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Synthesis of enantioenriched spirocyclic oxindoles catalyzed by bifunctional thiourea†

Xue-Wei Qian, [ab] Hong Lin,[c] Tianjiao Hu,[d] Xiaodi Yang *[c] and Xing-Wen Sun *[a]

The spirocyclic oxindole scaffold, prevalent in natural products and bioactive compounds, holds paramount significance in organic chemistry. We report an efficient strategy for the construction of enantioenriched spirocyclic oxindoles bearing four consecutive stereogenic centers *via* a Michael–Mannich cascade reaction catalyzed by a bifunctional thiourea. The desired products were obtained in excellent yields (up to 99%) with high stereoselectivities (up to >20 : 1 d.r., >99% ee). A scaled-up reaction variant proceeded smoothly, highlighting the potential applicability of this method in the synthesis of bioactive compound libraries.

The spirocyclic oxindole architecture has immense importance in modern organic chemistry because of its prevalence in both natural products and bioactive compound.[1] For example, surugatoxin,[2] prosurugatoxin, and neosurugatoxin are a family of spirocyclic oxindole alkaloids that have demonstrated nanomolar activity for neuronal nicotinic acetylcholine receptors (Fig. 1). Enantiopure five-membered spirocyclic oxindoles have garnered significant attention due to their diverse bioactivities and structural complexity. Enantioselective methods for the construction of spirocyclic oxindoles, which constitute the core of numerous potent drugs, remain notably scarce.[3] A major challenge in constructing these architectures lies in the stereoselective formation of multiple stereogenic centers, particularly when two adjacent quaternary centers are involved.[4] The biological activity of drug molecules is often closely linked to their stereochemistry. As the number of chiral centers in a molecule increases, the challenge of synthesizing a single stereoisomer becomes significantly more demanding. Consequently, the development of new strategies enabling the efficient and selective synthesis of such spirocyclic oxindoles from readily available starting materials remains highly sought after.

In recent years, significant strides have been taken in the development of enantioselective techniques for the synthesis of five-membered spirocyclic oxindoles. A pivotal breakthrough occurred in 2007 when Trost and coworkers introduced a palladium-catalyzed [3+2] cycloaddition as a viable strategy for constructing such compounds (Fig. 2a).[5] Concurrently, organocatalytic cascade reactions have emerged as a potent alternative for spirocyclic oxindole synthesis. In line with the contemporary trends of chemical research, the pursuit of innovative annulation methodologies has garnered substantial attention over the past few decades. Significantly, [3+2] annulations have emerged as potent strategies for the construction of multi-functionalized five-membered carbo- and heterocyclic compounds. Among these strategies, tertiary phosphine-catalyzed asymmetric [3+2] cycloaddition reactions involving methyleneindolinones with MBH carbonates or allenoates,[6] along with various organocatalytic tandem reactions such as Michael/Henry,[7] Michael-aldol,[8] Michael-alkylation,[9] and Michael/Michael additions,[10] represent common

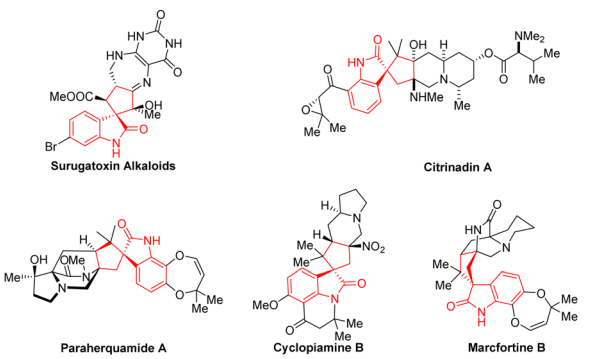

Fig. 1 Bioactive five-membered spirocyclic oxindoles.

[a] *Department of Chemistry, Fudan University, 200433, Shanghai, China. E-mail: sunxingwen@fudan.edu.cn*
[b] *State Key Laboratory of Molecular Engineering of Polymers, Fudan University, 200433, Shanghai, China*
[c] *The Research Center of Chiral Drugs, Innovation Research Institute of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine, 201203, Shanghai, China*
[d] *Department of Chemistry, College of Sciences, Shanghai University, 200444, Shanghai, China*

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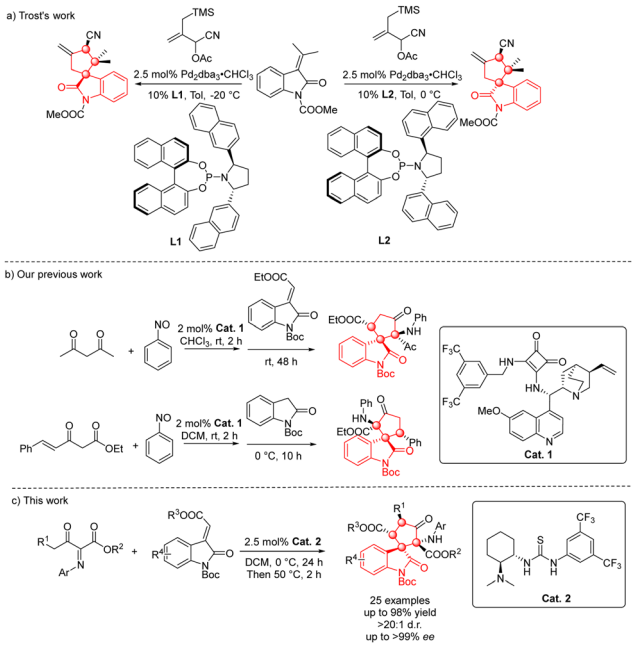


Fig. 2 Synthesis of spirocyclic oxindoles.

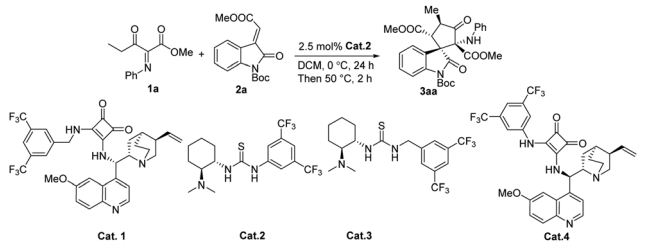
approaches for the synthesis of these alkaloids. In 2015, our group devised an efficient method for crafting chiral spirocyclopentane oxindoles through a tandem Michael/Mannich reaction involving methyleneindolinones and ketimines, achieved *via* a polarity reversal strategy.[11] A novel approach was introduced leading to the formation of spirocyclic oxindoles featuring an α-amino-β-keto ester moiety in 2018 (Fig. 2b).[12]

Spirocyclic oxindoles obtained by the above methods feature three consecutive chiral centers, rendering the synthesis of single configurations highly challenging. Compounds such as surugatoxins, which contain fully substituted five-membered carbon rings with four consecutive chiral centers, further exemplify the synthetic complexity. Notably, the methods to access spirocyclic oxindole scaffolds bearing four consecutive chiral centers are underdeveloped.[13] 1,3-Dicarbonyl ketimines have been demonstrated as versatile imine synthons capable of participating in diverse addition reactions.[14] Building on this foundation, ketimine precursors featuring two nucleophilic sites were efficiently prepared from readily available propionyl acetate derivatives and nitrosobenzene compounds.[15] By extensively optimizing the reaction conditions, we developed an efficient Michael–Mannich sequence to access enantiomerically enriched spiroindoles with fully substituted all-carbon quaternary spiro stereogenic centers on the cyclopentane ring, incorporating four consecutive stereogenic centers (Fig. 2c).

In our previous works, a series of spirocyclohexane oxindoles and spirocyclopentane oxindoles were successfully synthesized with high selectivities through squaramide-catalyzed multicomponent reactions.[16] Highly enantioselective synthesis of 3,3′-spirooxindole γ-lactams with thiourea was also achieved recently.[17] Building on previous work, the synthesis of fully substituted spirocyclic indoles was explored by using squaramide and thiourea catalysts. In initial experiments, the starting material was fully consumed, yielding the major product. However, during separation and purification by column chromatography, the product's configuration underwent transformation. Significant chemical shift changes of the products were observed in the ^{1}H NMR spectrum (for details, see the ESI†). Further investigation indicated that the heat generated during column chromatography facilitated the conversion of the kinetic product to the thermodynamic product. To address this, post-reaction processing was optimized. After the reaction was completed with the kinetic product obtained at low temperature, the reaction was further stirred at elevated temperature to drive the full conversion of the kinetic product to the thermodynamic product. This approach enabled the preparation of a single-configuration product with high selectivity. Ultimately, highly stereoselective formation of a single configuration was achieved under the conditions employing **Cat.2** in nearly quantitative yield in dichloromethane at 0 °C for 24 h followed by 2 h stirring at 50 °C (Table 1, entry 1, 99% yield, >20:1 d.r., >99% ee).

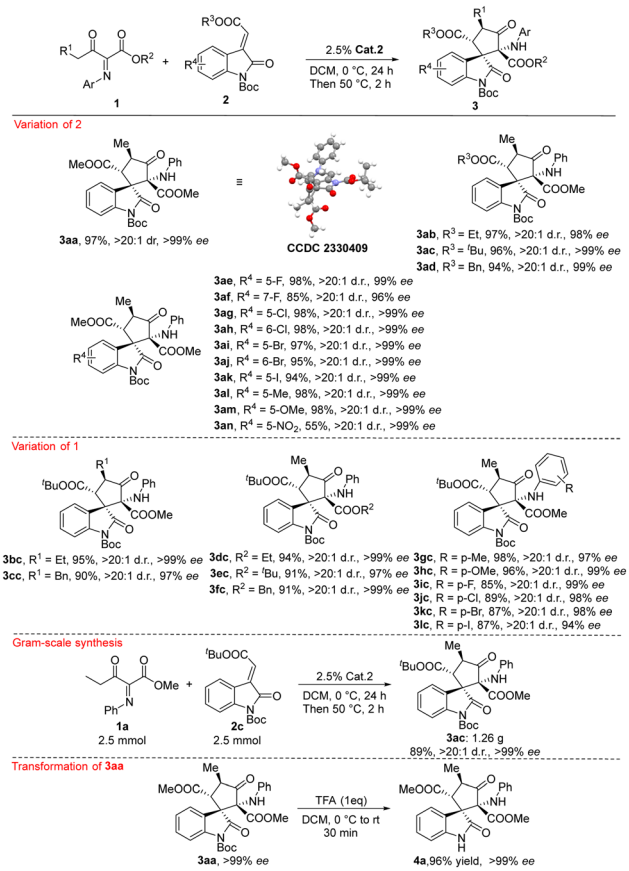
Control experiments revealed that other catalysts also promoted this reaction effectively, and various catalysts enabled complete conversion of the starting materials; however, the stereoselectivity of the reaction decreases to varying extents when alternative catalysts are employed (entries 2–4). Temperature studies showed that lower reaction temperatures decreased the reaction rate, preventing complete conversion of the starting materials within 24 h (entry 5). Increasing the temperature to ambient conditions, however, led to reduced stereoselectivity (entry 6). The investigation of various solvents demonstrated that

Table 1 Optimization of the reaction conditions[a]



Entry	Variation from the "standard conditions"	d.r.[b]	ee[c]/%	Yield[d]/%
1	None	>20:1	>99	99
2	**Cat.1** instead of **Cat.2**	4:1	95	79
3	**Cat.3** instead of **Cat.2**	11:1	>99	86
4	**Cat.4** instead of **Cat.2**	19:1	96	95
5	−20 °C instead of 0 °C	>20:1	>99	77
6	rt instead of 0 °C	19:1	98	95
7	Tol instead of DCM	>20:1	94	99
8	EA instead of DCM	>20:1	95	95
9	Dioxane instead of DCM	>20:1	96	97
10	THF instead of DCM	>20:1	92	42
11	MeCN instead of DCM	>20:1	98	74
12	EtOH instead of DCM	>20:1	97	63

[a] Unless noted otherwise, the reaction was performed with 0.4 mmol of **1a**, 0.4 mmol of **2a** and 2.5% mmol of **Cat.** in 0.5 mL of DCM. [b] The d.r. was determined by ^{1}H NMR spectroscopy of the crude reaction mixtures. [c] The ee was determined by HPLC analysis on a chiral stationary phase. [d] Yield of major diastereoisomer determined by ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.



Scheme 1 Scope of the reaction. Reaction conditions: **1** (0.40 mmol), **2** (1.0 equiv.), and **Cat. 2** (2.5 mol%) in DCM (0.5 mL) at 0 °C for 24 h followed by 50 °C for 2 h. Yield from column isolation.

the catalytic system exhibited notable stereoselectivity across different solvents. Among the solvents tested, dichloromethane proved optimal, affording the highest yield and stereoselectivity. In contrast, alternative solvents led to reductions in both yield and stereoselectivity to varying extents (entries 7–12). Additional screening conditions are provided in the ESI.†

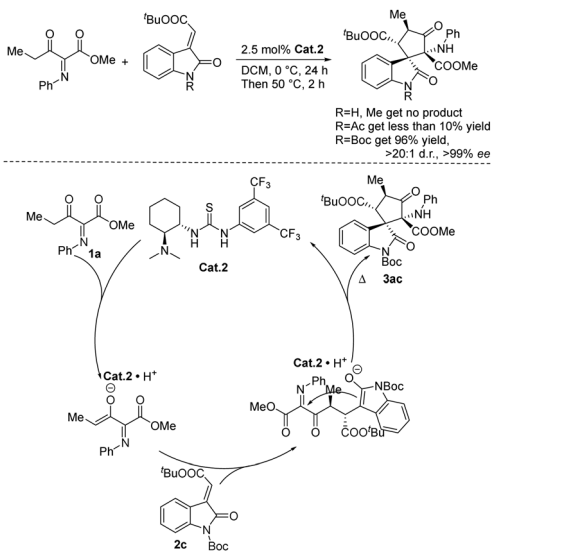
Armed with the optimized conditions, an extensive investigation of the substrate scope was conducted within the framework of the asymmetric [3+2] annulation strategy for the synthesis of spirocyclic oxindoles. Consistently promising results were obtained, with the spirocyclic oxindoles isolated in good to excellent yields (55–98%) and displaying high stereoselectivity (>20 : 1 d.r., 94 to >99% ee) (Scheme 1).

Initial studies focused on methyleneindolinones, which are versatile and highly reactive substrates. Reactions with structurally diverse methyleneindolinones afforded various spirocyclic oxindoles, as shown in Scheme 1. Notably, ester-substituted methyleneindolinones provided the desired products in high yields (**3aa–3ad**). To demonstrate the preparative utility of this asymmetric reaction, gram-scale reactions were conducted under standard conditions, yielding spirocyclic oxindole **3ac** in 89% yield with excellent stereoselectivity (>20 : 1 d.r., >99% ee). Substituents on the phenyl ring were well tolerated, including both electron-withdrawing and electron-donating groups (**3ae–3am**), except for nitro-substituted methyleneindolinones (**3an**, 55% yield).

The ketimine component was also examined, revealing that ketimines with varying carbon chain lengths achieved high yields (**3bc**, 95%; **3cc**, 90%) and excellent stereoselectivity (>20 : 1 d.r., >99% ee and 97% ee) under the optimized conditions. Similarly, the ester functionality in the ketimine yielded products with excellent efficiency and stereoselectivity (**3dc–3fc**). Finally, the electronic effects of *N*-substituted aromatic groups in the ketimines were evaluated. *N*-Aryl ketimines bearing various substituents delivered the desired products in high yields (**3gc–3lc**, 85–98%) while maintaining high stereoselectivity (>20 : 1 d.r., 94–99% ee). The products could easily undergo further transformations. Boc deprotection product **4a** was obtained in 96% yield and >99% ee by trifluoroacetic acid.

To investigate the stereochemical outcome of this reaction, specific control experiments were designed and performed. Unprotected or Me- or Ac-protected methyleneindolinones did not afford the desired products. Boc-protected methyleneindolinone furnished the desired product with excellent yield and enantioselectivity. These results demonstrate that the Boc group, which is a hydrogen bond acceptor and electron-deficient, is essential for activating the methyleneindolinones. Also, the steric hindrance of the Boc moiety is beneficial to the enantioselectivity of the reaction (Scheme 2).

A proposed mechanism is illustrated in Scheme 2. The tertiary amine moiety of the bifunctional thiourea catalyst serves as a base, facilitating the enolization of the ketimine to generate the corresponding enolate. Simultaneously, the methyleneindolinone is activated by hydrogen bonding with the thiourea catalyst.[18] The process proceeds through an intermolecular Michael addition, and this step is the stereoselectivity-determining step from which the first chiral center is generated, followed by an irreversible cyclization step. Upon completion of cyclization,



Scheme 2 Control experiments and proposed mechanism for the reaction.

the kinetic product undergoes thermal isomerization to afford the thermodynamic product.

The structure of **3aa** was established through X-ray crystallography. Unfortunately, the absolute configuration of the compound could not be confidently determined. Therefore, the assignment of the absolute configuration was carried out using the electronic circular dichroism (ECD) method. By comparing the calculated ECD with the experimental data,[19] it was determined that compound **3aa** has the absolute configuration of (1*S*,2*R*,4*R*,5*R*) (for details, see the ESI†).

In summary, an efficient method for the synthesis of spirocyclic oxindoles under mild conditions has been developed. This approach enables the direct and efficient construction of five-membered spirocyclic oxindoles bearing four consecutive chiral centers *via* a Michael–Mannich cascade reaction of ketimines catalyzed by bifunctional thioureas. The method affords excellent yields (up to 98%) and exceptional stereoselectivities (up to >20 : 1 d.r., >99% ee). Furthermore, the reaction is highly scalable, requiring only 2.5 mol% of a simple thiourea catalyst to proceed efficiently. Gram-scale reactions provided excellent results, highlighting the scalability and utility of this strategy for the synthesis of spirocyclic oxindoles with four consecutive chiral centers, including structures relevant to surugatoxin.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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