NHC-Catalyzed Ester Activation: Access to Sterically Congested Spirocyclic Oxindoles via Reaction of α-Aryl Esters and Unsaturated Imines

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Abstract: Carboxylic esters can be readily obtained at low cost. Therefore, asymmetric catalytic activation of esters should provide useful strategies for organic synthesis. Here we report a N-heterocyclic carbene (NHC)-mediated reaction of α-aryl acetic esters with oxindole-derived α,β-unsaturated imines. The reaction involves the formation of NHC-bound ester enolate intermediate from an ester as a key step, and furnishes spirocyclic oxindole products. The sterically congested spirocyclic oxindole bears a newly formed six-membered δ-lactams and cannot be easily prepared using other methods.

Key words: N-heterocyclic carbene, ester activation, enolate, spirocyclic, oxindole

Spirocyclic oxindole is a unique scaffold found in bioactive natural and synthetic products (Figure 1).[1] Organocatalytic synthesis of this class of molecules has received considerable attentions in recent years. Representative organocatalysts for spirocyclic oxindole synthesis include amines,[2] cinchona alkaloids,[3] thioureas,[4] phosphines,[5] and phosphoric acids,[6] as reported by Barbas, Melchiorre, Chen, Wang, Gong, Williams, Scheidt, and others. In the area of NHC catalysis,[7] the activation of enals or ketenes to react with isatin and its derivatives has furnished spirocyclic oxindole β- and γ-lactones or lactams, as disclosed by Nair,[8] Ye,[9] and our own laboratory.[10]

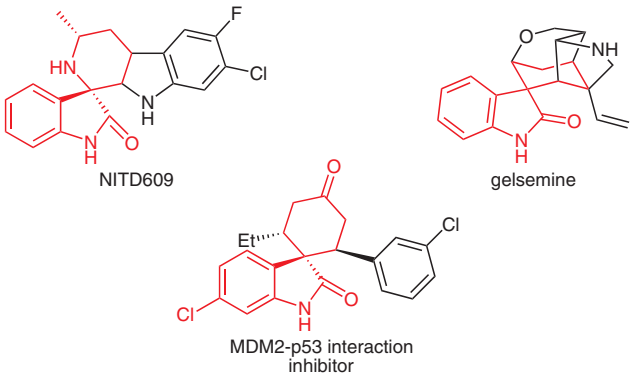
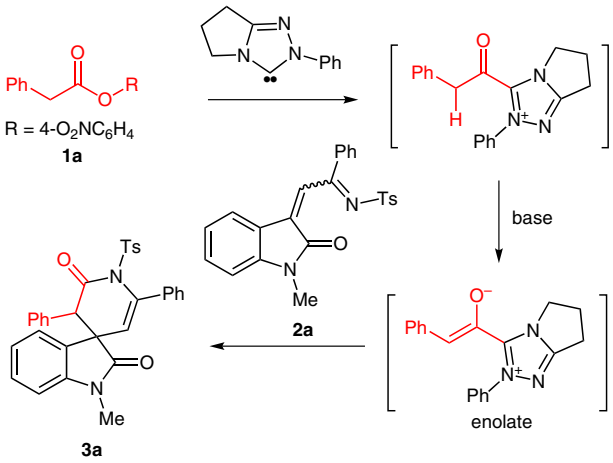


Figure 1 Natural products and synthetic inhibitors with spirocyclic oxindole moiety containing six-membered rings

We are interested in the activation of readily available and stable carboxylic esters via NHC to generate enolate and other intermediates for asymmetric synthesis.[11] Here we report the synthesis of spirocyclic oxindole derivatives containing a newly formed six-membered δ-lactam ring via NHC-catalyzed activation of α-aryl ester as a key step (Scheme 1). The six-membered lactam product bears a sterically bulky aryl substituent right adjacent to the spirocyclic carbon center and cannot be easily accessed using other approaches such as those based on enal[8,9b,9c,10] or ketene substrates.[9a] Notably, the majority of previous methods for spirocyclic oxindole synthesis via NHC and other organocatalysis led to spirooxindoles with a newly formed five-membered ring (γ-lactam).[9c,10b] In contrast, fewer studies[9d] were directed toward six-membered ring-fused spirooxindoles structures (e.g., δ-lactams). This may limit the exploration of these molecules for biological activities. For instance, the spiroindolone NITD609 (Figure 1) has recently been found to kill blood stages of *Plasmodium falciparum* and *Plasmodium vivax* at a low nanomolar concentration.[1b] This indicates that six-membered-ring-containing spirooxindole compounds have potentials for the treatment of malaria.



Scheme 1 NHC-catalyzed activation of α-aryl ester to synthesize spirocyclic oxindole δ-lactams

We started by using phenyl acetic ester **1a** and isatin-derived azadiene **2a** as model substrates (Table 1). Evaluations on the NHC catalysts showed that triazolium-based precatalyst **A** and **B** could mediate the reaction to afford **3a** with DIPEA as a suitable base (Table 1, entries 2 and

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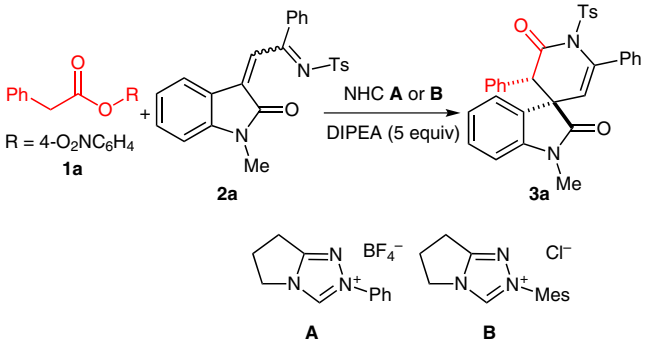
3). No product was observed in the absence of NHC catalysts (Table 1, entry 1). A comparison of catalysts **A** (with an *N*-phenyl substituent) and **B** (with an *N*-mesityl substituent) indicated that the sterically demanding catalyst **B** was less effective, leading to a much lower yield (Table 1, entry 3). We then attempted to optimize the reaction using catalyst **A**. For example, running the reaction at 60 °C could afford **3a** with an improved 71% yield (Table 1, entry 7). By using 30 mol% catalyst **A** with excess DIPEA as the base, **3a** could be isolated in 78% yield at room temperature (Table 1, entry 8).[12] The diastereoselectivity (ca. 2:1 dr) of this reaction was low under a large range of conditions (including the use of chiral NHC catalysts).

Table 1 Screening of Conditions[a]



Entry	NHC (mol%)	Solvent	Temp	Yield (%)[b]	dr[c]
1	–	DCE	r.t. or 60 °C	<5	–
2	**A** (20)	DCE	r.t.	61	67:33
3	**B** (20)	DCE	r.t.	25	55:45
4	**A** (20)	$CHCl_3$	r.t.	35	70:30
5	**A** (20)	CH_2Cl_2	r.t.	53	75:25
6	**A** (20)	DCE	40 °C	65	68:32
7[d]	**A** (20)	DCE	60 °C	71	67:33
8	**A** (30)	DCE	r.t.	78	65:35

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.10 mmol), solvent (0.5 mL).
[b] Isolated yield (both diastereomers) based on **2a**.
[c] Diasteromeric ratio of **3a** determined via ^{1}H NMR analysis of unpurified reaction mixtures.
[d] Conditions: 10 equiv of DIPEA was used. Compound **2a** was used as a mixture of isomers with *E*- and *Z*- configurations of the carbon–carbon double bond. The *E*- or *Z*-configuration of **2a** did not have observable effect on the reaction yield and dr.

In general, the enantioselective introduction of an asymmetric quaternary carbon atom still remains challenging in organic synthesis.[13] Reactions using this type of isatin derivatives were found to give relatively low diastereoselectivities in a few previous studies by Nair[8] and ourselves.[10a] New catalysts and strategies to address this issue are yet to be developed. The diastereoselectivity and efficiency of this reaction were not affected by the *E*- or *Z*-configuration of the carbon–carbon double bond of imine substrate **2a**. Similar observation was reported previously by us in reactions of enals and this type of unsaturated imines.[10a] This result suggested the catalytic reaction likely went through a stepwise Michael addition followed by lactam formation, rather than a concerted Diels–Alder pathway. The relative configuration of the major diastereomer of **3a** was assigned based on X-ray crystallographic analysis (Figure 2).

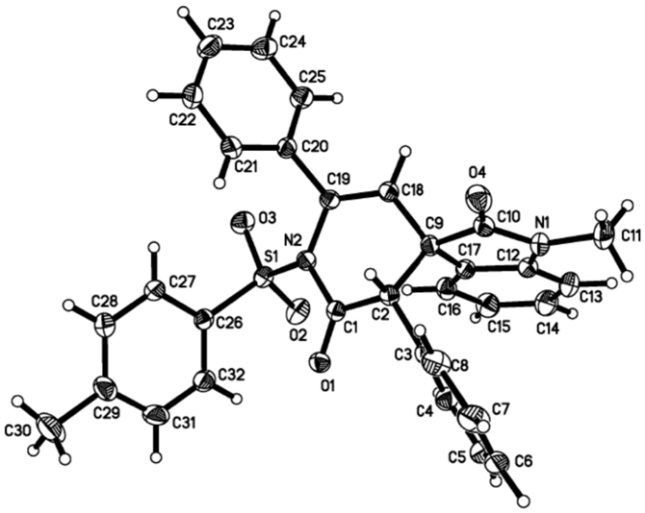
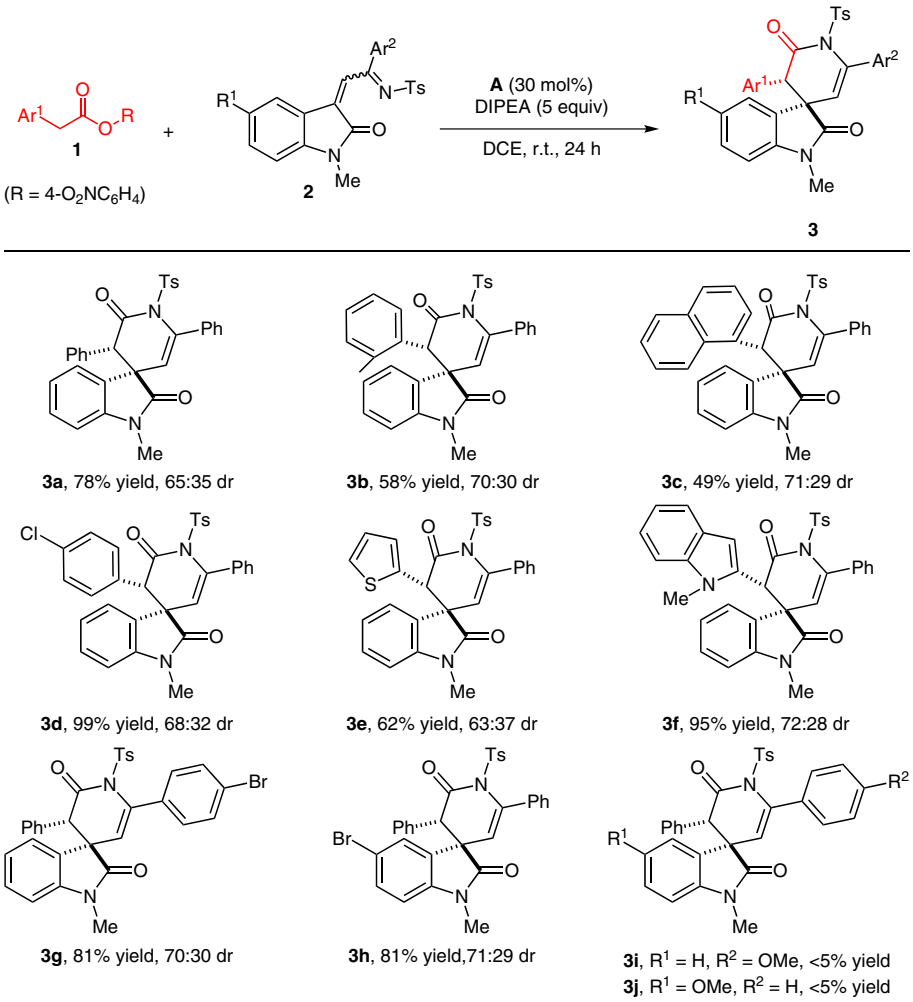


Figure 2 X-ray crystal structure of **3a**

We next evaluated the effects of the arylacetic ester substrates (Scheme 2). The aryl group of esters **1** with a methyl substituent showed lower reactivities (**3b**). Sterically bulkier esters with a naphthyl substituent **3c** led to product with moderate yield. Esters with electron-deficient aryl group **3d** or heteroaryl substituents **3e**,**f** were efficient substrates, giving products with good to excellent yields. We next examined isatin-derived α,β-unsaturated imines under the optimized conditions (Scheme 2). Electron-deficient imines **3g**,**h** were suitable substrates whereas electron-rich imines (substituted with OMe) failed to give the desired products under these conditions.

We also evaluated chiral NHC catalysts for this transformation (Scheme 3). Due to the sterically congested nature of the substrates, the common chiral triazolium NHC catalysts that had been successful in our earlier studies on reaction between α-aryl esters and simple unsaturated imines were not effective here.[11] The reaction yields were low even at elevated temperature (60 °C) in the presence of various chiral NHC catalysts (Scheme 3). Nevertheless, chiral inductions were possible. With triazolium **C** as the catalyst, the reaction could afford **3a** with 50% yield, 2:1 diastereomeric ratio, and 40% enantiomeric excess (major diastereomer). Increasing the sterics of the NHC catalysts (e.g., **D** or **E**) led to ineffective reaction (e.g., less than 5% yield). L-Phenylalanine-derived triazolium salt **F** performed slightly better than **C**, leading to the lactam product with 45% yield with 62% enantiomeric excess.



Scheme 2 The scope of the α-aryl acetic esters and imines. Reaction conditions are the same as in Table 1, entry 8. Yields are isolated yield (of both diastereomers) based on **2**. Diasteromeric ratio of **3** determined via ^{1}H NMR analysis of unpurified reaction mixtures.

In summary, we have developed a catalytic method for spirocyclic oxindole δ-lactam derivatives via NHC-mediated enolization of stable α-aryl acetic esters. Due to the steric nature of isatin-derived imines and the α-aryl enolate intermediate, diasterero- and enantioselectivities remain challenging at this moment. Further studies in search of new strategies for asymmetric synthesis of challenging spirocyclic molecules using ester substrates are in progress in our laboratory.

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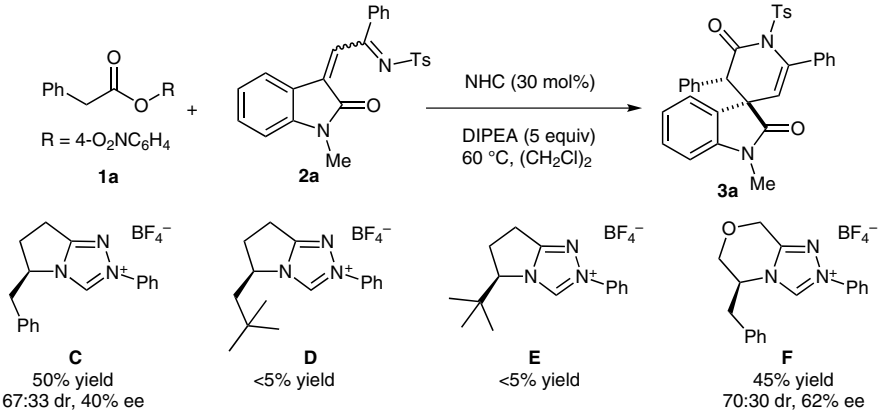

Scheme 3 Chiral NHC catalysts

Board (EDB), GlaxoSmithKline (GSK), and Nanyang Technological University (NTU).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(12) **General Procedure for the Synthesis of 3**
To a 10 mL two-necked oven-dried flask was added ester **1** (0.10 mmol, 2.0 equiv), α,β-unsaturated imine **2** (0.05 mmol) and triazolium salt **A** (0.015mmol). The flask was then evacuated and refilled with argon. Anhyd $(CH_2Cl)_2$ (0.5 mL) was added, followed by an injection of DIPEA (0.25 mmol). The mixture was stirred at r.t. for 24 h. Solvent was removed under reduced pressure, and the residue was purified via column chromatography on silica gel with hexanes–EtOAc as eluent to afford the desired products **3**. Compound **3a**: yield 78%; 65:35 dr; colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47 (s, 3 H), 2.84 (s, 3 H), 4.50 (s, 1 H), 5.83 (s, 1 H), 6.61 (d, 1 H, *J* = 7.8 Hz), 6.80 (d, 2 H, *J* = 7.3 Hz), 7.07 (t, 2 H, *J* = 8.0 Hz), 7.14–7.40 (m, 10 H), 7.88–7.92 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.7, 26.0, 53.5, 58.3, 108.2, 119.2, 123.6, 125.1, 126.4, 126.5, 127.6, 128.0, 128.2, 128.6, 129.1, 129.5, 129.8, 130.2, 131.7, 135.9, 136.8, 142.0, 143.3, 145.4, 171.0, 176.0. ESI-HRMS: *m/z* calcd for $[C_{32}H_{27}N_2O_4S]^+$: 535.1692; found: 535.1682. HPLC analysis [Chiralcel IA, *i*-PrOH–hexane (20:80), 0.7 mL/min]: t_R (major) = 11.9 min; t_R (minor) = 31.2 min; er = 81:19.

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