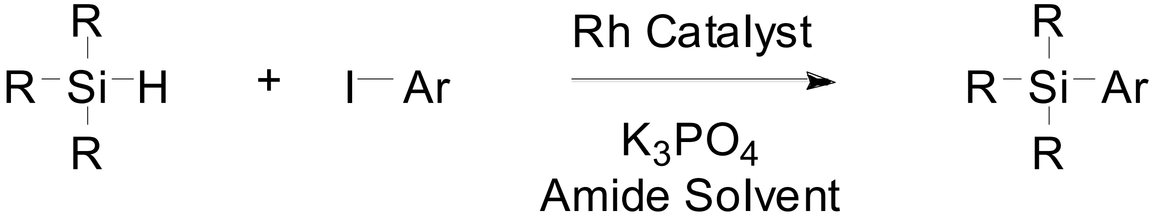
Direct and Selective Arylation of Tertiary Silanes with Rhodium Catalyst



$$R_3Si{-}H + I{-}Ar \xrightarrow[\text{K}_3\text{PO}_4\ \text{Amide Solvent}]{\text{Rh Catalyst}} R_3Si{-}Ar$$

J. Org. Chem. **2008** ASAP Article.

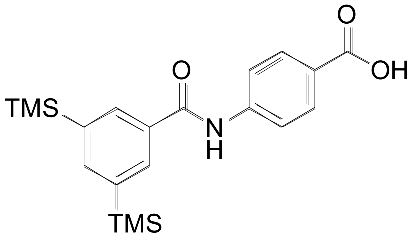
Yoshinori Yamanoi and Hiroshi Nishihara

Current Literature: 8/30/08

David Arnold

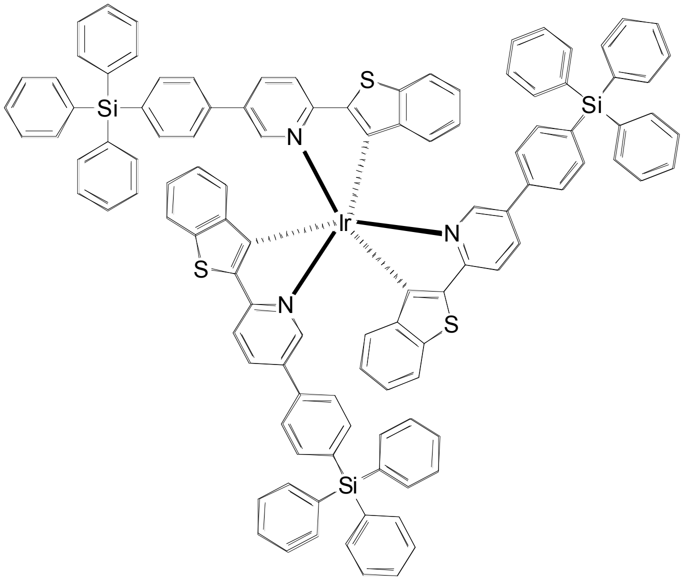
Importance of Arylsilanes: Applications to Biological and Material Sciences

- Cancer Theraputics:



TAC-101: Phase 1 clinical trials
for the treatment of lung cancer

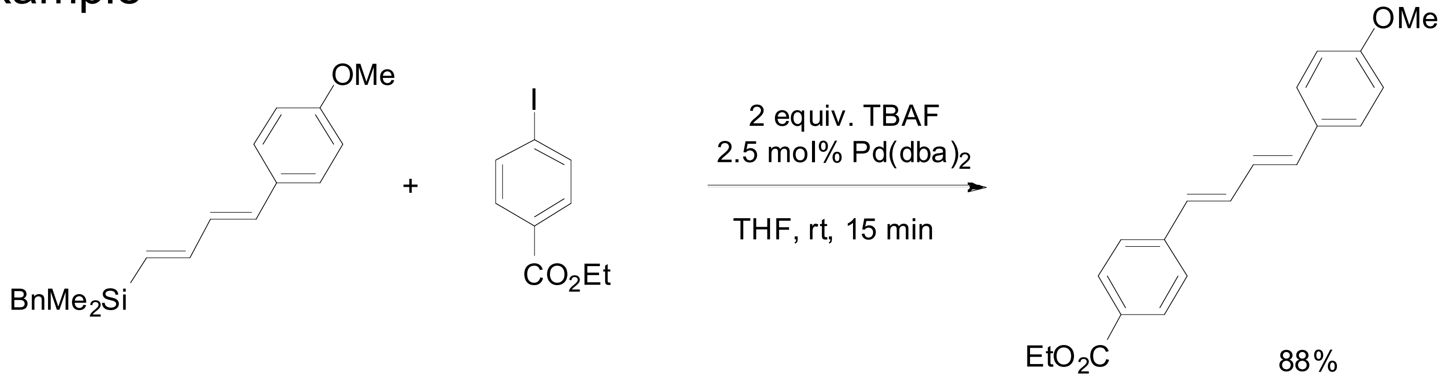
- Material Sciences: Organic Phosphorescent Materials: Organic Light Omitting Diodes



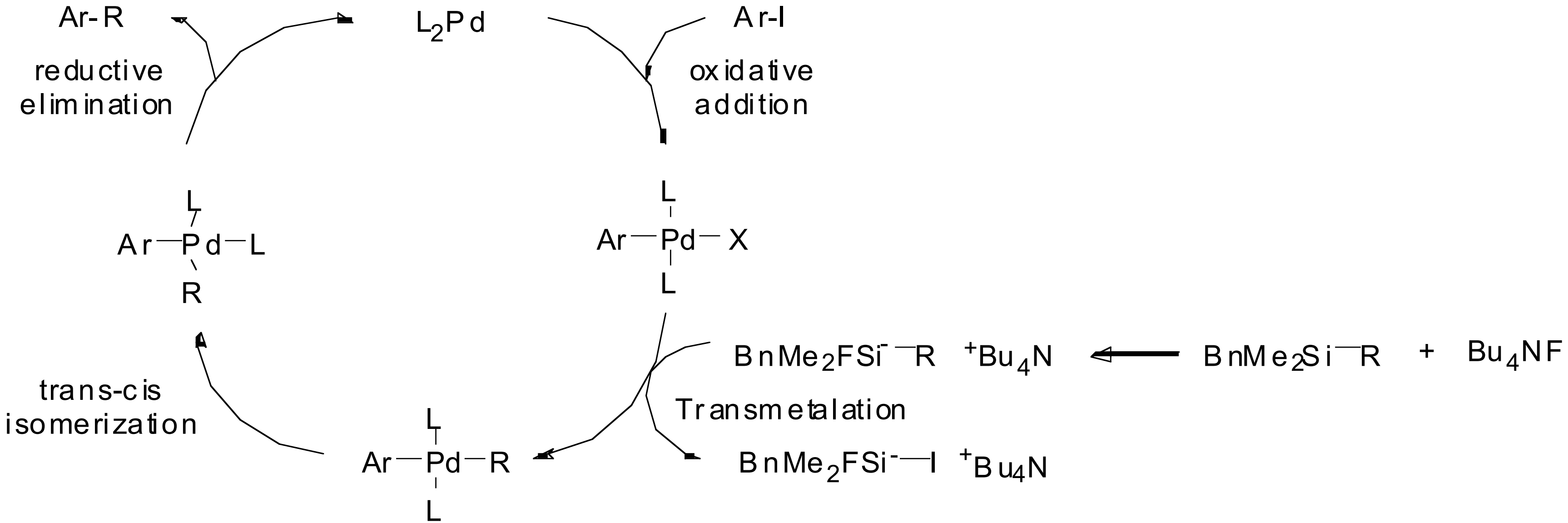
DDT **2003**, *8*, 551; *J. Org. Chem.* **2007**, *72*, 6241.

Application to Organic Synthesis: Substrates for Fluoride-Promoted Hiyama Coupling Reactions

- Example



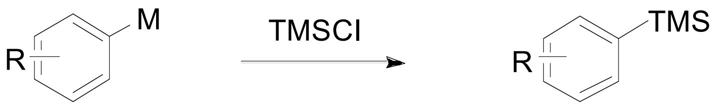
- Mechanism



J. Am. Chem. Soc. **2005**, *127*, 8004.

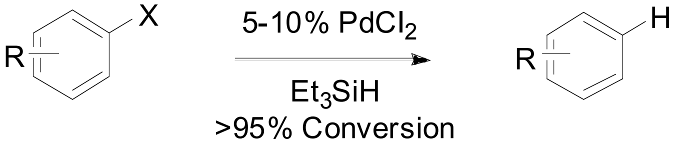
Traditional Methods Used to Access Arylsilanes and Early Studies in Palladium Catalyzed Reactions

- Reaction of Grignard or organolithium reagents:

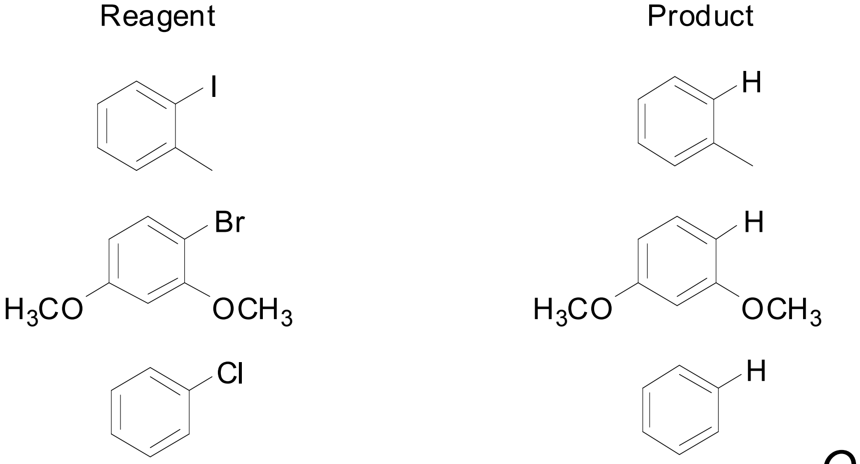


M = MgX, Li
R = alkyl, OMe, NMe_2

- $PdCl_2$ catalyzed reactions between aryl halides and Et_3SiH resulted in reduction products:

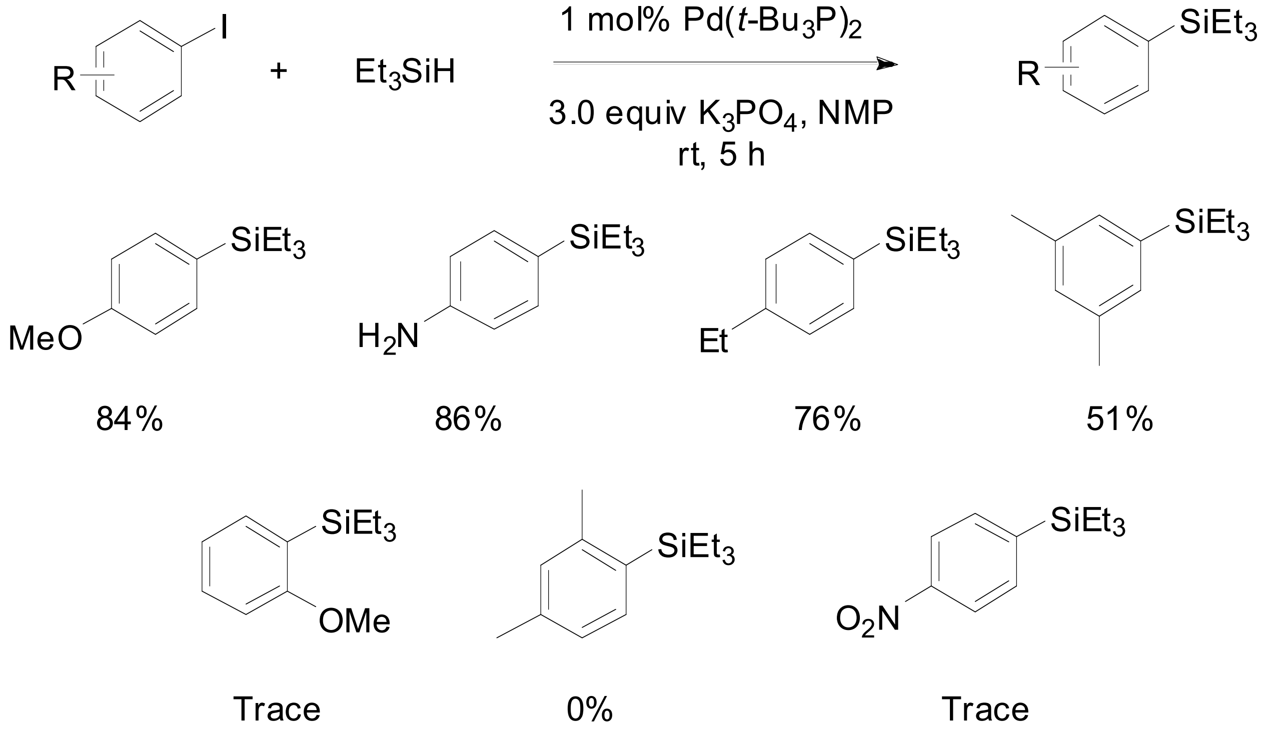


X = I, Br, Cl



Organometallics **1996**, *15*, 1508.
Silicon Reagents in Organic Synthesis: Academic Press; London, UK, **1988**.

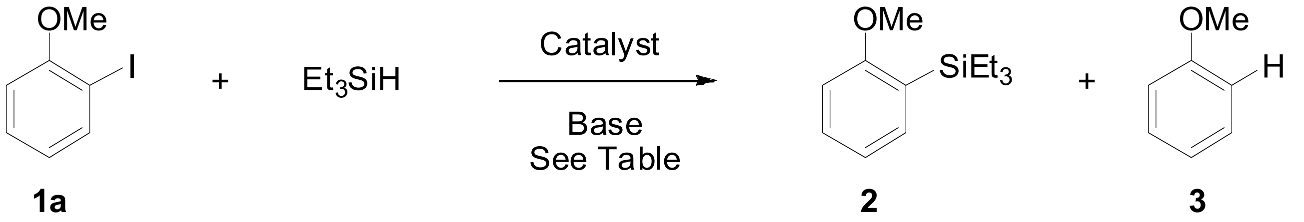
Author’s Earlier Work on Palladium-Catalyzed Silylations of Aryl Halides

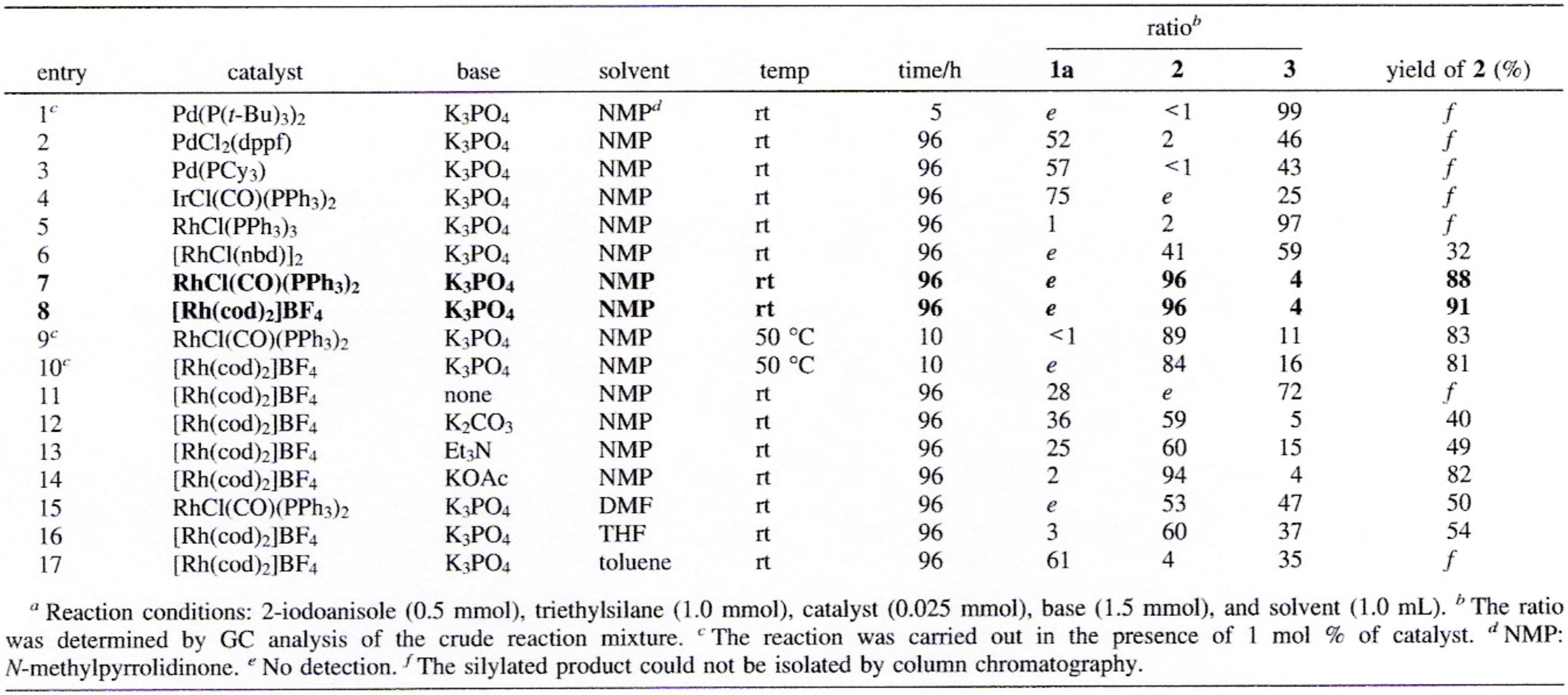


- Aryl halide reactivity was found to be Ar-I > Ar-Br > Ar-Cl.
- Addition of base was found to essential to suppress the formation of the reduction product.
- The reaction was found to be intolerable of *o*-substitution or electron-withdrawing groups on the aryl halide.

J. Org. Chem. **2005**, *70*, 9607.

Reaction Optimization





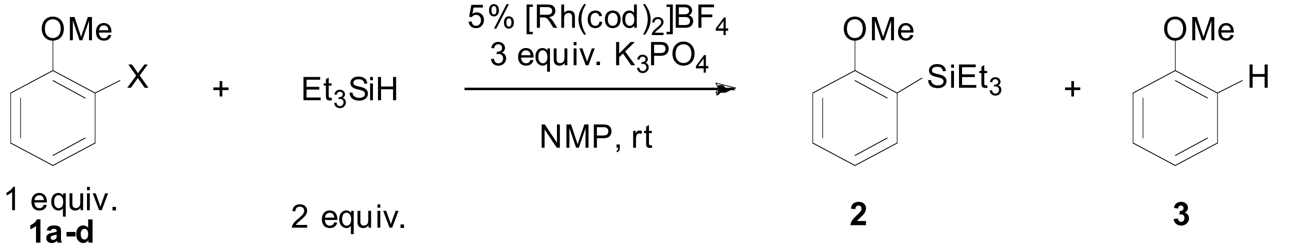
entry	catalyst	base	solvent	temp	time/h	ratio[b] 1a	2	3	yield of **2** (%)
1[c]	$Pd(P(t\text{-}Bu)_3)_2$	K_3PO_4	NMP[d]	rt	5	*e*	<1	99	*f*
2	$PdCl_2(dppf)$	K_3PO_4	NMP	rt	96	52	2	46	*f*
3	$Pd(PCy_3)$	K_3PO_4	NMP	rt	96	57	<1	43	*f*
4	$IrCl(CO)(PPh_3)_2$	K_3PO_4	NMP	rt	96	75	*e*	25	*f*
5	$RhCl(PPh_3)_3$	K_3PO_4	NMP	rt	96	1	2	97	*f*
6	$[RhCl(nbd)]_2$	K_3PO_4	NMP	rt	96	*e*	41	59	32
7	**$RhCl(CO)(PPh_3)_2$**	**K_3PO_4**	**NMP**	**rt**	**96**	***e***	**96**	**4**	**88**
8	**$[Rh(cod)_2]BF_4$**	**K_3PO_4**	**NMP**	**rt**	**96**	***e***	**96**	**4**	**91**
9[c]	$RhCl(CO)(PPh_3)_2$	K_3PO_4	NMP	50 °C	10	<1	89	11	83
10[c]	$[Rh(cod)_2]BF_4$	K_3PO_4	NMP	50 °C	10	*e*	84	16	81
11	$[Rh(cod)_2]BF_4$	none	NMP	rt	96	28	*e*	72	*f*
12	$[Rh(cod)_2]BF_4$	K_2CO_3	NMP	rt	96	36	59	5	40
13	$[Rh(cod)_2]BF_4$	Et_3N	NMP	rt	96	25	60	15	49
14	$[Rh(cod)_2]BF_4$	KOAc	NMP	rt	96	2	94	4	82
15	$RhCl(CO)(PPh_3)_2$	K_3PO_4	DMF	rt	96	*e*	53	47	50
16	$[Rh(cod)_2]BF_4$	K_3PO_4	THF	rt	96	3	60	37	54
17	$[Rh(cod)_2]BF_4$	K_3PO_4	toluene	rt	96	61	4	35	*f*

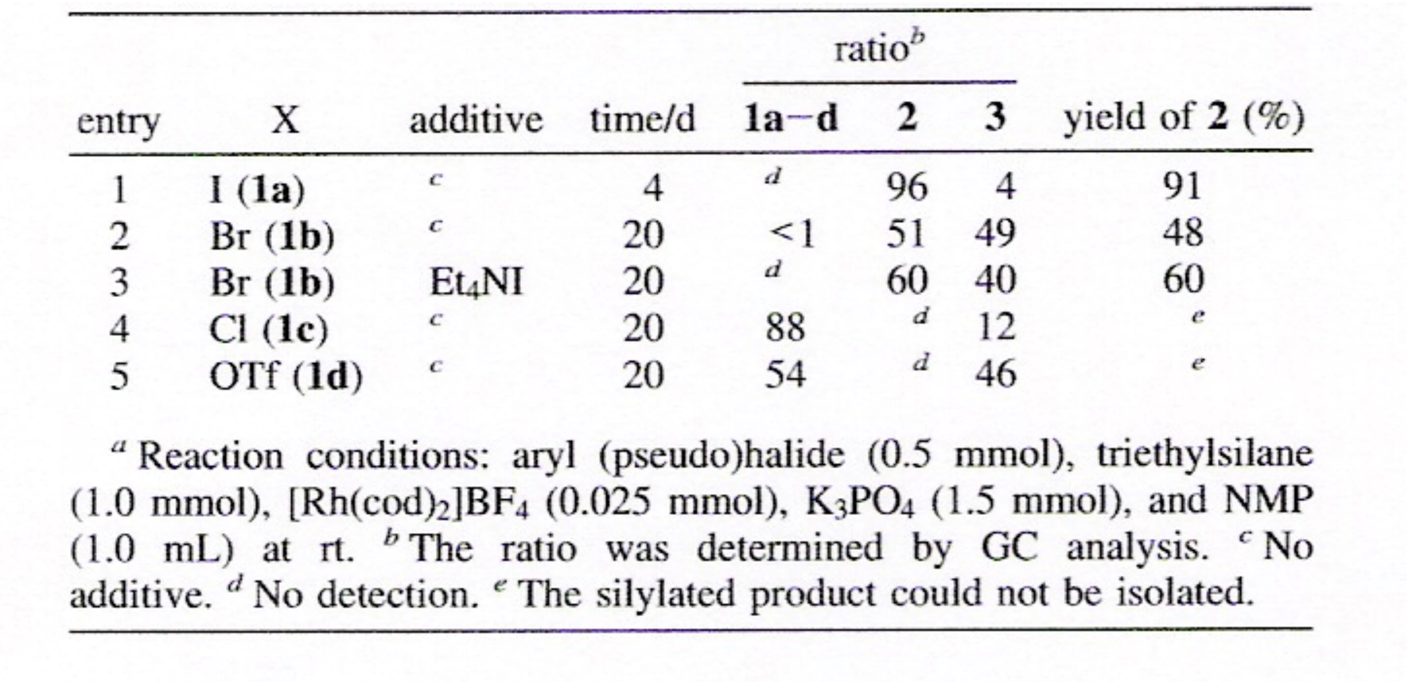
[a] Reaction conditions: 2-iodoanisole (0.5 mmol), triethylsilane (1.0 mmol), catalyst (0.025 mmol), base (1.5 mmol), and solvent (1.0 mL). [b] The ratio was determined by GC analysis of the crude reaction mixture. [c] The reaction was carried out in the presence of 1 mol % of catalyst. [d] NMP: *N*-methylpyrrolidinone. [e] No detection. [f] The silylated product could not be isolated by column chromatography.

- Optimized Conditions Found by GC Analysis:

  Catalyst: 5% $RhCl(CO)(PPh_3)_2$ or 5% $[Rh(cod)_2]BF_4$
  Solvent: NMP
  Base: 3 equiv. K_3PO_4

Relative Reactivities of Aryl Halides and Triflates Under Optimized Conditions



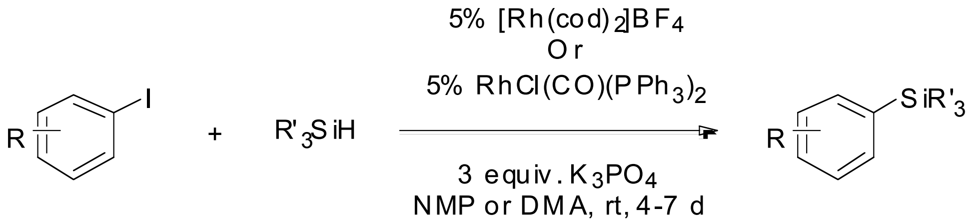


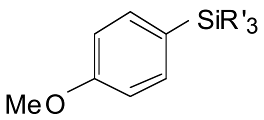
				ratio[b]			
entry	X	additive	time/d	**1a−d**	**2**	**3**	yield of **2** (%)
1	I (**1a**)	[c]	4	[d]	96	4	91
2	Br (**1b**)	[c]	20	<1	51	49	48
3	Br (**1b**)	Et_4NI	20	[d]	60	40	60
4	Cl (**1c**)	[c]	20	88	[d]	12	[e]
5	OTf (**1d**)	[c]	20	54	[d]	46	[e]

[a] Reaction conditions: aryl (pseudo)halide (0.5 mmol), triethylsilane (1.0 mmol), $[Rh(cod)_2]BF_4$ (0.025 mmol), K_3PO_4 (1.5 mmol), and NMP (1.0 mL) at rt. [b] The ratio was determined by GC analysis. [c] No additive. [d] No detection. [e] The silylated product could not be isolated.

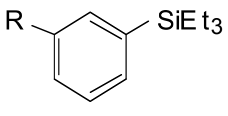
- Reactivity Order: Ar-I > Ar-Br > Ar-Cl, Ar-OTf.

Reaction Scope

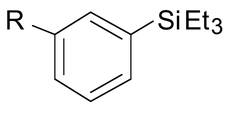




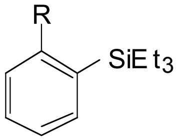
Variation of Hydrosilane
R' = -Et$_3$ (99%); -*i*-Pr$_3$ (83%)
-*t*-BuMe$_2$ (99%); -Ph$_2$Me (98%)



Electron-Donating Substituents
R = -OMe (78%); -Me$_2$N (81%);
-OH (99%); -NH$_2$ (98%)



Electron-Withdrawing Substituents
R = -CO$_2$Et (77%); -C(O)Me (83%);
-CF$_3$ (72%); -CN (72%)

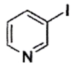
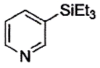
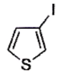
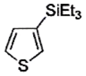
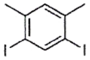
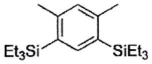
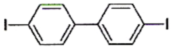
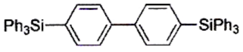
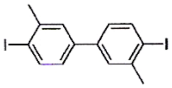
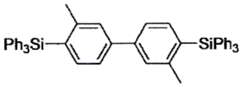
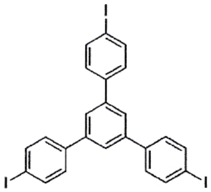
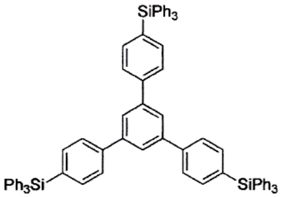
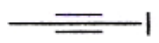
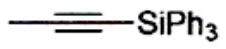
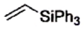
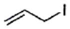
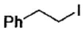


Sterically Hindered Ortho-Substituted Substrates
Alkyl: R = -Me (99%); -Et (79%); -*i*-Pr (68%); -Ph (0%); *t*-Bu (0%)
Electron-Donating Groups: -OMe (91%); -SMe (99%); -OH (99%); -NH$_2$(99%)
Electron-Withdrawing Groups: -CO$_2$Et (0%); -C(O)Me (0%); -CF$_3$ (0%); -CN (0%)

- Good functional group tolarance with *meta*- and *para*-substituted aryl iodides: -alkyl, -OMe, -SMe,-OH, -NMe$_2$, -NH$_2$, -CO$_2$Et, -C(O)Me, -CF$_3$ and –CN
- The reaction is sensitive to both steric and electronic effects for *ortho*-substituted aryl iodides.

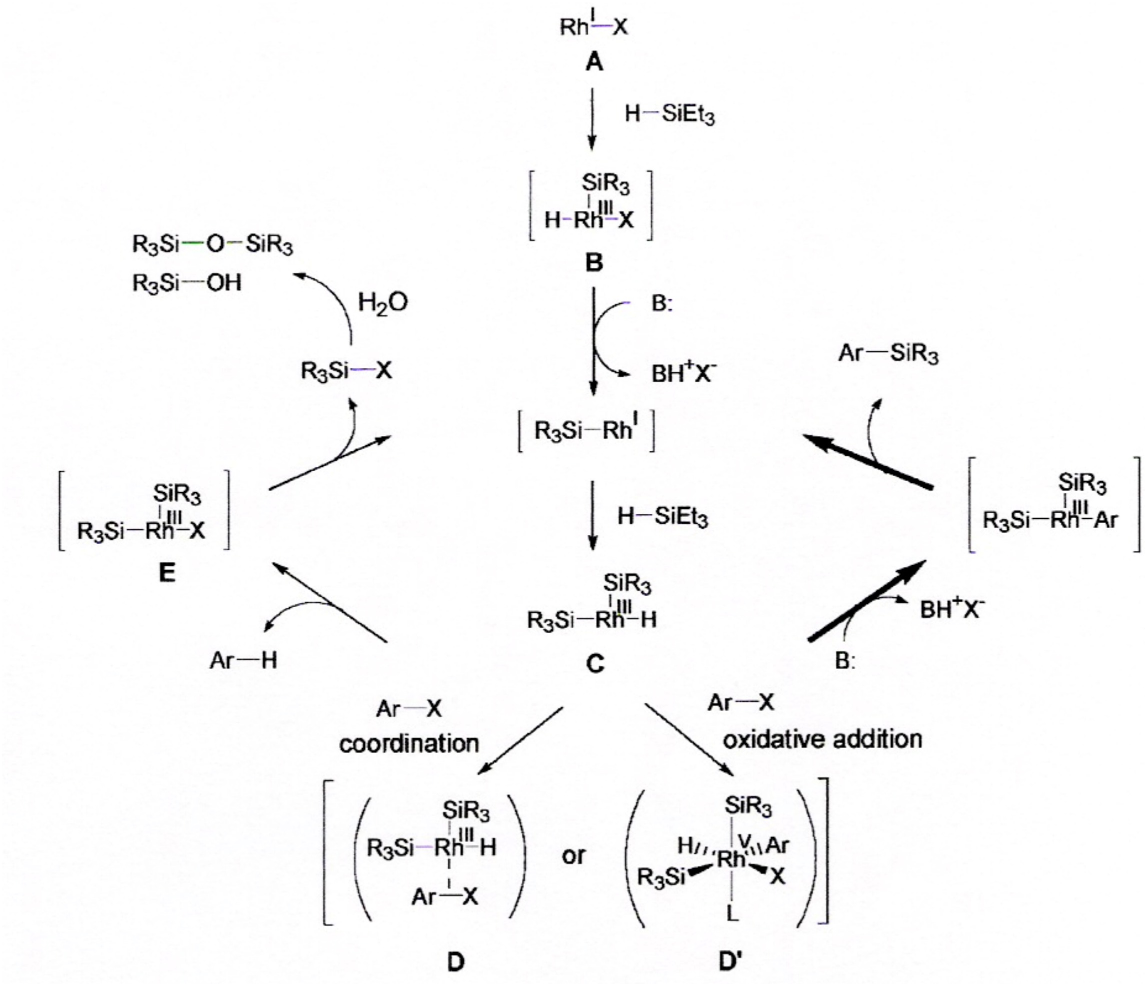
Advanced Substrate Scope: Aromatic Heterocycles, Multiple Couplings and Non-Aromatic Couplings

$$\text{R–I} + \text{H–SiR}_3 \xrightarrow[\text{conditions}]{} \text{R–SiPh}_3$$

entry	R–I	R_3	conditions[a]	product	yield (%)
1		Et_3	A	 **39**	71
2		Et_3	B	 **40**	88
3		Et_3	B	 **41**	73
4		Ph_3	B	 **42**	86
5		Ph_3	B	 **43**	54
6		Ph_3	B	 **44**	55
7		Ph_3	C	 **45**	38[b]
8		Ph_3	D	 **46**	49[b]
9		Ph_3	D	—	c
10		Ph_3	A	—	c

[a] Conditions: (A) R-I (0.5 mmol), $HSiR_3$ (2.0 equiv), K_3PO_4 (3.0 equiv), $RhCl(CO)(PPh_3)_2$ (5 mol %), NMP (1.0 mL), rt, 4 d. (B) R-I (0.5 mmol), $HSiR_3$ (2.0 equiv), $[Rh(cod)_2]BF_4$ (5 mol %), NMP (1.0 mL), rt, 6 d. (C) Ph_3SiH (1.0 mmol), R-I (3.0 equiv), K_3PO_4 (3.0 equiv), rt, 4 d. (D) Ph_3SiH (1.0 mmol), R-I (3.0 equiv), K_3PO_4 (3.0 equiv), 0 °C, 6 d. [b] The yield was based on the amount of triphenylsilane. No silylated product was obtained.

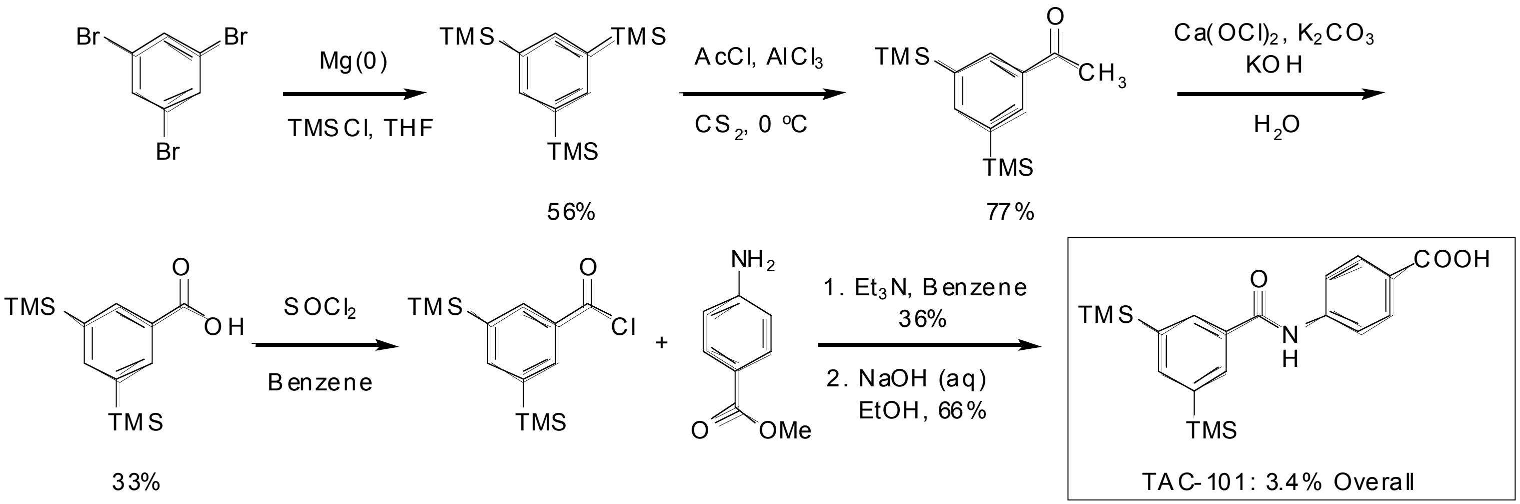
Proposed Mechanism



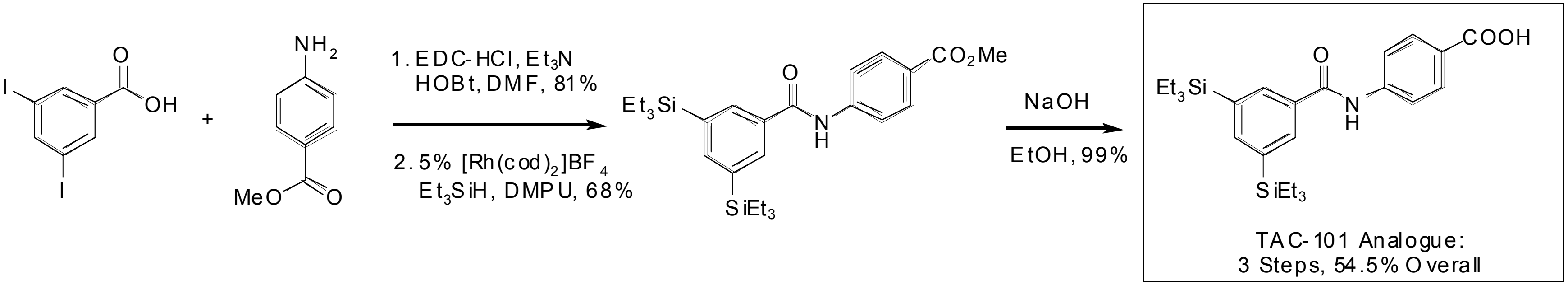
- Key Catalytic Species: $Rh(H)(SiR_3)_2$

Application of Methodology

- Previously Reported Synthesis of TAC-101:



- Application of Methodology to the Synthesis of a TAC-101 Analogue:



J. Med. Chem. **1990**, *33*, 1430.

Conclusions

- The authors have developed a novel rhodium catalyzed reaction between trialkylsilanes and aryl halides to produce arylsilanes.

- The reaction developed through this methodology demonstrated good functional group compatibility and substrate scope.

- The developed methodology has wide application in the fields of organic synthesis, medicinal chemistry and material sciences.