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Catalytic Asymmetric Synthesis of Morpholines. Using Mechanistic Insights To Realize the Enantioselective Synthesis of Piperazines

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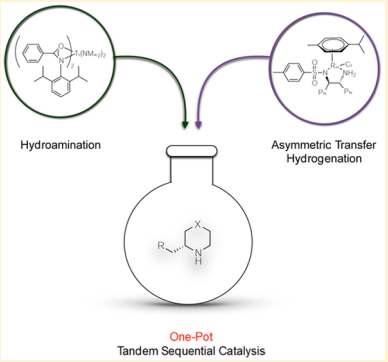
Supporting Information

ABSTRACT: An efficient and practical catalytic approach for the enantioselective synthesis of 3-substituted morpholines through a tandem sequential one-pot reaction employing both hydroamination and asymmetric transfer hydrogenation reactions is described. Starting from ether-containing aminoalkyne substrates, a commercially available bis(amidate)bis(amido)Ti catalyst is utilized to yield a cyclic imine that is subsequently reduced using the Noyori−Ikariya catalyst, RuCl [(*S*,*S*)-Ts-DPEN] (η^6-*p*-cymene), to afford chiral 3-substituted morpholines in good yield and enantiomeric excesses of >95%. A wide range of functional groups is tolerated. Substrate scope investigations suggest that hydrogen-bonding interactions between the oxygen in the backbone of the ether-containing substrate and the [(*S*,*S*)-Ts-DPEN] ligand of the Ru catalyst are crucial for obtaining high ee's. This insight led to a mechanistic proposal that predicts the observed absolute stereochemistry. Most importantly, this mechanistic insight allowed for the extension of this strategy to include N as an alternative hydrogen bond acceptor that could be incorporated into the substrate. Thus, the catalytic, enantioselective synthesis of 3-substituted piperazines is also demonstrated.



INTRODUCTION

The synthesis of enantiopure 3-substituted morpholines is of interest in contemporary organic chemistry.[1] These structural motifs are prevalent in biologically relevant compounds, and they present an important research challenge in the development of new tools for the preparation of potential pharmaceuticals. Traditional synthetic approaches to enantiopure, substituted morpholines generally employ a stepwise synthetic strategy from enantioenriched starting materials that are derived from naturally occurring chiral amino acids.[2] These syntheses are not catalytic, and they result in stoichiometric amounts of byproducts and waste. In addition, the reliance on enantiopure starting materials poses a limitation on the morpholine products that can be accessed by these routes, as most affordable commercial starting materials are derived from naturally occurring amino acids.[2a,3] Here, our strategy instead focuses on the assembly of prochiral substrates, with variable substituent patterns and functional group incorporation, to realize the selective synthesis of either enantiomer by using tandem hydroamination, asymmetric-transfer hydrogenation.

Prochiral substrates can be used to construct 3-substituted morpholine products in both a diastereoselective and enantioselective fashion. Bode and co-workers have recently reported the preparation of racemic 3-substituted morpholines and piperazines and the diastereoselective synthesis of disubstituted 2,3-morpholines from commercially available SnAP reagents and aldehydes.[5] Enantioenriched 2-substituted morpholines with moderate ee values (up to 60%) can be realized through Pd-catalyzed allylic substitution reactions.[6] Examples of other catalytic strategies from prochiral starting materials include enantioselective α-chlorination of aldehydes followed by reductive amination and base-induced cyclization,[7] oxyamination,[8] Pd-catalyzed carboamination,[3c] and hydroamination of functionalized aminoalkenes to arrive at disubstituted morpholines diastereoselectively.[9] The enantioselective preparation of *N*-heterocycles with substitutions α to N is of interest due to the biological relevance of α-chiral amines;[10] however, none of these aforementioned approaches can be used to synthesize such morpholine products in an enantioselective manner.

Catalytic hydroamination, the direct addition of an N−H bond across a C−C unsaturation, is an efficient and atom-economical transformation to yield new C−N bonds.[11] Our research group has developed the bis(amidate)bis(amido) titanium precatalyst **1** for the hydroamination of alkynes.[12] We previously reported a tandem sequential, one-pot catalytic approach to 3-substituted morpholines by hydroamination of functionalized aminoalkynes to yield cyclic imines, which can then be reduced enantioselectively by Ru-catalyzed asymmetric-transfer hydrogenation (ATH, Scheme 1).[9b] This route effectively affords the first catalytic, enantioselective approach for the synthesis of 3-substituted morpholine products in good yields. Furthermore, our results show that the known oxophilicity of Group 4 catalytic systems does not preclude their application in the synthesis of biologically relevant morpholines.

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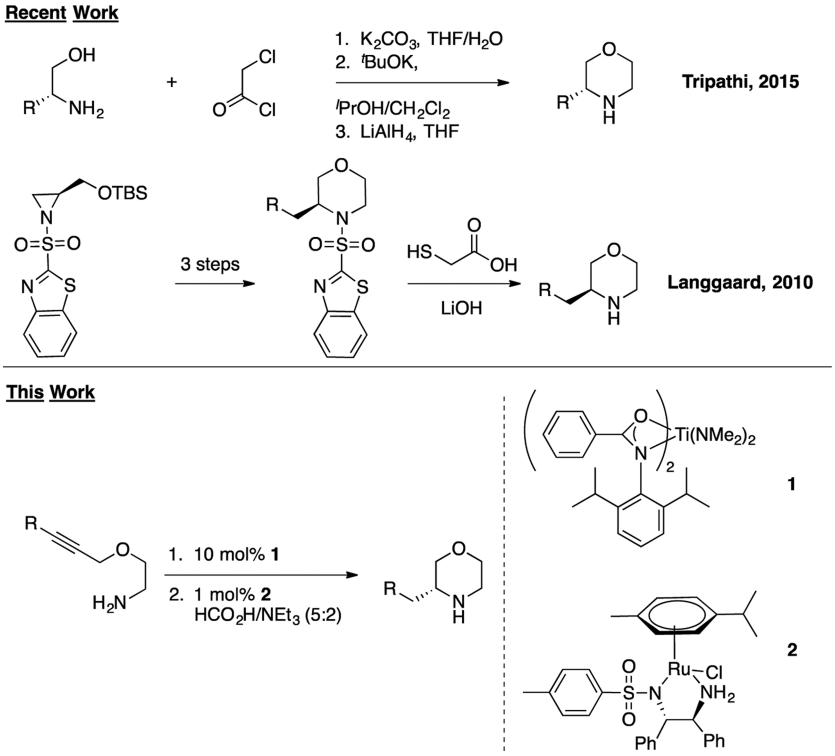
Scheme 1. Strategies for Synthesizing Enantioenriched 3-Morpholines[2c,4]



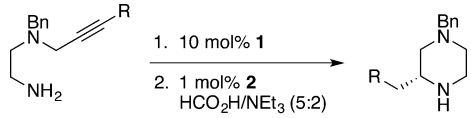
Asymmetric-transfer hydrogenation is an industrially important synthetic method for reliably reducing ketones to chiral alcohols under mild conditions; however, the application of this synthetic protocol to the reduction of imines to yield amines is only consistently applicable for select aryl-substituted substrates.[13] Specifically, the Noyori–Ikariya catalyst (**2**)[9b] yields outstanding enantioselectivities with isoquinolines or cyclic imine substrates that bear adjacent steric bulk and aromatic groups. Mechanistic proposals rationalizing the high enantioselectivities have suggested that these aromatic substituents participate in important stabilizing CH/π interactions with the η^6-cymene ring of the Ru catalyst as well as CH/π interactions with the TSPEN ligand.[14] This proposal is consistent with the low ee's previously reported in the preparation of 2-substituted piperidines via asymmetric-transfer hydrogenation of precursor cyclic imines.[15] Interestingly, in our case excellent enantioselectivities are observed for a wide range of alkyl-substituted morpholine products.[9b]

Here, we explore the substrate scope of this one-pot synthetic protocol in the synthesis of a wide range of 3-substituted morpholines in good yields with excellent enantioselectivities. Based upon substrate scope observations, we put forward a mechanistic proposal that implicates hydrogen-bonding interactions between the cyclic imine substrates and the Ru catalyst **2** to afford morpholine products with high ee's. Furthermore, this mechanistic insight points toward a new application of this synthetic strategy: the catalytic preparation of selectively substituted piperazines with good ee's (Scheme 2).

RESULTS AND DISCUSSION

Synthesis of Aminoalkyne Substrates. Our initial efforts into this new synthetic methodology were preceded by the search for a facile, modular preparation for the assembly

Scheme 2. Asymmetric Synthesis of 3-Alkylated *N*-Benzylpiperazine via Hydroamination and Asymmetric-Transfer Hydrogenation



of aminoalkyne substrates required for tandem catalysis investigations. By using a flexible approach, aminoalkyne substrates could be prepared using a modular three step synthetic route featuring modified literature procedures (Scheme 3).

Boc-protected ethanolamine and a propargyl bromide substrate were reacted under modified Williamson ether synthesis conditions to yield the corresponding ether.[16] When propargyl bromide is used as a reagent, the reaction proceeds smoothly at room temperature to give protected terminal aminoalkyne **3** in 79% yield. For alkyl-substituted propargyl bromides, elevated temperatures are required for the reaction to progress, affording **4i–l** in 69–81% yield. The preparation of aryl-substituted aminoalkyne substrates (**4a–g**, yields = 37–91%) was easily achieved using Sonagashira cross-coupling conditions starting from *tert*-butyl (2-(prop-2-yn-1-yloxy)ethyl)carbamate (**3**).[17] These protected aminoethers undergo Boc deprotection using acidic conditions to give the requisite primary aminoalkyne substrates (**5a–l**, yields = 51%-quantitative; see the Experimental Section and Table 2).

Morpholine Synthesis. We initiated our investigations of intramolecular hydroamination using aminoalkyne **5a** with 5 mol % of precatalyst **1** at 110 °C in toluene (Table 1, entry 1), in accordance with previously established catalytic conditions.[12b] Even with increased reaction temperatures (entry 2) and extended reaction times (entry 3), this reaction did not go

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Scheme 3. General Synthetic Route for the Preparation of Aminoalkyne Substrates

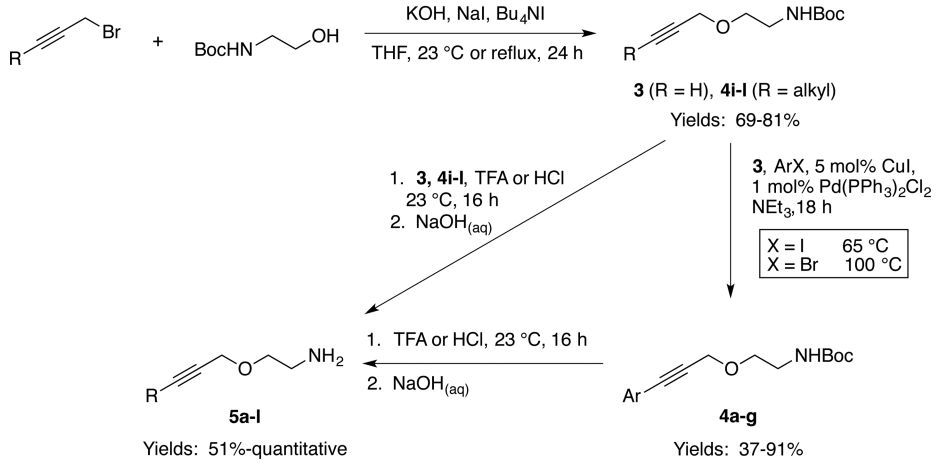
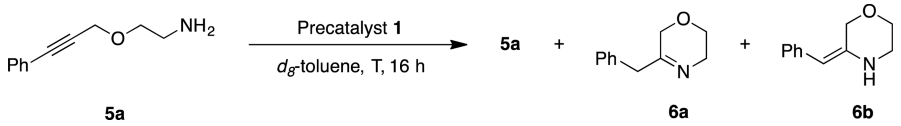


Table 1. Optimization of Hydroamination Reaction Conditions

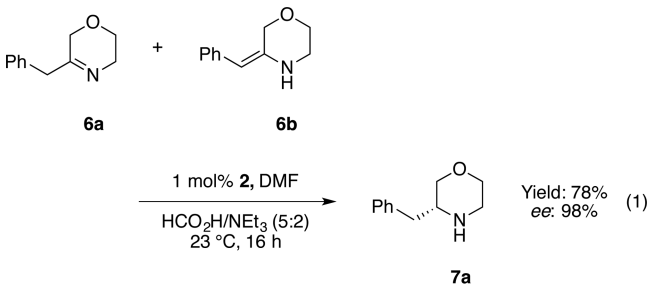


entry	precatalyst loading[a] (mol %)	temp (°C)	ratio[b]
1	5	110	3:1: 0.1
2	5	120	3:1: 0.1
3[c]	5	130	3:1: 0.1
4	10	110	0:1: 0.1

[a]Precatalyst loading calculated with resepect to 0.2 mmol of **5a**. Reactions conducted in a sealed J-Young NMR tube in 0.5 mL of d_8-toluene. [b]Determined by ^{13}C NMR spectroscopy (400 MHz, 298 K). [c]Reaction time extended to 24 h.

to completion. We attribute this sluggish reactivity to the presence of the potentially chelating oxygen heteroatom in this class of aminoalkyne substrates. When 10 mol % of precatalyst **1** was used, the hydroamination reaction proceeded smoothly to completion at 110 °C overnight to produce imine **6a**, along with the enamine isomer **6b**. These reactions were monitored using ^{13}C NMR spectroscopy by observing the disappearance of signals corresponding to the alkyne carbons (~90−75 ppm) and the formation of a diagnostic imine signal at ~165 ppm.

Notably, hydroamination and asymmetric-transfer hydrogenation can be performed in a facile one-pot tandem sequential fashion without isolation and purification of the imine intermediate. The crude mixture of imine and enamine isomers was enantioselectively reduced using 1 mol % of commercially available RuCl [(*S*,*S*)-Ts-DPEN] (η^6-*p*-cymene) (**2**) as a catalyst (eq 1).[18] Notably, the presence of the Ti



hydroamination catalyst in the enamine/imine mixture does not hinder subsequent transfer hydrogenation reactivity. The crude morpholine product was purified by acid−base extraction to afford **7a** in 78% yield with 98% ee, as determined by supercritical fluid chromatography (Table 2, entry 1). Even while avoiding column chromatography, this product was >95% pure, as determined by ^{1}H NMR spectroscopy (see the SI). The (*R*)-configuration of product **7a** was determined by comparing the optical rotation of the pure product with the literature value of the isolated (*S*)-enantiomer, which was synthesized from enantiopure (*S*)-phenylalanol.[19] The absolute configurations for all other examples here were assigned by analogy.

With optimized reaction conditions in hand, we explored the substrate scope for this method using 10 mol % of precatalyst **1**, followed by 1 mol % of **2** as catalyst (Table 2). Good yields and excellent enantioselectivities were obtained with morpholine products containing variously substituted aromatic ring systems (Table 2, entries 1−7). Both Ti and Ru catalysts display tolerance to electron-donating substituents (Table 2, entry 5) and electron-withdrawing substituents (Table 2, entries 3 and 4) on the aromatic ring. Aryl bromide functionalities are permitted (**7b**), and the product retains an important functional group amenable to further synthetic manipulations such as cross coupling.[20] Nitrogen-containing heteroaromatic systems, such as pyridine (Table 2, entry 6), are also tolerated.

To our delight, good yields and high enantioselectivities were also obtained with aminoalkyne substrates containing alkyl groups (Table 2, entries 8−12). Imines with minimal steric bulk such as those substituted with simple methyl and *n*-propyl substituents yielding products **7h** and **7i** are reduced with good enantioselectivities. Notably, substrate **5k** bearing a

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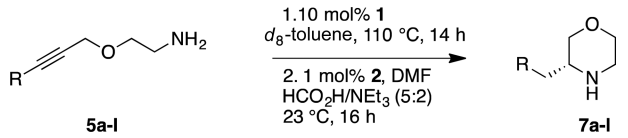
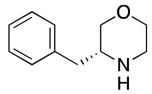
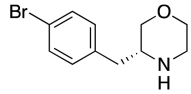
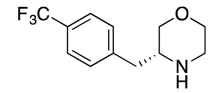
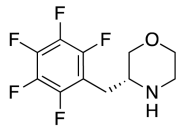
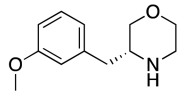
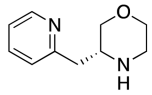
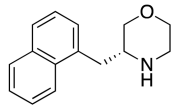
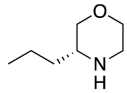
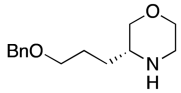
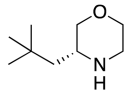
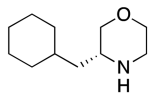
Table 2. Synthesis of 3-Substituted Morpholines by Tandem Hydroamination and Asymmetric Transfer Hydrogenation



5a-l **7a-l**

Entry	R		Product		Yield (%)[a]	ee (%)[b]
1	Ph	**5a**		**7a**	78%	98%
2	*p*-Br-Ph	**5b**		**7b**	80%	97%
3	*p*-CF_3-Ph	**5c**		**7c**	52%	98%
4	C_6F_5	**5d**		**7d**	77%	98%
5	*m*-OMe-Ph	**5e**		**7e**	57%	94%
6	2-py	**5f**		**7f**	66%[d]	99%
7	1-Np	**5g**		**7g**	72%	93%
8	H	**5h**		**7h**	65%	>99%[c,e]
9	Et	**5i**		**7i**	78%	97%[c]
10	$BnOCH_2CH_2$	**5j**		**7j**	79%	97%[c]
11	*t*-Bu	**5k**		**7k**	74%	74%[c]
12	cyclohexane	**5l**		**7l**	51%	95%[c]

[a]Crude yield (>95% pure). [b]Determined by supercritical fluid chromatography. [c]Determined by supercritical fluid chromatography after derivatization with tosyl chloride. [d]Isolated yield after flash chromatography. [e]Isolated by derivatization into oxalate salt (vide infra).

tert-butyl group afforded **7k** in 74% yield with only 74% ee. This lowered enantioselectivity is attributed to the increased steric bulk of the *tert*-butyl group interfering with the transfer hydrogenation step of the synthetic sequence (*vide infra*).

While the crude 3-substituted morpholines described in Table 2 are synthesized in more than 95% purity in most cases, further purification of the resulting products can be readily achieved through isolation of the oxalate salt of the amine.

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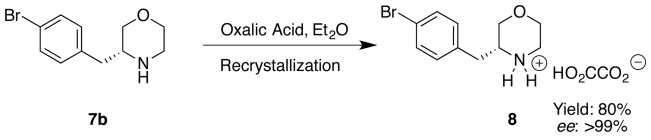
Recrystallization of the oxalate salt of **7b** from diethyl ether resulted in a further increase in enantioselectivity resulting in >99% ee (Scheme 4).

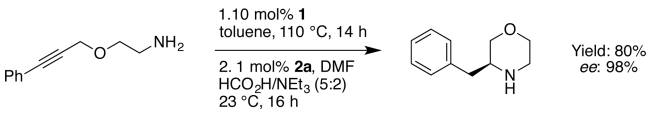
Scheme 4. Derivatization of Morpholine 7b into Oxalate Salt 8



7b 8

As illustrated in Table 2, the use of commercially available RuCl [(*S*,*S*)-Ts-DPEN] (η^6-*p*-cymene) for asymmetric transfer hydrogenation with the cyclic imines generated by hydroamination affords enantioenriched 3-substituted morpholine products. For product **7a**, the corresponding (*S*)-enantiomer can be synthesized through the use of commercially available RuCl [(*R*,*R*)-Ts-DPEN] (η^6-*p*-cymene) (**2a**) with comparable yields and enantioselectivies as the (*S*,*S*)-Ru catalyst (Scheme 5). The optical rotation of the resulting product matches the (*S*)-enantiomer, which was previously reported in the literature.[19]

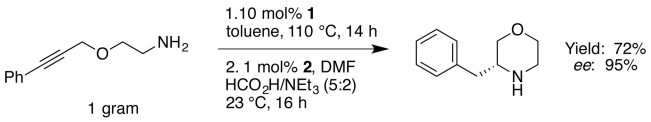
Scheme 5. Synthesis of (*S*)-3-Benzylmorpholine (9)



5a 9

Furthermore, this synthetic protocol for the enantioselective synthesis of morpholines is also amenable to gram-scale synthesis (Scheme 6). Starting from 1 g of aminoalkyne **5a**,

Scheme 6. Gram-Scale Synthesis of (*R*)-3-Benzylmorpholine

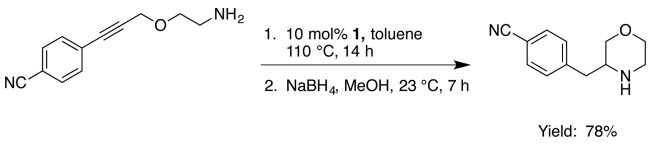


5a 7a

(*R*)-3-benzylmorpholine (**7a**) can be synthesized. Purification through simple acid–base extraction yields the desired product in 72% yield with 95% ee, which is comparable to the results obtained on smaller scale as presented in Table 2. No further purification by column chromatography or recrystallization was required.

During the exploration of the substrate scope of this method, an aminoalkyne substrate containing a nitrile group was synthesized (**10**, Scheme 7). Nitrile groups are versatile

Scheme 7. Synthesis of Nitrile-Containing Morpholine Product 11



10 11

functionalities that can undergo a variety of further synthetic transformations.[21] There are many examples of late-transition-metal hydroamination catalysts which display functional group tolerance toward nitrile groups, but examples of such functional group tolerance with early-transition-metal catalysts are noticeably lacking in the literature.[22]

Hydroamination of **10** occurred successfully to yield the corresponding cyclic imine, which was subsequently reduced with sodium borohydride to afford racemic morpholine product **11** in good yield (78%) and purity. While the racemic morpholine was successfully isolated, reduction of the cyclic imine with RuCl [(*S*,*S*)-Ts-DPEN] (η^6-*p*-cymene) failed to yield the analogous enantiomerically enriched morpholine product. This demonstrates that the titanium hydroamination catalyst is tolerant to the nitrile functionality and C–N unsaturations; however, the nitrile group interferes with the asymmetric transfer hydrogenation, as an intractable mixture of products is obtained after this step of the reaction.

Probing Mechanism. A wide range of substrates are compatible with our tandem sequential catalysis method to form 3-substituted morpholines with excellent enantioselectivies (Table 2). Most importantly, this protocol does not demand aromatic substituents or sterically demanding substrates to realize excellent ee's. These results are particularly intriguing considering all previous reports require aromatic substituents to access excellent enantioselectivities.[13a,b,14b] One hypothesis for the excellent enantioselectivies in our case could be that the residual Lewis acidic titanium species remaining after the hydroamination step has an advantageous effect on the ATH reaction. As a control experiment, the volatile aminoalkyne **5h** was selected to probe the role of the titanium residue on the ATH reaction (Scheme 8). The toluene solvent and the intermediate imine formed upon hydroamination could be vacuum transferred away from the titanium catalyst and into a clean reaction vessel. Complex **2** and all other reagents for ATH were then added, and upon reaction completion **7h** was obtained in 90% ee (average ee after the experiment was performed in triplicate) in contrast to the one-pot procedure where **7h** was yielded with >99% ee (Table 2, entry 8), indicating that indeed the presence of the titanium catalyst has a notable impact.[23]

Next, we examined the use of additives in the second step of the reaction in Scheme 7 in an effort to restore the enantioselectivity to the >99% ee observed in the one-pot process (Table 3). First, we carried out the sequence shown in Scheme 8 and then added titanium complex **1** into the ATH reaction (a stepwise reaction rather than a one-pot reaction), and interestingly, the observed ee was raised from 90% ee to 94% ee, but was less than the one-pot reaction (entry 1).[24] To test if this effect was due to the Lewis acidic character of residual [Ti] species, $Ti(NMe_2)_4$ was used as an additive, and a similar ee value was achieved (entry 2). However, this effect was not limited to titanium, as the addition of $Zr(NMe_2)_4$ also increased the enantiomeric excess to 94% (entry 3). However, when the late transition metal Lewis acid AgOTf was used, a dramatic decline in ee to 71% was observed (entry 4), suggesting that perhaps the slight restoration in ee is not a Lewis acid effect, but rather an amine or amide ligand effect arising from the use of precatalyst **1**. Interestingly, the addition of 20 mol % of just proligand resulted in an increase in ee to 93% (entry 5), while the addition of a simple amine additive also raised the ee's to 95% (entry 6). The compilation of these data highlight that hydrogen bonding interactions alone affect

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Scheme 8. Asymmetric Transfer Hydrogenation of 5h in the Absence of [Ti]

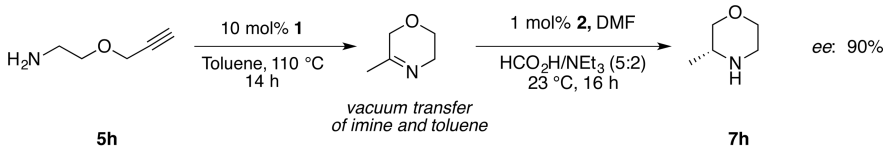
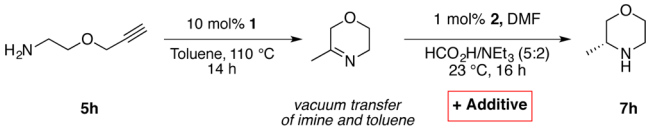
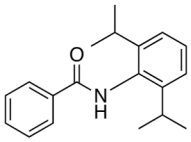


Table 3. Asymmetric Transfer Hydrogenation of 5h in the Absence of [Ti]



Entry	Additive	mol loading (%)	ee (%)[a,b]
1	**1**	10%	94%
2	$Ti(NMe_2)_4$	10%	94%
3	$Zr(NMe_2)_4$	10%	93%
4	AgOTf	10%	71%
5		20%	93%
6	$HNEt_2$	20%	95%

[a]Determined by supercritical fluid chromatography after derivitization with tosyl chloride. [b]Experiments performed in duplicate, and ee value presented is the average of the two runs.

the ee's of ATH, and the presence of added metal is not required. However, the combination of the residual Ti catalyst mixture that remains in the reaction mixture during the one-pot protocol cannot be duplicated through the use of precatalyst, proligand, or other Lewis acidic additives alone. Efforts to characterize the residual Ti catalyst mixture have not been successful.

Proposal. The proposed mechanism of ATH of carbonyl substrates postulates a concerted cyclic six-membered transition state, where hydride and proton transfer from the catalyst to the substrate occurs without coordination of the substrate to the metal center.[13g,14b,c,25] A more recent DFT investigation concludes that this proposed transition state is only applicable to gas-phase calculations and in solution, the reaction is a two-step process where transfer of the hydride from the Ru catalyst occurs, followed by a proton transfer from either the solvent or the TsDPEN ligand.[26]

Experimental and computational investigations into the mechanism of ATH for imines suggest that these substrates undergo reduction via a different reaction pathway. First, acidic activation of the imine by either a Brønsted or a Lewis acid is required for these reactions to proceed.[18,27] Gas phase calculations by Kačer and co-workers show that the imine substrates are protonated by formic acid that is present under catalytic reaction conditions, and the substrate can interact with the oxygen atoms of the sulfonyl group through hydrogen bonding to stabilize the transition state.[14a,b] Other significant

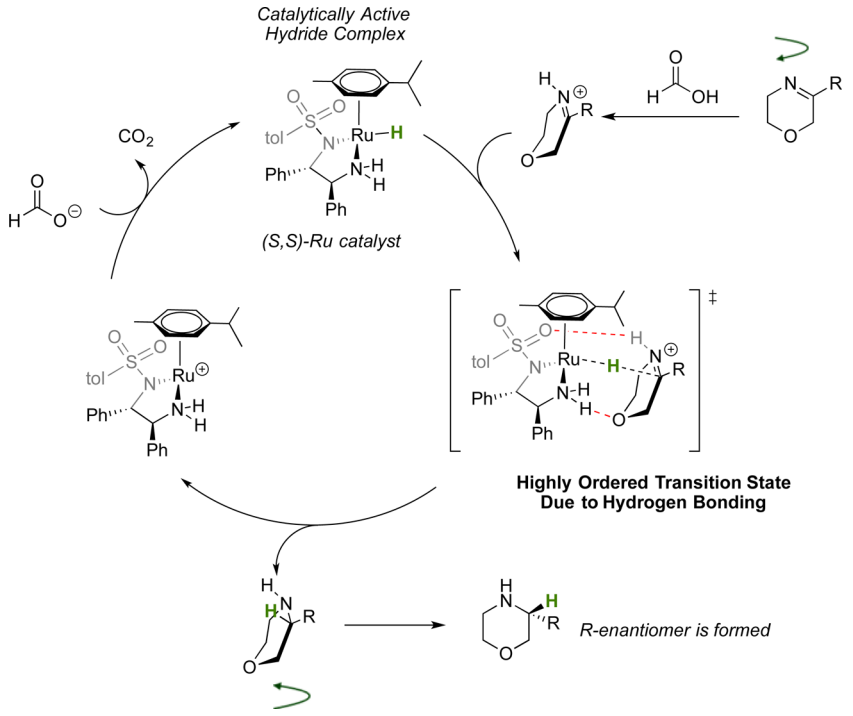


Figure 1. Proposed mechanistic rationale for asymmetric transfer hydrogenation invoking key role of heteroatom in favorable H-bonding interactions.

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effects include CH/π interactions between the substrate and the η^6-arene ring of the Ru catalyst, which can lower the overall energy of the transition state up to 12.3 kJ/mol.[14c] This rationalizes how substrates with aromatic rings adjacent to the C═N bond are known to give high ee's with the Noyori–Ikariya catalyst.[14a,b,15,18] However, in our studies, excellent enantioselectivities are achieved even with nonsterically demanding alkyl-substituted imines that cannot access the crucial CH/π interactions discussed above. In the case of morpholine, we have the O in the ring which could engage in further hydrogen-bonding interactions. Computational work presented by Kačer and co-workers inspired us to propose the mechanistic rationale shown in (Figure 1). We propose that a highly ordered transition state for the hydrogen transfer process can be accessed in which two key hydrogen-bonding interactions between the substrate and the chiral ligand are imperative for enantioselectivity: one between the proton of the iminium moiety and the oxygen atoms of the TsDPEN ligand the second between the oxygen heteroatom of the imine substrate and the hydrogen atoms of the neutrally bound ethylenediamine ligand. Note that this simplified proposed mechanism focuses on the profound effect of the Noyori–Ikariya catalyst and does not consider the more subtle effect of residual Ti catalyst.[14a,b]

The substrate enters the catalytic cycle as an iminium ion due to protonation by the formic acid that is present in the reaction medium. The protonated substrate approaches the catalytically active Ru hydride complex from the side away from the chiral ligand, facilitating hydride transfer to the electrophilic imine C. The orientation of the imine substrate for reduction is proposed to occur as depicted in Figure 1 to facilitate two key hydrogen-bonding interactions. The predicted stereochemical outcome resulting from this proposed mechanism is in agreement with observed experimental results. In particular, the (*S*,*S*)-Ru catalyst affords the *R*-enantiomeric product and the (*R*,*R*)-Ru catalyst yields the corresponding *S*-enantiomer product. An alternative approach of the substrate promoting hydride delivery to the *Re* face of the imine would have the R-substituent oriented down toward the TsDPEN ligand of **2**; however, this creates major steric congestion between the substrate and the cymene ligand (Figure 2). Also,

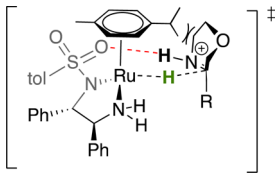
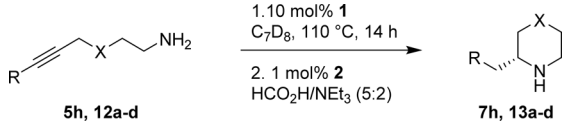


Figure 2. Alternative transition state for asymmetric transfer hydrogenation.

favorable hydrogen bonding interactions with the oxygen cannot be accommodated in this alternative transition state model. Therefore, Figure 1 suggests the relatively less sterically demanding substrate trajectory and gives rise to the possibility of effective hydrogen bonding between the O atom and the ethylene diamine ligand. The experimental observation that sterically demanding R groups yield products with reduced ee's (**7k**, ee = 74%) is consistent with this proposal, as the additional steric bulk on the imine substrate perturbs this approach into the catalyst active site. Therefore, high ee's can be achieved for the synthesis of a range of alkyl- and aryl-CH_2 substituted morpholines without the need for CH/π interactions with the substrate.

The necessity for secondary hydrogen-bonding interactions between the oxygen in the backbone of the cyclic imine and the TsDPEN ligand for high enantioselectivities is further corroborated by experimental results when this synthetic strategy is applied to the synthesis of other *N*-heterocycles (Table 4). For example, as was reported previously,[15]

Table 4. Synthesis of Substituted *N*-Heterocycles by Tandem Hydroamination and Asymmetric Transfer Hydrogenation



5h, 12a-d → **7h, 13a-d**

Entry	X	R		Product		Yield (%)[a]	*ee* (%)[b]
1	O	H	**5h**		**7h**	65%	>99%[c]
2	C	Ph	**12a**		**13a**	87%	24%
3	S	H	**12b**		**13b**	71%	66%[c]
4	NTs	H	**12c**		**13c**	80%	70%
5	NBn	H	**12d**		**13d**	58%	>98%[d]

[a]Crude yield. [b]Determined by supercritical fluid chromatography. [c]Determined by supercritical fluid chromatography after derivitization with tosyl chloride. [d]Determined by ^{19}F NMR spectroscopy after derivitization with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride.

piperidines, with no potential for hydrogen bonding in the 4-position, see dramatic reductions in ee's (24%, entry 2). However, when hydrogen bonding slightly larger thiomorpholines (with longer C–S bonds (1.82 Å) vs (C–O) (1.46 Å),[28] the ee's are somewhat restored (66%, entry 3). Using the tosyl-protected piperazines, the observed ee is only 70% (entry 4). We suggest that the impeding steric bulk and variable hydrogen-bonding character of the tosyl group reduces the potential for favorable interactions with the N of the ring. However, this result suggests that the incorporation of a substituent on N that is neither capable of hydrogen bonding nor sterically demanding should favor the desirable hydrogen-bonding interactions with the ethylene diamine ligand.

To test this hypothesis, the non-hydrogen-bonding benzyl-protected diaminoalkyne was prepared (Scheme 6) and used in our one-pot enantioselective protocol (Table 4, entry 5).

Aminoalkyne **12d** was synthesized by starting from reductive amination of BOC-protected ethylene diamine and benzaldehyde to yield **14**,[29] followed by the installation of the

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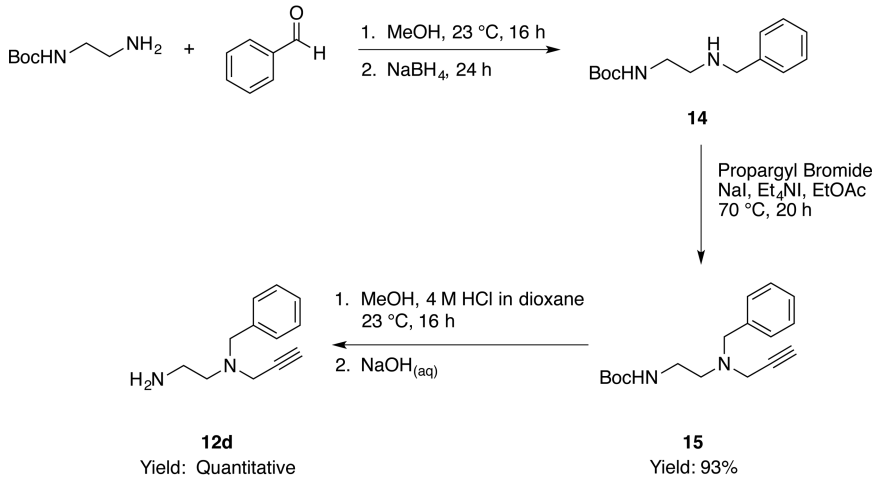
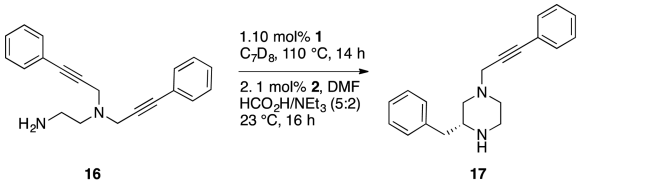
Scheme 9. Synthetic Route to 12d



propargylic functional group through base mediated alkylation conditions (Scheme 9). Removal of the BOC protecting group using 4 M HCl in dioxane yields the substrate **12d**, which was subjected to the general reaction conditions for hydroamination, but complete conversion to the cyclic imine was not observed, suggesting catalyst deactivation by this potentially chelating substrate. Catalyst deactivation was observed to be slow, as partial conversion to the imine was observed after 14 h by NMR spectroscopy; however, no further conversion was observed with prolonged reaction times and increased reaction temperatures. Conversion to the desired cyclic imine can be improved through a second addition of 10 mol % of **1** and increased reaction time. The introduction of a second portion of Ti catalyst reacts with uncyclized aminoalkyne substrates after the first portion of Ti is no longer catalytically active. Finally, the cyclic imine was reduced using standard ATH reaction conditions to yield (*R*)-1-benzyl-3-methylpiperazine. Derivatization with (*R*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride allowed for ee determination by *in situ* ^{19}F NMR spectroscopy.[30] Gratifyingly, only one enantiomer was observed (Table 4, entry 5).

This synthetic strategy may be extended for the preparation of other piperazine compounds with high enantioselectivities. The synthesis of (*R*)-3-benzyl-1-(3-phenylprop-2-yn-1-yl)-piperazine (**17**) from aminoalkyne (**16**) successfully yielded the desired product with a high ee of 96% (Scheme 10). This target compound is amenable to further synthetic manipulations through the pendent alkyne functionality; however, the yield for **17** is low (14%), and the desired product was inseparable from the starting material as the product was isolated as a mixture containing the aminoalkyne starting material. Similar to the preparation of **13d**, incomplete conversion in the hydroamination step was observed by NMR spectroscopy, due to possible catalyst deactivation of **1** by the potentially chelating aminoalkyne substrate. Nevertheless, these data demonstrate that the scope for ATH of cyclic imines is no longer limited to substrates containing aromatic groups, but cyclic imines with hydrogen-bond acceptors incorporated into the substrate can be reduced with good enantioselectivities, providing that other destabilizing interactions can be avoided. This achievement is a powerful extension of ATH to access more chiral heterocycles using this catalytic strategy and provides new insights for the development of alternative approaches for enantioselective morpholine and piperazine synthesis.

Scheme 10. Synthesis of (*R*)-3-Benzyl-1-(3-phenylprop-2-yn-1-yl)piperazine



Further extension of the substrate scope of *N*-benzyl 2-substituted piperazines was explored. Good ee's were obtained for piperazine products **19** (87%) and **21** (81%, Scheme 11); however, complete conversion to the desired product was not achieved. Even with sequential loading of the catalyst, yields ranging from 8−10% after tosylation were achieved and further investigations to improve the conversion of the hydroamination step are currently underway. Interestingly, unlike the morpholine case, the asymmetric reduction to yield the desired piperazine products showed greater variation in enantioselectivies with changes to the R group of the cyclic imine. Even with the minor increase in steric bulk moving from methyl to ethyl, a significant impact on the selectivity is observed (**13d** vs **21**). While the ee's of the benzyl-protected piperazine products are lower than those achieved with the oxygen containing substrates, they are improved from the tosyl-protected piperazine (Table 4, entry 2 vs entry 5), highlighting the importance of carefully considering the accessibility of the hydrogen-bond accepting site in the substrate for effective ATH.

CONCLUSIONS

An efficient and practical one-pot tandem sequential approach to enantioenriched 3-substituted morpholines through the use of Ti-catalyzed hydroamination and Ru-catalyzed asymmetric transfer hydrogenation was presented. Precatalysts **1** and **2** are tolerant to a wide range of functional groups and give morpholine products with good yields and excellent ee's of >95% in most cases. From experimental observations, a mechanistic proposal was derived in which key hydrogen-bonding interactions between cyclic imine substrates and Ru

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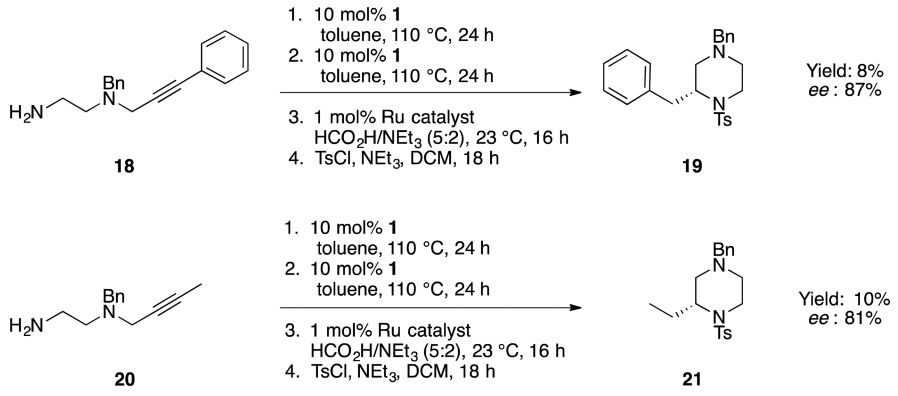
Scheme 11. Synthesis of Piperazines 19 and 21



catalytically active species give rise to the resulting high enantioselectivities. This proposal led to a substrate scope extension of this method to include benzyl-protected 3-substituted piperazines. Good ee's were achieved with the piperazine products (>81%), highlighting that good to excellent enantioselectivities can be achieved with asymmetric transfer hydrogenation of imine substrates to access enantioenriched piperazine products. Other methods for the generation of imine substrates that can exploit such hydrogen bonding capabilities are currently being designed and investigated for the synthesis of α-chiral substituted amines.

EXPERIMENTAL SECTION

General Methods. Synthesis of metal complexes and subsequent reactions involving these precatalysts were performed under an inert atmosphere of nitrogen using standard Schlenk line or glovebox techniques. Tetrahydrofuran, diethyl ether, and toluene were purified by passage over activated alumina. Dichloromethane was dried over CaH_2 and distilled. Toluene-d_8 was degassed via three cycles of freeze−pump−thaw and stored over 4 Å molecular sieves in the glovebox. Thin-layer chromatography (TLC) was performed on fluorescence UV silica plates (60 Å thick). All chemicals were purchased from commercial sources and used as received. Hydroamination precatalyst **1** was prepared using the literature procedure.[12a,31] The following compounds were synthesized using known literature procedures, and the spectral data were in accordance with those previously published: *tert*-butyl (2-hydroxyethyl)carbamate,[16] *tert*-butyl (2-(prop-2-yn-1-yloxy)ethyl)carbamate (**3**),[16] *tert*-butyl (2-aminoethyl)carbamate,[32] *tert*-butyl (2-(benzylamino)ethyl)carbamate (**14**),[33] 3-phenylprop-2-yn-1-ol,[34] and (3-bromoprop-1-yn-1-yl)-benzene.[34,35] The following compounds were synthesized as described in our previously published report: *tert*-butyl (2-((3-phenylprop-2-yn-1-yl)oxy)ethyl)carbamate (**4a**), *tert*-butyl (2-((3-(4-bromophenyl)-prop-2-yn-1-yl)oxy)ethyl)carbamate (**4b**), *tert*-butyl (2-((3-(perfluorophenyl)prop-2-yn-1-yl)oxy)ethyl)carbamate (**4d**), *tert*-butyl (2-((3-(pyridin-2-yl)prop-2-yn-1-yl)oxy)ethyl)carbamate (**4f**), *tert*-butyl (2-(pent-2-yn-1-yloxy)ethyl)carbamate (**4i**), *tert*-butyl (2-((5-(benzyloxy)pent-2-yn-1-yl)oxy)ethyl)carbamate (**4j**), *tert*-butyl (2-((4,4-dimethylpent-2-yn-1-yl)oxy)ethyl)carbamate (**4k**), (*R*)-3-benzylmorpholine (**7a**), (*R*)-3-(4-bromobenzyl)morpholine (**7b**), (*R*)-3-((perfluorophenyl)methyl)morpholine (**7d**), (*R*)-3-(pyridin-2-ylmethyl)morpholine (**7f**), (*R*)-3-methylmorpholine (**7h**), (*R*)-3-propylmorpholine (**7i**), (*R*)-3-(3-(benzyloxy)propyl)morpholine (**7j**), (*R*)-3-neopentylmorpholine (**7k**), and (*R*)-3-(4-bromobenzyl)-morpholine oxalate salt (**8**), (*S*)-2-benzylpiperidine (**13a**), (*R*)-3-methylthiomorpholine (**13b**), and (*R*)-3-methyl-1-tosylpiperazine (**13c**).[9b]

Instrumentation. Proton (^{1}H NMR) and carbon (^{13}C{^{1}H} NMR) spectra were recorded in deuterochloroform at 300 or 400 MHz for ^{1}H NMR spectra and 75 or 100 MHz for ^{13}C{^{1}H} NMR spectra. Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of deuterochloroform (7.27 ppm for ^{1}H NMR spectra and 77.0 ppm ^{13}C NMR spectra). Assignment of ^{13}C{^{1}H} NMR shifts have been made by DEPT-135 experiments. High-resolution mass spectra (HRMS) were obtained by time-of-flight (TOF) electrospray ionization (ESI). Optical rotations were recorded with a polarimeter using a sample cell with a path length of 1 dm. The enantiomeric excess values were measured by supercritical fluid chromatography (SFC), ^{19}F NMR after *in situ* derivatization with (*R*)-α-methoxy-α-trifluoromethylphenylacetic acid chloride, or chiral HPLC. Fourier transform infrared (FTIR) spectra were collected neat on NaCl disks and are reported in cm^{-1}.

General Procedure A for Sonagashira Cross Coupling. CuI (5 mol %), *tert*-butyl (2-(prop-2-yn-1-yloxy)ethyl)carbamate (5−10 mmol, 1 equiv), and triethylamine (12.0 mL) were added into a Schlenk flask under N_2. ArX (1.1 equiv) and $Pd(PPh_3)_2Cl_2$ (2 mol %) were added, and the mixture was heated at 60 °C (X = I) or 100 °C (X = Br) for 16 h. The solvent was diluted with CH_2Cl_2 (40 mL), washed with aqueous HCl (1 M, 2 × 20 mL) and brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The dark residue was purified by flash chromatography (15% ethyl acetate in hexanes).

General Procedure B for BOC Deprotection. To a solution of the *N*-Boc-protected amine (1−8 mmol, 1 equiv) in methanol (15 mL) was added HCl in dioxane (4 M, 2−4.0 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then 14 h at room temperature. The solvent was evaporated, diethyl ether (30 mL) was added, and the solid was filtered and washed with diethyl ether (15 mL). The free base was obtained by neutralization of the HCl salt with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, and concentrated to about 6 mL. The CH_2Cl_2 solution was further dried with CaH_2, filtered, and concentrated to afford the anhydrous primary amine, which was vacuum-dried at 65 °C overnight before being transferred to the glovebox.

General Procedure C for the Tandem Intramolecular Hydroamination followed by $NaBH_4$ Reduction. A J. Young NMR tube was charged with a solution precatalyst (10 mol %) and the aminoalkyne (0.25−0.5 mmol,1 equiv) dissolved in anhydrous d_8-toluene (0.5 mL). The tube was sealed and maintained at 110 °C for 14 h. After the reaction mixture was allowed to cool to room temperature, the resulting mixture from the hydroamination reaction was diluted with MeOH (7 mL). $NaBH_4$ (4.0 equiv) was added, and the reaction mixture was stirred for 2 h at room temperature. After removal of the solvent in vacuo, the residue was diluted with EtOAc (8 mL) and washed with aqueous HCl (1 M, 3 × 5 mL). The combined aqueous layers were basified with saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 8 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to provide light yellow oil as the corresponding racemic 3-substituted morpholine with >95% purity in most cases. The racemic 3-morpholine products were used for development of SFC methods for ee determination.

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General Procedure D for the Tandem Intramolecular Hydroamination followed by Catalytic Asymmetric Transfer Hydrogenation. All hydroamination reactions were prepared in a N_2-filled glovebox. A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with a solution of precatalyst (10 mol %) and the aminoalkyne (0.25−0.4 mmol), dissolved in anhydrous toluene (0.5 mL). The Schlenk tube was sealed and maintained at 110 °C for 14 h. After the reaction mixture was allowed to cool to room temperature, RuCl[(*S*,*S*)-TsDPEN(*p*-cymene)] (1 mol %) in dry DMF (0.1 mL) was added followed by a 5:2 mixture of formic acid/triethylamine (0.1 mL), and the reaction mixture was stirred at room temperature for 14 h under nitrogen. The solution was diluted with 8 mL of EtOAc and washed with water (5 mL) and aqueous HCl (1 M, 2 × 5 mL). The combined aqueous layers were washed with EtOAc (5 mL), basified with saturated aqueous $NaHCO_3$ (15 mL), and extracted with EtOAc (3 × 8 mL). The combined organic layers were washed with water (2 × 5 mL) and brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to provide a brownish yellow oil as the corresponding 3-substituted morpholine with above 95% purity in most cases.

General Procedure E for the Synthesis of *N*-Tosylated Morpholines. Tosyl chloride (1.1 equiv) was added to a solution of crude 3-substituted morpholine (1.0 equiv) and triethylamine (2.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C, and the resulting solution was stirred at 0 °C for 1 h and then overnight at room temperature. The reaction mixture was washed with aqueous HCl (1 M, 3 mL), saturated aqueous $NaHCO_3$ (3 mL), and brine before being dried over Na_2SO_4 and filtered. The solvent was removed by rotary evaporation, and the residue was purified by flash chromatography (15% EtOAc/hexanes).

Synthesis and Characterization of Compounds. *tert-Butyl (2-((3-(4-(Trifluoromethyl)phenyl)prop-2-yn-1-yl)oxy)ethyl)carbamate (**4c**).* Following the general procedure A, the reaction of *tert*-butyl (2-(prop-2-yn-1-yloxy)ethyl)carbamate (**3**, 0.500 g, 2.5 mmol)[16] and 4-iodobenzotrifluoride (0.748 g, 2.8 mmol) afforded the title compound **4c** (0.723 g, 91%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58−7.51 (m, 4H), 4.94 (br s, 1H), 4.38 (s, 2H), 3.64 (t, J = 5.1 Hz, 2H), 3.37 (q, J = 5.1 Hz, 2H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.8 (C), 131.8 (CH), 130.0 (q, J = 32.4 Hz, C), 126.2 (C), 123.7 (q, J = 270 Hz, C), 125.0 (q, J = 3.3 Hz, CH), 87.4 (C), 84.7 (C), 78.9 (C), 69.0 (CH_2), 58.5 (CH_2), 40.2 (CH_2), 28.1 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.2; IR (NaCl, cm^{-1}) 3357, 2975, 29718, 1713, 1169; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{20}NO_3F_3Na$ 366.1293 found 366.1288.

*tert-Butyl (2-((3-(3-Methoxyphenyl)prop-2-yn-1-yl)oxy)ethyl)carbamate (**4e**).* Following the general procedure A, the reaction of *tert*-butyl (2-(prop-2-yn-1-yloxy)ethyl)carbamate (**3**, 1.000 g, 5.0 mmol)[16] and 3-bromoanisole (1.028 g, 5.5 mmol) afforded the title compound **4e** (0.560 g, 37%) as a brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, J = 7.8 Hz, 1H), 7.03 (d, J = 7.5 Hz, 1H), 6.97 (t, J = 1.2 Hz, 1H), 6.87 (dd, J = 7.8, 2.1 Hz, 1H), 4.95 (br s, 1 H), 4.37 (s, 2 H), 3.79 (s, 3H), 3.64 (t, J = 5.1 Hz, 2 H), 3.37 (q, J = 5.4 Hz, 2 H), 1.43 (s, 9 H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.4 (C), 156.1 (C), 129.5(CH), 124.4 (CH), 123.5 (C), 116.7 (CH), 115.3 (CH), 86.5 (C), 84.7 (C), 79.4 (CH_2), 69.3 (CH_2), 59.1 (CH_2), 55.4 (CH_3), 40.5 (CH_2), 28.5 (CH_3); IR (NaCl, cm^{-1}) 3364, 2975, 2931, 1713; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{23}NO_4Na$ 328.1525, found 328.1523.

*tert-Butyl (2-((3-(Naphthalen-1-yl)prop-2-yn-1-yl)oxy)ethyl)carbamate (**4g**).* Following the general procedure A, the reaction of *tert*-butyl (2-(prop-2-yn-1-yloxy)ethyl)carbamate (**3**, 1.000 g, 5.0 mmol)[16] and 4-iodonapthalene (0.699 g, 2.8 mmol) afforded the title compound **4g** (0.439 g, 54%) as a light brown oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 4.2 Hz, 1H), 7.84−7.80 (m, 2H), 7.69 (dd, J = 7.2, 1.2 Hz, 1H), 7.54 (m, 2H), 7.40 (dd, J = 8.1, 6.9 Hz, 1H), 5.09 (br s, 1H), 4.52 (s, 2H), 3.73 (t, J = 5.1 Hz, 2H), 3.42 (q, J = 5.1 Hz, 2H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 156.0 (C), 133.3 (C), 133.1 (C), 130.8 (CH), 129.0 (CH), 128.3 (CH), 126.8 (CH), 126.4 (CH), 126.0 (CH), 125.1 (CH), 120.1 (C), 89.7 (C), 84.6 (C), 79.3 (C), 69.2 (CH_2), 59.2 (CH_2), 40.5 (CH_2), 28.4 (CH_3); IR (NaCl, cm^{-1}) 3359, 3059, 2932, 2248, 1714; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{20}H_{23}NO_3Na$ 348.1576, found 348.1591.

*tert-Butyl (2-((3-Cyclohexylprop-2-yn-1-yl)oxy)ethyl)carbamate (**4l**).* 4-Cyclohexylbut-2-yn-1-ol (0.500 g, 3.6 mmol, synthesized using known literature procedure)[36] and triphenylphosphine (1.415 g, 5.4 mmol) were dissolved in CH_2Cl_2 (50 mL), and the solution was cooled to 0 °C. Carbon tetrabromide (1.890 g, 5.7 mmol) in CH_2Cl_2 (10 mL) was added dropwise. After 15 min of stirring at 0 °C, the cold solution was diluted with hexanes (30 mL) and filtered through a plug of silica gel. The solvent was removed by rotary evaporation, followed by a second filtration through a short pad of silica gel with 5% of EtOAc in hexanes to provide (3-bromoprop-1-yn-1-yl)cyclohexane as a pale yellow oil (0.667 g, 92%). (3-Bromoprop-1-yn-1-yl)cyclohexane is a known compound and spectral data are in agreement with those previously reported: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (d, J = 2.4 Hz, 2H), 2.46−2.40 (m, 1H), 1.83−1.64 (m, 4H), 1.55−1.26 (m, 6H).[37] *tert*-Butyl (2-hydroxyethyl)-carbamate (0.458 g, 2.8 mmol)[16] and (3-bromoprop-1-yn-1-yl)-cyclohexane (0.630 g, 3.1 mmol) were stirred in THF (10 mL). Tetrabutylammonium iodide (0.103 g, 0.28 mmol) and sodium iodide (0.042 g, 0.28 mmol) were added, followed by portionwise addition of KOH (0.930 g, 5.6 mmol). The reaction mixture was stirred at room temperature for 72 h. The solvent was removed in vacuo, and the residue was dissolved in H_2O (30 mL) and extracted with EtOAc (3 × 30 mL). The organic extracts were combined, washed with 10% metabisulfite solution (30 mL) and brine, dried over $NaSO_4$, filtered, and concentrated. Purification by column chromatography (10% EtOAc in hexanes) yielded **4l** as pale yellow oil (0.573 g, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (br s, 1 H), 4.15 (d, J = 3 Hz, 2 H), 3.56 (t, J = 4.8 Hz, 2 H), 3.33 (q, J = 5.4 Hz, 2 H), 2.43−2.37 (m, 1H), 1.84−1.65 (m, 4H), 1.52−1.18 (m, 6H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 156.0 (C), 91.6 (C), 79.3 (C), 75.6 (C), 68.8 (CH_2), 58.9 (CH_2), 40.5 (CH_2), 32.7 (CH_2), 29.2 (CH), 28.5 (CH_3), 25.9 (CH_2), 25.0 (CH_2); IR (NaCl, cm^{-1}) 3382, 2992, 2856, 1692, 1519; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{16}H_{27}NO_3Na$ 304.1889, found 304.1892.

*2-((3-(4-(Trifluoromethyl)phenyl)prop-2-yn-1-yl)oxy)ethanamine (**5c**).* Following general procedure B, **4c** (0.476 g, 1.6 mmol) was deprotected to yield **5c** as a yellow oil (0.497 g, quantitative): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.37 (m, 4H), 4.26 (s, 2H), 3.74 (t, J = 5.4 Hz, 2H), 2.77 (t, J = 5.1 Hz, 2H), 1.61 (br s, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 131.8 (CH), 129.8 (q, J = 32 Hz, C), 126.3 (C), 124.7 (q, J = 271 Hz, C), 125.0 (q, J = 3.3 Hz, C), 87.6 (C), 84.6 (C), 72.3 (CH_2), 58.6 (CH_2), 41.5 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.4; IR (NaCl, cm^{-1}) 3299, 2923, 2854, 1324; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{12}H_{13}NOF_3$ 244.0949, found 244.0950.

*2-((3-(3-Methoxyphenyl)prop-2-yn-1-yl)oxy)ethanamine (**5e**).* Following general procedure B, **4e** (0.476 g, 1.6 mmol) was deprotected to yield **5e** as a yellow oil (0.304 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, J = 8.1 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 6.97 (t, J = 1.2 Hz, 1H), 6.87 (dd, J = 8.4, 2.7 Hz, 1H), 4.39 (s, 2 H), 3.79 (s, 3H), 3.62 (t, J = 5.1 Hz, 2 H), 2.93 (br s, 2 H), 1.8 (br s, 2 H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.1 (C), 129.2 (CH), 124.1 (CH), 123.4 (C), 116.5 (CH), 114.9 (CH), 86.1 (C), 84.8 (C), 70.5 (CH_2), 69.3 (CH_2), 58.8 (CH_2), 55.1 (CH_3), 40.9 (CH_2); IR (NaCl, cm^{-1}) 3369, 2937, 2858, 1158; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{12}H_{16}NO_2$ 206.1181, found 206.1179.

*2-((3-(Naphthalen-1-yl)prop-2-yn-1-yl)oxy)ethanamine (**5g**).* Following general procedure B, **4g** (0.439 g, 1.4 mmol) was deprotected to yield **5g** as a yellow oil (0.287 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, J = 8.7 Hz, 1H), 7.76 (t, J = 7.2 Hz, 2H), 7.66 (d, J = 7.2 Hz, 1H), 7.56−7.42 (m, 2H), 7.35 (dd, J = 8.4, 7.5 Hz, 1H), 4.48 (s, 2H), 3.62 (t, J = 5.1 Hz, 2H), 2.87 (t, J = 5.1 Hz, 2H), 1.38 (br s, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 133.1 (C), 132.9 (C), 130.5 (CH), 128.8 (CH), 128.1 (CH), 126.6 (CH), 126.2 (CH), 125.9 (CH), 125.0 (CH), 120.1 (C), 90.0 (C), 84.1 (C), 72.3 (CH_2), 59.0 (CH_2), 41.7 (CH_2); IR (NaCl, cm^{-1}) 3370, 3057, 2925, 2858,

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1586; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{15}H_{16}NO$ 226.1232, found 226.1228.

*2-((3-Cyclohexylprop-2-yn-1-yl)oxy)ethanamine (**5l**).* Following general procedure B, **4l** (0.560 g, 2.0 mmol) was deprotected to yield **5l** as a yellow oil (0.270 g, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (d, J = 2.1 Hz, 2H), 3.52 (t, J = 5.4 Hz, 2H), 2.87 (t, J = 5.1 Hz, 2H), 2.42−2.35 (m, 1H), 1.82−1.24 (m, 10H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 91.2 (C), 75.7 (C), 71.9 (CH_2), 58.9 (CH_2), 41.8 (CH_2), 32.6 (CH_2), 29.1 (CH), 25.8 (CH_2), 25.0 (CH_2); IR (NaCl, cm^{-1}) 3370, 2929, 2853, 1449; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{11}H_{20}NO$ 182.1545, found 182.1542.

*(3R)-3-(4-(Trifluoromethyl)benzyl)morpholine (**7c**).* Following general procedure D, the reaction of **5c** (0.055 g, 0.23 mmol) afforded the title compound **7c** as a light brown oil (0.029 g, 52%, ee = 98%): $[\alpha]_D$ = +4 (c = 8.8, chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 3.82−3.75 (m, 2H), 3.57−3.49 (m, 1H), 3.27 (dd, J = 11, 9.6 Hz, 1H), 3.07−2.98 (m, 1H), 2.92−2.82 (m, 2H), 2.71 (dd, J = 14, 5.1 Hz, 1H), 2.55 (dd, J = 14, 8.7 Hz, 1H), 1.89 (br s, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.2 (C), 129.6 (CH), 129.1 (q, J = 19.8 Hz, C), 127.9 (q, J = 270 Hz, CF_3), 125.7 (q, J = 3.3 Hz, CH), 72.4 (CH_2), 67.6 (CH_2), 56.0 (CH), 46.2 (CH_2), 38.8 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.8; IR (NaCl, cm^{-1}) 3426, 2922, 2851, 1164; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{12}H_{15}NOF_3$ 246.1106, found 246.1104.

*(R)-3-(3-Methoxybenzyl)morpholine (**7e**).* Following general procedure D, the reaction of **5e** (0.050 g, 0.24 mmol) afforded the title compound **7e** as a light brown oil (0.043 g, 85%, ee = 94%): $[\alpha]_D$ = +80 (c = 0.9, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (dd, J = 15, 7.8 Hz, 1H), 6.84−6.78 (m, 3H), 3.88−3.80 (m, 2H), 3.83 (s, 3H), 3.62−3.54 (m, 1H), 3.31 (t, J = 9.6 Hz, 1H), 3.08−3.00 (m, 1H), 2.95−2.84 (m, 2H), 2.68 (dd, J = 13, 4.8 Hz, 1H), 2.49 (dd, J = 13, 9.3 Hz, 1H), 1.97 (br s, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 159.1 (C), 139.2 (C), 129.7 (CH), 121.6 (CH), 114.9 (CH), 112.0 (CH), 72.5 (CH_2), 67.5 (CH_2), 56.2 (CH), 55.3 (CH_3), 46.3 (CH_2), 39.0 (CH_2); IR (NaCl, cm^{-1}) 3321, 2952, 2849, 1599, 1583, 1488; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{12}H_{18}NO_2$ 208.1339, found 208.1338.

*(R)-3-(Naphthalen-1-ylmethyl)morpholine (**7g**).* Following general procedure D, the reaction of **5g** (0.050 g, 0.24 mmol) afforded the title compound **7g** as a light brown oil (0.036 g, 72%, ee = 93%): $[\alpha]_D$ = +40 (c = 0.2, methanol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08−8.01 (m, 1H), 7.90−7.84 (m, 1H), 7.76 (d, 1H), 7.57−7.47 (m, 2H), 7.43−7.34 (m, 2H), 3.90 (dd, J = 11, 2.7 Hz, 1H), 3.78 (dt, J = 11, 2.7 Hz, 1H), 3.65−3.52 (m, 1H), 3.40 (dd, J = 11, 9 Hz, 1H), 3.24−3.16 (m, 2H), 2.95−2.76 (m, 3H), 1.95 (br s, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 134.2 (C), 133.9 (C), 132.1 (C), 129.0 (CH), 127.6 (CH), 126.2 (CH), 125.9 (CH), 125.5 (CH), 123.8 (CH), 72.7 (CH_2), 67.5 (CH_2), 55.36 (CH_2), 46.3 (CH_2), 36.0 (CH); IR (NaCl, cm^{-1}) 2922, 2850, 1453, 1105; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{15}H_{18}NO$ 228.1388, found 228.1384.

*(R)-3-(Cyclohexylmethyl)morpholine (**7l**).* Following general procedure D, the reaction of **5l** (0.104 g, 0.24 mmol) afforded the title compound **7l** as a light brown oil (0.053 g, 85%): $[\alpha]_D$ = +92 (c = 1.0, dichloromethane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (dt, J = 11, 3.0 Hz, 2H), 3.46 (dt, J = 11, 3.0 Hz, 1H), 3.09 (t, J = 9.9 Hz, 1H), 2.97−2.80 (m, 1H), 2.35 (br s, 1H), 1.68−1.59 (m, 4H), 1.33−0.76 (m, 7H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 73.2 (CH_2), 67.6 (CH_2), 52.2 (CH), 46.3 (CH_2), 40.2 (CH_2), 34.1 (CH), 33.7 (CH_2), 33.3 (CH_2), 26.6 (CH_2), 26.3 (CH_2), 26.2 (CH_2); IR (NaCl, cm^{-1}) 3320, 2921, 2850, 1448, 1107; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{11}H_{22}NO$ 184.1701, found 184.1704.

*(R)-3-(Cyclohexylmethyl)-4-tosylmorpholine (**7l-Ts**).* Following general procedure E, the reaction of **7l** (0.048 g, 0.26 mmol) afforded the title compound **7l-Ts** as a clear, colorless oil (0.057 g, 85%, ee = 95%): $[\alpha]_D$ = −14 (c = 0.4, chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.1 Hz, 2H), 3.85 (dt, J = 7.8, 2.4 Hz, 1H), 3.69 (dd, J = 12, 3.3 Hz, 1H), 3.60 (d, J = 11 Hz, 1H), 3.53 (d, J = 13 Hz, 1H), 3.43 (dd, J = 12, 3 Hz, 1H), 3.38−3.18 (m, 2H), 2.41 (s, 3H), 1.73−1.36 (m, 7H), 1.21−1.11 (m, 4H), 0.92−0.72 (m, 2H); ^{13}C{ ^{1}H} NMR (75 MHz, $CDCl_3$) δ 143.4 (C), 138.2 (C), 129.8 (CH), 127.2 (CH), 69.0 (CH_2), 66.2 (CH_2), 51.1 (CH), 40.7 (CH_2), 35.5 (CH_2), 34.3 (CH), 33.4 (CH_2), 33.2 (CH_2), 26.2 (CH_2), 26.2 (CH_2), 21.6 (CH_3); IR (NaCl, cm^{-1}) 2923, 2852, 1449,1347; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{18}H_{27}NO_3SNa$ 360.1609, found 360.1616.

*(S)-3-Benzylmorpholine (**9**).* Known compound[19] synthesized from 2-((3-phenylprop-2-yn-1-yl)oxy)ethan-1-amine[9b] (0.047 g, 0.27 mmol) using general procedure D, except 1 mol % RuCl[(*R*,*R*)-TsDPEN(*p*-cymene)] catalyst was used. The title compound was isolated as a light brown oil (0.038 mmol, 80%, 95% ee): $[\alpha]_D$ = −39 (c = 1.6, methanol; lit. $[\alpha]_D$ = −38.2, c = 0.056, methanol);[19] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.18 (m, 5 H), 3.81 (dt, J = 10, 3 Hz, 2H), 3.61−3.52 (m, 1H), 3.30 (t, J = 10 Hz, 1H), 3.07−2.96 (m, 1H), 2.93−2.83 (m, 2H), 2.65 (dd, J = 13, 4.8 Hz, 1H), 2.49 (dd, J = 13, 9 Hz, 1H), 2.29 (br s, 1H); HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{11}H_{16}NO$ 178.1232, found 178.1228.

*4-(3-(2-Aminoethoxy)prop-1-yn-1-yl)benzonitrile (**10**).* Following general procedure A, the reaction of *tert*-butyl (2-(prop-2-yn-1-yloxy)ethyl)carbamate[1] (0.500 g, 2.5 mmol) and 4-iodobenzonitrile (0.630 g, 2.8 mmol) afforded *tert*-butyl (2-((3-(4-cyanophenyl)prop-2-yn-1-yl)oxy)ethyl)carbamate (0.776 g, 52%) as a light brown oil (**10a**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 5.04 (br s, 1H), 4.30 (s, 2H), 3.55 (t, J = 5.1 Hz, 2H), 3.27 (q, J = 5.1 Hz, 2H), 1.33 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 155.8 (C), 132.0 (CH), 131.8 (CH), 127.2 (C), 118.1 (C), 111.7 (C), 89.4 (C), 84.6 (C), 69.2 (CH_2), 58.6 (CH_2), 40.1 (CH_2), 28.2 (CH_3); IR (NaCl, cm^{-1}) 3365, 2977, 2933, 2229, 1713; HRMS-ESI (m/z) [M + Na]$^+$ calcd for $C_{17}H_{20}N_2O_3Na$ 323.1372, found 323.1372. Following general procedure B, *tert*-butyl (2-((3-(4-cyanophenyl)prop-2-yn-1-yl)oxy)ethyl)carbamate (0.776 g, 2.6 mmol) was deprotected to yield **10** as a light brown oil (0.452 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.4 Hz, 2H), 4.40 (s, 2H), 3.60 (t, J = 5.1 Hz, 2H), 2.91 (t, J = 5.4 Hz, 2H), 1.42 (br s, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 132.4 (CH), 132.1 (CH), 127.6 (C), 118.4 (C), 112.0 (C), 89.9 (C), 84.7 (C), 72.8 (CH_2), 59.0 (CH_2), 41.9 (CH_2); IR (NaCl, cm^{-1}) 3340, 2924, 2856, 2228, 1604; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{12}H_{13}N_2O$ 201.1028, found 201.1029.

*4-(Morpholin-3-ylmethyl)benzonitrile (**11**).* Following general procedure C, **10** (50 mg, 0.25 mmol) was reacted to yield **11** as a light brown oil (39 mg, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 8.1 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 3.76 (dd, J = 11, 2.7 Hz, 2H), 3.53−3.45 (m, 1H), 3.23 (t, J = 9.6 Hz, 1H), 3.05−2.96 (m, 1H), 2.90−2.80 (m, 2H), 2.69 (dd, J = 13, 5.1 Hz, 1H), 2.55 (dd, J = 13, 8.7 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 143.8 (C), 132.5 (CH), 130.0 (CH), 118.8 (C), 110.7 (C), 72.2 (CH_2), 67.5 (C), 55.8 (CH_2), 46.1 (CH_2), 39.1 (CH_2); IR (NaCl, cm^{-1}) 3309, 2954, 2852, 2227, 1607; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{12}H_{15}N_2O$ 203.1184, found 203.1178.

*N^1-Benzyl-N^1-(prop-2-yn-1-yl)ethane-1,2-diamine (**12d**).* Following general procedure B, *tert*-butyl (2-(benzyl(prop-2-yn-1-yl)amino)-ethyl)carbamate (**15**, 1.77 g, 4.8 mmol) was deprotected to yield N^1-benzyl-N^1-(prop-2-yn-1-yl)ethane-1,2-diamine (**12d**) as a light brown oil (1.27 g, quantitative): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5H), 3.64 (s, 2H), 3.31 (d, J = 1.6 Hz, 2H), 2.77 (t, J = 5.6 Hz, 2H), 2.64 (t, J = 6.0 Hz, 2H), 2.23 (t, 2.4 H, 1H), 1.66 (br s, 2H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 138.3 (C), 128.7 (CH), 127.9 (CH), 126.8 (C), 78.2 (C), 72.9 (C), 57.5 (CH $_2$), 55.7 (CH_2), 41.2 (CH_2), 39.0 (CH_2); IR (NaCl, cm^{-1}) 30556, 2926, 2822, 1489; HRMS-ESI (m/z) [M + H]$^+$ calcd for $C_{12}H_{17}N_2$ 189.1392, found 189.1396.

*(R)-1-Benzyl-3-methylpiperazine (**13d**).* Known compound[38] synthesized from N^1-benzyl-N^1-(prop-2-yn-1-yl)ethane-1,2-diamine (**12d**, 0.100 g, 0.53 mmol) using general procedure D, except after reaction with **1** at 110 °C for 14 h, an additional 10 mol % of **1** was added, and the reaction mixture was heated to 110 °C for an additional 14 h. Compound **13d** was isolated as a brown oil (0.058 g, 58%). $[\alpha]_D$ = +7.1 (c = 0.65, chloroform; lit. $[\alpha]_D$ = +7.3, c = 0.68, chloroform).[38] >98% ee as determined by derivatization with (*R*)-α-

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methoxy-α-(trifluoromethyl)phenylacetic acid chloride in situ using the previously described experimental procedure,[39] ^{19}F NMR (292 MHz, $CDCl_3$) δ −72.1. Derivatization of the opposite enantiomer synthesized using RuCl[(*R*,*R*)-TsDPEN(*p*-cymene) with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride in situ using previously described experimental procedure,[39] ^{19}F NMR (292 MHz, $CDCl_3$) δ −73.4. Following general procedure E, **13d** was isolated as the tosylated piperazine compound as a colorless oil (0.062 g, 60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.0 Hz, 2H), 7.30 (m, 7H), 4.06−4.04 (m, 1H), 3.58 (d, *J* =13 Hz, 1H), 3.47 (d, *J* = 13 Hz, 1H), 3.37 (d, *J* = 13 Hz, 1H), 3.23 (dt, *J* = 12, 2.8 Hz, 1H), 2.71 (d, *J* = 10 Hz, 1H), 2.52 (d, *J* = 11 Hz, 1H), 2.43 (s, 3H), 2.16 (dd, *J* = 11, 3.6 Hz, 1H), 2.05 (dt, *J* = 12, 3.6 Hz, 1H), 1.16 (d, *J* = 6.4 Hz, 3H); ^{13}C{ ^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.0 (C), 138.1 (C), 137.9 (C), 129.6 (CH), 128.7 (CH), 128.2 (CH), 127.1 (CH), 62.5 (CH_2), 57.8 (CH_2), 52.7 (CH), 49.6 (CH_2), 40.9 (CH_2), 21.5 (CH_3), 15.4 (CH_3); IR (NaCl, cm^{-1}) 2920, 2849, 1663; HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{19}H_{25}N_2O_2S$ 345.1637, found 345.1633.

*tert-Butyl (2-(Benzyl(prop-2-yn-1-yl)amino)ethyl)carbamate (**15**).* *tert*-Butyl (2-(benzylamino)ethyl)carbamate (3.26 g, 13 mmol) was dissolved in EtOAc (100 mL). NaI (0.300 g, 2 mmol), Et_4NI (0.300 g, 1 mmol), and K_2CO_3 (3.59 g, 26 mmol) were added, and the suspension was heated to 70 °C for 20 h. The reaction mixture was cooled to room temperature, and H_2O was added (50 mL). The resulting layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined and washed with 10% metabisulfite solution (50 mL) and brine (50 mL) before drying over Na_2SO_4. The crude reaction mixture was purified by flash chromatography (15% EtOAc in hexanes) to yield the title compound as a pale yellow oil (**15**, 3.47 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.23 (m, 5H), 3.64 (s, 2H), 3.31 (d, *J* = 2.4 Hz, 2H), 3.24 (q, *J* = 5.1 Hz, 2H), 2.69 (t, *J* = 6.0 Hz, 2H), 2.24 (t, *J* = 2.4 Hz, 1H), 1.62 (br s, 1H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.0 (C), 138.3 (CH), 129.1 (CH), 128.5 (CH), 127.4 (C), 79.2 (C), 78.2 (C), 73.5 (CH_2), 57.6 (CH_2), 52.4 (CH_2), 41.4 (CH_2), 37.9 (C), 28.5 (CH_3), IR (NaCl, cm^{-1}) 3426, 3298, 2976, 2834, 1712, 1495; HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{17}H_{25}N_2O_2$ 289.1916, found 289.1917.

*N^1,N^1-Bis(3-phenylprop-2-yn-1-yl)ethane-1,2-diamine (**16**).* DBU (1.06 g, 7.0 mmol, 1.04 mL) was added to (3-bromoprop-1-yn-1-yl)benzene (1.34 g, 7.0 mmol) dissolved in toluene (10 mL), resulting in a dark brown reaction mixture. A solution of *tert*-butyl (2-aminoethyl)carbamate (1.12 g, 7.0 mmol) in toluene (10 mL) was added, and the reaction mixture was stirred at room temperature for 48 h. The solvent was removed in vacuo, and the residue was dissolved in DCM (50 mL) and washed with 10% metabisulfite solution (30 mL) and brine before drying over Na_2SO_4, filtering, and concentrating into a brown oil. The crude material was purified by flash chromatography (15% EtOAc in hexanes) to afford (2-(bis(3-phenylprop-2-yn-1-yl)amino)ethyl)carbamate as a yellow oil (**16a**, 0.235 g, 9%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.41 (m, 4H), 7.29−7.23 (m, 6H), 5.14 (br s, 1H), 3.70 (s, 4H), 3.30 (q, *J* = 4.8 Hz, 2H), 2.81 (t, *J* = 6.0 Hz, 2H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 156.0 (C), 131.8 (CH), 128.3 (CH), 128.2 (CH), 122.9 (C), 85.4 (C), 84.4 (C), 79.1 (C), 52.1 (CH_2), 43.3 (CH_2), 37.9 (C), 28.4 (CH_3); IR (NaCl, cm^{-1}) 3427, 3056, 2976, 2930, 1711, 1490; HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{25}H_{29}N_2O_2$ 389.2222, found 389.2229. (2-(Bis(3-phenylprop-2-yn-1-yl)amino)ethyl)carbamate (0.230 g, 0.59 mmol) was deprotected using general procedure B to yield *N*^{1},*N*^{1}-bis(3-phenylprop-2-yn-1-yl)ethane-1,2-diamine as a yellow oil (**16**, 0.168 g, quantitative): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46−7.40 (m, 4H), 7.30−7.27 (m, 6H), 3.72 (s, 2H), 2.86 (t, *J* = 5.7 Hz, 2H), 2.76 (t, *J* = 5.7 Hz, 2H), 2.12 (br s, 2H); ^{13}C{ ^{1}H} NMR (75 MHz, $CDCl_3$) δ 131.8 (CH), 128.3 (CH), 128.1 (CH), 123.0 (C), 85.2 (C), 84.7 (C), 55.8 (CH_2), 43.5 (CH_2), 39.4 (CH_2); IR (NaCl, cm^{-1}) 3363, 2923, 2850, 1597, 1573. HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{20}H_{21}N_2$ 289.1705, found 289.1699.

*(R)-3-Benzyl-1-(3-phenylprop-2-yn-1-yl)piperazine (**17**).* Following general procedure D, **16** (0.073 g, 0.25 mmol) was reacted to yield **17** in a mixture with unreacted **16** as brown oil (NMR yield: 14%, 96% ee): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23−7.20 (m, Ar−H), 4.11 (apparent quartet, 1H), 3.51(s, 2H), 3.08−2.92 (m, 2H), 2.61 (dd, *J* = 14, 9 Hz, 1H), 2.39 (dt, *J* = 11, 3 Hz, 1H), 2.13 (t, *J* = 10 Hz, 1H); HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{20}H_{23}N_2$ 291.1861, found 291.1858.

*N^1-Benzyl-N^1-(3-phenylprop-2-yn-1-yl)ethane-1,2-diamine (**18**).* Following general procedure A, the reaction of *tert*-butyl (2-(benzyl(prop-2-yn-1-yl)amino)ethyl)carbamate (1.000 g, 3.5 mmol) and iodobenzene (0.785 g, 3.9 mmol, 0.43 mL) afforded *tert*-butyl (2-(benzyl(3-phenylprop-2-yn-1-yl)amino)ethyl)carbamate (**18a**, 1.155 g, 91% yield) as a brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.45 (m, 2H), 7.38−7.28 (m, 8H), 4.99 (br s, 1H), 3.72 (s, 2H), 3.53 (s, 2H), 3.32−3.27 (m, 2H), 2.77 (t, *J* = 5.6 Hz, 2H), 1.46 (2, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1 (C), 138.5 (C), 131.9 (CH), 129.3 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.4 (CH), 123.2 (C), 85.9 (C), 84.1 (C), 79.2 (C), 58.0 (CH_2), 52.7 (CH_3), 42.3 (CH_2), 38.0 (CH_2), 28.6 (CH_3); IR (NaCl, cm^{-1}) 3426, 3299, 2976, 2835, 1712, 1485; HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{23}H_{29}N_2O_2$ 365.2229, found 365.2232. Following general procedure B, *tert*-butyl (2-(benzyl(3-phenylprop-2-yn-1-yl)amino)ethyl)-carbamate (**18a**, 1.01 g, 2.8 mmol) was deprotected to yield **18** as a brown oil (0.789 g, quantitative): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.45 (m, 2H), 7.40−7.25 (m, 8H), 3.73 (s, 2H), 3.54 (s, 2H), 2.83 (t, *J* = 6 HZ, 2H), 2.72 (t, *J* = 6.4 Hz, 2H), 1.61 (br s, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.9 (C), 131.8 (CH), 129.2 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.2 (CH), 123.3 (C), 85.6 (C), 84.4 (C), 58.2 (CH_2), 56.4 (CH_2), 42.5 (CH_2), 39.5 (CH_2); IR (NaCl, cm^{-1}) HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{18}H_{21}N_2$ 265.1705, found 265.1704.

*(R)-1,3-Dibenzylpiperazine (**19**).* Following general procedure D, amino alkyne **18** (0.050 g, 0.38 mmol) was reacted; after reaction with **1** at 110 °C for 14 h, an additional 10 mol % of **1** was added, and the reaction mixture was heated to 110 °C for an additional 14 h. Subsequent reduction with **2** yielded crude **19** as a brown oil (0.042 g, 84%). Following general procedure E, **19** was isolated as the tosylated piperazine compound (0.005 g, 8%, 87% ee): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.34−7.24 (m, 7H), 7.15−7.13 (m, 3H), 6.98−6.96 (m, 2H), 4.07−4.04 (m, 1H), 3.70 (d, *J* = 14 Hz, 1H), 3.45 (d, *J* = 13 Hz, 1H), 3.35−3.28 (m, 2H), 3.17 (dd, *J* = 13, 11 Hz, 1H), 2.78 (d, *J* = 12 Hz, 1H), 2.65 (dd, *J* = 12, 4 Hz, 1H), 2.62 (d, *J* = 12 Hz, 1H), 2.41 (s, 3H), 2.05 (dt, *J* = 12, 3.2 Hz, 1H), 1.90 (dd, *J* = 11, 3.2 Hz, 1H); ^{13}C{ ^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.2 (C), 138.8 (C), 138.2 (C), 138.7 (C), 129.8 (CH), 129.5 (CH), 129.4 (CH), 128.5 (CH), 128.4 (CH), 127.4 (CH), 127.2 (CH), 126.4 (CH), 62.9 (CH_2), 55.8 (CH_2), 53.3 (CH), 52.9 (CH_2), 41.5 (CH_2), 35.4 (CH_2), 29.9 (CH_2), 21.7 (CH_2); IR (NaCl, cm^{-1}) 2923, 2853, 1351, 1161; HRMS-ESI (*m*/*z*) [M + H]$^+$ calcd for $C_{25}H_{29}N_2O_2S$ 421.1950, found 421.1957.

*N^1-Benzyl-N^1-(but-2-yn-1-yl)ethane-1,2-diamine (**20**).* 2-Butyn-1-ol was stirred in THF, and the solution was cooled to 0 °C. Triethylamine was added, followed by methanesulfonyl chloride dropwise. The resulting reaction mixture was an orange solution with a white precipitate. The reaction mixture was stirred for 15 min before the precipitate was filtered off, and the filtrate was concentrated into clear orange oil. The oil was dissolved in acetonitrile (10 mL) and added to *tert*-butyl (2-(benzylamino)ethyl)-carbamate (1.401 g, 5.5 mmol) and potassium carbonate (2.509 g, 18 mmol) in acetonitrile (20 mL). The reaction mixture was heated to a reflux for 64 h. The reaction mixture was cooled to room temperature, and the solvent was removed in vacuo. The residue was dissolved in water (50 mL), and the aqueous solution was extracted with ethyl acetate (3 × 50 mL). The organic fractions were combined, washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated into brown oil. The crude material was purified by column chromatography (5−15% ethyl acetate in hexanes) to yield *tert*-butyl (2-(benzyl(but-2-yn-1-yl)amino)ethyl)-carbamate as a clear, colorless oil (**20a**, 0.514 g, 31%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.23 (m, 5H), 5.02 (br s, 1H), 3.62 (s, 2H), 3.26−3.20 (m, 4H), 2.65 (t, *J* = 6.0 Hz, 2H), 1.86 (s, 3H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.0 (C), 138.6 (C),

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129.0 (CH), 128.3 (CH), 127.1 (CH), 80.9 (C), 78.9 (C), 73.4 (C), 57.7 (CH_2), 52.3 (CH_2), 41.7 (CH_2), 37.9 (CH_2), 28.4 (CH_3), 3.43 (CH_3). IR (NaCl, cm^{-1}) 3359, 2913, 2849, 1712, 1494; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{18}H_{27}N_2O_2$ 303.2073, found 303.2066. Following general procedure B, *tert*-butyl (2-(benzyl(but-2-yn-1-yl)amino)ethyl)carbamate was deprotected to yield N^1-benzyl-N^1-(but-2-yn-1-yl)ethane-1,2-diamine (**20**) as a clear, colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.19 (m, 5H), 3.60 (s, 2H), 3.24 (s, 2H), 2.74 (t, J = 5.6 Hz, 2H), 2.58 (t, J = 4.8 Hz, 2H), 1.83 (s, 3H), 1.34 (br s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.6 (C), 129.0 (CH), 128.1 (CH), 126.9 (CH), 80.6 (C), 73.7 (C), 57.9 (CH_2), 56.1 (CH_2), 41.9 (CH_2), 39.5 (CH_2), 3.40 (CH_3); IR (NaCl, cm^{-1}) 3356, 2913, 2849, 1577, 1452; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{13}H_{19}N_2$ 203.1548, found 203.1545.

*(R)-1-Benzyl-3-ethylpiperazine (**21**).* Following general procedure D, amino alkyne **20** (0.100 g, 0.49 mmol) was reacted; however, after reaction with **1** at 110 °C for 14 h, an additional 10 mol % of **1** was added and the reaction mixture was heated to 110 °C for an additional 14 h. Subsequent reduction with **2** yielded crude **21** as a brown oil (0.025 g, 24%). Following general procedure E, **21** was isolated as the tosylated piperazine compound (0.004 g, 10%, 81% ee): ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 11 Hz, 2H), 7.29−7.20 (m, 7H), 3.80−3.75 (m, 1H), 3.66 (d, J = 19 Hz, 1H), 3.43 (d, J = 18 Hz, 1H), 3.30−3.18 (m, 2H), 2.61 (d, J = 15 Hz, 2H), 2.43 (s, 3H), 1.90 (dt, J = 16, 4.4 Hz, 2H), 1.70 (sextet, J = 10 Hz, 2H), 0.78 (t, J =10 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.1 (C), 138.9 (C), 138.2 (C), 129.8 (CH), 128.8 (CH), 128.4 (CH), 127.3 (CH), 127.2 (CH), 62.8 (CH_2), 55.7 (CH_2), 52.5 (CH), 52.9 (CH_2), 41.3 (CH_2), 29.9 (CH_3), 22.5 (CH_2), 11.0 (CH_3). IR (NaCl, cm^{-1}) 2923, 2850, 1460, 1163; HRMS-ESI (m/z) $[M + H]^+$ calcd for $C_{20}H_{27}N_2O_2S$ 359.1793, found 359.1786.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01884.

^1H and $^{13}C\{^1H\}$-spectra for new compounds and chromatograms used for ee determination (PDF)

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Notes

The authors declare no competing financial interest.

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