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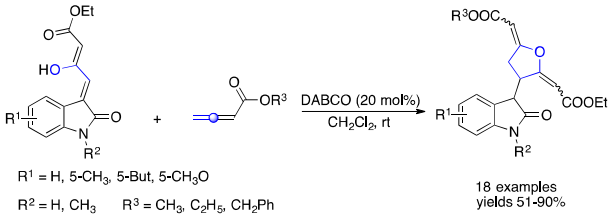

A DABCO catalyzed domino reaction between 3-oxo-4-(2-oxoindolin-3-ylidene)butanoates and allenoates furnished 2,3,5-substituted tetrahydrofuran furan derivatives bearing oxindole moiety and two exocyclic double bonds in high yield.

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COMMUNICATION

Convenient Synthesis of Substituted Tetrahydrofuran via Lewis Base Catalyzed [3+2] Domino Reactions†

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A DABCO catalyzed domino reaction between 3-oxo-4-(2-oxoindolin-3-ylidene)butanoates and allenoates furnished 2,3,5-substituted tetrahydrofuran furan derivatives bearing oxindole moiety and two exocyclic double bonds in high yield. During this reaction, two carbon atoms and one oxygen atom of 3-oxo-4-(2-oxoindolin-3-ylidene)butanoates participated. Moreover, four isomers were synthesized and two of them can be isolated in this reaction.

The remarkable significance of substituted tetrahydrofuran derivatives in natural products has motivated chemists to develop various approaches for their construction (Fig. 1).[1] Owing to the significance of the tetrahydrofuran scaffolds, extensive efforts have been made for the efficient synthesis of these heterocycles.[2] Despite the presence of various methodologies, an efficient, eco-friendly, straightforward synthetic method toward tetrahydrofuran derivatives still represents a challenging task for chemists. On the other hand, over the past decade, organocatalytic domino reactions have been used for the rapid construction of numerous pharmaceuticals, natural products, and synthetically valuable building blocks.[3] Such reactions have many advantages, as they are atom-economical and have reduced synthetic steps, minimized the amount of purification required and removed the need for protecting group strategies. Among the organocatalytic domino reactions, allenoates have attracted much attention due to the versatile reaction modes. After the pioneering work of Lu's [3+2] cycloaddition,[4] significant advances have been made in the organocatalytic cycloaddition reactions, such as [4+2], [3+3], and [4+1] cycloadditions.[5] Furthermore, very recently, many groups have developed [3+2] cyclizations between allenoates and methyleneoxindoles to efficiently access spirooxindoles.[6] Therefore, we directed our efforts toward study of the reaction between easily accessible methyleneoxindoles with allenoates.

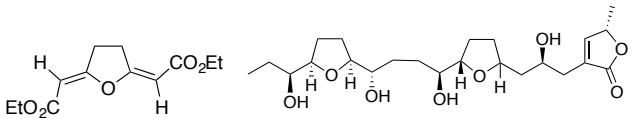
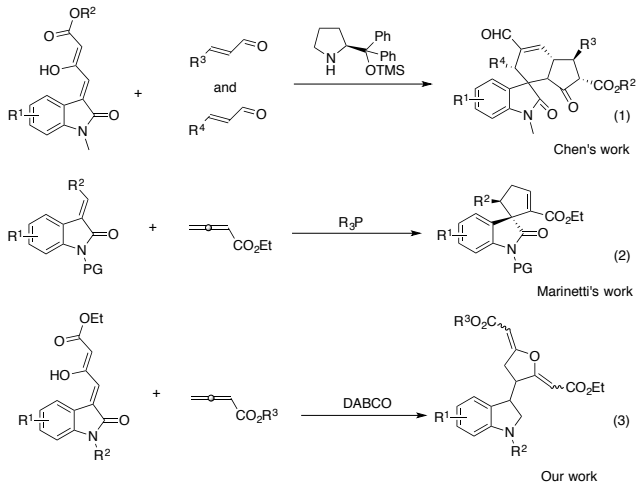


Fig. 1 Medicinally important tetrahydrofuran derivatives.

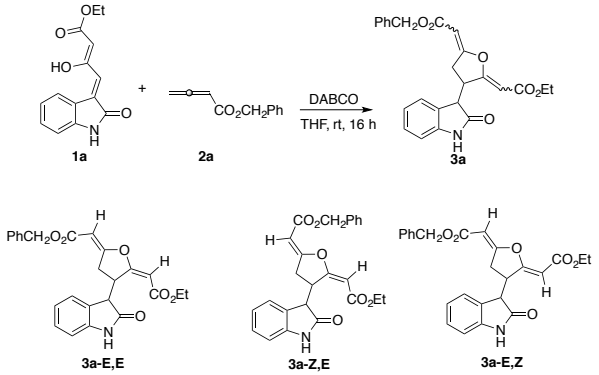
C3-substituted oxindoles demonstrate a diverse array of biological and pharmacological activities.[7] Accordingly, much effort has been devoted in the past years in the preparation of these compounds, especially C3 spirooxindoles via organocatalytic strategies.[8] For example, in 2010, Chen's group reported a three-component domino reaction of methyleneoxindoles with two molecules of α,β-unsaturated aldehyde catalyzed by chiral amine, to obtain a spectrum of spirooxindoles (Scheme 1, eq. 1).[9] Marinetti's group developed a [3+2] cyclization between methyleneoxindoles and allenoates catalyzed by BINOL-derived phosphine, resulting in the formation of spirocyclopentane oxindoles (Scheme 1, eq. 2).[10] Notably, for most of examples, N-protected isatins were seclected as the substrates. Therefore, the development reactions of N-without protected reactions is still highly desirable for practical synthetic application. Our group has had a long-standing interest in developing new domino reactions for construction carbocycles and heterocycles due to their versatility in medicinal chemistry, in natural product synthesis, Given the recent discovery of methyleneoxindoles as versatile substrate in the organocatalytic reaction, we envisioned that domino reactions between methyleneoxindoles and allenoates would yield the desired tetrahydrofuran derivatives. Herein, we wish to report a new domino reaction of 3-oxo-4-(2-oxoindolin-3-ylidene) butanoates with allenoates to form substituted tetrahydrofuran derivatives (Scheme 1, eq. 3).



Scheme 1 Seclected examples of organocatalyzed reactions of methyleneoxindoles.

We began our study with **1a** and **2a** as the model substrates, and the results were summarized in Table 1. When **1a** (1.0 equiv.), **2a** (1.2 equiv.) and 20 mol% DABCO were stirred in

THF at room temperature for 16 h, three new compounds were obtained and part of **1a** was recovered based on TLC analysis (Scheme 2). All of the new products were characterized by using conventional spectroscopic methods including ^{1}H NMR, ^{13}C NMR, DEPT-135, HMQC, NOE, HRMS (ESI), and conclusive evidence for their structure and stereochemistry was derived from single crystal X-ray analysis (Fig. 2 (a)).[11] To our surprise, a 2,3,5-trisubstituted tetrahydrofuran derivative with two exocyclic double bonds was obtained via [3+2] annulation reaction with four isomers. Among these four isomers, two of them can be isolated by column chromatography (**3a-E,E**; **3a-Z,E** (double bond configuration as evidenced by NOESY, see the ESI), and the third isomers (**3a-E,Z**) mixed with trace another isomer in some cases. In view of the surprising result and the fact that tetrahydrofuran derivatives are important compounds, it was obligatory to promote us to continue to optimize the reaction conditions.



Scheme 2 Preliminary results of the [3+2] domino reaction.

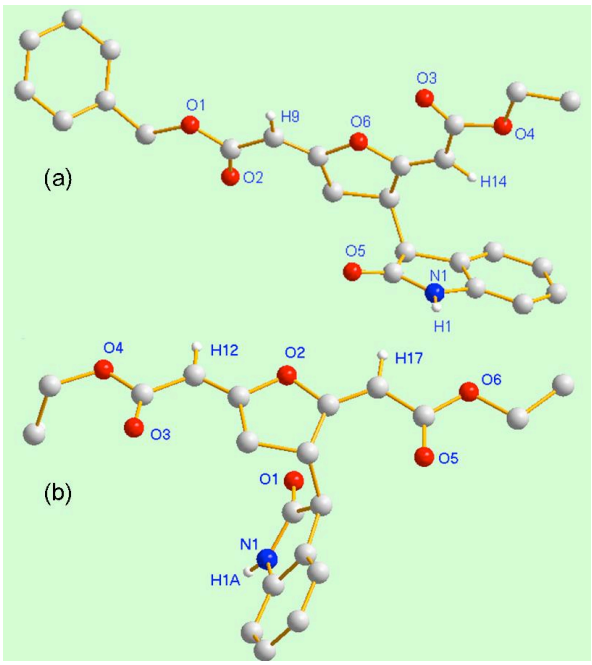
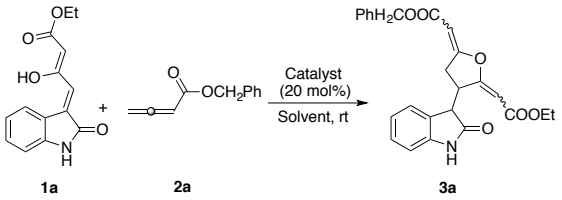


Fig. 2 Crystal structure of **3a-E,Z** (a) and **3c-E,E** (b).

Among the other amines were tested (Table 1), N,N-dimethyl-4-aminopyridine (DMAP) also promoted the domino reaction to give the desired product, however, at least two unknown products also obtained (entry 2). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) exhibited no catalytic activity (entry 3). Triphenyl phosphine used as the catalyst, resulted in a complex mixture which was hard to be analyzed (entry 4). Therefore, we selected DABCO as the best catalyst to optimize the reaction conditions further. During screening solvents, to our delight, the yield can be improved to 90% using CH_2Cl_2. While, the yields of this reaction failed to improve when using toluene, CH_3CN, $CHCl_3$, DMSO and EtOH (entries 6-10). Furthermore, increasing the amount of **2a** to 3 equivalents yield no obviously increased (entry 11). In addition, we did the reaction at 0 ^{o}C or using 10 mol% DABCO as catalyst, a prolonged reaction time was required and the Z/E selectivity of **3a** did not increased (entries 12 and 13). Finally, we used 9-OMe quninine as catalyst, the Z/E selectivity still not improved obviously (Entry 14). Thus, we finally established the optimal reaction conditions for this reaction: using 20 mol% of DABCO as a catalyst and CH_2Cl_2 as a solvent to perform the reaction at room tempetature.

Table 1 Screening catalysts and solvents for the domino reactions[a]



Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]	E,E: Z,E:E,Z[c]
1	DABCO	THF	16	40	1:2:3
2	DMAP	THF	2	50	1:1:2
3	DBU	THF	3	0	-
4	PPh_3	THF	4	complex	-
5	DABCO	CH_2Cl_2	2.5	90	1:2:3
6	DABCO	EtOH	2	62	1:1:3
7	DABCO	CH_3CN	6	20	1:2:3
8	DABCO	toluene	2	30	1:2:3
9	DABCO	$CHCl_3$	2	65	1:2:2
10	DABCO	DMSO	0.5	40	1:1:3
11[d]	DABCO	CH_2Cl_2	2.5	78	1:2:3
12[e]	DABCO	CH_2Cl_2	10	58	1:1:2
13[f]	DABCO	CH_2Cl_2	10	55	1:1:2
14	9-OMe-Quinine	CH_2Cl_2	36	74	1:2:2

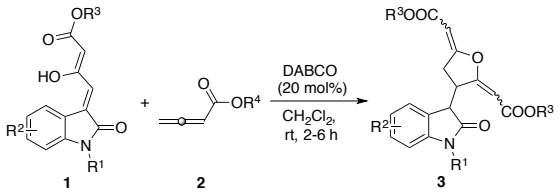
[a] Unless otherwise noted, all reactions are conducted with 0.1 mmol **1a**, 0.12 mmol **2a**, 20 mol% catalyst in 2 mL solvents. [b] Isolated yields. [c] Determined by NMR. [d] 3.0 equiv. **2a** was used. [e] Reaction temperature is 0 ^{o}C. [f] 10 mol% DABCO is used.

Having this optimized condition in hand, we next focused our efforts on exploring the substrate scope with respect to substitution on both methyleneoxindoles substrate (**1**) and allenoates (**2**). The results are summarized in Table 2. We first tested the substituted groups on their benzene ring of methyleneoxindoles (**1**), for 5, 6 or 7 substituted substrates, the corresponding 3-tetrahydrofuran indolones have been isolated in good yields (entries 1-16, except 4).[12] Concerning the electron properties of substituents of **1**, electron-neutral and electron-donating substituents were compatible under the optimized

reaction condition. However, when 6-methoxyl substituted **1d** was surveyed, the 3-tetrahydrofuran indolone derivatives **3j** was isolated in 68% yield with longer reaction time. The reason was that the 6-methoxyl group decreased the activity of the substrate **1d** (entry 10). Next, we examined the effect of substituents on N atom. N-methyl protected substrates (**1**) underwent this reaction in the presence of DABCO, resulting in the corresponding 3-tetrahydrofuran indolone derivatives with excellent yields (entries 12-16). Furthermore, for the N without protecting group substrates, a slightly decreased yield was obtained, with moderate stereoselectivity (entries 1-3 and 5-11). This is because some unknown side reactions occurred. Moreover, we also examined the effect of ester group of **1**, the Z/E selectivity of **3** was not increased when **1j** was used (entry 18). The structure of the product **3c-E,E** (Fig. 2 (b)) and **3m-E,E** (ESI) were confirmed by X-ray structure analysis.[11]

Next, we examined the scope of the reaction with various allenoates. Benzyl buta-2,3-dienoate **2a**, methyl buta-2,3-dienoate **2b**, and ethyl buta-2,3-dienoate **2c** were accommodated in the reaction, leading to the generation of desired products in high yields (Table 2, except entry 4). However, no desired product was isolated when *tert*-butyl buta-2,3-dienoate **2d** was used (Table 2, entry 4).

Table 2 Scope of the DABCO catalyzed domino reactions[a]



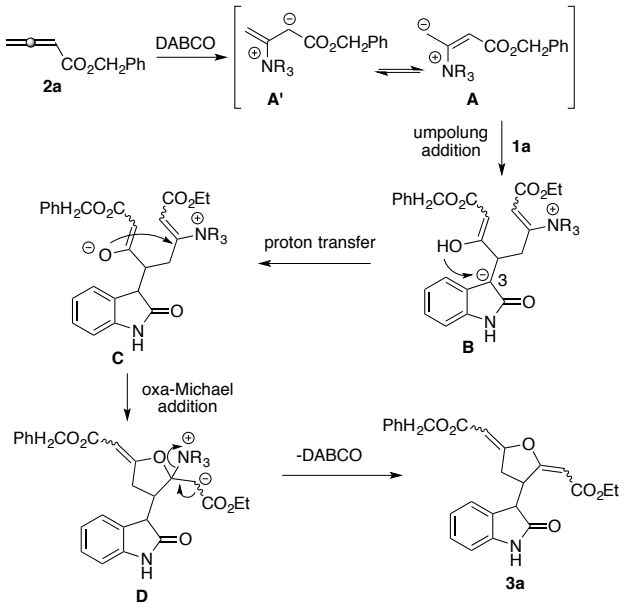
1a: R^1 = H, R^2 = H, R^3 = OEt; **1b**: R^1 = H, R^2 = 5-CH_3, R^3 = OEt; **1c**: R^1 = H, R^2 = 5-OCH_3, R^3 = OEt; **1d**: R^1 = H, R^2 = 6-OCH_3, R^3 = OEt; **1e**: R^1 = H, R^2 = 7-CH_3, R^3 = OEt; **1f**: R^1 = CH_3, R^2 = H, R^3 = OEt; **1g**: R^1 = CH_3, R^2 = 5-CH_3, R^3 = OEt; **1h**: R^1 = CH_3, R^2 = 5-^{t}Bu, R^3 = OEt; **1i**: R^1 = H, R^2 = 5-Cl, R^3 = OEt; **1j**: R^1 = H, R^2 = H, R^3 = $OCH(CH_3)_2$.

2a: R^4 = CH_2Ph, **2b**: R^4 = CH_3, **2c**: R^4 = C_2H_5, **2d**: R^4 = ^{t}Bu

Entry	1	2	Tmie (h)	3 Yield (%)[b]	E,E: Z,E: E,Z[c]
1	**1a**	**2a**	2.5	90	1:2:3
2	**1a**	**2b**	2	51	1:1:1
3	**1a**	**2c**	3	62	1:2:3
4	**1a**	**2d**	6	0	-
5	**1b**	**2a**	3	62	1:1:2
6	**1b**	**2b**	3	73	1:2:3
7	**1b**	**2c**	3	79	1:1:1
8	**1c**	**2a**	2	72	1:3:4
9	**1c**	**2c**	3	70	1:1:1
10	**1d**	**2a**	3	68	1:1:2
11	**1e**	**2a**	1.5	74	1:2:3
12	**1f**	**2a**	1	90	1:1:1
13	**1f**	**2c**	5	75	1:1:2
14	**1g**	**2b**	4	51	1:1:2
15	**1g**	**2c**	5	76	1:1:1
16	**1h**	**2a**	1	89	1:2:2
17	**1i**	**2a**	1	46	1:3:5
18	**1j**	**2a**	3	66	1:2:4

[a] Reaction conditions: **1** (0.1 mmol), allenoates **2** (0.12 mmol), DABCO (0.02 mmol) in 2 ml CH_2Cl_2 at rt. [b] Isolated yields. [c] Determined by isolated yields.

On the basis of our experimental results and some related literature,[13, 14] a possible mechanism for this domino reaction is outlined in Scheme 3. The DABCO acted as a nucleophilic trigger and attacked the β carbon of allenoates to produce the allylic carbanion intermediate **A**, which subsequently underwent an umpolung addition to **1a** to give the intermediate **B**. After proton transfer from enol (OH) to carbanion (3 position), the enol anion **C** produced, which was through oxa-Michael addition to form **D**, and then elimination of DABCO to furnish the desired product **3a**.



Scheme 3 Possible reaction mechanism.

Conclusions

In conclusion, we have developed a convenient and efficient organocatalytic domino strategy for the synthesis of tetrahedydrofuran derivatives containing two exocyclic double bonds from readily available and simple starting materials. From the synthetic point of view, this protocol represents an extremely simple and atom-economic way to construct four 2,3,5-trisubstituted tetrahydrofuran derivatives in one pot. Further studies on the expansion of the substrate scope, asymmetric catalytic reactions and the application of this methodology to total synthesis are currently underway and will be reported in due course.

Acknowledgements

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Notes and references

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[b] K. Zhang, Department of Chemistry and Biochemistry, University of California, Los Angeles
‡ These authors contribute to this work equally.
† Electronic supplementary information (ESI) available: Experimental procedures, structural proofs, CIF file of CCDC-1015270 (**3c-E,E**), CCDC-1015271(**3a-E,Z**) and CCDC-1015272 (**3m-E,E**). See DOI: 10.1039/b000000x/

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