Palladium-Catalyzed Direct α-Arylation of Ketones. Rate Acceleration by Sterically Hindered Chelating Ligands and Reductive Elimination from a Transition Metal Enolate Complex

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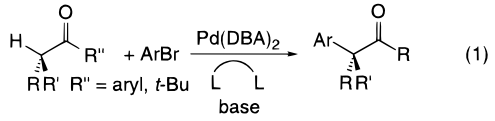
The palladium-catalyzed coupling to form C−C bonds between aryl and vinyl halides or triflates and a carbon nucleophile is one of the most widely used transition-metal-catalyzed reactions.[1−3] However, cross-coupling reactions involving ketone enolates as the nucleophile are limited, and typically occur in modest yields.[4] Further, many transition metal-catalyzed approaches to ketone arylation using preformed main group enol ethers[4−14] or using bismuth or lead reagents[15,16] have been investigated, and each has its drawbacks.[13] The simple direct reaction of an aryl halide and a ketone with base in the presence of a transition metal catalyst has not been reported. Given the success of our recent palladium-catalyzed chemistry that produces aryl amines from aryl halides, amines, and an appropriate base,[17,18] and the similar pK_a values of arylamines and ketones,[19] it seems likely that our amination procedures could be extended to the direct arylation of ketones. We report here our initial results on the arylation of ketones to form secondary, tertiary, and quaternary carbon centers, along with independent generation of the palladium enolate intermediate and the unusual direct observation of its C−C bond-forming reductive elimination.

The catalytic chemistry we report is shown in a general form in eq 1, and specific examples and the yields of isolated pure products are provided in Table 1. This chemistry resulted from an attempt to conduct palladium-catalyzed aminations of aryl halides in acetone solvent. The reaction procedure is simple,



(1)

and although conducted under N_2 with solvents distilled under N_2, the reaction is not highly air-sensitive. The addition of the ketone, typically used directly from a commercial source, to a combination of $Pd(DBA)_2$ and ligand, solvent, and either $KN(SiMe_3)_2$ or NaO-*t*-Bu base generated the aryl ketone in high yields after heating in refluxing THF for several hours and after silica gel chromatography. Reactions involving electron neutral or electron rich aryl halides were more selective for monoarylation when $KN(SiMe_3)_2$ was used. With electron poor aryl halides, NaO-*t*-Bu gave good selectivity and did not lead to direct decomposition of the aryl halide.

Table 1. Palladium-Catalyzed a-Arylation of Ketones

Entry	Aryl Halide	Ketone	Product	Procedure[a]	Yield[b]
1				A B	84% 76%
2				A B	71% 47%
3				A	79%
4				C	55%
5				A	94%
6				A	85%
7				D	73%
8				A	69%
9				A	79%
10				A	68%
11				A	57%
12				A	51%

[a] Procedures: (A) 7.5 mol % $Pd(DBA)_2$, 9 mol % DTPF, 2.2 equiv of $KN(SiMe_3)_2$, refluxing THF, 0.75 h: (B) 7.5 mol % $Pd(DBA)_2$, 9.0 mol % DPPF, 2.2 equiv of $KN(SiMe_3)_2$, refluxing THF, 2 h; (C) 10 mol % $Pd(DBA)_2$, 15 mol % DTPF, 1.2 equiv of $KN(SiMe_3)_2$, refluxing THF, 5 h; (D) 7.5 mol % $Pd(DBA)_2$, 9.0 mol % DTPF, 2.2 equiv of NaO-*t*-Bu, refluxing THF, 0.75 h. [b] Yields are for pure isolated product and are an average of 2 runs on a 1 mmol scale.

DPPF-ligated palladium complexes (DPPF = bis(diphenylphosphino)ferrocene) were active catalysts for this transformation. However, we also surveyed a combination of several DPPF derivatives as ligands for the palladium catalysts and

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(21) 1,1′-Bis[bis(2-methylphenyl)phosphino]ferrocene. Ferrocene (2.280 g, 12.26 mmol) was mixed with 2.1 equiv of *n*-butyllithium (2.66 M in hexanes, 9.68 mL, 25.74 mmol), 2.1 equiv of TMEDA (3.88 mL, 25.74 mmol), and hexane (50 mL) in an oven dried flask fitted with a condenser, addition funnel, and an N_2 inlet. The reaction was heated to reflux for 5 h before being cooled to −40 °C. A solution of bis(2-methylphenyl)-chlorophosphine (6.400 g, 25.73 mmol) in THF (15 mL) was added dropwise to the reaction over 10 min. The reaction was allowed to warm slowly to room temperature and stirred for 12 h. The crude reaction was concentrated to approximately 20% of its original volume, and the yellow solids were filtered. The solids were then washed with 1 M HCl (20 mL), H_2O (20 mL), ethanol (20 mL), and ether (20 mL). The solids were dried under vacuum to give 6.214 g of product (83% yield). ^{1}H NMR ($CDCl_3$): δ 7.17−6.96 (m, 16H), 4.25 (bs, 4H), 4.06 (bs, 4H), 2.46 (s, 12H); ^{13}C-{^{1}H} NMR ($CDCl_3$): δ 141.64 (d, J = 26.3 Hz), 137.51 (d, J = 10.6 Hz), 133.29, 129.41 (d, J = 5.1 Hz), 128.4, 125.50, 76.52, 74.15 (d, J = 15.1 Hz), 72.13 (d, J = 3.0 Hz), 21.29 (d, J = 21.6 Hz); ^{31}P{1H} NMR: ($CDCl_3$): δ −36.81. Anal. Calcd. for $C_{38}H_{36}FeP_2$: C, 74.76; H, 5.94. Found: C, 74.31; H, 6.08.

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found that the sterically hindered chelating ligand 1,1′-bis(di-*o*-tolylphosphino)ferrocene[20,21] (DTPF) gave faster reaction rates and higher yields than did DPPF. For example, on a small scale, the reaction of phenyl bromide with acetophenone was complete after 40 min for reactions involving DTPF, while aryl halide remained in identical reactions involving either DPPF or BINAP. As shown in entries 1 and 2, the final yields were also 10−25% higher when using DTPF than when using DPPF. Although DTPF is not commercially available, it is trivial to prepare by methods analogous to those used to prepare DPPF,[22] and we readily prepared multigram quantities in high yield. Thus, we used this ligand for the majority of our studies, although useful yields were observed when using DPPF.

As one can see from Table 1, this chemistry is general for alkyl aryl ketones. Aryl iodides (entry 3) and aryl bromides are both accommodated in the coupling process. Sterically hindered (entry 5), electron poor (entry 7), and electron rich (entry 8) aryl halides are all viable substrates. Both aryl and heteroaryl ketones give moderate to good yields. We have not extensively studied this chemistry for dialkyl ketones, but entry 12 shows that this class of ketones can participate in the coupling process.

It is unusual for the coupling chemistry to occur with ketones that would generate palladium−enolate intermediates bearing β-hydrogens. Transmetalation of tin reagents typically requires an open coordination site in the palladium square plane for rapid reactions,[23,24] and therefore, monodentate phosphines are the best ligands for reactions with tin enolates. However, monodentate ligands allow for β-hydrogen elimination since they can dissociate to generate the open coordination site required for this competing side reaction.[25] In our case, the use of alkali enolates allows for the transmetalation to occur rapidly for complexes containing chelating phosphines and, therefore, allows for the use of chelating phosphines that retard β-hydrogen elimination relative to reductive elimination.

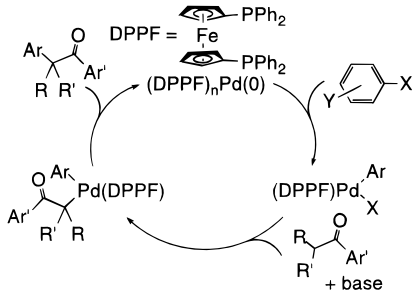
As a result, it seemed likely that our chemistry involving DPPF and its derivatives could occur in high yields for enolates that bear β-hydrogens. Indeed, this chemistry was conducted successfully with ethyl phenyl ketone using a catalyst combination of $Pd(DBA)_2$ and either DPPF or DTPF (entry 2).

Considering the instability of tertiary alkyl complexes toward decomposition by either β-hydrogen elimination or M−C bond homolysis, it is remarkable that these enolate arylations occur intermolecularly to form quaternary centers in useful yields. Reaction of bromobenzene with isobutyrophenone catalyzed by 10 mol % $Pd(DBA)_2$ and DTPF in the presence of $KN(TMS)_2$ gave the arylation product in 55% yield. The yield using DPPF was a substantially lower by GC, and the reaction with this catalyst was not pursued. Stereoselective enolate couplings with chiral bidentate ligands should be possible in future studies.

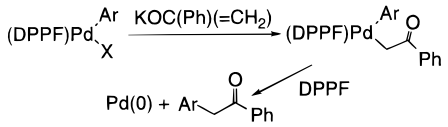
A likely catalytic cycle is shown in Scheme 1. No DBA is observed by GC during these reactions. It is consumed in the reaction medium and is unlikely to participate in these reactions, except in the initial stages. Oxidative addition of the aryl halide to a (DPPF)Pd(0) complex, followed by reaction of the aryl halide with the alkali enolate would form the enolate aryl complex. C−C bond-forming reductive elimination would occur to form the product, but such a reductive elimination involving an enolate complex is uncommon.

Thus, we conducted some initial studies shown in Scheme 2 to observe directly the enolate aryl complex that would undergo this unusual stoichiometric reaction. Indeed, reaction of the potassium enolate of acetophenone with (DPPF)Pd(p-C_6H_4-*t*-Bu)Br[26] cleanly generated a new complex that was isolated in 45% yield, as a solid containing roughly 10% of Pd(0)−DPPF, but was definitively characterized by $^{31}P\{^1H\}$ and ^1H NMR spectroscopies. Two new doublets (δ 20.0, 18.7; J_{PP} = 25.5 Hz) were observed by ^{31}P NMR spectroscopy, and a new *tert*-butyl group was observed, along with a new set of DPPF Cp resonances. Most important, a ^1H resonance with intensity of two hydrogens was observed at δ 3.40. This signal was a single resonance (confirmed at different magnetic fields) that was a virtual triplet (J_{HP} = 10.7), showing coupling to the two phosphine ligands that was confirmed by $^1H\{^{31}P\}$ NMR spectroscopy. This resonance is, therefore, due to a metal-bound methylene and indicates that the enolate is C-bound. This complex underwent reductive elimination at room temperature to form the α-aryl ketone in 74−87% yield (^1H NMR with internal standard) with a half-life of 2 h at room temperature or with complete consumption of enolate after 1 h at 50 °C. This rapid reductive elimination prevented the isolation of the enolate complex in pure form at this time but did demonstrate that this complex is most likely the C−C bond-forming intermediate in the catalysis.

Scheme 1



Scheme 2



A number of mechanistic questions need to be addressed in the future. The product ketone contains α-hydrogens, and it is not clear whether the high selectivity for monoarylation results from steric or electronic effects. Furthermore, the origin of the rate acceleration by DTPF relative to DPPF is not clear; neither nor are the reactions that lead to catalyst deactivation. These issues, as well as broadening the scope of the carbonyl substrates will be the subject of future studies.

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Supporting Information Available: A representative procedure for the ketone arylation process, literature references to the aryl ketone products, and ^1H NMR, ^{13}C NMR, and mass spectra of the arylation products (42 pages). See any current masthead page for ordering and Internet access information.

Note Added in Proof: An example of a related ketone arylation appeared after submission of this manuscript (Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1740−1741), and Buchwald has reported related chemistry that uses BINAP as ligand (Palucki, M.; Buchwald, S. J. *J. Am. Chem. Soc.* In press).

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