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Chiral Phosphoric Acid-Governed Anti-Diastereoselective and Enantioselective Hetero-Diels−Alder Reaction of Glyoxylate

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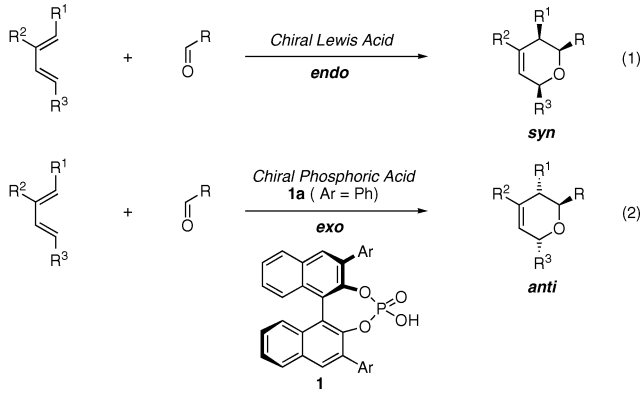
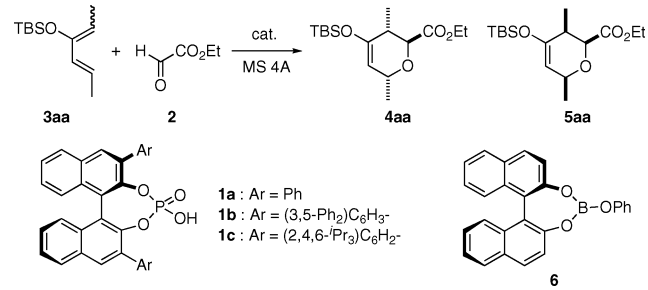
Hetero-Diels−Alder reactions between dienes and carbonyl compounds have served as an extremely valuable method for the preparation of dihydropyrans.[1] The development of catalytic enantio- and diastereoselective variants is an area of considerable importance.[2] Previous studies mainly have demonstrated the use of chiral Lewis acid catalysts to control high levels of stereoselectivity (eq 1).[3] It is noteworthy that vicinal substituents of the dihydropyran were established exclusively with **syn** selectivity. Presumably, the syn selectivity observed in previous reports is due to the following intrinsic nature of the chiral Lewis acid catalyst: (i) dominant secondary π-orbital interactions and (ii) the steric demand of the chiral Lewis acid catalyst, as the diene could approach the aldehyde with an endo alignment to avoid the steric repulsion between the incoming diene and the catalyst.[4] In contrast, instances of alternative exo-oriented enantioselective processes, which would correspond to **anti** selectivity, have yet to be fully developed.[5] We now report the first example of a highly enantio- and **anti**-selective hetero-Diels−Alder reaction between a glyoxylate and siloxy- or methoxydienes induced by chiral binaphthol-derived phosphoric acid **1a** as a catalyst (eq 2).



In view of our previous success in promoting catalytic asymmetric reactions using chiral phosphoric acids,[6] we began to investigate the corresponding process using (2*Z*,4*E*)-*tert*-butyldimethylsilyloxy-2,4-hexadiene (**3aa**) in the presence of chiral phosphoric acid **1a** and 4 Å molecular sieves. Initial results with **1a** revealed that although chiral Lewis acids have typically provided the optically active syn adduct, chiral phosphoric acid **1a** was uniquely efficient in affording anti adduct **4aa** in 95% yield with 99% ee as a single diastereomer (Table 1, entry 1).[7] Even with 2 mol % catalyst loading, adduct **4aa** was obtained in excellent yield without detrimental effects on the enantioselectivity and anti diastereoselectivity (Table 1, entry 2).

Having achieved this unprecedented **anti** selectivity, we directed our subsequent efforts toward considering the diastereoselectivity in this reaction. At first, reactions between ethyl glyoxylate **2** and siloxydiene **3aa** were conducted to evaluate the effect of the Lewis

Table 1. Preliminary Study[a]



entry	cat. (mol %)	conditions	yield, %[b]	*anti*:*syn* [c]	**4aa**/**5aa** ee, %[d]
1	**1a** (5)	toluene, r.t., 24 h	95	>99:1	99/−
2	**1a** (2)	toluene, r.t., 24 h	92	>99:1	97/−
3	BF_3·OEt_2 (100)	toluene, −78 °C, 1 h	70	1:1	−/−
4	**6** (100)	CH_2Cl_2, −78 °C, 1 h	43	1:2	3/3
5	**1b** (5)	toluene, r.t., 24 h	62	1:5	−/65
6	**1c** (5)	toluene, r.t., 24 h	50	1:25	−/29

[a] The reactions were conducted with **2** and **3aa** in the presence of catalyst. [b] Isolated yield. [c] Determined by ^{1}H NMR (see the Supporting Information). [d] Determined by chiral GC.

acid catalyst on the diastereoselectivity, using either BF_3·OEt_2 as a monodentate Lewis acid or binaphthol-derived **6**[8] as a slightly bulkier catalyst (Table 1, entries 3 and 4). In both cases, diastereomeric mixtures of the products were obtained in moderate to good yields. More importantly, the reaction using **6** exhibited a slightly higher syn selectivity than that using BF_3·OEt_2. The resulting diastereoselectivities indicate that (i) the secondary π-orbital interactions are weak in the present hetero-Diels−Alder reaction and (ii) the steric demand of the catalyst seems to be the dominant factor in increasing the syn selectivity. To support these considerations, the diastereoselectivity was evaluated using the representative chiral phosphoric acids **1b** and **1c**, which possess bulkier aryl groups at the 3 and 3′ positions, thus constraining the area around the activation site (Table 1, entries 5 and 6). In each of these two cases, the *syn*-dihydropyran **5aa** was obtained as the major product, in accordance with the diastereoselectivity that was previously reported. The significant enhancement of the syn diastereoselectivities using **1b** and **1c** suggests that the substituents at the 3 and 3′ positions of the chiral phosphoric acid provide an important element of stereochemical control in the transition state (TS).

Among previously proposed mechanisms, although Mukaiyama aldol mechanism cannot be excluded completely, the differences in diastereoselectivities can be rationalized by TS structures via the concerted [4 + 2] cycloaddition mechanism (Scheme 1).[9] For **1b**- and **1c**-catalyzed reactions, the endo orientation of the diene to the aldehyde (TS1) is preferred over the exo orientation (TS2) because of the steric hindrance between the diene substituents and the bulky aryl groups of the catalyst around the activation site. For

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Scheme 1. Plausible Transition-State Structures

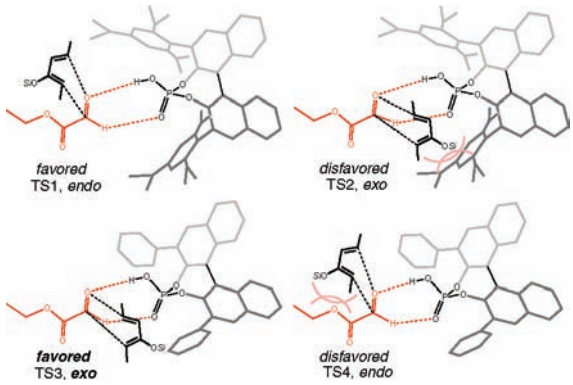
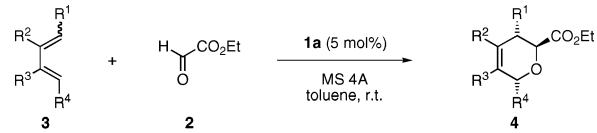
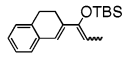


Table 2. Scope of Siloxy and Methoxy Dienes[a]



3a : R^2 = OTBS, **3b** : R^4 = OMe

entry	diene	yield, %[b]	*anti* : *syn*[c]	ee of **4**, %[d]
1	**3aa** : R^1 = Me, R^3 = H, R^4 = Me	95	>99 : 1	99
2	**3ab** : R^1 = H, R^3 = H, R^4 = Me	92	>99 : 1	98
3	**3ac** : R^1 = Me, R^3 = H, R^4 = Ph	92	>99 : 1	97
4	**3ad** : R^1 = Me, R^3 = H, R^4 = -CH=CHMe	75	>95 : <5	99
5	**3ae** : R^1 = *n*-Pr, R^3 = H, R^4 = Ph	90	>99 : 1	98
6	**3af** : 	56	79 : 21	99
7	**3ba** : R^1 = H, R^2 = H, R^3 = H	84	93 : 7	98
8	**3bb** : R^1 = Me, R^2 = H, R^3 = H	93	91 : 9	99
9	**3bc** : R^1 = Me, R^2 = H, R^3 = Me	51	94 : 6	95
10	**3bd** : R^1, R^2 = -$(CH_2)_4$- R^3 = H	75	95 : 5	97

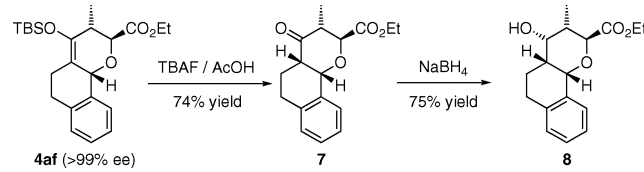
[a] The reactions were conducted with **2** and **3** in the presence of 5 mol % **1a**. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Determined by chiral GC or HPLC (see the Supporting Information).

the **1a**-catalyzed reaction, the much smaller phenyl groups at the 3 and 3′ positions of **1a** allow the dienes to occupy an exo orientation (TS3). The endo selectivity (TS4) is not favorable because of the steric repulsion between the diene substituents and glyoxylate **2**.

The scope of the anti-diastereoselective and enantioselective reaction was investigated under optimized reaction conditions (Table 2). In general, the siloxydienes provided the desired adducts in high yields with excellent enantioselectivities and anti-diastereoselectivities (entries 1−3 and 5). The alkenyl-substituted siloxydiene resulted in a decrease in reactivity, although high stereoselectivity was maintained (entry 4). Furthermore, methoxydienes (**3b**) were also well-tolerated, providing the corresponding *anti*-dihydropyrans **4** predominantly with excellent enantioselectivities (entries 7−10).

Dihydropyran **4af** can also function as an excellent substrate for enolate-based stereoselective transformations (Scheme 2). **4af** was selectively protonated using acetic acid to afford the 5,6-*anti*-ketone

Scheme 2. Stereoselective Elaboration of Dihydropyrans



4af (>99% ee) **7** **8**

7. Reduction of **7** with $NaBH_4$ afforded the 3,4-*syn*-alcohol **8** with excellent diastereoselectivity. No loss of stereochemical integrity was observed during any of these processes.

In summary, we have developed a chiral phosphoric acid-catalyzed completely enantioselective and anti-diastereoselective hetero-Diels−Alder reaction of ethyl glyoxylates that displays a wide substrate scope for a series of siloxy- and methoxydienes. The diastereoselectivities presented are disparate to those previously reported for hetero-Diels−Alder reactions catalyzed by a chiral Lewis acid. The method described herein provides a practical approach for the stereoselective construction of dihydropyran derivatives. Further mechanistic studies regarding these stereochemistries are ongoing and will be reported in due course.[10]

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Supporting Information Available: Experimental details, characterization data, GC and HPLC enantiomer analysis, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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