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Palladium-catalyzed cross-coupling reaction of aryl(trialkyl)silanes with aryl nitriles

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ABSTRACT

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Introduction

Biaryls represent the mostly common structural motifs in a broad range from naturally occurring, potentially useful therapeutic agents to versatile building materials for light-emitting diodes and liquid crystals. Metal-catalyzed cross-coupling reactions have innovated a number of synthetic processes to access these structural motifs.^{1,2} While a number of protocols have been developed using a wide range of conventional electrophiles (aryl halides, aryl sulfonates, etc.), further extension of cross-coupling reaction involving extremely challenged electrophilic partner recently has attracted much attention to this field, such as cleavage of C-C bond.^{3–5} Owing to its strength (>100 kcal mol⁻¹), the carbon– carbon σ -bond of C-CN bond to be broken is kinetically inert, and its activation is usually limited to systems in which relief of strain or aromatization serves as the driving force.⁶ Nevertheless, low-valent metal complexes containing Ni,⁷⁻⁹ Rh,^{10,11} Pd,^{12,13} etc.,^{14,15} are able to cleave the carbon–carbon bond, and make C-CN bond an attractive electrophile used in an array of transformations, such as cross-coupling,¹⁶⁻¹⁸ silylation,¹⁹ borylation,²⁰ and carbocynation²¹⁻²⁴ of alkenes and alkynes. With respect to arylation of C-CN bond to form biaryls, Miller et al., for example, reported several cross-coupling reactions of aryl nitriles with aryl Grignard reagents,^{16,17} and Shi and co-workers also developed a boron-based cross-coupling reaction of aryl nitriles.²⁵ However, the CN group acting as leaving group in cross coupling is, to date, limited to the reaction with active organometallics (Mg, Zn, B) via Ni catalyst. Increasing demands for chemoselectivity, availability, stability, and non-toxicity have made arylsilanes an attractive alternative to conventionally employed organomagnesium and organoboron reagents in cross-coupling reaction.²⁶⁻⁴¹ Owing to the weak nucleophilic feature of organosilanes, such protocols have rarely met with success in silicon-based cross-coupling reaction of aryl nitriles. On the other hand, we recently developed a robust aryl(trialkyl)silane reagent that could participate in the cross-coupling reaction of aryl chlorides and tosylates.⁴² The attractive organosilane (HOMSi reagent) bearing a proximal hydroxyl group close to the silyl species allows fluoride-free intramolecular activation, and formation of pentacoordinate silicates and/or metal alkoxides is likely responsible for the transmetallation under mild conditions with a carbonate salt as activator.^{43–45} With the background in mind, we examined a silicon-based aryl-aryl cross-coupling reaction of aryl nitriles. We found that the newly developed arylsilanes also achieve highly chemoselective C-C bond forming reaction by the cleavage of C-CN bond. Herein, we report a palladium-catalyzed aryl-aryl cross-coupling reaction of the aryl(trialkyl)silanes with aryl nitriles.

Using highly stable, readily accessible, and recyclable 2-(2-hydroxyprop-2-yl)cyclohexyl-substituted

arylsilanes activated by a mild phosphate base, palladium-catalyzed silicon-based aryl-aryl cross-cou-

pling reaction proceeds for the first time with aryl nitriles in a highly chemoselective manner.

Results and discussion

In the course of our research project aiming at metal-catalyzed silicon-based arylation of C–CN bond, the cross-coupling reaction of ethyl 4-cyanobenzonate **2a** with phenyl[2-(2-hydroxyprop-2-yl)





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Table 1

Optimization of conditions for Pd-catalyzed cross-coupling of 1a with 2a^a



 $Ar^1 = EtO_2C-C_6H_4$

Entry	Metal	Ligand	Yield of 3a ^b (%)	Yield of 4a^c (%)
1	Ni(cod) ₂	PMe ₃	46	>95
2	Ni(cod) ₂	PEt ₃	<10	>95
3	[Pd(allyl)Cl] ₂	PMe ₃	85	>95
4	[Pd(allyl)Cl] ₂	PEt ₃	<10	>95
5	[Pd(allyl)Cl] ₂	$P(i-Pr)_3$	Trace	>95
6	[Pd(allyl)Cl] ₂	PCyP ₃	Trace	>95
7	[Pd(allyl)Cl] ₂	$P(n-Bu)_3$	Trace	>95
8	[Pd(allyl)Cl] ₂	PCy ₃	Trace	>95
9	[Pd(allyl)Cl] ₂	PPhMe ₂	Trace	>95
10	$Pd(OAc)_2$	PMe ₃	58	>95
11	Pd(dba) ₂	PMe ₃	34	>95
12	$Pd(CH_3CN)_2Cl_2$	PMe ₃	61	>95
13	PdCl ₂	PMe ₃	<10	>95
14 ^d	[Pd(allyl)Cl] ₂	PMe ₃	67	>95
15 ^e	[Pd(allyl)Cl] ₂	PMe ₃	27	52
16 ^f	[Pd(allyl)Cl] ₂	PMe ₃	<10	20

 $^{\rm a}~$ Reaction conditions: $1a~(0.4~mmol),\,2a~(0.2~mmol),\,metal$ source (10 mol % with respect to metal), K₃PO₄ (0.8 mmol), ligand (0.04 mmol), toluene (1 mL), 110 °C, 24 h.

^b The yield was determined by GC.

The yield was, with respect to **1a**, determined by GC.

^d Using a 2.5 mol % of [Pd(allyl)Cl]₂.

K₃PO₄ was replaced with K₂CO₃.

^f K₃PO₄ was replaced with Na₂CO₃.

cyclohexyl]dimethylsilane 1a was firstly conducted to screen the optimal reaction conditions (Table 1). In an initial experiment, we delightedly observed the formation of desired coupling product 3a in a 46% yield when the reaction was catalyzed by Ni(cod)₂ (5 mol %) in the presence of PMe₃ (entry 1). Further investigation revealed the yield was dramatically increased to 85% when the metal Ni was switched to Pd (entry 3). Moreover, the reusable silyl ether 4a was also formed in almost quantitative yield by GC. Only a trace amount of product 3a was detected when other phosphine ligands were screened. However, we also observed a quantitative recovery of the cyclic silyl ether 4a by GC regardless of efficiency of crosscoupling, which could be in part due to the protiodesilylation of aryl silane to give **4a** (entries 4–9).⁴⁶ Further screening of Pd sources revealed [Pd(allyl)Cl]₂ as the best choice (entries 10–13). The reduction of Pd loading retarded the reaction, and gave an unparallel yield (entry 14). Na₂CO₃ and K₂CO₃ resulted in the part recovery of **1a**, and thus afforded **3a** in a poor yield (entries 15 and 16).

With the optimization conditions in hand, we next investigated the substrate scope of the reaction. We were pleased to find that phenyl[2-(2-hydroxyprop-2-yl)cyclohexyl]dimethylsilane 1a could couple efficiently with a wide array of aryl nitriles to yield various biaryls in moderate to good yield irrespective of steric and electronic character of the substituent groups. For example, *p*-methylphenyl, *p*-methoxylphenyl, 3-dimethoxylpheny nitriles **2b–2d** proceeded the cross-coupling reaction in moderate yield (Table 2, entries 2–4). Notably, substituents ortho to cyano group, even simple methyl group, would retard the coupling reaction somewhat (entry 5). In addition, various functional groups, such as carboxylic, trifluoromethyl, and fluoro groups, could tolerate the conditions (entries 6–8). Next, we are very pleased to find that silicon-based protecting groups successfully tolerated the coupling condition in contrast to the conventional fluoride-activation which results in desilylation (entry 9). The reaction of 3-cyanopyridine 2j

Table 2

Pd-catalyzed cross-coupling reactions of aryl nitriles and aryl(trialkyl)silanes^a



Ar = 4-Me-C₆H₄ (**1b**), 2-Me-C₆H₄ (**1c**), 4-CF₃-C₆H₄(**1d**), 4-F-C₆H₄ (**1e**)

Time (h)	Yield of 3^{b} (%)
24	78 (3a)
24	65 (3b)
36	51 (3c)
36	62 (3d)
36	35 (3e)
24	71 (3f)
24	69 (3g)
24	60 (3h)
24	51 (3i)
36	42 (3j)
24	<5 (3k)
36	67 (3I)
24	73 (3m)
24	63 (3n)
24	68 (30)
24	62 (3f)
	Time (h) 24 24 36 36 36 24 24 24 24 36 24 36 24 36 24 24 24 24 24 24 24 24 24 24

^a Reaction conditions: **1** (1 mmol), **2** (0.5 mmol), [Pd(allyl)Cl]₂ (5 mol%), K₃PO₄ (4 equiv), PMe₃ (0.1 mmol), toluene (2 mL), 110 °C.

Isolated vield

could also afford desired heteroarene 3j, the yield, but, decreased to some extent. While styryl nitrile 2k did not undergo arylation, the reaction of 2-naththyl nitrile 2l gave a 67% yield of 3l (entries 11 and 12). Sequentially, we attempted to probe the efficiency of other aryl(trialkyl)silanes prepared similarly from the corresponding aryl Grignard reagents. We were pleased to find that 4-tolyl silane 1b and 2-tolyl silane 1c underwent the cross-coupling reaction in good yield (entries 13 and 14). Additionally, 4-trifluoromethyphenyl silane 1d and 4-fluorophenyl silane 1e also proceeds the reaction to furnish corresponding fluoro-containing biaryls, which would provide a new alternative to other type of organometallics (Mg, B, etc.) in the synthesis of pharmaceutically important fluoroarenes (entries 15 and 16).

A working mechanism was also proposed as outlined in Figure 1 for the palladium-catalyzed silicon-based cross-coupling reaction on the basis of previously reported mechanism. 42-45 Firstly, in situ reduction of Pd precursor forms LnPd(0), followed by oxidative addition of aryl nitrile to generate LnPd(II)(Ar)(CN), and then intermediate LnPd(II)(Ar)(CN) is transmetallated by the pentacoordinated silicate intermediate A originating from intermolecular activation of aryl(trialkyl)silane using K₃PO₄ as an activator, and the resulted LnPd(II)(Ar¹)(Ar) finally proceeds the reductive elimination to give desired biaryls (Ar^1-Ar) , as well as Pd(0) to involve next catalytic cycles. It is worth to mention that the by-product, a cyclic silvl ether 4a, is reusable by treating with ArMgBr.

In summary, we have demonstrated that a robust aryl(trialkyl)silane proceeded fluoride-free cross-coupling reaction with extremely inert but synthetically interesting C-CN bond for the first time. It is worth to mention merits including the recycle of organosilane and fluoride-free manner would enhance the widespread acceptability of silicon-based cross-coupling protocol. Additionally, it represents a rare example of silicon-based C–C bond activation, and provides a novel pathway to redirect the synthetic strategy for the construction of C-C bond. Further efforts to expand utilization scope of the robust aryl(trialkyl)silanes in organic synthesis are current issues in our laboratory.



Figure 1. A possible mechanistic pathway.

Experimental section

All manipulations of oxygen- and moisture-sensitive materials were conducted with a Schlenk technique or in a dry box under a nitrogen or argon atmosphere. Flash column chromatography was performed using EM Silica gel 60 (300–400 mesh). Visualization was accomplished with UV light (254 nm) and/or an aqueous alkaline KMnO₄ solution followed by heating. Proton and carbon nuclear magnetic resonance spectra (¹H and ¹³C NMR) were recorded on a Varian Mercury 400 (¹H NMR, 400 MHz; ¹³C NMR 101 MHz) spectrometer with solvent resonance as the internal standard (¹H NMR, CHCl₃ at 7.26 ppm; ¹³C NMR, CDCl₃ at 77.0 ppm). Unless otherwise noted, reagents were commercially available and were used without further purification. Anhydrous toluene was distilled from sodium/benzophenone prior to use. Preparation of aryl(trialkyl)silanes (**1a–1d**) and **4a** are described in our previous publications.⁴²

Preparation of 4-fluorophenyl[2-(hydroxypro-2yl)cyclohexyl]dimethylsilane (1e)

To a suspension of Mg (0.26 g, 11 mmol) in THF (2 mL) was added dropwise a solution of 4-bromofluorobenzene (1.7 g, 10 mmol) in THF (10 mL) over 15 min at rt, and the resulting mixture was stirred at rt for 0.5 h. To the solution of the aryl Grignard reagent thus obtained was added 4a (0.99 g, 5.0 mmol) at 0 °C. After being stirred at rt overnight, the reaction mixture was quenched with a saturated NH₄Cl aqueous solution at 0 °C. The aqueous layer was extracted with diethyl ether, and the combined organic layers were dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give the title compound (1.2 g, 83%) as a colorless oil, $R_f 0.30$ (hexaneethyl acetate = 10:1). ¹H NMR (400 MHz, CDCl₃) δ 7.50–7.40 (m, 2H), 7.04-6.95 (m, 2H), 1.91-1.86 (m, 1H), 1.76-1.50 (m, 3H), 1.41 (td, J = 9.3 Hz, 3.4 Hz, 1H), 1.34–0.94 (m, 5H), 1.15 (s, 3H), 0.98 (s, 3H), 0.84 (s, 1H), 0.33 (s, 3H), 0.31 (s, 3H): ¹³C NMR (101 MHz, CDCl₃) δ 162.86 (d, I = 246.9 Hz), 137.42 (d, 3.8 Hz), 135.29 (d, 6.9 Hz), 114.62 (d, 19.2 Hz), 74.32, 49.80, 31.34, 29.67, 28.33, 27.40, 26.11, 25.70, 24.15, -0.86, -1.33. Anal. Calculated for C₁₇H₂₇FOSi: C, 69.34; H, 9.24; Found: C, 69.09; H, 9.24.

General procedure for cross-coupling reaction of aryl(trialkyl)silanes with aryl nitriles

All reactions and manipulations were run under nitrogen atmosphere. Under nitrogen atmosphere, a reaction tube was charged with Aryl nitrile **2** (0.5 mmol), aryl(trialkyl)silane **1** (1.0 mmol), [Pd(allyl)Cl]₂ (9.2 mg, 13 µmol), PMe₃ (7.6 mg, 0.1 mmol), K₃PO₄ (0.42 g, 2.0 mmol), and toluene (2 mL). The mixture was stirred at 110 °C until a GC analysis showed complete consumption of the starting materials (usually 24–36 h), the solvent was evaporated under reduced pressure and the resulted mixture was filtered through a Florisil pad, diluted with Et₂O, and washed with water and then brine. The organic layer was dried over anhydrous MgSO₄ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give the corresponding biaryl.

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- 46. Under the basic catalytic conditions, somewhat protiodesilylation of aryl[2-(hydroxyprop-2-yl)cyclopentyl]dimethylsilanes was detected, competing with desired cross-coupling, which is shown as follows:

