Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201900065

Link to VoR: http://dx.doi.org/10.1002/adsc.201900065

10.1002/adsc.201900065

Very Important Publication

COMMUNICATION

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

N-Heterocyclic Carbene Catalyzed Asymmetric Synthesis of Pentacyclic Spirooxindoles via [3+3] Annulations of Isatin-Derived Enals and Cyclic N-Sulfonyl Ketimines

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Received: ((will be filled in by the editorial staff))

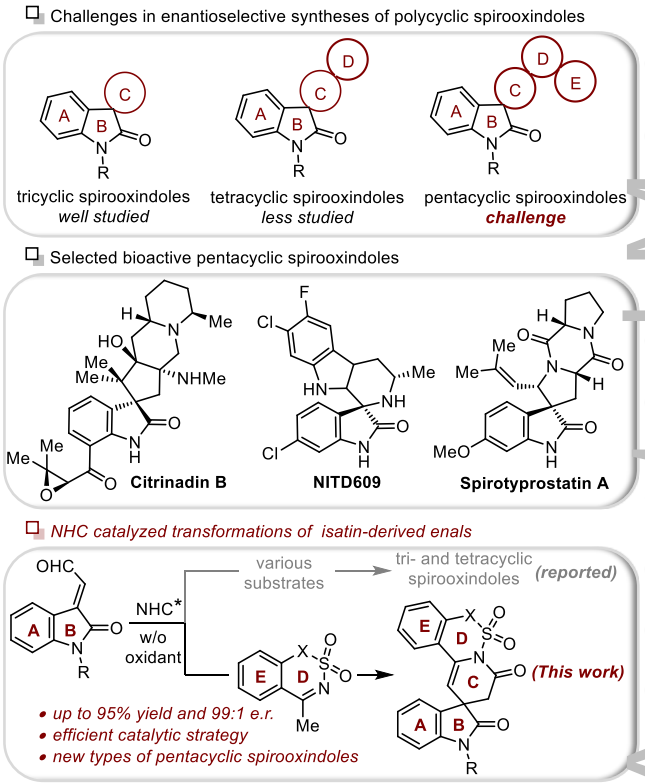
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract: A convenient enantioselective route to new types of pentacyclic spirooxindoles via [3+3] annulation reactions of isatin-derived enals and cyclic N-sulfonyl ketimines, using N-heterocyclic carbene (NHC) catalysis has been developed. The new protocol leads to pentacyclic spirooxindoles bearing a quaternary spiro-stereocenter in good yields and good to high enantiomeric ratios.

Keywords: pentacyclic spirooxindoles; N-heterocyclic carbenes; isatin-derived enals; cyclic ketimines; asymmetric synthesis

Structurally complex molecules such as polycyclic spirooxindoles exist in a variety of pharmaceutically relevant compounds and natural products.[1] Tremendous efforts have been devoted for their synthesis and synthetic protocols to tri- and tetracyclic spirooxindoles have been well developed (Scheme 1, top).[2] Despite this progress, the pentacyclic spirooxindoles are still a relatively underexplored class of complex molecules, even if they have impressive activities as pharmaceuticals, including citrinadin B,[3] NITD609[4] and spirotryprostatin A (Scheme 1, middle).[5] This might be due to the lack of practical, asymmetric strategies for their synthesis.

In the last few decades, dramatic progress in the field of N-heterocyclic carbene (NHC) catalysis has enabled the development of efficient methods to build complex highly enantioenriched molecules.[6] A series of tri- and tetracyclic spirooxindoles have been synthesized by annulations of isatin derivtives with enolate, homoenolate, dienolate or α,β-unsaturated acyl azolium intermediates.[7] In 2016 we successfully developed a practical alternate entry to spirooxindoles by using isatin-derived enals as three-carbon homoenolate components.[8] Since then, a series of NHC-catalyzed [3+n] annulation of isatin-derived enals was developed, by our and other groups for a variety of tri- and tetracyclic spirooxindoles.[9]

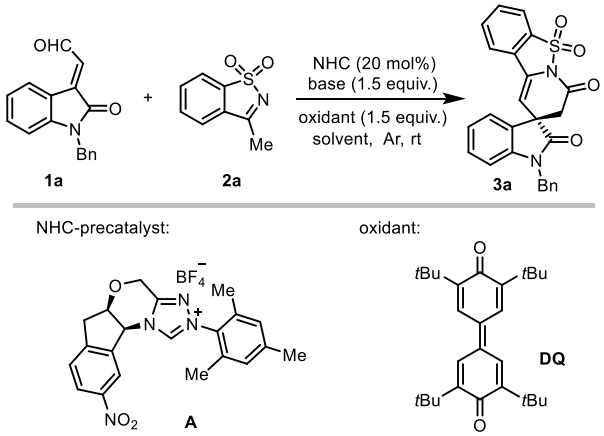


Scheme 1. NHC-Catalyzed reactions via α,β-unsaturated acyl azolium intermediates.

Encouraged by these previous developments, we set out to develop the first NHC-catalyzed synthesis of pentacyclic spirooxindoles via [3+3] annulation reactions of isatin-derived enals and cyclic N-sulfonyl ketimines[10] (Scheme 1, bottom).

To validate the feasibility of the proposed process, the model reaction of the isatin-derived enal **1a** with the cyclic N-sulfonyl ketimine **2a** was investigated under NHC catalysis (Table 1). In the presence of the tetracyclic NHC precatalyst **A**,[11] K_2CO_3 as the base and diphenoquinone (DQ) as the oxidant, the desired product **3a** could be obtained in 30% yield with 84:16 e.r. (entry 1). Encouraged by this promising result, different types of bases were then screened, such as the inorganic bases Cs_2CO_3, Na_2CO_3, KOAc, NaOAc, CsOAc, K_3PO_4 and the organic bases DIPEA, NEt_3, TMEDA, DABCO, DMAP (entries 2-12). The results indicated that NaOAc was the best choice and furnished the desired product in 80% yield with 85:15 e.r. (entry 5). Further screening of solvents showed that the reaction in DCM, DCE, $CHCl_3$, 1,4-dioxane, EA or toluene provided poorer results than in CH_3CN (entries 13-19). It should be noted that poor results resulted when 4 Å molecular sieves were added (entry 20) or the reaction was carried out at 0 °C (entry 21).

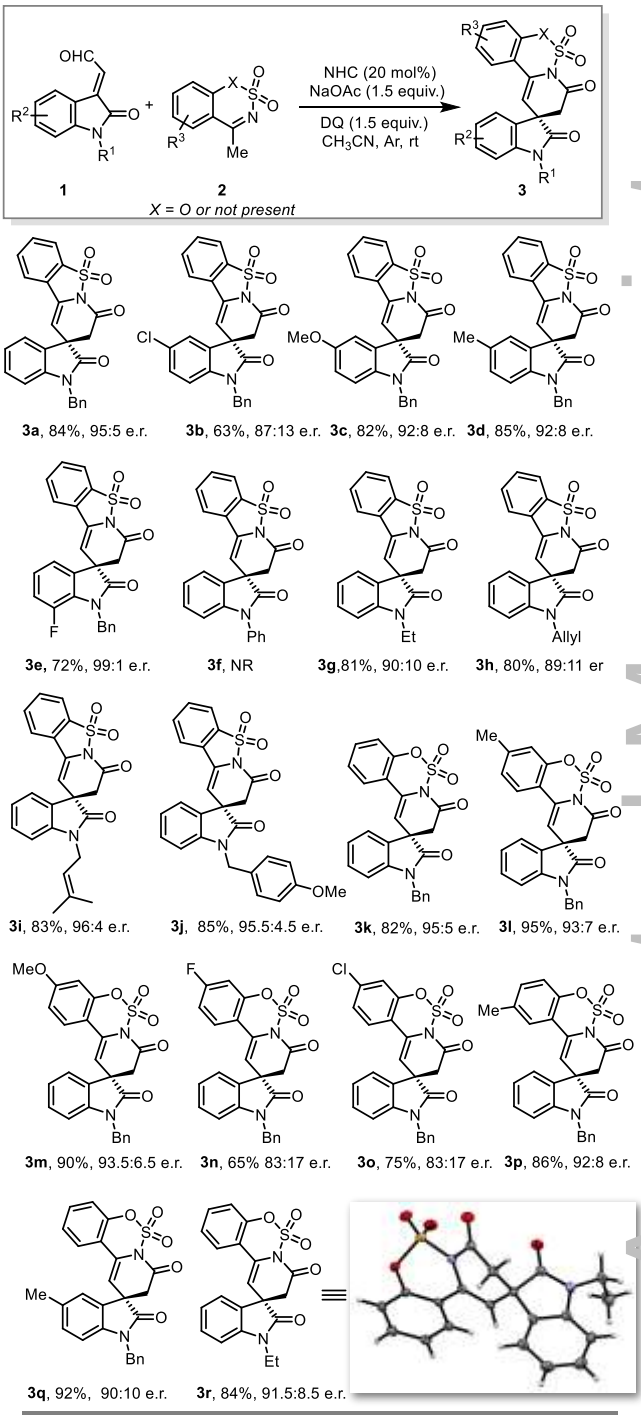
Table 1. Optimization of the reaction conditions[a]



Entry	Base	Solvent	Yield[b] (%)	E.r. [c]
1	K_2CO_3	THF	30	84:16
2	Cs_2CO_3	THF	Trace	-
3	Na_2CO_3	THF	Trace	-
4	KOAc	THF	Trace	-
5	NaOAc	THF	80	85:15
6	CsOAc	THF	Trace	-
7	K_3PO_4	THF	Trace	-
8	DIPEA	THF	80	82:18
9	NEt_3	THF	76	82.5:17.5
10	TMEDA	THF	75	88:12
11	DABCO	THF	78	84:16
12	DMAP	THF	72	80.5:19.5
13	NaOAc	DCM	74	89:11
14	NaOAc	DCE	73	88:12
15	NaOAc	$CHCl_3$	78	85.5:14.5
16	NaOAc	CH_3CN	84	95:5
17	NaOAc	Dioxane	50	85.5:14.5
18	NaOAc	Toluene	60	79:21
19	NaOAc	EA	65	85:15
20[d]	NaOAc	CH_3CN	84	89.5:10.5
21[e]	NaOAc	CH_3CN	70	78:22

[a] Unless noted, a mixture of **1a** (0.3 mmol), **2a** (0.2 mmol), base (0.3 mmol) and catalyst (20 mol%) in the solvent (2.0 mL) was stirred at room temperature for 24 h.
[b] Yield of isolated **3a**.
[c] Determined by HPLC analysis using a chiral stationary phase.
[d] 4 Å molecular sieves were added.
[e] The reaction was carried out at 0 °C.

Table 2. Reaction scope [a][b]



[a] Yields of isolated products **3** after chromatography.
[b] The e.r. value was determined by HPLC analysis of the purified product using a chiral stationary phase.

With the optimized conditions in hand, the reaction scope with respect to the cyclic N-sulfonyl ketimines

and the isatin-derived enals was examined (Table 2). Initially, a variety of substituted isatin derived enals were explored. Both electron-withdrawing (5-Cl and 7-F) and electron-donating (5-MeO and 5-Me) groups on the isatin ring were tolerable to afford the desired products **3b-e** in good yields with good to excellent enantiomeric ratios. The isatin derived enals with different nitrogen protecting groups were also studied. The N-ethyl, allyl and 4-methoxy benzyl isatin derived enals **1g-j** worked as well to give the desired products **3g-j** in 80-85% yield with good enantiomeric ratios. Unfortunately, the current reaction condition is not suitable for the N-phenyl isatin derived enal **1f**, and a complex mixture was observed with no starting material left. Various substituted six-membered cyclic N-sulfonyl ketimines (X = O) were also evaluated under the optimized conditions. As expected, a range of sulfamate-derived cyclic imines reacted well with the isatin derived enal **1a** to give the desired pentacyclic spirooxindoles **3k-p** in 65-95% yield with 83:17-93.5:6.5 enantiomeric ratios. In addition, the isatin derived enals **1q** and **r** also worked well to give **3q** and **r** in very good yields with good asymmetric inductions.

The absolute configuration of the product **3r** was determined to be (*S*) according to an X-ray crystallographic analysis (Table 2, bottom) while the other product configurations were assigned by analogy. [12]

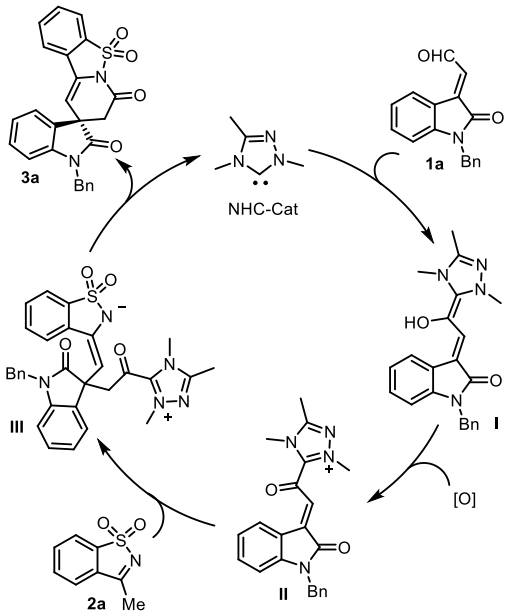


Figure 1. Plausible catalytic cycle.

A plausible catalytic cycle is depicted in Figure 1. The addition of the NHC catalyst to the isatin-derived enal **1a** gives the Breslow intermediate **I**, which is oxidized by the bisquinone to afford the α,β−unsaturated acyl azolium intermediate **II**. In the presence of a base, the Michael addition of the sulfonyl ketimine **2a** to **II** leads after a proton-shift to the adduct **III**. The final intramolecular lactamization of **III** furnishes the product **3a** and regenerates the NHC catalyst.

In conclusion, the NHC-catalyzed enantioselective [3+3] annulation of cyclic sulfonyl ketimines and isatin-derived enals was developed. This protocol enables the direct organocatalytic assembly of a variety of pentacyclic spirooxindoles in good yields with good to high enantioselectivities.

Experimental Section

To a solution of isatin-derived enal **1** (0.3 mmol, 1.5 equiv) in CH_3CN (2 mL), was added the substrates **2** (0.2 mmol, 1.0 equiv), oxidant **DQ** (0.3 mmol, 1.5 equiv),NHC precursor **A** (0.04 mmol, 0.2 equiv) and NaOAc (0.3 mmol, 1.5 equiv). The resulting mixture was stirred at room temperature under argon for 12 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (pentane/EtOAc as the eluent) to furnish the corresponding products **3**.

Acknowledgements

Q. Liu thanks the China Scholarship Council for a fellowship

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[12] CCDC 1889531 (**3r**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

10.1002/adsc.201900065

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