Synthesis of Cp*CH_2PPh_2 and its use as a ligand for the nickel-catalysed cross-coupling reaction of alkyl halides with aryl Grignard reagents†

Minoru Uemura, Hideki Yorimitsu* and Koichiro Oshima*

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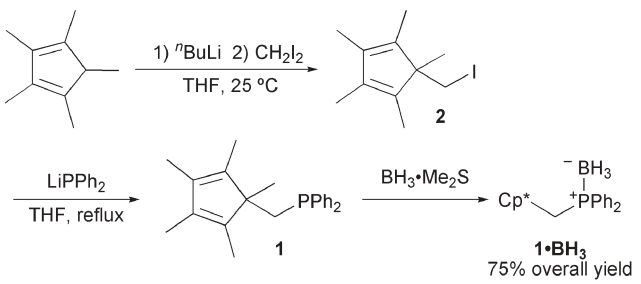
A new ligand, Cp*CH_2PPh_2 (Cp* = 1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl), was prepared, and was used as a ligand for nickel-catalysed cross-coupling reaction of alkyl halides with aryl Grignard reagents, which nickel–phosphine complexes had never made possible.

Phosphine ligands play important roles in organic synthesis, as clearly demonstrated in transition metal catalysis. Among them, monophosphine ligands having an additional intramolecular coordinating site are an important class.[1] Recently, monophosphine ligands having a coordinating alkene moiety was developed and applied to highly enantioselective transformations.[2] Here we introduce Cp*CH_2PPh_2 (**1**, Cp* = 1,2,3,4,5-pentamethyl-2,4-cyclopentadienyl), a monophosphine ligand with a pendant 1,3-diene moiety. We envisioned that the 1,3-diene part as well as the phosphorous atom would coordinate to transition metal and that **1** would thus serve as a new six-electron donating ligand.

The synthesis of **1** is outlined in Scheme 1.[3] The reaction of Cp*Li with diiodomethane provided iodide **2**. Treatment of **2** with lithium diphenylphosphide in refluxing THF afforded **1** in high yield. Since **1** is sensitive to oxygen, we converted the ligand to a phosphine–borane complex and handled it. The phosphine **1** was regenerated *in situ* by removing borane with 1,8-diazabicyclo[2.2.2]octane (DABCO) prior to use as a ligand.

Cross-coupling reactions of alkyl halides are rather difficult reactions, compared to those of aryl or alkenyl halides, since



Scheme 1 Synthesis of Cp*CH_2PPh_2.

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto-daigaku Katsura, Nishikyo-ku, Kyoto 615-8510, Japan. E-mail: yori@orgrxn.mbox.media.kyoto-u.ac.jp; oshima@orgrxn.mbox.media.kyoto-u.ac.jp; Fax: +81-75-383-2438; Tel: +81-75-383-2437

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intermediary alkylmetal complexes are prone to undergo β-hydride elimination.[4,5] We expected that the diene moiety of **1** could advantageously occupy vacant coordination sites necessary for the β-hydride elimination. We thus chose nickel-catalysed cross-coupling reaction of 1-bromooctane with phenylmagnesium bromide as a model reaction (eqn (1), Table 1). Although several nickel complexes catalyse such a difficult coupling reaction,[4b,4c,5] there are no reports on the cross-coupling reaction catalysed by nickel–phosphine complexes.[6]

$$\underset{(0.50\ \text{mmol})}{{}^{n}C_8H_{17}Br} + \underset{(1.5\ \text{eq})}{PhMgBr} \xrightarrow[\text{Et}_2\text{O (0.5 mL)}]{\substack{NiCl_2\ (5\ \text{mol\%}) \\ \text{Ligand (10 mol\%)}}}{}^{n}C_8H_{17}Ph \qquad (1)$$

The nickel-catalysed reaction using **1** was indeed successful, quantitatively yielding octylbenzene (entry 1).[7,8] It is worth noting that we could obtain a mixture of **1** (27 μmol, 54% recovery) and the oxide of **1** (22 μmol, 43% recovery) after the reaction. The recovery suggests that a bis(π-allyl)nickel complex which is a suitable catalyst for similar coupling reactions[4b] is not generated from **1** in the reaction mixture.

Other conventional phosphines such as triphenylphosphine, tricyclohexylphosphine, and tri(*tert*-butyl)phosphine did not assist the coupling reaction efficiently (entries 2–4). Use of neopentyldiphenylphosphine that is as bulky as **1** failed to afford octylbenzene (entry 5). It is worth noting that a homologue of **1**, Cp*$CH_2CH_2PPh_2$ (**3**), was far less effective (entry 6). Hexamethylcyclopentadiene (**4**) is not a suitable ligand by itself

Table 1 Effect of ligands on nickel-catalysed cross-coupling reaction of 1-bromooctane with phenylmagnesium bromide[a]

Entry	Ligand	NMR yield[d] (%)
1	**1**[b]	Quant.
2	PPh_3	29
3	$P({}^{c}C_6H_{11})_3$	14
4	$P({}^{t}Bu)_3$	11
5	$P(CH_2{}^{t}Bu)Ph_2$[b]	9
6	Cp*$CH_2CH_2PPh_2$ (**3**)[b]	13
7	Cp*Me (**4**)	4
8	**4** + PPh_3[c]	38
9	none	5

[a] Reaction conditions are shown in eqn (1). [b] Generated *in situ* by treatment of the relevant phoshphine–borane with DABCO. [c] 10 mol% of both **4** and PPh_3. [d] The yields were determined as follows. After extractive workup and evaporation, bromoform was added to a crude oil. Comparison of the ^1H signals of bromoform and octylbenzene revealed the NMR yield.

(entry 7). Interestingly, combined use of **4** and triphenylphosphine resulted in formation of octylbenzene in moderate yield (entry 8). Without any ligands, a 5% yield of octylbenzene was obtained (entry 9).

Diethyl ether is the best solvent. The reactions in toluene, THF, dioxane, and hexane provided octylbenzene in 88, 81, 65, and 64% yields, respectively, under the $NiCl_2$(**1**) catalysis.

Other alkyl halides underwent the nickel-catalysed phenylation with the aid of **1** (eqn (2), Table 2). The reactions of primary alkyl bromides provided the corresponding phenylated products in high yields (entries 1,[9] 4–9). Typical protective groups such as THP and 1,3-dioxolane survived under the reaction conditions (entries 6, 7), while carbonyl groups were not tolerant. 8-Bromo-1-octene was phenylated, leaving the terminal olefinic group untouched (entry 9). Primary alkyl iodide was as reactive as bromide (entry 3). In contrast, alkyl chloride completely resisted the reaction. Unfortunately, an attempted cross-coupling reaction of a secondary alkyl bromide resulted in an unsatisfactory yield of cyclohexylbenzene (entry 10).

$$\underset{(0.50\ \text{mmol})}{R-SX} + \underset{(X\ \text{eq})}{PhMgBr} \xrightarrow[\substack{Et_2O\,(0.5\ \text{mL})\\ 25\,^{\circ}C,\,3\ \text{h}}]{\substack{NiCl_2\,(5\ \text{mol}\%)\\ 1\,(10\ \text{mol}\%)}} R-SPh \qquad (2)$$

The cross-coupling reaction is believed to involve a radical process as justified by the following two experiments. Treatment of cyclopropylmethyl bromide with *p*-methoxyphenylmagnesium bromide furnished *p*-(3-butenyl)anisole (eqn (3)). No cyclopropane skeletons were observed in the crude oil. In addition, the reaction of 6-halo-1-hexene derivative **5** afforded benzyl-substituted pyrrolidine **6**, in addition to unphenylated pyrrolidine **7** (eqn (4)). Ring-opening of a cyclopropylmethyl radical and ring-closure of a 5-hexenyl radical are well-known isomerization reactions,[10] suggesting the intermediacy of carbon-centered radicals. Oxidative addition *via* a single electron transfer process is most probable.[4]

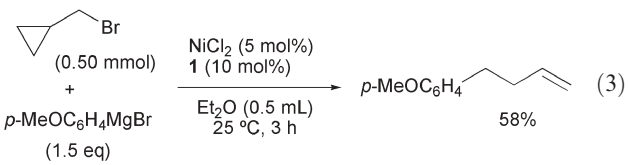
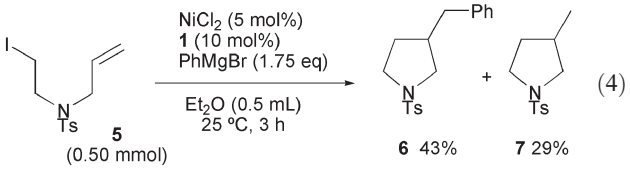


Table 2 Reactions of various alkyl halides with phenylmagnesium bromide[a]

Entry	Substrate	X eq.	Isolated yield (%)
1	$^{n}C_8H_{17}Br$	1.50	83
2	$^{n}C_8H_{17}Br$	1.50	84[b]
3	$^{n}C_{12}H_{25}I$	1.75	80
4	$PhCH_2CH_2Br$	1.75	60
5	$PhCH_2CH_2CH_2Br$	1.75	70
6	$THPO(CH_2)_5Br$[c]	1.75	76
7	$(OCH_2CH_2O)CH(CH_2)_4Br$	2.50	76
8	$Br(CH_2)_6Br$	3.00	68
9	$CH_2{=}CH(CH_2)_6Br$	2.00	62
10	$^{c}C_6H_{11}Br$	1.50	36

[a] Reaction conditions are shown in eqn (2). Ligand **1** was generated *in situ* by treatment of **1**·BH_3 with DABCO. [b] *p*-$MeOC_6H_4MgBr$ was used instead of PhMgBr. [c] THP = Tetrahydropyranyl.



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3 Synthesis of **1**·BH_3: a solution of *n*BuLi in hexane (1.60 M, 8.75 mL, 14 mmol) was added to a solution of 1,2,3,4,5-pentamethyl-1,3-cyclopentadiene (2.5 mL, 15 mmol) in THF (50 mL) at −20 °C. The mixture was stirred for 30 min at the same temperature. Diiodomethane (0.81 mL, 10 mmol) was added to the reaction mixture, and the mixture was stirred for 12 h at room temperature. The reaction was quenched with water, and the mixture was extracted with hexane. The combined organic parts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give a crude oil. The oil was filtered through a short pad of silica gel (hexane) to afford 5-iodomethyl-1,2,3,4,5-pentamethyl-1,3-cyclopentadiene, which was used for the next step without further purification. A solution of *n*BuLi in hexane (1.60 M, 5.29 mL, 8.46 mmol) was added to a solution of diphenylphosphine (1.33 mL, 7.69 mmol) in THF (38 mL) at 0 °C. The mixture was stirred for 10 min at the same temperature. Cp*CH_2I in THF (10 mL) was added to the reaction mixture, and the mixture was stirred for 3 h at 70 °C. Borane–dimethyl sulfide complex (0.88 mL, 9.23 mmol) was added to the mixture at 0 °C, and the resulting mixture was stirred for 30 min at 0 °C. The reaction was quenched with water, and the mixture was extracted with ethyl acetate. The combined organic parts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to give a crude oil. The oil was purified by chromatography on silica gel (Wakogel C–200, hexane–ethyl acetate = 20 : 1) to afford **1**·BH_3 (2.02 g, 5.80 mmol, 75%). IR (nujol) 694, 736, 866, 1058, 1436, 2385 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 0.40–1.20 (br, 3H), 0.98 (d, J = 2.5 Hz, 3H), 1.39 (s, 6H), 1.59 (s, 6H), 2.53 (d, J = 11.0 Hz, 2H), 7.33–7.56 (m, 10H); ^{13}C NMR ($CDCl_3$) δ (ppm) 10.09 (2C), 11.02 (2C), 24.87 (d, J = 13.8 Hz), 31.31 (d, J = 32.9 Hz), 53.51, 128.00 (d, J = 9.5 Hz, 4C), 130.47 (d, J = 2.4 Hz, 2C), 131.12 (d, J = 54.9 Hz, 2C), 132.56 (d, J = 9.1 Hz, 4C), 135.75 (2C), 138.21 (2C); ^{31}P NMR ($CDCl_3$) δ (ppm) 9.08 (m); found: C, 79.11; H, 8.62%. Calcd for $C_{23}H_{30}BP$: C, 79.32; H, 8.68%. mp: 85.0–85.5 °C.

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5 The reactions in ref. 4*b* and 4*c* use 1,3-butadiene and pyridine derivatives, respectively, as a ligand. Nickel-salen complexes catalysed the phenylation of alkyl bromide: P. Styring, C. Grindon and C. M. Fisher, *Catal. Lett.*, 2001, **77**, 219.

6 ^{31}P NMR analysis of a mixture of $Ni(cod)_2$ and **1** in C_6D_6 showed one clean signal at δ = 38.38 ppm. A ^{31}P signal of **1** alone appeared at δ = −23.58 ppm. We are tempted to conjecture the formation of a nickel–phosphine complex. However, there remains a possibility that

nickel-nanoparticles were formed. See ref. 4*g*. In addition, we have no exact evidence for the interaction between the diene moiety and the nickel.
7 The reaction using BH_3-free ligand **1** also yielded octylbenzene quantitatively. DABCO has no influence on the reaction. We preferred using **1·BH$_3$** because of easy handling.
8 The reaction of 1-bromooctane proceeded under the catalysis of $NiCl_2$ (5 mol%) and **1** (5 mol%) to afford octylbenzene quantitatively. However, in some cases in Table 2 and eqn (3) and (4), $NiCl_2$ (5 mol%) and **1** (10 mol%) was required to guarantee high yields.
9 General procedure for nickel-catalysed coupling reaction: $NiCl_2$ (3.2 mg, 0.025 mmol), phosphine–borane complex **1·BH$_3$** (17.4 mg, 0.050 mmol), and DABCO (8.4 mg, 0.075 mmol) in toluene (0.2 mL) were stirred for 30 min at 60 °C. Diethyl ether (0.5 mL) and 1-bromooctane (0.086 mL, 0.50 mmol) were added to the resulting mixture. Phenylmagnesium bromide in THF (1.99 M, 0.38 mL, 0.75 mmol) was added to the reaction mixture. The mixture was stirred for 3 h at room temperature. The reaction was quenched with saturated ammonium chloride solution, and the mixture was extracted with hexane. The combined organic layer was dried over Na_2SO_4 and concentrated. Silica gel column purification (Wakogel C-200, hexane) of the crude product provided octylbenzene (78.9 mg, 0.41 mmol, 83%). Octylbenzene was visualized by UV on TLC.
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