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Catalytic asymmetric induction of planar chirality: Palladium-catalyzed asymmetric cross-coupling of *meso* tricarbonyl(arene)chromium complexes with alkenyl- and arylboronic acids

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Abstract

Asymmetric cross-coupling of tricarbonyl(*o*-dichlorobenzene)chromium with alkenyl- and arylmetals in the presence of a chiral phosphine-palladium catalyst gave the mono-coupling products at up to 69% ee.

Key words: (Arene)chromium; Planar chirality; Catalytic asymmetric cross-coupling; Chiral ligand

1. Introduction

Tricarbonyl(η^6-arene)chromium complexes can exist in two enantiomeric forms due to planar chirality when the arene ring is substituted with different groups at the *ortho*- or *meta*-position. This planar chirality of the (arene)chromium complexes can be transferred into a new central chirality with high selectivity by means of appropriate organic reactions [1], and the tricarbonylchromium group can easily be removed from the reaction products to give the metal-free organic compounds in an optically active form after the transformation. Therefore, the preparation of optically pure (arene)chromium complexes has great potential for stereoselective transformations and asymmetric syntheses [1,2]. The availability of simple and selective methods capable of use on a larger scale would greatly aid the application of the enantiopure (η^6-arene)chromium complexes. The usual method for preparation of the optically active (arene)chromium complexes is the resolution via recrystallization [3] or column chromatography [4] of the corresponding diastereomers derived from racemic (arene)chromium complexes and suitable chiral reagents. Biocatalysts have been used for the optical resolution of racemic (*o*-substituted benzaldehyde)$Cr(CO)_3$ and (*o*-substituted benzylalcohol)$Cr(CO)_3$ [5,6]. The diastereoselective *ortho* lithiation of chiral benzaldehyde acetal chromium complex [7] and the stereoselective chromium complexation of the *o*-substituted benzaldehyde chiral diamines [8] have been also reported to produce the corresponding optically active (arene)chromium complexes. However, employment of the stoichiometric amount of the chiral reagents is required for the preparation of the chiral tricarbonyl(arene)chromium complexes in these methods. The use of a catalytic amount of chiral reagents is an attractive method for the preparation of the enantiomeric pure organometallic π-complexes. In this article, we wish to report the first catalytic asymmetric synthesis of optically active (arene)chromium complexes, achieved by asymmetric cross-coupling of a

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meso (arene)chromium complex in the presence of a chiral palladium catalyst.

2. Results and discussion

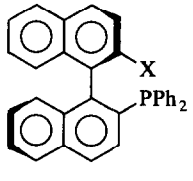
Palladium-catalyzed cross-coupling reactions involve oxidative addition of organic halides to palladium(0) as one of the key steps in the catalytic cycle. Although oxidative addition of the C–Cl bond of the arene compounds is usually difficult, it has been reported that the coordination of an electron-withdrawing tricarbonylchromium group to the arene ring facilitates the oxidative addition of the C–Cl bond [9]. A selective mono-coupling of one of the enantiotopic chlorine atoms of tricarbonyl(*o*-dichlorobenzene)chromium complex (**1**) would result in the formation of optically active (*o*-substituted chlorobenzene)chromium complexes. In this context, we have investigated the asymmetric mono-substitution reactions of complex **1** with various organometals in the presence of chiral phosphine-palladium catalysts [10].

The results obtained for reaction of tricarbonyl(*o*-dichlorobenzene)chromium (**1**) with vinylic metals in the presence of chiral palladium catalysts are summarized in Table 1. Reaction of **1** with tributyl(vinyl)stannane catalyzed by palladium complex coordinated with chiral ligands, BINAP [11] and PPFA [12], gave good yields of the mono-coupling product, tricarbonyl(*o*-chlorostyrene)chromium (**2a**), though in a racemic form (entries 1 and 2). In the presence of chiral monophosphine ligand, MeO-MOP [13], the reaction of vinylstannane gave the di-coupling product **3a** selectively, the mono-coupling product not being obtained (entry 3). To improve the yield of the mono-coupling product, one of the electron-withdrawing three carbonyl ligands on the chromium was replaced by an electron-donating

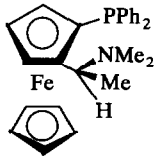
TABLE 1 Catalytic asymmetric cross-coupling of (*o*-dichlorobenzene)$Cr(CO)_3$ with vinylic metals [a]

Entry	Vinylic metal	Ligand (L*)	°C, h	Ratio [b] of **2**:**3** (yield [c] %)	% ee [d] of **2** (abs config)
1 [e]	$CH{=}CHSnBu_3$	(*R*)-BINAP	40, 18	75:25 (80)	0
2 [e]	$CH_2{=}CHSnBu_3$	(*S*)-(*R*)-PPFA	40, 18	87:13 (46)	0
3 [e]	$CH_2{=}CHSnBu_3$	(*R*)-MeO-MOP [f]	0, 18	0:100 (46)	–
4 [e]	$CH_2{=}CHMgBr$	(*S*)-(*R*)-PPFA	50, 48	75:25 (8)	–
5 [e]	$CH_2{=}CHZnCl$	(*S*)-(*R*)-PPFA	40, 18	67:33 (56)	42(1*S*, 2*R*)
6 [e]	$CH_2{=}CHZnCl$	(*R*)-MeO-MOP	0, 18	24:76 (93)	0
7 [e]	$CH_2{=}CHZnCl$	(*S*, *S*)-DIOP	40, 18	70:30 (33)	0
8 [g]	$CH_2{=}CHB(OH)_2$	(*S*)-(*R*)-PPFA	23, 48	73:27 (59)	38 (1*S*, 2*R*)
9 [h]	$CH_2{=}CHB(OH)_2$	(*S*)-(*R*)-PPFA	22, 5	52:48 (67)	13 (1*S*, 2*R*)
10 [g]	$CH_2{=}CHB(OH)_2$	(*S*)-Valphos [i]	25, 48	92:8 (48)	10 (1*S*, 2*R*)
11 [g]	$CH_2{=}CMeB(OH)_2$	(*S*)-(*R*)-PPFA	27, 48	95:5 (64)	44 (1*S*, 2*R*)
12 [g]	$CH_2{=}CMeB(OH)_2$	(*R*)-BINAP	35, 48	47:53 (93)	25 (1*S*, 2*R*)
13 [g]	$CH_2{=}CMeB(OH)_2$	(*S*)-(*R*)-BPPFA	27, 10	91:9 (67)	2 (1*S*, 2*R*)
14 [j]	$CH_2{=}CMeB[O(CH_2)_3O]$	(*S*)-(*R*)-PPFA	35, 48	76:24 (63)	39 (1*S*, 2*R*)
15 [g]	$CH_2{=}CMeZnCl$	(*S*)-(*R*)-PPFA	35, 48	74:26 (70)	22 (1*S*, 2*R*)
16 [g]	(*E*)-^{n}BuCH=$CH_2B(OH)_2$	(*S*)-(*R*)-PPFA	27, 18	77:23 (53)	44 (1*S*, 2*R*)

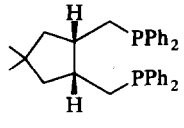
[a] Molar ratio; complex **1**/vinylic metal (RM)/chiral ligand (L*)/palladium = 1.0/3.0/0.12/0.10.
[b] Ratio was determined by HPLC or ^{1}H NMR.
[c] Isolated yield.
[d] Enantiomeric excess was determined by HPLC (Daicel Chiralcel OD eluted with 10% 2-propanol in hexane).
[e] THF was used as solvent.
[f] Ratio of MeO-MOP/palladium = 0.24/0.10.
[g] Reaction with vinyl boronic acids was carried out in the presence of 3 equiv of 0.4 M TlOH in aqueous THF solution.
[h] Potassium carbonate (3 equiv) as base was used in a mixture of MeOH and H_2O.
[i] Ref. 15.
[j] In the presence of 3 equiv of NaOEt in ethanol.



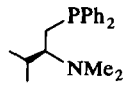
X = PPh_2: (*R*)-BINAP
X = OME: (*R*)-MeO-MOP



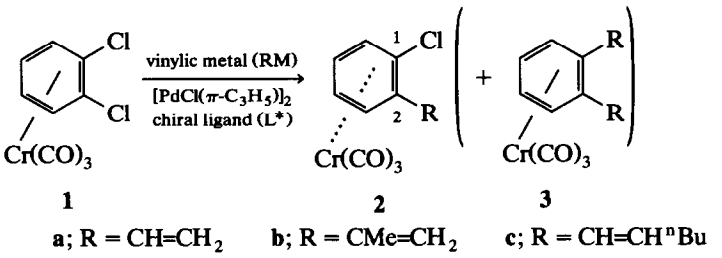
(*S*)-(*R*)-PPFA



(*S*)-(*S*)-DIOP



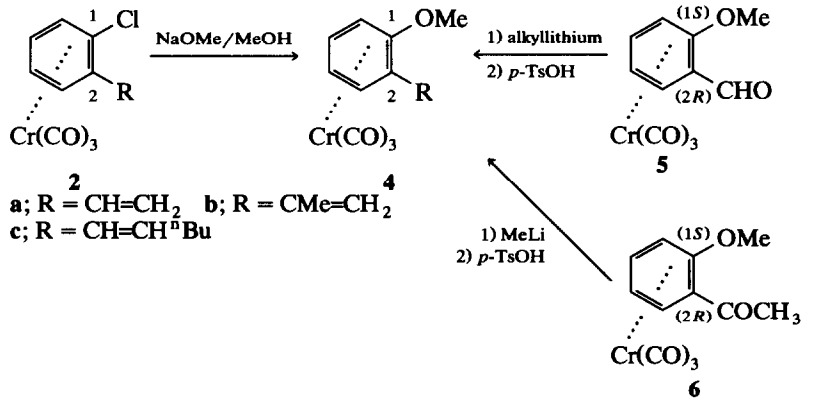
(*S*)-Valphos



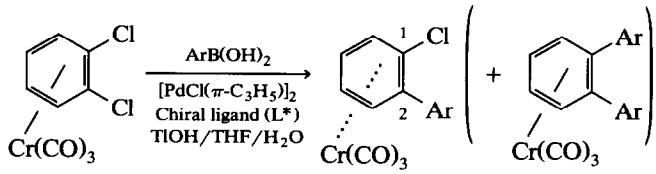
Scheme 1.

phosphine ligand by photo-irradiation in the presence of triphenylphosphine [14]. Unfortunately the corresponding dicarbonyl(triphenylphosphine)(*o*-dichlorobenzene)chromium gave no coupling products. Since no enantioselectivity was observed in the coupling reaction of tricarbonylchromium complex **1** with vinylstannane reagent, we turned our attention to other vinylic metals. Although vinylmagnesium bromide gave a low yield of the coupling products (entry 4), vinylzinc chloride afforded mono-coupling product **2a** of 42% ee ($[\alpha]_D^{17}$ − 115.4° (*c* 0.32, EtOH)) in 44% yield in the reaction catalyzed by 5 mol% of di-μ-chlorobis(π-allyl)palladium(II) and 12 mol% of (*S*)-(*R*)-PPFA in THF (entry 5). The enantiomeric excess can be easily determined by an HPLC analysis (Daicel Chiralcel OD eluted with 10% isopropanol in hexane). The asymmetric coupling reaction with vinylboronic acid [16] catalyzed by palladium-PPFA in aqueous thallium hydroxide gave 38% ee of the mono-coupling product (entry 8). Use of potassium carbonate instead of thallium hydroxide as base in aqueous methanol resulted in lower enantioselectivity (entry 9). From these results, moderate enantioselectivity in the formation of the mono-coupling product is found to be achieved by use of simple vinylboronic acid or vinylzinc chloride in the presence of the chiral aminophosphine ligand, PPFA. With substituted vinylboronic acids, α-methylvinylboronic acid or hexenylboronic acid, comparable enantioselectivities (44% ee) were observed in the cross-coupling in the presence of PPFA (entries 11 and 16). The ratio of mono- to di-coupling product was improved with α-methylvinylboronic acid, probably due to the stereoelectronic effects of the electron-donating methyl group. Reaction with the corresponding boric ester gave similar enantioselectivity (entry 14).

The absolute configurations of the mono-coupling products **2a–c** were easily determined as follows (Scheme 2). Nucleophilic substitution [17] of the remaining chlorine atom of the mono-coupling product (−)-**2a** (40% ee) with sodium methoxide in refluxing methanol for 18 h gave (−)-tricarbonyl(*o*-methoxystyrene)chromium (**4a**) ($[\alpha]_D^{20}$ − 122.9° (EtOH)) in 50% yield. On the other hand, enantiomerically pure (−)-(1*S*,2*R*)-tricarbonyl(*o*-anisaldehyde)chromium (**5**), obtained by the resolution through oxazolidine derivatives of (*L*)-valinol according to the literature method [4b,4c], was converted to (−)-(*o*-methoxystyrene)chromium (**4a**) ($[\alpha]_D^{20}$ − 492° (EtOH)) in 75% yield by treatment with methyllithium followed by dehydration with *p*-toluenesulfonic acid in benzene. It follows that the absolute configuration of the cross-coupling product (−)-**2a** is (1*S*,2*R*). The absolute configuration of the mono-coupling compounds **2b** ($[\alpha]_D^{27}$ − 8.1° (EtOH)) and **2c** ($[\alpha]_D^{27}$ − 212.0° (EtOH)) was similarly confirmed



Scheme 2. Determination of absolute configuration of coupling products.



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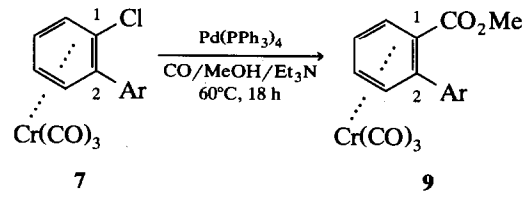
a; Ar = C_6H_5, **b**; Ar = *o*-MeC_6H_4, **c**; Ar = *o*-$MeOC_6H_4$

Scheme 3.



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Scheme 4.

as (1*S*,2*R*). Thus, the reaction of (−)-**2b** and (−)-**2c** with sodium methoxide gave the corresponding nucleophilic substitution products (+)-**4b** ($[\alpha]_D^{27}$ + 48.8° (EtOH)) and (−)-**4c** ($[\alpha]_D^{23}$ − 104.3° (EtOH)), respectively. The stereodefined authentic compounds, **4b** and **4c**, were prepared as follows. (−)-(1*S*,2*R*)-tricarbonyl (*o*-methoxyacetophenone)chromium (**6**), derived from the stereodefined (−)-(1*S*,2*R*)-(*o*-anisaldehyde)chromium complex (**5**) by treatment with MeLi followed by oxidation with DMSO/acetic anhydride [18], gave (+)-tricarbonyl(*o*-methoxy-α-methylstyrene)chromium (**4b**) by reaction with MeLi followed by dehydration. Also, (−)-**5** was converted to (−)-tricarbonyl((1-(*E*)-(*o*-methoxyphenyl)hexene)chromium (**4c**) by treatment with pentyllithium followed by dehydration.

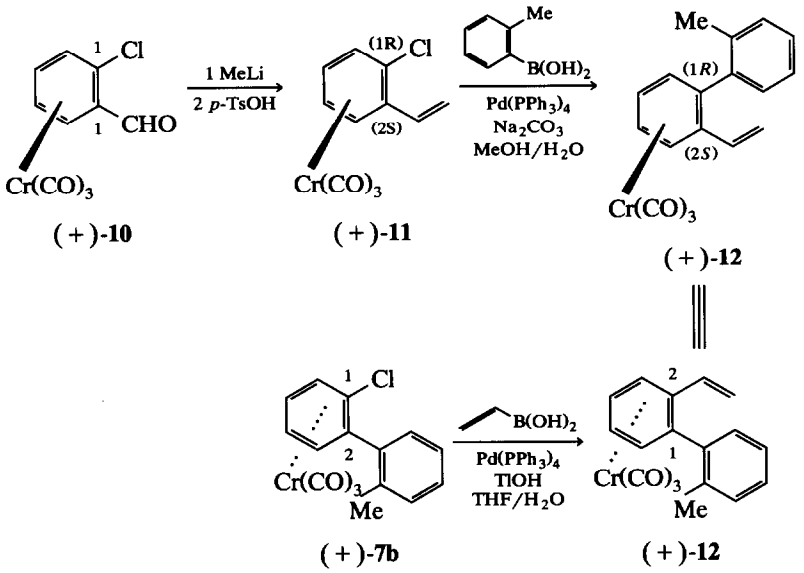
Since the catalytic asymmetric cross-coupling of the *meso*(*o*-dichlorobenzene)chromium complex (**1**) with vinylic boronic acids in the presence of PPFA can be achieved in moderate enantioselectivities, we next studied asymmetric coupling reactions with arylboronic acids catalyzed by the chiral palladium (Scheme 3, Table 2). Reaction of **1** with phenylboronic acid catalyzed by the palladium complex coordinated with (*S*)-(*R*)-PPFA at 28°C for 18 h gave (+)-tricarbonyl(*o*-phenyl chlorobenzene)chromium (**7a**) in 16% yield, along with 2% yield of the di-coupling product. The enantiomeric excess was determined to be 49.5% by HPLC analysis with Chiralcel OD-H after conversion into the corresponding methyl ester complex **9a** by treatment with a catalytic amount of $Pd(PPh_3)_4$ in a solution of MeOH and Et_3N under 1 atmosphere of carbon monoxide (Scheme 4). At higher reaction temperature (50°C, 18 h), the enantiomeric excess of the mono-coupling product **7a** ($[\alpha]_D^{28}$ + 41.9° (*c* 0.25, EtOH)) was increased to 69.1% ee in 40% yield (entry 2). With *o*-methylphenylboronic acid, the optical purity of the mono-coupling product (+)-**7b** ($[\alpha]_D^{26}$ + 29.7° (EtOH)) was 55.5% ee. With MeO-MOP ligand, enantioselectivity was lower (entry 4). The optical purities of mono-coupling products in the asymmetric reaction with *o*-substituted arylboronic acids largely depend on the nature of the *ortho* substituent. Thus, *o*-methoxyphenylboronic acid resulted in a very low yield of the coupling products (entry 5).

The absolute configuration of the mono-aryl coupling product (+)-**7b** was determined as follows (Scheme 5). Optical resolution of racemic (*o*-chlorobenzaldehyde)$Cr(CO)_3$ was carried out under the same procedure as that for (*o*-anisaldehyde)chromium mentioned above. The optically resolved (+)-(*o*-chlorobenzaldehyde)$Cr(CO)_3$ (**10**) ($[\alpha]_D^{27}$ + 635.2° (*c* 0.38, EtOH) > 99% ee) was converted to (+)-(*o*-chlorostyrene) chromium (**11**) ($[\alpha]_D^{27}$ + 358.0° (*c* 0.30, EtOH)) which was determined to have (1*R*,2*S*)-configuration by comparison of the optical rotation value with the stereodefined authentic sample (−)-(1*S*,2*R*)-**2a** obtained by the asymmetric coupling of vinylboronic acid. (1*R*,2*S*)-(+)-tricarbonyl(*o*-chlorostyrene)chromium (**11**) was allowed to react with *o*-methyl-phenylboronic acid catalyzed by $Pd(PPh_3)_4$ to give coupling product, (+)-(*o*-

TABLE 2. Catalytic asymmetric cross-copuling of **1** with arylboronic acids

Entry	Arylboronic acid	Ligand (L*)	°C, h	Ratio of **7**:**8** (yield %)	% ee of **7** (abs config)
1	$C_6H_5B(OH)_2$	(*S*)-(*R*)-PPFA	28 18	89:11 (18)	49 (1*S*,2*R*)
2	$C_6H_5B(OH)_2$	(*S*)-(*R*)-PPFA	50 18	73:27 (55)	69 (1*S*,2*R*)
3	*o*-$MeC_6H_4B(OH)_2$	(*S*)-(*R*)-PPFA	50 40	80:20 (64)	55 (1*S*,2*R*)
4	*o*-$MeC_6H_4B(OH)_2$	(*R*)-MeO-MOP	25 18	84:16 (69)	21 (1*S*,2*R*)
5 [a]	*o*-$MeOC_6H_4B(OH)_2$	(*S*)-(*R*)-PPFA	70 20	33:67 (13)	40 (−) [b]

[a] Reaction catalyzed by non-chiral $Pd(PPh_3)_4$ gave 88% yield of mono-coupling product.
[b] Absolute configuration was not determined.

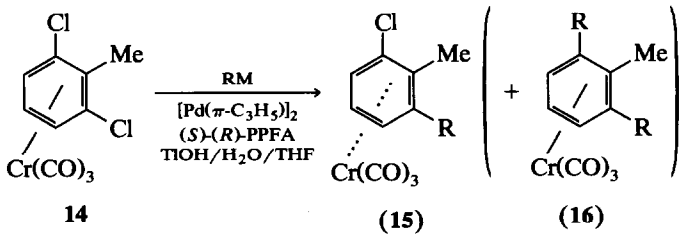


Scheme 5. Determination of absolute configuration of (+)-**7b**.

(2-tolyl)styrene)chromium (**12**) ($[\alpha]_D^{24}$ + 470.5° (*c* 0.84, EtOH)). On the other hand, the monoarylation product (+)-**7b** (55% ee), obtained in the asymmetric coupling, was coupled with vinylboronic acid in the presence of $Pd(PPh_3)_4$ to give (+)-**12** ($[\alpha]_D^{29}$ + 290.2° (*c* 0.13, EtOH)). Therefore, absolute configuration of the mono-coupling product (+)-**7b** in the catalytic asymmetric reaction was confirmed as (1*S*,2*R*).

Another *meso* (arene)chromium complex, tricarbonyl(2,6-dichlorotoluene)chromium (**14**) gave unsatisfactory results in both chemical yield of the mono-coupling product and enantioselectivity in the coupling with vinylic boronic acids catalyzed by (*S*)-(*R*)-PPFA-palladium (Table 3).

In summary, we have achieved, for the first time, the catalytic asymmetric synthesis of optically active molecules whose chirality is based on planar chirality due to the 1,2-asymmetrically substituted (η^6-arene) chromium structure. The stereochemical outcome in the present catalytic asymmetric cross-coupling reaction should be determined at the oxidative addition step to the chiral palladium where one of the enantiotopic carbon–chlorine bonds reacts stereoselectively with the chiral palladium(0) species forming a palladium–carbon bond. It is interesting that the enantioselectivity largely depends on the metals of the vinylating or arylating reagents. With the stannane reagent, the mono-coupling product resulted in racemic compound, while the organoboron or zinc reagent gave coupling products with moderate to good enantioselectivity. Among the organoboron reagents, arylboronic acids showed higher enantioselectivity in the cross-coupling reaction. It is likely that the metals of vinylating or arylating reagents play an important role in the enantioselection at the oxidative addition step of the (*o*-dichlorobenzene)chromium complex (**1**). Although the precise mechanism for asymmetric induction in the cross-coupling reaction is not clarified in such a way as to prove that the enantiomeric excesses depend on the vinylating metals, we propose that the oxidative addition step would occur enantiomerically with the complexed reagents derived from palladium/chiral phos-



Scheme 6.

TABLE 3. Asymmetric cross-coupling of **14** with vinylboronic acids in the presence of (*S*)-(*R*)-PPFA

Entry	RM	Reaction conditions °C, h	Ratio of 15:16 (yield%)	% ee [a] of 15
1	CH_2=CMeB(OH)$_2$	5, 48	53:47 (59)	5
2	CH_2=CMeB(OH)$_2$	40, 15	24:76 (17)	8
3	CH_2=CHB(OH)$_2$	5, 48	75:25 (5)	–

[a] Enantiomeric excess was determined by HPLC (Chiralcel OD-H) after a conversion of remaining chlorine atom to the corresponding methyl ester. Absolute configuration was not determined.

phine ligand/vinylating metal, not with the simple chiral palladium reagent. Further mechanistic investigations are in course.

3. Experimental details

All manipulations involving organometallics were carried out under an atmosphere of nitrogen or argon and using inert gas/vacuum double-manifold techniques. All melting points were determined on a Yanagimoto MPJ-2 micromelting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Hitachi R-90 or a JEOL GX-400. All NMR spectra were recorded in $CDCl_3$ solvent with tetramethylsilane as an internal reference. IR spectra were determined on a JASCO A-100 spectrometer. Mass spectra were taken on a JEOL D-300 or a JEOL AX-500 spectrometer. Elemental analysis was performed on a Perkin-Elmer Model 240 elemental analyzer. Optical rotations were obtained on a JASCO DIP-370 automatic polarimeter at wavelength 589 nm (sodium D line) using a 1.0 dm cell with a total volume of 3 ml. $Cr(CO)_6$ was commercially obtained (Sterm Chemicals) and used as received.

3.1. Preparation of tricarbonyl(o-dichlorobenzene)chromium (1)

A mixture of *o*-dichlorobenzene (4.4 g, 30 mmol) and $Cr(CO)_6$ (3.3 g, 15 mmol) in dibutyl ether (300 ml), n-heptane (30 ml) and THF (30 ml) was refluxed at 120°C for 24 h under nitrogen. After cooling to room temperature, the solvents and excess hexacarbonylchromium were evaporated *in vacuo*. The residue was dissolved in ether and the precipitate filtered off. The yellow ether solution was reduced *in vacuo*, and the residue was purified with silica gel chromatography (60 g, ether/hexane; 1/20) to afford 1.42 g (16% yield) of **1**. mp. 101°C; ^{1}H NMR (90 MHz) δ 5.12–5.31 (m, 2H), 5.60–5.68 (m, 2H); IR ($CHCl_3$) 1980, 1905, 1420, 1115 cm^{-1}.

3.2. Catalytic asymmetric cross-coupling of the (o-dichlorobenzene)chromium with alkenyl- or aryl-boronic acids in the presence of (S)-(R)-PPFA

3.2.1. Typical procedure for palladium(0) catalyzed reaction of 1 with α-methylvinylboronic acid (1S,2R)-Tricarbonyl(o-chloro α-methylstyrene)chromium (2b)

A solution of (*o*-dichlorobenzene)$Cr(CO)_3$ (28 mg, 0.10 mmol), α-methylvinylboronic acid (26 mg, 0.30 mmol), $[PdCl(\pi\text{-}C_3H_5)]_2$ (1.8 mg, 0.005 mmol), (*S*)-(*R*)-PPFA (5.3 mg, 0.012 mmol) and thallium hydroxide (0.75 ml, 0.4 M in water, 0.30 mmol) in THF (1 ml) was degassed by three cycles of freeze/pump/thaw, and stirred at 27°C for 48 h under argon. The reaction mixture was quenched with water and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel chromatography (ether/hexane = 1/20) to produce a mono-coupling product **2b** (18 mg, 61%); mp 61°C; $[\alpha]_D^{20}$ – 8.1° (*c* 0.32, EtOH). ^{1}H NMR (400 MHz) δ 2.02 (s, 3H), 4.92 (dt, J = 6.1, 1.2 Hz, 1H), 5.24 (s, 1H), 5.32 (s, 1H), 5.34 (d, J = 6.1 Hz, 1H), 5.46 (dt, J = 6.1, 1.2 Hz, 1H), 5.49 (dd, J = 6.1, 1.2 Hz, 1H); IR ($CHCl_3$) 1975, 1900, 1210, 1065, 920 cm^{-1}. Anal. Calcd for $C_{12}H_9O_3ClCr$: C, 49.93; H, 3.14. Found: C, 49.87; H, 3.15%. The optical purity (44% ee) of **2b** was determined by HPLC with Daicel Chiralcel OD (eluted with 10% of 2-propanol in hexane; flow rate 0.5 ml/min; UV detector 254 nm; temperature 26°C; retention time; 15.8 min for (1*R*,2*S*)-isomer, 17.3 min for (1*S*,2*R*)-isomer.

3.2.2. (1S,2R)-Tricarbonyl(o-chlorostyrene)chromium (2a)

Mp. 74°C; $[\alpha]_D^{20}$ – 110.2° (*c* 0.35, EtOH). ^{1}H NMR (400 MHz) δ 5.12 (dd, J = 6.1, 6.7 Hz, 1H), 5.36 (dd, J = 6.1, 6.7 Hz, 1H), 5.45 (d, J = 11.0 Hz, 1H), 5.50 (d, J = 6.7 Hz, 1H), 5.70 (d, J = 6.1 Hz, 1H), 5.74 (d, J = 17.7 Hz, 1H), 6.77 (dd, J = 11.0, 17.7 Hz, 1H); IR ($CHCl_3$) 1980, 1900, 1440, 1200, 1055 cm^{-1}. Anal. Calcd. for $C_{11}H_7O_3ClCr$: C, 48.11; H, 2.57. Found: C, 48.21; H, 2.62%. Retention time on HPLC (Chiralcel OD, 10% of 2-propanol in hexane, 0.5 ml/min); 23.20 min for (1*R*,2*S*)-isomer, 28.39 min for (1*S*,2*R*)-isomer.

3.2.3. (1S,2R)-Tricarbonyl(1-(E)-(o-chlorophenyl)hexene))chromium (2c)

Yellow oil; $[\alpha]_D^{27}$ – 212.0° (*c* 0.14, EtOH). ^{1}H NMR (400 MHz) δ 0.90 (t, J = 7.0 Hz, 3H), 1.31 ~ 2.22 (m, 6H), 5.12 (t, J = 6.1 Hz, 1H), 5.29 (t, J = 6.1 Hz, 1H), 5.48 (d, J = 6.7 Hz, 1H), 5.66 (d, J = 6.7 Hz, 1H), 6.20 (dt, J = 15.9, 6.7 Hz), 6.38 (d, J = 15.9 Hz, 1H); IR

($CHCl_3$) 1975, 1905, 1205, 910 cm^{-1}; mass spectrum (relative intensity), *m/e* 330 (M^+, 15), 246 ($M^+ - 3CO$, 22), 194 ($M^+ - Cr(CO)_3$, 45), 138 (100); high resolution mass spectrum Calcd. for $C_{15}H_{15}O_3ClCr$: 330.0115. Found: 330.0091. Retention time on HPLC (Chiralcel OD, 10% of 2-propanol in hexane, 0.5 ml/min); 14.56 min for (1*R*,2*S*)-isomer, 17.73 min for (1*S*,2*R*)-isomer.

3.2.4. (1S,2R)-Tricarbonyl(o-phenyl chlorobenzene)-chromium (7a)

Yellow oil; $[\alpha]_D^{28} + 41.9°$ (*c* 0.25, EtOH). 69.1% ee; ^1H NMR (90 MHz) δ 5.05 ~ 5.25 (m, 2H), 5.50 ~ 5.80 (m, 2H), 7.37 ~ 7.46 (m, 3H), 7.48 ~ 7.54 (m, 2H); IR ($CHCl_3$) 1980, 1900, 1440, 1085 cm^{-1}; mass spectrum (relative intensity), *m/e* 324 (M^+, 25), 240 ($M^+ - 3CO$, 100); high resolution mass spectrum Calcd. for $C_{15}H_9O_3ClCr$: 323.9645. Found: 323.9655.

3.2.5. (1S,2R)-Tricarbonyl(o-(o-tolyl) chlorobenzene) chromium (7b)

Yellow oil; $[\alpha]_D^{26} + 29.7°$ (*c* 0.68, EtOH); ^1H NMR (400 MHz) 2.18 (s, 3H), 4.99 (t, *J* = 6.1 Hz, 1H), 5.45 (d, *J* = 6.1 Hz, 1H), 5.56 (d, *J* = 6.1 Hz, 1H), 5.61 (t, *J* = 6.1 Hz, 1H), 7.20 ~ 7.25 (m, 1H), 7.30 ~ 7.34 (m, 1H), 7.48 ~ 7.50 (m, 1H); IR ($CHCl_3$) 1970, 1900, 1450, 1060, 910 cm^{-1}; mass spectrum (relative intensity), *m/e* 338 (M^+, 41), 254 ($M^+ - 3CO$, 65), 220 (100); high resolution mass spectrum Calcd. for $C_{16}H_{11}O_3ClCr$: 337.9801. Found: 337.9776.

3.3. Nucleophilic substitution of coupling products with sodium methoxide

3.3.1. Typical procedure; (1S,2R)-tricarbonyl(o-methoxystyrene)chromium (4a)

A solution of (−)-(1*S*,2*R*)-tricarbonyl(*o*-chlorostyrene)chromium (**2a**) (27 mg, 0.10 mmol) and sodium methoxide (108 mg, 2.0 mmol) in dry methanol (2 ml) was refluxed for 18 h under nitrogen. The reaction mixture was quenched with cold water and extracted with ether. The extract was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by SiO_2 chromatography (hexane/ether = 20/1) to give 2.7 mg of **4a**. MP 97°C; $[\alpha]_D^{27} - 122.9°$ (*c* 0.17, EtOH); ^1H NMR (400 MHz) δ 3.77 (s, 3H), 4.93 (dd, *J* = 6.1, 6.7 Hz, 1H), 5.07 (d, *J* = 6.7 Hz, 1H), 5.25 (d, *J* = 11.6 Hz, 1H), 5.48 (ddd, *J* = 6.7, 6.1, 1.2 Hz, 1H), 5.61 (d, *J* = 17.7 Hz, 1H), 5.83 (dd, *J* = 6.1, 1.2 Hz, 1H), 6.70 (dd, *J* = 17.7, 11.6 Hz, 1H); IR ($CHCl_3$) 1965, 1890, 1460, 1415, 1245 cm^{-1}. Anal. Calcd. for $C_{12}H_{10}O_4Cr$: C, 53.34; H, 3.73. Found: C, 53.01; H, 3.75%. The optical purity (40% ee) of **4a** was determined by HPLC with Chiralcel OF (eluted with 10% 2-propanol in hexane; flow rate 1.0 ml/min; UV detector 254 nm; temperature 30°C. Retention time; 11.45 min for (1*S*,2*R*)-isomer, 13.35 min for (1*R*,2*S*)-isomer.

3.3.2. (1S,2R)-Tricarbonyl(o-methoxy α-methylstyrene)chromium (4b)

Mp, 97°C. $[\alpha]_D^{28} + 48.8°$(*c* 0.15, EtOH). ^1H NMR (400 MHz) δ 2.07 (s, 3H), 3.74 (s, 3H), 4.79 (t, *J* = 6.1 Hz, 1H), 4.97 (d, *J* = 6.7 Hz, 1H), 5.18 (s, 1H), 5.20 (s, 1H), 5.53 (dt, *J* = 6.4, 1.2 Hz, 1H), 5.61 (dd, *J* = 6.4, 1.2 Hz, 1H); IR ($CHCl_3$) 1880, 1470, 1410, 1015 cm^{-1}. Anal. Calcd. for $C_{13}H_{12}O_4Cr$: C, 54.94; H, 4.26. Found: C, 54.71; H, 4.22%. Retention time on HPLC (Chiralcel OF, 10% 2-propanol in hexane, 0.5 ml/min); 16.47 min for (1*R*,2*S*)-isomer; 18.17 min for (1*S*,2*R*)-isomer.

3.3.3. (1S,2R)-Tricarbonyl(1-(E)-(o-methoxyphenyl)-hexene))chromium (4c)

Yellow oil; $[\alpha]_D^{23} - 104.3°$ (*c* 0.10, EtOH). ^1H NMR (400 MHz) δ 0.89 (t, *J* = 7.0 Hz, 3H), 1.28 ~ 1.45 (m, 4H), 2.14 (q, *J* = 6.7 Hz, 2H), 3.76 (s, 3H), 4.93 (t, *J* = 6.1 Hz, 1H), 5.08 (d, *J* = 6.7 Hz, 1H), 5.42 (dt, *J* = 6.7, 1.2 Hz, 1H), 5.79 (dd, *J* = 6.7, 1.2 Hz, 1H), 6.12 (dt, *J* = 15.9, 6.7 Hz, 1H), 6.34 (d, *J* = 15.9 Hz, 1H); IR ($CHCl_3$) 1960, 1880, 1465, 1245, 1050, 1030 cm^{-1}; mass spectrum (relative intensity) *m/e* 326 (M^+, 11), 242 ($M^+ - 3CO$, 33), 200 (54), 52 (100); high resolution mass spectrum Calcd. for $C_{16}H_{18}O_4Cr$: 326.0610. Found: 326.0629. Retention time on HPLC (Chiralcel OF, 10% 2-propanol in hexane, 0.5 ml/min); 13.85 min for (1*R*,2*S*)-isomer; 14.87 min for (1*S*,2*R*)-isomer.

3.4. Carbonylation of mono-aryl coupling product

3.4.1. Typical procedure for (+)-(1S,2R)-tricarbonyl-(o-tolyl methylbenzoate)chromium (9b)

A mixture of (+)-**7b** (37 mg), $Pd(PPh_3)_4$ (159 mg, 0.14 mmol) and triethylamine (42 mg, 0.42 mmol) in methanol under 1 atmosphere of carbon monoxide was stirred at 60°C for 18 h. The reaction mixture was filtered and the filtrate was reduced *in vacuo*. Water was added to the residue. The residue was extracted with ether, washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Purification by silica gel chromatography (ether/hexane = 1/10) gave 22 mg of **9b**. Yellow oil; $[\alpha]_D^{25} + 97.0°$ (*c* 0.10, EtOH); ^1H NMR (400 MHz) δ 2.09 (s, 3H), 3.61 (s, 3H), 5.31 (d, *J* = 6.7 Hz, 1H), 5.42 (t, *J* = 6.1 Hz, 1H), 5.52 (t, *J* = 6.4 Hz, 1H), 5.94 (d, *J* = 6.1 Hz, 1H), 7.16 ~ 7.19 (m, 1H), 7.24 ~ 7.28 (m, 1H), 7.34 ~ 7.41 (m, 1H); IR ($CHCl_3$) 1980, 1900, 1720, 910 cm^{-1}; mass spectrum (relative intensity) *m/e* 362 (M^+, 27), 306 ($M^+ - 2CO$, 5), 278 ($M^+ - 3CO$,

100); high resolution mass spectrum Calcd. for $C_{18}H_{14}O_5Cr$: 362.0246. Found: 362.0241. The optical purity (55% ee) was determined by HPLC with Chiralpack AS (eluted with 5% of 2-propanol in hexane, flow rate 0.5 ml/min, UV detector 254 nm, temperature 40°C, retention time; 15.99 min for (1*S*,2*R*)-isomer, 17.48 min for (1*R*,2*S*)-isomer.

3.4.2. (1S,2R)-Tricarbonyl(o-phenyl methylbenzoate)-chromium (9a)

Yellow oil; $[\alpha]_D^{27}$ + 64.4° (*c* 0.14, EtOH); ^{1}H NMR (90 MHz) δ 3.65 (s, 3H), 5.25 ~ 5.60 (m, 3H), 5.95 (d, J = 6.7 Hz, 1H), 7.29 (s, 5H); IR ($CHCl_3$) 1985, 1920, 1720, 1470, 1380 cm^{-1}; mass spectrum (relative intensity) *m/e* 348 (M^+ 25), 264 ($M^+ - 3CO$, 100), 206 ($M^+ - 3CO - CO_2Me$, 70); high resolution mass spectrum Calcd. for $C_{17}H_{12}O_5Cr$: 348.0090. Found: 348.0070. The optical purity (69.1% ee) was determined by HPLC with Chiralcel OD-H (eluted with 10% of 2-propanol in hexane, flow rate 0.5 ml/min, UV detector 254 nm, temperature 40°C). Retention time; 43.32 min for (1*S*,2*R*)-isomer, 46.32 min for (1*R*,2*S*)-isomer.

3.5. Optical resolution of racemic (o-chlorobenzaldehyde)chromium

A mixture of racemic (*o*-chlorobenzaldehyde)chromium (600 mg, 2.3 mmol), *L*-valinol (710 mg, 6.9 mmol), *p*-tolenesulfonic acid (10 mg) and molecular sieves (4 Å, 500 mg) in dry ether (50 ml) was stirred at 20°C for 18 h under nitrogen. The reaction mixture was filtered and the filtrate evaporated *in vacuo*. The residue was separated into two fractions by alumina column chromatography (ICN Biomedicals, Alumina N, Akt IV, 50 g, ether/hexane = 1/10). Both fractions were separately reduced *in vacuo*, and dissolved in a mixture of 15% aqueous THF (100 ml) and conc. HCl (1 ml), and both the mixtures were stirred at room temperature for 1 h under nitrogen, and saturated aqueous sodium bicarbonate was added to the reaction mixture. The reaction mixture was extracted with ether, washed with brine and dried over $MgSO_4$. Both the organic layers were separately reduced *in vacuo* and purified by silica gel chromatography (50 g, ether/hexane = 1/10). The first fraction part gave 256 mg of (−)-enriched (*o*-chlorobenzaldehyde)chromium and the second one afforded 158 mg of the corresponding (+)-isomer ($[\alpha]_D^{27}$ + 635.2°, (*c* 0.38, EtOH). The enantiomeric purities were determined by HPLC (Chiralcel OJ, 10% 2-propanol in hexane, 0.5 ml/min, 40°C, UV detector 254 nm). Retention time; 34.15 min for (+)-isomer; 38.08 min for (−)-isomer; % ee > 99% for (+)-isomer, 65% for (−)-isomer.

3.6. (+)-(1R,2S)-Tricarbonyl(o-chrorostyrene)chromium (11)

A solution of methyllithium (1.5 M in ether, 0.05 ml, 0.071 mmol) was added to a solution of (+)-tricarbonyl(*o*-chlorobenzaldehyde) (**10**) (13.1 mg, 0.047 mmol) in dry ether (3 ml) by syringe at −78°C under nitrogen and the reaction mixture was warmed to 0°C over 2 h, and quenched with water. The mixture was extracted with ether, washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was dissolved in a mixture of *p*-toluenesulfonic acid (5 mg) and benzene (2 ml), and refluxed for 1 h under nitrogen. The mixture was extracted with ether, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel chromatography with ether/hexane (1/15) to afford 7.8 mg of **11**. The ^{1}H NMR spectrum of **11** was consistent with that of the catalytic asymmetric coupling product **2a**. $[\alpha]_D^{27}$ + 358.0° (*c* 0.30, EtOH).

3.7. (+)-(1R,2S)-Tricarbonyl(o-(2-tolyl)styrene)chromium (12)

A mixture of (+)-(1*R*,2*S*)-tricarbonyl(*o*-chlorostyrene)chromium (**11**) (20 mg, 0.073 mmol), *o*-methylphenylboronic acid (20 mg, 0.15 mmol), $Pd(PPh_3)_4$ (8.5 mg, 0.0073 mmol), TlOH (33.4 mg, 0.15 mmol) in water (0.38 ml) and THF (2 ml) was heated at 60°C for 3 h under nitrogen. Usual workup gave 16.8 mg (70%) of **12** as yellow oil. ^{1}H NMR (400 MHz) δ 2.09 (s, 3H), 5.19 (t, J = 6.7 Hz, 1H), 5.22 (d, J = 11.0 Hz, 1H), 5.46 (d, J = 5.5 Hz, 1H), 5.50 (d, J = 6.7 Hz, 1H), 5.63 (d, J = 17.7 Hz, 1H), 5.65 (t, J = 6.7 Hz, 1H), 6.11 (dd, J = 11.0, 17.1 Hz, 1H), 7.21 (d, J = 7.9 Hz, 1H), 7.27 (t, J = 6.7 Hz, 1H), 7.29 (t, J = 6.7 Hz, 1H), 7.49 (d, J = 7.9 Hz, 1H); IR ($CHCl_3$) 1965, 1890, 1450, 1200, 930 cm^{-1}; $[\alpha]_D^{24}$ + 470.5° (*c* 0.84, EtOH). MS spectrum (relative intensity) *m/e* 330 (M^+, 20), 246 ($M^+ - 3CO$, 100); high resolution mass spectrum Calcd. for $C_{18}H_{14}O_3Cr$: 330.0348. Found: 330.0360.

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