Literature Report

Rhodium-Catalyzed Intermolecular C-H Silylation of Arenes with High Steric Regiocontrol

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Date: 2015-03-31

Hartwig, J. F. *et al.*
Science **2014**, *343*, 853–857.

University of California
Berkeley

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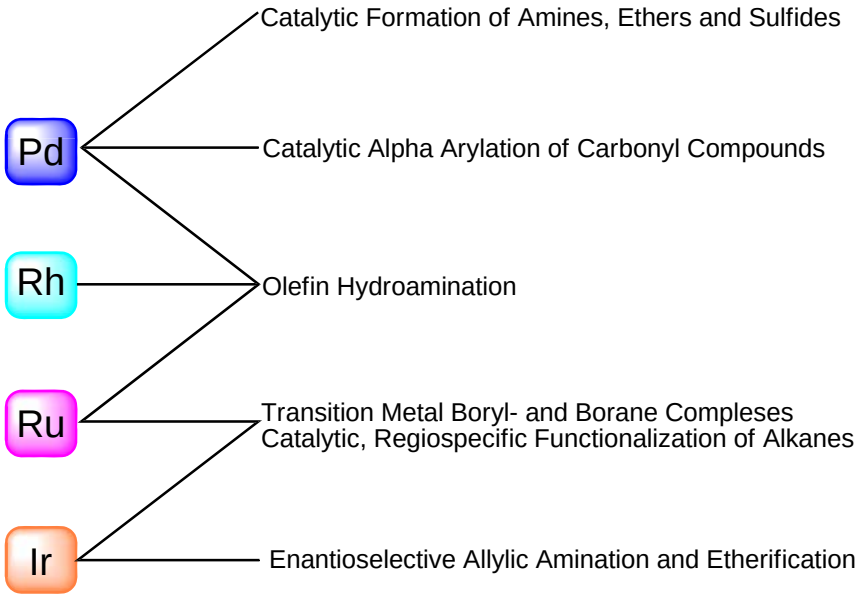
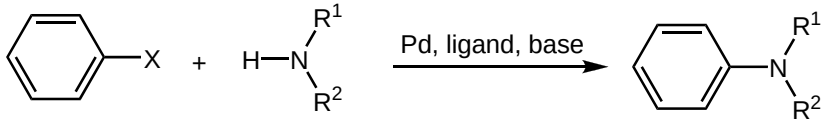
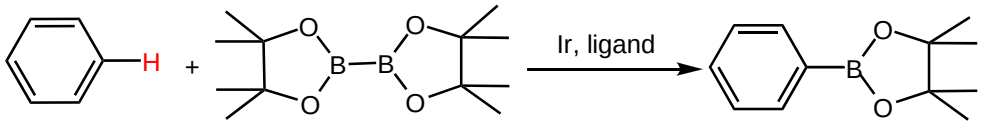
Introduction



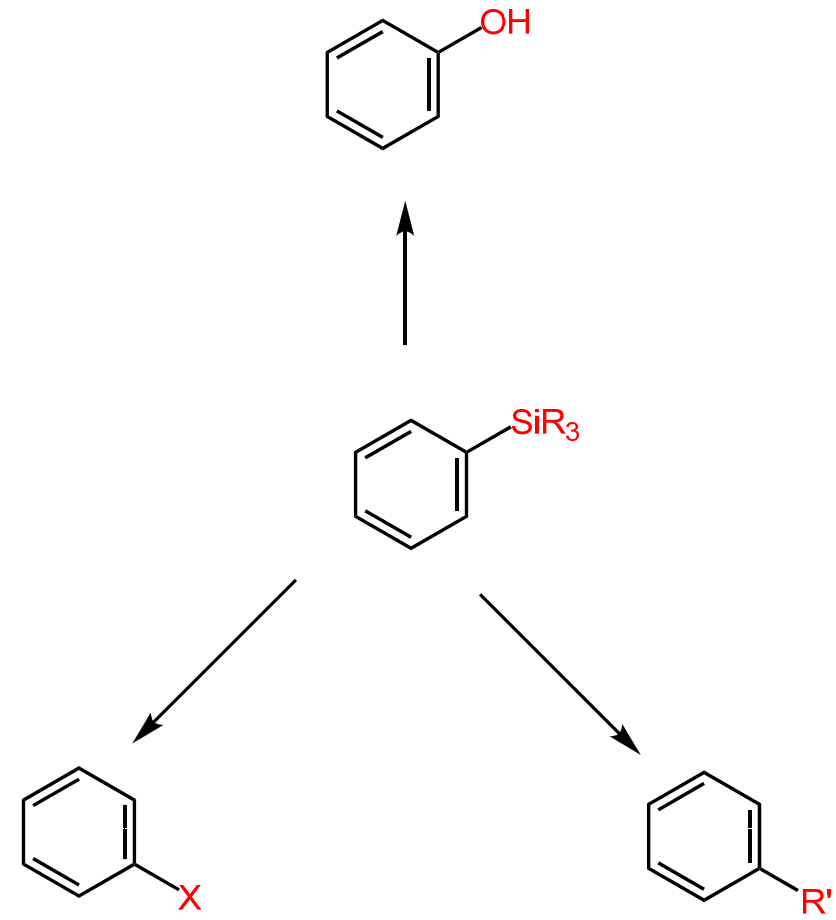
Buchwald-Hartwig Cross Coupling Reaction



Miyaura-Ishiyama-Hartwig Borylation



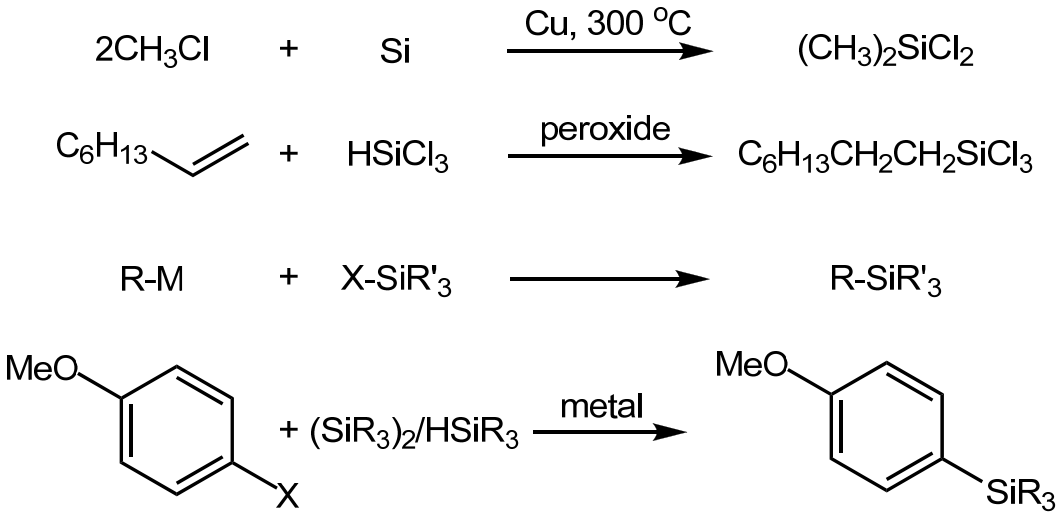
Introduction



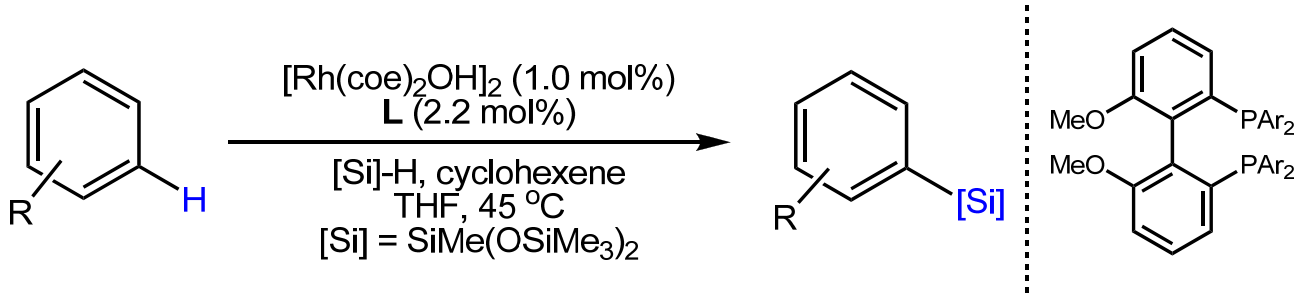
X = I, Br

R' = Aryl, *N*-Heterocycle, *et al*

Introduction



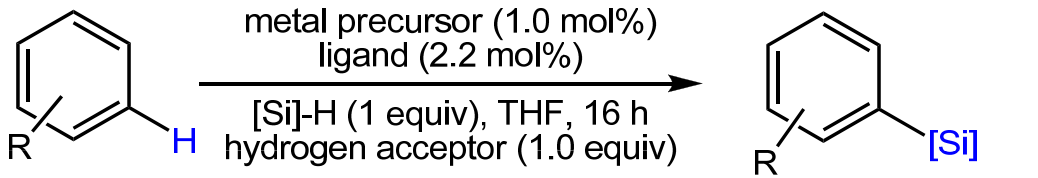
Rhodium-Catalyzed Intermolecular C-H Silylation of Arenes with High Steric Regiocontrol



- high functional group tolerance
- under mild, neutral conditions

Hartwig, J. F. *et al. Science* **2014**, *343*, 853-857.

Evaluation of the Reaction Conditions for the Silylation of Arenes



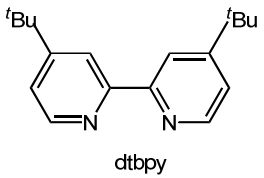
[Si] = $SiMe(OTMS)_2$

Entry	Arene	Metal precursor	Ligand	Acceptor	T (^{o} C)	Yield (%)[a]
1	Benzene	$[Ir(cod)OMe]_2$	dtbpy	None	80	8
2	Benzene	$[Ir(cod)OMe]_2$	Me_4Phen	None	80	11
3	Benzene	$[Ir(cod)OMe]_2$	2-MePhen	None	80	16
4	Benzene	$[Ir(cod)OMe]_2$	2-MePhen	Cyclohexene	80	29
5	Benzene	$[Rh(cod)Cl]_2$	dppb	Cyclohexene	80	0
6	Benzene	$[Rh(cod)Cl]_2$	dcpe	Cyclohexene	80	0
7	Benzene	$[Rh(cod)Cl]_2$	**L3**	Cyclohexene	80	68

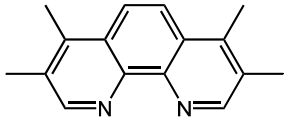
Evaluation of the Reaction Conditions for the Silylation of Arenes

Entry	Arene	Metal precursor	Ligand	Acceptor	T (° C)	Yield (%)
8	1,3-Xylene	$[Rh(coe)_2OH]_2$	**L3**	Cyclohexene	50	64
9	1,3-Xylene	$[Rh(coe)_2OH]_2$	**L1**	Cyclohexene	50	68
10	1,3-Xylene	$[Rh(coe)_2OH]_2$	**L2**	Cyclohexene	50	75
11	1,3-Xylene	$[Rh(coe)_2OH]_2$	**L2**	Cyclohexene	45	92[b]

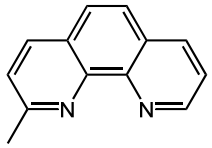
[a] Yields determined by GC analysis. [b] Yield determined by ^1H NMR spectroscopy. Reaction run with two equivalents of silane and cyclohexane



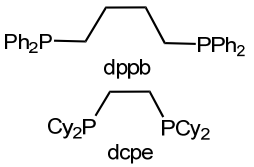
dtbpy

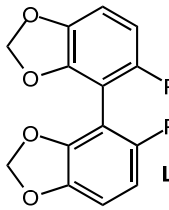


Me_4Phen

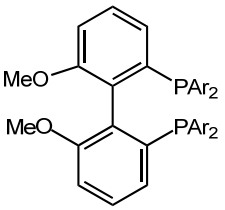


2-MePhen





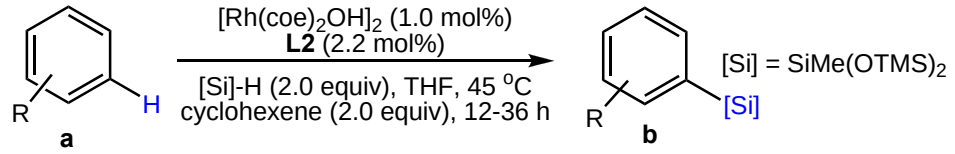
L3 Ar = 3,5-^{t}Bu$_2$-4-MeO-C_6H_2

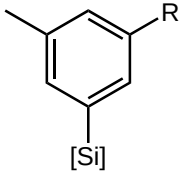


L1 Ar = 3,5-^{t}Bu$_2$-4-MeO-C_6H_2

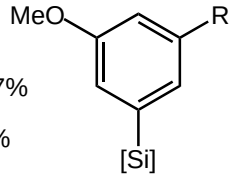
L2 Ar = 3,4,5-$(MeO)_3$-C_6H_2

The Regioselective Silylation of Arenes



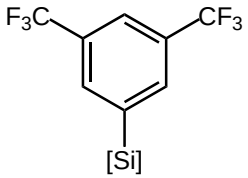


1b (R = Me) 83%
2b (R = OMe) 82%
3b (R = Cl) 86%
4b (R = $OSiMe_2{}^tBu$) 67%
5b (R = NMe_2) 65%
6b (R = $C(O)NEt_2$) 96%
7b (R = Bpin) 96%

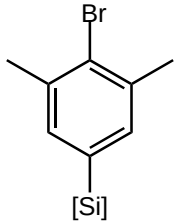


8b (R = OMe) 89%
9b (R = CH_2CH_2Cl) 93%

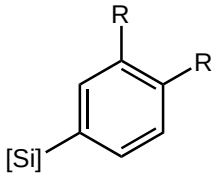
10b (R = ) 91%



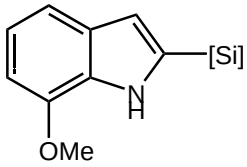
11b 78%



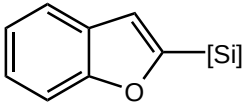
12b 48%



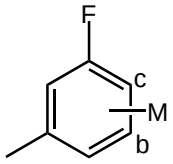
13b (R = OMe) 95%
14b (R = Me) 85%
15b (R,R = $-(CH_2)_3-$) 90%



16b 85%



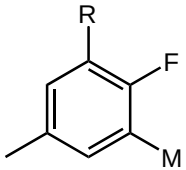
17b 83%



18

M = [Si]: 72%
(89:11 b:c)

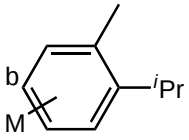
M = [B]: (> 95%)
(49:41:10 b:c:di)



19 b (R = H)
c (R = M)

M = [Si]: 98%
(96:4 b:c)

M = [B]: (> 95%)
(53:47 b:c)



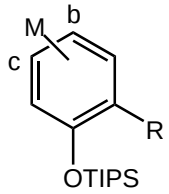
20

M = [Si]: 69%
(82:18 b:c)

M = [B]: 78%
(42:58 b:c)

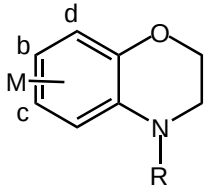
[Si] = $Si(Me)(OSiMe_3)_2$; [B] = Bpin, pin = 2,3-dimethyl-2,3-butanediolate (pinacolate)

The Regioselective Silylation of Arenes



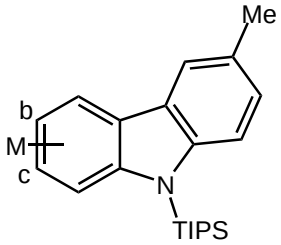
21 (R = Me)
M = [Si]: 90% (>99:1 b:c)
M = [B]: 81% (28:72 b:c)

22 (R = OMe)
M = [Si]: 94% (89:11 b:c)
M = [B]: 80% (51:49 b:c)

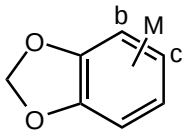


23 (R =TIPS)
M = [Si]: 53% (>99:1 b:c)
M = [B]: 44% (49:45:6 b:c:d)

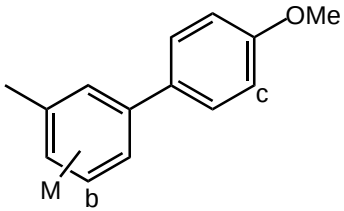
24 (R = Me)
M = [Si]: 95% (83:17 b:c)
M = [B]: 79% (46:47:7 b:c:d)



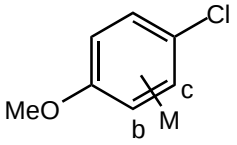
25 M = [Si]: 90% (97:3 b:c)
M = [B]: 44% (33:67 b:c)



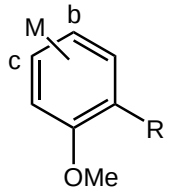
26 M = [Si]: 91% (92:8 b:c)
M = [B]: 74% (4:96 b:c)



27 M = [Si]: 80% (97:3 b:c)
M = [B]: 76% (87:13 b:c)



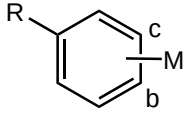
28 M = [Si]: 83% (98:2 b:c)
M = [B]: 88% (43::19:38 b:c:di)



29 (R = CF_3)
M = [Si]: 92% (98:2 b:c)
M = [B]: (>95%) (31:69 b:c)

30 (R = Cl)
M = [Si]: 86% (94:6 b:c)
M = [B]: 94% (40:60 b:c)

31 (R = Me)
M = [Si]: 93% (86:14 b:c)
M = [B]: 75% (25:75 b:c)



32 (R = NMe_2)
M = [Si]: 84% (92:8 b:c)
M = [B]: 53% (21:75:4 b:c:di)

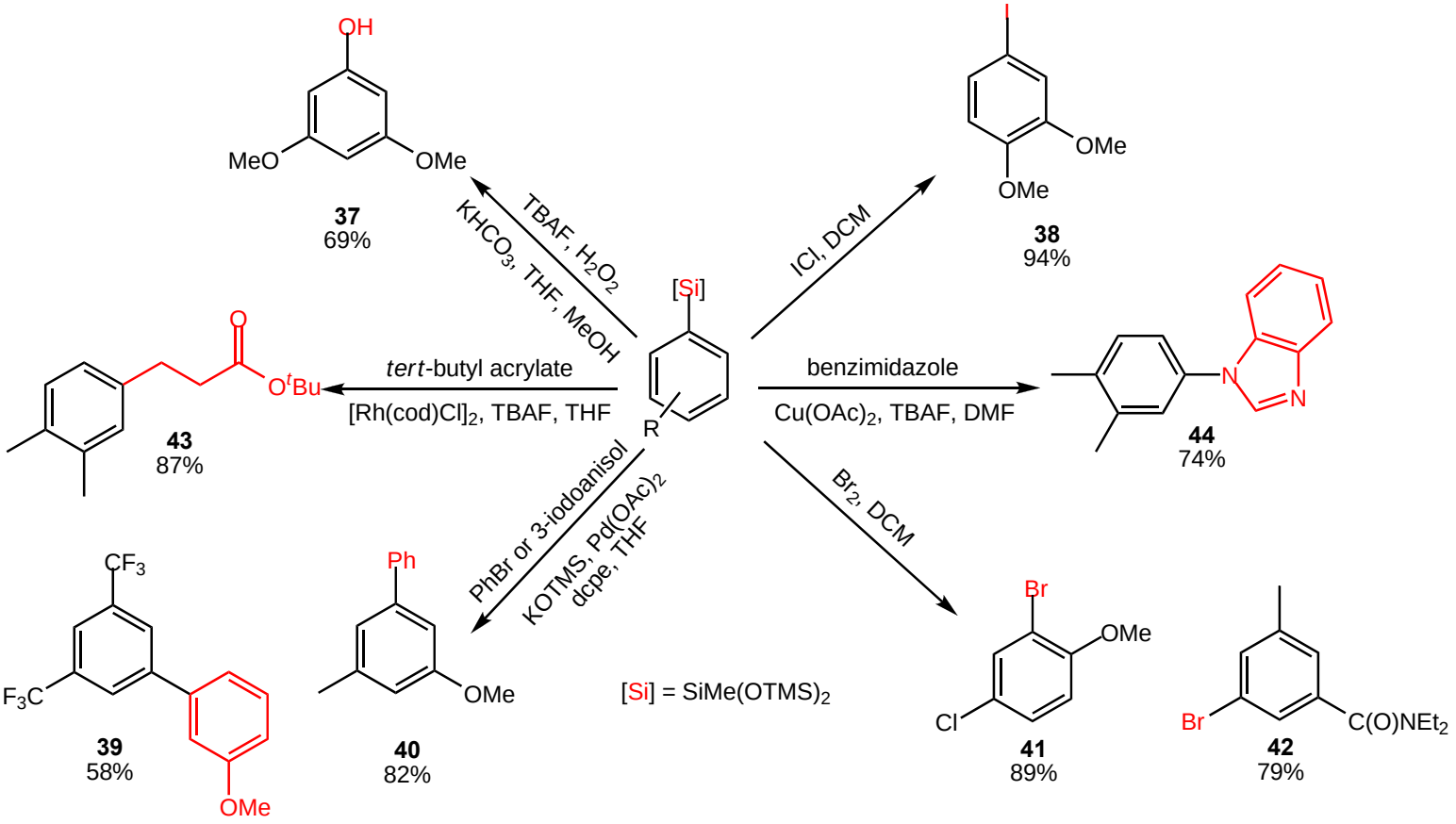
33 (R = OMe)
M = [Si]: 94% (80:20 b:c)
M = [B]: 76% (16:68:16 b:c:di)

34 (R = CF_3)
M = [Si]: 82% (22:77:1 b:c:di)
M = [B]: >99% (31:29:40 b:c:di)

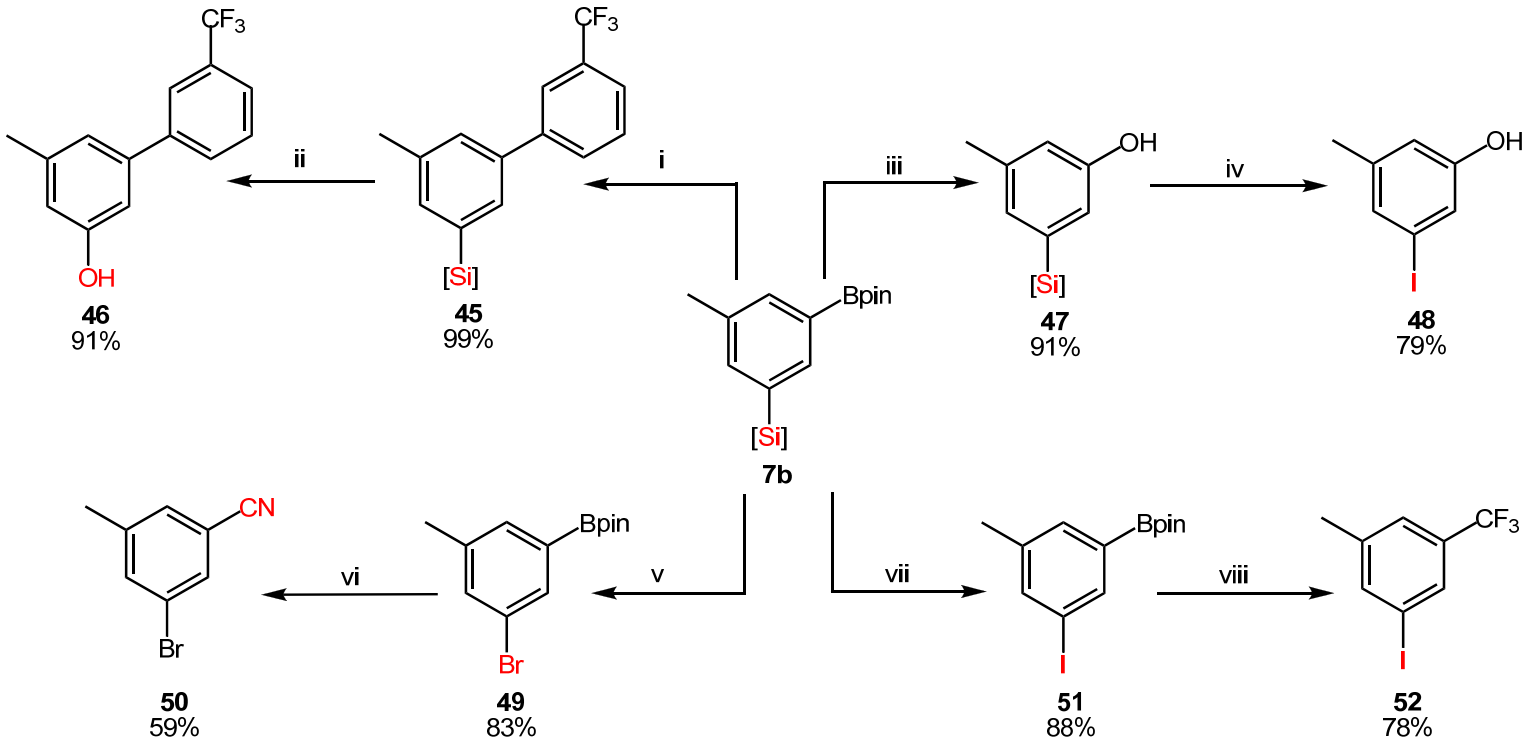
35 (R = $SiMe_3$)
M = [Si]: 58% (67:33 b:c)
M = [B]: 52% (28:56:16 b:c:di)

36 (R = [Si])
M = [Si]: 48% (96:4 b:c)
M = [B]: 91% (43:41:16 b:c:di)

Functionalization of the Arylsilane Products

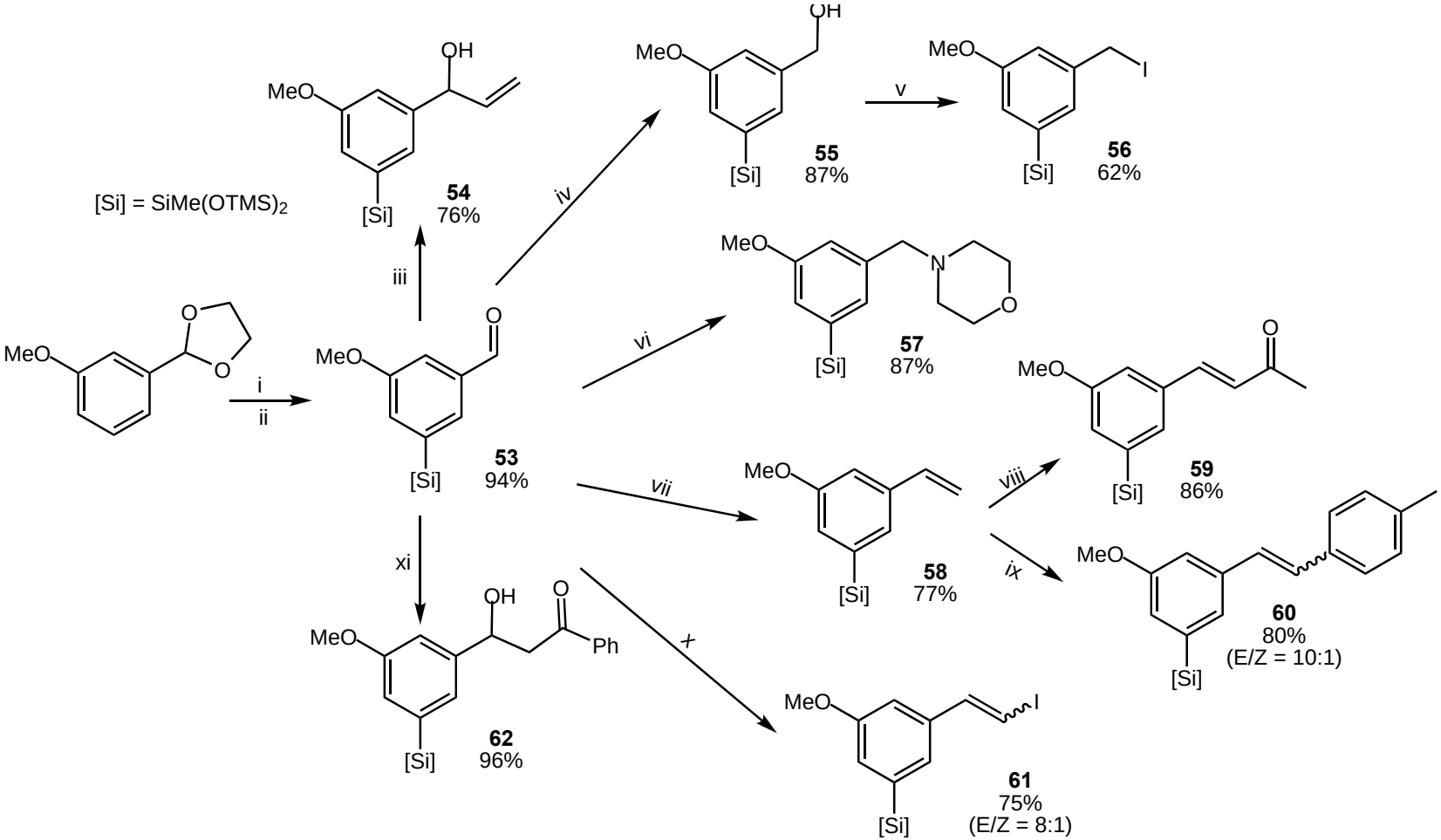


Functionalization of the Arylsilane Products



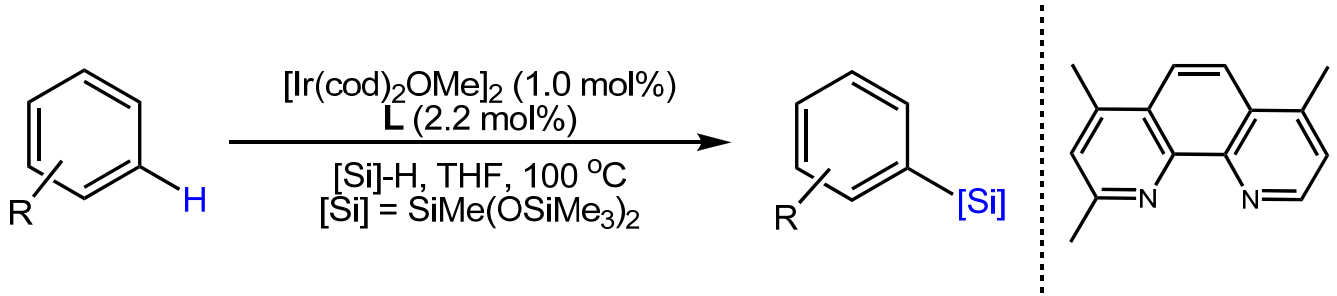
Reaction coditions: (i) $Pd(dppf)Cl_2$, 3-CF_3-C_6H_4Br, K_2CO_3, THF; (ii) TBAF, H_2O_2, $KHCO_3$, MeOH; (iii) NaOH, H_2O_2, THF, H_2O; (iv) ICl, DCM; (v) Br_2, DCM; (vi) $Cu(NO_3)_2 \bullet 3H_2O$, $Zn(CN)_2$,CsF, MeOH, H_2O; (vii) ICl, DCM; (viii) (Phenanthroline)$Cu(CF_3)$, KF, DMF.

Silylarenes as Useful Building Blocks



Reaction conditions: (i) $[Rh(coe)_2OH]_2$, **L2**, $HSiMe(OTMS)_2$, cyclohexene, THF; (ii) $Pd(MeCN)_2Cl_2$, acetone; (iii) vinylmagnesium bromide THF; (iv) $NaBH_4$, THF; (v) Ph_3P, I_2, imidazole, THF; (vi) morpholine, $NaHB(OAc)_3$, 1,2-dichloroethane; (vii) ^nBuLi, Ph_3PMeI, THF; (viii) Grubbs catalyst, methyl vinyl ketone, DCM; (ix) $Pd(OAc)_2$, 4-bromotoluene, triethanolamine, THF; (x) CHI_3, $CrCl_2$, dioxane, THF; (xi) acetophenone, $MgBr_2$, $(^iPr)_2NEt$, DCM

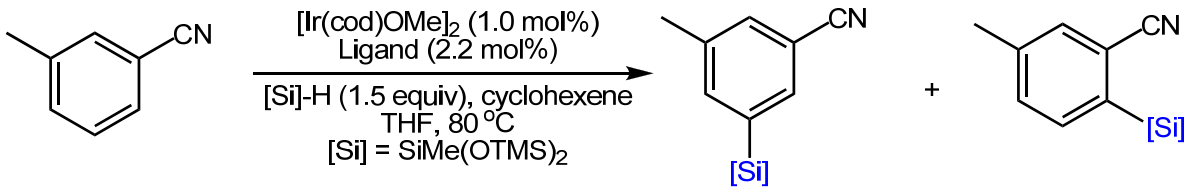
Iridium-Catalyzed Silylation of Aryl C−H Bonds



- high functional group tolerance
- broad scope with heteroarenes

Hartwig, J. F. *et al. J. Am. Chem. Soc*. **2015**, *137*, 592–595.

Evaluation of Reaction Conditions



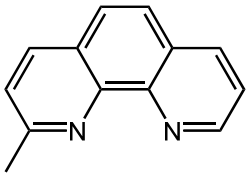
Entry	Ligands	Conversion (%) [a]	Yield (%) [a,b]	**1a**:**1b** [a]
1	**L1**	29	26	19:1
2	**L2**	6	0	/
3	**L3**	38	36	26:1
4	**L4**	39	35	26:1
5	**L5**	34	30	24:1
6	**L6**	9	7	20:1
7	**L7**	22	19	6:1

[a] Determined by GC. [b] Combined yield of **1a** and **1b**

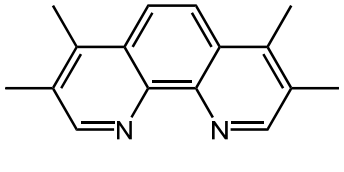
Evaluation of Reaction Conditions

Entry	Ligands	Conversion (%) [a]	Yield (%) [a,b]	**1a**:**1b** [a]
8	**L8**	31	0	/
9	**L9**	45	38	11:1
10[c]	**L3**	53	49	26:1
11[c,d]	**L3**	93	90	25:1

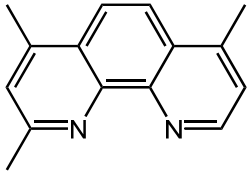
[a] Determined by GC. [b] Combined yield of **1a** and **1b.** [c] Reaction run with 1 equiv of cyclohexene. [d] Reaction run at 100 °C.



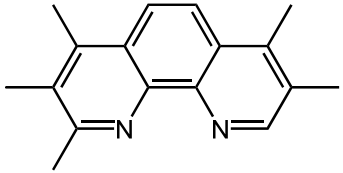
L1



L2



L3



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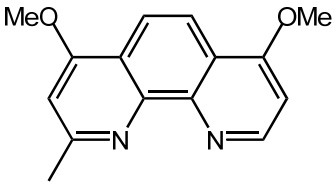
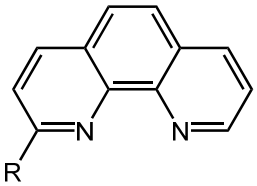
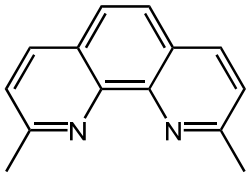


L5

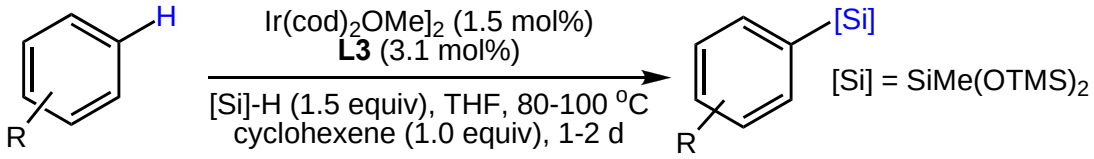


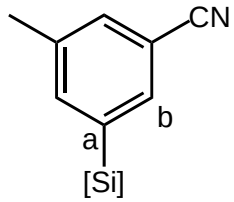
L6, R = Et
L7, R = OMe
L8, R = *t*Bu



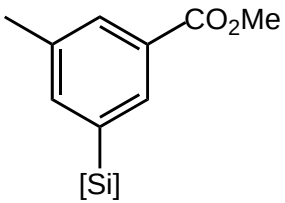
L9

C−H Silylation of Arenes

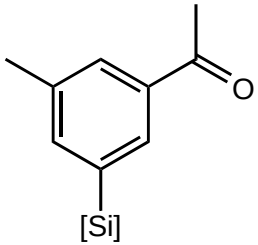




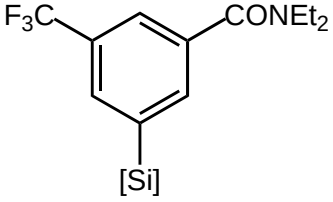
1
77% (a:b = 96:4)



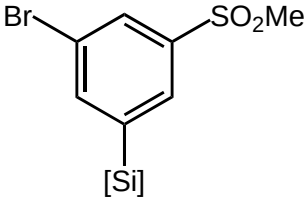
2
92%



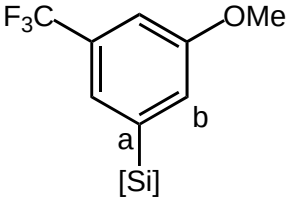
3
68%



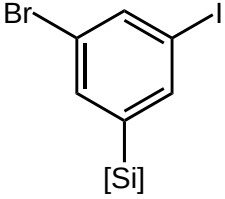
4
84%



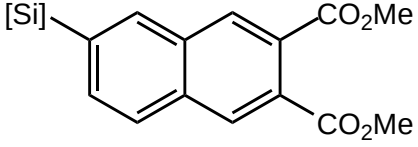
5
82%



6
86% (a:b = 96:4)

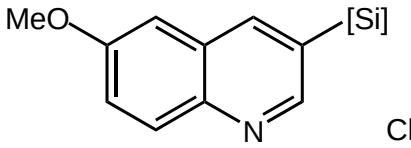


7
69%

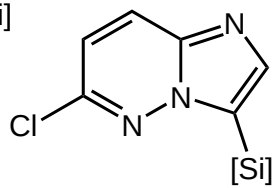


8
94%

C−H Silylation of Heteroarenes



9
83%



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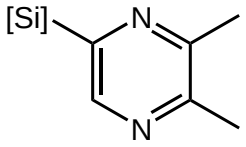
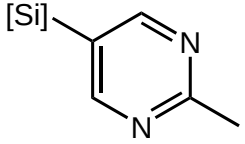
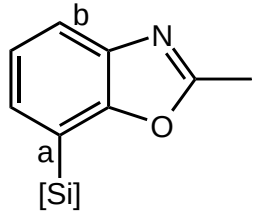
68%



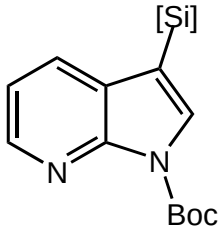
11
73%



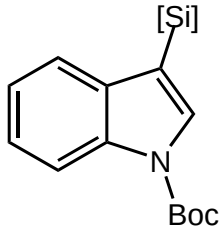
12
94%



13
65% (a:b = 94:6)



14
90%



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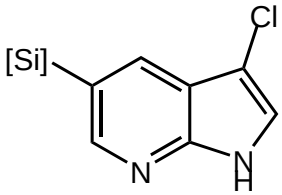
95%



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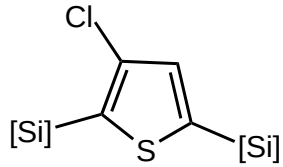
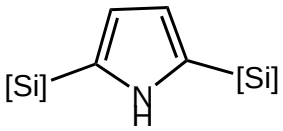
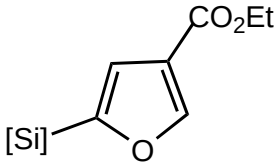


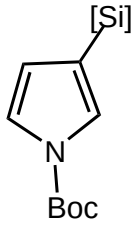
17
99%



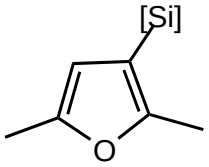
18
45%



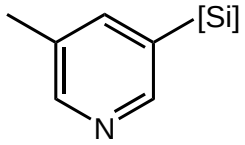
19
82%



20
97%

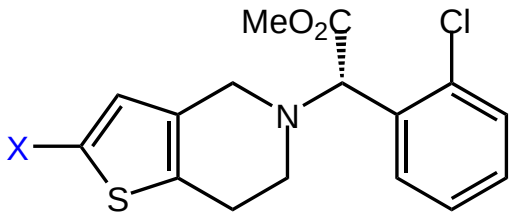


21
80%

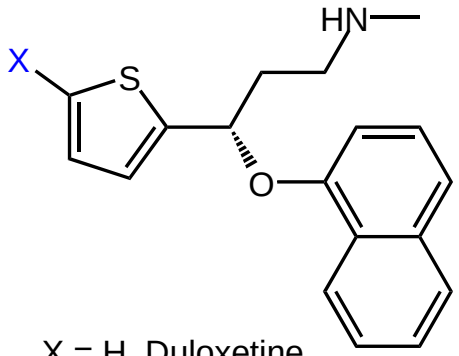


22
80%

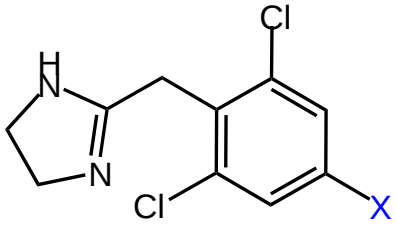
C−H Silylation of Pharmaceutical Compounds



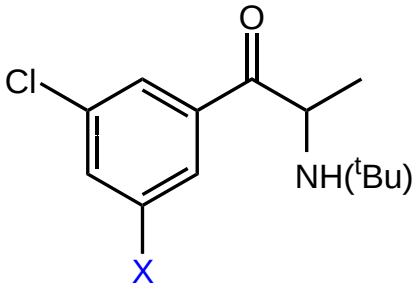
X = H, Clopidogrel
(antiaggregant)
23 X = [Si], 88%



X = H, Duloxetine
(antidepressant)
24 X = [Si], 86%

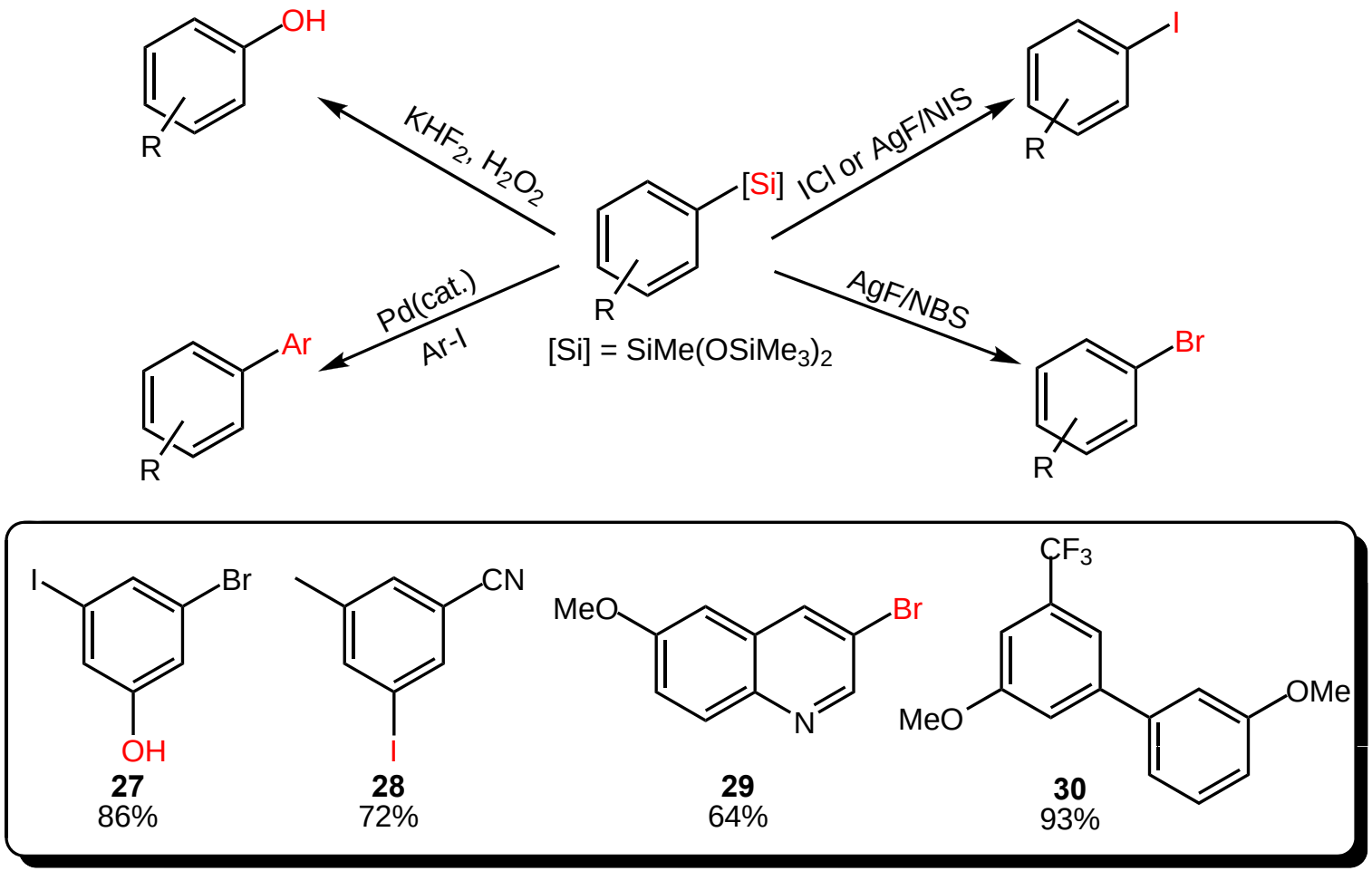


X = H, Clonidine
(hypertension treatment)
25 X = [Si], 87%

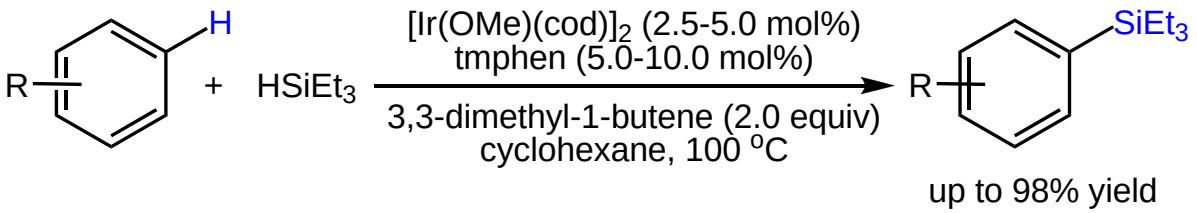


X = H, Bupropion
(antidepressant)
26 X = [Si], 69%

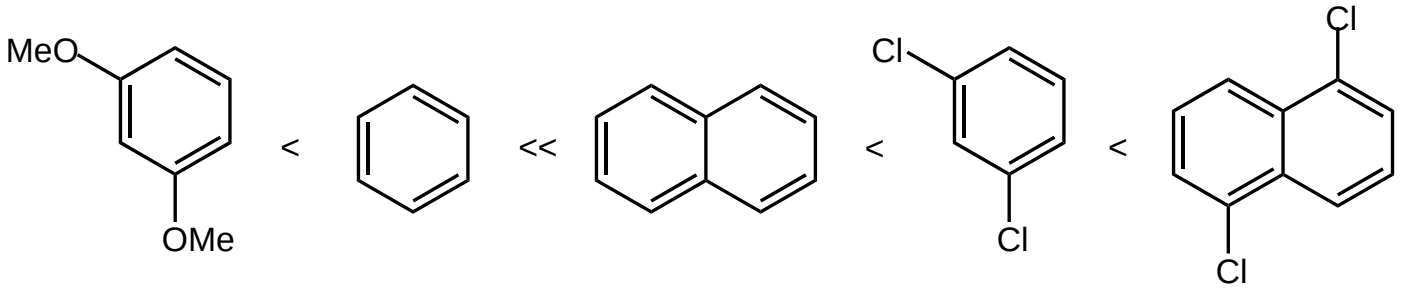
Functionalization of Silylarene Products



Iridium-Catalyzed Intermolecular Dehydrogenative Silylation of Polycyclic Aromatic Compounds without Directing Groups



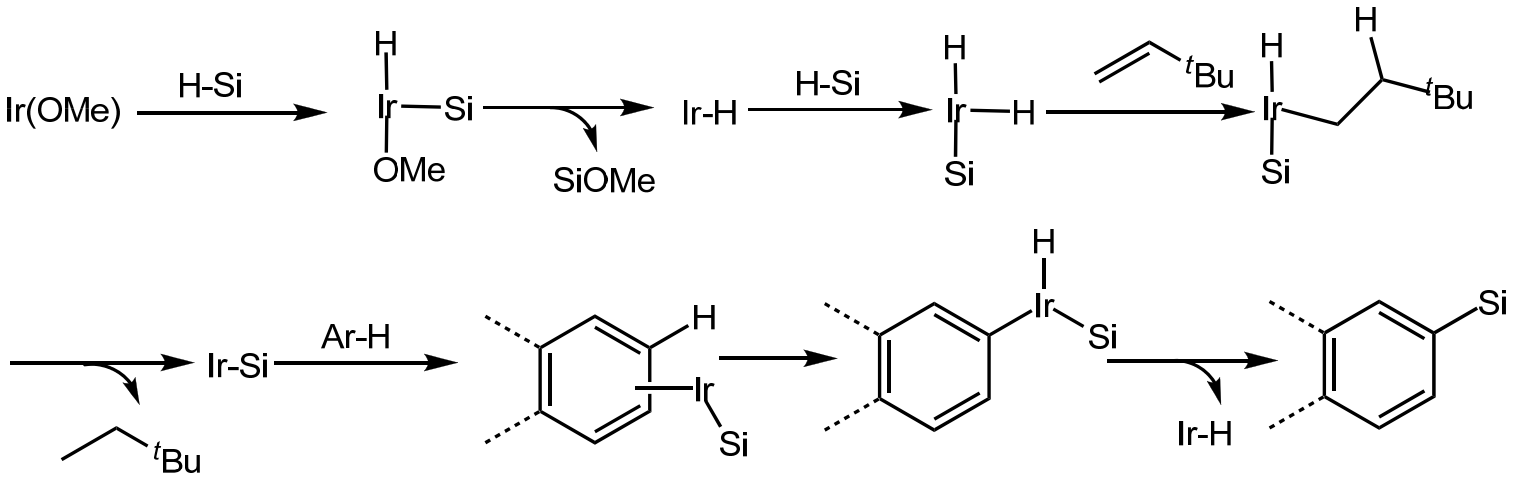
up to 98% yield



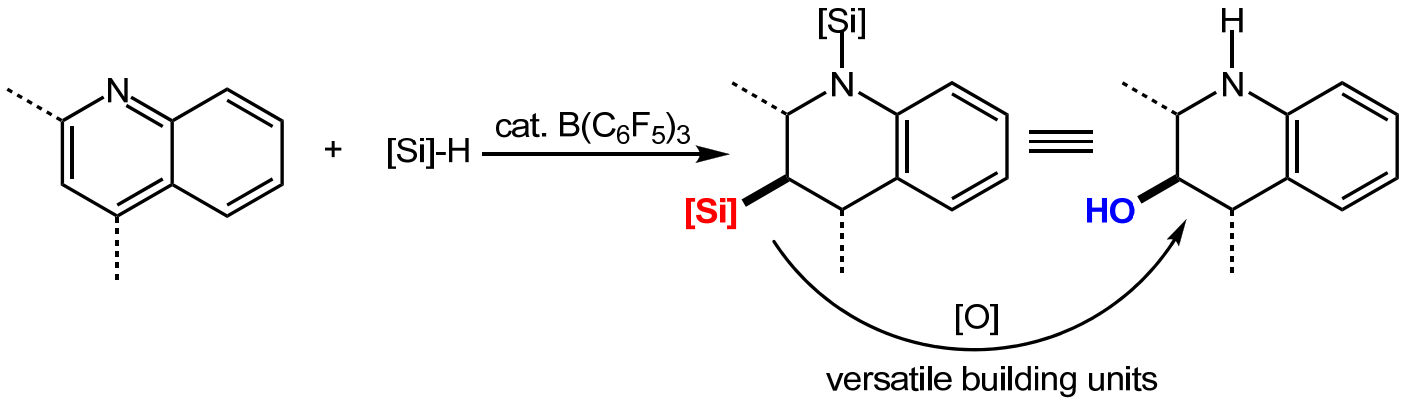
Reactivity of arenes for the current Ir-catalyzed dehydrogenative silylation

Takai, K. *et al. Chem. Eur. J*. **2015**, *21*, 4566-4570.

Plausible Reaction Mechanism



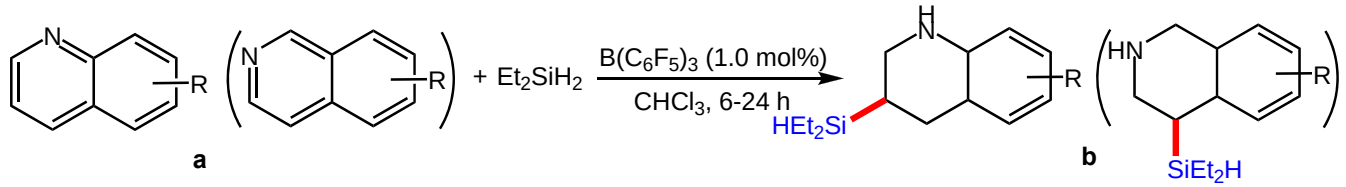
Boron-Catalyzed Silylative Reduction of Quinolines: Selective sp^3 C−Si Bond Formation



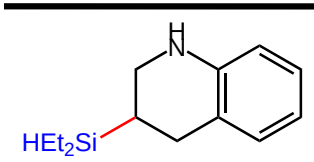
- first catalytic silylative dearomatization
- high TON, scalable, broad scope
- chemo-, regio-, stereoselective
- asymmetric induction

Chang, S. *et al. J. Am. Chem. Soc*. **2014**, *136*, 16780–16783.

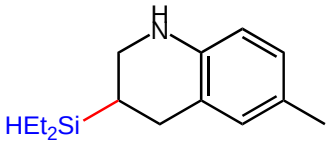
Substrate Scope in the Silylative Reduction



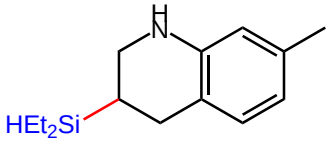
a b



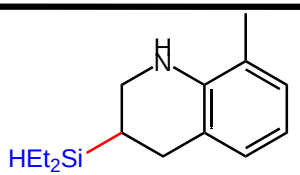
1b 86%
6 h at 65 °C



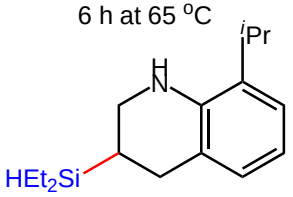
2b 82%
6 h at 65 °C



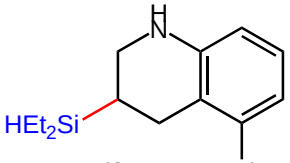
3b 81%
6 h at 65 °C



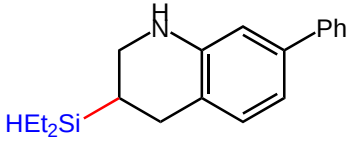
4b 96%
6 h at 65 °C



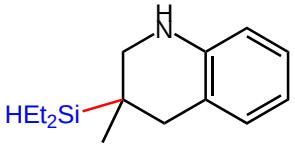
5b 90%
6 h at 65 °C



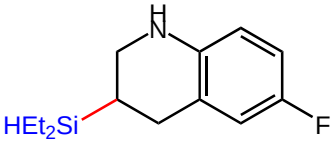
6b 70%
12 h at 65 °C



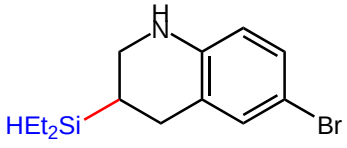
7b 61%
6 h at 65 °C



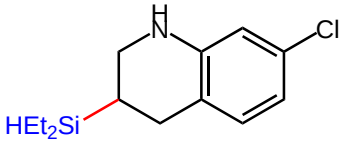
8b 96%
24 h at 65 °C



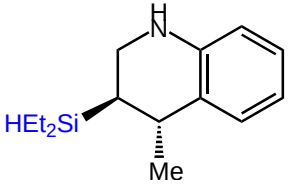
9b 73%
6 h at 65 °C



10b 94%
12 h at 65 °C

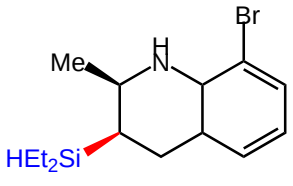


11b 87%
6 h at 65 °C

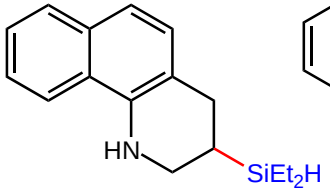


12b 95%
24 h at 65 °C

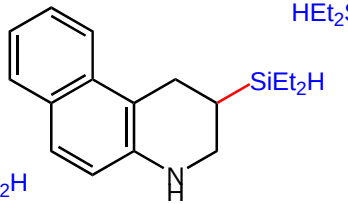
Substrate Scope in the Silylative Reduction



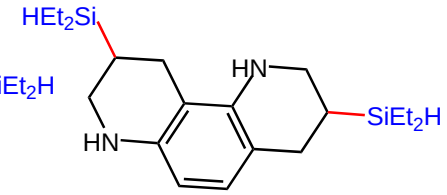
13b 81%
6 h at 23 °C



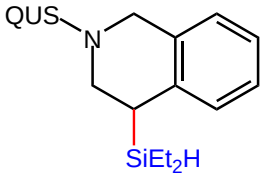
14b 94%
6 h at 65 °C



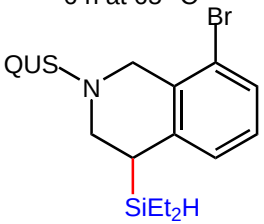
15b 85%
6 h at 65 °C



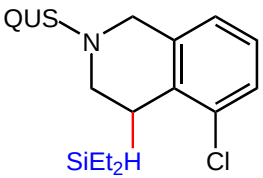
16b 72%
6 h at 65 °C



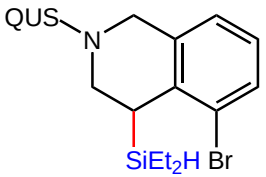
17b 44%
24 h at 100 °C



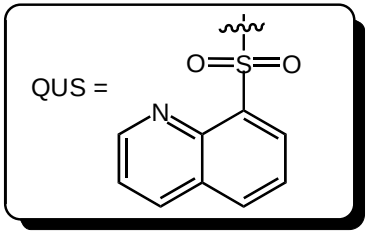
18b 66%
24 h at 100 °C



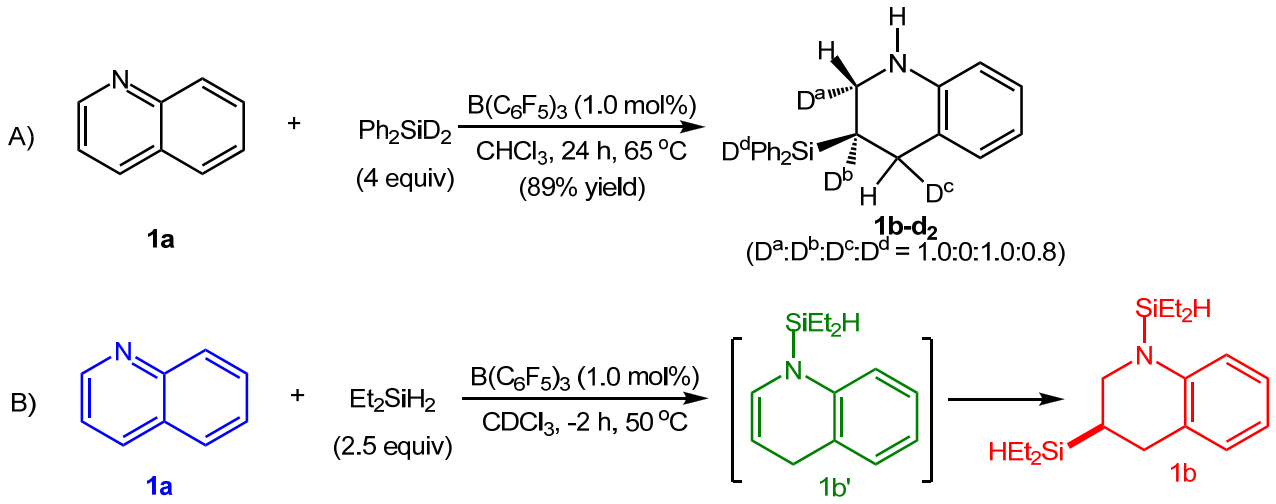
19b 81%
24 h at 100 °C

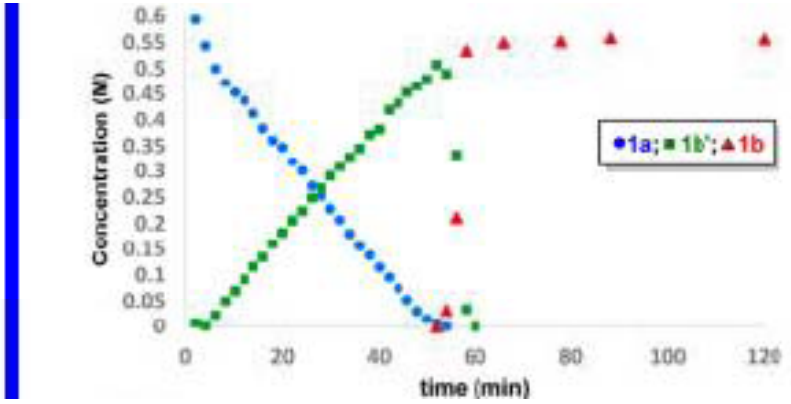


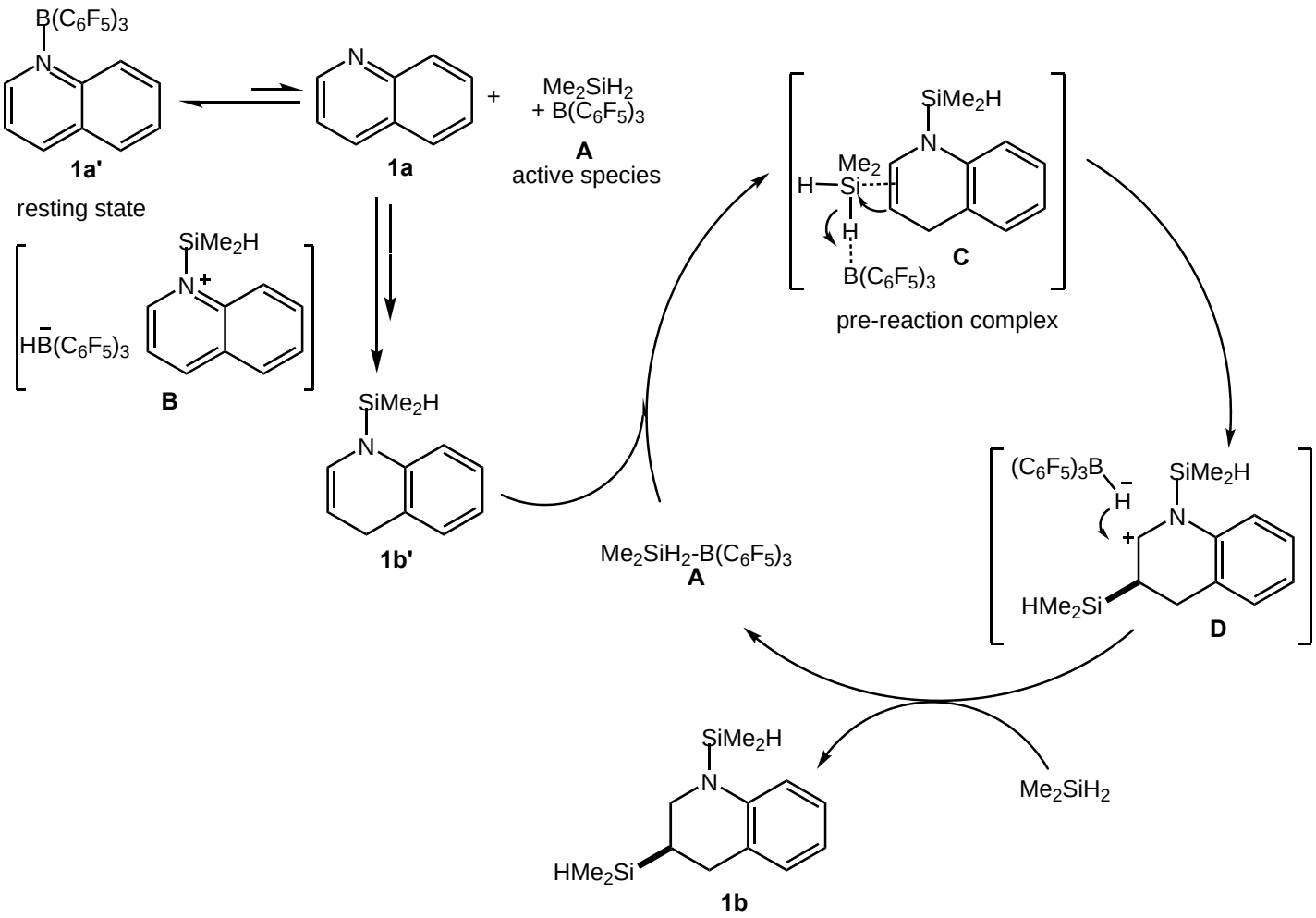
20b 71%
24 h at 100 °C



Preliminary Mechanistic Studies

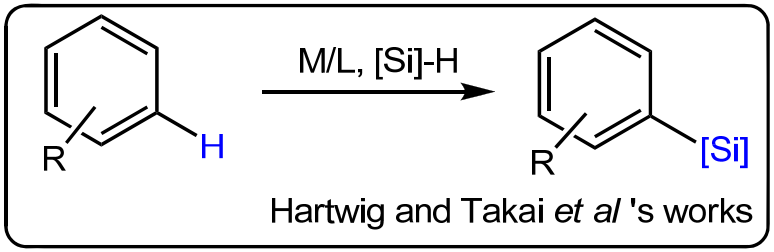




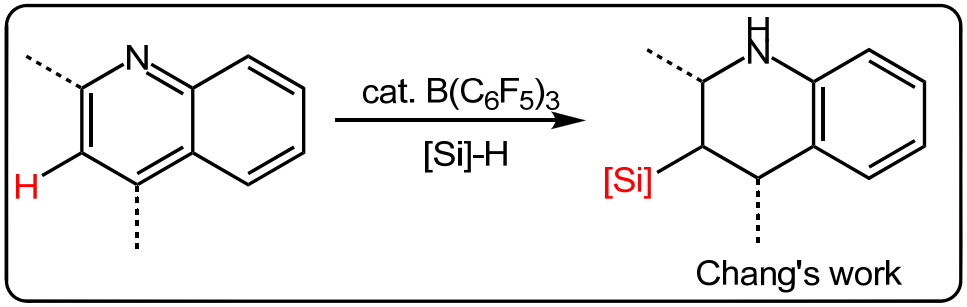

B(C6F5)3
1a'
resting state
1a
Me2SiH2
+ B(C6F5)3
A
active species
SiMe2H
HB(C6F5)3
B
1b'
Me2SiH2-B(C6F5)3
A
SiMe2H
Me2
H
Si
H
B(C6F5)3
C
pre-reaction complex
(C6F5)3B
H
SiMe2H
HMe2Si
D
SiMe2H
HMe2Si
1b
Me2SiH2

Summary

Metal-catalyzed silylation of arenes



Boron-catalyzed silylation of arenes



Methods for the selective functionalization of aromatic C–H bonds under mild, neutral conditions have synthetic applications in fields ranging from materials science to medicinal chemistry. Perhaps most important for the utility of C–H bond functionalization is the control of site selectivity. Regioselectivity in classical electrophilic aromatic substitution reactions is governed by the electronic properties of the substituents on the arene. In catalytic C–H functionalization of arenes, regiocontrol has been achieved in some cases by substituents on the arene that bind to the catalyst and direct the reaction to an *ortho*- or *meta*-C–H bond. In other cases, such as in the widely used iridium-catalyzed borylation of arenes, the regioselectivity results from the steric properties of substituents *ortho* to a reacting C–H bond. However, reactions that occur with selectivity derived from the steric properties of groups distal to a potential site of reactivity on arenes have been challenging to develop. Groups in these positions are assumed to have minor steric effects on a reaction site, so much so that a classical method for probing the electronic effects of an aromatic ring on a chemical reaction is to introduce substituents *meta* or *para* to a site of reactivity.

The intermolecular, rhodium-catalyzed silylation of arenes that we report here occurs under mild conditions, with arene as the limiting reagent and with regioselectivities that complement or surpass those of other arene functionalizations. Several factors lead to the selectivity and synthetic utility of the silylation reaction. First, the silicon reagent is sterically demanding. Assuming the intermediate that cleaves the aryl C–H bond contains a silyl group on the metal, the size of the silane reagent, along with the size of the ancillary ligands, control the degree of regioselectivity. Second, two of the substituents on the silane are bound to silicon through oxygen, and a silicon heteroatom bond is typically required for many of the transformations of arylsilanes at the C–Si bond. The origin of the remote selectivity remains to be defined. However, our results suggest that a wide scope of functionalization reactions with remote regiocontrol should be achievable through judicious choice of ancillary ligands and reagents with appropriate steric bulk.