

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

Grace Mann,[‡] Christopher Incarvito,[†]
Arnold L. Rheingold,[†] and John F. Hartwig^{*,‡}

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.^{1–6} The importance of aryl ether substructures has created a synthetic challenge to prepare the aryl–oxygen linkage in a general fashion under mild conditions.^{7–11} Pd-catalyzed C–O coupling^{4,12–15} could be a solution to this synthetic problem, but the reductive elimination of acyclic ethers^{4–6} 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,^{4–6,13} 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*-butylphosphino)ferrocene) (1) in amination of aryl halides¹⁶ led us to seek improvements in aryl halide etherification using this ligand. The reaction in eq 1 containing catalytic amounts of Pd(OAc)₂ 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(C₆H₅)(O-*p*-C₆H₄OMe) (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

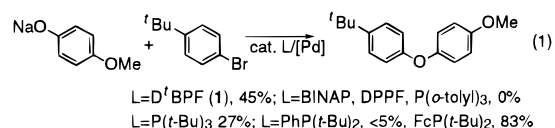
Table 1. Palladium-Catalyzed Conversion of Aryl Halides to Aryl Ethers with FcP(*t*-Bu)₂ or P(*t*-Bu)₃ As Ligand

| | ArX | NaOR | Product | cond. | Yield % ^a |
|----|-----|-------------------|---------|-------------|----------------------|
| 1 | | | | 9h, 80 °C | 82 |
| 2 | | | | 12h, 80 °C | 85 |
| 3 | | | | 12h, 110 °C | 74 |
| 4 | | | | 12h, 110 °C | 63 |
| 5 | | | | 24h, 110 °C | 81 ^b |
| 6 | | NaO- <i>t</i> -Bu | | 12h, 85 °C | 71 ^c |
| 7 | | NaO- <i>t</i> -Bu | | 12h, 100 °C | 68 ^{c,d} |
| 8 | | NaO- <i>t</i> -Bu | | 12h, 110 °C | 62 ^{c,d} |
| 9 | | NaO- <i>t</i> -Bu | | 6h, 85 °C | 84 |
| 10 | | NaO- <i>t</i> -Bu | | 3h, 80 °C | 78 |

^a All the reactions were performed in toluene solvent with a 0.2–0.3 M concentration of aryl halide, 2–5 mol % Pd(dba)₂, 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. ^b 5 mol % Pd(dba)₂ and 5 mol % P(*t*-Bu)₃ were used as catalyst. The product was isolated in >96% purity. ^c After heating, the reaction mixture was treated with CF₃CO₂H and CF₃SO₃H. ^d 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)¹⁷ and ferrocenyldi-*tert*-butylphosphine (4). These ligands were prepared, each in one step, and used in combination with Pd(OAc)₂ as catalyst for the reaction in eq 1. Reactions catalyzed by 3 and Pd(OAc)₂ gave less than



5% diaryl ether, but reactions catalyzed by 4 and Pd(OAc)₂ 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)₂ 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)₃ were used as catalyst (4 = 85%,

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[‡] Yale University.
[†] University of Delaware.

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