

Asymmetric Catalysis

PyBidine/Copper Catalyst: Asymmetric *exo'*-Selective [3+2] Cycloaddition using Imino Ester and Electrophilic Indole**

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Abstract: Electrophilic indoles having two electron-withdrawing groups undergo nucleophilic attack at C2 and electrophilic functionalization at C3. This is the first enantioselective formal [3+2] cycloaddition using electrophilic indoles. The PyBidine/Cu catalyst smoothly promoted highly enantio- and *exo'*-selective [3+2] cycloaddition using imino esters and 3-nitroindoles. This reaction provides a method for the preparation of diverse and complex chiral pyrroloindoline compounds.

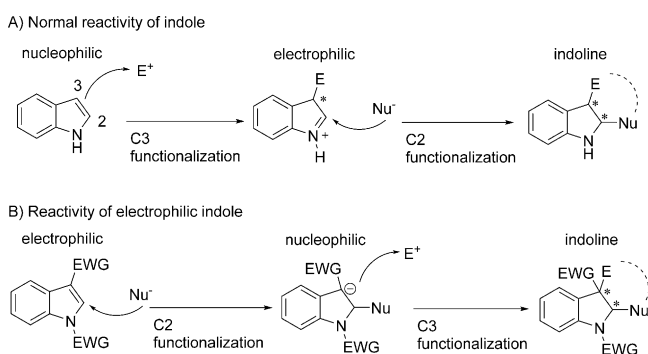
The indole skeleton is found in numerous biologically active compounds and pharmaceutical drugs.^[1] Reactions involving indoles generally occur through nucleophilic attack at the C3-position, such as a Friedel–Crafts reaction.^[2] Nucleophilic reaction at the C3-position acts as a trigger, thus trapping the iminium intermediate, which provides an elegant synthetic route for indoline derivatives (Scheme 1 A).^[3] However, an indole containing two electron-withdrawing groups can

from those indolines made using electron-enriched indoles. An example of a racemic reaction using electrophilic indoles was reported by Gribble and co-workers, who succeeded in synthesizing nonchiral pyrrolo[2,3-b]indole by an unusual Barton–Zard reaction of 3-nitroindoles with isocyanoacetate.^[4a] Mancini et al. applied electrophilic indoles to a Diels–Alder reaction.^[4d,g] Recently, Piettre et al. reported a [3+2] cycloaddition of an azomethine ylide with 3-nitroindoles.^[4m] However, no example of a catalytic asymmetric reaction using electrophilic indoles has been reported.

In a study on catalytic asymmetric [3+2] cycloaddition reactions,^[5] the bis(imidazolidine)pyridine (PyBidine)^[6] and imidazoline aminophenol (IAP) ligands^[7] were developed. The PyBidine/Cu complex catalyzed the *endo*-selective asymmetric [3+2] cycloaddition of nitroalkenes with imino esters.^[6a] An *exo'*-selective enantioselective cyclization also has been achieved using a chiral IAP/Ni catalyst.^[7a,b,8] We present herein a catalytic asymmetric [3+2] cycloaddition between imino esters and electrophilic indoles for diversity-oriented asymmetric catalysis (DOAC).^[9,10] This strategy allows synthesis of pyrrolo[3,4-b]indole derivatives,^[11,12] having a quaternary carbon center, which are structural isomers of cyclotryptamines.^[13]

Initially, the effect of chiral catalysts on the [3+2] cycloaddition using 1-tosyl-3-nitroindole was first investigated (Table 1). The IAP/Ni catalyst gave the desired product with moderate enantioselectivity and lower diastereoselectivity. However, the IAP/Cu catalyst did not promote [3+2] cycloaddition. In contrast, the PyBidine/Cu catalyst smoothly catalyzed the reaction to give high diastereo- and enantioselectivity (entry 3). X-ray crystallographic analysis confirmed that the major isomer was of the *exo'* form (see the Supporting Information).^[14] Some of the chiral ligands examined (entries 4–7)^[15] resulted in reduced catalyst activity, while the binap/Ag catalyst promoted *exo* selectivity. The use of Cs₂CO₃ as the base improved enantioselectivity (entry 9), and the catalyst loading was reduced to 5 mol% to obtain results similar to those shown in entry 3 (entry 10). The highly *exo'*-selective reaction is easily scaled up and maintains the excellent enantioselectivity (entry 11).

After optimization of the reaction conditions, the substrate scope for catalytic asymmetric [3+2] cycloaddition was investigated. Various substituted N-Ts-protected 3-indoles provided products with excellent stereoselectivities (Table 2, entries 1–5). Cycloaddition of the 5-chloro-3-nitroindole compound was conducted at 25 °C in 1,4-dioxane to ensure dissolution of the substrate (entry 2). 6-Methyl- and 7-chloro-3-nitroindoles required a longer reaction time (entries 6 and 7). Another sulfonyl protecting group, such as *p*-nitro- or *p*-methoxybenzenesulfonyl, was also compatible in the PyBi-



Scheme 1. Reactivity of indole substrates.

behave as an electrophilic alkene.^[4] These indoles undergo nucleophilic functionalization at the C2-position and attack electrophiles at the C3-position in an inverse manner (Scheme 1 B). The inverse reaction using electrophilic indoles provides highly functionalized indolines which are different

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[**] This work was supported by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (Japan), and by the Workshop on Chirality at Chiba University (WCCU). PyBidine = bis(imidazolidine)pyridine.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201405223>.

Table 1: Optimization of reaction conditions.

No.	Ligand	Metal salt	<i>t</i> [h]	Yield [%] ^[a]	<i>exo'</i> / <i>exo</i> / <i>endo</i> (or <i>endo'</i>) ^[b]	<i>ee</i> [%] (<i>exo'</i>)
1	IAP	Ni(OAc) ₂	20	61	56:44:n.d.	62
2	IAP	Cu(OTf) ₂	20	trace	—	—
3	PyBidine	Cu(OTf) ₂	20	75	>99:n.d.:n.d.	98
4	Pybim	Cu(OTf) ₂	20	trace	—	—
5	(<i>S,S</i>)- <i>t</i> Bu-box ^[c]	Cu(OTf) ₂	20	54	24:55:21	4
6	(<i>R</i>)-binap	Cu(OTf) ₂	20	99	69:24:7	79
7	(<i>R</i>)-binap	AgClO ₄	5	92	33:49:18	—55
8 ^[d]	PyBidine	Cu(OTf) ₂	8	78	>99:n.d.:n.d.	98.9
9 ^[c,d]	PyBidine	Cu(OTf) ₂	20	97	>99:n.d.:n.d.	99.6
10 ^[c,d,e]	PyBidine	Cu(OTf) ₂	48	91	>99:n.d.:n.d.	98
11 ^[c,f]	PyBidine	Cu(OTf) ₂	20	86	99:n.d.:n.d.	99

[a] Combined yield of diastereomers. [b] Determined by ¹H NMR analysis of crude reaction mixture. [c] Cs₂CO₃ was used instead of NEt₃. [d] Conducted at 10 °C. [e] 5 mol % catalyst and Cs₂CO₃ were used.

[f] 1 mmol scale (427 mg of *exo'*-pyrroloindoline product were obtained). binap = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl, (*S,S*)-*t*Bu-box = 2,2'-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline], Ts = 4-toluenesulfonyl, Tf = trifluoromethanesulfonyl.

dine/Cu-catalyzed reaction. The N-acetylated or alkoxy-carbonylated 3-nitroindoles gave chiral pyrroloindolines with satisfactory selectivity (entries 10–12).

Various imino esters gave products with good diastereoselectivity, and the major products possessed high enantioselectivity (Table 3, entries 1–5). Although the *o*-bromo substituent decreased enantioselectivity, an *o*-methyl group showed high enantiomeric excess (entries 6 and 7). Imino esters with a bicyclic skeleton also were converted into their corresponding *exo'* products (entries 8 and 9).

Chemical transformation of the indoline product is shown in Scheme 2. The nitro functionality on the quaternary carbon center was reduced to the amine **4a** using zinc powder and TMSiCl.^[16] The radical denitration proceeded selectively to produce **5a** in 72 % yield without loss of diastereoselectivity.^[17] Enantiomeric excess was retained in these transformations.

The X-ray crystallographic analysis of **3a** revealed the (*S,S*)-diphenylethylene-diamine-derived PyBidine/Cu(OTf)₂ complex gave the *exo'*-(*R,S,R,R*)-cycloadduct as described in Table 1 (see the Supporting Information). The *exo'*-selective cycloaddition can be explained by a double *anti*-selective

Table 2: Substrate scope of 3-nitroindoles.

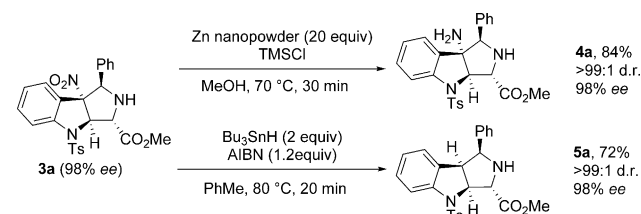
No.	1 (R ¹ , R ²)	<i>t</i> [h]	3	Yield [%] ^[a]	<i>exo'</i> / <i>exo</i> / <i>endo</i> (or <i>endo'</i>) ^[b]	<i>ee</i> [%] (<i>exo'</i>)
1	1b (5-Br, Ts)	48	3b	99	97:3:n.d.	99
2 ^[c]	1c (5-Cl, Ts)	40	3c	78	93:7:n.d.	96
3	1d (5-F, Ts)	19	3d	97	>99:n.d.:n.d.	99
4	1e (5-CN, Ts)	19	3e	99	>99:n.d.:n.d.	99
5	1f (5-BzO, Ts)	21	3f	82	>99:n.d.:n.d.	99
6	1g (6-Me, Ts)	46	3g	93	>99:n.d.:n.d.	99
7	1h (7-Cl, Ts)	48	3h	91	>99:n.d.:n.d.	99
8	1i (H, Nos)	24	3i	82	>99:n.d.:n.d.	99
9	1j (H, Mbs)	22	3j	99	90:10	91
10 ^[c]	1k (H, Ac)	17	3k	98	>99:n.d.:n.d.	98
11	1l (H, CO ₂ Et)	22	3l	94	>99:n.d.:n.d.	97
12 ^[c]	1m (H, Boc)	18	3m	82	>99:n.d.:n.d.	97

[a] Combined yield of diastereomers. [b] Determined by ¹H NMR analysis of the crude reaction mixture. [c] Conducted at 25 °C. Boc = *tert*-butoxycarbonyl, Mbs = *p*-methoxybenzenesulfonyl, Nos = *p*-nitrobenzenesulfonyl.

Table 3: Substrate scope of imino esters.

No.	2 (R ³)	<i>t</i> [h]	3	Yield [%] ^[a]	<i>exo'</i> / <i>exo</i> / <i>endo</i> (or <i>endo'</i>) ^[b]	<i>ee</i> [%] (<i>exo'</i>)
1	2b (4-BrC ₆ H ₄)	20	3n	99	>99:n.d.:n.d.	99
2	2c (4-FC ₆ H ₄)	27	3o	84	>99:n.d.:n.d.	96
3	2d (4-MeC ₆ H ₄)	20	3p	92	>99:n.d.:n.d.	98
4	2e (4-MeOC ₆ H ₄)	26	3q	81	>99:n.d.:n.d.	99
5	2f (3-ClC ₆ H ₄)	24	3r	77	>99:n.d.:n.d.	98
6 ^[c]	2g (2-BrC ₆ H ₄)	24	3s	73	86:14:n.d.	65
7	2h (2-MeC ₆ H ₄)	27	3t	90	95:5:n.d.	96
8	2i (3,4-(OCH ₂ O)-C ₆ H ₃)	24	3u	92	>99:n.d.:n.d.	99
9	2j (1-naphthyl)	30	3v	80	92:8:n.d.	97

[a] Combined yield of diastereomers. [b] Determined by ¹H NMR analysis of the crude reaction mixture. [c] Conducted at 25 °C.


Scheme 2. Transformation of reaction products. AIBN = 2,2'-azobis(2-methylpropanitrile).

Michael/Mannich reaction (see a proposed transition state and the catalytic cycle in the Supporting Information).^[18,19]

Although the PyBidine/Cu catalyst gave the *endo* product in the [3+2] cycloaddition of an imino ester with *trans*- β -nitrostyrene,^[6a] the enantioface selection of the first Michael reaction is the same in both cases.

In summary, the PyBidine/Cu complex catalyzed an enantioselective formal [3+2] cycloaddition using imino esters and 3-nitroindoles. The highly enantiomerically enriched pyrrolindoline compounds were obtained with *exo'* selectivity. This reaction represents the first report of the catalytic asymmetric formal [3+2] cycloaddition using electrophilic indoles. This reaction provides an efficient method for constructing diverse and complex chiral pyrrolindoline compounds. Research into further applications of this enantioselective [3+2] cycloaddition with 3-nitroindoles is in progress.

Experimental Section

Procedure for the catalytic asymmetric [3+2] cycloaddition of imino ester with 3-nitroindoles (entry 11, Table 1): PyBidine (0.110 mmol) and Cu(OTf)₂ (0.100 mmol) were added to a two-necked round-bottomed flask containing a stir bar under Ar. 1,4-Dioxane (5 mL) was added to the flask and the mixture was stirred for 2 h. To the resulting solution, imino ester (1.20 mmol), and Cs₂CO₃ (0.100 mmol) were added subsequently at RT, then 3-nitroindole (1.00 mmol) was added at 25 °C. After being stirred for 20 h, the reaction mixture was quenched by water. The organic layer was extracted with chloroform. The collected organic layer was dried over Na₂SO₄. After removal of the solvent under reduced pressure, the resulting crude reaction mixture was subjected to short column chromatography (Hex/AcOEt = 2:1) to remove decomposed imino esters. Column chromatography (Hex/AcOEt = 5:1) gave the product as white solid (427 mg). The enantiomeric excesses of the products were determined by chiral-phase HPLC using a Daicel Chiralpak IA column. ¹H NMR (500 MHz, CDCl₃): δ = 7.76 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.23–7.18 (m, 6H), 7.04 (d, *J* = 7.4 Hz, 2H), 7.41 (dd, *J* = 7.4, 7.9 Hz, 1H), 6.00 (d, *J* = 7.9 Hz, 1H), 5.68 (s, 1H), 4.91 (s, 1H), 4.57 (s, 1H), 3.93 (s, 3H), 2.73 (br, 1H), 2.32 ppm (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 171.8, 145.0, 143.9, 135.1, 132.6, 131.6, 129.9, 129.0, 128.7, 128.1, 127.9, 127.4, 123.3, 122.8, 114.8, 101.3, 72.7, 69.8, 66.0, 53.1, 21.5 ppm; HRMS calcd for C₂₅H₂₄N₃O₆ [*M*+H]⁺: 494.1380, found: *m/z* 494.1370; Enantiomeric excess was determined by HPLC with a Chiralpak IA column (80:20 hexane:2-propanol, 1.0 mL min⁻¹, 254 nm); minor enantiomer *t*_r = 11.1 min, major enantiomer *t*_r = 21.2 min; [α]_D²⁵ = +100.9 (*c* = 1.0, CHCl₃, 99% *ee*).

Received: May 13, 2014

Revised: June 23, 2014

Published online: July 31, 2014

Keywords: asymmetric catalysis · copper · cycloaddition · heterocycles · synthetic methods

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