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PyBidine–Ni(OAc)$_2$-Catalyzed Michael/Aldol Reaction of Methyleneindolinones and Thiosalicylaldehydes for Stereochemically Divergent Thiochromanyl-spirooxindoles

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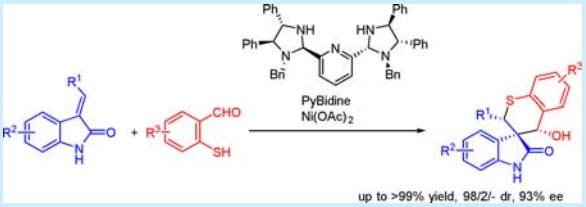
Supporting Information

ABSTRACT: (*S*,*S*)-Diphenylethylenediamine-derived bis(imidazolidine)pyridine (PyBidine)–Ni(OAc)$_2$ complex catalyzed the asymmetric Michael/aldol reaction of methyleneindolinone and thiosalicylaldehyde to produce (2′*R*,3*S*,4′*R*)-thiochromanyl-spirooxindole having three contiguous stereogenic centers.



Spirooxindoles are complex skeletal structures with significant biological activity that are found in many naturally occurring alkaloids. Spirotryprostatin A isolated from *Aspergillus fumigatus* inhibits the cell cycle at the G2/M phase in a mouse cdc2 mutant cell line, tsFT210 (Figure 1).[1] Gelsemium

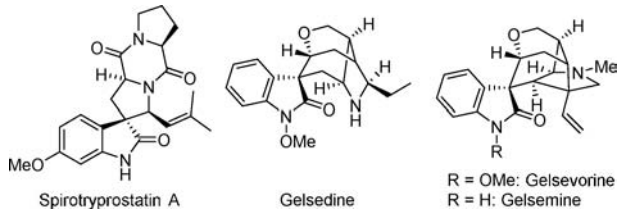


Figure 1. Examples of biologically significant spirooxindoles.

spirooxindole alkaloids (e.g., glesedine, gelsevorine, and gelsemine) isolated from the ancient medicine yakatsu stored in the Shosoin Repository exhibit a wide range of biological activities, including analgesic, antiinflammatory, and antitumor effects.[2]

Among a wide range of approaches directed toward the spirooxindole structure, synthesis using catalytic asymmetric reaction can provide a powerful methodology for accessing novel pharmacophores, not just the naturally occurring compounds.[3,4] For example, artificial pyrrolidinyl-spirooxindoles, which contain a five-membered ring, have been constructed using the catalytic asymmetric [3 + 2] cycloaddition of methyleneindolinones and imino esters.[5] For catalytic access to spirooxindole structures with a six-membered heterocycle, asymmetric tandem Michael/Michael reactions using methyleneindolinones have been investigated, and Zhao has pioneered a thiourea-catalyzed synthesis of tetrahydroquinolinyl-spirooxindoles.[6a]

Zhu also reported the asymmetric syntheses of tetrahydroquinolinyl-spirooxindoles using a (DHQD)$_2$PHAL catalyst and chromanyl-3,3′-oxindoles using a squaramide catalyst.[7] Quite recently, Enders succeeded in the catalytic asymmetric synthesis of chromanyloxindoles by a chiral thiourea-catalyzed oxa-Michael/1,6-addition.[8,9] However, successful syntheses of sulfur-containing chiral versions are limited, although replacement of the oxygen atom by sulfur can be a rational strategy for improving pharmacological activity.[6b,10,11]

The present report describes the first catalytic asymmetric synthesis of thiochromanyl-spirooxindoles.[12] A program on diversity-oriented asymmetric catalysis (DOAC) led to the catalytic asymmetric synthesis of stereochemically diversified pyrrolidinyl-spirooxindoles. An imidazoline aminophenol (IAP)–Ni(OAc)$_2$ promoted the first general *exo*′-selective [3 + 2] cycloaddition (Scheme 1 (1)).[13a] Bis(imidazolidine)-pyridine (PyBidine)–Cu(OTf)$_2$ was used as the catalyst for the highly *endo*-selective [3 + 2] cycloaddition of methyleneindolinone and iminoesters (Scheme 1 (2)).[13b] The DOAC of thiochromanes also was achieved using the IAP–Ni(OAc)$_2$ catalyst (Scheme 1 (3)).[14]

By combining the chemistry shown in Scheme 1, the synthesis of chiral thiochromanyl-spirooxindoles was investigated by determining the appropriate catalyst for the reaction of asymmetric Michael/aldol reaction of methyleneindolinone (**1a**) and thiosalicylaldehyde (**2a**) (Table 1).

When the IAP–Ni(OAc)$_2$ catalyst was used in the reaction of **1a** and **2a**, the reaction proceeded at −78 °C to give the desired thiochromanyl-spirooxindole (**3a**) in a diastereoselective manner; however, the major diastereomer was obtained in racemic form (Table 1, entry 1). Although an effort was made to obtain optically active **3a**, promoting the asymmetric induction for **3a** using the IAP–metal catalyst was very difficult. In contrast, the use of PyBidine–Cu(OTf)$_2$, which was effective in the *endo*-selective [3 + 2] cycloaddition of

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Scheme 1. IAP− and PyBidine−Metal-Catalyzed Asymmetric Synthesis of Pyrrolidinyl-spirooxindoles and Thiochromanes

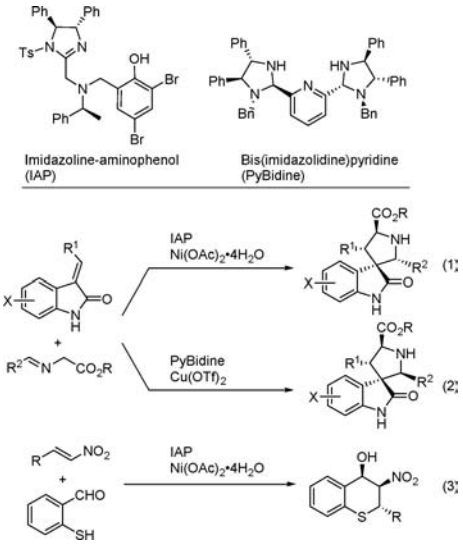
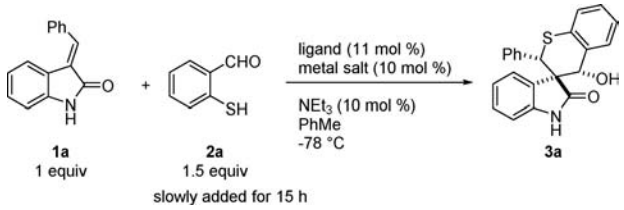


Table 1. Catalyst Exploration for Michael/Aldol Reaction of Methyleneindolinone and Thiosalicylaldehyde



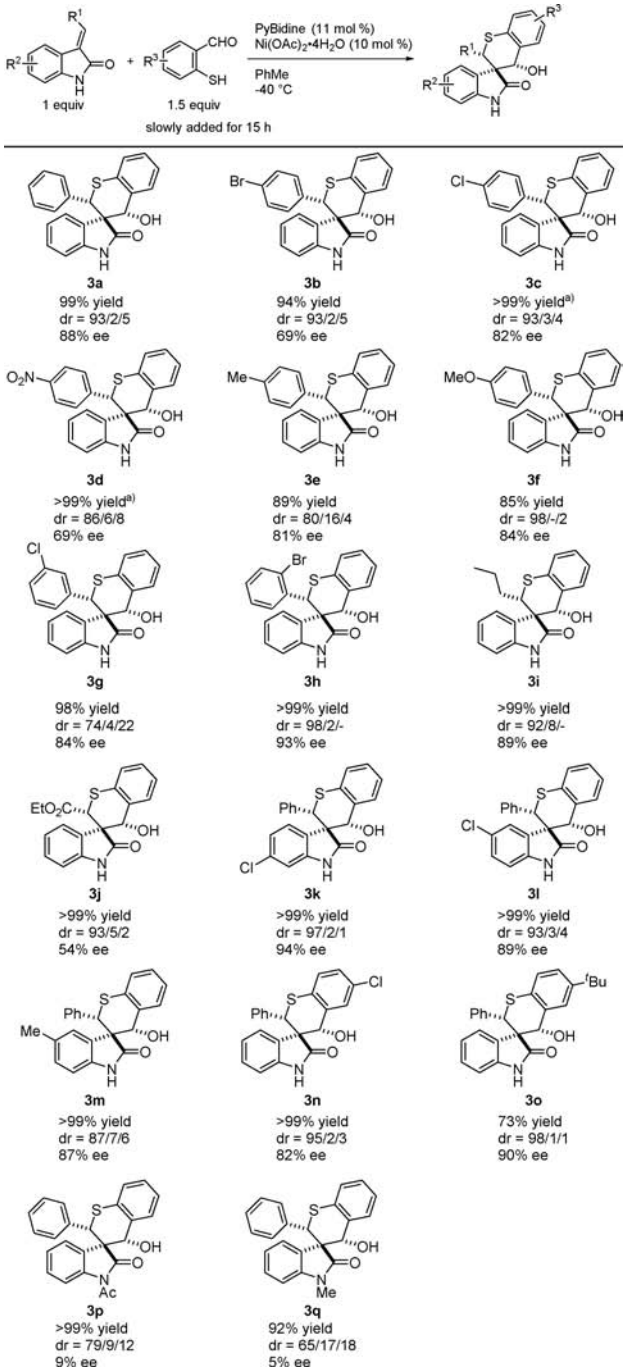
entry	ligand	metal salt	yield[a] (%)	diastereomeric ratio 3a/3a′/3a″	ee[b] (%)
1	IAP	$Ni(OAc)_2$[c]	48	74/15/11	*rac*
2	PyBidine	$Cu(OTf)_2$	27	64/23/13	−12
3	PyBidine	$Cu(OAc)_2$	70	67/15/18	−7
4	PyBidine	$Co(OAc)_2$[c]	65	74/7/19	−8
5	PyBidine	$Ni(OAc)_2$[c]	79	80/6/14	50
6	PyBidine	$Zn(OAc)_2$	99	74/10/16	4
7[d]	PyBidine	$Ni(OAc)_2$[c]	99	82/4/14	66
8[d,e]	PyBidine	$Ni(OAc)_2$[c]	99	93/2/5	88
9[d–f]	PyBidine	$Ni(OAc)_2$[c]	99	91/3/6	76

[a]Combined yield of diastereomers. [b]ee of major diastereomer **3a**. [c]Tetrahydrate was used. [d]Without NEt_3. [e]Reaction was performed at −40 °C. [f]**2a** was slowly added over 0.5 h.

methyleneindolinones, resulted in the production of **3a** with 12% ee. The PyBidine−$Cu(OAc)_2$ showed greater catalytic activity and provided the product in 70% yield. Among the acetates of first-row transition metals examined, the PyBidine−$Ni(OAc)_2$ catalyst gave thiochromanyl-spirooxindoles in a 79% combined yield with a diastereomeric ratio (dr) of 80/6/14 and **3a** as the major isomer with 50% ee (Table 1, entry 5). After optimization (reaction at −40 °C without NEt_3), the thiochromanyl-spirooxindoles were produced in 99% yield with up to 93/2/5 diastereoselectivity, with **3a** being produced in 88% ee (entry 8). (Detailed optimization conditions are available in the Supporting Information.)

The applicability of the PyBidine−$Ni(OAc)_2$-catalyzed asymmetric synthesis of thiochromanyl-spirooxindoles is outlined in Table 2.

Table 2. Asymmetric Michael/Aldol Reaction of Methyleneindolinones and Thiosalicylaldehydes Using PyBidine−$Ni(OAc)_2$ Catalyst



[a]**2a** was slowly added over 0.5 h.

For aryl-substituted methyleneindolinones, both electron-deficient and -donating groups on the benzene ring were used successfully to yield thiochromanyl-spirooxindoles with high diastereoselectivity, and **3h** with an *o*-Br substituent was obtained with up to 93% ee. Slow addition of **2a** over 0.5 h gave better asymmetric induction when using electron-deficient methyleneindolinones to give **3c** and **3d**. Alkyl-substituted methyleneindolinone also was compatible and yielded **3i** with 89% ee. Introduction of chloro and methyl groups on the indolinone ring provided **3k**−**m**. Furthermore, substituted

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thiosalicylaldehydes gave **3n** and **3o** with 82% ee and 90% ee, respectively.

The absolute structure of the main diastereomer was determined by single-crystal X-ray crystallography of **3h** (Figure 2). Using the (*S*,*S*)-diphenylethylenediamine-derived PyBidine−Ni(OAc)$_2$ catalyst, (2′*S*,3*S*,4′*R*)-4′-hydroxy-2′-phenylspiro[indoline-3,3′-thiochroman]-2-one (**3h**) was obtained as the major product.

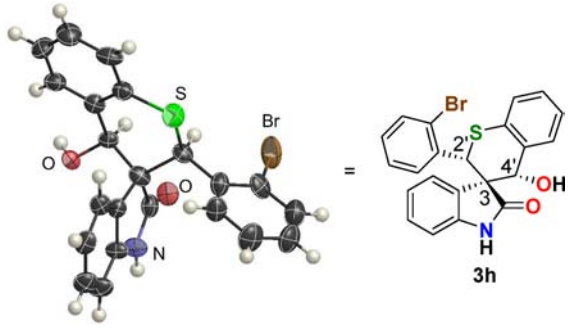
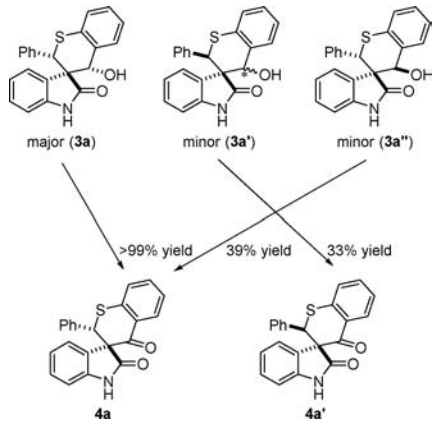


Figure 2. X-ray structure of major diastereomer **3h**.

To obtain stereochemically divergent products from thiochromanyl-spirooxindoles, **3a** and its diastereomers (**3a′** and **3a″**) were oxidized by the Dess−Martin reagent as shown in Scheme 2.

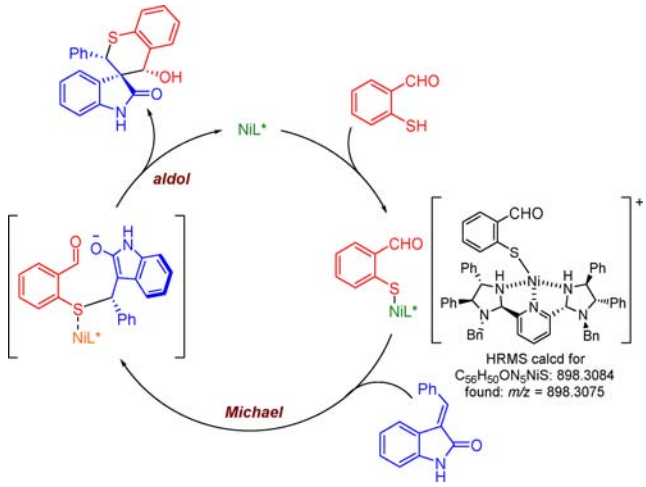
Scheme 2. Oxidation of Michael/Aldol Adducts of Methyleneindolinone (1a) and Thiosalicylaldehyde (2a) (Dess−Martin Reagent, CH_2Cl_2, rt, 17 h)



The oxidation of both **3a** and **3a″** gave the same ketone **4a**, which suggested that **3a″** was an epimer at the 4′-hydroxyl group of **3a**. As expected, oxidation of the remaining isomer **3a′**, which is an epimer at the phenyl position, gave **4a′**.

The proposed catalytic cycle for the PyBidine−Ni(OAc)$_2$-catalyzed asymmetric reaction of methyleneindolinone and thiosalicylaldehyde is provided in Scheme 3. When PyBidine−Ni(OAc)$_2$ was mixed with thiosalicylaldehyde (**2a**), HRMS analysis provided a peak at m/z = 898.3075, which corresponded to [PyBidine−Ni−S(C_6H_4)CHO]$^+$. Due to the strong affinity of the soft thiol functional group for the late transition metal, reaction began with formation of the nickel thiolate of thiosalicylaldehyde. The nickel−thiolate then attacked the methyleneindolinone in a Michael reaction to provide the enolate of indolinone. Further intramolecular aldol

Scheme 3. Proposed Catalytic Cycle



reaction of the nickel enolate furnished the thiochromanyl-spirooxindole with regeneration of the PyBidine−Ni catalyst.

Details of the reaction using the (*S*,*S*)-diphenylethylenediamine-derived PyBidine−Ni(OAc)$_2$ catalyst is shown in Figure 3. By following the catalytic cycle, the PyBidine−Ni(OAc)$_2$ complex generated the nickel thiolate. The methyleneindolinone also was activated in the second quadrant of the PyBidine−Ni(OAc)$_2$ complex using hydrogen bonding through the NH of the imidazolidine ring.[13b] The hydrogen bonding controlled the direction of methyleneindolinone for acceptance of nucleophilic addition of thiolate and guided the following aldol reaction to provide (2′*S*,3*S*,4′*R*)-4′-hydroxy-2′-phenylspiro[indoline-3,3′-thiochroman]-2-one **3** as the major product (Figure 3).

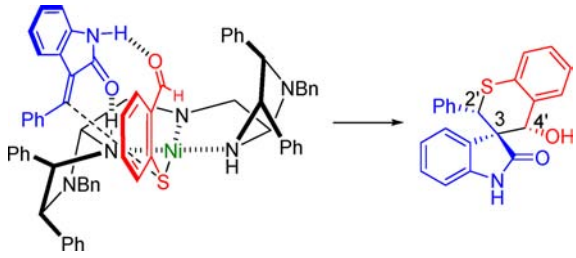


Figure 3. Plausible reaction mode for the yield of major diastereomer **3a**.

In this plausible reaction model, an additional hydrogen-bonding network between the NH of methyleneindolinone and thiosalicylaldehyde controlled attachment of the 4′*R*-hydroxy group, which is supported by the low asymmetric induction for giving N-acetylated **3p** and *N*-methylated **3q** (Table 2).

In conclusion, this is the first example of a highly diastereoselective asymmetric Michael/aldol reaction of methyleneindolinones and thiosalicylaldehydes catalyzed by bis(imidazolidine)pyridine (PyBidine)−Ni(OAc)$_2$ to produce thiochromanyl-spirooxindoles. This provides a wide range of diverse thiochromanyl-spirooxindoles that show promise for application as biologically active pharmaceuticals.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02783.

Experimental procedure and analytical data (PDF)
X-ray crystallographic data for **3h** (CIF)

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Notes

The authors declare no competing financial interest.

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