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A Highly Practical and General Route for α-Arylations of Ketones Using Bis-phosphinoferrocene-Based Palladium Catalysts

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Abstract:

Well-defined, air-stable Pd complexes of bis-phosphinoferrocene family of catalysts have been studied in the arylation of various ketones with aryl chlorides and aryl bromides. Bis(di-*tert*-butyl)phosphinoferrocene (DtBPF)-based catalysts such as (DtBPF)$PdCl_2$ and (DtBPF)$PdBr_2$ have been identified as two of the most active catalysts for the α-arylation of a model reaction involving propiophenone and 4-chlorotoluene. The scope of the (DtBPF)-$PdCl_2$ catalyst has been efficiently expanded to the arylation of various ketones with aryl chlorides and bromides with up to 97% isolated yields, under relatively mild reaction conditions at low catalyst loadings. The efficacy of the (DtBPF)$PdCl_2$ catalyst was demonstrated at very low catalyst loadings with *S/C* 10,000 for the difficult aryl bromide, 4-bromoanisole, and 2000 for the electron-neutral aryl chloride, 4-chlorotoluene, on ~10-g scale with excellent isolated yields and lower Pd in the product (6 and 48 ppm, respectively). Comparative studies on the Pd:DtBPF molar ratios between *in situ* catalysts and preisolated catalysts revealed that preisolated (DtBPF)PdX_2 (X = Cl, Br) are the catalysts of choice due to various practical reasons.

Introduction

The α-aryl carbonyl moiety is ubiquitous in many organic compounds with interesting pharmacological and biological properties.[1] Stoichiometric reactions between a stabilized ketone enolate carbanion and an aryl electrophile serve as a classical C−C bond-forming technology toward the synthesis of α-aryl carbonyl compounds.[2] However, these transformations suffer from many practical drawbacks, such as functional group compatibility and air and moisture sensitivity, in addition to the toxicity of the reagents. To alleviate some of these limitations, recently metal-catalysed α-arylation of carbonyl compounds has been developed as a new and novel class of C−C bond-forming reactions, mainly because of the pioneering work of Hartwig[3] and Buchwald.[4] Subsequent contributions from Nolan,[5] Ackerman,[6] and Chan[7] are also significant.

Our laboratory has been involved in designing practical, elegant, and simple catalytic solutions to various name reactions in the area of cross-coupling. In this context, we identified bidentate phosphines featuring the ferrocene backbone as an interesting class of ligands in a variety of transition metal-catalysed reactions in organic synthesis.[8] Palladium complexes of 1,1′-bis-substituted ferrocenylphosphines have been utilized efficiently as practical commercial catalysts for a number of cross-coupling reactions.[9] Recent work from our group successfully demonstrated the application of an air-stable, yet highly active, preformed catalyst: 1,1′-bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (DtBPF)$PdCl_2$ in the Suzuki coupling of a wide variety of unactivated aryl halides.[10] Very recently, we also successfully explored the suitability of (DtBPF)$PdCl_2$ catalyst in the α-arylation of ketone enolates with aryl chlorides.[11] As a continuation of our studies toward developing simple, elegant, and general catalytic processes for C−C bond-forming reactions, we present herein a detailed study on the use of bis-phosphinoferrocene-based Pd(II) complexes as preformed catalysts (Figure 1) in the α-arylation of ketone enolates with aryl-bromides and -chlorides. From an organic process development point of view, there are several parameters

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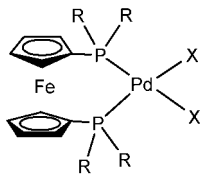


R	X	catalyst
^{t}Bu	Cl	(DtBPF)$PdCl_2$
^{t}Bu	Br	(DtBPF)$PdBr_2$
^{t}Bu	I	(DtBPF)PdI_2
^{i}Pr	Cl	(DiPPF)$PdCl_2$
Cy	Cl	(DCPF)$PdCl_2$
Ph	Cl	(DPPF)$PdCl_2$

Figure 1. **Palladium catalysts.**

Table 1. **Performance of Pd-bis-phosphinoferrocene-based catalysts in the arylation of propiophenone with 4-chlorotoluene**[a]

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

in a cross-coupling reaction such as palladium precursor, ligand, additive, solvent, temperature, *in situ* vs fully formed catalyst, etc., and there are, correspondingly, a large number of protocols for accomplishing the transformation, the choice of which depends on the electronic and steric match between the catalysts and the reactants. In this study, we investigated the role of these parameters and protocols, with a view to develop economically viable and environmentally friendly processes relevant to the fine chemical and pharmaceutical industries. The results of the study are discussed below.

Results

Figure 1 shows the various preformed Pd complexes of bis-phosphinoferrocenes employed in the study. All these catalysts have been isolated in very good yield and purity and are commercially available through Johnson Matthey Catalysis and Chiral Technologies. Based on our experience in catalysis, in general, we prefer preformed catalysts, as Pd-catalysts generated *in situ* require high catalyst loadings and therefore may suffer from reproducibility issues. In addition, certain free ligands such as tris- *tert*- butylphosphine employed in coupling are often air sensitive or even pyrophoric.

Effect of the Catalyst on the α-Arylation of Propiophenone with 4-Chlorotoluene. The structure–activity relationship of the catalysts (1,1′-bis(phosphinoferrocene)palladium dihalide) was studied in the α-arylation of propiophenone with an electron-neutral substrate, 4-chlorotoluene, in the presence of NaO^{t}Bu base at 60 °C with 1 M substrate concentration in THF. Table 1 summarizes the relative activities of both isolated as well as *in situ* catalysts. As expected, among the preisolated 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.[10] The DtBFP-based catalysts (DtBPF)PdX_2 (X = Br, Cl) gave moderate to high conversions within 3 h (Table 1, entries 2 and 3), while the corresponding *in situ* system, $Pd_2(dba)_3$/DtBPF gave no activity under identical conditions (Table 1, entry 1 vs entries 2 and 3). In order to further understand its superior activity, we have determined the X-ray molecular structure of (DtBPF)$PdCl_2$ complex[11] and compared its bonding characteristics with other similar complexes (Figure 2). Notably, the P−Pd−P bite angle of the bidentate ligand in (DtBPF)$PdCl_2$ is the largest (104.22 °) in the series of bis-phosphinoferrocene complexes of $PdCl_2$ (Figure 2).[9a,12] Interestingly, the bite angle of the isopropyl analog, (DiPPF)$PdCl_2$ (103.95 °) is close to that of (DtBPF)$PdCl_2$.[12a] However, (DiPPF)$PdCl_2$ catalyst has not been very active either in the α-arylation (Table 1, entry 6) or Suzuki coupling involving arylchlorides.[10] The unique activity of (DtBPF)$PdCl_2$ could be due to its larger bite angle, coupled with the steric and electronic effects of the *tert*-butyl group. Surprisingly, among the (DtBPF)-PdX_2 series, (DtBPF)PdI_2 catalyst gave only 12% conversion. Current study is in progress to understand its structure–activity relationship in catalysis.

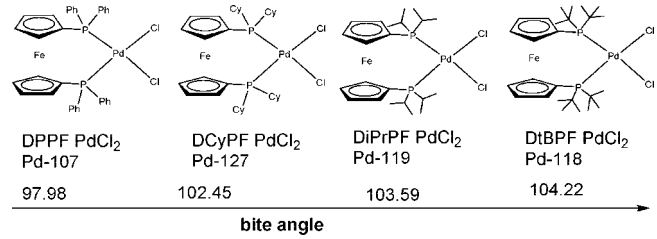


Figure 2. **Bite angle variation for bis-phosphinoferrocene $PdCl_2$ complexes.**[9a,12]

Effect of Solvent and Base in the α-Arylation of Propiophenone. The catalysts such as (DtBPF)$PdCl_2$, (DtBPF)-$PdBr_2$ and (DCPF)$PdCl_2$, which gave reasonably good conversions, were selected for further optimization in terms of understanding the solvent and base effect at 1% catalyst loading (Chart 1). Both (DtBPF)$PdCl_2$ and (DtBPF)$PdBr_2$ showed high conversion in dioxane solvent, while the (DCPF)$PdCl_2$ catalyst, inversely, led to increased conversions in the following order: THF < dioxane < Toluene ≈ MTBE. This difference in behavior indicates that solvent–catalyst combination is indeed important even when the structural differences of the catalysts are very subtle.

The type of the base and its ratio to the substrates are also important factors in the α-arylation of ketone enolates. Investigation of different alkoxide bases in the model reaction showed that NaO^{t}Bu was the best base of choice (Table 2, entries 1–5). Although bis-silylamides have been previously shown to work in the α-arylation of ketones with aryl bromides and iodides,[3c] in our model reaction involving an aryl chloride substrate in the presence of (DtBPF)$PdCl_2$ catalyst, KN(Me_3Si)$_2$ has led to modest conversion (Table 2, entry 7). Other inorganic bases (e.g., hydroxides, carbonates, or phosphates) have given no arylation products, presumably due to their poor basicity to

(12) (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) (DCPF)$PdCl_2$: P−Pd−P = 102.45; see ref 23. (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.

Chart 1. **Solvent effect in the bis(phosphinoferrocene)palladium dichloride-catalysed arylations**

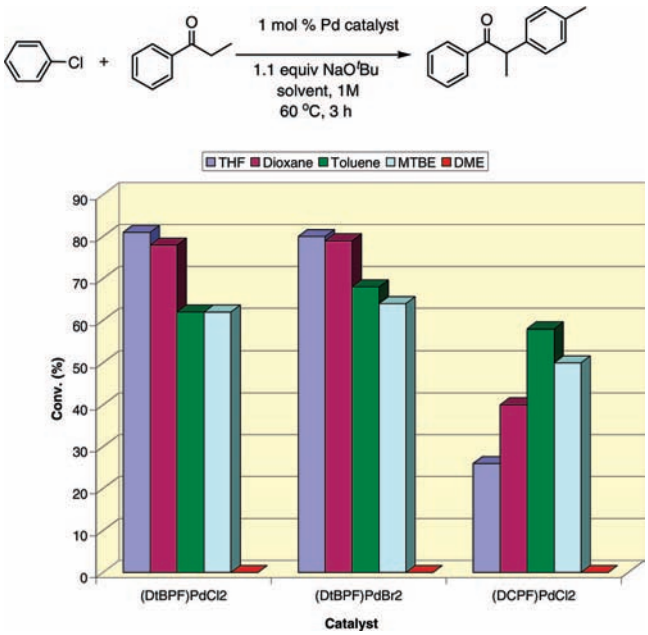
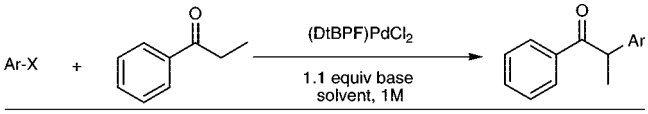


Table 2. **Base effect in the (DtBPF)$PdCl_2$−catalysed α-arylation**



entry	base	catalyst (mol %)	solvent	time (h)	T (°C)	conv (%)[a]
			4-chlorotoluene			
1	NaO^{t}Bu	1	THF	3	60	80
2	KO^{t}Bu	1	THF	3	60	68
3	NaO^{i}Pr	1	THF	3	60	9
4	KOMe	1	THF	3	60	15
5	NaOMe	1	THF	3	60	33
6	LiN(Me_3Si)$_2$	1	THF	3	60	NR
7	KN(Me_3Si)$_2$	1	THF	3	60	24
			2-bromopyridine			
8	NaO^{t}Bu	2	THF	24	25	46
9	KO^{t}Am[b,c]	2	toluene	4	110	48
10	KO^{t}Am[b,d]	2	toluene	24	110	48
11	LiN(Me_3Si)$_2$	2	THF	3	25	17
12	NaN(Me_3Si)$_2$	2	THF	3	25	39
13	KN(Me_3Si)$_2$	2	THF	3	25	33
14	KN(Me_3Si)$_2$[e]	2	THF	3	25	30
15	KN(Me_3Si)$_2$[f]	2	THF	3	25	23
16	KN(Me_3Si)$_2$	2	THF	6	60	50
17	K_3PO_4[g]	2	THF	24	60	6
			2-chloropyridine			
18	KN(Me_3Si)$_2$	2	THF	6	60	62

[a] Conversion was determined by GC. [b] 25% solution in toluene. [c] Base solution added dropwise over 4 h. [d] 2-Br-pyridine added slowly over approximately 3 h. [e] 0.5 M substrate concentration. [f] 1.5 equiv KN(Me_3Si)$_2$ relative to substrate. [g] 20 mol % *p*-methoxyphenol relative to the substrate was added.

generate the ketone enolate, necessary to facilitate the "transmetalation" step.

We also decided to study the arylation of heterocyclic halides due to their importance in the production of pharmaceutically active ingredients.[13] However, the use of a strong base/nucleophile in the α-arylation using nitrogen-containing heteroaryl halides is known to pose problems, due to the base sensitivity of these substrates. Therefore, we investigated the effect of the base in the arylation of propiophenone with 2-bromopyridine, under various reaction conditions (Table 2, entries 8–17) using (DtBPF)$PdCl_2$ catalyst. Although the reaction proceeded at room temperature with the full consumption of 2-bromopyridine in the presence of NaO^{t}Bu base, only 46% of the coupled product was observed. The remaining starting material was consumed by the base concomitantly, therefore limiting the complete formation of the desired product. In an attempt to limit the residence time of the unreacted 2-bromopyridine with the base, controlled addition of the substrate or base was performed in a dropwise manner. The results shown in Table 2, entries 9 and 10 suggest that even when the reagent addition is controlled, the reaction of the substrate with the base competes with the coupling reaction, leading again to the moderate formation of the arylated product. When weaker bases, such as NaN(Me_3Si)$_2$ and KN(Me_3Si)$_2$, were investigated at rt, only 30–40% conversion to the desired product was observed. Notably, in the case of these bases, the starting material 2-bromopyridine was not fully consumed by the base even after 24 h of reaction time. Decreasing the substrate concentration or increasing the amount of base did not have any effect on the product conversion (Table 2, entries 14 and 15), while increasing the temperature to 60 °C gave moderate conversion (Table 2, entry 16). Interestingly, under similar conditions, 2-chloropyridine also gave 60% conversion (Table 2, entry 18). We have not yet made any attempts to further optimize the reaction by increasing the reaction temperature, changing the solvent, and changing the substrate concentration. Although Buchwald demonstrated an efficient α-arylation of ketones with halonitroarenes by using Pd-based bulky monodentate phosphines in the presence of K_3PO_4 in conjunction with 20% *p*-methoxyphenol as additive,[14] we observed no reaction under similar conditions in the (DtBPF)-$PdCl_2$-catalysed α-arylation of propiophenone with 2-bromopyridine (Table 2, entry 17).

Scope of (DtBPF)$PdCl_2$-Catalysed α-Arylation. The identification of the preisolated 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 both aryl halides and ketones. Catalysis using (DtBPF)$PdCl_2$ led to high conversions in the arylation of various ketones with challenging aryl halides (Table 3). Electron rich and neutral aryl bromides were efficiently converted to the desired product at room temperature (Table 3, entries 1 and 3). This methodology (room temperature) also allowed us to carryout selective arylation using a bromochloroarene substrate, where C−C bond formation occurred only at the C−Br center (Table 3, entry 2). While electron neutral aryl chlorides such as 4-chlorotoluene and chlorobenzene proceeded smoothly at 60 °C in high conversions (Table 3, entries 9 and 10), the electron rich 4-chloroanisole required higher temperature to reach high conversion in the reactions with both aromatic and cyclic ketones such as tetralones (Table 3, entries 6–8).

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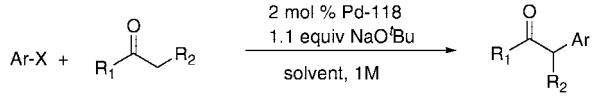
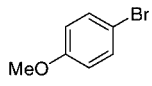
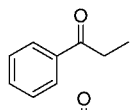
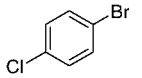
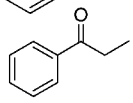
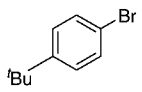
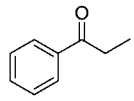
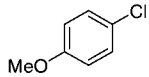
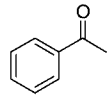
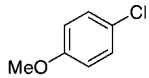
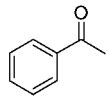
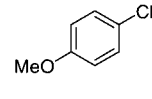
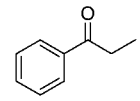
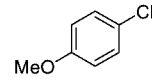
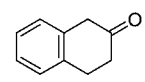
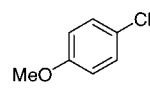
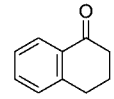
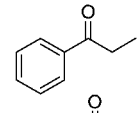
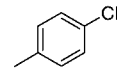
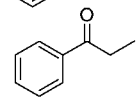
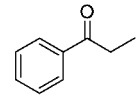
(14) Rutherford, J. L.; Rainka, M. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 15168.

Table 3. **(DtBPF)$PdCl_2$-catalysed α-arylation of aryl bromides and chlorides with various ketones**



entry	Ar-X	ketone	conditions	conv (isol)[a]
1			THF rt	99 (97)
2			THF rt	94 (92)
3			THF rt	98 (96)
4[b]			Dioxane 100 °C	53
5[c]			Dioxane 100 °C	98 (90)

entry	substrate	product	conditions	conv (isol)[a]
6			Dioxane 100 °C	99 (94)
7			Dioxane 100 °C	79
8			Dioxane 100 °C	75
9			THF 60 °C	99 (91)
10			THF 60 °C	96 (95)
11			Dioxane 100 °C	48

[a] Conversion was determined by GC. Isolated yields reported in parentheses. [b] 47% bis-arylation product. [c] 2 equiv 4-chloroanisole and 2.2 equiv NaO^{t}Bu were used; bis-arylation product was formed exclusively.

We also tried to understand the effect of substrate, base and stoichiometry on monoarylation versus diarylation. Sterically less hindered substrates such as 4-chloroanisole led to both mono- and bisarylation products even when stoichiometric amount of the reagents was used (Table 3, entry 4). The selectivity towards the monoarylated product was however increased by increasing the amount of base, while the selectivity to the bisarylated product was improved by using excess of 4-cholroanisole (Table 3, entry 5). 2-Chlorothiophene, a fairly difficult substrate in coupling reactions, was reacted with propiophenone at 100 °C in the presence of 2 mol % (DtBPF)$PdCl_2$ and gave 48% conversion to the desired product (Table 3, entry 11).

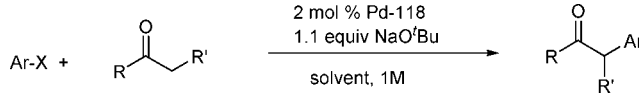
The versatility of (DtBPF)$PdCl_2$ catalyst has also been tested in the arylation of various ketones with sterically hindered substrates (Table 4). While sterically hindered and electron rich aryl bromides such as 2-methyl-4-bromoanisole proceeded smoothly at room temperature (Table 4, entries 4–6), highly sterically hindered substrates such as, 2,6-diisopropyl-bromobenzene gave very low conversions. The effect of the ketone substrate was also studied by using various acetophenone derivatives, which reacted efficiently with sterically hindered aryl halides to give the products in excellent isolated yields, without the formation of the bisarylated byproducts.

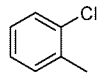
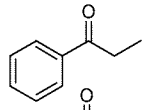
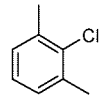
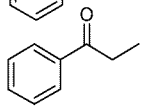
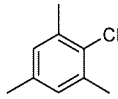
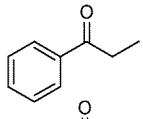
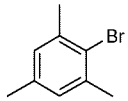
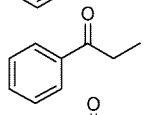
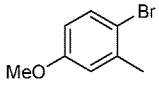
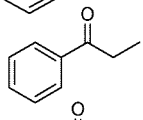
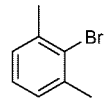
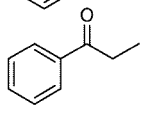
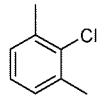
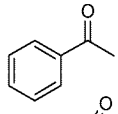
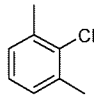
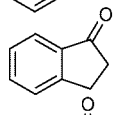
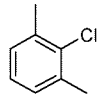
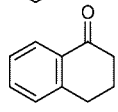
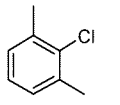
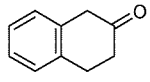
Catalyst Loading Optimization, Scale-Up at Low Catalyst Loadings, Workup and Palladium Removal. The comparative catalytic activities of (DtBPF)$PdCl_2$ and (DtBPF)$PdBr_2$ catalysts were tested at lower catalyst loadings using both aryl chloride and challenging aryl bromide substrates (Table 5, entries corresponding to fresh dioxane). The arylation of propiophenone with 4-chlorotoluene in dioxane (1 M substrate concentration) at 100 °C showed high conversion in the case of both catalysts at substrate to catalyst ratios (*S/C*) of 1000 in less than 3 h. Lowering further the catalyst loading to *S/C* 2000 still gave high conversion in the case of (DtBPF)$PdCl_2$ catalyst, while (DtBPF)$PdBr_2$ catalyst reached 78% conversion after 24 h (Table 5, entries 4 and 8). Similar activity tests were also performed using 4-bromoanisole at much lower catalyst loadings (*S/C* 10,000), with ca. 90% conversion (Table 5, entries 11 and 14). To our knowledge this is the lowest catalyst loading that has ever been reported in an arylation of a ketone.

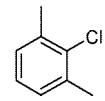
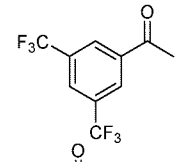
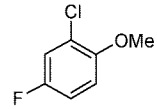
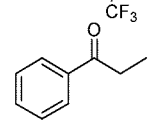
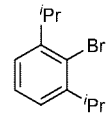
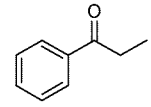
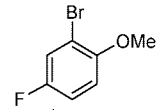
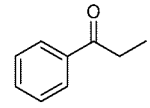
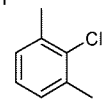
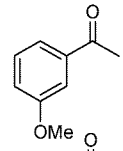
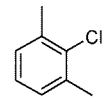
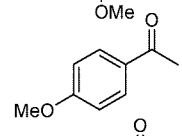
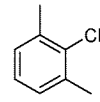
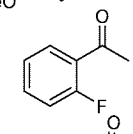
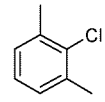
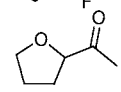
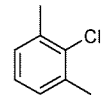
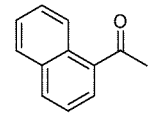
In our preliminary catalyst loading optimization studies involving an undegassed bottle of a previously opened dioxane, much lower conversions were observed in comparison to the freshly opened bottle of solvent (see Table 5). This might be due to the hygroscopic nature of the dioxane, coupled with the potential formation of peroxide. It is fairly established that moisture content in the solvent can affect the enolate formation in the α-arylation of enolates, while peroxide can poison the catalyst. Interestingly, when a fresh bottle of anhydrous dioxane was used, significantly higher conversions were consistently observed with excellent reproducibility on both 5mmol and 40mmol scale of reactions. This indicates that subtle changes are important in the process optimization of a catalytic reaction such as this.

The best reaction conditions were reproduced successfully on 9-g scale synthesis using (DtBPF)$PdCl_2$ catalyst at *S/C* 2000 in the case of 4-chlorotoluene substrate (Scheme 1), when the

Table 4. **(DtBPF)$PdCl_2$-catalysed α-arylation of ketones with sterically hindered aryl halides**



entry	Ar-X	ketone	conditions	conv (isol)[a]
1			THF 60 °C	99 (93)
2			THF 60 °C	99 (86)
3			THF 60 °C	91 (90)
4			THF rt	86 (81)
5			THF rt	99 (97)
6			THF rt	99 (80)
7			Dioxane 100 °C	99 (92)
8			Dioxane 100 °C	99
9			Dioxane 100 °C	91
10			Dioxane 100 °C	99

entry	Ar-X	ketone	conditions	conv (isol)[a]
11			Dioxane 100 °C	98 (60)
12			THF 60 °C	93 (61)
13			THF rt	13
14			THF rt	86 (65)
15			Dioxane 100 °C	98 (91)
16			Dioxane 100 °C	99 (82)
17			Dioxane 100 °C	99 (95)
18			Dioxane 100 °C	61
19			Dioxane 100 °C	99 (95)

[a] Conversion was determined by GC. Isolated yields reported in parentheses.

starting materials were consumed within 6 h. A simple workup procedure involving filtration through a silica pad to remove solids afforded 96% recovery of the product in >98.5% purity. The high conversion at low catalyst loading not only enabled the high yield recovery of the product *via* simple filtration but also facilitated lower residual Pd and Fe contents (48 ppm Pd and 34 ppm Fe) in the product.[15] In the case of 4-bromoanisole even at much lower catalyst loading (*S/C* 10000), 95% conversion was observed within 24 h of the reaction period (Scheme 2). The unreacted starting materials in this case have been removed by recrystallization of the crude product from MTBE/hexane, affording the product in 88% isolated yield, >99.8% purity, and 6 ppm residual Pd.

Effect Pd/DtBPF Ratio on the α-Arylation of Propiophenone with 4-Chlorotoluene. In our preliminary catalyst testing, we observed that the *in situ* generated catalyst using $Pd_2(dba)_3$ and DtBPF ligand showed no conversion in the model reaction, where the Pd:DtBPF molar ratio is 1:1, although there are reports on the use of DtBPF ligand in conjunction with Pd precursors in Suzuki,[16] Buchwald−Hartwig amination,[17] ketone α-arylation,[3b] and Heck coupling.[18] This observation prompted us to look more closely at the influence of this parameter in the ketone α-arylation reactions (Table 6). A control experiment in the absence of DtBPF was performed to ensure no conversion in the absence of a ligand. When $Pd_2(dba)_3$ and DtBPF were employed in 1:0.5 molar ratio at 1 M substrate concentration,

(15) The same-scale reaction was complete in less than 1 h at *S/C* 200. In this case, the higher residual metal content (theoretical, Pd = 2378 ppm, Fe = 1250 ppm) was reduced by recrystallization of the crude product from MTBE/hexane (83% recovery of the product in >99% purity, found: Pd = 600 ppm, Fe = 200 ppm).

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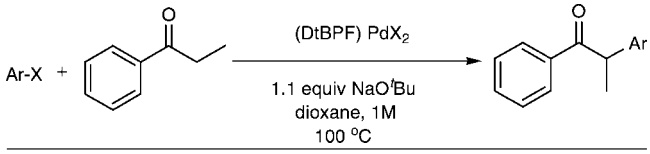
(17) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.
(18) (a) Shaughnessy, K. H.; Kim, P.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 2123. (b) Boyles, A. L.; Butler, I. R.; Quayle, S. C. *Tetrahedron Lett.* **1998**, *39*, 7766.

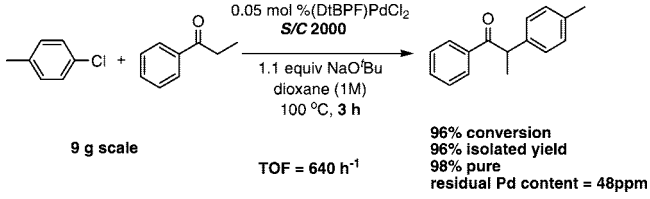
Table 5. **Effect of substrate to catalyst (*S/C*) ratio and solvent purity on the activity**



			fresh dioxane		old dioxane	
entry	Pd catalyst	*S/C*	time (h)	conv (%)[a]	time (h)	conv (%)[a]
		4-cholorotoluene[b]				
1	(DtBPF)$PdCl_2$	200	1	98	24	90
2	(DtBPF)$PdCl_2$	400	3	99	24	60
3	(DtBPF)$PdCl_2$	1000	3	96	24	52
4	(DtBPF)$PdCl_2$	2000	3	90	NA[d]	NA
5	(DtBPF)$PdBr_2$	200	1	97	24	100
6	(DtBPF)$PdBr_2$	400	1	94	24	77
7	(DtBPF)$PdBr_2$	1000	3	94	24	42
8	(DtBPF)$PdBr_2$	2000	24	78	NA	NA
		4-bromoanisole[c]				
9	(DtBPF)$PdCl_2$	1000	1	96	24	78
10	(DtBPF)$PdCl_2$	2000	3	95	24	71
11	(DtBPF)$PdCl_2$	10000	24	91	24	51
12	(DtBPF)$PdBr_2$	1000	1	96	24	61
13	(DtBPF)$PdBr_2$	2000	3	89	24	60
14	(DtBPF)$PdBr_2$	10000	24	80	24	49

[a] Conversion was determined by GC; average of two runs. [b] 4-chlorotoluene (3 mmol, 355 μL), propiophenone (3.3 mmol, 440 μL), (DtBPF)PdX_2 catalyst, NaO^{t}Bu (3.3 mmol, 317 mg), dioxane (3 mL), 100 °C. [c] 4-bromoanisole (5 mmol, 626 μL), propiophenone (5.5 mmol, 730 μL), (DtBPF)PdX_2 catalyst, NaO^{t}Bu (5.5 mmol, 530 mg), dioxane (5 mL), 100 °C. [d] NA = not available.

Scheme 1. **Nine-gram scale α-arylation of 4-chlorotoluene at *S/C* 2000**



70% conversion to the desired product was observed, while no conversion was observed when the Pd:L mole ratio was 1:1 (Table 6, entry 2 vs entry 3). A similar behavior was observed for other Pd precursors such as $Pd(OAc)_2$ and $Pd(acac)_2$ (Table 6, entry 4 vs entry 5 and entry 6 vs entry 7). Interestingly, at lower substrate concentrations, and hence lower catalyst concentrations, a Pd:DtBPF ratio of 1:1 led to modest to moderate conversions (Table 6, entries 8 and 9). Very interestingly, the use of the preisolated catalyst (DtBPF)$PdCl_2$ with a formal Pd:DtBPF ratio of 1:1 led to the highest conversion within 3 h at 1 mol % catalyst loading and 1 M substrate concentration at 60 °C (Table 6, entry 10).

The results in Table 6 suggest that *in situ* generated catalysts are highly dependent on the reaction conditions. At high substrate concentration, the optimum Pd:DtBPF ratio is 1:0.5, while the activity of the 1:1 Pd:DtBPF system slightly increased with lowering the substrate concentration. This behavior could be correlated with the formation of a $Pd(0)(DtBPF)_2$ species and slow release of the active species Pd(0)(DtBPF) at lower concentration.[11] A similar observation has been made by Buchwald on the influence of Pd:L ratios in an amination reaction involving $Pd(dba)_2$/XantPhos under *in situ* conditions.[19]

Discussion

Scheme 3 represents the catalytic cycle involving a bidentate fully formed complex. However, complication can occur due to β-hydrogen elimination, mono- vs diarylation, and thermodynamic stability of Pd−O coordinated species vs Pd−C coordinated species in the reductive elimination step.

While much progress has been achieved in the Pd-catalysed cross couplings of aryl halides and pesudohalides with various coupling partners, this area is still very much open to the role of reaction conditions in finding an optimal and practical "catalyst system". An ideal catalyst system may be the result of the apt metal to ligand ratio in addition to the fine balance of several factors: nature of ancillary ligands (electronic and steric factors), Pd precursor, solvent, base, additive, and counterion (from the Pd precursor, base, or aryl electrophile substrate). The results presented in this study clearly illustrate the role of these parameters in devising a practical catalyst system for the arylation of ketones.

As shown in the mechanism, a preformed complex is indeed superior to the *in situ* catalyst system, when DtBPF ligand is used. This is due to the formation of a well-defined species, and therefore more control in activity and selectivity during the scale-up. This study also indicates that bis-phosphinoferrocene $PdCl_2$ catalyst family follows the general trends: electron-rich substituents favor the oxidative addition of aryl chlorides, while the steric bulk and bite angle play an active role in the reductive elimination step (Table 1 and Figure 2). Although theoretically catalyst activation of the (DtBPF)PdX_2 series may lead to the same active (DtBPF)Pd(0) species, this study suggests that catalyst activity has been also influenced by the nature of the halide counterion (Table 1). We are currently studying the relationship between the nature of the palladium precursor and activity in coupling reactions (for both preisolated and *in situ* systems). We believe that this factor has an important influence on the precatalyst activation in generating the active Pd(0) species and, hence, influencing the difference in activity.

Conclusions

A general protocol for the efficient α-arylation of aryl chlorides and bromides without the need of special handling of catalyst, solvent, and reagents was devised efficiently, although the reactions were performed under inert conditions. Air-stable (DtBPF)PdX_2 (X = Cl, Br) catalysts were identified for the arylation of various ketones with a variety of aryl chlorides and aryl bromides, with excellent yields and selectivity. This study gives the lowest catalyst loadings (*S/C* loading up to 10,000/1) that have been reported for an α-arylation reaction with very good reproducibility. We have been able to perform scale up on two substrates and isolated the products in high yields and purity, with low residual metal in the product using simple work up procedures. Therefore, our current technology might be useful for plant scale up involving similar substrates. Investigation of the Pd:DtBPF ratios of the preformed and *in situ* systems in catalysis indicated that the well-defined catalyst (DtBPF)$PdCl_2$ is a preferred catalyst of choice. The investigation of this catalyst family in other coupling reactions

Scheme 2. **Nine-gram scale α-arylation of 4-bromoanisole at *S/C* 10000**

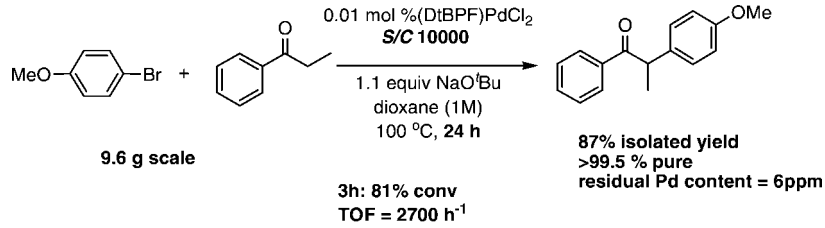
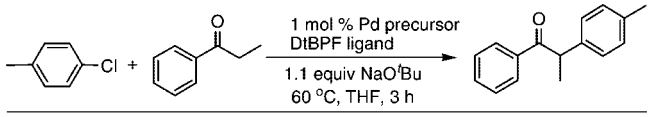


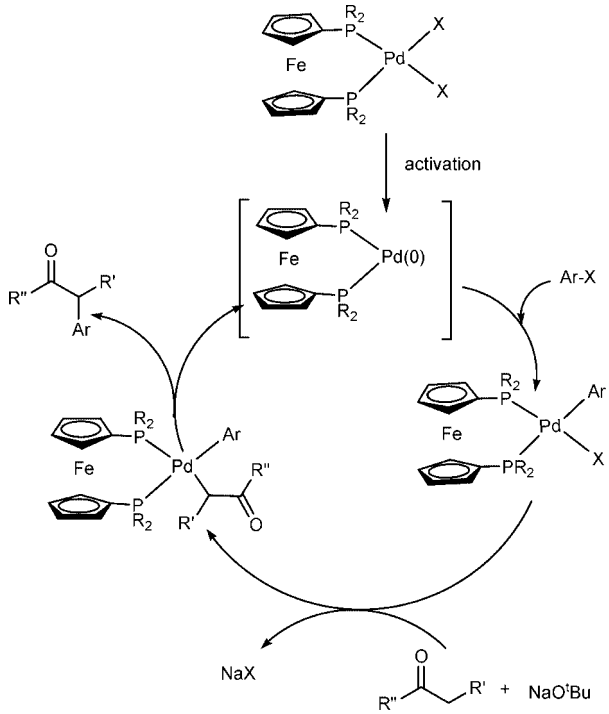
Table 6. **Effect of Pd:L ratio and concentration on the activity**



entry	Pd precursor	[S] (mmol/mL)	Pd:DtBPF molarratio	conv (%)[a]
1	$Pd_2(dba)_3$	1	no ligand	NR
2	$Pd_2(dba)_3$	1	1:0.5	70
3	$Pd_2(dba)_3$	1	1:1	NR
4	$Pd(OAc)_2$[b]	1	1:1	NR
5	$Pd(OAc)_2$	1	1:0.5	40
6	$Pd(acac)_2$[b]	1	1:1	NR
7	$Pd(acac)_2$	1	1:0.5	56
8	$Pd_2(dba)_3$	0.5	1:1	35
9	$Pd_2(dba)_3$	0.33	1:1	31
10	$(DtBPF)PdCl_2$	1	1:1	80

[a] Conversion was determined by GC. [b] 2 mol % Pd precursor was used.

Scheme 3. **Proposed catalytic cycle for ketone α-arylation using bis-phosphinoferrocene PdX_2 catalysts**



as well as the mechanistic and structural studies to understand the lower activity of $(DtBPF)PdI_2$ in comparison to its analogous chloride and bromide counterparts are currently under investigation.

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Experimental Section

General. All solvents and reagents were purchased from commercial sources and used as received. All catalysts, ligands, or precious metal precursors are commercially available from Johnson Matthey, Catalysis and Chiral Technologies. Flash chromatography was performed on silica gel 60, 0.040–0.063 mm (230–400 mesh) (Alfa Aesar) using hexane/methyl-*tert*-butyl ether. ^1H and ^{13}C NMR and spectra were recorded on Bruker-400 MHz spectrometer at ambient temperature in $CDCl_3$ (Alfa Aesar). GC analyses were performed on a Perkin-Elmer Autosystem XL gas chromatograph equipped with a Varian CP SIL 5CB capillary column. All reactions were carried out under inert atmosphere in 12-place Radleys carousels or in Schlenk tubes with magnetic stirring, unless otherwise indicated. The purity of the isolated products was >95% as determined by ^{1}HNMR, GC, and/or elemental analysis. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ 07904.

General Procedure for α-Arylation of Ketones with Aryl Halides. $(DtBPF)PdCl_2$ (2 mol %, 0.04 mmol, 26 mg) and NaO^{t}Bu (2.2 mmol, 212 mg) were loaded in a 25 mL Schlenk tube. The tube was evacuated by performing three vacuum/nitrogen refill cycles, and 2 mL of anhydrous, degassed THF or dioxane was injected, followed by the addition of the aryl halide (2 mmol) and ketone (2 mmol). The resulting mixture was stirred at the indicated temperature, and conversion was monitored by GC. The reaction mixture was purified directly by flash chromatography using 5–10% methyl-*tert*-butyl ether (MTBE)/hexane. **2-(2,6-Dimethylphenyl)-1-(3-methoxyphenyl)ethanone** (Table 4, entry 15). The general procedure afforded the title compound in 91% isolated yield (439 mg, white solid). **^{1}H NMR**($CDCl_3$): δ 7.72 (d, $J = 7.6$, 1H, ArH), 7.6 (m, $J = 7.6$, 1H, ArH), 7.45 (t, $J = 8.2$, 1H, ArH), 7.1 (m, 4H, ArH), 4.39 (s, 2H, $CH_2(CO)$), 3.4 (s, 3H, OCH_3), 2.25 (s, 6H, CH_3). **^{13}C NMR**($CDCl_3$): δ 197, 160, 138, 137, 132, 130, 128, 127, 120, 119, 113, 55, 40, 20. **Elemental analysis**: Calcd C, 80.28; H, 7.13; Found C, 80.41; H, 7.19.

General Procedure for α-Arylation of 4-Chlorotoluene at Low Catalyst Loadings (Table 5, entries 1–8). $(DtBPF)PdX_2$ (X = Cl, Br) and NaO^{t}Bu (3.3 mmol, 317 mg) were loaded in a Radleys carousel tube. The tube was evacuated by performing three vacuum/nitrogen refill cycles, and anhydrous dioxane (3 mL), 4-chlorotoluene (3 mmol, 0.355 mL), and propiophenone (3.3 mmol, 0.44 mL) were injected. The resulting mixture was degassed by performing three vacuum/nitrogen refill cycles, stirred at 100 °C, and conversion monitored by GC.

General Procedure for α-Arylation of 4-Bromoanisole at Low Catalyst Loadings (Table 5, entries 9–15). (DtBPF)-PdX_2 (X = Cl, Br) and NaO^{t}Bu (5.5 mmol, 530 mg) were loaded in a Radley carousel tube. The tube was evacuated by performing three vacuum/nitrogen refill cycles and anhydrous dioxane (5 mL), 4-bromoanisole (5 mmol, 0.626 mL) and propiophenone (5.5 mmol, 0.73 mL) were injected. The resulting mixture was degassed by performing three vacuum/nitrogen refill cycles, stirred at 100 °C, and conversion monitored by GC.

Scale-up and Isolation of α-Arylation of 4-Chlorotoluene at *S/C* 2000. (DtBPF)$PdCl_2$ (*S/C* 2000, 0.1 mol %, 0.02 mmol, 13 mg) and NaO^{t}Bu (40.4 mmol, 4g) were loaded in a 100 mL Schlenk flask. The flask was evacuated by performing three vacuum/nitrogen refill cycles, and anhydrous dioxane (30 mL), 4-chlorotoluene (40 mmol, 4.7 mL), and propiophenone (40.4 mmol, 5.4 mL) were injected. The resulting mixture was degassed by performing three vacuum/nitrogen refill cycles, lowered in a preheated oil bath at 100 °C and stirred, and conversion was monitored by GC. After 6 h, the reaction reached 99% conversion. The flask was cooled down, the resulting mixture filtered through a silica pad (30 g), and the silca pad washed with 250 mL MTBE. The filtrate was evaporated, and the resulting off-white solid was dried under high vacuum (8.36 g, 37.4 mmol, 96% isolated yield, >98.5% by GC). **1-Phenyl-2-*p*-tolylpropan-1-one: Elemental analysis**: Calcd C, 85.79; H, 7.19; Found C, 85.46; H, 7.28. Residual Pd and Fe content: Theoretical Pd, 238 ppm; Fe, 125 ppm; Found Pd, 48 ppm; Fe, 34 ppm. **^{1}H NMR** ($CDCl_3$): δ 8.07 (d, J = 7.2, 2H, ArH), 7.46 (t, J = 7.6, 1H, ArH), 7.38 (t, J = 7.6, 2H, ArH), 7.23 (d, J = 8, 2H, ArH),), 7.13 (d, J = 8, 2H, ArH), 4.7 (q, J = 6.8, 1H, CH(CO)), 2.3 (s, 3H, CH_3),1.57 (d, J = 6.8, 3H, CH_3). **^{13}C NMR** ($CDCl_3$): δ 200, 139, 136.7, 136.5, 133, 130, 129, 128.5, 128, 47.6, 21, 20.

Scale-up and Isolation of α-Arylation of 4-Bromoanisole at *S/C* 10000. (DtBPF)$PdCl_2$ (*S/C* 10000, 0.01 mol %, 0.004 mmol, 2.6 mg) and NaO^{t}Bu (40.4 mmol, 4 g) were loaded in a 100 mL Schlenk flask. The flask was evacuated by performing three vacuum/nitrogen refill cycles and anhydrous dioxane (30 mL), 4-bromoanisole (40 mmol, 5 mL), and propiophenone (40.4 mmol, 5.4 mL) were injected. The resulting mixture was degassed by performing three vacuum/nitrogen refill cycles, lowered in a preheated oil bath at 100 °C, stirred, and conversion was monitored by GC. After 24 h, the reaction reached 95% conversion. The flask was cooled down, the resulting mixture was filtered through a silica pad (10 g), and the silca pad was washed with 250 mL of MTBE. The filtrate was evaporated and the resulting sticky white solid was dried under high vacuum. The GC analysis of the crude solid showed 94% product, 3% 4-bromoanisole, and 3% propiophenone. The crude solid was recrystallized from MTBE/hexane (10 mL/200 mL) at –60 °C, filtered, and dried under high vacuum (8.4 g of white solid, 35 mmol, 88% isolated yield, >99.5% by GC). **2(4-methoxyphenyl)-1-phenylpropan-1-one: Elemental analysis**: Calcd. C, 82.05; H, 6.68; Found C, 79.74; H, 6.75. Residual Pd and Fe content: Theoretical Pd, 44 ppm; Fe, 23 ppm; Found Pd, 6 ppm; Fe, 13 ppm. **^{1}H NMR**($CDCl_3$): δ 7.95 (d, J = 7.6, 2H, ArH), 7.45 (t, J = 7.2, 1H, ArH), 7.36 (t, J = 7.6, 2H, ArH), 7.2 (d, J = 8.4, 2H, ArH),), 6.82 (d, J = 8.4, 2H, ArH), 4.64 (q, J = 6.9, 1H, CH(CO)), 3.73 (s, 3H, CH_3),1.51 (d, J = 6.8, 3H, CH_3). **^{13}C NMR**($CDCl_3$): δ 200, 159,133, 129, 128.8, 128.5, 114, 55, 47, 20.

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Supporting Information Available

Copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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