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1,3-Dipolar cycloaddition of isatin *N*,*N*′-cyclic azomethine imines with α,β-unsaturated aldehydes catalyzed by DBU in water†

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A simple and green procedure was established by [3 + 3] cycloaddition reaction of isatin derived cyclic imine 1,3-dipoles with α,β-unsaturated aldehydes, giving the desired spiro heterocyclic oxindoles with aza-quaternary centers in good yields and diastereoselectivities. It should be noted that water can be employed as a suitable solvent for the improvement of diastereoselectivity.

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Aza-quaternary centers are pivotal structural units, which exist in a variety of bioactive molecules and natural products.[1] In particular, spirooxindoles at the C3 position bearing a quaternarized N-heterocycle have attracted considerable attention because of their privileged structural units with attractive bioactivities,[2] for example, antimalarial,[3] anti-HIV,[4] antitumor,[5] anticancer,[6] inhibitor at the vanilloid receptor,[7] antituberculosis,[8] *etc.* (Fig. 1). Due to their remarkable biological importance, great efforts have been made to access spiro heterocyclic oxindoles with aza-quaternary centers. These methods include cycloaddition of imines,[9] 1,3-dipolar cycloaddition,[10] multicomponent cyclization reaction[11] and metal-catalyzed cycloaddition.[12] Among them, 1,3-dipolar cycloaddition is one of the most powerful tools for the construction of diverse spirooxindole fused N-heterocyclic scaffolds. Of these, *N*,*N*′-cyclic azomethine imines were widely studied for constructing various types of N-heterocyclic skeletons with spirooxindole as a stable and easily accessed 1,3-dipoles. In 2013, Wang's group reported their pioneering studies on Et_3N-catalyzed diastereoselective [3 + 3] annulation of *N*,*N*′-cyclic azomethine imines with isothiocyanatooxindoles to build 3,3′-triazinylspirooxindoles. In 2017, Wang *et al.* developed a new isatin-derived *N*,*N*′-cyclic azomethine imine 1,3-dipoles, and successfully applied in the [3 + 2] cycloaddition reaction for the construction of spirooxindoles bearing N-heterocycles (Scheme 1a).[10c] Very recently, Jin's group reported a Cs_2CO_3-catalyzed [3 + 4] annulation of isatin-derived 1,3-dipole with aza-oQMs (Scheme 1b).[10d] Furthermore, Moghaddam and coworkers developed an efficient method for the synthesis of pyridazine-fused spirooxindole scaffolds by 1,3-dipolar [3 + 3] cycloadditions (Scheme 1c).[10e] On the other hand, α,β-unsaturated aldehydes and their analogs as readily available substrates are also important building blocks in the synthesis of heterocyclic compounds which are widely applied in N-heterocyclic carbenes catalysis and other organocatalysis.[13] Inspired by these great works and our continuing efforts towards green synthesis of spirooxindole skeletons. We envisioned a quick and efficient way of [3 + 3] cyclization reaction of α,β-unsaturated aldehydes with the new isatin *N*,*N*′-cyclic azomethine imine 1,3-dipoles *via* oxindole C3 umpolung. We wish to disclose herein that a green and practical access to synthesize pharmacologically interesting spirooxindole derivatives by involving isatin *N*,*N*′-cyclic azomethine imine 1,3-dipole as nucleophiles and various α,β-unsaturated aldehydes in water using DBU as organocatalyst. Our initial examinations were carried out using isatin derivated cyclic imine 1,3-dipole **1a** (0.1 mmol) and α,β-unsaturated aldehyde **2a** (0.12 mmol) as the model substrates, the results of condition optimization are shown in Table 1. At the outset, without catalyst condition and with catalysts were investigated at room temperature in dichloromethane (DCM)

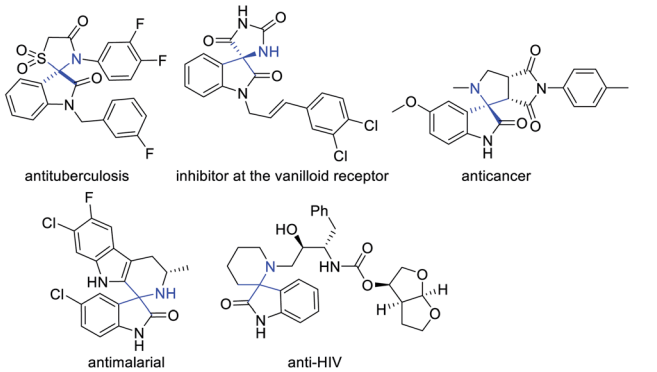

Fig. 1 Selected bioactive products of C3-spirooxindoles with aza-quaternary centers.

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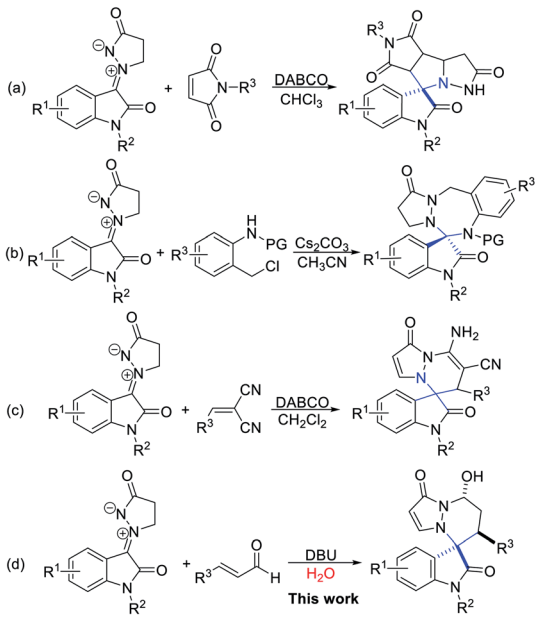
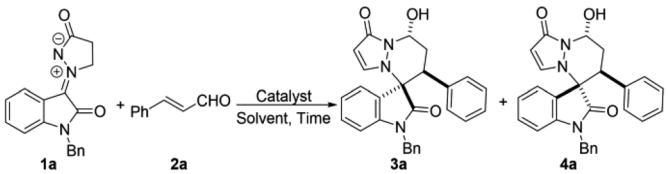


Scheme 1 Isatin-derived *N,N′*-cyclic azomethine imine 1,3-dipoles participated in the construction of N-heterocyclic skeletons with C3-spirooxindole.

Table 1 Optimization of the reaction conditions[a]

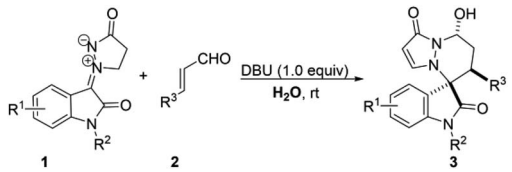


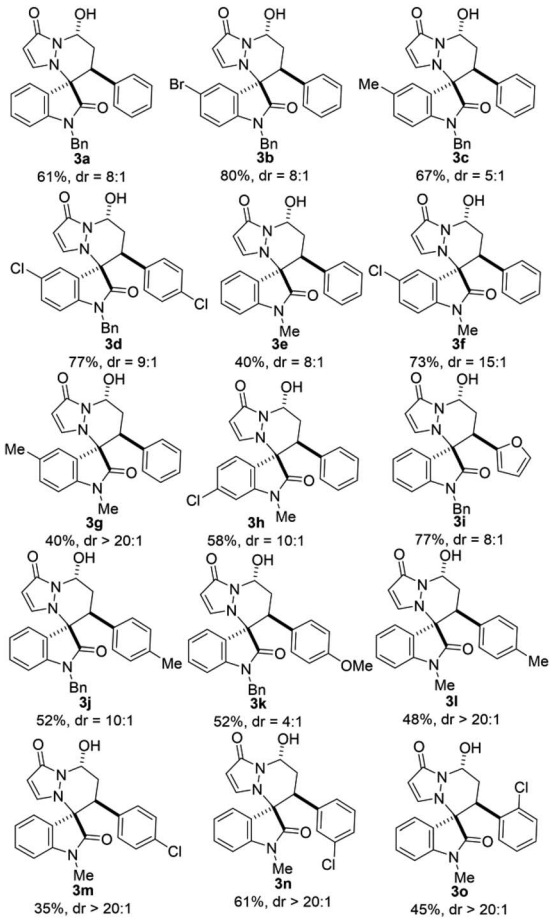
Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	3a : 4a[c]
1	—	DCM	24	—	—
2	DABCO	DCM	24	Trace	—
3	DMAP	DCM	24	Trace	—
4	NEt_3	DCM	3	25	1 : 3.4
5	DIPEA	DCM	24	Trace	—
6	DBU	DCM	0.1	75	1.7 : 1
7	Cs_2CO_3	DCM	1	34	1 : 2.4
8	$KOBu^t$	DCM	0.1	25	1 : 2.4
9	PPh_3	DCM	24	Trace	—
10	Pyrrolidine	DCM	24	59	1.6 : 1
11[d]	DBU	DCM	24	61	1.8 : 1
12	DBU	Toluene	0.2	75	1.3 : 1
13	DBU	CH_3CN	0.1	20	2.3 : 1
14	DBU	THF	0.1	85	1.2 : 1
15	DBU	$CHCl_3$	0.1	86	1.7 : 1
16[e]	DBU	$CHCl_3$	0.1	86	1.5 : 1
17	DBU	EtOH	24	62	1.8 : 1
18	Na_2CO_3	EtOH	24	46	1 : 1.6
19	DBU	H_2O	24	61	8 : 1

[a] Otherwise specified, all reactions were carried out using **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (0.1 mmol), solvent (1 ml). [b] Isolated yields of diastereoisomeric mixture. [c] Determined by ^{1}H NMR. [d] Catalyst (0.01 mmol). [e] Performed at reflux.

(Table 1, entries 1–10). The results show that catalyst had a significant effect on the yields. However, it has negligible effect on the diastereoselectivities. Organic bases, such as DABCO, DMAP, Et_3N, DIPEA (*N,N*-diisopropylethylamine), DBU, were compared and found that DBU could improve the yield obviously with 75% yield (Table 1, entry 6 *vs.* entries 1–5). While the inorganic bases were used, such as Cs_2CO_3, $KOBu^t$, failed to improve the reaction yields (Table 1, entries 7, 8). Other catalysts were also tested, but no better results were found (Table 1, entries 9, 10). When the catalyst loading was reduced to 10 mol%, the yield decreased with increasing the reaction time (Table 1, entry 11). Subsequently, a series of solvents were further investigated (Table 1, entries 12–

Table 2 The scope of the [3 + 3] annulation[a,b,c]





[a] All reactions were carried out using **1** (0.1 mmol), **2** (0.12 mmol), DBU (1.0 equiv.) in water (1.0 ml) at room temperature. [b] Isolated yields were diastereoisomeric mixture. [c] dr was determined by ^{1}H NMR in the crude products.

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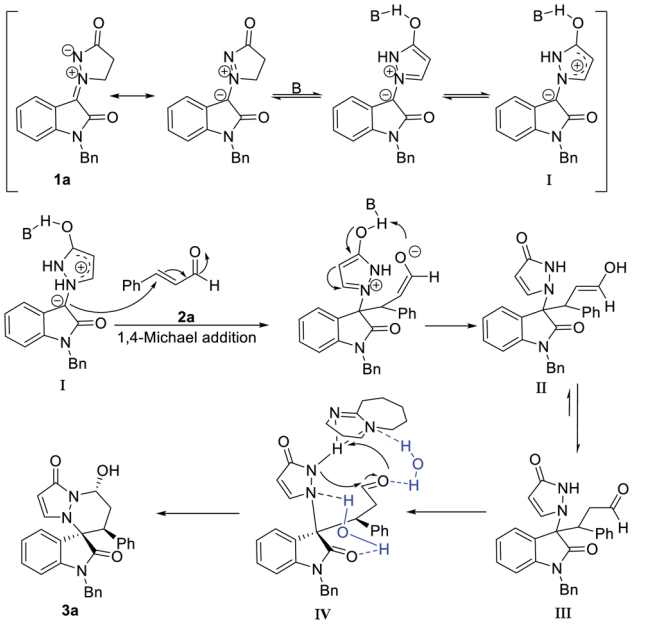
17). Solvents such as THF and $CHCl_3$ slightly improved the yields but no positive results were obtained for the diastereoselectivities (Table 1, entries 14, 15). A higher reaction temperature gave no better result (Table 1, entry 16). When DBU or Na_2CO_3 was used in ethanol also gave no satisfactory results (Table 1, entries 17, 18). With the hope of further improving diastereoselectivity, water was chosen as the solvent, the diastereoselectivity was significantly improved but the yield was decreased to 61% (Table 1, entry 19). Finally the optimum process conditions were carried out as follows: **1a**/**2a**/DBU = 1.0 : 1.2 : 1.0 molar ratio, in water at room temperature (Table 1, entry 19).

Under the optimal reaction conditions, the generality of this reaction was next investigated. As can be seen from Table 2, all reactions proceeded well to give the desired products **3** in moderate to good yields with good to high diastereoselectivities under identical conditions. The scope of isatin derivated cyclic imine 1,3-dipoles **1** were examined under the optimal reaction conditions, both N-Bn **1a** and N-Me **1e** substituted isatin derivated cyclic imine 1,3-dipoles could proceed smoothly and gave the desired products with moderate results (**3a** and **3e**). The 5-substituted electron-withdrawing groups on the aromatic ring of isatin derivated cyclic imine 1,3-dipoles **1** gave better yields compared with the electron-donating counterparts (**3b** *vs.* **3c**, and **3f** *vs.* **3g**). Subsequently, the electronic characteristics of α,β-unsaturated aldehydes **2** were studied, while both electron-donating (**3j**, **3k** and **3l**) and mildly electron-withdrawing groups (**3d**, **3m**) on phenyl ring had only a slight impact on yields and diastereoselectivities. Reaction involving heteroaryl aldehyde such as 2-furanacrolein **2i** also gave product **3i** in 77% yield with high diastereoselectivity (8 : 1 dr). Sterically hindered substituent on α,β-unsaturated aldehyde **2o** had little influence on the yield and diastereoselectivity.

Based on our results and previous studies, a plausible catalytic cycle is proposed in Scheme 2. **1a** was promoted by a base to form more stable intermediate **I**. After this, intermediate **I** underwent 1,4-Michael addition with α,β-unsaturated aldehyde **2a** to form **II**. Next, keto–enol tautomerism occurred to form intermediate **III**. To avoid the steric hindrance, the intermediate **III** attack preferentially to the Re-face of aldehyde, leading to the formation of the major product **3a**.

In conclusion, we have disclosed a novel metal-free DBU-catalyzed [3 + 3] cycloaddition reaction *via* C3 umpolung strategy of oxindole. Varieties of isatin derivated cyclic imine 1,3-dipoles and α,β-unsaturated aldehydes were compatible with this protocol under mild conditions, and afforded spiro heterocyclic oxindoles with aza-quaternary center in good yields with good to high diastereoselectivities. Notably, water as a green solvent had positive effect on the diastereoselectivities.



Scheme 2 A plausible catalytic cycle.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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