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Mechanistic Studies on a Dipeptide-Promoted Asymmetric Cyclopropanation of Unfunctionalized Olefins

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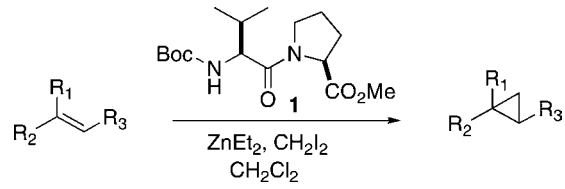
ABSTRACT



This paper describes mechanistic studies on a dipeptide-promoted asymmetric cyclopropanation system for unfunctionalized olefins. Zinc species generated from the deprotonation of the N−H of the dipeptide ligand have been investigated by NMR and X-ray structure studies and are likely to be responsible for asymmetric cyclopropanation. ZnI_2 plays an important role in promoting the reaction.

The asymmetric Simmons−Smith reaction presents an important approach to the synthesis of optically active cyclopropanes from olefins.[1] Various effective systems have been developed using chiral auxiliaries,[2] reagents,[3] or catalysts.[4] In most of these methods, substrates usually contain heteroatoms as directing groups to enhance both reactivity and stereocontrol. Asymmetric Simmons−Smith-type cyclopropanation for prochiral olefins without effective directing groups generally presents a formidable challenge.[5]

Our earlier studies have shown that encouragingly high enantioselectivity (72−91% ee) can be achieved for the cyclopropanation of unfunctionalized olefins using a stoichiometric amount of dipeptide *N*-Boc-L-Val-L-Pro-OMe (**1**),

(1) For leading reviews, see: (a) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (d) Denmark, S. E.; Beutner, G. *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. (f) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041.

(2) For leading references, see: (a) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254. (b) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256. (c) Sugimura, T.; Futagawa, T.; Tai, A. *Tetrahedron Lett.* **1988**, *29*, 5775. (d) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986. (e) Charette, A. B.; Côté, B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1991**, *113*, 8166. (f) Kang, J.; Lim, G. J.; Yoon, S. K.; Kim, M. Y. *J. Org. Chem.* **1995**, *60*, 564. (g) Charette, A. B.; Côté, B. *J. Am. Chem. Soc.* **1995**, *117*, 12721. (h) Song, Z.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, C.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069.

(3) For leading references on chiral reagents for 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) Kitajima, H.; Aoki, Y.; Ito, K.; Katsuki, T. *Chem. Lett.* **1995**, 1113. (f) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943.

(4) For leading references on chiral catalysts for allylic alcohols, see: (a) Takahashi, H.; Yoshioka, M.; Ohno, M.; Kobayashi, S. *Tetrahedron Lett.* **1992**, *33*, 2575. (b) Imai, N.; Sakamoto, K.; Takahashi, H.; Kobayashi, S. *Tetrahedron Lett.* **1994**, *35*, 7045. (c) Denmark, S. E.; Christenson, B. L.; Coe, D. M.; O'Connor, S. P. *Tetrahedron Lett.* **1995**, *36*, 2215. (d) Charette, A. B.; Brochu, C. *J. Am. Chem. Soc.* **1995**, *117*, 11367. (e) Imai, N.; Sakamoto, K.; Maeda, M.; Kouge, K.; Yoshizane, K.; Nokami, J. *Tetrahedron Lett.* **1997**, *38*, 1423. (f) Denmark, S. E.; O'Connor, S. P. *J. Org. Chem.* **1997**, *62*, 3390. (g) Balsells, J.; Walsh, P. J. *J. Org. Chem.* **2000**, *65*, 5005. (h) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12168. (i) Shitama, H.; Katsuki, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 2450.

(5) (a) Sawada, S.; Oda, J.; Inouye, Y. *J. Org. Chem.* **1968**, *33*, 2141. (b) Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron Lett.* **1968**, 3495. (c) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621. (d) Charette, A. B.; Francocur, S.; Martel, J.; Wilb, N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4539. (e) Lorenz, J. C.; Long, J.; Yang, Z.; Xue, S.; Xie, Y.; Shi, Y. *J. Org. Chem.* **2004**, *69*, 327.

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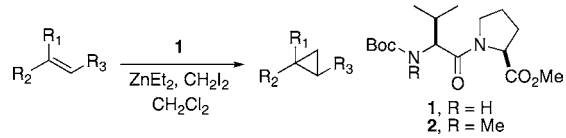
$ZnEt_2$, and CH_2I_2 (Scheme 1).[6a] Subsequent studies showed that a catalytic process for this cyclopropanation is feasible

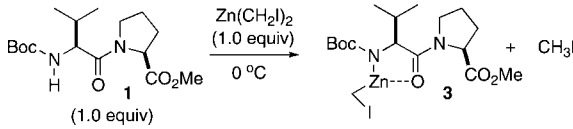
Scheme 1



when an achiral ligand such as ethyl methoxyacetate (EMA) is added to coordinate with $Zn(CH_2I)_2$ to reduce background reaction.[6b,c,7] It was observed that addition of ZnI_2 can facilitate the cyclopropanation, particularly when the reaction is carried out at low temperature.[6b,c,8] A better mechanistic understanding of this cyclopropanation system would be beneficial for further development. Herein we wish to report our preliminary efforts on this subject.

In contrast to dipeptide **1**, no conversion was obtained for 1-phenyl-3,4-dihydronaphthalene when a methylated dipeptide, *N*-Boc-*N*-Me-L-Val-L-Pro-OMe (**2**), was used. This indicates that the N−H of dipeptide **1** was important for the asymmetric cyclopropanation. When dipeptide **1** was treated with $Zn(CH_2I)_2$ at 0 °C, MeI was slowly formed as judged by the ^{1}H NMR spectrum, suggesting that compound **1** was slowly deprotonated by $Zn(CH_2I)_2$ to form a peptide bound zinc reagent, putatively drawn as **3** (Scheme 2). When the

Scheme 2



cyclopropanation of 1-phenyl-3,4-dihydronaphthalene was performed with 1.0 equiv of **1** and 1.0 equiv of $Zn(CH_2I)_2$, 30% conversion and 85% ee were obtained for the product after 24 h at 0 °C (Figure 1, curve A). The product ee was found to increase with time (from 70% ee at 1 h to 85% ee at 14 h), indicating that more and more asymmetric cyclopropanation via a chiral species occurred with time, which is consistent with compound **3** being involved for the asymmetric cyclopropanation as it was formed gradually from dipeptide **1** and $Zn(CH_2I)_2$.

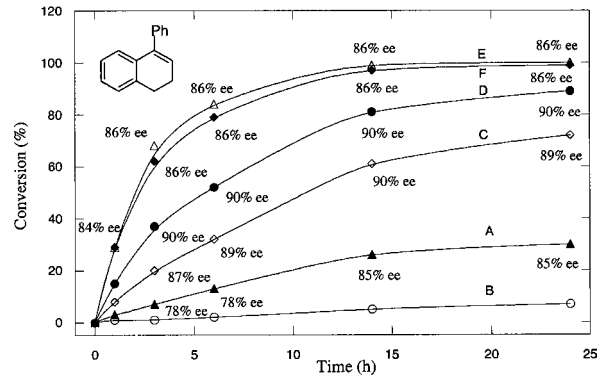
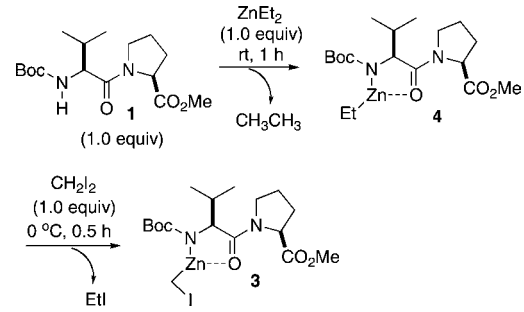


Figure 1. Plot of the conversion of 1-phenyl-3,4-dihydronaphthalene against time (h). The curves presented are: (A) $Zn(CH_2I)_2$ (1.0 equiv) + *N*-Boc-L-Val-L-Pro-OMe (**1**) (1.0 equiv); (B) L*-$ZnCH_2I$ (**3**) (2.0 equiv); (C) L*-$ZnCH_2I$ (**3**) (2.0 equiv) + ZnI_2 (0.4 equiv); (D) L*-$ZnCH_2I$ (**3**) (2.0 equiv) + ZnI_2 (1.0 equiv); (E) L*-$ZnCH_2I$ (**3**) (1.0 equiv) + $Zn(CH_2I)_2$ (1.0 equiv); (F) L*-ZnI (**9**) (1.0 equiv) + $Zn(CH_2I)_2$ (1.0 equiv) (L* = *N*-Boc-L-Val-L-Pro-OMe). All reactions were carried out in CH_2Cl_2 at 0 °C.

Compound **3** can be generated more cleanly by treating dipeptide **1** with $ZnEt_2$, followed by CH_2I_2 (Scheme 3). The

Scheme 3



transformations can be readily monitored by the formation of CH_3CH_3 and EtI. The ^{1}H and ^{13}C NMR data are consistent with the structures of compounds **3** and **4** (see Supporting Information). For compound **3**, the *N*-$ZnCH_2I$ signal overlapped with the signal of the Boc group. To avoid this complication, a Cbz-protected dipeptide Cbz-L-Val-L-Pro-OMe (**5**) was then used for further NMR study. In this case, the methylene signal of *N*-$ZnCH_2I$ displayed two clear doublets at ~1.5 ppm (see Supporting Information), which is consistent with the CH_2 group being placed in a chiral environment. Obtaining a crystal structure for compounds **3**, **4**, or related compounds proved to be extremely challenging. A suitable single crystal of **7** derived from ligand **6** and $ZnEt_2$ was finally obtained after much experimentation. The X-ray structure (Figure 2) shows that a dimer is formed via a complexing carbonyl of the Boc and amide groups with zinc atoms. At this moment, it is not clear whether the dimerization plays an important role in catalysis. No

(6) (a) Long, J.; Yuan, Y.; Shi, Y. *J. Am. Chem. Soc.* **2003**, *125*, 13632. (b) Long, J.; Du, H.; Li, K.; Shi, Y. *Tetrahedron Lett.* **2005**, *46*, 2737. (c) Du, H.; Long, J.; Shi, Y. *Org. Lett.* **2006**, *8*, 2827.

(7) For recent reports on asymmetric cyclopropanation using chiral phosphoric acid derived Zn reagents, see: (a) Lacasse, M.-C.; Poulard, C.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 12440. (b) Voituriez, A.; Charette, A. B. *Adv. Synth. Catal.* **2006**, *348*, 2363.

(8) For theoretical studies and discussion on the effect of ZnX_2, see: (a) Nakamura, E.; Hirai, A.; Nakamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5844. (b) Zhao, C.; Wang, D.; Phillips, D. L. *J. Am. Chem. Soc.* **2002**, *124*, 12903. (c) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 2341.

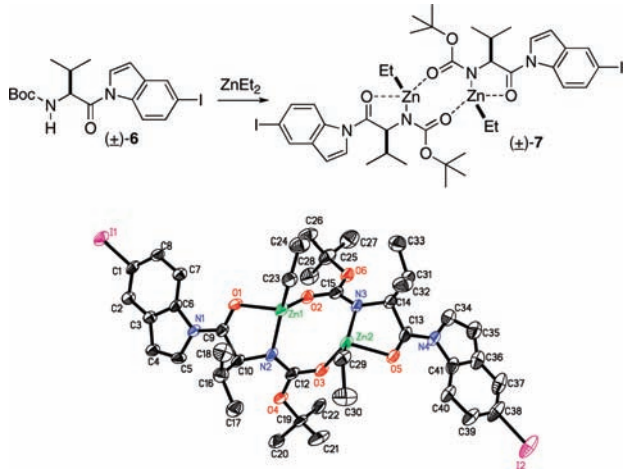


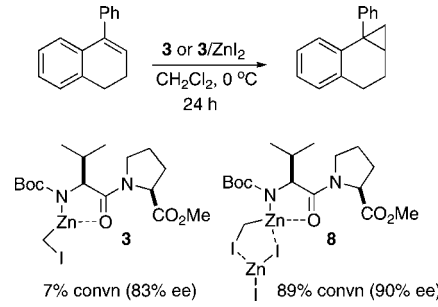
Figure 2. Structure of compound **7**.

nonlinear effects were observed for the cyclopropanation of 1-phenyl-3,4-dihydronaphthalene with dipeptide **1**.

Interestingly, compound **3** prepared via the aforementioned method (Scheme 3) was not effective for cyclopropanation, giving only 7% conversion (83% ee) for 1-phenyl-3,4-dihydronaphthalene after 24 h at 0 °C (Figure 1, curve B). It was surmised that higher reactivity obtained with 1.0 equiv of $Zn(CH_2I)_2$ and 1.0 equiv of **1** (Figure 1, curve A) could be due to the fact that the cyclopropanation might be facilitated by ZnI_2 or related species resulting from the decomposition of $Zn(CH_2I)_2$[9] and/or background reaction of the olefin with $Zn(CH_2I)_2$. Subsequent studies showed that the cyclopropanation with **3** was indeed enhanced by the addition of ZnI_2 (Figure 1, curves C and D), giving 89% conversion and 90% ee with 2.0 equiv of **3** and 1.0 equiv of ZnI_2 after 24 h at 0 °C.

The effects of ZnX_2 on Simmons−Smith cyclopropanation have been described and discussed.[4c,f,8,10] For example, Denmark and co-workers reported that ZnI_2 has a favorable effect on the bissulfonamide-catalyzed cyclopropanation of allylic alcohols.[4c,f] The increased reaction rate and enantioselectivity caused by ZnI_2 is attributed to the formation of the more reactive and selective $IZnCH_2I$ species via a Schlenk equilibrium. In their theoretical studies, Nakamura and co-workers proposed that ZnX_2 could accelerate the cyclopropanation as a Lewis acid via a five-centered transition state.[8a,c] The precise role of ZnI_2 in the current system awaits further study.[11] ZnI_2 could activate **3** via a five-membered species (**8**) (Scheme 4), following the proposed model by Nakamura.[8a,c] ZnI_2 could also facilitate the cyclopropanation by breaking possible dimers analogous to **7**, or it could facilitate the opening of a vacant orbital on

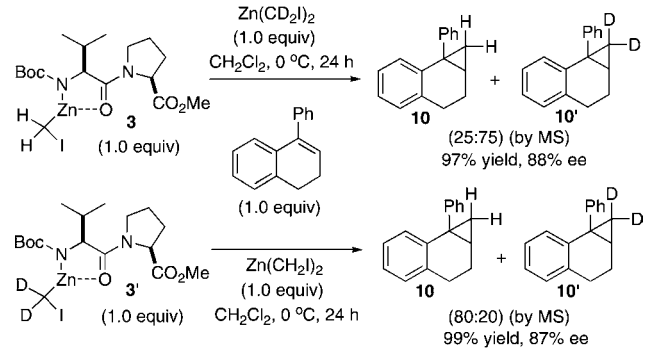
Scheme 4



the Zn atom for iodine to coordinate, activating the methylene group toward cyclopropanation.[5c]

The cyclopropanation proceeded efficiently with 1.0 equiv of **3** and 1 equiv of $Zn(CH_2I)_2$ without addition of ZnI_2 (Figure 1, curve E), suggesting that ZnI_2 or related species, formed in situ from the decomposition and/or background reaction of $Zn(CH_2I)_2$, was effective in promoting the cyclopropanation. High ee's obtained in this study also suggested that the asymmetric process is faster than the background reaction. When the cyclopropanation was performed with 1.0 equiv of L*-ZnI (**9**) (L* = *N*-Boc-L-Val-L-Pro-OMe) and 1.0 equiv of $Zn(CH_2I)_2$, 99% conversion and 86% ee were obtained after 24 h at 0 °C (Figure 1, curve F). In this case, cyclopropanating species **3** was probably generated in situ via the transmetalation between L*-ZnI (**9**) and $Zn(CH_2I)_2$. NMR studies also indicated that L*-ZnI (**9**) can undergo rapid transmetalation with $Zn(CH_2I)_2$.[12] The facile transmetalation between the chiral Zn species and $Zn(CH_2I)_2$ was also observed in a deuterium labeling study in which a mixture of labeled and unlabeled products was formed regardless of whether L*-$ZnCH_2I$ (**3**) and $Zn(CD_2I)_2$ or L*-$ZnCD_2I$ (**3′**) and $Zn(CH_2I)_2$ were used (Scheme 5).

Scheme 5



On the basis of these results, a plausible catalytic cycle is shown in Scheme 6. Compound **3**, generated from dipeptide **1** by deprotonation with $ZnEt_2$ and subsequent halogen

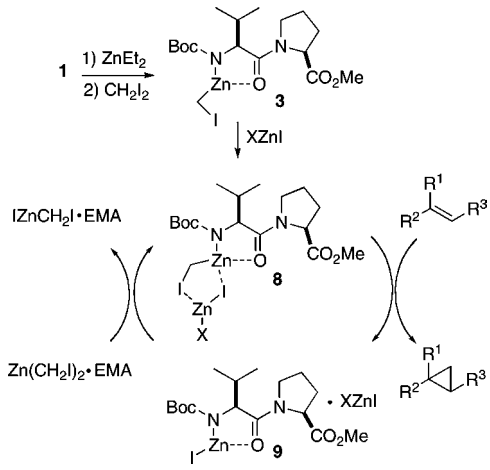
(9) For a leading reference, see: Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 4539.

(10) For leading references on studies and discussion on the effect of ZnX_2, also see: (a) Charette, A. B.; Beauchemin, A.; Francoeur, S. *J. Am. Chem. Soc.* **2001**, *123*, 8139. (b) Fournier, J.-F.; Charette, A. B. *Eur. J. Org. Chem.* **2004**, 1401.

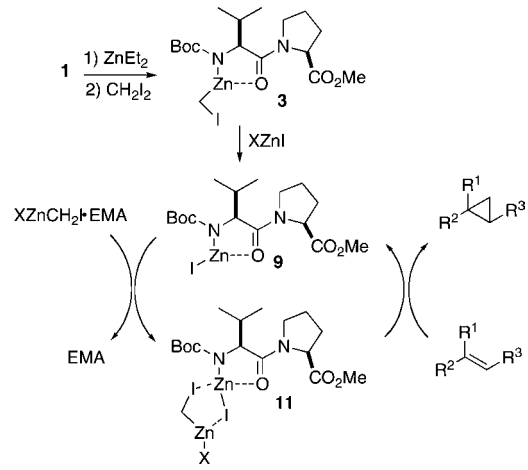
(11) Other Lewis acids can also promote the cyclopropanation of 1-phenyl-3,4-dihydronaphthalene at 0 °C, such as BF_3·Et_2O (72% conv., 87% ee) and $ZnBr_2$ (44% conv., 88% ee).

(12) For a leading reference on transmetallation of zinc reagents, see: Dessy, R. E.; Coe, G. R. *J. Org. Chem.* **1963**, *28*, 3592.

Scheme 6



Scheme 7



exchange with CH_2I_2, is activated by XZnI to form complex **8**, which then cyclopropanates the olefin to form **9**. Active species **8** is regenerated upon transmetalation between **9** and $Zn(CH_2I)_2$ to complete the cycle. Alternatively, compound **9** could act as a chiral Lewis acid to activate $XZnCH_2I$ for cyclopropanation (Scheme 7). Some zinc species involved in the reaction pathways could also exist and/or function as dimers structurally similar to compound **7**. The dimer structures may also be important for the creation of an effective chiral environment for asymmetric induction. A precise reaction mechanism awaits further study.

In summary, studies have shown that zinc species generated from the deprotonation of the N−H of dipeptide ligand **1** are likely to be responsible for asymmetric cyclopropanation and that ZnI_2 plays an important role in promoting cyclopropanation. Rapid transmetalations among various zinc species are involved in the catalytic cycle. These results provide a better understanding for the peptide-promoted asymmetric cyclopropanation and lay the foundation for future development. Further search for an effective catalytic process with high reactivity and enantioselectivity is 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 experimental procedures for Figure 1 and Scheme 6, and NMR studies of compounds **3**, **4**, and **9** along with the X-ray structure of compound **7** and the NMR spectra of **3**, **4**, **9**, and related compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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