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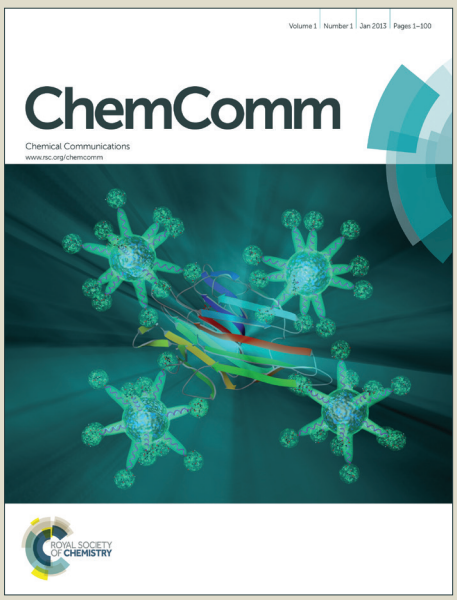

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COMMUNICATION

Cooperative catalysis of N-heterocyclic carbene and Brønsted acid for a highly enantioselective route to unprotected spiro-indoline-pyrans

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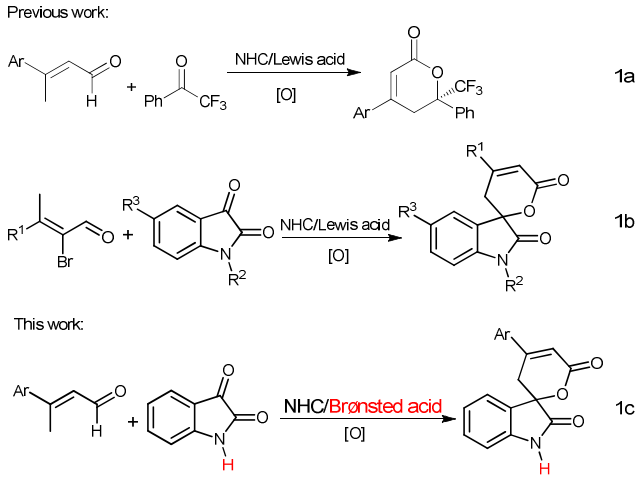
A chiral cooperative catalysis of NHC and Brønsted acid for formal [4+2] reaction of unprotected isatins and enals was developed for the direct synthesis of unprotected spiro[indoline-3,2'-pyran]-2,6'(3'H)-diones in good to excellent yields (up to 95%) with high enantioselectivities (up to >93% ee).

3'-Spirooxindoles are key motifs encountered throughout natural products and pharmacueticals;[1] thus, the preparation of chiral 3'-spirooxindoles has been of great interest and has motivated a tremendous wealth of strategies for their synthesis.[2] While, due to the severely uncontrollable reactivity of N-H in isatin derivatives, no examples with unprotected isatin electrophiles has been documented and the synthesis of 3'-spirooxindole compounds must be realized *via* multistep protocols, in which substrate protection and prefunctionalization are typically required.

N-Heterocyclic carbenes (NHCs), with their special electronic characteristics, not only serve as excellent ligands in organometallic catalysis,[3] but also act as organocatalysts.[4] With NHC catalysis, the reactions of aldehydes, enals, or ketenes with isatins as activated ketone electrophiles can afford hetero-spirocyclic oxindoles (oxindole β- or γ-lactones), has been disclosed.[5] In the past decade, great advances have been achieved in the development of N-heterocyclic carbene (NHC) as organocatalysts. Besides the umpolung of aldehydes (acyl anion intermediates),[6] NHC organocatalysis has been extended for the activation of the α-carbon (enolate intermediate)[7] and beta-carbon (homoenolate intermediate)[8] of enals. Recently, NHC-catalyzed γ-carbon activation, developed by Chi and co-workers, opens up a new avenue for the synthesis of target molecules (Scheme 1, eq 1a).[9]

We have disclosed a chiral NHC-catalyzed hetero-Diels-Alder reaction of *in situ* generated enolate species and formal [3+2] cylcoaddition reaction of homoeolate species.[10] Our ongoing interest in NHC-catalyzed reaction of *in situ* generated vinyl enolate species prompted us to investigate the cycloaddition with unprotected isatin to afford unprotected spiro-indoline-pyran moieties, which are important building blocks in the synthesis of many natural products, and biologically active compounds.

A study that was carried out by Yao and coworkers presented a chiral NHC-catalyzed formal [4+2] cycloddition of α-bromo-α,β-unsaturated aldehydes with isatin derivatives yielding spirocyclic oxindole–dihydropyranones (Scheme 1, eq 1b).[11] However, the unprotected isatin electrophiles have not been investigated and the direct synthesis of unprotected 3'-spirooxindoles is still in challege.



Scheme 1. NHC Catalyzed γ-Addition Reaction of Enals

To address the challenge of direct synthesis of non-protected 3'-spirooxindole compounds, NHC-catalyzed annulation reactions of *in situ* generated vinyl enolate species with commercial available non-protected isatain was chosen as the model reactions. N-mesityl-substituted triazolium salt (refer to cat.) was determined as the catalyst for this reaction. Enals **1** was used as vinyl enolate precursor. Unfortunately, the desired product was afforded in low enantioselectivity and yield with/without cooperative catalysis of NHC and Lewis acid. We wondered that cooperative catalysis of NHC and Brønsted acid maybe helpful for high enantioselectivity and high yield. To our surprise, when pivalic acid was explored as cocatalyst in the reaction, excellent enantioselectivities could be realized due to the highly steric effect of *tert*-butyl group on the acid structure.

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We hypothesized that excellent enantioselectivities can be rationalized by the cooperative catalysis of NHC and Brønsted acid due to forming hydrogen bonding of pivalic acid to unprotected isatin and vinyl enolate intermediates. The Brønsted acid is known to have good affinities for carbonyl oxygens on vinyl enolate intermediates and hydrogen atom on N of isatin derivatives. So it is involved in multisite coordination to bring isatin derivatives into close proximity with vinyl enolate intermediate generated by enal **1** and NHC catalyst.

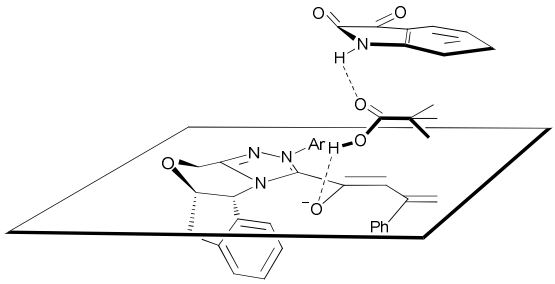


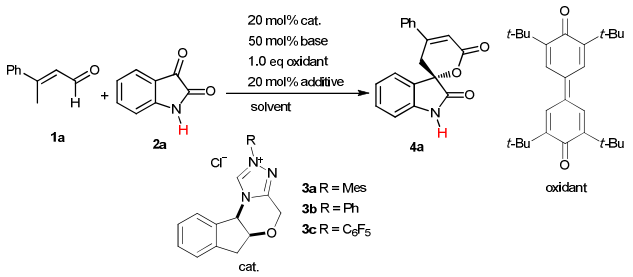
Figure 1. The proposed transtion state

We initiated our studies by evaluating the reaction between enal **1a** and isatin **1b** with N-mesityl-substituted triazolium salt in presence of base (Table 1). It was found that the reaction could proceed and afforded the desired product albeit with moderate yield and poor enantioselectivity (44% ee). Even worse results were obtained by cooperative catalysis of NHC and lewis acid (Table 1, entries 4-8). To obttain better results, we turned our attention towards cooperative catalysis of NHC and Brønsted acid with the aim of increasing its potential to hydrogen bond between isatin N-H and Brønsted acid. We therefore used the simple acetic acid and to our delight, both yield and enantioselectivity were increased (Table 1, entry 9). Inspired by this result, pivalic acid with bulky group (Table 1, entry 11) was tried with good yield and high enantioselectivity. Next, the use of different solvents and bases was evaluated for this reaction. The screening of solvents revealed that mixed solvent THF/ether in 1:1 was the most ideal (Table 1, entry 17), constracting to result of 65% yield, 80% ee (Table 1, entry 14) by using THF as sole solvent and ether afforded comparable enantioselectivity albeit with low yield (Table 1, entry 12).

K_2CO_3 was found to be the most ideal base for this reaction (Table 1, entry 17). When Cs_2CO_3 was employed, the yield decreased dramatically with a loss in enantioselectivity (Table 1, entry 18). NaOAc afforded comparable yield to that of K_2CO_3 with decreasing enantioselectivity (Table 1, entry 21). We observed that the organic bases were deemed to be unsuitable to the reaction as they led to lowered yields and enantioselectivities (Table 1, entries 19). It is particularly noteworthy that only 2.5 mol% cocatalyst (pivalic acid) was used to obtain good enantioselectivity and yield for the reaction.

With the optimal reaction conditions established, the scope of this cooperative NHC/BA catalysis reaction was explored (Table 2). The reaction proceeded smoothly for a broad spectrum of enals to afford the desired products in good yields and excellent optical purity. Both electron-donating and electron-withdrawing substitutents on beta-phenyl group were tolerated. Replacing beta-phenyl group with a naphthyl group did not significantly change the reaction result in yield and enantionselectivity (Table 2, 4g). The scope of substituted isatin substrate was also examined under the optimized conditions (Table 2, 4i-4o). 5-Fluro substituted isatin gave the best enantioselectivity (93% ee) with good yield (Table 2, 4k).

Table 1. Screening of catalysts, solvent, base and additive[a]



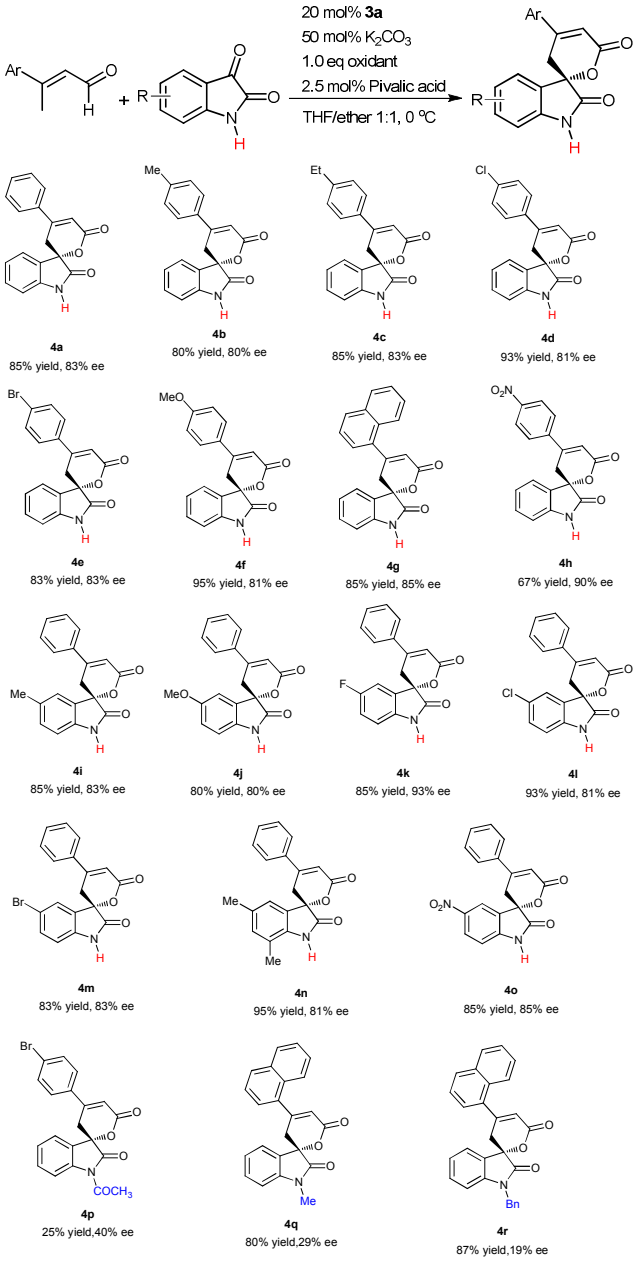
Entry	Cat	Solvent	Base	Additive	Yield (%)[b]	ee (%)[c]
1	3a	THF	K_2CO_3	-	50	44
2	3b	THF	K_2CO_3	-	25	35
3	3c	THF	K_2CO_3	-	trace	n.d
4	3a	THF	K_2CO_3	$Sc(OTF)_2$	23	34
5	3a	THF	K_2CO_3	$Mg(OTF)_2$	35	24
6	3a	THF	K_2CO_3	LiOTF	40	46
7	3a	THF	K_2CO_3	$LiBF_4$	26	10
8	3a	THF	K_2CO_3	LiCl	25	20
9	3a	THF	K_2CO_3	AcOH	63	60
10	3a	THF	K_2CO_3	propanoic acid	67	74
11	3a	THF	K_2CO_3	pivalic acid	68	76
12	3a	THF	K_2CO_3	pivalic acid	65	80
13	3a	ether	K_2CO_3	pivalic acid	25	82
14	3a	MTBE	K_2CO_3	pivalic acid	46	74
15	3a	toluene	K_2CO_3	pivalic acid	59	68
16	3a	CH_2Cl_2	K_2CO_3	pivalic acid	45	34
17[d]	**3a**	**THF/ether 1:1**	**K_2CO_3**	**pivalic acid**	**85**	**83**
18	3a	THF/ether 1:1	Cs_2CO_3	pivalic acid	40	70
19	3a	THF/ether 1:1	Et_3N	pivalic acid	75	72
20	3a	THF/ether 1:1	DIPEA	pivalic acid	82	76
21	3a	THF/ether 1:1	NaOAc	pivalic acid	85	70
22	3a	THF/ether 1:1	DMAP	pivalic acid	70	76

[a] Unless other specified, reaction was performed in 0.2 mmol scale in solvent (2 mL) at 0 °C. [b] Yield of isolated products. [c] ee value determined by HPLC analysis on Chiralcel column (see the supplementary information). [d] The scale of additive could be decreased to 2.5 mol% with the same results.

Similarly, electron-donating groups on isatin were also well-tolerated (Table 2, 4i, 4j, 4n). It is worth mentioning that the

different protected counterparts were bad-tolerated in the reaction, affording very low enantioselectivities (Table 2, 4p, 4q, 4r). When the hydrogen atom was protected, the hydrogen bond between isatin and pivalic acid would be broken and this cocatalyst could not play its role on bringing two substrates into close proximity and this is consistent with the proposed transition state.

Table 2. Substrate scope of NHC-catalyzed synthesis of unprotected spiro-indoline-pyrans



To determine the stereochemistry of the spiro-indoline-pyran product obtained from the NHC/BA cooperative catalysis reactions of enal and unprotected isatin, the X-ray crystallographic analysis of the product **4d** was performed to provide the absolute configuration (Figure 2, CCDC1052930). The (*1R,2S*)-cis-N-mesityl substituted triazolium salt prepared from (1R,2S)-(+)-cis-1-aminoindan-2-ol afforded exclusively provided (S)- spiro[indoline-3,2'-pyran]-dione **4d**.

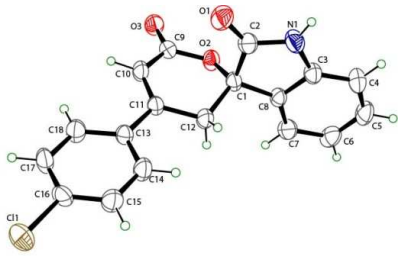
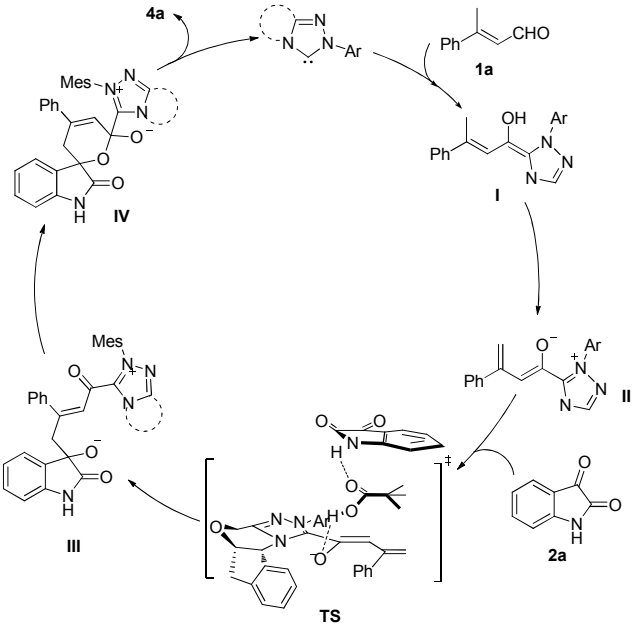


Figure 2. X-ray crystal structure of **4d**. Thermal ellipsoids were shown at 50% probability.

Our proposed pathway for cooperative NHC/Brønsted acid catalysis for oxidative gama-addition reaction of enal to unprotected isatin first involves the nuclephilic addition of the NHC organocatalyst to the enals to afford Breslow intermediate I. It is followed by oxidation and γ-deprotonation to afford vinyl enolate intermediate (II). Vinyl enolate II then undergoes nucleophilic addition to unprotected isatin **2a**, eventually affording product **4a**. Pivalic acid is involved in multisite coordination to bring the isatin electrophile into close proximity with vinyl enolate intermediate II by forming binary hydrogen bonds, as illustrated in the transition state (TS). The binary hydrogen bonds and bulky substituted (by *tert*-butyl group) Brønsted acid magnify chiral induction by chiral NHC catalyst. Then aldol reaction is followed by carbonyl addition to afford cycloaddition adduct IV. Subsequent acylation completes the catalytic cycle and releases the enantioenriched spiro-indoline-pyrans and regenerated the NHC catalyst.



Scheme 2. The proposed mechanism

Conclusions

In conclusion, a cooperative NHC/BA catalyzed [4+2] direct cycloaddition reaction of vinyl enolate with isatin was developed

for the synthesis of unprotected spiro-indoline-pyrans in good to excellent yields with high enantioselectivities. The remote chiral control was realized by cooperative catalysis of NHC and Brønsted acid. This protocol holds great potential in direct synthesis of biologically active unprotected 3'-spirooxindole derivatives in high enantiomeric purity and further investigation is undergoing.

Acknowlegement

We thank the NSFC (21302032 and 21373073) and the PCSIRT (IRT 1231) for financial support. G.Z. appreciated a Qianjiang Scholar from Zhejiang Province in China.

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Graphical Abstract:

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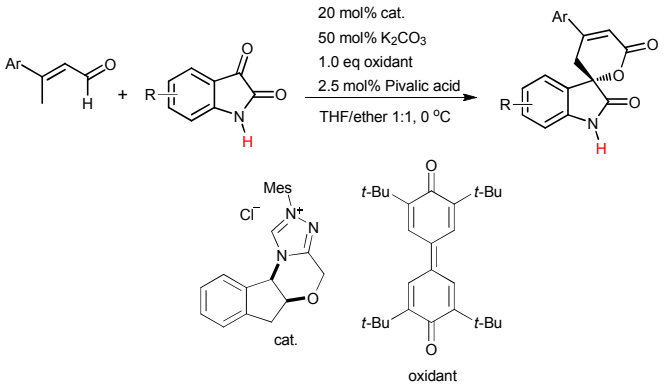

A chiral cooperative catalysis of NHC and Brønsted acid for formal [4+2] reaction of unprotected isatins and enals was developed for the direct synthesis of unprotected spiro[indoline-3,2'-pyran]-2,6'(3'H)-diones in good to excellent yields (up to 95%) with high enantioselectivities (up to >93% ee).