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Catalytic Asymmetric Simmons–Smith Cyclopropanation of Silyl Enol Ethers. Efficient Synthesis of Optically Active Cyclopropanol Derivatives

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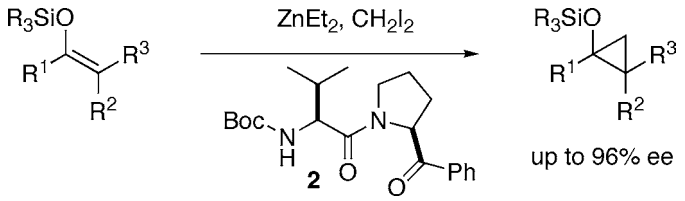
ABSTRACT



This paper describes a catalytic asymmetric Simmons–Smith cyclopropanation of silyl enol ethers using dipeptide 2 as the ligand. A variety of optically active cyclopropyl silyl ethers can be obtained in high yields. Up to 96% ee was obtained. The dipeptide can be recovered after the reaction in good yield and reused without the loss of reactivity or enantioselectivity.

Cyclopropanols and their derivatives are versatile building blocks for organic synthesis because of their ability to undergo various synthetically useful transformations.[1] Asymmetric Simmons−Smith cyclopropanation of prochiral enol ethers would provide an effective route to a variety of cyclopropanol derivatives.[2−4] However, such transformations are still highly challenging because currently successful asymmetric Simmons−Smith cyclopropanations usually require the presence of hydroxyl groups to direct the reaction.[5,6]

In 1998, we reported that a new class of (iodomethyl)-zinc species ($RXZnCH_2I$) generated by reacting RXH with an appropriate organozinc reagent (Scheme 1) are highly effective for the cyclopropanation of various olefins including substrates which were previously unreactive.[7a,b] A wide range of RXH from alcohols to acids (such as CF_3COOH and CF_3SO_3H) can be used to generate the (iodomethyl)zinc species, and the reactivity of these reagents toward cyclopropanation can be regulated by adjusting the electronic and/or steric nature of the modifier RXH. Importantly, we observed that the asymmetric cyclopropanation of unfunctionalized olefins

(1) For recent reviews, see: (a) Kulinkovich, O. G. *Chem. Rev.* **2003**, *103*, 2597. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151.

(2) For a leading review on the metal-catalyzed asymmetric cyclopropanation of enol ethers using transition-metal-based carbenoids generated from diazocarbonyl compounds, giving a carbonyl-containing cyclopropane product, see: ref 1b.

(3) For recent reviews on Simmons−Smith cyclopropanation, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (c) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1. (d) Denmark, S. E.; Beutner, G. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2002; p 85. (e) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

(4) For leading references on chiral enol ether-based asymmetric cyclopropanations, see: (a) Sugimura, T.; Futagawa, T.; Tai, A. *Tetrahedron Lett.* **1988**, *29*, 5775. (b) Sugimura, T.; Koguro, K.; Tai, A. *Tetrahedron Lett.* **1993**, *34*, 509. (c) Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Katagiri, T.; Miyashige, R.; Mizuguchi, M.; Nagano, S.; Sugimori, S.; Tai, A.; Tei, T.; Okuyama, T. *Tetrahedron* **2001**, *61*, 7495.

(5) For leading references on chiral reagent-based asymmetric cyclopropanations of allylic alcohols, see: (a) Ukaji, Y.; Nishimura, M.; Fujisawa, T. *Chem. Lett.* **1992**, 61. (b) Denmark, S. E.; Edwards, J. P. *Synlett* **1992**, 229. (c) Ukaji, Y.; Sada, K.; Inomata, K. *Chem. Lett.* **1993**, 1227. (d) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651. (e) Charette, A. B.; Prescott, S.; Brochu, C. *J. Org. Chem.* **1995**, *60*, 1081. (f) Kitajima, H.; Aoki, Y.; Ito, K.; Katsuki, T. *Chem. Lett.* **1995**, 1113. (g) Charette, A. B.; Juteau, H.; Lebel, H.; Deschênes, D. *Tetrahedron Lett.* **1996**, *37*, 7925. (h) Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207. (i) Charette, A. B.; Lemay, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1090. (j) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943.

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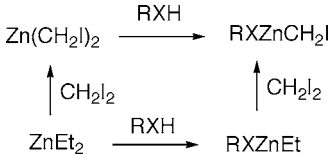
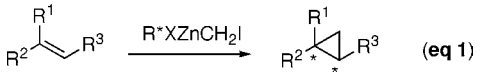
Scheme 1

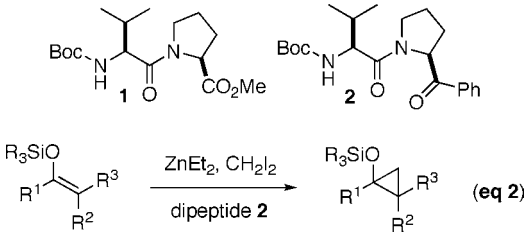


was possible when chiral R*XH was used,[7a,b] which provides an approach for the development of asymmetric cyclopropanation of various olefins (eq 1).



(eq 1)

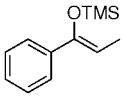
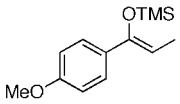
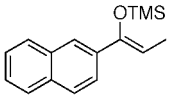
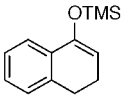
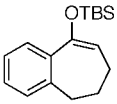
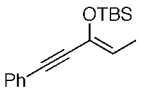
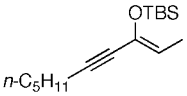
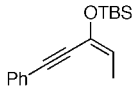
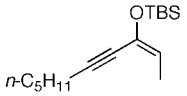
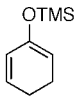
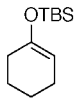
On the basis of this study, we have continued our efforts to develop an asymmetric Simmons−Smith cyclopropanation which does not require a specific directing functional group.[7] We recently reported a cyclopropanation system using a stoichiometric amount of dipeptide *N*-Boc-L-Val-L-Pro-OMe (**1**) as the chiral ligand, and up to 91% ee was obtained for unfunctionalized olefins.[8] Subsequently, we found that a catalytic process is feasible.[9,10] Herein, we wish to report a highly enantioselective cyclopropanation of silyl enol ethers using this system (eq 2).



(eq 2)

Our initial studies with (*Z*)-1-phenyl-1-(trimethylsilyloxy)-1-propene using 25 mol % of dipeptide **1**, $ZnEt_2$, CH_2I_2, ZnI_2, and ethyl methoxyacetate (EMA) gave the cyclopropane product in 87% ee.[9] When the cyclopropanation was carried out with 25 mol % of a modified dipeptide **2**, 93% ee was obtained (Table 1, entry 1).[11] Moreover, about 90% of this dipeptide could be recovered after the reaction, and the

Table 1. Asymmetric Cyclopropanation of Olefins with Dipeptide **2**[a]

entry	substrate	yield (%)[b]	ee (%)
1		99	93[d,7b]
2		97	93[d,13]
3		80	95[e,13]
4		97	93[d,14]
5		72	96[f]
6		89	86[f,12]
7		86	86[f]
8		91	93[f,12]
9		83	93[f]
10		79[c]	92[d,15]
11		90	72[f,16]
12		77	89[f]

[a] The cyclopropanation was carried out with silyl enol ether (1.2 mmol), peptide **2** (0.3 mmol), ethyl methoxyacetate (EMA) (1.2 mmol), CH_2I_2 (2.7 mmol), $ZnEt_2$ (1.5 mmol), ZnI_2 (0.30 mmol, prepared from I_2 and $ZnEt_2$ in situ) in CH_2Cl_2 at −40 °C for 24−72 h. For entries 1−4 and 12, the reaction time is 48 h; for entries 5−9 and 11, the reaction time is 72 h; for entry 10, the reaction time is 24 h. [b] Isolated yield. [c] The isolated product contains ca. 10% biscyclopropanes. [d] Enantioselectivity was determined by GC (Chiraldex B-DM). [e] Enantioselectivity was determined by HPLC (Chiralcel OD Column). [f] Enantioselectivity was determined by GC (Chiraldex B-DM) after desilylation by TBAF.

(6) For leading references on chiral catalyst-based asymmetric cyclopropanations of allylic alcohols, see: (a) Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575. (b) Imai, N.; Takahashi, H.; Kobayashi, S. *Chem. Lett.* **1994**, 177. (c) Imai, N.; Sakamoto, K.; Takahashi, H.; Kobayashi, S. *Tetrahedron Lett.* **1994**, *35*, 7045. (d) Denmark, S. E.; Christenson, B. L.; Coe, D. M.; O'Connor, S. P. *Tetrahedron Lett.* **1995**, *36*, 2215. (e) Denmark, S. E.; Christenson, B. L.; O'Connor, S. P. *Tetrahedron Lett.* **1995**, *36*, 2219. (f) Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. *Tetrahedron* **1995**, *51*, 12013. (g) Charette, A. B.; Brochu, C. *J. Am. Chem. Soc.* **1995**, *117*, 11367. (h) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 584. (i) Imai, N.; Sakamoto, K.; Maeda, M.; Kouge, K.; Yoshizane, K.; Nokami, J. *Tetrahedron Lett.* **1997**, *38*, 1423. (j) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 3390. (k) Denmark, S. E.; O'Connor, S. P.; Wilson, S. R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1149. (l) Balsells, J.; Walsh, P. J. *J. Org. Chem.* **2000**, *65*, 5005. (m) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168.

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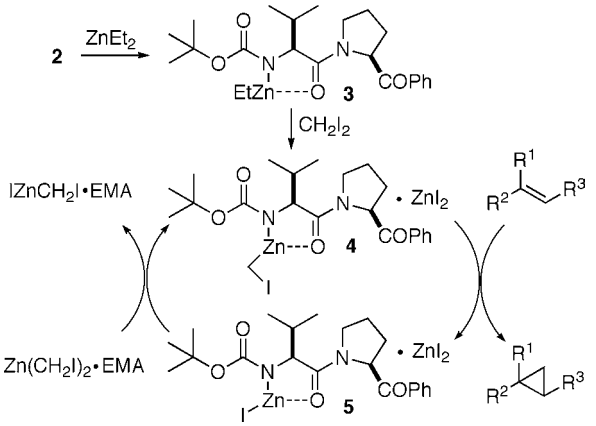
(8) Long, J.; Yuan, Y.; Shi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13632.

(9) Long, J.; Du, H.; Li, K.; Shi, Y. *Tetrahedron Lett.* **2005**, *46*, 2737.

(10) For a recent report on asymmetric cyclopropanation of allylic and homoallylic ethers using chiral phosphoric acids, see: Lacasse, M.-C.; Poulard, C.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 12440.

recovered ligand provided similar reactivity and enantioselectivity for the cyclopropanation. Encouraged by this result, a series of silyl enol ethers were examined for the asymmetric cyclopropanation using 25 mol % of **2** as the ligand. As shown in Table 1, cyclopropanation reactions proceeded smoothly, giving corresponding cyclopropyl silyl ethers in high yields and ee's. Up to 96% ee was obtained for the aromatic silyl enol ethers (Table 1, entry 5). Alkynyl enol ethers are also effective substrates (Table 1, entries 6−9), and higher ee's (93% ee) were obtained with (*E*)-isomers. Desilylation of the cyclopropane products with TBAF provided optically active alkynylcyclopropanols which can be used for further transformations.[12] For 2-(trimethylsilyloxy)-1,3-cyclohexadiene (Table 1, entry 10), the cyclopropanation predominately occurred on the enol ether, giving the vinyl cyclopropane in 92% ee. No noticeable kinetic resolution was observed in this case. For simple cyclic silyl enol ethers, somewhat lower ee's were obtained (Table 1, entries 11 and 12). Although a detailed understanding of the reaction mechanism awaits further study, a plausible catalytic cycle is shown in Scheme 2. Compound **4** could be generated from dipeptide **2** by deprotonation with $ZnEt_2$, followed by halogen exchange with CH_2I_2. Compound **4** could then cyclopropanate the olefin to form **5**, which could regenerate **4** by exchange with $Zn(CH_2I)_2$ to complete the cycle.

Scheme 2



In summary, we have found that a dipeptide-catalyzed asymmetric cyclopropanation is very effective for silyl enol ethers. A variety of cyclopropyl silyl ethers can be obtained in high yields and ee's. The dipeptide can be recovered after the reaction in high yield and reused without the loss of reactivity or enantioselectivity. Structural studies of the peptide ligand on enantioselectivity as well as the search for a more effective catalytic process are currently underway.

Acknowledgment. We are grateful for the generous financial support from the National Science Foundation CAREER Award program (CHE-9875497).

Supporting Information Available: The characterization data of dipeptide **2**, the cyclopropanation procedure, and the characterization data of cyclopropyl silyl ethers, along with the GC and HPLC data for the determination of the enantiomeric excess of cyclopropanes (14 pages). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The reaction rate and enantioselectivity are dependent upon the amount of catalyst used and the reaction temperature: at 0 °C for 3 h, 25 mol % of **2**, 100% conversion, 87% ee; 10 mol % of **2**, 100% conversion, 85% ee; 5 mol % of **2**, 99% conversion, 82% ee. At room temperature for 2 h, 25 mol % of **2**, 100% conversion, 83% ee; 10 mol % of **2**, 100% conversion, 79% ee; 5 mol % of **2**, 100% conversion, 73% ee.

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(15) Rinderhagen, H.; Mattay, J. *Chem.−Eur. J*. **2004**, *10*, 851.

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