## Palladium-Catalyzed C-O Coupling Involving Unactivated Aryl Halides. Sterically Induced Reductive Elimination To Form the C-O Bond in **Diaryl Ethers**

Grace Mann,<sup>‡</sup> Christopher Incarvito,<sup>†</sup> Arnold L. Rheingold,<sup>†</sup> and John F. Hartwig<sup>\*,‡</sup>

> Department of Chemistry, Yale University P.O. Box 208107, New Haven, Connecticut 06520-8107 Department of Chemistry, University of Delaware Newark, Delaware 19716

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The reductive elimination of ethers from transition metal complexes is a rare elementary reaction that is limited to special cases.<sup>1-6</sup> The importance of aryl ether substructures has created a synthetic challenge to prepare the aryl-oxygen linkage in a general fashion under mild conditions.<sup>7-11</sup> Pd-catalyzed C-O coupling<sup>4,12–15</sup> could be a solution to this synthetic problem, but the reductive elimination of acyclic ethers<sup>4-6</sup> that is the crucial step for this catalytic process has been limited to palladium complexes with aromatic systems that are highly activated and undergo direct, uncatalyzed nucleophilic aromatic substitution chemistry. Thus, it is unactivated aryl halides that are crucial substrates to include in transition metal-catalyzed C-O coupling chemistry,<sup>4-6,13</sup> and we report that Pd complexes with sterically hindered alkylphosphines (1) undergo thermal reductive elimination to form the C–O bond in diaryl ethers from complexes with unactivated metal-bound aryl groups and (2) catalyze the formation of diaryl ethers and protected phenols from unactivated aryl halides. These findings demonstrate the concept that sterically hindered alkylphosphines accelerate reductive elimination.

Our recent success with D'BPF (1,1'-bis(di-tert-butylphosphinoferrocene)) (1) in amination of aryl halides<sup>16</sup> led us to seek improvements in aryl halide etherification using this ligand. The reaction in eq 1 containing catalytic amounts of Pd(OAc)<sub>2</sub> and D'BPF gave diaryl ether in 45% yield. The same reaction with BINAP, DPPF, or  $P(o-tolyl)_3$  as ligand gave no ether. The origin of this reactivity difference was complex and led to the discovery of a new ferrocenyl monophosphine.

The presumed arylpalladium phenoxide intermediate (D'BPF)- $Pd(C_6H_5)(O-p-C_6H_4OMe)$  (2) was isolated after reaction of (D'BPF)Pd(Ph)(Br) with sodium aryloxide in THF. Surprisingly, thermolysis of 2 at 110 °C in the presence or absence of sodium aryloxide and added ligand as trap for Pd(0) produced no diaryl ether. Either reductive elimination does not occur during the

<sup>‡</sup> Yale University.

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Fable 1.	Palladium-Catalyzed Conversion of Aryl Halides to Aryl
Ethers wit	h FcP $(t-Bu)_2$ or $P(t-Bu)_3$ As Ligand

	ArX	NaOR	Product	cond.	Yield %a
1	C-ci	NaO	C O OMe	9h, 80 °C	82
2	⟨Br	NaO	CCO OMe	12h, 80 °C	<b>8</b> 5
3	<sup>t</sup> Bu—	NaO	<sup>r</sup> Bu O OMe	12h, 110 ℃	74
4	O Ph → Br	NaO-	Ph(O)C	12h, 110 °C	63
5	CI	NaO	OMe	24h, 110 °C	81 <sup>b</sup>
6		NaO- <i>t</i> -Bu	ОН	12h, 85 °C	71 <sup>C</sup>
7	→Br	NaO- <i>t</i> -Bu	-C-	12h, 100 °C	68c,d
8	-	NaO- <i>t</i> -Bu	OH —	12h, 110 °C	62C,d
9	'Bu- Br	NaO- <i>t</i> -Bu	<sup>t</sup> Bu————————————————————————————————————	6h, 85 ℃	84
10	С			3h, 80 °C	78
	+ NaO- <i>t</i> -Bu				

<sup>a</sup> All the reactions were performed in toluene solvent with a 0.2-0.3 M concentration of aryl halide, 2-5 mol % Pd(dba)<sub>2</sub>, 2-5 mol % 4, and 1.2 equiv of NaOR unless otherwise stated. Ligand 4 is oxygen sensitive in solution. All reagents were weighed in a glovebox. Isolated yields were from an average of two runs.<sup>b</sup> 5 mol <sup>%</sup> Pd(dba)<sub>2</sub> and 5 mol %  $P(t-Bu)_3$  were used as catalyst. The product was isolated in >96% purity. <sup>c</sup> After heating, the reaction mixture was treated with CF<sub>3</sub>CO<sub>2</sub>H and CF<sub>3</sub>SO<sub>3</sub>H. <sup>d</sup> Yield was determined by GC analysis with an internal standard.

catalytic cycle or a D'BPF-ligated palladium complex is not the product-forming intermediate.

Careful analysis of all reaction products by GC/MS showed the latter to be true: D'BPF cleaved into the two monophosphines, phenyldi-tert-butylphosphine (3)<sup>17</sup> and ferrocenyldi-tert-butylphosphine (4). These ligands were prepared, each in one step, and used in combination with Pd(OAc)<sub>2</sub> as catalyst for the reaction in eq 1. Reactions catalyzed by 3 and  $Pd(OAc)_2$  gave less than



L=D<sup>t</sup> BPF (1), 45%; L=BINAP, DPPF, P(o-tolyl)<sub>3</sub>, 0% L=P(t-Bu)3 27%; L=PhP(t-Bu)2, <5%, FcP(t-Bu)2, 83%

5% diaryl ether, but reactions catalyzed by 4 and Pd(OAc)<sub>2</sub> gave 83% yield of diaryl ether by GC analysis. Thus, palladium complexes of ligand 4 produce the true catalyst, and this catalyst is superior to any previous transition metal system for the formation of diaryl ethers from unactivated aryl halides.

A survey of the catalytic formation of diaryl ethers with ligand 4 is provided in Table 1. Reactions were faster when using Pd-(dba)<sub>2</sub> as the palladium source. Aryl bromides or chlorides with electron-withdrawing acyl or electron-donating alkyl groups reacted to form diaryl ethers in good yields. Aryl iodides gave low conversions. Aryl halides with ortho substituents reacted faster (80 °C) than unhindered aryl halides (110 °C). Similar yields of diaryl ether were obtained from hindered aryl halides when Pd- $(dba)_2$  and ligand 4 or P(*t*-Bu)<sub>3</sub> were used as catalyst (4 = 85%,

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 $P(t-Bu)_3 = 83\%$ ), but unhindered aryl halides gave higher yields of diaryl ether when using ligand 4 (4 = 74%, P(t-Bu)<sub>3</sub> = 27\%). Electron-rich sodium aryl oxides, sodium phenoxide, and a sodium aryl oxide bearing an ortho methoxy substituent all gave diaryl ether product in good yields.<sup>18</sup>

Aryl halides were also converted to tert-butyl aryl ethers, which serve as precursors to aryl alcohols, using NaO-t-Bu as reagent and a catalyst bearing ligand 4 or  $P(t-Bu)_3$ . The complex formed from ligand 4 and Pd(dba)<sub>2</sub> catalyzed the formation of aryl ether at a faster rate than that formed from  $P(t-Bu)_3$ . This type of C-O bond formation occurred for electron-rich aryl bromides, iodides, and chlorides, and occurred cleanly to produce O heterocycles.<sup>14</sup> In general, a catalyst loading of 2-5% was sufficient for formation of both diaryl and tert-butyl aryl ethers. Lower catalyst loads led to longer reaction times. A 1:1 or even a 1:0.5 ratio of Pd to ligand was sufficient. Entry 9 shows that yields are higher, temperatures are lower, and times are shorter than previous reactions conducted with BINAP15 or DPPF.13

With the correct ligand for diaryl ether formation, we prepared potential reaction intermediates. Palladium(0) complex {Pd- $[(P(Fc)(t-Bu)_2)]_2$  (5) was isolated in analytically pure form by reaction of ligand 4 with  $(\eta^3$ -allyl) $(\eta^5$ -cyclopentadienyl)Pd at room temperature or with Pd[(P(o-tolyl)<sub>3</sub>]<sub>2</sub> at 65 °C for 1 h. An X-ray diffraction study showed a perfectly linear geometry for 5 (Scheme 1).<sup>19</sup> Dimeric palladium-bromide complex {[Pd(P(Fc)- $(t-Bu)_2)(o-MeC_6H_4)(\mu-Br)]_2$  (6) was prepared by phosphine exchange between 4 and  $[(P(o-tolyl)_3)Pd(Ar)(\mu-Br)]_2$ . Aryl oxide complexes {Pd[P(Fc)(t-Bu)<sub>2</sub>](Ar)( $\mu$ -O-p-C<sub>6</sub>H<sub>4</sub>OMe)}<sub>2</sub> (Ar = o-MeC<sub>6</sub>H<sub>4</sub>, **7a**; Ar = p-MeC<sub>6</sub>H<sub>4</sub>, **7b**) were synthesized by addition of sodium aryl oxide to 6, formed in situ by the phosphine exchange in THF solvent. The X-ray structure (Scheme 1) of 7b shows square-planar Pd centers with a sum of the four angles at the metal equal to 361.7° and a dimeric core with a puckered geometry containing a Pd–O–Pd–O torsion angle of 33.2 °.19

Thermolysis of isolated palladium aryl oxide 7a at 70 °C for 30 min in the presence of 20 equiv of  $P(t-Bu)_3$  gave diaryl ether

in 95% yield (eq 2). This observation constitutes the first reductive



elimination of diaryl ether and a rare reductive elimination of ether with an unactivated aryl group.<sup>20</sup> Surprisingly, thermolysis of 7a without added  $P(t-Bu)_3$  gave diaryl ether in only 25% yield in the presence or absence of sodium aryl oxide, aryl bromide, or ligand 4 (eq 2). Similarly, 7a generated in situ by addition of sodium aryl oxide to 6 gave aryl ether in 22% yield. Finally, reaction of p-tolyl complex 7b in the presence of 10 equiv of  $P(t-Bu)_3$  gave diaryl ether in 25% yield. Ligand exchange presumably induces elimination of diaryl ether in the presence of added  $P(t-Bu)_3$ , consistent with lower reaction rates and lower yields with decreasing quantities of added  $P(t-Bu)_3$ . The instability of P(t-Bu)<sub>3</sub>-ligated aryl halide complexes prevented direct synthesis of  $P(t-Bu)_3$ -ligated aryl oxide complexes.

The contrast between the modest yield of ether from the stoichiometric reductive eliminations without added  $P(t-Bu)_3$  and the excellent yields of catalytic reactions with only 4 as ligand indicates that dimeric 6 and 7 are not the precise intermediates on the catalytic cycle. Indeed, the proposed catalytic cycle in Scheme 1 involves monomeric versions of the isolated arylpalladium complexes.<sup>21</sup> Monomeric complexes are almost certainly the intermediate because (1) reductive eliminations are more common from a single metal center, (2) lower yields and/or slower rates for the reductive elimination of sulfides and amines from dimeric vs monomeric Pd(II) thiolate and amido complexes have been observed previously,<sup>22,23</sup> (3) higher yields of the catalytic chemistry were observed at lower concentrations (82% at 0.2 M aryl halide vs 23% at 1 M aryl halide), and (4) <sup>31</sup>P NMR spectrometry showed that monomeric Pd(0) 5 was the resting state, creating low concentrations of arylpalladium intermediates and favoring reactions from monomeric species in solution.

The catalytic and stoichiometric results presented here contrast the more common C-C bond formation between aryl halides and phenoxides with use of more conventional arylphosphines.<sup>24-26</sup> The difference in products as a function of steric effects shows that changes in ligand size can dramatically change the chemoselectivity of coupling with phenols. Apparently, coordination of ligand 4 or  $P(t-Bu)_3^{27,28}$  to arylpalladium phenoxides makes reductive elimination of ethers much faster than it is from complexes containing more conventional arylphosphine ligands.

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Supporting Information Available: Experimental procedures, spectroscopic data, and analytical data for 2 and 4-7; X-ray diffraction data for 5 and 7b and literature references to previously reported products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Another possibility for forming the true intermediate is an exchange of phosphorus substituents by P-C cleavage processes to create small quantities of P(t-Bu)3 that are bound to the actual catalyst. However, higher yields and faster rates for the reactions of unhindered substrates with ligand **4** instead of  $P(t-Bu)_3$  rule out this possibility.

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<sup>(18)</sup> Only a trace of the more common product from C-C bond formation was present in the isolated material.

<sup>(19)</sup> Crystallographic characterization. For (5): monoclinic, C2/c, yellow (19) Crystanographic characterization for (3) inducting (22), yenow blade, a = 22.4159(2) Å, b = 10.1684(2) Å, c = 15.8735(2) Å,  $\beta = 106.9971-(2)^\circ$ , V = 3460.05(6) Å<sup>3</sup>, Z = 4, R(F) = 3.36%, GOF = 1.169. For (**7b**): monoclinic, C2/c, orange irregular block, a = 20.070(1) Å, b = 27.723(2) Å, c = 14.542(1) Å,  $\beta = 128.047(3)^\circ$ , V = 6372.1(7) Å<sup>3</sup>, Z = 8, R(F) = 0.056, GOF = 1.83