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Carbon–Heteroatom Bond-Forming Reductive Elimination. Mechanism, Importance of Trapping Reagents, and Unusual Electronic Effects during Formation of Aryl Sulfides
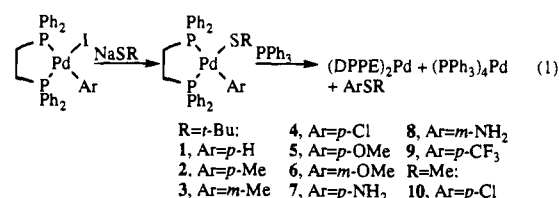
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Reductive elimination is perhaps the most fundamental reaction in organometallic chemistry and provides the key bond-forming step in catalytic transformations ranging from small-scale laboratory preparations to large-scale manufacturing.[1] Reductive elimination reactions that form carbon–carbon and carbon–hydrogen bonds are now common.[2] Analogous reactions that form carbon–heteroatom bonds are rare,[3-5] particularly those that form simple sulfides, ethers, and amines.[6] We felt that the handful of palladium-catalyzed hetero-cross-coupling reactions[7-16] pointed toward systems that would undergo this undeveloped but potentially fundamental primary reaction. We report the preparation of palladium thiolato aryl complexes [(DPPE)Pd(SR)(Ar)] that undergo reductive elimination of alkyl aryl sulfides, the importance of effective trapping reagents for high product yields, and our initial mechanistic studies that suggest strikingly different electronic properties of the transition state from those involved in more common C–C and C–H bond-forming reductive eliminations.

Addition of sodium alkyl thiolates to the palladium aryl halide complexes provided aryl *tert*-butyl thiolato complexes **1–8** and **10** that were stable at room temperature (eq 1). These com-

R=*t*-Bu: **4**, Ar=*p*-Cl   **8**, Ar=*m*-NH₂
1, Ar=*p*-H   **5**, Ar=*p*-OMe   **9**, Ar=*p*-CF₃
2, Ar=*p*-Me   **6**, Ar=*m*-OMe   R=Me:
3, Ar=*m*-Me   **7**, Ar=*p*-NH₂   **10**, Ar=*p*-Cl

pounds were isolated as yellow hydrocarbon-soluble crystalline solids in 40–70% yields. We also cleanly generated C_6D_6 solutions of complex **9** possessing a *p*-CF₃ substituent that was too reactive to be isolated. All of the compounds are only mildly air sensitive and are water stable. All substitution reactions occurred in >90% yield when monitored by ^{31}P NMR spectroscopy.

Warming a benzene solution of **1–10** at 50 °C in the presence of triphenylphosphine formed the corresponding alkyl aryl sulfide in quantitative yield and the two Pd(0) phosphine compounds (eq 1).[17] In the absence of a reagent to trap the Pd(0) fragment, the sulfide product was formed in only 45–65% yield (^1H NMR spectroscopy with internal standard), with competitive formation of biaryl products derived from the palladium-bound aryl group and the phosphine phenyls.[18] Addition of 10 equiv (0.12 M) of diphenylacetylene or *p*-tolyl iodide as trapping reagent gave >95% yield of the desired sulfide and formed the Pd(0) acetylene complex as the organometallic product or regenerated the aryl iodide complex used to synthesize the thiolato aryl complexes. Reaction rates in the presence of acetylene or aryl halide were within 20% of those measured with added phosphine. Thus, reductive elimination does not involve the added reagent, but high yields of the desired organic product require efficient trapping of the palladium fragment [(DPPE)Pd]. The addition of aryl halide, substitution of thiolate for the resulting palladium halide, and reductive elimination of sulfide constitute catalytic formation of aryl sulfides from aryl halides and main group thiolates.[7-11] Addition of the potential radical inhibitors dihydroanthracene or tri-*o*-tolylphoshine alone gave similar products to reactions conducted in the absence of any added reagent. Quantitative rate studies were not conducted, but reactions run side by side showed no effect of these reagents on reaction rates in the presence or absence of added PPh₃.

Carbon–carbon bond-forming reductive elimination reactions have been shown to occur from five-coordinate species in analogous nickel systems[19] and to be accelerated by alkyl iodides in Pd(II) systems.[20-22] However, the sulfide eliminations were zero order in trapping reagent. Reaction rates were clearly independent of phosphine concentration, and no evidence for the buildup of a five-coordinate species was observed at concentrations up to 0.25 M. Reaction from a three-coordinate species is more difficult to probe, and the presence or absence of such a complex cannot be deduced from rate behavior because of the ligand chelation. Therefore, we prepared the *o,o*-bis-(diphenylphosphino)benzene compound [L₂Pd(C₆H₄-*p*-Me)(S-*t*-Bu)] (**11**) containing a more rigid chelate. Should the mechanism involve a three-coordinate species, then complex **11** would undergo elimination at a slower rate than the DPPE analog. Instead, the rate of sulfide elimination from **11** was $(1.9 \pm 0.1) \times 10^{-4}$, or roughly 1.5 times faster than that from **2**, due to the slightly weaker electron-donating ability of this phosphine. Although these data do not rigorously rule out phosphine dissociation that would reversibly open the stable five-membered chelate ring before elimination from a three-coordinate species, they do suggest direct elimination from the isolated and observed four-coordinate complex.

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(17) Thermodynamically, the mixed phosphine complex [Pd(PPh₃)₂-(DPPE)] is less favorable than the two homoleptic compounds. Addition of 1 equiv of (DPPE) to Pd(PPh₃)₄ gives 0.5 equiv of Pd(DPPE)₂ and remaining Pd(PPh₃)₄. At high concentrations of PPh₃, some mixed complex can be detected.

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Table 1. Rate Constants (s^{-1} × 10^4) as a Function of Aryl Substituent

substituent	k	substituent	k
p-H	2.4	*m*-OMe	2.4
p-Cl	1.1	*p*-NH$_2$	0.36
p-Me	1.2	*m*-NH$_2$	2.5
m-Me	2.3	*p*-CF$_3$	14
p-OMe	0.33		

Kinetic experiments indicate that there are at least two reaction pathways with different rate-determining steps in the absence of trapping reagent. One pathway is the desired sulfide elimination, while others lead to products including organic biaryl compounds. The rate of reaction of phenyl compound **1** in the absence of trap was $(3.5 \pm 0.5) \times 10^{-4}$ s^{-1}, although it deviated from first-order behavior after two half-lives. For this sample, the yield of phenyl *tert*-butyl sulfide was 65%. The side reactions were suppressed by adding PPh$_3$, PhCCPh, or ArI as trapping reagents, since sulfide yields were quantitative. The rate of reaction of **1** in the presence of 0.06 M PPh$_3$ was $(2.4 \pm 0.2) \times 10^{-4}$, or 69% of that in the absence of trap. Thus, the trapping reagents inhibit all pathways but the desired sulfide elimination reaction, rather than affecting the selectivity of an intermediate formed after the rate-determining step or accelerating the rate of the sulfide elimination.

Warming compounds **2**−**8** in the absence of trapping reagent revealed an exchange of the phosphine and palladium-bound aryl groups that occurs on a time scale similar to that of the reductive elimination reaction. Tolyl compound **2** yielded phenyl- as well as *p*-tolyl *tert*-butyl sulfide product in a 1.3:1 ratio (65% overall yield) in the absence of trap. Careful monitoring of the reaction allowed observation of increasing ratios of rearranged to unrearranged starting complex in addition to increasing ratios of phenyl to *p*-tolyl sulfide product. The mechanism for biaryl formation and aryl exchange is not clear at this point, but exchange behavior with added dihydroanthracene or tri-*o*-tolylphosphine that was similar to that with no trap suggests the absence of radical pathways. Importantly, added trapping reagent shuts down this exchange process and allows clean formation of substituted aryl sulfides.[23]
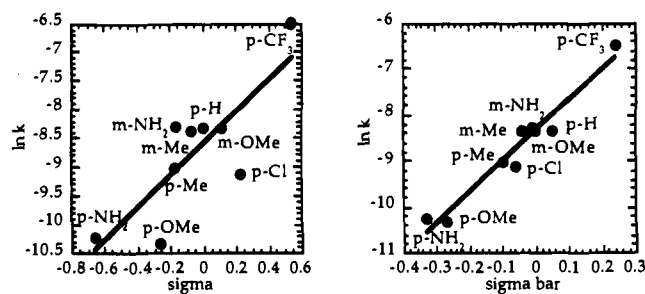
Simple, nucleophilic aromatic substitution reactions display a strong rate acceleration by electron-withdrawing substituents at the aromatic ring.[24] Carbon−carbon and carbon−hydrogen bond-forming reductive eliminations are accelerated by electron-donating groups.[25] We sought to determine if these carbon−heteroatom bond-forming reductive eliminations would display electronic effects more similar to an intramolecular nucleophilic aromatic substitution or to well-known reductive eliminations that form nonpolar bonds.

In order to address this issue, we prepared a number of complexes containing substituted aryl systems and measured the rates of reductive elimination in each case. The effects of varying the aryl substituent on reaction rates were similar to, but smaller than those for uncatalyzed nucleophilic aromatic substitution by thiolates. Moreover, the trends were different from those believed to exist for C−C and C−H bond formations. Table 1 shows the reaction rates for compounds **1**−**9** and demonstrates that electron-donating substituents have an overall decelerating effect on the reaction rate. The order of reaction

Figure 1. Free energy relationships for the reductive elimination reaction.

rates for five of the *p*-substituted compounds was *p*-CF$_3$ > *p*-H > *p*-Me > *p*-OMe ≈ *p*-NH$_2$ and showed the rough trend, although *p*-Cl compound **4** underwent reductive elimination with a rate that was slower than that of the parent phenyl compound, despite its small, positive σ value. The left plot in Figure 1 shows that the substituent effects do not follow a linear free energy relationship with the simple σ values derived from benzoic acid acidity. Instead, a synthetic σ value that is constructed from separate resonance and inductive parameters, with the resonance effect weighted more heavily than the inductive effect, provides the more linear relationship in the right of Figure 1. The treatment of these data parallels studies describing the separation of inductive and resonance effects in the reactions of organic compounds[24,26] and provides the inductive and resonance ϱ values of $\varrho_I = 1.7$ and $\varrho_{R^-} = 5.0$ ($R = 0.97$).[27]

The sulfide elimination from **2** provided a rate ((8.9 ± 0.9) × 10^{-5}) in THF solvent similar to that in benzene. The absence of a measurable solvent effect is consistent with modest ϱ values, although solvent effects are typically less pronounced for reactions of organometallic compounds than for purely organic molecules.

In conclusion, we have presented a rare example of carbon−heteroatom bond-forming reductive elimination that is a crucial step in the catalytic hetero-cross-coupling reactions catalyzed by palladium compounds. In contrast to C−C bond-forming eliminations, a trapping reagent for [(DPPE)Pd] is necessary for high yields. Moreover, it is clear from our preliminary mechanistic data that the intimate mechanism for these C−X bond-forming processes differs markedly from more common C−C and C−H bond-forming reactions, and the rate acceleration by electron-withdrawing groups points to a transition state that contains some character analogous to nucleophilic aromatic substitutions.

(23) Exchange between phosphine- and palladium aryl groups has been observed in [Pd(PPh$_3$)$_2$Ar(I)] compounds and was inhibited by added phosphine. In our case, the presence of a chelating ligand rules out inhibition by added phosphine that displaces a dissociative pre-equilibrium, as was suggested in ref 18.

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