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Asymmetric Diels–Alder reaction between furans and propiolates

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ABSTRACT

We report the first asymmetric Diels–Alder reaction between furan and propiolates. Propiolate, a dienophile, was equipped with an Evans' auxiliary and a sulfonyl group to control and facilitate diastereoselective cycloaddition. Treatment with furan as a diene and aluminium Lewis acid afforded a 7-oxabicyclo[2.2.1]heptadiene skeleton diastereoselectively. The origin of diastereoselectivity can be explained by chelation of aluminium center to carbonyl groups and oxygen of furan. Friedel–Crafts-type products were obtained when pyrrole was used as diene.

Introduction

Enantioselective Diels–Alder reactions have been developed using either chiral auxiliaries [1] or asymmetric catalysts [2,3]. In particular, when an enone and a cyclic diene are used, bicyclic Diels–Alder adducts can be obtained with good stereoselectivity [4–6]. Secondary orbital interaction [7] limits the direction from which the diene approaches, thus single adduct can obtained if face-selectivity is achieved. Four stereogenic centers are constructed in a single reaction as shown in Scheme 1A.

In contrast to the alkene-diene Diels–Alder reaction, the Diels–Alder reaction between an *alkyne* and diene remains underdeveloped. The most important reason for this is the difficulty of stereochemical control. Unlike the case of enones described above, an alkyne has two degenerated π-orbitals distributed uniformly around its sp-hybridized carbons, meaning that there is no face or planarity (Scheme 1B). This leaves no means for stereochemical control based on the approach of the diene. To our knowledge, there are limited examples of diastereo- or *enantio*-controlled Diels–Alder reactions between an alkyne and diene [8–23]. Although asymmetric metal-catalyzed formal [4 + 2] cycloaddition reactions using alkynes and linear dienes have been also developed [24–30], there have been no example of constructing a bridged bicyclic skeleton by this method so far.

The bicyclo[2.2.1]heptadiene skeleton is one of the adducts of a Diels–Alder reaction between an alkyne and cyclic diene. Here, if the two olefins are non-uniformly substituted, the bridgehead carbons become chiral centers, giving a possible pair of enantiomers. Yet, despite extensive reports of the asymmetric synthesis of the corresponding bicycloheptene core [4–6,31–35], enantioselective synthesis of the bicycloheptadiene core by Diels–Alder reaction has been a difficult task.

In particular, 7-oxabicyclo[2.2.1]heptadiene, which can be prepared by Diels–Alder reaction between an alkyne and furan, has recently garnered much attention. The oxabicycloheptadiene skeleton has been extensively studied as a chemical probe for thiols [36–43]. Although bicycloheptadiene skeletons are stable under normal conditions, thiol adducts can induce a controllable *retro*-Diels–Alder reaction (Scheme 1C). However, racemic mixtures have been used for this research, and the reactivity of the individual enantiomers has not been discussed. Considering the three-dimensional structures of bioactive proteins and peptides, an enantioselective supply of this skeleton would be beneficial for further fine-tuning the characteristics of the *retro*-Diels–Alder reaction.

This bicycloheptadiene skeleton is also an attractive starting point for constructing complex polycyclic structure. After the appropriate introduction of substituents, the *endo*-cis-disubstituted bicycloheptadiene would be obtained by chemoselective functionalization of the resultant Diels–Alder adduct. This partial structure can be found in a number of acetogenin natural product such as maneonenes (Scheme 1D) [44,45]. Although a *trans*-disubstituted [46] or *exo*-cis bicyclic core [47–50] can be obtained with good selectivity in a few steps, the enantioselective synthesis of the *endo*-cis bicyclic skeleton has so far been limited to enzymatic desymmetrization after saturation of a double bond, reduction, and acylation [51–53]. Herein, we report the first example of an intermolecular asymmetric Diels–Alder reaction between propiolates and furans.

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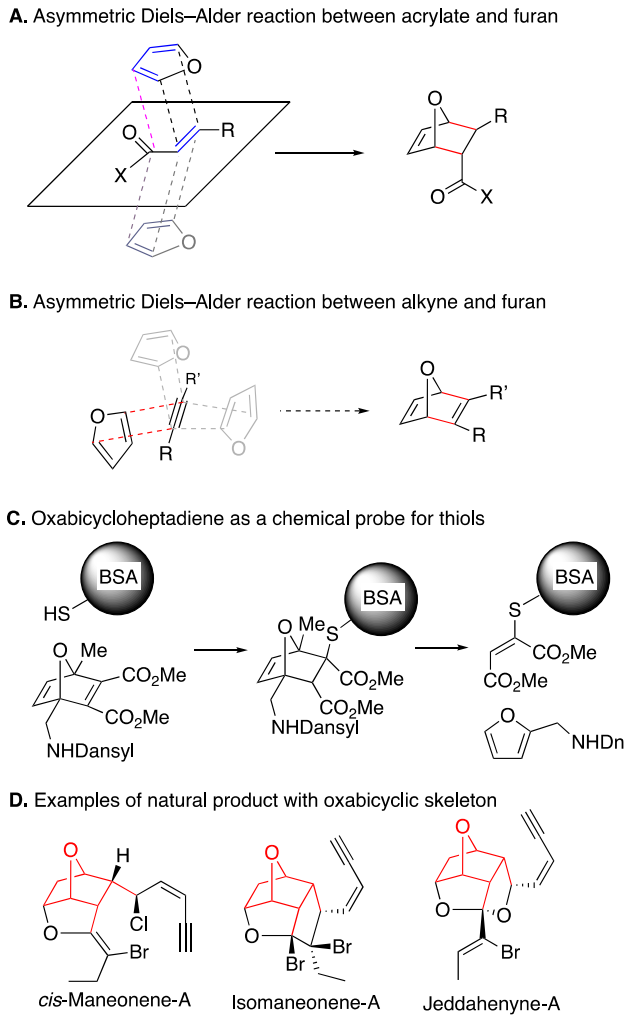


Scheme 1. Synthesis and applications of the oxabicycloheptadiene core.

Result and discussion

Sulfonylated propiolamide was selected as a substrate and subjected to the Diels–Alder reaction with furan. Conjugation with a carbonyl group and a sulfonyl group was considered beneficial for promoting the Diels–Alder reaction while also distinguishing the two resultant sp^2 carbons [54]. Introduction of the carbonyl group was also advantageous because the LUMO of the dienophile is fixed orthogonal to the carbonyl-alkyne plane (Fig. 1A) [15]. Several attempts have been made to use asymmetric catalysts, but they did not achieve asymmetric induction. We attributed this to the spatial distance between the carbonyl group and the alkyne. Unlike acrylates, the alkyne is directed away from the carbonyl group, which is the coordination center for the catalyst [13]. Therefore, we decided to utilize a chiral oxazolidinone-based approach by Evans [23,55], anticipating that the auxiliary would cover the chemical space far from the carbonyl group (Fig. 1B).

The synthesis of the substrate is shown in Scheme 2. Protected propiolic acid **1** was condensed with valine-derived oxazolidinone **2** [55] to afford protected propiolamide **3**. Removal of the terminal silyl group followed by terminal phenylthiolation provided sulfide **4**. Subsequent oxidation afforded substrate **5**. Other substrates with various pendant groups were prepared similarly from known chiral auxiliaries [56–62].

With substrates in hand, we next turned to optimizing the reaction conditions (Table 1). Substrate **5** was treated with furan and a

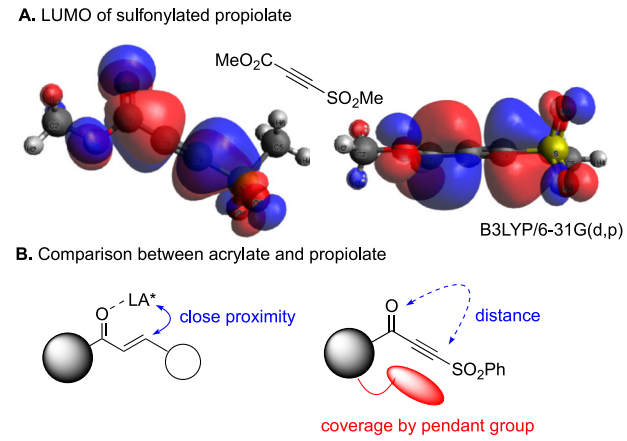
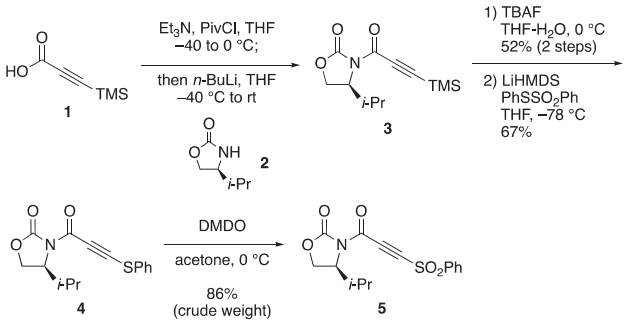
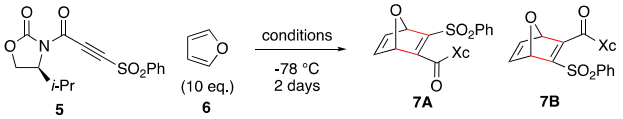


Fig. 1. Characteristics of propiolates.



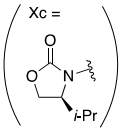
Scheme 2. Preparation of substrate.

Table 1
Optimization of reaction conditions.



entry	Lewis acid	eq.	solvent	conc.	yield[a]	A : B
1	none	–	CH_2Cl_2	0.1 M	31%	1 : 1
2	$TiCl_4$	5.8	CH_2Cl_2	0.1 M	decomp.	–
3	$Cu(OTf)_2$	2.0	CH_2Cl_2	0.1 M	53%	1 : 1
4	$AlCl_3$	2.0	CH_2Cl_2	0.1 M	77%	1 : 1
5	$AlCl_3$	2.0	tolulene	0.1 M	68%	1 : 1
6	$AlCl_3$	2.0	THF	0.1 M	58%	1.2 : 1
7	$AlCl_3$	2.0	Et_2O	0.1 M	51%	3 : 1
8	$AlCl_3$	0.5	Et_2O	0.1 M	54%	1.2 : 1
9	$AlCl_3$	2.0	Et_2O	0.5 M	48%	2 : 1
10	$AlCl_3$	2.0	Et_2O	0.01 M	57%	6 : 1

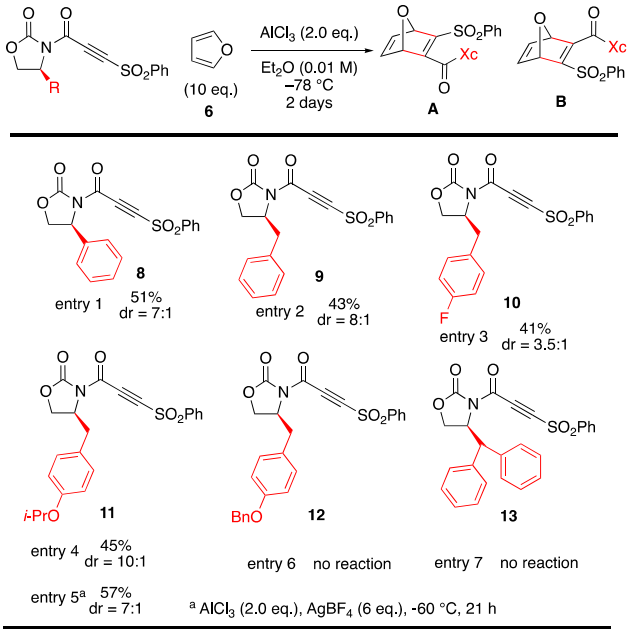
Xc =



Lewis acid, and the expected Diels–Alder reaction products **7A** and **7B** were obtained (entries 1–4). Although diastereoselectivity was not observed, use of aluminum chloride as the Lewis acid gave the highest yield (entry 4). Solvent screening revealed that moderate stereoselectivity could be achieved in ethereal solvent (entries 5–7). Although usage of substoichiometric amount of the Lewis acid deteriorated the selectivity (entry 8), a dilution improved the selectivity (entries 9 and 10).

Having optimized the reaction conditions, effects of the pendant group were investigated (Table 2). Bulkier substituents gave

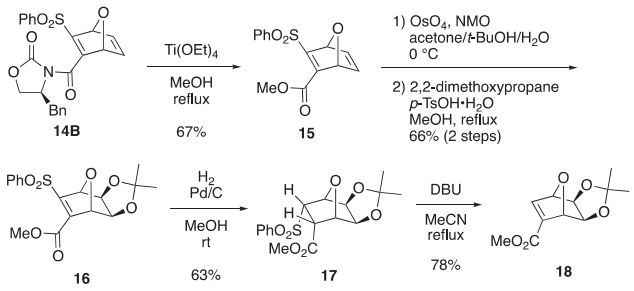
Table 2
Optimization of the pendant group.



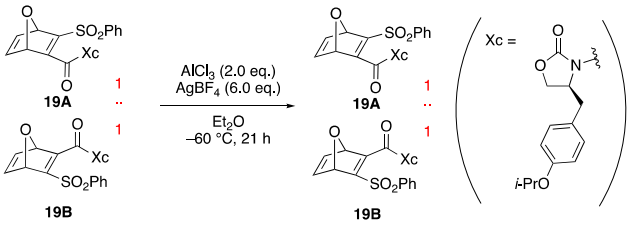
higher diastereoselectivity, accompanied by a slight decrease in yield. Phenylglycine or substituted phenylalanine derivatives generally gave good results (entries 1–5), and an electron-donating group further improved the selectivity. The best diastereoselectivity was achieved with isopropylated tyrosine derivative **11**, which gave a satisfactory dr of 10:1 (entry 4). Use of silver tetrafluoroborate as an additive prevented Michael addition of chloride ion to alkyne moiety and improved yield, but slightly lowered dr (entry 5). Notably, the bulkier substituents benzyloxybenzyl and diphenylmethyl substitution completely inhibited the reaction (entries 6 and 7).

The auxiliary can be removed in a single step. For example, **14B**, a minor adduct from **9** and furan, was treated with titanium ethoxide to afford **15** without giving any byproduct (Scheme 3). This was further converted to a known desulfonylated compound **18** [31] via 4-step sequence. The absolute configuration of the Diels–Alder adducts was thus confirmed.

Because the Diels–Alder adduct of furan is susceptible to the *retro*-Diels–Alder reaction, a control experiment was performed to determine whether the stereoselectivity was the result of kinetic or thermodynamic control. Thus, a 1:1 diastereomeric mixture of the bicyclic moiety was again subjected to the Diels–Alder reaction conditions (Scheme 4). The substrate remained intact, indicating



Scheme 3. Confirmation of the absolute configuration.



Scheme 4. Reaction reversibility test.

that no *retro*-Diels–Alder reaction or selective decomposition of one diastereomer occurred under these conditions, and the reaction therefore gives kinetic product.

We explain the origin of the stereoselectivity as shown in Fig. 2. As proposed by Evans [23], the carbonyl groups are expected to be parallel and are activated by coordination to aluminum. Diethyl ether may also coordinate to the aluminum centers, forming clusters. At the same time, the pendant group of the oxazolidinone moiety covers one of the alkyne 'faces' by stacking, restricting the reactive face of the LUMO (see also Fig. 1). Then, furan approaches the propiolate by way of coordination to aluminum. Although an unparallel coordination model has been proposed to explain the selectivity of an oxazolidinone-based auxiliary [63], the large difference in reactivity between **9** and **13** is likely to be better explained by the steric bulk around the alkyne moiety (see also Table 2).

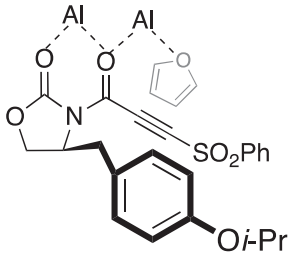


Fig. 2. Proposed origin of stereoselectivity.

Table 3
Substrate scope.

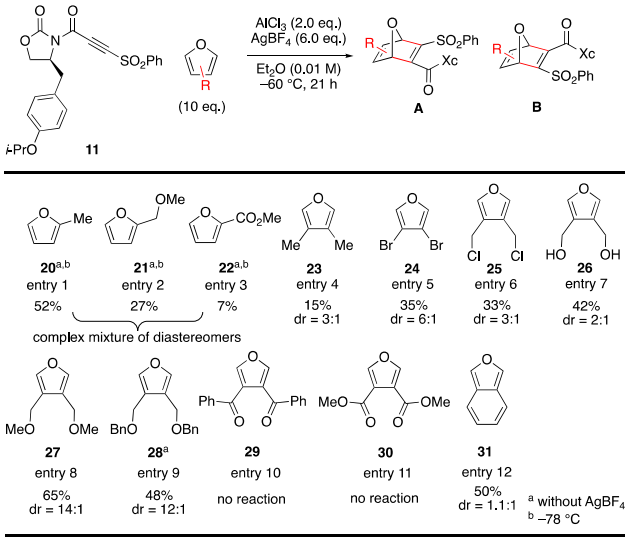
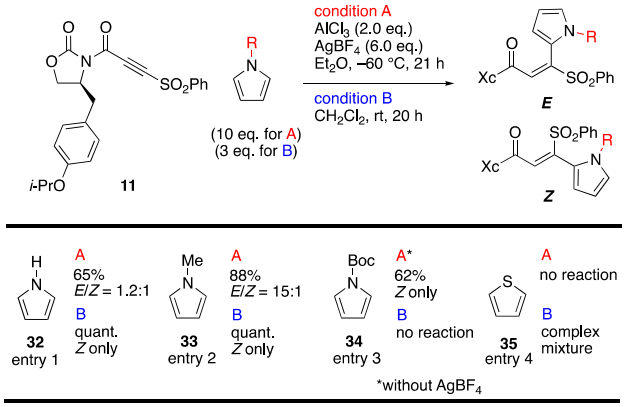
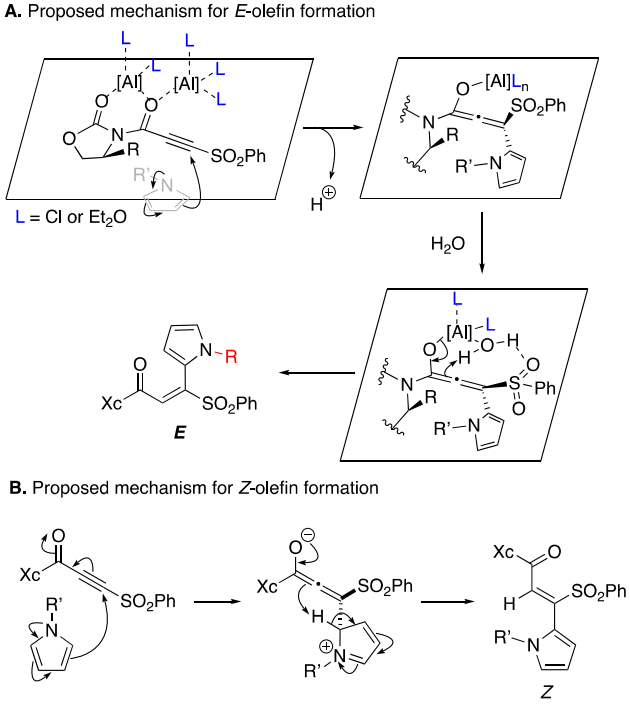


Table 4
Reaction with other heteroaromatics.



Following optimization of the reaction conditions, we examined various substituted furans as the reaction partner (Table 3). Asymmetrically substituted furans **20**–**22** led to an inseparable complex mixture of diastereomers, suggesting regioselectivity was difficult to achieve (entries 1–3). Removal of the chiral auxiliary from these adducts failed, possibly due to a competing *retro*-Diels–Alder reaction because substitution at the bridgehead position and coordination of a Lewis acid to the carbonyl group resulted in increased steric repulsion. Therefore, we decided to focus on 3,4-disubstituted furan derivatives. Moderate to good stereoselectivity was observed for alkyl- or halogen-substituted furans **23**–**28** (entries 4–9), and especially high selectivity and yield was achieved when 3,4-bis(methoxymethyl)furan **27** or 3,4-bis(benzyloxymethyl)furan **28** was used (entries 8 and 9). On the other hand, electron-withdrawing groups in **29** and **30** completely inhibited the reaction (entries 10 and 11). Isobenzofuran **31** was reactive but had little selectivity (entry 12).



Scheme 5. Proposed rationale for *E*/*Z*-geometry.

Heteroaromatics other than furan were also subjected to reaction conditions (Table 4). Reaction with *N*-substituted pyrroles proceeded smoothly, but Friedel–Crafts-type products were generated. Interestingly, *E*/*Z* selectivity of products was dependent on reaction conditions: reaction with $AlCl_3$ in ether at low temperature afforded the *E*-acrylate preferentially (entries 1 and 2). On the other hand, only the *Z*-acrylate was obtained without $AlCl_3$ in dichloromethane at room temperature (entries 1 and 2). In the case of Boc-protected pyrrole, *Z* isomer was selectively obtained in good yield (entry 3). Thiophene, the isostere of furan, resulted in no reaction or a complex mixture in both conditions (entry 4).

The selectivity in *E*/*Z*-geometry can be rationalized as described in Scheme 5: the pyrrole attacks the β-position of activated propiolamide from bottom side to afford allenoate (Scheme 5A, right top). Then, upon aqueous workup, water molecule approaches the allenoate by way of coordination to aluminium center and hydrogen bonding to sulfone moiety (right bottom). Thus α-position is protonated from the same side as sulfone to afford *E*-acrylate. In the case of *N*-Boc-protected **34**, the carbamate moiety might act better as hydrogen bond acceptor than sulfone to yield *Z*-acrylate. On the other hand, in the absence of aluminium, the conjugate addition occurs to inactivated propiolamide, hence higher temperature required for **32** and **33**, to afford zwitterion intermediate (Scheme 5B, center). Subsequent deprotonation-protonation takes place in intramolecular fashion to provide *Z*-acrylate.

Conclusion

In conclusion, we have achieved the first intermolecular asymmetric Diels–Alder reaction between propiolates and furans. A chiral auxiliary worked effectively to control the reaction 'face' of the alkyne carbons, and a three-dimensional structure was constructed from the combination of one- and two-dimensional substrates. Further studies to improve the yield and selectivity of the reaction and apply it in the total synthesis of natural product are under way in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153075.

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