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(2+2) Cycloaddition Reaction of Alkyl Enol Ethers with Acrylates by *in Situ* Generated Silyl Triflic Imide Catalyst

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We describe here (2+2) cycloaddition reaction of alkyl enol ethers with acrylates catalyzed by triethylsilyl triflic imide (Et_3SiNTf_2), which was *in situ* generated from triethylsilane and triflic imide. The reaction efficiently provides substituted cyclobutanes bearing alkoxy function in a stereoselective manner.

Key words (2+2) cycloaddition; cyclobutane; triflic imide; silane

Although cyclobutane ring is one of the fundamental carbocyclic skeletons, only a limited number of synthetic methods exists for the synthesis.[1—3] As one of the solutions, we have reported (2+2) cycloaddition reaction of silyl enol ethers with α,β-unsaturated esters catalyzed by $EtAlCl_2$ (*ca.* 20 mol% catalyst loading) to produce substituted cyclobutanes bearing siloxy moiety with high stereoselectivity.[4—6] Recently, Corey's group developed its asymmetric variant giving enantiomerically enriched cyclobutanes using a chiral oxazaborolidine-$AlBr_3$ catalyst.[7] In the course of our continuous study directed to develop the practical process, we have found trifluoromethenesulfonimide (Tf_2NH) efficiently catalyses the (2+2) cycloaddition reaction.[8,9] The method displays several synthetic advantages, such as high stereoselectivity, wide substrate scope, low catalyst loading (*ca.* 0.1 mol%), and applicability for multi-gram scale synthesis. In the cycloaddition reaction, silyl triflic imide (R_3SiNTf_2) *in situ* generated from Tf_2NH and silyl enol ether substrate is recognized as an actual catalyst showing strong Lewis acidity.[10—14] Actually, we observed pre-assembled R_3SiNTf_2 activates the cycloaddition reaction. However, our reported method using Tf_2NH includes the following problems. First, if R_3SiNTf_2 is used, it is hard to handle the catalyst owing to its air sensitivity. Second, only silyl enol ethers can be used as substrates for the Tf_2NH-catalyzed (2+2) cycloaddition reaction. R_3SiNTf_2 does not *in situ* formed with the other electron-rich olefins, such as alkyl enol ethers. In this paper, we wish to report (2+2) cycloaddition reaction of alkyl enol ethers with acrylates in the presence of pre-assembled silyl triflic imide from silyl hydride and Tf_2NH.

First of all, we examined (2+2) cycloaddition reaction of 1-methoxycyclohexene (**1a**) with benzyl acrylate (**2a**) in the presence of either Tf_2NH or trimethylsilyl triflic imide (Me_3SiNTf_2). $TMSNTf_2$ was prepared from trimethylsilyl chloride and silver triflic imide ($AgNTf_2$) and isolated according as Ghosez's method (Chart 1).[10] In the presence of Tf_2NH (10 mol%), no reaction occurred in CH_2Cl_2. On the contrary, Me_3SiNTf_2 (10 mol%) promoted (2+2) cycloaddition reaction to furnish cycloadduct **3aa** as a single diastereomer at −78 °C in 44% yield. The relative steteochemistry of **3aa** was tentatively assigned by comparison of the spectral data with structurally related compounds.[4] Although reaction time was prolonged, chemical yield of **3aa** does not increased and **1a** was still remained.

We were intrigued by *in situ* generation of silyl triflic imide during the reaction can achieve a simple operation protocol for (2+2) cycloaddition reaction of alkyl enol ethers. Ghosez and his co-workers reported Me_3SiNTf_2 could be synthesized from trimethylsilane and Tf_2NH at ambient temperature by only mixing under neat conditions.[11] Owing to its easier handling and commercially availability, we decided to use triethylsilane (Et_3SiH) for generation of triflic imide. However, when reaction of **1a** with **2a** was carried out in the presence of a catalytic amount of Et_3SiH and Tf_2NH at −78 °C, no (2+2) cycloaddition reaction proceeded at all (Table 1, entry 1). Notably, no side reaction, such as reduction of acrylate with Et_3SiH, occurred under the conditions. On the contrary, when the reaction was performed at 50 °C, only trace amount of **3aa** was formed but oligomerized product of **2a** was observed (entry 2). Next, we examined premixing of Et_3SiH and Tf_2NH to prepare Et_3SiNTf_2[15] *in situ* (without isolation) before cycloaddition reaction. Namely, after Et_3SiH (15 mol%) was treated with Tf_2NH (10 mol%) in toluene at ambient temperature for 15 min, the solution was added to a mixture of **1a** (1.4 eq) and **2a** (1.0 eq) in CH_2Cl_2 at −78 °C and stirred for 1 h to afford **3aa** as a sole stereoisomer in 47% yield (entry 3). Further optimization study revealed the catalyst was effectively generated in toluene at 50 °C for 10 min (entry 4), which resulted in the formation of **3aa** in 83%. On the other hand, generation of Et_3SiNTf_2 in CH_2Cl_2 was not so efficient (entry 5). Although microwave (MW) technique was submitted to prepare the actual catalyst *in situ*, the chemical yield of **3** was not improved (entry 6).

Under the optimal conditions for *in situ* generation of Et_3SiNTf_2 in hand, reaction with methyl acrylate (**2b**) afforded **3ab** in 84% yield (entry 7, Table 1). Ethyl enol ether **1b** is also employable (entry 8). However, (2+2) cycloaddition reaction was not successful in the reaction of less substi-

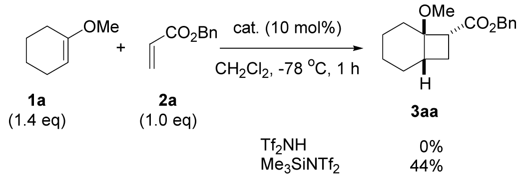

Chart 1. (2+2) Cycloaddition Reaction of Alkyl Enol Ether (**1a**) with Acrylate (**2a**)

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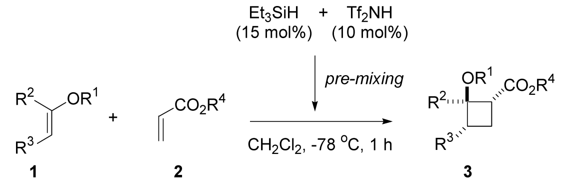
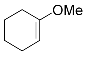
Table 1. (2+2) Cycloaddition Reaction of Alkyl Enol Ethers with Acrylates in the Presence of Tf_2NH and Et_3SiH[a)]

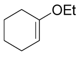


Entry	Substrate		Pre-mixing conditions		% yield of **3**
	1	**2** (R^4)	Temp (°C)	Time (min)	
1	**1a**	**2a** (Bn)	−78	0	0
2	**1a**	**2a**	50	0	Trace
3	**1a**	**2a**	rt	15	47
4	**1a**	**2a**	50	10	83
5[b)]	**1a**	**2a**	50	10	37
6[c)]	**1a**	**2a**	50	2	32
7	**1b**	**2a**	50	10	52
8	**1a**	**2b** (Me)	50	10	84
9	**1c**	**2a**	50	10	0
10	**1d**	**2a**	50	10	0

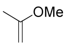
a) Standard conditions: (pre-mixing) Et_3SiH (15 mol%), Tf_2NH (10 mol%) in toluene, (cycloaddition reaction) **1** (1.4 eq), **2** (1.0 eq) in CH_2Cl_2 at −78 °C for 1 h. Yield was calculated based on **2**. *b*) (pre-mixing) In CH_2Cl_2. *c*) (pre-mixing) Under microwave irradiation.



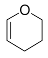
1a



1b



1c



1d

tuted enol ethers, such as 2-methoxypropene (**1c**) and dihydropyrane (**1d**). In the reaction of **1c**, **1c** was fully consumed by cationic oligomerization (entries 9, 10).

In summary, we have developed (2+2) cycloaddition reaction of alkyl enol ethers catalyzed by silyl triflic imide, which was *in situ* generated from triethylsilane and triflic imide. It provides substituted cyclobutanes bearing alkoxy function in a stereoselective manner.

Experimental

Typical Procedure for the Catalytic (2+2) Cycloaddition Reaction To a toluene solution of Tf_2NH (0.2 M in toluene, 100 μl, 20 μmol) was added triethylsilane (3.5 mg, 30 μmol) at 50 °C and stirred for 10 min at the same temperature. After cooled to −78 °C, the mixture was diluted with CH_2Cl_2 (2.0 ml). To the solution were added 1-methoxycyclohexene (**1a**) (31 mg, 0.28 mmol) and benzyl acrylate (**2a**) (32 mg, 0.20 mmol), and stirred for additional 1 h at −78 °C. The resulting mixture was quenched with Et_3N (14 μl, 0.10 mmol), and then concentrated *in vacuo*. The residue was purified by chromatography on silica gel in hexane–AcOEt (10 : 1) to afford **3aa** (45 mg, 83% yield) as a single diastereomer.

(1*R**,6*S**,8*R**)-8-(Benzyloxycarbonyl)methoxybicyclo[4.2.0]octane (**3aa**): Coloress oil. IR (neat) cm^{-1}: 2930, 2856, 2829, 1732, 1454. ^1H-NMR (400 MHz, $CDCl_3$) δ: 1.17—1.81 (10H, m), 2.35 (1H, m), 3.03 (1H, dd, J=8.1, 1.0 Hz), 3.28 (3H, s), 5.09 (1H, d, J=12.4 Hz), 5.16 (1H, d, J=12.4 Hz), 7.34 (5H, m). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 172.7, 79.7, 51.5, 50.7, 45.6, 36.4, 26.5, 23.9, 21.3, 20.4, 18.8. LR-MS *m/z*: 274 (M^+). HR-MS *m/z*: Calcd for $C_{17}H_{22}O_3$ 274.1569 (M^+), Found 274.1552.

(1*R**,6*S**,8*R**)-8-(Methoxycarbonyl)methoxybicyclo[4.2.0]octane (**3ab**): Colorless oil. IR (neat) cm^{-1}: 2932, 2858, 1732, 1435, 1219, 1182, 1103, 1080. ^1H-NMR (400 MHz, $CDCl_3$) δ: 1.25—1.87 (m, 10H), 2.38 (m, 1H), 3.0 (dd, J=7.9, 1.0 Hz, 1H), 3.32 (s, 3H), 3.68 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 172.7, 79.7, 51.5, 50.7, 45.6, 36.4, 26.5, 23.9, 21.3, 20.4, 18.8. LR-MS *m/z*: 198 (M^+). HR-MS *m/z*: Calcd for $C_{11}H_{18}O_3$ 198.1256 (M^+), Found 198.1247.

(1*R**,6*S**,8*R**)-8-(Benzyloxycarbonyl)ethoxybicyclo[4.2.0]octane (**3ba**): Colorless oil. IR (neat) cm^{-1}: 2927, 2850, 2828, 1730, 1455. ^1H-NMR (400 MHz, $CDCl_3$) δ: 1.2 (t, J=8 Hz, 3H), 1.25—1.91 (m, 10H), 2.35 (m, 1H), 3.02 (dd, J=8.2, 1.0 Hz, 1H), 3.33 (q, J=8.0 Hz), 5.08 (d, J=12 Hz, 1H), 5.15 (d, J=12 Hz, 1H), 7.65 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 172.1, 135.9, 128.5, 128.4, 128.2, 128,1, 128.0, 79.9, 66.1, 50.7, 45.7, 36.2, 26.3, 23.8, 21.3, 20.2, 18.8. LR-MS *m/z*: 286 (M^+). HR-MS *m/z*: Calcd for $C_{18}H_{24}O_3$ 288.1725 (M^+), Found 288.1738.

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References

1) Baldwin J. E., "Comprehensive Organic Synthesis," Vol. 5, ed. by Trost B. M., Fleming I., Pergamon Press, Oxford, 1991, pp. 63—84.
2) Crimmins M. T., "Comprehensive Organic Synthesis," Vol. 5, ed. by Trost B. M., Fleming I., Pergamon Press, Oxford, 1991, pp. 123—150.
3) Lee-Ruff E., Mladenova G., *Chem. Rev.*, **103**, 1449—1483 (2003).
4) Takasu K., Ueno M., Inanaga K., Ihara M., *J. Org. Chem.*, **69**, 517—521 (2004).
5) Takasu K., Nagao S., Ueno M., Ihara M., *Tetrahedron*, **60**, 2071—2078 (2004).
6) Inanaga K., Takasu K., Ihara M., *J. Am. Chem. Soc.*, **126**, 1352—1353 (2004).
7) Canales E., Corey E. J., *J. Am. Chem. Soc.*, **129**, 12686—12687 (2007).
8) Inanaga K., Takasu K., Ihara M., *J. Am. Chem. Soc.*, **127**, 3669—3670 (2005).
9) Takasu K., Ishii T., Inanaga K., Ihara M., *Org. Synth.*, **83**, 193—199 (2006).
10) Mathieu B., Ghosez L., *Tetrahedron Lett.*, **38**, 5497—5500 (1997).
11) Mathieu B., Ghosez L., *Tetrahedron*, **58**, 8219—8226 (2002).
12) Ishihara K., Hiraiwa Y., Yamamoto H., *Synlett*, **2001**, 1851—1854 (2001).
13) Boxer M. B., Yamamoto H., *J. Am. Chem. Soc.*, **128**, 48—49 (2006).
14) Takasu K., Hosokawa N., Inanaga K., Ihara M., *Tetrahedron Lett.*, **47**, 6053—6056 (2006).
15) Mikami K., Jpn. Kokai Tokkyo Koho, JP 10330293 (1988) [*Chem. Abstr.*, **130**, 81199].