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3-(Methoxycarbonyl)cyclobutenone as a Reactive Dienophile in Enantioselective Diels–Alder Reactions Catalyzed by Chiral Oxazaborolidinium Ions

Peng Yan, Changxu Zhong, Jie Zhang, Yu Liu, Huayi Fang, and Ping Lu*

Abstract: Cyclobutenone has been used as a highly reactive dienophile in Diels-Alder reactions, however, no enantioselective example has been reported. We disclose herein a chiral oxazaborolidine-aluminum bromide catalyzed enantioselective Diels–Alder reaction of 3-alkoxycarbonyl cyclobutenone with a variety of dienes. Furthermore, a total synthesis of (–)-kingianin F was completed for the first time via enantioenriched cycloadduct bicyclo[4.2.0]octane derivative.

Cyclobutenones have shown unique reactivity due to their inherent ring strain, thus they have been recognized as important building blocks in organic synthesis for decades.[1] Strain–release driven ring opening of cyclobutenones enable rapid assembly of complex molecules.[2] However, functionalization of cyclobutenones to access enantiomerically pure four–membered ring moiety is less studied.[3]

Bicyclo[4.2.0]octane motifs exist in many natural products, some representative examples are depicted in Figure 1. About 80 protoilludanes and related sesquiterpenes have been isolated and these molecules feature a common tricyclic 5/6/4-framework.[4] SNF4435 C and D, featuring a core bicyclo[4.2.0]octadiene motif, possess immunosuppressive and anticancer activity.[5] Kingianins A-N, a family of bicyclo[4.2.0]octadiene dimers, showed significant binding affinity for the protein Bcl-xL.[6]

Several strategies to synthesize enantioenriched bicyclo[4.2.0]octane moiety have been developed,[7] however, the intermolecular Diels–Alder reaction of cyclobutenone has not been explored yet.

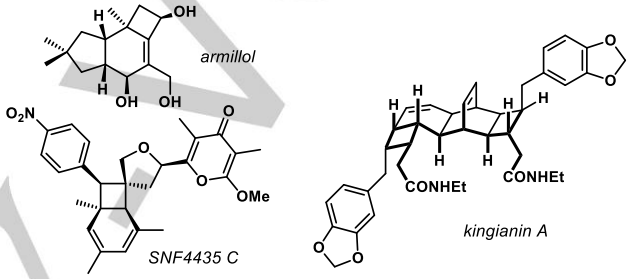
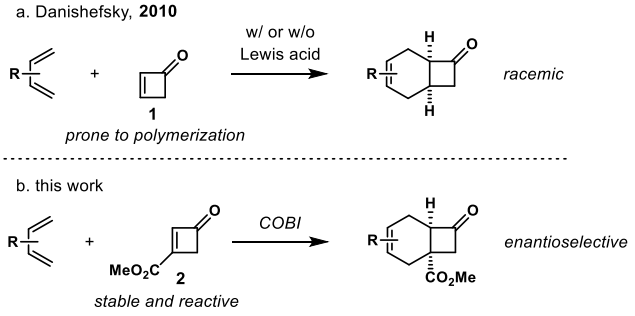


Figure 1. Selected natural products with a bicyclo[4.2.0]octane scaffold.

Diels–Alder reaction has proved to be a fundamental transformation to generate complex molecules efficiently both in academic and industry areas.[8] In 2010, Danishefsky disclosed that Diels–Alder reaction of the parent cyclobutenone **1** and an array of dienes gave diverse bicyclo[4.2.0]octene derivatives in good yields under mild conditions (Scheme 1a).[9] Later, the preparation of a more reactive dienophile 2-bromocyclobutenone was further explored.[10,11] Of note, cyclobutenone **1** and 2-bromocyclobutenone had to be stored in solution to inhibit polymerization. We envisioned that a highly reactive cyclobutenone with better stability would provide a practical approach to access enantioenriched bicyclo[4.2.0]octane derivatives. Herein we report our work on unique reactivity of 3-methoxycarbonylcyclobutenone **2** as dienophile in enantioselective Diels–Alder reaction under the catalysis of chiral oxazaborolidinium ion[12,13] (Scheme 1b).



Scheme 1. The Diels–Alder reaction of cyclobutenone.

[*] P. Yan, C. Zhong, Prof. Dr. P. Lu
Department of Research Center for Molecular Recognition and Synthesis, Department of Chemistry, Fudan University
220 Handan Lu, Shanghai 200433, P. R. China
E-mail: plu@fudan.edu.cn
Homepage: http://rcmrs.fudan.edu.cn/Data/View/173
J. Zhang, Prof. Dr. Y. Liu
College of Chemistry and Life, Advanced Institute of Materials Science, Changchun University of Technology, Changchun 130012, P. R. China
Prof. Dr. H. Fang
School of Materials Science and Engineering, Tianjin Key Lab for Rare Earth Materials and Applications, Nankai University, Tianjin, 300350, P. R. China

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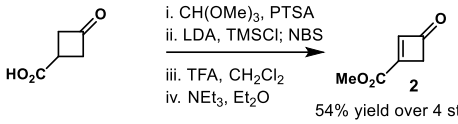
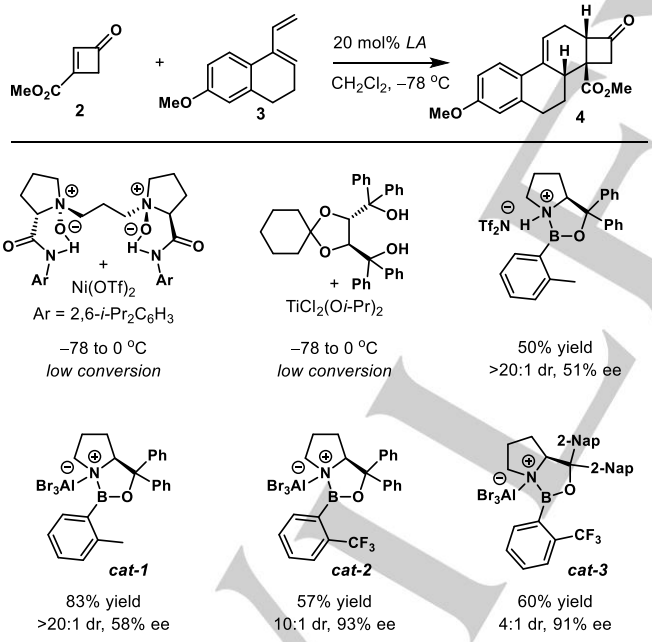
The cyclobutenone **2** was easily prepared from commercially available 3-oxocyclobutane-1-carboxylic acid on a multigram scale (Scheme 2). In contrast to parent cyclobutenone **1**, the product **2** was purified by column chromatography and could be stored in a neat state for months in a freezer without any decomposition.



Scheme 2. The preparation of cyclobutenone **2**.

We commenced our studies with the reaction of dienophile **2** and Dane's diene **3** (Table 1). Treatment of **2** and **3** in CH_2Cl_2 at room temperature afforded the adduct **4** smoothly in 79% yield with a 2:1 diastereoselectivity. Several chiral Lewis acid and Brϕnsted acid catalytic systems were then examined, including chiral phosphoric acid,[14] Feng's *N*,*N*-dioxide-metal complex[15] and chiral titanium complex,[16] only low conversion was obtained in these cases. Gladly, when Corey's chiral oxazaborolidinium ion (COBI) catalytic system was employed,[17,18] the reaction gave the desired adduct **4** in good yield and high diastereoselectivity. After optimization, we found ***cat-2*** furnished adduct **4** in 93% ee and 10:1 dr.[19]

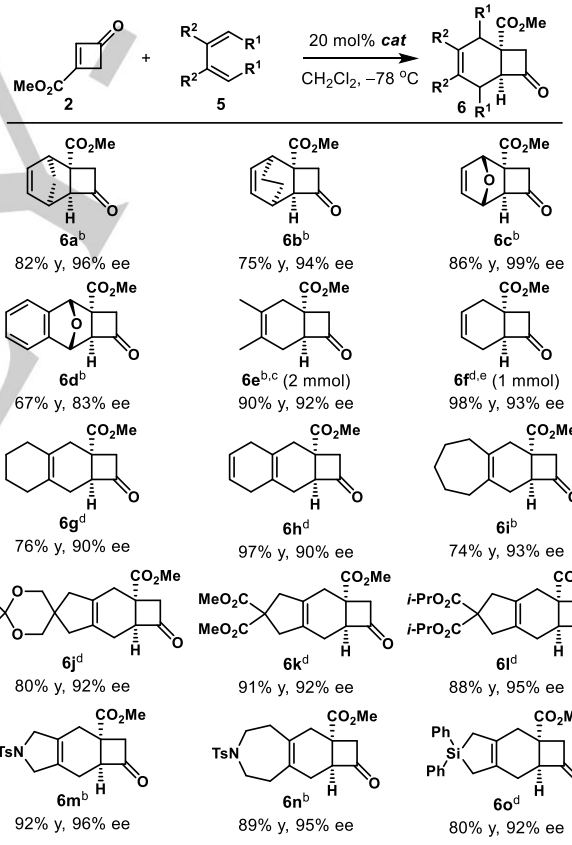
Table 1. Optimization of enantioselective Diels–Alder reaction[a]



[a]**2** (0.2 mmol), **3** (0.3 mmol), LA (20 mol%), CH_2Cl_2, –78 °C. The ee values were determined by HPLC analysis on a chiral stationary phase. All results are corrected to (S)-catalyst. See Supporting Information (SI) for more details. Tf = trifluoromethanesulfonyl; 2-Nap = 2-naphthyl.

We next examined the Diels-Alder reaction of cyclobutenone **2** with an array of symmetric 1,3-diene **5** under the catalysis of COBI (Table 2). The reaction of 1,3-cyclopentadiene and 1,3-cyclohexadiene with cyclobutenone **2** afforded the corresponding *endo* adducts **6a** and **6b** in high yield and enantioselectivity in the presence of ***cat-1***. The *exo* products **6c** and **6d** were obtained when furan and benzofuran were employed. The absolute configuration of adduct **6c** was determined by X-ray crystallographic analysis,[19] and the stereochemical outcome of the reaction could be preliminarily explained by the depicted model for complex ***cat-1***-cyclobutenone **3** in Figure 2. Low catalyst loading (5 mol%) was sufficient in the 2 mmol-scale reaction of 2,3-dimethyl-1,3-butadiene, and the corresponding product **6e** was achieved in 90% yield and 92% ee. The cycloaddition reaction of 1,3-butadiene (in CH_2Cl_2 or hexane) provided product **6f** in 98% yield and 93% ee in the presence of 10 mol% ***cat-3***. In addition, exocyclic conjugate dienes were applicable to the reaction of cyclobutenone **2**, giving the corresponding adducts **6g**-**6l** in 74-97% yield and 90-95% ee. Oxidation of **6h** with DDQ led to tetrahydronaphthalene **6h'** (see SI), which could be viewed as the cycloadduct from *o*-quinodimethane and cyclobutenone **2**. Heterocyclic dienes were also tolerated under above conditions, and the products **6m**-**6o** were furnished in 80-92% yield and 92-96% ee.

Table 2. Substrate scope of symmetric 1,3-diene[a]



[a]**2** (0.2 mmol), **5** (0.3-2 mmol), ***cat*** (20 mol%), CH_2Cl_2. All results are corrected to (*S*)-catalyst. The ee values were determined by HPLC analysis. [b]***cat-1*** was used. [c] 5 mol% ***cat-1*** was used. [d]***cat-3*** was used. [e]10 mol% ***cat-3*** was used. Ts = *p*-toluenesulfonyl.

An array of 2-substituted 1,3-dienes **7** was also explored (Table 3). The reaction of 2-bromofuran and cyclobutenone **3** provided the *exo* product **8a** in 84% yield and 98% ee in the presence of ***cat-1***. The absolute configuration of **8a** was determined by X-ray crystallographic analysis.[19] The reaction of 2-benzyloxycarbonyl

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cyclobutenone **2'** with isoprene or myrcene gave the corresponding adducts **8b** and **8c** in good regioselectivity and

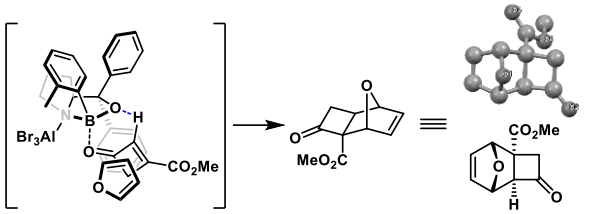
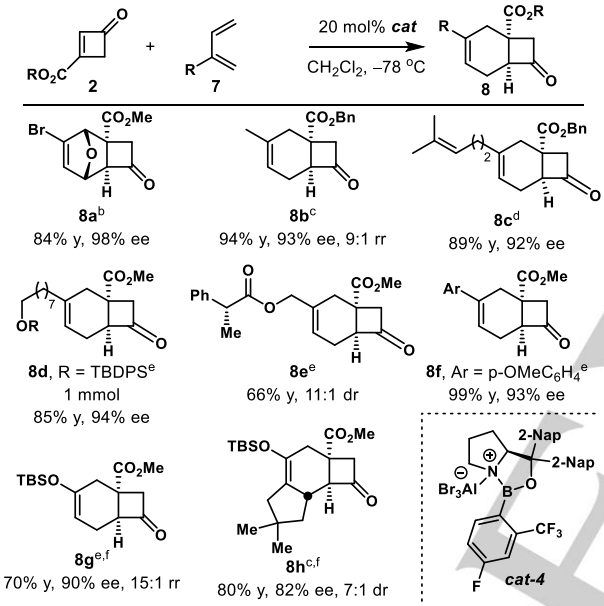


Figure 2. Proposed model for the reactive complex of ***cat-1*** and cyclobutenone **2**.

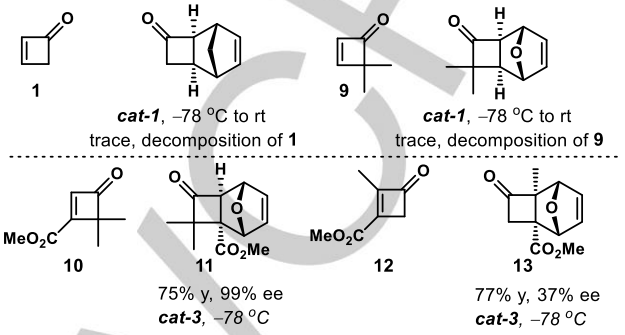
Table 3. Substrate Scope of Unsymmetric 1,3-Diene[a]



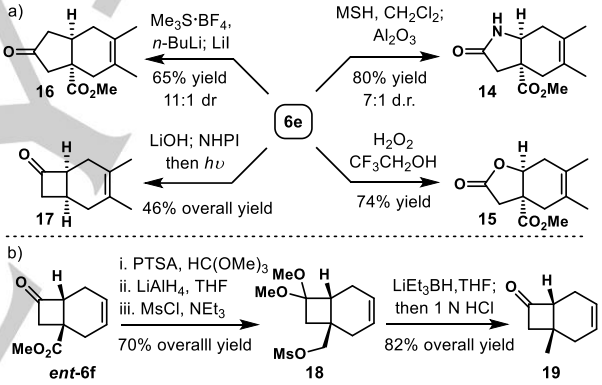
[a]**2** (0.2 mmol), **7** (0.3-2 mmol), ***cat*** (20 mol%), CH_2Cl_2. See SI for details. All results are corrected to (*S*)-catalyst. The ee values were determined by HPLC analysis. [b]***cat-1*** was used. [c]***cat-3*** was used. [d]***cat-4*** was used. [e]***cat-2*** was used. [f]–90 °C. TBS = *t*-butyldimethylsilyl; TBDPS = *t*-butyldiphenylsilyl.

enantioselectivity. 2-Alkyl and aryl substituted 1,3-butadienes **7d-7f** afforded the corresponding products **8d-8f** in good yield and selectivity. In addition, cycloadduct **8g** could be obtained in 70% yield and 90% ee in the presence of ***cat-2*** at –90 °C. Besides, the *exo* adduct **8h**, bearing a tricyclic 5/6/4-framework, could be furnished in 80% yield and 82% ee. The structure of **8h** was determined by X-ray crystallographic analysis of its desilylation derivative (**8h'**, see SI).[19]

We next turned to compare the different reactivity of cyclobutenones (Scheme 3). Surprisingly, the reaction of cyclobutenones **1** and **9** gave no conversion under standard conditions at –78 °C, while these two cyclobutenones led to decomposition after elevating reaction temperature. Gladly, the [4+2]-reaction of cyclobutenone **10** and furan provided desired adduct **11** in 75% yield and 99% ee. Of note, the *gem*-dimethylcyclobutane moiety was found in a variety of classes of natural products.[20] Cyclobutanone **12**, with methyl group at the 2-position, afforded adduct **13** in 37% ee, indicating the importance of α-CH-O interaction between cyclobutenone and COBI catalyst (Figure 2). We assumed that the steric hindrance posed by 3-substitution group would inhibit decomposition or polymerization of cyclobutenone under strong Lewis acid.[21] In addition, the electron deficient methoxycarbonyl group in **2** would enhance the reactivity of C=C double bond, leading to the successful COBI-catalyzed cycloaddition.



Scheme 3. Comparison of Reactivity and Natural Charge Analysis of Cycobutanones.



Scheme 4. Further transformations of cycloadducts **6e** and *ent*-**6f**. MSH = *O*-(mesitylsulfonyl)hydroxylamine; NHPI = *N*-hydroxyphthalimide; PTSA = *p*-toluenesulfonamide; Ms = methanesulfonyl.

As shown by Danishefsky, bicyclo [4.2.0]octane motifs could be transformed to ring expansion products, viewed as otherwise directly inaccessible Diels-Alder products.[9] Thus adduct **6e**, bearing a quaternary methoxycarbonyl group, was examined under ring expansion conditions (Scheme 4a). Lactone **14** and lactam **15** were obtained in good yield and regioselectivity uneventfully. Cyclopentanone **16** could also be achieved via a two-step sequence ($Me_3S{\bullet}BF_4$; LiI).[22] In addition, photo induced decarboxylation of **6e** afforded product **17** in 46% yield over three steps.[23] Furthermore, the methoxycarbonyl group of *ent*-**6f** could be transformed to methyl group smoothly (Scheme 4b).

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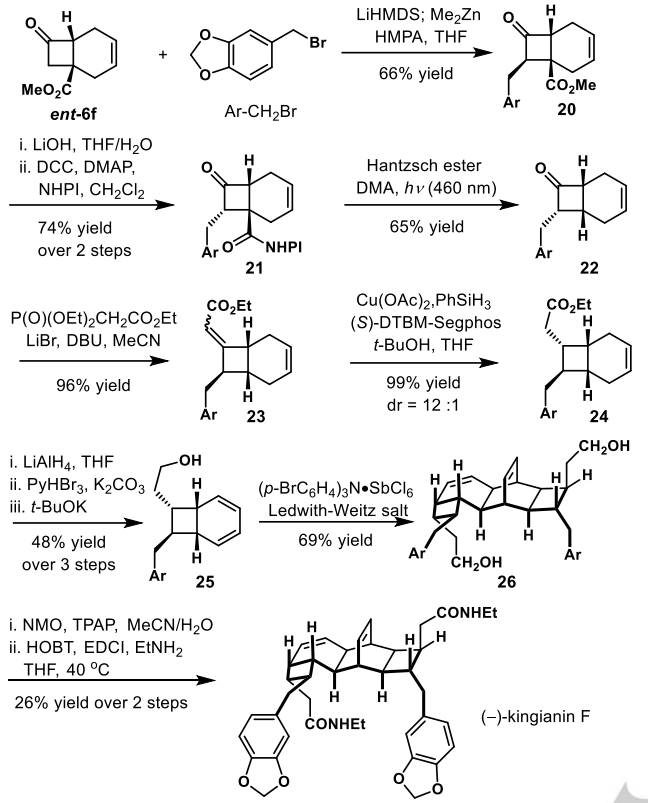

Scheme 5. Synthesis of (–)-kingianin F. HMPA = hexamethylphosphoramide; DCC = *N*,*N*'-dicyclohexylcarbodiimide; DAMP = 4-(dimethylamino)pyridine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; NMO = *N*-methylmorpholine *N*-oxide; TPAP = tetrapropylammonium perruthenate; HOBT = hydroxybenzotriazole; EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; Hantzsch ester = diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate; (*S*)-DTBM-Segphos = (*S*)-(+)-5,5'-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole.

The kingianins (A-N) were isolated from the barks of Endiandra kingiana (*Lauraceae*) and featured a common pentacyclic scaffold, arising from dimeric Diels-Alder reaction of bicyclo[4.2.0]octadienes.[6] Although isolated as racemic mixtures, the levorotatory enantiomers showed the more potent binding affinity for Bcl-xL than dextrorotatory counterparts.[6b] Several elegant biomimetic syntheses have been completed, and electrocyclization strategy was utilized to access racemic bicyclo[4.2.0]octadiene moiety.[24,25] We envisioned that our Diels-Alder reaction of cyclobutenone would offer a different approach to synthesize enantioenriched kingianins and determine their absolute configurations (Scheme 5). Starting from *ent*-**6f**, alkylation of *in-situ* generated zinc enolate provided **20** as a single diastereomer.[26] Photo-induced decarboxylation gave cyclobutanone **22** via redox-active ester **21** in 65% yield.[23,27] Then Horner-Wadsworth-Emmons reaction furnished enoate **23** in 96% yield as a 2:1 isomer.[27,28] Highly selective reduction of above enoate **23** was achieved using CuH/(*S*)-DTBM-Segphos, giving *trans*-**24** in 99% yield and 12:1 dr.[29] Sequential $LiAlH_4$ reduction, bromination and dehydrobromination gave known diene **25**[24a] in 48% overall yield. Finally (–)-kingianin F was completed in a further three-step sequence as reported by Sherburn.[24a]

In conclusion, we reported here a chiral oxazaborolidinium ion catalyzed highly enantioselective and regioselective Diels-Alder reaction of 3-alkoxycarbonyl cyclobutenone with a series of dienes. 3-Alkoxycarbonyl group played a critical role in reactivity and stability of dienophile cyclobutenone. Enantioenriched cycloadduct bicyclo[4.2.0]octene derivatives could be used as versatile intermediates in the total synthesis of related natural products, leading to the first completion of (–)-kingianin F.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cyclobutenone • chiral oxazaborolidinium ion • Diels-Alder reaction • strain-released driven• bicyclo[4.2.0]octane

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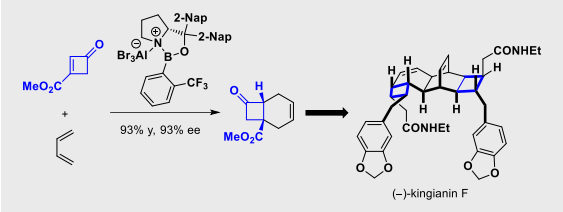

The first enantioselective Diels-Alder reaction of cyclobutenone has been developed, and 3-methoxycarbonyl group shows remarkable effect on stability and reactivity. Based on enantioenriched adduct, the total synthesis of (–)-kingianin F was completed.

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3-Alkoxycarbonyl Cyclobutenone as a Reactive Dienophile in Chiral Oxazaborolidinium Ion Catalyzed Enantioselective Diels–Alder Reaction