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Organocatalytic oxa/aza-Michael–Michael Cascade Strategy for the Construction of Spiro [Chroman/Tetrahydroquinoline-3,3′-oxindole] Scaffolds

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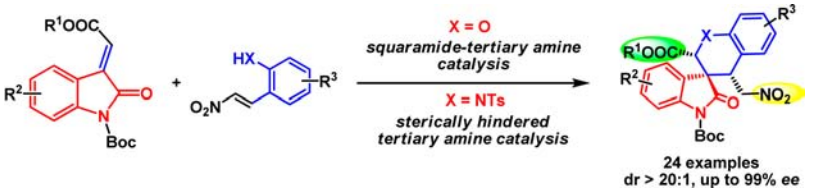
ABSTRACT



A new useful and effective chiral amine-catalyzed oxa- and aza-Michael–Michael cascade methodology for the construction of enantiomerically enriched indolinones spiro-fused with chromans or tetrahydroquinolines is reported. By employing suitable organocatalysts depending on the different Michael donors (Ar-OH/Ar-NHR), the processes offered excellent stereocontrol (dr >20:1, >99% ee) under mild conditions.

Spirooxindole,[1] chroman,[2] and tetrahydroquinoline[3] skeletons containing multiple stereogenic centers are privileged heterocyclic ring systems that are featured in a large number of bioactive alkaloids and medicinally relevant compounds. Furthermore, some sophisticated structures in which the oxindole core is fused with a chroman/tetrahydroquinoline moiety at the C3-position were documented as possessing remarkable biological activities.[4] Because of the significant medicinal value and structural complexities, these intriguing frameworks have emerged as attractive synthetic targets (Scheme 1a).[5] However, the efficient asymmetric synthetic methodology to construct these rigid spiroarchitectures with multistereocenters is deficient. Very recently, Shi and Tu realized the highly stereoselective synthesis of spiro [tetrahydroquinoline-2,3′-oxindole] derivatives through an isatin-involved Povarov reaction (Scheme 1b).[6] Nevertheless, enantiomerically enriched spiro [chroman/tetrahydroquinoline-3,3′-oxindole] scaffolds possessing the potential as an important pharmacophore have not been constructed until now.

Asymmetric organocatalytic domino reactions[7] which proceed consecutively and under the same reaction

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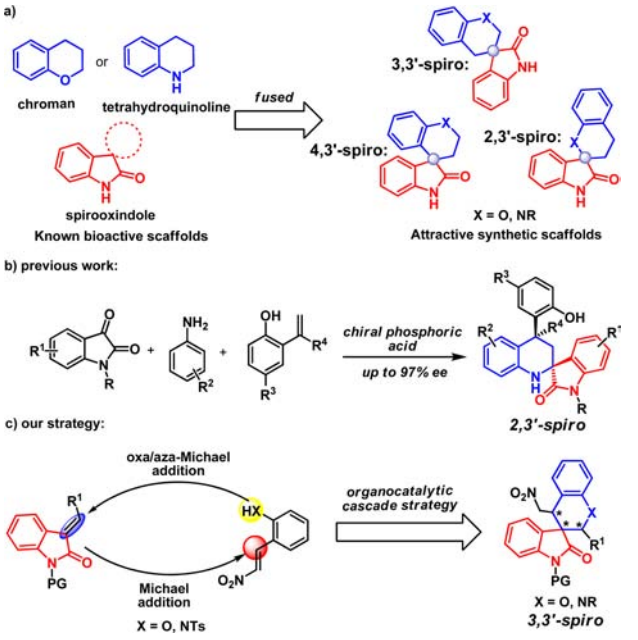
Scheme 1. Spiro [Chroman/Tetrahydroquinoline-3,3′-oxindole] Scaffold Synthesis



conditions to construct complex frameworks from simple precursors are characterized by high efficiencies, excellent stereoselectivities, and environmental friendliness. Therefore, organocatalytic domino reactions are widely regarded as powerful tools in contemporary organic synthesis. Recently, methyleneindolinones were selected to enantioselectively construct spirooxindole scaffolds in organocatalytic domino reactions and cycloadditions.[8] (*E*)-2-(2-Nitrovinyl)phenols bearing both a Michael donor and Michael acceptor were important starting materials for affording chiral chromene or chroman cores, particularly in organocatalytic *Michael*−*hemiacetalization* cascade reactions with carbonyl compounds.[9] However, chiral Lewis base catalyzed *oxa-Michael*−*Michael* cascade reactions of (*E*)-2-(2-nitrovinyl)phenol derivatives with electron-deficient olefins are less developed;[10] the asymmetric reactions involving (*E*)-2-(2-nitrovinyl)aniline derivatives have not even been reported. Inspired by the pioneering work of Wang on the use of bifunctional tertiary amine-hydrogen-bond donor catalysts in asymmetric domino reactions,[11] and also in conjunction with the construction of spiro [chroman/tetrahydro-quinoline-3,3′-oxindole] skeletons, herein, we described our results on chiral Lewis base catalyzed *oxa/aza-Michael*−*Michael* cascade sequences between methyleneindolinones and (*E*)-2-(2-nitrovinyl) phenol/aniline derivatives (Scheme 1c).

Initial examinations were carried out by using variously *N*-protected methyleneindolinones **2** and (*E*)-2-(2-nitrovinyl)-phenol **3a** in the presence of 20 mol % DABCO (Table 1, entries 1−4). The preliminary studies revealed that the reaction efficiency highly depended on the protection form of the nitrogen. The promising racemic product was obtained only when Boc was used (Table 1, entry 4). Inspired by this result, we examined a number of chiral tertiary amines (**1a**−**1d**) and bifunctional tertiary amine-hydrogen-bond donor catalysts (**1e**−**1h**) for the enantioinduction of the reaction using *N*-Boc protected methyleneindolinone **2a** as the Michael acceptor (Table 1, entries 5−12). This led to identification of squaramide-cinchona bifunctional catalyst **1h** as the optimal catalyst, which provided the desired product in 71% yield with 85% ee, 10:1 dr (Table 1, entry 12). To further increase the reaction diastereo- and enantioselectivity, we focused on varying reaction parameters including solvent, temperature, and concentration of the reactants (see Supporting Information (SI), Table S1). After investigating these parameters, the optimized conditions were established to afford spiro [chroman-3,3′-oxindole] **4a** in 72% yield with > 20:1 dr and 92% ee in CH_2Cl_2 (0.05 mol/L) at 0 °C (Table S1, entry 11).

With optimized reaction conditions in hand, we examined an array of *N*-Boc protected methyleneindolinones **2** and 2-(*E*)-(2-nitrovinyl)phenol derivatives **3** to explore the generality of this asymmetric oxa-Michael−Michael cascade reaction. The results are summarized in Scheme 2. The scope of the reaction could be successfully extended to *N*-Boc protected methyleneindolinones with various ester groups, and high stereoselectivities (> 20:1 dr, 92%-98% ee) were generally achieved (Scheme 2, **4a**−**4e**). Further exploration of the substrate scope focused on the 2-(*E*)-(2-nitrovinyl)phenol derivatives **3** (Scheme 2, **4f**−**4l**). These results indicated that enantioselectivities were almost

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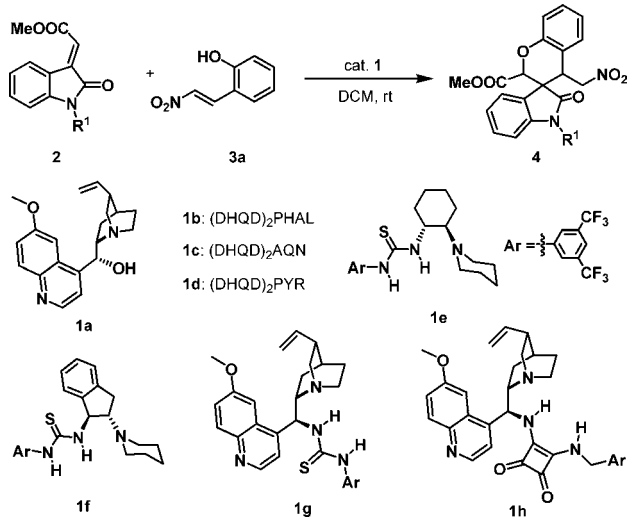
Table 1. Screening for the Optimal Catalyst[a]



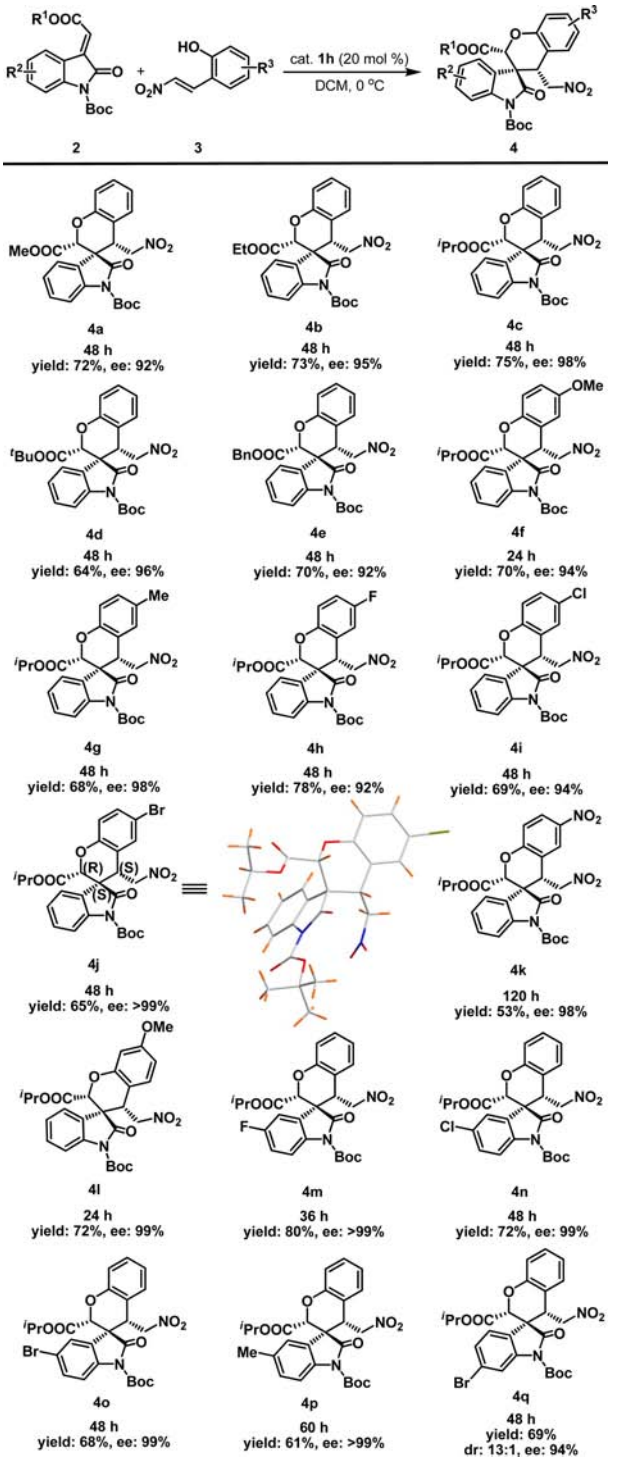
entry	R^1	cat.	t (h)	yield (%)[b]	dr[c]	*ee* (%)[d]
1	H	DABCO	96	0	–	–
2	Ac	DABCO	96	0	–	–
3	Bn	DABCO	96	trace	–	–
4	Boc	DABCO	24	68	–	–
5[e]	Boc	**1a**	24	53	13:1	−10
6	Boc	**1b**	24	82	>20:1	80
7	Boc	**1c**	24	78	>20:1	73
8	Boc	**1d**	24	75	>20:1	63
9	Boc	**1e**	24	68	9:1	28
10	Boc	**1f**	24	64	9:1	36
11	Boc	**1g**	24	67	10:1	56
12	**Boc**	**1h**	**24**	**71**	**10:1**	**85**

[a] Unless otherwise noted, the reaction was carried out with 0.20 mmol of **2**, 0.10 mmol of **3a**, 20 mol % of catalyst **1** (0.02 mmol) in CH_2Cl_2 (1 mL) at rt. [b] Yield of isolated product. [c] Determined by ^1H NMR analysis of the crude products. [d] *ee* values of the major diastereoisomer were determined by chiral HPLC analysis. [e] The opposite configuration.

independent of the nature [halides (**4h**−**4j**), electron-donating (**4f**, **4g**, **4l**), and electron-withdrawing (**4k**) groups] and position (**4f**, **4l**) of the substituent on the aromatic ring of **3**. When a series of methyleneindolinones **2** with various substituents on the aromatic ring were employed as the substrate, the asymmetric transformation could also be completed with excellent stereoselectivities in moderate-to-good yields (Scheme 2, **4m**−**4q**). Functional groups, such as fluoro (**4m**), chloro (**4n**), and bromo (**4o**, **4q**) groups, were well tolerated under the reaction conditions. Moreover, the absolute configurations of the stereogenic centers of product **4j** were confirmed by X-ray crystallographic analysis.[12a]

To demonstrate the practical utility of our domino protocol, we examined the preparation of **4c** on a gram scale (see SI). When the reaction was conducted in 4 mmol amounts, 1.27 g of optically pure **4c** (64% yield, up to 99% ee) could be obtained after recrystallization from CH_2Cl_2/*n*-hexane.

Scheme 2. Synthesis of 4-(Nitromethyl)spiro [Chroman-3,3′-oxindole] Derivatives **4**[a,b]



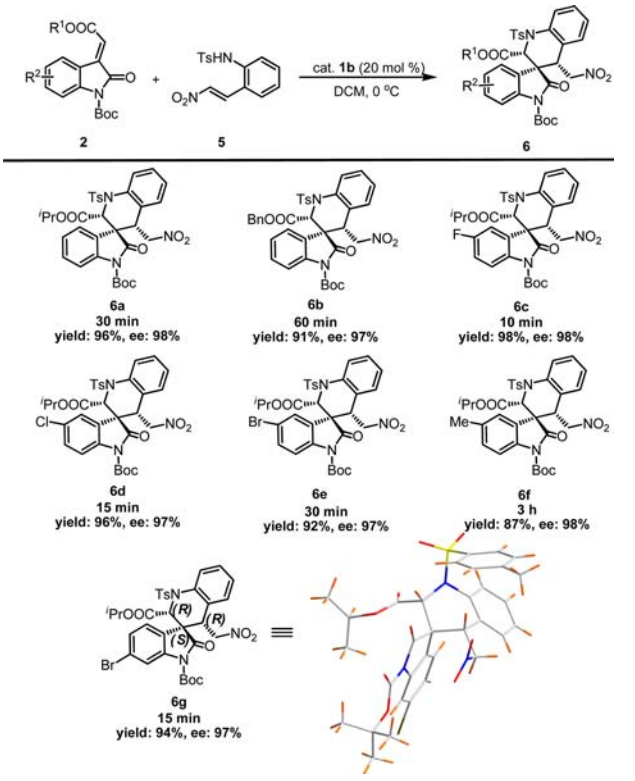
[a] The reaction was carried out with 0.20 mmol of **2**, 0.10 mmol of **3**, and 20 mol % of catalyst for 1 h in CH_2Cl_2 (2.0 mL) at 0 °C. [b] Yield of isolated product; ee values were determined by chiral HPLC analysis; dr was determined by ^1H NMR analysis of the crude products, and unless otherwise noted, dr values of compound **4** were greater than 20:1.

(12) (a) CCDC 913217 contains the supplementary crystallographic data of the product **4j** for this paper. (b) CCDC 933342 contains the supplementary crystallographic data of the product **6g** 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.

Next, we wished to construct another attractive synthetic target: spiro [tetrahydroquinoline-3,3′-oxindole] skeleton **6** through an asymmetric aza-Michael−Michael cascade sequence between methyleneindolinones **2** and *N*-Ts-2-(*E*)-(2-nitrovinyl)aniline **5**. However, to our surprise, the enantioselectivity of the reaction employing **1h** as the catalyst under the above optimized conditions was low (30% ee) though the yield (94%) and diastereoselectivity (> 20:1) remained relatively high. This result spurred us to seek another catalyst for the purpose of obtaining enantiomerically enriched spiro [tetrahydroquinoline-3,3′-oxindole]. After screening the catalyst library of Table 1 again, we excitedly found that excellent stereoselectivity (> 20:1 dr and 98% ee) could be achieved in quantitative yield (96%) when chiral tertiary amine **1b** was used. Inspired by this result, we then evaluated a number of *N*-Boc protected methyleneindolinones **2** to determine the substrate generality of this new catalytic system, and the results are summarized in Scheme 3. Ester groups did not substantially impact the yield or stereoselectivity (Scheme 3, **6a**−**6b**). Moreover, both electron-donating and -withdrawing substituents at different positions on the aromatic ring afforded the products with 97%−98% ee and excellent dr values in good yields (Scheme 3, **6c**−**6g**). In consideration of employing this new catalyst, the absolute configurations of the stereogenic centers of the spiro [tetrahydroquinoline-3,3′-oxindole] skeletons were confirmed once again by X-ray crystallographic analysis (Scheme 3, **6g**).[12b]

In summary, we have developed a convenient and efficient organocatalytic cascade strategy for the asymmetric synthesis of spiro [chroman/tetrahydro-quinoline-3,3′-oxindole] skeletons from readily available and simple starting materials. The oxa-Michael−Michael reaction sequence catalyzed by a squaramide-tertiary amine proceeded well under mild conditions to furnish a series of spiro [chroman-3,3′-oxindole] derivatives containing three contiguous stereocenters, including one spiro quaternary chiral center. This straightforward process offered excellent stereocontrol (> 20:1 dr and > 99% ee) even on a preparative scale. Significantly, when the sterically hindered chiral tertiary amine was used as the organocatalyst, the aza-Michael−Michael reactions of methyleneindolinones **2** with the rational designed *N*-Ts-2-(*E*)-(2-nitrovinyl)aniline **5** provided the densely functionalized spiro [tetrahydroquinoline-3,3′-oxindole] derivatives in almost quantitative yields with excellent stereoselectivities (> 20:1 dr and up to 98% ee). Further studies on the biological activity of this intriguing class of spirocyclic compounds are underway in our laboratory.

Scheme 3. Synthesis of Spiro [Tetrahydroquinoline-3,3′-oxindole] Derivatives **6**[a,b]



[a] The reaction was carried out with 0.20 mmol of **2**, 0.10 mmol of **5**, and 20 mol % of catalyst **1b** in CH_2Cl_2 (2.0 mL) at 0 °C. [b] Yield of isolated product; *ee* values were determined by chiral HPLC analysis; dr was determined by ^1H NMR analysis of the crude products, and dr values of all **6** compounds were greater than 20:1.

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Supporting Information Available. Representative experimental procedures, analytical data for all the compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.