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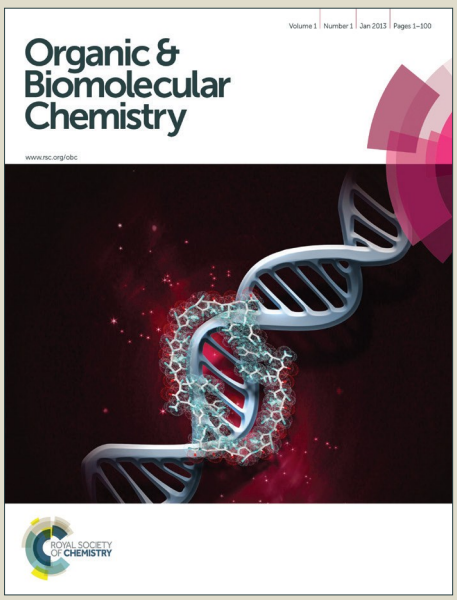

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DABCO-catalyzed unusual [4+2] cycloaddition reaction: non-substituted allenoate acts as a four-carbon synthon and facile synthesis of spirooxindoles

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A DABCO-catalyzed domino reaction between methyleneoxindoles and allenoate which enables the direct synthesis of spirooxindoles is reported. This is the first example of a non-substituted allenoate to act as a four-carbon synthon in a tertiary amine-catalyzed reaction.

Over the past two decades, organocatalytic domino reactions involving electron-deficient allenoates have been well studied. A number of new allenoate-based reactions with high synthetic potentials have also been developed.[1] The pioneering work of Lu's [3+2] cycloaddition has led to many significant advances in Lewis base-catalyzed annulation reactions.[2] Many of these reactions are based on phosphine and amine catalysts. The types of phosphine-catalyzed reactions are much more than amine-catalyzed reactions. In amine-catalyzed domino reactions involving allenoates, the allenoates usually act as two-carbon (β, γ or α, β) synthons (Fig. 1a, 1b).[3] There is only one example of an α-substituted allenoate acting as a four-carbon synthon in a tertiary amine-catalyzed cycloaddition reaction (Fig. 1c).[4] To the best of our knowledge, non-substituted allenoates acting as four-carbon synthons in tertiary amine-catalyzed reactions has not been reported before.[5]

Spirooxindoles are ubiquitous motifs of biologically active compounds (Fig. 2). Because of their considerable medicinal potential, researchers have been trying to design efficient synthetic methods for spirooxindole-scaffold systems. In particular, organocatalytic domino reactions have proven effective for constructing spirooxindoles.[6] However, despite the considerable effort that has been made in this field, more efficient synthetic strategies are required to diversify the spirooxindole product library. Herein, we wish to report an unusual DABCO-catalyzed [4+2] cycloaddition reaction between methyleneoxindoles and allenoate (Fig. 1d). To the best of our knowledge, this is the first report of a non-substituted allenoate acting as a four-carbon synthon in a tertiary amine-catalyzed reaction.[7]

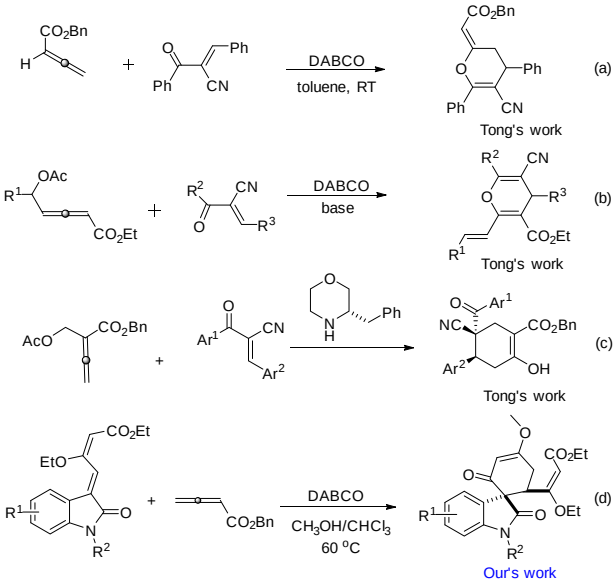

Fig. 1 Tertiary amine-catalyzed domino reactions of allenoates

During our ongoing investigation of organocatalyzed domino reactions, we synthesized methyleneoxindole **1**.[8] As shown in Scheme 1, methyleneoxindole **1** has many reaction sites and is

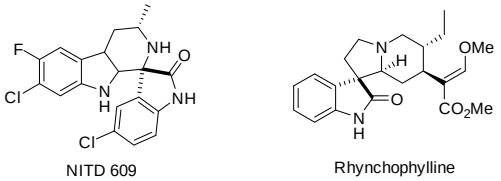

Fig. 2 Representative examples of pharmaceutical molecules containing a spirooxindole core structure.

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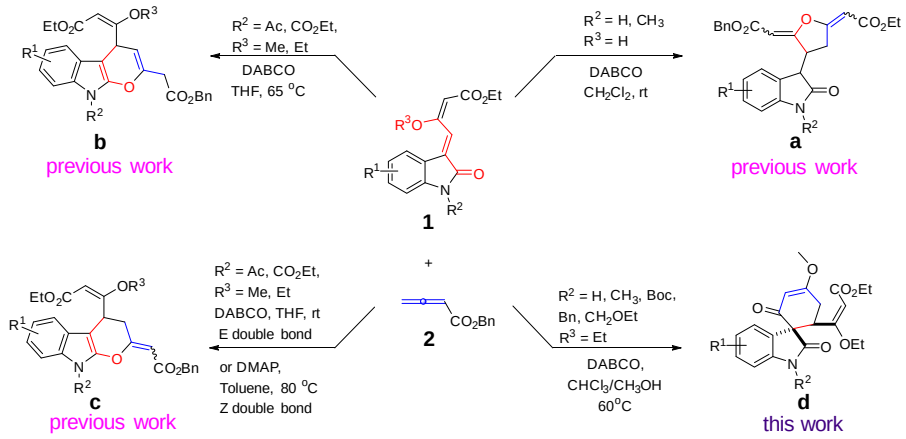


Scheme 1. Reactions between methyleneoxindoles and allenoates catalyzed by organocatalysts.

a versatile reaction partner. For example, when R^3 = H, the reaction of **1** and allenoate **2** gives tetrahydrofuran derivatives (Scheme 1a). After protecting the enol as an ester, we can control the reaction to obtain pyrano[2,3-b]indol or dihydropyrano[2,3-b]indol derivatives (Scheme 1 b, c). On the basis of these results, we envisioned that tertiary amines might be able to catalyze methyleneoxindole and allenoate to form spirooxindoles by adjusting the N protective groups (Scheme 1d).

In order to test our postulation, we synthesized a series of N-non-protected substrates **1**,[9] and studied their reactivity with allenoate. We selected **1a** and **2a** as model substrates and the results are summarized in Table 1. When **1a** (0.5 mmol), **2a** (1 mmol) and DABCO (1,4-diazabicyclo[2.2.2]octane) (30 mol%) were stirred in MeOH (2 mL) at room temperature, the new product **3a** was obtained in 18% yield as a single diastereomer, and 76% **1a** was recovered. After purification by column chromatography, **3a** was characterized by ^{1}H NMR, ^{13}C NMR, HRMS, and conclusive evidence for the structure and stereochemistry was obtained by single crystal X-ray analysis (Fig. 3).[9] Multiple events were involved in this reaction, including: (1) spirooxindoles were obtained via a DABCO-catalyzed domino reaction, (2) two C-C bonds and one C-O bond were formed, (3) non-substituted allenoate **2a** acted as a four-carbon synthon, and (4) the methoxy group acted as a nucleophilic reagent and appeared in the final product.

The new reactivity we observed prompted us to optimize reaction conditions to improve yield. Results can be found in Table 1. We found that performing the reaction at 60 °C in MeOH improved the yield to 43% (entry 2). Changing the solvent from MeOH to $CHCl_3$ gave **3a-OBn** in 30% yield (entry 3).[10] When toluene was selected as solvent, **3a-OBn** was obtained in 40% (entry 4). MeOH plays an important role in

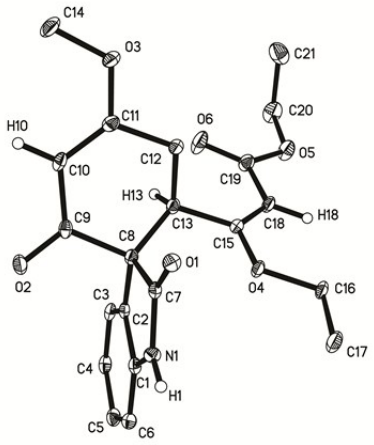
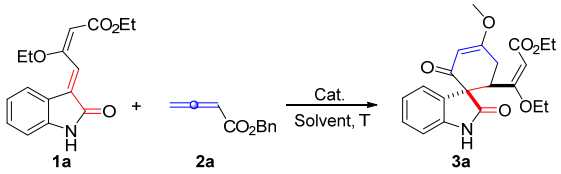


Fig. 3 Crystal structure of **3a**

this reaction as carrying out the reaction in other solvents such as CH_3CN, THF, dioxane, DMF, DMSO gave no desired product (entries 5-8). In order to continue improving the yield, we tested mixed solvent systems. Using toluene and MeOH as solvent (v:v = 1:1.5) yielded only 36% **3a** (entry 9). To our surprise, using a 1:1.5 volume solution of $CHCl_3$ and MeOH gave an improved yield of 47% (entry 10). It is important to note that for all cases, the reaction did not proceed to full conversion even after an extended reaction time. To further improve conversion, using $CHCl_3$ and MeOH as the solvent (v:v = 1:1.5), and adding DABCO (12 mol% per batch) and **2a** (1 eq. per batch) in three batches led to an improved yield of 53% (entry 11). Other ratios of $CHCl_3$/CH_3OH or using methyl buta-2,3-dienoateinstead of **2a** did not produce better results (entries 12-15). Other Lewis bases such as DMAP (4-dimethylaminopyridine), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), NEt_3, and PPh_3 were examined but were all inefficient

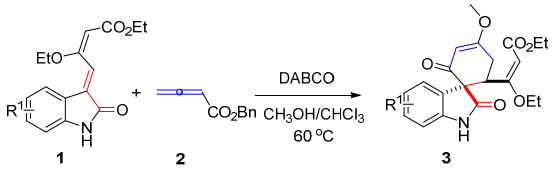
Table 1. Optimization of the domino reaction[a]



Entry	Cat.	Solvent	Time (h)	Yield (%)[b]
1[c]	DABCO	CH_3OH	6	18
2[d]	DABCO	CH_3OH	6	43
3[d]	DABCO	$CHCl_3$	6	30
4[d]	DABCO	Toluene	6	40
5[d]	DABCO	CH_3CN	6	0
6[d]	DABCO	Dioxane	6	0
7[d]	DABCO	DMF	6	0
8[d]	DABCO	DMSO	6	0
9[d]	DABCO	toluene/CH_3OH (1:1.5)	7	36
10[d]	DABCO	$CHCl_3$/CH_3OH (1:1.5)	7	47
11[e]	DABCO	$CHCl_3$/CH_3OH (1:1.5)	7	53
12[e]	DABCO	$CHCl_3$/CH_3OH (1:1)	7	39
13[e]	DABCO	$CHCl_3$/CH_3OH (1:2)	7	36.5
14[e]	DABCO	$CHCl_3$/CH_3OH (1:3)	7	37
15[f]	DABCO	$CHCl_3$/CH_3OH (1:1.5)	7	51
16[e]	DMAP	$CHCl_3$/CH_3OH (1:1.5)	7	17
17[e]	DBU	$CHCl_3$/CH_3OH (1:1.5)	7	trace
18[e]	Et_3N	$CHCl_3$/CH_3OH (1:1.5)	7	0
19[e]	PPh_3	$CHCl_3$/CH_3OH (1:1.5)	7	0
20[g]	$(DHQ)_2PHAL$	$CHCl_3$/CH_3OH (1:1.5)	7	32

[a] Reaction conditions: **1a** (0.5 mmol), allenoate **2a** (1 mmol) and catalyst (30 mol%) in 2 mL solvent. [b] Isolated yields [c] Run at room temperature. [d] Run at 60 °C. [e] Run at 60 °C and added DABCO (12 mol%) and **2a** (1.0 eq) in three batches. [f] Methyl buta-2,3-dienoate instead of **2a** was used. [g] $(DHQ)_2PHAL$ is hydroquinine 1,4-phthalazinediyl diether.

Table 2. Scope of the DABCO-catalyzed domino reaction of non-protected substrates[a]



Entry	R^1	Time (h)	**3**	Yield (%)[b]
1	H (**1a**)	7	**3a**	53 (63)[c]
2	5-CH_3 (**1b**)	7	**3b**	42 (57)[c]
3	5-OCH_3 (**1c**)	7	**3c**	40 (73)[c]
4	5-F (**1d**)	7	**3d**	86
5	5-Cl (**1e**)	7	**3e**	90
6	5-Br (**1f**)	7	**3f**	77
7	5-I (**1g**)	7	**3g**	68
8	5-OCF_3 (**1h**)	6	**3h**	67
9	5-NO_2 (**1i**)	5	**3i**	64
10	6-F (**1j**)	7	**3j**	66
11	6-Cl (**1k**)	7	**3k**	33
12	6-Br (**1l**)	7	**3l**	76
13	7-F (**1m**)	7	**3m**	84
14	7-Cl (**1n**)	7	**3n**	86
15	7-Br (**1o**)	7	**3o**	88
16	5,6-di-F (**1p**)	7	**3p**	66

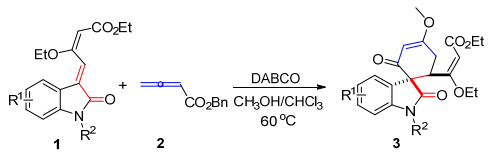
[a] Reaction conditions: **1** (0.5 mmol), allenoate **2a** (0.5 mmol× 3), DABCO (12 mol% ×3) in $CHCl_3$/MeOH (1:1.5, 2 mL) at 60 °C. [b] Isolated yields. [c] Allenoate **2a** (0.5 mmol× 5), DABCO (12 mol% ×5), reaction time 10 h.

(entries 16-19). When the chiral tertiary amine $(DHQ)_2PHAL$ (hydroquinine 1,4-phthalazinediyl diether) was used, only a 32% yield and a 5% ee were observed (entry 20).

Having established the optimal reaction conditions, we explored the substrate scope with respect to substitutions on methyleneoxindoles **1**. The results are summarized in Table 2. The functionalized methyleneoxindoles **1** bearing diverse electron-withdrawing or electron-donating aryl groups at the C5, C6 or C7 positions were well tolerated and gave the desired product in 33-90% (entries 1-16). Methyleneoxindoles with electron-withdrawing groups were transformed in higher yield, while methyleneoxindoles with electron-donating groups gave lower yields. For example, 5-halo substituted methyleneoxindoles reacted with **2a** to afford the corresponding **3d**-**3g** in 68-90% yield (entries 4-7). Reaction with **1d** (5-F) and **1e** (5-Cl) especially led to high yields. On the other hand, reaction with **1b** (5-CH_3) and **1c** (5-CH_3O) gave **3b** and **3c** in 42% and 40% yield, respectively (entries 2-3). In order to improve these reaction yields, we added DABCO and **2a** in five batches; this produced good yields (entries 1-3). It is important to note that the tolerance of the iodo- and bromo- group on the phenyl ring is especially synthetically useful and this provides an opportunity for further functionalization (entries 6-7). For substrate **1i** bearing a strong electron-withdrawing group (-NO_2), the reaction also gave the desired product **3i** in 64% yield (entry 9). In addition, when trifluoromethoxy group (**1h**) was installed at the C5 position of **1**, the desired product **3h** was obtained in moderate yield (entry 8). A range of C7-substituted **1** was also investigated. The methyleneoxindoles **1m** (7-F), **1n** (7-Cl) and **1o** (7-Br) reacted and produced good yields (entries 13-15). Moreover, when C6 substituted substrates were used in the reaction, equally excellent results were obtained except for **1k** that only led to 33% yield (entries 10-12). Furthermore, substrate **1p** (5,7-difluoro) also afforded product **3p** in 66% yield (entry 16). It is important to note that C4-substituted methyleneoxindoles were unreactive for this domino reaction under identical reaction conditions. This is likely due to steric hindrance.

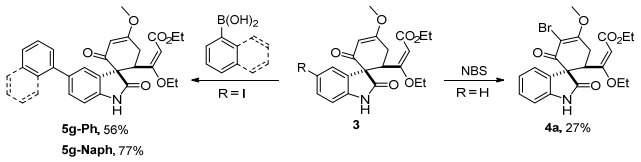
The scope of this domino reaction with regard to N-protected **1** was then explored. The results are shown in Table 3. The -CH_3, -Bn, -Boc, and -CH_2OEt protected substrates gave

Table 3. Scope of the DABCO catalyzed domino reaction of N-protected substrates[a]



Entry	R^1	R^2	Time (h)	3	Yield(%)[b]
1	H (**1q**)	CH_3	7	**3q**	68
2	5-Cl (**1r**)	CH_3	6	**3r**	82
3	5-Br (**1s**)	CH_3	7	**3s**	80
4	H (**1t**)	Bn	7	**3t**	77
5	5-Cl (**1u**)	Bn	4	**3u**	90
6	5-Br (**1v**)	Bn	4	**3v**	90
7	H (**1w**)	Boc	7	**3w**	62
8	H (**1x**)	CH_2OEt	6	**3x**	81

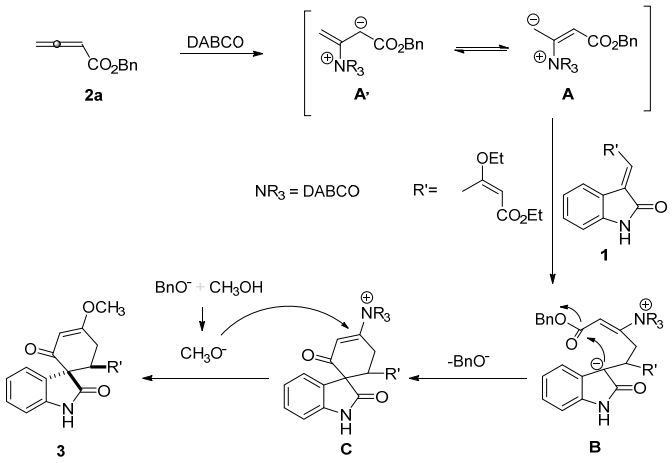
[a] Reaction conditions: **1** (0.5 mmol), allenoate **2a** (0.5 mmol×3), DABCO (12 mol% × 3) in $CHCl_3$/MeOH (1:1.5, 2 mL) at 60 °C. [b] Isolated yields.



Scheme 2. Chemical transformations of **3**.

the corresponding products. The results showed that the electronic nature of substituents on the methyleneoxindoles had a pronounced effect on the efficiency of this domino reaction. For example, substrates **1** containing chloro- or bromo- group at the C5 position was converted more effectively (entries 2, 3, 5, 6). Furthermore, among these N-protective substrates, N-Bn substrates **1t**, **1u** and **1v** were converted more efficiently than the corresponding N-CH_3 substrates. We were also intrigued to find that substrate **1w** (N-tert-butoxycarbonyl) and **1x** (N-ethoxymethyl group) exhibited good performance and gave the corresponding product **3w** and **3x** in 62% and 81% yield, respectively (entries 7-8). It should be noted that the N-protected substrates were more efficiently converted than the non-protected substrates (Table 3 vs Table 2). The structure of product **3s** was unambiguously assigned by X-ray diffraction.[9]

All of the test reactions were performed at small scale but scale-up was easily accomplished. For example, the desired spirooxindole **3e** was obtained in 88% yield when the reaction was scaled up to 500 mg of **1e** under the optimized reaction conditions. Furthermore, the resulting highly functionalized spirooxindoles offer many opportunities for chemical transformations. For example (Scheme 2), the bromination reaction of **3a** was easily conducted with NBS in CCl_4 and



Scheme 3. Possible mechanism of this domino reaction.

afforded **4a** in 27% yield. The Suzuki coupling reaction of **3g** with phenylboronic acid and naphthalen-2-ylboronic acid gave the desired products **5g-Ph** and **5g-Naph** in 56% and 77% yields, respectively.

Although the mechanism of the above cyclization reaction has not been unequivocally established, one reasonable pathway is outlined in Scheme 3. DABCO acts as a nucleophilic trigger and attacks the β carbon of the allenoate to produce intermediates **A** and **A'**. The allylic carbanion **A** then subsequently attacks substrate **1** to give intermediate **B**. Through intramolecular addition, **B** becomes intermediate **C**. Finally, the nucleophilic reagent (CH_3O^-) attacks **C** to give the desired product and regenerate DABCO.

In conclusion, we have developed the first example of an amine-catalyzed [4+2] cycloaddition reaction in which non-substituted allenoate acted as a four-carbon synthon. This domino reaction afforded an efficient method for the synthesis of spirooxindoles bearing the 3-alkyloxycyclohex-2-en-1-one moiety. Further investigations of an asymmetric version and its applications in the synthesis of biologically interesting molecules are underway, and the results will be reported in due course.

Acknowledgments

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9 CCDC: 1418019 (**1h**), 1418021 (**3a**), and 1418020 (**3s**).

10 The structure of **3a-OBn** is similar to **3a** with a methoxyl group substituted by a benzyloxy group.