Stereoselective Induction of an Axial Chirality by Suzuki Cross Coupling of Tricarbonyl(arene)chromium Complexes with Arylboronic Acids

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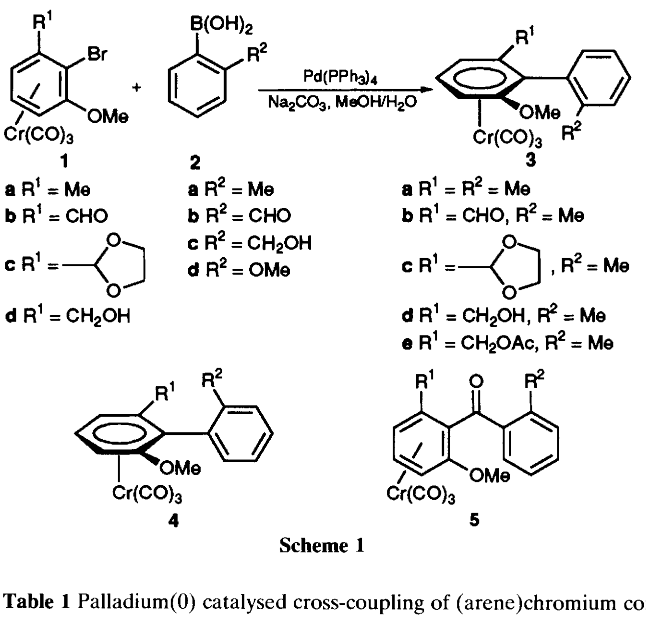
Tricarbonyl(2,6-disubstituted-1-bromobenzene)chromium was treated with *ortho*-substituted phenylboronic acids in the presence of a palladium(0) catalyst to give mono-Cr(CO)$_3$ complexes of biphenyl compounds with a complementary axial chirality depending upon the nature of *ortho*-substituent of the phenylboronic acids

Biphenyl or binaphthyl compounds with axial chirality are attractive targets not only as chiral ligands in asymmetric reactions but also for the synthesis of biologically active natural products.[1] Here we report the palladium(0) catalysed Suzuki cross-coupling reaction[2] giving mono-Cr(CO)$_3$ complexed biphenyl compounds, where the stereoselectivity is controlled by the nature of the *ortho*-substituent of the phenylboronic acid used.[3]

Oxidative addition of arylhalides to the palladium(0) is accelerated by coordination of an electron-withdrawing tricarbonylchromium group to the arene.[4] Tricarbonyl(2-methoxy-6-methyl-1-bromobenzene)chromium **1a** was treated with *o*-methylphenylboronic acid **2a** catalysed by 10 mol% of Pd(PPh$_3$)$_4$ in the presence of sodium carbonate in aqueous MeOH at 75 °C to give the cross-coupling product **3a** in 96% yield without any formation of the corresponding atropisomer (Scheme 1). The stereochemistry of **3a** was assigned as (*S**,*S**)† by comparison with an authentic sample derived from a stereodefined complex **3e** the configuration of which was determined by X-ray crystallography.[5] The methyl group on the *B*-ring of the complex **3a** is directed toward the tricarbonylchromium group with respect to the complexed arene *A*-ring in spite of a severe steric interaction between the methyl and Cr(CO)$_3$ groups. Similarly, the cross-coupling reaction of *o*-methylphenylboronic acid **2a** with the other chromium complexes **1b**, **c** and **d** gave the products **3b**, **c** and **d** with the same axial chirality (entries 2, 3, 4, Table 1). With *o*-methoxyphenylboronic acid **2d**, the (*S**,*S**)-coupling products **3** were obtained as major products along with stereoisomeric complexes **4** (entries 10, 11, Table 1). Whereas the coupling of *o*-formylphenylboronic acid **2b** with complexes **1a**, **b** and **c** gave diastereoisomeric (*S**,*R**)-chromium complexes **4** (R^2 = CHO) as the only isolated products (entries 5, 6, 7, Table 1). Formation of these products **4** can be attributed to a thermodynamically controlled reaction *via* isomerization of the kinetically controlled coupling products (*S**,*S**)-**3** to the corresponding axial isomeric (*S**,*R**)-complexes **4** under coupling reaction conditions, since oxidation of complex **3d** to **3b** at room temp. with Me$_2$SO–Ac$_2$O gave the corresponding diastereomerically axial complex **4** without isolation of **3b**. Coupling of *o*-hydroxymethyl phenylboronic acid **2c** with the complexes **1** catalysed by Pd(PPh$_3$)$_4$ produced the (*S**,*S**)-chromium complex **3** and CO inserted product **5** in various ratios depending upon the *ortho*-substituent of the chromium complex (entries 8, 9, Table 1). Thus, reaction of **1a** with *o*-hydroxymethylphenylboronic acid **2c** produced (*S**,*S**)-**3** as the major product, whereas coupling with **1c** afforded only CO inserted compound **5**. It is obvious from the results that the stereochemistry of axial chirality of the coupling products is unambiguously controlled by the nature of *ortho*-substituent of phenylboronic acids.

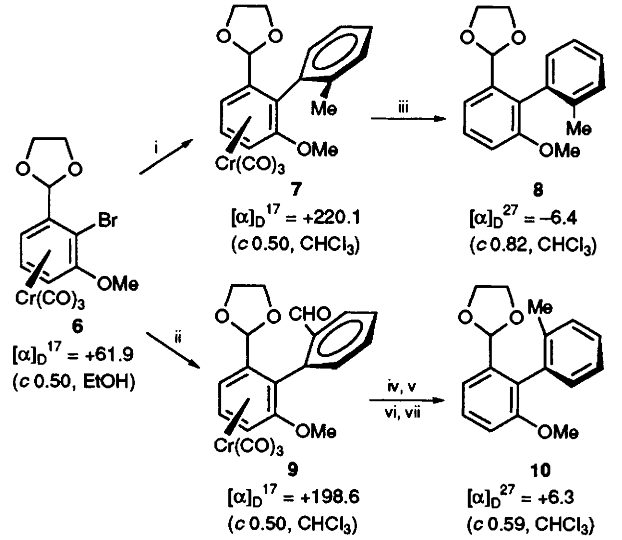
This diastereoselective cross-coupling reaction provides a promising approach to the formation of the enantiomerically pure biphenyl compounds with axial chirality in both enantiomeric forms from a single arene chromium complex (Scheme 2). Enantiomerically pure (+)-chromium complex **6**‡ was coupled with *o*-methylphenylboronic acid **2a** to give (+)-(*R*,*R*)-complex **7**, which was converted to (−)-(*R*)-2-methoxy-2′-methyl-6-(1,3-dioxolanyl)biphenyl **8**§ on exposure to sunlight, in good yield. Alternatively, diastereoisomeric (+)-(*R*,*S*)-chromium complex **9** was obtained by the coupling of complex **6** with *o*-formylphenylboronic acid **2b**.



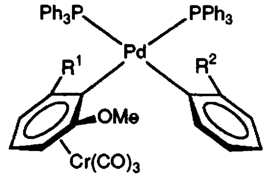
Scheme 1

Table 1 Palladium(0) catalysed cross-coupling of (arene)chromium complexes **1** with arylboronic acids **2**

Entry	Complex	Phenylboronic acid	Product	R^1	R^2	Yield (%) 3	4	5
1	**1a**	**2a**	**3a**	Me	Me	96	—	—
2	**1b**	**2a**	**3b**, **5**	CHO	Me	82	—	7
3	**1c**	**2a**	**3c**	$\overline{\text{CHO(CH}_2)_2\text{O}}$	Me	81	—	—
4	**1d**	**2a**	**3d**	CH$_2$OH	Me	77	—	—
5	**1a**	**2b**	**4**	Me	CHO	—	95	—
6	**1b**	**2b**	**4**	CHO	CHO	—	43	—
7	**1c**	**2b**	**4**	$\overline{\text{CHO(CH}_2)_2\text{O}}$	CHO	—	52	—
8	**1a**	**2c**	**3**, **5**	Me	CH$_2$OH	55	—	13
9	**1c**	**2c**	**5**	$\overline{\text{CHO(CH}_2)_2\text{O}}$	CH$_2$OH	—	—	40
10	**1a**	**2d**	**3**, **4**	Me	OMe	91	3	—
11	**1d**	**2d**	**3**, **4**	CH$_2$OH	OMe	85	5	—



Scheme 2 *Reagents and conditions*: i, *o*-methylphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, H_2O, 70 °C, 30 min, 81%; ii, *o*-formylphenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, MeOH, H_2O, 70 °C, 30 min, 52%; iii, hν–O_2, 90%; iv, LAH, diethyl ether, 62%; v, MsCl, py, 38%; vi, LAH, diethyl ether, 51%; vii, hν–O_2, diethyl ether, 90%



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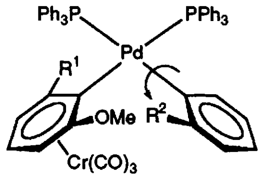

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The biphenyl complex **9** was converted to the antipode (+)-(*S*)-biphenyl compound **10**§ by reduction of the formyl group to a methyl group followed by demetallation.

Although the precise mechanism of the cross-coupling reaction is not clear enough to prove that the stereochemistry of the axial chirality depends on the *ortho*-substituent of the phenylboronic acids, the observed stereoselectivity can be rationalized by examining the transision states and palladium intermediates. Two *cis* diorgano palladium(II) intermediates **11** and **12** with a square configuration are the transient species prior to biaryl carbon–carbon bond formation. Complex **11** depicts a crowded system in which the R^2 substituent on the *B*-ring is close to the sterically larger R^1 substituent. The alternative complex **12** appears to be free of any severe non-bonded interaction, in which the R^2 substituent is close to the smaller methoxy group, and the tricarbonylchromium group is further away from the bulky triphenylphosphine. In complex **12**, both arene rings are coupled *via* overlapping[7] of p-orbitals with evasion of severe non-bonding interactions between R^2 and the triphenylphosphine groups, giving the products **3**.

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Footnotes

† (*S**,*S**) *etc*: the first symbol indicates a configuration of planar chirality of the chromium complexed arene ring (at C-1 position), and the second represents axial chirality. The * indicates a racemate but only one enantiomer is shown for clarity.

‡ Optically pure (+)-complex **6** ($[\alpha]_D^{17}$ +61.9 (*c* 0.5, EtOH) was prepared from optically resolved (−)-tricarbonyl(2-bromo-3-methoxybenzaldehyde)chromium {$[\alpha]_D^{24}$ −347.2 (*c* 1.415, $CHCl_3$)} by reaction with ethylene glycol and a catalytic amount of *p*-TsOH in MeCN at room temp. Resolution of the racemic tricarbonyl(2-bromo-3-methoxybenzaldehyde)chromium was achieved by the Davies method.[6]

§ The optical purity of the biphenyl compounds **8** and **10** was determined by HPLC with Chiralcel OJ (eluted with hexane–ethanol 75 : 25; column temperature 25 °C; flow rate 0.5 ml min^{-1}); retention times; 12.72 min for (−)-**8**; 15.44 min for (+)-**10**.

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