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Novel Rh Catalysis in Cross-Coupling between Alkyl Halides and Arylzinc Compounds Possessing *ortho*-COX ($X = OR, NMe_2$, or Ph) Groups

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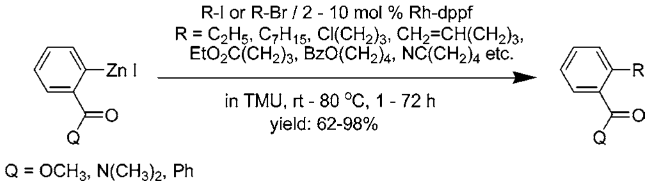
ABSTRACT



Rh–dppf was found to be an efficient catalyst for the cross-coupling between primary alkyl halides bearing β-hydrogens and arylzinc compounds possessing carbonyl groups such as ester, amide, or ketone at the ortho position. Various functional groups such as ester, nitrile, or acyloxylate moieties on the halides were tolerated under the catalysis conditions. Arylzinc compounds free of *ortho*-carbonyl groups reacted well with ethyl 3-iodopropanoate, suggesting that the essential intramolecular interaction between carbonyl groups and Rh promotes the reductive elimination.

Transition-metal-catalyzed cross-coupling of organometallic compounds (R−m) with organic halides (R′−X) has become one of the most useful methods for constructing carbon−carbon bonds in organic synthesis.[1] The present utility and efficiency of catalysis have been mainly achieved by refining auxiliary components of the catalyst system such as ligands, additives, and/or solvents with fixed metallic centers of Pd or Ni, which at the same time eliminate the incidental drawbacks stemming from the reluctant catalytic reaction.[1] This was exemplified by the recently reported successful application of novel Ni-4-(trifluoromethyl)styrene,[2a] Pd−P(c-C_6H_{11})$_3$,[2b] or Pd−P(c-C_5H_9)$_3$ catalytic systems[2c] to the difficult cross-coupling between R−m (R = aryl; m = ZnX) and R′−X (R′ = alkyl; X = I, Br, or Cl).[3,4] Hereupon, we envisaged the necessity for reinvestigating the catalytic activity of other transition metals, particularly Rh, in the cross-coupling reaction. Although only a few papers exist on Rh-catalyzed cross-coupling between R−m and R′−X,[5] Rh catalysis is intriguing in view of the following: (1) Rh may commence the catalytic cycle with transmetalation (path A, Scheme 1) instead of with more conventional oxidative addition (path B) and (2) the number of d-electrons, d^6 or d^8, and the coordination numbers, CN = 4 or 6, of the metallic species involved differ from those of Pd or Ni

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(1) (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.

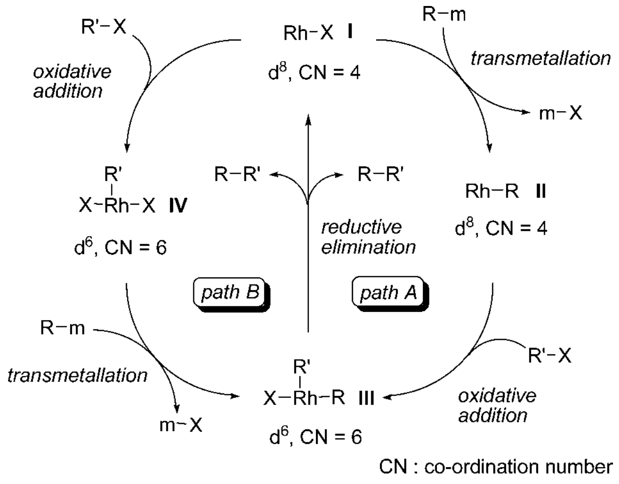
(2) (a) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186−11187. (b) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056−4059. (c) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527−12530.

(3) (a) Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688. (b) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, *100*, 3187−3204.

(4) Among various combinations of reaction components, the catalytic cross-couplings of R = aryl and R′ = alkyl are the most problematic because alkyl electrophiles, aryl nucleophiles, or the resulting oxidative adducts are less susceptible to oxidative addition, transmetalation, or reductive elimination caused by overwhelmingly facile side reactions such as β-elimination, respectively.[3a]

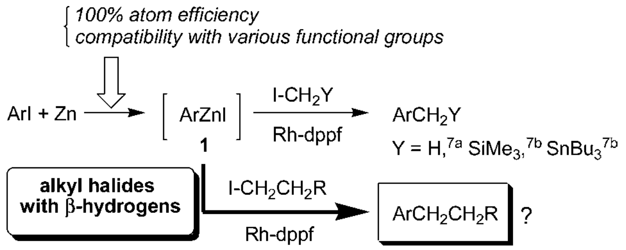
10.1021/ol060969d CCC: $33.50

Scheme 1. Two Possible Catalytic Cycles for Rh-Catalyzed Cross-Coupling between R−m and R′−X



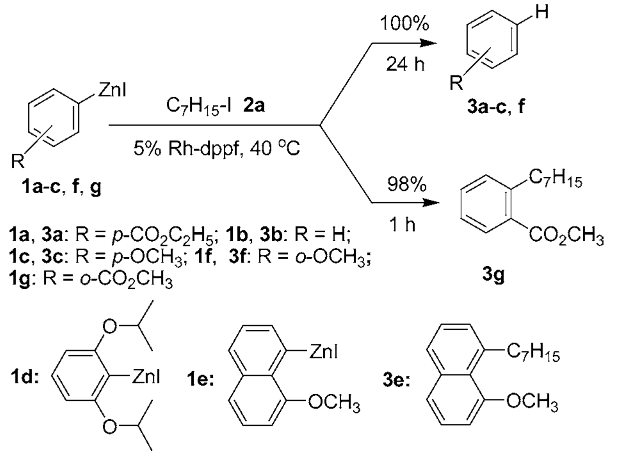
catalysis (d^8 or d^{10} and CN = 4), which perhaps is the cause for complication with conventional catalysts.[5b,6,7b] Furthermore, along with the long-standing Cu catalysis,[8] recently disclosed Fe or Co catalysis[9] suggests the latent catalytic activity of transition metals other than Pd or Ni toward the cross-coupling with R′ = alkyl. On the basis of these phenomena, we previously initiated an investigation of the catalytic activity of Rh toward the cross-coupling reaction of our arylzinc compounds **1** (Scheme 2)[10] with alkyl halides and found that the catalyst system composed of Rh and 1,1′-bis(diphenylphosphino)ferrocene (dppf) exhibits excellent catalytic activity toward the reaction between **1** and alkyl halides such as iodomethane, (iodomethyl)trimethylsilane, or (iodomethyl)tributyltin.[7] In this study, we applied the Rh−dppf catalyst system to the reaction of **1** with alkyl halides containing β-hydrogens (Scheme 2).

Scheme 2. Rh−dppf-Catalyzed Cross-Coupling of Arylzinc Compounds with Alkyl Halides



The reaction solution composed of **1**, 1-iodoheptane **2a** (1.1 equiv), and 5 mol % of Rh−dppf, generated in situ from 2.5 mol % of [RhCl(cod)]$_2$ and 5 mol % of dppf, in *N*,*N*,*N′*,*N′*-tetramethylurea (TMU) was stirred at 40 °C for 24 h under nitrogen. As shown in Scheme 3, arylzinc compounds **1a**−**c** were converted into the protodezincation products **3a**−**c** quantitatively, indicating that the β-elimination of alkyl−Rh intermediates **III** and/or **IV** took place rapidly under these conditions. The coexistence of 5 mol % of PPh$_3$ in the reaction solution inhibited all reactions including the β-elimination where 92% of **1a** was recovered after the reaction. Even without any additives, **1d** was quantitatively recovered after exposure to the catalytic system and **1e** afforded the desired cross-coupled product **3e** in 13% yield (17% conversion) from the reaction at 80 °C for 12 h with 10 mol % of Rh−dppf. **1f** afforded the protodezincation product **3f**, quantitatively.[11] To our delight, the cross-coupled product **3g** was quantitatively formed in the reaction of **1g** and **2a** at 40 °C for 1 h under Rh−dppf catalysis. As shown in Table 1, the reaction proceeded smoothly at room temperature (entry 2) or with 2 mol % of Rh−dppf at 80 °C (entry 3) to provide **3g** in good yield.

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



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(5) (a) 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) Andrianome, M.; Delmond, B. *J. Org. Chem.* **1988**, *53*, 542−545. (d) Andrianome, M.; Haberle, K.; Delmond, B. *Tetrahedron* **1989**, *45*, 1079−1088. (e) Uemura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229−2231. (f) Evans, P. A.; Uraguchi, D. *J. Am. Chem. Soc.* **2003**, *125*, 7158−7159. (g) Evans, P. A.; Leahy, D. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974−8975.

(6) (a) Schwartz, J.; Hart, D. W.; Holden, J. L. *J. Am. Chem. Soc.* **1972**, *94*, 9269−9271. (b) Semmelhack, M. F.; Ryono, L. *Tetrahedron Lett.* **1973**, 2967−2970. (c) Hegedus, L. S.; Kendall, P. M.; Lo, S. M.; Sheats, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 5448−5452. (d) Fanizzi, F. P.; Sunley, G. J.; Maitlis, P. M. *J. Organomet. Chem.* **1987**, *330*, C31−C32.

(7) (a) Hossain, K. M.; Takagi, K. *Chem. Lett.* **1999**, 1241−1242. (b) Takahashi, H.; Hossain, K. M.; Nishihara, Y.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2006**, *71*, 671−675.

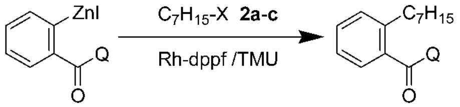
(8) Kochi, J. K. *J. Organomet. Chem.* **2002**, *653*, 11−19.

(9) (a) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, 2081−2091. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337−2364. (c) Furstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 626−629.

(10) For our synthesis of arylzinc compounds, see: (a) Takagi, K. *Chem. Lett.* **1993**, 469−472. (b) Ogawa, Y.; Saiga, A.; Mori, M.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2000**, *65*, 1031−1036. (c) Ikegami, R.; Koresawa, A.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2003**, *68*, 2195−2199. Except for Zn, other arylmetal compounds such as those of B, Si, Sn, Bi, or Ti are not available via synthesis from aryl halides and simple substances as metallic sources.

(11) None of the **1**'s including 2-isopropoxy-, 2-acetoxy-, 2-(methoxy)methyl-, or 2-(trifluoromethyl)phenylzinc iodide afforded the desired cross-coupling products. However, the rates of protodezincation of **1** depended on the substituents and decreased in the order of 2-acetoxy, 2-(methoxy)methyl > 2-trifluoromethyl > 2-isopropoxy. The coexistence of 1 equiv of benzophenone in the reaction solution of **1b** did not change the course of the reaction.

Table 1. Reaction between **1** with an *ortho*-Carbonyl Group and 1-Haloheptane **2a**−**c**[a]



1g-i **3g-i**

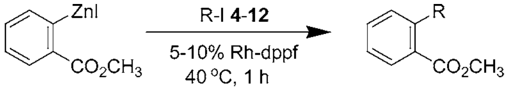
1g, **3g**: Q = OCH_3; **1h**, **3h**: Q = $N(CH_3)_2$; **1i**, **3i**: Q = Ph
2a; X = I; **2b**; X = Br; **2c**; X = Cl

entry	1	2	catalyst/mol %	temp/°C time/h	yield[b] 3	1/%
1	**1g**	**2a**	5	40/1	**3g**	98 (74)
2	**1g**	**2a**	5	rt/1	**3g**	92
3	**1g**	**2a**	2	80/3	**3g**	72
4	**1g**	**2b**	10	80/1	**3g**	78
5	**1g**	**2b**	10	rt/72	**3g**	71
6[c]	**1g**	**2c**	10	40/24	**3g**	98
7	**1h**	**2a**	10	40/2	**3h**	(75)
8	**1i**	**2a**	10	40/12	**3i**	(63)

[a] **1** (0.44 mmol), **2** (0.40 mmol), Rh−dppf (0.008−0.04 mmol), and TMU (0.22 mL) were employed for all entries. [b] GLC yield. Values in parentheses are isolated yields. [c] NaI (1.2 mmol) was added.

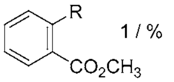
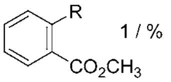
1-Bromoheptane **2b** was also successful in the reaction, though stirring at 80 °C (entry 4) or for a long time (entry 5) was required. In the presence of 3 equiv of NaI, 1-chloroheptane **2c** favorably reacted with **1g** under catalysis by Rh−dppf to afford the desired cross-coupled product **3g** in good yield (entry 6). Besides **1g**, **1h** and **1i** also reacted with **2a** to afford the desired cross-coupled products **3h** and **3i** in good yield under similar conditions (entries 7 and 8). As shown in Table 2, various substituents such as chloro **5**, ethoxycarbonyl **6**, alkenyl **7**, benzoyloxy **8**, cyano **9**, alkoxy **10**, or phenyl **11** on the alkyl chains at the C2−C5 positions were tolerated under catalysis by Rh−dppf giving the desired cross-coupled products **13**−**20**, all isolated in good yields (entries 2−9). Under similar conditions, *sec*-alkyl iodide **12** did not afford the cross-coupling product at all (entry 10). To our knowledge, this is the first example of Rh-catalyzed cross-coupling of alkyl halides containing β-hydrogens with any organometallic compounds. Furthermore, it provides a facile synthetic method for alkylbenzenes possessing *ortho*-carbonyl groups, with the beneficial features of simplicity, a great degree of functional group tolerance, and utility of readily available starting materials.[12]

Table 2. Reaction between **1g** and Various Iodoalkanes **4**−**12**[a]



1g **13-21**

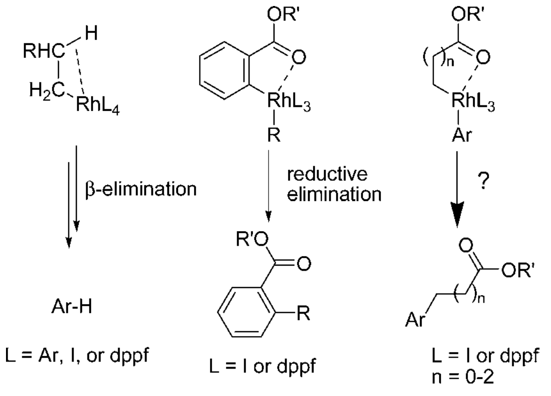
4, **13**: R = CH_3CH_2; **5**, **14**: R = $ClCH_2CH_2CH_2$;
6, **15**: R = $C_2H_5O_2CCH_2CH_2CH_2$; **7**, **16**: R = $CH_2{=}CHCH_2CH_2CH_2$;
8, **17**: R = $PhCO_2CH_2CH_2CH_2CH_2$; **9**, **18**: R = $NCCH_2CH_2CH_2CH_2$;
10, **19**: R = $THPOCH_2CH_2CH_2CH_2CH_2$; **11**, **20**: R = $PhCH_2CH_2$;
12, **21**: R = $CH_3CH_2(CH_3)CH$

		yield[b]				yield[b]	
entry	R-I		1 / %	entry	R-I		1 / %
1	**4**	**13**	65	6	**8**	**17**	62
2	**5**	**14**	57 (99)	7	**9**	**18**	77
3	**6**	**15**	60 (99)	8	**10**	**19**	62
4	**7**	**16**	57 (99)	9	**11**	**20**	70
5[c]	**22**	**16**	68	10	**12**	**21**	0

[a] **1** (0.44 mmmol), **4**−**12** (0.40 mmol), Rh−dppf (0.02−0.04 mmol), and TMU (0.22 mL) were employed for all entries. [b] Isolated yield. Yields in parentheses determined by GLC. [c] 5-Bromo-1-pentene **22** was used in place of **7**. The reaction temperature was 80 °C.

Although the detailed mechanism still remains to be clarified, the critical effect exerted by the *ortho*-carbonyl groups in **1** was made apparent for the Rh−dppf-catalyzed reaction of **1** with alkyl halides. As a d^6 complex, our alkyl−Rh intermediates, **III** and/or **IV**, have a vacant coordination site, which must be responsible for the occurrence of the β-elimination, resulting in protodezincation of **1** (Scheme 4).[13] Hence, it might be reasonable to speculate that the carbonyl group occupies the sixth site preventing elimination. However, a simple occupation of the site by some groups was inadequate for the promotion of cross-coupling, as could be seen in the reactions between **2a** and **1a** with PPh_3 or **1d** or **1f** (vide supra).[14] Consequently, the activating effect

Scheme 4



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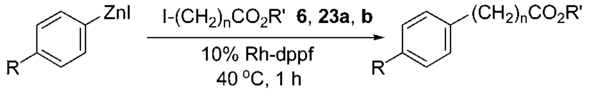
[12] Arylzinc compounds containing *ortho*-carbonyl groups are readily prepared from the corresponding iodoarenes and zinc powder.[10] Directed ortho metalation of arenes containing carbonyl groups provides another route to the compounds; see, for example: (a) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539−3540. (b) Mills, R. J.; Taylor, N. J.; Snieckus, V. *J. Org. Chem.* **1989**, *54*, 4372−4385.

[13] Depending on the kinds of **1**, the reaction course was selected from both protodezincation of **1** and cross-coupling of **1** with R. This result possibly means that the cross-coupling products were formed through path A.

[14] The *o*-MeO group is known to interact with the rhodium center in *o*-anisylrhodium complexes; see, for example: (a) Jones, R. A.; Wilkinson, G. *J. Chem. Soc., Dalton Trans.* **1979**, 472−477. (b) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169−196.

exerted by the coordination of carbonyl groups to the metallic center is conceivable to control the following course of reactions (Scheme 4). To clarify this, the reactions of **1**, free of *ortho*-carbonyl groups, with alkyl halides possessing an ester group at the α-, β-, or γ-position of **23a**, **23b**, or **6** were examined. As shown in Table 3, methyl 3-iodopropanoate **23b** readily reacted with **1a**, **1j**, or **1k** to afford the cross-coupled products **25**−**27** in moderate to good yield and with **1c** to afford **28** in a low yield (entries 2−6) under the conditions[15] where the reaction between **1a** and **2a** afforded the protodezincation product **3a** quantitatively (vide supra). On the other hand, ethyl iodoacetate **23a** or ethyl 4-iodobutanoate **6** afforded a trace and low yield of the cross-coupled products **24** and **29**, respectively (entries 1 and 7), probably suggesting that an intramolecular interaction between the carbonyl group and Rh is essential to induce the reductive elimination.[16]

Table 3. Reaction between **1** and Iodoalkane Bearing an Ester Group **6**, **23a**,**b**[a]



1a, **c**, **j**, **k** **24-29**

1a: R = $CO_2C_2H_5$; **1c**: R = OCH_3; **1j**: R = COPh; **1k**: R = Cl
6: n = 3, R' = C_2H_5; **23a**: n = 1, R' = C_2H_5; **23b**: n = 2, R' = CH_3
24: R = $CO_2C_2H_5$, n =1, R' = C_2H_5; **25**: R = $CO_2C_2H_5$, n = 2, R' = CH_3;
26: R = COPh, n = 2, R' = CH_3; **27**: R = Cl, n = 2, R' = CH_3;
28: R = OCH_3, n = 2, R' = CH_3; **29**: R = $CO_2C_2H_5$, n = 3, R' = C_2H_5

			yield[b]	
entry	1	23	24−29	1/%
1	**1a**	**23a**	**24**	0
2	**1a**	**23b**	**25**	55 (89)
3[c]	**1a**	**23b**	**25**	(92)
4	**1j**	**23b**	**26**	57
5	**1k**	**23b**	**27**	47
6	**1c**	**23b**	**28**	21
7	**1a**	**6**	**29**	6

[a] **1** (0.44 mmmol), **23** (0.40 mmol), Rh−dppf (0.04 mmol), and TMU (0.22 mL) were employed for all entries. [b] Isolated yield. Yields in parenthesese determined by GLC. [c] BINAP was used in place of dppf.

In conclusion, the novel and efficient Rh catalysis of the cross-coupling of primary alkyl halides with arylzinc compounds possessing carbonyl groups at the ortho position was disclosed, which provides a facile synthetic method for polyfunctionalized alkylbenzenes.

Acknowledgment. We are grateful to Prof. Hiroshi Nakazawa and Dr. Masami Itazaki at Osaka City University for measurements of HRMS.

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

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(15) As a ligand, BINAP was equally effective, but others such as PPh_3 or 1,3-bis(diphenylphosphino)propane were less effective than dppf.

(16) The desired effect not only was limited to β- or γ-carbonyl substituents in alkyl halides but also included ketone additives in the Ni-catalyzed cross-coupling between two C sp^3 centers: Giovannini, R.; Studemann, T.; Devasagayaraj, A.; Dussin, G.; Knochel, P. *J. Org. Chem.* **1999**, *64*, 3544−3553.