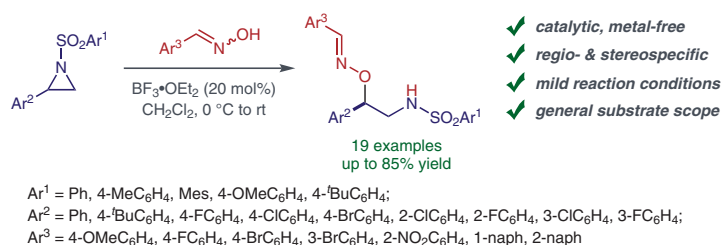


Facile Synthesis of Oxime Amino Ethers via Lewis Acid Catalyzed S_N2 -Type Ring Opening of Activated Aziridines with Aryl Aldehyde Oximes

Aditya Bhattacharyya^{1b}
 Subhomoy Das
 Navya Chauhan
 Pronay K. Biswas
 Manas K. Ghorai^{1b}

Indian Institute of Technology Kanpur, Kanpur 208016, Uttar Pradesh, India
 mkghorai@iitk.ac.in



Received: 20.12.2019
 Accepted after revision: 21.01.2020
 Published online: 02.03.2020
 DOI: 10.1055/s-0039-1691596; Art ID: st-2019-k0681-l

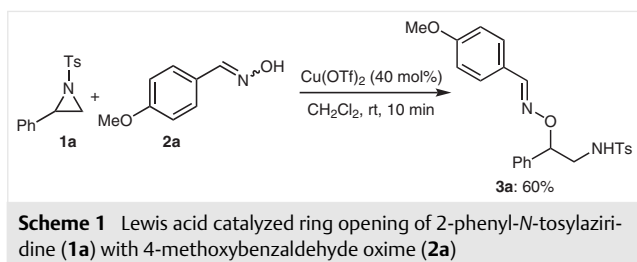
Abstract A simple strategy to access a wide range of substituted oxime amino ethers in good to high yields via Lewis acid catalyzed S_N2 -type ring opening of activated aziridines with aryl aldehyde oximes is reported.

Key words aziridine, oxime, oxime ether, Lewis acid catalyst, S_N2 -type ring opening, stereoselectivity

Oxime ethers have been used as valuable synthons for the preparation of a wide spectrum of biologically significant molecular moieties such as chiral α -, β -, and γ -amino acid derivatives,¹ γ -butyrolactones,² primary amines,³ benzofurans,⁴ pyrrolidines and piperidines,⁵ C-glycosylthreonine and allothreonine,⁶ chiral ligands,⁷ and α -amino esters.⁸ In addition, oxime ethers have also been used as a suitable class of radical acceptors under various photochemical⁹ and nonphotochemical conditions,^{1b,c} as auxiliary linkers,¹⁰ as directing group for C–H functionalization,¹¹ and as coupling partners in annulation reactions with olefins.¹² The available reports for the synthesis of oxime ethers mainly involve etherification of oximes¹³ – another valuable functional group in organic synthesis.¹⁴ Dehydrogenative cross-coupling reaction between allylic sp^3 C–H bonds with oximes¹⁵ have also been performed to access oxime ethers. In this context, we realized that regio- and stereospecific synthetic routes to functionalized and structurally diverse oxime amino ethers are scarce in the literature which could nonetheless emerge as potential synthons for valuable biologically active compounds.

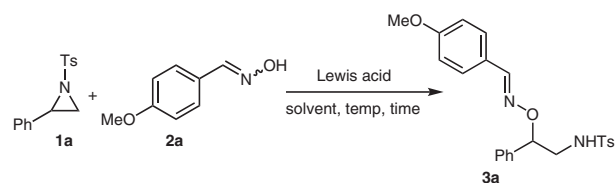
In recent years, the small-ring aza-heterocycles have emerged as one of the most advantageous building blocks in organic synthesis.¹⁶ We have been working on Lewis acid catalyzed S_N2 -type ring-opening transformations of activated aziridines and azetidines to access various value-added aza-heterocyclic compounds either by ring-opening cyclization (ROC)¹⁷ or by domino ring-opening cyclization (DROC)¹⁸ strategies. Notably, aziridin-1-yl oximes have drawn attention from the synthetic chemists owing to their cytotoxic activity that make them potential anticancer agents.¹⁹ Its prevalent chemistry involves the intramolecular ring-opening reactions of the aziridine functionality with the hydroxylamine group under suitable reaction conditions.^{19,20} A very few literature reports describe intermolecular ring opening of aziridines with hydroxylamine anions in the presence of a strong base,²¹ or with the nitrogen center of the oximes²² or with α -carbanion of the oxime functionalities.²³ Ring opening of aziridines with nitrones is also documented.^{18c} We anticipated that a wide variety of oxime amino ethers could easily be obtained via Lewis acid catalyzed intermolecular S_N2 -type ring opening of activated aziridines with aryl aldehyde oximes. Herein, we wish to report our preliminary results as a letter.

To test the viability of our approach, we performed a preliminary experiment with the reaction of racemic 2-phenyl-*N*-tosylaziridine (**1a**) with 1.5 equivalents of 4-methoxybenzaldehyde oxime (**2a**) in the presence of 40 mol % Cu(OTf)₂ as the Lewis acid in dichloromethane at room temperature. To our delight, the ring opening of the aziridine **1a** occurred at the benzylic position, and the corresponding 2-phenyl substituted oxime amino ether derivative **3a** was formed in 60% yield as a single regioisomer (Scheme 1). The molecular structure of **3a** was characterized by its spectral and analytical data.²⁴



Next to optimize the reaction conditions for achieving better yields of the product, several other non-nucleophilic metal salts as the Lewis acids and solvents, such as 1,2-dichloroethane and tetrahydrofuran, were screened.

Table 1 Optimization Studies for the Lewis Acid Catalyzed Ring Opening of 2-Phenyl-*N*-tosylaziridine (**1a**) with 4-Methoxybenzaldehyde Oxime (**2a**)

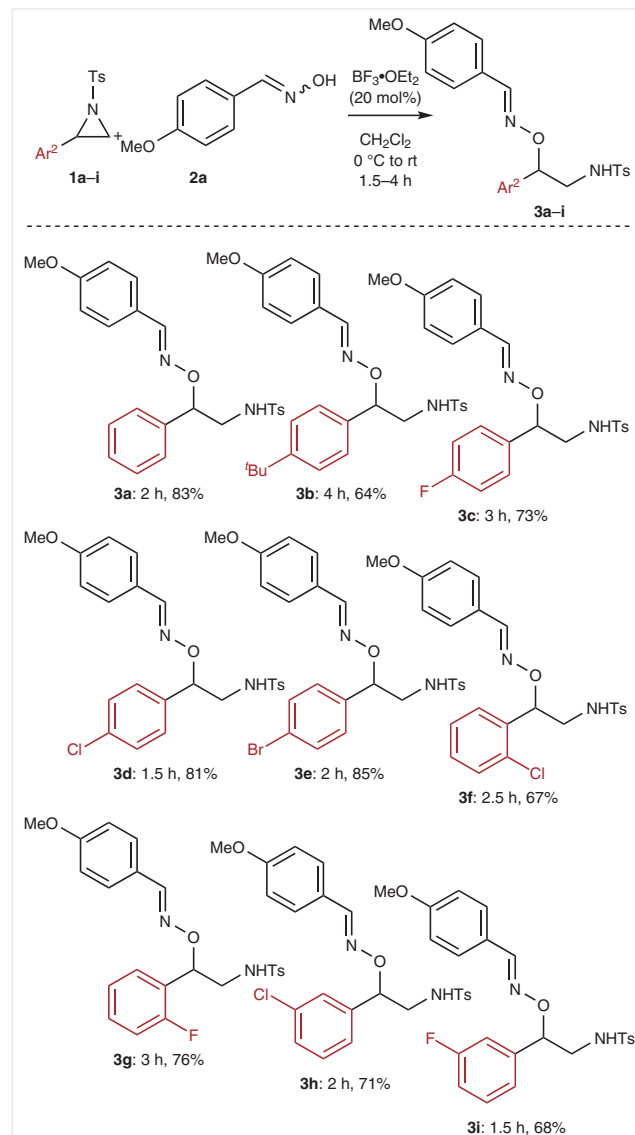


Entry	Lewis acid (mol%)	Solvent	Temp	Time	Yield (%) ^a
1	Cu(OTf) ₂ (40)	CH ₂ Cl ₂	rt	10 min	60
2	Cu(OTf) ₂ (40)	THF	rt	3 h	43
3	Cu(OTf) ₂ (40)	(CH ₂) ₂ Cl ₂	rt	30 min	55
4	Sc(OTf) ₃ (40)	CH ₂ Cl ₂	rt	1 h	53
5	Zn(OTf) ₂ (40)	CH ₂ Cl ₂	rt	1.5 h	68
6	Yb(OTf) ₃ (40)	CH ₂ Cl ₂	rt	2 h	41
7	Mg(OTf) ₂ (40)	CH ₂ Cl ₂	rt	24 h	nr
8	BF ₃ ·OEt ₂ (40)	CH ₂ Cl ₂	rt	1 h	76
9	BF ₃ ·OEt ₂ (20)	CH ₂ Cl ₂	0 °C to rt	2 h	83

^a Yields of isolated products after column chromatographic purification.

All the results are shown in Table 1. The use of Cu(OTf)₂ furnished the product in short time with moderate yield (entry 1). Changing the solvents from CH₂Cl₂ to either THF (entry 2) or 1,2-DCE (entry 3) led to the formation of the product **3a** with reduced yields. The yield of the reaction further decreased with Sc(OTf)₃ (53%, entry 4). Encouraging result was obtained with Zn(OTf)₂, and the desired product could be obtained in 68% yield in 1.5 h (entry 5). The use of water-resistant Lewis acid Yb(OTf)₃ afforded **3a** in poor yield (41%, entry 6). No reaction was observed when a milder Lewis acid such as Mg(OTf)₂ was used (entry 7). Notable increase in the yield was observed when 40 mol% BF₃·OEt₂ was used, and **3a** was obtained in 76% yield (entry 8). The best result was obtained with 20 mol % BF₃·OEt₂ as the

Lewis acid at 0 °C to room temperature, and **3a** was obtained in 83% yield (entry 9). When the amount of Lewis acid was further decreased, the reaction was found to be sluggish.

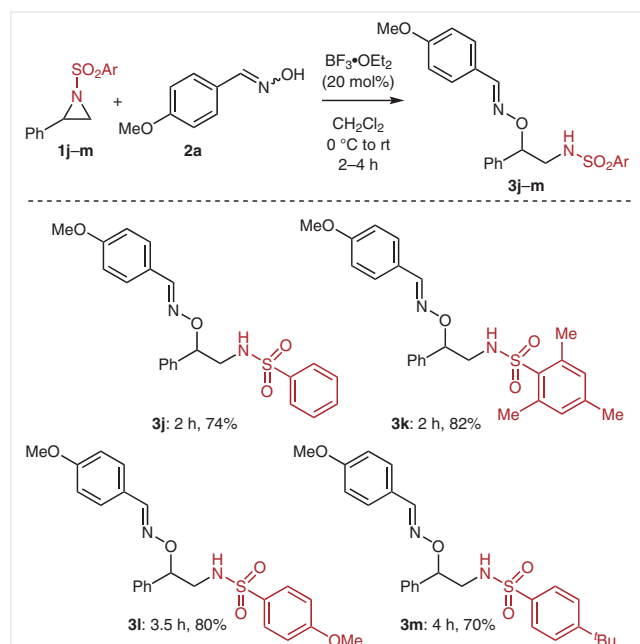


To generalize the strategy a wide range of 2-aryl-*N*-tosylaziridines bearing variety of substitution patterns on the aryl groups under the optimized reaction condition were studied. All the results are tabulated in Scheme 2. When the aziridine **1b** with a strong electron-donating *tert*-butyl group at the 4-position of the 2-phenyl group was used, the corresponding ring-opened product **3b** was formed as a single regioisomer in good yield (64%). Interestingly, when aziridines **1c-e** bearing halogen groups (F, Cl, and Br) at the 4-position of the 2-phenyl group were reacted, the respective oxime amino ethers **3c-e** were obtained in high yields.

With relatively more sterically constrained aziridines with halogen groups at the 2-position of the 2-phenyl groups **1f** (Cl) and **1g** (F), the respective oxime amino ethers **3f** and **3g** were obtained in 67% and 76% yields.

A marginal reduction in yield was observed with 2-(3-halophenyl)-substituted aziridines **1h** (Cl) and **1i** (F), and the corresponding ring-opened products **3h** and **3i** were furnished in 71% and 68% yields, respectively.

To study the electronic effect of the *N*-arylsulfonyl groups, a variety of *N*-arylsulfonylaziridines **1j–m** with varying electron-withdrawing ability on the nitrogen were reacted with 4-methoxybenzaldehyde oxime (**2a**) under the optimized reaction conditions, and the results are shown in Scheme 3.

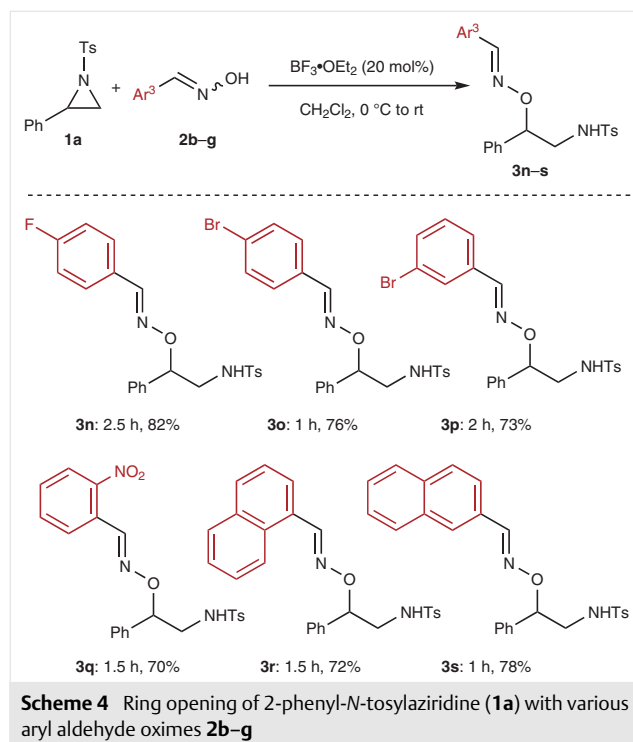


Scheme 3 Ring opening of various 2-phenyl-*N*-arylsulfonylaziridines **1j–m** with 4-methoxybenzaldehyde oxime (**2a**)

The *N*-benzenesulfonyl aziridine **1j** reacted smoothly with **2a** and furnished the corresponding product **3j** in 74% yield. On the other hand, with strong electron-donating groups such as 2,4,6- Me_3 (mesityl; **1k**), OMe (**1l**), or *t*-Bu (**1m**) attached with the phenylsulfonyl group of the aziridine, the respective oxime amino ethers **3k–m** were formed as single regioisomers in excellent yield (up to 82%).

To further investigate the substrate tolerance, a wide range of aryl aldehyde oximes **2b–g** were employed as the nucleophiles. Accordingly, when *p*-halo-substituted benzaldehyde oxime derivatives **2b** (F) and **2c** (Br) reacted with **1a**, the corresponding oxime amino ethers **3n** and **3o** were obtained in 82% and 76% yields, respectively. The 3-Br variant **2d** was also reacted efficiently, and **3p** was formed in good yield (73%). When **2e** with a nitro group at the 2-position of the aryl group was reacted with **1a**, the correspond-

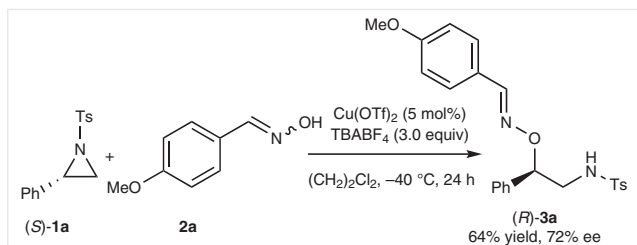
ing product **3q** was obtained in 70% yield. Interestingly, when sterically congested 1-naphthaldehyde oxime (**2f**) and 2-naphthaldehyde oxime (**2g**) were employed as the nucleophiles, the reactions proceeded well, and the products **3r** and **3s** were obtained in 72% and 78% yields, respectively, in short time. All the results are summarized in Scheme 4.



Scheme 4 Ring opening of 2-phenyl-*N*-tosylaziridine (**1a**) with various aryl aldehyde oximes **2b–g**

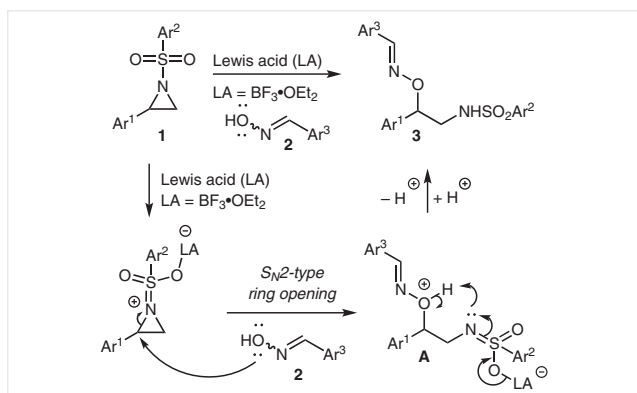
Additional significance of our protocol was validated in the synthesis of nonracemic oxime amino ether derivative (*R*)-**3a** from (*S*)-**1a**. As we demonstrated in our earlier reports that the tetraalkylammonium salts could effectively control the racemization process of the enantiopure aziridines during the reaction,²⁵ we used a number of such salts in stoichiometric amount to enhance the stereospecificity of the product. After several screenings when (*S*)-**1a** was treated with 10.0 equivalents of **2a** at -40 °C in the presence of 5 mol% $\text{Cu}(\text{OTf})_2$ as the Lewis acid and 3.0 equivalents of tetrabutylammonium tetrafluoroborate (TBABF_4) as the additive using 1,2-dichloroethane as the solvent, the desired product **3a** was obtained in good yield with up to 72% enantiomeric excess (Scheme 5).

A plausible mechanistic pathway is shown in Scheme 6. Based on the experimental observations, we propose that the Lewis acid catalyzed ring opening of the activated aziridines with aryl aldehyde oximes proceeds via an $\text{S}_\text{N}2$ -type pathway as demonstrated by us earlier.^{17,18} At first, the Lewis acid gets coordinated with the nitrogen of the aziridine ring (or with the sulfonyl oxygen) and thereby further activates the aziridine towards nucleophilic attack. Then, the



Scheme 5 Stereospecific synthesis of nonracemic oxime amino ether (*R*)-**3a** from (*S*)-**1a**

oxygen of the oxime functionality attacks at the benzylic position of the aziridine and after protonation/deprotonation produces the corresponding ring-opened product with high stereospecificity.



Scheme 6 Plausible mechanistic pathway for the formation of oxime amino ethers from activated aziridines and aryl aldehyde oximes

In conclusion, we have developed an operationally simple synthetic route to a wide variety of substituted racemic and nonracemic oxime amino ethers in good to high yields via Lewis acid catalyzed S_N2 -type ring opening of activated aziridines with aryl aldehyde oximes.²⁶ We believe that the developed methodology will be useful to the organic and medicinal chemists.

Funding Information

M.K.G. is thankful to the Department of Science and Technology (DST), India for financial support. A.B. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, India for a research fellowship. S.D. and N.C. thank University Grants Commission (UGC), New Delhi, India for Senior Research Fellowships.

Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0039-1691596>.

References and Notes

- (1) (a) Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 6190. (b) Fujino, H.; Nagatomo, M.; Paudel, A.; Panthee, S.; Hamamoto, H.; Sekimizu, K.; Inoue, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 11865. (c) Nagatomo, M.; Nishiyama, H.; Fujino, H.; Inoue, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 1537. (d) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454. (e) Miyabe, H.; Fujii, K.; Naito, T. *Org. Biomol. Chem.* **2003**, *1*, 381. (f) Miyabe, H.; Konishi, C.; Naito, T. *Org. Lett.* **2000**, *2*, 1443. (g) Miyata, O.; Muroya, K.; Kobayashi, T.; Yamanaka, R.; Kajisa, S.; Koide, J.; Naito, T. *Tetrahedron* **2002**, *58*, 4459.
- (2) Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 5618.
- (3) Huang, X.; Ortiz-Marciales, M.; Huang, K.; Stepanenko, V.; Merced, F. G.; Ayala, A. M.; Correa, W.; De Jesús, M. *Org. Lett.* **2007**, *9*, 1793.
- (4) Takeda, N.; Miyata, O.; Naito, T. *Eur. J. Org. Chem.* **2007**, 1491.
- (5) Miyata, O.; Takahashi, S.; Tamura, A.; Ueda, M.; Naito, T. *Tetrahedron* **2008**, *64*, 1270.
- (6) Bragnier, N.; Guillot, R.; Scherrmann, M.-C. *Org. Biomol. Chem.* **2009**, *7*, 3918.
- (7) Cooper, T. S.; Larigo, A. S.; Laurent, P.; Moody, C. J.; Takle, A. K. *Org. Biomol. Chem.* **2005**, *3*, 1252.
- (8) Jeon, G.-H.; Yoon, J.-Y.; Kim, S.; Kim, S. S. *Synlett* **2000**, 128.
- (9) Wu, G.; Wang, J.; Liu, C.; Sun, M.; Zhang, L.; Ma, Y.; Cheng, R.; Ye, J. *Org. Chem. Front.* **2019**, *6*, 2245.
- (10) Dong, Y.; Liu, G. *J. Org. Chem.* **2017**, *82*, 3864.
- (11) Saha, R.; Perveen, N.; Nihesh, N.; Sekar, G. *Adv. Synth. Catal.* **2019**, *361*, 510.
- (12) (a) Fu, X.; Yang, J.; Deng, K.; Shao, L.; Xia, C.; Ji, Y. *Org. Lett.* **2019**, *21*, 3505. (b) Li, Y.; Chen, H.; Qu, L.-B.; Houk, K. N.; Lan, Y. *ACS Catal.* **2019**, *9*, 7154. (c) Behnke, N. E.; Lovato, K.; Yousufuddin, M.; Kürti, L. *Angew. Chem.* **2019**, *131*, 14357. (d) Huang, F.; Zhang, S. *Org. Lett.* **2019**, *21*, 7430.
- (13) (a) Cao, Z.; Liu, Z.; Liu, Y.; Du, H. *J. Org. Chem.* **2011**, *76*, 6401. (b) Li, C.; Zhang, H.; Cui, Y.; Zhang, S.; Zhao, Z.; Choi, M. C. K.; Chan, A. S. C. *Synth. Commun.* **2003**, *33*, 543. (c) Soltani, Rad. M. N.; Khalafi-Nezhad, A.; Karimitabar, F.; Behrouz, S. *Synthesis* **2010**, 1724. (d) Jia, X.; Wang, X.; Yang, C.; Da, Y.; Yang, L.; Liu, Z. *Tetrahedron* **2009**, *65*, 2334. (e) Zeng, H.; Zhu, C.; Jiang, H. *Org. Lett.* **2019**, *21*, 1130.
- (14) Abele, E.; Lukevics, E. *Synthesis of Heterocycles from Oximes*, In *The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids. The Chemistry of Functional Groups*; Rappoport, Z.; Liebman, J. F., Ed.; John Wiley & Sons: Chichester, **2008**, 233.
- (15) Jin, J.; Li, Y.; Wang, Z.-J.; Qian, W.-X.; Bao, W.-L. *Eur. J. Org. Chem.* **2010**, 1235.
- (16) (a) Ghorai, M. K.; Bhattacharyya, A.; Das, S.; Chauhan, N. *Top. Heterocycl. Chem.* **2016**, *41*, 49. (b) Dolfen, J.; De Kimpe, N.; D'hooghe, M. *Synlett* **2016**, 27, 1486. (c) Takeda, Y.; Kuroda, A.; Sameera, W. M. C.; Morokuma, K.; Minakata, S. *Chem. Sci.* **2016**, *7*, 6141. (d) Takeda, Y.; Ikeda, Y.; Kuroda, A.; Tanaka, S.; Minakata, S. *J. Am. Chem. Soc.* **2014**, *136*, 8544. (e) Callebaut, G.; Meiresonne, T.; De Kimpe, N.; Mangelinckx, S. *Chem. Rev.* **2014**, *114*, 7954. (f) Schneider, C. *Angew. Chem. Int. Ed.* **2009**, *48*, 2082. (g) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, **2006**, 517. (h) Stankovic, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643. (i) Dolfen, J.;

- Vervisch, K.; De Kimpe, N.; D'hooghe, M. *Chem. Eur. J.* **2016**, *22*, 4945. (j) D'hooghe, M.; Ha, H.-J.; Macha, L. *Synthesis* **2019**, *51*, 1491. (k) Remete, A. M.; Kiss, L. *Eur. J. Org. Chem.* **2019**, 5574.
- (17) (a) Mal, A.; Goswami, G.; Ahmad, Wani, I.; Ghorai, M. K. *Chem. Commun.* **2017**, *53*, 10263. (b) Pradhan, S.; Shahi, C. K.; Bhattacharyya, A.; Chauhan, N.; Ghorai, M. K. *Org. Lett.* **2017**, *19*, 3438. (c) Shahi, C. K.; Bhattacharyya, A.; Nanaji, Y.; Ghorai, M. K. *J. Org. Chem.* **2017**, *82*, 37. (d) Pradhan, S.; Shahi, C. K.; Bhattacharyya, A.; Ghorai, M. K. *Chem. Commun.* **2018**, *54*, 8583. (e) Chauhan, N.; Pradhan, S.; Ghorai, M. K. *J. Org. Chem.* **2019**, *84*, 1757.
- (18) (a) Bhattacharyya, A.; Kavitha, C. V.; Ghorai, M. K. *J. Org. Chem.* **2016**, *81*, 6433. (b) Ghorai, M. K.; Tiwari, D. P. *J. Org. Chem.* **2013**, *78*, 2617. (c) Wani, I. A.; Sayyad, M.; Ghorai, M. K. *Chem. Commun.* **2017**, *53*, 4386. (d) Mal, A.; Sayyad, M.; Wani, I. A.; Ghorai, M. K. *J. Org. Chem.* **2017**, *82*, 4. (e) Lin, T.-Y.; Wu, H.-H.; Feng, J.-J.; Zhang, J. *Org. Lett.* **2017**, *19*, 6526. (f) Bhattacharyya, A.; Shahi, C. K.; Pradhan, S.; Ghorai, M. K. *Org. Lett.* **2018**, *20*, 2925.
- (19) (a) Nikitjuka, A.; Jirgensons, A. *Chem. Heterocycl. Compd.* **2014**, *49*, 1544. (b) Nikitjuka, A.; Shestakova, I.; Romanchikova, N.; Jirgensons, A. *Chem. Heterocycl. Compd.* **2015**, *51*, 647.
- (20) Abele, E. *Heterocycl. Lett.* **2013**, *3*, 229.
- (21) Tabarki, M. A.; Besbes, R. *Tetrahedron* **2014**, *70*, 1060.
- (22) Dondas, H. A.; Cummins, J. E.; Grigg, R.; Thornton-Pett, M. *Tetrahedron* **2001**, *57*, 7951.
- (23) Chen, D.-D.; Ding, C.-H.; Hou, X.-L.; Dai, L.-X. *Chem. J. Chin. Univ.* **2011**, *32*, 694.
- (24) See the Supporting Information for details.
- (25) Ghorai, M. K.; Shukla, D.; Bhattacharyya, A. *J. Org. Chem.* **2012**, *77*, 3740.
- (26) **Representative Experimental Procedure for the BF₃·OEt₂-Catalyzed Ring Opening of Aziridines with Aldehyde Oximes (Scheme 2)** To a solution of the aziridine **1a-i** (50 mg, 1.0 equiv)

and 4-methoxybenzaldehyde oxime (**2a**, 1.5 equiv) in 2.0 mL dry dichloromethane was added anhydrous BF₃·OEt₂ (0.2 equiv) with a microsyringe at 0 °C under an argon atmosphere. The reaction mixture was stirred for an appropriate time (Scheme 2) at an appropriate temperature while the progress of the reaction was monitored by TLC. Upon completion the reaction was quenched with saturated aqueous NaHCO₃ solution. The aqueous layer was extracted with CH₂Cl₂ (3 × 5.0 mL) and it was washed with brine solution. The combined organic layers were dried over anhydrous Na₂SO₄, and the solvent was removed under reduced pressure. The crude concentrate was purified by flash column chromatography on silica gel (230–400 mesh) using 10% ethyl acetate in petroleum ether to provide the pure products **3a-i**.

(E)-N-(2-[(4-methoxybenzylidene)amino]oxy)-2-phenylethyl)-4-methylbenzenesulfonamide (3a**)**

The general method described above was followed when the aziridine **1a** (50.0 mg, 0.1829 mmol, 1.0 equiv) was reacted with the 4-methoxybenzaldehyde oxime (**2a**, 41.5 mg, 0.274 mmol, 1.5 equiv) in the presence of BF₃·OEt₂ (4.6 μL, 0.037 mmol, 20 mol %) in dichloromethane (2.0 mL) at 0 °C to rt for 2 h to afford the product **3a** (64.5 mg, 0.1518 mmol) as a white solid in 83 % yield; mp 98–100 °C. *R*_f = 0.30 (EtOAc/petroleum ether, 3:7). IR (KBr): 3283, 2955, 2925, 2854, 1606, 1572, 1513, 1495, 1454, 1419, 1329, 1306, 1252, 1161, 1092, 1063, 1029, 955, 832, 814, 756, 701, 664, 602, 550 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ = 8.00 (s, 1 H), 7.71 (d, 2 H, *J* = 8.3 Hz), 7.42 (d, 2 H, *J* = 8.6 Hz), 7.33–7.23 (m, 7 H), 6.86 (d, 2 H, *J* = 8.6 Hz), 5.18 (dd, 1 H, *J* = 8.3, 3.9 Hz), 5.01–4.99 (m, 1 H), 3.82 (s, 3 H), 3.46–3.41 (m, 1 H), 3.37–3.32 (m, 1 H), 2.39 (s, 3 H). ¹³C{¹H} NMR (125 MHz, CDCl₃): δ = 161.3, 149.7, 143.5, 138.3, 137.0, 129.8, 128.7, 128.6, 128.3, 127.2, 126.7, 124.3, 114.2, 82.9, 55.4, 48.1, 29.8, 21.6. HRMS (ESI-TOF): *m/z* calcd for C₂₃H₂₅N₂O₄S [M + H]⁺: 425.1535; found: 425.1529