Alkenyl- and Aryl[2-(hydroxymethyl)phenyl]dimethylsilanes: An Entry to Tetraorganosilicon Reagents for the Silicon-Based Cross-Coupling Reaction

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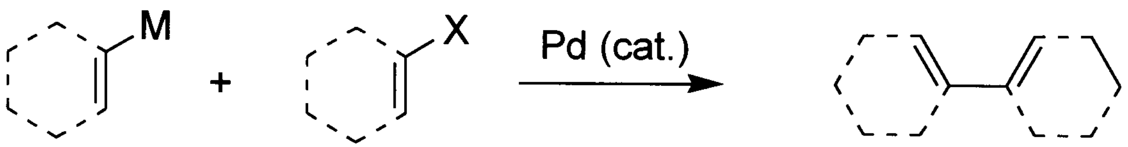
ASAP

4/30/05 Current Literature
Erikah Englund

Outline

- Silicon Coupling Intro
- Some Varieties of Silicon Reagents
  - Fluorosilanes
  - Alkoxysilanes
- Fluoride Free Conditions
  - Silanols
  - Tetraorganosilanes
- Title Paper
- Conclusion



M = **SnR_3** (*Stille-Migita-Kosugi*)
BR_2 or $B(OR)_2$ (*Suzuki-Miyaura*)
$SiR_{(3-n)}F_n$ (*Hiyama*)
$Si(OR)_3$ (*Tamao-Ito*)

- **Sn and B**
  - **Advantages:**
    - non-reactive in absence of catalyst
    - Several different methods for synthesis
  - **Disadvantages:**
    - High molecular weight
    - Toxicity (Sn)
    - Limited stability and coupling effeciency (B)
- **Si**
  - **Advantages:**
    - Non-Toxicity
    - Stability
    - Ease of Preparation
  - **Disadvantages:**
    - Use of F^- source (expensive and incompatible with other functional groups)
    - F^- free coupling conditions often need strong acid or base

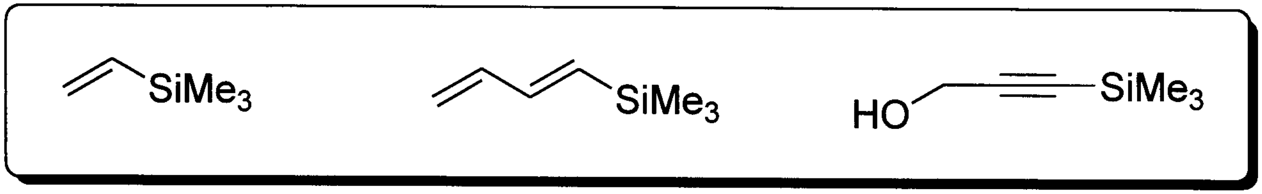
Denmark, *Acc.Chem.Res.* **2002**, *35*, 835

Silicon Challenges in Cross Coupling

- Small electronegativity difference in Si-C bond = weak nucleophile (too stable to cross couple)
- Hypothesis: Forming the Si “ate” complex will increase the aptitude to cross couple
- Hiyama and Hatanaka (*J.O.C.* **1988**, *53*, 918) demonstrated the first synthetically viable cross coupling of vinyl and propargyl silicon reagents with aryl and alkenyl iodides in the presence of Pd catalyst and fluoride source.

$$R^1X \quad + \quad R^2SiMe_3 \xrightarrow[\text{HMPA, 50°C, 2 h}]{F^-\text{, Pd, THF,}} R^1\text{-}R^2$$

Representative silanes used:

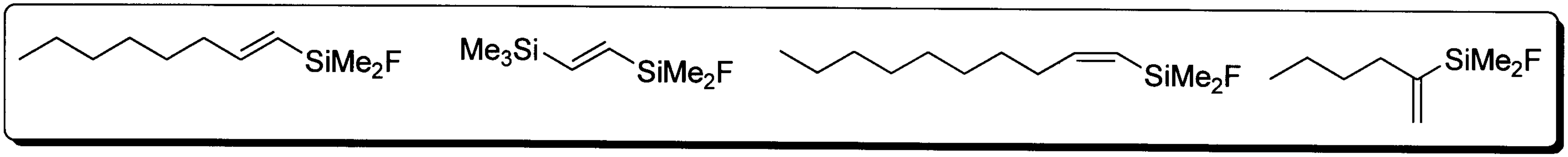


Early Advances:

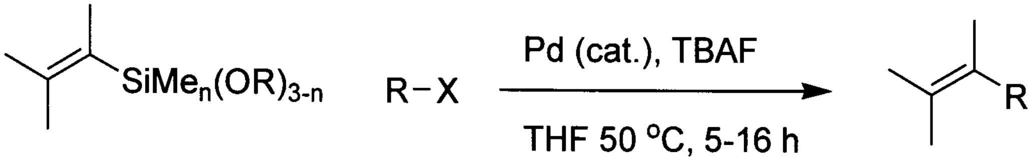
- Fluorosilanes (Hiyama, *J.O.C.* **1989**, *54*, 268)

$$R^1X \quad + \quad R^2SiF_nMe_{3-n} \xrightarrow[\text{60 °C, 16 h}]{\text{F}^-\text{, Pd, THF,}} R^1\text{–}R^2$$

Representative silanes used:

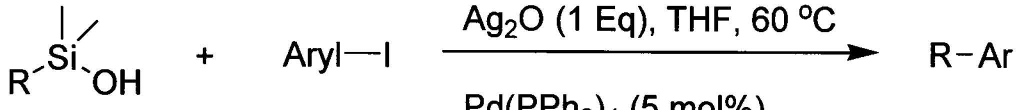


- Alkoxysilanes (Tamao, *Tet. Lett.* **1989**, *30*, 6051)



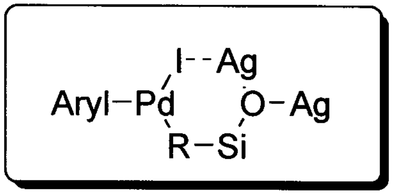
Fluoride Free Conditions

- Silanols with Ag_2O (Hiyama, *J.O.C.* **2000**, *65*, 5342)

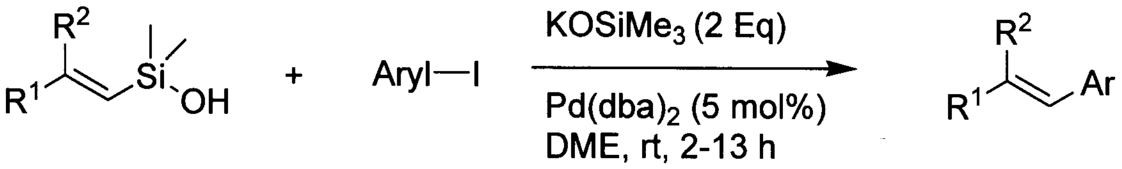


R = aryl or vinyl

Proposed Intermediate:

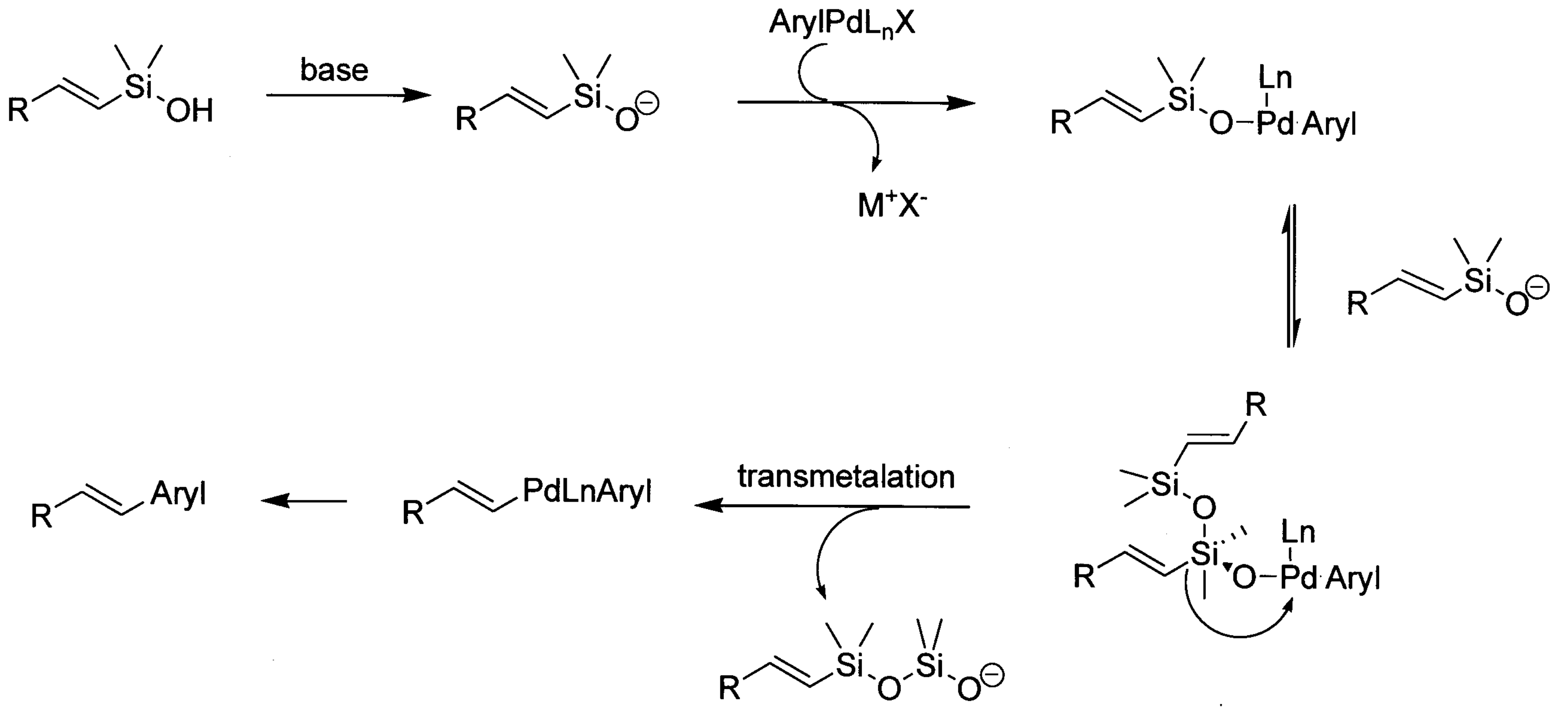


- Silanols with base (Denmark, *J.A.C.S.* **2001**, *123*, 6439)

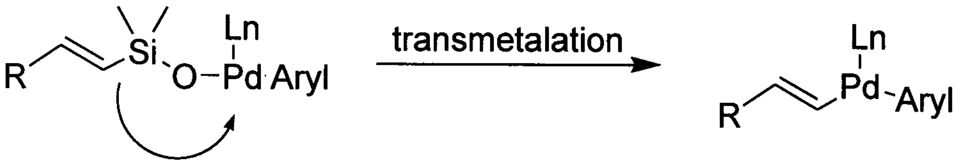


Compatible with TBS protected alcohols

- Expected Mechanism from Denmark conditions:



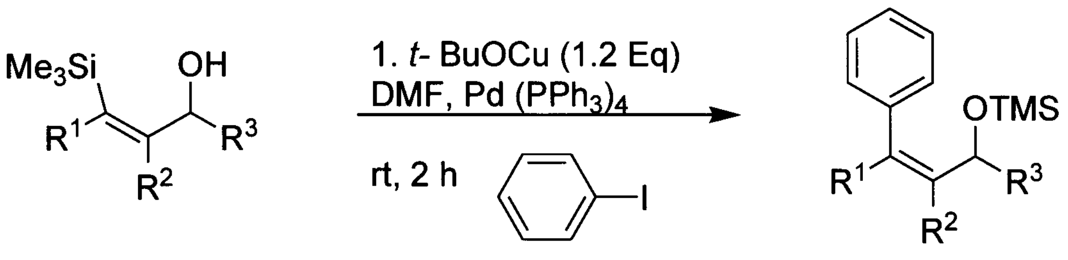
- Found Mechanism (from rate law studies)



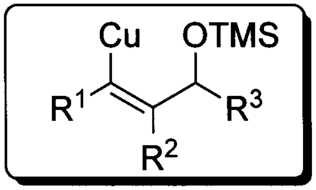
Denmark, *J.A.C.S.* **2004**, *126*, 4876

Fluoride Free Cond. (cont.)

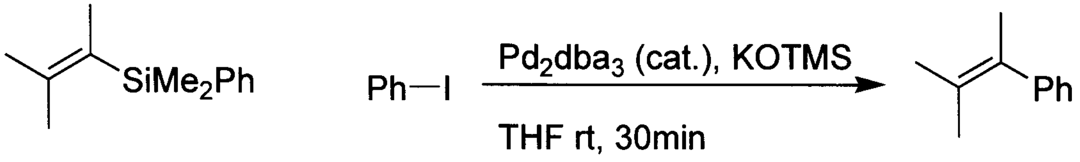
- Tetraorganosilanes
  - Stoichiometric Cu (Takeda, *J. O. C.* **2002**, 8450)



Proposed Intermediate:

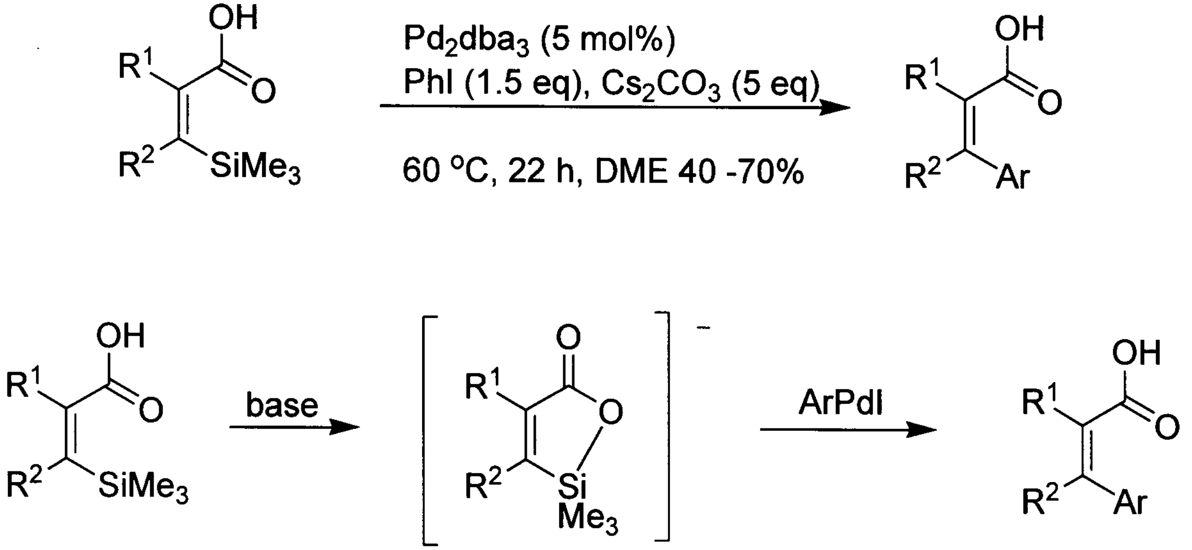


  - Strong Base (Anderson, *J.O.C.* **2004**, *69*, 8971)



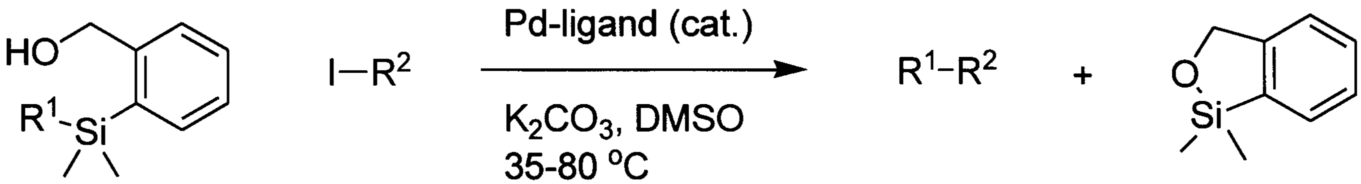
Tetraorgano Silanes (cont.)

- Intramolecular activation (Shindo, *SynLett*, **2005**, 1, 176)

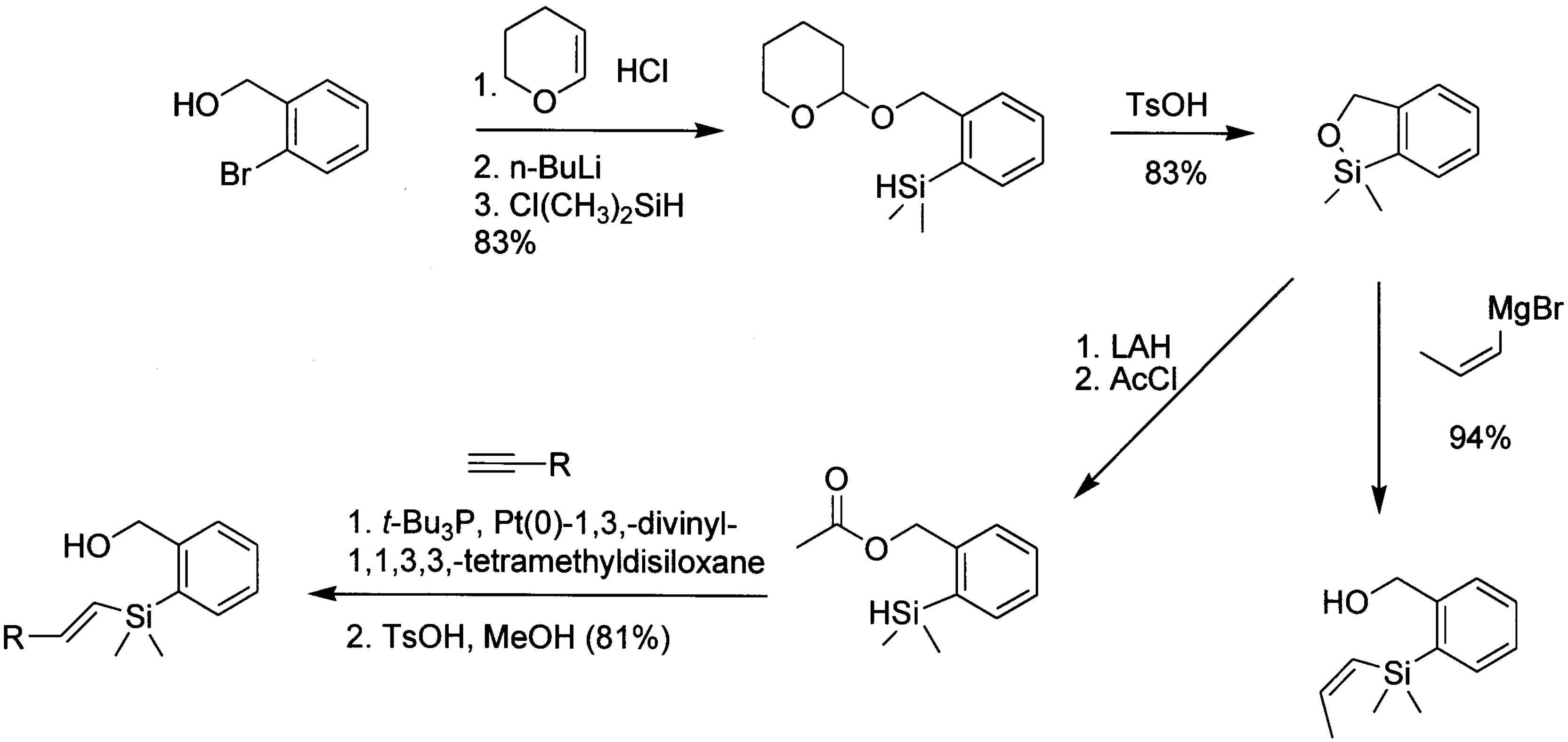


Title Paper

Hiyama (*J.A.C.S.* A.S.A.P.)



Prep of Silicon Reagents



Cross-Coupling of **1** with Aryl and Alkenyl Iodides

R = (E)-HexCH=CH **1a**
(E)-NC$(CH_2)_3$CH=CH **b**
(E)-PhCH=CH **c**
MeCH=CH **d**
H_2C=CMe **e**
H_2C=CPh **f**
(E)-PrCH=CPr **g**
Me_2C=CH **h**

entry	alkenylsilane	aryl and alkenyl Iodide	time (h)	yield (%)[b]
1	**1a**	4-NC-C_6H_4	20	93
2	**1a**	4-EtO_2C-C_6H_4	18	96
3	**1a**	4-Me(O)C-C_6H_4	17	94
4	**1a**	4-H(O)C-C_6H_4	20	94
5	**1a**	4-O_2N-C_6H_4	26	99
6	**1a**	4-Cl-C_6H_4	19	93
7	**1a**	4-MeO-C_6H_4	40	89
8	**1a**	3-*t*-$BuMe_2SiOCH_2$-C_6H_4	23	98
9	**1a**	3-$HOCH_2$-C_6H_4	47	88
10	**1a**	2-Me-C_6H_4	47	94
11	**1a**	1-naphthyl	23	91
12	**1a**	3-pyridyl	23	80
13	**1a**	2-thienyl	23	99
14	**1b**	4-EtO_2C-C_6H_4	19	95
15	**1c**	4-EtO_2C-C_6H_4	19	88
16	**1d**	4-EtO_2C-C_6H_4	19	91[c]
17	**1e**	4-EtO_2C-C_6H_4	24	96
18	**1f**	4-EtO_2C-C_6H_4	25	95
19[d,e]	**1f**	4-MeO-C_6H_4	12	80[f]
20[d]	**1g**	4-EtO_2C-C_6H_4	29	92
21	**1h**	4-EtO_2C-C_6H_4	25	96
22[g]	**1b**	(*E*)-HexCH=CH	3	73
23[g]	**1b**	(*Z*)-HexCH=CH	2	78

Cross Coupling of **2** Aryl Iodides

R = Ph **2a**

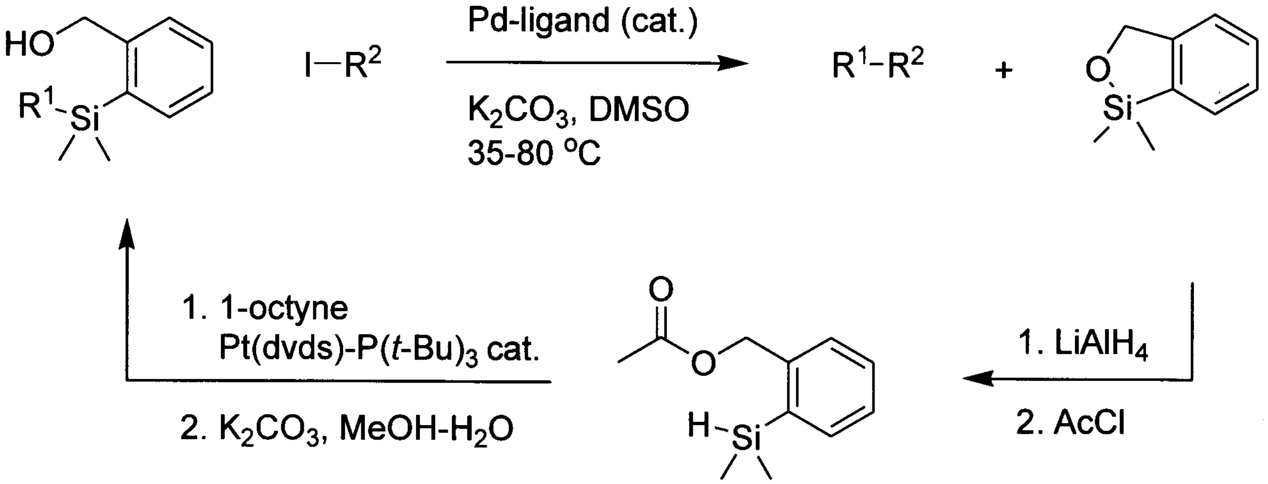
4-F-C_6H_4 **b**

2-Me-C_6H_4 **c**

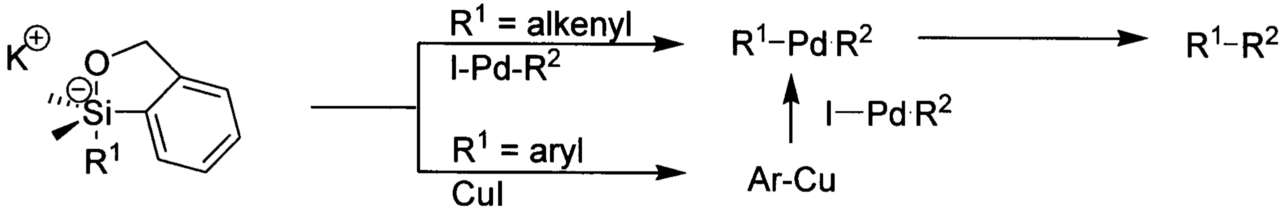
2-thienyl **d**

entry	arylsilane	Aryl iodide	time (h)	yield (%)[b]
1	**2a**	4-NC-C_6H_4	7	97
2	**2a**	4-MeO-C_6H_4	16	99
3	**2a**	2,6-Me_2-C_6H_3	13	94
4	**2a**	2-pyridyl	13	96
5	**2a**	2-thienyl	13	93
6	**2b**	4-EtO_2C-C_6H_4	3	91
7[c]	**2c**	4-EtO_2C-C_6H_4	5	81
8	**2d**	4-EtO_2C-C_6H_4	10	93

Recycling the Silicon Reagent



Proposed Reaction Pathway



Conclusions

- Silicon coupling reagents are desirable due to their non-toxicity, stability and synthetic availability.
- Many of the reaction conditions previously developed were too harsh (strong base), incompatible with other functionality (fluoride mediated) or required a stoichiometric amount of an additional metal.
- Mild reaction conditions have been developed for coupling with tetraorganosilanes and aryl or alkenyl iodides.
- For the first time, the metal residue used in the coupling reaction can be recovered and recycled.