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# Asymmetric Mukaiyama–Michael Addition of Acyclic Enones Catalyzed by *allo*-Threonine-Derived *B*-Aryloxazaborolidinones

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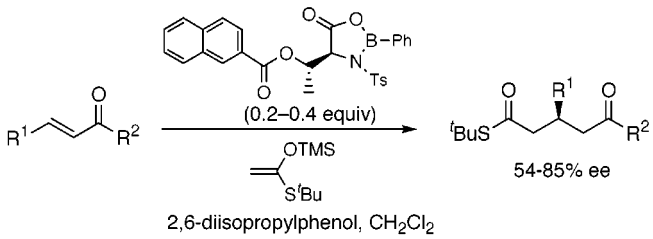
## ABSTRACT




***O*-(2-Naphthoyl)-*N*-tosyl-L-*allo*-threonine-derived *B*-phenyloxazaborolidinone catalyzes the asymmetric Mukaiyama–Michael addition of simple acyclic enones to give adducts of 54–85% ee. 2,6-Diisopropylphenol as an additive is demonstrated to effectively retard the undesirable *Si*$^+$-catalyzed racemic pathway.**

The Lewis acid-promoted conjugate addition of silyl ketene acetals and enolsilanes to α,β-unsaturated carbonyl compounds, the Mukaiyama−Michael addition,[1] has become a powerful method for the preparation of 1,5-dicarbonyl compounds. However, only limited advances have been made toward the enantioselective version of the reaction using a chiral Lewis acid catalyst.[2] Most recently, Evans et al. demonstrated the utility of $C_2$-symmetric chiral Cu(II) Lewis acids for the reaction of bidentate Michael acceptors such as alkylidene malonates and alkenoyl oxazolidinones.[3] Herein we wish to report that L-*allo*-threonine-derived oxazaborolidinones **1** are efficient catalysts for the asymmetric Mukaiyama−Michael addition of *simple acyclic enones*. The use of 2,6-diisopropylphenol as an additive to retard the undesirable *Si*$^+$-catalyzed racemic pathway is also described.

Oxazaborolidinone **1a** was prepared by the reaction of *O*-benzoyl-*N*-tosyl-L-*allo*-threonine[4,5] with dichlorophenylboron in $CH_2Cl_2$. Slow addition of benzalacetone (**2**) during 4 h to a solution of TBS ketene *S*,*O*-acetal **3a** (1.5 equiv) and **1a** (0.4 equiv) in $CH_2Cl_2$ at −78 °C afforded enantiomerically enriched Michael adduct (*S*)-**4a**[6,7] (83% ee) and

(1) Narasaka, T.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223−1224.

(2) (a) Kobayashi, S.; Suda, S.; Yamada, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 97−100. (b) Bernardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921−8924. (c) Bernardi, A.; Karamfilova, K.; Sanguinetti, S. Scolastico, C. *Tetrahedron* **1997**, *53*, 13009−13026. (d) Kitajima, H.; Ito, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 17015−17028. (e) Nishikori, H.; Ito, K.; Katsuki, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1165−1170.

(3) (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994−1995. (b) Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865−868. (c) Evans, D. A.; Johnston, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649. (d) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134−9142.

(4) *O*-Acyl-*N*-sulfonyl-L-*allo*-threonines **1a**−**i** were prepared from L-*allo*-threonine[5] by the following sequence: (1) $R^1SO_2Cl$, ether, aqueous $NaHCO_3$, (2) BnOH, TsOH, toluene reflux, (3) $R^2COCl$, pyridine, (4) $H_2$, Pd/C.

(5) Elliot, D. F. *J. Chem. Soc.* **1950**, 62−68.

(6) The absolute configuration of **2a** was determined by converting to the methyl ester derivative[7] on treatment of **2a** with silver trifluoroacetate in methanol.

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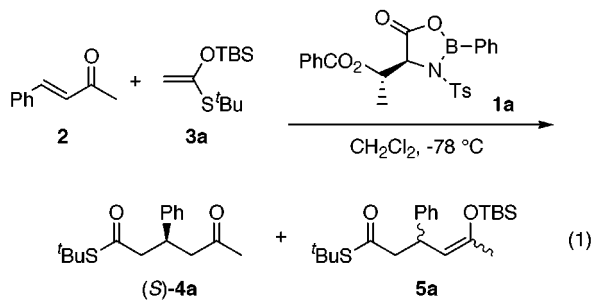
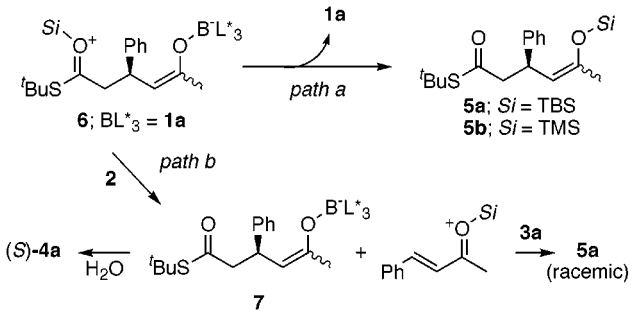
racemic enolsilane **5a** (2% ee) in 6% and 71% yield, respectively (eq 1). The result implies the intrinsically high

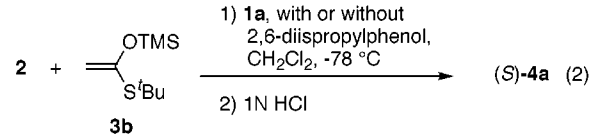



enantioselectivity of oxazaborolidinone **1a**. Thus, plausible intermediate **6** (*Si* = TBS) might undergo intermolecular silyl group transfer to enone **2** to catalyze a nonenantioselective reaction (path b),[8] rather than undergoing intramolecular transfer to the enolate oxygen atom to regenerate **1a** (path a) (Scheme 1). The adduct (*S*)-**4a** of high ee might be derived from boron enolate **7**, thus formed.

**Scheme 1.** Chiral Lewis Acid- vs *Si*$^+$-Promoted Pathways




Under similar conditions, the reaction of the enone with TMS ketene *S*,*O*-acetal **3b** in the presence of **1a** (0.4 equiv) afforded the corresponding enolsilane **5b** exclusively, which was hydrolyzed with 1 N HCl to give adduct (*S*)-**4a** of 32% ee in 76% yield (eq 2). The formation of nonracemic




enolsilane **5b** as an initial product suggests the regeneration of the catalyst from the intermediate **6b** (*Si* = TMS) (path a). However, the *Si*$^+$-catalyzed racemic pathway (path b) might still be predominant, lowering the enantioselectivity of the adduct.

(7) Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967−4970.

(8) (a) Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323−4326. (b) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837−8838. (c) Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570−4581.

It was anticipated that a phenol as an additive would react with intermediate **6b** (*Si* = TMS) to give adduct **4a** and the corresponding aryl silyl ether with simultaneous regeneration of the catalyst **1a**.[9] Indeed, slow addition (4 h) of a mixture of enone **2** and 2,6-diisopropylphenol (1.0 equiv) to a solution of **3b** and oxazaborolidinone **1a** (0.4 equiv) in $CH_2Cl_2$ at −78 °C afforded **4a** in 50% ee (80% yield) together with the formation of diisopropylphenyl trimethylsilyl ether. Examination of a variety of substituted phenols as additives revealed that steric environment around the hydroxy group is crucial. 2,6-Dimethylphenol, for example, did not give a good result (25% ee) probably due to the complexation of the phenol with **1a**. On the other hand, sterically hindered 2,6-di(*tert*-butyl)phenol could not trap the TMS group, resulting in a low ee (24%) of the adduct.

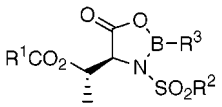
We then focused our attention to the optimization of the structure of *allo*-threonine-derived oxazaborolidinones. For this purpose, the reaction of **2** with TBS ketene *S*,*O*-acetal **3a** was chosen because the ee of **4a** in this reaction might tell us the intrinsic enantioselectivity of the catalyst not obscured by the racemic pathway. As shown in the results summarized in Table 1, the modification of the aryl group

**Table 1.** Asymmetric Michael Addition of **2** and **3a** with Oxazaborolidinones **1a**−**i**[a]

| 1 | $R^1$ | $R^2SO_2$ | $R^3$ | ee (%) of **4a**[b] |
|---|---|---|---|---|
| **1a** | $C_6H_5$ | Ts | $C_6H_5$ | 83 |
| **1b** | $C_6H_5$ | Ts | *p*-$ClC_6H_4$ | 83 |
| **1c** | $C_6H_5$ | Ts | *m*-$ClC_6H_4$ | 82 |
| **1d** | $C_6H_5$ | Ms | $C_6H_5$ | 82 |
| **1e** | $CH_3$ | Ts | $C_6H_5$ | 67 |
| **1f** | 3,5-$(MeO)_2C_6H_3$ | Ts | $C_6H_5$ | 87 |
| **1g** | 2-naphthyl | Ts | $C_6H_5$ | 88 |
| **1h** | 2-naphthyl | Ts | *m*-$ClC_6H_4$ | 89 |
| **1i** | 2-naphthyl | Ts | *p*-$ClC_6H_4$ | 89 |

[a] The reaction was carried out by adding a solution of **2** in $CH_2Cl_2$ to a solution of **3a** (1.5 equiv) and **1a**−**i** (0.4 equiv) in $CH_2Cl_2$ during 4 h at −78 °C. The yields of (*S*)-**4a** were 6−36%. [b] Determined by chiral HPLC using a Chirapak AD column.

attached to the boron atom of *O*-benzoyl derivative **1a** did not affect the enantioselectivity of the resulting oxazaborolidinones (**1b**,**c**).[10,11] *N*-Methanesulfonyl derivative **1d** also exhibited a similar ee of 82%. On the other hand, the enantioselectivity was influenced by the structure of the *O*-acyl group. An improved enantioselectivity was observed for 3,5-dimethoxybenzoyl derivative **1f** and 2-naphthoyl derivatives **1g**−**i**. The later exhibited high ee values (88−89%) irrespective of the structures of the *B*-aryl group.




**1a-i**

The reaction of enone **2** with TMS ketene acetal **3b** was examined by using *O*-(2-naphthoyl) derivatives **1g**,**h** in the

**Table 2.** Asymmetric Michael Addition of **2** and **3b** with Oxazaborolidinones **1a**,**g**,**h** in the Presence of 2,6-Diisopropylphenol[a]

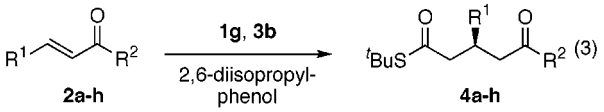
| entry | catalyst | **3b** (equiv) | additive (equiv) | concn[b] (M) | product yield (%) | product ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | **1a** | 1.5 | 1.0 | 0.1 | 80 | 50 |
| 2 | | 1.5 | 1.0 | 0.2 | 64 | 59 |
| 3 | **1g** | 1.5 | 1.0 | 0.1 | 89 | 64 |
| 4 | | 3.0 | 3.0 | 0.1 | 81 | 74 |
| 5 | | 3.0 | 3.0 | 0.2 | 77 | 81 |
| 6[d] | | 3.0 | 3.0 | 0.1 | 88 | 79 |
| 7 | **1h** | 1.5 | 1.0 | 0.1 | 66 | 63 |
| 8 | | 3.0 | 3.0 | 0.1 | 67 | 80 |

[a] Unless otherwise noted, 0.4 equiv of a catalyst was used. [b] The initial concentration of a catalyst in $CH_2Cl_2$. [c] Determined by chiral HPLC using a Chirapak AD column eluting with hexane−2-propanol mixtures. [d] 0.2 equiv of a catalyst was used.

presence of 2,6-diisopropylphenol (Table 2). These oxazaborolidinones exhibited higher ee values than *O*-benzoyl derivative **1a** under the reaction conditions in which 1.5 equiv of **3b** and 1.0 equiv of the additive were used at 0.1 M in $CH_2Cl_2$ (entries 3 and 7 vs entry 1). *B*-(*m*-Chlorophenyl) derivative **1h** of higher Lewis acidity promoted the Mukaiyama−aldol reaction of the adduct as well, resulting in its lower chemical yield. The use of the additive in excess (3 equiv) considerably improved the enantioselectivity (entries 4 and 8). The best result of 81% ee was obtained when the reaction was conducted with **1g** at higher concentration (0.2 M) (entry 5). The reaction using 0.2 equiv of the catalyst afforded a comparable ee (79%) as well as a high chemical yield (entry 6).[12]

Asymmetric Michael addition of other acyclic enones was examined by using **1g** as a catalyst (Table 3). Of the

**Table 3.** Asymmetric Michael Addition of Acyclic Enones[a]




| entry | | enone **2** $R^1$ | enone **2** $R^2$ | **3g** (equiv) | yield (%) | ee[b,c] (%) |
|---|---|---|---|---|---|---|
| 1 | **2a** | Ph | $CH_3$ | 0.2 | 88 | 79 |
| 2 | **2b** | *p*-$MeC_6H_4$ | $CH_3$ | 0.2 | 57 | 54 |
| 3 | **2c** | *p*-$ClC_6H_4$ | $CH_3$ | 0.2 | 94 | 85 |
| 4 | **2d** | *m*-$ClC_6H_4$ | $CH_3$ | 0.2 | 69 | 69 |
| 5 | **2e** | Ph | $CH_3CH_2$ | 0.4 | 93 | 61 |
| 6 | **2f** | Ph | $(CH_3)_2CH$ | 0.4 | 71 | 81 |
| 7 | **2g** | Ph | $(CH_3)_3C$ | 0.4 | 72 | 16 |
| 8 | **2h**[d] | $CH_3$ | $CH_3$ | 0.4 | 60 | 84 |

[a] The reaction was carried out by using **3b** (3.0 equiv) and 2,6-diisopropylphenol (3.0 equiv) at −78 °C in $CH_2Cl_2$. [b] ee was determined by chiral HPLC using a Chirapak AD or a Chirapak ADH column eluting with hexane−2-propanol mixtures. [c] The absolute configurations of **4a**,**e** and **4h** were determined by specific rotation of the methyl ester derivative[7] and $^1$H NMR analysis of the (*R*)-1-(α-naphthyl)ethylamide derivative,[13] respectively. [d] Contains 30% mesityl oxide.

substituted benzalacetones, the *p*-chloro derivative exhibited the highest enantioselectivity of 85% ee (entry 3). The structure of the alkyl group attached to the carbonyl influences the enantioselectivity. Although the reaction of the *tert*-butyl derivative was nonselective (entry 7), an enantioselectivity comparable to that of benzalacetone was obtained for the isopropyl derivative (entry 6). It should be noted that the present reaction could be equally applicable to a simple aliphatic enone (entry 8).

In summary, we have developed *O*-aroyl-L-*allo*-threonine-derived oxazaborolidinones **1** as Lewis acid catalysts for the asymmetric Mukaiyama−Michael addition. The enantioselective reaction of simple acyclic enones has been achieved for the first time by using *O*-(2-naphthoyl) derivative **1g**. 2,6-Diisopropylphenol as an additive was demonstrated to effectively retard the undesirable $Si^+$-catalyzed racemic pathway.

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**Supporting Information Available:** Preparation of *O*-(2-naphthoyl)-*N*-tosyl-L-*allo*-threonine and characterization data for the products in Table 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Hexafluoro-2-propanol which has been reported to be an effective additive for a similar purpose[2d,3b] did not give us improved enantioselectivity.

(10) The oxazaborolidinones were prepared by using the corresponding aryldibromoboranes.[11]

(11) Haubold, W.; Herdtle, J.; Gollinger, W.; Einholz, W. *J. Organomet. Chem.* **1986**, *315*, 1−8.

(12) **Experimental procedure for the preparation of (*S*)-4a (Table 2, entry 6).** To a solution of *O*-(2-naphthoyl)-*N*-tosyl-L-*allo*-threonine (85 mg, 0.20 mmol) in $CH_2Cl_2$ (2 mL) under a nitrogen atmosphere at room temperature was added dichlorophenylborane (26 μL, 0.20 mmol). After being stirred for 1 h, the mixture was concentrated in vacuo. To a solution of the resulting oxazaborolidinone **1g** and silyl ketene acetal **3b** (612 mg, 3.0 mmol) in $CH_2Cl_2$ (2 mL) at −78 °C were added a $CH_2Cl_2$ (2 mL) solution of enone **2a** (146 mg, 1.0 mmol) and 2,6-diisopropylphenol (535 mg, 3.0 mmol) during 4 h by using a syringe pump. After completion of the addition, the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and the solution was filtered. The filtrate was extracted three times with hexane, dried ($Na_2SO_4$), and concentrated in vacuo. The residue was dissolved in 1 N HCl (4 mL)−THF (20 mL), and the resulting solution was stirred at room temperature for 30 min. The mixture was poured into aqueous $NaHCO_3$ and extracted three times with ether. The organic layers were dried ($Na_2SO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography ($SiO_2$, 5% ethyl acetate in hexane) gave 245 mg (88%) of adduct (*S*)-**4a** (79% ee).

(13) Hoye, T. R.; Koltun, D. O. *J. Am. Chem. Soc.* **1998**, *120*, 4638−4643.