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# Cleavage of Activated Cyclic Amines: Unprecedented Approach toward 2-Substituted Cyclobutanones

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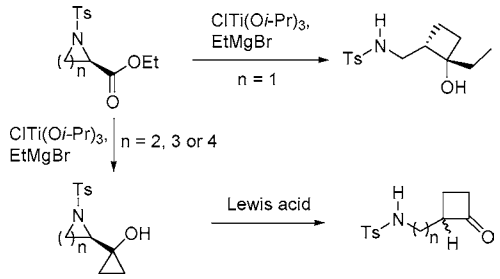
## ABSTRACT




**We report, for the first time, ring opening of activated four- to six-membered cyclic amines followed by an intramolecular expansion of cyclopropanol to cyclobutanone via carbocation intermediate. In the case of a *N*-tosylaziridine ester, a cyclobutanol was formed in a stereospecific manner during the Kulinkovich reaction step.**

Strained compounds such as cyclopropanol[1] and cyclobutanone[2] are very useful in organic synthesis. The synthetic utility of the latter is associated with the highly electrophilic carbonyl group whose reactivity is considerably different from that of carbonyls in larger rings due to high strain energy (ca. 25 kcal/mol). Cyclobutanone and its derivatives have served as useful precursors for ring expansion reactions,[3,4] which are widely used in organic synthesis. In general, a four-membered ketone ring system is synthesized either by [2+2] cycloaddition of ketenes and olefins[5] or by ring expansion of cyclopropyl precursors.[6,7] While working on the synthesis of natural products and a Lewis acid-catalyzed cycloaddition of four-membered cyclic amines with nitriles,[8] we envisioned that cyclopropanol may undergo rearrangement with α-substituted activated cyclic amines.

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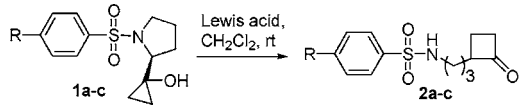
As anticipated, the rearrangement occurred smoothly and we describe our results in this Letter. Very few examples of rearrangements or fragmentations of the activated five-membered ring are known.[9] *To our knowledge, this will be the first report for ring opening of an activated cyclic amine followed by an intramolecular expansion of a cyclopropanol to a 2-substituted cyclobutanone*. The methodology would widen the chemistry of three- to six-membered cyclic amines for synthesis of functionalized cyclobutanones.

At the outset, it was planned to test the methodology by taking five-membered cyclic amine. The requisite precursor **1a** was synthesized from L-proline ester by activating the secondary amine as a tosylate and converting the ester into a cyclopropanol by using Kulinkovich reaction.[1,10] On treatment of **1a** with 1 equiv of $Sn(OTf)_2$ in $CH_2Cl_2$ at room temperature for 4 h, a cyclobutanone derivative **2a** was obtained in 70% yield (Scheme 1).[11] It was observed that

**Scheme 1.** Opening of *N*-Activated Cyclic Amine in the Presence of Lewis Acids

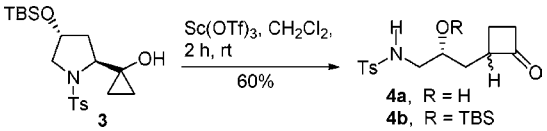



| R | Lewis acid | time | product | yield |
|---|---|---|---|---|
| Me | $Sn(OTf)_2$ | 04 h | 2a | 70% |
| Br | $Cu(OTf)_2$ | 02 h | 2b | 52% |
| OMe | $Yb(OTf)_3$ | 24 h | 2c | 40% |

the reaction also took place to almost the same extent (65% yield) with 0.5 equiv of the Lewis acid, but the reaction time was longer (24 h). Other metal triflates such as $Cu(OTf)_2$ (40%, 12 h), $Sc(OTf)_3$ (60%, 10 h), $In(OTf)_3$ (55%, 12 h), and $Yb(OTf)_3$ (65%, 24 h) also facilitated the reaction, but isolated yields were inferior as shown in parentheses against each Lewis acid. It is important to mention here that traditional Lewis acids such as $BF_3{\cdot}OEt_2$ and $TiCl_4$ gave less than 25% yield of the cyclobutanone derivative. Ti(O-*i*-Pr)$_4$, ClTi(O-*i*-Pr)$_3$, $LiClO_4$, and $Zn(OTf)_2$ did not initiate this rearrangement even after 20 h at room temperature. On the basis of the results from Scheme 1, it was concluded that tosylate worked best as an activating group in this reaction.

In the above reaction the optically active precursor **1a** gave **2a** as a racemic product, which could not be separated on chiral columns. To establish a mechanism, we synthesized a precursor **3** that had one more chiral center with the hope that the diastereomeric products will show separation. It was indeed the case. The exposure of the **3** to $Sc(OTf)_3$ for 4 h provided a mixture of rearranged products **4a** and **4b** with a ratio of 1:2 suggesting that the TBS group was desilylated to some extent. Other Lewis acids such as $Cu(OTf)_2$, $Sn(OTf)_2$, and $In(OTf)_3$ were equally good for the rearrangement, but only **4a** could be isolated where the TBS group was deprotected completely (Scheme 2). $^1$H NMR and

**Scheme 2**




HPLC analysis of the rearranged product **4b** showed it to be a 1:1 mixture of diastereomers. Thus, during the rearrangement, the chirality at the carbon α to the ketone in the cyclobutanone derivative **4b** is lost. This indicated an involvement of a discreet carbocation at this center.

On the basis of the above experimental evidence, a mechanism for the formation of cyclobutanone derivative has been proposed (Figure 1). The Lewis acid chelation to

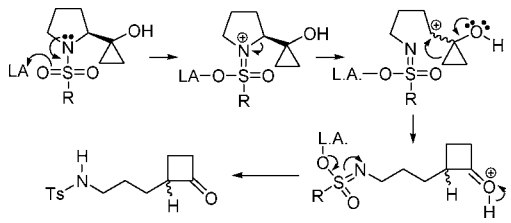



**Figure 1.** Possible mechanism for the ring opening of five-memberd activated cyclic amine.

the oxygen of the sulfonyl group would weaken the C−N bond leading to a cleavage of the pyrrolidine ring. This would result in the formation of a carbocation at the chiral center. Subsequent expansion of the cyclopropanol provided a racemic mixture of a cyclobutanone derivative.

Although base-induced ring opening of cyclopropanols in aprotic solvents probably involves formation of the corresponding homoenolate anions as intermediates, only a limited number of successful trappings of these species with carbon centered electrophiles have been reported.[12] The exposure of **1a** to bases such as DBU, *t*-BuOK, *n*-BuLi, and NaH did not affect it even after 24 h. Thus, it was confirmed that the rearrangement occurs only in the presence of a suitable Lewis acid and there is no reaction in the presence of a base.

(9) (a) Farcas, S.; Namy, J.-L. *Tetrahedron Lett.* **2000**, *41*, 7299−7302. (b) Honda, T.; Ishikawa, F. *Chem. Commun.* **1999**, 1065−1066. (c) Bon, E.; Bigg, D. C. H.; Bertrand, G. *J. Org. Chem.* **1994**, *59*, 1904−1906. (d) Dixit, A. N.; Tandel, S. K.; Rajappa, S. *Tetrahedron Lett.***1994**, *35*, 6133−6134.

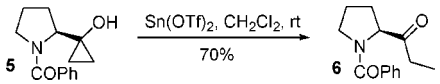
(10) (a) For theoretical study on the mechansim, see: Wu, Y.-D.; Yu, Z.-X. *J. Am. Chem. Soc.* **2001**, *123*, 5777−5786. (b) Also see: Casey, C. P.; Strotman, N. A. *J. Am. Chem. Soc.* **2004**, *126*, 1699−1704.

(11) Under the specified Kulinkovich condition, the reaction failed to give any corresponding cyclopropanol when R = *p*-F. The reaction was messy when R = *p*-$NO_2$.

(12) (a) Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365−390 and references therein. (b) Takeda, K.; Nakatani, J.; Nakamura, H.; Sako, K.; Yoshii, E.; Yamaguchi, K. *Synlett* **1993**, 841−843. (c) Carey, J. T.; Knors, C.; Helquist, P. *J. Am. Chem. Soc.* **1986**, *108*, 8313−8314. (d) Carey, J. T.; Helquist, P. *Tetrahedron Lett.* **1988**, *29*, 1243−1246. (e) Sunder, N. M.; Patil, P. A.; Narasimhan, N. S. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1331−1334.

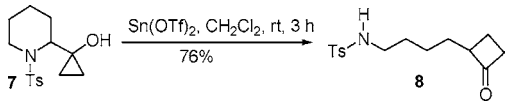
Having established the mechanism of the reaction, it was decided to see the effect of other activating groups such as benzoate on the nitrogen. Thus, compound **5** was treated with $Sn(OTf)_2$ and, to our surprise, no cyclobutanone derivative was obtained. Instead, a ketone[13] **6** was isolated in 70% yield. Thus, it indicated that the benzoate is not strong enough to activate the pyrrolidine ring so that the C−N bond can cleave (Scheme 3).

**Scheme 3**




To extend the scope of the study, the reaction was carried out at a six-membered cyclic amine. It was heartening to note that compound **7**, on exposure to $Sn(OTf)_2$, afforded a 2-substituted cyclobutanone derivative **8** in 76% yield as the only product (Scheme 4). It is worth mentioning here

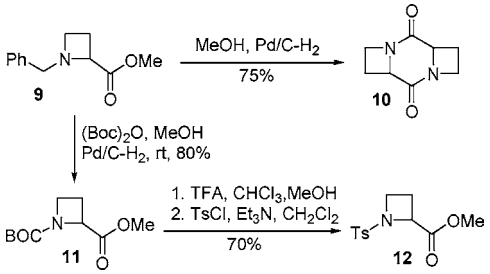
**Scheme 4**




that the cleavage of the six-membered piperdine ring was smoother.

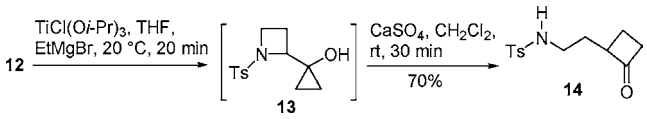
After successful demonstration of the ring-opening of five- and six-membered *N*-activated rings, we extended the reaction to a four-membered cyclic amine. Thus, we thought that the required precursor can be synthesized from compound **9**[14] using standard chemistry. Unfortunately, while doing hydrogenation of the *N*-benzyl compound **9** with 10% Pd/C in methanol, a dimerized product **10** was isolated. To avoid the dimerization, we adopted an alternative strategy for the synthesis of *N*-tosyl azetidine ester **12** (Scheme 5).

**Scheme 5**



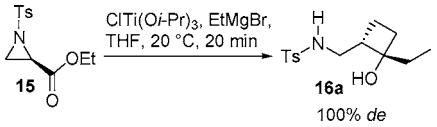

The ester **12**, under the Kulinkovich condition, furnished *N*-tosyl azetidine cyclopropanol **13**, which appeared to be unstable during purification over silica gel and only the required rearranged product **14** was obtained.[15] It indicated that a very mild Lewis acid should be sufficient to mediate this rearrangement on four-membered cyclic amines. Thus, the crude product, obtained after the Kulinkovich reaction, was treated with $CaSO_4$ at room temperature for a brief period. To our delight, a clean cyclobutanone derivative **14** was obtained in an overall yield of 70% (Scheme 6).

**Scheme 6**




Interestingly, a chiral *N*-tosyl aziridine ester **15**, under the Kulinkovich condition, furnished a chiral cyclobutanol derivative **16a** in 52% yield. There was no trace of the expected cyclopropanol product or even the final cyclobutanone derivative (Table 1).

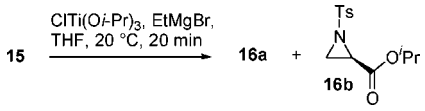
**Table 1.** Optimization for the Formation of Cyclobutanol




| entry | Lewis acid | mol % | EtMgBr, equiv | yield, % |
|---|---|---|---|---|
| 1 | $ClTi(O\text{-}i\text{-}Pr)_3$ | 50 | 1 | 0 |
| 2 | $ClTi(O\text{-}i\text{-}Pr)_3$ | 75 | 2 | 0 |
| 3 | $ClTi(O\text{-}i\text{-}Pr)_3$ | 100 | 3 | 14 |
| 4 | $ClTi(O\text{-}i\text{-}Pr)_3$ | 50 | 4 | 36 |
| 5 | $ClTi(O\text{-}i\text{-}Pr)_3$ | 75 | 4 | 40 |
| 6 | $ClTi(O\text{-}i\text{-}Pr)_3$ | 100 | 4 | 52 |
| 7 | $ClTi(O\text{-}i\text{-}Pr)_3$ | 150 | 4 | 50 |
| 8 | $Ti(O\text{-}i\text{-}Pr)_4$ | 50 | 4 | 32 |
| 9 | $Ti(O\text{-}i\text{-}Pr)_4$ | 75 | 4 | 45 |
| 10 | $Ti(O\text{-}i\text{-}Pr)_4$ | 100 | 4 | 47 |
| 11 | $Ti(OEt)_4$ | 100 | 4 | 23 |

The same reaction was studied at various temperatures and it was observed that only transesterified product **16b** was obtained at lower temperatures (Table 2).

**Table 2.** Effect of Temperature




| entry | temp, °C | product | yield, % |
|---|---|---|---|
| 1 | 20 | **16a** | 52 |
| 2 | 0 | **16a** | 30 |
| 3 | −40 | **16b** | 68 |
| 4 | −78 | **16b** | 70 |

The structure of the **16a** was confirmed by a single-crystal X-ray crystallographic analysis (Figure 2). It appeared that

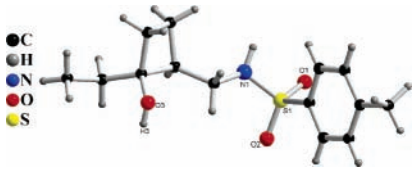
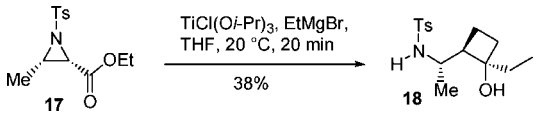



**Figure 2.** X-ray structure of compound **16a**.

the cleavage of the aziridine ring and expansion of a cyclopropanol occurred in a concerted manner followed by an addition of an ethyl group to the cyclobutanone, formed in situ, in a stereoselective manner.

To confirm that the reaction is highly stereoselective, compound **17**[16] with two chiral centers was subjected to Kulinkovich conditions. As predicted from the above aziridine case, only one stereoisomer of a cyclobutanol derivative **18** was isolated (Scheme 7).

**Scheme 7**




On the basis of the above experimental evidence the follwing mechanism has been proposed. After formation of cyclopropanol the oxygens of sulfonyl and hydroxyl groups can chelate the titanium. After chelation, the ring expansion of cyclopropane and the opening of *N*-tosylaziridine occur simultaneously to give a titanium cyclobutanone complex. Now, the ethyl group attacks the carbonyl group of cyclobutanone on the exposed site to give cyclobutanol in a highly stereospecific manner (Figure 3).

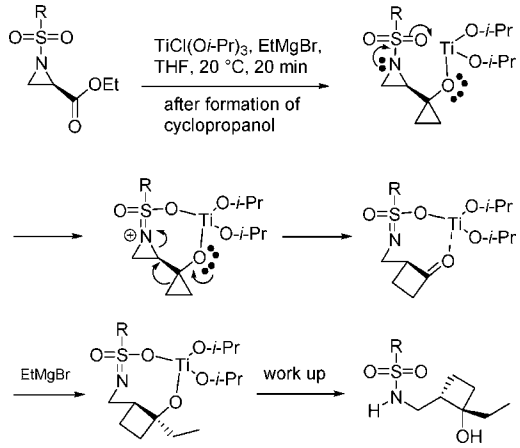



**Figure 3.** Possbile mechanism for formation of the chiral cyclobutanol.

In summary, we have reported for the first time ring opening of activated four- to six-membered cyclic amines followed by intramolecular expansion of cyclopropanols to 2-substituted cyclobutanones. In the case of a *N*-tosylaziridine ester, cleavage of the aziridine ring and expansion of a cyclopropanol occurred in a concerted manner. This was followed by an addition of an ethyl group to the cyclobutanone system, formed in situ, in a stereoselective manner.

**Acknowledgment.** We thank DST and CSIR (Government of India) for financial support. S.B. and S.S. thank CSIR for research fellowships. We also thank Mr. P. Thilagar, Department of Chemistry, IIT Kanpur for solving the crystal structure.

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

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(14) Wasserman, H. H.; Lipshutz, B. H.; Tremper, A. W.; Wu, J. S. *J. Org. Chem.* **1981**, *46*, 2991−2999.

(15) Azetidine cyclopropanol **13**, on purification over radial chromatography, gave complete conversion to cyclobutanone derivative. It was later realized that the rearrangement was initiated by the binder ($CaSO_4$) present in the silica gel.

(16) Starmans, W. A. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1998**, *54*, 629−636.