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Assembly of Spirooxindole Derivatives Containing Four Consecutive Stereocenters via Organocatalytic Michael–Henry Cascade Reactions

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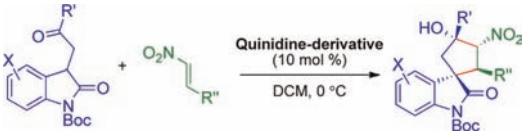
ABSTRACT



A novel organocatalytic strategy for the synthesis of highly substituted spirocyclopentaneoxindoles was developed employing simple nitrostyrenes and 3-substituted oxindoles as starting materials. Michael–Henry cascade reactions, enabled through cinchona alkaloid organocatalysis, provided products in high yield and excellent enantioselectivity in a single step.

A spirocyclic-3,3′-oxindole core is a structural centerpiece found in a number of biologically active synthetic[1] and natural products[2] with activities in a variety of disease areas (Figure 1). A multiply substituted pentane ring fused with an oxindole moiety, together with their medicinal relevance, makes the asymmetric assembly of this family of molecules an attractive but challenging task. Recently, significant attention has been focused on this class of molecules;[3] however, the stereoselective catalytic synthesis of all-carbon pentacyclic-spirooxindole-ring systems are not well-developed.[3t] Processes involving transition metals such cycloadditions[3r] or cyclizations of silyloxy-1,6-enynes[3n] together with organocatalytic asymmetric transformations involving nucleophilic phosphine catalysis,[3t,v] cycloaddition processes,[3n] and cinchona alkaloid catalyzed cascade reactions[3x] have been disclosed.

From their origin in the organocatalytic Robinson annulation reaction,[4a] the power of organocascade reactions to create complex molecular structures has grown tremendously.[4] With respect to our studies here, several laboratories, including our own, have shown that 3-substituted oxindoles are versatile nucleophiles in organocatalytic Michael reactions.[5]

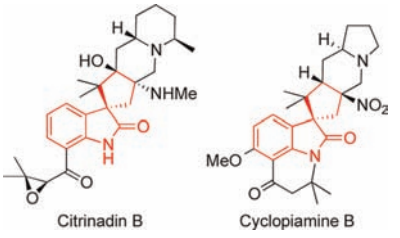


Figure 1. Natural products and bioactive drug candidates containing spirooxindole core structures.

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Encouraged by these results and our own laboratory's recent success in the construction of bispirooxindoles,[3x] we designed a novel Michael–Henry tandem process to construct highly substituted carbocyclic 3,3′-spirooxindole core units from simple 3-substituted oxindoles and nitrostyrenes, catalyzed by cinchona alkaloids (Figure 2).

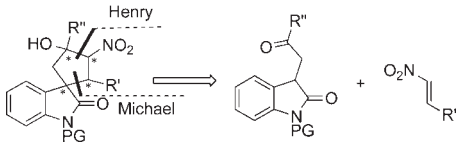

Figure 2. Retrosynthetic analysis for the construction of spirocyclo-3,3-oxindoles via a Michael–Henry cascade reaction.

Successfully executed, this strategy would allow four consecutive stereocenters, including one quaternary spirocarbon center, to be set in a single step. Herein, we report the realization of this goal with the organocatalytic synthesis of a collection of spirocyclic-3,3′-oxindoles in excellent chemical and optical yield.

In an effort to identify a suitable catalyst for our proposed transformation, those shown in Figure 3, including several chiral tertiary amine derivatives (**I**–**VII**) and

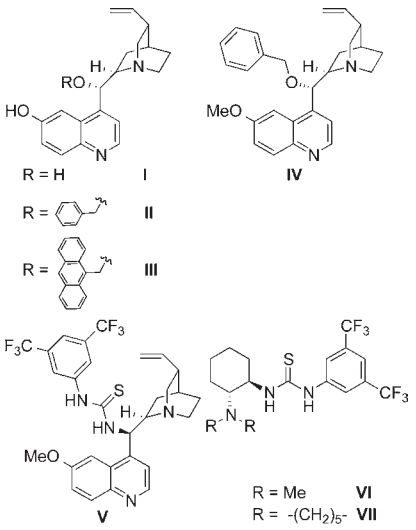

Figure 3. Organocatalysts employed in the asymmetric Michael–Henry cascade reaction.

those with thiourea moieties (**V**–**VII**), were evaluated in a model reaction of oxindole derivatives **1a**–**d** and nitrostyrene **2a**. Benzyl-protected catalyst **II**[6] provided reaction product **3a** with a dr of 1:1:1 and an enantiomeric excess of 66% ee (Table 1, entry 2). The replacement of the benzyl group by the sterically more demanding 9-anthracenylmethyl group (**III**) led to an improvement in selectivity. Only two diastereomers (dr 1:3) with an enantiomeric excess of 78% were obtained (entry 3), whereas use of thiourea-containing catalyst **V**[7] resulted in 1:4 dr and −43% ee (entry 5). A Takemoto-type catalyst **VI**,[8] containing a bismethylated cyclohexylamine functionality, provided product **3a** with a 1:3 diastereoselectivity and an enantiomeric excess of 58% (entry 6). Use of **VII**,[9] in which the amine moiety is incorporated in a cyclic C_5-tether, resulted in a similar dr; however, the ee was increased to 78% (entry 7).

Encouraged by these results, further experiments were undertaken to better understand the catalytic system.

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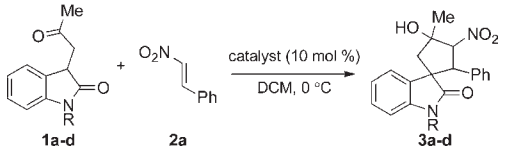
Table 1. Catalyst Screen and Optimization Studies[a]



entry	catalyst	R	time (h)	product	conversion[b] (%)	dr[c] (%)	ee[d] (%)
1	**I**	H	24	**3a**	no reaction	–	–
2	**II**	H	24	**3a**	>99	1:1[i]:1	66
3	**III**	H	24	**3a**	92	1:3	78
4	**IV**	H	24	**3a**	40	1:1[i]	5
5	**V**	H	24	**3a**	>99	1:4	−43
6	**VI**	H	24	**3a**	91	1:3	58
7	**VII**	H	24	**3a**	98	1:3	78
9[e]	**III**	Bn	2	**3b**	70	2:1	n.d.
10[e]	**III**	CBZ	2	**3c**	>99	11:1	80
11[e]	**III**	Boc	2	**3d**	>99	8:1	95
12[e]	**VII**	Boc	2	**3d**	>99	1:10	88
13[f]	**III**	Boc	2	**3d**	>99	11:1	94
14[g,h]	**III**	Boc	2	**3d**	>99	11:1	94

[a] Reaction conditions unless otherwise noted were 3-substituted oxindole (0.052 mmol, 1 equiv); nitrostyrene (0.16 mmol, 3 equiv); catalyst (0.0052 mmol, 0.1 equiv); DCM (0.5 mL, 0.1 M); workup: NH_4Cl. [b] Determined by ^1H NMR of crude product. [c] Determined by ^1H NMR of crude product. [d] Determined by chiral HPLC analysis of major diastereomer. [e] DCM (2 mL, 0.025 M). [f] Workup: ice cold HCl (1 M). [g] Nitrostyrene (0.15 mmol, 1.5 equiv). [h] If 1 equiv of nitrostyrene is used, reaction yield is 80%. [i] Ee determined.

Quinidine derivative **I**[6] containing two unprotected hydroxyl groups was found to be inactive under the selected reaction conditions (Table 1, entry 1). The phenolic hydroxyl group on the quinoline moiety of quinidine-derived catalyst **II** was protected as a methyl ether to provide **IV**.[6] Through this derivatization, the selectivity of the catalyst was compromised (entry 4), demonstrating the importance of a free hydroxyl functionality at this position.

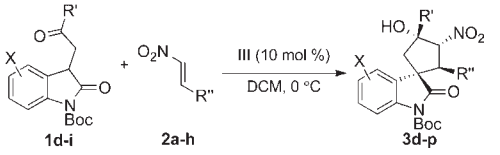
In attempts to further improve the catalytic process, simple protecting group manipulations were carried out. In the presence of catalyst **III**, benzyl-protected oxindole **1b** and nitrostyrene **2a** gave product **3b** in low selectivity after 2 h (entry 9). However, when 3-substituted oxindoles modified with protecting groups such as CBZ or Boc were employed, products with an excellent dr of 11:1 (80% ee) and 8:1 (95% ee), respectively, were obtained in under 2 h (entries 10–11). Catalyst **VII** was less selective than **III** if employed together with Boc-protected starting material **1d** (1:10 dr, 88% ee)(entry 12). Interestingly, Takemoto-type catalyst **VII** provided mainly the minor diastereomer as compared to the diastereomer obtained with cinchona alkaloid derivative **III**. Both CBZ and Boc are attractive protecting groups due to the relative ease with which they may be removed from the reaction product.

Further improvement of the selectivity of the Boc protected substrate was obtained through an alteration of the workup procedure (entry 13). The dr was improved to 11:1 while the ee remained at 94% when 1 M HCl was employed in the extractive workup. Product epimerization caused by incomplete removal of catalyst during NH_4Cl workup is likely avoided under these conditions. Finally reaction economy was improved by reducing the nitrostyrene component to 1.5 equiv without affecting the yield or selectivity (entry 14).

Different solvents were then tested in the presence of catalyst **III** together with Boc-protected oxindole derivative **1d** and nitrostyrene **2a** in order to further improve the selectivity of the reaction.[10] Aprotic solvents such as DCM and chloroform were best suited of those tested. Remarkably, brine also afforded products with good selectivity (6:1 dr and 84% ee) and in 50% yield; solubility limited the progress of this reaction. When DCM and brine were used in combination, the reaction yield was improved to 75%; however, the selectivity dropped slightly.

With optimized reaction conditions in hand, the scope of the methodology was investigated in reactions with various oxindole derivatives (**1e**–**i**) as well as a series of nitrostyrenes (**2a**–**h**) as starting materials in the presence of catalyst **III** in DCM at 0 °C for 2 h (Table 2).

Table 2. Scope of the Reaction[a]



entry	R′	R″	X	product	yield[b] (%)	dr[c] (%)	ee[d] (%)
1	Me	Ph	H	**3d**	93	11:1	94
2	Me	4-Me-Ph	H	**3e**	90	9:1	91
3	Me	4-OMe-Ph	H	**3f**	88	9:1	92
4	Me	4-Br-Ph	H	**3g**	85	8:1	94
5	Me	3,5-Cl-Ph	H	**3h**	95	12:1	95
6	Me	2-NO_2-Ph	H	**3i**	96	10:1	98
7	Me	2-thienyl	H	**3j**	94	6:1	92
8	Me	2-furyl	H	**3k**	95	7:1	97
9	Me	Ph	5-Me	**3l**	95	10:1	91
10	Me	Ph	5-OMe	**3m**	90	7:1	92
11	Me	Ph	6-Cl	**3n**	97	8:1	90
12	Et	Ph	H	**3o**	96	11:1	91
13	Ph	Ph	H	**3p**	89	18:1	93

[a] General reaction conditions: 3-substituted oxindole (0.1 mmol, 1 equiv); nitrostyrene (0.15 mmol, 1 equiv); catalyst (0.01 mmol, 0.1 equiv); DCM 2 mL, (0.025 M); workup: ice cold HCl (1 M). [b] Determined by ^1H NMR of crude product. [c] Determined by ^1H NMR of crude product. [d] Determined by chiral-phase HPLC analysis of major diastereomer.

A range of substituted nitrostyrenes provided reaction products in high chemical and optical yield. Electron-donating

(10) See Supporting Information for data on solvent screen.

substitutions on the aryl ring of the nitrostyrenes were well tolerated; however, diastereomeric ratios of 9:1 and enantiomeric excesses of 91% and 92%, respectively (entries 2−3), were slightly lower than with optimal reactants. Strongly electron-withdrawing substituents, such as nitro, provided product **3i** (entry 6) in excellent selectivity (10:1 dr, 98% ee). Use of reactants with various substitution patterns on the aromatic system provided products **3g**−**h** with excellent diastereomeric ratios between 8:1 and 12:1 and in enantiomeric excesses ranging between 94% and 95% (entries 4−5). It is worth mentioning that 3,5-bischloro substituted nitrostyrenes (entry 5) provided products with higher selectivity than did the unsubstituted phenyl ring in **3d** (entry 1). Various other aromatic systems, including 2-thienyl-1-nitroethene **2g** and 2-furyl-1-nitroethene **2h**, were also acceptable starting materials and provided dr's of 6:1 and 7:1 with ee's of 92% and 97% (entries 7−8).

Various oxindole derivatives were also successfully introduced ranging from unsubstituted (entry 1) to electron-donating 5-methyl (**3l**, entry 9) and 5-methoxy substituents (**3m**, entry 10). Chlorine-substituted oxindole **1g** provided product **3n** in an 8:1 dr and 90% ee (entry 11). In addition to methyl-substituted alkylketone-derived oxindoles, sterically more demanding ethyl-modified substrates were tolerated in this transformation without loss of selectivity (entry 12). Significantly, less reactive arylketone-derived oxindole **1i** underwent the Michael−Henry cascade reaction to afford product **3p** in an excellent dr of 18:1 and ee of 93% (entry 13), although a slightly longer reaction time of 5 h was required to complete the reaction.

The absolute configuration of the products obtained in the Michael−Henry cascade reaction was determined by X-ray crystallography analysis of compound **3d** (see Supporting Information).

In summary, we have developed a highly selective organocatalytic Michael−Henry cascade reaction that provides spirooxindole core structures with four consecutive stereogenic centers, including an all-carbon spiro quaternary center in excellent chemical and optical yield. This simple and effective reaction provides rapid entry to stereochemically complex core structures common to a variety of bioactive molecules and should facilitate future studies and discoveries involving this intriguing class of molecules.

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Supporting Information Available. Experimental procedures and compound characterization (^{1}H NMR, ^{13}C NMR, HPLC) including X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.