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Catalytic Enantioselective Synthesis of Atropisomeric Indoles with an N–C Chiral Axis

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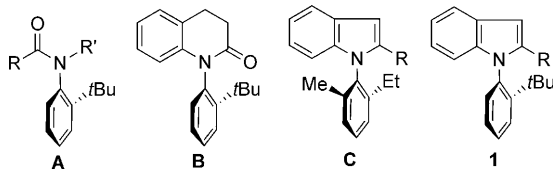
Atropisomeric compounds, owing to rotation restriction around an N–C bond, have received much attention recently as novel chiral molecules.[1] *ortho-tert*-Butylanilide derivatives are typical examples of such atropisomeric compounds.[2] In 2005, we succeeded in the highly enantioselective synthesis of atropisomeric *ortho-tert*-butylanilides **A** and *N*-(*ortho-tert*-butylphenyl)lactams **B** through chiral, Pd-catalyzed, inter- and intramolecular N-arylation of achiral NH-anilides.[3] These reactions were the first practical, catalytic, asymmetric synthesis of compounds with N–C axial chirality.[4]

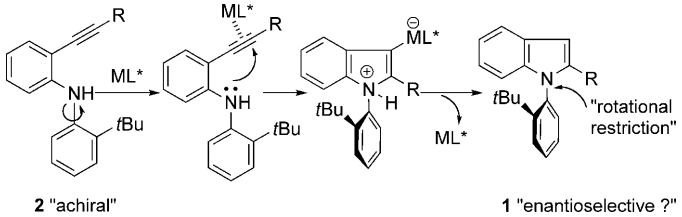


After the publication of that work,[3a] catalytic, asymmetric syntheses of similar compounds with N–C axial chirality were reported by several other groups, all of which are of amide-type compounds, such as anilides, imides, and ureas.[5] On the other hand, the catalytic, asymmetric synthesis of non-amide compounds with N–C axial chirality has not been reported so far.

Several N–C axially chiral compounds with non-amide skeletons have also been found.[1a,6] For example, Uemura and Kamikawa recently reported that indole derivatives possessing a 2,6-disubstituted phenyl group on the nitrogen atom (**C**) have a high rotational energy barrier around the N–Ar bond; however, in their synthesis of the optically active form, a stoichiometric chiral source is required.[6c] We predicted that similar to indoles **C**, *N*-(*ortho-tert*-butylphenyl)-indoles **1**, also have stable atropisomeric structures.

In this paper, we report the catalytic, enantioselective synthesis of axially chiral indoles **1** (non-amide compounds with N–C axial chirality) through the chiral, Pd^{II}-catalyzed, 5-*endo*-hydroaminocyclization of *ortho*-alkynylanilines. Furthermore, the stereochemical assignment of the axial chirality in indole products **1** is described.

For a catalytic, asymmetric synthetic method for atropisomeric *N*-(*ortho-tert*-butylphenyl)indole derivative **1**, we chose 5-*endo*-hydroaminocyclization of *ortho*-alkynylanilines. This reaction, which proceeds in the presence of a transition-metal catalyst or basic reagent, has been investigated by many groups as an efficient synthetic method of creating an indole skeleton,[7] but, to the best of our knowledge, its application to an asymmetric reaction has not been reported to date. We expected that optically active atropisomeric indoles **1** could be obtained through chiral, transition-metal-catalyzed (ML*) 5-*endo*-hydroaminocycliztion of achiral *N*-(*ortho-tert*-butylphenyl)-2-alkynylanilines **2** (Scheme 1).



Scheme 1. Catalytic enantioselective synthesis of atropisomeric indoles.

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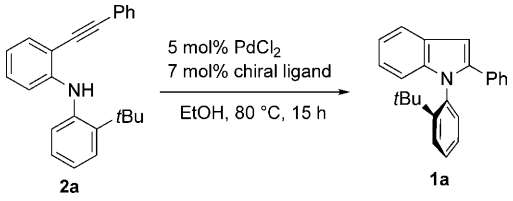
Before the asymmetric reaction was attempted, the optimization of the reaction conditions (transition metal and solvent) was investigated by using *N*-(*ortho-tert*-butylphenyl)-2-(phenylethynyl)aniline (**2a**) as the substrate. It was found that when the reaction was performed in EtOH, in the presence of $PdCl_2$ (5 mol%), for 4 h, at 80°C the 5-*endo*-cyclization product, **1a**, was obtained in excellent yield (99%).

Subsequently, under these optimized conditions, a survey of various chiral ligands was performed (Table 1). The best result was obtained by the use of (*R*)-SEGPHOS as the ligand.[8] In this case, atropisomeric indole **1a**, containing a chiral N–C axis, was obtained in 60% *ee* (Table 1, entry 10). In general, the reaction in the presence of a chiral ligand required a longer reaction time in comparison with that of the ligand-free reaction.

Table 1. Survey of chiral ligands for the catalytic, enantioselective 5-*exo*-aminocyclization of **2a**.



2a **1a**

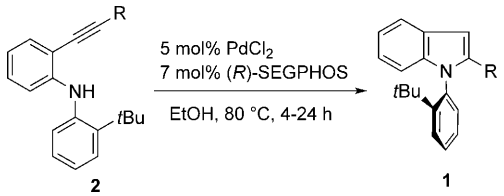
Entry	Ligand[a]	Yield [%][b]	*ee* [%][c]
1	(*R*)-BINAP	82	0
2	(*R*)-MOP	69	2
3	(*S*,*S*)-Trost ligand	trace	–
4	(*R*)-(*S*)-BPPFA	14	3
5	(*R*)-DTBM-SEGPHOS	8	0
6	P,N-ligand	trace	–
7	(*R*,*R*)-*t*Bu-BOX	85	11
8	(*R*)-DIFLUOROPHOS	89	26
9	(*R*)-SYNPHOS	99	55
10	(*R*)-SEGPHOS	93	60

[a] BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; (*R*)-MOP = (*R*)-2-(diarylphosphino)-1,1′-binaphthalene; (*S*,*S*)-Trost Ligand = 2-diphenylphosphanyl-*N*-[(*1S,2S*)-2-[(2-diphenylphosphanylbenzoyl)amino]cyclohexyl]benzamide; (*R*)-(*S*)-BPPFA = (R)-*N*,*N*-dimethyl-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine; (*R*)-DTBM-SEGPHOS = (*R*)-(−)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole; P,N-ligand = (*S*)-(−)-2-[2-(diphenylphosphino)phenyl]-4-(1-methylethyl)-4,5-dihydrooxazole; (*R*,*R*)-*t*Bu-BOX = (*R*,*R*)-2,2′-methylenebis(4-*tert*-butyl-2-oxazoline); (*R*)-DIFLUOROPHOS = (*R*)-(−)-5,5′-bis(diphenylphosphino)-2,2,2′,2′-tetrafluoro-4,4′-bi-1,3-benzodioxole; (*R*)-SYNPHOS = [(5,6),(5′,6′)-bis(ethylenedioxy)biphenyl-2,2′-diyl]bis(diphenylphosphine); SEGPHOS = 5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole. [b] Isolated yield. [c] The *ee* was determined by HPLC analysis using a chiral column.

The chiral axis of indole **1a** was confirmed to have a high rotational-energy barrier. That is, even when the isolated **1a** was heated in EtOH for 24 h at 80°C, no appreciable change in the *ee* was detected.[9] Thus, it is evident that the racemization of indole product **1a** does not occur under the reaction conditions.

The reactions of various *ortho*-alkynylanilines (**2b**–**2i**) were then investigated in the presence of the (*R*)-SEGPHOS–$PdCl_2$ catalyst (Table 2). In contrast to **2a**, the reaction of **2b**, which has an aliphatic substituent, in this case an *n*Bu group, barely proceeded under the optimized conditions. In the reaction of such less reactive substrates the addition of AgOTf (5 mol%), which leads to the generation of a more reactive cationic-Pd species, was effective. In this case, indole product **1b** was obtained in a good yield (84%), although a decrease in the enantioselectivity was observed in comparison with that of phenyl derivative **2a** (35% *ee*, Table 2, entries 1 and 2). The reaction of *para*-methylphenyl derivative **2c** also resulted in a decrease in the enantioselectivity (49% *ee*, Table 2, entries 1 and 3). On the other hand, with *ortho*-methylphenyl derivative **2d**, a slight increase in the enantioselectivity was observed (67% *ee*, Table 2, entries 1 and 4). These results may indicate that the presence of an *ortho*-substituent is important for improving the enantioselectivity.

Table 2. Catalytic enantioselective 5-*exo*-aminocyclization with various *ortho*-alkynylanilines **2**.



2 **1**

Entry	**2**	R	Time [h]	**1**	Yield [%][a]	*ee* [%][b]
1	**2a**	C_6H_5	4	**1a**	93	60
2[c]	**2b**	nC_4H_9	24	**1b**	84	35
3	**2c**	4-MeC_6H_4	7	**1c**	89	49
4	**2d**	2-MeC_6H_4	9	**1d**	95	67
5	**2e**	2-$MOMOCH_2C_6H_4$[d]	7	**1e**	71	77
6	**2f**	2-$iPrC_6H_4$	12	**1f**	90	80
7[c]	**2g**	2-$NO_2C_6H_4$	24	**1g**	67	82
8	**2h**	2-ClC_6H_4	13	**1h**	85	83
9	**2i**	2-BrC_6H_4	23	**1i**	90	83

[a] Isolated yield. [b] The *ee* was determined by HPLC analysis using a chiral column. [c] 5 mol% of Ag(OTf) was added. [d] MOMO = methoxymethoxy.

Subsequently, the reactions with substrates **2e**–**2i,** containing various *ortho*-substituents were examined (Table 1, entries 5–9). The bulkier *ortho*-substituents were found to bring about a further increase in the enantioselectivity. For example, the reactions of *ortho*-methoxymethoxymethyl derivative **2e** and *ortho*-isopropyl derivative **2f** gave the indole products **1e** and **1f** in 77 and 80% *ee*, respectively (Table 2, entries 5 and 6). In the reactions of **2g**, **2h**, and **2i**, containing either a nitro group or a halogen atom as the *ortho*-substituent, the best enantioselectivities were observed (82–83% *ee*, Table 2, entries 7–9). For the less reactive *ortho*-nitro derivative **2g**, the addition of AgOTf was required to obtain **1g** in a good yield.

The increase in the enantioselectivity caused by *ortho*-substitution may be due to the dynamic axial chirality generated around the $C_{alkynyl}$–C_{phenyl} bond (Figure 1). That is, in the present reaction, the construction of the N–C axial chirality occurs in the N–C bond-forming step; direct enantio-

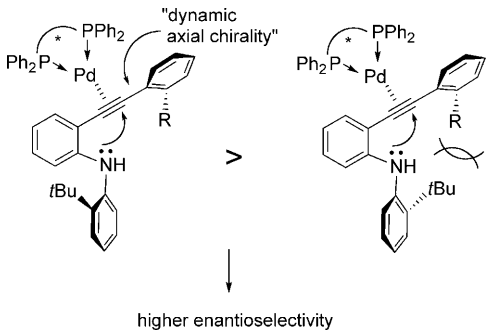
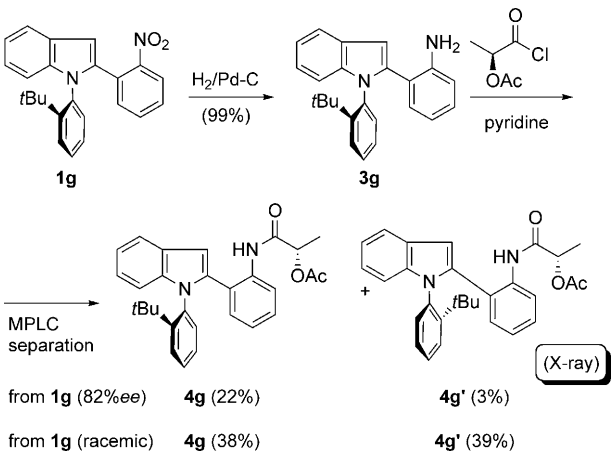


Figure 1. Possible mechanism for the increase in the enantioselectivity caused by the *ortho*-substituent.

control by the chiral ligand on the Pd atom would be difficult, because the chiral ligand is relatively far way from the N–C axis being constructed. In the reaction of substrates containing a bulky *ortho* substituent, chiral information from (*R*)-SEGPHOS may be effectively transferred to the N–C bond through the axially chiral $C_{alkynyl}$–C_{phenyl} bond (dynamic axial chirality).

The absolute configuration of the enantiomers in atropisomeric indole product **1g** (82% *ee*) were determined in accordance with Scheme 2; reduction of the nitro group and



Scheme 2. Stereochemical assignment of the major enantiomer in **1g**.

subsequent condensation with (*S*)-acetoxypropionyl chloride gave diastereomeric amides **4g** and **4g′**. By MPLC separation of **4g** and **4g′**, followed by X-ray crystallographic analysis of the minor diastereomer (**4g′**) (Figure 2),[10] the major enantiomer in **1g** was determined to be the *S* configuration. The major enantiomer in *ortho*-bromo derivative **1h** was also confirmed to be the *S* configuration on the basis of correlation with benzylamino phenyl derivative **5**, which can be formed from both **1h** (84% *ee*) and **1g** (82% *ee*) in accordance with Scheme 3.

In conclusion, we succeeded in the enantioselective synthesis of atropisomeric indole derivatives with an N–C chiral axis through the (*R*)-SEGPHOS–$PdCl_2$-catalyzed 5-

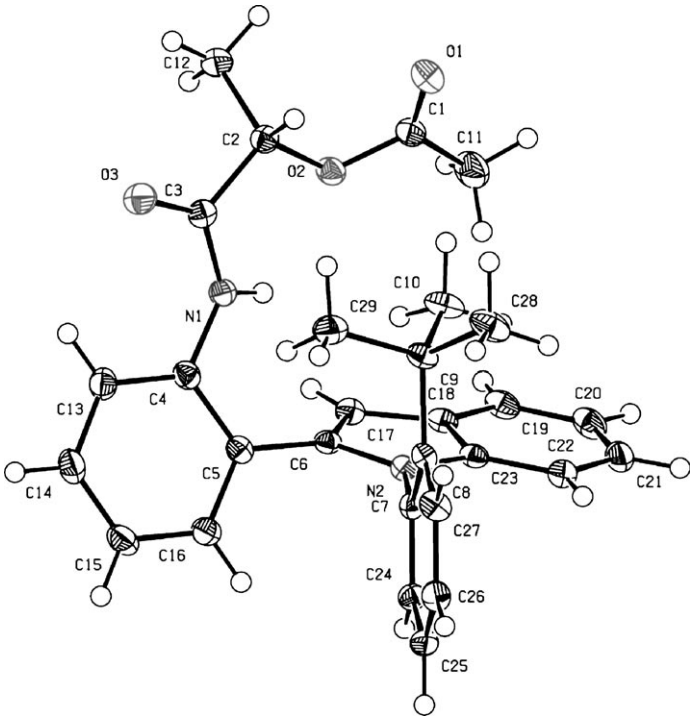
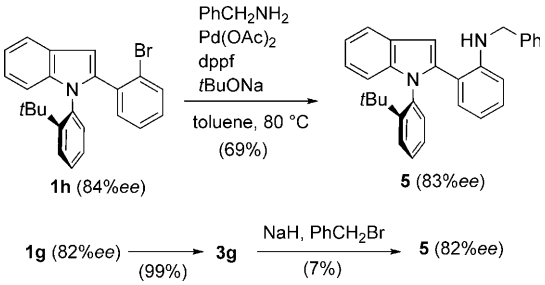


Figure 2. X-ray crystal structure of **4g′**.



Scheme 3. Stereochemical assignment of the major enantiomer in **1h**; dppf = 1,1′-bis(diphenylphosphanyl)ferrocene.

endo-hydroaminocyclization of achiral *ortho*-alkynylanilines (up to 83% *ee*). The present reaction is the first asymmetric version of indole synthesis through 5-*endo*-hydroaminocyclization of *ortho*-alkynylanilines, as well as the first example of the catalytic, enantioselective synthesis of non-amide N–C axially chiral compounds.

Experimental Section

***N*-(*ortho-tert*-Butylphenyl)-2-(2-nitrophenyl)-1*H*-indole (1g)**: A solution of $PdCl_2$ (6.8 mg, 0.038 mmol) and (*R*)-SEGPHOS (32.8 mg, 0.054 mmol) in EtOH (2.5 mL) was stirred for 10 min at RT and then AgOTf (10.0 mg, 0.038 mmol) was added to the reaction mixture. After being stirred for a further 10 min at 80 °C, **2g** (285 mg, 0.77 mmol) in EtOH (5.0 mL) was added and the mixture was stirred for 24 h at 80 °C. The solvent was evaporated to dryness. Purification by column chromatography (hexane/AcOEt = 50:1) and subsequent MPLC (hexane/AcOEt = 150:1) gave **1g** (192 mg, 67%). The *ee* (82%) of **1g** was determined by HPLC

analysis using a CHIRALCEL OD-3 column [25 cm x 0.46 cm i.d.; 1.0% *i*PrOH in hexane; flow rate: 1.5 mL min^{-1}; (+)-**1g** (major); t_R = 6.1 min, (−)-**1g** (minor); t_R = 6.9 min]. **1g**: pale yellow solid; m.p. 103–104 °C; $[\alpha]_D^{25}$ = +107.7 (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.54–7.50 (m, 2H), 7.39 (dd, J = 1.2, 8.2 Hz, 1H), 7.27–7.17(m, 4H), 7.09–6.98 (m, 4H), 6.74 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 0.6 Hz, 1H), 0.81 ppm (s, 9H,); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 150.1, 148.5, 140.9, 135.7, 133.8, 132.7, 132.6, 131.4, 130.0, 128.9, 128.6, 127.5, 126.94, 126.90, 124.0, 122.9, 120.8, 120.3, 111.6, 104.7, 36.0, 31.5 ppm; IR (KBr): $\tilde{\nu}$ = 3057 cm^{-1}; MS: m/z: 371 $[M+H]^+$; HRMS: m/z calcd for $C_{24}H_{23}N_2O_2$: 371.1760 $[M+H]^+$; found: 371.1744.

***N*-(*ortho-tert*-Butylphenyl)-2-(2-bromophenyl)-1*H*-indole (1i)**: A solution of $PdCl_2$ (2.7 mg, 0.015 mmol) and (*R*)-SEGPHOS (12.8 mg, 0.021 mmol) in EtOH (2 mL) was stirred for 5 min at RT and then **2i** (121 mg, 0.30 mmol) in EtOH (2 mL) was added to the reaction mixture. After being stirred for 23 h at 80 °C, the EtOH was evaporated to dryness. Purification by column chromatography (hexane only) and subsequent MPLC (hexane/AcOEt = 100:1) gave **1i** (109 mg, 90%). The *ee* (83%) of **1i** was determined by HPLC analysis using a CHIRALCEL OD-3 column [25 cm x 0.46 cm i.d.; hexane only; flow rate: 1.5 mL min^{-1}; (+)-**1i** (minor); t_R = 11.8 min, (−)-**1i** (major); t_R = 18.1 min]. **1i**: pale yellow solid; m.p. 51–52 °C; $[\alpha]_D^{25}$ = −75.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.76–7.72 (m, 1H), 7.69–7.65 (m, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.41–7.35 (m, 1H), 7.27–7.24 (m, 2H), 7.23–7.18 (m, 3H), 7.10–7.04 (m, 2H), 6.99 (t, J = 0.8 Hz, 1H), 6.94–6.90 (m, 1H), 1.04 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 148.7, 140.2, 138.7, 134.8, 133.6, 133.3, 133.1, 132.0, 129.9, 128.9, 128.7, 127.0, 126.32, 126.31, 124.8, 122.4, 120.6, 120.1, 111.7, 106.2, 36.1, 31.5 ppm; IR (KBr): $\tilde{\nu}$ = 3059 cm^{-1}; MS: m/z: 404 $[M+H, {}^{79}Br]^+$, 406 $[M+H, {}^{81}Br]^+$; elemental analysis calcd (%) for $C_{24}H_{22}NBr$: C 71.29, H 5.48, N 3.46; found: C 71.27, H 5.48, N 3.49.

Acknowledgements

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Keywords: atropisomerism · enantioselectivity · indoles · palladium · phosphane ligands

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[9] A high rotational barrier around the N–C chiral axis of the atropisomeric indole was also confirmed by using **1g** (83% *ee*). That is, no appreciable change in the *ee* was detected even after heating **1g** in EtOH for 24 h, at 80 °C.

[10] CCDC-763524 (**4g′**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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