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Highly Enantioselective Construction of Spiro[*4H*-pyran-3,3′-oxindoles] Through a Domino Knoevenagel/Michael/Cyclization Sequence Catalyzed by Cupreine

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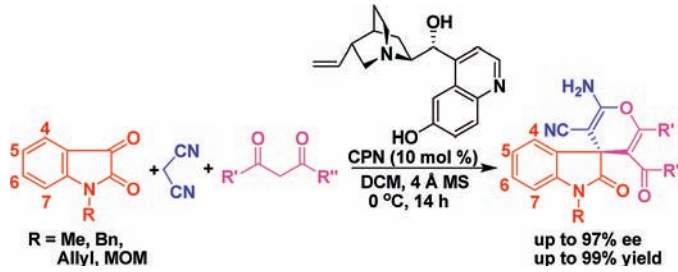
ABSTRACT



The first enantioselective organocatalytic two- and three-component reactions via a domino Knoevenagel/Michael/cyclization sequence with cupreine as catalyst have been developed. A wide range of optically active spiro[*4H*-pyran-3,3′-oxindoles] were obtained in excellent yields (up to 99%) with good to excellent enantioselectivities (up to 97%) from simple and readily available starting materials under mild reaction conditions. These heterocyclic spirooxindoles will provide promising candidates for chemical biology and drug discovery.

The heterocyclic spirooxindoles are attractive targets in organic synthesis because of their highly pronounced biological activities as well as wide-ranging utility as synthetic intermediates for alkaloids, drug candidates, and clinical pharmaceuticals.[1] Therefore, searching for efficient methods for the synthesis of these compounds is interesting in organic synthesis, and numerous impressive successes have been recorded for the synthesis of diversely structured spirocyclic oxindoles over the past years.[2,3] However, the construction of one unique spirocyclic oxindole, incorporating a 2-amino-4*H*-pyran-3-carbonitrile ring at the C3 position of oxindole, is still limited.[4] To the best of our knowledge, no asymmetric protocol to access optically active spiro[4*H*-pyran-3,3′-oxindole] derivatives has yet been reported. In this context, considering the broad biological activities of some spirocyclic oxindoles containing a six-membered spirocyclic moiety at the C3 position,[5] we can envision that an efficient catalytic

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asymmetric tactic to access spiro[4*H*-pyran-3,3′-oxindole] compounds is particularly promising as well as strongly desired.

One of the desirable goals in organic chemistry is the catalytic asymmetric assembly of simple and readily available precursor molecules into stereochemically complex products.[6] In addition, asymmetric organocatalysis has recently emerged as a promising synthetic tool for the organic synthesis.[7] Therefore, as a continuation of our intense research on asymmetric organocatalysis[8a−c] and the preparation of chiral oxindole derivatives,[8d] we have recently become interested in the stereoselective construction of the spiro[4*H*-pyran-3,3′-oxindole] motifs. Herein, we will report the first asymmetric organocatalytic two- and three-component reactions via a domino Knoevenagel/Michael/cyclization sequence that provide a series of spiro[4*H*-pyran-3,3′-oxindoles] in excellent yield (up to 99%) with good to excellent ee values (up to 97% ee) from simple and readily available starting materials.

At the outset of the study, a variety of chiral organocatalysts **cat. 1**−**10** (Figure 1) were tested in the selected reaction of substrates **1c** and **2a** in 1,2-dichloroethane (DCE) at 0 °C, and the results are summarized in Table 1. As shown, cupreine (**CPN**),[9,10] quinine's C6′-OH derivative, gave the best results (92% yield, 85% ee) among these tested organocatalysts (Table 1, entry 8 vs 1−7 and 9−10). Then, with **CPN** as catalyst, the screening of the ratio of substrates **1c** to **2a** revealed that 5.0 equiv of **2a** to **1c** was the optimal ratio (Table 1, entry 11).

Afterward, during the investigation of the protecting groups on the N1 of isatylidene malononitrile derivatives, methoxymethyl (MOM−) was superior to H-, Boc-, and Ac-groups in light of the reactivity and enantioselectivity (Table 2, entries 1−4). Gratifyingly, a subsequent solvent screen resulted in selection of conditions that significantly increased the ee value without diminishing the yield (Table 2, entries 3 and 5−9). Further, adding 4 Å molecular sieves (MS) led to fast reaction (14 h) and a slightly higher ee value of 95% (Table 1, entry 10). Finally, 0 °C was found to be the most suitable reaction temperature (Table 2, entries 10−12). In summary, acetylacetone/isatylidene malononitriles (5/1),

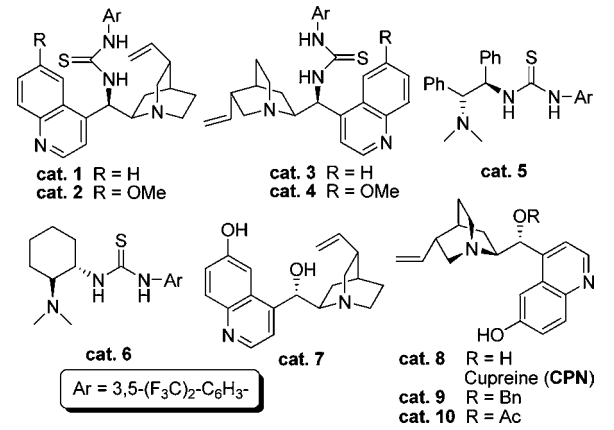
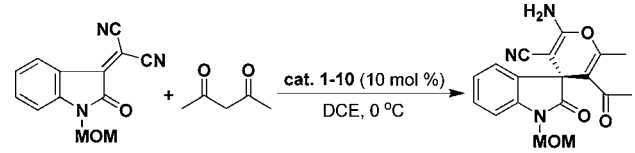


Figure 1. Chiral organocatalysts tested in this study.

Table 1. Screening of Different Chiral Organocatalysts and the Ratio of Substrates **1c** to **2a**[a]



1c **2a** **3c**

entry	cat.	1c:2a	time (h)	yield (%)[b]	ee (%)[c]
1	**cat. 1**	1:10	16	60	−2
2	**cat. 2**	1:10	16	94	0
3	**cat. 3**	1:10	34	58	−36
4	**cat. 4**	1:10	34	75	0
5	**cat. 5**	1:10	34	88	−3
6	**cat. 6**	1:10	36	trace	nd
7	**cat. 7**	1:10	24	trace	nd
8	**cat. 8**	1:10	12	92	85
9	**cat. 9**	1:10	36	82	7
10	**cat. 10**	1:10	36	90	54
11	**cat. 8**	1:5	16	92	86
12	**cat. 8**	1:2	36	90	84

[a] Reactions were performed on a 0.1 mmol scale in 1.0 mL of DCE at 0 °C. [b] Isolated yield. [c] Determined by HPLC.

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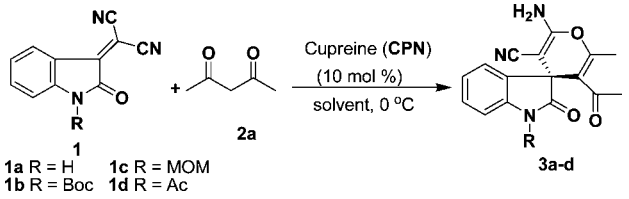
CPN (10 mol %), and 4 Å MS in CH_2Cl_2 (DCM) at 0 °C became our standard reaction conditions for the synthesis of various spiro[4*H*-pyran-3,3′-oxindole] derivatives.

Table 2. Optimization of Reaction Conditions[a]

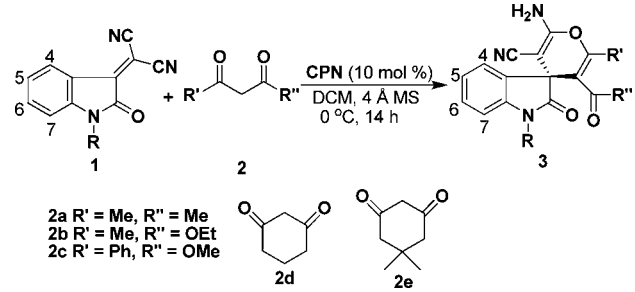


entry	1	solvent	time (h)	3/yield (%)[b]	ee (%)[c]
1	**1a**	DCE	28	**3a**/90	78
2	**1b**	DCE	48	**3b**/trace	nd
3	**1c**	DCE	20	**3c**/92	86
4	**1d**	DCE	60	**3d**/76	55
5	**1c**	THF	36	**3c**/91	6
6	**1c**	DMF	14	**3c**/92	−14
7	**1c**	toluene	13	**3c**/94	70
8	**1c**	CH_2Cl_2	18	**3c**/95	94
9	**1c**	$CHCl_3$	18	**3c**/93	55
10	**1c**	CH_2Cl_2	14	**3c**/95	95[d]
11	**1c**	CH_2Cl_2	24	**3c**/94	95[d,e]
12	**1c**	CH_2Cl_2	14	**3c**/94	92[d,f]

[a] Unless noted, the reactions were carried out with **1** (0.1 mmol), **2a** (0.5 mmol), and **CPN** (0.01 mmol) in 1.0 mL of solvent at 0 °C. [b] Isolated yield. [c] Determined by HPLC. [d] 4 Å MS (30 mg) was used. [e] −20 °C. [f] 25 °C.

The optimized protocol was then expanded to a variety of isatylidene malononitrile derivatives **1** and 1,3-diones (**2a**, **2d**−**e**) or β-oxo esters (**2b**−**c**). As shown in Table 3, variation of the electronic properties of the substituents at either C4 or C5 or C6 of *N*-MOM isatylidene malononitriles was tolerable with excellent yields ranging from 93% to 98% and enantioselectivities ranging from 92% to 97% ee (entries 2−9). It is worth noting that the reaction between **1c** and **2a** proceeded cleanly for only 3 h and afforded the corresponding spirocyclic oxindole product **3e** in 97% yield with 92% ee (entry 2). Electron-donating groups on the N1 of isatylidene malononitrile also proved to be amenable to this procedure with very high yields and ee values (entries 10−12). Additionally, another precursor **2b** also reacted well with different electron-types of *N*-MOM isatylidene malononitriles (entries 13−15) and *N*-Bn isatylidene malononitrile (entry 16). In these cases, the desired spirooxindole products were obtained smoothly in high yields (89−95%) but with good enantioselectivities (72−82% ee), despite using a large amount of solvent (entries 13−16).[11] Moreover, methyl 3-oxo-3-phenylpropanoate (**2c**) also gave the corresponding product in 92% yield with 79% ee for 24 h (entry 17). We also observed that 1,3-cyclohexanediones **2d** and **2e** presented very high reaction activities, completing the reactions in 30 and 15 min, respectively. However, very poor enantioselectivities were obtained for **3u** and **3v** (entries 18 and 19).

Table 3. Asymmetric Synthesis of Spiro[4*H*-pyran-3,3′-oxindoles] with Two-Component Reactions[a]



entry	1	2	3/yield (%)[b]	ee (%)[c]
1	R = MOM	**2a**	**3c**/95	95
2	R = MOM, 4-Cl	**2a**	**3e**/97	92[d,e]
3	R = MOM, 5-F	**2a**	**3f**/93	96[f]
4	R = MOM, 5-Cl	**2a**	**3g**/95	97[f]
5	R = MOM, 6-Cl	**2a**	**3h**/95	94
6	R = MOM, 5-Br	**2a**	**3i**/95	97[e,g]
7	R = MOM, 6-Br	**2a**	**3j**/98	95
8	R = MOM, 5-Me	**2a**	**3k**/96	93
9	R = MOM, 5-OMe	**2a**	**3l**/98	96
10	R = Me	**2a**	**3m**/94	95
11	R = Bn	**2a**	**3n**/95	94
12	R = Allyl	**2a**	**3o**/87	94
13	R = MOM	**2b**	**3p**/89	72[h]
14	R = MOM, 5-Cl	**2b**	**3q**/95	77[h]
15	R = MOM, 5-OMe	**2b**	**3r**/95	82[h]
16	R = Bn	**2b**	**3s**/92	74[i]
17	R = MOM	**2c**	**3t**/92	77[j]
18	R = MOM	**2d**	**3u**/95	0[k]
19	R = MOM	**2e**	**3v**/95	8[l]

[a] For reaction conditions, see Supporting Information. [b] Isolated yield. [c] Determined by HPLC. [d] Run for 3 h. [e] In 6.0 mL of DCE.[11] [f] In 6.0 mL of DCM.[11] [g] The absolute configuration of **3i** was assigned as *R* configuration by X-ray analysis (see Supporting Information), by inference, those of all of the products of this reaction. [h] In 18.0 mL of DCM.[11] [i] In 18.0 mL of DCE.[11] [j] Run for 24 h. [k] Run for 30 min. [l] Run for 15 min in 10 mL of DCM.[11]

More importantly, under our optimal reaction conditions, one-pot, three-component reactions among various isatins **4**, malononitrile (**5**), and **2a**−**c** could proceed smoothly to provide the desired products in excellent yields and good to excellent enantioselectivities (Table 4, entries 1−14). Moreover, there appears to be significant tolerance toward structural and electronic variations of isatins **4**, to enable access to a variety of complex spiro[4*H*-pyran-3,3′-oxindole] derivatives. As to substrates **2d** and **2e**, results very similar to the two-component reaction (Table 3, entries 18 and 19) were obtained (Table 4, entries 15 and 16). All in all,

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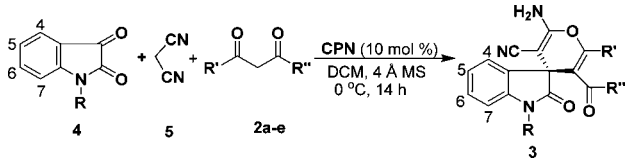
compared with two-component reactions, hardly any deleterious effects on reactivity and enantioselectivity may be observed in the one-pot, three-component reactions (Table 3 vs Table 4).

Table 4. Asymmetric Synthesis of Spiro[4*H*-pyran-3,3′-oxindoles] with One-Pot, Three-Component Reactions[a]



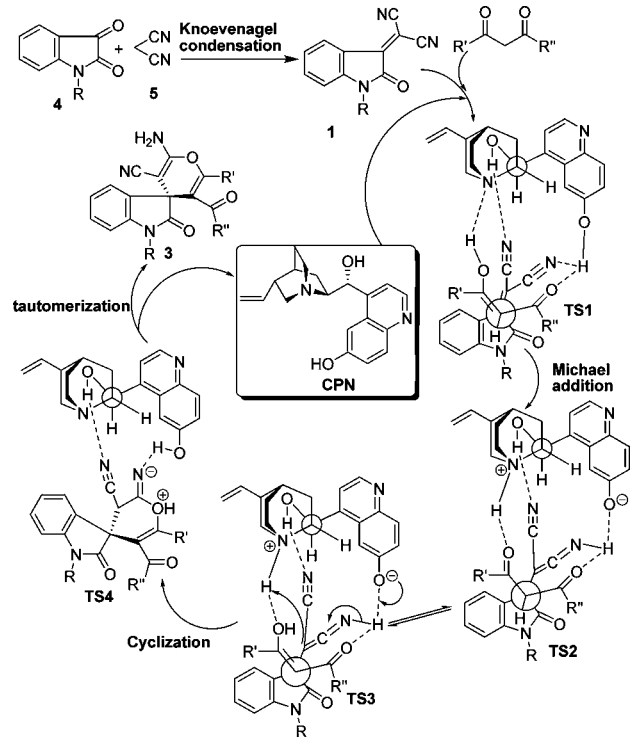
entry	4	2	3/yield (%)[b]	ee (%)[c]
1	R = MOM	**2a**	**3c**/93	95
2	R = MOM, 5-F	**2a**	**3f**/93	95[d]
3	R = MOM, 5-Cl	**2a**	**3g**/95	95[e]
4	R = MOM, 6-Cl	**2a**	**3h**/92	95
5	R = MOM, 6-Br	**2a**	**3j**/95	94
6	R = MOM, 5-Me	**2a**	**3k**/90	92
7	R = MOM, 5-OMe	**2a**	**3l**/99	96
8	R = Me	**2a**	**3m**/94	95
9	R = Bn	**2a**	**3n**/92	95
10	R = Allyl	**2a**	**3o**/85	94
11	R = MOM	**2b**	**3p**/90	72[f]
12	R = MOM, 5-Cl	**2b**	**3q**/95	72[f]
13	R = MOM, 5-OMe	**2b**	**3r**/98	80[f]
14	R = MOM	**2c**	**3t**/90	79[g]
15	R = MOM	**2d**	**3u**/95	5[h]
16	R = MOM	**2e**	**3v**/96	7[h,i]

[a] For reaction conditions, see Supporting Information. [b] Isolated yield. [c] Determined by HPLC. [d] In 6.0 mL of DCM.[11] [e] In 6.0 mL of DCE.[11] [f] In 18.0 mL of DCM.[11] [g] Run for 24 h. [h] Run for 2 h. [i] In 10 mL of DCM.[11]

Although the exact mechanism awaits further study, we suggest Scheme 1 as a working hypothesis. The isatin **4** first condenses with malononitrile (**5**) to afford **1** through fast Knoevenagel condensation. Subsequently, we propose that the Michael addition of **2** to **1** catalyzed by **CPN** proceeds via transition-state **TS1** to generate **TS2**. **TS2** and **TS3** coexist as a keto−enol tautomerism equilibrium in the reaction system. Then, the intramolecular cycloaddition, involving the CN group activated by the phenolic OH as the electrophile, occurs via **TS3** to form **TS4**. Finally, molecular tautomerization leads to the formation of the desired product spiro[4*H*-pyran-3,3′-oxindole] derivatives **3** and concurrently releases catalyst **CPN** back into the catalytic cycle. As shown by transition-state models **TS1**−**4** illustrated in Scheme 1, the stereochemical outcome of this asymmetric cascade reaction catalyzed by **CPN** results from a network of hydrogen-bonding interactions among the sequence Michael addition, keto−enol tautomerization, cyclization, and tautomerization sequence steps.

(11) The reaction was performed under diluted conditions to improve the enantioselectivity.

Scheme 1. Working Hypothesis for the Formation of Product **3**



In summary, we have developed the first enantioselective synthesis of spiro[4*H*-pyran-3,3′-oxindole] derivatives catalyzed by readily available cupreine as the catalyst. This catalytic system can be accommodated in the two-component reaction for the formation of a spectrum of optically active heterocyclic spirooxindoles in very high yields and enantioselectivities. Moreover, the direct organocatalytic asymmetric one-pot, three-component reaction through a domino Knoevenagel/Michael/cyclization sequence for efficient construction of spiro[4*H*-pyran-3,3′-oxindole] compounds has also been successfully explored. These heterocyclic spirooxindole compounds will provide promising candidates for chemical biology and drug discovery. More intense research on the development of catalytic asymmetric approaches applicable to the preparation of structure-diversified spirooxindole derivatives is underway in our laboratory.

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Supporting Information Available: Experimental procedures, spectral data, X-ray crystal structure, and a CIF. This material is available free of charge via the Internet at http://pubs.acs.org.

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