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Chiral Bis(imidazolidine)iodobenzene (I-Bidine) Organocatalyst for Thiochromane Synthesis Using an Asymmetric Michael/Henry Reaction

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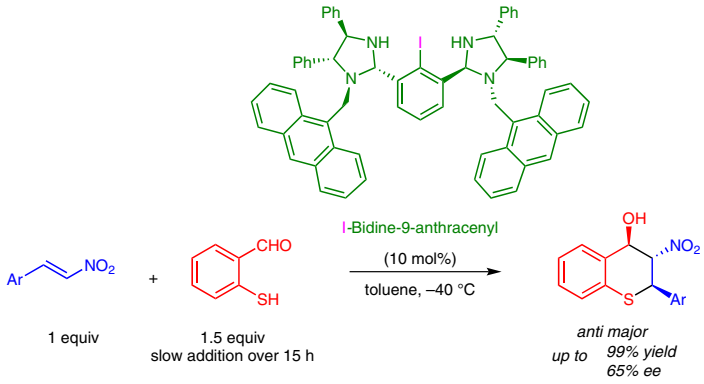

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Abstract Bis(imidazolidine)iodobenzene (I-Bidine) was designed as an organocatalyst based on previously reported imidazolidine- or oxazolidine-containing chiral metal catalysts. I-Bidine showed catalytic activity for the Michael/Henry reaction of thiosalicyl aldehydes with nitroalkenes to give optically active thiochromanes with moderate enantiomeric excesses.

Key words organocatalyst, thiochromane, tandem reaction, asymmetric synthesis

The chemistry of asymmetric organocatalysis has developed rapidly to become a fundamentally important process for providing optically active compounds.[1] The successful development of organocatalysis depends on optimizing catalyst–substrate interactions, especially the hydrogen bonding network and steric effects. This report describes a new approach to designing imidazolidine-containing iodobenzene organocatalyst based on the parent chiral imidazolidine-metal catalyst.

For the development of novel asymmetric catalysts, a series of imidazolidine- and oxazolidine-containing chiral ligands have been developed, such as bis(imidazolidine)pyridine (PyBidine)[2] and bis(oxazolidine)pyridine (PyBodine),[3] which enabled various metal-catalyzed asymmetric reactions. Bis(imidazolidine)-containing NCN-pincer Pd and Rh complexes also have been developed.[4] These imidazolidine- and oxazolidine-containing catalysts possess unique catalytic activities that cannot be explained by the activity of the simple metal center. To provide highly stereoselective reactions, the metal center must cooperate with the hydrogen bonding from the NH of the imidazolidine (or oxazolidine), as suggested by structural analysis of the catalyst, experimental studies on the reaction mechanism, and density functional theory (DFT) studies.[5–7] Based on these results, a new bis(imidazolidine)-containing organocatalyst was designed (Figure 1). For this catalyst, the metal center of PyBidine-metal and the NCN pincer complex was replaced by iodine because of the potential use of the halogen bonding facilitated by the Lewis acidity of the iodine.[8,9]

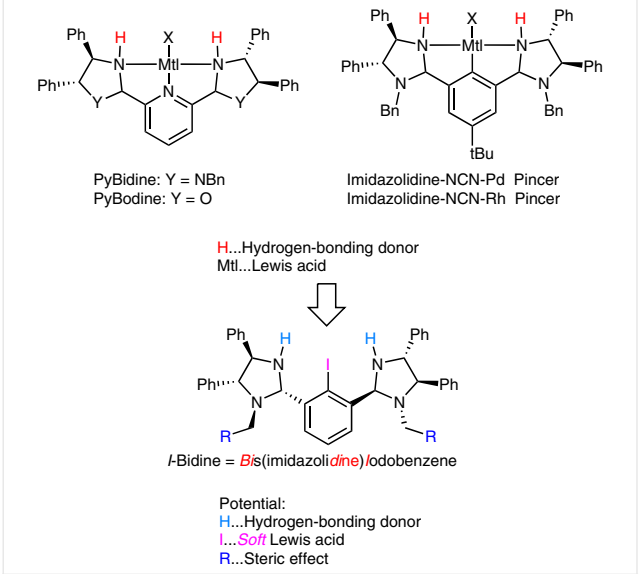
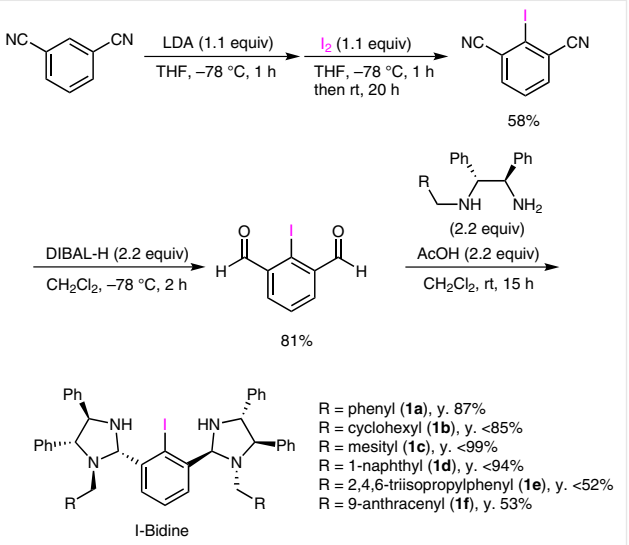


Figure 1 Design of bis(imidazolidine) iodobenzene (I-Bidine) from imidazolidine (or oxazolidine)-containing chiral metal catalysts

The synthesis of bis(imidazolidine) iodobenzene (I-Bidine) is shown in Scheme 1.[10] After iodination of phthalonitrile, the nitrile was reduced by DIBAL-H to give the aldehyde. Condensation with monobenzyl diphenylethylenediamine using acetic acid in dichloromethane gave I-Bidine (**1a**). I-Bidine analogues **1b–f** were prepared by following the same procedure.[11]



Scheme 1 Synthesis of bis(imidazolidine) iodobenzene (I-Bidine)

Highly stereoselective imidazolidine ring formation was confirmed from the ^{1}H NMR spectrum of **1a** (Figure 2). The ^{1}H NMR data for the analogues are provided in the Supporting Information.

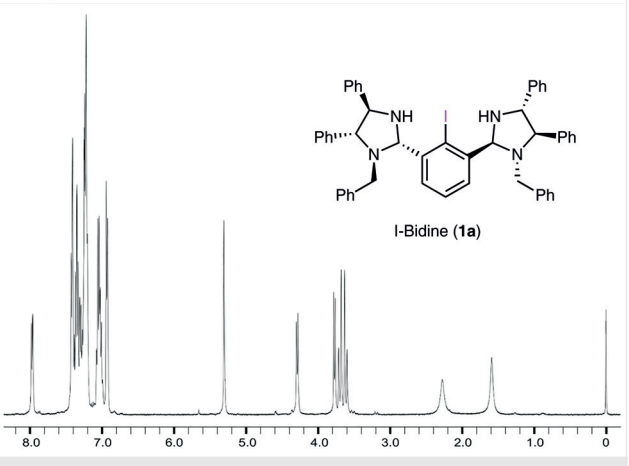


Figure 2 ^{1}H NMR spectrum of I-Bidine (**1a**)

X-ray crystallographic analysis of **1a** revealed an all-*trans* configuration of the imidazolidine ring (Figure 3).[12] In the structure of **1a**, derived from (*R*,*R*)-diphenylethylenediamine, the NH protons of imidazolidine appear in the second and fourth quadrants, although the imidazolidine rings do not appear to have any direct interaction with iodine.

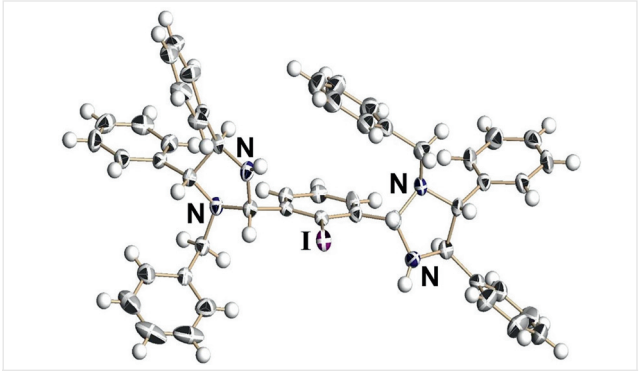


Figure 3 X-ray crystal structure of **1a**

Considering the soft Lewis acidity of iodine in I-Bidine, the synthesis of thiochromane using nitroalkene (**2**) and thiosalicyl aldehyde (**3**) was selected as a target reaction.[13] Using 10 mol% I-Bidine (**1a**), the reaction of nitrostyrene (**2a**) with thiosalicyl aldehyde (**3**) gave *syn*-nitroaldol (*syn*-**4a**) with 13% ee and racemic *anti*-nitroaldol (*anti*-**4a**) in toluene at –40 °C (Table 1, entry 1). Addition of a thiosalicyl aldehyde using a syringe pump improved the enantiomeric excess of *syn*-**4a** to 40% ee, although racemic *anti*-**4a** was also obtained (entry 2). The different enantiomeric excess values for *syn*- and *anti*-**4a** suggest that I-Bidine catalyst also affects asymmetric induction in the Henry reaction, not only the first step of the Michael reaction.

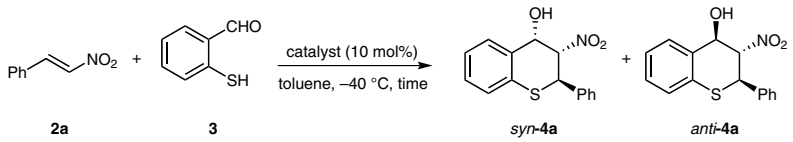
The use of catalyst **5** without iodine and bis(imidazoline)iodobenzene **6** resulted in lower enantiomeric excesses for *syn*-**4a** (Table 1, entries 3 and 4), though some asymmetric inductions were observed on *anti*-**4a** using **5** and **6**.

Using a syringe pump technique, catalyst screening was conducted in order to evaluate the steric effects of *N*-alkyl substituents in I-Bidines (Table 2).

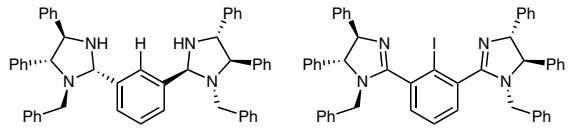
In all cases, *anti*-**4a** was the major isomer formed. The sterically hindered I-Bidines (**1b–f**) underwent asymmetric induction to form the major isomer *anti*-**4a**. For both diastereomers and catalytic activity, I-Bidine **1f** was selected to examine the generality of the thiochromane synthesis (Scheme 2).

Because the obtained thiochromanes epimerized partially during silica gel column chromatography, the yields and dr determined by ^{1}H NMR analysis of the crude products are provided with the isolated values after the silica gel column chromatography. Various nitrostyrenes with electron-donating and -withdrawing substituents were successfully employed for the I-Bidine (**1f**)-catalyzed Michael/Henry reaction with thiosalicyl aldehyde to give chiral thiochromanes with moderate enantiomeric excess.[14] A thiophenyl nitroalkene also was transformed to thiochromane **4f**. For the *p*-methoxy nitrostyrene, *syn*-**4h** with 63% ee was obtained along with *anti*-**4h** with 65% ee. The abso-

Table 1 Reaction Optimization of I-Bidine (**1a**)-Catalyzed Michael/Henry Reaction of Nitroalkene (**2**) and Thiosalicyl Aldehyde (**3**)



2a **3** *syn*-**4a** *anti*-**4a**

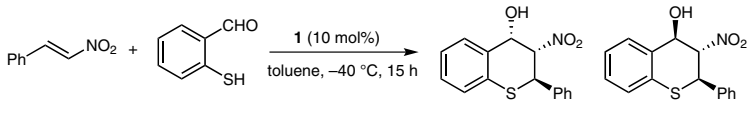


5 **6**

Entry	Catalyst	Time (h)	Yield[a] (%)	*syn*/*anti*[a]	ee of *syn* (%)	ee of *anti* (%)
1[b]	**1a**	0.5	99	52:48	13	*rac*
2	**1a**	15[c]	99	48:52	40	*rac*
3	**5**	15[c]	93	23:77	14	–15
4	**6**	15[c]	94	23:77	9	27

[a] Yields and diastereomeric ratios (dr) were determined by the ^{1}H NMR analysis of the crude product.
[b] Compound **3** was added in one portion.
[c] Compound **3** was added using a syringe pump over 15 h.

Table 2 Catalyst Screening for the Catalytic Asymmetric Synthesis of Thiochromane[a]



2a 1 equiv **3** 1.5 equiv slow addition over 15 h *syn*-**4a** *anti*-**4a**

Entry	Catalyst	Yield[b] (%)	*syn*/*anti*[b]	ee of *syn* (%)	ee of *anti* (%)
1	**1a**	99	48:52	40	*rac*
2	**1b**	68	40:60	21	16
3	**1c**	84	32:68	64	59
4	**1d**	75	31:69	33	8
5	**1e**	99	39:61	67	63
6	**1f**	99	44:56	69	53

[a] Compound **3** was added using a syringe pump over 15 h.
[b] Yields and dr were determined by the ^{1}H NMR analysis of the crude product.

lute structure of thiochromane **4d** was determined by comparison of the HPLC retention time with that reported previously.[13e,m] Using (*R*,*R*)-diphenylethylenediamine-derived **1f**, (2*R*,3*S*,4*R*)-**4d** was obtained as the major *anti*-isomer and (2*R*,3*S*,4*S*)-**4d** was obtained as the *syn*-isomer.

In conclusion, bis(imidazolidine)iodobenzene (I-Bidine) was developed as an organocatalyst based on imidazolidine- or oxazolidine-containing chiral metal catalysts. The I-Bidine possessed catalytic activity for the Michael/Henry reaction of thiosalicyl aldehydes with nitroalkenes to give optically active thiochromanes. The development of more efficient organocatalysts based on cooperative function is ongoing.

Acknowledgment

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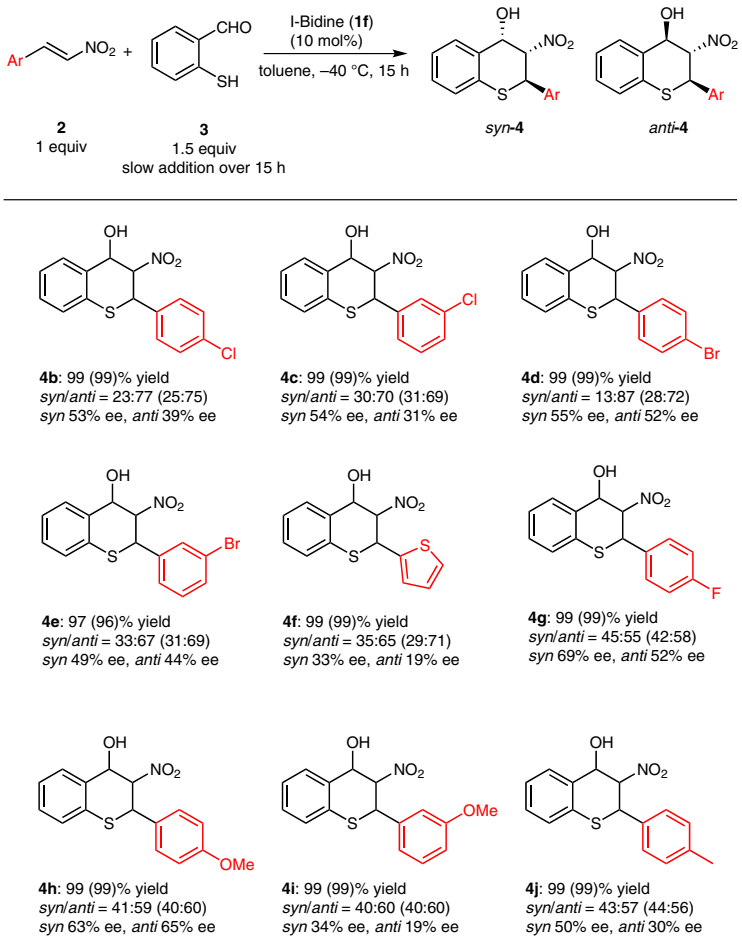

Scheme 2 Catalytic asymmetric synthesis of thiochromane.[a] a) Yields and dr were determined by ^{1}H NMR analysis of the crude product. Values in parentheses represent yields and dr after silica gel column chromatography.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588614.

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(11) **Synthesis of I-Bidines (1); General Procedure**: To a stirred solution of 2-iodoisophthalaldehyde (1 equiv) in CH_2Cl_2 (0.067 M) were added monoarylmethyl-(1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (2.2 equiv), and AcOH (2.2 equiv) at rt. After being stirred for appropriate time, the reaction mixture was quenched by H_2O, and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to afford the product.

I-Bidine (1a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 7.2 Hz, 2 H), 7.21–7.43 (m, 21 H), 7.00–7.08 (m, 6 H), 6.94 (d, *J* = 7.4 Hz, 4 H), 5.31 (s, 2 H), 4.29 (d, *J* = 7.9 Hz, 2 H), 3.77 (d, *J* = 8.1 Hz, 2 H), 3.70 (d, *J* = 13.7 Hz, 2 H), 3.62 (d, *J* = 13.9 Hz, 2 H), 2.27 (br s, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.9, 141.7, 139.8, 135.6, 129.9, 129.3, 128.5, 128.4, 128.2, 128.1, 127.6, 127.5, 127.10, 127.06, 126.7, 106.4, 84.0, 75.4, 68.5, 53.5. HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{50}H_{46}IN_4$: 829.2762; found: 829.2771. IR (neat) 3083, 3060, 3027, 2972, 2926, 2844, 1602, 1494, 1454, 1048, 880, 759, 699 cm^{-1}.

(12) Crystal Data for I-Bidine (**1a**): $C_{50}H_{45}IN_4$: MW = 828.80, monoclinic, P_{21}, *a* = 10.1466(13) Å, *b* = 12.5687(15) Å, *c* = 16.297(2) Å; α = 90°, β = 101.573(2)°, γ = 90°, *V* = 2036.1(4) Å^3, *Z* = 2, R = 0.0390 and *w*R = 0.0647. CCDC 1425335 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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(14) **General Procedure for Asymmetric Michael/Henry Reaction**: To a two-necked round-bottomed flask were added I-Bidine (0.015 mmol), nitrostyrene (0.15 mmol), and anhyd toluene (1 mL) under argon, and the mixture was cooled to –40 °C. Slow addition of 2-mercaptobenzaldehyde (0.225 mmol, ca. 75% purity) in anhyd toluene (5 mL) using syringe pump was conducted for 15 h. Then the completion of the reaction was checked by TLC and the solvent was removed under reduced pressure. Yield and diastereomeric ratio of the product were determined by crude ^{1}H NMR. The crude mixture was purified by silica gel column chromatography to afford the 2-aryl-3-nitrothiochroman-4-ol. The enantiomeric excesses of the product were determined by chiral stationary phase HPLC using a Daicel Chiralpak AD-H, AS-H, and Chiralcel OD-H column.

(2*R*,3*S*,4*R*)-3-Nitro-2-phenylthiochroman-4-ol (*anti*-4a): ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.72–7.74 (m, 1 H), 7.53 (dd, *J* = 1.6, 8.5 Hz, 2 H), 7.36–7.43 (m, 3 H), 7.22–7.29 (m, 2 H), 7.11–7.14 (m, 1 H), 5.69 (d, *J* = 8.3 Hz, 1 H), 5.36–5.45 (m, 2 H), 5.15 (d, *J* = 10.8 Hz, 1 H). ^{13}C NMR (125 MHz, acetone-d_6): δ = 136.4, 135.9, 132.5, 130.0, 129.8, 129.3, 129.1, 128.6, 126.0, 125.4, 94.1, 72.3, 47.4. HRMS: *m*/*z* [M + NH_4]$^+$ calcd for $C_{15}H_{17}N_2O_3S$: 305.0954; found: 305.0954. IR (neat): 3380, 3062, 3024, 1587, 1555, 1037, 753, 741, 702 cm^{-1}. $[\alpha]_D^{26.5}$ +7.0 (c = 0.05, MeOH, 53% ee); enantiomeric excess was determined by HPLC with a Chiralpak AD-H column [hexane–2-propanol (85:15), flow rate: 0.7 mL/min, λ = 254 nm]; t_R (minor enantiomer) = 16.4 min, t_R (major enantiomer) = 17.7 min; 53% ee.

(2*R*,3*S*,4*S*)-3-Nitro-2-phenylthiochroman-4-ol (*syn*-4a): ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.59–7.62 (m, 2 H), 7.49 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.33–7.43 (m, 3 H), 7.30 (dt, *J* = 1.5, 7.6 Hz, 1 H), 7.20 (dt, *J* = 1.4, 7.5 Hz, 1 H), 7.15 (dd, *J* = 1.4, 7.9 Hz, 1 H), 5.71

(dd, J = 2.9, 11.7 Hz, 1 H), 5.48 (d, J = 5.8 Hz, 1 H), 5.41 (dd, J = 2.9, 5.6 Hz, 1 H), 5.28 (d, J = 11.7 Hz, 1 H). ^{13}C NMR (100 MHz, acetone-d_6): δ = 137.7, 134.5, 133.5, 132.0, 129.9, 129.6, 129.22, 129.19, 125.7, 125.4, 90.1, 70.6, 41.4. HRMS: m/z [M + NH_4]$^+$ calcd for $C_{15}H_{17}N_2O_3S$: 305.0954; found: 305.0957. IR (neat): 3389, 3061, 2925, 2853, 1702, 1644, 1586, 1555, 1520, 1439, 1316, 1036, 762 cm^{-1}. $[\alpha]_D^{25.9}$ +78.9 (c = 0.05, MeOH, 69% ee); enantiomeric excess was determined by HPLC with a Chiralpak AD-H column [hexane:2-propanol (85:15), flow rate: 0.7 mL/min, λ = 254 nm]; t_R (minor enantiomer) = 21.4 min; t_R (major enantiomer) = 14.2 min; 69% ee.