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

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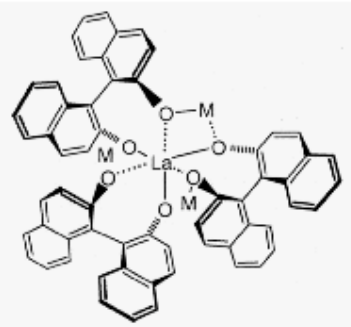
J. Am. Chem. Soc. **2003**, 125, 15837-15845

Professor Masakatsu Shibasaki

Masakatsu Shibasaki was born in 1947 in Saitama, Japan, and received his Ph.D. from The University of Tokyo in 1974 under the direction of the late Professor Shun-ichi Yamada before doing postdoctoral studies with Professor E. J. Corey at Harvard University. In 1977 he returned to Japan and joined Teikyo University as an associate professor. In 1983 he moved to Sagami Chemical Research Center as a group leader, and in 1986 took up a professorship at Hokkaido University, before returning to The University of Tokyo as a professor in 1991. He was a visiting professor at Philipps-Universität Marburg during 1995. He has received the Pharmaceutical Society of Japan Award for Young Scientists (1981), Inoue Prize for Science (1994), Fluka Prize (Reagent of the Year, 1996), the Elsevier Award for Inventiveness in Organic Chemistry (1998), the Pharmaceutical Society of Japan Award (1999), Molecular Chirality Award (1999), the Naito Foundation Research Prize for 2001 (2002), and ACS Award (Arthur C. Cope Senior Scholar Award) (2002). His research interests include asymmetric catalysis, including asymmetric Heck reactions and reactions promoted by asymmetric bifunctional complexes, and also the medicinal chemistry of biologically significant compounds.

Reagent of the year 1996

The Reagent

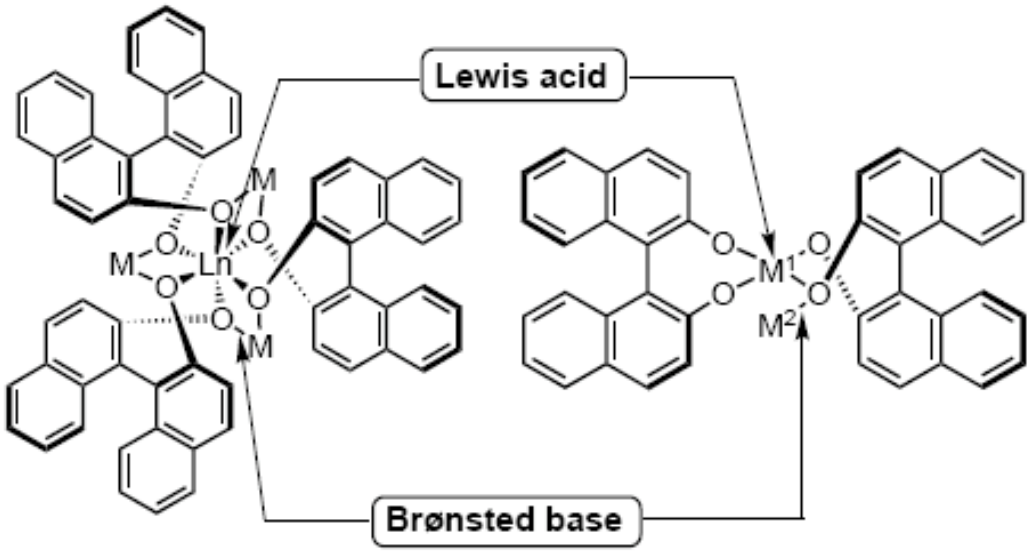


Three new, chiral, hetero-bimetallic, multifunctional complexes constitute the Fluka Prize winning reagent of the year 1996.Each complex consists of a central lanthanum atom, three alkali metal atoms (lithium sodium or potassium) and three molecules of either R(+)- or S(-)-1,1'-bi(2-naphtol)[(R)or (S)-BINOL](Fluka 14383 and 14384)[1]. They function as proton acceptors as well as Lewis acids in catalytical, enantioselective addition of nucleophiles to either carbonyl compounds or imines. The complexes are effective as chiral catalysts in enantioselective transformations of the following types:

- Nitroaldol reactions [2]-[12] (preferentially with lithium as a constituent of the complex), leading to 1,2-nitroalcohols and then to 1,2-aminoalcohols which represent a class of highly interesting compounds with respect to their biological activity.
- Michael additions [13][14][18] (preferentially with sodium as a constituent of the complex). So far malonic ester additions to 2-cycloalkenones have been shown to proceed with high enantioselectivity.
- Hydrophosphonylation of both imines [15] and aldehydes, [16][17] with potassium containing catalysts being preferred for the former, and lithium containig catalysts for the latter. The reaction mechanism has been studied in the case of Michael additions: A basic BINOL-dianion ligand abstracts a proton from the malonic ester and the resulting enolate coordinates to the catalyst through an alkali metal center. Also, the Lewis acidic La-center complexes with the carbonyl compound, thereby activating it and holding this species in place for enantioselective attack by the nucleophile. These catalytically active complexes are easily prepared by mixing LaCl3 (Fluka 61490) with the BINOL-di-alkali metal salt in THF in the presence of NaOH and H_2O [3][5]. The complexes can also be formed by using lanthanum 2-propoxide, BINOL (3 eq) and either BuLi, NaO-t-Bu, or KHMDS, for the lithium, sodium, and potassium complexes respectively [6][15].

http://www.sigmaaldrich.com/suite7/Brands/Fluka___Riedel_Home/Miscellaneous/Reagent_of_the_Year/1996.html

Figure 1. Heterobimetallic multifunctional complexes



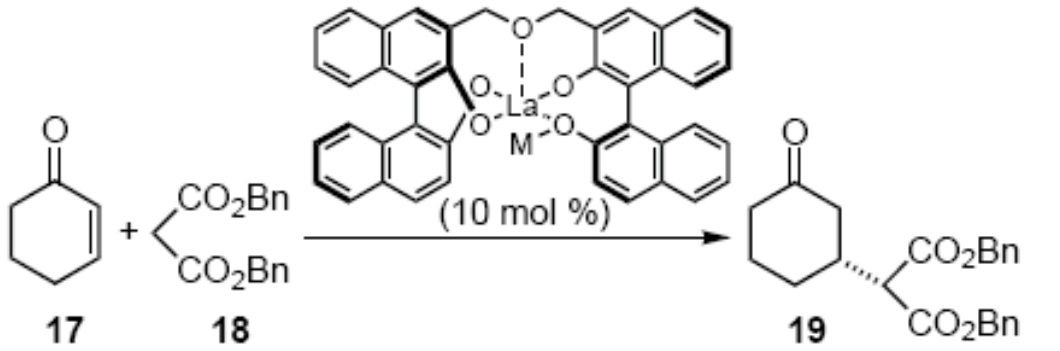
Ln = La, M = Li : LLB **1**

M^1 = Al, M^2 = Li : ALB **2**

M^1 = Ga, M^2 = Li : GaLB **3**

Review: Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal*. **2002**, 1, 344

Table 2. Catalytic asymmetric Michael reaction promoted by (*R*,*R*)-La-M-linked-BINOL complexes.



17 **18** **19**

entry	M	solvent	temp. (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	Li	THF	0	24	21	35
2	Na	THF	0	24	41	43 [c]
3	K	THF	–20	24	16	54 [c]
4	H (**20**)	THF	0	45	53	85
5	H (**20**)	DME	rt	72	94	>99

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The mirror image enantiomer was formed.

Scheme 4. Proposed mechanism for the Michael reaction of enones with malonates.

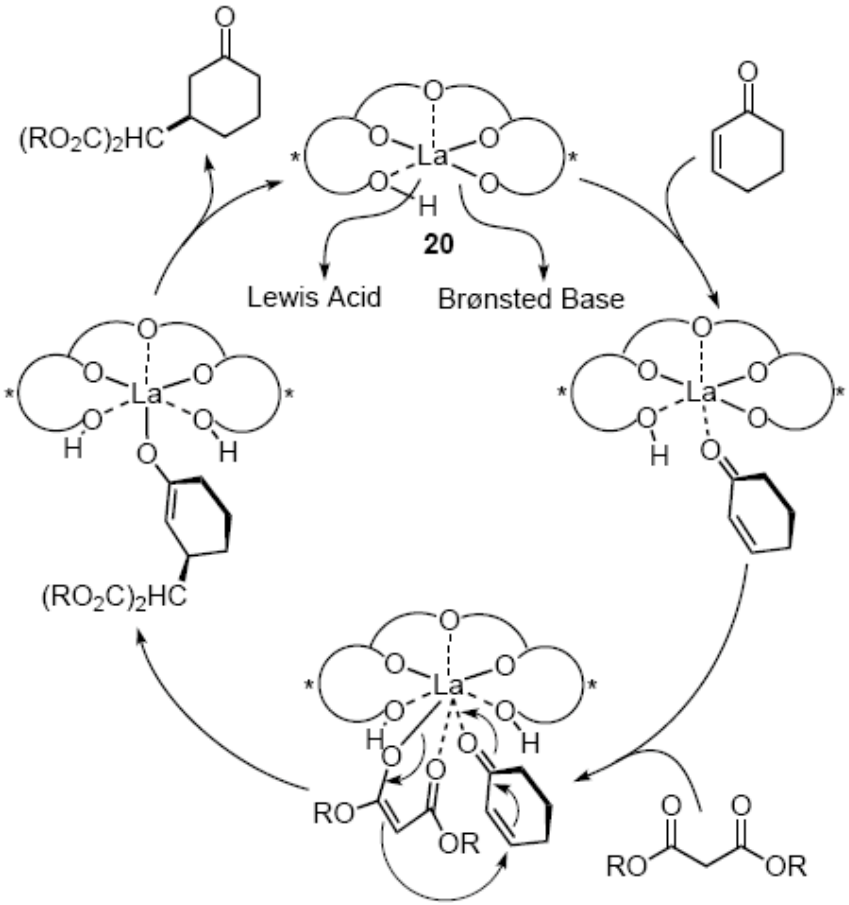
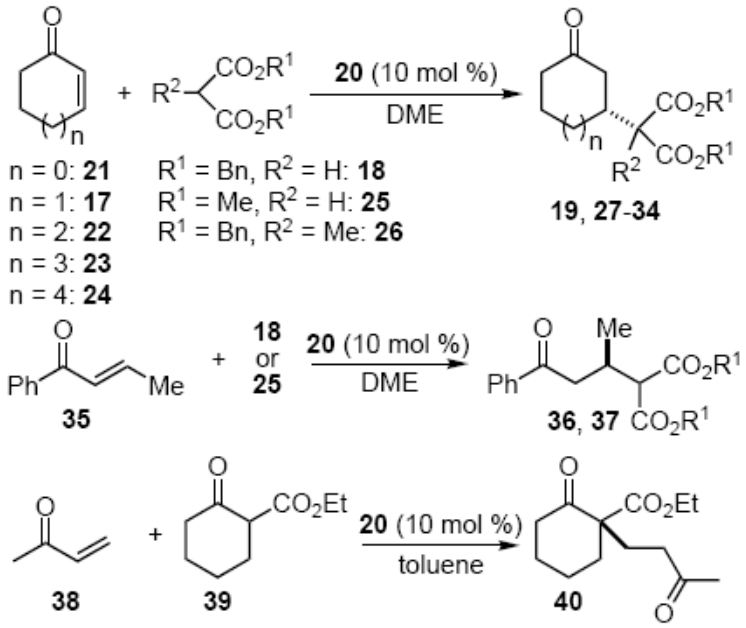


Table 3. Catalytic asymmetric Michael reactions promoted by (*R*,*R*)-La-linked-BINOL **20**.[a]



entry	enone	β-dicarbonyl compounds	temp. (°C)	time (h)	product	yield[b] (%)	ee[c] (%)
1	**21**	**18**	4	85	**27**	85	>99
2	**21**	**25**	4	85	**28**	96	>99
3	**17**	**18**	rt	72	**19**	94	>99
4	**17**	**18**	4	85	**19**	98	>99
5	**17**	**25**	rt	72	**29**	95	>99
6[d]	**17**	**26**	rt	84	**30**	84	98
7	**22**	**18**	4	85	**31**	96	>99
8	**22**	**25**	4	85	**32**	97	>99
9[d]	**23**	**25**	rt	96	**33**	82	99
10	**24**	**18**	4	120	**34**	61	82
11	**35**	**18**	–40	56	**36**	97	78
12	**35**	**25**	–40	56	**37**	95	74
13[e]	**38**	**39**	–30	36	**40**	97	75

[a] In all cases, the reaction was run on 0.6 mmol scale at 0.4 M in enone and malonate.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] The reaction was carried out in DME/THF (9:1).
[e] **24** was added dropwise over 24 h.

Figure 8. Preparation of the stock air-stable powdered (*R*,*R*)-La-linked-BINOL complex **20.**

Catalytic asymmetric Michael reaction

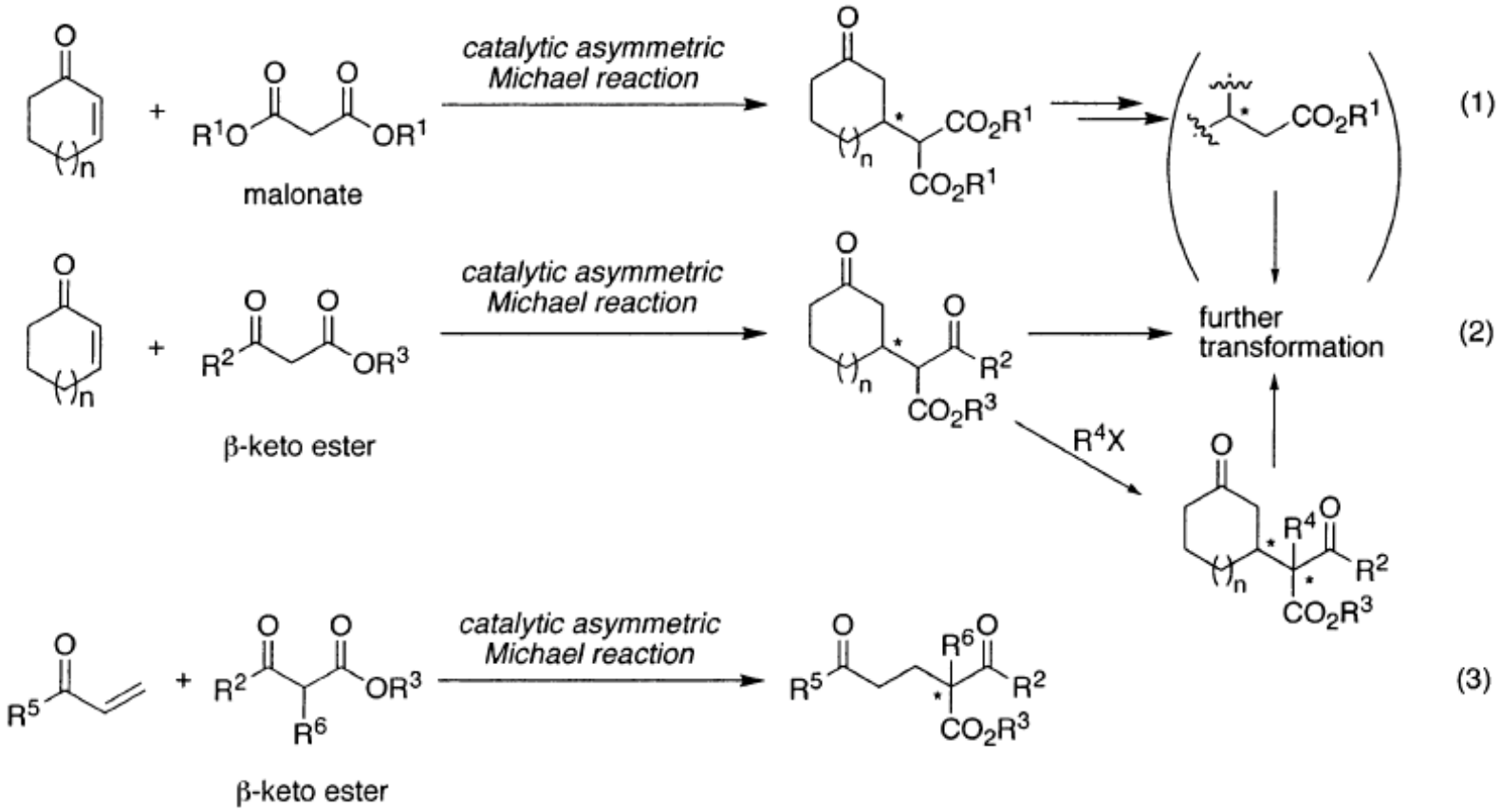
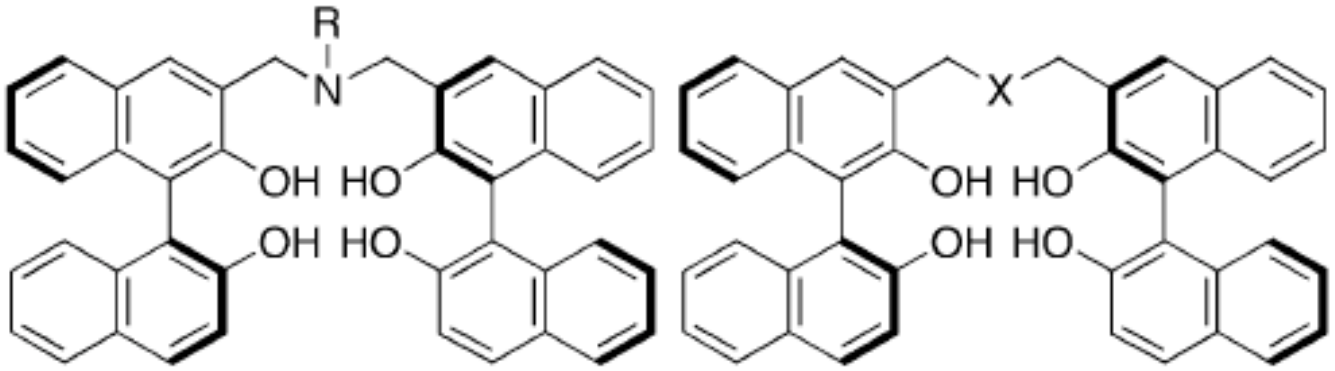


Figure 1. Structures of (*S*,*S*)-NR-linked-BINOLs **1**−**4**, (*S*,*S*)-O-linked-BINOL **5**, and (*S*,*S*)-S-linked-BINOL **6**.



R = H: (*S*,*S*)-**1**
R = Me: (*S*,*S*)-**2**
R = Et: (*S*,*S*)-**3**
R = CH_2CF_3: (*S*,*S*)-**4**

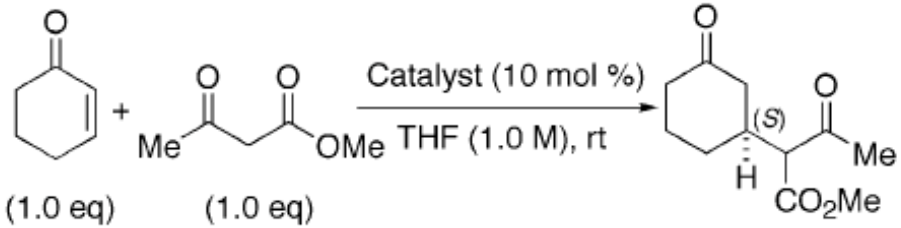
X = O: (*S*,*S*)-**5**
X = S: (*S*,*S*)-**6**

Preparation:

La(OiPr)3 + NR-Linked-BINOL —Remove solvent→ La-NR-Linked-BINOL

Pale-yellow powder

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



(1.0 eq) **7b** (1.0 eq) **8a** **9ba**

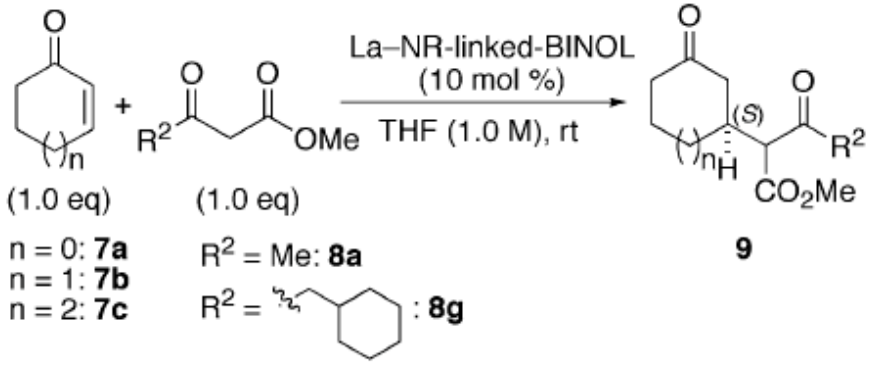
entry	catalyst	time (h)	yield[b] (%)	ee[c] (%)
1	(*S*)-LSB	39	72	6
2	(*S*)-ALB	94	24	0
3	La-(*S*,*S*)-**5** (O)	60	66	74
4	Pr-(*S*,*S*)-**5** (O)	42	19	51
5	Sm-(*S*,*S*)-**5** (O)	36	nr[d]	nd[e]
6	La-(*S*,*S*)-**6** (S)	24	24	58
7	La-(*S*,*S*)-**1** (NH)	24	65	90
8	La-(*S*,*S*)-**2** (NMe)	24	77	92
9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

LSB: Lanthanide-containing chiral heterometallic complex

ALB: Aluminum-containing chiral heterobimetallic complex

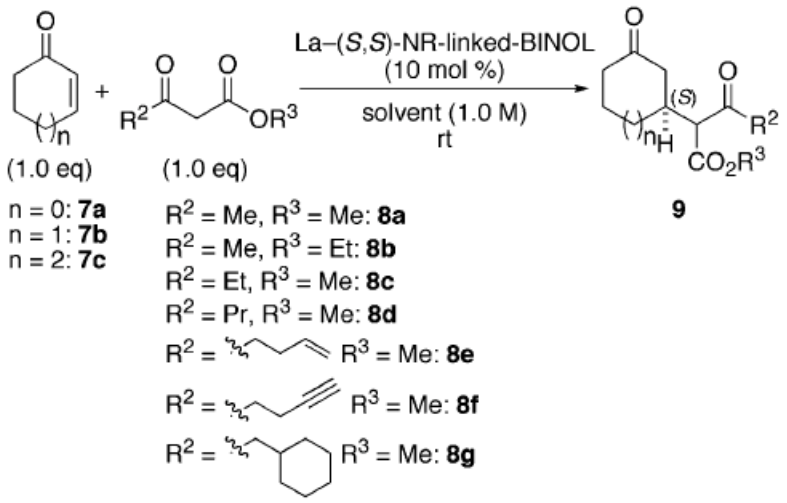
Table 2. Effects of the Substituent (R) on the NR-Linked-BINOL Ligand[a]



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.

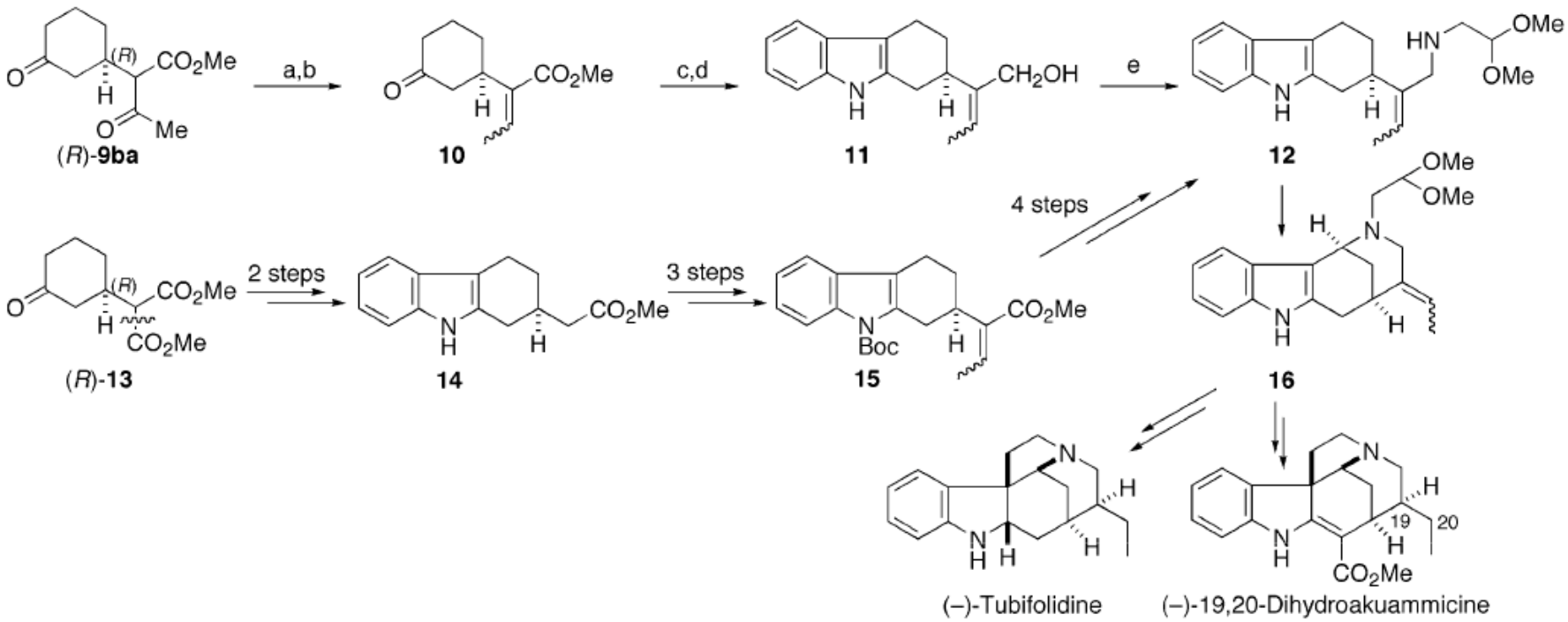
Table 3. Catalytic Asymmetric Michael Reaction of β-Keto Esters to Enones Using the La–NR-Linked-BINOL Complexes[a]



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.

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) $PhNHNH_2 \cdot HCl$, 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

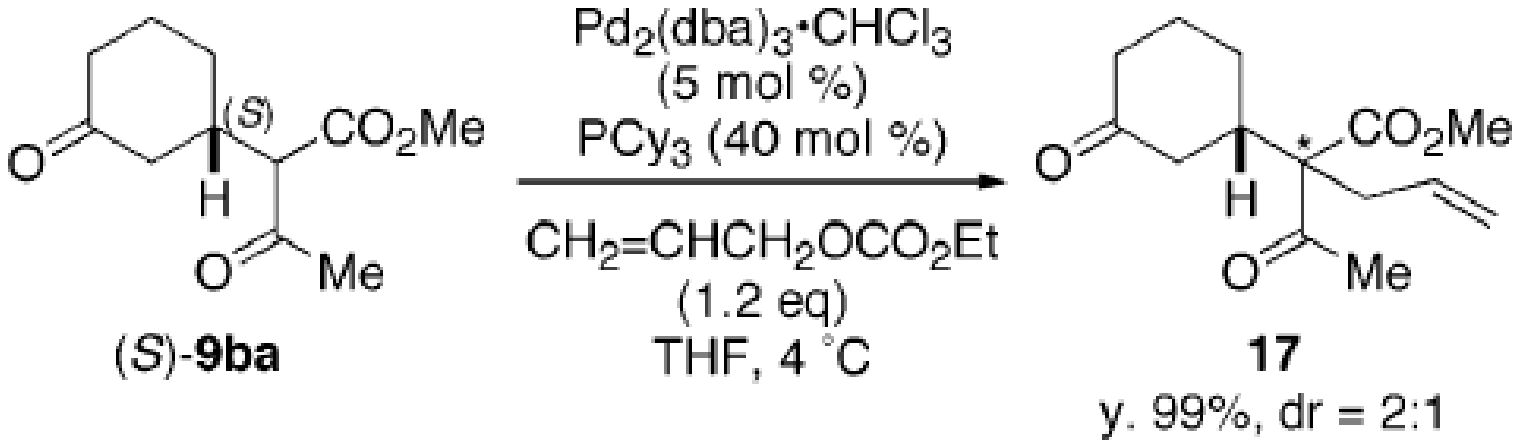


Figure 2. ESI-MS (positive mode) spectra of solutions of La−NMe-linked-BINOL with or without β-keto ester **8a**.

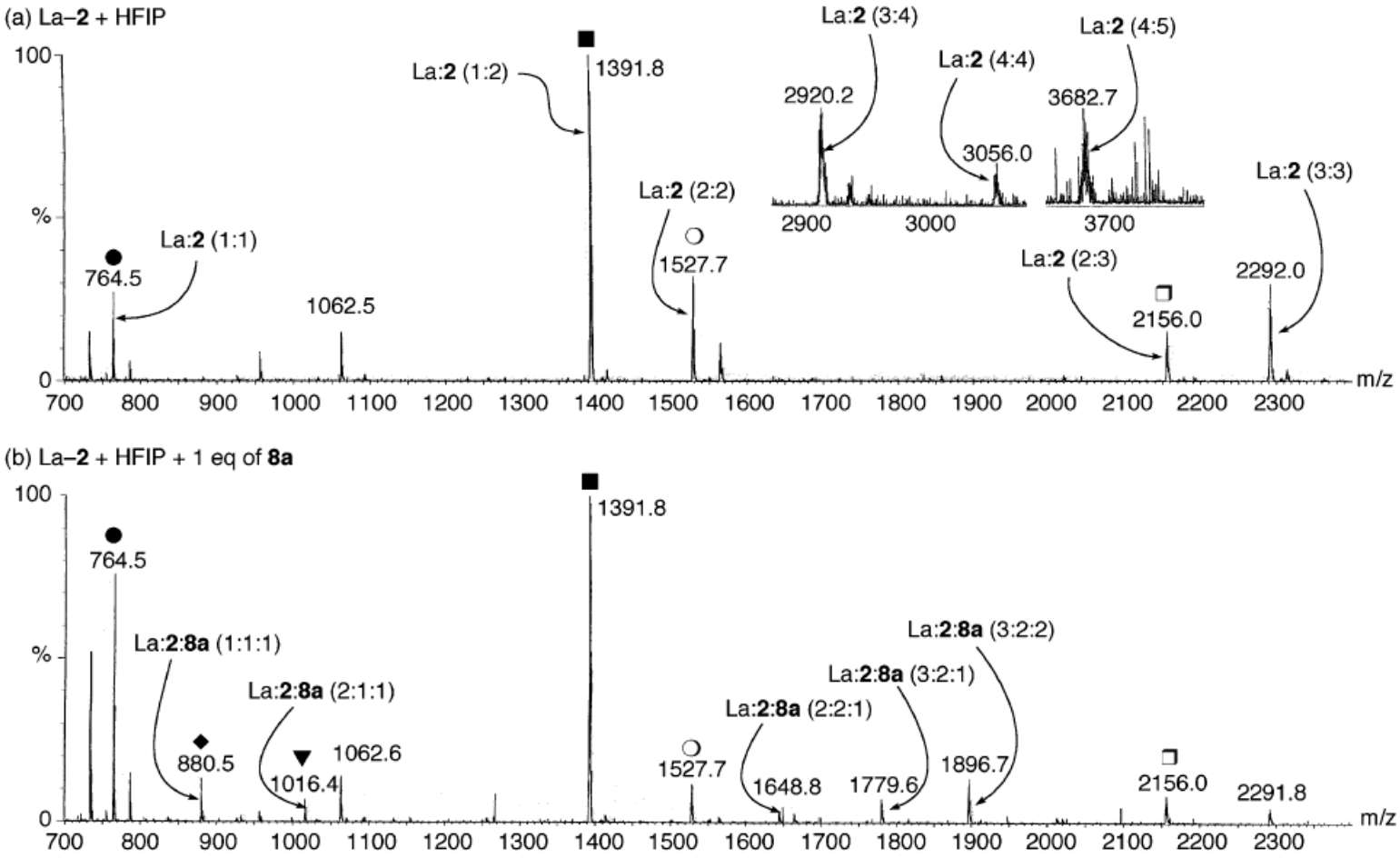


Figure 2. ESI-MS (positive mode) spectra of solutions of La−NMe-linked-BINOL with or without β-keto ester **8a**.

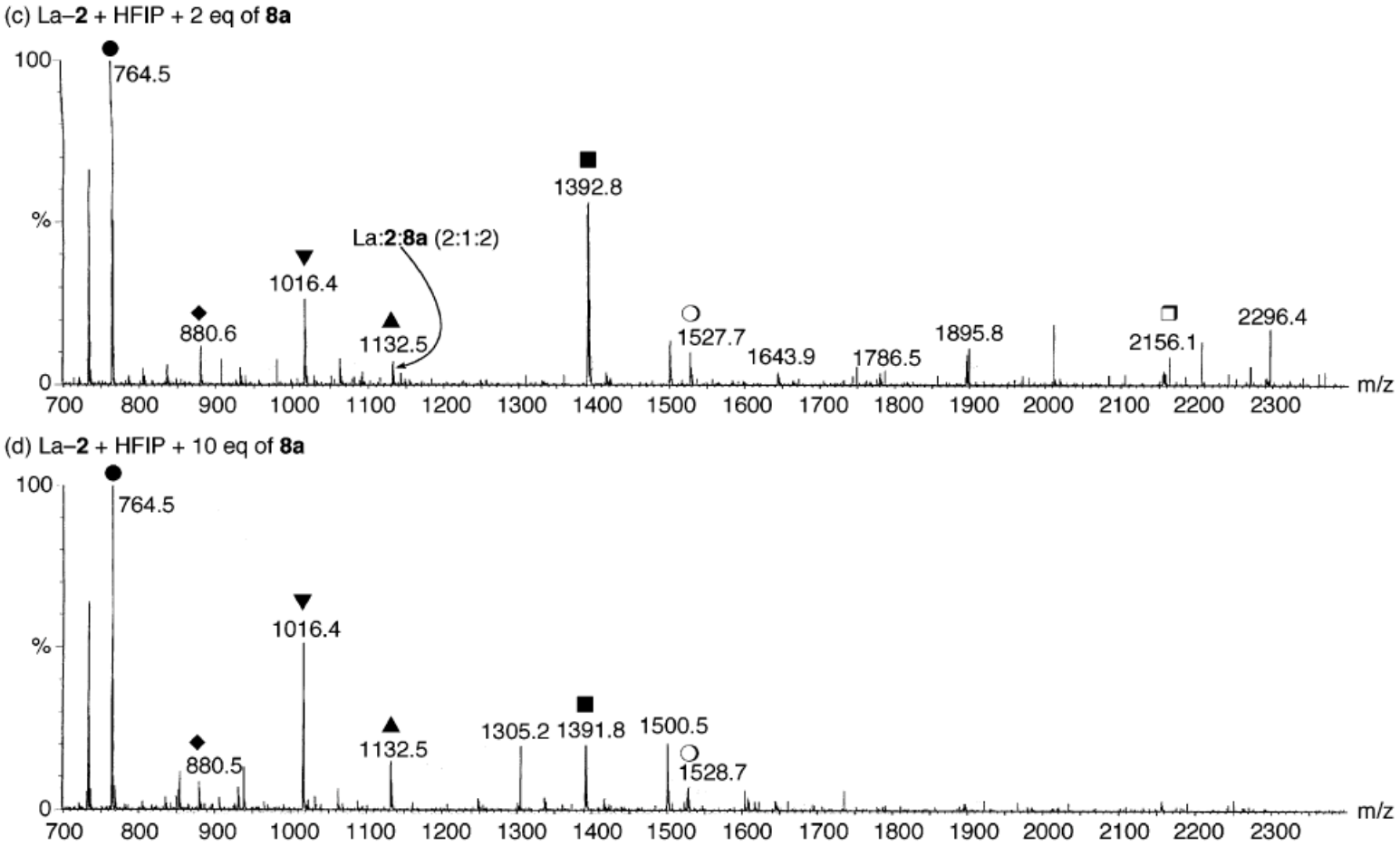
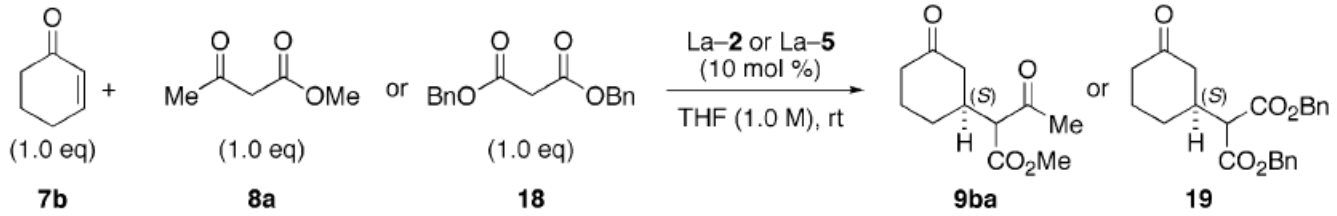


Figure 3. Effects of nonenantiopure ligands (nonlinear effects) (●, ee of the product; ▲, yield).



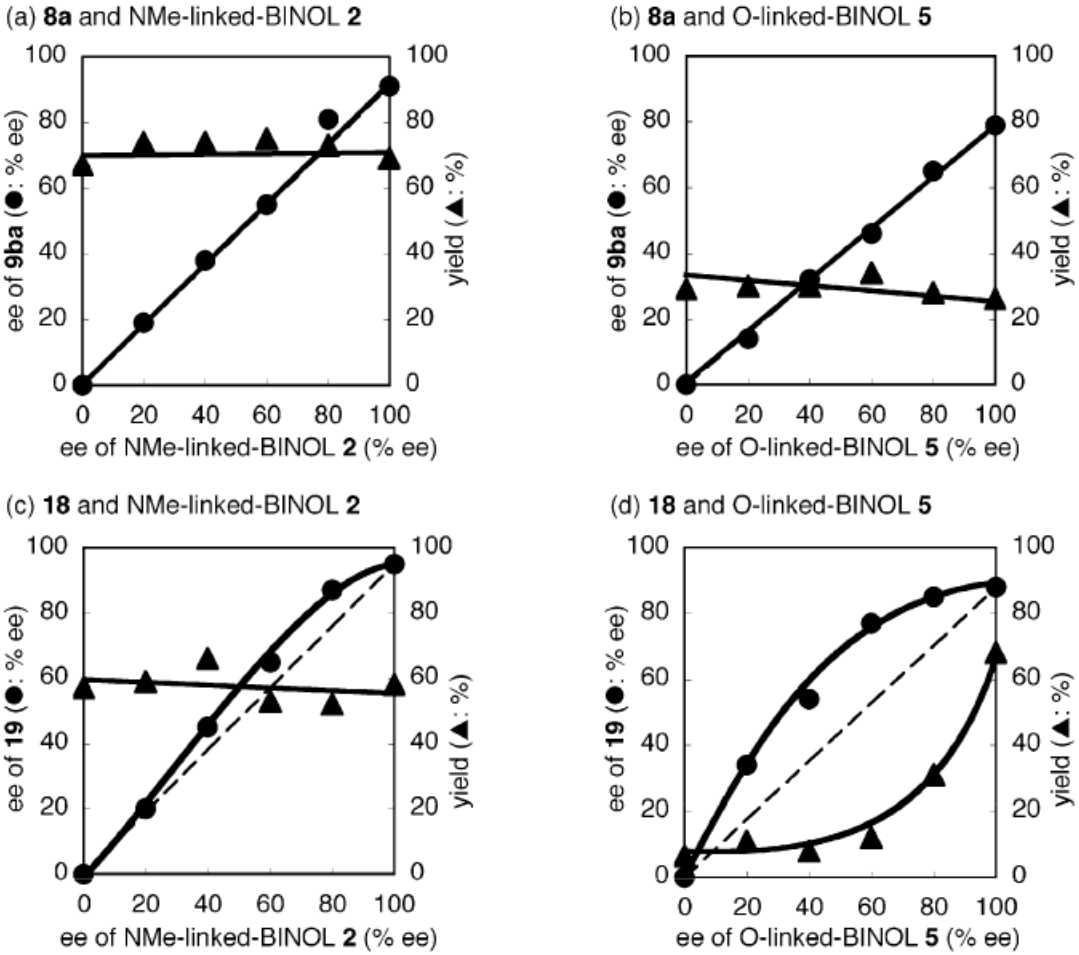
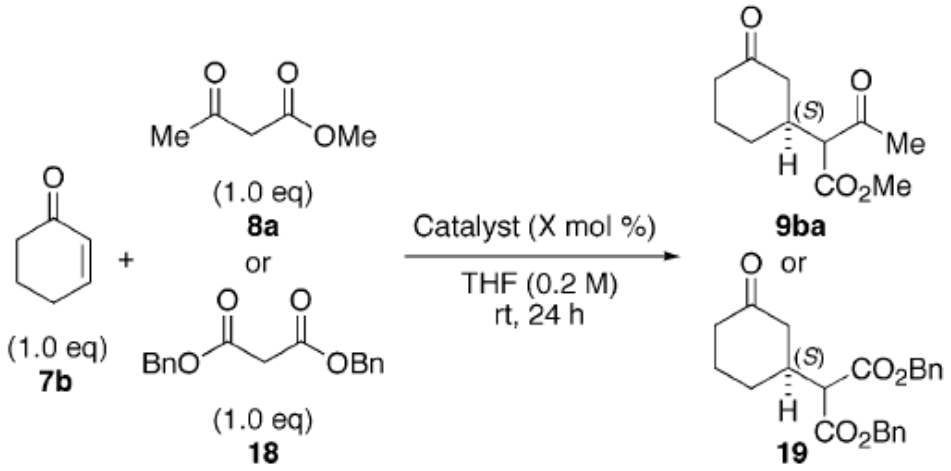


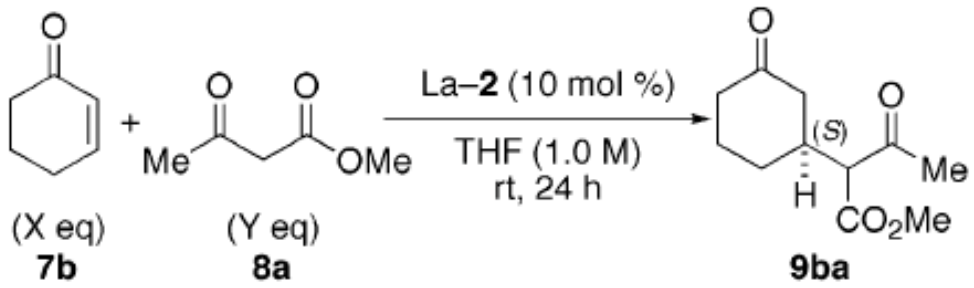
Table 4. Effects of the Catalyst Loading[a]



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]

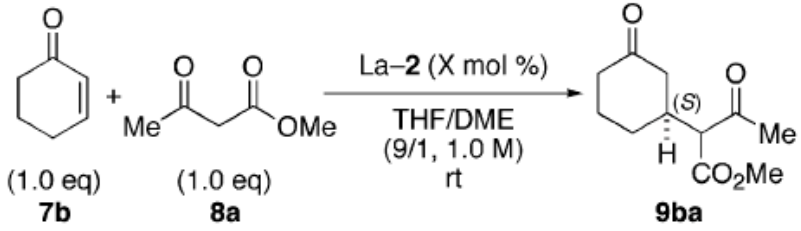


(X eq) **7b** (Y eq) **8a** **9ba**

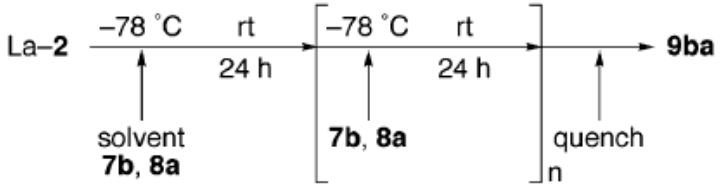
entry	*X* (mol %)	*Y* (mol %)	La–2:8a ratio	yield[b] (%)	ee[c] (%)
1	10	1	1:10	quant	91
2	2.5	1	1:10	quant	91
3	1	1	1:10	77	92
4	1	1.1	1:11	69	91
5	1	1.2	1:12	63	89
6	1	1.3	1:13	59	88
7	1	1.4	1:14	56	87

[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.

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.

Conclusion

1. Asymmetric induction occurs at the beta-position of Michael acceptor was achieved by using La-NR-linked-BINOL (R=H or Me) complex
2. A linker heteroatom in linked-BINOL can tune the catalyst profile electronically and sterically. In general, NMe ligand 2 was suitable for the combination of both small enones and beta-keto esters, and the NH ligand 1 was suitable for bulkier substrate.
3. To generate the desired active species effectively, maintaining the ration of the La-NMe-linked-BINOL complex and beta-keto ester at 1:2 to 1:10 was very important.