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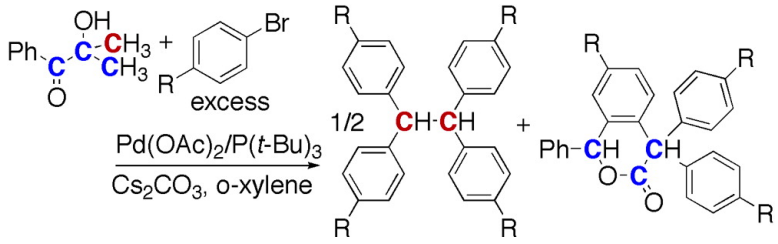

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Palladium-Catalyzed Reaction of 2-Hydroxy-2-methylpropiophenone with Aryl Bromides: A Unique Multiple Arylation via Successive C−C and C−H Bond Cleavages

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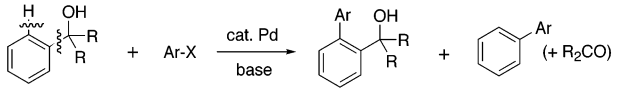
Transition metal-catalyzed organic reactions via cleavage of C−H[1] and C−C[2] bonds have recently attracted much attention from atom-economic and chemoselective points of view, and various catalytic processes involving different modes to activate the relatively inert bonds have been developed. We reported that phenols, aromatic ketones, and benzamides undergo regioselective aromatic arylation via C−H bond cleavage upon treatment with aryl halides in the presence of palladium catalysts.[3a−d] Coordination of the functional groups to arylpalladium(II) intermediates is the key to the reaction. The arylation of *tert*-benzyl alcohols was found to occur not only via C−H bond cleavage but also via C−C bond cleavage (Scheme 1), and the systematic studies of factors affecting the reaction revealed that the C−C bond cleavage predominates by using an appropriate ligand such as PCy_3.[4,5] We now report our new findings that a structurally related substrate to the alcohols, 2-hydroxy-2-methylpropiophenone (**1**), undergoes unexpected successive multiple arylation via C−C and C−H bond cleavages upon treatment with excess bromobenzenes (Scheme 2),[3] which appears to proceed through an intriguing catalytic sequence.

When ketone **1** (0.5 mmol) was treated with bromobenzene (**2a**) (2.5 mmol) in the presence of $Pd(OAc)_2$ (0.025 mmol), PPh_3 (0.15 mmol), and Cs_2CO_3 (2.5 mmol) in refluxing *o*-xylene for 20 h, 1,1,2,2-tetraphenylethane (**3a**) was formed in 62% yield (calculated as 2 × [**3a**]/[**1a**], see below) as the single major product (Scheme 2 and entry 1 in Table 1). Use of *p*-bromotoluene (**2b**) in place of **2a** gave 1,1,2,2-tetra(*p*-tolyl)ethane (**3b**) (74%) (entry 3), suggesting that the four aryl groups come from the bromide. In this case, P(*p*-tolyl)$_3$ was used as ligand for preventing the contamination of the phenyl group in PPh_3.[6] It was of interest that with P(*t*-Bu)$_3$ as ligand not only **3b** was formed in a quantitative yield, but also another structurally attractive compound, that is, 1-phenyl-4,4-di(*p*-tolyl)-7-methylisochroman-3-one (**4b**), was produced in substantial yield (entry 5). Similarly, the reaction with *p*-bromoanisole (**2c**) gave ethane **3c** and isochromanone **4c** (entry 6). Using **2a** and *p*-bromofluorobenzene (**2d**) in the presence of P(*t*-Bu)$_3$, ethanes **3a** and **3d** were formed in good yields as expected, but the yields of the corresponding isochromanones were low (entries 2 and 7). The yield of **4a** could not be improved with an increased amount of **2a** (3.5 mmol), while that of **3a** was quantitative. The structure of **4a** was verified by X-ray analysis (see Supporting Information). It is noted that no products via the reaction similar to Scheme 1 were detected in these reactions.

To rationalize the formation of tetraarylethanes **3** and isochromanones **4**, we assumed the sequence illustrated in Scheme 3. The first step involves the α-ketol rearrangement of **1** to **5**, that is 1,2-methyl-migration.[7] The successive catalytic α,α-diarylation of ketone **5** to give **6** takes place in a usual manner.[1f,8] The reverse α-ketol rearrangement of **6** occurs to give ketol **7**. The diarylmethyl moiety in **7** dimerizes to give **3** accompanied by formation of diketone **8**, and the triarylation of **8** leads to **4**.

Scheme 1



Scheme 2

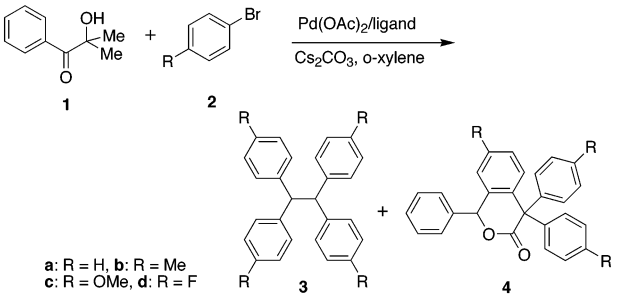
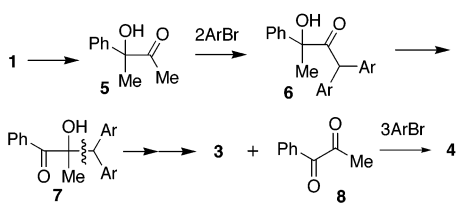


Table 1. Reaction of 2-Hydroxy-2-methylpropiophenone (**1**) with Aryl Bromides (**2**)[a]

				% yield[b]	
entry	bromide	ligand	time (h)	**3**	**4**
1	**2a**	PPh_3	20	62	*c*
2	**2a**	P(*t*-Bu)$_3$	6	>98 (79)	13 (9)
3	**2b**	P(*p*-tolyl)$_3$	12	74	*c*
4	**2b**	PCy_3	6	78	*c*
5	**2b**	P(*t*-Bu)$_3$	6	>98 (73)	45 (33)
6	**2c**	P(*t*-Bu)$_3$	6	(80)	(40)
7	**2d**	P(*t*-Bu)$_3$	6	(71)	*d*

[a] Reaction conditions: [**1**]:[**2**]:[$Pd(OAc)_2$]:[ligand]:[Cs_2CO_3] = 0.5:2.5:0.025:0.15:2.5 (in mmol), in refluxing *o*-xylene under N_2. [b] GLC yield based on amount of **1a** used. Value in parentheses indicates yield after purification. [c] Not detected. [d] Detected (ca. 5%) by GC−MS.

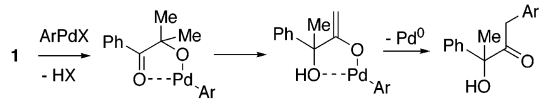
Scheme 3



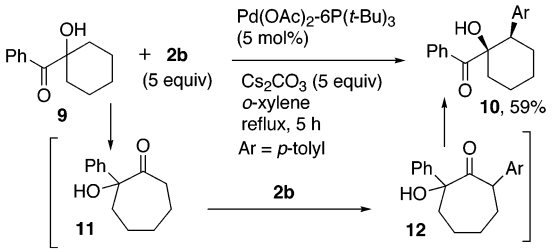
It seems reasonable to consider that the initial α-ketol rearrangement is catalyzed by ArPd(II) species, which is followed by the first arylation (Scheme 4). It should be described that the reaction of 1-benzoyl-1-hydroxycyclohexane (**9**) with **2b** under the same conditions used for the reactions in Scheme 2 gave compound **10**, which is a monoarylation product at the 2-position of **9**, in 59% yield as a sterically stable, single isomer (Scheme 5).[9] This implies that **10** is formed by α-ketol rearrangement to **11** and α-arylation to **12**,[7b,c] which may occur as in Scheme 4. The product appears to

10.1021/ja0477874 CCC: $27.50

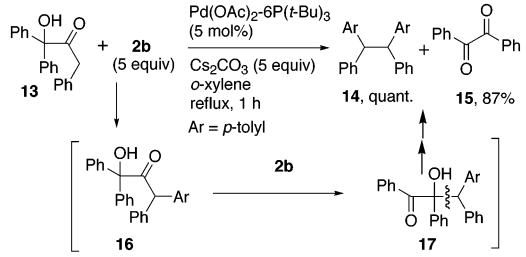
Scheme 4



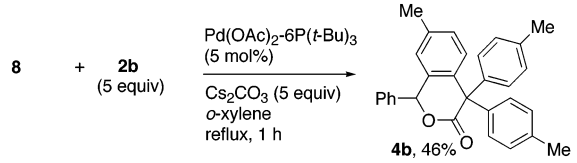
Scheme 5



Scheme 6



Scheme 7



be relatively less reactive under the conditions, so that there is very little further arylation. 1-Hydroxy-1,1,3-triphenyl-2-propanone (**13**),[10] which is a model substrate of mono-arylation product of **5**, was also treated with **2b**. As expected, 1,2-diphenyl-1,2-di(*p*-tolyl)ethane (**14**) was obtained in quantitative yield as a mixture of two possible diastereomers (ca. 3:2) together with benzil (**15**) (Scheme 6). These compounds may be formed via intermediary products **16** and **17** as in Scheme 3. As a relevant reaction to the transformation of **17** to **14** and **15** as well as that of **7** to **3** and **8**, Ru-catalyzed dimerization of diphenylmethanol to give **3a** has been reported.[11] In the present reaction, a diarylmethylpalladium(II) species, which is formed via β-carbon elimination of the corresponding palladium-(II) alcoholate, seems to participate.[12]

It was also confirmed that treatment of diketone **8** with **2b** afforded isochromanone **4b** in 46% yield (Scheme 7). Although the precise mechanism for the cyclization accompanied by C−H bond cleavage along with lactonization is not clear at the present stage, it seems to involve an electrophilic character since the reactions with **2b** and **2c**, each of which has an electron-donating substituent, afforded relatively good yields of **4**, while in the case of **2d**, nonproductive consumption of **8** predominated.[13]

Thus, the reactions in Schemes 5−7 seem to be satisfactorily in harmony with our hypothesis shown in Scheme 3, although further studies are required to establish the details.

In summary, we have described a unique reaction for the effective production of 1,1,2,2-tetraarylethanes by a 2:4 coupling under palladium catalysis that involves C−C bond cleavages. An interesting arylative cyclization involving C−H bond cleavage to give substituted isochroman-3-ones has also been shown. These unprecedented reactions seem to provide useful information for designing new catalytic cycles that occur via C−C and C−H cleavages.

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Supporting Information Available: Standard experimental procedures and characterization data for new compounds: This material is available free of charge via the Internet at http://www.pubs.acs.org.

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(9) Two-dimensional NMR analysis indicated that it has a cis arrangement. MOPAC PM-3 caluculation suggested the coumpound is more stable than its trans isomer by 1.9 kcal/mol.

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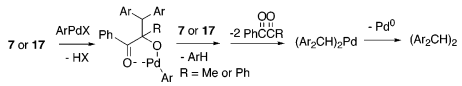
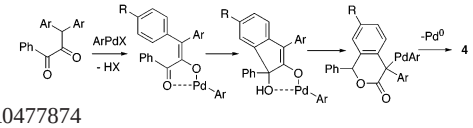
(12) In the present case, aryl bromide may act as oxidant.[3c,4b] One of the possible sequences is as follows:



(13) A palladium enolate may be involved as the key intermediate. One of the possible sequences is as follows:



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