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α-Arylation of Ketones Using Highly Active, Air-Stable (DtBPF)PdX_2 (X = Cl, Br) Catalysts

Gabriela A. Grasa and Thomas J. Colacot*

Johnson Matthey Catalysis and Chiral Technologies, 2001 Nolte Drive, West Deptford, New Jersey 08066

colactj@jmusa.com

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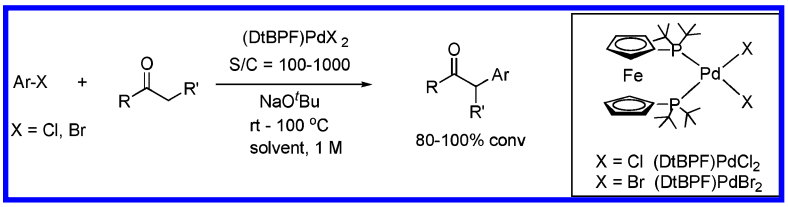
ABSTRACT



α-Arylation of various ketones with aryl chlorides and bromides using the well-defined and air-stable (DtBPF)PdX_2 (X = Cl, Br) catalysts gave 80–100% yield of the coupled products under relatively mild conditions at low catalyst loadings. The X-ray structure of (DtBPF)$PdCl_2$ revealed the largest P–Pd–P bite angle (104.2°) for a ferrocenyl bisphosphine ligand. ^{31}P NMR monitoring of (DtBPF)$PdCl_2$-catalyzed reaction of 4-chlorotoluene with propiophenone indicated that DtBPF remained coordinated in a bidentate mode during the catalytic cycle.

Toward the end of the last century, there was a paradigm shift in the area of C−C bond forming reactions, in designing complex organic molecules via Pd-catalyzed coupling.[1] Among the various cross-coupling reactions, such as Heck, Suzuki, Stille, Sonogashira, Negishi, and Kumada, Pd-catalyzed α-arylation of carbonyl compounds has emerged as a powerful new C−C bond forming method. Seminal work from the groups of Hartwig[2] and Buchwald[3] identified palladium precursors such as $Pd(OAc)_2$ and $Pd_2(dba)_3$ in conjunction with bulky, electron-rich monodentate or bidentate phosphines as viable catalytic systems for such transformations. Nolan[4] and Ackerman[5] have also effectively studied the applications of Pd-based N-heterocyclic carbenes and diaminochlorophosphines, respectively, for α-arylation of ketone enolates, while Chan[6a] and Buchwald[6b] have independently reported asymmetric α-arylation using chiral atropoisomeric bisphosphine-based nickel catalysts.

By virtue of their adjustable electronic, steric, and bite angle properties, bidentate ferrocenylphosphines have become a very important class of ligands in transition-metal-catalyzed reactions in organic synthesis.[7] 1,1′-Bis-substituted ferrocenylphosphines have been particularly successful for a wide range of Pd-catalyzed C−C and C−heteroatom cross-coupling reactions.[8] Recently, our group has reported the superior catalytic activity of the air-stable, preformed catalyst 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium dichlo-

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(7) (a) *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: Weinheim, Germany, 1995. (b) Stepnicka, P. *Ferrocenes: From Materials and Chemistry to Biology*; Wiley: Chichester, UK, in press.

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ride (DtBPF)$PdCl_2$ in Suzuki coupling of a wide variety of aryl chlorides.[9] In continuation of our studies toward developing simple and elegant catalytic processes for C−C bond forming reactions, we report herein the application studies of (DtBPF)$PdCl_2$ and its analogous bromide complex in the α-arylation of ketone enolates with aryl bromides and chlorides. We also report the X-ray crystal structure of (DtBPF)$PdCl_2$ with a view to understand its unique catalytic activity in comparison to the respective in situ catalytic systems and other examples of palladium complexes of 1,1′-bis-substituted, bidentate ferrocenylphosphines.

Figure 1 illustrates the various Pd complexes of ferrocenylphosphines employed in this study, while Table 1 shows their relative reactivity in the arylation of a model system

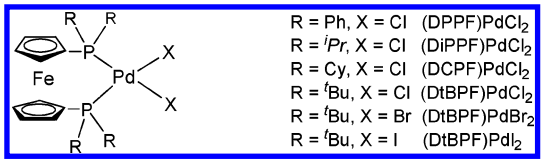

Figure 1. Bis(phosphino)ferrocene−PdX_2 complexes.

Table 1. Performance of Pd−Bisphosphinoferrocene-Based Catalysts in the Arylation of Propiophenone with 4-Chlorotoluene[a]

entry	precatalyst	conv[b] (%)
1	(DPPF)$PdCl_2$	NR
2	(DiPPF)$PdCl_2$	14
3	(DCPF)$PdCl_2$	42
4	(DtBPF)$PdCl_2$	88
5	(DtBPF)$PdBr_2$	89
6	(DtBPF)PdI_2	12
7	$Pd_2(dba)_3$/DtBPF	NR

[a] Reaction conditions: 3 mmol of 4-chlorotoluene, 3.3 mmol of propiophenone, 0.06 mmol of catalyst, 3.3 mmol of NaO^{t}Bu, 3 mL of THF, 60 °C, 3 h reaction time. [b] Conversion was determined by GC.

(propiophenone with electron neutral *para*-chlorotoluene) at 1 M substrate concentration in THF solvent at 60 °C for a reaction period of 3 h. Both (DtBPF)$PdCl_2$ and (DtBPF)-$PdBr_2$ led to high conversions, while the Pd_2dba_3/DtBPF in situ generated catalyst gave no activity under identical conditions (Table 1, entries 4 and 5 vs entry 7). Among the preformed catalysts, the activity increased in the order Ph < *i*-Pr < Cy < *t*-Bu. This observation was similar to our earlier observation on Suzuki coupling of aryl chlorides[9] and Buchwald−Hartwig aminations.[10] Surprisingly, (DtBPF)PdI_2 catalyst gave only 12% conversion.

The X-ray structure determination of (DtBPF)$PdCl_2$ (Figure 2) has been useful in explaining the structure−activity

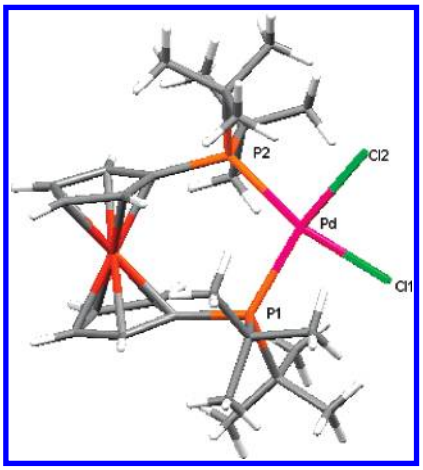

Figure 2. (DtBPF)$PdCl_2$ complex. Selected bond lengths (Å) and angles (deg): Pd−P1 2.3466(16), Pd−P2 2.3503(15), Pd−Cl1 2.3607(15), Pd−Cl2 2.3532(15); P1−Pd−P2 104.22(5), Cl1−Pd−Cl2 83.66(5), P1−Pd−Cl2 159.98(6), P2−Pd−Cl2 88.17(5), P1−Pd−Cl1 88.74(5), P2−Pd−Cl1 160.82(5).

relationship of the catalyst. As shown in Figure 2, Pd has a distorted square planar geometry with the two phosphorus atoms in a *cis* configuration. Notably, the P−Pd−P bite angle of the bidentate ligand in (DtBPF)$PdCl_2$ is the largest (104.22°) in the series of bisphosphinoferrocene complexes of $PdCl_2$.[8a,11] This is in agreement with the X-ray structure of an oxidative addition product, (DtBPF)Pd(Br)(4-CN−C_6H_5) (104.28°), reported by Hartwig et al.[12] Although the reported bite angle of the isopropyl analogue (DiPPF)$PdCl_2$ is 103.95°,[11a] this catalyst has not been very active for α-arylation and aryl chloride Suzuki coupling.[9] This suggests that, in addition to the larger bite angle, the bulky, electron rich *t*-Bu groups on the phosphorus atoms play a crucial role in providing the apt electronic and steric balance necessary to facilitate the oxidative addition and subsequent reductive elimination steps during the coupling of challenging substrates, such as aryl chlorides.

The in situ catalyst system generated from $Pd_2(dba)_3$ and DtBPF ligand in 1:1 molar ratio has shown no activity in the model reaction after 3 h (Table 1, entry 7), although there are reports on the use of DtBPF ligand in conjunction with Pd precursors in Suzuki,[13] Buchwald−Hartwig amination,[14]

(8) (a) Colacot, T. J.; Parisel, S. *Ferrocenes: From Materials and Chemistry to Biology*; Wiley: Chichester, UK, in press. (b) Colacot, T. J. *Chem Rev.* **2003**, *103*, 3101 (see references therein). (c) Colacot, T. J. *Platinum Met. Rev.* **2001**, *45*, 22. (d) Colacot, T. J.; Quian, H.; Cea-Olivares, R.; Hernandez-Ortega, S. *J. Organomet. Chem.* **2001**, *637*−*639*, 691.

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(10) Hagopian, L. E.; Campbell, A. N.; Golen, J. A.; Rheingold, A. L.; Nataro, C. *J. Organomet. Chem.* **2006**, *691*, 4890.

(11) (a) (DiPrPF)$PdCl_2$: P−Pd−P = 103.59°: Elsagir, A. R.; Gassner, F.; Gorls, H.; Dinjus, E. *J. Organomet. Chem.* **2000**, *597*, 139. (b) (DCyPF)-$PdCl_2$: P−Pd−P = 102.45°: see ref 10. (c) (DMPF)$PdCl_2$: P−Pd−P = 99.3°: Bianchini, C.; Meli, A.; Oberhauser, W.; Parisel, S.; Passaglia, E.; Ciardelli, F.; Gusev, O. V.; Kal'sin, A. M.; Vologdin, N. V. *Organometallics* **2005**, *24*, 1018. (d) (DPPF)$PdCl_2$: P−Pd−P = 97.98°: Butler, I. R.; Cullen, W. R.; Kim, T. J.; Rettig, S. J.; Trotter, J. *Organometallics* **1985**, *4*, 972.

(12) Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775.

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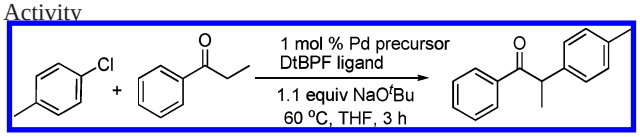
(14) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem Soc.* **1998**, *120*, 7369.

ketone α-arylation,[2b] and Heck coupling.[15] This observation prompted us to have a closer look at the influence of stoichiometry of Pd:DtBPF in the ketone α-arylation reactions (Table 2). A control experiment performed in the

Table 2. Effect of Pd:L Ratio and Concentration on the Activity



entry	Pd precursor	[S] (mmol/mL)	Pd:DtBPF mole ratio	conv[a] (%)
1	$Pd_2(dba)_3$	1	no ligand	NR
2	$Pd_2(dba)_3$	1	1:0.5	70
3	$Pd_2(dba)_3$	0.5	1:1	35
4	$Pd_2(dba)_3$	0.33	1:1	31
5	$(DtBPF)PdCl_2$	1	1:1	80

[a] Conversion was determined by GC.

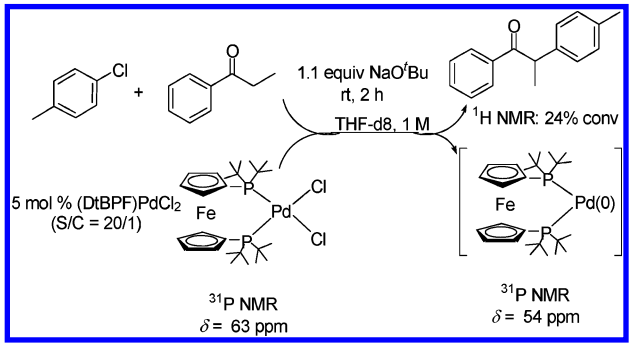
absence of DtBPF gave no reaction. Interestingly, when $Pd_2(dba)_3$ and DtBPF were employed in a 1:0.5 molar ratio at 1 M substrate concentration, 70% conversion to the desired product was observed (Table 2, entry 2 vs Table 1, entry 7).

However, at lower substrate/catalyst concentrations, a Pd:DtBPF ratio of 1:1 gave modest to moderate conversions (Table 2, entries 4 and 5). Very interestingly, the preformed complex, $(DtBPF)PdCl_2$, with a formal Pd:DtBPF ratio of 1:1 gave the highest conversion within 3 h at 1 mol % catalyst loading, even at high substrate concentration (Table 2, entry 6). The above results indicate that, for the in situ systems, the optimum Pd:DtBPF ratio is 1:0.5.[16] This difference in reactivity behavior could be explained based on the formation of $Pd(0)(DtBPF)_n$ and differential release of the ligand to form the active species at various ligand ratios and concentrations. This is in agreement with Buchwald's observations on the influence of Pd:L ratios in amination using $Pd(dba)_2$/XantPhos in situ systems.[17]

Hartwig also observed that a $Pd(dba)_2$/DtBPF molar ratio of 1:0.5 is optimal in the α-arylation of ketones.[2b] Using ^{31}P NMR spectroscopy, his group monitored the stoichiometric reaction of the oxidative addition product and postulated that one of the phosphorus atoms may decoordinate to form a tricoordinate palladium center upon enolate coordination. To test this hypothesis, we also monitored the fate of the preformed $(DtBPF)PdCl_2$ catalyst in α-arylation by NMR (Scheme 1).

While reacting 4-chlorotoluene with propiophenone in THF-d_8 at 1 M substrate concentration, in the presence of NaO^{t}Bu base and 5 mol % of $(DtBPF)PdCl_2$ loading, 24% conversion was observed after 2 h at rt. Furthermore, the

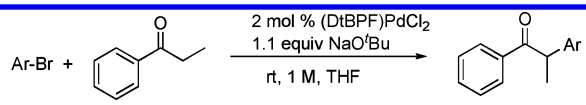
Scheme 1

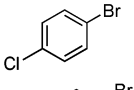
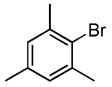
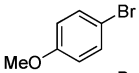
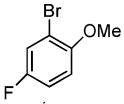
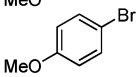
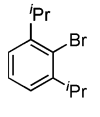
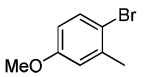
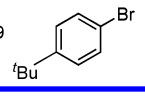
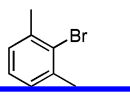


peak characteristic of $(DtBPF)PdCl_2$ complex (~63 ppm) completely disappeared during the catalytic cycle with the formation of a new singlet at ~54 ppm. This singlet could be attributed to an active catalytic species, (DtBPF)Pd(0).[2b,12] The absence of a peak at ca. 25 ppm,[2b] characteristic of a mono-uncoordinated bidentate ligand, unlike in the case of the stoichiometric reaction, indicates that DtBPF ligand possibly retains its bidentate coordination mode during catalysis, under these conditions. The fact that no transient species are detected in the NMR time scale suggests that (η^2-DtBPF)Pd(0) could be the ground state of the reaction.[18]

The identification of the pre-isolated complexes $(DtBPF)PdCl_2$ and $(DtBPF)PdBr_2$ as efficient catalysts in the α-arylation of propiophenone with 4-chlorotoluene prompted us to investigate their generality with respect to various other substrates. Catalysis using $(DtBPF)PdCl_2$ led to high conversions at room temperature in the arylation of propiophenone

Table 3. Room Temperature $(DtBPF)PdCl_2$-Catalyzed α-Arylation of Aryl Bromides



entry	substrate	conv[a] (%)	entry	substrate	conv[a] (%)
1		94 (92)	6		86 (81)
2		99 (97)	7		86 (65)
3		78[b]	8		13
4		99 (97)	9		98 (96)
5		99 (80)			

[a] Conversion was determined by GC. Isolated yields reported in parentheses. [b] With 0.1 mol % of $(DtBPF)PdCl_2$, 100 °C, dioxane.

with challenging aryl bromides (Table 3). Electron-rich substrates as well as sterically hindered substrates were

(15) (a) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123. (b) Boyles, A. L.; Butler, I. R.; Quayle, S. C. *Tetrahedron Lett.* **1998**, *39*, 7766.

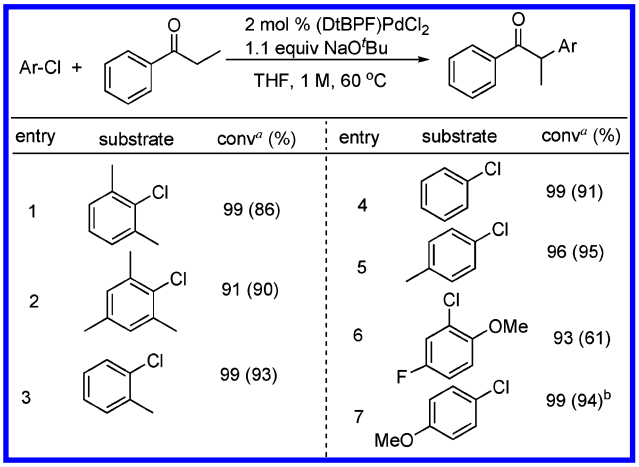
(16) A reviewer suggested that free dba ligand released from the reaction of $Pd_2(dba)_3$ with DtBPF might inhibit the catalysis. We are also currently studying the reaction of $Pd_2(dba)_3$ with DtBPF at different stoichiometries.

(17) Klingensmith, L. M.; Streiter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, *25*, 82.

efficiently converted to the desired product under mild reaction conditions (Table 3, entries 2−6 and 8). However, highly sterically hindered substrates, such as 2,6-diisopropylbromobenzene, gave very low conversions. This method (room temperature) also allowed us to carry out selective arylation using a dihalogenated arene substrate, where coupling occurred only at the C−Br center (Table 3, entry 1). (DtBPF)$PdCl_2$ was tested at low loadings (*S*/*C* 1000/1) for an unactivated bromide with high conversion (Table 3, entry 3).

The activity of (DtBPF)$PdCl_2$ catalyst in the ketone α-arylation was tested using very challenging aryl chloride substrates (Table 4). While sterically hindered aryl chlorides,

Table 4. Effect of the Aryl Chloride Substrate in the (DtBPF)$PdCl_2$-Catalyzed α-Arylation of Propiophenone



entry	substrate	conv[a] (%)	entry	substrate	conv[a] (%)
1		99 (86)	4		99 (91)
2		91 (90)	5		96 (95)
3		99 (93)	6		93 (61)
			7		99 (94)[b]

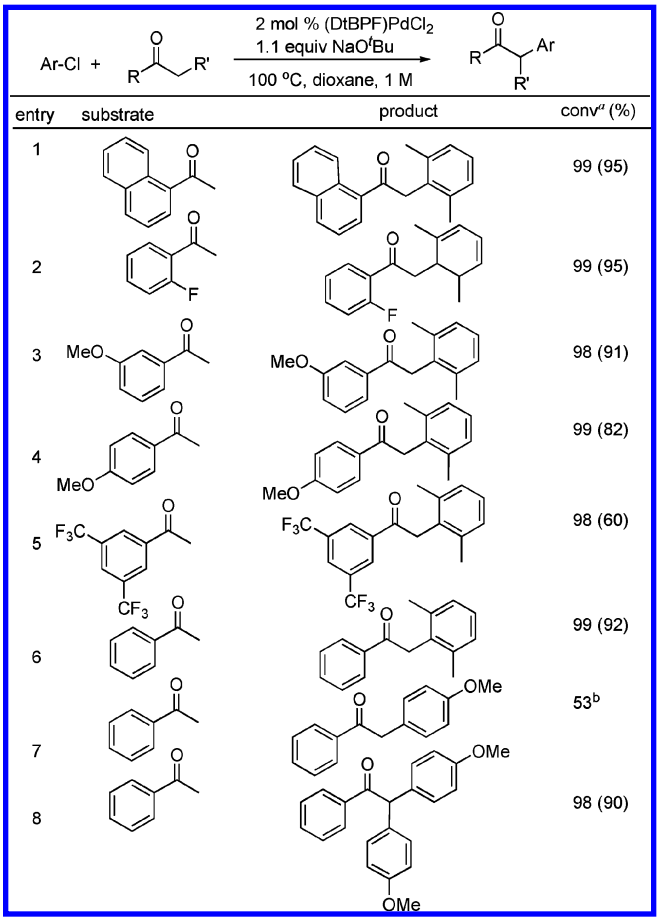
[a] Conversion was determined by GC. Isolated yields reported in parentheses. [b] The reaction was performed using dioxane at 100 °C.

such as 2-chloro-*m*-xylene and chloromesitylene, proceeded smoothly at 60 °C in high conversions (Table 4, entries 1−6), the electron-rich 4-chloroanisole required higher temperature to reach full conversion (Table 4, entry 7). Inversely, the effect of the ketone substrate was also studied using difficult aryl chlorides, such as 2-chloro-*m*-xylene and 4-chloroanisole (Table 5). Various acetophenone derivatives reacted efficiently with sterically hindered 2-chloro-*m*-xylene to give the products in excellent isolated yields (Table 5, entries 1−6).

We also tried to understand the effect of substrate, base, and stoichiometry on monoarylation versus diarylation. Sterically crowded aryl halides (e.g., 2-chloro-*m*-xylene) gave only monoarylation products, while sterically less hindered substrates such as 4-chloroanisole led to both mono- and bisarylation products even when stoichiometric amounts of the reagents were used (Table 4, entry 7). The selectivity toward the monoarylated product was, however, increased by increasing the amount of base, while the selectivity of the bisarylated product was improved by using excess of 4-chloroanisole (Table 5, entry 8).

(18) No free ArP^tBu_2 due to DtBPF cleavage under catalytic α-arylation conditions was observed. For DtBPF cleavage under O-arylation conditions, see: Shelby, Q.; Kataoka, N.; Mann, G.; Hartwig, J. F. *J. Am. Chem Soc.* **2000**, *122*, 10718.

Table 5. Effect of the Ketone Substrate in the (DtBPF)$PdCl_2$-Catalyzed α-Arylation



entry	substrate	product	conv[a] (%)
1			99 (95)
2			99 (95)
3			98 (91)
4			99 (82)
5			98 (60)
6			99 (92)
7			53[b]
8			98 (90)

[a] Conversion was determined by GC. Isolated yields reported in parentheses. [b] 47% bisarylation product determined by GC.

In conclusion, we have identified well-defined and air-stable (DtBPF)PdX_2 (X = Cl, Br) catalysts for the arylation of various ketones with aryl chlorides and bromides in excellent yields, under mild reaction conditions, and low catalyst loadings (*S*/*C* loading up to 1000/1) with very good reproducibility, in comparison to the respective in situ systems. Preliminary NMR investigation of the Pd:DtBPF ratios of the preformed and in situ systems in catalysis indicates that the well-defined catalyst (DtBPF)$PdCl_2$ is a preferred choice. The mechanistic and structural studies to understand the lower activity of (DtBPF)PdI_2, in comparison to that of its analogous chloride and bromide counterparts, are in progress.

Acknowledgment. We thank Dr. Glenn Yap of University of Delaware for X-ray structure determination. Fred Hancock and Bill Tamblyn, Johnson Matthey CCT, are acknowledged for useful discussion and encouragement.

Supporting Information Available: Experimental procedures, characterization data, and a X-ray crystallographic data of (DtBPF)$PdCl_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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