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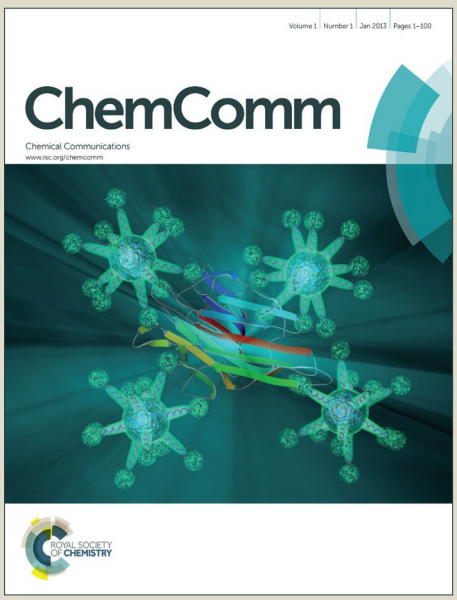

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Asymmetric assembly of spirooxindole dihydropyranones through direct enantioselective organocatalytic vinylogous aldol–cyclization cascade reaction of 3-alkylidene oxindoles with isatins

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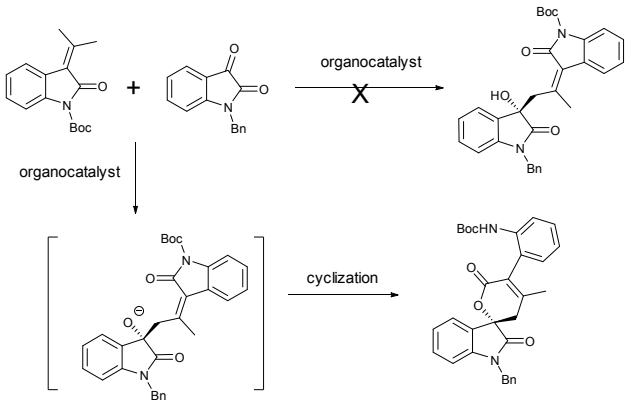
A highly enantioselective organocatalytic vinylogous aldol–cyclization cascade reaction of 3-akylidene oxindoles to isatins has been acheived by using bifuctional organocatalysts. The unexpected intramolecular lactonization which follows the initial aldol reaction, leading to the cleavage of the oxindole ring and generation of enantioenriched spirooxindole dihydropyranones in good to excellent yields with high enantioselectivities.

Over the last decades, the research involving vinylogous reactions is rapidly growing since the vinylogous reaction is one of the most efficient protocols for the direct formation of allylic compounds, which are widely used in organic synthesis.[1] As such, the control of the stereochemical outcome of the new remote carbon center inspired many organic chemist to design new mode of vinylogous reactions.[2-8] The vinylogous reactions of enolate derived from 3-alkylidene oxindole derivatives are of special interest because this scaffolds are found in many biologically active compounds.[9]

Recently, Casiraghi and coworkers reported the first example of organocatalyzed vinylogous Michael addition of 3-alkylidene oxindoles to nitroalkenes by using the bifunctional cinchona alkaloid/thiourea catalysts.[8a-b] They discovered that the 3-alkylidene oxindoles could act as a vinylogous nucleophile to functionalize at the γ-position with electrophiles. Later, many efficient and elegant methodologies have been created using 3-alkylidene oxindoles as nucleophiles.[8c-g] However, the development of other efficient methods for the chiral γ-substituted 3-alkylidene oxindoles is of considerable synthetic and biological importance.

The vinylogous aldol reaction is an efficient synthetic methodology for the construction of α, β-unsaturated δ-hydroxy carbonyl compounds whose motif are present in many natural products.[1g] Casiraghi and coworkers developed the asymmetric vinylogous Mukaiyama-type aldol reaction of 3-alkenyl-2-silyloxyindoles with aromatic aldehydes to generate the chiral homoallylic hydroxylated oxindoles by using a catalytic Lewis base system.[10] However, to the best of our knowledge, the direct vinylogous aldol reaction with 3-alkylidene oxindoles is still under-explored. We presumed that the 3-alkylidene oxindoles could react with isatins to provide biologically relevant 3-hydroxyoxindole derivatives.[11] However, to our surprise, our results show the 3-alkylidene oxindoles not only reacted with isatins smoothly, but further cyclized to cleave the oxindole ring and construct spirooxindole dihydropyranones (Scheme 1).



Scheme 1 Vinylogous Aldol-cyclization Cascade Reaction of 3-Alkylidene Oxindoles with Isatins.

Spirooxindole dihydropyranones are a key structure element in a number of natural products and synthetic bioactive molecules.[12] Reports of catalytic asymmetric transformation to chiral spirooxindole dihydropyranone derivatives are still limited. Ye,[13a] Chi,[13c] and Yao[13b,d,g] developed elegant methods to synthesized spirooxindole dihydropyranone derivatives using NHC-catalysis. Wu[13e] reported the formation of spirooxindole dihydropyranones form vinylogous aldol-

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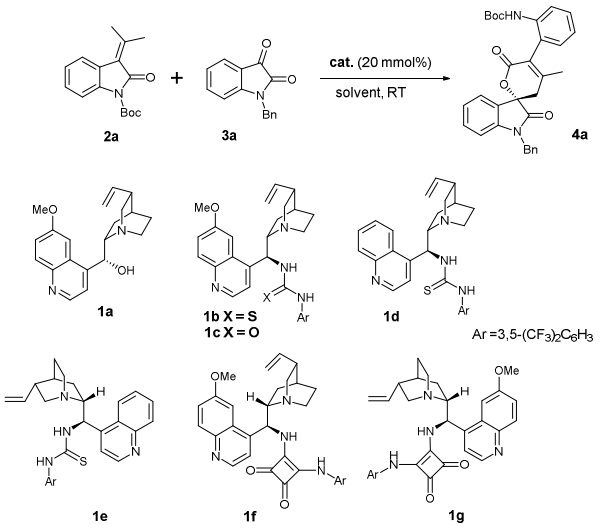
cyclization cascade reaction of allyl pyrazoleamides with isatins. Xu[13f] achieved an efficient hetero-Diels-Alder reaction of olefinic azlactone with isatins to construct spirooxindole dihydropyranone derivatives. Therefore, we herein reported a catalytic direct asymmetric convenient vinylogous aldol-cyclization cascade reaction of 3-alkylidene oxindoles with isatins. By using chiral cinchona alkaloid-squaramide bifunctional organocatalysts system, high yields and enantioselectivities were achieved for spirooxindole dihydro-pyranones.

To investigate the reactivity of 3-alkylidene oxindoles with isatins, we initially carried out the vinylogous aldol reaction with oxindole **2a** (1.5 equiv.) and isatin **3a** (1 equiv.) by using quinine **1a** (20 mol %) as the catalyst in 0.5 mL toluene and at room temperature (Table 1, entry 1).

Table1. Conditions Optimization[a]



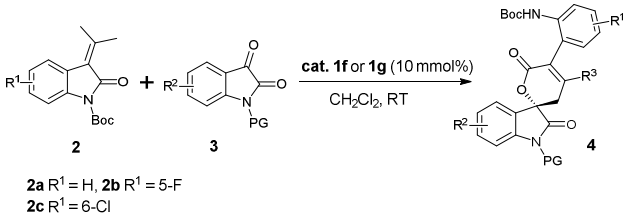
Entry	Cat.	Solvet	Time(h)	Yield (%)[b]	ee (%)[c]
1	**1a**	toluene	48h	50%	12
2	**1b**	toluene	12h	99%	50
3	**1c**	toluene	48h	87%	62
4	**1d**	toluene	12h	93%	48
5	**1e**	toluene	12h	88%	68[d]
6	**1f**	toluene	12h	81%	94
7	**1f**	THF	48h	71%	92
8	**1f**	CH_2Cl_2	12h	94%	95
9	**1f**	CH_3CN	12h	80%	92
10[e]	**1f**	CH_2Cl_2	18h	99%	96
11[f]	**1f**	CH_2Cl_2	48h	99%	96
12[d,e]	**1g**	CH_2Cl_2	18h	94%	99[d]

[a]Unless otherwise noted, the reaction was carried out by using 0.1 mmol of **3a**, 1.5 equiv of **2a**, and 20 mmol % of catalyst in 0.5 mL of solvent at RT for indicated time. [b]Isolated yields. [c]Determinated by chiral HPLC analysis. [d]ee of ***ent*-4a**. [e]10 mmol % of catalyst was used. [f]5 mmol % of catalyst was used.

To our delight, the reaction proceeded smoothly after 48h and afforded the desired product **4a** with moderate yield, albeit in low enantioselectivity. The screening of a variety of bifunctional thiourea/squaramide catalysts showed the quinine-derived squaramide catalyst **1f** gave the best results (81% yield, 94% ee, Table 1, entry 2-6). We then turned our attention to the solvent screening and found CH_2Cl_2 was shown to be the ideal solvent as **4a** was generated with better yield and enantioselectivity (94% yield, 95% ee, Table 1, entry 7-9). Lowering the amounts of catalyst **1f** resulted in slightly increasing the yield and enantioselectivity (99% yield, 96% ee) although the reaction time was also increased (Table 1, entry 10-11). Finally, the optimal conditions were chosen by conducting the reaction at room temperature in CH_2Cl_2 with 10 mol% of catalyst **1f** (Table 1, entry 10). By using the quinidine-derived squaramide catalyst **1g**, the opposite enantiomer ***ent*-4a** was obtained in 99% yield and 99% ee (Table 1, entry 12).

With the optimized conditions in hand, the general substrate scope of both 3-alkylidene oxindoles **2** and isatins **3** were examined, and the results are shown in table 2.

Table 2 Substrate Scope Examination[a]



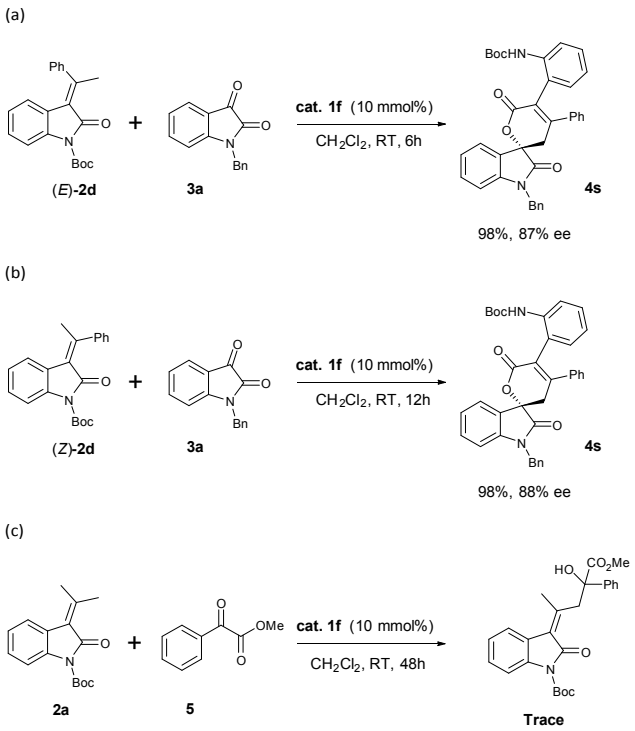
Entry	R^1	R^2	PG	**4**	Yield (%)[b]	ee (%)[d]
1	H	H	Bn	**4a**	99	96 (99)
2	H	H	Me	**4b**	92	95 (96)
3	H	H	Et	**4c**	94	94 (98)
4	H	H	Allyl	**4d**	95	95 (95)
5	H	H	H	**4e**	90	95 (96)
6	H	5-Cl	Bn	**4f**	92	90 (97)
7	H	6-Cl	Bn	**4g**	80	98 (98)
8	H	7-Cl	Bn	**4h**	99	91 (90)
9	H	5-F	Bn	**4i**	99	99 (99)
10	H	7-F	Bn	**4j**	91	94 (95)
11	H	5-Br	Bn	**4k**	87	98 (99)
12	H	5-Me	Bn	**4l**	95	97 (99)
13	H	5-OMe	Bn	**4m**	85	94 (91)
14	H	5-NO_2	Bn	**4n**	62	98 (97)
15	5-F	H	Bn	**4o**	98	98 (99)
16	5-F	5-OMe	Bn	**4p**	96	97 (96)
17	5-F	5-NO_2	Bn	**4q**	84	98 (90)
18	6-Cl	H	Bn	**4r**	96	87 (87)

[a]All reaction was carried out by using 0.1 mmol of **3**, 1.5 equiv of **2**, and 10 mmol % of catalyst in 0.5 mL of CH_2Cl_2 at RT for 18h. [b]Isolated yields. [c]Determinated by ^{1}H NMR. [d]Determinated by chiral HPLC analysis. Values in parentheses refer to reactions catalyzed by the quinidine-derived squaramide catalyst **1g**.

Generally, all reactions proceeded smoothly to give the corresponding spirooxindole dihydropyranones in good to excellent yields (up to 99%) and excellent enantioselectivities (up to 99%). The effect of different of N-substituted isatins was first investigated. *N*-methyl, *N*-ethyl, and *N*-allyl substituted isatins all showed good tolerance to this cascade reaction and gave the products **4b-d** in excellent yields and

enantioselectivities (Table 2, entry 2-4). To our delight, it was found the unprotected isatin **3e** also took part into the cascade reaction and deliver the product **4e** in 90% yield and 95% ee (Table 2, entry 5). Isatins with different-positioned halogens (Table 2, entry 6-11), electron-donating groups (Table 2, entry 12-13), and electron-withdrawing groups (Table 2, entry 14) reacted well with oxindole **2a** to afford the products **4f-n** in good yields and high enantioselectivities albeit the yield of **4n** (62%) is slight lower compared to others. We then turned our attention to the vinylogous aldol-cyclization cascade reaction of 5-fluoro substituted oxindole **2b** with *N*-benzyl, 5-methoxy, and 5-nitro substituted isatins. It was found the reactions proceeded smoothly to give the desired spirooxindole products **4o-q** in high yields and enantioselectivities (Table 2, entry 15-17). The 6-chloro substituted oxindole **2c** reacted well with isatin **3a** and gave the product **4r** in 96% yield, but lower enantioselectivities was obtained (87% ee, Table 2, entry 18). The unprotected oxindole, in contrast, delivered no desired product. The N-benzyl protected oxindole provided the vinylogous aldol product. These results shown the occurrence of intramolecular lactonization was probably due to an increasing reactivity of the oxindole ring by placing the Boc protecting group on nitrogen atom. (See ESI† for details)

We next evaluated the vinylogous aldol-cyclization cascade reaction of 3-arylidene oxindole **2d** with isatin **3a**. As shown in scheme 2, we prepared oxindoles (*Z*)[10] and (*E*)-2d[8f] and separately reacted with isatin **3a** under the optimal conditions. Intriguingly, it was found that only spirooxindole **4s** was obtained in high yield and enantioselectivity regardless of (*Z*) or (*E*)-**2d** were used (Scheme 2a and 2b).



Scheme 2 Further Substrate Scope Examination

The reaction of oxindole **2a** with methyl benzoylformate **5** under our optimal conditions was also evaluated. As shown in scheme 2c, only trace amount of vinylogous aldol product was found, no cyclization was observed.

The absolute configuration of the products was assigned based on the X-ray crystallographic analysis.[14] Taking advantage of the crystallographic structure of spirooxindole-dihydropyranone **4k**, all other product configurations were deduced by referring to that of **4k** (Figure 1).

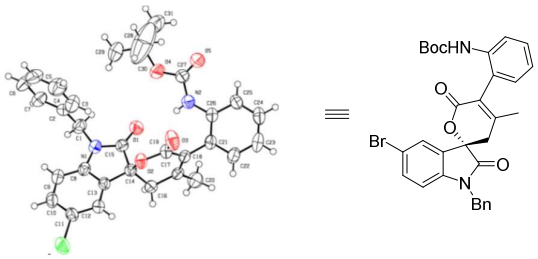
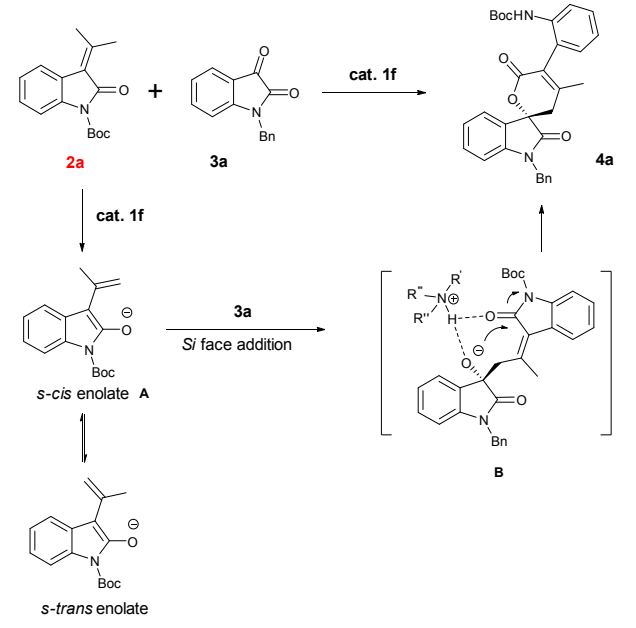


Figure 1 X-ray crystal structure of **4k**

A plausible reaction mechanism for this vinylogous aldol-cyclization cascade reaction is illustrated in scheme 3. According to the absolute configuration, and the proposed mechanism reported from Bencivenni group,[15] the oxindole **2a** was deprotonated by catalyst **1f** and generate *s-cis* enolate **A**, which then added through *Si* face to isatin **3a** to give alkoxide intermediate **B**. After cyclization and protonation of the intermediate **B**, the desired product **4a** was delivered and catalyst **1f** was regenerated. Another possible direct hetero-Diels-Alder reaction pathway reported by Xu cannot be ruled out.[13f] The possible model of dual activation of both nucleophile and electrophile by means of catalyst **1g** was also proposed. (See Figure S1 in the ESI†)



Scheme 3 A Plausible Reaction Mechanism

In summary, we have developed the organocatalyzed vinylogous aldol-cyclization of 3-Akylidene oxindoles with various substituted isatins by using cinchona alkaloid-squaramide bifunctional organocatalysts. A broad range of enantioenriched spirooxindole dihydropyranones with a quaternary stereocenter could be smoothly synthesized in good to excellent yields with high enantioselectivities. The 3-arylidene oxindole **2d** could also give the spirooxindole **4s** through the same cascade reaction. The detailed mechanistic study and further applications of this chemistry toward other reaction design are currently underway.

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