

Catalytic Asymmetric Synthesis of Spirooxindoles by a Mannich-Type Reaction of Isothiocyanato Oxindoles**

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Spirooxindoles are privileged structural motifs found in many alkaloids and unnatural biologically active compounds.^[1] Inspired by these important scaffolds, various synthetic methods for producing chiral spirooxindoles, especially applications to natural product synthesis, have been investigated over the last decade.^[2] As a state-of-the-art method, catalytic asymmetric one-step construction of spirooxindoles has also been intensively studied.^[3–5] However, most of the studies reported to date have focused on the catalytic asymmetric synthesis of spirooxindoles bearing an all-carbon quaternary stereocenter at the C3' position of the oxindole, such as in a spirocycloalkaneoxindole core^[4] and a spiro[pyrrolidin-3,3'-oxindole] core.^[5] On the other hand, catalytic asymmetric methods for spirooxindoles bearing a nitrogen atom at the C3' position of the oxindole unit are still limited,^[6,7] despite their importance for the design of medically important compounds (Figure 1), such as a CRTH2 antagonist with good oral bioavailability,^[8] a selective inhibitor of *Mycobacterium tuberculosis* protein tyrosine phosphatase B,^[9] a potent antimalarial agent,^[10] and an inhibitor of the interaction between the tumor suppressor p53 and its negative regulator Hdm2.^[11] Thus, expansion of the scope of available chiral spirooxindole cores is in high demand. Herein, we report a highly diastereo- and enantioselective synthesis of a spiro[imidazolidine-4,3'-oxindole] core by an asymmetric Mannich-type reaction of isothiocyanato oxindoles catalyzed by a strontium/Schiff base complex **1** (Figure 2). The transformation of a Mannich adduct into a spiro[imidazolidine-4,3'-oxindole] core is also described.

As part of our ongoing investigation of the synthesis of chiral oxindoles^[12] and asymmetric reactions with isothiocya-

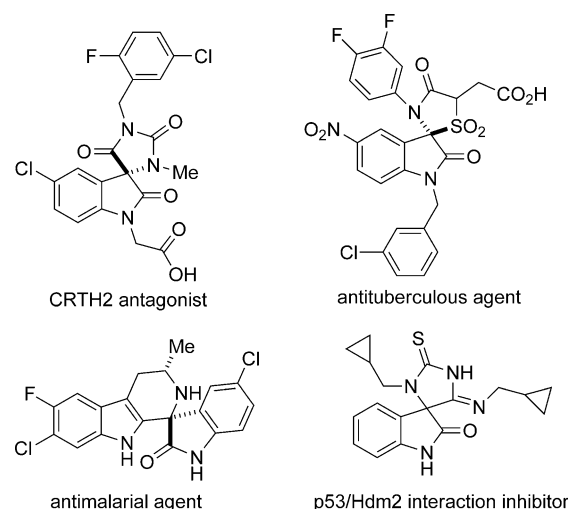


Figure 1. Spirooxindoles bearing a nitrogen atom at the C3' position of the oxindole unit; a CRTH2 antagonist with good oral bioavailability, an antituberculous agent, an antimalarial agent, and an inhibitor of p53/Hdm2 interaction.

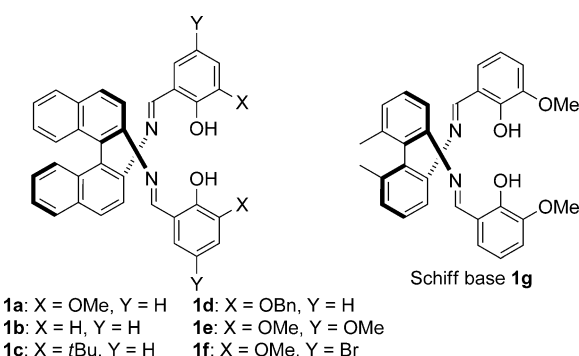


Figure 2. Structures of Schiff bases (R)-**1a–g**. Bn = benzyl.

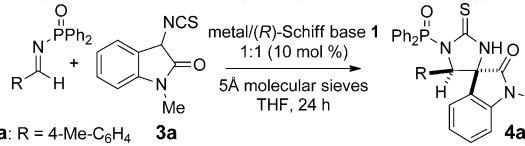
nato esters as donors^[13,14] under bifunctional metal/Schiff base catalysis,^[15] we studied the reaction of imine **2a** and 3-isothiocyanato oxindole **3a**. Initial screenings of various metal/Schiff base catalysts developed in our group showed promising results, in particular with group 2 metal/Schiff base **1a** (Figure 2). The optimization studies are summarized in Table 1. Bu₂Mg/Schiff base **1a**, which was suitable for reactions using isothiocyanato esters as donors,^[13a] promoted the reaction with high diastereoselectivity (Table 1, entry 1, 98:2 d.r.), but with only poor enantioselectivity (5% *ee*). Among the group 2 metals screened (Table 1, entries 1–4), Sr(OiPr)₂ afforded the best enantioselectivity (93% *ee*; entry 3). Enantioselectivity was much poorer when using

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Table 1: Optimization of the catalytic asymmetric Mannich-type reaction.



Entry	Metal source	1	T [°C]	Yield [%] ^[a]	d.r. ^[a]	ee [%] ^[b]
1	Bu ₂ Mg	1a	−40	60	98:2	5
2	Ca(OiPr) ₂	1a	−40	96	87:13	1
3	Sr(OiPr) ₂	1a	−40	95	91:9	93
4	Ba(OiPr) ₂	1a	−40	62	91:9	9
5	Al(OiPr) ₃	1a	−40	92	55:45	30
6	Ni(OAc) ₂	1a	−40	99	91:9	10
7	Sr(OiPr) ₂	1b	−40	68	76:24	1
8	Sr(OiPr) ₂	1c	−40	90	76:24	3
9	Sr(OiPr) ₂	1d	−40	91	71:29	5
10	Sr(OiPr) ₂	1e	−40	92	89:11	76
11	Sr(OiPr) ₂	1f	−40	87	84:16	89
12	Sr(OiPr) ₂	1g	−40	95	97:3	95
13 ^[c]	Sr(OiPr) ₂	1g	−60	88 ^[d]	98:2	97

[a] Determined by ¹H NMR spectroscopic analysis of the crude mixture.

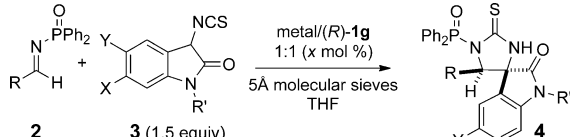
[b] Determined by chiral stationary phase HPLC analysis. [c] Reaction was run for 12 h. [d] Yield of isolated **4aa** after purification by silica gel column chromatography.

other metal sources, such as Al(OiPr)₃ and Ni(OAc)₂ (entries 5 and 6). To improve the diastereoselectivity with Sr(OiPr)₂, several Schiff bases were investigated (entries 7–12). Schiff bases **1b–1d**, which lack an *ortho*-MeO substituent, resulted in poor diastereo- and enantioselectivity, thus suggesting the importance of the MeO-group. Electronic tuning of the ligands using **1e** and **1f** resulted in less satisfactory selectivity (entries 10 and 11). Modification of the diamine backbone was effective, and Schiff base **1g**, which bears a 2,2'-biphenyldiamine backbone, gave product **4aa** in 97:3 d.r. and 95% ee at −40°C (entry 12). After further optimization of the reaction temperature and the reaction time with Schiff base **1g**, product **4aa** was isolated in 88% yield, 98:2 d.r., and 97% ee after 12 h at −60°C (entry 13).

The substrate scope of the Mannich-type reaction under optimized reaction conditions is summarized in Table 2.^[16] Substituents at the *para*-, *meta*-, and even the sterically hindered *ortho*-positions on the aromatic ring of imines **2a–2c** were compatible, and the products were obtained in 97–96% ee and 98:2–92:8 d.r. (Table 2, entries 1–3). In the case of the less reactive 4-MeO-substituted imine **2d**, Schiff base **1a** with the binaphthyl backbone showed better reactivity, and product **4da** was obtained in 92% yield and 93% ee at −20°C, albeit with only moderate diastereoselectivity (81:19 d.r.; entry 4). Catalyst loading was successfully reduced to 5 mol% and then to 2.5 mol% with imine **2e**. Although a longer reaction time was required with reduced catalyst loading, high diastereoselectivity and enantioselectivity were observed (entries 6 and 7). Imines **2f–2i**, which bear electron-withdrawing substituents, also resulted in high selectivity, 99–97% ee and 98:2–87:13 d.r. (entries 8–12). Aside from **3a**, the oxindole donors Cl-substituted oxindole **3b** and Me-substituted oxindole **3c** also gave the respective products in

Table 2: Sr-catalyzed asymmetric Mannich-type reaction of isothiocyanato oxindoles.^[a]

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2 + **3** (1.5 equiv) $\xrightarrow[5\text{\AA molecular sieves, THF}]{\text{metal/(R)-1g 1:1 (x mol \%)}}$ **4**

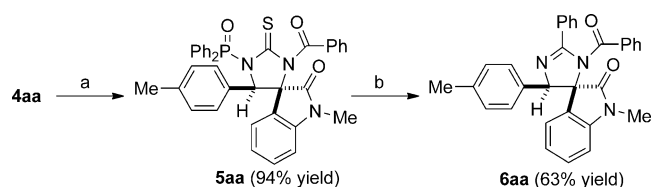
3a: X = H, Y = H, R' = Me
3b: X = Cl, Y = H, R' = Me
3c: X = H, Y = Me, R' = Me
3d: X = H, Y = H, R' = $\text{CH}_2\text{CH=CH}_2$

	R	2	3	x ^[b]	4	T [°C]	t [h]	Yield [%] ^[c]	d.r. ^[d]	ee [%] ^[e]
1	4-Me-C ₆ H ₄	2a	3a	10	4aa	−60	12	88	98:2	97
2 ^[f]	3-Me-C ₆ H ₄	2b	3a	10	4ba	−60	9	98	92:8	97
3 ^[f]	2-Me-C ₆ H ₄	2c	3a	10	4ca	−60	9	95	94:6	96
4 ^[g]	4-MeO-C ₆ H ₄	2d	3a	10	4da	−20	12	92	81:19	93
5 ^[f]	Ph	2e	3a	10	4ea	−60	9	99	96:4	98
6	Ph	2e	3a	5	4ea	−60	24	96	95:5	97
7	Ph	2e	3a	2.5	4ea	−60	48	96	95:5	95
8 ^[f]	4-F-C ₆ H ₄	2f	3a	10	4fa	−60	8	95	87:13	99
9	3-F-C ₆ H ₄	2g	3a	10	4ga	−60	12	98	98:2	99
10	4-Cl-C ₆ H ₄	2h	3b	10	4hb	−60	11	87	97:3	97
11	4-Cl-C ₆ H ₄	2h	3c	10	4hc	−60	9	93	97:3	97
12	4-Br-C ₆ H ₄	2i	3a	10	4ia	−60	9	99	97:3	98
13 ^[f]	3-thienyl	2j	3a	10	4ja	−60	9	98	83:17	94
14 ^[g]	2-furyl	2k	3d	10	4kd	−40	9	88	89:11	98
15 ^[g]	4-Me-C ₆ H ₄	2a	3d	10	4ad	−40	12	90	98:2	94

[a] Unless otherwise noted, reactions were run in THF (0.17 M) using imine **2** (0.20 mmol), isothiocyanato oxindole **3** (1.5 equiv), Sr(OiPr)₂ (10 mol %), and (R)-**1g** with 5 Å molecular sieves (40 mg). [b] x = mol % of catalyst used. [c] Yield of isolated **4** after purification by silica gel column chromatography. [d] Determined by ¹H NMR spectroscopic analysis of the crude mixture. [e] Determined by chiral stationary phase HPLC analysis. [f] Schiff base (S)-**1g** was used instead of (R)-**1g**, and *ent*-**4** was obtained as the major product. [g] Schiff base (S)-**1a** was used instead of (R)-**1g**, and *ent*-**4** was obtained as the major product.

excellent diastereo- and enantioselectivity (entries 10 and 11). For *N*-allyl protected oxindole donor **3d**, Schiff base **1a** had better reactivity and stereoselectivity, and the Mannich adducts were obtained in comparably good yield, diastereoselectivity, and enantioselectivity with *N*-Me oxindole donors **3a–3c** (entries 14 and 15). These results with a removable *N*-protecting group on the oxindole unit are important for future synthetic applications using the present method.

To demonstrate the synthetic utility of the products, we transformed the spiro[imidazolidine-4,3'-oxindole] core in **4aa** into a spiro[imidazoline-4,3'-oxindole] core (Scheme 1). After benzylation of **4aa** (94% yield), **5aa** was subjected to Pd-catalyzed desulfurative cross-coupling conditions.^[17] Removal of a diphenylphosphinoyl group and cross-coupling with PhB(OH)₂ proceeded simultaneously at 50°C in THF, and the spiro[imidazoline-4,3'-oxindole] product **6aa** was obtained in 63% yield. Product **6aa** has a *cis*-diaryl relationship, and can be regarded as a hybrid of two species: 1) Nutlin,^[18] an imidazole-based inhibitor of p53/E3-ubiquitin ligase Mdm2 interaction, and 2) MI-219,^[19] a spiro[pyrrolidine-3,3'-oxindole]-based p53/Mdm2 inhibitor. Because of this, the present method would be useful in the field of



Scheme 1. Transformation of Mannich adduct **4aa** into spiro(imidazoline-4,3'-oxindole) **6aa**. Reagents and conditions: a) Benzoyl chloride (1.5 equiv), Et₃N (1.5 equiv), DMAP (10 mol%), CH₂Cl₂, RT, 4 h. b) PhB(OH)₂ (2 equiv), CuTC (3 equiv), Pd(PPh₃)₄ (10 mol%), THF, 50°C, 1 h. DMAP = *N,N*-dimethyl-4-aminopyridine, TC = thiophen-2-carboxylate.

medicinal chemistry for the design and synthesis of new potent anti-tumor agents.^[20]

In summary, we have developed an asymmetric Mannich-type reaction of isothiocyanato oxindoles catalyzed by a Sr/Schiff base complex, which provides concise access to enantiomerically enriched spiro[imidazolidine-4,3'-oxindole] compounds, as well as a spiro[imidazoline-4,3'-oxindole] through a two-step conversion from the Mannich adduct. In an effort to develop a new anti-tumor agent, library syntheses of divergent spiro[imidazoline-4,3'-oxindole] compounds is ongoing and will be reported together with the biological activity of the products in due course.

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