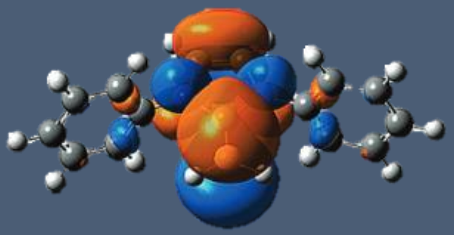
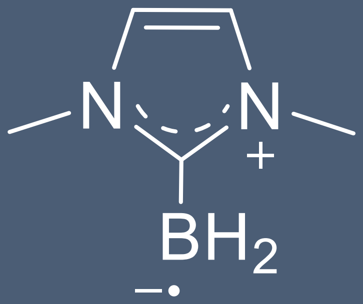
UNIVERSITY OF ILLINOIS URBANA-CHAMPAIGN

Lewis Base-Boryl Radical Enabled Reactions

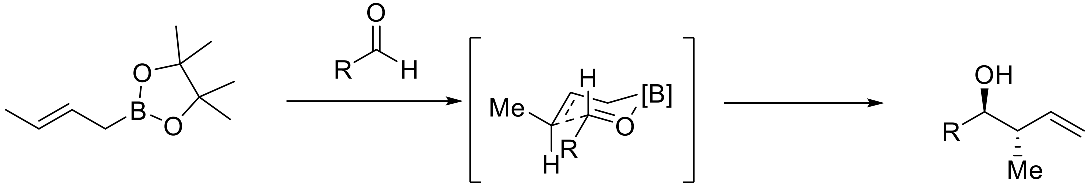


Blake Ocampo
February 21, 2023

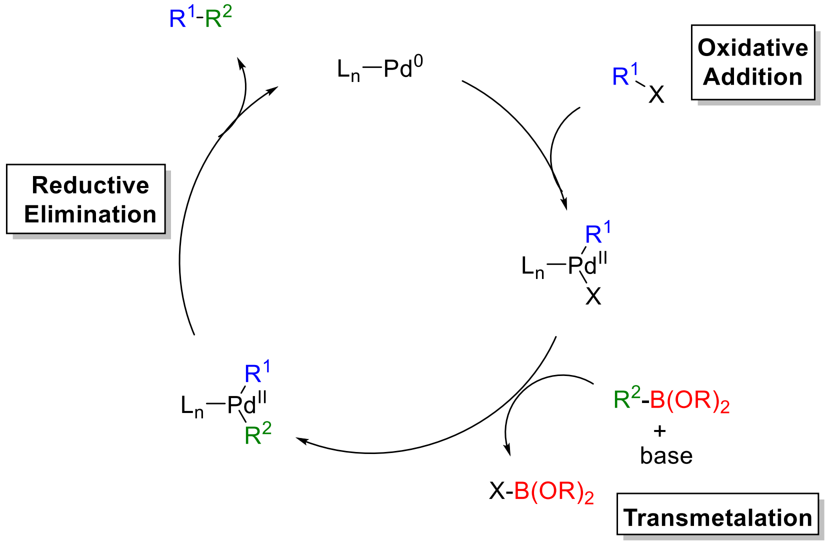


Classic Uses of Boron as a Lewis Acid

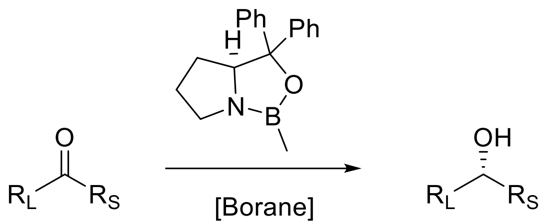
Allylation



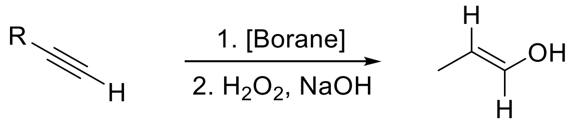
Suzuki Cross-Coupling



Reduction

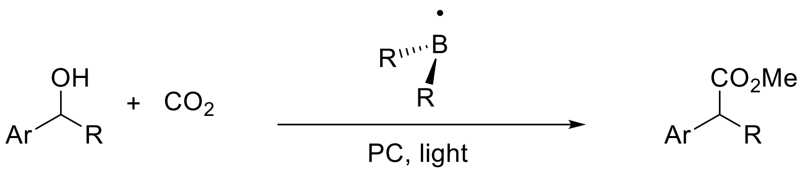


cis Hydroboration

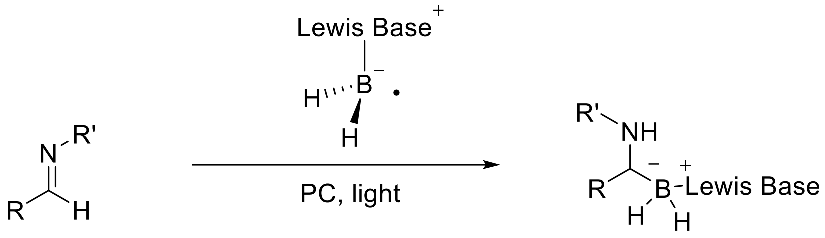


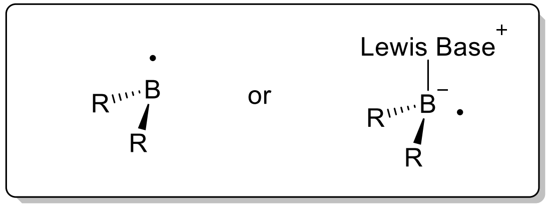
Why Care about Boryl Radicals?

Cross-Electrophile Coupling

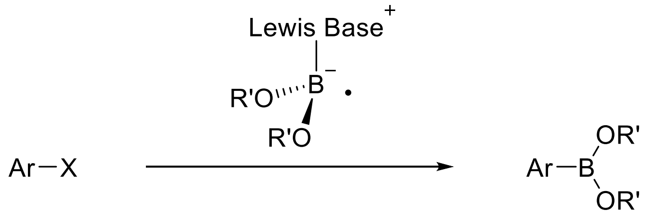


"Inverse" Hydroboration

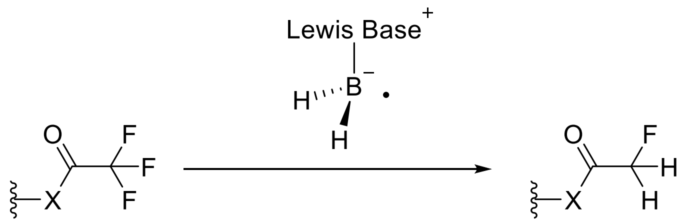




Radical Borylation of Arenes



Selective Dehalogenation of C-F bonds



Acc. Chem. Res. 2023, 56, 169–186

Outline

I. Initial Discovery of Stable Boryl-Radicals, Structural Features, and Early Reaction Rationalization

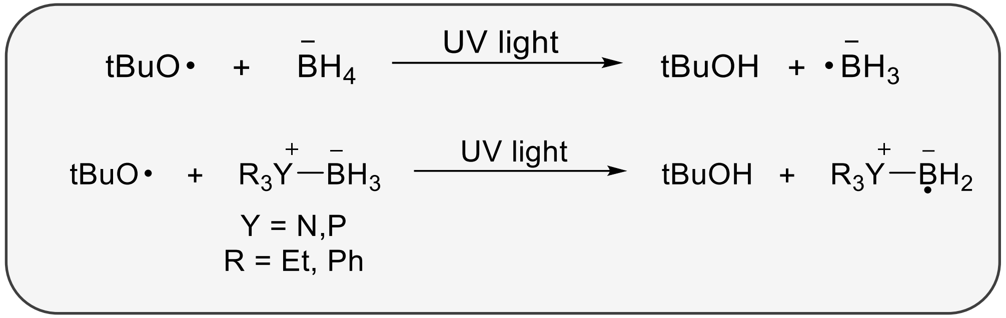
II. NHC-Borane complexes and Extension into Modern Applications

III. Non-NHC Borane Reactivities and other Modern Advances

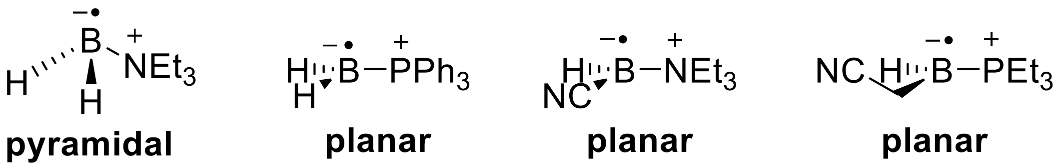
Acc. Chem. Res. **2023**, 56, 169–186

Initial Amine and Phosphine Boryl Radical Investigation

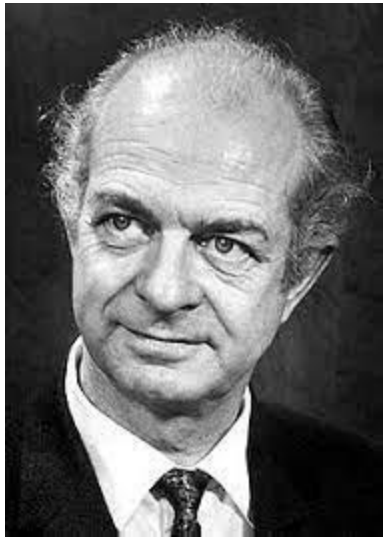
Roberts Studies 3 bond, 7 electron Boryl Radicals



EPR Result Suggested:



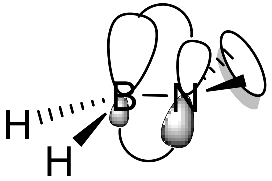
Rationalizing "Ideal" Radical Geometry With Carbon Radicals



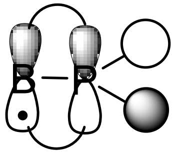
Linus Pauling

1. If $\chi_X = \chi_C$, energy minimized when bonding orbitals have the greatest energy (B(*sp*^{3}))
2. If $\chi_X < \chi_C$, energy minimized with more s character to the bonding orbitals (B(*sp*^{2}))
3. If $\chi_X > \chi_C$, energy minimized with more s character to the odd electron orbital (B(*sp*^{3}))

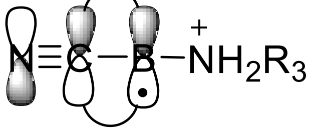
Some Key MO Interactions:



Filled B(SOMO) with Filled N(π), Reduced interaction when pyramidal



Filled B(SOMO) with lower energy P(π*), Better interaction when planar

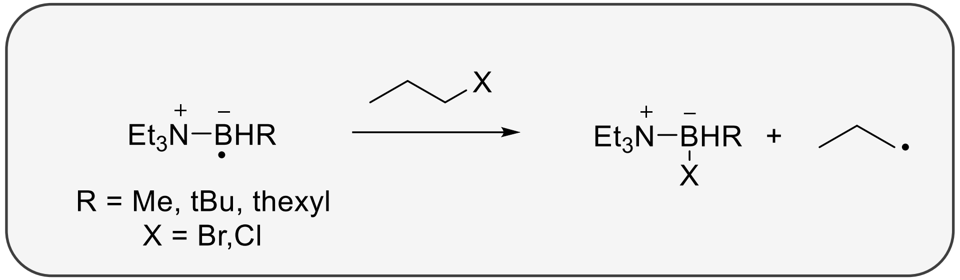


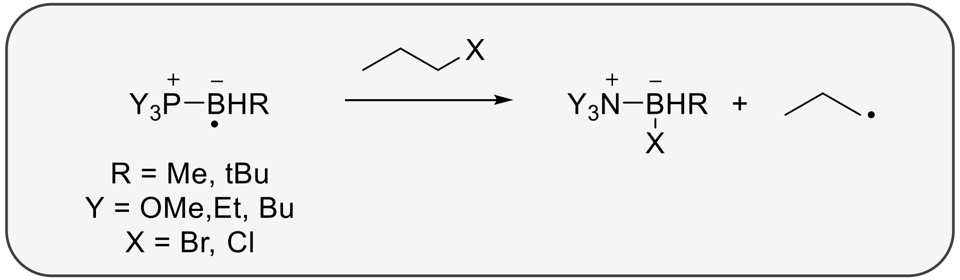
Filled B(SOMO) with lower energy CN(π*) Better interaction when planar

J. Chem. Soc., Chem. Commun., **1983**, 1224-1226
J. Chem. Phys. **1969**, 51, 2767

Reactivity of Amine and Phosphine Boryl Radicals

Halogen Atom Abstraction

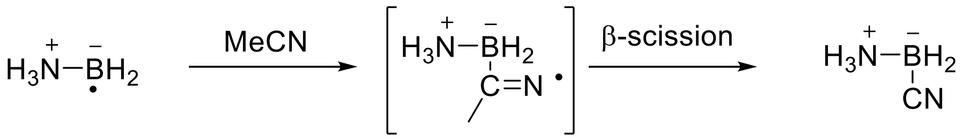


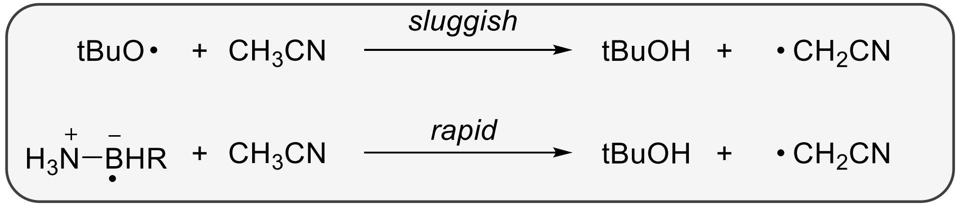


- ❖ Occurs at 173 K readily with substitution on borane
- ❖ Higher reactivity, close to 1:1 rate constant between tertiary and primary alkyl halide

- ❖ Significantly lower reactivity with Cl, even with borane substitution
- ❖ Higher selectivity for tertiary alkyl halides

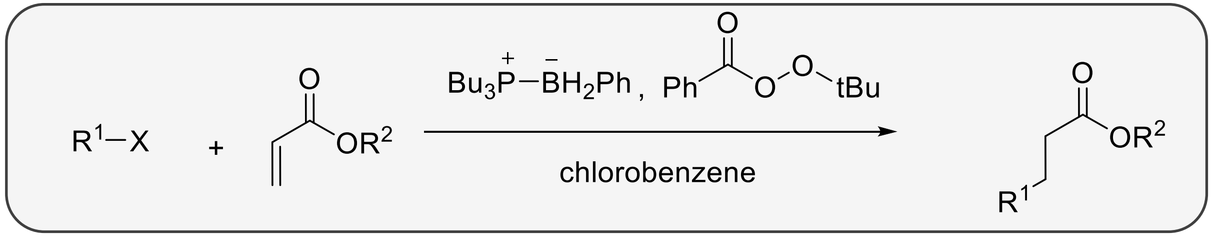
Nitrile Reactivity and Polarity Reversal

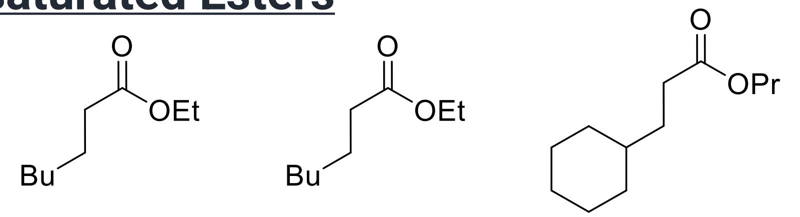




- ❖ Radical addition can occur with unsubstituted boranes
- ❖ An "electrophilic" radical is converted to "nucleophilic" radical

Addition of Alkyl Radicals into α,β-Unsaturated Esters



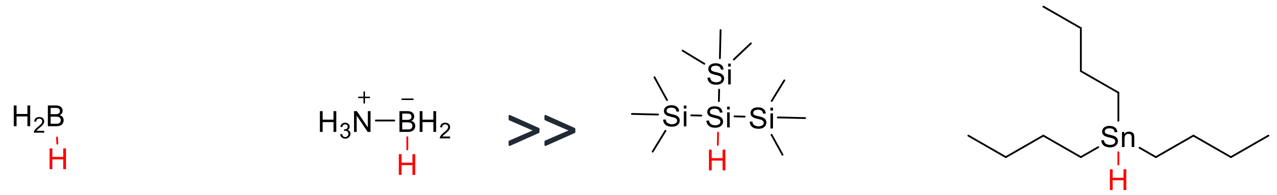


59% yield (X = I) | 25% yield (X =Br) | 44% yield (X = I)

J. Chem. Soc., Chem. Commun., **1983**, 1224-1226
J. Chem. Soc., Perkin Trans. **1988**, 2, 1183-1193
J. Chem. Soc., Perkin Trans. **1988**, 2, 1195-1200
Chem. Soc. Rev., **1999**, 28, 25–35

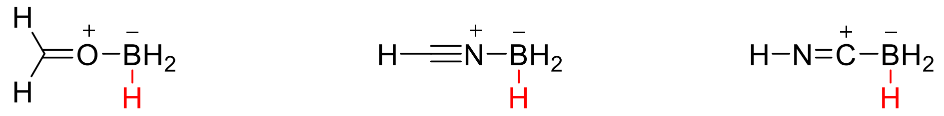
Why did Boryl Radicals Receive So Little Attention?

1. Ligated and non-ligated boranes had much higher BDEs than Sn and Si for radical hydrogen donors



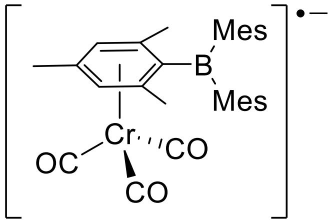
106.6 kcal/mol | 101 kcal/mol | 79 kcal/mol | 74 kcal/mol

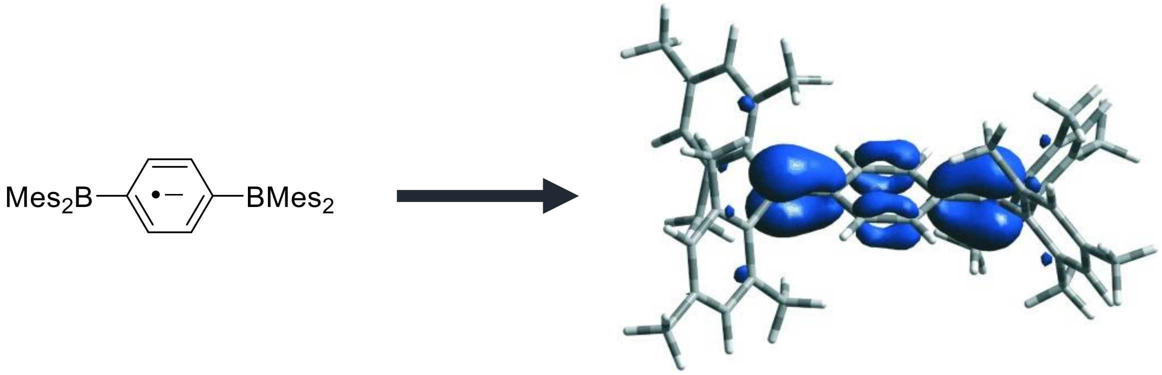
2. Calculations of structures with lower BDEs involved transitory compounds and reaction incompatibility



56.1 kcal/mol | 72.8 kcal/mol | 75.2 kcal/mol

3. Most work focused on boryl radicals from materials and computational perspectives

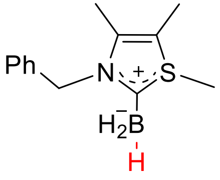




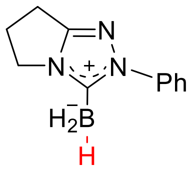
J. Am. Chem. Soc. **2008**, 130, 31, 10082-10083
Angew. Chem. Int. Ed. **2009**, 48, 28, 5082-5091
J. Am. Chem. Soc. **1997**, 119, 35, 8350-8360
Coord. Chem. Rev. **2017**, 352, 346-378
J. Am. Chem. Soc. **2010**, 132, 2350–2358

Expanding Boryl Radical Chemistry through NHCs

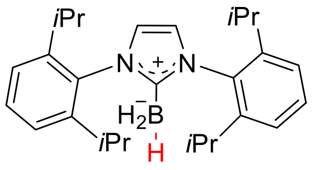
Calculation of B-H BDEs



74 kcal/mol



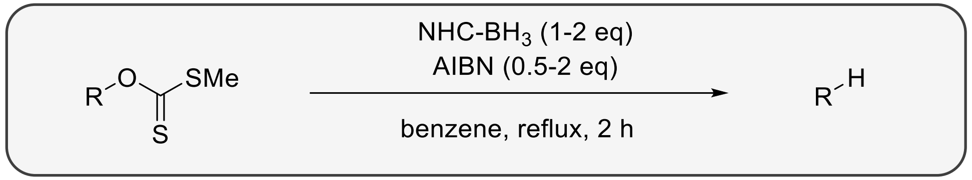
79 kcal/mol

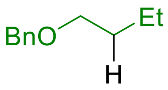


80 kcal/mol

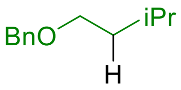
UB3LYP/LACVP* level

Curran Applies NHC-Borane to Xanthates

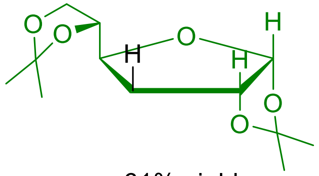




70% yield

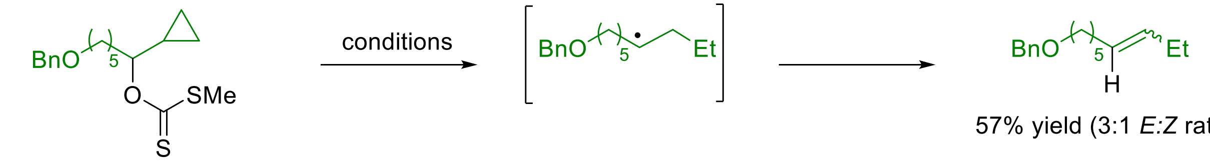


64% yield

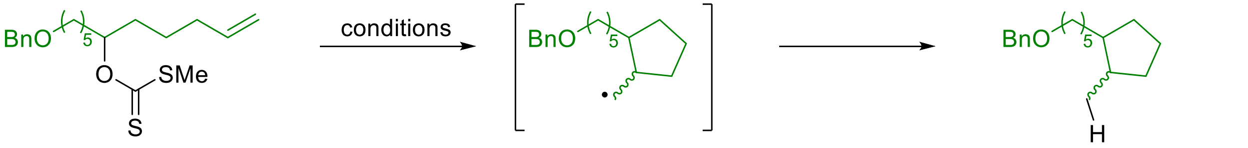


61% yield

Radical Clock Experiment



57% yield (3:1 *E:Z* ratio)

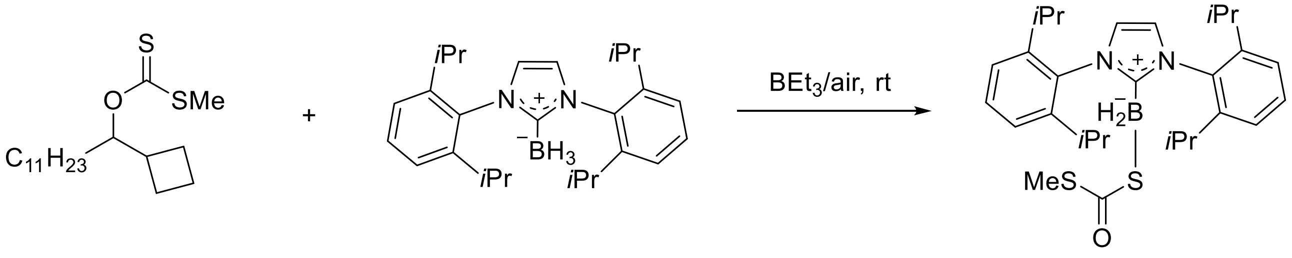


67% yield

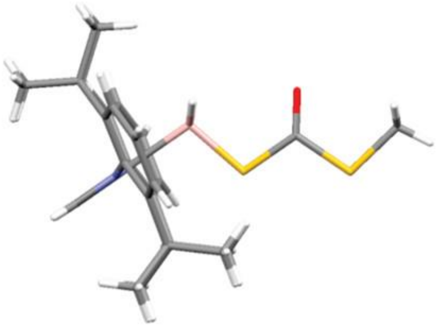
- NHC-Boranes are competent radical hydrogen atom donors
- Tunable ligands may be able to affect various reactivities

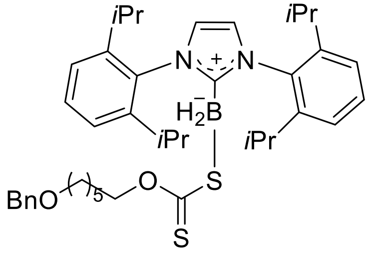
Evidence to Support a Radical Chain Mechanism

Isolated Compounds



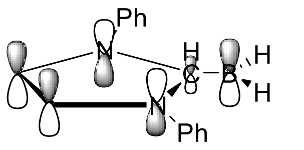
79% yield

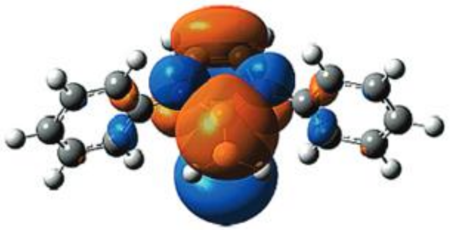




9% yield

Representative SOMO for NHC



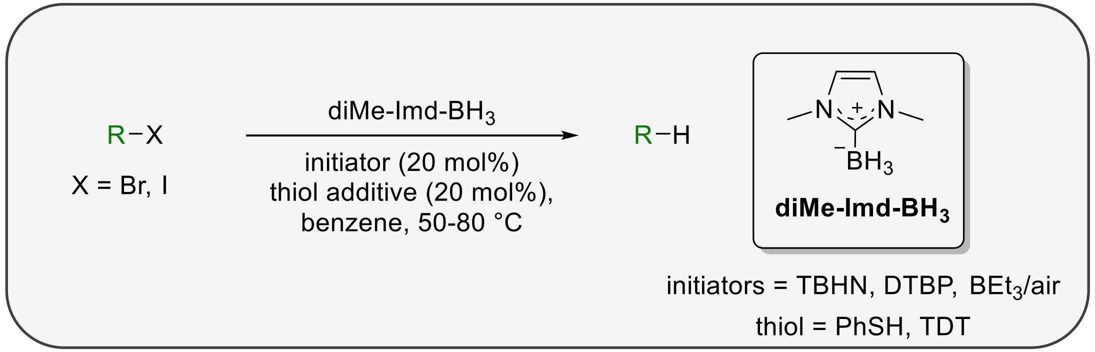


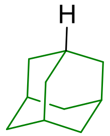
- Planar NHC boryl radical observed by EPR
- Xanthate Reduction determined to be $3.4 \times 10^4\ M^{-1}s^{-1}$
  - $(TMS)_3$Si-H = $3.9 \times 10^5\ M^{-1}s^{-1}$
  - Bu_3Sn-H = $9 \times 10^6\ M^{-1}s^{-1}$
  - Et_3Si-H = $6.4 \times 10^2\ M^{-1}s^{-1}$

J. Am. Chem. Soc. **2008**, 130, 31, 10082-10083
J. Am. Chem. Soc. **2009**, 131, 31, 11256-11262

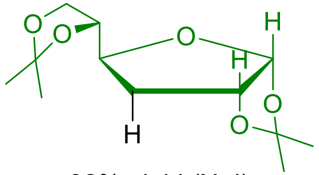
Extend Reactivity to Simple Alkyl and Aryl Halides

Curran Utilizes Thiol Additives

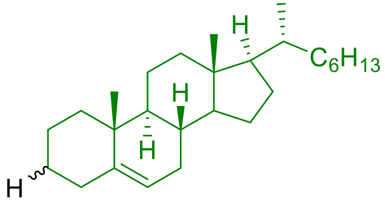




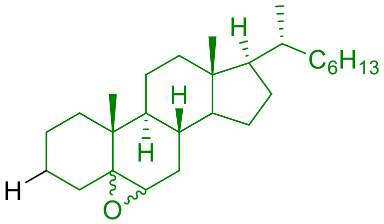
97% yield (X=Br)
92% yield (X=I)



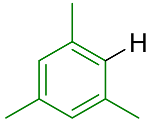
82% yield (X=I)



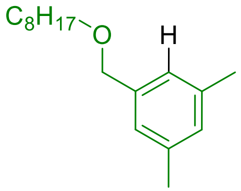
96% yield (X=Br)
95% yield (X=I)



96% yield (X=Br)

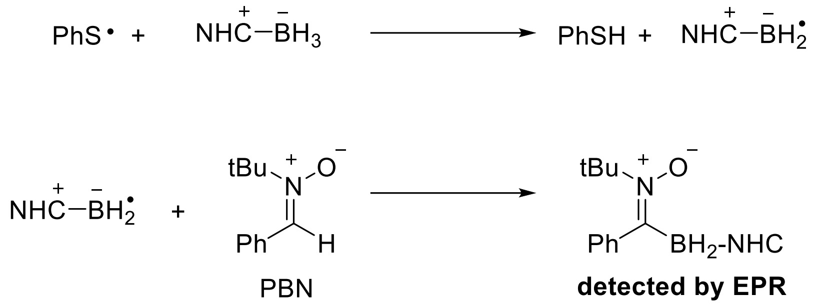


96% yield (X=Br)



86% yield (X=Br)
82% yield (X=I)

Spin Trapping For Hydrogen Transfer



Suggested Propagation Steps

$$\mathrm{NHC\overset{+}{}\!-\!\overset{-}{B}H_2^{\bullet}} + R{-}X \xrightarrow{k_1 > 10^5} \mathrm{NHC\!-\!BH_2X} + R^{\bullet}$$

$$\mathrm{NHC\!-\!BH_3} + R^{\bullet} \xrightarrow{k_2 < 10^5} \mathrm{NHC\!-\!BH_2^{\bullet}} + R{-}H$$

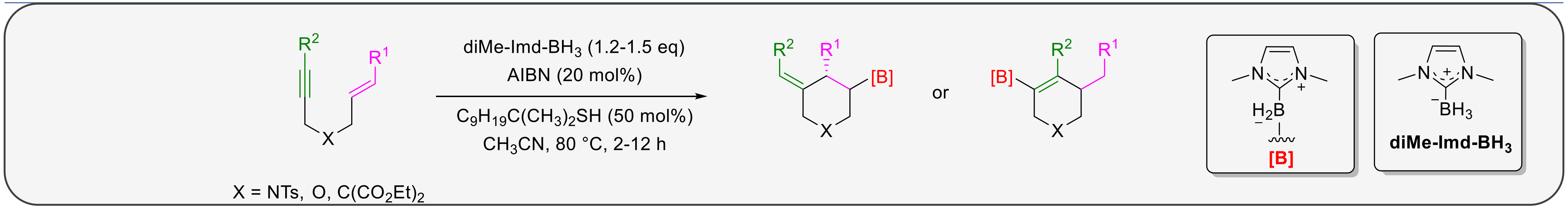
$$\mathrm{PhSH} + R^{\bullet} \xrightarrow{k_3 \approx 10^8} \mathrm{PhS^{\bullet}} + R{-}H$$

$$\mathrm{PhS^{\bullet}} + \mathrm{NHC\!-\!BH_3} \xrightarrow{k_4 = 1.2 \times 10^8} \mathrm{PhSH} + \mathrm{NHC\!-\!BH_2^{\bullet}}$$

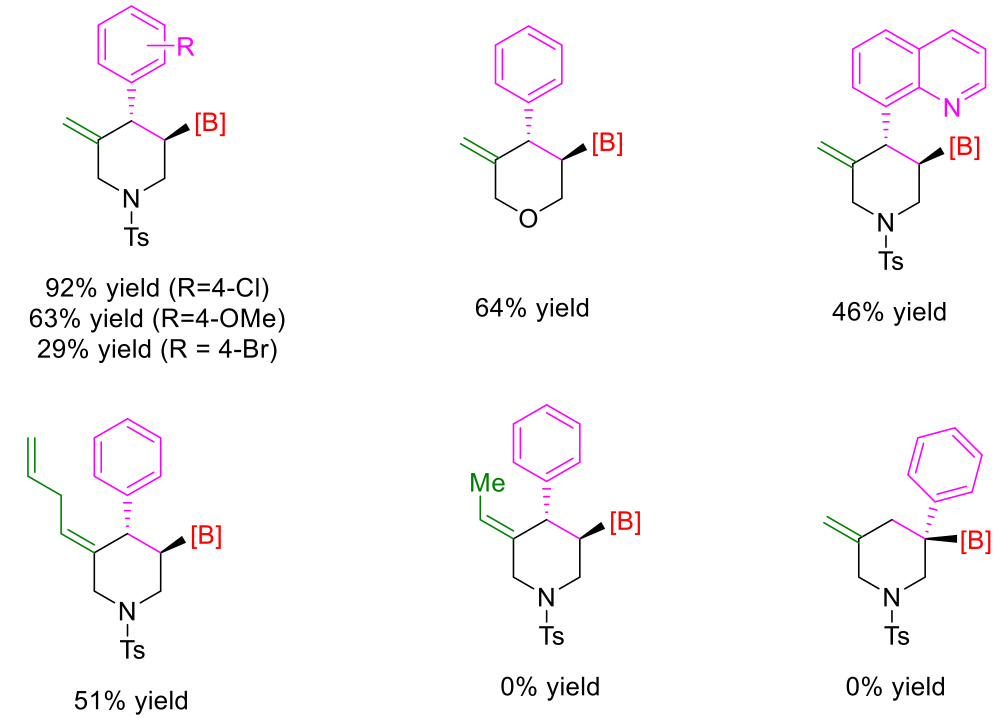
- ❖ Thiol accelerates radical HAT
- ❖ This is still however a thermodynamically unfavorable process

J. Am. Chem. Soc. **2010**, 132, 2350
Angew. Chem. **2008**, 120, 7538-7542
J. Am. Chem. Soc. **2012**, 134, 5669-5674

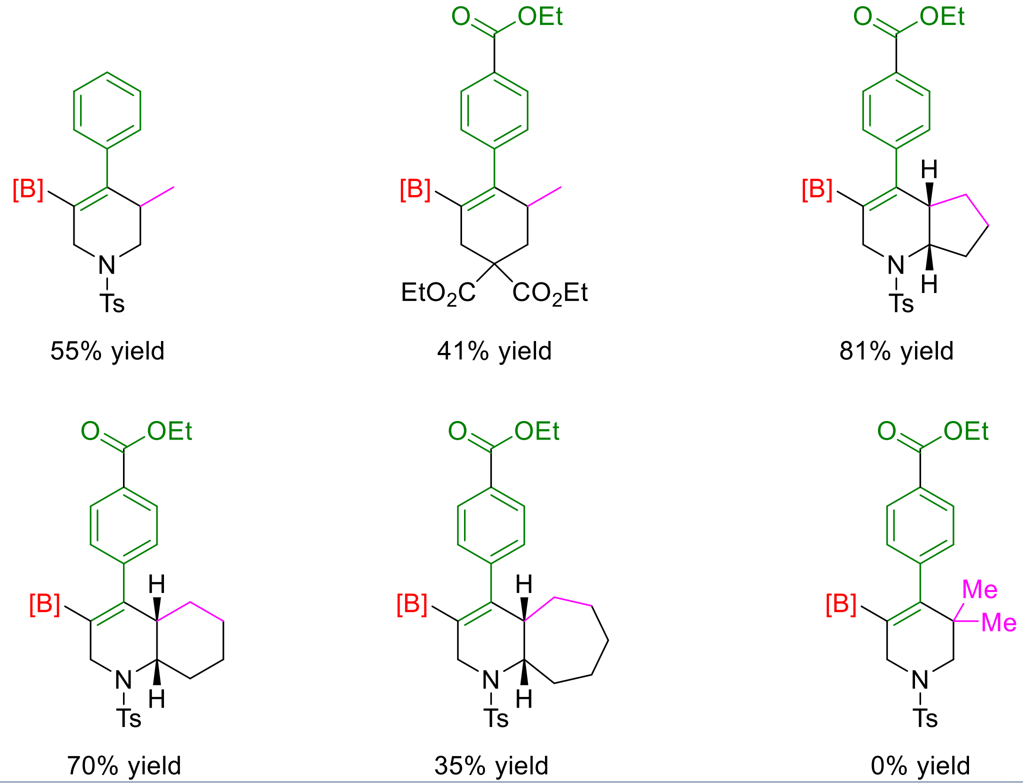
Wang Utilizes Thiol Catalysis for Borylation/Cyclization



Alkene Radical Initiated



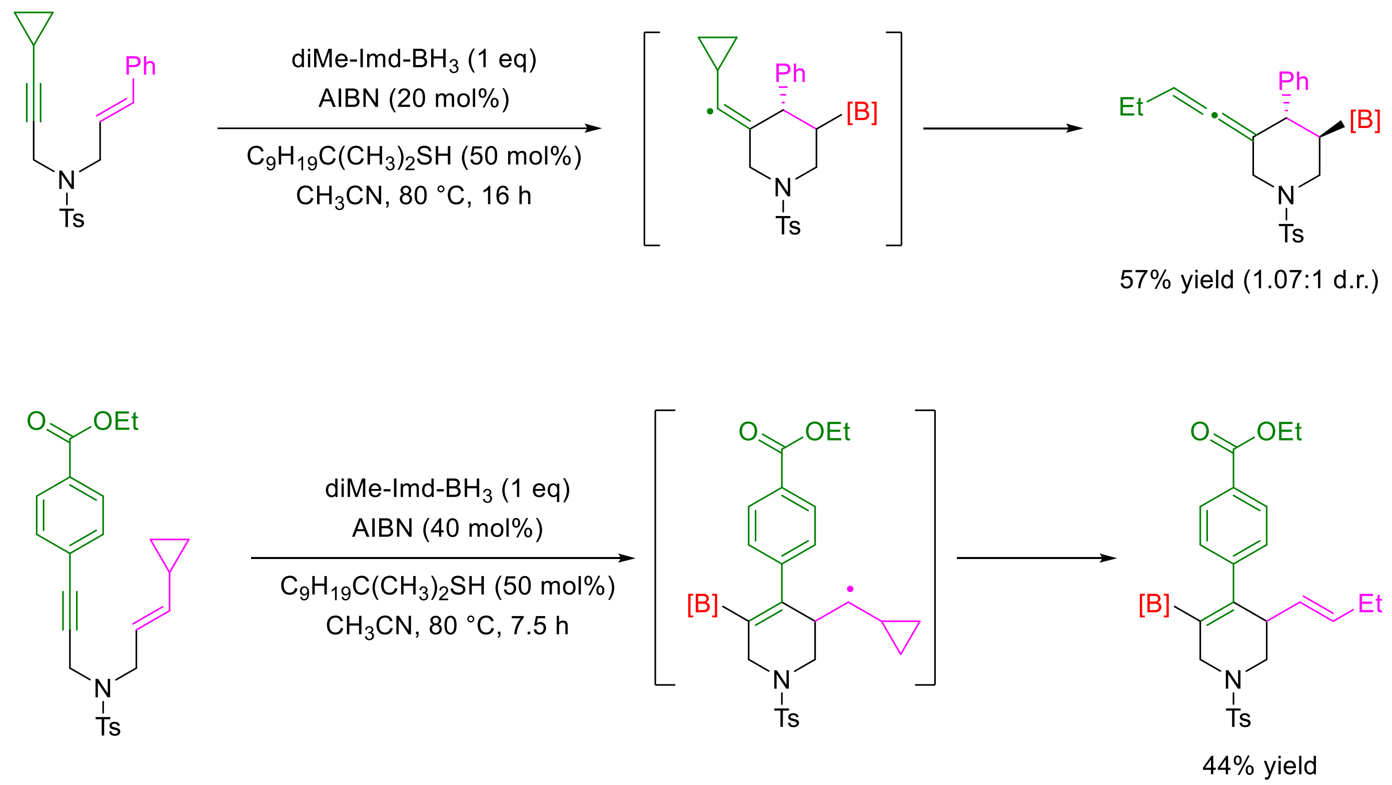
Alkyne Radical Initiated



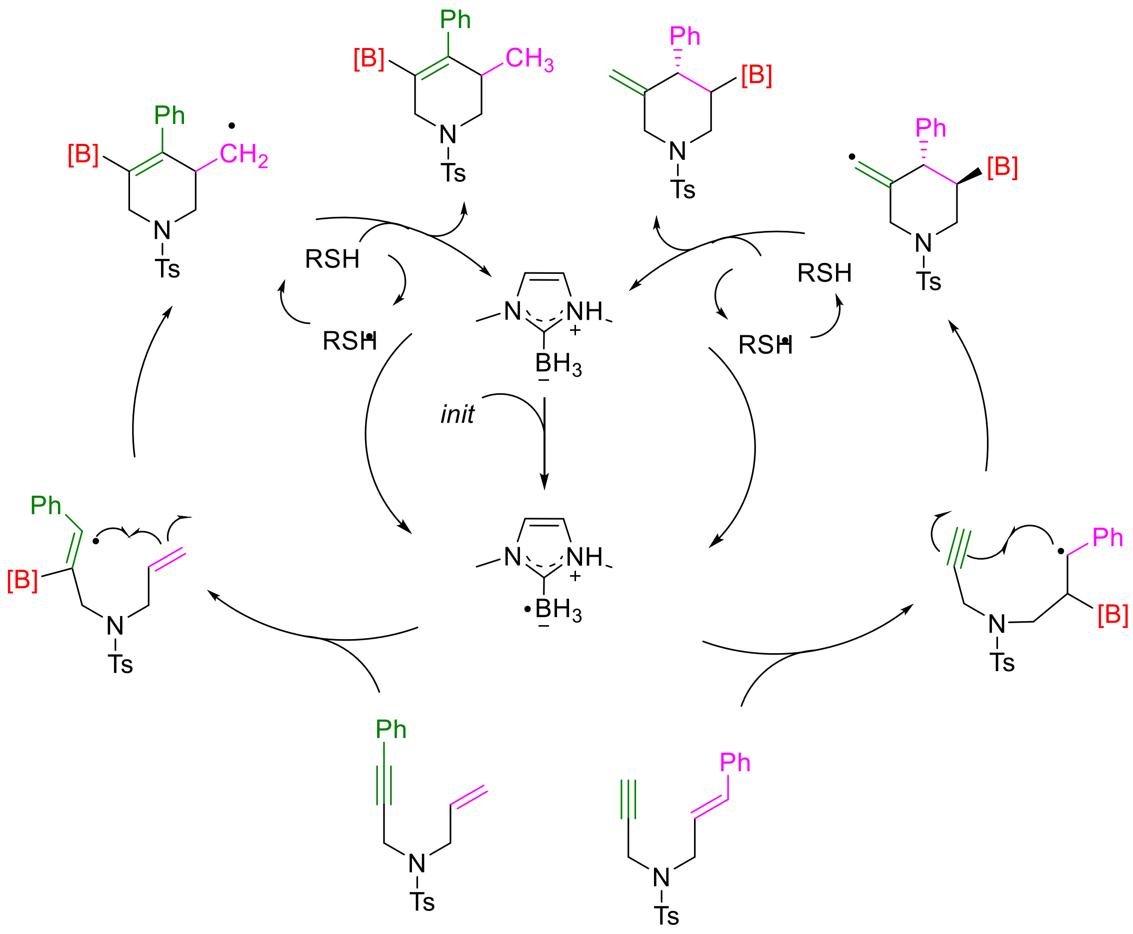
J. Am. Chem. Soc. **2017**, 139, 6050-6053

Borylation/Cyclization Mechanism

Radical Clock Experiments



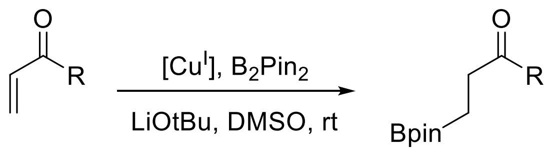
Proposed Mechanism



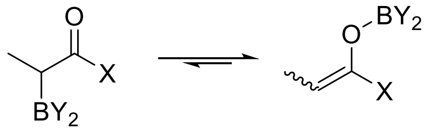
α-borylation of unsaturated esters

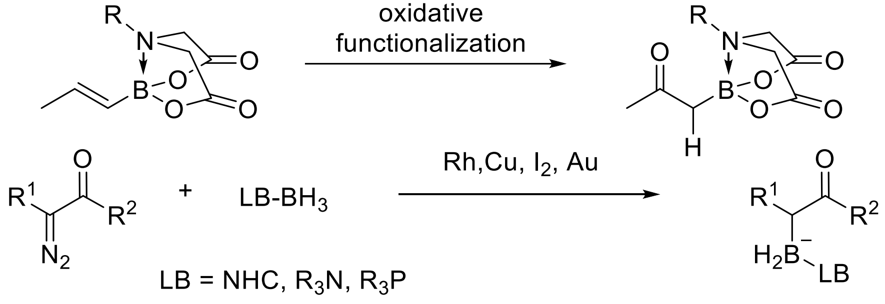
Comparing α vs. β borylation

Oestrich β-borylation



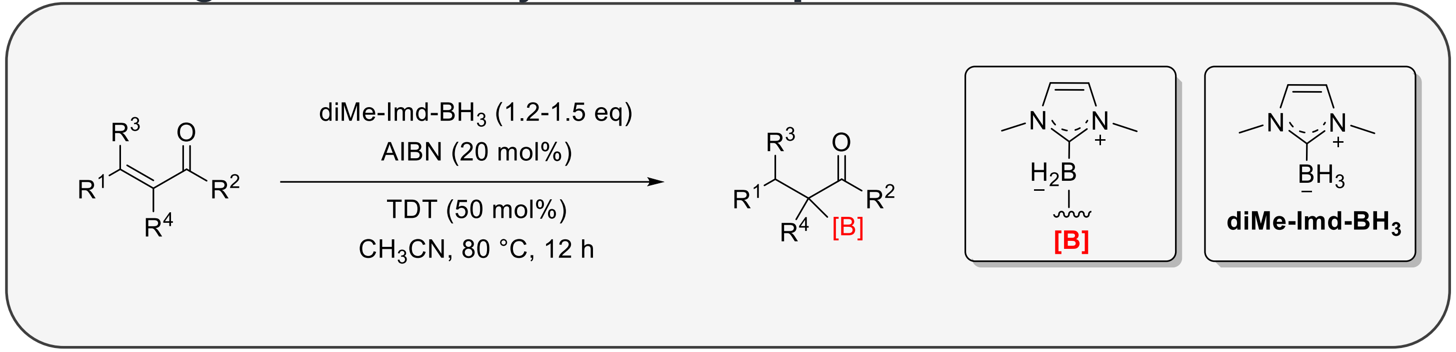
C to O-boron isomerization in α-borylation

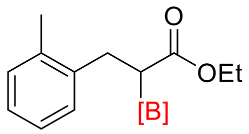




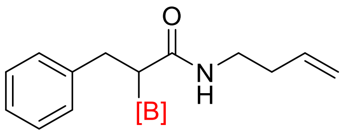
- *O*-Boron enolates occur due to 1,3-boron shift and are thermodynamically driven
- Existing methodology still relies on multi-step synthesis rather than direct conversion

Wang Utilizes a Boryl Radical to promote a C-bound Boron

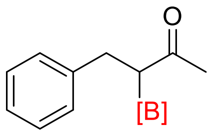




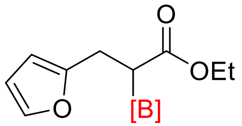
78% yield



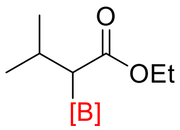
89% yield



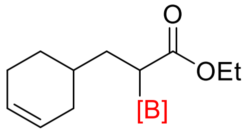
94% yield



95% yield



56% yield



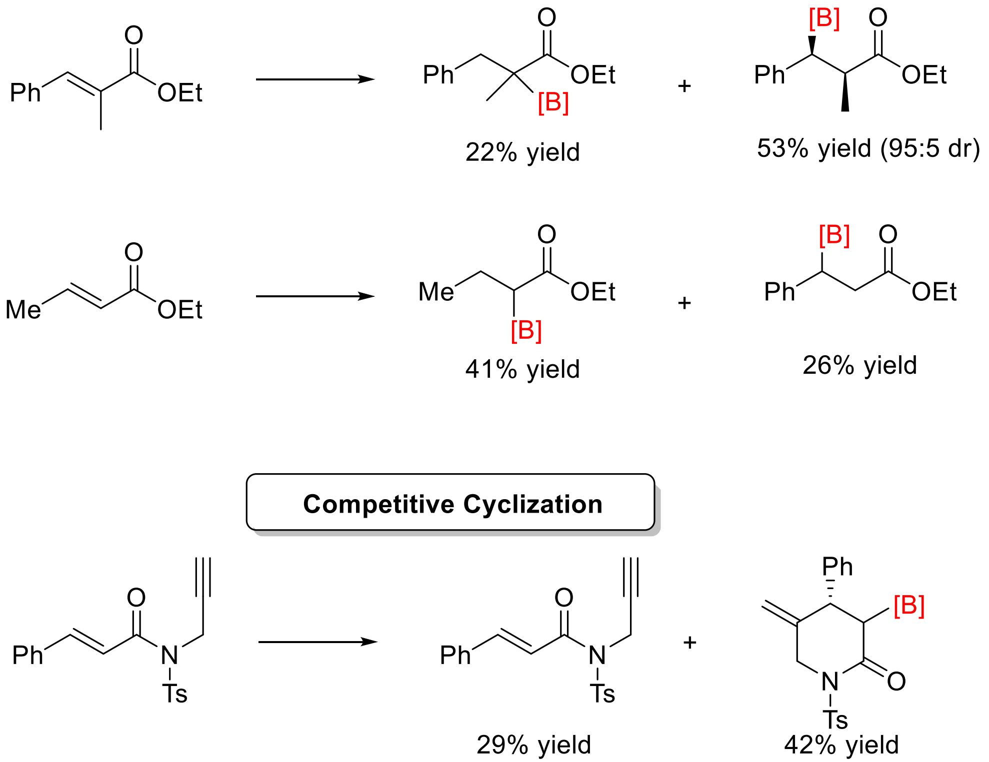
39% yield

Nat. Commun. 2019, 10, 1934
Chem. Sci., 2019, 10, 1434–144

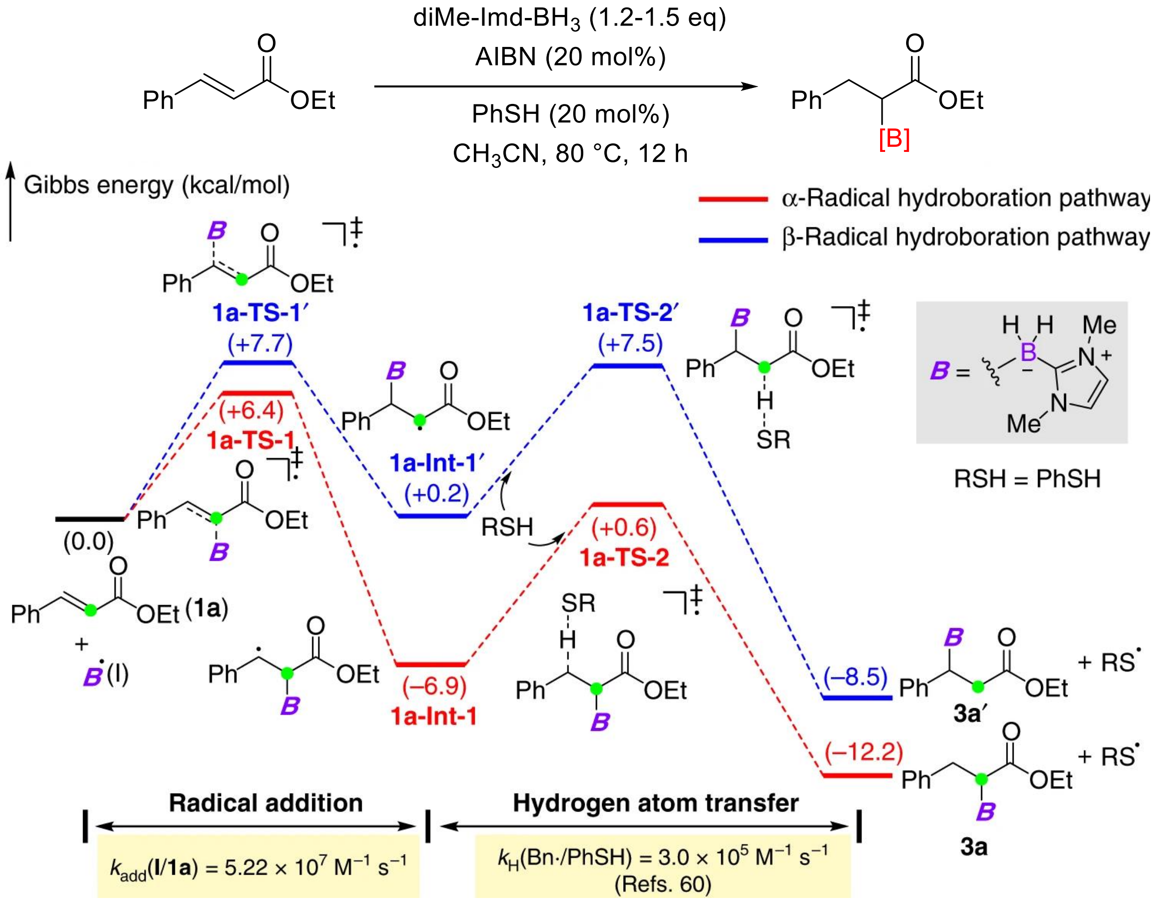
Defining a Mechanism for Selective α-Borylation

Limitations of the Method

Competitive α vs. β borylation



DFT Investigation

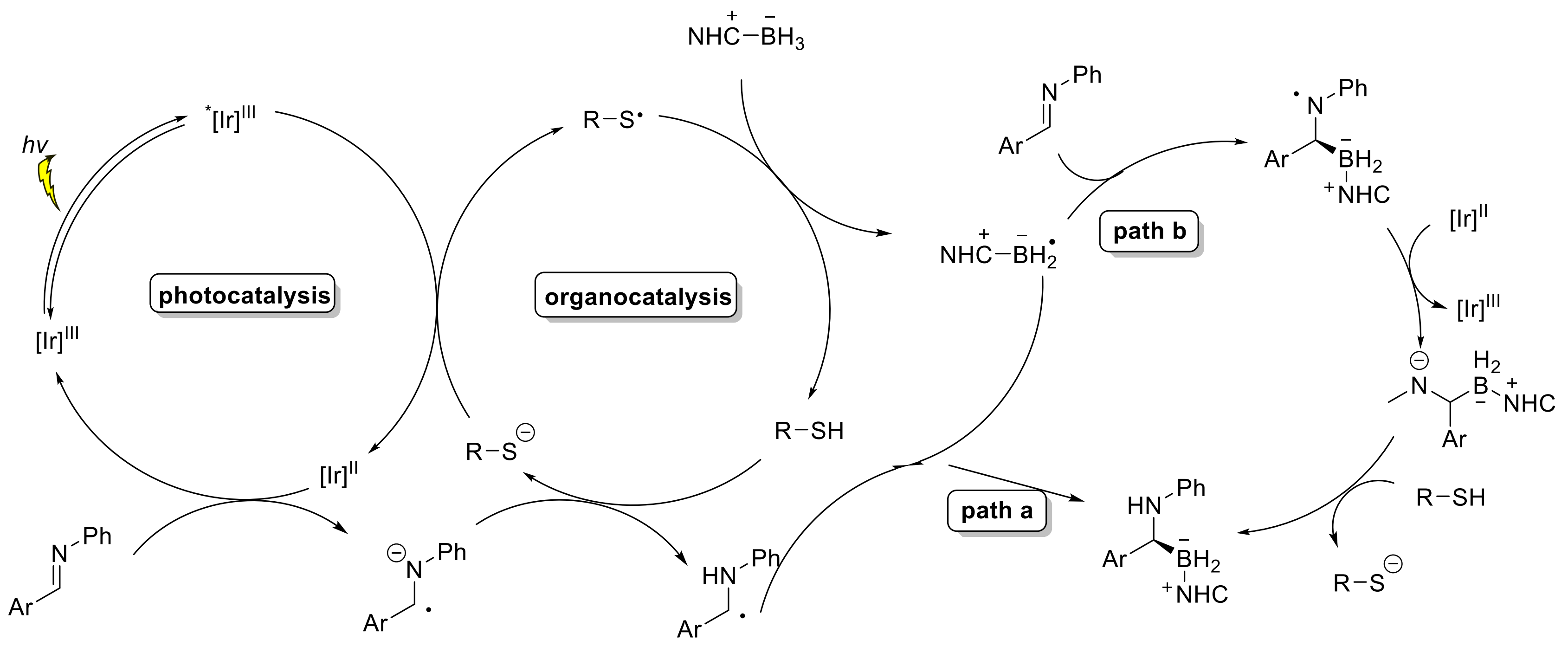


- ➢ α and β-borylation are differentiated through reversibility of β-addition/elimination

Nat. Commun. 2019, 10, 1934
Chem. Sci., 2019, 10, 1434–144

A Hypothesis about Moving from 1,3 to 1,2 borylation

Xie and Zhu form a Mechanistic Hypothesis



Path A

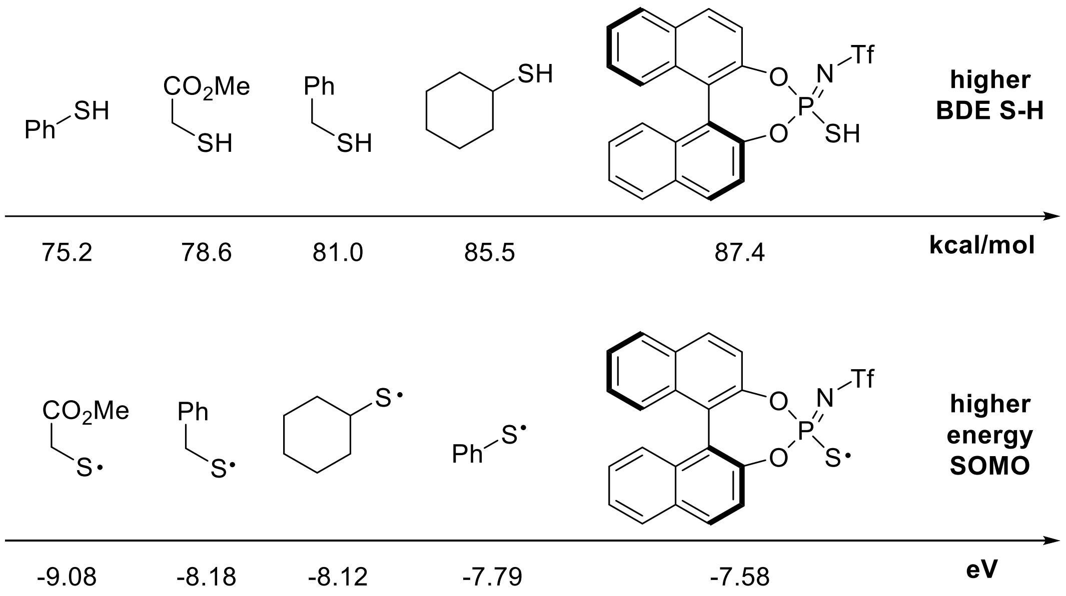
SET reduction of imine with a reductive Ir^{II} could be followed by radical-radical C-B cross-coupling

Path B

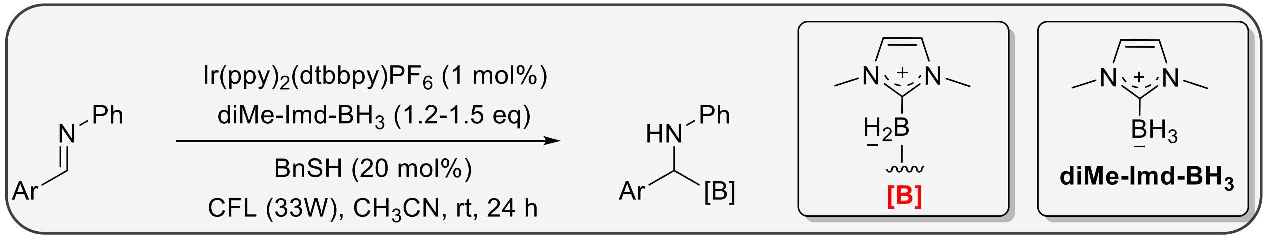
NHC-boryl radical addition occurs then SET reduction of the nitrogen-centered radical

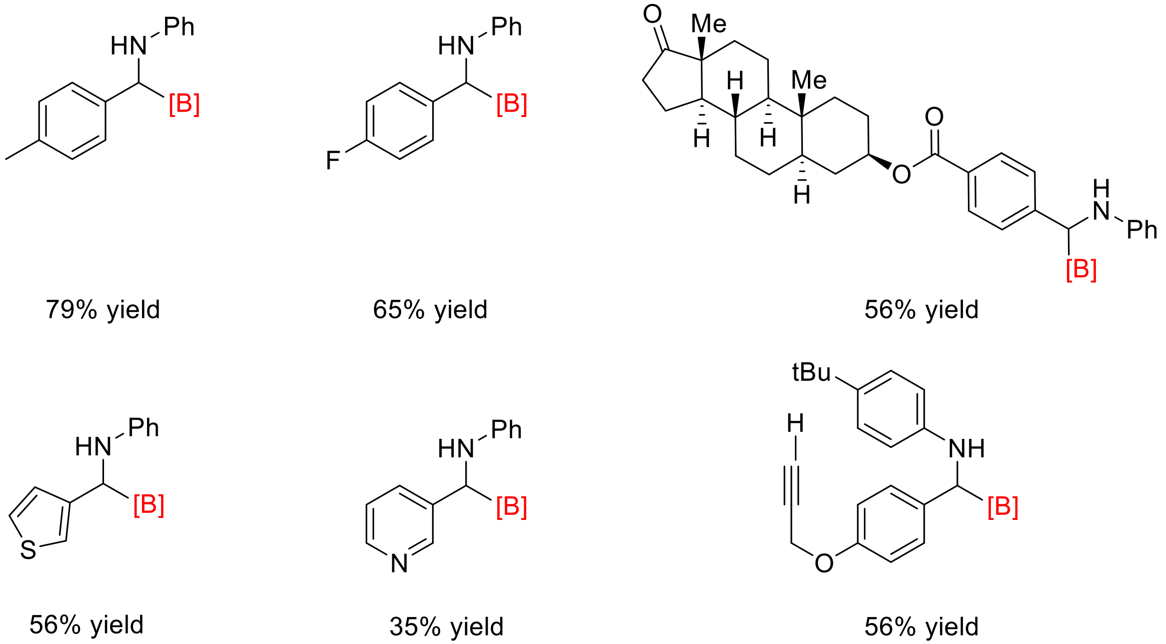
Developing a Method for "Inverse Hydroboration"

Varying Thiol Reactivity



Reaction Conditions



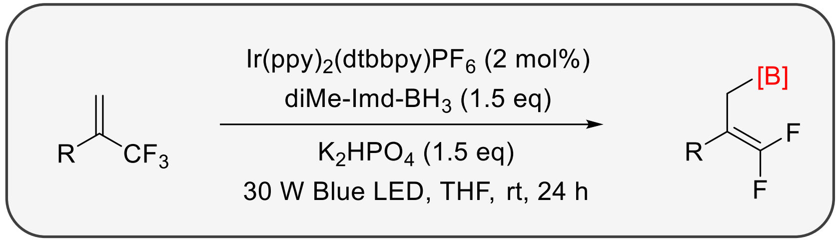


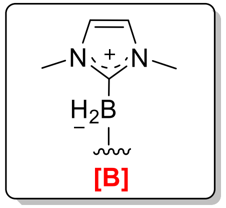
- BnSH suppresses reduction of the imine
  - Capable of rapid HAA
- Cyclohexanethiol promotes reactivity
  - Still shows significant reduction

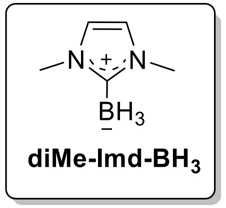
Mechanistic studies were unfortunately unable to differentiate **Path A** vs. **Path B**, but low quantum yield of 35% did suggest **Path B** is less likely.

Towards Non-Initiator Type NHC-Borane Reactivity

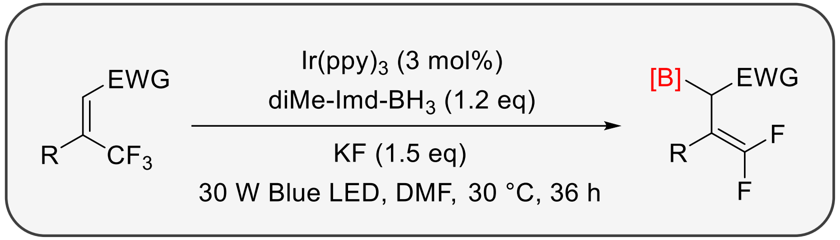
Yang's Photoredox System

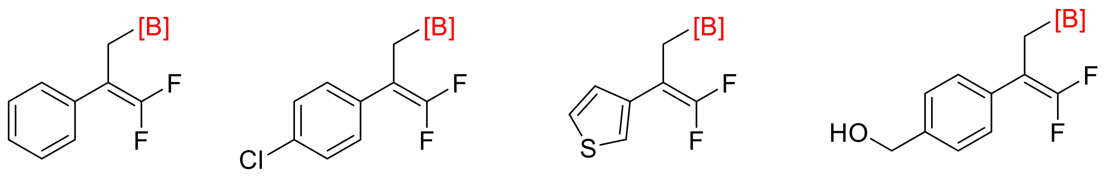




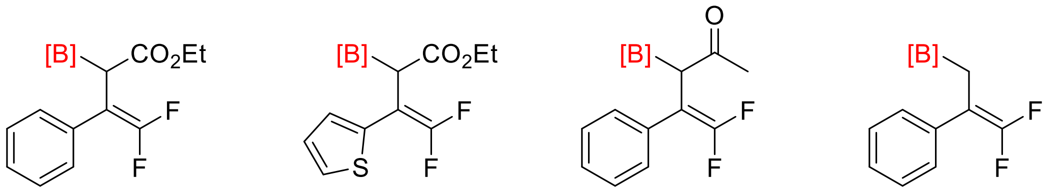


Wang's Photoredox System

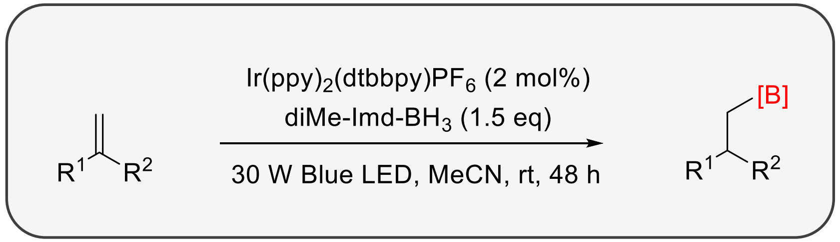


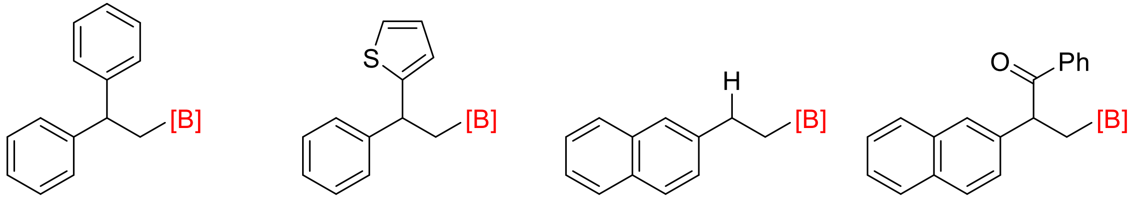


87% yield | 89% yield | 80% yield | 87% yield

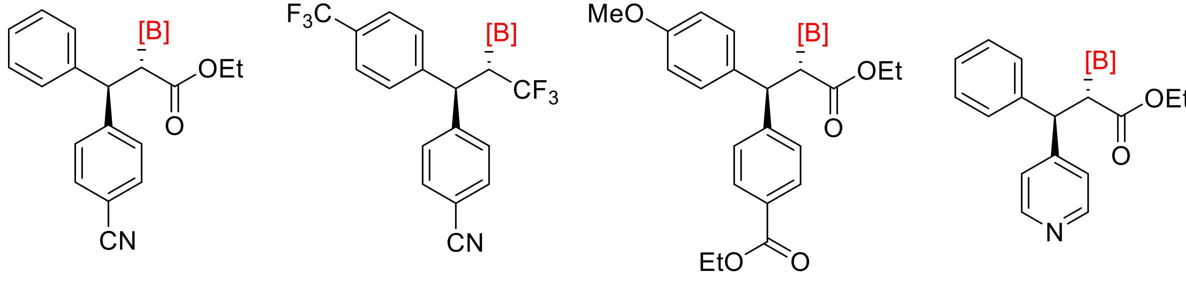


65% yield | 60% yield | 48% yield | 0% yield





54% yield | 55% yield | 55% yield | 72% yield



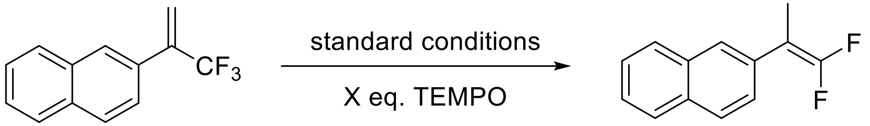
50% yield | 40% yield | 40% yield | 40% yield

Angew. Chem. Int. Ed. **2020**, 59, 6706 –6710 (Yang)
Angew. Chem. Int. Ed. **2020**, 59, 12876–12884 (Wang)

Individual Mechanism Investigations

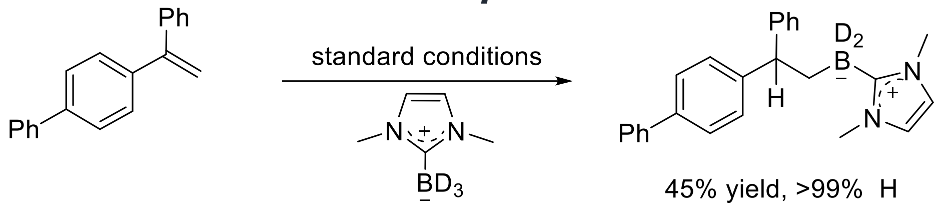
Yang's Mechanism Investigation

Radical Trap Experiment

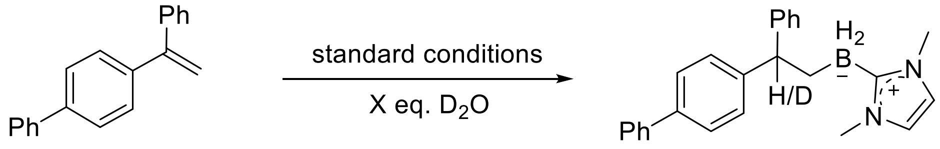


21% yield (2 eq)
0% yield (4 eq)

Deuterium Experiments

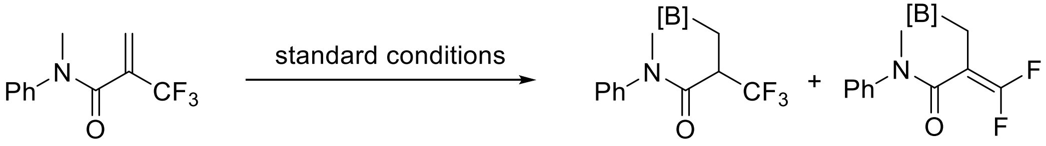


45% yield, >99% H



55:45 H:D (100 eq of D_2O)
12:88 H:D (150 eq of D_2O)

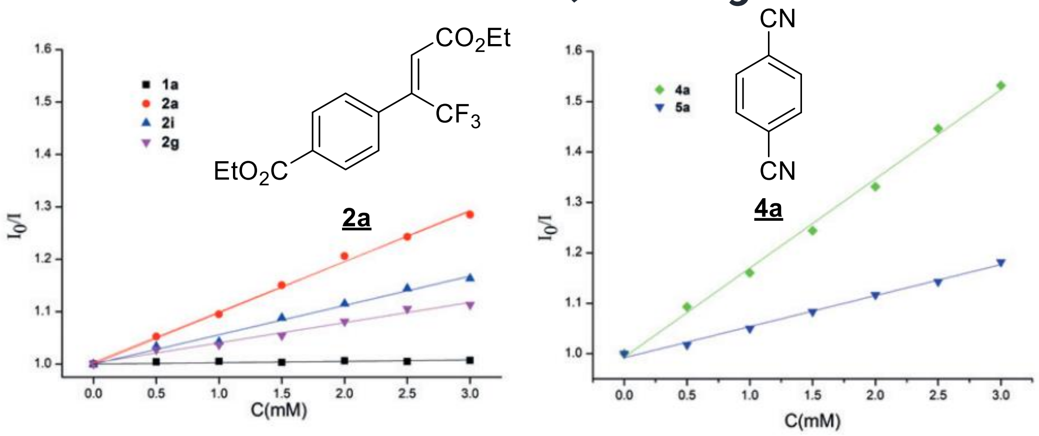
1,4 Addition Experiment



detected by HRMS

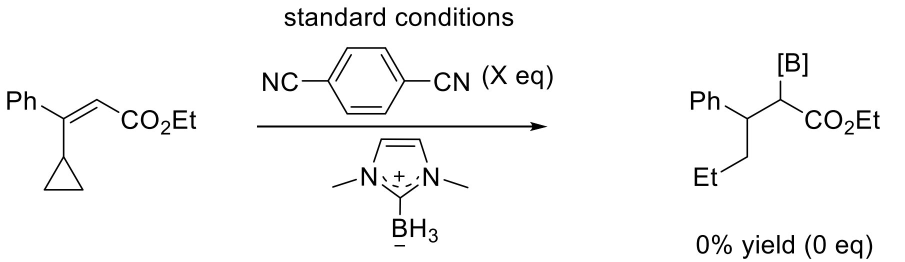
Wang's Mechanism Investigation

Stern-Volmer Quenching



❖ NHC-Borane shows no oxidative quenching for Wang, UNLIKE Yang

Radical Clock Experiment



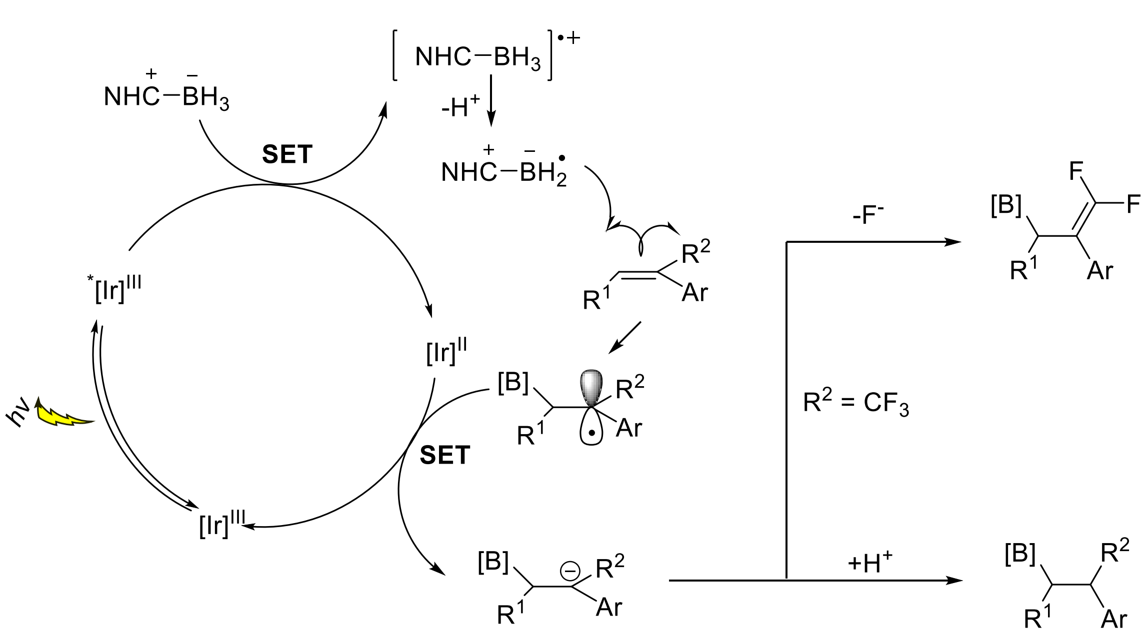
0% yield (0 eq)
39% yield (0.2 eq)

❖ Arene plays a role as an oxidant in this cycle

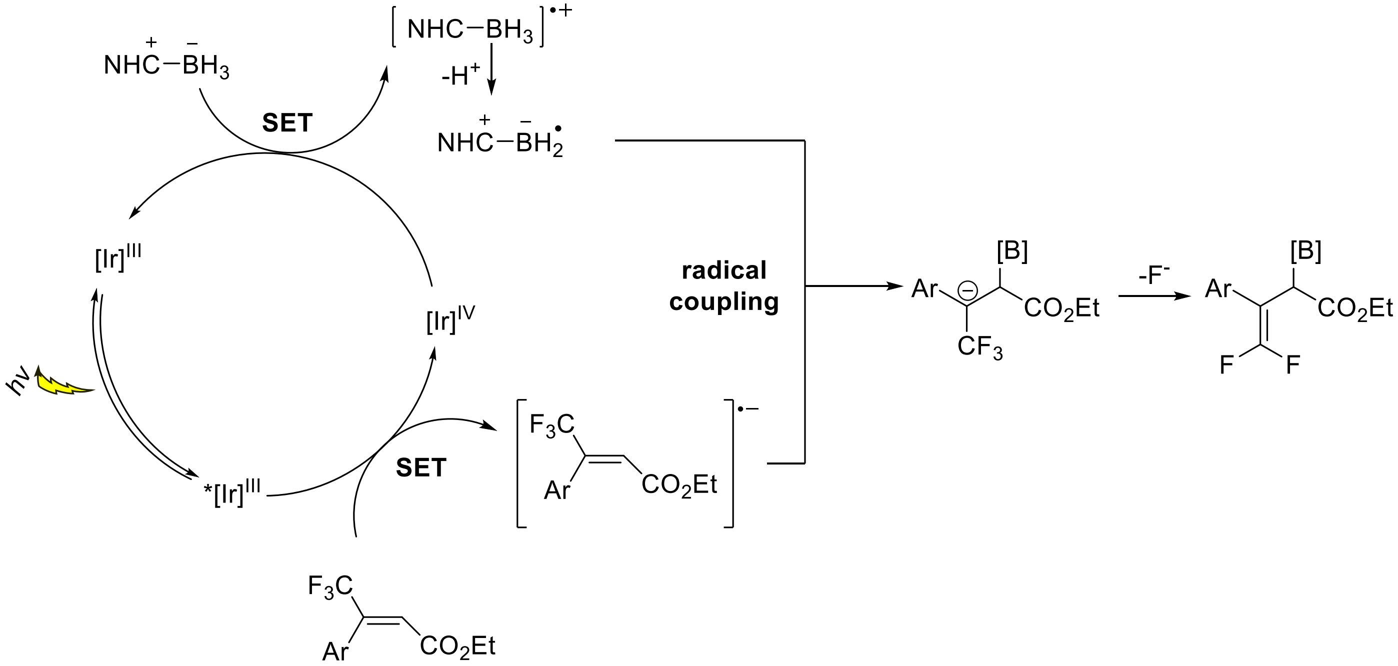
Angew. Chem. Int. Ed. **2020**, 59, 6706 –6710 (Yang)
Angew. Chem. Int. Ed. **2020**, 59, 12876–12884 (Wang)

Two Separate Reaction Manifolds

Yang's Ir(II)/Ir(III) Proposed Mechanism

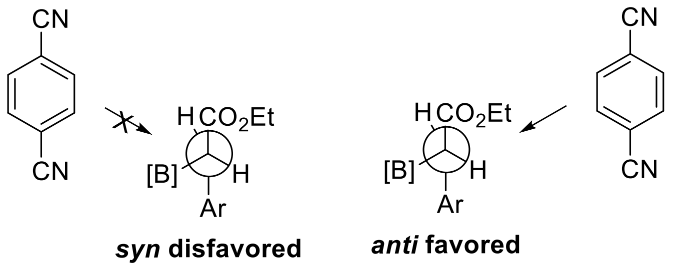


Wang's Ir(III)/Ir(IV) Proposed Mechanism



Rational Design Can Access Different Manifolds of Reactivity!

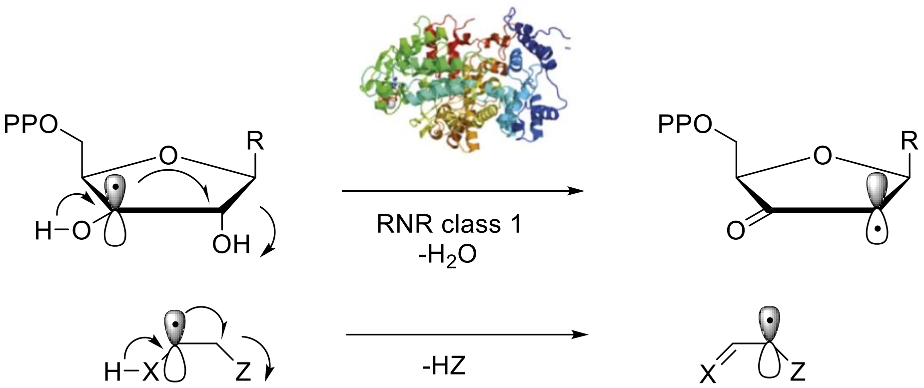
Radical Coupling Stereochemistry Rationale



Angew. Chem. Int. Ed. **2020**, 59, 6706 –6710 (Yang)
Angew. Chem. Int. Ed. **2020**, 59, 12876–12884 (Wang)

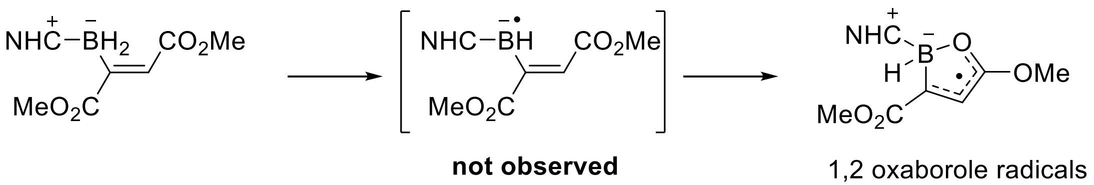
Boryl-Radical Mediated Defluorination

Spin-Center Shifts in Chemistry



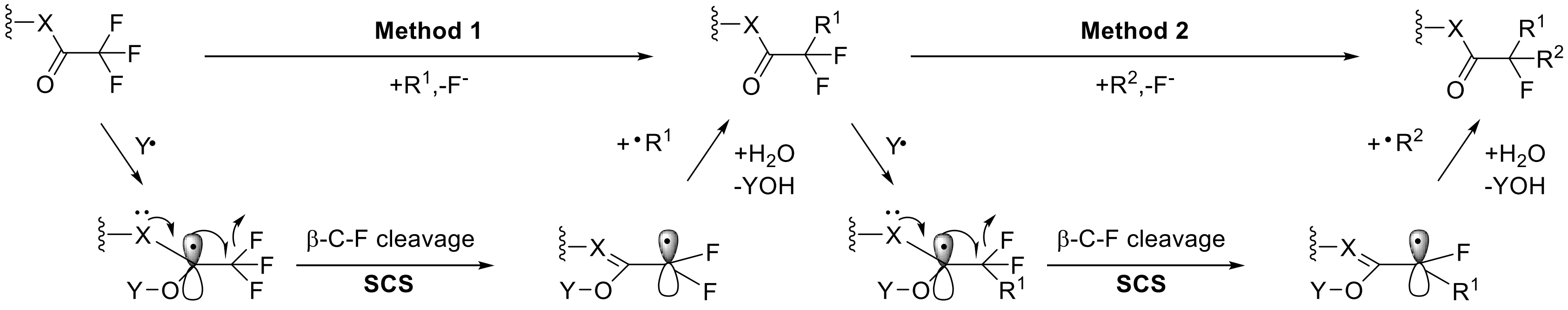
X = O, NR
Z = Br, Cl, OR

Key Finding by Curran and Walton



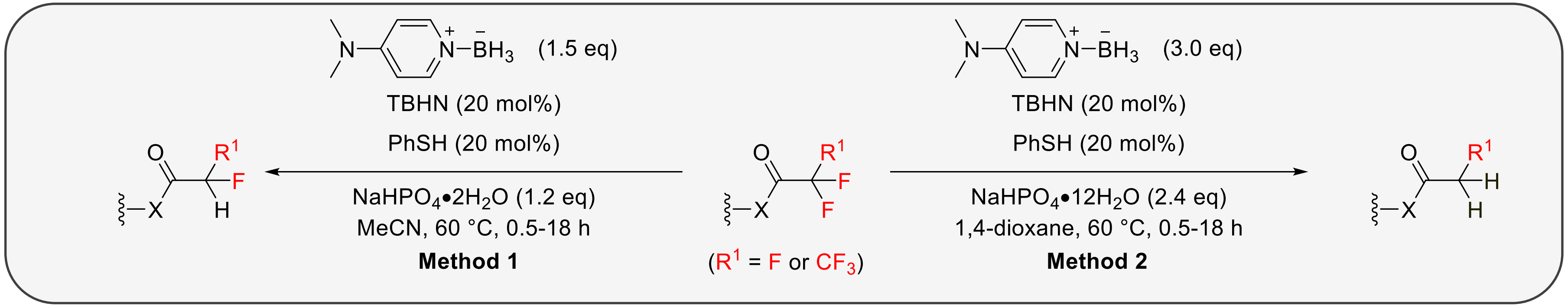
Boryl Radicals can be nucleophilic to towards carbonyls!

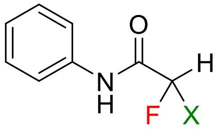
The Ideal Reaction Manifold for Step-Wise Defluorination



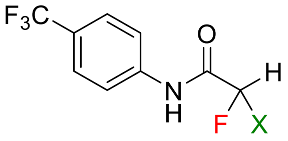
Science **2021**, 371, 1232-1240
Nature **2015**, 525, 87-90
J. Am. Chem. Soc. **2018**, 140, 15868-1875

Boryl-Radical Mediated Defluorination Methodology

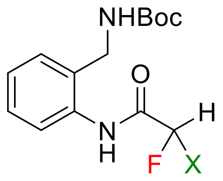




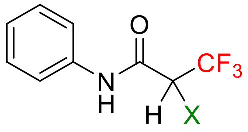
82% yield (X=F)
85% yield (X=H)



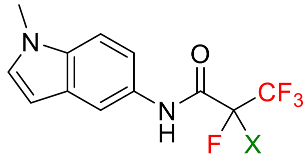
58% yield (X=F)
73% yield (X=H)



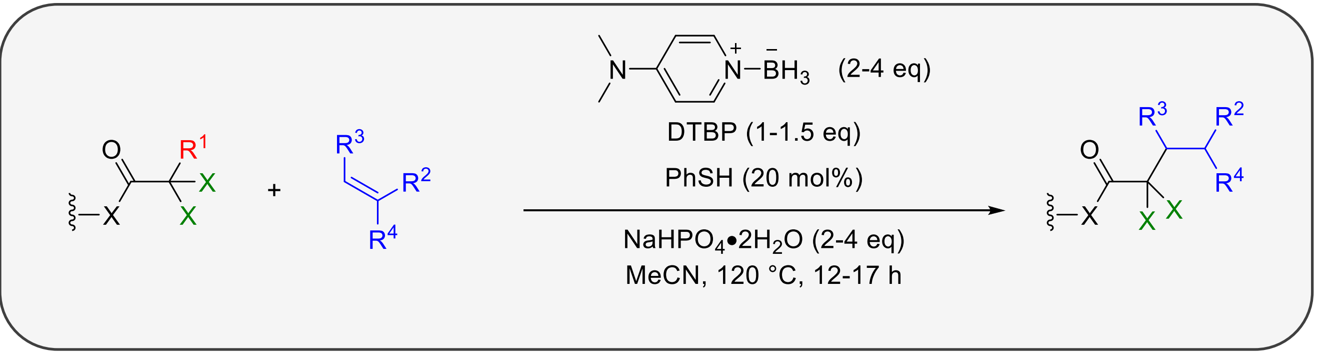
65% yield (X=F)
80% yield (X=H)

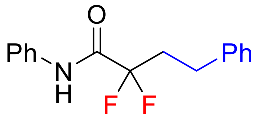


92% yield (X=F)
94% yield (X=H)

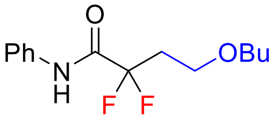


84% yield (X=F)
55% yield (X=H)

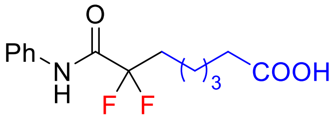




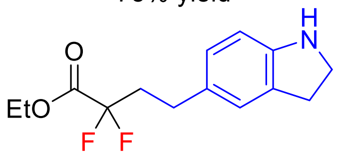
75% yield



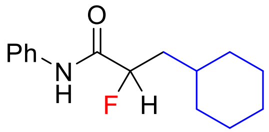
56% yield



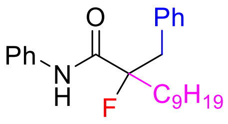
35% yield



52% yield



61% yield

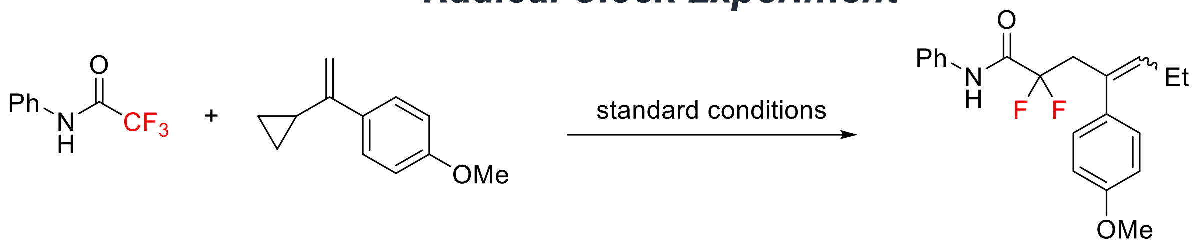


61% yield

Science **2021**, 371, 1232-1240
Nature **2015**, 525, 87-90
J. Am. Chem. Soc. **2018**, 140, 15868-1875

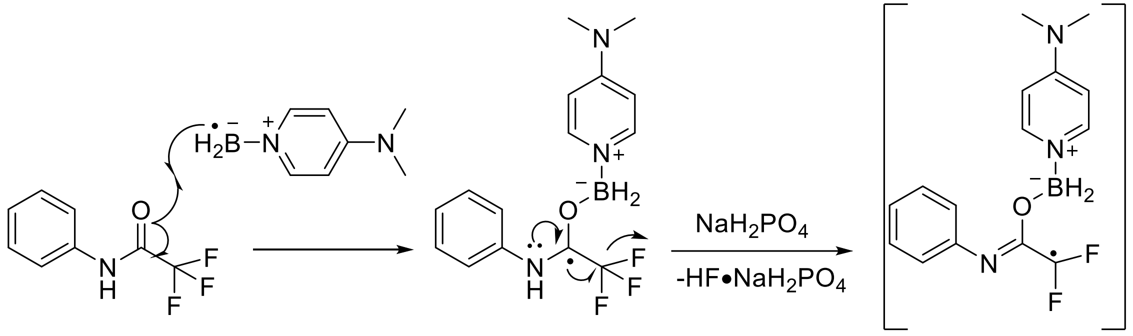
Mechanistic Investigations for Defluorination

Radical Clock Experiment



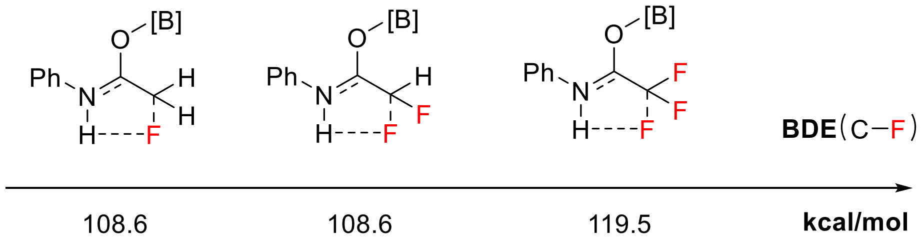
43% (E/Z isomers)

Proposed Intermediate

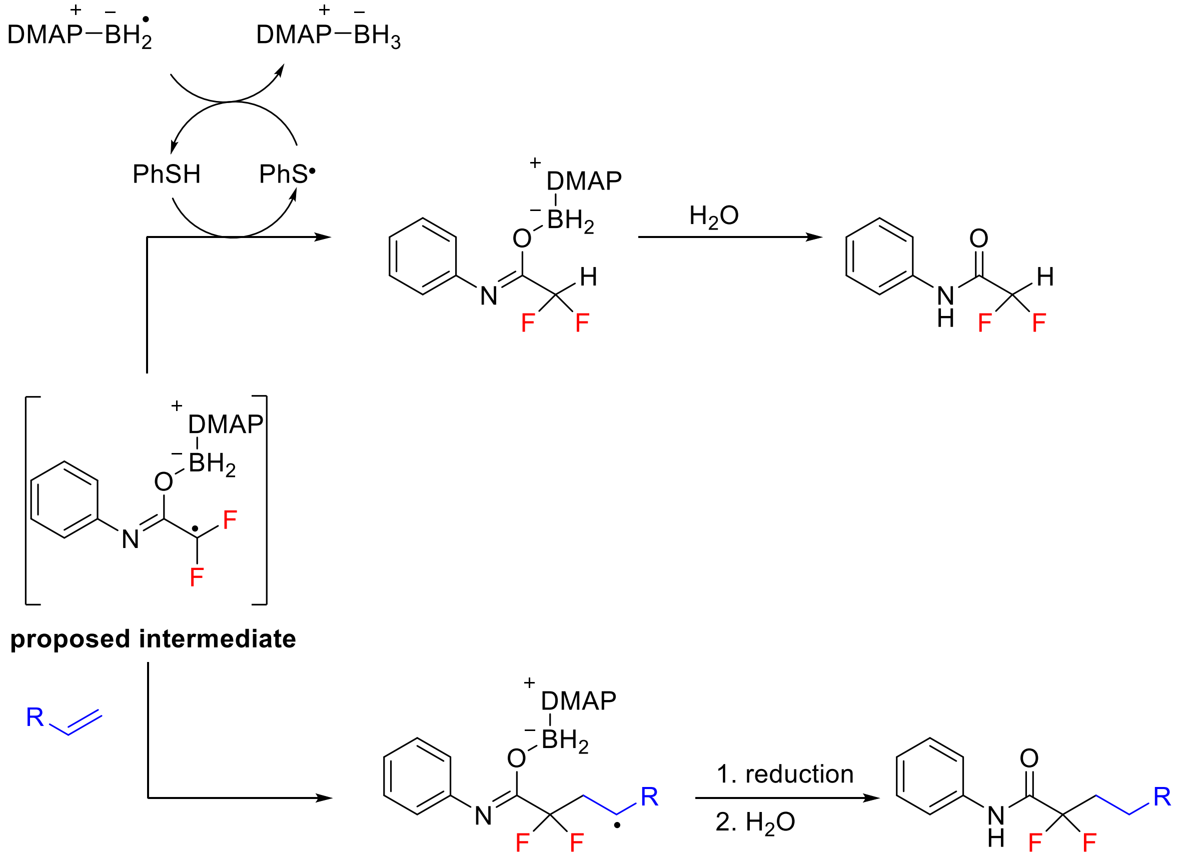


proposed intermediate

Bond Dissociation Energies for SCS



Proposed Pathway

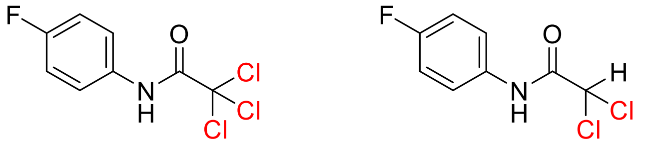


Science **2021**, 371, 1232-1240

Extending Dehalogenation Methods to Chlorine

Developing Method with Reaction Screening

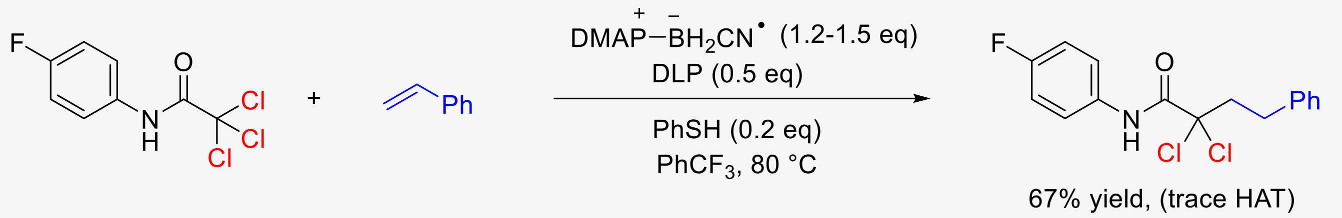
Quenching Rate Constants



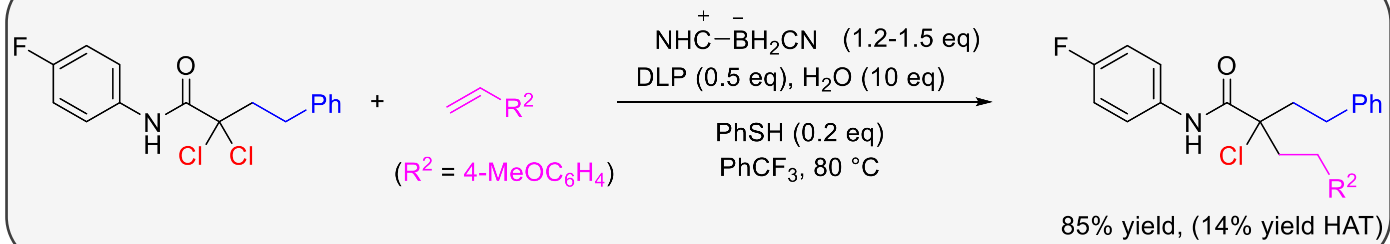
Boryl Radical	k_Q ($M^{-1}s^{-1}$) at rt	k_Q ($M^{-1}s^{-1}$) at rt
$DMAP^{+}-BH_2^{-\bullet}$	**3.9 × 10^{8}**	**3.7 × 10^{7}**
$H_2NHC^{+}-BH_2^{-\bullet}$	**2.5 × 10^{8}**	**4.2 × 10^{7}**
$DMAP^{+}-BH_2CN^{-\bullet}$	**2.9 × 10^{8}**	**1.3 × 10^{7}**
$NHC^{+}-BH_2CN^{-\bullet}$	**8.4 × 10^{6}**	**2.1 × 10^{6}**

- ➢ Chemoselectivity for chlorine is high
  - ❖ Unable to see quenching of radical for monochlorine

Dechlorinative Coupling from Trichloromethyl Group



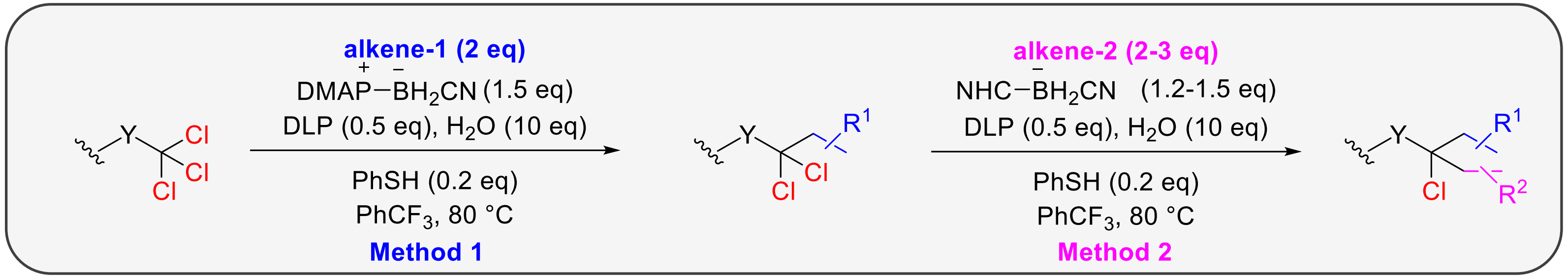
Dechlorinative Coupling from Dichloromethyl Group

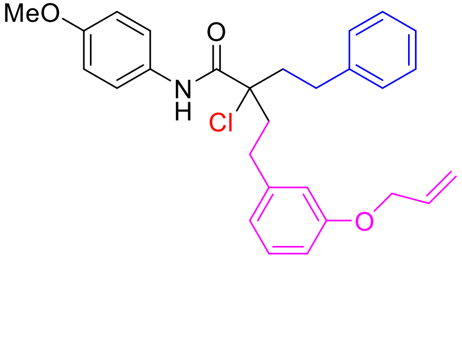


- ➢ $NHC-BH_2CN$ is the only borane that goes to completion for dichloromethyl group
  - ❖ Note: This “NHC” is referring to diMe-Imd-BH3

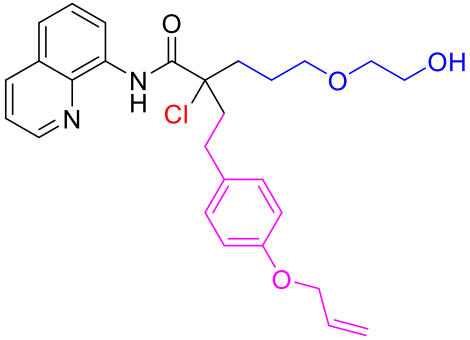
J. Am. Chem. Soc. **2022**, 144, 33, 15275-15285

Boryl-Radical Mediated Dechlorinative Coupling

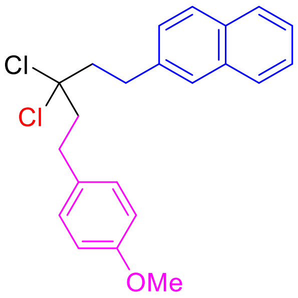




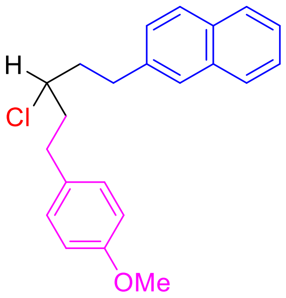
72% yield; 64% yield



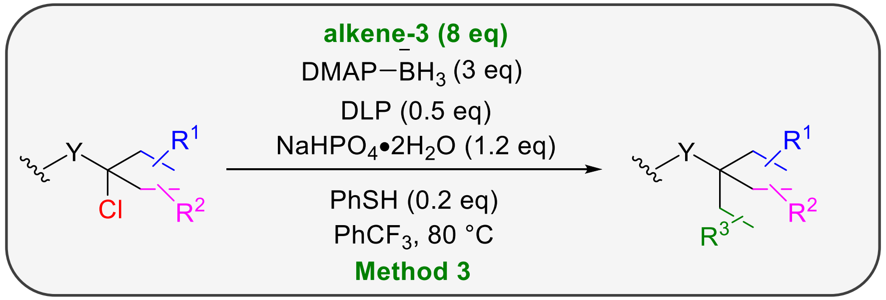
52% yield; 55% yield

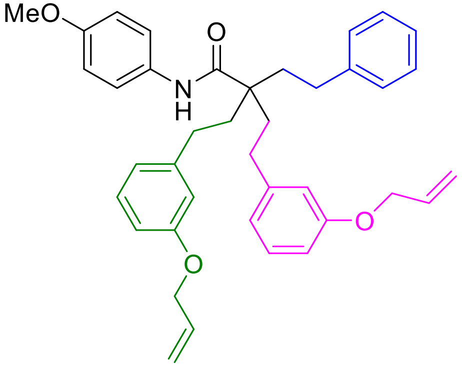


86% yield; 71% yield

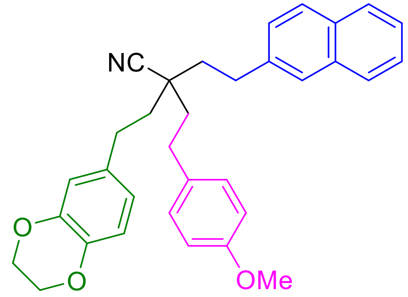


70% yield; trace yield





49% yield



47% yield

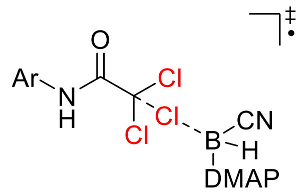
Note: If BDE of C-Cl ~81 kcal/mol, the substrate was inert for the third dechlorination

J. Am. Chem. Soc. **2022**, 144, 33, 15275-15285

Changes in the Mechanism from C-F to C-Cl

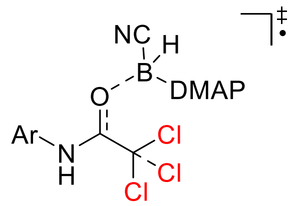
Possible Reaction Pathways

Halogen Atom Transfer vs. *Carbonyl Attack*

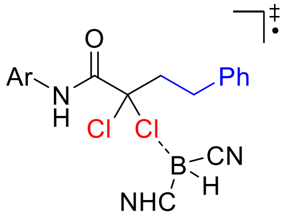


$\Delta G^{\ddagger} = 7.0\ kcal/mol$

vs.

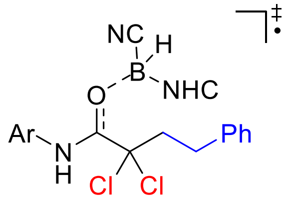


$\Delta G^{\ddagger} = 9.7\ kcal/mol$

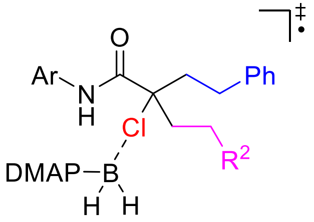


$\Delta G^{\ddagger} = 12.3\ kcal/mol$

vs.

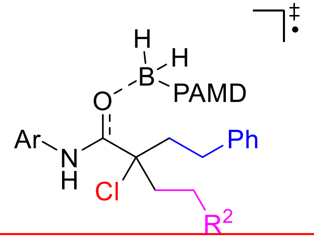


$\Delta G^{\ddagger} = 16.6\ kcal/mol$



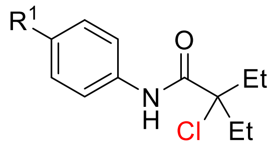
$\Delta G^{\ddagger} = 14.6\ kcal/mol$

vs.



$\Delta G^{\ddagger} = 13.7\ kcal/mol$

Possible Reaction Pathways



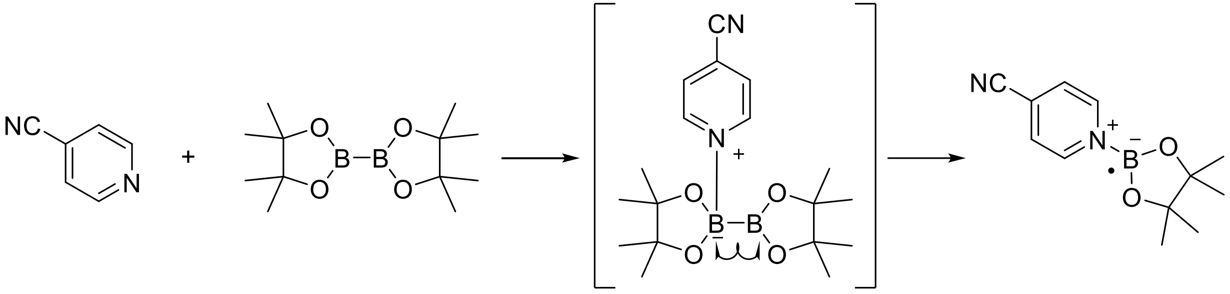
R^1	k_Q ($M^{-1}s^{-1}$) at 72 °C	SOMO/LUMO gap (eV)
-CN	1.21×10^6	3.41
-Ph	0.97×10^6	4.37
-OMe	$< 10^5$	4.55

- This suggests that the boryl radical prefers to attack the carbonyl oxygen atom, which would induce a SCS to eliminate HCl
- The mechanism is then proposed as halogen atom transfer for tri- and dichloromethyl substituents, but an SCS for mono-chloro species

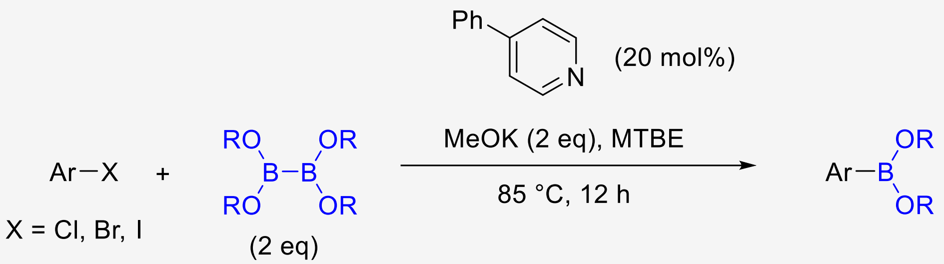
J. Am. Chem. Soc. **2022**, 144, 33, 15275-15285

Radical Borylation Methodology with B_2Pin_2

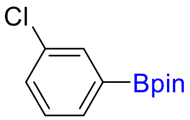
Zhu Designs Catalyst for Homolytic Cleavage of B_2Pin_2



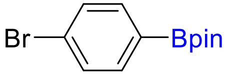
Jiao Applies This To Radical Borylation of Arenes



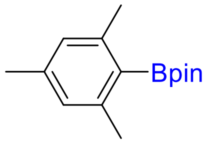
85% yield (X=I)
72% yield (X=Br)



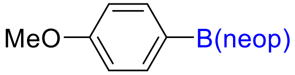
68% yield (X=I)



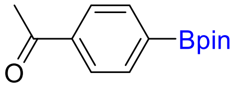
66% yield (96:4 mono:di)



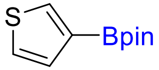
83% yield (X=I)



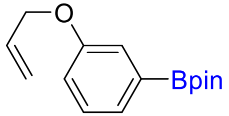
62% (X = I)



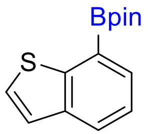
62% yield (X=I)
61% yield (X=Cl)



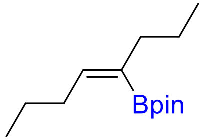
51% yield (X=I)



58% yield (X = I)



55% yield (X=Br)

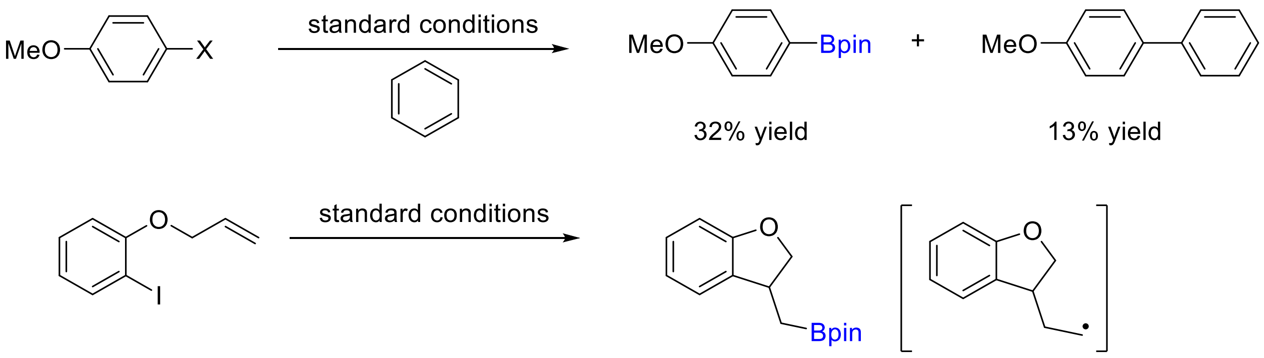


70% yield (X=Br)

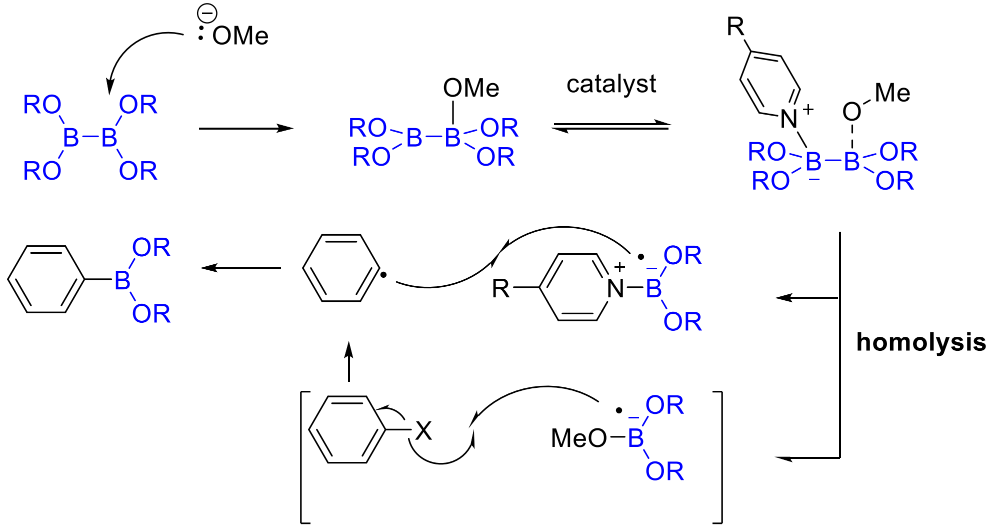
J. Am. Chem. Soc. **2017**, 139, 2, 607-610
Angew. Chem. Int. Ed., **2016**, 55, 5985

Confirming the Mechanism

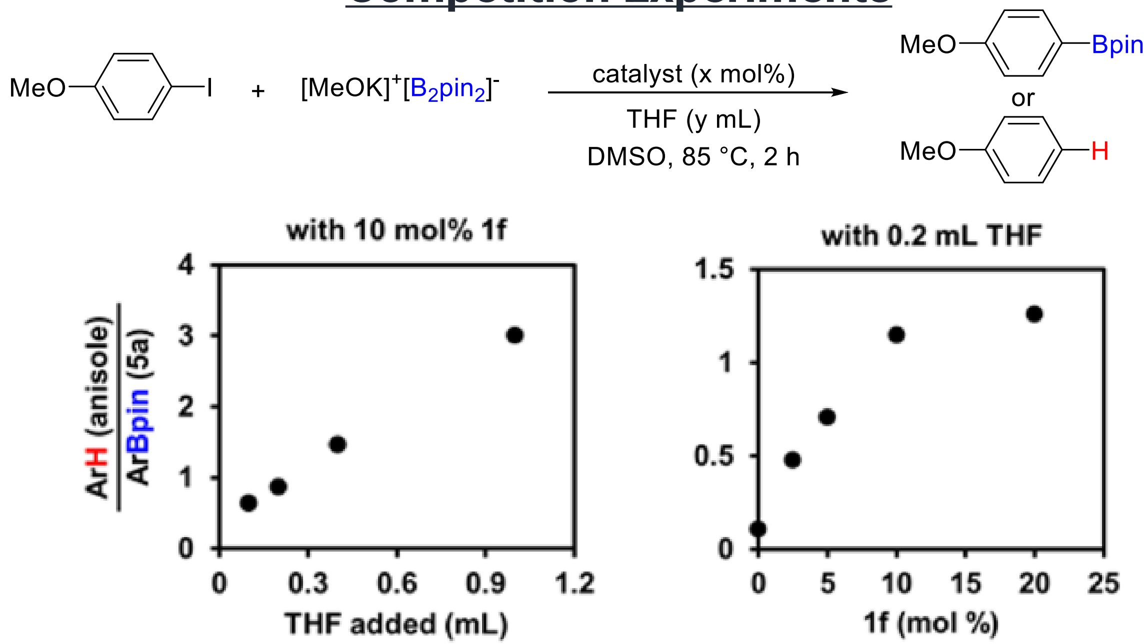
Radical Studies



Plausible Reaction Mechanism



Competition Experiments

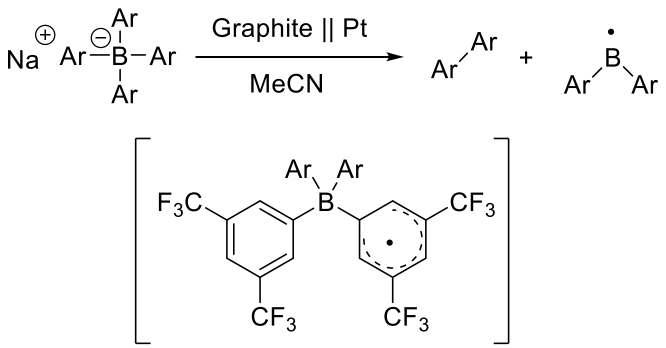


- Suggests ate complex is formed with B_2pin_2
- Two operative species:
  - Persistent Boryl Radical for Coupling
  - Electron Donor for SET

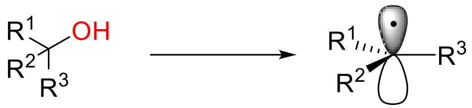
J. Am. Chem. Soc. **2017**, 139, 2, 607-610

Designing a non-ligated boryl-radical system

Waldvogel reports 2 bond, 5 e$^-$ boron generation

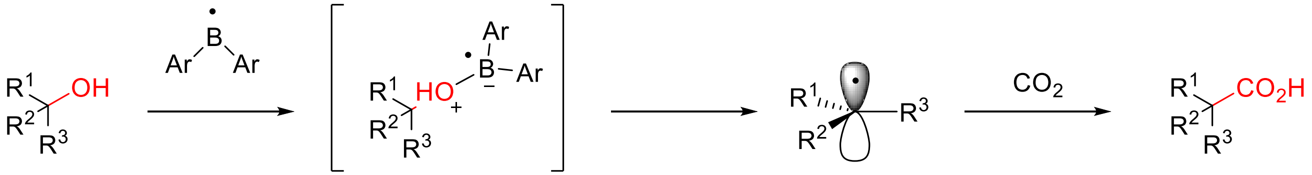


Transforming an Tertiary Alcohol to a Radical



- High BDE (96 kcal/mol)
- Can be accomplished by Ti(III), cationic phosphine radicals, or functional group interconversion

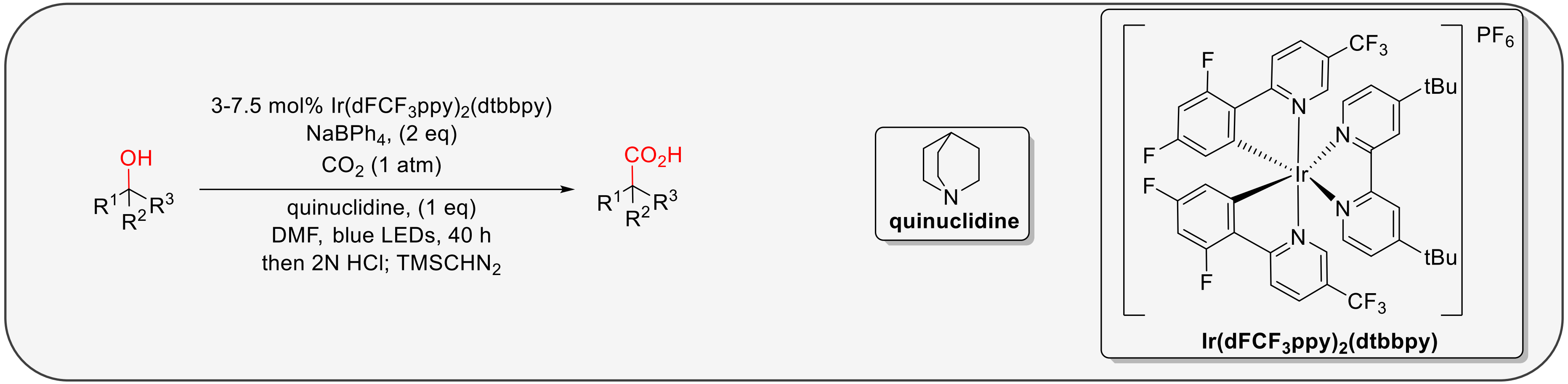
Hypothesis

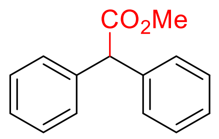


Capture of the unstable neutral boryl radical species by oxygen could allow for activation of the C-O bond for homolysis

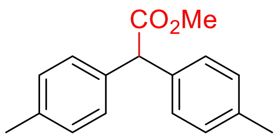
Chem. Commun. 2018, 54, 6128-6131
J. Am. Chem. Soc. 2022, 144, 8551-8559

Boryl Radical Activation of Benzylic C-OH

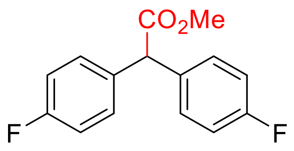




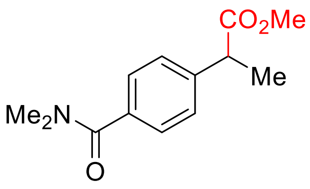
78% yield



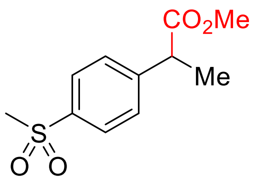
45% yield



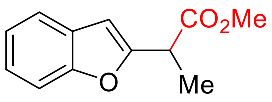
50% yield



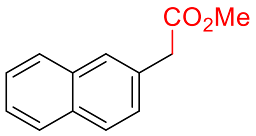
65% yield



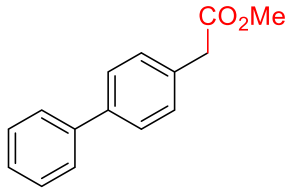
60% yield



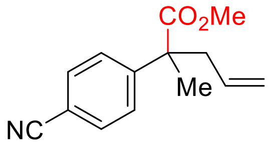
40% yield



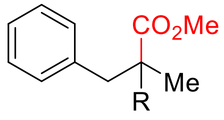
40% yield



78% yield



40% yield

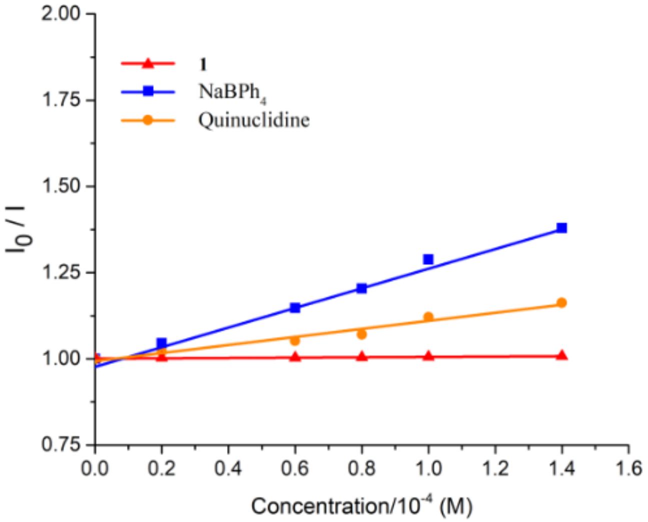


0% yield (R=H)
0% yield (R=Me)

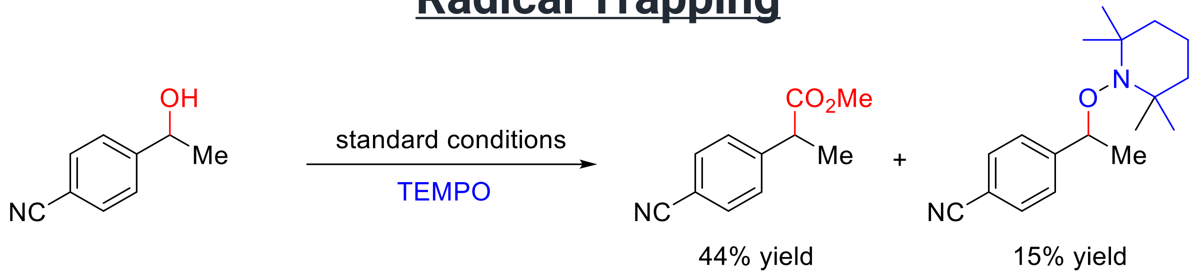
Chem. Commun. **2018**, 54, 6128-6131
J. Am. Chem. Soc. **2022**, 144, 8551-8559

Probing Reactive Species

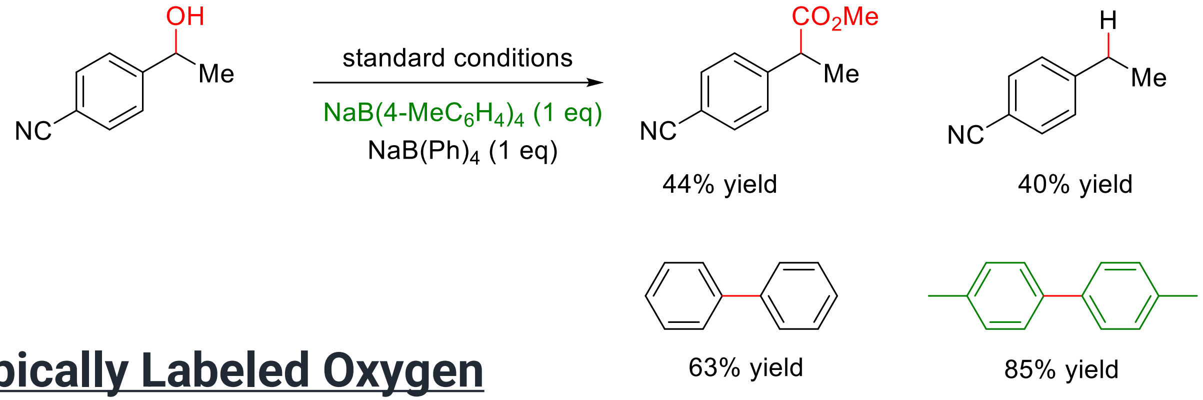
Stern-Volmer Analysis



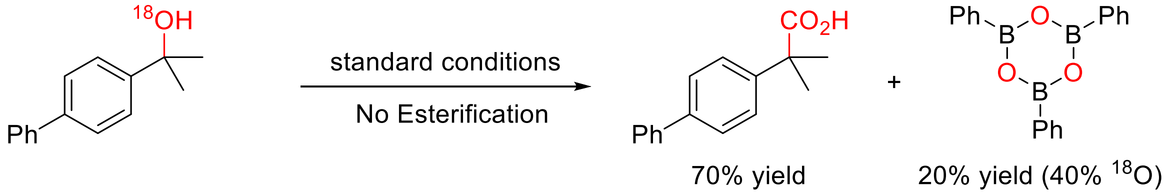
Radical Trapping



Crossover Experiment



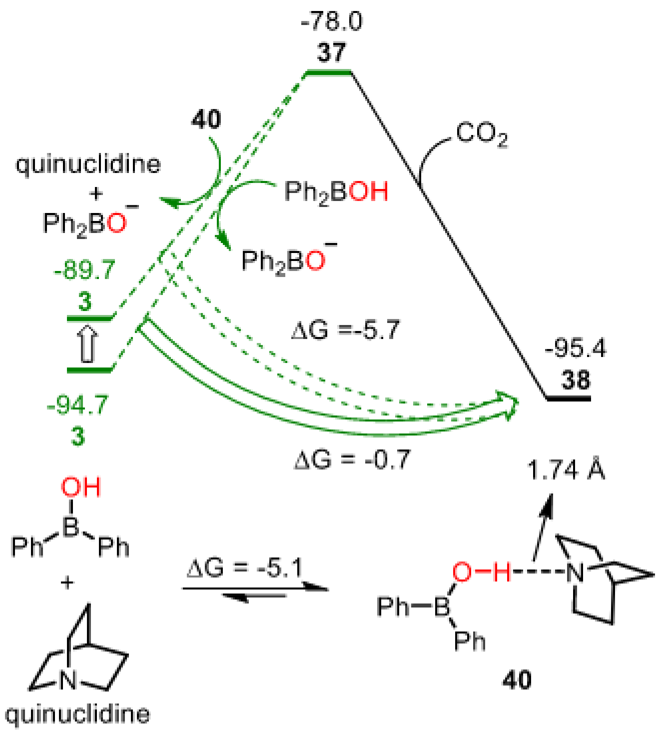
Isotopically Labeled Oxygen



Chem. Commun. **2018**, 54, 6128-6131
J. Am. Chem. Soc. **2022**, 144, 8551-8559

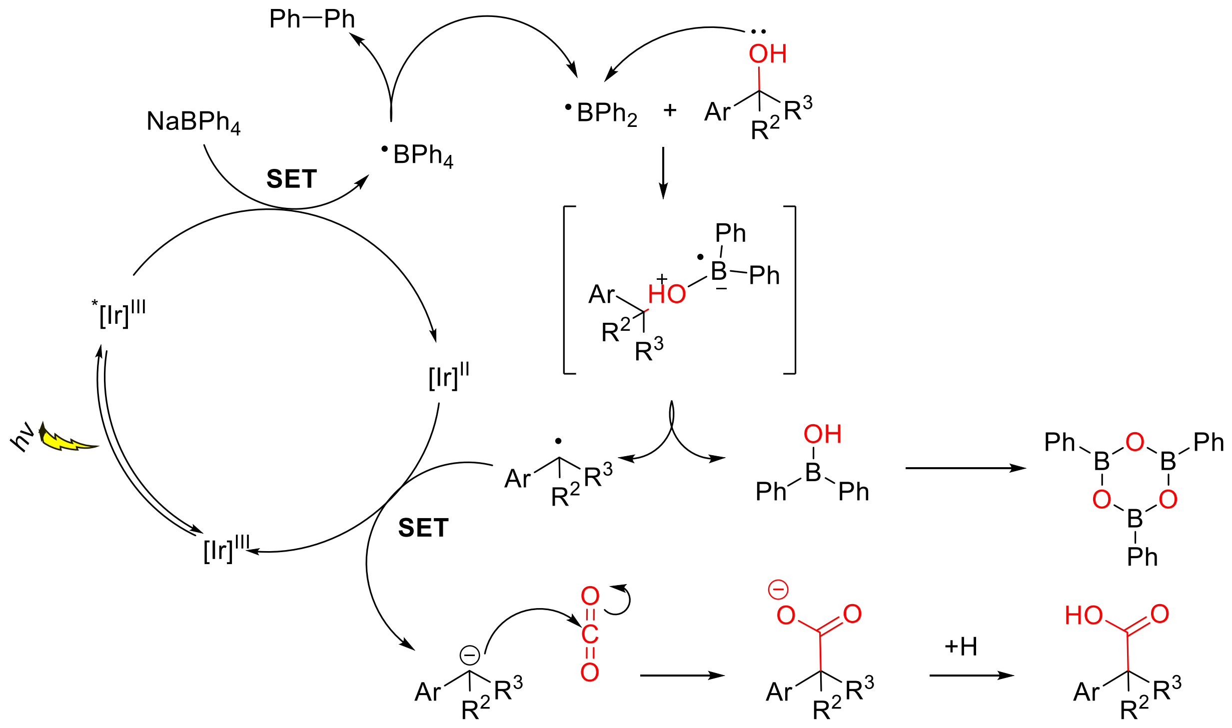
Final Mechanism Proposal

About Quinuclidine's Role



❖ Functions to Suppress Proton Transfer to Benzylic Anion

Plausible Reaction Mechanism



Summary of Reactivities

Pros

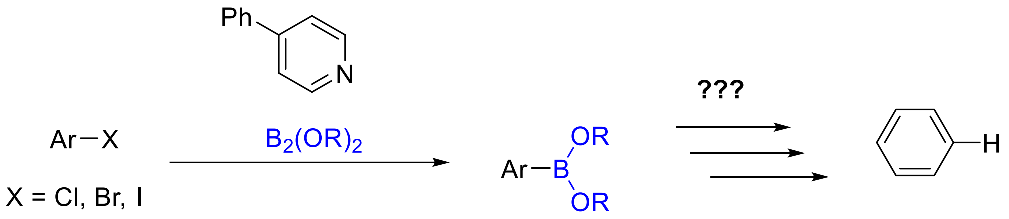
- Very tunable reactivity based on the ligand
- Many precursors to boryl radicals are easily accessible and bench-top stable
- Can access "inverse" reactivity compared to standard boron chemistry
- Can be used to activate normally inert bonds

Cons

- Reaction development requires either extensive trial/error or computational investigation
- Often require H-atom donors with temperature or photocatalysis
- Other radical chain precursors still often perform better for these transformations
- Most NHC-based methods still utilize the the *N*-methyl NHC

Future Directions

Direct C-H Radical Borylation

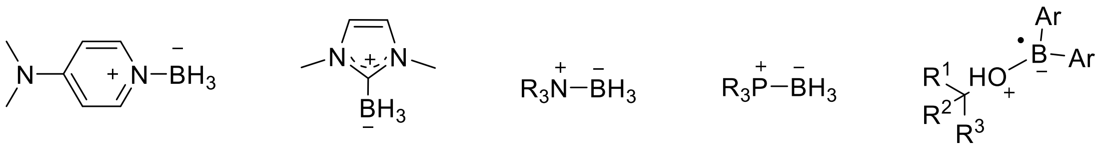


- This will almost certainly involve photoredox applications/new boron ligand development

Additional Carbon-Heteroatom Activation Development

- Substrate scope compatibility is still limited

Additional Investigation into how the Lewis Base Alters the Chemical Reactivity



- The field is rich in different complexes, but reaction development is difficult

Acc. Chem. Res. 2023, 56, 169–186

Reviews of Interest

Guobing Yan, Dayun Huang, Xiangmei Wu

Recent Advances in C–B Bond Formation through a Free Radical Pathway

Adv. Synth. Catal. **2018**, 360, 1040-1053

Tian-Yu Peng, Feng-Lian Zhang, and Yi-Feng Wang

Lewis Base−Boryl Radicals Enabled Borylation Reactions and Selective Activation of Carbon−Heteroatom Bonds

Acc. Chem. Res. **2023**, 56, 169−186

Florian W. Friese and Armido Studer

New avenues for C-B bond formation *via* radical intermediates

Chem. Sci. **2019**, 10, 8503-8518

Emy Andre-Joyaux, Lars Gnagi, Manuel Gnagi-Lux, Camilo Andres Melendez Becerra, Valentin Soulard, Nicholas D. C. Tappin, and Phillipe Renaud

Boron-Mediated Radical Reactions

Organoboron Compounds, **2022**, 1-102