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Communication

Silver-Catalyzed Enantioselective Propargylic C−H Bond Amination through Rational Ligand Design

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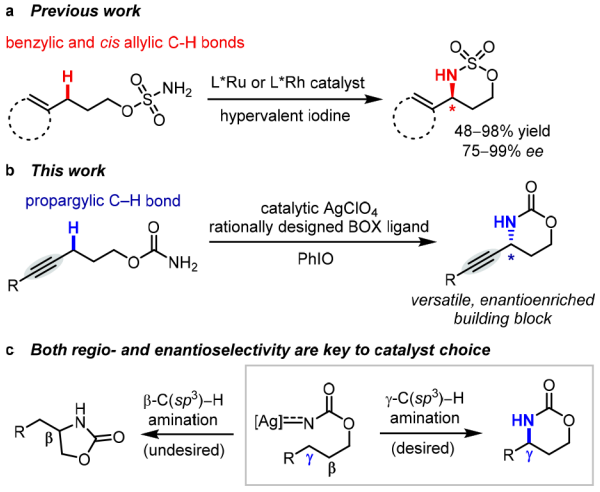
ABSTRACT: Asymmetric C−H amination via nitrene transfer is a powerful tool to prepare enantioenriched amine precursors from abundant C−H bonds. Herein, we report a regio- and enantioselective synthesis of γ-alkynyl γ-aminoalcohols via a silver-catalyzed propargylic C−H amination. The protocol was enabled by a new bis(oxazoline) (BOX) ligand designed via a rapid structure−activity relationship (SAR) analysis. The method utilizes accessible carbamate esters bearing γ-propargylic C−H bonds and furnishes versatile products in good yields and excellent enantioselectivity (90−99% *ee*). The putative Ag−nitrene is proposed to undergo enantiodetermining hydrogen-atom transfer (HAT) during the C−H amination event. Density functional theory calculations shed insight into the origin of enantioselectivity in the HAT step.

Enantioselective syntheses of γ-aminoalcohols are attractive, as diverse bioactive molecules contain this motif,[1] including antibiotics negamycin and nikkomycin Z[1a−c] and HIV drugs lopinavir and ritonavir.[1e−g] γ-Aminoalcohols are valuable precursors to β-amino acids, which are incorporated into peptides to modulate their drug-like properties,[2] and function as asymmetric ligands.[3] Enantioenriched γ-aminoalcohols are commonly prepared by diastereoselective reductions of chiral imines or carbonyls;[4−9] however, asymmetric Mannich-based[4−6] or chiral auxiliary-directed[7−9] strategies require additional chemical steps. Direct, asymmetric transformations of C−H to C−N bonds via transition-metal-catalyzed nitrene transfer (NT) can streamline access to γ-aminoalcohols from abundant alcohols, as shown independently by the Blakey and Du Bois groups in asymmetric aminations of benzylic and allylic C−H bonds using chiral Ru and Rh catalysts, respectively (Scheme 1a).[10,11] Recent examples of asymmetric NT of propargylic C−H bonds include Ir- and Ru-catalyzed syntheses of γ-lactams and Fe- and Co-catalyzed transformations of sulfamoyl azides to sulfamides.[12,13] Although these reports achieve enantioselective propargylic C−H amination, they do require specific dioxazolone or sulfamoyl azide precursors and cannot be applied to the synthesis of versatile γ-aminoalcohol building blocks.

Since He's first reports of Ag-catalyzed NT,[14] the diverse coordination of Ag(I) supported by *N*-coordinating ligands has been exploited to achieve tunable NT with excellent chemoselectivity and site-selectivity.[15,16] This flexibility makes silver an ideal platform to develop general catalysts for asymmetric NT. In 2017, we reported the first chemoselective, Ag-catalyzed asymmetric aziridination using a 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] ((*S*,*S*)-^{t}Bu-BOX) ligand,[16e] while Bach disclosed a site-selective and enantioselective C−H amination of 2-quinolones and 2-pyridones catalyzed by a heteroleptic Ag(I) bis-(phenanthroline) complex.[17] Herein, we couple the versatility of silver with the rational design of new ligands to achieve asymmetric amination of propargylic C−H bonds to enantioenriched γ-alkynyl γ-aminoalcohols (Scheme 1b).

Scheme 1. Prior and Proposed Asymmetric C−H Bond Amination



Several factors were considered in ligand design, particularly site-selectivity, as a metal nitrene generated from a carbamate can engage either a β- or γ-C(sp^3)−H bond (Scheme 1c) to form a 5- or 6-membered heterocycle. We previously

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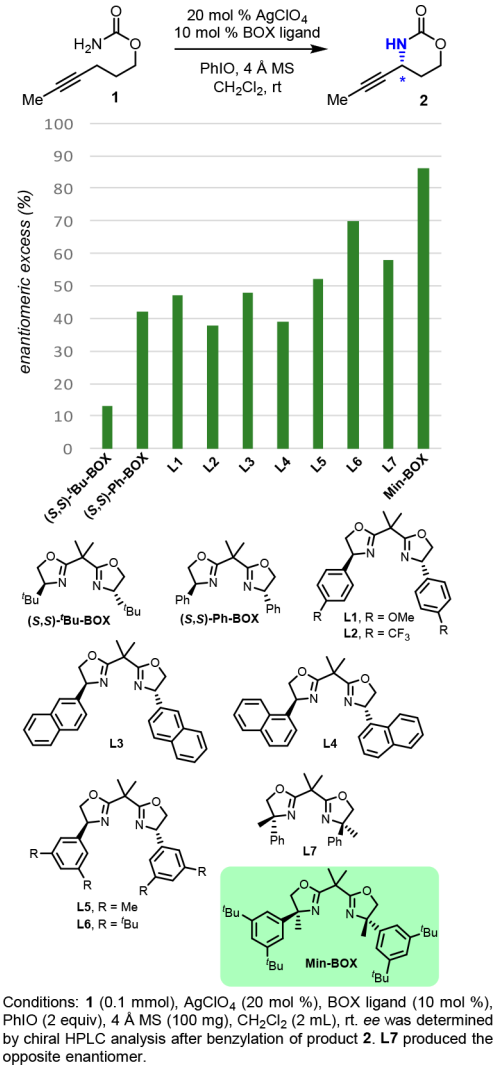
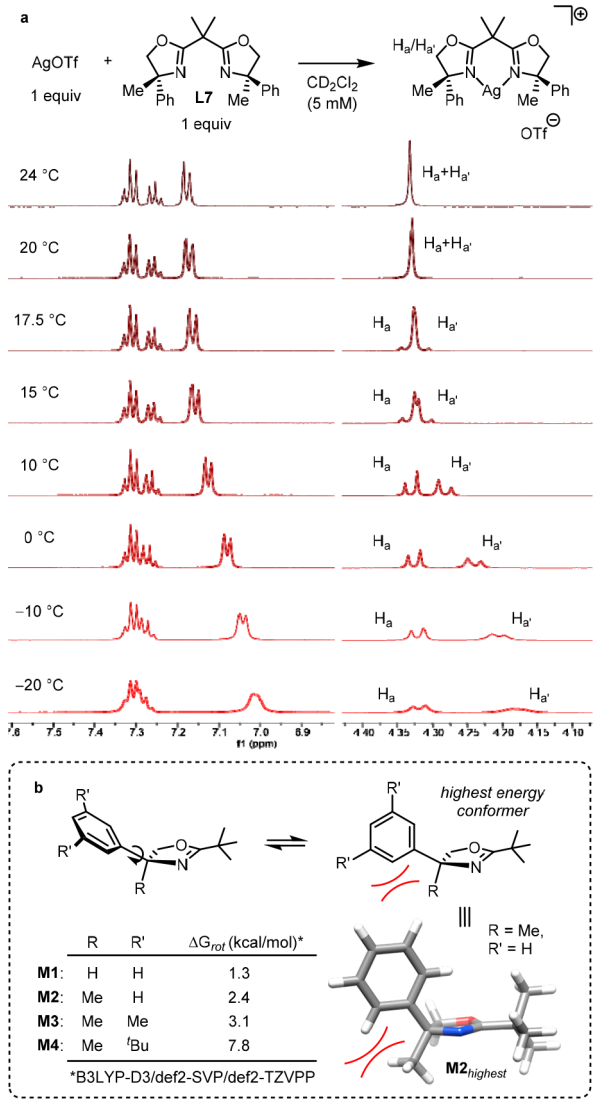


Conditions: **1** (0.1 mmol), $AgClO_4$ (20 mol %), BOX ligand (10 mol %), PhIO (2 equiv), 4 Å MS (100 mg), CH_2Cl_2 (2 mL), rt. *ee* was determined by chiral HPLC analysis after benzylation of product **2**. **L7** produced the opposite enantiomer.

Figure 1. Ligand optimization for C−H bond amination of **1**.



	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 α-Me substitution in the ligand. (a) VT-NMR studies of [Ag(**L7**)]OTf. (b) Increased rotational barrier (ΔG_{rot}) for the Ar-group, as supported by DFT calculations.

demonstrated ligand choice is key to tunable catalyst control over ring size, with the bidentate, achiral 2,2′-isopropylidene-bis[4,4-dimethyl-2-oxazoline] (dmBOX) showing strong preference for γ-C−H bond amination.[16i] A second concern involved minimizing dynamic behavior of the Ag(I) complex to ensure good transfer of stereochemical information from catalyst to product. Previous diffusion-ordered spectroscopy (DOSY) and variable-temperature (VT) NMR studies of silver complexes formed from dmBOX and $AgClO_4$ revealed no equilibrium between monomeric/dimeric species and no fluxional ligand behavior.[16i] Finally, challenges inherent in differentiating between prochiral hydrogens on the carbon adjacent to the alkyne required a modular ligand design, with the BOX scaffold ideal for further investigations.[18]

Studies were initiated with carbamate ester **1**, bearing two propargylic C−H bonds at the γ-position. A variety of chiral BOX ligands were explored (Figure 1; see Supporting Information (SI) for details) to rapidly identify a promising candidate. Subjecting **1** to $AgClO_4$/(*S*,*S*)-^{t}Bu-BOX[16e] gave a good yield of **2**, but in only 13% *ee*. Interestingly, when ^{t}Bu was substituted with Ph ((*S*,*S*)-Ph-BOX), the *ee* was enhanced to 42%. This was promising, as aryl-substituted BOX ligands enable ready tuning of sterics and electronics.[18] Aryl groups containing *para*-electron-donating (**L1**) or electron-withdrawing (**L2**) groups gave **2** in 47% and 38% *ee*, respectively, suggesting substrate−ligand π−π or metal−ligand cation−π interactions do not exert much influence on *ee*. BOX ligands substituted with 2-naphthyl (**L3**) or 1-naphthyl groups (**L4**) indicated increased steric bulk at the aryl *meta*-site (**L3**, 48% *ee*) is more beneficial than substitution at the *ortho*-position (**L4**, 39% *ee*). Indeed, installation of *meta*-Me and ^{t}Bu groups on the aryl rings of **L5** and **L6** improved the *ee* to 70% 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%.[19] Gratifyingly, combining all the features that improve *ee* into a single **Min-BOX** ligand gave 86% *ee* and a near-quantitative yield of **2** at rt, optimized to 90% *ee* at −10 °C (see SI for details).

The beneficial effect of the fully substituted stereocenter α to the nitrogens in **L7** and **Min-BOX** appeared 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 steric congestion near the silver.[20] Previous observations showed certain *N*-chelating ligands for Ag(I) give equilibrating

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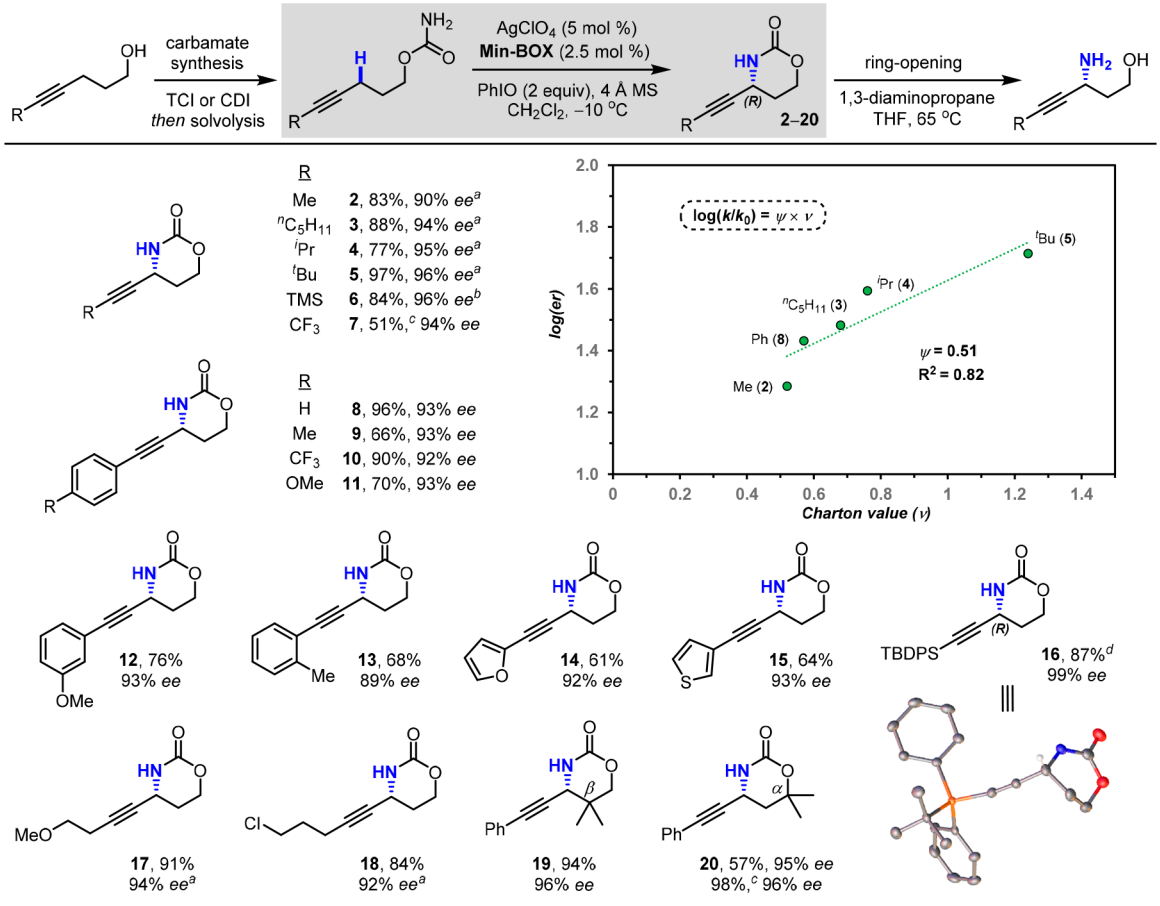

Conditions: carbamate ester (0.2 mmol), $AgClO_4$ (5 mol %), **Min-BOX** (2.5 mol %), PhIO (2 equiv), 4 Å MS (200 mg), CH_2Cl_2 (4 mL), −10 °C. Isolated yields indicated; *ee* determined by chiral HPLC analysis. [a]*ee* determined after benzylation. [b]*ee* determined after benzoylation. [c]Reaction 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 propargylic C−H bond amination.

mixtures of mono- vs bis-ligated species, as well as monomeric/dimeric complexes,[16a,i,20c] which can result in loss of selectivity. Gratifyingly, NMR studies of a silver complex supported by **L7** showed no equilibrium between mono- and bis-ligated species (see SI for details); rather, the data suggested altered conformer populations in Ag(**L7**)OTf at different temperatures (Figure 2a). VT ^{1}H NMR spectra of Ag(**L7**)OTf in CD_2Cl_2 (5 mM) showed substantial changes in the chemical shift of diastereotopic protons H_a and $H_{a'}$ as the temperature decreased. No changes in 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 unresolved at −90 °C, a relatively high energy barrier for rotation around single bonds was implied.[21] DFT calculations on truncated mono-oxazoline models shed insight into the influence of the fully substituted carbon center on bond rotation (Figure 2b; see 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 (**M2**) increases bond rotation energy relative to the **M1** model ($\Delta\Delta G_{rot}$ = +1.1 kcal/mol from **M1** to **M2**). Successful bond rotation with this increased hindrance places the *ortho*-proton within ∼2.2−2.4 Å of 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 α-Me group substitution and the restricted rotation of the aryl ring in **L7** and **Min-BOX** rigidify the enantiodetermining transition state (TS) and enhance asymmetric induction.

With optimized conditions in hand, the reaction scope was explored (Figure 3). In general, substrates containing bulky alkyl or aryl substitution at the distal alkyne carbon gave excellent yields and *ee*. For example, altering R from a methyl in **2** to *n*-pentyl (**3**), isopropyl (**4**), or *tert*-butyl (**5**) increased the *ee* to 94−96%. Notably, *ee* was not affected by electronic modifications to the alkyne. Both **6** (R = TMS) and **7** (R = CF_3) gave excellent *ee*; increased catalyst loading was required for CF_3-substituted alkyne **7**, due to slow conversion and ruled out the likelihood of alkyne−Ag interactions playing a critical role in the enantiodetermining step. Phenyl-substituted alkyne **8** and derivatives possessing both electron-donating (**9** and **11**) and electron-withdrawing groups (**10**) at the *para*-position were successfully transformed into 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 lowered *ee* (**13**). Alkynes bearing heterocyclic groups, including furan (**14**) and thiophene (**15**), were also tolerated.

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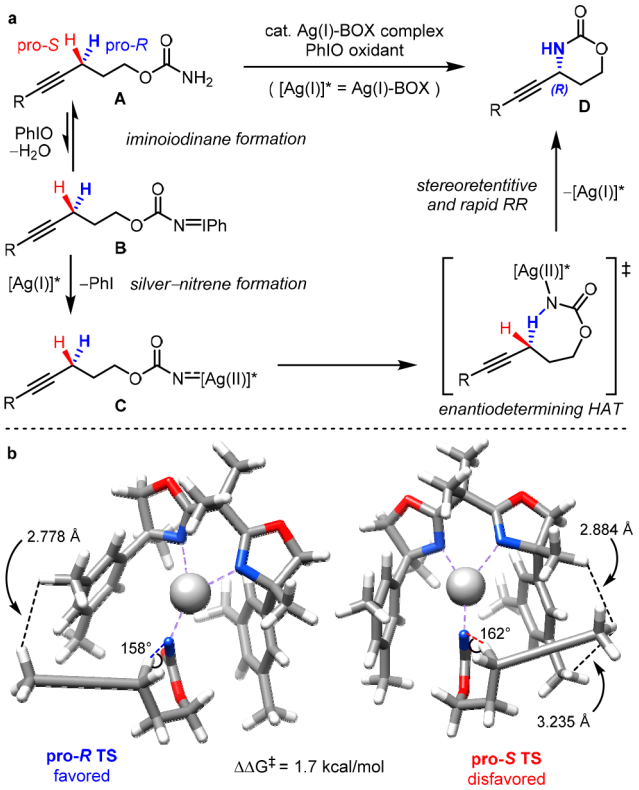

Figure 4. (a) Proposed mechanism of Ag-catalyzed enantioselective propargylic C–H amination. (b) B3LYP-D3/def2-SVP/def2-TZVPP transition state models of pro-*R* and pro-*S* HAT pathways employing substrate **1** and Ag(**L8**)$^+$ complex.

The impact of steric bulk at the distal alkyne carbon on *ee* was further examined through linear free-energy relationships (LFER) using Charton's steric parameters and the modified Taft equation.[22] The relationship between the relative rate (k/k_0) and steric parameters (ν) is described by $\log(k/k_0) = \psi\nu$, with ν defined from measurements of steric effects on rates of methyl ester hydrolysis. As k/k_0 = enantiomeric ratio (*er*) when evaluating an asymmetric reaction, log(*er*) is proportional to the product of ψ (the sensitivity factor) and ν.[23] An LFER with a good correlation ($R^2 = 0.82$) was observed in a plot of log(*er*) vs ν 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 *tert*-butyldiphenylsilyl (TBDPS) group was installed on the alkyne, and asymmetric C–H amination gave **16** in 99% *ee*. The absolute configuration of **16** was assigned as (*R*) by X-ray crystallography; other configurations were assigned by analogy. The oxazinanone ring of **16** was opened under mild conditions to give a 92% NMR yield of the corresponding γ-aminoalcohol, while preserving the TBDPS group. Substrates bearing alkyl ethers (**17**) or alkyl chlorides (**18**) were well-tolerated, furnishing an *ee* of 93% and 92%, respectively. Substitution in the tether at both the α- and β-positions had no detrimental effect on *ee* (**19**–**20**, 95–96% *ee*). The carbamate ester precursor to **20** is particularly noteworthy, as tertiary alcohols cannot effectively form the sulfamate precursors required for Ru- and Rh-catalyzed NT.[10,11] While α-substitution in **20** led to a drop in conversion under standard conditions, a higher catalyst loading restored reactivity.

Experimental and computational studies of Ag-catalyzed NT suggest the mechanistic pathway in Figure 4a. Nitrene precursor **A** initially undergoes ligand exchange with the iodosobenzene (PhIO) oxidant to form iminoiodinane species **B**.[16e,20c,24] A silver–nitrene complex **C** results from reaction of **B** with a chiral Ag(I) catalyst. According to our previous DFT studies, reactive intermediate **C** is best described as a Ag(II)–nitrene radical anion, which abstracts a prochiral propargylic hydrogen in an H-atom transfer (HAT) step, followed by a rapid radical recombination (RR).[16d,f,20c,25] The radical species is not a stationary point on the potential energy surface, as the RR displays no energy barrier; experimentally, no radical intermediates are trapped. Previous observations confirm the C–H amination is stereoretentive, further supporting the rapid nature of the RR[16i,j,20b] and suggesting the initial HAT is the enantio-determining step in this chemistry.

To probe the origin of enantioselectivity in the HAT, TS modeling of the two prochiral pathways was conducted on **1** using a silver catalyst supported by a model BOX ligand **L8** (truncated from **Min-BOX**: *meta*-^{t}Bu → Me) (Figure 4b). The computed silver complex Ag(**L8**)$^+$ was supported by a single BOX ligand, as DOSY NMR experiments show Ag-BOX complexes in solution are monomeric.[16i,26] We were delighted to find DFT calculations successfully predicted the observed (*R*) 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 Ar-ring (2.794 Å) to avoid steric interactions with the fully substituted carbon center. The alkyne faces away from the ligand scaffold, with an alkyne···*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 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.[16i] In accordance with the expected 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 *meta*-alkyl substitution in the aryl ring of the **Min-BOX** reduces the ability of the ligand to minimize steric interactions in the disfavored pro-*S* pathway.

In conclusion, we report the first general silver catalyst for intramolecular, enantioselective propargylic C–H amination proceeding via an NT pathway. A new **Min-BOX** ligand was rationally designed to transform carbamate esters bearing two prochiral γ-propargylic C–H bonds to γ-aminoalcohol motifs in good yields and *ee*. Charton's modified Taft equation and steric parameters established an LFER between the sterics of groups on the distal alkyne carbon and *ee*. DFT calculations further validated that the design features introduced into **Min-BOX** can effectively differentiate between prochiral protons during the enantio-determining HAT step. Oxazinanones generated from this method are easily deprotected to enantioenriched aminoalcohols that may serve as building blocks for diverse molecules, including the platelet aggregation inhibitor Xemilofiban,[27] antimalarial falcipain-2 inhibitors,[28] and other useful amines.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c05726.

Characterization data, optimization tables, and additional substrates/catalysts (PDF)

Atomic xyz coordinate data (conformational analyses, intermediate, reactant complexes, transition states) (ZIP)

X-ray crystallographic information for **16** (deposited with the CCDC as 2005980) (CIF)

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Notes

The authors declare no competing financial interest.

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