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Asymmetric Synthesis of Spirooxindole δ-Lactones with Vicinal Tertiary and Quaternary Stereocenters via Regio-, Diastereo-, and Enantioselective Organocatalytic Vinylogous Aldol−cyclization Cascade Reaction

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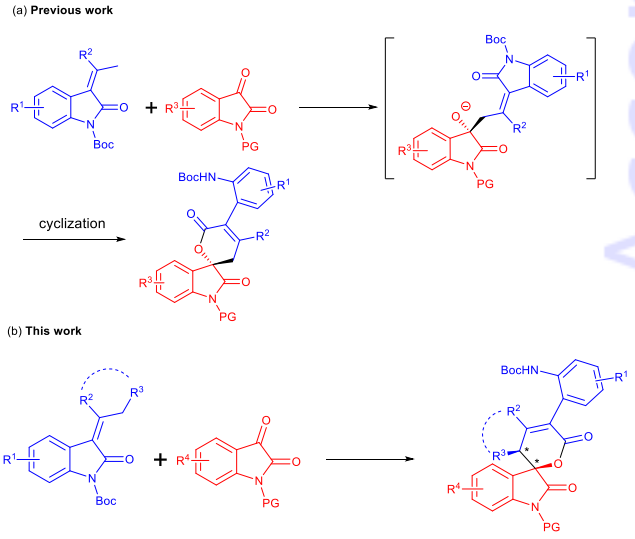
Abstract. A highly region-, diastereo-, and enantioselective organocatalytic vinylogous aldol−cyclization cascade reaction of prochiral 3-akylidene oxindoles to isatins has been achieved by using bifuctional organocatalysts. A variety of enantioenriched spirooxindole δ-lactones with vicinal tertiary and quaternary stereocenters were generated in good to excellent yields with good to high diastereoselectivities and enantioselectivities.

Keywords: Organocatalysis; 3-Akylidene oxindoles; Spirooxindole δ-lactones; Vinylogous aldol−cyclization.

Spirooxindole δ-lactone is a key structure element found in a variety of natural products and biologically active molecules.[1] The catalytic asymmetric transformations to chiral spirooxindole δ-lactone derivatives had been less studied. Ye,[2a] Chi, [2c] and Yao[2b,d,g] developed elegant methods to synthesized spirooxindole δ-lactone derivatives using NHC-catalysis. Wu[2e] reported the formation of spirooxindole δ-lactones from vinylogous aldol-cyclization cascade reaction of allyl pyrazoleamides with isatins. Xu[2f] achieved an efficient hetero-Diels-Alder reaction of olefinic azlactones with isatins to construct spirooxindole δ-lactone derivatives. Shi[2h-k] and coworkers utilized the enolizable homophthalic anhydride to react with istains to synthesize enantioenriched spirooxindole δ-lactones. The development of other efficient methods for the chiral spirooxindole δ-lactones is still of considerable synthetic and biological importance.

The vicinal tertiary and quaternary stereocenters are present in many natural products and biologically important molecules. A number of effort have been made towards the asymmetric synthesis of continuous tertiary and quaternary stereocenters.[3] However, it always required more harsh reaction conditions to stereoselective construct the quaternary stereocenters due to steric hindrance.[4] Hence, there is still a need for the development of catalytic and effective methods for generating of vicinal quaternary and tertiary stereocenters.

3-Alkylidene oxindoles have been documented as a vinylogous nucleophile to functionalize at the γ-position with a variety of electrophiles[5] employing hydrogen-bonding organocatalysts for substrate activation and diverse synthesis of optically pure compounds.[6] Our group recently has described an unexpected catalytic direct asymmetric vinylogous aldol[7]-cyclization cascade reaction of 3-alkylidene oxindoles with isatins using quinine-derived chiral squaramides as hydrogen-bonding organocatalysts,[8] a protocol that let to optically pure spirooxindole δ-lactones bearing a quaternary center.[9] The key transformation of this cascade reaction was the 3-alkylidene oxindoles could react with isatins via vinylogous aldol reaction, followed by an unusual cyclization to cleave the oxindole ring and construct spirooxindole δ-lactones (Scheme 1a).



Scheme 1. Previous and current construction of spirooxindole δ-lactones using vinylogous aldol−cyclization cascade reaction.

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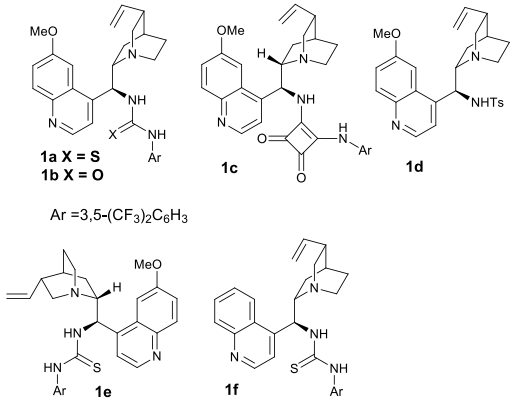
Continuing on this work, we expected this organo-catalytic vinylogous aldol-cyclization cascade reaction might be extended to the reaction of 3-alkylidene oxindoles bearing a prochiral site at the γ-position, which could be proceeded smoothly to deliver spirooxindole δ-lactones with the vicinal quaternary and tertiary stereocenters at the γ- and δ-positions (Scheme 1b). To the best of our knowledge, there is no mild, catalytic and efficient method to synthesize chiral polycyclic spirooxindole δ-lactones with the vicinal quaternary and tertiary stereocenters until today. We herein describe the first example of this transformation with perfect regioselective control, high enantioselectivities and high diastereo-selectivities.

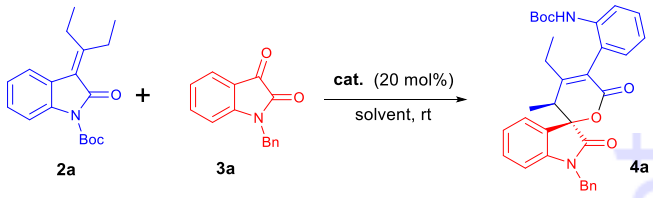
We initiated the investigation by carrying out the cascade reaction with oxindole **2a** (1.5 equiv.) and isatin **3a** (1 equiv.) by using quinie-derived thiourea catalyst **1a** (20 mol %, Scheme 2) as the catalyst in 0.5 mL toluene and at room temperature (Table 1, entry 1).



Scheme 2. Catalysts evaluated in this study.

reaction at room temperature in toluene with 15 mol% of catalyst **1a** at 0.4M substrate concentration. By using the quinidine-derived thiourea catalyst **1e**, the opposite enantiomer ***ent*-4a** was obtained in 88% yield, >20:1 diastereoselectivity and >99% *ee* (Table 1, entry 11).

Table 1. Optimization of reaction conditions.[a]



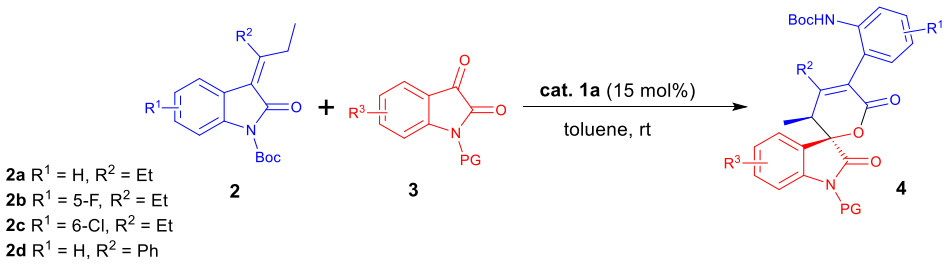
Entry	Cat.	Solvent	Time [h]	Yield [%][b]	dr[c]	*ee* [%][d]
1	**1a**	toluene	42	92	>20:1	>99
2	**1b**	toluene	218	56	>20:1	>99
3	**1c**	toluene	218	trace	-	-
4	**1d**	toluene	218	trace	-	-
5	**1a**	CH_2Cl_2	69	97	>20:1	>99
6	**1a**	THF	146	84	>20:1	>99
7	**1a**	CH_3CN	74	54	>20:1	>99
8	**1a**	DMF	218	trace	-	-
9[e]	**1a**	toluene	121	98	>20:1	>99
10[e,f]	**1a**	toluene	70	93	>20:1	>99
11[e,f]	**1e**	toluene	194	88	>20:1	>99[g]

[a] Unless otherwise noted, the reaction was carried out by using 0.1 mmol of **3a**, 1.5 equiv of **2a**, and 20 mol % of catalyst in 0.5 mL of solvent at rt (26-28℃)for indicated time. [b] Isolated yields. [c] Determinated by crude NMR analysis. [d] Determinated by chiral HPLC analysis. [e] 15 mol % of catalyst was used. [f] 0.25 mL of toluene. [g] *ee* of ***ent*-4a**.

To our delight, the reaction proceeded smoothly after 42h and afforded the desired product **4a** in 92% isolated yield, with exclusive γ-site- and *Z*-selectivities, and with excellent diastereoselectivity (>20:1) and enantioselectivity (>99% *ee*). Urea catalyst **1b** also reacted well with isatin **3a**, but resulted in lower product yield (56%) and longer reaction time (218h) (Table 1, entry 2). Squaramide **1c** and sulfonamide **1d** proved unproductive and afforded only trace amount of product **4a** (Table 1, entries 3-4). The screening of several polar and apolar solvents such as CH_2Cl_2, THF, CH_3CN, and DMF showed longer reaction time or lower product yield outcomes as compared to reactions conducted in toluene (Table 1, entries 5-8). Lowering the amounts of catalyst **1a** resulted in slightly increasing the yield (98% yield) and no enantioselectivity erosion although the reaction time was also increased (Table 1, entry 9). Increasing the reaction concentration from 0.2M to 0.4M shortened the reaction time without any disruption of yield, diastereoselectivity, and enantioselectivity (Table 1, entry 10). Finally, the optimal conditions were chosen by conducting the

With the optimal conditions established, we next explored the general substrate scope of both acyclic 3-alkylidene oxindoles **2** and isatins **3**. As shown in Table 2, all reactions genereally proceeded well to deliver the corresponding spirooxindole δ-lactones in good to high isolated yields, with excellent levels of γ-site selectivities, enantioselectivities and diastereo-selectivities. 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, diastereoselectivities and enantio-selectivities although the dr value of **4d** is lower compared to others (Table 2, entries 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 99% yield, >20:1 diastereoselectivity and 83% *ee* (Table 2, entry 5). Basically, the position and the electronic properties of the aromatic ring substituent, regardless of electron-donating or electron-withdrawing groups, did not alter the reaction performance significantly (Table 2, entries 6-13).

Table 2. Substrate scope examination.[a]



Entry	R^1	R^2	R^3	**2**	PG	**4**	Time [h]	Yield [%][b]	dr[c]	*ee* [%][d]
1	H	Et	H	**2a**	Bn	**4a**	70	93	>20:1	>99
2	H	Et	H	**2a**	Me	**4b**	62	93	>20:1	84
3	H	Et	H	**2a**	Et	**4c**	28	96	>20:1	92
4	H	Et	H	**2a**	Allyl	**4d**	48	93	9:1	92
5	H	Et	H	**2a**	H	**4e**	90	99	>20:1	82
6	H	Et	5-F	**2a**	Bn	**4f**	72	83	>20:1	>99
7	H	Et	7-F	**2a**	Bn	**4g**	71	78	11:1	96
8	H	Et	5-Cl	**2a**	Bn	**4h**	93	70	6:1	>99
9	H	Et	6-Cl	**2a**	Bn	**4i**	69	75	10:1	92
10	H	Et	5-Br	**2a**	Bn	**4j**	69	70	7:1	97
11	H	Et	5-Me	**2a**	Bn	**4k**	62	99	>20:1	94
12	H	Et	5-OMe	**2a**	Bn	**4l**	38	82	>20:1	99
13	H	Et	5-NO_2	**2a**	Bn	**4m**	128	99	10:1	>99
14	5-F	Et	H	**2b**	Bn	**4n**	20	99	>20:1	>99
15	6-Cl	Et	H	**2c**	Bn	**4o**	13	99	>20:1	>99
16	H	Ph	H	**2d**	Bn	**4p**	92	99	>20:1	73

[a] Unless otherwise noted, the reaction was carried out by using 0.1 mmol of **3a**, 1.5 equiv of **2a**, and 15 mol % of catalyst in 0.25 mL of solvent at rt (26-28℃)for indicated time. [b] Isolated yields. [c] Determinated by crude NMR analysis. [d] Determinated by chiral HPLC analysis.

However, the halogen-substituted isatins **3g-j** gave the product **4g-j** in excellent enantioselectivities, but slightly reduced product yields and diastereoselectivities (Table 2, entries 7-10). Variation of the alkylidene donors was then surveyed in reactions with isatin **3a** (Table 2, entries 14-15).

The 5-F substituted oxindole **2b** and 6-Cl substituted oxindole **2c** were found to be compatible and competent substrates in this cascade reaction and afforded the spirooxindole δ-lactones **4n-o** in excellent yields, diastereoselectivities and enantioselectivities.

We then turned our attention to the vinylogous aldol-cyclization cascade reaction of 3-alkylidene oxindoles bearing a phenyl substituent at the β-position with isatin **3a**. The alkylidene derivative (*E*)-**2d**, prepared according the literatures,[10] could also be productively engaged in this asymmetric transformation, and delivered the corresponding product **4p** with good results in terms of yield and diastereoselectivity, albeit with modest enantioselectivity (Table 2, entries 16).

The unprotected oxindole, in contrast, delivered no desired product. This indicated 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.

After studying the reaction with isatins and oxindoles with acyclic substituents, we focused our attention in the use of various cyclic ring-substituted oxindoles as nucleophiles in this cascade reaction. This reaction could be extended to the construction of polycyclic spirooxindole δ-lactones, which were potential scaffolds to medicinal chemistry.[1]

We initiated our studies by evaluating the cascade reaction of oxidole **2e** and isatin **3a** in our optimized conditions. To our disappointment, the desired product **5a** was obtained in low enantioselectivity although the yield and diastereoselectivity were satisfied (Table 3, entries 1). However, the enantioselectivity (69% *ee*) was improved dramatically when the reaction was conducted in dichloromethane (Table 3, entries 2). Examination of other cinchona-alkaloid bifunctional organocatalysts showed the catalyst **1c** gave the highest enantioselectivity with excellent product yield and diastereoselectivity (Table 3, entries 3-5). Intriguingly, the opposite enantiomer of **5a** was obtained. The reason for the enantioselectivity switch is still not clear. After screening of catalyst loadings, various solvents and reaction temperature, the final optimal conditions were chosen by perfoming the reaction at room temperature in CH_2Cl_2 with 15 mol% of catalyst **1c** (Table 3, entries 6).

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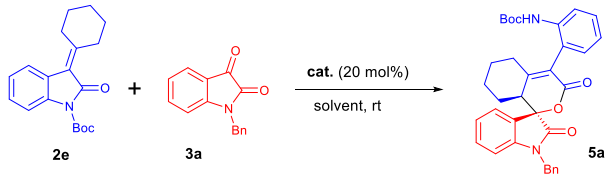
Table 3. Reaction conditions optimization.[a]

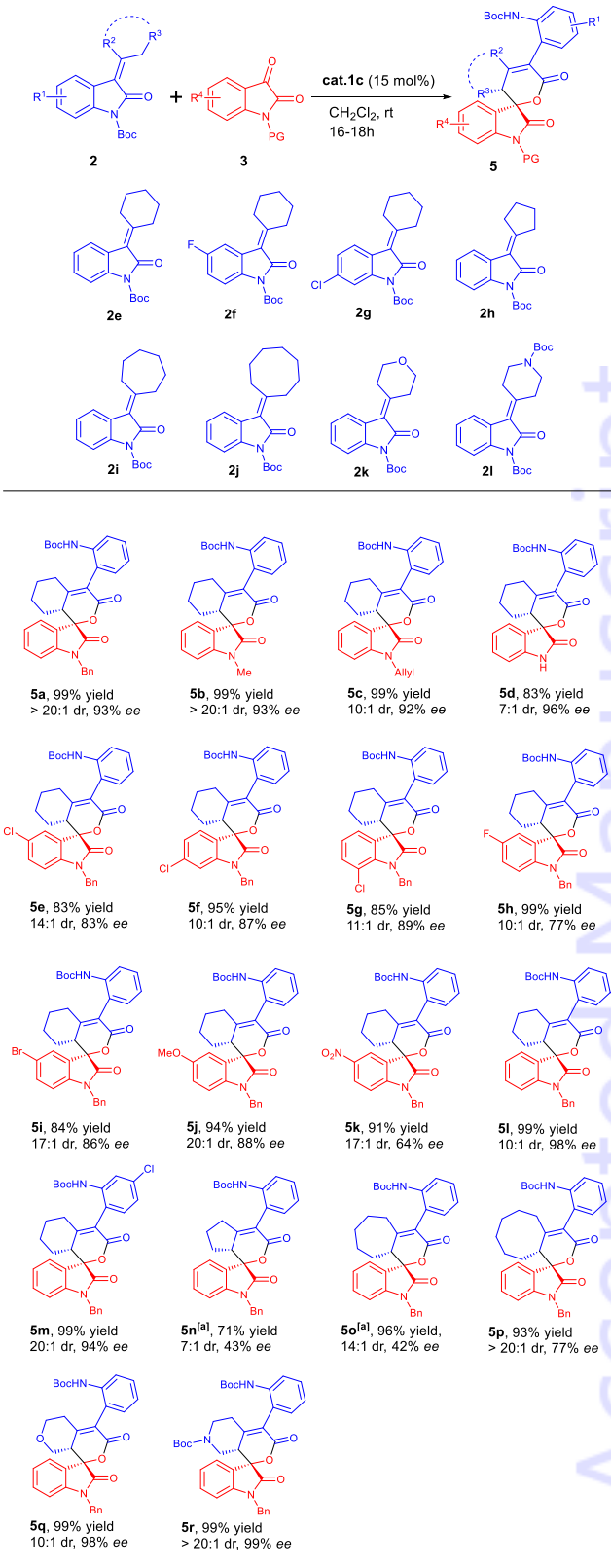


Entry	Cat.	Solvent	Time [h]	Yield [%][b]	dr[c]	*ee* [%][d]
1	**1a**	toluene	31	99	7:1	29
2	**1a**	CH_2Cl_2	18	96	>20:1	69
3	**1b**	CH_2Cl_2	18	98	>20:1	31
4	**1c**	CH_2Cl_2	18	99	>20:1	93[e]
5	**1f**	CH_2Cl_2	18	99	>20:1	6
6[f]	**1c**	CH_2Cl_2	18	99	>20:1	93[e]
7[g]	**1c**	CH_2Cl_2	18	84	>20:1	89[e]
8[h]	**1c**	CH_2Cl_2	18	54	>20:1	88[e]
9	**1c**	THF	72	93	>20:1	93[e]
10	**1c**	CH_3CN	12	95	>20:1	91[e]
11	**1c**	$CHCl_3$	18	90	>20:1	92[e]
12	**1c**	$Cl(CH_2)_2Cl$	18	91	>20:1	94[e]
13[i]	**1c**	CH_2Cl_2	24	93	>20:1	87[e]
14[j]	**1c**	CH_2Cl_2	24	93	>20:1	90[e]

[a] Unless otherwise noted, the reaction was carried out by using 0.1 mmol of **3a**, 1.5 equiv of **2a**, and 20 mol % of catalyst in 0.5 mL of solvent at rt (20-22℃)for indicated time. [b] Isolated yields. [c] Determinated by crude NMR analysis. [d] Determinated by chiral HPLC analysis. [e] Opposite enantiomer. [f]15 mol % of catalyst [g] 10 mol % of catalyst. [h] 5 mol % of catalyst. [i] 0℃. [j] 10℃.

We then focused our attention on establishing the scope with respect to both the cyclic ring-substituted oxindoles **2e-l** and isatins **3** (Scheme 3). Most isatins with different N-protecting groups, electron-donating and electron-withdrawing groups (**5a-5k**) were well tolerated, obtaining high yields, good to high diastereoselectivities (7:1 to >20:1) and good to high enantiomeric excesses (83% to 96% *ee*), except for products **5h** (77% *ee*)and **5k** (64% *ee*). The oxindoles bearing a halogen substituent gave products **5l** and **5m** in excellent yields and enantioselectivities. Remarkably, the oxindoles with different ring-size, tetrahydropyran and piperidine substituents (**2h-l**) were also worked well in this cascade reaction. However, only oxindole **2k** and **2l** delivered the products **5q** and **5r** in excellent yields (99%), diastereoselectivities (10:1 and >20:1) and enantiomeric excesses (98% and 99% *ee*).

The relative and absolute configurations of **4j** and **5i**, bearing a Br atom, were unambiguously and respectively determined as (C15*R*, C16*S*) and (C15*S*, C16*R*) configuration with a *syn*-structure by X-ray crystallographic analysis (Figure 1). [11] The configuration of the other products in Table 2 and Scheme 3 were assigned by analogy assuming the reactions retained a uniform stereochemical outcome.



Scheme 3. Scope of the cascade reaction of cyclic ring-substituted oxindoles: 0.1 mmol of **3**, 1.5 equiv of **2**, and 15 mol % of catalyst in 0.5 mL of CH_2Cl_2 at rt (20-22℃)for 16-18h. Isolated yields. Diastereomer ratios were determinated by crude NMR analysis. Enantiomeric excesses were determinated by chiral HPLC analysis. [a] 30 mol% of catalyst.

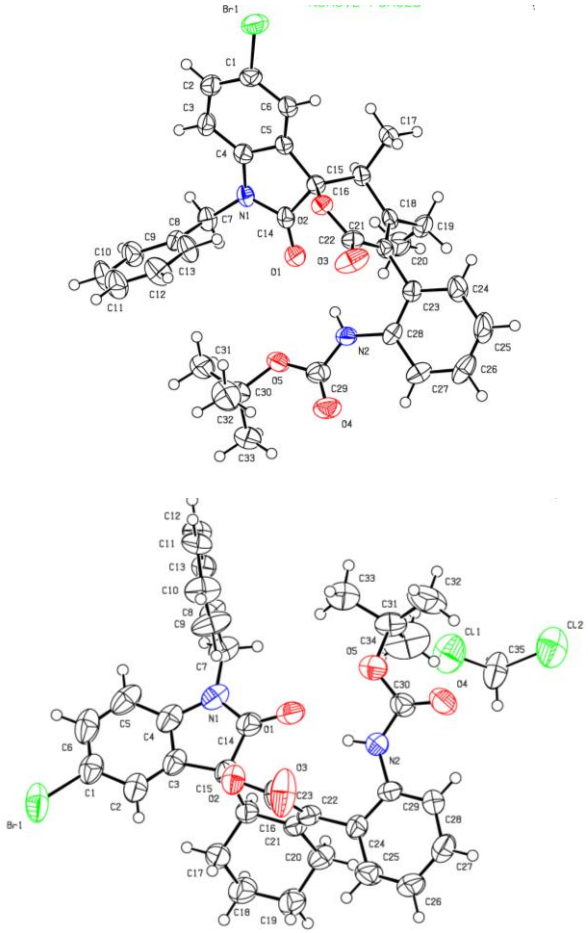


Figure 1. Relative and absolute stereochemistry of brominated products **4j** (*top*) and **5i** (*bottom*) were determinated by single crystal X-ray analysis.

To explain the detail stereochemistry outcome of this cascade reaction, a plausible transition model utilizing *Cinchona* catalysts-promoted activation models was proposed. As outlined in Figure 2, the quinuclidine base of the catalyst deprotonated the H atom from the γ-position of oxindoles **2** and generated *s-cis* enolate through hydrogen bonding. Meanwhile, the isatins **3** also developed hydrogen bonding with the thiourea moiety of the catalyst and finally two substrates were synergistically activated based on the activation pathway proposed by Takemoto and coworkers.[12] The stereochemistry of products **4** was speculatively determined in the first vinylogous aldol addition step. Through the close spatial proximity, the oxindole nucleophile, which the methyl group at the γ-position and R^3 were projected in *trans* geometry, preferably added to *Si*, *Si*-face trajectory of isatins **3** and afforded the spirooxindoles **4** with (C15*R*, C16*S*) configuration and *syn*-conformation (Figure 2a). It is likely due to the steric repulsion between methyl group and R^3, the *anti*-conformation products were the minor isomers observed in this cascade reaction (Figure 2b). The X-ray crystallographic analysis shows the configuration of **5** (C15*S*, C16*R*) were opposite to spirooxindoles **4** and the conformation **(***syn*) were the same as **4**. These results indicated the stereochemistry of polycyclic spirooxindoles **5** went through the same mechanistic pathway as **4**.

However, the other possible dual activation model proposed by Pápai[13] and Zhong[14] cannot be excluded. The nucleophile is activated by the thiourea group of the catalyst, while the protonated quinuclidine nitrogen generated hydrogen bonding with the isatins **3**. The detailed mechanistic study of this chemistry using DFT calculations is currently underway in our laboratories.

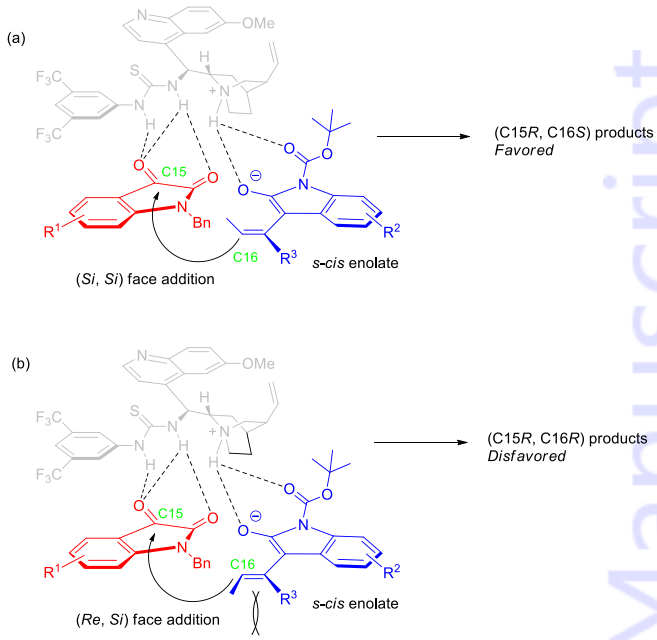


Figure 2. Possible transition states for stereochemistry.

In summary, we have developed a highly region-, diastereo-, and enantioselective organocatalytic vinylogous aldol−cyclization cascade reaction of prochiral 3-akylidene oxindoles to various substituted isatins by using cinchona alkaloid bifunctional organocatalysts. A broad range of enantioenriched spirooxindole δ-lactones with vicinal quaternary and tertiary stereocenters could be smoothly synthesized in good to excellent yields, high enantioselectivities and diastereoselectivities. Especially, this methodology could be extended to the construction of complex polycyclic spirooxindole δ-lactones. We expect that these novel spirooxindole products emerging from these studies will be valuable for organic synthesis and pharmaceutical chemistry communities.

Experimental Section

Typical Procedure for the Enantioselective Organocatalytic Vinylogous Aldol−cyclization Cascade Reaction

To a solution of 3-alkylidene oxindoles **2** (0.15 mmol) and catalyst **1a** or **1c** (0.015 mmol) in solvent was added isatins **3** (0.10 mmol) at room temperature until **3** was consumed (determined by TLC). The reaction solution was

concentrated in vacuum and the crude was purified by silica gel flash chromatography (Hexane/EA 5:1 to 3:1) to afford the pure products **4** or **5**. The enantiomeric ratio was determined by HPLC on a chiral stationary phase. The corresponding opposite enantiomers (***ent*-4**) were obtained by using catalyst **1e** under the same reaction conditions.

Acknowledgements

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[11] CCDC 1497412 (**4j**) and CCDC 1567444 (**5i**) contain 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.

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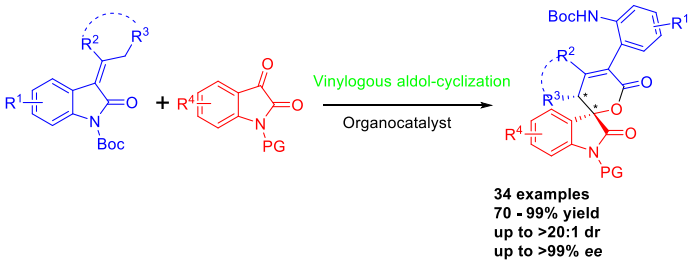
UPDATE

Asymmetric Synthesis of Spirooxindole δ-Lactones with Vicinal Tertiary and Quaternary Stereocenters via Regio-, Diastereo-, and Enantioselective Organocatalytic Vinylogous Aldol− cyclization Cascade Reaction



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