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Phosphine Oxides as Stabilizing Ligands for the Palladium-Catalyzed Cross-Coupling of Potassium Aryldimethylsilanolates

Scott E. Denmark^{*}, Russell C. Smith, and Steven A. Tymonko

Roger Adams Laboratory, Department of Chemistry, University of Illinois, 600 S. Mathews Avenue, Urbana, Illinois 61801

Abstract

The palladium-catalyzed cross-coupling reaction of potassium (4-methoxyphenyl)dimethylsilanolate (K^+1^-) with aryl bromides has been demonstrated using triphenylphosphine oxide as a stabilizing ligand. Unsymmetrical biaryls can be prepared from a variety of aryl bromides in good yield with short reaction times. Qualitative kinetics studies compared effects of different phosphine oxides on the rate of cross-coupling and established the beneficial effect of these ligands in the reaction of electron-rich arylsilanolates. The improved yield and reproducibility of the cross-coupling of several bromides was demonstrated by direct comparison of reactions performed with and without triphenylphosphine oxide under non-rigorous exclusion of oxygen.

Keywords

cross-coupling; biaryls; phosphine oxides; silanols

1. Introduction

The palladium-catalyzed cross-coupling reaction of organometallic nucleophiles is one of the premier methods for carbon-carbon bond formation.ⁱ The use of organostannanes,ⁱⁱ organoboranes,ⁱⁱⁱ and organozinc^{iv} reagents has been comprehensively studied as the nucleophilic partner and has been elevated to name reaction status.^v Although these reactions have been used extensively for myriad synthetic transformations, there are nevertheless inherent limitations that warrant the development of new methods. Organosilanes, initially investigated by Hiyama and coworkers, have become an attractive alternative to some of the more commonly used donors. Early implementation of organosilanes as donors with different transferable groups required the use of fluoride to promote the cross-coupling process (Hiyama-Hatanaka paradigm).^{vi} Despite the broad applicability of this procedure for the cross-coupling of organosilanes, the requirement for fluoride activation is a significant disadvantage because of, inter alia, the incompatibility

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Address Correspondence to: Professor Scott E. Denmark, 245 Roger Adams Laboratory, Box 18, Department of Chemistry, University of Illinois, 600 S. Mathews Avenue, Urbana, IL 61801, phone: (217) 333-0066, fax: (217) 333-3984, denmark@scs.uiuc.edu.

Supporting Information **Available**: Complete experimental details for all preparative procedures along with full characterization of all starting materials and products as well as raw data for kinetic analyses (46 pages) are provided.

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with silicon protecting groups and the aggressive nature of fluoride. Therefore, the development of fluoride-free, cross-coupling reactions of organosilanols that display the same substrate scope and rate as the fluoride-promoted processes would be valuable.^{vii} This objective has been realized, in part, with the introduction of Ag_2O ^{viii} and KOSiMe_3 as activators for the cross-coupling of alkenyl-^{viiib} and alkynylsilanols.^{ix}

However, the formation of biaryls from cross-coupling of the corresponding arylsilanes (such as aryl(halo)silanes,^x aryl(halo)silylcyclobutanes,^{viiic} aryl(triallyl)silanes^{xi} and aryl(trialkoxy)silanes^{xii}) has been dominated by the use of fluoride activation.^{xiii} Although these reactions are effective, the coupling of the arylsilanes requires more forcing conditions. To address this concern, and remove the requirement for fluoride activation, we have recently demonstrated that electron-rich aryl(dimethyl)silanols undergo cross-coupling reactions with aryl iodides and bromides under the action of Cs_2CO_3 .^{xiv} Although the scope of electrophile for the cross-coupling of (4-methoxyphenyl)dimethylsilanol (**1**) is good, the reactions are slow (3-24 h), additives are needed to suppress homocoupling, and other arylsilanols are poor substrates.^{xivb} Because of our continued interest in the development of milder and more general cross-coupling reactions of organosilanes, we made recourse our to recent discovery that alkali metal silanolates are key reactive intermediates in these transformations.^{xv,xvi} The ease of preparation, stability and competence of metal silanolates has been illustrated in the cross-coupling of both alkenyl^{xvii} and heteroaryl^{xviii} silanolates. The preformed silanolate can be directly charged into the reaction mixture and affords a significant rate increase compared to the use of TMSOK as the activator.^{xix} Thus, we sought to develop cross-coupling conditions for the formation of biaryls with preformed silanolates to improve both the reaction time as well as the scope of the substrate.

2. Results

2.1. Orienting Experiments

Initial studies focused on the cross-coupling of preformed, alkali metal silanolates in the presence of various additives. Because the previous conditions for the coupling of silanols employed phosphine ligands in conjunction with the $\text{Cs}_2\text{CO}_3 / \text{H}_2\text{O}$ activator,^{xiv} we were concerned about the in-situ formation of phosphine oxides through reduction of the palladium(II) precatalyst, allylpalladium(II)chloride dimer (APC) by the phosphine.^{xx} The cross-coupling of potassium (4-methoxyphenyl)dimethylsilanolate K^+I^- with 4-bromobenzotrifluoride using APC (2.5 mol%) and dppb (5 mol%) in toluene at 90 °C reached 80% conversion in a 100 min, Figure 1 (compared to ca. 180 min with $\text{Cs}_2\text{CO}_3 / \text{H}_2\text{O}$). To test the affect of phosphine oxides on the reaction rate and efficiency, the mono-oxide, dppb(O), was employed and a similar conversion was reached, but in a shorter time (70 min). Much to our surprise the use of dppb(O)₂ dramatically increased the rate and the reaction went to completion in *less than 15 min!* Other phosphine oxides were then tested to establish if this phenomenon was unique to dppb(O)₂. A more basic, chelating bis phosphine oxide, dppf(O)₂ gave identical results. Remarkably either 1 and 2 equiv of triphenylphosphine oxide per palladium gave rates and conversions nearly indistinguishable from those with dppb(O)₂. The beneficial effect of phosphine oxide ligands was clearly demonstrated in the “ligandless” experiment shown in Figure 1. Under identical conditions but without a phosphine oxide additive, the initial rate of the coupling is good, nearly matching the rate in the presence of dppb(O), however, the reaction stalled after 30 min with the obvious formation of palladium black.

Although control experiments have unambiguously established that phosphine oxides are not formed from the reduction of APC,^{xx} our misconception has lead to the serendipitous discovery that phosphine oxides are useful ligands that allow for considerably faster cross-coupling reactions compared to the use of phosphine ligands. On the basis of these insights,

we undertook a systematic study of the effect of triphenylphosphine oxide on the cross-coupling of K^+I^- with a variety of electronically and sterically demanding aryl bromides to expand the scope of biaryl synthesis with arylsilanolates.

2.2. Expansion of Scope of Aryl Bromide

To establish the utility of phosphine oxides in a preparative cross-coupling reaction, K^+I^- and 4-bromobenzotrifluoride **2c** were combined in toluene at 90 °C with APC (2.5 mol%) and triphenylphosphine oxide ($Ph_3P(O)$, 5 mol%). The cross-coupling product was obtained in good yield (79%) after only 30 min. From this initial encouraging result, the cross-coupling with a variety of aryl bromides in the presence of $Ph_3P(O)$ was undertaken to fully establish reaction scope. The results are compiled in Table 1. Gratifyingly, aryl bromides of diverse structural and electronic nature underwent smooth cross-coupling to form unsymmetrical biaryl products rapidly and in good yield. Both electron-deficient (entry 1-3) and electron-rich (entry 5-7) 4-substituted aryl bromides reacted within 60 min to afford moderate to good yields. Unexpectedly, these reaction conditions were not compatible with certain sensitive functional groups. For example, aryl bromides containing a keto or cyano substituent led to poor conversions (< 10%) in contrast to their behavior in Cs_2CO_3 -promoted cross-coupling reactions.^{xiv} Further complications arose in the reaction of ethyl 4-bromobenzoate where unproductive consumption of the starting aryl bromide was observed. The loss of starting material was attributed to ester cleavage by the arylsilanolate at elevated temperatures. This problem could be easily remedied by making recourse to a *tert*-butyl ester. Compound **2a** reacted smoothly to afford an 82% yield of the desired biaryl product (Table 1, entry 1). In all cases, the symmetrical biaryl formed through homocoupling of the bromide was the primary side product (7-14% yield).

The rate of reaction was not sensitive to sterically demanding groups on the aryl bromide. Indeed, the 2-substituted aryl bromides reacted at a rate comparable to the corresponding 4-substituted isomers. Substrates bearing both electron-withdrawing (Table 1, entry 10) and electron-donating (Table 1, entry 11) substituents at the 2-position reacted to give the desired biaryl products in good yields. The successful coupling of the sterically hindered 2-bromomesitylene dramatically illustrated this point (Table 1, entry 13). The standard reaction conditions afforded only a 60% conversion with visible formation of Pd black after 10 min. Using 1.5 equiv of the arylsilanolate and the hemilabile ligand dppbO, the reaction was complete in 90 min and the biaryl product was isolated in good yield (77%). Cross-coupling reactions of aryl bromides bearing a heteroatom substituent at the 2-position were problematic and provided only 20% conversion in the best case. These groups containing Lewis basic atoms (e.g. O, N) most likely coordinate the metal center and thus inhibit productive cross-coupling from occurring.^{xxi} On the other hand, reaction of K^+I^- with *meta*-substituted aryl bromides proceeded smoothly as both the 3-chloro as well as the labile 3-triethylsilyloxy methyl substituents were compatible (Table 1, entries 8-9). The stability of the sensitive silicon-protecting group illustrates the mildness of the reaction conditions even at elevated temperatures.

Although the effectiveness of $Ph_3P(O)$ as a ligand had been established for the cross-coupling of K^+I^- , we nonetheless needed to perform the preparative reactions in the absence of a ligand for direct comparisons. Therefore, a representative set of substrates were subjected to the cross-coupling reaction conditions in the absence of $Ph_3P(O)$. Surprisingly, the preparative cross-coupling of K^+I^- with 4-bromobenzotrifluoride using APC (2.5 mol%) in toluene at 90 °C went to completion in 30 min without $Ph_3P(O)$. This result was contrary to the results obtained during the kinetic studies of this system. Interestingly, the cross-coupling in the absence of the ligand was rapid and general for the cases tested (Table 2). Both *ortho* and *para*-substituted aryl bromides reacted quickly all reaching >99%

conversion. The reaction with the 4-bromobenzotrifluoride was repeated on a preparative scale and a 76% isolated yield was achieved with 7% undesired homocoupling product. These results contradicted those obtained during the kinetic analysis of this system. Thus, to reconcile the disparate behavior, it was necessary to revisit the previous examples to more precisely understand the effect of added phosphine oxide.

2.3 The Role of Phosphine Oxide

The principle difference between the kinetic runs illustrated in Figure 1, and the results in Table 2 was the frequent sampling of the former reactions that could have compromised the inert atmosphere. To identify the impact of phosphine oxide additives on the rate and reproducibility of the cross-coupling under *non-optimal reaction conditions*, several representative bromides (**2b**, **2c**, **2f**, **2k**) were reexamined. For operational simplicity and to assay the robustness of the procedure, all reagents (except the hygroscopic silanolate) were weighed open to the atmosphere and added to the reaction flask without taking the usual precautions to remove oxygen. Each reaction (0.5 mmol) was performed in triplicate in side-by-side experiments both with and without $\text{Ph}_3\text{P}(\text{O})$ and the progress was monitored by GC analysis. The graphs in Figure 2 show the results for each of the four substrates. The blue lines represent the reactions run with $\text{Ph}_3\text{P}(\text{O})$ and the red lines represent those without. As indicated in the legend, pairs of experiments executed side-by-side are represented by the same icons (squares, circles, diamonds, etc.). In addition, the effect of scale was examined and is illustrated by the dashed lines (2.0 mmol scale) on the charts for **2c** and **2f**. The beneficial effect of $\text{Ph}_3\text{P}(\text{O})$ is immediately apparent in the coupling with **2b** (Figure 2). In the presence of this ligand, the reaction proceeded smoothly and with excellent reproducibility (conversions 59–67%). In contrast, in the absence of $\text{Ph}_3\text{P}(\text{O})$ the reaction was irreproducible and afforded consistently lower yields (18–57%). A similar irreproducibility was seen with **2c**. In the presence of $\text{Ph}_3\text{P}(\text{O})$ the reactions tracked nearly identically affording 76–78% conversion in 35 min, whereas the ligandless runs afforded 34–62% conversion in the same time. When the scale was increased four-fold, the yields for both reaction improved, nonetheless, the yield in the presence of $\text{Ph}_3\text{P}(\text{O})$ remained higher (89 vs. 74%). Similar results were seen with bromides **2f** and **2k**. In both cases the presence of $\text{PPh}_3(\text{O})$ resulted in improved conversion and reproducibility of the reaction. The striking behavior of 2-bromotoluene (**2k**) deserves comment. Despite the steric encumbrance, this substrate reacted faster than any other in the group reaching completion in less than 10 min in the presence of the ligand. As clearly seen in the graph, the ligandless reactions were slower and less reproducible.

3. Discussion

The results in Table 1 and Figure 2 clearly show that the phosphine oxide additive has a salutary effect in the cross-coupling reaction. However, the origin of this effect is not well understood, but may arise from a weak stabilizing interaction with the palladium catalyst. Because these reactions are performed in a non-coordinating solvent (toluene), stabilization from the solvent is not likely. Therefore, the phosphine oxide could be serving as a labile ligand that can prevent catalyst decomposition by a number of mechanisms including oxidation or agglomeration.

Although phosphine oxides are not generally recognized as good ligands for late transition metals^{xxii} a $\text{dppf}(\text{O})_2$ palladium(II) Cl_2 complex has been reported.^{xxiii} The existence of this complex demonstrates the ability of phosphine oxides to bind directly to Pd(II), but no discrete coordination chemistry to Pd(0) has been reported and no synthetic transformation of these species has been described. On the other hand, there is a wealth of knowledge (both structural and synthetic) on the use of bisphosphine *mono oxides* as “hemilabile” ligands for palladium. Hemilabile ligands, which contain both soft and hard coordinating atoms are a

promising new class of ligands for a variety of synthetic transformations.^{xxiv} The ability for these ligands to stabilize late transition metals while forming weak metal complexes affording more active metal centers is of interest. The bisphosphine monoxides are effective in reactions such as carbonylation,^{xxv} cycloaddition,^{xxvi} and oligomerization of olefins.^{xxvii}

How then does $\text{Ph}_3\text{P}(\text{O})$ influence the coupling reactions by itself? An intriguing hypothesis is that the phosphine oxide stabilizes the $\text{Pd}(0)$ atoms/particles formed from direct reduction of APC by the silanolate.^{xx} The reduction of APC leads to the formation of highly active Pd nanoparticles that can readily catalyze reactions, but that can also form inactive clusters.^{xxviii} Several methods have been developed to stabilize Pd nanoparticles, such as the use of aminomethylated TentaGel in a resin form.^{xxix} In addition, Li has described the use of *secondary* phosphine oxides (P-bound) in the palladium-catalyzed coupling of aryl chlorides with phenylboronic acid.^{xxx} One of the more creative uses of phosphine oxides as labile ligands was reported by Bawendi and coworkers who prepared a poly(ethylene glycol) phosphine oxide polymer to stabilize water-soluble palladium nanoparticles.^{xxxi} Interestingly, an example of a Suzuki cross-coupling was provided, clearly demonstrating the ability of phosphine oxides to intervene productively in catalytic processes. In addition, phosphine oxides have been used extensively to stabilize nanoparticles of other metals.^{xxxii}

The weak coordination of the phosphine oxide to the palladium catalyst prevents the precipitation of palladium black. Therefore, a constant catalyst loading is maintained throughout the reaction resulting in good reaction rates and reproducible yields. In the absence of this additive, the reactions proceed, but with varying rates and conversions. The irreproducibility might arise from variable degrees of oxygen contamination of the reaction apparatus resulting in inconsistent rates of catalyst decomposition. Thus, under rigorously controlled anaerobic conditions, the effect of the phosphine oxide is negligible and reactions proceed rapidly and with excellent conversion as was seen in the control experiments in Table 2. However, the reactions become more robust and do not require special precautions if $\text{Ph}_3\text{P}(\text{O})$ is added. In this sense, the phosphine oxide can be seen as a “buffer” or scavenger that allows reactions to proceed, even under less than ideal conditions.

4. Conclusions

In summary, the cross-coupling of an electron-rich arylsilanolate with a variety of aryl bromides proceeds smoothly with $\text{Ph}_3\text{P}(\text{O})$ as a ligand. The use of a preformed arylsilanolate in combination with an extremely labile ligand to provide unsymmetrical biaryls compares very favorably with the use of Cs_2CO_3 and arylsilanols. This method has the additional advantage that the silanolate is easily prepared and stored, and can be charged directly into the reaction vessel. Although the cross-coupling reactions also function in the absence of ligands, control studies showed that this process has a sensitivity to oxygen or moisture and the $\text{Ph}_3\text{P}(\text{O})$ can serve as a “buffering” ligand that helps to stabilize highly active palladium nanoparticles throughout the catalytic cycle. Further studies to extend this process to other arylsilanolates along with investigations into the mechanism of the homocoupling pathway are ongoing and will be reported in due course.

5. Experimental Section

5.1. General Experimental Methods

See the Supporting Information

5.2. General Procedure I: Analysis and Kinetic Measurements for Cross-coupling of K^+I^- with 4-Bromobenzotrifluoride Using Different Phosphines (Oxides)

5.2.1. Kinetic measurement using 1,3-bis(diphenylphosphino)butane dioxide (dppb(O)₂)—In a dry box, naphthalene (48 mg), APC (4.6 mg, 0.0125 mmol, 0.025 equiv), dppb(O)₂ (11.0 mg, 0.025 mmol, 0.05 equiv), and 4-bromobenzotrifluoride (70 μ L, 0.50 mmol, 1.0 equiv) were dissolved in dry toluene (1.0 mL) at room temperature in a one-neck, 5-mL round-bottom flask with a magnetic stir bar and fitted with a reflux condenser and three-way stop-cock (fitted with an argon inlet and a rubber septum). To this solution was added K^+I^- (165 mg, 0.75 mmol, 1.5 equiv). The flask was removed from the dry box, the stopcock purged with argon, and was placed in a 90 °C oil bath. Reaction progress was monitored by GC analysis. Sampling of the reaction was performed by removing 30- μ L aliquots of the mixture by syringe and quenching the aliquots at regular intervals. The quench was performed as follows: the withdrawn aliquot of the reaction mixture was injected into 100 μ L of a 10% aqueous solution of 2-dimethylaminoethanethiol hydrochloride. This yellow solution was diluted with 1.5 mL of ether and the organic layer was filtered through a 0.5 \times 1.0 cm plug of silica gel. The filtrate was analyzed by GC. Naphthalene, t_R 1.53 min; **3c**, t_R 5.72 min (HP-1, 170 °C (5 min), 50 °C/min, 225 °C (2 min), 16 psi).

5.3. General Procedure II: Cross-Coupling of Potassium Dimethyl(4-methoxyphenyl)silanolate with Aryl Bromides (Table 1)

5.3.1. Butyl 4'-methoxy-4-biphenylcarboxylate (3a) (Table 1, entry 1)—In a dry box, an oven-dried, 5-mL, 1-necked, round-bottomed flask containing a magnetic stir bar equipped with a reflux condenser and a three-way argon inlet capped with a septum, APC (9 mg, 0.025 mmol, 2.5 mol %) and triphenylphosphine oxide (Ph₃P(O), 14 mg, 0.05 mmol, 5 mol %) were combined. Dry, deoxygenated toluene (2.0 mL) and 4-bromo(*tert*-butyl)benzoate (257 mg, 1.0 mmol, 1.0 equiv) were added followed by potassium dimethyl(4-methoxyphenyl)silanolate K^+I^- (286 mg, 1.3 mmol, 1.3 equiv). The flask was closed-off to the atmosphere and transferred to a hood. The reaction mixture was heated to 90 °C under argon. After TLC analysis showed complete consumption of the aryl bromide, the mixture was cooled to rt and subjected to an aqueous work-up. The reaction mixture was poured onto H₂O (10 mL) and was extracted with ethyl acetate (3 \times 10 mL). The organics were washed with brine (10 mL) and dried (Mg₂SO₄). The combined organics were concentrated *in vacuo* and the residue was purified by column chromatography (SiO₂, 30 \times 200 mm SiO₂, CH₂Cl₂/hexanes, 1/1) followed by recrystallization from ethanol to afford 234 mg of **3a** as analytically pure colorless plates. mp 107-108 °C (EtOH); ¹H NMR (500 MHz, CDCl₃) δ 8.04 (d, 2 H, *J* = 8.8 Hz, HC(3)), 7.60 (d, 2 H, *J* = 8.8 Hz, HC(2)), 7.57 (d, 2 H, *J* = 8.8 Hz, HC(2')), 7.00 (d, 2 H, *J* = 8.8 Hz, HC(3')), 3.86 (s, 3 H, H₃CO(3'')), 1.62 (s, 9 H, H₃C(2'')); ¹³C NMR (126 MHz, CDCl₃) δ 165.7 C(5), 159.7 C(4'), 144.7 C(2'), 132.5 C(1), 130.1 C(1'), 129.9 C(3), 128.3 C(2'), 126.3 C(2), 114.3 C(3'), 80.8 C(1''), 55.3 C(3''), 28.2 C(2''); IR (KBr) 2979 (m), 2925 (m), 2827 (w), 1938 (w), 1892 (w), 1871 (w), 1709 (s), 1601 (s), 1531 (m), 1497 (m), 1452 (m), 1372 (m), 1301 (s), 1170 (s), 1112 (s), 1037 (s), 1015 (m), 833 (s), 774 (s), 698 (w) cm⁻¹; MS (EI, 70eV) *m/z* 284 (M⁺, 4), 228 (100), 213 (21), 185 (21), 139 (12), 117 (9), 91 (6); *R_f* 0.30 (hexanes/CH₂Cl₂, 2/1) [silica gel, UV (256, 366)]; Anal. Calcd for C₁₈H₂₀O₃: C, 76.03; H, 7.09. Found: C, 75.86; H, 7.22.

5.3.2. 4-Butoxy-4'-methoxybiphenyl (3f) (Table 1, entry 6)—Following General Procedure II, APC (15 mg, 0.025 mmol, 2.5 mol %), Ph₃P(O) (23 mg, 0.05 mmol, 5 mol %), toluene (3.3 mL), 1-bromo-4-butoxybenzene (174 μ L, 1.0 mmol, 1.0 equiv) and K^+I^- (286 mg, 1.3 mmol, 1.3 equiv) were combined and heated to 90 °C. After 60 min, the mixture was cooled to rt and subjected to an aqueous work-up. Purification by column chromatography (SiO₂, 40 mm \times 200 mm, hexanes/CH₂Cl₂, gradient 4/1 to 2/1) followed by

recrystallization afforded 155 mg (61%) of **3f** as colorless plates. mp 132-133 °C (EtOH); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.49 (d, 2 H, $J = 8.6$ Hz, HC(2)), 7.48 (d, 2 H, $J = 8.8$ Hz, HC(2')), 6.97 (d, 2 H, $J = 8.6$ Hz, HC(3)), 6.96 (d, 2 H, $J = 8.8$ Hz, HC(3')), 4.01 (t, 2 H, $J = 6.5$ Hz, HC(1'')), 3.85 (s, 3 H, HC(1'')), 1.80 (tt, 2 H, $J_1 = 6.5$ Hz, $J_2 = 7.5$ Hz, HC(2'')), 1.52 (tq, 2 H, $J_1 = J_2 = 7.5$ Hz, HC(3'')), 1.00 (t, 3 H, $J = 7.5$ Hz, HC(4'')); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 158.6 C(4), 158.3 C(4'), 133.5 C(1), 133.2 C(1'), 127.7 C(2), 127.7 C(2'), 114.7 C(3), 114.1 C(3'), 67.7 C(1''), 55.3 C(1''), 31.3 C(2''), 19.2 C(3''), 13.8 C(4''); IR (KBr) 2950 (s), 2925 (s), 2873 (m), 2372 (w), 2056 (w), 1891 (w), 1602 (s), 1501 (s), 1470 (m), 1398 (m), 1323 (m), 1274 (s), 1263 (s), 1178 (s), 1137 (m), 1121 (m), 1075 (w), 1044 (s), 1005 (m), 969 (w), 819 (s), 806 (s) cm^{-1} ; MS (EI, 70eV) m/z 256 (M^+ , 91), 200 (100), 185 (49), 157 (15), 128 (12), 102 (3); R_f 0.27 (hexanes/ CH_2Cl_2 , 2/1) [silica gel, UV]; Anal. Calcd for $\text{C}_{17}\text{H}_{20}\text{O}_2$: C, 79.65; H, 7.86. Found: C, 79.85; H, 7.90.

5.3.3. 3-Chloro-4'-methoxybiphenyl (3h) (Table 7, entry 8)—Following General Procedure II, APC (9 mg, 0.025 mmol, 2.5 mol %), $\text{Ph}_3\text{P}(\text{O})$ (14 mg, 0.05 mmol, 5 mol %), toluene (2.0 mL), 3-chlorobromobenzene (117 μL , 1.0 mmol, 1.0 equiv) and K^+I^- (286 mg, 1.3 mmol, 1.3 equiv) were combined and heated to 90 °C. After 60 min, the mixture was cooled to rt and subjected to an aqueous work-up. Purification by column chromatography (SiO_2 , 30 mm \times 200 mm, hexanes/ CH_2Cl_2 , gradient 7/1 to 6/1) followed by recrystallization afforded 189 mg (86%) of **3h** as analytically pure colorless plates. mp 56-57 °C (EtOH); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.55 (t, 1 H, $J_1 = J_2 = 1.9$ Hz, HC(2)), 7.51 (d, 2 H, $J = 8.8$ Hz, HC(2')), 7.43 (dt, 1 H, $J_1 = J_2 = 1.3$ Hz, $J_3 = 7.7$ Hz, HC(4)), 7.34 (t, 1 H, $J = 7.7$ Hz, HC(5)), 7.28 (dq, 1 H, $J_1 = 1.3$ Hz, $J_2 = 2.1$ Hz, $J_3 = 7.7$ Hz, HC(6)), 6.99 (d, 2 H, $J = 8.8$ Hz, HC(3')), 3.86 (s, 3 H, $\text{H}_3\text{CO}(1'')$); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 159.5 C(4'), 142.6 C(1), 134.6 C(3), 132.2 C(1'), 129.9 C(5), 128.1 C(2'), 126.8 C(2), 126.6 C(6), 124.8 C(4), 114.3 C(3'), 55.3 C(1''); IR (KBr) 3059 (w), 2956 (m), 2935 (w), 2904 (w), 2832 (w), 2362 (m), 2341 (w), 1894 (w), 1605 (m), 1576 (m), 1561 (m), 1512 (m), 1470 (m), 1390 (w), 1290 (m), 1279 (m), 1248 (s), 1184 (m), 1101 (m), 1021 (s), 884 (w), 832 (s), 786 (s), 687 (s), 667 (m) cm^{-1} ; MS (EI, 70eV) m/z 220 (33), 218 (M^+ , 100), 205 (12), 203 (38), 177 (13), 175 (41), 168 (3), 149 (15), 139 (15), 113 (9), 98 (5), 87 (13), 75 (19), 63 (27); R_f 0.28 (hexanes/ CH_2Cl_2 , 6/1) [silica gel, UV]; Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{ClO}$: C, 71.40; H, 4.99. Found: C, 71.25; H, 4.99.

5.3.4. 4'-Methoxy-3-(triethylsiloxymethyl)biphenyl (3i) (Table 1, entry 9)—Following General Procedure II, APC (9 mg, 0.025 mmol, 2.5 mol %), $\text{Ph}_3\text{P}(\text{O})$ (14 mg, 0.05 mmol, 5 mol %), toluene (2.0 mL), 1-bromo-3-(triethylsiloxymethyl)benzene (301 mg, 1.0 mmol, 1.0 equiv) and K^+I^- (286 mg, 1.3 mmol, 1.3 equiv) were combined and heated to 90 °C. After 60 min, the mixture was cooled to rt and subjected to an aqueous work-up. Purification by column chromatography (SiO_2 , 30 mm \times 220 mm, hexanes/ CH_2Cl_2 , 6/1) followed by reverse phase chromatography (reverse phase silica, 20 mm & times; 150 mm, MeOH/ H_2O , 12/1) afforded 220 mg (67 %) of **3i** as a colorless oil. $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.57 (m, 1 H, HC(2)), 7.56 (d, 2 H, $J = 8.8$ Hz, HC(2')), 7.46 (d, 1 H, $J = 7.6$ Hz, HC(6)), 7.40 (t, 1 H, $J = 7.6$ Hz, HC(5)), 7.31 (d, 1 H, $J = 7.6$ Hz, HC(4)), 7.00 (d, 2 H, $J = 8.8$ Hz, HC(3')), 4.82 (s, 2 H, HC(2'')), 3.87 (s, 3 H, HC(1'')), 1.03 (t, 9 H, $J = 7.8$ Hz, HC(4'')), 0.70 (q, 6 H, $J = 7.8$ Hz, HC(3'')); $^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 159.1 C(4), 141.7 C(3), 140.7 C(1'), 133.8 C(1), 128.6 C(5), 128.1 C(2), C(2'), 125.4 C(6), 124.6 C(4), 114.1 C(3'), 64.8 C(7), 55.3 C(1''), 6.8 C(3''), 4.5 C(2''); IR (neat) 3023 (w), 2950 (s), 2909 (s), 2863 (s), 2361 (w), 2046 (w), 1886 (w), 1697 (w), 1607 (s), 1519 (s), 1483 (s), 1460 (s), 1439 (s), 1411 (m), 1372 (m), 1284 (s), 1248 (s), 1181 (s), 1108 (s), 1074 (s), 1008 (s), 971 (m), 858 (m), 829 (s), 783 (s), 744 (s) cm^{-1} ; MS (EI, 70eV) m/z 328 (M^+ , 56), 299 (70), 269 (26), 197 (100), 165 (9), 154 (7), 99 (9), 59 (4); HRMS (EI, 70eV) m/z calcd for

$C_{20}H_{28}O_2Si$ (M^+): 328.1859; found: 328.1862; R_f 0.38 (hexanes/ CH_2Cl_2 , 1/1) [silica gel, UV, CAN]; GC t_R = 9.00 min (HP-1, 150 °C, 2 min, 50 °C/min, 250 °C, 6.5 min, 16 psi).

5.3.5. 2-Chloro-4'-methoxybiphenyl (3j) (Table 1, entry 10)—Following General Procedure II, APC (9 mg, 0.025 mmol, 2.5 mol %), $Ph_3P(O)$ (14 mg, 0.05 mmol, 5 mol %), toluene (2.0 mL), 2-chlorobromobenzene (116 μ L, 1.0 mmol, 1.0 equiv) and K^+Ic^- (286 mg, 1.3 mmol, 1.3 equiv) were combined and heated to 90 °C. After 30 min, the mixture was cooled to rt and subjected to an aqueous work-up. Purification by column chromatography (SiO_2 , 30 mm \times 220 mm, hexanes/ CH_2Cl_2 , 6/1) followed by Kugelrohr distillation afforded 188 mg (86%) of **3j** as an analytically pure, colorless oil. Bp 130 °C (ABT, 0.2 mmHg); 1H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, 1 H, J_1 = 1.3 Hz, J_2 = 7.9 Hz, HC(3)), 7.42 (d, 2 H, J = 8.8 Hz, HC(2')), 7.36 (dd, 1 H, J_1 = 1.9 Hz, J_2 = 7.3 Hz, HC(6)), 7.32 (ddd, 1 H, J_1 = 1.5 Hz, J_2 = J_3 = 7.9 Hz, HC(5)), 7.28 (ddd, 1 H, J_1 = 1.9 Hz, J_2 = J_3 = 7.9 Hz, HC(4)), 7.01 (d, 2 H, J = 8.8 Hz, HC(6)), 3.88 (s, 3 H, $H_3CO(1'')$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1 C(4'), 140.1 C(1), 132.6 C(2), 131.7 C(1'), 131.4 C(6), 130.6 C(2'), 129.9 C(3), 128.2 C(4), 126.8 C(5), 113.4 C(3'), 55.2 C(1''); IR (neat) 3062 (m), 3002 (m), 2957 (m), 2935 (m), 2836 (m), 2546 (w), 2359 (w), 2047 (w), 1888 (w), 1613 (w), 1579 (m), 1516 (s), 1469 (s), 1441 (s), 1408 (m), 1296 (s), 1250 (s), 1179 (s), 1126 (m), 1109 (m), 1074 (m), 1037 (s), 1018 (m), 1002 (m), 946 (w), 831 (s), 805 (m), 757 (s), 733 (s), 665 (m) cm^{-1} ; MS (EI, 70eV) m/z 220 (36), 218 (M^+ , 100), 205 (5), 203 (15), 177 (5), 175 (13), 149 (4), 139 (10), 115 (3), 75 (2), 63 (2); TLC R_f 0.43 (hexanes/ CH_2Cl_2 , 6/1) [silica gel, UV]; Anal. Calcd for $C_{13}H_{11}ClO$: C, 71.40; H, 5.07. Found: C, 71.21; H, 4.99.

5.4. General Procedure III: Cross-Coupling of Potassium Dimethyl(4-methoxyphenyl)silanolate with Aryl Bromides Without a Ligand (Table 2)

5.4.1. 4'-Methoxy-4-(trifluoromethyl)biphenyl (3c) (Table 2, entry 2)—In an oven-dried, 5-mL, 1-necked, round-bottomed flask containing a magnetic stir bar equipped with a reflux condenser and an argon inlet capped with a septum, was charged APC (9 mg, 0.025 mmol, 2.5 mol %). The flask was sequentially evacuated and purged with argon twice. Toluene (1.0 mL), and 4-bromobenzotrifluoride (138 μ L, 1.0 mmol, 1.0 equiv) were added followed by dimethyl(4-methoxyphenyl)silanolate K^+Ic^- (286 mg, 1.3 mmol, 1.3 equiv). The reaction mixture was heated to 90 °C under argon. After TLC analysis showed complete consumption of the aryl bromide, the mixture was cooled to rt and subjected to an aqueous work-up. The reaction mixture was poured onto H_2O (10 mL) and was extracted with ethyl acetate (3 \times 10 mL). The organics were washed with brine (10 mL) and dried (Mg_2SO_4). The combined organics were concentrated *in vacuo* and the residue was purified by column chromatography (SiO_2 , 30 \times 200 mm SiO_2 , hexanes/ CH_2Cl_2 , 5/1) followed by recrystallization from ethanol to afford 191 mg of **3c** as colorless flake crystals. The spectroscopic data matched those from the literature.^{xiv} mp 121–122 °C (EtOH); 1H NMR (500 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4 H, HC(2), HC(3)), 7.55 (d, 2 H, J = 8.8 Hz, HC(2')), 7.01 (d, 2 H, J = 8.8 Hz, HC(3')), 3.87 (s, 3 H, $H_3CO(1'')$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.9 C(4'), 144.3 C(1), 132.2 C(1'), 128.7 (q, J_{CF} = 32.2 Hz, C(4)), 128.3 C(2'), 126.9 C(2), 125.7 (q, J_{CF} = 3.7 Hz, C(3)), 124.4 (q, J_{CF} = 271.6 Hz, C(5)), 114.4 C(3'), 55.3 C(1''); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6 $CF_3(5)$; TLC R_f 0.63 (hexanes/ CH_2Cl_2 , 4/1) [silica gel, UV]; GC t_R = 6.55 min (HP-1, 150 °C (5 min), 50 °C/min, 250 °C (2 min), 16 psi).

5.5. General Procedure IV: Comparison of Cross-Coupling of Potassium Dimethyl(4-methoxyphenyl)silanolate with Aryl Bromides with and without Triphenylphosphine Oxide

5.5.1. 4-Bromobenzotrifluoride using $Ph_3P(O)$ —In a dry box, K^+Ic^- (143 mg, 0.50 mmol, 13 equiv) was charged into an oven-dried vial and sealed. The vial was transferred from the dry box into the hood. Naphthalene (31.7 mg), APC (4.6 mg, 0.0125 mmol, 0.025

equiv), $\text{Ph}_3\text{P}(\text{O})$ (7.0 mg, 0.025 mmol, 0.05 equiv) were charged into a one-neck, 5-mL round-bottom flask with a magnetic stir bar and fitted with a reflux condenser (during weighing, the round-bottom flask was kept open to an ambient atmosphere). The condenser capped with an argon adapter and the solids were dissolved in dry toluene (1.0 mL) resulting in a yellow solution. 4-Bromobenzotrifluoride (69 μL , 0.5 mmol, 1.0 equiv) was then added by removing the argon adapter and adding the material via syringe. To this solution was added the solid K^+I^- by again removing the argon adapter and adding the material as a solid. The flask was opened to an argon atmosphere, and was placed in a 90- $^\circ\text{C}$ oil bath. Reaction progress was monitored by GC analysis. The reaction was sampled by removing 30- μL aliquots of the mixture syringe and quenching the aliquots at regular intervals (5 min). The quench was performed as follows: the withdrawn aliquot of the reaction mixture was injected into 100 μL of a 10% aqueous solution of 2-dimethylaminoethanethiol hydrochloride. This yellow solution was diluted with 1.5 mL of ether and the organic layer was filtered through a 0.5 \times 1.0 cm plug of silica gel. The filtrate was subjected to GC analysis. Naphthalene, t_{R} 1.53 min; **3c**, t_{R} 5.72 min (HP-1, 170 $^\circ\text{C}$ (5 min), 50 $^\circ\text{C}/\text{min}$, 225 $^\circ\text{C}$ (2 min), 16 psi).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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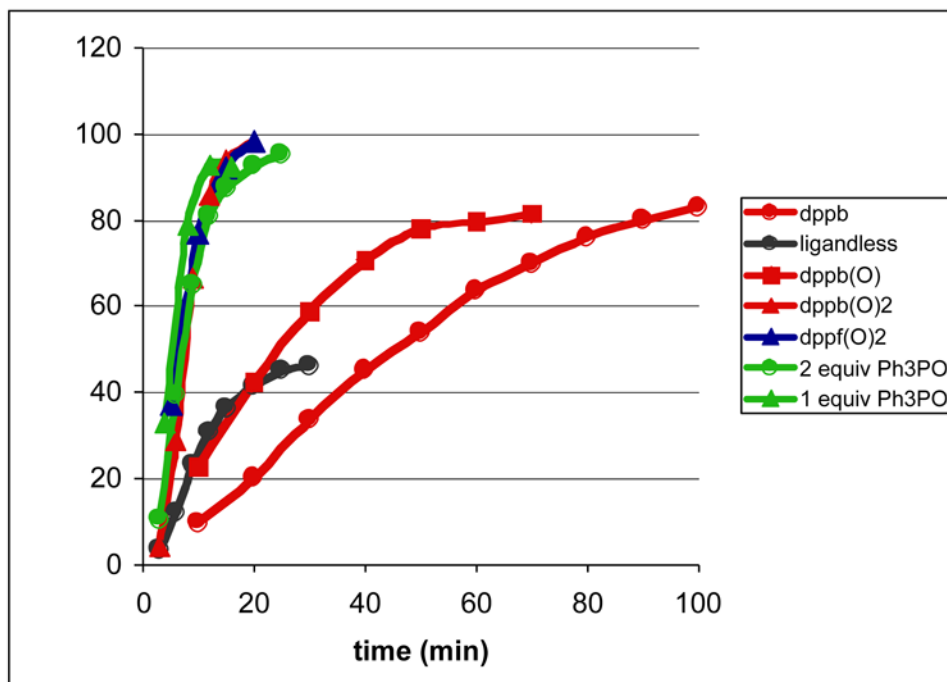
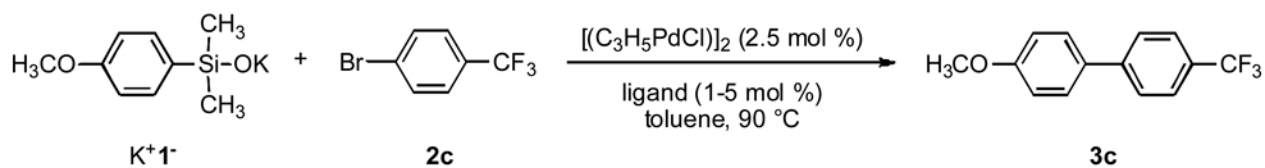


Figure 1.
Rate of cross-coupling as a function of ligand.

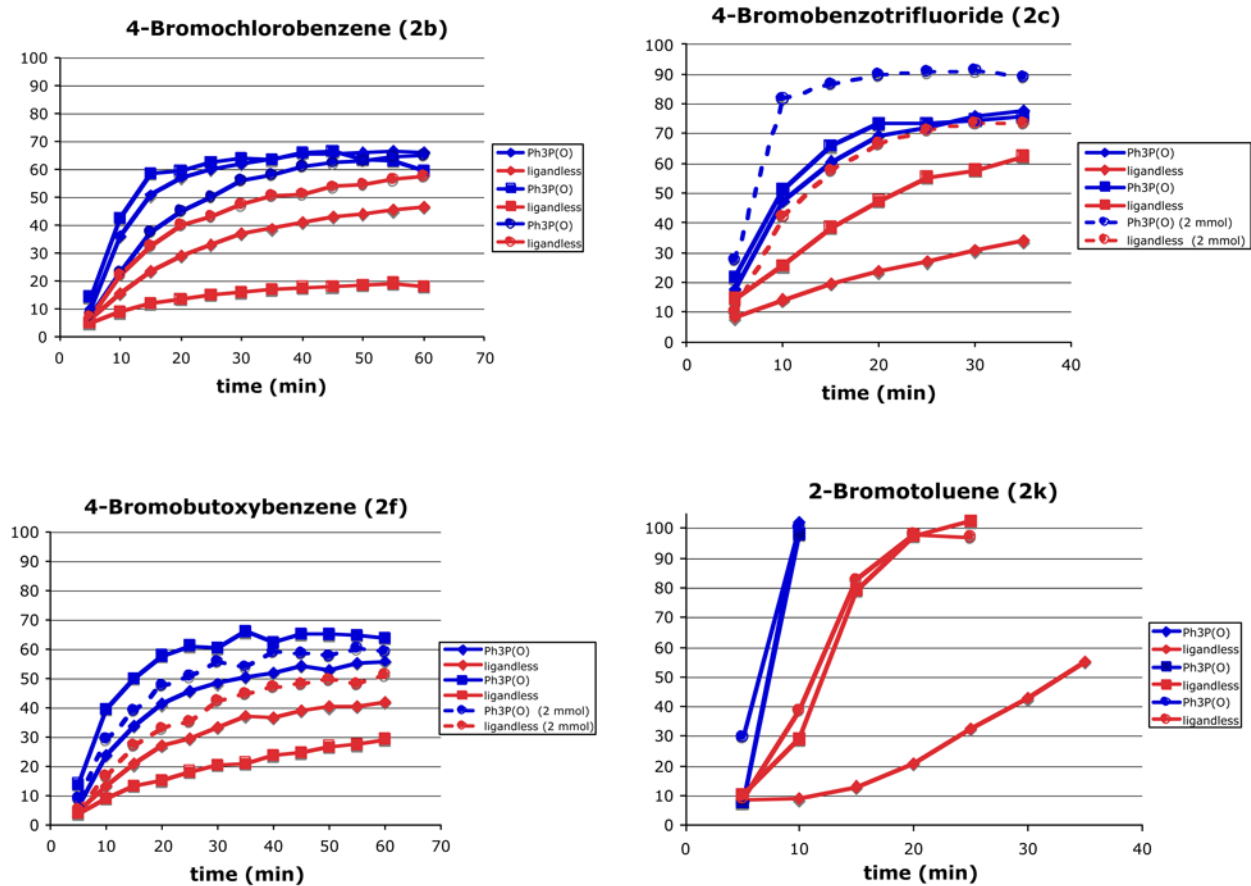
















Figure 2.
Comparison of reaction profiles.

Table 1
Cross-Coupling of K⁺I⁻ with Substituted Aryl Bromides Using Phosphine Oxides^a

entry	aryl bromide	product	time, min	yield, % ^b	product ratio ^c (cross/homocoupling, 3:4)
1			60	82	98:2
2			45	80	90:10
3			30	79	-
4			30	72	88:12
5			35	63	83:17
6			60	61	82:18
7			60	81	-



entry	aryl bromide	product	time, min	yield, % ^b	product ratio ^c (cross/homocoupling, 3:4)
8			60	86	93:7
9			60	67 ^d	-
10			30	86	-
11			30	85	-
12			35	85	-
13 ^e			60	77	-
14 ^e			90	80 ^f	99:1 ^g

^aReaction employed 1.3 equiv of K^+I^- .

^bYields are based on chromatographically homogeneous products.

^cRatios of cross/homocoupling are based on isolated yields unless otherwise mentioned.

^dProduct was found to be 97% pure by GC analysis

^eReaction employed 1.5 equiv of K^+I^- and dppbO (5 mol%).

^fYield based on conversion as determined by 1H NMR.

^gRatio of cross-/homocoupling determined by 1H NMR integration.

Table 2
Ligandless Cross-Coupling of K^+I^- with Substituted Aryl Bromides^a

entry	aryl bromide	product	time, min	conversion, % ^b
1		3b	60	100
2		3c	30	100 (76%) ^{c,d}
3		3f	60	> 99
4		3j	30	100
5		3k	30	> 95

^aReaction employed 1.3 equiv of K^+I^- .

^bConversion determined by ¹H NMR integration of the corresponding aryl bromide

^cYield in parentheses based on pure, isolated material

^d7% homocoupling product isolated