Formation and Reactivity of Hetero-Atom–Centered Radicals

Xue-Song Zhou

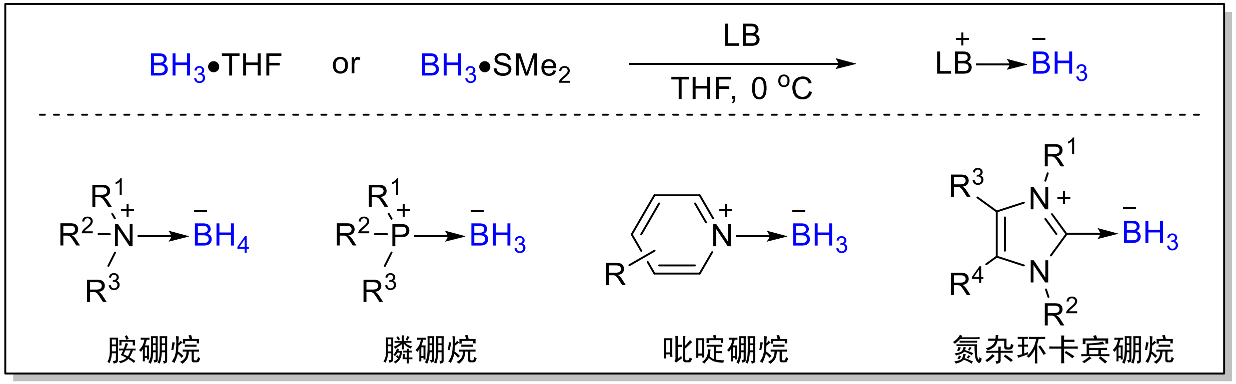
Feb. 18, 2023

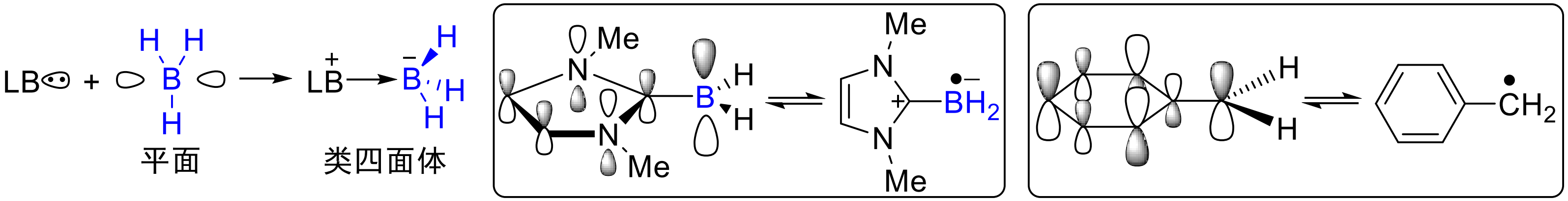
Outline

- Discovery of boryl radicals
- Reduction reaction promoted by boryl radicals
- Cyclization cascade reaction promoted by boryl radicals
- Hydroboration reaction promoted by boryl radicals
- Minisci reaction promoted by boryl radicals

Discovery of boryl radicals

Type and structure of LB-BH_3 complexs





Discovery of boryl radicals

Early studies for boron radical

$$^{t}BuOO^{t}Bu \xrightarrow{h\nu} {}^{t}BuO\cdot$$

$$Et_3N\text{-}BH_3 + {}^{t}BuO\cdot \longrightarrow Et_3N\text{-}\dot{B}H_2 + {}^{t}BuOH$$

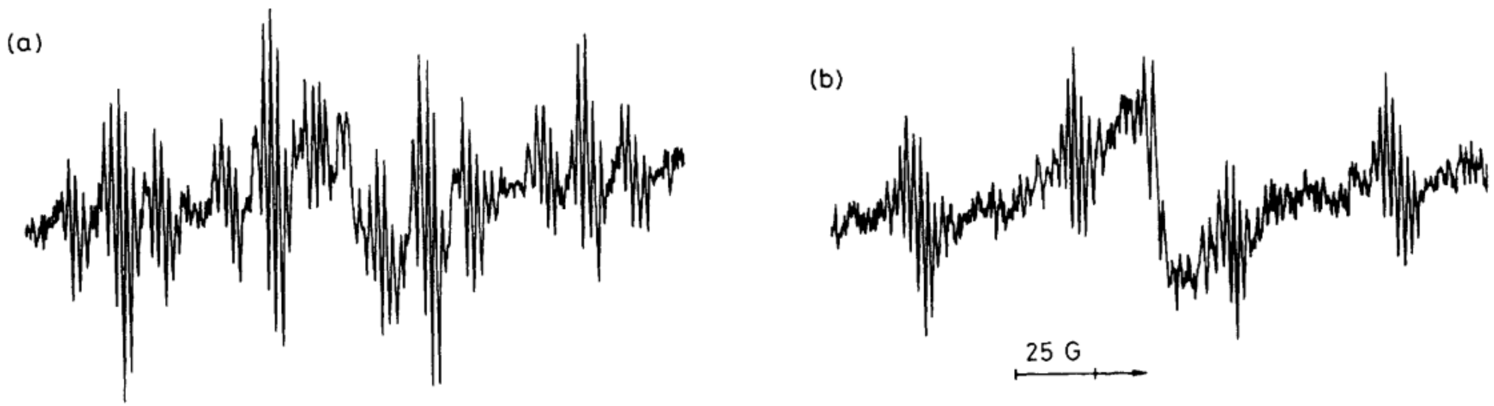
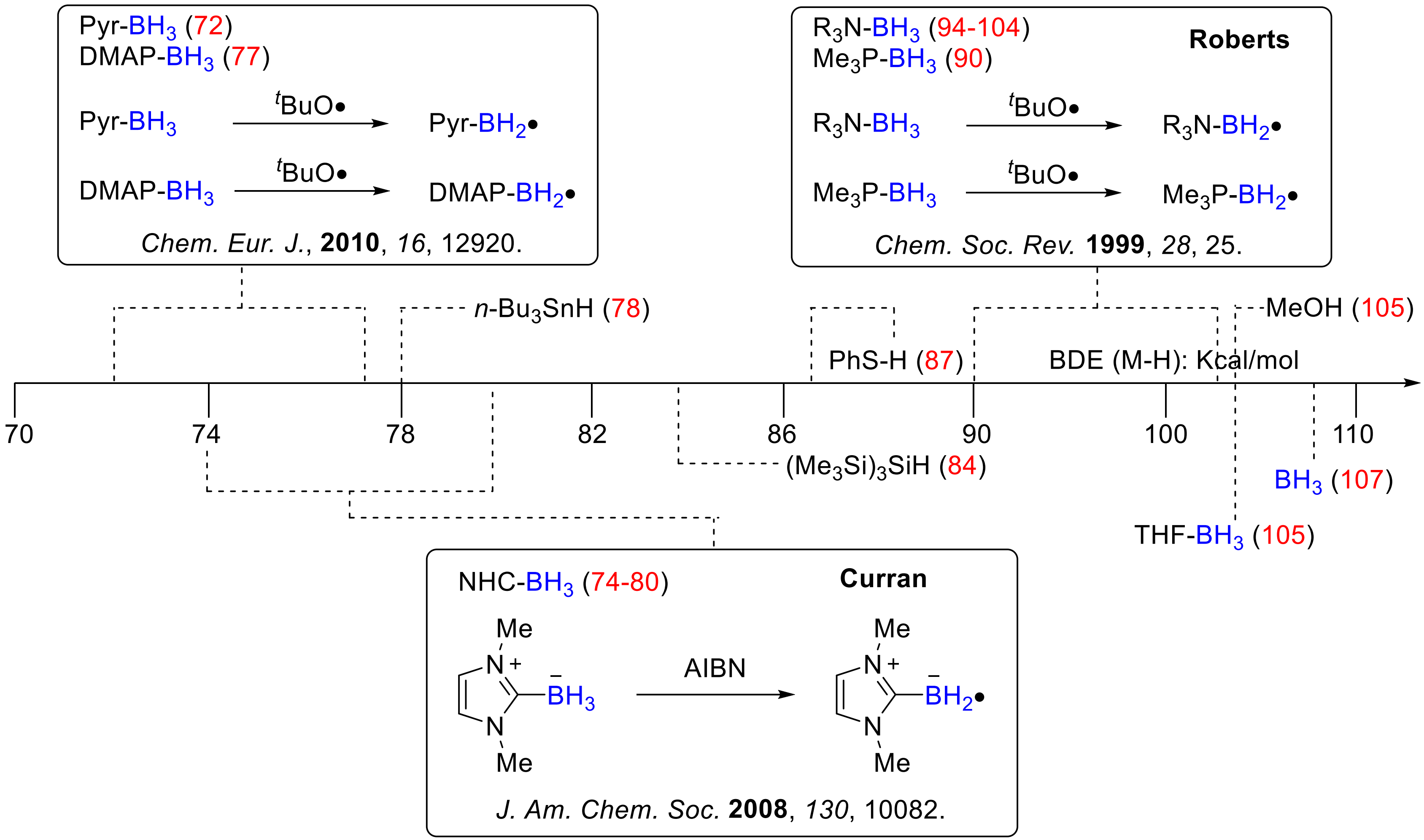


Figure 1. E.s.r. spectra at 193 K of (a) $Et_3\overset{+}{N}\text{–}\overset{-}{B}H_2^{\bullet}$ generated from $Et_3\overset{+}{N}\text{–}\overset{-}{B}H_3$ (97.5 atom% ^{11}B) in cyclopropane–THF (3:1 v/v) and (b) $Et_3\overset{+}{N}\text{–}\overset{-}{B}D_2^{\bullet}$ generated from $Et_3\overset{+}{N}\text{–}\overset{-}{B}D_3$ (81.2 atom% ^{11}B) in cyclopropane–[$^2H_8$]THF (3:1 v/v). Some unidentified lines are present in both spectra. No e.s.r. signals were observed during photolysis of $Et_3\overset{+}{N}\text{–}\overset{-}{B}H_3$ alone in cyclopropane–THF.

B. P. Roberts, et. al. *J. Chem. Soc.*, Chem. Commun. **1983**, 1224.

Discovery of boryl radicals

BDE of LB-BH_3 complexs



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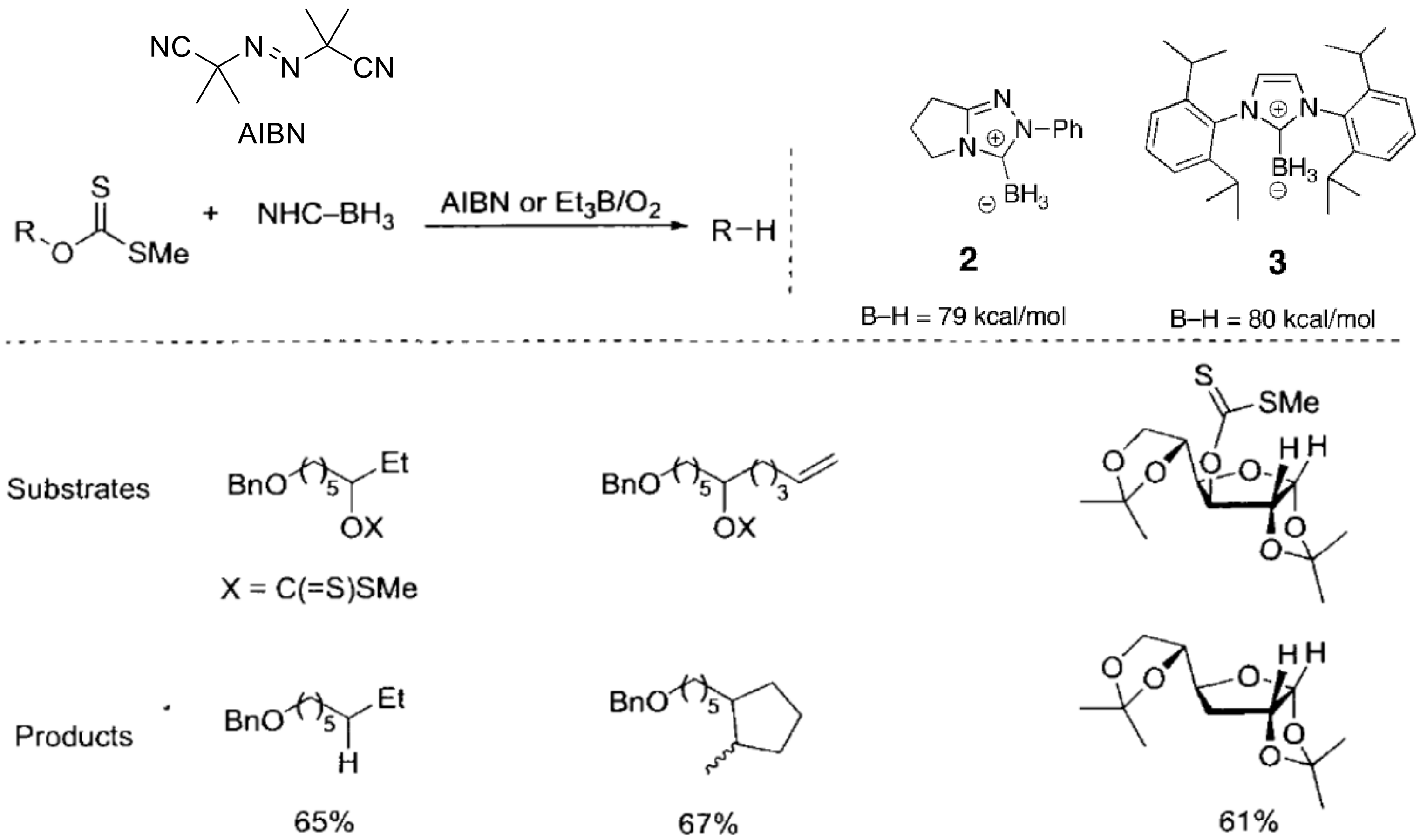
Reduction reaction promoted by boryl radicals

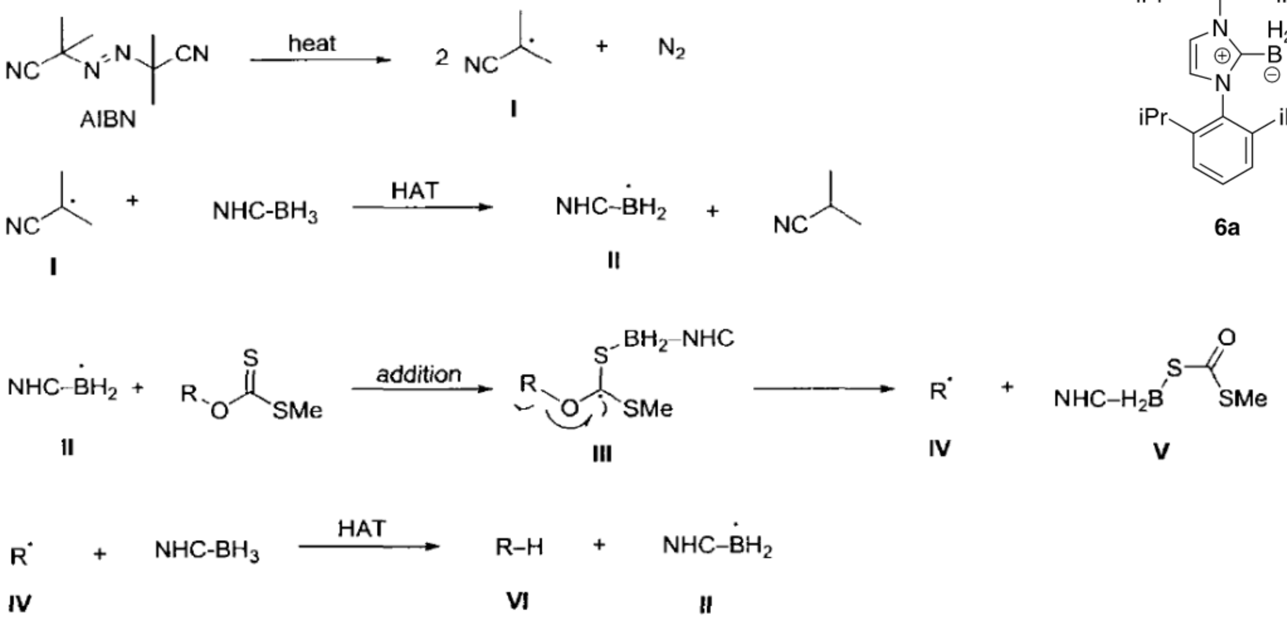
- NHC-BH_3 mediated Barton-McCombie deoxygenation reaction

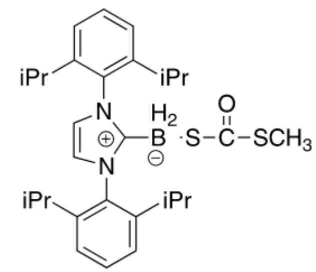


D. P. Curran, et. al. *J. Am. Chem. Soc.* **2008**, *130*, 10082.

Reduction reaction promoted by boryl radicals

- **NHC-BH_3 mediated Barton-McCombie deoxygenation reaction**





6a

precursor	isolated yield **6a**
2a	79%
2b	66%
2c	70%

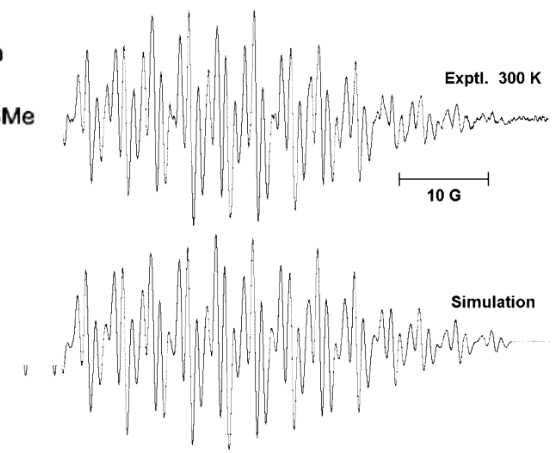
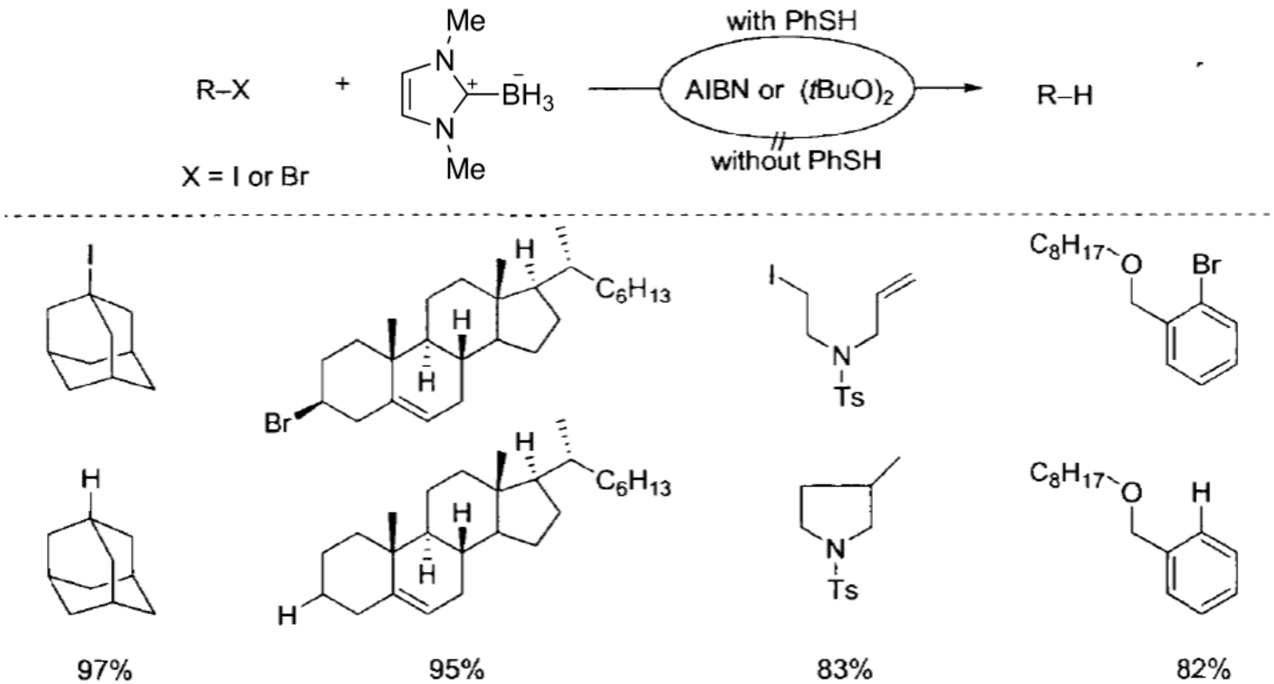


Figure 7. Solution EPR spectrum of NHC-BH_2• radical **3a**. Top: First derivative experimental spectrum at 300 K in *t*-BuPh. Bottom: Computer simulation with parameters noted in Table 1.

D. P. Curran, et. al. *J. Am. Chem. Soc.* **2009**, *131*, 11256.

Reduction reaction promoted by boryl radicals

- **NHC-BH_3 mediated radical reductions of halides**



D. P. Curran, et. al. *J. Am. Chem. Soc*. **2012**, *134*, 5669.

Reduction reaction promoted by boryl radicals

■ NHC-BH$_3$ mediated radical reductions of halides

$$\text{NHC–BH}_2\bullet + \text{R–X} \xrightarrow[k_1 > 10^5\ \text{M}^{-1}\ \text{s}^{-1}]{\text{fast}} \text{NHC-BH}_2\text{X} + \text{R}\bullet \quad (1)$$

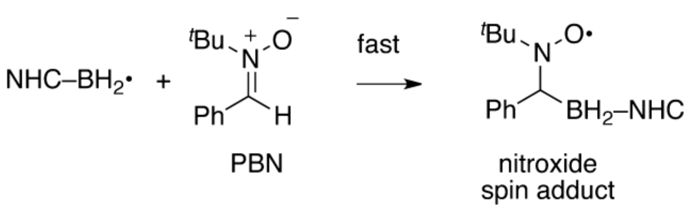
$$\text{NHC–BH}_3 + \text{R}\bullet \xrightarrow[k_2 < 10^5\ \text{M}^{-1}\ \text{s}^{-1}]{\text{slow}} \text{NHC–BH}_2\bullet + \text{R–H} \quad (2)$$

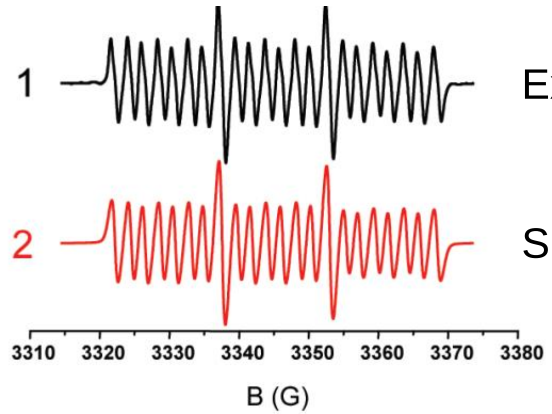
$$\text{PhS–H} + \text{R}\bullet \xrightarrow[k_3 \approx 10^8\ \text{M}^{-1}\ \text{s}^{-1}]{\text{fast}} \text{PhS}\bullet + \text{R–H} \quad (3)$$

$$\text{NHC–BH}_3 + \text{PhS}\bullet \xrightarrow[k_4 = 1.2 \times 10^8\ \text{M}^{-1}\ \text{s}^{-1}]{\text{fast}} \text{NHC-BH}_2\bullet + \text{PhS–H} \quad (4)$$

for rxn of **1** with PhS•

$$\text{PhS}\bullet + \text{NHC–BH}_3 \longrightarrow \text{PhSH} + \text{NHC–BH}_2\bullet \quad (4)$$





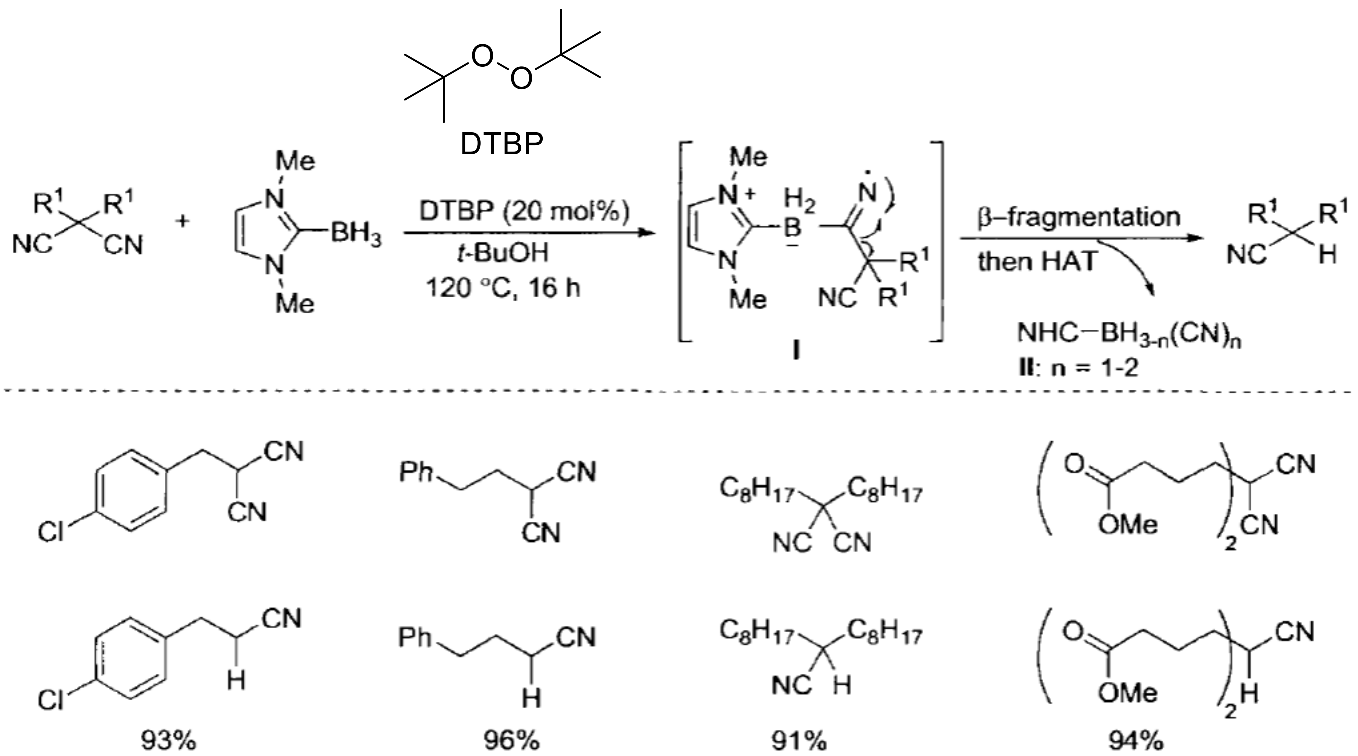
Experimental spectra

Simulated spectra

D. P. Curran, et. al. *J. Am. Chem. Soc*. **2012**, *134*, 5669.

Reduction reaction promoted by boryl radicals

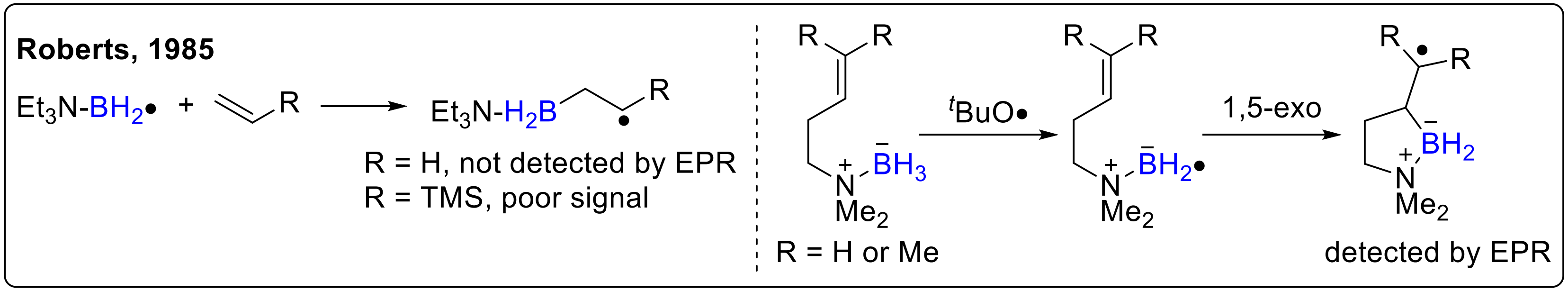
- **NHC-BH_3 mediated reductive decyanation**

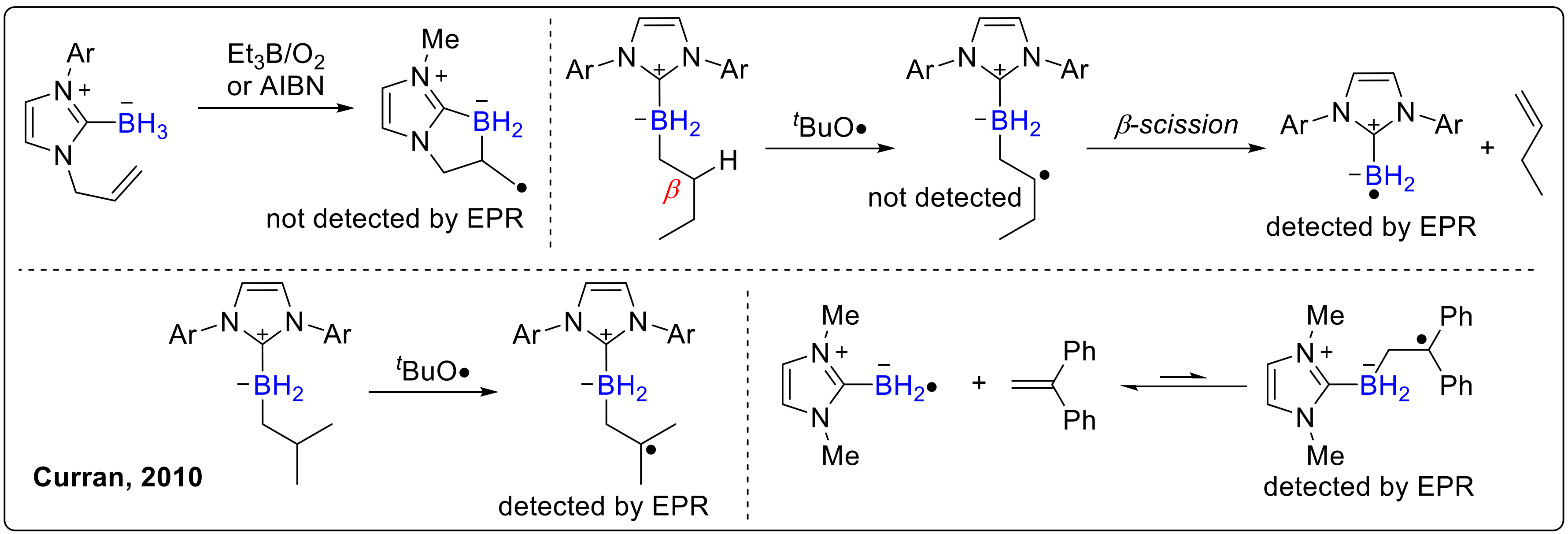


D. P. Curran, et. al. *J. Am. Chem. Soc*. **2015**, *137*, 8617.

Background

Early studies for boron radical addition reaction





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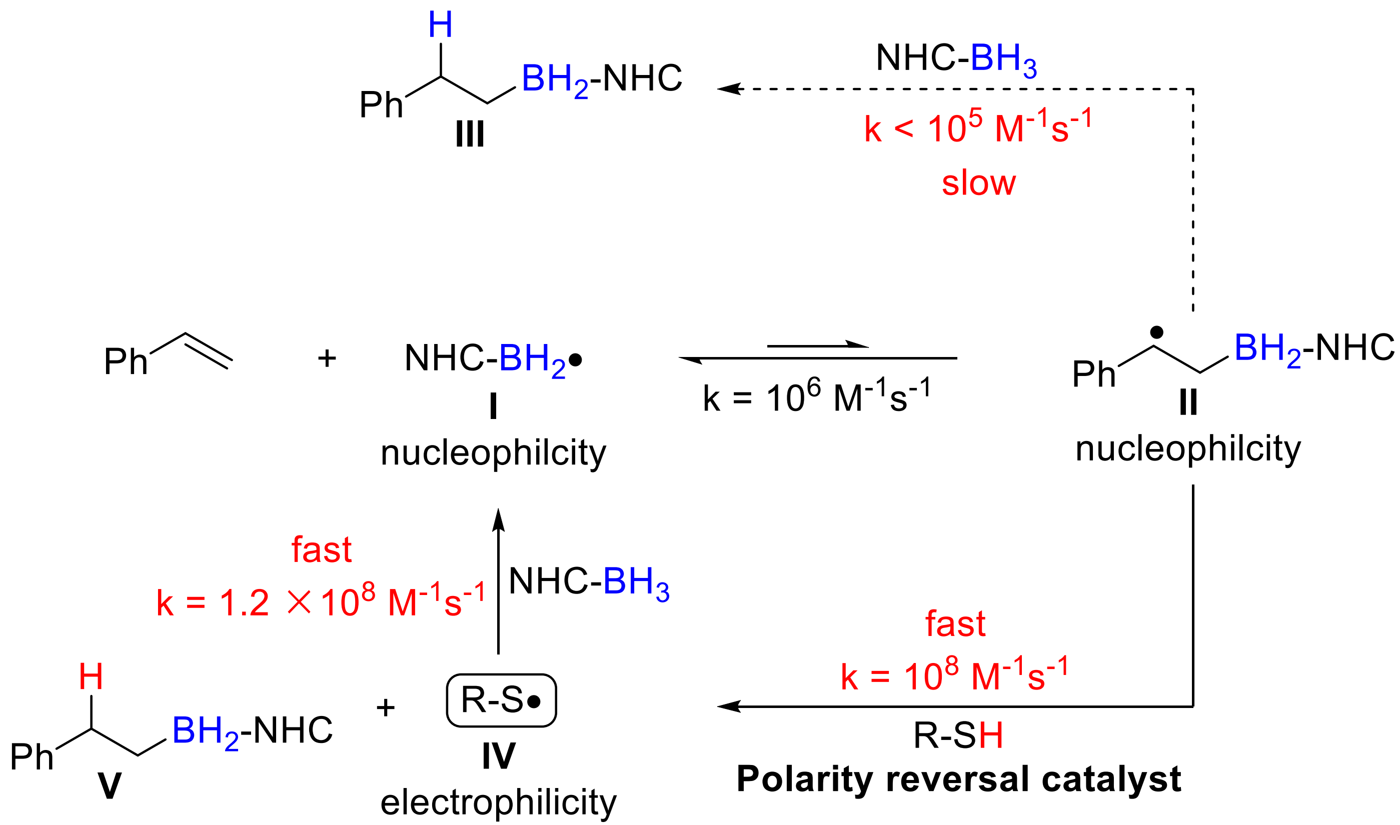
Background

■ **Possible process for boron radical addition reaction**



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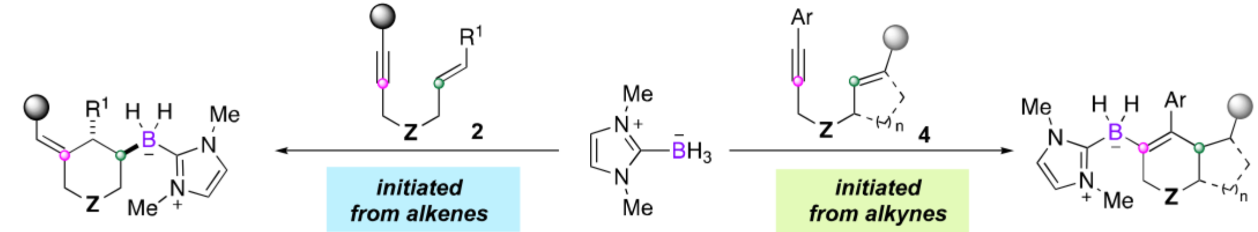
Cyclization cascade reaction promoted by boryl radicals

Radical borylation/cyclization cascade of 1,6-enynes



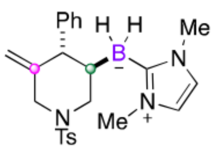
3, 16 examples, 29-92% yield

1a

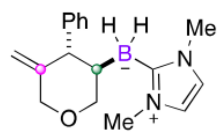
5, 13 examples, 35-81% yield

conditions: AIBN (20 mol%), $C_9H_{19}C(CH_3)_2SH$ (50 mol%), MeCN, 80 °C, 2-12 h;
R^1 = Ar, CO_2Me, **Z** = NTs, $C(CO_2Et)_2$, n = 1, 2, 3; AIBN = 2,2'-azobis(isobutyronitrile)

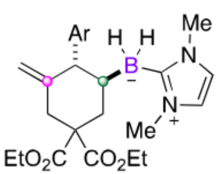
representative products initiated from alkenes



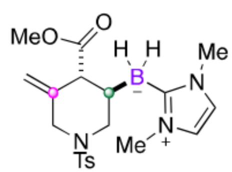
3a, 84%



3b, 52%

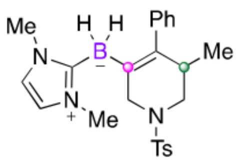


3c, 70%
(Ar = 4-$CO_2EtC_6H_4$)

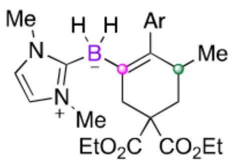


3d, 58%

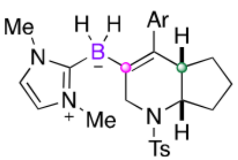
representative products initiated from alkynes



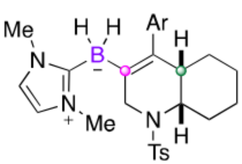
5a, 55%



5b, 41%
(Ar = 4-$CO_2EtC_6H_4$)



5c, 81%
(Ar = 4-$CO_2EtC_6H_4$)

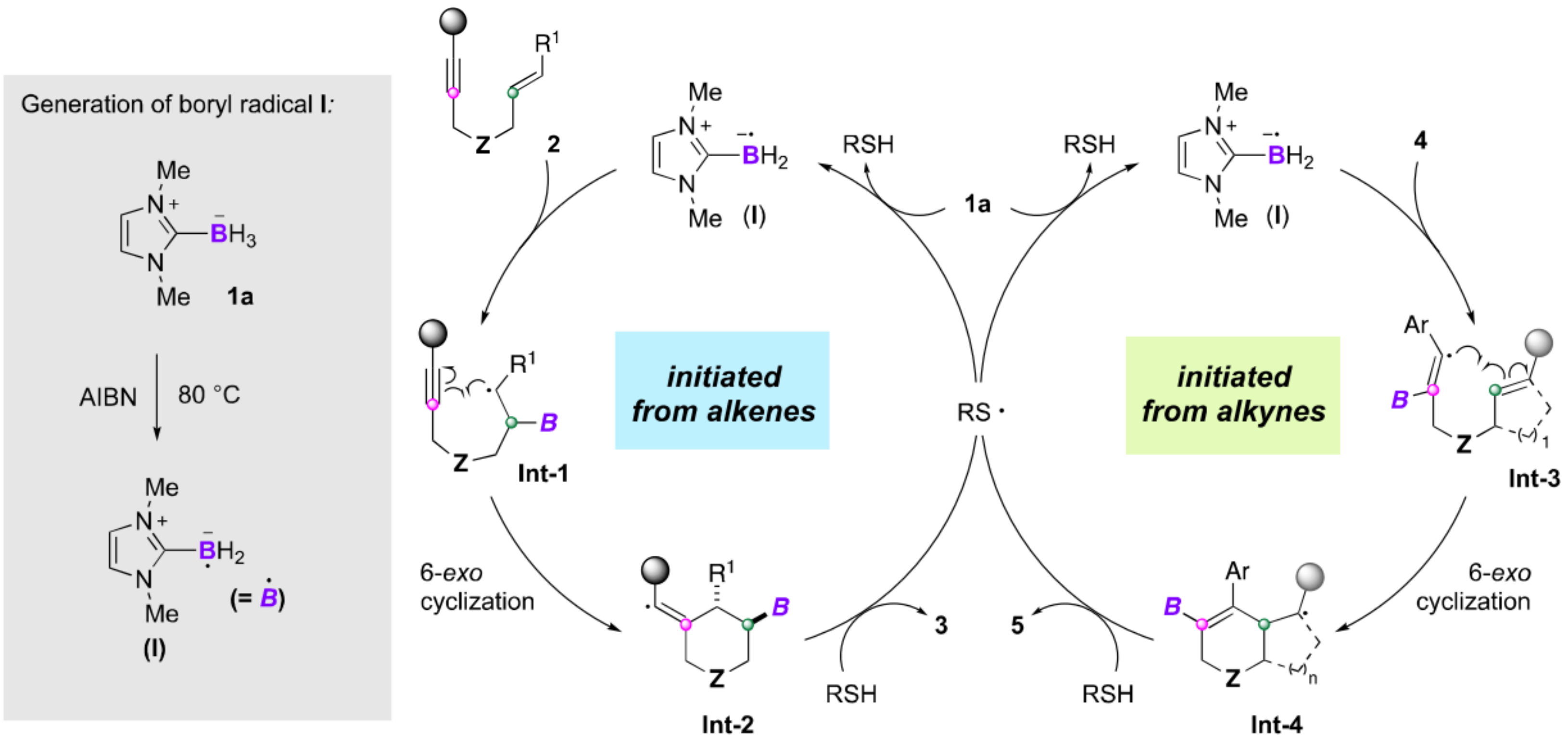


5d, 60%
(Ar = 2-ClC_6H_4)

Y.-F. Wang, et. al. *J. Am. Chem. Soc*. **2017**, *139*, 6050.

Cyclization cascade reaction promoted by boryl radicals

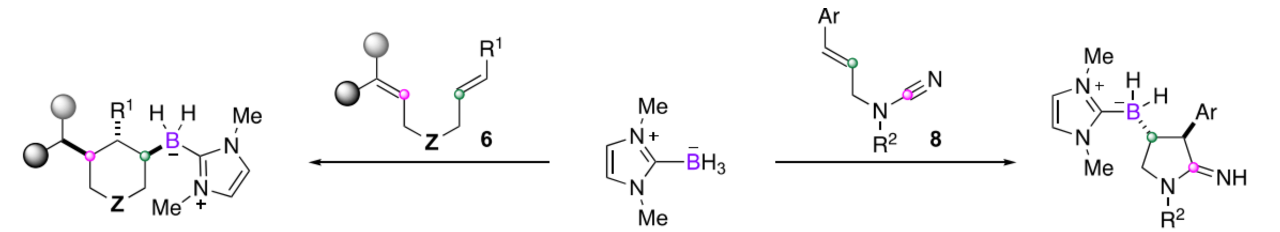
■ Radical borylation/cyclization cascade of 1,6-enynes



Y.-F. Wang, et. al. *J. Am. Chem. Soc*. **2017**, *139*, 6050.

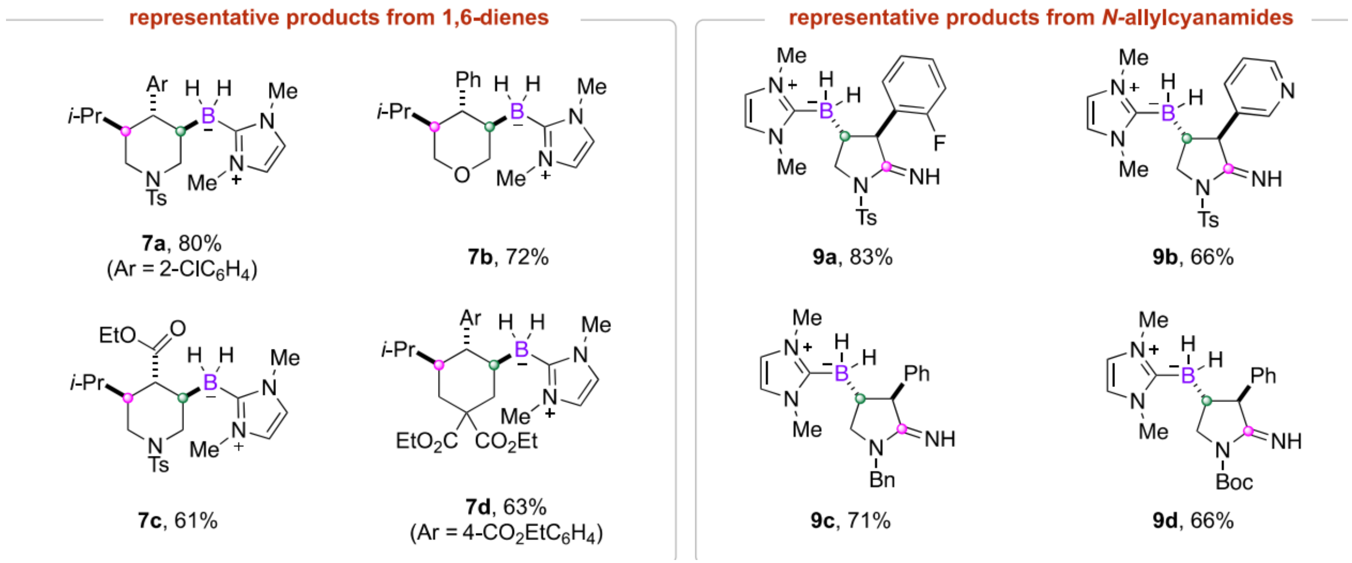
Cyclization cascade reaction promoted by boryl radicals

Radical borylation/cyclization cascade of 1,6-dienes and N-allylcyanamides



7, 18 examples, 42-90% yield | **1a** | **9**, 17 examples, 51-91% yield

condition: AIBN (20 mol%), $C_9H_{19}C(CH_3)_2SH$ (20 mol%), CH_3CN, 80 °C, 12 h
R^1 = Ar, CO_2Et, $CONEt_2$, R^2 = Ts, Ar, Bn, Boc, **Z** = NTs, O, $C(CO_2Et)_2$



Y.-F. Wang, et. al. *Org. Lett.* **2018**, *20*, 2360.
Y.-F. Wang, et. al. *Org. Lett.* **2018**, *20*, 7558.

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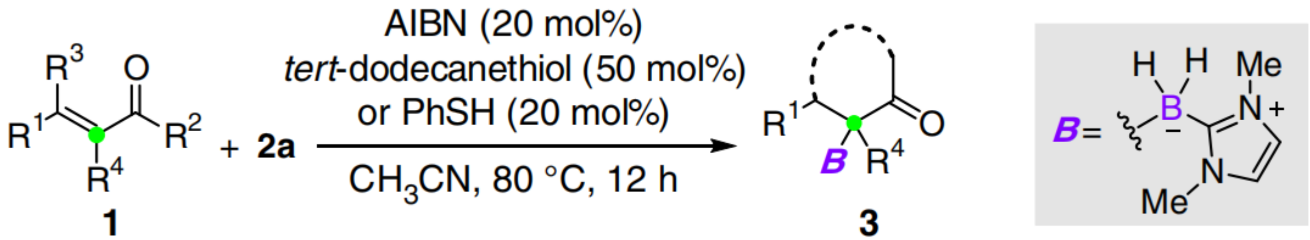
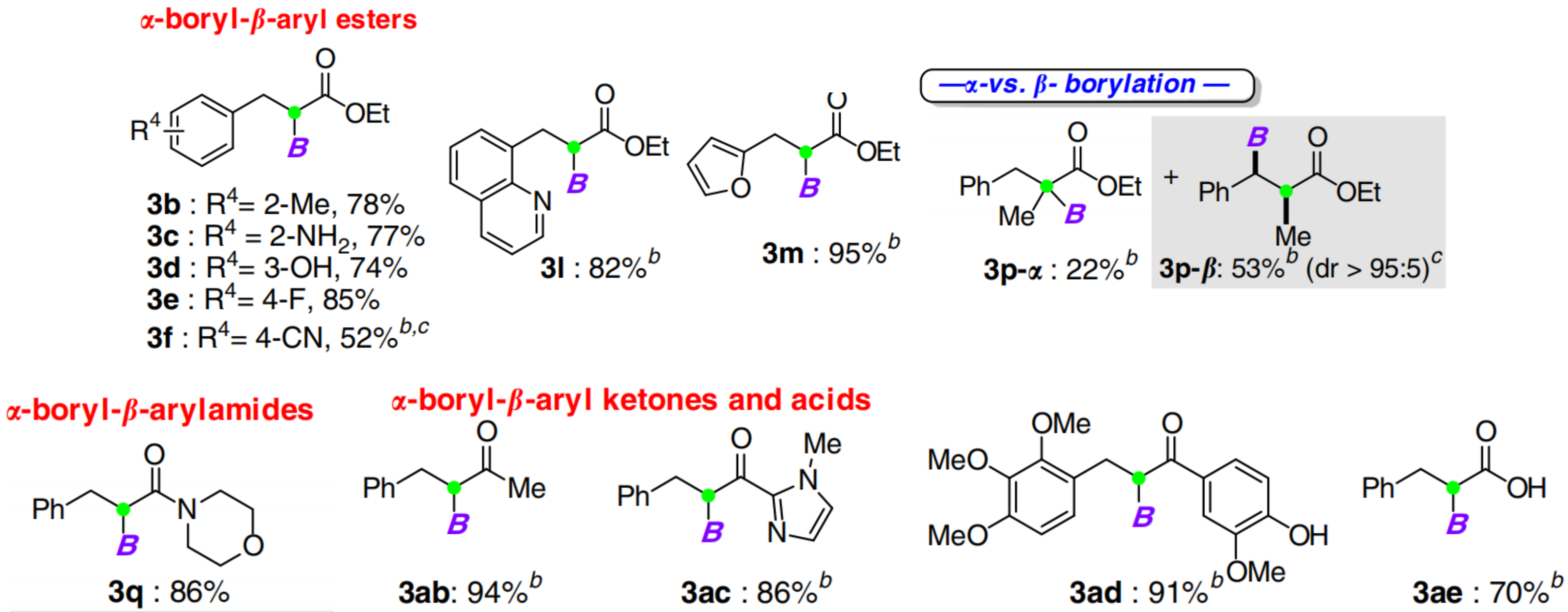
Hydroboration reaction promoted by boryl radicals

α-Regioselective radical hydroboration of activated alkenes

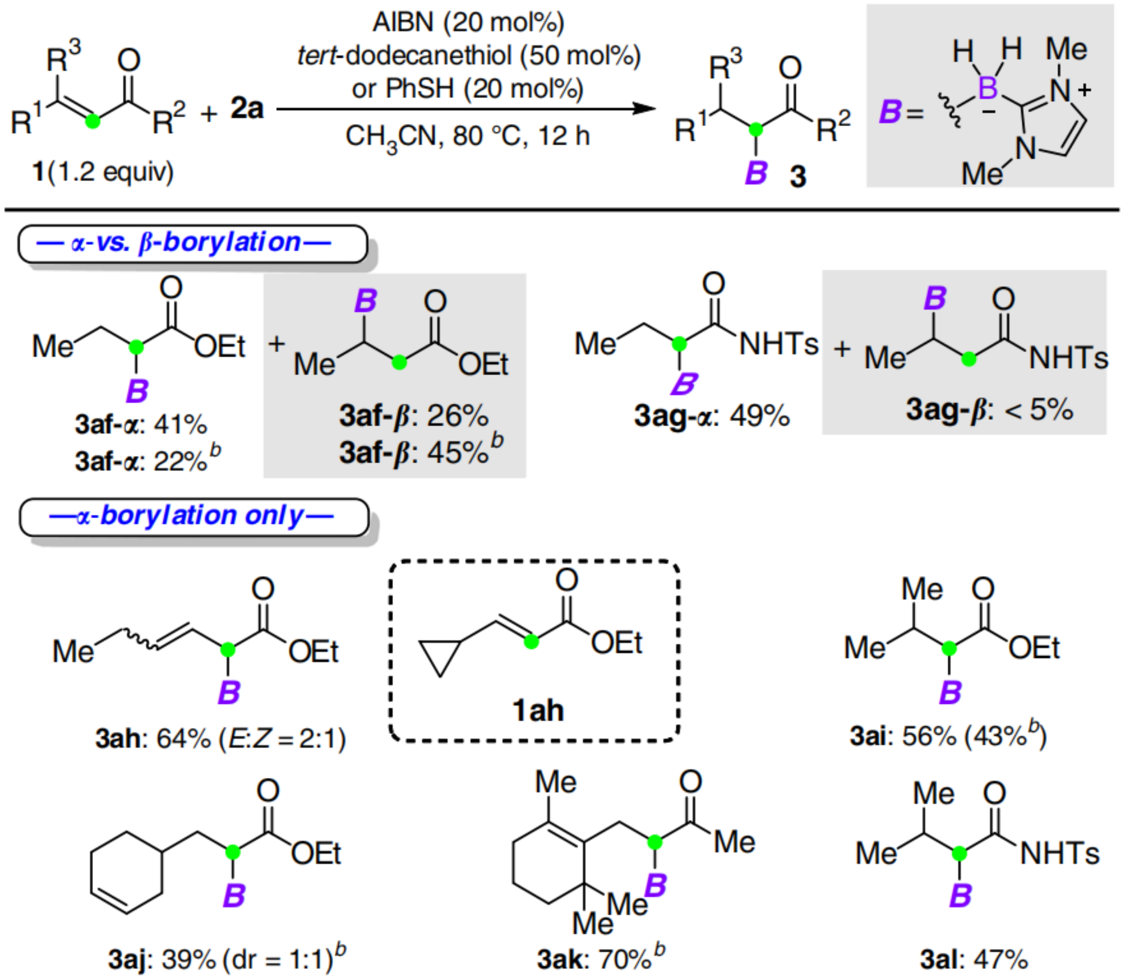




Y.-F. Wang, et. al. *Nat. Commun*. **2019**, *10*, 1934.

Hydroboration reaction promoted by boryl radicals

■ α-Regioselective radical hydroboration of activated alkenes



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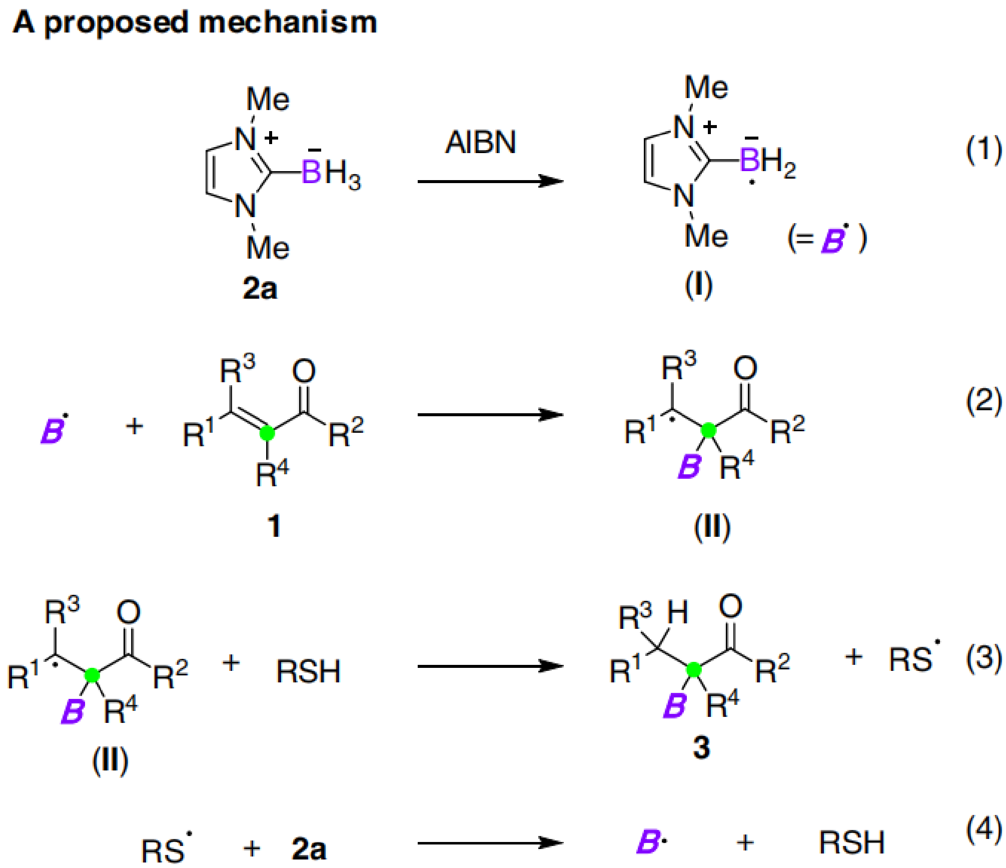

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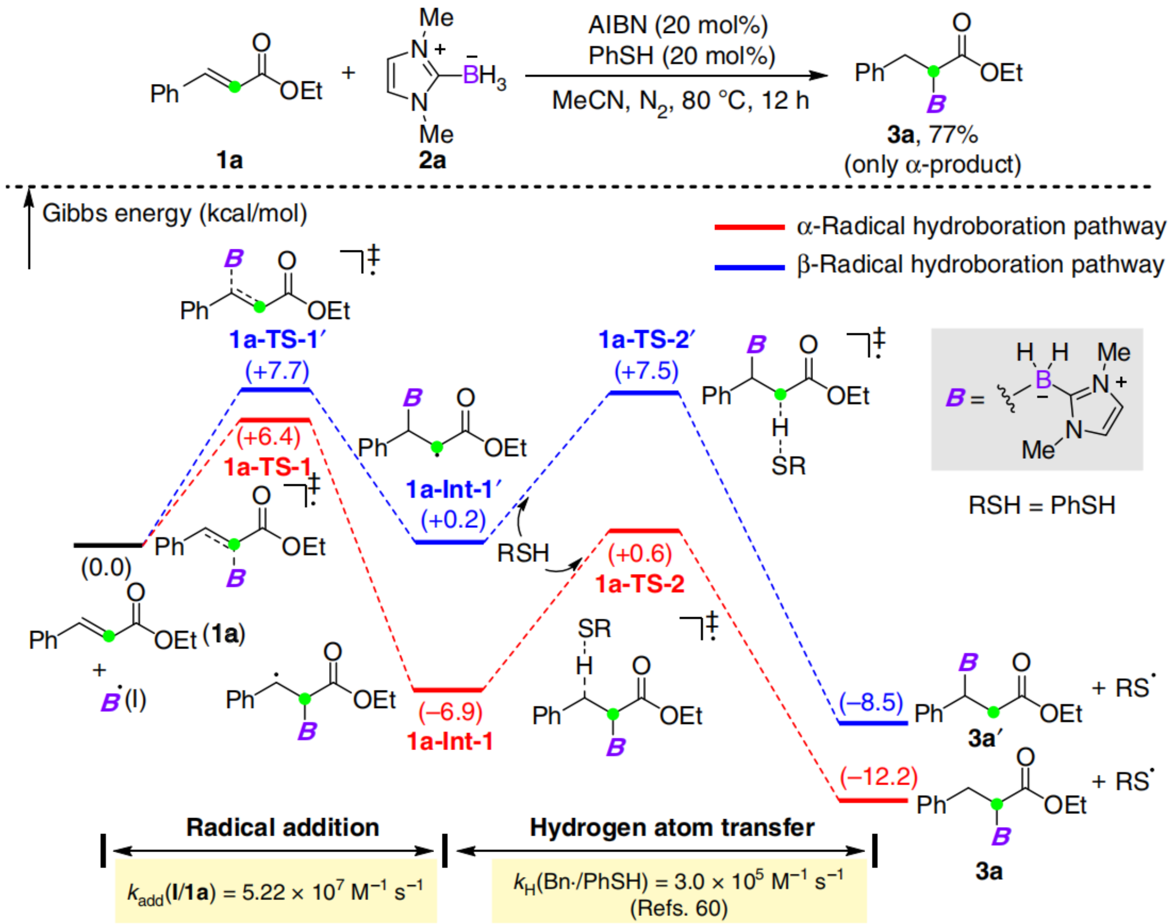

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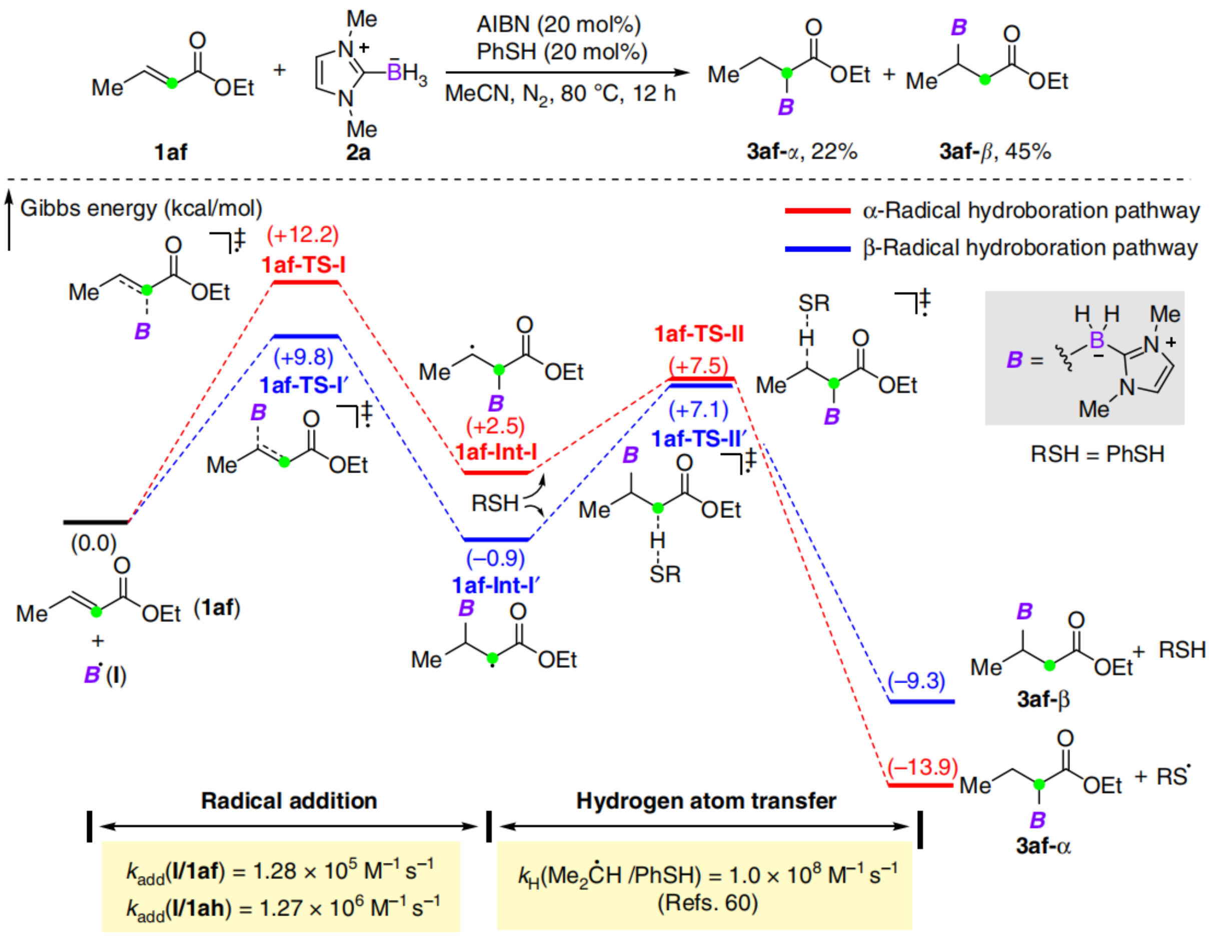
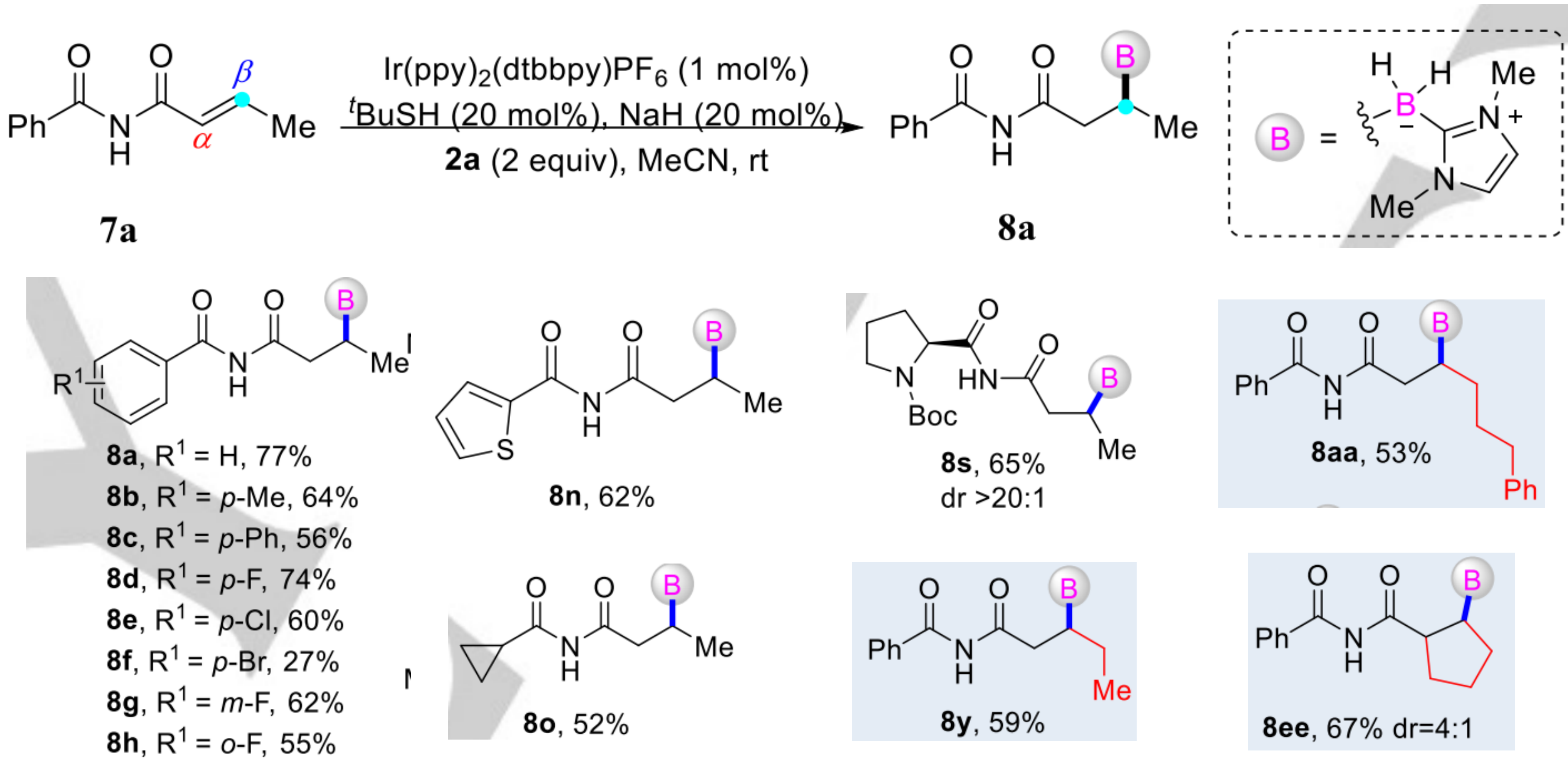


Y.-F. Wang, et. al. *Nat. Commun*. **2019**, *10*, 1934.

Hydroboration reaction promoted by boryl radicals

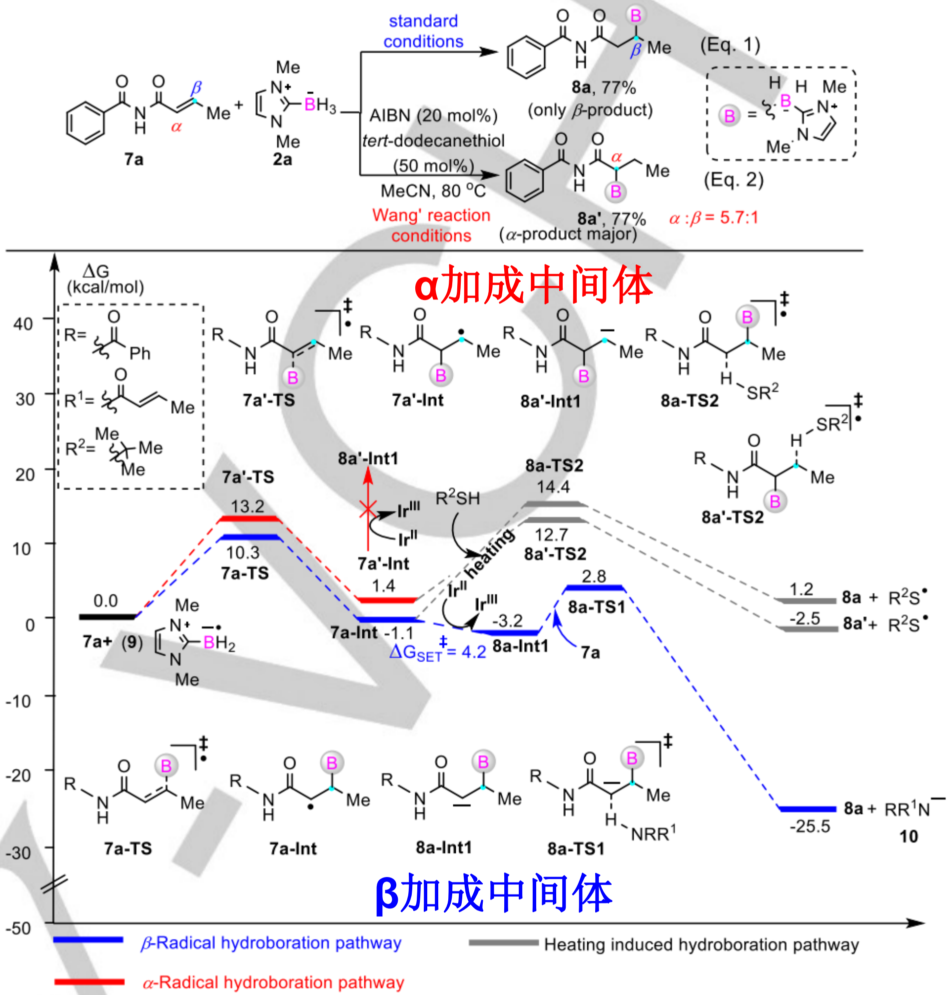
β-Regioselective radical hydroboration of activated alkenes



J. Xie; S.-H. Li; C.-J. Zhu, et. al. *Angew. Chem. Int. Ed.* **2020**, *59*, 12817.

Hydroboration reaction promoted by boryl radicals

β-Regioselective radical hydroboration of activated alkenes



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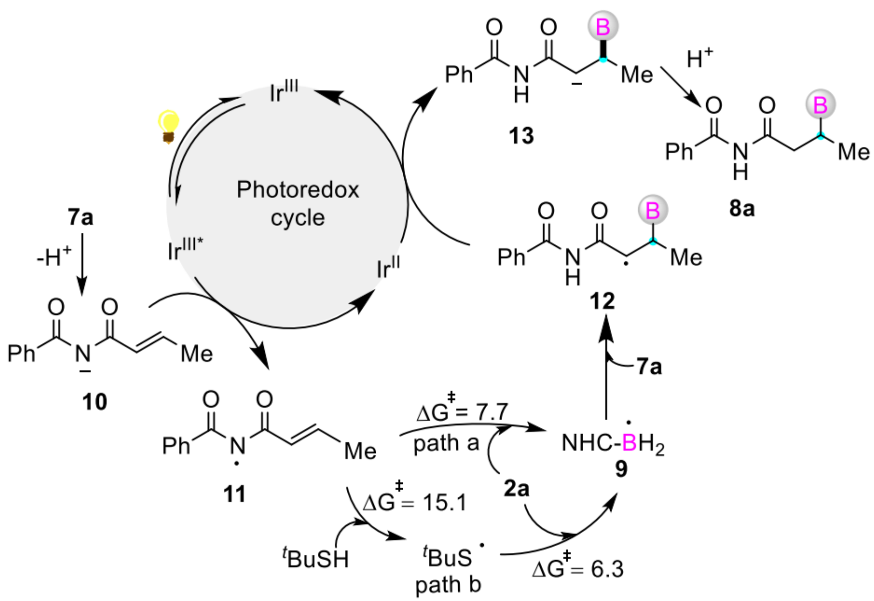
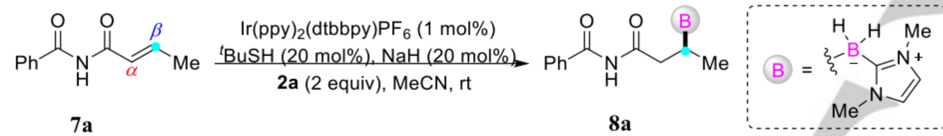




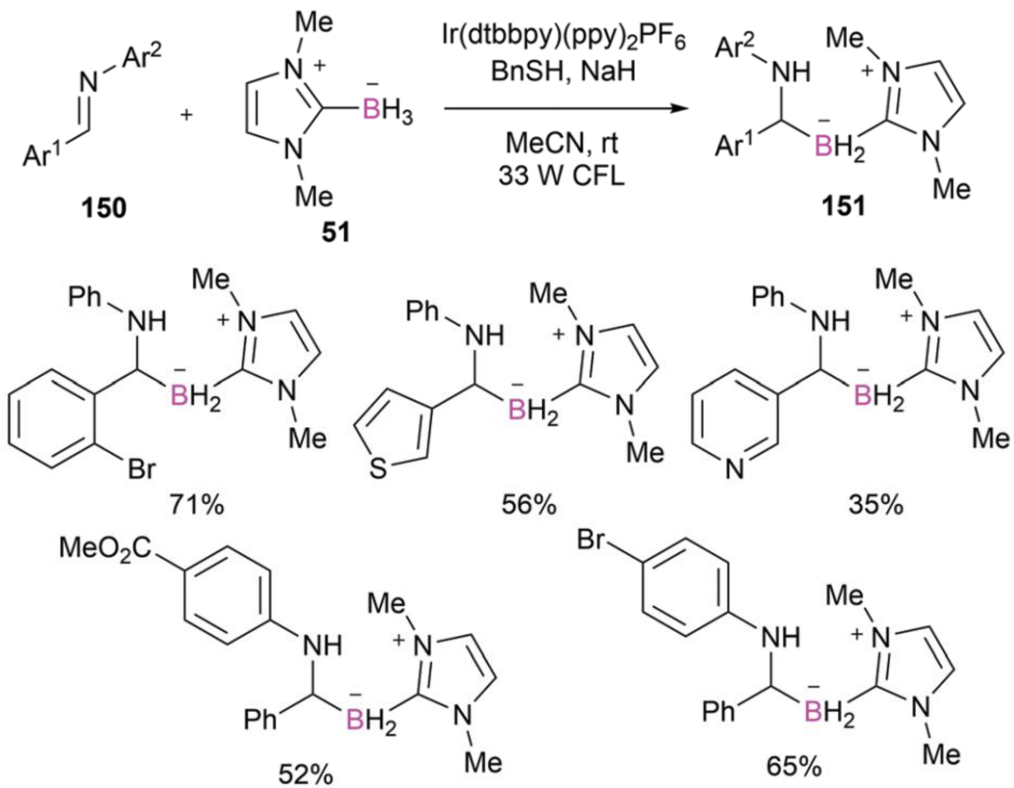
Entry	Variation of standard conditions	Yield [%][b]
1	**None**	**77**
2	$Ru(bpy)_3Cl_2$	ND
3	4CZIPN	ND
4	Eosin Y	trace
5	blue LEDs instead CFL	25
6	without ^{t}BuSH	27
7	without light	ND
8	Without photocatalyst	ND

measurements always mean these should be taken only as guidelines. The oxidation potentials of Amide aonic (**10**) ($E_{1/2}^{\text{oxidation}}$ = 0.53 V vs SCE), ^{t}BuS$^-$ ($E_{1/2}^{\text{oxidation}}$ = 0.52 V vs SCE). The oxidation potentials of Amide ionic and ^{t}BuS$^-$ is similar, both of them are lower than photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ ($E_{1/2}$*III/II = +0.66 V vs SCE) [3].

J. Xie; S.-H. Li; C.-J. Zhu, et. al. *Angew. Chem. Int. Ed.* **2020**, *59*, 12817.

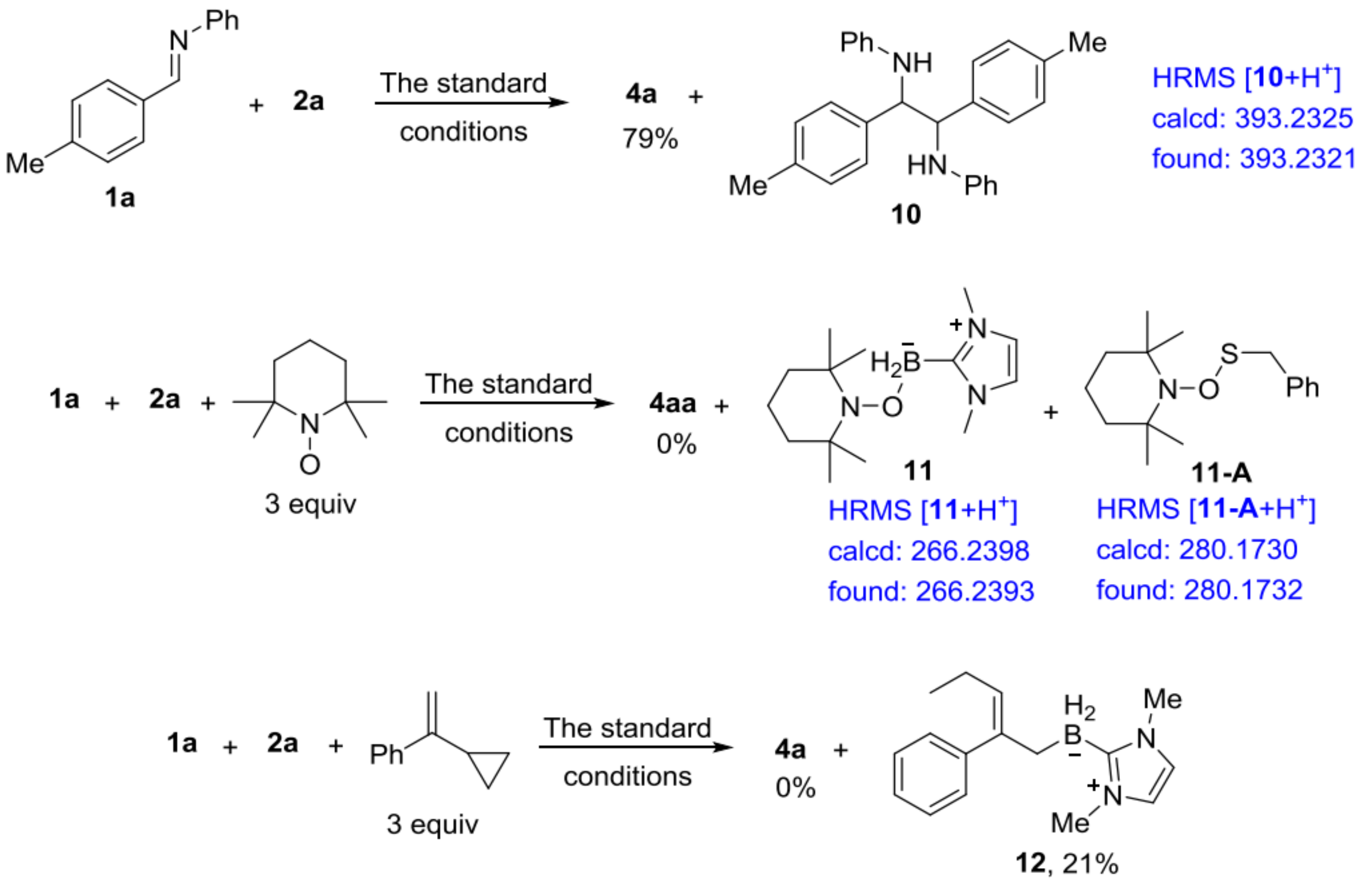
Hydroboration reaction promoted by boryl radicals

■ Radical hydroboration of imines



J. Xie; C.-J. Zhu, et. al. *Angew. Chem. Int. Ed.* **2018**, *57*, 3990.

Radical hydroboration of imines



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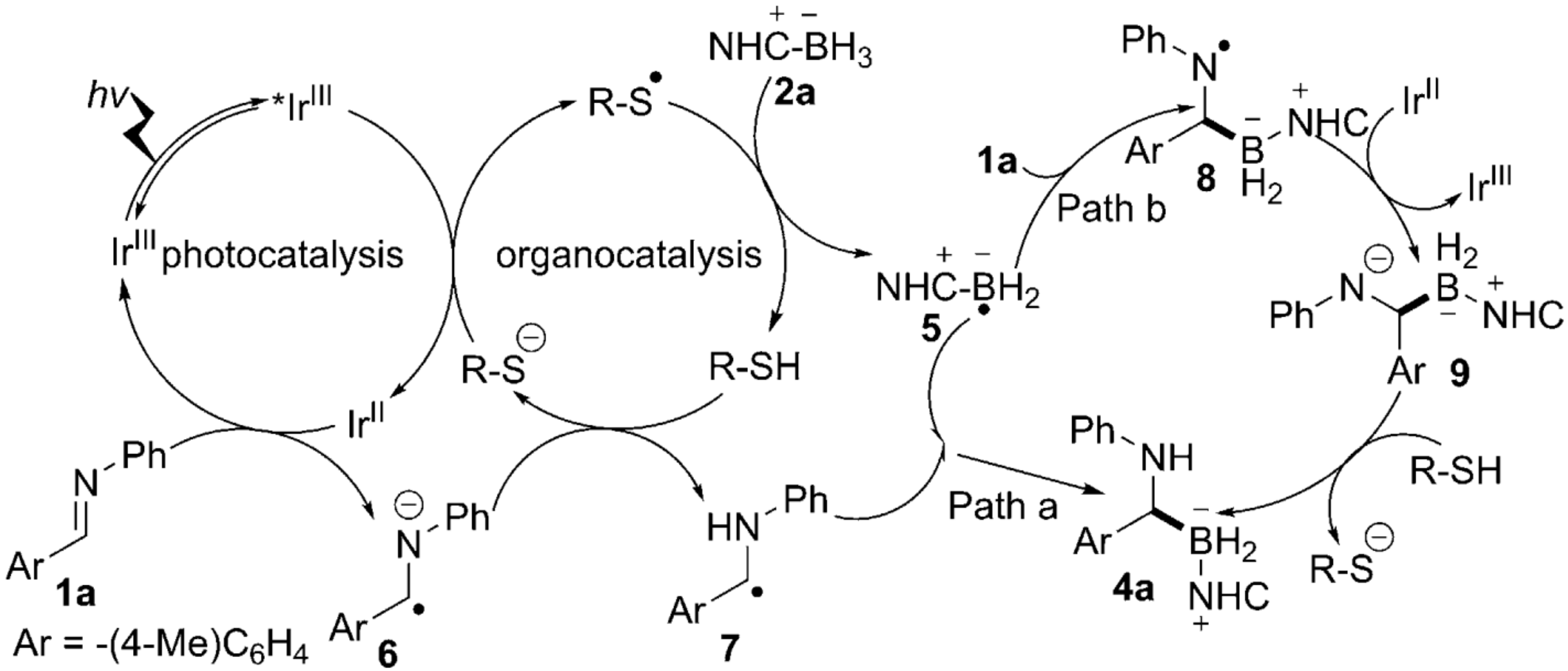
Hydroboration reaction promoted by boryl radicals

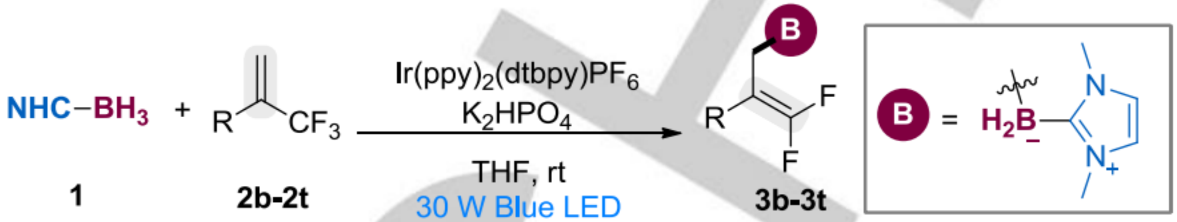
Radical hydroboration of imines



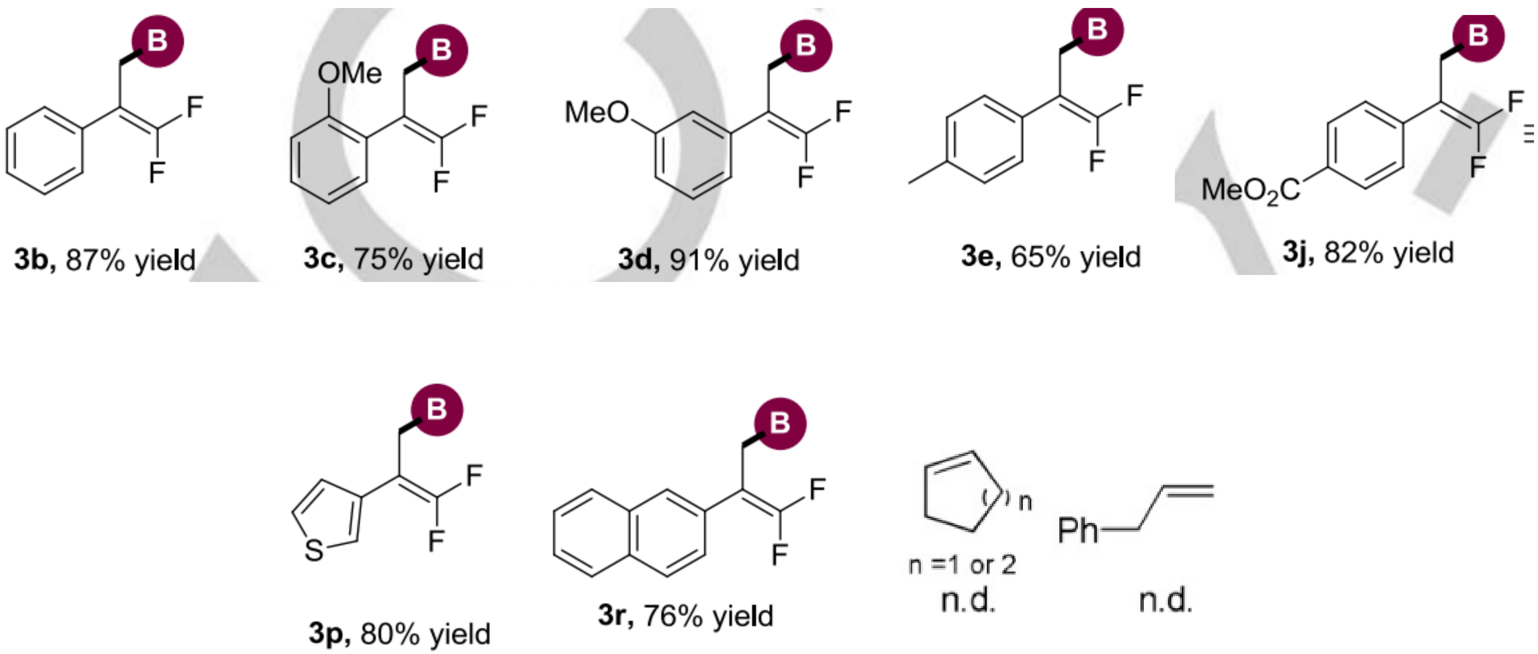
J. Xie; C.-J. Zhu, et. al. *Angew. Chem. Int. Ed.* **2018**, *57*, 3990.

Hydroboration reaction promoted by boryl radicals

■ Radical hydroboration of activated alkenes by photoredox catalysis



$E_{1/2} \approx 0.34$ V



H.-Y. Xiang; X.-Q. Chen, H, Yang, et. al. *Angew. Chem. Int. Ed.* **2020**, *59*, 6706.

Hydroboration reaction promoted by boryl radicals

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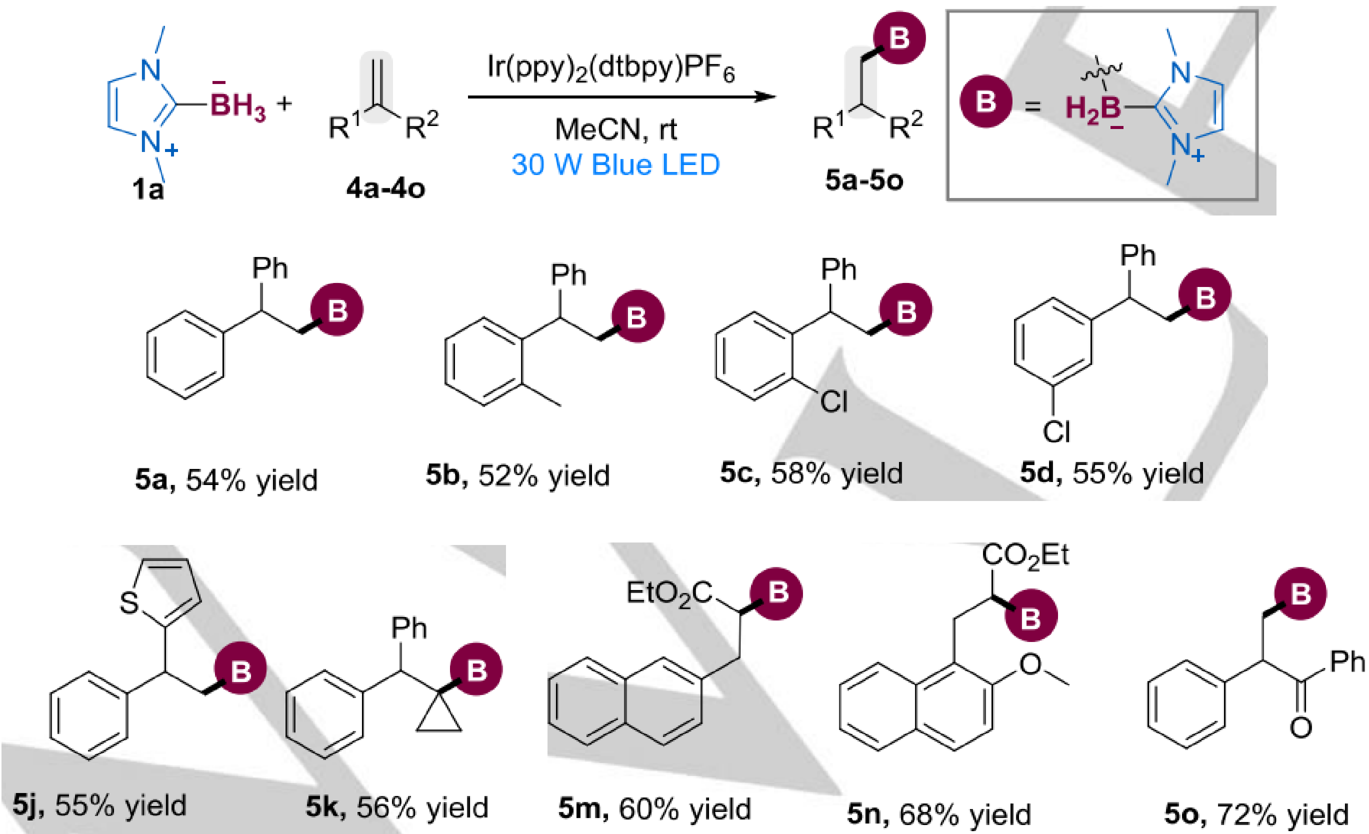

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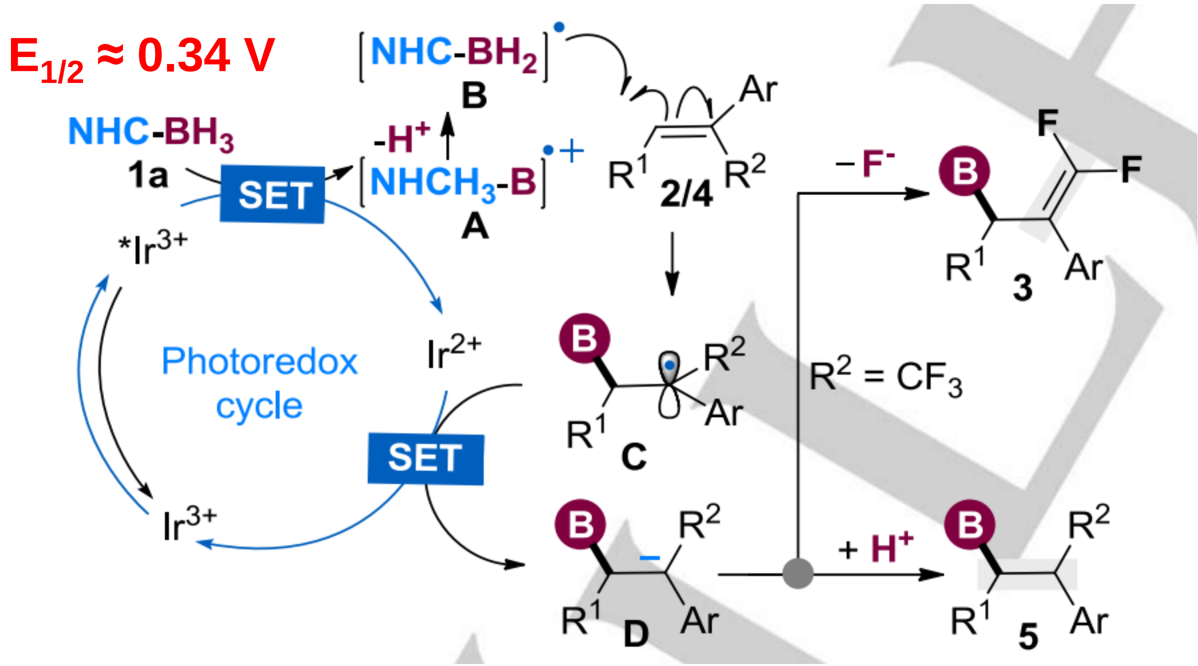

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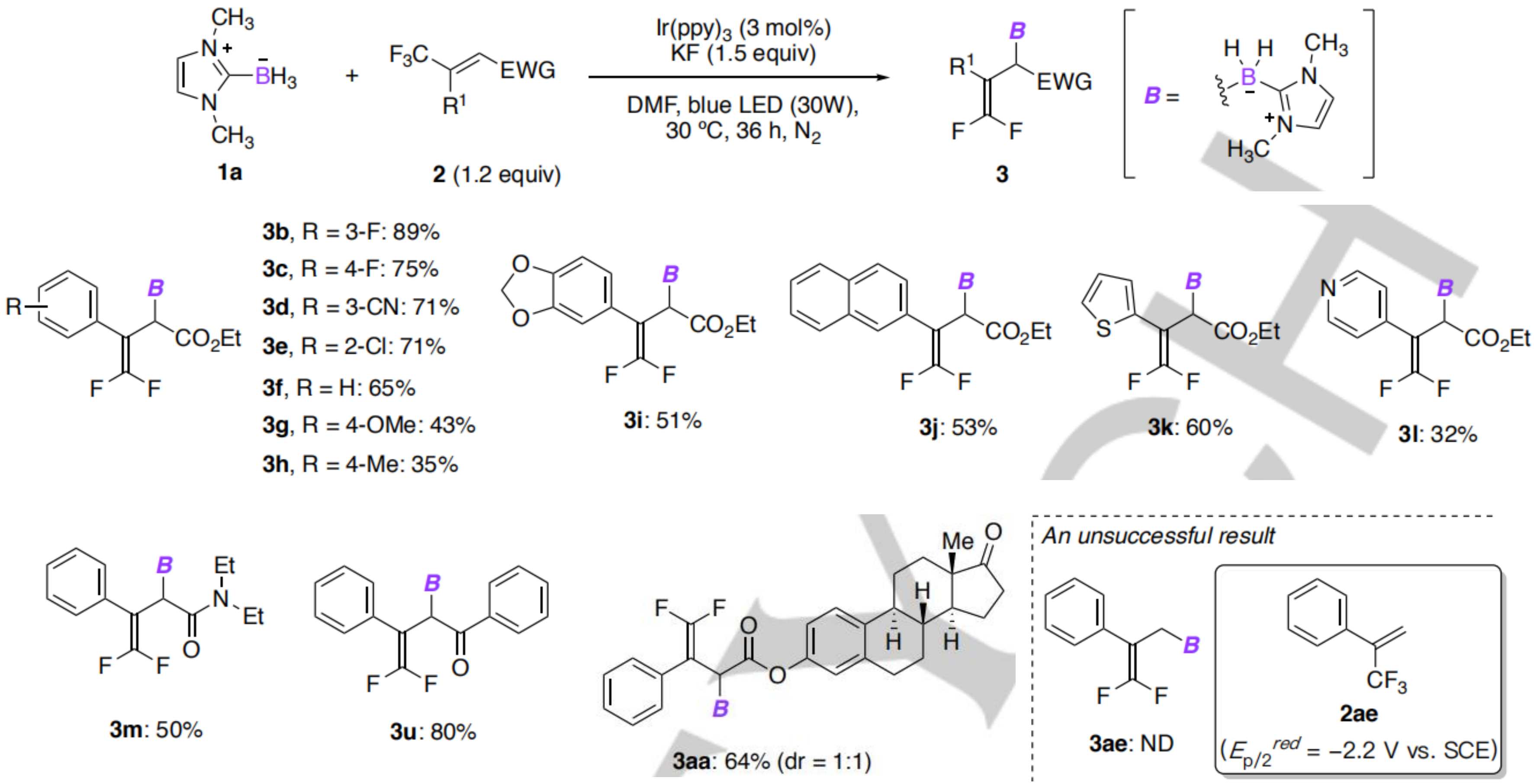
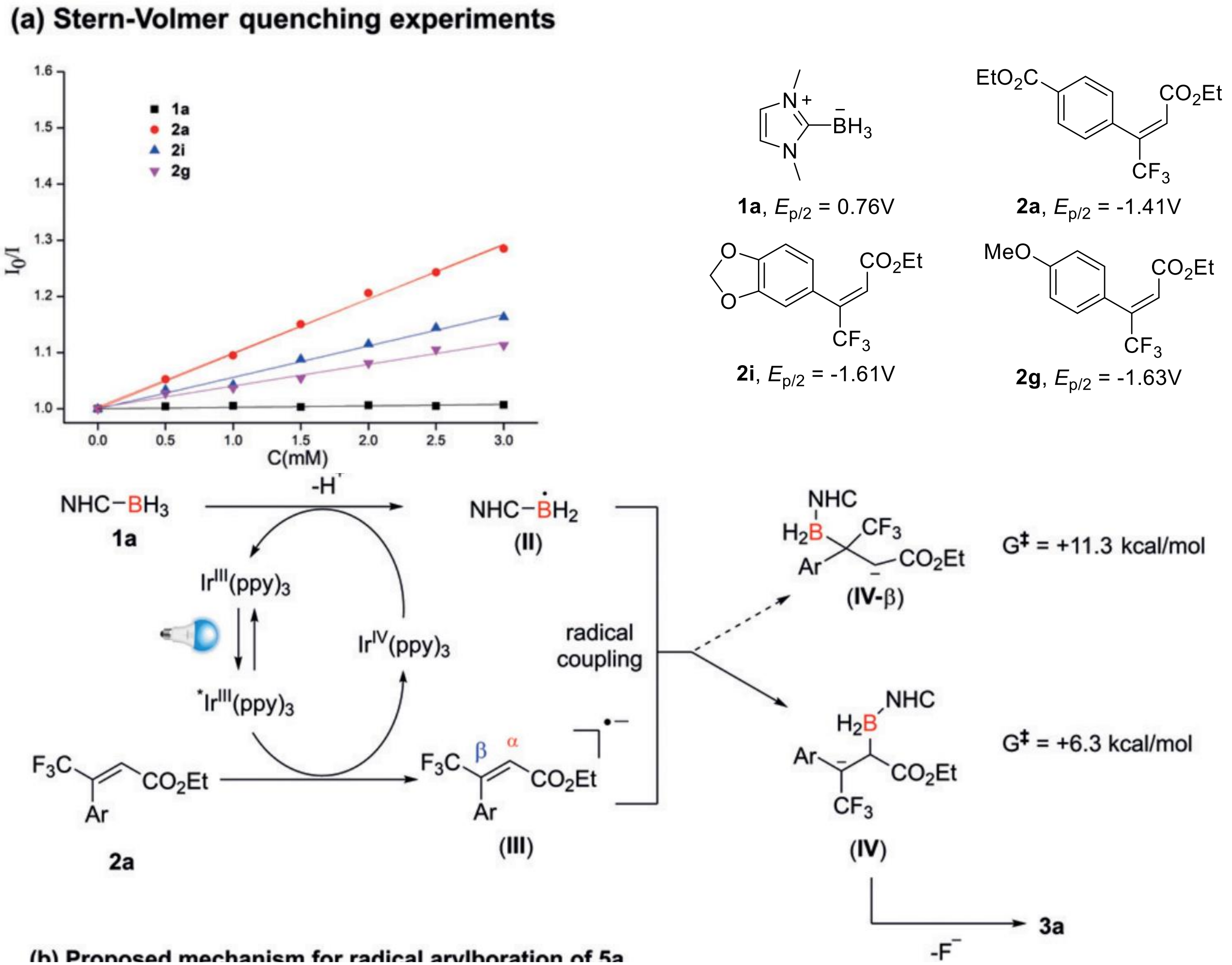


Y.-F. Wang, et. al. *Angew. Chem. Int. Ed.* **2020**, *59*, 12876.

Hydroboration reaction promoted by boryl radicals

Radical hydroboration of activated alkenes by photoredox catalysis



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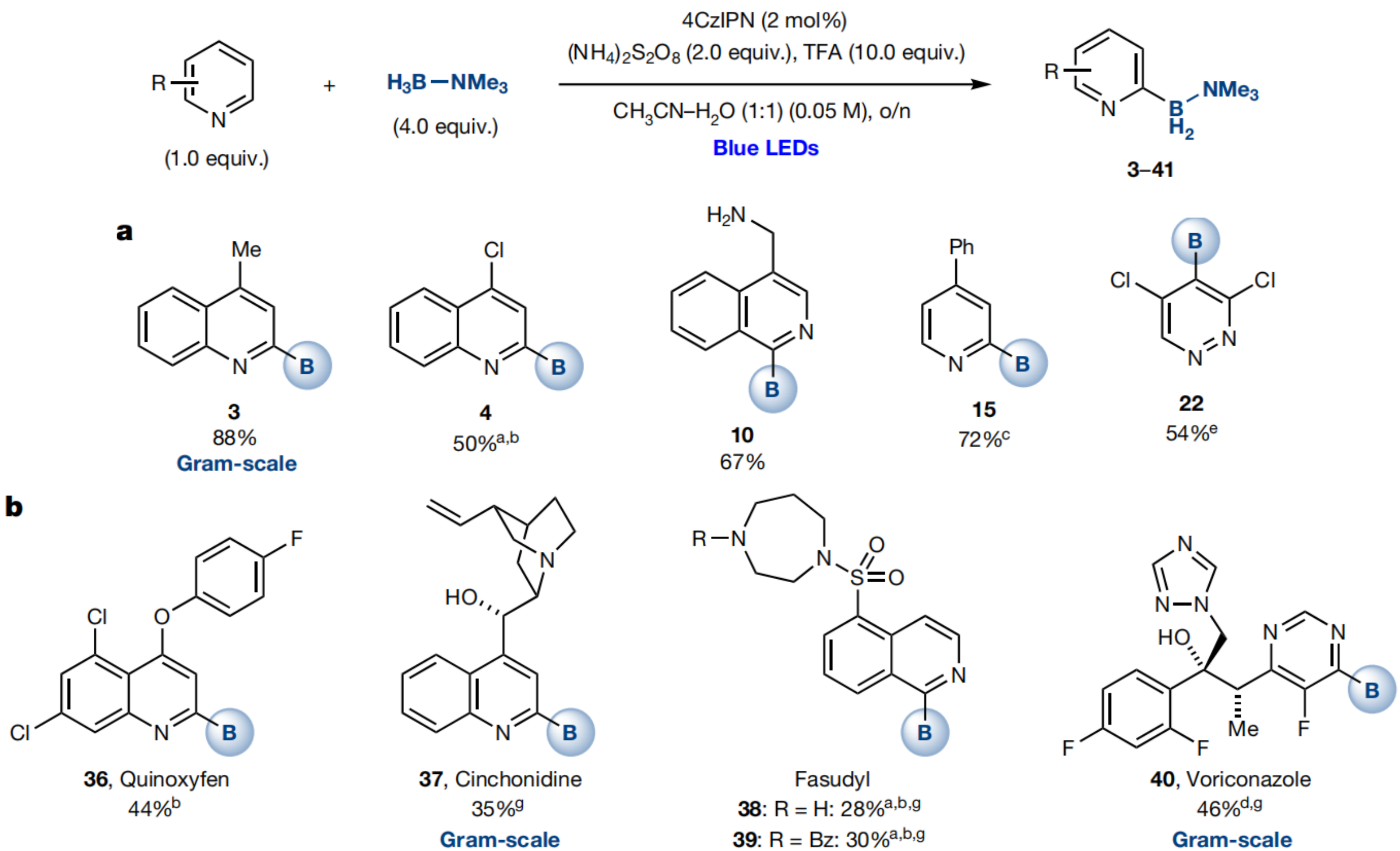
Outline

- Discovery of boryl radicals
- Reduction reaction promoted by boryl radicals
- Cyclization cascade reaction promoted by boryl radicals
- Hydroboration reaction promoted by boryl radicals
- **Minisci reaction promoted by boryl radicals**

Minisci reaction promoted by boryl radicals

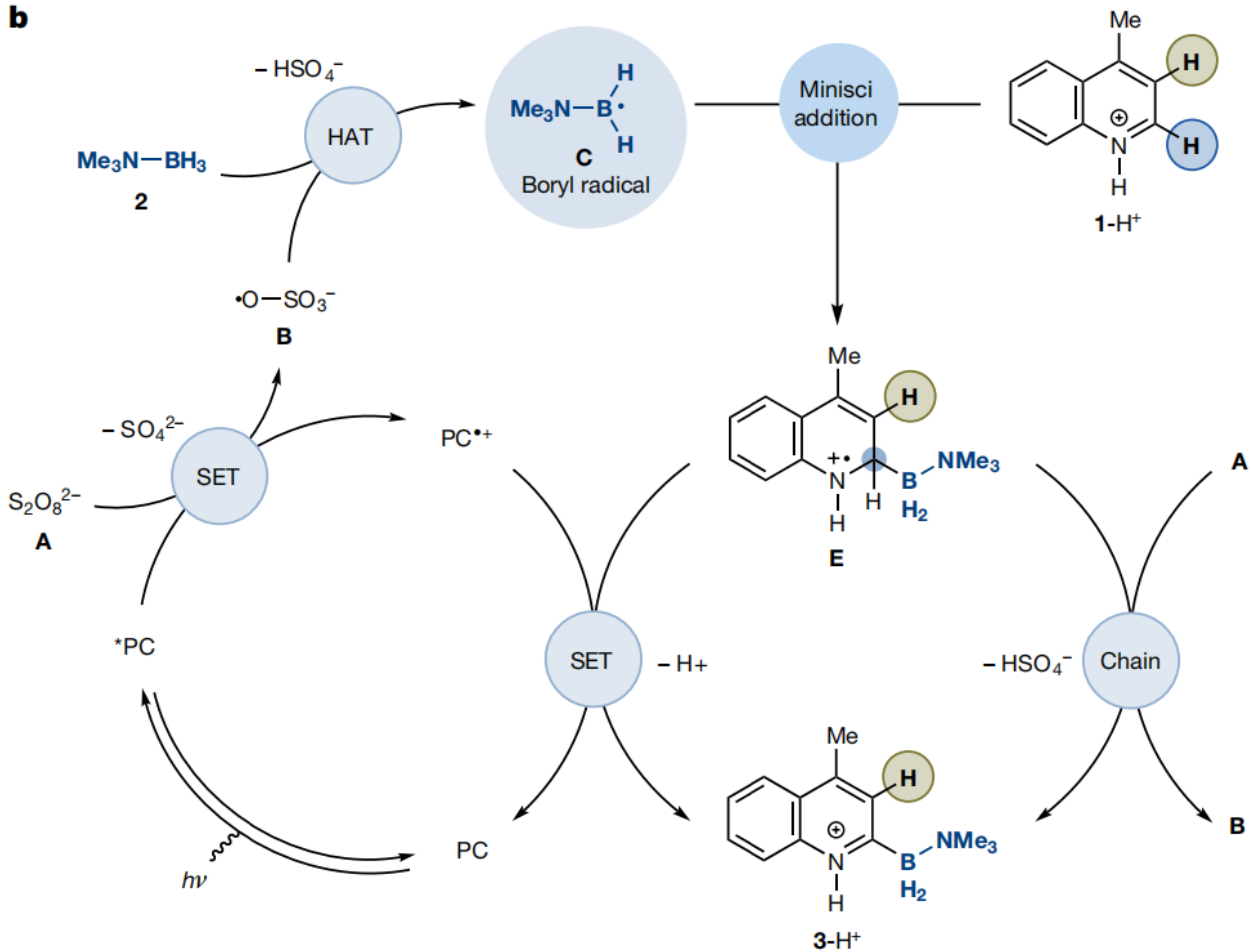
A radical approach for the selective C–H borylation of azines



D. Leonori, et. al. *Nature* **2021**, *595*, 677.

Minisci reaction promoted by boryl radicals

- A radical approach for the selective C–H borylation of azines



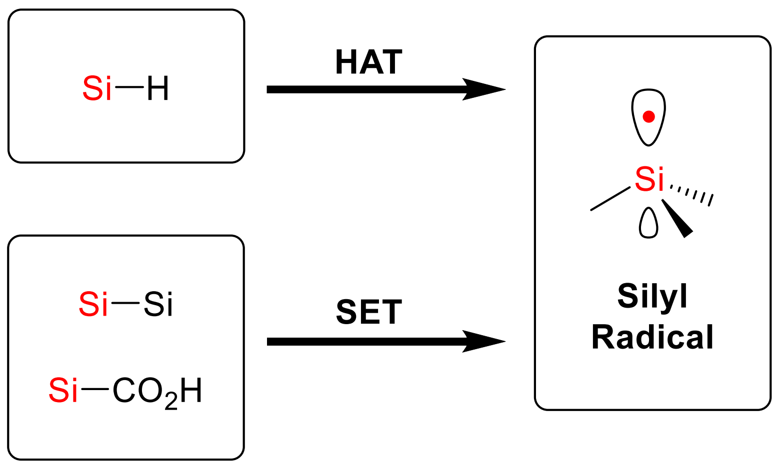
D. Leonori, et. al. *Nature* **2021**, *595*, 677.

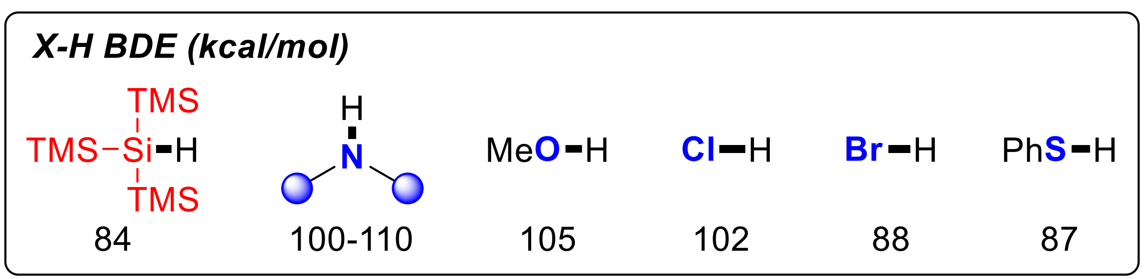
Outline

- Discovery of silyl radicals
- Generation of silyl radicals from Si–H reagents
- Generation of silyl radicals from Si–Si reagents
- Generation of silyl radicals from Si–CO_2H reagents

Background

Silyl radical precursor



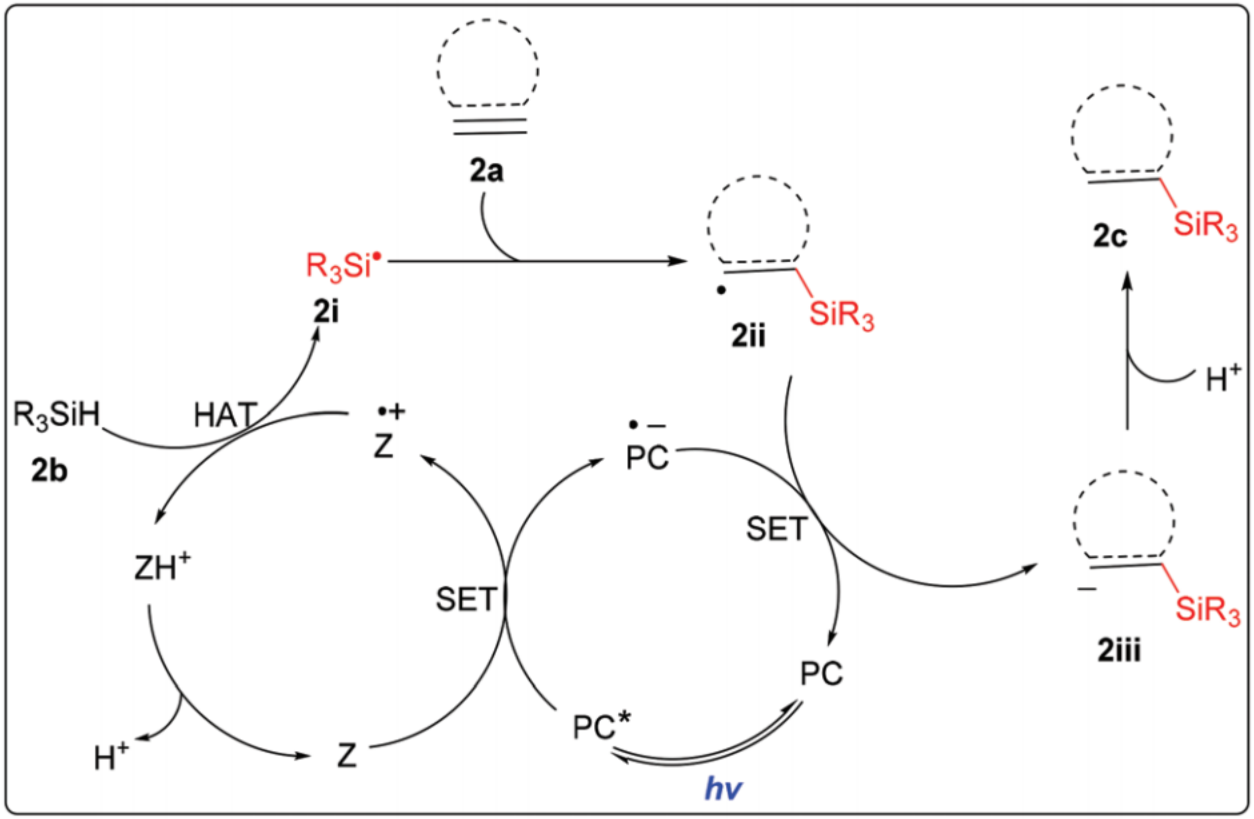


Outline

- Discovery of silyl radicals
- **Generation of silyl radicals from Si–H reagents**
- Generation of silyl radicals from Si–Si reagents
- Generation of silyl radicals from Si–CO_2H reagents

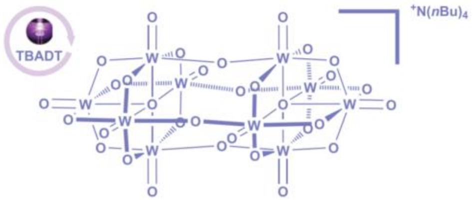
Generation of silyl radicals from Si–H reagents

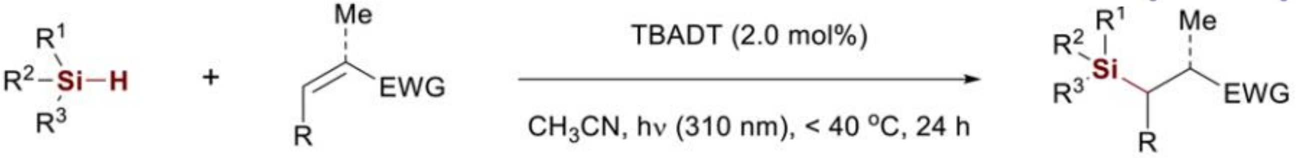
- **General mechanism for hydrosilylation of alkenes via HAT**



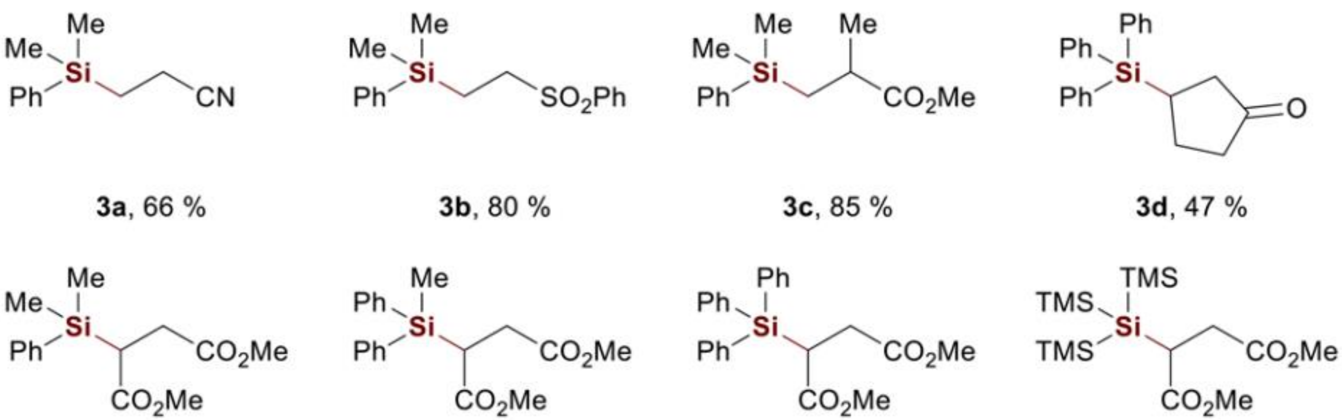
Generation of silyl radicals from Si–H reagents

Hydrosilylation of alkenes via HAT



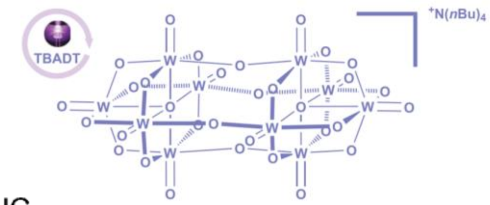


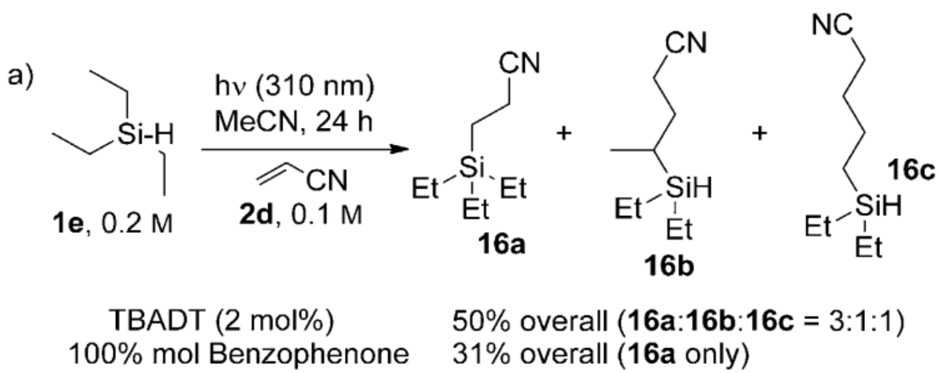
selected examples

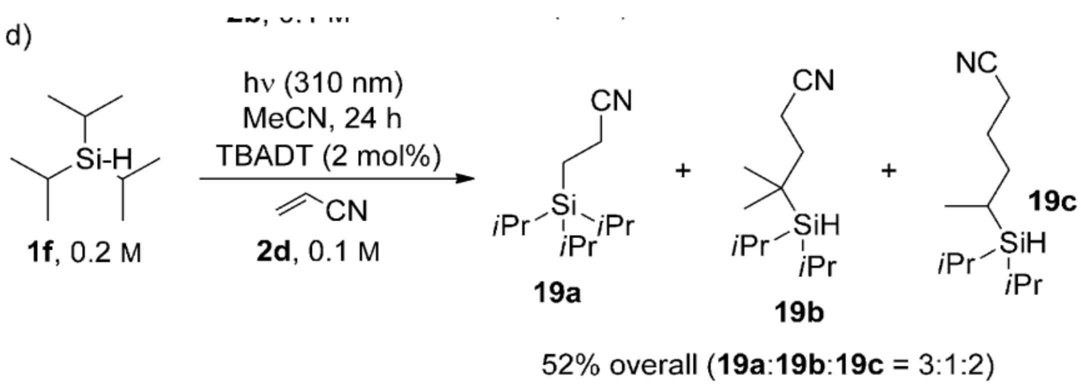


M. Fagnoni, et. al. *ChemCatChem*, **2015**, *7*, 3350.

Hydrosilylation of alkenes via HAT



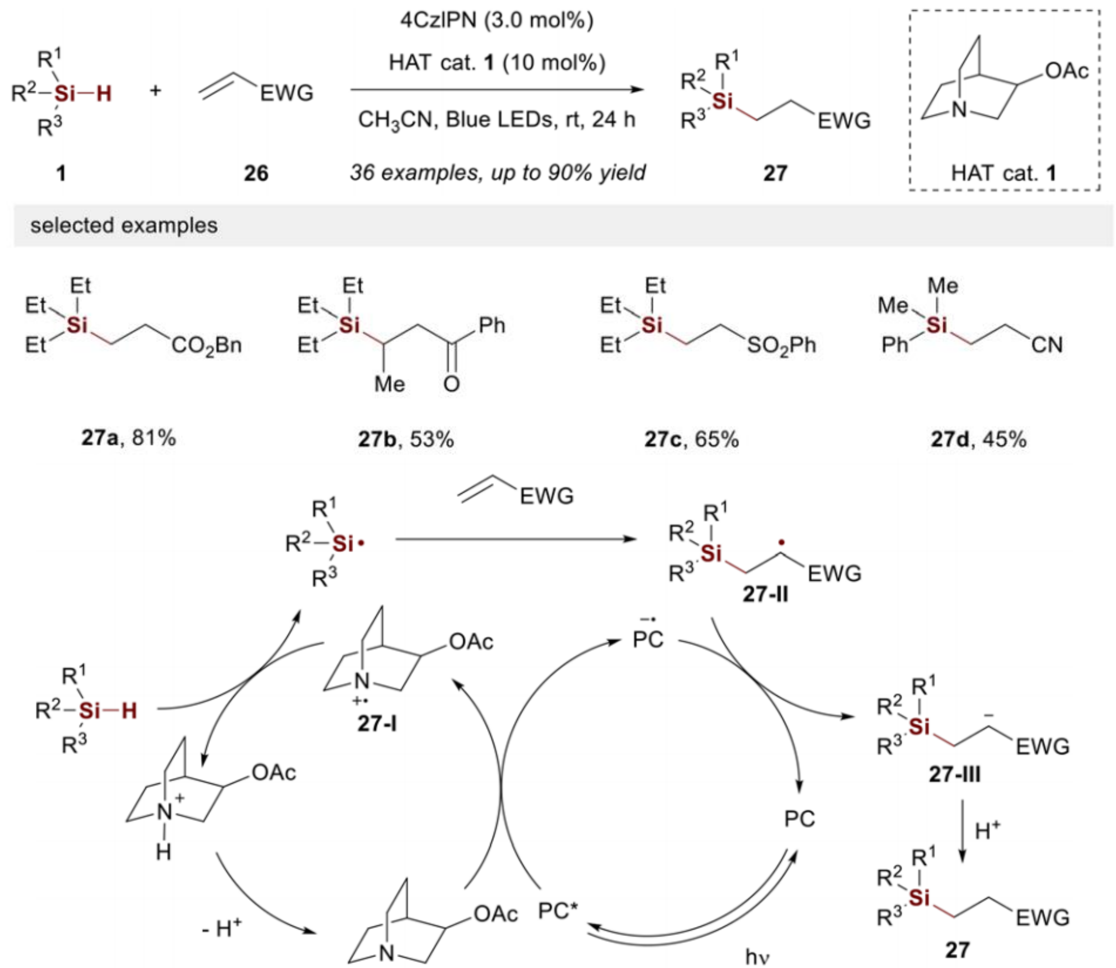




M. Fagnoni, et. al. *ChemCatChem*, **2015**, *7*, 3350.

Generation of silyl radicals from Si–H reagents

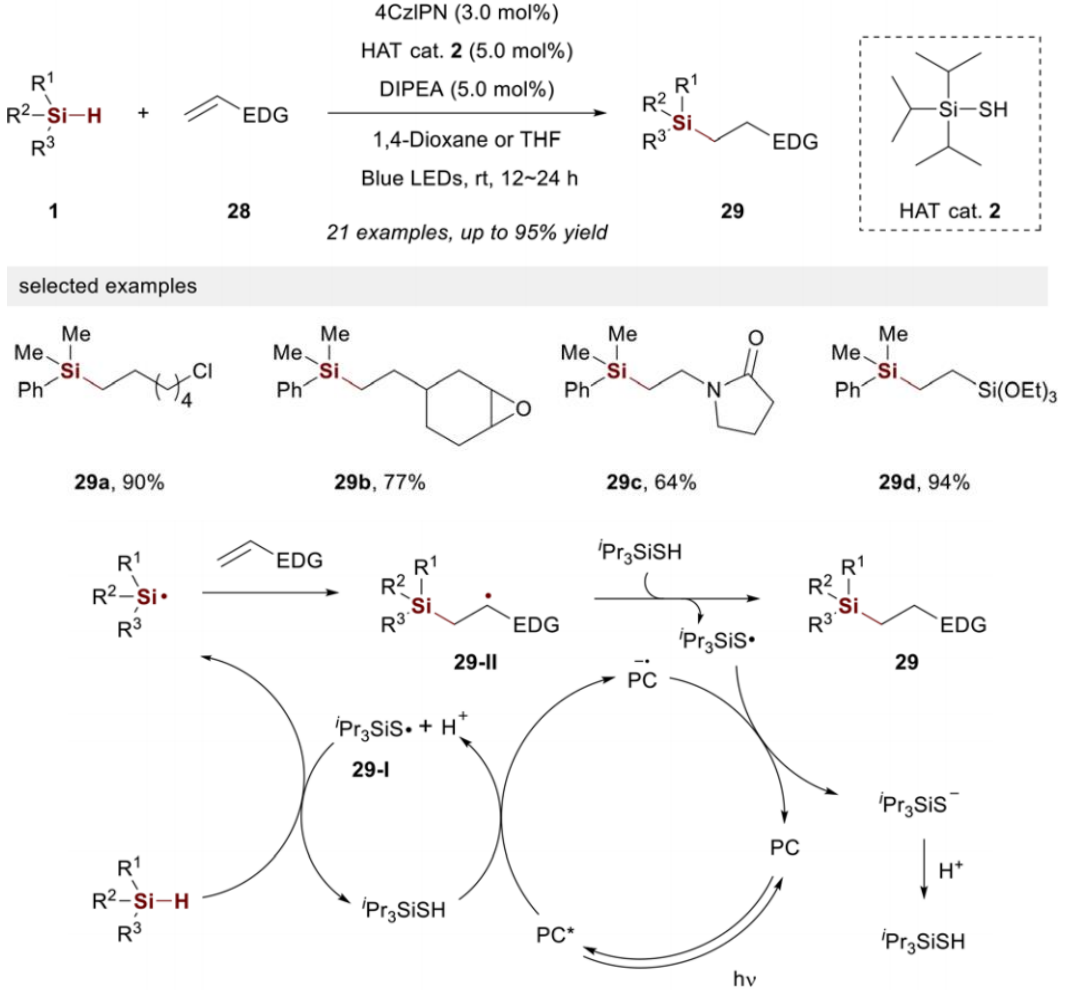
Hydrosilylation of alkenes via HAT



J. Wu, et. al. *Angew. Chem. Int. Ed.* **2017**, *56*, 16621.

Generation of silyl radicals from Si–H reagents

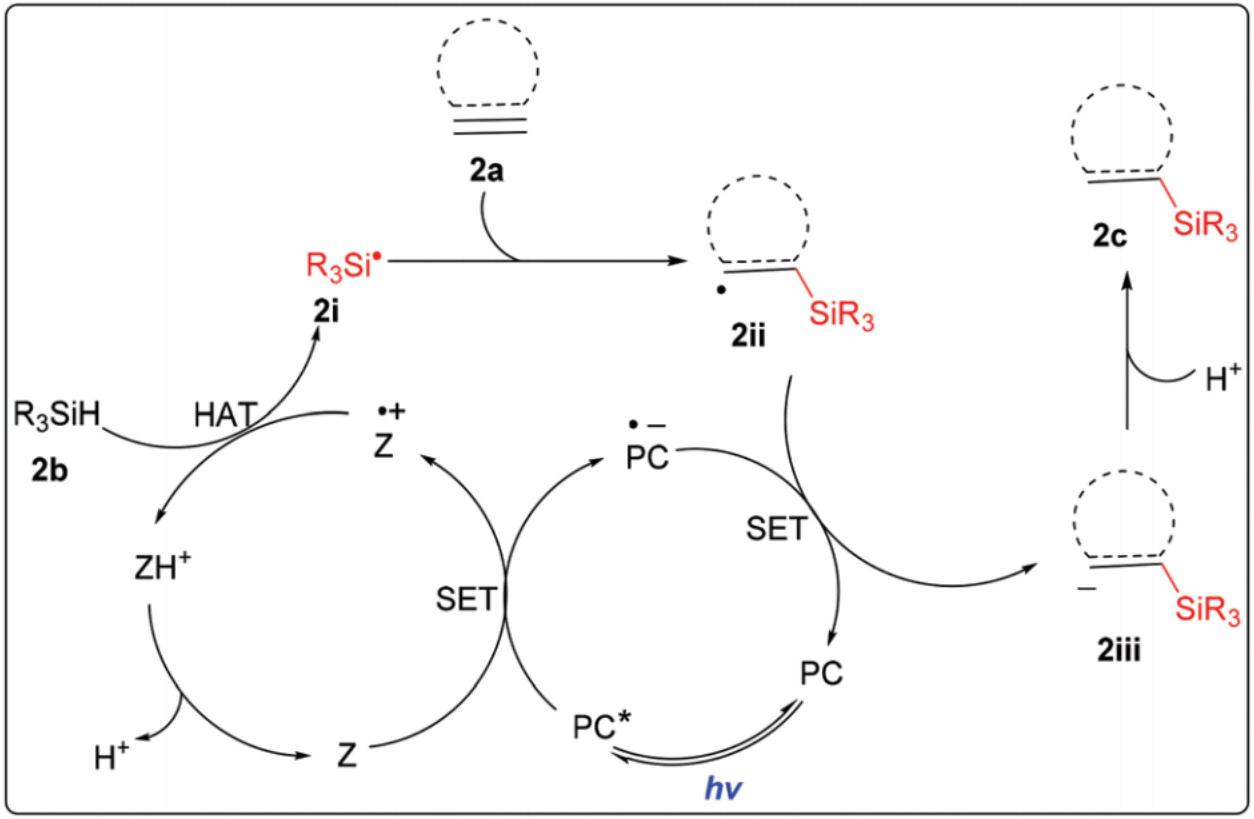
Hydrosilylation of alkenes via HAT



J. Wu, et. al. *Angew. Chem. Int. Ed.* **2017**, *56*, 16621.

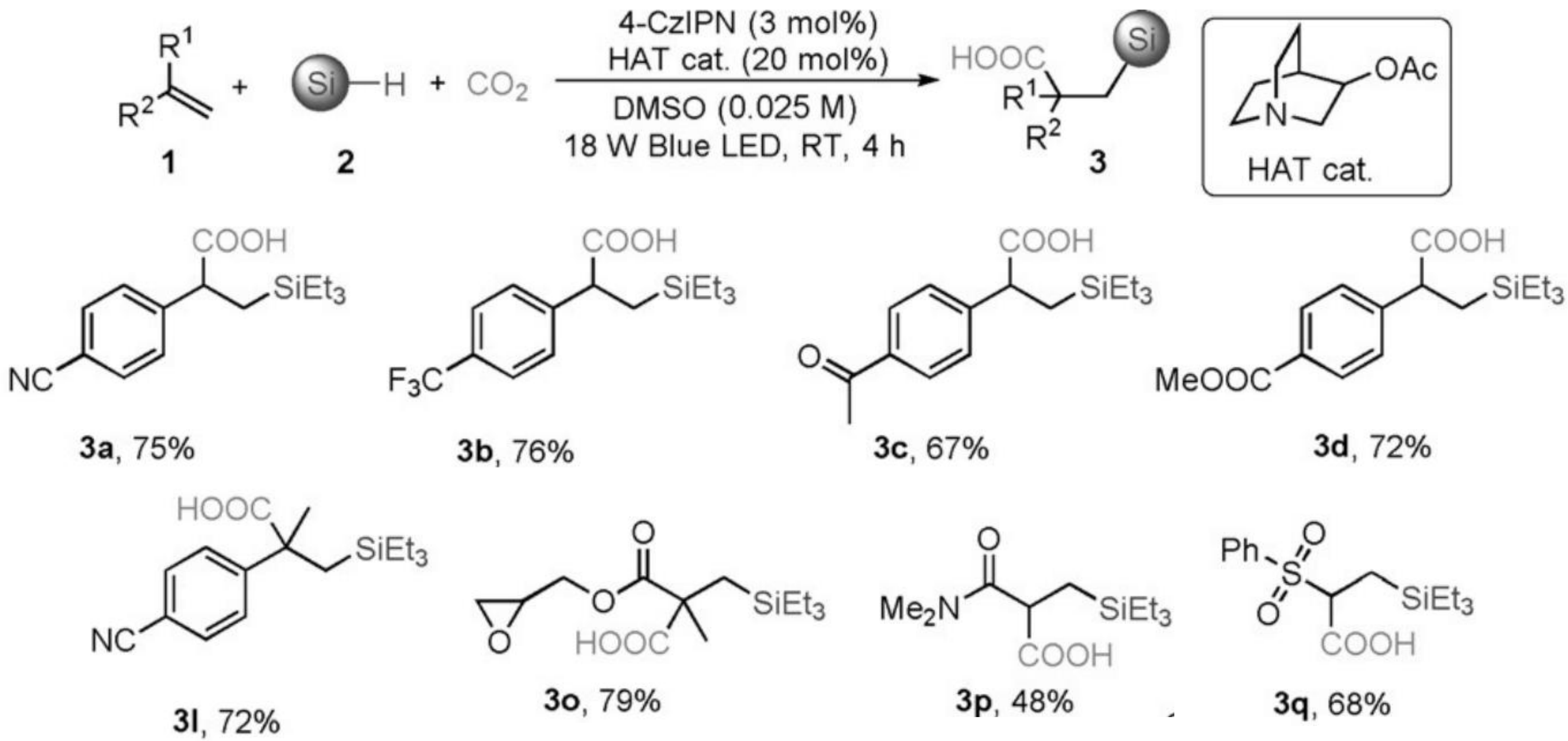
Generation of silyl radicals from Si–H reagents

- **General mechanism for hydrosilylation of alkenes via HAT**



Generation of silyl radicals from Si–H reagents

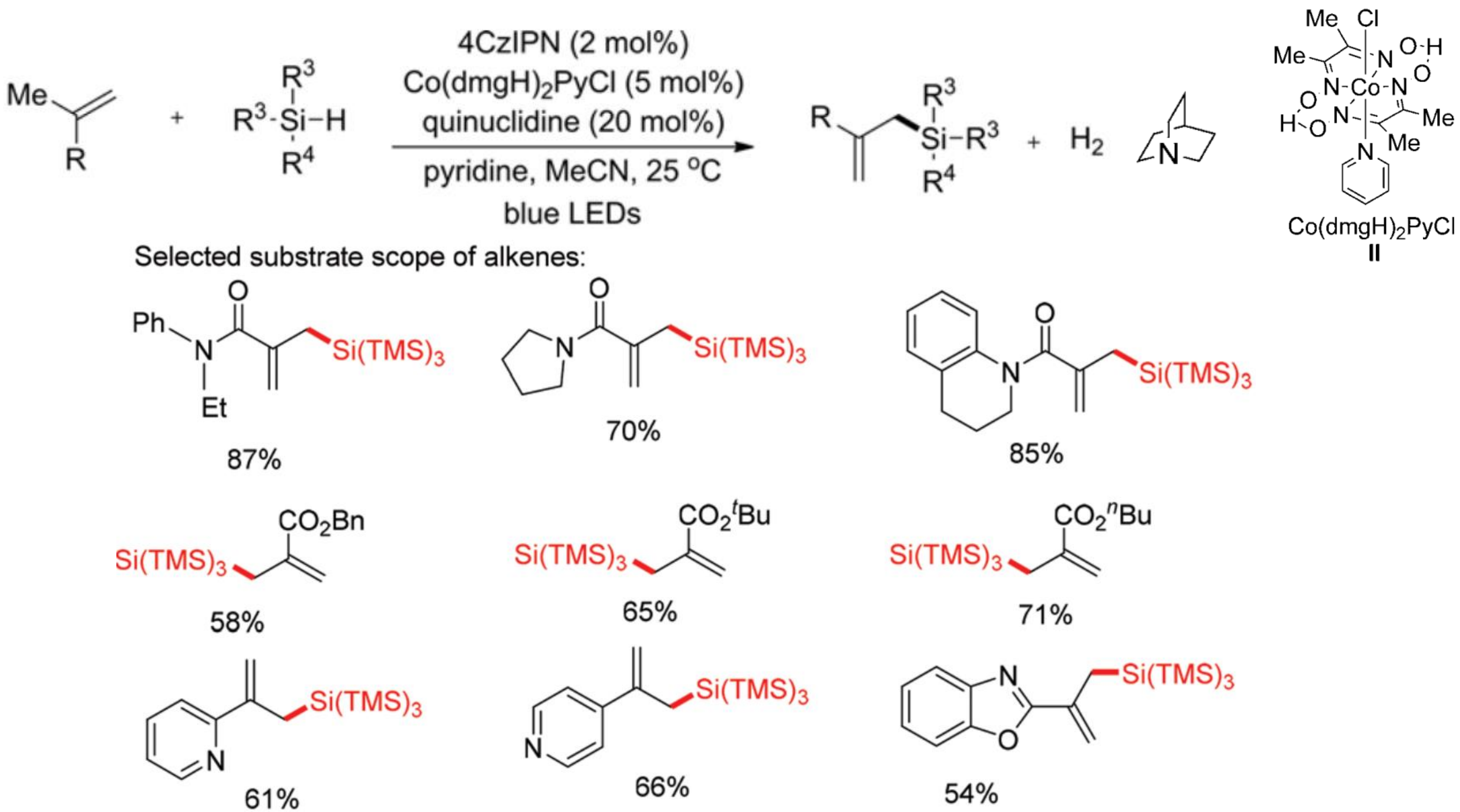
■ **Silacarboxylation of alkenes via HAT**



J. Wu, et. al. *Angew. Chem. Int. Ed.* **2018**, *57*, 17720.

Generation of silyl radicals from Si–H reagents

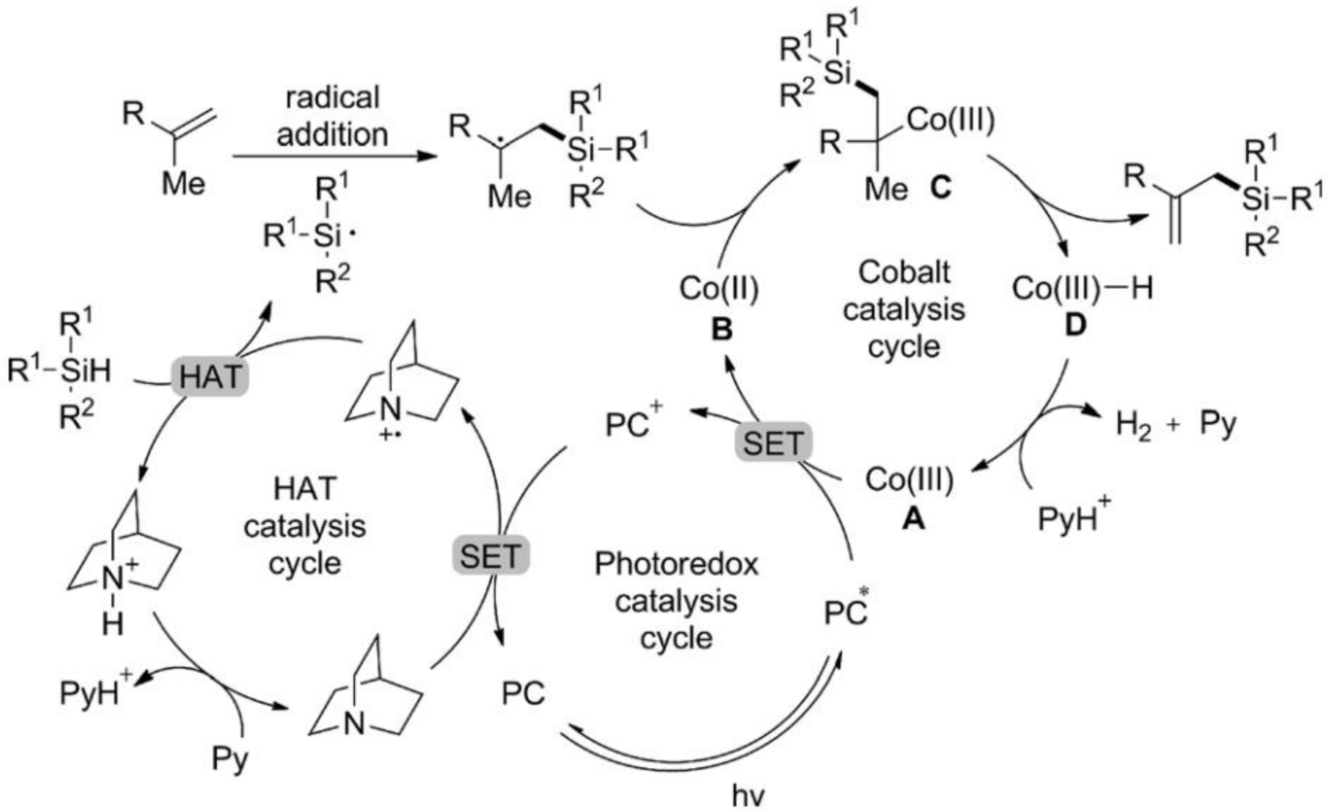
Dehydrogenative silylation of alkenes via HAT



P.-F. Xu, et. al. *Angew. Chem. Int. Ed.* **2019**, *58*, 10941.

Generation of silyl radicals from Si–H reagents

Dehydrogenative silylation of alkenes via HAT

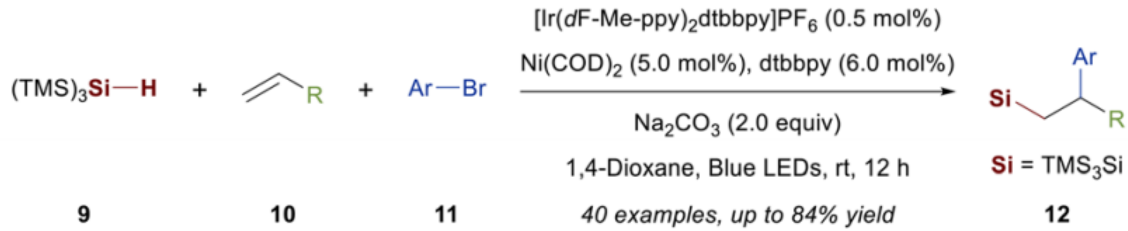


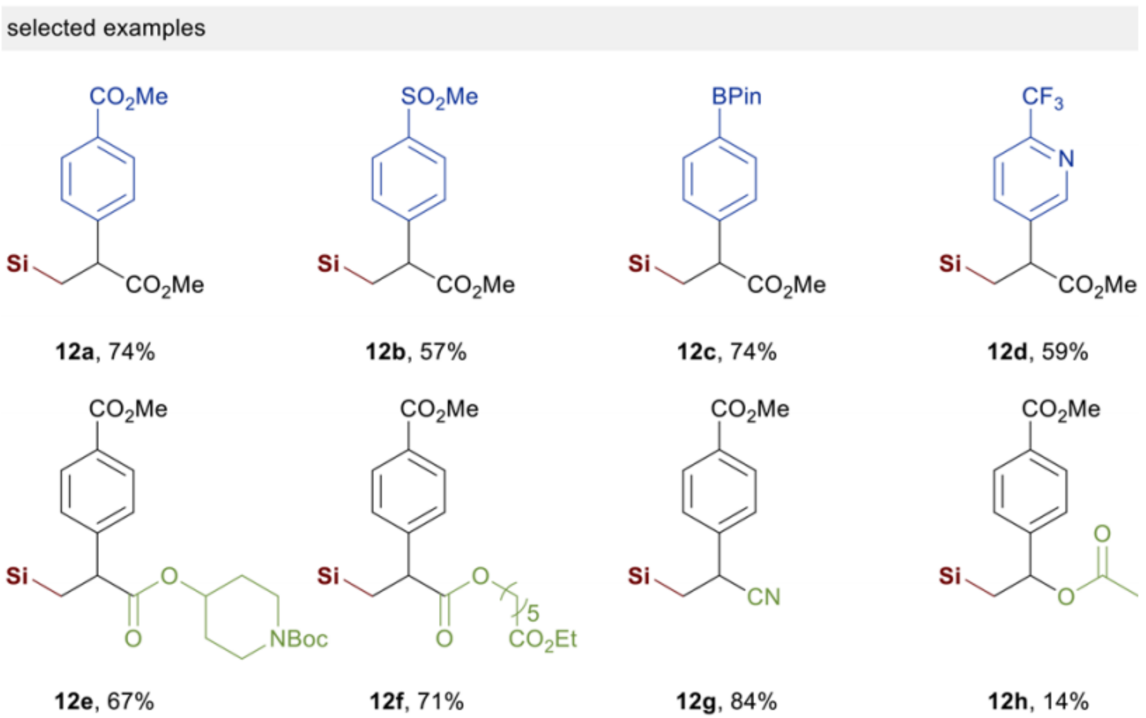
Scheme 3. A proposed mechanism.

P.-F. Xu, et. al. *Angew. Chem. Int. Ed.* **2019**, *58*, 10941.

Generation of silyl radicals from Si–H reagents

■ Arylsilylation of alkenes via HAT

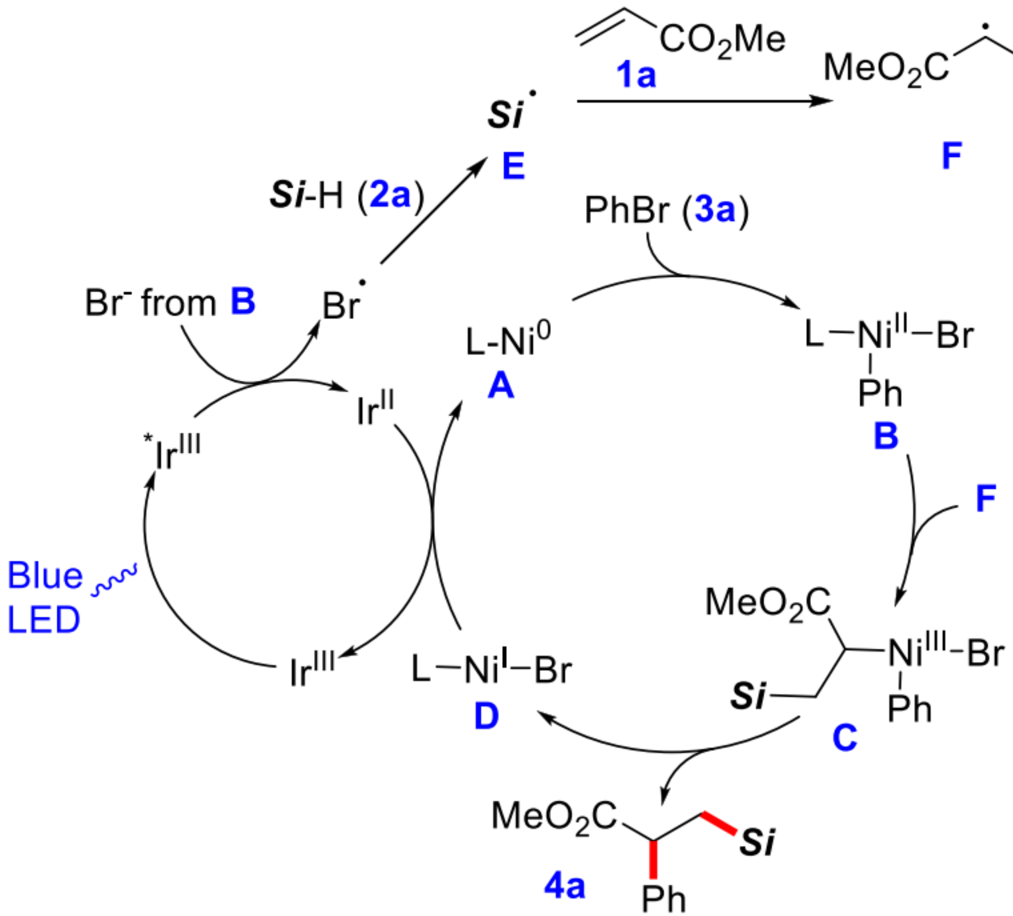




X.-L. Hu, et. al. *ACS Catal*. **2020**, *10*, 777.

Generation of silyl radicals from Si–H reagents

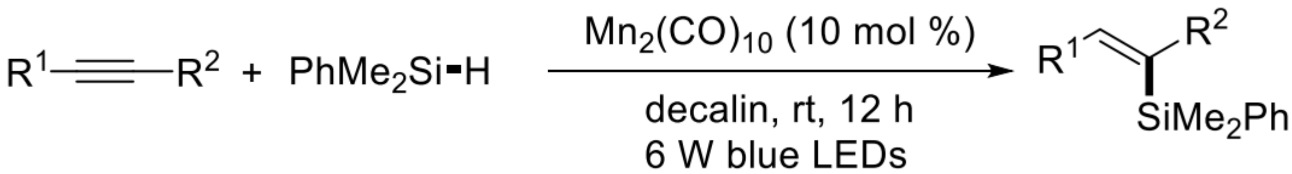
Arylsilylation of alkenes via HAT

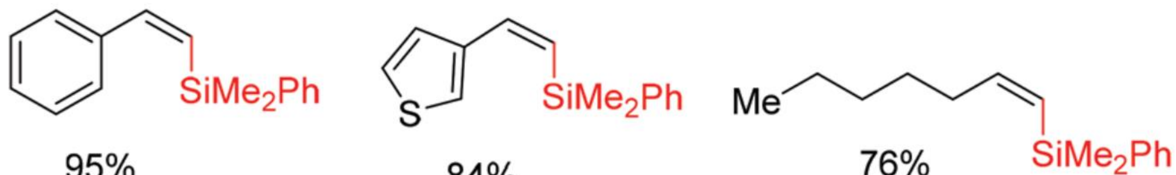


X.-L. Hu, et. al. *ACS Catal*. **2020**, *10*, 777.

Generation of silyl radicals from Si–H reagents

Hydrosilylation of alkynes via HAT

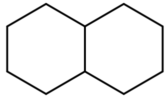




95% Z/E : > 99:1

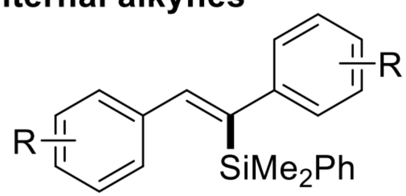
84% Z/E : > 99:1

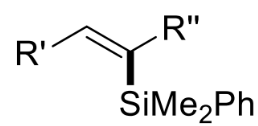
76% Z/E : = 93:7



decalin
十氢化萘

(b) Internal alkynes[c]





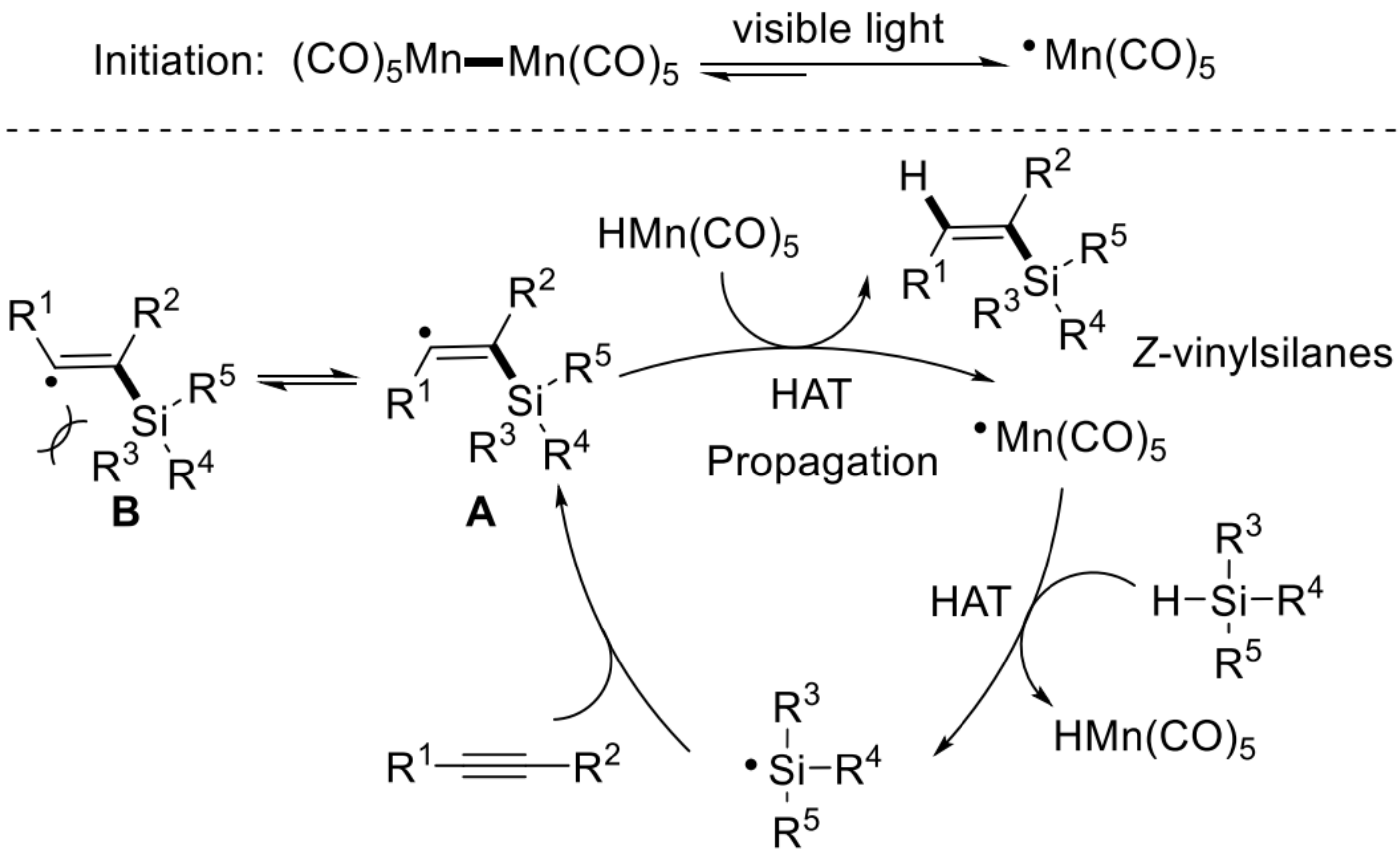
25, R = H, 95% (*Z*/*E* = 97:3)
26, R = 4-Me, 75% (*Z*/*E* > 99:1)
27, R = 4-F, 85% (*Z*/*E* = 95:5)
28, R = 3-Me, 71% (*Z*/*E* > 99:1)

29, R' = Ph, R" = Me, 82% (*Z*/*E* = 97:3)
30, R' = Ph, R" = Et, 81% (*Z*/*E* = 98:2)
31, R' = Ph, R" = *n*Pr, 90% (*Z*/*E* = 96:4)
32, R' = Et, R" = Et, 65% (*Z*/*E* = 98:2)

Z.-H. Zhang, B. Zhang, et. al. *Org. Lett.* **2019**, *21*, 2750.

Generation of silyl radicals from Si–H reagents

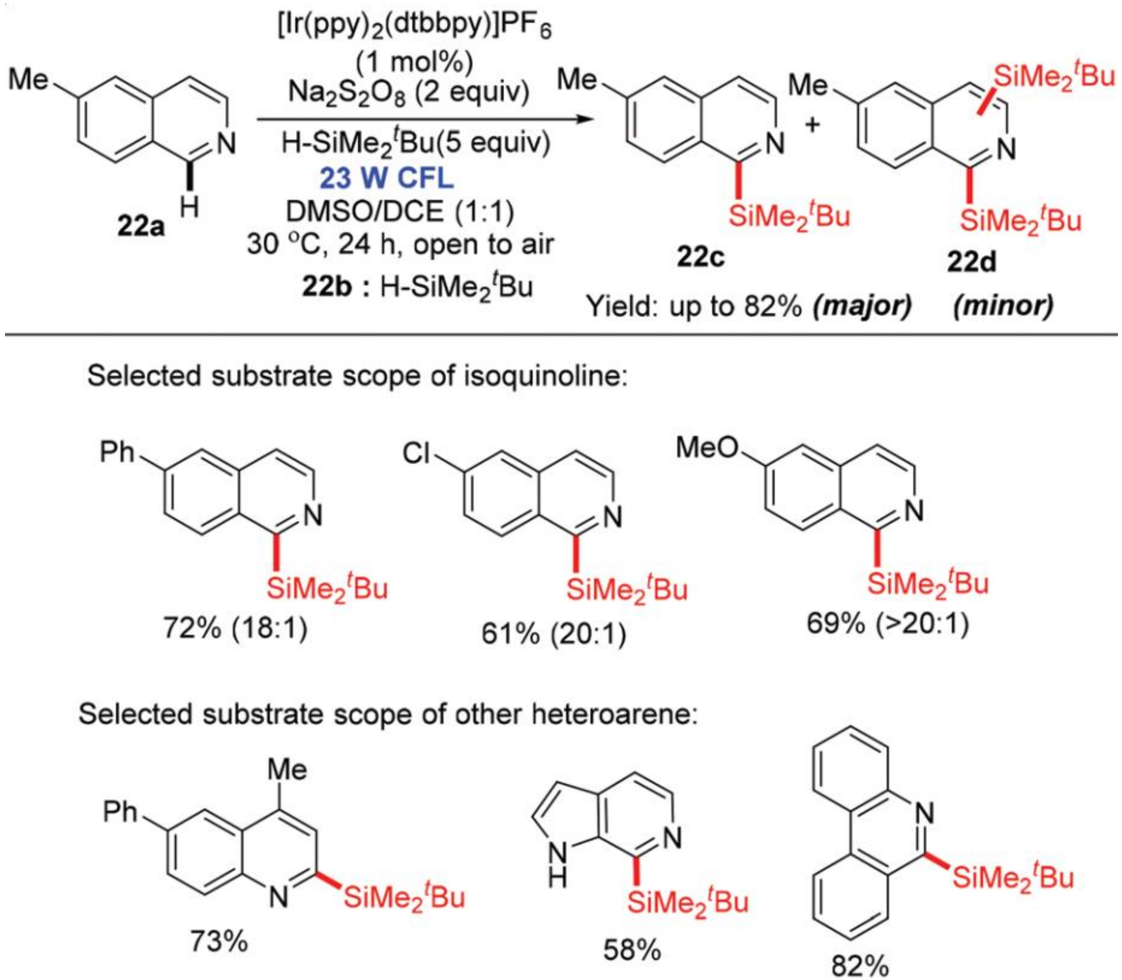
Hydrosilylation of alkynes via HAT



Z.-H. Zhang, B. Zhang, et. al. *Org. Lett.* **2019**, *21*, 2750.

Generation of silyl radicals from Si–H reagents

C–H silylation of heteroarenes via HAT



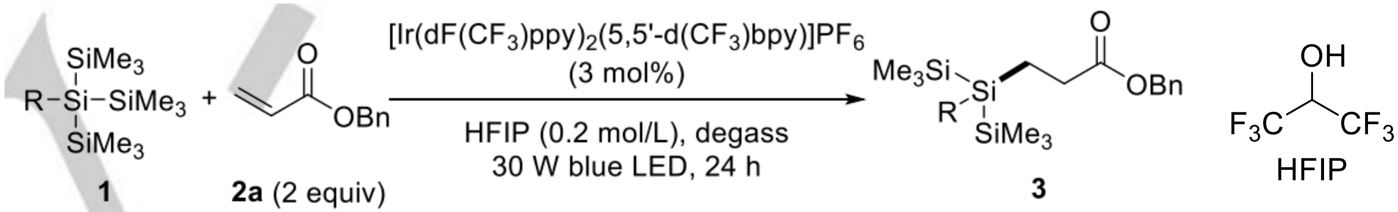
H. Li, W. Wang, Y.-Q. Zhang, et. al. *Chem. Sci.* **2019**, *10*, 3817.

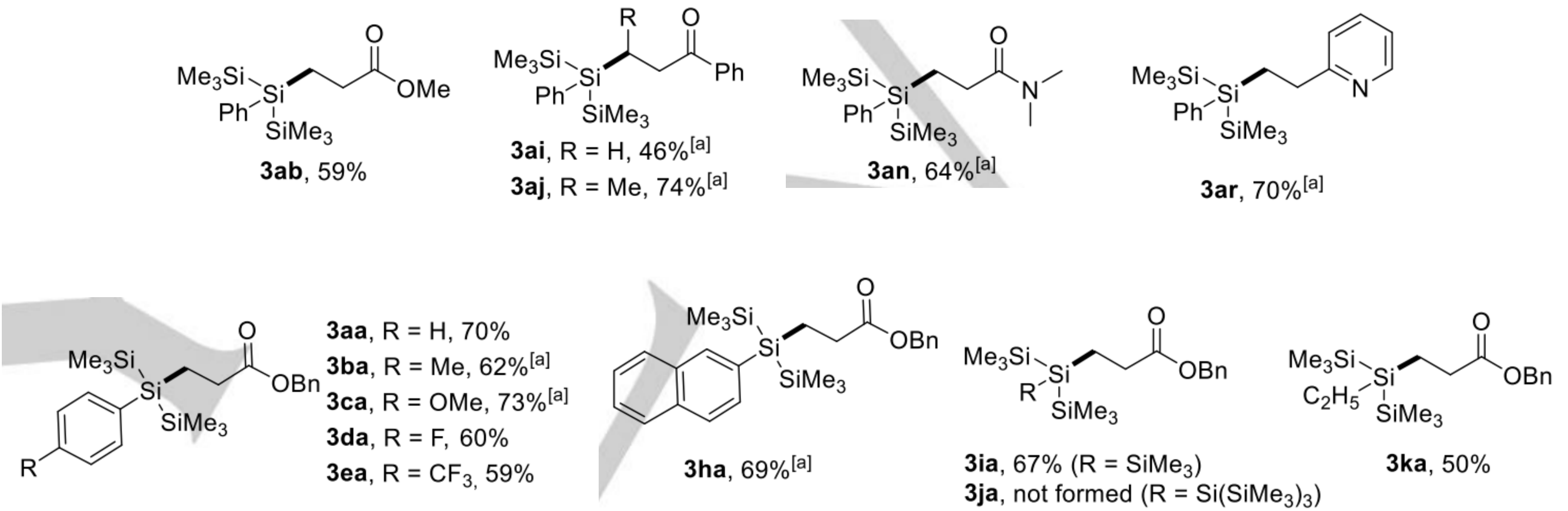
Outline

- Discovery of silyl radicals
- Generation of silyl radicals from Si–H reagents
- **Generation of silyl radicals from Si–Si reagents**
- Generation of silyl radicals from Si–CO_2H reagents

Generation of silyl radicals from Si–Si reagents

Hydrosilylation of alkenes via oxidative Si−Si bond cleavage

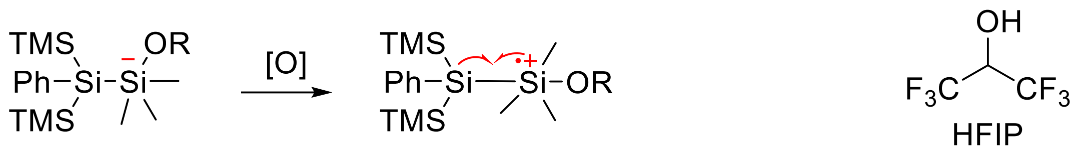


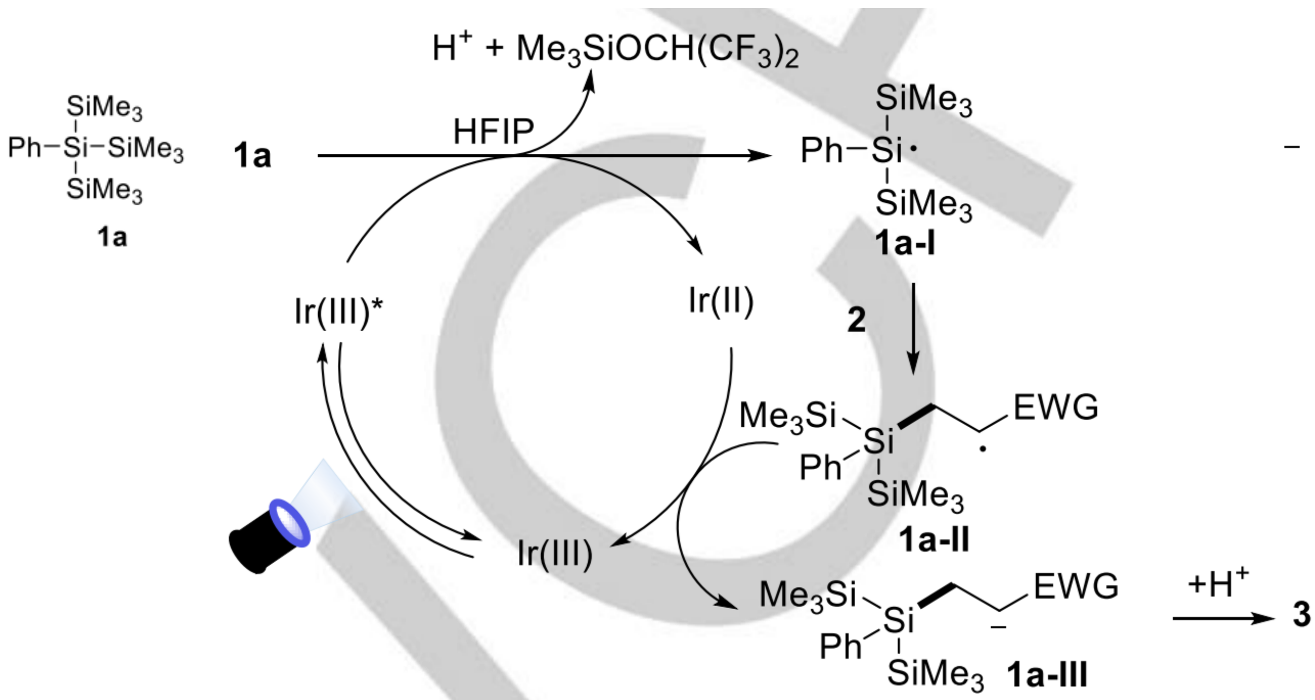


A. Studer, et. al. *Angew. Chem. Int. Ed.* **2021**, *60*, 675.

Generation of silyl radicals from Si–Si reagents

■ Hydrosilylation of alkenes via oxidative Si−Si bond cleavage

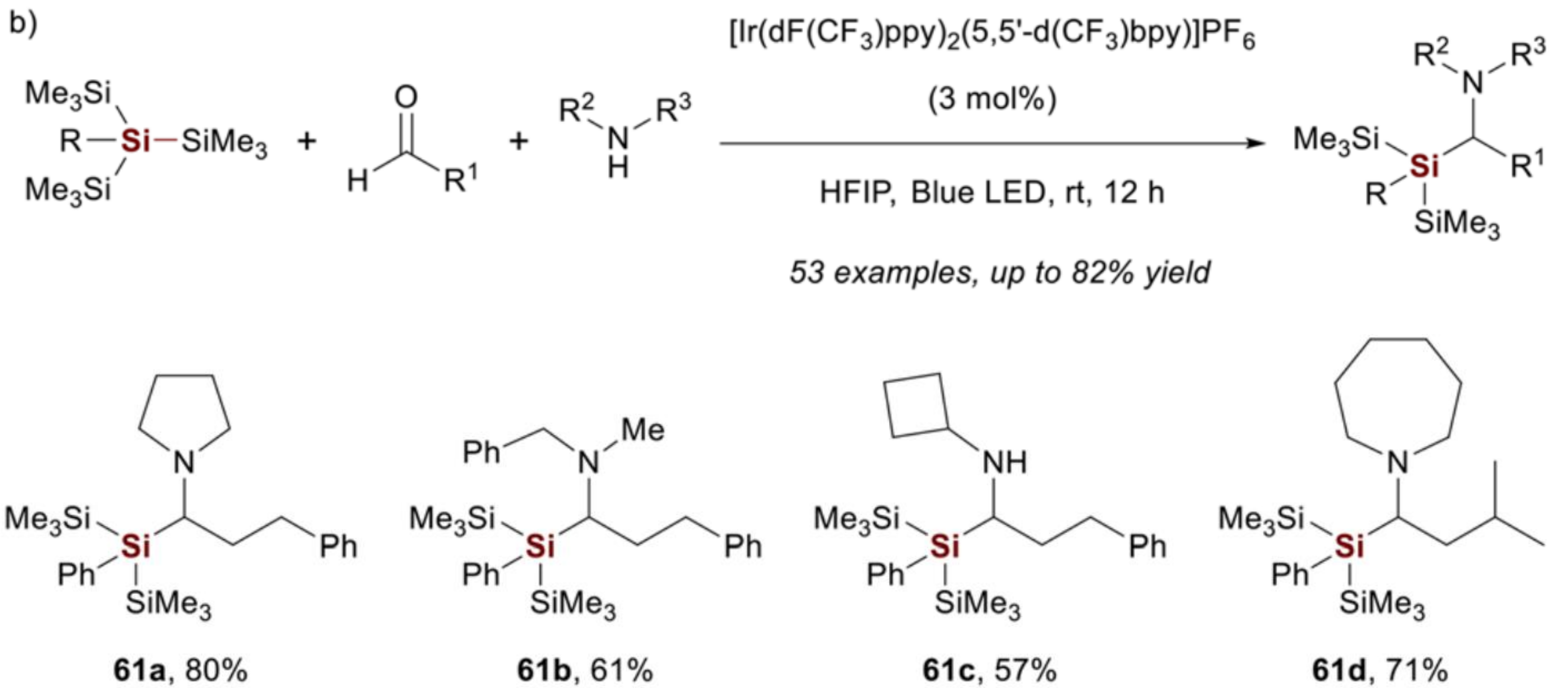




A. Studer, et. al. *Angew. Chem. Int. Ed.* **2021**, *60*, 675.

Generation of silyl radicals from Si–Si reagents

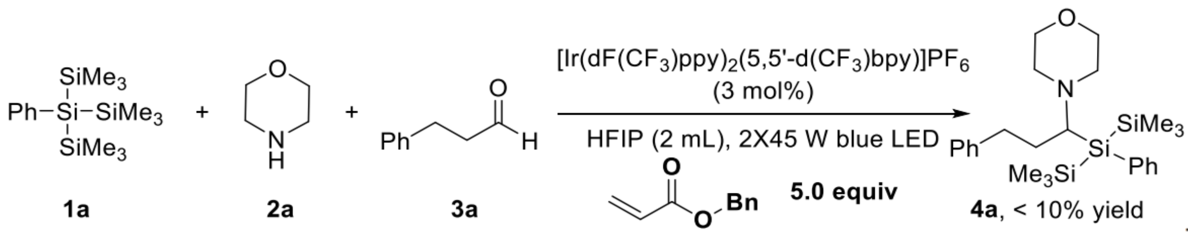
Hydrosilylation of imines via oxidative Si−Si bond cleavage

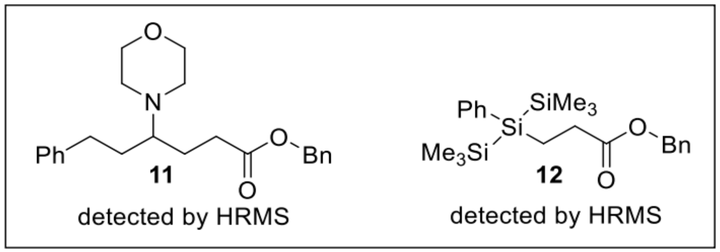


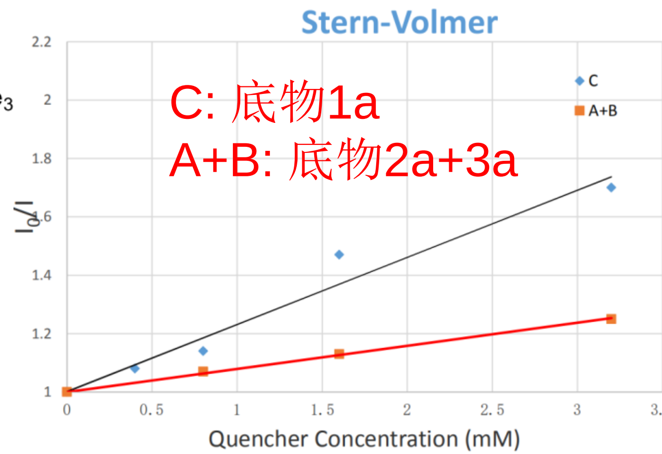
A. Studer, et. al. *Angew. Chem. Int. Ed.* **2021**, *60*, 23335.

Generation of silyl radicals from Si–Si reagents

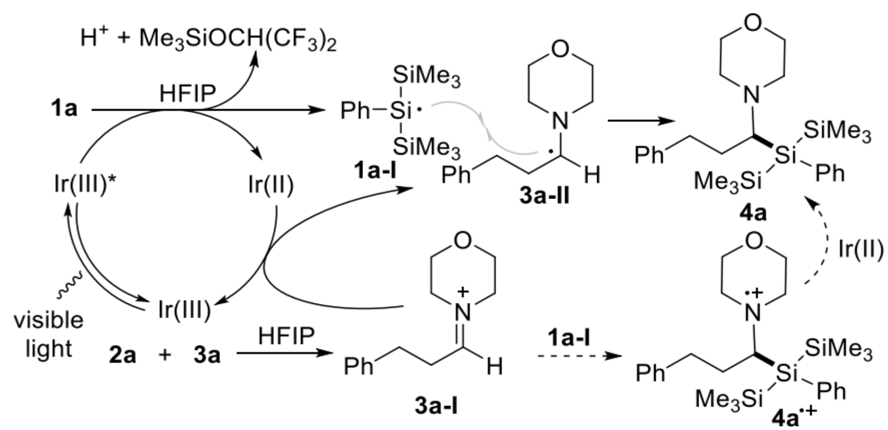
Hydrosilylation of imines via oxidative Si−Si bond cleavage







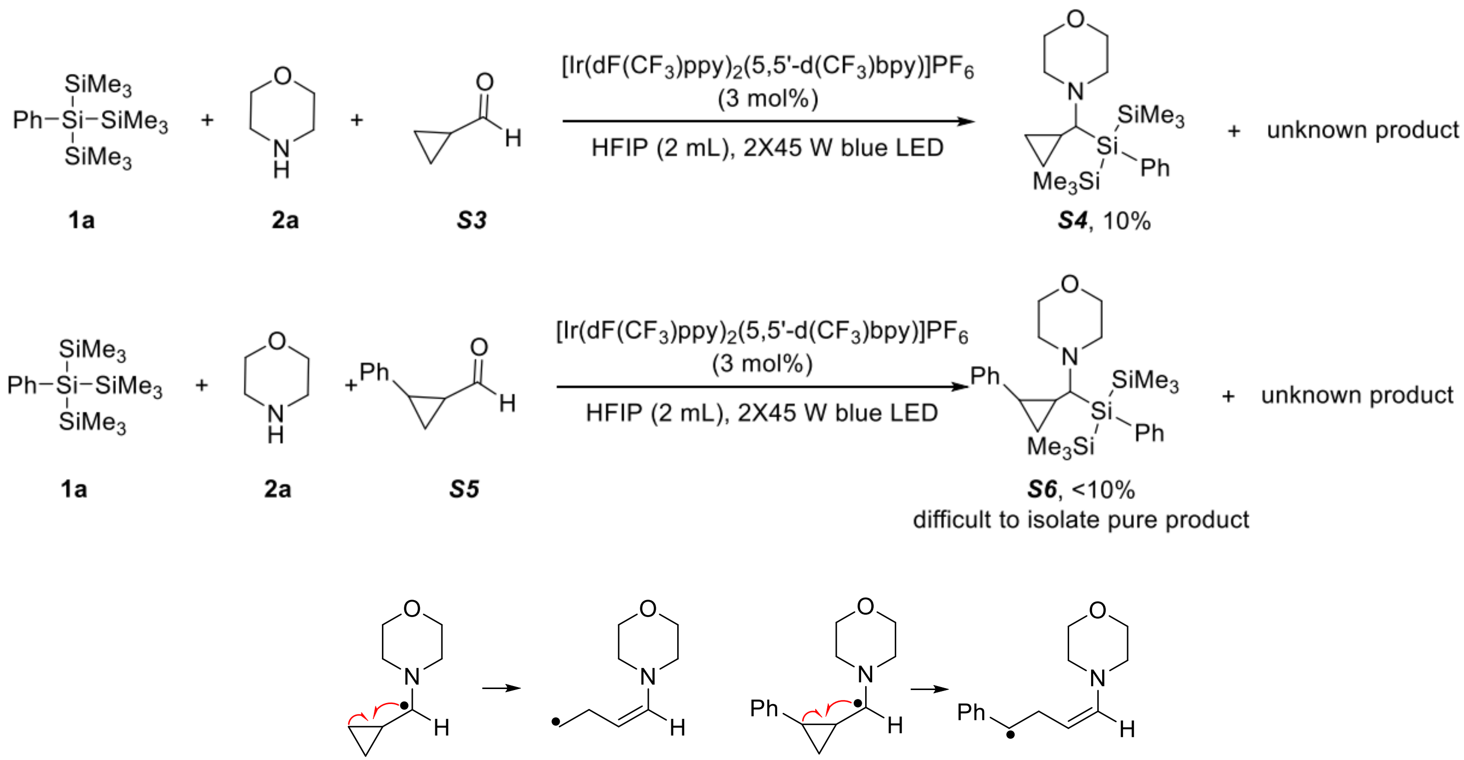
d) *Proposed mechanism*



A. Studer, et. al. *Angew. Chem. Int. Ed.* **2021**, *60*, 23335.

Generation of silyl radicals from Si–Si reagents

■ Hydrosilylation of imines via oxidative Si−Si bond cleavage



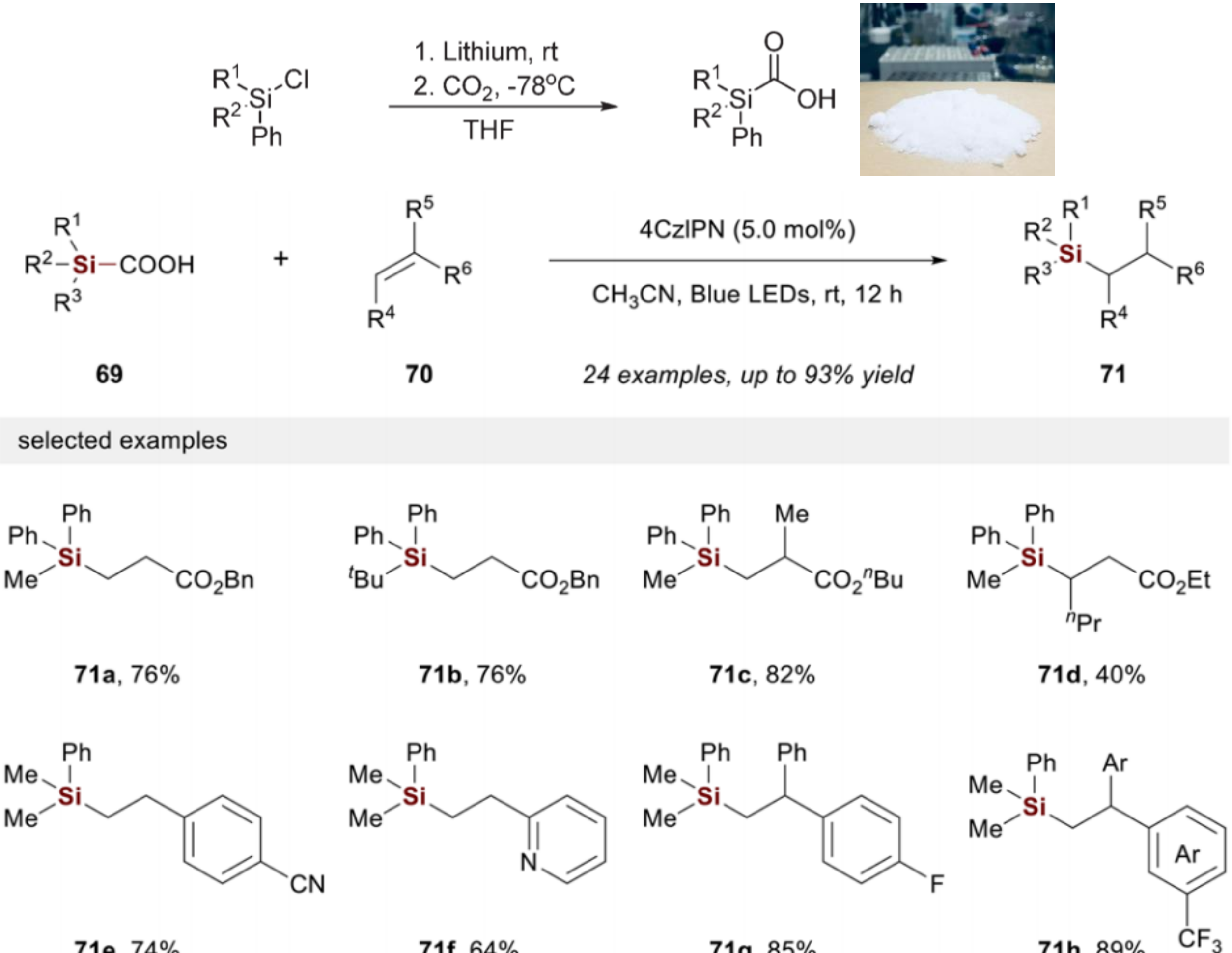
A. Studer, et. al. *Angew. Chem. Int. Ed.* **2021**, *60*, 23335.

Outline

- Discovery of silyl radicals
- Generation of silyl radicals from Si–H reagents
- Generation of silyl radicals from Si–Si reagents
- **Generation of silyl radicals from Si–CO_2H reagents**

Generation of silyl radicals from Si–CO_2H reagents

Hydrosilylation of alkenes via decarboxylation of silacarboxylic acids

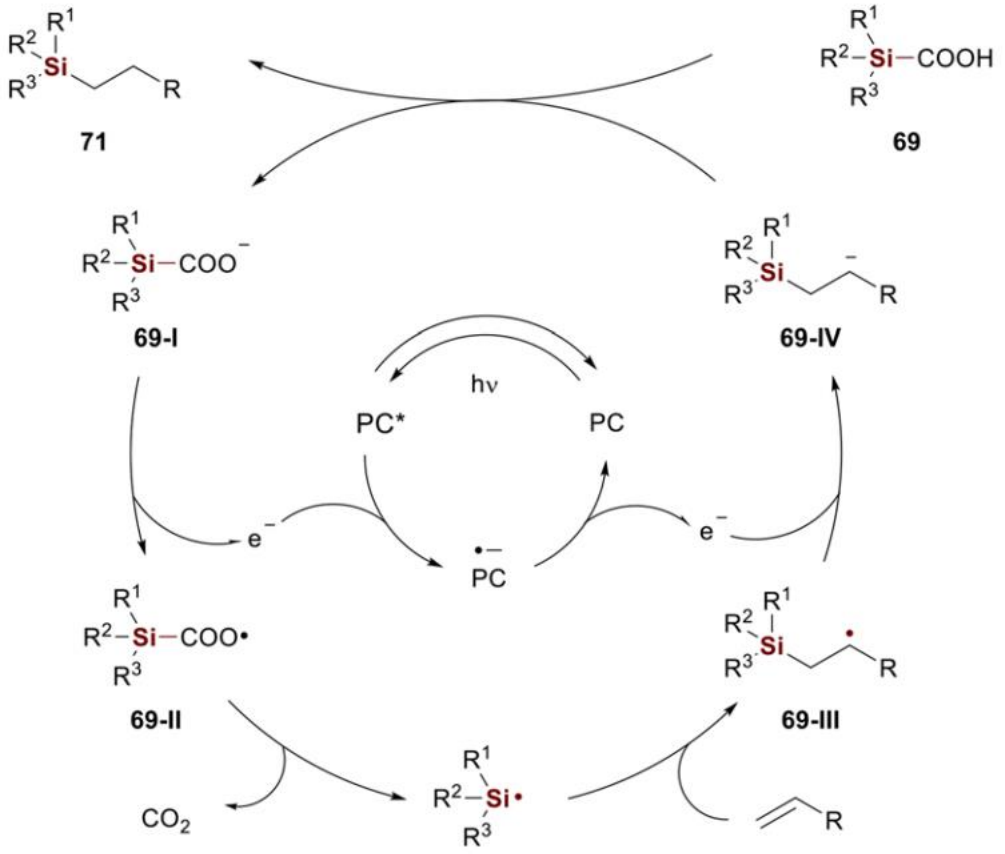


C. Wang, M. Uchiyama, et. al. *Angew. Chem. Int. Ed.* **2020**, *59*, 10629.

Generation of silyl radicals from Si–CO_2H reagents

■ **Hydrosilylation of alkenes via decarboxylation of silacarboxylic acids**

$E^{1/2}(PC^*/PC^{\bullet-}) = +1.35V$ $E^{1/2}(Ph_2MeSiCOO\bullet/Ph_2MeSiCOO^-) = +1.32V$



C. Wang, M. Uchiyama, et. al. *Angew. Chem. Int. Ed.* **2020**, *59*, 10629.

Seminal reviews

Reviews for boryl radicals

- **Lewis base-boryl radicals enabled borylation reactions and selective activation of carbon-heteroatom bonds**. Y.-F. Wang, et. al. *Acc. Chem. Res.* **2023**, *56*, 169.
- **Advances in chemistry of N-heterocyclic carbene boryl radicals**. T. Taniguchi, *Chem. Soc. Rev*. **2021**. *50*. 8995.
- **Boryl radical addition to multiple bonds in organic synthesis**. T. Taniguchi, *Eur. J. Org. Chem*. **2019**, *2019*, 6308.

Reviews for silyl radicals

- **Recent development of photo-mediated generation of silyl radicals and their application in organic synthesis**. J. Wu, et. al. *ChemPhotoChem*. **2018**, *2*, 839.
- **Recent advances in photo- and electro-enabled radical silylation**. C. He, *Org. Chem. Front.*, **2022**, *9*, 6400.

Conclusion and future prospects

- 杂原子自由基的产生条件越来越温和，其自由基前体越来越丰富；
- 探索新的杂原子自由基前体以及杂原子自由基受体；
- 如何实现烯烃的双官能团化，一步引入两个杂原子；
- 如何通过杂原子自由基中间体实现含杂原子的手性分子构建。