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Synthesis of cyclobutanones and four-membered enol ethers by using a rearrangement reaction of enol triflates

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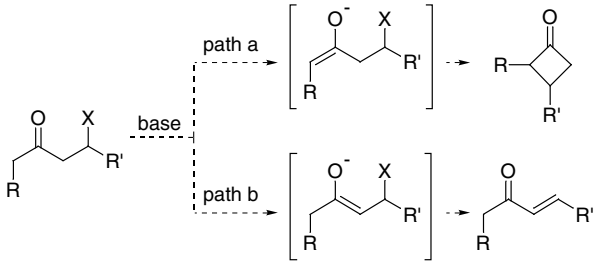
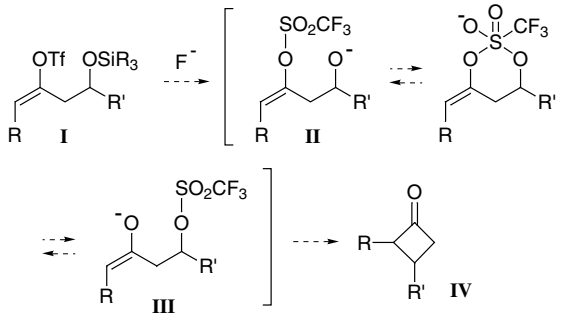
Abstract—A new synthetic method of cyclobutanone derivatives and four-membered enol ethers via an intramolecular cyclization of a ketone enolate was developed. The cyclization precursors, enol triflates having a silyloxy group at the β′-position, were synthesized from the corresponding β-hydroxy ketones, which were prepared via an aldol reaction of a cycloalkanone and an aldehyde. Under the influence of TBAF, the enol triflates afforded a cyclobutanone or a four-membered enol ether through rearrangement of the trifluoromethanesulfonyl group followed by an intramolecular *C*- or *O*-alkylation reaction.

Development of an efficient method for constructing highly strained molecules is one of the most challenging subjects in synthetic organic chemistry. Although formation of three-membered rings, for example, cyclopropanes and epoxides, is a kinetically favored process, cyclization reactions giving rise to four-membered compounds are far more difficult. Therefore, four-membered ketones are commonly prepared through a [2+2] cycloaddition reaction of a ketene with an olefin,[1] while there are only a few methods for synthesizing cyclobutanones via a direct intramolecular cyclization reaction. For example, solvolysis of a trifluoromethanesulfonyl ester of a 1-alkyn-4-ol affords a cyclobutanone derivative via a π-cyclization reaction.[2] An intramolecular alkylation reaction of a ketone enolate having a good leaving group at the β′-position provides an alternative way for cyclobutanone synthesis (path a in Scheme 1).[3] This type of approach, however, suffers from generation of a regio isomer of the enolate, which merely lead to an enone via a β-elimination reaction (path b). Indeed, successful results have been reported only in the cases that an α,α-disubstituted ketone, which cannot choose path b, is used as a cyclization precursor.



Scheme 1. Reactions of enolates generated from a ketone having a leaving group at the β-position.

With a view to overcome the limitation mentioned above, we designed enol triflate **I** having a siloxy group at the β′-position as a cyclization precursor (Scheme 2).



Scheme 2. Enol triflates as a precursor of a cyclobutanone derivatives.

Keywords: Cyclobutanone; Oxetane; Enol ether; Cyclization; Enol triflate.
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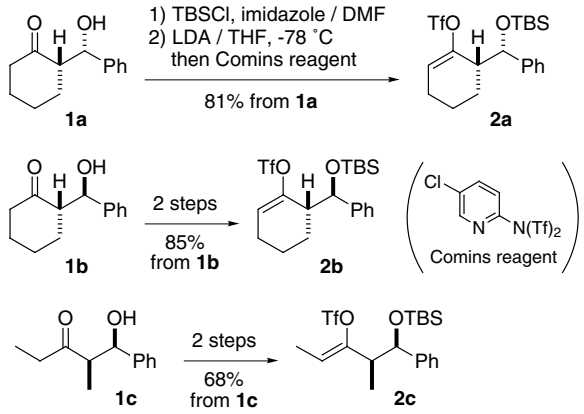
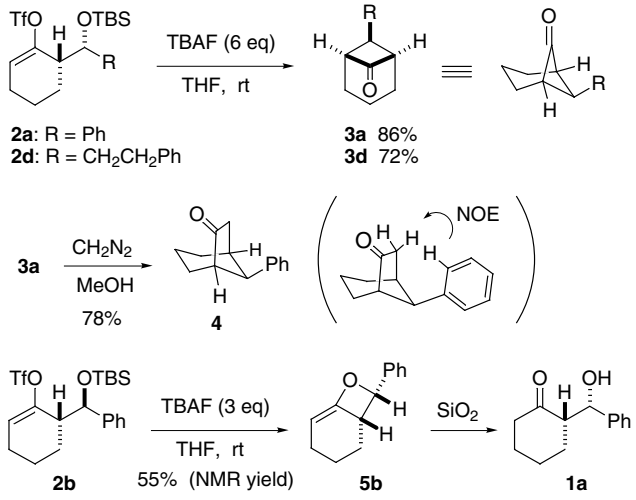


Scheme 3. Preparation of cyclization precursors from aldol derivatives.

Under the influence of a fluoride ion, silyl ether **I** will give alkoxide **II** that could be transformed into enolate **III** through an intramolecular rearrangement of the trifluoromethanesulfonyl group.[4] The resulting enolate **III** having a trifluoromethanesulfonyloxy group, a very good leaving group,[5] at the β′-position would rapidly undergo a cyclization reaction to afford a cyclobutanone derivative **IV**.

To this end, cyclization precursors were successfully synthesized from the corresponding β-hydroxy ketones, which are readily accessible via an aldol reaction of a ketone and an aldehyde,[6] in two steps (Scheme 3). Thus, after protection of the hydroxyl group with a *tert*-butyldimethylsilyl group,[7] the ketone was converted to an enol triflate[8] through regioselective formation of a lithium enolate under kinetic control.

The cyclization reaction was performed by treating the substrate with tetrabutylammonium fluoride[7] (TBAF) in THF, and the desired cyclobutanone **3a** was obtained from enol triflate **2a** as a single isomer in high yield (Scheme 4).

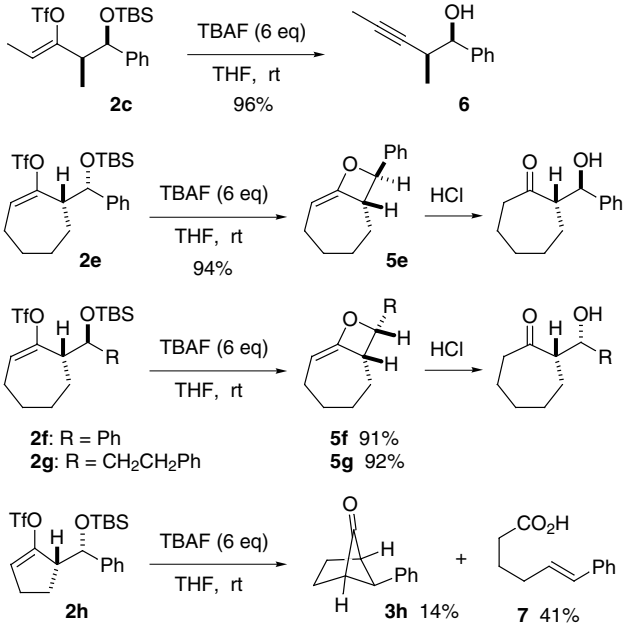


Scheme 4. Cyclization reactions of six-membered enol triflates.

Since determination of the stereochemistry of the product was difficult, cyclobutanone **3a** was transformed into cyclopentanone derivative **4** through one-carbon ring expansion by diazomethane.[9] The *syn*-configuration between the phenyl group and the ketone moiety was unambiguously confirmed by an NOE experiment of **4**, which indicates that the cyclization step giving rise to **3a** involves inversion of the configuration at the benzylic carbon. High reactivity at the benzylic position to enhance the cyclization step seems not essential for the cyclobutanone synthesis, because enol triflate **2d** having an aliphatic side chain instead of a phenyl group also afforded **3d** in good yield.

On the other hand, the reaction of the corresponding diastereomer **2b** resulted in the formation of a mixture containing no desired cyclobutanone derivative. Silica gel column chromatography of the mixture afforded aldol **1a** as the major product, although it was never detected in the ^{1}H NMR spectra of the crude mixture. Careful analysis of the reaction of **2b** led us to find oxetane derivative **5b**, a highly strained enol ether[10] that easily undergoes hydrolysis during column chromatography to give aldol **1a**, as a main product. Since the stereochemistry of oxetane **5b** confirmed by an NOE experiment was identical with that of aldol **1a**, conversion of the former to the latter would proceed through protonation of the olefin moiety.

Next, scope and limitation of the fluoride-mediated intramolecular cyclization reaction was investigated (Scheme 5). Acyclic enol triflate **2c** failed to give any cyclization product, and alkynyl alcohol **6** arising from a β-elimination reaction was obtained almost quantitatively. The result suggests that the use of an enol triflate prepared from a cycloalkanone is effective to avoid a β-elimination reaction giving rise to a highly strained cycloalkyne.



Scheme 5. Cyclization reactions of various enol triflates.

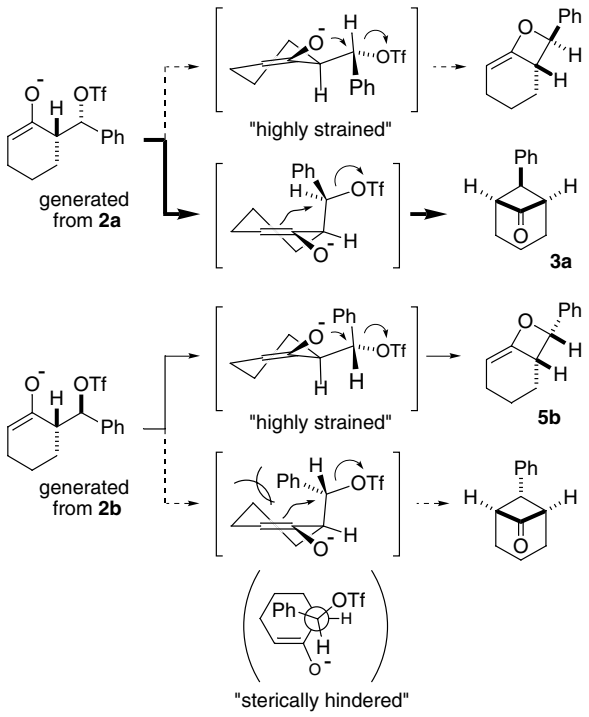
Interestingly, the ring size of substrates was found to play an important role in selection of the reaction pathway, namely, *C*-alkylation versus *O*-alkylation. Thus, both enol triflates **2e** and **2f** derived from cycloheptanone underwent an *O*-alkylation reaction regardless of their stereochemistry in excellent yields, while five-membered substrate **2h** afforded cyclobutanone **3h** in low yield along with fragmentation product **7**. It is noteworthy that oxetanes **5e**, **5f**, and **5g** exhibited much higher stability than **5b**, which allowed us to isolate them in high yield after silica gel column chromatography. In order to determine the stereochemistry, the enol ethers were subjected to hydrolysis promoted by diluted hydrochloric acid and the corresponding *syn* and *anti* aldol derivatives were obtained, respectively.

The different behavior of the cyclic enol triflates **2a**, **2b**, **2e**, **2f**, and **2h** can be rationalized as follows. The cyclization step proceeds through an intermediate having a quaternary ammonium enolate moiety and an alkyl triflate moiety (**III** in Scheme 2). It should be noted that a quaternary ammonium enolate and an alkyl triflate are classified as a 'hard nucleophile' and a 'hard electrophile', respectively.[11] Combination of these 'hard' species should be advantageous to an *O*-alkylation reaction, and oxetanes **5b**, **5e**, and **5f** are formed via this pathway. On the other hand, these four-membered enol ethers having an sp^2 carbon at the angular position are highly strained especially in the case that the size of the carbocycle is small. Indeed, cyclohexene derivative **5b** exhibits higher lability than the seven-membered analogues **5e** and **5f**, and an *O*-alkylation pathway from five-membered enol triflate **2h** suffered from extremely high strain energy of a bicyclo[3.2.0]heptane skeleton.

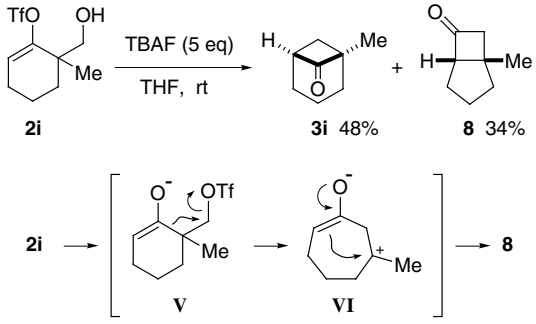
Selective formation of cyclobutanones from six-membered enol triflates **2a** and **2d** can also be explained similarly, although the corresponding *syn*-isomer **2b** yielded enol ether **5b**. As depicted in Scheme 6, the exceptional behavior of enol triflate **2b** would come from steric repulsion between the phenyl group and the ring carbon in the transition state leading to a cyclobutanone derivative.

Finally, a cyclization reaction of a six-membered enol triflate having a substituent at the α′-position was examined (Scheme 7). In this case, increased steric hindrance around the silyloxy group prevented the desilylation step, and the substrate was previously treated with HF to remove the silyl group under more mild conditions. The reaction of β′-hydroxy enol triflate **2i** with TBAF afforded cyclobutanone **3i** along with unusual product **8** in high combined yield. It is reported that a similar result was obtained from the reaction of 2-methyl-2-(tosyloxymethyl)cyclohexanone with a base.[3,12] We assumed that the unusual product **8** would arise from ring expansion of enolate **V** to give zwitter ion intermediate **VI** followed by transannular cyclization.

In order to prove the hypothesis, we designed enol triflates **2j** and **2k** having a methoxyl group at the α′-position, as a substrate (Scheme 8). We envisioned that the electron donation by the methoxyl group would strongly



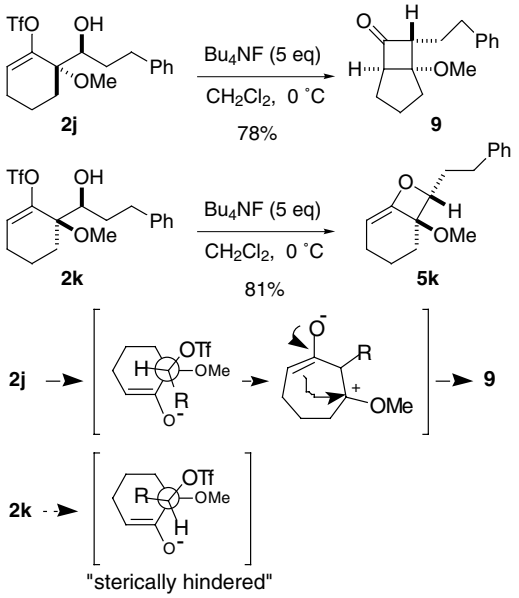
Scheme 6. Transition state models of the cyclization reactions.



Scheme 7. Cyclization reaction of α′-substituted enol triflate **2i**.

stabilize the zwitter ion intermediate like **VI** in Scheme 7, which leads to selective formation of the cyclization product with a bicyclo[3.2.0]heptane skeleton. Indeed, the reaction of triflate **2j** afforded the expected cyclobutanone **9** via a ring expansion pathway, while the corresponding *anti*-isomer **2k** underwent an *O*-alkylation reaction. The different behavior between these *syn*- and *anti*-isomers is quite similar with that of **2a** and **2b** in Scheme 6, and the results can be rationalized by using a similar transition state model. While the ring expansion reaction of **2j** proceeds through a transition state in which the ring carbon and the triflate moiety are antiparallel to each other, **2k** cannot undergo a similar reaction because of steric repulsion between the side chain and the six-membered ring.

In conclusion, a new synthetic method of cyclobutanone derivatives and four-membered enol ethers was developed on the basis of intramolecular cyclization of a ketone enolate. The cyclization precursors, enol triflates



Scheme 8. Cyclization reactions of α′-methoxy enol triflates **2j** and **2k**.

having a silyloxy group at the β′-position, were synthesized from the corresponding β-hydroxy ketones, which were prepared via an aldol reaction of a cycloalkanone and an aldehyde. Under the influence of TBAF, the enol triflates afforded a cyclobutanone or a four-membered enol ether through rearrangement of the trifluoromethanesulfonyl group followed by an intramolecular *C*- or *O*-alkylation reaction.[13] Synthetic applications of the products having a highly strained skeleton are currently under investigation.

Acknowledgements

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13. Typical procedure: enol triflate **2g** (0.54 g, 1.1 mmol) was diluted with a 1.0 M THF solution of TBAF (6.6 mL, 6.6 mmol) at room temperature. After being stirred for 1 h, aqueous $NaHCO_3$ solution was added. The aqueous layer was extracted with ether, and the combined organic layer was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by silica gel column chromatography (hexane–AcOEt, 20:1) afforded oxetane **5g** (0.23 g, 92%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.19–2.25 (m, 10H), 2.60 (ddd, J = 6.9, 9.6, 13.7 Hz, 1H), 2.79 (ddd, J = 5.1, 9.9, 13.7 Hz, 1H), 3.46–3.57 (m, 1H), 4.74 (ddd, J = 4.3, 7.6, 9.6 Hz, 1H), 4.79–4.85 (m, 1H), 7.16–7.32 (m, 5 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 25.36, 25.41, 29.72, 30.51, 31.44, 33.38, 44.95, 81.62, 95.25, 125.89, 128.33, 128.38, 141.26, 163.86.