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Palladium-Catalyzed Formation of Diaryl Ethers from Aryl Bromides. Electron Poor Phosphines Enhance Reaction Yields

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Abstract: Aryl bromides were converted to diaryl ethers with sodium aryl oxides in the presence of catalytic amounts of $Pd(DBA)_2$ and DPPF. Isolated yields of over 90% were achieved in reactions with electron deficient aryl bromides and electron rich sodium aryl oxides. Electron poor DPPF derivatives led to increased reaction yields. © 1997 Elsevier Science Ltd.

The biaryl ether linkage is found in many important classes of molecules such as isodityrosine natural products, ligands for inorganic complexes, and polyphenylene oxide polymers. The importance of isodityrosines in the pharmaceutical industry has challenged synthetic chemists to devise mild methods for the synthesis of diaryl ethers.[1] The common reactions that generate diaryl ethers from aryl halides are nucleophilic aromatic substitution[2] and Ullmann couplings.[3] Unfortunately, nucleophilic aromatic substitutions are most favorable with the more expensive and less available aryl fluorides, and these reactions must be conducted in highly polar solvents that can be difficult to remove completely. Ullmann ether synthesis can be conducted with aryl bromide substrates, but these reactions involve high temperatures. Alternatives to diaryl ether formation in natural product synthesis that are stoichiometric in metal complex have also been developed.[4]

Our efforts in this area have been directed toward the use of palladium catalysts and chelating phosphine ligands to mediate the transformation of aryl halides to aryl ethers. Our group and subsequently Buchwald's, recently published the intermolecular formation of alkyl aryl ethers from aryl halides and alkoxides using palladium or nickel catalysts.[5-8] We observed that C-O bond-forming reductive elimination from DPPF-ligated Pd complexes was facile from complexes containing electron deficient aryl groups, but complexes containing electron neutral aryl groups did not undergo C-O bond-forming reductive elimination. From this observation, and parallel studies from our lab on C-N and C-S bond-forming reductive elimination, it is clear that the aryl group acts as an electrophile, while the alkoxide, amide, or thiolate acts as a nucleophile during the C-X bond-forming reductive elimination.[9] Because phenoxides are even less nucleophilic than alkoxides, the formation of diaryl ethers is a difficult problem to address with palladium-catalyzed chemistry, and high yields may require ligand modification. We report our results on diaryl ether formation from aryl halides and aryl oxides catalyzed by palladium complexes (Eq. 1), along with our initial results on how ligand modifications can improve reaction yields.[10]

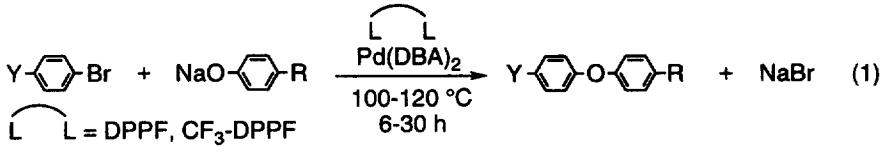
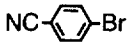
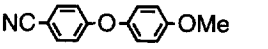
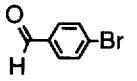
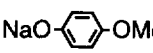
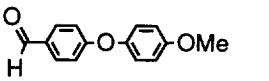
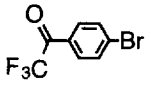
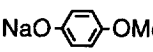
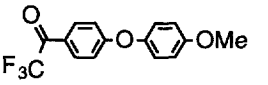
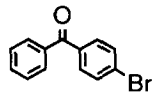
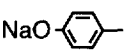
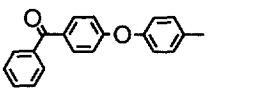
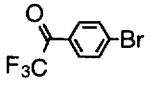
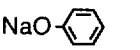
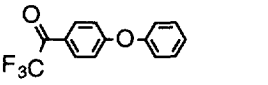
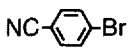
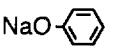
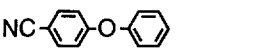
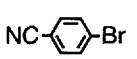
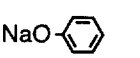
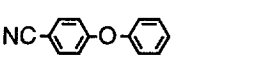


Table 1. Palladium-catalyzed Formation of Diaryl Ethers using DPPF as ligand.[a]

	ArBr	Aryl oxide	Product	Solvent	Yield[b]
1				tol/thf	92%
2				tol/thf	91%
3				tol/thf	67%
4				tol/thf	63%
5				tol/thf	76%
6				tol/thf	51%
7				glyme	29%

[a]Reactions were conducted with 5 - 10 mol % $Pd(DBA)_2$, 6 - 11 mol % DPPF and heated for 6 - 30 h at 100 - 120 °C in a 9:1 toluene/THF mixture. [b]Isolated yields from the average of two runs.

Reaction of aryl bromide (1 equiv) and sodium aryl oxide (1.2 equiv) in a mixture of toluene and THF solvent, in the presence of $Pd(DBA)_2$ (5 - 10%) and DPPF (6 - 11%), produced diaryl ethers in 29-92 % isolated yields at 100 - 120 °C after 6-30 h. (Table 1, DBA = dibenzylideneacetone, DPPF = 1,1'-diphenylphosphinoferrocene). All diaryl ethers were purified by column chromatography and gave suitable elemental analyses. Control experiments conducted in the same solvent mixture in the absence of the catalyst gave no diaryl ether. A catalyst loading of less than 5 % resulted in incomplete consumption of the starting aryl halide.

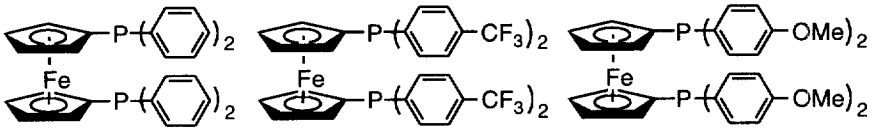
The yields for the palladium-catalyzed formation of diaryl ethers from aryl bromides varied with substrate. This reaction is thus far limited to electron deficient aryl bromides, but products such as 4-aryloxybenzaldehyde can be converted to 4-aryloxyphenol, an electron rich aryl ether, by Baeyer-Villager oxidation.[11] Isolated yields of the diaryl ether in excess of 90% were obtained when electron deficient aryl bromides were used in conjunction with electron rich aryl oxides. Yields were lower for reactions involving less electron rich aryl oxides when DPPF was used as ligand (entry 1 and 6). Reaction of the sterically hindered 2-chloro- or 2-methoxyphenol with 4-bromobenzonitrile under the standard reaction conditions did not form any diaryl ether. The use of a polyether solvent such as glyme also did not increase the yield of diaryl ether (entry 7).

The electronic properties of the DPPF ligand affected substantially the reaction yields, as shown in Table 2. In related studies on aryl halide aminations, ligand electronics did not have a dramatic affect on reaction yields.[12] The small affect that was observed showed slightly reduced yields for electron poor ligands, due to increased amounts of arene product formed from several reaction pathways. In the case of diaryl ether

Table 2. A Comparison of Different DPPF Derivatives for the Palladium-catalyzed Formation of Diaryl Ethers.[a]

	ArBr	Aryl oxide	Product	Ligand	Yield[b]
1	NC-C$_6$H$_4$-Br	NaO-C$_6$H$_5$	NC-C$_6$H$_4$-O-C$_6$H$_5$	DPPF	51%
2	NC-C$_6$H$_4$-Br	NaO-C$_6$H$_5$	NC-C$_6$H$_4$-O-C$_6$H$_5$	CF_3-DPPF[c]	74%
3	NC-C$_6$H$_4$-Br	HO-C$_6$H$_5$ + NaO-C$_6$H$_3$(t-Bu)$_2$ (2,6-t-Bu)	NC-C$_6$H$_4$-O-C$_6$H$_5$	CF_3-DPPF[c]	78%[e]
4	NC-C$_6$H$_4$-Br	NaO-C$_6$H$_5$	NC-C$_6$H$_4$-O-C$_6$H$_5$	OMe-DPPF[d]	8.5%[e]
5	NC-C$_6$H$_4$-Br	HO-C$_6$H$_5$ + Cs_2CO_3	NC-C$_6$H$_4$-O-C$_6$H$_5$	CF_3-DPPF[c]	24%

[a]Reactions were conducted with 5 - 10 mol % $Pd(DBA)_2$, 6 - 11 mol % DPPF in a 9:1 toluene:THF mixture and were heated for 6 - 30 h at 100 - 120 °C. [b]Isolated yields from the average of two runs. [c]CF_3-DPPF = 1,1'-bis[di((4-trifluoromethyl)phenyl)phosphino]ferrocene. [d]OMe-DPPF = 1,1'-bis[di((4-methoxy)phenyl)phosphino]ferrocene. [e]GC yield with reference to an internal standard.



DPPF CF_3-DPPF OMe-DPPF

synthesis, reduction through β-hydrogen elimination cannot occur and we expected that electron poor ligands would accelerate the reductive elimination process and increase reaction yields.

Indeed, the use of the electron poor *p*-CF_3-substituted DPPF, 1,1'-di[bis(4-(trifluoromethyl)phenyl)phosphino]ferrocene (CF_3-DPPF), increased reaction yields in reactions of the electron neutral aryl oxide with 4-bromobenzonitrile, as shown in Table 2. The use of the electron rich *p*-OMe-substituted DPPF, 1,1'-di[bis(4-methoxyphenyl)phosphino]ferrocene (OMe-DPPF), gave low reaction yields. For example, the reaction of NaOPh with 4-bromobenzonitrile catalyzed by a combination of $Pd(DBA)_2$ and DPPF occurred in only 51% yield (Entry 1), but the reaction catalyzed by combination of $Pd(DBA)_2$ and CF_3-DPPF[13] occurred in 74% yield (entries 2 and 3). When *p*-OMe-substituted DPPF[14] along with $Pd(DBA)_2$ were used as catalyst, the reaction occurred in only 8.5% yield (entry 4). In addition, reactions employing CF_3-DPPF as ligand were somewhat faster. Reactions catalyzed by CF_3-DPPF and $Pd(DBA)_2$ were complete in 20 h at 118 °C while the reactions catalyzed by DPPF required heating for 29 h at the same temperature. The use of Cs_2CO_3 as base (entry 5) gave lower reaction yields than did the use of pre-formed aryl oxide (entry 2) or aryl oxide and a hindered phenoxide base (entry 3).

In summary, we have developed a new method for the formation of diaryl ethers from aryl bromides using palladium catalysts and DPPF or modified DPPF ligands. Ligand electronic properties have a dramatic effect on the reaction yields in some cases, and this result may lead to the design of catalysts that will allow for a general metal-catalyzed method to form diaryl ethers. Further work will also be directed toward the

understanding of the carbon-oxygen bond forming step in the catalytic cycle and the effect of ligand electronic properties on this reaction.

Representative procedure: A screw-capped vial was charged with 30.4 mg (0.0530 mmol) of $Pd(DBA)_2$, 51.5 mg (0.0623 mmol) of CF_3-DPPF, 78.9 mg (0.680 mmol) of sodium phenoxide, and 98.9 mg (0.543 mmol) of 4-bromobenzonitrile in a mixture of toluene and THF (9 mL/1 mL). The vial was immersed in a 120 °C oil bath for 20 h. After this time the solvent was removed, and the crude material was adsorbed onto silica, and the product, 4-phenoxybenzonitrile, (81.5 mg, 79.6%) was isolated by elution with 20:1 hexanes/ethyl acetate.

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