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Catalytic Asymmetric Michael Reaction of β-Keto Esters: Effects of the Linker Heteroatom in Linked-BINOL

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Abstract: We describe the development of a general catalytic asymmetric Michael reaction of acyclic β-keto esters to cyclic enones, in which asymmetric induction occurs at the β-position of the acceptors. Among the various asymmetric catalyst systems examined, the newly developed La−NR-linked-BINOL complexes (R = H or Me) afforded the best results in terms of reactivity and selectivity. In general, the NMe ligand **2** was suitable for the combination of small enones and small β-keto esters, and the NH ligand **1** was suitable for bulkier substrates (steric tuning of the catalyst). Using the La−NMe-linked-BINOL complex, the Michael reaction of methyl acetoacetate (**8a**) to 2-cyclohexen-1-one (**7b**) gave the corresponding Michael adduct **9ba** in 82% yield and 92% ee. The linker heteroatom in linked-BINOL is crucial for achieving high reactivity and selectivity in the Michael reaction of β-keto esters. The amine moiety in the NR-linked-BINOL can also tune the Lewis acidity of the central metal (electronic tuning of the catalyst), which was supported by density functional studies and experimental results. Another advantage of the NR-linked-BINOL ligand as compared with O-linked-BINOL is the ease of modifying a substituent on the amine moiety, making it possible to synthesize a variety of NR-linked-BINOL ligands for further improvement or development of new asymmetric catalyses by introducing additional functionality on the linker with the amine moiety. The efficiency of the present asymmetric catalysis was demonstrated by the synthesis of the key intermediate of (−)-tubifolidine and (−)-19,20-dihydroakuammicine in only five steps compared to the nine steps required by the original process from the Michael product of malonate. This strategy is much more atom economical. On the basis of the results of mechanistic studies, we propose that a β-keto ester serves as a ligand as well as a substrate and at least one β-keto ester should be included in the active catalyst complex. Further improvement of the reaction by maintaining an appropriate ratio of the La−NMe-linked-BINOL complex and β-keto esters is also described.

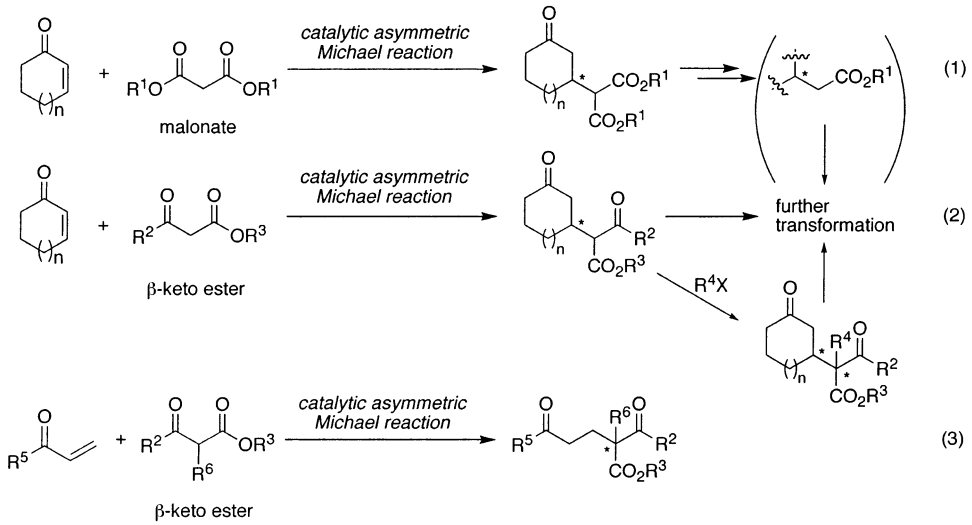
Introduction

The catalytic asymmetric Michael reaction of enolates to α,β-unsaturated carbonyl compounds is one of the most important carbon−carbon bond forming reactions due to the ready availability of both substrates, usefulness of enantiomerically enriched Michael products, and high atom economy.[1] Thus, the development of catalytic asymmetric Michael reactions has been extensively studied with several great successes, such as the Lewis acid-promoted addition of enol silyl ethers to α,β-unsaturated carbonyl compounds (Mukaiyama−Michael reaction),[2] which use stoichiometric amounts of silyl reagents and bases for the preparation of substrates. The atom-economically more desirable direct catalytic asymmetric Michael reaction was recently developed by several groups.[1,3] Among them, the catalytic asymmetric Michael reaction of malonates to enones, in which asymmetric induction occurs at the β-position of the

(1) For recent reviews of catalytic asymmetric Michael reactions, see: (a) Kanai, M.; Shibasaki, M. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000; pp 569−592. (b) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.1. (c) Sibi, M.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (d) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171. (e) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221. (f) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688.

(2) For recent examples using a metal and chiral ligand complex, see: (a) Kobayashi, S.; Suda, S.; Yamada, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 97. (b) Benardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921. (c) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, W.; Tedrow, J. *J. Am. Chem. Soc.* **2000**, *122*, 9134. (d) Evans, D. A.; Scheidt, K. A.; Johnston, N.; Willis, M. *J. Am. Chem. Soc.* **2001**, *123*, 4480. For recent examples using a chiral organocatalyst, see: (e) Zhang, F-. Y.; Corey, E. J. *Org. Lett.* **2001**, *3*, 639. (f) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am Chem Soc.* **2003**, *125*, 1192. (g) Ooi, T.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.

(3) Recently, a direct catalytic asymmetric Michael reaction of unmodified ketones and aldehydes was reported, although Michael donors and/or Michael acceptors were rather limited. For examples using unmodified ketones as donors, see: (a) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097. (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III. *Tetrahedron Lett.* **2001**, *42*, 4441. (c) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (d) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 4251. (e) Enders, D.; Seki, A. *Synlett* **2002**, 26. (f) Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2582. (g) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559. For examples using unmodified aldehydes as donors, see: (h) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737. (i) Alexakis, A.; Andrey, O. *Org. Lett.* **2002**, *4*, 3611. (j) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151. For examples using α-cyano esters as donors, see: (k) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295. (l) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron* **1994**, *50*, 4439. (m) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204.



enones, has been widely examined, and several excellent catalysts were developed (eq 1).[4,5] This methodology was successfully applied to the syntheses of several natural products[6] such as *Strychnos* alkaloids.[6b−d] Structurally related β-keto esters have also been studied as Michael donors because of the higher potential of the corresponding Michael products to be useful in further transformations (eq 2).[7] In this case, appropriate substituents can be introduced into the ketone unit (R^2) prior to the Michael reaction, while one of the ester units in the Michael product of malonate is often removed by decarboxylation during the synthetic process (vide infra).[6a−d,8] Moreover, the characteristic reactivity of β-keto esters allows for additional substituents (R^4) to be more efficiently introduced at the α-position of β-keto esters to construct quaternary carbon stereocenters in the presence of a ketone moiety other than malonate (vide infra).

Despite the usefulness of the above-mentioned reactions (shown in eq 2), the catalytic asymmetric Michael reaction of α-substituted β-keto esters, especially indan-1-one-2-carboxylate, to methyl vinyl ketone was mainly studied; thus, the chiral center was constructed at the α-position of the β-keto esters (eq 3).[9,10] In contrast to the successful asymmetric induction at the α-position of β-keto esters (eq 3), only a few asymmetric Michael reactions of β-keto esters to β-substituted enones, such as cyclic enones, achieved asymmetric induction at the β-position of the acceptor (eq 2).[11−13] This was probably due to the preferential coordination of Michael donors (malonates or β-keto esters) to a chiral complex in a bidentate chelating manner rather than to Michael acceptors (enones),[9,10] resulting in difficulty in controlling the facial selectivity of the Michael acceptors. Barnes, Ji, and co-workers reported a Michael reaction of β-keto esters to nitrostyrenes using the chiral bisoxazoline−Mg complex and amine base.[11] Jørgensen and co-workers recently employed the chiral bisoxazoline−Cu complex to promote a Michael reaction of several cyclic β-keto esters such as 4-hydroxycoumarins to β,γ-unsaturated α-keto esters.[12] Ikariya and co-workers recently reported the catalytic asymmetric Michael reaction of methyl acetoacetate to an enone, cyclopentenone, using a chiral Ru complex.[13] While the level of enantioselection for these reactions is encouraging, there remains room for improvement in terms of substrate generality. Herein,

(4) For catalytic asymmetric Michael reactions of malonates reported by our group, see: (a) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571. (b) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194. (c) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104. (d) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (e) Xu, Y.; Ohori, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **2002**, *58*, 2585. (f) Takita, R.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 4661. For reviews, see: (g) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236. (h) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. For a review of O-linked-BINOL, see: (i) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *343*, 1.

(5) For other examples of catalytic asymmetric Michael reactions of malonates, see: (a) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520. (b) Perrard, T.; Plaquevent, J.-C.; Desmurs, J.-R.; Hebrault, D. *Org. Lett.* **2000**, *2*, 2959. (c) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661. (d) Annamalai, V.; DiMauro, E. F.; Carroll, P. J.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 1973. See also ref 1b.

(6) (a) Yamada, K.-i.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 3666. (b) Shimizu, S.; Ohori, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 7547. (c) Ohori, K.; Shimizu, S.; Ohshima, T.; Shibasaki, M. *Chirality* **2000**, *12*, 400. (d) Ohshima, T.; Xu, Y.; Takita, R.; Shimizu, S.; Zhong, D.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14546 (Additions and Corrections **2003**, *125*, 2014). (e) Nara, S.; Toshima, H.; Ichihara, A. *Tetrahedron Lett.* **1996**, *37*, 6745. (f) Nara, S.; Toshima, H.; Ichihara, A. *Tetrahedron* **1997**, *53*, 9509.

(7) For a general review of β-keto esters describing the ubiquitous importance of β-keto esters in organic chemistry, see: Benetti, S.; Romagnoli, R.; Risi, C. D.; Spalluto, G.; Zanirato, V. *Chem. Rev.* **1995**, *95*, 1065.

(8) The intermediate of strychnine synthesis (ref 6d) can be synthesized from the Michael product of β-keto ester in one step, a shorter process than that reported using the Michael product of malonate. For preliminary results, see the Supporting Information.

(9) (a) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238. (b) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. (c) Brunner, H.; Hammer, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 312. (d) Desimoni, G.; Dusi, G.; Faita, G.; Quadrelli, P.; Righetti, P. *Tetrahedron* **1995**, *51*, 4131. (e) Sasai, H.; Emori, E.; Arai, T.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 5561. (f) Christoffers, J.; Rössler, U.; Werner, T. *Eur. J. Org. Chem.* **2000**, 701. (g) Nakajima, M.; Yamaguchi, Y.; Hashimoto, S. *Chem. Commun.* **2001**, 1596. (h) Suzuki, T.; Torii, T. *Tetrahedron: Asymmetry* **2001**, *12*, 1077.

(10) For high substrate generality using chiral palladium complexes, see: (a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240. (b) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, *5*, 3225.

(11) For Michael reaction of β-keto esters to nitrostyrene derivatives (six examples), see: (a) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215. (b) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. *J. Am. Chem. Soc.* **2002**, *124*, 13097.

(12) For Michael reaction of several cyclic β-keto esters such as 4-hydroxycoumarins to β,γ-unsaturated α-keto esters (several examples), see: (a) Halland, N.; Velgaard, T.; Jørgensen, K. A. *J. Org. Chem.* **2003**, 5067. (b) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955.

(13) For Michael reaction of β-keto ester to enone (one example), see: Watanabe, M.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2003**, *125*, 7508. The authors proposed that the reactions might proceed through a transition state similar to that postulated for transfer hydrogenation, in which enone might be fixed in the chiral catalyst complex through a hydrogen bond between the carbonyl oxygen of enone and the amine proton of a chiral ligand.

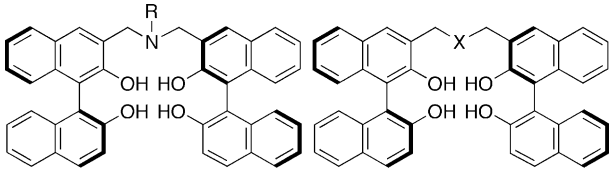
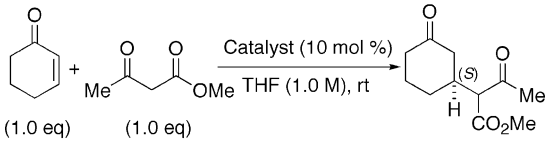


Figure 1. Structures of (*S*,*S*)-NR-linked-BINOLs **1**−**4**, (*S*,*S*)-O-linked-BINOL **5**, and (*S*,*S*)-S-linked-BINOL **6**.

Table 1. Catalyst Screening for Catalytic Asymmetric Michael Reaction of β-Keto Ester[a]



entry	catalyst	time (h)	yield[b] (%)	ee[c] (%)
1	(*S*)-LSB	39	72	6
2	(*S*)-ALB	94	24	0
3	La-(*S*,*S*)-**5** (O)	60	66	74
4	Pr-(*S*,*S*)-**5** (O)	42	19	51
5	Sm-(*S*,*S*)-**5** (O)	36	nr[d]	nd[e]
6	La-(*S*,*S*)-**6** (S)	24	24	58
7	La-(*S*,*S*)-**1** (NH)	24	65	90
8	La-(*S*,*S*)-**2** (NMe)	24	77	92
9	La-(*S*,*S*)-**3** (NEt)	24	60	88
10	La-(*S*,*S*)-**4** (NCH_2CF_3)	24	11	24

[a] The product was obtained as a 1:1 mixture of diastereomers. [b] Isolated yield. [c] The enatiomeric excess was determined by GC analysis after conversion to the appropriate derivatives; see the Supporting Information. [d] No reaction. [e] Not determined.

we report a general catalytic asymmetric Michael reaction of β-keto esters to cyclic enones using the newly developed La−NR-linked-BINOL (R = H (**1**) or Me (**2**), Figure 1) complexes. An amine moiety in the NR-linked-BINOL can electronically tune the Lewis acidity of the central metal and sterically tune the chiral environment of the La−NR-linked-BINOL complex. The selectivity of this reaction is highly dependent on the bulkiness of the β-keto esters, and high reactivity and selectivity were accomplished by an appropriate choice of the substituent (R) in the NR-linked-BINOL ligand. In addition, we demonstrated the usefulness of the corresponding Michael product by synthesis of the key intermediate of (−)-tubifolidine and (−)-19,20-dihydroakuammicine. Using the Michael adduct of the β-keto ester, the key intermediate was synthesized in fewer steps as compared with using the Michael adduct of malonates (five steps vs nine steps). Finally, several mechanistic investigations of the Michael reactions are discussed to gain insight into the active catalyst species.

Results and Discussion

Catalyst Development for the Asymmetric Michael Reaction of β-Keto Esters. In our preliminary studies, asymmetric induction in the Michael reaction of β-keto ester **8a** to **7b** was not observed even when using excellent catalysts for the Michael reaction of malonates, such as LSB[4b] and ALB[4c,e] complexes (Table 1, entries 1 and 2). Only the La−O-linked-BINOL complex[4d,f,i] afforded **9ba** in moderate yield and enantiomeric excess (entry 3). Other more Lewis acidic lanthanide metals gave unsatisfactory results (entries 4 and 5). These findings suggested that the use of β-keto esters as ligands would prevent dissociation of the product from the complex or form undesired complexes with more Lewis acidic Ln catalysts.[14] Thus, a less Lewis acidic metal was expected to be more suitable for the reaction of β-keto esters. Because La is the weakest Lewis acid of the lanthanide metals, we expected that a linker heteroatom on linked-BINOL would electronically tune the properties of the La catalyst. We examined S-linked-BINOL **6**[15] (entry 6) and NR-linked-BINOLs **1** (R = H) and **2** (R = Me) (entries 7 and 8) and found that nitrogen on the linker accelerates the reaction with high selectivity (up to 92% ee). Coordination of the electron-rich amine moiety to the central metal might decrease the Lewis acidity of the central metal. Although on the basis of the oxophilicity of hard lanthanide metals, an oxygen linker would be expected to decrease the Lewis acidity more than a nitrogen linker; in this case, the high electron-donating ability of the amine moiety, which is spatially fixed in the vicinity of the central metal by two BINOL units, might effectively influence the Lewis acidity of the central metal. The electronic effects of the NR moiety were demonstrated by comparing the NEt ligand **3** with the NCH_2CF_3 ligand **4** (entries 9 and 10). The size of the trifluoroethyl group is regarded to be the same as that of the ethyl group, but the electronic properties of the trifluoroethyl group are quite different from those of the ethyl group because of the electron-withdrawing nature of the fluorine atom. As we presumed, NCH_2CF_3 ligand **4** had much lower reactivity and selectivity (11% yield, 24% ee, entry 10) than the NEt ligand **3** (60% yield, 88% ee, entry 9). These results directly support our hypothesis that the amine moiety of NR-linked-BINOL can tune the Lewis acidity of the central metal. This hypothesis was also supported by B3LYP[16] density functional studies.[17] One advantage of the NR-linked-BINOL ligand is its versatility; the ligand can be readily synthesized from the corresponding primary amine,[18] making electronic as well as steric fine-tuning of the catalyst possible. The ease of handling the La−NR-linked-BINOL complexes is equivalent to that of the La−O-linked-BINOL complex.[4d,i] It is easily prepared as a pale-yellow powder by simply mixing La(O-*i*-

(14) Although, in general, there is a linear relation between pK_a and log *K* (stability constant of the chelating agent), acetylacetone has a greater stability constant value (log *K* = 17.4) than ethyl acetoacetate (log *K* = 14.2). See: (a) Calvin, M.; Wilson, K. W. *J. Am. Chem. Soc.* **1945**, *67*, 2003. This discrepancy would result from the interference of the strong ester resonance of the ethyl acetate, which prevents the carbonyl group from taking part fully in the resonance of the chelate ring like the chelation of acetylacetone to metal. See also: (b) Martell, E.; Calvin, M. *Chemistry of the Metal Chelate Compounds*; Prentice Hall: New York, 1952. In addition, in the case of β-diketone complexes of lanthanide ions, more acidic β-diketone complexes show higher stability. For example, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium [Eu(fod)$_3$] is more stable than tris(dipivalomethanato)europium [Eu(dpm)$_3$] against carboxylic acids and phenols. See: (c) Liu, K.-T.; Hsu, M.-F.; Chen, J.-S. *Tetrahedron Lett.* **1974**, *25*, 2179. A logical extension of these results is that the β-keto ester would form more stable lanthanide complexes than malonates.

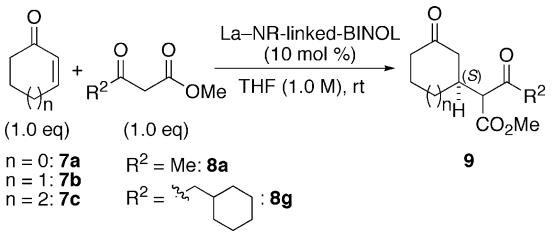
(15) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169.

(16) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(17) Final geometry optimization and calculation of atomic charges (Mulliken charges) of the La complexes were performed by means of the B3LYP hybrid density functional method using a LanL2DZ basis set with Gaussian 98. Further examination of natural bond orbital analysis (Pop = NPA) and more desirable calculations using the MP2 method for the calculation of atomic charges was not possible due to the existence of lanthanum atoms in the molecule. For details, see the Supporting Information.

(18) For details, see the Supporting Information.

Table 2. Effects of the Substituent (R) on the NR-Linked-BINOL Ligand[a]



entry	enone	β-keto ester	ligand R	time (h)	yield[b] (%)	ee[c] (%)
1	**7a**	**8a**	H (**1**)	24	67	65
2	**7a**	**8a**	Me (**2**)	24	82	73
3	**7b**	**8a**	H (**1**)	24	69	90
4	**7b**	**8a**	Me (**2**)	24	77	92
5	**7b**	**8a**	Et (**3**)	24	60	88
6	**7c**	**8a**	H (**1**)	24	83	91
7	**7c**	**8a**	Me (**2**)	24	52	90
8	**7b**	**8g**	H (**1**)	48	67	73
9	**7b**	**8g**	Me (**2**)	48	40	21

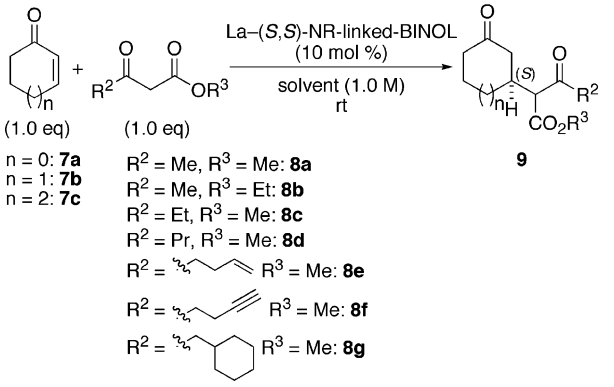
[a] Products were obtained as a 1:1 mixture of diastereomers. [b] Isolated yield. [c] The enantiomeric excess was determined by GC analysis after conversion to the appropriate derivatives. For the determination of the absolute configuration, see the Supporting Information.

Pr)$_3$ and NR-linked-BINOL, and removing the solvent.[18] Moreover, the complex can be stored under air (>6 weeks).[18]

Effects of the Substituent (R) on the NR-Linked-BINOL Ligand. Before optimization of the reaction conditions, we further examined the effects of the substituent (R) on the NR-linked-BINOL ligand using combinations of selected substrates (Table 2). When the smallest β-keto ester, methyl acetoacetate (**8a**), was used for the Michael reactions to cyclic enones **7a**−**c** (five- to seven-membered ring), the NMe ligand **2** gave the highest selectivity (entries 1−7). In the case of 2-cyclohepten-1-one (**7c**), however, there was a considerable decrease in reactivity using the NMe ligand **2** (24 h, 52% yield, entry 7) as compared with the reaction using the smaller NH ligand **1** (24 h, 83% yield, entry 6). When a bulkier β-keto ester **8g** was used, there was a great difference in enantioselectivity between the reaction of the NH ligand **1** (73% ee, entry 8) and NMe ligand **2** (21% ee, entry 9). In general, the NMe ligand **2** was suitable for the combination of small enones and small β-keto esters, and the NH ligand **1** was suitable for bulkier substrates, suggesting that substituents of the linker nitrogen can sterically tune the chiral environment of the catalyst. This tendency was also observed with other combinations of substrates (see Table 3). An NEt ligand **3**, electronically more suitable than NMe ligand **2** or NH ligand **1**, was expected to give better results; however, there was slightly lower reactivity and selectivity (entry 5). In this case, the strict steric effects of amine substituents might exceed the electronic effects.

Scope and Limitations of the Catalytic Asymmetric Michael Reaction of β-Keto Esters Using La−NR-Linked-BINOL Complexes. We then investigated the scope and limitations of several substrates after optimizing the reaction conditions, e.g., solvent composition and concentration. For the reaction using the NMe ligand **2**, the addition of DME (THF:DME = 9:1) often improved the reactivity with the same enantioselectivity. On the other hand, when the NH ligand **1** was used, the addition of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)[4f] sometimes had positive effects in terms of reactivity

Table 3. Catalytic Asymmetric Michael Reaction of β-Keto Esters to Enones Using the La−NR-Linked-BINOL Complexes[a]



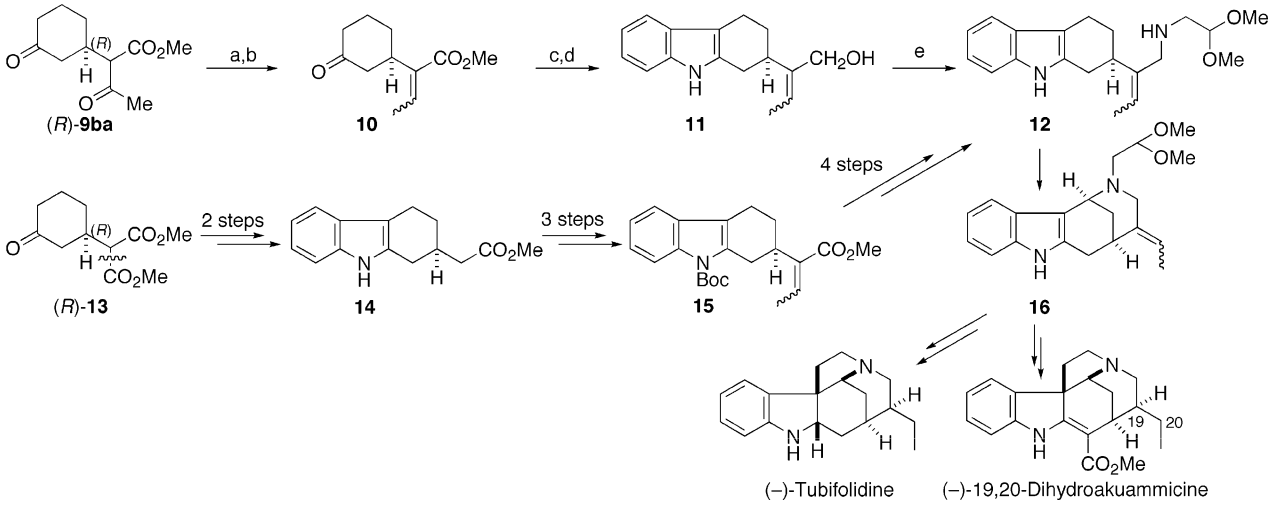
entry	enone	β-keto ester	ligand	product	time (h)	yield[b] (%)	ee[c] (%)
1[d]	**7a**	**8a**	**2**	**9aa**	24	94	73
2[d]	**7a**	**8c**	**2**	**9ac**	24	85	80
3[e]	**7a**	**8d**	**1**	**9ad**	24	75	75
4[e]	**7a**[h]	**8e**	**1**	**9ae**	48	84	72
5[d]	**7b**	**8a**	**2**	**9ba**	24	82	92
6[d]	**7b**	**8b**	**2**	**9bb**	42	71	88
7[d]	**7b**	**8c**	**2**	**9bc**	24	71	91
8[d]	**7b**	**8d**	**2**	**9bd**	36	81	87
9[e]	**7b**[h]	**8e**	**1**	**9be**	48	73	80
10[f]	**7b**[h]	**8f**	**1**	**9bf**	48	65	73
11[e]	**7b**[h]	**8g**	**1**	**9bg**	48	67	73
12[d]	**7c**	**8a**	**2**	**9ca**	42	83	92
13[g]	**7c**	**8b**	**1**	**9cb**	24	88	89
14[g]	**7c**	**8c**	**1**	**9cc**	24	91	90
15[g]	**7c**	**8d**	**1**	**9cd**	24	87	88
16[f]	**7c**[h]	**8e**	**1**	**9ce**	48	83	83
17[e]	**7c**[h]	**8f**	**1**	**9cf**	48	74	77
18[e]	**7c**[h]	**8g**	**1**	**9cg**	48	66	69

[a] Products were obtained as a 1:1 mixture of diastereomers. [b] Isolated yield. [c] The enantiomeric excess was determined by GC analysis after conversion to the appropriate derivatives. For the determination of the absolute configuration, see the Supporting Information. [d] Solvent composition, THF/DME (9:1). [e] THF. [f] THF/HFIP (19:1). [g] THF/HFIP (19:1), 2.0 M. [h] A 1.2 equiv sample of enone was used.

while maintaining selectivity. For example, the yield of **9ba** was improved from 77% (entry 4, Table 2) to 82% (entry 3, Table 5) by the addition of DME. As shown in Table 3, the Michael reaction of a variety of acyclic β-keto esters, **8a**−**g**, to cyclic enones **7a**−**c** was promoted by the La−NR-linked-BINOL complex to afford Michael adducts with moderate to good enantiomeric excess. To the best of our knowledge, this is the first example of a general catalytic asymmetric Michael reaction of acyclic β-keto esters to cyclic enones in which asymmetric induction occurs at the β-position of the enones (eq 2).

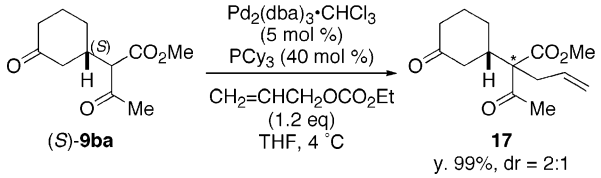
Synthetic Application of the Michael Product of β-Keto Ester. The usefulness of the Michael product of β-keto esters was demonstrated (Scheme 1). Indole **12** is the key intermediate of (−)-tubifolidine[6b] and (−)-19,20-dihydroakuammicine,[6c] which were synthesized from the Michael product of malonate (*R*)-**13** through a C−C bond cleavage (decarboxylation) and formation (aldol reaction). Using (*R*)-**9ba** as a starting material, which was prepared using the (*R*,*R*)-NMe ligand **2** (82%, 92% ee), the key intermediate **12** was synthesized more efficiently in terms of atom economy. The chemoselective reduction of the β-ketone by the Ru catalyst[20] and dehydration by DCC−CuCl[21] provided **10** in good yield (84% and 81%, respectively), which was further converted to indole product by Fisher's indole

Scheme 1. Synthesis of the Key Intermediate of (−)-Tubifolidine and (−)-19,20-Dihydroakuammicine[a]



[a] Key: (a) catalytic $RuCl_3$, catalytic DPPB, MeOH, H_2 (30 atm), 50 °C, 84%; (b) CuCl, DCC, benzene, reflux, 81%; (c) $PhNHNH_2$·HCl, AcOH, reflux; (d) DIBAL-H, toluene, −78 °C, 72% (two steps); (e) Ms_2O, *i*-Pr_2NEt, CH_2Cl_2, −20 °C, then $H_2NCH_2CH(OMe)_2$, 4 °C, 60%.

Scheme 2. Chemoselective Allylation at the α-Position of the β-Keto Ester



synthesis. After a 1,2-reduction of the α,β-unsaturated ester, the resulting alcohol was displaced by aminoacetaldehyde dimethyl acetal through methanesulfonyl ester to provide the key intermediate **12**.[22] Compared with the previous synthesis using the Michael adduct of malonate as a starting material (**13** to **12**), the present synthesis requires fewer steps (five steps vs nine steps) and all the carbon atoms of the Michael donor were efficiently utilized for the construction of the carbon skeleton of **12** without C−C bond cleavage.

Using the characteristic reactivity of β-keto ester, an additional substituent can be chemoselectively introduced at the α-position of β-keto esters in the presence of another ketone in the molecule, making it possible to construct a quaternary carbon stereocenter. Although high levels of diastereoselectivity have not yet been achieved (2:1), the allyl substituent was successfully introduced at the α-position of the β-keto ester in 99% yield to afford **17** (Scheme 2),[23] which can be utilized for further transformations to synthesize complex compounds.

Mechanistic Studies. Although many asymmetric catalysts for the Michael reaction have been developed, it is still difficult to characterize the active species and there are no reports of detailed mechanistic investigations except for a few examples of the reactions catalyzed by the lanthanide-containing chiral heterobimetallic complex (LSB),[4b] the aluminum-containing chiral heterobimetallic complex (ALB),[4c] and chiral transition-metal complexes.[10a,13,24] Although, as mentioned, we developed an efficient asymmetric Michael reaction of malonate catalyzed by the La−O-linked-BINOL complex,[4d,f,i] the details of the reaction are not yet clear due to the difficulty in determining the catalyst structure of alkali-metal-free lanthanide complexes.[25] In contrast to the successful structural determination of heterobimetallic complexes containing a lanthanide metal, alkali metals, and BINOL,[4b,g,h] there had been only a little information on the structure of alkali-metal-free Ln−BINOL complexes available before we elucidated the structure of the La−BINOL−Ph_3As=O complex,[25a] which promoted the catalytic asymmetric epoxidation of a variety of α,β-unsaturated carbonyl compounds.[25a,26] In the absence of Ph_3As=O, the La−BINOL complex should exist as a mixture of oligomeric species on the basis of the results of laser desorption/ionization time-of-flight mass spectrometry, the obscure ^{13}C NMR spectrum, and asymmetric amplification in the epoxidation, making it difficult to determine the structure of the La−BINOL complex.[25a] Ph_3As=O is an effective additive to realize high reactivity and selectivity, and the role of Ph_3As=O was elucidated to promote the formation of the monomeric species by the coordination of Ph_3As=O to the lanthanum metal, leading to the structural determination (including X-ray analysis).[25a] On the basis of the high stability of La−1,3-diketone complexes such as $Ln(acac)_3$

(19) Although it is possible that the role of the amine is to enolize the β-keto ester, it might not be very feasible on the basis of the results of the corresponding La−O-linked-BINOL, which promoted the reaction in a way similar to that of La−NR-linked-BINOL. See the Mechanistic Studies.

(20) For the first example of catalytic asymmetric hydrogenation of 1,3-dicarbonyl compounds using an Ru catalyst, see: (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. For review, see: (b) Ager, D. J.; Laneman, S. *Tetrahedron: Asymmetry* **1997**, *8*, 3327 and references therein. For in situ generation of Ru−diphosphine catalysts from anhydrous $RuCl_3$, see: (c) Madec, J.; Pfister, X.; Phansavath, P.; Vidal, V. R.; Genêt, J.-P. *Tetrahedron* **2001**, *57*, 2563.

(21) (a) Alexandre, C.; Rouessac, F. *Bull. Soc. Chim. Fr.* **1971**, 1837. For an example of synthetic application, see: (b) Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776. See also ref 6d.

(22) Spectroscopic data were identical to the reported data (ref 6b).

(23) Tsuji, J.; Shimizu, I.; Minami, I.; Ohashi, Y.; Sugiura, T.; Takahashi, K. *J. Org. Chem.* **1985**, *50*, 1523.

(24) For an example of mechanistic investigation and improvement based on the mechanism of Rh-catalyzed asymmetric Michael-type reaction, see: Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(25) (a) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725. Kobayashi et al. reported the structural information on Yb− and Sc−BINOL complexes prepared from $Yb(OTf)_3$ or $Sc(OTf)_3$, BINOL, and a tertiary amine, see: (b) Kobayashi, S.; Ishitani, H.; Hachiya, I.; Araki, M. *Tetrahedron* **1994**, *40*, 11623 and references therein.

(26) (a) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Synth. Org. Chem. Jpn.* **2002**, *60*. 94. (b) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9474. (c) Nemoto, T.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *Chirality* **2003**, *15*, 306. (d) Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14544. (e) Tosaki, S.-y.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 495. (f) Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Fukuta, Y.; Nemoto, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 11206.

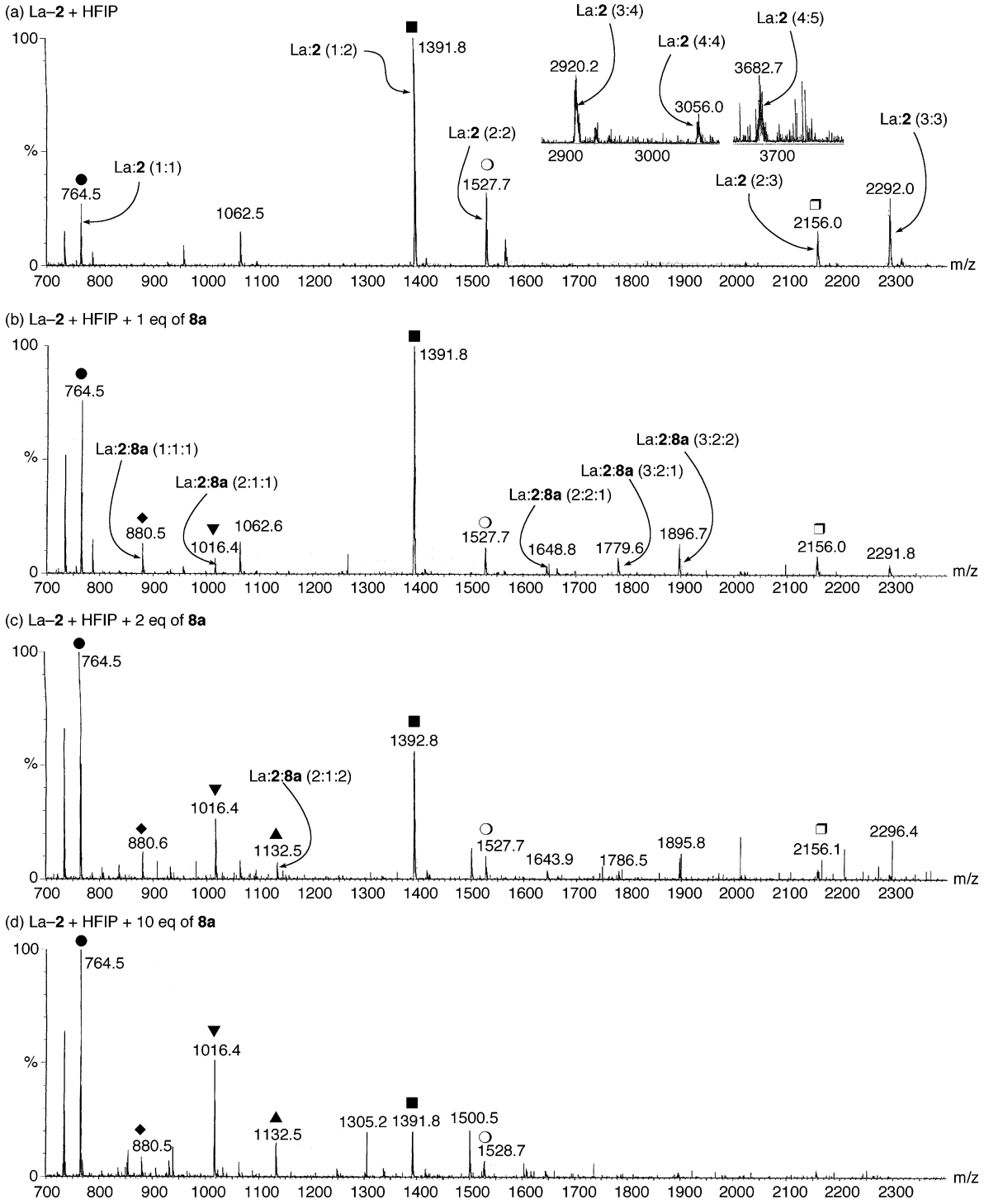


Figure 2. ESI-MS (positive mode) spectra of solutions of La−NMe-linked-BINOL with or without β-keto ester **8a**.

complexes, β-keto ester should have a high affinity for lanthanide metals.[14] Thus, we expected that the β-keto ester could stabilize the monomeric species in a way similar to that of $Ph_3As{=}O$. Despite numerous attempts to obtain a crystal for X-ray analysis or an informational NMR spectrum with or without β-keto ester, only unsatisfactory results were obtained, suggesting that even in the presence of the β-keto ester, the La−NR-linked-BINOL complexes exist as a mixture of several species in solution.

To gain insight into the structure of La−NR-linked-BINOL complexes in solution *directly*, we performed electrospray ionization mass spectrometry (ESI-MS) analysis. The ESI-MS spectrum of the solution generated from the La(O-*i*-Pr)$_3$ and NMe-linked-BINOL **2** in a ratio of 1:1 is shown in Figure 2a. There were several peaks assigned to the complexes of La:**2** = 1:1 to 4:5, supporting our assumption that the La−**2** complex itself exists as a mixture of oligomeric species. When β-keto ester **8a** (1 equiv with respect to the La−**2** complex) was added to a solution of the La−**2** (1:1) complex (Figure 2b), the relative intensities of the peaks of higher order oligomers (La:**2** = 2:2 to 4:5) decreased and several peaks derived from the β-keto ester-containing species (La:**2**:**8a** = 1:1:1 to 3:2:2) appeared.[27]

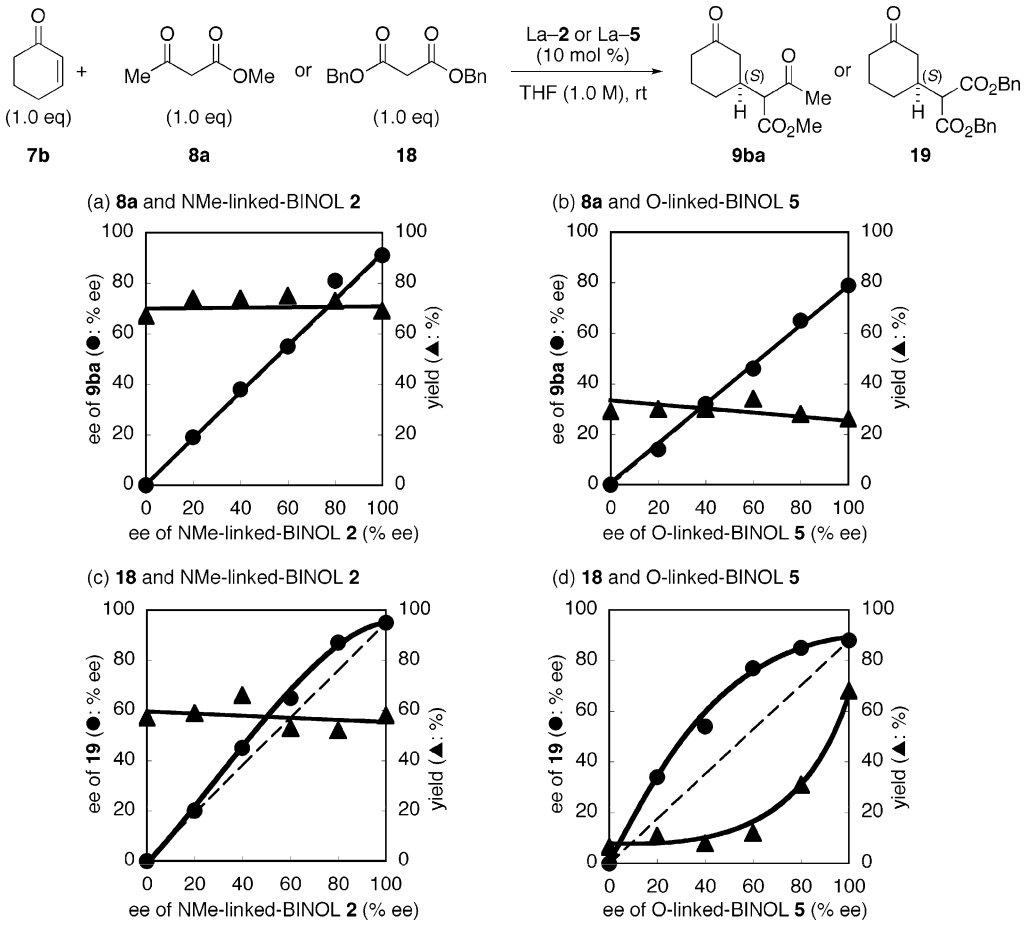


Figure 3. Effects of nonenantiopure ligands (nonlinear effects) (●, ee of the product; ▲, yield).

Further addition of β-keto ester (2−10 equiv with respect to the La−**2** complex, Figure 2c,d) made the peaks in the high molecular weight region (MW > 1500) almost disappear.[18] When 4 or 10 equiv of β-keto ester was added, five main peaks were detected; two were derived from the complexes of La:**2** = 1:1 or 1:2, and the other three peaks were derived from the species that contain β-keto ester(s) and only one molecule of NMe ligand **2** (La:**2**:**8a** = 1:1:1, 2:1:1, and 2:1:2). Although the complex did not converge to one species, even after the addition of excess β-keto ester, these results support our expectation that several relatively stable monomeric species are formed by the coordination of β-keto ester to the lanthanum metal.[28] Using malonate [dibenzyl malonate (**18**)] instead of β-keto ester, however, only obscure ESI-MS spectra were obtained.[29]

To obtain further information about the active species, we next examined the Michael reaction using the nonenantiopure La−NMe-linked-BINOL complex. As shown in Figure 3a, there was a clear linear relation between the enantiomeric excess of NMe ligand **2** and that of the Michael adduct **9ba**. When the La−O-linked-BINOL complex was used for the reaction of β-keto ester, a linear relation was observed again (Figure 3b). On the other hand, in the reaction of malonate **18**, both La−NMe-linked-BINOL and La−O-linked-BINOL complexes displayed positive nonlinear effects[30] (Figure 3c,d). These findings indicate that the structures of the active species of both the La−NMe-linked-BINOL complex and the La−O-linked-BINOL complex are similar. Thus, the differences between La−NMe-linked-BINOL and La−O-linked-BINOL complexes in the asymmetric Michael reaction would be caused mainly by the electronic property of the linker heteroatom (vide supra). Moreover, the results of ESI-MS analysis as well as the clear linear relation between the enantiomeric excess of the NMe ligand **2** and that of Michael adduct **9ba** suggested that the active species in the Michael reaction of β-keto ester promoted by La−NMe-linked-BINOL complex is a monomeric species.

Examinations of the nonlinear effects shown in Figure 3 and ESI-MS analysis led us to suppose that the active species in the Michael reaction of β-keto ester would be different from that of malonate; the former would be a monomeric species, and the latter would be an oligomeric species. In addition, it is reasonable to assume that the active species includes at least one β-keto ester other than the substrate. β-Keto ester can function as a ligand to promote the fragmentation of the

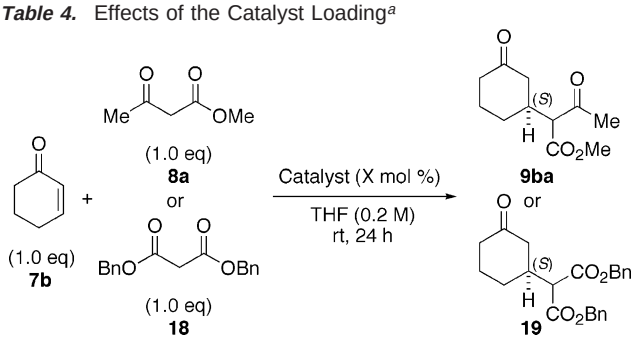
(27) Because lanthanum has essentially only one stable isotope, it is difficult to confirm the assignment by the ion distribution pattern of the observed peaks. Thus, we performed ESI-MS analysis using ethyl acetoacetate (**8b**) instead of methyl acetoacetate (**8a**). In this case, peaks corresponding to the complexes of La:**2**:**8b** = 1:1:1 to 3:2:2 were detected.

(28) The existence of large peaks assigned to the La:**2** = 1:1 and 1:2 complexes, even in the presence of excess β-keto ester, might be caused by fragmentation through ionization on ESI(+)-MS analysis, although other possibilities cannot be excluded.

(29) This might be due to the lower coordination ability of malonate to the lanthanum metal. See ref 14. In addition, when O-linked-BINOL **5** or NH-linked-BINOL **1** was used as a chiral ligand instead of NMe-linked-BINOL **2**, only obscure spectra were obtained. Furthermore, the addition of enone had no effect on the ESI-MS spectrum in the presence of β-keto ester.

(30) (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922. (b) Kagan, H. B. *Synlett* **2001**, 888.

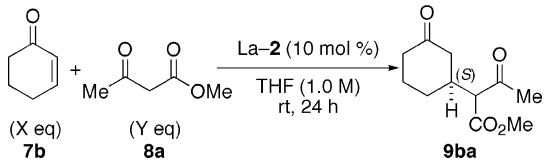
Table 4. Effects of the Catalyst Loading[a]



entry	ligand	product	*X* (mol %)	**La–2**:**8a** ratio	yield[b] (%)	ee[c] (%)
1	**2**	**9ba**	10	1:10	42	89
2	**2**	**9ba**	25	1:4	52	89
3	**2**	**9ba**	50	1:2	49	85
4	**2**	**9ba**	75	1:1.3	39	79
5	**2**	**9ba**	100	1:1	32	79
6[d]	**2**	**9ba**	100	1:2	68	87
7[e]	**2**	**9ba**	100	1:1	53	80
8	**2**	**19**	10		61	96
9	**2**	**19**	100		91	91
10	**5**	**9ba**	10	1:10	7	68
11	**5**	**9ba**	100	1:1	22	44
12	**5**	**19**	10		39	88
13	**5**	**19**	100		80	93

[a] Products were obtained as a 1:1 mixture of diastereomers. [b] Isolated yield. [c] The enantiomeric excess was determined by GC analysis after conversion to the appropriate derivatives. For the determination of the absolute configuration, see the Supporting Information. [d] A 2.0 equiv sample of **8a** was used. [e] A 2.0 equiv sample of **7b** was used.

Table 5. Effects of the Equivalence of Enone or *β*-Keto Ester[a]



entry	*X* (mol %)	*Y* (mol %)	**La–2**:**8a** ratio	yield[b] (%)	ee[c] (%)
1	10	1	1:10	quant	91
2	2.5	1	1:10	quant	91
3	1	1	1:10	77	92
4	1	1.1	1:11	69	91
5	1	1.2	1:12	63	89
6	1	1.3	1:13	59	88
7	1	1.4	1:14	56	87

[a] Products were obtained as a 1:1 mixture of diastereomers. [b] Isolated yield. [c] The enantiomeric excess was determined by GC analysis after conversion to the appropriate derivatives. For the determination of the absolute configuration, see the Supporting Information.

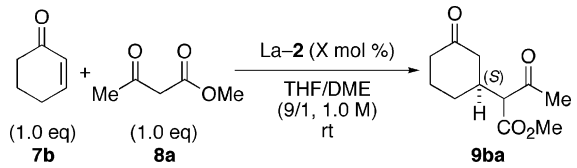
oligomeric species into a monomeric species. The role of *β*-keto ester as a ligand was elucidated by the following experiments. The effects of catalyst loading of the Michael reaction of *β*-keto ester **8a** or malonate **18** to enone **7b** were investigated using the NMe-linked-BINOL **2** or O-linked-BINOL **5** ligand. When *β*-keto ester **8a** was used as a Michael donor, higher catalyst loading (≥50 mol % La−NMe-linked-BINOL complex) decreased the reactivity and selectivity (entries 3−5, Table 4).[31] In the presence of 100 mol % La−NMe-linked-BINOL complex, 2.0 equiv of *β*-keto ester **8a** gave a much higher yield and better enantiomeric excess (entry 6) than 1.0 equiv of **8a** (entry 5), while 2.0 equiv of enone **7b** increased only the reactivity (entry 7). From these results, more than 2 equiv of *β*-keto ester with respect to the La−NMe-linked-BINOL complex is necessary to realize high reactivity and selectivity. On the other hand, in the Michael reaction of malonate **18**, higher catalyst loading increased the reactivity with only a slight loss of selectivity (entries 8 and 9). The same tendency was observed using O-linked-BINOL **5** instead of NMe-linked-BINOL **2** (entries 10−13). An additional 1 equiv of *β*-keto ester seems to tune the structure of the chiral La−ligand complex, affording high reactivity and selectivity.

The effects of the ratio of the La−NMe-linked-BINOL complex and *β*-keto ester as well as enone were further investigated using 10 mol % La−NMe-linked-BINOL complex (Table 5). As with using stoichiometric amounts of the La−NMe-linked-BINOL complex (entry 7, Table 4), an excess amount of enone had positive effects only on the reactivity (entries 1 and 2, Table 5). In contrast, although the results shown in Table 4 suggested that more *β*-keto ester gave better results, in this case, only amounts slightly larger than 1.0 equiv of *β*-keto ester gave a lower yield and enantiomeric excess (entries 4−7, Table 5). While the reason for this is not yet clear, it is possible that excess *β*-keto ester leads to the production of undesired complexes or the prevention of the coordination of enone. On the basis of the results shown in Tables 4 and 5, the appropriate ratio between the La−NMe-linked-BINOL complex and *β*-keto ester to generate the desired active species effectively is 1:2 to 1:10. The tendency for the effects of *β*-keto ester in the Michael reaction is very similar to that of $Ph_3As{=}O$ in epoxidation, in which the addition of 1 equiv of $Ph_3As{=}O$ afforded the best results in terms of reactivity and selectivity.[25a] Therefore, we propose that *β*-keto ester has a role not only as a substrate but also as a ligand to promote the generation of an active monomeric species in a way similar to that of $Ph_3As{=}O$.

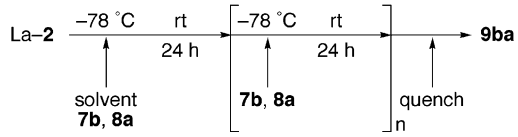
Improvement of the Catalytic Asymmetric Michael Reaction of *β*-Keto Ester Based on the Reaction Mechanism. The above-mentioned finding prompted us to determine how to *maintain the appropriate ratio of the La−NMe-linked-BINOL complex and β-keto ester in the course of the reaction* to realize higher catalyst activity. When the catalyst amount was reduced to 5 mol % La−NMe-linked-BINOL complex (the initial ratio of La−**2** and *β*-keto ester was 1:20), the Michael adduct **9ba** was obtained in 62% yield and 87% ee even after 48 h (Table 6, entry 2). To maintain the appropriate ratio and decrease the catalyst loading, the substrates were added in several portions. When the substrates were added in two portions, even 5 mol % La−**2** complex gave results (77% yield, 92% ee, entry 3) comparable to those of the standard reaction conditions (10 mol % La−**2** complex, one portion, entry 1). This procedure made it possible to achieve a high turnover number (TON; around 50) using only 1.25 mol % La−**2** complex (entry 5). Because an excess amount of enone increased the reactivity without a loss of selectivity, enone **7b** was added in one portion with a two-portion addition of *β*-keto ester **8a**, resulting in an improvement of yield from 77% (entry 3) to 81% (entry 6). Slow addition of *β*-keto ester was also examined, but only a slight improvement was observed as compared with multiportion

(31) Because of low solubility of the catalyst in high loading, the concentration of the substrate was set to 0.2 M. This condition afforded a lower yield and enantiomeric excess (0.2 M, 42%, 89% ee, entry 1, Table 4) than optimized reaction conditions (1.0 M, 82%, 92% ee, entry 5, Table 3).

Table 6. Low Catalyst Loading Maintaining the Appropriate Ratio of La−**2** and **8a**[a]



Procedure



entry	initial La–**2**:**8a** ratio	*X* (mol %)	n	time (h)	yield[b] (%)	ee[c] (%)	TON
1	1:10	10	0	24	79	92	8
2	1:20	5	0	48	62	87	12
3	1:10	5	1	48	77	92	15
4	1:10	2.5	2	72	62	89	25
5	1:10	1.25	3	96	61	87	49
6[d]	1:10	5	1	48	81	92	16

[a] Products were obtained as a 1:1 mixtures of diastereomers. [b] Isolated yield. [c] The enantiomeric excess was determined by GC analysis after conversion to the appropriate derivatives. For the determination of the absolute configuration, see the Supporting Information. [d] **7b** was added in one portion at first.

addition. While this method has not been fully optimized, it will enable the practical use of this reaction.

Conclusion

We successfully developed a general catalytic asymmetric Michael reaction of acyclic β-keto esters to cyclic enones, in which asymmetric induction occurs at the β-position of the acceptor, using novel La−NR-linked-BINOL (R = H (**1**) or Me (**2**)) complexes (up to 92% ee). In addition, we demonstrated that a linker heteroatom in linked-BINOL can tune the catalyst profile electronically and sterically. In general, the NMe ligand **2** was suitable for the combination of both small enones and β-keto esters, and the NH ligand **1** was suitable for bulkier substrates. The usefulness of the Michael product was demonstrated by the synthesis of the key intermediate **12** of (−)-tubifolidine and (−)-19,20-dihydroakuammicine. Compared with previous syntheses using the Michael adduct of malonate as a starting material (**13** to **12**), the synthesis from the Michael adduct of β-keto esters (**9ba** to **12**) is a shorter process (five steps vs nine steps) and all the carbon atoms of the Michael donor were efficiently utilized for the construction of the carbon skeleton of **12** without C−C bond cleavage. Several mechanistic studies revealed that at least one β-keto ester served as a ligand to promote the generation of an active monomeric species in a way similar to that of $Ph_3As{=}O$ in a La−BINOL-promoted epoxidation. To generate the desired active species effectively, maintaining the ratio of the La−NMe-linked-BINOL complex and β-keto ester at 1:2 to 1:10 was very important. On the basis of this finding, we succeeded in reducing the catalyst amount by multiportion addition of β-keto ester. Further studies are currently under investigation in our group.

Acknowledgment. This work was supported by RFTF and a Grant-in-Aid for Encouragements for Young Scientists (A) from the Japan Society for the Promotion of Science (JSPS).

Supporting Information Available: Experimental procedures and characterization of the products and other detailed results and discussion (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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