HETEROCYCLES, Vol. 79, 2009, pp. 229 - 242. © The Japan Institute of Heterocyclic Chemistry
Received, 24th September, 2008, Accepted, 21st November, 2008, Published online, 28th November, 2008.
DOI: 10.3987/REV-08-SR(D)8

ENANTIOSELECTIVE RADICAL CYCLIZATION FOR THE SYNTHESIS OF CYCLIC COMPOUNDS

Eito Yoshioka, Shigeru Kohtani, and Hideto Miyabe*

School of Pharmacy, Hyogo University of Health Sciences, Chuo-ku, Minatojima, Kobe 650-8530, Japan. E-mail: miyabe@huhs.ac.jp

Abstract – This review highlights the enantioselective radical cyclization reactions catalyzed by chiral Lewis acid as well as organocatalyst. The results of the radical cyclization controlled by chiral Al, Ti, Mg, Yb and Zn reagents, the oxidative cyclization using chiral amine, the chiral complexing agent-catalyzed reductive cyclization, transfer of chirality in radical cyclization, and so on are summarized.

1. INTRODUCTION

Free radical-mediated reactions have been developed as a powerful method for constructing the carbon-carbon bond. Particularly, the control of stereoselectivity in radical reactions has been of great importance to organic synthesis.[1] Hence, new concepts and methods for controlling stereoselectivity of radical reactions are emerging continuously. In the last ten years, the chiral Lewis acid-catalyzed radical reaction has become a field of central importance for asymmetric synthesis. Significant progress has been made in enantioselective radical addition reaction, allylation, and H-atom transfer reactions.[2-5] However, studies on enantioselective radical reactions have concentrated on intermolecular reactions, and stereocontrol in intramolecular reactions still remains a major challenge. This review highlights the recent remarkable success in enantioselective radical cyclization reactions catalyzed by chiral Lewis acid as well as organocatalyst or chiral complexing agent.

2. CHIRAL LEWIS ACID-CATALYZED CYCLIZATION

In recent years, studies on enantioselective intermolecular radical addition reactions and radical allylation reactions have been achieved remarkable success by using chiral Lewis acid.[2-5] In contrast, only a handful of reports describes the chiral Lewis acid-mediated enantioselective radical cyclizations, which can be classified into three types by the nature of coordination with a chiral Lewis acid (Type **I**, Type **II**, and Type **III**, Figure 1).

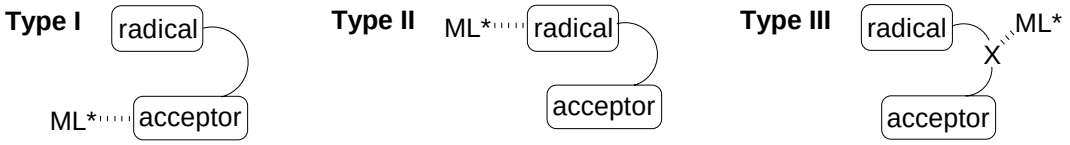
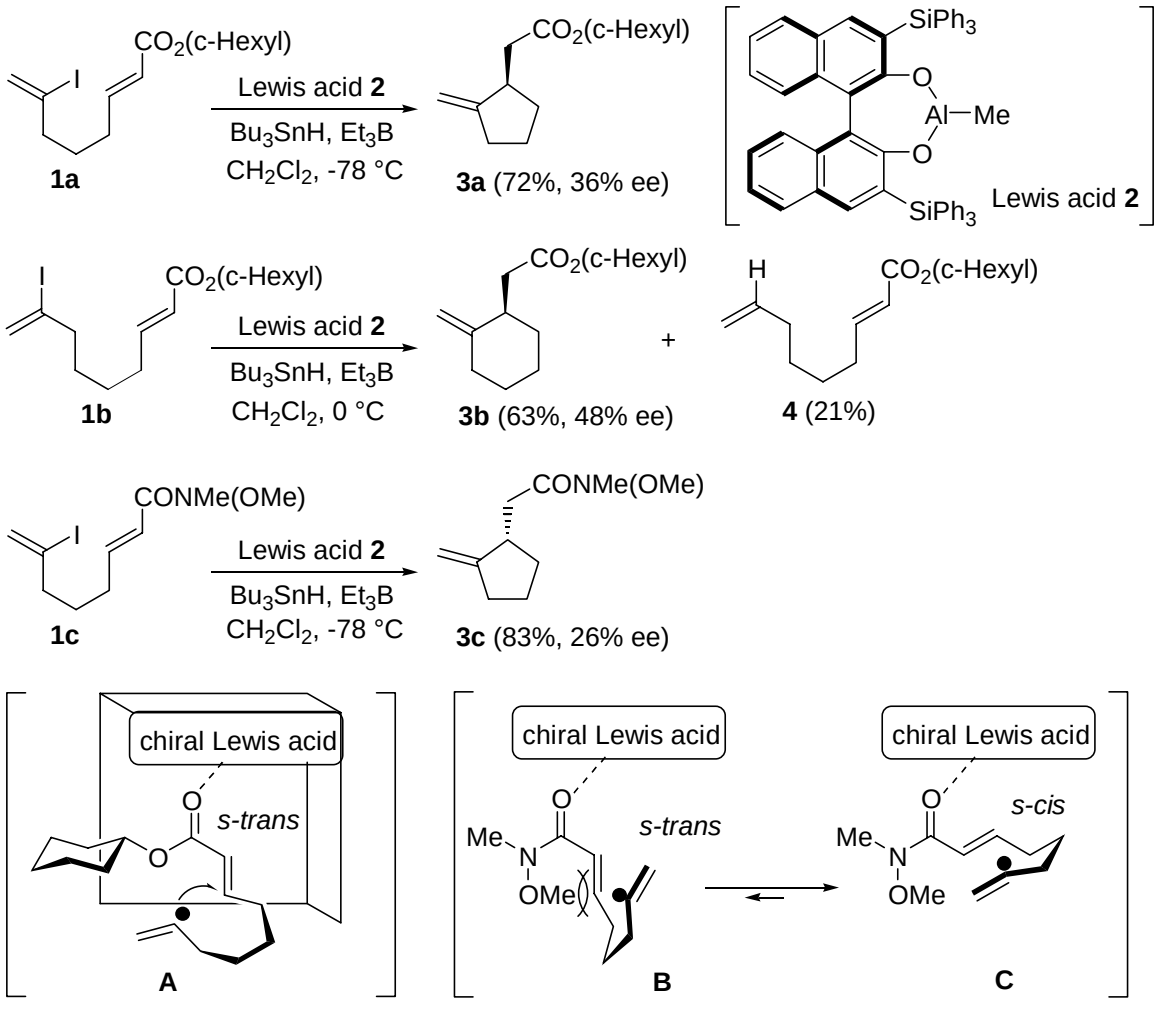


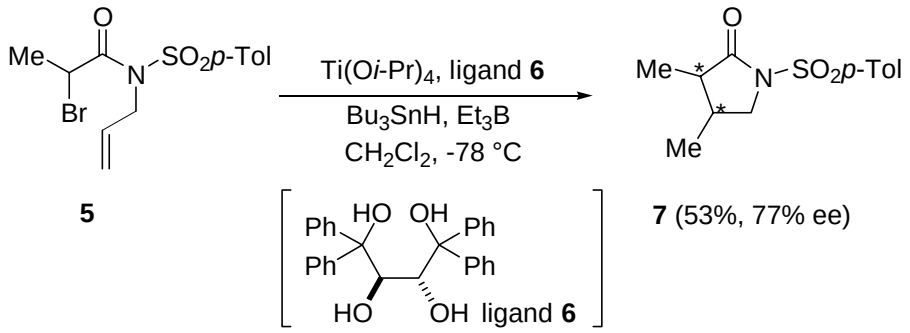
Figure 1. Chiral Lewis Acid-Catalyzed Cyclizations

Early work on chiral Lewis acid-mediated enantioselective radical type **I** cyclization was reported by Nishida's group (Scheme 1).[6] The cyclization of α,β-unsaturated ester **1a** at -78 °C in the presence of 4 equiv of chiral aluminum Lewis acid **2** gave the cyclic compound **3a** in 72% yield and with 36% ee, although the use of 1 equiv of **2** gave the low selectivity. The 6-*exo* cyclization of ester **1b** was inefficient at -78 °C and the reduced product **4** was obtained as a major product. The cyclic product **3b** was obtained in 63% yield with 48% ee by performing the reaction at 0 °C. These reactions would proceed *via s-trans* conformation **A**. In contrast to esters **1a** and **1b** giving (*R*)-products **3a** and **3b**, the amide **1c** gave (*S*)-product **3c** as a major isomer *via s-cis* conformation **C**.



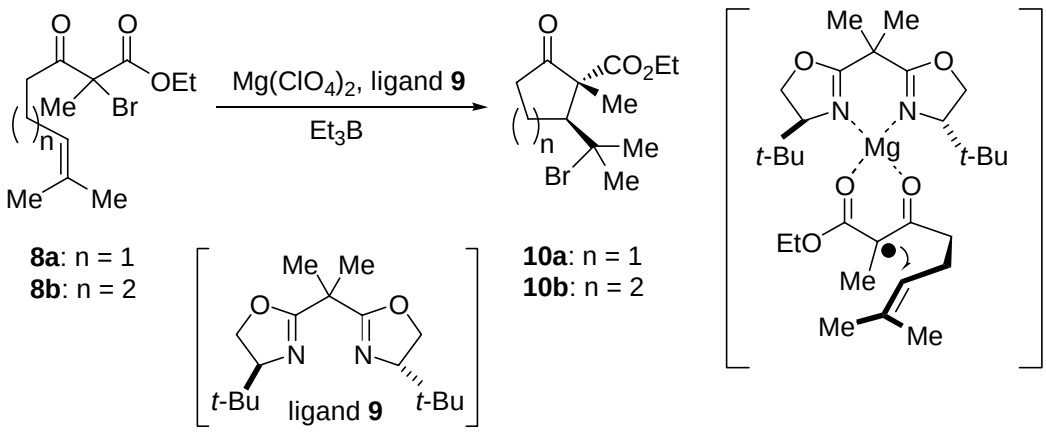
Scheme 1. Cyclizations Controlled by Chiral Aluminum Reagent

Enantioselective cyclization of α-bromo-*N*-allylamides was studied by Ishii's group (Scheme 2).[7] Among several substrates evaluated, sulfonamide **5** with *p*-toluenesulfonyl substituent gave good enantioselectivity. When the reaction of **5** was carried out in CH_2Cl_2 at -78 °C with Bu_3SnH (2 equiv) and Lewis acid (1 equiv) derived from Ti(O*i*-Pr)$_4$ (1 equiv) and chiral ligand **6** (1 equiv), the product **7** was obtained in 53% yield with 77% ee.



Scheme 2. Cyclizations Controlled by Lewis Acid Derived from Ti(O*i*-Pr)$_4$ and Chiral Alcohol

In 2001, a high degree of stereocontrol was achieved in type **II** cyclizations by Yang and coworkers (Scheme 2).[8] The α-radical, generated from β-keto ester, was introduced as a coordination site for the asymmetric cyclization. Atom-transfer cyclization of unsaturated β-keto esters **8a** and **8b** proceeded smoothly to give the cyclized products **10a** and **10b**, respectively. Good enantioselectivities were observed when chiral ligand **9** and $Mg(ClO_4)_2$ were employed (Table 1). As a solvent effect, toluene generally gave higher enantioselectivities than CH_2Cl_2 (entries 1 and 2). The addition of activated molecular sieves not only led to an increase in yields and enantioselectivities, but also made it possible for the use of catalytic amounts of the chiral Lewis acid (entries 3, 4 and 6). High enantioselectivity was attained even when using 0.3 equiv of the chiral Lewis acid catalyst (entry 4).



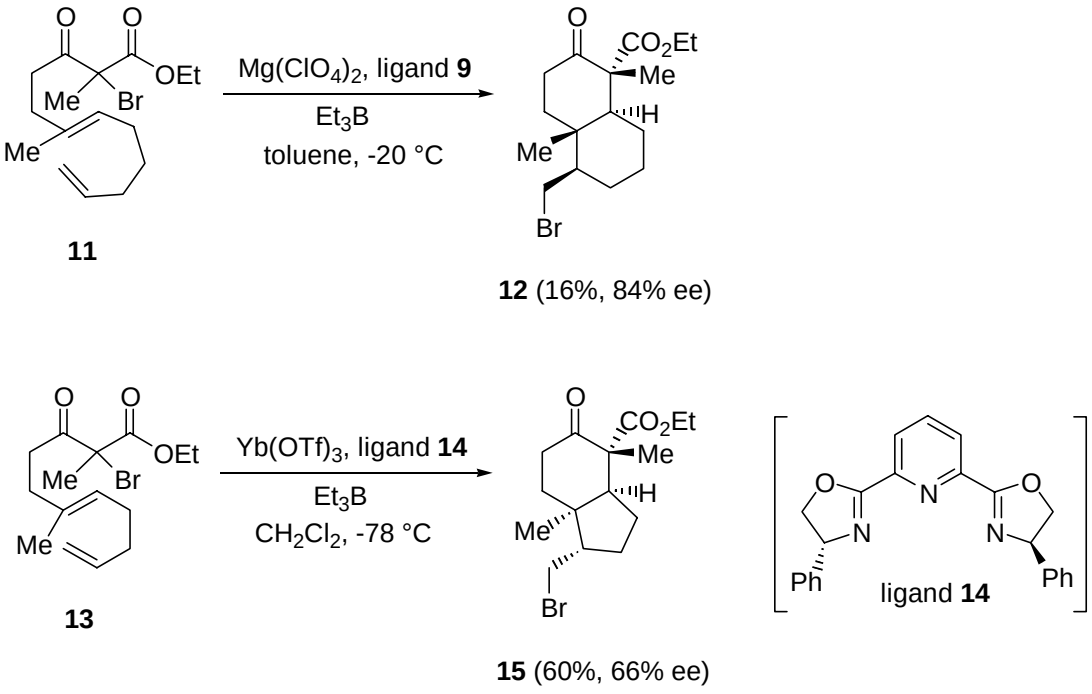
Scheme 3. Cyclizations Controlled by Lewis Acid Derived from $Mg(ClO_4)_2$ and Box Ligand

Table 1. Atom-Transfer Cyclizations of **8a** and **8b**[a]

Entry	Substrate	Catalyst (equiv)	Solvent	Additive	Yield (%)[b]	Ee (%)
1	**8a**	1.1	CH_2Cl_2	none	68	71
2	**8a**	1.1	toluene	none	67	94
3	**8a**	0.5	toluene	MS 4Å	65	93
4	**8a**	0.3	toluene	MS 4Å	68	92
5	**8b**	1.1	toluene	none	62	93
6	**8b**	0.5	toluene	MS 4Å	53	94

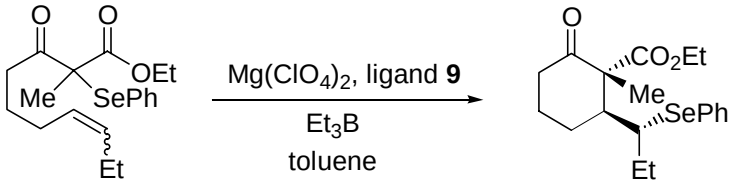
[a] Reactions were carried out with Et_3B (3 equiv) at -78 °C. [b] Isolated yield.

Enantioselective tandem or cascade radical cyclizations continue to attract much interest, since highly functionalized compounds with multiple stereocenter are available. The type **II** cyclization was applied to cascade cyclization. Yang reported the enantioselective atom-transfer cascade cyclization of α-bromo β-keto esters (Scheme 4).[9] The 6-*endo*/6-*exo* cyclization of **11** was performed with ligand **9** and $Mg(ClO_4)_2$. Good enantioselectivity of the fused ring product **12** was observed when reaction was carried out in toluene at -20 °C, but the yield of the product **12** was low. The asymmetric 6-*endo*/5-*exo* cyclization of **13** was evaluated by using $Yb(OTf)_3$. The combination of Pybox ligand **14** and $Yb(OTf)_3$ in CH_2Cl_2 gave the best result.



Scheme 4. Cascade Cyclizations Controlled by Chiral Lewis Acid

Catalytic enantioselective group-transfer radical cyclization was also studied by Yang (Scheme 5),[10] who investigated the PhSe-group-transfer cyclization of α-phenylseleno β-keto ester **16**. Chiral Lewis acid, derived from $Mg(ClO_4)_2$ and box ligand **9**, was the suitable catalyst for this cyclization. The addition of activated molecular sieves accelerated the reaction. The 6-*exo* product **17** was obtained with 89% ee, when β-keto ester (*Z*)-**16** was employed as a substrate (Table 2, entry 1). When a catalytic amount (0.3 equiv) of chiral Lewis acid was used, the enantioselectivity slightly decreased to 84% ee (entry 2). Additionally, β-keto ester (*E*)-**16** gave the same product **17** in comparable yields and enantioselectivities (entries 4 and 5).



16 **17**

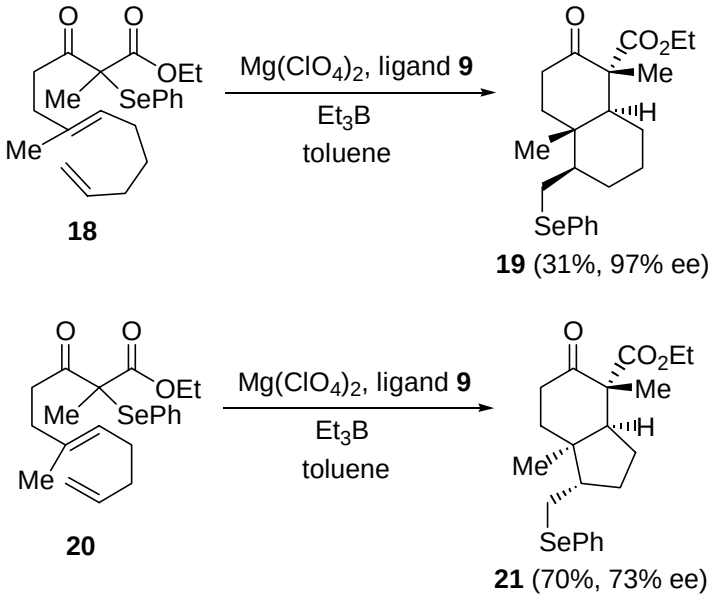
Scheme 5. Cyclization of **16** Controlled by Chiral Lewis Acid

Table 2. PhSe-Group-Transfer Cyclization of (*Z*)-**16** and (*E*)-**16**[a]

Entry	Substrate	Catalyst (equiv)	Time (h)	Yield (%)[b]	Ee (%)
1	(*Z*)-**16**	1.0	6	82	89
2	(*Z*)-**16**	0.3	10	81	84
3	(*E*)-**16**	1.0	7	71	81
4	(*E*)-**16**	0.3	10	66	87

[a] Reactions were carried out with Et_3B (5 equiv) in toluene at -78 °C in the presence of MS 4Å.
[b] Isolated yield.

Yang reported that PhSe-group-transfer reaction was ideal in terms of both reaction efficiency and enantioselectivity for the cascade cyclization (Scheme 6).[10] Substrate **18** underwent the 6-*endo*/6-*exo* cyclization to give the fused ring product **19** with 97% ee albeit in low yield. In contrast to the low yield in the corresponding Br-transfer cascade cyclization,[9] the fused ring product **21** was obtained from substrate **20** in 70% yield with 73% ee. Good chemical yield of **21** was attained even when 0.3 equiv of the chiral Lewis acid catalyst was used. They assume that the lower transfer rate of the PhSe group to the intermediate alkyl radical and its bulk cause the PhSe group abstraction to be more stereoselective than that of Br-transfer cascade cyclization.



Scheme 6. Cascade Cyclizations of **18** and **20** Controlled by Chiral Lewis Acid

Most radical reactions proceed through early transition states; thus, the geometry of substrates play an important role for asymmetric reaction. The control of the rotamer population would be crucial for achieving high enantioselectivity in radical cyclization reactions.[11] We consider that the predominant formation of a single reactive rotamer must be achieved by the type **III** approach (Figure 1), which contains a coordination tether (X) between two acceptors.[12] To develop a highly efficient and stereoselective method, we have studied new approaches to control stereoselectivity of cascade radical addition-cyclization reaction by taking advantage of hydroxamate ester **23** (Figure 2).[13]

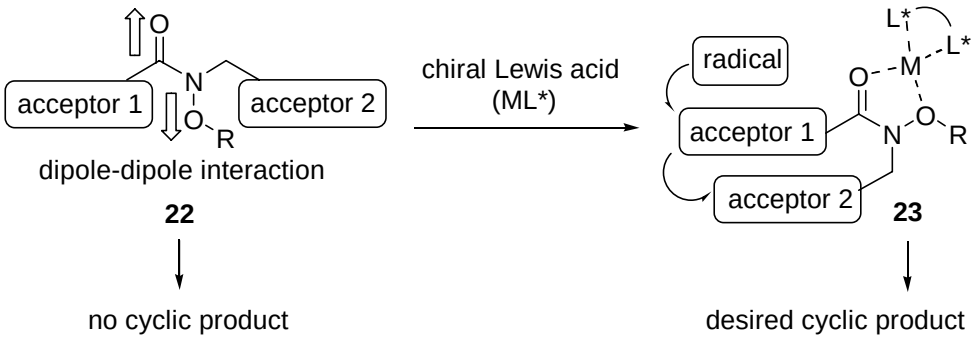
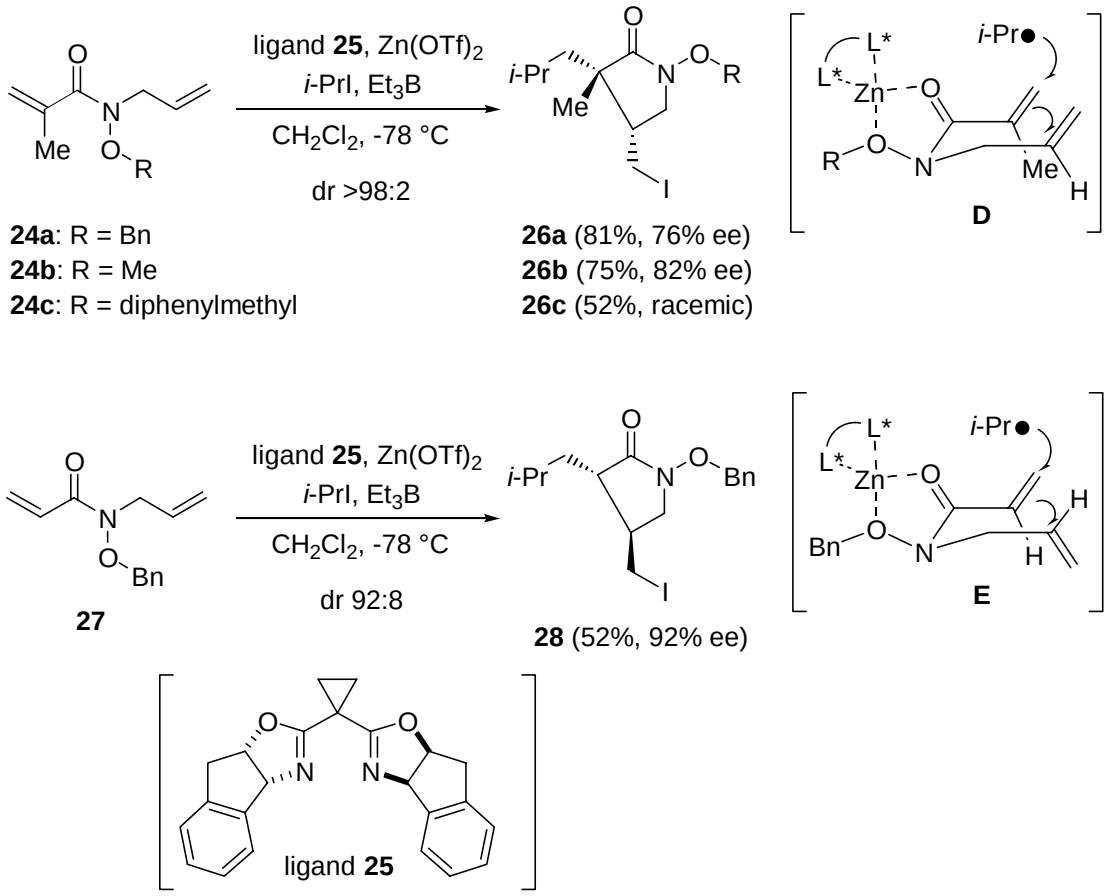


Figure 2. Chiral Lewis Acid-Catalyzed Cascade Reaction

There are no reports on enantioselective cascade reactions involving both inter- and intramolecular carbon-carbon bond forming processes. Therefore, the isopropyl radical addition-cyclization-trapping reaction of hydroxamate esters **24a-c** was studied (Scheme 7). In this reaction, the hydroxamate ester moiety could control the rotamer population of substrates through a stable five-membered chelation.

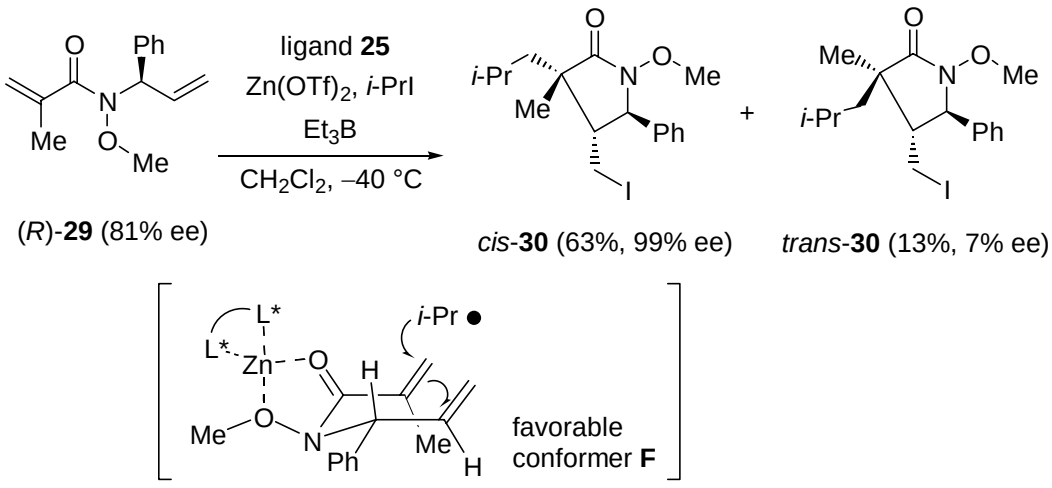


Scheme 7. Cascade Reactions Involving Both Inter- and Intramolecular Bond Forming Processes

While practically no reaction occurred in the absence of Lewis acid additive, the use of chiral Lewis acid led to an enhancement in chemical yield even at -78 °C. In the presence of stoichiometric amounts of the chiral Lewis acid prepared from $Zn(OTf)_2$ and box ligand **25**, cascade reaction of **24a** proceeded smoothly to give the 5-*exo* cyclization product **26a** in 81% yield with good enantioselectivity and high *cis* diastereoselectivity. We were also interested in probing the effect of the fluxional substituent (R) of **24** on the stereochemistry.[14] Reaction of **24b**, which has a small methoxy group, led to high enantioselectivity. Interestingly, the size of the fluxional substituent (R) had an impact on enantioselectivity, with larger groups leading to lower ee values. The use of substrate **24c** with a diphenylmethyl group gave the racemic product **26c**, probably as a result of dissonance between the chiral Lewis acid and bulky substituent. Cyclization of **24a-c** leading to the major *cis* diastereomer occurs *via* the conformer **D**, in which two olefin units adopt a *cis* arrangement probably due to the effect of orbital symmetry reported by Beckwith and Houk.[15]

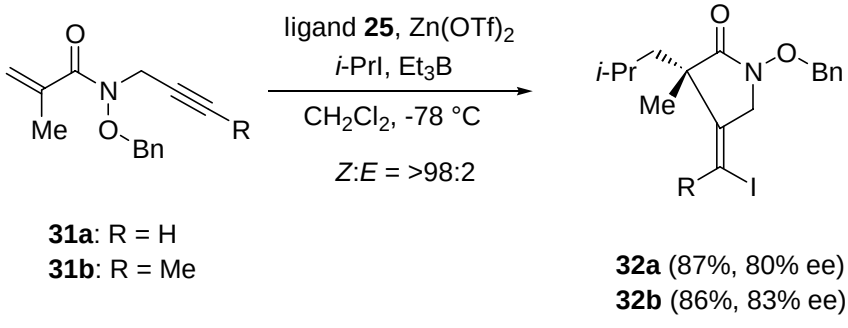
Outstanding level of enantioselectivity was obtained in the cascade reaction of acrylated substrate **27**. In marked contrast to methacrylated substrates **24a-c**, the *trans* diastereoselectivity was observed. The *trans*-selectivity in reaction of **27** was regarded as the result of steric repulsion between two olefin units and the reaction proceeded *via* the stable conformer **E**.

Next, the cascade reaction of chiral substrate (*R*)-**29** was investigated (Scheme 8). The reaction of (*R*)-**29** (81% ee) gave a 63% yield of (*S*)-*cis*-**30** with 99% ee, accompanied by a small amount of *trans*-**30** with low enantiomeric excess. The enhanced enantioselectivity of *cis*-**30** can be explained by kinetic resolution of an intermediate chiral radical. The major cyclization proceeded *via* the favorable conformer **F** minimizing the allylic 1,3-strain effect.



Scheme 8. Cascade Reaction of Chiral Substrate (*R*)-**29**

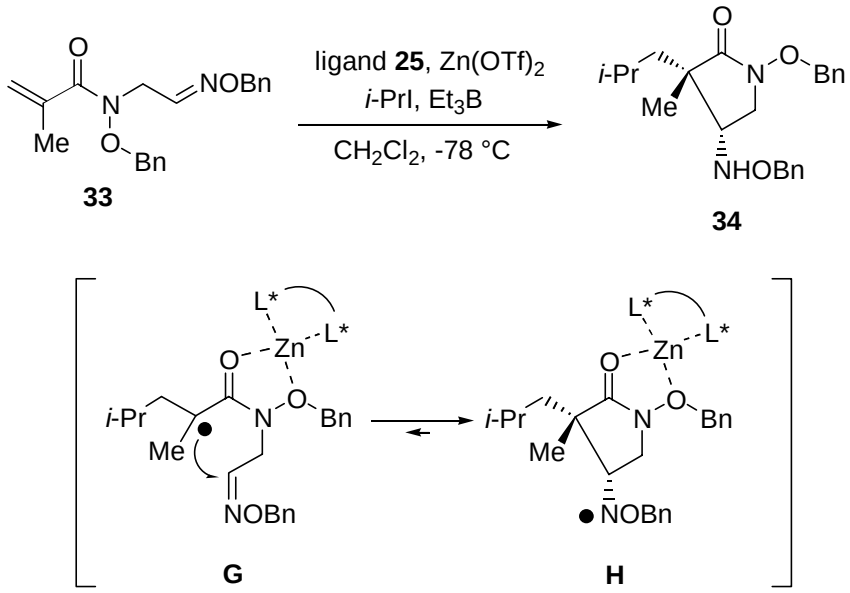
Chiral Lewis acid promoted the reaction of substrates **31a** and **31b** having carbon-carbon triple bond to afford the cyclized products **32a** and **32b** in high yields and with good enantioselectivities (Scheme 9). The high *Z*/*E* selectivity of products indicates that the iodine atom-transfer from *i*-PrI to reactive intermediate vinyl radical was effective and directed the *Z* selectivity.



Scheme 9. Cascade Reactions of Substrate **31a** and **31b**

Nothing has been known about the enantioselective radical cyclization of imines;[16] thus, we next explored the cascade reaction of oxime ether **33** (Scheme 10).[17] Interestingly, the amount of triethylborane and the reaction time had an impact on enantioselectivity (Table 3). Increasing the amount of triethylborane from 2.5 equiv to 20 equiv improved the enantioselectivity (compare entry 1 with entry 2). Additionally, a

prolonged reaction led to lower selectivity (entry 3). Improvement of enantioselectivity was also observed by changing the reaction time from 3 h to 1 h (entry 4). Result from these studies shows that the slow trapping reaction of an aminyl radical **H** with triethylborane would allow the reversibility between intermediate **G** and aminyl radical **H**, leading to erosion of enantioselectivity.



Scheme 10. Cascade Reaction of Oxime Ether **33**

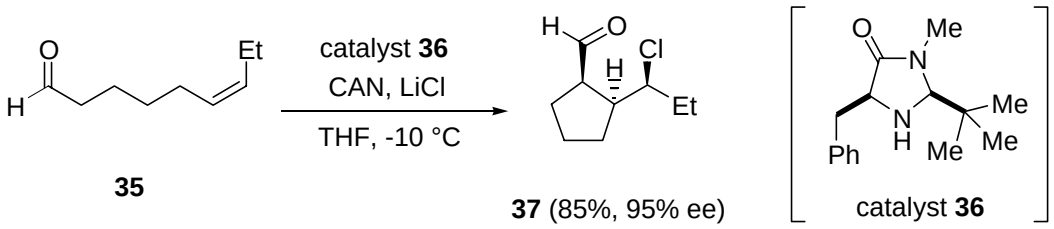
Table 3. Cyclization of Oxime Ether **33**[a]

Entry	Et_3B (equiv)	Time (h)	Yield (%)[b]	Ratio *cis*:*trans*	Ee (%) of *cis*-isomer
1	2.5	3	69	84:16	68
2	20	3	70	82:18	85
3	2.5	24	91	76:24	64
4	2.5	1	17	89:11	77

[a] Reactions were carried out with isopropyl iodide (30 equiv) in CH_2Cl_2 at -78 °C. [b] Isolated yield.

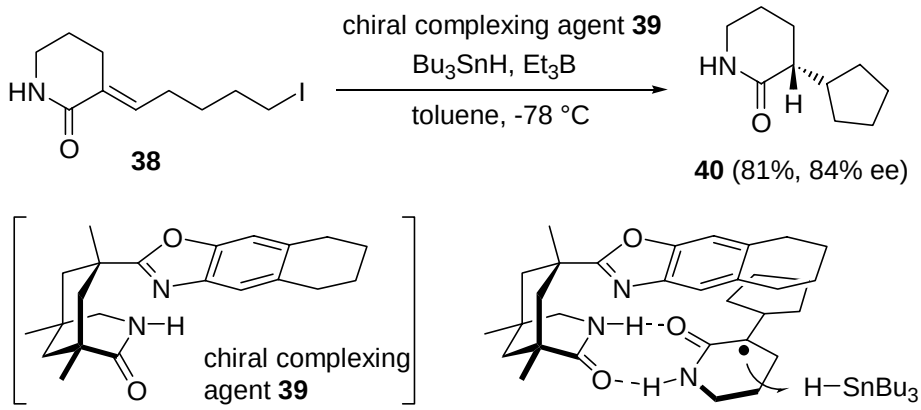
3 CYCLIZATION USING ORGANOCATALYST OR CHIRAL COMPLEXING AGENT

MacMillan has studied the oxidative radical reactions using chiral organocatalyst.[18] Enantioselective cyclization of unsaturated aldehyde **35** was investigated in the presence of ceric ammonium nitrate (CAN) as the stoichiometric oxidant (Scheme 11). In this reaction, chiral amine catalyst **36** activates aldehyde **35** by the formation of enamine, which gives a transient radical cation intermediate by single-electron oxidation. In the presence of LiCl, aldehyde **35** underwent the 5-*exo* cyclization to give the halogenated product **37** with 95% ee with good diastereoselectivity.



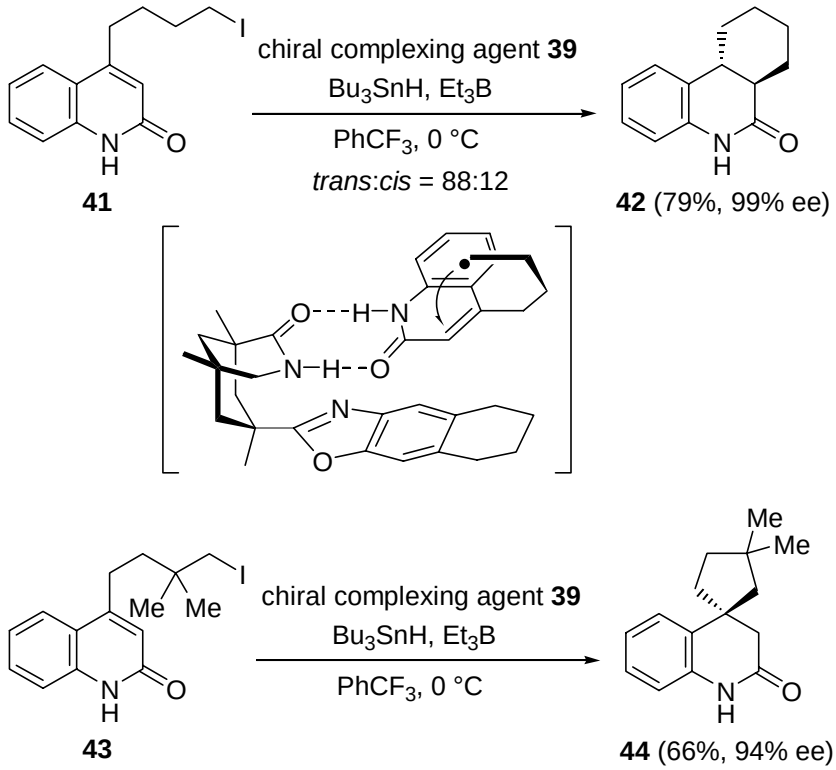
Scheme 11. Reaction Using Organocatalyst

The enantioselective radical cyclization was also achieved by Bach's group, who relied on an unique hydrogen-bonding chiral complexing agent (Scheme 12).[19] Chiral complexing agent **39** features a hydrogen bond donor (NH) site and a hydrogen bond acceptor (C=O) site. The reductive radical cyclization of piperidin-2-one **38** was investigated in the presence of Bu_3SnH and Et_3B. When chiral complexing agent **39** (2.5 equiv) was employed in toluene at -78 °C, the cyclic product **40** was obtained in 81% yield with 84% ee. In nonpolar solvents, chiral complexing agent **39** binds lactam moiety in **38** and **40**, facilitating a differentiation of enantiotopic faces. However, this reaction can not be categorized to direct stereocontrol in radical cyclizations, because the stereodetermining step is hydrogen transfer from Bu_3SnH to intermediate radical.



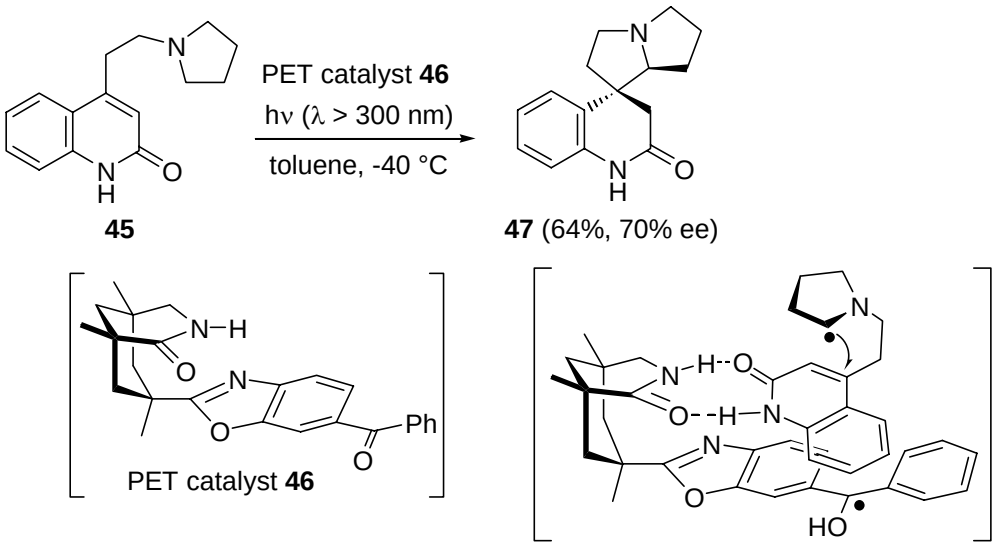
Scheme 12. Reaction Using Chiral Complexing Agent

Chiral complexing agent-mediated direct stereocontrol in radical cyclizations was achieved by using quinolones as substrates (Scheme 13).[20] The reaction of the unsubstituted iodide **41** gave 6-*endo* cyclization product **42**. When chiral complexing agent **39** (2.5 equiv) was employed in $PhCF_3$ at 0 °C, the cyclic product **42** was obtained with 99% ee. In addition, the cyclized product **42** was obtained with 55% ee even in the presence of only 0.1 equiv of chiral complexing agent. The cyclization of substituted iodide **43** occurred with regioselectivity different from that of **41**. When chiral complexing agent **39** (2.5 equiv) was employed in $PhCF_3$ at 0 °C, the 5-*exo* cyclization product **44** was formed predominantly with excellent enantioselectivity.



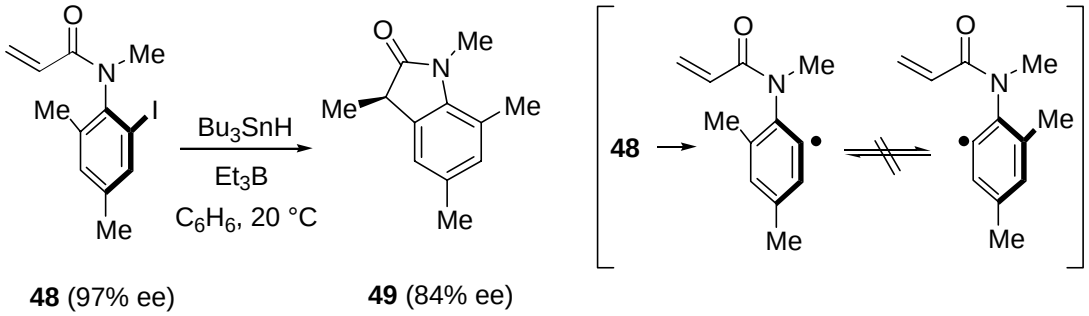
Scheme 13. Cyclizations of Quinolones Using Chiral Complexing Agent

Bach studied the catalytic enantioselective radical cyclization driven by photoinduced electron transfer (PET).[21] The electron accepting chiral catalyst **46** was explored for enantioselective radical cyclization of quinolone **45** (Scheme 14). The chiral catalyst **46** serves not only as a PET agent, but also as stereocontrolling device. By employing catalyst **46**, the desired reaction proceeded to give the spirocyclic product **47** in good yield. The enantiomeric excess reached 70% for a catalyst loading of 30 mol%. This performance suggests that photochemical reactions may find use in general asymmetric synthesis.[22]



Scheme 14. Cyclization of Quinolones Using Chiral Complexing Agent

As unique cyclization procedure, transfer of chirality was investigated by Curran's group (Scheme 15).[23] Even though the chiral axis is destroyed in cyclization process, the products faithfully remember the configuration of the precursors. The axial chirality of **48** was transferred into a new stereocenter of **49** with retention of chirality as a result of the almost complete absence of racemization of radical intermediates.



Scheme 15. Transfer of Chirality in Radical Cyclization

4 CONCLUSION AND OUTLOOK

Synthetic strategies involving radical cyclizations would be desirable tools for preparing organic compounds. Enantioselective radical cyclizations continue to attract much interest, since highly functionalized compounds with multiple stereocenter can be provided. The new concept and approach for controlling stereochemistry of radical reactions offer opportunities for further exploration with intriguing possibilities in enantioselective radical cyclization.

ACKNOWLEDGEMENTS

This work was supported in part by a Grant-in-Aid for Young Scientists (B) (to E.Y.) and for Scientific Research (C) (to H.M.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and Hyogo Science and Technology Association (to H.M.).

REFERENCES

1. D. P. Curran, N. A. Porter, and B. Giese, 'Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications' VCH: Weinheim, 1996; 'Radicals in Organic Synthesis' Vols. 1 and 2, ed. by P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001.
2. For selected examples of enantioselective radical addition reactions and allylations, see: M. P. Sibi, G. Petrovic, and J. Zimmerman, *J. Am. Chem. Soc.*, 2005, **127**, 2390; M. P. Sibi, J. Zimmerman, and T. Rheault, *Angew. Chem. Int. Ed.*, 2003, **42**, 4521; Y. Watanabe, N. Mase, R. Furue, and T. Toru,

Tetrahedron Lett., 2001, **42**, 2981; U. Iserloh, D. P. Curran, and S. Kanemasa, *Tetrahedron: Asymmetry*, 1999, **10**, 2417; M. Murakata, T. Jono, Y. Mizuno, and O. Hoshino, *J. Am. Chem. Soc.*, 1997, **119**, 11713; M. P. Sibi, J. Ji, J. H. Wu, S. Gürtler, and N. A. Porter, *J. Am. Chem. Soc.*, 1996, **118**, 9200; J. H. Wu, R. Radinov, and N. A. Porter, *J. Am. Chem. Soc.*, 1995, **117**, 11029.

3. For selected examples of enantioselective H-atom transfer reactions, see: M. P. Sibi and K. Patil, *Angew. Chem. Int. Ed.*, 2004, **43**, 1235; M. P. Sibi, Y. Asano, and J. B. Sausker, *Angew. Chem. Int. Ed.*, 2001, **40**, 1293; M. Murakata, H. Tsutsui, N. Takeuchi, and O. Hoshino, *Tetrahedron*, 1999, **55**, 10295.
4. For selective examples of enantioselective reductions using chiral H-atom transfer reagents, see: Y. Cai, B. P. Roberts, and D. A. Tocher, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1376; D. Dakternieks and C. H. Schiesser, *Aust. J. Chem.*, 2001, **54**, 89; M. Blumenstein, K. Schwarzkopf, and J. O. Metzger, *Angew. Chem. Int. Ed.*, 1997, **36**, 235; D. Nanni and D. P. Curran, *Tetrahedron: Asymmetry*, 1996, **7**, 2417.
5. For general information details for enantioselective radical reactions, see: P. Renaud and M. Gerster, *Angew. Chem. Int. Ed.*, 1998, **37**, 2562; M. P. Sibi and N. A. Porter, *Acc. Chem. Res.*, 1999, **32**, 163; G. Bar and A. F. Parsons, *Chem. Soc. Rev.*, 2003, **32**, 251; M. P. Sibi, S. Manyem, and J. Zimmerman, *Chem. Rev.*, 2003, **103**, 3263.
6. M. Nishida, H. Hayashi, A. Nishida, and N. Kawahara, *Chem. Commun.*, 1996, 579.
7. K. Hiroi and M. Ishii, *Tetrahedron Lett.*, 2000, **41**, 7071.
8. D. Yang, S. Gu, Y.-L. Yan, N.-Y. Zhu, and K.-K. Cheung, *J. Am. Chem. Soc.*, 2001, **123**, 8612; D. Yang, Y.-L. Yan, K.-L. Law, and N.-Y. Zhu, *Tetrahedron*, 2003, **59**, 10465.
9. D. Yang, S. Gu, Y.-L. Yan, H.-W. Zhao, and N.-Y. Zhu, *Angew. Chem. Int. Ed.*, 2002, **41**, 3014.
10. D. Yang, B.-F. Zheng, Q. Gao, S. Gu, and N.-Y. Zhu, *Angew. Chem. Int. Ed.*, 2006, **45**, 255.
11. M. P. Sibi and J. Ji, *J. Am. Chem. Soc.*, 1996, **118**, 3063.
12. H. Miyabe, R. Asada, A. Toyoda, and Y. Takemoto, *Angew. Chem. Int. Ed.*, 2006, **45**, 5863; H. Miyabe and Y. Takemoto, *Chem. Eur. J.*, 2007, **13**, 7280.
13. O. Corminboeuf and P. Renaud, *Org. Lett.*, 2002, **4**, 1731; O. Corminboeuf and P. Renaud, *Org. Lett.*, 2002, **4**, 1735.
14. O. Corminboeuf, L. Quaranta, P. Renaud, M. Liu, C. P. Jasperse, and M. P. Sibi, *Chem. Eur. J.*, 2003, **9**, 28.
15. A. L. J. Beckwith, *Tetrahedron*, 1981, **37**, 3073; D. C. Spellmeyer and K. N. Houk, *J. Org. Chem.*, 1987, **52**, 959.
16. For reviews, see: T. Naito, *Heterocycles*, 1999, **50**, 505; A. G. Fallis and I. M. Brinza, *Tetrahedron*, 1997, **53**, 17543; G. K. Friestad, *Tetrahedron*, 2001, **57**, 5461; H. Miyabe, M. Ueda, and T. Naito,

Synlett, 2004, 1140.

17. H. Miyabe, A. Toyoda, and Y. Takemoto, *Synlett*, 2007, 1885.
18. T. D. Beeson, A. Mastracchio, J.-B. Hong, K. Ashton, and D. W. C. MacMillan, *Science*, 2007, **316**, 582.
19. T. Aechtner, M. Dressel, and T. Bach, *Angew. Chem. Int. Ed.*, 2004, **43**, 5849; M. Dressel, T. Aechtner, and T. Bach, *Synthesis*, 2006, 2206.
20. M. Dressel and T. Bach, *Org. Lett.*, 2006, **8**, 3145.
21. A. Bauer, F. Westkämper, S. Grimme, and T. Bach, *Nature*, 2005, **436**, 1139.
22. P. Wessig, *Angew. Chem. Int. Ed.*, 2006, **45**, 2168.
23. D. P. Curran, W. Liu, and C. H.-T. Chen, *J. Am. Chem. Soc.*, 1999, **121**, 11012.

Eito Yoshioka has been an Assistant Professor at the School of Pharmacy, Hyogo University of Health Sciences since 2008. He received his B. Sc. (2000) and Ph. D. degrees (2005) from Osaka University. Then, he worked as a postdoctoral fellow with Prof. Takeshi Imanishi until 2006. He worked as a researcher at RIKEN Molecular Imaging Research Program in 2006.

Shigeru Kohtani has been a Lecturer at the School of Pharmacy, Hyogo University of Health Sciences since 2007. He received his B. Sc. degree (1990) from Kanazawa University and M. Sc. degree (1992) from Tokyo Institute of Technology. He joined the Faculty of Pharmaceutical Sciences, Kanazawa University as a Technical Assistant in 1992 and was promoted to Research Associate in 1997. He received his Ph. D. in 1997 under the supervision of Professor Michiya Itoh at Kanazawa University.

Hideto Miyabe has been a Professor at the School of Pharmacy, Hyogo University of Health Sciences since 2007. He received his B. Sc. (1991) and Ph. D. degrees (1996) from Osaka University. He joined Kobe Pharmaceutical University as an Assistant Professor in 1996. He worked as a JSPS postdoctoral fellow with Prof. M. P. Sibi at North Dakota State University from 2001. He moved to the Graduate School of Pharmaceutical Sciences, Kyoto University as a Lecturer in 2002 and was promoted to Associate Professor in 2004. He received the Pharmaceutical Society of Japan Award for Young Scientists in 2003.