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Rhodium-Catalyzed Multicomponent-Coupling Reactions Involving a Carborhodation–Cross-Coupling Sequence

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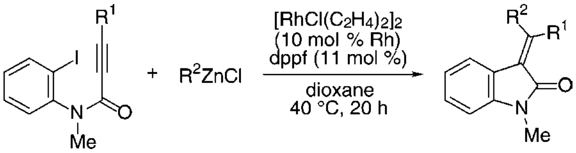
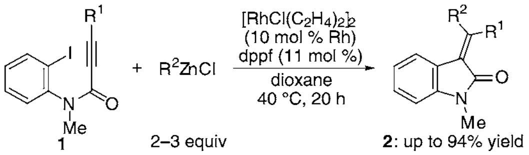
ABSTRACT



A rhodium-catalyzed multicomponent-coupling reaction has been developed that involves a cross-coupling with organohalides as part of the reaction sequence. Through several experiments toward mechanistic investigations, it has also been demonstrated that the reaction most likely proceeds via a carborhodation–oxidative addition–reductive elimination pathway, which clearly contrasts to the corresponding palladium-catalyzed processes.

Rhodium-catalyzed addition of organometallic reagents to carbon−carbon or carbon−heteroatom unsaturated bonds provides a mild and efficient way of constructing new carbon−carbon bonds,[1] and several multicomponent-coupling reactions based on this technology have been described,[2] creating two or more new carbon−carbon bonds in a single step to furnish rather complex molecules from simple organic fragments. On the other hand, rhodium-catalyzed cross-coupling reactions of organometallic reagents with organohalides have been much less studied,[3] while the palladium-catalyzed cross-couplings have reached a mature stage by extensive studies in the past few decades.[4] Here we describe the development of a catalytic multiple carbon−carbon bond-forming reaction by incorporating a rhodium-catalyzed cross-coupling with organohalides as part of the reaction sequence (eq 1). We also demonstrate our mechanistic investigations, highlighting the difference from the conventional palladium-catalyzed analogous processes.[5]



(1)

Initially, we chose alkyne-tethered iodoarene **1a** as a model substrate to examine the reaction with phenylzinc chloride in the presence of a catalytic amount of $[RhCl(cod)]_2$ at 40 °C, and we found that desired product **2a** was successfully formed, albeit in low yield (17% yield; Table 1, entry 1).

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(1) (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (b) Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918. (c) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279. For reviews, see: (d) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (e) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (f) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284.

(2) For selected examples, see: (a) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Organomet. Chem.* **2002**, *648*, 297. (b) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984. (c) Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 1110. (d) Lautens, M.; Mancuso, J. *J. Org. Chem.* **2004**, *69*, 3478. (e) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54. (f) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094.

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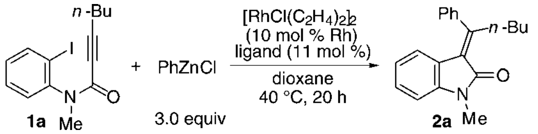
Table 1. Rhodium-Catalyzed Phenylation−Cross-Coupling Reaction of **1a**:Ligand Effect

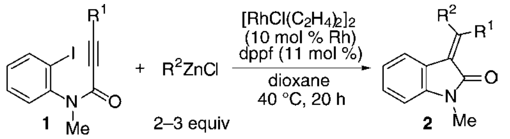


entry	ligand	yield (%)[a]
1[b]	cod	17
2	dppp	13
3	dppb	13
4	dppf	87[c]

[a] Determined by ^{1}H NMR against an internal standard ($MeNO_2$). [b] $[RhCl(cod)]_2$ was used as a catalyst. [c] Isolated yield.

We subsequently discovered that the reaction progress is highly dependent on the ligand employed. Thus, the use of dppp or dppb as a ligand resulted in low yield of **2a** (13% yield; entries 2 and 3), but the employment of dppf (1,1′-bis(diphenylphoshphino)ferrocene)[6] dramatically improved the reactivity, furnishing **2a** in 87% yield (entry 4).[7]

Table 2. Rhodium-Catalyzed Arylation−Cross-Coupling Reaction of **1**: Scope



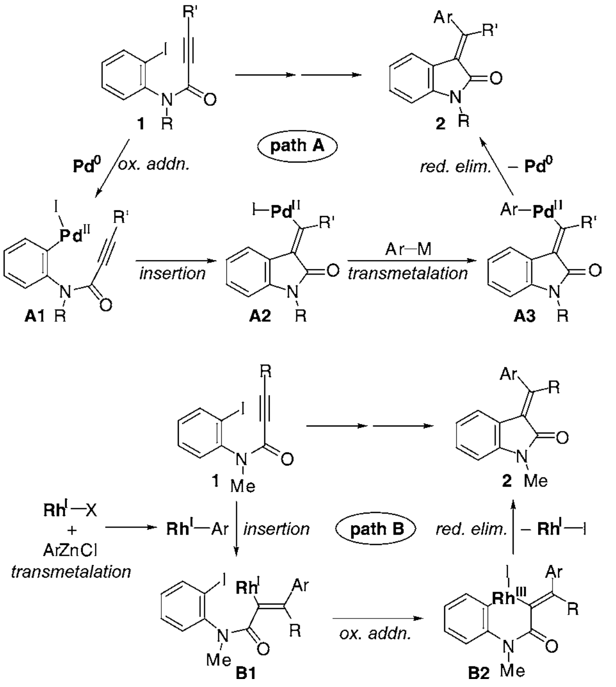
entry	product	yield (%)[a]
1	$R^1 = n$-Bu, R^2 = Ph (**2a**)	87
2[b]	$R^1 = n$-Bu, R^2 = Ph (**2a**)	78
3	$R^1 = (CH_2)_3OMe$, R^2 = Ph (**2b**)	84
4	$R^1 = i$-Bu, R^2 = Ph (**2c**)	94
5	$R^1 = i$-Pr, R^2 = Ph (**2d**)	57
6	R^1 = Ph, R^2 = Ph (**2e**)	85
7	$R^1 = n$-Bu, $R^2 = 3\text{-}MeOC_6H_4$ (**2f**)	77
8	$R^1 = n$-Bu, $R^2 = 3\text{-}MeC_6H_4$ (**2g**)	80
9	$R^1 = n$-Bu, $R^2 = 3\text{-}ClC_6H_4$ (**2h**)	78[c]
10	$R^1 = n$-Bu, $R^2 = 4\text{-}MeOC_6H_4$ (**2i**)	77
11	$R^1 = n$-Bu, R^2 = Me (**2j**)	75

[a] Isolated yield. [b] The reaction was conducted with 3 mol % catalyst loading. [c] Contaminated with ~5% impurity.

Under these conditions with dppf as the ligand, the scope of this reaction is illustrated in Table 2.[8] The catalyst loading can be lowered to 3 mol % with minimal decrease of the yield (78% yield; entry 2). Primary and secondary alkyl groups as well as aryl groups can be used as substituents on the alkyne (R^1) in the reaction with phenylzinc chloride (entries 1−6). With respect to the nucleophilic component, not only various arylzinc chlorides (entries 7−10) but also methylzinc chloride (entry 11) provide the desired products in high yield (75−80% yield).[9]

With regard to the reaction mechanism, path A is generally believed for the palladium-catalyzed analogous processes (Scheme 1).[5c] Thus, initial oxidative addition of the iodoarene of substrate **1** to palladium(0) generates arylpalladium(II) intermediate **A1**. Intramolecular insertion of the alkyne to this carbon−palladium bond affords alkenylpalladium(II) species **A2**. Subsequent transmetalation of the aryl group gives bis(organo)palladium(II) **A3**, and reductive elimination releases product **2** to regenerate the palladium(0) complex. One can propose a similar mechanism for the present rhodium catalysis just by changing Pd(0)/Pd(II) to Rh(I)/

Scheme 1. Catalytic Cycle for the Palladium-Catalyzed Formation of Compound **2** (path A) and Proposed Catalytic Cycle for the Rhodium-Catalyzed Formation of Compound **2** (path B)



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(3) (a) Hossain, K. M.; Takagi, K. *Chem. Lett.* **1999**, 1241. (b) Takahashi, H.; Hossain, K. M.; Nishihara, Y.; Shibata, T.; Takagi, K. *J. Org. Chem.* **2006**, *71*, 671. (c) Takahashi, H.; Inagaki, S.; Nishihara, Y.; Shibata, T.; Takagi, K. *Org. Lett.* **2006**, *8*, 3037. (d) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229. See also: (e) Yasui, H.; Mizutani, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 1410.

(4) For recent reviews, see: (a) Negishi, E., Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons: Hoboken, NJ, 2002; Vol. 1. (b) Netherton, M. R.; Fu, G. C. In *Topics in Organometallic Chemistry*: *Palladium in Organic Synthesis*; Tsuji, J., Ed.; Springer: New York, 2005; p 85.

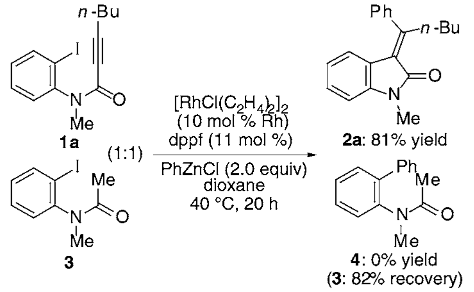
(5) (a) Cheung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741. (b) Yanada, R.; Obika, S.; Inokuma, T.; Yanada, K.; Yamashita, M.; Ohta, S.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 6972. (c) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153. (d) Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511. See also: (e) Yanada, R.; Obika, S.; Oyama, M.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 2825.

(6) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

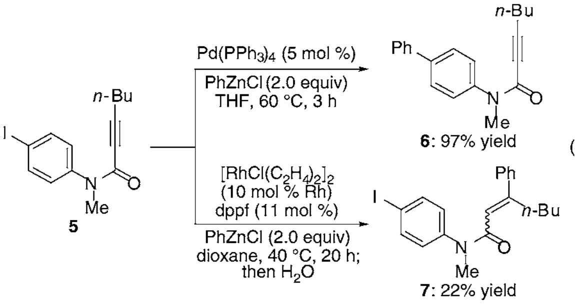
(7) The reaction can be conducted in other solvents with similar efficiency (72% yield in THF, 86% yield in DME, 78% yield in toluene, and 75% yield in dichloromethane).

Rh(III), but another pathway, path B, may be more legitimate, because rhodium(I) complexes are known to undergo facile transmetalation with organometallic reagents and the resulting organorhodium(I) species are known to add to a variety of unsaturated bonds including carbon−carbon triple bonds.[1] Thus, path B involves an initial formation of an arylrhodium(I) species by transmetalation of an aryl group from zinc to rhodium. The alkyne of substrate **1** then inserts to this carbon−rhodium bond to generate alkenylrhodium(I) intermediate **B1**.[1b] Intramolecular oxidative addition of the iodoarene gives bis(organo)rhodium(III) species **B2**, which undergoes reductive elimination to furnish product **2** along with the regeneration of the rhodium(I) complex.[10]

To understand which reaction pathway is more plausible under our standard conditions, we conducted some experiments as follows. First, we carried out a competition reaction between **1a** and **3** with phenylzinc chloride under rhodium catalysis (eq 2), and found that compound **2a** was obtained as a sole product in 81% yield and none of the simple cross-coupling product **4** was generated. In contrast, when this reaction was conducted in the presence of a palladium catalyst, a significant amount of **4** (31%) was formed along with **2a** (61%). Furthermore, although a reaction of **5** with phenylzinc chloride in the presence of Pd(PPh_3)$_4$ gave only cross-coupling product **6** (97% yield; eq 3), the use of Rh/dppf as a catalyst provided 1,4-addition product **7** (22% yield (not optimized)) with no formation of **6**. These experimental results strongly indicate that path B in Scheme 1 is more likely the actual reaction pathway in the present rhodium-catalyzed formation of **2**.

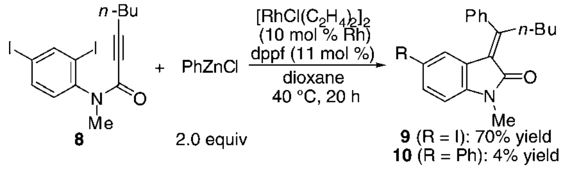


(2)



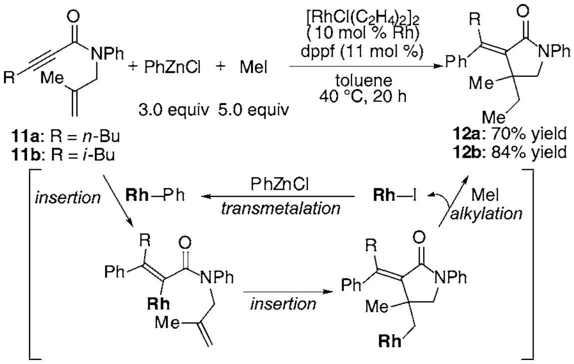
(3)

Because the present rhodium catalysis starts with arylrhodation of an alkyne, rather than oxidative addition of an iodoarene, diiodo-substrate **8** can be converted to iodo-remaining product **9** in 70% yield with a minimal amount of phenylated product **10** (eq 4). In contrast, when a palladium catalyst (e.g., Pd(PPh_3)$_4$) is employed in the reaction of **8**, compound **10** becomes the major product (61% yield) with no formation of **9**.



(4)

By further taking advantage of this reaction mechanism, we have also devised a rhodium-catalyzed three-molecule, four-component coupling reaction of 1,6-enyne **11**, phenylzinc chloride, and iodomethane, furnishing highly functionalized γ-lactam **12** in high yield as shown in eq 5.[11]



(5)

In summary, we have developed a rhodium-catalyzed multicomponent-coupling reaction involving a cross-coupling with organohalides as part of the reaction sequence. Through several experiments toward mechanistic investigations, we have also demonstrated that the reaction most likely proceeds via a carborhodation−oxidative addition−reductive elimination pathway, which clearly contrasts to the corresponding palladium-catalyzed processes.

Acknowledgment. Support has been provided in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (21 COE on Kyoto University Alliance for Chemistry).

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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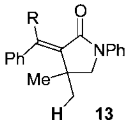
(8) General procedure for Table 2: A solution of [RhCl(C_2H_4)$_2$]$_2$ (3.9 mg, 20 μmol Rh) and dppf (12.2 mg, 22.0 μmol) in dioxane (10 mL) was stirred for 10 min at room temperature. Substrate **1** (0.20 mmol) and ArZnCl (0.33−0.60 mL, 0.40−0.60 mmol; 0.67−1.22 M solution in THF) were added to it, and the mixture was stirred for 20 h at 40 °C. The reaction was quenched with water (80 μL), passed through a pad of silica gel with EtOAc, and concentrated under vacuum. The residue was purified by silica gel preparative TLC with CH_2Cl_2 to afford product **2**.

(9) For an example of the rhodium-catalyzed addition of dimethylzinc, see: Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Org. Lett.* **2006**, *8*, 979.

(10) For discussion on the mechanism of the rhodium-catalyzed cross-couplings, see ref 3b.

(11) Ca. 3% of protonated product **13** is contaminated.



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