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Solid phase cross-coupling reaction of aryl(halo)silanes with 4-iodobenzoic acid

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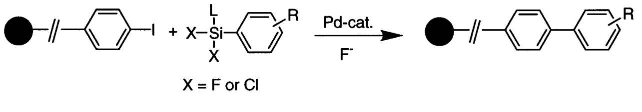
Abstract

Aryl(alkyl)(halo)silanes undergo facile and efficient palladium catalyzed cross-coupling reaction with iodobenzoic acid tethered to the Wang resin. Acid cleavage releases unsymmetrical biaryl carboxylic acids with high conversions, purities and yields. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Solid phase; Cross-coupling reaction; Pd; Silanes; Wang resin

1. Introduction

Transition-metal catalyzed cross-coupling reactions constitute today one of the most important class of carbon–carbon bond forming reaction [1] in the hands of organic chemists. Of the metals that have been used, some have gained extensive use, in particular, boron and tin in combination with Pd catalysts and have found widespread applications. One aspect of such applications is the cross-coupling reaction of aryl compounds to obtain unsymmetrical biaryls that are important pharmacophore [2] in a variety of biologically active compounds as well as key mesogenic unit in the liquid crystalline technology. With the renewed interest in solid phase organic synthesis as a powerful tool for combinatorial chemistry came new challenges for the organic chemist: developing solid-phase reactions and transferring successful solution-phase reactions to solid phase. In testimony for this very active new research area are publications of many review articles [3] and books [4] in the past few years. It is no surprise then that some of the earliest efforts were aimed at transferring several of the well-known Pd-catalyzed coupling reactions to solid phase [5] and disclosed in several articles [6]. A recent comprehensive review discusses the applications of transition metal-catalyzed reactions to solid phase synthesis [7].



Scheme 1.

The palladium catalyzed cross-coupling reaction of aryl(halo)silanes [8] with iodoarenes has been shown to give good to high yields of unsymmetrical biaryls. Our research goal was to transfer this reaction from solution phase to solid phase and identify a general set of conditions that allow complete conversion to products from a wide range of substrates (Scheme 1). In a recent publication [9], we have shown that, under the appropriate set of conditions, the reaction of aryl(alkyl)(difluoro)silanes with 4-iodobenzoic acid tethered to the Wang resin proceeds with high efficiency. In the present paper a detailed description of our results are presented.

2. Results and discussion

Optimization of conditions was carried out based on our model reaction shown in Scheme 2.

Resin **1** was obtained by esterification of the Wang resin with 4-iodobenzoic acid [10]. Chlorosilanes **2a**–**2h** and fluorosilanes **2a′**, **2b′**, and **2g′** were prepared ac-

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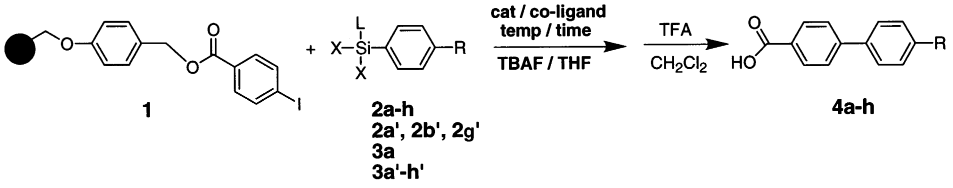
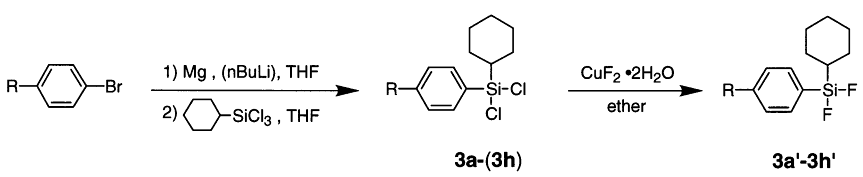


	R =	*p*-Bu	*p*-MeO	H	*p*-Me	*o*-Me	*m*-Me	*p*-F	*p*-CF$_3$
L = ethyl	X = Cl	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**
	X = F	**2a'**	**2b'**					**2g'**	
L = cyclohexyl	X = Cl	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**
	X = F	**3a'**	**3b'**	**3c'**	**3d'**	**3e'**	**3f'**	**3g'**	**3h'**

Scheme 2.



Scheme 3.

cording to the previously published procedure [8a]. Fluorosilanes **3a**′–**3h**′ were prepared as shown in Scheme 3.

Compounds **3a**–**3h** were prepared in one step from reaction of the corresponding Grignard reagents with cyclohexyltrichlorosilane. For compound **3h**, however, since the synthesis via the Grignard was unsuccessful, we first prepared the lithiated intermediate at −78°C, which was subsequently reacted with cyclohexyltrichlorosilane to give the desired product. Dichlorosilanes **3a**–**3h** were then converted to the corresponding difluorosilanes **3a**′–**3h**′ with CuF_2–$2H_2O$ in diethylether.

When we started our study, we initially synthesized compounds **2a**′, **2b**′ and **2g**′ as the representative silanes and used silane **2a**′ for reaction optimization. The intermediate resin, obtained after coupling, was cleaved with trifluoroacetic acid in dichloromethane, and the product analyzed by proton NMR. The results are shown in Table 1.

Our initial reaction optimization studies were carried with the Merrifield resin [11] using the optimized conditions for solution phase developed by us. As shown in Table 1 (entry 1), only 50% conversion was obtained with 1.5 equivalents of silane, two equivalents of KF, 5 mol% of $(\eta^3\text{-}C_3H_5PdCl)_2$ at 100°C for 24 h. In entry 2, KF was replaced with TBAF, and the reaction time was increased to 48 h, but only a small increase in conversion was obtained (70%). In entry 3 the amount of TBAF was increased to three equivalents, while lowering the temperature and reaction time to 80°C and 24 h, respectively. Again only 70% conversion was obtained. In entry 4 the reaction time was increased to 48 h, but similar conversion was obtained (70%).

While carrying out these preliminary studies, the optimal washing sequence for the intermediate resin obtained after cross-coupling had to be optimized. After several trials the following sequence was adopted for all our subsequent reactions: 3 × THF, 3 × DMF, briefly with 2 × dilute KCN in DMSO [12], 3 × DMF, 3 × MeOH, 3 × CH_2Cl_2, and finally 2 × MeOH. In addition, we also found that ester cleavage of the final product according to the described method (NaOMe, MeOH, THF) gave at times the product with varying degree of purity and yield under identical coupling and cleavage conditions [13].

To resolve this problem we replaced the Merrifield resin with Wang resin, which can be quickly and efficiently cleaved with 30% TFA in CH_2Cl_2. In entry 5 (Table 1), where two equivalents of silane, four equivalents of KF, 5 mol% of $(\eta^3\text{-}C_3H_5PdCl)_2$ at 100°C for 48 h were used, we obtained 72% conversion. In entry 6 with ten equivalents of tri(2-furyl)phosphine (Fu_3P) added relative to the catalyst, and the reaction time increased to 72 h, good conversion was observed, but the product contained the ethyl-coupled product as a major byproduct. In entries 7 and 8, we replaced $(\eta^3\text{-}C_3H_5PdCl)_2$ with $Pd(OAc)_2$, but the conversions were very low, 30 and 50%, respectively. In addition, in entry 8 where (Fu_3P) was added, the ethyl-coupled product was again present as a major byproduct. In entry 9 where $Pd(PPh_3)_4$ was used as catalyst we obtained 80%

conversion, and the purity was the highest obtained so far. However, as with the previous trials, the resin was sticky and difficult to wash, probably due to the high temperature and reaction time.

In order to avoid this problem, in entry 10 we replaced KF with TBAF, and lowered the temperature to 80°C and shortened the reaction time to 35 h. While the conversion was very slightly lower than with entry 9, the crude product obtained contained only the starting material as a byproduct. In order to obtain complete conversion we added PPh_3 in entry 11 as a co-ligand but obtained the ethyl-coupled product as the major byproduct. Finally, in entry 12 we simply increased the amount of silane and TBAF to five equivalents and observed 100% conversion.

When we tested the optimized reaction conditions with *p*-methoxyphenylsilane **2b′**, we obtained product **4b** with quantitative conversion in 98% yield. With *p*-fluorophenylsilane derivative **2g′**, a complex mixture resulted including an ethyl-coupled product as an important byproduct. This competitive reaction of the ethyl group precludes the use of any electron-deficient partner on the silane, and therefore prompted us to search for an alternative dummy ligand. As a replacement for the ethyl ligand we chose a cyclohexyl group. In addition to commercial availability of (cyclohexyl)trichlorosilane, this dummy ligand has advantages of being more stable and less prone to migration, since the cross-coupling step proceeds with an organosilicon reagent as a nucleophile. Thus, compounds **3a′**–**3h′** were prepared and their coupling results are given in Table 2.

Table 1
Reaction optimization for the cross-coupling reactions of 4-butylphenyl(difluoro)(ethyl)silane with iodobenzoic acid tethered to Merrifield and Wang resins [a]

Entry	**2a**/eq.	F^- (eq.)	5 mol% cat/mol% co-ligand	Temp. (°C)/time (h)	% Conv. [b]
Merrifield resin [c]					
1	1.5	KF (2)	$(\eta^3\text{-}C_3H_5PdCl)_2$	100/24	50 [d]
2	1.5	TBAF (2)	$(\eta^3\text{-}C_3H_5PdCl)_2$	100/48	70 [d]
3	1.5	TBAF (3)	$(\eta^3\text{-}C_3H_5PdCl)_2$	80/24	70 [d]
4	1.5	TBAF (3)	$(\eta^3\text{-}C_3H_5PdCl)_2$	80/48	70 [d]
Wang resin [e]					
5	2	KF (4)	$(\eta^3\text{-}C_3H_5PdCl)_2$	100/48	72
6	2	KF (4)	$(\eta^3\text{-}C_3H_5PdCl)_2/10Fu_3P$	100/72	90 [f]
7	2	KF (4)	$Pd(OAc)_2$	100/24	30
8	2	KF (4)	$Pd(OAc)_2/10\ Fu_3P$	100/72	50 [f]
9	2	KF (4)	$Pd(PPh_3)_4$	90/72	80
10	4	TBAF (4)	$Pd(PPh_3)_4$	80/35	76
11	4	TBAF (4)	$Pd(PPh_3)_4/10PPh_3$	80/35	78 [f]
12	5	TBAF (5)	$Pd(PPh_3)_4$	80/35	100

[a] All reactions were carried on 0.1 g of resin in DMF (5 ml) with KF and THF (5 ml) with TBAF.
[b] Based on the NMR of the crude product after TFA cleavage.
[c] Particle size of 100–200 mesh, 1–2% cross-linked, 0.67 mmol g^{-1} of iodobenzoate.
[d] Product cleaved as methyl ester.
[e] Particle size of 100–200 mesh, 1–2% cross-linked 0.88 mmol g^{-1} of iodobenzoate.
[f] Contaminated by the ethyl cross-coupling product.

Table 2
Cross-coupling of aryl(cyclohexyl)(difluoro)silanes with Wang resin-tethered 4-iodobenzoic acid [a]

Entry	Silane	eq. Silane	eq. TBAF	Time (h)	% Conv. [b] (**4**, % yield) [c]
1	**3a′**	5	5	30	>99 (**4a**, quant.)
2	**3b′**	5	5	30	>99 (**4b**, quant.)
3	**3c′**	10	10	48	>99 (**4c**, 96)
4	**3d′**	10	10	48	>99 (**4d**, 94)
5	**3e′**	10	10	48	>99 (**4e**, 93)
6	**3f′**	10	10	48	>98 (**4f**, 94)
7	**3g′**	10	10	48	<40
8	**3g′**	10	10	72	>94 (**4g**, 91)

[a] All reactions were run at 80°C in THF with 5 mol% $Pd(PPh_3)_4$.
[b] Conversion based on ^{1}H-NMR and HPLC.
[c] Isolated yield based on the incorporation of 4-iodobenzoic acid on the resin.

Table 3
Cross-coupling of aryl(ethyl)(dichloro)silanes with Wang resin-tethered 4-iodobenzoic acid [a]

Entry	Silane	eq. Silane	eq. KF	Pd/Fu_3P (mol%)	Time (h)	Product, % conv. [b]
1	**2a**	3	15	5	44	**4a**, 100
2	**2b**	3	15	5	44	**4b**, 83
3	**2b**	3	15	10	44	**4b**, 100
4	**2c**	3	15	10	44	**4c**, 83
5	**2c**	3	15	10	72	**4c**, 90
6	**2d**	3	15	10	44	**4c**, 82
7	**2e**	3	15	10	44	**4e**, 82
8	**2f**	3	15	5	44	**4f**, 94
9	**2g**	3	15	10	44	**4g**, 76
10	**2g**	5	25	5	44	**4g**, 91

[a] All the reactions were carried out with KF (15 eq.) in DMF (1 ml), $Pd(OAc)_2$ (5 or 10 mol%) and Fu_3P (5 or 10 mol%) at 120°C.
[b] Conversion was estimated by ^1H-NMR of each freed coupled product.

As seen from Table 2, with *p*-butylphenyl derivative **3a**′, we obtained **4a** with over 99% conversion in quantitative yield (entry 1). Similar results were obtained for *p*-methoxyphenyl derivative **3b**′: over 99% conversion and quantitative yield of **4b** resulted (entry 2). With phenyl- (**3c**′), *p*-methylphenyl- (**3d**′), or *o*-methylphenylsilane (**3e**′), we obtained low conversions under the optimized conditions. However, when the number of equivalents of both the silane and TBAF were increased to ten, and the reaction time to 48 h, over 99% conversions were obtained for all three derivatives, with yields of 96, 94 and 93%, respectively (entries 3–5). With *m*-substituted phenylsilane **3f**′, the conversion was only 15% with five equivalents of silane. However, with ten equivalents of **3f**′ and longer reaction time, we attained 98% conversion and 94% yield of **4f** (entry 6). With *p*-fluorophenylsilane **3g**′ under the optimized conditions, low conversion in **4g** resulted. Under the modified conditions (entry 7) the conversion was improved to 40%. When we further increased the reaction time to 72 h (entry 8), the conversion exceeded 94% and gave **4g** in 91% yield. Finally with *p*-(trifluoromethyl)phenylsilane **3h**′, 30% conversion at best was obtained even after 48 or 72 h of a reaction period.

Subsequently, we studied the cross-coupling reaction by means of (aryl)(dichloro)(cyclohexyl)silanes. We used **3a** and examined the coupling conditions. Because **3a** is assumed to be converted into difluoro derivative [8e] **3a**′, we first used three equivalents of TBAF ($Pd(PPh_3)_4$, 80°C, 30 h) to observe 8% conversion. All attempts using KF in lieu of TBAF, or increasing the amounts of reagents could not improve the conversion drastically.

Since the reaction of **3a** was unexpectedly sluggish, we decided to revert to ethyl derivative **2a**. We reexamined the reagents and conditions. Typical results are shown in Table 3.

We reexamined the catalysts, fluoride ion reagents, solvents, amounts, and reaction temperatures for the coupling of **2a** and found that use of **2a** (three equivalents), KF (15 equivalents) in the presence of $Pd(OAc)_2$ (5 mol%) and Fu_3P (5 mol%) at 120°C afforded **4a** quantitatively (Table 3, entry 1). Without the ligand, the conversion was 92%. The conditions were applied to the other dichlorosilanes.

The optimized condition were then applied to silanes **2b**–**2g**. With *p*-methoxyphenylsilane derivative **2b**, **4b** was obtained with over 83% conversion (entry 2). When the amount of both catalyst and $(Fu)_3P$ were increased to 10 mol%, we achieved 100% conversion (entry 3). With phenylsilane **2c**, under the conditions of entry 3, only 66% conversion was obtained. Using 10 mol% catalyst and co-ligand (entry 4), 83% conversion was obtained. When the reaction time was extended to 72 h (entry 5), conversion became 90% and we obtained **4c** in 90% yield. For *p*-methylphenylsilane **2d**, 10 mol% catalyst and co-ligand gave 82% conversion (entry 6). Under similar conditions *o*-methylphenylsilane **2e** (entry 7) reacted with 82% conversion. *m*-Tolylsilane **2f** was converted into **4f** with 94% conversion (entry 8). Fluorophenylsilane **2g** coupled with 76% conversion, but when the amounts of **2g** and KF were increased and the amounts of catalyst and co-ligand were lowered, over 90% conversion was achieved. In any event, the (aryl)(dichloro)(ethyl)silanes are equally or slightly less efficient in the conversions of the coupling.

3. Conclusion

We have shown that under the appropriate set of conditions the palladium catalyzed cross-coupling reaction of (aryl)(cyclohexyl)(difluoro)silanes with 4-iodobenzoic acid tethered to the Wang resin proceeds with high efficiency, and the reaction of (aryl)(ethyl)(dichloro)silanes with equal or slightly less efficiency.

4. Experimental

NMR spectra were measured in a $CDCl_3$ solution, unless otherwise noted, the chemical shifts being given in ppm. ^{1}H-NMR and ^{13}C-NMR spectra (tetramethylsilane as an internal standard) and ^{19}F-NMR spectra ($CFCl_3$ as an internal standard) were measured on a Varian Mercury 200 spectrometer. Elemental analyses were carried out at Elemental Analysis Center, Kyoto University.

All silanes were prepared under an argon atmosphere, and all coupling reactions were carried in a screw-capped test tube. THF and pentane were distilled from sodium/benzophenone and stored under an argon atmosphere. (Ethyl)(trichloro)silane and (trichloro)(cyclohexyl)silane were purchased from Tokyo Kasei Kogyo and used without further purification. CuF_2–H_2O was purchased from Kanto Chemical and used without further purification. Palladium catalyst ($Pd(PPh_3)_4$) was prepared according to the corresponding literature [14]. Finally, all the resin used in our study were purchased from Advanced ChemTech.

All cross-coupling products were analyzed by HPLC (eluent: 40% aq 0.3% H_3PO_4: 60% acetonitrile).

4.1. General procedure for preparation of (aryl)(dichloro)(ethyl) silanes

4.1.1. (4-Butylphenyl)(dichloro)(ethyl)silane ***(2a)***

To a solution of ethyltrichlorosilane (15.4 g, 94 mmol) in THF (40 ml) was added at 0°C with stirring 4-butylphenylmagnesium bromide prepared from 1-bromo-4-butylbenzene (10.0 g, 47 mmol) and magnesium (1.48 g, 61 mmol) in THF (20 ml). The mixture was stirred at room temperature (r.t.) overnight; bulk of the solvent was removed under reduced pressure; dry pentane was added to the reaction mixture. The resulting slurry was filtered over Celite, and the filtrate was concentrated to give a brown oil, which was distilled at 95°C (0.4 mmHg) to afford (4-butylphenyl)(dichloro)(ethyl)silane as a colorless oil (10.8 g, 88% yield). ^{1}H-NMR (200 MHz) δ 0.90 (t, $J = 8.0$ Hz, 3 H), 1.18 (t, $J = 8.0$ Hz, 3 H), 1.40 (m, 4 H), 1.46–1.68 (m, 2 H), 2.62 (t, $J = 7.2$ Hz, 2H), 7.25 (d, $J = 9.0$ Hz, 2H), 7.64 (d, $J = 9.0$ Hz, 2H). ^{13}C-NMR (200 MHz) δ 6.27, 13.11, 13.92, 22.36, 33.34, 35.75, 128.47, 133.40. Anal. Calc. for $C_{12}H_{18}Cl_2Si$: C, 55.17; H, 6.94. Found: C, 55.45; H, 6.81%.

The following were prepared according to the general procedure.

4.1.2. (Dichloro)(ethyl) (4-methoxyphenyl)silane ***(2b)*** *[8a]*

Colorless oil (4.5 g, 71% yield), b.p. 78°C (1 mmHg). ^{1}H-NMR (200 MHz) δ 1.17 (t, $J = 8.0$ Hz, 3H), 1.25 (t, $J = 8.0$ Hz, 2H), 3.80 (s, 3H), 6.95 (d, $J = 9.0$ Hz, 2H), 7.40 (d, $J = 9.0$ Hz, 2H). ^{13}C-NMR (200 MHz) δ 6.26, 13.17, 55.09, 113.98, 135.13.

4.1.3. (Dichloro)(ethyl)(phenyl)silane ***(2c)*** *[15]*

Colorless oil (3.4 g, 70% yield), b.p. 55°C (0.5 mmHg). ^{1}H-NMR (200 MHz) δ 1.22 (t, $J = 2.2$ Hz, 3H), 1.40 (t, $J = 2.2$ Hz, 2H), 7.42–7.60 (m, 3H), 7.78–7.85 (m, 2H). ^{13}C-NMR (200 MHz) δ 6.22, 13.01, 128.31 (2C), 131.56, 132.34, 133.36 (2C).

4.1.4. (Dichloro)(ethyl)(4-methylphenyl) silane ***(2d)*** *[15]*

Colorless oil (5.4 g, 68% yield), b.p. 50°C (0.6 mmHg). ^{1}H-NMR (200 MHz) δ 1.21 (t, $J = 2.2$ Hz, 3H), 1.41 (t, $J = 2.2$ Hz, 2H), 2.46 (s, 3H), 7.34 (d, $J = 4.6$ Hz, 2H), 7.68 (d, $J = 4.6$ Hz, 2H). ^{13}C-NMR (200 MHz) δ 6.25, 13.09, 21.60, 128.86, 129.10, 133.39, 141.93.

4.1.5. (Dichloro)(ethyl)(2-methylphenyl)silane ***(2e)***

Colorless oil (2.2 g, 35% yield), b.p. 62°C (0.8 mmHg). ^{1}H-NMR (200 MHz) δ 1.24 (t, $J = 1.2$ Hz, 3H), 1.48 (t, $J = 1.2$ Hz, 2H), 2.66 (s, 3H), 7.28–7.36 (m, 2H), 7.44–7.48 (m, 1H), 7.78–7.82 (m, 1H). ^{13}C-NMR (200 MHz) δ 6.35, 13.47, 22.70, 125.30, 130.42, 130.78, 131.86, 134.66, 143.62.

4.1.6. (Dichloro)(ethyl)(3-methylphenyl)silane ***(2f)***

Colorless oil (4.6 g, 72% yield), b.p. 52°C (0.6 mmHg). H-NMR (200 MHz) δ 1.22 (t, $J = 2.0$ Hz, 3H), 1.42 (t, $J = 2.0$ Hz, 2H), 2.46 (s, 3H), 7.37–7.46 (m, 2H), 7.57–7.62 (m, 2H). ^{13}C-NMR (200 MHz) δ 6.24, 13.01, 21.42, 128.22, 130.38, 132.14, 132.39, 133.84, 137.90.

4.1.7. (Dichloro)(ethyl)(4-fluorophenyl)silane ***(2g)***

Colorless oil (6.1 g, 80% yield), b.p. 82°C (4 mmHg). ^{1}H-NMR (200 MHz) δ 1.17 (t, $J = 8.0$ Hz, 3H), 1.25 (t, $J = 8.0$ Hz, 2H), 7.10 (d, $J = 9.5$ Hz, 2H), 7.70 (dd, $J = 9.5$, 7.6 Hz, 2H). ^{13}C-NMR (200 MHz) δ 6.16, 13.12, 115.69 (d, 2C), 128.15 (d), 135.81 (d, 2C), 164.03 (d). Anal. Calc. for $C_8H_9FCl_2Si$: C, 43.06; H, 4.07. Found: C, 43.06; H, 4.07%.

4.2. A typical procedure for preparation (aryl)(ethyl)(difluoro)silanes

4.2.1. (4-Butylphenyl)(difluoro)(ethyl)silane ***(2a′)***

(4-Butylphenyl)(dichloro)(ethyl) silane (10.8 g, 41 mmol) in dry diethyl ether (30 ml) was added slowly to CuF_2–$2H_2O$ (11.4 g, 83 mmol) in dry ether (30 ml) at 0°C. The resulting slurry was stirred at r.t. overnight, diluted with pentane, and filtered over Celite. The filtrate was concentrated to give a brown oil, which was distilled at 65°C (0.8 mmHg) to give (4-butylphenyl)(difluoro)(ethyl)silane as a colorless oil (7.8 g, 83% yield). ^{1}H-NMR (200 MHz) δ 0.95 (t, $J = 8.0$

Hz, 3H), 1.00–1.20 (m, 5H), 1.22–1.45 (m, 2H), 1.45–1.65 (m, 2H), 2.62 (t, $J = 7.2$ Hz, 2H), 7.25 (d, $J = 9.0$ Hz, 2H), 7.64 (d, $J = 9.0$ Hz, 2H). ^{13}C-NMR (50 MHz) δ 4.10 (t), 5.13, 13.86, 22.38, 33.40, 35.87, 125.75 (t), 128.48, 133.72, 147.02. Anal. Calc. for $C_{12}H_{18}F_2Si$: C, 63.12; H, 7.94. Found: C, 62.27; H, 8.06%.

The following were prepared according to the typical procedure.

4.2.2. (Ethyl)(difluoro)(4-methoxyphenyl)silane (**2b′**) [8a]

Colorless oil (2.7 g, 70% yield), b.p. 51°C (1 mmHg). ^{1}H-NMR (200 MHz) δ 1.00–1.20 (m, 5H), 3.80 (s, 3H), 6.95 (d, $J = 9.0$ Hz, 2H), 7.40 (d, $J = 9.0$ Hz, 2H).

4.2.3. (Ethyl)(Difluoro)(4-fluorophenyl)silane (**2g′**)

Colorless oil (2.9 g, 57% yield), b.p. 45°C (7 mmHg). ^{1}H-NMR (200 MHz) δ 1.00–1.2 (m, 5H), 7.10 (d, $J = 9.0$ Hz, 2H), 7.70 (dd, $J = 9.0$, 1.8 Hz, 2H). ^{13}C-NMR (50 MHz) δ 3.98 (t), 4.97 (t), 115.70 (d, 2C), 124.85 (td), 136.05 (dt, 2C), 165 (d). Anal. Calc. for $C_8H_9FCl_2Si$: C, 50.51; H, 4.77. Found: C, 50.49; H, 4.74%.

4.3. A typical procedure for preparation of aryl(cyclohexyl)(dichloro)silanes

4.3.1. (4-Butylphenyl)(dichloro)(cyclohexyl)silane (**3a**)

To a solution of cyclohexyltrichlorosilane (10.0 g, 46 mmol) in THF (20 ml) was added at 0°C with stirring 4-butylphenylmagnesium bromide prepared from 1-bromo-4-butylbenzene (5.0 g, 23 mmol) and magnesium (0.73 g, 30 mmol) in THF (20 ml). The mixture was stirred at r.t. overnight; bulk of the solvent was removed under reduced pressure; dry pentane was added to the reaction mixture. The resulting slurry was filtered over Celite, and the filtrate was concentrated to give a brown oil. Distillation of this oil at 145°C (0.8 mmHg) afforded (4-butylphenyl)(dichloro)(cyclohexyl)silane as a colorless oil (7.25 g, 90% yield). ^{1}H-NMR (200 MHz) δ 0.95 (t, $J = 6.8$ Hz, 3H), 1.05–1.40 (m, 8H), 1.44–2.00 (m, 7H), 2.60 (t, $J = 6.8$ Hz, 2H), 7.25 (d, $J = 6.8$ Hz, 2H), 7.65 (d, $J = 6.8$ Hz, 2H). ^{13}C-NMR (50 MHz) δ 13.92, 22.37, 25.77 (2C), 26.23, 27.11 (2C), 30.41, 33.32, 35.73, 128.19, 128.35 (2C), 133.88 (2C), 146.64. Anal. Calc. for $C_{16}H_{24}Cl_2Si$: C, 60.94; H, 7.67. Found: C, 60.88; H, 7.69%.

The following were prepared according to the typical procedure.

4.3.2. (Dichloro)(cyclohexyl)(4-methoxyphenyl)silane (**3b**)

Colorless oil (5.8 g, 74% yield), b.p. 140°C (0.8 mmHg). ^{1}H-NMR (200 MHz) δ 1.10–1.40 (m, 6H), 1.60–2.00 (m, 5H), 3.80 (s, 3H), 6.95 (d, $J = 8.0$ Hz, 2H), 7.65 (d, $J = 8.0$ Hz, 2H). ^{13}C-NMR (50 MHz) δ 25.77 (2C), 26.20, 27.08 (2C), 30.52, 55.11, 113.88 (2C), 122.33, 135.58 (2C), 162.11. Anal. Calc. for $C_{13}H_{18}OCl_2Si$: C, 53.98; H, 6.27. Found: C, 53.95; H, 6.25%.

4.3.3. (Dichloro)(cyclohexyl)(phenyl)silane (**3c**)

Colorless oil (6.8 g, 82% yield), b.p. 101°C (0.3 mmHg). ^{1}H-NMR (200 MHz) δ 1.10–1.50 (m, 6H), 1.60–2.10 (m, 5H), 7.40–7.60 (m, 3H), 7.60–7.90 (m, 2H). ^{13}C-NMR (50 MHz) δ 25.72 (2C), 26.20, 27.07 (2C), 30.32, 128.17 (2C), 131.38, 131.46, 133.81 (2C). Anal. Calc. for $C_{12}H_{16}Cl_2Si$: C, 55.60; H, 6.22. Found: C, 55.63; H, 6.21.

4.3.4. (Dichloro)(cyclohexyl)(4-methylphenyl)silane (**3d**)

Colorless oil (5.3 g, 66% yield), b.p. 112°C (0.15 mmHg). ^{1}H-NMR (200 MHz) δ 1.10–1.40 (m, 6H), 1.50–1.90 (m, 5H), 2.40 (s, 3H), 7.25 (d, $J = 7.5$ Hz, 2H), 7.60 (d, $J = 7.5$ Hz, 2H). ^{13}C-NMR (50 MHz) δ 21.61, 25.76 (2C), 26.21, 27.10 (2C), 30.41, 127.96, 128.99 (2C), 133.87 (2C), 141.74. Anal. Calc. for $C_{13}H_{18}Cl_2Si$: C, 57.14; H, 6.64. Found: C, 57.08; H, 6.60%.

4.3.5. (Dichloro)(cyclohexyl)(2-methylphenyl)silane (**3e**)

Colorless oil (2.3 g, 30% yield), b.p. 120°C (0.3 mmHg). ^{1}H-NMR (200 MHz) δ 1.20–1.50 (m, 6H), 1.70–1.90 (m, 5H), 2.60 (s, 3H), 7.18–7.30 (m, 2H), 7.40 (m, 1H), 7.80 (m, 1H). ^{13}C-NMR (50 MHz) δ 23.06, 25.95 (2C), 26.28, 27.25 (2C), 30.38, 125.29, 129.61, 130.75, 131.67, 135.43, 143.51. Anal. Calc. for $C_{13}H_{18}Cl_2Si$: C, 57.14; H, 6.64. Found: C, 57.11; H, 6.63%.

4.3.6. (Dichloro)(cyclohexyl)(3-methylphenyl)silane (**3f**)

Colorless oil (6.6 g, 82% yield), b.p. 115°C (0.95 mmHg). ^{1}H-NMR (200 MHz) δ 1.20–1.40 (m, 6H), 1.60–1.98 (m, 5H), 2.40 (s, 3H), 7.30 (m, 2H), 7.50 (m, 2H). ^{13}C-NMR (50 MHz) δ 21.40, 25.71 (2C), 26.17, 27.05 (2C), 30.30, 128.03, 130.84, 131.23, 132.18, 134.24, 137.70. Anal. Calc. for $C_{13}H_{18}Cl_2Si$: C, 57.14; H, 6.64. Found: C, 57.10; H, 6.62%.

4.3.7. (Dichloro)(cyclohexyl)(4-fluorophenyl)silane (**3g**)

Colorless oil (2.2 g, 69% yield), b.p. 93°C (0.6 mmHg). ^{1}H-NMR (200 MHz) δ 1.10–1.40 (m, 6H), 1.60–1.95 (m, 5H), 7.10 (t, $J = 8.6$ Hz, 2H), 7.70 (dd, $J = 8.6$, 7.1 Hz, 2H). ^{13}C-NMR (50 MHz) δ 25.93 (2C), 26.17, 27.05 (2C), 30.40, 115.56 (d, 2C), 127.24 (d), 136.22 (d, 2C), 164.94 (d). Anal. Calc. for $C_{12}H_{15}FCl_2Si$: C, 51.99; H, 5.45. Found: C, 51.90; H, 5.35%.

4.3.8. (Dichloro)(cyclohexyl)[4-(trifluoromethyl)-phenyl]silane (***3h***)

To a solution of 4-bromobenzotrifluoride (2.0 g, 8.9 mmol) in dry THF (30 ml) at -78°C, was added dropwise butyllithium (5.7 ml, 1.57 M in hexane). The reaction mixture was stirred for 10 min and transferred via canula to a solution of cyclohexyltrichlorosilane (2.3 g, 10.7 mmol) in THF (30 ml) at -78°C. After the resulting mixture was stirred for 1 h, the cooling bath was removed, and the reaction mixture stirred for an additional 3 h. Subsequently the bulk of the solvent was removed under reduced pressure, and dry hexane was added to the reaction mixture. The resulting slurry was filtered over Celite, and the filtrate was concentrated to give a brown oil. Distillation of this oil at 92°C (0.15 mmHg) afforded (dichloro)(cyclohexyl)[4-(trifluoromethyl)phenyl]silane as a colorless oil (1.3 g, 46% yield). ^{1}H-NMR (200 MHz) δ 1.10–1.40 (m, 6H), 1.60–2.00 (m, 5H), 7.70 (t, $J = 6.9$ Hz, 2H), 7.70 (d, $J = 6.9$ Hz, 2H). ^{19}F-NMR (188 MHz) δ -63.8 (s). Anal. Calc. for $C_{13}H_{15}Cl_2\ F_3Si$: C, 47.71; H, 4.62. Found: C, 47.60; H, 4.58%.

4.4. Typical procedure for preparation aryl(cyclohexyl)(difluoro)silanes

4.4.1. (4-Butylphenyl)(cyclohexyl)(difluoro)silane (***3a′***)

(4-Butylphenyl) (dichloro)(cyclohexyl)silane (6.5 g, 21 mmol) in dry diethylether (20 ml) was added slowly to CuF_2-$2H_2O$ (5.7 g, 41 mmol) in dry diethylether (20 ml) at 0°C. The resulting slurry was stirred at r.t. overnight, diluted with pentane, filtered through a Celite pad, and the filtrate was concentrated to give a brown oil. Distillation at 105°C (0.3 mmHg) afforded (4-butylphenyl)-(cyclohexyl)(difluoro)silane as a colorless oil (4.9 g, 85% yield). ^{1}H-NMR (200 MHz) δ 0.90 (t, $J = 6.7$ Hz, 3H), 1.10–1.50 (m, 8H), 1.50–1.90 (m, 7H), 2.60 (t, $J = 6.7$ Hz, 2H), 7.25 (d, $J = 6.7$ Hz, 2H), 7.55 (d, $J = 6.7$ Hz, 2H). ^{13}C-NMR (50 MHz) δ 14.90, 23.54, 24.52 (t), 26.31 (2C), 27.36, 28.09 (2C), 34.34, 36.83, 126.21 (t), 129.38 (2C), 134.91 (t, 2C), 147.84. ^{19}F-NMR (188 MHz) δ -148.8 (s). Anal. Calc. for $C_{16}H_{24}F_2Si$: C, 68.04; H, 8.56. Found: C, 67.90; H, 8.63%.

Followings were prepared according to the typical procedure.

4.4.2. (Cyclohexyl)(difluoro)(4-methoxyphenyl)silane (***3b′***)

Colorless oil (4.6 g, 90% yield), b.p. 104°C (0.6 mmHg). ^{1}H-NMR (200 MHz) δ 1.10–1.50 (m, 6H), 1.60–1.90 (m, 5H), 3.80 (s, 3H), 6.95 (d, $J = 8.0$ Hz, 2H), 7.58 (d, $J = 8.0$ Hz, 2H). ^{13}C-NMR (50 MHz) δ 23.60 (t), 26.37 (2C), 26.39, 27.10 (2C), 55.06, 114.00 (2C), 119.40 (t), 135.64 (2C), 162.30. ^{19}F-NMR (188 MHz) δ -146.7 (s). Anal. Calc. for $C_{13}H_{18}Fl_2Si$: C, 60.98; H, 7.19. Found: C, 60.91; H, 7.08%.

4.4.3. (Cyclohexyl)(difluoro)(phenyl)silane (***3c′***)

Colorless oil (5.1 g, 87% yield), b.p. 71°C (1.5 mmHg). ^{1}H-NMR (200 MHz) δ 1.10–1.50 (m, 6H), 1.60–1.90 (m, 5H), 7.38–7.60 (m, 3H), 7.60–7.70 (m, 2H). ^{13}C-NMR (50 MHz) δ 23.45 (t), 25.28 (2C), 26.35, 27.06 (2C), 128.21 (2C), 128.44, 131.64, 133.87 (2C). ^{19}F-NMR (188 MHz) δ -148.2 (s). Anal. Calc. for $C_{12}H_{16}F_2Si$: C, 63.68; H, 7.13. Found: C, 63.21; H, 7.13%.

4.4.4. (Cyclohexyl)(difluoro)(4-methylphenyl)silane (***3d′***)

Colorless oil (4.0 g, 85% yield), b.p. 74°C (0.2 mmHg). ^{1}H-NMR (200 MHz) δ 1.10–1.50 (m, 6H), 1.60–1.90 (m, 5H), 2.40 (s, 3H), 7.30 (d, $J = 7.5$ Hz, 2H), 7.60 (d, $J = 7.5$ Hz, 2H). ^{13}C-NMR (50 MHz) δ 21.63, 23.51 (t), 25.30 (2C), 26.35, 27.06 (2C), 124.86 (t), 128.99 (2C), 133.89 (2C), 141.91. ^{19}F-NMR (188 MHz) δ -148.0 (s). Anal. Calc. for $C_{13}H_{18}Cl_2Si$: C, 64.96; H, 7.55. Found: C, 64.99; H, 7.39%.

4.4.5. (Cyclohexyl)(difluoro)(2-methylphenyl)silane (***3e′***)

Colorless oil (1.2 g, 61% yield), b.p. 90°C (2 mmHg). ^{1}H-NMR (200 MHz) δ 1.10–1.50 (m, 6H), 1.60–1.90 (m, 5H), 2.50 (s, 3H), 7.15–7.25 (m, 2H), 7.40 (m, 1H), 7.60 (m, 1H). ^{13}C-NMR (50 MHz) δ 22.62, 24.18 (t), 25.39 (2C), 26.38, 27.16 (2C), 125.10, 127.89 (t), 130.05, 131.63, 134.93 (t), 143.91. ^{19}F-NMR (188 MHz) δ -145.5 (s). Anal. Calc. for $C_{13}H_{18}F_2Si$: C, 64.91; H, 7.55. Found: C, 65.19; H, 7.45%.

4.4.6. (Cyclohexyl)(difluoro)(3-methylphenyl)silane (***3f′***)

Colorless oil (5.0 g, 87% yield), b.p. 71°C (0.35 mmHg). ^{1}H-NMR (200 MHz) δ 1.10–1.25 (m, 6H), 1.60–1.90 (m, 5H), 2.40 (s, 3H), 7.30 (m, 2H), 7.45 (m, 2H). ^{13}C-NMR (50 MHz) δ 21.40, 23.46 (t), 25.28 (2C), 26.35, 27.07 (2C), 128.13, 130.86 (t), 130.94, 132.44, 134.36, 137.75. ^{19}F-NMR (188 MHz) δ -148.2 (s). Anal. Calc. for $C_{13}H_{18}F_2Si$: C, 64.96; H, 7.55. Found: C, 64.91; H, 7.42%.

4.4.7. (Cyclohexyl)(difluoro)(4-fluorophenyl)silane (***3g′***)

Colorless oil (1.93 g, 69% yield), b.p. 55°C (0.4 mmHg). ^{1}H-NMR (200 MHz) δ 1.10–1.45 (m, 6H), 1.60–1.90 (m, 5H), 7.10 (t, $J = 8.6$ Hz, 2H), 7.65 (dd, $J = 8.6$, 7.1 Hz, 2H). ^{13}C-NMR (50 MHz) δ 23.42 (t), 25.24 (2C), 26.31, 27.01 (2C), 115.67 (d, 2C), 136.24 (d, 2C), 146.21, 165.14 (d). ^{19}F-NMR (188 MHz) δ -107.25 (m, 1 F), -147.25 (s, 2 F). Anal. Calc. for $C_{12}H_{15}F_3Si$: C, 58.92; H, 6.13. Found: C, 58.99; H, 6.19%.

4.4.8. (Cyclohexyl)(difluoro)[4-(trifluoromethyl)-phenyl]silane (***3h′***)

(Dichloro)(cyclohexyl)[4 - (trifluoromethyl)phenyl]silane (4.7 g, 14.5 mmol) in dry diethylether (20 ml) was added slowly to CuF_2–$2H_2O$ (4.0 g, 29 mmol) in dry diethylether (20 ml) at 0°C. The resulting slurry was stirred at r.t. overnight, diluted with pentane, filtered over Celite, and the filtrate was concentrated to give a brown oil which distillated at 77°C (0.15 mmHg) to afford (cyclohexyl)(difluoro)[4-(trifluoromethyl)phenyl]-silane as a colorless oil (2.8 g, 65% yield). ^{1}H-NMR (200 MHz) δ 1.10–1.50 (m, 6H), 1.60–1.95 (m, 5H), 7.60–7.90 (m, 4H). ^{13}C-NMR (50 MHz) δ 23.39 (t), 25.21 (2C), 26.32, 27.02 (2C), 123.91 (q), 124.88 (q, 2C), 133.13 (t), 133.60 (q), 134.40 (t, 2C). ^{19}F-NMR (188 MHz) δ -64.00 (s, 3 F), -148.00 (s, 2 F). Anal. Calc. for $C_{13}H_{15}F_5Si$: C, 53.05; H, 5.14. Found: C, 53.20; H, 5.20%.

4.5. General procedure for the solid phase cross-coupling of (aryl)(difluoro)silanes with Wang resin-tethered iodobenzoic acid

*4.5.1. 4′-Butyl-biphenyl-4-carboxylic acid (**4a**)*

To 0.1 g of resin **1** (0.88 mmol g^{-1}, 0.088 mmol) was added 5 ml of dry THF. After swelling for 30 min, the following were added in sequential order $Pd(PPh_3)_4$ (0.010 g, 5 mol%), **3a**′ (0.20 g, 0.88 mmol), and TBAF (0.88 ml, 1 M in THF). The test tube was then capped, and the reaction mixture was stirred at 80°C for 30 h. Subsequently, the resin was filtered and washed successively with 3 × THF, 3 × DMF, briefly with 2 × dilute KCN in DMSO, 3 × DMF, 3 × MeOH, 3 × CH_2Cl_2, and finally 2 × MeOH. After drying to a constant weight, the resin was cleaved with TFA–CH_2Cl_2 (1:3, 4 ml) for 1 h to give **4a** (22 mg), quantitative yield. ^{1}H-NMR (200 MHz, acetone-d_6) δ 0.85–1.00 (t, $J = 7.4$ Hz, 3H), 1.25–1.50 (m, 2H), 1.50–1.78 (m, 2H), 2.60–2.75 (t, $J = 7.4$ Hz, 3H), 7.30 (d, $J = 8.1$ Hz, 2H), 7.57 (d, $J = 8.1$ Hz, 2H), 7.70 (d, $J = 8.1$ Hz, 2H), 8.20 (d, $J = 8.1$ Hz, 2H). ^{13}C-NMR (50 MHz, DMSO-d_6) δ 12.45, 20.87, 32.07, 33.80, 125.28 (2C), 125.57 (2C), 127.09, 127.48 (2C), 128.54 (2C), 135.73, 141.62, 144.07, 165.54. Anal. Calc. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.25; H, 7.16%.

*4.5.2. 4′-Methoxybiphenyl-4-carboxylic acid (**4b**)*

^{1}H-NMR (200 MHz, acetone-d_6) δ 3.80 (s, 3H), 7.10 (d, $J = 8.3$ Hz, 2H), 7.65 (d, $J = 8.3$ Hz, 2H), 7.75 (d, $J = 8.3$ Hz, 2H), 7.95 (d, $J = 8.3$ Hz, 2H). ^{13}C-NMR (50 MHz, DMSO-d_6) δ 53.86, 112.84 (2C), 124.94 (2C), 126.69, 126.84 (2C), 128.54 (2C), 130.87, 143.68, 158.30, 165.55. Anal. Calc. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.65; H, 5.25%.

*4.5.3. Biphenyl-4-carboxylic acid (**4c**)*

^{1}H-NMR (200 MHz, acetone-d_6) δ 7.35–7.6 (m, 3H), 7.70 (d, $J = 6.9$ Hz, 2H), 7.80 (d, $J = 6.9$ Hz, 2H), 8.15 (d, $J = 6.9$ Hz, 2H). ^{13}C-NMR (50 MHz, DMSO-d_6) δ 127.78 (2C), 127.93 (2C), 129.26, 130.05 (2C), 130.61, 130.93 (2C), 140.00, 145.25, 168.12. Anal. Calc. for $C_{13}H_{10}O_2$: C, 78.77; H, 5.08. Found: C, 78.72; H, 5.01%.

*4.5.4. 4′-Methylbiphenyl-4-carboxylic acid (**4d**)*

^{1}H-NMR (200 MHz, acetone-d_6) δ 2.40 (s, 3H), 7.35 (d, $J = 7.8$ Hz, 2H), 7.60 (d, $J = 7.8$ Hz, 2H), 7.80 (d, $J = 7.8$ Hz, 2H), 8.15 (d, $J = 7.8$ Hz, 2H). ^{13}C-NMR (50 MHz, DMSO-d_6) δ 21.69, 127.44 (2C), 127.74 (2C), 130.27, 130.65 (2C), 130.92 (2C), 137.07, 138.75, 145.18, 168.14. Anal. Calc. for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.20; H, 5.65%.

*4.5.5. 2′-Methylbiphenyl-4-carboxylic acid (**4e**)*

^{1}H-NMR (200 MHz, acetone-d_6) δ 2.20 (s, 3H), 7.10–7.2 (m, 4H), 7.35 (d, $J = 8.5$ Hz, 2H), 8.00 (d, $J = 8.5$ Hz, 2H). ^{13}C-NMR (50 MHz, DMSO-d_6) δ 21.07, 126.03, 127.05, 128.84, 130.23 (2C), 131.46, 135.63, 138.56, 140.37, 141.29, 145.20, 168.16. Anal. Calc. for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.28; H, 5.67%.

*4.5.6. 3′-Methylbiphenyl-4-carboxylic acid (**4f**)*

^{1}H-NMR (200 MHz, acetone-d_6) δ 2.40 (s, 3H), 7.22 (m, 1H), 7.38 (m, 1H), 7.50 (m, 1H), 7.80 (d, $J = 8.0$ Hz, 2H), 8.10 (d, $J = 8.0$ Hz, 2H). ^{13}C-NMR (50 MHz, DMSO-d_6) δ 22.04, 125.04, 127.75 (2C), 128.57, 129.94, 130.89 (2C), 139.25, 139.95, 145.38, 168.15. Anal. Calc. for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.19; H, 5.63%.

*4.5.7. 4′-Fluorobiphenyl-4-carboxylic acid (**4g**)*

^{1}H-NMR (200 MHz, acetone-d_6) δ 7.20–7.35 (m, 2H), 7.75–7.85 (m, 4H), 8.10 (d, $J = 8.5$ Hz, 2H). ^{13}C-NMR (50 MHz, DMSO-d_6) δ 113.37, 116.44 (d, 2C), 118.18, 127.06 (2C), 130.03 (d, 2C), 130.33, 143.60, 162.70, 167.51. Anal. Calc. for $C_{13}H_9FO_2$: C, 72.22; H, 4.20. Found: C, 72.05; H, 4.05%.

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