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Enantio- and diastereoselective construction of vicinal quaternary and tertiary carbon centers by catalytic Michael reaction of α-substituted β-keto esters to cyclic enones

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Abstract—A catalytic enantio- and diastereoselective Michael reaction was achieved to construct vicinal quaternary and tertiary carbon centers in one step. Using 5 mol% of La(O-*i*-Pr)$_3$ and 10 mol% of a new *N*-linked-BINOL type ligand, the reaction of α-substituted β-keto esters to cyclic enones provided the corresponding Michael adducts in up to quantitative yield with a diastereomeric ratio up to 86/14 and enantiomeric excess up to 86% for the major isomer. An alternative catalyst preparation method using La(OTf)$_3$ instead of La(O-*i*-Pr)$_3$ was also examined.

The enantioselective construction of quaternary carbon centers, that is, carbon centers with four different non-hydrogen substituents, represents a very challenging and dynamic area in organic synthesis.[1] An attractive approach to this goal involves the generation of nucleophilic species by in situ generation of acidic hydrocarbons because of its operationally simple, atom economical, and functional group-tolerant features. A catalytic enantioselective direct Michael reaction[2] of prochiral trisubstituted carbon nucleophiles to electron-deficient C–C double bonds is one of the most efficient candidates. In fact, several efficient catalytic enantioselective Michael reactions of α-substituted β-keto esters to methyl vinyl ketone, which construct a quaternary carbon center at the Michael donor, were reported.[3] To expand the usefulness of this catalysis, a catalytic stereoselective Michael reaction of prochiral trisubstituted carbon nucleophiles to prochiral β-substituted electron-deficient C–C double bonds is highly desirable because it can construct vicinal quaternary and tertiary carbon centers from simple precursors in one step. This reaction, however, requires a catalyst that simultaneously constructs both the quaternary and tertiary carbon centers in sterically demanding positions. Thus, only a few highly enantio- and diastereoselective catalytic reactions have been reported, such as Michael reactions of α-substituted β-keto esters to acyclic β-substituted enones[3i] and β-substituted nitroolefins,[4] α-substituted α-cyanoester to α,β-unsaturated imides,[5] substituted indoles to β-substituted α,β-unsaturated aldehydes,[6] and α,α-disubstituted aldehydes to β-substituted nitroolefins.[7] On the other hand, there are no reports of a Michael reaction of prochiral trisubstituted carbon nucleophiles to *s-trans* type Michael acceptors such as cyclic enones. Herein, we report a catalytic enantio- and diastereoselective Michael reaction of α-substituted β-keto esters to *cyclic enones* to construct vicinal quaternary and tertiary carbon centers in one step. Tuning the linker length and the N-substituent in NR-linked-BINOL ligands was critical to achieve high reactivity and good stereoselectivity. Moreover, we describe a new convenient catalyst preparation method of La complexes from La(OTf)$_3$.

The catalytic asymmetric Michael reaction of malonates to β-substituted enones, which constructs tertiary carbon centers at the Michael acceptors, has been widely examined by our group[8] and others[9] with much success. Recently, we also developed a catalytic asymmetric Michael reaction of α-non-substituted β-keto esters to cyclic enones using a chiral La complex prepared from La(O-*i*-Pr)$_3$ and NR-linked-BINOLs (R = H: **1a**, R = Me: **1b**, Scheme 1) in a ratio of 1:1, in which the newly generated stereocenter at the α-position of β-keto ester is

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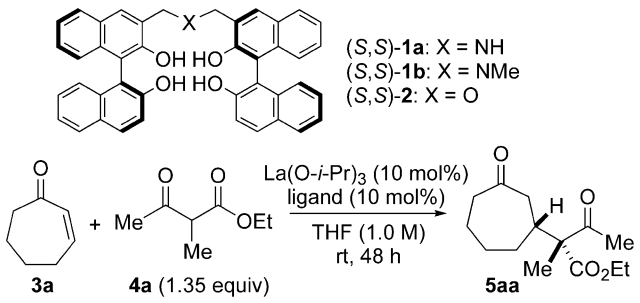
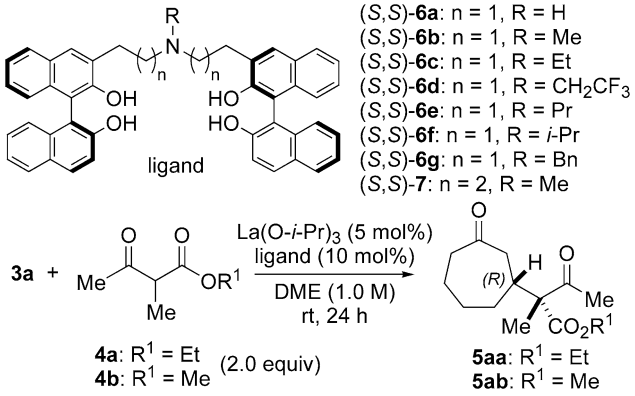


Scheme 1. Catalytic enantio- and diastereoselective Michael reaction of **4a** to **3a** using chiral La complex.

readily epimerized and affords an almost 1:1 mixture of diastereomers.[10] Based on these results, we first examined a Michael reaction of ethyl 2-methylacetoacetate (**4a**) to 2-cyclohepten-1-one (**3a**) using La–**1** (1:1) complexes.[11] The Michael reaction using these complexes, however, gave the corresponding Michael adduct **5aa** in low yield and selectivity (La–**1a** complex: 19% yield, 65/35 dr, 8% ee for the major isomer; La–**1b** complex: 25% yield, 63/37 dr, 25% ee for the major isomer). The use of the La–**2** (1:1) complex, which is an efficient catalyst for the Michael reaction of malonates,[8d,f] produced very low reactivity (4% yield).

The steric effects of the substituent at the α-position of β-keto ester might prevent formation of an active catalyst complex.[12] To create enough chiral space for the reaction of α-substituted β-keto ester, we designed and synthesized various new types of NMe-linked-BINOL **6b** ($n = 1$) and **7** ($n = 2$) (Table 1).[13] When 10 mol% of La–**6b** (1:1) complex was used, reactivity was greatly improved (entry 2). On the other hand, ligand **7**, which has a longer linker than **6**, negatively affected this reaction (entry 9). Thus, the reaction conditions, such as solvent composition, concentration of the substrates, equivalence of the substrates, and ratio of La and ligand, were optimized using the La–**6b** complex. As a result, using DME, 2.0 equiv of **4a** to **3a**, and a 1:2 ratio of La and **6b** produced much higher reactivity and stereoselectivity to afford **5aa** in 72% yield, although the enantiomeric excess of the major diastereomer was still moderate (55% ee, entry 3). To further improve the enantioselectivity, the N-substituent of the ligand was investigated. In our previous studies on the catalytic enantioselective Michael reaction of α-non-substituted β-keto esters to cyclic enones, the N-substituent electronically tuned the Lewis acidity of the central metal and sterically tuned the chiral environment. Therefore, ligands **6a**,**c**–**g** were synthesized and examined for the reaction of **4a** to **3a**. The La–**6c** (1:2) complex, which has an ethyl group as the N-substituent, produced the highest reactivity and enantio- and diastereoselectivity among the La–**6** complexes examined (entry 4). The electronic effects of the N-substituent were demonstrated by comparing the ligands **6c** and **d**.[10] More electron-withdrawing ligand

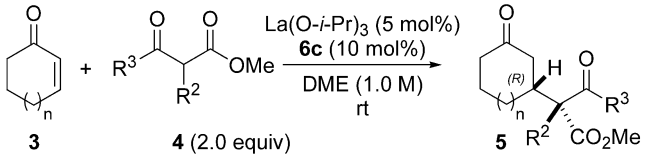
Table 1. Ligand screening for the catalytic enantio- and diastereoselective Michael reaction



Entry	Ligand	β-Keto ester	Yield[a] (%)	dr (major/minor)[b]	ee (%) (major/minor)[c]
1	**6a**	**4a**	5	65/35	nd[d]
2[e]	**6b**	**4a**	58	70/30	43/41
3	**6b**	**4a**	72	76/24	55/72
4	**6c**	**4a**	86	83/17	75/81
5	**6d**	**4a**	33	80/20	8[f]/20
6	**6e**	**4a**	88	77/23	61/76
7	**6f**	**4a**	82	79/21	59/77
8	**6g**	**4a**	60	74/26	47/64
9[e]	**7**	**4a**	30	62/38	14/3[f]
10	**6b**	**4b**	67	75/25	81/76
11	**6c**	**4b**	89	86/14	82/82

[a] Isolated yield.
[b] dr was determined by ^{1}H NMR analysis of the crude product.
[c] ee was determined by chiral GC analysis after acetalization of the cyclic ketone of **5**.
[d] Not determined.
[e] Reaction conditions were the same as those in Scheme 1.
[f] Enantiomer was obtained.

Table 2. The catalytic enantio- and diastereoselective Michael reaction of α-substituted β-keto esters to cyclic enones



3 4 (2.0 equiv) 5

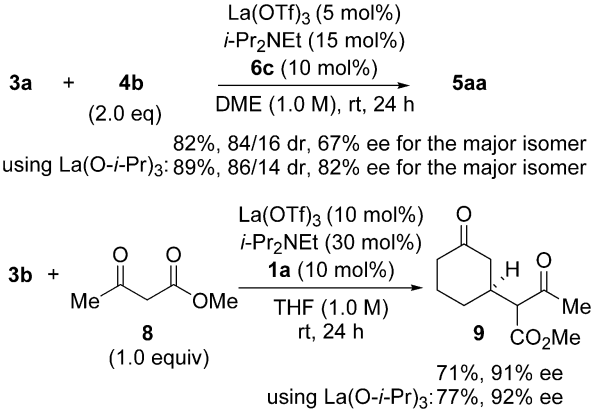
Entry	Enone **3**	β-Keto ester **4**	Product	Time (h)	Yield (%)[a]	dr (major/minor)[b]	ee (%) (major/minor)[c]
1	**3c**: $n = 0$	**4b**: R^2 = Me, R^3 = Me	**5cb**	24	100	76/24	79[d]/73[d]
2[e]	**3c**: $n = 0$	**4c**: R^2 = allyl, R^3 = Me	**5cc**	70	86	77/23	56/63
3[e]	**3c**: $n = 0$	**4d**: R^2 = propargyl, R^3 = Me	**5cd**	70	76	73/27	61[d]/50[d]
4[e]	**3c**: $n = 0$	**4f**: $R^2 = (CH_2)_3Ph$, R^3 = Me	**5cf**	48	80	73/27	41/81
5	**3c**: $n = 0$	**4g**: R^2 = Me, R^3 = Et	**5cg**	38	93	80/20	64[d]/60[d]
6[e]	**3c**: $n = 0$	**4h**: R^2 = Me, R^3 = *i*-Pr	**5ch**	96	71	86/14	63/16
7	**3b**: $n = 1$	**4b**: R^2 = Me, R^3 = Me	**5bb**	24	92	86/14	86/80
8	**3b**: $n = 1$	**4c**: R^2 = allyl, R^3 = Me	**5bc**	48	75	72/28	62/84
9	**3b**: $n = 1$	**4d**: R^2 = propargyl, R^3 = Me	**5bd**	48	64	79/21	66[d]/42[d]
10[e]	**3b**: $n = 1$	**4e**: R^2 = Et, R^3 = Me	**5be**	48	65	77/23	67/78
11[e]	**3b**: $n = 1$	**4f**: $R^2 = (CH_2)_3Ph$, R^3 = Me	**5bf**	70	37	68/32	56/86
12	**3b**: $n = 1$	**4g**: R^2 = Me, R^3 = Et	**5bg**	38	83	80/20	85[d]/55[d]
13[e]	**3b**: $n = 1$	**4h**: R^2 = Me, R^3 = *i*-Pr	**5bh**	96	42	84/16	80[d]/35[d]
14	**3a**: $n = 2$	**4b**: R^2 = Me, R^3 = Me	**5ab**	24	89	86/14	82[d]/82[d]
15	**3a**: $n = 2$	**4c**: R^2 = allyl, R^3 = Me	**5ac**	96	69	74/26	42/72
16	**3a**: $n = 2$	**4d**: R^2 = propargyl, R^3 = Me	**5ad**	96	58	84/16	70/84
17	**3a**: $n = 2$	**4f**: $R^2 = (CH_2)_3Ph$, R^3 = Me	**5af**	96	45	81/19	39/67

[a] Isolated yield.
[b] dr was determined by ^{1}H NMR analysis of the crude product.
[c] ee was determined by chiral GC analysis (entry 14) or chiral HPLC analysis (entries 1–13 and 15–17).
[d] ee was determined after acetalization of the cyclic ketone.
[e] 4.0 equiv of compound **4** was used.

6d had much lower reactivity and enantioselectivity than ligand **6c** (entry 5). Ligands **6e–g** had lower enantioselectivity than **6c**, probably due to the steric and electronic nature of these ligands (entries 6–8). In contrast to our previous studies,[10] the NH ligand **6a** had quite low reactivity and selectivity (entry 1). Furthermore, when sterically less demanding **4b** (R^1 = Me) was used as a Michael donor, **5ab** was obtained in 89% yield, 86/14 dr, and 82% ee for both diastereomers (entry 11).

We then investigated the scope and limitations of several substrates.[14] The results are summarized in Table 2.[15] The Michael reaction of variety of α-substituted β-keto esters **4** to cyclic enones **3** (5- to 7-membered rings) was promoted by the La–**6c** (1:2) complex to afford the corresponding Michael adducts **5** with moderate diastereoselectivity (68/32–86/14 dr) and moderate to good enantioselectivity for the major isomers (39–86% ee). Substitution at the γ-position of **4** (R^3) was tolerated (**4g** and **h**, entries 5, 6, 12, and 13). When **3c** was used as a Michael acceptor, high reactivity was obtained (71–100% yield, entries 1–6). The reactivity decreased as the ring size of **3** increased in this reaction system. Thus, when **3a** was used as a Michael acceptor, a long reaction time (96 h) was necessary except when using **4b** as a Michael donor. For several low reactive substrates, 4.0 equiv of **4** were used to obtain better results (entries 2–4, 6, 10, 11, and 13). Although there is room for improvement in the reactivity and the enantioselectivity, to the best of our knowledge, this is the first example of a catalytic enantio- and diastereoselective Michael reaction of α-substituted β-keto esters to cyclic enones.

To further enhance the usefulness of this reaction, we investigated use of $La(OTf)_3$ as an alternative La metal source because of the commercial availability of $La(OTf)_3$ and its high tolerance to air and water. Our preliminary studies revealed that alkali metal salts had negative effects on this system. Thus, we investigated the combination of $La(OTf)_3$ and an amine base. Using 5 mol% of $La(OTf)_3$, 15 mol% of *i*-Pr_2NEt, and 10 mol% of ligand **6c**, almost the same reactivity and diastereoselectivity were obtained as with the original catalyst preparation method, although the enantioselectivity was decreased (Scheme 2). The new catalyst preparation method was also applicable to the catalytic enantioselective Michael reaction of α-non-substituted β-keto ester to cyclic enone. In this case, identical



Scheme 2. Catalytic enantioselective Michael reaction using a catalyst prepared from $La(OTf)_3$ and *i*-Pr_2NEt.

enantioselectivity was obtained. These observations suggest that the combination of lanthanide triflate ($Ln(OTf)_3$) and an amine base can also be used to access a chiral alkali metal free lanthanide complex.

In conclusion, we developed a catalytic enantio- and diastereoselective Michael reaction of α-substituted β-keto esters to cyclic enones to construct vicinal quaternary and tertiary carbon centers using the La–**6c** (1:2) complex. The linker length of the NR-linked-BINOL type ligand and the N-substituent were critical to obtain good reactivity and stereoselectivity. This reaction was also promoted by a catalyst prepared from $La(OTf)_3$ and *i*-Pr_2NEt. Further studies of the reaction mechanism, catalyst structure, and application to natural product synthesis are in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version at doi:10.1016/j.tetlet.2005.05.139.

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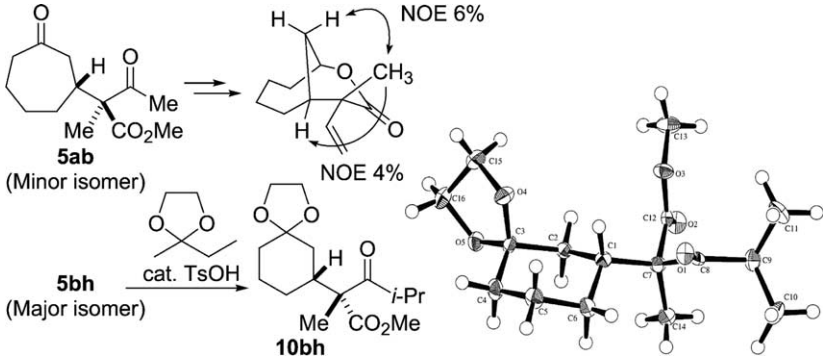
11. For the screening of reaction conditions, we used **3a** and **4a** as substrates because enantiomeric excess of the product **5aa** was easily determined by chiral GC analysis after acetalization of the cyclic ketone.
12. In the catalytic enantioselective Michael reaction of α-non-substituted β-keto esters to cyclic enones, we proposed that at least one β-keto ester should be included in the active catalyst complex. See Ref. 10.
13. For the syntheses of ligands **6a**–**g** and **7**, see Supplementary data.
14. General procedure for the catalytic enantio- and diastereoselective Michael reaction promoted by La(O-*i*-Pr)$_3$ and ligand–**6c** (1:2) complex: to a stirred solution of **6c** (14.4 mg, including 7.0 w/w% solvent (THF and hexane), 0.02 mmol) in THF (0.18 mL) at −78 °C was added a solution of La(O-*i*-Pr)$_3$ (50 μL, 0.01 mmol, 0.2 M in THF, freshly prepared from the powder of La(O-*i*-Pr)$_3$ and dry THF, La(O-*i*-Pr)$_3$ was purchased from Kojundo Chemical Laboratory CO., LTD., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (fax: +81 492 84 1351)). The solution was stirred for 2.5 h at room temperature and then the solvent was evaporated under reduced pressure. DME (0.2 mL) were added to the catalyst complex in a flask at −78 °C and the mixture was stirred for 5 min at the same temperature. Then, 2-cyclohepten-1-one (**3a**) (22.3 μL, 0.2 mmol) and methyl 2-methylacetoacetate (**4b**) (49.6 μL, 0.4 mmol) were added. The mixture was stirred at −78 °C for 5 min, then the dry-ice acetone bath was removed, and the reaction mixture was stirred at room temperature. After 24 h, the reaction mixture was diluted with ethyl acetate, washed with saturated aqueous NH_4Cl, and dried over Na_2SO_4. After evaporation, the residue was

purified by flash column chromatography (SiO_2, hexane/ethyl acetate, 9/1) to give **5ab** (43.3 mg, 0.18 mmol, 89%, 86/14 dr, 82% ee for both diastereomers).



15. In all entries, the absolute configurations of β-position of the acceptors were determined to be *R* by chemical correlation. The relative configurations were determined by NOE (**5ab** and **bc**), X-ray (**5bh**), and chemical correlation (**5aa**,**ac**,**ad**,**af**,**bb**,**bd**,**be**,**bf**,**bg**,**cc**,**cd**, and **cf**). For details, see Supplementary data.

Crystallographic data for **10bh** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 272617.