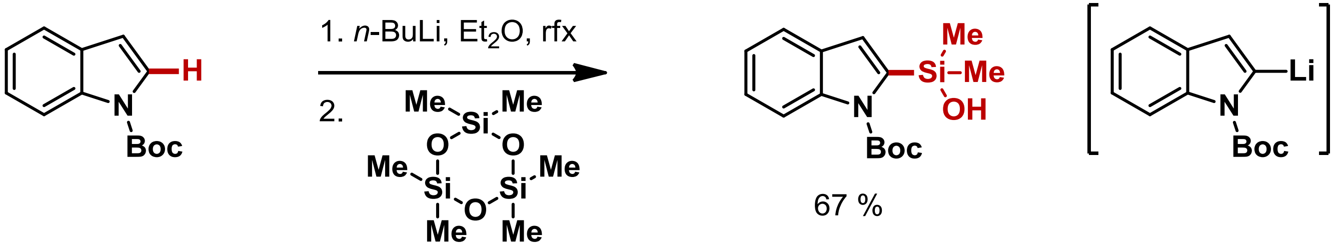
19
K
potassium

Silylation of C-H bonds in aromatic heterocycles by an Earth-abundant metal catalyst

A. A. Toutov, W.-B. Liu, K. N. Betz, A. Fedorov, B. M. Stoltz, R. H. Grubbs, *Nature*, **2015**, *518*, 80.

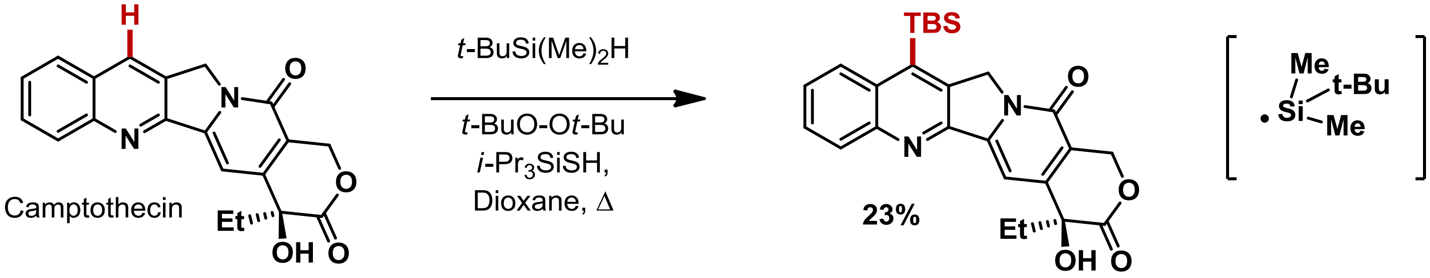
Stoichiometric Approaches

Interception of heteroaryl Li or Mg reagent



Denmark et *al*. *Org. Lett*, **2004**, *6*, 3649

Sila-Minisci Reaction

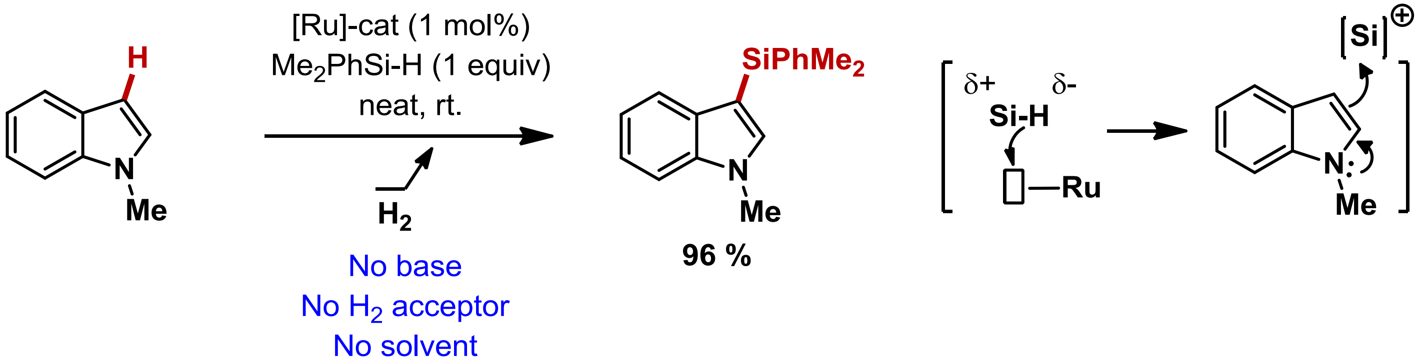


Camptothecin

Curran et *al*. *Bioorg. Med. Chem.* **2003**, *11*, 451

Previous Reports

Ru-catalyzed Friedel-Crafts reaction



[Ru]-cat (1 mol%)
Me_2PhSi-H (1 equiv)
neat, rt.

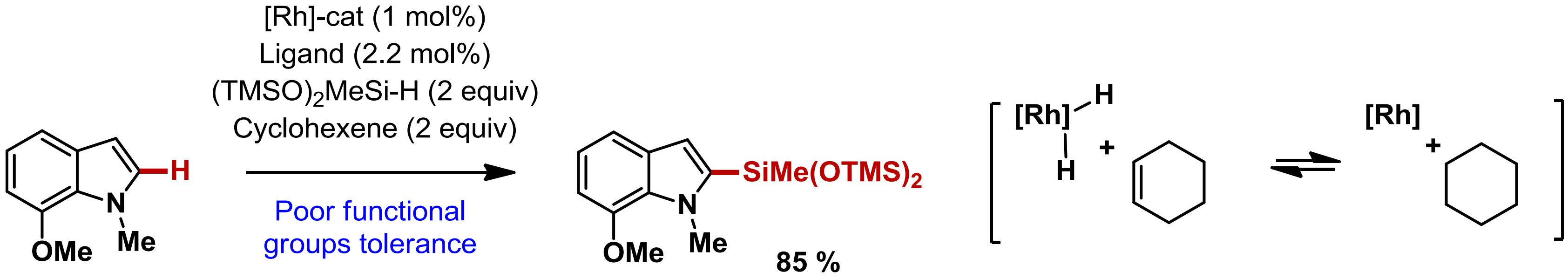
H_2

96 %

No base
No H_2 acceptor
No solvent

M. Oestreich, Y. Okhi, K. Tatsumi *et al.*, *JACS*, **2011**, *133*, 3312

Rh-catalyzed silylation



[Rh]-cat (1 mol%)
Ligand (2.2 mol%)
$(TMSO)_2MeSi$-H (2 equiv)
Cyclohexene (2 equiv)

Poor functional
groups tolerance

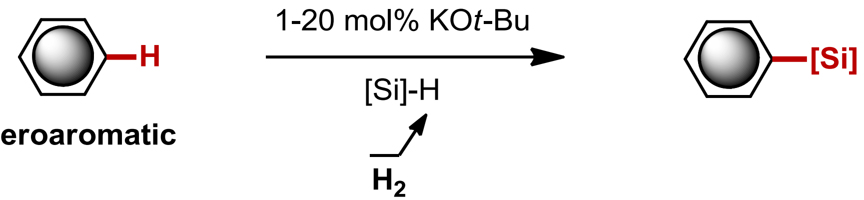
85 %

Hartwig *et al*. *Science*, **2014**, *343*, 853

⇨ **Iridium catalyst improves the versatility of the reaction**

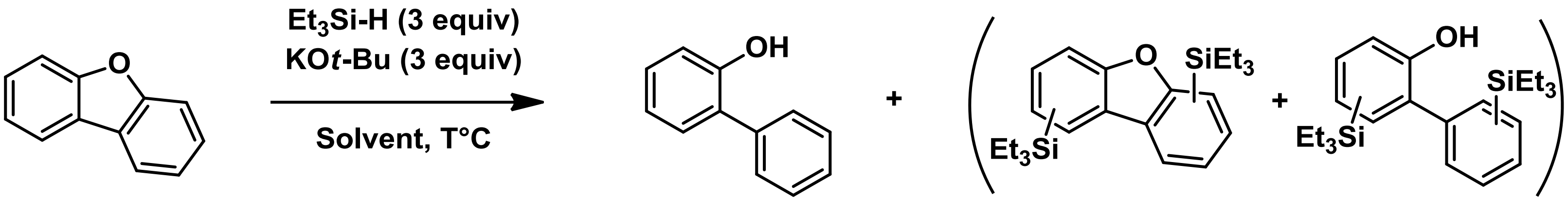
Hartwig *et al*. *JACS*, **2015**, *137*, 592

This Work



- **Earth-abundant metal [K] catalyst**
- **No H_2 acceptor or additives**
- **Mild reaction conditions**
- **Chemo- and regioselective**
- **TON up to 92**
- **> 100 g scale**

An example of serendipity

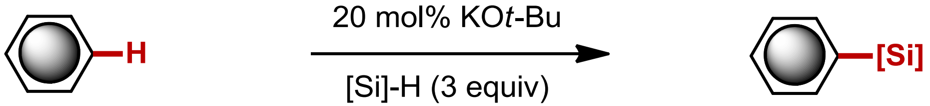


MAJ

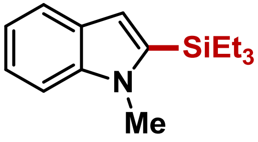
Min

Grubbs *et al*. *Chem. Sci.* **2013**, *4*, 1640

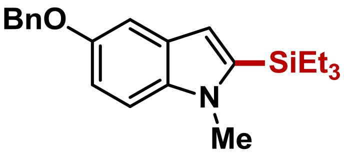
Selected Reaction Scope



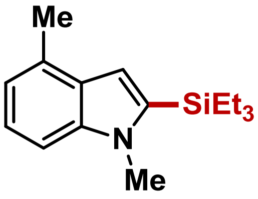
>50 examples



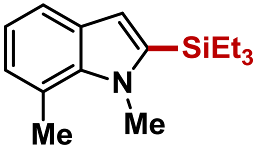
Neat, 45°C
C2:C3 > 20:1
78%



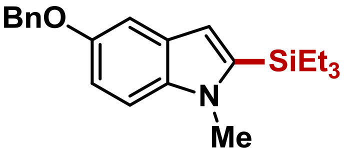
THF, 25°C
C2:C3 > 20:1
68%



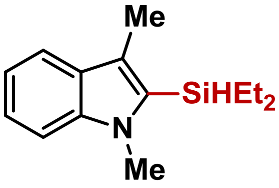
Neat, 45°C
C2:C3 > 20:1
69%



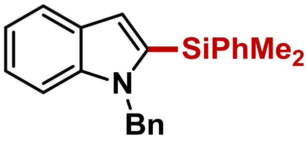
Neat, 45°C
C2:C3 > 20:1
61%



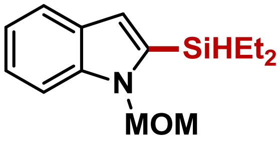
THF, 45°C
C2:C3 > 20:1
48%



THF, 65°C
65%

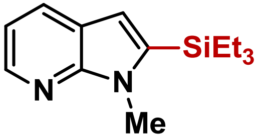


THF, 45°C
C2:C3 > 20:1
58%

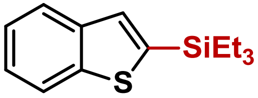


Neat, 60°C
C2:C3 = 14:1
66%

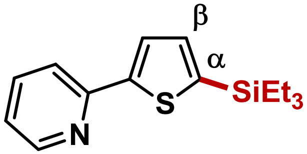
Selected Reaction Scope



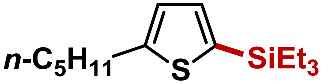
THF, 35°C
C2:C3 > 20:1
71%



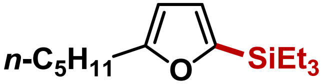
THF, 25°C
C2:C3 > 20:1
93%



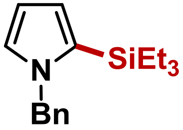
THF, 25°C
α:β > 20:1
94%



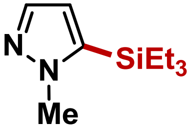
THF, 25°C
α:β > 20:1
92%



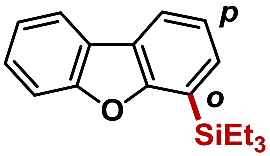
THF, 25°C
α:β > 20:1
95%



THF, 25°C
mono:bis = 20:1
95%

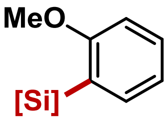


THF, 25°C
α:β > 20:1
71%

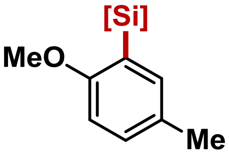


THF, 65°C
o:*p* > 20:1
mono:bis = 15:1
71%

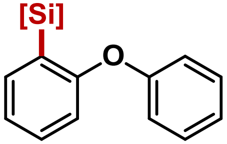
Oxygen-directed silylation



o:(*m* + *p*) > 20:1
43%

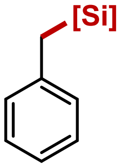


42%

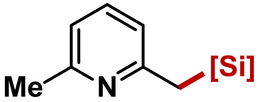


o:(*m* + *p*) > 20:1
55%

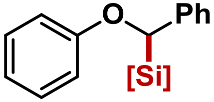
C(*sp3*)-silylation



C(*sp*^{3}):C(*sp*^{2}) > 18:1
24%

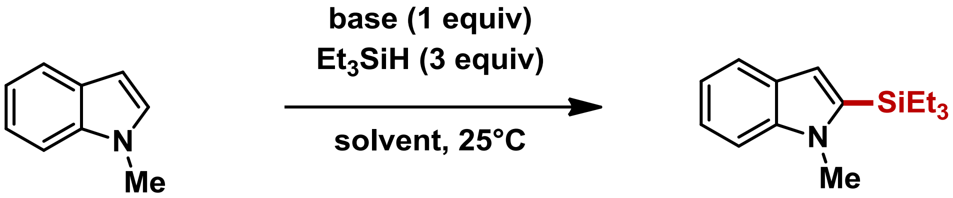


Mono:bis > 20:1
24%

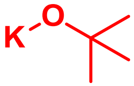


46%

Optimization

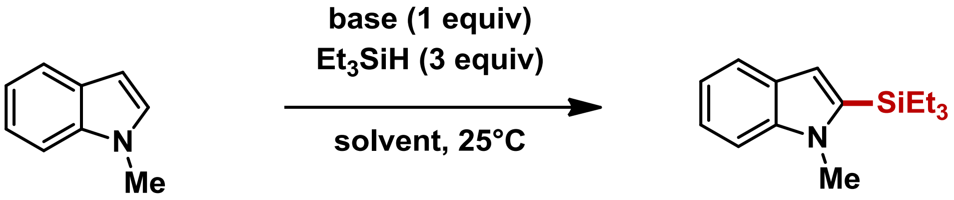


C2-silylation

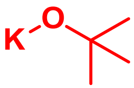


67%

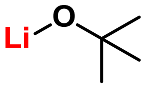
Optimization

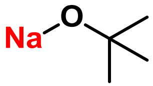


C2-silylation



67%





0%	0%

Cations

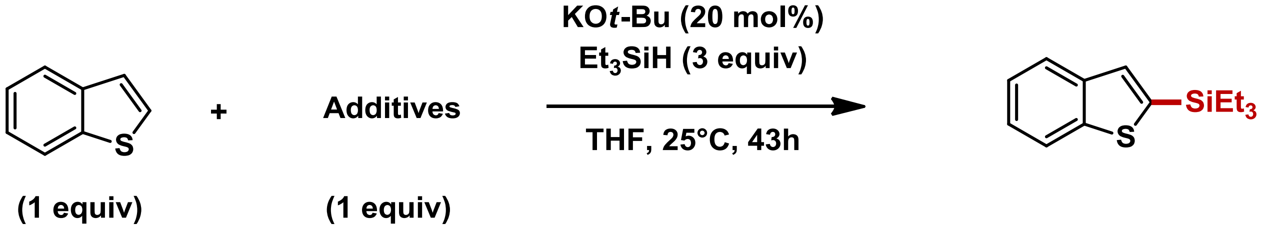
K-H	K-OH	K-OMe	K-OEt	K-HMDS
0%	0%	0%	14%	44%

Anions

K-F	TBA-F
0%	0%

Fluorides

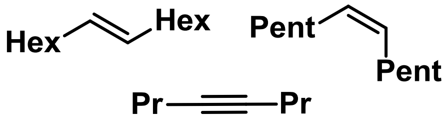
Functional group compatibility



Glorius *et al*. *Nature Chem*, **2013**, *5*, 597

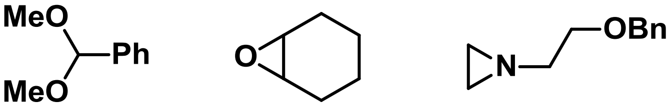
Tolerated

Alkenes, Alkynes :



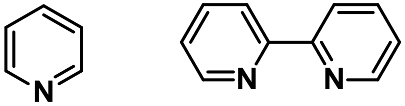
Aryl-X : Ph-F Ph-Cl $Ph-CF_3$ $Ph-NMe_2$

Acetals, epoxides, aziridines :



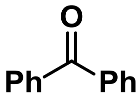
PPh_3

Pyridine derivatives :



Non-tolerated

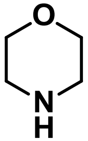
Carbonyl groups:



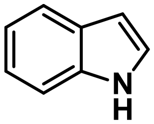
$PhCO_2Me$

Aryl-X : Ph-Br Ph-I $Ph-NO_2$ Ph-CN

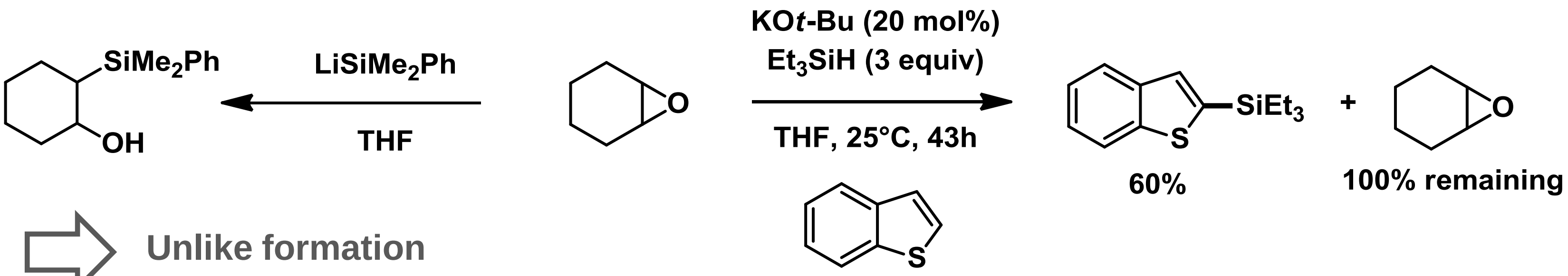
Free amines and alcohols :



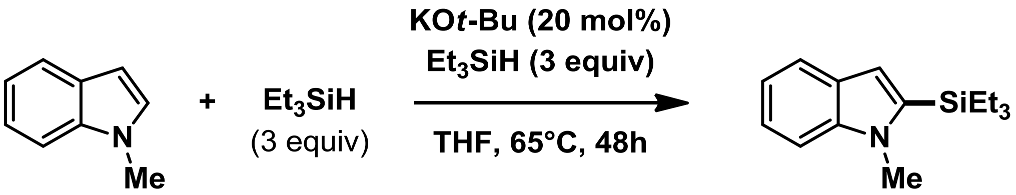
BnOH



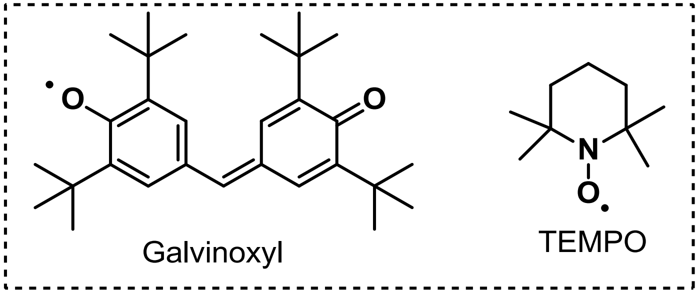
Toward a Radical Pathway



Unlike formation
of discrete silyl anions

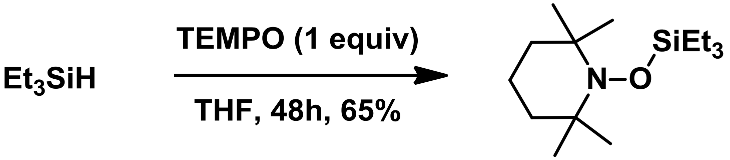


without additive	74%
with Galvinoxyl (20 mol%)	ND
with TEMPO (20 mol%)	ND



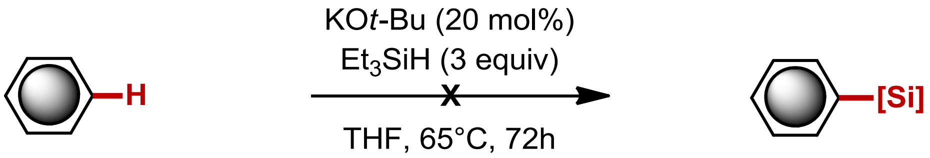
Formation of a silyl-radical
with KO*t*-BU

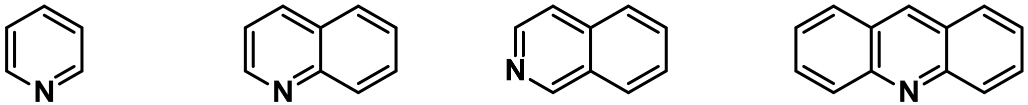
• SiR_3



without KO*t*-Bu	ND
with KO*t*-Bu (20 mol%)	Major product

An Unknown Mechanism

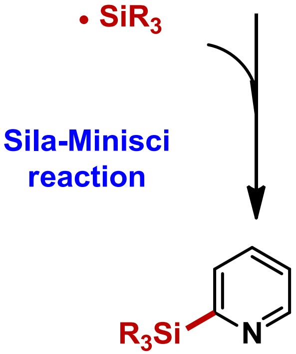


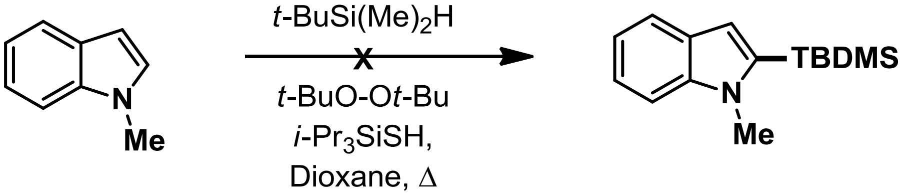


Pyridine Quinoline Isoquinoline Acridine

No reaction

Favorable substrates for Minisci-type





Curran's sila-Minisci conditions

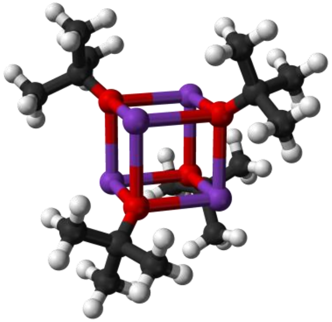
Curran et *al*. *Bioorg. Med. Chem.* **2003**, *11*, 451

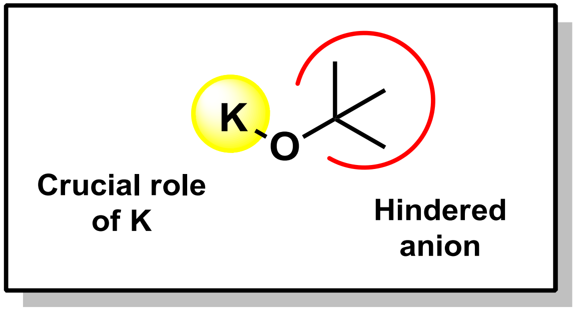
No reaction

Conclusion

- **A new simple and cheap procedure for the direct silylation of heteroaromatic compounds**

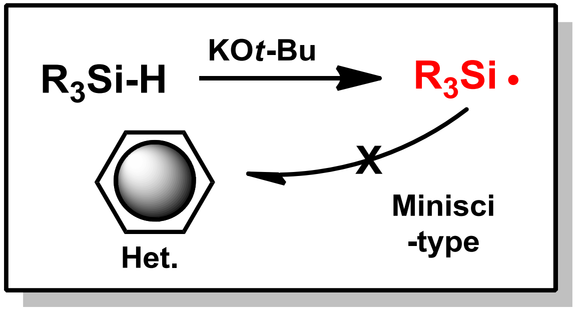
- **Unknown mechanism : new reactivity of KO*t*-Bu as a catalyst**



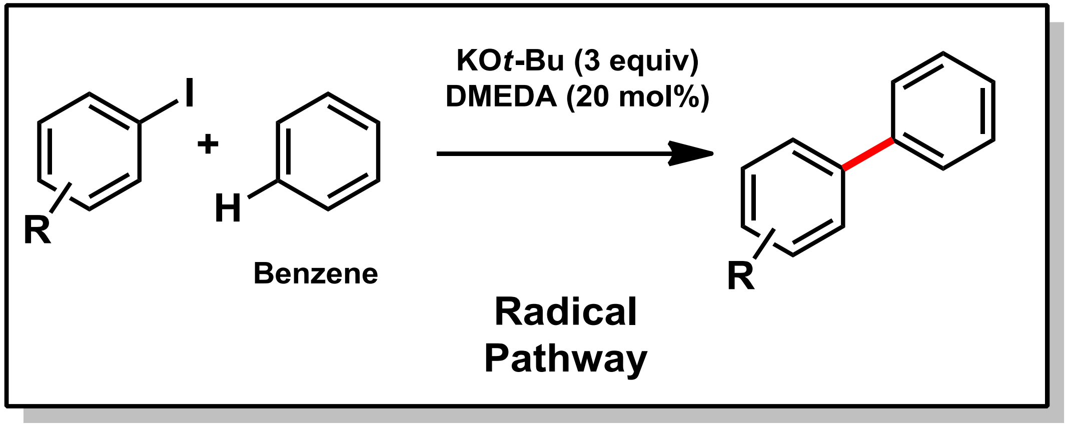


Crucial role of K

Hindered anion



Minisci -type



Radical Pathway