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New Chiral Phosphine Ligands Containing (η^6-Arene)chromium and Catalytic Asymmetric Cross-Coupling Reactions

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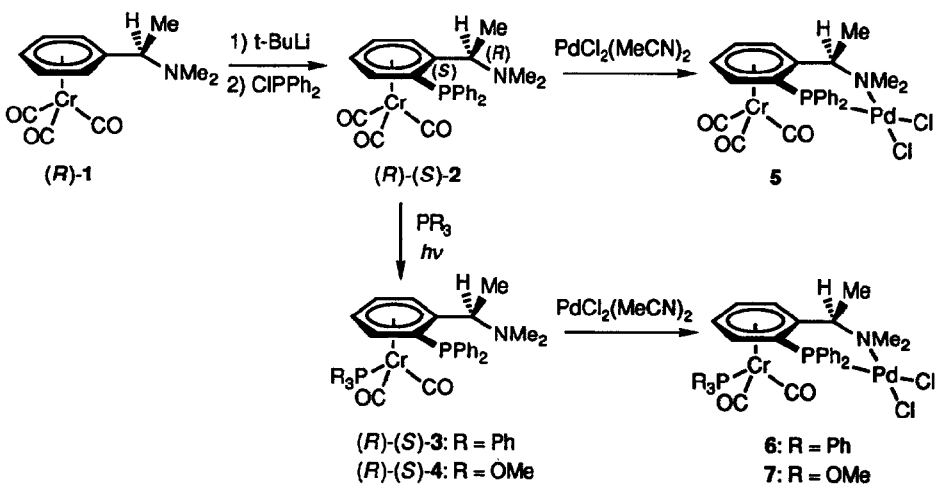
Abstract: New chiral monophosphine ligands **2-4** containing (η^6-arene)chromium were prepared via the stereoselective ortho-lithiation of ((*R*)-*N*,*N*-dimethyl-1-phenylethylamine)-$Cr(CO)_3$ (**1**). Asymmetric cross-coupling of 1-phenylethylmagnesium or -zinc reagent with vinyl bromides in the presence of palladium or nickel catalysts complexed with the chiral (η^6-arene)chromium ligands gave the coupling products of up to 61% ee.

There has been great interest in asymmetric synthesis catalyzed by chiral phosphine-transition metal complexes,[1] and the preparation of chiral phosphine ligands which are capable of bringing about high enantioselectivity is essential for development of the catalytic asymmetric synthesis. Chiral ferrocenylphosphines, which have a ferrocene planar chirality and functional groups on the side chain, have been proven to be highly enantioselective ligands for a variety of catalytic asymmetric reactions.[2-4] Here we wish to describe the preparation of novel optically active phosphine ligands **2-4** which are analogous to the ferrocenylphosphines but contain (η^6-arene)chromium moiety and their use for the catalytic asymmetric cross-coupling.[5]

Scheme 1



The new chiral phosphine ligands are readily prepared by way of diastereoselective lithiation of ((*R*)-*N*,*N*-dimethyl-1-phenylethylamine)$Cr(CO)_3$ ((*R*)-**1**) (Scheme 1). According to the procedure reported by Davies[7] and Heppert[8] groups, (*R*)-**1** (0.35 mmol) was metalated with *t*-butyllithium (0.42 mmol) in 5 mL of ether at –40 °C. THF (0.3 mL) was added and the mixture was treated with ether (2 mL) solution of chlorodiphenylphosphine (0.70 mmol). Aqueous work-up followed by column chromatography on silica gel (hexane/ether = 5/1) gave 80% yield of diastereomerically pure chiral phosphine (*R*)-(*S*)-**2**.[9,10] Yellow crystals of (*R*)-(*S*)-**2** (mp 154 °C, $[\alpha]_D^{19}$ –42 (*c* 1.1, chloroform)) were obtained by recrystallization from ether and hexane. The planar chirality of the (η^6-arene)chromium moiety is deduced to be *S*[9,11] from the stereochemistry in the lithiation of **1**,[7-9] where one of the diastereotopic ortho hydrogens is selectively replaced. One of the three carbon monoxide molecules on the chromium of **2** was replaced by triphenylphosphine or trimethyl phosphite under irradiation with a high pressure mercury lamp to give another phosphine ligand (*R*)-(*S*)-**3**[10] (49% yield) or (*R*)-(*S*)-**4**[10] (70% yield), respectively.

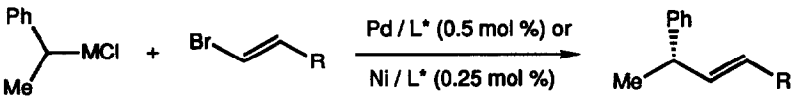
The new optically active (η^6-arene)chromium-phosphines **2**-**4** were used as chiral ligands for the palladium- or nickel-catalyzed asymmetric cross-coupling reactions (Scheme 2). The reaction conditions and results obtained are summarized in Table 1. Reaction of 1-phenylethylmagnesium chloride (**8**) with vinyl bromide (**10a**) in the presence of nickel catalyst, generated in situ by mixing anhydrous nickel chloride with ligand (*R*)-(*S*)-**2**, under the standard reaction conditions[5] gave (*S*)-3-phenyl-1-butene (**11a**) of 53% ee (entry 1). The enantiomeric purity was determined by HPLC analysis (Sumichiral OA-1000 or OA-2000) of *N*-phenyl-2-phenylpropanamide, which was obtained by oxidation ($KMnO_4/NaIO_4$) of the coupling product **11a** followed by anilide formation ($PhNH_2$/DCC) of the resulting 2-phenylpropanoic acid. Use of zinc reagent **9** increased the stereoselectivity to 61% ee (entry 2). Palladium complex **5**,[12] which was prepared from (*R*)-(*S*)-**2**

Table 1. Catalytic Asymmetric Cross-Coupling of PhCH(Me)MCl (M = Mg (**8**) or Zn (**9**)) with Alkenyl Bromide **10**.[a]

entry	PhCH(Me)MCl (**8**) or (**9**)	bromide (**10**)	catalyst (metal/ligand)	product	yield[b] (%)	% ee[c] (config)
1	**8** (M = Mg)	**10a** (R = H)	$NiCl_2$/(*R*)-(*S*)-**2**[d]	**11a**	53	53 (*S*)
2	**9** (M = Zn)	**10a** (R = H)	$NiCl_2$/(*R*)-(*S*)-**2**[d]	**11a**	44	61 (*S*)
3	**8** (M = Mg)	**10a** (R = H)	**5** ($PdCl_2$[(*R*)-(*S*)-**2**])	**11a**	56	13 (*S*)
4	**9** (M = Zn)	**10a** (R = H)	**5** ($PdCl_2$[(*R*)-(*S*)-**2**])	**11a**	67	61 (*S*)
5	**8** (M = Mg)	**10b** (R = Ph)	**5** ($PdCl_2$[(*R*)-(*S*)-**2**])	**11b**	81	43 (*S*)
6	**9** (M = Zn)	**10b** (R = Ph)	**5** ($PdCl_2$[(*R*)-(*S*)-**2**])	**11b**	75	58 (*S*)
7	**9** (M = Zn)	**10a** (R = H)	**6** ($PdCl_2$[(*R*)-(*S*)-**3**])	**11a**	94	37 (*S*)
8	**9** (M = Zn)	**10b** (R = Ph)	**6** ($PdCl_2$[(*R*)-(*S*)-**3**])	**11b**	72	53 (*S*)
9	**9** (M = Zn)	**10a** (R = H)	**7** ($PdCl_2$[(*R*)-(*S*)-**4**])	**11a**	72	17 (*S*)

[a] All reactions were carried out at 0 °C for 18 h in ether and THF in the presence of 0.5 mol % of the catalyst unless otherwise noted. PhCH(Me)MCl/bromide = 2.5-3.0. [b] Isolated yield by distillation followed by preparative GLC (Silicone DC550). [c] Determined by HPLC analysis of *N*-phenyl-2-phenylpropanamide prepared by oxidation ($KMnO_4/NaIO_4/K_2CO_3$/*t*-BuOH/H_2O) of coupling products **11** followed by anilide formation ($PhNH_2$/DCC) (see text). [d] Catalyst of 0.25 mol % was used.

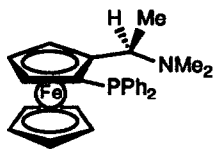
Scheme 2



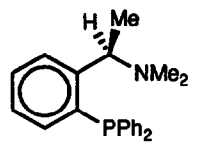
8: M = Mg
9: M = Zn

10a: R = H
10b: R = Ph

(*S*)-**11a**: R = H
(*S*)-**11b**: R = Ph



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



12

and dichlorobis(acetonitrile)palladium(II), also catalyzed the cross-coupling reaction of the zinc reagent to give (*S*)-**11a** of the same enantiomeric purity (61% ee) (entry 4). A little lower stereoselectivity was observed with palladium catalysts **6** and **7** (entries 7-9). It was shown by ^{1}H NMR that both the phosphorus and nitrogen atoms in the ligand of palladium complexes **5-7** are coordinated to the palladium forming a chelate.[12]

The stereoselectivity attained here is comparable with those observed for the cross-coupling reaction of **8** in the presence of the chiral ferrocenylmonophosphine ligands represented by (*R*)-(*S*)-PPFA,[5c] which gave (*S*)-**11a** of 56-68% ee. A chiral aminoalkylphosphine ligand, (*R*)-1-(2-diphenylphosphinophenyl)ethyl-*N*,*N*-dimethylamine (**12**), which is analogous to (*R*)-(*S*)-**2** but lacks the chromium coordination, has been reported[13] to be less enantioselective (40% ee) than **2**, indicating that the tricarbonylchromium group coordinated to the phenyl ring contributes to enhancing the stereoselectivity.[14,15]

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9 Preparation of racemic phosphine (*R**)-(*S**)-**2** has been reported (ref 8).

10 (*R*)-(*S*)-**2**: mp 154 °C (ether/hexane). $[\alpha]_D^{19}$ –42 (*c* 1.1, chloroform). ^{1}H NMR ($CDCl_3$): δ 1.10 (d, *J* = 7 Hz, 3 H), 1.73 (s, 6 H), 4.48 (m, 1 H), 4.96 (d, *J* = 6 Hz, 1 H), 5.10 (t, *J* = 6 Hz, 1 H), 5.14 (m, 1 H), 5.51 (t, *J* = 6 Hz, 1 H), 7.31 (m, 10 H). (*R*)-(*S*)-**3**: mp 151 °C (ether/hexane). $[\alpha]_D^{22}$ –344 (*c* 0.58, chloroform). ^{1}H NMR ($CDCl_3$): δ 0.85 (d, *J* = 6 Hz, 3 H), 1.65 (s, 6 H), 3.80 (m, 1 H), 4.45-4.70 (m, 4 H), 7.25-7.60 (m, 25 H). (*R*)-(*S*)-**4**: mp 117 °C (ether/hexane). $[\alpha]_D^{26}$ –381 (*c* 0.32, chloroform). ^{1}H NMR ($CDCl_3$): δ 1.10 (d, *J* = 7 Hz, 3 H), 1.72 (s, 6 H), 3.48 (d, *J* = 11 Hz, 9 H), 4.50 (m, 1 H), 4.69 (d, *J* = 6 Hz, 1 H), 4.80 (t, *J* = 6 Hz, 1 H), 4.86 (m, 1 H), 5.20 (q, *J* = 6 Hz, 1 H), 7.26-7.41 (m, 10 H).

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12 **5** ($PdCl_2$[(*R*)-(*S*)-**2**]): mp 153 °C (ether/dichloromethane). $[\alpha]_D^{15}$ +786 (*c* 0.18, chloroform). ^{1}H NMR ($CDCl_3$): δ 1.32 (d, *J* = 6 Hz, 3 H), 2.80 (s, 3 H), 3.39 (s, 3 H), 3.68 (m, 1 H), 5.01-5.20 (m, 3 H), 5.82 (m, 1 H), 7.45-7.72 (m, 8 H), 8.65 (m, 2 H). **6** ($PdCl_2$[(*R*)-(*S*)-**3**]): mp 184 °C (ether/dichloromethane). $[\alpha]_D^{15}$ +1348 (*c* 0.14, chloroform). ^{1}H NMR ($CDCl_3$): δ 1.13 (d, *J* = 6 Hz, 3 H), 2.70 (s, 3 H), 3.29 (s, 3 H), 3.61 (m, 1 H), 4.03 (m, 1 H), 4.45 (m, 1 H), 4.84 (m, 2 H), 7.32-7.70 (m, 23 H), 8.65 (m, 2 H). **7** ($PdCl_2$[(*R*)-(*S*)-**4**]): mp 153 °C (ether/dichloromethane). $[\alpha]_D^{14}$ +1540 (*c* 0.15, chloroform). ^{1}H NMR ($CDCl_3$): δ 1.30 (d, *J* = 6 Hz, 3 H), 2.80 (s, 3 H), 3.33 (s, 3 H), 3.51 (d, *J* = 11 Hz, 9 H), 3.60-3.75 (m, 1 H), 4.68-4.82 (m, 3 H), 5.55 (m, 1 H), 7.35-7.69 (m, 8 H), 8.80 (m, 2 H).

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