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Catalytic and Enantioselective Diels–Alder Reactions of (*E*)-4-Oxopent-2-enoates

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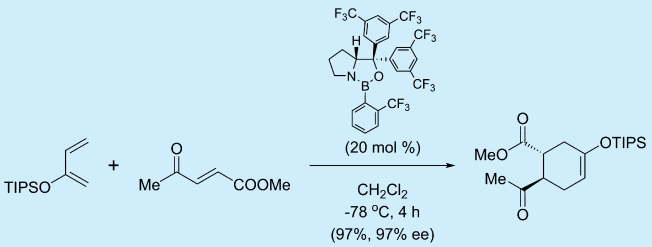
Supporting Information

ABSTRACT: Novel oxazaborolidines activated by the strong acid triflimide or $AlBr_3$ form cationic chiral catalysts. These are effective catalysts for highly regio- and enantioselective Diels–Alder reactions using substituted (*E*)-4-oxopent-2-enoates as dienophiles.



1,2-Disubstituted dienophiles with two different electron-withdrawing groups[1] are good partners in the Diels–Alder reaction because of their LUMO-lowering properties.[2] In this context, substituted (*E*)-4-oxopent-2-enoates (**A** in Figure 1) are

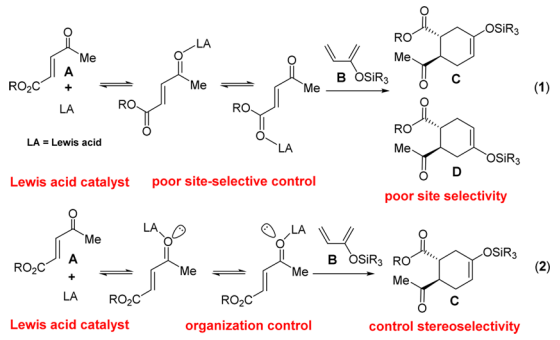


Figure 1. Diels–Alder reactions of (*E*)-4-oxopent-2-enoates.

unique because they can coordinate with Lewis acids. This increases the reactivity of the dienophiles and induces enantioselectivity in the presence of asymmetric catalysts in the Diels–Alder reactions.

However, the usefulness of (*E*)-4-oxopent-2-enoates in the asymmetric synthesis via Diels–Alder reactions is diminished both by the low site selectivity of coordination of its two carbonyl groups to Lewis acids[3] (eq 1 in Figure 1) and by the lower selectivity of Lewis acid coordination with its ketone moiety because the ketone is positioned in a similar steric environment[4] (eq 2 in Figure 1).

Both these issues arise in the Lewis acid association step, an organizational event that is essential for stereo- and regioselective control, which presents a challenge in the development of a catalytic asymmetric variant of Diels–Alder reaction. Herein, we describe the development of an enantioselective Diels–Alder reaction of (*E*)-4-oxopent-2-enoates (**A**) using modified oxazaborolidine-based catalysts.

We recently reported that Hayashi's ligand **E** was an effective catalyst in the enantioselective synthesis of aldehyde **3** (eq 1 in Scheme 1), which was then converted to ketone **4**, a key intermediate in our asymmetric total synthesis of the natural product propindilactone G.[5] However, the process would be more attractive if ketone **4** could be directly constructed from diene **1** and (*E*)-4-oxopent-2-enoate-based dienophile **5**. We, therefore, began to explore this concise synthesis.

Cationic chiral oxazaborolidiniums **7**, **8**, and **9** (eq 2 in Scheme 1) are the most versatile and electrophilic chiral catalysts, which are obtained by activation of the (*R*)-oxazaborolidine **6** with either triflic acid, triflimide, or $AlBr_3$.[6,4b] Because these catalysts are effective in a variety of Diels–Alder reactions with high enantio- and diastereoselectivities,[7] we initially investigated the enantioselective synthesis of **4** from diene **1** and dienophile **5** using catalysts **7**–**9**.

Table 1 shows the results. When catalysts **7** and **8** were used, both reactions proceeded in the presence of catalyst (10 mol %) in CH_2Cl_2 at 0 °C to give product **4** in 85% yield with 63% ee and 88% yield with 54% ee, respectively (Table 1, entries 1 and 2). When **9** was used as the catalyst, the reaction at −78 °C gave **4** in 94% yield with 57% ee (entry 3), indicating that catalyst **9** was more potent than catalysts **7** and **8**. Although catalyst **9** afforded the desired product in high yield, its enantioselectivity was

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Scheme 1. Diels–Alder Reactions and Cationic Chiral Oxazaborolidines

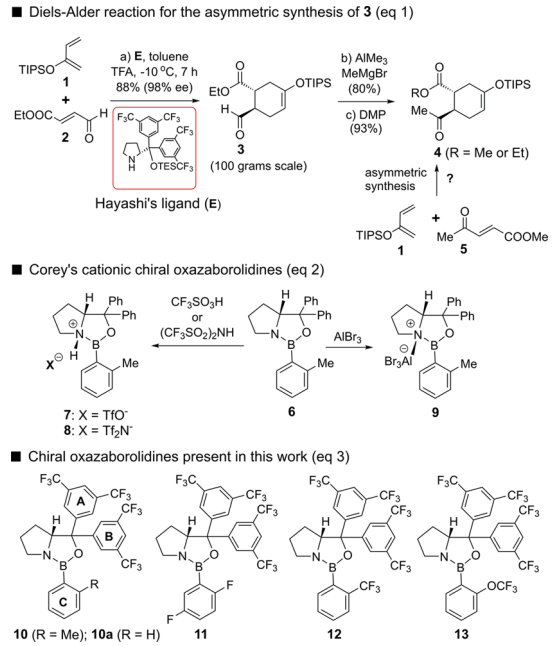
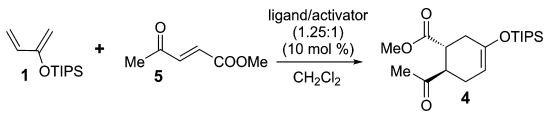


Table 1. Corey's Oxazaborolidine-Based Catalysts in the Diels–Alder Reaction of Diene 1 and Ketoester 5[a]



entry	activator	catalyst	temp	time (h)	yield (%)	ee[b,c] (%)
1	TfOH	**7**	0 °C	7	85	63
2	Tf_2NH	**8**	0 °C	5	88	54
3	$AlBr_3$	**9**	−78 °C	1.5	94	57

[a]Reagents and conditions: to a solution of catalyst in CH_2Cl_2 prepared by mixing ligand (1.25 equiv) and activator (1.0 equiv) was added the solution of diene **1** (2 equiv) and dienophile **5** (1 equiv) in CH_2Cl_2 at the given temperature, and the reaction was carried out under the conditions listed above. [b]Product ratios determined by chiral HPLC. [c]Absolute configuration of product **4** was determined by chemical correlation to a known compound.

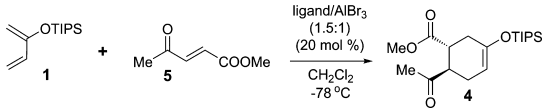
unsatisfactory. We, therefore, decided to initiate a program to identify more efficient catalysts that give high yields and high enantioselectivities in the proposed Diels–Alder reaction.

Recently, Corey and co-workers reported that the fluorine substituents in the chiral oxazaborolidinium ligands can lead to more potent chiral oxazaborolidinium cationic catalysts.[8] The effectiveness of Hayashi's ligand, which bears four trifluoromethyl groups on its two phenyl rings, in the Diels–Alder reaction for the synthesis of **3** from diene **1** and dienophile **2** inspired us to prepare a modified oxazaborolidine ligand **10** (eq 3 in Scheme 1). We expected that this type of ligand would be effective in the enantioselective synthesis of ketone **4** from diene **1** and dienophile **5** because the four electron-deficient trifluoromethyl groups would significantly reduce the electron density on the *gem*-biaryl rings. This would enhance coordination of the boron atom in catalyst **10** with the carbonyl group in dienophile **5**.

To test our proposal, ligand **10** was prepared according to the reported protocol,[9] and the details are given in the Supporting Information (SI). To evaluate the effect of the methyl group on the C ring of ligand **10** on the outcome of the Diels–Alder reaction, we also made the ligand **10a** (eq 3 in Scheme 1) by replacing this methyl group with a hydrogen.

We then performed the Diels–Alder reactions. First, ligand **10** and $AlBr_3$ were mixed in CH_2Cl_2 at −25 °C, which was then cooled to −78 °C. To this solution was added a solution of diene **1** and dienophile **5** in CH_2Cl_2 in a dropwise manner at −78 °C, and the resultant mixture was then stirred at −78 °C for 1.5 h. The reaction was then quenched by addition of Et_3N (0.2 mL). The desired product **4** was obtained in 80% yield with 90% ee (Table 2, entry 1). We also ran the same reactions under the

Table 2. CF_3-Derived Oxazaborolidines As Catalysts in the Diels–Alder Reaction of Diene 1 and Ketoester 5



entry	catalyst	time (h)	yield (%)	ee (%)
1	**10**	1.5	80	90
2	**10a**	5.5	80	94

identical conditions in the presence of ligand **10a** for comparison. The data in Table 2 show that **10a** catalyzed the Diels–Alder reaction to give **4** in 80% yield with 94% ee.

The absolute stereochemistry of **4** was confirmed by comparison of its NMR spectrum and optical rotation with those of compound **4** derived from the Hayashi-ligand-catalyzed Diels–Alder reaction, which is a key intermediate in our asymmetric total synthesis of propindilactone G.[5]

Mechanistically, the optimal structure of ketone-binding substrate–oxazaborolidinium complex **A** shown in Figure 2

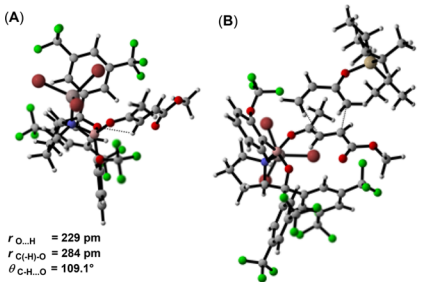


Figure 2. Optimal conformations of the substrate–oxazaborolidinium complex (A) and favored transition state structure (B).[11]

exhibits characters similar to previous studies:[4b,10] (1) the ketone favors coordinating to the boron atom from the less congested convex face of the fused 5/5 ring system; (2) in the complex, the coordinating C=O double bond favors an s-*trans* configuration relative to the C=C double bond; (3) the remaining lone pair on the carbonyl oxygen adopts a *trans*-planar conformation relative to B–O bond, probably due to secondary orbital interaction; and (4) for the nonclassical C–H···O hydrogen bond, the O···H distance and C(–H)···O distance are short, at around 230 and 285 pm, respectively, although the C–H···O angle is relatively sharp, at around 110°.

The favorable substrate–oxazaborolidinium complex **A** has a coordinate site from its convex face, which led the diene **1** to attack **A** from its less hindered direction. The reaction of the resulting borane complex **A** with diene **1** would proceed via

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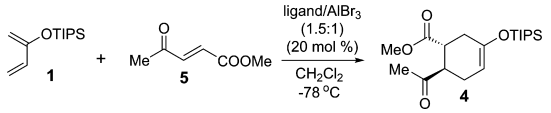
transition state **B** in which the bonding is principally between the β-carbon of the binding carbonyl group in the dienophile **5** and C(1) of diene **1**. The enhanced enantioselectivities of ligands **10** and **10a** indicate that electron-deficient groups (CF_3–) on the oxazaborolidine scaffold could benefit the asymmetric synthesis of product **4**.

To support this analysis, ligands **11**, **12**, and **13** (eq 3 in Scheme 1) were synthesized accordingly. Ligand **11** was made by replacement of the C ring of ligand **10** by a 2,5-difluoro-phenyl group,[8] and ligands **12** and **13** were prepared by replacement of the C ring of ligand **10** by a 2-(trifluoromethyl)phenyl group and a 2-(trifluoromethoxy)phenyl group, respectively. With these ligands in hand, we then carried out their Diels–Alder reactions of diene **1** with dienophile **5**. As illustrated Table 3, all the reactions could afford the desired product **4**, and the catalyst derived from ligand **12** gave both the highest yield and ee (Table 3, entry 2).

Table 3. Diels–Alder Reactions Catalyzed by Oxazaborolidines 11–13 Derived Catalysts

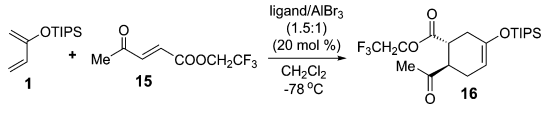


entry	catalyst	time (h)	yield (%)	ee (%)
1	**11**	4	87	88
2	**12**	4	97	97
3	**13**	36	85	79

In an attempt to decipher the enhanced enantioselectivity, we then carried out computational experiments. Our results reveal a general trend that the bonding between the carbonyl oxygen and oxazaborolidinium boron atom is strengthened by the electron-withdrawing aryl groups on the oxazaborolidinium. As a result, the bond distance between the carbonyl oxygen of dienophile and the boron atom of oxazaborolidinium is shortened, which coincides with the observed increase of enantioselectivity (details in SI).[11,12]

To examine the electronic effect of the ester in dienophile on the outcome of Diels–Alder reaction, we prepared dienophile **15** bearing a trifluoroethyl ester[13] and ran its Diels–Alder reaction with diene **1** in the presence of the catalysts derived from **11**, **12**, and **13**; the results are given in Table 4. When the catalyst derived

Table 4. Diels–Alder Reactions with Dienophile 15

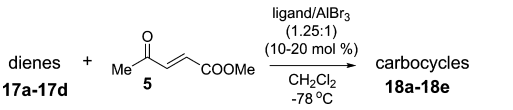


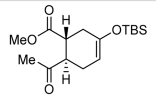
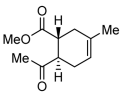
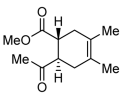
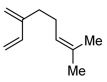
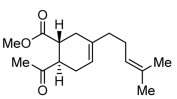
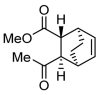
entry	catalyst	time (h)	yield (%)	ee (%)
1	**11**	5	80	73
2	**12**	4	42	89
3	**13**	18	77	75

from **11** was used in the Diels–Alder reaction, **16** was formed in 80% yield with 73% ee. In the case of the catalyst derived from **12**, the yield of adduct **16** decreased significantly, and the ee was slightly higher (Table 4, entry 2). However, moderated yield and ee of adduct **16** were obtained when ligand **13** was used in the reaction (Table 4, entry 3). The observed results are presumably because of the low site selectivity of the coordination of its two carbonyl groups of dienophile **15** to the catalysts caused by reducing the electron density on the ester group.

With this chemistry in mind, we then began to synthesize carbocycles **18a–18e** using catalysts derived from **10**, **12**, and **13**. As shown in Table 5, all the selected substrates could afford the

Table 5. Enantioselective Synthesis of Carbocycles 18a–18e



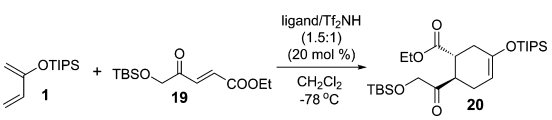
entry	catalyst (mol %)	diene	product	time (h)	yield (%)	ee (%)
1	**10** (10)			9	92	73
	12 (20)			16	79	90
	13 (20)	**17a**	**18a**	36	82	83
2	**10** (10)			5	91	93
	12 (20)			18	72	74
	13 (20)	**17b**	**18b**	4	99	96
3	**10** (10)			6	90	92
	12 (20)			3	92	98
	13 (20)	**17c**	**18c**	5	99	93
4	**10** (10)			15	84	79
	12 (20)			9	83	79
	13 (20)	**17d**	**18d**	6[a]	86	95
5	**13** (20)			6[b]	73[c]	85
		17e	**18e**			

[a]The reaction was conducted at −60 °C. [b]The reaction was conducted at −70 °C. [c]The ratio of endo/exo for the product **18e** is >99:1.

expected annulated products in good yields with good ee values. It is worthwhile to mention that different substrates need different catalyst and various combinations of catalyst loadings and reaction times to achieve better results.

To extend the reaction scope, we used the developed method for the enantioselective synthesis of carbocycle **20**, which is a key intermediate in our asymmetric total synthesis of naturally occurring complex triterpenoid lancifodilactone G.[14] A pre-cooled solution of diene **1** and dienophile **19** was added to the freshly prepared catalyst, either **10**, **10a**, **12**, or **13**, and the reaction was run under the conditions listed in Table 6. The results show that the catalysts derived from ligands **12** and **13** (entries 3 and 4) afforded the desired product **20** in excellent

Table 6. Enantioselective Synthesis of Carbocycle 20



entry	catalyst	time (h)	yield (%)	ee (%)
1	**10**	6	87	87
2	**10a**	2	85	92
3	**12**	1	97	94
4	**13**	1	95	96

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yield and with good ee value. This shows that the ligands are robust in the construction of useful starting materials for the asymmetric total synthesis of complex natural products.

In conclusion, the development of an enantioselective Diels–Alder reaction using substituted (*E*)-4-oxopent-2-enoates as dienophiles was achieved by using the catalysts derived from Corey's oxazaborolidinium cations. The developed method was used to synthesize structurally diverse carbocycles, some of which are the key intermediates in the asymmetric total synthesis of complex natural products. The use of such ligands in Diels–Alder reactions of (*E*)-1,2-disubstituted dienophiles with two different electron-withdrawing groups is currently being investigated in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01692.

Experimental procedures, spectral, and other characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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