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Negishi Alkyl−Aryl Cross-Coupling Catalyzed by Rh: Efficiency of Novel Tripodal 3-Diphenylphosphino-2-(diphenylphosphino)methyl-2-methylpropyl Acetate Ligand

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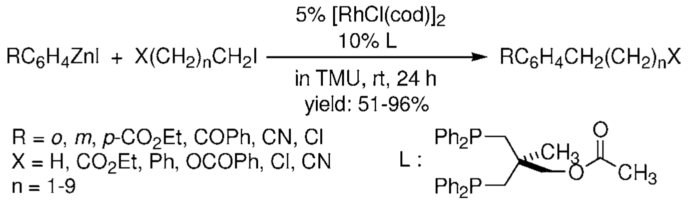
ABSTRACT



3-Diphenylphosphino-2-(diphenylphoshino)methyl-2-methylpropyl acetate acted as an efficient ligand for a Rh catalyst, achieving cross-coupling between arylzinc compounds bearing electron-withdrawing groups and alkyl electrophiles. The beneficial effect of the tripodal ligand and such aryl nucleophiles was discussed with regard to the specificity of the Rh catalysis.

Pd- or Ni-catalyzed cross-coupling between carbon electrophiles, R−X (R = alkenyl, aryl, or alkynyl; X = halides, sulfonates, etc.), and organometallic nucleophiles, R′−m (R′ = alkyl, alkenyl, aryl, or alkynyl; m = Mg, Zn, B, Sn, Si, etc.), provides one of the most valuable methods for constructing carbon−carbon bonds in organic synthesis.[1] However, alkyl electrophiles, especially when R is an alkyl group possessing β-hydrogens, are not readily available for the reaction, since these electrophiles react far more reluctantly with the catalyst than other commonly employed ones. Additionally, the resulting intermediates, oxidative adducts, are apt to suffer from β-hydride elimination. Subsequently, the yields of the desired cross-coupling products are diminished.[2] To solve these problems of alkyl cross-coupling, a number of investigations have been undertaken in recent years to develop efficient catalyst systems, with the aid of novel ligands such as trif1uoromethylstyrenes,[3a] 1,3-butadiene,[3b] $P(c\text{-}C_6H_{11})_3$,[3c] N-heterocyclic carbenes,[3d] bathophenanthroline,[3e] $P(t\text{-}Bu)_2Me$,[3f] and pincers[3g] of a Pd or Ni catalyst[2] or with the aid of novel metallic species such

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(1) For reviews, see: (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002. (c) Tsuji, J. *Palladium Reagents and Catalysis: Innovation in Organic Synthesis*; John Wiley & Sons: New York, 1995.

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(3) Ni−Mg: (a) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186–11187. (b) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223. Pd−Mg: (c) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056–4059. (d) Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403–409. Ni−Sn: (e) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341. Pd−Sn: (f) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910–3912. Pincer Ni−Mg: (g) Vechorkin, O.; Hu, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 2937–2940.

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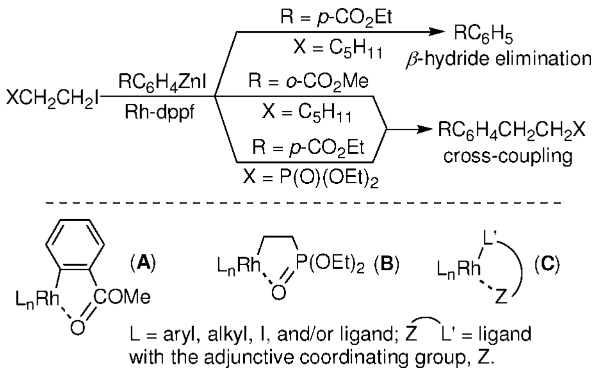
as Fe[2a,4] or Co.[2a,5] In our continuing studies on the synthesis and synthetic applications of arylzinc compounds,[6] the utility of Rh catalysts in the Negishi alkyl−aryl cross-coupling was examined for the first time. These studies revealed that catalytic cross-coupling takes place smoothly in the presence of Rh−1,1′-bis(diphenylphosphino)ferrocene (dppf), provided either of the coupling components, ArZnX or R−X, contains functional groups like carbonyl or phosphoryl near the reaction centers (Scheme 1).[7] In these instances, the vacant sites of the oxidative adducts are favorably occupied by the coupling components to prevent β-hydride elimination (**A** and **B**, Scheme 1). Here, we describe the design and development of new efficient ligands such that the role preveously exerted by the substituents is now performed by the ligands themselves (**C**, Scheme 1).

Scheme 1. Effect of Coordinating Functional Groups on the Rh-Catalyzed Negishi Alkyl−Aryl Cross-Coupling



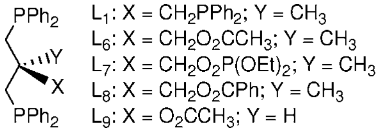
The effect of adjunctive groups in the ligand molecules was examined in the reaction of *p*- ethoxycarbonylphenylzinc iodide **1a** and 1-iodoheptane **2a** (1.5−3 equiv) in the presence of 5 mol % of $[RhCl(cod)]_2$ (cod = 1,5-cyclooctadiene) in *N*,*N*,*N*′,*N*′-tetramethylurea (TMU) at room temperature for 24 h, and the results are summarized in Table 1. At first, L_1, containing the phosphorus adjunctive group, quenched every catalytic reaction (entry 1), though the parent molecule, 1,3-bis(diphenylphosphino)propane (dppp), was a slightly better ligand than dppf (entry 2 and Scheme 1). Similarly, tripodal ligand L_2 and L_3 were ineffective (entries 3 and 4), which implies that simple occupation of the vacant site is insufficient to promote the alkyl−aryl cross-coupling by Rh catalysis. The adjunctive ester group did not work well in the monodentate phosphorus ligands L_4 and L_5 (entries 5 and 6), but the adjunctive ester and phosphoryl groups worked successfully in the bidentate phosphorus ligands L_6 and L_7, affording the desired product **3aa** predominantly (entries 7 and 8). L_8 and L_9 were less effective (entries 9 and 10). β-Hydride elimination is suppressed completely after the removal of cod in the catalyst precursor $[RhCl(cod)]_2$ from the reaction solution (entries 11 and 12), and this procedure was applied in every subsequent run. For the solvent, *N*,*N*-dimethylformamide (DMF) was also compatible with the reaction but THF was not (entries 13 and 14). In the presence of NaI, 1-bromoheptane reacted favorably with **1a** to afford the desired cross-coupling product in good yield (entry 15). Thus, with typical alkyl electrophiles, i.e., ones possessing β-hydrogens and no special coordinating groups near the reaction cnter, Rh-catalyzed Negishi alkyl-aryl cross-coupling was achieved for the first time by means of the utility of L_6.

Table 1. Effect of Ligand on the Rh-Catalyzed Reaction between **1a** and **2a**[a]

$$\underset{\textbf{1a}}{p\text{-EtO}_2CC_6H_4ZnI} + \underset{\textbf{2a}}{C_7H_{15}I} \xrightarrow[\text{TMU, rt, 24 h}]{5\%\ [RhCl(cod)]_2,\ \text{ligand}} \underset{\textbf{3aa}}{p\text{-EtO}_2CC_6H_4C_7H_{15}}$$

entry	ligand	yield[b] (%)
1	L_1	>5
2	dppp	13
3	L_2	>5
4	L_3	>5
5	$EtO_2CCH_2PPh_2$ (L_4)	>5
6	o-$MeO_2CC_6H_4PPh_2$ (L_5)	9
7	L_6	66
8	L_7	64
9	L_8	36
10	L_9	14
11	L_6	99
12	L_7	83
13[c]	L_6	82
14[d]	L_6	>5
15[e]	L_6	99

[a] **1a** (0.20 mmol), **2a** (0.60 mmol), $[RhCl(cod)]_2$ (0.01 mmol), Ligand (0.02 mmol), and TMU (0.1 mL) were employed for all entries, except for entries 11−15, where **2a** of 0.30 mmol was used, and entries 5 and 6, where Ligand of 0.06 mmol was used. In entries 11−15, cod was removed from the reaction solution. [b] GLC yield. [c] DMF was used in place of TMU. [d] THF was used in place of TMU. [e] C_7H_5Br was used in place of **2a**. NaI (0.60 mmol) was added.



L_1: X = CH_2PPh_2; Y = CH_3
L_6: X = $CH_2O_2CCH_3$; Y = CH_3
L_7: X = $CH_2O_2P(OEt)_2$; Y = CH_3
L_8: X = CH_2O_2CPh; Y = CH_3
L_9: X = O_2CCH_3; Y = H
L_2: $PhP(CH_2CH_2PPh_2)_2$
L_3: $P(CH_2CH_2PPh_2)_3$

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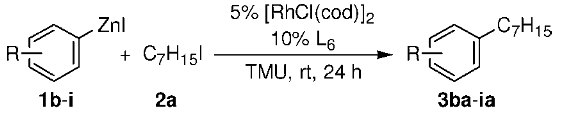
(8) To our knowledge, six catalytic alkyl−aryl cross-couplings have been accomplished using arylmetallic nucleophiles, containing such reactive functional groups as ester, nitrile, and nitro,[3a,e,8a−d] which utilized an unstable catalyst,[3a] a high reaction temperature (60−80 °C),[3e,8a,b] manipulated nucleophiles ($ArZnCH_2TMS$),[8c] or special procedures:[8a,d] (a) Duncton, M. A. J.; Estiarte, M. A.; Tan, D.; Kaub, C.; O'Mahony, D. J. R.; Johnson, R. J.; Cox, M.; Edwards, W. T.; Wan, M.; Kincaid, J.; Kelly, M. G *Org. Lett.* **2008**, *10*, 3259–3262. (b) Lu, F.; Chi, S.-W.; Kim, D.-H.; Han, K.-H.; Kuntz, I. D.; Guy, R. K. *J. Comb. Chem.* **2006**, *8*, 315–325. (c) Nakamura, M.; Ito, S.; Matsuo, K.; Nakamura, E. *Synlett* **2005**, 1794–1798. (d) Vechorkin, O.; Proust, V.; Hu, X. *J. Am. Chem. Soc.* **2009**, *131*, 12078–12079.

Arylzinc compounds containing electron-withdrawing groups such as CN, COPh, CO_2Me, or Cl at the *para*, *meta*, or *ortho* positions **1b**−**f** readily underwent catalysis by Rh−L_6 in the reaction with **2a** to afford the coupling products in moderate to good yields (entries 1−5, Table 2). Under similar conditions, arylzinc compounds containing electron-donating groups such as alkyl or OCH_3 (**1h**,**i**) as well as unsubstituted compound **1g** gave the cross-coupling products in minor amounts, instead affording Ar-H derived from β-hydride elimination as the main products (entries 6−8). As for the alkyl electrophile, various substituents such as CO_2Et, Ph, OBz, Cl, or CN on the chain at the C_2−C_4 positions (**2b**,**c**,**e**−**g**) were tolerated under catalysis by Rh-L_6, giving the desired cross-coupling products **3ab**,**ac**,**bd**−**bg**,**cb**,**cg**,**jg** in good yields (entries 1−8, Table 3). The *o*-tolylzinc compound afforded the desired product **3jg** in 54% yield (entry 9). Although quite a number of catalytic alkyl−aryl cross-couplings have been developed recently,[2,3] there exist few examples using functionalized arylmetallic nucleophiles as coupling components.[8] Therefore, the present reaction, featuring the availability of such nucleophiles,[6] along with the mildness of the reaction conditions and the facility of the reaction procedure,[8] provides efficient and novel access to polyfunctionalized alkylbenzenes.

Table 2. Rh-L_6-Catalyzed Cross-Coupling between Various Arylzinc Compounds and 2a[a]

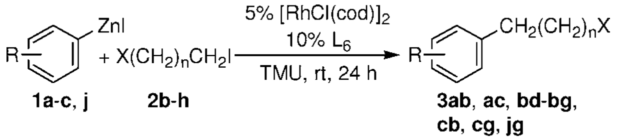


1b, **3ba**: R = *p*-CN; **1c**, **3ca**: R = *p*-COPh; **1d**, **3da**: R = *p*-Cl; **1e**, **3ea**: R = *m*-CO_2Me; **1f**, **3fa**: R = *o*-CO_2Me; **1g**, **3ga**: R = H; **1h**, **3ha**: R = *p*-Et; **1i**, **3ia**: R = *p*-OMe

entry	RC_6H_4ZnI	$RC_6H_4C_7H_{15}$	yield[b] (%)
1	**1b**	**3ba**	99
2	**1c**	**3ca**	80
3	**1d**	**3da**	51
4	**1e**	**3ea**	(90)
5	**1f**	**3fa**	(90)
6	**1g**	**3ga**	23
7	**1h**	**3ha**	27
8	**1i**	**3ia**	21

[a] RC_6H_4ZnI (0.20 mmol), **2a** (0.30 mmol), $[RhCl(cod)]_2$ (0.01 mmol), L_6 (0.02 mmol), and TMU (0.1 mL) were employed for all entries, except for entries 4 and 5, where every component was doubled. [b] GLC yield. Values in parentheses are isolated yields.

Table 3. Rh-L_6-Catalyzed Synthesis of Functionalized Alkylbenzenes[a]



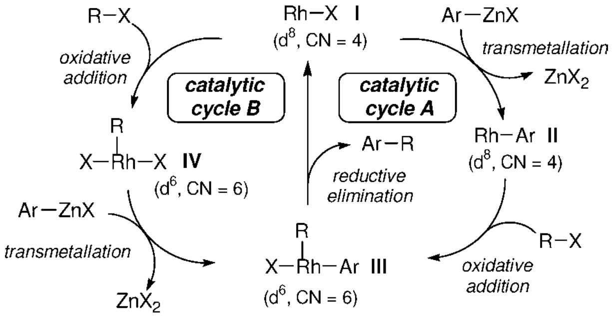
1a, **3ab**, **3ac**: R = *p*-CO_2Et; **1b**, **3bd**, **3be**, **3bf**, **3bg**: R = *p*-CN; **1c**, **3cb**, **3cg**: R = *p*-COPh; **1j**, **3jh**: R = *o*-Me; **2b**, **3ab**, **3cb**: n = 2, X = CO_2Et; **2c**, **3ac**: n = 1, X = Ph; **2d**, **3bd**: n = 9, X = H; **2e**, **3be**: n = 3, X = OCOPh; **2f**, **3bf**: n = 2, X = Cl; **2g**, **3bg**, **3cg**, **3jg**: n = 3, X = CN

entry	RC_6H_4ZnI	$X(CH_2)_nCH_2I$	$RC_6H_4CH_2(CH_2)_nX$	yield[b] (%)
1	**1a**	**2b**	**3ab**	85
2	**1a**	**2c**	**3ac**	96
3	**1b**	**2d**	**3bd**	83
4	**1b**	**2e**	**3be**	96
5	**1b**	**2f**	**3bf**	95
6	**1b**	**2g**	**3bg**	79
7	**1c**	**2b**	**3cb**	95
8	**1c**	**2g**	**3cg**	90
9	**1j**	**2g**	**3jg**	54

[a] RC_6H_4ZnI (0.40 mmol), **2a** (0.60 mmol), $[RhCl(cod)]_2$ (0.02 mmol), L_6 (0.04 mmol), and TMU (0.2 mL) were employed for all entries. [b] Isolated yield.

Although a detailed mechanism remains to be clarified, the observed unique specificity of the reaction might provide some insight into the catalytic properties of Rh in the cross-coupling.[7,9] In Rh-catalyzed cross-coupling, two catalytic cycles are possible, one commencing with transmetalation and the other with oxidative addition (catalytic cycle A and B, respectively, Scheme 2). In both cases, Rh^{3+} species (intermediates **III** and **IV**) are formed by the oxidative addition of the alkyl electrophile. Binding of either the third functional group of the tripod ligand L_6 or the β-C−H bond in the alkyl electrophile to the empty orbital is then possible, since the coordination number (CN) is increased via the

Scheme 2. Two Possible Catalytic Cycles for Rh-Catalyzed Cross-Coupling between R-X and Ar-ZnX



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(9) In comparison with the vast numbers of Pd- or Ni-catalyzed cross-couplings of R−X and R′−m, Rh-catalyzed ones are few: Larock, R. C.; Hershberger, S. S *J. Organomet. Chem.* **1982**, *225*, 31–41. (b) Larock, R. C.; Narayanan, K.; Hershberger, S. S. *J. Org. Chem.* **1983**, *48*, 4377–4380. (c) Evans, P. A.; Uraguchi, D. *J. Am. Chem. Soc.* **2003**, *125*, 7158–7159. (d) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974–8975. (e) Uemura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229–2231. (f) Yasui, H.; Mizutani, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 1410–1415. (g) Wu, J.; Zhang, L.; Luo, Y. *Tetrahedron Lett.* **2006**, *47*, 6747–6750. (h) Wu, J.; Zhang, L.; Gao, K. *Eur. J. Org. Chem.* **2006**, 5260–5263. (i) Kantam, M. L.; Roy, S.; Roy, M.; Sreedhar, B.; Choudary, B. M.; De, R. L. *J. Mol. Catal. A: Chem.* **2007**, *273*, 26–31. (j) Zhang, L.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 2409–2413. (k) Yu, J.-Y.; Kuwano, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 7217–7219.

change in the oxidation state of Rh from +1 to +3. Notably, the reaction using a 1:1 molar mixture of **1a** and **1g** with **2a** afforded **3aa** (89%) and **3ga** (16%) (Scheme 3), which coincides well with the reactions using **1a** and **1g** individually (entry 12, Table 1, and entry 6, Table 2). These results suggest that there is no free HX derived from β-hydride elimination in the reaction solution: HX would decompose ArZnX, resulting in a reduced yield of **3aa**. Thus, Ar-H was likely derived from the oxidative adduct **III** through the intermediate **V** (bold arrow, Scheme 4). Therefore, the catalytic cycle A most likely operates in the present reaction,[10] where **III** is a common intermediate before the reaction diverges between cross-coupling and β-hydride elimination (Schemes 2 and 4). Accordingly, from the fact that electron-deficient arylzinc nucleophiles and/or tripodal ligand L_6 exert a beneficial effect on the cross-coupling, while relatively restraining the β-hydride elimination, the carbon−carbon bond-forming reductive elimination of intermediate **III** is speculated to be accelerated by the electron transfer from an alkyl ligand[11] to an aryl ligand[12] and by the concomitant acceptance of the electrons on the metallic center by the carbonyl group of L_6 (Scheme 5).[13,14]

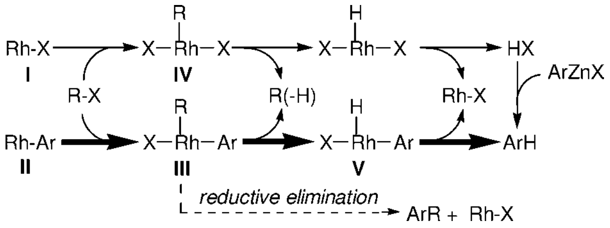
Scheme 3. Reaction between **1a**, **1g**, and **2a**

$$\mathbf{1a} + \mathbf{1g} + \mathbf{2a} \xrightarrow[\text{TMU, rt, 24 h}]{5\%\ [\text{RhCl(cod)}]_2,\ 10\%\ \text{L}_6} \mathbf{3aa} + \mathbf{3ga}$$

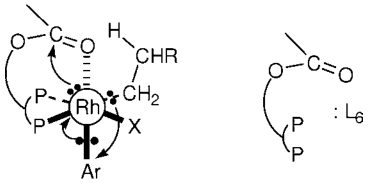
1a/**1g**/**2a**/Rh-L_6 = 1/1/2/0.1 89% 16%

1a: *p*-$\text{EtO}_2\text{CC}_6\text{H}_4\text{ZnI}$; **1g**: $\text{C}_6\text{H}_5\text{ZnI}$; **2a**: $\text{C}_7\text{H}_{15}\text{I}$;
3aa: *p*-$\text{EtO}_2\text{CC}_6\text{H}_4\text{C}_7\text{H}_{15}$; **3ga**: $\text{C}_6\text{H}_5\text{C}_7\text{H}_{15}$

Scheme 4. β-Hydride Elimination from Intermediate **III** or **IV**



Scheme 5. Supeculative View of Reductive Elimination



In conclusion, the novel Rh catalysis enables the cross-coupling of alkyl halides with arylzinc compounds bearing electron-withdrawing groups by means of the efficient assistance of tripodal ligand, L_6, which provides a facile and useful synthetic method of polyfunctionalized alkylbenzenes.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (No. 20550043) from the Japan Society for the Promotion of Science.

Supporting Information Available: Experimental procedures, compound characterization data, and DFT calculation. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] Catalytic cycle A was believed to operate in the Rh-catalyzed Negishi alkyl−aryl cross-coupling utilizing TMSCH_2I as an alkyl electrophile: Takahashi, H.; Hossain, K. M.; Nishihara, Y.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2006**, *71*, 671–675.

[11] In the Rh-catalyzed alkyl−aryl cross-coupling between ArZnX and YCH_2I (Y = H, OMe, or CN), the higher the electronic density of the YCH_2 fragment is, the larger the reactivity becomes: Hossain, K. M.; Takagi, K. *Chem. Lett.* **1999**, 1241–1242.

[12] The electronic deficiency of the aryl fragment is known to promote the reductive elimination of certain aryl transition-metal complexes, which generally retards the process. See: (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232–8245. (b) Mann, G.; Baranano, D.; Hartwig, J. F.; Reingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205–9219. (c) Shekhar, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 13016–13027.

[13] Electron-accepting ligands are known to promote the reductive elimination, yielding a carbon−carbon bond between aryl and alkyl fragments See ref 3a.

[14] The DFT calculation established that little interaction exists between Rh and either the third arm of L_6 or the alkyl group in the analogue of intermediate **III** itself. See the Supporting Information.