Palladium-catalyzed Coupling of Benzoyl Halides with Aryltrifluorosilanes Leading to Diaryl Ketones

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Acyl–aryl Hiyama coupling of acyl halides with arylsilanes has been achieved by employing a palladium/phosphine catalyst system. A variety of acyl chlorides and fluorides can be applied for coupling with arylsilicon reagents, and unsymmetrical benzophenone derivatives can be prepared using this protocol.

In modern synthetic chemistry, the transition-metal-catalyzed cross-coupling reaction is a powerful tool for the formation of a carbon–carbon bond. Organosilicon compounds are among the most attractive coupling reagents because of their chemical stability, high availability, and low toxicity. Hence, a cross-coupling using organosilicon compounds (Hiyama coupling) ranks high on the list of the most important carbon–carbon bond formation strategies.[1] Numerous researchers have developed a variety of useful and straightforward methodologies for the transition-metal-catalyzed coupling for the construction of diaryl ketones, which function as important building blocks in organic and pharmaceutical chemistry. The three most recent approaches to silicon-based cross-coupling for diaryl ketone synthesis are summarized in Scheme 1: (A) carbonylative coupling of aryl halides with arylsilanes;[2] (B) coupling of aryl halides with acylsilanes;[3] and (C) coupling of acyl electrophiles with arylsilanes.[4]

Hiyama and co-workers reported the palladium-catalyzed carbonylative coupling of aryl iodides with arylfluorosilanes. The striking features of this reaction were that carbon monoxide was embedded in the diary ketone framework under only 1 atm, and the use of an organosilane containing more than one fluorine atom was essential for the coupling; in the case of tetraorgano-silanes, the major formation of an acyl fluoride is considered a demerit (Scheme 1A).[2] Another approach was the coupling of aryl halides with acylsilanes, such as in 2011, when Krska and co-workers developed a coupling of aryl bromides with aryl trimethylsilyl ketone as an acyl anion equivalent in the presence of a palladium catalyst (Scheme 1B).[3] Numerous efficient cross-coupling reactions of acid halides with a variety of organo-metallic reagents, which is classified as a (C)-type coupling, have been reported, such as B,[5] Mg,[6] Al,[7] Zn,[8] In,[9] Sn,[10] Hg,[11] and Bi,[12] are also available for coupling with carboxylic acid derivatives.[13] In contrast, as far as we could ascertain, there has been no report of the direct preparation of diaryl ketones via coupling with organosilicon compounds, with one notable exception: coupling of phenylbenzothioates with ArSi(OMe)$_3$ in the presence of CuI, TBAF, and Pd(PPh$_3$)$_4$ as the catalyst (Scheme 1C).[4]

However, the acyl derivative used in that procedure was limited to a thioester, and the use of other acyl electrophiles as a counter partner for a similar cross-coupling with organosilicon compounds remains unexplored.[14] Hence, the development of a transition-metal-catalyzed coupling reaction of organosilicon compounds with typical acyl halides leading to the preparation of diaryl ketones is considered one of the most effective and attractive routes, and both these substrates are extremely economical and widely available. In this communication, we describe a novel (C)-type coupling preparation of diaryl ketones, which is a palladium-catalyzed acyl–aryl Hiyama cross-coupling using an acid halide, or a pseudohalide, such as an acid chloride and an acyl fluoride, as the acyl electrophiles.

Initially, we investigated the reaction conditions caused by the coupling of 3,5-dimethylbenzoyl chloride (**1a**) with a phenylsilicon reagent in the presence of 3.5 equiv of CsF in xylene at 140 °C for 24 h (Table 1).[15] When the reaction was performed using phenyltrifluorosilane (**2a**) with a catalytic amount of Pd(OAc)$_2$/PPh$_3$, 23% of the desired diaryl ketone **3aa** was detected by GC analysis (Entry 1). Ligand screening was then conducted to improve the chemical yield. The electron-withdrawing triarylphosphine, P(4-CF$_3$C$_6$H$_4$)$_3$, showed a similar effect as PPh$_3$ (Entry 2). By contrast, the use of a more electron-donating methoxy-substituted triarylphosphine improved the yield of the ketone (Entry 3). Although the use of PCy$_3$ did not give the product (Entry 4), the use of P^{t}Bu$_3$ as a ligand effectively promoted the coupling to give diaryl ketone **3aa** in 75% isolated yield (Entry 5). It is well known that a Pd/P^{t}Bu$_3$-based catalyst system often exhibits high reactivity for a variety of cross-couplings because of its steric bulkiness and electron richness.[16] However, other bulky and electron-rich phosphines or carbenes, such as XPhos and IMes, were ineffective for this coupling (Entries 6 and 7). The effect of a silyl substituent on the
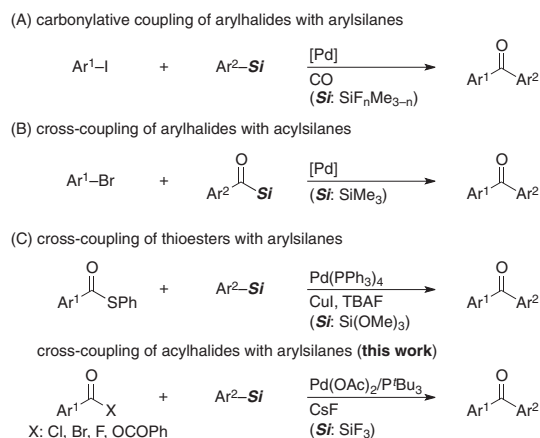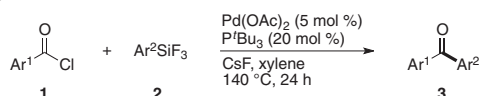

Scheme 1. Palladium-catalyzed silicon-based coupling for diaryl ketone.

Table 1. Optimization of the reaction conditions[a]
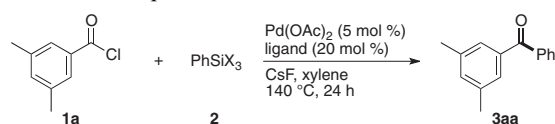
Entry	PhSiX$_3$	Ligand	Yield/%[b]
1	PhSiF$_3$ (2a)	PPh$_3$	23
2	2a	P(4-CF$_3$C$_6$H$_4$)$_3$	25
3	2a	P(4-MeOC$_6$H$_4$)$_3$	41
4	2a	PCy$_3$	nd[c]
5	2a	P^{t}Bu$_3$	75[d]
6	2a	XPhos	37
7	2a	IMes[e]	31
8	PhSi(OEt)$_3$	P^{t}Bu$_3$	3[f]

[a]Reaction conditions: **1a** (0.4 mmol), PhSiX$_3$ (1.2 mmol), Pd(OAc)$_2$ (0.02 mmol), ligand (0.08 mmol), and CsF (1.4 mmol) in xylene (0.4 mL) at 140 °C for 24 h. [b]GC yield. [c]Not detected. [d]Isolated yield. [e]IMes was generated in situ from IMes·HCl with ^{t}BuOK (1:1). [f]Ethyl 3,5-dimethylbenzoate was determined in an 80% NMR yield.

Table 2. Pd/P^{t}Bu$_3$-catalyzed coupling of benzoyl chlorides **1** with aryltrifluorosilane **2**[a]

[a]Reaction conditions: **1** (0.4 mmol), **2** (1.2 mmol), Pd(OAc)$_2$ (0.02 mmol), P^{t}Bu$_3$ (0.08 mmol), and CsF (1.4 mmol) in xylene (0.4 mL) at 140 °C for 24 h. Isolated yields are shown. [b]1 mmol scale.

employed phenylsilane was critical to this transformation; when using a trialkoxylsilane, PhSi(OEt)$_3$, acid chloride **1a** was converted into the corresponding ethyl ester in 80% yield, and only 3% of the desired ketone **3aa** was detected (Entry 8).

The formation of various diaryl ketones was then performed using benzoyl chlorides **1** with aryltrifluorosilanes **2** under the optimal conditions described for Entry 5 in Table 1 (Table 2). The reaction of benzoyl chloride (**1b**) with phenyltrifluorosilane (**2a**) afforded benzophenone (**3ba**) in good yield. Acid chlorides **1c–1e** bearing a methyl group on the aromatic ring, at the 2-, 3-,

Table 3. Palladium-catalyzed Hiyama coupling of various acyl electrophiles with phenylsilane **2a**[a]
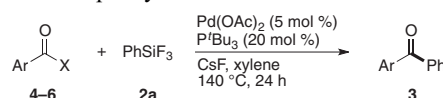
Entry	Substrate	Ar	X	Product	Yield/%[b]
1	4a	3,5-Me$_2$C$_6$H$_3$	F	3aa	54[c]
2	4b	Ph	F	3ba	63[c]
3	4c	2-MeC$_6$H$_4$	F	3ca	50
4	4d	3-MeC$_6$H$_4$	F	3da	59
5	4e	4-MeC$_6$H$_4$	F	3ea	47
6	4f	4-MeOC$_6$H$_4$	F	3fa	33
7	4h	4-CF$_3$C$_6$H$_4$	F	3ha	55
8	4k	2-naphthyl	F	3ka	55
9	4m	cynnamyl	F	3ma	10
10	5	Ph	Br	3ba	37[c]
11	6	(4-MeC$_6$H$_4$CO)$_2$O		3ea	23[c]

[a]Reaction conditions: acyl halides, or pseudohalides, **4–6** (1 mmol), **2a** (3 mmol), Pd(OAc)$_2$ (0.05 mmol), P^{t}Bu$_3$ (0.2 mmol), and CsF (3.5 mmol) in xylene (1 mL) at 140 °C for 24 h. [b]GC yield. [c]0.4 mmol scale.

or 4-positions, were applied to the coupling with phenylsilane **2a** to give asymmetric diaryl ketones **3ca–3ea** in 58–64% isolated yields. The coupling of various benzoyl chlorides **1f–1j** bearing either electron-donating or electron-withdrawing groups, such as a methoxy, fluoro, trifluoromethyl, nitro, and cyano group, at the 4-position with phenylsilane **2a** formed diaryl ketones **3fa–3ja** in moderate to good yields. Substrates bearing 2-naphthyl, 2-thienyl, and cinnamyl moieties can be also applicable to the coupling with **2a**, though the yields were decreased, to afford the coupling products **3ka**, **3la**, and **3ma**. Methyl-substituted unsymmetrical- and symmetrical diaryl ketones **3ab–3ad** were prepared from a combination of 3,5-dimethylbenzoyl chloride (**1a**) and the corresponding arylsilanes **2b–2d**. Further, 3-methylbenzophenone (**3da**) was obtained from benzoyl chloride (**1b**) and 3-methylated arylsilane **2c**, as well as the reaction of benzoyl chloride **1d** with **2a**.

This protocol was then expanded to other acid derivatives (Table 3). Compared with a typical acid chloride, acyl fluorides generally behave as more stable electrophiles toward a nucleophile, such as water, and they can be easily prepared from the corresponding carboxylic acids or acyl chlorides.[17] Hence, the utility of acyl fluorides as an electrophile is considered to be significant for this type of a coupling. Moreover, the catalytic conversion of acyl fluorides to diaryl ketones has been rare, except for one example with a nickel catalyst reported by Rovis and co-workers.[8e] When the reaction of acyl fluoride **4a** with arylsilane **2a** was conducted using a catalytic system composed of Pd(OAc)$_2$/P^{t}Bu$_3$ and CsF at 140 °C for 24 h, the desired coupling product **3aa**, which would have been formed via an acyl C–F bond cleavage, was produced in 54% GC yield, (Entry 1). Several acyl fluorides **4b–4f**, **4h**, **4k**, and **4m** can also be used in the coupling to give benzophenone derivatives **3ba–3ma**, respectively (Entries 2–9). When both acyl bromide **5** and acid anhydride **6** were applied to the substrate, the corresponding benzophenone derivatives **3ba** and **3ea** were obtained in moderate yields (Entries 10 and 11).

Although the mechanistic investigations of this coupling are yet to be conducted, it is assumed that the reaction would proceed in a manner similar to a typical Hiyama cross-coupling process: (i) oxidative addition of an acyl halide to palladium(0); (ii) transmetalation of the aryl group on the pentacoordinate silicate, which is generated from an arylsilane with CsF, to the acyl palladium complex; and (iii) reductive elimination to produce a diaryl ketone, with the regeneration of palladium(0).

In summary, we have demonstrated the first Hiyama cross-coupling of acyl halides, or pseudohalides, with aryltrifluorosilanes, leading to the preparation of diaryl ketones, using a $Pd(OAc)_2/P^tBu_3$ catalyst system. Noteworthy features of this method include the applicability of the transformation to highly versatile acyl chlorides and to an inactive acyl fluoride, and the achievement of this conversion by a combination of commercially and readily available catalysts and substrates. A key factor in our success was the utilization of a bulky and electron-rich trialkylphosphine ligand and a fluoride-substituted organosilicon transmetalating reagent. Efforts are underway to further optimize and mechanistically study this coupling, along with other applications for this catalyst system.

Supporting Information is available on http://dx.doi.org/10.1246/cl.160223.

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