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Diversity-Oriented Synthesis of Spirocyclohexene Indane-1,3-diones and Coumarin-Fused Cyclopentanes via an Organobase-Controlled Cascade Reaction

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Abstract. An organobase-controlled, divergent cascade reaction to construct spirocyclohexene indane-1,3-diones and coumarin-fused cyclopentanes is reported. The cascade reaction is triggered by the 1,6-addition of 3-homoacylcoumarins to the indanedione-derived acceptors and further regio/chemoselective reaction that preferentially resulted in spiro systems and fused cyclopentanes in a diversity-oriented manner. The 1,6-addition/aldol and 1,6-addition/vinylogous Michael addition cascade processes were controlled by different base/solvent systems to the predominant formation of one of the two carbocyclic compounds.

Keywords: Diversity-oriented synthesis; 1,6-addition; aldol reaction; vinylogous Michael addition; spiro and fused systems

Introduction

Diversity-oriented synthesis via an organocatalytic approach offers a cost-effective strategy to access vast libraries of bioactive molecules.[1] The generation of molecular diversity and complexity plays a crucial role in drug discovery to ascertain a variety of structurally diverse compounds.[2] Synthesis of spiro/fused systems is a topic of recent interest because of their numerous applications in medicinal chemistry.[3] In recent years, elegant methods were reported for cascade reactions initiated by 1,6-addition to generate complex structural motifs.[4] Competing from the 1,4-addition reaction, facilitation of 1,6-addition and further cascade reaction is a great challenge in synthetic chemistry due to the presence of more reactive β-position in extended conjugation.[5] A few strategies have been adopted to overcome such complications, such as increasing steric crowding at the β-position or by activating δ-position with a suitable catalyst.[6] The LUMO-lowering strategy has also been one of the most frequently employed activation modes to realize 1,6-addition reactions.[7] On the other hand, vinylogous Michael addition reaction has long attracted the attention of synthetic chemists due to the potential to construct a C-C bond at remote γ-position.[8] The difficult control of regioselectivity is a major challenge in vinylogous Michael addition and 1,6-addition reactions. Comprising both of these two reactions in a single cascade is the most challenging task and the development of those cascade reactions has attracted great interest.

Indanedione-derived spiro six-membered carbocycles were found in many natural products and bioactive molecules, most of those are generated via 1,4-addition reactions of 1,3-indanedione systems.[9] Several conjugated systems were found as acceptors in the 1,6-addition reaction to activate a remote δ-position.[10] However, 1,3-indanedione bearing an extended conjugation was rarely explored as an acceptor in 1,6-addition initiated cascade reactions.[11] On the other hand, coumarin and its derivatives are privileged heterocyclic scaffolds, and their numerous applications have been found in medicinal and materials chemistry.[12] Furthermore, these compounds tend to show diverse reactivity, which can be tuned by proper functionalization.[13] Owing to their immense biological activities and their applications in medicinal chemistry (Figure 1),[14] the development of an efficient method that could

provide both of the spiro and fused systems is highly desirable.

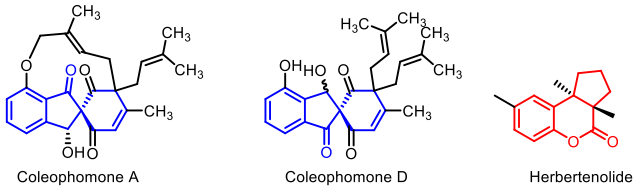
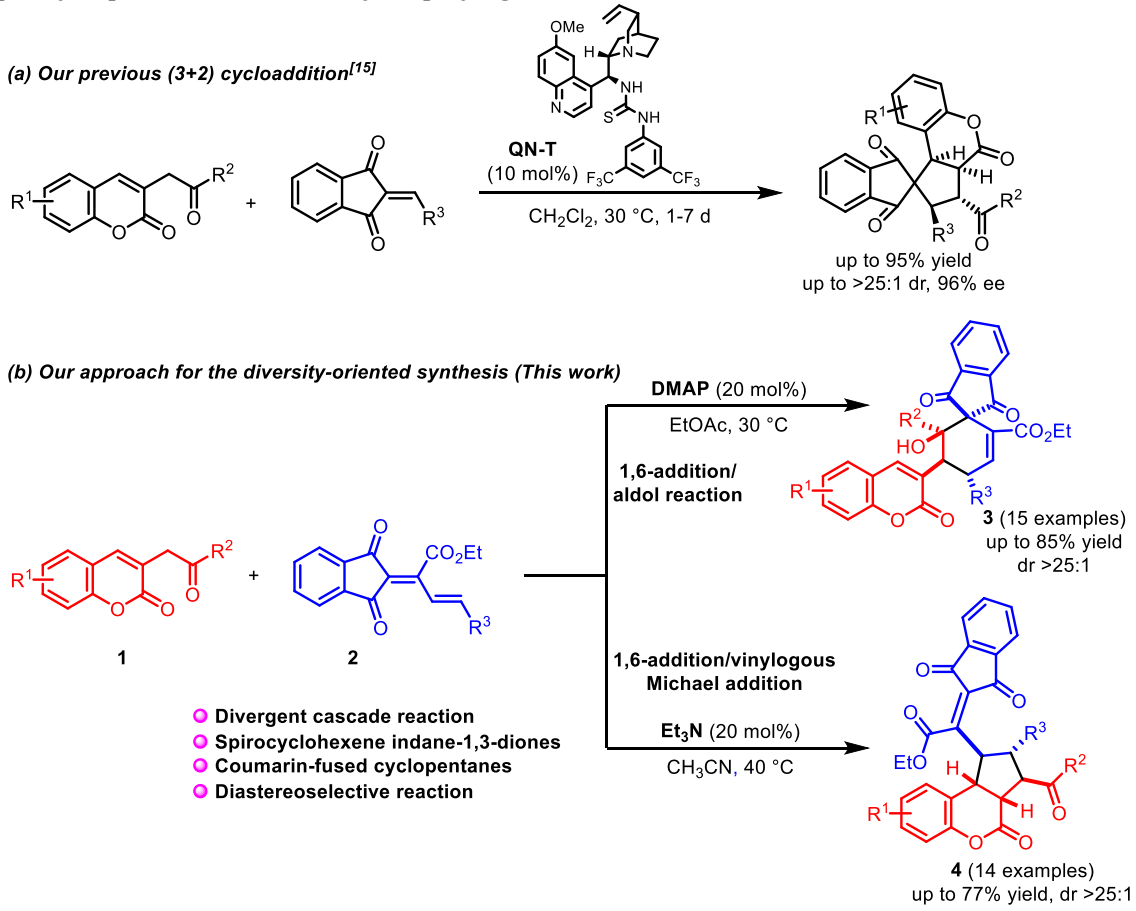


Figure 1. Natural products with spirocyclic 1,3-indanedione and coumarin-fused cyclopentane moieties

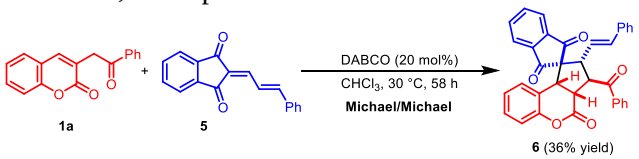
Recently, we have reported a (3+2) cycloaddition reaction for the generation of coumarin/indanedione-fused spirocyclopentane derivatives by employing 3-homoacylcoumarin as an all-carbon 1,3-dipole precursor with 2-arylidene-1,3-indanedione (Scheme 1).[15] In continuation of our efforts for the development of novel cascade reactions,[16] we envisioned that complex structural motifs could be synthesized via an organocatalytic cascade strategy initiated by 1,6-addition, and that could turn into a divergent synthesis of spiro and fused carbocycles. In this context, we report a diversity-oriented construction of spirocyclohexene indane-1,3-diones and coumarin-fused cyclopentanes in good yields with high diastereoselectivities from 3-homoacylcoumarin and 1,3-indanedione-derived 1,6-acceptor as reacting partners via an organobase-controlled cascade reaction.



Scheme 1. (a) Synthesis of coumarin/indandione-fused spirocyclopentanes (b) Our design for the synthesis of spiro and fused systems.

Results and Discussion

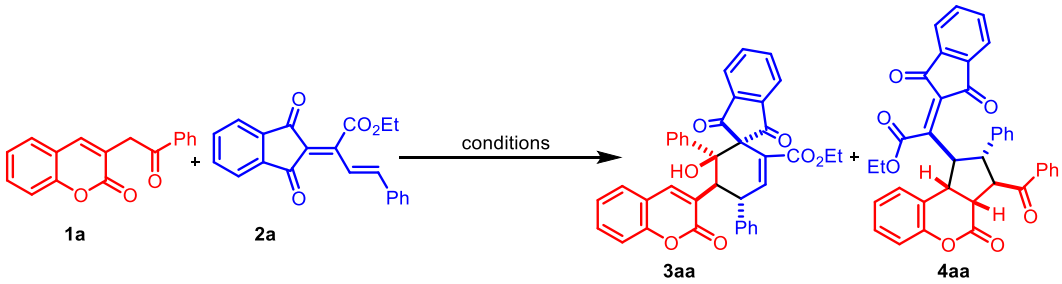
Initially, we have examined the reaction with 3-homoacylcoumarin **1a** and 2-(3-phenylallylidene)-1,3-indanedione **5** in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) at 30 °C. It was found that a double Michael cascade reaction took place to generate compound **6** in 36% yield (Scheme 2). To realize our objective, we envisioned that if we could incorporate a group at the more reactive *β*-position, the nucleophile would be possible to attack at *δ*-position and that would further lead to a cascade reaction. Thus, the substrate **2a** has been designed as a model 1,6-acceptor for our studies.



Scheme 2. Double Michael addition reaction of 3-homoacylcoumarin **1a** with **5**.

Accordingly, we have carried out the reaction with 3-homoacylcoumarin derivative **1a** and 1,3-indanedione-derived 1,6-acceptor **2a** in the presence of DABCO in $CHCl_3$ at 30 °C. The products **3aa** and **4aa** were observed in 24% yield and a trace amount of yield, respectively (Table 1, entry 1). To optimize the reaction conditions, different bases and various solvents were screened (entries 2–10). Notably, the strong bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and 1,1,3,3-tetramethylguanidine (TMG) employed in the reaction conditions for the efficient deprotonation of 3-homoacylcoumarin, but only trace amount of desired products **3aa** and **4aa** were found after 48–60 h (entries 3 and 4). Delightfully, product **3aa** was obtained in 61% yield along with a trace amount of product **4aa** using 4-dimethylamino pyridine (DMAP) as a base in chlorobenzene or EtOAc as solvent (entries 7 and 8). The yield of the product **3aa** was further increased to 73% by using dry EtOAc as solvent under anhydrous conditions (entry 11). Significantly, by employing the 1.2 equiv of **2a** was found to furnish the desired product **3aa** in 84% yield in a 1,6-addition/aldol cascade reaction (entry 12). We have also found that raising the reaction temperature to 50 °C did not improve the yield of the product (entry 13). When the reaction conditions were screened with different bases, we have found the formation of two types of products in a few cases. These results opened up the possibility of diversity-oriented synthesis by altering the reaction conditions. Further optimization of the reaction using Et_3N as a base furnished the products **3aa** and **4aa** in 27% and 5% yields in EtOAc (entry 14). To our surprise, the reaction in acetone solvent afforded the products **3aa** and **4aa** in 20% and 50% yields, respectively (entry 15). The screening of solvents, temperature and utilizing dry solvents revealed that the reaction in CH_3CN at 40 °C furnished the fused ring systems in good yields (entries 16–21). Finally, the optimal conditions for the selective synthesis of products **3aa** and **4aa** were determined as listed in entries 12 and 17, respectively. Therefore, the outcome of 1,6-addition/aldol and 1,6-addition/vinylogous Michael addition cascade reactions can be tuned by appropriate selection of the reaction conditions from one of the DMAP/EtOAc and Et_3N/CH_3CN systems. The structures of the compounds **3aa** and **4aa** were further confirmed by X-ray diffraction analysis (see Supporting Information for detailed optimization and crystal data).[17]

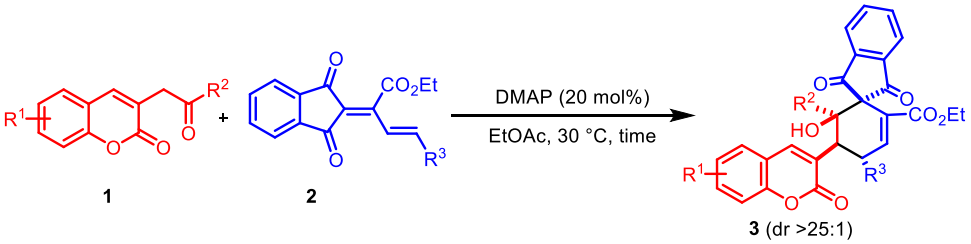
Table 1. Optimization of the reaction conditions.[a]



Entry	Base	Solvent	T (°C)	*t* (h)	**3aa**/**4aa** (%)[b]
1	DABCO	$CHCl_3$	30	60	24/trace
2	DIPEA	$CHCl_3$	30	60	23/trace
3	DBU	$CHCl_3$	30	48	trace/trace
4	TMG	$CHCl_3$	30	60	trace/6
5	DMAP	$CHCl_3$	30	60	38/trace
6	DMAP	toluene	30	60	40/trace
7	DMAP	PhCl	30	60	61/trace
8	DMAP	EtOAc	30	60	61/trace
9	DMAP	THF	30	60	53/trace
10	DMAP	CH_3CN	30	60	39/trace
11[c]	DMAP	EtOAc	30	84	73/trace
12[c,d]	DMAP	EtOAc	30	84	84[e]/trace
13[c,d]	DMAP	EtOAc	50	48	70/8
14	Et_3N	EtOAc	30	60	27/5
15	Et_3N	acetone	30	60	20/50
16	Et_3N	CH_3CN	30	84	10/53
17	Et_3N	CH_3CN	40	60	10/65
18	Et_3N	$CHCl_3$	40	60	13/trace
19	Et_3N	EtOAc	40	60	16/trace
20	Et_3N	acetone	40	72	16/50
21[f]	Et_3N	CH_3CN	40	60	14/47

[a]Unless otherwise specified, all reactions were carried out using **1a** (0.1 mmol), **2a** (1.0 equiv), and base (20 mol%) in the given solvent (0.5 mL). [b]Yield was determined by ^{1}H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard. [c]The reaction was carried out using dry EtOAc as solvent under argon. [d] 1.2 equiv of **2a** was used. [e]Isolated yield of **3aa**. [f]The reaction was carried out using dry CH_3CN as a solvent.

Table 2. Substrate scope of 1,6-addition/aldol cascade reaction.[a,b]



Entry	R^1/R^2	R^3	*t* (h)	**3** (%)[c]
1	H/Ph (**1a**)	Ph (**2a**)	84	84 (**3aa**)
2	6-Cl/Ph (**1b**)	Ph (**2a**)	72	60 (**3ba**)
3	6-Br/Ph (**1c**)	Ph (**2a**)	252	59 (**3ca**)
4	6-OMe/Ph (**1d**)	Ph (**2a**)	168	66 (**3da**)
5	7-OMe/Ph (**1e**)	Ph (**2a**)	240	43 (**3ea**)
6	8-OMe/Ph (**1f**)	Ph (**2a**)	48	trace (**3fa**)
7	6,8-Cl_2/Ph (**1g**)	Ph (**2a**)	96	34 (**3ga**)
8	H/4-Cl-Ph (**1h**)	Ph (**2a**)	84	45 (**3ha**)
9	H/4-OMe-Ph (**1i**)	Ph (**2a**)	240	20 (**3ia**)
10	H/CH_3 (**1j**)	Ph (**2a**)	72	66 (**3ja**)
11	H/Ph (**1a**)	2-Cl-Ph (**2b**)	240	58 (**3ab**)
12	H/Ph (**1a**)	3-Cl-Ph (**2c**)	72	76 (**3ac**)
13	H/Ph (**1a**)	4-Cl-Ph (**2d**)	84	85 (**3ad**)
14	H/Ph (**1a**)	4-Br-Ph (**2e**)	72	79 (**3ae**)
15	H/Ph (**1a**)	4-NO_2-Ph (**2f**)	60	74 (**3af**)
16	H/Ph (**1a**)	4-OMe-Ph (**2g**)	240	20 (**3ag**)

[a]Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol), **2** (1.2 equiv), and DMAP (20 mol%) in dry EtOAc (1.0 mL) under argon and stirred at 30 °C. [b]Trace amount of product **4** was determined by ^{1}H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard in all the cases. [c]Isolated yield of the product **3**.

Having established the optimal conditions, the substrate scope of spirocyclohexene indane-1,3-diones **3** was further investigated (Table 2). Examination of different substituents (R^1 and R^2) of 3-homoacylcoumarin **1** for the reaction with **2a** afforded the desired products **3** in moderate to good yields with high diastereoselectivities. The electronic properties of R^1 substituents on the coumarin ring did not follow any trend. For example, 6-Cl, 6-Br, and 6-OMe groups on the coumarin ring provided desired products up to 59–66% yields, albeit with different rates of the reaction (entries 2–4). However, the position of substituent on the coumarin ring has a significant impact on the reaction outcome. The coumarin derivatives bearing 7-OMe, 8-OMe, and 6,8-Cl_2 substituents on the coumarin ring reacted with **2a** to afford the corresponding products in low to moderate yields (entries 5–7). Furthermore, we have carried out the reactions of different R^2 substitutions of the coumarin **1** with **2a** under the optimized conditions. A substrate **1h** with chloro group at *para*-position of the aryl ring is more efficient than the substrate **1i** bearing methoxy group (entries 8 and 9). The coumarin derivative with methyl (R^2) group **1j** also well-tolerated, and the desired product **3ja** was obtained in 66% yield (entry 10).

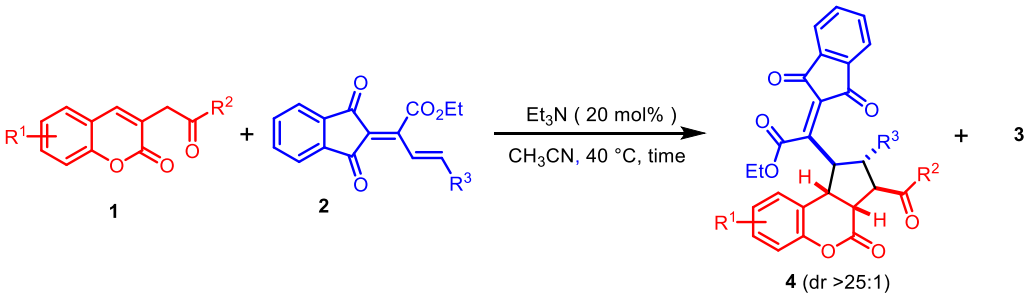
Furthermore, indanedione-derived acceptors **2** bearing different R^3 substitutions were also examined with **1a** in 1,6-addition/aldol cascade reaction. Substrates **2c**–**2f** with electron-withdrawing R^3 groups provided the products **3ac**–**3af** in good yields as compared with the substrate **2g** bearing 4-OMe (R^3) group, irrespective of their position (entries 11–15). Interestingly, substrate **2b** with chloro group at the *ortho*-position of the aryl ring also afforded the corresponding product **3ab** in 58% yield under the reaction conditions (entry 11). Along with the desired products **3** in DMAP/EtOAc system, the formation of a trace amount of product **4** was observed in all the reactions.

Next, we investigated the substrate scope of 1,6-addition/vinylogous Michael addition adducts under the optimal conditions (Table 1, entry 17). A series of coumarin-fused cyclopentanes **4** was generated, and

the results are shown in Table 3. Substrates with electron-withdrawing R^1 groups at coumarin ring **1b** and **1c** efficiently facilitated the reaction to afford the desired fused adducts in good yields when compared with substrates bearing electron-donating groups **1d**–**1f**, regardless of their position (entries 2–6). Again substrate having 8-OMe on coumarin ring shows a poor reactivity under the optimized conditions (entry 6). The substrates bearing an electron-donating group as R^1 substituent would prevent the intramolecular Michael addition reaction by enhancing the electron density at the reactive site. As a result, the lower yield of the product **4** and lower **4**/**3** ratios were observed when substrates with electron-releasing groups were employed (entries 4 and 5). The reaction of coumarin with different acyl R^2 substitutions also reacted well with **2a** and furnished the corresponding products **4ha**–**4ja** in up to 60% yields (entries 8–10). The substrate bearing R^2 as an electron-withdrawing group would enhance the reactivity of the carbonyl group, which may facilitate the intramolecular aldol reaction to give the product **3**. This could contribute to the observed lower **4**/**3** ratios (entry 8).

Furthermore, different indanedione R^3 substitutions were also tested with **1a** for the 1,6-addition/vinylogous Michael addition cascade reaction. Substrates with electron-withdrawing groups at the *ortho*, *meta*, and *para* positions were well-tolerated and afforded the corresponding products **4ab**–**4af** in up to 65% yields. Based on our observation, the sterically hindered R^3 substituent may favour the formation of product **4**. In the cases of *para*-substituted R^3 substrates, less steric hindrance observed in the reacting model and that favours the formation of products **3**, which results in the lower **4**/**3** ratios (entries 13-15). However, the electron-donating 4-OMe substituent **2g** did not provide the desired product under the optimal reaction conditions. Besides the desired products **4**, 4% to 25% yields of the spiro compounds **3** were observed as minor products in all the cases. The cascade reactions under Et_3N catalysis gave the corresponding mixture of products (**3** and **4**) in good yields. However, the selective formation of fused products **4** was moderate due to the aromatic-like character of the coumarin ring, which would prevent the addition of nucleophilic vinylogous enolate to the coumarin ring in an 1,4-addition manner.

Table 3. Substrate scope of 1,6-addition/vinylogous Michael addition cascade reaction.[a]



Entry	R^1/R^2	R^3	*t* (h)	**4**[b] (%)	**3**[c] (%)
1	H/Ph (**1a**)	Ph (**2a**)	60	63 (**4aa**)	11 (**3aa**)
2	6-Cl/Ph (**1b**)	Ph (**2a**)	52	75 (**4ba**)	4 (**3ba**)
3	6-Br/Ph (**1c**)	Ph (**2a**)	48	77 (**4ca**)	9 (**3ca**)
4	6-OMe/Ph (**1d**)	Ph (**2a**)	56	42 (**4da**)	15 (**3da**)
5	7-OMe/Ph (**1e**)	Ph (**2a**)	56	34 (**4ea**)	20 (**3ea**)
6	8-OMe/Ph (**1f**)	Ph (**2a**)	72	trace (**4fa**)	trace (**3fa**)
7	6,8-Cl_2/Ph (**1g**)	Ph (**2a**)	52	45 (**4ga**)	12 (**3ga**)
8	H/4-Cl-Ph (**1h**)	Ph (**2a**)	56	44 (**4ha**)	23 (**3ha**)
9	H/4-OMe-Ph (**1i**)	Ph (**2a**)	56	60 (**4ia**)	7 (**3ia**)
10	H/CH_3 (**1j**)	Ph (**2a**)	60	47 (**4ja**)	16 (**3ja**)
11	H/Ph (**1a**)	2-Cl-Ph (**2b**)	60	49 (**4ab**)	7 (**3ab**)
12	H/Ph (**1a**)	3-Cl-Ph (**2c**)	96	65 (**4ac**)	11 (**3ac**)
13	H/Ph (**1a**)	4-Cl-Ph (**2d**)	56	45 (**4ad**)	24 (**3ad**)
14	H/Ph (**1a**)	4-Br-Ph (**2e**)	48	54 (**4ae**)	25 (**3ae**)
15	H/Ph (**1a**)	4-NO_2-Ph (**2f**)	48	41 (**4af**)	19 (**3af**)
16	H/Ph (**1a**)	4-OMe-Ph (**2g**)	48	nr	nr

[a]Unless otherwise specified, all reactions were carried out using **1** (0.2 mmol), **2** (1.0 equiv), and Et_3N (20 mol%) in CH_3CN (1.0 mL) and stirred at 40 °C (Some of the reactions were scaled up to 0.8 mmol due to the moderate yields of **4**). [b]Isolated yield of the product **4**. [c]Yield of the product **3** was determined by ^1H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard. nr: no reaction.

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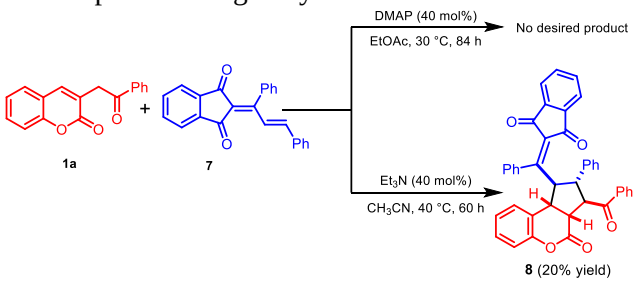
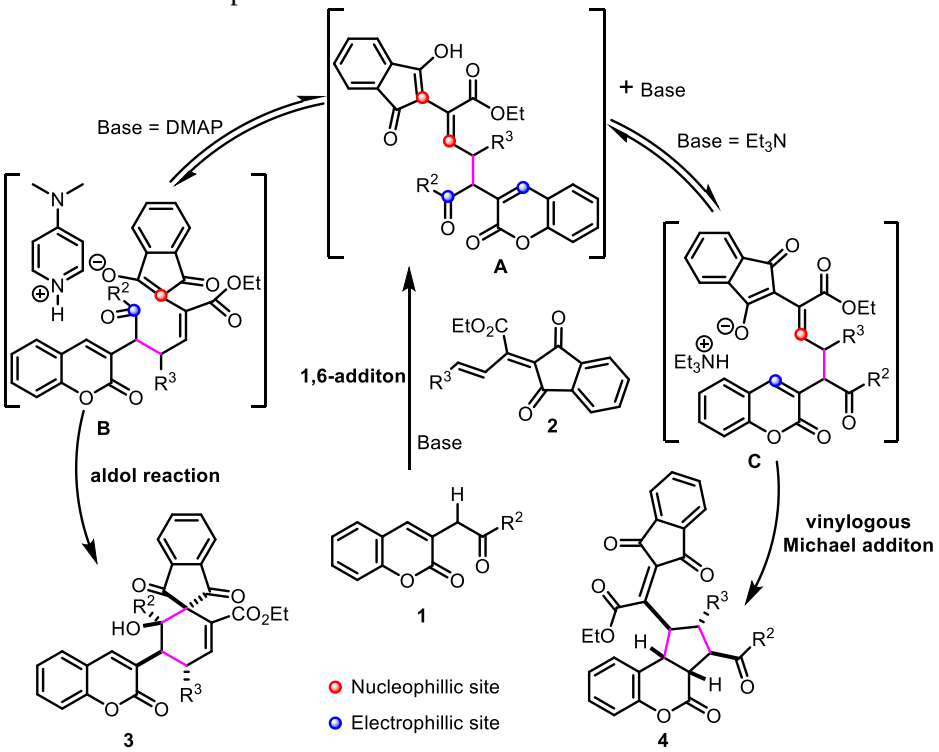
Furthermore, the indane-1,3-dione derivative bearing a phenyl group at β-position **7** was tested for its reactivity towards the construction of the corresponding spiro and fused compounds. Although the reaction under DMAP catalysis did not furnish the expected spiro product, the corresponding fused product **8** was obtained in only 20% yield in the presence of Et_3N when increasing the catalyst loading to 40 mol% (Scheme 3). It indicates that the strong electron-withdrawing group at β-position would facilitate the reaction more efficiently to afford the desired products in good yields.

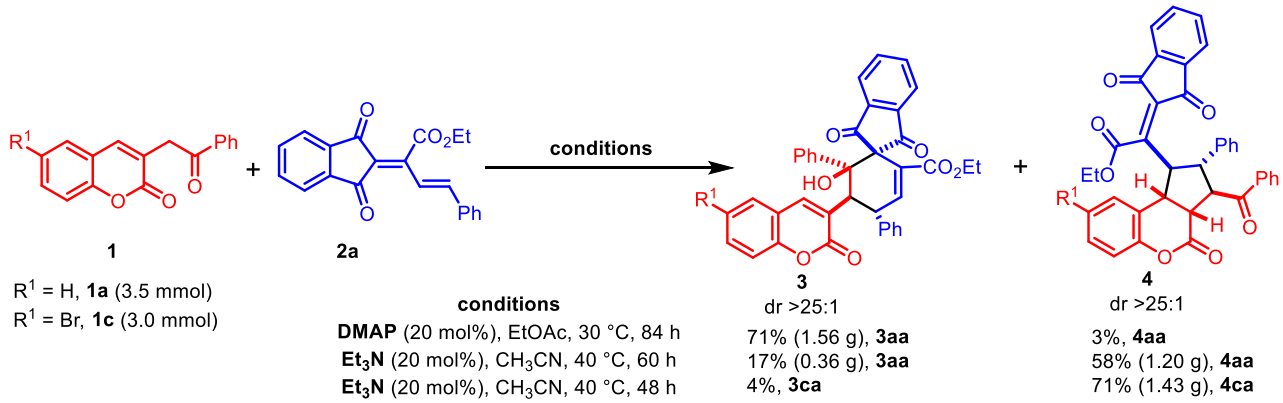


Scheme 3. Reactions of indane-1,3-dione **7** bearing phenyl group at β-position with **1a**.

On the basis of the results, a plausible reaction mechanism is illustrated in Scheme 4. The reaction initiated by 1,6-addition of 3-homoacylcoumarin **1** to the indanedione derivative **2** in the presence of a base would provide a common intermediate **A** for both the 1,6-addition/aldol and 1,6-addition/vinylogous Michael addition cascade reactions. On the one hand, deprotonation of intermediate **A** by DMAP, corresponding conjugate acid would engage with dienolate which is resulted from **A**, to provide an intermediate **B**. Further, a regio and chemoselective intramolecular aldol reaction of intermediate **B** leads to a desired spirocyclic product **3**. On the other hand, in the presence of Et_3N, the intermediate **A** would form dienolate, and that would associate with respective conjugate acid to generate intermediate **C**. An intramolecular vinylogous Michael addition upon intermediate **C** results in the desired product **4** in regio and chemoselective manner under the reaction conditions. Although the regio-selectivity observed in the second step is not clear, it could be attributed to the use of different base and solvent systems. The respective conjugate acids of DMAP and Et_3N would have different hydrogen-bonding interactions accompanied by steric hindrance with a key dienolate intermediate, which would lead to two different transition states and result in the formation of products in a divergent manner. However, chemoselectivity would be controlled by the active α and γ positions of dienolate intermediate to provide favoured ring systems over unfavoured ones (6 membered over 7 and 5 membered over 4).

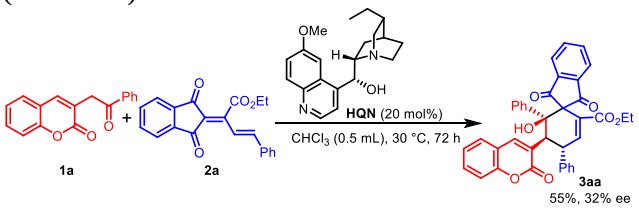


Scheme 4. Plausible mechanism.



Scheme 5. Gram-scale synthesis of **3aa**, **4aa**, and **4ca**.

To demonstrate the feasibility of the cascade reactions, we also carried out the gram-scale reactions for the synthesis of spiro and fused carbocyclic systems. The desired products **3aa**, **4aa**, and **4ca** were obtained in more substantial quantities with similar efficiency and selectivity as shown in Scheme 5. Furthermore, we tested our protocol in an asymmetric version under cinchona-alkaloid derived hydrogen-bonding catalyst reaction conditions. Unfortunately, the efforts to optimize the reaction under various conditions gave the inferior results in our hand (see SI for the experimental details). The cascade reaction of **1a** with **2a** in $CHCl_3$ has been examined in the presence of **HQN**-catalyst [(*R*)-((1*S*,2*S*,4*S*,5*R*)-5-ethylquinuclidin-2-yl)(6-methoxy quincolin-4-yl)methanol]. The corresponding product **3aa** was obtained in 55% yield with 32% ee in 72 h (Scheme 6).



Scheme 6. Attempt to prepare the chiral **3aa**.

Conclusions

In summary, a novel switchable organocatalytic reaction has been developed for the synthesis of spiro and fused carbocyclic systems in moderate to good yields. The tunable reactivity of the key 1,6-addition intermediate resulted from 3-homoacylcoumarin and indanedione derivative has been utilized as an advantage to realize diversity-oriented synthesis. In the presence of DMAP, 1,6-addition/aldol cascade reaction furnished the spirocyclic systems, whereas the 1,6-addition/vinylogous Michael addition sequence resulted in fused ring systems by using Et_3N as a base. Besides, the diversity-oriented switchable reactions have been reported in recent years by choosing appropriate base/solvent systems or controlled by the substrate or the catalyst.[18,19] Therefore, the diversity-oriented cascade reactions described here could have good potential to generate molecular diversity and complex structures in organic synthesis.

Experimental Section

General procedure for the preparation of spirocyclohexene indane-1,3-diones 3: A dry and argon-flushed two-neck reaction tube equipped with a magnetic stir bar was charged with **1** (0.2 mmol), **2** (1.2 equiv), DMAP (4.9 mg, 20 mol%), and dry EtOAc (1.0 mL) and stirred at 30 °C. The progress of the reaction was monitored by TLC and ^1H NMR data analysis. After the completion of the reaction, the reaction mixture was quenched with 2N HCl (0.25 mL) and extracted with CH_2Cl_2 (3x2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo, and the residue was purified by silica gel flash chromatography to afford the pure spiro compound **3**.

General procedure for the preparation of coumarin-fused cyclopentanes 4: A capped glass vial equipped with a magnetic stir bar was charged with **1** (0.1 mmol), **2** (1 equiv), Et_3N (2.8 µL, 20 mol%), and CH_3CN (0.5 mL) and stirred at 40 °C. The progress of the reaction was monitored by TLC and ^1H NMR data analysis. After the completion of the reaction, the reaction mixture was quenched with 2N HCl (0.25 mL) and extracted with CH_2Cl_2 (3x2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, then concentrated in vacuo, and the residue was purified by silica gel flash chromatography to afford the pure fused compound **4**.

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FULL PAPER

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