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Syntheses of Chiral β- and γ-Amino Ethers, Morpholines, and Their Homologues via Nucleophilic Ring-Opening of Chiral Activated Aziridines and Azetidines

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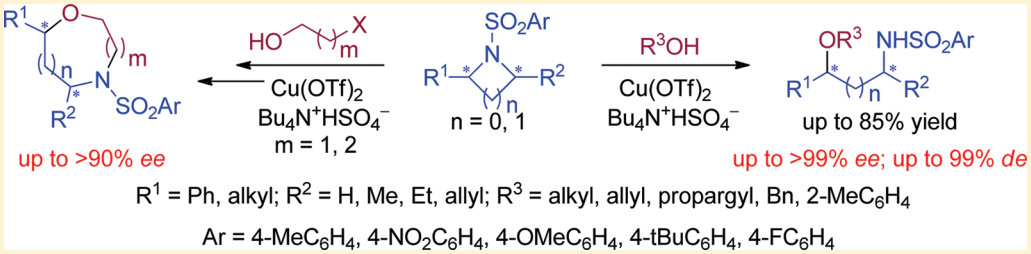
Supporting Information



ABSTRACT: Lewis acid catalyzed quaternary ammonium salt mediated highly regioselective ring-opening of chiral activated aziridines and azetidines with alcohols to nonracemic β- and γ-amino ethers has been developed. The reaction mainly proceeds via an S_N2 pathway, and the partial racemization of the starting substrate was effectively controlled by using quaternary ammonium salts. β- and γ-amino ethers are obtained with high enantio- and diastereospecificity (ee up to >99%, de up to 99%). The methodology was further extended to synthesize morpholines and their homologues with high enantiospecificity (ee up to 90%) when halo alcohols were employed as the nucleophiles.

INTRODUCTION

In recent years, ring-opening transformations of small ring aza-heterocycles have been extensively exploited to provide excellent routes for the construction of important synthetic targets via nucleophilic ring-opening, cycloaddition, and rearrangement reactions.[1−5] Lewis acid (LA) mediated ring-opening of 2-phenyl-*N*-tosylaziridines and -azetidines with several nucleophiles to afford nonracemic products in high enantiomeric excess have been reported by us. We demonstrated the reaction to proceed through a prevalent S_N2 pathway, and the partial loss of enantiopurity in all the cases was due to partial racemization of the starting aziridines or azetidines.[5]

Very recently, we have reported S_N2-type ring-opening of aziridines and azetidines using (i) quaternary ammonium salts with nucleophilic halides as the counterions in the presence of $BF_3{\cdot}Et_2O$[6a] and (ii) quaternary ammonium salt with non-nucleophilic counteranions in the presence of metal halides as Lewis acids[6b] to afford haloamines with excellent enantiospecificity. We believe that the dipolar quaternary ammonium salt stabilizes the dipolar intermediate generated from the interaction of aziridine with the LA and controls the racemization of the starting aziridine affording the haloalkylamines with excellent ee (up to 99%).

We anticipated that it could be possible to achieve the Lewis acid-catalyzed ring-opening of aziridines and azetidines by nucleophiles in the presence of quaternary ammonium salts with non-nucleophilic anions which allow the products to be formed with higher enantiospecificity than those previously obtained in the absence of these ammonium salts, e.g., nonracemic β- and γ-amino ethers with high ee.[5i] To demonstrate the efficiency of our present synthetic methodology, we chose the same nucleophile (i.e., alcohols) as the products amino ethers are an important class of compounds from biological perspectives. Enantiopure β-amino ethers are key precursors in the preparation of a wide variety of pharmaceutical compounds. The β-amino ether mexiletine[7] is a popular antiarrhythmic,[8] antimyotonic,[9] and analgesic agent.[10] It has also been proposed for the treatment of tinnitus.[11] β-Amino ethers are essential fragments in many glucopeptide antibiotics[12] and ether-containing peptide bond surrogate units.[13] There are several reports available for the syntheses of β-amino ethers in the literature.[14] General methods include alkoxide or Brønsted acid mediated alcoholyses of aziridines,[14a] opening of *N*-nosylaziridines by MeOH,[14b] KSF clay,[14c] or Lewis acid mediated ring-opening of aziridines.[14d] Ring-opening of resin-bound aziridines with phenol nucleophiles has been reported recently.[14e] Syntheses of β-amino ethers by substitution of the β-hydroxy ether have also been reported.[14f] Their homologues, γ-amino ethers, are widely used for the treatment of anxiety and depression, e.g., fluoxetine, a novel antidepressant, is widely used for treatment of various types of psychiatric disorders, as well as other clinical conditions.[15−18] Syntheses of γ-amino ethers are known from chiral alcohol intermediates,[19] *N*-alkylazetidinols,[20] and 2-aryl-*N*-tosylazeti-

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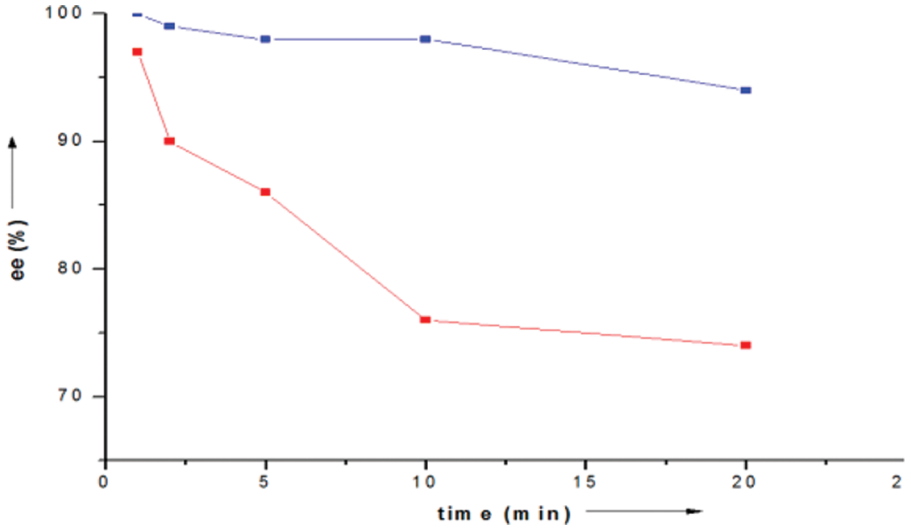


Figure 1. Comparative racemization study of (*R*)-**1a** with $Cu(OTf)_2$ at 0 °C in DCM with TBAHS (blue line) and without TBAHS (red line) up to 20 min.

dines.[21,22] Various synthetic protocols like chemical or enzymatic resolution, asymmetric reduction of the prochiral ketones, dihydroxylation or Sharpless epoxidation of styrene, and carbonyl−ene reaction of benzaldehyde have been employed for the syntheses of γ-amino ethers. We report herein copper(II) triflate-catalyzed and tetrabutylammonium hydrogen sulfate (TBAHS)-mediated ring-opening of aziridines and azetidines with alcohols to afford nonracemic amino ethers in excellent diastereo- and enantiospecificity.

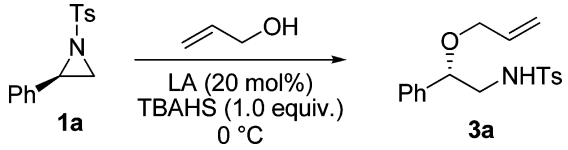
RESULTS AND DISCUSSION

To test the feasibility of our approach, at first we studied the racemization of enantiopure (*R*)-2-phenyl-*N*-tosylaziridine **1a** with $Cu(OTf)_2$ (20 mol %) in dichloromethane without any nucleophile in the presence of TBAHS. Our earlier studies showed that the rate of racemization of (*R*)-2-phenyl-*N*-tosylaziridine **1a** was very fast with $Cu(OTf)_2$ in dichloromethane; the ee of (*R*)-**1a** after 5 min was found to be 86%, and after 20 min it was reduced to 74%.

In the presence of TBAHS, to our great pleasure, we observed that the racemization of (*R*)-**1a** with $Cu(OTf)_2$ (20 mol %) could be controlled to an appreciable extent; the ee of (*R*)-**1a** after 5 min was slightly reduced (ee 98%), and after 20 min it became 94% (Figure 1, details are provided in the Supporting Information).

Next, we studied the ring-opening of aziridine (*R*)-**1a** with allyl alcohol in the presence of a catalytic amount of LA and TBAHS (Scheme 1). When (*R*)-**1a** was treated with allyl alcohol in the presence of 20 mol % of $Cu(OTf)_2$ and 1.0 equiv of TBAHS at 0 °C for 15 min, nonracemic β-amino ether **3a** was obtained in good yield and excellent ee (88%) as the only regioisomer.

Scheme 1. Nucleophilic Ring-Opening of 2-Phenyl-*N*-tosylaziridine by Allyl Alcohol in the Presence of Lewis Acid and Quaternary Ammonium Salt



To optimize the reaction conditions for better yield and ee, various other Lewis acids were screened; however, other Lewis acids took a longer time for completion of the reaction, and the products were obtained with reduced ee in some cases. The reaction was found to be more efficient using only 5 mol % of $Cu(OTf)_2$ and 2.0 equiv of TBAHS to produce the amino ether **3a** with 92% ee (entry 7, Table 1). All of the results have been summarized in Table 1.

Table 1. Screening of Lewis Acids for Regioselective Nucleophilic Ring-Opening of (*R*)-1a with Allyl Alcohol in the Presence of TBAHS[a]

entry	Lewis acid (20 mol %)	time	yield[b] (%)	ee[c] (%)
1	$Sc(OTf)_3$	4.5 h	73	88
2	$Zn(OTf)_2$	4.5 h	74	89
3	$BF_3{\cdot}OEt_2$	1.5 h	37	78
4	$Yb(OTf)_3$	2 h	78	77
5	AgOTf	4 h	77	82
6	$Cu(OTf)_2$	15 min	75	88
7[d]	$Cu(OTf)_2$	30 min	76	92
8[d,e]	$Cu(OTf)_2$	25 min	75	71

[a]Allyl alcohol was used as the solvent in all the cases. [b]After column chromatographic purification. [c]The ee was determined by Chiralpak AS-H column. [d]5 mol % of $Cu(OTf)_2$ and 2.0 equiv of TBAHS were used. [e]The reaction was performed at room temperature.

After observing the enhanced enantiospecificity of the reaction with catalytic amount of $Cu(OTf)_2$ and TBAHS, we explored the reaction with other quaternary ammonium salts having different non-nucleophilic counteranions viz. hexafluorophosphate, triflate, perchlorate, and tetrafluoroborate (Scheme 2). However, it took a longer time for the completion of the reaction in all of the cases affording the product with poor yield and comparatively low enantiospecificity. TBAHS was found to be the best salt for the Lewis acid catalyzed ring-opening reaction with alcohols (entry 1, Table 2). The results are summarized in Table 2.

Under the optimized reaction conditions, the ring-opening of (*R*)-**1a** was generalized with a number of alcohols (propargyl,

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Scheme 2. Nucleophilic Ring-Opening of (*R*)-2-Phenyl-*N*-tosylaziridine by Allyl Alcohol in the Presence of $Cu(OTf)_2$ and Quaternary Ammonium Salt

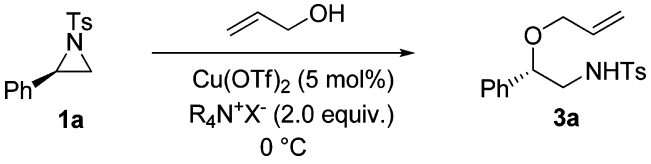


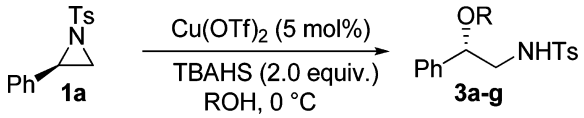
Table 2. Optimization of Quaternary Ammonium Salts[a]

entry	$R_4N^+X^-$	time (h)	yield[b] (%)	ee[c] (%)
1	$Bu_4N^+HSO_4^-$	0.5	76	92
2	$Bu_4N^+PF_6^-$	3.0	56	88
3	$Bu_4N^+OTf^-$	2.0	30	85
4	$Bu_4N^+ClO_4^-$	1.75	56	79
5	$Bu_4N^+BF_4^-$	2.5	62	89

[a]Allyl alcohol was used as the solvent in all the cases. [b]After column chromatographic purification. [c]The ee was determined by Chiralpak AS-H column.

benzyl, isopropyl, etc., Scheme 3), and the results are shown in Table 3. It was observed that under catalytic conditions using

Scheme 3. $Cu(OTf)_2$-Catalyzed TBAHS-Mediated Regioselective Nucleophilic Ring-Opening of (*R*)-2-Phenyl-*N*-tosylaziridine with Different Alcohols



2.0 equiv of TBAHS, there was 7−20% enhancement in ee in all the cases by comparison with results obtained in the absence of the quaternary ammonium salts.[23]

In the course of performing of the experiments described in Table 3, it has been observed that the rate of reactions varied in different alcohols. The dielectric constants of the alcohols are as follows: MeOH (33.0), allyl alcohol (19.7), propargyl alcohol (20.8), 2-chloroethanol (25.80), 2-propanol (20.18), tBuOH (17.26), benzyl alcohol (11.916), and *o*-cresol (6.76).[24] Probably the combination of solvent polarity (depends on dielectric constant) and hydrogen bonding governs the reactivity of a particular alcohol. MeOH being the most polar stabilizes the dipolar intermediate before nucleophilic attack and probably because of H-bonding nucleophilicity of MeOH is reduced (reaction becomes slower). Other alcohols are comparatively less polar and better nucleophiles. As a result, they stabilize the reactive intermediate to a lesser extent, and there is a possibility of a double S_N2 attack at the reactive site. This might contribute to the faster reaction but with decreased stereospecificity.

When more sterically crowded 2-methyl-2-propanol was used, (*R*)-**1a** (Table 3, entry 6) afforded the corresponding amino ether with excellent enantiospecificity at 25 °C. It is worth mentioning that 2-methyl-2-propanol failed to give any ring-opening product with (*R*)-**1a** in the absence of TBAHS. When propargyl alcohol was used as the solvent, (*R*)-**1a** produced the amino ether **3c** with 80% ee within 2 min at 0 °C (Table 3, entry 3). When the same reaction was performed in dichloromethane as the solvent with 5.0 equiv of the alcohol at −50 °C (reaction duration 6 h), the enantiospecificity was enhanced (ee 92%). However, other alcohols did not react at lower temperature. The absolute configuration of the amino ether **3b** as a representative example has been determined to be (*S*) in our previous report.[5i]

To study the electronic effect of the *N*-arylsulfonyl group, a variety of *N*-arylsulfonylaziridines **1b−e** (ee > 99%)[5j] were treated with methanol in the presence of catalytic amount of $Cu(OTf)_2$ and stoichiometric amount of TBAHS to afford the corresponding amino ethers **3h−k** in good yield and excellent ee (Scheme 4, Table 4). When (*R*)-2-phenyl-*N*-nosylaziridne **1b** was employed, the corresponding product **3h** was formed in good yield and excellent enantiospecificity (Table 4, entry 1). The nosyl group can be easily deprotected under mild reaction conditions without affecting the enantiomeric excess of the corresponding product.[5b] In this context chiral (*R*)-2-phenyl-*N*-acetylaziridine was synthesized utilizing modified reported procedure,[23,25] and its ring-opening reactions with alcohols (MeOH and allyl alcohol) were studied applying the present reaction conditions. Unfortunately, with *N*-acetylaziridine we were not successful to get any ring-opening product. The aziridine **1d** bearing a weak electron-withdrawing group on nitrogen took a longer time for the reaction to complete, and the yield of the reaction was also found to be poor in this case (Table 4, entry 3). As the preparation of *N*-tosylaziridnes are very easy (both racemic and chiral), we have employed the *N*-tosylaziridines for most of our studies.

To broaden the scope of this methodology further, a variety of 2-alkyl-*N*-tosylaziridines **1f−i** (ee > 99%)[5j] prepared from the corresponding amino acids were reacted with methanol under the same reaction conditions (Scheme 5).

Ring-opening of alkyl aziridines **1f−i** with methanol was found to be comparatively slower than arylaziridines (Table 5) and produced the corresponding amino ethers as a mixture of regioisomers **3l−o** and **4l−o** arising from internal attack and terminal attack, respectively, which could not be separated by column chromatography. Structures of the regioisomers could not be interpreted from the ^1H NMR of the crude reaction mixture as regioisomeric proton signals were found to be mostly inseparable, although ^{13}C NMR clearly showed the presence of amino ethers **3l−o** and **4l−o**.

The regioisomeric ratio was determined by HPLC analysis. The structure of the major regioisomer **4** was confirmed indirectly by comparing with an authentic compound. As a representative example, **4m** was converted to the corresponding *N*-methyl derivative (Scheme 6), and its spectral data (^1H and ^{13}C NMR) were compared with the authentic compound **5** prepared from (*S*)-phenylalanine.[5i,17]

The strategy was further extended to enantiopure *trans*-2,3-disubstituted aziridines **1j−m**.[6] Ring-opening of enantiopure **1j−m** (de up to 99%) in the presence of 5 mol % of copper triflate and 2.0 equiv of TBAHS with methanol afforded the corresponding anti amino ethers **3p−s** as the major diasteromers (Scheme 7, Table 6, entries 1−4) with high yield and excellent de. However, the reaction did not proceed in the absence of TBAHS using catalytic amount of Lewis acid.

After successful demonstration of the strategy for the ring-opening of aziridines, we envisaged that the ring-opening of enantiopure (*S*)-2-phenyl-*N*-tosylazetidine **2a** (ee > 99%) with alcohols in the presence of catalytic amount of LA and stoichiometric amount of quaternary ammonium salt would also afford γ-amino ethers **6** with better specificity. Initially, we studied the ring-opening of (*S*)-**2a** with methanol in the

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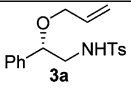
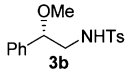
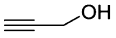
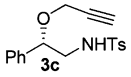
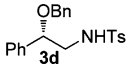
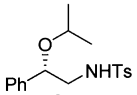
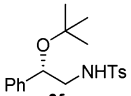
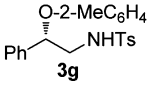
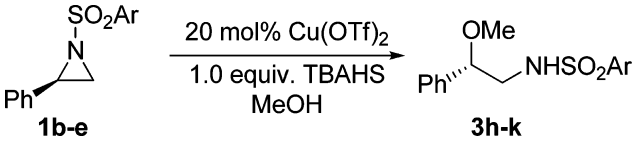
Table 3. Cu(OTf)$_2$-Catalyzed TBAHS-Mediated Regioselective Nucleophilic Ring-Opening of (*R*)-2-Phenyl-*N*-tosylaziridine with Different Alcohols[a]

entry	alcohols	amino ether	time	yield[b] (%)	ee[c] (%)
1		 **3a**	0.5 h	76	92
2	MeOH	 **3b**	2 h	80	>99
3		 **3c**	2 min	75	80
4	BnOH	 **3d**	15 min	72	92
5	iPrOH	 **3e**	2 h	77	91
6[d]	tBuOH	 **3f**	1.5 h	70	88
7[d,e]	*o*-Cresol	 **3g**	20 min	65[f]	nd

[a]Alcohols were used as the solvent in all the cases. [b]After column chromatographic purification. [c]The ee was determined by chiral HPLC analysis. [d]The reaction was performed at 25 °C. [e]The other regioisomer **4g** (from terminal attack) was also obtained in a 2:1 ratio. [f]Combined yield of regioisomers **3g** and **4g** after column chromatographic purification.

Scheme 4. Cu(OTf)$_2$-Catalyzed TBAHS-Mediated Regioselective Nucleophilic Ring-Opening of Various (*R*)-2-Phenyl-*N*-sulfonylaziridines with Methanol



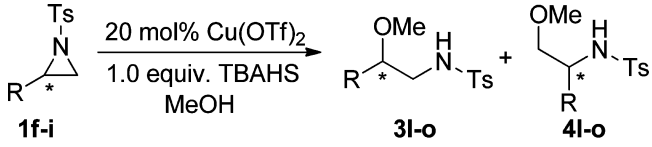
presence of 30 mol % of Cu(OTf)$_2$ and a stoichiometric amount of quaternary ammonium salt at 0 °C to produce amino ether **6a** in high yield (82%) and excellent ee (94%).

Table 4. Cu(OTf)$_2$-Catalyzed TBAHS-Mediated Regioselective Nucleophilic Ring-Opening of Various (*R*)-2-Phenyl-*N*-sulfonylaziridines with Methanol[a]

entry	aziridine, Ar	amino ether	time (h)	yield[b] (%)	ee[c] (%)
1	**1b**, 4-$NO_2C_6H_4$	**3h**	4	85	>99
2	**1c**, 4-$MeOC_6H_4$	**3i**	3.5	77	98
3	**1d**, 4-FC_6H_4	**3j**	12	51	97
4	**1e**, 4-tBuC_6H_4	**3k**	4	67	95

[a]Methanol was used as solvent in all the cases. [b]After column chromatographic purification. [c]The ee was determined by chiral HPLC analysis.

Scheme 5. Nucleophilic Ring-Opening of 2-Alkyl-*N*-tosylaziridines with Methanol



R = **1f**: (*R*) Me, **1g**: (*S*) Bn, **1h**: (*R*) iPr,**1i**: (*R*) iBu

The strategy was generalized for the ring-opening of (*S*)-**2a** with a number of alcohols, and the results are summarized in Table 7. In this case, also we have observed 6−20% enhancement in ee and appreciable reduction in reaction time.[23]

The scope of the methodology was further extended for the ring-opening of enantiopure *cis*- and *trans*-2,4-disubstituted azetidines **2b−e** with methanol to afford the corresponding 1,3-amino ethers **6g−j**. The ring-opening of enantiomerically pure *trans*-(2*R*,4*S*)-2-allyl-4-phenyl-*N*-tosylazetidine **2d** affords amino ether **6i** as the major diastereomer with syn configuration, whereas ring-opening of *cis*-**2e** affords amino ether **6j** with the anti configuration as the major diastereomer (Scheme 9, Table 8, entries 3 and 4).

The 1,3-relative stereochemistry of the diastereomers **6i** and **6j** was determined by NOESY experiment. When protons H_a

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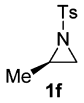
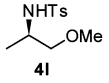
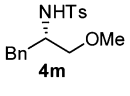
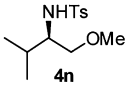
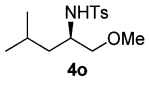
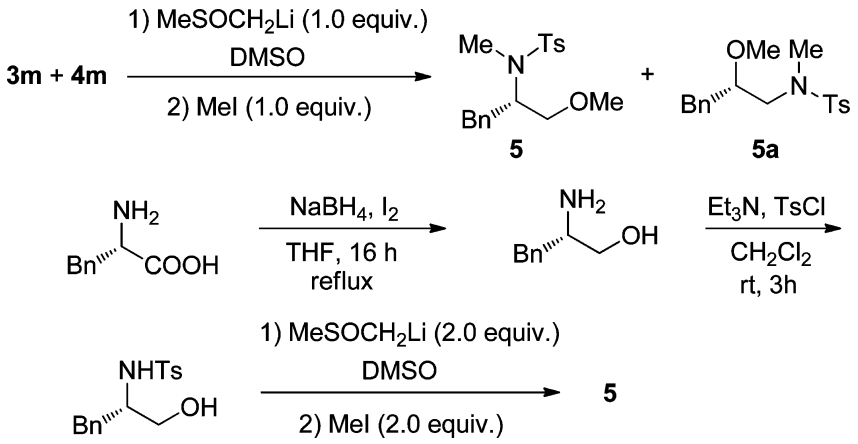
Table 5. Cu(OTf)$_2$-Catalyzed TBAHS-Mediated Nucleophilic Ring-Opening of 2-Alkyl-*N*-tosylaziridines with Methanol[a]

entry	aziridine	amino ether	time (h)	yield[b] (%)	ratio **4**:**3**
1	 **1f**	 **4l**	2	66	70:30
2	 **1g**	 **4m**	1	88	89:11
3	 **1h**	 **4n**	7	53	84:16
4	 **1i**	 **4o**	10	64	52:48

[a]Methanol was used as the solvent in all the cases. [b]After column chromatographic purification. [c]The ratio was determined by HPLC analysis.

Scheme 6. Synthesis of Authentic Compound 5



Scheme 7. Cu(OTf)$_2$-Catalyzed TBAHS-Mediated Regioselective Nucleophilic Ring-Opening of 2,3-Disubstituted *N*-Tosylaziridines with Methanol

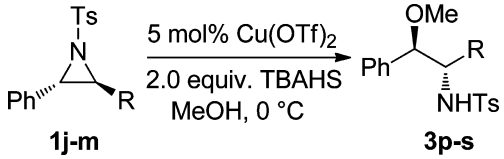
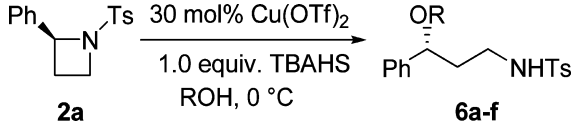


Table 6. Cu(OTf)$_2$-Catalyzed TBAHS-Mediated Regioselective Nucleophilic Ring-Opening of 2,3-Disubstituted *N*-Tosylaziridines with Methanol[a]

entry	aziridine	amino ether	time (h)	yield[b] (%)	de[c] (%)
1	R = Et, **1j**	**3p**	1	90	>99
2	R = Me, **1k**	**3q**	1	84	>99
3	R = nPr, **1l**	**3r**	1.5	68	>99
4[d]	R = allyl, **1m**	**3s**	2	70	92

[a]Methanol was used as solvent in all the cases. [b]After column chromatographic purification. [c]The de was determined by ^{1}H NMR and chiral HPLC analysis. [d]The de of starting aziridine was 92%.

Scheme 8. Cu(OTf)$_2$-Catalyzed TBAHS-Mediated Regioselective Nucleophilic Ring-Opening of 2-Phenyl-*N*-tosylazetidine with Various Alcohols



and H_b were irradiated, peak enhancement for the *cis*-diastereomer was comparatively more than for the *trans*-diastereomer (Figure 2).

However, in order to get mechanistic insight and to demonstrate the effect of TBAHS, we performed the following set of experiments in dichloromethane using limited excess of alcohols as the nucleophiles. To our anticipation, the enantiospecificity of the reactions increased appreciably in all the cases.

In order to showcase the efficiency of our present methodology, we have further extended this protocol for the synthesis of morpholines and homomorpholines by the ring-opening of various aziridines and azetidines with halo alcohols. When (*R*)-2-phenyl-*N*-sulfonylaziridines (*R*)-**1a,c,d** were treated with 2-chloroethanol in the presence of 5 mol % of Cu(OTf)$_2$ and a stoichiometric amount of tetrabutylammo-

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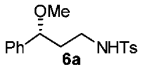
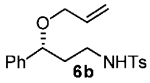
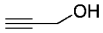
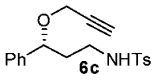
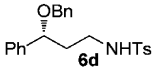
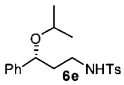
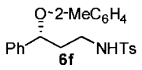
Table 7. Cu(OTf)$_2$-Catalyzed TBAHS-Mediated Regioselective Nucleophilic Ring-Opening of 2-Phenyl-*N*-tosylazetidine with Various Alcohols[a]

entry	alcohols	amino ether	time	yield[b] (%)	ee[c] (%)
1	MeOH	 **6a**	7 h	82	94
2		 **6b**	4 h	75	84
3		 **6c**	5 min	80	86
4	BnOH	 **6d**	15 min	68	91
5	iPrOH	 **6e**	72 h	77	88
6	*o*-Cresol[d,e]	 **6f**	5 min	70[f]	46

[a]Alcohols were used as solvent in all cases. [b]After column chromatographic purification. [c]The ee was determined by chiral HPLC analysis. [d]The reaction was performed at 25 °C. [e]The other regioisomer **7f** (from terminal attack) was also obtained in 2:1 ratio. [f]Combined yield of regioisomers **6f** and **7f** after column chromatographic purification.

Scheme 9. Cu(OTf)$_2$-Catalyzed TBAHS-Mediated Regioselective Nucleophilic Ring-Opening of 2,4-Disubstituted *N*-tTosylazetidine with Methanol

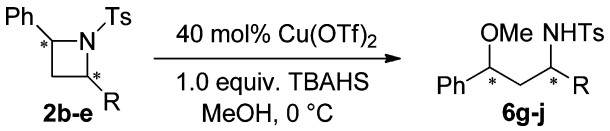


Table 8. Cu(OTf)$_2$-Catalyzed TBAHS-Mediated Regioselective Nucleophilic Ring-Opening of 2,4-Disubstituted *N*-Tosylazetidine with Methanol[a]

entry	azetidine	amino ether	time (h)	yield[b] (%)	dr[c]
1	 **2b**	 **6g**	24	86	97:3
2	 **2c**	 **6h**	48	80	98:2
3	 **2d**	 **6i**	18	95	91:9
4	 **2e**	 **6j**	40	90	99:1

[a]Methanol was used as solvents in all the cases. [b]After column chromatographic purification. [c]The dr was determined by ^{1}H NMR.

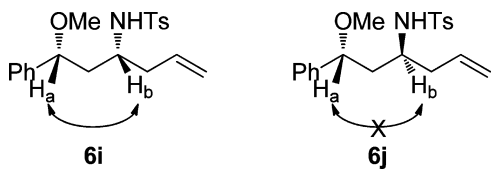


Figure 2. Diagnostic NOE observation for the amino ethers **6i** and **6j**.

nium hydrogen sulfate at 0 °C, it afforded the corresponding chloroethoxy amines which upon further treatment with KOH afforded the *N*-sulfonylmorpholines **7a–c** with improved ee (Scheme 10, Table 10).

When the ring-opening reaction of (*R*)-**1a** with 2-chloroethanol in the presence of 5 mol % of Cu(OTf)$_2$ and stoichiometric amount of TBAHS was performed at −50 °C in dichloromethane solvent, it afforded the morpholine **7a** with 90% ee (Table 10, entry 4).

The reaction was also successful in the case of azetidine. When the ring-opening reaction of (*S*)-**2a** with 3-chloropropanol in the presence of 40 mol % of Cu(OTf)$_2$ and a stoichiometric amount of TBAHS was performed at 0 °C in dichloromethane solvent, it afforded the oxazocane **8**, the two-carbon higher homologue of morpholines with 78% ee in 50% overall yield (Scheme 11).

MECHANISM

The reaction follows an S_N2-type mechanism as proposed previously by us.[6] Based on our racemization studies of (*R*)-**1a** and (*S*)-**2a** in the presence of quaternary ammonium salt, we believe that Cu(OTf)$_2$ reacts with aziridine or azetidine to generate a highly reactive intermediate **9** or **10** that is stabilized by tetraalkylammonium salt and the rate of racemization of (*R*)-**1a** or (*S*)-**2a** is retarded. The alcohol as the nucleophile then attacks at the benzylic position of **9** or **10** affording the amino ether with enhanced enantiospecificity (Scheme 12).

CONCLUSION

In conclusion, we have developed a simple strategy for the synthesis of optically enriched or enantiopure β- and γ-amino ethers via Lewis acid catalyzed quaternary ammonium salt mediated ring-opening of aziridines and azetidines with

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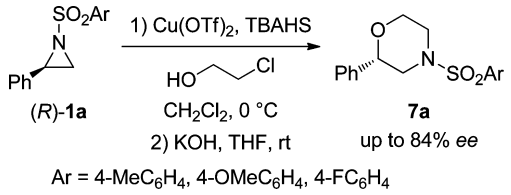
Table 9. Comparative Experimental Study of Ring-Opening of (*R*)-2-Phenyl-*N*-tosylaziridine and (*S*)-2-Phenyl-*N*-tosylazetidine with Various Alcohols as Nucleophiles in Dichloromethane with and without TBAHS

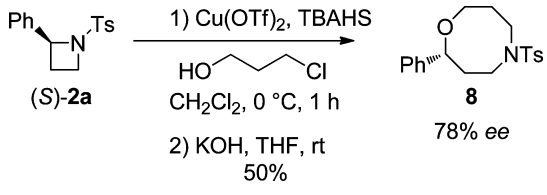
entry	substrate	alcohol	without TBAHS			with TBAHS		
			time	yield[c] (%)	ee[d] (%)	time	yield[c] (%)	ee[d] (%)
1[a]	(*R*)-**1a**		3.5 h	83	49	2 h	45	83
2[a]	(*R*)-**1a**		35 min	86	21	15 min	43	70
3[a]	(*R*)-**1a**	BnOH	1.5 h	66	25	30 min	47	74
4[b]	(*S*)-**2a**		10 h	88	31	7.5 h	53	42
5[b]	(*S*)-**2a**		15 min	85	28	10 min	54	32

[a]0.1 equiv of $Cu(OTf)_2$, 1.0 equiv of TBAHS, and 5.0 equiv of alcohol were used. [b]0.4 equiv of $Cu(OTf)_2$, 1.0 equiv of TBAHS, and 5.0 equiv of alcohol were used. [c]After column chromatographic purification. [d]The ee was determined by chiral HPLC analysis.

Scheme 10. One-Pot Ring-Opening of Chiral 2-Phenyl-*N*-sulfonylaziridines in the Presence of $Cu(OTf)_2$ and TBAHS by Chloroethanol

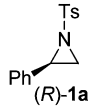
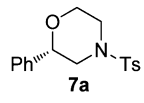
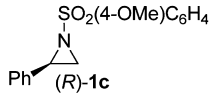
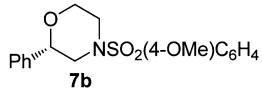
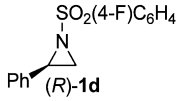
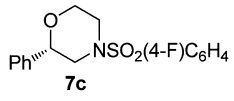
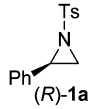
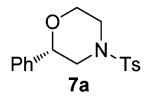


Scheme 11. Ring-Opening of (*S*)-2-Phenyl-*N*-tosylazetidine in the Presence of $Cu(OTf)_2$ and TBAHS by 3-Chloropropanol at 0 °C



alcohols under very mild reaction conditions. The methodology was further extended for the synthesis of morpholines and their higher homologues. The present strategy can be treated as a general methodology which stands superior than other reports including our earlier results for the preparation of β- and γ-amino ethers based on the following experimental observations: (i) using the quaternary ammonium salt the ring-opening reactions of aziridines and azetidines could be made possible using catalytic amount of Lewis acid; (ii) the reaction time becomes considerably shorter when quaternary ammonium salt is used; (iii) reaction with less reactive nucleophiles (e.g., 2-methyl-2-propanol) which do not react at all, are made successful using the quaternary ammonium salt as the additive; (iv) by adding quaternary ammonium salt in the reaction

Table 10. One-Pot Synthesis of Morpholines and Higher Homologues via Ring-Opening of Aziridines and Azetidines with 2-Chloroethanol in the Presence of TBAHS[a]

entry	aziridine or azetidine	time (ring opening)	product	yield[b] (%)	ee[c] (%)
1	 (*R*)-**1a**	20 min	 **7a**	62	82
2	 (*R*)-**1c**	40 min	 **7b**	58	84
3	 (*R*)-**1d**	30 min	 **7c**	56	86
4[d]	 (*R*)-**1a**	6 h	 **7a**	59	90

[a]In all cases, the alcohol served as the solvent and a stoichiometric amount of TBAHS was used. [b]After column chromatographic purification. [c]Determined by HPLC analysis using Chiralpak AD-H or Chiralcel OD-H. [d]The reaction was performed at −50 °C.

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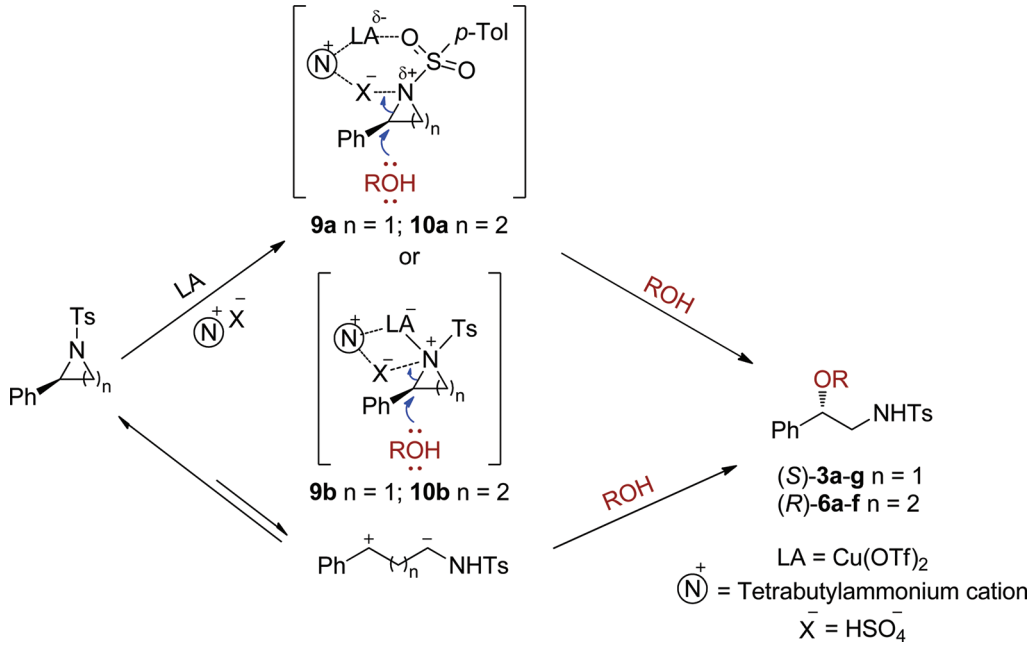
Scheme 12. Plausible Mechanism for the Ring-Opening of Aziridines and Azetidines with Alcohols



mixture the competitive racemization of chiral aziridines and azetidines are controlled; (v) up to 20−24% increase in enantiospecificity were observed when the quaternary ammonium salt was used in the reaction along with the catalytic amount of Lewis acid.

EXPERIMENTAL SECTION

General Procedures. Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F_{254} precoated plates. Visualizations were accomplished with a UV lamp or I_2 stain. Silica gel 100−200 and 230−400 mesh size were used for column chromatography using the combination of ethyl acetate and petroleum ether as an eluent. Unless noted, all of the reactions were carried out in oven-dried glassware under an atmosphere of nitrogen using anhydrous solvents. Where appropriate, solvents and all reagents were purified prior to use following the guidelines of Perrin and Armarego.[26] $Cu(OTf)_2$ used in all reactions was prepared using a literature procedure.[27] All commercial reagents were used as received. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 400 or 500 MHz. Chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethyl silane (δ 0.00). ^{1}H NMR splitting patterns are designated as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), or multiplet (m). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 100 or 125 MHz. Mass spectra (MS) were obtained using FAB and ESI mass spectrometer. Melting points were determined using a hot stage apparatus and are reported as uncorrected. Enantiomeric excess (ee) was determined by HPLC using a Chiralcel OD-H or Chiralpak AD-H or AS-H analytical column (detection at 254 nm). Optical rotations are reported as $[\alpha]^{25}_D$ (c in g per 100 mL solvent).

General Procedure for the $Cu(OTf)_2$-Catalyzed TBAHS-Mediated Ring-Opening of Aziridines. *Method A.* A solution of the aziridine (*R*)-**1a** (1.0 equiv) and TBAHS (2.0 equiv) in 1.0 mL alcohol was added to anhydrous $Cu(OTf)_2$ (0.05 equiv) at an appropriate temperature under an argon atmosphere. The mixture was stirred for an appropriate time (entries 1−7, Table 3 and 6), and then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 5.0 mL) and was washed with brine solution. The organic layers were collected and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (230−400 mesh) using 15% ethyl acetate in petroleum ether to provide the pure product.

Method B. A solution of the aziridine (1.0 equiv) and TBAHS (1.0 equiv) in 1.0 mL of methanol was added to anhydrous $Cu(OTf)_2$ (0.2 equiv) at an appropriate temperature under an argon atmosphere. The mixture was stirred for an appropriate time (Tables 4 and 5), and then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 5.0 mL) and was washed with brine solution. The organic layers were collected and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (230−400 mesh) using 15% ethyl acetate in petroleum ether to provide the pure product.

General Procedure for the $Cu(OTf)_2$-Catalyzed TBAHS-Mediated Ring-Opening of Azetidines. *Method C.* A solution of the azetidine (*S*)-**2a** (0.087 mmol, 1.0 equiv) and TBAHS (0.087 mmol, 1.0 equiv) in alcohol was added to anhydrous $Cu(OTf)_2$ (0.0261 mmol, 0.3 equiv) at an appropriate temperature under an argon atmosphere. The mixture was stirred for an appropriate time (entries 1−6, Table 7), and then the reaction mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 5.0 mL) and was washed with brine solution. The organic layers were collected and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (230−400 mesh) using 15% ethyl acetate in petroleum ether to provide the pure product.

Method D. A solution of the azetidine **2b−e** (1.0 equiv) and TBAHS (1.0 equiv) in methanol was added to anhydrous $Cu(OTf)_2$ (0.4 equiv) at an appropriate temperature under an argon atmosphere. The mixture was stirred for an appropriate time (entries 1−4, Table 8), and then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 5.0 mL) and was washed with brine solution. The organic layers were collected and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography on silica gel (230−400 mesh) using 15% ethyl acetate in petroleum ether to provide the pure product.

General Procedure for the $Cu(OTf)_2$-Catalyzed TBAHS-Mediated One-Pot Ring-Opening/Cyclization of Aziridines with Halo Alcohols. *Method E.* A solution of the aziridines

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1a, **1c**, and **1d** (1.0 equiv) in halo alcohol (10 equiv) was added at 0 °C to anhydrous copper triflate (5 mol %) and 1 equiv of TBAHS under an argon atmosphere. The mixture was stirred for an appropriate time, and then it was further treated with KOH in THF to afford the *N*-sulfonylmorpholines **7a−c** with improved ee. The reaction was quenched with water, and then the mixture was extracted with dichloromethane (3 × 5.0 mL) and dried over anhydrous sodium sulfate. The crude product was purified by flash column chromatography on silica gel (230−400 mesh) using 10% ethyl acetate in petroleum ether to provide the pure product.

General Procedure for the $Cu(OTf)_2$-Catalyzed TBAHS-Mediated One-Pot Ring-Opening/Cyclization of Azetidines with Halo Alcohols. *Method F.* A solution of the azetidine **2a** (1.0 equiv) in halo alcohol (10 equiv) was added at 0 °C to anhydrous copper triflate (40 mol %) and 1 equiv of TBAHS under an argon atmosphere. The mixture was stirred for an appropriate time, and then it was further treated with KOH in THF to afford the *N*-sulfonyloxazocane **8** with improved ee. The reaction was quenched with water, and then it was extracted with dichloromethane (3 × 5.0 mL) and dried over anhydrous sodium sulfate. The crude product was purified by flash column chromatography on silica gel (230−400 mesh) using 10% ethyl acetate in petroleum ether to provide the pure product.

*(S)-N-(2-(Allyloxy)-2-phenylethyl)-4-methylbenzenesulfonamide (**3a**).* The general method A described above was followed when (*R*)-**1a** (25 mg, 0.091 mmol) reacted with allyl alcohol at 0 °C to afford **3a** as a dense liquid (22.0 mg, 76% yield): $[\alpha]^{25}_D$ +88.2 (*c* 0.17 in $CHCl_3$) for a 92% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AS-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 37.1 min (minor), t_R 2: 54.7 min (major): R_f 0.41 (EtOAc/petroleum ether, 3: 7); IR ν_{max} (KBr, cm^{-1}) 3273, 2914, 2862, 1648, 1597, 1405, 1327, 1163, 1098, 924, 813, 760, 702, 664, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, 2H, *J* = 8.0 Hz), 7.27−7.13 (m, 7H), 5.80−5.70 (m, 1H), 5.11 (dd, 1H, *J* = 15.6, 1.4 Hz), 5.06 (br s, 1H, NH), 4.94 (dd, 1H, *J* = 9.0, 2.7 Hz), 4.30 (dd, 1H, *J* = 9.3, 3.7 Hz), 3.80 (dd, 1H, *J* = 12.4, 5.4 Hz), 3.62 (dd, 1H, *J* = 12.4, 6.1 Hz), 3.18−3.11 (m, 1H), 2.96−2.89 (m, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.4, 136.9, 134.0, 129.7, 128.6, 128.4, 127.0, 126.6, 117.5, 79.6, 69.6, 49.3, 21.5; HRMS (ESI) calcd for $C_{18}H_{21}NO_3S$ $(M + H)^+$ 332.1320, found 332.1326.

*(S)-N-(2-Methoxy-2-phenylethyl)-4-methylbenzenesulfonamide (**3b**).* The general method A described above was followed when (*R*)-**1a** (25 mg, 0.091 mmol) reacted with methanol to afford **3b** as white solid (21.6 mg, 80% yield): mp 105 °C; $[\alpha]^{25}_D$ +47.5 (*c* = 0.16 in $CHCl_3$) for a >99% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min: t_R 1: 34.2 min (major): R_f 0.34 (EtOAc/petroleum ether, 3:7); IR ν_{max} (KBr, cm^{-1}) 3284, 2910, 2820, 1600, 1448, 1321, 1160, 1074, 900, 812, 761, 700, 548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 2H, *J* = 8.3 Hz), 7.34−7.17 (m, 7H), 4.94 (br m, 1H, NH), 4.17 (dd, 1H, *J* = 9.3, 3.7 Hz), 3.21−3.16 (m, 1H), 3.15 (s, 3H), 2.95−2.89 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.2, 136.8, 129.8, 129.6, 128.6, 127.0, 126.5, 82.4, 56.8, 49.3, 21.5; HRMS (ESI) calcd for $C_{16}H_{19}NO_3S$ $(M + H)^+$ 306.1163, found 306.1168.

*(S)-4-Methyl-N-(2-phenyl-2-(prop-2-ynyloxy)ethyl)-benzenesulfonamide (**3c**).* The general method A described above was followed when (*R*)-**1a** (25 mg, 0.091 mmol) reacted with propargyl alcohol to afford **3c** as a dense liquid (21.6 mg, 75% yield): $[\alpha]^{25}_D$ +15.8 (*c* 0.19 in $CHCl_3$) for an 80% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 27.71 min (minor), t_R 2: 33.56 min (major): R_f 0.38 (EtOAc/petroleum ether, 3: 7); IR ν_{max} (film, cm^{-1}) 3284, 2920, 2859, 2118, 1597, 1411, 1328, 1159, 1086, 868, 813, 701, 665, 546; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 2H, *J* = 8.3 Hz), 7.35−7.20 (m, 7H), 4.99−4.97 (m, 1H, NH), 4.55 (dd, 1H, *J* = 7.8, 3.6 Hz), 4.06 (dd, 1H, *J* = 15.8, 2.4 Hz), 3.81 (dd, 1H, *J* = 15.8, 2.5 Hz), 3.26−3.20 (m, 1H), 3.06−3.01 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 143.6, 137.3, 137.0, 129.8, 128.9, 127.2, 126.9, 79.4, 79.1, 75.1, 56.0, 49.1, 21.6; HRMS (ESI) calcd for $C_{18}H_{19}NO_3S$ $(M + H)^+$ 330.1163, found 330.1167.

*(S)-N-(2-(Benzyloxy)-2-phenylethyl)-4-methylbenzenesulfonamide (**3d**).* The general method A described above was followed when (*R*)-**1a** (25 mg, 0.091 mmol) was reacted with benzyl alcohol to afford **3d** as a dense liquid (23.7 mg, 72% yield); $[\alpha]^{25}_D$ +17.8 (*c* 0.216 in $CHCl_3$) for a 92% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 35.61 min (major), t_R 2: 41.11 min (minor): R_f 0.38 (EtOAc/petroleum ether, 3: 7); IR ν_{max} (film, cm^{-1}) 3253, 2917, 2865, 1597, 1419, 1324, 1163, 1088, 901, 850, 815, 753, 549; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, 2H, *J* = 8.3 Hz), 7.37−7.30 (m, 12H), 4.87 (br s, 1H, NH), 4.42−4.39 (m, 2H), 4.18(d, 1H, *J* = 11.4 Hz), 3.25−3.20 (m, 1H), 3.06−3.01 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 138.4, 137.5, 136.9, 129.7, 128.8, 128.5, 128.0, 127.9, 127.0, 126.8, 79.9, 70.7, 49.3, 21.5; HRMS (ESI) calcd for $C_{22}H_{23}NO_3S$ $(M + H)^+$ 382.1476, found 382.1479.

*(S)-N-(2-Isopropoxy-2-phenylethyl)-4-methylbenzenesulfonamide (**3e**).* The general method A described above was followed when (*R*)-**1a** (25 mg, 0.091 mmol) reacted with 2-propanol to afford **3e** as a white solid (22.4 mg, 77% yield): mp 98−100 °C; $[\alpha]^{25}_D$ +42.0 (*c* 0.10 in $CHCl_3$) for a 91% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AS-H column), hexane−2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 30.74 min (minor), t_R 2: 48.32 min (major): R_f 0.36 (EtOAc/petroleum ether, 1: 5); IR ν_{max} (KBr, cm^{-1}) 3447, 3275, 2972, 2922, 1399, 1328, 1168, 1091, 704, 561; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, 2H, *J* = 8.3 Hz), 7.33−7.21 (m, 7H), 4.92−4.90 (br m, 1H, NH), 4.44 (dd, 1H, *J* = 9.3, 3.8 Hz), 3.48−3.43 (m, 1H), 3.20−3.15 (m, 1H), 2.93−2.88 (m, 1H), 2.41 (s, 3H), 1.10 (d, 3H, *J* = 6.2 Hz), 1.04 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 139.6, 136.9, 129.7, 128.5, 128.2, 127.1, 126.5, 76.7, 69.3, 49.5, 23.3, 21.5, 21.0; HRMS (ESI) calcd for $C_{18}H_{23}NO_3S$ $(M + H)^+$ 334.1476, found 334.1477.

*(S)-N-(2-tert-Butoxy-2-phenylethyl)-4-methylbenzenesulfonamide (**3f**).* The general method A described above was followed when (*R*)-**1a** (25 mg, 0.091 mmol) reacted with 2-methyl-2-propanol to afford **3f** as a white solid (21.0 mg, 70% yield): mp 92−94 °C; $[\alpha]^{25}_D$ +85.7 (*c* 0.084 in $CHCl_3$) for a 88% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AS-H column), hexane−2-propanol, 95:5; flow rate =1.0 mL/min; t_R 1: 23.53 min (minor), t_R 2: 33.24 min (major): R_f 0.36 (EtOAc/petroleum ether, 1:5); IR ν_{max} (KBr, cm^{-1}) 3447, 3274, 2974, 2924, 1457, 1398, 1367, 1191, 1164, 1090, 704, 557; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 2H, *J* = 8.3 Hz), 7.30−7.22(m, 7H), 4.75 (br m, 1H, NH), 4.60 (dd, 1H, *J* = 8.9, 3.8 Hz), 3.13−3.07 (m, 1H), 2.85−2.80 (m, 1H), 2.41 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 142.4, 136.9, 129.7, 128.4, 127.6, 127.1, 126.2, 75.2, 73.3, 50.1, 28.7, 21.5; HRMS (ESI) calcd for $C_{19}H_{25}NO_3S$ $(M + H)^+$ 348.1633, found 348.1635.

*(S)-4-Methyl-N-(2-phenyl-2-(o-tolyloxy)ethyl)-benzenesulfonamide (**3g**).* The general method A described above was followed when (*R*)-**1a** (25 mg, 0.091 mmol) reacted with *o*-cresol to afford **3g** and **4g** as a regioisomeric mixture in 2.5:1 ratio. **3g**: 21.1 mg (65% yield), white solid; mp 100−102 °C; $[\alpha]^{25}_D$ +15.9 (*c* 0.119 in $CHCl_3$); IR ν_{max} (KBr, cm^{-1}) 3287, 2923, 1596, 1493, 1331, 1237, 1161, 1094, 751, 548; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, 2H, *J* = 8.3 Hz), 7.70−7.24 (m, 7H), 7.10−7.09 (m, 1H), 6.93−6.89 (m, 1H), 6.80−6.77 (m, 1H), 6.43−6.41 (m, 1H), 5.13 (dd, 1H, J = 8.9, 4.5 Hz), 4.88−4.87 (br m, 1H, NH), 3.45−3.40 (m, 1H), 3.33−3.29 (m, 1H), 2.40 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 143.7, 138.1, 137.2, 130.9, 129.9, 128.9, 128.5, 127.1, 126.8, 126.7, 126.1, 121.1, 112.8, 78.2, 49.6, 21.6, 16.6; HRMS (ESI) calcd for $C_{22}H_{23}NO_3S$ $(M + H)^+$ 382.1477, found 382.1479.

*(R)-4-Methyl-N-(1-phenyl-2-(o-tolyloxy)ethyl)-benzenesulfonamide (**4g**):* dense liquid (8.1 mg, 30% yield); $[\alpha]^{25}_D$ −2.6 (*c* 0.074 in $CHCl_3$); R_f 0.42 (EtOAc/petroleum ether, 3:7); IR ν_{max} (KBr, cm^{-1}) 3472, 3261, 2926, 1596, 1464, 1309, 1151, 1091, 706, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 2H, *J* = 8.3 Hz), 7.23−7.13 (m, 7H), 7.08−7.06 (m, 1H), 6.94−6.92 (m, 1H), 6.75−

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6.67 (m, 2H), 4.37 (t, 2H, J = 7.56), 3.53−3.45 (m, 2H), 2.37 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 143.6, 140.4, 136.8, 129.8, 129.7, 128.9, 128.2, 127.3, 126.8, 125.9, 123.9, 120.8, 46.5, 44.4, 21.6, 15.9; HRMS (ESI) calcd for $C_{22}H_{23}NO_3S$ (M + H)$^+$ 382.1477, found 382.1475.

*(S)-N-(2-Methoxy-2-phenylethyl)-4-nitrobenzenesulfonamide (**3h**).* The general method A described above was followed when (*R*)-**1b** (25 mg, 0.0822 mmol) reacted with methanol to afford **3h** as a white solid (22.7 mg, 85% yield): mp 86−88 °C; $[\alpha]^{25}_D$ +46.1 (*c* 0.24 in $CHCl_3$) for a >99% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 25.88 min (major). R_f 0.42 (EtOAc/petroleum ether, 2:3); IR ν_{max} (KBr, cm^{-1}) 3445, 3276, 2923, 2854, 1532, 1348, 1164, 1072, 704, 546; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.25 (m, 2H), 7.95−7.92 (m, 2H), 7.29−7.24 (m, 3H), 7.15−7.12 (m, 2H), 5.13 (dd, 1H, NH, J = 8.6, 2.7 Hz), 4.19 (dd, 1H, J = 9.0, 3.6 Hz), 3.28−3.21 (m, 1H), 3.12 (s, 3H), 2.97−2.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 145.8, 137.7, 128.8, 128.6, 128.2, 126.5, 124.4, 81.9, 56.8, 49.3; HRMS (ESI) calcd for $C_{15}H_{17}N_2O_5S$ (M + H)$^+$ 337.0858, found 337.0854.

*(S)-4-Methoxy-N-(2-methoxy-2-phenylethyl)benzenesulfonamide (**3i**).* The general method B described above was followed when (*R*)-**1c** (25 mg, 0.0864 mmol) reacted with methanol to afford **3i** as white solid (20.5 mg, 77% yield): mp >350 °C; $[\alpha]^{25}_D$ +18.3 (*c* 0.163 in $CHCl_3$) for a 98% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 23.3 min (minor), t_R 2: 26.6 min (major); R_f 0.46 (EtOAc/petroleum ether, 2:3); IR ν_{max} (KBr, cm^{-1}) 3284, 2926, 1597, 1498, 1330, 1260, 1156, 1092, 1026, 762, 563; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72−7.69 (m, 2H), 7.29−7.21 (m, 3H), 7.14−7.12 (m, 2H), 6.91−6.87 (m, 2H), 4.89 (dd, 1H, J = 12.0, 8.0 Hz), 4.13 (dd, 1H, J = 12.0, 4.0 Hz), 3.79 (s, 3H), 3.15−3.10 (m, 1H), 3.09 (s, 3H), 2.90−2.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 138.2, 131.4, 129.2, 128.7, 128.4, 126.6, 114.2, 81.9, 56.8, 55.6, 49.3; HRMS (ESI) calcd for $C_{16}H_{19}NO_4S$ (M + H)$^+$ 322.1113, found 322.1117.

*(S)-4-Fluoro-N-(2-methoxy-2-phenylethyl)benzenesulfonamide (**3j**).* The general method B described above was followed when (*R*)-**1d** (25 mg, 0.0902 mmol) reacted with methanol to afford **3j** as a white solid (12.5 mg, 51% yield): mp 102−104 °C; $[\alpha]^{25}_D$ +107.8 (*c* 0.213 in $CHCl_3$) for a 97% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 13.2 min (major), t_R 2: 18.8 min (minor); R_f 0.57 (EtOAc/petroleum ether, 2:3); IR ν_{max} (KBr, cm^{-1}) 3441, 3273, 2918, 1596, 1498, 1332, 1161, 1072, 867, 705, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79−7.75 (m, 2H), 7.29−7.22 (m, 3H), 7.15−7.08 (m, 4H), 4.96−4.95 (m, 1H), 4.15 (dd, 1H, J = 9.3, 3.7 Hz), 3.19−3.14 (m, 1H), 3.12 (s, 3H), 2.92−2.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 129.8, 129.7, 128.7, 128.5, 126.6, 116.4, 116.2, 81.9, 56.8, 49.3; HRMS (ESI) calcd for $C_{15}H_{16}FNO_3S$ (M − H)$^+$ 308.0756, found 308.0754.

*(S)-4-tert-Butyl-N-(2-methoxy-2-phenylethyl)-benzenesulfonamide (**3k**).* The general method B described above was followed when (*R*)-**1e** (25 mg, 0.0793 mmol) reacted with methanol to afford **3k** as a white solid (17.3 mg, 67% yield): $[\alpha]^{25}_D$ +72.4 (*c* 0.25 in $CHCl_3$) for a 95% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol, 90:10; flow rate =1.0 mL/min; t_R 1: 10.7 min (major), t_R 2: 18.0 min (minor); R_f 0.32 (EtOAc/petroleum ether, 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 2H), 7.45−7.42 (m, 2 H), 7.29−7.12 (m, 5H), 4.93 (dd, 1H, J = 8.0, 4.0 Hz), 4.14 (dd, 1H, J = 8.0, 4.0 Hz), 3.18−3.10 (m, 3H), 2.94−2.87 (m, 1H), 1.25 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4, 138.3, 136.9, 136.8, 128.7, 128.4, 126.9, 126.6, 126.1, 82.1, 56.8, 56.7, 49,3, 35.1, 31.2; HRMS (ESI) calcd for $C_{19}H_{25}NO_3S$ (M + H)$^+$ 348.1633, found 348.1661.

*(R)-N-(1-Methoxypropan-2-yl)-4-methylbenzenesulfonamide (**4l**).* The general method B described above was followed when (*R*)-**1f** (25 mg, 0.1183 mmol) reacted with methanol to afford **3l** and **4l** as a dense liquid as an inseparable mixture (17.8 mg, 66% yield): $[\alpha]^{25}_D$ −24.0 (*c* 0.075 in $CHCl_3$). Regioisomeric ratio was determined by chiral HPLC analysis (Chiralpak AS-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 28.73 min (major), t_R 2: 33.33 min (minor): R_f 0.21 (EtOAc/petroleum ether, 1:5); IR ν_{max} (KBr, cm^{-1}) 3280, 2977, 2929, 2829, 1599, 1494, 1452, 1380, 1328, 1257, 1161, 1092, 1055, 1019, 907, 846, 815, 706, 666, 553, 456; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.66 (m, 2H), 7.25−7.20 (m, 2H), 4.81 (br s, 1H), 3.32−3.30 (m, 1H), 3.17 (s, 3H), 3.03−3.00 (m, 1H), 2.70−2.65 (m, 1H), 2.36 (s, 3H), 1.03−1.00 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 136.9, 129.8, 129.7, 127.1, 75.1, 56.3, 48.1, 21.6, 16.5 (for major regioisomer); HRMS (ESI) calcd for $C_{11}H_{17}NO_3S$ (M + H)$^+$ 244.1007, found 244.1009.

*(S)-N-(1-Methoxy-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide (**4m**).* The general method B described above was followed when (*S*)-**1g** (25 mg, 0.087 mmol) was reacted with methanol to afford **3m** and **4m** as a dense liquid as an inseparable mixture (23.8 mg, 88% yield): $[\alpha]^{25}_D$ +13.3 (*c* 0.03 in $CHCl_3$). The regioisomeric ratio was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 9.10 min (major), t_R 2: 13.81 min (minor); R_f 0.29 (EtOAc/petroleum ether, 1:5); IR ν_{max} (KBr, cm^{-1}) 3283, 2925, 1599, 1453, 1329, 1159, 1091, 702, 551; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, 2H, J = 8.0 Hz), 7.25−7.17 (m, 5H), 7.03−7.02 (m, 2H), 4.78 (d, 1H, J = 7.7 Hz), 3.52−3.49 (m, 1H), 3.25−3.20 (m, 1H), 3.21 (s, 3H), 3.19−3.12 (m, 1H), 2.78−2.77 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 137.7, 137.3, 129.8, 129.7, 129.4, 128.6, 127.2, 127.1, 126.7, 72.5, 58.9, 54.6, 38.3, 21.6; HRMS (ESI) calcd for $C_{17}H_{22}NO_3S$ (M + H)$^+$ 320.1320, found 320.1321.

*(R)-N-(1-Methoxy-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (**4n**).* The general method B described above was followed when (*R*)-**1h** (25 mg, 0.1045 mmol) reacted with methanol to afford **3n** and **4n** as a dense liquid as an inseparable mixture (13.4 mg, 53% yield): $[\alpha]^{25}_D$ +46.6 (*c* 0.03 in $CHCl_3$). Regioisomeric ratio was determined by chiral HPLC analysis (Chiralpak AS-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 19.82 min (minor), t_R 2: 25.28 min (major); R_f 0.32 (EtOAc/petroleum ether, 1:5); IR ν_{max} (KBr, cm^{-1}) 3290, 2959, 2924, 1440, 1329, 1162, 1086, 680, 550; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 2H), 7.26−7.20 (m, 2H), 4.73 (br s, 1H), 3.26−3.22 (m, 1H), 3.09 (s, 3H), 2.99−2.96 (m, 1H), 2.36 (s, 3H), 1.81−1.76 (m, 1H), 0.82−0.72 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 138.2, 129.7, 129.5, 127.1, 84.3, 71.7, 58.9, 58.7, 29.7, 21.5, 18.9, 18.5; HRMS (ESI) calcd for $C_{13}H_{22}NO_3S$ (M + H)$^+$ 272.1320, found 272.1324.

*(R)-N-(1-Methoxy-4-methylpentan-2-yl)-4-methylbenzenesulfonamide (**4o**).* The general method A described above was followed when (*R*)-**1i** (25 mg, 0.0987 mmol) reacted with methanol to afford **3o** and **4o** as a dense liquid as an inseparable mixture (16.7 mg, 64% yield): $[\alpha]^{25}_D$ −11.0 (*c* 0.11 in $CHCl_3$). The regioisomeric ratio was determined by chiral HPLC analysis (Chiralpak AS-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 19.06 min (major), t_R 2: 25.90 min (minor); R_f 0.36 (EtOAc/petroleum ether, 1:5); IR ν_{max} (KBr, cm^{-1}) 3281, 2955, 2929, 1461, 1329, 1160, 1093, 814, 706, 552; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 2H), 7.26−7.20 (m, 2H), 4.82 (br s, 1H), 3.20−3.00 (m, 5H), 2.71−2.68 (m, 1H), 2.35(s, 3H), 1.53−1.46 (m, 1H), 1.38−1.31 (m, 1H), 1.29−1.20 (m, 1H), 1.09−1.02 (m, 1H), 0.81−0.75 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.4, 139.1, 138.2, 129.7, 129.5, 127.0, 74.0, 58.9, 56.6, 51.7, 45.7, 41.6, 40.4, 24.5, 24.3, 22.9, 22.8, 22.5, 21.9, 21.5; HRMS (ESI) calcd for $C_{14}H_{24}NO_3S$ (M + H)$^+$ 286.1477, found 286.1475.

*(S)-N-(1-Methoxy-3-phenylpropan-2-yl)-N,4-dimethylbenzenesulfonamide (**5**).* A hexane solution of nBuLi (0.18 mL, 0.2893 mmol, 1.6 M) was added carefully to anhydrous DMSO (0.18 mL) in a two-necked round-bottomed flask. (*S*)-*N*-(1-Methoxy-3-phenylpropan-2-yl)-4-methylbenzenesulfonamide **4m** (42 mg, 0.1315 mmol) in 2.5 mL of DMSO was added, and the resulting solution was stirred under nitrogen for 2 h. MeI (40 μL, 0.639 mmol) was then added, and the reaction mixture was stirred for 1 h. The reaction mixture was poured into H_2O and extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4, and the solvent

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was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (230−400 mesh) using 10% ethyl acetate in petroleum ether to provide 5 (31.5 mg, 75%): $[\alpha]^{25}_{D}$ −11.0 (*c* 0.11 in $CHCl_3$); IR ν_{max} (film, cm^{-1}) 2923, 2371, 1594, 1452, 1328, 1153, 939, 812, 699, 655, 548; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, 2H, *J* = 8.6 Hz), 7.26−7.17 (m, 5H), 7.13−7.12 (m, 2H), 4.33−4.30 (m, 1H), 3.33−3.32 (m, 2H), 3.20 (s, 3H), 2.89−2.85 (dd, 1H, *J* = 13.5, 8.3 Hz), 2.81 (s, 3H), 2.59 (dd, 1H, *J* = 13.4, 6.7 Hz), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.9, 138.1, 136.9, 129.5, 129.2, 128.6, 127.4, 126.6, 72.7, 58.8, 58.0, 35.4, 29.7, 21.6; HRMS (ESI) calcd for $C_{18}H_{23}NO_3S$ (M + H)$^+$ 334.1476, found 334.1474.

*N-((1R,2S)-1-Methoxy-1-phenylbutan-2-yl)-4-methylbenzenesulfonamide (**3p**).* The general method A described above was followed when **1j** (25 mg, 0.083 mmol) reacted with methanol to afford **3p** as a colorless liquid (24.3 mg, 90% yield); de of the sample was found to be >99% from ^1H NMR: R_f 0.32 (EtOAc/petroleum ether, 1:5); IR ν_{max} (film, cm^{-1}) 3290, 2923, 2852, 1452, 1329, 1159, 1093, 1027, 815, 705, 663, 571, 550; ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, 2H, *J* = 8.6 Hz), 7.31−7.23 (m, 5H), 7.09 (d, 2H, *J* = 7.3 Hz), 4.80 (d, 1H, *J* = 10.0 Hz), 4.06 (d, 1H, *J* = 3.1 Hz), 3.29−3.24 (m, 1H), 3.14 (s, 3H), 2.42 (s, 3H), 1.33−1.23 (m, 2H), 0.67 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2, 138.5, 137.9, 129.6, 128.4, 127.6, 127.1, 126.5, 84.8, 60.5, 57.7, 29.7, 21.5, 20.8, 10.4; HRMS (ESI) calcd for $C_{18}H_{24}NO_3S$ (M + H)$^+$ 334.1476, found 334.1475.

*N-((1R,2S)-1-Methoxy-1-phenylpropan-2-yl)-4-methylbenzenesulfonamide (**3q**).* The general method A described above was followed when **1k** (25 mg, 0.087 mmol) reacted with methanol to afford **3q** as a colorless liquid (22.6 mg, 84% yield); de of the sample was found to be >99% from ^1H NMR: R_f 0.36 (EtOAc/petroleum ether, 1:5); IR ν_{max} (film, cm^{-1}) 3281, 2983, 1329, 1160, 1089, 704, 667, 552; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 2H, *J* = 8.3 Hz), 7.27−7.17 (m, 5H), 7.06 (d, 2H, *J* = 7.1 Hz), 4.82 (d, 1H, *J* = 9.0 Hz), 4.06 (d, 1H, *J* = 3.2 Hz), 3.46−3.41 (m, 1H), 3.13 (s, 3H), 2.35 (s, 3H), 0.79 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 138.5, 138.0, 129.6, 128.4, 128.2, 127.8, 127.0, 126.6, 85.4, 57.5, 54.5, 29.7, 21.5, 14.6; HRMS (ESI) calcd for $C_{17}H_{21}NO_3S$ (M + H)$^+$ 320.1320, found 320.1323.

*N-((1R,2S)-1-Methoxy-1-phenylpentan-2-yl)-4-methylbenzenesulfonamide (**3r**).* The general method B described above was followed when **1l** (25 mg, 0.079 mmol) reacted with methanol to afford **3r** as a colorless liquid (17.5 mg, 68% yield); de of the sample was found to be >99% from ^1H NMR: R_f 0.38 (EtOAc/petroleum ether, 1:5); IR ν_{max} (film, cm^{-1}) 3295, 2928, 2872, 1451, 1419, 1323, 1160, 1096, 1034, 815, 706, 663, 584, 550; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, 2H, *J* = 8.4 Hz), 7.32−7.29 (m, 4H), 7.26−7.23 (m, 1H), 7.09 (d, 2H, *J* = 7.3 Hz), 4.84 (d, 1H, *J* = 9.6 Hz), 4.05 (d, 1H, *J* = 3.1 Hz), 3.38−3.34 (m, 1H), 3.12 (s, 3H), 2.42 (s, 3H), 1.39−1.23 (m, 2H), 1.16−1.13 (m, 1H), 0.95−0.87 (m, 1H), 0.65 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 138.6, 137.9, 129.6, 129.5, 128.4, 127.6, 127.1, 126.5, 84.9, 58.8, 57.7, 29.8, 21.5, 18.9, 13.5; HRMS (ESI) calcd for $C_{19}H_{25}NO_3S$ (M + H)$^+$ 348.1633, found 348.1637.

*N-((1R,2S)-1-Methoxy-1-phenylpent-4-en-2-yl)-4-methylbenzenesulfonamide (**3s**).* The general method B described above was followed when **1m** (25 mg, 0.079 mmol) reacted with methanol to afford **3s** as colorless liquid (17.3 mg, 70% yield); de of the sample was found to be 92% from ^1H NMR: R_f 0.36 (EtOAc/petroleum ether, 1:5); IR ν_{max} (film, cm^{-1}) 3286, 2921, 2851, 1598, 1494, 1452, 1419, 1329, 1185, 1160, 1114, 1093, 1049, 990, 814, 759, 705, 663, 550, 419; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, 2H, *J* = 8.3 Hz), 7.32−7.24 (m, 5H), 7.15 (d, 2H, *J* = 7.5 Hz), 5.46−5.41 (m, 1H), 4.90 (s, 1H), 4.87 (d, 1H, *J* = 7.5 Hz), 4.79 (d, 1H, *J* = 8.9 Hz), 4.20 (d, 1H, *J* = 3.7 Hz), 3.44−3.40 (m, 1H), 3.18 (s, 3H), 2.41 (s, 3H), 2.18−2.11 (m, 1H), 2.01−1.97 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 138.1, 138.0, 134.4, 129.7, 129.6, 128.6, 128.5, 127.9, 127.3, 127.2, 126.7, 126.6, 118.2, 84.7, 58.4, 57.8, 32.7, 21.6; HRMS (ESI) calcd for $C_{19}H_{23}NO_3S$ (M + H)$^+$ 346.1474, found 346.1476.

*(R)-N-(3-Methoxy-3-phenylpropyl)-4-methylbenzenesulfonamide (**6a**).* The general method C described above was followed when (*S*)-**2a** (25 mg, 0.087 mmol) reacted with MeOH in the presence of 30 mol % of $Cu(OTf)_2$ and 1.0 equiv of TBAHS at 0 °C for 7 h to afford **6a** as a white solid (22.0 mg, 82% yield): mp 108 −110 °C; $[\alpha]^{25}_{D}$ +44.5 (*c* 0.20 in $CHCl_3$) for a 94% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 35.5 min (major), t_R 2: 43.7 min (minor): R_f 0.28 (EtOAc/petroleum ether, 3: 7); IR ν_{max} (KBr, cm^{-1}) 3300, 3267, 2923, 1416, 1321, 1162, 1086, 814, 763, 701, 666, 547; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, 2H, *J* = 8.3 Hz), 7.25−7.17 (m, 5H), 7.08−7.06 (m, 2H), 5.15 (br s, 1H, NH), 4.12 (dd, 1H, *J* = 7.6, 5.1 Hz), 3.08 (s, 3H), 3.06−3.02 (m, 1H), 2.97−2.92 (m, 1H), 2.37 (s, 3H), 1.77−1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 140.8, 136.9, 129.7, 128.5, 127.8, 127.1, 126.3, 83.1, 56.7, 41.0, 36.9, 21.5; HRMS (ESI) calcd for $C_{17}H_{21}NO_3S$ (M + H)$^+$ 320.1320, found 320.1328.

*(R)-N-(3-(Allyloxy)-3-phenylpropyl)-4-methylbenzenesulfonamide (**6b**).* The general method C described above was followed when (*S*)-**2a** (25 mg, 0.087 mmol) reacted with allyl alcohol to afford **6b** as a dense liquid (21.5 mg, 75% yield): $[\alpha]^{25}_{D}$ +45.6 (*c* 0.16 in $CHCl_3$) for an 84% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AS-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 30.94 min (major), t_R 2: 35.80 min (minor): R_f 0.38 (EtOAc/petroleum ether, 3: 7); IR ν_{max} (film, cm^{-1}) 3286, 2924, 2859, 1598, 1418, 1326, 1158, 1092, 813, 702, 664; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 2H, *J* = 8.3 Hz), 7.25−7.18 (m, 5H), 7.08 (d, 2H, *J* = 7.8 Hz), 5.78−5.70 (m, 1H), 5.18 (t, 1H, *J* = 4.9 Hz), 5.14−5.08 (m, 2H), 4.30 (q, 1H, *J* = 8.0, 4.4 Hz), 3.79 (dd, 1H, *J* = 12.4, 4.9 Hz), 3.59 (dd, 1H, *J* = 12.7, 6.1 Hz), 3.08−3.02 (m, 1H), 2.98−2.92 (m, 1H), 2.37 (s, 3H), 1.82−1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 141.0, 136.9, 134.3, 129.6, 128.5, 127.8, 127.1, 126.3, 117.3, 80.4, 69.5, 41.0, 36.9, 21.5; HRMS (ESI) calcd for $C_{19}H_{23}NO_3S$ (M + H)$^+$ 346.1476, found 346.1475.

*(R)-4-Methyl-N-(3-phenyl-3-(prop-2-ynyloxy)propyl)-benzenesulfonamide (**6c**).* The general method C described above was followed when (*S*)-**2a** (25 mg, 0.087 mmol) reacted with propargyl alcohol to afford **6c** as a dense liquid (22.9 mg, 80% yield); $[\alpha]^{25}_{D}$ +77.8 (*c* 0.14 in $CHCl_3$) for a 86% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column) 90:10 hexane−2-propanol, flow rate = 1.0 mL/min; t_R 1: 20.28 min (major), t_R 2: 27.96 min (minor): R_f 0.28 (EtOAc/petroleum ether, 3: 7); IR ν_{max} (film, cm^{-1}) 3286, 2923, 2856, 2117, 1598, 1325, 1159, 1091, 813,702, 634; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, 2H, *J* = 8.0 Hz), 7.26−7.19 (m, 5H), 7.10 (dd, 1H, *J* = 7.3, 1.2 Hz), 5.03 (t, 1H, *J* = 5.9 Hz), 4.48 (q, 1H, *J* = 4.4 Hz), 4.02 (dd, 1H, *J* = 15.9, 2.4 Hz), 3.70 (dd, 1H, *J* = 15.9, 2.2 Hz), 3.11−3.06 (m, 1H), 3.05−2.96 (m, 1H), 2.37 (s, 3H), 2.36−2.35 (m, 1H), 1.83−1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 139.9, 136.9, 129.6, 128.6, 128.2, 127.1, 126.5, 79.6, 79.1, 74.7, 55.5, 40.7, 36.8. 21.5; HRMS (ESI) calcd for $C_{19}H_{21}NO_3S$ (M + H)$^+$ 344.1320, found 344.1320.

*(R)-N-(3-(Benzyloxy)-3-phenylpropyl)-4-methylbenzenesulfonamide (**6d**).* The general method C described above was followed when (*S*)-**2a** (25 mg, 0.087 mmol) reacted with benzyl alcohol to afford **6d** as a dense liquid (21.9 mg, 68% yield): $[\alpha]^{25}_{D}$ +60.9 (*c* 0.141 in $CHCl_3$) for a 82% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralpak AD-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 16.36 min (minor), t_R 2: 18.92 min (major): R_f 0.34 (EtOAc/petroleum ether, 3: 7); IR ν_{max} (film, cm^{-1}) 3284, 2924, 2863, 1597, 1450, 1416, 1326, 1158, 1092, 814, 742, 700, 664; ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, 2H, *J* = 8.3 Hz), 7.36−7.18 (m, 12H), 5.05 (br s, 1H, NH), 4.42 (d, 1H, *J* = 11.6 Hz), 4.37 (dd, 1H, *J* = 8.6, 4.0 Hz), 4.15 (d, 1H, *J* = 11.6 Hz), 3.15−3.09 (m, 1H), 3.02−2.98 (m, 1H), 2.44 (s, 3H), 1.88−1.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 141.0, 137.8, 137.0, 129.6, 128.6, 128.5, 128.0, 127.9, 127.1, 126.4, 79.8, 70.4, 40.8, 37.1, 21.5; HRMS (ESI) calcd for $C_{23}H_{25}NO_3S$ (M + H)$^+$ 396.1633, found 396.1631.

*(R)-N-(3-Isopropoxy-3-phenylpropyl)-4-methylbenzenesulfonamide (**6e**).* The general method C described above was followed when (*S*)-**2a** (25 mg, 0.087 mmol) reacted with isopropyl alcohol to afford **6e** as a dense liquid (22.3 mg, 77% yield): $[\alpha]^{25}_{D}$ +46.5 (*c* 0.18 in $CHCl_3$) for a 88% ee sample. Optical purity was determined by chiral

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HPLC analysis (Chiralcel OD-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; t_R 1: 17.9 min (major), t_R 2: 28.3 min (minor): R_f 0.28 (EtOAc/petroleum ether, 3: 7); IR ν_{max} (film, cm^{-1}) 3284, 2970, 1598, 1327, 1161, 1093, 814, 703, 551; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76−7.74 (m, 2H), 7.32−7.11 (m, 7H), 5.38−5.36 (m, 1H), 4.43 (t, 1H, J = 12.35, 6.2 Hz), 3.43−3.38 (m, 1H), 3.11−3.06 (m, 1H), 3.02−2.95 (m, 1H), 2.44 (s, 3H), 1.79−1.59 (m, 2H), 1.07−0.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 142.0, 137.0, 129.6, 128.4, 127.6, 127.2, 126.2, 78.4, 69.1, 41.2, 36.9, 23.4, 21.5, 21.0. HRMS (ESI) calcd for $C_{19}H_{25}NO_3S$ (M + H)$^+$ 348.1633, found 348.1632.

*(R)-4-Methyl-N-(3-phenyl-3-(o-tolyloxy)propyl)-benzenesulfonamide (**6f**).* The general method C described above was followed when (*S*)-**2a** (25 mg, 0.087 mmol) reacted with *o*-cresol to afford a mixture of regioisomers **6f** and **7f** (2:1 ratio) as a dense liquid (22.6 mg, 70% combined yield); regioisomer **6f**: $[\alpha]^{25}_D$ +48.5 (*c* 0.20 in $CHCl_3$) for a 46% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−2-propanol, 85:15; flow rate = 1.0 mL/min; t_R 1: 13.4 min (major), t_R 2: 18.0 min (minor): R_f 0.34 (EtOAc/petroleum ether, 3: 7); IR ν_{max} (Neat, cm^{-1}) 3493, 3288, 2924, 2871, 1653, 1490, 1322, 1155, 1092, 814, 739, 700, 662; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, 2H, J = 8.3 Hz), 7.19−7.08 (m, 8H), 6.90−6.83 (m, 2H), 6.70 (t, 1H, J = 7.6 Hz), 4.65 (br s, 1H, NH), 4.26 (t, 1H, J = 7.8 Hz), 2.96−2.91 (m, 1H), 2.79−2.76 (m, 1H), 2.33 (s, 3H), 2.13 (s, 3H), 2.12−2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 143.4, 143.1, 136.8, 129.7, 129.0. 128.6, 128.0, 127.1, 126.5, 125.9, 123.6, 120.7, 41.5, 40.5, 34.5, 21.5, 16.0; HRMS (ESI) calcd for $C_{23}H_{25}NO_3S$ (M + H)$^+$ 396.1633, found 396.1634.

*3-(o-Tolyloxy)-1-phenyl-N-tosylpropan-1-amine (regiosomer **7f**).* $[\alpha]^{25}_D$ −35.6 (*c* 0.10 in $CHCl_3$) for a 51% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−2-propanol, 85:15; flow rate =1.0 mL/min; t_R 1: 34.1 min (major), t_R 2: 49.2 min (minor): R_f 0.22 (EtOAc/petroleum ether, 3: 7); IR ν_{max} (Film, cm^{-1}) 3445, 3291, 2925, 1599, 1506, 1320, 1155, 1092, 814, 735, 701, 663; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 2H, J = 8.3 Hz), 7.20−7.03 (m, 8H), 6.80−6.75 (m, 2H), 6.58 (d, 1H, J = 8.1 Hz), 4.28 (br s, 1H), 3.75 (t, 1H, J = 8.0 Hz), 2.83 (t, 2H, J = 6.1 Hz), 2.35 (s, 3H), 2.13−2.06 (m, 2H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 144.1, 143.4, 136.7, 135.7, 130.3, 129.7, 128.6, 127.5, 127.1, 126.3, 126.1, 123.8, 114.9, 47.4, 41.7, 35.5, 21.5, 15.9; HRMS (ESI) calcd for $C_{23}H_{25}NO_3S$ (M + H)$^+$ 396.1633, found 396.1634.

*N-((1R,3R)-1-Methoxy-1-phenylpentan-3-yl)-4-methylbenzenesulfonamide (**6g**).* The general method D described above was followed when **2b** (25 mg, 0.079 mmol) reacted with methanol to afford **6g** as a dense colorless liquid (22.9 mg, 86% yield): R_f 0.39 (EtOAc/petroleum ether, 1:4); IR ν_{max} (film, cm^{-1}) 3282, 3029, 2926, 1734, 1599, 1494, 1453, 1418, 1160, 1094, 1044, 963, 843, 815, 759, 702, 665. 551; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 1H, J = 8.0 Hz), 7.32−7.25 (m, 5H), 7.11 (d, 2H, J = 6.8 Hz), 5.37 (br d, 1H, NH), 4.27 (dd, 1H, J = 10.2, 2.7 Hz), 3.38−3.34 (m, 1H), 3.11 (s, 3H), 2.43 (s, 3H), 1.67−1.43 (m, 4H), 0.85 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 141.5, 138.6, 129.5, 128.5, 127.7, 127.2, 126.3, 80.6, 56.4, 53.3 41.7, 27.7, 21.5, 10.1; HRMS (ESI) calcd for $C_{19}H_{25}NO_3S$ (M + H)$^+$ 348.1633, found 348.1638.

*N-((1R,3S)-1-Methoxy-1-phenylpentan-3-yl)-4-methylbenzenesulfonamide (**6h**).* The general method D described above was followed when **2c** (25 mg, 0.079 mmol) reacted with methanol to afford **6h** as a dense colorless liquid (21.2 mg, 80% yield): R_f 0.32 (EtOAc/petroleum ether, 1:4); IR ν_{max} (film, cm^{-1}) 3279, 3030, 2929, 2823, 1599, 1494, 1454, 1326, 1161, 1093, 1042, 1006, 912, 815, 759, 703, 665, 551; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, 2H, J = 8.3 Hz), 7.31−7.23 (m, 5H), 7.10 (d, 2H, J = 6.9 Hz), 5.37 (d, 1H, NH, J = 8.9 Hz), 4.27 (dd, 1H, J = 10.6, 2.9 Hz), 3.37−3.35 (m, 1H), 3.11 (s, 3H), 2.42 (s, 3H), 1.65−1.60 (m, 2H). 1.53−1.44 (m, 2H), 0.75 (t, 3H, J = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 141.3, 138.1, 129.6, 129.5, 128.5, 127.9, 127.2, 126.5, 82.6, 82.5, 56.3, 56.2, 41.7, 28.0, 21.5, 8.9; HRMS (ESI) calcd for $C_{19}H_{25}NO_3S$ (M + H)$^+$ 348.1633, found 348.1631.

*N-((1R,3R)-1-Methoxy-1-phenylhex-5-en-3-yl)-4-methylbenzenesulfonamide (**6i**).* The general method D described above was followed when **2d** (25 mg, 0.0695 mmol) reacted with methanol to afford **6i** as a dense colorless liquid (25.6 mg, 95% yield): R_f 0.36 (EtOAc/petroleum ether, 1: 4); IR ν_{max} (film, cm^{-1}) 3277, 3064, 2924, 1641, 1599, 1494, 1453, 1325, 1160, 1093, 1039, 996, 916, 815, 760, 703, 665, 551; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, 1H, J = 8.0 Hz), 7.32−7.12 (m, 7H), 5.62−5.54 (m, 1H), 5.37 (d, 1H, NH), 4.99 (d, 1H, J = 10.1 Hz), 4.93 (d, 1H, J = 17.2 Hz), 4.00 (dd, 1H, J = 8.9, 3.8 Hz), 3.39−3.35 (m, 1H), 3.05 (s, 3H), 2.44 (s, 3H), 2.29−2.16 (m, 2H), 1.86−1.80 (m, 1H), 1.68−1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 141.2, 137.9, 133.3, 129.7, 128.7, 128.1, 127.4, 126.6, 118.9, 82.5, 56.4, 52.7, 41.9, 39.7, 21.6; HRMS (ESI) calcd for $C_{20}H_{25}NO_3S$ 360.1633, found (M + H)$^+$ 360.1636.

*N-((1R,3S)-1-Methoxy-1-phenylhex-5-en-3-yl)-4-methylbenzenesulfonamide (**6j**).* The general method D described above was followed when **2e** (25 mg, 0.0695 mmol) reacted with methanol to afford **6j** as a dense colorless liquid (24.0 mg, 90% yield); R_f 0.43 (EtOAc/petroleum ether, 1:4); IR ν_{max} (film, cm^{-1}) 3280, 3064, 2923, 2852, 1736, 1641, 1599, 1494, 1453, 1418, 1327, 1261, 1159, 1093, 1037, 918, 842, 814, 760, 702, 664, 629, 586, 551; ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, 1H, J = 6.9 Hz), 7.32−7.23 (m, 5H), 7.13 (d, 1H, J = 17.3 Hz), 4.29 (dd, 1H, J = 10.3, 3.7 Hz), 3.59−3.56 (m, 1H), 3.12 (s, 3H), 2.42 (s, 3H), 2.28−2.23 (m, 1H), 2.15−2.06 (m, 1H), 1.70−1.65 (m, 1H), 1.52−1.49 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.1, 141.5, 138.3, 133.4, 129.7, 129.6, 128.5, 127.7, 127.2, 126.3, 118.7, 80.2, 56.4, 50.9, 42.3, 39.3, 21.5; HRMS (ESI) calcd for $C_{20}H_{25}NO_3S$ (M + H)$^+$ 360.1633, found 360.1634.

*(S)-2-Phenyl-4-tosylmorpholine (**7a**).* The general method E described above was followed when **1a** reacted with KOH at room temperature for 30 min in dry THF to afford **7a** as a white solid (62% yield), mp 102−104 °C. Optical rotation: $[\alpha]^{25}_D$ +160.8 (*c* 0.049, $CHCl_3$) for a 82% ee sample. Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−2-propanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 18.15 min (major), t_R 2: 36.14 min (minor): R_f 0.37 (ethyl acetate/hexane, 1:4); IR ν_{max} (film, cm^{-1}) 2963, 2924, 2855, 1448, 1342, 1306, 1167, 1109, 964, 814, 745, 588; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, 2H, J = 8.3 Hz), 7.29−7.21 (m, 7H), 4.53 (dd, 1H, J = 10.5, 2.7 Hz), 4.00 (dd, 1H, J = 11.7, 2.2 Hz), 3.78 (ddd, 1H, J = 14.2, 11.4, 2.4 Hz), 3.71−3.67 (m, 1H), 3.58−3.55 (m, 1H), 2.43 (ddd, 1H, J = 14.9, 11.5, 3.4), 2.36 (s, 3H), 2.20−2.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 138.7, 132.3, 129.8, 128.5, 128.3, 127.9, 127.8, 126.0, 77.4, 66.2, 51.9, 45.4, 21.5; HRMS (ESI) calcd for $C_{17}H_{19}NO_3S$ (M + H)$^+$ 318.1165, found 318.1165.

*(S)-4-(4-Methoxyphenylsulfonyl)-2-phenylmorpholine (**7b**).* The general method E described above was followed when **1c** reacted with KOH in THF at rt for 1 h to afford **7b** as a white solid (58% yield); mp 95−97 °C; optical rotation $[\alpha]^{25}_D$ +41.7 (*c* 0.15, $CHCl_3$) for a 84% ee sample; enantiomeric purity was determined by chiral HPLC analysis (Chiralpak AS-H column), hexane−2-propanol, 95:5, flow rate = 1.0 mL/min; t_R 1: 36.46 min (minor), t_R 2: 42.77 min (major): R_f 0.41 (ethyl acetate/hexane, 3: 7); IR ν_{max} (KBr, cm^{-1}) 2921, 1594, 1498, 1351, 1258, 1165, 1094, 957, 804, 699, 564; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, 2H, J = 8.8 Hz), 7.29−7.21 (m, 5H), 6.93 (d, 1H, J = 9.0 Hz), 4.53 (dd, 1H, J = 10.3, 2.4 Hz), 4.03−3.99 (m, 1H), 3.80 (s, 3H), 3.78 (ddd, 1H, J = 11.7, 8.3, 2.7 Hz), 3.70−3.66 (m, 1H), 3.57−3.54 (m, 1H), 2.43 (ddd, 1H, J = 11.5, 11.5, 3.4 Hz), 2.16, (dd, 1H, J = 10.4, 10.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 138.8, 129.9, 128.5, 128.2, 126.0, 114.4, 77.4, 66.2, 55.6, 51.9, 45.4; HRMS (ESI) calcd for $C_{17}H_{19}NO_4S$ (M + H)$^+$ 334.1113, found 334.1113.

*(S)-4-(4-Fluorophenylsulfonyl)-2-phenylmorpholine (**7c**).* The general method E described above was followed when **1d** reacted with KOH in THF at rt for 20 min to afford **7c** as a white solid (56% yield): mp 98−101 °C; optical rotation: $[\alpha]^{25}_D$ +144.6 (*c* 0.057, $CHCl_3$) for a 86% ee sample. Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−2-propanol, 95:5; flow rate =1.0 mL/min; t_R 1: 18.31 min (major), t_R 2: 34.54 min (minor): R_f 0.45 (ethyl acetate/hexane, 3:7); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.67 (m, 2H), 7.30−7.12 (m, 7H), 4.53 (d, 1H, J = 10

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Hz), 4.02 (dd, 1H, J = 11.7, 3.2 Hz), 3.80 (ddd, 1H, J = 11.5, 11.5, 2.4 Hz), 3.71−3.68 (m, 1H), 3.59−3.56 (m, 1H), 2.44 (ddd, 1H, J = 11.5, 11.5, 3.4 Hz), 2.20−2.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 130.5, 130.4, 128.6, 128.4, 126.0, 116.6, 116.4, 66.2, 51.9, 45.4; HRMS (ESI) calcd for $C_{16}H_{16}FNO_3S$ $(M + H)^+$ 322.0913, found 322.0916.

*(R)-2-Phenyl-5-tosyl-1,5-oxazocane (**8**).* General procedure F for one-pot synthesis of morpholine homologues was followed when (*S*)-**2a** was reacted with bromopropanol at 0 °C for 30 min followed by cyclization with excess KOH in dry THF at rt for 28 h to afford **8** as a dense liquid (50% yield); optical rotation $[\alpha]^{25}_D$ +82.8 (*c* 0.16, $CHCl_3$) for a 78% ee sample. Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−2-propanol, 95:5, flow rate = 1.0 mL/min; t_R 1: 13.17 min (major), t_R 2: 15.06 min (minor): R_f 0.30 (ethyl acetate/hexane, 1: 4); IR ν_{max} (neat, cm^{-1}) 2922, 2854, 1335, 1156, 1104, 713, 697, 549; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 2H, J = 8.0 Hz), 7.27−7.18 (m, 7H), 4.66 (dd, 1H, J = 10.0, 4.2 Hz), 3.82−3.78 (m, 1H), 3.72−3.62 (m, 2H), 3.52−3.48 (m, 1H), 3.17−3.11 (m, 1H), 2.99−2.93 (m, 1H), 2.36 (s, 3H), 2.23−2.14 (m, 2H), 1.84−1.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 129.7, 128.3, 126.9, 125.7, 66.5, 49.0. 47.6, 37.4, 30.4, 21.5; HRMS (ESI) calcd for $C_{19}H_{23}NO_3S$ $(M + Na)^+$ 368.1296, found 368.1292.

■ ASSOCIATED CONTENT

Supporting Information

Details of the racemization studies, copies of ^{1}H and ^{13}C NMR spectra of the compounds, and HPLC chromatograms for ee determination. This material is available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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