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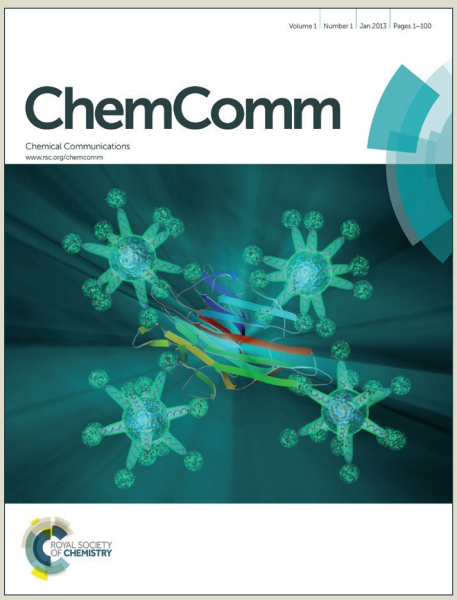





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# Graphic Abstract

**Organocatalytic Cascade Michael/Michael Reaction for the Asymmetric Synthesis of Spirooxindoles Containing Five Contiguous Stereocenters**

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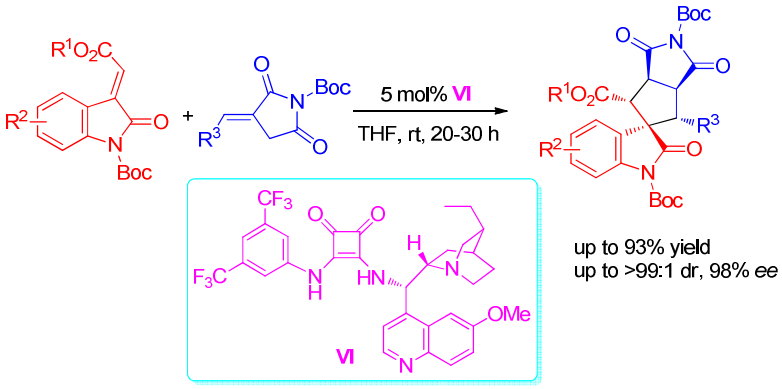


Squaramide-catalyzed cascade Michael/Michael reaction for the asymmetric synthesis of five-membered spirooxindoles containing five contiguous stereocenters is presented.

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# Organocatalytic Cascade Michael/Michael Reaction for the Asymmetric Synthesis of Spirooxindoles Containing Five Contiguous Stereocenters

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A bifunctional squaramide-catalyzed Michael/Michael cascade reaction for the construction of five-membered spirooxindoles was developed. This reaction afforded the corresponding products with five contiguous stereocenters including one quaternary center in good to excellent yields (up to 93%) with excellent stereoselectivities (up to >99:1 dr, 98% *ee*). Meanwhile, the practicality of this methodology was illustrated by a gram-scale synthesis, one-pot four-component reaction and synthetic transformation of the resulting adduct.

The spirooxindole architecture is a privileged scaffold that is prevalent in both natural products and synthetic bioactive molecules.[1] In particular, enantiopure five-membered spirooxindoles are considered to be more important skeletons associated with their diverse bioactivities and structural complexity (Figure 1),[2] which have inspired organic chemists to pursue efficient methods to synthesize them. The key challenge for the construction of such structures is the formation of multiple stereocenters. Therefore, the development of efficient and highly stereoselective new strategies for the synthesis of such spirooxindoles from readily available starting materials are always in great demand.

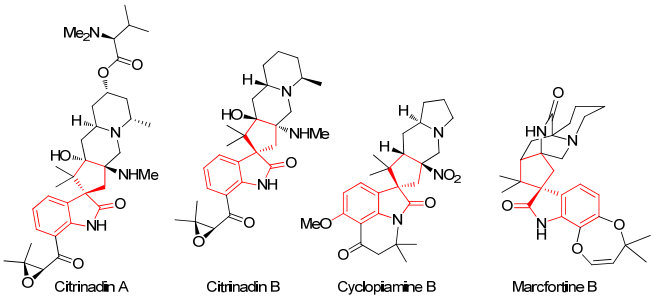
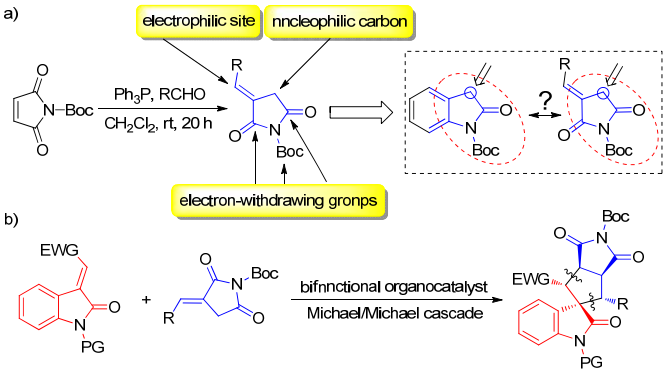



**Figure 1** Examples of bioactive five-membered spirooxindole derivatives.

In the development of new strategies for catalytic asymmetric synthesis of five-membered spirooxindoles, the spiro[pyrrolidin-3,3'-oxindole] scaffolds have been well studied.[3] However, there are few enantioselective methods for synthesis of cyclopentane fused spirooxindoles.[4] Recently, an asymmetric catalytic synthesis of such compounds via scandium(III)/indapybox complex catalyzed [3+2] cycloaddition was reported by Franz and co-workers.[5] Currently, the organocatalytic enantioselective domino or cascade reaction is an alternative powerful strategy to the synthesis of complex compounds with contiguous multiple stereocenters except from transition-metal catalysis.[6] More recently, Lin and co-workers developed a squaramide-catalyzed Michael/Mannich cascade reaction for highly stereoselective synthesis of five-membered spirooxindoles.[7] However, despite the considerable effort that has been devoted in this field, further research is needed to develop more flexible synthetic strategies, to expand structural and stereochemical diversity, and to extend the functional pattern of spirooxindoles.




**Scheme 1** Proposed strategy towards spirooxindoles. EWG = electron-withdrawing group, PG = protecting group.

Maleimides are an important class of substrates, which have been successfully used in asymmetric organocatalytic synthesis of chiral succinimide derivatives.[8] Furthermore, α-alkylidene succinimides are very useful synthons bearing multiple electron withdrawing groups, nucleophilic and electrophilic sites. These compounds have similar structure to oxindoles

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that have been successfully used as donor in the asymmetric reactions (Scheme 1a),[9] but there is still few reports in asymmetric synthesis of chiral succinimide derivatives.[10] We envisoned that α-alkylidene succinimides should also be used as tandem reagents to trigger the asymmetric cascade Michael/Michael reaction with 3-olefinic oxindoles in the presence of bifunctional organocatalyst to give the corresponding spirocyclopentane derivative bearing a disubstituted succinimide unit (Scheme 1b). To the best of our knowledge, such compounds have not been used as nucleophilic reagents triggering a cascade reaction thus far. Herein, we present one novel squaramide-catalyzed[11] diastereo-and enantioselective cascade Michael/Michael reaction for the asymmetric synthesis of five-membered spirooxindoles.

Our study of the catalytic asymmetric reaction began with the finding appropriate α-alkylidene succinimide. Initially, the unprotected α-alkylidene succinimide **2a** was chosen as tandem reagent to evaluate the feasibility of asymmetric cascade Michael/Michael reaction with the isatin derived enoate **1a** in the presence of the squaramide **I** (5 mol%) in toluene at room temperature (Table 1, entry 1). Unfortunately, no reaction was observed, perhaps due to the relatively low reactivity of unprotected α-alkylidene succinimide. When *N*-Bn and *N*-Ph α-alkylidene succinimides **2b** and **2c** were used as the tandem reagents, a trace amount of products was detected by TLC (Table 1, entries 2 and 3). On the other hand, when the R substituent on the nitrogen of the α-alkylidene succinimide **2** was changed to a *t*-butyloxy carbonyl (Boc) group, the corresponding substrate **2d** reacted smoothly with **1a** under the same condition to afford **3a** as the major diastereomer (76:24 dr) in moderate yield with excellent enantioselectivity (98% *ee*). This result indicates that the *t*-butyloxy carbonyl group can enhance the reactivity of α-alkylidene succinimide.

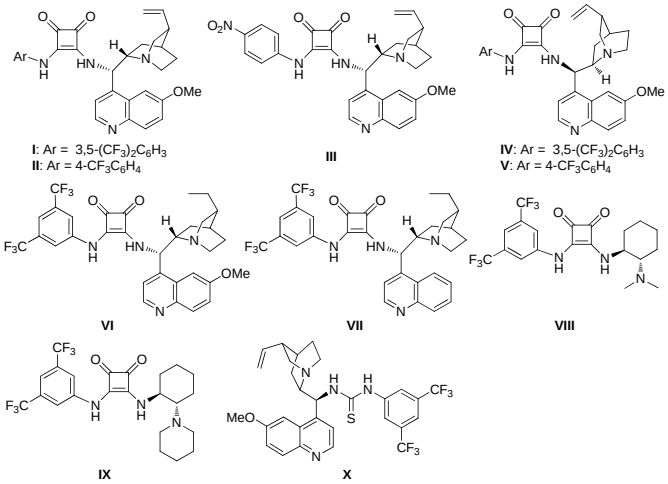
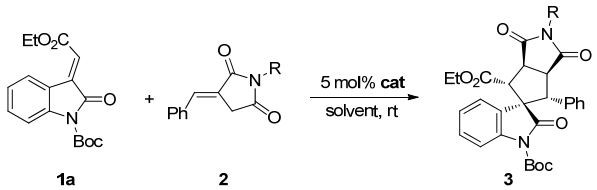



**Figure 2** Squaramide and thiourea organocatalysts.

With the above excellent result in hand, we evaluated a small library of organocatalysts (Figure 2) for this cascade process. Quinine-derived squaramide **II** bearing 4-$CF_3$ group on the aromatic ring gave an inferior result (Table 1, entry 5). When squaramides **III** was used, a little better result was obtained (Table 1, entry 6). Squaramides **IV** and **V** derived from quinidine afforded the desired adduct with low diastereoselectivity and opposite configuration (Table 1, entries 7 and 8). A little improvement in yield and diastereoselectivity was obtained when hydroquinine-derived squaramide **VI** was used as the catalyst (Table 1, entry 9). Squaramide **VII** derived from hydrocinchonidine offered inferior outcomes (Table 1, entry 10). Squaramides **VIII** and **IX** derived from (1*S*,2*S*)-1,2-diaminocyclohexane- were also examined, but no improvements were observed (Table 1, entries 11 and 12). In addition, for comparison with the used squaramides, the corresponding quinine-derived thiourea **X** was also screened (Table1, entry 13). Unfortunately, there is a significant decline in yield with similar stereoselectivity. At last, we chose hydroquinine-derived squaramide **VI** as the optimal catalyst.

**Table 1** Screening of organocatalysts and optimization of reaction conditions for the asymmetric synthesis of spirooxindole **3**.[a]




**1a** **2** **3**

| Entry | solvent | R | catalyst | t [h] | Yield[b][%] | dr[c] | *ee*[c] |
|---|---|---|---|---|---|---|---|
| 1 | PhMe | H (**2a**) | **I** | 72 | — | — | — |
| 2 | PhMe | Bn (**2b**) | **I** | 72 | trace | — | — |
| 3 | PhMe | Ph (**2c**) | **I** | 72 | trace | — | — |
| 4 | PhMe | Boc (**2d**) | **I** | 10 | 57 (**3a**) | 76:24 | 98 |
| 5 | PhMe | Boc (**2d**) | **II** | 10 | 52 (**3a**) | 74:26 | 98 |
| 6 | PhMe | Boc (**2d**) | **III** | 10 | 60 (**3a**) | 79:21 | 98 |
| 7 | PhMe | Boc (**2d**) | **IV** | 10 | 62 (**3a**) | 61:39 | -99 |
| 8 | PhMe | Boc (**2d**) | **V** | 10 | 57 (**3a**) | 48:52 | -97 |
| 9 | PhMe | Boc (**2d**) | **VI** | 10 | 63 (**3a**) | 82:18 | 98 |
| 10 | PhMe | Boc (**2d**) | **VII** | 10 | 48 (**3a**) | 56:44 | 88 |
| 11 | PhMe | Boc (**2d**) | **VIII** | 10 | 50 (**3a**) | 79:21 | 88 |
| 12 | PhMe | Boc (**2d**) | **IX** | 10 | 53 (**3a**) | 79:21 | 98 |
| 13 | PhMe | Boc (**2d**) | **X** | 10 | 38 (**3a**) | 73:27 | 99 |
| 14 | $CH_2Cl_2$ | Boc (**2d**) | **VI** | 3 | 39 (**3a**) | 79:21 | 98 |
| 15 | $CHCl_3$ | Boc (**2d**) | **VI** | 3 | 30 (**3a**) | 68:32 | 67 |
| 16 | $ClCH_2CH_2Cl$ | Boc (**2d**) | **VI** | 3 | 36 (**3a**) | 83:17 | 98 |
| 17 | MeCN | Boc (**2d**) | **VI** | 10 | 62 (**3a**) | 69:31 | 96 |
| 18 | THF | Boc (**2d**) | **VI** | 20 | 83 (**3a**) | 86:14 | 98 |
| 19 | $Et_2O$ | Boc (**2d**) | **VI** | 20 | 79 (**3a**) | 72:28 | 96 |
| 20 | 1,4-dioxane | Boc (**2d**) | **VI** | 20 | 74 (**3a**) | 86:14 | 96 |
| 21[d] | THF | Boc (**2d**) | **VI** | 40 | 80 (**3a**) | 78:22 | 98 |
| 22[e] | THF | Boc (**2d**) | **VI** | 20 | 85 (**3a**) | 81:19 | 97 |
| 23[f] | THF | Boc (**2d**) | **VI** | 40 | 76 (**3a**) | 78:22 | 95 |

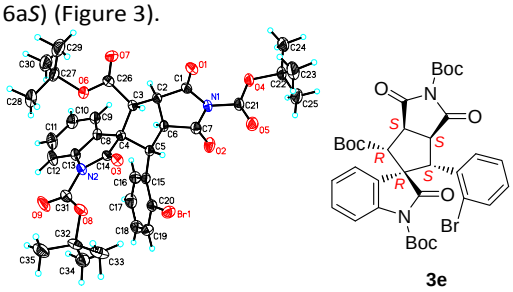
[a] Reaction conditions: **1a** (0.11 mmol), **2** (0.1 mmol), catalyst (5 mol%) in 0.5 mL solvent at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The reaction was performed at −10 °C. [e] 10 mol% catalyst was used. [f] 2.5 mol% catalyst was used.

To improve the yield and diastereoselectivity of this cascade Michael/Michael reaction, further optimization was performed using squaramide **VI**. The effect of solvent, temperature and catalyst loading were evaluated for the optimal reaction conditions (Table1, entries 14−23). The reaction afforded the desired **3a** in higher yield and diastereoselectivity when THF was used as the solvent (Table1, entry 18), but with a longer reaction time. When the temperature was reduced to −10 °C,

no improvement was obtained (Table 1, entry 21). Neither increasing nor reducing the catalyst loading could improve the result obviously (Table 1, entries 22 and 23). From the above evaluations, the optimal catalyst loading was finally determined to be 5 mol%.

With the optimized conditions in hand, we next examined the substrate scope of the asymmetric cascade reaction for the synthesis of highly functionalized spirooxindoles. The 3-olefinic oxindole **1b** bearing a *tert*-butyl ester was tested firstly. The improvements in yield and diastereoselectivity were observed with a slightly decrease in enantioselectivity. Next, a variety of α-alkylidene succinimides were examined, and the corresponding products **3c–l** were obtained. The presence of either electron-withdrawing (**3c–f**) or electron-donating groups (**3g–i**) on the aromatic rings of α-alkylidene succinimides is well tolerated, which indicate that the electronic nature of the substituents on the aromatic rings has little influence on this cascade process. The position of the substituent on the aromatic ring of α-alkylidene succinimides also has little effect on stereoselectivity (**3e**, **3f**, **3h** and **3i**). Additionally, heterocyclic substrate was also amenable to this cascade reaction and afforded the corresponding product **3k** with excellent result. Meanwhile, the diastereo- and enantioselectivity were maintained for the less reactive phenylethyl substituted α-alkylidene succinimide and afforded the corresponding product **3l** with longer reaction time in decreased yield. Then, a variety of 5-substituted 3-olefinic oxindoles containing *tert*-butyl ester were tested, and all these substrates could smoothly undergo the cascade Michael/Michael reaction to afford the desired spirooxindoles **3m–r**. However, the substrates with electron-withdrawing groups, such as F and $NO_2$, afforded the corresponding products **3m** and **3r** in lower yields. A kind of 6-substituted 3-olefinic oxindole was also evaluated, and the desired spirooxindole **3s** was obtained with better stereoselectivity.

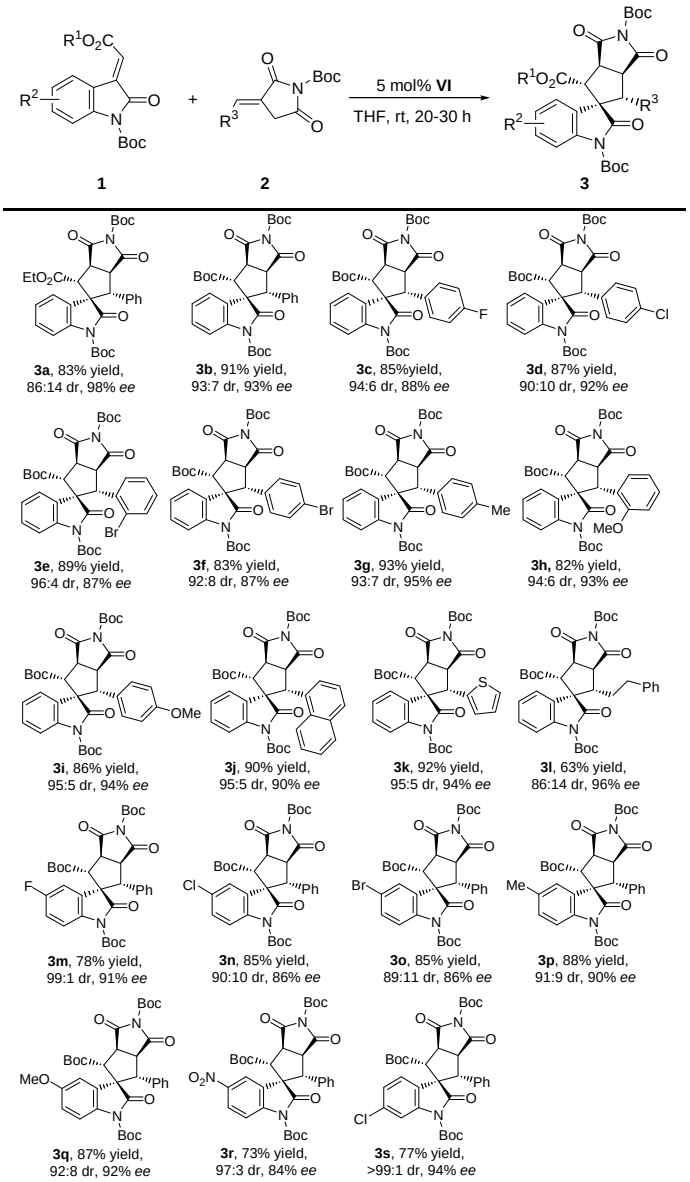
The absolute configuration of the product was elucidated by single crystal X-ray diffraction analysis of **3e**.[12] The exo' selectivity of the reaction was confirmed unambiguously, and the absolute configuration was determined as (3a*S*, 3'*R*, 4*S*, 6*R*, 6a*S*) (Figure 3).



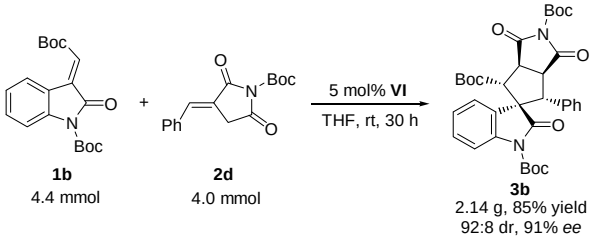
**3e**

**Figure 3** X-ray crystal structure of **3e**.

To illustrate the preparative utility of this asymmetric cascade Michael/Michael reaction, a gram-scale reaction was also conducted under same conditions (Scheme 3). The five-membered spirooxindole **3b** was obtained in 85% yield with excellent diastereoselectivity (92:8 dr) and slightly decreased enantioselectivity (91% *ee*).



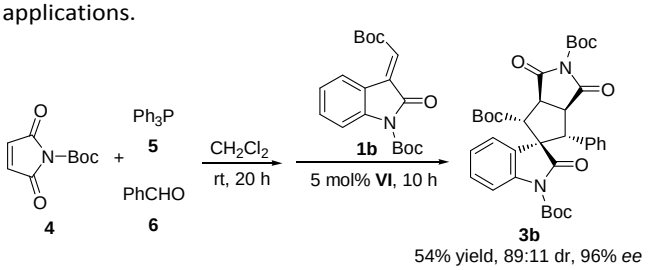

**Scheme 2** Substrate scope. Reaction conditions: **1** (0.22 mmol), **2** (0.2 mmol), and catalyst **VI** (5 mol%) in 1.0 mL THF was stirred at room temperature. The dr and *ee* value of all products were determined by HPLC except the dr of product **3d**.The dr of **3d** was determined by weighing the quality of isolated diastereomers.



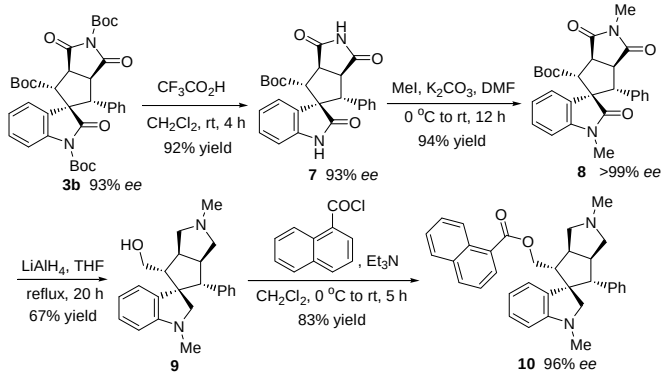

**Scheme 3** Gram-scale synthesis of **3b**.

One-pot reaction of four available starting materials was tested using the $CH_2Cl_2$ as the solvent (Scheme 4). The reaction proceeded smoothly and giving the desired product **3b** in 54% yield with good diastereoselectivity (89:11 dr) and excellent enantioselectivity (96% *ee*). This one-pot four-component

reaction would be more convenient in potential industrial applications.




**Scheme 4** One-pot four-component reaction.




**Scheme 5** Synthetic transformation of adduct **3b**.

To further extend the potential of this protocol a facile route to obtain enantiomerically pure analogue of spirooxindole for potential clinical application, the derivatization of the major diastereomer of **3b** was also investigated (Scheme 5). The *N*-Boc protecting group in **3b** can be removed smoothly using $CF_3CO_2H$ at room temperature for 4 h, the corresponding product **7** was obtained in 92% yield without erosion of enantioselectivity (93% *ee*). The product **7** can be easily transformed into *N*-methyl substituted product **8** in 94% yield using methyl iodide. A subsequent $LiAlH_4$ reduction of compound **8** in refluxing THF for 20 h afforded spiro[octahydrocyclopenta[*c*]pyrrole-3,3'-indoline] **9** in 67% yield. Due to the fact that enantiomers of **9** couldn't be separated by HPLC, further esterification of **9** led to the synthesis of ester **10** in 83% yield with 96% *ee* using naphthoyl chloride. The enantiomers of **10** could be well separated by HPLC. This methodology provides additional opportunities for preparing this intriguing class of compounds and might be useful in medicinal chemistry.

In summary, we have successfully developed an efficient cascade Michael/Michael reaction catalyzed by a bifunctional tertiary amine-squaramide catalyst for the asymmetric synthesis of five-membered spirooxindoles containing five contiguous stereocenters with a broad scope of substrates. The corresponding products were obtained in good yields with excellent diastereoselectivities and enantioselectivities (up to > 99:1 dr, 98% *ee)*. Importantly, this cascade reaction could be easily scaled up and one-pot four-component reaction was also successfully applied to the synthesis of spirooxindole. Specifically, an asymmetric synthesis of the core structure of spiro[octahydrocyclopenta-[*c*]pyrrole-3,3'-indoline] derivatives has been efficiently achieved within several synthetic steps.

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12 Crystallographic data for compound-**3e** (CCDC-1446037) has been provided as CIF file in supporting information.