Palladium-Catalyzed α-Arylation of Ketones

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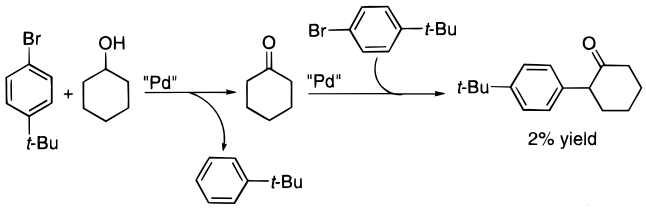
The synthesis of α-aryl ketones has received much attention over the past two decades.[1] A number of stoichiometric arylating reagents have been successfully developed for this purpose; however, their utility is decreased because each synthesis of an α-aryl ketone requires the synthesis of a different arylating reagent.[2,3] In contrast, the direct coupling of aryl halides with ketones would provide a convenient method for the synthesis of α-aryl ketones. Semmelhack et al. have demonstrated that $Ni(COD)_2$ (COD = cyclooctadiene) catalyzes the intramolecular coupling of an aryl iodide with a ketone enolate.[4] While there are reports of Pd- or Ni-catalyzed intermolecular coupling reactions that afford α-aryl ketones, these methods require the use of stoichiometric amounts of tin reagents and/or the use of enol ether, enamine, or α-chloro ketone derivatives instead of the ketone.[5,6] Thus, a general method which utilizes readily available starting materials and affords products in high regioselectivity has not been realized. Herein, we describe a novel Pd-catalyzed method for the direct cross coupling of aryl halides with ketones.

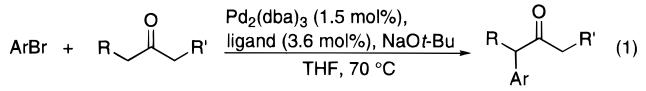
We have previously shown that a mixture of $Pd_2(dba)_3$ (dba = dibenzylidene acetone) and Tol-BINAP catalyzes the coupling of sodium alkoxides (generated *in situ* by reaction of the alcohol with NaH) with electron-deficient aryl bromides to form aryl ethers.[7] In addition, we found that reaction of electron neutral or electron-rich aryl bromides with sodium alkoxides (generated from primary or secondary alcohols) provides the reduced arene as the major product with concomitant oxidation of the alcohol

Scheme 1



to the corresponding ketone. It was during this latter study that we unexpectedly observed small amounts of α-aryl ketone products. For example, GC analysis of the crude reaction mixture of the attempted Pd-catalyzed coupling of 1-bromo-4-*tert*-butylbenzene with cyclohexanol showed that *tert*-butylbenzene was the major product along with small amounts of 2-(4-*tert*-butylphenyl)cyclohexanone (2%), Scheme 1.[8]

Realizing the need for a general method for the synthesis of α-aryl ketones, we began to focus on optimizing the formation of this product. After some experimentation, we found that the combination of $Pd_2(dba)_3$ and Tol-BINAP or BINAP in the presence of NaO-*t*-Bu effectively catalyzes the desired coupling reaction, eq 1.[9] We found that 3 mol % Pd and 3.6 mol %



(1)

ligand were sufficient to obtain complete conversion of starting aryl bromide. Under the conditions employed, α-aryl ketones were not formed in the absence of catalyst. A broad study on the generality of this reaction was undertaken, and the results are shown in Table 1.[10,11]

As illustrated in Table 1, the Pd-catalyzed arylation of ketones provides a general method for obtaining a wide variety of α-aryl ketones. The mild reaction conditions are compatible with a wide variety of functional groups including nitriles, ethers, imines, amides, aryl chlorides, and acetals. Reaction times are typically 4−12 h using 3 mol % palladium and 3.6 mol % ligand. Reaction of 2-bromo-*p*-xylene with 3′,4′-(methylenedioxy)acetophenone required 5 mol % Pd and 18 h for complete conversion of the starting aryl halide (entry 12).[12]

The regioselectivity of the Pd-catalyzed arylation of ketones is quite remarkable. Ketones containing α,α′-hydrogens are

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(9) Tol-BINAP = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

(10) Representative procedure: In a fume hood, an oven-dried Schlenk tube containing a stir bar was charged with $Pd_2(dba)_3$ (6.9 mg, 0.0075 mmol), Tol-BINAP (12.2 mg, 0.018 mmol), and NaO-*t*-Bu (65 mg, 0.65 mmol). The Schlenk tube was evacuated and back filled with argon. THF (2 mL) was added followed by 2-(3-bromophenyl)-1,3-dioxolane (76 μL, 0.5 mmol), 3-methyl-2-butanone (64 μL, 0.60 mmol), and additional THF (1 mL). The resulting red mixture was heated under argon in a 70 °C oil bath until the starting halide had been consumed as judged by GC analysis. The Schlenk tube was cooled to room temperature, and diethyl ether (25 mL) and H_2O (25 mL) were added. The aqueous layer was separated and extracted with diethyl ether (25 mL). The organic layers were combined, washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel to give 90 mg (76% yield) of a colorless oil.

(11) Other ligands examined in the Pd-catalyzed coupling of cyclohexanone with 1-bromo-4-*tert*-butylbenzene include tri-*o*-tolylphosphine, 1,2-bis(diphenylphosphino)ethane (DPPE), 1,2-bis(diphenylphosphino)propane (DPPP), and 1,1′-bis(diphenylphosphino)ferrocene (DPPF). The use of DPPF provided the desired product in 50% yield (GC); however, *tert*-butylbenzene was formed in 25% yield (GC). Use of Tol-BINAP afforded >90% yield (GC, uncorrected for response factors) of the desired product and <1% yield (GC) of *tert*-butylbenzene.

(12) The reaction of 4-chloroacetophenone and of 4-methoxyacetophenone with 2-bromo-*p*-xylene proceeded to only ca. 90% conversion of the starting aryl halide using 5 mol % Pd and 6 mol % ligand. The reaction of 2-bromo-*p*-xylene with 3-methyl-2-butanone using 7 mol % Pd and 8.4 mol % ligand gave complete conversion of the starting aryl halide, but the isolated product was <95% pure.

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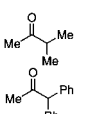
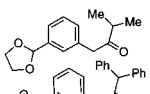
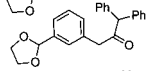
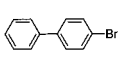
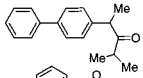
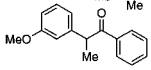
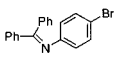
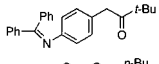
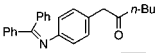
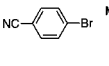
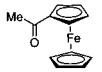
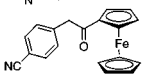
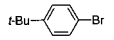
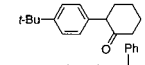
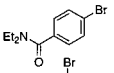
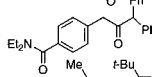
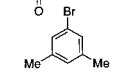
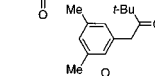
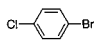
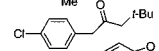
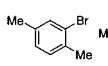
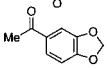
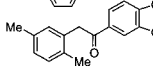
Table 1. Palladium-Catalyzed Coupling of Aryl Bromides with Ketones[a]

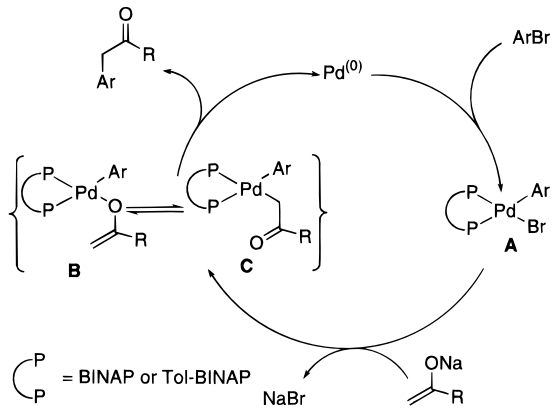
entry	aryl bromide	ketone	ketone:ArBr	ligand	product	monoarylation / diarylation	yield (%)[b]
1			1.2	Tol-BINAP		13:1	76
2			1.2	Tol-BINAP		--	72
3			1.2	Tol-BINAP		--	93
4			1.2	BINAP		--	91
5			1.2	Tol-BINAP		--	78
6			1.2 2.0	BINAP BINAP		10:1 28:1	64[c] 63[d]
7			1.2 2.0	BINAP BINAP		20:1 27:1	64 75
8			1.2 2.0	Tol-BINAP Tol-BINAP		30:1 33:1	67 83
9			1.2	Tol-BINAP		--	69
10			1.2	Tol-BINAP		--	93
11			1.2 2.0	Tol-BINAP Tol-BINAP		7:1 16:1	71 88
12			1.2	BINAP		--	84[e]

[a] Reaction conditions are as follows: 1.0 equiv of ArBr, 1.2 or 2.0 equiv of ketone, 1.3 equiv of NaO*t*-Bu, 1.5 mol % of $Pd_2(dba)_3$, 3.6 mol % of ligand in THF (ArBr = 0.17 M), 70 °C. [b] Yields refer to the average of isolated yields for two runs. [c] Isolated as a 20:1 mixture of regioisomers. [d] Isolated as a 16:1 mixture of regioisomers. [e] Reaction performed using 5 mol % Pd and 6 mol % BINAP.

preferentially arylated at the least-hindered side (methyl > methylene ≫ methine). For example, NMR analysis of the crude reaction mixture of the coupling of 2-(3-bromophenyl)-1,3-dioxolane with 3-methyl-2-butanone showed no evidence of arylation at the methine carbon and a 13:1 mixture of monoarylation:diarylation of the methyl ketone (entry 1). Likewise, NMR analysis of the crude reaction mixture of the coupling of 4-bromobiphenyl with 2-methyl-3-pentanone revealed that coupling occurred exclusively at the methylene carbon (entry 3). Coupling of 1,1-diphenylacetone to 2-(3-bromophenyl)-1,3-dioxolane (entry 2) or *N*,*N*-diethyl-*p*-bromobenzamide (entry 9) occured exclusively at the methyl group despite the significantly greater acidity of the methine proton.

Further examples illustrating the high degree of regioselectivity can be seen in the reaction of *N*-(diphenylmethylene)-4-bromoaniline with 2-hexanone (entry 6). Although the degree of regioselectivity (arylation of methyl vs methylene) decreased slightly upon increasing the relative concentration of ketone, the amount of diarylation of the methyl ketone decreased from 9% to 3%, as determined by NMR analysis of the crude reaction mixture. Diarylation was observed only for methyl ketones which are relatively unhindered at the α′-position. Thus, no diarylation was observed for 1,1-diphenylacetone (entries 2 and 9), 3-methyl-2-butanone (entry 1), and pinacolone (entries 5 and 10). In addition, no diarylation was observed in the coupling of 2-bromo-*p*-xylene with 3′,4′-(methylenedioxy)acetophenone, presumably because of the steric hindrance provided by the *o*-methyl group (entry 12). Arylation of methine carbons was not observed under these conditions. Attempts at coupling 1-bromo-4-*tert*-butylbenzene with 2,6-dimethylcyclohexanone

Scheme 2



gave, after 14 h, <2% of the desired 2,6-dimethyl-2-(4-*tert*-butylphenyl)cyclohexanone.[13]

Although little mechanistic information has been obtained about the Pd-catalyzed arylation of ketones, we believe that the reaction proceeds via the mechanism shown in Scheme 2. Oxidative addition of the $Pd(0)L_n$ with the aryl bromide affords the Pd(II) organometallic intermediate **A**. Ligand substitution of the bromide by the sodium enolate provides the Pd(II) organometallic intermediate **B** or **C**. Given the high degree of regioselectivity of arylation, we believe that deprotonation of the ketone occurs prior to coordination to the Pd center. Finally, reductive elimination from intermediate **B** or **C** provides the α-aryl ketone and regenerates the $Pd(0)L_n$ catalyst. That **C** does not decompose via a *β*-hydride elimination pathway (in cases where both α-carbons are substituted) further attests to the ability of BINAP and Tol-BINAP to render such complexes 4-coordinate.[14]

In summary, we have developed a general method for the direct synthesis of α-aryl ketones from ketones and aryl bromides.[15,16] This process displays good functional group tolerance and high regioselectivity. Efforts to extend the substrate scope to other classes of substrates such as esters and amides and to develop an asymmetric variant are currently under progress.

Acknowledgment. Financial support from the National Science Foundation, the National Institutes of Health (postdoctoral fellowship to M.P.) and Pfizer are gratefully acknowledged. We thank Joseph P. Sadighi for providing *N*-(diphenylmethylene)-4-bromoaniline.

Supporting Information Available: Details of experimental procedures and spectroscopic and analytical data (7 pages). See any current masthead page for ordering and Internet access instructions.

Note Added in Proof. Hamann and Hartwig have independently discovered and conducted a study of the catalytic arylation of ketones.[16a] In addition, Miura and co-workers have reported the catalytic conversion of 1,3-diphenylacetone to 1,1,3,3-tetraphenylacetone via a similar transformation.[16b]

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(13) Determined by GC and GC/MS analysis of the crude reaction mixture.

(14) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216.

(15) After completion of this work, an abstract describing similar work appeared: Hamann, B. C.; Hartwig, J. F. *Abstracts of Papers*, 214th ACS National Meeting of the American Chemical Society, Division of Inorganic Chemistry, Las Vegas, NV, September 7−11, 1997; American Chemical Society: Washington, DC, 1997; INORG 444.

(16) (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* In press. (b) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew Chem., Int. Ed. Engl.* **1997**, *36*, 1740−1742.