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Catalytic asymmetric Simmons–Smith cyclopropanation of unfunctionalized olefins

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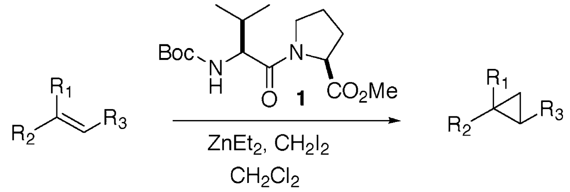
Abstract—This paper describes a catalytic asymmetric cyclopropanation system for unfunctionalized olefins using readily available dipeptide *N*-Boc-L-Val-L-Pro-OMe (**1**) as ligand.

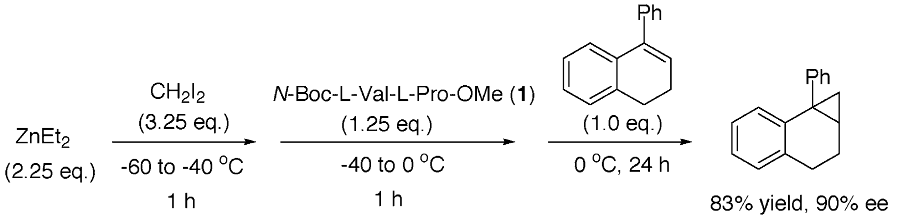
Cyclopropanes are present in many biologically and medicinally important molecules, and the Simmons–Smith reaction is a widely used method for the synthesis of cyclopropanes from olefins.[1] Great progress has been made in asymmetric cyclopropanations using chiral auxiliaries,[2] reagents,[3] and catalysts.[4] In these methods, heteroatoms present in substrates act as directing groups to enhance the reaction rate via the proximity effect and to create an orderly transition state to achieve effective stereocontrol. Removal of the directing group is unfavorable for both reactivity and stereoselectivity. Thus, asymmetric Simmons–Smith type cyclopropanation of unfunctionalized olefins via transfer of a simple methylene group presents a formidable challenge.[5]



Scheme 1.

In our efforts to develop such a process, we recently discovered that a system using a stoichiometric amount of dipeptide *N*-Boc-L-Val-L-Pro-OMe (**1**), $ZnEt_2$, and CH_2I_2 provided encouragingly high enantioselectivity (72–91% ee) for olefins without directing groups (Scheme 1).[6] To further develop the process, a key question is whether such system can be catalytic, thus requiring substoichiometric amounts of chiral ligand. Herein we wish to report our preliminary efforts on this subject.

In our original stoichiometric procedure,[6] the cyclopropanation was carried out in the sequence as outlined in Scheme 2 using 2.25 equiv of $ZnEt_2$, 3.25 equiv of



Scheme 2.

Keywords: Asymmetric cyclopropanation; Peptide ligand; Simmons–Smith cyclopropanation; Unfunctionalized olefins.

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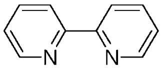
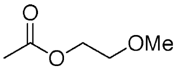
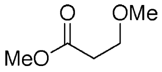
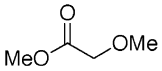
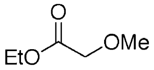
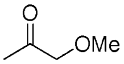
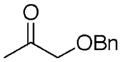
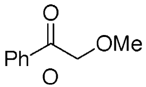
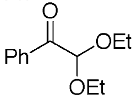
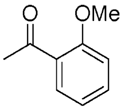
Table 1. The effect of achiral additives on asymmetric cyclopropanation of olefins[a]

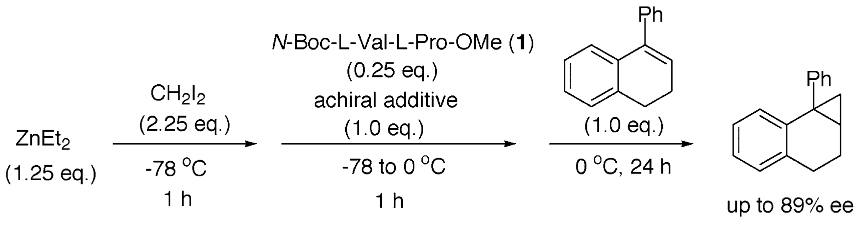
Entry	Additive	Conv. (ee)[b] (%)
1	None	57 (52)
2		2 (8)
3		91 (69)
4		65 (87)
5		68 (88)
6		73 (89)
7		49 (88)
8		52 (89)
9		45 (89)
10		32 (85)
11		85 (78)

[a] The cyclopropanation was carried out with olefin (1.0 equiv), $ZnEt_2$ (1.25 equiv), CH_2I_2 (2.25 equiv), achiral additive (1.0 equiv), and dipeptide **1** (0.25 equiv) in CH_2Cl_2 at 0 °C for 24 h.

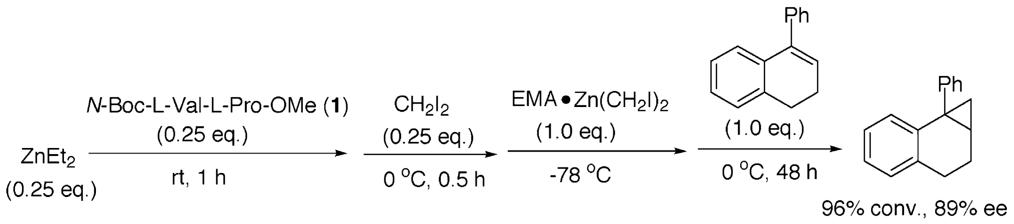
[b] The conversion and enantioselectivity were determined by GC (Chiraldex B-DM).

CH_2I_2, and 1.25 equiv of *N*-Boc-L-Val-L-Pro-OMe (**1**). In the case of 1-phenyl-3,4-dihydronaphthalene, the cyclopropane product was obtained with 90% ee in 83% yield after 24 h at 0 °C. However, when the cyclopropanation was carried out with 0.25 equiv of the dipeptide, only 52% ee and 42% conversion were obtained (0 °C, 48 h). A similar ee (52%) was observed when less $ZnEt_2$ (1.25 equiv) and CH_2I_2 (2.25 equiv) were used (Table 1, entry 1). The lower ee's obtained with substoichiometric amounts of chiral ligand could be largely due to the enhanced background reaction from $Zn(CH_2I)_2$. Subsequently, we surmised that an achiral additive could be used to coordinate with $Zn(CH_2I)_2$ and reduce the background cyclopropanation,[7] thus enhancing the ee (Scheme 3). As shown in Table 1, the enantioselectivity was indeed increased by a variety of achiral additives. For example, 89% ee was obtained with ethyl methoxyacetate (EMA) (Table 1, entry 6). The ee was comparable to that obtained by the original stoichiometric procedure, showing that the chiral ligand could be used in substoichiometric amounts. Changing the reagent addition order as outlined in Scheme 4 further improved the reaction conversion. This catalytic process was illustrated with a number of substrates (Table 2), and the ee's obtained were similar to those previously obtained with a stoichiometric amount of chiral ligand. It was also observed that the cyclopropanation could be accelerated by addition of ZnI_2.[4c,f,8,9]

In summary, we have found that the readily available dipeptide *N*-Boc-L-Val-L-Pro-OMe (**1**) is an effective ligand to promote the catalytic asymmetric cyclopropanation of unfunctionalized olefins. While the turn-over efficiency and enantioselectivity need to be further improved, the current study has shown that a catalytic asymmetric cyclopropanation is conceptually feasible, and provides useful information for future development. Further mechanistic studies as well as the search for an effective catalytic process with high reactivity and enantioselectivity are currently underway.

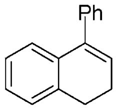
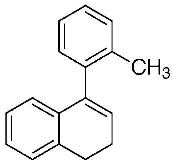
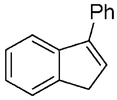
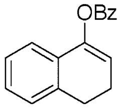
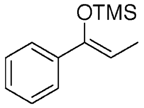


Scheme 3.



Scheme 4.

Table 2. Asymmetric cyclopropanation of olefins with *N*-Boc-L-Val-L-Pro-OMe (**1**)[a]

Entry	Substrate	Yield[b] (%)	ee[c] (%)
1		87	89
2		60	89
3		85	77
4		52	78
5		96	87

[a] The cyclopropanation was carried out with olefin (1.0 equiv), $ZnEt_2$ (1.25 equiv), CH_2I_2 (2.25 equiv), ethyl methoxyacetate (1.0 equiv), dipeptide **1** (0.25 equiv), and ZnI_2 (0.25 equiv) in CH_2Cl_2 at 0 °C for 48 h except for entry 5, where the reaction was carried out at −40 °C for 72 h.

[b] Isolated yield after purification. For entries 2 and 4, the cyclopropane products were isolated after removing the unreacted olefins by epoxidation with *m*-CPBA in CH_2Cl_2. The cyclopropane products gave satisfactory spectroscopic characterization.

[c] Enantioselectivity was determined by chiral GC (Chiraldex B-DM).

Acknowledgements

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9. *Representative catalytic asymmetric cyclopropanation procedure* (Table 2, entry 1): To a flame-dried and Ar-filled 10 mL Schlenk tube (tube A) was added a solution of *N*-Boc-L-Val-L-Pro-OMe (**1**) (98.5 mg, 0.3 mmol, 0.25 equiv) in freshly distilled CH_2Cl_2 (1.0 mL), followed by addition of neat $ZnEt_2$ (37.0 mg, 31 μL, 0.3 mmol, 0.25 equiv). The solution was stirred at room temperature for 1 h. Upon cooling to 0 °C under argon, CH_2I_2 (80.4 mg, 24 μL, 0.3 mmol, 0.25 equiv) was added dropwise and the reaction mixture was stirred at 0 °C for 0.5 h. Upon cooling to −78 °C under argon, ZnI_2 (95.8 mg, 0.3 mmol, 0.25 equiv) was added.
Simultaneously, to another flame-dried and Ar-filled 10 mL Schlenk tube (tube B) were added neat $ZnEt_2$ (148.2 mg, 123 μL, 1.2 mmol, 1.0 equiv) and freshly distilled CH_2Cl_2 (1.0 mL). Upon cooling to −78 °C under argon, CH_2I_2 (642.8 mg, 193 μL, 2.4 mmol, 2.0 equiv) was added. After the resulting mixture was stirred at this temperature for 1 h (a white precipitate formed after ~2 min), ethyl

methoxyacetate (EMA) (141.8 mg, 141 μL, 1.2 mmol, 1.0 equiv) was added. Upon warming to −40 °C over several minutes and staying at this temperature for 5 min (a homogeneous solution was formed), the reaction mixture was then cooled to −78 °C.

The solution in tube B was transferred to tube A via a cannula at −78 °C, followed by addition of 1-phenyl-3,4-dihydronaphthalene (247.5 mg, 1.2 mmol, 1.0 equiv). Upon warming to 0 °C and stirring at this temperature for 48 h, the reaction mixture was diluted with CH_2Cl_2 (50 mL), quenched with saturated NH_4Cl solution (10 mL), and stirred for 20 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and hexane (2 × 20 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by flash chromatography (hexane) to give the cyclopropane as a white powder (230.4 mg, 87% yield, 89% ee).