Facile isomerization of silyl enol ethers catalyzed by triflic imide and its application to one-pot isomerization–(2 + 2) cycloaddition

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Abstract
A triflic imide (Tf\textsubscript{2}NH) catalyzed isomerization of kinetically favourable silyl enol ethers into thermodynamically stable ones was developed. We also demonstrated a one-pot catalytic reaction consisting of (2 + 2) cycloaddition and isomerization. In the reaction sequence, Tf\textsubscript{2}NH catalyzes both of the reactions.

Introduction
Silyl enol ethers, which are isolable equivalents of metal enolates, are useful and important intermediates in synthetic chemistry [1-3]. They react as a good nucleophile for the introduction of a carbon skeleton or a functional group at the α-position of a carbonyl group under appropriate conditions. Although silyl enol ethers are easily prepared from the corresponding ketones, the regiochemical issue would arise in the case of asymmetric ketones. Treatment with a strong base such as lithium diisopropylamide (LDA), followed by silyl chloride, under cryogenic conditions selectively affords kinetically favourable silyl enol ethers. On the other hand, thermodynamically stable ones can be predominantly obtained by the reaction with a silylating agent in the presence of a weak base, such as triethylamine, under equilibration conditions. Although the preparation of silyl enol ethers has been extensively studied, there have only been a limited number of studies on their isomerization [4-7]. Deyin\textsuperscript{e} reported that a catalytic amount of triethylammonium chloride promotes the isomerization to give thermodynamically favourable ones in moderate yield [5]. However, harsh conditions (reaction temperature: ca. 100 to 200 °C) were required for the complete equilibration. Yamamoto and co-workers reported that a SnCl\textsubscript{4}–(BINOL
monomethyl ether) complex (5–10 mol %) catalyzes the isomerization of silyl enol ethers at −78 °C [6]. By using this catalyst, they remarkably achieved the kinetic resolution of racemic silyl enol ethers. To make this isomerization synthetically useful and valuable, the development of more-reactive catalysts and a facile procedure would be required. In this communication, we describe isomerization of silyl enol ethers by an organocatalyst under mild conditions and its application to a one-pot catalytic reaction involving isomerization of silyl enol ethers and (2 + 2) cycloaddition.

Results and Discussion

During our research on triflic imide (Tf$_2$NH)-catalyzed reactions [8], we accidentally found that the isomerization of kinetically favourable silyl enol ethers into thermodynamically stable ones occurs smoothly in the presence of Tf$_2$NH. When the TBS enol ether 1a was treated with a catalytic amount of Tf$_2$NH (1.0 mol %) in CH$_2$Cl$_2$ at ambient temperature, isomerization resulted in the thermodynamically stable 2a in 92% yield along with the recovered 1a and ketone 3 (Table 1, entry 1). Equilibrium was reached within 5 min. The reaction using 20 mol % of Tf$_2$NH resulted in an increase of decomposition into 3 (entry 2). When the reaction was performed at −10 °C, the chemical yield of 2 was slightly improved (entry 3). In contrast, no isomerization was observed at −78 °C even after 1 h (entry 4). The catalytic isomerization reaction also proceeded in toluene (entry 5), but no (or almost no) isomerization occurred in CH$_3$CN (entry 6). When 10-camphorsulfonic acid (5 mol %) was used as a catalyst for 1 h, the isomerization was incomplete (entry 7). Enol ethers bearing typical silyl groups were also isomerized (entries 8–12). The decomposition of TMS enol ether 1b into 3b slightly increased at ambient temperature compared to that at −10 °C (entries 8 and 9). In the reaction of TIPS enol ether 1d, the reaction rate decreased and more catalyst (5 mol %) was necessary to achieve equilibrium within 5 min (entry 12).

Several silyl enol ethers were explored for catalytic isomerization under the optimized conditions (1 mol % of Tf$_2$NH, −10 °C, CH$_2$Cl$_2$). The results are summarized in Table 2. All the kinetically favourable silyl enol ethers 1 were smoothly isomerized to the thermodynamically stable 2 in the presence of Tf$_2$NH.

A plausible mechanism for the catalytic isomerization is shown in Scheme 1. Silyl enol ether 1 is rapidly protonated by a catalytic amount of Tf$_2$NH to give the corresponding siloxonium cation 4, and, then, another molecule of silyl enol ether 1 deprotonates the α-position of 4. Equilibration results in the selective production of the thermodynamically more stable 2.

As a side reaction, the counter anion, Tf$_2$N$^-$, could attack the silicon atom of 2 to produce silyl triflic imide (R$_2$SiNTf$_2$) [8-12] and the corresponding ketone 3. Therefore, the use of a large amount of Tf$_2$NH causes decomposition into 3 (Table 1, entry 2).

| Table 1: Tf$_2$NH-catalyzed isomerization of silyl enol ethers.$^{a,b}$ |
|---|---|---|---|---|
| entry | 1 (SiR$_3$) | solvent | temp. (°C) | % yield |
| 2 | 1 (recovd.) | 3 |
| 1 | 1a (TBS) | CH$_2$Cl$_2$ | rt | 92 | 6 | 2 |
| 2 | 1a | CH$_2$Cl$_2$ | rt | 71 | 4 | 25 |
| 3 | 1a | CH$_2$Cl$_2$ | −10 | 93 | 4 | 3 |
| 4 | 1a | CH$_2$Cl$_2$ | −78 | 3 | 97 | 2 |
| 5 | 1a | toluene | −10 | 92 | 5 | 2 |
| 6 | 1a | CH$_3$CN | −10 | 2 | 96 | 2 |
| 7 | 1a | CH$_2$Cl$_2$ | −10 | 25 | 64 | 11 |
| 8 | 1b (TMS) | CH$_2$Cl$_2$ | rt | 85 | 6 | 9 |
| 9 | 1b | CH$_2$Cl$_2$ | −10 | 91 | 4 | 5 |
| 10 | 1b | CH$_2$Cl$_2$ | −78 | 0 | 95 | 5 |
| 11 | 1c (TES) | CH$_2$Cl$_2$ | −10 | 78 | 5 | 17 |
| 12 | 1d (TIPS) | CH$_2$Cl$_2$ | −10 | 92 | 3 | 5 |

$^{a,b}$Yields were determined by GC–MS. $^b$Regiosomer 1 (>99% purity) was used as a substrate. $^{c}$20 mol % of catalyst was used. $^{d}$Reactions were carried out for 1 h. $^{e}$5 mol % of catalyst was used. $^{f}$10-Camphorsulfonic acid was used as a catalyst.
We have previously reported the Tf$_2$NH catalyzed (2 + 2) cycloaddition of silyl enol ethers with acrylates generating substituted cyclobutanes [10]. We are intrigued that the isomerization of silyl enol ethers and successive (2 + 2) cycloaddition could be promoted by Tf$_2$NH in a one-pot reaction. When 1a was treated with Tf$_2$NH (1 mol%) under the isomerization conditions (−10 °C), followed by the addition of methyl acrylate (5) at −78 °C, 6-methylbicyclo[4.2.0]octane 6 and its diastereomer were obtained in 86% and 6%, respectively (Scheme 2a). No formation of their regioisomers was observed.

The obtained compound 6 is identical to the product in the reaction of 2a with 5 [10,13]. It is noteworthy that two different reactions, isomerization and (2 + 2) cycloaddition, are catalyzed by Tf$_2$NH [14-18]. By contrast, when 1a reacted with 5 in the presence of Tf$_2$NH at −78 °C, (2 + 2) cycloaddition directly proceeded to give 2-methylbicyclo[4.2.0]octane 7 in 66% yield along with the formation of two diastereomers (Scheme 2b). Obviously, at this temperature, no isomerization of 1a occurred.

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only the separation to remove the corresponding kinetically favourable regioisomer, but also loss of the undesired regioisomer.

**Conclusion**

In summary, we have developed a new catalytic isomerization reaction of silyl enol ethers. Kinetically favourable silyl enol ethers were smoothly converted into thermodynamically stable ones by treatment with a catalytic amount of Tf₂NH under mild conditions. Moreover, we demonstrated that the one-pot reaction involves two different catalytic reactions, an isomerization and a (2 + 2) cycloaddition.

**Supporting Information**

Supporting Information File 1
Experimental details and spectral data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-73-S1.pdf]

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**References**


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