Direct Aryl Halide Phenol Coupling

The Catalytic Intermolecular Orthoarylation of Phenols**

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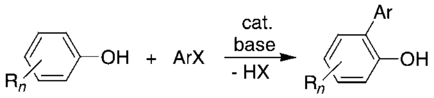
The biaryl subunit is an important structural motif that is found in a wide range of compounds such as natural products, polymers, liquid crystals, and ligands for homogeneous transition-metal catalysts.[1] One class of reaction that provides particular challenges for the catalytic chemist is the synthesis of orthoarylated phenols. Currently the most commonly used catalytic routes to these compounds employ Suzuki or Stille coupling reactions.[2] These require the introduction and subsequent loss of stoichiometric amounts of either boronic acid/ester or organotin functions. Therefore the ability to couple an aryl halide *directly* with a phenol (Scheme 1) without the need for a sacrificial electrophilic boron or tin fragment would be highly desirable from both synthetic and atom-economic points of view.



Scheme 1. The catalytic orthoarylation of phenols.

The transition-metal-catalyzed *ortho*-selective arylation of phenols has been limited to a few examples of *intramolecular* couplings of aryl halides that are tethered to the phenolic substrates,[3] and the reactions of aryl halides with 1-naphthol or 2-aryl-substituted phenols.[4] In all cases the reactions proceed via the formation of stable five- or six-membered metallacycles. Simple phenols avoid orthometalation reactions with late transition metals as this would give unfavorably strained, four-membered metallacycles.[5] However when aryloxide groups are incorporated into phosphorus donors such as phosphites, $P(OAr)_3$, or phosphinites, $PR_2(OAr)$, then facile orthometalation can occur to give low-strain, five-membered metallacyles. Lewis exploited this phenomenon when he demonstrated that ruthenium triarylphophite complexes catalyze the *ortho*-specific deuteration and ethylation of phenol.[6,7] These catalytic processes rely on the reversible in situ transesterification of catalytic amounts of triaylphosphite ligands with the substrate phenols. We were interested to see whether catalytic transesterification of phenols and their subsequent C–H activation by orthometalation could be used to realize the *intermolecular* orthoarylation of these substrates (Scheme 1), a process that, to the best of our knowledge, has not been previously reported. Such a process could allow the synthesis of a wide range of selectively 2-arylated phenols.[8]

The substrates used in optimization studies were 4-bromoacetophenone and the bulky phenol 2,4-di-*tert*-butylphenol, since phosphorus donors that incorporate this aryl oxide residue have been found to undergo particularly facile orthometalation reactions.[9] Initial experiments focused on the use of either 1) palladium catalysts formed in situ from dipalladium tris(dibenzylideneacetone) with the ligands tris(2,4-di-*tert*-butylphenyl)phosphite (**1**), (2,4-di-*tert*-butylphenyl) diphenyl phosphinite (**2**), or (2,4-di-*tert*-butylphenyl) diisopropyl phosphinite (**3a**) acting as cocatalysts, or 2) preformed palladacyclic catalysts containing these ligands.[9b,c] In all cases we observed either no reaction or the oxidative coupling of the phenol to give 2,2′,4,4′-tetra-*tert*-butylbiphenol (**4**).

By contrast when Wilkinson's catalyst is employed with an appropriate cocatalyst, then the reaction proceeds as shown in Scheme 1 to give the orthoarylated phenol, 2,4-di-*tert*-butyl-6-4′-acetylphenyl phenol (**5a**). The molecular structure of this new phenol was determined and is shown in Figure 1.[10] The choice of cocatalyst is important; the reaction works with the bulky triarylphosphite ligand **1**, but a large excess (3.5 equivalents) of aryl bromide is required otherwise the major product formed is again the homocoupled biphenol **4**. The triarylphosphinite ligand **2** also functions as a cocatalyst and does not require such a large excess of aryl bromide, but when it is replaced by the aryl dialkylphosphinite **3a** then the reaction is far more efficient and higher yields of the product are obtained. In principle any OAr functional group can be incorporated into the phosphinite cocatalyst, but for ease of product identification and purification we usually employed phosphinites that contain the substrate phenol. The data from the catalytic studies with Wilkinson's catalyst and the aryl dialkylphosphinite ligands acting as cocatalysts are summarized in Table 1.

As can be seen from Table 1, entries 1–6, good to excellent conversions to the 2-arylated phenols are obtained regardless of whether the aryl bromide used is activated, nonactivated, or deactivated with respect to oxidative addition. The

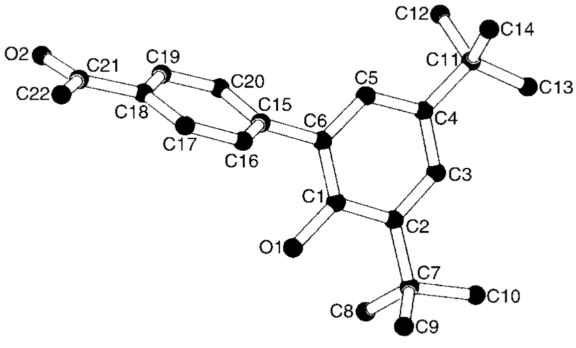


Figure 1. Molecular structure of compound **5a**.

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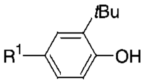
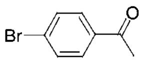
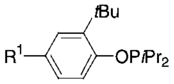
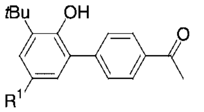
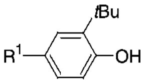
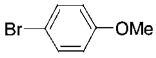
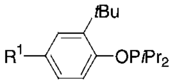
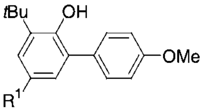
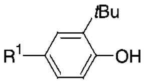
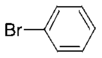
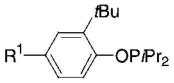
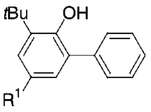
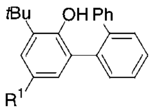
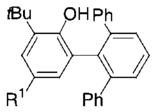
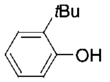
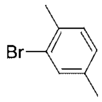
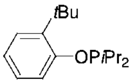
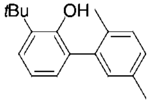
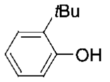
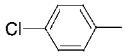
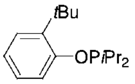
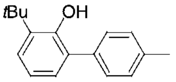
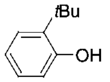
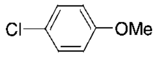
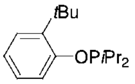
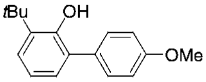
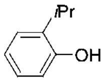
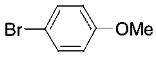
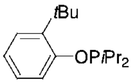
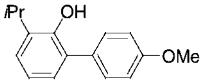
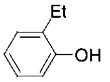
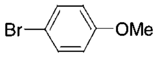
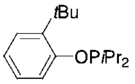
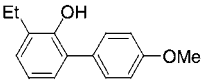
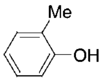
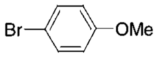
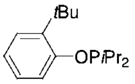
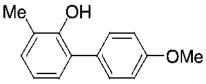
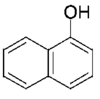
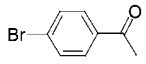
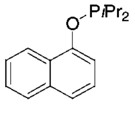
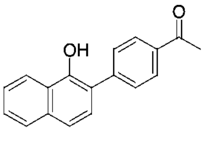
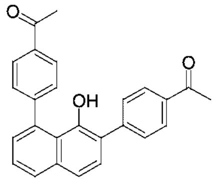
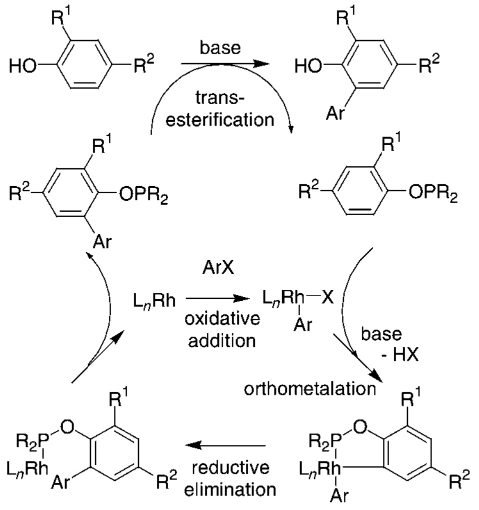
Table 1: Catalytic orthoarylation of phenols.[a]

Entry	Phenol	Aryl halide	Phosphinite cocatalyst	Product (yield [%])[b]		
1 ($R^1 = t$Bu) 2 ($R^1 =$ H)					**5a**: $R^1 = t$Bu (96) **5b**: $R^1 =$ H (96)	
3 ($R^1 = t$Bu) 4 ($R^1 =$ H)					**5c**: $R^1 = t$Bu (86) **5d**: $R^1 =$ H (79)	
5 ($R^1 = t$Bu) 6 ($R^1 =$ H)				 **5e**: $R^1 = t$Bu (81) **5f**: $R^1 =$ H (84)	 **6e**: $R^1 = t$Bu (6) **6f**: $R^1 =$ H (8)	 **7e**: $R^1 = t$Bu (5)
7					**5f** (100)	
8					**5g** (25)[c]	
9					**5h** (15)	
10					**5i** (68)	
11					**5j** (53)	
12					**5k** (21)[c]	
13				 **5m** (71)	 **8** (23)	

[a] Reaction conditions: Phenol (1.0 mmol), aryl halide (1.5 mmol), Cs_2CO_3 (1.7 mmol), $[RhCl(PPh_3)_3]$ (0.05 mmol), $PR_2(OAr)$ (0.15 mmol), toluene (10 mL), reflux, N_2, 18 h. [b] Yield of isolated product. [c] Estimated by ^{1}H NMR spectroscopy.

reaction also proceeds smoothly when the sterically hindered aryl bromide 2-bromo-*para*-xylene is employed (Table 1, entry 7). Even aryl chlorides can be used as substrates (Table 1, entries 8 and 9), although much lower yields of coupled products result. In all cases where the phenol substrate is unsubstituted at the 4-position only orthoarylation occurs; a simple electrophilic reaction of these substrates should also lead to the formation of paraarylated products. This demonstrates that the reaction is indeed *ortho*-selective, which in turn implies that the C–H activation of the phenol occurs after it has been incorporated into the phosphinite cocatalyst. In certain cases the reaction does not stop at the simple 2-arylated products and arylation of the previously introduced 2-aryl group occurs. Such multiple arylation reactions have been observed before.[4]

It is not necessary to have a bulky *tert*-butyl group in the 2-positon of the phenol for the reaction to proceed; the incorporation of progressively smaller groups such as isopropyl and ethyl still gives good yields of the products (Table 1, entries 10 and 11). Activity was even seen with 2-methylphenol (Table 1, entry 12), however in this case the yield was somewhat lower. No activity is observed with unsubstituted phenol. The reduction in catalytic activity with decreasing steric bulk implies that the rate-determining step is probably the orthometalation of the phosphinite ligand. To accelerate this process and thus facilitate the use of phenol as a substrate



Scheme 2. Plausible reaction mechanism.

we investigated the application of the bulkier phosphinite cocatalyst P*t*Bu$_2$(OPh) (**3b**), formed by reaction of P*t*Bu$_2$Cl with sodium phenoxide. In this case a number of products resulted that proved very difficult to separate. However it was possible to determine by ^{1}H NMR spectroscopy that roughly one third of the 4-bromoanisole used was incorporated into coupled products.

It is not necessary to have an alkyl group in the 2-position to facilitate the coupling reaction; 1-naphthol can also be used as a substrate (Table 1, entry 13). In this case a small amount of a second, 2,8-diarylated product (**8**), is observed. Presumably the 8-arylation occurs after the 2-arylation as there is no evidence for the formation of 8-arylated naphthol. It is possible that the 8-arylation does not proceed through the orthometalation of a phosphinite intermediate since 1-naphthol itself has been shown to undergo 8-arylation in the presence of a palladium catalyst.[4]

A plausible mechanism for the new reaction is given in Scheme 2, in which the phosphinite cocatalyst coordinates to and orthometalates at a rhodium(III) center formed previously by oxidative addition of the aryl halide. However, it is possible that the orthometalation step precedes the oxidative addition and occurs at a Rh$^{\mathrm{I}}$ center. Either way, subsequent reductive elimination of the orthometalated ligand and the aryl group leads to the reformation of the active catalyst and the liberation of a new 2-arylated aryl dialkylphosphinite ligand. This ligand then undergoes catalytic transesterification with the starting phenol to regenerate the cocatalyst and liberate the 2-arylated phenol product.

In summary, we have demonstrated for the first time the catalytic intermolecular *ortho*-selective arylation of phenols. We are currently examining the scope of this reaction with a range of phenols and related substrates and a variety of coupling partners.

Experimental Section

Typical catalytic procedure: Synthesis of **5a**: [RhCl(PPh$_3$)$_3$] (0.046 g, 0.05 mmol), **3a** (0.048 g, 0.15 mmol), 4-bromoacetophenone (0.300 g, 1.50 mmol), 2,4-di-*tert*-butylphenol (0.206 g, 1.00 mmol), and Cs$_2$CO$_3$ (0.550 g, 1.70 mmol) in toluene (10 mL) were heated at reflux under N$_2$ for 18 h, cooled and quenched with HCl (aq) (2 M, 5 mL). The mixture was extracted with CH$_2$Cl$_2$ (3 × 25 mL), dried (MgSO$_4$), filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (silica, CHCl$_3$/hexane 1:1) to give **5a** as a colorless solid (0.313 g, 96 %).

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[1] a) S. P. Stanforth, *Tetrahedron* **1998**, *54*, 263–303; b) G. Bringmann, R. Walter, R. Weirich, *Angew. Chem.* **1990**, *102*, 1006; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 977–991.

[2] For recent examples see: a) M. A. Zhuravel, S. T. Nguyen, *Tetrahedron Lett.* **2001**, *42*, 7925–7928; b) R. Kranich, K. Eis, O. Geis, S. Mühle, J. W. Bats, H.-G. Schmalz, *Chem. Eur. J.* **2000**, *6*, 2874–2894; c) K. B. Simonsen, K. V. Gothelf, K. A. Jørgensen, *J. Org. Chem.* **1998**, *63*, 7536–7538; d) D. E. Zembower, H. Zhang, *J. Org. Chem.* **1998**, *63*, 9300–9305; e) S. Yonezawa, T. Komurasaki, K. Kawada, T. Tsuri, M. Fuji, A. Kugimiya, N. Haga, S. Mitsumori, M. Inagaki, T. Nakatani, Y. Tamura, S. Takechi, T. Taishi, M. Ohtani, *J. Org. Chem.* **1998**, *63*, 5831–5837.

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[5] Miura and co-workers have demonstrated the 1-arylation of 2-naphthols. This pattern of reactivity presumably results from the high susceptibility of the 1-position to electrophilic attack rather than the formation of a highly strained four-membered palladacycle. See references [4].

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[10] CCDC-192419 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit @ccdc.cam.ac.uk).

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