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Catalytic asymmetric Michael reactions of dibenzyl malonate to α,β-unsaturated *N*-acylpyrroles using a La(O-*i*Pr)$_3$/*Ph*-linked-BINOL complex

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Abstract—Catalytic asymmetric Michael reactions of a malonate to acyclic α,β-unsaturated *N*-acylpyrroles as ester equivalent acceptors are described. A La(O-*i*Pr)$_3$/(*S*,*S*)-linked-BINOL complex, which is suitable for Michael addition to cyclic enones, is not suitable for acyclic α,β-unsaturated *N*-acylpyrroles. A new (*S*,*S*)-*Ph*-linked-BINOL chiral ligand was developed to improve enantioselectivity, and a La(O-*i*Pr)$_3$/(*S*,*S*)-*Ph*-linked-BINOL complex with the addition of HFIP afforded Michael adducts in good yield and enantioselectivity (up to 96% ee).

The Michael reaction is one of the most useful carbon–carbon bond-forming reactions, and the development of catalytic enantioselective variants has been an important topic of study over the last decade.[1] Previously, we reported that a La(O-*i*Pr)$_3$/linked-BINOL **1a** (Fig. 1) = 1:1 complex is effective for catalytic asymmetric Michael reaction of malonates to cyclic enones, giving Michael adducts in up to 99% ee.[2,3] Its application to acyclic substrates, however, is limited to a few enones, and it is not applicable to acyclic α,β-unsaturated esters. Despite recent progress in asymmetric Michael reactions to enones and nitroalkenes,[4,5] the use of acyclic carboxylic acid derivatives as acceptors in combination with 1,3-dicarbonyl donors is still limited.[6–9] Kanemasa et al. (malononitrile and 1,3-diketones),[6] Jacobsen and co-workers (malononitrile and cyano esters),[7] Evans et al. (β-keto esters),[8] and Takemoto and co-workers (malononitrile and cyano esters)[9] recently reported elegant systems giving Michael adducts from acyclic carboxylic acid derivatives in high enantioselectivity. The use of malonates as donors, however, is rare.[10,11] Herein we report a catalytic asymmetric Michael reaction of a malonate to α,β-unsaturated *N*-acylpyrrole derivatives.

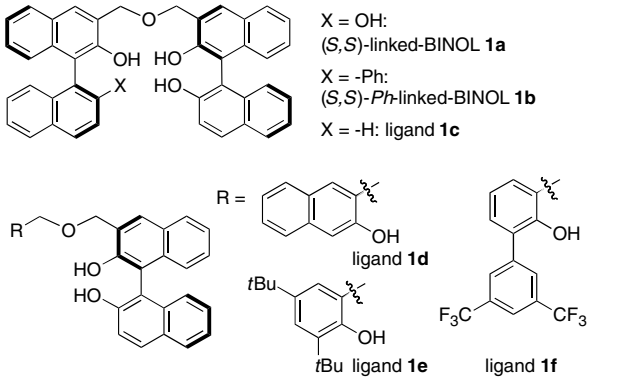

Figure 1. Structures of (*S*,*S*)-linked-BINOL **1a**, (*S*,*S*)-*Ph*-linked-BINOL **1b** and other non-C_2-symmetric linked-BINOL derivatives **1c–f**.

A new *Ph*-substituted linked-BINOL **1b** (Fig. 1) was effective for high enantioselectivity.

We recently reported the utility of α,β-unsaturated *N*-acylpyrroles in asymmetric conjugate additions.[12–14] Therefore, we initiated our studies with α,β-unsaturated *N*-acylpyrrole **2** and dibenzyl malonate **3** using the La(O-*i*Pr)$_3$/linked-BINOL **1a** = 1:1 complex. The optimization studies of the reaction conditions are summarized in Table 1. With *N*-acylpyrrole **2a**, only trace amount of product was obtained at −20 °C (entry 1).

Keywords: Asymmetric catalysis; Lanthanide; Linked-BINOL; Michael reaction.
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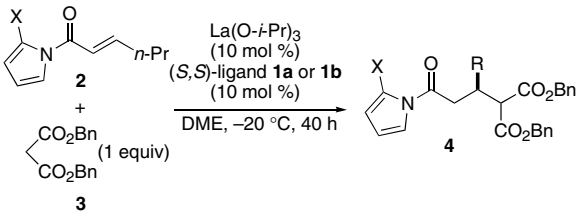
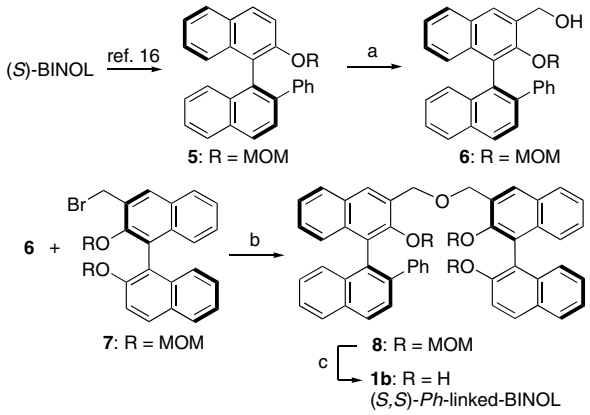
Table 1. Optimization of reaction conditions



Entry	*N*-Acylpyrrole X	Ligand	Additive	Yield (%)	% ee
1	H- : **2a**	**1a**	—	Trace	—
2	EtO : **2b**	**1a**	—	70	8
3	Me_2N : **2c**	**1a**	—	40	32
4	: **2d**	**1a**	—	50	41
5	**2d**	**1b**	—	23	86
6	**2d**	**1c**	—	83	40
7	**2d**	**1d**	—	80	18
8	**2d**	**1e**	—	81	2
9	**2d**	**1f**	—	92	10
10	**2d**	**1b**	HFIP[a]	78	80

[a] 0.1 equiv of HFIP (1,1,1,3,3,3-hexafluoroisopropanol) was added.

To improve the reactivity of *N*-acylpyrrole, *N*-acylpyrroles **2b**–**2d** with an electron-withdrawing group at the 2'-position were examined, and *N*-acylpyrrole **2d** produced promising reactivity and enantioselectivity. With **2d**, the reaction proceeded at −20 °C and Michael adduct **4d** was obtained in 50% yield and 41% ee after 40 h (entry 4). Further screening of the reaction conditions using ligand **1a**, with alterations in the solvent, metal, malonate, and reaction temperature, did not afford satisfactory results. Therefore, we modified the chiral ligand. We hypothesized that the bulkiness around the lanthanide metal center is important for improving enantioselectivity. Based on our recent report that non-C_2-symmetric linked-BINOL derivatives are effective in Zn-catalyzed reactions[15] and on Katsuki's salen ligand containing a binaphthyl group,[16] we designed non-C_2-symmetric *Ph*-linked-BINOL **1b** (Fig. 1). The synthetic scheme of (*S*,*S*)-*Ph*-linked-BINOL **1b** is summarized in Scheme 1. Compound **5** and **7** were synthesized from BINOL by following the reported procedures.[3a,16] A coupling reaction of **6** and **7**, followed by removal of the MOM group afforded **1b** in good yield. As expected, ligand **1b** improved enantioselectivity (86% ee, Table 1, entry 5), although reactivity decreased significantly (23% yield). In contrast, sterically less hindered non-C_2-symmetric linked-BINOL derivatives **1c**–**1f**, which were utilized in Zn-catalyzed reactions,[15] showed less satisfactory enantioselectivity (entries 6–9, **1c**–**1f**), albeit in better reactivity than **1b**. Ligand **1b** was selected for further studies in terms of enantioselectivity. The reaction rate was improved by the addition of 1,1,1,3,3,3-hexafluoroisopropanol (HIFP),[17] while maintaining good enantioselectivity (78% yield, 80% ee, entry 10). We assume that HIFP would accelerate the catalyst turnover step by efficiently protonating the intermediate La-enolate species to dissociate Michael product **4**.



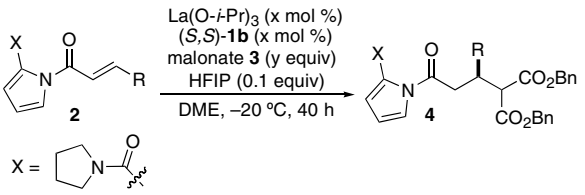
Scheme 1. Reagents and conditions: (a) (i) *t*-BuLi, THF, −78 °C; then DMF, −78 °C–rt, 4 h; (ii) $NaBH_4$, MeOH/THF, 0 °C–rt, 12 h, 77% yield (two steps from **5**); (b) NaH, **7**; then **6**, DMF, rt, 10 h, 83% yield; (c) *p*-TsOH·H_2O (cat.), MeOH/CH_2Cl_2, 40 °C, 24 h, 94% yield.

The substrate scope and limitations are summarized in Table 2. Both linear (**2d** and **2e**) and branched (**2f**) alkyl-substituted *N*-acylpyrroles gave good enantioselectivity. With branched substrate **2f**, however, 20 mol % of catalyst and 2 equiv of malonate **3** were required to achieve good conversion. With alkenyl substituents, the 1,4-addition proceeded predominantly over 1,6-addition, affording products **4g** and **4h** in high ee (entry 4: 96% ee, entry 5: 92% ee). β-Aryl-substituted *N*-acylpyrroles **2i** and **2j** were also applicable, although 20 mol % catalyst was required for good conversion (entries 6–7).

Although we and others have reported various useful transformations of *N*-acylpyrrole units,[12–14,18] transformation of the present amide-substituted *N*-acylpyrrole unit has not been reported. Gratifyingly, the transformations of the Michael adducts proceeded smoothly under mild conditions, as shown in Scheme 2. The amide-substituted *N*-acylpyrrole unit is more readily cleaved than the non-substituted *N*-acylpyrrole unit.[12,13] Methanolysis was promoted by 10 mol % of $Er(OTf)_3$ at room temperature, giving ester **9** in 96% yield.[19] Thioester **10** was obtained in 76% yield by treatment with EtSLi. Amide **11** was obtained in 92% yield by treatment with amine·HCl salt and imidazole. Amide **12** was also obtained in 82% yield by treatment with pyrrolidine at 25 °C. Treatment with $NaBH_4$ gave cyclized compound **13** in 85% yield.

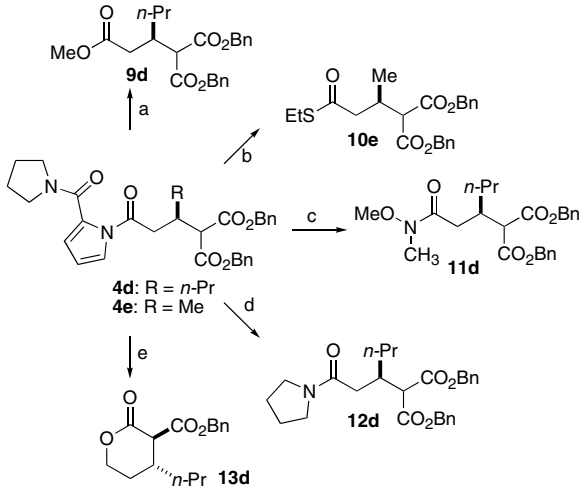
In summary, we developed a new La(O-*i*-Pr)$_3$/*Ph*-linked-BINOL **1b** = 1:1 complex for the catalytic asymmetric Michael reaction of dibenzyl malonate **3** to α,β-unsaturated 2′-amide-substituted *N*-acylpyrroles. The use of sterically hindered (*S*,*S*)-*Ph*-linked-BINOL **1b** was essential for high enantioselectivity, giving Michael adducts in 76–87% yield and in 78–96% ee.[20] Further application of (*S*,*S*)-*Ph*-linked-BINOL **1b** is ongoing.

Table 2. Michael reaction of various α,β-unsaturated *N*-acylpyrroles



Entry	*N*-Acylpyrrole R	Product	Conditions[a]	Yield[b] (%)	% ee[c]
1	**2d**: *n*-Pr	**4d**	A	78	80
2	**2e**: Me	**4e**	A	85	90
3	**2f**: Cyclohexyl	**4f**	B	87	88
4	**2g**: –CH=CHCH$_3$	**4g**	B	80	96
5	**2h**: –CH=CH(CH$_2$)$_2$CH$_3$	**4h**	A	83	92
6	**2i**: Ph	**4i**	B	76	78
7	**2j**: 4-Cl–C$_6$H$_4$	**4j**	B	80	86

[a] Conditions A: 10 mol % of La(O-*i*Pr)$_3$, 10 mol % of (*S*,*S*)-**1b**, and 1 equiv of malonate **3** were used; Conditions B: 20 mol % of La(O-*i*Pr)$_3$, 20 mol % of (*S*,*S*)-**1b**, and 2 equiv of malonate **3** were used.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.



Scheme 2. Transformations of *N*-acylpyrrole unit; Reagents and conditions: (a) Er(OTf)$_3$ (10 mol %), MeOH/CH$_3$CN, 25 °C, 24 h, 96% yield; (b) EtSLi (1.5 equiv), THF, 0 °C, 15 min, 77% yield; (c) *N*,*O*-dimethylhydroxylamine·HCl (3 equiv), imidazole (9 equiv), CH$_2$Cl$_2$, 0 °C, 22 h, 92% yield; (d) pyrrolidine (2.2 equiv), THF, 25 °C, 1 h, 82% yield; (e) NaBH$_4$, MeOH/THF, 0 °C, 1 h, 85% yield.

Acknowledgements

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20. *Representative procedure of catalytic asymmetric Michael reaction*: To a solution of (*S*,*S*)-P*h*-linked-BINOL **1b** (10 mg, 15 μmol) in THF (0.2 mL) was added La(O-*i*Pr)$_3$ (0.2 M in THF, 75 μL, 15 μmol). The mixture was stirred for 30 min at 25 °C, then the solvent was removed under reduced pressure. The residue was dried in vaccuo for 5 h to remove *i*PrOH to afford La-**1b** catalyst. To the La-**1b** catalyst was added DME (0.25 mL), and then the mixture was cooled to −20 °C. To the solution were added HIFP (15 μmol), *N*-acylpyrrole **2** (0.15 mmol), and then malonate **3** (0.15 mmol), and the reaction mixture was stirred at −20 °C for 40 h. The mixture was quenched with sat. aq. NH_4Cl, and extracted with ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. After evaporation, the residue was purified by flash silica gel column chromatography to afford Michael adduct **4**. Absolute configuration of Michael adduct **4j** was determined after conversion into *N*-acylpyrrole moiety into a known methyl ester, see Ref. 10a.