JOC Article

Palladium-Catalyzed Arylation of α,α-Disubstituted Arylmethanols via Cleavage of a C−C or a C−H Bond To Give Biaryls

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The palladium-catalyzed arylation of α,α-disubstituted arylmethanols with aryl halides proceeds not only via C−H bond cleavage at the ortho-position, but also via cleavage of the sp^2-sp^3 C−C bond with the liberation of ketones (*β*-carbon elimination) to give the corresponding biaryls. Both reactions appear to occur through common arylpalladium(II) alcoholate intermediates. The results of systematic studies with respect to which C−C or C−H bond is preferentially cleaved in the arylation are reported. Among the important findings is the selective elimination of ortho-substituted aryl groups even from aryl(diphenyl)methanols due to steric reasons. Thus, various biaryls having ortho-substituents can be produced efficiently by treatment of the corresponding aryl(diphenyl or dimethyl)methanols with aryl bromides and chlorides.

Introduction

Transition metal-catalyzed cross-coupling is now recognized to be one of the most useful C−C bond formation reactions.[1] For the synthesis of biaryls, whose skeletons are found in a wide range of important compounds including natural products and organic functional materials,[2] palladium- or nickel-catalyzed coupling of arylmetals (metal = Mg, Zn, B, Sn, Si, etc.) with aryl halides via transmetalation is very often employed.

Meanwhile, transition metal-catalyzed organic reactions via cleavage of C−H[3,4d] and C−C[4] bonds have attracted much attention from atom-economic and chemoselective points of view, and various catalytic processes involving different modes to activate the relatively inert bonds have been developed, especially for the past decade. Among the most promising activation strategies is to utilize the proximate effect by coordination of a functional group in a given substrate to the metal center of a catalyst.

As an example of aryl−aryl coupling via C−H bond cleavage, we reported that appropriately functionalized aromatic substrates such as phenols[5a,b] and aromatic ketones[5c] and amides[5d,e] efficiently undergo direct intermolecular *ortho*-arylation on treatment with aryl halides in the presence of palladium catalysts, in which coordination of the functional groups to intermediary arylpalladium(II) species is the key. In the course of our study on the reaction, we also found another unique aryl−aryl coupling via C−C bond cleavage. Thus, aromatic alcohols such as α,α-disubstituted arylmethanols react with aryl halides not only via the C−H bond cleavage, but also via cleavage of the sp^2-sp^3 C−C bond with the liberation of ketones to give biaryls (Scheme 1).[6−8] The reaction of the alcohols appears to be of importance in both mechanistic and synthetic aspects. It proceeds via *β*-carbon elimination in competition with *ortho*-metalation. The catalytic examples of *β*-carbon elimination in transition metal alcoholates are very limited, although some efficient

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(2) (a) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263. (c) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, 525.

(3) Reviews: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Kakiuchi, F.; Murai, S. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, Germany, 1999; p 47. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (d) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (f) Miura, M.; Nomura, M. In *Cross-Coupling Reactions*; Springer: Berlin, Germany, 2002; p 211.

(4) Reviews: (a) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245. (b) Rybtchinski, B.; Milstein, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 870. (c) Murakami, M.; Ito, Y. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, Germany, 1999; p 97. (d) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem. Eur. J.* **2002**, *8*, 2423.

(5) (a) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997,** *36*, 1740. (b) Kawamura, Y.; Satoh, T.; Miura, M.; Nomura, M. *Chem. Lett.* **1999**, 961. (c) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2001**, *57*, 5967. (d) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655. (e) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286.

(6) Preliminary communication: Terao, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2001**, *123*, 10407.

(7) Related catalytic aryl−aryl coupling via C−H bond cleavage. Rh: (a) Oi, S.; Fukita, S.; Inoue. Y. *Chem. Commun.* **1998**, 2439. (b) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112. Ru: (c) Oi, S.; Fukita, S.; Hitrata, N.; Wakatsuki, N.; Miyano, S.; Inoue, Y. *Org. Lett.* **2001**, *3*, 2579. (d) Oi. S.; Ogino, Y.; Fukita, S.; Inoue, Y. *Org. Lett.* **2002**, *4*, 1783. (e) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698.

(8) Related catalytic aryl−aryl coupling via C−C bond cleavage. Pd: (a) Satoh, T.; Jones, W. D. *Organometallics* **2001**, *20*, 2916. Ni: (b) Miller, J. A. *Tetrahedron Lett.* **2001**, *42*, 6991.

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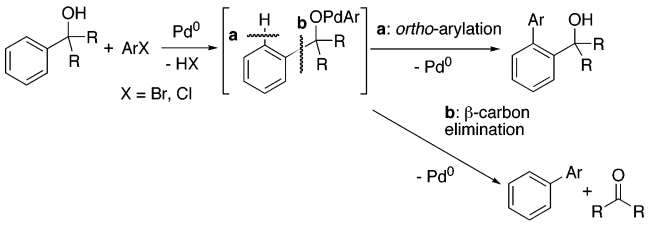
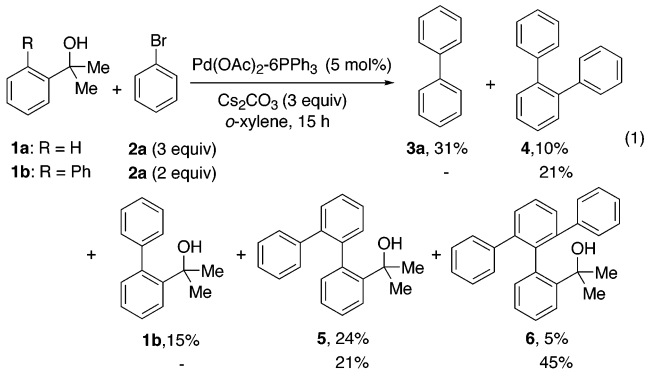
SCHEME 1



Pd-catalyzed ring-opening reactions of cyclic compounds[9−11] and a Ru-catalyzed fragmentation of homoallyl alcohols[12] involving the cleavage mode have recently been reported.[13] Furthermore, the present reaction via C−C bond cleavage is expected to be useful as a new complement of conventional coupling methods. Consequently, we have carried out a detailed study using various arylmethanols to gain an insight into the factors affecting the arylative coupling via the cleavage of a C−C bond as well as that of a C−H bond and to reveal scope and limitations of the reaction. The results are described herein.

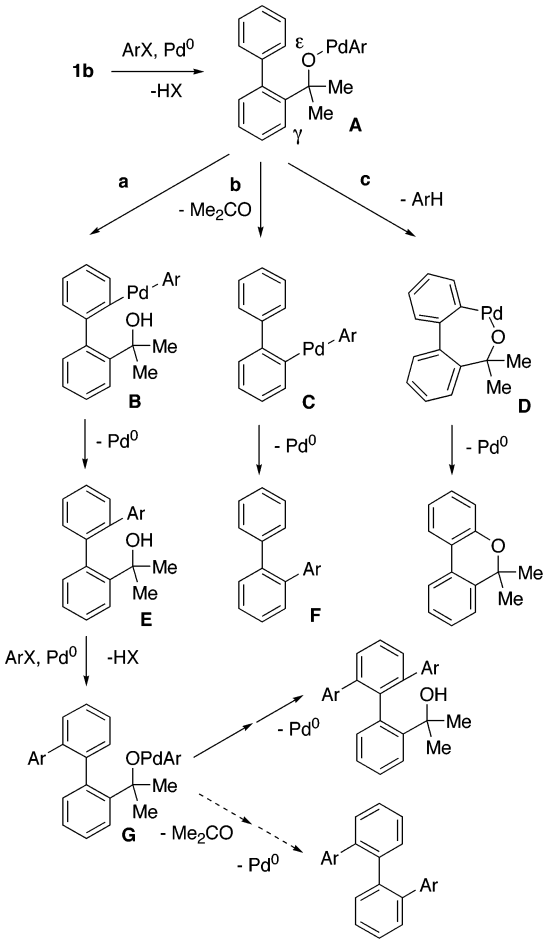
Results and Discussion

(A) Factors Affecting the Ratio of *ortho*-Arylation to Arylative *β*-Carbon Elimination. When the reaction of 2-phenyl-2-propanol (**1a**) (1 mmol) with bromobenzene (**2a**) (3 equiv) was carried out in the presence of $Pd(OAc)_2$-$6PPh_3$ (5 mol %) with Cs_2CO_3 as base in refluxing *o*-xylene for 15 h, mono-, di-, and triphenylated products (**1b**, **5**, and **6**; path a in Schemes 1 and 2) were produced via successive C−H bond cleavage together with biphenyl (**3a**) and *o*-terphenyl (**4**) (eq 1, yields by GC based on the



amount of **1a**). The latter products are considered to be formed by the phenylative C−C bond cleavage of **1a** and **1b**, respectively (path b). The fact that only a negligible amount of quaterphenyl (less than 1%) was detected by GC-MS suggests that in the corresponding alcoholate intermediate **G** (Scheme 2), it is difficult for the large terphenyl moiety to stand ready for *syn*-elimination. The lack of products via *β*-carbon elimination with one of the methyl groups is attributable to the fact that such a reaction with an sp^3 carbon is energetically unfavorable. It should be cited that in a 2-methyl-2-phenyl-1-propylpalladium(II) complex, selective *β*-phenyl elimination has been reported to occur.[14]

SCHEME 2



The reaction started with **1b** afforded the 1,2,3-triphenylbenzene derivative **6** with an enhanced yield of 45% (eq 1).[15] The fact that the arylation via C−H bond cleavage only takes place at the 2′-position and not at all at the 3-position suggests that *ϵ*-palladation is more preferable than *γ*-palladation in this case, although the latter occurs in the reaction of **1a**. It was of considerable interest that the reaction of alcohol **1b** with 2-bromotoluene (**2b**) gave a sterically more crowded triphenylbenzene **7** in a higher yield of 76% along with minor

(9) Cyclic allylic carbonates: Harayama, H.; Kuroki, T.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2352.

(10) Cyclobutanols: (a) Arylative ring-opening: Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **1999**, *121*, 11010. (b) Nishimura, T.; Ohe, K.; Uemura, S. *J. Org. Chem*. **2001**, *66*, 1455. (c) Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2000**, *122*, 12049. See also: (d) Larock, R. C.; Reddy, C. K. *J. Org. Chem*. **2002**, *67*, 2027.

(11) Cyclopropanols: (a) Park S.-B.; Cha, J. K. *Org. Lett*. **2000**, *2*, 147. (b) Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* **2000**, 629.

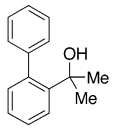
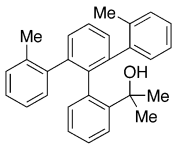
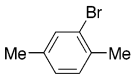
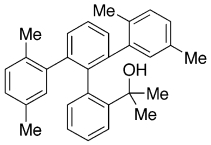
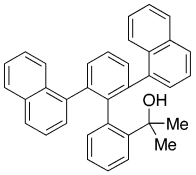
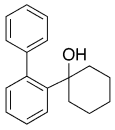
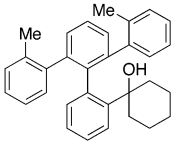
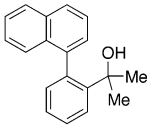
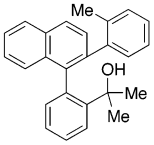
(12) Kondo, T.; Kodoi, K.; Nishinaga, E.; Okada, T.; Morisaki, Y.; Watanabe, Y.; Mitsudo, T. *J. Am. Chem. Soc.* **1998**, *120*, 5587.

(13) Pd-catalyzed reaction of alkynols with aryl halides to form sp^2−sp bonds 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.; Y. Yeung, Y.-Y. *J. Org. Chem*. **2001**, *66*, 1910. (c) Choi, C.-K.; Tomita, I.; Endo, T. *Chem. Lett*. **1999**, 1253.

(14) Cámpora, J.; Gutiérrez-Puebla, E.; López, J. A.; Monge, A.; Palma, P.; del Río, D.; Carmona, E. *Angew. Chem., Int. Ed*. **2001**, *40*, 3641.

(15) The reaction with $Pd(OAc)_2$-$4PPh_3$ for 24 h, however, gave **6** with a lower yield of 13% together with **4** (22%) and **5** (60%), which may be due to catalyst deactivation. Precipitation of Pd black was observed after the reaction.

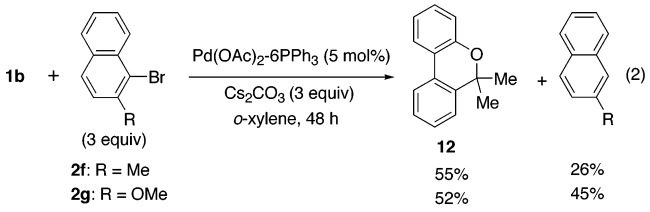
TABLE 1. Reaction of Alcohols 1b−d with Ortho-Substituted Aryl Bromides 2[a]

entry	1	ArBr	time, h	product, %[b]
1	 **1b**	 **2b**	24	 **7**, 76 (55)
2		 **2d**	30	 **8**, 80 (50)
3		 **2e**	49	 **9**, 66 (40)
4	 **1c**	**2b**	47	 **10**, 60 (35)
5	 **1d**	**2b**	48	 **11**, 59 (32)

[a] Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.15 mmol), Cs_2CO_3 (1.5 mmol) in refluxing *o*-xylene. [b] Determined by GC analysis. The value in parentheses is the isolated yield.

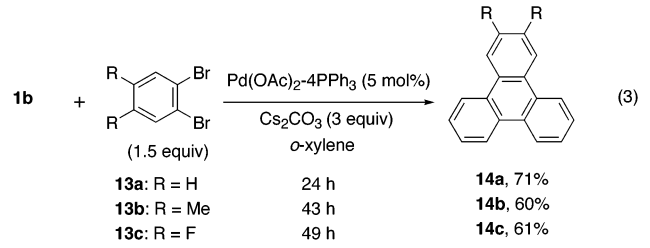
amounts of other products (Table 1, entry 1), while that with 4-bromotoluene (**2c**) was not successful due to scrambling of the aryl moiety with a phenyl group of the ligand.[16] It is noted that the structure of **7** could be unambiguously verified by X-ray analysis (see Supporting Information).[17] The result with **2b** indicates that the second arylation effectively occurs with the relatively bulky bromide probably due to the fact that the key palladium(II) alcoholate intermediates **A** and **G** (Scheme 2) are so congested that β-carbon elimination can hardly occur, and nevertheless, the aromatic carbons at which the substitution takes place can turn appropriately to the metal center. In harmony with this consideration, the reactions of **1b** with 2,5-dimethylbromobenzene (**2d**) and 1-bromonaphthalene (**2e**) and of 1-(biphenyl-2-yl)cyclohexanol (**1c**) with **2b** gave the corresponding diarylated products **8**−**10** in substantial yields. 2-[2-(1-Naphthyl)-phenyl]-2-propanol (**1d**) reacted with **2b** to give monophenylated product **11**.

The reaction of alcohol **1b** with a further hindered bromide, 1-bromo-2-methylnaphthalene (**2f**), gave 6,6-dimethyl-6*H*-benzo[*c*]chromene (**12**) (55%) as the major product along with 2-methylnaphthalene (26% based on **2f**, 79% based on **1b**) (eq 2). Compound **12** was also



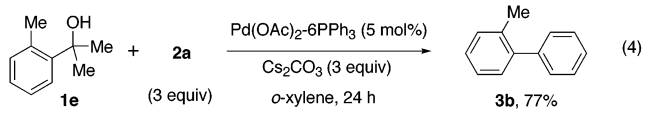
formed with use of 1-bromo-2-methoxynaphthalene (**2g**). The formation of **12** suggests that in intermediate **A**, the third reaction pattern via C−H bond cleavage to yield palladacycle **D** along with an arene (path c) takes place when aryl bromide is too bulky.[18]

The reaction of **1b** was found to be applied to the synthesis of triphenylenes by using 1,2-dibromobenzenes (**13**). Thus, treatment of **1b** with dibromides **13a**−**c** gave triphenylene and its derivatives **14a**−**c** in good yields (eq 3). Analysis of the reaction mixture with **13a** at the early



stage by GC-MS confirmed formation of two possible intermediates, which corresponds to **E** and **F** (Ar = 2-BrC_6H_4) in comparable amounts. Thus, triphenylenes are considered to be formed via both paths a and b.

The reaction of 2-methylphenyl-2-propanol (**1e**) with **2a** under similar conditions employed for eq 1 selectively gave 2-methylbiphenyl (**3b**) in 77% yield, **1e** (20%) being recovered (eq 4). This indicates that an appropriate ortho-



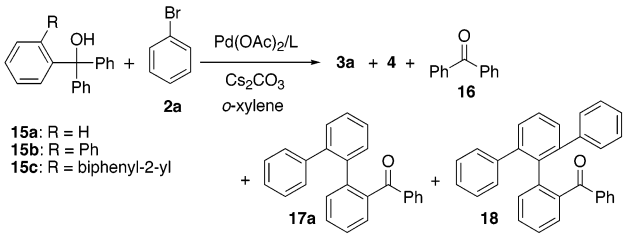
substituent on 2-phenyl-2-propanol other than a phenyl group can selectively induce β-carbon elimination. Re-

(16) (a) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441. (b) Grushin, V. V. *Organometallics* **2000**, *19*, 1888.

(17) ^{1}H NMR of **7** at room temperature showed 4 peaks for each methyl group, suggesting that there exists three possible rotamers of syn-syn, syn-anti, and anti-anti in solution. The peaks coalesced at 150 °C, giving two peaks as expected (see Supporting Information). Similar ^{1}H NMR spectra were obtained in the case of compounds **8**−**11**. Their methyl peaks also coalesced by heating with the exception of those of **9**.

(18) The formation of palladacycle **D** from **A** may involve electrophilic attack of the palladium on the ϵ-carbon followed by elimination of an arene, although participation of another path via a Pd(IV) species cannot be excluded. See: (a) Dyker, G. *Chem. Ber. Recl.* **1997**, *130*, 1567. (b) Catellani, M. *Synlett* **2003**, 298. The formation of 2-substituted naphthalenes with higher yields than those expected suggests participation of another reduction mechanism. However, the details are unclear.

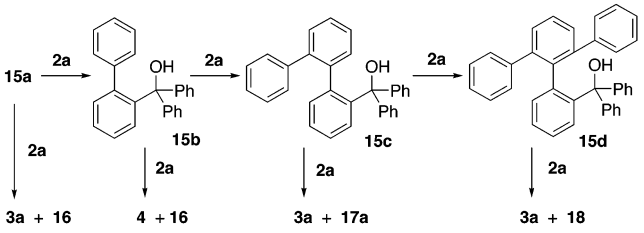
TABLE 2. Reaction of Triphenylmethanols (15a−c) with Bromobenzene (2a)[a]



entry	15	ligand	time, h	products, % yield[b]
1	**15a**	PPh_3	24	**3a**, 98; **4**, 7; **16**, 55; **17a**, 35; **18**, 7
2	**15a**	PCy_3	18	**3a**, 93; **4**, 6; **16**, 88
3[c]	**15a**	PCy_3	22	**3a**, 80; **4**, 7; **16**, 84
4[c,d]	**15a**	PCy_3	22	**3a**, 4; **16**, 3
5[c,e]	**15a**	PCy_3	22	N.R.
6[f]	**15a**	(*R*)-BINAP	10	**3a**, 93; **4**, 9; **16**, 62; **17a**, 30;**18**, 9
7[f]	**15a**	DPPF	36	**3a**, 83; **4**,17; **16**, 65; **17a**, 23; **18**,10
8	**15a**	P(*t*-Bu)$_3$	30	**3a**, 74; **4**, 6; **16**, 67; **17a**, 21
9	**15a**	P(*o*-Tolyl)$_3$	6	**3a**, 63; **16**, 99
10[g]	**15b**	PPh_3	24	**3a**, 60; **4**, 40; **16**, 38; **17a**, 29; **18**, 33
11[g]	**15c**	PPh_3	18	**3a**, 100; **17a**, 39; **18**, 60

[a] Reaction conditions: **15** (1 mmol), **2a** (3 mmol), Cs_2CO_3 (3 mmol), $Pd(OAc)_2$ (0.05 mmol), ligand (0.2 mmol) in refluxing *o*-xylene. [b] Determined by GC analysis. [c] **2a** (1.2 mmol) and Cs_2CO_3 (1.2 mmol) were used. [d] K_2CO_3 was used in place of Cs_2CO_3. [e] Reaction in refluxing toluene. [f] Ligand (0.1 mmol) was used. [g] **15** (0.5 mmol), **2a** (1.5 mmol), Cs_2CO_3 (1.5 mmol), $Pd(OAc)_2$ (0.025 mmol), and PPh_3 (0.2 mmol) were used.

SCHEME 3

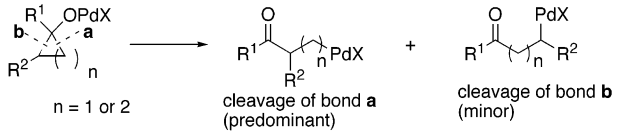


sults with various ortho-substituted 2-phenyl-2-propanols are described later.

The reaction with triphenylmethanol (**15a**) also gave useful mechanistic information. When **15a** was treated with **2a** (3 equiv) in the presence of $Pd(OAc)_2$-4PPh_3 for 24 h, **3a** (98%) and **4** (7%) were formed together with benzophenone (**16**) (55%) and di- and triphenylated benzophenones **17a** (35%) and **18** (7%) (Table 2, entry 1).[19] Monophenylated benzophenone was not detected. It is reasonable to consider that mono-, di-, and triphenylations of **15a** successively occur via C−H bond cleavage to give the corresponding alcohols **15b−d** as in the reaction of **1a**, and then, phenylative β-carbon elimination of **15a−d** affords **3a** and **4** together with the benzophenones (Scheme 3). The phenylated alcohols could be detected by GC-MS analysis of the reaction mixture at the early stage. It was also confirmed that the reaction of separately prepared **15b** with **2a** gave **3a** and **4** along with benzophenones **16−18** (Table 2, entry 10). From the reaction of **15c** was produced only **3a**

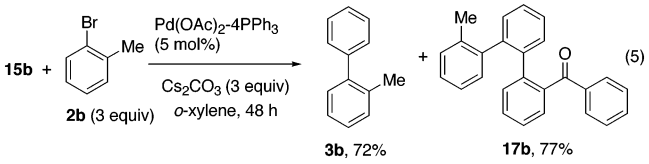
(19) The fact that the total yield of **3a** and **4** is somewhat greater than 100% may be due to the participation of homocoupling of **1a** to some extent. However, formation of homocoupling products was not observed or was negligible (less than 2%) in the other reactions.

SCHEME 4



together with **17a** and **18** (Table 2, entry 11). Thus, as for the β-carbon elimination, alcohol **15b** releases the biphenyl group, whereas one of the phenyl groups is eliminated from **15c** and **15d**, each reaction being highly selective. This suggests that as in the reaction of 2-phenyl-2-propanols, an ortho-substituent on triphenylmethanol significantly affects the ease and direction of C−C bond cleavage. Detailed results with various monosubstituted triphenylmethanols are described in the next section.

The reaction of alcohol **15b** with bromide **2b** selectively gave monoarylated benzophenone **17b** and 2-methylbiphenyl (**4b**) along with other minor products (eq 5), indicating that the ortho-substituent on bromobenzene does not interfere with the first *ortho*-arylation, but then, induces C−C cleavage selectively due to steric reasons.



The product distribution in the reaction of **15a** and **2a** with various phosphine ligands is also shown in Table 2. Bulky phosphines such as PCy_3, P(*t*-Bu)$_3$, and P(*o*-Tolyl)$_3$ seem to promote C−C bond cleavage (entries 2, 8, and 9). PCy_3 afforded biphenyl (**3a**) and benzophenone (**16**) in 93% and 88% yields, respectively, and only a minor amount of *o*-terphenyl (**4**) (6%) was observed as the sole byproduct. P(*o*-Tolyl)$_3$ gave no product via C−H bond cleavage. In this case, however, the yield of **3a** (63%) was considerably low and analysis of the reaction mixture by GC-MS suggested formation of a considerable amount of the ligand phenylated.[20] The reason PCy_3 more effectively enhances C−C bond cleavage than P(*t*-Bu)$_3$ is not definitive.

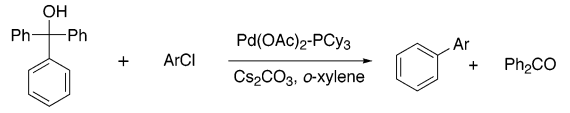
(B) Substituent Electronic and Steric Effects in the Arylative β-Carbon Elimination of Triphenylmethanols. The palladium(II)-catalyzed reactions of tertiary alcohols involving β-carbon elimination reported to date are mainly those with cyclobutanol[10] and cyclopropanol[11] derivatives, in which a less-substituted aliphatic carbon is eliminated selectively (Scheme 4). In the relevant transition metal-catalyzed ring-opening reactions involving cyclopropyl-[21] and cyclobutylmethylmetal[22] intermediates, the elimination of less-substituted carbon also occurs, often exclusively. However, more substituted cyclopropane bonds can also be cleaved

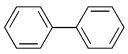
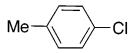
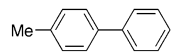
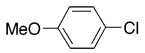
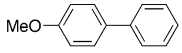
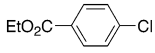
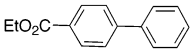
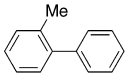
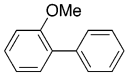
(20) Goodson, F. E.; Hauck, S. I.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 7527.

(21) Pd: (a) Lautens, M.; Meyer, C.; Lorenz, A. *J. Am. Chem. Soc.* **1996**, *118*, 10676. Rh: (b) Wender, P. A.; Dyckman, A. J.; Husfeld, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442. (c) Wender, P. A.; Pedersen, T. M.; Scanio, M. J. C. *J. Am. Chem. Soc.* **2002**, *124*, 15154. Ru: (d) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379.

(22) Rh: Murakami, M.; Takahashi, K.; Amii, H.; Ito, Y. *J. Am. Chem. Soc.* **1997**, *119*, 9307.

TABLE 3. Reaction of Triphenylmethanol with Aryl Chlorides[a]



entry	ArCl	biaryl, %yield[b]	Ph_2CO, %yield[b]
1			89	91
2			93	91
3			74	80
4			94	88
5			77	70
6			98	96

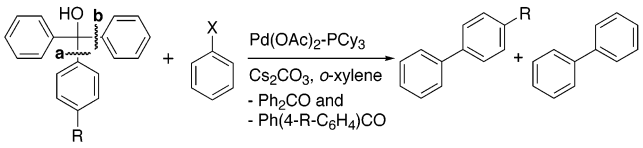
[a] Reaction conditions: alcohol (0.5 mmol), aryl chloride (1 mmol), Cs_2CO_3 (1 mmol), $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.05 mmol) in refluxing *o*-xylene for 20−24 h. [b] Determined by GC analysis.

selectively in some cases due to substituent electronic and conformational effects.[21d]

As for the present arylative coupling via the elimination of aromatic carbon, a systematic set of triphenylmethanols having an electron-donating or -withdrawing group at a para- or ortho-position may provide useful information with respect to which factor is dominant in the reaction, provided that their reactions occur selectively via C−C bond cleavage. Fortunately, as described above, it was found that the reaction of triphenylmethanol with an appropriate ligand such as PCy_3 induces *β*-carbon elimination selectively. The bulky and electron-rich phosphine was also found to allow use of chlorobenzene in place of bromobenzene in the present system, as has been shown in other palladium-catalyzed reactions with aryl halides.[23,24] Various 4- or 2-substituted chlorobenzenes reacted with the alcohol to give the corresponding biphenyls with good yields along with benzophenone (Table 3).

The reaction of 4-methylphenyl(diphenyl)methanol with bromobenzene gave a mixture of 4-methylbiphenyl and biphenyl in a ratio of 33:67 together with the corresponding benzophenones (Table 4, entry 1). Using chlorobenzene gave the same product ratio (entry 2). These results indicate that each of the three sp^2-sp^3 C−C bonds is cleaved statistically. In the reaction of 4-methoxyphenyl(diphenyl)methanol, the amount of 4-methoxybiphenyl was almost equal to that of biphenyl, showing that the electron-donating 4-methoxy group enhances the bond cleavage by a factor of 2 (entries 3 and 4). The electron-withdrawing 4-trifluoromethyl group was also found to promote the cleavage by a factor of 1.5 (entries 5 and 6).

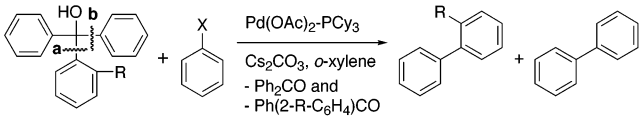
TABLE 4. Reaction of 4-Substituted Triphenylmethanols with Bromo- and Chlorobenzenes[a]



entry	R	X	time, h	total yield, %[b]	**a**:**b**
1[c]	Me	Br	20	79	33:67
2	Me	Cl	20	92	33:67
3[c]	OMe	Br	22	74	49:51
4	OMe	Cl	12	88	49:51
5[c]	CF_3	Br	22	69	43:57
6	CF_3	Cl	16	85	44:56

[a] Reaction conditions: alcohol (0.5 mmol), PhBr (0.6 mmol) or PhCl (1 mmol), $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.05 mmol) in refluxing *o*-xylene. [PhBr or PhCl] = [Cs_2CO_3]. [b] Determined by GC analysis. [c] PCy_3 (0.1 mmol) was used.

TABLE 5. Reaction of 2-Substituted Triphenylmethanols with Bromo- and Chlorobenzenes[a]



entry	R	X	time, h	total yield, %[b]	**a**:**b**
1[c]	Me	Br	22	100	93:7
2	Me	Cl	20	94	91:9
3[d]	Me	Br	22	94	88:12
4[c]	OMe	Br	8	99	>99:1
5	OMe	Cl	10	100	>99:1
6[d]	OMe	Br	22	96	97:3
7	CF_3	Cl	2	99	98:2

[a] Reaction conditions: alcohol (0.5 mmol), PhBr (0.6 mmol) or PhCl (1 mmol), $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.05 mmol) in refluxing *o*-xylene. [PhBr or PhCl] = [Cs_2CO_3]. [b] Determined by GC analysis. [c] PCy_3 (0.1 mmol) was used. [d] PPh_3 (0.1 mmol) was used.

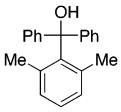
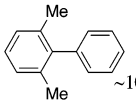
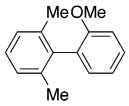
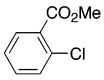
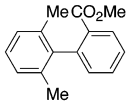
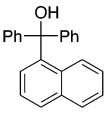
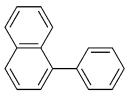
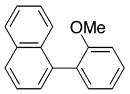
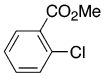
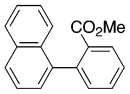
The reactions in entries 10 and 11 of Table 2 suggest that the ease of elimination of a phenyl group from ortho-substituted triphenylmethanols depends on the bulkiness of the substituents. Therefore, a number of the ortho-substituted substrates were subjected to the reaction with bromo- and chlorobenzenes (Table 5). The reaction of 2-methylphenyl(diphenyl)methanol gave 2-methylbiphenyl in more than 90% selectivities and yields (entries 1 and 2). It should be noted that the coupling efficiently and selectively proceeded even with PPh_3 in the case of bromobenzene (entry 3). From the reactions of 2-methoxy- and 2-trifluoromethylphenyl(diphenyl)methanols were produced the corresponding 2-substituted biphenyls almost exclusively with high yields (entries 4−7). The substituent steric effect together with the electronic enhancement could lead to the high selectivities.

A further bulky 2,6-dimethylphenyl group was also eliminated exclusively (Table 6). Thus, 2,6-dimethylphenyl(diphenyl)methanol quantitatively coupled even with ortho-substituted chlorobenzenes to give the correspond-

(23) (a) Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047. (b) Grushin, V. V.; Alper, H. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, Germany, 1999; p 193.

(24) Review for the recent development of Pd-catalyzed arylation reactions with aryl chlorides including aryl−aryl coupling with use of arylmetals: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

TABLE 6. Reaction of 2-(2,6-Dimethylphenyl)- and 2-(1-Naphthyl)diphenylmethanols with Aryl Halides[a]

entry	alcohol	ArX (mmol)	time, h	product, %yield[b]
1[c]			8	 ~100 (71)
2			2	98
3			2	 ~100
4			4	 ~100
5[c]			8	 97
6			4	98
7			2	 97(91)
8			18	 97

[a] Reaction conditions: alcohol (0.5 mmol), PhBr (0.6 mmol) or PhCl (1 mmol), $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.05 mmol) in refluxing *o*-xylene. [PhBr or PhCl] = [Cs_2CO_3]. [b] Determined by GC analysis. [c] PCy_3 (0.1 mmol) was used.

ing biaryls (entries 1−4). The 1-Naphthyl group was also eliminated exclusively (entries 5−8).

The above results show (a) both electron-donating and electron-withdrawing groups on triphenylmethanol make *β*-carbon elimination favorable in small, but meaningful extents, and (b) the phenyl group having one or two ortho-substituent(s) is selectively eliminated even in the reactions with ortho-substituted aryl chlorides as coupling partners. The latter contrasts with the ring-opening reaction of cycloalkanols cited above (Scheme 4). The selective phenyl elimination from alcohols **15c** and **15d** (Scheme 3) seems to be rather exceptional.

The present arylative coupling of triphenylmethanols is considered to occur via transition states I and II in Scheme 5. An electron-donating group may enhance the interaction between the metal and *ipso*-aromatic carbon, while the sp^2-sp^3 C−C bond may be weakened by an electron-withdrawing group. These two factors seem to perturb the reactivity of the phenyl group. Apart from the intuitive direction with respect to which bond is cleaved, the activation energy of transition state I leading to ortho-substituted biphenyl usually should be lower than that of transition state II to less-substituted biphenyl, so that steric effects due to the ortho-substituents allow the selective elimination. Steric repulsion between the ortho-substituted phenyl group and the bulky ligand

SCHEME 5

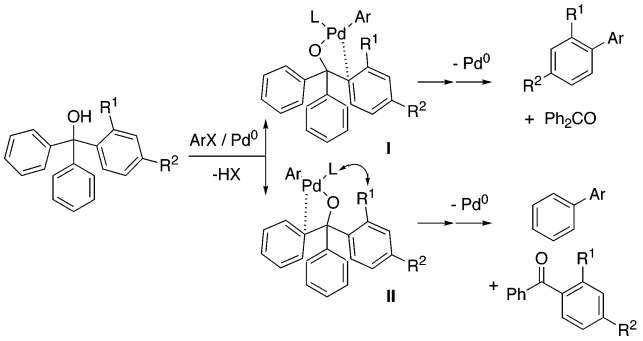
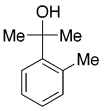
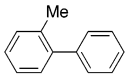
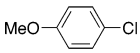
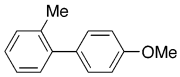
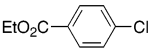
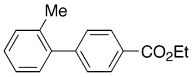
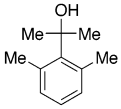
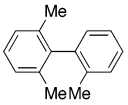
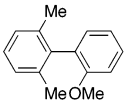
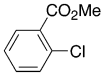
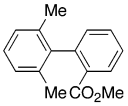
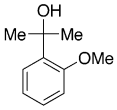
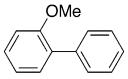
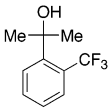
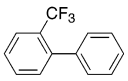


TABLE 7. Reaction of 2-(2-Substituted phenyl)-2-propanols with Aryl Chlorides[a]

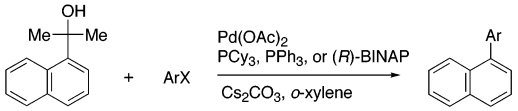
entry	alcohol	ArCl	time, h	product, %yield[b]
1			28	 76
2			8	 91 (78)
3			44	 82 (70)
4[c]			4	 97
5[d]			2	 90 (88)
6[d]			20	 96 (81)
7			22	 86 (81)
8			4	 65 (61)

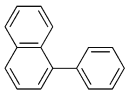
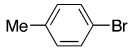
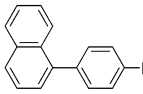
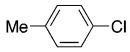
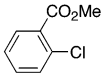
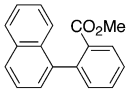
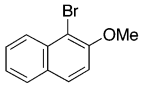
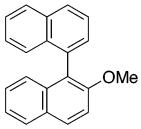
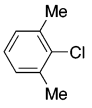
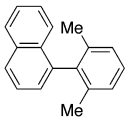
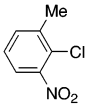
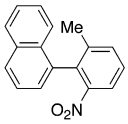
[a] Reaction conditions: alcohol (0.5 mmol), aryl chloride (1.5 mmol), Cs_2CO_3 (1.5 mmol), $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.05 mmol) in refluxing *o*-xylene. [b] Determined by GC analysis. The value in parentheses is the isolated yield. [c] ArCl (0.6 mmol) and Cs_2CO_3 (0.6 mmol) were used. [d] ArCl (1 mmol) and Cs_2CO_3 (1 mmol) were used.

seems to make transition state II unfavorable, while further studies are required to establish this. The result with alcohol **15c** (Table 2, entry 11), however, indicates that the relative activation energies of I and II can be changed in a special case.

Additional factors leading to selective elimination have also been found. (a) The reaction of 9-phenylxanthen-9-ol with 4-bromo- and 4-chlototoluenes cleanly proceeded to give 4-methylbiphenyl quantitatively along with xanthone (eq 6). The alcohol seems to be configurationally

TABLE 8. Reaction of 2-(1-Naphthyl)-2-propanol with Aryl Halides[a]



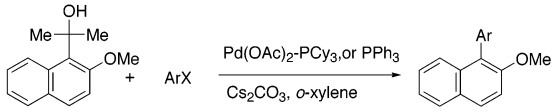
entry	ArX (mmol)	time, h	product, % yield[b]
1[c]	 (1.5)	6	 94
2[d]	 (1.5)	22	86
3[d]	 (1.5)	8	 94 (82)
4	 (1.5)	22	76
5	 (1)	4	 ~100 (89)
6[e]	 (0.5)	4	 ~100 (83)[f]
7	 (1)	4	 99 (78)
8	 (1)	22	 75 (73)

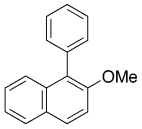
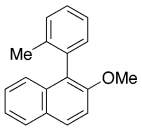
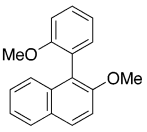
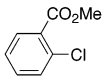
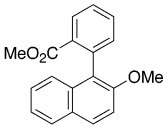
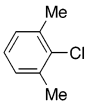
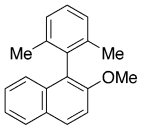
[a] Reaction conditions: alcohol (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.05 mmol) in refluxing *o*-xylene. [ArCl] = [Cs_2CO_3]. [b] Determined by GC analysis. The value in parentheses is the isolated yield. [c] PPh_3 (0.1 mmol) was used in place of PCy_3. [d] PCy_3 (0.1 mmol) was used. [e] Alcohol (0.75 mmol) and (*R*)-BINAP (0.05 mmol) were used. [f] 63% ee.

suitable for the selective β-carbon elimination. (b) In contrast, 9-phenylfluoren-9-ol reacted via ring-opening β-carbon elimination (eq 7). This may be attributed to ring-strain.[10a] (c) 2-Thienyl- and 2-furyl(diphenyl)methanols were found to be reactive, and the reactions with chlorobenzene were completed within 2 h to give 2-phenylthiophene and 2-phenylfuran, selectively, formation of biphenyl being negligible (eq 8). High reactivity of the heteroaryl groups may be due to the coordination ability of the internal heteroatoms.

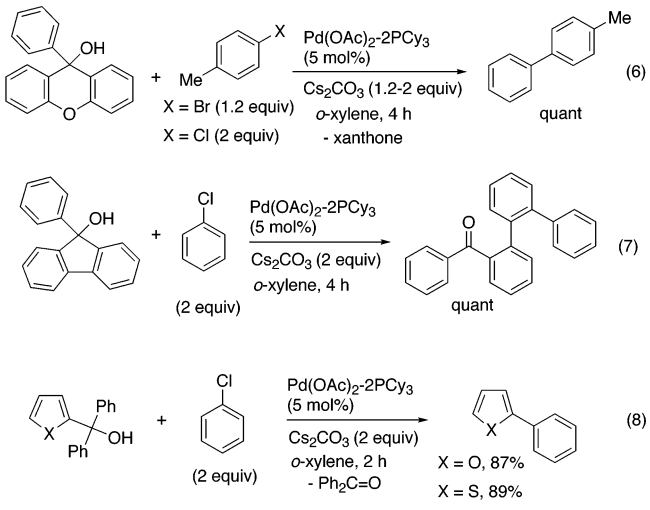
(C) Selective Formation of Biaryls with 2-Aryl-2-propanols and Aryl Bromides or Chlorides. While various biaryls can be obtained selectively with use of substituted triphenylmethanols and aryl bromides or chlorides under the present conditions, the use of 2-aryl-2-propanols appears to be synthetically advantageous, since it will make product isolation easier. The result shown in eq 4 suggests that ortho-substituted 2-phenyl-2-propanols may be good substrates for the present coupling. Consequently, a number of such substrates were subjected to the reaction. The results with 2-methyl-, 2,6-dimethyl-, 2-methoxy-, and 2-trifluoromethylphenyl-2-propanols together with a number of chlorobenzenes are shown in Table 7. In each case the reaction

TABLE 9. Reaction of 2-(2-Methoxy-1-naphthyl)-2-propanol with Aryl Halides[a]



entry	ArX (mmol)	time, h	products, %yield[b]
1[c]	 (0.6)	2.5	 93 (92)
2[d]		24	92
3	 (0.6)	4	 93 (92)
4	 (1)	4	 ~100 (89)
5[e]	(3)	4	(93)
6[f]	(1)	4	94
7	 (1)	2	 ~100 (83)
8	 (1)	4	 47 (45)

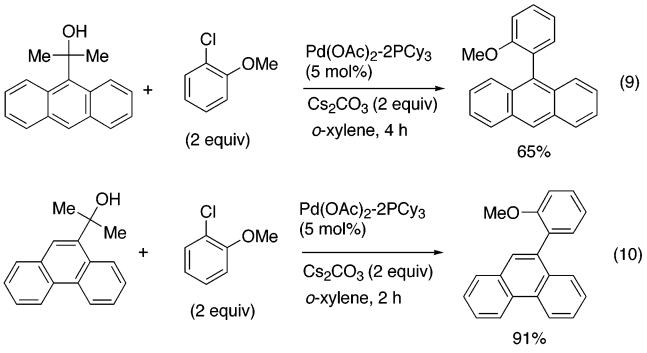
[a] Reaction conditions: alcohol (0.5 mmol), $Pd(OAc)_2$ (0.025 mmol), PCy_3 (0.05 mmol) in refluxing *o*-xylene. [ArX] = [Cs_2CO_3]. [b] Determined by GC analysis. The value in parentheses is the isolated yield. [c] PPh_3 (0.1 mmol) was used in place of PCy_3. [d] $Pd(OAc)_2$ (0.005 mmol) and PCy_3 (0.02 mmol) were used. [e] Alcohol (2.5 mmol) was used. [f] $[PhPd(OH)PCy_3]_2$ (0.0058 mmol) was used as the catalyst system.



proceeded selectively to give the corresponding biaryl. Notably, the reactions of 2,6-dimethylphenyl-2-propanol with ortho-substituted chlorobenzenes were completed in short periods of time to give 2,6,2′-trisubstituted biaryls in high yields (entries 4−6), as in the reactions with the corresponding triphenylmethanol (Table 6).

2-(1-Naphthyl)-2-propanol as an ortho-substituted 2-phenyl-2-propanol was also suitable for the aryl−aryl coupling. Tables 8 and 9 show the results with the propanol and its 2-methoxy derivative, respectively. The reactions proceeded smoothly in relatively short periods of time. The product yields are generally good with the exception of that of entry 8 in Table 9, where a formally 2,6,2′,6′-tetrasubstituted biphenyl was produced with a moderate yield. The reaction of 2-(1-naphthyl)-2-propanol and 1-bromo-2-methoxynaphthalene with (*R*)-BINAP gave the corresponding (*R*)-enantiomer-enriched binaphthyl with 63% ee (Table 8, entry 6), indicating that asymmetric induction is possible in the present coupling.[25,26] It was confirmed in some cases that comparable product yields could be obtained by using 1 mol % of the catalyst (Table 9, entries 2 and 5). A dimeric Pd complex with a 1:1 ratio of Pd to PCy_3 $[PhPd(OH)PCy_3]_2$[27] (1.2 mol % of Pd) was found to be acceptable (Table 9, entry 6).[28]

As expected from their structures, 2-(9-anthryl)- and 2-(9-phenanthryl)-2-propanols could also be used as substrates (eqs 9 and 10).



Conclusions

We have carried out a systematic study on the palladium-catalyzed arylation of α,α-disubstituted arylmethanols with aryl halides. The results are summarized as follows. (a) While the reaction of triphenylmethanol proceeds via both C−H and C−C bond cleavages, using a bulky phosphine ligand such as PCy_3 selectively affords products via the latter cleavage. Using the simple and tractable PCy_3 also enables aryl chlorides to react efficiently in the present system. (b) The results with a set of monosubstituted triphenylmethanols with PCy_3 as ligand indicate that substituent steric effects rather than electronic perturbations are significant. Thus, the aryl groups having an ortho-substituent are eliminated selectively with the exception of only a few examples. (c) The reaction of 2-(biphenyl-2-yl)-2-propanols mainly proceeds via C−H cleavage at the 2′-position, not at the 3-position. Interestingly, their diarylation occurs efficiently with use of ortho-substituted aryl bromides to produce sterically crowded 1,2,3-triphenylbenzene derivatives. (d) In contrast, 2-aryl-2-propanols having one or two ortho-substituent(s) other than a phenyl group undergo selective coupling with aryl bromides and chlorides via C−C bond cleavage to give the corresponding biaryls having ortho-substituents with good yields. The aryl−aryl coupling that does not use arylmetals seems to be an effective complement of conventional methods, especially for preparing biaryls having ortho-substituents.

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Supporting Information Available: Standard experimental procedure, characterization data of products, and an ORTEP drawing for compound **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0344034

(25) Catalytic asymmetric aryl−aryl coupling: (a) For review: Ogasawara, M.; Hayashi, T. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; John Wiley Sons: New York, 2000; p 651. (b) Cammidge, A. N.; Crépy, K. V. L. *Chem. Commun.* **2000**, 1723. (c) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

(26) Asymmetric Kumada−Tamao coupling to give the same binaphthyl with up to 37% ee: Frejd, T.; Klingstedt, T. *Acta Chem. Scand.* **1989**, *43*, 670.

(27) Grushin, V. V.; Alper, H. *Organometallics* **1993**, *12*, 1890.

(28) The reaction with $Pd(OAc)_2$-2P(*t*-Bu)$_3$, however, did not proceed. The reason is not definitive at the present stage.