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Asymmetric Synthesis of Axially Chiral Biaryls: Inversion of Planar Chirality vs Axial Isomerization and Functionalization at the Side Chain of Biaryl Chromium Complexes

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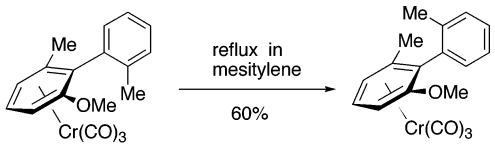
Axially chiral *syn*-biaryl chromium complexes having a coordinating heteroatom substituent at the benzylic position gave *anti*-biaryl chromium complexes **5** with inversion of the planar chirality by heating in a nonaromatic solvent, while *syn*-biaryl chromium complexes with an *o*-methyl or formyl substituent afforded axially isomerized *anti*-biaryl chromium complexes under heating in an aromatic solvent. *syn*-Biaryl and both enantiomeric *anti*-biaryl chromium complexes with the *o*-formyl group were stereoselectively prepared from an identical planar chiral arene chromium complex as chiral source. The formyl group of the axially chiral chromium complexes was functionalized by radical cyclization and β-lactam formation, and hetero-Diels−Alder reaction.

Introduction

Axially chiral biaryl compounds are of importance not only as chiral ligands in asymmetric reactions but also for biologically active natural products. There is currently considerable interest in the development of efficient methodology for the synthesis of axial biaryls in enantiomerically pure form.[1] Nucleophilic displacement of an *o*-methoxy group of chiral aryl oxazolines with aryl Grignard reagents has been widely employed in asymmetric biaryl syntheses.[2] Other interesting methods have been reported for the preparation of axially chiral biaryls.[3] However, it is usually difficult to prepare both enantiomers of axially chiral biaryls from a single chiral source in these asymmetric reactions.

We have developed a unique method for the synthesis of both enantiomers of axially chiral biaryls starting from an identical planar chiral arene chromium complex as the chiral source.[4] Thus, palladium(0)-catalyzed cross-coupling of planar chiral 2,6-disubstituted bromobenzene chromium complexes with *o*-substituted arylboronic acids gave *syn*-biaryl chromium complexes under reflux in aqueous methanol in the presence of sodium carbonate. The obtained *syn*-biaryl chromium complexes, e.g., (η-1,2,3,4,5,6)-tricarbonyl(2-methoxy-2′,6-dimethylbiphenyl-)chromium complex (**1**),[4a] underwent a central bond rotation under reflux in mesitylene to give thermodynamically stable *anti*-biaryl chromium complex **2**[4a] (Scheme 1).

SCHEME 1. Axial Isomerization under Thermal Conditions



1 — *syn*; $Cr(CO)_3$ / Me — $[\alpha]_D^{33}$ −242 (*c* 0.1, $CHCl_3$)

2 — *anti*; $Cr(CO)_3$ / Me — $[\alpha]_D^{32}$ −200 (*c* 0.1, $CHCl_3$)

In this way, both diastereomers of chromium-complexed axially chiral biaryls can be stereoselectively

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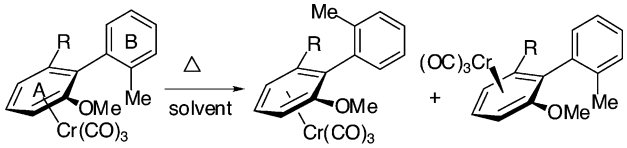
prepared from an identical planar chiral arene chromium complex. On the other hand, we furthermore found that the tricarbonylchromium fragment of a *syn*-biaryl chromium complex migrated to the reversed arene face without axial isomerization under thermal conditions during a synthetic study of atropodiastereomeric korupensamines A and B.[5] The question was raised to us which path, that is, axial isomerization or tricarbonylchromium migration to the revesed arene face, takes place predominantly in *syn*-biaryl chromium complexes under thermal conditions.[6] These interesting results prompted us to undertake a systematic investigation of the stereochemical behavior under thermal conditions for further development of the asymmetric reaction of axially chiral biaryl chromium complexes.

Results and Discussion

Axial Isomerization vs Tricarbonylchromium Migration under Thermal Conditions. Biaryl chromium complexes having both planar and axial chiralities are useful building blocks in asymmetric transformations such as natural product synthesis.[5,7] If stereoisomers of these biaryl chromium complexes could be stereoselectively prepared as enantiomerically pure compounds from an identical planar chiral 2,6-disubstituted bromobenzene chromium complex, synthetic development of the asymmetric reaction would be further advanced. Accordingly, we examined the stereochemical behavior of *syn*-biaryl chromium complexes under thermal conditions for the preparation of stereoisomers as optically pure forms. Initially, we studied the effect of an ortho-substituent on the stereochemical behavior: axial isomerization vs tricarbonylchromium migration of *syn*-biaryl chromium complexes under thermal conditions. Treatment of an enantiomerically pure *syn*-(2-methoxy-6-hydroxymethyl-2′-methylbiphenyl)chromium complex (**3a**) ($[\alpha]^{28}_D$ −254.0) refluxed in xylene gave (xylene)$Cr(CO)_3$ complex in 58% yield without the axial isomerization (Table 1, entry 1). The coordinating benzylic oxygen of the chromium complex **3a** accelerates a facile migration of the tricarbonylchromium fragment to the aromatic solvent by weakening the chromium−arene bond. Coordinating donor solvents is also known to accelerate ligand exchange to other arenes.[8] Therefore, xylene was next changed to a nonaromatic coordinating solvent for thermal behavior. We selected a 1:1 mixture of di-*n*-butyl ether and 1,2-dichloroethane as the solvent system under thermal conditions by considering the solubility and boiling point. Heating of **3a** at 120 °C in a 1:1 mixture of di-*n*-butyl ether and 1,2-dichloroethane for 2 h gave predominantly the thermodynamically stable *anti*-biphenyl chromium complex **5a** ($[\alpha]^{31}_D$ +140.0) as a major product (entry 2). The stereochemistry of **5a** was confirmed by ^{1}H NMR spectra as the anti-relationship between the methyl group on the chromium uncomplexed B-ring and the chromium tricarbonyl fragment. Thus, the methyl signal of the thermally isomerized *anti*-complex **5a** appeared at 2.09 ppm, while the corresponding methyl of the *syn*-biaryl chromium complex **3a** was shifted to low field at 2.64 ppm. The low-field shift of the methyl signal in the *syn*-biaryl chromium complex is due to an anisotropic effect of the $Cr(CO)_3$ fragment.[9] However, the thermally isomerized *anti*-chromium complex **5a** was found not to be the central bond rotated *anti*-chromium complex **4a** by comparison of optical rotation values and HPLC behavior with the chiral stational phase of chromium-free (*S*)-2-methoxy-6-hydroxymethyl-2′-methylbiphenyl derived from the chromium complexes **5a** and **3a**.[10] These results indicate, obviously, that inversion of the planar chirality took place without central bond rotation in the *syn*-biaryl chromium complex **3a**. Thus, the tricarbonylchromium fragment migrates to the reversed arene face.[11] To survey the effect of benzylic alcohol functionality for the inversion of planar chirality, we next examined methoxymethyl-substituted *syn*-biphenyl complex **3b**. It was found that *anti*-biaryl chromium complex **5b** with inversion of planar chirality was also predominantly

TABLE 1. Axial Isomerization vs $Cr(CO)_3$ Migration under Thermal Conditions



3 *syn*; $Cr(CO)_3$ / Me — **4** *anti*; $Cr(CO)_3$ / Me — **5** *anti*; $Cr(CO)_3$ / Me

entry	complex	R	condition[e]	ratio **4**:**5**	yield (%)
1[a]	**3a**	CH_2OH	A	–	–
2	**3a**	CH_2OH	B	5:95	55
3	**3b**	CH_2OMe	B	6:94	69
4[b]	**3c**	$CH_2OTBDMS$	C	27:73	24
5	**3c**	$CH_2OTBDMS$	D	49:51	80
6	**3d**	$CH(OMe)_2$	A	1:>99	55
7	**3d**	$CH(OMe)_2$	C	1:>99	69
8	**3e**	CH_2NHMe	B	3:97	32
9[c]	**3f**[d]	Me	E	–	–
10	**3g**	CHO	F	>99:1	98
11	**3h**	CO_2Me	A	90:10	38
12	**3i**	CH=NMe	A	80:20	46
13	**3j**	COMe	A	99:1	37

[a] (Xylene)$Cr(CO)_3$ was obtained in 58% yield as an isomeric mixture. [b] De-tricarbonylchromium compound was the major product. [c] Starting material was recovered. [d] Complex **3f** listed in Table 1 is identical with **1** in Scheme 1. [e] Conditions: (A) xylene, 140 °C; (B) *n*-Bu_2O, $(CH_2Cl)_2$, 120 °C; (C) *n*-Bu_2O, $(CH_2Cl)_2$, 140 °C; (D) mesitylene, 140 °C; (E) isoamyl ether, $(CH_2Cl)_2$, 160 °C; (F) toulene, 110 °C.

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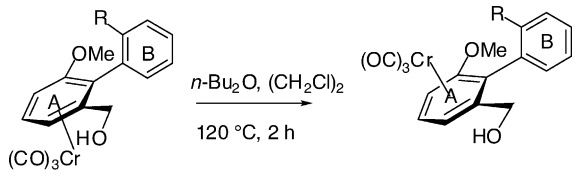
TABLE 2. $Cr(CO)_3$ Migration to the Inverted Arene Face under Thermal Conditions



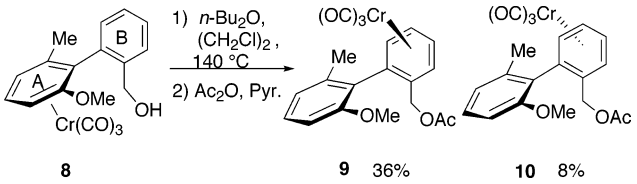
6 *anti-* **7** *syn-*

entry	complex	R	ratio **6**:**7**	yield (%)
1	**6a**	H	95:5	77
2	**6b**	Me	>99:<1	99

obtained (entry 3). However, in the case of complex **3c** possessing a bulky *tert*-butyldimethylsilyl protecting group, the ratio of the axially isomerized product **4c** increased (entries 4 and 5). Extremely high diastereoselective chromium migration to the reversed arene face was achieved with dimethylacetal-substituted *syn*-complex **3d** under refluxing in either aromatic or nonaromatic solvents (entries 6 and 7). In analogy with benzylic oxygen, the corresponding *N*-methylamino-substituted *syn*-biaryl chromium complex **3e** gave predominantly the chromium-migrated *anti*-biaryl complex **5e** (entry 8). On the other hand, the axially isomerized products **4g**, **4h**, **4i**, and **4j** were obtained when R substituents were sterically less sp^2-carbon atoms such as formyl, methoxycarbonyl, *N*-methylimine, and methyl ketone (entries 10∼13). These results indicate that the coordinating heteroatom[6,12] at the sp^3-benzylic position plays an important role for the inversion of planar chirality. The solvent effect was also significant for not only the inversion of planar chirality but also axial isomerization. The *syn*-biaryl complex **3f** underwent axial isomerization by reflux in an aromatic solvent, while heating in a nonaromatic solvent resulted in recovery of the starting material (entry 9). Thus, an aromatic solvent accelerates the axial isomerization.

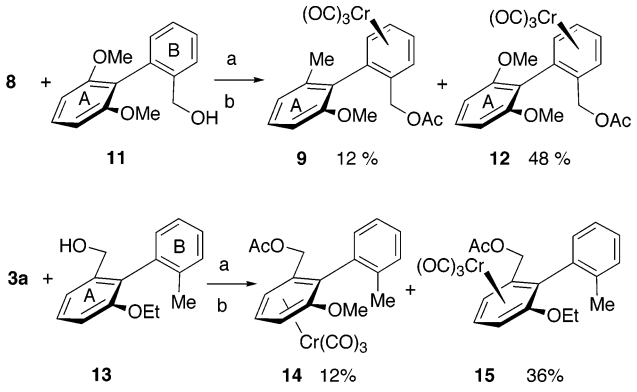
We next examined the steric effect of the relative stereochemistry between the substituent on the non-chromium complexed arene B-ring and the $Cr(CO)_3$ fragment for the stereochemical behavior (Table 2). The racemization of the less hindered biaryl chromium complex **6a** lacking the ortho-substituent on the B-ring was sluggish (entry 1). Similarly, *anti*-biaryl chromium complex **6b** with a hydroxymethyl group resulted in recovery of the starting material (entry 2). Thus, the inversion of planar chirality was induced by steric repulsion between the substituent on the non-chromium complexed arene B-ring and the $Cr(CO)_3$ fragment.

SCHEME 2. Migration of the $Cr(CO)_3$ Fragment of 8



8 **9** 36% **10** 8%

SCHEME 3. Crossover Reaction[a]



11 **9** 12 % **12** 48 %

13 **14** 12% **15** 36%

[a] Reagents and conditions: (a) *n*-Bu_2O, $(CH_2Cl)_2$, 120 °C, 2 h; (b) Ac_2O, Pyr.

We next focused on the stereochemical behavior under thermal conditions of *syn*-biaryl chromium complexes having hydroxymethyl on the chromium-uncomplexed B-ring (Scheme 2). *syn*-(η-1,2,3,4,5,6)-Tricarbonyl-(2-methoxy-6-methyl-2′-hydroxymethylbiphenyl)chromium complex (**8**) was refluxed and the following acetylation gave the tricarbonylchromium migration products **9** and **10** as a diastereomeric mixture in 44% yield along with a 37% yield of a dechromium product. The relative stereochemistry of the chromium complexes **9** and **10** was easily determined by chemical shift of the ^1H NMR spectra. Neither the central bond rotation nor the chromium migration to the reversed arene A-ring was observed under these conditions. Thus, the $Cr(CO)_3$ fragment migrates exclusively to the arene ring substituted with the hydroxymethyl group regardless of the electron density of the arene ring.

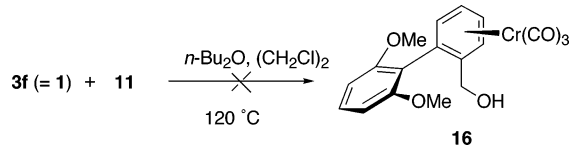
For clarification of the reaction mechanism, we next studied a crossover reaction between a *syn*-biaryl chromium complex and a chromium uncomplexed biaryl under thermal conditions. A 1:1 mixture of *syn*-biaryl chromium complex **8** and 2,6-dimethoxy-2′-hydroxymethyl biphenyl (**11**) in di-*n*-butyl ether and dichloroethane was heated at 120 °C for 2 h, and the reaction products were analyzed after acetylation (Scheme 3). The $Cr(CO)_3$ fragment of complex **8** migrated to the B-ring of the biaryl compound **11** giving biaryl complex **12** as a major chromium complex. Similarly, a crossover reaction between **3a** and 2-ethoxy-6-hydroxymethyl-2′-methylbiphenyl (**13**) gave *anti*-(η-1,2,3,4,5,6)-tricarbonyl(2-ethoxy-6-acetoxymethyl-2′-methylbiphenyl)chromium com-

(10) Optical rotation of chromium free (*S*)-2-methoxy-6-hydroxymethyl-2′-methylbiphenyl derived from the *anti*-chromium complexes, which is an inseparable 95:5 mixture of **5a** and **4a**, is $[\alpha]^{28}_D$ +31.8 (*c* 0.12, $CHCl_3$); the corresponding value of chromium free compound obtained from *syn*-biaryl chromium complex **3a** is $[\alpha]^{27}_D$ +32.2 (*c* 0.28, $CHCl_3$). Optical purities of *anti*-biphenyl chromium complexes, **4a** and **5a**, and the correspomding chromium free 2-methyl-6-hydroxymethyl-2′-methylbiphenyl were determined by chiral HPLC. For **4a** and **5a**: chiralcel OD, hexane/2-propanol (9/1), flow rate 0.5 mL/min, 40 °C, retention time 13.8 (**4a**) and 16.2 min (**5a**). For 2-methyl-6-hydroxymethyl-2′-methylbiphenyl: chiralcel OJ-H, hexane/2-propanol (50/1), flow rate 0.5 mL/min, 40 °C, retention time 46.5 and 53.7 min. Optically active 2-methyl-6-hydroxymethyl-2′-methylbiphenyl from **3a** and **5a**: retention time 46.5 min.

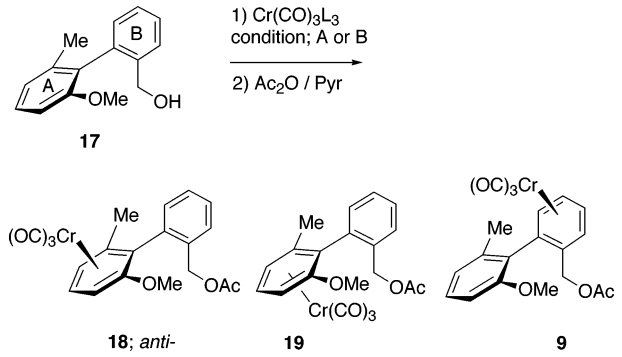
(11) See our preliminary report: Kamikawa, K.; Sakamoto, T.; Uemura, M. *Synlett* **2003**, 516−518.

(12) The chromium−arene bond is weakened by assistance with the coordinating benzylic oxygen. Tricarbonyl(1-*exo*-vinyl-1-*endo*-indanol)-chromium complexes were heated in the presenece of functionalized arenes, 2-methyl-1,3-cyclopentadione, and a catalytic amount of Triton-B to give the corresponding tricarbonylchromium migration products to the exsisting arenes. (a) Meyer, A.; Jaouen, G. *J. Organomet. Chem*. **1975**, *97*, C21−C23. (b) Goasmat, F.; Dabard, R.; Patin, H. *Tetrahedron Lett*. **1975**, *16*, 2359−2362.

SCHEME 4



SCHEME 5. Direct Chromium Complexation of 17[a]



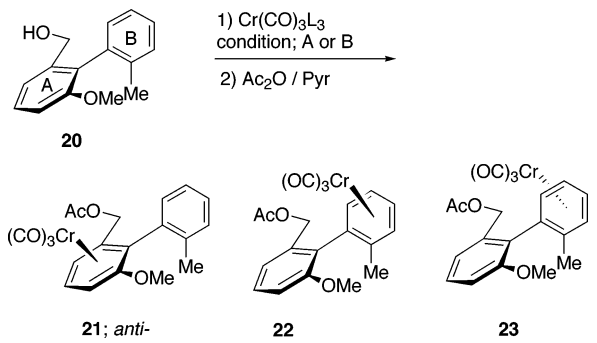
[a] Reagenets and conditions: (A) $Cr(CO)_6$, *n*-Bu_2O/THF (10/1), 120 °C, 18 h; **18** (40%), **19** (2%), **9** (28%); (B) (naphthalene)$Cr(CO)_3$, THF/ether (10/1), 70 °C, 4 h; **18** (3%), **19** (17%), **9** (41%).

plex (**15**) as a major product along with formation of the corresponding acetate chromium complex **14**[4a] derived from the starting material **3a**. Although the reaction was performed under conditions which induce inversion of planar chirality, the reason for recovering the *syn*-biaryl chromium complex even though a minor product is unclear. In both cases, the tricarbonylchromium fragment migrates to the arene ring substituted with the hydroxymethyl group. These results indicate that the inversion of the planar chirality of chromium complexes **3** with benzylic heteroatom substituents under thermal conditions proceeds in an *intermolecular* fashion.

Moreover, it was found that an "*intramolecular* coordination of the heteroatom" with the tricarbonylchromium fragment is essential for the chromium migration. Thus, heating a mixture of *syn*-biaryl chromium complex **3f** with an *o*-methyl group and 2,6-dimethoxy-2′-hydroxymethyl biphenyl (**11**) resulted in recovering the starting materials without formation of the chromium migration product **16** (Scheme 4).

It is important for clarification of the inversion of planar chirality to see if the tricarbonylchromium migration is attributed to a recomplexation path to chromium-free biaryl compounds derived from *syn*-biaryl chromium complexes. Direct chromium complexation of 2-methoxy-6-methyl-2′-hydroxymethylbiphenyl (**17**) with $Cr(CO)_6$ afforded thermodynamically stable *anti*-biphenyl complex **18** and the B-ring chromium-coordinated compound **9** under heating in di-*n*-butyl ether and THF at 120 °C (Scheme 5). The *anti*-biphenyl complex **18** coordinated on the electron-rich A-ring was obtained as a major product in direct chromium complexation. As shown in Scheme 2, the *syn*-biaryl chromium complex **8** gave predominantly chromium migration products **9** and **10** to the B-ring with the hydroxymethyl group under thermal conditions. From these results, the chromium migration reaction seems to rule out a process of recomplexation of the generated chromium-free biaryl compounds from *syn*-biaryl complxes. However, chromium complexation of **17** with (naphthalene)$Cr(CO)_3$ under heating in THF and ether at 70 °C gave B-ring coordination product **9** and A-ring coordinated *syn*-biaryl chromium complex **19**. Both chromium complexes **9** and **19** would be formed via a coordination intermediate of the benzylic oxygen with the chromium fragment. Obviously, the reaction path for the chromium complexation of **17** with (naphthalene)$Cr(CO)_3$ is distinct from that of thermodynamic conditions with $Cr(CO)_6$.

SCHEME 6 [a]



[a] Reagents and conditions: (A) $Cr(CO)_6$, *n*-Bu_2O/THF (10/1), 120 °C, 24 h; **21** (60%), **22** (8%), **23** (−); (B) (naphthalene)$Cr(CO)_3$, THF/ether (10/1), 70 °C, 4 h; **21** (28%), **22** (6%), **23** (17%).

We have already reported[9a] that 2-methoxy-6-hydroxymethyl-2′-methylbiphenyl (**20**) afforded thermodynamically stable *anti*-biphenyl complex **21** coordinated to the hydroxymethyl-substituted electron-rich arene A-ring as a major compound under both conditions (Scheme 6). The chromium complex **23** was obtained via a coordination intermediate of the benzylic hydroxy with chromium by complexation with (naphthalene)$Cr(CO)_3$.

Obviously, the reaction path for the tricarbonylchromium migration under thermal conditions is initiated by intramolecular coordination of the benzylic heteroatom with the chromium fragment followed by transfer of the chromium to the benzylic heteroatom-substituted arene ring. The reaction products of the chromium migration under thermal conditions are not completely consistent with those of chromium complexation with (naphthalene)$Cr(CO)_3$, although the benzylic heteroatom is significant for the chromium migration for both reactions. It is noted that the chromium migration of the *syn*-biaryl chromium complexes under thermal conditions gives predominantly *anti*-biaryl chromium complexes with high diastereoselectivity, while direct chromium complexation of biaryls, regardless of the complexation reagents, afforded regio- and stereoisomeric mixture in various ratios.

A kinetic study of the migration reaction of *syn*-biaryl chromium complex **3d** was carried out (Figure 1). The decrease of concentration of complex **3d** was monitored by HPLC with ferrocene as an internal standard. Kinetic plots are accurately first order in the chromium complex **3d**. The first-order rate constant k_{obs} and the half-life at 110 °C were estimated as 1.97×10^{-3} and 0.10 h. This result indicates that arene−metal bond cleavage requires the most energy in these migration reactions, and would be the rate-determining step.

On the basis of these observations, a plausible mechanism for the stereoselective chromium migration to the

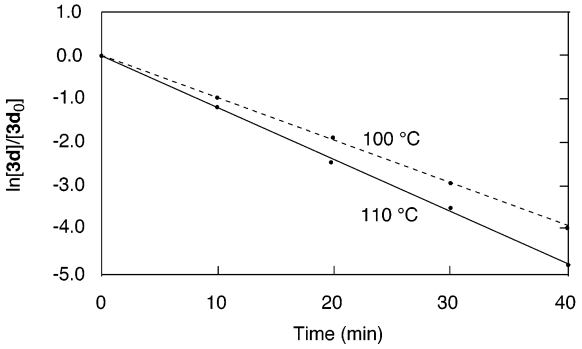
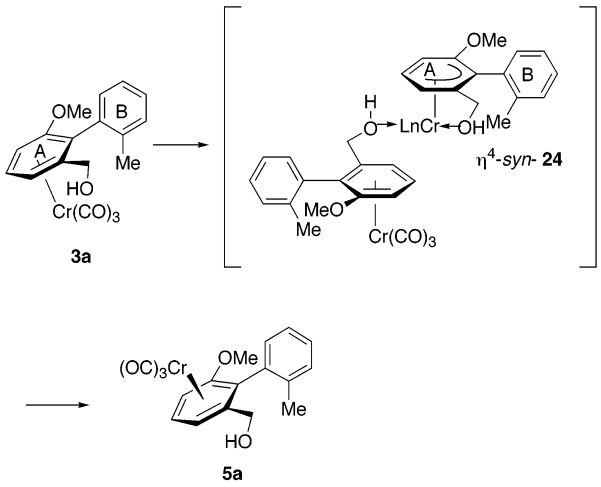


FIGURE 1. First-order kinetics plots for disappearance of *syn*-biaryl **3d** in migration reaction.

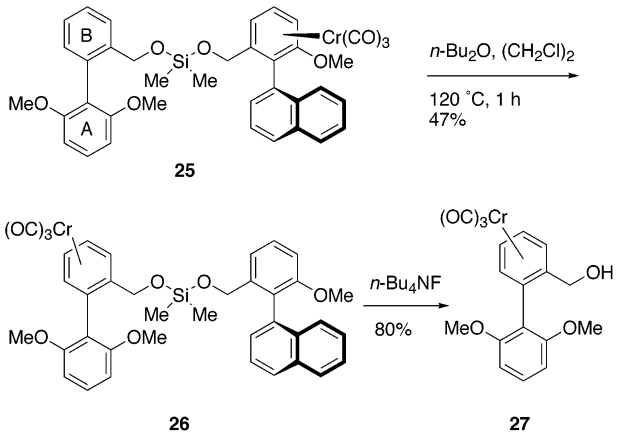
SCHEME 7. Proposed Reaction Mechanism for Face Inversion



reversed face is proposed in Scheme 7. The tricarbonylchromium unit of the *syn*-biphenyl complex **3a** can slip to the η^4-*syn*-**24** intermediate via intramolecular coordination of the chromium with the benzylic heteroatom and a coordinating solvent. Judging from the first-order kinetic study, this initial step requiring the disruption of aromaticity would be the rate-determining step. Regardless of electron density, the chromium migration reaction proceeds on the arene ring possessing a heteroatom at the benzylic position. Subsequently, another benzyl alcohol of the *syn*-biaryl chromium complex could coordinate with the chromium of the η^4-*syn*-**24** intermediate for a dual activation. In this way, a labile tricarbonylchromium species could generate and coordinate to the less hindered side of the A-ring giving *anti*-biaryl chromium complex **5a**. However, the precise reaction mechanism is still unclear.

Internal Chromium Migration Reaction in a Bis-biaryl Chromium Complex. For further development of an efficient chromium migration reaction, we next studied an internal chromium migration reaction to another arene ring. The "internal" migration reaction proceeds about two times faster than the "external" reaction already mentioned above. We selected bis-biaryl chromium complex **25** as a model compound, in which the *syn*-biaryl chromium complex unit was linked with another biaryl unit. Heating of **25** in di-*n*-butyl ether and dichloroethane at 120 °C gave tricarbonylchromium migration product to another biaryl B-ring **26** in 47% yield (Scheme 8). Desilylation of **26** with *n*-Bu_4NF gave chromium complex **27** in 80% yield. As both benzylic hydroxy groups of complex **25** are protected with the dimethylsilyl group, the coordination ability with the chromium seems to be poor. Nevertheless, the tricarbonylchromium fragment migrated selectively to the B-ring of the chromium-free biaryl unit, not to the electron-rich A-ring. As the *syn*-biaryl chromium complex unit of **25** has both planar and axial chiralities, it is expected to open avenues for stereoselective chromium tricarbonyl migration to prochiral arene compounds with *distinction of the arene face*. In line with this idea, we are now planning asymmetric chromium migration on arene compounds substituted with a free-*o*-hydroxymethyl unit to increase the coordination ability with the chromium fragment.

SCHEME 8

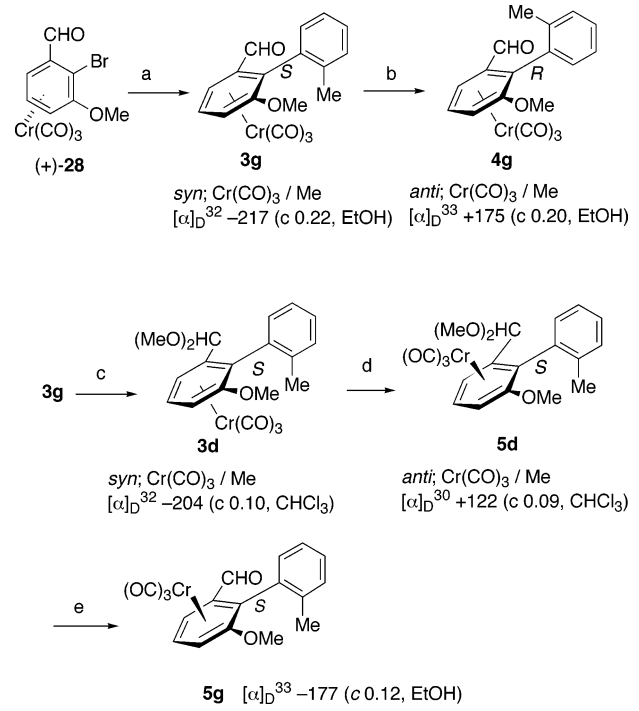


Stereoselective Functionalization of Axially Chiral Biaryl Chromium Complexes. As part of our exploration of the planar chiral arene chromium complexes, we have developed diastereoselective cross-coupling with *o*-substituted arylboronic acids giving *syn*-biaryl chromium complexes and subsequent axial isomerization and inversion of planar chirality of the *syn*-biaryl chromium complexes depending on the nature of the ortho substituents and reaction conditions. We next studied stereoselective fuctionalization at the side chain of biaryl chromium complexes. Since planar chiral *o*-substituted benzaldehyde chromium complexes are versatile compounds in asymmetric synthesis,[13] we initially prepared *syn*- and both enantiomeric *anti*-(η-1,2,3,4,5,6)-tricarbonyl(2-methoxy-6-formyl-2′-methylbiphenyl)chromium complexes, **3g**, **4g**, and *ent*-**4g**, from an identical planar chiral arene chromium complex (+)-**28** according to the above-mentioned procedure (Scheme 9).

Similarly, analogous axially chiral *syn*- and *anti*-biaryl chromium complexes with a naphthalene fragment were prepared in a similar sequence (Scheme 10).[4a] Face inversion was achieved with hydroxymethyl-substituted *syn*-chromium complex **31**. Heating of **31** in a 1:1 mixture of di-*n*-butyl ether and 1,2-dichloroethane gave *anti*-complex **32** with $Cr(CO)_3$ fragment migration with high selectivity (ratio 99:1). Oxidation[14] of **32** with DMSO and acetic anhydride afforded *ent*-**30**.

Having established the method for the preparation of axially chiral *syn*-biaryl and both enantiomers of *anti*-biaryl chromium complexes starting from a single planar chiral arene chromium complex, the synthetic utility for

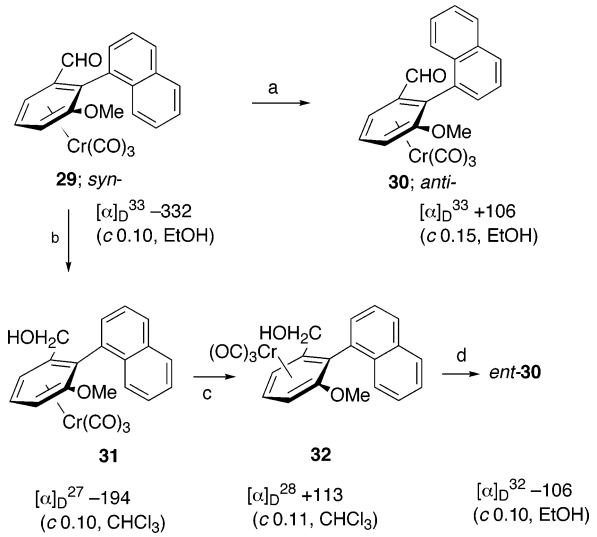
SCHEME 9 [a]



[a] Reagents and conditions: (a) *o*-methylphenylboronic acid, 5 mol % of $Pd(PPh_3)_4$, Na_2CO_3, MeOH, H_2O, 75 °C (74%); (b) xylene, 140 °C, 2 h (70%); (c) $CH(OMe)_3$, MeOH, *p*-TsOH, rt (70%); (d) *n*-Bu_2O, $(CH_2Cl)_2$, 120 °C, 3 h (50%); (e) 6 N HCl, THF, rt (92%).

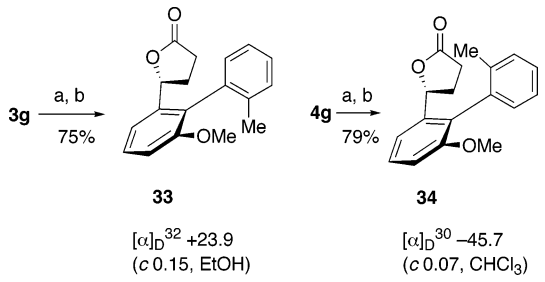
stereoselective fuctionalization at the side chain of biaryl chromium complexes was investigated.[15] Initially, stereoselective addition to the *o*-formyl group of biaryl chromium complexes was examined. The samarium iodide-mediated coupling reaction of the chromium-complexed benzaldehydes **3g** and **4g** with methyl acrylate gave optically pure γ-lactone compounds **33** and **34**, respectively, as shown in Scheme 11. No stereoisomers at the benzylic position were detected, and high diastereoselectivity is based on stereoselective attack of the samarium iodide to the *anti*-oriented carbonyl group[16]

SCHEME 10 [a]



[a] Reagents and conditions: (a) xylene, 140 °C, 2 h (98%); (b) $NaBH_4$, MeOH, 0 °C (100%); (c) *n*-Bu_2O, $(CH_2Cl)_2$, 120 °C, 2 h (65%); (d) DMSO, Ac_2O, rt (64%).

SCHEME 11. Stereoselective Addition Reaction to the Formyl Group[a]



[a] Reagents and conditons: (a) SmI_2, $CH_2{=}CHCO_2Me$, *t*-BuOH, THF; (b) $h\nu$, air, ether.

and stable configuration of the generated chromium-complexed ketyl radical intermediate without racemization at the benzylic position.[17] *ent*-**4g** was also converted to the corresponding γ-lactone compound *ent*-**34**.

Cycloaddition to the corresponding imine group of the axially chiral biaryl chromium complexes was also observed (Scheme 12). Treatment of chromium-complexed benzaldimines **35**, **38**, and antipode of **38** with phenoxy acetyl chloride in the presence of triethylamine gave *cis*-β-lactam derivatives without any formation of stereoisomers in good yields.[18,19] Similarly, reaction[20] with Dan-

(13) Some representative references: (a) Pache, S.; Romanens, P.; Kündig, E. P. *Organometallics* **2003**, *22*, 377−380. (b) Wang, Q.; Foersterling, F. H.; Hossain, M. M. *Organometallics* **2002**, *21*, 2596−2598. (c) Tanaka, Y.; Taniguchi, N.; Uemura, M. *J. Org. Chem*. **2002**, *67*, 9227−9237. (d) Gibson, S. E.; Ibrahim, H. *Chem. Commun*. **2002**, *21*, 2465−2473. (e) Rose-Munch, F.; Rose, E. *Eur. J. Inorg. Chem*. **2002**, 1269−1283. (f) Tanaka, Y.; Taniguchi, N.; Uemura, M. *Org. Lett*. **2002**, *4*, 835−838. (g) Netz, A.; Polborn, K.; Müeller, T. J. *J. Am. Chem. Soc*. **2001**, *123*, 3441−3453. (h) Baldoli, C.; Del Buttero, P.; Perdicchia, D.; Pilati, T. *Tetrahedron* **1999**, *55*, 14089−14096. (i) Rose-Munch, F.; Rose, E. *Curr. Org. Chem*. **1999**, *3*, 445−467. (j) Han, J. W.; Son, S. U.; Chung, Y. K. *J. Org. Chem*. **1997**, *62*, 8264−8267. (k) Fretzen, A.; Kündig, E. P. *Helv. Chim. Acta* **1997**, *80*, 2023−2026. (l) Alexakis, A.; Kanger, T.; Mangeney, P.; Rose-Munch, F.; Perrotey, A.; Rose, E. *Tetrahedron*: *Asymmetry* **1995**, *6*, 2135−2138. (m) Baldoli, C.; Del Buttero, P. *J. Chem. Soc., Chem. Commun*. **1991**, 982−984. (n) Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A. *J. Chem. Soc., Chem. Commun*. **1987**, 762−764. (o) Davies, S. G.; McCarthy, T. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier Science, Ltd.: Oxford, UK, 1995; Vol. 12, pp 1039−1070. (p) Schmalz, H.-G.; Siegel, S. In *Transition Metals for Fine Chemicals and Organic Synthesis*; Bolm, C., Beller, M., Eds.; VCH: Weinheim, Germany, 1998; Vol. 1

(14) Levine, S. G.; Gopalakrshnan, B. *Tetrahedron Lett*. **1982**, *23*, 1239−1240.

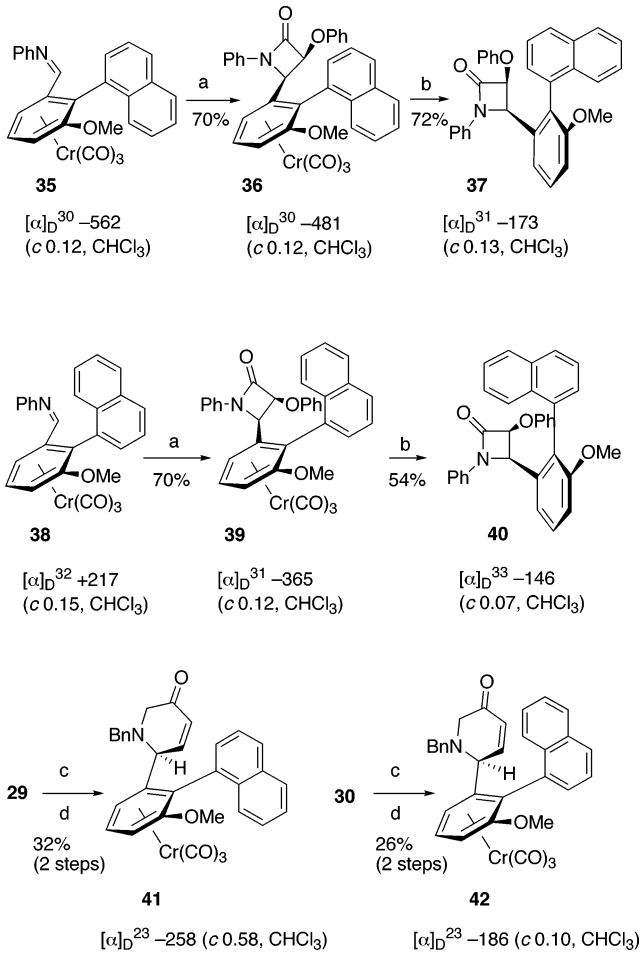
(15) Tanaka, Y.; Sakamoto, T.; Kamikawa, K.; Uemura, M. *Synlett* **2003**, 519−521.

(16) For some reviews see: (a) Solladié-Cavallo, A. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1, p 99. (b) Davies, S. G.; Coote, S. J.; Goodfellow, C. L. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S. Ed.; JAI Press: Greenwich, CT, 1991; Vol. 2, p 1. (c) Uemura, M. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI Press: Greenwich, CT, 1991; Vol. 2, p 195. (d) Davies, S. G.; Donohoe, T. J. *Synlett* **1993**, 323−332.

(17) (a) Taniguchi, N.; Uemura, M. *Tetrahedron Lett*. **1997**, *38*, 7199−7202. (b) Merlic, C. A.; Walsh, J. C. *Tetrahedron Lett*. **1998**, *39*, 2083−2086.

(18) (a) Baldoli, C.; Del Buttero, P.; Licandro, E.; Maiorana, S.; Papagni, A. *Tetrahedron*: *Asymmetry* **1994**, *5*, 809−812. (b) Del Buttero, P.; Baldoli, C.; Molteni, G.; Pilati, T. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1927−1941.

SCHEME 12. Stereoselective Cycloaddition Reaction to the Imine Group[a]



[a] Reagents and conditions: (a) $PhOCH_2COCl$, Et_3N, CH_2Cl_2, 0 °C to rt; (b) *hν*, air, ether; (c) $BnNH_2$, p-TsOH, ether; (d) *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene, $SnCl_4$, THF, −78 to 0 °C.

ishefsky's diene in the presence of $SnCl_4$ gave 2,3-dihydro-4-pyridinone chromium complexes **41** and **42**.

In conclusion, we have demonstrated stereoselective tricarbonylchromium migration to the inverted arene face by heating of the chromium-complexed *syn*-biaryls having a coordinating group at the benzylic position in a non-aromatic donor solvent. Moreover, we have reported asymmetric synthesis of axially chiral *syn*-biaryl and both *anti*-biaryl chromium complexes starting from a single planar chiral arene chromium complex as a chiral source, and stereoselective fuctionalization at the side chain of biaryl chromium complexes. Further exploration such as stereoselective chromium tricarbonyl migration to the other arene ring is under investigation.

(19) Crystallographic data for racemic **39** have been deposited with Cambridge Crystallographic Data Center, No. CCDC-1195543. Empirical formula $C_{35}H_{25}NO_6Cr$, M = 607.58, orthorhombic, space group $Pca2_1$, a = 12.633 Å, b = 10.3860 Å, c = 21.752 Å, V = 2853.9(5) Å^3, Z = 4, D_c = 1.414 g/cm^3, F_{000} = 1256.00, Mo Kα (λ = 0.71075 Å), no. of reflections measured 26037, reflections with $I > 3.00\sigma(I)$, R = 0.049, R_w = 0.095.

(20) (a) Ratni, H.; Crousse, B.; Kündig, E. P. *Synlett* **1999**, 626−628. (b) Kündig, E. P.; Xu, L. H.; Romanens, P.; Bernardinelli, G. *Synlett* **1996**, 270−272. (c) Baldoli, C.; Del Buttero, P.; Ciolo, M. D.; Mariorana, S.; Papagni, A. *Synlett* **1996**, 258−260.

Experimental Section

All manipulations involving organometallics were carried out under an atmosphere of nitrogen or argon and with inert gas/vacuum double manifold techniques. All NMR spectra were recorded in $CDCl_3$ or acetone-d_6 solvent with tetramethylsilane as an internal reference. Mass spectra were determined with the EI mode. Optical rotations were obtained at a wavelength of 589 nm (sodium D line), using a 1.0-dm cell with a total volume of 5 mL. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl immediately before use. Toluene, di-*n*-butyl ether, and dichloroethane were used as received.

General Procedure for the Thermal Reaction of the Biaryl Chromium Complex. A solution of *syn*-biaryl complex **3** (0.25 mmol) in a mixture of di-*n*-butyl ether (2.0 mL) and dichroloethane (2.0 mL) was stirred at 120 °C for 2 h. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give *anti*-biaryl complexes **4** and **5**. The ratio of axially isomerized *anti*-complex **4** and face-inverted *anti*-complex **5** was determined by HPLC with the chiral stationary phase.

(+)-(*R,S*)-Tricarbonyl[(η-1,2,3,4,5,6)-2-methoxy-6-(hydroxymethyl)-2′-methylbiphenyl)chromium (5a): mp 122 °C; $[\alpha]^{31}_D$ +140.0 (*c* 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.72 (1H, s), 2.09 (3H, s), 3.66 (3H, s), 4.20 (2H, d, J = 5.5 Hz), 5.06 (1H, d, J = 6.5 Hz), 5.15 (1H, d, J = 6.5 Hz), 5.79 (1H, t, J = 6.5 Hz), 7.23−7.33 (3H, m), 7.42−7.45 (1H, m); IR ($CHCl_3$) 1950, 1870, 1530, 1450, 1420, 1260, 1030 cm^{-1}. Anal. Calcd for $C_{18}H_{16}O_5Cr$: C, 59.34; H, 4.43. Found: C, 59.34; H, 4.50. HPLC conditions: Chiralcel OD; hexane/2-propanol 9/1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm; retention time for racemate 13.8, 16.2 min, retention time for complex **5a** 16.2 min, retention time for complex **4a** 13.8 min.

(+)-(*R,S*)-Tricarbonyl[(η-1,2,3,4,5,6)-2-methoxy-6-(methoxymethyl)-2′-methylbiphenyl)chromium (5b): $[\alpha]^{29}_D$ +114.3 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.09 (3H, s), 3.24 (3H, s), 3.65 (3H, s), 3.84 (1H, d, J = 12.5 Hz), 3.96 (1H, d, J = 12.5 Hz), 5.03 (1H, d, J = 6.6 Hz), 5.10 (1H, d, J = 6.6 Hz), 5.76 (1H, t, J = 6.6 Hz), 7.23−7.33 (3H, m), 7.42−7.45 (1H, m); MS (rel intensity) *m/z* 378 (M^+, 8), 294 (47), 263 (4), 249 (75), 231 (13), 169 (23), 131 (32), 119 (32), 100 (7), 69 (100); HRMS calcd for $C_{19}H_{18}O_5Cr$ 378.0559, found 378.0556. HPLC conditions: Chiralcel OD; hexane/2-propanol 9/1; flow rate 0.5 mL/min; column temperature 40 °C; UV detector 254 nm; retention time for racemate, 14.3, 15.8 min, retention time for complex **5b**, 15.8 min, retention time for complex **4b**, 14.3 min.

(*R,S*)-Tricarbonyl[(η-1,2,3,4,5,6)-2-methoxy-6-(*tert*-butyldimethylsilyloxymethyl)-2′-methylbiphenyl)chromium (5c): mp 131 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.11 (3H, s), −0.06 (3H, s), 0.83 (9H, s), 2.08 (3H, s), 3.64 (3H, s), 4.04 (1H, d, J = 12.8 Hz), 4.17 (1H, d, J = 12.8 Hz), 5.02 (1H, d, J = 6.6 Hz), 5.14 (1H, d, J = 6.2 Hz), 5.75 (1H, dd, J = 6.2, 6.6 Hz), 7.21−7.31 (3H, m), 7.42 (1H, dd, J = 1.5, 6.2 Hz); IR ($CHCl_3$) 1950, 1860, 1460, 1420, 1260, 1120, 1060 cm^{-1}. Anal. Calcd for $C_{24}H_{30}O_5CrSi$: C, 60.23; H, 6.32. Found: C, 60.31; H, 6.11. The ratio of **5c** and **4c** was determined after transforming into complexes **5a** and **4a**.

(+)-(*R,S*)-Tricarbonyl[(η-1,2,3,4,5,6)-2-methoxy-6-(dimethoxymethyl)-2′-methylbiphenyl)chromium (5d): mp 148 °C; $[\alpha]^{30}_D$ +122.0 (*c* 0.09, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (3H, s), 2.99 (3H, s), 3.48 (3H, s), 3.63 (3H, s), 4.88 (1H, s), 5.03 (1H, d, J = 6.1 Hz), 5.20 (1H, d, J = 6.1 Hz), 5.75 (1H, t, J = 6.1 Hz), 7.26−7.30 (3H, m), 7.48 (1H, d, J = 5.9 Hz); IR ($CHCl_3$) 1960, 1880, 1540, 1420, 1260, 1060 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_6Cr$: C, 58.82; H, 4.94. Found: C, 58.62; H, 5.00. HPLC conditions: Chiralcel OJ; hexane/2-propanol 9/1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm; retention time for racemate, 9.1, 11.1 min, retention time for complex **5d**, 11.1 min, retention time for complex **4d**, 9.1 min.

(+)-(*R*,*S*)-Tricarbonyl[(η-1,2,3,4,5,6)-2-methoxy-6-(*N*-methylaminomethyl)-2′-methylbiphenyl)chromium (5e): $[\alpha]^{31}_D$ +103.0 (*c* 0.13, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.61 (1H, s), 2.09 (3H, s), 2.34 (3H, s), 3.27 (2H, s), 3.65 (3H, s), 5.04 (1H, d, *J* = 6.5 Hz), 5.14 (1H, d, *J* = 6.5 Hz), 5.75 (1H, t, *J* = 6.5 Hz), 7.25−7.32 (3H, m), 7.43−7.46 (1H, m); IR ($CHCl_3$) 1940, 1860, 1530, 1420, 1250, 1050 cm^{-1}; MS (rel intensity) *m*/*z* 377 (M^+, 1), 349 (6), 293 (100), 249 (87); HRMS calcd for $C_{19}H_{19}O_4NCr$ 377.0719, found 377.0713. HPLC conditions: Chiralcel AD; hexane/2-propanol/Et_2NH 200/10/1; flow rate 0.5 mL/min; column temperature 40 °C; UV detector 254 nm; retention time for racemate, 19.8, 21.9 min, retention time for complex **5e**, 19.8 min, retention time for complex **4e**, 21.9 min.

(+)-(*S*,*R*)-Tricarbonyl[(η-1,2,3,4,5,6)-2-methoxy-6-formyl-2′-methylbiphenyl]chromium (4g): mp 130 °C; $[\alpha]^{33}_D$ +175.0 (*c* 0.20, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (3H, s), 3.67 (3H, s), 5.27 (1H, d, *J* = 6.7 Hz), 5.43 (1H, d, *J* = 6.7 Hz), 5.80 (1H, t, *J* = 6.7 Hz), 7.26 (1H, d, *J* = 7.3 Hz), 7.32−7.39 (2H, m), 7.57 (1H, d, *J* = 7.3 Hz), 9.41 (1H, s); IR ($CHCl_3$) 1980, 1910, 1700 cm^{-1}. Anal. Calcd for $C_{18}H_{14}O_5Cr$: C, 59.67; H, 3.89. Found: C, 59.61; H, 3.92. HPLC conditions: Chiralcel AS; hexane/2-propanol 9/1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm; retention time for racemate, 13.3, 27.0 min, retention time for complex **5g**, 27.0 min, retention time for complex **4g**, 13.3 min.

(−)-(*S*,*R*)-Tricarbonyl[(η-1,2,3,4,5,6)-2-methoxy-6-(methoxycarbonyl)-2′-methylbiphenyl]chromium (4h): mp 128 °C; $[\alpha]^{29}_D$ −170.0 (*c* 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.07 (3H, s), 3.58 (3H, s), 3.66 (3H, s), 5.14 (1H, d, *J* = 6.7 Hz), 5.39 (1H, d, *J* = 6.7 Hz), 5.76 (1H, d, *J* = 6.7 Hz), 7.18−7.32 (3H, m), 7.39−7.42 (1H, m); IR ($CHCl_3$) 1960, 1880, 1700, 1420, 1250, 1050 cm^{-1}. Anal. Calcd for $C_{19}H_{16}O_6Cr$: C, 58.17; H, 4.11. Found: C, 57.98; H, 4.13. HPLC conditions: Chiralcel OF; hexane/2-propanol 100/1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm; retention time for racemate, 37.8, 42.9 min, retention time for complex **4h**, 37.8 min, retention time for **5h**, 42.9 min.

(+)-(*S*,*R*)-Tricarbonyl[(η-1,2,3,4,5,6)-2-methoxy-6-(*N*-methylimino)-2′-methylbiphenyl]chromium (4i): mp 117 °C; $[\alpha]^{31}_D$ +85.4 (*c* 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.05 (3H, s), 3.33 (3H, s), 3.65 (3H, s), 5.11 (1H, d, *J* = 6.5 Hz), 5.58 (1H, d, *J* = 6.5 Hz), 5.80 (1H, d, *J* = 6.5 Hz), 7.24−7.38 (3H, m), 7.38−7.59 (2H, m); IR ($CHCl_3$) 1940, 1860, 1620, 1480, 1410, 1260 cm^{-1}. Anal. Calcd for $C_{19}H_{17}NO_4Cr$: C, 60.80; H, 4.57. Found: C, 61.06; H, 4.46. The ratio of **5i** and **4i** was determined after transforming into complexes **5g** and **4g**.

(+)-(*S*,*R*)-Tricarbonyl[(η-1,2,3,4,5,6)-6-acetyl-2-methoxy-2′-methylbiphenyl]chromium (4j): $[\alpha]^{25}_D$ +91.5 (*c* 0.094, $CHCl_3$); ^{1}H NMR δ1.88 (3H, s), 2.06 (3H, s), 3.66 (3H, s), 5.19 (1H, d, *J* = 6.6 Hz), 5.23 (1H, d, *J* = 6.6 Hz), 5.76 (1H, t, *J* = 6.6 Hz), 7.21−7.33 (3H, m), 7.52 (1H, d, *J* = 7.0 Hz); IR ($CHCl_3$) 1970, 1900, 1685, 1275, 1040 cm^{-1}; MS (rel intensity) *m*/*z* 376 (M^+, 2), 348 (2), 320 (6), 292 (100); HRMS calcd for $C_{19}H_{16}O_5Cr$ 376.0402, found 376.0424. HPLC conditions: Chiralcel AS; hexane/2-propanol 9/1; flow rate 1.0 mL/min; column temperature 40 °C; UV detector 254 nm; retention time for racemate, 11.3, 15.1 min, retention time for complex **4j**, 15.1 min, retention time for complex **5j**, 11.3 min.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 14078101, Reaction Control of Dynamic Complexes) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental details for the preparation of complexes and spectral characterization; kinetic study of complex **3d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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