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Silicon Directed *ipso*-Substitution of Polymer Bound Arylsilanes: Preparation of Biaryls *via* the Suzuki Cross-Coupling Reaction[1]

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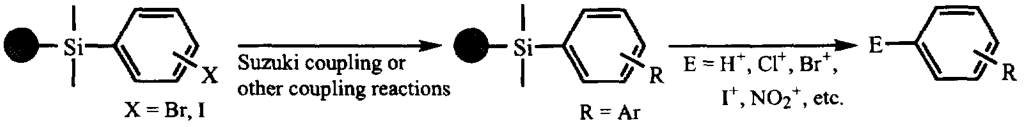
Abstract: *A method for attaching haloarylsilanes to polymer support was developed. The polymer bound arylhalides were reacted with a variety of* $ArB(OH)_2$ *under the Suzuki cross-coupling reaction conditions and the coupled resins were cleaved by different electrophiles to give ipso-substitution products in good yields.* Copyright © 1996 Elsevier Science Ltd

Constructing libraries of nonpolymeric, small organic molecules by solid phase techniques has been the recent focus of combinatorial synthesis.[2] While many pharmacologically interesting molecules such as 1,4-benzodiazepines,[3] hydantoins,[3e] ureas,[4] γ-butyrolactones,[5] benzylpiperazines,[6] aryl ethers,[7] pyrrolidines,[8] tertiary amines,[9] cyclic ethers[10] and isoquinolines,[11] etc., have been prepared on solid support in the last few years, most of the linkers (e.g., OH, COOH, NHR) employed in these syntheses are inherited from those used in generating peptide, oligonucleotide and oligosacharride libraries. During the preparation of this manuscript, Plunkett and Ellman[3a] reported the first application of silicon as a cleavable linker for solid phase synthesis and most recently Chenera *et al.*[12] described another protiodetachable silicon linker. Herein we report an alternative silicon based linking technology which is complementary to the existing strategies in that the linker itself can be converted to nonpolar functions such as H, I, Br, etc.. The new technique should allow further diversification of libraries in the cleavage step, permitting a multifold increase in the number of molecular entities generated.

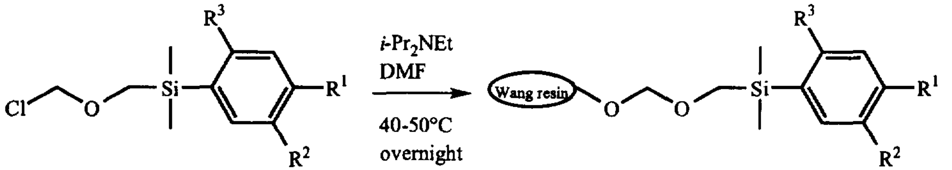
The central motif of our strategy is outlined in **Scheme 1**. We envisaged that a polymer bound library (represented by R) attached through an arylsilane linker could be cleaved with a variety of electrophiles such as H^+, I^+, Br^+, Cl^+, Ac^+, NO_2^+, etc., giving rise to different sets of libraries according to the electrophiles used.



Scheme 1

Silicon directed *ipso*-substitution of arylsilanes is a facile and well studied process in solution.[13] Yet few examples of this reaction on solid support have appeared in the literature. We report herein a simple and efficient method for attaching arylsilanes to solid support. Linker **1** (see scheme in notes)[14,15] was prepared from 1,4-dibromobenzene in 85% overall yield. In similar fashions, linkers **2** (from 1,3-dibrombenzene, 77% overall), **3**[16] (from 1,2-dibromobenzene, 69% overall), and **4**[17] (from 2,4-dibromoanisole, 30% overall) were prepared.

The attachment of linkers to solid support was straightforward. For example, reaction of commercially available Wang resin (Novabiochem) with **1** in DMF at 40-50 °C overnight in the presence of Hünig's base under a nitrogen atmosphere resulted in the modified resin **P-1**. Loading of Wang resin was confirmed by the IR spectrum (disappearance of the hydroxyl absorption band at 3500 cm^{-1} of the starting resin). Linkers **2**, **3** and **4** were loaded to Wang resin to give polymers **P-2**, **P-3** and **P-4**, respectively.



1: $R^1 = Br, R^2 = R^3 = H$
2: $R^2 = Br, R^1 = R^3 = H$
3: $R^3 = Br, R^1 = R^2 = H$
4: $R^1 = H, R^2 = Br, R^3 = OMe$

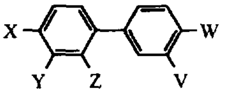
P-1: $R^1 = Br, R^2 = R^3 = H$
P-2: $R^2 = Br, R^1 = R^3 = H$
P-3: $R^3 = Br, R^1 = R^2 = H$
P-4: $R^1 = H, R^2 = Br, R^3 = OMe$

The stability of the linkers was investigated using resin **P-1** as an example. It was found that **P-1** was very stable towards bases or fluorides. For instance, treating the resin with NaOH (0.1 M in DME, refluxing, 24h), or NaOMe (0.1 M in MeOH, r.t., 1 week), or KF (10eq, DME/H_2O, 18-crown-6, refluxing, 24h), or KF (10eq, DMF/H_2O, 80°C, 24h) did not result in an appreciable amount of linker cleavage.

Electrophilic cleavage [iododesilylation with iodine monochloride (ICl, 3eq) in CH_2Cl_2, bromodesilylation with Br_2(6eq)/pyridine(3eq) in CH_2Cl_2 and protiodesilylation with CF_3COOH/CH_2Cl_2(1/1 vol, +5% Me_2S)] of the modified resins was first carried out to test the feasibility of *ipso*-sustitution on solid support. The desired *ipso*-substitution products were obtained (except **P-1** in the protiodesilylation).[18] The rates for the solid phase reactions were comparable with those in solution.[13b,18] Encouraged by the observation, we then applied the technology for the preparation of a variety of biphenyls. The Suzuki coupling reaction on solid support, studied by Frenette and Friesen,[19] was employed as the key C-C bond forming reaction due to its mildness and tolerance of a wide scope of functionalities. The resins were first reacted with $ArB(OH)_2$ (3eq) under either the standard aqueous[19] [3%$Pd(PPh_3)_4$, 2M Na_2CO_3, DME, refluxing overnight] or anhydrous[20] [3% $Pd(PPh_3)_4$, 1:1 Et_3N/DMF, refluxing for 24 h] conditions. The coupled resins were then subjected to electrophilic cleavage to determine the yield as well as the extent of the coupling reactions. These results are summarized in **Table 1**.

P-1 and phenylboronic acid were used as probes to determine suitable conditions for the coupling and comparable results were obtained under both anhydrous and aqueous conditions (Entries 1,2). As shown, a wide range of functionalized boronic acids can be used. The products obtained are generally free of contamination from the bromide. An exception was found in the case of a strongly electron deficient boronic acid (Entry 8) in which the reaction did not reach completion (33% yield + starting material) after 24 h under anhydrous conditions. Standard aqueous coupling conditions (Entry 9), however, afforded solely the desired product (82% after iododesilylation). In the case of 4-(hydroxymethyl)phenylboronic acid (Entry 5), direct cleavage of the coupled resin with ICl afforded the desired alcohol in poor yield (36%).[21] However, protection of the hydroxyl group as an acetate (Ac_2O, pyr, DMAP, CH_2Cl_2) followed by ICl cleavage furnished the corresponding ester in good yield (80%, Entry 6). The yields for bromodesilylation (Entries 15-18) were excellent in all cases. With an electron rich system (Entry 17), bisbromination took place to yield the dibromobiphenyl. Electrophilic cleavage after coupling with 4-(hydroxymethyl)-phenylboronic acid (Entry 18) furnished two products, the desired alcohol as well as the corresponding aldehyde. The ratio of the two compounds was dependent upon the cleavage time. When the reaction was stopped after 1-2 h, the alcohol was obtained as the predominate product. Allowing the reaction to proceed overnight produced the aldehyde exclusively. The protiodesilylation ($CF_3COOH/CH_2Cl_2/Me_2S$) (Entries 19-22) afforded the coupled products in poor to moderate yields. This may be a reflection of the difficulty in isolating these simple biphenyl products (they are quite volatile and sublime slowly even at room temperature).

Table 1. Suzuki Coupling and Electrophilic Cleavage of the Coupled Resins.

Entry	Resin	$ArB(OH)_2$[a] (3eq)	Condition[b] A or B	Electrophile		Yield(%)[c]
1	**P-1**	**1**	**A**	ICl	X=I,Y=Z=V=W=H	98
2	**P-1**	**1**	**B**	ICl	X=I,Y=Z=V=W=H	85
3	**P-1**	**2**	**A**	ICl	X=I,W=Me,Y=Z=V=H	97
4	**P-1**	**3**	**A**	ICl	X=I,W=OMe,Y=X=V=H	96
5	**P-1**	**4**	**A**	ICl	X=I,W=CH_2OH,Y=Z=V=H	36
6	**P-1**	**4**	**A**	ICl	X=I,W=CH_2OAc,Y=Z=V=H	80[d]
7	**P-1**	**5**	**A**	ICl	X=I,W=Cl,Y=Z=V=H	90
8	**P-1**	**6**	**A**	ICl	X=I,Y=Z=W=H,V=NO_2	33
9	**P-1**	**6**	**B**	ICl	X=I,Y=Z=W=H,V=NO_2	82
10	**P-2**	1	**A**	ICl	Y=I,X=Z=W=V=H	99
11	**P-2**	**2**	**A**	ICl	Y=I,W=Me,X=Z=V=H	99
12	**P-2**	**3**	**A**	ICl	Y=I,W=OMe,X=Z=V=H	83
13	**P-3**	1	**A**	ICl	Z=I,X=Y=W=V=H	98
14	**P-4**	1	**A**	ICl	X=OMe,Y=I,Z=W=V=H	55
15	**P-1**	1	**A**	Br_2/pyr	X=Br,Y=Z=W=V=H	97
16	**P-1**	**2**	**A**	Br_2/pyr	X=Br,W=Me,Y=Z=V=H	99
17	**P-1**	**3**	**A**	Br_2/pyr	X=V=Br,W=OMe,Y=Z=H	99
18	**P-1**	**4**	**A**	Br_2/pyr	X=Br,W=CH_2OH,Y=Z=V=H + X=Br,W=CHO,Y=Z=V=H	83
19	**P-1**	**3**	**A**	CF_3COOH	X=Y=Z=V=H,W=OMe	54[e]
20	**P-2**	1	**A**	CF_3COOH	X=Y=Z=W=V=H	39
21	**P-2**	**3**	**A**	CF_3COOH	X=Y=Z=V=H,W=OMe	20[f]
22	**P-4**	1	**A**	CF_3COOH	X=Y=Z=V=H,W=OMe	60

[a] $ArB(OH)_2$: **1**, phenyl; **2**, 4-methylphenyl; **3**, 4-methoxyphenyl; **4**, 4-hydroxymethylphenyl (provided by Dr. R. Ruel at Merck Frosst); **5**, 4-chlorophenyl; **6**, 3-nitrophenyl. [b] Condition **A**: Et_3N/DMF (1:1vol), 80-90°C, 24h; **B**: Na_2CO_3(2M)/DME, reflux overnight. [c] Isolated yields based on loading level of modified resin. [d] The coupled resin was first reacted with Ac_2O in CH_2Cl_2 in the presence of pyridine and DMAP and then cleaved with ICl in CH_2Cl_2. [e] All protiodesilylations were carried out for 24h except for Entry 20 (44h). [f] This reaction was substantially slower compared to Entries 19 and 22, several unidentified products were also observed on the crude ^1H NMR spectrum

In conclusion, we have demonstrated the versatility and utility of novel bromoarylsilane linkers for solid phase synthesis. The linkers are fully amenable to C-C bond formation under the Suzuki reaction conditions and can tolerate a broad array of arylboronic acid substrates. Electrophilic cleavage of the coupled products from the resin proceeds quickly and with generally high yields.

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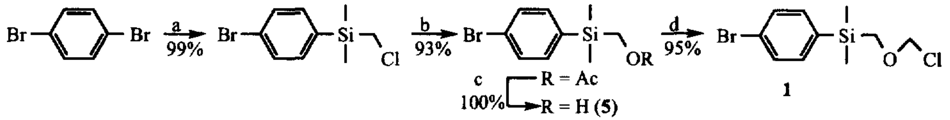
14. Linker **1** was prepared according to the following scheme:



a. i) n-BuLi(1eq), THF, -78°C, 5 min; ii) $(CH_3)_2Si(Cl)CH_2Cl$(1eq), 5 min, -78°C. b. NaOAc(1.2eq), DMF, n-Bu_4NI(0.3eq), 80°C, 24h. c. Dibal-H(2.1eq), toluene, -78 to 0°C, 2h. d. trioxane(1.2eq), HCl(g).[15]

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17. In the reaction of the corresponding alcohol with HCl(g) and trioxane to yield linker **4**, substantial amount of protiodesilylation (@50%) took place.
18. The iodination of **P-1**and **P-4** with ICl (3eq) in CH_2Cl_2 was nearly instantaneous. Greater than 90% of the product was released from the solid support within 10 min. Longer reaction time (2-24h) usually resulted in contamination with various silicon species (observed on the ^1H NMR of the crude products). **P-2** and **P-3** reacted at a slower rate. Nevertheless, good yields of the desired products were obtained.The brominative cleavage of resins with bromine (6eq)/pyr(3eq) in CH_2Cl_2 was equally efficient for **P-1** and **P-4**. The reactions were usually finished in 2h at 0°C. **P-3** reacted at a slower rate (61% in 24h) and **P-2** was the slowest to react (36% in 24h). Protiodesilylation (CF_3COOH /CH_2Cl_2/Me_2S) of **P-1** did not furnish the desired cleavage product (bromobenzene). Instead, the corresponding trifluoroacetate of alcohol **5** was obtained in greater than 90% yield (cleavage occurred at either the benzylic position of Wang resin or the acetal linkage). In a separate experiment, treatment of alcohol **5** with CF_3COOH in CH_2Cl_2 afforded the same product in quantitative yield. **P-4**, however, reacted smoothly to afford 67% yield of the desired product (*p*-bromoanisole)
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