

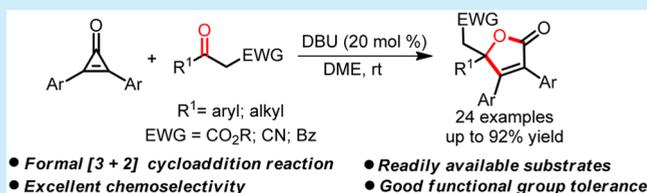
Organocatalyzed [3 + 2] Annulation of Cyclopropenones and β -Ketoesters: An Approach to Substituted Butenolides with a Quaternary Center

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S Supporting Information

ABSTRACT: An unprecedented organocatalyzed [3 + 2] annulation of cyclopropenones and β -ketoesters has been developed. This reaction provides a direct approach to highly substituted butenolides with a quaternary center in moderate to good yields. The preliminary mechanism study verified that the enol intermediate is crucial to the reaction outcome and the intermolecular esterification and intramolecular Michael addition process were involved.



Butenolides as privileged structural motifs are widely found in a variety of pharmaceuticals and natural products, such as butyrolactone I,^{1a} triptolide,^{1b} triptidiolide,^{1b} rofecoxib,^{1c} vitamin C,^{1d} lanthellidone G,^{1e} and lanthellidone H^{1e} (Figure 1). They also serve as important synthetic building blocks in

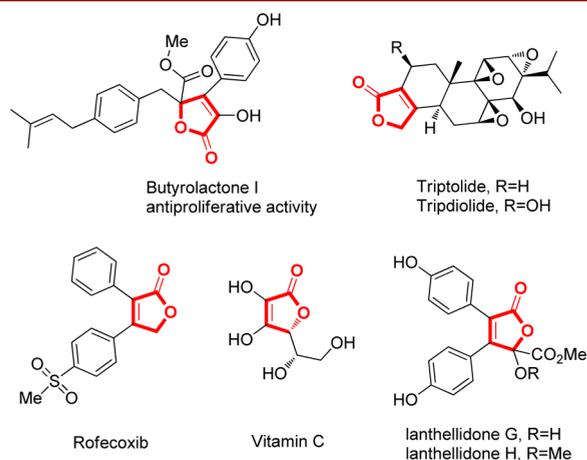


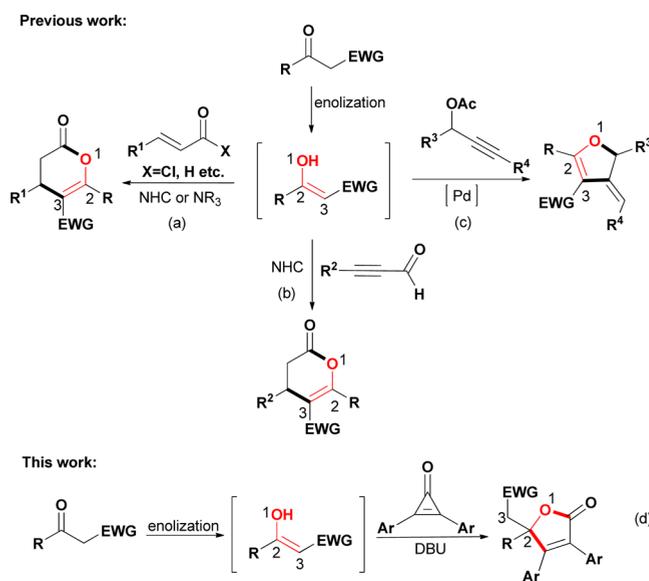
Figure 1. Selected bioactive compounds containing a butenolide structural motif.

complex molecule synthesis.² Generally, the strategies to construct butenolides rely on Au-catalyzed intramolecular cyclization of enynes,³ Ru-catalyzed intramolecular cyclization of acrylates,⁴ Rh-catalyzed intramolecular cyclization of alkynoates,⁵ the acid-promoted intramolecular cyclization of butanoic acids,⁶ or intermolecular cyclization of keto acids and tertiary alcohols.⁷ Although much progress has been achieved in this area, the use of expensive transition-metal catalysts, the complicated operation, and/or harsh reaction conditions limited their wide applicability. Hence, the development of a

promising strategy for the synthesis of highly substituted butenolides from simple starting materials under mild reaction conditions is still highly desirable.

β -Ketoesters as accessible building blocks have been used to react with α,β -unsaturated aldehydes or acyl chlorides to construct dihydropyranones under NHCs or tertiary amine catalyzed [3 + 3] annulation (Scheme 1a and 1b)^{8,9} or with propargylic esters to form dihydrofurans under Pd-catalyzed [3 + 2] annulation (Scheme 1c).¹⁰ All of the above-mentioned

Scheme 1. Cycloaddition Reaction of β -Ketoesters

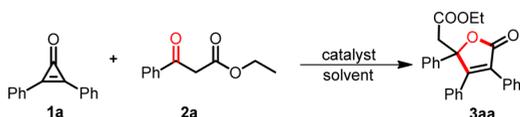


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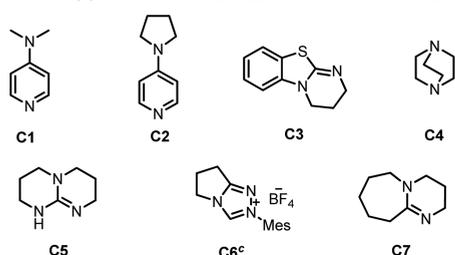
examples normally underwent intermolecular Michael addition and intramolecular esterification/cyclization processes because the enolization of β -ketoesters made the methylene of β -ketoesters a prior nucleophilic site and the oxygen atom of keto group another nucleophilic site. As part of the evolution of the application of β -ketoesters, herein we describe an unprecedented organocatalyzed [3 + 2] annulation between β -ketoesters and cyclopropenones,¹¹ affording the butenolides with a quaternary center in good yields with excellent chemoselectivity (Scheme 1d). In this reaction, the enolization of β -ketoesters made the oxygen atom of keto group a prior nucleophilic site that reacted with cyclopropenones to realize ring-opening and intermolecular esterification processes, and subsequent intramolecular Michael addition delivered the corresponding butenolides.

We initiated our exploration by investigating the reaction between 2,3-diphenylcycloprop-2-enone **1a** and ethyl benzoylacetate **2a**. When the reaction was performed in CH₂Cl₂ at room temperature, the desired compound **3aa** could not be obtained under the catalysis of DMAP (**C1**), 4-PPy (**C2**), and DHPB (**C3**) (Table 1, entries 1–3). When DABCO (**C4**), TBD (**C5**), and NHC precatalyst (**C6**) were tested, **3aa** could be obtained in low yields (Table 1, entries 4–6). To our delight, the yield of **3aa** was dramatically improved to 79% when DBU (**C7**) was used as the catalyst (Table 1, entry 7).

Table 1. Optimization of Reaction Conditions^{a,b}



entry	cat.	solvent	yield (%)
1	C1	CH ₂ Cl ₂	NR
2	C2	CH ₂ Cl ₂	NR
3	C3	CH ₂ Cl ₂	NR
4	C4	CH ₂ Cl ₂	3
5	C5	CH ₂ Cl ₂	7
6	C6	CH ₂ Cl ₂	13
7	C7	CH ₂ Cl ₂	79
8 ^d	C7	CH ₂ Cl ₂	50
9	C7	toluene	58
10	C7	THF	71
11	C7	1,4-dioxane	80
12	C7	Et ₂ O	86
13	C7	DME	91



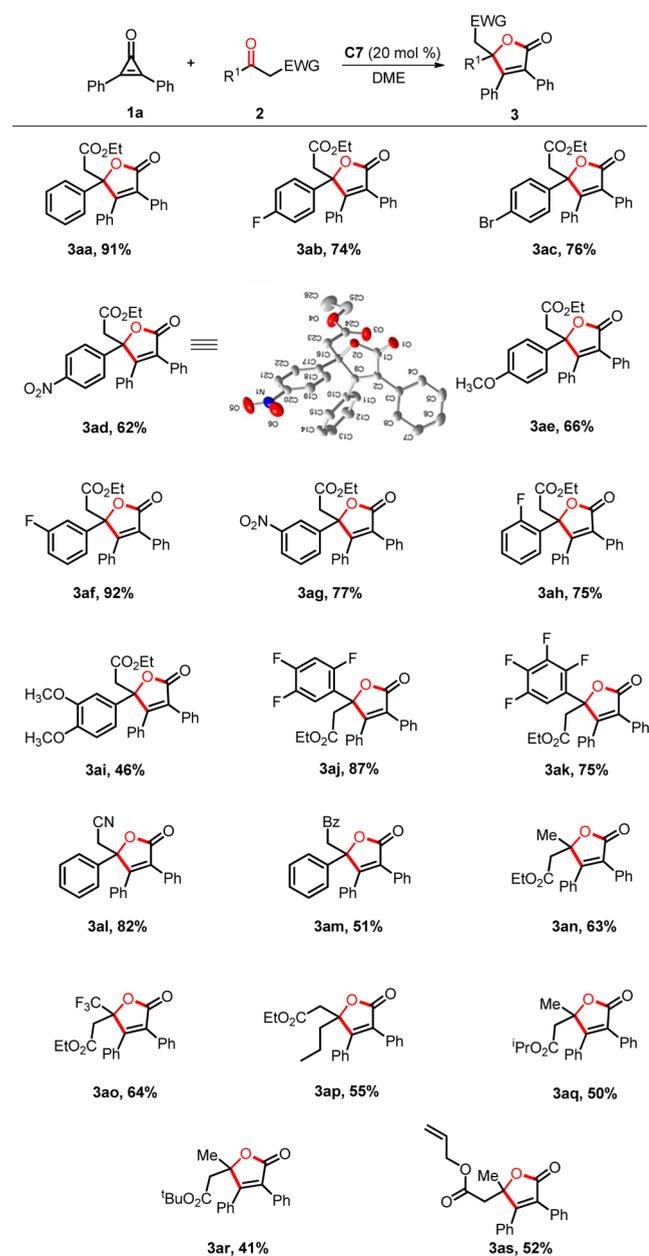
C1: N,N-dimethylpyridin-4-amine; **C2**: 4-pyrrolidylpyridine; **C3**: 1,2,3,4-tetrahydro-1H-benzothiazole; **C4**: 1,4-diazabicyclo[2.2.2]octane; **C5**: 1,4-diazabicyclo[2.2.2]octane; **C6^c**: 1,2,3,4-tetrahydro-1H-benzothiazole; **C7**: 1,4-diazabicyclo[2.2.2]octane.

^aReaction conditions: **1a** (0.15 mmol, 1.5 equiv), **2a** (0.1 mmol, 1.0 equiv), catalyst (20 mol %) in solvent (1.0 mL) at ambient temperature for 24 h. ^bIsolated yield. ^cWith 20 mol % of K₂CO₃. ^d10 mol % of DBU was used.

Decreasing catalyst loading resulted in lower yield (Table 1, entry 8). Screening of solvents revealed that the yield of **3aa** could be increased to 91% when DME was employed as the solvent (Table 1, entries 9–13).

With the optimized conditions in hand, we then tested an array of β -ketoesters and cyclopropenones to explore the generality of this novel [3 + 2] annulation reaction, and the results are summarized in Scheme 2. First, a series of ethyl benzoylacetates bearing electron-withdrawing or electron-donating groups at the C4-position of the benzene ring were examined, and the corresponding butenolides **3aa**–**ae** were achieved in 62–91% yields. The structure of **3ad** was determined by X-ray crystal structure analysis.¹² The

Scheme 2. Scope of the β -Ketoesters^{a,b}

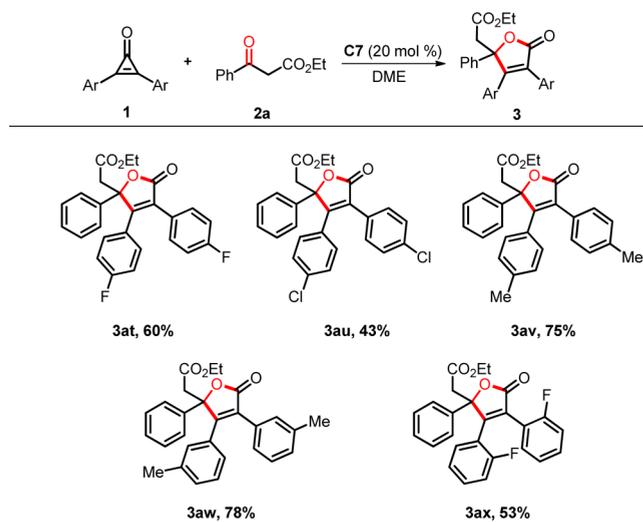


^aReaction conditions: **1a** (0.15 mmol, 1.5 equiv), **2** (0.1 mmol, 1.0 equiv), **C7** (20 mol %) in DME (1.0 mL) at ambient temperature for 24 h. ^bIsolated yields.

compounds **3af–ah** with *meta* or *ortho* substituents at the benzene ring were obtained in 75–92% yields. Multifluorine-substituted benzoylacetates **2j** and **2k** resulted **3j** and **3k** in 87% and 75% yields. When a CN group or Bz group was used to replace the ester group, the **3al** and **3am** could also be obtained in 82% and 51% yields. Methyl-, trifluoromethyl-, or *n*-propyl-substituted β -ketoesters afforded **3an**, **3ao**, and **3ap** in 63%, 64%, and 55% yields. The use of isopropyl ester, *tert*-butyl ester, or allyl ester afforded **3aq–as** in moderate yields.

The substrate scope of cyclopropenones was then examined, and the results are shown in Scheme 3. The 2,3-diary-

Scheme 3. Scope of the Cyclopropenones^{a,b}



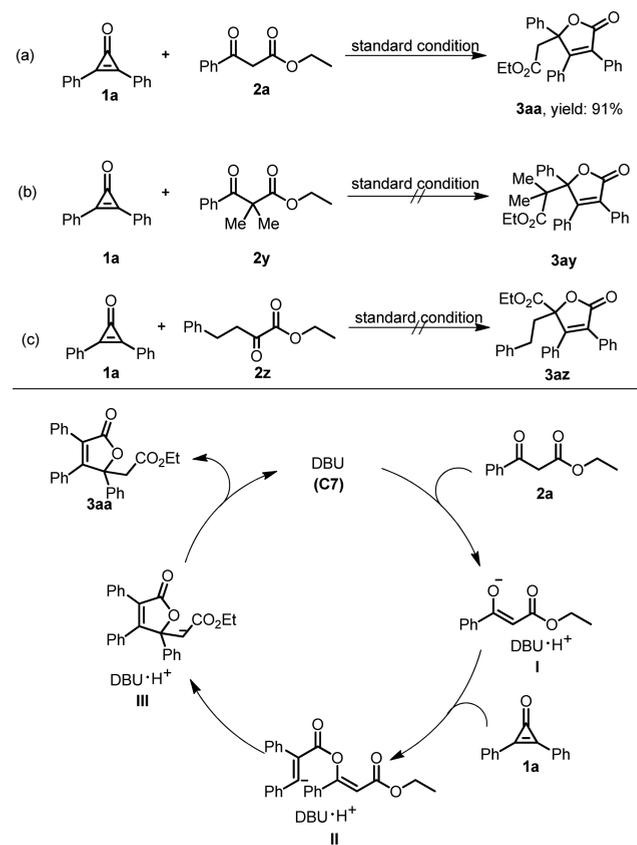
^aReaction conditions: **1** (0.15 mmol, 1.5 equiv), **2a** (0.1 mmol, 1.0 equiv), **C7** (20 mol %) in DME (1.0 mL) at ambient temperature for 24 h. ^bIsolated yields.

lucycloprop-2-enone with a methyl group at the C4-position of the phenyl ring afforded **3av** in 75% yield. Electron-withdrawing groups on the C4-position showed slightly lower reactivity and furnished **3at** and **3au** in 60% and 43% yields. The **3aw** with a C3-methyl group and **3ax** with a C2-fluorine group could also be obtained in 78% and 53% yields.

To explore the reaction mechanism, control experiments were performed as shown in Scheme 4. When ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate **2y** reacted with cyclopropenone **1a**, no corresponding product **3ay** was achieved (Scheme 4b), and this result demonstrated that the enol intermediate is crucial to the reaction outcome and the reaction did not go through intermolecular nucleophilic addition and intramolecular esterification processes. When ethyl 2-oxo-4-phenylbutanoate **2z** was tested, although it could easily offer enolization under base conditions, we did not detect the corresponding product **3az** (Scheme 4c). This phenomenon implied that the in situ formation of a Michael addition acceptor during the enolization is also important to achieve the annulation.

On the basis of previous reports^{11a–g} and our control experiments, a plausible mechanism for this [3 + 2] annulation between cyclopropenones and β -ketoesters is proposed in Scheme 4. Deprotonation of β -ketoester **2a** by DBU (**C7**) generates the enol intermediate **I**. The in situ formed nucleophilic oxygen anion attacks the carbonyl group of cyclopropenone **1a**, realizing the ring-opening process and

Scheme 4. Control Experiment and Proposed Mechanism



affording the intermediate **II**. Subsequently, the intramolecular Michael addition of **II** delivers intermediate **III**. Finally, the product **3aa** could be obtained after protonation.

In conclusion, we have developed an unprecedented organocatalyzed [3 + 2] annulation for the construction of highly substituted butenolides with a quaternary center from cyclopropenones and β -ketoesters with excellent chemoselectivity. The method obviated the need for metal catalyst and proceeded well under mild conditions and simple operation. Further, this reaction expands the application of β -ketoesters in cycloaddition reaction and pioneers a new model to achieve new chemistry of β -ketoesters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03737.

General procedures, ¹H and ¹³C NMR spectra for all new compounds, and X-ray crystal structure of **3ad** (PDF) X-ray crystallographic data for **3ad** (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

- (1) (a) Braña, M. F.; García, M. L.; López, B. L.; Pascual-Teresa, B. d.; Ramos, A.; Pozuelo, J. M.; Domínguez, M. T. *Org. Biomol. Chem.* **2004**, *2*, 1864. (b) Kupchan, S. M.; Court, W. A.; Dailey, R. G.; Gilmore, J. C. J.; Bryan, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 7194. (c) Bhat, A.-S.; Tandan, S. K.; Kumar, D.; Krishna, V.; Prakash, V. R. *Eur. J. Pharmacol.* **2007**, *556*, 190. (d) *Vitamin C: Its Chemistry and Biochemistry*; Davies, M. B., Austin, J., Partridge, D. A., Eds.; Royal Society of Chemistry: Cambridge, U.K., 1991. (e) Zhang, H.; Conte, M. M.; Huang, X.-C.; Khalil, Z.; Capon, R. J. *Org. Biomol. Chem.* **2012**, *10*, 2656.
- (2) For selected examples, see: (a) Fournier, J.; Lozano, O.; Menozzi, C.; Arseniyadis, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1257. (b) Fournier, J.; Arseniyadis, S.; Cossy, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7562. (c) Yavorsky, A.; Shvydkiv, O.; Hoffmann, N.; Nolan, K.; Oelgemöller, M. *Org. Lett.* **2012**, *14*, 4342. (d) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (f) Paquette, L. A.; Wang, T.-Z.; Sivik, M. R. *J. Am. Chem. Soc.* **1994**, *116*, 2665.
- (3) Liu, Y.; Song, F.; Guo, S. *J. Am. Chem. Soc.* **2006**, *128*, 11332.
- (4) Bassetti, M.; D'Annibale, A.; Fanfoni, A.; Minissi, F. *Org. Lett.* **2005**, *7*, 1805.
- (5) Alfonsi, M.; Arcadi, A.; Chiarini, M.; Marinelli, F. *J. Org. Chem.* **2007**, *72*, 9510.
- (6) Browne, D. M.; Niyomura, O.; Wirth, T. *Org. Lett.* **2007**, *9*, 3169.
- (7) For selected examples, see: (a) Mao, W.; Zhu, C. *Org. Lett.* **2015**, *17*, 5710. (b) Cheikh, N.; Villemin, D.; Bar, N.; Lohier, J.-F.; Choukchou-Braham, N.; Mostefa-Kara, B.; Sopkova, J. *Tetrahedron* **2013**, *69*, 1234.
- (8) For selected examples, see: (a) De Sarkar, S.; Studer, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 9266. (b) Rong, Z.-Q.; Jia, M.-Q.; You, S.-L. *Org. Lett.* **2011**, *13*, 4080. (c) Wang, G.; Chen, X.; Miao, G.; Yao, W.; Ma, C. *J. Org. Chem.* **2013**, *78*, 6223. (d) Vellalath, S.; Van, K. N.; Romo, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 13688. (e) Ni, Q.; Xiong, J.; Song, X.; Raabe, G.; Enders, D. *Chem. Commun.* **2015**, *51*, 14628.
- (9) Zhu, Z.-Q.; Zheng, X.-L.; Jiang, N.-F.; Wan, X.; Xiao, J.-C. *Chem. Commun.* **2011**, *47*, 8670.
- (10) Zhou, Y.; Zhu, F.-L.; Liu, Z.-T.; Zhou, X.-M.; Hu, X.-P. *Org. Lett.* **2016**, *18*, 2734.
- (11) For selected examples of cyclopropenone in cycloaddition reactions, see: (a) Kascheres, A.; Rodrigues, J. A. R. *J. Org. Chem.* **1975**, *40*, 1440. (b) Wadsworth, D. H.; Weidner, C. H.; Bender, S. L.; Nuttall, R. H.; Luss, H. R. *J. Org. Chem.* **1989**, *54*, 3652. (c) Weidner, C. H.; Michaels, F. M.; Beltman, D. J.; Montgomery, C. J.; Wadsworth, D. H.; Briggs, B. T.; Picone, M. L. *J. Org. Chem.* **1991**, *56*, 5594. (d) Wender, P. A.; Paxton, T. J.; Williams, T. J. *J. Am. Chem. Soc.* **2006**, *128*, 14814. (e) Hemming, K.; Khan, M. N.; Kondakal, V. V. R.; Pitard, A.; Qamar, M. I.; Rice, C. R. *Org. Lett.* **2012**, *14*, 126. (f) Matsuda, T.; Sakurai, Y. *J. Org. Chem.* **2014**, *79*, 2739. (g) Rivero, A. R.; Fernández, I.; Arellano, C. R. d.; Sierra, M. A. *J. Org. Chem.* **2015**, *80*, 1207. (h) Matsuda, T.; Sakurai, Y. *Eur. J. Org. Chem.* **2013**, *2013*, 4219. (i) Rao, B.; Tang, H.; Zeng, X.; Liu, L.; Melaimi, M.; Bertrand, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 14915. (j) Xie, F.; Yu, S.; Qi, Z.; Li, X. *Angew. Chem., Int. Ed.* **2016**, *55*, 15351. (k) Wallbaum, J.; Jones, P.; Werz, D. B. *J. Org. Chem.* **2015**, *80*, 3730. (l) Schuster-Haberhauer, A.; Gleiter, R.; Körner, O.; Leskovar, A.; Werz, D. B.; Fischer, F. R.; Rominger, F. *Organometallics* **2008**, *27*, 1361. (m) Werz, D. B.; Klatt,

G.; Raskatov, J. A.; Köppel, H.; Gleiter, R. *Organometallics* **2009**, *28*, 1675.

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