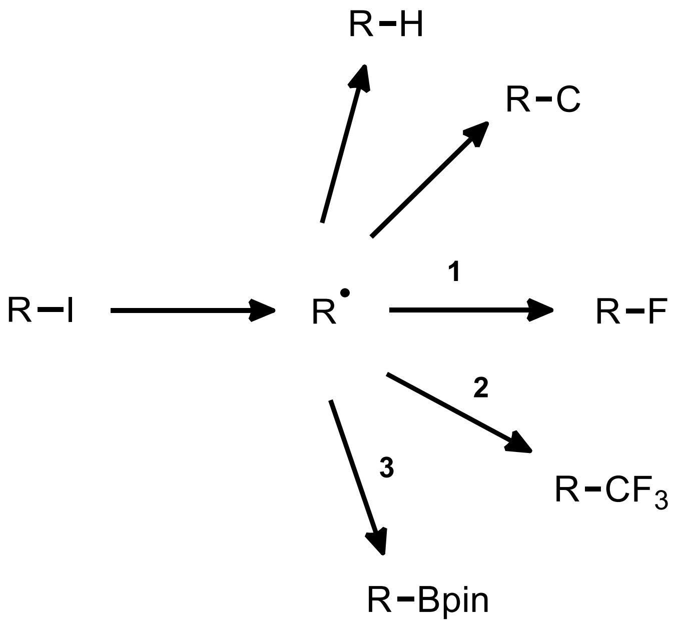
Deaminative Functionalization of Primary Alkyl Amines by a Radical Mechanism

Group Literature Meeting

Kate Berger

April 2, 2020

Alkyl Radical Functionalization



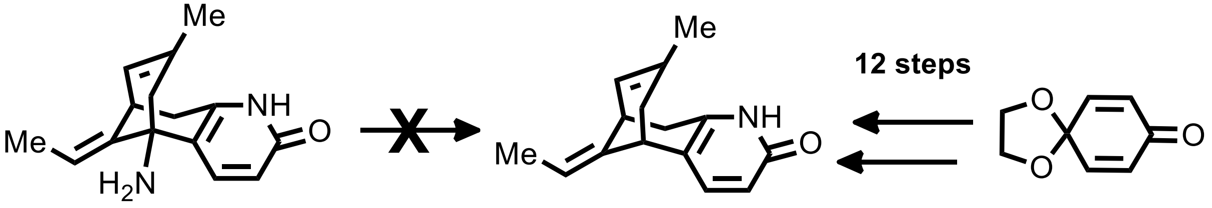
-Conversion to alkanes by use of a hydrogen atom transfer reagent (HAT)
- C-C bond formation by numerous methods including Giese type coupling with olefins, Minisci type coupling with aromatics and Ni catalyzed transformations

1. Meyer, D.; Jangra, H.; Walther, F.; Zipse, H.; Renaud, P. *Nat. Commun.* **2018,** *9* (1), 4888.
2. Shen, H.; Liu, Z.; Zhang, P.; Tan, X.; Zhang, Z.; Li, C. *J. Am. Chem. Soc.* **2017,** *139* (29), 9843.
3. Cheng, Y.; Mück-Lichtenfeld, C.; Studer, A. *Angew. Chem. Int. Ed.* **2018,** *57* (51), 16832-16836.

For a review see: Lekkala, R.; Lekkala, R.; Moku, B.; Rakesh, K. P.; Qin, H.-L., Recent Developments in Radical-Mediated Transformations of Organohalides. *Eur. J. Org. Chem.* **2019,** *2019* (17), 2769.

Demand for Deaminative Functionalization

“As an example of their prevalence, a search of Pfizer’s internal chemical store revealed over 47 000 alkyl primary amines vs about 28 000 primary and secondary alkyl halides.”[1]



natural product huperzine A

desired deaminated derivative

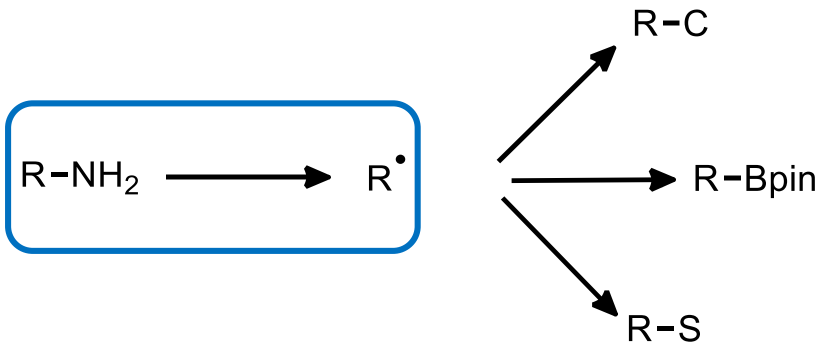
$$\mathrm{R{-}NH_2} \xrightarrow{\mathrm{HNO_2}} \mathrm{R{-}\overset{+}{N}{\equiv}N} \xrightarrow[-\,\mathrm{N_2}]{} \mathrm{R^+} \xrightarrow{\text{Sandmeyer Conditions}} \mathrm{R{-}X}$$

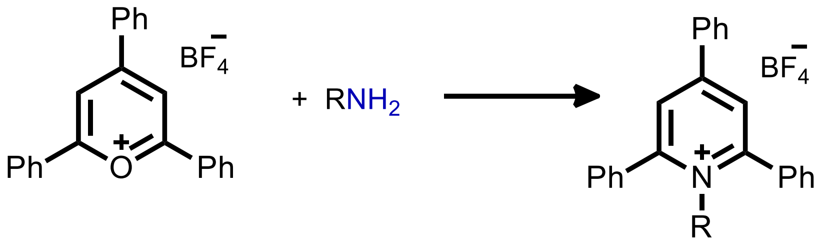
Diazotization: R is arene only,
harsh conditions, explosion risk

X: halide, alcohol, nitrile

1. Plunkett, S.; Basch, C. H.; Santana, S. O.; Watson, M. P. *J. Am. Chem. Soc.* **2019,** *141* (6), 2257.
2. Högenauer, K.; Baumann, K.; Enz, A.; Mulzer, J. *Bioorg. Med. Chem. Lett.* **2001,** *11* (19), 2627.

Deaminative Radical Functionalization





Katritzky Salts

- deamination to produce alkyl radical species has the potential to convert primary amines to a wide range of functional groups
- recent advances in radical deaminative functionalization have resulted in new methods for C-C, C-B and C-S bond formation
- Organized broadly by method: Ni catalyzed cross coupling and photoredox

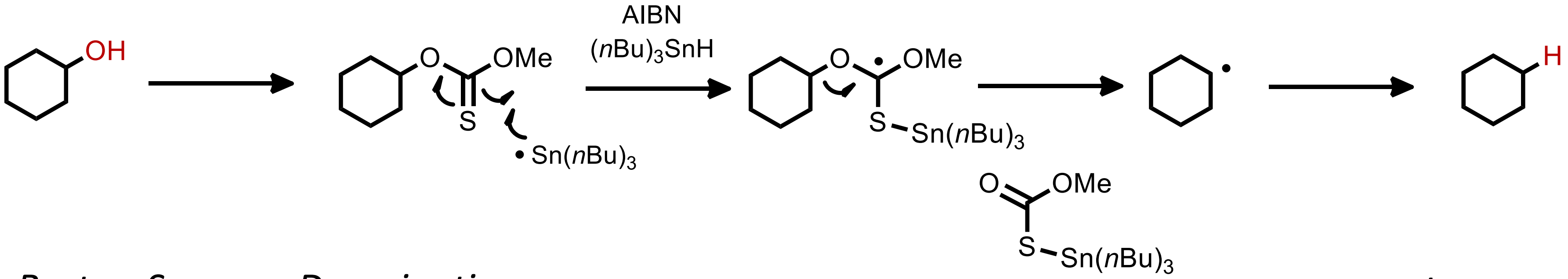
For two recent reviews see:

Pang, Y.; Moser, D.; Cornella, J., Pyrylium Salts: Selective Reagents for the Activation of Primary Amino Groups in Organic Synthesis. *Synthesis* **2020,** *52* (04), 489-503

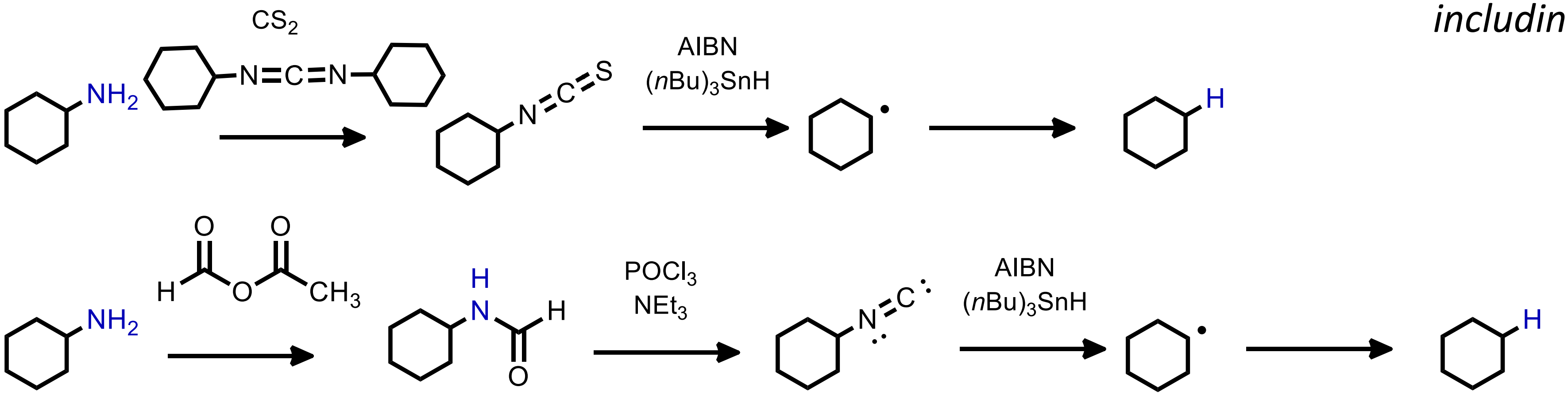
M. Correia, J. T.; A. Fernandes, V.; Matsuo, B. T.; C. Delgado, J. A.; de Souza, W. C.; Paixão, M. W., Photoinduced deaminative strategies: Katritzky salts as alkyl radical precursors. *Chem. Commun.* **2020,** *56* (4), 503.

Early Attempts at Radical Deamination

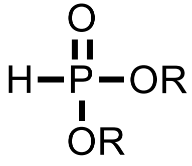
Barton-McCombie Deoxygenation



Barton-Saegusa Deamination

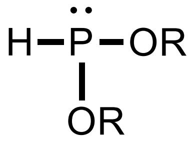


Later expanded to other radical reagents including hypophosphorus acid



$H-P(=O)(OR)-OR$

AIBN



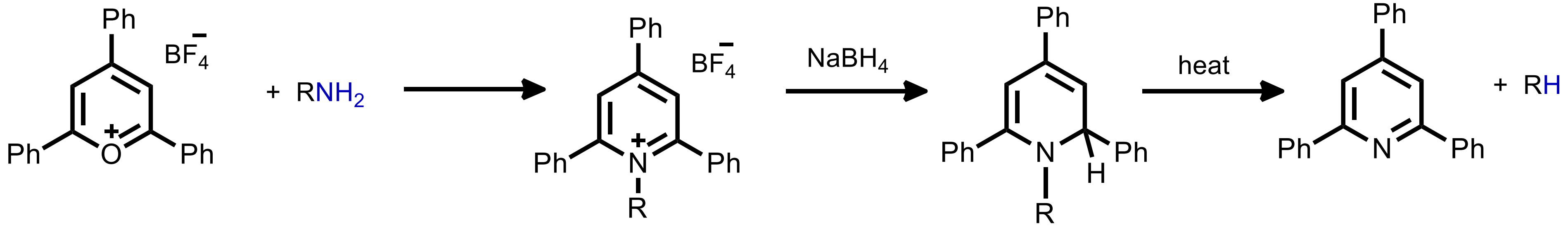
$H-\ddot{P}(OR)-OR$

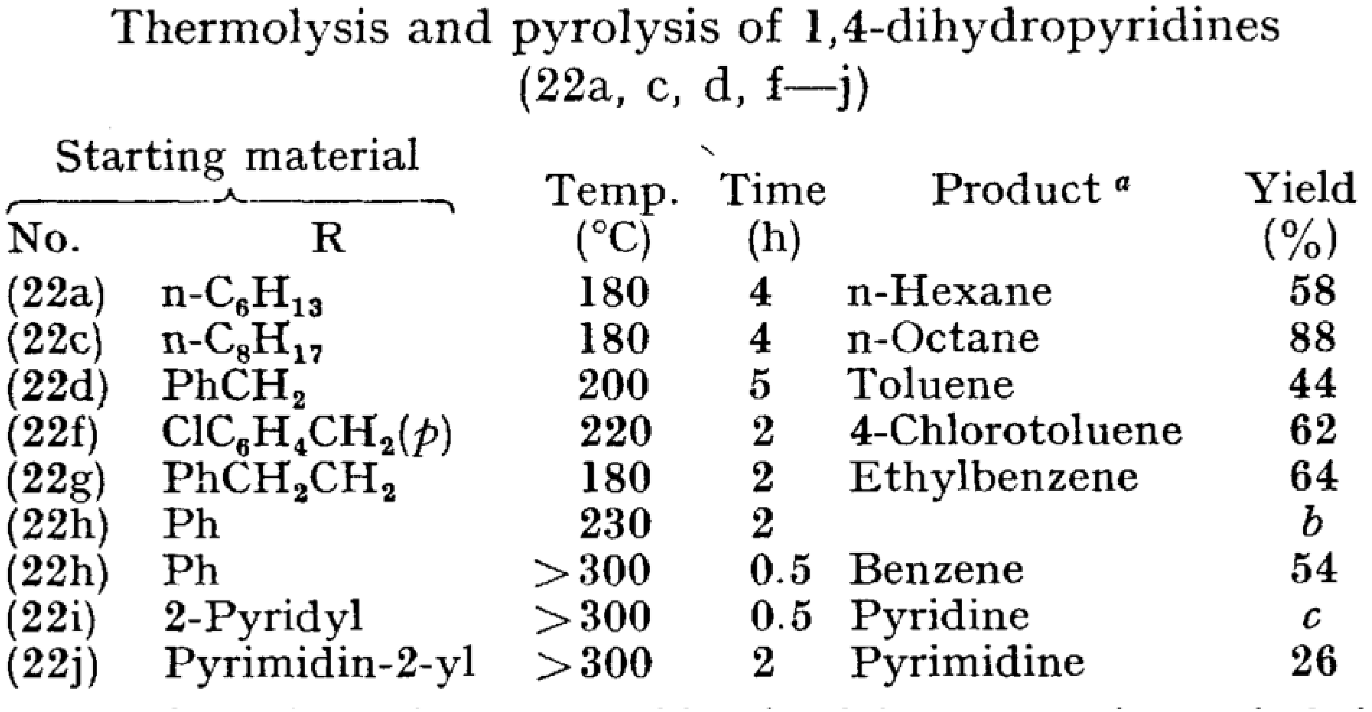
benyzol peroxide

Barton, D. H. R.; Bringman, G.; Lamotte, G.; Hay Motherwell, R. S.; Motherwell, W. B. *Tet. Lett.* **1979,** *20* (24), 2291.

Barton, D. H. R.; Ok Jang, D.; Jaszberenyi, J. C., *Tet. Lett.* **1992,** *33* (39), 5709.

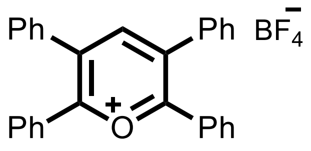
Reductive Amination with Katritzky Salts





Thermolysis and pyrolysis of 1,4-dihydropyridines (22a, c, d, f—j)

Starting material		Temp. (°C)	Time (h)	Product [a]	Yield (%)
No.	R				
(22a)	n-C_6H_{13}	180	4	n-Hexane	58
(22c)	n-C_8H_{17}	180	4	n-Octane	88
(22d)	$PhCH_2$	200	5	Toluene	44
(22f)	$ClC_6H_4CH_2$(*p*)	220	2	4-Chlorotoluene	62
(22g)	$PhCH_2CH_2$	180	2	Ethylbenzene	64
(22h)	Ph	230	2		*b*
(22h)	Ph	>300	0.5	Benzene	54
(22i)	2-Pyridyl	>300	0.5	Pyridine	*c*
(22j)	Pyrimidin-2-yl	>300	2	Pyrimidine	26

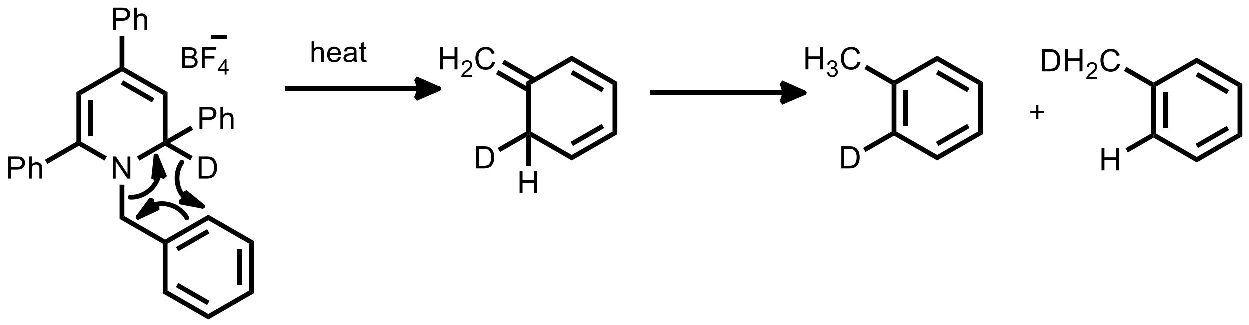


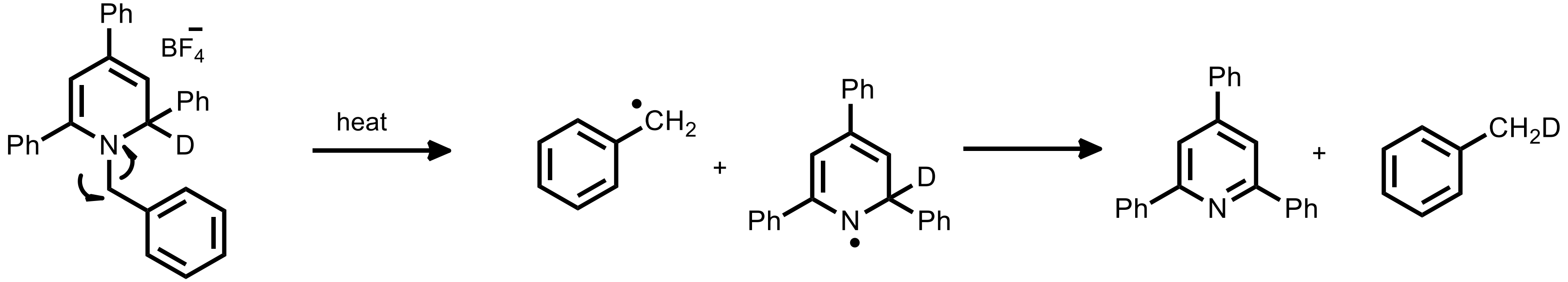
Katritzky, A. R.; Horvath, K.; Plau, B. *J. Chem. Soc. Chem. Comm.* **1979,** (6), 300.

Katritzky, A. R.; Marson, C. M. *Angew. Chem. Int. Ed.* **1984,** *23* (6), 420.

Katritzky, A. R.; Horvath, K.; Plau, B. *J. Chem. Soc. Perkin Trans. I.* **1980**, 2554.

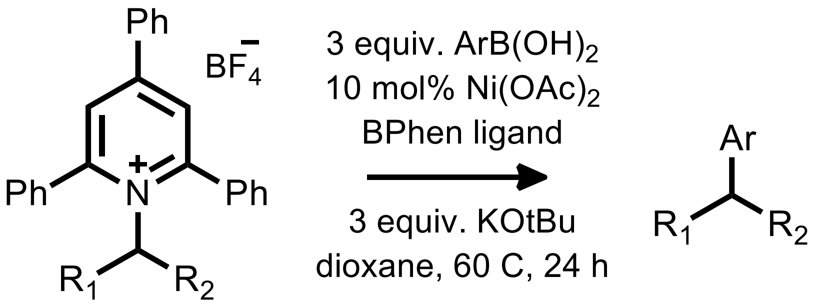
Katritzky Salts: Evidence for a Radical Mechanism

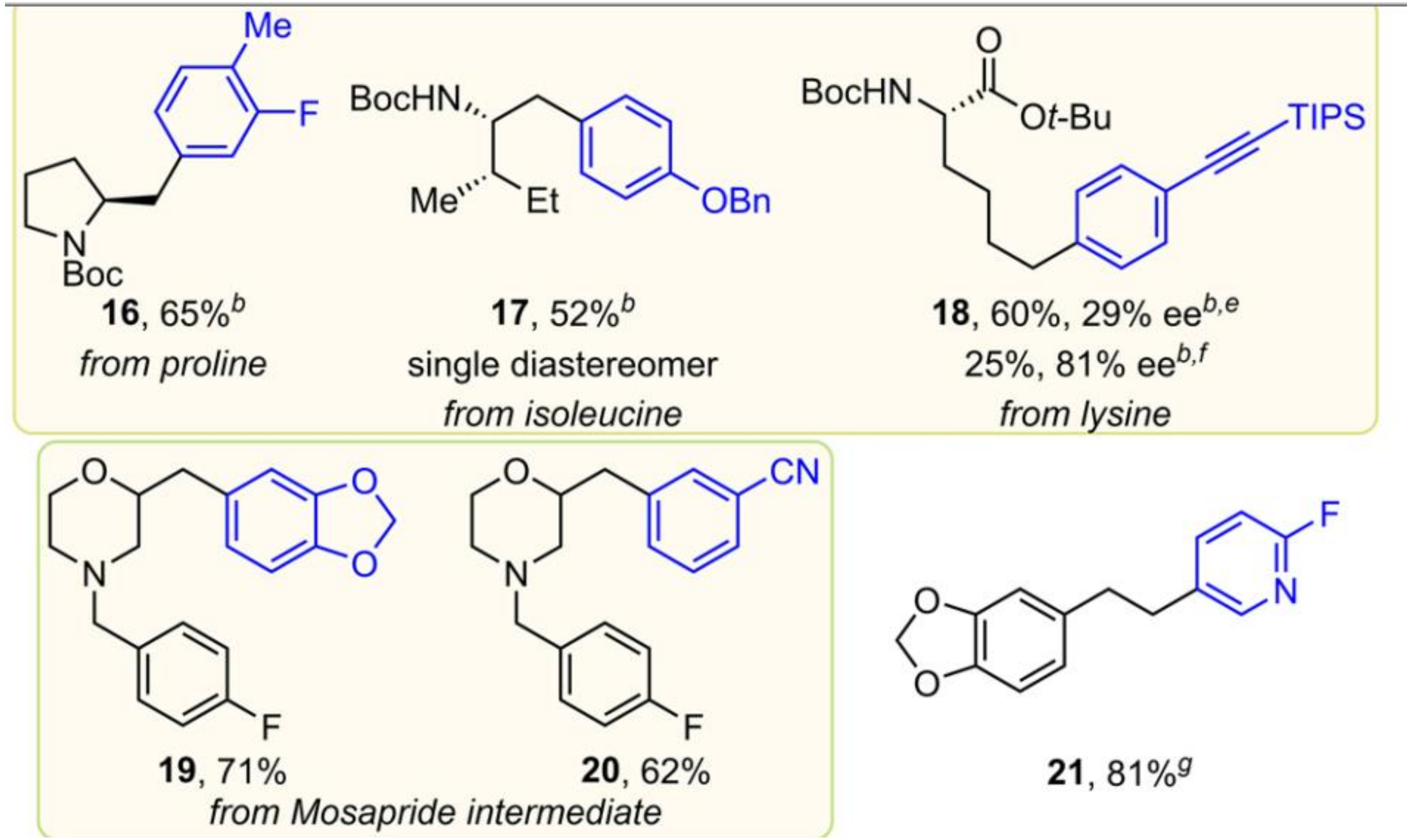




Katritzky, A. R.; Horvath, K.; Plau, B. *J. Chem. Soc. Perkin Trans. I.* **1980**, 2554.

Modern Applications of Katritzky Salts: Ni Cross Coupling





16, 65%^{b} *from proline*

17, 52%^{b} single diastereomer *from isoleucine*

18, 60%, 29% ee^{b,e} 25%, 81% ee^{b,f} *from lysine*

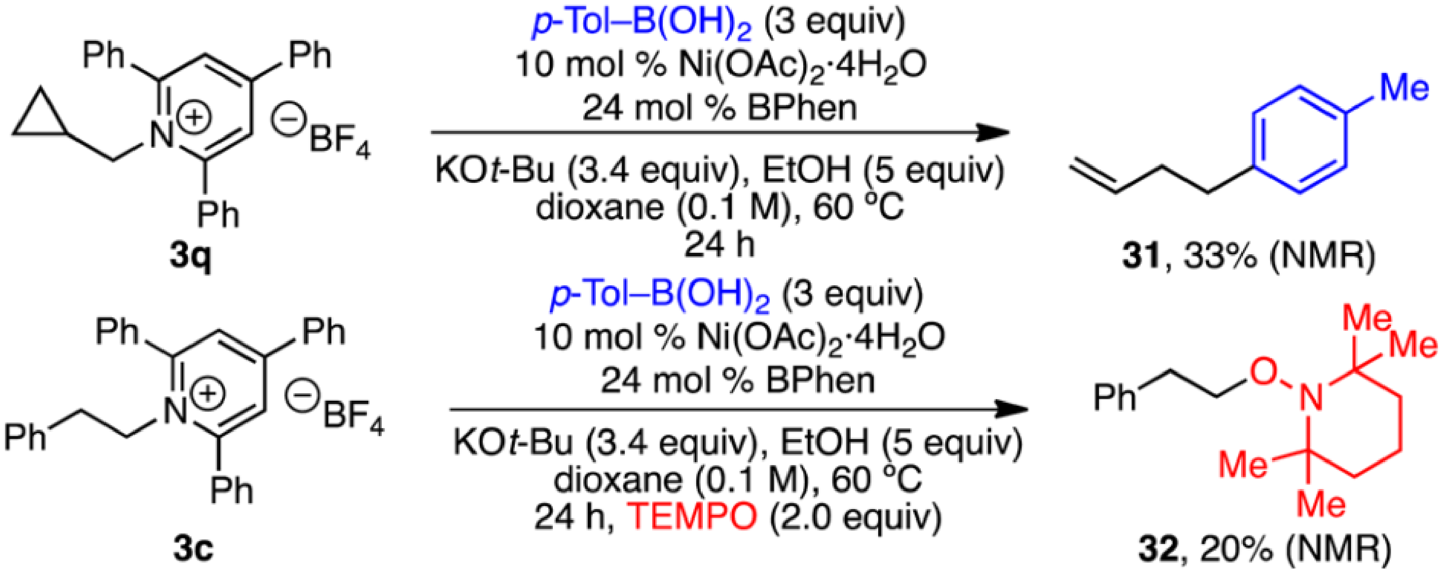
19, 71% **20**, 62% *from Mosapride intermediate*

21, 81%^{g}

Functional Group Tolerance:
esters, amides, nitriles

Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P., *J. Am. Chem. Soc.* **2017,** *139* (15), 5313.

Modern Applications of Katritzky Salts: Ni Cross Coupling



3q

p-Tol–$B(OH)_2$ (3 equiv)
10 mol % $Ni(OAc)_2 \cdot 4H_2O$
24 mol % BPhen

KO*t*-Bu (3.4 equiv), EtOH (5 equiv)
dioxane (0.1 M), 60 °C
24 h

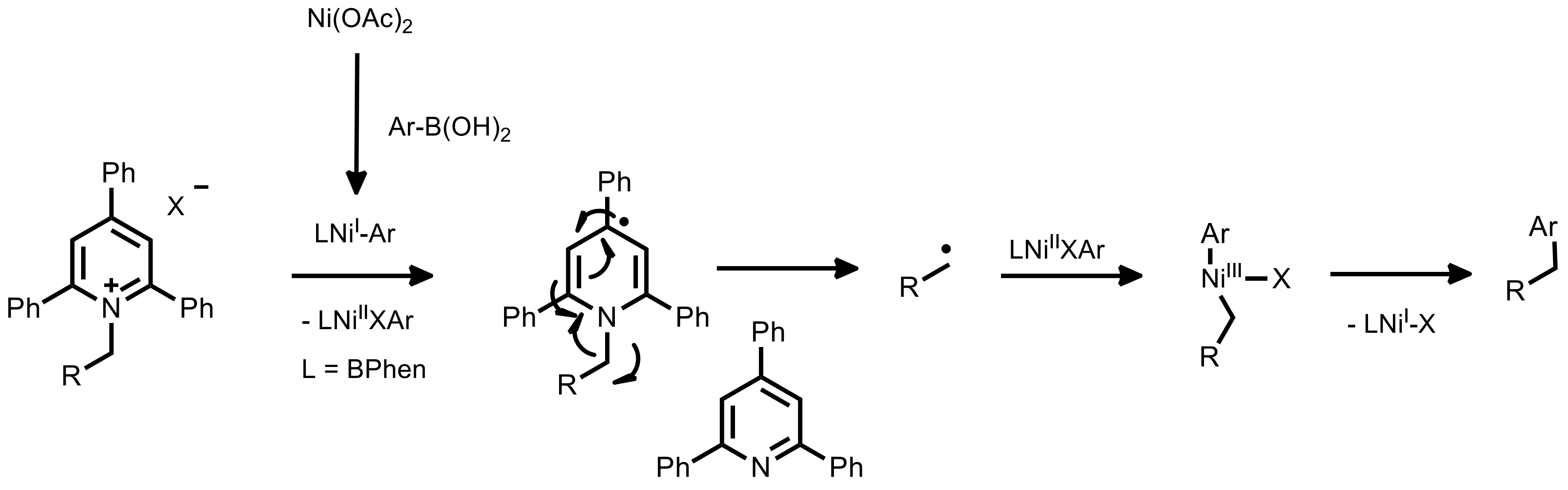
31, 33% (NMR)

3c

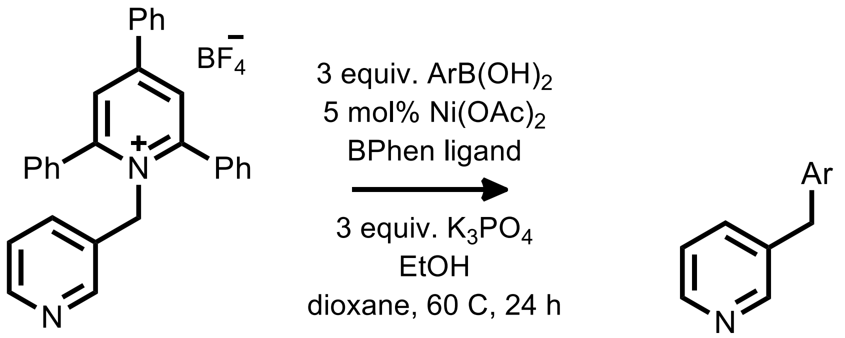
p-Tol–$B(OH)_2$ (3 equiv)
10 mol % $Ni(OAc)_2 \cdot 4H_2O$
24 mol % BPhen

KO*t*-Bu (3.4 equiv), EtOH (5 equiv)
dioxane (0.1 M), 60 °C
24 h, TEMPO (2.0 equiv)

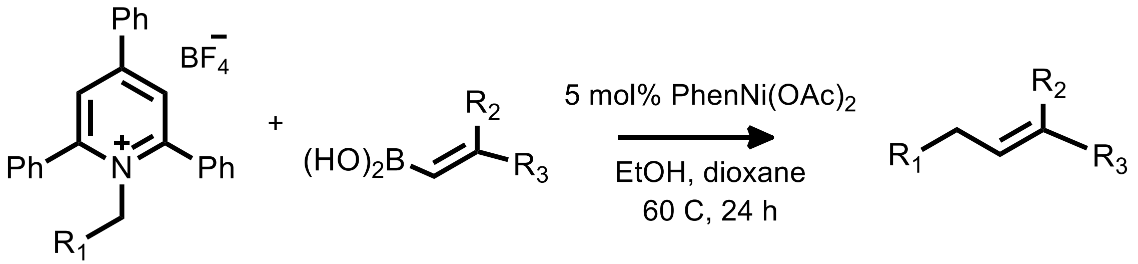
32, 20% (NMR)



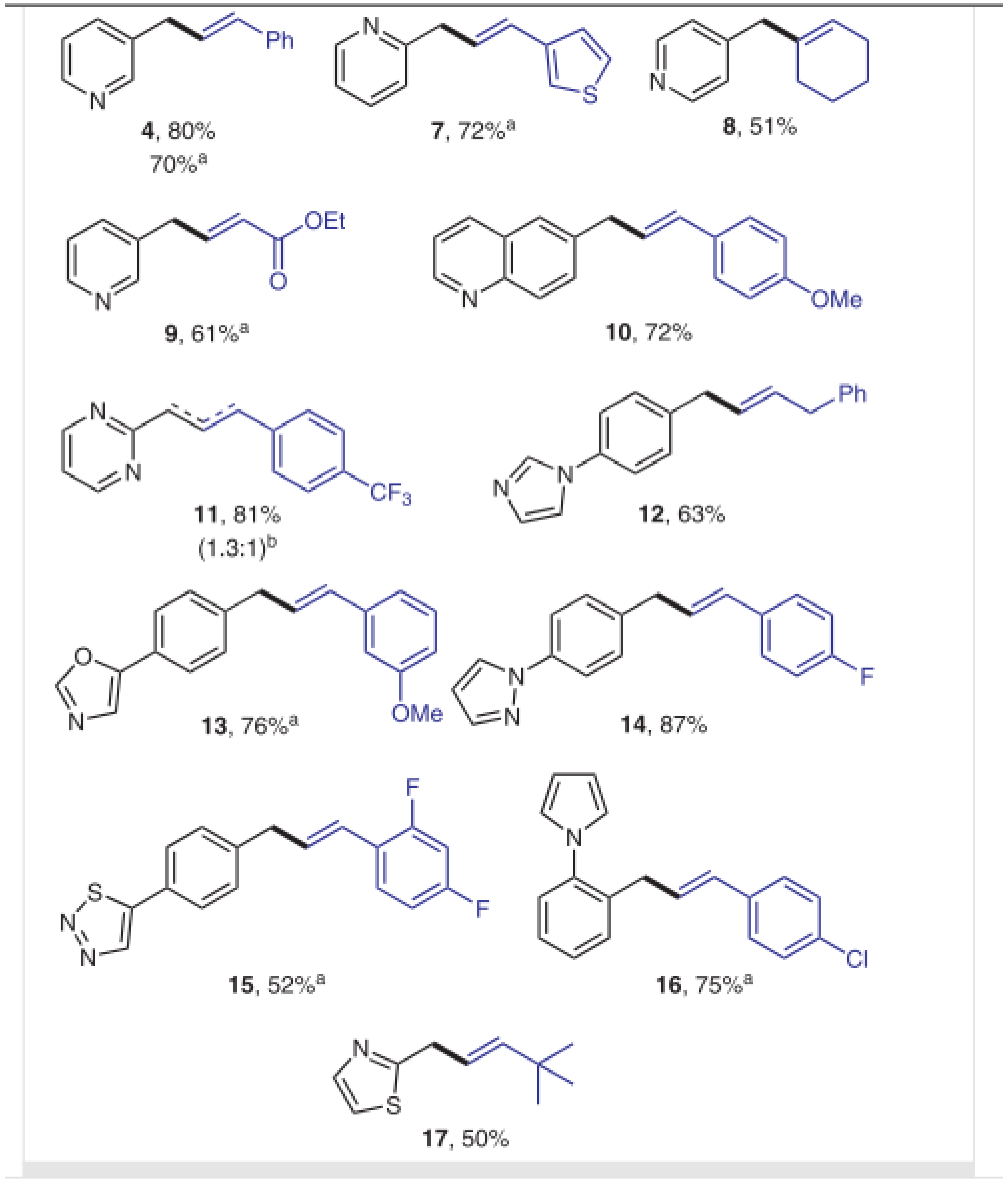
Additional Cross Coupling Examples



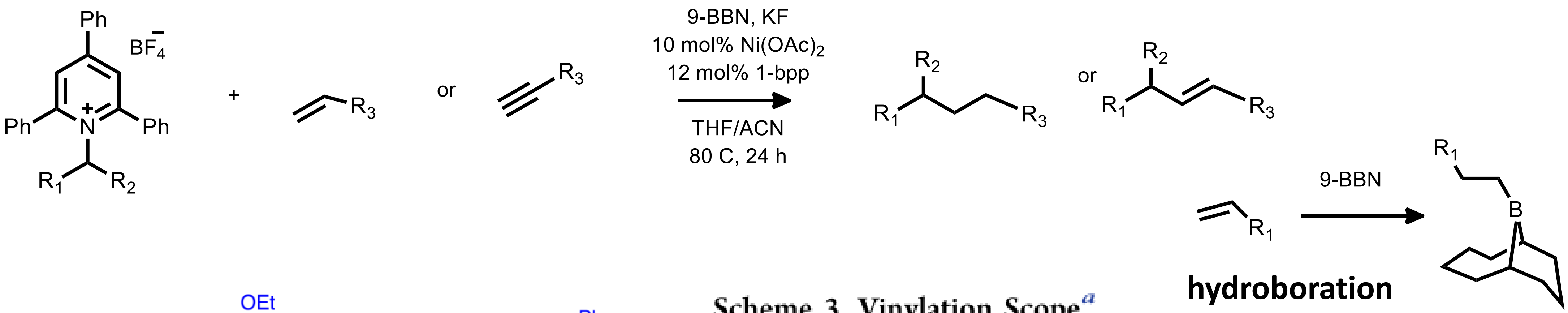
Guan, W.; Liao, J.; Watson, M. P. *Synthesis* **2018,** *50* (16), 3231.



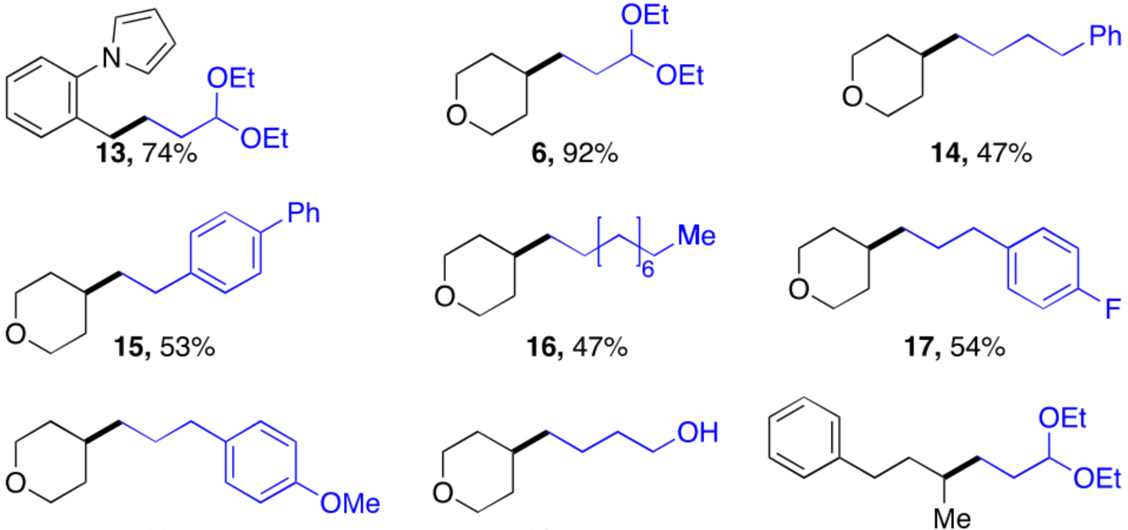
Liao, J.; Guan, W.; Boscoe, B. P.; Tucker, J. W.; Tomlin, J. W.; Garnsey, M. R.; Watson, M. P. *Org. Lett.* **2018,** *20* (10), 3030.



Deaminative Cross Coupling via Hydroboration



hydroboration



13, 74%

6, 92%

14, 47%

15, 53%

16, 47%

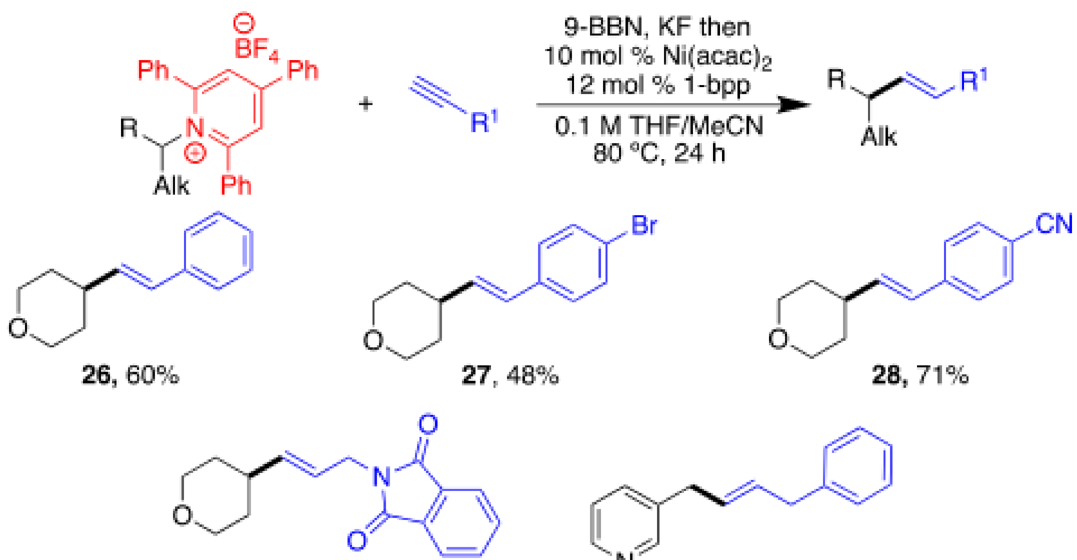
17, 54%

18, 78%

19, 69%

20, 68%

Scheme 3. Vinylation Scope[a]



26, 60%

27, 48%

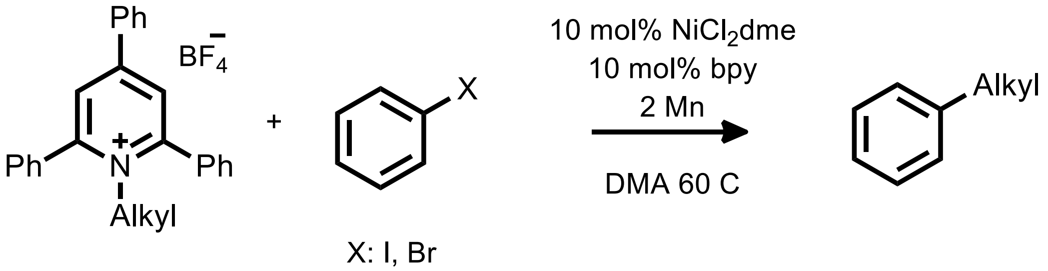
28, 71%

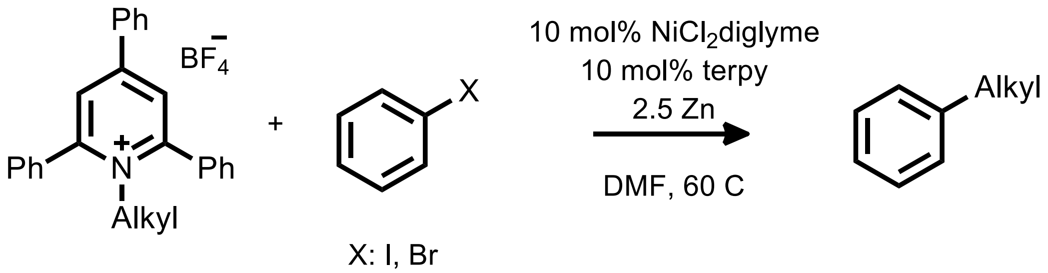
29, 53%

30, 59%

Baker, K. M.; Lucas Baca, D.; Plunkett, S.; Daneker, M. E.; Watson, M. P. *Org. Lett.* **2019,** *21* (23), 9738.

Reductive Cross Couplings of Halides





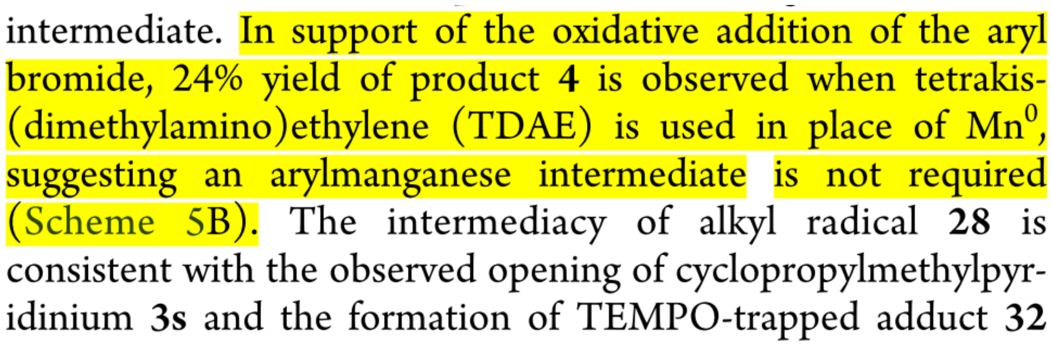
Yue, H.; Zhu, C.; Shen, L.; Geng, Q.; Hock, K. J.; Yuan, T.; Cavallo, L.; Rueping, M. *Chem. Sci.* **2019,** *10* (16), 4430.

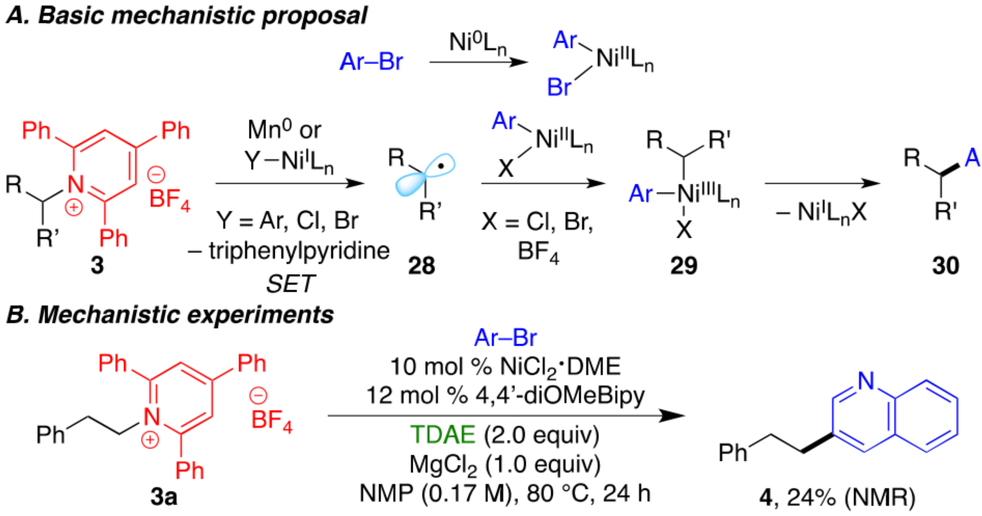
Liao, J.; Basch, C. H.; Hoerrner, M. E.; Talley, M. R.; Boscoe, B. P.; Tucker, J. W.; Garnsey, M. R.; Watson, M. P. *Org. Lett.* **2019,** *21* (8), 2941.

Martin-Montero, R.; Yatham, V. R.; Yin, H.; Davies, J.; Martin, R. *Org. Lett.* **2019,** *21* (8), 2947.

Ni, S.; Li, C.-X.; Mao, Y.; Han, J.; Wang, Y.; Yan, H.; Pan, Y. *Sci. Adv.* **2019,** *5* (6), eaaw9516.

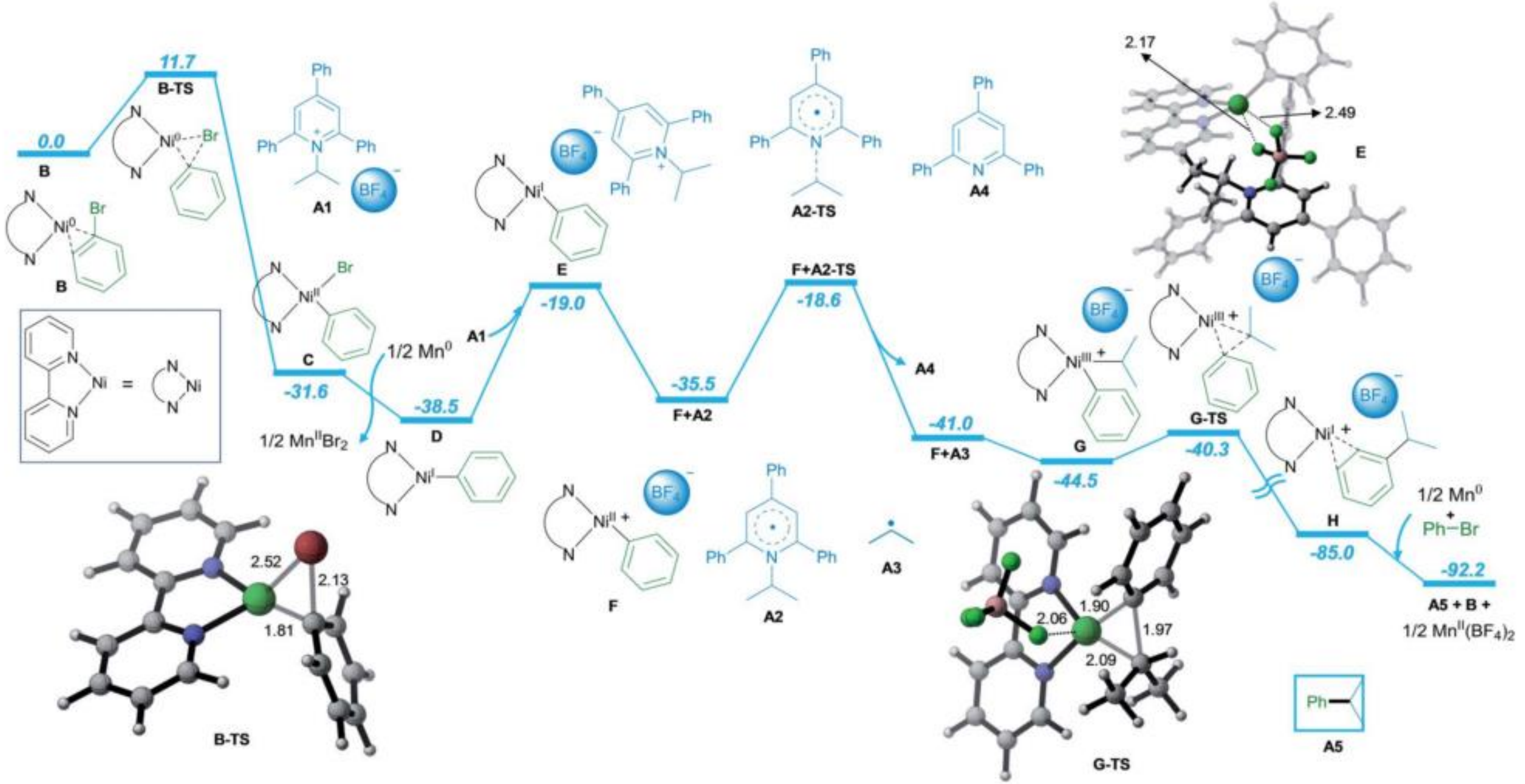
Functional group tolerance: ketones, nitriles, ethers, thiophene, pyridine, alcohol,


intermediate. In support of the oxidative addition of the aryl bromide, 24% yield of product **4** is observed when tetrakis(dimethylamino)ethylene (TDAE) is used in place of Mn^0, suggesting an arylmanganese intermediate is not required (Scheme 5B). The intermediacy of alkyl radical **28** is consistent with the observed opening of cyclopropylmethylpyridinium **3s** and the formation of TEMPO-trapped adduct **32**


A. Basic mechanistic proposal

B. Mechanistic experiments

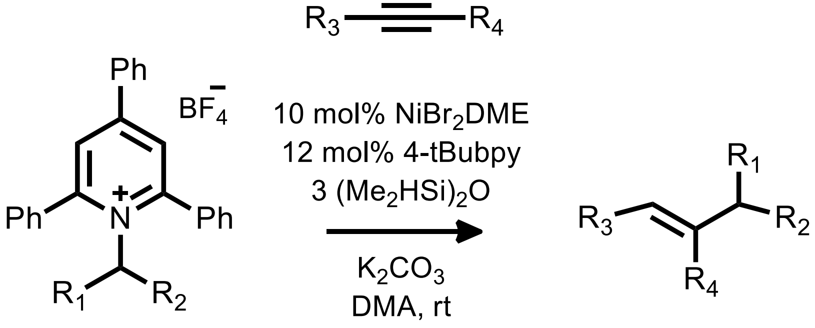
Reductive Cross Couplings of Halides: DFT Mechanism



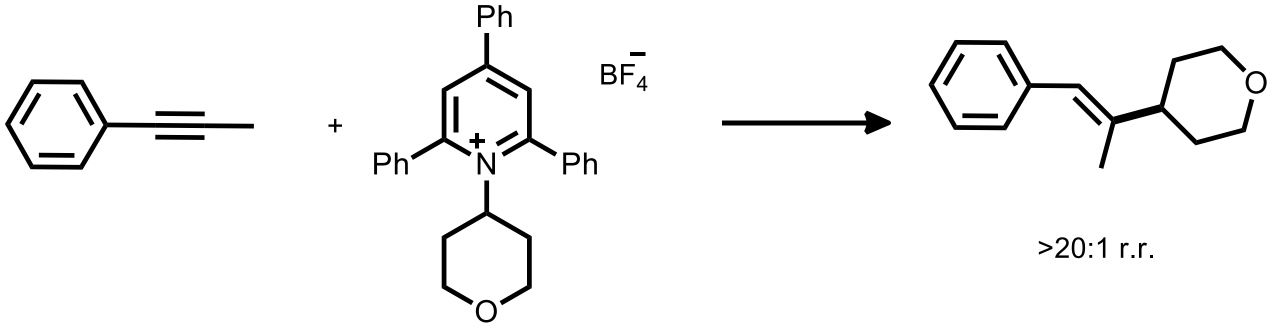
Scheme 3 DFT-Computed energy profile for the nickel-catalyzed reductive cross-coupling reaction of aryl halides and pyridinium salts. Free energies in solution (in kcal mol^{-1}) at the SMD(DMA)-M06/Def2-QZVPP//ωB97xD/Def2-TZVP(Ni,Mn)/Def2-SVP (non-metal) level are displayed.

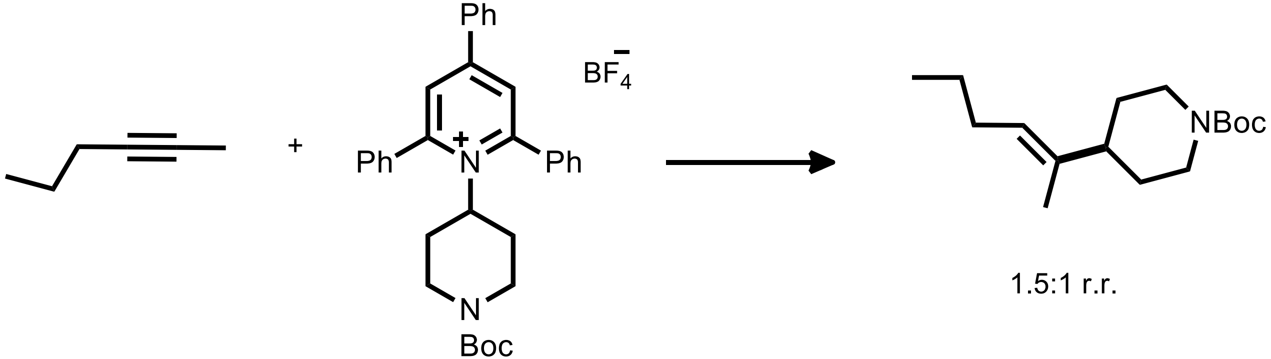
Yue, H.; Zhu, C.; Shen, L.; Geng, Q.; Hock, K. J.; Yuan, T.; Cavallo, L.; Rueping, M. *Chem. Sci.* **2019,** *10* (16), 4430.

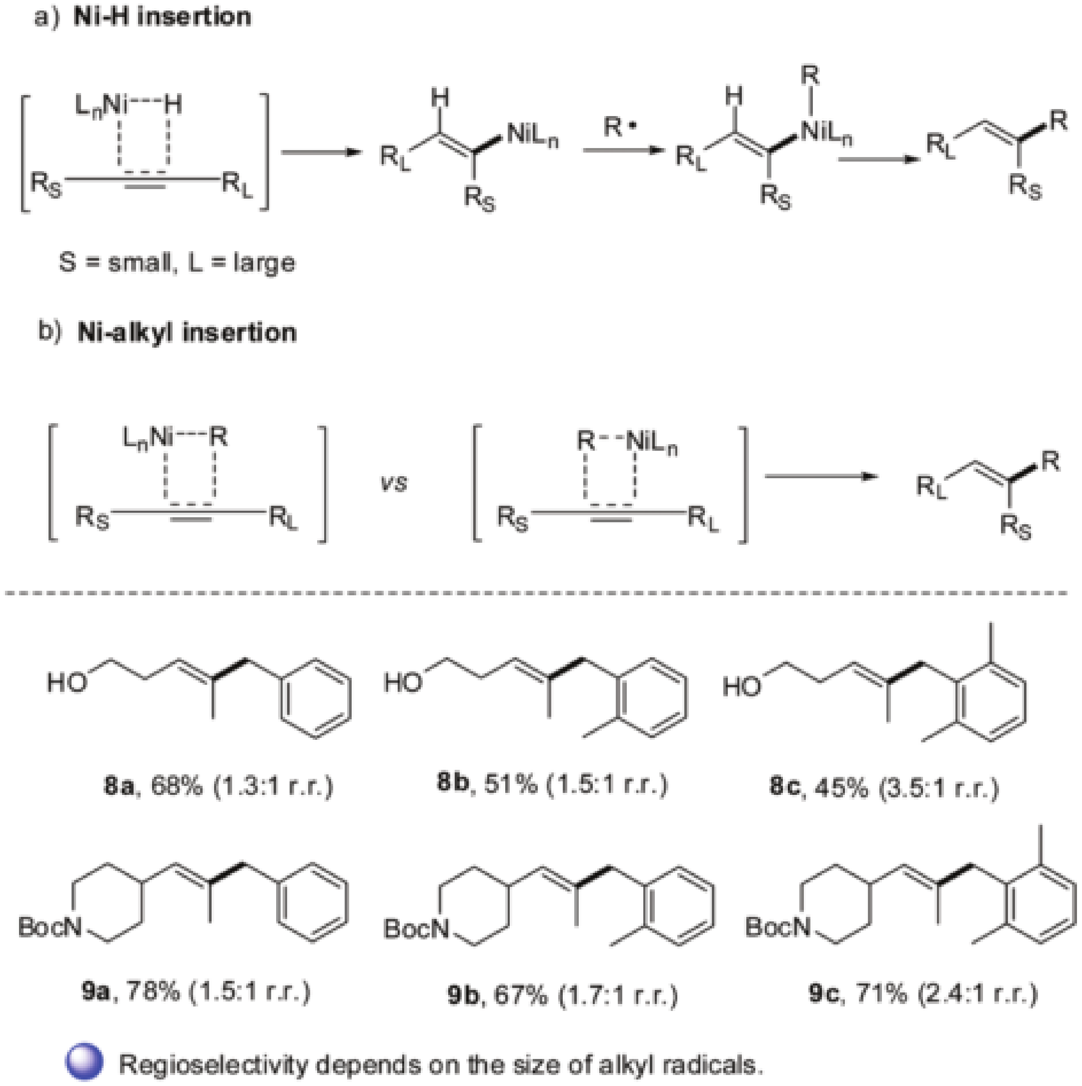
Cis-Hydroalkylation of Alkynes



Functional group tolerance: amides, esters, sulfides, alcohol



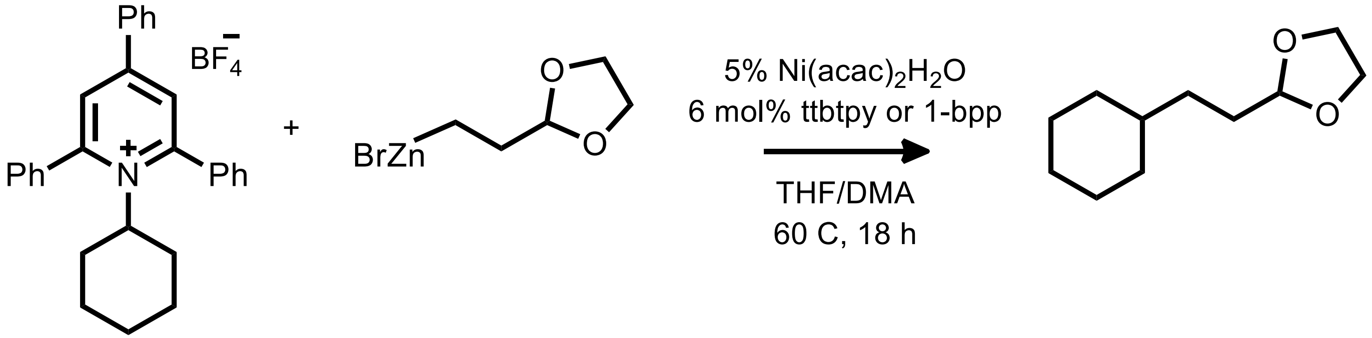




Scheme 3 Further investigation on regioselectivity.

Zhu, Z.-F.; Tu, J.-L.; Liu, F. *Chem. Commun.* **2019,** *55* (76), 11478.

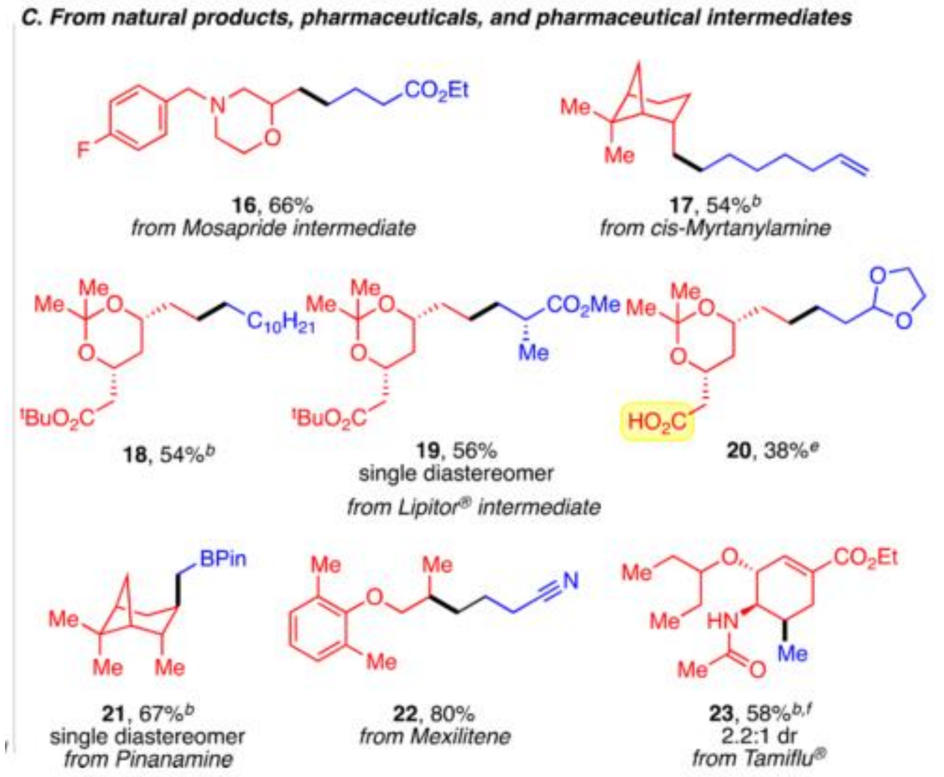
Negishi Alkyl-Alkyl Cross Coupling



5% Ni(acac)$_2$H$_2$O
6 mol% ttbtpy or 1-bpp
THF/DMA
60 C, 18 h

Reaction Scope:

- primary and secondary alkyl pyridinium salts
- tolerance for benzodioxole, thiophene, pyridine, pyrimidine, azetidine rings
- acetal, ester, nitrile, oxetane
- methylzinc iodide can also be coupled resulting in NH_2 being replaced by CH_3 isostere
- borylation by methylpinacolboronatezinc bromide


C. From natural products, pharmaceuticals, and pharmaceutical intermediates

16, 66%
from Mosapride intermediate

17, 54%^{b}
from cis-Myrtanylamine

18, 54%^{b}

19, 56%
single diastereomer
from Lipitor® intermediate

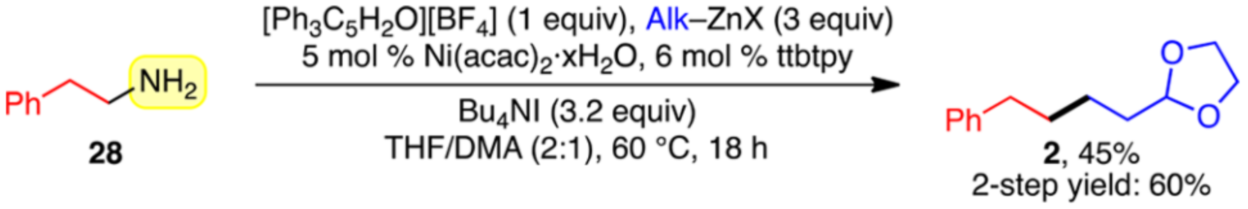
20, 38%^{e}

21, 67%^{b}
single diastereomer
from Pinanamine

22, 80%
from Mexilitene

23, 58%^{b,f}
2.2:1 dr
from Tamiflu®

Scheme 4. One-Pot Activation and Cross-Coupling



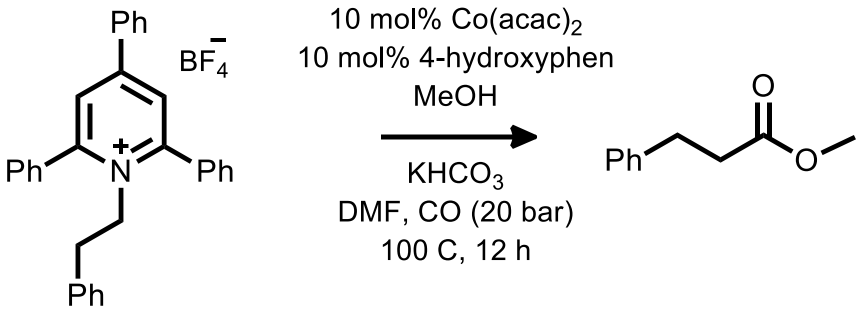
28

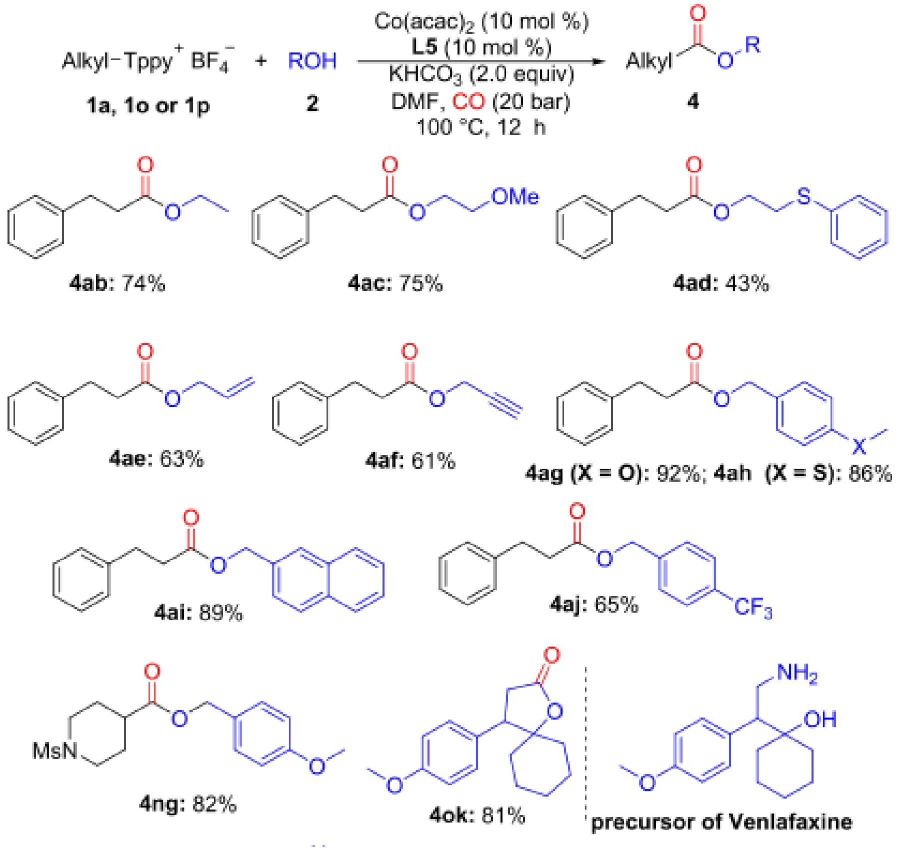
[Ph$_3$C$_5$H$_2$O][BF$_4$] (1 equiv), Alk–ZnX (3 equiv)
5 mol % Ni(acac)$_2$·xH$_2$O, 6 mol % ttbtpy
Bu$_4$NI (3.2 equiv)
THF/DMA (2:1), 60 °C, 18 h

2, 45%
2-step yield: 60%

Plunkett, S.; Basch, C. H.; Santana, S. O.; Watson, M. P. *J. Am. Chem. Soc.* **2019,** *141* (6), 2257.

Deaminative Alkoxycarbonylation

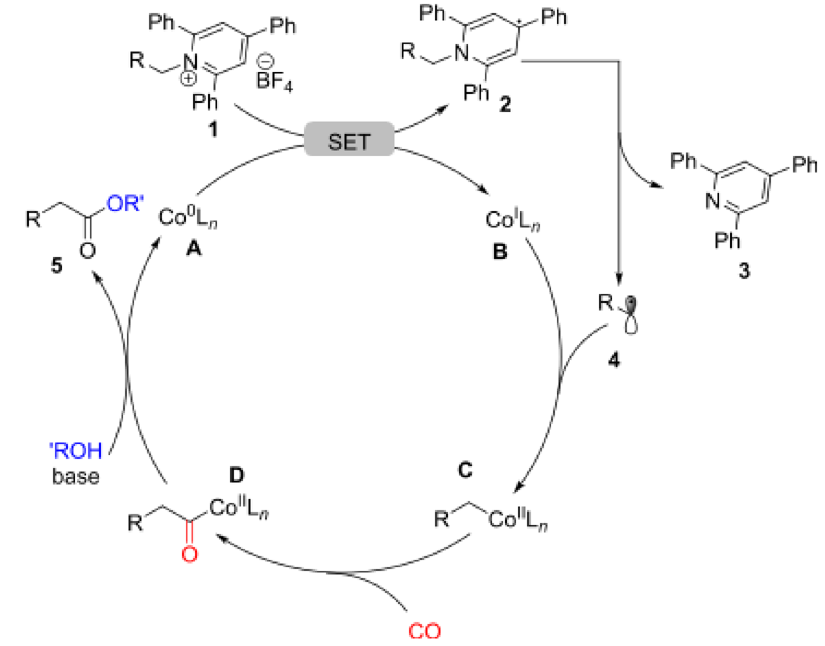




Functional group tolerance:

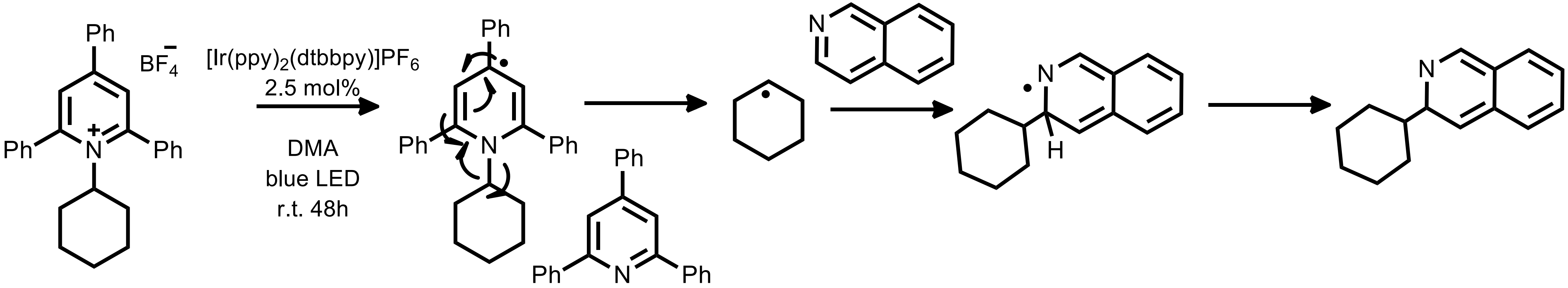
- indole substituted primary alkyl amine
- ether, bromide, chloride
- cannot have EWG such as nitro

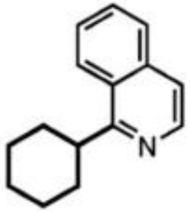
Scheme 3. Proposed Mechanism



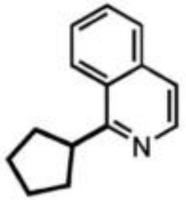
Li, C.-L.; Jiang, X.; Lu, L.-Q.; Xiao, W.-J.; Wu, X.-F. *Org. Lett.* **2019,** *21* (17), 6919.

Modern Applications of Katritzky Salts: Photoredox

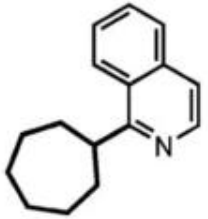




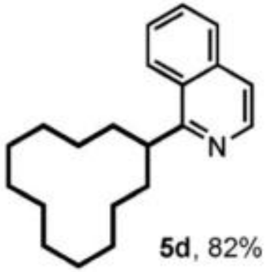
5a, 83%



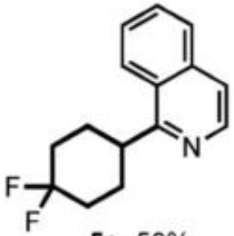
5b, 91%



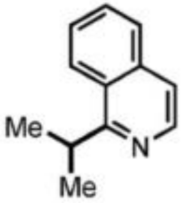
5c, 88%



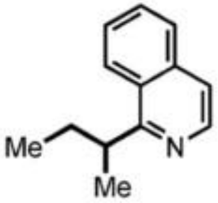
5d, 82%



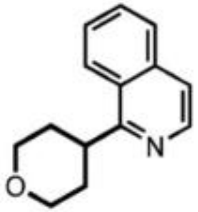
5e, 58%



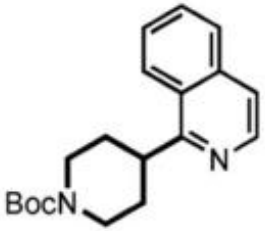
5f, 66%



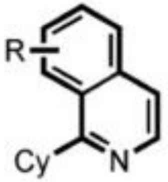
5g, 63%



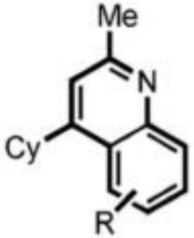
5h, 82%



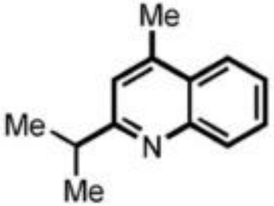
5i, 86%

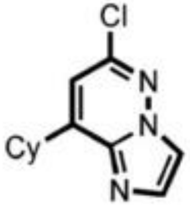


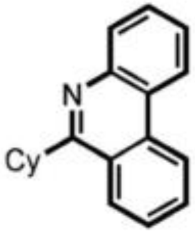
5j, R = 3-Me, 65%
5k, R = 6-Me, 47%
5l, R = 6-Br, 59%

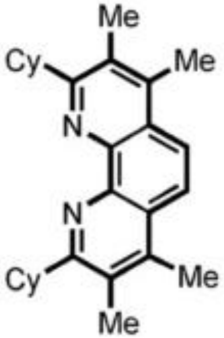


5m, R = H, 86%
5n, R = 7-F, 48%
5o, R = 8-Cl, 32%
5p, R = 6-Br, 67%



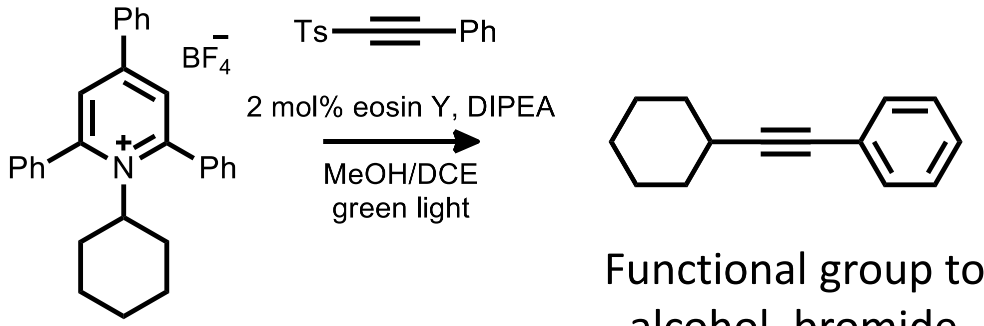




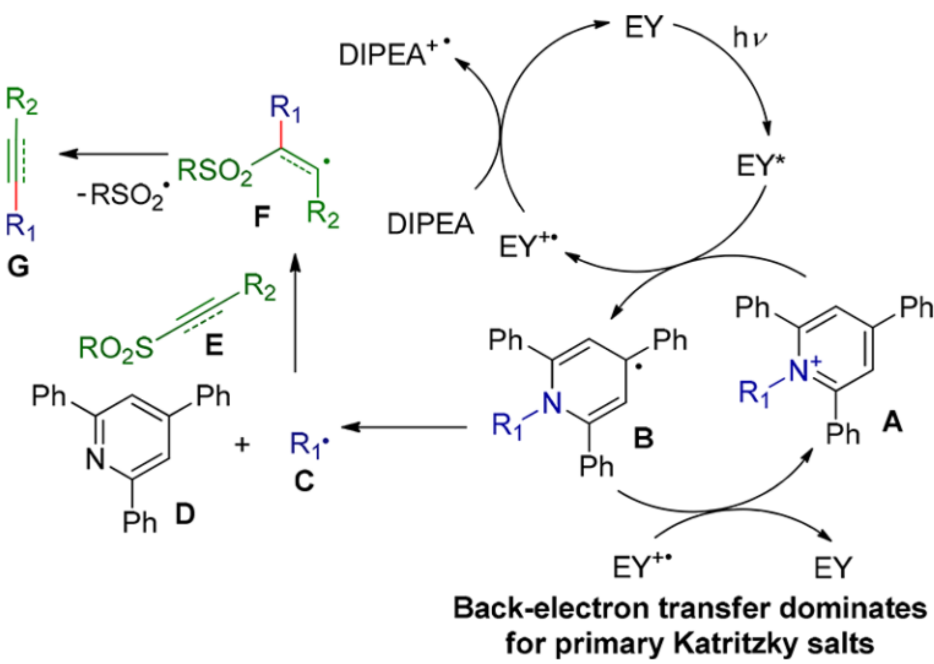


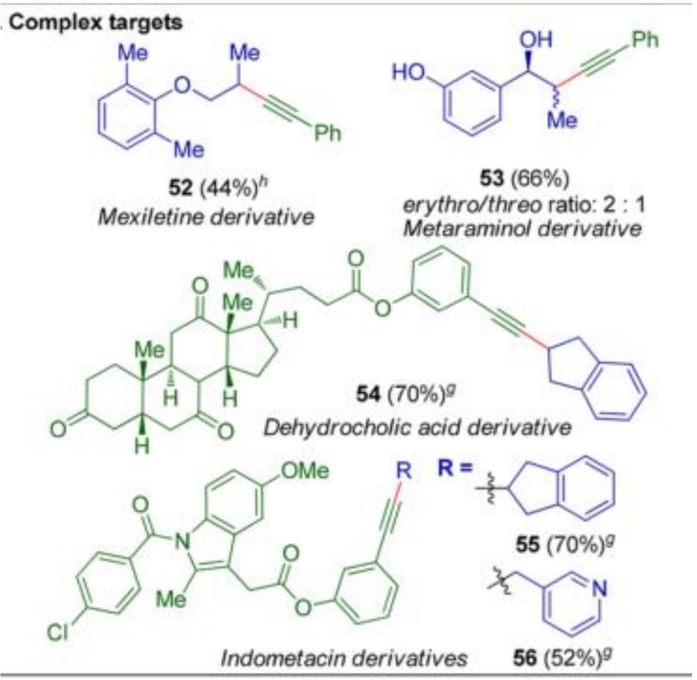
Klauck, F. J. R.; James, M. J.; Glorius, F. *Angew. Chem. Int. Ed.* **2017,** *56* (40), 12336.

Photoredox Alkynylation

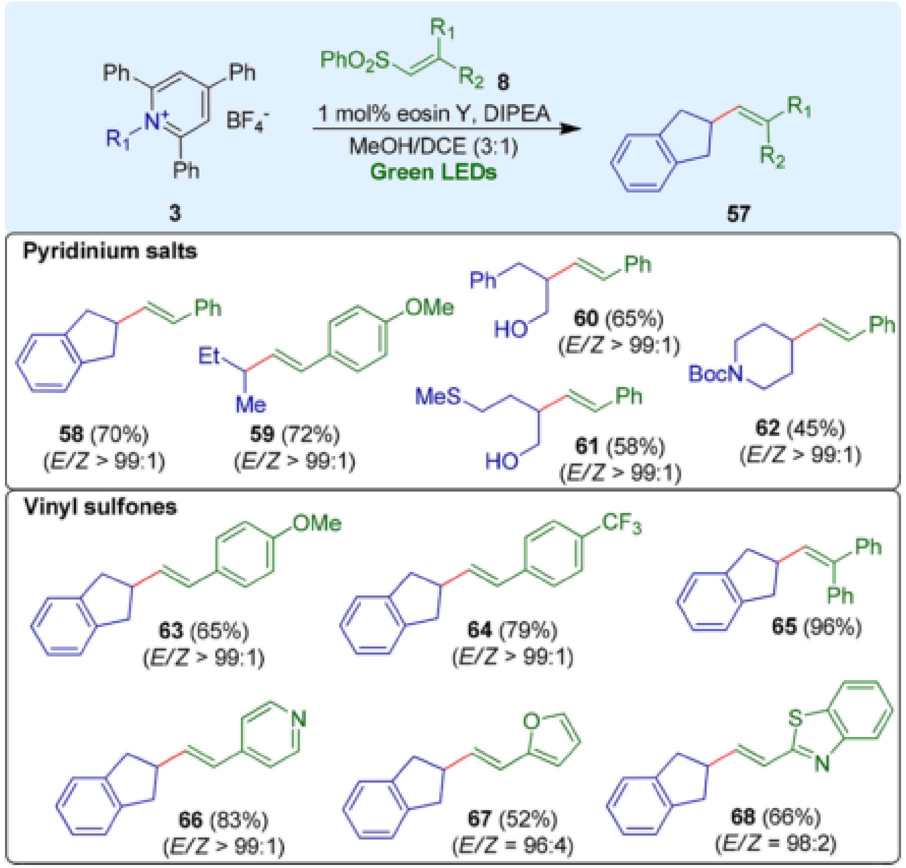


Functional group tolerance:
- alcohol, bromide, chloride, thiophene





Scheme 3. Scope of Deaminative Alkenylation^a

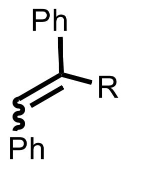


Ociepa, M.; Turkowska, J.; Gryko, D. *ACS Catal.* **2018,** *8* (12), 11362.

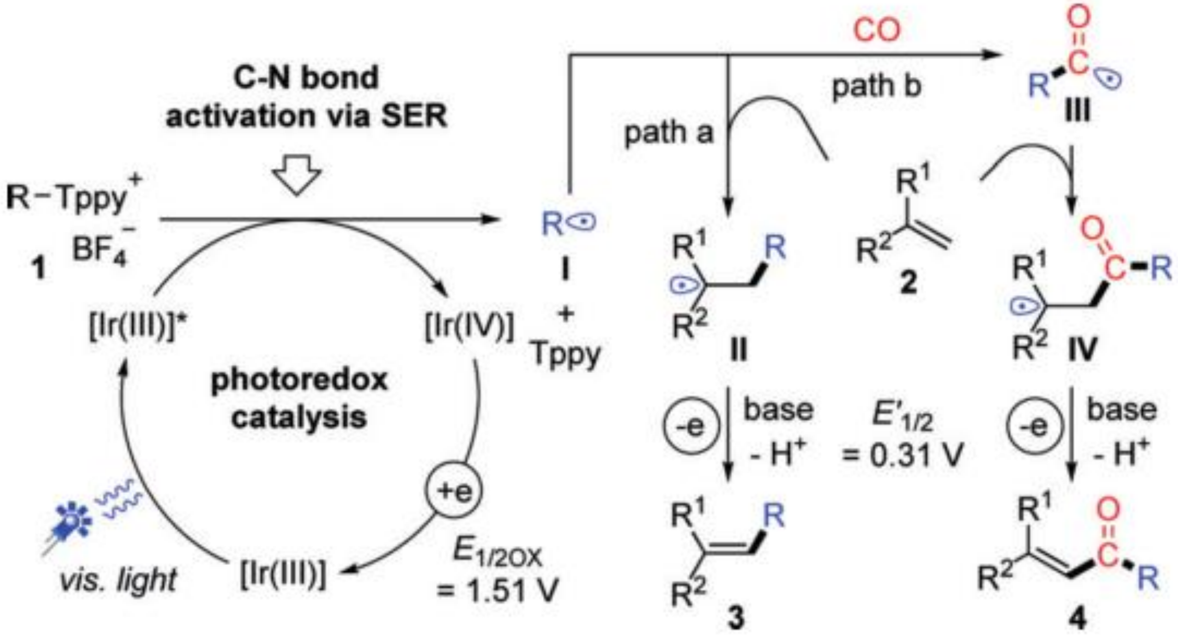
Photoredox Deaminative Carbonylative Alkyl-Heck

Functional group tolerance:
- nitriles, esters

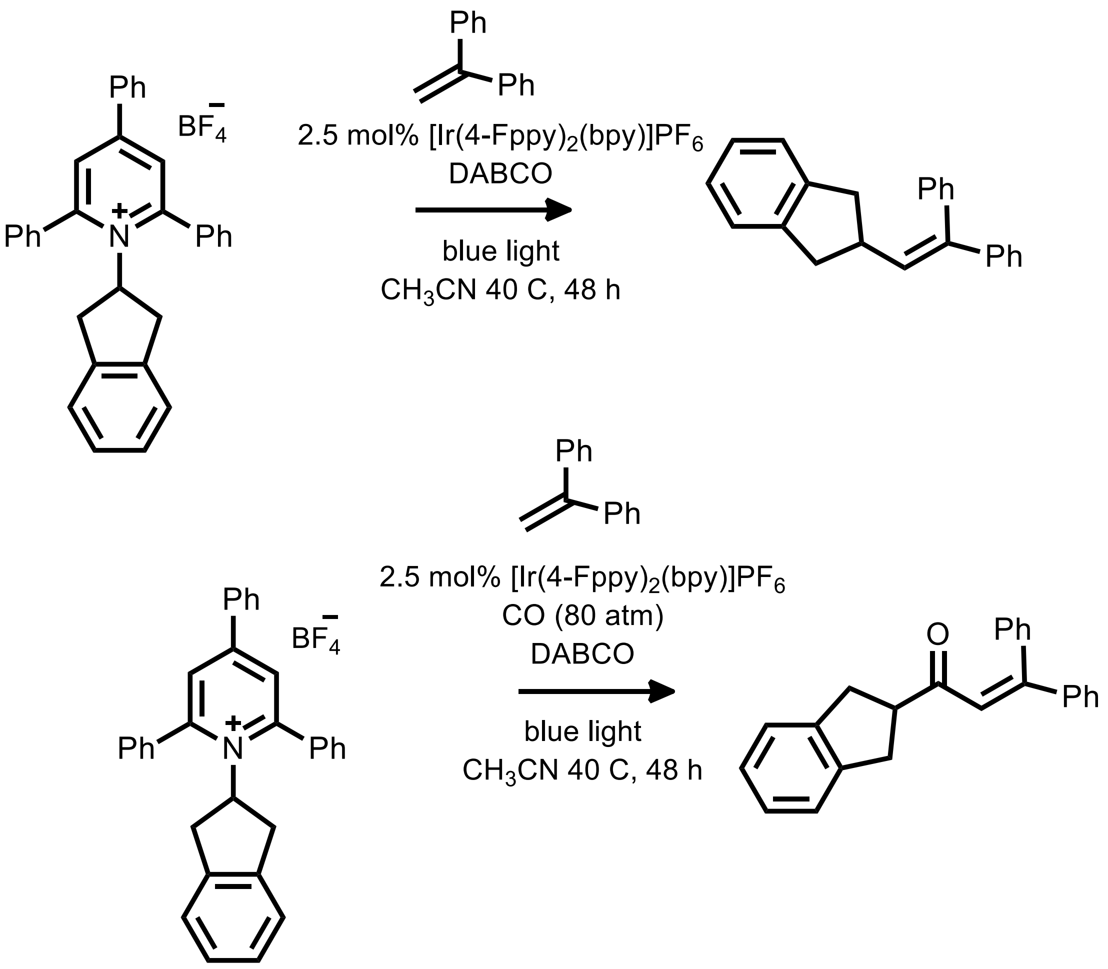
Mostly use symmetrical alkenes



8:1 E:Z

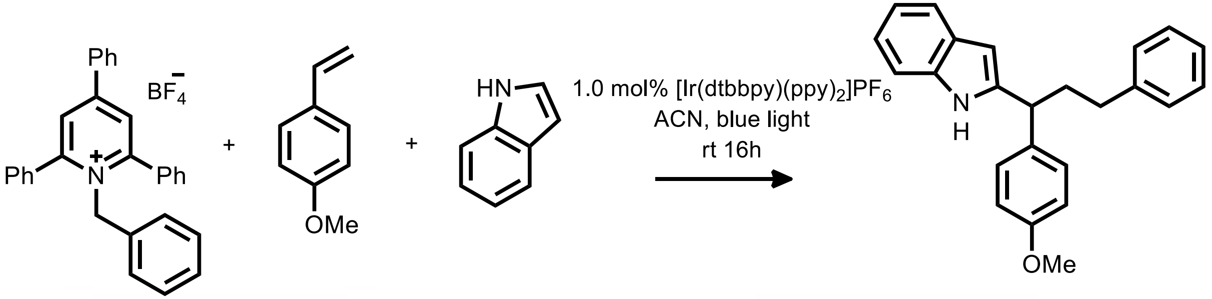


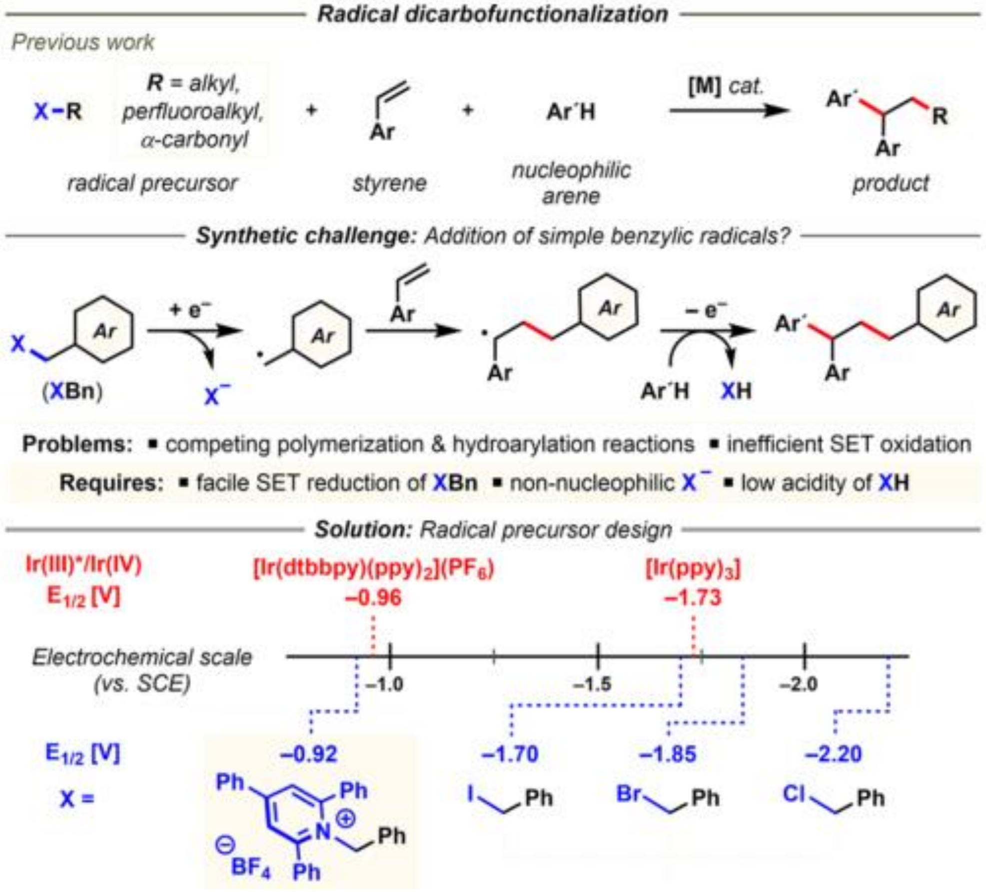
Scheme 2. Proposed mechanism.



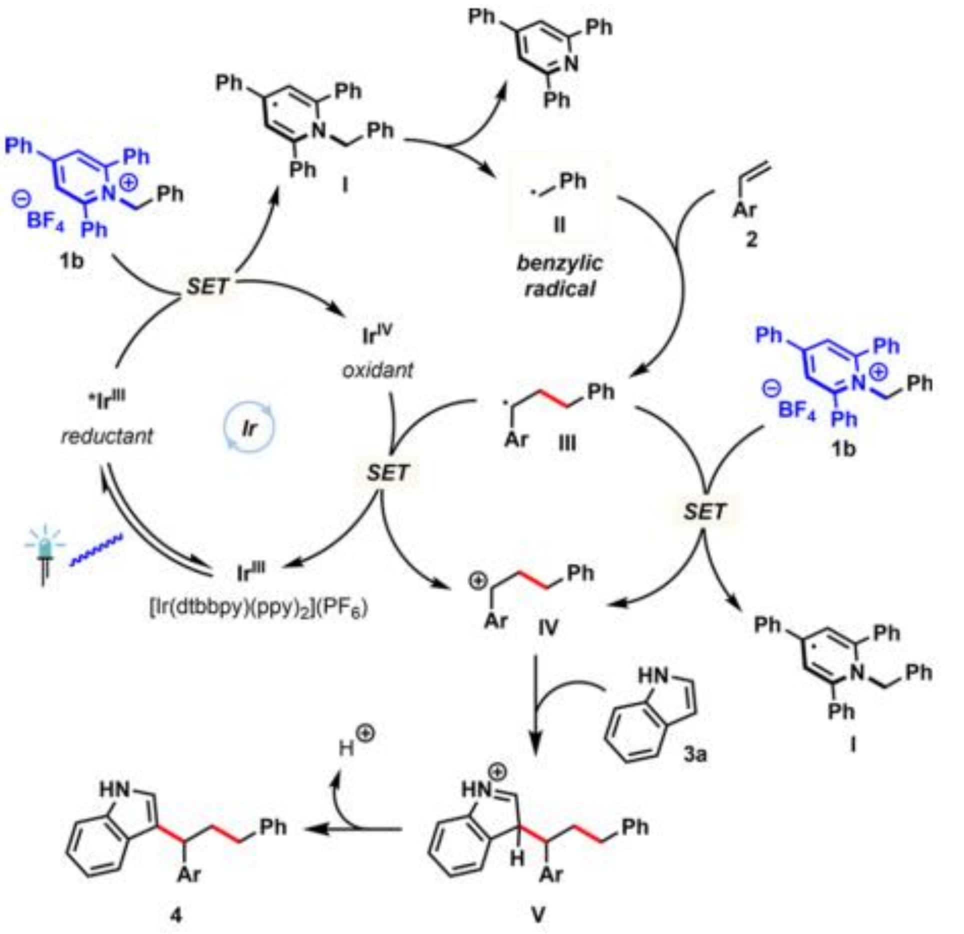
Jiang, X.; Zhang, M.-M.; Xiong, W.; Lu, L.-Q.; Xiao, W.-J., *Angew. Chem. Int. Ed.* **2019,** *58* (8), 2402.

Three Component Dicarbofunctionalization



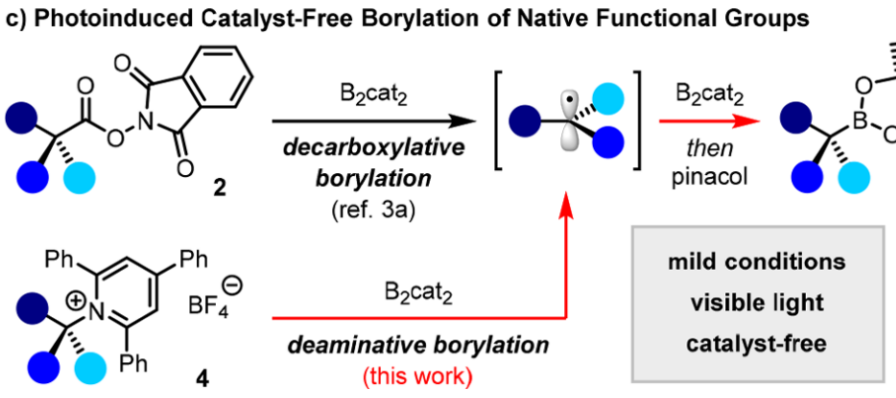


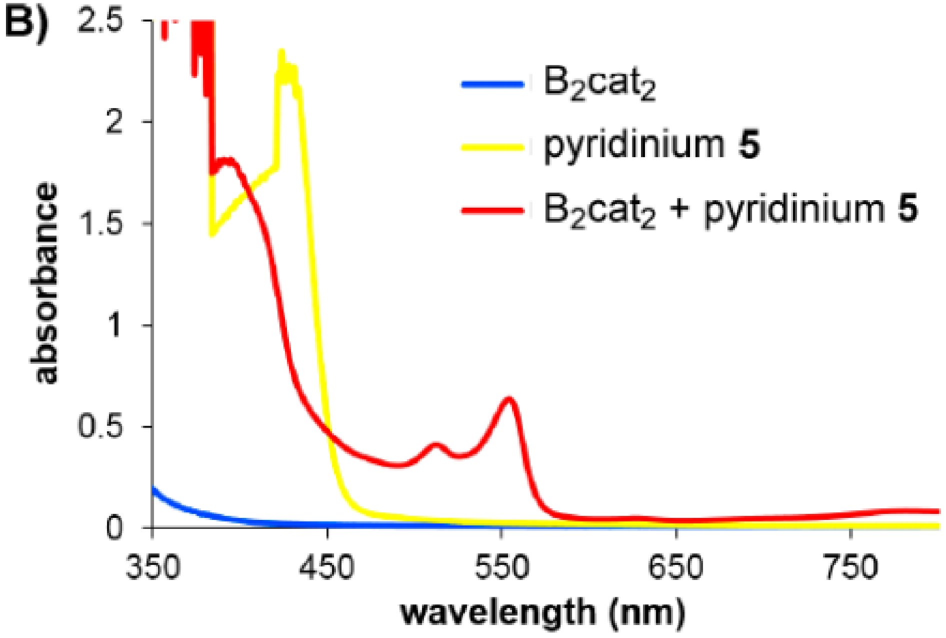
Scheme 4. Proposed Mechanism of the Deaminative Dicarbofunctionalization Using Katritzky Salts as Radical Precursors

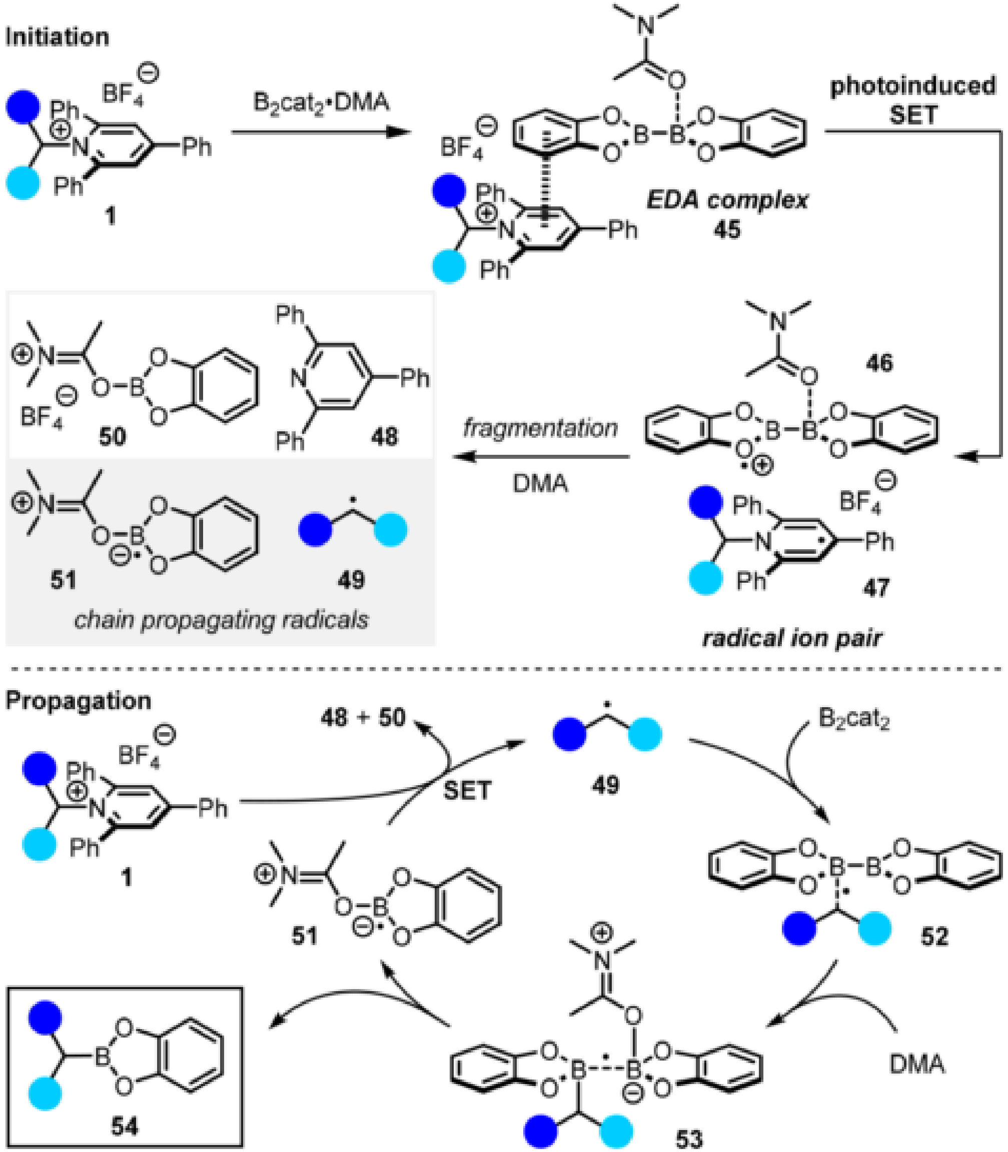


Klauck, F. J. R.; Yoon, H.; James, M. J.; Lautens, M.; Glorius, F. *ACS Catal.* **2019,** *9* (1), 236.

Deaminative Borylation via an EDA Complex


c) Photoinduced Catalyst-Free Borylation of Native Functional Groups

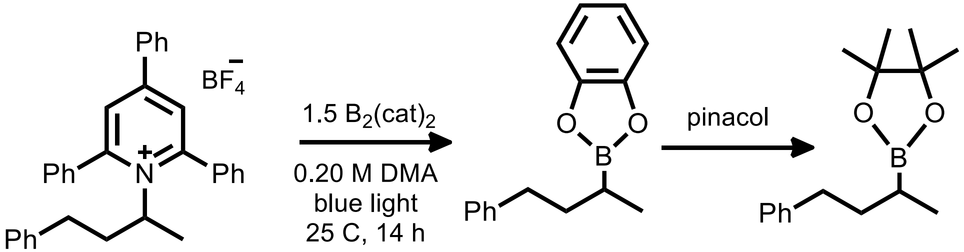




Wu, J.; He, L.; Noble, A.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2018,** *140* (34), 10700.

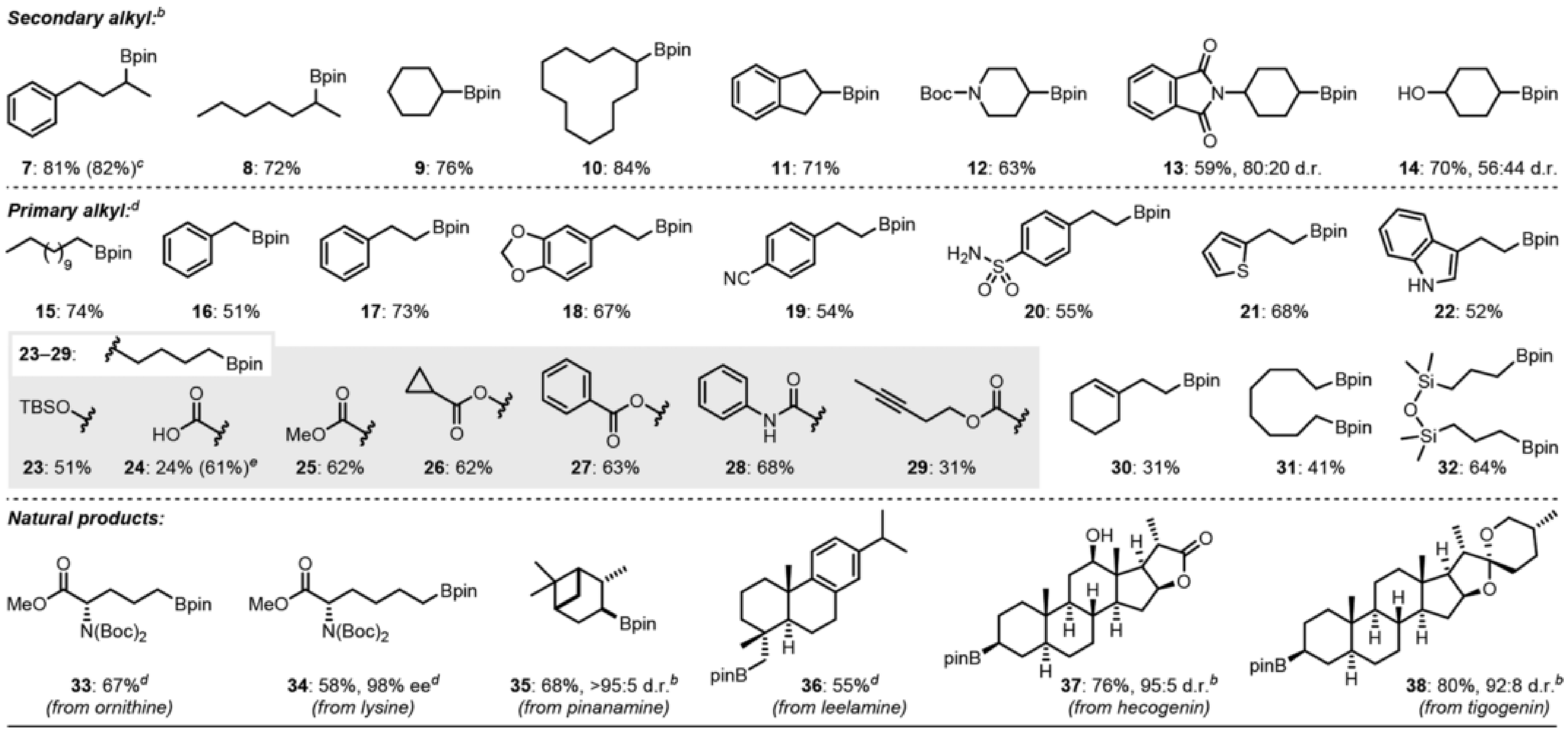
quantum yield of 7

Deaminative Borylation via an EDA Complex



Functional Group Tolerance:
ester, nitrile, sulfonamide, alcohols

Table 2. Substrate Scope[a]

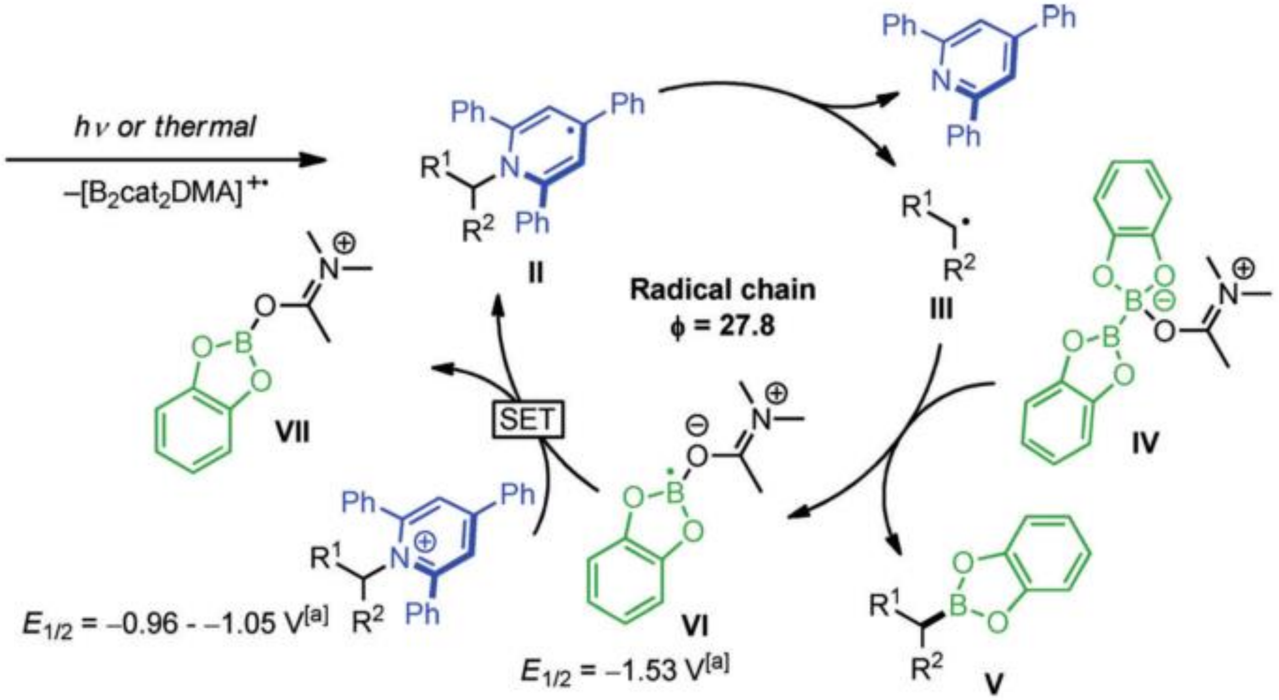


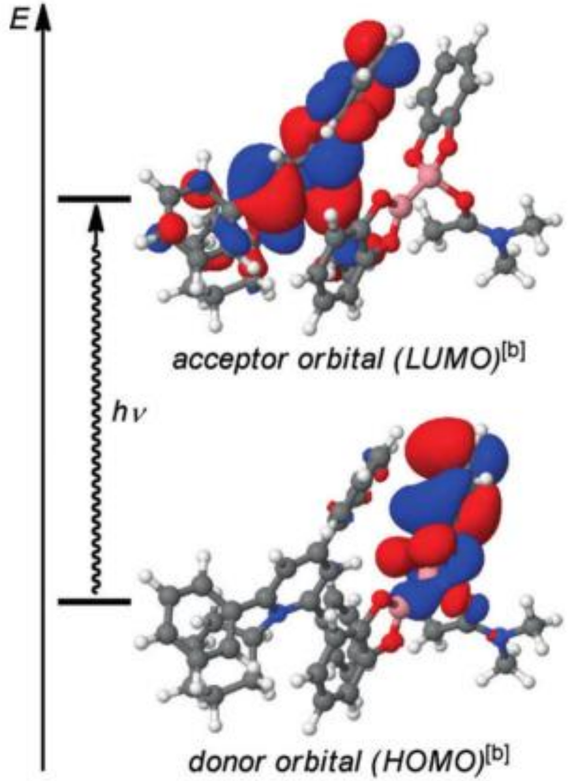
Wu, J.; He, L.; Noble, A.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2018,** *140* (34), 10700.

Deaminative Borylation via an EDA Complex

A. Proposed mechanism

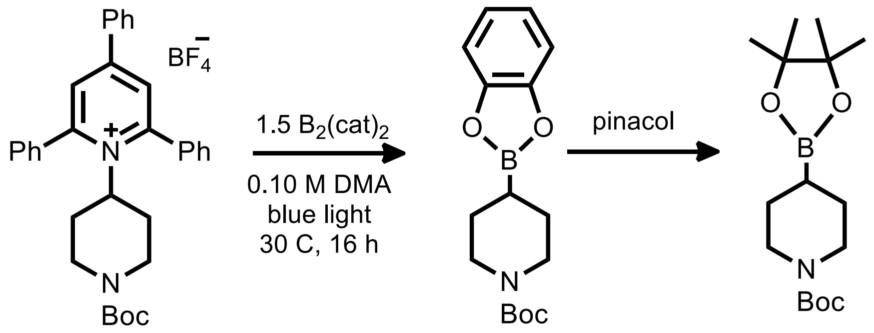
EDA complex, **I**





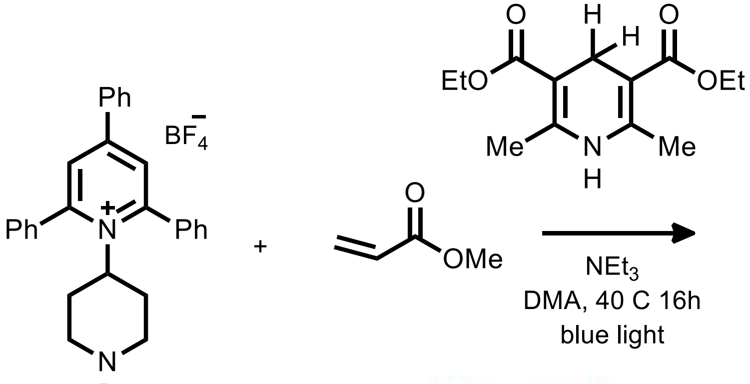
acceptor orbital (LUMO)[b]

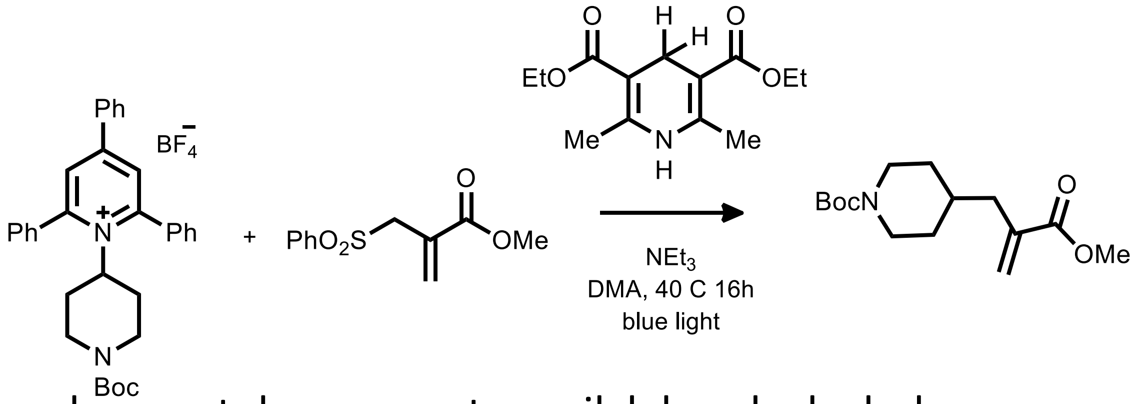
donor orbital (HOMO)[b]



Sandfort, F.; Strieth-Kalthoff, F.; Klauck, F. J. R.; James, M. J.; Glorius, F. *Chem. Eur. J.* **2018,** *24* (65), 17210.

Other Deaminative Functionalizations via an EDA Complex





Functional group tolerance: esters, silyl, boryl, alcohol

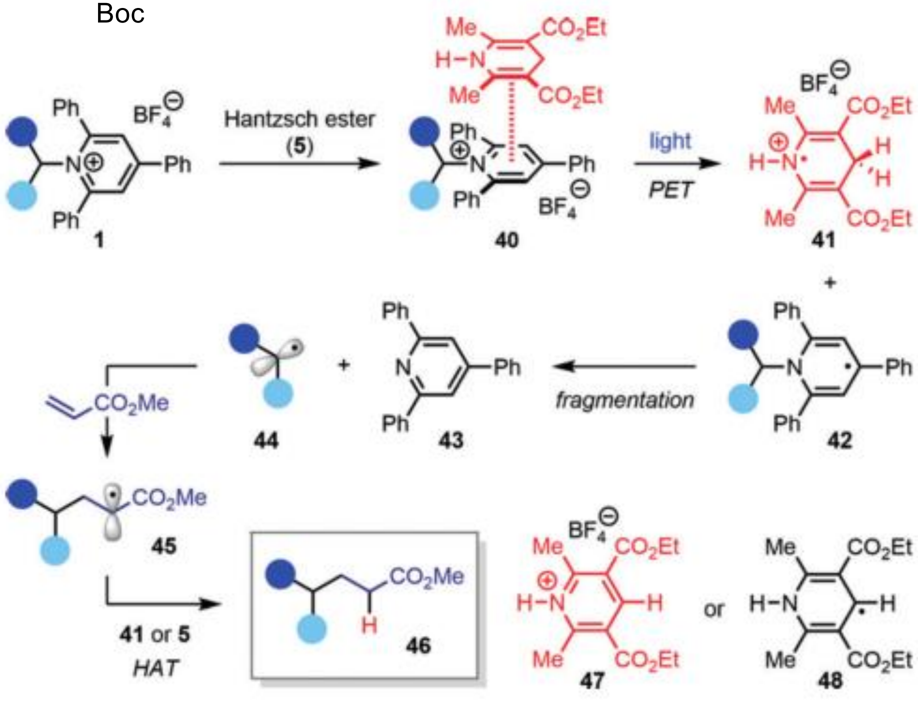
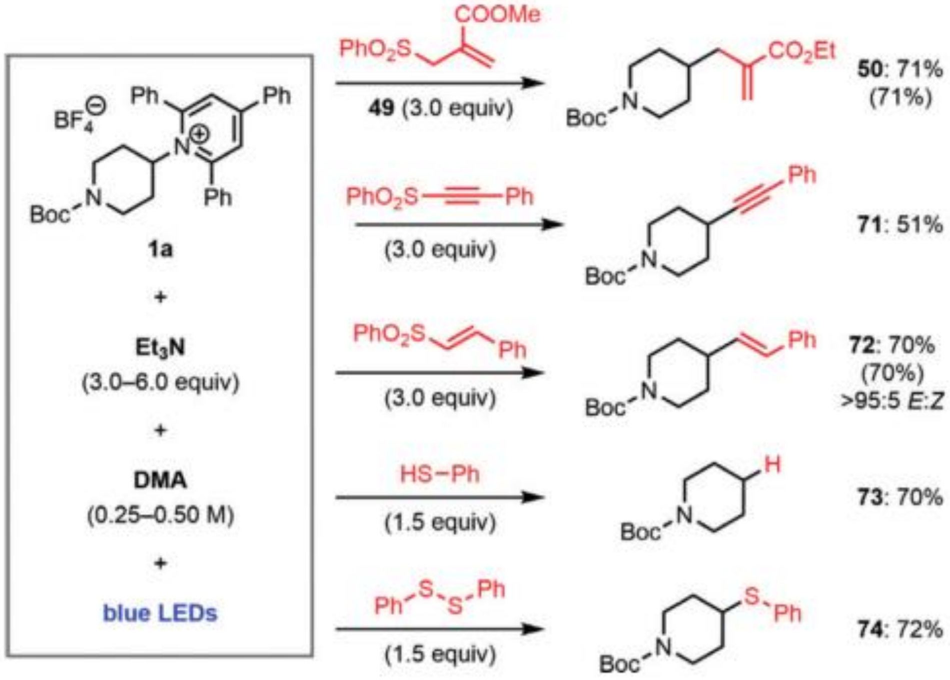


Figure 2. Proposed mechanism.



Wu, J.; Grant, P. S.; Li, X.; Noble, A.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2019,** *58* (17), 5697.

Other Deaminative Functionalizations via an EDA Complex

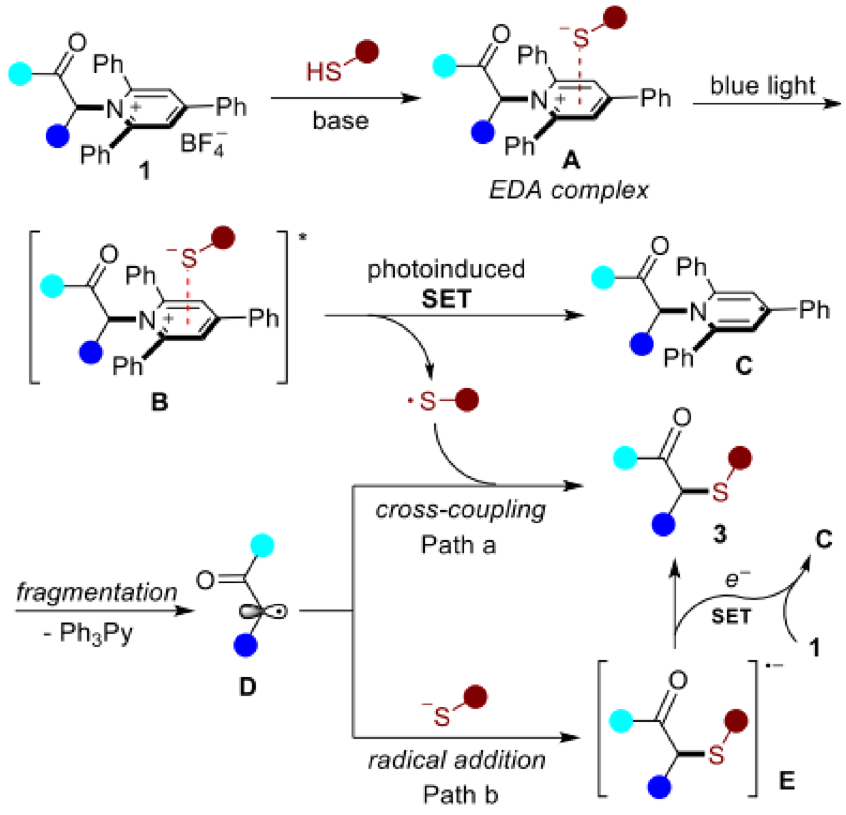
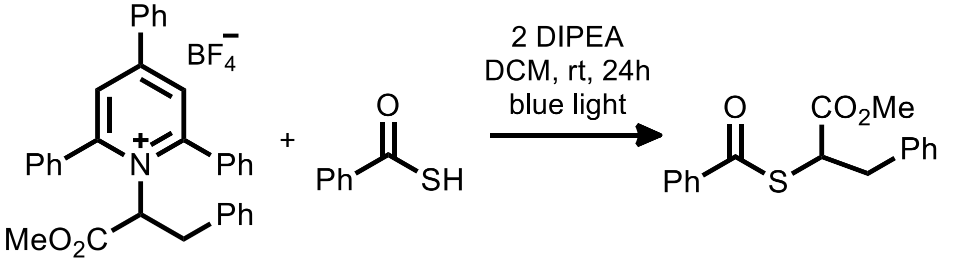
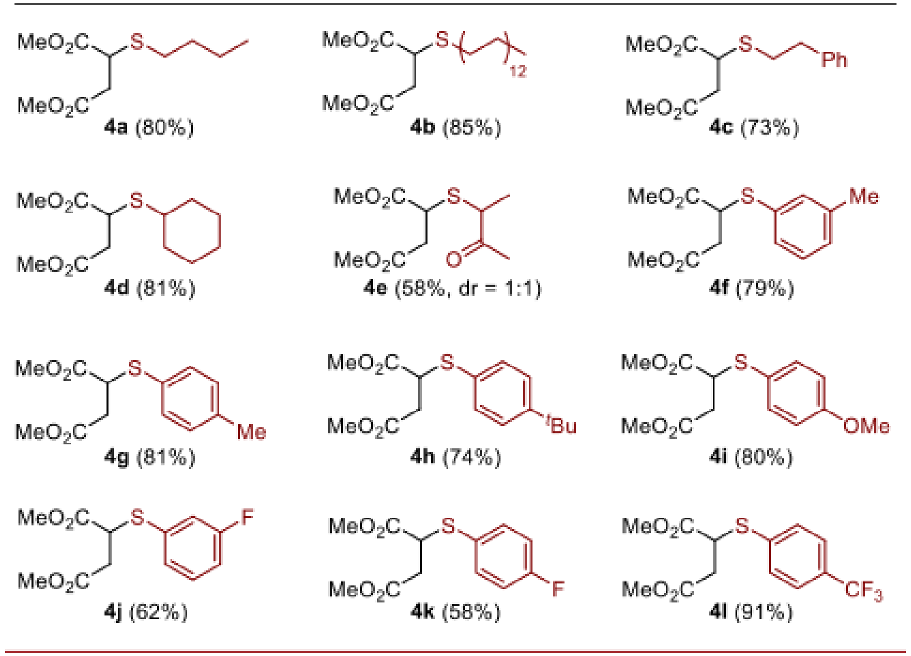


Figure 4. Proposed mechanism for the photoinduced thioesterfication.

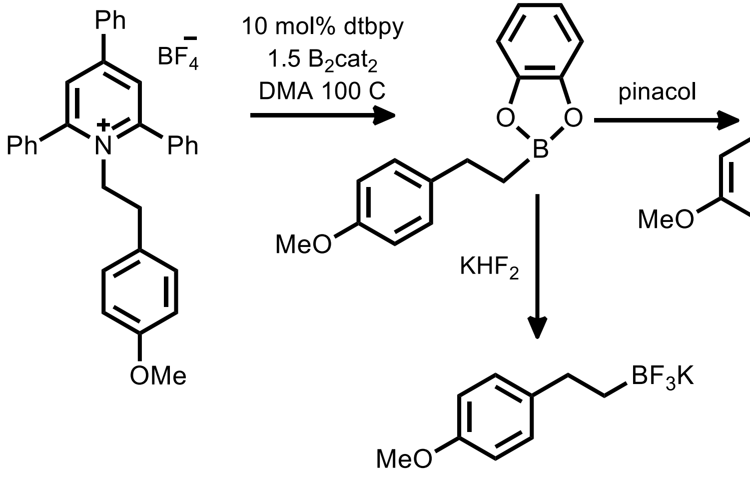


Used a variety of amino acid derivates with carboxylic acid protected



Yi, J.; Badir, S. O.; Kammer, L. M.; Ribagorda, M.; Molander, G. A. *Org. Lett.* **2019,** *21* (9), 3346.

Deaminative Borylation by a Lewis Base



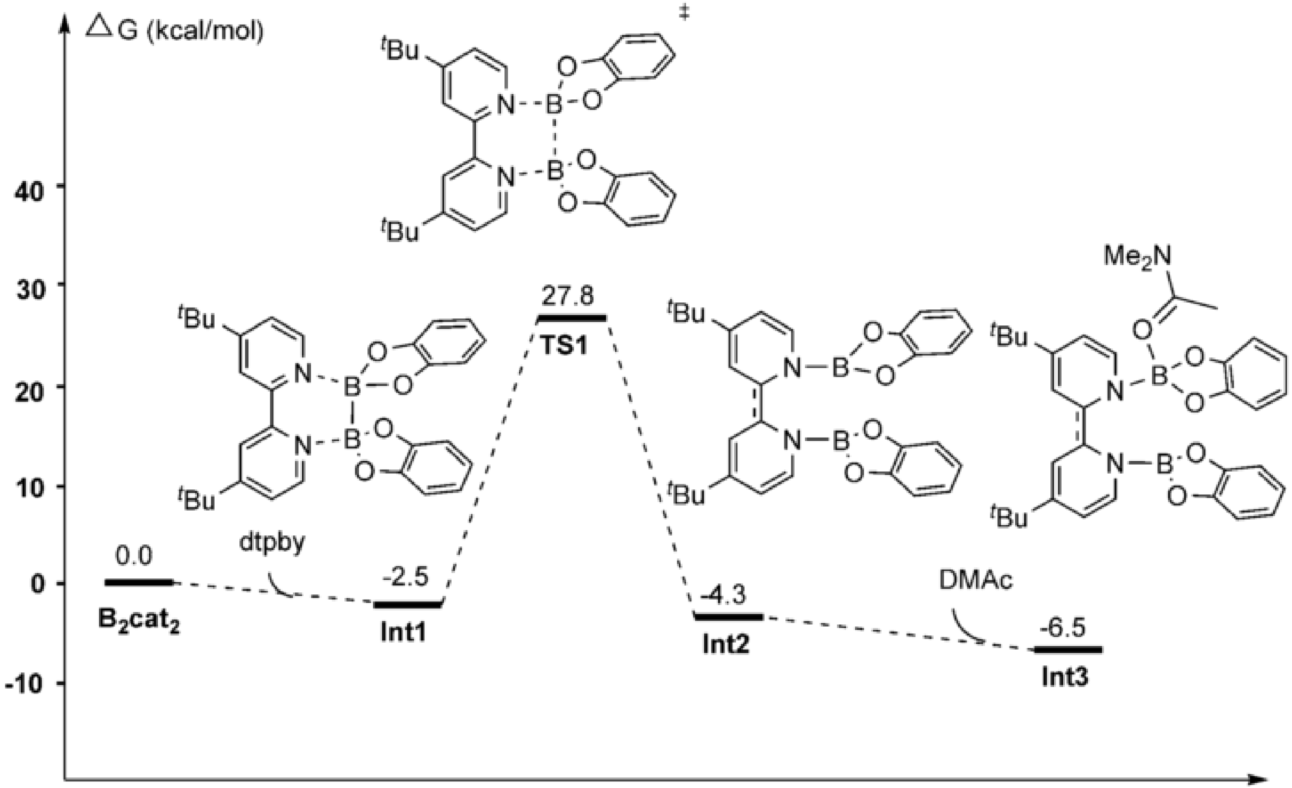
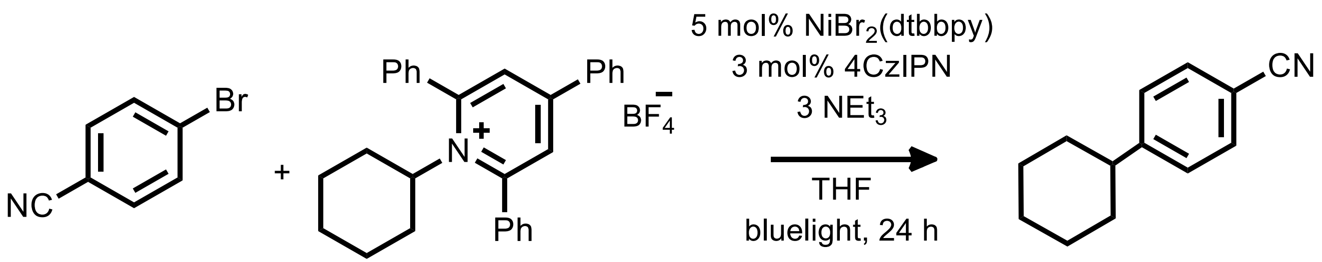
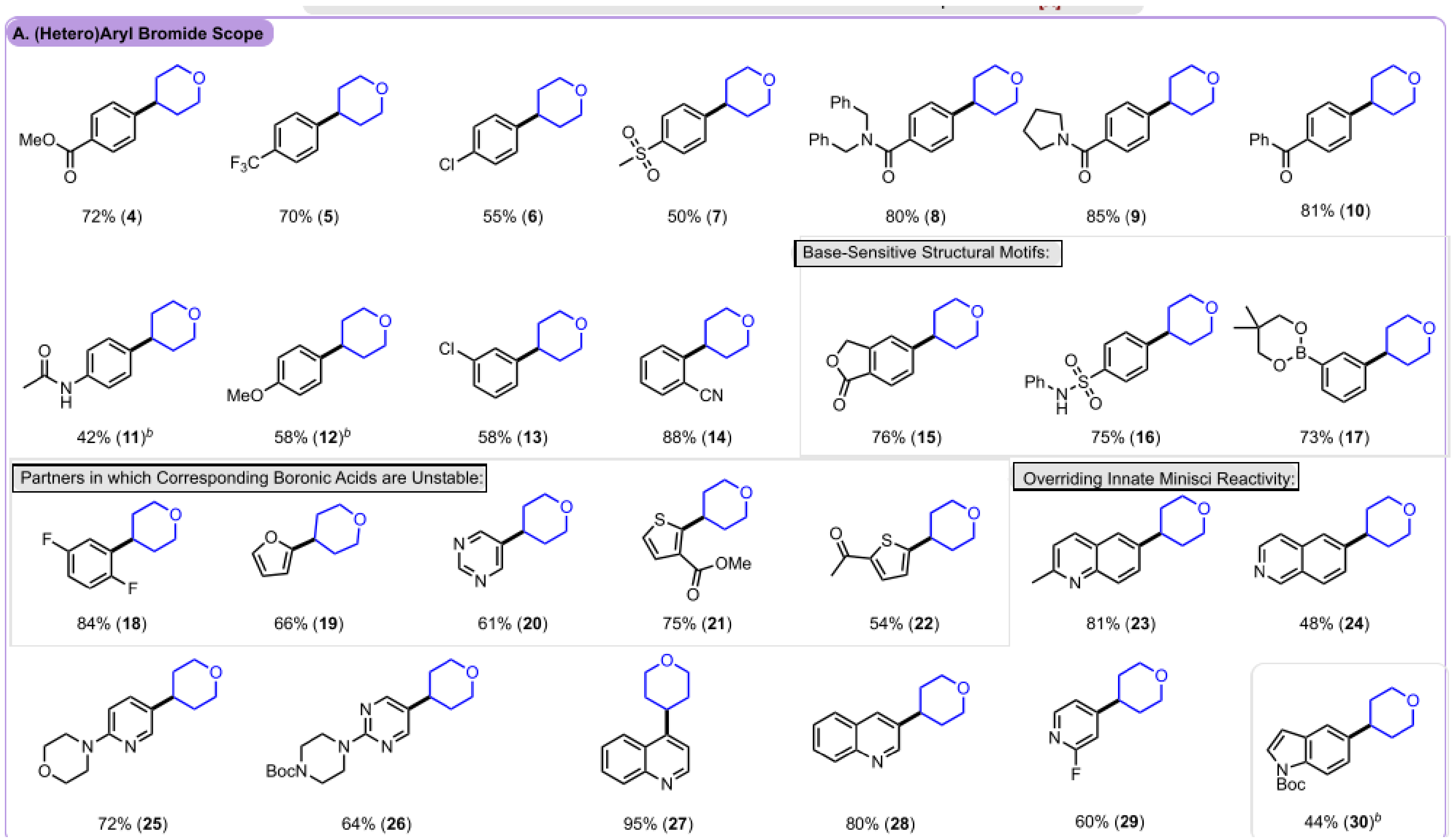


Figure 2. Gibbs free energy profile for the dtpby induced cleavage of the B—B bond of B_2cat_2 (all energies are given in kcal mol^{-1}).

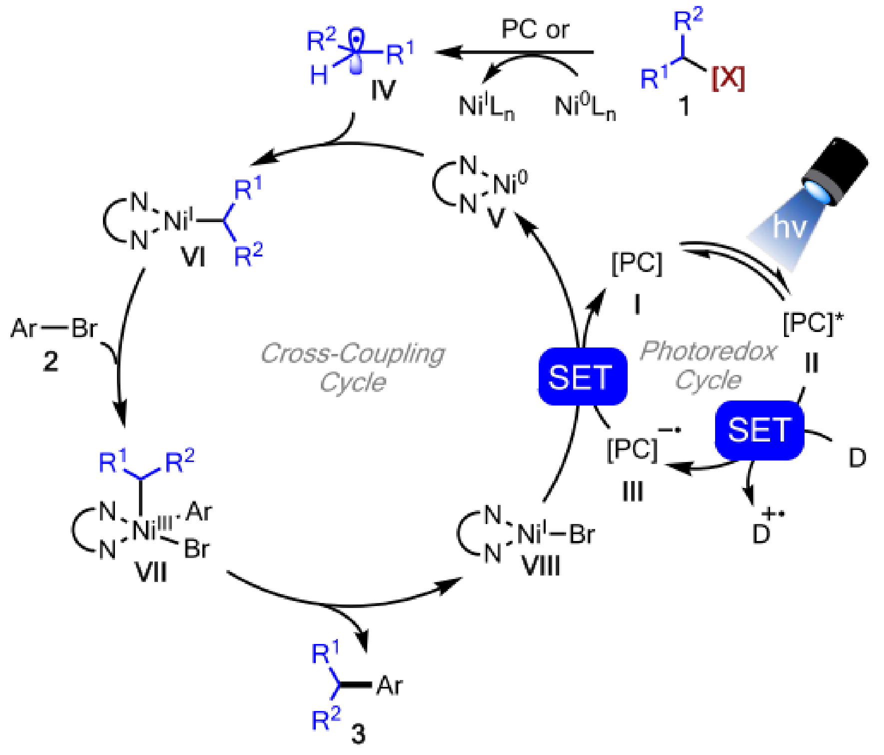
Hu, J.; Wang, G.; Li, S.; Shi, Z. *Angew. Chem. Int. Ed.* **2018,** *57* (46), 15227.

You Guessed It: Dual Photoredox Ni Cross Coupling

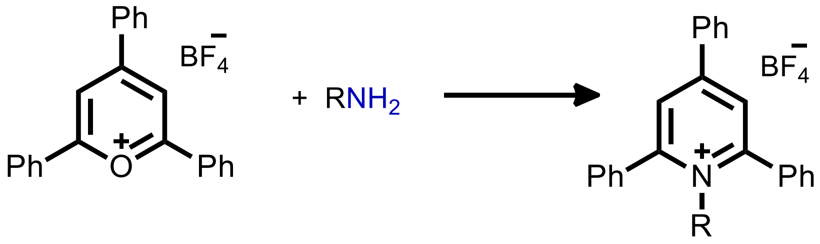


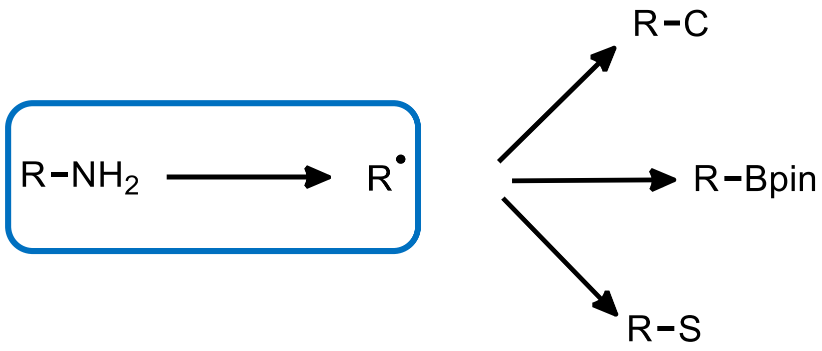


Scheme 5. Reductive Nickel/Photoredox Dual Catalysis: Mechanistic Rationale



Conclusion and Outlook




$R{-}NH_2 \longrightarrow R^{\bullet}$

R–C

R–Bpin

R–S

There is clearly a high demand for new radical deaminative strategies because when one new strategy was reported it led to an explosion of new research.