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A CONVENIENT SYNTHESIS OF SUBSTITUTED HETEROAROMATIC COMPOUNDS VIA THE PALLADIUM-CATALYZED CROSS-COUPLING REACTION OF ORGANOSILICON COMPOUNDS

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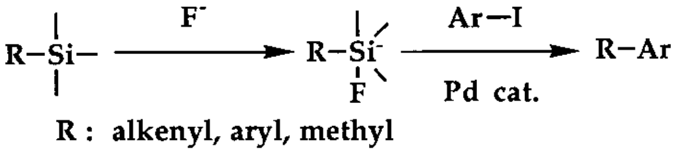
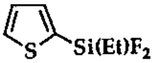
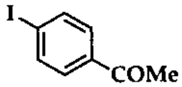
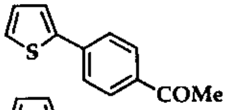
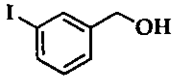
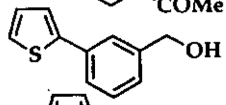
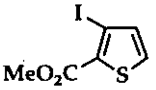
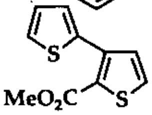
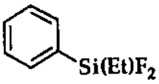
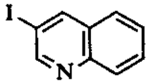
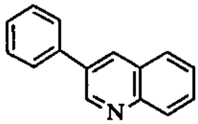
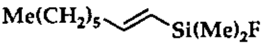
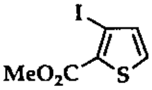
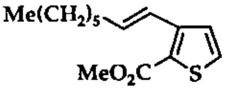
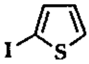
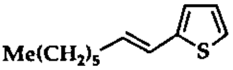
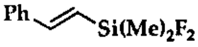
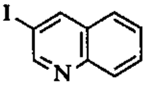
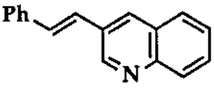
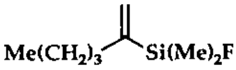
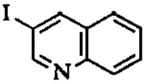
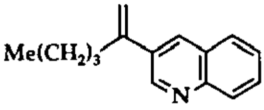
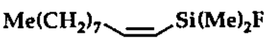
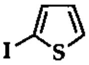
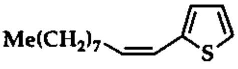
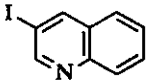
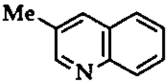
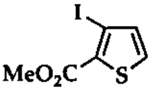
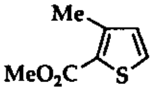
Abstract-The silicon-based cross-coupling reaction promoted by fluoride ion and a Pd catalyst provides us with a new entry to substituted heteroaromatic compounds.

We have recently developed the fluoride ion and Pd catalyst promoted cross-coupling reaction of organosilicon compounds with organic halides.[1] The reaction is characterized by its high stereospecificity, chemoselectivity and ready availability of the organosilicon substrates. We have extended the cross-coupling method to the synthesis of a wide variety of heteroaromatic compounds and found the reaction is indeed effective. Preliminary results are reported herein.



We first studied the aryl-aryl cross-coupling[1e] of ethyl(2-thienyl)difluorosilane and ethyl(phenyl)-difluorosilane with aryl iodides. Table 1 summarizes the results obtained. The reaction proceeded smoothly in *N,N*-dimethylformamide (DMF) solvent at 100 °C with 2.5 mol% of $(\eta^3\text{-}C_3H_5PdCl)_2$ as the catalyst in the presence of 2.0 equiv. of potassium fluoride to afford the desired unsymmetrical heterobiaryls in excellent yields (conditions A, entries 1 - 4). As we previously reported[1b] introduction of a fluorine atom into the silyl group of organosilanes accelerated the rate of the cross-coupling reaction. High chemoselectivity was also observed; not only cabonyl groups like ketone (entry 1) and ester (entry 3) but hydroxyl (entry 2) tolerated the reaction conditions. Though tetrabutylammonium fluoride (TBAF) equally works well, inexpensive potassium fluoride used herein has an advantage in economical view point.

Table 1. Pd-Catalyzed Cross-Coupling of Organosilicon Compounds with Organic Halides

Entry	Organosilicon compound	Aryl iodide	Reaction conditions [a)] Reaction time (h)	Product	(Yield/%)[b)]
1			A 24		(96)
2			A 64		(81)
3			A 12		(82)
4			A 12		(68)
5			B 36		(74)
6			B 12		(78)
7			B 18		(84)
8			B 44		(64)
9			C 5		(62)
10	$(Et_2N)_3S \cdot Me_3SiF_2$		D 24		(66)
11			D 24		(79)

a) All the reactions were carried out by using 3 mol of the organosilicon compound and 2 mol of the aryl iodode under the following conditions. A: $(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5 mol%) in DMF, 2.0 equiv of KF, 100 °C. B: $(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5 mol%) in THF, 1.5 mol of TBAF, 60 °C. C: $(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5 mol%) in DMF, 1.0 mol of TASF, 60 °C. D: $(\eta^3\text{-}C_3H_5PdCl)_2$ (2.5 mol%) in DMF, 80 °C.

b) Isolated yields are given.

Alkenyldimethylfluorosilanes also could couple with iodothiophenes and 3-iodoquinoline,[1b] using an organic fluoride salt like TBAF or tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF).[2] Potassium fluoride was completely ineffective to this type of coupling reaction. The most effective catalyst is $(\eta^3\text{-}C_3H_5PdCl)_2$ in THF (conditions B, entries 5 - 8) for the reaction of (E)-alkenylfluorosilane. However, in the reaction of (Z)-1-(dimethylfluorosilyl)-1-decene with 2-iodothiophene, the conditions B gave a significant amount of isomerized product, 2-[(E)-1-octenyl]thiophene, along with the desired (Z) isomer. The best result was obtained by using $(\eta^3\text{-}C_3H_5PdCl)_2$ as the catalyst and DMF as the solvent (conditions C, entry 9). With the appropriate catalyst and the solvent, the cross-coupling proceeded with retention of the configuration of the alkenylsilanes. Thus, the method is demonstrated to be highly effective for the one-pot construction of the stereo-defined alkenylsubstituted heteroaromatic compounds.

Methylation of heteroaryl iodides with TASF took place effectively to give methylated heteroaryl compounds (entries 10 and 11).[1c] The highest yields of coupling products were obtained by using DMF as the solvent and $(\eta^3\text{-}C_3H_5PdCl)_2$ as the catalyst (conditions D).

The following procedure (conditions A) for the entry 3 of Table 1 is representative. To a mixture of potassium fluoride (0.17 g, 3 mmol), $(\eta^3\text{-}C_3H_5PdCl)_2$ (9 mg, 2.5 mol%) and methyl 3-iodo-2-thiophenecarboxylate (0.27 g, 1.0 mmol) in dry DMF (5 ml) was added ethyl(2-thienyl)difluorosilane (0.27 g, 1.5 mmol) under an argon atmosphere. The reaction mixture was stirred at 100 °C for 12 h. The mixture was diluted with ether and washed with aq. sodium bicarbonate. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (silica gel column, hexane-EtOAc 10 : 1) afforded methyl 3-(2-thienyl)-2-thiophenecarboxylate as a colorless oil (0.18 g, 0.82 mmol, 82%).[3]

Though the transition-metal catalyzed cross-coupling by means of organoboron,[4] organotin,[5] organozinc,[6] and Grignard reagents[6] has been applied to the synthesis of substituted heteroaromatics and heterobiaryls, all of these have a problem in view of practicability. The boron, tin, and zinc reagents must be prepared through rather tedious operations. The Grignard reagents lack the functional group compatibility. All organosilicon compounds employed in this work are commercially available or readily prepared in excellent yields through the Pd-catalyzed silylation of aryl halides with disilanes,[7] decarbonylative silylation of aroyl chlorides with chlorodisilanes,[8] hydrosilylation of alkyne with chlorodimethylsilane,[9] followed by fluorination using SbF_3[10] or CuF_2.[11] Aryl- and alkenylfluorosilanes are insensitive to moisture and easy to be handled.

In summary, the Pd-catalyzed cross-coupling of organofluorosilicon compounds with aryl iodides is found to be a chemoselective and stereospecific route to highly functionalized heterobiaryls, alkenyl- and methyl-substituted heteroaromatic compounds. Ready availability of various types of organofluorosilicon reagents should find wide application to the synthesis of a various array of heteroaromatic compounds.

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3) ^{1}H Nmr (90 MHz, $CDCl_3$) δ 3.85 (s, 3H), 7.00 - 7.63 (m, 5H); ir (neat) 3120, 2960, 1715, 1430, 1260, 1235, 1070, 770, 700 cm^{-1}; ms *m/z* (relative intensity) 224 (M^+, 87), 193 (100), 121 (51), 69 (18), 45(29).

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