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Chemoselective Silver-Catalyzed Nitrene Transfer: Tunable Syntheses of Azepines and Cyclic Carbamimidates

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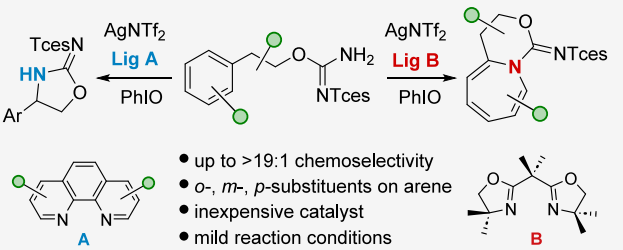
ABSTRACT: Azepines and their saturated azepane counterparts are important moieties in bioactive molecules but are under-represented in current drug screening libraries. Herein, we report a mild and efficient azepine formation via silver-catalyzed dearomative nitrene transfer. A 2,2,2-trichloroethoxysulfonyl (Tces)-protected carbamimidate nitrene precursor, coupled with the appropriate ligand for silver, is essential for achieving the unexpected chemoselectivity between arene dearomatization and benzylic C(sp^3)−H amination. Potential applications in the late-stage diversification of azepines to complex molecular scaffolds and diastereoselective hydrogenations to sp^3-rich derivatives are also highlighted.



INTRODUCTION

N-Heterocycles are common motifs in natural products and drugs; approximately 60% of the Food and Drug Administration (FDA)-approved small-molecule drugs contain at least one heterocycle.[1] Of these, seven-membered rings containing one nitrogen atom, including azepines and azepanes, are unrepresented in the current drug libraries. However, this is not due to a lack of bioactivity, as there are examples of azepanes that function as glycosidase inhibitors, antidiabetics, anticancer agents, and antiviral compounds (Scheme 1A).[1]

Common strategies for the syntheses of substituted azepanes (Scheme 1B) include various types of intramolecular cyclizations, [4 + 3] and related cycloadditions, expansion of strained ring intermediates, and ring-closing metathesis.[2] However, these *de novo* approaches largely require preinstallation of desired functionality and stereochemistry into the precursors and are not particularly modular; thus, there is intense interest in new methods for the synthesis of seven-membered *N*-heterocycles that employ readily available precursors. Based on our group's long-standing interest in transition metal-catalyzed nitrene transfer (NT), we were intrigued by an underexplored strategy involving nitrene insertion into an aromatic ring to form the seven-membered heterocycle. While the Büchner reaction to insert a carbene into an arene to form a seven-membered carbocycle is well known,[3a−h] the analogous "aza-Büchner" involving insertion of a nitrene into an aromatic precursor is underexplored. Early examples employed sulfonylazide[4a] or carbamate[4b] precursors, high temperatures, and/or pressures to generate the key free nitrene intermediate. As a result of these harsh conditions, reactions were generally low-yielding and exhibited poor chemoselectivity between competing reactions of free nitrene. More recently, the Wei group reported a $Rh_2(esp)_2$-catalyzed (esp: α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid) insertion of a nitrene formed from a carbamoyl azide precursor to furnish azepine scaffolds.[5] However, inconsistent selectivity between nitrogen insertion and C(sp^2)−H amination, coupled with the need for high temperatures, high Rh loadings, and prolonged reaction time, limited the versatility of this chemistry. Luan and co-workers similarly reported the synthesis of azepinones via the aminative dearomatization of naphthols,[6] although high temperatures and arene functionality at the *ortho* position were required. The Leonori group reported an elegant synthesis of azepines via a singlet aryl nitrene generated from photolysis of a nitroarene (Scheme 1C) followed by reduction of the azepines to their respective azepanes.[7] A large excess of $P(O^iPr)_3$ in the presence of blue LEDs was required to generate the nitrene intermediate, with the amine reagent required to trap the resultant ketimine en route to the 1*H*-azepine product. Thus, functionality at the *ortho* position of the nitroarene is not tolerated, and high loadings of Pd and/or Pt catalysts were typically needed for reduction to the saturated azepane.

Our group has reported several examples of chemo- and site-selective silver-catalyzed nitrene transfer (NT), where the identity of the nitrene precursor and the ligand can be fine-

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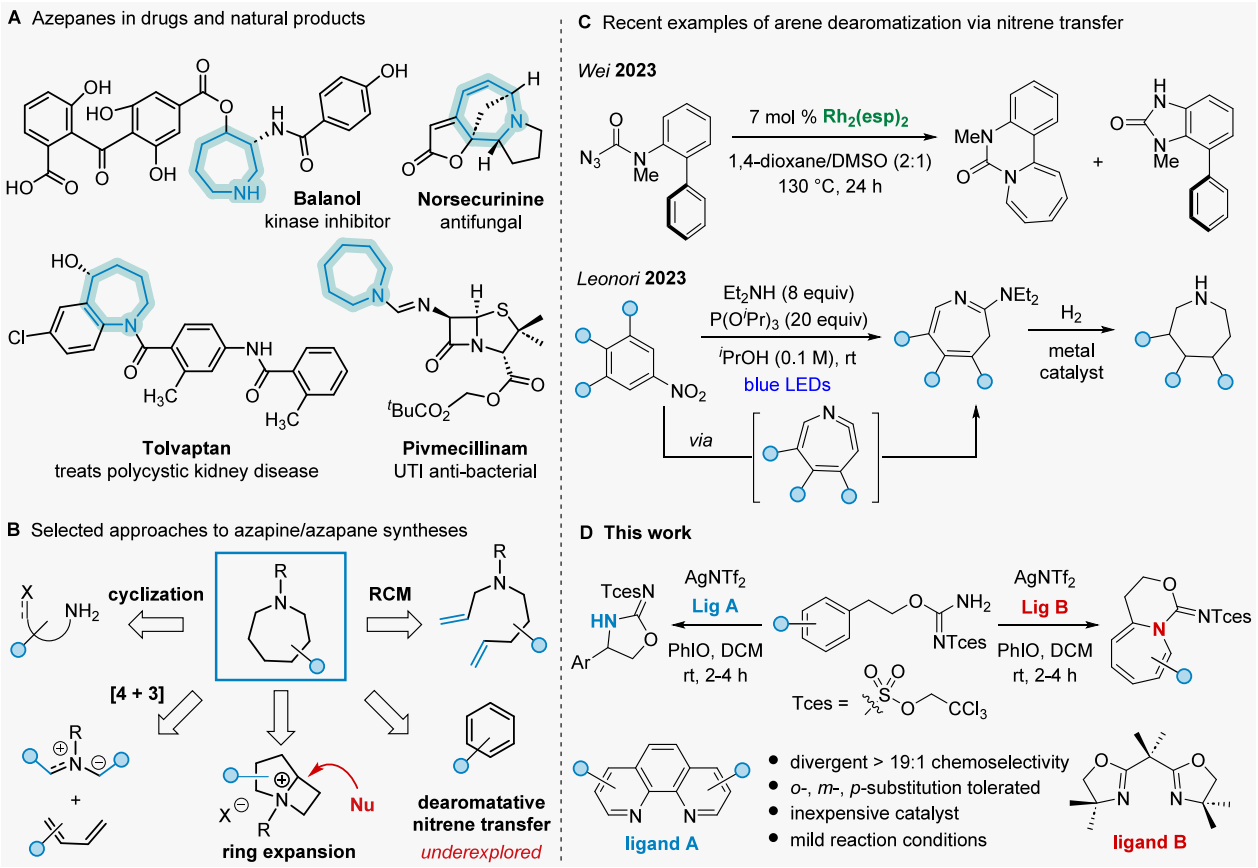
Scheme 1. (A–D) Previous Approaches to Azepine Synthesis and Chemoselective Silver-Catalyzed Dearomative Ring Expansion



tuned to control the reaction outcome.[8] We envisioned that the combination of a suitable nitrene precursor and an appropriate ligand would enable us to selectively toggle between either benzylic C–H amination or insertion of the nitrene into the aromatic ring in an aza-Büchner-type reaction (Scheme 1D). Herein, we report a chemoselective method for the synthesis of either azepines or cyclic carbamimidates using silver-catalyzed nitrene transfer. Highlights of our method include the replacement of expensive Rh complexes with cheaper silver salts, no need for photolysis, excellent chemoselectivity for either C–H insertion or aziridination, mild reaction conditions, the ability to tolerate substitution at any carbon of the arene, and the ability for diverse postfunctionalizations of the azepine products.

RESULTS AND DISCUSSION

Research Strategy and Approach. Our group has harnessed the diversity of coordination environments available to Ag(I) complexes to achieve catalyst-controlled NT.[8] For example, simple changes to the ratio of 1,10-phenanthroline (phen):AgOTf (Scheme 2A) enabled tuning for aziridination vs C–H amination using carbamates as nitrene precursors.[8a] More recently, we reported a highly chemo- and enantioselective intramolecular aziridination catalyzed by a silver catalyst supported by an indan-based bis(oxazoline) (BOX) ligand **A** (Scheme 2A).[9] Interestingly, large differences in the *ee* of the product aziridine were noted based on the identity of the nitrene precursor.[9,10] When a carbamate was employed, the use of (*S*,*S*)-indanBOX (**A**; Scheme 2A) resulted in only 32% *ee* of the aziridine.[10] However, the carbamimidate furnished an 86% yield and 94% *ee* of the aziridine. These observations, coupled with other works from our group showing divergent site selectivity in C–H amidation that can be achieved by using either a carbamate or sulfamate in tandem with the optimal ligands,[8i] highlight our ability to "match" the steric bulk of the nitrene precursor with that of the ligand to influence the reaction outcome.[9]

We were intrigued by the potential to achieve a unique example of a tunable and chemoselective NT using carbamimidates, which are underexplored as nitrene precursors; indeed, prior to our work, only one example of aziridination was reported by the Dauban group.[11] We were curious whether the steric bulk of a Tces-protected carbamimidate, combined with the appropriate ligands, might enable selective tuning for either amination at a benzylic C–H bond or dearomative NT via an aza-Büchner reaction (Scheme 2C) to generate a transient fused aziridine. The intermediate could then undergo an electrocyclic ring-opening along Path 1 to furnish the azepine or rearomatize via Path 2 to deliver a product that represents the formal amination of a C(sp^2)–H bond. It should be mentioned that this mode of reactivity has not been observed using sulfamates or carbamates as nitrene precursors, despite significant effort.

Two main elements of the reaction design were used to guide our hypothesis for catalyst-controlled chemoselectivity (Scheme 2D). First, we proposed that the sp^2-hybridized nitrogen of the carbamimidate would behave similarly to the carbamate oxygen in our previous work, binding to the Lewis

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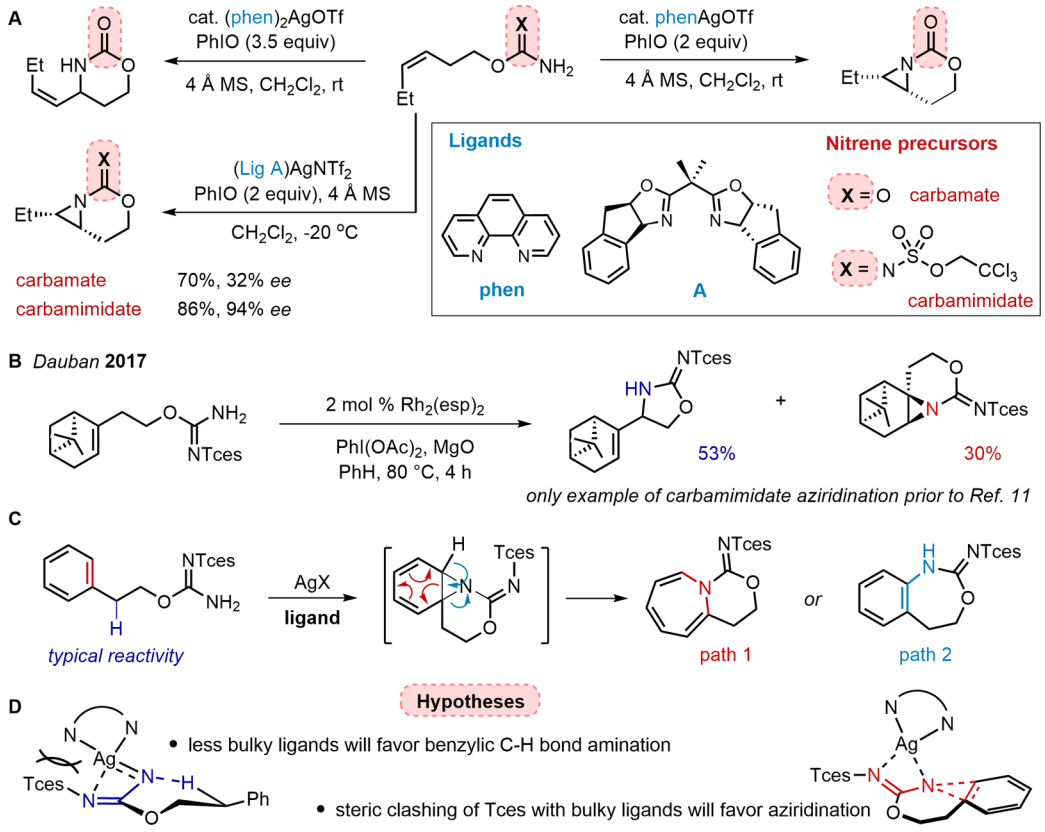
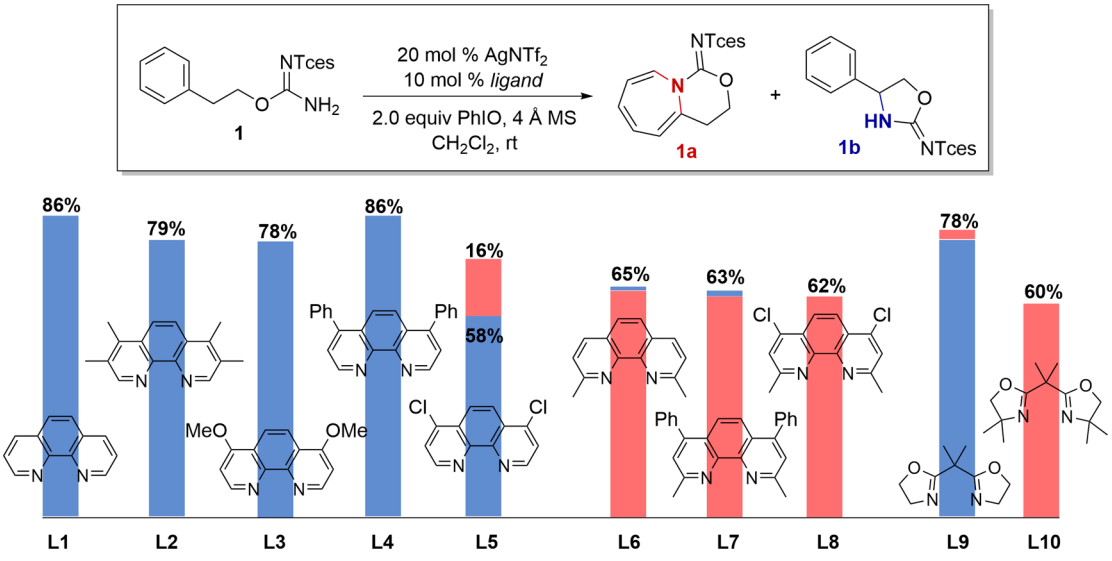
Scheme 2. (A–D) Precedent and Reaction Design for Silver-Catalyzed Chemoselective NT with Carbamimidates



Scheme 3. Ligand Screening for Silver-Catalyzed Chemoselective Nitrene Transfer



acidic silver and enforcing a square-planar geometry in the transition state of the NT.[8i] Second, we reasoned that combining the bulky Tces-protected carbamimidate with a sterically undemanding ligand would favor typical benzylic C–H amination. In contrast, employing a bulky ligand would lead to clashing between the ligand and the Tces group and might favor competing aziridine despite the energy penalty associated with disrupting aromaticity.

Results. The impact of diverse bidentate ligands on the chemoselectivity of silver-catalyzed amination of model Tces-protected carbamimidate **1** was investigated (Scheme 3). A 2:1 silver/ligand ratio was initially employed for two reasons: first, it is expected to preferentially form a monomeric silver complex in solution to promote reactivity, and second, we have previously noted that excess silver salt aids in breaking down the polymeric PhIO.[8a,12] A series of substituted phenanthroline ligands **L1**–**L5** favored the C–H insertion product **1b**; more electron-rich ligands **L2** and **L3** gave slightly lower yields compared to electron-neutral **L1** and **L4**. Excitingly, installing an electron-withdrawing chlorine on **L5** gave the first indication of desired azepine **1a**, albeit in a 3.6:1 ratio of **1b**:**1a**. This result highlights the ability of electronic effects to

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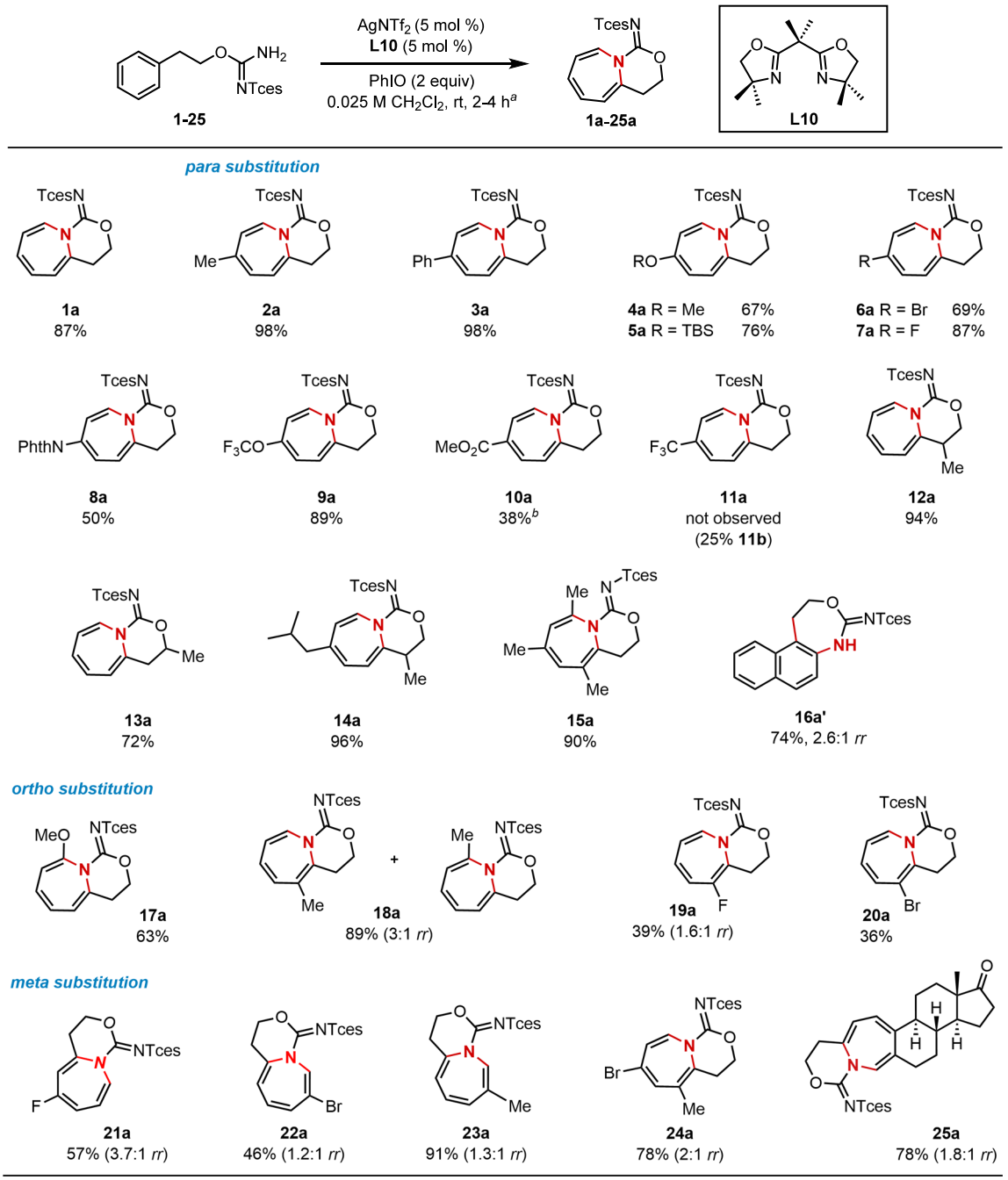
Table 1. Scope of Chemoselective Silver-Catalyzed Ring Expansion of Carbamimidates to Azepines



[a]Yields determined by ^{1}H NMR using trimethylphenyl silane as an internal standard. [b]Heated at 50 °C for 4 h.

exert an impact on chemoselectivity. Ultimately, more sterically demanding ligands, as exemplified by the neocuproine ligands **L6**–**L8** and the dmBOX ligand **L10**, strongly favored formation of the azepine **1a**, with minimal-to-undetectable formation of **1b** by ^{1}H NMR. Previous density functional theory (DFT) calculations on the transition state of silver-catalyzed NT catalyzed by (dmBOX)$AgClO_4$ showed that a seven-membered transition state was required to accommodate the near-linear geometry needed for the hydrogen atom transfer step;[8b,c] coordination of carbonyl oxygen of the carbamate to silver was key to favoring the larger transition state. The results in Scheme 3 support our hypothesis that the imidate nitrogen binds the Ag similarly, with the increased steric congestion of the bulky Tces protecting group further destabilizing the smaller transition state that leads to competing C–H insertion.

With the identification of **L10** as the best ligand for the formation of azepine **1a**, further optimization was carried out prior to exploring the scope of the chemistry. Decreasing both the catalyst loading and the concentration to minimize product degradation resulted in an improved yield of **1a** to 87% (see the Supporting Information for details). The optimal conditions were applied to a range of substituted arenes to ascertain the scope of the azepine formation (Table 1), with excellent chemoselectivity observed across the majority of substrates. A variety of *para* substituents on the arene were

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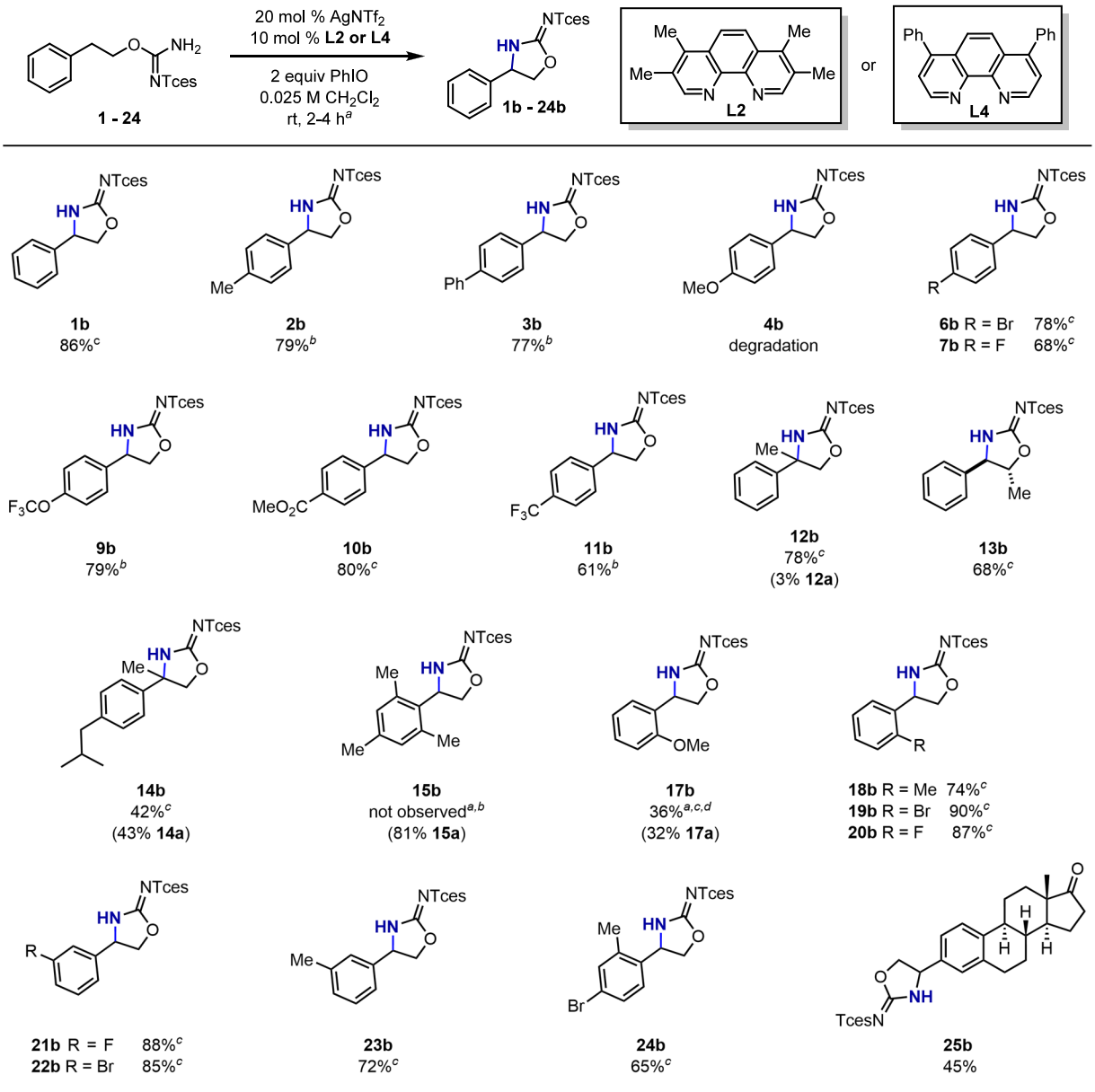
Table 2. Scope of Chemoselective Silver-Catalyzed C(sp^3)−H Amination



[a]Yields determined by ^{1}H NMR using trimethylphenylsilane as the internal standard. [b]Me_4phen was used. [c]Bathophen was used. [d]Decomposition upon workup.

tolerated, including a methyl in **2a**, a phenyl in **3a**, protected amine and alcohol functional groups in **4a**−**5a** and **8a**, halogens in **6a** and **7a**, an ester in **10a**, and a trifluoromethoxy group in **9a**. Excellent-to-good yields were observed with electron-neutral and electron-donating substituents, while diminished yields were observed with the electron-withdrawing ester group in **10a**. As expected, no formation of azepine **11a** was noted with a highly electron-deficient arene; competing C−H insertion to **11b** was observed instead. Modifications to the carbamimidate tether to furnish **12a** and **13a** were well tolerated. A carbamimidate derived from ibuprofen delivered **14a** in 96% yield, while we were pleased to see that both *ortho* and *para* substitution precursors **24** and **15** successfully furnished a 78% yield of trisubstituted azepine **24a** and a 90% yield of the tetrasubstituted azepine **15a**. Due to the high propensity of the intermediate aziridine to rearomatize, naphthalene-derived carbamimidate **16** did not furnish the azepine but instead yielded the formal C(sp^2)−H insertion products **16a′** and **16a″** through Path 2 in Scheme 2C; efforts are ongoing to identify conditions tunable for both Paths 1 and 2.

The ring expansion was next investigated with a series of *o*-substituted carbamimidates **17**−**20**. An electron-donating OMe group in **17** resulted in a single regioisomer **17a**. The *o*-Me substituted carbamimidate **18** favored aziridination at the less substituted alkene of the arene, presumably due to increased steric hindrance. The presence of the electronegative, albeit small, F group in carbamimidate **19**, resulted in a 1.6:1 mixture of isomers of **19a**, where aziridination was favored at the less substituted C═C bond of the arene, likely due to electronic effects. In contrast, the increased steric demand of the bromine in **20** significantly improved the regioselectivity

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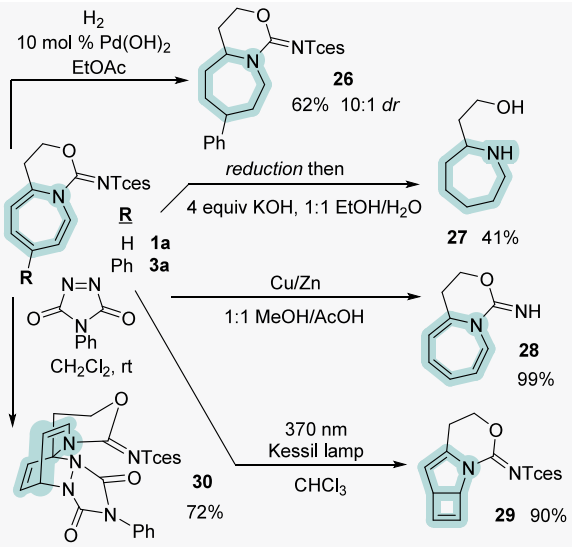
for the aziridination at the less substituted double bond, resulting in the observation of only one regioisomer **20a**. These results provide insight into the likely regiochemical behavior of arenes containing substituents that vary in their steric and electronic properties.

The electronic effects of the *meta* substituents in **21**−**23** were diminished compared to their *ortho*-substituted counterparts, and essentially a 1:1 mixture of regioisomeric products was observed in **22a** and **23a**. However, a moderate regioselectivity of 3.7:1 in favor of the initial aziridination of a less substituted alkene of the precursor was observed in the reaction of the *m*-F carbamimidate **21**−**21a**. This improved regioselectivity suggested that the steric and electronic effects of various substituents can be biased toward different regioisomers. The small, electronegative fluorine promotes formation of the electronically favored azepine isomer, while bulkier electron-neutral to slightly donating substituents show little bias. The potential for the ring expansion strategy to be employed in late-stage functionalizations of complex molecules is highlighted by the reaction of the estrone-derived carbamimidate **25** under mild conditions to furnish the azepines **25a** in 78% yield. This result also showcases the ability of the chemistry to accommodate substituents at both the *meta* and *para* positions of the arene.

The scope of the benzylic C(sp^3)−H bond amination was examined next by using either 3,4,7,8-tetramethylphenanthroline **L2** or bathophenanthroline **L4** as the ligand (Table 2). Similar to the azepine formation, precursors **1**−**3** bearing electron-neutral substituents gave excellent yields of the C−H amination products **1b**−**3b**. Strong electron-donating groups in the *p*-position, such as the −OMe group of **4**, resulted in amination of the benzylic C−H bond, but product **4b** rapidly decomposed under the reaction conditions. Halogens in **6**−**7** gave the corresponding benzylic amines in good yields. Interestingly, replacing the −OMe group of **4** with a $-OCF_3$ group in **9** furnished **9b** in 79% yield with no decomposition. Compared to the azepine formation, the precursors **10**−**11**, bearing electron-withdrawing substituents, furnished better yields and chemoselectivity for the C−H amination, including a 61% yield of **11b**. Substituents in the carbamimidate tethers of **12** and **13** successfully delivered **12b** and **13b**, respectively. The stereochemistry in **13b** was validated through the collection of an X-ray crystallographic structure (see the Supporting Information for details). However, precursors bearing electron-donating groups on the arene showed competing azepine formation. For example, **14** derived from ibuprofen gave a 1:1 mixture of **14a**:**14b**; sterics at the benzylic carbon may also play a role in controlling the reaction outcome. In the case of the mesityl carbamimidate **15**, no **15b** was observed and an 81% yield of the azepine **15a** was obtained, even using the typical C(sp^3)−H amination conditions; a similar result was noted for **17**. The naphthyl-derived precursor **16** gave only 3% **16b** and 14% of a 4:1 mixture **16a′**:**16a″** (see the Supporting Information for details). Halogens and alkyl groups at both the *ortho* and *meta* positions of the arene in **18**−**23** gave the desired products **18b**−**24b** in good yields. Finally, the estrone-derived **25** furnished the C−H amination product **25b** in moderate yield, highlighting the ability of this chemistry to be employed for chemoselective nitrene transfer in more complex molecule settings.

The azepine scaffolds could be postfunctionalized in diverse ways to generate high Fsp^3 (number of sp^3-hybridized carbons/total carbon count) scaffolds and unusual nitrogen-containing molecular architectures (Scheme 4). Hydrogenation of azepine **3a** gave **26** in a good yield and 10:1 diastereoselectivity, highlighting the promising potential of this approach for modular and stereocontrolled syntheses of highly substituted azepanes. Reduction of **1a**, followed by further hydrolysis, yielded 1,3-amino alcohol **27**. The Tces protecting group of **1a** was also easily removed under mild conditions in essentially quantitative yield to give **28**. The bicyclic azepines serve as convenient precursors for the construction of more complex scaffolds. For example, irradiation of **1a** in degassed $CHCl_3$ using a 370 nm Kessil lamp furnished the [4.5.6] tricyclic product **29** in 90% yield.[13] Furthermore, the unusual, bridged tricycle **30** could be prepared in good yield via a regio- and stereoselective intermolecular hetero-Diels−Alder reaction.[14]

Scheme 4. Selective Diversifications of Azepine Scaffolds



CONCLUSIONS

In conclusion, we have developed a highly chemoselective NT of aryl-substituted carbamimidates where the nature of the ligand controls the reaction outcome. More sterically hindered bidentate ligands promote dearomative ring expansion to deliver substituted azepines in good yields, while less congested ligands yield C−H amination products. The interaction of the steric bulk of the Tces protecting group with the ligand controls the favored transition state in the NT to achieve the observed chemoselectivity. Arenes bearing a wide range of functional groups and varying electronics were tolerated in the chemistry. Simple postfunctionalizations of the azepine products produced substituted azepanes with good yield and *dr* as well as complex fused and bridged compounds. Ongoing efforts are focused on expanding this chemistry to heteroarenes and achieving intermolecular aza-Büchner reaction selectivity on a broad range of substituted arenes.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c08249.

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Characterization data, optimization tables, additional substrates/catalysts, and details of computational methods (PDF)

Accession Codes

CCDC 2363662−2363663 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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