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Diastereoselective Synthesis of Axially Chiral Biaryls via Nucleophilic Addition to (Arene)chromium Complexes with Grignard Reagents

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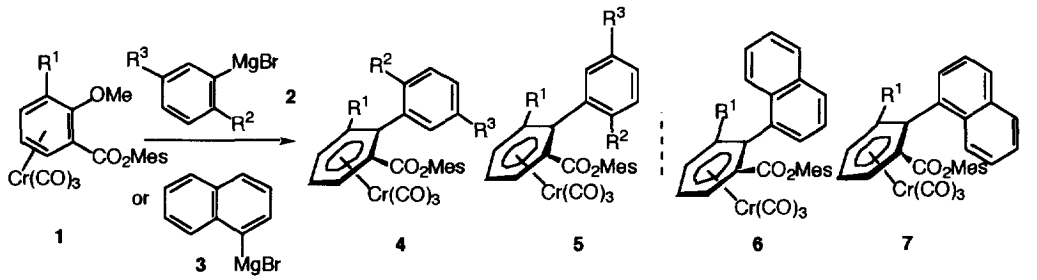
Abstract: Nucleophilic substitution of tricarbonyl(2,4,6-trimethylphenyl 2-methoxybenzoate)-chromium complexes with aryl Grignard reagents affords stereoselectively axially chiral biaryls.

Axially chiral biaryls are of potential importance not only as chiral ligands for asymmetric reactions but also as intermediates for the synthesis of biologically active natural products. There is considerable current interest in development of methodologies for synthesis of enantiomerically pure axial biaryls.[1] Nucleophilic substitution of an *o*-alkoxy group of activated arenes with electron-withdrawing substituents such as oxazoline, ester, sulfinyl, sulfonyl and diphenylphosphinyl groups with aryl Grignard reagents produce biaryl compounds.[1,2] These nucleophilic substitutions of the activated *o*-alkoxy arenes with chiral auxiliaries provide atropisomerically active biaryls. Recently, Miyano et al. reported that the nucleophilic substitution of 2-menthoxybenzoates with aryl Grignard reagents gave axially chiral biphenyl-2-carboxylates with various diastereoselectivities depending upon the Grignard reagents.[2b] The strong electron-withdrawing property of the tricarbonylchromium accelerates the nucleophilic addition,[3] and the (arene)$Cr(CO)_3$ complexes possessing different substituents at *ortho*- or *meta*-positions can exist in two enantiomeric forms based on a planar chirality. We have recently reported that the planar chirality of the arene ring is diastereoselectively transferred to the axial chirality of biaryls by palladium(0)-catalyzed cross-coupling of (η^6-arylhalide)$Cr(CO)_3$ with arylboronic acids.[4,5] Here, we wish to report stereoselective synthesis of axially chiral biaryls by nucleophilic addition of aryl Grignards to planar chiral (arene)chromium complexes.

A solution of tricarbonyl(2,4,6-trimethylphenyl 2,3-dimethoxybenzoate)chromium (**1**) (R^1 = OMe) and *o*-tolylmagnesium bromide in a mixture of ether/benzene (1/4) was refluxed for 30 min to afford the nucleophilic substitution products as a diastereomeric mixture in a ratio of 98 : 2 (entry 1).[6] The relative stereochemistry of the major product **4** was easily elucidated by ^{1}H-NMR spectra, in which a lower field methyl signal (δ 2.64 ppm) was assigned to the *syn*-methyl protons to the $Cr(CO)_3$ fragment, while the corresponding *anti*-methyl protons appeared at 2.10 ppm. Generally, NMR signals of the protons *syn* to the $Cr(CO)_3$ fragment are shifted to far lower field than are those of the *anti*-protons due to an anisotropic effect of the $Cr(CO)_3$ fragment.[7] Other reaction results are summarized in Table, and some facts are worthy of comment. Generally, high *anti*



Mes = 2,4,6-trimethylphenyl

Table. Nucleophilc Substitution of (Arene)chromium Complexes with Aryl Grignards

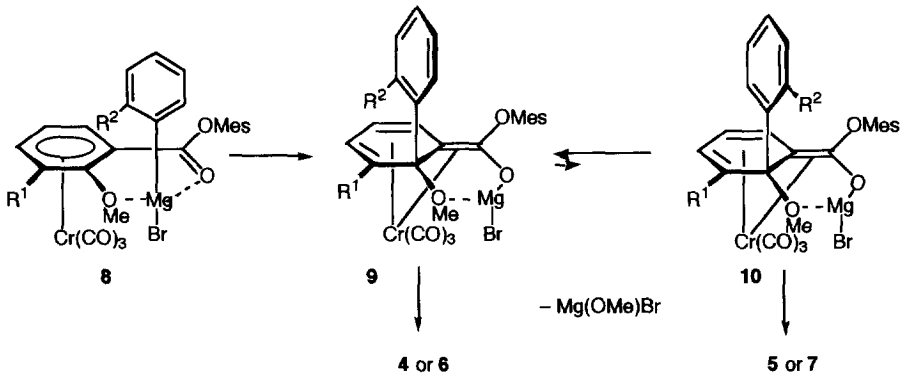
Entry	Complex **1**	Grignard reagents **2** or **3**	Reflux (solv. min)	Yield (%)	Ratio **4** : **5** (or **6** : **7**)
1	R^1 = OMe	**2**: R^2 = Me, R^3 = H	benzene 30	68	98 : 2
2	R^1 = Me	**2**: R^2 = Me, R^3 = H	benzene 30	68	99 : 1
3	R^1 = Me	**2**: R^2 = R^3 = Me	xylene 90	81	99 : 1
4	R^1 = Me	**2**: R^2 = OMe, R^3 = H	benzene 30	–[a]	
5	R^1 = OMe	**2**: R^2 = OMe, R^3 = H	benzene 30	–[a]	
6	R^1 = OMe	**2**: R^2 = OCH_2OMe, R^3 = H	benzene 30	–[a]	
7	R^1 = OMe	**3**	benzene 30	68	91 : 9
8	R^1 = OMe	**3**	mesitylene 120	60	>99 : 1
9	R^1 = Me	**3**	benzene 30	70	95 : 5
10	R^1 = Me	**3**	mesitylene 120	76	>99 : 1

a; Complexed mixture

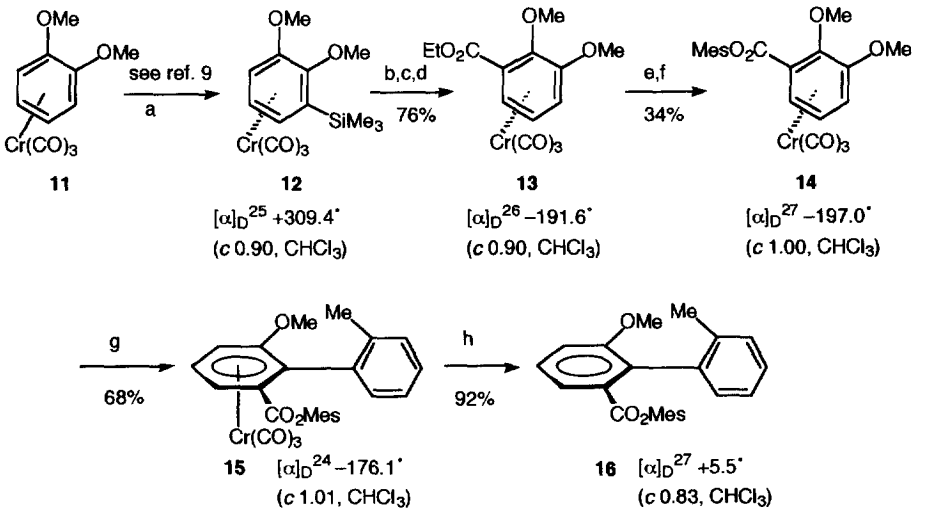
diastereoselectivities were achieved by the nucleophilic additions of aryl Grignard reagents to the planar chiral (arene)chromium complexes. The diastereoselectivity was found to be dependent on the reaction temperature. Thus, reflux of **1** and α-naphthymagnesium bromide in benzene afforded **6** with 82~90% de, while the reaction under mesitylene refluxing gave **6** exclusively (entries 7 vs 8; 9 vs 10). This higher selectivity is a result of axial isomerization of the sterically unfavored *syn*-isomers **7** to the thermodynamically controlled *anti*-isomers **6** under reflux in higher boiling point solvent.[4c,8] Surprisingly, the reaction of aryl Grignards having an oxygen function at the *ortho*-position with (2-methoxy-*3-substituted* benzoate)$Cr(CO)_3$ complex **1** ($R^1 \neq H$) afforded a complexed mixture without formation of the desired nucleophilic addition/elimination product (entries 4~6). However, (2-methoxy benzoate)$Cr(CO)_3$ complex **1** (R^1 = H) was reacted with *o*-anisyl Grignard giving the corresponding nucleophilic addition/elimination product in good yield.

The plausible reaction mechanism for high diastereoselectivity would be mostly indebted to the proposed model by Meyers.[1b,9] The Grignards approach from the *exo*-side via coordination of magnesium with two oxygen atoms to form **8**. From the chelated intermediate **8**, the aryl group migrates to the C_{ipso} position of the methoxy forming σ-complexed enolate transition states **9** and **10**. When the enolate intermediate rearomatizes giving the biaryl compounds with loss of the methoxy, the axial chirality is controlled by the steric interactions between the *ortho* substituent R^2 and $Cr(CO)_3$ fragment. Therefore, the biaryl compound **4** is predominantly obtained through the sterically favored enolate **9**. In the case of the *o*-oxygenated aryl Grignard reagents,

magnesium would further coordinate with oxygen of the R^2 substituent forming the enolate **10**, which might be the cause for the non-formation of the desired addition/elimination products.



Finally, enantiomerically pure biaryl was synthesized from the planar chiral arene chromium complex. (1,2-Dimethoxybenzene)chromium (**11**) was converted to (+)-(2,3-dimethoxytrimethylsilylbenzene)chromium (**12**) in 90-97% ee by the known procedure.[10] Further *ortho* lithiation of **12** followed by quenching with ethyl chloroformate, and de-silylation with the fluoride ion gave enantiomerically pure (–)-complex **13** in 76% overall yield after one recrystallization from ether/hexane. Basic hydrolysis of **13** and subsequent reaction with 2,4,6-trimethylphenol produced **14** in 34% yield. Nucleophilic addition of **14** with *o*-tolyl Grignard followed by exposure to sunlight afforded axially chiral (*S*)-biphenyl **16** with 98% ee.[11]



Reagents and Conditions

a) Lithium bis[(*R*)-α-phenylethyl]amide, THF, Me_3SiCl (83%); b) *n*-BuLi, THF, TMEDA, -78°C, 1h; c) $ClCO_2Et$, THF, -78°C; d) *n*-Bu_4F, THF; e) 1M-KOH, THF, H_2O; f) 2,4,6-trimethylphenol, $(CF_3CO)_2O$, reflux; g) *o*-tolylmagnesium bromide, benzene, reflux; h) *hν*-O_2, ether

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6 Typical procedure: To a solution of complex **1** (R^1 = Me) (200mg, 0.48mmol) in dry benzene (4 mL) was added a solution of *o*-tolylmagnesium bromide (1M in ether, 1.0 mL, 1.0mmol) under argon, and the mixture was refluxed for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by SiO_2 chromatography to give 157 mg of **4** (R^1 = R^2 = Me, R^3 = H). mp 148°C, ^{1}H-NMR (400MHz, $CDCl_3$) δ 1.88 (3H, s), 1.96 (6H, s), 2.08 (3H, s), 2.19 (3H, s), 5.36 (1H, d, *J* = 6.4 Hz), 5.67 (1H, t, *J* = 6.4 Hz), 5.97 (1H, d, *J* = 6.4 Hz), 6.77 (2H, s), 7.16-7.26 (3H, m), 7.49 (1H, dd, *J* = 6.3, 7.1 Hz).

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11 Optical purity of **16** was determined by HPLC (Daicel Chiracel OF, hexane/2-propanol). The absolute configuration was assigned by the reaction mechanism and a comparison of signs of optical rotation with those of the related compounds.[4c]

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