Silver-Catalyzed Enantioselective Propargylic C–H Bond Amination Through Rational Ligand Design

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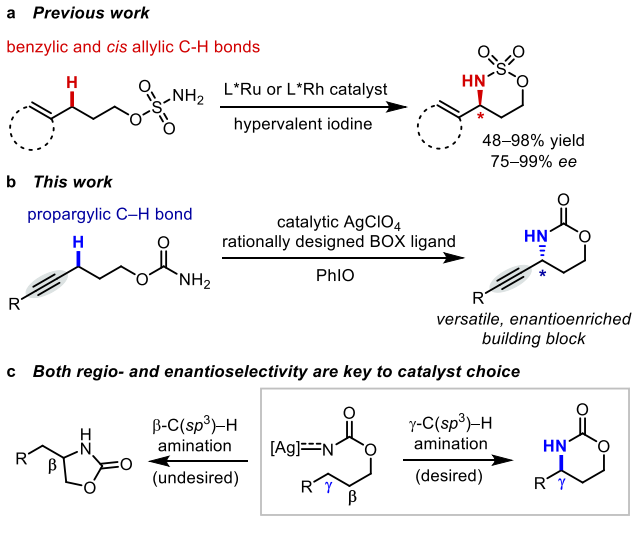
ABSTRACT: Asymmetric C–H amination via nitrene transfer (NT) is a powerful tool for the preparation of enantioenriched amine building blocks from abundant C–H bonds. Herein, we report a highly regio- and enantioselective synthesis of γ-alkynyl γ-amino alcohol motifs via a silver-catalyzed propargylic C–H amination. The protocol was enabled by development of a new bis(oxazoline) (BOX) ligand through a rapid structure-activity relationship (SAR) analysis. The method utilizes readily accessible carbamate ester substrates bearing γ-propargylic C–H bonds and furnishes versatile products in good yields and with excellent enantioselectivity (90–99% *ee*). A putative Ag–nitrene intermediate is proposed to undergo an enantiodetermining hydrogen-atom transfer (HAT) during the C–H amination event. Density functional theory (DFT) calculations were performed to investigate the origin of enantioselectivity in the HAT step.

Enantioselective syntheses of γ-amino alcohols is an attractive goal, as diverse biologically active molecules contain this motif,[1] including the antibiotics negamycin and nikkomycin Z,[1a-c] and the HIV treatments lopinavir and ritonavir.[1e-g] γ-Amino alcohols are valuable precursors to β-amino acids, which can be incorporated into peptides as a strategy to modulate their drug-like properties,[2] and are also convenient sources of chirality for diverse asymmetric transformations.[3] A popular strategy to prepare enantioenriched γ-amino alcohols involves formation of chiral imine or carbonyl intermediates, followed by diastereoselective reduction of the C=X (X = N or O) bond.[4-9] However, these asymmetric Mannich-based[4-6] or chiral auxiliary-directed[7-9] strategies require additional chemical steps. The direct asymmetric transformation of C–H to C–N bonds via transition metal-catalyzed nitrene transfer (NT) offers the potential for streamlined access to γ-amino alcohols from simple, abundant alcohol precursors.[10] In 2008, the Blakey and Du Bois groups independently reported the first examples of asymmetric amination of benzylic and allylic C–H bonds to furnish enantioenriched γ-amino alcohols in good *ee* using chiral Ru and Rh catalysts, respectively (Scheme 1a).[11,12]

Since He's first reports of Ag-catalyzed NT,[13] we and others have exploited the diverse coordination of Ag(I) species supported by sp^2 *N*-coordinating ligands to achieve tunable and predictable NT reactions with excellent control over chemo- and site-selectivity.[14,15] The flexibility of ligands capable of supporting Ag-catalyzed NT make this metal an ideal platform for developing general catalysts for asymmetric NT reactions. In 2017, we reported the first examples of chemoselective, Ag-catalyzed asymmetric aziridination using a 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] ((*S*,*S*)-^{t}Bu-BOX) ligand,[15e] while Bach recently disclosed a site- and enantioselective C–H amination of 2-quinolones and 2-pyridones catalyzed by a heteroleptic Ag(I) bis(phenanthroline) complex.[16] In this communication, we describe coupling the flexibility of silver-catalyzed NT with the rational design of new ligands for the asymmetric amination of propargylic C–H bonds (Scheme 1b) to enantioenriched γ-alkynyl γ-amino alcohol building blocks.

Several factors were considered in our ligand design. One important issue is site-selectivity, as the putative metal nitrene generated from a carbamate precursor can engage a β- or γ-C(*sp*^{3})–H bond (Scheme 1c) to form either a 5- or 6-member heterocycle *en route* to 1,2- or 1,3-amino alcohol products. We previously demonstrated that ligand choice is key to achieving tunable catalyst control over ring size, with

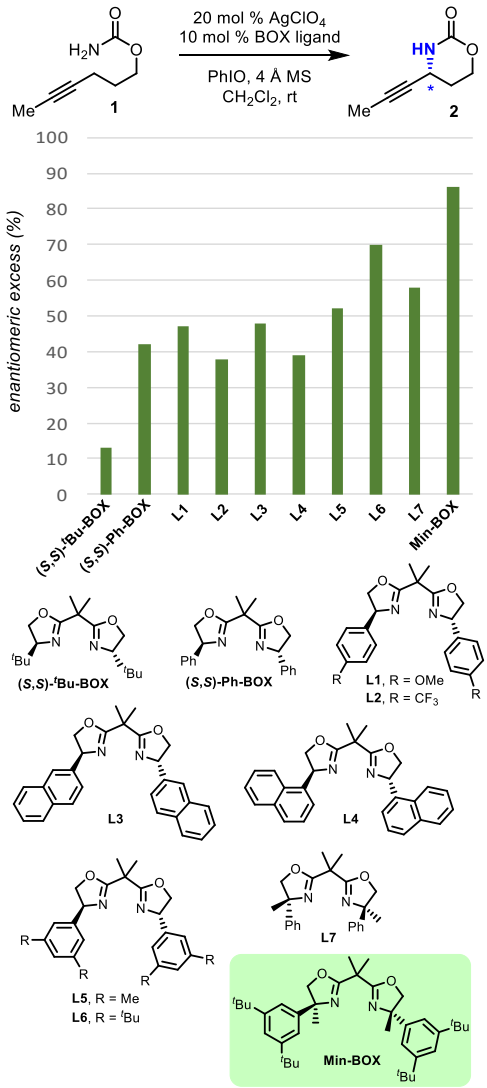
Scheme 1. Prior and proposed asymmetric C–H bond amination.



a bidentate, achiral 2,2′-isopropylidenebis[4,4-dimethyl-2-oxazoline] (dmBOX) ligand showing a strong preference for γ-C–H bond amination.[15i] A second concern involved mini-

mizing dynamic behavior of the Ag(I) complex in solution to ensure good transfer of stereochemical information from catalyst to product. Previous diffusion-ordered spectroscopy (DOSY) and variable temperature (VT) NMR studies of a silver complex formed from dmBOX and $AgClO_4$ revealed no equilibrium between monomeric and dimeric species, and no fluxional behavior of the ligand.[15i] Finally, the challenges inherent in differentiating between two prochiral hydrogen atoms on a carbon adjacent to the linear, compact alkyne group required a modular, readily tunable ligand scaffold. Given these considerations, BOX ligands were a logical choice to investigate to achieve our goal of site- and enantioselective propargylic C–H bond amination.

Studies were initiated with carbamate ester **1**, bearing two activated propargylic C–H bonds at the γ-position. A variety of chiral BOX ligands were explored (Figure 1, full details in the Supporting Information) using simple structure-activity

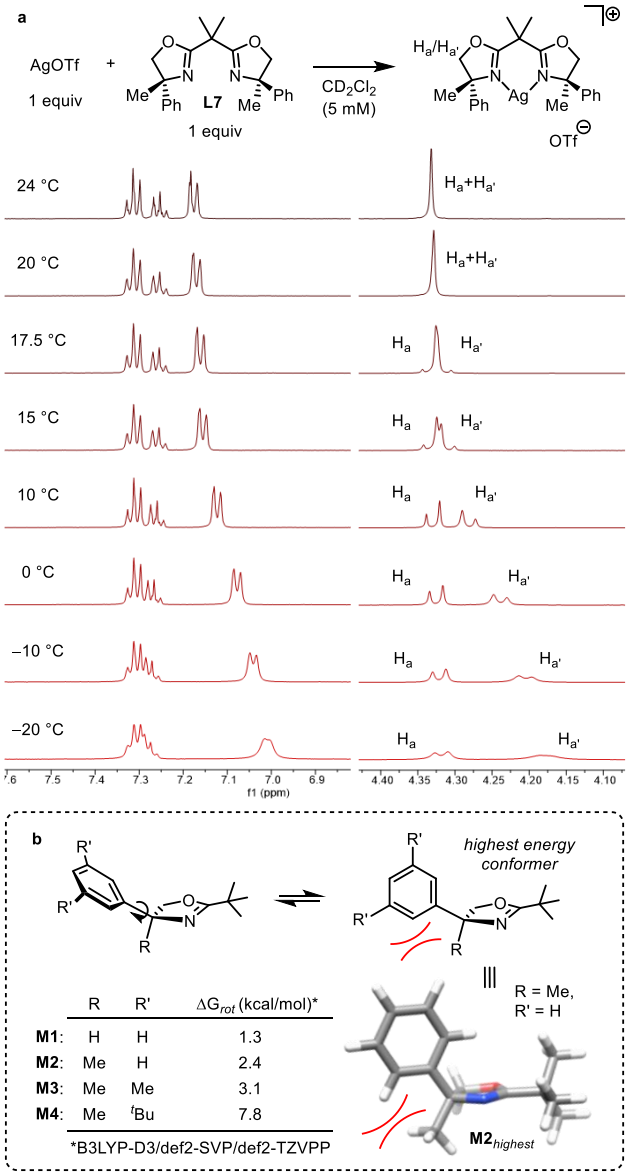


Conditions: **1** (0.1 mmol), $AgClO_4$ (20 mol %), BOX ligand (10 mol %), PhIO (2 equiv), 4 Å MS (100 mg), CH_2Cl_2 (2 mL), rt. *ee* was determined by chiral HPLC analysis after benzylation of product **2**. **L7** produced the opposite enantiomer.

Figure 1. SAR between BOX ligand modification and enantioselectivity in Ag-catalyzed propargylic C–H bond amination of **1**.

relationships (SAR) to rapidly identify a promising candidate. Subjecting **1** to conditions for enantioselective aziridination with commercially available (*S*,*S*)-^{t}Bu-BOX ligand,[15e] resulted in a good yield of oxazinanone **2**, but in only 13% *ee.* Interestingly, when the ^{t}Bu was substituted with a Ph group ((*S*,*S*)-Ph-BOX), a significant enhancement to 42% *ee* was observed. This was a promising lead, as the aryl-substituted BOX scaffold is highly modular and the steric and electronic features of the ligand can be readily tuned.[17] Electronic modifications to the aryl groups in **L1** and **L2** were used to probe if substrate-ligand π–π or metal-ligand cation–π interactions might influence *ee*.[15f,18] Neither electron-donating (**L1**) nor electron-withdrawing groups (**L2**) at the *para* position had much impact, giving 47% and 38% *ee*, respectively. BOX ligands substituted with a 2-naphthyl (**L3**) or 1-naphthyl group (**L4**) indicated increasing steric bulk at the *meta* position of the aryl group (**L3**) had a positive impact on the *ee* of **2** (48% *ee*), while substitution at the *ortho* position of the aryl group (**L4**) decreased the *ee* to 39%. Indeed, installation of *meta*-Me and ^{t}Bu groups on the aromatic ring of BOX ligands **L5** and **L6** improved the *ee* significantly, up to 70% *ee* in the case of **L6**. Replacing the hydrogens at the chiral carbons of (*S*,*S*)-Ph-BOX with Me groups to yield fully substituted carbon centers in **L7** improved *ee* from 42% to 58%. Gratifyingly, combining the features that improve *ee* into a single **Min-BOX** ligand gave 86% *ee* and a near-quantitative yield of **2** at room temperature. The *ee* was further improved at lower temperatures, furnishing up to 90% *ee* at –10 °C (see the SI for details of optimization).

The beneficial effect of additional substitution at the stereocenter α to the coordinating *N* atoms in **L7** and **Min-BOX** ligands was at first counterintuitive, as replacing H with Me should reduce facial discrimination in the NT event. We hypothesized this modification suppressed detrimental dynamic behavior of the complex by increasing the steric congestion near the silver center.[19] Previous observations showed certain *N*-chelating ligands for Ag(I) lead to equilibrating mixtures of mono- *vs.* bis-ligated species, as well as monomeric *vs.* dimeric complexes;[15a,15i,19c] the presence of multiple potential catalytic species leads to a loss of selectivity. Indeed, NMR studies of silver complexes supported by **L7** and **Min-BOX** did not show any equilibrium between mono- and bis-ligated species (see the SI for details). Rather, the data suggested the presence of altered conformer populations in the Ag(**L7**)OTf complex at different temperatures (Figure 2a). The VT ^{1}H NMR spectra of Ag(**L7**)OTf in CD_2Cl_2 (5 mM) showed substantial changes in the chemical shifts of the diastereotopic protons H_a and $H_{a'}$ and the aromatic protons as the temperature was decreased, while no changes in chemical shift were observed in Ag complexes supported by BOX ligands lacking a fully substituted carbon center. Although individual conformer signals of Ag(**L7**)OTf were not resolved even at –90 °C, this implies a relatively high energy barrier for the rotations around single bond(s).[20] DFT calculations were carried out on truncated mono-oxazoline models to shed further insight into the influence of the fully substituted carbon center on bond rotation (Figure 2b, see the SI for details). Relaxed surface scans were conducted by rotating the N–C–C–C dihedral angle (10° increments, 36 steps) to assess the energetic penalty of rotating the aromatic ring (ΔG_{rot}). Installation of the α-Me group (**M2**) increases bond rotation energy relative to the



	R	R'	ΔG$_{rot}$ (kcal/mol)*
M1:	H	H	1.3
M2:	Me	H	2.4
M3:	Me	Me	3.1
M4:	Me	^{t}Bu	7.8

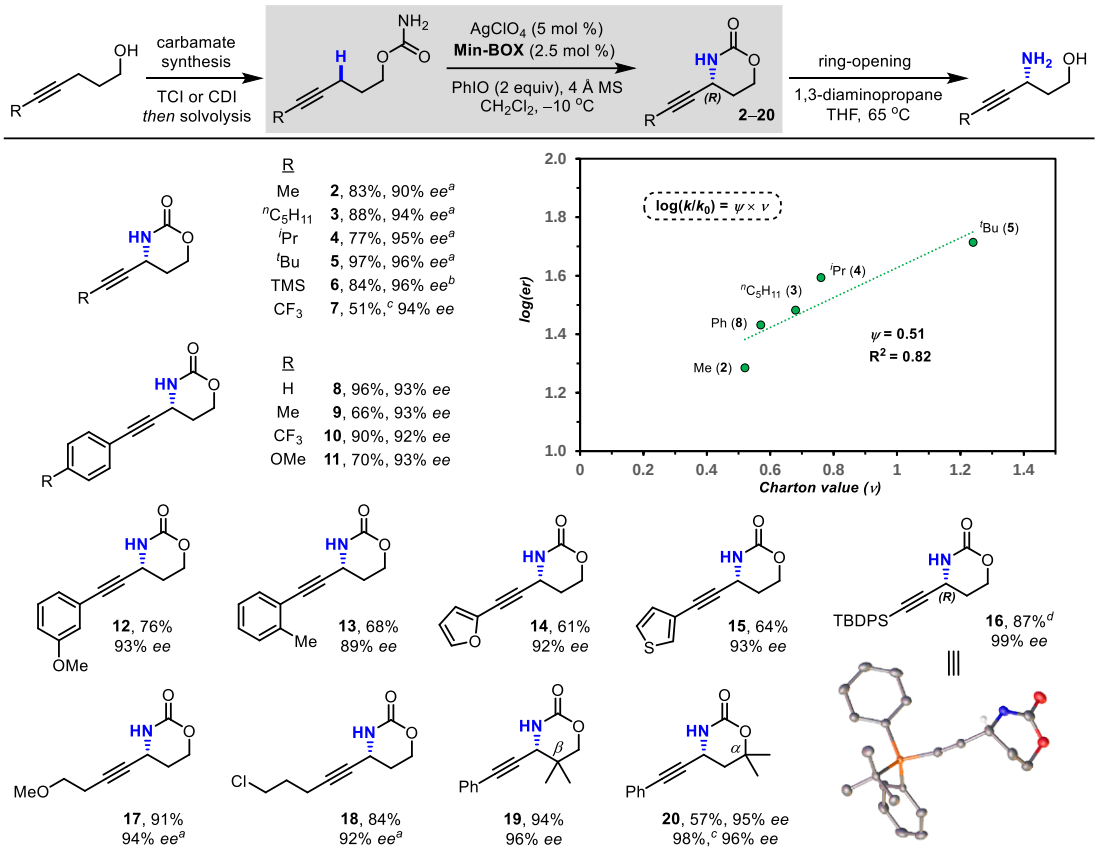
Figure 2. Effect of the additional Me substitution in the ligand. (a) VT-NMR studies of [Ag(**L7**)]OTf complex. (b) Increased rotational barrier (ΔG$_{rot}$) for the Ar group, as supported by DFT calculations.

M1 model (ΔΔG$_{rot}$ = +1.1 kcal/mol from **M1** to **M2**). Successful bond rotation with this increased steric hindrance involves placing the *ortho*-proton within ~2.2–2.4 Å from two of the α-Me protons. In agreement with the observed *ee* enhancement, introduction of *meta*-Me substitution on the aryl ring increased the bond rotation energy to 3.1 kcal/mol (**M3**). Further steric crowding with *meta*-^{t}Bu groups gave a 7.8 kcal/mol bond rotation energy (**M4**), nearly 6.5 kcal/mol greater than the **M1** model. We postulate the increased rotational barrier introduced by the α-Me group substitution and the restricted rotation of the aryl ring in BOX ligands **L7** and **Min-BOX** rigidify the enantiodetermining transition state (TS) and enhance asymmetric induction.

With optimized conditions in hand, the scope of the reaction was explored (Figure 3). In general, substrates containing bulky alkyl or aryl substitution at the distal carbon of the alkyne gave excellent yields and *ee*. For example, altering the distal R group from the initial methyl group in **2** to bulkier substituents, such as *n*-pentyl (**3**), *i*-propyl (**4**) or *t*-butyl groups (**5**), resulted in increased *ee* to 94–96%. Notably, the enantioselectivities were not affected by electronic modifications to the alkyne precursors. Both **6** (R = TMS) and **7** (R = CF_3) gave excellent *ee*, although an increased catalyst loading was required for the CF_3-substituted alkyne **7**, due to slow conversion. These results helped to rule out the possibility of alkyne–Ag interactions playing a critical role in the enantiodetermining step. Carbamate esters containing a Ph group attached to the distal alkyne carbon (**8**), as well as derivatives possessing both electron-donating (**9** and **11**) and an electron-withdrawing groups (**10**) at the *para*-position were successfully transformed into the corresponding oxazinanones in high *ee* (92–93%). Addition of –OMe at the *meta*-position of the Ar substituent was tolerated (**12**), while *ortho*-Me-substitution slightly diminished the *ee* (**13**). Alkynes bearing heterocyclic groups, such as a furan (**14**) and a thiophene (**15**), were also tolerated under the reaction conditions.

The impact of the steric bulk of the substituents at the distal carbon of the alkyne precursors on *ee* was further examined through linear free-energy relationships (LFER) using the steric parameters and modified Taft equation developed by Charton.[21] The equation $\log(k/k_0) = \psi\nu$ describes a relationship between the relative rate (k/k_0) and steric parameters (ν), with ν defined from measuring steric effects in the rates of methyl ester hydrolysis. The k/k_0 is equal to the enantiomeric ratio (*er*) when evaluating an asymmetric reaction; therefore, log(*er*) is proportional to the product of ψ (the sensitivity factor) and ν.[22] A LFER with a good correlation (R^2 = 0.82) was observed when log(*er*) was plotted *vs.* ν values for **2**–**5** and **8**. The positive sensitivity factor ψ and high correlation with Charton's steric parameters indicate that larger groups on the distal alkyne carbon should yield higher *ee*. To test this prediction, a substrate containing an alkyne protected with a *t*-butyldiphenylsilyl (TBDPS) group was prepared and subjected to asymmetric C–H amination to give **16** in 99% *ee*. The oxazinanone **16** was subjected to a mild ring-opening conditions to give a 92% NMR yield of the corresponding γ-amino alcohol, while preserving the TBDPS group. The absolute configuration of **16** was determined to be (*R*) by X-ray crystallography; other product configurations assigned by analogy to **16**. Additionally, substrates bearing an alkyl ether (**17**) or an alkyl chloride (**18**) were well-tolerated in this chemistry, furnishing excellent *ee* of 93% and 92%, respectively. Substitution in the tether was also possible at both the α- and β-positions and had no detrimental effect on the enantioselectivity of the reaction (**19**–**20**, 95–96% *ee*). The carbamate ester precursor to **20** is particularly noteworthy, as it is derived from a tertiary alcohol that does not effectively form the sulfamate precursor required for Ru- and Rh-catalyzed NT.[11,12] While α-substitution in **20** led to a drop in conversion under standard conditions, a higher catalyst loading restored reactivity; this approach is also effective for substrates with electron-poor propargylic C–H bonds, such as the precursor to **7**.

Previously reported experimental and computational studies on Ag-catalyzed NT reactions suggest the mechanistic pathway proposed in Figure 4a. The carbamate ester



Conditions: carbamate ester (0.2 mmol), $AgClO_4$ (5 mol %), **Min-BOX** (2.5 mol %), PhIO (2 equiv), 4 Å MS (200 mg), CH_2Cl_2 (4 mL), –10 °C. Isolated yields indicated; *ee* determined by chiral HPLC analysis. [a]*ee* determined after benzylation. [b]*ee* determined after benzoylation. [c]Reaction used 2x catalyst loading (10 mol % $AgClO_4$ / 5 mol % **Min-BOX**). [d]The free 1,3-amino alcohol was obtained in 92% NMR yield after deprotection with 1,3-diaminopropane (20 equiv), THF (0.1 M), 65 °C.

Figure 3. Substrate scope and LFER study of Ag-catalyzed enantioselective amination of propargylic C–H bonds

nitrene precursor **A** initially undergoes ligand exchange with the iodosobenzene (PhIO) oxidant to form an iminoiodinane species **B** (Figure 4a).[15e,23] A silver–nitrene complex **C** is generated by reacting the iminoiodinane species with a chiral Ag(I) catalyst. According to our previous DFT studies, the reactive intermediate **C** is best described as Ag(II)–nitrene radical anion, which abstracts a prochiral propargylic hydrogen in a hydrogen atom transfer (HAT) step, followed by a rapid radical recombination (RR) step.[14d,14f,18c] The radical species is not a stationary point on the potential energy surface, as the RR step displays no energy barrier; experimentally, no radical intermediates are intercepted or trapped. Previous observations confirm the C–H amination is stereoretentive, further supporting the rapid nature of the RR step[15i-j,19b] and suggesting the initial HAT is the enantiodetermining step in the asymmetric C–H bond amination.

In order to probe the origin of enantioselectivity in the HAT, TS modeling of the two prochiral pathways was conducted on the propargylic C–H amination of carbamate ester **1** using a silver catalyst supported by a model BOX ligand **L8** (truncated from **Min-BOX**: *meta*-^{t}Bu→Me) (Figure 4b). The silver complex Ag(**L8**)$^+$ in the calculations was supported by a single BOX ligand, as DOSY NMR experiments show Ag-BOX complexes in solution are monomeric.[15i,24] We were delighted to find the DFT calculations successfully predicted the observed (*R*) absolute configuration, with the pro-*R* pathway favored by 1.7 kcal/mol. The pro-*R* TS places the substrate tail in close proximity to the *para*-position of the aryl ring (2.794 Å) to avoid steric interactions with the fully substituted carbon center. The alkyne position faces away from the ligand scaffold, with an alkyne substituent···*meta*-Me distance of (2.778 Å). Conversely, the disfavored pro-*S* TS places the alkyne tail near the *ortho*-proton of the aryl ring (2.546 Å), with an alkyne Me···*meta*-Me distance of 3.235 Å. This alkyne orientation introduces steric interactions between the substrate tail and the α-Me group of the fully substituted carbon center (2.884 Å), which is absent in the pro-*R* pathway. Though these TS models differ in their steric interactions, near-linear N···H···C geometries were observed for both the pro-*R* (158.3°) and pro-*S* (161.7°) TS in the HAT, consistent with our previous computational studies.[15i] In accordance with the anticipated rigidity of **L8**, the aryl ring rotations from pro-*R* to pro-*S* only deviate up to 7.5°; indeed, introduction of the fully substituted carbon center and the *meta* alkyl substitution in the aryl ring of the **Min-BOX** reduces the ability of the ligand scaffold to minimize steric interactions in the disfavored pro-*S* pathway.

In conclusion, we report the first general catalyst for intramolecular, enantioselective propargylic C–H amination proceeding via an Ag-catalyzed NT pathway. A new **Min-BOX** ligand was rationally designed to transform carbamate

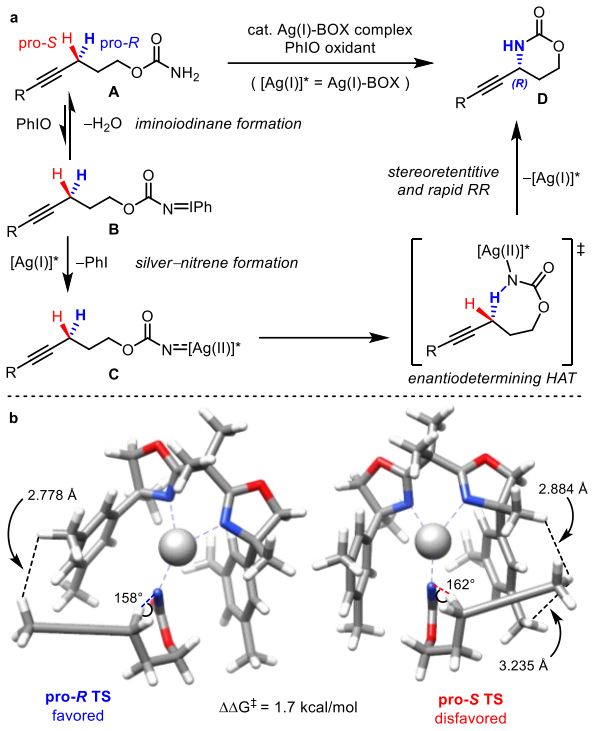


Figure 4. (a) Proposed mechanism of Ag-catalyzed enantioselective propargylic C–H amination. (b) B3LYP-D3/def2-SVP/def2-TZVPP transition state models of pro-*R* and pro-*S* HAT pathways employing substrate **1** and Ag(**L8**)$^+$ complex.

ester substrates bearing two prochiral γ-propargylic C–H bonds to γ-amino alcohol motifs in good yields and *ee*. Charton's modified Taft equation and steric parameters established a LFER between the size of groups on the distal alkyne carbon and the *ee* of the NT. DFT calculations further validated that the design features introduced into **Min-BOX** effectively differentiate between the pro-*R* and pro-*S* protons during the enantiodetermining HAT step. The oxazinanones generated from this method are easily deprotected and derivatized to enantioenriched amino alcohols that can serve as useful building blocks for diverse molecules, including the platelet aggregation inhibitor, Xemilofiban,[25] anti-malarial falcipain-2 inhibitors,[26] and other amines.

ASSOCIATED CONTENT

Characterization data, optimization tables, and additional substrates/catalysts are included in the supplementary materials, which are available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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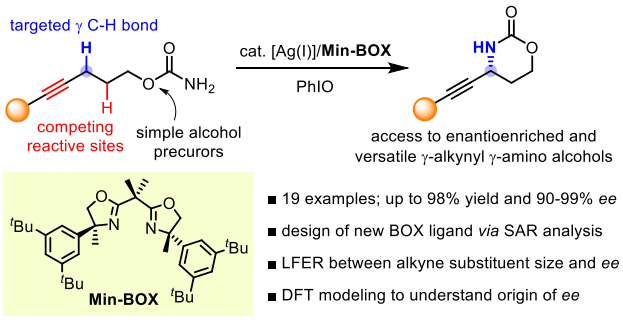

- 19 examples; up to 98% yield and 90-99% *ee*
- design of new BOX ligand *via* SAR analysis
- LFER between alkyne substituent size and *ee*
- DFT modeling to understand origin of *ee*