

Chiral Counteranion Synergistic Organocatalysis under High Temperature: Efficient Construction of Optically Pure Spiro[cyclohexanone-oxindole] Backbone

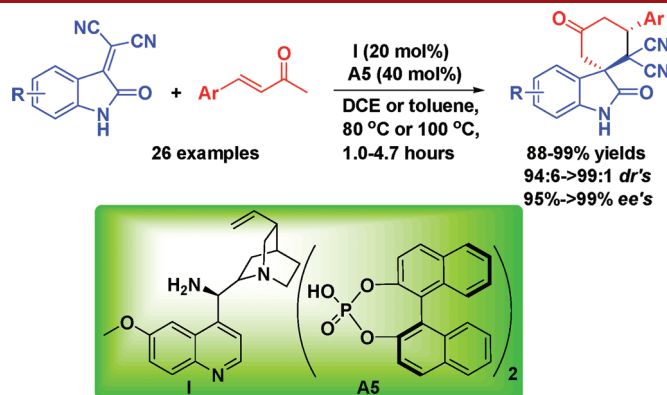
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ABSTRACT



The combination of a cinchona-based chiral primary amine and a BINOL-phosphoric acid has been demonstrated as a powerful and synergistic catalyst system for the double Michael addition of isatylidene malononitriles with α,β -unsaturated ketones, to provide the novel chiral spiro[cyclohexanone-1,3'-indoline]-2',3'-diones in high yields (88–99%) with excellent diastereo- and enantioselectivities (94:6–99:1 dr's, 95–99% ee's).

The spirooxindole alkaloids represent a great family of natural products and pharmaceutically relevant compounds with remarkable structural complexity and interesting biological activities.¹ Consequently, various synthetic protocols have been developed over the past decades for the construction of the multistereogenic spirocyclic oxindoles.² Among these procedures, several types of

organo-catalyzed domino transformations that have emerged very recently in the literature are especially attractive by virtue of features such as highly efficient multistereogenic formation, operational simplicity, and excellent stereoselective control in the synthetic reactions.³ Specifically, the spirocyclic oxindole family with a chiral spiro[cyclohexanone-1,3'-indoline] core, an intriguing combination of multistereogenic cyclohexanone and oxindole motifs, is a promising subset with potential

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bioactivity.⁴ The asymmetric synthesis of this class of compounds involves the stereocontrolled installation of a spiro-quaternary chiral carbon center, which has been a challenging goal for synthetic chemists. In 2009, Melchiorre and co-workers reported the first example of a one-step synthesis of multistereogenic spiro[cyclohexane-1,3'-indoline]-2',4-diones via a tandem iminium and enamine catalytic sequence (Figure 1).⁵ Shortly after, Gong's group disclosed a highly enantioselective synthesis via the reaction between methyleneindolinones and Nazarov reagents catalyzed by Brønsted acid-Lewis base bifunctional organocatalysts.⁶ Very recently, Wang et al. reported a highly enantioselective procedure to the similar types of spirocyclic oxindoles by using a primary amine-catalyzed double Michael reaction of 3-nonsubstituted oxindoles with dienones (Figure 1).⁷ However, to the best of our knowledge, so far no results have been reported in the literature for the enantioselective synthesis of spiro[cyclohexane-1,3'-indoline]-2',3-diones (Figure 1). Herein, we disclosed that optically pure spiro[cyclohexane-1,3'-indoline]-2',3-diones could be efficiently synthesized in high yields with excellent diastereo- and enantioselectivities through the cascade Michael additions of isatylidene malononitriles **1**⁸ with α,β -unsaturated ketones **2** via the catalysis of a cinchona alkaloid-derived primary amine together with an acidic additive.

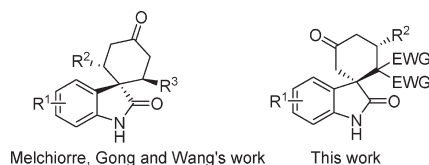


Figure 1. Spiro[cyclohexanone-oxindole] backbones.

Inspired by the established fact that the combination of a cinchona alkaloid-derived primary amine with a chiral or

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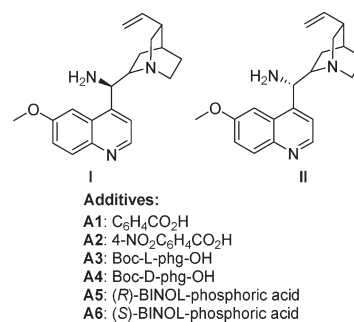


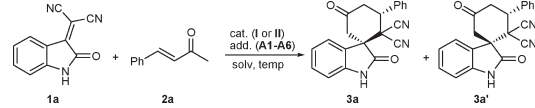
Figure 2. Screened catalysts.

achiral protic acid⁹ can act as powerful catalyst in asymmetric enamine and iminium ion transformation,¹⁰ we began the investigation by testing the model reaction between **1a** and **2a** with 20 mol % quinidine-derived primary amine **I** or its pseudoenantiomer **II** as the catalyst and 40 mol % protic acids **A1–A6** (Figure 2) as the additives. After an initial screening of additives for the reactions performed at room temperature (Table S1, Supporting Information), it was found that the combination of amine catalyst **I** and BINOL-derived chiral phosphoric acid¹¹ **A5** was optimal in terms of both diastereo- and enantioselectivities, affording the corresponding spiro[cyclohexane-1,3'-indoline]-2',3-dione **3a** in 90% yield with excellent optical purity (98:2 dr, 98% ee). However, in this case the reaction was found to be somewhat sluggish, which took several days to completion. Therefore, the reaction conditions were further optimized by examination of the effects of temperature and solvent, as well as the potential matched/mismatched combinations¹⁰ of catalysts **I** or **II** with chiral **A1–A6**, and the results were shown in Table 1. Gratifyingly, the **I/A5** catalyzed reaction in 1,2-dichloroethane (DCE) proceeded much faster with the elevation of temperature from rt to 80 °C, to furnish the product **3a** in nearly quantitative yields without sacrificing of either diastereoselectivities or enantioselectivities (entries 1–8). Further screening of the other catalyst/additive pairs reveals that **I/A5** was the matched combination, affording the product in

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Table 1. Evaluation of Catalyst/Additive Combination and Optimization of Reaction Conditions^a



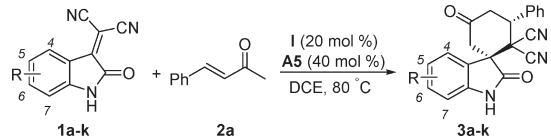
entry	cat./add. (mol %)	solv	temp (°C)	time (h)	yield (%) ^b	dr (%) ^c	ee (%) ^c
1	I (20)/ A1 (40)	DCE	rt	42	85	16:84	99
2	I (20)/ A5 (40)	DCE	rt	84	90	98:2	98
3	I (20)/ A5 (40)	DCE	40	14	92	98:2	98
4	I (20)/ A5 (40)	DCE	60	2.5	95	98:2	98
5	I (20)/ A5 (40)	DCE	80	1.5	99	>99:1	98
6	I (20)/ A6 (40)	DCE	80	2.0	99	>99:1	97
7	II (20)/ A5 (40)	DCE	80	1.0	99	93:7	–86
8	II (20)/ A6 (40)	DCE	80	30	99	85:15	–90
9	I (20)/ A2 (40)	DCE	80	7.0	92	17:83	90
10	I (20)/ A3 (40)	DCE	80	7.0	80	34:66	91
11	I (20)/ A4 (40)	DCE	80	6.0	97	41:59	94
12	I (20)/ A5 (40)	DCM	40	48	99	>99:1	98
13	I (20)/ A5 (40)	THF	65	6.0	99	>99:1	98
14	I (20)/ A5 (40)	CHCl ₃	60	6.5	99	>99:1	98
15	I (20)/ A5 (40)	CH ₃ CN	80	2.0	95	83:17	95
16	I (20)/ A5 (40)	Toluene	80	1.5	94	>99:1	97
17	I (20)/ A5 (40)	Toluene	100	1.0	99	>99:1	95
18	I (15)/ A5 (30)	DCE	80	6.5	92	>99:1	94
19	I (10)/ A5 (20)	DCE	80	10	94	>99:1	98
20	I (5)/ A5 (10)	DCE	80	26	90	>99:1	98

^a Reactions were performed with **1a** (0.1 mmol), **2a** (0.2 mmol) and primary amine catalyst loading **I** and **II** (5–20 mol %) and the additives **A1**–**A6** (10–40 mol %) in solvent (1.0 mL) under the reaction temperature of rt–100 °C. ^b Isolated yields. ^c Determined by chiral HPLC.

optimal diastereo- and enantioselectivities (entry 5 vs entries 9–11). Whereafter, several common solvents were examined for this transformation in the presence of catalyst **I/A5**, from which 1,2-dichloroethane and toluene turned out to be the best choice in terms of both the reactivity and selectivities (entries 12–17). Finally, a screening of catalyst loading in the range of 5–20 mol % indicates that the diastereo- and enantioselectivities were almost retained, albeit the reactivity dropped considerably with the decreased catalyst loadings (entries 18–20 vs entry 5).

Encouraged by these promising results, we further examined the scope of the **I/A5**-catalyzed double Michael addition between substituted isatylidene malononitriles **1a–k** and benzylideneacetone **2a**. The reactions were performed in DCE under the above optimized reaction conditions, and the results were shown in Table 2. Excellent diastereo- and enantioselectivities were obtained by using this catalytic system, irrespective of the variations in electronic and steric properties of the substituents attached to the phenyl rings of the oxindole backbones. Thus, reactions of various 2-(2-oxoindolin-3-ylidene) malononitriles **1a–k** and benzylideneacetone **2a** proceeded smoothly to afford the spiro[cyclohexane-1,3'-indoline]-2',3-diones **3a–k** in 88–99% yields with 96:4–99:1 dr's and 97–99% ee's (entries 1–11). For the reactions involving substrates **1b** or

Table 2. Substrate Scope of **I/A5**-Catalyzed Double Michael Addition of Isatylidene Malononitriles **1a–k** with Benzylideneacetone **2a**^a



entry	R	time (h)	yield (%) ^b	dr (%) ^c	ee (%) ^c
1	H (1a)	1.5	3a /99	>99:1	98
2 ^d	4-Cl (1b)	36	3b /90	99:1	98
3 ^d	4-Br (1c)	36	3c /88	>99:1	98
4	5-CH ₃ O (1d)	2.0	3d /99	>99:1	98
5	5-CH ₃ (1e)	4.7	3e /92	98:2	97
6	5-F (1f)	2.5	3f /99	>99:1	98
7	5-Cl (1g)	5.0	3g /92	>99:1	97
8	5-Br (1h)	3.5	3h /95	99:1	97
9	6-Br (1i)	3.0	3i /99	99:1	>99
10	5,6-F ₂ (1j)	4.0	3j /96	>99:1	98
11	7-FCF ₃ (1k)	1.5	3k /99	96:4	97

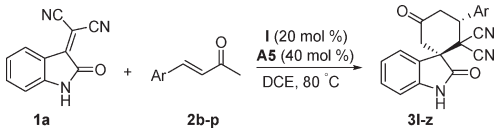
^a Reactions were performed with **1a–k** (0.1 mmol), **2a** (0.2 mmol) and catalyst loading **I** (20 mol %)/**A5** (40 mol %), in DCE (1.0 mL). ^b Isolated yields. ^c Determined by chiral HPLC. ^d Reactions were performed at 40 °C.

1c, the -Cl or -F substituent at the 4-position of the oxindole backbones seems to have a detrimental effect on both the diastereo- and enantioselectivities at the relatively higher reaction temperature of 80 °C. Nevertheless, the corresponding products **3b** and **3c** could still be obtained in high yields and excellent diastereo- and enantioselectivities when the reactions were carried out at 40 °C, albeit at the cost of some losses in reactivity in these cases (entries 2 and 3).

We found that the combination **I/A5** is also an excellent catalytic system with respect to the double Michael addition of **1a** with various α,β -unsaturated ketones **2b–p**. The reactions were carried out in DCE in the presence of 20 mol % catalyst **I** at 80 °C, and the results are shown in Table 3. For the enone substrates **2b–m** bearing either electron-donating or electron-withdrawing substituents on the β -phenyl group, the adducts **3l–w** were obtained in 90–99% yields with 94:6–99:1 dr's and 97–99% ee's (entries 1–12). Moreover, the α,β -unsaturated ketones **2n–p** containing heteroaromatic or fused aromatic rings were also suitable substrates for this reaction, affording the corresponding products **3x–z** in 92–98% yields with 97:3–99:1 dr's and 97–99% ee's (entries 13–15).

Intriguingly, we have also found that this double Michael addition may proceed smoothly under relatively high temperature (100 °C) without significant loss of stereoselectivities, thus providing an effective way to improve the efficiency of the catalysis. Several reactions of isatylidene malononitriles and α,β -unsaturated ketones **2** were reinvestigated in the presence of 20 mol % of catalyst **I/A5** (1/2 molar ratio) in toluene at 100 °C, and the results are summarized in Table 4. The desired products **3a**, **3d**, **3i**, **3k**, **3n**,

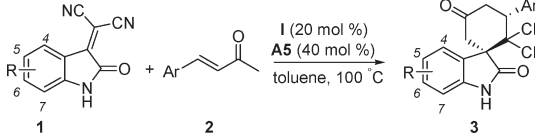
Table 3. Substrate Scope of **I/A5**-Catalyzed Double Michael Addition of Isatylidene Malononitrile **1a** with α,β -Unsaturated Ketones **2b–p**^a



entry	Ar	time (h)	yield (%) ^b	dr (%) ^c	ee (%) ^c
1	<i>o</i> -MeOC ₆ H ₄ (2b)	1.5	3l /91	94:6	>99
2	<i>o</i> -FC ₆ H ₄ (2c)	3.0	3m /99	>99:1	97
3	<i>o</i> -ClC ₆ H ₄ (2d)	2.0	3n /90	>99:1	99
4	<i>m</i> -ClC ₆ H ₄ (2e)	3.0	3o /93	98:2	99
5	<i>p</i> -MeOC ₆ H ₄ (2f)	2.0	3p /99	99:1	>99
6	<i>p</i> -MeC ₆ H ₄ (2g)	1.5	3q /99	>99:1	98
7	<i>p</i> - ⁱ PrC ₆ H ₄ (2h)	2.0	3r /99	>99:1	99
8	<i>p</i> -FC ₆ H ₄ (2i)	3.5	3s /95	97:3	98
9	<i>p</i> -ClC ₆ H ₄ (2j)	2.5	3t /92	>99:1	>99
10	<i>p</i> -BrC ₆ H ₄ (2k)	2.5	3u /99	>99:1	97
11	<i>p</i> -CF ₃ C ₆ H ₄ (2l)	3.0	3v /95	>99:1	99
12	<i>o,p</i> -(MeO) ₂ C ₆ H ₃ (2m)	2.0	3w /96	96:4	98
13	2-thienyl (2n)	2.5	3x /93	>99:1	>99
14	2-furyl (2o)	3.0	3y /98	97:3	>99
15	1-naphthyl (2p)	2.0	3z /92	>99:1	97

^aReactions were performed with **1a** (0.1 mmol), **2b–p** (0.2 mmol) and catalyst loading **I** (20 mol %)/**A5** (40 mol %), in DCE (1.0 mL).
^bIsolated yields. ^cDetermined by chiral HPLC.

Table 4. **I/A5**-Catalyzed Double Michael Addition of Isatylidene Malononitriles **1** with α,β -Unsaturated Ketones **2** in Toluene at 100 °C^a



entry	R	Ar	time (h)	yield (%) ^b	dr (%) ^c	ee (%) ^c
1	H (1a)	C ₆ H ₅ (2a)	1.0	3a /99	>99:1	95
2	5-CH ₃ O (1d)	C ₆ H ₅ (2a)	1.5	3d /99	99:1	95
3	6-Br (1i)	C ₆ H ₅ (2a)	2.0	3i /98	99:1	>99
4	7-CF ₃ (1k)	C ₆ H ₅ (2a)	1.5	3k /96	95:5	97
5	H (1a)	<i>o</i> -ClC ₆ H ₄ (2d)	2.5	3n /97	97:3	>99
6	H (1a)	<i>p</i> -CF ₃ C ₆ H ₄ (2l)	2.5	3v /95	97:3	97
7	H (1a)	<i>p</i> -MeOC ₆ H ₄ (2f)	1.4	3p /99	>99:1	98

^aReactions were performed with **1** (0.1 mmol), **2** (0.2 mmol) and catalyst loading **I** (20 mol %)/**A5** (40 mol %), in toluene (1.0 mL).
^bIsolated yields. ^cDetermined by chiral HPLC.

3v, and **3p** were obtained in 95–99% yields within 1.0–2.5 h, with 95:5–99:1 dr's and 95–99% ee's (entries 1–7). Finally, we were fortunate to obtain single crystals of compound **3i**, for which the absolute configuration was unambiguously established on the basis of the X-ray crystallographic analysis (see Supporting Information).

Mechanistically, we envisioned that the construction of a spiro[cyclohexane-1,3'-indoline]-2',3-dione core might be accomplished with isatylidene malononitriles acting both as an acceptor and a latent donor in a double Michael addition sequence. The α,β -unsaturated ketones can be activated by condensation with the chiral primary amine catalyst with the assistance of a protic acid (HX), leading to the formation of a chiral nucleophilic dienamine intermediate, that will stereoselectively attack the 3-C of the isatylidene moiety. Herein the regioselectivity would be determined by the dicyano groups, which are more electron-withdrawing than the carbonyl group in the isatin moiety. The resulting Michael adduct would further undergo an iminium catalyzed intramolecular conjugate addition, thus affording the desired product in a one-pot fashion. In addition, excellent diastereo- and enantioselectivities of the present catalytic system indicate that the chiral counteranion provides additional stereo-discrimination in the transition state (Figure 3).

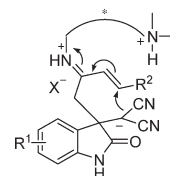


Figure 3. Proposed transition state.

In summary, the combination of a cinchona-based chiral primary amine and a BINOL-phosphoric acid has been demonstrated as a powerful and synergistic catalyst system for the double Michael addition of isatylidene malononitriles with α,β -unsaturated ketones, to provide the novel chiral spiro [cyclohexane-1,3'-indoline]-2',3-diones in high yields (88–99%) with excellent diastereo- and enantioselectivities (94:6–99:1 dr's, 95–99% ee's). Salient features of the present protocol include excellent stereoselective control in the multi-stereogenic formation, operational simplicity, and highly efficient one-pot synthesis of the sophisticated spiro oxindole structures. The dicyano groups in the products provide a convenient handle for synthetic manipulations; further work along this line is undergoing in this laboratory.

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Supporting Information Available. Experimental procedures and characterization data, HPLC data and X-ray data for **3i** (CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.