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Communication

Highly efficient enantioselective synthesis of bispiro[benzofuran-oxindole/benzofuran-chromanone]s through organocatalytic inter-/intramolecular Michael cycloaddition

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ABSTRACT

A quinine-derived thiourea-catalyzed inter-/intramolecular Michael cycloaddition of chromone-oxindole/benzofuranone synthons with 3-substituted methylenebenzofuranones has been established, which constructed enantiomerically pure bispiro[benzofuran-oxindole/benzofuran-chromanone]s bearing five consecutive stereocenters including two spiro quaternary carton centers in good yields (up to 93%) with high diastereoselectivities (up to >20:1 dr) and good enantioselectivities (up to >99% *ee*). Moreover, this is the first example of bifunctional chromone-benzofuranone synthon directed organocatalytic tandem reaction, and also the first example of the bispiro[benzofuran-oxindole] and bispirobenzofuranone, potentially useful in medicinal chemistry.

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The rich structural diversity and complexity of molecules has always captured the attention of chemists to design cost-effective and sustainable synthetic ways [1], especially diversity-oriented synthesis of known natural and synthetic bioactive compounds [2]. In this context, spirocyclic benzofuranones have attracted considerable interest due to their privileged structural motifs found in natural and unnatural compounds with diverse and important biological activities (Fig. 1) [3]. There are some examples, concerning the catalytic asymmetric construction of such typically spirocyclic benzofuranones, have been disclosed [4,5]. In spite of these elegant progresses, catalytic asymmetric methods for catalytic asymmetric assembly of spirocyclohexane-based benzofuranones have been less studied (Scheme 1a).

Spirocyclic oxindoles [6] with carbocyclic six-membered rings are also important substructures that are widely present in numerous bioactive natural products (Fig. 1) [7]. Consequently, considerable effort has been devoted to asymmetric approaches to access enantioenriched spirocyclohexane oxindoles [7,8]. However, highly efficient, diastereoselective, and enantioselective reactions generating complex and structurally diverse chiral spirocyclohexane oxindoles in one step remain a challenging but highly desirable goal in organic synthesis (Scheme 1a).

Chromanones are an important class of heterocycles containing the core structure of dihydrobenzopyranone. Even though there exist many strategies for the asymmetric synthesis of chiral chromanones with only one chiral center [9], attempts toward the direct asymmetric synthesis of enantioenriched fused chromanone systems bearing two consecutive stereocenters are limited [10]. Especially, fused ring chromanone skeletons are also abundant in natural products like cyclopentene, cyclohexanone or cyclohexane fused chromanones (Fig. 1) [11]. The use of readily available chromones as a class of two-carbon building blocks to participate Michael cycloaddition reactions presents a promising one [12]. However the activation of the chemically inert chromones retards the development of this methold. Therefore, the stereoselective construction of fused ring chromanones is also a highly desirable but challenging goal.

Considering the wide occurrence of chromanones, spirocyclohexanebenzofuranones and spirocyclohexaneoxindoles in natural products and drugs, integrating these medicinally relevant motifs to generate unprecedented polycyclic skeletons would be highly desirable [1,2]. The intimating challenge lies in the scarcity of efficient pathways to rapidly install these structural units simultaneously. Herein, we hypothesized that highly functionalized chiral bispiro[benzofuran-oxindole/benzofuran-chromanone]s could be constructed *via* an organocatalytic domino inter-/intramolecular Michael cycloaddition of 3-substituted methylenebenzofuranone and bifunctional chromone-oxindole/benzofuran synthon. To the best of our knowledge, if successful, this is the first example of

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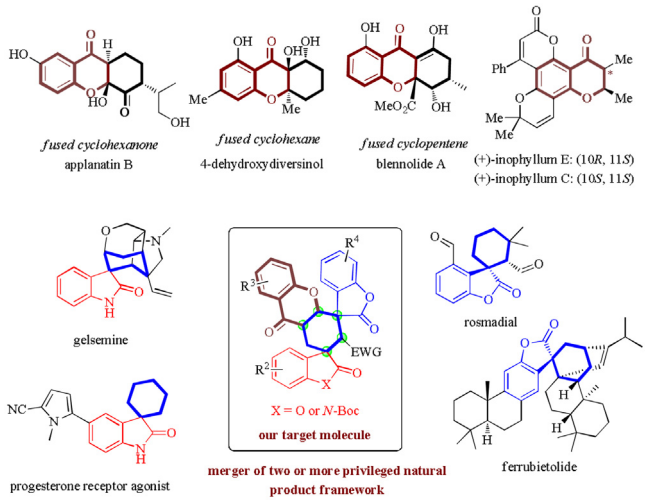


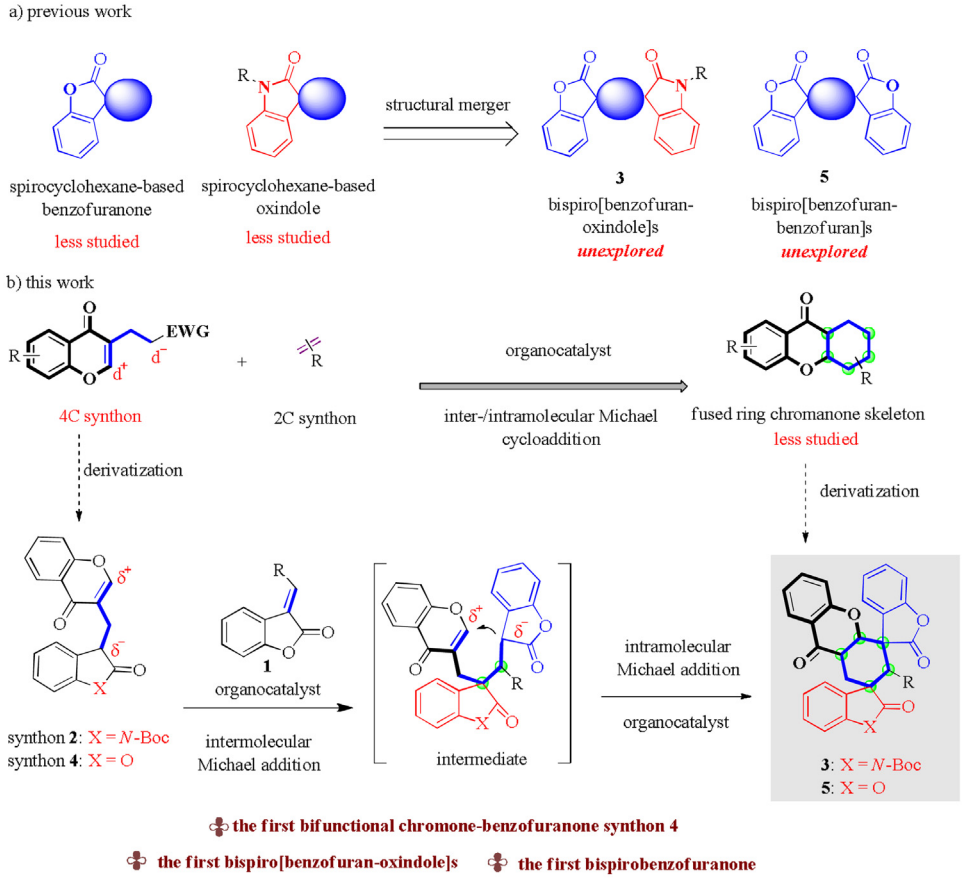
Fig. 1. Representative natural products and our target molecule.

bifunctional chromone-benzofuranone synthon directed organocatalytic tandem reaction, and also the first example of the bispiro[benzofuran-oxindole]s and bispirobenzofuranone (Scheme 1b).

Initially, the reaction of *tert*-butyl ester substituted methylenebenzofuranone **1a** with chromone-oxindole synthon **2a** [13] was investigated under the catalysis of quinine-derived squaramide-tertiary amine **C1** (Fig. 2) (Table 1, entry 1). Gratifyingly, the designed inter-/intramolecular Michael cycloaddition reaction indeed afforded the desired product **3a** in a 78% yield albeit with 99% *ee* and >20:1 dr. This preliminary result demonstrated the feasibility of our design. In order to improve the yield, other chiral bifunctional tertiary amine catalysts **C2**-**C10** (Fig. 2) were utilized as catalysts in the reaction (entries 2–10). It was found that 10 mol% of quinine-derived thiourea-tertiary amine catalyst **C2** fully converted chromone-oxindole synthon **1a** into the desired product **3a** with good control over the stereochemistry (90% yield, 99% *ee*, >20:1 dr) (entry 2). The subsequent evaluation of solvents discovered that Et_2O could deliver the cycloaddition with better enantioselectivity than other solvents (entry 2 *vs.* entries 11–13). Thus, the optimal reaction conditions were chosen as those illustrated in entry 2.

After establishing the optimal reaction conditions, the substrate scope and limitations were explored. Initially, the possibility to employ various 3-substituted methylenebenzofuranones **1** was evaluated using chromone-oxindole synthon **2a** as a model substrate (Scheme 2, products **3a**-**d**). The reaction proved unbiased towards the substituents of substrates **1**. Notably, in all of the cases high yields and high stereoselectivities were observed. Replacement of a *tert*-butyl ester substituent with an ethyl ester group in **2** was also well tolerated, could deliver the desired products **3** with excellent dr and *ee* (products **3b**, **3d**, **3f**, **3h**, **3j**, **3m**, **3o** and **3q**). Moreover, the reaction was shown to work well with benzoyl substituted substrates **1** to give the desired products **3t**-**w** with very good yields (70%–85%), diastereoselectivities (all cases >20:1 dr), and good enantioselectivities (93%–98% *ee*).

Then, various chromone-oxindole synthons **2** were reacted with 3-substituted methylenebenzofuranones **1** (Scheme 2). To our delight, a highly efficient synthesis was observed under the reaction conditions in highly enantioselective fashions (products **3e**-**s** with 96% to >99% *ee*). The reactions were shown to work well with a range of chromone-oxindole synthons **2** bearing either



Scheme 1. Design of chiral bispiro[benzofuran-oxindole/benzofuran-chromanone]s.

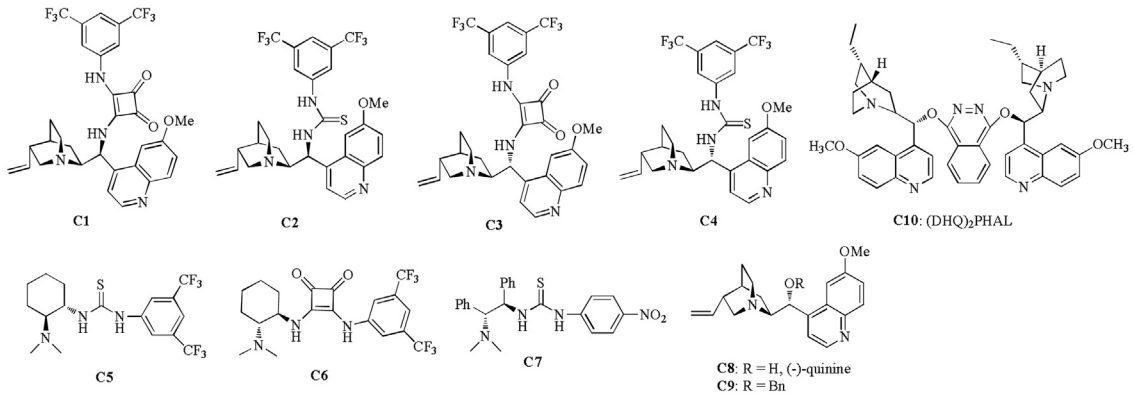
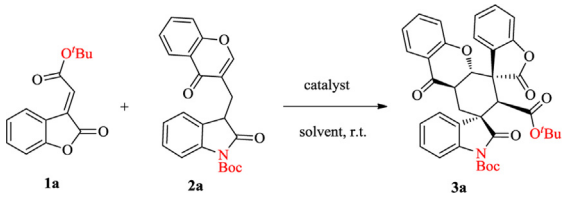


Fig. 2. Structures of organocatalysts screened in this text.

Table 1
Optimization of reaction conditions for synthesis of compound **3a**.[a]



Entry	Catalyst	Solvent	Time (d)	Yield (%)	dr[b]	*ee* (%)[c]
1	**C1**	Et_2O	3	78	>20:1	99 (+)
2	**C2**	Et_2O	3	90	>20:1	99 (+)
3	**C3**	Et_2O	3	30	>20:1	90 (-)
4	**C4**	Et_2O	3	<10	–	–
5	**C5**	Et_2O	3	43	>20:1	58 (+)
6	**C6**	Et_2O	3	50	>20:1	80 (-)
7	**C7**	Et_2O	3	40	>20:1	88 (+)
8	**C8**	Et_2O	3	51	3:1	10 (-)
9	**C9**	Et_2O	3	52	4:1	19 (-)
10	**C10**	Et_2O	3	55	>20:1	80 (-)
11	**C2**	CH_2Cl_2	3	87	>20:1	97 (+)
12	**C2**	$CHCl_3$	3	88	>20:1	95 (+)
13	**C2**	Toluene	3	83	>20:1	92 (+)
14[d]	**C2**	Et_2O	5	89	>20:1	87 (+)

[a] Unless otherwise noted, the reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol), catalyst (10 mol%) in 3.0 mL solvent at r.t. for 3 d.
[b] Determined by ^1H NMR analysis.
[c] Determined by chiral HPLC analysis.
[d] Run with 5 mol% of catalyst **C2** at r.t. for 5 d.

electronwithdrawing or electron-donating groups in the chromone ring to give the desired products **3e**-**k** and **3s** with very good yields (up to 93%), excellent diastereoselectivities (all cases >20:1 dr) and enantioselectivities (96% to >99% *ee*).

Inspired by the success in the chromone-oxindole synthons **2**, and based on diverse structural library design, considering that bispiro[bibenzofuran-chromanone]s **5** would be medicinally important hybrids for the development of new biological molecules, subsequently, we further designed and synthesized a novel bifunctional benzofuran-chromone **4** as a 4C synthon and was then subjected to methylene benzofuranone **1** in 3.0 mL of Et_2O/DCM (1:1, v/v) at room temperature for 3 day. The reaction proceeded smoothly, affording the medicinally important bispiro [benzofuran-benzofuran-chromanone]s **5a** in 68% yield with 98% *ee*, 92:8 dr. The reaction scope generally proved to be broad with respect to a wide variety of electron-rich and -poor reagents **1** and **4** to give diversely substituted bispiro[bibenzofuran-chromanone]s **5a**-**k** in 58%–80% yields with 93% to >99% *ee* and up to >20:1 dr.

The absolute configuration was unambiguously assigned on the basis of the X-ray analysis of the products **3a**, **3c** and **5a** (Fig. 3). The absolute configurations of all remaining products **3** and **5** were given by analogy.

Based on the experimental results, we suggested a possible bifunctional catalytic mode to account for the observed stereoselectivities (Scheme 3), The tertiary amine group of the catalyst **C2** acted as a base to deprotonate the OH group of the enolized substrate **2** or **4**. Meanwhile, the carbonyl group of substrate **1** was activated by catalyst **C2** *via* forming a hydrogen bond. Subsequently, the Re-face of the **1** was preferably attacked by the Si-face of enolated substrate **2** or **4**, delivering the transient Michael adduct intermediate under this dual activating mode of chiral catalyst **C2**. Finally, the α-position of the resulting prochiral nucleophile intermediate initiates an intermolecular annulation process through the attack to the Si-face of the electron-defficient chromone moiety to accomplish the desired (C1'*S*, C2'*R*, C4'*S*, C5'*S*, C6'*S*)-configured **3** or **5**.

Subsequently, we carried out two gram-scale inter-/intramolecular Michael cycloadditions to examine the applicability of the reaction. As shown in Scheme 4, the gram-scale reaction could smoothly take place to give products **3c** and **5a** with excellent enantio- and, diastereoselectivities, which was similar to the results of the small-scale reaction (for details, see the Supporting infomation).

In summary, we have demonstrated that a wide range of complex bispiro[benzofuran-oxindole/benzofuran-chromanone]s **3** and **5** can be efficiently assembled in high stereoselectivity in a single step from bifunctional chromone-oxindole/benzofuran synthons **2** and **4** servring as starting materials. The transformation provides products **3** and **5** comprised of five consecutive stereocenters including two spiro quaternary carton centers, in high yields and stereoselectivities (up to 93% yield, >20:1 dr and >99% *ee*). Moreover, this is the first example of the bifunctional chromone-benzofuranone synthon **4** directed organocatalytic tandem reaction, and also the first example of the bispiro[benzofuran-oxindole] and bispirobenzofuranone, potentially useful in medicinal chemistry. We believe this strategy would broaden the synthetic utility of bifunctional chromone synthon in the assembly of biologically valuable compounds.

Acknowledgments

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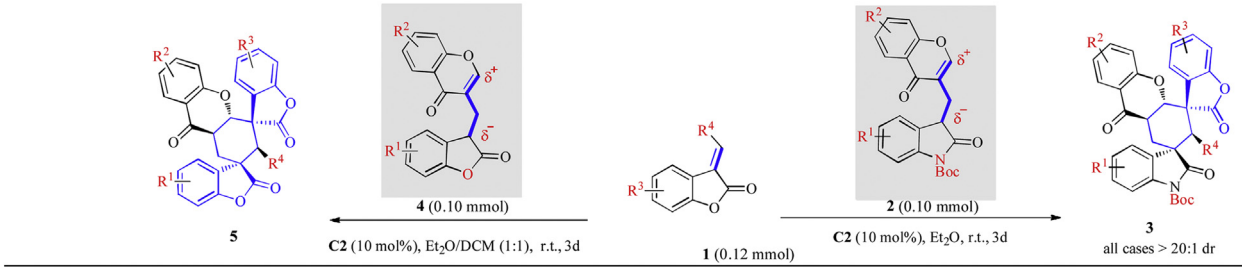
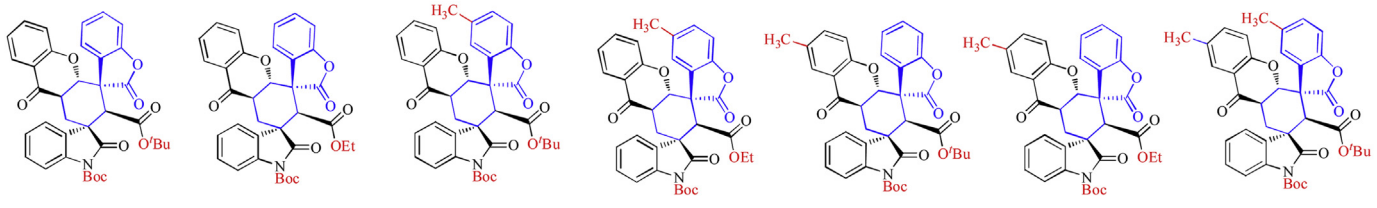
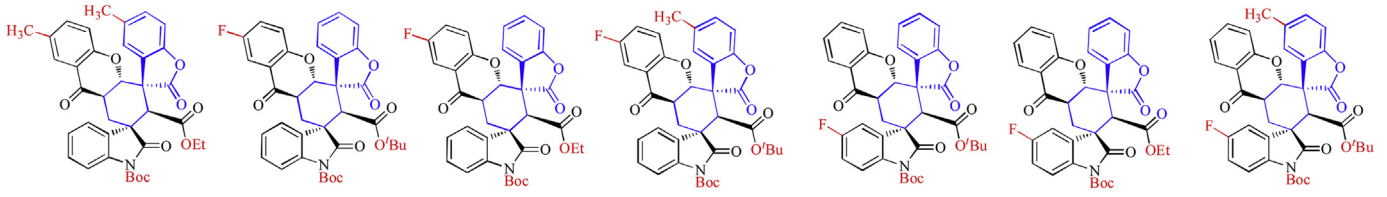
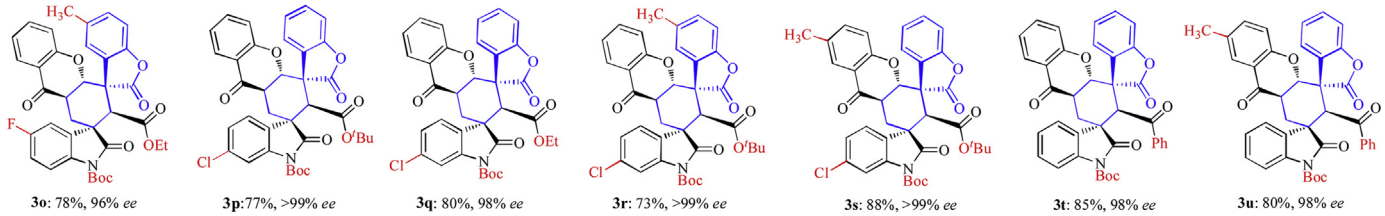




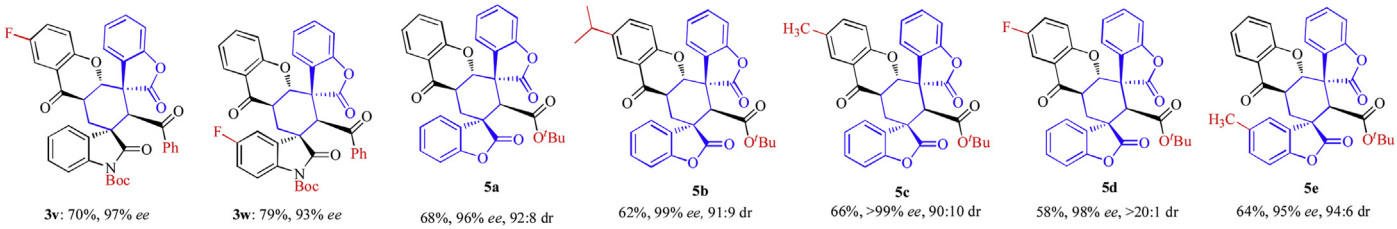
3a: 90%, 99% *ee* **3b**: 90%, 99% *ee* **3c**: 91%, 97% *ee* **3d**: 93%, 97% *ee* **3e**: 89%, >99% *ee* **3f**: 93%, >99% *ee* **3g**: 85%, 99% *ee*



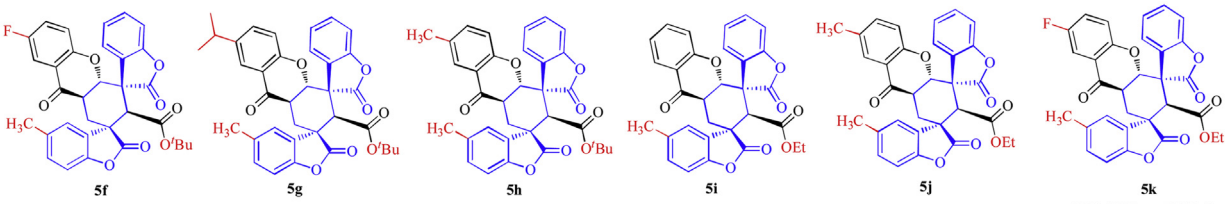
3h: 77%, 98% *ee* **3i**: 91%, 98% *ee* **3j**: 86%, 96% *ee* **3k**: 90%, 99% *ee* **3l**: 84%, 98% *ee* **3m**: 81%, 97% *ee* **3n**: 83%, 97% *ee*



3o: 78%, 96% *ee* **3p**:77%, >99% *ee* **3q**: 80%, 98% *ee* **3r**: 73%, >99% *ee* **3s**: 88%, >99% *ee* **3t**: 85%, 98% *ee* **3u**: 80%, 98% *ee*



3v: 70%, 97% *ee* **3w**: 79%, 93% *ee* **5a** 68%, 96% *ee*, 92:8 dr **5b** 62%, 99% *ee*, 91:9 dr **5c** 66%, >99% *ee*, 90:10 dr **5d** 58%, 98% *ee*, >20:1 dr **5e** 64%, 95% *ee*, 94:6 dr



5f 76%, 96% *ee*, >20:1 dr **5g** 77%, 93% *ee*, 93:7 dr **5h** 80%, 99% *ee*, 94:6 dr **5i** 77%, >99% *ee*, >20:1 dr **5j** 67%, >99% *ee*, >20:1 dr **5k** 76%, 96% *ee*, >20:1 dr

Scheme 2. Substrate scope to compounds **3** and **5**.

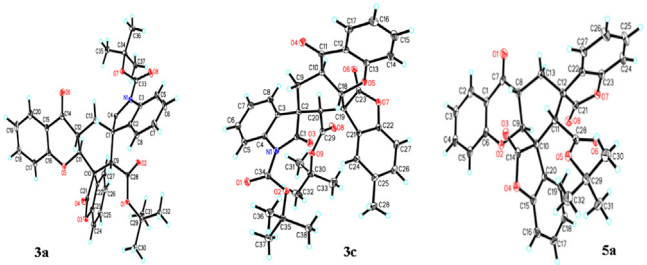
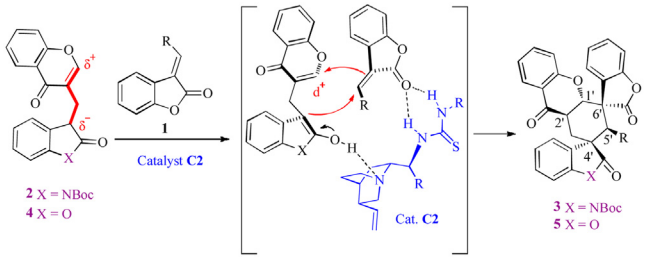
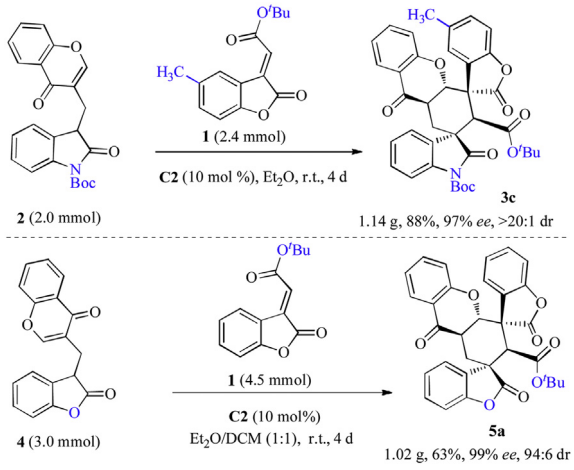


Fig. 3. The X-ray crystal structures of enantiopure **3a**, **3c** and **5a**.



Scheme 3. A plausible reaction mechanism.



Scheme 4. Scale-up reaction.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.06.015.

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