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$B(C_6F_5)_3$: A New Class of Strong and Bulky Lewis Acid for *Exo*-Selective Intermolecular Diels–Alder Reactions of Unreactive Acyclic Dienes with *α,β*-Enals

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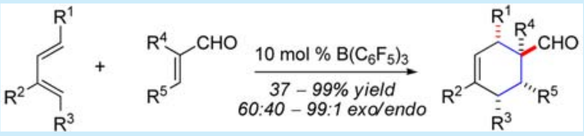
Supporting Information

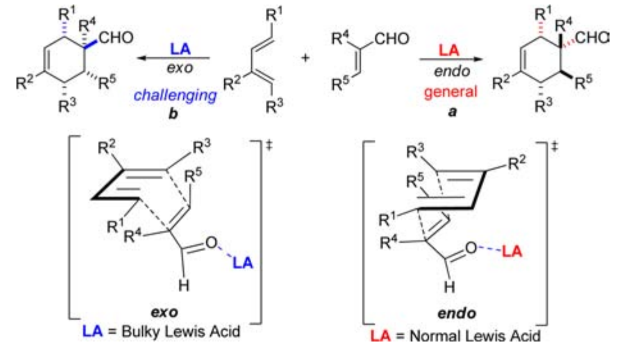
ABSTRACT: Lewis acid $B(C_6F_5)_3$ catalyzed the Diels–Alder reactions of multisubstituted open-chain dienes and *α,β*-enals to afford the desired products with high *exo*-selectivities are reported. The substituent effect of the dienes and dienophiles on the product's stereoselectivity was thoroughly investigated, and it was found that most of the desired *exo*-Diels–Alder products could be obtained in good yields and with high *exo*-stereoselectivities.



The Lewis acid catalyzed intermolecular Diels–Alder (DA) reaction is one of the most important organic transformations in organic synthesis as it provides one of the most efficient entries to six-membered ring-containing compounds.[1] Due to the many methods available for the control of relative and absolute stereochemistries, this method is now widely used for the construction of complex natural products and pharmaceuticals.[2] Despite the fact that it is often employed in organic synthesis, there are still reactivity and selectivity problems associated with the less reactive multisubstituted open-chain dienes.[3] In most cases, the *endo*-selective products were obtained as the major products due to favorable secondary orbital interactions.[4] Therefore, a major challenge in this area is the design of a general method to obtain the highly *exo*-selective DA reaction for this type of system that can lead to different stereochemical control in the resulting products (Scheme 1).[5]

Except for a few special cases of Diels–Alder reactions that employed highly reactive dienes such as cyclopentadienes,[6] 1-amino-3-siloxy dienes,[7] Danishefsky dienes,[8] silyloxy dienes,[9] silylated dienes,[10] or bulky dienes[11] with dienophiles such as carbene complexes,[12] highly substituted dienophiles,[13] to the best of our knowledge, the intermolecular *exo*-selective DA reactions of unreactive simple open-chain dienes with *α,β*-unsaturated enals have rarely been reported.[9,14] The need to use special substrates such as reactive dienes as well as poor selectivities observed in some of these cases highlight the huge potential for further development in this field.

Scheme 1. Diels–Alder Reaction of Open-Chain Dienes and Enals



Therefore, there is a need to discover a new and more reactive catalyst that can catalyze the *exo*-DA reaction of less reactive open-chain dienes and dienophiles. We envisage that a bulky Lewis acid will steer the reaction to the *exo* pathway instead of the usual *endo* pathway due to unfavorable steric repulsion between the Lewis acid and the diene. On the basis of this thinking, we embarked on the search for highly *exo*-selective intermolecular Diels–Alder reaction using open-chain dienes and simple *α,β*-unsaturated enals as dienophiles.

Initial screening of the reaction using diene **1a** with the easily accessible *E*-isomer of dienophile **2a** (Table 1) revealed that when a variety of common Lewis acids such as $In(OTf)_3$, $InBr_3$, $FeCl_3$, $Sc(OTf)_3$, and $Yb(OTf)_3$ were employed (Table 1, entries 1–5), no reaction was observed. On the other hand, using the more reactive Lewis acids such as $BF_3{\cdot}OEt_2$, $SnCl_4$,[15] and $AlCl_3$ led to the formation of the desired products in low to moderate to good yields. As expected, the *endo*-selective [4 + 2] Diels–Alder product was obtained as the major product. To test our hypothesis using bulky Lewis acid, we first explored the use of bulky aluminum tris(2,6-diphenylphenoxide) (ATPH) as catalyst as previously reported by Yamamoto. While this catalyst works with reactive dienes, no reaction was observed in

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Table 1. Diels–Alder Studies Using Different Lewis Acids[a,b]

entry	Lewis cid	yield (%) (**3aa**:**3aa′**:**3aa″**)[c]
1	$In(OTf)_3$	
2	In Br_3	
3	$FeCl_3$	
4	$Yb(OTf)_3$	
5	$Sc(OTf)_3$	
6	ATPH[6b]	
7	$SnCl_4$	65 (29:57:14)
8	$AlCl_3$	23 (30:70:0)
9	BF_3 OEt_2	99 (0:24:76)
10	$B(C_6F_5)_3$	80 (88:12:0)[d]; 73[e]; 55[f]

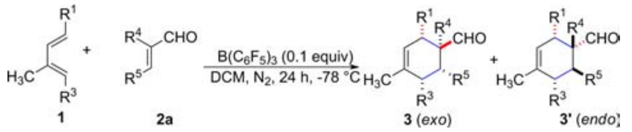
[a] Diels–Alder reactions were run with 0.5 equiv of Lewis acid, 1 equiv of dienophile (0.2 mmol), and 2.0 equiv of diene (0.4 mmol) under N_2 atmosphere at −78 °C. [b] Isolated yield of *exo* and *endo* isomers. [c] Diastereomeric ratios were based on ^1H and ^{13}C NMR analysis. [d] 88:12 dr ratio of **3aa** and **3aa′** was determined from the crude ^1H NMR spectra of the reaction. [e,f] Conversion yield determined according to ^1H NMR spectra analysis (0.2 equiv and 0.1 equiv of $B(C_6F_5)_3$ was used, respectively).

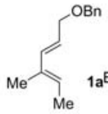
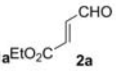
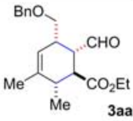
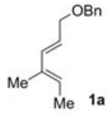
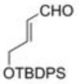
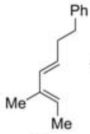
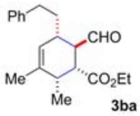
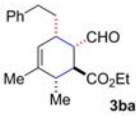
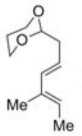
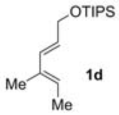
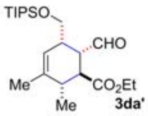
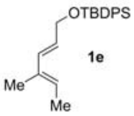
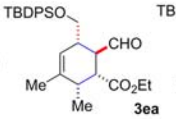
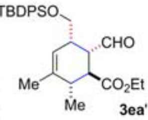
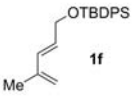
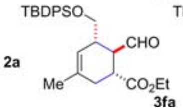
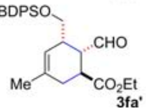
this DA reaction with open-chain dienes even when a stoichiometric amount of the Lewis acid was used. Therefore, a more reactive bulky Lewis acid is needed to effect this transformation. We decided to explore the use of $B(C_6F_5)_3$, a bulky Lewis acid used widely in the synthesis of frustrated Lewis pairs (FLP).[16] To our delight, *exo*-selective compound **3aa** could be obtained as the major product in high yield when 50 mol % of $B(C_6F_5)_3$ was used in this reaction (Table 1, entry 10).

With this exciting discovery, we then turned our attention to investigate the substituent effect of the dienophiles and dienes.[17] It was found that no desired product could be detected when the bulky silyl-protected enal **2b** was applied in the reaction (Table 2, entry 2). In addition, in the case of diene **1b**, with a linear alkyl-substituted diene, a good yield with a dominant *exo*-selective isomer could be obtained under the standard reaction conditions (Table 2, entry 3). The diene with an acetal protecting group resulted in a mixture of *exo*- and *endo*-selective products in 37% yield and with a 60/40 ratio (Table 2, entry 4). Further screening showed that when the diene's protecting group was changed to a triisopropylsilyl group, the product of **3da** was obtained in high yield and with good *exo* stereoselectivity (Table 2, entry 5). To our delight, excellent yield and *exo*/*endo* stereoselectivity of the DA product could be observed when the *tert*-butyldiphenylsilyl was applied as the protecting group (Table 2, entry 6). It was also noted that the removal of the methyl group at the C-1 position of the diene would slightly decrease the product's *exo*/*endo* stereoselectivity (Table 2, entry 7).

Further exploration of the substrate scopes using various dienes and dienophiles were carried out (Figure 1). We are pleased to find that all of the reactive β-substituted enals and multisubstituted dienes worked well to afford the desired products in moderate to good yields. First, different substituted enals were tested as the dienophiles. Comparing the results, it was found that the enals with electron-deficient substituents at the β-position (Figure 1, **3ea**) could react easily in the DA reaction. However, only moderate yields but high *exo*-selectivities of the desired products could be obtained by using enals with an electron-rich group (Figure 1, **3ed**). Moreover, the α,α,β-trisubstituted enal with a more bulky protecting group also can be used in the DA cycloaddition reaction to give the corresponding product **3ag** (the relative configuration was determined by X-ray crystallographic analysis) in an acceptable yield. Next, various dienes were also synthesized and examined in this reaction. It was observed that the dienes with linear alkyl or alkenyl substituents all could afford the products in high yields with high selectivities when reacted with enal **2a** (Figure 1, **3ga**, **3ha**, **3ia**, **3ja**, and **3ka**). Furthermore, the replacement of the 2-Me on the diene with phenyl group (Figure 1, **3ma** and **3na**) led to significantly decreased yields but without damaging the *exo*-selectivities of the products (the relative configuration of **3ma** was determined by X-ray crystallographic analysis).

Table 2. Substituent Effect of Diene in Diels–Alder Reaction Catalyzed by $B(C_6F_5)_3$[a]



entry[a]	diene	dienophile	exo	endo	yield/%[b]
1	 **1a**	 **2a**	 **3aa**	 **3aa'**	55[d] **3aa**:**3aa'** (87:13)[c]
2	 **1a**	 **2b**	—	—	NR
3	 **1b**	**2a**	 **3ba**	 **3ba'**	50 **3ba**:**3ba'** (67:33)[c]
4	 **1c**	**2a**	 **3ca**	 **3ca'**	37 **3ca**:**3ca'** (60:40)[c]
5	 **1d**	**2a**	 **3da**	 **3da'**	84 **3da**:**3da'** (88:12)[c]
6	 **1e**	**2a**	 **3ea**	 **3ea'**	99 **3ea**:**3ea'** (94:6)[c]
7	 **1f**	**2a**	 **3fa**	 **3fa'**	90 **3fa**:**3fa'** (81:19)[c]

[a] Diels–Alder reactions were run with 0.1 equiv of $B(C_6F_5)_3$, 1 equiv of dienophile (0.2 mmol), and 2.0 equiv of diene (0.4 mmol) in DCM under N_2 atmosphere at −78 °C for 48 h. [b] Isolated yield of *exo* and *endo* isomers. [c] Diastereomeric ratios were based on ^1H NMR analyses. [d] Conversion yield was determined according to ^1H NMR spectral analysis.

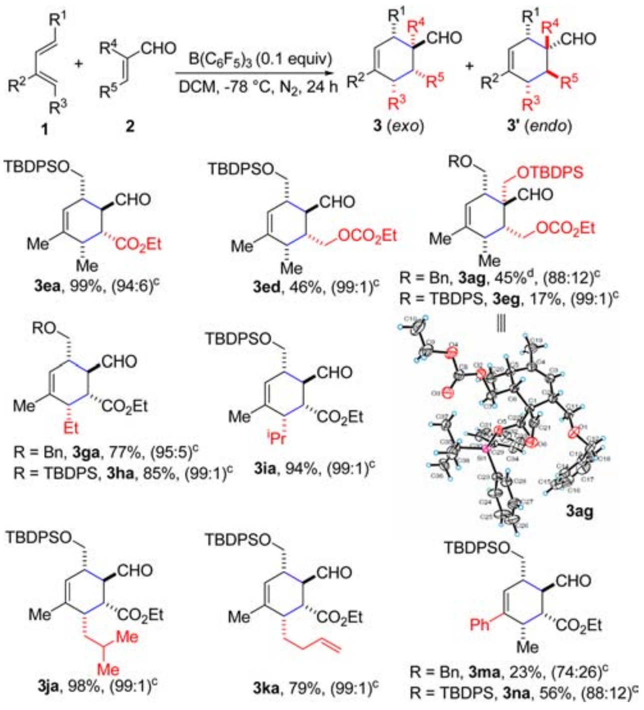
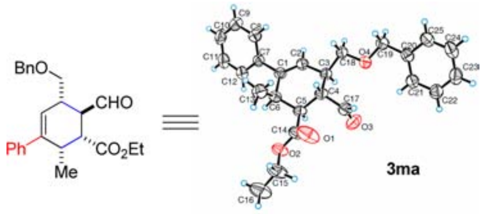


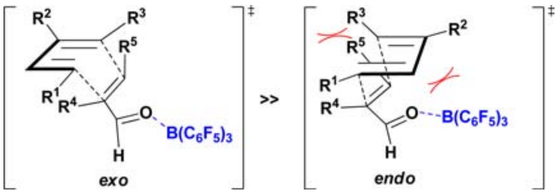
Figure 1. Multisubstituted open-chain dienes and dienophiles in Diels−Alder reactions catalyzed by $B(C_6F_5)_3$. (a) Diels−Alder reactions were run with 0.1 equiv of $B(C_6F_5)_3$, 1 equiv of dienophile (0.2 mmol), and 2.0 equiv of diene (0.4 mmol) under N_2 atmosphere for 48 h. (b) Isolated yield of *exo* and *endo* isomers. (c) Diastereomeric ratios were based on ^{1}H NMR analysis. (d) Diels−Alder reactions were run with 0.5 equiv of Lewis acid.



The remarkable *exo*-selectivities of the products in this reaction may be due to the steric interaction between the bulky Lewis acid $B(C_6F_5)_3$ with the dienes as well as the interaction between the substituents R_5 and R^5 that it disfavors the *endo* transition state, which has been well discussed by Gouverneur and Houk (Scheme 2).[10]

In conclusion, we have developed a $B(C_6F_5)_3$-catalyzed *exo*-Diels−Alder reaction utilizing common multisubstituted open-chain dienes and dienophiles to construct six-membered ring systems with high *exo*-stereoselectivity. This study provides a direct and simple method for the synthesis of a series of *exo*-selective DA products. The use of $B(C_6F_5)_3$ as a reactive bulky Lewis acid to effect abnormal selectivity in other organic transformations as well as application of this *exo*-Diels−Alder reactions for the synthesis of complex molecules are in progress.

Scheme 2. Transition States for $B(C_6F_5)_3$-Catalyzed *exo*-Diels−Alder Reaction



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02066.

Experimental procedures and spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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