Highly Efficient and Accelerated Suzuki Aryl Couplings Mediated by Phosphine-Free Palladium Sources

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Suzuki aryl cross-couplings employing aryl bromides and aryl iodides proceed under mild conditions (65 °C) with high efficiency (substrate-to-catalyst ratios in excess of 500) in the presence of phosphine-free palladium catalysts derived from palladium acetate, $Pd_2(dba)_3{\cdot}C_6H_6$ (dba = dibenzylideneacetone), and $[(\eta^3\text{-}C_3H_5)PdCl]_2$. Phosphine inhibition is shown to play a key role in limiting catalytic efficiency; qualitative comparison studies show that the phosphine-free systems are 1–2 orders of magnitude more active than phosphine-supported catalytic systems. $Pd[P(Ph)_3]_4$ proved to be the least active of the catalytic species screened. The phosphine-free methodology appears to be generally applicable; cross-couplings of aryl iodides yielding biaryls **6** and **7** proceed without noticeable steric or electronic effects. Cross-couplings employing aryl bromides are insensitive to electronic effects in the synthesis of **6** but are slowed by steric hindrance in the synthesis of **7**. Acceleration of cross-coupling is observed in the presence of polar cosolvents and at high pH.

Introduction

Palladium-mediated cross-coupling reactions of aryl halides and aryl sulfonates with arylmetal reagents,[1] particularly arylstannanes (Stille coupling)[2] and arylboronic acids (Suzuki coupling),[3] are versatile methods for synthesizing unsymmetrical biaryls. Both couplings employ accessible substrates and proceed under mild conditions; Suzuki couplings offer the additional advantages of being largely unaffected by the presence of water, tolerating a broad range of functionality, and yielding nontoxic byproducts. As a consequence, they have been used extensively in the synthesis of natural products, nucleoside analogs, and pharmaceuticals.

Our principal interest in Suzuki aryl couplings is their application in poly(arylene) synthesis.[4] Step-growth polymerizations of this type are notoriously sensitive to any process which generates endcaps or other imperfections in the growing polymer.[5] For this reason, side reactions in Pd-mediated couplings which have only a limited impact on the synthesis of small molecules (*vide infra*) become vitally important in polymerization because they both result in endcaps[6] and dramatically affect macromolecular architecture.[7] In order to synthesize high molecular weight linear poly(arylenes) we required a catalytic system with significantly greater activity, efficiency, and specificity than the widely employed Suzuki protocol.[8]

In this paper, we demonstrate that phosphine inhibition plays a key role in limiting catalytic efficiency in Suzuki aryl couplings and show that extraordinarily mild, efficient, and clean catalysis occurs in the complete absence of phosphines. These findings expand on extensive development of "ligandless" catalysis for a variety of Pd-mediated reactions by Beletskaya *et al.*[9] Indeed, the first reported example of an aqueous Suzuki aryl coupling describes the production of phenylbenzoates from iodobenzoates and phenylboric acid in the presence of "ligandless" palladium acetate.[10] In addition, we present a series of solvent, pH, and substituent studies which explore optimal conditions for Suzuki aryl couplings and the generality of the phosphine-free method.

Results and Discussion

Phosphine Inhibition. To examine phosphine inhibition, we chose to study the cross-coupling of 4-halonitrobenzenes with phenylboric acid to yield 4-nitrobiphenyl (Table 1). Similar trends in catalytic activity hold for 4-iodo- and 4-bromonitrobenzene with the latter being slightly less reactive than the former. $Pd[P(Ph)_3]_4$ (**1**), $ArPd(PPh_3)_2I$ (Ar = 4-$NO_2C_6H_4$ or 4-$CF_3C_6H_4$) complexes **2**, palladium acetate (**3**), $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (**4**), and $Pd_2(dba)_3{\cdot}C_6H_6$ (**5**) (dba = dibenzylideneacetone) were examined as catalyst precursors. Phosphine-free precursors **3**–**5** are approximately 1 order of magnitude more active than **2** (entries 2 and 7, Table 1), which are in turn markedly more active than **1**.[11] The role of phosphines as inhibitors was confirmed further by spiking both **2** and **5** with 2 additional equiv per metal of triphenylphosphine; reactivity identical to **1** and **2**, respectively, was

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Table 1. Effect of Catalyst Precursor on Cross-Coupling To Yield 4-Nitrobiphenyl[a]

entry	precursor	time (h)	% convn[b] (% yield)[c]
	4-Iodonitrobenzene		
1	**1**	8.0	23
2	**2**	0.33	53
3	**2**	8.0	>98 (91)
4	**2** + $2PPh_3$	8.0	21
5	**3**	0.75	>98 (97)
6	**4**	1.0	>98 (99)
7	**5**	0.33	98
8	**5**	0.75	>98 (98)
9	**5** + $2PPh_3$	8.0[d]	>98 (97)
10	**5** (0.02%)	8.0	>98 (99)
	4-Bromonitrobenzene		
11	**1**	12.0	89
12	**2**	12.0	>98 (94)
13	**3**	2.5	>98 (96)
14	**4**	2.0	79
15	**5**	2.0	>98 (97)

[a] All couplings were carried out at 65 °C in aqueous acetone in the presence of 0.2% catalyst precursor and 2.5 equiv of K_2CO_3 unless noted otherwise. [b] Percent conversion is defined as [biaryl/(biaryl + aryl halide)]100 and was determined by ^1H NMR of the crude reaction extract. [c] Percent yield refers to isolated sublimate (≥99% pure as determined by GC/MS of selected runs). [d] Shorter reaction times resulted in incomplete reaction.

Table 2. Cosolvent Effects on Cross-Coupling[a]

cosolvent	time (h)	% convn (% yield)[b]
acetone	8.0	>98 (91)
THF	8.0	>98 (98)
DME	8.0	97
CH_3CN	8.0	94
toluene	8.0	59
benzene	8.0	51

[a] All couplings were carried out using 0.2% catalyst precursor **2** and 4-iodonitrobenzene. [b] Percent conversion and percent yield are defined as in Table 1.

observed (entries 4 and 9, Table 1). Couplings employing **2-5** can be routinely conducted at substrate-to-catalyst ratios of 500. Quantitative coupling at a substrate-to-catalyst ratio of 5000 demonstrates the efficiency attainable with phosphine-free precursors (entry 10, Table 1).

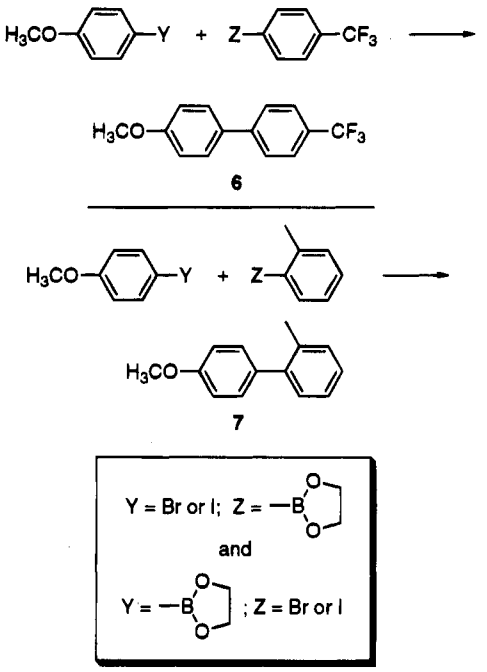
Optimization Studies. Additional studies demonstrated that water-miscible, polar, weakly coordinating cosolvents such as acetone or THF are optimal; DME and acetonitrile inhibit cross-coupling mildly, and nonpolar cosolvents slow the reaction markedly (Table 2).[12] Attempts to accelerate cross-couplings in nonpolar solvents by use of phase-transfer catalysts met with uniform failure. pH plays a role in cross-coupling as well (Table 3). Reactions carried out in the presence of a bicarbonate:carbonic acid buffer (pH = 7–8.5) are retarded relative to cross-couplings buffered with a carbonate:bicarbonate buffer (pH = 9.5–11). Changes in solvent and catalyst do not alter this effect. The pK_A of phenylboric acid is 8.8,[13] suggesting the possiblity of two active species with different reactivities: the hydroxyboronate anion at pH > pK_A and the free boronic acid at pH < pK_A. Alternatively, the reaction may proceed *via* equilibrium concentrations of the hydroxyboronate anion at pH < pK_A. The

Table 3. pH and Substrate Effects on Cross-Coupling[a]

base	cosolvent	precursor	time (h)	% convn (% yield)[b]
$KHCO_3$	acetone	**2**	8.0	67
$KHCO_3$	acetone	**3**	0.75	59
$KHCO_3$	THF[c]	**2**	15.0	70
K_2CO_3	acetone	**2**	8.0	>98 (99)[d]

[a] All couplings were carried out using 0.2% catalyst precursor, 4-iodonitrobenzene, and 4 equiv of $KHCO_3$ unless noted otherwise. [b] Percent conversion and percent yield are defined as in Table 1. [c] Carried out in 70:30 THF:H_2O. [d] 2-Phenyl-1,3,2-dioxaborolane employed. (Compare entry 3 in Table 1.)

Scheme 1



facilitation of Suzuki coupling with strong bases has been noted;[14] faster reaction of the hydroxyboronate anion is consistent with the characteristic electrophilic reactivity of arylboronates.[15] Under these conditions, 2-phenyl-1,3,2-dioxaborolane was found to be as reactive as phenylboric acid, presumably due to rapid hydrolysis of the boronate ester (entry 4, Table 3).

Generality Studies. In order to explore the generality of the phosphine-free methodology, several permutations of the synthesis of 4-methoxy-4′-(trifluoromethyl)-biphenyl (**6**) and 4-methoxy-2′-methylbiphenyl (**7**) were conducted (Scheme 1 and Table 4). Cross-coupling yielded both products quantitatively and proceeded without noticeable electronic or steric effects when aryl iodides were used.[16] Aryl bromides coupled smoothly to yield **6** but demonstrated some sensitivity to steric hindrance in the synthesis of **7**. When 2-(2-methylphenyl)-1,3,2-dioxaborolane was employed (entry 8, Table 4), reactions using 0.2% **3** reproducibly attained approximately 50% conversion for reaction times ranging from 3 to 16 h. Raising the amount of **3** to 0.5 and 1.0% increased the conversion to 60 and 81%, respectively. It

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Table 4. Electronic and Steric Permutations of Phosphine-Free Cross-Couplings[a]

entry	Y	Z	time (h)	% convn (% yield)[b]
		Biaryl **6**		
1	I	$B(OCH_2)_2$	0.67	[c](97)
2	Br	$B(OCH_2)_2$	4.0	>98 (98)
3	$B(OCH_2)_2$	I	0.67	>98 (99)
4	$B(OCH_2)_2$	Br	4.0	[c](97)
		Biaryl **7**		
5	I	$B(OCH_2)_2$	0.67	>98 (98)
6	Br	$B(OCH_2)_2$[d]	16.0	98 (92)
7	$B(OCH_2)_2$	I	0.67	>98 (97)
8	$B(OCH_2)_2$	Br	3.0–16.0	50–81[e]

[a] All couplings were carried out using 0.2% catalyst precursor **3** in aqueous acetone. [b] Percent conversion and percent yield are defined as in Table 1; for **7**, percent yield refers to isolated distillate. [c] Not determined. [d] 1.2 equiv of boronate. [e] See text.

is unclear whether poor results in this coupling arise because of catalyst deactivation or due to accelerated deboronation of the *ortho*-substituted boronate.[17] Slower coupling was also observed when the functionality of the aryl substrates was reversed (entry 6, Table 4). In this case, however, quantitative consumption of aryl bromide was attained by employing 1.2 equiv of boronate and longer reaction times.

Catalytic Species. Whereas reactions carried out using **1** and **2** most likely proceed by the catalytic pathway generally invoked for Suzuki couplings,[18] the nature of the catalytic species generated from precursors **3**, **4** and **5** is unclear. Zero-valent Pd is not known to exist as a molecular species in solution in the absence of strong donor or acceptor ligands.[19] Ligand-free ArPdX complexes (Ar = C_6H_5) have been prepared by metal-vapor deposition and are stable at −116 °C; at higher temperatures, rapid disproportionation and reductive coupling occur, yielding Pd, PdX_2, and biphenyl.[20] In the absence of credible molecular intermediates on the catalytic pathway, we cannot discount the possibility that phosphine-free cross-couplings are heterogeneous processes.[21] Reactions carried out with **3**–**5** darken immediately on addition of the catalyst precursor and precipitate metal particles even at 0 °C, yet remain highly active. Regardless of the identity of the active species, phosphine-free couplings can be routinely carried out at substrate-to-catalyst ratios 1–2 orders of magnitude greater than standard Pd-mediated coupling reactions.

It has been shown that **3** mediates the stoichiometric reductive coupling of aryl boronates.[22] This process and accompanying side reactions appear to be responsible for converting **3** to a catalytically active Pd(0) species. Reaction of **3** with 2 equiv of 2-[4-(trifluoromethyl)-phenyl]-1,3,2-dioxaborolane in basic aqueous acetone yielded 4,4′-bis(trifluoromethyl)biphenyl, 4-(trifluoromethyl)phenol, and unconsumed 4-(trifluoromethyl)-phenylboronic acid in addition to Pd black.

Side Reactions in Cross-Couplings. Protodeboronation. The mild hydrolytic instability of arylboronic acids has been extensively documented. Protodeboronation occurs *via* an electrophilic *ipso*- substitution and proceeds by acid-, base-, and metal-ion-catalyzed pathways.[15,17] Since deboronation can be expected to occur with a rate constant independent of aryl coupling, some loss of reagent due to this process is inevitable.[23] In most standard cases, addition of a 10% excess of boronate ensures quantitative consumption of the aryl halide. In situations where expensive or rare boronates are employed or where careful matching of reactive functional groups is necessary, such as in step-growth polymerization, the use of excess boronate may not be desirable. Accelerated cross-coupling should minimize deboronation and thus facilitate higher reaction efficiency in these instances.

Aryl Scrambling (Homocoupling). Traces of homocoupled materials are frequently observed in Pd-mediated cross-couplings.[24] We find that homocoupled byproducts are undetectable by GC/MS analysis of the products obtained from cross-couplings employing **3**.[25]

Phosphine-Related Side Reactions. Exchange of metal-bound aryls and phosphine-bound aryls occurs reversibly in Pd complexes analogous to **2** at 50 °C.[26] Since these compounds are key intermediates in the proposed cross-coupling pathway, aryl exchange allows ligand-bound phenyl groups to enter the cross-coupling cycle *in lieu* of the desired aryl halide-derived aryl moieties and hence to contaminate reaction products.[27] Tetraarylphosphonium salts can be synthesized by the Pd-catalyzed reaction of iodoarenes and triarylphosphines.[28] To the degree that phosphine arylation occurs during cross-coupling, it represents a nonproductive consumption of aryl halides. Both of these phosphine related side reactions can be eliminated by employing catalyst precursors such as **3**–**5**.

Further studies exploring the nature of the active catalyst in these couplings and the applicability of phosphine-free catalysis to related cross-coupling reactions are underway.[29] We will present the details of an ongoing mechanistic investigation of catalysis in aqueous Suzuki couplings in the near future.

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Experimental Section

General. Schlenk-line techniques were used for all manipulations. ^{1}H NMR spectra were acquired at 300, 400, or 500 MHz using Bruker AM-series and AMX-series spectrometers; ^{13}C and ^{19}F spectra were obtained at corresponding frequencies. Mass spectrometric analyses were performed by the University of California, Berkeley Mass Spectrometry Laboratory, or with a Hewlett-Packard 5890A gas chromatograph equipped with a 5970 mass-selective detector. Melting points are uncorrected.

Reagents. Solvents were purified by standard methods, deoxygenated by four freeze–pump–thaw cycles, and stored under argon. Water was obtained from a Millipore Milli-Q Water System and was deoxygenated in a similar manner. Palladium acetate was obtained from Aldrich Chemical Co. Complexes **1**,[30] **4**,[31] and **5**[32] were synthesized by standard methods. $ArPd(PPh_3)_2I$ compounds **2** (Ar = 4-$NO_2C_6H_4$,[33] 4-$CF_3C_6H_4$[34]) were synthesized by reaction of 1 equiv of (Pd) **5** with 2 equiv PPh_3 in the presence of 1 equiv of the appropriate aryl iodide in THF at ambient temperature and were recrystallized from THF/hexanes. Aryl halides were obtained commercially, purified by sublimation or distillation at reduced pressure, and stored under argon at −20 °C prior to use. Phenylboric anhydride was prepared from recrystallized phenylboric acid by dehydration *in vacuo* followed by sublimation. Substituted 2-aryl-1,3,2-dioxaborolanes were prepared from the corresponding aryl bromides by standard methods.[35]

Cross-Couplings. Scrupulous care must be used to exclude atmospheric oxygen from these reactions. We observed irreproducible results upon deviating significantly from the representative protocol outlined below.

4-Nitrobiphenyl (92–93–3) (registry numbers supplied by author). To a thick-walled glass tube equipped with a sidearm and Teflon stopcock were added a stir-bar, 0.248 g of 4-iodonitrobenzene (1.00 mmol), 0.106 g of phenylboric anhydride (0.35 mmol, 1.05 equiv as phenylboric acid), and 0.346 g of K_2CO_3 (2.5 mmol). The tube was flushed with argon and equipped with a rubber septum. Acetone (2.0 mL) and 2.5 mL of water were added with a gas-tight syringe. The septum was replaced by a Teflon stopcock, and two freeze–pump–thaw cycles were performed. A 4.0 mM solution of **3** in acetone (0.5 mL, 0.002 mmol) was then introduced under an argon backflow. Two additional freeze–pump–thaw cycles were performed, and the flask was capped with argon, sealed, and heated at 65 °C for 45 min. The contents were extracted with ether (4 × 10 mL), pooled, back-extracted with 10 mL of water, and concentrated *in vacuo*. This crude isolate contained no starting materials detectable by ^{1}H NMR. Sublimation (80 °C, 10 mTorr) gave 0.194 g (97% yield) of 4-nitrobiphenyl. No contamination by 4,4′-dinitrobiphenyl or biphenyl was detectable by GC/MS analysis of the sublimate: mp 113–115 °C (CH_3OH) (lit.[36] mp 112–114 °C); ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 1H), 7.49 (m, 2H), 7.62 (m, 2H), 7.73 (d, J = 8.8 Hz, 2H), 8.29 (d, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 124.1, 127.4, 127.8, 128.9, 129.1, 138.8, 147.1, 147.6; MS (m/z) 199.

4-Methoxy-4′-(trifluoromethyl)biphenyl (6) (10355–12–1). An identical procedure employing 0.187 g (1.00 mmol) of 4-bromoanisole and 0.227 g of 2-[4-(trifluoromethyl)phenyl]-1,3,2-dioxaborolane (1.05 mmol) yielded, after 4.0 h at 65 °C, 0.244 g of sublimed **6** (97%). No contamination by 4,4′-bis(trifluoromethyl)biphenyl or 4,4′-dimethoxybiphenyl was detectable by GC/MS: mp 122–124 °C (CH_3OH) (lit.[37] mp 124–126 °C); ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H); 6.99 (d, J = 8.8 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H), 7.64 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 55.3, 114.4, 124.4 (q, $^1J_{CF}$ = 270.8 Hz), 125.7 (q, $^3J_{CF}$ = 3.8 Hz), 126.8, 128.3, 128.7 (q, $^2J_{CF}$ = 32.5 Hz), 132.2, 144.3, 159.9; ^{19}F NMR ($CDCl_3$) δ −62.3; MS (m/z) 252.

4-Methoxy-2′-methylbiphenyl (7) (92495–54–0). An identical procedure employing 0.234 g (1.00 mmol) of 4-iodoanisole and 0.172 g of 2-(2-methylphenyl-1,3,2-dioxaborolane (1.05 mmol) yielded, after 40 min at 65 °C, 0.193 g of **7** (97%) as a colorless distillate[24b] (Kugelrohr, ot 60–65 °C, 10 mTorr). No contamination by 2,2′-dimethylbiphenyl or 4,4′-dimethoxybiphenyl was detectable by GC/MS: ^{1}H NMR ($CDCl_3$) identical to spectrum reported in ref 24b; ^{13}C NMR ($CDCl_3$) δ 20.5, 55.3, 113.5, 125.7, 126.9, 129.9, 130.2, 134.4, 135.5, 141.5, 158.5; MS (m/z) 198.

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Supplementary Material Available: Appropriate ^{1}H, ^{13}C, and ^{19}F NMR spectral tabulations and other characterization data for the 2-aryl-1,3,2-dioxaborolanes (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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