Unusual in Situ Ligand Modification to Generate a Catalyst for Room Temperature Aromatic C−O Bond Formation

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The lifetime of a catalyst is generally controlled by its decomposition pathways, such as ligand degradation. Generally, one seeks to identify these decomposition pathways and to then prevent them. We report an unusual example of the opposite scanario: a surprising in situ structural change that transforms a phosphine-ligated, transition-metal complex displaying low catalytic activity into another system exhibiting high activity. Identification of the modified catalyst and independent synthesis of it has led to a series of room-temperature couplings of aryl bromides with phenoxides, alkoxides, and siloxides, including cyclizations to form oxygenated heterocycles. Our results emphasize that many factors underlie apparent catalyst structure−reactivity relationships, including the potential to form unexpected complexes displaying high activity.

Mild, aromatic carbon−oxygen bond formation is a difficult transformation. For reactions of unactivated aryl halides, direct, uncatalyzed substitutions and copper-mediated couplings typically require temperatures of 100 °C or greater.[1−3] Diazotization and displacement with oxygen nucleophiles is generally limited to phenol synthesis and uses stoichiometric amounts of copper in its mildest form.[4] We recently reported the first palladium catalysts for the formation of diaryl and alkyl aryl ethers from unactivated aryl halides.[5] Yet, our system, as well as that reported recently by Buchwald,[6] required temperatures similar to those for copper-mediated processes.[1−3,7,8]

We felt that a deep-seated understanding of how catalyst structure affects reactivity could improve this process. Two results suggested that the system we recently studied was more complex than expected and that it would serve as an illustrative example of how in situ changes in structure can affect catalyst activity. First, reactions of aryl halides with sodium phenoxides catalyzed by complexes generated from $Pd(dba)_2$ and $PFc(t\text{-}Bu)_2$ occurred in high yields, but stoichiometric reductive elimination from the presumed arylpalladium phenoxide intermediate occurred in much lower yields (Scheme 1).[5] Second, careful monitoring of the catalytic reactions (Figure 1) showed that aryl halide was consumed initially without formation of diaryl ether and that the time dependence for formation of this product was sigmoidal. These results suggested the presence of an induction period.

Several mechanistic hypotheses were tested to explain one or both of these observations. First, we considered whether cleavage of the isolated dimer was slower than direct decomposition to form products other than diaryl ether, a hypothesis that would explain the discrepancy in yields. Thus, we conducted the crossover experiment in eq 1. Thermolysis of the two arylpalladium phenoxides would produce two ether products if dimer cleavage prior to reductive elimination was irreversible, but it would produce four diaryl ethers if dimer cleavage was rapid and reversible. This experiment produced nearly equal amounts of the four ethers, suggesting that dimer cleavage was reversible, and that another explanation for the discrepancy was required.

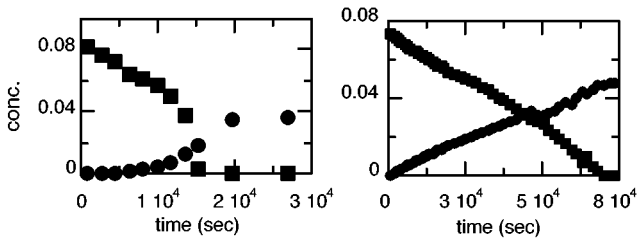
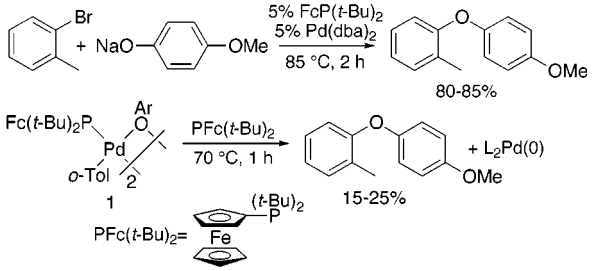
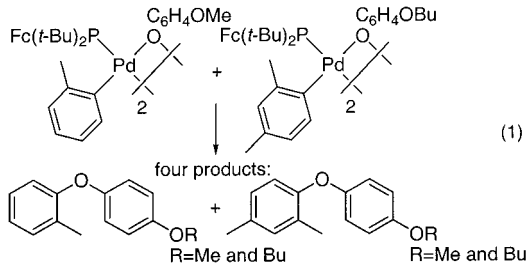


Figure 1. Decay of ArBr and appearance of ArOAr′ vs time for reaction of 2-bromotoluene (0.08 M) with $NaOC_6H_4$-4-OMe catalyzed by 5% $Pd(dba)_2$ and 7.5% $PFc(t\text{-}Bu)_2$ at 70 °C (left) and catalyzed by 5% $Pd(dba)_2$ and $Ph_5FeP(t\text{-}Bu)_3$ at 40 °C (right).

Scheme 1





Second, we evaluated whether the active catalyst was a species other than that generated by simple ligation of $PFc(P\text{-}t\text{-}Bu)_2$ to the metal center. We evaluated possible ligand modifications by heating palladium acetate with 20 equiv of ligand relative to palladium and sodium *tert*-butoxide in chlorobenzene at 110 °C. During this experiment with large amounts of phosphine, we could analyze for changes in the ligand structure. We observed the remarkable catalytic perphenylation of the unsubstituted cyclopentadienyl group (eq 2).[9] This material was formed in essentially quantitative yields, and was isolated in 60−70% yields. This result suggested that $FcP(t\text{-}Bu)_2$ underwent arylation in the catalytic system to provide the ligand of the active catalyst.

Several additional results indicated that arylated ferrocenyl ligands were components of the active catalyst. For example, the catalytic reaction of excess ligand with PhCl using phenoxide as base provided several arylated ligands, including $Ph_5FcP(t\text{-}Bu)_2$. In addition, ^1H and ^{31}P NMR spectra of reactions of PhBr with

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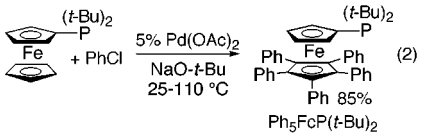
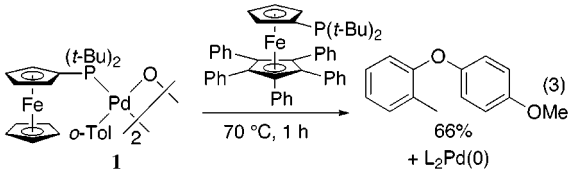


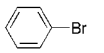
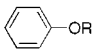
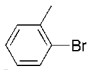
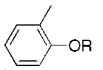
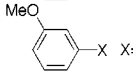
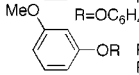
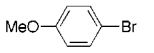
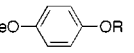
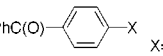
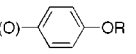
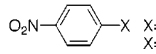
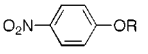
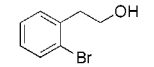
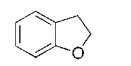
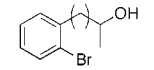
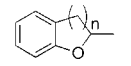
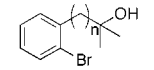
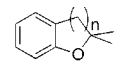
NaO-*t*-Bu using a more conventional 1.1:1 ratio of FcP(*t*-Bu)$_2$ to Pd(dba)$_2$ as catalyst showed the decay of FcP(*t*-Bu)$_2$ and growth of $Ph_5FcP(t\text{-}Bu)_2$ and its Pd(0) complex $\{Pd[Ph_5FcP(t\text{-}Bu)_2]\}_2$. This complex was identified by the formation of $[Pd(PCy_3)_2]$ and additional free $Ph_5FcP(t\text{-}Bu)_2$ after treatment of the reaction solution with PCy_3 and by independently generating the same species by addition of ligand to Pd(dba)$_2$ at room temperature or CpPd(allyl) at 50 °C. Finally, reactions catalyzed by a combination of Pd(dba)$_2$ and $Ph_5FcP(t\text{-}Bu)_2$ as ligand occurred more rapidly than those employing PFc(*t*-Bu)$_2$, occurred in higher yield, and occurred without a large induction period (Figure 1). Reaction of 2-MeC_6H_4Br with NaOC_6H_4-*p*-OMe at 80 °C gave complete reaction after 1 h, and reaction at room temperature gave quantitative yields after 70 h.

If complexes containing $Ar_5FcP(t\text{-}Bu)_2$ as ligand are the true catalysts in the formation of diaryl ethers, then reaction yields for reductive elimination of diaryl ether should be higher when this ligand is bound to the arylpalladium phenoxide fragment. Due to the steric properties of this ligand, we have not been able to isolate arylpalladium halide or phenoxide complexes containing this ligand. However, addition of a 20-fold excess of $Ph_5FcP(t\text{-}Bu)_2$ to FcP(*t*-Bu)$_2$-ligated phenoxide **1** led to the reductive elimination of diaryl ether with rates that were faster and with yields that were higher than in the absence of this ligand. Reaction at 70 °C for 1 h occurred in 66% yield (eq 3). Reactions conducted with a smaller excess of $P(Ph_5Fc)(t\text{-}Bu)_2$ gave lower yields and slower rates. Endothermic ligand exchange to generate the $Ph_5FcP(t\text{-}Bu)_2$ analogue of **1** and rapid reductive elimination from this complex accounts for this observation.



The use of isolated $Ph_5FcP(t\text{-}Bu)_2$ in combination with a palladium catalyst precursor may then provide faster rates and higher yields than previous catalysts for this process. Indeed, we found that a combination of $Ph_5FcP(t\text{-}Bu)_2$ and Pd(dba)$_2$ catalyzes the formation of several types of aromatic carbon−oxygen bonds at room temperature. Table 1 summarizes this chemistry. As stated above, reaction of 2-MeC_6H_4Br with NaOC_6H_4-*p*-OMe occurred at room temperature in 70 h. Reaction of NaO-*t*-Bu with a variety of electron-neutral or electron-poor aryl bromides also occurred at room temperature. Deactivated substrates such as 4-bromoanisole required heating but gave the protected phenol as product in good yield. Similar chemistry occurred with the siloxide NaOSi(*t*-Bu)Me$_2$ to give TBS-protected phenol products. Again, reactions with electron-neutral or electron-poor substrates occurred in good yield. The most deactivated substrates gave low yields. Intramolecular formation of aryl alkyl ethers also occurred under these conditions. Entries 15−19 show examples of cyclizations to form oxygen heterocycles rapidly at room temperature. Importantly, this ligand system allows for the reaction of substrates that bear β-hydrogens. The reactions in entries 17 and 19 occur in much higher yield than observed previously.[10] In all cases, we compared qualitatively the rates of these reactions to those catalyzed by Pd(dba)$_2$ and FcP(*t*-Bu)$_2$ or by 2-methyl, 2-(di-*tert*-butylphosphino)-1,1-biphenyl;[6] little or no reaction occurred at room temperature with these ligands. Although we have not explored in detail the activity of catalysts generated from $Ph_4FcP(t\text{-}Bu)_2$, preliminary data have suggested that these complexes are much less reactive than those generated from $Ph_5FcP(t\text{-}Bu)_2$.

Table 1. Aromatic C−O Bond Formation Catalyzed by 5 mol % Pd(dba)$_2$/$Ph_5FcP(t\text{-}Bu)_2$ [a]

Entry	Aryl Halide	Product	Temp, Time	Yield
1		 R=O-*t*-Bu	RT, 17 h	96%
2		 R=O-*t*-Bu	RT, 14 h	79%
3		R=OTBS	RT, 16 h	99%
4		 R=OC_6H_4-4-OMe	RT, 70 h	99%
5	X=Br	R=O-*t*-Bu	RT, 19 h	77%
6		R=OTBS	80 °C, 12 h	79%
7	X=Cl	R=O-*t*-Bu	80 °C, 6 h	92%
8		R=OTBS	80 °C, 12h	78%
9		 R=O-*t*-Bu	80 °C, 12h	67%
10	 X=Br	 R=O-*t*-Bu	RT, 6 h	98%
11	X=Br	R=OTBS	RT, 21 h	94%
12	X=Cl	R=O-*t*-Bu	RT, 4 h	98%
13	 X=Br	 R=O-*t*-Bu	RT, 9 h	98%
14	X=Cl	R=O-*t*-Bu	RT, 5 h	93%
15			80 °C, 0.5 h	58%
16			n=1, RT, 5 h	59%
17			n=2, RT, 0.5 h	64%
18			n=1, RT, 15 h	77%
19			n=2, RT, 10 min	93%

[a] Reactions conducted in toluene solvent with 0.5 mmol aryl halide substrate and 1.2 equiv of alkoxide or siloxide in 2 mL of toluene. Isolated yields are an average of at least two runs.

Modification of this ligand structure by altering the steric and electronic properties of the Cp-bound aryl group will be investigated in the future to improve catalyst activity further. Moreover, the stability of the current catalysts and the mild conditions for the process should allow for future kinetic studies on this process and for future synthetic studies on related couplings.

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Supporting Information Available: Ligand preparation procedures and representative catalytic reaction procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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