JOC*Note*

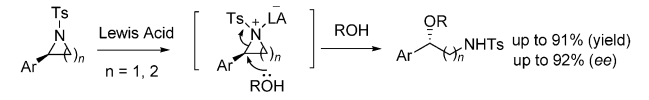
Lewis Acid-Mediated Highly Regioselective S_N2-Type Ring-Opening of 2-Aryl-*N*-tosylazetidines and Aziridines by Alcohols

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

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

mkghorai@iitk.ac.in

Received March 6, 2007



Lewis acid-mediated highly regioselective S_N2-type ring-opening of 2-aryl-*N*-tosylazetidines with alcohols to afford various 1,3-amino ethers in excellent yields with good enantiomeric excess is described. Similar S_N2-type ring-opening of chiral 2-phenyl-*N*-tosylaziridine with various alcohols produces the corresponding nonracemic 1,2-amino ethers in excellent yields and good ee. The mechanism of the ring-opening of aziridines and azetidines *via* an S_N2 pathway is supported by the formation of nonracemic amino ethers.

Aziridines and azetidines are valuable building blocks in organic synthesis because of their ability to undergo ring-opening,[1] cycloaddition,[2] and fragmentation[3] reactions. We have recently reported Lewis acid (LA)-mediated nucleophilic ring-opening and cycloaddition of 2-aryl-*N*-tosylazetidines and aziridines to provide nonracemic products, and a mechanism was proposed *via* an S_N2-type pathway to rationalize the formation of nonracemic products.[4] We anticipated LA-mediated ring-opening of aziridines and azetidines to follow S_N2 pathways which would enable the design of enantioselective ring-opening reactions of chiral aziridines and azetidines toward enantiopure targets.

During our synthetic and mechanistic investigations on LA-mediated ring-opening of azetidines, we have developed an efficient strategy for nucleophilic ring-opening of 2-aryl-*N*-sulfonylazetidines followed by (i) a novel rearrangement to allylamines[5a] and (ii) [4 + 2] cycloaddition with carbonyl compounds to nonracemic 1,3-oxazinanes.[5b] Our observations provide convincing evidence that the rearrangement or the cycloaddition proceeds through an S_N2-type pathway, instead of a 1,4-dipole as invoked earlier.[2e−g] We have also demonstrated the ring-opening of chiral 2-phenyl-*N*-tosylaziridine followed by cycloaddition with carbonyl compounds to give a variety of nonracemic 1,3-oxazolidines *via* an S_N2-type pathway.[5c] To rule out the S_N1 pathway through the intermediacy of a stable 1,4-dipole, the nucleophilic ring-opening of 2-aryl-*N*-tosylazetidines **1** in polar and protic alcohol (methyl, benzyl, propargyl, etc.) medium was studied where the solvent served as the nucleophile. We report, herein, an expedient approach for a direct access to nonracemic 1,3-amino ethers with excellent yields and high ee (up to 90%) by the regioselective nucleophilic ring-opening of chiral 2-phenyl-*N*-tosylazetidine with alcohols. Biologically active amino ethers of general structure **2** (Figure 1) are widely used for the treatment of anxiety and depression and their analogues belong to a class of potent and selective serotonin and norepinephrin reuptake inhibitors.[6−9]

Although few reports are available in the literature for the synthesis of 1,3-amino ethers,[10] there is no report for the synthesis of these amino ethers *via* LA-mediated nucleophilic ring-opening of 2-aryl-*N*-tosylazetidines with alcohols. Chiral 1,2-amino ethers as essential fragments in many glycopeptide antibiotics[11] and ether-containing peptide bond surrogate units[12] are important for several biological processes. Alkoxide- or

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

(1) For ring opening of aziridines: (a) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701−2743 and references cited therein. (b) Minakata, S.; Okada, Y.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett*. **2005**, *7*, 3509−3512. (c) Ding, C. H.; Dai, L. X.; Hou, X. L. *Tetrahedron* **2005**, *61*, 9586−9593. (d) Pineschi, M.; Bertolini, F.; Haak, R. M.; Crotti, P.; Macchia, F. *Chem. Commun*. **2005**, 1426−1428. (e) Minakata, S.; Hotta, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2006**, *71*, 7471−7472. (f) Fukuta, Y.; Mita, T.; Fukuda, N.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2006**, *128*, 6312−6313. (g) De Kimpe, N. Three- and Four-Membered Rings, With All Fused Systems Containing Three- and Four-Membered Rings. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Elsevier: Oxford 1996; Vol. 1, Chapter 1.21. For ring opening of azetidines: (h) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1994**, *50*, 5775−5782. (i) Akiyama, T.; Daidouji, K.; Fuchibe, K. *Org. Lett*. **2003**, *5*, 3691−3693. (j) Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett*. **2005**, *7*, 5861−5864. (k) Domostoj, M.; Ungureanu, I.; Schoenfelder, A.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2006**, *47*, 2205−2208. (l) Van Brabandt, W.; Van Landeghem, R.; De Kimpe, N. *Org. Lett*. **2006**, *8*, 1105−1108. (m) Golding, P; Millar, R. W.; Paul, N. C.; Richards, D. H. *Tetrahedron* **1995**, *51*, 5073−5082. (n) Vanecko, J. A.; West, F. G. *Org. Lett*. **2005**, *7*, 2949−2952.

(2) For cycloaddition of aziridines: (a) Concellón, J. M.; Riego, E.; Suárez, J. R.; García-Granda, S.; Díaz, M. R. *Org. Lett.* **2004**, *6*, 4499−4501. (b) Zhu, W.; Cai, G.; Ma, D. *Org. Lett*. **2005**, *7*, 5545−5548. (c) Ghorai, M. K.; Ghosh, K.; Das, K. *Tetrahedron Lett.* **2006**, *47*, 5399−5403 and references cited therein. For cycloaddition of azetidines: (d) Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Chem. Commun*. **2001**, 958−959. (e) Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Tetrahedron Lett.* **2001**, *42*, 6087−6091. (f) Prasad, B. A. B.; Bisai, A.; Singh, V. K. *Org. Lett.* **2004**, *6*, 4829−4831. (g) Yadav, V. K.; Sriramurthy, V. *J. Am. Chem. Soc*. **2005**, *127*, 16366−16367. (h) Baeg, J. O.; Bensimon, C.; Alper, H. *J. Org. Chem*. **1995**, *60*, 253−256. (i) Baeg, J. O.; Bensimon, C.; Alper, H. *Ibid*. **1995**, *60*, 3092−3095.

(3) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Salgado, N. R. *J. Org. Chem*. **1999**, *64*, 9596−9604 and the referrences cited therein.

(4) (a) Ghorai, M. K.; Das, K.; Kumar, A.; Ghosh, K. *Tetrahedron Lett.* **2005**, *46*, 4103−4106. (b) Ghorai, M. K.; Das, K.; Kumar, A.; Das, A. *Tetrahedron Lett.* **2006**, *47*, 5393−5397. (c) Ghorai, M. K.; Ghosh, K.: Das, K. *Tetrahedron Lett.* **2006**, *47*, 5399−5403.

(5) (a) Ghorai, M. K.; Kumar, A.; Das, K. Unpublished results. (b) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, doi: 10.1016/j.tetlet.2007.04.097. (c) Ghorai, M. K.; Ghosh, K. *Tetrahedron Lett*. **2007**, *48*, 3191−3195.

(6) Robertson, D. W.; Jones, N. D.; Swartzendruber, J. K.; Yang, K. S.; Wong, D. T. *J. Med. Chem*. **1988**, *31*, 185−189 and references cited therein.

(7) Silver, H. *Int. Clin. Psychopharm.* **2003**, *18*, 305−313.

(8) Wong, D. T.; Bymaster, F. P.; Engleman, E. A. *Life Sci*. **1995**, *57*, 411−441.

(9) Chouinard, G.; Annable, L.; Bradwejn, J. *Psychopharmacology* **1984**, *83*, 126−128.

10.1021/jo0703294 CCC: $37.00
Published on Web 06/26/2007

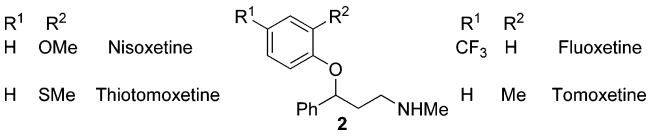
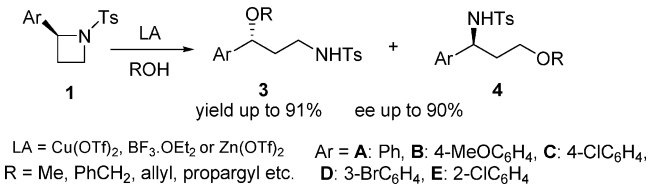


FIGURE 1. Representative biologically active amino ethers.

SCHEME 1. Lewis Acid-Mediated Regioselective Nucleophilic Ring-Opening of 2-Aryl-*N*-tosylazetidines with Alcohols

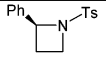
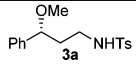
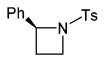
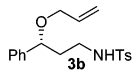
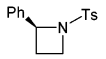
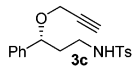
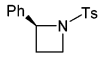
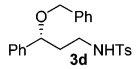
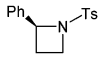
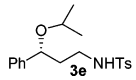


LA = $Cu(OTf)_2$, $BF_3.OEt_2$ or $Zn(OTf)_2$ Ar = **A**: Ph, **B**: 4-$MeOC_6H_4$, **C**: 4-ClC_6H_4,
R = Me, $PhCH_2$, allyl, propargyl etc. **D**: 3-BrC_6H_4, **E**: 2-ClC_6H_4

Bronsted acid-mediated alcoholyses of aziridines has been reported by Stamm et al. where a borderline S_N2-type mechanism was mentioned.[13a] Similar opening of *N*-nosyl aziridine[13b] by MeOH is reported by Maligres et al. There are few reports known for KSF clay[13c] or LA-mediated[13d] ring-opening of aziridines with alcohols to racemic 1,2-amino ethers without illustrating proper mechanism of the reaction.[13c,d] Some amino ethers prepared from other methods have been effectively used as chiral ligands for asymmetric transformations.[14] In this article, we describe a direct route to nonracemic 1,2-amino ethers (up to 92% ee) by LA-mediated regioselective nucleophilic ring-opening of chiral 2-phenyl-*N*-tosylaziridine **5** with alcohols *via* an S_N2 pathway.

Our study began with the ring-opening of enantiomerically pure (*S*)-2-phenyl-*N*-tosylazetidine **1A** (ee >99%)[15] in polar protic solvents, such as various alcohols. When (*S*)-**1A** was treated with MeOH in the presence of LA, to our great pleasure, we observed the formation of nonracemic 1,3-amino ether **3a** in good yield with excellent ee (86−90%) (Scheme 1). Ring-opening of **1A** with MeOH in the presence of $Cu(OTf)_2$ was found to be highly regioselective and only one regioisomer **3a** was formed as indicated by the ^1H NMR of the crude reaction mixture.

TABLE 1. $Cu(OTf)_2$-Mediated Regioselective Nucleophilic Ring-Opening of 2-Phenyl-*N*-tosylazetidine with Alcohols[a]

entry	azetidine **1A**	alcohols	product **3**	time (h)	temp (°C)	yield (%)[b]	*ee* (%)[c]
1		MeOH	 **3a**	4 h	60	70	86[d]
2			 **3b**	24 h	25	87	78
3			 **3c**	1.5 h	-25	91	82[e]
4		$PhCH_2OH$	 **3d**	1 h	0	55	68
5			 **3e**	24 h	25	63	64[f]

[a] In all the cases the alcohol served as the solvent. [b] Yield of isolated product after column chromatographic purification. [c] Determined by chiral HPLC. [d] 90% ee was obtained at 40 °C. [e] At 0 °C reaction was completed in 10 min and 76% ee was obtained. [f] 20% CH_2Cl_2 in ^{i}PrOH was used as the solvent.

Formation of the other regioisomer **4a** from the terminal attack of **1A** was not observed. To demonstrate the general value of this strategy, ring-opening of (*S*)-**1A** was studied with a number of alcohols (allyl, benzyl, propargyl, etc.), and the results are summarized in Table 1. (*S*)-**1A** gave ring opened product **3c** in 91% yield with 76% ee within 10 min at 0 °C when propargyl alcohol was used in the presence of $Cu(OTf)_2$. The reaction time was reduced to 5 min for the same reaction performed in CH_2Cl_2 as the solvent with 5 equiv of the alcohol; however, the enantioselectivity was found to be poor (ee 44%). A little variation of ee was observed when $BF_3{\cdot}OEt_2$ or $Zn(OTf)_2$ was used as the LA. **1A** was found to be less reactive with secondary alcohol (^{i}PrOH) and a reduced yield of the corresponding amino ether **3e** was obtained at ambient temperature. Under similar reaction conditions, more sterically crowded ^{t}butyl alcohol failed to give any ring-opening product with **1A**. The reaction did not proceed well with catalytic amount (0.3 equiv) of LA and 1 equiv of catalyst was required for completion of the reaction. To broaden the scope of this strategy, the ring-opening of a number of substituted *N*-tosylazetidines **1B**−**E** with various alcohols was studied, and the corresponding 1,3-amino ethers **3f**−**m** were obtained in excellent yields (Table 2). Azetidines **1D**,**E** (entries 7, 8, Table-2) reacted slowly with propargyl alcohol in comparison with **1A**−**C** (entry 3 Table 1 and entries 1, 5, Table 2). All azetidines reacted faster with propargyl and benzyl alcohols compared to other alcohols. However, 2-benzyl-*N*-tosylazetidine reacted slowly (10 h) with propargyl alcohol to produce 4-phenyl-3-(prop-2-ynyloxy)-*N*-tosylbutan-1-amine in 51% yield.[16] The reaction was found to be more facile in CH_2Cl_2 instead of alcohols serving as the solvent. Using *o*-cresol in CH_2Cl_2, **1A** furnished regioisomers **3i** and **4i** in a 1:1 ratio. The formation of other regioisomer **4i** can be ascribed to the steric repulsion caused by methyl group in *o*-cresol during nucleophilic attack at benzylic position.

(10) (a) Li, Y.; Li, Z.; Li, F.; Wang, Q.; Tao, F. *Org. Bimol. Chem.* **2005**, *3*, 2513−2518. (b) Watanabe, M.; Murata, K.; Ikariya, T. *J. Org. Chem.* **2002**, *67*, 1712−1715. (c) O'Brien, P.; Phillips, D. W.; Towers, T. D. *Tetrahedron Lett.* **2002**, *43*, 7333−7335. (d) Kumar, P.; Upadhyay, R. K.; Pandey, R. K. *Tetrahedron: Asymmetry* **2004**, *15*, 3955−3959. (e) Kamal, A.; Khanna, G. B. R.; Ramu, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2039−2051. (f) Bhandari, K.; Srivastava, S.; Shanker, G.; Nath, C. *Bioorg. Med. Chem.* **2005**, *13*, 1739−1747.

(11) Boger, D. L.; Kim, S. H.; Mori, Y.; Weng, J. H.; Rogel, O.; Castle, S. L.; McAtee, J. J. *J. Am. Chem. Soc.* **2001**, *123*, 1862−1871 and references cited there in.

(12) Ho, M.; Chung, J. K. K.; Tang, N. *Tetrahedron Lett.* **1993**, *34*, 6513−6516.

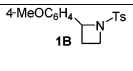
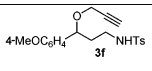
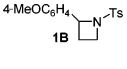
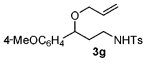
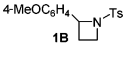
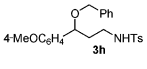
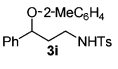
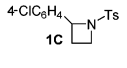
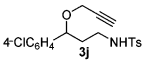
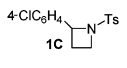
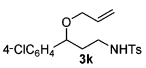
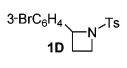
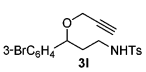
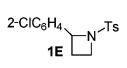
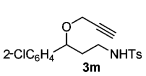
(13) (a) Bucholz, B.; Stamm, H. *Isr. J. Chem.* **1986**, *27*, 17−23. (b) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253−5256. (c) Yadav, J. S.; Reddy, B. V. S.; Balanarsaiah, E.; Raghavendra, S. *Tetrahedron Lett.* **2002**, *43*, 5105−5107. (d) Prasad, B. A. B.; Sanghi, R.; Singh, V, K. *Tetrahedron* **2002**, *58*, 7355−7363.

(14) (a) Hodgson, D. M.; Štefane, B.; Miles, T. J.; Witherington, J. *Chem. Commun.* **2004**, 2234−2235. (b) Furth, P. S.; Reitman, M. S.; Gentles, R.; Cook, A. F. *Tetrahedron Lett.* **1997**, *38*, 6643−6646. (c) Sott, R.; Granander, J.; Hilmersson, G. *J. Am. Chem. Soc.* **2004**, *126*, 6798−6805. (d) Ramírez, A.; Lobkovsky, E.; Collum, D. B.; *J. Am. Chem. Soc.* **2003**, *125*, 15376−15387. (e) Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585−4586. (e) Inoue, I.; Shindo, M.; Koga, K.; Tomioka, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1603−1606. (f) Periasamy, M.; Seenivasaperumal, M.; Rao, V. D. *Tetrahedron: Asymmetry* **2004**, *15*, 3847−3852. (g) Aravind, A.; Mohanty, S. K.; Pratap, T. V.; Baskaran, S. *Tetrahedron Lett.* **2005**, *46*, 2965−2968.

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

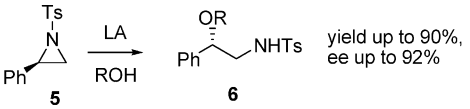
(16) Details are provided in the Supporting Information.

TABLE 2. Cu(OTf)$_2$-mediated Nucleophilic Ring-Opening of Racemic 2-Aryl-*N*-tosylazetidines with Alcohols[a]

entry	azetidine **1**	alcohols	product **3**	time (h)	temp (°C)	yield (%)[b]	ratio **3**:**4**[c]
1	 **1B**		 **3f**	5 min	0	91	100:0
2	 **1B**		 **3g**	15 min	0	85	100:0
3	 **1B**	$PhCH_2OH$	 **3h**	15 min	25	55	100:0
4	 **1A**	*o*-cresol	 **3i**	10 min	0	30[d]	50:50
5	 **1C**		 **3j**	30 min	0	91	100:0
6	 **1C**		 **3k**	6 h	25	85	100:0
7	 **1D**		 **3l**	1.5 h	25	87	100:0
8	 **1E**		 **3m**	3 h	25	85	100:0

[a] In all the cases CH_2Cl_2 served as the solvent. [b] Yield of isolated product after column chromatographic purification. [c] Determined by ^{1}H NMR. [d] Additionally 30% of **4i** were received.

SCHEME 2. LA-Mediated Regioselective Nucleophilic Ring-Opening of (*R*)-5 with Alcohols

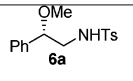
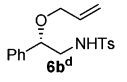
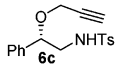
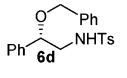


LA = Cu(OTf)$_2$, BF_3.OEt$_2$ or Zn(OTf)$_2$ R = **a**: Me, **b**: allyl, **c**: propargyl,**d**: $PhCH_2$

After successful demonstration of the strategy for the ring-opening of azetidines, we envisaged that a straightforward approach to nonracemic 1,2-amino ethers **6** would be realized by the ring-opening of enantiomerically pure (*R*)-2-phenyl-*N*-tosylaziridine **5** (ee >99%) with alcohols in the presence of LA (Scheme 2). We have studied the ring-opening of (*R*)-**5** with various alcohols, and in all the cases corresponding amino ethers **6** were obtained in high yields with good to excellent ee (Table 3). When (*R*)-2-phenyl-*N*-nosylaziridine (>99% ee) was reacted with methanol, the reaction was completed in 2.5 h to produce the corresponding amino ether in 91% yield with 94% ee.[16] The nucleophilic ring-opening of 2-phenyl-*N*-tosylaziridines with alcohols was found to be more facile compared to 2-phenyl-*N*-tosylazetidines. This is probably because of more inherent strain present in the aziridine nucleus in comparison with azetidine.

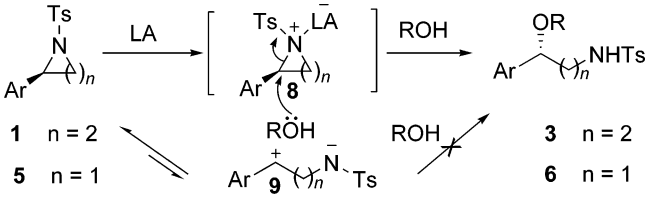
The full mechanistic interpretations for the ring-opening of optically active (*S*)-2-phenyl-*N*-tosylazetidine **1A** and (*R*)-2-phenyl-*N*-tosylaziridine **5** with alcohols *via* S_N2 pathways have been firmly established by the generation of nonracemic amino ethers (**3a** and **6a**, respectively) with inverted absolute configurations. In order to determine the absolute configuration of the major enantiomer of **3a** obtained from the nucleophilic ring-opening of (*S*)-**1A** with MeOH, it was converted into (*R*)-3-methoxy-*N*-methyl-3-phenyl-*N*-tosylpropan-1-amine and its absolute configuration was assigned by comparing optical rotation and chiral HPLC analysis with an authentic sample[17] prepared from (*S*)-mandelic acid with ee >99%. Similarly, the absolute

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

entry	aziridine **5**	alcohols	product **6**	time (h)	temp (°C)	yield (%)[b]	*ee* (%)[c]
1		MeOH	 **6a**	4 h	25	82	92
2			 **6b**[d]	25 min	25	85	-
3			 **6c**	5 min	0	90	60
4		$PhCH_2OH$	 **6d**	15 min	25	76	80

[a] In all the cases the alcohol served as the solvent. [b] Yield of isolated product after column chromatographic purification. [c] Determined by chiral HPLC. [d] Nonracemic **6b** is inseparable in both AD and OD HPLC columns.

SCHEME 3. Mechanism for the LA-Mediated Ring-Opening of 2-Phenyl-*N*-tosylazetidines and Aziridine with Alcohols



LA = Cu(OTf)$_2$, BF_3.OEt$_2$ or Zn(OTf)$_2$

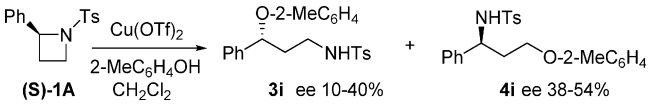
configuration of 1,2-amino ether **6a** was ascertained.[18] On the basis of the above facts, we suggest that the ring-opening of chiral 2-phenyl-*N*-tosylazetidine and aziridine with alcohols proceeds *via* an S_N2 pathway as depicted in Scheme 3. LA is coordinated to the azetidine **1** ($n = 2$) or aziridine **5** ($n = 1$) nitrogen, generating a highly reactive species **8**, which undergoes nucleophilic attack by alcohols in an S_N2 fashion to provide nonracemic **3** or **6**, respectively.

It is clear that the reaction does not proceed through a stable benzylic carbocation intermediate **9** from which a racemic product could be expected either from enantiomerically pure (*S*)-**1A** or (*R*)-**5**. We rationalized that the reduced enantioselectivity in all the cases was due to partial racemization of starting azetidine or aziridine (through the interconversion of **1**/**5** and **9**) before the nucleophilic ring-opening step as shown in Scheme 3. This mechanistic proposal is supported by the formation of racemized amino ether **4i** (38−54% ee) from the reaction of (*S*)-**1A** with varying amount of *o*-cresol in CH_2Cl_2 where enantiomerically pure **4i** could be expected from enantiomerically pure (*S*)-**1A** (Scheme 4). Furthermore, (*S*)-**1A** was found to be racemized in the presence of Cu(OTf)$_2$ without any nucleophile.[16]

(17) The absolute configuration of 1,3-amino ether prepared from (*S*)-mandelic acid and that obtained from (*S*)-2-phenyl-*N*-tosylazetidine is the same. Details of the preparation of authentic compound are provided in the Supporting Information.

(18) The absolute stereochemistry for the major enantiomer of **6a** was determined by compairing optical rotation and chiral HPLC analysis of an authentic compound (ee 98%) prepared from (*S*)-mandelic acid (ee > 99%). The absolute configuration of 1,2-amino ether prepared from (*S*)-mandelic acid and that obtained from (*R*)-2-phenyl-*N*-tosylaziridine is the same. Details of the preparation of authentic compound for (*S*)-**6a** is provided in the Supporting Information.

SCHEME 4. LA-Mediated Ring-Opening of (*S*)-1A with *o*-Cresol



In conclusion, we have demonstrated that the nucleophilic ring-opening of 2-aryl-*N*-tosylazetidines or aziridines does proceed through an S_N2 pathway instead of a stable 1,4- or 1,3-dipolar intermediate, respectively. We report a direct synthesis of optically active 1,3- and 1,2-amino ethers from enantiopure *N*-tosylazetidine and aziridine, respectively. Utilizing this approach, biologically active amino ether precursors could be obtained easily. Further applications of this methodology are under investigation in our laboratory.

Experimental Section

General Procedure for the $Cu(OTf)_2$-Mediated Ring-Opening of 2-Aryl-*N*-tosylazetidine and -aziridine with Alcohols (method A). A solution of the azetidine (0.087 mmol, 1.0 equiv) or azirdine (0.091 mmol, 1.0 equiv) in 1.0 mL of alcohol was added to anhydrous $Cu(OTf)_2$ (1.0 equiv) at an appropriate temperature under an argon atmosphere. The mixture was stirred for an appropriate time (Table 1/Table 3), and then the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (3 × 5.0 mL) and dried over anhydrous Na_2SO_4. 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 nonracemic products. Important note: In CH_2Cl_2 reaction was completed in a shorter time with better yields; however, the enantioselectivity was reduced. General experimental method B is described in the Supporting Information.

(***R*)-3-Phenyl-3-(prop-2-ynyloxy)-*N*-tosylpropan-1-amine** (**3c**). The general method A described above was followed when (*S*)-**1A** reacted with propargyl alcohol to afford **3c** as a dense liquid in 91% yield; $[\alpha]_D^{25}$ +67.5 (*c* 0.126 in $CHCl_3$) for a 76% ee sample (ee 82% when the reaction was performed at −25 °C for 1.5 h). Optical purity was determined by chiral HPLC analysis (Chiralcel OD-H column), hexane−2-propanol, 90:10; flow rate = 1.0 mL/min; $T_R(1)$: 18.12 min (major), $T_R(2)$: 23.84 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, 2H, J = 7.3, 1.2 Hz), 5.03 (t, 1H, J = 5.9 Hz), 4.48 (dd, 1H, J = 9.0, 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, ESI-MS *m*/*z* = 344 (M^+ + 1); Anal. Calcd (%) for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08; Found (%) C, 66.39; H, 6.29; N, 4.29.

(*S*)-2-Methoxy-2-phenyl-*N*-tosylethanamine (**6a**). The general method A described above was followed when (*R*)-**5** reacted with MeOH to afford **6a** as a white solid in 82% yield, mp 105 °C; $[\alpha]_D^{25}$ +89.8 (*c* 0.345 in $CHCl_3$) for a 92% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel AD-H column), hexane−2-propanol, 95:5; flow rate = 1.0 mL/min; $T_R(1)$: 26.04 min (minor), $T_R(2)$: 28.08 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; ^1H 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, 128.6, 128.4, 127.0, 126.5, 82.4, 56.8, 49.3, 21.5; Anal. Calcd (%) for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59; Found (%) C, 62.65; H, 6.19; N, 4.55.

Acknowledgment. M.K.G. is grateful to IIT-Kanpur and DST, India. K. Das and D. Shukla thank IIT-Kanpur, India, for research fellowships.

Supporting Information Available: General experimental procedures, spectroscopic data, copies of ^1H and ^{13}C spectra for all new compounds and HPLC chromatograms for ee determination. This material is available free of charge *via* the Internet at http://pubs.acs.org.

JO0703294