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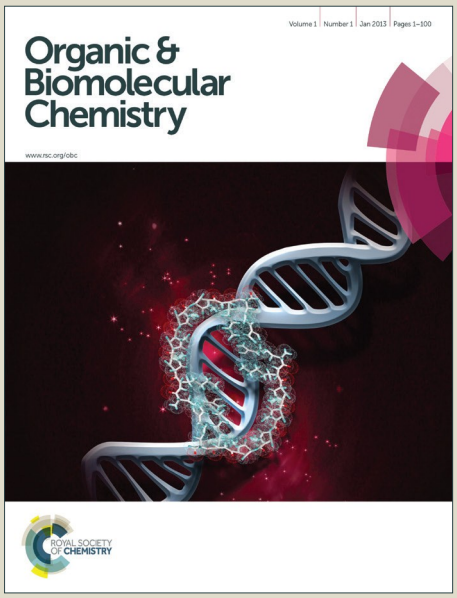

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Base-catalyzed controllable reaction of 3-ylideneoxindoles with O-Boc hydroxycarbamates for the synthesis of amidoacrylates and spiroaziridine oxindoles

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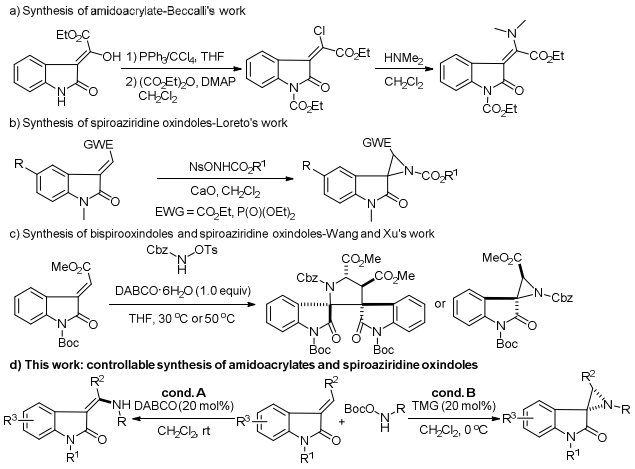
A base-catalyzed divergent reaction of 3-ylideneoxindoles with O-Boc hydroxycarbamates has been developed to provide an efficient access to various amidoacrylates and spiroaziridine oxindoles with generally high yields, which should be potentially useful in drug discovery.

Amidoacrylates and aziridines are two important classes of versatile synthons with wide applications in organic synthesis.[1,2] For example, amidoacrylate derivatives are often employed as dipolarophiles in 1,3-dipolar cycloaddition,[3] dienophiles in Diels-Alder reaction,[4] electrophiles in Michael-type reactions,[5] coupling reagents in the Heck[6] and Suzuki[7] reactions, Friedel-Crafts alkylation[8] and other cycloaddition reactions.[9] Employing these transformations, a variety of synthetically and biologically important nitrogen-containing compounds, such as unnatural amino acids and heterocycles can be efficiently obtained. Moreover, aziridines can also undergo a diverse range of synthetically useful transformations, such as nucleophilic ring-opening and ring-expansion because of the high strain energy of the aziridine ring.[10] Thus, a plethora of efficient protocols have been developed for efficient construction of various structurally diverse amidoacrylates and aziridines. In this context, however, the incorporation of the privileged oxindole motif into the amidoacrylate and aziridine scaffolds remains largely unexplored.[11]

As for the synthesis of amidoacrylates containing oxindole motif, to our knowledge, only one report from the Becalli group described an efficient route to access the α-dimethylamine-substituted acrylate via a multi-step procedure (Scheme 1a).[12] The group of Loreto developed a direct aziridination of easily accessible 3-ylideneoxindoles for facile synthesis of highly functionalized spiroaziridine oxindoles (Scheme 1b).[13] Peng disclosed an example of enantioselective synthesis of spiroaziridine oxindole by intramolecular S_N2-cyclization of chiral Mannich products, obtained from an organocatalytic asymmetric Mannich reaction of 3-bromooxindoles with N-Ts-imines.[14] It has also been recently reported by Marsini[15a] and Hajra[15b] respectively that the aza-Corey-Chaykovsky aziridination reaction of isatin-derived chiral N-tert-butanesulfinyl ketimines with in situ-generated sulfur ylides provided a highly diastereoselective access to various optically active spiroaziridine oxindoles. During the course of our study, the group of Wang and Xu reported an elegant stoichiometric base-mediated domino reaction of 3-methyleneindolinones with N-tosyloxycarbamates, providing a divergent approach for the synthesis of various bispirooxindoles and spiroaziridine oxindoles by tuning the substrate ratio (Scheme 1c).[16] Despite these advances, the development of new methods to construct diversely functionalized amidoacrylates and aziridines with oxindole moiety is still highly desirable for drug discovery and medicinal chemistry.

Base on our continuing interest in heterocycle synthesis,[17] we recently achieved a base-catalyzed divergent reaction of 3-methyleneindolinones with O-Boc hydroxycarbamates in a controllable manner (Scheme 1d). In contrast to Wang's work, our reaction gave the oxindole-containing acrylates and spiroaziridine oxindoles in generally high yields by using suitable bases.



Scheme 1 Reaction design with 3-methyleneindolinones.

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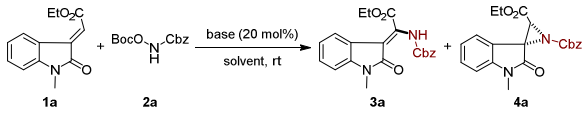
Inspired by the recent successful applications of the hydroxycarbamate derivatives in aziridination reaction,[18] we initially investigated the reaction of 3-ylideneoxindole **1a** with O-Boc hydroxycarbamate **2a** by evaluating various inorganic or organic bases as the catalysts in CH_2Cl_2 as the solvent (Table 1). Interestingly, in the most cases, the reaction proceeded smoothly to give a mixture of unexpected amidoacrylate **3a** and spiroaziridine oxindole **4a** with variable ratios (entries 1-6). For example, in the presence 20 mol% of DABCO (triethylenediamine), the reaction worked very well to give a 99% yield of **3a** (entry 5); meanwhile, the reaction with 20 mol% of TMG (tetramethylguanidine) as the catalyst proceeded smoothly to furnish **4a** in 75% yield (entry 6). With these two organic bases identified, we then briefly examined other commonly used solvents as well as reaction temperature to further improve the reaction efficiency and yield. As for the formation of product **3a**, it was found that the combination of DABCO and CH_2Cl_2 was still the best of choice, resulting in the best isolated yield and chemoselectivity (entries 5 vs. 7-11). Moreover, a combination of TMG with CH_2Cl_2 gave rise to the best results for the formation of **4a** with up to 82% yield at 0 °C (entries 12 vs. 13-17). Notably, the structures of the products **3a** and **4a** were fully characterized (see the ESI) and unambiguously confirmed by X-ray single crystal analysis (Fig. 1).[19]

Table 1 Optimization studies[a]



Entry	Base	Solvent	Time (h)	3a Yield[b] (%)	4a Yield[b] (%)
1	KOH	CH_2Cl_2	7	<5	37
2	NaOH	CH_2Cl_2	7	<5	53
3	K_2CO_3	CH_2Cl_2	7	<5	20
4	Cs_2CO_3	CH_2Cl_2	15	33	18
5	**DABCO**	**CH_2Cl_2**	**24**	**99**	**0**
6	**TMG**	**CH_2Cl_2**	**0.25**	**<5**	**75**
7	DABCO	THF	72	99	0
8	DABCO	Et_2O	96	98	0
9	DABCO	toluene	96	99	0
10	DABCO	DMF	26	99	0
11	DABCO	DMSO	26	89	0
12[c]	**TMG**	**CH_2Cl_2**	**2.5**	**<5**	**82**
13[c]	TMG	THF	2.5	<5	64
14[c]	TMG	Et_2O	2.5	<5	77
15[c]	TMG	CH_3CN	2.5	<5	68
16[c]	TMG	DMF	2.5	<5	57
17[c]	TMG	$CHCl_3$	2.5	<5	56

[a] Unless noted, reactions were performed with **1a** (0.2 mmol), **2a** (0.24 mmol), base (20 mol%) in the solvent (1 mL) at room temperature. [b] Isolated yield after column chromatography. [c] Reactions were carried out on a scale of 0.3 mmol in 5 mL of solvent at 0 °C.

With the optimized reaction conditions established, we first investigated the substrate scope for the synthesis of diversely substituted amidoacrylates **3**. As shown in Table 2, the reaction tolerated a wide range of diversely substituted 3-ylideneoxindoles. For instance, a series of N-free and N-substitued 3-ylideneoxindoles with various electron-withdrawing, aryl and aliphatic groups on the

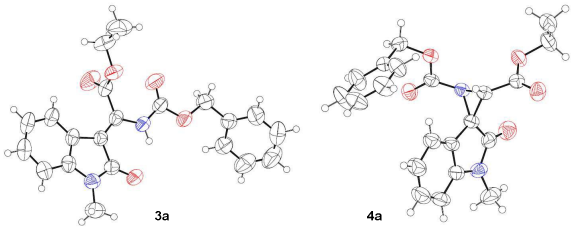
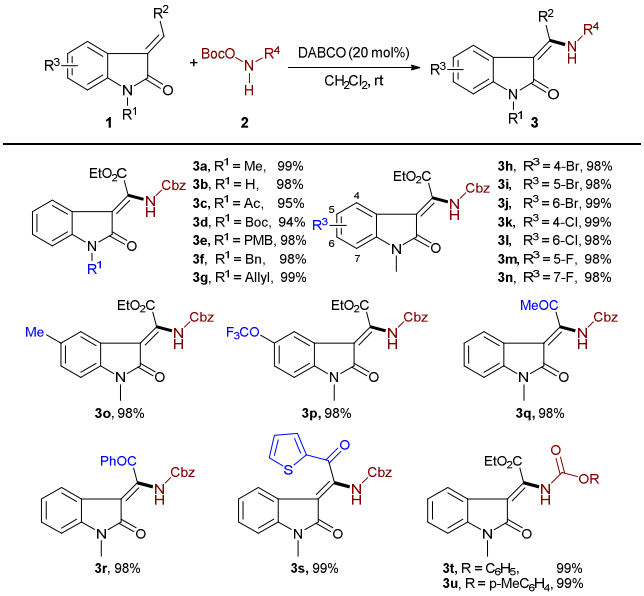


Fig. 1 X-ray crystal structures of compounds **3a** and **4a**.

nitrogen all turned out to be suitable for the reaction, giving the corresponding products **3a-g** with excellent yields (94-99%). Moreover, the electronic property and substitution patterns of the phenyl ring of 3-ylideneoxindoles have no obvious effect on the reaction; and the corresponding products **3h-p** were obtained in quantitative yields. Notably, these Cl-, and Br-substituted amidoacrylates **3h-l** could be used for further transition metal-catalyzed coupling, and the fluororine-containing products (i.e., **3m-n** and **3p**) are of great biological interest. Replacement of the ester moiety by the other carbonyl groups still furnished the expected products (i.e., **3q-s**) in high yields. As demonstrated in the synthesis of **3t-u**, variation of the carbamate also has no effect on the reaction efficiency and chemoselectivity.

Table 2 Substrate scope for amidoacrylate synthesis[a,b]



[a] Conditions: reactions were performed with **1** (0.2 mmol), **2** (0.24 mmol), DABCO (0.04 mmol) and 1 mL of CH_2Cl_2. The solution was stirred for 24 h at room temperature. [b] Isolated yield after column chromatography.

Next, we explored the generality of the reaction for the synthesis of synthetically and biologically important spiroaziridine oxindoles using O-Boc hydroxycarbamate **2a** (Table 3). As for the ester moiety in the N-methyl-protected 3-ylideneoxindoles, the variation of the ester moiety has very slight effects on the yields; and the

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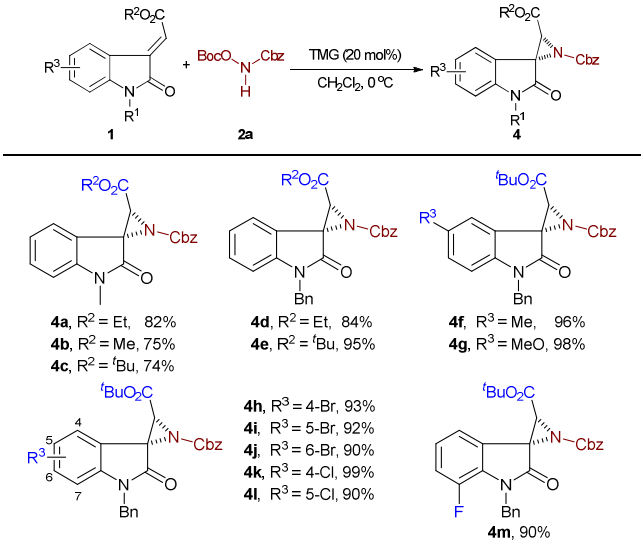
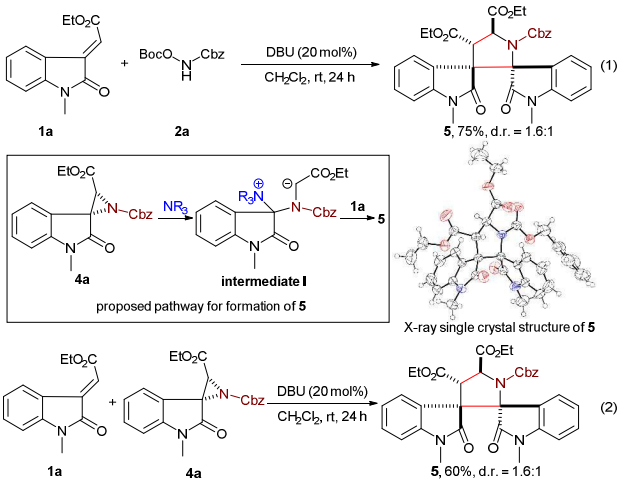
corresponding products **4a-c** were obtained in good yields. In contrast, in the case of N-benzyl-protected 3-ylideneoxindoles, the sterically more demanding ester group resulted in an increase of the yield (i.e., **4d-e**). Then, we continued to investigate the influence of the electronic property and substitution patterns of the aromatic ring on this aziridination reaction. A series of electron-donating (Me, MeO) and electron-withdrawing (Br, Cl, F) functional groups could be well incorporated into the C-4, C-5, C-6, and C-7 positions, producing the corresponding aziridines as single diastereomers in generally high yields (90-99%). The excellent diastereoselectivity observed in the aziridination can probably be attributed to the high stereodirecting effect of Cbz (carbobenzyloxy) group and the cyclic transition. The N-free 3-ylideneoxindole failed to give the desired aziridination product (not shown).

Table 3 Substrate scope for the synthesis of spiroaziridine oxindoles[a,b]



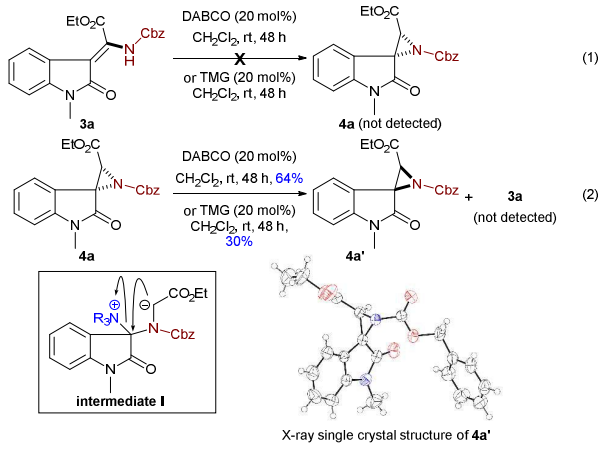
[a] Conditions: reactions were performed with **1** (0.3 mmol), **2a** (0.36 mmol), TMG (0.06 mmol) and 5 mL of CH_2Cl_2. The solution was stirred for 15 min to 6 h at 0 °C. [b] Isolated yield of the single diastereomer after column chromatography.

In accordance with Wang's observation, we also found that the reaction of **1a** and **2a** with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as the catalyst could also lead to the formation of a 75% yield of bispirooxindole **5** albeit with moderate diastereoselectivity, which was confirmed by X-ray single crystal analysis (Scheme 2, eqn 1).[19] Moreover, it was found that treatment of a mixture of **1a** and **4a** with a catalytic amount of DBU could also lead to the bispirooxindole **5** in 60% yield, suggesting that **4a** might be involved as the key intermediate for bispirooxindole formation (Scheme 2, eqn 2). Based on these results and Wang's model,[16] we then postulated that the formation of bispirooxindole **5** should arise from the base-catalyzed formal [3+2] cycloaddition of the initially formed spiroaziridine oxindole **4a** with another molecule of 3-ylideneoxindole **1a** through the intermediate **I**, which was formed from ring-opening of the initially formed aziridine **4a** by nucleophilic attack of the tertiary amine catalyst (Scheme 2).



Scheme 2. Formation of bispirooxindole.

To gain some insights into the reaction mechanism, we performed several more control experiments (Scheme 3). When amidoacrylate **3a** was subjected to the standard conditions, we did not detect any spiroaziridine oxindole **4a**, and **3a** remained intact (Scheme 3, eqn 1). Interestingly, subjectiong of the spiroaziridine oxindole **4a** to the standard conditions only gave rise to its diastereomer **4a'** with moderate yields, which might be formed by intermediate **I** via a base-catalyzed ring-opening process (Scheme 3, eqn 2). It should be noted that the reaction of 3-ylideneoxindole **1a** with O-Boc hydroxycarbamate **2a** using TMG as the base still lead to the exclusive formation of **4a** with comparable yield, even when the reaction time was prolonged to 24 h. These observations indicated that the products amidoacrylate **3a** and spiroaziridine oxindole **4a** should be formed through different reaction pathways. Not surprisingly, the spiroaziridine oxindole **4a** should be formed by a classical aziridination process.[18]



Scheme 3. Control experiments.

Although the detailed mechanism is not clear at this stage, we proposed a possible mechanism for the formation of **3a** (Scheme 4). Initially, 3-ylideneoxindole **1a** undergoes a base-catalyzed aza-Michael addition with O-Boc hydroxycarbamate **2a** to give the intermediate **6**,[20] which further undergoes a tertiary amine-

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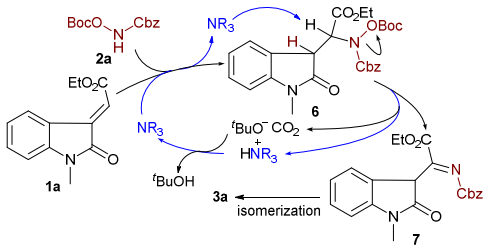
promoted elimination to furnish the imine **7**. Then, the imine **7** isomerizes easily into the corresponding more stable amidoacrylate **3a**. The tertiary amine catalyst would be regenerated through a deprotonation process by the *tert*-butoxide anion for the next cycle.



Scheme 4. Proposed catalytic cycle for the formation of **3a**.

In conclusion, we have developed a base-catalyzed controllable and divergent reaction of 3-ylideneoxindoles with O-Boc hydroxycarbamates under mild conditions. Employing the simple organic bases, DABCO or TMG, as the catalysts, a wide variety of highly functionalized amidoacrylates and spiroaziridine oxindoles were obtained in generally excellent yields. The products should be potentially useful in drug discovery. Studies on the application of these products and the development of catalytic asymmetric versions to access chiral aziridines and bispirooxindoles are currently underway in our laboratory.

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