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Oxazaborolidinone-Catalyzed Enantioselective Diels−Alder Reaction of Acyclic α,β-Unsaturated Ketones

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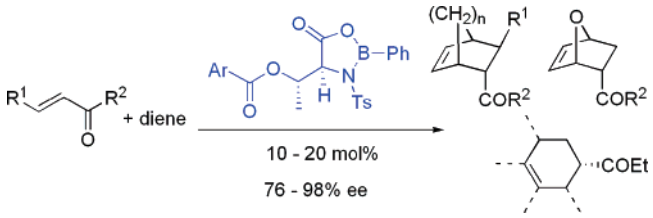
Received September 17, 2007



allo-Threonine-derived *O*-acyl-*B*-phenyl-oxazaborolidinones are demonstrated to be powerful and highly enantioselective Lewis acid catalysts for the Diels−Alder reaction of simple acyclic enone dienophiles, expanding the scope of ketone dienophiles and dienes. With 10 to 20 mol % of catalyst, the Diels−Alder adducts are obtained in 76−98% ee with high *endo*-selectivity. The catalyst exhibits high activity for the reaction with the less reactive β-substituted dienophiles and the less reactive 1,3-cycohexadiene and 1,3-butadiene derivatives. The application of the catalysts to the Diels−Alder reaction of furan is also described.

Introduction

Lewis acid-catalyzed asymmetric Diels−Alder reactions have attracted great attention for their ability to construct complex carbocyclic frameworks in an enantiomerically enriched form starting from simple substrates.[1] The reaction of unsaturated aldehydes, especially with an α-substituent,[2] and bidentate alkenoyl-oxazolidinones[3] as dienophiles has been extensively developed in earlier studies. On the other hand, the asymmetric Diels−Alder reaction of ketone dienophiles has been reported most recently,[4−7] in spite of the prevalence of enantiopure ketones in natural products. The carbonyl oxygen of a ketone has sterically and electronically similar lone pairs, difficult to be discriminated in complexation by chiral Lewis acids. In addition, the less electron-deficient nature of the ketone dienophiles necessitates enhanced acidity of catalysts.

Corey and co-workers reported that a cationic oxazaborolidine **1a** of high Lewis acidity is a highly enantioselective catalyst for the asymmetric Diels−Alder reaction of ketone dienophiles.[4] A wide application of the cationic boron catalyst has been established in natural product syntheses.[8] Yamamoto and co-workers reported oxazaborolidine-derived catalyst **1b** whose

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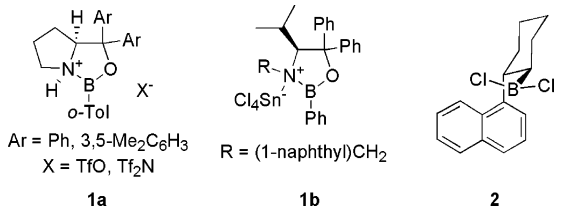
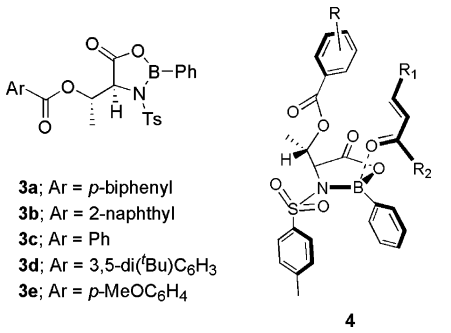
10.1021/jo702043g CCC: $40.75
Published on Web 12/06/2007

acidity is enhanced by another Lewis acid, $SnCl_4$.[6,9] Hawkins and co-workers showed that dichloroboron complex **2**, developed previously for ester dienophiles,[10] also catalyzes the reaction of ketone dienophiles with high selectivity.[5]



1a **1b** **2**

We have recently reported that *allo*-threonine-derived oxazaborolidinones (OXB) **3** are efficient catalysts for asymmetric Michael reaction of simple acyclic enones with silyl ketene *S*,*O*-acetals.[11,12] The high enantioselectivity and absolute stereochemical course of the reaction are rationalized in terms of the activated complex model shown in **4**.[11b] Although the recently developed catalysts are well designed to obviate inherent difficulties in the asymmetric Diels−Alder reaction of ketones, the scope of ketone dienophiles and dienes should be expanded further in view of the high synthetic utility of the enantioselective transformation. Herein, we wish to report that OXB catalysts **3** are also effective in the asymmetric Diels−Alder reaction of acyclic enones.[13] The OXB catalysts exhibited high enantioselectivity predicted from the activated complex model **4**. In spite of their apparently weaker Lewis acidity, OXB catalysts **3** showed high activity in the reaction of the less reactive dienes and dienophiles.



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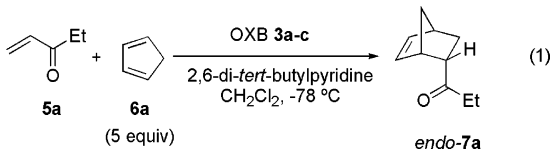
Results

The potential of the OXB catalysts **3** in the ketone Diels−Alder reaction was first evaluated with ethyl vinyl ketone (**5a**) and cyclopentadiene (**6a**) (eq 1, Table 1).



(1)

5a **6a**

TABLE 1. Asymmetric Diels−Alder Reaction of Ethyl Vinyl Ketone and Cyclopentadiene Catalyzed by OXB 3a−c[a]

entry	catalyst	mol %	yield (%)	*endo*:*exo*	ee (%)[b]
1[c]	**3a**	40	74	96:4	84
2	**3a**	40	80	98:2	91
3	**3a**	20	75	96:4	91
4	**3a**	10	88	96:4	92
5	**3b**	10	82	96:4	72
6	**3c**	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 **3**) 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.

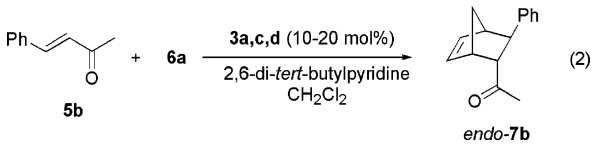
TABLE 2. Asymmetric Diels−Alder Reaction of Benzalacetone with Cyclopentadiene Catalyzed by OXB 3a,c,d[a]

entry	OXB	mol %	temp (°C)	time (h)	yield (%)	*endo*:*exo*[b]	ee[c] (%)
1	**3a**	20	−60	24	65	>98:2	90
2	**3a**	20	−60	72	77	>98:2	91
3	**3c**	20	−60	24	95	>98:2	92
4	**3c**	10	−60	72	96	>98:2	91
5	**3c**	10	−78	72	15	>98:2	92
6	**3d**	20	−60	72	90	>98:2	88

[a] Reactions were carried out by using cyclopentadiene (5 equiv) and 2,6-di-*tert*-butylpyridine (0.25 equiv with respect to **3**) in CH_2Cl_2. [b] Determined by ^1H NMR analysis (500 MHz, $CDCl_3$). [c] The ee was determined by chiral phase HPLC.

In the presence of *O*-*p*-biphenoyl OXB **3a** (40 mol %), the Diels−Alder reaction proceeded smoothly at −78 °C to give the corresponding *endo* adduct **7a** diastereo- and enantioselectively (entry 1). The addition of 2,6-di-*tert*-butylpyridine (0.25 equiv with respect to catalyst **3a**) improved the enantioselectivity (entry 2). The additive was used to trap a trace amount of HCl that could contaminate the catalyst in preparation from *O*-(*p*-biphenoyl)-*N*-tosyl-(L)-*allo*-threonine and dichlorophenylborane. Under these conditions, the amount of catalyst could be reduced to 10 mol % keeping the superior level of enantioselectivity (92% ee) as well as high *endo* selectivity (96:4) (entry 4). The enantioselectivity was dependent upon the *O*-acyl group in OXB catalysts. For the reaction of ethyl vinyl ketone with cyclopentadiene, the selectivity was decreased in the order of *O*-*p*-biphenoyl **3a**, *O*-2-naphthoyl **3b**, and *O*-benzoyl **3c** (entries 5 and 6). The trend in enantioselectivity is similar to that observed in the asymmetric Michael reaction.[11c]

A phenyl group in *β*-position reduces the reactivity of dienophile[14] and, to the best of our knowledge, there was no precedent for their asymmetric Diels−Alder reaction. To access the activity of OXB catalysts **3**, we examined the reaction of benzalacetone (**5b**) with cyclopentadiene (eq 2, Table 2). At



(2)

5b **6a**

−60 °C for 24 h, the reaction of **5b** was catalyzed by **3a** (20 mol %) to give the corresponding adduct *endo*-**7b** in 65% yield

(9) For the activation of an oxazaborolidine by $AlBr_3$, see ref 4e.

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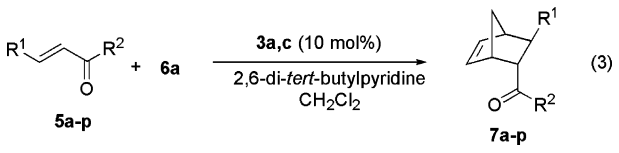
TABLE 3. OXB-Catalyzed Asymmetric Diels−Alder Reaction of Ketone Dienophiles 5a−p[a]

entry	dienophile	R^1	R^2	OXB	cond.[b]	product	yield (%)	*endo*:*exo*[c]	ee[d] (%)
1	**5c**	H	Me	**3a**	A	**7c**	52	>98:2	85
2	**5a**	H	Et	**3a**	A	**7a**	88	96:4	92
3	**5d**	Me	Me	**3a**	A	**7d**	85	>98:2	87
4	**5e**	Me	Et	**3a**	A	**7e**	90	>98:2	94
5	**5b**	Ph	Me	**3c**	B	**7b**	95	>98:2	92
6	**5f**	*p*-FC_6H_4	Me	**3c**	B	**7f**	83	>98:2	91
7	**5g**	*p*-ClC_6H_4	Me	**3c**	B	**7g**	96	>98:2	91
8	**5h**	***m***-ClC_6H_4	Me	**3c**	B	**7h**	97	>98:2	91
9	**5i**	*p*-$CF_3C_6H_4$	Me	**3c**	B	**7i**	98	>98:2	90
10	**5j**	*m*-$CF_3C_6H_4$	Me	**3c**	B	**7j**	91	>98:2	93
11	**5k**	*p*-MeC_6H_4	Me	**3c**	B	**7k**	53	>98:2	90
12[e]	**5k**			**3c**	B	**7k**	91	>98:2	91
13	**5*l***	*p*-$MeOC_6H_4$	Me	**3c**	B	**7*l***	4	>98:2	90
14	**5m**	Ph	Et	**3c**	B	**7m**	95	>98:2	93
15[e]	**5n**	Ph	*i*-Pr	**3a**	B	**7n**	71	98:2	61
16[e,f]	**5o**	Ph	H	**3a**	B	**7o**	33	84:16	8
17[e]	**5p**	2-cyclohexenone		**3a**	B	**7p**	25	>98:2	44

[a] Unless otherwise noted, reaction was carried out with cyclopentadiene (5 equiv), OXB **3a**,**c** (10 mol %), and 2,6-di-*tert*-butylpyridine (2.5 mol %) in CH_2Cl_2. [b] Condition A: at −78 °C for 24 h. Condition B: at −60 °C for 72 h. [c] Determined by 500 MHz ^1H NMR analysis. [d] Determined by chiral stationary phase GC or HPLC. [e] 20 mol % of the catalyst was used. [f] The reaction was carried out for 44 h.

together with the recovery of **5b** (26%) (entry 1). The product was obtained with high *endo* selectivity and with satisfactory enantioselectivity (90% ee). Full conversion of **5b** was not attained even after 72 h under these conditions (entry 2). In contrast, *O*-benzoyl OXB **3c** exhibited higher activity. The reaction was accomplished within 24 and 72 h with a 20 and 10 mol % catalyst loading, respectively (entries 3 and 4). Although OXB **3c** exhibited reduced enantioselectivity in the reaction of ethyl vinyl ketone (Table 1, entry 6), high selectivity (91−92% ee) comparable to that of the *O*-biphenoyl derivative was obtained. At −78 °C, the reaction was sluggish owing to the deposition of both dienophile **5b** and catalyst **3c** (entry 5). *O*-(3,5-Di(*tert*-butyl)benzoyl) OXB **3d** exhibited a catalytic activity comparable to **3c** but with slight lowering of the enantioselectivity (entry 6).

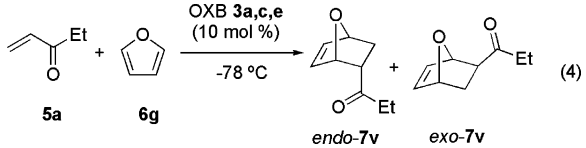
The scope of ketone dienophiles in the OXB-catalyzed asymmetric Diels−Alder reaction was demonstrated by the results summarized in Table 3. At −78 °C with 10 mol % of OXB **3a**, not only vinyl ketones **5a**,**c** but also propenyl ketones **5d**,**e** reacted with cyclopentadiene to give the corresponding *endo* adducts in high ee (entries 1−4). By using OXB **3c** (10 mol %) at −60 °C, a variety of benzalacetone derivatives with an electron-withdrawing group at the para- or meta-position underwent smooth reaction to give the *endo* adducts enantioselectively (90−93% ee) (entries 6−10).[15] Substitution of an electron-donating group, however, significantly lowered the reactivity of dienophiles. A 20 mol % catalyst loading was required for the reaction of *p*-methylbenzalacetone (**5k**) (entry 12). The reaction of *p*-methoxy derivative **5*l*** was very sluggish (entry 13). Enantioselectivity was always higher for ethyl ketones than the corresponding methyl ketones derivatives (entry 1 vs 2, 3 vs 4, and 5 vs 14). Decreased enantioselectivity was observed for isopropyl ketone **5n** (entry 15). OXB catalyst **3a** did not show enantioselectivity for the reaction of unsaturated aldehyde **5o** and cyclic ketone **5p** (entries 16 and 17).



(3)

With the high catalytic activity of OXB **3a**,**c** established in the Diels−Alder reactions of cyclopentadiene, attention was directed to the less reactive dienes. It has been reported that the reactivity of 1,3-cyclohexadiene (**6b**), 2,3-dimethyl-2,3-butadiene (**6c**), and 2,4-hexadiene (**6d**) is 2600, 1500, and 1300 times lower than that of cyclopentadiene.[16] OXB **3a** was found to catalyze the reaction of these less reactive dienes (Table 4). By using 20 mol % of catalyst **3a** at −78 °C, reaction of **6b**−**d** with ethyl vinyl ketone proceeded in an efficient manner to give the corresponding adducts **7q**−**s** in relatively high ee as well as with high diastereoselectivity (entries 1−3). The reaction of ethyl vinyl ketone with 1-phenylthiobutadiene (**6e**)[17] and 1-(benzyloxycarbonylamino)butadiene (**6f**),[18] employing 20 mol % of catalyst **3c** at −40 °C, afforded the corresponding adducts **7t**,**u** in low yield, but with high *endo* selectivity and moderate ee (entries 4 and 5). The apparent lower reactivity of dienes **6e**,**f** is probably due to their low solubility under the reaction conditions.

Diels−Alder Reaction of Furan. The Diels−Alder reaction of furan provides potentially useful, stereoselectively functionalized intermediates, 7-oxabicyclo[2.2.1]hept-2-enes. However, furan is generally held to be a poor diene.[3,19,20] A few examples of the catalytic asymmetric Diels−Alder reaction of furans have been reported for α-haloacroleins,[21] acryl oxazolidinones,[3] and 2,2,2-trifluoroethyl acrylate.[9] No report has appeared on the reaction of ketone dienophiles. The Diels−Alder reaction of ethyl vinyl ketone (**5a**) with furan (**6g**) was investigated by using OXB catalyst **3** (eq 4).



(4)

Under the standard conditions (10 mol % OXB **3a**, −78 °C, in CH_2Cl_2), the reaction of **5a** with **6g** proceeded rapidly to give, after 0.3 h, the adduct **7v** in 59% yield as a 22:78 mixture of *exo* and *endo* isomers, both of which were produced in low ee (Table 5, entry 1). Enantioselectivity was almost lost when the reaction was carried out for 2 h under otherwise the

TABLE 4. Asymmetric Diels−Alder Reaction of Dienes 6b−f with Ethyl Viniyl Ketone[a]

entry	diene	OXB	product	yield (%)	*endo*:*exo* [b]	ee [c] (%)
1	**6b**	**3a**	**7q**	88	98:2	88
2	**6c**	**3a**	**7r**	80	-	81
3	**6d**	**3a**	**7s**	70	93:7	80
4 [d]	**6e**	**3c**	**7t**	26	>98:2	76
5 [d]	**6f**	**3c**	**7u**	23	>98:2	86

[a] Unless otherwise noted, reaction was carried out with a diene (5 equiv), a catalyst (20 mol %), and 2,6-di-*tert*-butylpyridine (2.5 mol %) in CH_2Cl_2 at −78 °C for 22 h. [b] Determined by 500 MHz ^{1}H NMR analysis. [c] Determined by chiral stationary phase GC or HPLC. [d] Reaction was carried out at −40 °C for 24 h with 3 and 1.5 equiv of a diene for entries 4 and 5.

TABLE 5. OXB-Catalyzed Asymmetric Diels−Alder Reaction of Ethyl Vinyl Ketone with Furan [a]

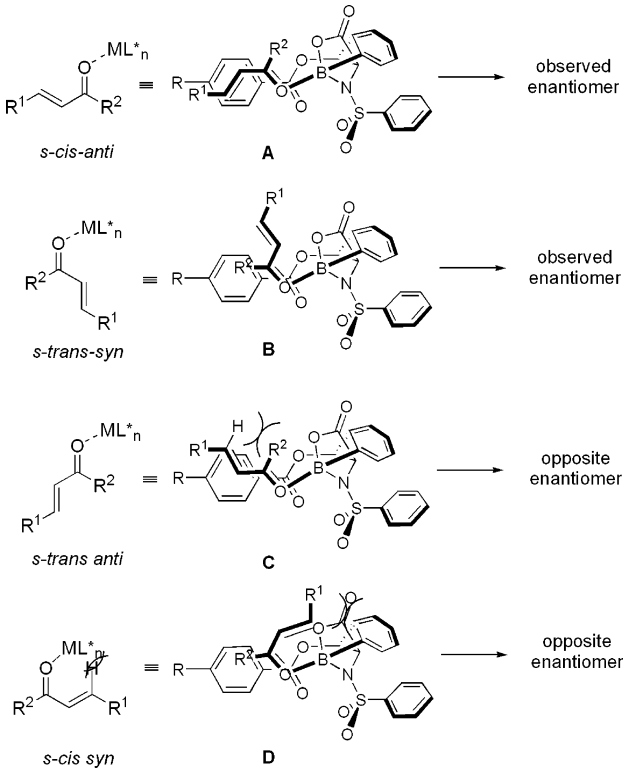
entry	OXB	solvent	time (h)	yield (%)	*endo*:*exo*[b]	*endo* ee (%)[c]	*exo* ee (%)[c]
1	**3a**	CH_2Cl_2	0.3	59	22:78	24	15
2			2	39	21:79	5	8
3		Et_2O	0.3	18	72:28	95	24
4			2	21	66:34	94	21[d]
5		toluene	0.3	80	82:18	91	17
6			2	75	57:43	76	30[d]
7	**3c**		0.3	88	93:7	98	36
8			2	75	81:19	95	0
9	**3e**		0.3	68	84:16	95	21
10			2	70	81:19	95	10

[a] Reaction was carried out with furan (5 equiv) and a catalyst (10 mol %) at −78 °C. [b] Determined by 500 MHz ^{1}H NMR analysis. [c] Determined by chiral stationary phase GC after converting into *exo*- and *endo*-1-(7-oxabicyclo[2.2.1]hept-2-yl)propan-1-one by hydrogenation with Pd/C. [d] Enriched with the opposite enantiomer.

same conditions (entry 2). Marked effect of solvent was observed on diastereo- and enantioselectivity in the Diels−Alder reaction with furan. *Endo*-selectivity and high enantioselectivity were observed by carrying out the reaction in ether for 0.3 h whereas the product yield was low (entry 3). High yield (80%), as well as high enantioselectivity (91% ee), was obtained with *endo*-selectivity by carrying out the reaction in toluene (entry 5). Diastereoselectivity was decreased by the longer reaction time in ether or toluene (entries 4 and 6). Interestingly, the

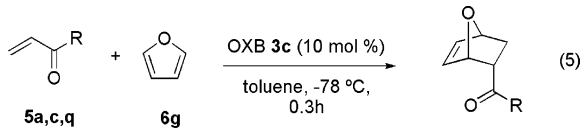
(15) The absolute structure of **7g** was established by the crystallographic analysis. See the Supporting Information.

SCHEME 1



reversal in the absolute configuration of the *exo*-enantiomer was observed in these reactions. Further improvement was obtained by employing *O*-benzoyl OXB **3c** (10 mol %) in toluene (entry 7). Under these conditions, *endo*-**7v** was obtained in 98% ee with high diastereoselectivity (*endo*:*exo* = 93:7). *O*-*p*-Anisoyl OXB **3e** exhibited selectivities between those of **3a** and **3c** (entry 9).

Under the optimal conditions with 10 mol % of **3c** in toluene at −78 °C for 0.3 h, not only **5a** but also methyl vinyl ketone (**5c**) and pentyl vinyl ketone (**5q**) reacted with furan to give the corresponding *endo* adduct **7w**,**x** in high enantioselectivity (eq 5). Attempted reaction of *β*-substituted enones such as **5d** did not give the corresponding cycloadducts.



endo-**7v**; R = Et; 88% yield, 93:7, 98% ee
endo-**7w**; R = Me; 58% yield, 67:33, 93% ee
endo-**7x**; R = C_5H_{11}; 94% yield, 86:14, 98% ee

Discussion

There are four possible coordination modes of an acyclic enone to Lewis acids (ML*$_n$) (Scheme 1). Except for the

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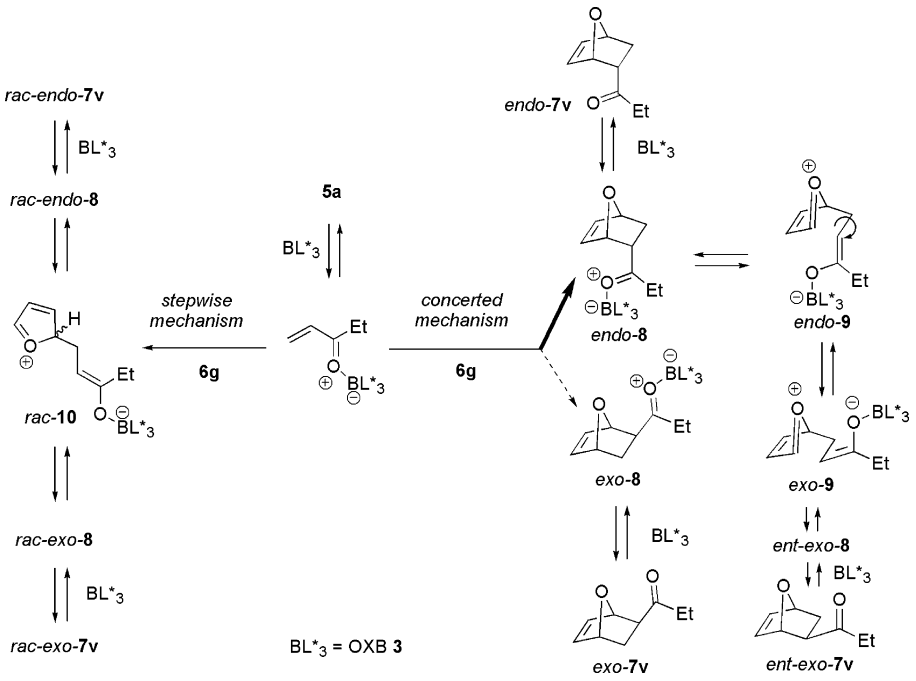
SCHEME 2



sterically congested *s-cis-syn* isomer, other isomers are seemingly feasible for activated complexes. We have recently shown that OXBs have a strong tendency to be coordinated by pyridine derivatives from the face syn to the substituent attached to the oxazaborolidinone ring.[22] Assuming a similar facial selectivity for enone coordination with respect to the OXB ring, four possible activated complex models (**A**−**D**) are conceivable corresponding to the four coordination modes.

The approach of dienes from the open front side of the activated complex **A** (*s-cis-anti*) (=**4**) and **B** (*s-trans-syn*) would lead to the enantiomers obtained in the OXB-catalyzed reaction while, on the other hand, **C** (*s-trans-anti*) and **D** (*s-cis-syn*) would give the opposite enantiomer. Low enantioselectivity was observed for cyclic enone **5p** with the fixed *s-trans* structure (Table 3, entry 17). Low selectivity was also observed for isopropyl ketone **5n** in which anti coordination by OXB **3** might be sterically less favorable (entry 15). These observations suggest strongly that the OXB-catalyzed Diels−Alder reaction of acyclic enones proceeds not through *s-trans-syn* complex **B** but through *s-cis-anti* complex **A**.

In contrast to the high enantioselectivity observed for acyclic enones, OXB **3a** did not show selectivity for cinnamaldehyde (**5o**) (entry 16). The result implies that the reaction of the enal (R^2 = H) proceeded concurrently through complexes **A** and **C**. For ketone dienophiles, *s-trans-anti* complex **C** ($R^2 \neq$ H) is unfavorable owing to an 1,3-allylic strain, which might be a major factor for the preference of the *s-cis-anti* complex **A** in the reaction of acyclic enones. The allylic interaction in complex **C** also might be responsible for the general trend of slightly higher enantioselectivity for ethyl ketones ($R^2 = CH_3CH_2$) in comparison with methyl ketones ($R^2 = CH_3$).

The catalytic activity of OXB **3** is unexpectedly high in view of the moderate acidity of boron-based neutral Lewis acids.[23] The observed activity of OXB **3a**,**c** is comparable or even higher than that of cationic boron catalyst **1a**,**b**[4,6.9] or dichloroboron complex **2**[5] judging from reaction temperatures, catalyst amounts, and applicability to the less reactive dienes and dienophiles. In comparison with these catalysts, OXB **3** has a less rigid chiral environment around the boron atom, which might be responsible for its high activity. The acyloxy moiety of **3** is conformationally flexible to some extent due to the presence of three rotatable bonds (CHMe−O, O−CO, and CO−Ar), serving as a "soft fence" to induce enantioselectivity. The activated complex **4** (=**A** in Scheme 1) could accommodate space for structural change in the transition state to stabilize the transition state and facilitate the Diels−Alder reaction.

In the reaction of benzalacetone (**5b**), *O*-benzoyl OXB **3c** showed higher catalytic activity in comparison with *O-p*-biphenoyl derivative **3a**. The observation can be rationalized by considering an unfavorable interaction in the transition state between the phenyl group of **5b** and the *p*-phenyl group of **3a**. The approach of cyclopentadiene toward activated complex **A** (R, R^1 = Ph) would result in a steric congestion in the transition state between these phenyl groups, which could not be fully accommodated by the structural modification of the acyloxy moiety.

The mechanism of the Diels−Alder reaction has long been a topic of discussion.[24] The reaction may take place through either a concerted or a stepwise mechanism involving the formation of a zwitterion or biradical intermediate. Recent experimental[25] and theoretical studies[26,25b] on the reaction of furans point out that the mechanism changes from concerted to stepwise with an increased electron deficiency in the dienophile. In the OXB-catalyzed furan Diels−Alder reaction, solvents and reaction time

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had a remarkable effect on the diastereo- and enantioselectivity (Table 5). High enantioselectivity was obtained with *endo*-selectivity by carrying out the reaction in toluene for 0.3 h (entries 5, 7, and 9). Diastereoselectivity was decreased by the longer reaction time together with a decrease in the enantioselectivity (entries 8 and 10) or reversal in the absolute configuration of the minor *exo*-enantiomer (entry 6). While the observation is difficult to rationalize based on the retro-Diels−Alder reaction,[27] it can be understood by postulating a limiting concerted and a stepwise mechanism (Scheme 2). The concerted Diels−Alder reaction of furan catalyzed by OXB **3** would produce *endo*-**7v** as a major diastereomer and enantiomer. Assuming an activated complex model **4**, the major enantiomer of a minor *exo* adduct (*exo*-**7v**) would be the one with 1*R*,2*S*,4*R* configuration.[28] The stepwise reaction of furan would proceed without enantioselectivity to give racemic zwitterion intermediate *rac*-**10**, which would cyclized to give *rac*-*exo*-**7v** as a major diastereomer with minor formation of *rac*-*endo*-**7v**. Due to the stabilization of intermediate *rac*-**10** in CH_2Cl_2, the Diels−Alder reaction of furan in this solvent proceeded mainly through the stepwise mechanism, with minor competition of the concerted pathway, resulting in *exo* selective formation of the adducts in low enantioselectivity (entries 1 and 2). On the other hand, in the less polar toluene, the reaction proceeded primarily through the concerted pathway to give *endo*-**7v** diastereo- and enantioselectively (entries 5, 7, and 9). In toluene, however, the initially produced *endo*-**7v** is slowly transformed to the thermodynamically more stable *ent*-*exo*-**7v** through tight ion pair *endo*-**9** and *exo*-**9**. As a result, in the reaction for 2 h, the enantioselectivity of the *exo* adducts was decreased with OXB **3c** and **3e** (entries 8 and 10) or reversed with OXB **3a** (entry 6).

Conclusion

The results in this report demonstrate that *allo*-threonine-derived OXB catalysts, especially *O*-*p*-biphenoyl and *O*-benzoyl OXB **3a**,**c**, are highly effective in asymmetric Diels−Alder reactions of acyclic ketone dienophiles. With 10 to 20 mol % of the catalysts, the Diels−Alder adducts were obtained in high *endo* selectivity and enantioselectivity. The catalysts exhibit high activity for the less reactive dienophiles such as benzalacetone derivatives and for the less reactive dienes such as 1,3-cyclopentadiene. The application of catalyst **3c** to the Diels−Alder reaction of furan has also proven to be possible by using toluene as a solvent. The remarkable solvent effect as well as isomerization of the kinetically favored *endo* adduct to the thermodynamically favored *exo* adduct was discussed in terms of a limiting concerted and a stepwise mechanism. The observed absolute structures of the Diels−Alder adducts are consistent with the activation complex model **4**. The moderately flexible nature of the acyloxy was proposed to be responsible for the high activity of the neutral boron complex **3**.

Experimental Section

1-[(1*S*,2*S*,4*S*)-Bicyclo[2.2.1]hept-5-en-2-yl]propan-1-one[4a] (7a): Typical Procedure for Asymmetric Diels−Alder Reaction. To a solution of *O*-(*p*-biphenoyl)-*N*-tosyl-(L)-*allo*-threonine[8c] (140 mg, 0.309 mmol) in CH_2Cl_2 (2.5 mL) under argon atmosphere 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 **3a** 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 (2.72 mmol, 88%) of the adduct **7a**: $[\alpha]^{23}_D$ −104 (*c* 1.1, $CHCl_3$) (92% ee). Lit.[4a] for the (1*R*,2*R*,4*R*)-enantiomer: $[\alpha]^{23}_D$ +111 (*c* 0.76, $CHCl_3$) (97% ee). *Endo*−*exo* ratio was determined by GC analysis, using a OV-1 column (30 m, 1.8 kg/cm^2, initial temperature 50 °C, 10 deg/min ramp to 320 °C); retention times 6.5 (*endo*) and 6.2 min (*exo*). Enantioselectivity was determined by GC analysis, using a Chrompack Cp-Cyclodextrin-β-236-M-19 column (30 m, 1.8 kg/cm^2, initial temperature 50 °C, 2 deg/min ramp to 200 °C); retention times 26.9 (major) and 26.7 min (minor).

1-[(1*S*,2*S*,4*S*)-7-Oxabicyclo[2.2.1]hept-5-en-2-yl]propan-1-one (7v): Typical Procedure for Asymmetric Diels−Alder Reaction with Furan. To a solution of *O*-(benzoyl)-*N*-tosyl-(L)-*allo*-threonine[3c] (75.5 mg, 0.200 mmol) in CH_2Cl_2 (2 mL) under argon atmosphere at room temperature was added dichlorophenylborane (28.5 μL, 0.22 mmol). After being stirred for 30 min, the mixture was concentrated in vacuo. To a mixture of the resulting OXB **3c** in toluene (6.4 mL) at −78 °C were added ethyl vinyl ketone (168 mg, 2.00 mmol) and furan (0.73 mL, 10 mmol). The resulting solution was stirred at −78 °C for 0.3 h. The mixture was quenched by the addition of saturated aqueous $NaHCO_3$ and filtered. The filtrate was extracted three times with ether, dried ($MgSO_4$), and concentrated in vacuo. The toluene solution of the crude product was subjected to a flash chromatography (SiO_2, gradient elution with 0−25% Et_2O in hexane) to obtain 269 mg (1.77 mmol, 88%) of a 93:7 mixture of *endo*-**7v** and *exo*-**7v**. The *endo* and *exo* adducts were isolated by flash chromatography. *endo*-**7v** (98% ee): R_f 0.33 (SiO_2, 30% ethyl acetate in hexane); $[\alpha]^{23}_D$ −75.2 (*c* 1.00, $CHCl_3$) (96% ee);[29] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.03 (3H, t, J = 7.2 Hz), 1.59 (1H, dd, J = 4.0 and 11.2 Hz), 2.00 (1H, ddd, J = 4.8, 9.1, and 11.3 Hz), 2.33−2.50 (2H, m), 3.20 (1H, td, J = 4.3 and 9.0 Hz), 5.01 (1H, dd, J = 1.1 and 4.7 Hz), 5.17 (1H, br d, J = 4.7 Hz), 6.15 (1H, dd, J = 1.5 and 5.9 Hz), 6.40 (1H, dd, J = 1.7 and 5.9 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 7.6, 27.4, 35.8, 50.8, 78.9, 79.2, 134.8, 136.8, 208.9; HRMS (EI) calcd for $C_9H_{12}O$ 152.0837, found 152.0838. *exo*-**7v** (36% ee): R_f 0.27 (SiO_2, 30% ethyl acetate in hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (3H, t, J = 7.3 Hz), 1.51 (1H, dd, J = 8.5 and 11.4 Hz), 1.62 (1H, br s), 2.03 (1H, td, J = 4.4 and 11.4 Hz), 2.47−2.61 (3H, m), 5.07 (1H, br d, J = 4.4 Hz), 5.09 (1H, d, J = 1.0 Hz), 6.36 (1H, dd, J = 1.6 and 5.8 Hz), 6.38 (1H, dd, J = 1.6 and 5.8 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 7.9. 28.4, 34.5, 49.8, 78.0, 79.9, 134.9, 136.8, 210.9; HRMS (EI) calcd for $C_9H_{12}O$ 152.0837, found 152.0832.

Endo−*exo* ratio was determined by 500 MHz ^{1}H NMR analysis. The absolute stereochemistry was assumed by analogy. A 93:7 mixture of the *endo* and *exo* adduct was hydrogenated in the presence of Pd/C (10%) in hexane to give 1-(7-oxabicyclo[2.2.1]-hept-2-yl)propan-1-one as a mixture of *endo* and *exo* isomers. Enantioselectivity was determined by GC analysis, using a BETA DEX 225 (m) column (30 m, 1.8 kg/cm^2, initial temperature

(27) If retro-Diels−Alder reaction were responsible for the *endo*-*exo* isomerization, complete racemization of *exo*-**7v** (entry 8) would be observed in full equilibrium, where the thermodynamically more stable *exo* isomer would be a major component.

(28) In accord with this supposition, treatment of a 85:15 mixture of *endo*-**7v** (87% ee) and *exo*-**7v** (50% ee) with aq KOH (1 M)/Et_2O at room temperature gave a 48:52 mixture of *endo*-**7v** (64% ee) and *ent*-*exo*-**7v** (56% ee) in 31% yield.

(29) Specific rotation was measured for the product of the reaction with OXB **3c** (5 mol %) at −78 °C for 0.3 h in toluene (34% yield, *endo*:*exo* = 86:14, *endo*; 96% ee, *exo*; 23% ee).

90 °C, 1 deg/min ramp to 170 °C); retention times 26.3 (major *endo* enantiomer), 28.2 (minor *endo* enantiomer), 37.9 (major *exo* enantiomer), and 36.9 min (minor *exo* enantiomer). *endo*-1-(7-Oxabicyclo[2.2.1]hept-2-yl)propan-1-one: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (3H, t, J = 7.4 Hz), 1.38 (1H, m), 1.50 (1H, m), 1.58 (1H, m), 1.63−1.77 (2H, m), 1.98 (1H, dd, J = 4.7 and 11.8 Hz), 2.33−2.48 (2H, m), 3.18 (1H, m), 4.59 (1H, t, J = 5.3 Hz), 4.76 (1H, t, J = 5.2 Hz), a minor *exo*-isomer resonates at 4.64 (1H, t, J = 5.0 Hz) and 4.72 (1H, d, J = 4.9 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 7.6, 20.1, 29.9, 31.6, 36.6, 55.7, 77.4, 78.1, 209.2.

Acknowledgment. Financial support from the Ministry of Education, Science, Sports and Culture of the Japanese Government [Grant-in-Aid for Scientific Research (No. 17550101)] is gratefully acknowledged.

Supporting Information Available: Preparation of OXB ligands and data for Diels−Alder adducts **7a**−**x**, including X-ray data of **7g**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702043G