Induction of axially chiral N–C bonds in *N*-aryl acridane and related complexes by chromium tricarbonyl migration reactions†

Akiyoshi Mori,[a] Shunsuke Kinoshita,[a] Masaru Furusyo[b] and Ken Kamikawa*[a]

Received 9th April 2010, Accepted 30th July 2010
DOI: 10.1039/c0cc00836b

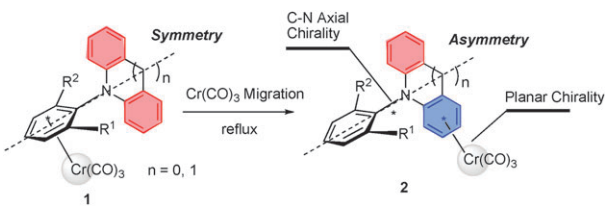
The thermal chromium tricarbonyl migration reaction induced axially chiral N–C bonds of *N*-aryl acridane and related complexes in good yield with outstanding enantiomeric excess.

The stereoselective synthesis of axially chiral N–C bonds is gaining increasing attention[1] because of their potential use in asymmetric reactions[2] and as intermediates for the synthesis of biologically active natural products,[3] agricultural herbicides, and fungicides.[4] Among the compounds with axially chiral N–C bonds, the stereoselective synthesis of axially chiral anilide has been intensively studied and some outstanding methods involving catalytic and enantioselective syntheses have been reported.[5] On the other hand, we previously reported the diastereoselective synthesis of *N*-aryl indoles, another class of compounds with axially chiral N–C bonds.[6] During the course of our study, we found that the chromium tricarbonyl ($Cr(CO)_3$) group migrates[7] to the benzene ring of indole in a diastereoselective manner. This result prompted us to investigate the possibility of exploring novel types of axially chiral induction involving $Cr(CO)_3$ migration. The concept of this research is shown in Scheme 1.

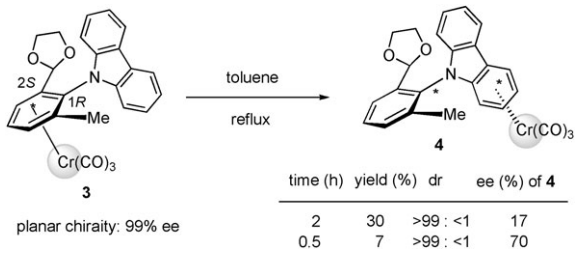
If the $Cr(CO)_3$ group in complex **1** that has a prochiral N–C bond axis could stereoselectively migrate to the neighboring arene ring while avoiding steric hindrance, not only planar chirality but also N–C axial chirality would be simultaneously induced by the desymmetrization in complex **2**.

In line with this idea, the induction of an axially chiral N–C bond utilizing an *N*-aryl carbazole chromium complex was initially investigated.

First, optically active complex **3**[8] was refluxed in toluene solution for two hours. As a result, migrated complex **4** was



Scheme 1 Concept for induction of axially chiral N–C bond by chromium tricarbonyl migration reaction.

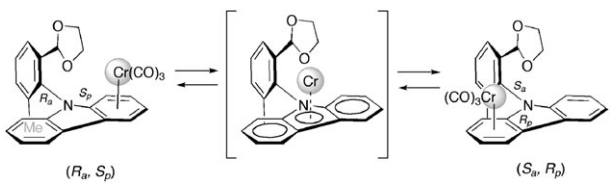


Scheme 2 Induction of axially chiral N–C bond utilizing *N*-aryl carbazole chromium complex.

obtained in 30% yield in the diastereomerically pure form. The stereochemistry of **4** was judged from ^{1}H-NMR that the $Cr(CO)_3$ group oriented toward the same side as the dioxolane group, since the chemical shift of the methine proton in a dioxolanyl group shifted 0.46 ppm lower field than that of **3** due to the anisotropic effect of the $Cr(CO)_3$ group.[9] However, it was found that the enantiomeric excess (ee) of **4**, which indicates not only the ee of the planar chirality but also that of the N–C axial chirality induced by desymmetrization, was only 17% (Scheme 2). On the other hand, when this migration reaction was stopped at 30 min, the ee of **4** was improved to 70%. The results indicate that the racemization proceeds from the enantiomerically enriched migrated complex during reflux for a long time.[10] This would be caused by the slippage of the $Cr(CO)_3$ group through the conjugated aromatic system of carbazoles (Scheme 3).[11]

When the slippage occurred from one benzene ring to the other benzene ring of carbazole, both axial and planar chiralities were simultaneously inverted to form the corresponding enantiomer. Thus, this process is presumed to cause racemization of the newly formed $Cr(CO)_3$ migrated complex.

Therefore, if this π-conjugated system of carbazoles was changed to a *non-conjugated* one, such as acridane, the racemization *via* slippage of the $Cr(CO)_3$ group would be suppressed. To confirm this hypothesis, we next examined the $Cr(CO)_3$ migration reaction utilizing symmetrical *non-conjugated* *N*-aryl complexes (Table 1). To our delight, the migration reaction of *N*-aryl acridane chromium complex **5a** proceeded smoothly to give product **6a** in 78% yield with 99% ee without any loss of enantiomeric purity of the planar chirality of **5a**. Therefore,

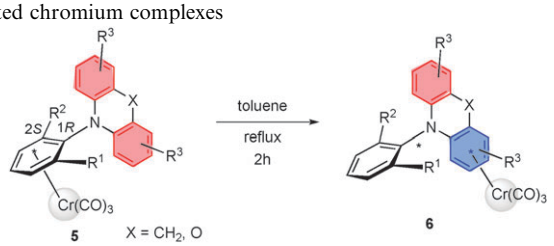


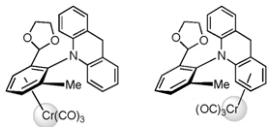
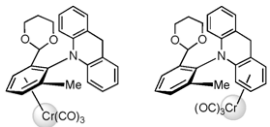
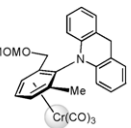
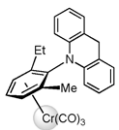
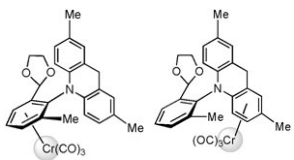
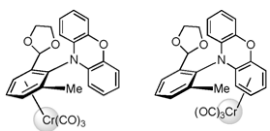
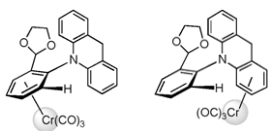
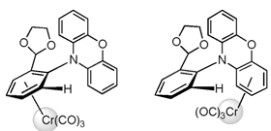
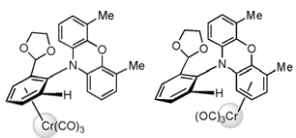
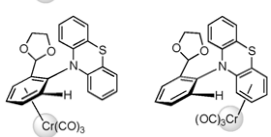
Scheme 3 Racemization *via* slippage.

[a] *Department of Chemistry, Graduate School of Science, Osaka Prefecture University Sakai, Osaka 599-8531, Japan. E-mail: kamikawa@c.s.osakafu-u.ac.jp; Fax: +81 72-254-9931; Tel: +81 72-254-9721*
[b] *Analysis Technology Research Center, Sumitomo Electric Industries Ltd., 1-1-1, Koyakita, Itami, Hyogo, 664-0016, Japan*

† Electronic supplementary information (ESI) available: Details of synthetic methods, analyses. CCDC 768398 (**7**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc00836b

Table 1 Induction of axially chiral N–C bonds in acridane and related chromium complexes



Entry	Substrate	Product	Yield (%)	dr	ee (%)
1	**5a**		78	>99 : <1	99
2	**5b**		70	>99 : <1	89
3	**5c**		—	—[a]	—	—
4	**5d**		—	—[a]	—	—
5[b]	**5e**		42	>99 : <1	98
6	**5f**		60	>99 : <1	94
7	**5g**		61	87 : 13	99
8	**5h**		73	85 : 15	95
9	**5i**		60	>99 : <1	95
10	**5j**		71	>99 : <1	85

[a] Starting material was recovered. [b] The reaction was carried out for 4.5 h.

both planar and N–C axial chiralities were induced with high stereoselectivity.[12] The stereochemistry of the migrated chromium complex **6a** was confirmed by the X-ray analysis of hydrolyzing complex **7**.‡ It was revealed that the $Cr(CO)_3$ group oriented toward the same side as the aldehyde group, and therefore, the $Cr(CO)_3$ group was directed toward the acetal group in complex **6a**. This result is in good agreement with our previous studies (Fig. 1).[6]

These migration reactions required the acetal group as a directing group. When the acetal group was changed to a 1,3-dioxane group, the ee of the product was decreased to 89%. Other functional groups, such as $MOMOCH_2$ or ethyl groups, are not effective for the migration reaction (entries 3 and 4). When 2,7-dimethylacridane complex **5e** was used, the migration reaction proceeded slowly and required a longer time (4.5 h). As a result, the ee of the migrated product was slightly decreased to 98% (entry 5). Phenoxazine complex **5f** gave the product with 94% ee (entry 6). Then, *ortho*-trisubstituted complexes were also examined. When *N*-arylacridane complex **5g** was refluxed, the migrated product was formed in 61% yield with 99% ee along with an inseparable diastereomer based on the planar chirality and the axial one (entry 7).[13] In the case of phenoxazine complexes **5h** and **5i**, the ee of the product was slightly decreased to 95% (entries 8 and 9). When phenothiazine complex **5j** was used, ee dropped markedly to 85% (entry 10).

We also conducted the diastereoselective transformation of **6a** utilizing a newly formed planar chirality of the complex (Scheme 4). Thus, complex **6a** was treated with *n*BuLi and subsequent trapping with MeI from the *exo* side of the $Cr(CO)_3$ group to give complex **8** as a single diastereomer. Therefore, the central chirality was also introduced from a single mobile chiral auxiliary.

Interestingly, identical **8** was also synthesized *via* a nucleophilic reaction with 9-methylacridane and a subsequent diastereoselective $Cr(CO)_3$ migration in one pot. Thus, planar, axial, and central chiralities were newly formed at the same time in a stereoselective manner (Scheme 5). The stereoselective formation of complex **8** would be caused by a structural difference between complexes **10** and **11** which were formed in the course of the reaction as an inseparable mixture. The chromium tricarbonyl migration would preferentially occur from diastereomer **11** whose methyl group in an acridane fragment oriented toward the opposite side as the directing group.

We have succeeded in the induction of axially chiral N–C bonds of *N*-aryl acridane and related chromium complexes by

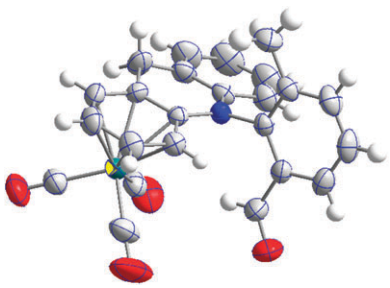
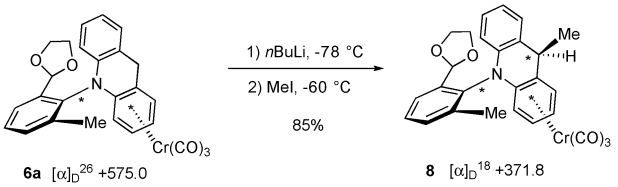
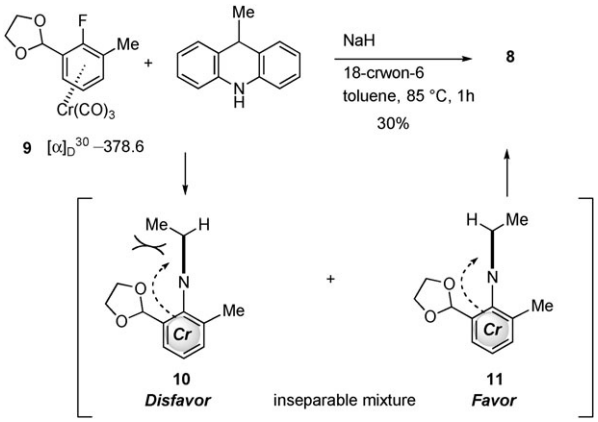


Fig. 1 ORTEP drawing of complex **7**.



Scheme 4 Diastereoselective transformation utilizing the migrated planar chirality of complex **6a**.



Scheme 5 Synthesis of complex **8** by nucleophilic substitution and chromium tricarbonyl migration reaction in one pot.

diastereoselective $Cr(CO)_3$ migration. Further applications are under investigation in our laboratory.

Notes and references

‡ Crystal data for **7**: $C_{27.5}H_{23}CrNO_4$, M = 483.48, triclinic, $P\bar{1}$, a = 10.867(4), b = 14.490(7), c = 14.911(4), V = 2293.2(1) Å^3, Z = 4, D_c = 1.4000 g cm^{-3}, μ(MoKα) = 0.71075 mm^{-1}, F(000) = 1004.00, T = 296 K, 22 335 reflections collected, 10 174 unique (R_{int} = 0.024), R_1 = 0.047 ($I > 3\sigma(I)$), wR_2 = 0.145 ($I > 3\sigma(I)$), S = 1.03. Data collection was carried out using the RIGAKU RAXIS RAPID, and SHELXL97 programs were used for the structure solution and refinement.

1 *Tetrahedron Symposium in-print on Axially Chiral Amide*, ed. J. Clayden, *Tetrahedron*, 2004, vol. 60, p. 4325.

2 (*a*) T. Mino, Y. Tanaka, Y. Hattori, T. Yabusaki, H. Saotome, M. Sakamoto and T. Fujita, *J. Org. Chem.*, 2006, **71**, 7346; (*b*) Y. Z. Chen, M. D. Smith and K. D. Shimizu, *Tetrahedron Lett.*, 2001, **42**, 7185; (*c*) X. Dai and S. C. Virgil, *Tetrahedron Lett.*, 1999, **40**, 1245; (*d*) X. Dai, A. Wong and S. C. Virgil, *J. Org. Chem.*, 1998, **63**, 2597.

3 (*a*) G. Bringmann, S. Tasler, H. Endress, J. Kraus, K. Messer, M. Wohlfarth and W. Lobin, *J. Am. Chem. Soc.*, 2001, **123**, 2703; (*b*) G. Bringmann, T. Gulder, M. Reichert and F. Meyer, *Org. Lett.*, 2006, **8**, 1037.

4 (*a*) F. Spindler and T. Früh, in *Chirality in Agrochemicals*, ed. N. Kurihara and J. Miyamoto, John Wiley & Sons, 1998, pp. 142–173; (*b*) R. J. Brown, G. Annis, A. Casalnuovo, D. Chan, R. Shapiro and W. J. Marshall, *Tetrahedron*, 2004, **60**, 4361.

5 (*a*) D. J. Bennett, P. L. Pickering and N. S. Simpkins, *Chem. Commun.*, 2004, 1392; (*b*) H. Koide, T. Hata and M. Uemura, *J. Org. Chem.*, 2002, **67**, 1929; (*c*) A. Ates and D. P. Curran, *J. Am. Chem. Soc.*, 2001, **123**, 5130; (*d*) D. P. Curran, H. Qi, S. J. Geib and N. C. DeMello, *J. Am. Chem. Soc.*, 1994, **116**, 3131; (*e*) J. Terauchi and D. P. Curran, *Tetrahedron: Asymmetry*, 2003, **14**, 587; (*f*) A. J. B. Lapierre, S. J. Geib and D. P. Curran, *J. Am. Chem. Soc.*, 2007, **129**, 494; (*g*) K. Tanaka, K. Takeishi and K. Noguchi, *J. Am. Chem. Soc.*, 2006, **128**, 4586; (*h*) K. Tanaka and K. Takeishi, *Synthesis*, 2007, 2920; (*i*) O. Kitagawa, M. Yoshikawa, H. Tanabe, T. Morita, M. Takahashi, Y. Dobashi and T. Taguchi, *J. Am. Chem. Soc.*, 2006, **128**, 12923; (*j*) O. Kitagawa, M. Takahashi, M. Yoshikawa and T. Taguchi, *J. Am. Chem. Soc.*, 2005, **127**, 3676; (*k*) S. Brandes, M. Bella, A. Kjærsgaard and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2006, **45**, 1147.

6 (*a*) K. Kamikawa, S. Kinoshita, H. Matsuzaka and M. Uemura, *Org. Lett.*, 2006, **8**, 1097; (*b*) K. Kamikawa, S. Kinoshita, M. Furusyo, S. Takemoto, H. Matsuzaka and M. Uemura, *J. Org. Chem.*, 2007, **72**, 3394.

7 For the migration of chromium carbonyl group to other arene rings, see: (*a*) T. G. Traylor and K. J. Stewart, *J. Am. Chem. Soc.*, 1986, **108**, 6977; (*b*) J. A. S. Howell, P. C. Yates, N. F. Ashford, D. T. Dixon and R. Warren, *J. Chem. Soc., Dalton Trans.*, 1996, 3959; (*c*) E. P. Kündig, M. Kondratenko and P. Romanens, *Angew. Chem., Int. Ed.*, 1998, **37**, 3146; (*d*) K. Kamikawa, T. Sakamoto, Y. Tanaka and M. Uemura, *J. Org. Chem.*, 2003, **68**, 9356; (*e*) M. F. Semmelhack, A. Chlenov and D. M. Ho, *J. Am. Chem. Soc.*, 2005, **127**, 7759; (*f*) J. Pan, J. W. Kampf and A. J. Ashe III, *Organometallics*, 2006, **25**, 197; (*g*) H. C. Jahr, M. Nieger and K. H. Dötz, *Chem. Commun.*, 2003, 2866.

8 The absolute stereochemistry of the planar chirality in the complex **3** was determined as (1*R*, 2*S*). See ESI† for details.

9 (*a*) M. Uemura, H. Nishimura, K. Kamikawa and M. Shiro, *Inorg. Chim. Acta*, 1994, **222**, 63; (*b*) G. Bringmann, L. Göbel, K. Peters, E. M. Peters and H. G. von Schnering, *Inorg. Chim. Acta*, 1994, **222**, 255.

10 Isolated complex **4** was refluxed in toluene for further 2 h, however formation of complex **3** was not observed.

11 (*a*) T. A. Albright, P. Hofmann, R. Hoffmann, C. P. Lillya and P. A. Dobosh, *J. Am. Chem. Soc.*, 1983, **105**, 3396; (*b*) S. D. Cunningham, K. Ofele and B. R. Willeford, *J. Am. Chem. Soc.*, 1983, **105**, 3724; (*c*) G. Zhu, J. M. Tanski, D. G. Churchill, K. E. Janak and G. Parkin, *J. Am. Chem. Soc.*, 2002, **124**, 13658; (*d*) G. Zhu, K. Pang and G. Parkin, *J. Am. Chem. Soc.*, 2008, **130**, 1564.

12 Direct chromium complexation with $Cr(CO)_6$ in non-chromium coordinated *N*-arylacridane **5a** gave complex mixture of mono- and dichromium coordinated complexes.

13 The rotational barrier of **6g** was estimated by B3LYP/6-31(d,p). See ESI† for details.

