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Efficient Cross-Coupling Reactions of Aryl Chlorides and Bromides with Phenyl- or Vinyltrimethoxysilane Mediated by a Palladium/Imidazolium Chloride System

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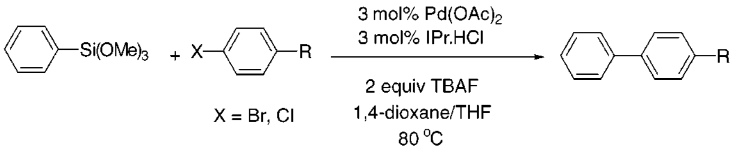
ABSTRACT



A combination of palladium acetate and the imidazolium salt IPr·HCl (1, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) has proven to be highly efficient in the cross coupling reactions of aryl bromides and electron-deficient aryl chlorides with phenyltrimethoxysilane or vinyltrimethoxysilane. The catalytic performance of this system was found to be comparable to that of systems using PCy_3 and $P(o\text{-tol})_3$.

Pd-catalyzed C−C bond formation is one of the most fundamental and important reactions in organic synthesis.[1] It represents the key step in a wide range of preparative organic processes, from the synthesis of natural products[2] to supramolecular chemistry and material science.[3] Common methodologies used are the palladium mediated coupling of organic halides or halide equivalents with Grignard reagent[4] (Kumada reaction), organotin[5] (Stille reaction) or organoboron[6] reagents (Suzuki reaction) where monodentate phosphines are usually employed as ancillary ligands.

The use of silicon-derived compounds as transmetalation reagents has attracted much attention as a viable option to these processes for its low cost, easy availability, nontoxic byproducts, and stability to many reaction conditions.[7] High catalyst and phosphine loading are usually required to produce high yields for unactivated aryl halides using this methodology.

Nucleophilic N-heterocyclic carbenes, or so-called “phosphine mimics”, have attracted considerable attention as

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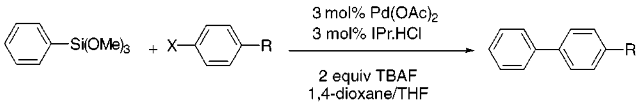
possible alternatives for the widely used phosphine ligands in homogeneous catalysis.[8] Recently, we and others have found that the combination of $Pd_2(dba)_3$ or $Pd(OAc)_2$ and IPr·HCl (**1**) (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) or IMes·HCl (**2**) (IMes = bis-(1,3-(2,4,6-trimethylphenyl)imidazol-2-ylidene) was highly efficient in Suzuki coupling,[9] Kumada coupling[10] and amination of aryl chlorides.[11] Therefore, it was of interest to expand the scope of these catalytic systems to silicon-derived reagents as the coupling partner. We now wish to report the use of Pd(II)/IPr.HCl in the cross coupling reaction of aryl halides with phenyltrimethoxysilane. A preliminary study on vinylation of aryl bromides using vinyltrimethoxysilane had also been performed.

Treatment of aryl halide (1 equiv) with phenyltrimethoxysilane (2 equiv) in the presence of 3 mol % of $Pd(OAc)_2$ and 3 mol % of IPr·HCl in 1,4-dioxane/THF at 80 °C was found to lead to coupling products[12] (Table 1).[13] In general, excellent yields of cross-coupled products were obtained for aryl bromides (entries 1−3). In fact, for the electron-deficient substrate 4-bromoacetophenone, quantitative conversion was obtained in less than 1 h (entry 3). Longer reaction times were required for electron−neutral aryl bromides (entries 1−2).

Table 1. Pd−IPr-Catalyzed Cross-Coupling of Aryl Halides with Phenyltrimethoxysilane



entry	X	R	time (h)	yield[a] (%)
1	Br	H	3	100
2	Br	Me	6	93[b]
3	Br	COMe	1	100
4	Cl	OMe	17	19[c]
5	Cl	Me	4	29
6	Cl	COMe	3	100
7	Cl	CN	2	100

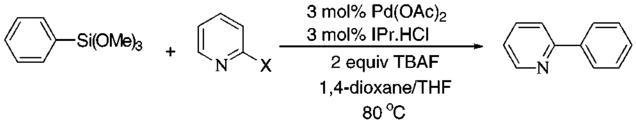
[a] GC yields. [b] 60 °C; 3 equiv of $PhSi(OMe)_3$. [c] Isolated yield.

The catalytic system also proved to be highly efficient for electron-deficient aryl chlorides (entries 6−7). Complete conversion was readily obtained for 4-chloroacetophenone, although a slightly longer reaction time compared with the bromo-analogue was required, which is consistent with the general trend that aryl chlorides are less reactive than aryl bromides as observed in Stille,[5] Suzuki[6] and Kumada coupling.[4] It is worth mentioning that by using a $Pd(II)/PPh_3$ or P(*o*-toly)$_3$ system, 4-chloroacetophenone could not be activated in the coupling reaction with phenytrimethoxysilane.[7a] Subsequently a more sophisticated phosphine (Buchwald's ligand)[14] and high catalyst loading were required to provide moderate yields of the desired product. In the present system, coupling involving the electron deficient 4-chlorobenzonitrile gave quantitative conversion in 2 h (entry 7).

In contrast to our findings in Suzuki[9a] and Kumada coupling,[10] the catalyst/ligand system was not suitable for electron-neutral or electron-donating aryl chlorides in siloxane cross coupling reactions (entries 4−5). The reaction with 4-chlorotoluene gave only a 29% yield of cross-coupled product in 4 h. Attempt to prolong the reaction time did not lead to an increase in yield. Presumably, the catalytic system degenerated after 4 h which was consistent with the observation of palladium black deposition. A 19% isolated yield of biaryl product was obtained for 4-chloroanisole (entry 4).

As illustrated in Table 2, the siloxane cross coupling technology based on the Pd(II)/IPr·HCl is also applicable to heteroaryl halides. Using 2-bromopyridine as substrate gave 81% yield of 2-phenylpyridine in 7 h (entry 1). The chloro-

Table 2. Pd-IPr-Catalyzed Cross-Coupling of 2-Chloro- and 2-Bromopyridine with Phenyltrimethoxysilane



entry	X	time (h)	yield (%)
1	Br	7	81[a]
2	Cl	7.5	81[b]

[a] Isolated yield. [b] GC yield.

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(12) Application of these conditions to the substrate 4-bromotoluene resulted in small amount of homocoupled product formation. By lowering the temperature to 60 °C and using 3 equiv of phenyltrimethoxysilane, the amount of homocoupled product was effectively reduced. These conditions are general for all other substrates described in this study.

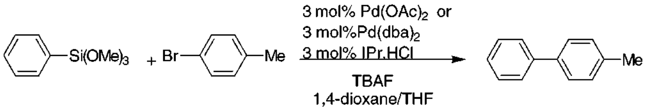
(13) **General procedure for cross coupling reactions:** Under an atmosphere of argon 1,4-dioxane (3 mL), aryl halide (1.0 mmol), phenyltrimethoxysilane (2.0 mmol) and TBAF (2 mL, 2.00 mmol) were added in turn to a screw-capped vial with a septum charged with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), **1** (13 mg, 0.03 mmol), and a magnetic stirring bar. The vial was placed in an 80 °C oil bath and stirred. The reaction was monitored by GC. In some cases, the yields were determined by GC using biphenyl as internal standard. The mixture was then allowed to cool to room temperature. The reaction was quenched (30 mL H_2O) and extracted (4 × 30 mL Et_2O). The organic layers were dried over $MgSO_4$, concentrated in vacuo and then purified by flash chromatography. All coupling products were found to be identical by ^1H NMR with literature data.

(14) Buchwald's ligand = 2-(Dicyclohexylphosphino)biphenyl.

analogue gave an identical yield (entry 2). It is worth noting that this latter reaction using 4-chloropyridine has not previously been reported in silicon-derived coupling reactions using phosphines as ancillary ligands.[7a]

As stated above, common C–C bond coupling technologies employed phosphines as ancillary ligand. Thus, it was of interest to compare the catalytic performances of the imidazolylidene ligands IPr and IMes with the commonly employed phosphines in siloxane cross coupling. As shown in Table 3, both PCy_3 and P(*o*-tolyl)$_3$ are highly effective in the coupling reaction of 4-bromotoluene with phenyltrimethoxysilane (entries 1–2). Comparable catalytic activity could also be obtained with IPr•HCl, although a slightly longer reaction time was required (entry 4). Consistent with previous findings, IMes•HCl, with a smaller steric bulk, was less efficient than IPr•HCl (entry 3).

Table 3. Effect of Ancillary Ligand for the Pd–IPr-Catalyzed Cross-Coupling of 4-Bromotoluene with Phenyltrimethoxysilane

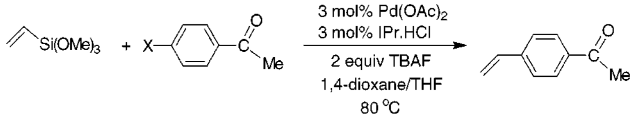


entry	Pd	L	time (h)	yield[a] (%)
1	Pd (0)	PCy_3	1.5	100[b]
2	Pd (0)	P(*o*-tol)$_3$	1	100[b]
3	Pd (II)	IMes•HCl	2	60[c]
4	Pd (II)	IPr•HCl	6	93[c]

[a] GC yield. [b] 80 °C; 2 equiv of $PhSi(OMe)_3$. [c] 60 °C; 3 equiv of $PhSi(OMe)_3$.

A preliminary study was performed to see if the catalytic system Pd(II)/IPr•HCl could also mediate the coupling reaction of aryl halides with vinyltrimethoxysilane to produce substituted styrene. A similar protocol to the preparation of biaryls using phenyltrimethoxysilane was employed. As shown in entry 1 of Table 4, the coupling reaction of 4-bromoacetophenone with vinyltrimethoxysilane to 4-acetylstyrene was completed in 8 h. Reaction with the chloro-analogue required a longer reaction time to reach completion (entry 2). These early results show great promise as the methodology could find applications as a substitute for Stille coupling where the generated tin byproducts are environmentally undesirable.

Table 4. Pd-IPr Catalyzed Coupling of 4-Bromo-acetophenone with Vinyltrimethoxysilane



entry	X	time (h)	conversion (%)
1	Br	8	100
2	Cl	18	100

In summary, the Pd/imidazolium chloride system has been successfully extended to the siloxane cross coupling methodology. The Pd(II)/IPr•HCl system is highly efficient in activating aryl bromides and electron-deficient aryl chlorides. Investigations into the use of other siloxane derivatives and applications to pharmaceutical intermediate synthesis are ongoing.

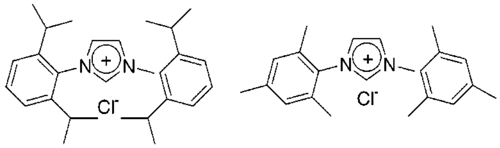


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Figure 1. Imadazolium salts.

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Supporting Information Available: Experimental procedures, details of reaction conditions, and spectroscopic and analytic data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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