Asymmetric Catalysis

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Catalytic Asymmetric Synthesis of 3-Indolyl Methanamines Using Unprotected Indoles and N-Boc Imines under Basic Conditions

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Abstract: *A chiral imidazolidine-containing NCN/Pd-OTf catalyst (**C4**) promoted the nucleophilic addition of unprotected indoles to N-Boc imines. Using sulfinyl amines as the N-Boc imine precursors, the combined use of **C4** with K_2CO_3 activated the NH indoles to give chiral 3-indolyl methanamines with up to 98% ee. Compared with conventional acid-catalyzed Friedel–Crafts reactions, this reaction proceeds under mildly basic conditions and is advantageous for the use of acid-sensitive substrates.*

The chiral 3-indolyl methanamine skeleton occurs widely in biologically active natural products such as strychnine and vindoline-related indole alkaloids (Figure 1).[1] PS121912, which possesses vitamin D receptor (VDR)/coactivator inhibitor activity,[2] and (*R*)-IBR 120, which has RAD51 inhibitory activity,[3] were discovered in a chemical library of small molecules.

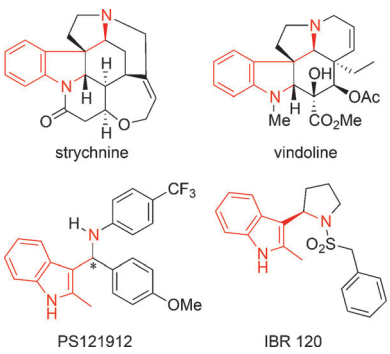

Figure 1. Examples of biologically active 3-indolyl methanamines.

For the catalytic synthesis of chiral 3-indolyl methanamines, asymmetric Friedel–Crafts reaction of indoles with imine substrates is the most direct method.[4] In 1999, Johannsen reported the first catalytic asymmetric Friedel–Crafts reaction of indoles with N-Ts-iminoesters of ethyl glyoxylate using a chiral Cu^I/Tol-BINAP catalyst.[5] Deng and co-workers reported the Friedel–Crafts reaction of indoles with N-Ts imines using a chiral thiourea organocatalyst.[6]

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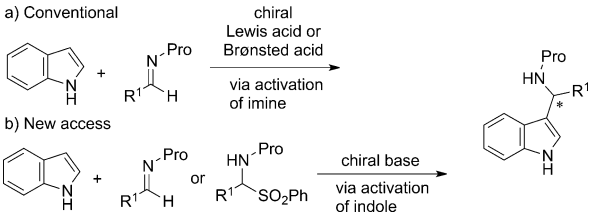
After the report by Terada and co-workers on using a chiral phosphoric acid with N-Boc imines,[7] various imines were examined in the catalytic asymmetric Friedel–Crafts reaction of indoles.[8] In these pioneering works, conventional catalytic asymmetric Friedel–Crafts reactions of indoles with imine substrates were conducted using chiral Lewis acids or Brønsted acids (Scheme 1a). However, acidic conditions are often problematic for the synthesis of complex molecules. The present report describes a new route for chiral 3-indolyl methanamines using unprotected indoles and N-Boc imines under basic conditions.[9]

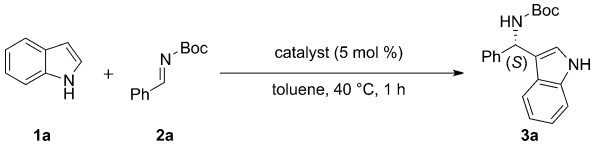


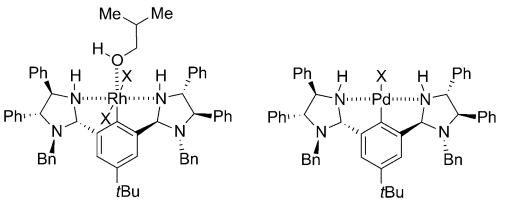
Scheme 1. a) Conventional acid-catalyzed Friedel–Crafts reaction. b) New base-promoted access.

For catalytic asymmetric reactions under mild reaction conditions, we developed a series of imidazolidine-containing NCN-pincer metal complexes.[10,11] In particular, the NCN/Rh-OAc complex **C2** (see Table 1) is an efficient basic catalyst for the Mannich reaction of malononitrile nucleophiles with N-Boc imines.[10b] Our initial study was focused on the development of the most efficient catalyst for the reaction of indole (**1a**) with the N-Boc imine **2a** (Table 1). The use of imidazolidine-containing NCN-metal catalysts (**C1**–**C4**) resulted in low asymmetric induction (entries 1–3, and 5). In the presence of 1 equivalent K_2CO_3, **C1** and **C2** did not exhibit significant catalytic effects, while **C3** and **C4** gave **3a** with 76 and 57% *ee*, respectively (entries 4 and 6). In all cases, the chemical yield of **3a** was moderate because of the hydrolysis of **2a**.

Preliminary success for asymmetric catalysis of unprotected indole with N-Boc imine under mild basic conditions prompted the use of a sulfinyl amine as an imine precursor.[12] The optimal reaction conditions for the reaction of **1a** with the sulfinyl amine **4a** were explored (Table 2). By using 1–3 equivalents of K_2CO_3, reactions with **C3** and **C4** proceeded, but inconsistent *ee* values were recorded for **3a** (entries 1 and 2). After increasing the amount of K_2CO_3 to 6 equivalents, 5 mol% **C4** gave **3a** in 95% yield and 95% *ee* with good reproducibility, and the use of **C3** gave **3a** in 85% yield and

Table 1: Catalyst screening for reaction of indole **1a** with the N-Boc imine **2a**.





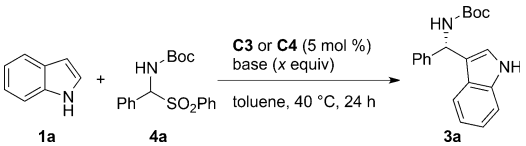
X = Cl: **C1**
X = OAc: **C2**

X = Cl: **C3**
X = OTf: **C4**

Entry	Catalyst	Yield [%][a]	*ee* [%][b]
1	**C1**	42	14 (*S*)
2	**C2**	32	*rac*
3	**C3**	59	18 (*S*)
4[c]	**C3**	41	76 (*S*)
5	**C4**	72	4 (*R*)
6[c]	**C4**	70	57 (*S*)

[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Using 1 equiv K_2CO_3. Boc = *tert*-butoxycarbonyl, Tf = trifluoromethanesulfonyl.

Table 2: Optimized reaction conditions for reaction of **1a** with the sulfinyl amine **4a**.



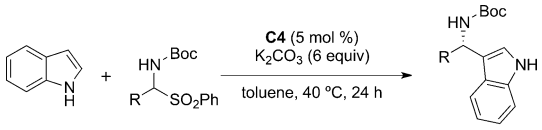
Entry	Catalyst	Base (equiv)	Yield [%][a]	*ee* [%][b]
1	**C3**	K_2CO_3 (1-3 equiv)	ca.50	65–80
2	**C4**	K_2CO_3 (1-3 equiv)	60–80	40–90
3	**C3**	K_2CO_3 (6 equiv)	85	94
4	**C4**	K_2CO_3 (6 equiv)	95	95
5	**C4**	K_2CO_3 (9 equiv)	97	94
6	**C4**	Na_2CO_3 (6 equiv)	33	4
7	**C4**	Cs_2CO_3 (6 equiv)	22	94
8	**C4**	Et_3N (6 equiv)	24	6

[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase.

94% *ee* under similar reaction conditions (entries 3 and 4). Among the bases tested, K_2CO_3 was the most effective for enhancing the activity of **C4** to provide **3a** with high *ee* values (see the Supporting Information).

Under the optimized reaction conditions, the substrate scope of sulfinyl amines was examined (Table 3). For substituted benzaldehyde-derived sulfinyl amines, both electron-donating and electron-withdrawing groups at the *ortho*, *meta*, and *para* positions on the benzene ring were used successfully to give adducts ranging from 92 to 95% *ee* (**3b–f**), although the *ortho*-fluoro adduct **3g** was obtained with 70% *ee*. 2-Naphthyl- and 1-naphthylaldehyde-derived N-Boc imines

Table 3: Substrate scope with respect to the sulfinyl amine **4**.



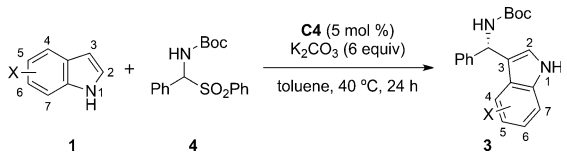
Entry	R	Yield [%][a]	*ee* [%][b]
1	4-MeC_6H_4 (**3b**)	99	95
2	3-MeC_6H_4 (**3c**)	90	94
3	2-MeC_6H_4 (**3d**)	90	92
4	4-FC_6H_4 (**3e**)	82	93
5	3-FC_6H_4 (**3f**)	92	94
6	2-FC_6H_4 (**3g**)	92	70
7	4-ClC_6H_4 (**3h**)	88	94
8	2-naphthyl (**3i**)	83	96
9	1-naphthyl (**3j**)	99	89
10[c]	cyclohexyl (**3k**)	94	97

[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Using isolated N-Boc imine (2 equiv) with 50 mg molecular sieves (4Å) for 1.0 mL of toluene.

were used to give the 3-indolyl methanamines **3i** and **3j**, respectively, with reasonably high enantiomeric excesses. Remarkable results were obtained using aliphatic imines. Although the sulfinyl amine did not promote the reaction, use of the isolated imine gave **3k** in 94% yield with 97% *ee* under similar basic conditions.

The applicability of the substituted indoles was also examined (Table 4). NH indoles (**3m–o**) containing a methyl substituent on the benzene ring were obtained in over 91% *ee*, although the 7-methyl indole showed less reactivity and gave **3p** with 86% *ee*. The reaction using 2-methyl indole resulted in **3l** with 77% *ee*. Electron-withdrawing groups at the 5-position of indole tended to produce greater enantiomeric excesses of up to 98% for **3s**, although an electron-

Table 4: Substrate scope with respect to the indole **1**.

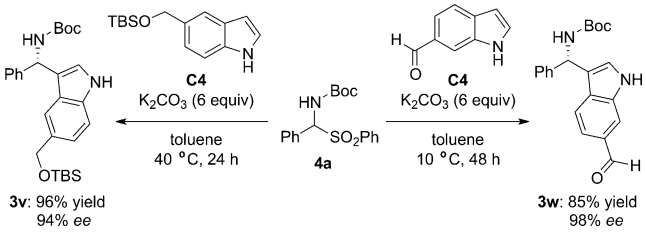


Entry	X	Yield [%][a]	*ee* [%][b]
1	2-Me (**3l**)	86	77
2	4-Me (**3m**)	86	92
3	5-Me (**3n**)	99	91
4	6-Me (**3o**)	96	94
5	7-Me (**3p**)	46	86
6	5-F (**3q**)	99	96
7	5-Cl (**3r**)	99	97
8	5-Br (**3s**)	98	98
9	5-MeO (**3t**)	99	91
10	1-Me (**3u**)	< 16	*rac*

[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase.

donating group was also tolerated to give **3t** with 91% *ee*. The N-methyl indole resulted in the formation of racemic **3u**.

The synthetic advantages of the reaction under basic conditions are shown in Scheme 2. The TBS-protected 5-hydroxymethylindole was smoothly transformed into **3v** with 94% *ee* while retaining the silyl protecting group. The 6-formyl indole was converted directly into **3w** with 98% *ee*. These transformations are difficult to perform under conventional Friedel–Crafts reaction conditions using Brønsted acids or Lewis acids.



3v: 96% yield
94% *ee*

3w: 85% yield
98% *ee*

Scheme 2. Catalytic asymmetric reaction of N-Boc imines with unprotected indoles containing acid-sensitive functionality. TBS = *tert*-butyldimethylsilyl.

The interaction of **C4** with substrates was examined to investigate the reaction mechanism. Although simple mixing **C4** with indole, or **C4** with K_2CO_3, did not produce any obvious changes in the ^{1}H NMR spectra (Figure 2b), addition of K_2CO_3 to the mixture resulted in the disappearance of the NH proton of the indole at $\delta = 11.0$ ppm, and a change in the chemical shifts of the imidazolidine ring of **C4** (Figure 2c). The interaction between **C4** with N-Boc imine was not supported by similar ^{1}H NMR experiments.

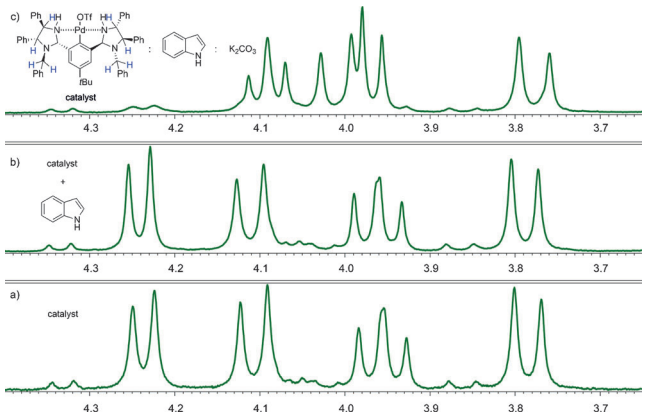


Figure 2. ^{1}H NMR spectra (in [D$_6$]DMSO) of a) **C4**, b) indole + **C4** (1:1), and c) indole + **C4** + K_2CO_3 (1:1:120). See details of the preparation of NMR samples in the Supporting Information. DMSO = dimethylsulfoxide.

Using the (*R*,*R*)-diphenylethylenediamine-derived **C4**, the *S*-enriched product was obtained, and confirmed by X-ray crystallographic analysis of **3s** (Figure 3).

A plausible reaction mechanism is depicted in Scheme 3. The NH indole is activated by **C4** with the assistance of K_2CO_3. The formation of the intermediate **A** is supported by

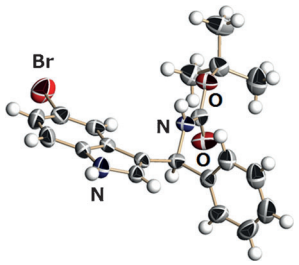


Figure 3. X-ray crystallographic analysis of (*S*)-**3s**.[14]

the non-acceleration by **C4** to give racemic **3u**, and by the reduction in enantioselectivity when 2- and 7-substituted indoles were used. ESI-MS analysis on the mixture of **C4** and 5-bromoindole with K_2CO_3 gave a new ion peak at $m/z = 1056.2861$, thus corresponding to [**C4** + 5-bromoindole − TfOH − H^+]$^-$. Along with the generation of **A**, additional K_2CO_3 generates the N-Boc imine from the sulfinyl amine substrate. The electron-deficient substituents on the indole promote smooth and strong interactions with **C4** to produce adducts with excellent enantiomeric excesses. To elicit details of the role of the catalyst, a commercially available (*S*,*S*)-diphenylethylenediamine-derived imidazoline-containing NCN-Pd catalyst (**C5**) was examined as shown in Scheme 4.[13]

Although the reaction was smoothly promoted by **C5** under similar basic conditions, surprisingly, **3a** was obtained in *S*-enriched form, which was the same stereoisomer obtained using **C4**. The different sense of asymmetric induction between **C4** and **C5** is attributed to the hydrogen bonding of the NH proton of the imidazolidine ligand in **C4**. The working model provided within brackets in Scheme 3 agrees with formation of the *S*-enriched 3-indolyl methanamine, in which a weak interaction between palladium and N-Boc imine might contribute to stabilize the transition state.[10,13]

In conclusion, the chiral imidazolidine-containing NCN/Pd-OTf catalyst **C4** promoted the nucleophilic addition of unprotected indoles to N-Boc imines in a highly enantioselective manner. The use of **C4** in basic media has advantages for transformations of acid-sensitive substrates. Further studies on catalyst development and application to the total synthesis of complex molecules are underway.

Acknowledgments

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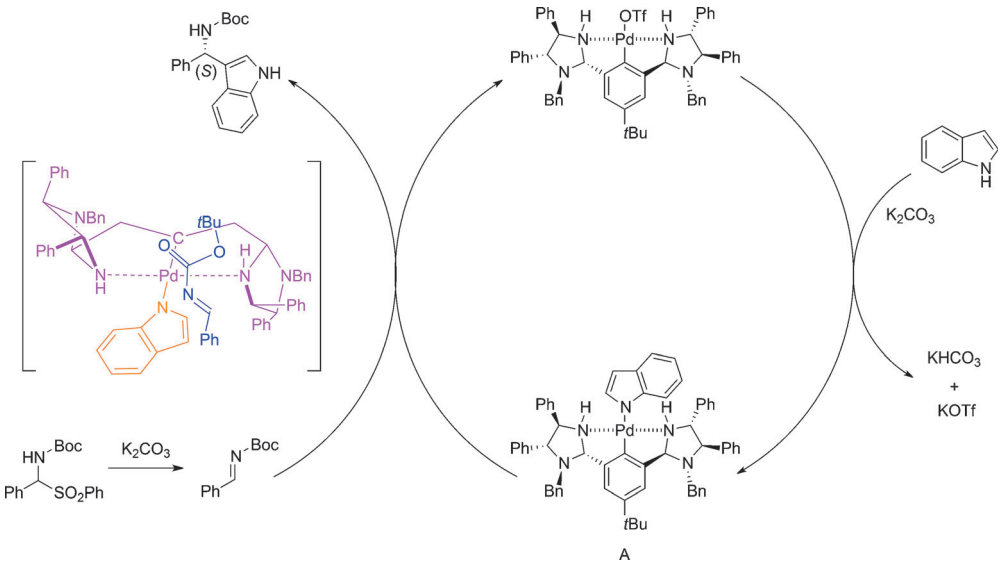
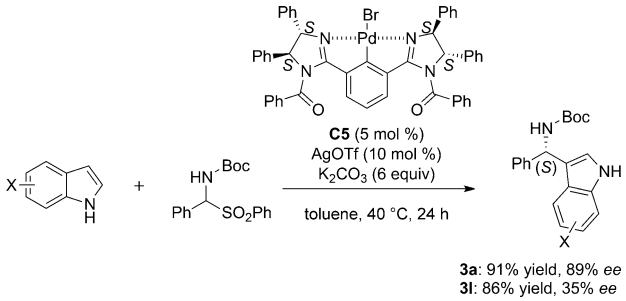
Keywords: asymmetric catalysis · imines · indole · ligands · palladium



Scheme 3. Plausible mechanism for the reaction of N-Boc imine with unprotected indole.



Scheme 4. (*S*,*S*)-Diphenylethylenediamine-derived imidazoline-containing NCN-Pd (**C5**) catalyzed reaction.

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[14] CCDC 1496464 [(*S*)-**3s**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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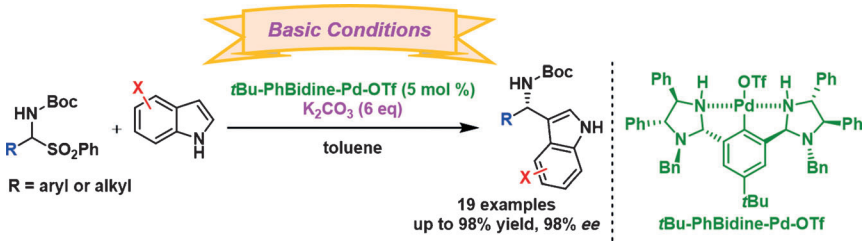
Communications

Asymmetric Catalysis

T. Arai,* J. Kakino _____ ▮▮▮▮–▮▮▮▮

Catalytic Asymmetric Synthesis of 3-Indolyl Methanamines Using Unprotected Indoles and N-Boc Imines under Basic Conditions



Basic still active: A chiral imidazolidine-containing NCN/Pd-OTf catalyst promoted the title reaction. By using sulfinyl amines as the N-Boc imine precursors, the combined use of the catalyst with K_2CO_3 activated the NH indoles to give chiral 3-indolyl methanamines with up to 98% *ee*. Compared with conventional acid-catalyzed Friedel–Crafts reactions, this reaction proceeds under mildly basic conditions and is advantageous for the use of acid-sensitive substrates.

