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Catalytic Enantioselective Henry Reactions of Isatins: Application in the Concise Synthesis of (*S*)-(−)-Spirobrassinin

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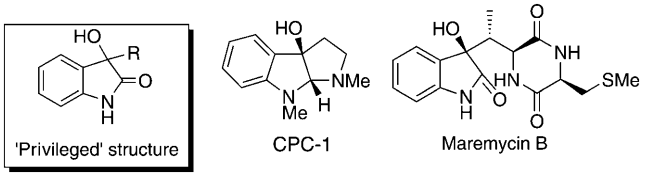
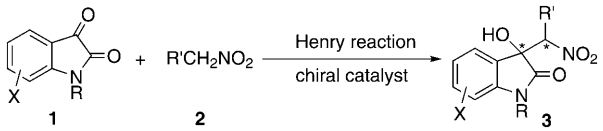
3-Substituted 3-hydroxyoxindoles are the core structural unit in a large array of fascinating natural products with a broad spectrum of intriguing biological activities .[1] CPC-



1,[2a] convolutamydines,[2b] maremycins,[2c] diazonamide A,[2d] leptosin D,[2e] *o*-hydroxyglucoisatisin,[2f] witindolinone C,[2g] TMC-95A-D,[2h] celogentin K,[2i] arundaphine,[2j] paratunamides A–D,[2k] and neuroprotectins A and B[2l] are representative examples. Notably, the scaffold has emerged as a "privileged" structure in drug discovery.[2a] Accordingly, the development of efficient methods for the construction of functionalized frameworks with this structure is of considerable synthetic and biological importance.

Herein, we wish to disclose a simple, cupreine-catalyzed, enantioselective Henry reaction of readily accessible nitroalkanes with isatins under mild reaction conditions to make the valuable chiral 3-substituted 3-hydroxyoxindoles. Good to high enantioselectivities and high yields have been obtained. Furthermore, the enantioselectivities can be readily improved to excellent levels (94–99%) by simple treatment of the solid products. These features render this synthetic tool particularly attractive for practical application in drug discovery, development, and production. Moreover, the synthetic value has been demonstrated in the efficient synthesis of natural product (*S*)-(−)-spirobrassinin in four steps for the first time without requiring protecting groups.

Asymmetric aldol reactions with isatins[3] give direct entry to the chiral 3-substituted 3-hydroxyoxindole framework (Scheme 1). Significant effort has been focused on the catalytic enantioselective aldol reactions of aldehydes and ketones.[4] Nevertheless, the asymmetric Henry (nitroaldol) reaction of isatins with readily available nitroalkanes remains elusive.[5] These aldol adducts are highly valuable building blocks for the total synthesis of 3-substituted 3-hydroxyoxindole-derived natural products and their analogues because the versatile nitro functionality can easily be transformed into a variety of functional groups, such as amine, nitrile oxide, ketone, carboxylic acid, hydrogen, and so forth.[6] Despite this, to the best of our knowledge, no such process has been reported so far.



Scheme 1. The catalytic asymmetric Henry reaction of isatins with nitroalkanes.

The creation of a chiral quaternary center is a challenging subject in asymmetric synthesis.[7] To date, the development of enantioselective nitroaldol reactions with ketones has met with limited success. In reported studies, acyclic α-keto esters and very active trifluoromethyl ketones are exclusively employed.[8] However, the use of useful cyclic ketones, such as isatins, has not been disclosed. Due to the sensitive nature of substrate structures, the enantioselectivity and reaction yield of each aldol reaction varies significantly.

In noncovalent bifunctional Brønsted acid–base mediated asymmetric catalysis, the conventional wisdom is that nonpolar aprotic solvents are preferred since they can minimize the interruption of interactions between the substrates and the catalyst.[9] However, in our initial investigation of the catalytic asymmetric Henry reaction of isatin (**1a**) with ni-

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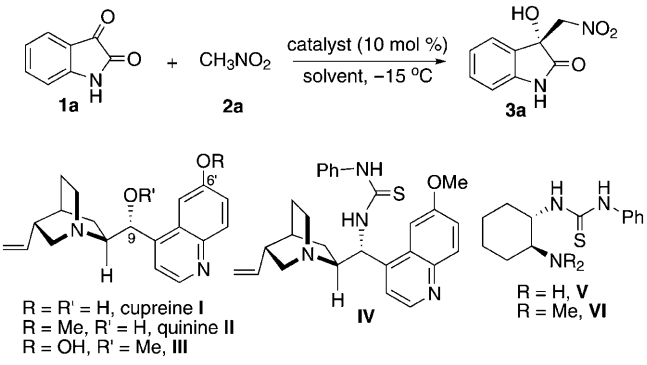
Table 1. Exploration of the catalytic asymmetric Henry reaction of isatin with nitromethane.[a]



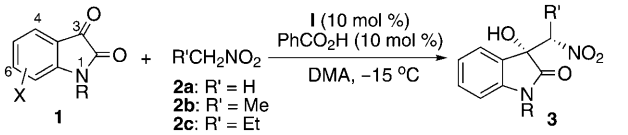
	Catalyst	Solvent	Additive	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**I**	CH_2Cl_2	none	10	97	4
2	**II**	CH_2Cl_2	none	14	92	0
3	**IV**	CH_2Cl_2	none	14	90	0
4	**V**	CH_2Cl_2	none	10	95	0
5	**VI**	CH_2Cl_2	none	24	95	0
6	**I**	DMF	none	3	95	86
7	**II**	DMF	none	5	96	4
8	**III**	DMF	none	10	94	58
9	**IV**	DMF	none	12	97	34
10	**I**	DMA	none	3	96	88
11	**I**	DMSO	none	4	98	23
12	**I**	THF	none	12	99	87
13	**I**	MeCN	none	18	96	64
14	**I**	DMA	H_2O	2	99	88
15	**I**	DMA	$PhCO_2H$	3	99	91 (99)[d]
16	**I**	DMA	Na_2HPO_4	2	95	85

[a] Unless specified, see the Experimental Section. [b] Yield after workup. [c] Determined by chiral HPLC analysis (Chiralpak AD-H). [d] This *ee* refers to after the solid product was washed with CH_2Cl_2.

tromethane (**2a**) in the presence of various bifunctional organocatalysts (**I**–**VI**; Table 1),[10–12] we found that in nonpolar aprotic CH_2Cl_2 very little enantioselectivity (0–4% *ee*) was observed in spite of the high yields (Table 1, entries 1–5). Interestingly, high enantioselectivity (86%, Table 1, entry 6) was obtained if the reaction was carried out in polar DMF with cupreine (**I**),[9g,10] although catalysts **II**–**IV**[11] displayed poor enantioselectivity (Table 1, entries 7–9). These studies indicate that both the 6′- and 9-OH groups were critical for the stereocontrol of the reaction (Table 1, entries 6–9). Notably, in DMF, the reaction time was significantly reduced and the desired product **3a** was produced in an almost quantitative yield (Table 1, entry 6). Probing the effect of solvent (Table 1, entries 6, and 10–13) revealed that polar dimethylacetamide (DMA) was optimal for the process (Table 1, entry 10). Finally, an acidic additive, $PhCO_2H$, was found to be beneficial to the enantioselectivity of the Henry reaction (91% *ee*, Table 1, entry 15). We found that pure product **3a** could be obtained in a high yield without column chromatography after workup. Moreover, the enantioselectivity could be further improved (99% *ee*) by washing the product with CH_2Cl_2 (Table 1, entry 15).

Having established a standard reaction protocol, we then probed a variety of isatins (**1**) and nitroalkanes (**2**) to determine the scope of this asymmetric transformation. As revealed in Table 2, the process proves to be a general strategy for the synthesis of useful chiral 3-substituted 3-hydroxyoxindoles (**3**) with significant structural variations. Impressively, in all cases, the reactions proceeded quickly (1.5–13 h), in excellent yields (99%), without purification by chromatography, and with good to high overall enantioselectivities (74–93% *ee*). The crude product was sufficiently pure (>95% purity) for yield calculation, characterization, and chiral HPLC analysis. In the case of products obtained as a solid (all except **3k**–**m**, which are oils), the enantioselectivity could be further improved to excellent levels (94–99%, Table 2, entries 1–10 and 14) by washing with CH_2Cl_2 (see the Experimental Section for details). It should be noted that, in some cases (e.g., products **3a**–**c**, **e**, **f**, **i**, **j**, and **n**, *ee* values shown in parenthesis), the obtained solid had a higher enantiopurity based on chiral HPLC analysis. However, in the case **3d g**, and **h**, the filtrate exhibited a higher enantiopurity than the solid. It appears that isatins (**1**) with electron-neutral and -donating substituents exhibit slightly better enantioselectivity than those bearing electron-withdrawing groups (Table 2, entries 1–3 and 11–13 vs. 4–8 and 10). If nitroethane (**2b**) or nitropropane (**2c**) was used as the nucleophile, two stereogenic centers were created with high *ee* (88, 84, and 93%) and good d.r. (10:1, 3:1, and 7:1; Table 2, entries 9, 10, and 14). Again, the *ee* and d.r. values could be further improved by washing the solid with CH_2Cl_2. Finally, it seems that variation of the protecting group on the N atom in isatins (**1**) had limited impact on the enantioselectivity (Table 2, entries 11–13). The absolute

Table 2. Scope of **I**-catalyzed nitroaldol reactions with isatins.[a]



	X	R	R′	**3**	*T* [h]	Yield [%][b]	*ee* [%]
1	H	H	H	**3a**	3	99	91[c] (99)[d]
2	5-Me	H	H	**3b**	3	99	92[c] (99)[d]
3	5-MeO	H	H	**3c**	3	99	89[c] (98)[d]
4	4-Cl	H	H	**3d**	2	99	74[c] (95)[d]
5	5-Cl	H	H	**3e**	2	99	81[c] (97)[d]
6	6-Cl	H	H	**3f**	3	99	80[c] (99)[d]
7	7-Cl	H	H	**3g**	4	99	80[c] (99)[d]
8	5-F	H	H	**3h**	1.5	99	89[c] (98)[d]
9	H	H	Me	**3i**	12	99	88,[c] 10:1 d.r.[e] (99,[d] 25:1 d.r.[e])
10	6-Br	H	Me	**3j**	13	99	84,[c] 3:1 d.r.[e] (94,[d] 4:1 d.r.[e])
11	H	Me	H	**3k**	2	99	86[c]
12	H	Bn	H	**3l**	3	99	85[c]
13	H	CH_2CO_2Me	H	**3m**	2	99	83[c]
14	H	H	Et	**3n**	16	99	93,[c] 7:1 d.r.[e] (95,[d] 10:1 d.r.[e])

[a] Unless specified, see the Experimental Section. [b] The yield was obtained after workup. [c] This *ee* refers to the product without treatment with CH_2Cl_2. [d] This *ee* refers to the product after treatment with CH_2Cl_2. [e] Determined by ^1H NMR spectroscopy.

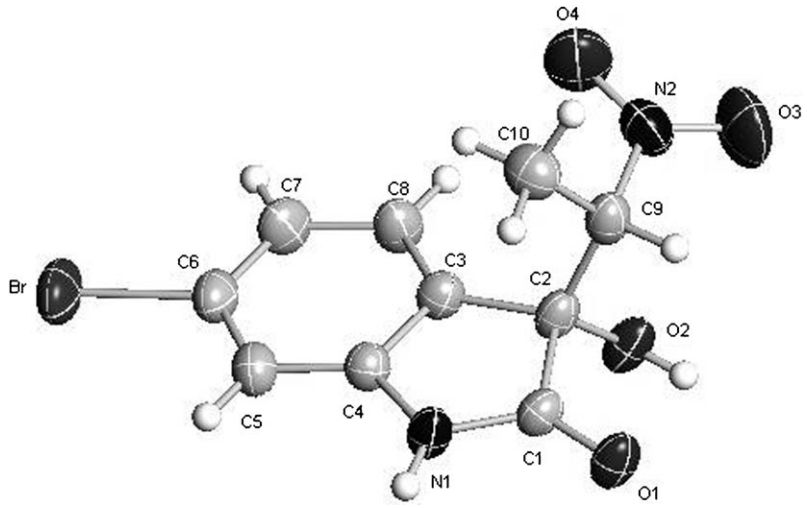
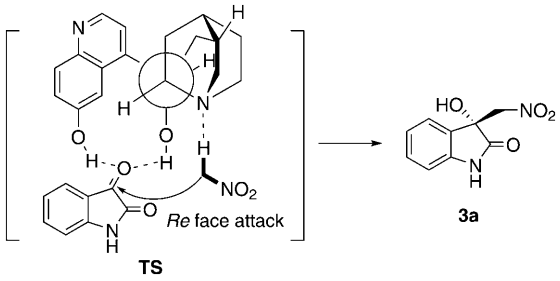


Figure 1. The X-ray crystal structure of compound **3j**.

stereochemistry of the nitroaldol adducts was determined by single crystal X-ray analysis of compound **3j** (Figure 1).[13]

A transition state (TS) model was proposed to rationalize the high enantioselectivity and the observed absolute configuration (*R*) of the cupreine-catalyzed Henry reaction (Scheme 2). Bifunctional catalyst **I** enables the simultaneous

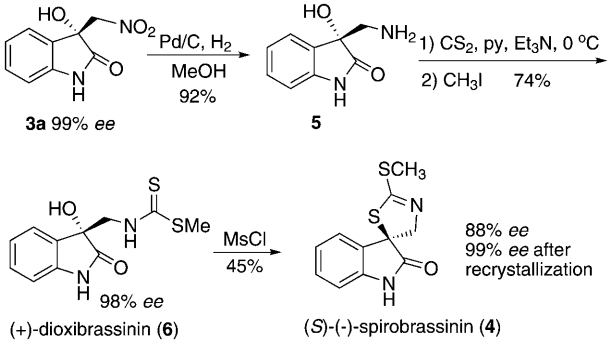


Scheme 2. A proposed transition state for the reaction.

activation of nucleophile **1a** through a base–acid interaction and of electrophile **2a** through the stronger double-hydrogen-bonding activation of the 6′- and 9-OH groups to deliver product **3a** with a high level of enantioselectivity, as observed in the investigation. Moreover, the amino group directs nitromethane **2a** to a *Re*-face attack of isatin **1a** to give adduct **3a** with the obtained *R* configuration.

To illustrate the synthetic utility of this methodology, we undertook the total synthesis of (*S*)-(−)-spirobrassinin (**4**; Scheme 3), a natural product isolated from *Pseudomonas cichorii* inoculated Chinese cabbages and Japanese radishes in 1987.[14] The compound displays various biological properties including plant defense,[15] antifungal,[16] and antitumor activities,[17] as well as oviposition stimulation.[18]. Therefore, a concise total synthesis of this natural product could provide a tool for access to analogues that may be valuable in biomedical studies that aim to elucidate the molecular mechanism underlying the biological activities of phytoalexins. For example, (−)-**4**, as a representative cruciferous phytoalexin, is a useful model for the study of a plant's chemical and biochemical defense mechanisms.[16] Herein, we present the first asymmetric synthesis of this target in four steps (Scheme 3).[19]

A related approach to that of the non-asymmetric version reported by Kutschy, Monde, and co-workers[19b] was explored to find an asymmetric synthesis by taking advantage of highly enantioenriched adduct **3a**. The



Scheme 3. A concise synthesis of (*S*)-(−)-spirobrassinin; py = pyridine.

nitro group in **3a** (99% *ee*) was reduced by Pd-catalyzed hydrogenation to give amine **5** in 92% yield. Conversion of the amino group to form dithiocarbamate **6** was achieved in 74% yield. No racemization was observed in this two-step transformation. Finally, an intramolecular nucleophilic substitution reaction by treatment of (+)-dioxibrassinin (**6**) with MsCl (Ms = mesylate) afforded the target (*S*)-(−)-spirobrassinin in 45% yield. A high enantioselectivity (88% *ee*) was obtained for this nucleophilic substitution reaction at a tertiary carbon atom. Its optical purity can be increased to 99% *ee* by recrystallization. The spectral data for **4** are in full agreement with those described in the literature ($[\alpha]_D^{25} = -135.5°$ ($c = 0.4$ in CH_2Cl_2); m.p. 140–142 °C; literature:[19b] $[\alpha]_D^{20} = -143.6$ ($c = 0.25$ in CH_2Cl_2, 92% *ee*); m.p.: 142–144 °C).

In conclusion, motivated by the "privileged" status of 3-substituted 3-hydroxyoxindoles, we have developed the first enantioselective synthesis of these compounds by using Henry reactions employing readily available isatins and nitroalkanes. The process is efficiently catalyzed by a simple natural product, cupreine, to give the aldol adducts in high yields and with good to high enantioselectivities under mild reaction conditions. This much less explored strategy[3o] rely-

ing on noncovalent-bond-mediated catalysis is different from the reported organocatalytic aldol reactions of isatins with carbonyls,[4] which use a covalent bond as the activation force. Moreover, the enantioselectivity can be improved to excellent levels by simple washing of the solid products. These features render this methodology synthetically viable and attractive in the efficient synthesis of biologically intriguing oxindole alkaloids, as demonstrated by the facile synthesis of (*S*)-(−)-spirobrassinin without using protecting groups.

Experimental Section

General Procedure (Table 2): Compound **2** (5.0 mmol) was added to a solution of **1** (1.0 mmol) and $PhCO_2H$ (12 mg, 0.1 mmol) in DMA (2 mL) in the presence of catalyst **I** (30 mg, 0.1 mmol) at −15 °C. The mixture was stirred at −15 °C for a specified time, monitored by utilizing the color change to light yellow and by TLC until these indicated reaction completion. An HCl solution (1 N, 10 mL) was added to the reaction mixture, which was then extracted with EtOAc (3×5 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo to provide a light yellow solid (for products **3a–j** and **n** Table 2, entries 1–10 and 14) or oil (for products **3k–m** Table 2, entries 11–13). The product was sufficiently pure (>95% purity) for yield calculation, characterization, and chiral HPLC analysis. Interestingly, it was found in some cases that, when a product was obtained as a solid (Table 2, entries 1–10 and 14), if it was washed with CH_2Cl_2 (3 mL) and then filtered the collected solid had a higher enantiopurity based on chiral HPLC analysis than prior to the washing (e.g., products **3a–c**, **e**, **f**, **i**, **j** and **n**, *ee* values shown in parenthesis in Table 2). However, in case of **3d**, **g**, and **h**, the filtrate exhibited a higher enantiopurity than the solid.

Acknowledgements

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Keywords: Henry reaction · isatins · natural products · organocatalysis · oxindoles

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