Organic LETTERS

Letter

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Anomalous Reactivity and Selectivity in the Intermolecular Diels–Alder Reactions of Multisubstituted Acyclic Dienes with Geometrical Isomers of Enals

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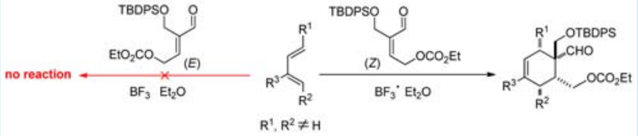
Supporting Information

ABSTRACT: A Lewis-acid catalyzed intermolecular Diels–Alder reaction between multisubstituted acyclic dienes and the *E* and *Z* isomers of *α*,*β*-enals was studied. It was found that the diene reacted selectively with the *Z*-isomer of the *α*,*β*-enal.



The intermolecular Diels–Alder reaction is probably one of the most efficient methods for the construction of six-membered rings.[1] Due to its predictable regioselectivity and highly stereoselective and convergent manner, the intermolecular Diels–Alder has been employed extensively for the construction of 6-membered ring containing natural products.[2] Furthermore, highly enantioselective methods using chiral catalysts have also emerged in recent years.[3] Surprisingly, detailed studies of the scope and limitations of the intermolecular version of Diels–Alder reaction employing highly substituted acyclic dienes and dienophiles are lacking.[4] In connection with our interest in the design of a general strategy for the total synthesis of cytochalasins,[5] the synthesis of a common advanced intermediate **3** via a Lewis acid-catalyzed intermolecular Diels–Alder reaction was desirable. We envisage that **3** could be obtained from a Diels–Alder reaction between highly functionalized acyclic diene **1** and dienophile **2**. If successful, this method provides an attractive strategy in controlling the stereochemistry of four of the six potential stereogenic carbon centers on the cyclohexane ring. However, during the course of this study, we found that this reaction diverges from the normal DA reaction in terms of

Scheme 1. Study of the Diels–Alder Reactions between Acyclic Dienes and Enals

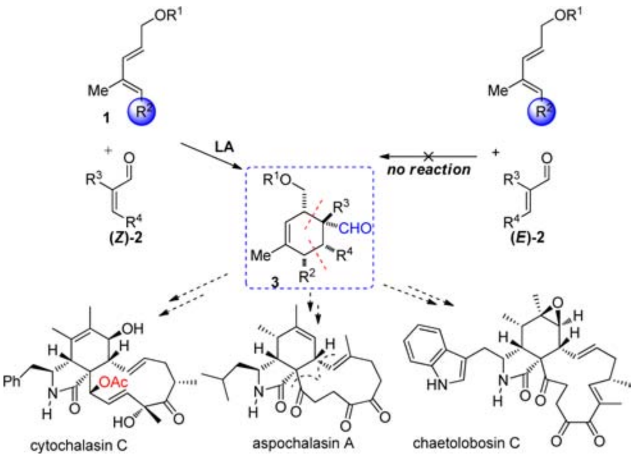
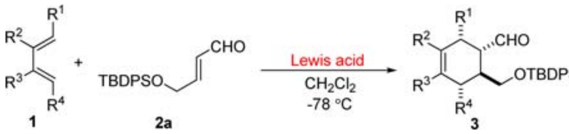
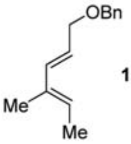
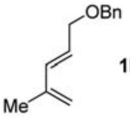
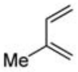
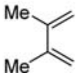


Table 1. Diels–Alder Reaction between Different Dienes and *trans*-Dienophile 2a Catalyzed by Lewis Acid[a]



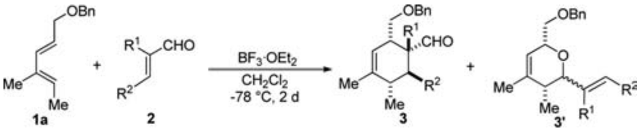
entry	diene		LA	yield (%)[b]	dr[c]
1		**1a**	$BF_3·OEt_2$ $SnCl_4$ $AlCl_3$ $In(OTf)_3$ $Sm(OTf)_3$ seal tube	n.r	—
2		**1b**	$BF_3·OEt_2$	76	> 99:1
3		**1c**	$BF_3·OEt_2$	84	> 99:1
4		**1d**	$BF_3·OEt_2$	85	--

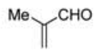
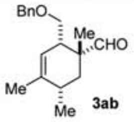
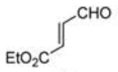
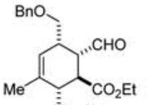
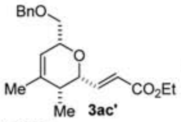
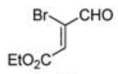
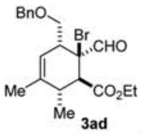
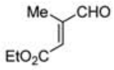
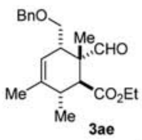
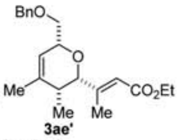
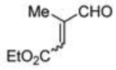
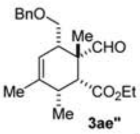
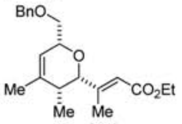
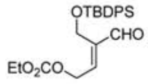
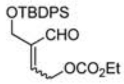
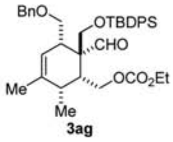
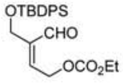
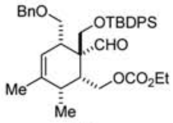
[a]Diels–Alder reactions were run with 0.1 equiv of $BF_3·OEt_2$, 1 equiv of dienophile **2a**, and 2 equiv of diene **1** at −78 °C under N_2 atmosphere. [b]Isolated yield. [c]Diastereomeric ratios were based on ^1H and ^{13}C NMR analysis.

Received: March 17, 2016
Published: May 2, 2016

DOI: 10.1021/acs.orglett.6b00783

Table 2. $BF_3 \cdot OEt_2$ Catalyzed Diels–Alder Studies Using Acyclic Diene 1a with Different Dienophile[a,b,c]



entry	dienophile	product		yield (%)	dr
1	 **2b**	 **3ab**		85	3ab (91:9)
2	 **2c**	 **3ac**	 **3ac'** 3ac:3ac' (25:75)	88	3ac (> 99:1) 3ac' (> 99:1)
3	 **2d**	 **3ad**	 **3ad'** 3ad:3ad' (33:67)	60[d]	3ad (69:31) 3ad' (70:30)
4	 **2e**	 **3ae**	 **3ae'** 3ae:3ae' (< 1:99)	38	3ae' (> 99:1)
5	 *Z*:*E* = 21:79	 **3ae''**	 **3ae'** 3ae'':3ae' (27:73)	54[d]	3ae'' (71:29) 3ae' (> 99:1)
6	 **2f**	—		—	
7	 *Z*:*E* = 40:60	 **3ag**		30	89:11
8	 **2g**	 **3ag**		95	88:12

[a] Diels–Alder reactions were run with 0.1 equiv of $BF_3 \cdot OEt_2$, 1 equiv of dienophile **2**, and 2 equiv of diene **1a** at −78 °C under N_2 atmosphere. [b] Isolated yield. [c] Diastereomeric ratios were based on ^1H and ^{13}C NMR analysis. [d] 0.5 equiv of Lewis acid was used.

reactivity and regioselectivity and proves more difficult than we had anticipated. In this letter, we report that the (*Z*)-geometrical isomer of the dienophile is more reactive than the (*E*)-isomer in the Lewis acid catalyzed intermolecular Diels–Alder reaction using multisubstituted acyclic dienes (Scheme 1).

First, we initiated our study by employing multisubstituted diene **1a** with the easily accessible *E*-isomer of dienophile **2a**, catalyzed by common Lewis acids (Table 1). Unfortunately, no reaction was observed when common Lewis acids ($SnCl_4$, $AlCl_3$, $In(OTf)_3$, and $Sm(OTf)_3$) were employed. In addition, carrying out the reaction in a sealed tube (toluene as solvent) was also unsuccessful. To probe the sluggishness of the reaction, we carried out the $BF_3 \cdot Et_2O$-catalyzed Diels–Alder reaction of *E*-**2a** using simpler terminal dienes such as **1c** and **1d** (entries 3 and 4). Interestingly, in both cases the desired normal Diels–Alder products were obtained in high yields. Moreover, acyclic dienes such as **1b** substituted one site also can afford good yield (entry 2), indicating how to catalyze inactive multisubstituted acyclic dienes with easy Lewis acid is still a great challenge.[6]

Next, we explored the Diels–Alder reaction of diene **1a** using various dienophiles in the presence of $BF_3 \cdot OEt_2$ as Lewis acid. The results are summarized in Table 2. As shown in Table 2 (entry 1), the reaction with methacrolein **2b** proceeded nicely to afford the *endo*-product in high yield with excellent *endo*-stereoselectivity. On the basis of the results from Table 1 and Table 2 (entry 1), we can conclude that the presence of substituents at the 4-position of the diene and the *β*-substituent of enal at the same time would reduce the reactivity of the Diels–Alder reaction. Therefore, for the Diels–Alder reaction of **1a** to react, a more reactive dienophile will be required. Inspired by the work of Corey,[7] we reacted aldehyde-ester dienophile **2c** with diene **1a** and we were rewarded with an unexpected outcome. Along with a normal Diels–Alder reaction, hetero-Diels–Alder reaction proceeded to generate 3,6-dihydro-2*H*-pyran derivative **3ac′** in high yield with good diasteroselectivity (Table 2, entry 2).[8] This accidental discovery provided a possible entry to highly functionalized *syn*-THP system (refer to Supporting Information for the determination of stereochemistry). Interestingly, when bromo- or methyl-substituted aldehyde-ester dienophile was employed, hetero-Diels–Alder reaction was favored but a decreased yield of the product was observed (Table 2, entry 3 and 4, respectively). Unfortunately, the Diels–Alder reaction did not proceed at all when the dienophile *E*-**2f** was used. The dienophile was completely recovered, while the diene was destroyed in the reaction (Table 2, entry 6). To our surprise, when the mixture of *Z*/*E* isomers of **2f** and **2g** was subjected to 2 equiv of diene, only *Z*-isomer **2g** took part in the Diels–Alder reaction.

E isomer remained unconsumed (Table 2, entry 7). The relative stereochemistries were confirmed by 2D NOESY experiments. When pure *Z*-isomer **2g** was used in the $BF_3 \cdot OEt_2$ catalyzed DA reaction, the desired *endo*-selective cyclization product **3ag** could be obtained in a high yield and good stereoselectivity (95% yield and 88:12 *endo*/*exo* stereoselectivity) (Table 2, entry 8; Figure 1). These results clearly suggest that the geometrical isomers of the dienophiles have different reactivity. The isomer with the aldehydic functionality cis to the *β*-substituent of the dienophile could afford the desired Diels–Alder cycloadducts. However, the

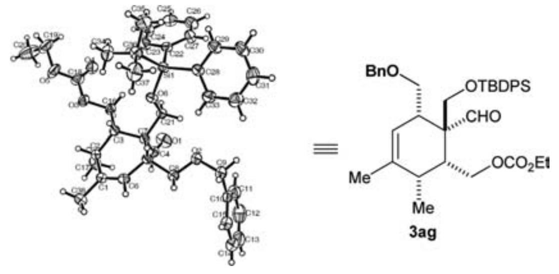
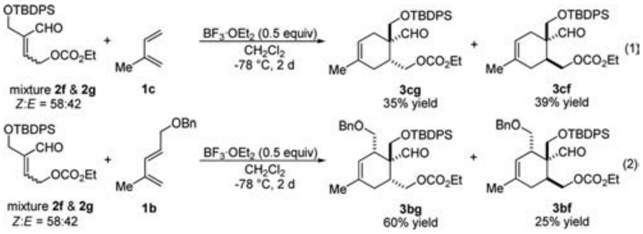


Figure 1. ORTEP Drawing of **3ag** with 30% thermal ellipsoids.

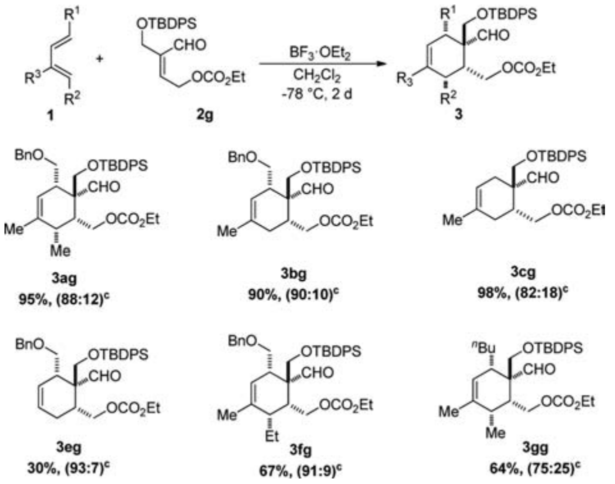
isomer with the aldehydic group trans to the β-substituent either gave the hetero-Diels−Alder product or was inert to the reaction.

Further investigations on different dienes reacting with the *Z*/*E* mixture of isomers **2f** and **2g** were carried out. It was noticed that the simpler acyclic diene could easily react with the dienophile regardless of the geometry of enals (eq 1). The substituent's effect of dienes also could be observed that the dienophile **2g** with *cis*-configuration more favored the transformation of the bulkier diene into the corresponding cyclization product (eq 2).



Therefore, various acyclic dienes were subjected to react with the *Z*-isomer dienophile **2g.** The results are summarized as shown in Scheme 2. Both simpler and multisubstituted dienes could react well with **2g** to furnish the desired products in excellent yields and high stereoselectivities. The effect of terminal substituents of the diene has also been screened. It was noted that the bulky group will diminish the product's yield significantly (Scheme 2, **3fg**). The good stereoselectivity of this reaction by using *Z*-configuration dienophiles could be rationalized by the less steric hindrance between the substituents R^2 on diene and R^5 on dienophile compared with the case of using *E*-configuration dienophiles (Scheme 3). It was noticed that only 30% yield of product **3eg** could be obtained when the unsubstituted diene was applied as the substrate in reaction. This was possibly caused by its difficulty in conversion into the s-*cis*-1,3-diene.

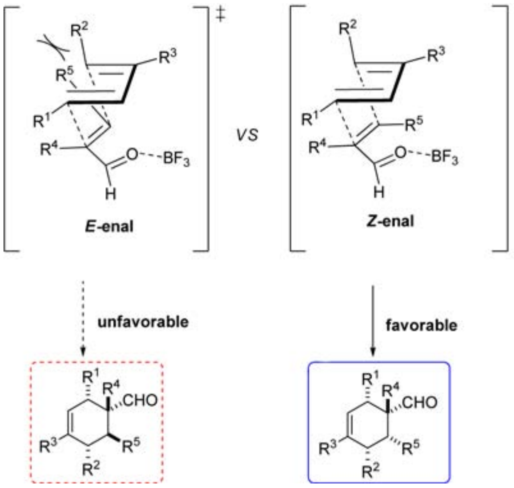
Scheme 2. Intermolecular Diels−Alder Reaction between Multisubstituted Acyclic Dienes and *cis*-Dienophile 2g Catalyzed by $BF_3{\cdot}OEt_2$[a,b,c]



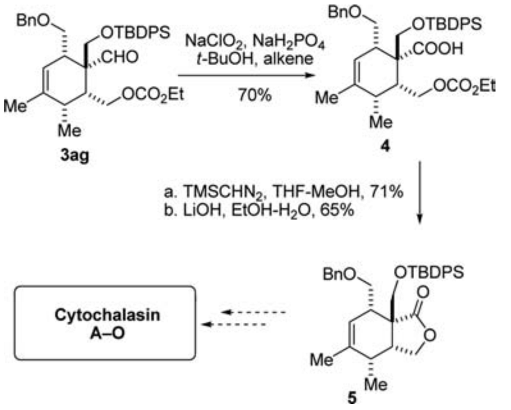
[a] Diels−Alder reactions were run with 0.1 equiv of $BF_3{\bullet}OEt_2$, 1 equiv of **2g**, and 2 equiv of diene **1** under N_2 atmosphere. [b] Isolated yield. [c] Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses.

The synthetic utility of the Lewis acid catalyzed Diels−Alder reaction using structurally complex dienes and dienophiles clearly demonstrated the versatility of our system in the construction of key intermediates **5** for cytochalasins synthesis as shown in Scheme 4.[9] The cycloadduct **3ag** could be utilized for further transformation to the compound **5** in a high yield.

Scheme 3. Insight of the Mechanism of the Diels−Alder Reaction



Scheme 4. Synthesis of Key Intermediate 5 for Natural Product Cytochalasins



In conclusion, we have developed a Lewis acid catalyzed intermolecular Diels−Alder reaction utilizing acyclic multifuctionalized diene and *Z*-enals to construct the six-membered ring systems. It was surprising to find that the *Z*-enals was more reactive than the *E*-enals in this system. This finding provides useful information for synthetic chemists interested in the use of Diels−Alder reaction for the construction of complex molecules and pharmaceuticals. The application of this method for the synthesis of complex molecules is in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00783.

Experimental procedures and spectral data for all new compounds (^1H NMR, ^{13}C NMR, HRMS)(PDF)
Crystallographic data of compound **3ag** (CCDC 1468127) (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (21372210) and the State Key Program of National Natural Science Foundation of China (21432009).

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DOI: 10.1021/acs.orglett.6b00783
Org. Lett. 2016, 18, 2355−2358