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Remarkable Tris(trimethylsilyl)silyl Group for Diastereoselective [2 + 2] Cyclizations

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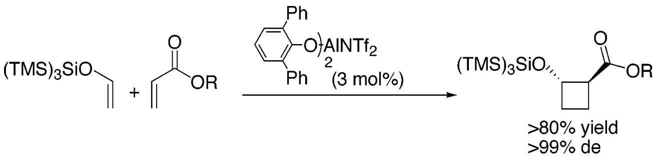
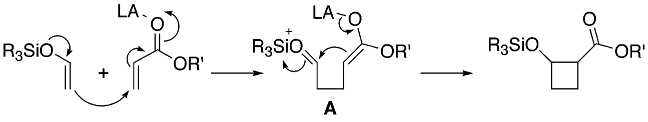
ABSTRACT



Diastereoselective [2 + 2] cyclizations of aldehyde- and ketone-derived silyl enol ethers with acrylates is described. The use of the tris(trimethylsilyl)silyl group allows for unprecedented reactivity, yields, and selectivity for these cyclizations. The presence of silicon–silicon bonds proved to be important for this transformation, where typical silyl groups (TBS and TIPS) failed to give any desired product. The bulky bis(2,6-diphenylphenoxide) aluminum triflimide catalyst was essential for high diastereoselectivity.

The cyclobutane core is found in various natural and unnatural bioactive molecules and is commonly found as a synthetic intermediate.[1] There are limited reports[1−3] for efficient synthesis of these four-membered rings via nonphotochemical [2 + 2] cycloadditions since the concerted [2 + 2] cyclization is disallowed by Woodward Hoffmann rules.[4] Thus, both thermal and ground-state catalytic reactions must proceed through a stepwise mechanism. Herein lies the difficulty, as the intermediates may be long lived, to give rise to undesired products. The use of aldehyde enol equivalents has been previously unattainable presumably due to this fact. In this communication, we wish to report the highly regio- and diastereoselective, aluminum-catalyzed [2 + 2] cycloaddition of silyl enol ethers (SEE) with α,*β*-unsaturated esters, which is believed to go through a Michael-aldol-type mechanism (Scheme 1).

Scheme 1. Proposed Michael-Aldol Mechanism for [2 + 2] Cyclization



To prevent side reactions potentially stemming from high-energy intermediates, we envisaged stabilizing **A** (Scheme 1) sterically and electronically. In fact, recently Ihara has released excellent reports on [2 + 2] cyclizations between TBS and TIPS enol ethers derived from ketones and esters.[2c−e] Unfortunately, however, use of simple acetalde-

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[1] For reviews on cyclobutane synthesis and reactions, see: (a) Nemoto, H.; Fukumoto, K. *Synlett* **1997**, 863 (b) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449.

[2] (a) Takasu, K.; Ueno, M.; Ihara, M. *Tetrahedron Lett.* **2000**, *41*, 2145. (b) Takasu, K.; Ueno, M.; Ihara, M. *J. Org. Chem.* **2001**, *66*, 4667. (c) Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. *J. Org. Chem.* **2004**, *69*, 517. (d) Takasu, K.; Nagao, S.; Ueno, M.; Ihara, M. *Tetrahedron* **2004**, *60*, 2071. (e) During manuscript prepartation, an example of Brønsted acid-catalyzed [2 + 2] cyclizations was reported: Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem Soc.* **2005**, *127*, 3666.

[3] Recent selected examples: (a) Hayashi Y.; Narasaka, K. *Chem. Lett.* **1989**, 793. (b) Ichikawa, Y.; Narita, A.; Shiozawa, A.; Hayashi, Y.; Narasaka, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1919 (c) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869 (d) Sweis, R. F.; Schramm, M. P.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 7442. (e) Ito, H.; Hasegawa, M.; Takenaka, Y.; Kobayashi, T.; Iguchi, Kazuo. *J. Am. Chem. Soc.* **2004**, *126*, 4520. (f) Avenoza, A.; Busto, J. H.; Canal, N.; Peregrina, J. M. *J. Org. Chem.* **2005**, *70*, 330.

[4] Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, Germany, 1970.

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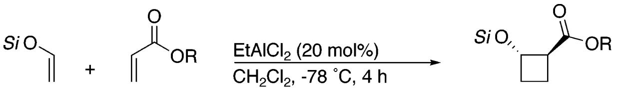
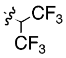
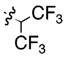
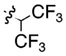
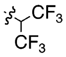
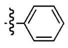
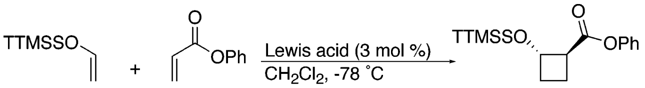
Table 1. Importance of Silyl Group and Ester[a]

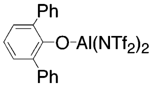
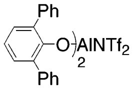
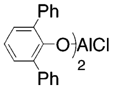


entry	*Si*	R	% yield[b] (trans/cis)[c]
1	TBS		0
2	TIPS		0
3	SiMe$_2$TMS		7 (1.5/1)
4	TTMSS		45 (2/1)
5	TTMSS		58 (5/1)

[a] Reactions were run with 1.2 mmol of silyl enol ether and 1.0 mmol of acrylate under a N_2 atmosphere. [b] Isolated yield. [c] Determined by ^1H NMR of crude material.

Table 2. Aluminum-Based Lewis Acid Screening[a]



entry	Lewis acid	time (h)	% yield[b] (trans/cis)[c]
1	EtAlCl$_2$	4	58 (5/1)
2	Al(NTf$_2$)$_3$	1	21[b] (6/1)
3	EtAl(NTf$_2$)$_2$	1	28[b] (6/1)
4	Et$_2$AlNTf$_2$	1	58 (5/1)
5		2	54 (7/1)
6		4	68 (10/1)
7		12	NR
8		6	NR[c]

[a] Reactions were run with 1.2 mmol of silyl enol ether and 1.0 mmol of acrylate under a N_2 atmosphere. [b] Isolated yield. [c] Determined by ^1H NMR of crude material. [d] Reaction run at room temperature.

hyde derived SEEs gave no [2 + 2] adducts, showing only decomposition of the SEE (Table 1, entries 1 and 2).

To compensate for the instability of the cationic portion in proposed intermediate **A**, an electron-donating substituent that provides increased hyperconjugation was employed. Use of the (dimethyl-trimethylsilyl)silyl-derived enol ether afforded the cyclobutane adduct in 7% yield (Table 1, entry 3). This represents the first example of a [2 + 2] condensation between an acetaldehyde silyl enol ether and an acrylic ester. Realizing that the introduction of one trimethylsilyl group was able to give the desired product, we next turned our attention to the tris(trimethylsilyl)silyl (TTMSS) group, which has three Si−Si bonds. It has been reported that the group is of comparable steric size to *tert*-butyl[5] and is among the strongest electron donators to π systems, lone pair centers, and molecular cations.[6] Therefore, TTMSS should be an excellent functional group for this reaction, and indeed TTMSS-derived silyl enol ether gave the [2 + 2] adduct in 45% yield (Table 1, entry 4). The effect of the R group of the ester was next investigated, and phenyl acrylate was shown to give the best yield and diastereoselectivity (Table 1, entry 5). Encouraged by these results, various Lewis acids were screened under identical reaction conditions as in Table 1; however, only the aluminum-based catalyst gave acceptable results, while $TiCl_4$, $GaCl_3$, $SnCl_4$, $AgNTf_2$, TMSOTf, and $HNTf_2$ all gave <10% of the desired product. Previously, we had observed that unwanted transfer of silyl groups during attempted asymmetric aldol synthesis could be prevented by using a bulky Lewis acid with the triflimide counteranion.[7]

Many aluminum−triflimide-based catalysts were examined, and significant results are summarized in Table 2.

It was found that a catalyst loading of 3 mol % was sufficient for good yields and a reasonable reaction time. While Al(NTf$_2$)$_3$ gave better diastereoselectivity than EtAlCl$_2$, the reactivity was too high, giving lower yields of the desired product, showing decomposition of the silyl enol ether (Table 2, entry 2). The use of EtAl(NTf$_2$)$_2$ and Et$_2$AlNTf$_2$ gave similar diastereoselectivity, and the latter gave a comparable yield with EtAlCl$_2$, with a decrease in reaction time (Table 2, entries 3 and 4 vs 1). In an effort to further increase the diastereoselectivity of the reaction, the use of bulky catalysts based on the methylaluminum bis(2,6-diphenylphenoxide) (MAPH)[8] scaffold was investigated. While the previous use of this catalyst was for the selective recognition of less hindered aldehydes for the Mukaiyama aldol reaction, implementation in this [2 + 2] reaction was imagined to increase the yield by imposing a steric environment that could concomitantly increase the diastereoselectivity during the ring-closing (aldol) step. The best result was obtained with bis(2,6-diphenylphenoxide) aluminum triflimide (BDAT) (Table 2, entry 6), while bis(2,6-diphenylphenoxide) aluminum chloride was unable to give the cyclobutane adduct even when warmed to room temperature (Table 2, entries 7 and 8).

To increase the scope and generality of the [2 + 2] reaction,[2c,d] nucleophiles with substitution at the β-position (aldehyde derived) as well as α-position (ketone derived) were investigated. The reaction was found to proceed smoothly in both cases at −40 °C with a 3 mol % catalyst

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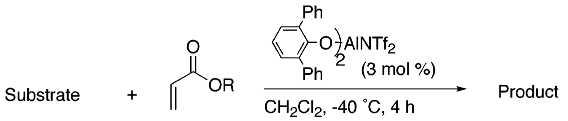
(5) Frey, J.; Schottland, E.; Rappoport, Z.; Bravo-Zhivotovskii, D.; Nakash, M.; Botoshansky, M.; Kaftory, M.; Apeloig, Y. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2555.

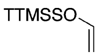
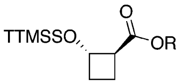
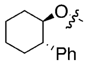
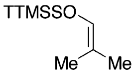
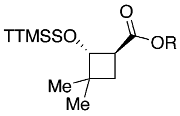
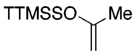
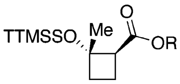
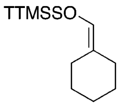
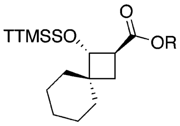
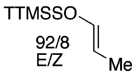
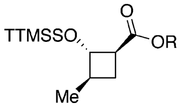
(6) Bock, H.; Meuret, J.; Baur, R.; Ruppert, K. *J. Organomet. Chem.* **1993**, *446*, 113.

(7) Hiraiwa, Yukihiro, Ph.D. Thesis, Department of Chemistry, University of Chicago, Chicago, IL, 2003.

(8) Marx, A.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 178.

Table 3. Diastereoselective [2 + 2] Cyclization of TTMSS-Enol Ether[a]



entry	substrate	R	% yield[b] (trans/cis)[c]	major product
1		Ph	84 (10/1)	
2[d]		Ph	82 (10/1)	
3[e]			81 (>99/1/0/0)[f]	
4		Ph	91 (>99/1)	
5		Ph	81 (25/1)	
6		Ph	94 (>99/1)	
7	 92/8 E/Z	Ph	93 (>99/1, 10/1[g])	

[a] Reactions were run with 1.2 mmol of silyl enol ether and 1.0 mmol of acrylate under a N_2 atmosphere. [b] Isolated yield. [c] Determined by ^{1}H NMR of crude material. [d] Performed with 1 mol % 24 h. [e] Reaction at 0 °C, 12 h. [f] Two isomers were found; the major is shown, while the minor was a trace amount of compound with inversion of the siloxy group. [g] Trans/cis for siloxy/methyl, with inversion of methyl being the minor isomer.

loading, giving exceedingly high yields with high trans/cis ratios (Table 3). Use of 1 mol % catalyst gave similar results, but extended reaction times were necessary (entry 2, Table 3). The acetaldehyde SEE was able to afford the cyclobutane adduct with >99/1/0/0 dr (Table 3, entry 3) by use of the chiral *trans*-(1*R*,2*S*)-2-phenylcyclohexanol-derived ester. Cleavage of the bulky silyl group is accomplished in identical fashion as the more common silicon groups by simple use of 1 equiv of TBAF, affording the free alcohol without a change in the diastereomeric ratio (see Supporting Information). Somewhat surprisingly, the highest-yielding reaction was the formation of the spiro compound (Table 3, entry 6), giving complete diastereoselectivity, and was confirmed by X-ray analysis.

In summary, we have developed the first diastereoselective [2 + 2] cyclization for aldehyde-derived silyl enol ethers. The use of the tris(trimethylsilyl)silyl group used in conjunction with the bulky BDAT catalyst allows for high yields and diastereoselectivity. Importantly, this [2 + 2] cyclization was unattainable with other typical silyl groups (i.e., TBS and TIPS). This reactivity is presumably due to the large steric size of the silyl group in conjunction with its superb electronic properties. These aldehyde enolate equivalents are stable, easy to handle, and appropriately reactive under Lewis acidic conditions. This reaction works with both aromatic- and aliphatic-based esters (Table 3), and use of a chiral auxiliary provides the hydroxycylcobutanecarboxylic esters in >99% ee.

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

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