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Stereoselective Synthesis of Axially Chiral N–C Bonds in *N*-Aryl Indoles

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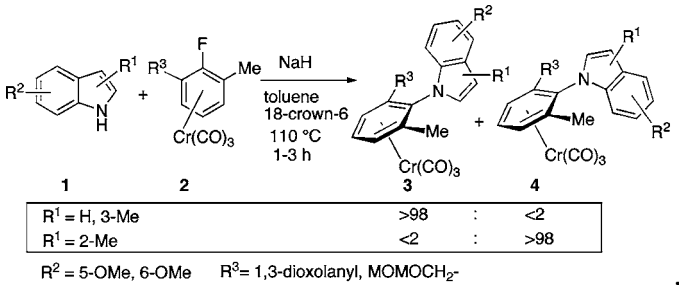
ABSTRACT



***N*-Aryl indoles with axially chiral N–C bonds were synthesized by stereoselective nucleophilic aromatic substitution reactions of planar chiral arene chromium complexes. Stereoselective chromium tricarbonyl migration was achieved in the sterically hindered *N*-aryl indole chromium complex by refluxing in toluene.**

o-Substituted anilides, *N*-aryl indoles, carbazoles, and related compounds possessing the chiral N−C bond have received much attention as novel atropisomeric compounds. As these axially chiral compounds are expected to be useful for asymmetric reactions and as molecular devices, their stereoselective syntheses have been the focus of recent studies.[1] The asymmetric synthesis of axially chiral anilides has been reported by several groups. Simpkins[2] and our group[3] reported the asymmetric desymmetrization of the ortho substituents in prochiral anilides with a stoichiometric amount of a chiral base. Recently, Taguchi[4] and Curran[5] developed the catalytic asymmetric synthesis of atropisomeric anilides by N-arylation or allylation reactions. On the other hand, the asymmetric synthesis of *N*-arylamines, including *N*-aryl indoles and carbazoles with axial chirality, has not been reported so far, although they have been receiving increasing attention for use as chiral ligands[6] and in such natural products as murrastifoline-F.[7] There is also no report on the stereoselective N−C bond formation of these axially chiral species. Recently, the palladium-catalyzed reaction involving N−C(aryl) bond formation has been actively studied and widely recognized as a useful method.[8] Another promising approach for the formation of N−C bonds is the aromatic nucleophilic substitution reaction of activated arenes;[9] however, this stereoselective reaction has not been successfully

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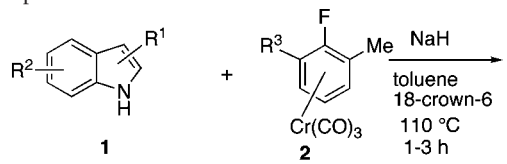
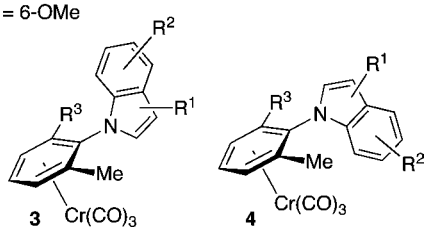
Table 1. Stereoselective Nucleophilic Substitution Reaction for the Synthesis of Axially Chiral *N*-Aryl Indole Chromium Complexes



1a: R^1 = H, R^2 = H
1b: R^1 = 2-Me, R^2 = H
1c: R^1 = 2-Me, R^2 = 5-OMe
1d: R^1 = 3-Me, R^2 = H
1e: R^1 = H, R^2 = 5-OMe
1f: R^1 = H, R^2 = 6-OMe

2a: R^3 = 1,3-dioxolanyl
2b: R^3 = $MOMOCH_2$-



entry	indole	complex	product	yield (%) **3** or **4**	ratio **3**:**4**
1	**1a**	**2a**	**3aa**	76	>98:<2
2	**1a**	**2b**	**3ab**	76	>98:<2
3	**1b**	**2a**	**4ba**	50	<2:>98
4	**1c**	**2a**	**4ca**	83	<2:>98
5	**1d**	**2a**	**3da**	77	>98:<2
6	**1e**	**2a**	**3ea**	70	>98:<2
7	**1f**	**2a**	**3fa**	86	>98:<2
8	**1f**	**2b**	**3fb**	65	>98:<2

carried out so far. Maiorana et al. reported the N-arylation of indoles by the nucleophilic substitution of haloarene chromium complexes to form the N−C(aryl) bond.[10] However, the synthesis of *N*-aryl indoles with an axially chiral N−C(aryl) bond could not be achieved because of steric hindrance. On the other hand, we have already reported the stereoselective synthesis of axially chiral biaryls by nucleophilic substitution reactions to planar chiral arene chromium complexes.[11] On the basis of these experiences, we have succeeded in the stereoselective synthesis of *N*-aryl indoles by the nucleophilic substitution reaction of haloarene chromium complexes. Herein, we report the details of the reactions.

The nucleophilic substitution reaction of a variety of indoles with planar chiral arene chromium complexes was examined, and the results are summarized in Table 1. Initially, we examined the nucleophilic substitution reaction

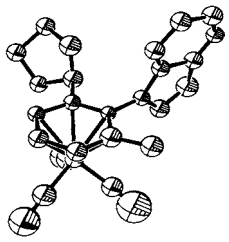


Figure 1. X-ray structure of complex **3aa**.

of an indolyl anion derived from indole (**1a**) with sodium hydride and optically active (+)-tricarbonyl{2-(1,3-dioxolanyl)-6-methyl-1-fluorobenzene} chromium (**2a**) ($[\alpha]^{22}_D$ +24 (*c* 0.03, $CHCl_3$)) in the presence of 18-crown-6 in toluene solution at 110 °C. The reaction proceeded smoothly to give *N*-aryl indole chromium complex **3aa** ($[\alpha]^{21}_D$ +68 (*c* 0.04, $CHCl_3$)) as a single diastereomer in 76% yield (entry 1). The stereochemistry of **3aa** was confirmed by X-ray analysis to have the anti configuration; i.e., the chromium tricarbonyl group and the benzene ring of the indole are in opposite directions with respect to the N−C bond (Figure 1). When chromium complex **2b** was used, *N*-aryl indole chromium complex **3ab** was obtained as a single diastereomer in a manner similar to that above (entry 2). Next, we examined the nucleophilic substitution reaction utilizing 2-methyl indole as the nucleophile (entry 3). Although it is a sterically hindered nucleophile, the reaction proceeded at 110 °C to give a product with high diastereoselectivity in 50% yield.[12] The stereochemistry of the product was confirmed to be **4ba** by X-ray analysis, wherein the benzene ring of the indole was directed toward the chromium tricarbonyl group. It is worth noting that the difference in bulkiness between the methyl group and the benzene ring of the indole was completely discriminated for the formation of the N−C bond, and the methyl group was considered to be a bulkier substituent than the benzene ring of the indole. A low-field shift of the C-7 proton of the indole fragment was observed (δ 8.08 ppm), which was caused by the anisotropic effect of the chromium tricarbonyl group.[13] When 2-methyl-5-methoxyindole (**1c**) was used as the nucleophile, **4ca**, which has the same stereochemical relationship as **4ba**, was obtained as a single diastereomer in good yield (entry 4). Other nucleophiles having substituents at a different position were also examined, and all of them gave moderate to good yields with high diastereoselectivities (entries 5−8). Judging from the ^{1}H NMR chemical shifts of the proton at the C-7 positon of the indole fragment, the stereochemsitry of these products was confirmed to be the thermodynamically stabele anti configration.

To estimate the rotational barrier of chromium-free *N*-aryl indole, we investigated the oxidative demetalation of opti-

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(12) 20% of the starting material was recovered, and 25% of decomplexed product was obtained.

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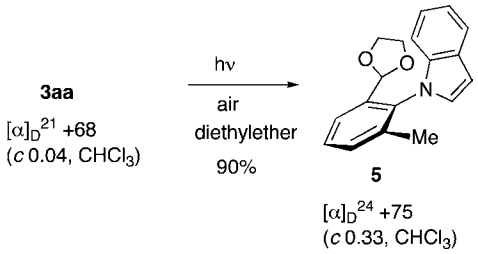
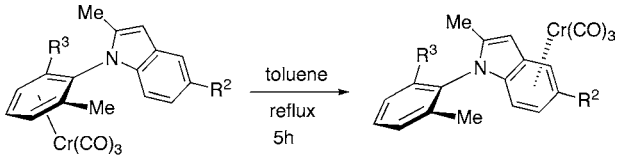
Scheme 1. Dechromium Complexation of **3aa**



cally active *N*-aryl indole chromium complex **3aa** (Scheme 1). A solution of (+)-**3aa** was exposed to sunlight at 0 °C until its yellow color disappeared. Demetalation product **5** exhibited positive optical rotation (($[\alpha]^{24}_D$ +75 (*c* 0.33, $CHCl_3$)) that did not change even after prolonged standing (24 h) at room temperature in chloroform solution. Therefore, axially chiral *N*-aryl indole **5** was refluxed in toluene solution and its optical purity was monitored by HPLC.[14] The optical purity of indole **5** did not decrease even after refluxing for 4 h. When the solvent was switched from toluene to xylene, indole **5** was decomposed under refluxing conditions to give an unidentified product. These results indicate that *N*-aryl indole **5** has a relatively high rotational barrier at the N−C axis and no racemization occurs under the above reaction conditions.

We also found that when sterically hindered *N*-aryl indole chromium complex **4ba** was refluxed in toluene for a long time (5 h), the stereoselective migration of the chromium tricarbonyl group to the arene ring of the indole occurred to give **6ba** in 60% yield as a single diastereomer (Table 2, entry 1).[15] X-ray analysis revealed that the chromium tricarbonyl group was directed toward the 1,3-dioxolane group. We found that the 1,3-dioxolane group is crucial for this reaction. When the substituent on the arene chromium complex of **4ba** was switched from the 1,3-dioxolane group to a methyl group, no chromium tricarbonyl transfer reaction took place under the same conditions (entry 2). Complexes

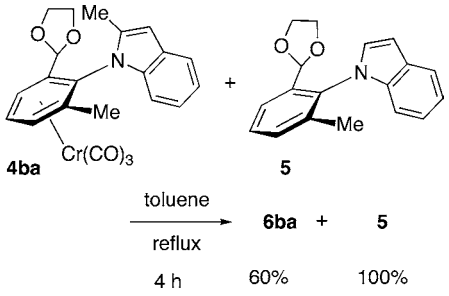
Table 2. Stereoselective Chromium Tricarbonyl Migration of Complex **4**



entry	complex	R^2	R^3	product	yield (%)
1	**4ba**	H	1,3-dioxolane	**6ba**	60
2	**4bc**	H	Me		[a]
3	**4bd**	H	$-CH_2OH$		[a]
4	**4be**	H	1,3-dithiolane		[a]
5	**4ca**	OMe	1,3-dioxolane	**6ca**	40

[a] Starting material was recovered.

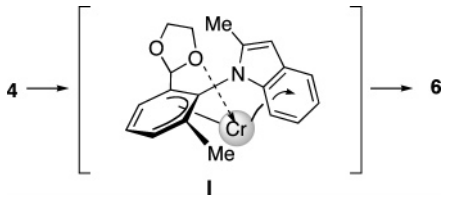
Scheme 2. Crossover Experiment



4bd and **4be**, having coordinating heteroatoms on the arene chromium ring, were also examined. However, no chromium tricarbonyl migration reaction took place and only the starting materials were recovered (entries 3 and 4). On the other hand, **4ca** with a 1,3-dioxolane group was transformed into **6ca** as a single diastereomer (entry 5). The role of the 1,3-dioxolane group might be to assist the transfer of the tricarbonyl chromium group by coordinating to a chromium atom; however, it remains unclear why only the 1,3-dioxolane group is effective for the migration reaction.

To clarify the reaction mechanism of this stereoselective chromium migration reaction, we conducted a crossover experiment using **4ba** and chromium uncomplexed *N*-aryl indole **5** (Scheme 2). A 1:1 mixture of **4ba** and **5** was refluxed in toluene for 4 h. The chromium tricarbonyl group migrated to the arene ring to give **6ba** in 60% yield and *N*-aryl indole **5** that was recovered unchanged. This indicates that the chromium tricarbonyl migration in **4ba** proceeds in an *intramolecular* fashion. On the basis of these observations, the plausible mechanism is proposed in Scheme 3. The chromium tricarbonyl group of indole **4ba** can slip into the η^4-intermediate via intramolecular coordination with the 1,3-dioxolane group. Labile chromium tricarbonyl species **I** is generated, in which chromium intramolecularly migrates to the arene face of the indole from the 1,3-dioxolane group to release steric repulsion.

Scheme 3. Proposed Mechanism for Stereoselective Chromium Tricarbonyl Migration Reaction



Tricarbonyl chromium coordinated indole derivatives exhibit unique properties due to the selective activation of

(14) HPLC conditions: chiralcel OD; hexane/2-propanol = 9:1; flow rate of 1.0 mL/min; column temperature = 40 °C; UV detector = 254 nm, retention time, racemate, 5.96 min for (+)-isomer and 6.74 min for (−)-isomer.

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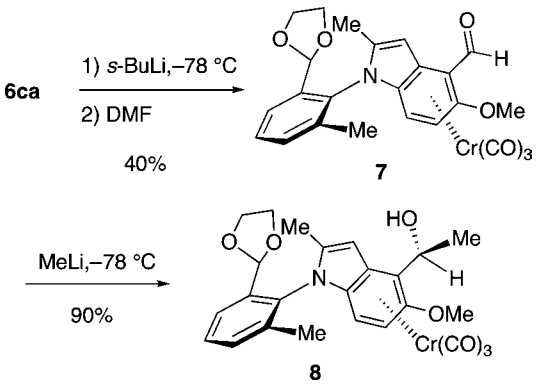
the six-membered ring. Thus, the chemo- and stereoselective transformation of **6ca** is possible utilizing the planar chiral indole fragment.

For the selective transformation of the chromium coordinated arene ring, nucleophilic dearomatization reactions and ortho-lithiation reactions are widely utilized.[16] For example, complex **6ca** was functionalized by treatment with *sec*-BuLi and subsequent trapping with DMF to give complex **7**, which was transformed at the C-4 position of the indole fragment, as the major product.[17] The stereoselective addition of **7** with methyllithium at −78 °C gave complex **8** as a single diastereomer (Scheme 4). Therefore, we succeeded in *controlling not only the axial chirality but also the chirality at the side chain from a single mobile chiral auxiliary*.

In conclusion, we have demonstrated the stereoselective synthesis of axially chiral *N*-aryl indoles by nucleophilic substitution reaction with high diastereoselectivities. Stereoselective chromium tricarbonyl migration was achieved by refluxing thermodynamically unstable **4ba** and **4ca** in toluene for a long time.

Together, these results indicate that we were able to control both the C−N axial chirality and the chirality at the side chain from a single chiral source. Studies of catalytic asymmetric synthesis of axially chiral *N*-aryl indoles are under way in our laboratory.

Scheme 4. Selective Transformation of Tricarbonylchromium Coordinated Indole



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Supporting Information Available: The general procedure for the stereoselective synthesis of *N*-aryl indole chromium complexes, their characterization and NMR spectra, and CIF files of complexes **3aa** (CCDC number, 286550), **4ba** (CCDC number, 286551), and **6ba** (CCDC number, 286552). This material is available free of charge via the Internet at http://pubs.acs.org.

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