

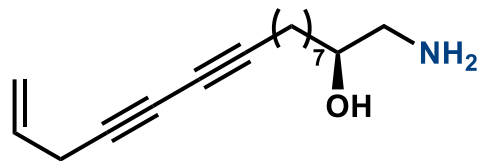


Deaminative Functionalizations of Unactivated Aliphatic Amines

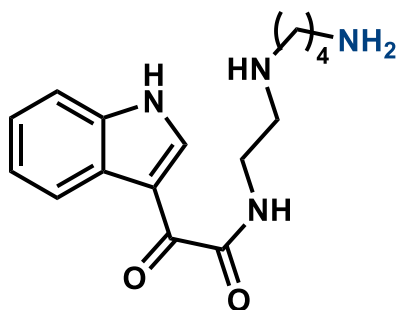
Reporter: Yuzhen Zhang
Supervisor: Prof. Quan Cai

Fudan University
2023-04-28

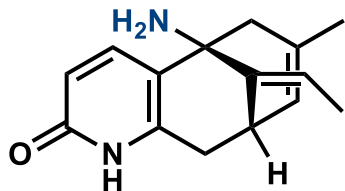
- **Background**
- **Deaminative Functionalizations via Katritzky-type Pyridinium Salts**
 - **By Transition Metal Catalysis and Lewis Base Catalysis**
 - **By Photoredox Catalysis and Electrochemical Catalysis**
- **Deaminative Functionalizations via Electron-rich Imines**
- **Direct Deaminative Functionalizations**
- **Summary and Outlook**



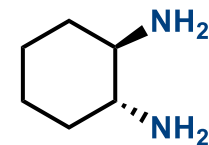
Distaminolyne A



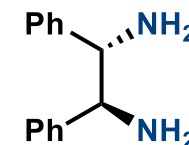
Didemnidine



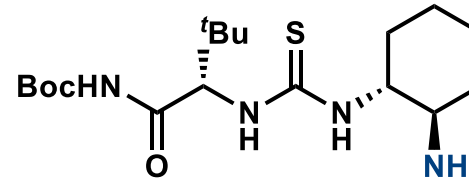
Huperzine A



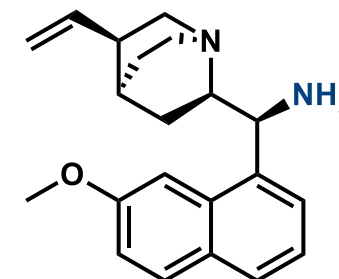
trans-1,2-Diaminocyclohexane



(1S, 2S)-(-)-DPEN



Amino-thiourea



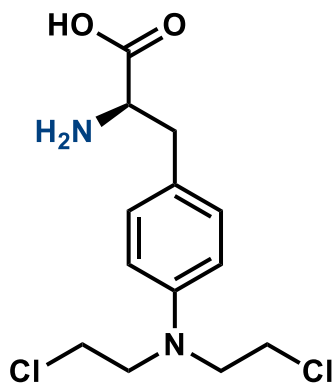
Cinchona Alkaloids

Natural Products

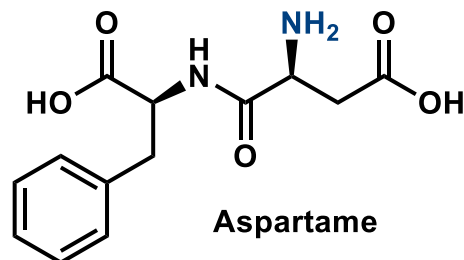
Catalysts/ Ligands

Aminoacids/ Peptides

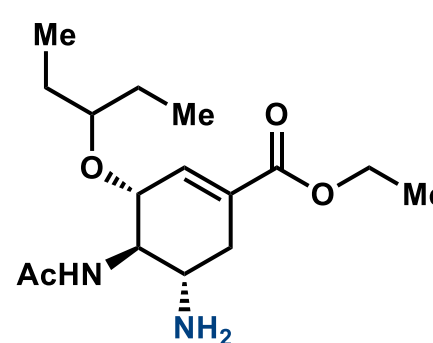
Pharmaceuticals



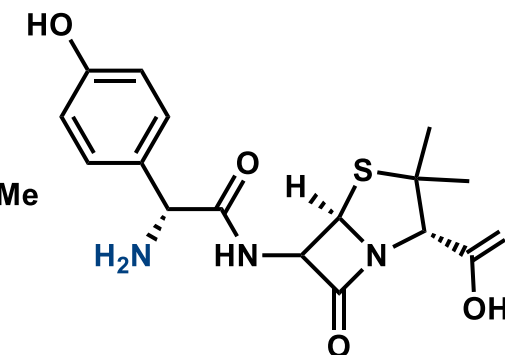
Melphalan



Aspartame



Tamiflu



Amoxicillin

C—H 414 kJ/mol

C—I 240 kJ/mol

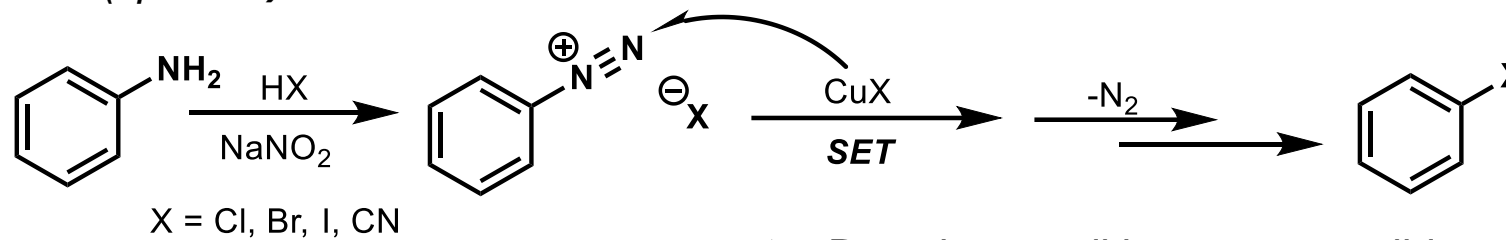
C—C 332 kJ/mol

C—N 305 kJ/mol



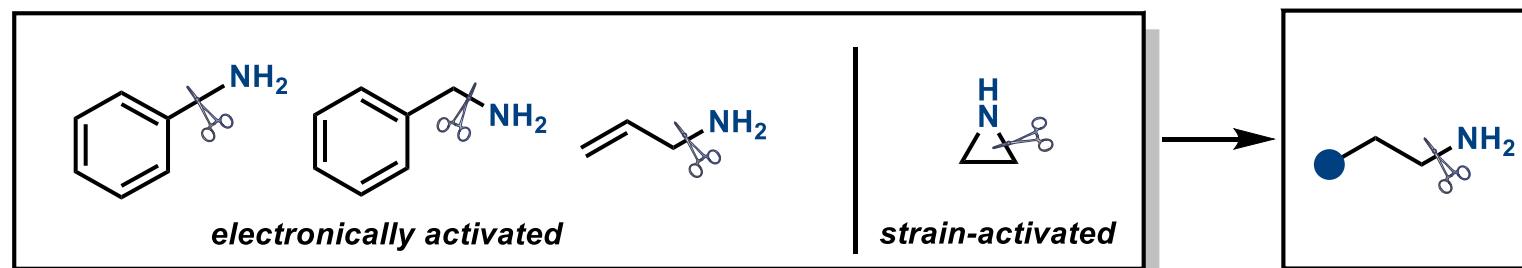
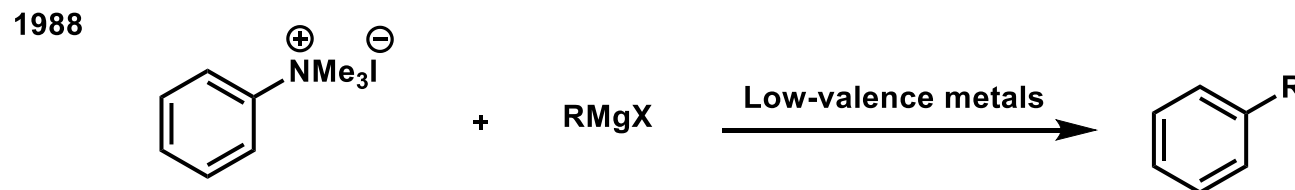
High bond energy
Poor leaving group ability

Sandmeyer Reaction (sp^2 C-N)



- Reaction conditions are not mild
- Strong acids and oxidants
- Instability of diazonium salts

Quaternary ammonium salts (sp^2 C-N & activated sp^3 C-N)



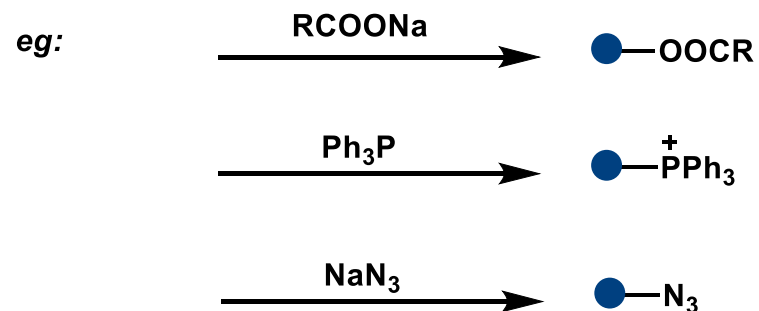
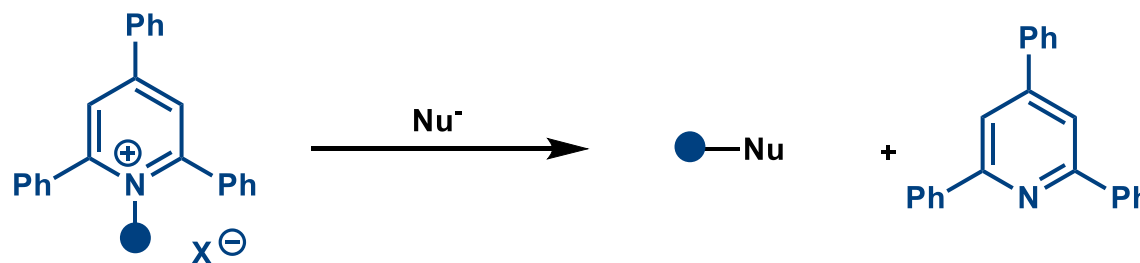
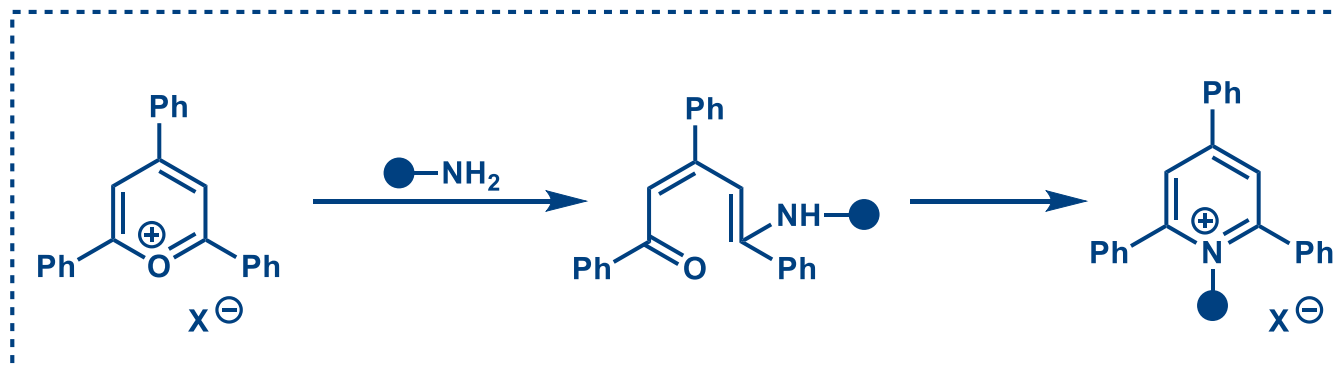
?

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Katritzky-type Pyridinium Salts



Alan Roy Katritzky
1928-2014



Katritzky, A. R.; Gruntz, U.; Kenny, D. H.; Rezende, M. C.; Sheikh, H. *J. Chem. Soc., Perkin Trans.* **1979**, 1, 430.

Katritzky, A. R.; Leahy, D.E. *J. Chem. Soc., Perkin Trans.* **2**, **1985**, 171.

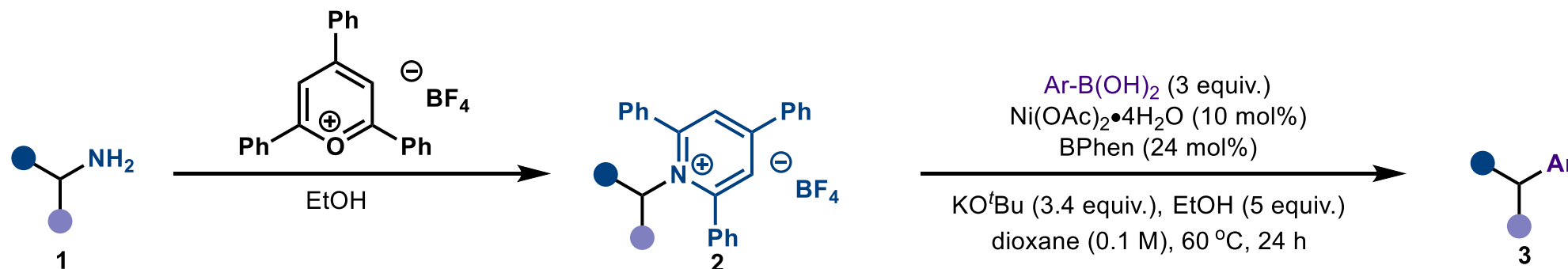
Katritzky, A. R.; Marson, C. M. *Angew. Chem., Int. Ed. Engl.* **1984**, 23, 420.

Said, S. A.; Fiksdahl, A. *Tetrahedron: Asymmetry* **2001**, 12, 1947.

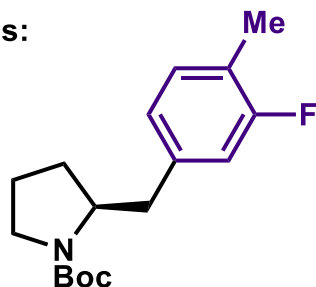
Deamination of Pyridinium Salts by TM Catalysis

Arylation

M. P. Watson

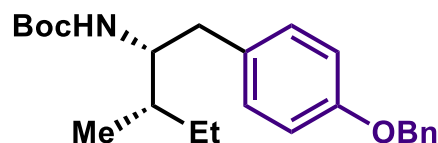


selected examples:



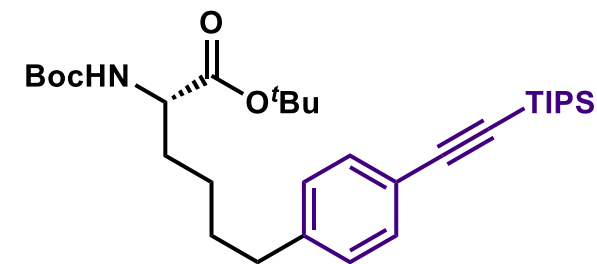
3a, 65%

From *proline*



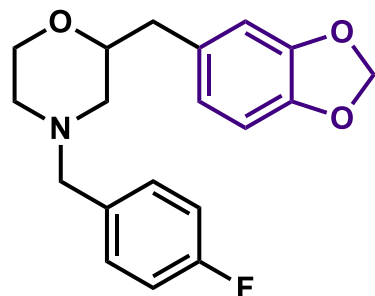
3b, 52%

From *isoleucine*



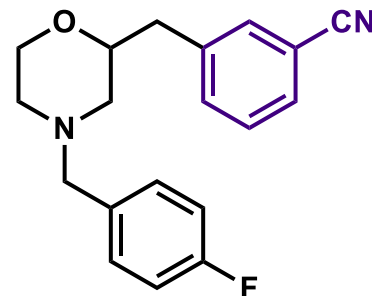
3c, 60%

From *lysine*

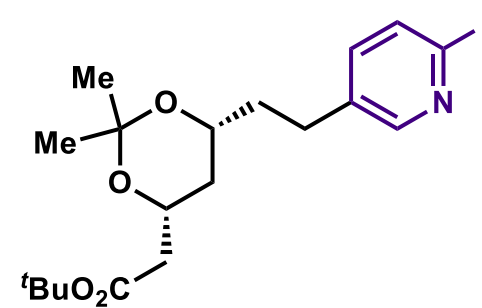


3d, 71%

From *Mosapride intermediate*



3e, 62%

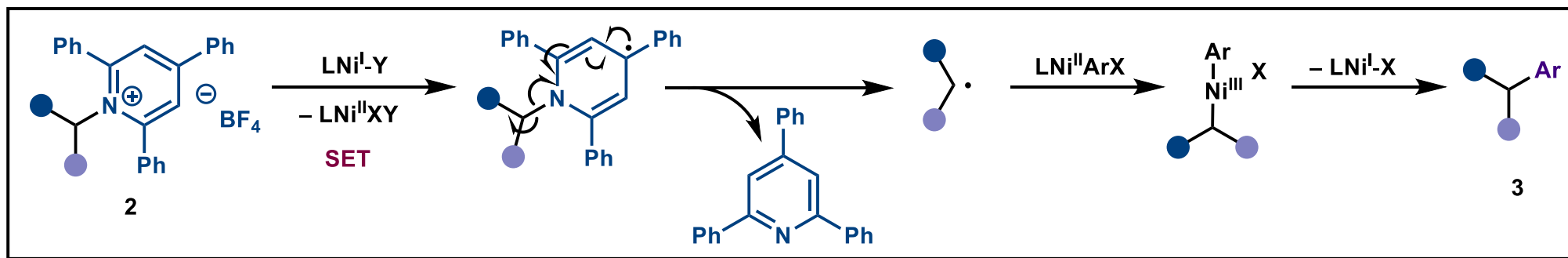
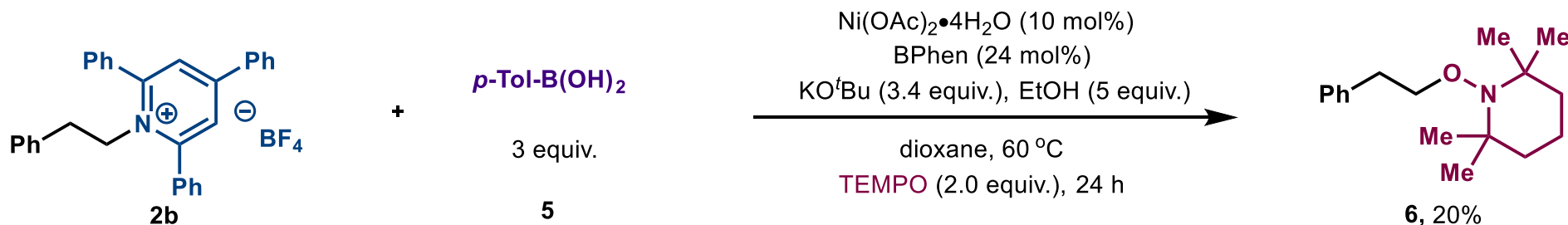
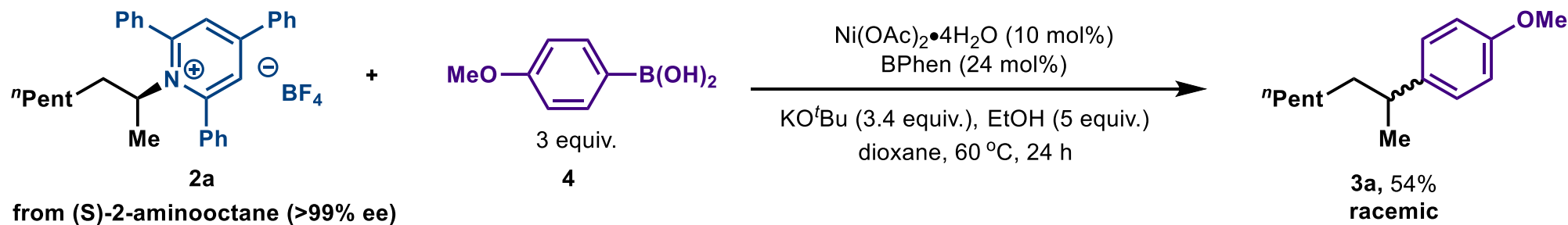


3f, 46%

From *Lipitor intermediate*

Deamination of Pyridinium Salts by TM Catalysis

Investigation of the reaction mechanism

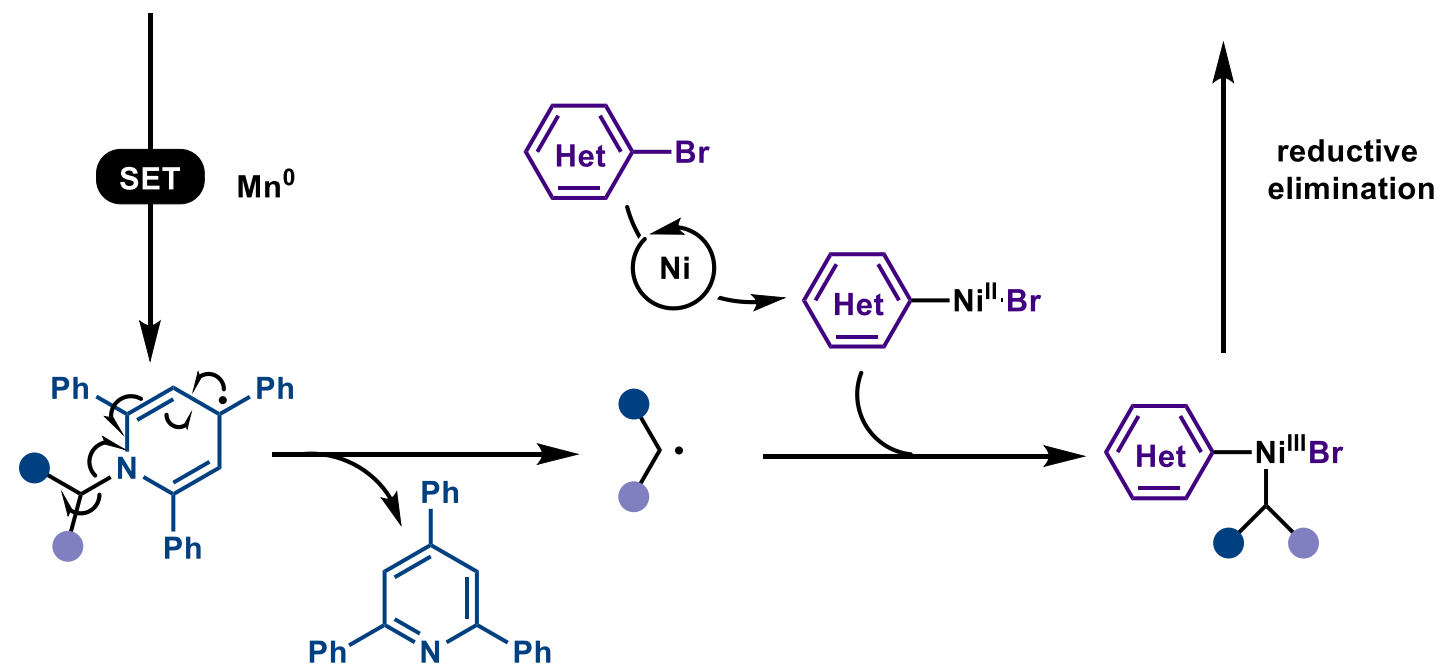
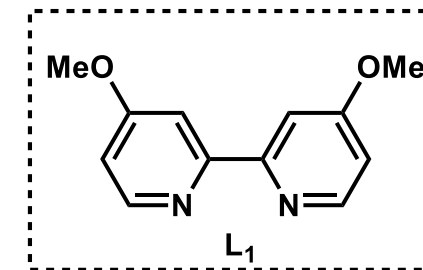
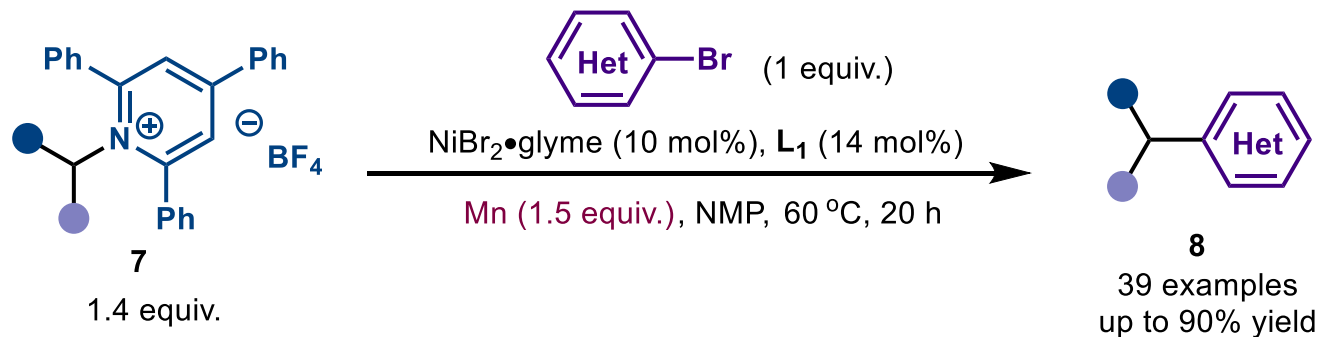


Deamination of Pyridinium Salts by TM Catalysis



Arylation

R. Martin

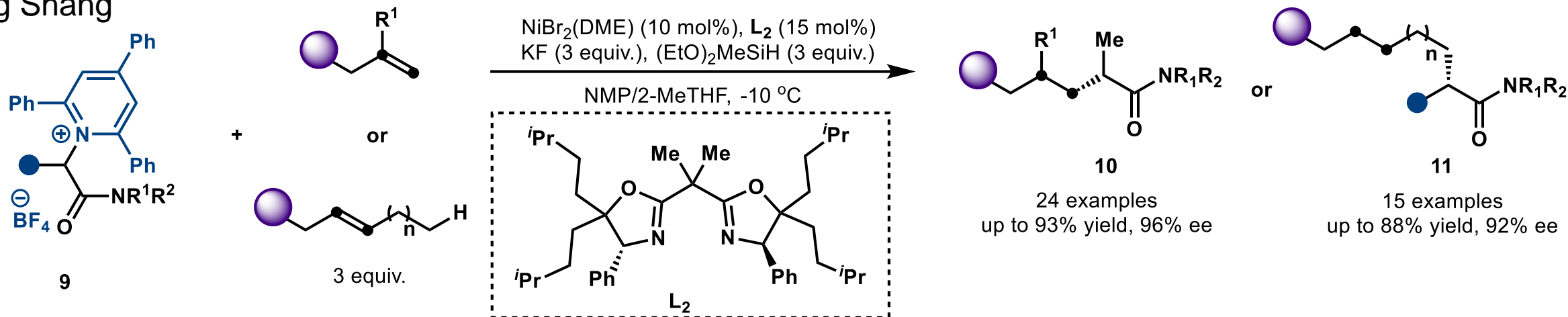


Deamination of Pyridinium Salts by TM Catalysis

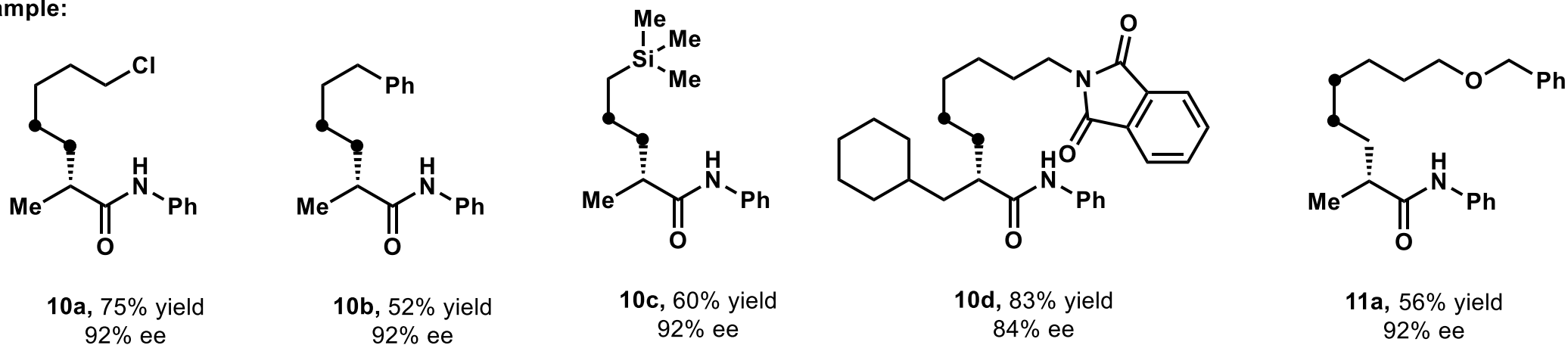


Dicarbon functionalization

Ming Shang



selected example:

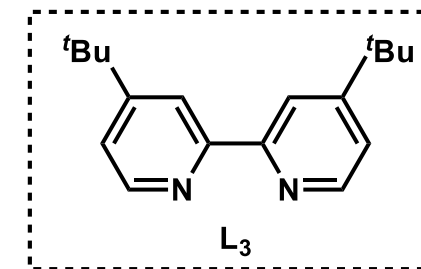
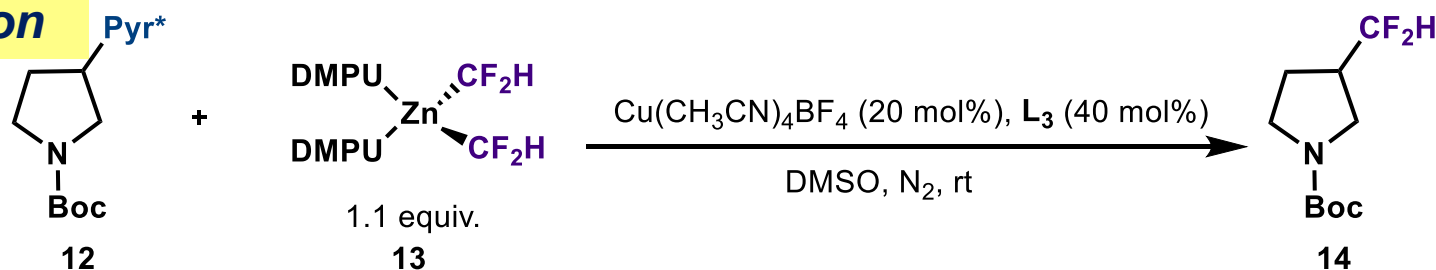


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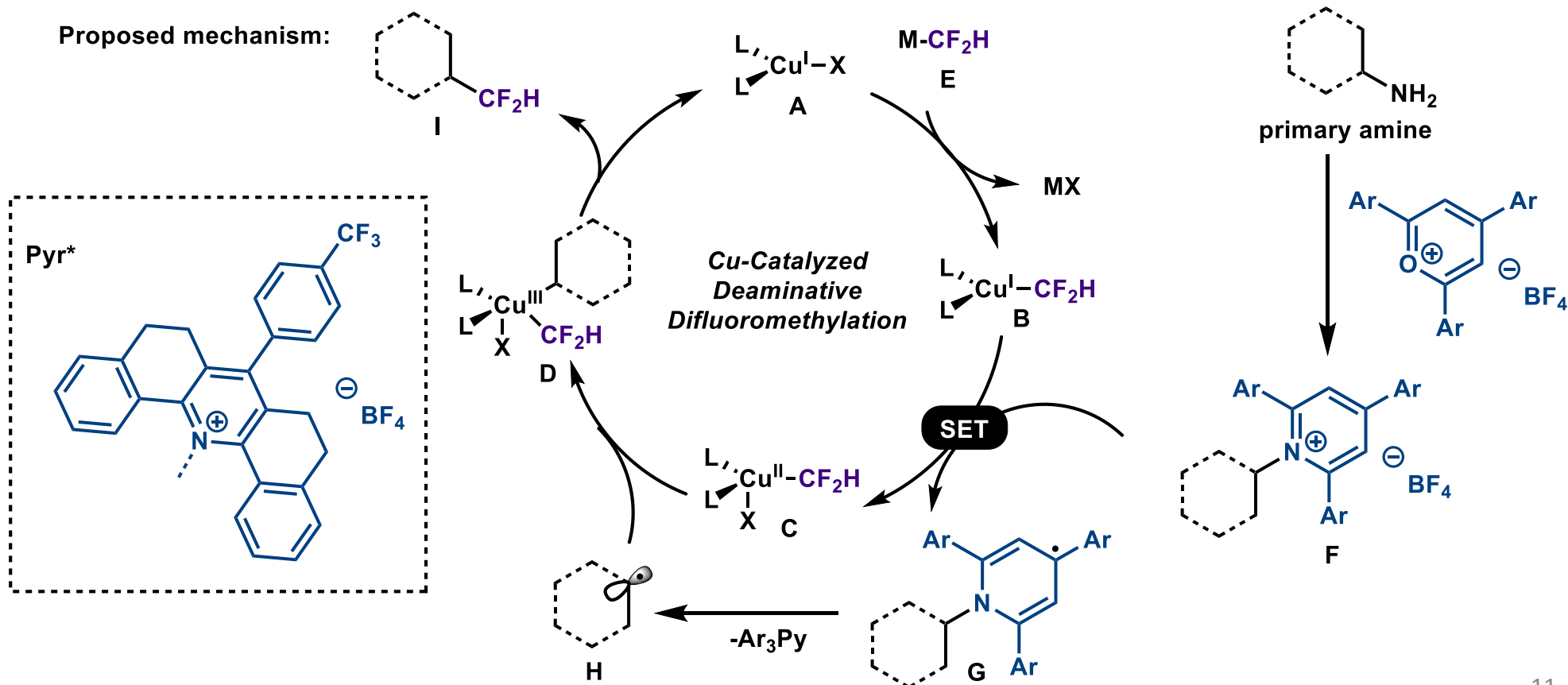


Difluoromethylation

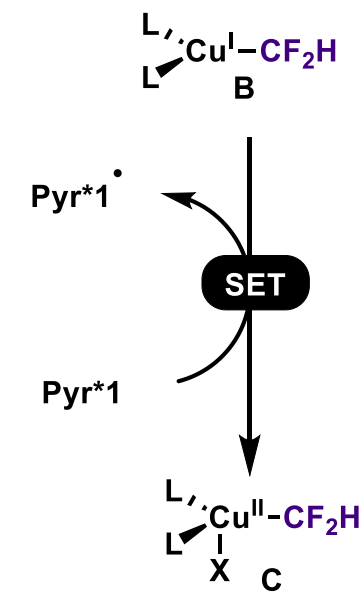
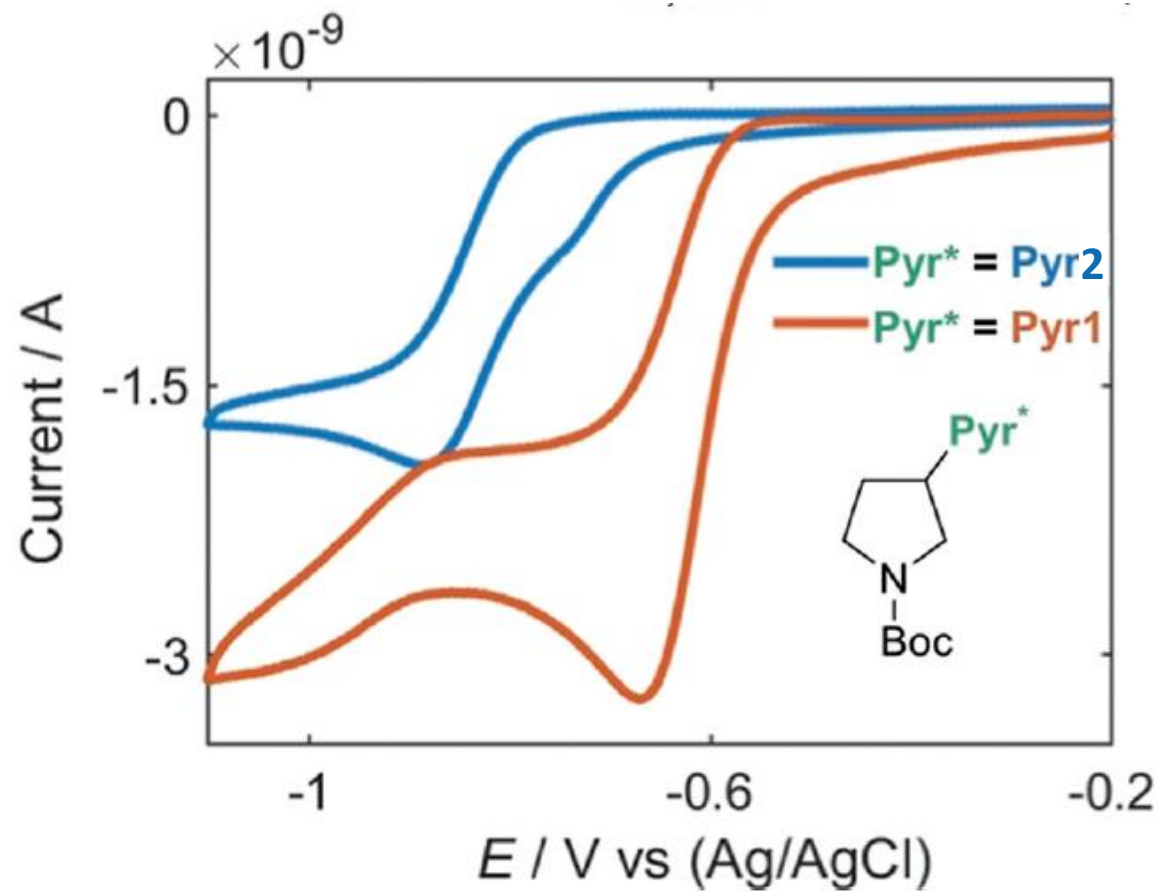
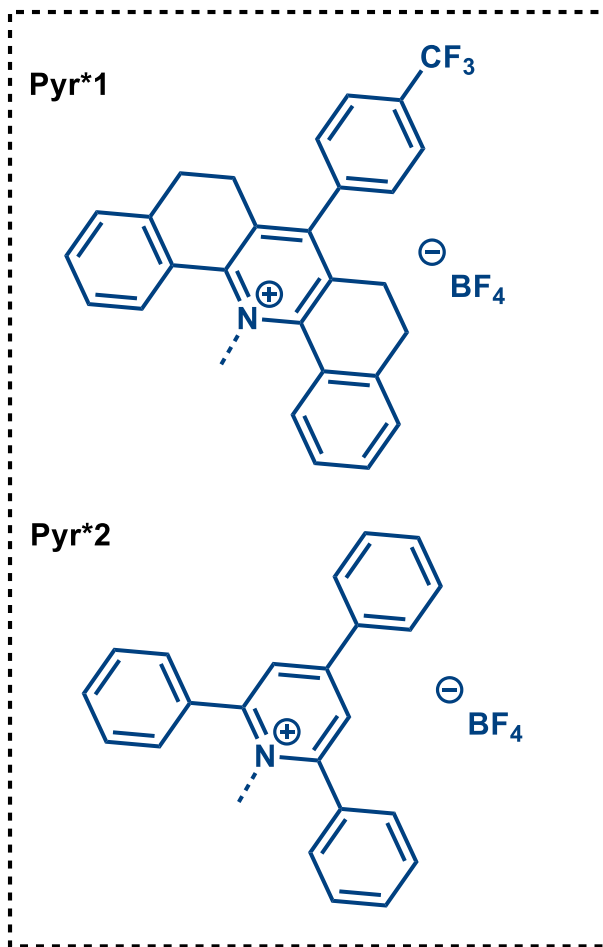
Liu Wei



Proposed mechanism:



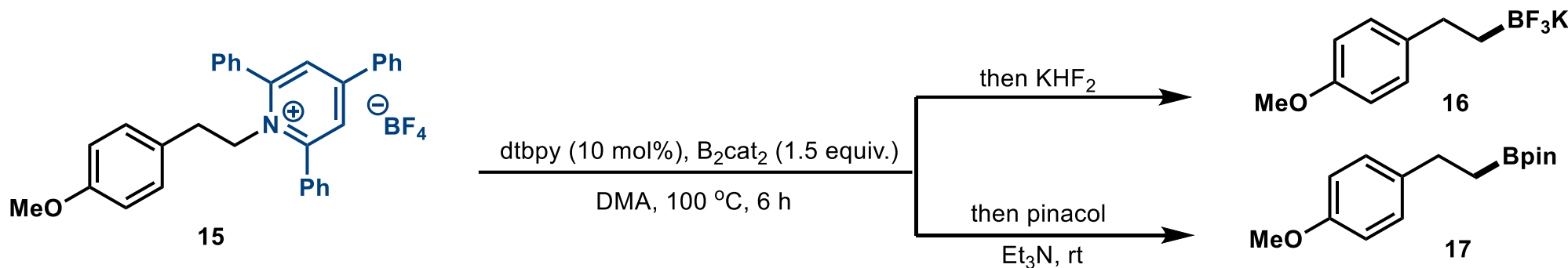
Deamination of Pyridinium Salts by TM Catalysis



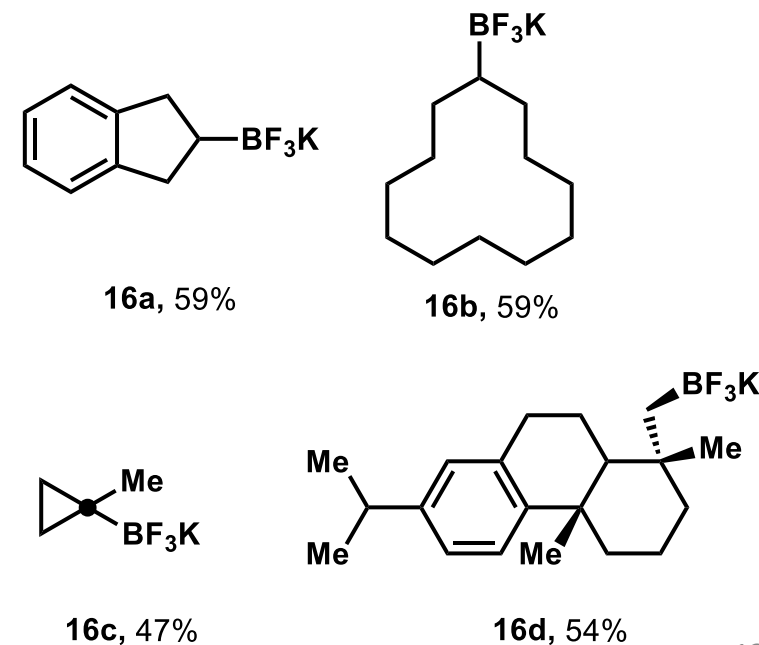
Deamination of Pyridinium Salts by LB Catalysis

Borylation

Shi Zhuangzhi
&
Li Shuhua



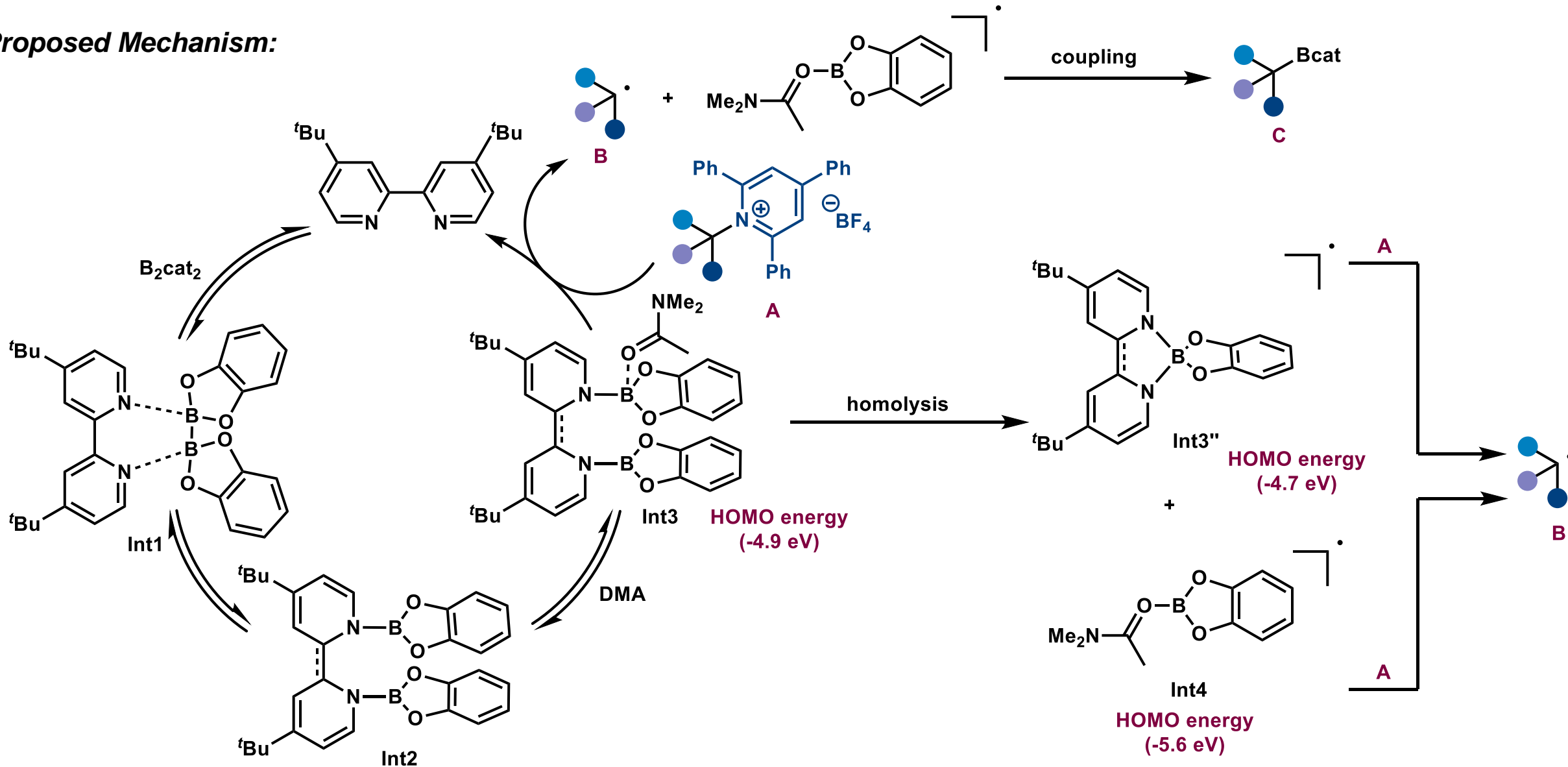
selected examples:



Entry	Variation from the standard conditions	yield
1	None	84
2	Without Lewis base	28
3	Without Lewis base, 24 h	49
4	B_2pin_2 instead of B_2cat_2	0
5	In the dark	80

Deamination of Pyridinium Salts by LB Catalysis

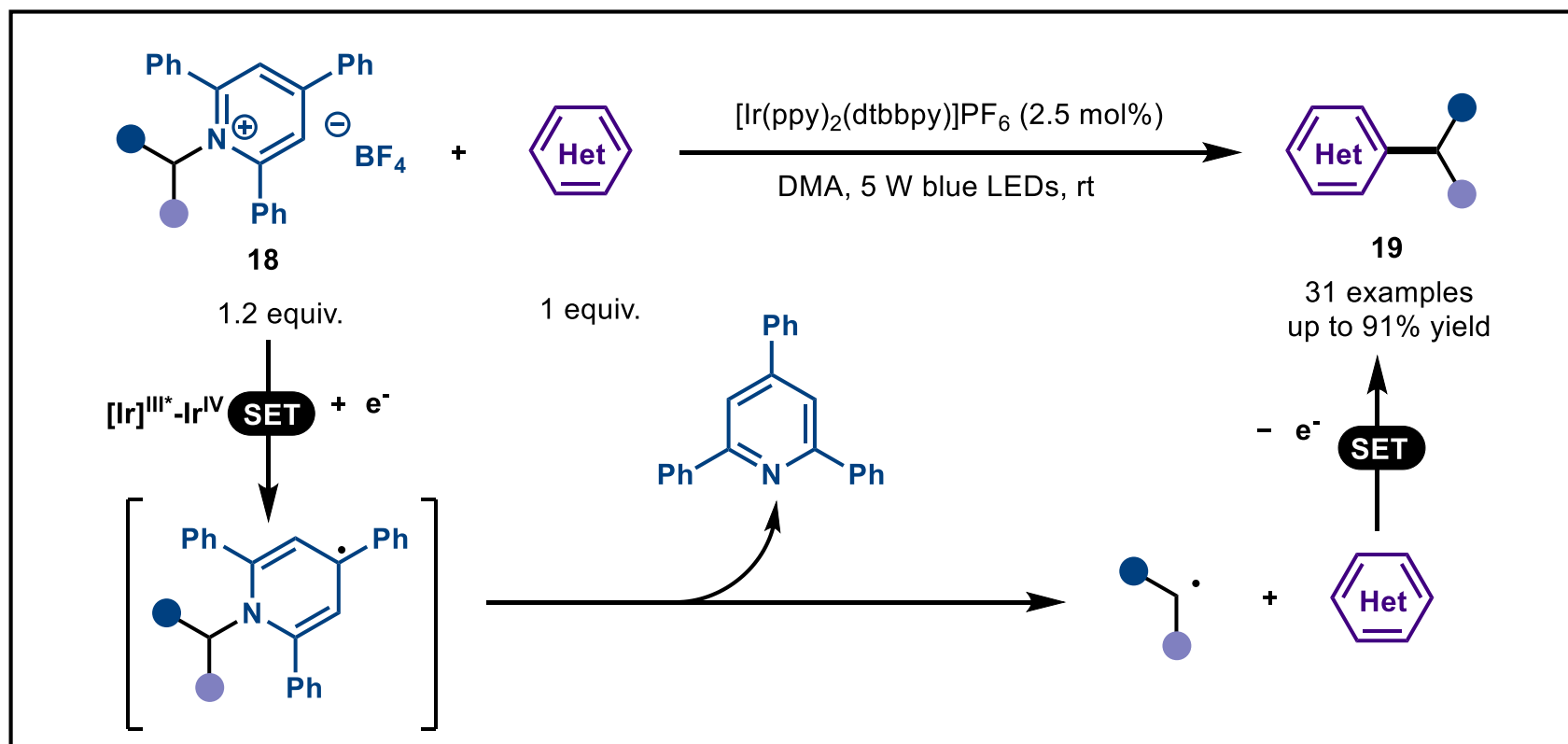
Proposed Mechanism:



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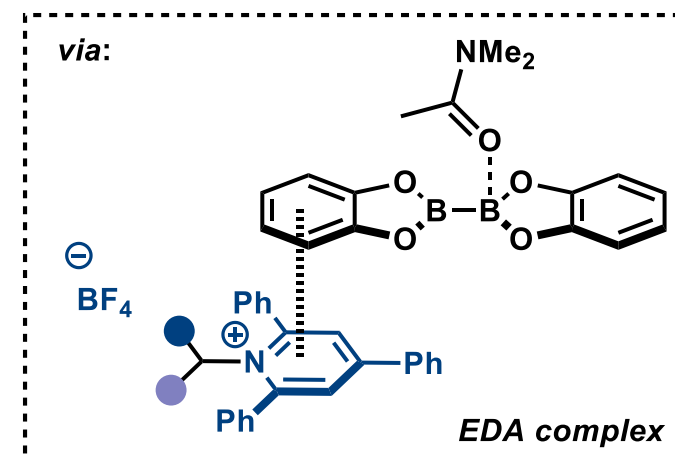
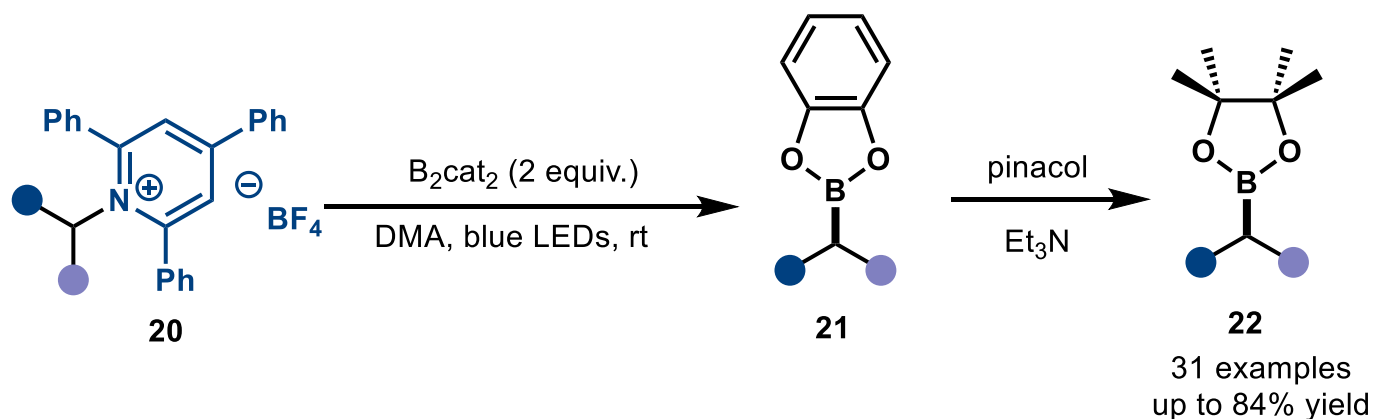
Heteroarylation

F. Glorius

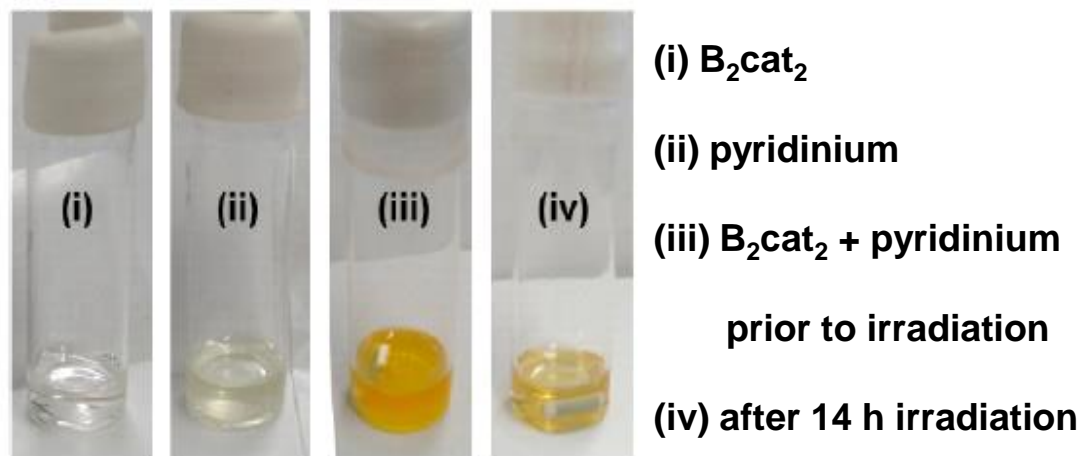


Deamination of Pyridinium Salts by Photocatalysis

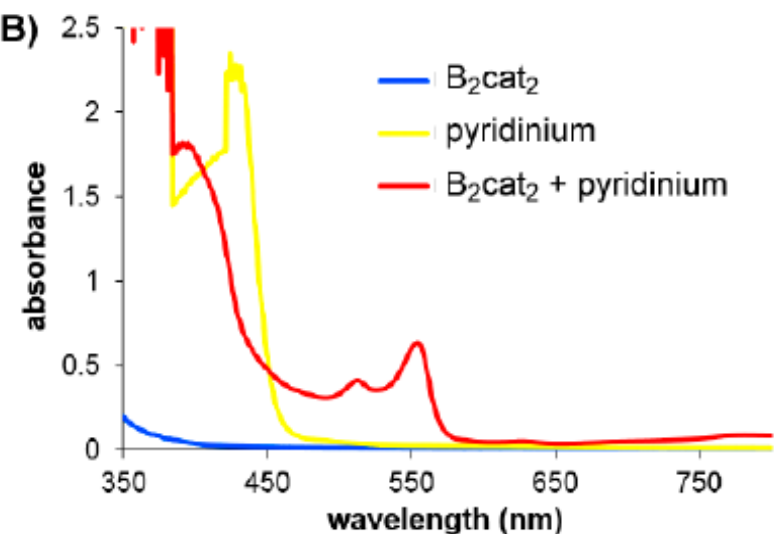
V. K. Aggarwal



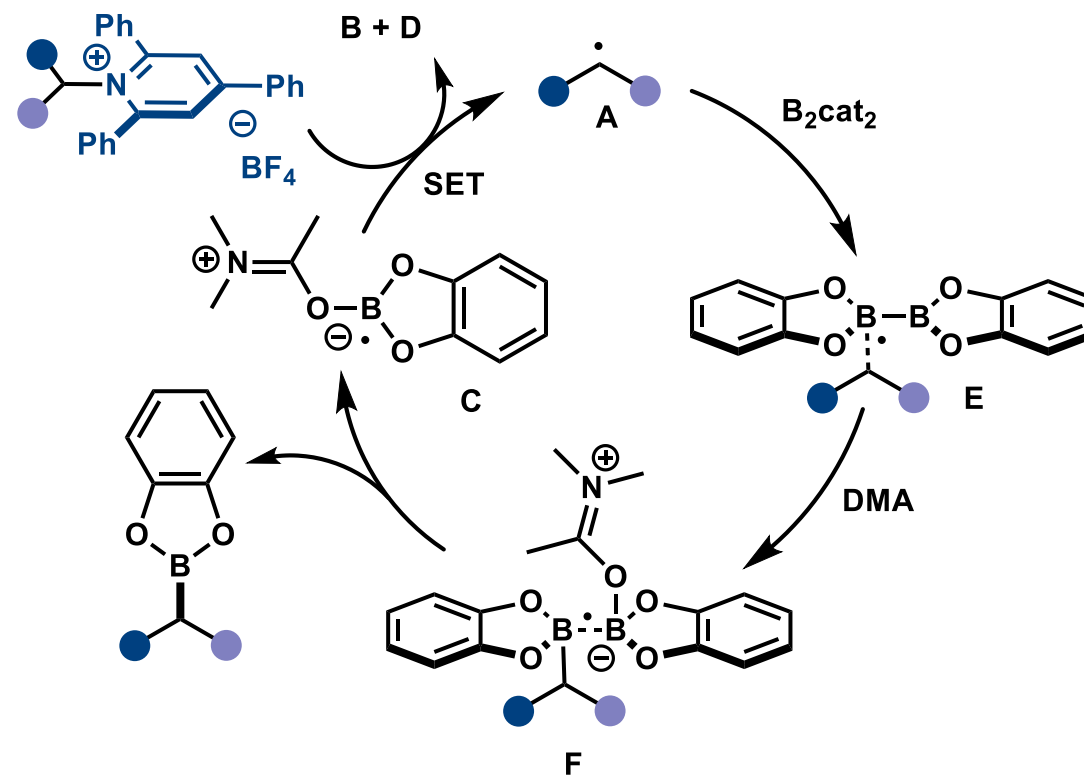
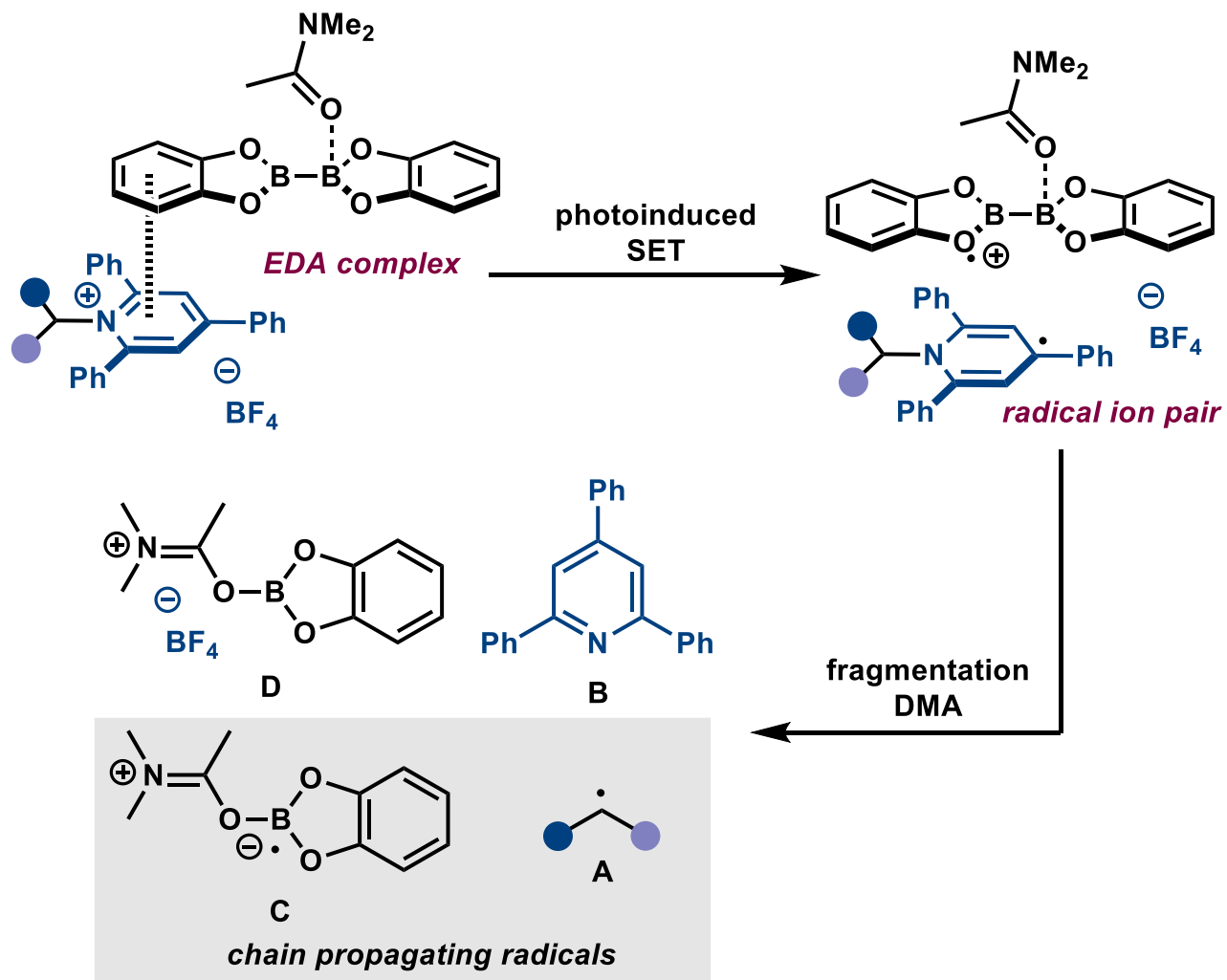
(A)



(B)

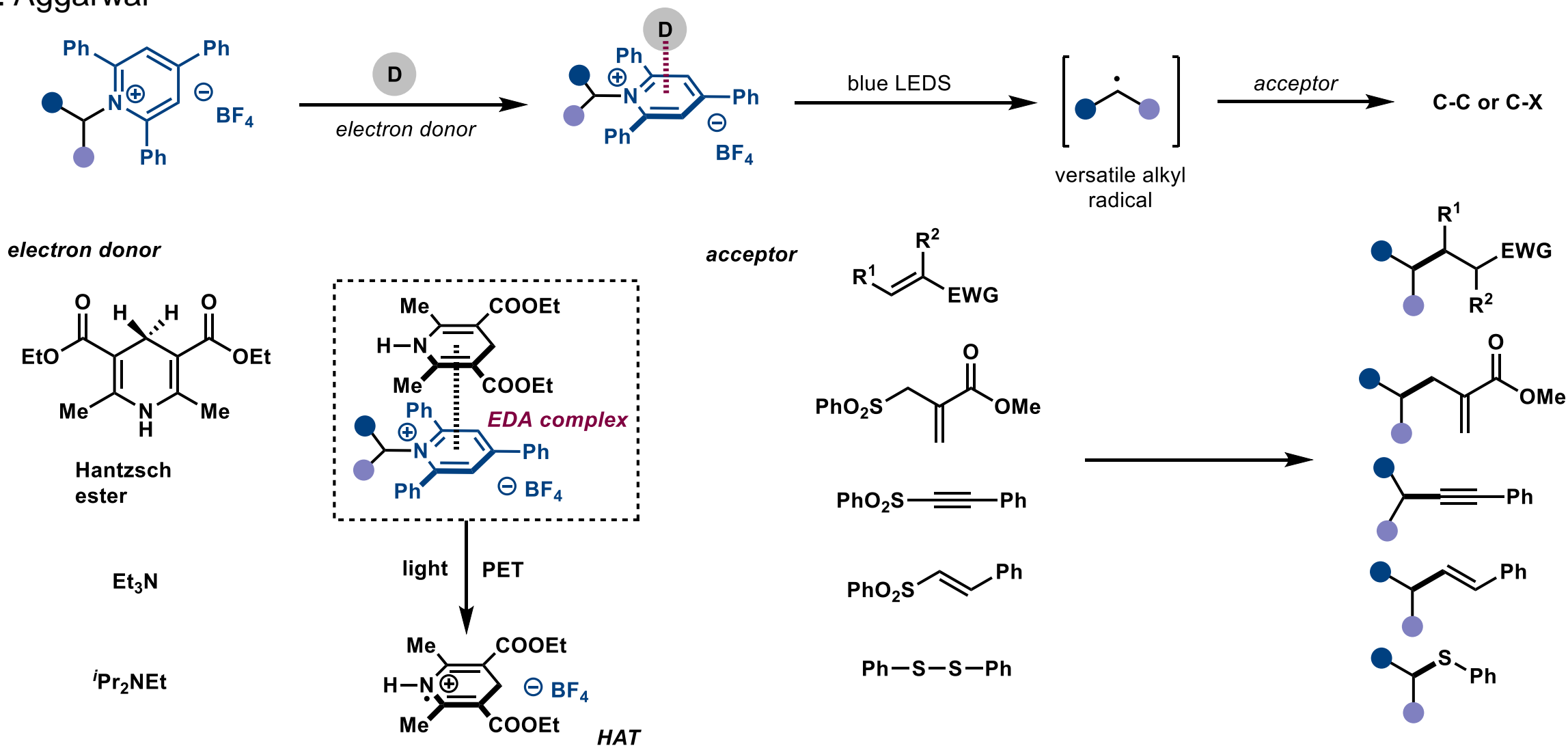


Proposed Mechanism:



Deamination of Pyridinium Salts by Photocatalysis

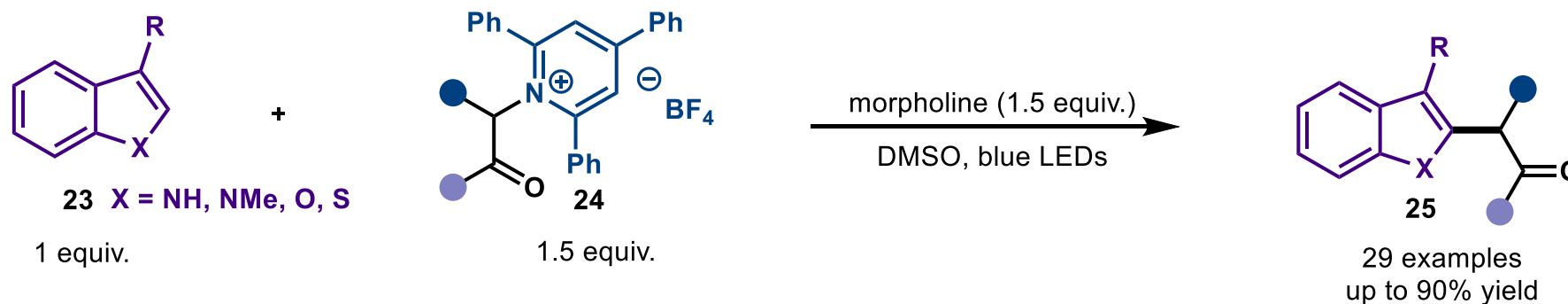
V. K. Aggarwal



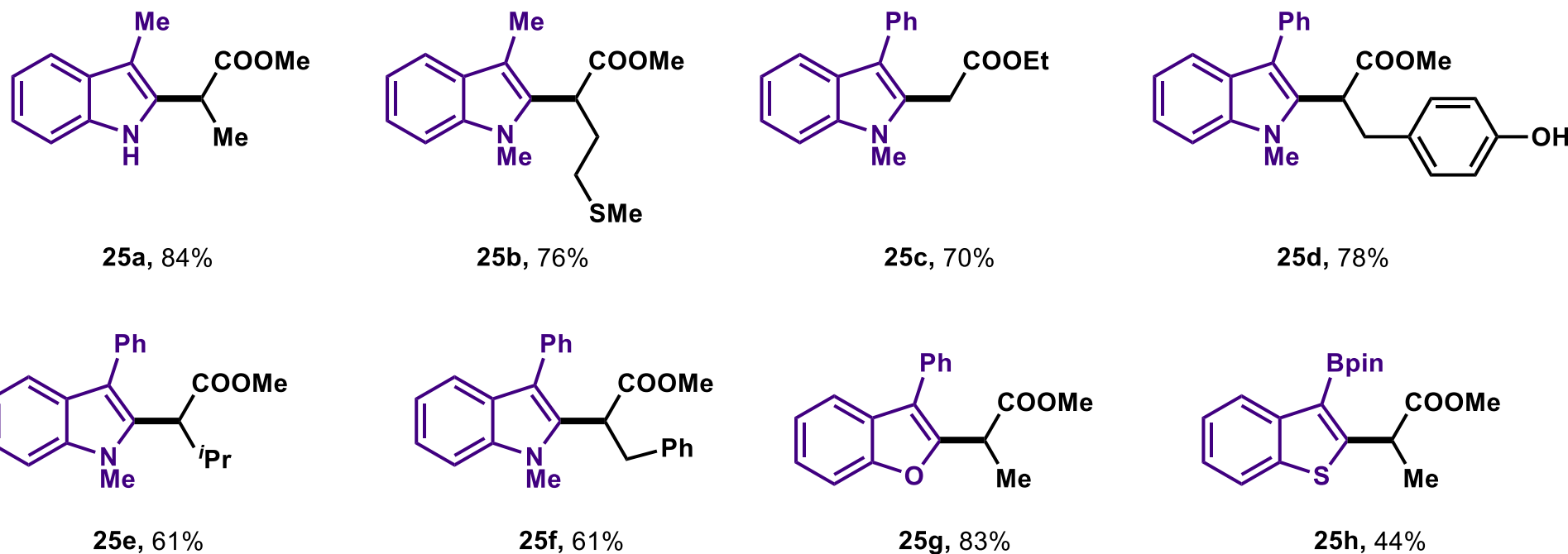
Deamination of Pyridinium Salts by Photocatalysis



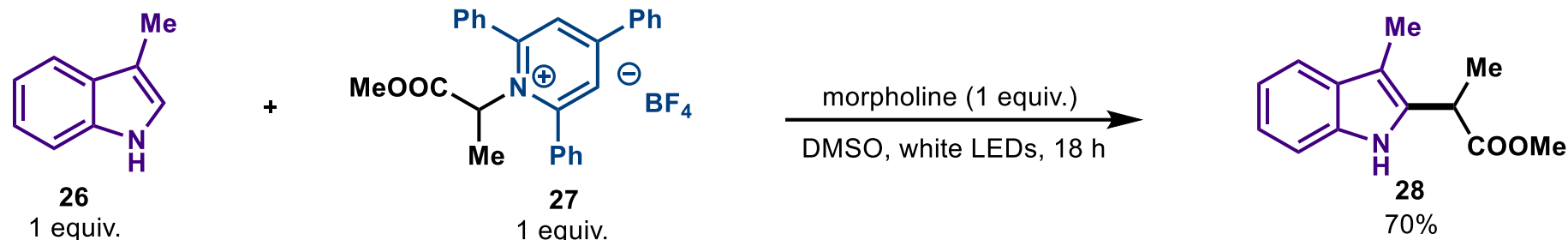
F. Glorius



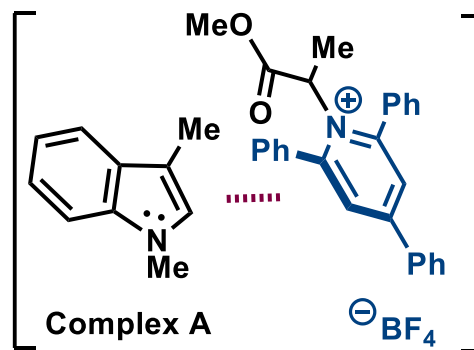
selected examples:



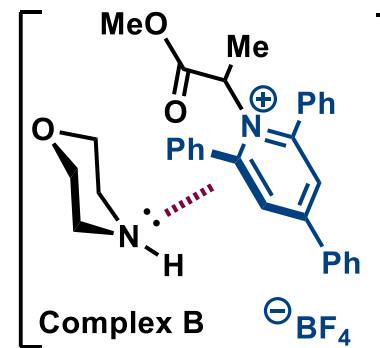
Deamination of Pyridinium Salts by Photocatalysis



Base	Yield
morph. No light	8%
morph. + O ₂	0%

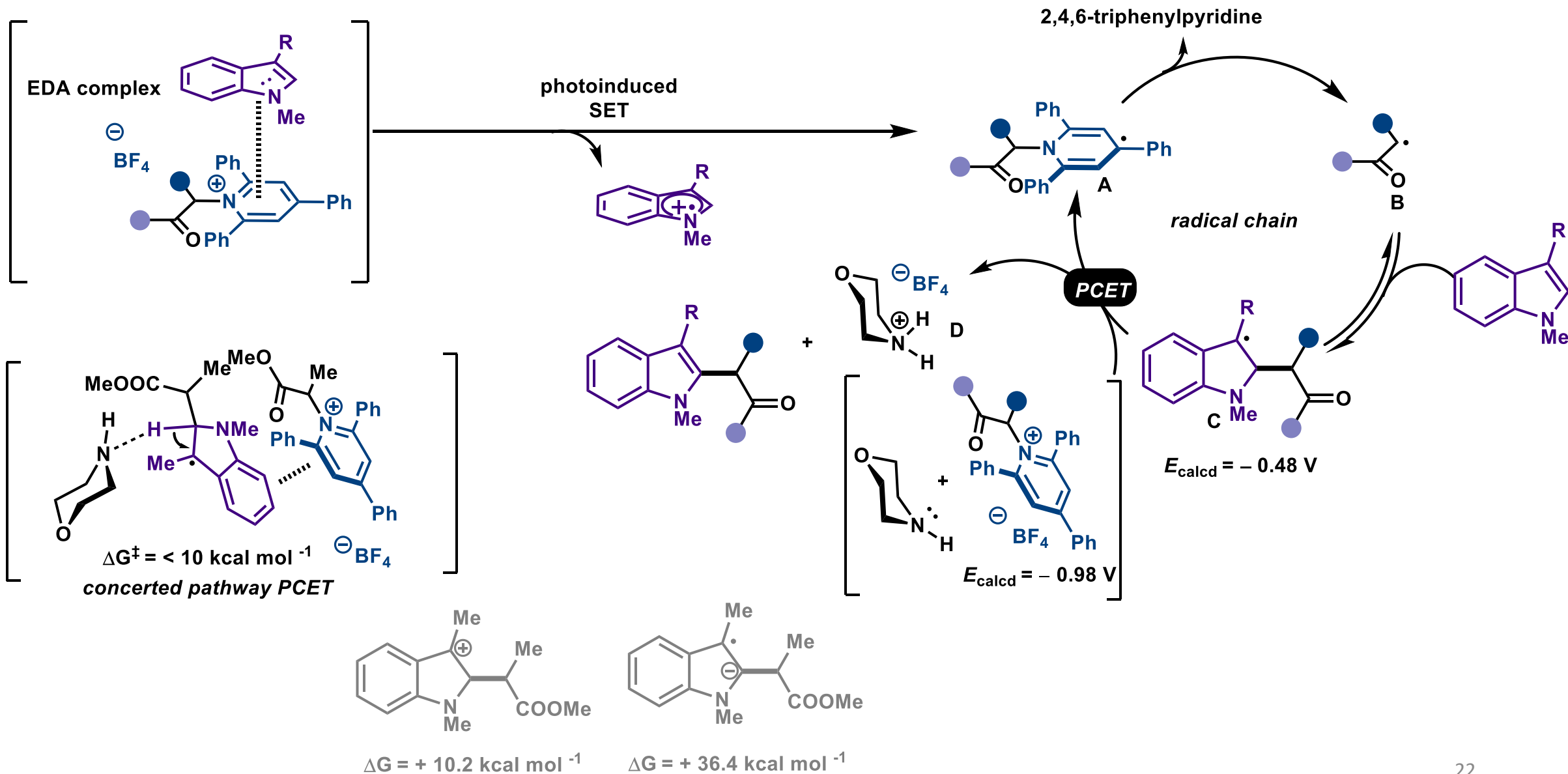


1:1 complex, $K_{\text{EDA}} = 2.1 \text{ M}^{-1}$
 $\epsilon_{\text{EDA}} (455 \text{ nm}) = 20.2 \text{ M}^{-1} \text{ cm}^{-1}$



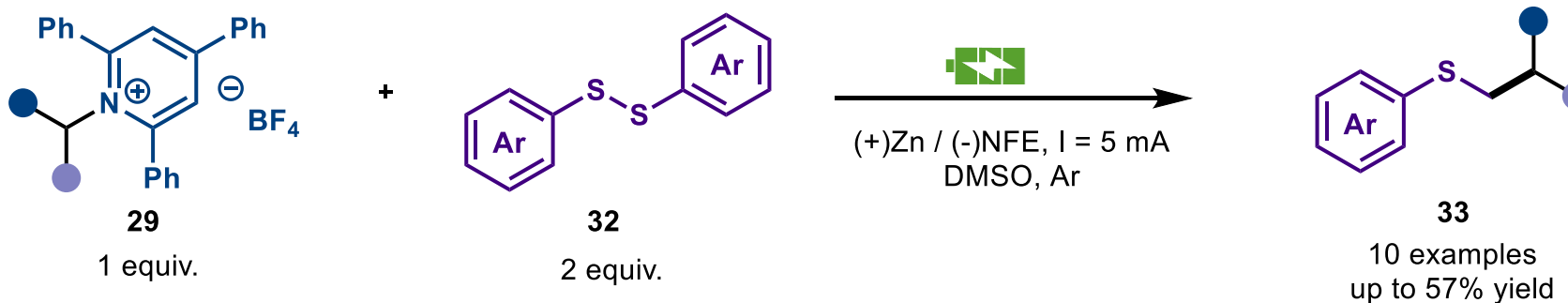
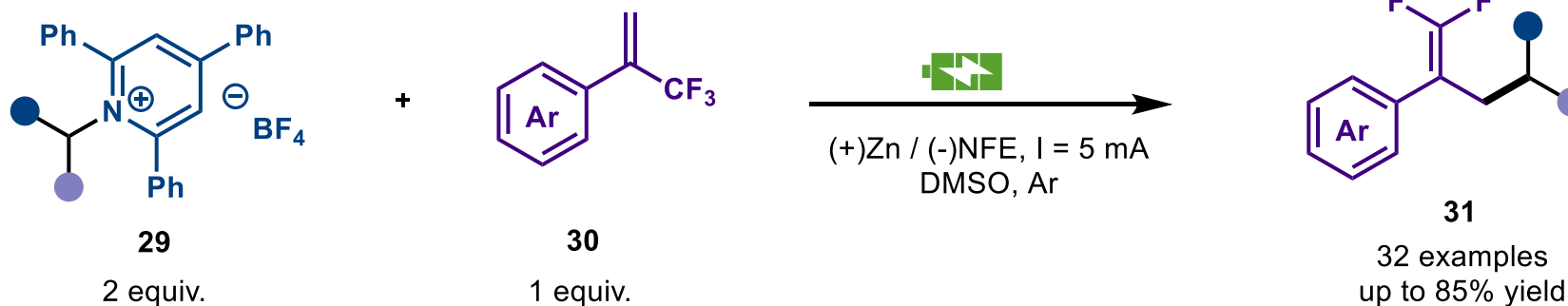
1:1 complex, $K_{\text{EDA}} = 8.8 \text{ M}^{-1}$
 $\epsilon_{\text{EDA}} (455 \text{ nm}) = 6.2 \times 10^{-3} \text{ M}^{-1} \text{ cm}^{-1}$

Deamination of Pyridinium Salts by Photocatalysis



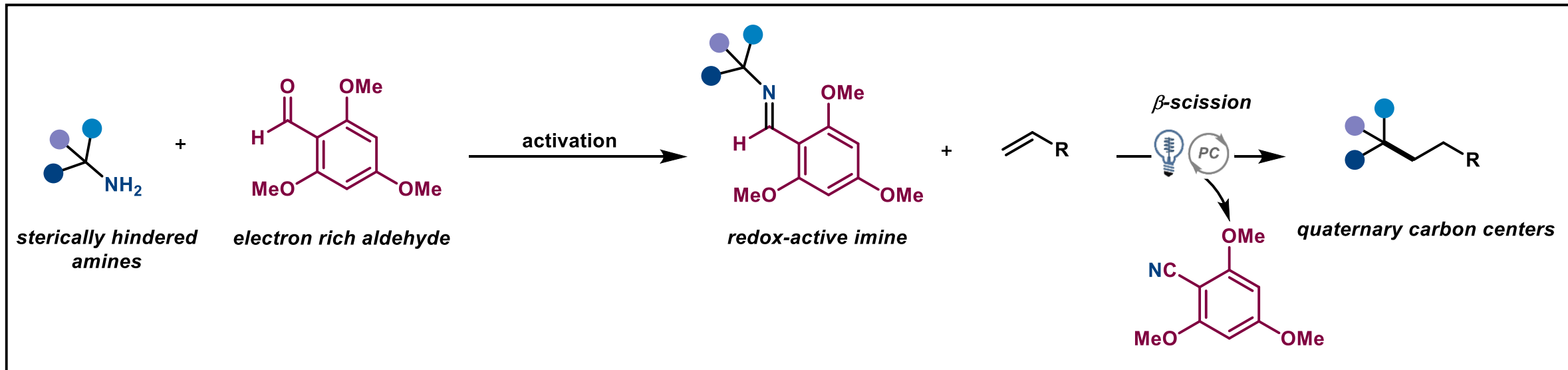
Fluoroalkenylation and Thiolation

Wang Yi
&
Pan Yi

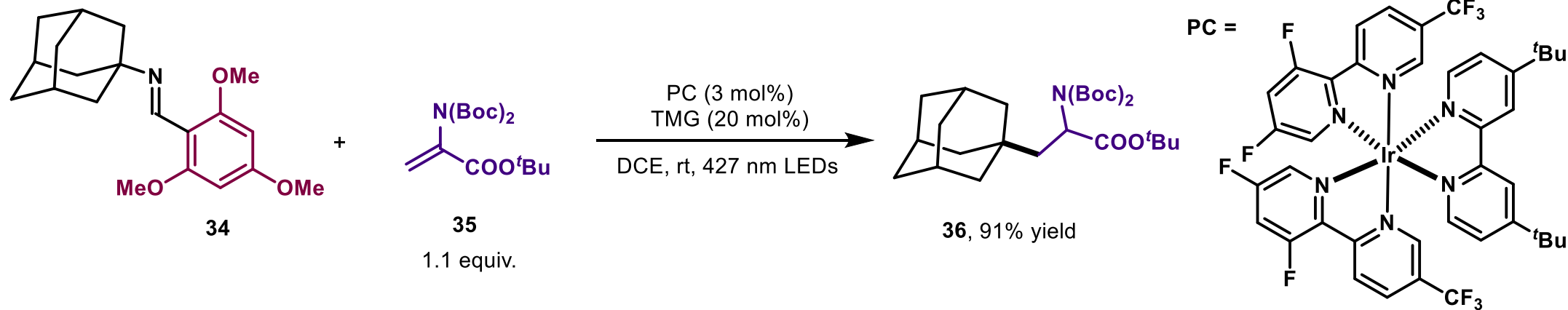


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Electron-rich Imines By Photocatalysis

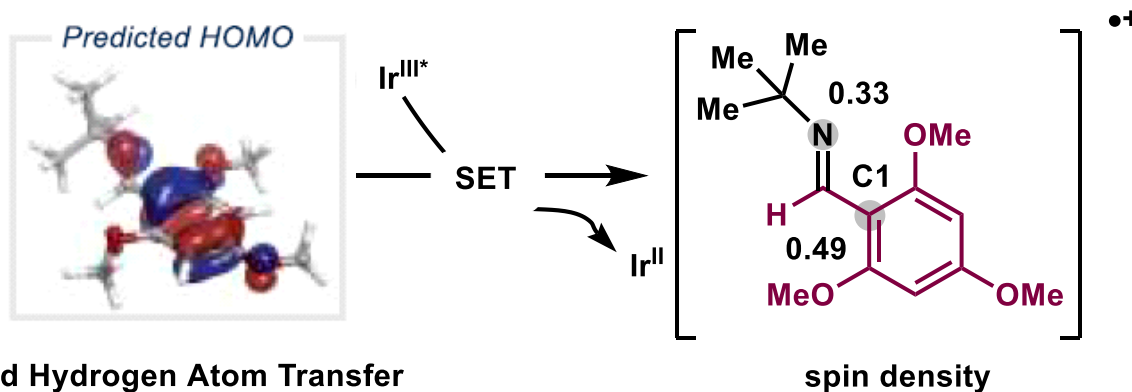


T. Rovis

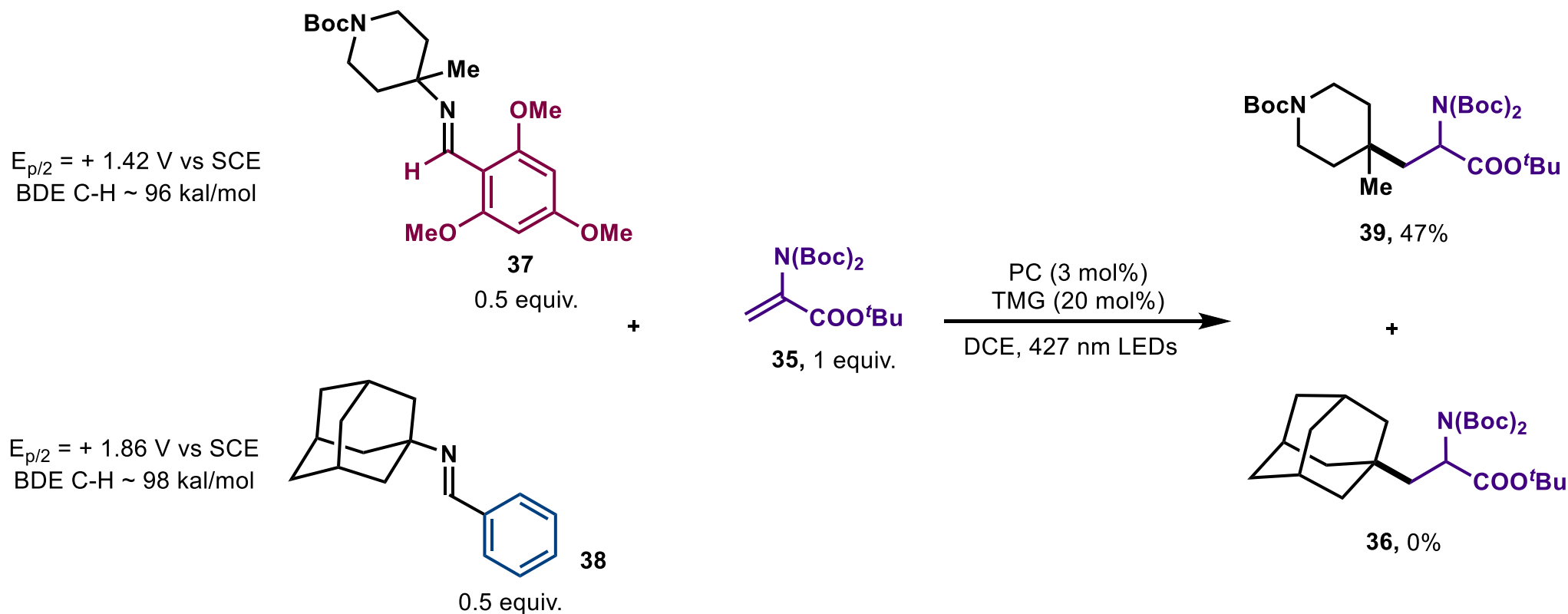


Electron-rich Imines By Photocatalysis

A. Potential Modes of Activation

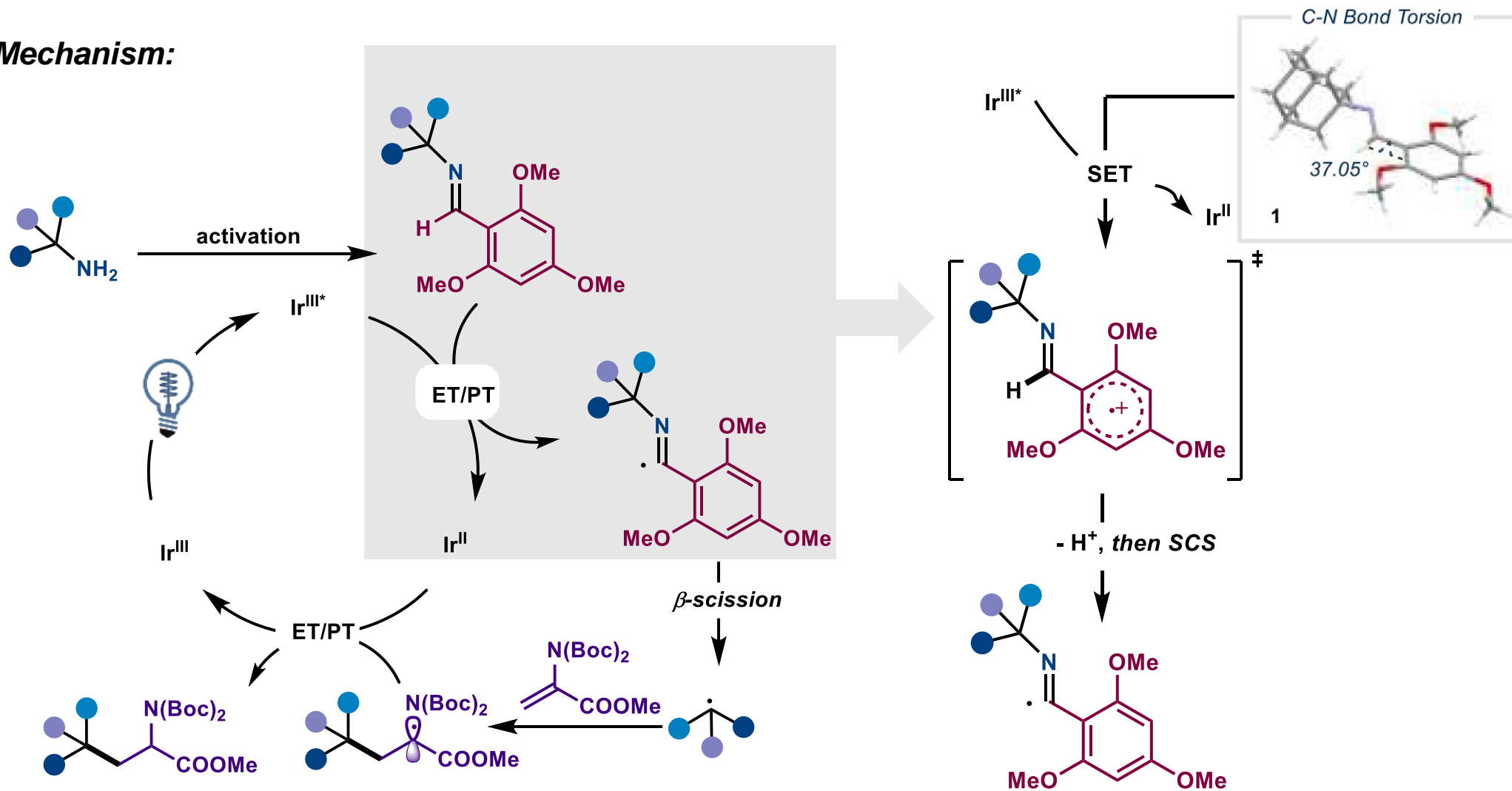


B. Testing for Iminyl Radical Promoted Hydrogen Atom Transfer



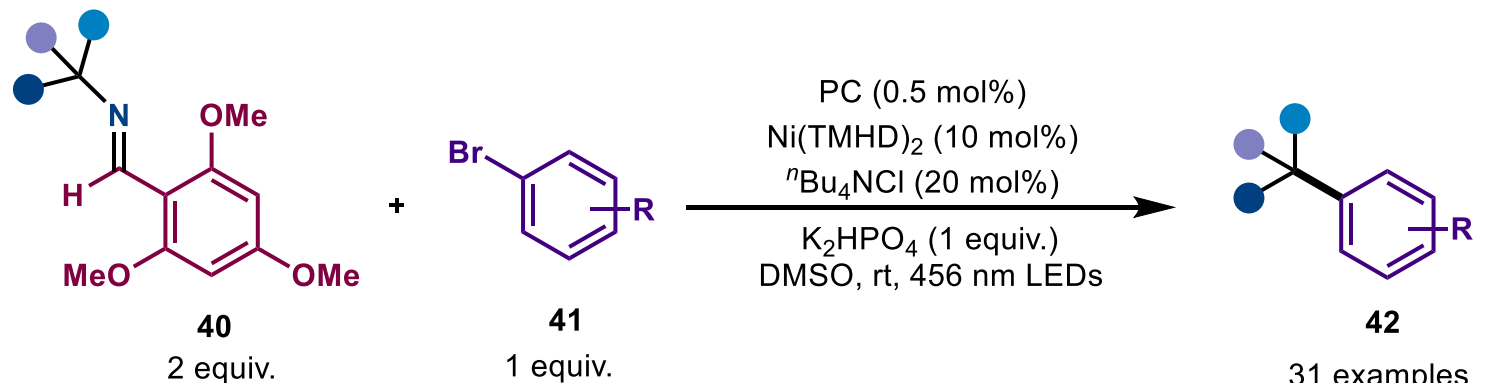
Electron-rich Imines By Photocatalysis

Proposed Mechanism:

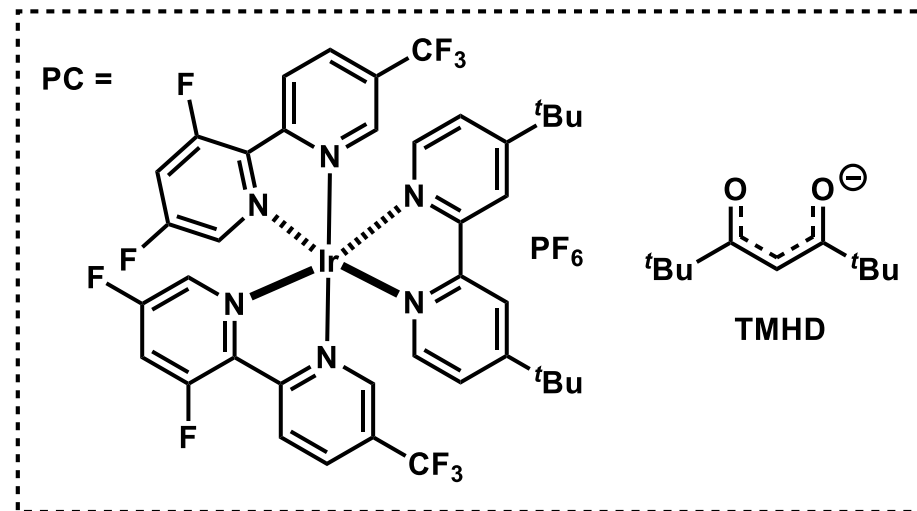


Electron-rich Imines By Nickel/Photo-Catalyzed

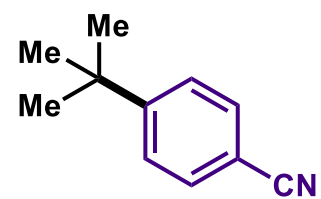
T. Rovis



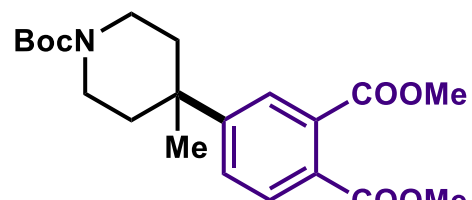
selected examples:



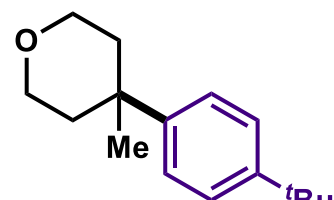
31 examples
up to 94% yield



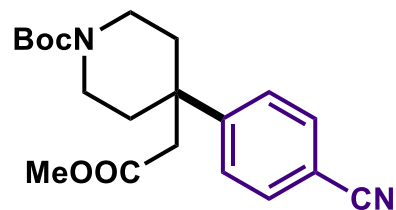
42a, 94%



42b, 61%

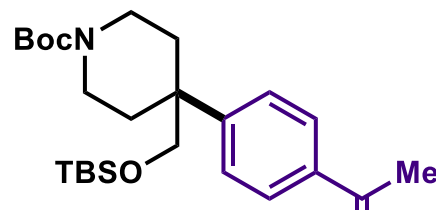


42c, 33%



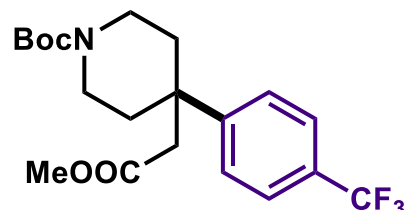
42d, 65%

from TACE Inhibitor intermediate



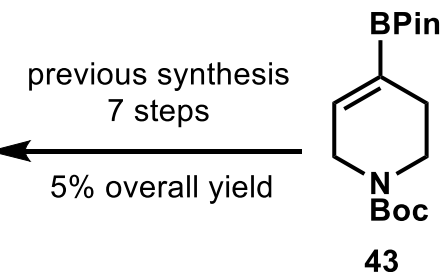
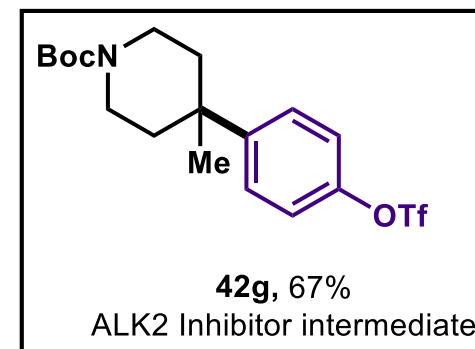
42e, 49%

NK₁ antagonist analog



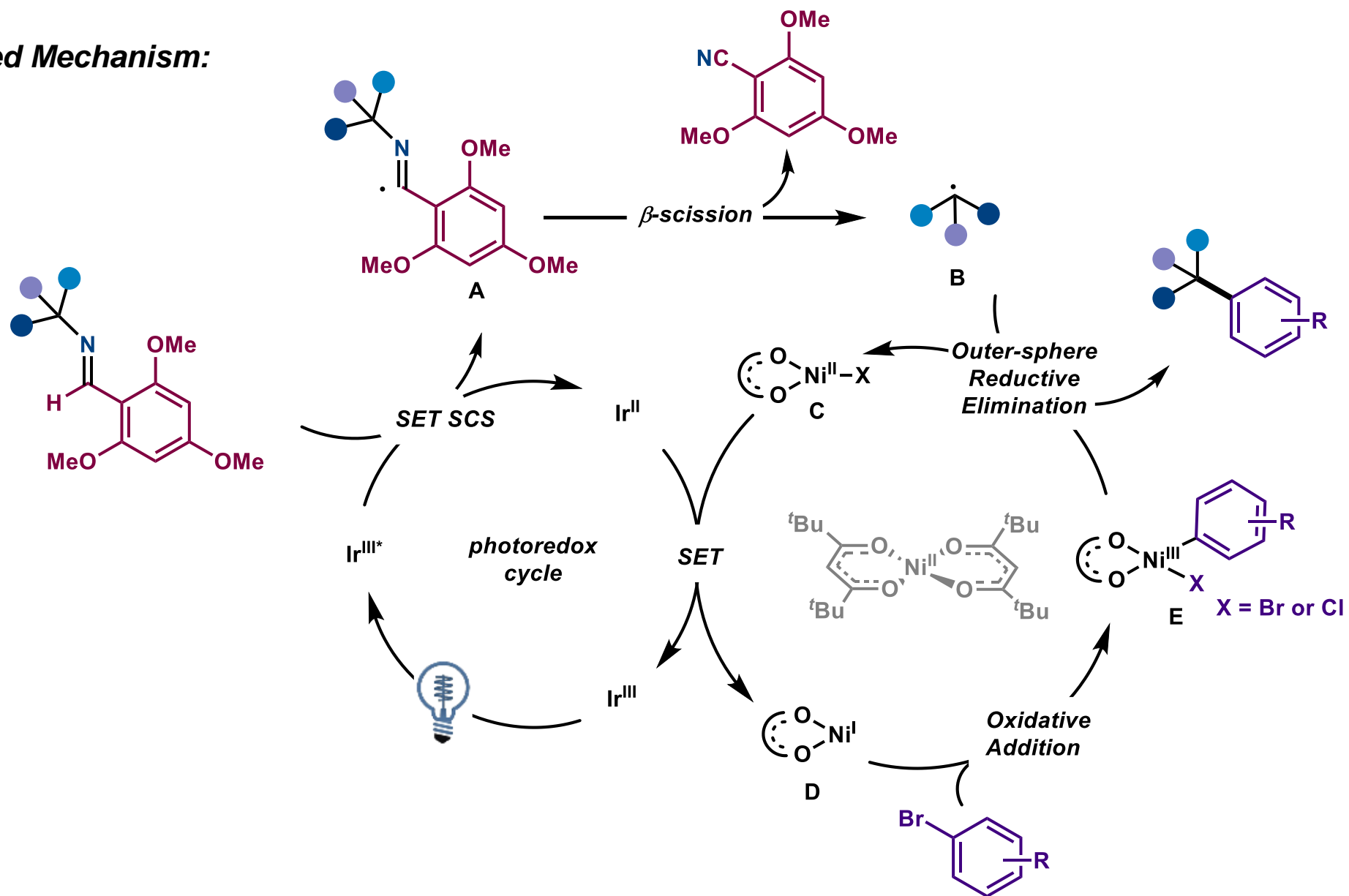
42f, 65%

CCR5 antagonist intermediate



Electron-rich Imines By Nickel/Photo-Catalyzed

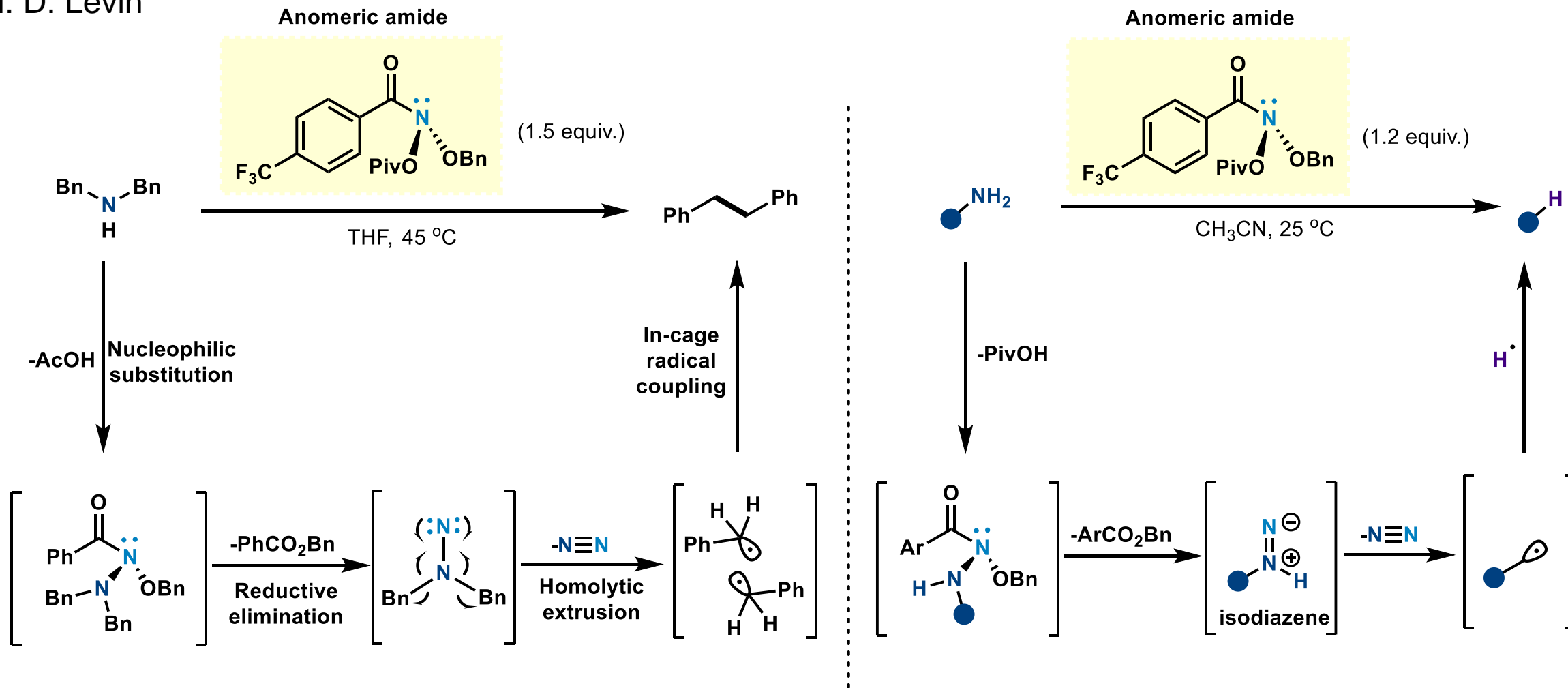
Proposed Mechanism:



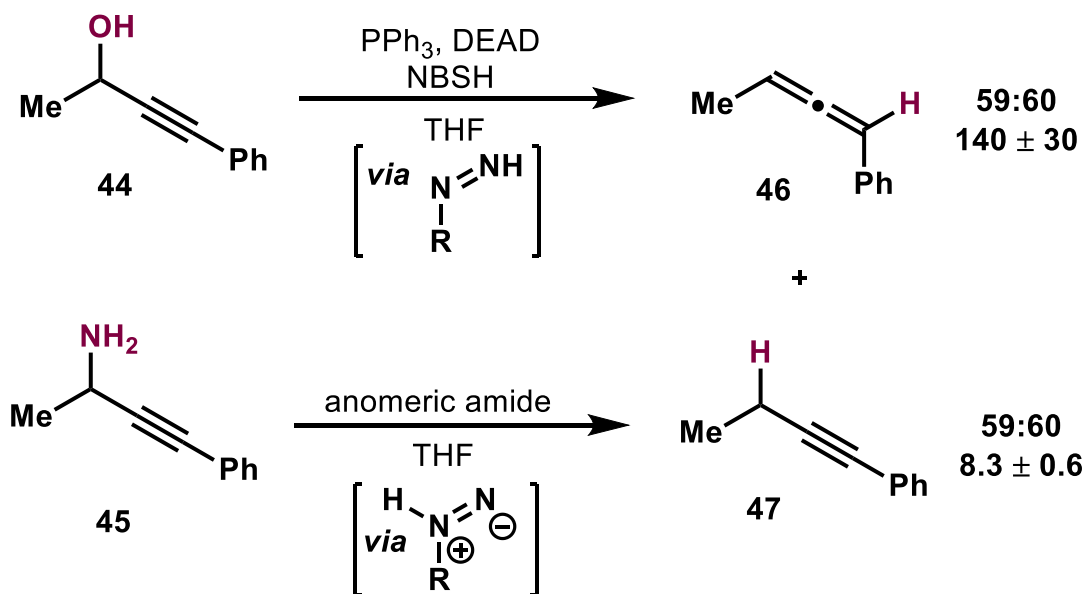
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- Summary and Outlook

Direct Deaminative Functionalizations

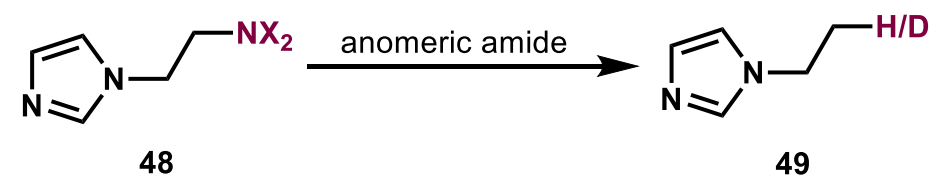
M. D. Levin



Comparison with the Myers allene synthesis

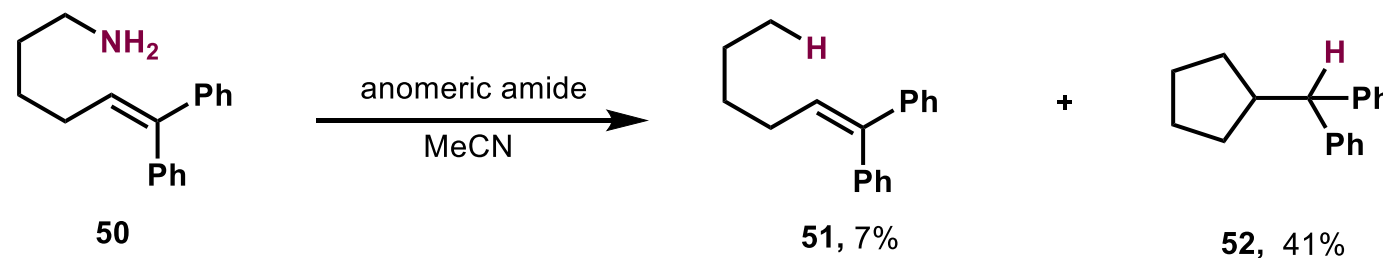


Deuterium labeling studies

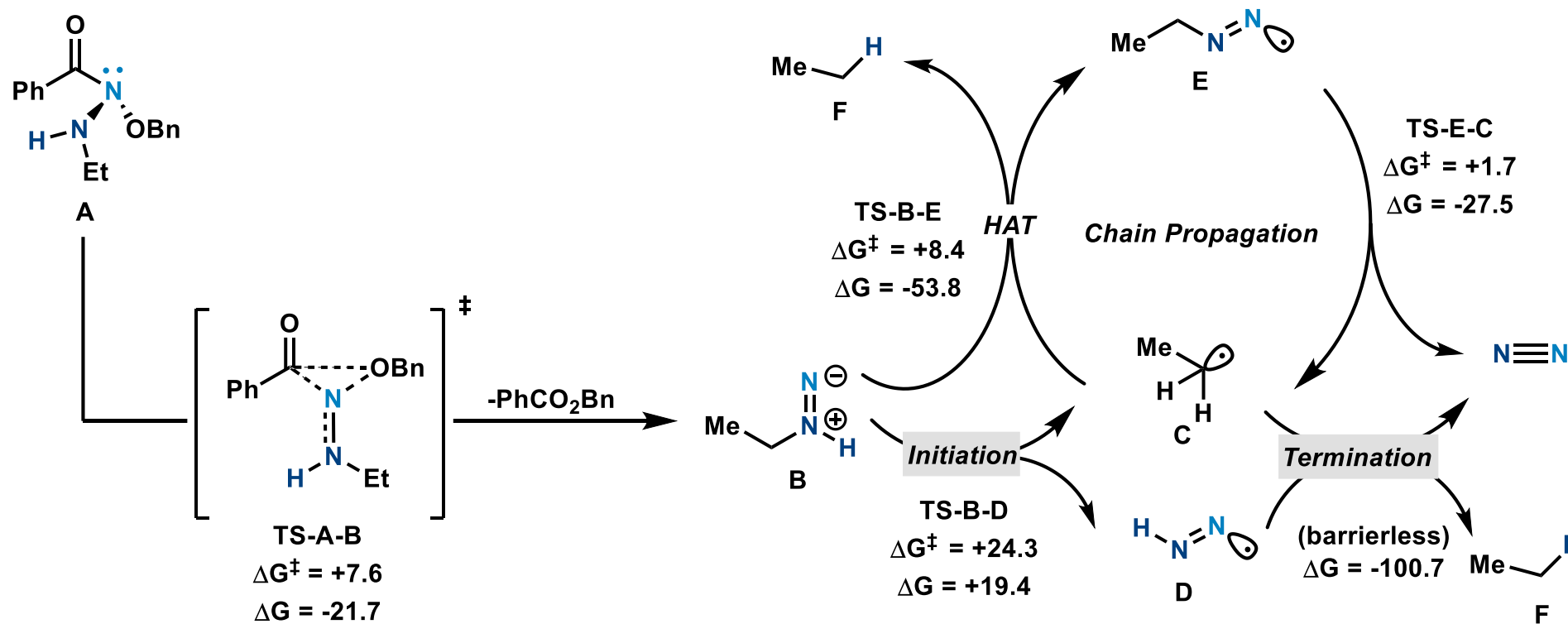


X ₂	Solvent	Product
X = H	MeCN-d ₃	0% D
X = D	MeCN	63 ± 9% D
X = H	96:4 MeCN/D ₂ O	73 ± 7% D
X = D	96:4 MeCN/D ₂ O	101 ± 4% D

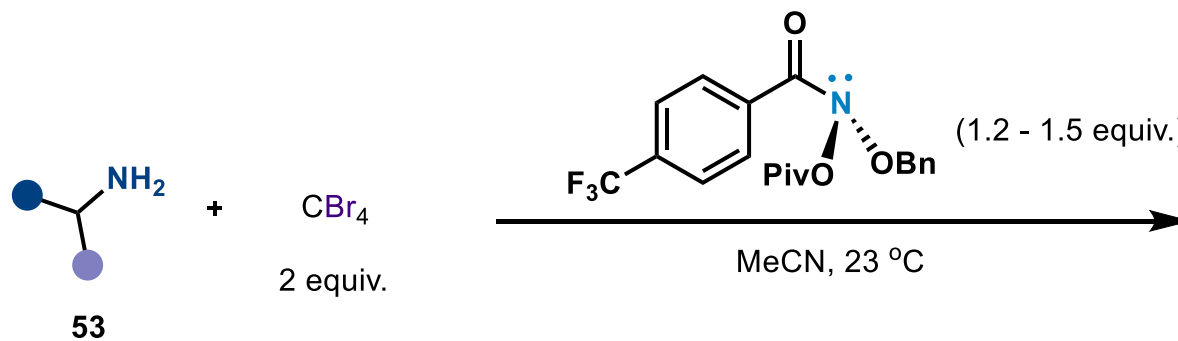
Radical clock experiments



Direct Deaminative Functionalizations

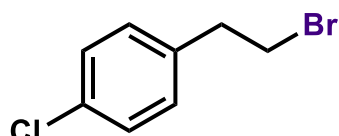


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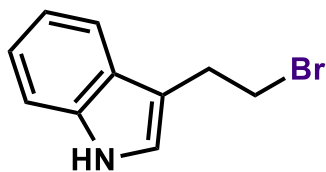


25 examples
up to 86% yield

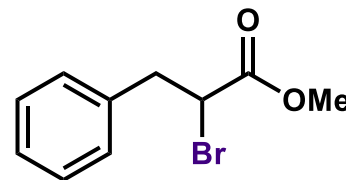
selected examples:



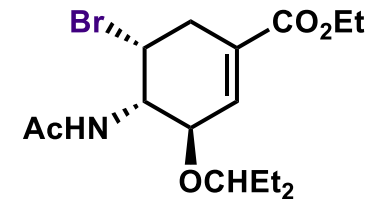
54a, 78%



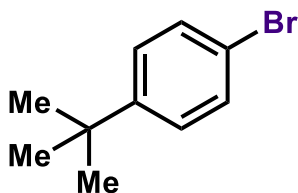
54b, 55%



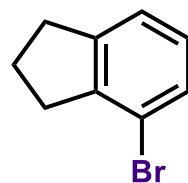
54c, 58%



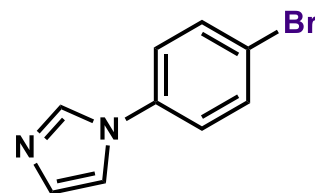
54d, 59%



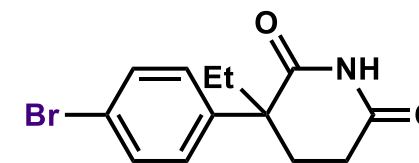
54e, 84%



54f, 86%



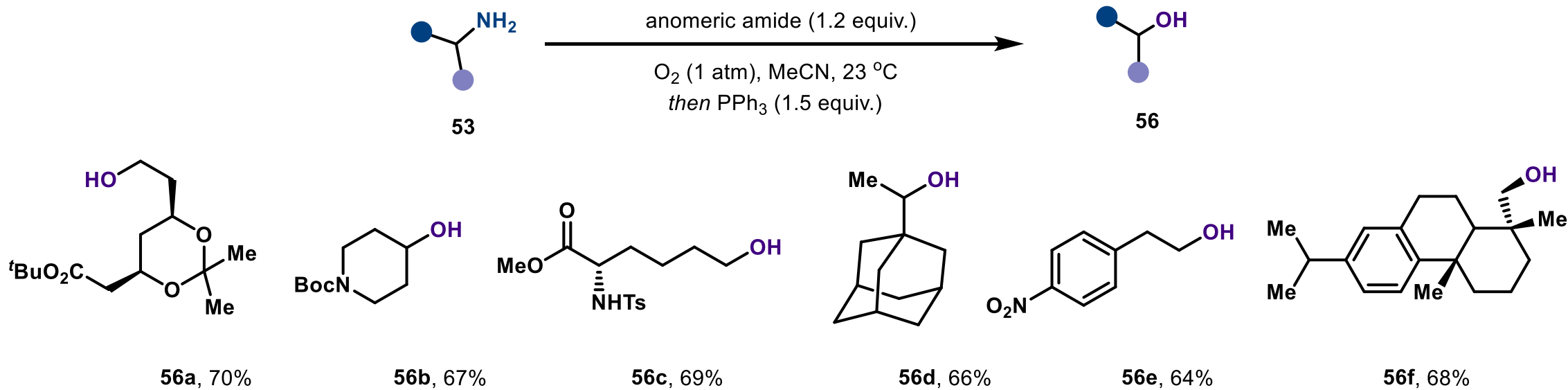
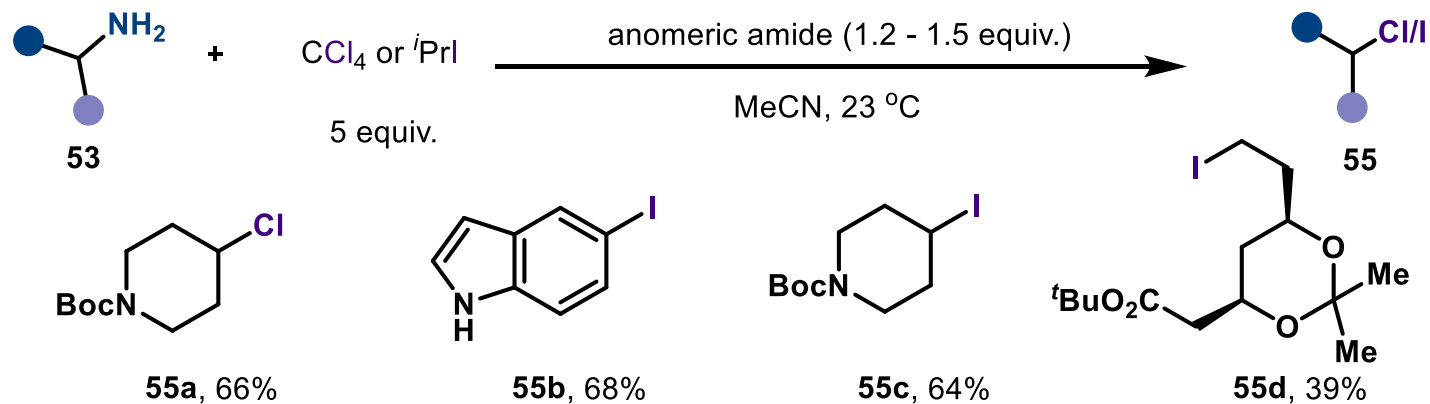
54g, 83%



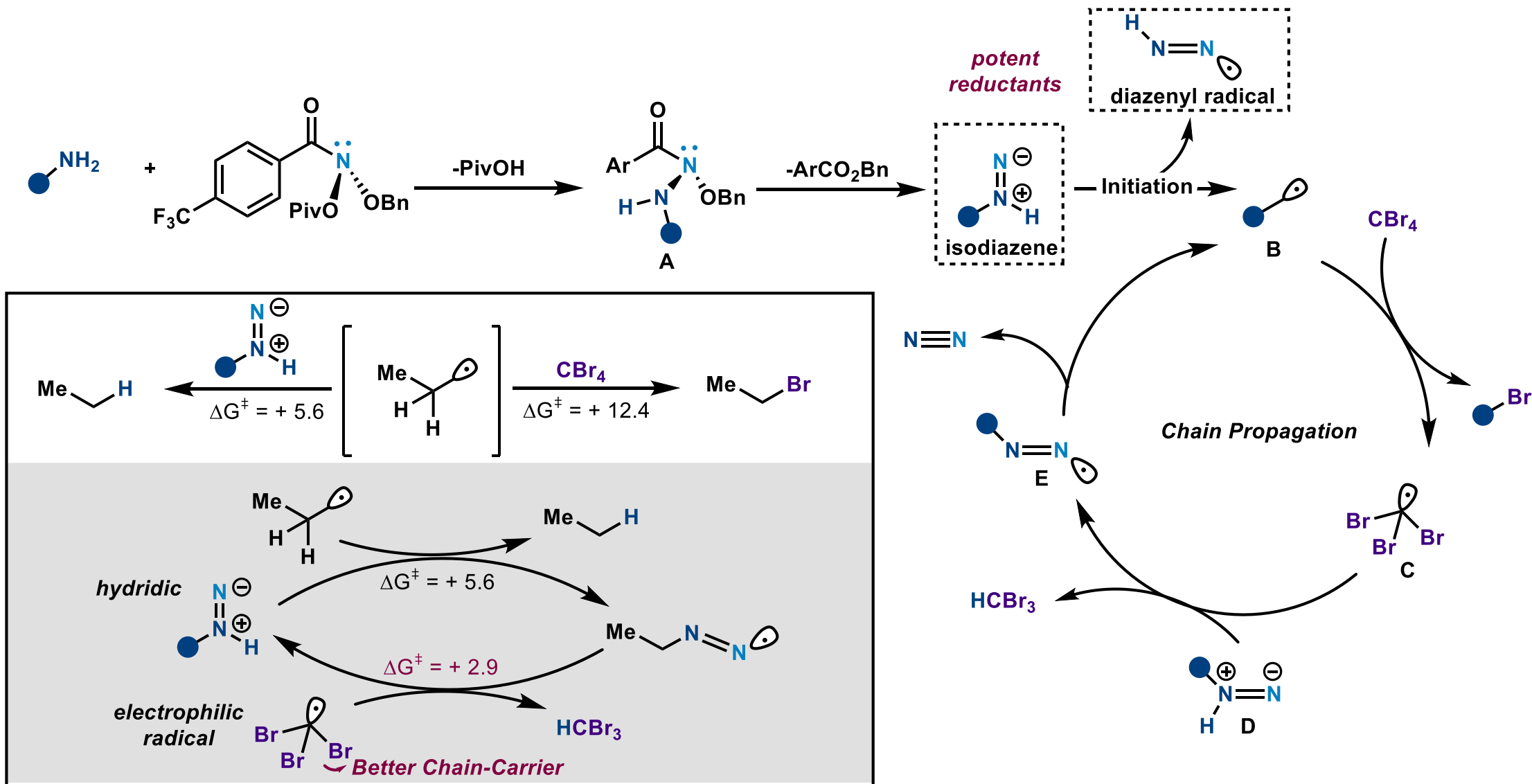
54h, 77%

Direct Deaminative Functionalizations

M. D. Levin

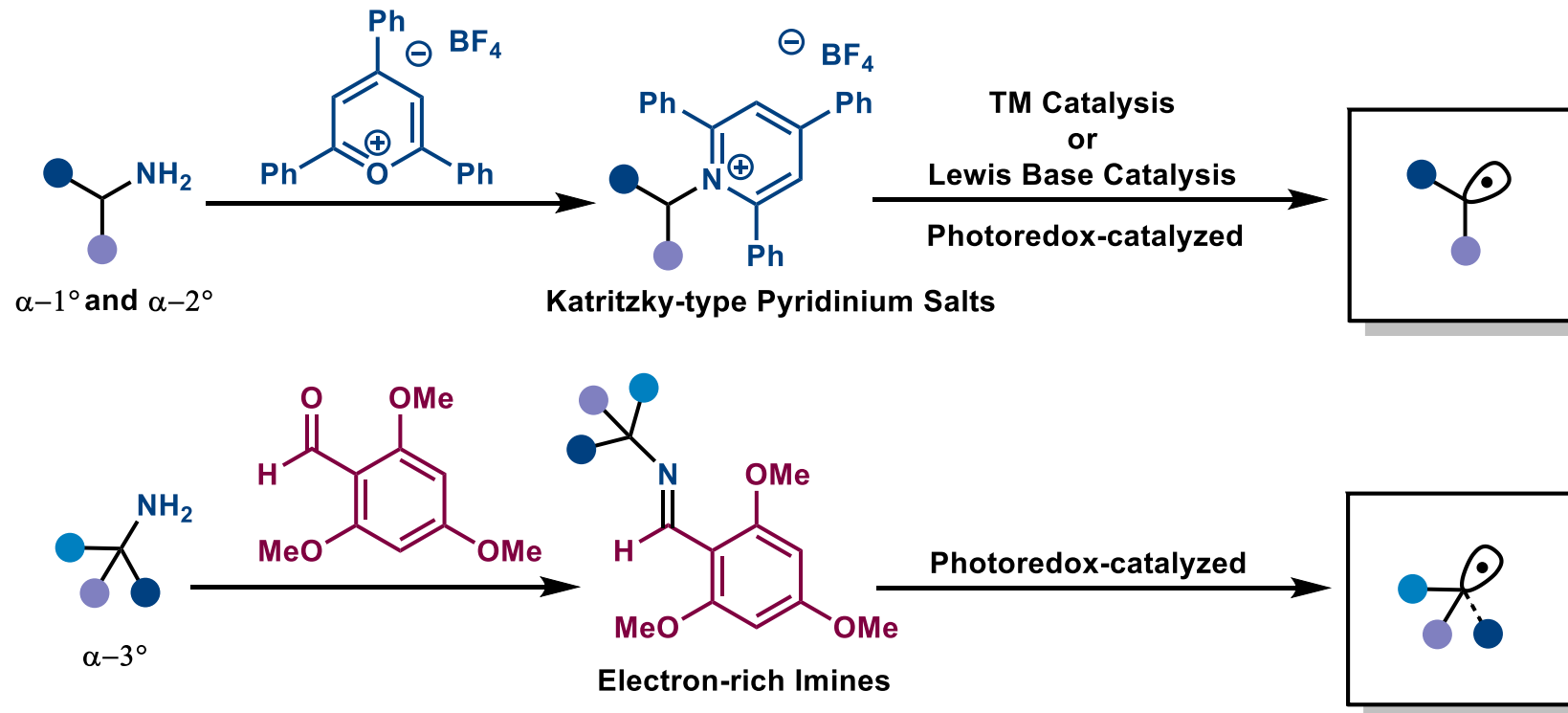


Direct Deaminative Functionalizations

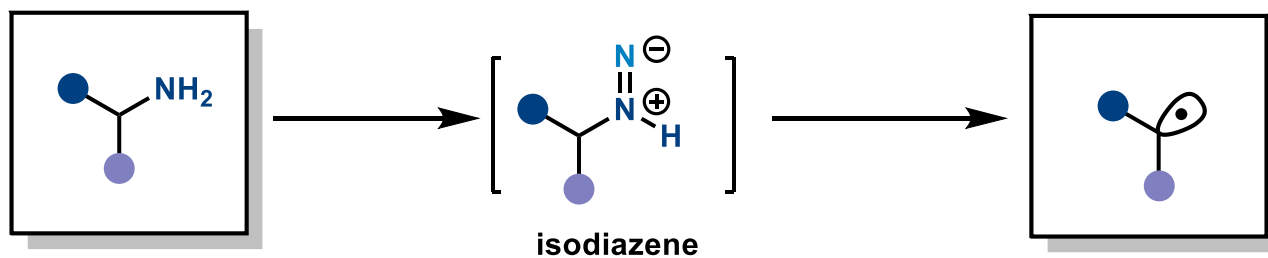


- Background
- Deaminative Functionalizations via Katritzky-type Pyridinium Salts
 - By Transition Metal Catalysis and Lewis Base Catalysis
 - By Photoredox Catalysis and Electrochemical Catalysis
- Deaminative Functionalizations via Electron-rich Imines
- Direct Deaminative Functionalizations
- **Summary and Outlook**

Indirect direct deaminative functionalizations via condensation of pyran or aldehyde

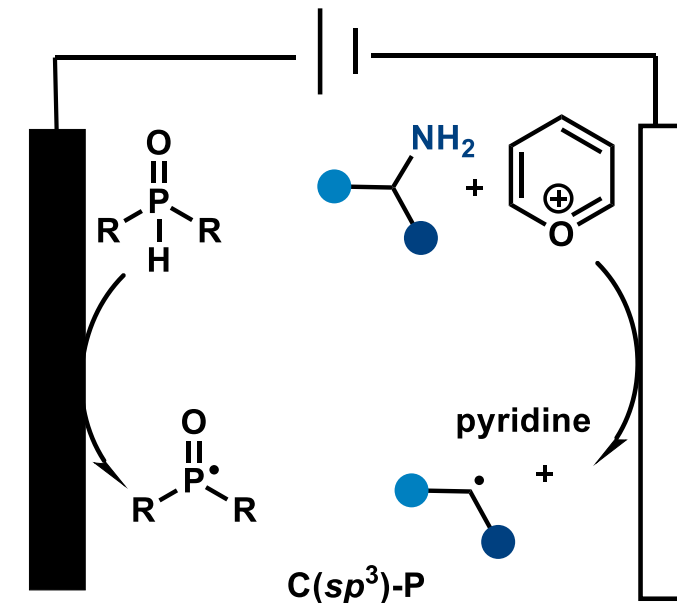


Direct deaminative functionalizations



Outlook

(i) In-situ generation (one pot)



(ii) Asymmetric version

(iii) Other reagent



Thanks for your
attention!