Communication

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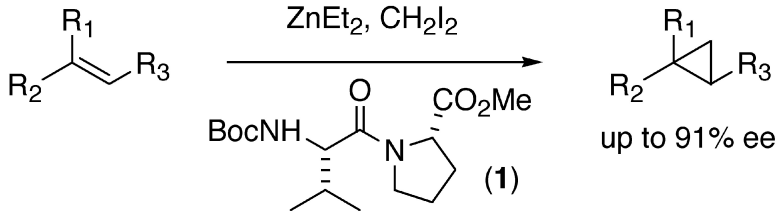
J. Am. Chem. Soc., **2003**, 125 (45), 13632-13633• DOI: 10.1021/ja030488e • Publication Date (Web): 18 October 2003



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Published on Web 10/18/2003

Asymmetric Simmons−Smith Cyclopropanation of Unfunctionalized Olefins

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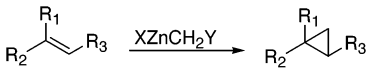
Cyclopropanes are an important class of molecules. The strain associated with the three-membered ring allows cyclopropanes to undergo a variety of synthetically useful ring-opening reactions.[1] The versatile reactivity of cyclopropanes also provides useful tools for the mechanistic study of many important chemical and biological transformations.[2] Furthermore, cyclopropanes are present in many biologically and medicinally important molecules, and their unique structural features provide important opportunities for drug design.

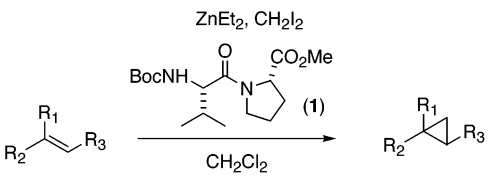
The Simmons−Smith reaction is a powerful method for the synthesis of cyclopropanes from olefins (Scheme 1),[3,4] and great progress has been made in this area. Efficient asymmetric cyclopropanations have been achieved using a variety of chiral auxiliaries including chiral ketals, allylic ethers, enol ethers, and vinyl boronic esters.[5−8] Enantioselective cyclopropanation of allylic alcohols has also been highly successful using either chiral reagents or catalysts.[9,10]

Scheme 1



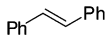
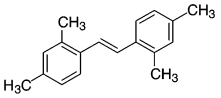
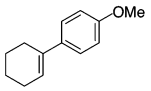
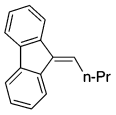
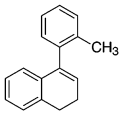
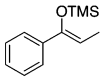
The common feature of these methods is the utilization of the directing function of heteroatoms present in the substrate. The coordination of the directing group to the Zn reagent not only greatly enhances the reaction rate via the effect of proximity, but also leads to an orderly transition state, thus providing effective stereocontrol. Therefore, removal of the directing group from the olefin substrate is detrimental to the stereochemical control of the reaction. The absence of the directing group also dramatically reduces the substrate's reactivity toward cyclopropanation, which itself is still an existing problem even for racemic cyclopropanation. Asymmetric Simmons−Smith type cyclopropanation of unfunctionalized olefins via transfer of a simple methylene group from a (halomethyl)zinc reagent faces issues of both reactivity and selectivity and is a challenging problem that remains unsolved.[11] To the best of our knowledge, prior to our initial studies,[12] only two reports appeared in the literature for asymmetric cyclopropanation of unfunctionalized olefins using (halomethyl)zinc reagents, and <4% ee was reported.[13a,b] In this communication, we wish to report a highly promising asymmetric cyclopropanation for unfunctionalized olefins.

Scheme 2



In our efforts to develop such a process, we discovered that treating a simple dipeptide *N*-Boc-L-Val-L-Pro-OMe (**1**) with $ZnEt_2$ and CH_2I_2 led to an active cyclopropanation system with encouragingly high enantioselectivity (Scheme 2). For example, when 3,4-dihydronaphthalene was used as substrate, the corresponding cyclopropanation product was formed in 71% yield and 72% ee (Table 1, entry 1). The high reactivity of this system is also illustrated in the case of normally sluggish stilbenes.[12] The

Table 1. Asymmetric Cyclopropanation of Olefins with *N*-Boc-L-Val-L-Pro-OMe (**1**)[a]

entry	substrate	yield (%)[d]	ee (%)
1		71	72[f]
2[b]		83	75[g]
3[c]		43	89[g]
4		71	75[g]
5[c]		78	90[f]
6		84	78[f] (98[h])
7		83	90[f] (99[h])
8		71	91[f] (99[h])
9		71	79[g] (98[h])
10		68[e]	85[f]

[a] The cyclopropanation was carried out with olefin (0.8 mmol), $ZnEt_2$ (1.8 mmol), CH_2I_2 (2.6 mmol), and peptide **1** (1.0 mmol) in CH_2Cl_2 at 0 °C for 24 h unless otherwise noted. For entry 1, the reaction was carried out at −30 °C for 48 h. For entries 4 and 10, the reaction was carried out at −40 °C for 72 and 15 h, respectively. [b] The reaction was carried out with olefin (0.8 mmol), $ZnEt_2$ (5.4 mmol), CH_2I_2 (7.8 mmol), and peptide **1** (3.0 mmol) in CH_2Cl_2 at 0 °C for 60 h. [c] The reaction was carried out with olefin (0.4 mmol), $ZnEt_2$ (1.8 mmol), CH_2I_2 (2.6 mmol), and peptide **1** (1.0 mmol) in CH_2Cl_2 at 0 °C for 48 h. [d] Isolated yield after purification. The cyclopropane products gave satisfactory spectroscopic characterization. [e] The product was isolated after desilylation by TBAF. [f] Enantioselectivity was determined by chiral GC (Chiraldex B-DM). [g] Enantioselectivity was determined by chiral HPLC (Chiralcel OJ). [h] The ee's after recrystallization from hexanes.

10.1021/ja030488e CCC: $25.00

cyclopropanes could be formed in reasonable yields with up to 89% ee (Table 1, entries 2 and 3). Further studies showed that various trisubstituted olefins were also effective substrates toward cyclopropanation (Table 1, entries 4−10). Up to 91% ee was attained (Table 1, entry 8).[14] Enol derivatives were found to be highly reactive substrates, and up to 85% ee was obtained (Table 1, entries 9 and 10). In some cases, the ee's could be further improved by recrystallization (Table 1, entries 6−9). While a stoichiometric amount of the dipeptide ligand was used in the current system, about 80% of the ligand could be recovered and the recovered ligand showed the same reactivity and selectivity. A detailed understanding of the mode of asymmetric induction for this system awaits further study.

In summary, we have found that the readily available dipeptide *N*-Boc-L-Val-L-Pro-OMe (**1**) is an effective ligand for asymmetric cyclopropanation of unfunctionalized olefins. Up to 91% ee has been attained. These results suggest that the development of a highly enantioselective Simmons−Smith type cyclopropanation of unfunctionalized olefins via transfer of a simple methylene group is a real possibility. Peptide **1** provides a promising lead for the optimization of the ligand structure to enhance the enantioselectivity. Mechanistic studies of this peptide-promoted cyclopropanation as well as the search for an effective catalytic process are currently underway.

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

Supporting Information Available: The cyclopropanation procedure and the GC and HPLC data for the determination of the enantiomeric excess of the cyclopropanes (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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JA030488E