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$Cp_2Fe(PR_2)_2PdCl_2$ (R = *i*-Pr, *t*-Bu) Complexes as Air-Stable Catalysts for Challenging Suzuki Coupling Reactions

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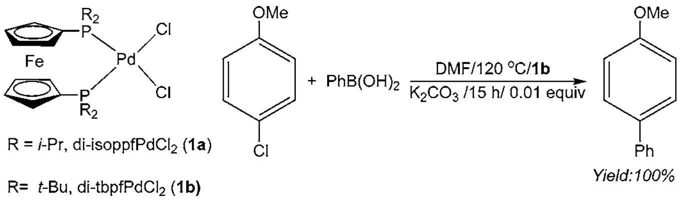
ABSTRACT



The use of $Cp_2Fe(PR_2)_2PdCl_2$ (R = *i*-Pr and *t*-Bu) in Suzuki coupling reactions were illustrated using a high throughput screening approach. The di-tbpfPdCl$_2$ catalyst was shown to be the more active catalyst for unactivated and sterically challenging aryl chlorides. Comparison studies using the commercial catalysts dppfPdCl$_2$, $(Ph_3P)_2PdCl_2$, $(Cy_3P)_2PdCl_2$, DPEPhosPdCl$_2$, dppbPdCl$_2$, dppePdCl$_2$, Pd(t-Bu$_3$P)$_2$, and [Pd-(μ-Br)(t-Bu$_3$P)]$_2$ were also done for selected cases to demonstrate the superior activities of di-tbpfPdCl$_2$ and di-isoppfPdCl$_2$.

During the past decade, carbon−carbon coupling chemistry took a quantum leap in the area of synthetic organic chemistry, mainly because of its applications in pharmaceutical and fine chemical industries for the construction of simple and complex organic molecules.[1] One of the reasons for such growth is demonstrated on the cover page of a recent issue of the *Journal of Organic Chemistry*, where Fu's assiduous work on the usage of Pd-based t-Bu$_3$P complexes is highlighted.[2] Fu's publications in this area, along with Koie's original work on amination, showed that t-Bu$_3$P, in conjunction with a Pd catalyst precursor, is a very good system for aryl chloride coupling chemistry, an important area that had very limited success for many years.[3] Following the work of Koie/Fu,[3] Hartwig[4] and Buchwald,[5] Li,[6] Guram,[7] Beller[8] and Reetz[9] applied a similar concept: the use of a bulky electron-rich organophosphine to accomplish similar chal-

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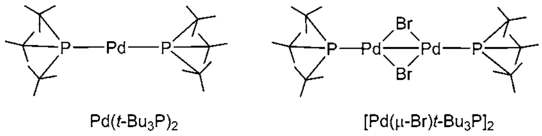

Figure 1. The structures[15] of Pd(t-Bu$_3$P)$_2$ and [t-Bu$_3$P(μ-Br)Pd]$_2$.

lenging transformations of aryl chlorides or related substrates. Carbenes are another class of electron-rich ligands that have been successfully tested for challenging coupling reactions, mostly by Nolan[10] and Herrmann.[11]

The use of air-stable, active catalysts is a preferred choice for many pharmaceutical and fine chemical companies. Although t-Bu$_3$P is a very active ligand for challenging coupling reactions, this pyrophoric, low melting solid requires special careful handling techniques. In addition, the in situ conditions often required to form the active species will sometimes cause formation of byproducts, leading to relatively lower yields and irreproducible results. The utilization of the known, fully formed Pd complexes of t-Bu$_3$P such as Pd(t-Bu$_3$P)$_2$ and [t-Bu$_3$P(μ-Br)Pd]$_2$ (Figure 1) to circumvent some of these problems was recently demonstrated by Fu[12] and Hartwig,[13] respectively. Prasad also studied the catalytic activity of [t-Bu$_3$P(μ-Br)Pd]$_2$ in amination reactions.[14] Although our group has been able to develop economical and novel commercial routes for these two catalysts, they undergo decomposition within hours if not stored properly. The decomposition occurs both in solution and solid phase, as evidenced by our in-house NMR studies.

As part of our continuing efforts to introduce new air-stable and active ferrocenylphosphine-based coupling catalysts,[16] herein we report the highly active, air-stable catalysts 1,1′- bis(di-isopropylphosphino)ferrocene palladium dichloride (di-isoppfPdCl$_2$) and 1,1′- bis(di-*tert*-butylphosphino)ferrocene palladium dichloride (di-tbpfPdCl$_2$) and their application in Suzuki coupling chemistry. Since the first report of these catalysts in the mid-1980s, only a half dozen citations are listed in the literature.[17] These articles contain limited details on synthesis or catalytic activity, in contrast to the corresponding phenyl derivative, dppfPdCl$_2$, which has been extensively studied and listed currently in about 500 publications. In this study, we also compared the reactivities of commercial catalysts, namely, Pd(t-Bu$_3$P)$_2$, [t-Bu$_3$P(μ-Br)Pd]$_2$, (Ph$_3$P)$_2$PdCl$_2$, (Cy$_3$P)$_2$PdCl$_2$, DPEPhos-PdCl$_2$ [bis(2-diphenylphosphinophenyl)ether palladium dichloride], dppfPdCl$_2$, dppbPdCl$_2$ and dppePdCl$_2$.

Table 1. Suzuki Coupling of Various Unactivated and Activated Substrates with PhB(OH)$_2$ Using Di-tbpfPdCl$_2$ (**1b**) under HTS Conditions

$$\text{ArX} + \text{PhB(OH)}_2 \xrightarrow[\text{K}_2\text{CO}_3\text{/ 15 h}]{\text{DMF/120 °C/}\mathbf{1b}} \text{Ar-Ph}$$

entry	substrate	catalyst loading	yield (%)
1	4-chlorotoluene	0.01 equiv	98
2	4-bromoanisole	0.01 equiv	100
3	4-chloroanisole	0.01 equiv	100
4	4-bromo-3-methylanisole	0.01 equiv	96
5	2-chlorothiophene	0.01 equiv	84
6	2-bromo-4-fluoroanisole	0.01 equiv	95
7	2-chloro-4-fluoroanisole	0.01 equiv	95
8	2-chloro-3-methylpyridine	0.01 equiv	89
9	2-chloro-4,6-dimethoxytriazine	0.01 equiv	100
10	bromomesitylene	0.01 equiv	85

Coupling of phenyl boronic acid with a variety of aryl chlorides and bromides was conducted using di-tbpfPdCl$_2$ as illustrated in Table 1. The structures of the electron-rich bidentate ferrocene-based catalysts employed in the study are given in Figure 2.

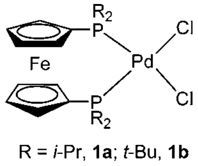

Figure 2. New catalysts, di-isoppfPdCl$_2$ (**1a**) and di-tbpfPdCl$_2$ (**1b**), employed in the study.

Most striking is the range of substrates with which the catalyst is quite reactive. Unactivated aryl chlorides such as chlorotoluene (entry 1) and chloroanisole (entry 3) gave nearly complete formation of the coupled products with a minimal amount of starting materials or byproducts. Additionally, sterically encumbered substrates such as 2-chloro-3-methyl pyridine, 2-chloro-4,6-dimethoxy triazine, and bromomesitylene gave good to excellent yields of the desired coupled product.

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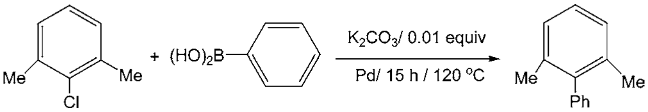
Table 2. Relative Reactivities of Pd Catalysts for the Coupling of 2-Chloro-*m*-xylene with $PhB(OH)_2$ in DMF



entry	catalyst	loading	yield (%)[a]
1	$(Ph_3P)_2PdCl_2$	0.01 equiv	0.0
2	Pd(*t*-$Bu_3P)_2$	0.01 equiv	64
3	[Pd(*μ*-Br)(*t*-$Bu_3P)]_2$	0.01 equiv	51
4	$dppfPdCl_2$	0.01 equiv	0.0
5	di-isoppf$PdCl_2$	0.01 equiv	37
6	di-tbpf$PdCl_2$	0.01 equiv	66

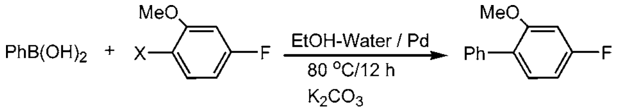
One of the more difficult systems in the present study seems to be 2-chlorothiophene (entry 5), which gave only 84% yield of the coupled product. In our earlier study, we found that even bromothiophene was a difficult system to couple, unlike bromopyridine, bromoanisole, and bromotoluene, when Ph_3P-Pd-based homogeneous or polymer-supported catalysts were employed.[18] Among the FibreCat 1000 series, a *t*-Bu_3P-based FibreCat-1032 (formerly known as "TunaCat") was the best catalyst of choice.[18]

Because *t*-Bu_3P-based preformed Pd(*t*-$Bu_3P)_2$ and [Pd(*μ*-Br)(*t*-$Bu_3P)]_2$ are considered to be two of the most active next generation catalysts despite their drawbacks (vide supra),[12−14] we decided to compare the relative activities in selected systems. The Suzuki coupling results using 2-chloro-*m*-xylene and phenyl boronic acid are summarized in Table 2.

These reactions are not optimized; however, they show a trend for this particular system. Both $dppfPdCl_2$ and $(Ph_3P)_2PdCl_2$ gave no conversion (entries 1 and 4) and were included as standards. Among the electron-rich catalysts, the isopropyl-based catalyst is the least active (entry 5), and *tert*-butyl ferrocenyl derivative (entry 6) is the most active. The activity of the Pd(0) catalyst seems to be comparable (entry 2) to that of **1b**, whereas that of the Pd(I) dimer (entry 3) is slightly lower. This shows that the activity of di-tbpf$PdCl_2$ is at least equal to or better than that of Pd(*t*-$Bu_3P)_2$ and [Pd(*μ*-Br)(*t*-$Bu_3P)]_2$ for very sterically hindered, unactivated substrates.

To demonstrate the significant reactivity differences between bromo- and chloro- substrates, we also studied the coupling of 2-bromo-4-fluoroanisole and 2-chloro-4-fluoroanisole using various air-stable Pd(II) catalysts. The results are summarized in Table 3.

Table 3. Demonstration of Superior Activity of Di-tbpf$PdCl_2$ in the Suzuki Coupling of 2-Chloro-4-fluoroanisole[a]



entry	catalyst	X	loading (equiv)	yield (%)
1	$(Ph_3P)_2PdCl_2$	Br	0.01	93
2	$(Cy_3P)_2PdCl_2$	Br	0.01	100
3	$dppePdCl_2$	Br	0.01	100
4	(*o*-$tol_3P)_2PdCl_2$	Br	0.01	100
5	$dppfPdCl_2$	Br	0.01	100
6	di-isoppf$PdCl_2$	Br	0.01	100
7	$(Ph_3P)_2PdCl_2$	Cl	0.01	2
8	$(Cy_3P)_2PdCl_2$	Cl	0.01	2
9	$dppePdCl_2$	Cl	0.01	5
10	$dppfPdCl_2$	Cl	0.01	4
11	(*o*-$tol_3P)_2PdCl_2$	Cl	0.01	7
12	(DPEPhos)$PdCl_2$	Cl	0.01	2
13	di-isoppf$PdCl_2$	Cl	0.01	9
14	di-tbpf$PdCl_2$	Cl	0.01	65
15	di-tbpf$PdCl_2$	Cl	0.01	100[a]

[a] All the reactions were conducted in EtOH−water (1:1) at 80 °C, except for entry 15, where DMF at 120 °C was used.

Although a majority of first and second generation Pd-based complexes (entries 1−5) gave complete conversion of 2-bromo-4-fluoroanisole to 2-phenyl-4-fluoroanisole, the corresponding chloro derivative was difficult to couple using a similar set of catalysts. Even the electron-rich di-isoppf$PdCl_2$ was not a good catalyst for this reaction. It is interesting to note that di-tbpf$PdCl_2$ was not only the best catalyst for this transformation but also significantly more reactive, demonstrating the importance of steric bulkiness and electron richness of the ligands in aryl chloride coupling reactions.

Both Butler and Hartwig have reported that di-isoppf and di-tbpf ligands with $PdCl_2$ were very active catalysts for Heck arylation of olefins[19] and amination[4] reactions. A report is also available on the use of these ligands in α-arylation of ketones.[20] However, these component phosphines are more air-sensitive than the corresponding Pd complexes and consequently are more difficult to handle in industrial processes.

For the first time, we demonstrated that di-tbpf$PdCl_2$ and di-isoppf$PdCl_2$ are excellent air-stable catalysts for aryl chloride Suzuki coupling reactions with relatively low metal loadings. The trend for reactivity of these catalysts is $dppfPdCl_2$ < di-isoppf$PdCl_2$ < di-tbpf$PdCl_2$. The increase in activity is attributed to the increase in steric bulk and electron density of the phosphine ligand.[3] The relatively larger bite angles of Pd complexes also seem to be important for the higher activity.[1f,17,21] On the basis of this work, these catalysts are superior to the *t*-Bu_3P-based Pd catalysts by considering the relative reactivity and air-stability. Work is in progress in demonstrating the activities of these catalysts in Buchwald−Hartwig, Kumada, Heck, Negishi, Stille, and Sonogashira coupling reactions. We also plan to develop

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conditions to obtain room-temperature Suzuki coupling.[1h]

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Supporting Information Available: Experimental details on the Suzuki coupling screening studies and characterization studies of di-isoppfPdCl$_2$ and di-tbpfPdCl$_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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