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Rh-Catalyzed Negishi Alkyl-Aryl Cross-Coupling Leading to α- or β-Phosphoryl-Substituted Alkylarenes

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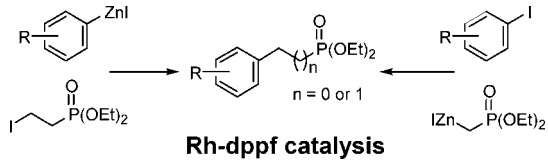
Received January 22, 2009



The catalytic cross-coupling between ArZnX and $ICH_2(CH_2)_nP(O)(OEt)_2$ ($n = 0-3$) has been investigated to determine the utility of the Rh catalyst during the alkyl-aryl cross-coupling and to develop a new synthetic method for phosphoryl-substituted alkylarenes. Rh-dppf exhibits an excellent catalytic activity for the reaction with the alkylphosphonate of $n = 1$, whereas for the reaction with those of $n = 2$ or 3, β-hydride elimination mainly takes place. As for the reaction with an alkylphosphonate of $n = 0$, a polarity inversion of the coupling components is necessary in order to provide the coupling products; the phosphoryl analogue of the Reformatsky reagent and ArI give the cross-coupling products in good yields through the catalysis by Rh-dppf.

Introduction

The Pd- or Ni-catalyzed cross-coupling of carbon electrophiles, R-X, with organometallic compounds, R′-m, is one of the most useful methods for constructing carbon−carbon bonds in organic synthesis.[1] Various kinds of coupling components such as aryl, alkenyl, alkynyl, and alkyl electrophiles and nucleophiles are applicable for this reaction; however, alkyl electrophiles, R = alkyl, are generally unsuitable because of the readily occurring side reaction, β-hydride elimination, under the catalytic conditions,[2] except for the activated ones containing functional groups such as $R = CH_2CO_2Et$ at the α-position.[3] Recently, the incidental drawbacks using conventional Pd or Ni catalysis have been overcome by using novel auxiliary components of the catalysts such as bulky and electron-rich phosphines,[4] chelating diamines,[5] *N*-heterocyclic carbenes,[6] 1,3-alkadienes,[7] or electron-poor alkenes,[8] which even allow the reactions with arylmetallic compounds, R′ = Ar, belonging to the relatively weak nucleophiles in the cross-coupling reactions[2a] (Figure 1). Furthermore, in certain instances, the catalysis is reported to be compatible with reactive functional groups such as an ester, ketone, nitrile, amide, or sulfoxide at carbons other than at the α-position of the alkyl chains,[4a,b,d−f,5b,6,8] thus expanding the synthetic utility of the reaction. During the course of our study of the catalytic efficiency of Rh in the Negishi

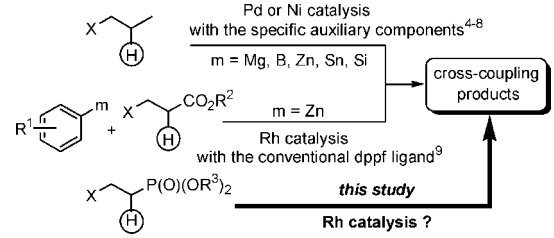


FIGURE 1. Alkyl-aryl cross-coupling: Pd or Ni catalysis versus Rh catalysis.

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10.1021/jo900142b CCC: $40.75
Published on Web 03/06/2009

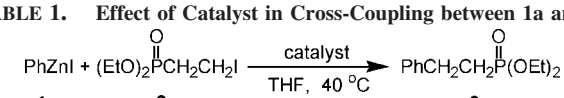
reaction, we found another methodology to achieve the alkyl-aryl cross-coupling with *nonactivated* alkyl electrophiles.[9] That is, in our reaction, it is not the auxiliary components of the catalysts but both the utility of the Rh as a catalyst and the manipulation of the coupling components by introduction of carbonyl groups near the reaction centers that could significantly suppress the β-hydride elimination. In this investigation, we studied the effect of phosphoryl groups on the alkyl-coupling partners during the Rh-catalyzed alkyl-aryl cross-coupling, intending to develop a new synthetic method for phosphoryl-substituted alkylarenes, a useful class of compounds in such fields as synthetic organic chemistry, represented by their utility as intermediates of the Horner−Wadsworth−Emmons reaction,[10] medicinal chemistry,[11] etc.[12]

Results and Discussion

A reaction solution composed of phenylzinc iodide (**1a**; 1.4 equiv), diethyl 2-iodoethylphosphonate (**2**; 1.0 equiv), and a Rh catalyst (2−5 mol %) in THF was stirred at 40 °C under nitrogen (Table 1). Throughout this study, the Rh catalysts were prepared in situ from $[RhCl(cod)]_2$ (cod = 1,5-cyclooctadiene) and various phosphorus ligands (Rh/P = 1:2), among which Rh-dppf (dppf = 1,1′-bis(diphenylphosphino)ferrocene) exhibited an excellent catalytic activity in the reaction, giving the desired coupling product **3a** in high yield (entries 1 and 2). Rh-BINAP was also effective for the reaction but required a longer reaction time than Rh-dppf (entry 3). On the other hand, Rh-PPh_3 and Rh-dppp (dppp = 1,3-bis(diphenylphosphino)propane) gave **3a** in low yields, though both starting materials **1a** and **2** were completely consumed under the stated conditions (entries 4 and 5). As the reaction solvent, TMU (TMU = *N*,*N*,*N*′,*N*′-tetramethylurea) was effective as THF (entry 6), but the reactivity of the bromide **4** was lower than **2** (entry 7). For the same reaction, the conventional Pd or Ni catalysts were far less effective than Rh-dppf, even if dppf was used as a ligand (entries 8−10), underlining the striking utility of Rh in the reaction.[9,13] To the best of our knowledge, this is the first example of synthesizing the phosphoryl substituted alkylarenes by the catalytic alkyl-aryl cross-coupling with nonactivated alkyl electrophiles.[14] Various arylzinc compounds containing such functional groups as CH_3 (entry 2), OCH_3 (entry 3), Cl (entry 4), or CO_2R (entries 5 and 6) at the para or meta position, **1b**−**f**, underwent catalysis by Rh-dppf during the reaction with **2** to afford the corresponding coupling products **3b**−**f** in good isolated yields, as shown in Table 2, whereas the substituent groups at the ortho position, **1g** and **1h**, completely inhibited the desired cross-coupling (entries 7 and 8).

The Rh-dppf catalyzed cross-coupling of **1a** with diethyl 3-iodopropylphosphonate (**5**) or diethyl 4-iodobutylphosphonate (**6**) took place far less selectively, producing the desired cross-coupling product **7** or **8** in reduced yields, i.e., 31% or 18%, respectively (Scheme 1). Together with the fact that in the Rh-dppf catalyzed reaction between **1a** and iodoethane (**9**) the yield

TABLE 1. Effect of Catalyst in Cross-Coupling between 1a and 2[a]



1a **2** **3a**

entry	catalyst	time (h)	yield[b] (%)
1	1/2[RhCl(cod)]$_2$/dppf	1	91
2	1/2[RhCl(cod)]$_2$/dppf	20	92
3	1/2[RhCl(cod)]$_2$/BINAP	20	70
4	1/2[RhCl(cod)]$_2$/PPh_3	1	<5
5	1/2[RhCl(cod)]$_2$/dppp	1	39
6[c]	1/2[RhCl(cod)]$_2$/dppf	1	92
7[d]	1/2[RhCl(cod)]$_2$/dppf	20	39
8	$Pd(PPh_3)_4$	20	<5
9	$PdCl_2$(dppf)	20	<5
10	$NiCl_2$(dppf)	20	14

[a] **1a** (0.56 mmol), **2** (0.4 mmol), catalyst (0.02 mmol), and THF (0.47 mL) were employed for all entries, except for entry 2, where 0.008 mmol of catalyst was used. [b] GLC yield. [c] TMU was used as solvent. [d] $BrCH_2CH_2P(O)(OEt)_2$ **4** was used in place of **2**.

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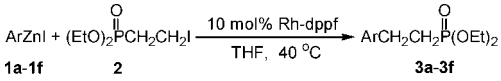
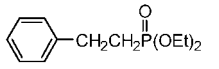
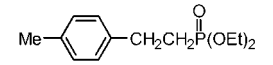
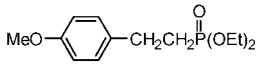
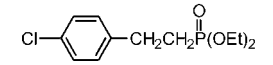
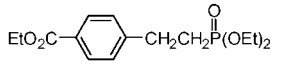
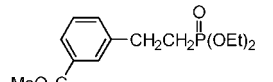
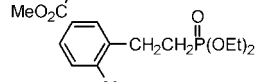
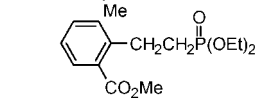
(14) There exists no precedent for the catalytic alkyl-aryl cross-coupling with alkyl electrophiles leading to phosphoryl-substituted alkylarenes, except for two examples using α-phosphoryl-substituted alkyl halides as an *activated* alkyl electrophile. Strotman, N. A.; Sommer, S.; Fu, G. C. *Angew. Chem., Int. Ed* **2007**, *47*, 3556–3558.

TABLE 2. Synthesis of Diethyl 2-Arylethylphosphonate[a]

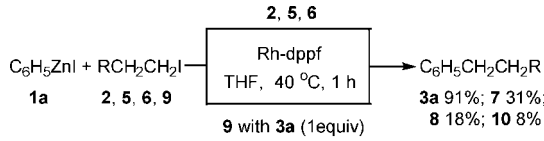


Ar = C_6H_5/**1a**,**3a**; *p*-MeC_6H_4/**1b**,**3b**; *p*-$MeOC_6H_4$/**1c**,**3c**; *p*-ClC_6H_4/**1d**,**3d**; *p*-$EtO_2CC_6H_4$/**1e**,**3e**; *m*-$MeO_2CC_6H_4$/**1f**,**3f**; *o*-MeC_6H_4/**1g**,**3g**; *o*-$MeO_2CC_6H_4$/**1h**,**3h**

entry	ArZnI	product		yield[b] (%)
1	**1a**		**3a**	86
2	**1b**		**3b**	81
3	**1c**		**3c**	67
4	**1d**		**3d**	76 (92)
5	**1e**		**3e**	61 (75)
6	**1f**		**3f**	62
7	**1g**		**3g**	<5
8	**1h**		**3h**	<5

[a] Molar ratio: $ArZnI/_2$/$[RhCl(cood)]_2$/dppf = 1.4:1:0.05:0.1. [b] Yields in parentheses were determined by GLC.

SCHEME 1. Reaction of 1a with 2, 5, 6, or 9



2, **3a**: R=$P(O)(OEt)_2$; **5**, **7**: R=$CH_2P(O)(OEt)_2$; **6**, **8**: R=$CH_2CH_2P(O)(OEt)_2$; **9**, **10**: R=H

of the cross-coupling product **10** was not increased by the addition of diethyl 2-phenylethylphosphonate (**3a**) in the reaction solutions (Scheme 1), these observations suggest the essential role exerted by the phosphoryl group, which exists in the reaction components and near the Rh center, to promote the cross-coupling with alkyl electrophiles possessing β-hydrogens (Figure 2).

A nearer phosphoryl group, for example, the one in diethyl 1-iodomethylphosphonate (**11**), however, did not assist the cross-coupling in its reaction with arylzinc compounds **1a,b,e**. Instead, the homocoupling products of the arylzinc compounds **12a,b,e** were obtained in quantitative yields (Scheme 2).[15] Fortunately, the addition of iodobenzene (**13a**) to the resulting solution, followed by heating of the obtained solution at 60 °C for 10 h,

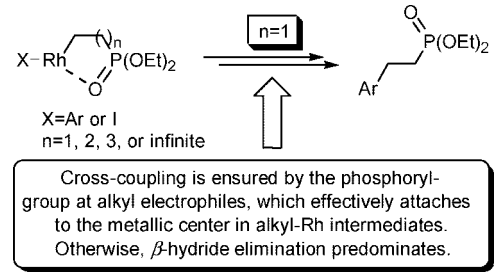


FIGURE 2. Effect of the phosphoryl group.

afforded the cross-coupling product **14a** in 80% yield based on the presumed intermediate **15**. Thus, alkyl-aryl cross-coupling with the alkyl electrophile **11** was achieved on the basis of the utility of the aryl electrophile **13a** via the polarity inversion of the alkyl electrophile **11** with 2 equiv of the arylzinc compounds **1a**.

More conveniently, the zinc compound **15**, a phosphoryl analogue of the Reformatsky reagent, was prepared by the reaction between **11** and zinc powder in THF[16,17] and was utilized in the reaction with **13a** in the presence of Rh-dppf, producing the desired product **14a** in 72% isolated yield as shown in Table 3 (entry 1). Various functional groups such as OCH_3 (entry 2), $CH_2OSi(CH_3)_2C(CH_3)_3$ (entry 3), $N(CH_3)_2$ (entry 4), Cl (entry 5), $CO_2C_2H_5$ (entry 6), or CN (entry 7) on the aryl electrophiles **13b**−**g** did not interfere with the Rh-dppf catalyzed reaction with **15** to afford the corresponding coupling products **14b**−**g** in good yields (entries 2−7). Meanwhile, among the substituent groups at the ortho position, some like CO_2CH_3 (entry 10) or COPh (entry 11) were tolerated in the reaction,[18] but some like OCH_3 (entry 8) or CN (entry 9) inhibited the reaction, analogous to the ones in **1g,h** (vide supra).

In conclusion, a novel, facile, and efficient synthetic method for α- or β-phosphoryl-substituted alkylarenes has been developed using the Rh-dppf catalyzed Negishi alkyl-aryl cross-coupling, featuring inhibition of the β-hydride elimination by the phosphoryl group at the β-carbons of the nonactivated alkyl electrophile or the utility of the phosphoryl analogue of the Reformatsky reagent as the alkyl nucleophile, which not only provides an alternative to precedents including the Arbuzov reaction under mild conditions but also assures the unique and specific catalysis by Rh in alkyl-aryl cross-coupling.

Experimental Section

Preparation of Diethyl (Iodozincio)methylphosphonate (15) in THF. In a reaction flask, Zn powder (1.31 g, 20 mmol) was heated by a heat-gun for 10 min under vacuum (1 Torr). To the solid were added diethyl 1-iodomethylphosphonate (**11**) (2.78 g, 10 mmol) and THF (5 mL), and the resulting mixture was stirred

(15) A similar reaction, the oxidative homo-coupling of arylmetallic compounds with activated alkyl electrophiles, was reported, in which arylboronic acids afford biaryls by catalysis with palladium using α-bromoacetate as the oxidant:(a) Goossen, L. K. *Chem. Commun.* **2001**, 669–670. (b) Lei, A.; Zhang, X. *Tetrahedron Lett.* **2002**, *43*, 2525–2528.

(16) To the best of our knowledge, there exists no precedent for the preparation of **15**, although the fluorine derivative of **15**, $(EtO)_2P(O)CF_2ZnI$, has been known for a long time and is widely utilized as a synthetic intermediate.[11a,b] (a) Qui, W.; Burton, D. J. *Tetrahedron Lett.* **1996**, *37*, 77–81. (b) Yokomatsu, T.; Abe, H.; Yamagishi, T.; Suemune, K.; Shibuya, S. *J. Org. Chem.* **1999**, *64*, 8413–8418.

(17) $[(MeO)_2P(O)CH_2]_2Zn$ was recently prepared by the deprotonation of $(MeO)_2P(O)CH_3$ with $Zn(tmp)_2$ (tmp = 2,2,6,6-tetramethylpiperidinyl anion), which was applied to the Pd-catalyzed cross-coupling with bromobenzene leading to $PhCH_2P(O)(OMe)_2$. We noticed that this is the only report that describes the catalytic synthesis of phosphoryl-substituted alkylarenes using non-fluoroalkyl nucleophiles as the coupling component: Hlavinka, M. L.; Hagadorn, J. R. *Organometallics* **2007**, *26*, 4105–4108.

(18) The beneficial effect of carbonyl groups at the ortho-position of arylzinc compounds is observed in the Rh-catalyzed cross-coupling with non-activated alkyl electrophiles.[9a]

SCHEME 2. Synthesis of 14a from 11

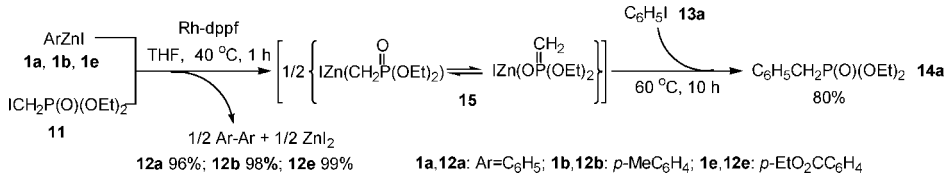
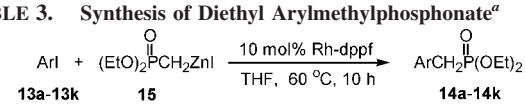
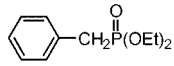
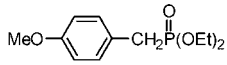
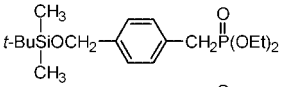
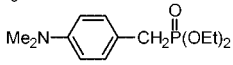
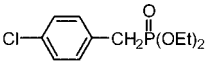
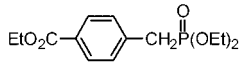
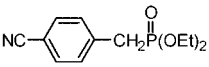
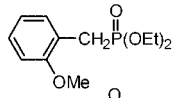
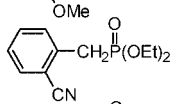
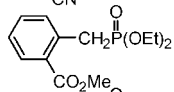
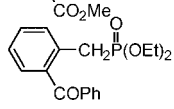


TABLE 3. Synthesis of Diethyl Arylmethylphosphonate[a]



Ar = C_6H_5/**13a**,**14a**; *p*-$MeOC_6H_4$/**13b**,**14b**; *p*-*t*-$BuMe_2SiOC_6H_4$/**13c**,**14c**; *p*-$Me_2NC_6H_4$/**13d**,**14d**; *p*-ClC_6H_4/**13e**,**14e**; *p*-$EtO_2CC_6H_4$/**13f**,**14f**; *p*-NCC_6H_4/**13g**,**14g**; *o*-$MeOC_6H_4$/**13h**,**14h**; *o*-NCC_6H_4/**13i**,**14i**; *o*-$MeO_2CC_6H_4$/**13j**,**14j**; *o*-$PhCOC_6H_4$/**13k**,**14k**

entry	ArI	product		yield (%)
1	**13a**		**14a**	72
2	**13b**		**14b**	68
3	**13c**		**14c**	71
4	**13d**		**14d**	50
5	**13e**		**14e**	68
6	**13f**		**14f**	74
7	**13g**		**14g**	62
8	**13h**		**14h**	<5
9	**13i**		**14i**	<5
10	**13j**		**14j**	86
11	**13k**		**14k**	85

[a] Molar ratio: ArI/**15**/[RhCl(cood)]$_2$/dppf = 1.4:1:0.05:0.1.

at ambient temperature for 24 h. Then, 0.30 mL of the supernatant solution was transferred to other flask containing chlorotrimethyltin (0.12 g, 0.60 mmol), and the mixture was stirred at the same temperature for 3 h. After the successive treatment of the resulting solution with aqueous KF and brine, the ether extract afforded 110 mg of diethyl (trimethylstannyl)methylphosphonate (**16**),[19] exhibiting the concentration of **15** to be 1.2 mol/L. **16**: oil; IR (neat) 1030, 1056, 1243 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.23 (t, J = 27.3 Hz, 9H), 1.08 (d, J = 17.7 Hz, 2H), 1.28 (t, J = 7.1 Hz, 6H), 3.98−4.06 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ −8.3 (d, J = 2.3 Hz), 5.9 (d, J = 134.6 Hz), 16.4 (d, J = 6.6 Hz), 61.0 (d, J = 6.3 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ 37.6.

Preparation of Diethyl 2-[4-(Ethoxycarbonyl)phenyl]ethylphosphonate (3e). Representative Procedure. To the mixture prepared by the reaction of [RhCl(cod)]$_2$ (10 mg, 0.02 mmol), dppf (22.2 mg, 0.04 mmol), and THF (0.05 mL) at ambient temperature for 10 min was added 0.47 mL of a 1.2 mol/L THF solution of **1e** (0.56 mmol), and the mixture was stirred for 5 min at the same temperature. To the resulting solution was added diethyl 2-iodoethylphosphonate (**2**) (0.075 mL, 0.4 mmol), and the mixture was stirred at 40 °C for 1 h. After the successive treatment of the resulting mixture with hydrazine monohydrate and brine, the ether extract was chromatographed on a silica gel column, affording 77 mg of **3e** (61%): oil; IR (neat) 1279, 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (dt, J = 7.1, 1.8 Hz, 6H), 1.36 (dt, J = 7.2, 1.8 Hz, 3H), 1.98−2.10 (m, 2H), 2.90−2.99 (m, 2H), 4.08 (quintet, J = 6.9 Hz, 4H), 4.34 (q, J = 7.1 Hz, 2H), 7.24 (d, J = 8.1 Hz, 2H), 7.95 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.2, 16.3 (d, J = 6.0 Hz), 27.1 (d, J = 140.5 Hz), 28.6 (d, J = 4.5 Hz), 60.8, 61.6 (d, J = 6.6 Hz), 128.0, 128.6, 129.8, 146.1 (d, J = 17.1 Hz), 166.4; ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.9; HRFAB-MS calcd for $C_{15}H_{24}O_5P$, 315.1361, found $(M + H)^+$ 315.1364.

Preparation of Diethyl (2-Benzoylphenyl)methylphosphonate (14k). Representative Procedure. To the mixture prepared by the reaction of [RhCl(cod)]$_2$ (10 mg, 0.02 mmol) and dppf (22.2 mg, 0.04 mmol) was added 0.47 mL of a 1.2 mol/L THF solution of **15** (0.56 mmol), and the mixture was stirred for 5 min at the same temperature. To the resulting solution was added (2-iodophenyl)phenylmethanone (**13k**) (123 mg, 0.4 mmol), and the mixture was stirred at 60 °C for 10 h. After the successive treatment of the resulting mixture with hydrazine monohydrate and brine, the ether extract was chromatographed on a silica gel column, affording 113 mg of **14k** (85%): oil; IR (neat) 1269, 1662 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 6H), 3.52 (d, J = 22.5 Hz, 2H), 3.83−3.95 (m, 4H), 7.28−7.32 (m, 2H), 7.41−7.48 (m, 4H), 7.54−7.56 (m, 1H), 7.79−7.83 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 16.1 (d, J = 6.0 Hz), 29.9 (d, J = 136.6 Hz), 61.9 (d, J = 6.7 Hz), 126.0 (d, J = 3.7 Hz), 128.2, 129.9 (d, J = 3.0 Hz), 130.4, 130.6 (d, J = 3.2 Hz), 131.6 (d, J = 10.0 Hz), 132.0 (d, J = 5.7 Hz), 133.0, 137.7, 138.2 (d, J = 6.6 Hz), 197.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.6; HRFAB-MS calcd for $C_{18}H_{22}O_4P$, 333.1256, found $(M + H)^+$ 333.1258.

Supporting Information Available: General methods, compound characterization data, and copies of the ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO900142B

(19) Weichmann, H.; Ochsler, B.; Duchek, I.; Tzschach, A. *J. Organomet. Chem.* **1979**, *182*, 465–476.