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Lewis acid mediated S_N2-type nucleophilic ring opening followed by [4+2] cycloaddition of *N*-tosylazetidines with aldehydes and ketones: synthesis of chiral 1,3-oxazinanes and 1,3-amino alcohols

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Abstract—A highly efficient strategy for $Cu(OTf)_2$ mediated S_N2-type nucleophilic ring opening followed by [4+2] cycloaddition reactions of enantiopure 2-phenyl-*N*-tosylazetidines with various aldehydes and ketones afforded a variety of substituted 1,3-oxazinanes and 1,3-amino alcohols in excellent yields, excellent de and good to excellent ee. The proposed S_N2-type mechanism of the cycloaddition reaction is supported by experimental evidence.

Azetidines are an important class of small ring N-heterocycles found in many naturally occurring and synthetically important organic compounds, which exhibit interesting biological and pharmacological properties.[1] In recent years, azetidines have been utilized in fragmentation,[2] ring opening[3a–c] or in association with ring expansion[3d–g] and cycloaddition reactions[4] to generate a wide variety of nitrogen-containing compounds. In spite of the great synthetic potential, the chemistry of azetidines has not been much explored, probably because of their exceptional stability[5] and the lack of availability of suitable methodologies. To date, $BF_3{\cdot}OEt_2$ mediated nucleophilic ring opening or [4+2] cycloaddition of 2-aryl-*N*-sulfonylazetidines are known where the reaction is believed to proceed through a stable 1,4-dipolar intermediate.[4a–c] Hence, the possibility of a stereoselective version of such reactions is restricted. Recently, we reported the ZnX_2 (X = I, OTf) mediated nucleophilic ring opening of 2-aryl-*N*-sulfonylazetidine leading to γ-iodoamines and tetrahydropyrimidines.[6]

In continuation of our synthetic and mechanistic investigations towards the chemistry of N-activated azetidines, herein, we report a highly efficient strategy for Lewis acid mediated nucleophilic ring opening of 2-phenyl-*N*-tosylazetidines in polar and coordinating solvents via an S_N2 pathway, followed by a [4+2] cycloaddition with carbonyl compounds to give non-racemic 1,3-oxazinanes and 1,3-amino alcohols. All these compounds are of considerable synthetic and pharmacological utility.[7–9] There are only a few reports in the literature on the synthesis of oxazinanes,[7a,b] which are important carbonyl equivalents[7d,e] and have been used for the syntheses of several biologically important molecules.[8] In the present paper, we report for the first time, a direct synthesis of non-racemic 1,3-oxazinanes via ring opening of enantiopure 2-phenyl-*N*-tosylazetidine followed by [4+2] cycloaddition reactions with various carbonyl compounds. The oxazinanes are easily converted to γ-amino alcohols, which are important precursors in medicinal chemistry.[9] Our observations provide convincing evidence that the cycloaddition proceeds through an S_N2-type pathway, and not through the intermediacy of a stable 1,4-dipolar intermediate as invoked earlier.

In order to elucidate the mechanism of nucleophilic ring opening of 2-phenyl-*N*-tosylazetidine **1**, we studied its fate in the presence of a Lewis acid (LA) in polar and coordinating solvents and discovered an unprecedented rearrangement to allylamine **2** as shown in Scheme 1.[10] Our study began with the nucleophilic ring opening of

Keywords: *N*-Tosylazetidine; Nucleophilic; Ring opening; Carbonyl; Lewis acid; $Cu(OTf)_2$; [4+2] Cycloaddition; 1,3-Oxazinane; 1,3-Amino alcohol; Non-racemic; S_N2; Mechanism.
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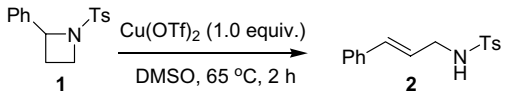
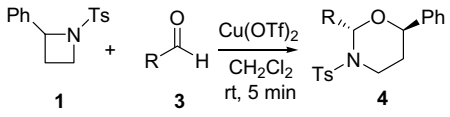


Scheme 1. Ring opening rearrangement of 2-phenyl-*N*-tosylazetidine.



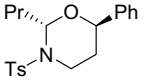
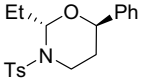
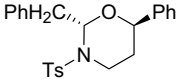
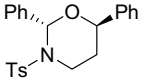
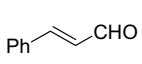
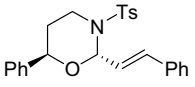
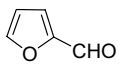
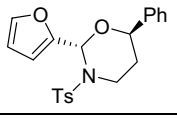
R = **a**: C_2H_5, **b**: C_3H_7, **c**: CH_2Ph, **d**: Ph **e**: -CH=CH-Ph, **f**: furyl

Scheme 2. $Cu(OTf)_2$ promoted [4+2] cycloaddition of 2-phenyl-*N*-tosylazetidine **1** with aldehydes.

2-phenyl-*N*-tosylazetidine **1** using acetone as the polar coordinating solvent in the presence of $Cu(OTf)_2$ as the LA at ambient temperature. The corresponding 1,3-amino alcohol **6** was obtained in 85% yield instead of **2** via a [4+2] cycloaddition reaction with acetone followed by hydrolysis within a very short period of time (Scheme 3). This observation prompted us to explore the ring opening of azetidines with carbonyl compounds and to investigate the mechanism of the reaction. Interestingly, when racemic **1** was treated with $Cu(OTf)_2$ as the Lewis acid and benzaldehyde as the solvent at ambient temperature,[11] the corresponding *trans*-1,3-oxazinane **4d**[12] was produced stereoselectively (de >99%) in 90% yield via a [4+2] cycloaddition reaction (Scheme 2). For easy purification, the same reaction was performed in CH_2Cl_2 using 5 equiv of the aldehyde and identical results were obtained. The progress of the reaction was comparatively slow when the reaction was performed using fewer equivalents of the Lewis acid, 1 equiv of the LA was necessary for completion of the reaction. Racemic **1** reacted smoothly with various aldehydes in CH_2Cl_2 at ambient temperature to produce *trans*-1,3-oxazinanes **4a**–**f**, stereoselectively (de 92–99%), in very high yields and the results are summarized in Table 1. All the products were fully characterized by spectroscopic techniques and elemental analyses. The trans stereochemistry of the 1,3-oxazinanes was determined by NOE measurements. Further the structure of 1,3-oxazinane **4c** was unambiguously confirmed by X-ray crystallography (Fig. 1).[13]

To investigate the mechanism of the cycloaddition we carried out the reaction with enantiomerically pure (*S*)-**1** (ee >99%).[14] The enantioselectivity for the cycloaddition of (*S*)-**1** with benzaldehyde in CH_2Cl_2 as the solvent was found to be poor (ee 18%). However, the ee increased gradually with increasing concentration of benzaldehyde (Fig. 2) and the maximum ee (75%) was obtained when benzaldehyde (neat) was used as the solvent (Table 1, entry 4). A number of aldehydes were studied with (*S*)-**1** and good enantioselectivity was observed in all the cases (Table 1). Little enhancement in the enantioselectivity was noted when $BF_3{\cdot}OEt_2$ or $Zn(OTf)_2$ was used as the Lewis acid. 1,3-Oxazinanes derived from ketones were found to be comparatively less stable and during work-up, these were hydrolyzed

Table 1. $Cu(OTf)_2$ promoted [4+2] cycloaddition of 2-phenyl-*N*-tosylazetidine **1** with aldehydes[a]

Entry	Carbonyl	Product	**4** de[b] (%)	ee[c] (%)	Yield[d] (%)
1	PrCHO		**4a** (94)	63	93
2	EtCHO		**4b** (92)	59	90
3	$PhCH_2CHO$		**4c**[e] (94)	62	89
4	PhCHO		**4d** (>99)	75	90
5			**4e** (>99)	65	85
6			**4f** (>99)	63	92

Reaction conditions:

[a] 1.0 equiv of $Cu(OTf)_2$, 5 equiv of aldehyde, unless otherwise mentioned all the reactions were performed in CH_2Cl_2 for 5 min at 25 °C.

[b] De was determined from the ^1H NMR of the crude reaction mixture.

[c] Determined by chiral HPLC, (*S*)-**1** was used and the aldehyde served as the solvent.

[d] Yield of the isolated trans diastereomer.

[e] Trans stereochemistry was determined by single-crystal X-ray analysis.

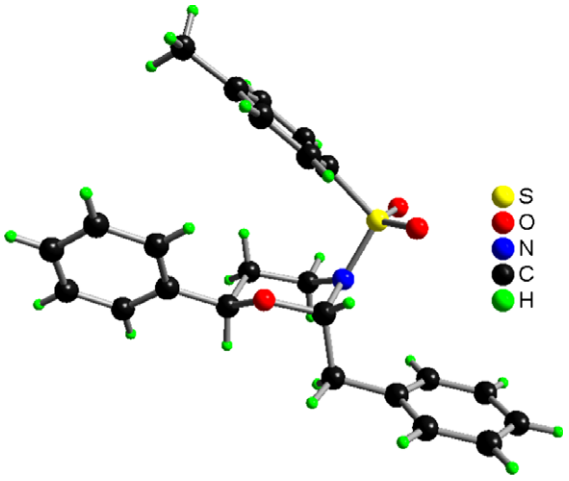


Figure 1. Crystal structure of **4c** (diamond view).

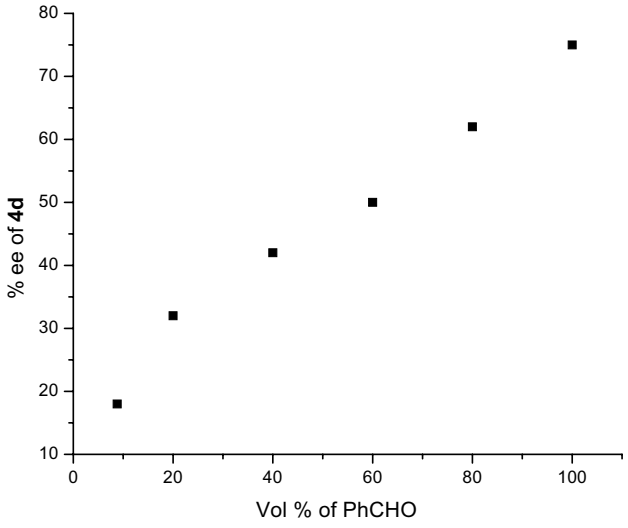


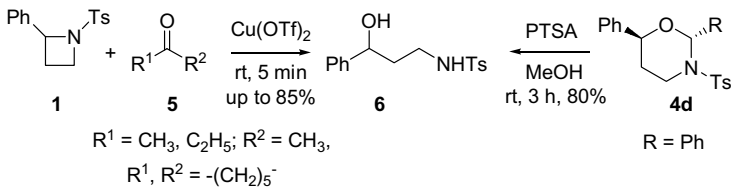
Figure 2. Effect of concentration of PhCHO on the % ee of **4d**.

to γ-amino alcohol **6**.[15] (*S*)-**1** provided non-racemic **6** in 85% yield with 62% ee when acetone was used as the solvent. 1,3-Oxazinane **4d** was easily hydrolyzed to the same amino alcohol **6** employing PTSA in MeOH (Scheme 3). The absolute stereochemistry of the major enantiomer of **6** was determined by comparison with the optical rotation and chiral HPLC analysis of an authentic sample of (*R*)-**6** (ee >98%) prepared from (*S*)-mandelic acid (ee >99%). The absolute configuration of 1,3-amino alcohol **6** prepared from (*S*)-mandelic acid and that obtained from (*S*)-2-phenyl-*N*-tosylazetidine (**1**) were the same. The formation of **6** with inverted stereochemistry (*R*) confirms the involvement of an S_N2-type pathway in the ring opening reaction of (*S*)-**1** by carbonyl compounds.

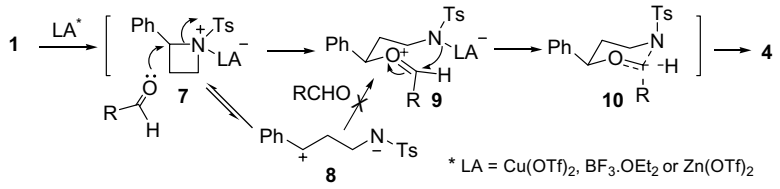
Based on, (i) the exclusive formation of trans-substituted-1,3-oxazinanes **4d–f** from the cycloaddition of racemic **1** with aldehydes and, (ii) the formation of non-racemic 1,3-oxazinanes and γ-amino alcohols with inverted stereochemistry from the cycloaddition of enantiomerically pure (*S*)-**1** with different aldehydes and ketones, respectively, we believe that the cycloaddition reaction proceeds through the mechanism shown in Scheme 4. The reactive species **7** undergoes S_N2-type nucleophilic ring opening followed by cyclization from the *si*-face of the carbonyl functionality of **9** to produce **4** via a six-membered TS **10**. The minor cis-diastereomers are formed because of possible cyclization from the *re*-face of the aldehydes having smaller alkyl substituents (Et, Pr). It is clear that the reaction does not proceed through a stable benzylic carbocation intermediate **8** from which a racemic product could be expected from enantiomerically pure (*S*)-**1** and in which **4** would have been formed as a diastereomeric mixture from racemic **1**. We rationalized the reduced enantioselectivity in all the cases being due to partial racemization (through a reversible ring opening and closing step) of the starting azetidine (*S*)-**1** before the nucleophilic ring opening step (Scheme 4).[16]

The scope of the methodology was further extended for the cycloaddition of enantiomerically pure *cis*-(2*S*,4*S*)-2-ethyl-4-phenyl-1-tosylazetidine **11**[14] with benzaldehyde in CH_2Cl_2 to give highly substituted oxazinane (2*R*,4*S*,6*R*)-4-ethyl-2,6-diphenyl-3-tosyl-1,3-oxazinane **12** with 4,6-trans geometry as the major diastereomer (**12**:**13** 89:11) in 90% combined yield (Scheme 5). The relative stereochemistry of oxazinanes **12** and **13** was determined by NOE measurements (Fig. 3). In this case, the relative stereochemistry of the starting azetidine **11** at C4 had been inverted in cycloaddition product **12**. The synthetic significance of the method was further demonstrated by the facile conversion of the inseparable diastereomeric mixture[17] of cycloadducts **12** and **13** into two diastereo- and enantiomerically pure substituted-1,3-amino alcohols **14** and **15**, by treatment with PTSA in MeOH (Scheme 5). 1,3-Amino alcohols **14** and **15** were obtained in pure forms by simple column chromatographic separation.

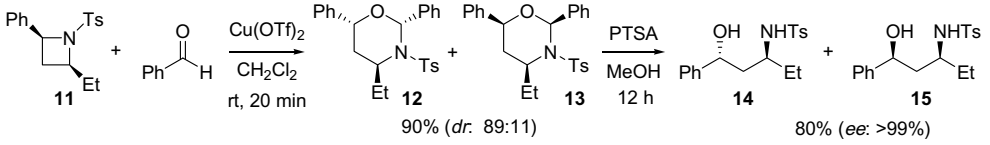
To conclude, we have demonstrated that the nucleophilic ring opening of 2-aryl-*N*-sulfonylazetidines proceeds through an S_N2 pathway. We report for the first



Scheme 3. $Cu(OTf)_2$ promoted [4+2] cycloaddition of 2-phenyl-*N*-tosylazetidine **1** with ketones.



Scheme 4. Proposed mechanism for the formation of **4** from **1**.



Scheme 5. Cycloaddition of 2,4-disubstituted-*N*-tosylazetidine **11** with benzaldehyde.

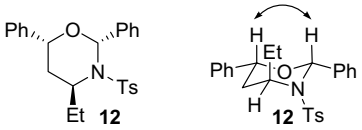


Figure 3. Diagnostic NOE observations for the oxazinane **12** (major diastereomer).

time a direct synthesis of non-racemic 1,3-oxazinanes by a [4+2] type cycloaddition of azetidines and carbonyl compounds. Our strategy is very important as numerous 1,3-amino alcohols can be synthesized in enantiomerically pure forms starting from the appropriate chiral disubstituted azetidines. Further applications of this methodology are in progress in our laboratory.

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10. Ghorai, M. K.; Kumar, A.; Das, K., unpublished results.
11. General procedure for the $Cu(OTf)_2$ mediated [4+2] cycloaddition of 2-phenyl-*N*-tosylzetidine with carbonyl compounds (Table 1): A solution of azetidine **1** (0.174 mmol) and carbonyl compound (0.870 mmol) in 0.7 mL of CH_2Cl_2 was added to a suspension of anhydrous $Cu(OTf)_2$ (0.174 mmol) in 0.3 mL of CH_2Cl_2 at 25 °C under an argon atmosphere. The mixture was stirred for 5 min 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 5% ethyl acetate in petroleum ether to provide the pure product. When chiral (*S*)-2-phenyl-*N*-tosylazetidine was used, non-racemic **4** was obtained. Greater enantioselectivity was observed when aldehydes or ketones were used as the solvent. In the case of ketones, the cycloaddition product was found to be very unstable and during work-up was hydrolyzed to the substituted 3-amino-1-phenyl-1-propanol.
12. Characterization data of 2,6-diphenyl-3-(4-methylphenylsulfonyl)-1,3-oxazinane **4d** (Table 1, entry 4): Following the general procedure outlined above, 2-phenyl-*N*-tosylazetidine **1** was reacted with benzaldehyde to afford a single trans diastereomer of **4d** as a white solid in 90% yield. R_f 0.35 (EtOAc/petroleum ether, 1:4); mp 135 °C; IR ν_{max} (KBr, cm^{-1}): 3057, 3028, 2965, 2924, 2845, 2370, 1598, 1491, 1451, 1330, 1213, 1157, 1056, 976, 925, 814, 739, 691, 649, 584; ^1H NMR (400 MHz, $CDCl_3$): δ 1.14–1.28 (m, 2H), 2.41 (s, 3H), 3.35–3.43 (m, 1H), 3.88–3.93 (m, 1H), 4.57 (dd, $J = 11.5$, 2.7 Hz, 1H), 6.84 (s, 1H), 6.86–6.88 (m, 2H), 7.17–7.21 (m, 3H), 7.26–7.38 (m, 5H), 7.45–7.47 (m, 2H), 7.90 (d, $J = 8.04$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 30.1, 40.2, 71.3, 84.4, 125.8, 127.0, 127.8, 127.9, 128.3, 128.4, 129.1, 129.8, 135.9, 138.1, 141.0, 143.7; FAB Mass = *m*/*z* 394 (M^++1). Anal. Calcd for $C_{23}H_{23}NO_3S$: C, 70.20; H, 5.89; N, 3.56. Found: C, 70.02; H, 5.86; N, 3.41. When chiral (*S*)-**1** (ee >99%) was used and benzaldehyde served as the solvent, non-racemic **4d** was obtained, optical rotation: $[\alpha]_D^{25}$ −19.30 (*c* 0.114, $CHCl_3$), with 75% ee [Chiracel AD-H column; hexane/isopropanol, 90:10; flow rate = 1.0 mL/min].
13. Crystallographic data of compound **4c** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 643311. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
14. Enantiomerically pure (*S*)-**1** and **11** were prepared using our reported method: Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 2471–2475.
15. Procedure for the synthesis of *N*-(3-hydroxy-3-phenylpropyl)-4-methyl-benzenesulfonamide **6**: The general procedure described above for the $Cu(OTf)_2$ mediated [4+2] cycloaddition of 2-phenyl-*N*-sulfonylazetidine with carbonyl compounds was followed except that ketone was used as the solvent instead of CH_2Cl_2. The crude compound was purified by flash column chromatography on silica gel (R_f 0.36, EtOAc/petroleum ether 1:1) to provide 3-amino alcohol **6** in up to 85% yield as a white solid, with a mp of 118 °C. When (*S*)-**1** was used and acetone served as the solvent, non-racemic 1,3-amino alcohol **6** was obtained. Optical rotation: $[\alpha]_D^{25}$ +24.0 (*c* 0.20, $CHCl_3$) for a 62% ee sample. Optical purity was determined by chiral HPLC analysis (Chiralcel AD-H column; hexane/isopropanol, 90:10; flow rate = 1.0 mL/min). 1,3-Oxazinanes **4** derived from aldehydes were hydrolyzed to the same amino alcohol **6** employing PTSA in MeOH. *N*-(3-Hydroxy-3-phenylpropyl)-4-methyl-benzenesulfonamide **6**:[9c] IR ν_{max} (KBr, cm^{-1}): 3453, 3176, 2922, 2868, 1596, 1322, 1155, 1094, 810, 747, 696, 549; ^1H NMR (400 MHz, $CDCl_3$): δ 1.75–1.80 (m, 2H), 2.36 (s, 3H), 2.95–3.01 (m, 1H), 3.06–3.13 (m, 1H), 4.73 (t, $J = 6.4$ Hz, 1H), 7.15–7.25 (m, 7H), 7.67 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 37.6, 40.8, 73.1, 125.5, 127.1, 127.8, 128.6, 129.7, 136.8, 143.3, 143.6; FAB Mass *m*/*z* = 306 (M^++1).
16. With increasing concentration of the carbonyl compound, (i) the concentration of the nucleophile increases and, (ii) **7** is better stabilized in more polar medium, thus the enantioselectivity of **4** is enhanced. In CH_2Cl_2, racemization of the starting azetidine (*S*)-**1** is appreciable and hence the enantioselectivity is reduced.
17. Although **12** and **13** are inseparable by TLC or simple column chromatography, they were separated by HPLC.