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Highly enantioselective catalytic Michael reaction of α-substituted malonates using La-linked-BINOL complex in the presence of HFIP (1,1,1,3,3,3-hexafluoroisopropanol)

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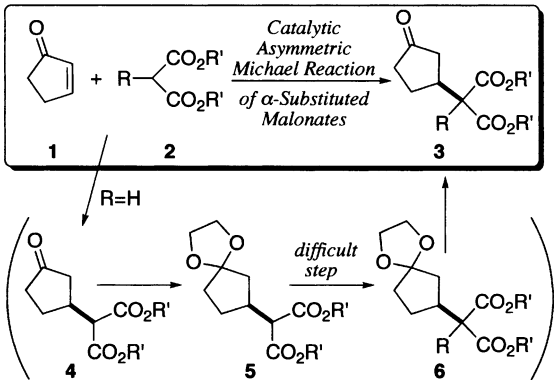
Abstract—A catalytic asymmetric Michael reaction of α-substituted malonates with broad generality was developed using the La-linked-BINOL complex. To enhance the reactivity of unreactive α-substituted malonates, we examined the effects of concentration and additives; 1.0 M was the best concentration and HFIP (1,1,1,3,3,3-hexafluoroisopropanol) accelerated the reaction efficiently. Under the optimized conditions, the catalytic asymmetric Michael reaction of a variety of α-substituted malonates proceeded successfully in high yield (up to 93%) and excellent enantiomeric excess (up to 99% ee). The addition of HFIP was also effective for the reaction of nonsubstituted malonates. In this case, 5 mol% of the La-linked-BINOL complex was sufficient for completion of the reaction in approximately 24 h. Moreover, several Michael adducts were readily converted to the bicyclic compounds.

The development of catalytic asymmetric carbon–carbon bond-forming reactions is a major goal in organic synthesis and a number of excellent asymmetric catalyses have been developed over the last two decades.[1] Only a few reactions, however, are commonly utilized in the catalytic asymmetric synthesis of complex molecules. One of the main reasons might be the limitation of the substrates. Thus, it is necessary to develop a useful catalytic asymmetric reaction with *extremely broad substrate generality*. The Michael reaction is one of the most powerful carbon–carbon bond-forming reactions and considerable efforts have been made to develop a catalytic asymmetric version of this reaction.[2–4] We succeeded in developing two excellent multifunctional asymmetric catalysts, the AlLibis(binaphthoxide) (ALB) complex[3a] and the La-linked-BINOL complex,[3b] for the asymmetric Michael reaction of malonates to enones. The ALB complex is highly active and readily applied for practical large-scale synthesis.[3d] The La-linked-BINOL complex, which was developed more recently, is suitable for use in research because it is stable to moisture, can be stored as a powder, is easily handled, and is effective for a variety of enones.[5,6] On the other hand, no catalytic asymmetric Michael reaction of α-substituted malonates, except for the α-methyl substituted malonate,[3a,b] has yet been reported,[7] despite the greater utility of substituted Michael adducts than nonsubstituted adducts for complex molecule synthesis. We report here the first example of a general catalytic asymmetric Michael reaction of α-substituted malonates. This reaction was realized by optimization of the La-linked-BINOL catalyst system in terms of reactivity, including the effects of concentration and addition of HFIP (1,1,1,3,3,3-hexafluoroisopropanol). We also report further effective transformation of Michael adducts to useful bicyclic compounds.



Scheme 1.

Keywords: catalytic asymmetric Michael reaction; α-substituted malonates; La-linked-BINOL complex; additive effects of HFIP (1,1,1,3,3,3-hexafluoroisopropanol).

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The Michael adduct **3**, which has a substituent at the α-position of the malonate moiety, is a useful intermediate, especially when the substituent contains functional groups, because it can be directly used for further transformation, such as the next ring construction (vide infra). Transformation from Michael adduct **4**, which is easily prepared using an already established asymmetric Michael reaction, to **3** requires three additional steps and usually the substituent-introduction step makes this process impractical due to the decreased nucleophilicity of the ester enolate derived from substrate **5**.[8] Therefore, direct preparation of the substituted Michael adduct **3** using a catalytic asymmetric Michael reaction of α-substituted malonates is very desirable (Scheme 1).

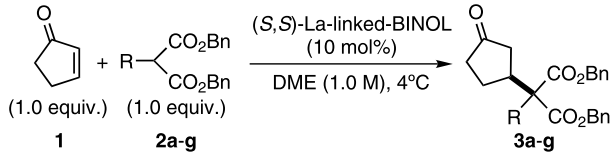
We first examined the catalytic asymmetric Michael reaction of dibenzyl allylmalonate (**2a**) to 2-cyclopentenone (**1**) using the ALB complex, however **2a** was unreactive and gave the Michael adduct **3a** in only 36% yield and 19% ee, even when using 20 mol% of the catalyst. We then examined the La-linked-BINOL complex because it has broad generality with respect to enones. Fortunately, previously reported conditions (10 mol% of the catalyst, 4°C, 0.4 M in DME)[3b] gave the Michael adduct in excellent enantiomeric excess (99% ee), although there was only moderate chemical yield (67%) even after 84 h. Therefore, we attempted to enhance the reactivity of the catalyst. After intensive optimization, the concentration of the reaction turned out to be a significant factor for improving chemical yield. The best concentration was 1.0 M,[9] and the Michael adduct **3a** was obtained in 86% yield without loss of enantiomeric excess (99% ee). In contrast to the ALB catalyst system,[3d] increasing the concentration further did not improve reactivity. The result of the scope and limitations of these improved conditions is summarized in Table 1.[10] Many types of α-substituted malonates, which contain additional functional groups, such as carbon–carbon double bonds, esters, and allylic acetates, can be used as a Michael donor, and enantioselectivity was nearly complete although the chemical yield was still unsatisfactory.

To further enhance reactivity, we examined several additives, which were previously reported to be beneficial during the improvement of our multifunctional catalysts. THF,[3b] additional bases (KO-*t*-Bu and LiHMDS),[3b] salts (LiCl, CsCl, $MgCl_2$), Et_2Zn,[3c] $Ph_3As{=}O$,[11] $Ph_3P{=}O$,[12] HMPA, MS4A,[11] etc. None of them, however, effectively improved this asymmetric Michael reaction system in terms of chemical yield and enantiomeric excess. Thus, we examined other types of additives. Alcohols had interesting effects.[13] That is, HFIP increased the reaction rate and chemical yield without decreasing the enantiomeric excess. 2,2,2-Trifluoroethanol also had a small positive effect on the chemical yield. On the other hand, MeOH and ArOH decreased both chemical yield and enantiomeric excess, and *i*-PrOH had almost no effect on the reaction. Under the best conditions (4°C, 1.0 M in 10/1 mixture of DME/HFIP), Michael adduct **3a** was obtained in 93% yield and 99% ee. The concentration of the reaction was also important in the presence of HFIP. The chemical yield of **3a** dropped to 86% when the concentration was 0.4 M.[14] These conditions were applicable to various α-substituted malonates (shown in Table 2).[15] In the presence of HFIP, all of the corresponding Michael adducts were obtained in higher yield compared with those shown in Table 1.[16]

In addition, HFIP effectively accelerated the Michael reaction of nonsubstituted malonates. Thus, only 5 mol% of catalyst forced the reaction to completion in approximately 24 h with 83–95% yield and >99% ee (Table 3). Under these decreased catalyst-loading conditions, the best ratio of DME and HFIP was 20:1, and the best concentration was 0.4 M to substrate (0.02 M to catalyst).

The reaction profile of the Michael reaction in the presence or absence of HFIP was investigated (Fig. 1). The addition of HFIP increased the initial reaction rate and the reaction proceeded more than twice as fast as in the absence of HFIP; as a result, nearly 90% conversion was observed within 24 h. The beneficial effect of

Table 1. Catalytic asymmetric Michael reaction of various α-substituted malonates **2a–g**



Entry	Malonate (R)	Product	Time (h)	Yield[a] (%)	Ee[b] (%)
1	**2a**: $CH_2CH{=}CH_2$	**3a**	86	86	99
2	**2b**: $(CH_2)_2CH{=}CH_2$	**3b**	88	65	99
3	**2c**: $(CH_2)_3CH{=}CH_2$	**3c**	106	66	96
4	**2d**: $(CH_2)_2CO_2Me$	**3d**	88	69	99
5	**2e**: $(CH_2)_2CO_2Et$	**3e**	92	62	98
6	**2f**: $(CH_2)_3CO_2Et$	**3f**	89	55	95
7[c]	**2g**: $CH_2CH{=}CHCH_2OAc$	**3g**	84	77	99

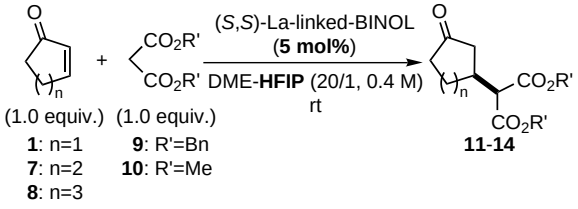
[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] *cis*/*trans* (~1/30) in both **2g** and **3g**. Enantiomeric excess was determined after ozonolysis.

Table 2. Catalytic asymmetric Michael reaction of various α-substituted malonates **2a–g** in the presence of HFIP

Entry	Malonate (R)	Product	Time (h)	Yield[a] (%)	Ee[b] (%)
1	**2a**: $CH_2CH{=}CH_2$	**3a**	87	93	99
2	**2b**: $(CH_2)_2CH{=}CH_2$	**3b**	85	80	98
3	**2c**: $(CH_2)_3CH{=}CH_2$	**3c**	88	84	96
4	**2d**: $(CH_2)_2CO_2Me$	**3d**	87	83	98
5	**2e**: $(CH_2)_2CO_2Et$	**3e**	92	75	96
6	**2f**: $(CH_2)_3CO_2Et$	**3f**	89	71	95
7[c]	**2g**: $CH_2CH{=}CHCH_2OAc$	**3g**	83	87	98

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] *cis*/*trans* (~1/30) in both **2g** and **3g**. Enantiomeric excess was determined after ozonolysis.

Table 3. Catalytic asymmetric Michael reaction of nonsubstituted malonates using 5 mol% of the catalyst



Entry	Enone	Malonate	Product	Time (h)	Yield[a] (%)	Ee[b] (%)
1	**1**	**9**	**11**	25	83	>99
2	**7**	**9**	**12**	24	95	>99
3[c]	**7**	**9**	**12**	24	79	>99
4	**7**	**10**	**13**	18	86	>99
5	**8**	**9**	**14**	30	85	>99

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The reaction was performed in DME without HFIP.

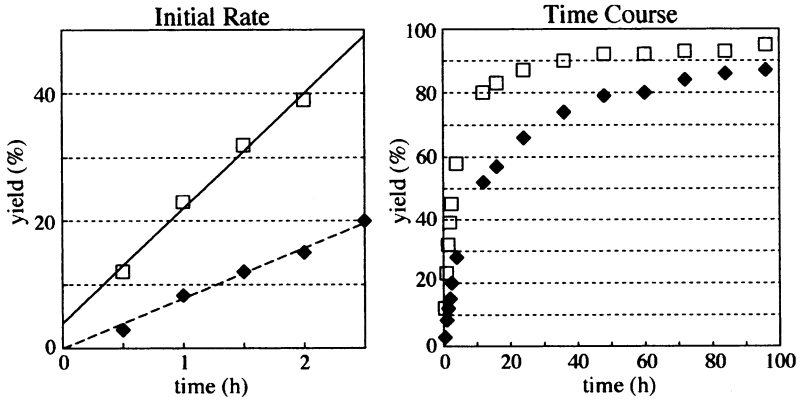
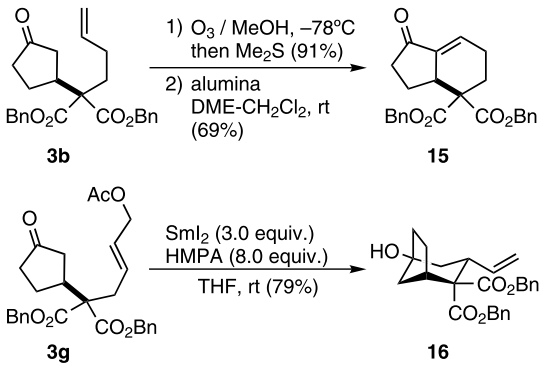


Figure 1. The initial rate and time course of the generation of **3a** in the presence or absence of HFIP. The yield of **3a** was determined by ^{1}H NMR: the reaction in the presence of HFIP (□) and in the absence of HFIP (◆).

HFIP was most prominent in the early stage of the reaction. Although the role of HFIP has not yet been clearly elucidated, we propose that this acidic (pK_a 17.9 in DMSO)[17] and sterically-hindered additive acts as a proton source[18] and assists in the dissociation of the product from the La complex.

Finally, the Michael adducts were successfully converted to the corresponding bicyclic compounds. Ozonolysis of Michael adduct **3b** (91% yield) followed by intramolecular aldol reaction using activated alumina (69% yield) furnished bicyclo[4.3.0]nonane derivative **15**. Reductive cyclization of compound **3g** using



Scheme 2.

SmI_2 directly produced the bicyclo[3.2.1]octane derivative **16** in 79% yield (Scheme 2). The fact that these bicyclic frameworks often occur in natural or unnatural bioactive compounds, such as hydrindan derivatives, makes these highly enantioselective short processes very useful.

In conclusion, we achieved the first general catalytic asymmetric Michael reaction of α-substituted malonates using the La-linked-BINOL complex in the presence of HFIP. HFIP accelerated the reaction of not only the α-substituted malonates, but also nonsubstituted malonates, efficiently. In the latter case, 5 mol% of the La-linked-BINOL complex was sufficient for completion of the reaction in approximately 24 h. Moreover, several Michael adducts were readily converted to the bicyclic compounds. Further studies of the reaction mechanism, catalyst structure, role of HFIP, and application to natural product synthesis are currently in progress.

Acknowledgements

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5. La(O-*i*-Pr)$_3$ can be purchased from Kojundo Chemical Laboratory Co., Ltd, 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (Fax: +(81)-492-84-1351). Freshly prepared La(O-*i*-Pr)$_3$ solution was used.
6. Both enantiomers of the La-linked-BINOL complex are now commercially available from STREM Chemicals, Inc., 7 Mulliken Way, Dexter Industrial Park, Newburyport, MA 01950-4098, USA (Fax: +(1)-978-465-3104). When they were used for the catalytic asymmetric Michael reaction of **9** to **7** (10 mol% of the catalyst was used in the reported conditions in Ref. 3b), the Michael adduct **12** was obtained in 57% yield and 94% ee.
7. The catalytic asymmetric Michael reaction of more reactive α-substituted β-keto esters and α-substituted α-cyano esters to very reactive enones were reported by us and others. See Ref. 2.
8. Only reactive electrophiles, such as allyl bromide (80%), reacted with **5** to give a reasonable yield, while other electrophiles, such as 5-bromo-1-pentene (30%), ethyl 4-bromobutanoate (15%), 4-bromo-1-butene (0%), and methyl acrylate (0%), gave highly unsatisfactory results.
9. Lower chemical yields were obtained in other concentrations (57% in 0.2 M and 80% in 2.0 M), although the enantiomeric excesses were unchanged in both cases (99% ee).
10. The absolute configurations of **3a**, **3c**, and **3f** were already determined by transformation of the known compound **4** to **3** via **5** and **6**; see Ref. 8. The absolute configurations of **3b**, **3d**, **3e**, and **3g** were tentatively determined on the basis of the absolute configuration of **3a** and previous results. See Ref. 3.
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14. Lower chemical yields were obtained in other concentrations (73% in 0.2 M and 93% in 2.0 M), although the enantiomeric excesses were unchanged in both cases (99% ee).
15. General procedure for the catalytic asymmetric Michael reaction promoted by (*S*,*S*)-La-linked-BINOL complex: DME (0.23 mL) was added to the (*S*,*S*)-La-linked-BINOL complex (18.8 mg, 0.25 mmol, prepared by the procedure in Ref. 3b) in a test tube at −78°C, and the mixture was stirred for 5 min at the same temperature. Then, 2-cyclopentene-1-one (**1**) (21 μL, 0.25 mmol) and dibenzyl allylmalonate (**2a**) (72 μL, $d=1.13$, 0.25 mmol) were added. Finally, HFIP (23 μL) was added and the mixture was stirred at −78°C for 5 min. The dry-ice acetone bath was then removed and the reaction mixture was stirred at 4°C. After 86 h, the mixture was diluted with ethyl acetate, washed with satd aq. NH_4Cl, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate 5/1) to give (−)-(*S*)-**3a** (94.7 mg, 0.233 mmol, yield 93%) in 99% ee [DAICEL CHIRALCEL OJ-H, hexane/2-propanol (90:10, v/v), flow rate: 0.8 mL/min, retention time: 55 min (*R*)-isomer and 63 min (*S*)-isomer, detected at 210 nm].
16. Using the best conditions, Michael reaction of **2a** to 2-cyclohexene-1-one (**7**) gave the corresponding (*S*)-Michael adduct in 63% yield and 94% ee, while the reaction to 2-cycloheptene-1-one (**8**) gave only trace amount of the corresponding Michael adduct.
17. The acidity of HFIP is nearly equal to that of phenol (pK_a 18.0 in DMSO).
18. In contrast, the addition of 1,1,1,3,3,3-hexafluoroisopropyl methyl ether did not accelerate the reaction.