Enantioselective Diels–Alder Reaction of Acyclic Enones Catalyzed by *allo*-Threonine-Derived Chiral Oxazaborolidinone

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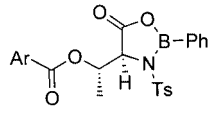
An *allo*-threonine-derived *O*-(*p*-biphenylcarbonyloxy)-*B*-phenyl-oxazaborolidinone is demonstrated to be a powerful and highly enantioselective Lewis acid catalyst for the enantioselective Diels–Alder reaction of simple acyclic enone dienophiles, expanding the scope of ketone dienophiles and dienes. With 10–20 mol % of the catalyst, the Diels–Alder adducts are obtained with up to 94 % *ee* and high *endo* selectivity. The catalyst exhibits a high activity in the reaction with the less reactive β-substituted dienophiles and the less reactive 1,3-cycohexadiene and 1,3-butadiene derivatives.

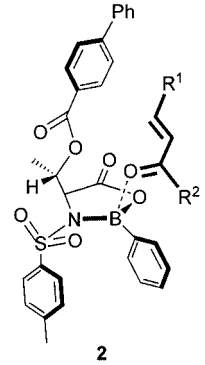
Introduction

Lewis acid catalyzed asymmetric Diels–Alder reaction has attracted great attention for their ability to construct complex carbocyclic frameworks in an enantiomerically enriched form starting from simple substrates.[1] Earlier studies have focused mainly on the reaction of unsaturated aldehydes, especially with an α-substituent,[2] and bidentate alkenoyl-oxazolidinones.[3] Despite of the prevalence of enantiopure ketones in natural products, the asymmetric Diels–Alder reaction of ketone dienophiles has been reported most recently.[4–6] The carbonyl oxygen atom of a ketone has sterically and electronically similar lone pairs which are difficult to be discriminated in complexation by chiral Lewis acids. In addition, the less electron-deficient nature of the ketone dienophiles necessitates an enhanced acidity of catalysts. Although recently developed catalysts are well designed to obviate such inherent difficulties,[4–6] the scope of ketone dienophiles and dienes is needed to be expanded further in view of the high synthetic utility of the enantioselective transformation.

We have recently reported that *allo*-threonine-derived oxazaborolidinone (OXB) **1a** is an efficient catalyst for the asymmetric Michael reaction of simple acyclic enones with silyl ketene S,O-acetals.[7] The high enantioselectivity and absolute stereochemical course of the reaction are rationalized in terms of the activated complex model shown in **2**.[7b] Herein, we wish to report that OXB **1a** serves as an efficient catalyst also for the asymmetric Diels–Alder reaction of acyclic enones exhibiting high enantioselectivity predicted from the activated complex **2** with the expansion of the scope of dienophiles and dienes.



1a; Ar = *p*-biphenyl
1b; Ar = 2-naphthyl
1c; Ar = Ph



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Results and Discussion

The potential of the OXB catalyst **1** in ketone Diels–Alder reactions was first evaluated with ethyl vinyl ketone and cyclopentadiene [Equation (1), Table 1]. The reaction with OXB **1a** (40 mol%) in dichloromethane at –78 °C gave the *endo* adduct in 84% *ee* (Entry 1). The enantioselectivity was improved in the presence of 2,6-di-*tert*-butylpyridine (0.25 equiv. with respect to catalyst **1a**) (Entry 2).[8] Under these conditions, the amount of the catalyst could be reduced to 10 mol% keeping the superior level of enantioselectivity (92% *ee*) as well as the high *endo* selectivity (96:4) (Entry 4). In accord with our previous observation in the asymmetric Michael reactions,[7b] the *O*-acyl group in the OXB catalysts is influential to the enantiofacial discrimination: 2-Naphthoyl and benzoyl derivatives **1b**,**c** exhibited a lower *ee* in comparison with the *p*-biphenylcarbonyloxy derivative (Entries 5 and 6).

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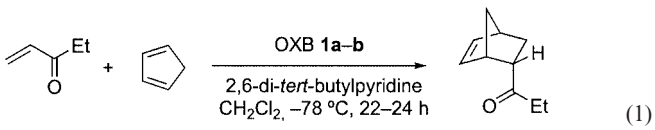
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



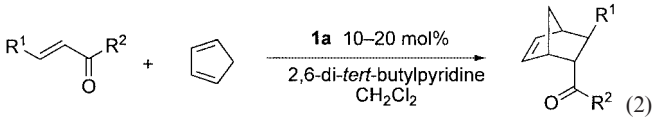
(1)

Table 1. Asymmetric Diels–Alder reaction of ethyl vinyl ketone and cyclopentadiene catalyzed by OXB **1a**–**c**.[a]

Entry	Catalyst	mol%	Yield (%)	*endo*/*exo*	*ee* (%)[b]
1[c]	**1a**	40	74	96:4	84
2	**1a**	40	80	98:2	91
3	**1a**	20	75	96:4	91
4	**1a**	10	88	96:4	92
5	**1b**	10	82	96:4	72
6	**1c**	10	74	94:6	68

[a] Unless otherwise noted, reactions were carried out by using cyclopentadiene (5 equiv.) and 2,6-di-*tert*-butylpyridine (0.25 equiv. with respect to **1**) in CH_2Cl_2 at –78 °C for 22–24 h. [b] Determined by chiral stationary phase GC. [c] The reaction was carried out in the absence of 2,6-di-*tert*-butylpyridine.

The scope of ketone dienophiles is demonstrated by the results summarized in Equation (2) and Table 2. At –78 °C with 10 mol% of **1a**, not only vinyl ketones but also propenyl ketones react with cyclopentadiene to give the corresponding *endo* adducts with high *ee* (Entries 1–4). A phenyl group in β-position reduces the reactivity of dienophiles and, to the best of our knowledge, there was no precedent for their asymmetric Diels–Alder reaction. A high level of enantioselectivity was obtained for the β-phenyl dienophiles by carrying out the reaction at –60 °C with 20 mol% of the catalyst (Entries 5 and 6). Decreased enantioselectivity was observed for a secondary alkyl ketone and cycloalkenone (Entries 7 and 8).



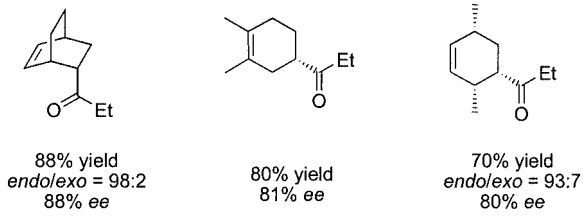
(2)

Table 2. OXB-catalyzed asymmetric Diels–Alder reaction of ketone dienophiles.[a]

Entry	Dienophile		Conditions	Yield	*endo*/*exo*	*ee*[b,c]
	R^1	R^2		(%)		(%)
1	H	Me	A	52	>98:2	85
2	H	Et	A	88	96:4	92
3	Me	Me	A	85	>98:2	87
4	Me	Et	A	90	>98:2	94
5	Ph	Me	B	77	>98:2	91
6	Ph	Et	B	59	98:2	90
7	Ph	*i*Pr	B	71	98:2	61
8	2-cyclohexenone		B	25	>98:2	44

[a] Conditions A: **1a** (10 mol%), –78 °C, 24 h. Condition B: **1a** (20 mol%), –60 °C, 72 h. [b] Product ratios determined by chiral stationary phase GC or HPLC. [c] Absolute configuration was determined by comparison wizh the literature optical rotation (Entries 1–4 and 8) or by analogy (Entries 5–7).

It has been reported that the reactivity of 1,3-cyclohexadiene, 2,3-dimethyl-2,3-butadiene, and 2,4-hexadiene is 2600, 1500, and 1300 times lower than that of cyclopentadiene.[9] OXB **1a** was found to catalyze the reaction of these less reactive dienes (Scheme 1). By using 20 mol% of catalyst **1a**, the reaction with ethyl vinyl ketone proceeded in an efficient manner at –78 °C for 22 h to give the corresponding adducts with relatively high *ee* as well as high diastereoselectivity.



Scheme 1.

The absolute configuration of the Diels–Alder adducts corresponds to the approach of dienes from the predicted open front side of the activated complex model **2** in which an acyclic enone is coordinated in an *s-cis-anti* fashion. The lower enantioselectivity for the secondary alkyl ketone and the cycloalkenone (Table 2, Entries 7 and 8) is also consistent with this model. Aside from a high enantiofacial discrimination of enones, the activity of catalyst **1a** for the less reactive substrates is unexpectedly high in view of the relatively lower acidity of the boron-based neutral Lewis acid complexes.[10] The acyloxy moiety in **2** is conformationally nonrigid due to the three rotatable bonds and could accommodate the space for the structural change in the transition state of the Diels–Alder reaction. The stabilization of the transition state in such a way might be the origin of the high Lewis acidity of the OXB catalyst **1a**.

In summary, OXB **1a** was demonstrated to be an efficient catalyst for asymmetric Diels–Alder reactions of acyclic enone dienophiles. With 10–20 mol% of the catalyst, the Diels–Alder adducts were obtained with up to 94% *ee* and high *endo* selectivity. The OXB catalyst exhibits a high activity for the reaction with the less reactive β-substituted dienophiles and the less reactive 1,3-cycohexadiene and 1,3-butadiene derivatives. It is noteworthy that the reactions with catalyst **1a** afford the enantiomers of adducts obtainable with previously reported catalysts[3–5] with a similar or higher level of enantioselectivity.

Experimental Section

1-[(1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-yl]propan-1-one:[4b] Typical procedure for the asymmetric Diels–Alder reaction (Table 2, Entry 2): To a solution of *O*-(*p*-biphenylcarbonyloxy)-*N*-tosyl-L-*allo*-threonine[7b] (140 mg, 0.309 mmol) in CH_2Cl_2 (2.5 mL) under argon at room temperature was added dichlorophenylborane (40 μL, 0.31 mmol). After being stirred for 30 min, the mixture was concentrated in vacuo. To a solution of the resulting OXB **1a** in CH_2Cl_2 (1.7 mL) at –78 °C were added 2,6-di-*tert*-butylpyridine (17 μL, 0.77 mmol), ethyl vinyl ketone (260 mg, 3.09 mmol), and 1,3-cyclopentadiene (1.04 mL, 15.5 mmol). The resulting solution was stirred at –78 °C for 24 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and filtered. The filtrate was

extracted three times with ether, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, gradient elution with 1–2% ethyl acetate in hexane) to give 408 mg (88%) of the adduct. $[\alpha]_D^{23} = -104$ ($c = 1.1$, $CHCl_3$) (92% *ee*); ref.[4b] for the (1*R*,2*R*,4*R*) enantiomer: $[\alpha]_D^{23} = +111$ ($c = 0.76$, $CHCl_3$) (97% *ee*). The *endo*/*exo* ratio and enantioselectivity were determined by GC analysis using an OV-1 (30 m) column and Chrompack Cp-Cyclodextrin-β-236-M-19 column (30 m), respectively.

Supporting Information: Describes experimental procedures and analytical data for the Diels–Alder products of this article (see also footnote on the first page of this article).

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