JOC Article
pubs.acs.org/joc

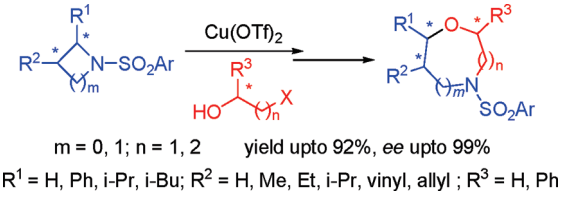
Enantioselective Syntheses of Morpholines and Their Homologues via S_N2-Type Ring Opening of Aziridines and Azetidines with Haloalcohols

Manas K. Ghorai,* Dipti Shukla, and Kalpataru Das

Department of Chemistry, Indian Institute of Technology, Kanpur 208016, India

mkghorai@iitk.ac.in

Received June 17, 2009



A highly regio- and stereoselective strategy for the syntheses in high yield and enantioselectivity of a variety of substituted nonracemic morpholines and their homologues is described. The reaction proceeds via an S_N2-type ring opening of activated aziridines and azetidines by suitable halogenated alcohols in the presence of Lewis acid followed by base-mediated intramolecular ring closure of the resulting haloalkoxy amine.

Introduction

Morpholines are an important class of heterocyclic compounds found in many naturally occurring or synthetically important organic molecules that exhibit interesting biological and pharmacological properties.[1] Particularly, *N*- and/or 2-substituted morpholines are drug candidates with a wide spectrum of biological activities (Figure 1). Morpholine such as reboxetine is an antidepressant drug,[2] and *cis*-2,3-disubstituted morpholine such as aprepitant (hNK1 antagonist) is used for chemotherapy-induced nausea and vomiting (CINV) and commercially available under the name of Emend.[3]

Furthermore, 2,6-disubstituted morpholines are used as antitumor agents,[4a] mild diuretics, and anorectics.[4b] The core structure of 1,4-oxazepanes is found in important natural products, such as neurotoxin batrachotoxin (BTX)[5] (Figure 1), and there are only a few reports for their synthesis.[6,16b] The synthesis and biological activities of 1,5-oxazocanes are also not well explored.[7] Apart from pharmacological utility, morpholines are also used frequently as simple bases, *N*-alkylating agents, catalysts, and chiral auxiliaries in various organic transformations.[8−10] Several efforts have been devoted toward the synthesis of morpholines from amino acids,[11] amino alcohols,[12] epoxides,[13] olefins,[14] carbohydrates,[15] vinyl sulfonium salts,[16] various other metal-catalyzed cyclizations,[17] and aziridines[18] or aziridinium ion intermediate.[19] However, a general synthetic approach to 2-substituted morpholines, 2,3-disubstituted morpholines,

*To whom correspondence should be addressed. Tel: +91-512-2597518; Fax: +91-512-2597436.

(1) Wijtmans, R.; Vink, M. K. S.; Schoemaker, H. E.; van Delft, F. L.; Blaauw, R. H.; Rutjes, F. P. J. T. *Synthesis* **2004**, 641-662 and references therein.

(2) (a) Hajos, M.; Fleishaker, J. C.; Filipiak-Reisner, J. K.; Brown, M. T.; Wong, E. H. F. *CNS Drug Rev*. **2004**, *10*, 23–44. (b) Versiani, M.; Cassano, G.; Perugi, G.; Benedetti, A.; Mastalli, L.; Nardi, A.; Savino, M. *J. Clin. Psychiatry* **2002**, *63*, 31. (c) Wong, E. H. F.; Sonders, M. S.; Amara, S. G.; Tinholt, P. M.; Piercey, M. F. P.; Hoffmann, W. P.; Hyslop, D. K.; Franklin, S.; Porsolt, R. D.; Bonsignori, A.; Carfagna, N.; McArthur, R. A. *Biol. Psychiatry* **2000**, *47*, 818.

(3) Pendergrass, K.; Hargreaves, R.; Petty, K. J.; Carides, A. D.; Evans, J. K.; Horgan, K. J. *Drugs Today* **2004**, *40*, 853.

(4) (a) Hikichi, M.; Yokokura, T.; Furuta, T.; Yaegashi, T. JP 62135472; *Chem. Abstr*. **1987**, *107*, 198358 (b) GB 831933; *Chem. Abstr*. **1961**, *55*, 2697.

(5) (a) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett*. **1994**, *45*, 8333–8336. (b) Grinsteiner, T. J.; Kishi, Y. *Tetrahedron Lett*. **1994**, *45*, 8337–8340.

(6) Clark, S. M.; Osborn, H. M. I. *Tetrahedron: Asymmetry* **2004**, *15*, 3643–3652.

(7) Glinka, R.; Kotelko, B. *Acta Pol. Pharm*. **1976**, *33*, 39–48.

(8) As catalyst (a) Mayer, S.; List, B. *Angew. Chem., Int. Ed*. **2006**, *45*, 4193–4195. (b) Quin, Y.-C.; Pu, L. *Angew. Chem., Int. Ed*. **2006**, *45*, 273–277. (c) Nelson, S. G.; Wang, K. *J. Am. Chem. Soc*. **2006**, *128*, 4232–4233. (d) Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett*. **2006**, *8*, 2559–2562. (e) Betancort, J. M.; Barbas, C. F. III *Org. Lett*. **2001**, *3*, 3737–3740.

(9) As auxiliary: (a) Ammazzalorso, A.; Amoroso, R.; Bettoni, G.; De Filippis, B.; Fantacuzzi, M.; Giampietro, L.; Maccallini, C.; Tricca, M. L. *Eur. J. Org. Chem*. **2006**, *71*, 4088–4091. (b) Jung, M. E.; Vaccaro, W. D.; Buszek, K. R. *Tetrahedron Lett*. **1989**, *30*, 1893–1896.

(10) C_2-symmetric chiral auxiliaries: (a) Enders, D.; Meyer, O.; Raabe, G.; Runsink, J. *Synthesis* **1994**, 66–72. (b) Takahata, H.; Takahashi, S.; Kouno, S.-I.; Momose, T. *J. Org. Chem*. **1998**, *63*, 2224–2227.

(11) (a) Dave, R.; Sasaki, N. A. *Org. Lett*. **2004**, *6*, 15–18. (b) Dave, R.; Sasaki, N. A. *Tetrahedron: Asymmetry* **2006**, *17*, 388–401. (c) Sladojevich, F.; Trabocchi, A.; Guarna, A. *J. Org. Chem*. **2007**, *72*, 4254–4257. (d) Bettoni, G.; Frachini, C.; Perrone, P.; Tortorella, V. *Tetrahedron* **1978**, *36*, 409–415.

DOI: 10.1021/jo901297d Published on Web 08/12/2009

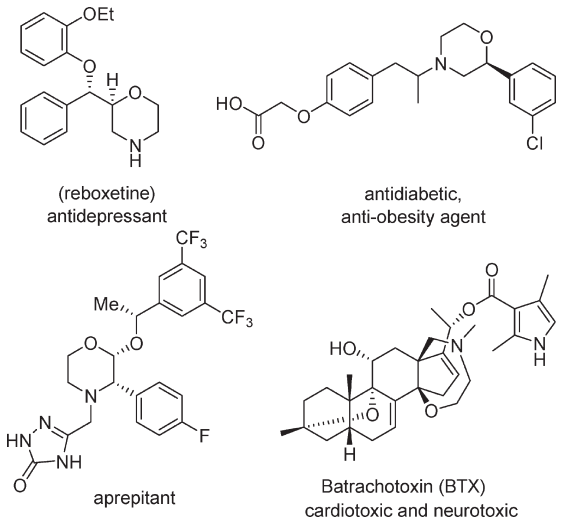


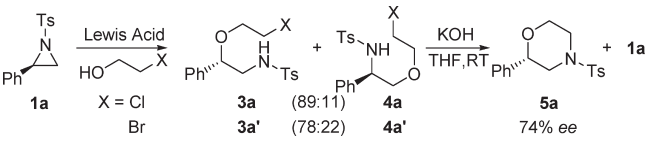
FIGURE 1. Pharmaceutically active compounds possessing a 2-substituted morpholine unit.

homomorpholines, and higher homologues is scarce in the literature.

We anticipated that 2-substituted nonracemic morpholines and homologues could easily be made from the ring opening of aziridines and azetidines by haloalcohols followed by cyclization.

Recently we have reported the Lewis acid (LA) mediated ring opening of enantiopure 2-aryl-*N*-tosylaziridines and azetidines by a number of nucleophiles such as alcohols, halides, nitriles, and carbonyls to provide nonracemic products in high enantiomeric excess.[20] We have demonstrated that the Lewis acid mediated nucleophilic ring opening of 2-aryl-*N*-tosylaziridines or azetidines does proceed through

SCHEME 1. Lewis Acid Mediated Ring Opening of (*R*)-2-Phenyl-*N*-tosylaziridines with Haloalcohols Followed by Cyclization to Morpholine



an S_N2-type pathway instead of stable 1,3- or 1,4-dipolar intermediates as invoked earlier.[21]

In continuation of our research activities in this area for designing enantioselective ring opening reactions of chiral aziridines and azetidines toward enantiopure targets, we have developed a simple strategy for the synthesis of nonracemic 2-substituted morpholines, 2,3-disubstituted morpholines, enantiopure 2,6-disubstituted morpholines, homomorpholines, and higher homologues via the ring opening of aziridines and azetidines with haloalcohols followed by intramolecular ring closure in the presence of a base. Herein, we report our results in detail.

Results and Discussion

Our investigation began with the ring opening of chiral (*R*)-2-phenyl-*N*-tosylaziridine **1a** (ee > 99%) with chloroethanol in the presence of stoichiometric amount of $Cu(OTf)_2$ at 0 °C, and we observed the formation of nonracemic chloroethoxy amine (*S*)-**3a**[22] and its regioisomer (*R*)-**4a** as an inseparable mixture. The same reaction when performed with bromoethanol produced the corresponding bromoethoxy amine **3a′** and its regioisomer **4a′** as an inseparable mixture.[23] When the mixture of **3a** and **4a** was treated with KOH at room temperature in THF, nonracemic morpholine **5a** was obtained in 70% yield (74% ee) along with aziridine **1a** (10% yield, 33% ee) (Scheme 1). A similar result was observed from the mixture of **3a′** and **4a′**. Comparing the ^{1}H NMR and COSY spectra of the mixture of **3a** and **4a** with that of pure **1a**, we could conclude that there was no trace of unreacted aziridine in the mixture of **3a** and **4a**. However, when this reaction mixture was treated with KOH, the ^{1}H NMR of the crude product indicates the presence of morpholine **5a** along with aziridine **1a**. To confirm that the reformed aziridine **1a** originates from **4a**, we treated **3a** with KOH, and the crude reaction mixture clearly indicated the presence of only **5a** in the sample.

Screening of Lewis Acid. To optimize the reaction condition to obtain better regioselectivity and yield, other Lewis acids such as $Zn(OTf)_2$, $ZnBr_2$, $BF_3 \cdot OEt_2$, and $Ti(O^iPr)_4$ were screened in chloroethanol as the solvent. However, there was not much improvement in regioselectivity of the ring opening and yield of the final product **5a** (Table 1). Interestingly, with a catalytic amount of $Cu(OTf)_2$ (20 mol %) and chloroethanol as the nucleophile, the reaction was found to be highly regioselective and **3a** (yield 87%, ee 78%) was produced as the only product; the other regioisomer **4a** did not form as indicated by the ^{1}H NMR of the crude reaction

(12) (a) Breuning, M.; Winnacker, M.; Steiner, M. *Eur. J. Org. Chem.* **2007**, *72*, 2100–2106. (b) Lanman, B. A.; Myers, A. G. *Org. Lett.* **2004**, *6*, 1045–1047. (c) Métro, T.-X.; Gomez Pardo, D.; Cossy, J. *J. Org. Chem.* **2008**, *73*, 707–710. (d) Brenner, E.; Baldwin, R. M.; Tamagnan, G. *Org. Lett.* **2005**, *7*, 937–940. (e) Cupples, C. A.; Morton, H. N. *PCT Int. Appl. WO 9638465*, **1996**.

(13) (a) Albanese, D.; Salsa, M.; Landini, D.; Lupi, V.; Penso, M. *Eur. J. Org. Chem.* **2007**, 2107–2113. (b) Abdel-Jalil, R. J.; Ali Shah, S. T.; Khan, K. M.; Voelter, W. *Lett. Org. Chem.* **2005**, *2*, 306. (c) Henegar, K. E. *J. Org. Chem.* **2008**, *73*, 3662–3665. (d) Lupi, V.; Albanese, D.; Landini, D.; Scaletti, D.; Penso, M. *Tetrahedron* **2004**, *60*, 11709–11718.

(14) (a) Siddiqui, S. A.; Narkhede, U. C.; Lahoti, R. J.; Srinivasan, K. V. *Synlett* **2006**, *11*, 1771–1773. (b) Nishi, T.; Ishibashi, K.; Nakajima, K.; Iio, Y.; Fukuzawa, T. *Tetrahedron: Asymmetry* **1998**, *9*, 3251–3262. (c) Takemoto, T.; Iio, Y.; Nishi, T. *Tetrahedron Lett.* **2000**, *41*, 1785–1788. (d) D'Arrigo, P.; Lattanzio, M.; Pedrocchi, G.; Servi, S. *Tetrahedron: Asymmetry* **1998**, *9*, 4021–4026. (e) Wilkinson, M. C. *Tetrahedron Lett.* **2005**, *46*, 4773–4775.

(15) (a) Grotenberg, G. M.; Christina, A. E.; Buizert, A. E. M.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M. *J. Org. Chem.* **2004**, *69*, 8331–8339. (b) Du, M.; Hindsgaul, O. *Synlett* **1997**, 395.

(16) (a) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3784–3786. (b) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 257–260.

(17) (a) Pedrosa, R.; Andres, C.; Mendiguchia, P.; Nieto, J. *J. Org. Chem.* **2006**, *71*, 8854–8863. (b) Yamazaki, A.; Achiwa, K. *Tetrahedron: Asymmetry* **1995**, *5*, 1021–1024.

(18) (a) Kogami, Y.; Okawa, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2963–2965. (b) Wang, L.; Liu, Q.-B.; Wang, D.-S.; Li, X.; Han, X.-W.; Xiao, W.-J.; Zhou, Y.-G. *Org. Lett.* **2009**, *11*, 1119–1122.

(19) D'hooghe, M.; Vanlangendonck, T.; Törnroos, K. W.; De Kimpe, N. *J. Org. Chem.* **2006**, *71*, 4678–4681.

(20) (a) Ghorai, M. K.; Das, K.; Shukla, D. *J. Org. Chem.* **2007**, *72*, 5859–5862. (b) Ghorai, M. K.; Kumar, A.; Das, K. *Org. Lett.* **2007**, *9*, 5441–5444. (c) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 4373–4377. (d) Ghorai, M. K.; Ghosh, K. *Tetrahedron Lett.* **2007**, *48*, 3191–3195. (e) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2009**, *50*, 1105-1109 and references cited therein.

(21) (a) Ungureanu, I.; Klotz, P.; Mann, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4615–4617. (b) Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Chem. Commun.* **2001**, 958–959.

(22) Absolute configuration of a similar compound was determined in our previous report; please see ref 20a.

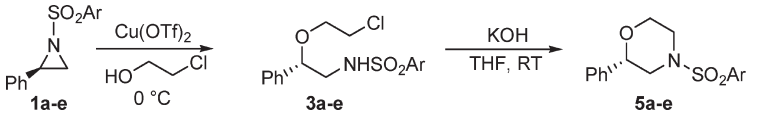
(23) See Supporting Information for details.

TABLE 1. Screening of Lewis Acids for Regioselective Nucleophilic Ring Opening of (*R*)-2-Phenyl-*N*-tosylaziridine with Chloroethanol[a]

entry	Lewis Acid (LA)	time (min)	ratio **3**:**4**[b]	yield (%)[c] of **3a** + **4a**	yield (%)[e] of **5a**	ee (%)[f] of **5a**
1	1.0 equiv $Cu(OTf)_2$	2	89:11	85	70	74
2	1.0 equiv $Zn(OTf)_2$	15	72:28	72	66	74
3	1.0 equiv $ZnBr_2$	10	76:24	45	60	74
4	1.0 equiv $BF_3 \cdot OEt_2$	1	81:19	68	72	74
5	1.0 equiv $Ti(O^iPr)_4$	10	77:23	55	73	74
6	0.2 equiv $Cu(OTf)_2$	5	100:0	87[d]	80	78
7	0.2 equiv $Cu(OTf)_2$	3	100:0	76[d]	80	35[g]

[a]Reaction condition: 1.0 equiv of LA was used, and unless noted otherwise all reactions were performed with (*R*)-**1a** in choloroethanol as the solvent at 0 °C. [b]Ratio was determined by ^1H NMR analysis of the crude reaction mixture. [c]Yield of isolated **3a** + **4a** after passing through plug of silica gel. [d]Yield of isolated **3a** after column chromatographic purification. [e]Yield of isolated **5a** after column chromatographic purification. [f]Determined by chiral HPLC. [g]Reaction was performed in CH_2Cl_2 with 5.0 equiv of chloroethanol.

TABLE 2. Two-Step Synthesis of Nonracemic 2-Phenyl-*N*-sulfonylmorpholines from (*R*)-2-Phenyl-*N*-sulfonylaziridines[a]



entry	substrates **1**	Ar	yield (%)[b] of chloroethoxy amine **3**	time (min)	yield (%)[b] of morpholines **5**	time	ee (%)[c] of **5a**
1	**1a**	$4\text{-}MeC_6H_4$	**3a** (87)	5	**5a** (80)	0.5 h	78
2	**1b**	$4\text{-}NO_2C_6H_4$	**3b** (81)	5	**5b** (85)	3 h	68
3	**1c**	$4\text{-}MeOC_6H_4$	**3c** (85)	10	**5c** (90)	1 h	75
4	**1d**	$4\text{-}FC_6H_4$	**3d** (82)	15	**5d** (86)	20 min	74
5	**1e**	$4\text{-}^tBuC_6H_4$	**3e** (88)	10	**5e** (72)	15 min	80

[a]0.2 equiv of $Cu(OTf)_2$ was used, and all reactions were performed with (*R*)-**1a**−**e** in choloroethanol as the solvent. [b]Yields of isolated **3** and **5** after column chromatographic purification are given in parentheses. [c]Determined by chiral HPLC using chiralcel OD-H or AS-H column.

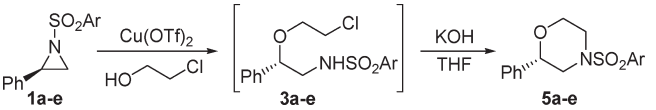
mixture. Next **3a** was treated with KOH at room temperature to produce morpholine **5a** in 80% yield. On the other hand, when the reaction was performed in CH_2Cl_2 as the solvent with 5.0 equiv of chloroethanol, it was completed in shorter time but the enantioselectivity of **5a** was found to be poor (ee 35%). Reaction was found to be highly efficient with choloroethanol as the solvent, and with other solvents such as DMF and THF the reaction was not successful.

To study the electronic effect of an *N*-arylsulfonyl group, a variety of *N*-arylsulfonyl aziridines **1a**−**e** were prepared from (*R*)-phenylglycinol.[23] With the optimized reaction condition, when (*R*)-2-phenyl-*N*-sulfonylaziridines **1a**−**e** with different arylsulfonyl groups on nitrogen were treated with chloroethanol in the presence of catalytic amount of $Cu(OTf)_2$, the corresponding chloroethoxy amines **3a**−**e** were produced in excellent yields (up to 88%) and were cyclized to the corresponding morpholines **5a**−**e** in good yield and ee (up to 80%) (Table 2). The reaction was found to be independent of the electronic effect of *N*-arylsulfonyl groups as the reaction time and yields of the products were almost same in all the cases (ring opening step). However, the ee was found to be lower with electron-withdrawing groups (Table 2, entries 2 and 4).

Encouraged by the aforementioned results, when we attempted the one-pot synthesis of **5a** via ring opening of **1a** with chloroethanol in the presence of 20 mol % $Cu(OTf)_2$ followed by KOH-assisted intramolecular cyclization, gratifyingly the reaction proceeded smoothly to furnish **5a** in 90% yield with 78% ee. Under identical reaction condition morpholines **5b**−**e** were obtained in excellent yields from the corresponding aziridines **1b**−**e** (Table 3).

To extend the scope of this methodology further, a variety of 2-alkyl-substituted aziridines **1f**−**h** prepared from

TABLE 3. $Cu(OTf)_2$-Catalyzed One-Pot Synthesis of 2-Phenyl-*N*-sulfonylmorpholines from (*R*)-2-Phenyl-*N*-sulfonylaziridines[a]



entry	aziridine	Ar	product	time (min)	yield (%)[b]	ee (%)[c]
1	**1a**	$4\text{-}MeC_6H_4$	**5a**	35	90	78
2	**1b**	$4\text{-}NO_2C_6H_4$	**5b**	185	92	68
3	**1c**	$4\text{-}MeOC_6H_4$	**5c**	70	83	75
4	**1d**	$4\text{-}FC_6H_4$	**5d**	35	91	74
5	**1e**	$4\text{-}^tBuC_6H_4$	**5e**	25	85	80

[a]0.2 equiv of $Cu(OTf)_2$ was used, and unless noted otherwise all reactions were performed with (*R*)-**1a**−**e** in choloroethanol as the solvent. [b]Yield of isolated **5** after column chromatographic purification. [c]Determined by chiral HPLC.

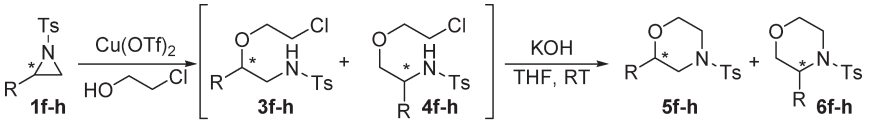
corresponding amino acids[24] were reacted under the same reaction conditions.

Ring opening of alkyl aziridines **1f**−**h** (ee > 99%) with chloroethanol was found to be slow, and the regioisomers **3f**−**h** and **4f**−**h** arising from internal attack and terminal attack, respectively, were obtained as an inseparable mixture (Scheme 2).

However, after cyclization and chromatographic separation 2-alkyl morpholines **5f**−**h** and 3-alkyl morpholines **6f**−**h** were obtained in pure forms with good yield (up to 72% overall yield)

(24) Aziridines **1f**−**h** were prepared from the corresponding amino acids L-Phe Ala, L-Val, L-Leu. These amino acids were reduced to corresponding 2-aminoethanols with $NaBH_4/I_2$ in THF, which were then transformed into *N*-tosyl derivatives with $TsCl/Et_3N$ in CH_2Cl_2. The *N*-tosyl derivatives were then cyclized to corresponding aziridines with TsCl/ KOH in THF to afford the corresponding aziridine in excellent yield.

SCHEME 2. Cu(OTf)$_2$-Catalyzed One-Pot Synthesis of 2- and 3-Alkyl-*N*-tosylmorpholines via the Ring Opening of Aziridines with Chloroethanol



R = **1f**: (*S*) Bn, **1g**: (*R*) ^{i}Pr,**1h**: (*R*) ^{i}Bu, *ee* upto 99%

TABLE 4. Cu(OTf)$_2$-Catalyzed One-Pot Synthesis of 2- and 3-Alkyl-*N*-tosylmorpholines via Ring Opening of Aziridines with Chloroethanol[a]

entry	aziridine **1**	morpholine **5** yield (%)[b]	morpholine **6** yield (%)[b]	time (h)	*ee* (%)[d] **5**	*ee* (%)[d] **6**
1	 **1f**	 **5f** (26)	 **6f** (51)	54[c]	98	99
2	 **1g**	 **5g** (29)	 **6g** (57)	11	96	98
3	 **1h**	 **5h** (68)	 **6h** (23)	27	94	97

[a]0.2 equiv of Cu(OTf)$_2$ was used, and unless noted otherwise all reactions were performed with **1f**−**h** in choloroethanol as the solvent. [b]Yield of isolated products after column chromatographic purification are given in parentheses. [c]1.0 equiv of Cu(OTf)$_2$ was used. [d]Determined by HPLC using Chiralcel AD-H or OD-H or AS-H.

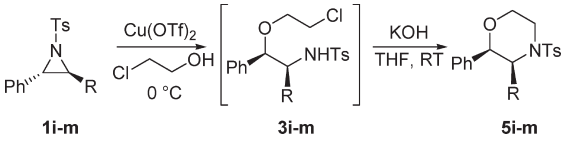
and excellent ee (up to 99%). Enhanced yield of the products were obtained when the reaction was performed under one-pot conditions, and the results are summarized in Table 4.

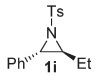
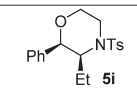
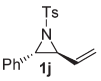
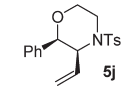
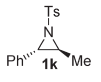
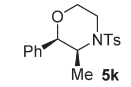
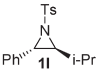
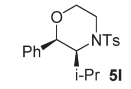
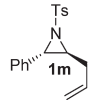
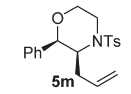
After establishing the synthesis of 2-substiuted morpholines, we envisioned that enantiopure 2,3-disubstituted morpholines could be made easily from enantiopure 2,3-disubstituted aziridines. The 2,3-disubstituted aziridines **1i**−**m** were prepared from L-phenylglycine using the method developed in our laboratory.[25] Ring opening of enantiopure *trans*-disubstituted aziridines **1i**−**m** (de up to 99%) with chloroethanol followed by cyclization in the presence of KOH under one-pot conditions afforded the corresponding *cis*-2,3-disubstituted morpholines as the major diastereomers (Table 5, entries 1−5) with high yield and excellent de.

The strategy was extended further for the syntheses of homomorpholines via the Cu(OTf)$_2$-catalyzed ring opening of (*R*)-2-phenyl-*N*-tosylaziridine **1a** with bromopropanol (10 equiv) to afford bromopropoxy amine **7** (yield 85%), which was cyclized in the presence of KOH to produce morpholine homologue 1,4-oxazepane **8** in good yield (76%) and ee (86%). The same reaction when performed under one-pot condition furnished nonracemic **8** in 87% yield and 86% ee (Scheme 3).

After successful demonstration of the strategy for the synthesis of morpholines and homomorpholines via the ring opening of aziridines, the synthetic potential of the strategy

TABLE 5. Cu(OTf)$_2$-Catalyzed One-Pot Synthesis of 2,3-disubstituted Morpholines via Ring Opening of 2,3-Disubstituted-*N*-tosylaziridines[a]



entry	aziridine **1**[b]	morpholine **5**	time (min)	yield (%)[c]	*de* (%)[d]
1	 **1i**	 **5i**	70	78	99
2	 **1j**	 **5j**	60	70	98
3	 **1k**	 **5k**	70	85	>99
4	 **1l**	 **5l**	90	72	94
5	 **1m**	 **5m**	55	75	92

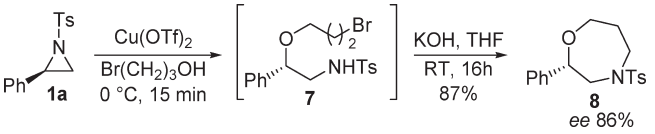
[a]In all the cases the alcohol served as the solvent. [b]Diasteromeric excess >99%, except for **1m** (92%). [c]Isolated yield of pure product (**5**) after column chromatographic purification. [d]Determined by ^{1}H NMR of crude reaction mixture, in all the cases ee of the product was found to be >99% as determined by chiral HPLC using Chiralcel AD-H or OD-H.

was further demonstrated by the straightforward synthesis of nonracemic seven- and eight-membered homologues of morpholine. The ring opening of enantiopure (*R*)-2-phenyl-*N*-tosylazetidine[26] **2a** (ee > 99%) with bromoethanol and bromopropanol in the presence of 50 mol % of Cu(OTf)$_2$ afforded **9a** and **10a**, respectively, which were cyclized in the presence of KOH to give morpholine homologues **11a** and **12a** with poor yields (up to 48%) and moderate ee (up to 56%). When the reaction was performed under one-pot condition, **11a** and **12a** were obtained with better yields

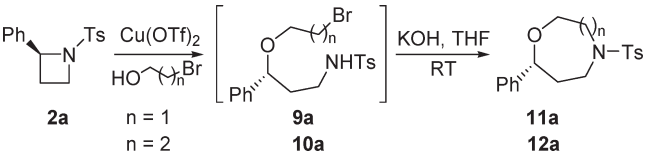
(25) Kumar, A. Ph.D. thesis submitted to IIT-Kanpur, India, **2009**.

(26) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 2471–2475.

SCHEME 3. Cu(OTf)$_2$-Catalyzed One-Pot Synthesis of Homomorpholine via the Ring Opening of (*R*)-2-Phenyl-*N*-tosylaziridine



SCHEME 4. One-Pot Synthesis of Homomorpholine and Higher Homologue via Ring Opening of 2-Phenyl-*N*-tosylazetidine



SCHEME 5. One-Pot Synthesis of Enantiopure Homomorpholines and Higher Homologue via Ring Opening of 2,4-Disubstituted-*N*-tosylazetidine

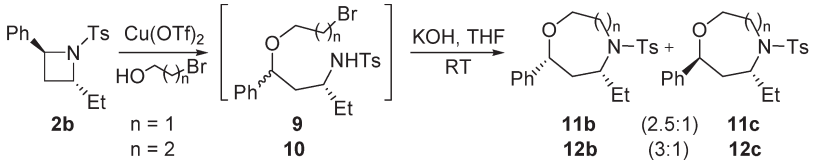
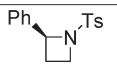
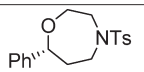
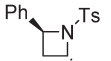
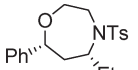
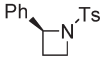
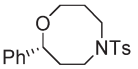
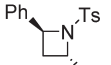
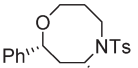


TABLE 6. One-Pot Synthesis of Homomorpholines and Higher Homologues via Ring Opening of Azetidines with Haloalcohols[a]

entry	azetidines **2**	haloalchols	major products (**11/12**)	yield (%)[b]	*ee* (%)[c]
1	 **2a**	$Br(CH_2)_2OH$	 **11a**	62	56
2	 **2b**	$Br(CH_2)_2OH$	 **11b**	70	99 (2.5:1)[d]
3	 **2a**	$Br(CH_2)_3OH$	 **12a**	60	50
4	 **2b**	$Br(CH_2)_3OH$	 **12b**	74	99 (3:1)[d]

[a]In all the cases the alcohol served as the solvent. [b]Yield of isolated product after column chromatographic purification. [c]Determined by HPLC using Chiralcel AD-H or OD-H column. [d]Determined by crude ^{1}H NMR.

(up to 62%) and the same ee (up to 56%) (Scheme 4, Table 6, entries 1 and 3).

Similarly, (2*R*,4*S*)-2-ethyl-4-phenyl-*N*-tosylazetidine[26] **2b** (ee > 99%) was reacted with bromoethanol and bromopropanol in the presence of 50 mol % of Cu(OTf)$_2$ followed by cyclization in the presence of KOH to produce homomorpholine **11b** and oxazocane **12b**, respectively, as the major products (Scheme 5, Table 6, entries 2 and 4).

Mechanistic Perspective. We do believe that the ring opening of chiral aziridines **1** and azetidines **2** with haloalcohols proceeds via an S_N2 pathway, which is illustrated in Scheme 6. The Lewis acid is coordinated to aziridine **1** or azetidine **2** nitrogen, generating a highly reactive species **13**, which undergoes nucleophilic attack by haloalcohols in S_N2 fashion to provide nonracemic **3**/**7** or **9**/**10**, respectively. These haloalkoxy amines undergo KOH-mediated intramolecular cyclization to form the corresponding morpholines.

We rationalized the reduced enantioselectivilty in all cases on the basis of partial racemization of **1** or **2** before the nucleophilic ring opening step, and this hypothesis is supported by the racemization of aziridine **1a**. We studied the racemization of enantiopure **1a** by performing the reaction with a catalytic amount of Cu(OTf)$_2$ (20 mol %) in CH_2Cl_2 at 0 °C without adding any nucleophile. The aliquots were taken out from the reaction mixture at different time intervals and analyzed by chiral HPLC. The reduced ee with time is shown in Figure 2. After 120 min, enantiopure (*R*)-**1a** was found to be almost racemized (ee 10%).[27]

(27) See Supporting Information for details of racemization study.

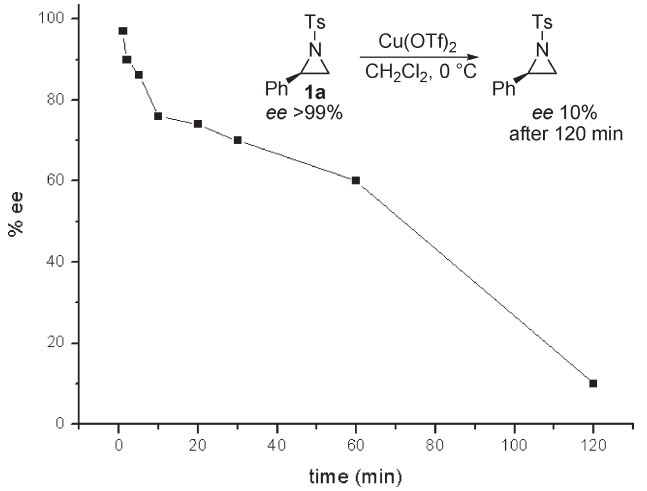
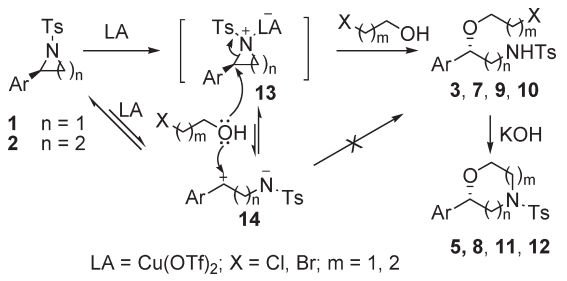


FIGURE 2. Racemization of (*R*)-**1a** in the presence of $Cu(OTf)_2$ in CH_2Cl_2 without any nucleophile.

SCHEME 6. Mechanism for the LA-Catalyzed Ring Opening of 2-Phenyl-*N*-tosylaziridines and Azetidines with Haloalcohols

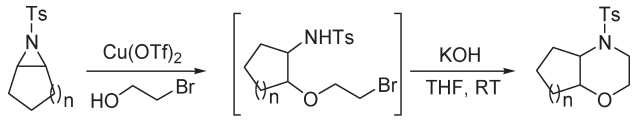


The observed high diasteroselectivities in the case of disubstituted aziridines **1i**−**m** are due to controlled and slow epimerization of the benzylic carbon center during the reaction. This is obvious as the epimerization would lead to the formation of less stable *cis*-aziridines from the corresponding more stable *trans*-aziridines. Moreover, the S_N2 reaction from the *cis*-isomer (if any) would be slower and less favorable for steric reasons. This rational has been evidenced from the very slow epimerization of **1m** compared to **1a** during the reaction; **1m** (de 92%) was treated with $Cu(OTf)_2$ (20 mol %) in CH_2Cl_2 solvent and after 10 min it was recovered without any loss of de (92%).[27]

Next the strategy was extended further to the synthesis of bicyclic morpholines via the ring opening of bicyclic aziridines. Aziridines **15** and **16** were reacted with bromoethanol in presence of catalytic amount (20 mol %) of $Cu(OTf)_2$ to afford the corresponding bromoethoxy amines **17** and **18** in good yield (up to 76%), which were cleanly cyclized in the presence of KOH to afford **19** and **20** (yield up to 80%). Under one-pot condition **19** and **20** were obtained in excellent overall yield (up to 84%) (Scheme 7). The bicyclic morpholines have been reported to be used in 2-(cyclic amino) pyrimidone derivatives as tau protein kinase 1 (TPK1) inhibitors.[28]

(28) Fukunaza, K.; Kohara, T.; Watanabe, K.; Usui, Y.; Uehera, F.; Yokoshima, S.; Sakai, D.; Kusaka, S.-I.; Nakayama, K. *PCT Int. Appl.* WO 2007119463, **2007**.

SCHEME 7. One-Pot Synthesis of Bicyclic Morpholines via Ring Opening of Bicyclic Aziridines



15 n = 1
16 n = 2

17
18

19 84%
20 78%

Finally, another application of this methodology is demonstrated by the synthesis of *cis*- and *trans*-2,6-diphenylmorpholine derivatives **25** and **26** in enantiopure form. Ring opening of racemic 2-phenyl *N*-tosylaziridine (**1a**) with (*R*)-methyl 2-hydroxy-2-phenylacetate in the presence of 20 mol % of $Cu(OTf)_2$ afforded corresponding products **21** and **22** in 1:1 ratio (Scheme 8).

Products **21** and **22** obtained in pure forms by column chromatographic separation were reduced to the corresponding alcohols **23** and **24** in excellent yield (up to 92%) by the treatment of lithium borohydride in THF. Alcohols **23** and **24** were then cyclized to the corresponding morpholines **25** and **26** (yield up to 81%), respectively, using *p*-toluene sulfonyl chloride and KOH in THF as the solvent (Scheme 8). Structures of **25** and **26** were unambiguously confirmed by X-ray crystallography (see Supporting Information).

Detosylation of **25** and **26** was carried out in sodium naphthalenide/tetrahydrofuran to get corresponding free morpholines **27** and **28** in good yield (scheme 9). C_2-symmetric morpholine **28** and its derivatives could find use as ligands, chiral auxiliaries, and catalysts in asymmetric transformations.

Conclusion

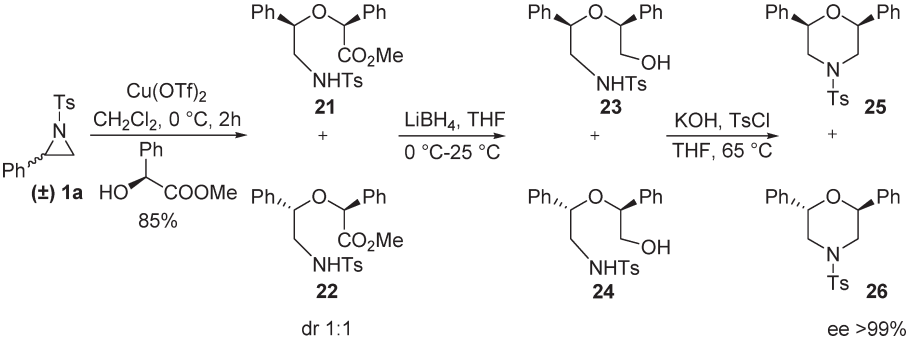
In conclusion, we have developed a simple and practical protocol for the synthesis of nonracemic 2-substituted morpholines, 2,3-disubstituted morpholines, enantiopure 2,6-disubstituted morpholines, homomorpholines, and higher homologues through a $Cu(OTf)_2$-catalyzed S_N2-type ring opening of *N*-activated aziridines and azetidines with haloalcohols. This method allows the use of a wide range of aziridines/azetidines and haloalcohols to construct six- to eight-membered N-O-heterocyles in excellent yield and enantioselectivity. The investigation on organocatalytic reaction of substituted morpholines and further study in this area is underway.

Experimental Section

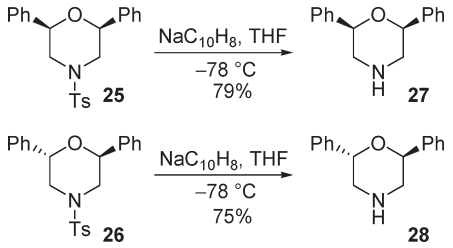
General Procedure for $Cu(OTf)_2$-Catalyzed Ring Opening of 2-Phenyl-*N*-sulfonylaziridines with Haloalcohols. A solution of aziridines **1a**−**e** (1.0 equiv) in haloalcohol (10 equiv) was added at 0 °C to anhydrous copper triflate (20 mol %) under an argon atmosphere. The mixture was stirred for appropriate time and then the reaction was quenched with saturated aqueous sodium bicarbonate solution. The aqueous layer 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 15% ethyl acetate in petroleum ether to provide the pure product.

(*S*)-*N*-(2-(2-Chloroethoxy)-2-phenylethyl)-4-methylbenzenesulfonamide (3a). The general method described above was

SCHEME 8. Synthesis of *cis*- and *trans*-2,6-Diphenylmorpholines



SCHEME 9. Cleavage of *N*-Tosyl Bond of 25 and 26



followed when **1a** (100 mg, 0.37 mmol) was reacted with chloroethanol (0.25 mL, 3.7 mmol) at 0 °C for 5 min to afford **3a** as a dense liquid (112 mg, 87% yield). $[\alpha]^{25}_{D}$ +133.6 (*c* 0.060, $CHCl_3$) for a 78% ee sample. Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−isopropanol, 95:5; flow rate = 1.0 mL/min; t_R 1: 21.92 min (major), t_R 2: 29.89 min (minor). R_f 0.35 (ethyl acetate−hexane, 1:4); IR ν_{max} (film, cm^{-1}) 3285, 2920, 1597, 1327, 1159, 1091, 810, 664, 552; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 8.1 Hz), 7.35−7.22 (m, 7H), 5.05 (dd, 1H, NH, J = 9.7, 2.9 Hz), 4.34 (dd, 1H, J = 9.2, 3.5 Hz), 3.62−3.56 (m, 3H), 3.47−3.43 (m, 1H), 3.25 (ddd, 1H, J = 13.2, 9.8, 3.5 Hz), 3.02 (ddd, 1H, J = 13.2, 9.2, 2.9 Hz), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 138.0, 137.1, 129.7, 128.9, 127.1, 126.5, 80.9, 68.9, 49.4, 43.0, 21.5; HRMS (ESI) $C_{17}H_{20}ClNO_3S$, $(M + H)^+$ found 354.0932, calcd 354.0930.

(*S*)-*N*-(2-(3-Bromopropoxy)-2-phenylethyl)-4-methylbenzenesulfonamide (7). The general method described above was followed when **1a** (100 mg, 0.37 mmol) was reacted with bromopropanol (0.33 mL, 3.7 mmol) at 0 °C for 15 min to afford **7** as a dense liquid (127 mg, 85% yield). R_f 0.39 (ethyl acetate−petroleum ether, 1:4); IR ν_{max} (film, cm^{-1}) 3293, 2924, 2874, 1327, 1160, 1092, 702, 664, 555; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, 2H, J = 8.0 Hz), 7.28−7.19 (m, 5H), 7.13 (d, 2H, J = 1.9 Hz), 4.90 (br s, 1H, NH), 4.21 (dd, 1H, J = 9.3, 3.9 Hz), 3.78−3.71 (m, 1H), 3.46−3.40 (m, 2H), 3.38−3.33 (m, 1H), 3.29−3.27 (m, 1H), 2.93−2.91 (m, 1H), 2.36 (s, 3H), 2.00−1.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 138.4, 129.7, 128.7, 128.5, 127.1, 126.5, 80.6, 66.4, 49.3, 32.5, 30.3, 21.5; HRMS (ESI) $C_{18}H_{22}BrNO_3S$, $(M + H)^+$ found 412.0584, calcd 412.0582.

(*R*)-*N*-(3-(2-Bromoethoxy)-3-phenylpropyl)-4-methylbenzenesulfonamide (9a). The general method described above was followed when **2a** (100 mg, 0.35 mmol) was reacted with bromoethanol (0.24 mL, 3.5 mmol) at 0 °C for 1 h to afford **9a** as a dense liquid (117 mg, 82% yield). R_f 0.25 (ethyl acetate−petroleum ether, 1:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, 2H, J = 8.3 Hz), 7.29−7.09 (m, 7H), 5.21 (br s, 1H, NH), 4.31 (dd, 1H, J = 8.8, 3.9 Hz), 3.61−3.56 (m, 1H), 3.43−3.34 (m, 3H), 3.17−3.13 (m, 1H), 3.03−2.98 (m, 1H), 2.37 (s, 3H), 1.84−1.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.4, 140.8, 137.1, 129.8, 128.8, 128.2, 127.3, 126.4, 81.8, 68.5, 41.1, 37.4, 31.5, 21.7; HRMS (ESI) $C_{18}H_{22}BrNO_3S$, $(M + H)^+$ found 412.0579, calcd 412.0582.

General Procedure for KOH-Mediated Ring Closure of Haloalkoxy Amines 3a−e to Corresponding Morpholines 5a−e. To a suspension of powdered KOH (2 equiv) in 1.0 mL dry THF was added a solution of haloalkoxy amine (1.0 equiv) in 5.0 mL dry THF. The mixture was stirred at room temperature for the appropriate time. After completion of the reaction, water was added, and the reaction mixture was extracted with ethyl acetate (3 × 5.0 mL). The combined organic layer was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel using 15% ethyl acetate and petroleum ether as the eluent.

(*S*)-2-Phenyl-4-tosylmorpholine (5a). The general method described above was followed when **3a** (100 mg, 0.28 mmol) was reacted with KOH (31 mg, 0.56 mmol) at rt for 30 min in dry THF to afford **5a** as a white solid (93 mg, 80% yield), mp 102−104 °C. $[\alpha]^{25}_{D}$ +153.0 (*c* 0.049, $CHCl_3$) for a 78% ee sample. Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−isopropanol, 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; ^{1}H 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) $C_{17}H_{19}NO_3S$ $(M + H)^+$ found 318.1165, calcd 318.1165.

General Procedure for One-Pot Synthesis of Morpholines and Homologues. A solution of the aziridine (1.0 equiv) in chloroethanol (10 equiv) was added to anhydrous copper triflate (20 mol %) at 0 °C under an argon atmosphere and stirred for the appropriate time. After completion of the reaction (as monitored by TLC) the reaction mixture was diluted with THF (2.0 mL), and excess KOH (12 equiv) was added to it. The reaction mixture was stirred further at rt for the appropriate time and then quenched with saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate (3 × 5.0 mL), washed with brine, and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel (230−400 mesh) using ethyl acetate in hexane as eluent to afford pure product.

(*S*)-4-(4-*tert*-Butylphenylsulfonyl)-2-phenylmorpholine (5e). The general procedure for one-pot synthesis of morpholine was followed when **1e** (100 mg, 0.32 mmol) was reacted with chloroethanol (0.21 mL, 3.2 mmol) at 0 °C for 10 min followed

by cyclization with excess KOH (215 mg, 3.83 mmol) in dry THF at rt for 15 min to afford pure **5e** as a white solid (102.5 mg, 90% yield); mp 112−115 °C; $[\alpha]^{25}_{D}$ +47.2 (*c* 0.072, $CHCl_3$) for a 80% ee sample. Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−isopropanol, 95:5, flow rate = 1.0 mL/min; t_R 1: 13.72 min (major), t_R 2: 22.37 min (minor). R_f 0.38 (ethyl acetate−hexane, 3:7); IR ν_{max} (KBr, cm^{-1}) 2923, 1343, 1170, 1101, 966, 772, 562; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, 2H, J = 8.5 Hz), 7.45 (d, 2H, J = 8.5 Hz), 7.28−7.23(m, 5H), 4.54 (dd, 1H, J = 10.2, 2.2 Hz), 4.01(dd, 1H, J = 10.7, 2.2 Hz), 3.80 (ddd, 1H, J = 11.7, 11.5, 2.7 Hz), 3.73−3.70 (m, 1H), 3.59−3.56 (m, 1H), 2.47 (ddd, 1H, J = 11.7, 11.5, 3.4 Hz), 2.23−2.18 (m, 1H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 138.7, 128.5, 128.3, 127.7, 126.1, 125.9, 77.3, 66.2, 51.9, 45.4, 31.0; HRMS (ESI) $C_{20}H_{25}NO_3S$, $(M + H)^+$ found 360.1631, calcd 360.1633.

(***S***)**-2-Isopropyl-4-tosylmorpholine (5g).** The general procedure for one-pot synthesis of morpholine was followed when **1g** (100 mg, 0.42 mmol) was reacted with chloroethanol (0.28 mL, 4.2 mmol) at rt for 9 h followed by cyclization with excess KOH (282 mg, 5.04 mmol) in dry THF at rt for 2 h to afford pure isomers **5g** and **6g** (1:2 ratio) as a white solid. Regioisomer **5g**: yield 29%, mp 93−95 °C; $[\alpha]^{25}_{D}$ +44.9 (*c* 0.069, $CHCl_3$) for a 96% ee sample. Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel AS-H column), hexane−isopropanol, 98:2, flow rate = 0.80 mL/min; t_R 1: 30.79 min (major), t_R 2: 34.44 min (minor). R_f 0.46 (ethyl acetate−hexane, 1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 2H, J = 8.0 Hz), 7.28 (d, 2H, J = 8.3 Hz), 3.83 (dd, 1H, J = 11.5, 3.2 Hz), 3.60−3.52 (m, 2H), 3.45−3.42 (m, 1H), 3.16−3.11 (m, 1H), 2.38 (s, 3H), 2.29 (ddd, 1H, J = 11.5, 11.2, 3.2 Hz), 2.03−1.98 (m, 1H), 1.58−1.53 (m, 1H), 0.85 (d, 3H, J = 6.8 Hz), 0.82 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 132.5, 129.7, 127.8, 80.3, 66.0, 48.3, 45.6, 45.5, 31.1, 21.5, 18.3; HRMS (ESI) $C_{14}H_{21}NO_3S$, $(M + H)^+$ found 284.1327, calcd 284.1320.

(***S***)**-3-Isopropyl-4-tosylmorpholine (6g).** White solid, yield 57%; mp 99−101 °C; $[\alpha]^{25}_{D}$ +39.4 (*c* 0.011, $CHCl_3$) for a 98% ee sample. Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel AS-H column), hexane−isopropanol, 98:2, flow rate = 0.80 mL/min; t_R 1: 21.62 min (minor), t_R 2: 26.08 min (major). R_f 0.38 (ethyl acetate−hexane, 1:5); IR ν_{max} (KBr, cm^{-1}) 2962, 2859, 1459, 1342, 1157, 926, 745, 677, 555; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, 2H, J = 8.3 Hz), 7.23 (d, 2H, J = 8.1 Hz), 3.75 (d, 1H, J=11.9 Hz), 3.56−3.51 (m, 2H), 3.27−3.05 (m, 4H), 2.36 (s, 3H), 2.26−2.18 (m, 1H), 0.90 (d, 3H, J = 6.6 Hz), 0.85 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 138.9, 129.8, 127.0, 66.2, 65.5, 59.7, 41.3, 25.4, 21.5, 19.9, 19.8; HRMS (ESI) $C_{14}H_{21}NO_3S$, $(M + H)^+$ found 284.1328, calcd 284.1320.

(**2*R*,3*S*)-3-Ethyl-2-phenyl-4-tosylmorpholine (5i).** The general procedure for one-pot synthesis of morpholine was followed when **1i** (100 mg, 0.33 mmol) was reacted with chloroethanol (0.22 mL, 3.3 mmol) at 0 °C for 10 min followed by cyclization with excess KOH (222 mg, 3.96 mmol) in dry THF at rt for 1 h to afford **5i** as a dense liquid (89 mg, 78% yield); de 99%; Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel AS-H column), hexane−isopropanol, 98:2, flow rate = 0.80 mL/min; t_R 1: 37.66 min (major), t_R 2: 45.79 min (minor). R_f 0.40 (ethyl acetate−hexane, 1:5); IR ν_{max} (neat, cm^{-1}) 2965, 2924, 2856, 1343, 1158, 1089, 995, 702, 552; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 8.3 Hz), 7.28−7.14 (m, 7H), 4.35 (d, 1H, J = 2.7 Hz), 3.89−3.86 (m, 1H), 3.84−3.80 (m, 1H), 3.68−3.60 (m, 1H), 3.43 (ddd, 1H, J = 12.2, 12.2, 2.9 Hz), 3.27−3.19 (m, 1H), 2.36 (s, 3H), 1.57−1.49 (m, 1H), 1.04−0.99 (m, 1H), 0.59 (t, 3H, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 138.8, 130.0, 128.4, 127.5, 127.1, 125.3, 79.3, 66.6, 59.5, 39.9, 21.6, 16.7, 10.6; HRMS (ESI) $C_{19}H_{23}NO_3S$, $(M + H)^+$ found 346.1475, calcd 346.1476.

(**2*R*,3*S*)-2-Phenyl-4-tosyl-3-vinylmorpholine (5j).** The general procedure for one-pot synthesis of morpholine was followed when **1j** (100 mg, 0.33 mmol) was reacted with chloroethanol (0.22 mL, 3.3 mmol) at 0 °C for 15 min followed by cyclization with excess KOH (222 mg, 3.96 mmol) in dry THF at rt for 45 min to afford **5j** as a dense liquid (80 mg, 70% yield); de 98%; Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel AS-H column), hexane−isopropanol, 95:5, flow rate = 1.0 mL/min; t_R 1: 17.58 min (minor), t_R 2: 21.43 min (major). R_f 0.43 (ethyl acetate−hexane, 1:5); IR ν_{max} (neat, cm^{-1}) 2924, 2854, 1728, 1345, 1274, 1163, 1111, 1019, 666, 567; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, 2H, J = 8.3 Hz), 7.32−7.21 (m, 7H), 5.59−5.52 (m, 1H), 4.90 (d, 1H, J = 10.6 Hz), 4.83 (d, 1H, J = 13.8 Hz), 4.72 (d, 1H, J = 2.9 Hz), 4.57−4.52 (m, 1H), 4.08 (dd, 1H, J = 11.5, 3.7 Hz), 3.79 (ddd, 1H, J = 11.5, 11.5, 3.2 Hz), 3.60 (dd, 1H, J = 12.9, 5.7 Hz), 3.22 (ddd, 1H, J = 12.3, 12.3, 3.7 Hz), 2.40 (s, 3H); HRMS (ESI) $C_{19}H_{21}NO_3S$, $(M + H)^+$ found 344.1245, calcd 344.1242.

(**2*R*,3*S*)-3-Methyl-2-phenyl-4-tosylmorpholine (5k).** The general procedure for one-pot synthesis of morpholine was followed when **1k** (100 mg, 0.35 mmol) was reacted with chloroethanol (0.24 mL, 3.5 mmol) at 0 °C for 10 min followed by cyclization with excess KOH (222 mg, 3.96 mmol) in THF at rt for 1 h to afford **5k** as a dense liquid (97.8 mg, 85% yield); de > 99%; Enantiopuric purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−isopropanol, 95:5, flow rate = 1.0 mL/min; t_R: 12.06 min. R_f 0.43 (ethyl acetate−hexane, 1:5); IR ν_{max} (neat, cm^{-1}) 2922, 2851, 1598, 1382, 1348, 1275, 1157, 1125, 1091, 1000, 920, 858, 701, 557; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 2H, J = 8.3 Hz), 7.28−7.17 (m, 7H), 4.56 (d, 1H, J = 2.7 Hz), 4.14−4.12 (m, 1H), 3.98 (dd, 1H, J = 11.5, 3.2 Hz), 3.64 (ddd, 1H, J = 14.6, 12.2, 3.2 Hz), 3.55−3.52 (dd, 1H, J = 12.9, 3.2 Hz), 3.18 (ddd, 1H, J=16.3, 12.4, 3.7 Hz), 2.36 (s, 1H), 0.65 (d, 3H, J = 6.8 Hz); HRMS (ESI) $C_{18}H_{21}NO_3S$, $(M + H)^+$ found 332.1326, calcd 332.1320.

(**2*R*,3*S*)-3-Isopropyl-2-phenyl-4-tosylmorpholine (5l).** The general procedure for one-pot synthesis of morpholine was followed when **1 L** (100 mg, 0.32 mmol) was reacted with chloroethanol (0.22 mL, 3.2 mmol) at 0 °C for 20 min followed by cyclization with excess KOH (222 mg, 3.96 mmol) in THF at rt for 70 min to afford **5 L** as a dense liquid (81 mg, 72% yield); de 94%; Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel AS-H column), hexane−isopropanol, 95:5, flow rate = 1.0 mL/min; t_R 1: 15.98 min (major), t_R 2: 18.23 min (minor). R_f 0.41 (ethyl acetate−hexane, 1:5); IR ν_{max} (neat, cm^{-1}) 2958, 2924, 2853, 1741, 1599, 1495, 1339, 1275, 1158, 1090, 936, 702, 554; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, 2H, J=8.3 Hz), 7.34−7.21 (m, 7H), 4.35 (d, 1H, J = 3.2 Hz), 3.87−3.85 (m, 1H), 3.80−8.78 (m, 1H), 3.75−3.72 (m, 1H), 3.42−3.37(m, 2H), 2.38(s, 3H), 2.02−1.97 (m, 1H), 0.84 (d, 3H, J = 6.6 Hz), 0.36 (d, 3H, J = 6.6 Hz); HRMS (ESI) $C_{20}H_{25}NO_3S$, $(M + H)^+$ found 360.1636, calcd 360.1633.

(**2*R*,3*S*)-3-Allyl-2-phenyl-4-tosylmorpholine (5m).** The general procedure for one-pot synthesis of morpholine was followed when **1m** (100 mg, 0.32 mmol) was reacted with chloroethanol (0.22 mL, 3.2 mmol) at 0 °C for 10 min followed by cyclization with excess KOH (222 mg, 3.96 mmol) in THF at rt for 45 min to afford **5m** as a dense liquid (86 mg, 75% yield); de 92%; R_f 0.44 (ethyl acetate−hexane, 1:5); IR ν_{max} (neat, cm^{-1}) 2922, 2854, 1639, 1493, 1336, 1159, 1091, 1023, 918, 814, 724, 702, 682, 557; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, 2H, J = 8.4 Hz), 7.34−7.23 (m, 7H), 5.42−5.36 (m, 1H), 4.83−4.81(m, 1H), 4.79 (s, 1H), 4.49 (d, 1H, J = 3.1 Hz), 4.16−4.13 (m, 1H), 3.93 (dd, 1H, J = 11.45, 3.5 Hz), 3.66 (dd, 1H, J = 14.2, 3.1 Hz), 3.56 (ddd, 1H, J = 15.3, 12.2, 3.1 Hz), 3.29 (ddd, 1H, J = 14.1, 12.2, 3.5 Hz), 2.42 (s, 3H), 2.36−2.29 (m, 1H), 1.86−1.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 138.5, 134.7, 129.9,

128.5, 127.6, 127.3, 125.3, 116.9, 79.3, 66.8, 57.5, 40.0, 29.8, 28.8, 21.6; HRMS (ESI) $C_{20}H_{23}NO_3S$, $(M + H)^+$ found 358.1478, calcd 358.1477.

(*S*)-2-Phenyl-4-tosyl-1,4-oxazepane (8). The general procedure for one-pot synthesis of homomorpholine was followed when **1a** (100 mg, 0.37 mmol) was reacted with bromopropanol (0.33 mL, 3.7 mmol) at 0 °C for 15 min followed by cyclization with excess KOH (249 mg, 4.44 mmol) in dry THF at rt for 16 h to afford **8** as a dense liquid (105 mg, 87% yield); $[\alpha]^{25}_D$ +158.3 (*c* 0.084, $CHCl_3$) for a 86% ee sample. Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−isopropanol, 95:5, flow rate = 1.0 mL/min; t_R 1: 12.26 min (major), t_R 2: 14.44 min (minor). R_f 0.41 (ethyl acetate−hexane, 3: 7); IR ν_{max} (neat, cm^{-1}) 2923, 2853, 1729, 1338, 1160, 1018, 700, 659, 549; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, 2H, J = 8.3 Hz), 7.27−7.19 (m, 7H), 4.56 (dd, 1H, J = 10.0, 2.4 Hz), 4.14- 4.08 (m, 1H), 3.92−3.89 (m, 1H), 3.84−3.77 (m, 2H), 2.99−2.92 (m, 1H), 2.74 (dd, 1H, J = 14.2, 10.0 Hz), 2.36 (s, 3H), 2.04−1.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 139.7, 136.4, 129.7, 128.5, 127.9, 126.9, 126.0, 83.9, 68.6, 57.7, 46.9, 30.6, 21.4; HRMS (ESI) $C_{18}H_{21}NO_3S$, $(M + H)^+$ found 332.1323, calcd 332.1320.

(*R*)-7-Phenyl-4-tosyl-1,4-oxazepane (11a). The general procedure for one-pot synthesis of morpholine homologues was followed when **2a** (100 mg, 0.35 mmol) was reacted with bromoethanol (0.24 mL, 3.5 mmol) at 0 °C for 1 h followed by cyclization with excess KOH (235.6 mg, 4.2 mmol) in dry THF at rt for 32 h to afford **11a** as a white solid (72 mg, 62% yield); mp 113−114 °C; $[\alpha]^{25}_D$ +22.5 (*c* 0.08, $CHCl_3$) for a 56% ee sample. Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−isopropanol, 95:5, flow rate = 1.0 mL/min; t_R 1: 21.72 min (major), t_R 2: 25.31 min (minor). R_f 0.32 (ethyl acetate−hexane, 1:4); ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, 2H, J = 8.0 Hz), 7.27−7.16 (m, 7H), 4.60 (dd, 1H, J = 9.5, 2.7 Hz), 4.04−4.00 (m, 1H), 3.73−3.51 (m, 3H), 3.28−3.20 (m, 1H), 3.19−3.14 (m, 1H), 2.37 (s, 3H), 2.25−2.21 (m, 1H), 1.98−1.95 (m, 1H); ^{13}C NMR (100 MHz $CDCl_3$) δ 143.1, 142.6, 129.5, 128.1, 127.1, 126.8, 125.3, 81.2, 69.7, 51.4, 46.0, 37.5, 21.2; HRMS (ESI) $C_{18}H_{21}NO_3S$, $(M + Na)^+$ found 354.1147, calcd 354.1140.

(5*R*,7*R*)-5-Ethyl-7-phenyl-4-tosyl-1,4-oxazepane (11b). The general procedure for one-pot synthesis of morpholine homologues was followed when **2b** (100 mg, 0.32 mmol) was reacted with bromoethanol (0.20 mL, 3.2 mmol) at 0 °C for 20 min followed by cyclization with excess KOH (215.5 mg, 3.8 mmol) in dry THF at rt for 40 h to afford **11b** as the major diastereomer as a dense liquid (68 mg, 60% yield); $[\alpha]^{25}_D$ +56.9 (*c* 0.20, $CHCl_3$) for a >99% ee sample. R_f 0.38 (ethyl acetate−hexane, 1:4); IR ν_{max} (neat, cm^{-1}) 2922, 2852, 1621, 1453, 1334, 1156, 1117, 1019, 813, 699, 547; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 2H, J = 8.3 Hz), 7.26−7.15 (m, 7H), 4.33 (d, 1H, J = 8.8 Hz), 4.02- 3.98 (m, 1H), 3.85−3.79 (m, 2H), 3.65 (dd, 1H, J = 12.9, 1.7 Hz), 3.28−3.23 (m, 1H), 2.37 (s, 3H),2.34−2.25 (m, 2H), 1.87−1.82 (m, 1H), 1.46−1.39 (m, 1H), 0.66 (t, 3H, J = 7.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 141.8, 138.5, 134.4, 129.6, 128.6, 128.0, 127.2, 126.3, 79.3, 69.4, 54.3, 41.9, 30.6, 21.6, 10.1; HRMS (ESI) $C_{20}H_{25}NO_3S$, $(M + H)^+$ found 360.1641, calcd 360.1633.

(*R*)-2-Phenyl-5-tosyl-1,5-oxazocane (12a). The general procedure for one-pot synthesis of morpholine homologues was followed when **2a** (100 mg, 0.35 mmol) was reacted with bromopropanol (0.32 mL, 3.5 mmol) at 0 °C for 30 min followed by cyclization with excess KOH (235.6 mg, 4.2 mmol) in dry THF at rt for 28 h to afford **12a** as a dense liquid (72 mg, 60% yield); $[\alpha]^{25}_D$ +53.1 (*c* 0.16, $CHCl_3$) for a 50% ee sample. Enantiomeric purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−isopropanol, 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; ^1H 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) $C_{19}H_{23}NO_3S$, $(M + Na)^+$ found 368.1292, calcd 368.1296.

(2*R*,4*R*)-4-Ethyl-2-phenyl-5-tosyl-1,5-oxazocane (12b). The general procedure for one-pot synthesis of morpholine homologues was followed when **2b** (100 mg, 0.32 mmol) reacts with bromopropanol (0.29 mL, 3.2 mmol) followed by cyclization with excess KOH (215.5 mg, 3.8 mmol) in dry THF at rt for 30 h to afford **12b** as the major diastereomer as a dense liquid (85 mg, 74% yield); $[\alpha]^{25}_D$ +63.5 (*c* 0.23, $CHCl_3$) for a >99% ee sample. R_f 0.37 (ethyl acetate−hexane, 1:4); IR ν_{max} (neat, cm^{-1}) 2922, 2854, 1335, 1156, 1104, 713, 697, 549; ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, 1H, J = 8.0 Hz), 7.30−7.21 (m, 7H), 4.52 (dd, 1H, J = 9.6, 1.6 Hz), 3.98−3.90 (m, 2H), 3.80−3.77 (m, 1H), 3.54−3.50 (m, 1H), 3.19−3.09 (m, 1H), 2.39 (s, 3H), 2.22−2.15 (m, 2H), 1.85−1.73 (m, 2H), 1.34−1.30 (m, 2H), 0.57 (t, 3H, J = 7.7 Hz); HRMS (ESI) $C_{21}H_{27}NO_3S$, $(M + H)^+$ found 374.1794, calcd 374.1789.

4-Tosyloctahydrocyclopenta[*b*][1,4]oxazine (19). The general procedure for one-pot synthesis of morpholines was followed when **15** (100 mg, 0.42 mmol) reacts with bromoethanol (0.38 mL, 4.2 mmol) at 0 °C for 7 h followed by cyclization with excess KOH (282 mg, 5.04 mmol) in dry THF at rt for 1 h to afford **19** as a white solid (99 mg, 84% yield); mp 115−116 °C; R_f 0.35 (ethyl acetate−hexane, 1:3); ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, 2H, J = 8.3 Hz), 7.29 (d, 2H, J = 8.1 Hz), 3.88 (dd, 1H, J = 10.5, 2.2 Hz), 3.71 (ddd, 1H, J = 11.7, 11.7, 2.4 Hz), 3.57−3.54 (m, 1H), 3.37−3.31 (m, 1H), 2.39 (s, 3H), 2.32 (ddd, 1H, J = 11.9, 11.7, 3.6 Hz), 2.16−2.13 (m, 1H), 1.99−1.81 (m, 3H), 1.67−1.60 (m, 1H), 1.37−1.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 131.9, 129.7, 128.0, 82.6, 67.1, 62.0, 47.7, 26.7, 25.3, 21.5, 17.1; HRMS (ESI) $C_{14}H_{19}NO_3S$, $(M + H)^+$ found 282.1162, calcd 282.1163.

(*S*)-Methyl-2-((*R*)-2-(4-methylphenylsulfonamido)-1-phenylethoxy)-2-phenylacetate (21). A solution of the aziridine (±) **1a** (200 mg, 0.732 mmol) and (*S*)-mandelic acid ester (304 mg, 1.83 mmol) in 5.0 mL dichloromethane was added to anhydrous copper triflate (52.9 mg, 0.146 mmol) at 0 °C under an argon atmosphere. The mixture was stirred for 2 h and then the reaction was quenched with aqueous saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane (3 × 5.0 mL) and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography using 15% ethyl acetate in hexane as eluent to afford pure products **21** and **22** as dense liquids in 1:1 ratio (272 mg, 85% combined yield); diastereomer **21**; R_f 0.28 (ethyl acetate−hexane, 3: 7); ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, 2H, J = 8.3 Hz), 7.27−7.19 (m, 10H), 7.09−7.07 (m, 2H), 5.96 (d, 1H, NH, J = 7.7 Hz), 4.67 (s, 1H), 4.37 (dd, 1H, J = 9.8, 2.7 Hz), 3.71 (s, 3H), 3.19−3.17 (m, 1H), 3.08−3.03 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 143.2, 137.6, 137.3, 135.9, 129.6, 128.7, 128.6, 128.5, 127.3, 127.0, 126.5, 80.8, 78.5, 52.6, 49.7, 21.5.

(*S*)-Methyl-2-(*S*)-2-(4-methylphenylsulfonamido)-1-phenylethoxy)-2-phenylacetate (22). Diastereomer **22**; R_f 0.24 (ethyl acetate−hexane, 3: 7); IR ν_{max} (neat, cm^{-1}) 2923, 1742, 1454, 1332, 1161, 1091, 701, 663, 554; ^1H NMR: (400 MHz, $CDCl_3$) δ 7.59 (d, 2H, J = 8.3 Hz), 7.39−7.38 (m, 2H), 7.33−7.12 (m, 12H), 5.09 (br s, 1H, NH), 4.64 (s, 1H), 4.23 (t, 1H, J = 6.8 Hz), 3.57 (s, 3H), 3.14 (d, 2H, J = 7.1 Hz), 2.39 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 143.2, 137.2,

135.5, 129.7, 129.2, 128.9, 128.8, 127.8, 127.1, 127.0, 78.2, 78.0, 52.2, 48.9, 21.5.

Acknowledgment. M.K.G. is grateful to IIT-Kanpur and DST, India. D.S. thanks IIT-Kanpur India for senior research fellowship.

Supporting Information Available: Spectroscopic data of other compounds, copies of ^{1}H and ^{13}C spectra for all new compounds, X-ray crystallographic structure of **25** and **26**, and HPLC chromatograms for ee determination. This material is available free of charge via the Internet at http://pubs.acs.org.