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Highly Efficient Enantioselective Construction of Bispirooxindoles Containing Three Stereocenters through an Organocatalytic Cascade Michael–Cyclization Reaction

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Abstract: Bispirooxindole derivatives containing three stereocenters, including two spiro quaternary centers, were synthesized in a high-yielding, atypically rapid, and stereocontrolled cascade Michael–cyclization reaction between methyleneindolinones and isothiocyanato oxindoles catalyzed by a bi- or multifunctional organocatalyst. Mild conditions were used to construct bispirooxindoles with excellent enantio- and diastereomeric purities within less than 1 min. Catalyst reconfiguration offered access to the opposite enantiomer. This exceptionally highly efficient procedure will allow diversity-oriented syntheses of this intriguing class of compounds with potential biological activities.

Keywords: asymmetric synthesis · cascade reactions · organocatalysis · spiro compounds · synthetic methods

Introduction

The structure complexity and well-defined three-dimensional architecture of natural molecules that act as the main sources of templates are generally correlated with specificity of drug action and potentially useful biological properties.[1] This complexity and richness in stereogenic centers has inspired generations of synthetic chemists to design new enantioselective strategies for assembling challenging target structures and reproducing the structural diversity occurring in natural molecules.[2]

The spirocyclic-oxindole scaffold defines the characteristic structural core of a large family of alkaloid natural products with strong bioactivity profiles and interesting structural properties (Figure 1).[3] Motivated by the varied and significant biological activities observed for this class of compounds, many remarkable advances have been made on enantioselective catalytic strategies for the construction of spirooxindoles, especially applications to natural product synthesis.[3a,4–6] For example, the groups of Wang and Barbas III, respectively, reported an elegant asymmetric cascade Michael–cyclization sequence or [3+2]-cycloaddition reaction between α-isothiocyanato imides and methyleneindolinones through dual activation by bifunctional organocatalysts, which provided excellent stereocontrol of the newly formed spirocyclic oxindoles.[4j,s] In this context, however, highly efficient methods for the enantioselective synthesis of bispirooxindole derivatives, which are featured in a large number of medicinal compounds, have been barely disclosed due to the required challenging simultaneous creation of multiple chiral centers including spiro quaternary ones in a single step.[7] Given the demand for new methodologies for the construction of bispirooxindole scaffolds, a simple and efficient synthetic method for the densely functionalized core scaffold with multiple stereogenic centers is highly desirable.

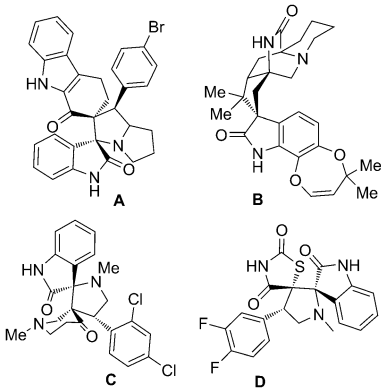

Figure 1. Some biologically active compounds with the spirocyclic oxindole core.

Recently, isothiocyanato oxindoles[4l,q,8] were used as efficient Michael donors and methyleneindolinones[4h,5a–c,7a] were used as highly reactive Michael acceptors. Encouraged by these achievements and the excellent synthetic art of

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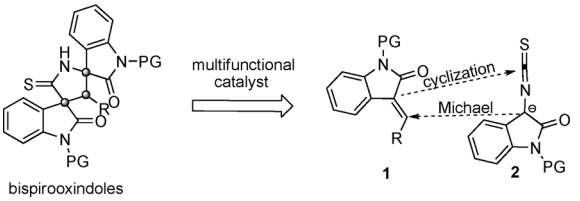
Wang, Barbas III, and their respective co-workers, we envisioned that bispirooxindole skeletons with multiple stereocenters, including two spiro quaternary centers,[2d,10] could be constructed by a cascade Michael–cyclization[11] reaction between rationally designed methyleneindolinones, **1**, and 3-isothiocyanato oxindoles, **2** (Scheme 1). However, three



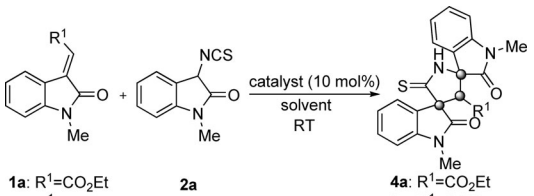
Scheme 1. Proposed strategy for the direct construction of bispirooxindoles through an organocatalytic cascade Michael–cyclization sequence. PG: protecting group.

challenges are associated with the performance of this cascade sequence in a single step: 1) the formation of a highly sterically congested spirocyclic pyrrolidinyl ring with five substituents; 2) the simultaneous creation of two chemical bonds and three stereocenters including two spiro quaternary centers in one step; and 3) the control of the diastereo- and enantioselectivity of the products. Herein, we present an exceptionally highly efficient strategy for the enantioselective construction of bispirooxindoles containing three stereocenters through a cascade Michael–cyclization reaction between methyleneindolinones, **1**, and isothiocyanato oxindoles, **2**. Under mild reaction conditions, all of the reactions were completed in less than one minute and afforded the bispirooxindole derivatives in almost quantitative yields with excellent enantiomeric and diastereomeric purities (up to 99% yield, up to >20:1 d.r., up to 99% *ee*) and significant opportunities for structural diversification.

Results and Discussion

In our initial investigation, several bi- or multifunctional organocatalysts (10 mol%) were screened to evaluate their ability to promote the cascade reaction between methyleneindolinone **1a** and 3-isothiocyanato oxindole **2a** in dichloromethane at room temperature (Table 1, Scheme 2). Gratifyingly and surprisingly, all of the catalysts exhibited high activity and the reaction finished, remarkably, in less than one minute with high yields, high diastereoselectivities, and moderate-to-high enantioselectivities (Table 1, entries 1–5). To our delight, the quinine-derived bifunctional thiourea catalyst **III** gave the desired bispirooxindole, **4a**, with 97% yield, >20:1 d.r., and 89% *ee* (Table 1, entry 3). Trifunctional catalyst **V**, designed by Barbas III and co-workers,[7a] only afforded moderate enantioselectivity (Table 1, entry 5). No significant improvement was achieved by changing solvents or lowering the temperature, although comparable enantioselectivities were obtained with chloroform and DCE

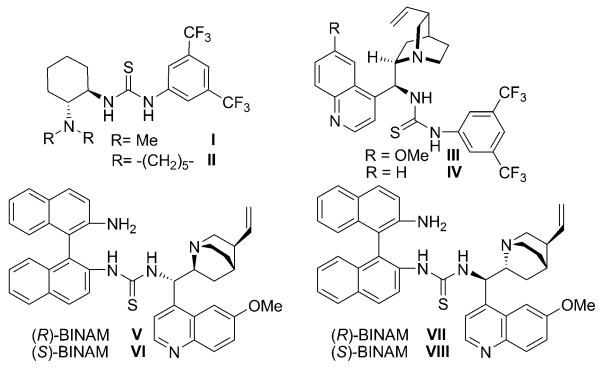
Table 1. Optimization of the organocatalytic cascade Michael–cyclization reactions.[a]



1a: R^1=CO_2Et **1b**: R^1=COPh — **2a** — **4a**: R^1=CO_2Et **3a**: R^1=COPh

Entry	Cat.	1	Solvent	*t* [min]	Yield [%][b]	*ee* [%][c]
1	**I**	**1a**	CH_2Cl_2	<1	93	74[g]
2	**II**	**1a**	CH_2Cl_2	<1	95	86[g]
3	**III**	**1a**	CH_2Cl_2	<1	97	89
4	**IV**	**1a**	CH_2Cl_2	<1	92	85
5	**V**	**1a**	CH_2Cl_2	<1	98	74[g]
6	**III**	**1a**	hexane	<1	89	59
7	**III**	**1a**	diethyl ether	<1	94	53
8	**III**	**1a**	THF	<1	90	67
9	**III**	**1a**	CH_3CN	<1	91	67
10	**III**	**1a**	toluene	<1	96	17
11	**III**	**1a**	$CHCl_3$	<1	97	84
12	**III**	**1a**	DCE	<1	95	89
13[d]	**III**	**1a**	CH_2Cl_2	35	86	90
14[e]	**III**	**1a**	CH_2Cl_2	<1	98	92
15[f]	**III**	**1a**	CH_2Cl_2	<1	97	90
16[e]	**III**	**1b**	CH_2Cl_2	<1	97	78
17[e]	**V**	**1b**	CH_2Cl_2	<1	98	94
18[e]	**VI**	**1b**	CH_2Cl_2	<1	96	18
19[e]	**VII**	**1b**	CH_2Cl_2	<1	95	88[g]
20[e]	**VIII**	**1b**	CH_2Cl_2	<1	95	95[g]

[a] Unless otherwise specified, all of the reactions were carried out by using **1** (0.11 mmol, 1.1 equiv) and **2** (0.1 mmol, 1 equiv) with 10 mol% of the catalyst in CH_2Cl_2 (1.0 mL) at room temperature. All of the diastereomeric ratios were >20:1 d.r. and were determined by ^{1}H NMR spectroscopy of the crude mixture. DCE: 1,2-dichloroethane. [b] Yields of the isolated diastereomeric mixture. [c] Major diastereoisomer determined by HPLC analysis. [d] The reaction was carried out at 0°C. [e] 15 mol% of catalyst was used. [f] 20 mol% of catalyst was used. [g] The opposite configuration of product to that obtained under the optimized reaction conditions.



Scheme 2. Bi- and multifunctional chiral organocatalysts studied.

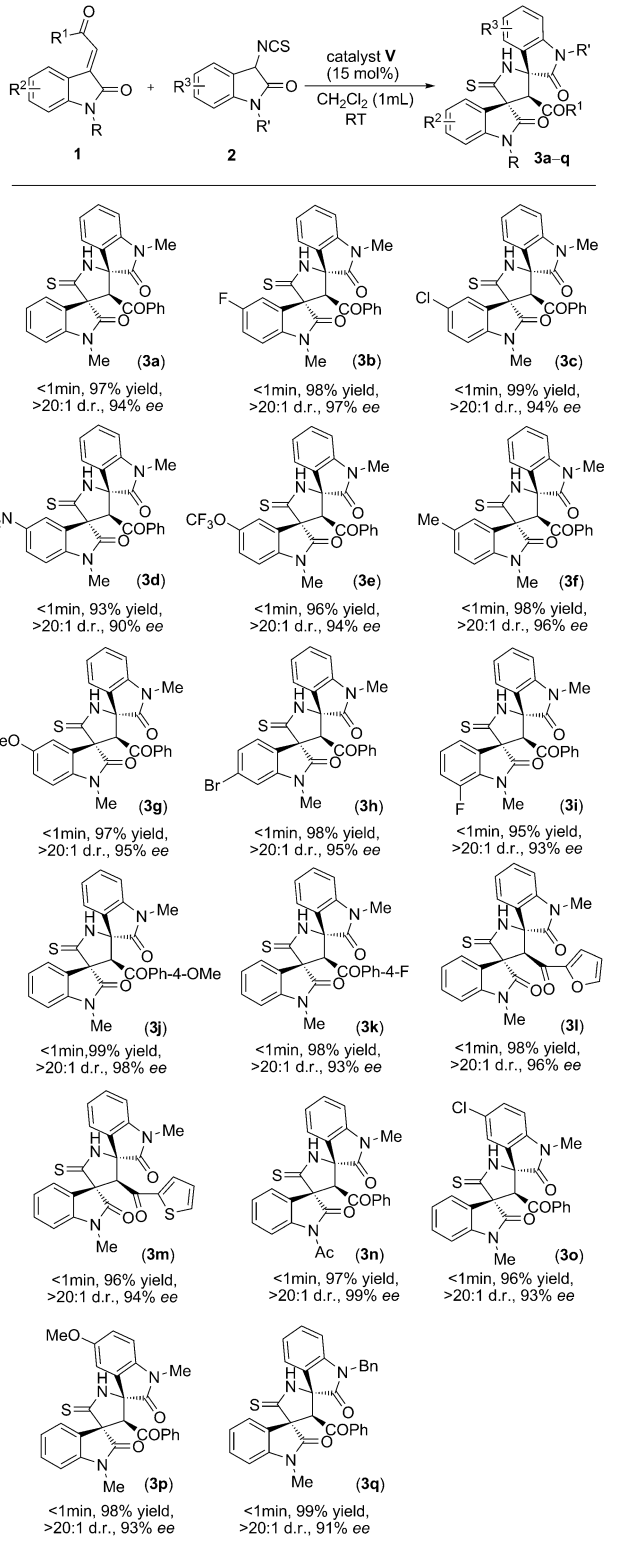
(Table 1, entries 6–13). The best enantioselectivity was obtained for product **4a** if the catalyst loading was increased to 15 mol% (Table 1, entry 14; 92% *ee*). On the basis that the different carbonyl group would have additional interactions with the catalyst, another methyleneindolinone, **1b**,

with a ketone group was employed in further investigations. Gratifyingly, in the presence of catalyst **V**, the reaction was accomplished in less than one minute and gave the desired product, **3a**, in almost quantitative yield with excellent enantioselectivity and diastereoselectivity (Table 1, entry 17; 98% yield, >20:1 d.r., 94% *ee*). Replacement of either the *R*-diamine component of the catalyst with an *S* diamine (catalyst **VI)** or of the quinine component with a quinidine (catalyst **VII**) did not lead to any improvement in enantioselectivity (Table 1, entries 18 and 19). However, replacement of both components, to generate catalyst **VIII**, afforded the opposite enantiomer of the product with excellent stereocontrol, which suggests that both of the two chiral elements of catalyst **V** played key roles in controlling the stereoselectivity (Table 1, entry 20).

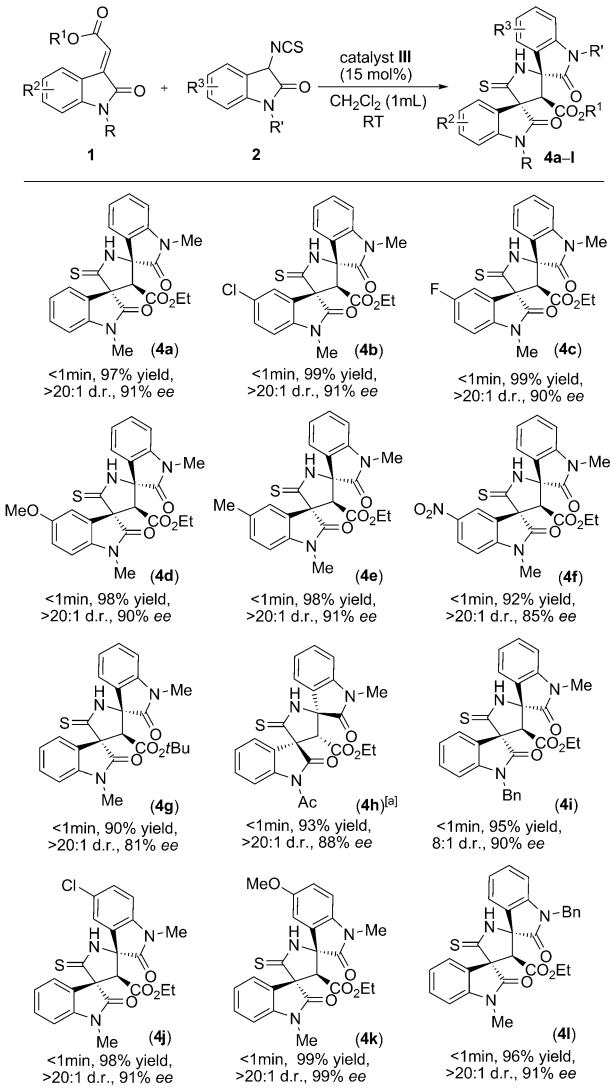
Our subsequent study probed the generality of our strategy in synthesizing substituted bispirooxindoles by focusing upon a variety of methyleneindolinones bearing different ketone substituents, **1**, and 3-isothiocyanato oxindoles, **2** (Scheme 3). All of the reactions catalyzed by catalyst **V** were completed within less than one minute and afforded high yields (93–99% yield), excellent diastereoselectivities (>20:1 d.r.), and excellent enantioselectivities (90–99% *ee*). Notably, minimal impact was observed on the efficiencies, enantioselectivities, and diastereoselectivities, regardless of the electronic nature, bulkiness, or positions of the substituents (Scheme 3, **3a–i**, **3o–p**). In addition to the phenyl group, other aromatic groups with both electron-withdrawing and electron-donating substituents, as well as heterocyclic analogues, were compatible under the optimized reaction conditions and provided excellent stereoselectivities (Scheme 3, **3j–m**). Various N-protecting groups of the two substrates with different electronic and steric parameters were tolerated (Scheme 3, **3n** and **3q**).

Further exploration of the substrate scope was focused upon methyleneindolinones bearing ester moieties, as summarized in Scheme 4. Catalyst **III** promoted the cascade Michael–cyclization sequence in less than one minute, thereby enabling access to a variety of bispirooxindole derivatives with excellent yields, diastereomeric ratios, and optical purities (90–99% yield, > 20:1 d.r., 81–99% *ee*). There appears to be significant tolerance towards electronic variations and positions of the substituents, as well as different N-protecting groups (Scheme 4, **4a–f**, **4h–l**). An increase in steric hindrance, introduced by a bulkier ester group, did not affect the efficiency and diastereoselectivity, but it did decrease the enantioselectivity (Scheme 4, **4g**; 81% *ee*). The absolute configurations of two bispirooxindoles with a ketone moiety (**3l**) and an ester moiety (**4l**), respectively, were unambiguously determined by X-ray crystallography (Figure 2 and 3).

Inspired by our successful work above, the opposite enantiomers of the products were synthesized by employing the catalyst **VIII**. The efficiency and stereocontrol of the reaction were not affected relative to those for the reactions catalyzed by catalyst **V** (Scheme 5). In support of the utility of our strategy, there was no change in reactivity or stereoselectivity if the reaction was carried out on a gram scale



Scheme 3. Synthesis of bispirooxindoles with ketone moieties and three contiguous stereocenters including two spiro quaternary centers. Unless otherwise specified, the reaction was carried out with **1** (0.11 mmol), **2** (0.10 mmol), and catalyst **V** (0.015 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. The reported yields are of the sum of the diastereoisomers. The d.r. values were determined by ^1H NMR spectroscopy of the crude mixture. The *ee* values were determined by chiral HPLC on a Chiralcel column. Bn: benzyl.



Scheme 4. Synthesis of bispirooxindoles with ester moieties and three contiguous stereocenters including two spiro quaternary centers. Unless otherwise specified, the reaction was carried out with **1** (0.11 mmol), **2** (0.10 mmol), and catalyst **III** (0.015 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. The reported yields are of the sum of the diastereoisomers. The d.r. values were determined by ^1H NMR spectroscopy of the crude mixture. The *ee* values were determined by chiral HPLC on a Chiralcel column. [a] Catalyst **V** was used to produce **4h**.

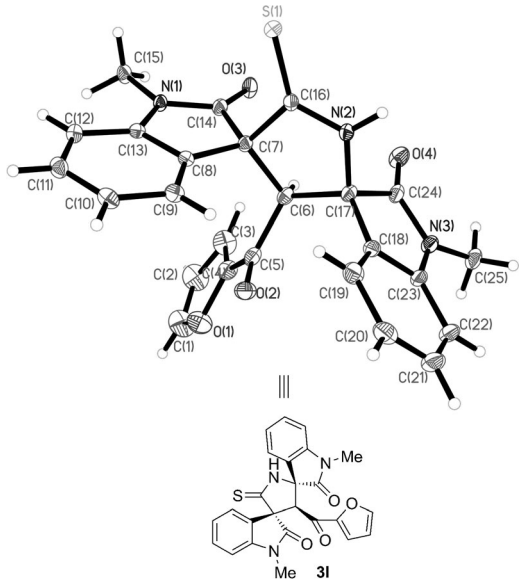


Figure 2. X-ray crystal structure of compound (3*S*,4′*S*,5′*S*)-**3l**.

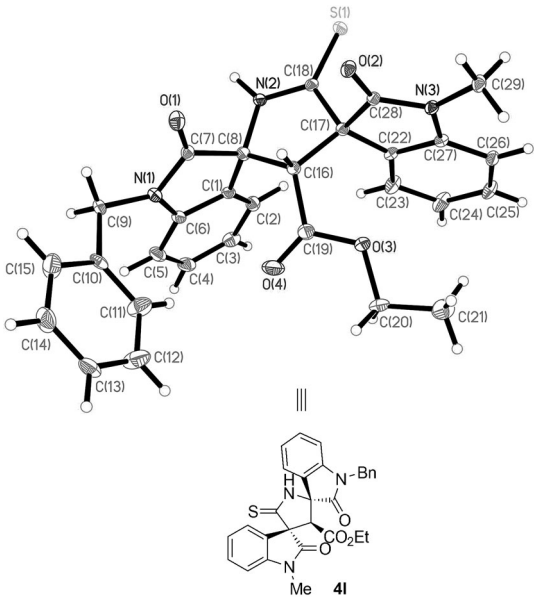
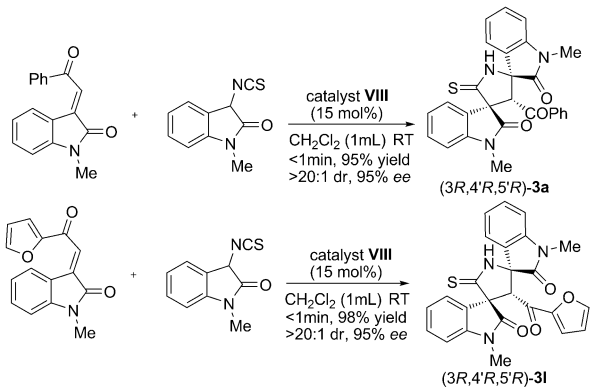


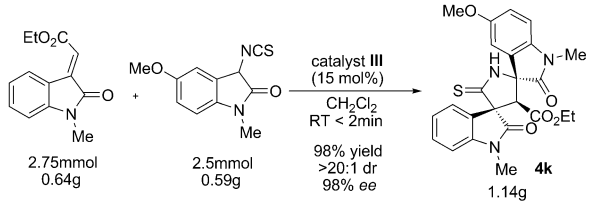
Figure 3. X-ray crystal structure of compound (3*S*,4′*S*,5′*S*)-**4l**.

(Scheme 6). To further expand the potential of this reaction, transformations of the products into other structurally diverse bispirooxindoles were performed. As illustrated in Scheme 7, the γ-thiolactam moiety of bispirooxindole **3b** was smoothly oxidized to form the γ-lactam in 89% yield by simple treatment with 30% aqueous hydrogen peroxide and formic acid in CH_2Cl_2. In addition, the γ-thiolactam moiety of bispirooxindole **4k** could be smoothly converted into a methylated thiolactam (in **6k**) according to the reported procedure.[12] It is worth noting that no great changes took place in the enantioselectivity during the above transformations.

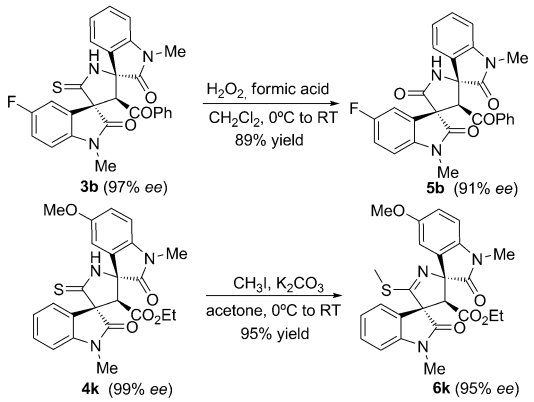
In light of the dual-activation model proposed by Takemoto and co-workers[13] and other recent studies,[4–6] we have proposed two possible models to account for the stereochemistry of the Michael–cyclization reaction (Scheme 8). When catalyst **V** promoted the reaction between methyleneindolinone ketone **1b** and 3-isothiocyanato oxindole **2a**, the two substrates were activated simultaneously by the catalyst **V**, as shown in Scheme 8a. MS experiments[14] by mixing catalyst **V** with **1b** and **2a** individually were investigated in order to support this mechanism. Despite no obvious evidence of interactions between catalyst **V** with **1b**, a new species was detected with the help of ESI-MS methods when



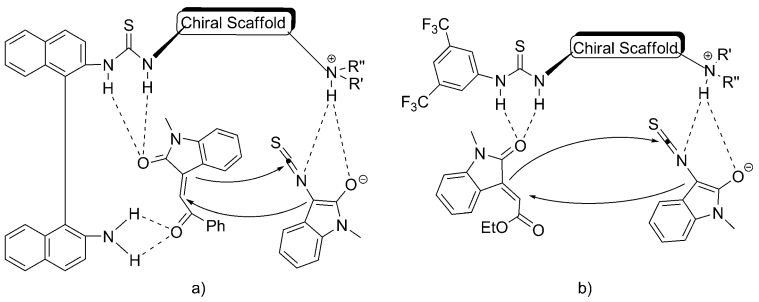
Scheme 5. Synthesis of enantiomers (3*R*,4′*R*,5′*R*)-**3a** and (3*R*,4′*R*,5′*R*)-**3l** by using catalyst **VIII**.



Scheme 6. Preparative-scale experiment.



Scheme 7. Transformation of the products into other bispirooxindoles.



Scheme 8. a) Proposed activation mode of the reaction between a ketone-bearing methyleneindolinone and isothiocyanato oxindole catalyzed by catalyst **V**. b) Proposed activation mode of the reaction between an ester-bearing methyleneindolinone with isothiocyanato oxindole catalyzed by catalyst **III**.

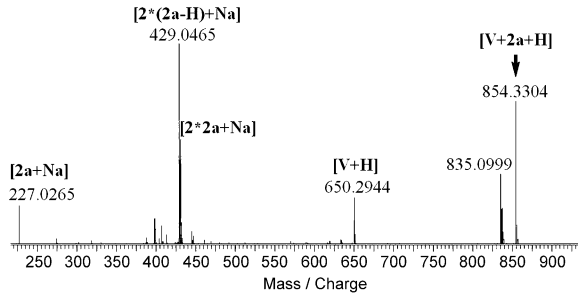
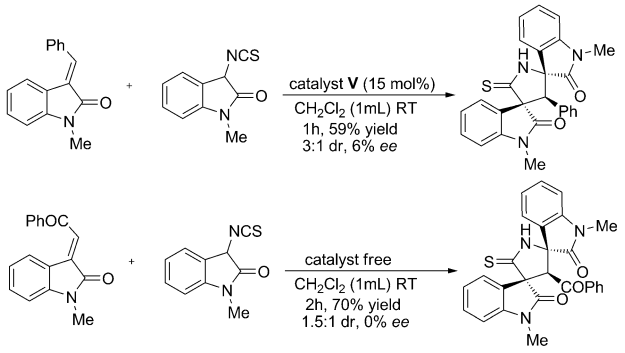


Figure 4. ESI-MS analysis indicating the peak of the new species in the solution of catalyst **V** and substrate **2a**.

catalyst **V** was combined with **2a** (Figure 4). This new species was characterized by a base peak at *m*/*z* 854.3304 and assigned as [**V**+**2a**]. This observation led us to propose a strong interaction between catalyst **V** and **2a**. Two further control experiments were investigated for mechanistic studies. Employment of a methyleneindolinone attached directly to a phenyl group with no ketone or ester moiety led to the desired product in only 59% yield, 3:1 d.r., and 6% *ee* (Scheme 9). In the absence of catalyst, the reaction was significantly slower and required several hours to reach completion (Scheme 9). These poor results supported the importance of the hydrogen-bonding interaction between catalyst **V** and **1b**. The above findings allow us to suggest our dual-activation model: **2a** interacts with the tertiary amine of catalyst **V** through multiple hydrogen bonds, which enhances the electrophilicity of the reacting carbon center. Concurrently, the ketone moiety and the carbonyl group of the indolinone in **1b** coordinate to the primary amine and thiourea moiety through hydrogen-bonding interactions that are crucial for stereocontrol (Scheme 8a).



Scheme 9. Control experiments for mechanism studies.

When catalyst **III** was used for the reaction between methyleneindolinone ester **1a** and isothiocyanato oxindole **2a**, the electron-deficient methyleneindolinone was activated by hydrogen bonds involving the carbonyl group in the indolinone and the thiourea moiety, while **2a** was enolized and activated by the tertiary amine at the same time (Scheme 8b).

Conclusion

We have developed an exceptionally highly efficient strategy for enantioselective construction of bispirocyclic oxindole derivatives through a simple organocatalytic cascade Michael–cyclization reaction. Under mild reaction conditions, all of the reactions catalyzed by bi- or multifunctional cinchona alkaloids finished in less than one minute, to provide bispirooxindoles containing three contiguous chiral centers, including two spiro quaternary stereocenters, in almost quantitative yields and with excellent stereocontrol. Significantly, catalyst reconfiguration offered access to the opposite enantiomer. The power of this straightforward process is highlighted by its extremely high efficiency in synthesizing the bispirooxindole skeletons in such a short time in one single operation, even if the experiment was performed on a gram scale. We believe that these novel compounds based on bispirocyclic oxindole skeletons will provide novel therapeutic agents and useful biological tools. The application of this strategy to synthesize more promising candidates for drug discovery and the biological evaluation of these compounds are currently underway.

Experimental Section

Typical experimental procedure for the catalytic asymmetric synthesis of a bispirooxindole with a ketone moiety (3a): Methyleneindolinone ketone **1b** (0.11 mmol, 1.1 equiv) and 3-isothiocyanato oxindole **2a** (0.10 mmol, 1.0 equiv) were added to a stirred solution of catalyst **V** (15 mol%) in CH_2Cl_2 (1.0 mL) at room temperature. The reaction was monitored by TLC. After complete consumption of 3-isothiocyanato oxindole **2a** (usually less than 1 min; the dark red solution turned light yellow), the crude product was purified by silica-gel chromatography to give the corresponding bispirocyclic oxindole derivative **3a**: $[\alpha]_D^{25} = +274.0$ ($c = 0.2$, CH_2Cl_2); HPLC: Chiralpak AD-H (hexane/*i*PrOH 70/30, flow rate 1 mL min^{-1}, $\lambda = 254$ nm); t_R (major) = 20.915 min, t_R (minor) = 23.269 min; 94% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.42$ (s, 1H), 7.64 (d, $J = 7.1$ Hz, 1H), 7.45 (d, $J = 7.3$ Hz, 1H), 7.39 (m, 1H), 7.30 (m, 1H), 7.23 (m, 2H), 7.11 (m, 5H), 6.79 (d, $J = 7.8$ Hz, 1H), 6.59 (d, $J = 7.7$ Hz, 1H), 5.66 (s, 1H), 3.19 (s, 3H), 3.08 ppm (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 201.36$, 194.15, 174.58, 174.25, 144.22, 143.09, 136.90, 132.73, 130.68, 129.61, 127.99, 127.64, 127.50, 126.40, 125.97, 124.82, 123.32, 123.00, 109.03, 108.56, 71.21, 68.89, 59.44, 27.12, 27.04 ppm; HRMS (ESI): *m/z* calcd for $C_{27}H_{21}N_3O_3S+H$ [*M*+H]: 468.1376; found: 468.1379.

Typical experimental procedure for the catalytic asymmetric synthesis of a bispirooxindole with an ester moiety (4a): Methyleneindolinone ester **1a** (0.11 mmol, 1.1 equiv) and 3-isothiocyanato oxindole **2a** (0.10 mmol, 1.0 equiv) were added to a stirred solution of catalyst **III** (15 mol%) in CH_2Cl_2 (1.0 mL) at room temperature. The reaction was monitored by TLC. After complete consumption of 3-isothiocyanato oxindole **2a** (usually less than 1 min; the dark yellow solution turned light yellow), the crude product was purified by silica-gel chromatography to give the corresponding bispirocyclic oxindole derivative **4a**: $[\alpha]_D^{25} = +125.8$ ($c = 0.6$, CH_2Cl_2); HPLC: Chiralpak AD-H (hexane/*i*PrOH 80/20, flow rate 1 mL min^{-1}, $\lambda = 254$ nm); t_R (minor) = 17.421 min, t_R (major) = 32.139 min; 92% *ee*; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.05$ (s, 1H), 7.62 (d, $J = 7.4$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 2H), 7.39 (t, $J = 7.6$ Hz, 1H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.12 (t, $J = 7.5$ Hz, 1H), 6.94 (d, $J = 7.7$ Hz, 2H), 4.92 (s, 1H), 3.52 (m, 2H), 3.33 (s, 3H), 3.31 (s, 3H), 0.53 ppm (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 201.43$, 174.20, 173.95, 165.59, 144.99, 144.00, 130.99, 129.70, 128.66, 126.12, 125.15, 123.77, 123.25, 122.82, 109.06, 108.80, 70.40, 68.16, 60.79, 56.66, 27.32, 27.24, 13.15 ppm; HRMS (ESI): *m/z* calcd for $C_{23}H_{21}N_3O_4S+H$ [*M*+H]: 463.1326; found: 463.1323.

Acknowledgements

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Asymmetric Synthesis

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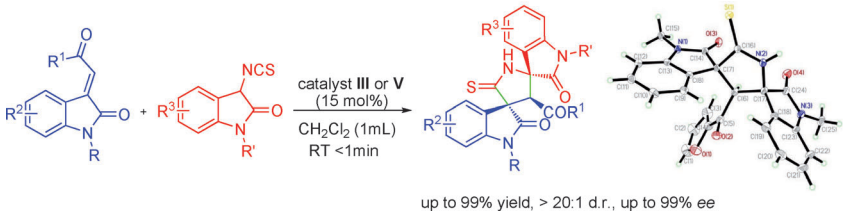
Highly Efficient Enantioselective Construction of Bispirooxindoles Containing Three Stereocenters through an Organocatalytic Cascade Michael–Cyclization Reaction



Cascade to complexity: Bispirooxindole derivatives containing three stereocenters, including two spiro quarternary centers, were synthesized in a high-yielding, atypically rapid, and stereocontrolled cascade Michael–cyclization reaction between methyleneindolinones and isothiocyanato oxindoles catalyzed by a bi- or multifunctional organocatalyst (see scheme).