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Palladium-Catalyzed Arylative Carbon−Carbon Bond Cleavage of α,α-Disubstituted Arylmethanols

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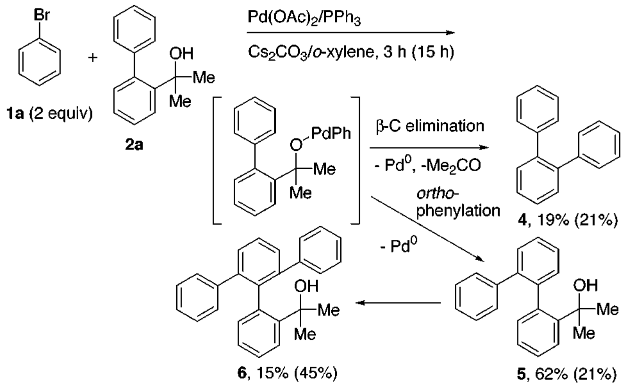
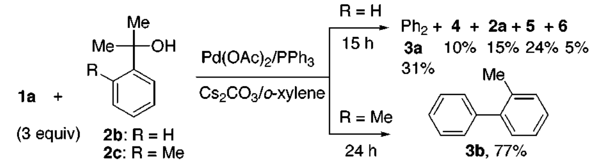
Transition metal-catalyzed organic reactions involving the cleavage of C−C single bonds have recently attracted much attention.[1] Although the cleavage is energetically unfavorable, various unique catalytic transformations including ring-expansion or ring-contraction, fragmentation, and coupling with another molecule can be realized when appropriately designed. Besides the reactions via oxidative addition of low-valent transition metals to a C−C bond,[1,2] catalytic cycles involving β-carbon elimination of heteroatom-coordinated species such as M−O−C−C may be constructed. Utilizing the latter cleavage to form M−C species and ketones (or aldehydes), Pd-catalyzed ring-opening reactions of cyclic allylic carbonates,[3] cyclobutanols,[4] and cyclopropanols[5] and a Ru-catalyzed fragmentation of homoallyl alcohols[6] have recently been developed. The driving force of these reactions originates from release of ring-strain or formation of a relatively stable π-allylmetal intermediate. In the course of our study of Pd-catalyzed new arylative C−C bond formation reactions,[7] it has been found that certain α,α-disubstituted arylmethanols, even acyclic ones, efficiently react with aryl bromides to give biaryls via cleavage of the sp^2−sp^3 C−C bond (eq 1),[4a,8,9] which is described herein.

$$\mathrm{Ar^1Br} \;+\; \mathrm{Ar^2}\wr\mathrm{C(R_2)OH} \;\xrightarrow[\text{base}]{\text{cat. Pd}}\; \mathrm{Ar^1\text{-}Ar^2} \;+\; \mathrm{R_2C{=}O} \qquad (1)$$

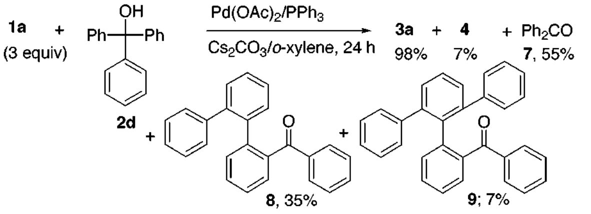
Scheme 1



Scheme 2



We previously reported that phenolic compounds as well as aromatic carbonyl compounds undergo *ortho*-arylation on treatment with aryl halides under the influence of palladium catalysts.[7a,b] For example, the phenylation of 2-phenylphenol with iodobenzene takes place regioselectively at the 2′-position. The reaction is a unique catalytic aryl−aryl coupling via cleavage of the aromatic C−H bond in which coordination of the phenolic oxygen to phenylpalladium(II) species is the key. To see the applicability of an alcohol function as the directing group in the arylation, we examined the reaction of 2-(biphenyl-2-yl)-2-propanol (**2a**) with bromobenzene (**1a**) (Scheme 1). When **2a** (0.5 mmol) was treated with **1a** (1 mmol) in the presence of Pd(OAc)$_2$ (0.025 mmol), PPh$_3$ (0.15 mmol), and Cs$_2$CO$_3$ (1 mmol) in refluxing *o*-xylene for 3 h, mono- and diphenylated products, **5** (62%) and **6** (15%), were produced along with *o*-terpheyl (**4**) (19%) (yields by GC based on the amount of **2a**). This suggests that in the key alkoxypalladium intermediate, not only anticipated *ortho*-phenylation of **2a** to produce **5** and **6** but also β-carbon elimination leading to **4** competitively occurs in a rate ratio of 8:2. By starting with 2-phenyl-2-propanol (**2b**) a mixture of biphenyl (**3a**), **2a**, and **4**−**6** was obtained, showing that the reaction similarly proceeds (Scheme 2). It was quite interesting that the reaction of 2-(2-methylphenyl)-2-propanol (**2c**) selectively proceeded via β-carbon elimination to give 2-methylbiphenyl (**3b**) (77%) as the single major product, **2c** (20%) being recovered. The reaction of triphenylmethanol (**2d**) with **1a** (3 equiv) also gave mechanistically important information (eq 2).[10] The product distribution indicates that both the processes via *ortho*-phenylation and β-carbon elimination occur in the initial step as in the reactions of **2a** and **2b**, and in this case, the successively *ortho*-phenylated products further undergo coupling with **1a** via β-carbon elimina-



(2)

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(8) Pd-catalyzed Sonogashira-type reaction of aryl halides with 2-alkynylpropanols is known. The reaction is generally considered to involve in situ generation of terminal alkynes, while it would proceed partly via β-carbon elimination. (a) Huynh, C.; Linstrumelle, G. *Tetrahedron* **1988**, *44*, 6337. (b) Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* **2001**, *66*, 1910. (c) Choi, C.-K.; Tomita, I.; Endo, T. *Chem. Lett.* **1999**, 1253.

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(10) The fact that the total yield of **3a** and **4** is somewhat greater than 100% may be due to the participation of homo-coupling of **1a** to some extent. However, formation of homo-coupling products was not observed or negligible (less than 2%) in the other reactions.

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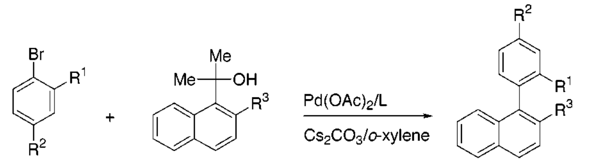
Table 1. Reaction of Aryl Bromides with 2-Naphthyl-2-propanols[a]

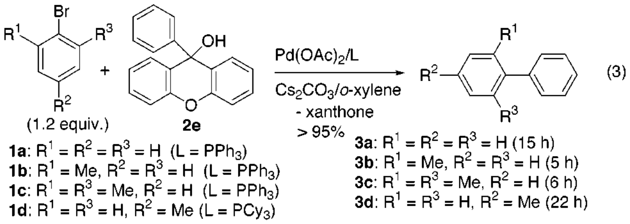


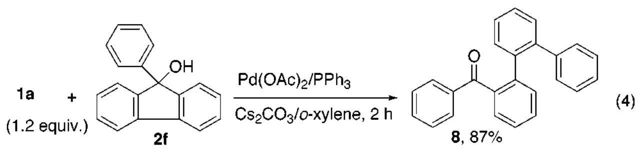
bromide **1** R^1, R^2 (mmol)	alcohol **2** R^3 (mmol)	L	time, h	product, %[b]
1a; H, H, (1.5)	**2g**; H (0.5)	PPh_3	6	**3e**, 94
1b; Me, H (0.6)	**2g**; H (0.5)	PPh_3	4	**3f**, 90 (72)
1d; H, Me (1.5)	**2g**; H (0.5)	PCy_3	8	**3g**, 94 (82)
1e; H, COOEt (0.8)	**2g**; H (0.5)	PPh_3	4	**3h**, 94 (91)
1a; H, H (0.6)	**2h**; OMe (0.5)	PPh_3	2.5	**3l**, 98 (82)
1a; H, H (0.6)	**2h**; OMe (0.5)	PPh_3	24[c]	**3l**, 92

[a] [**2**]:[$Ph(OAc)_2$]:[L] = 0.5:0.025:0.1 (in mmol), [**1**] = [Cs_2CO_3], in refluxing *o*-xylene. [b] Determined by GC analysis. Value in parentheses is isolated yield. [c] [$Pd(OAc)_2$]:[L] = 0.005:0.02.

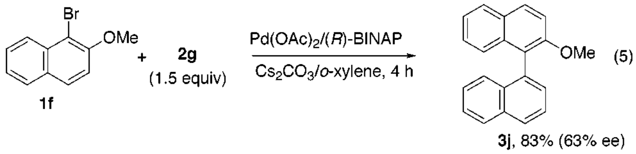
tion in a selective manner to give **3a** together with benzophenone derivatives **8** and **9**. It should be noted that in the reaction of **2a** (Scheme 1), prolonging the reaction time significantly increased the yield of **6**, but only a trace amount of quaterphenyl (less than 1%) was detected. These results imply that in the key intermediates $PhPdOC(Ar)R_2$, Ph−Ar coupling hardly occurs when Ar is too bulky. This is probably due to the fact that it is difficult for the intermediates to stand ready for *syn*-elimination. Thus, Ph−R coupling takes place when R is Ph or biphenyl, while β-carbon elimination with Me is energetically unfavorable and is not observed. On the other hand, the result with **2c** suggests that an appropriate *ortho*-substituent selectively induces β-carbon elimination.

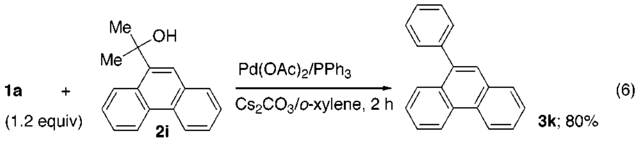
On the basis of the above information, selective catalytic systems for eq 1 may be constructed by using appropriate arylmethanols. We first designed that using 9-phenylxanthen-9-ol (**2e**). It was expected that the alcohol might be configurationally suitable for *syn*-elimination. Indeed, the reaction of **2e** with **1a** cleanly proceeded to give **3a** quantitatively along with xanthone (eq 3). It also reacted with 2-methyl-, 2,6-dimethyl-, and 4-methylbromobenzenes (**1b**−**d**) to give the corresponding biphenyls in 95% yields or in more than 95% yields. The reactions with **1b** and **1c** proceeded faster than that with **1a**, indicating that an *ortho*-substituent on bromobenzene promotes the coupling. In the case of **1d**, PCy_3 was found to be a suitable ligand. When PPh_3 was used, a considerable amount of **3a** (ca. 20%) was formed by contamination of a phenyl group in the phosphine, but it was completely suppressed by the use of PCy_3.[7d] In contrast to **2e**, 9-phenylfluoren-9-ol (**2f**) reacted with **1a** via ring-opening β-carbon elimination to give compound **8** selectively (eq 4). This may be attributed to ring-strain.





2-(1-Naphthyl)-2-propanol (**2g**) and its 2-methoxy derivative (**2h**) as the equivalents of *ortho*-substituted 2-phenyl-2-propanol were also found to be suitable substrates for eq 1 (Table 1). The reactions of **2g** with **1a**, **1b**, **1d**, and ethyl 4-bromobenzoate (**1e**) and of **2h** with **1a** smoothly proceeded to give the corresponding 1-phenylnaphthalenes **3e**−**i** in high yields. Treatment of **2g** with 1-bromo-2-methoxynaphthalene (**1f**) using (*R*)-BINAP as ligand gave (*R*)-(+)-enantiomer enriched binaphthyl **3j** with 63% ee, showing that asymmetric coupling can occur in the present system (eq 5).[11,12] As expected, 2-(9-phenanthryl)-2-propanol (**2i**) reacted with **1a** to afford 9-phenylphenanthrene (**3k**) (eq 6).





It should be cited that the Pd-catalyzed intramolecular nucleophilic cyclization of halophenyl-linked ketones to give five- and six-membered benzocycloalkanols has recently been reported.[13] The reaction proceeds via benzocycloalkanyl-OPd(II) species and the products are stable under heating conditions. Nevertheless, the present results show that the reverse β-carbon elimination can occur efficiently. This may be due to the fact that the present reaction involves energetically favorable diarylpalladium species, while further studies are required to establish this.

As is well-known, the Pd- or Ni-catalyzed cross-coupling of aryl halides with various arylmetals (metal = B, Sn, Mg, Zn, Si, etc.), which involves transmetalation, is a useful tool for making various natural products and organic functional materials having biaryl skeletons.[14,15] The present reaction is, to our knowledge, the first catalytic aryl−aryl coupling that proceeds via β-carbon elimination. The reaction systems that do not need arylmetal reagent appear to be a new, effective complement of the conventional method, especially for the synthesis of biaryls involving condensed aromatic moieties.

In summary, we have shown some important factors affecting the Pd-catalyzed arylative C−C bond cleavage of α,α-disubstituted arylmethanols and efficient aryl−aryl coupling systems. Further details of the reaction are under investigation in our laboratory.

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Supporting Information Available: Standard experimental procedure and characterization data for compounds **5**, **6**, **8**, and **9** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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