ORGANIC LETTERS

2007
Vol. 9, No. 26
5441−5444

Lewis Acid-Mediated Unprecedented Ring-Opening Rearrangement of 2-Aryl-*N*-tosylazetidines to Enantiopure (*E*)-Allylamines

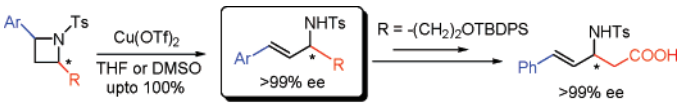
Manas K. Ghorai,* Amit Kumar, and Kalpataru Das

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

mkghorai@iitk.ac.in

Received September 24, 2007

ABSTRACT



Ar = Ph, 4-OMeC$_6$H$_4$, 4-ClC$_6$H$_4$, 2-ClC$_6$H$_4$, 3-BrC$_6$H$_4$
R = Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, -(CH$_2$)$_2$OTBDPS

A highly efficient strategy for Cu(OTf)$_2$-mediated ring-opening of 2-aryl-*N*-tosylazetidines in polar and coordinating solvents followed by an unprecedented rearrangement to substituted achiral and chiral (*E*)-allylamines (ee >99%) is reported. The methodology has been applied for the synthesis of γ-unsaturated-β-amino acids. A plausible mechanism for the rearrangement is also described.

Ring-opening transformations of small ring aza-heterocyles provide excellent routes for the construction of important synthetic targets.[1] In recent years, azetidines have been utilized in ring-opening[2] or in association with ring expansion,[3] fragmentation,[3c] rearrangement,[4] and cycloaddition reactions[5] to generate a wide variety of nitrogen-containing compounds of synthetic and pharmacological importance. Although nonactivated azetidines and azetidinium ions have been exploited extensively,[2a,b,3b,4] the chemistry of activated azetidines has not been much explored.

Recently, Lewis acid (LA)-mediated ring-opening of enantiopure 2-aryl-*N*-tosylazetidines by several nucleophiles such as halides,[6a] nitriles,[6a] carbonyls,[6b] and alcohols[6c] to provide nonracemic products in high enantiomeric excess has been reported by us (Scheme 1). We have demonstrated that the nucleophilic ring-opening of 2-aryl-*N*-tosylazetidines proceeds through an S$_N$2 pathway instead of a stable 1,4-dipolar intermediate as invoked earlier.[5a,b] Similar chemistry was observed for 2-aryl-*N*-tosylaziridines[6c,7] as well. In continuation of our research activities in this area to elucidate the mechanism of nucleophilic ring-opening of 2-aryl-*N*-

(1) (a) Davies, D. E.; Storr, R. C. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon: Oxford, UK, 1984; Vol. 7, Part 5, pp 237−284. (b) Moore, J. A.; Ayers, R. S. In *Chemistry of Heterocyclic Compounds—Small Ring Heterocycles*; Hassner, A., Ed.; Wiley: New York, 1983; Part 2, pp 1−217. (c) De Kimpe, N. In *Comprehensive Heterocyclic Chemistry II*; Padwa, A., Ed.; Elsevier: Oxford, UK, 1996; Vol. 1, Chapter 1.21. (d) Gribble, G. W.; Joule, J. A. In *Progress In Heterocyclic Chemistry*; Elsevier, Oxford, UK, 2004; Vol. 16, p 475.

(2) (a) Vargas-Sanchez, M.; Lakhdar, S.; Couty, F.; Evano, G. *Org. Lett.* **2006**, *8*, 5501. (b) Couty, F.; David, O.; Durrat, F. *Tetrahedron Lett.* **2007**, *48*, 1027. (c) Almena, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1994**, *50*, 5775. (d) Akiyama, T.; Daidouji, K.; Fuchibe, K. *Org. Lett.* **2003**, *5*, 3691. (e) Domostoj, M.; Ungureanu, I.; Schoenfelder, A.; Klotz, P.; Mann, A. *Tetrahedron Lett.* **2006**, *47*, 2205. (f) Dwivedi, S. K.; Gandhi, S.; Rastogi, N.; Singh, V. K. *Tetrahedron Lett.* **2007**, *48*, 5375. (g) Golding, P.; Millar, R. W.; Paul, N. C.; Richards, D. H. *Tetrahedron* **1995**, *51*, 5073.

(3) (a) Vanecko, J. A.; West, F. G. *Org. Lett.* **2005**, *7*, 2949. (b) Couty, F.; Durrat, F.; Evano, G.; Marrot, J. *Eur. J. Org. Chem.* **2006**, *18*, 4214. (c) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Salgado, N. R. *J. Org. Chem.* **1999**, *64*, 9596 and references cited therein.

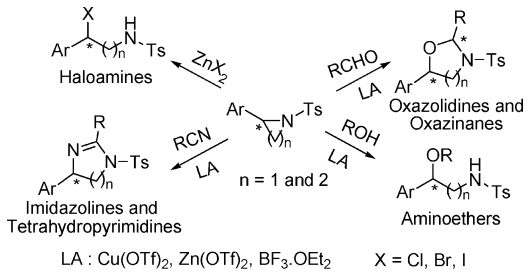
(4) (a) Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, *7*, 5861 and references cited therein. (b) De Kimpe, N.; Tehrani, K. A.; Fonck, G. *J. Org. Chem.* **1996**, *61*, 6500. (c) Van Brabandt, W.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1105. (d) Sulmon, P.; De Kimpe, N.; Schamp, N. *Tetrahedron* **1989**, *45*, 2937.

(5) (a) Ungureanu, I.; Klotz, P.; Schoenfelder, A.; Mann, A. *Chem. Commun.* **2001**, 958. (b) Prasad, B. A. B.; Bisai, A.; Singh, V. K. *Org. Lett.* **2004**, *6*, 4829. (c) Yadav, V. K.; Sriramurthy, V. *J. Am. Chem. Soc.* **2005**, *127*, 16366. (d) Baeg, J.-O.; Bensimon, C.; Alper, H. *J. Org. Chem.* **1995**, *60*, 253. (e) Baeg, J.-O.; Alper, H. *J. Org. Chem.* **1995**, *60*, 3092.

(6) For S$_N$2-type ring-opening of *N*-tosylazetidines: (a) Ghorai, M. K.; Das, K.; Kumar, A.; Das, A. *Tetrahedron Lett.* **2006**, *47*, 5393. (b) Ghorai, M. K.; Das, K.; Kumar, A. *Tetrahedron Lett.* **2007**, *48*, 4373. (c) Ghorai, M. K.; Das, K.; Shukla, D. *J. Org. Chem.* **2007**, *72*, 5859.

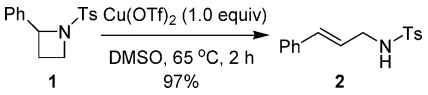
10.1021/ol7023218 CCC: $37.00
Published on Web 11/17/2007

Scheme 1. S_N2-Type Nucleophilic Ring-Opening of 2-Aryl-*N*-tosylazetidines and Aziridines



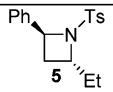
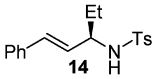
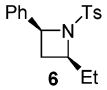
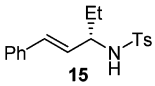
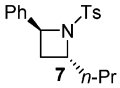
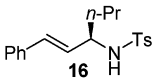
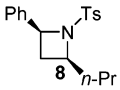
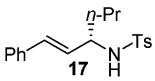
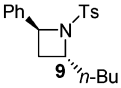
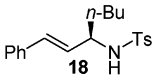
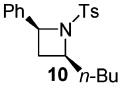
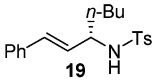
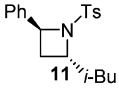
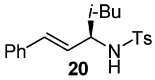
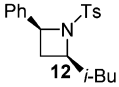
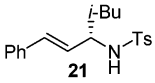
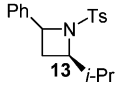
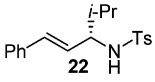
tosylazetidines, we studied their fate in the presence of Lewis acid in polar solvents and discovered an unprecedented rearrangement of azetidine **1** to allylamine **2** as shown in Scheme 2. The synthesis of allylamines has been an area of

Scheme 2. Ring-Opening Rearrangement in 2-Phenyl-*N*-tosylazetidine **1**



considerable research activity[8,9] primarily due to their key function as precursors or intermediates in organic synthesis,[10] as well as their presence in several biologically active compounds.[11] Moreover, these allylamines could be transformed into various important natural and unnatural amino acids upon oxidative cleavage of the olefinic bond.[9a] Herein, we report for the first time a highly efficient strategy for LA-mediated nucleophilic ring-opening followed by a novel rearrangement of 2-aryl-*N*-tosylazetidines to achiral and chiral allylamines. However, the ring-opening of other types of azetidinium intermediates toward allylamine derivatives has been reported earlier.[12] Allylamines obtained from suitably functionalized azetidines were easily converted into olefinic β-amino acids (Scheme 6), which are known to exhibit reversible or irreversible enzyme inhibition activity for a number of enzymes.[13,14]

Table 1. Synthesis of Chiral Allylamines from 2,4-Disubstituted Azetidines

entry	azetidine[a]	product[b]	yield (%)[c]
1	 **5**	 **14**	98
2	 **6**	 **15**	93
3	 **7**	 **16**	98
4	 **8**	 **17**	91
5	 **9**	 **18**	95
6	 **10**	 **19**	89
7	 **11**	 **20**	92
8	 **12**	 **21**	90
9	 **13**	 **22**	92

[a] All azetidine ee values were >99% (determined by chiral HPLC). [b] Stereochemistry and ee predicted based on precursor azetidine and supported by chiral HPLC. [c] Yield after column chromatographic purification.

When 2-phenyl-*N*-tosylazetidine **1** was treated with $Cu(OTf)_2$ as the Lewis acid with DMSO as the solvent at 65 °C, (*E*)-allylamine **2** was obtained in almost quantitative yield (Scheme 2). A series of Lewis acids such as $ZnCl_2$, $ZnBr_2$, $Zn(OTf)_2$, $InCl_3$, and $BF_3{\cdot}OEt_2$ were studied for the ring-opening of **1**. $Cu(OTf)_2$ was found to be the most efficient catalyst, although $BF_3{\cdot}OEt_2$ and $Zn(OTf)_2$ functioned in a similar fashion. In the absence of Lewis acid, no reaction was observed even at elevated temperatures. Solvent dependence of the reaction was studied in other coordinating solvents such as DMF, THF, and Et_2O with use of $Cu(OTf)_2$ as the Lewis acid. Similar reactions were observed in all these cases except Et_2O, where poor yield of **2** was obtained. Interestingly, when THF was served as the solvent, reaction was completed within 15 min at rt with use of 0.3 equiv of $Cu(OTf)_2$. With noncoordinating solvents such as CH_2Cl_2 or benzene, the reaction was found to be complicated and **2** was obtained in poor yield.

(7) For S_N2- type ring-opening of *N*-tosylaziridines: (a) Ghorai, M. K.; Das, K.; Kumar, A.; Ghosh, K. *Tetrahedron Lett.* **2005**, *46*, 4103. (b) Ghorai, M. K.; Ghosh, K.; Das, K. *Tetrahedron Lett.* **2006**, *47*, 5399. (c) Ghorai, M. K.; Ghosh, K. *Tetrahedron Lett.* **2007**, *48*, 3191.

(8) For reviews on Allylic amination, see: (a) Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685. (b) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.

(9) (a) Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225. (b) Concellón, J. M.; Suárez, J. R.; Del Solar, V. *Org. Lett.* **2006**, *8*, 349 and references cited therein. (c) Hodgson, D. M.; Fleming, M. J.; Stanway, S. J. *Org. Lett.* **2005**, *7*, 3295.

(10) (a) Nagashima, H.; Isono, Y.; Iwamatsu, S. *J. Org. Chem.* **2001**, *66*, 315. (b) Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2000**, *17*, 3007. (c) Oppolzer, W.; Stammen, B. *Tetrahedron* **1997**, *53*, 3577. (d) Davis, F. A.; Ramachandar, T.; Chai, J.; Skucas, E. *Tetrahedron Lett.* **2006**, *47*, 2743.

(11) (a) Magnus, P.; Lacour, J.; Coldham, I.; Mugrage, B.; Bauta, W. B. *Tetrahedron* **1995**, *51*, 11087. (b) Trost, B. M. *Angew. Chem., Int. Ed.* **1989**, *28*, 1173.

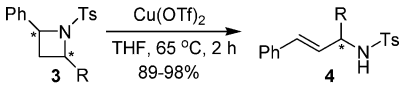
(12) D'hooghe, M.; Van Brabandt, W.; De Kimpe, N. *J. Org. Chem.* **2004**, *69*, 2703.

(13) For a review on olefinic amino acids, see: Berkowitz, D. B.; Charette, B. D.; Karukurichi, K. R.; McFadden, J. M. *Tetrahedron: Asymmetry* **2006**, *17*, 869.

(14) (a) Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 10677. (b) Baldwin, J. E.; Moloney, M. G.; North, M. *Tetrahedron* **1989**, *45*, 6319. (c) O'Donnell, M. E.; Sanvoisin, J.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1696 and references cited therein.

After getting this fascinating reactivity pattern of **1**, the scope of the reaction was extended to the synthesis of enantiomerically pure allylamines **14**−**22** from the chiral azetidines **5**−**13** (Table 1). Chiral disubstituted azetidines **5**−**13** were synthesized from amino acid precursors.[15] Azetidines **5**−**13** were treated with 1.0 equiv of $Cu(OTf)_2$ in refluxing THF for 2 h leading to enantiopure allylamines **14**−**22** in excellent yields (Scheme 3) and the results are

Scheme 3. Synthesis of Chiral Allylamines from 2,4-Disubstituted Azetidines

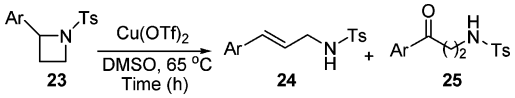


R = Et, *n*-Pr, *n*-Bu, *i*-Bu, *i*-Pr ee >99%

shown in Table 1. In all these cases 1.0 equiv of $Cu(OTf)_2$ and refluxing condition were necessary for complete conversion, the reaction was found to be slower with a lesser amount of $Cu(OTf)_2$ and at lower temperatures.

To investigate the mechanism of the reaction, azetidines **26**−**29** with different aryl groups were subjected to the reaction conditions mentioned in Scheme 2 and the results are summarized in Scheme 4. All azetidines (**26**−**29**) led to

Scheme 4. Effect of Aryl Group on the Reactivity of Azetidine

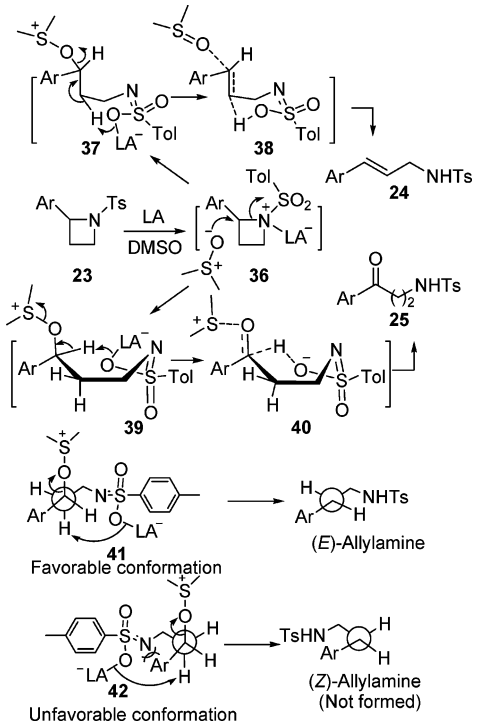


azetidine	time (h)	yield % (allylamine)	yield % (aminoketone)
Ar = Ph, **1**	2	97 (**2**)	0
Ar = 4-$MeOC_6H_4$, **26**	1	98 (**30**)	0
Ar = 4-ClC_6H_4, **27**	4	92 (**31**)	0
*Ar = 3-BrC_6H_4, **28**	15	55 (**32**)	31 (**34**)
*Ar = 2-ClC_6H_4, **29**	19	60 (**33**)	32 (**35**)

*$BF_3.OEt_2$ was used as the Lewis acid

the formation of allylamines **30**−**33** along with β-aminoketones **34**−**35** in some cases. β-Aminoketones **34**−**35** resulted as the minor products from the oxidative cleavage of **28**−**29** by DMSO. The probable mechanism of the ring-opening reaction is described in Scheme 5.[16] LA is coordinated to azetidine nitrogen generating a highly reactive species **36**, which undergoes nucleophilic attack by DMSO to give **37**. Subsequently, intramolecular E2 elimination from **37** is triggered by *N*-sulfoxonium ion via a six-membered transition state[17] **38** to produce **24**. Formation of **34**−**35** supports the involvement of DMSO in the reaction. The reaction is faster with an electron-donating substituent in aryl group (**26**),

Scheme 5. Proposed Mechanism for the Formation of Allylamine and β-Aminoketone from 2-Aryl-*N*-tosylazetidine



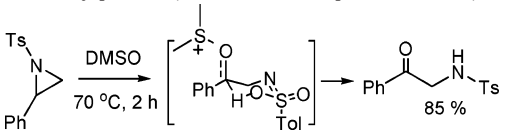
whereas it is retarded with an electron-withdrawing group (**28**−**29**) and competitive oxidative cleavage reaction takes place to generate β-aminoketones **34**−**35**. We suggest that β-aminoketones are formed by the elimination of dimethyl sulfide, probably via a higher energetic seven-membered transition state **40** as shown in Scheme 5. Stereoselective formation of (*E*)-allylamines can be rationalized by considering the E2 elimination from the favorable conformation **41** over **42** as shown in Scheme 5.

After demonstrating an efficient route to enantiopure allylamines, we further extended this strategy for the synthesis of olefinic β-amino acids.[13,14] Azetidines **43** and **46** (ee >99%) were conveniently prepared from (*R*)-phenylglycinol.[18] **43** and **46** when subjected to ring-opening rearrangement with $Cu(OTf)_2$ in refluxing THF, corresponding allylamines **44** and **47** were obtained in almost quantitative yields with ee >99%. Further, the silyl ether groups of **44** and **47** were unmasked to the corresponding alcohols by using TBAF in quantitative yields. Finally, oxidation[14a] of these alcohols by the Jones method produced

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

(16) A similar mechanism operates in other coordinating solvents (THF, DMF).

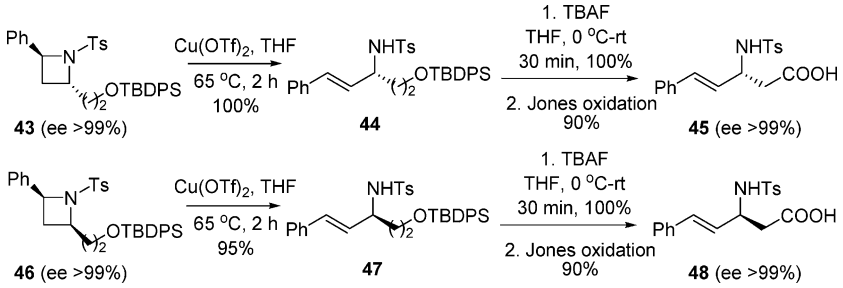
(17) (a) We proposed a similar type of six-membered transition state for oxidative cleavage of 2-phenyl-*N*-tosylaziridine by DMSO to α-amino ketone as the only product (Ghorai, M. K. Unpublished result).



(b) A similar oxidative ring-opening of aziridine-1-carboxylates to α-amino ketones by DMSO was reported earlier, see: Fujita, S.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1969**, *21*, 1677.

(18) The synthesis of azetidines **43** and **46** is described in the Supporting Information (pp S-12).

Scheme 6. Synthesis of of γ-Unsaturated-β-amino Acids **45** and **48**



N-tosyl-γ-unsaturated-β-amino acids **45** and **48** in excellent yields (Scheme 6).

In conclusion, we have developed a direct synthetic route to enantiopure (*E*)-allylamines via the ring-opening rearrangement of corresponding *N*-tosylazetidines. A plausible mechanism for the reaction is provided. The method has been utilized for the synthesis of important unnatural olefinic β-amino acids. More applications of this methodology and mechanistic exploration are under investigation in our laboratory.

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

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7023218