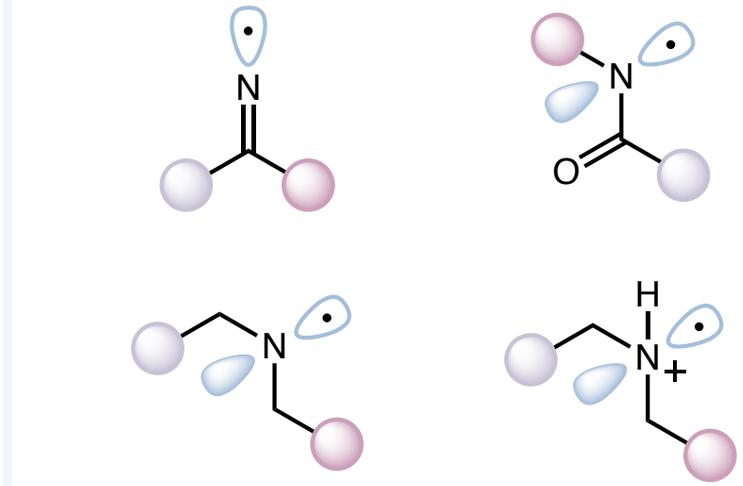
Formation and Reactivity of N–Centered Radicals



Amy Chan

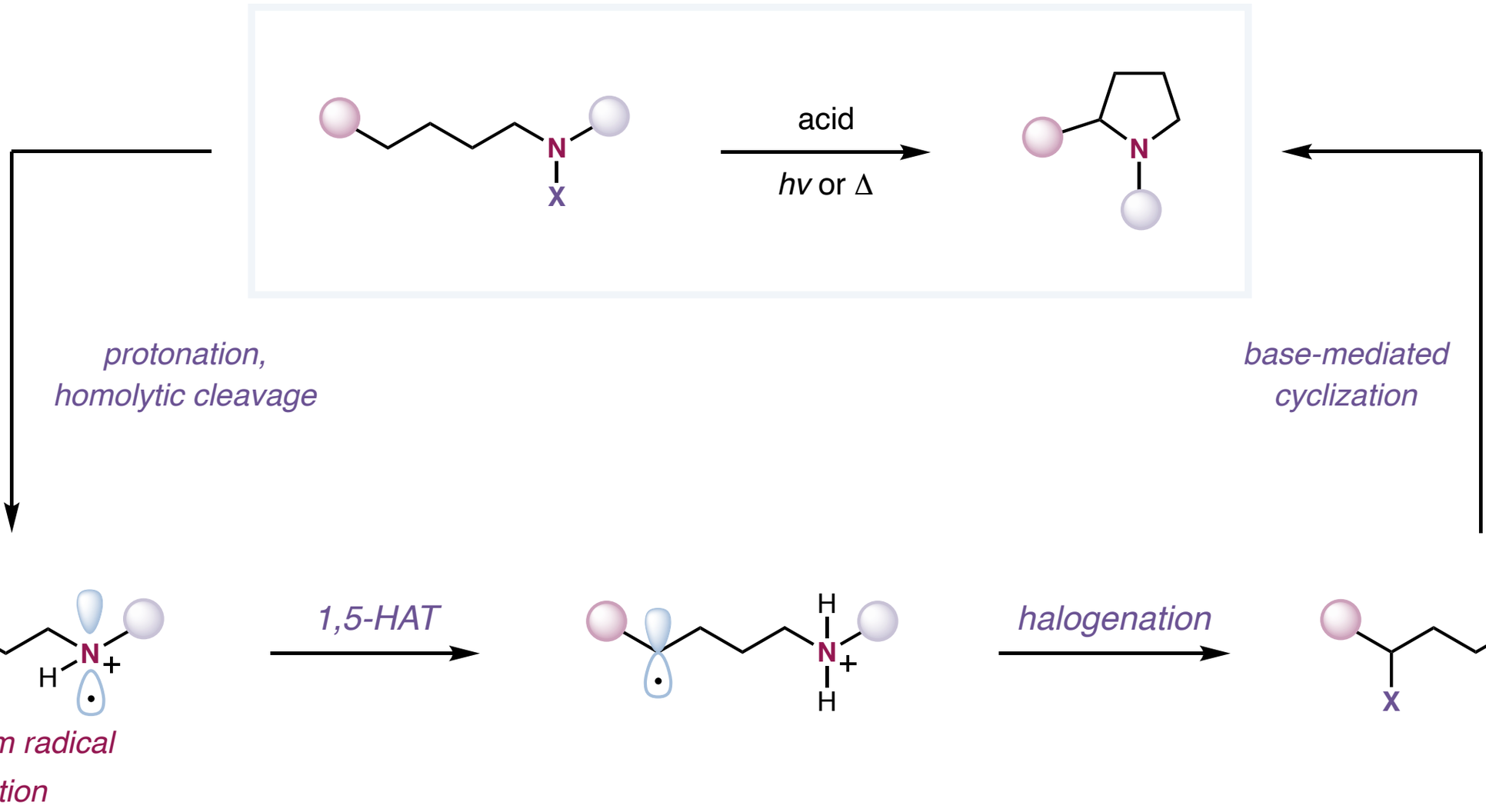
MacMillan Research Group

Group Meeting

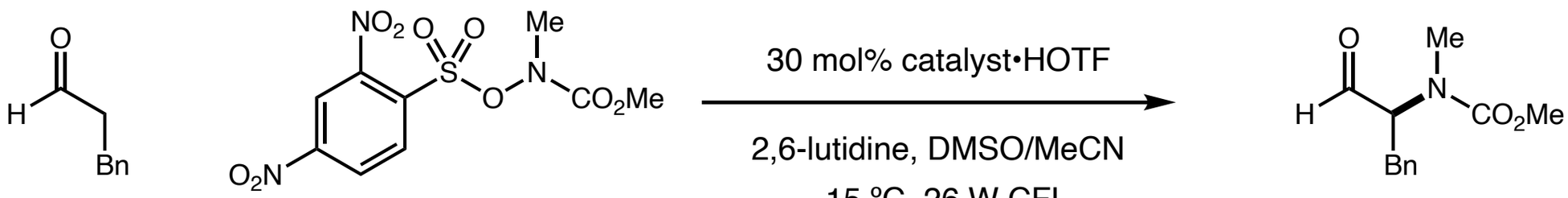
March 2nd, 2021

Early Application of N-Centered Radicals

Hoffmann-Loffler-Freytag cyclization

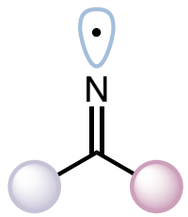
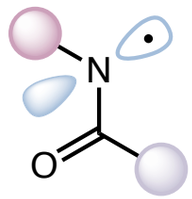
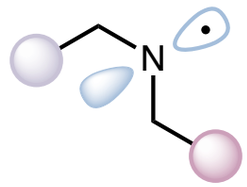
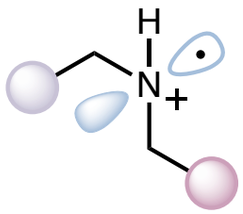


Application of N-Centered Radicals in Enamine Catalysis



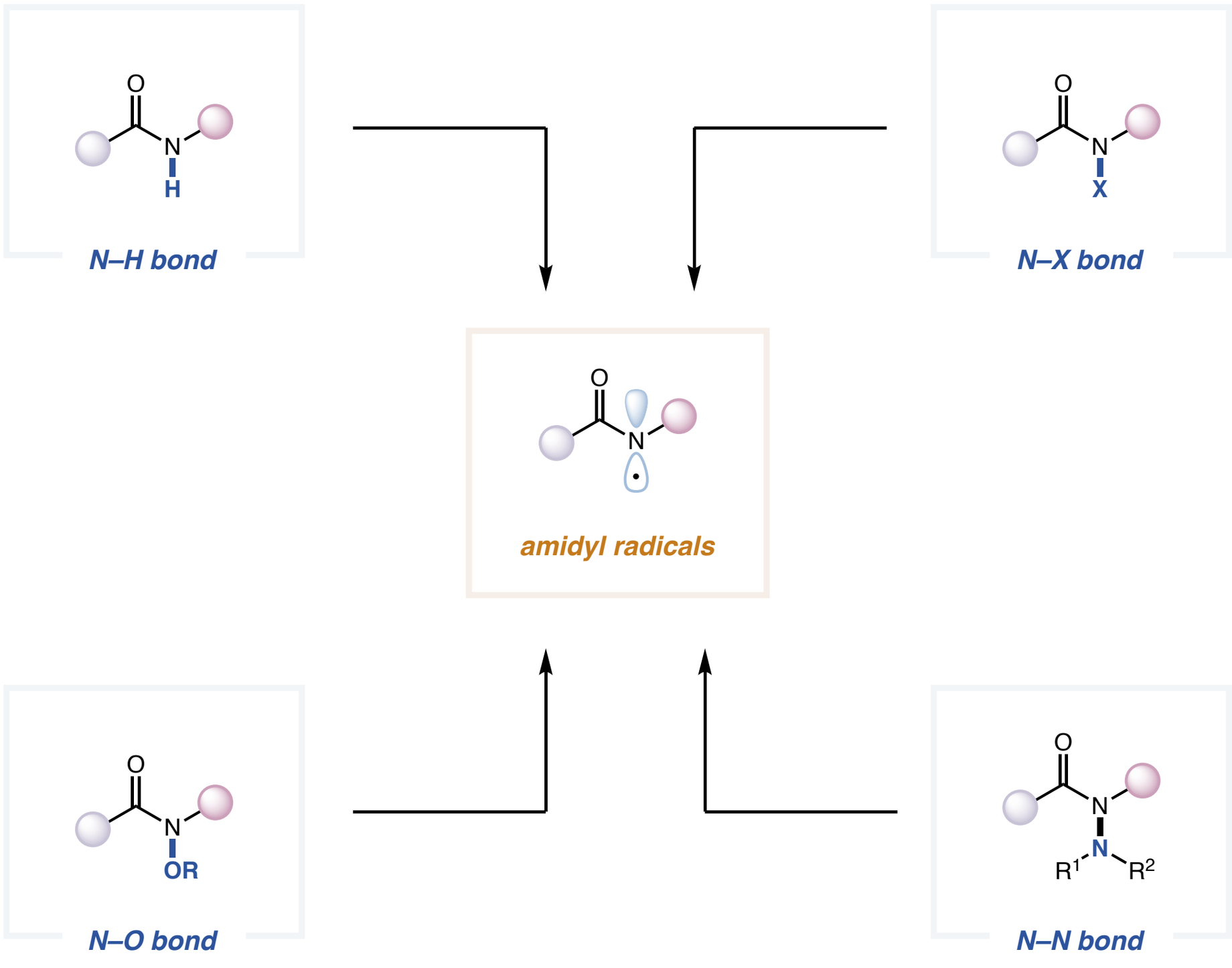
Cecere, G.; König, C. M.; Alleva, J. L., MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521.

Classification of N-Centered Radicals

				
Name	iminiyl	amidyl	aminyl	aminium
Configuration	σ	π	π	π
Philicity	ambiphilic	electrophilic	nucleophilic	electrophilic

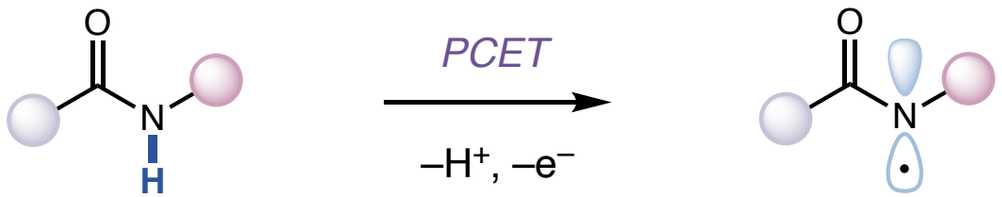
Davies, J.; Morcillo, S. P.; Douglas, J. J.; Leonori, D. *Chem. Eur. J.* **2018**, *24*, 12154.

Generation of N-Centered Radicals

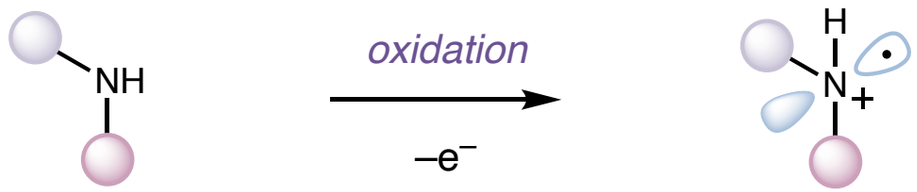


Generation of N-Centered Radicals

N–H bond cleavage



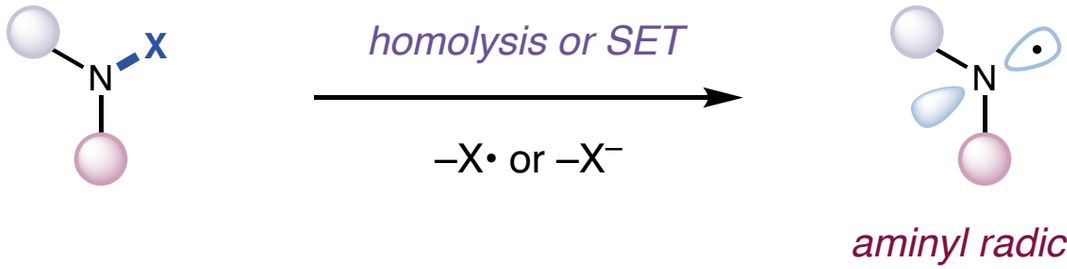
amidyl radical



aminium radical cation

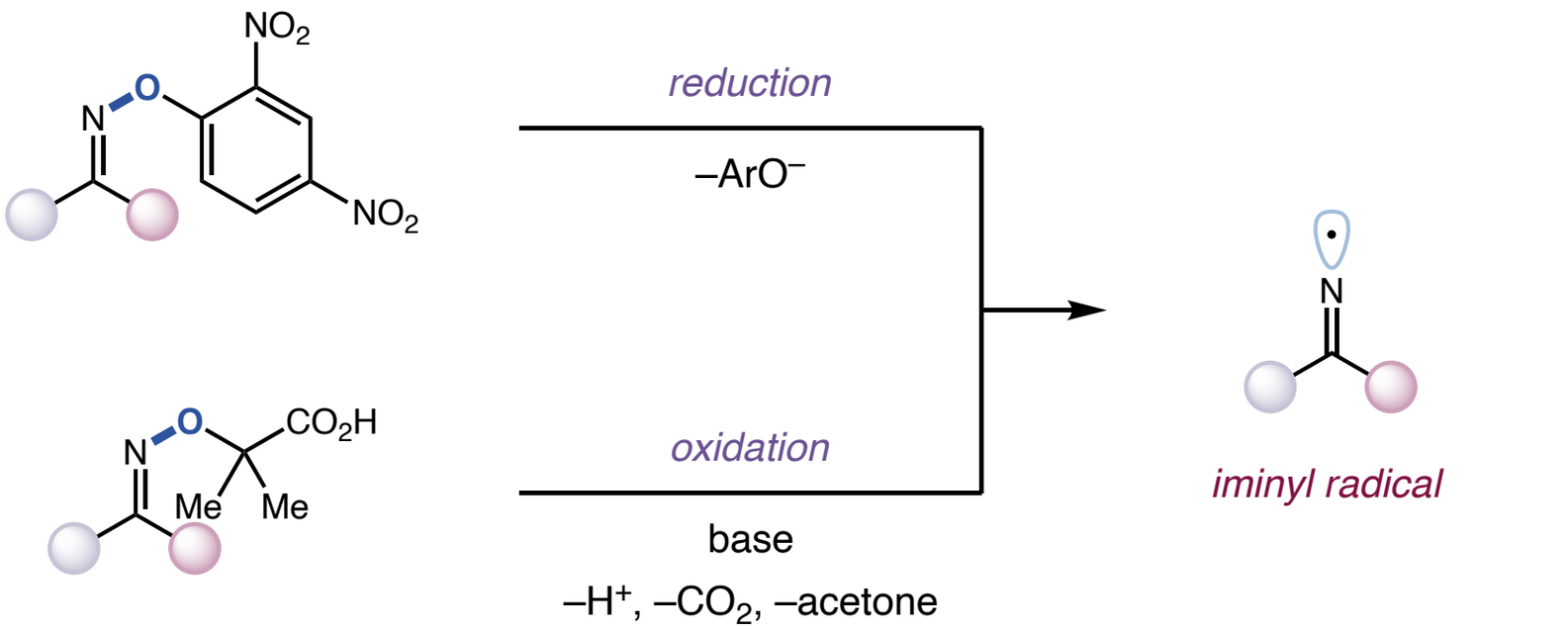
Generation of N-Centered Radicals

N–X bond cleavage



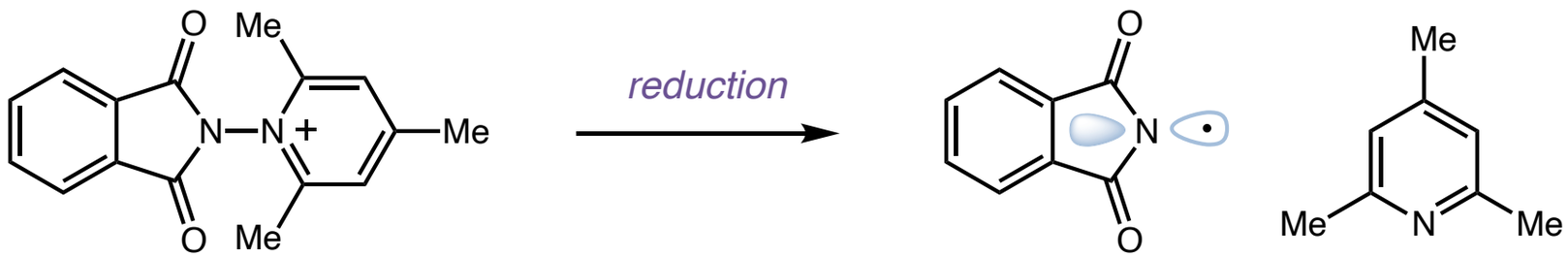
aminyl radical

N–O bond cleavage



iminyl radical

N–N bond cleavage



Outline

• Aminating reagents, forming sp^3 and sp^2 C–N bonds

• HAT reagents for sp^3 C–H functionalization, due to large BDEs of N–H bonds (up to 110 kcal/mol)

• Fragmentation (β-scission) is possible, but not universal

A. Formation of sp^3 C–N bonds: intramolecular cyclization

B. Formation of sp^3 C–N bonds: addition to olefins

C. Formation fo sp^2 C–N bonds: addition to aromatic compounds

D. *N*-centered radicals-mediated HAT of sp^3 C–H bonds

E. Fragmentation of *N*-centered radicals

Outline

- Aminating reagents, forming sp^3 and sp^2 C–N bonds
- HAT reagents for sp^3 C–H functionalization, due to large BDEs of N–H bonds (up to 110 kcal/mol)
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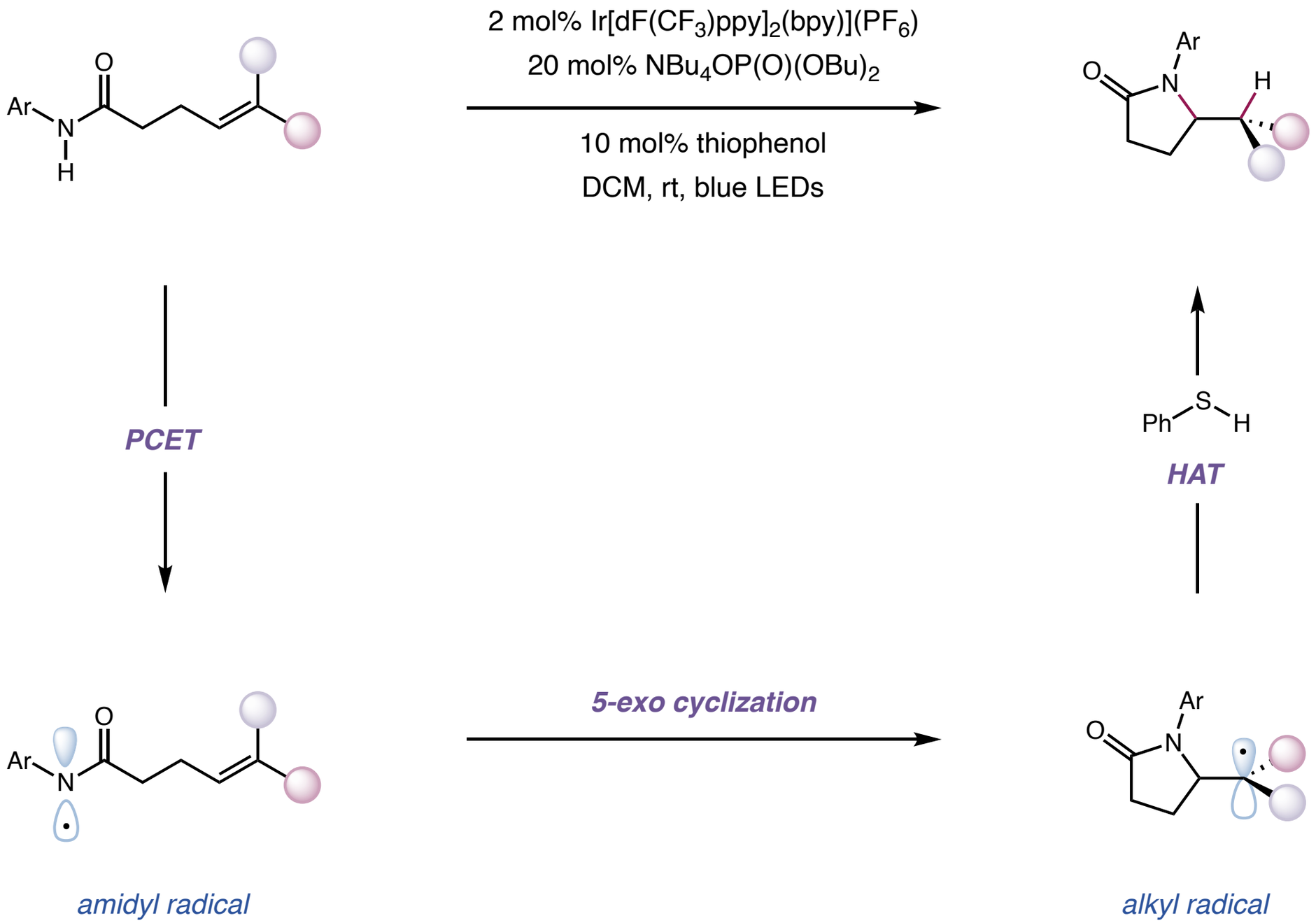
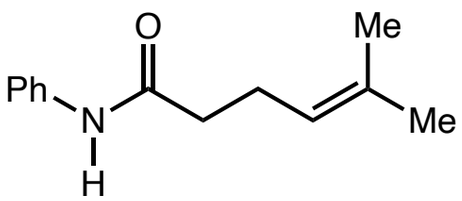
E. Fragmentation of *N*-centered radicals

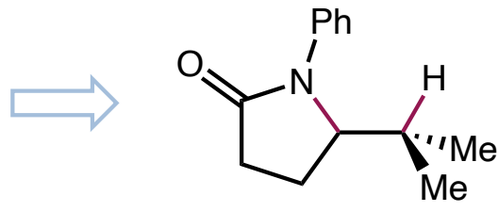
Amidyl Radical Cyclization: From Free N–H Compounds



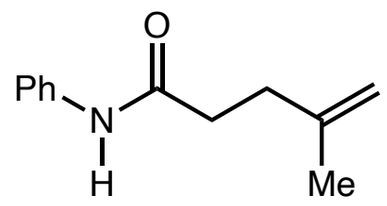
Miller, D. C.; Choi, G. J.; Orbe, H. S., Knowles, R. R. *J. Am. Chem Soc.* **2015**, *137*, 13492.

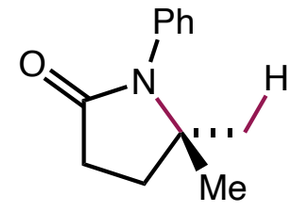
Amidyl Radical Cyclization: From Free N–H Compounds



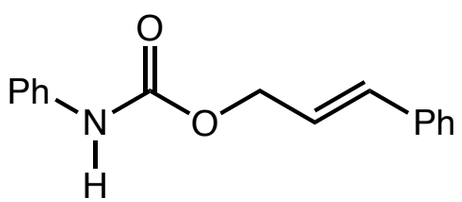


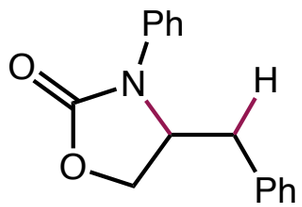
90% yield



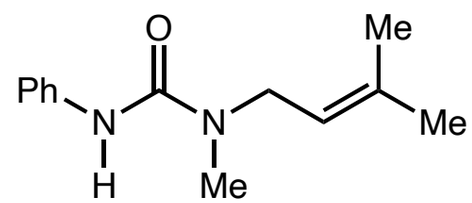


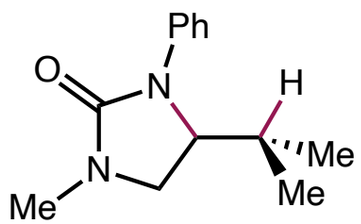
87% yield



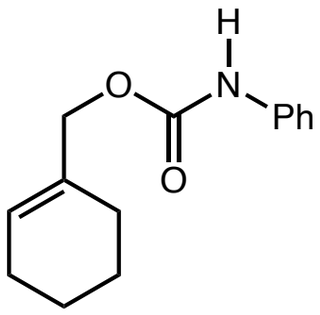


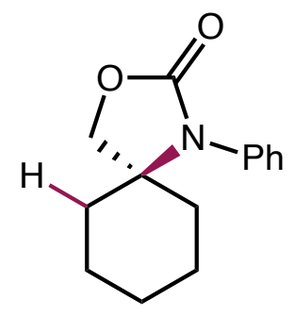
81% yield



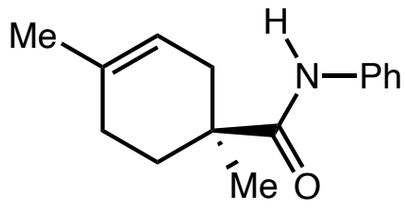


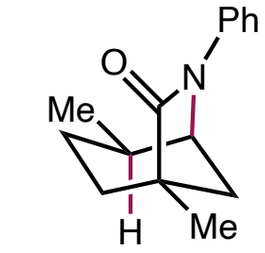
90% yield





86% yield

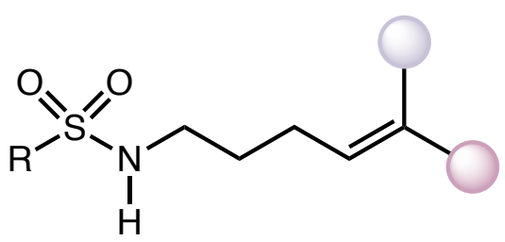




87% yield
5:1 dr

Miller, D. C.; Choi, G. J.; Orbe, H. S., Knowles, R. R. *J. Am. Chem Soc.* **2015**, *137*, 13492.

Amidyl Radical Cyclization: Enantioselective Hydroamination



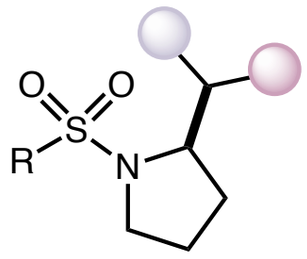
achiral sulfonamide

2 mol% $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}dCF_3bpy)]PF_6$

2.5 mol% chiral phosphate

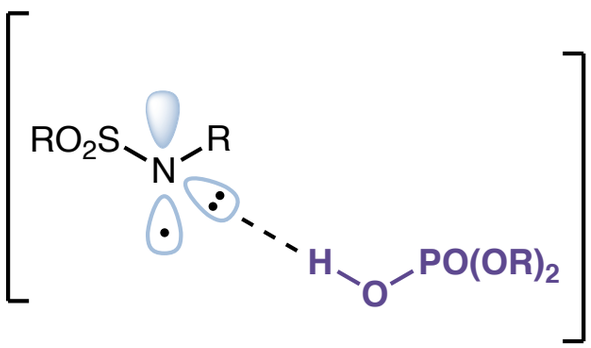
30 mol% TRIP thiol, $PhCF_3$

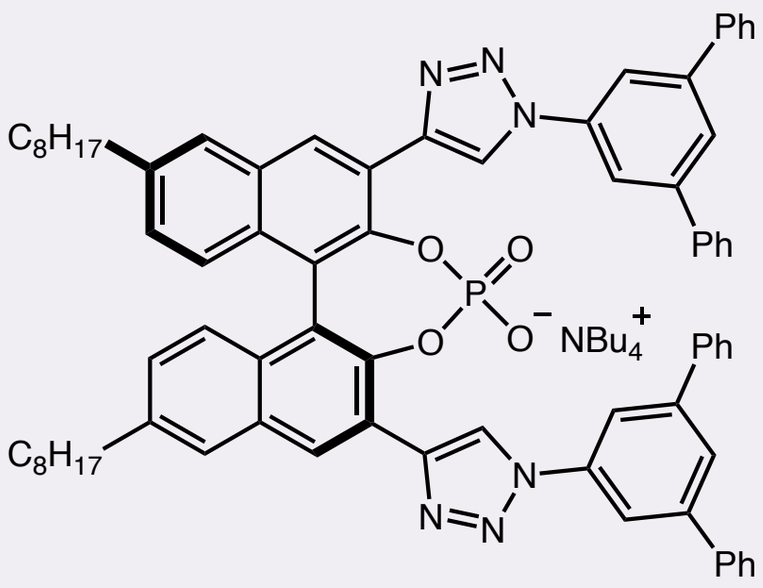
blue LEDs, –20 °C



enantioenriched product
up to 98:2 er

PCET

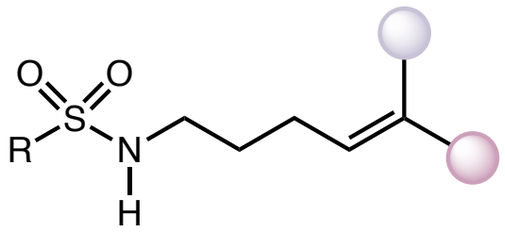




chiral phosphate catalyst

Roos, C. B.; Demaerel, J.; Graff, D. E.; Knowles, R. R. *J. Am. Chem. Soc.* **2020**, *142*, 5974.

Amidyl Radical Cyclization: Enantioselective Hydroamination



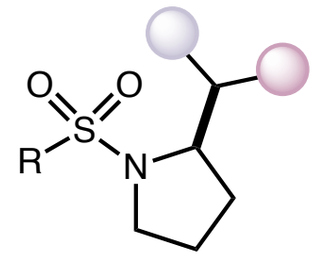
achiral sulfonamide

2 mol% $[Ir(dF(CF_3)ppy)_2(5,5'\text{-}dCF_3bpy)]PF_6$

2.5 mol% chiral phosphate

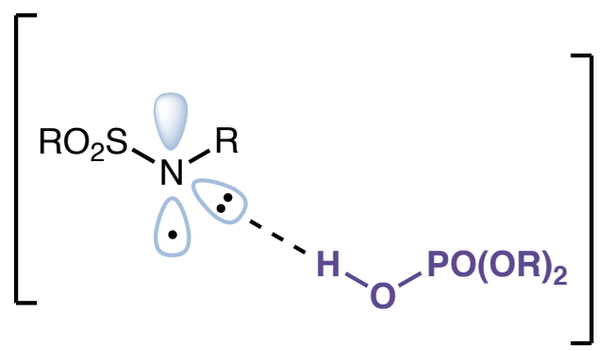
30 mol% TRIP thiol, $PhCF_3$

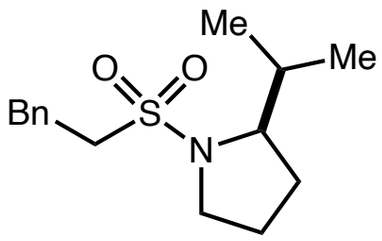
blue LEDs, –20 °C



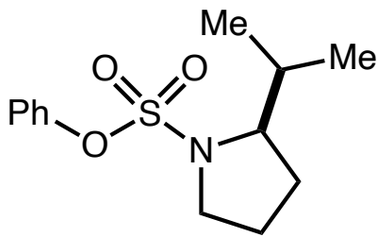
enantioenriched product
up to 98:2 er

PCET

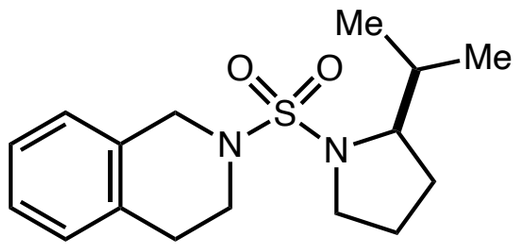




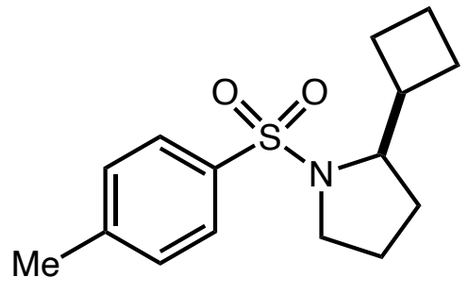
98% yield
92% ee



87% yield
84% ee



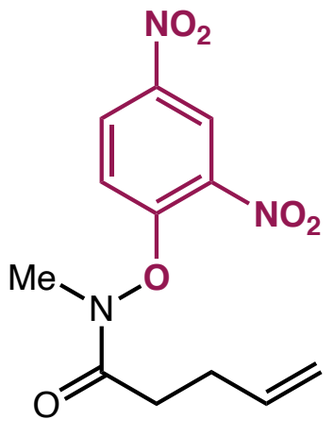
80% yield
88% ee

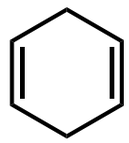


96% yield
90% ee

Roos, C. B.; Demaerel, J.; Graff, D. E.; Knowles, R. R. *J. Am. Chem. Soc.* **2020**, *142*, 5974.

Amidyl Radical Cyclization: Reductive N–O Cleavage

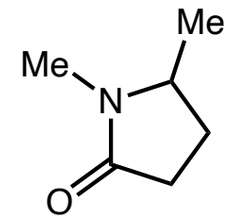




1,4-cyclohexadiene
(CHD)

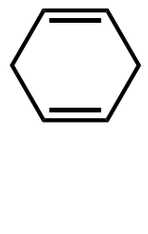
2 mol% **eosin Y**
2 equiv K_2CO_3

acetone, r.t., **green LEDs**

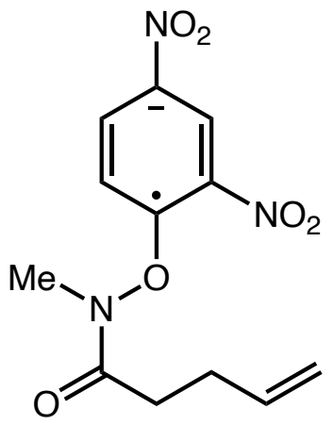


78% yield

SET reduction



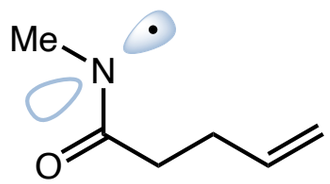
HAT



radical anion

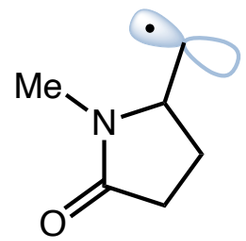
N–O cleavage

–ArO^-



amidyl radical

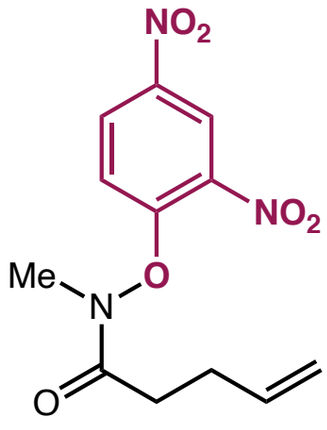
5-exo cyclization

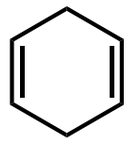


alkyl radical

Davies, J.; Svejstrup, T. D.; Reina, D. F.; Sheikh, N. S.; Leonori, D. *J. Am. Chem Soc.* **2016**, *138*, 8092.

Amidyl Radical Cyclization: Reductive N–O Cleavage

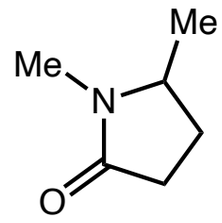




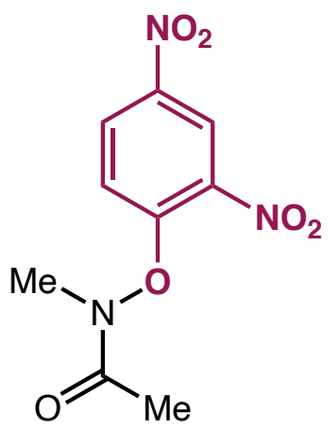
1,4-cyclohexadiene
(CHD)

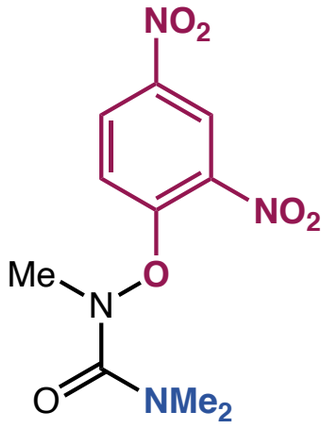
2 mol% **eosin Y**
2 equiv K_2CO_3

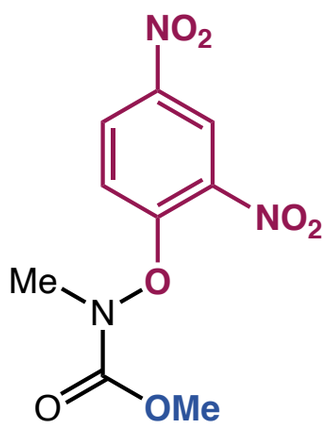
acetone, r.t., **green LEDs**



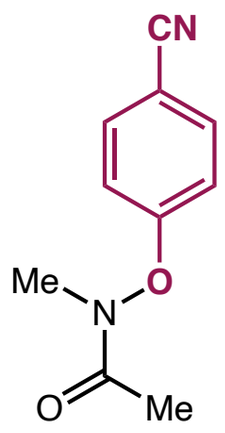
78% yield

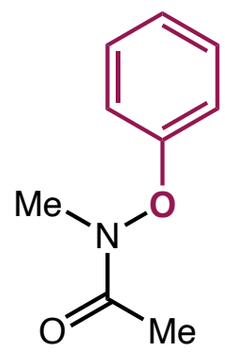






***eosin Y**

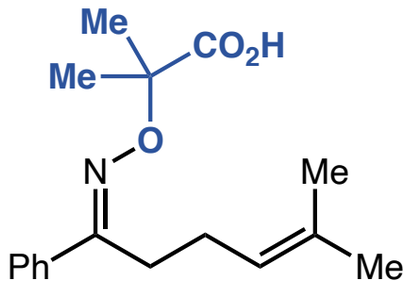




reductive potential (v.s. SCE)	–0.26 V	–0.37 V	–0.57 V	**–1.11 V**	–1.43 V	–2.10 V

Davies, J.; Svejstrup, T. D.; Reina, D. F.; Sheikh, N. S.; Leonory, D. *J. Am. Chem Soc.* **2016**, *138*, 8092.

Iminyl Radical Cyclization: Oxidative N–O Cleavage

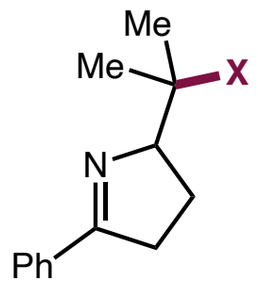


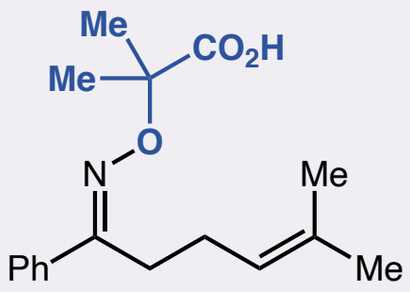
X–Y

SOMOphile

5 mol% Mes-Acr(ClO_4), base

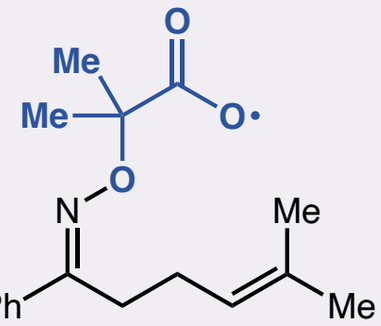
solvent, rt, blue LEDs





base

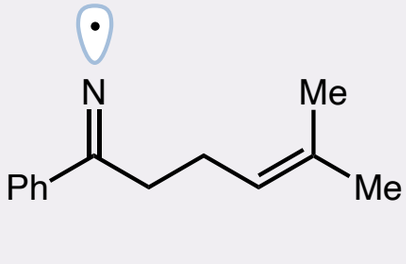
SET oxidation



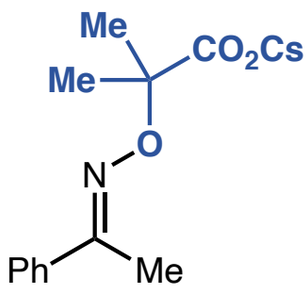
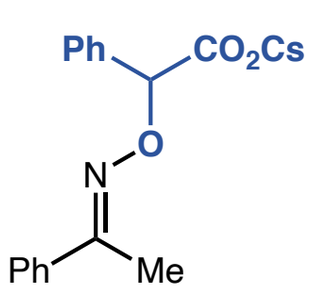
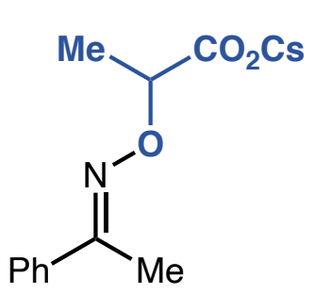
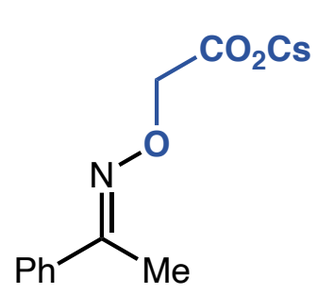
$-CO_2$, –acetone

decarboxylation

β-scission

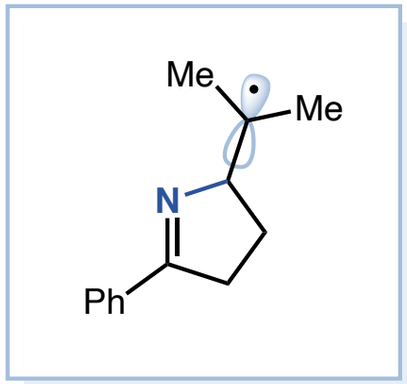


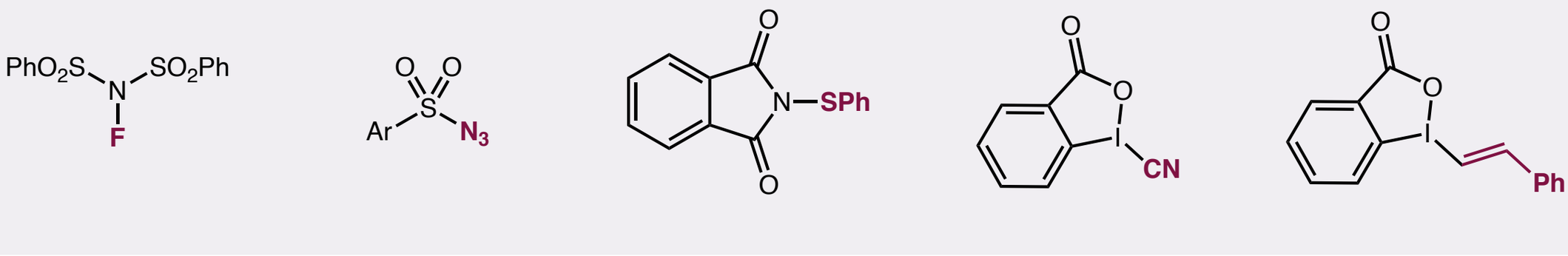
iminyl radical

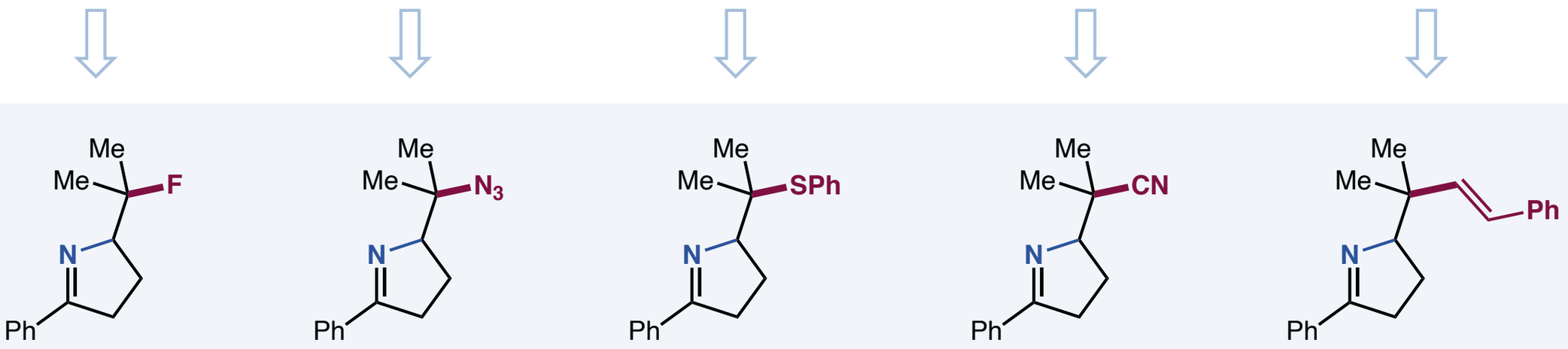
				***Mes-Acr⁺**	
oxidative potential (v.s. SCE)	+1.65 V	+1.75 V	+1.80 V	**+2.06 V**	+2.10 V

Davies, J.; Sheikh, N. S.; Leonori, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 13361.

Iminyl Radical Cyclization: Oxidative N–O Cleavage







80% yield *80% yield* *56% yield* *63% yield* *83% yield*

Davies, J.; Sheikh, N. S.; Leonori, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 13361.

Jiang, H.; Studer, A. *Angew. Chem. Int. Ed.* **2017**, *56*, 12273.

Outline

• Aminating reagents, forming sp^3 and sp^2 C–N bonds

• HAT reagents for sp^3 C–H functionalization, due to large BDEs of N–H bonds (up to 110 kcal/mol)

• Fragmentation (β-scission) is possible, but not universal

A. Formation of sp^3 C–N bonds: intramolecular cyclization

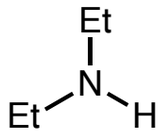
B. Formation of sp^3 C–N bonds: addition to olefins

C. Formation fo sp^2 C–N bonds: addition to aromatic compounds

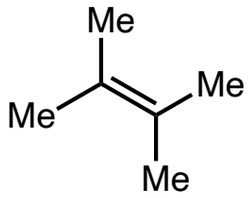
D. *N*-centered radicals-mediated HAT of sp^3 C–H bonds

E. Fragmentation of *N*-centered radicals

Intermolecular Hydroamination Using Secondary Alkyl Amines

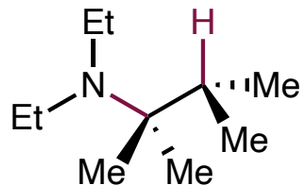


secondary alkyl amine

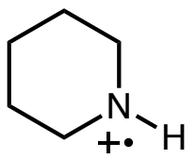


tetrasubstituted olefin

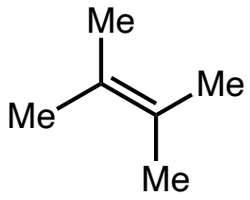
ΔG° = +4.9 kcal/mol



hydroaminated product

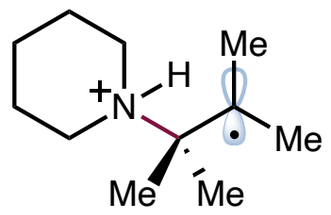


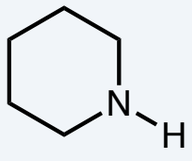
aminium radical cation

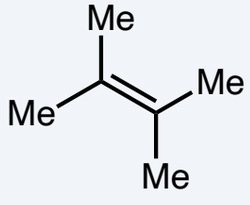


$k > 10^8\ M^{-1}s^{-1}$

kinetically facile



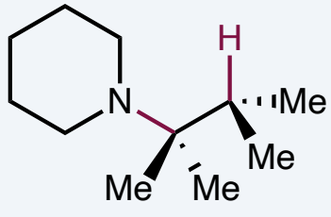




2 mol% $Ir[dF(Me)ppy]_2(dtbbpy)PF_6$

50 mol% TRIP thiol

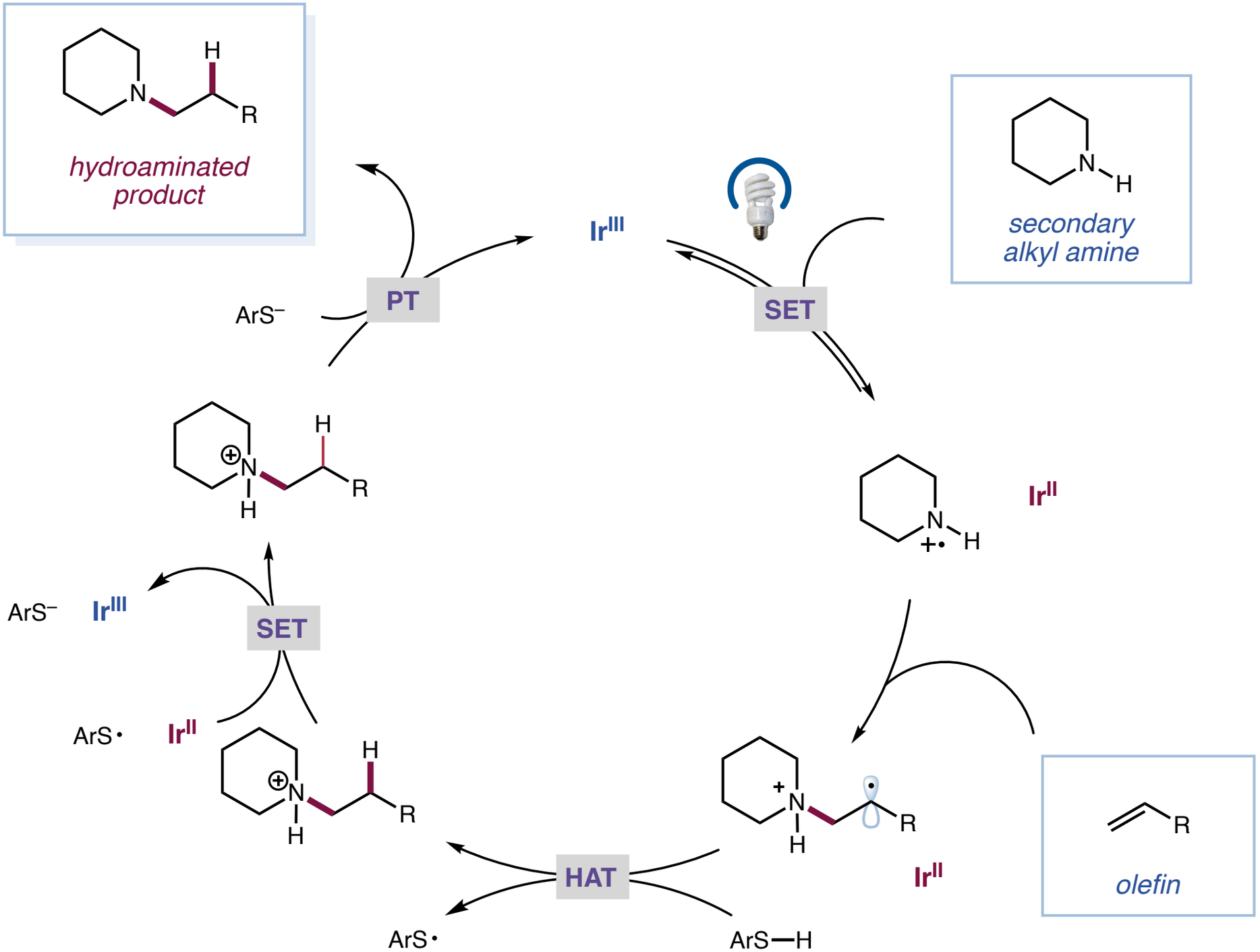
toluene, blue LEDs



91% yield

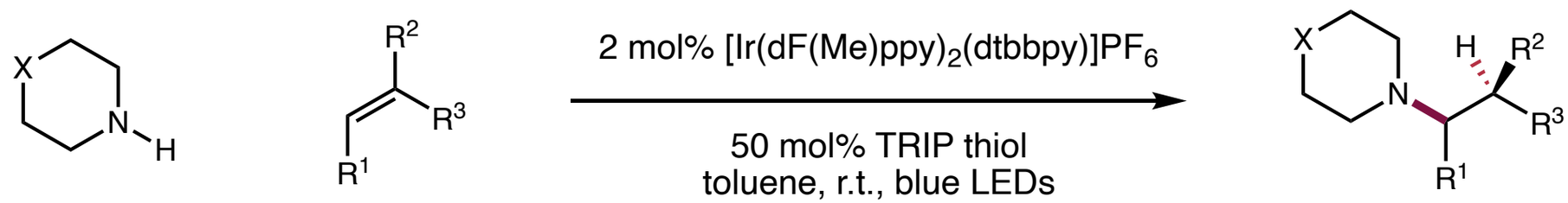
Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. *Science* **2017**, *355*, 727.

Intermolecular Hydroamination Using Secondary Alkyl Amines



Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. *Science* **2017**, *355*, 727.

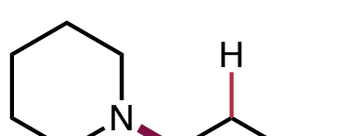
Intermolecular Hydroamination Using Secondary Alkyl Amines



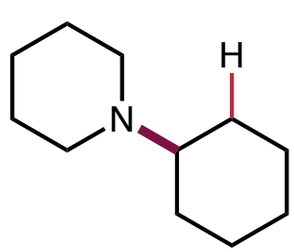
secondary alkyl amine

olefin

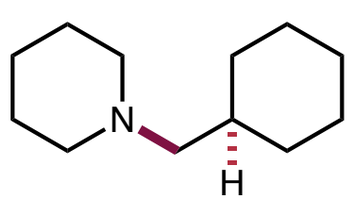
hydroaminated product



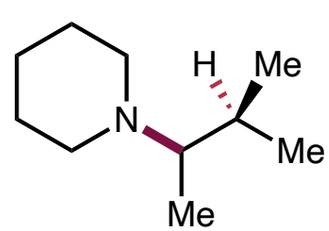
60% yield



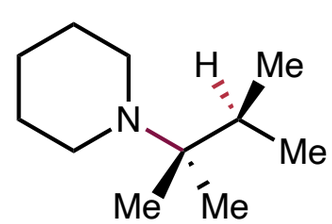
69% yield



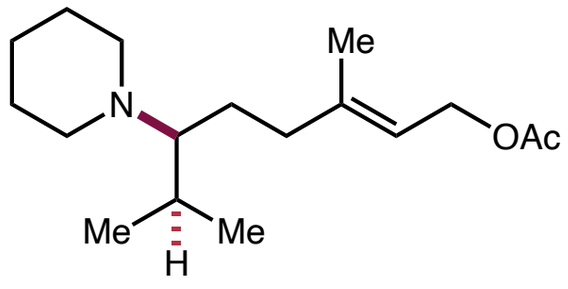
98% yield



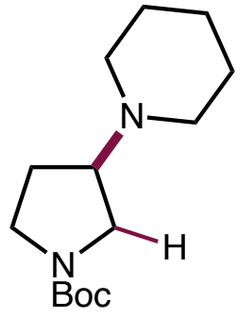
94% yield



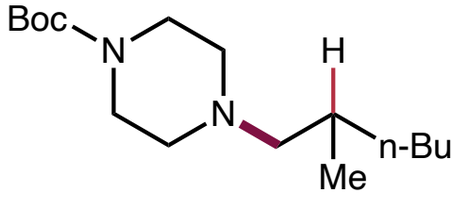
91% yield



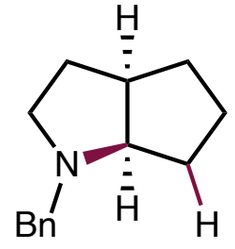
66% yield



81% yield



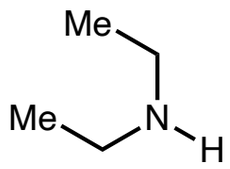
98% yield



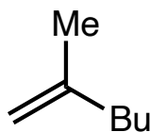
88% yield

Musacchio, A. J.; Lainhart, B. C.; Zhang, X.; Naguib, S. G.; Sherwood, T. C.; Knowles, R. R. *Science* **2017**, *355*, 727.

Intermolecular Hydroamination Using Primary Alkyl Amines



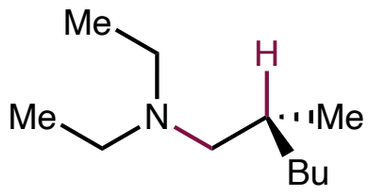
secondary alkyl amine



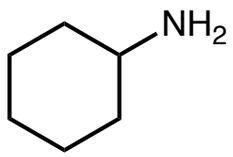
2 mol% $Ir[dF(Me)ppy]_2(dtbbpy)PF_6$

50 mol% TRIP thiol

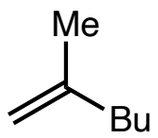
toluene, blue LEDs



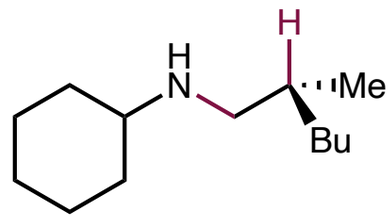
65% yield tertiary amine



primary alkyl amine

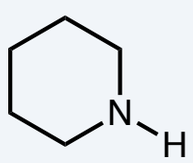


???

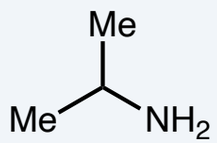


secondary amine

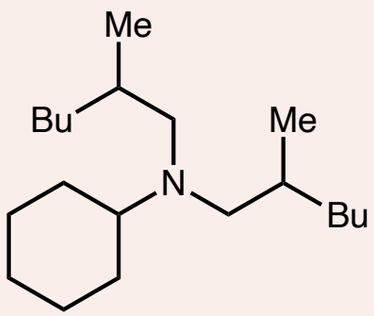
oxidation potential v.s. SCE



0.94 V



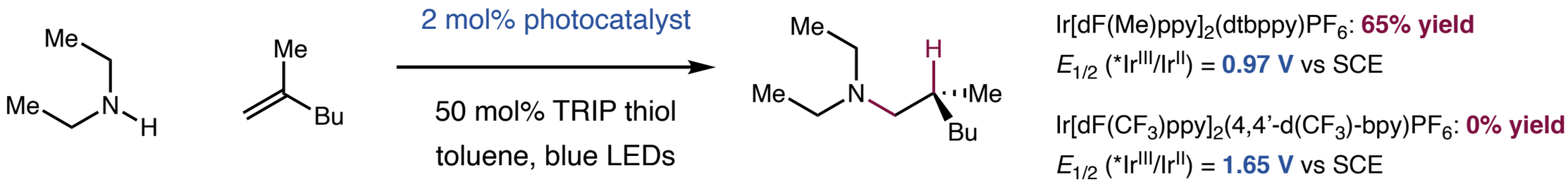
1.54 V

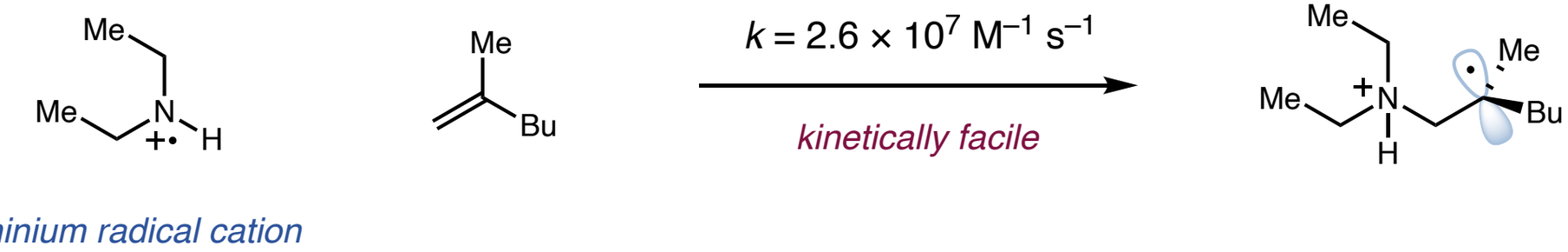


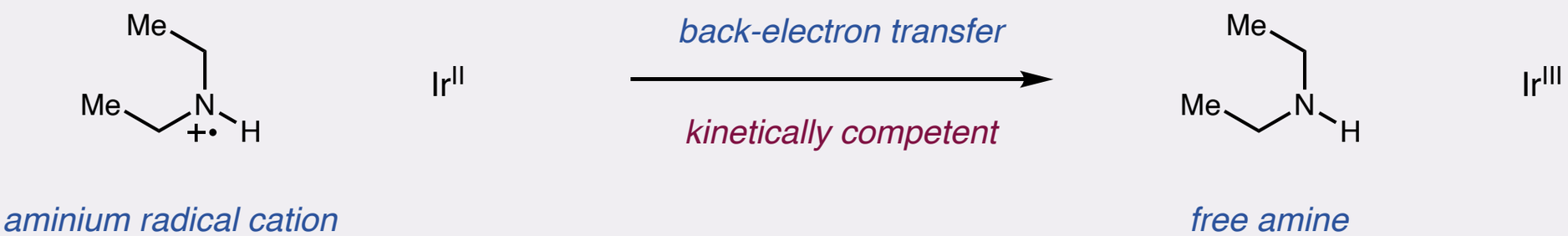
overalkylation

Miller, D. C.; Ganley, J. M.; Musacchio, A. J.; Sherwood, T. C.; Ewing, W. R.; Knowles, R. R. *J. Am. Chem. Soc.* **2019**, *141*, 16590.

Intermolecular Hydroamination Using Primary Alkyl Amines

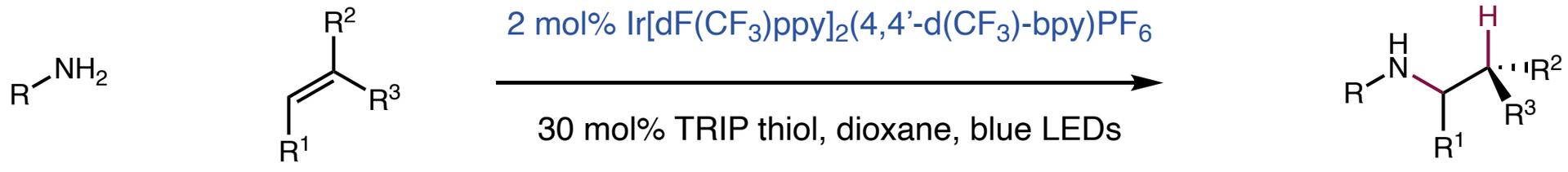






Miller, D. C.; Ganley, J. M.; Musacchio, A. J.; Sherwood, T. C.; Ewing, W. R.; Knowles, R. R. *J. Am. Chem. Soc.* **2019**, *141*, 16590.

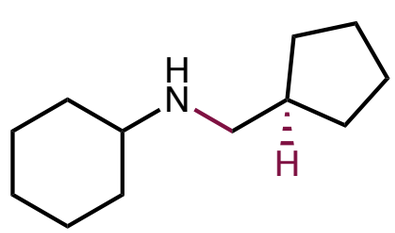
Intermolecular Hydroamination Using Primary Alkyl Amines



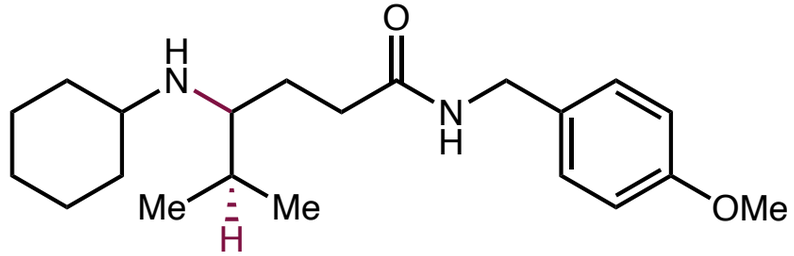
primary alkyl amine

olefin

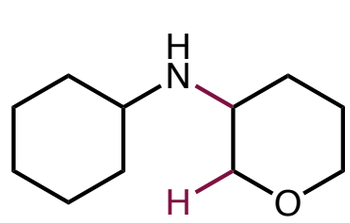
secondary alkyl amine
>20:1 mono-:overalkylation



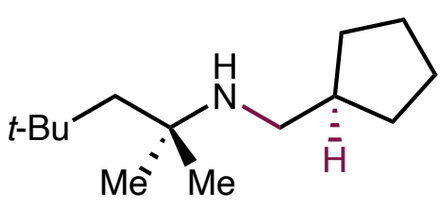
77% yield



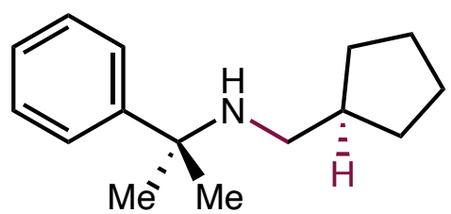
62% yield



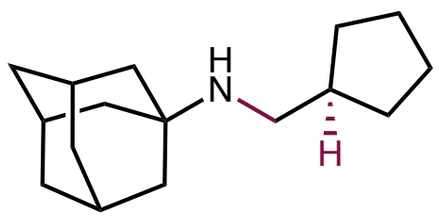
54% yield



59% yield



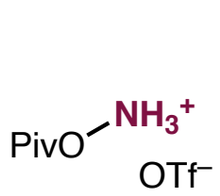
69% yield



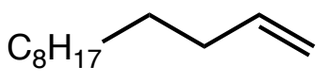
73% yield

Miller, D. C.; Ganley, J. M.; Musacchio, A. J.; Sherwood, T. C.; Ewing, W. R.; Knowles, R. R. *J. Am. Chem. Soc.* **2019**, *141*, 16590.

Incorporating Unprotected NH_2: Aminochlorination of Olefins



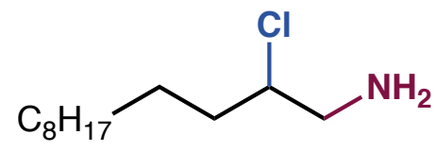
aminating reagent
2 steps from HO–NHBoc



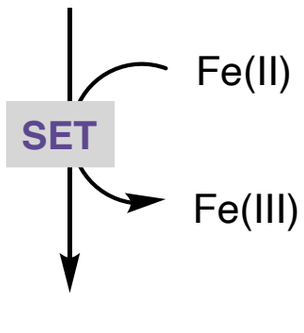
olefin

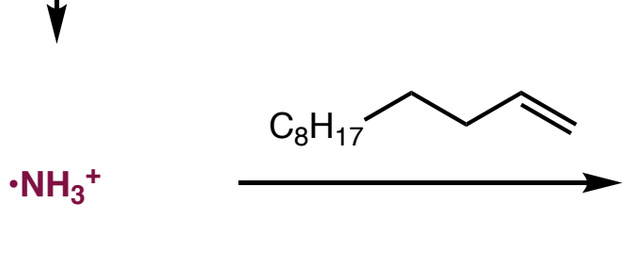
5 mol% $Fe(acac)_2$
1.05 equiv NaCl

MeOH/DCM, r.t.

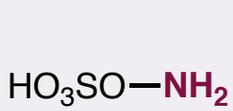


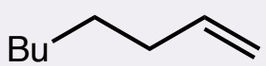
72% yield





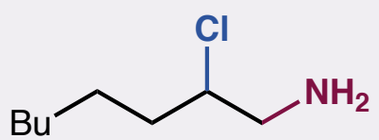
chlorine transfer
–Fe(II)





$FeCl_2$

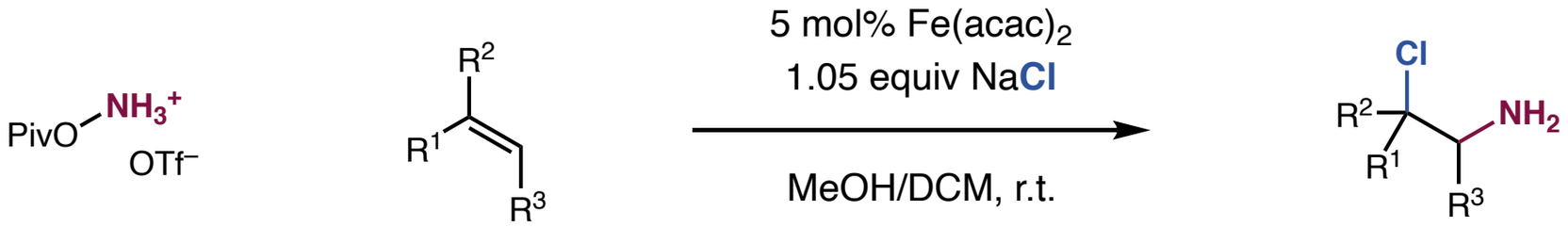
25–45% yield



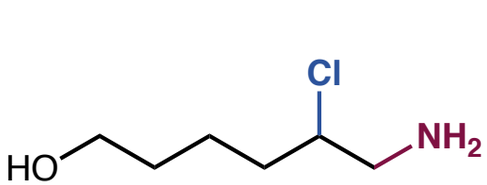
Legnani, L.; Prina-Cerai, G.; Delcaillau, T.; Willems, S.; Morandi, B. *Science* **2018**, *362*, 434.

Minisci, F.; Galli, R. *Tetrahedron Lett.* **1965**, *22*, 1679

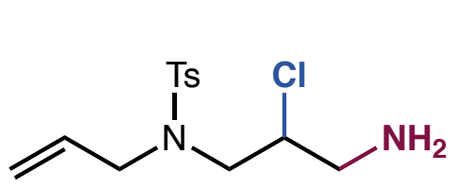
Incorporating Unprotected NH_2: Aminochlorination of Olefins



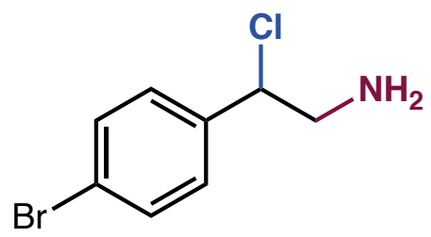
aminating reagent | *olefin* | *aminochlorination product*



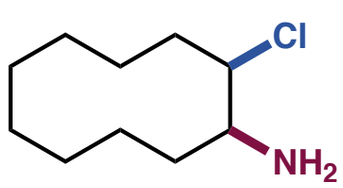
68% yield



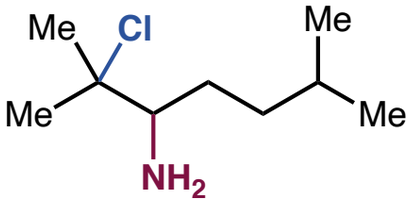
61% yield



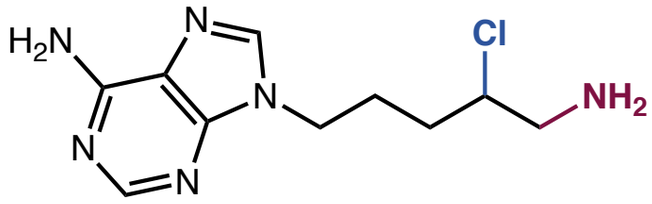
81% yield



73% yield, 14:1 dr from cis-olefin



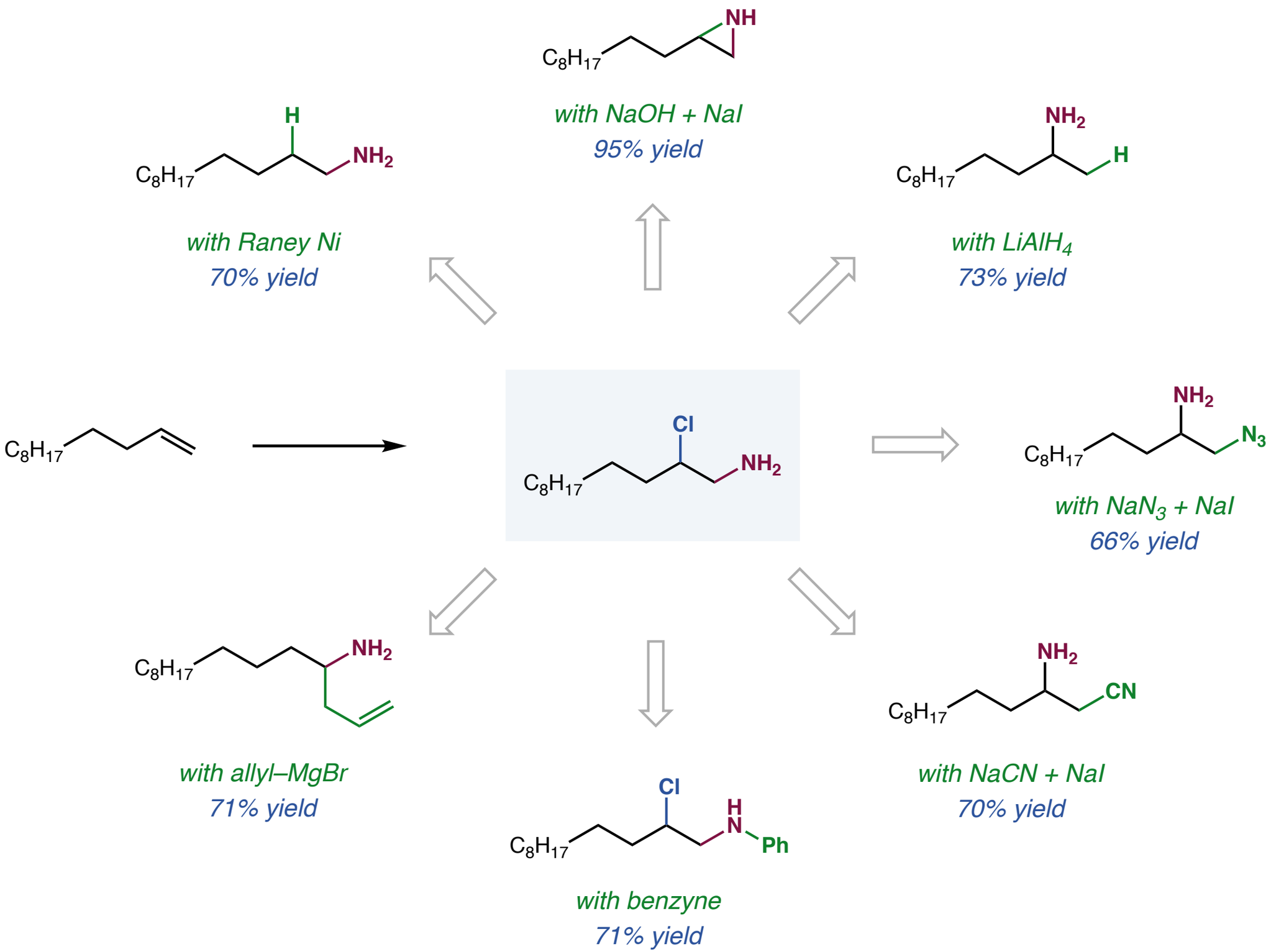
65% yield



58% yield

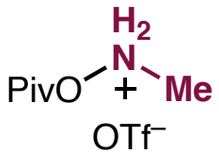
Legnani, L.; Prina-Cerai, G.; Delcaillau, T.; Willems, S.; Morandi, B. *Science* **2018**, *362*, 434.

Incorporating Unprotected NH_2: Aminochlorination of Olefins

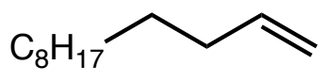


Legnani, L.; Prina-Cerai, G.; Delcaillau, T.; Willems, S.; Morandi, B. *Science* **2018**, *362*, 434.

Incorporating Alkyl Amines in Aminochlorination of Olefins



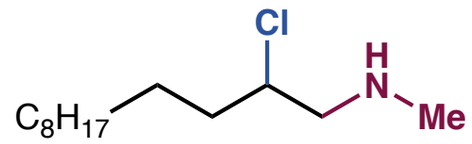
aminating reagent



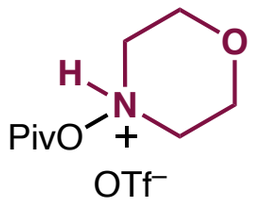
olefin

5 mol% $Fe(acac)_2$
7.5 mol% $Sc(OTf)_3$
1.05 equiv NaCl

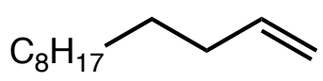
HFIP/DCM, r.t.



62% yield



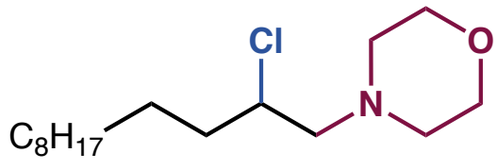
aminating reagent



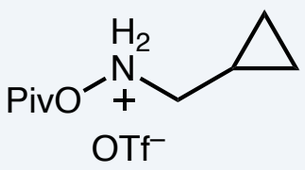
olefin

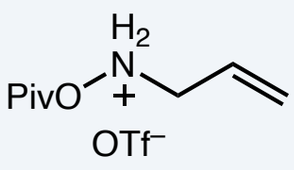
5 mol% $Fe(acac)_2$
10 mol% $AlCl_3$
1.05 equiv LiCl

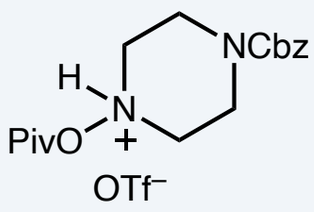
nBuOH/DCM, r.t.



57% yield



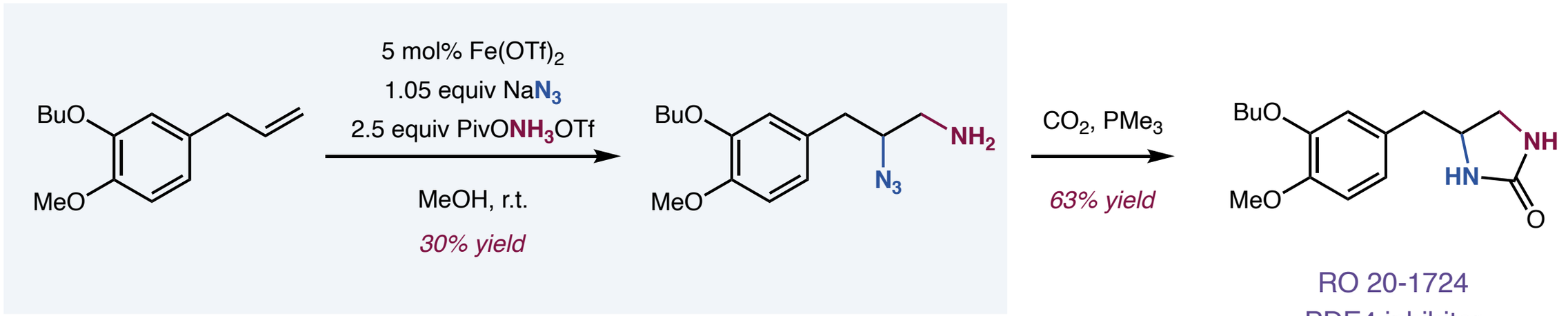




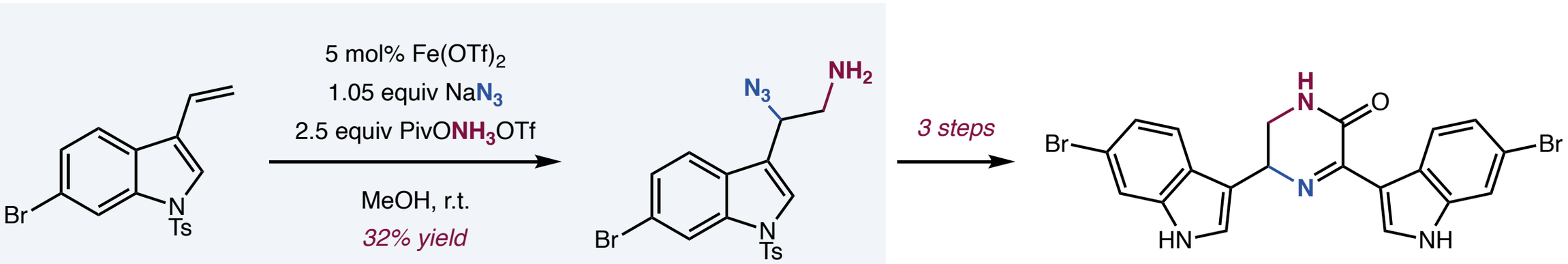
- *10 New aminating reagents developed*
- *Usually 3 steps from commercial materials*
- *Up to 30 grams synthesized*

Falk, E.; Makai, S.; Delcaillau, T.; Gurtler, L.; Morandi, B. *Angew. Chem. Int. Ed.* **2020**, *59*, 21064.

Incorporating Unprotected NH_2: Aminoazidation of Olefins



RO 20-1724
PDE4 inhibitor
previously **7 steps**



previously **7 steps**

hamacanthin B
antibacterial

Makai, S.; Falk, E.; Morandi, B. *J. Am. Chem. Soc.* **2020**, *142*, 21548.

Outline

• Aminating reagents, forming sp^3 and sp^2 C–N bonds

• HAT reagents for sp^3 C–H functionalization, due to large BDEs of N–H bonds (up to 110 kcal/mol)

• Fragmentation (β-scission) is possible, but not universal

A. Formation of sp^3 C–N bonds: intramolecular cyclization

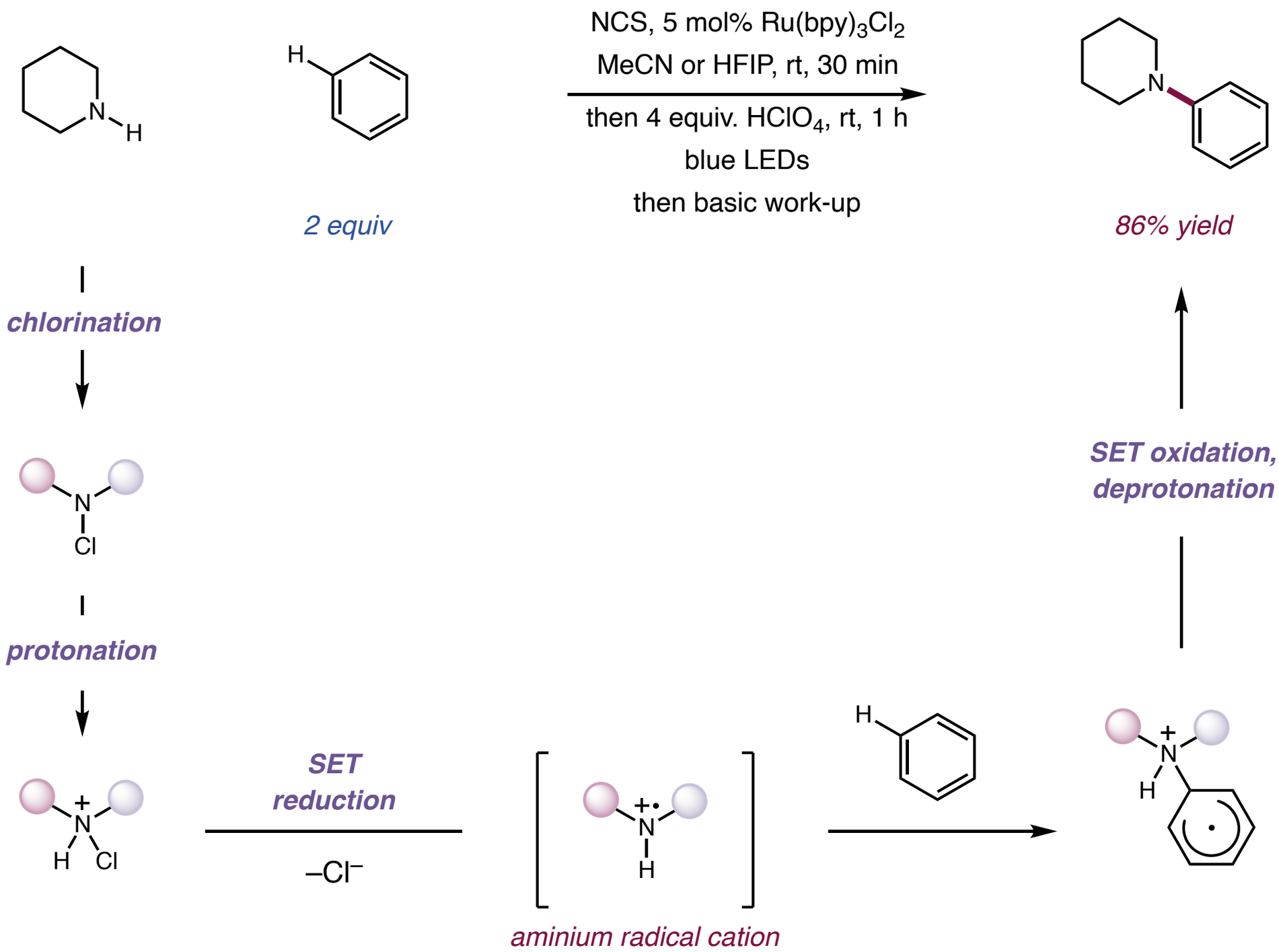
B. Formation of sp^3 C–N bonds: addition to olefins

C. Formation fo sp^2 C–N bonds: addition to aromatic compounds

D. *N*-centered radicals-mediated HAT of sp^3 C–H bonds

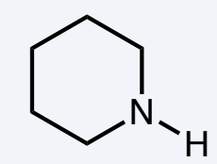
E. Fragmentation of *N*-centered radicals

Formation of C(sp^2)–N Bonds: Addition to Aromatics

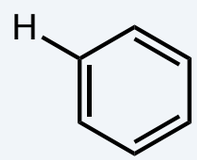


Ruffoni, A.; Juliá, F.; Svejstrup, T. D.; McMillan, A. J.; Douglas, J. J.; Leonori, D. *Nat. Chem.* **2019**, *11*, 426.

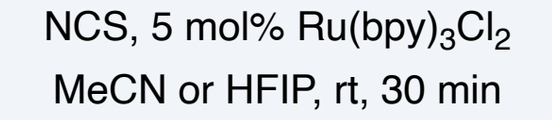
Formation of C(sp^2)–N Bonds: Addition to Aromatics

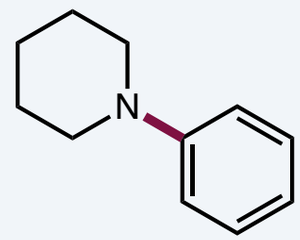


secondary amine

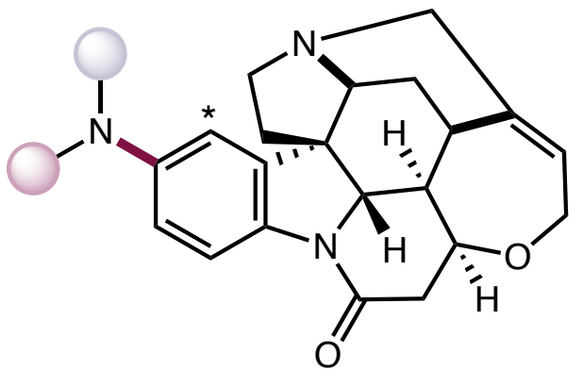


(hetero)arene

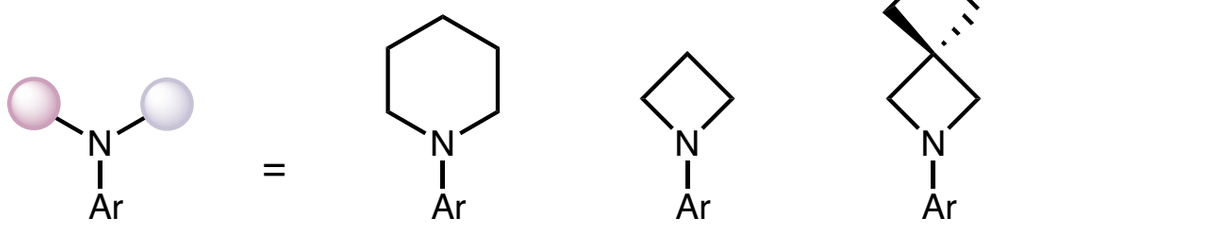


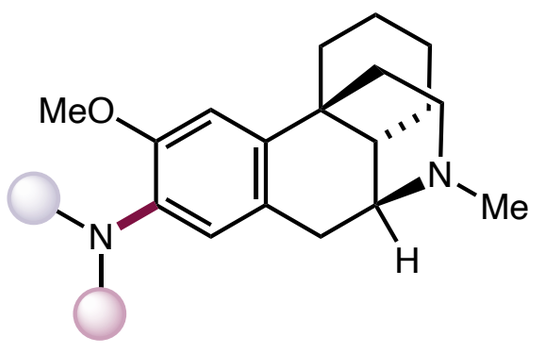


C–N coupled product

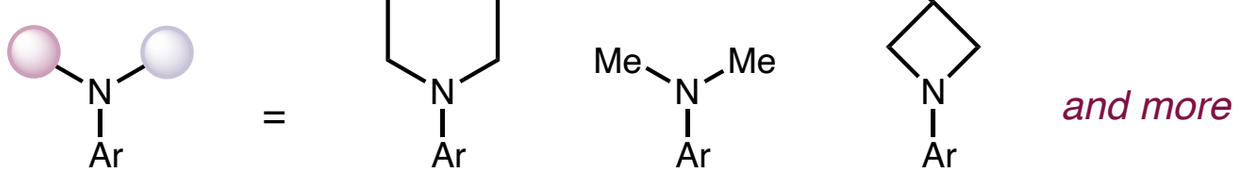


From strychnine





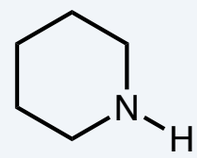
From Dextromethorphan (Robitussin)



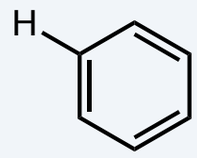
and more

Ruffoni, A.; Juliá, F.; Svejstrup, T. D.; McMillan, A. J.; Douglas, J. J.; Leonori, D. *Nat. Chem.* **2019**, *11*, 426.

Formation of C(sp^2)–N Bonds: Addition to Aromatics

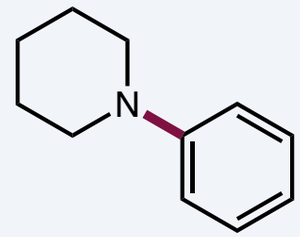


secondary amine

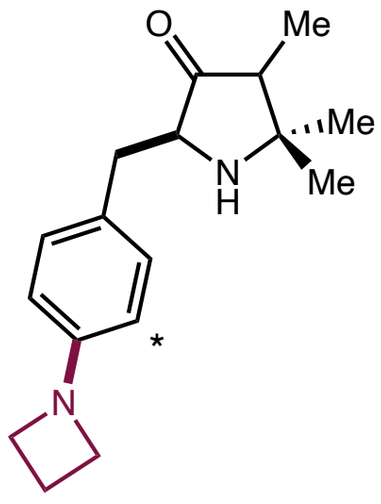


(hetero)arene

NCS, 5 mol% $Ru(bpy)_3Cl_2$
MeCN or HFIP, rt, 30 min
then 4 equiv. $HClO_4$, rt, 1 h
blue LEDs
then basic work-up

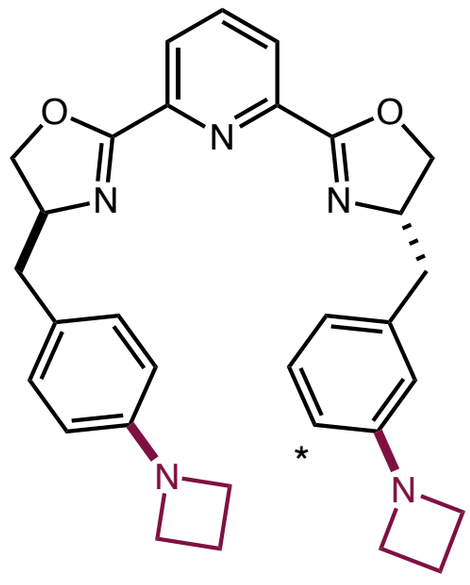


C–N coupled product



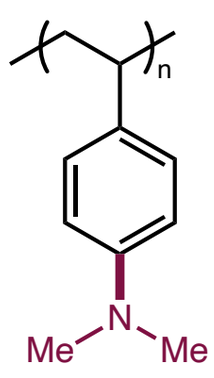
From MacMillan imidazolidinone

49% yield
2:1 r.r.



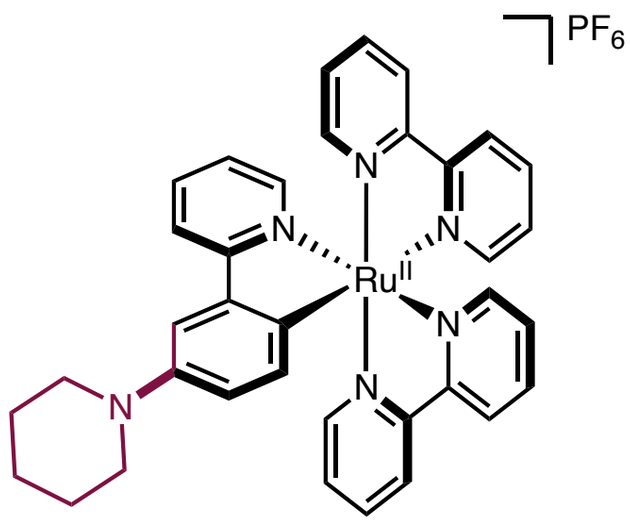
From PyBOX

90% yield
4:1 r.r.



From polystyrene

19% yield

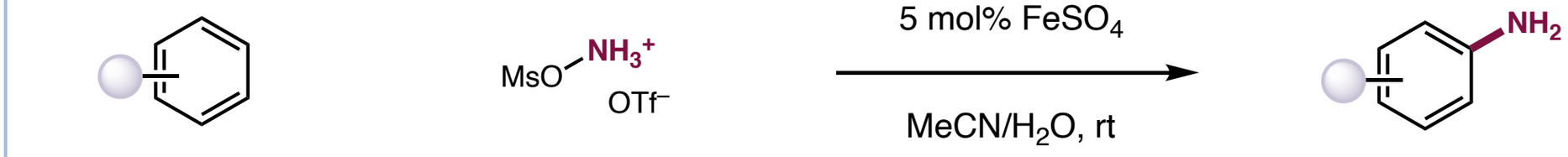


From $[Ru(ppy)(bpy)_2](PF_6)$

19% yield

Ruffoni, A.; Juliá, F.; Svejstrup, T. D.; McMillan, A. J.; Douglas, J. J.; Leonori, D. *Nat. Chem.* **2019**, *11*, 426.

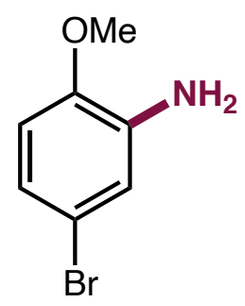
Formation of C(sp^2)–N Bonds: Addition to Aromatics



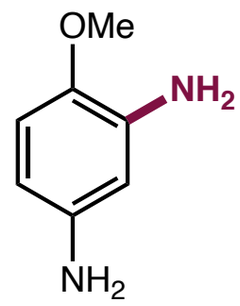
(hetero)arene
1 equiv

aminating reagent
2 steps from HO–NHBoc

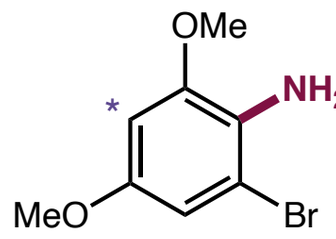
aniline



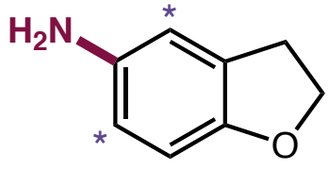
78% yield



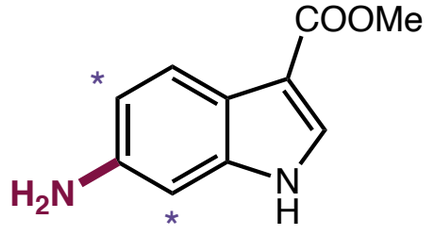
70% yield



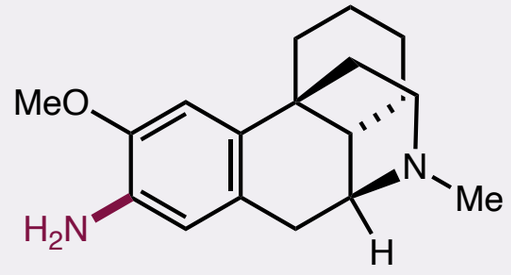
61% yield
1.8 : 1



88% yield
13.4 : 2 : 1



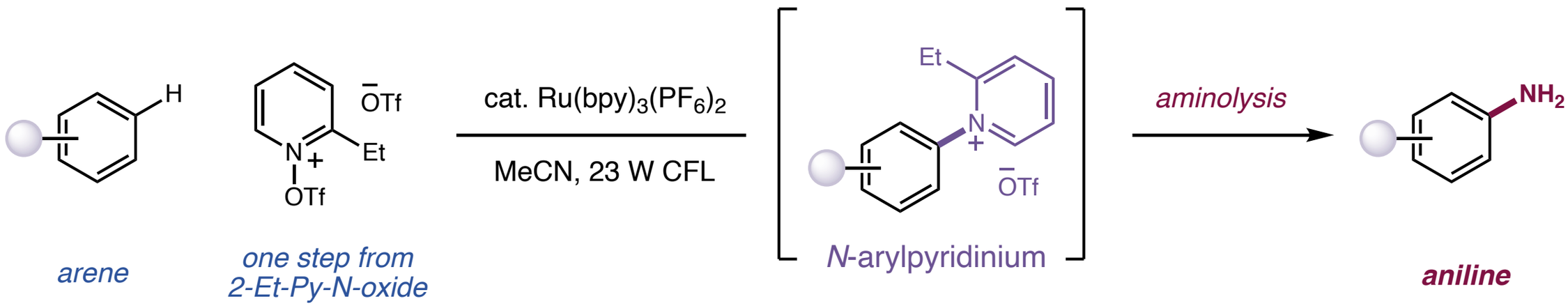
33% yield
2.3 : 1.6 : 1



From Robitussin
51% yield

Legnani, L.; Cerai, G. P.; Morandi, B. *ACS Catal.* **2016**, *6,* 8162.

Formation of C(sp^2)–N Bonds: Addition to Aromatics



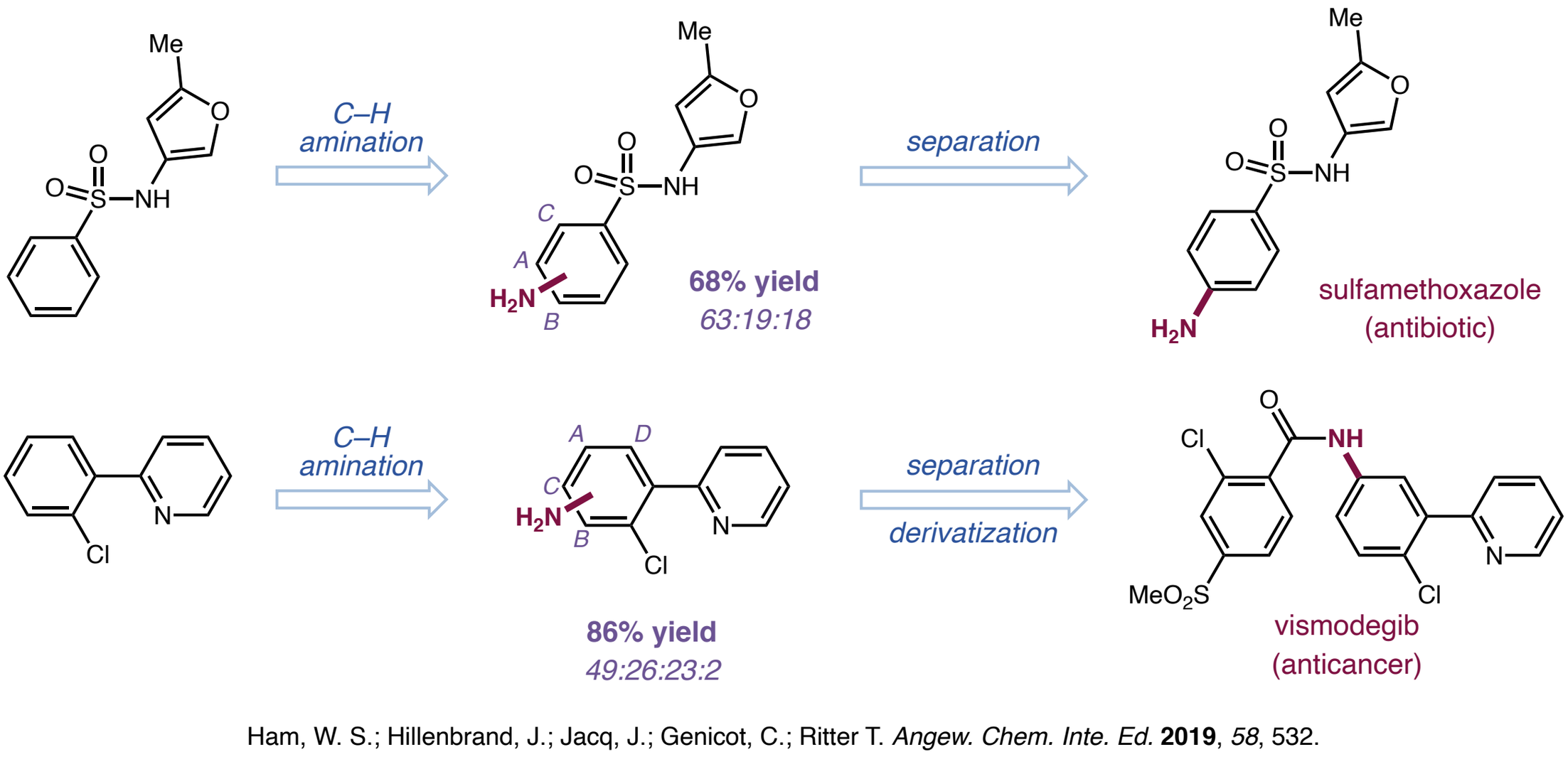
arene

one step from 2-Et-Py-N-oxide

N-arylpyridinium

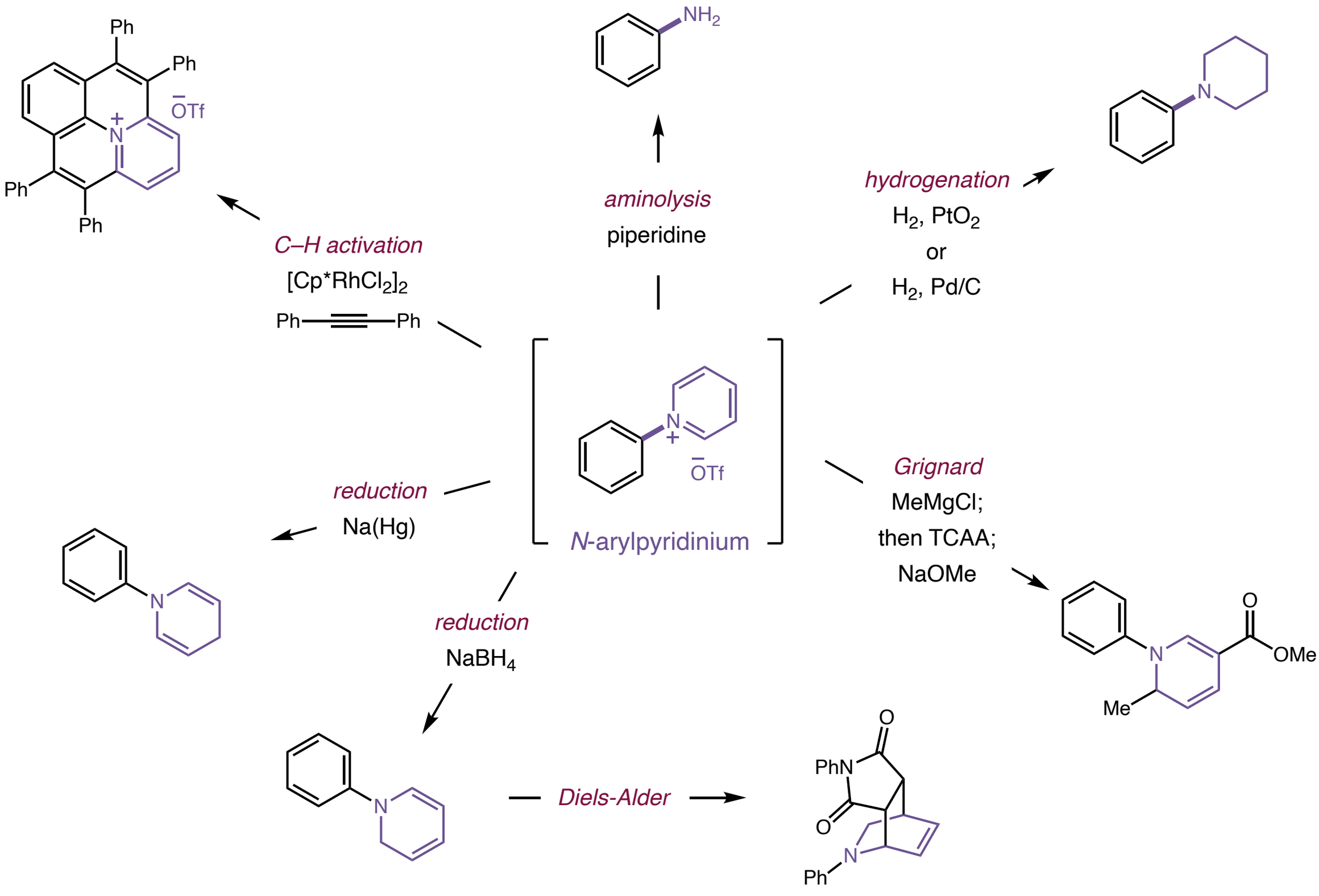
aniline

Utility of late-stage amination in drug discovery



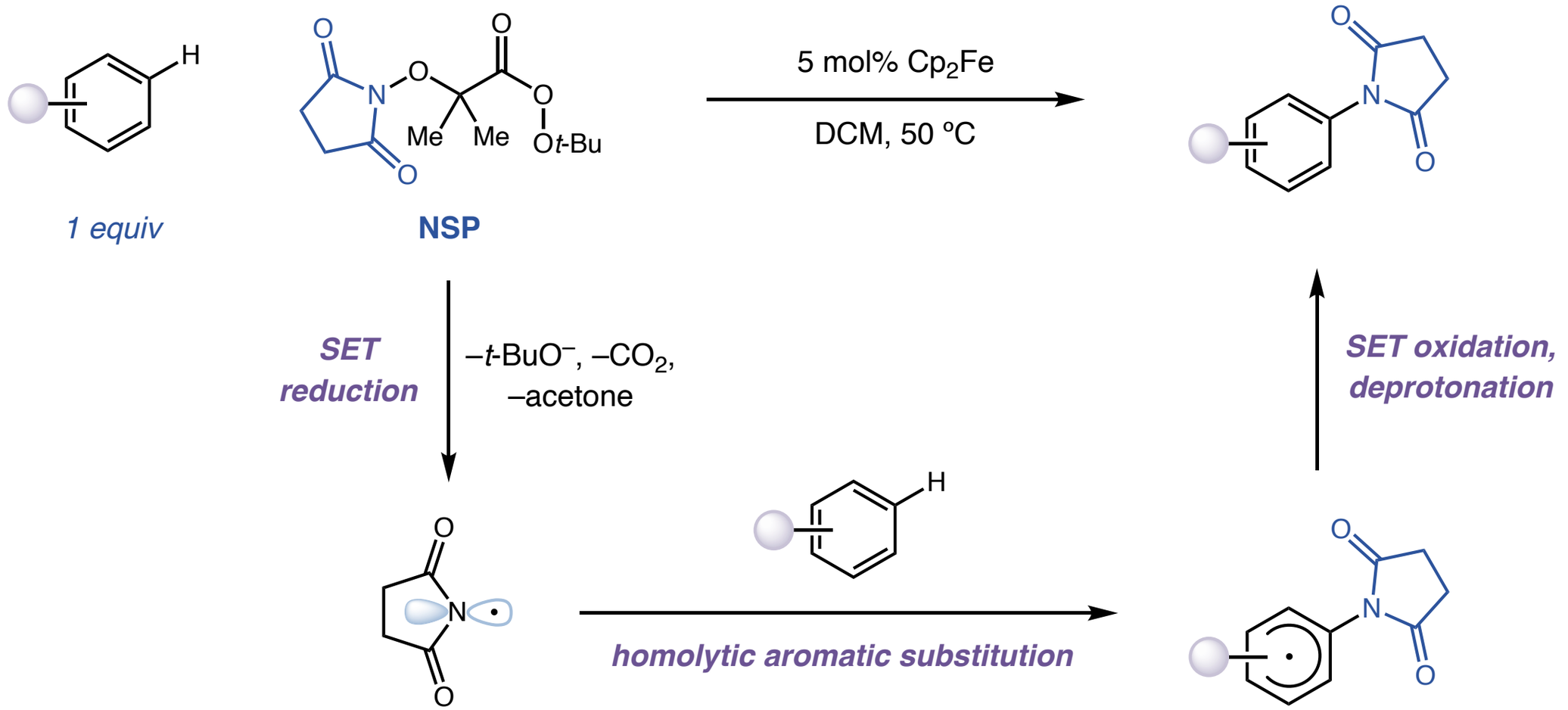
Ham, W. S.; Hillenbrand, J.; Jacq, J.; Genicot, C.; Ritter T. *Angew. Chem. Inte. Ed.* **2019**, *58*, 532.

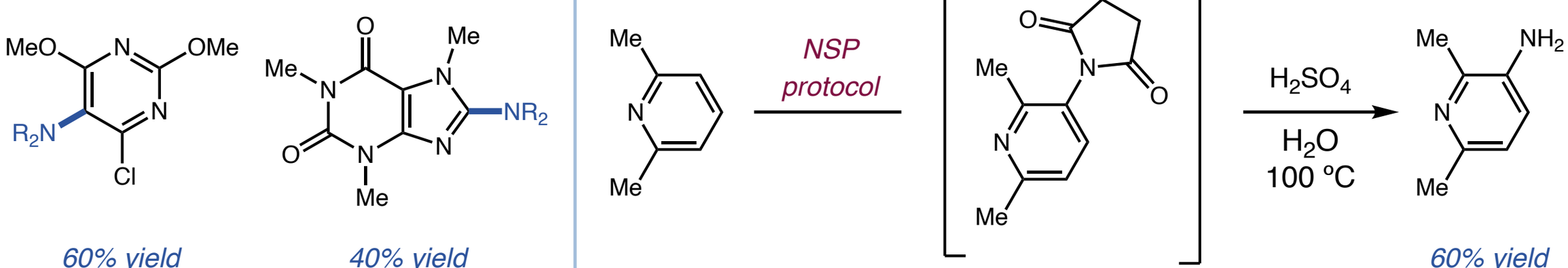
Formation of C(sp^2)–N Bonds: Addition to Aromatics



Rössler, S. L.; Jelier, B. J.; Tripet, P. F.; Shemet, A.; Jeschke, G.; Togni, A.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 526.

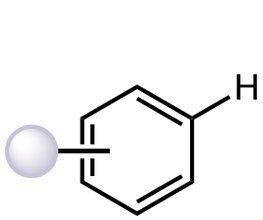
Formation of C(sp^2)–N Bonds: Addition to Aromatics



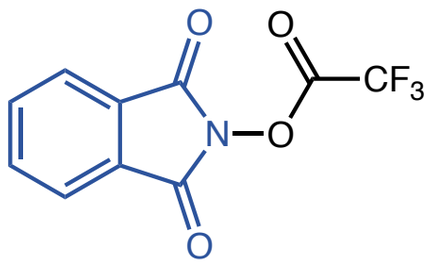


Foo, K.; Sella, E.; Thomé, I.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5279.

Formation of C(sp^2)–N Bonds: Addition to Aromatics

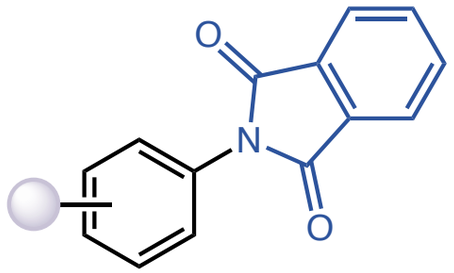


10 equiv



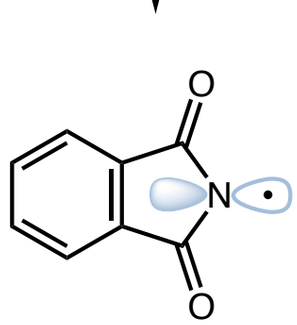
5 mol% $Ir(ppy)_3$

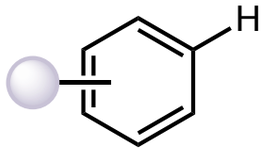
MeCN, rt
blue LEDs



SET reduction

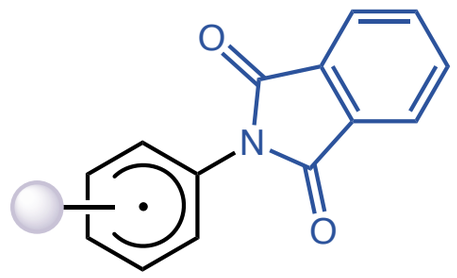
$-CF_3CO_2^-$

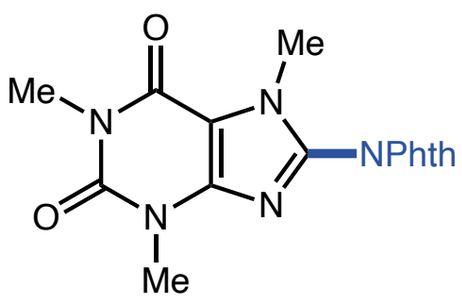




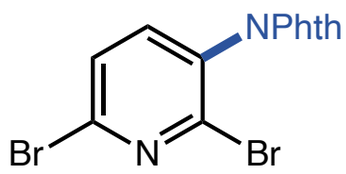
homolytic aromatic substitution

SET oxidation, deprotonation

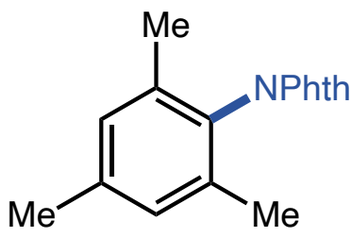




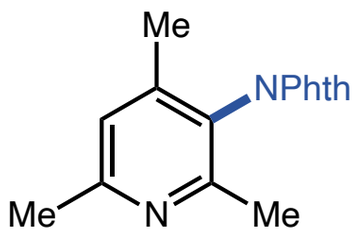
45% yield



32% yield



89% yield



66% yield

Allen, L. J.; Cabrera, P. J.; Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2014**, *136*, 5607.

Outline

• Aminating reagents, forming sp^3 and sp^2 C–N bonds

• HAT reagents for sp^3 C–H functionalization, due to large BDEs of N–H bonds (up to 110 kcal/mol)

• Fragmentation (β-scission) is possible, but not universal

A. Formation of sp^3 C–N bonds: intramolecular cyclization

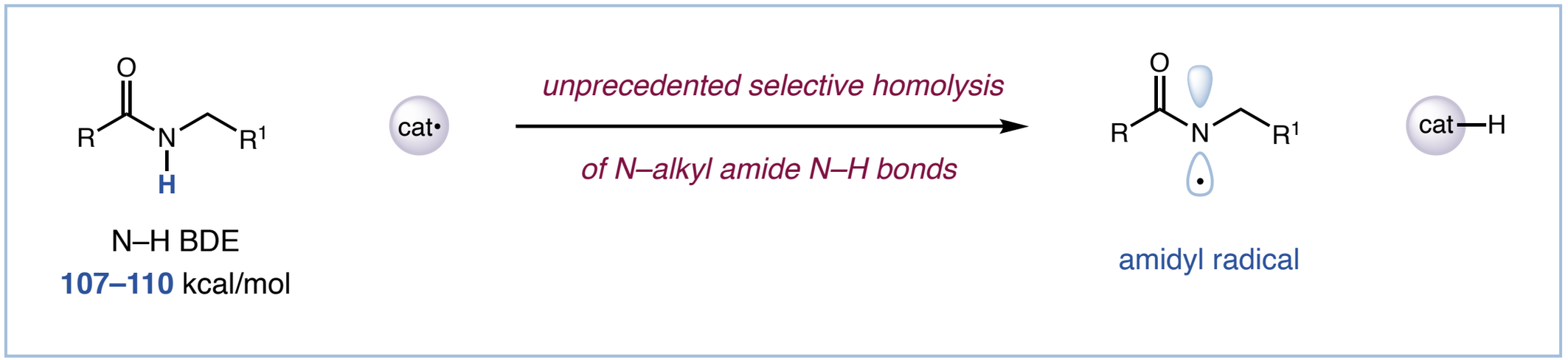
B. Formation of sp^3 C–N bonds: addition to olefins

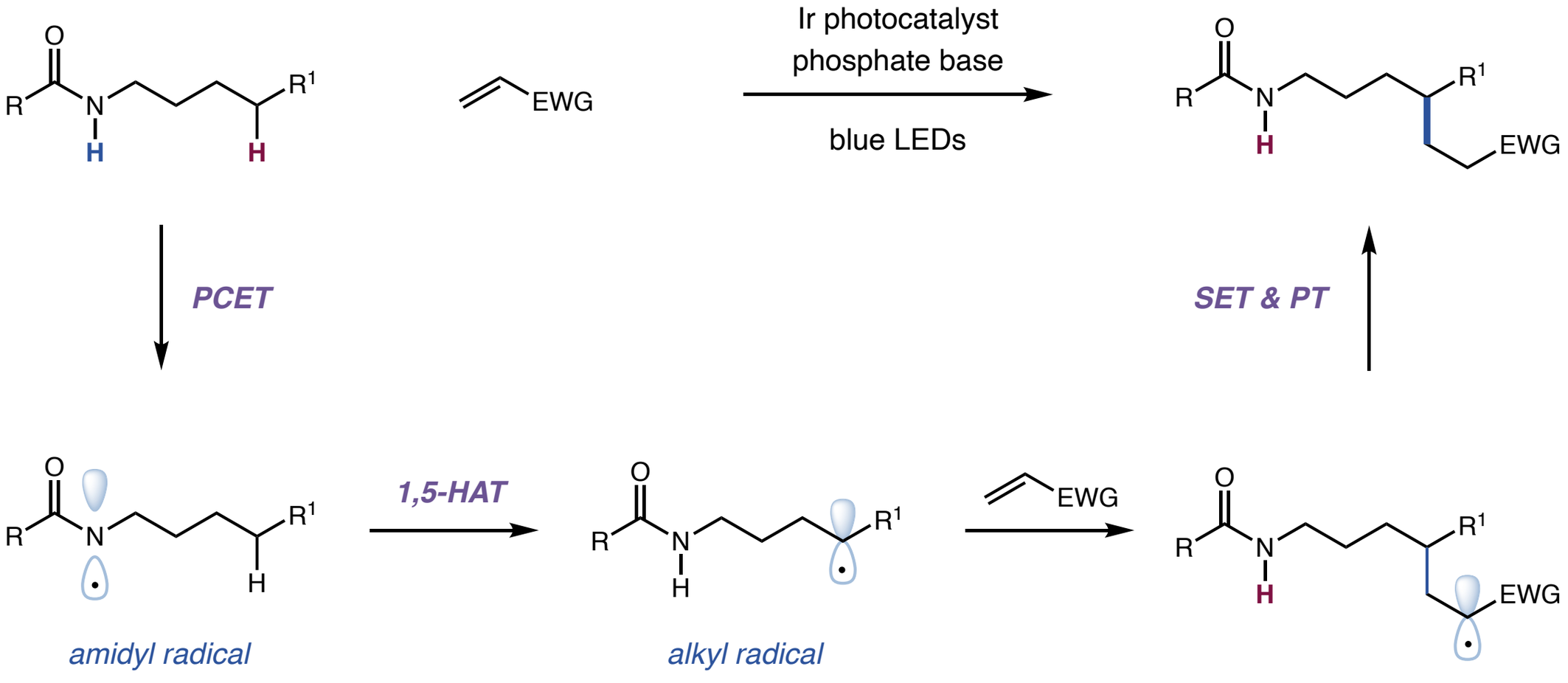
C. Formation fo sp^2 C–N bonds: addition to aromatic compounds

D. *N*-centered radicals-mediated HAT of sp^3 C–H bonds

E. Fragmentation of *N*-centered radicals

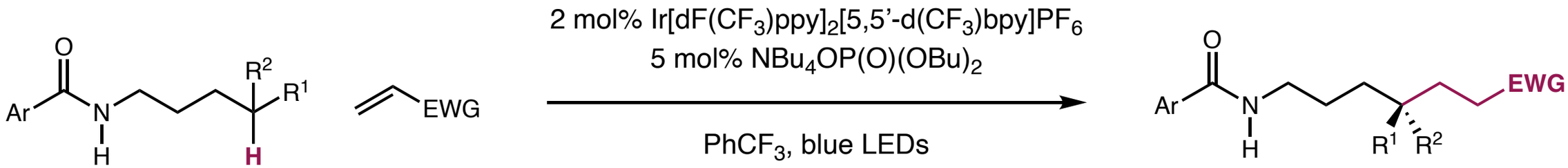
Amidyl Radical Induced 1,5-HAT for sp^3 C–H Functionalization

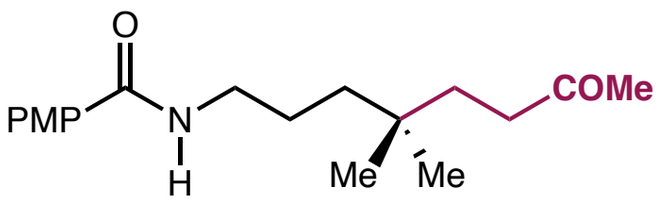




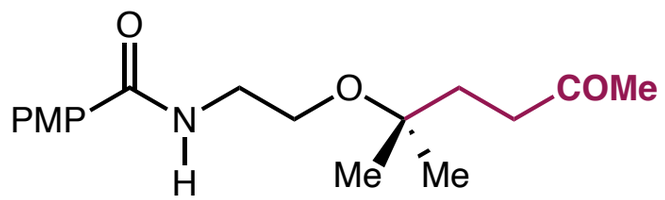
Choi, G, J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. *Nature* **2016**, *539*, 268.

Amidyl Radical Induced 1,5-HAT for sp^3 C–H Functionalization

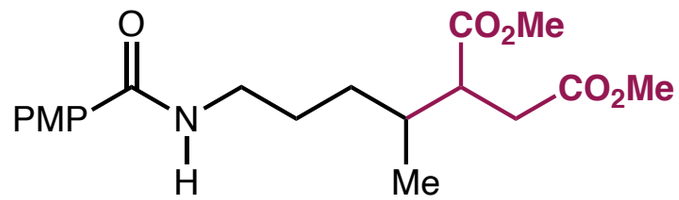




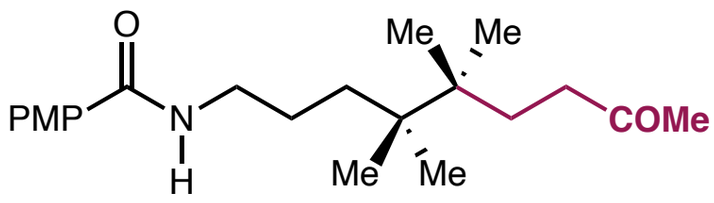
78% yield



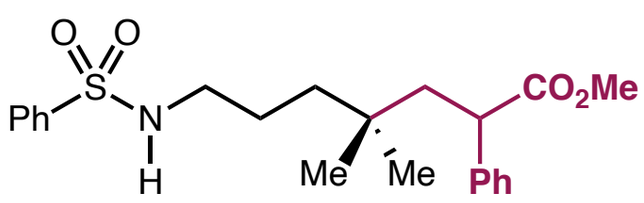
62% yield



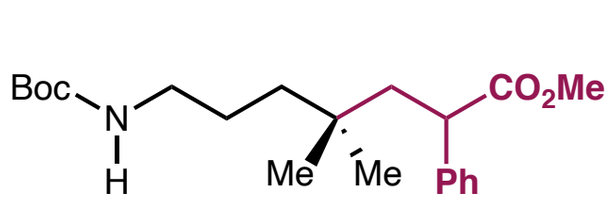
40% yield, 1:1 d.r.



57% yield



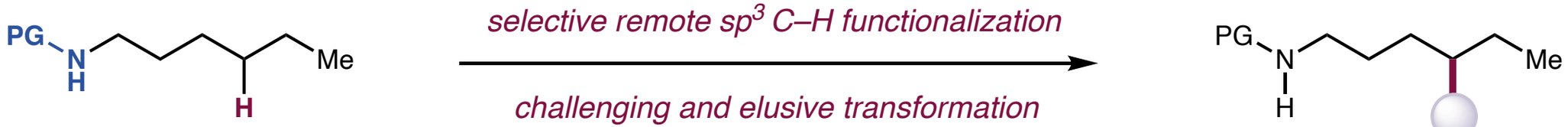
74% yield



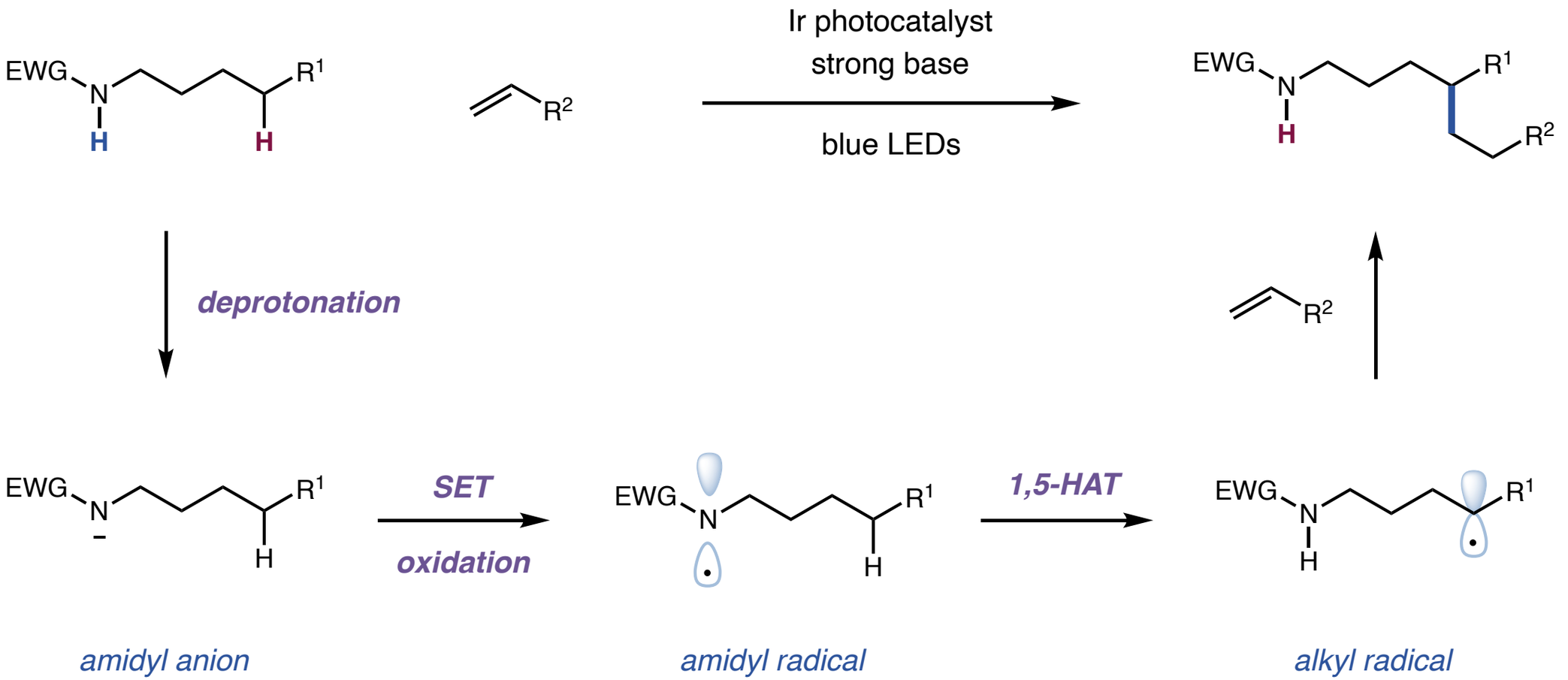
29% yield

Choi, G, J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. *Nature* **2016**, *539*, 268.

Amidyl Radical Induced 1,5-HAT for sp^3 C–H Functionalization



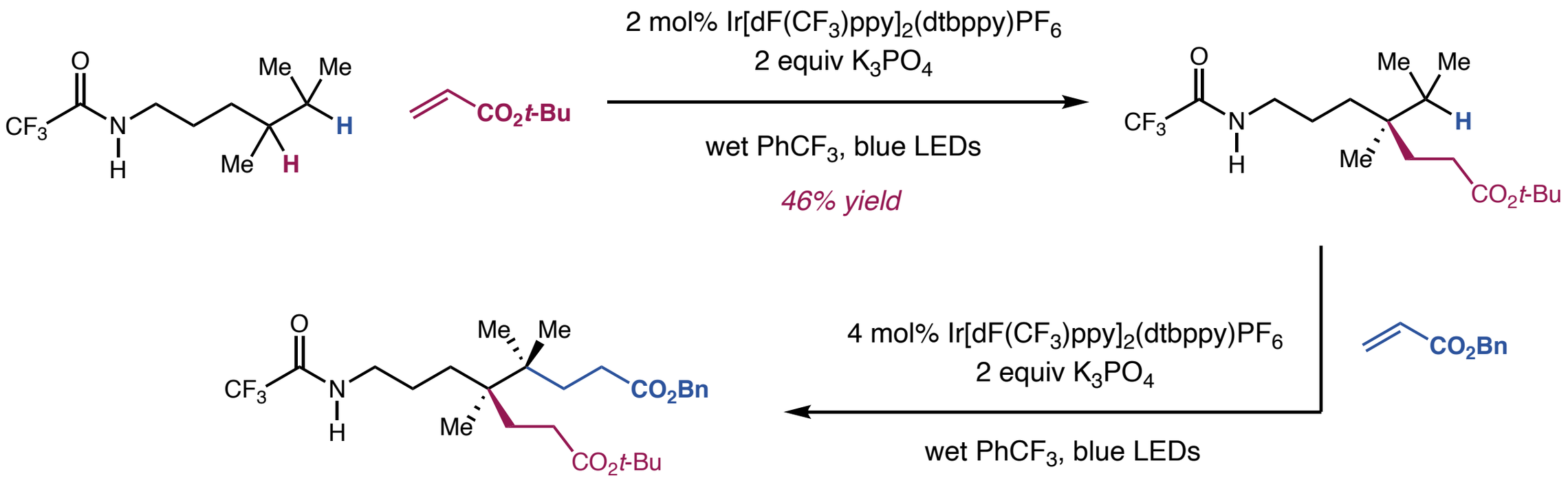
nitrogen motif as directing group

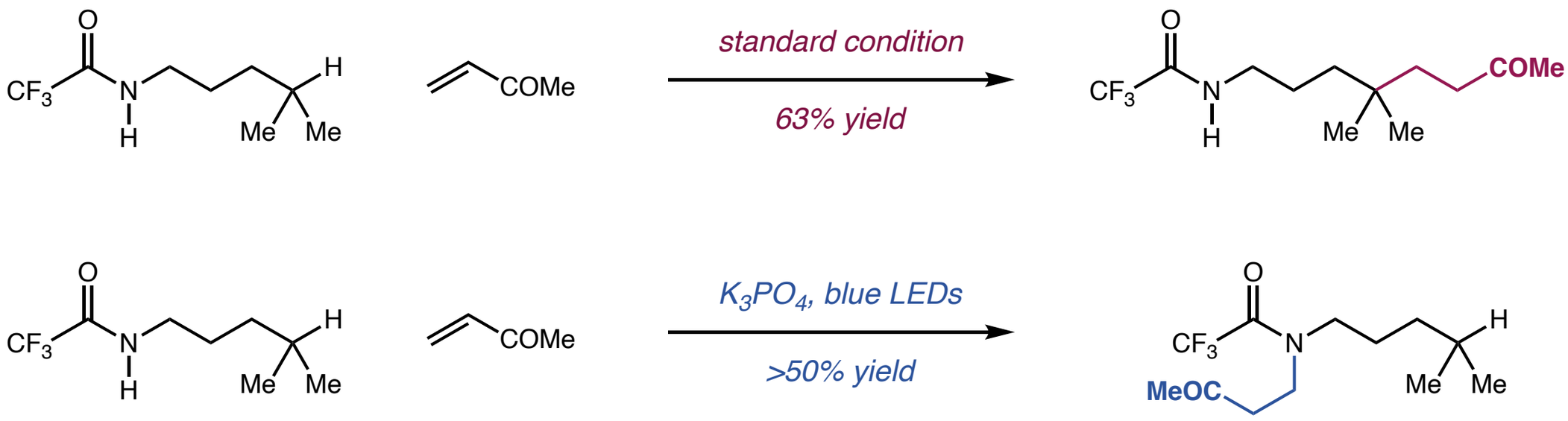


amidyl anion *amidyl radical* *alkyl radical*

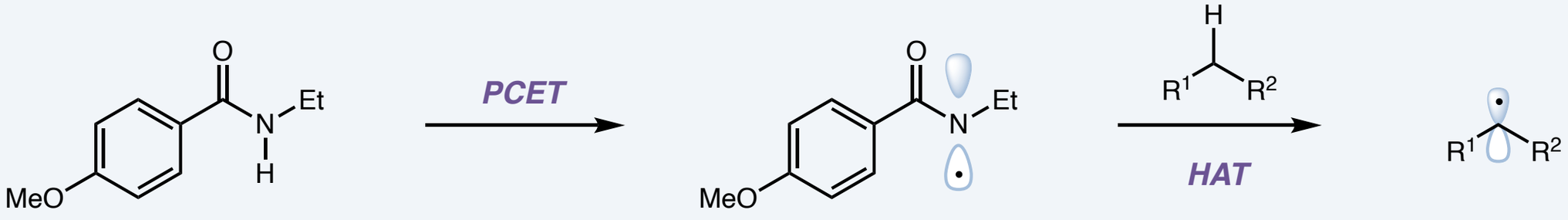
Chu, J. C. K.; Rovis, T. *Nature* **2016**, *539*, 272.

Amidyl Radical Induced 1,5-HAT for sp^3 C–H Functionalization





Amidyl Radical as HAT Reagent for Intermolecular sp^3 C–H Functionalization

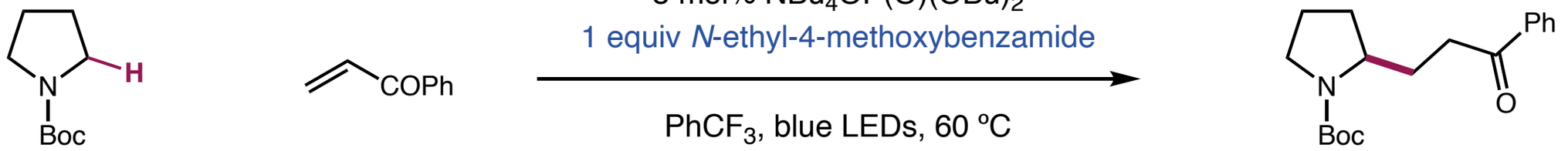


N-ethyl-4-methoxybenzamide

amidyl radical

1,5-HAT is not possible

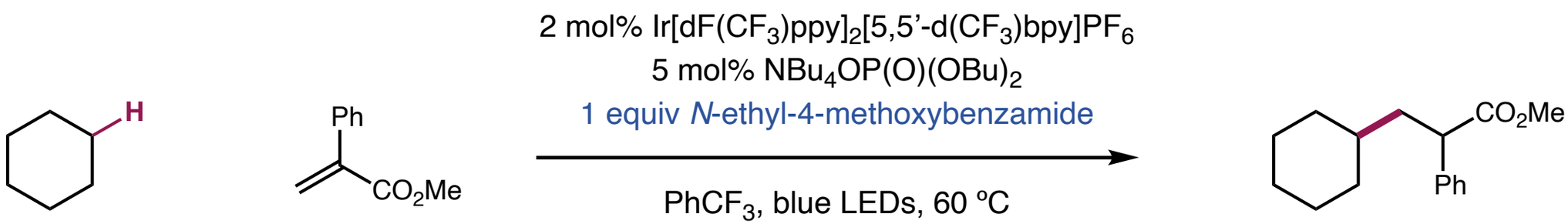
alkyl radical



10 equiv

1 equiv

60% yield



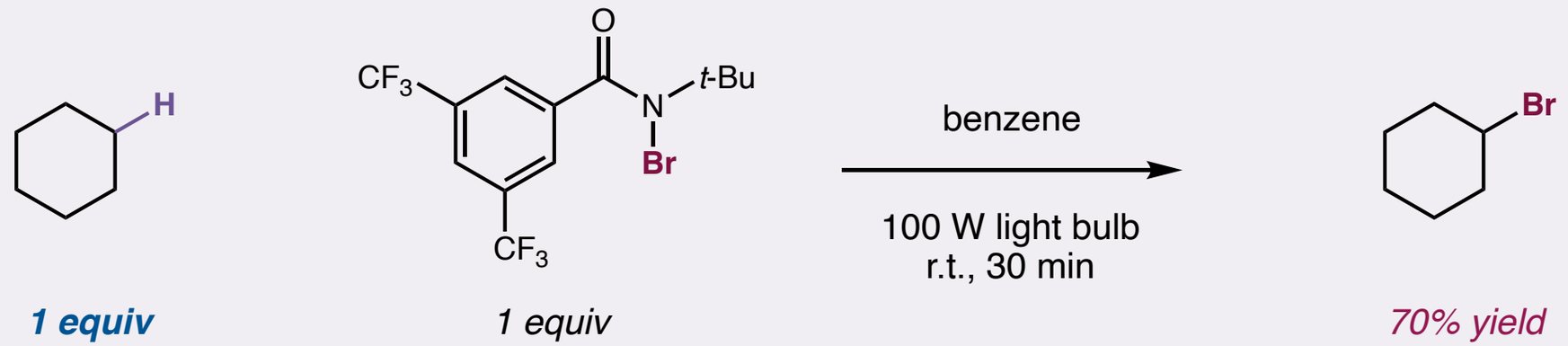
10 equiv

1 equiv

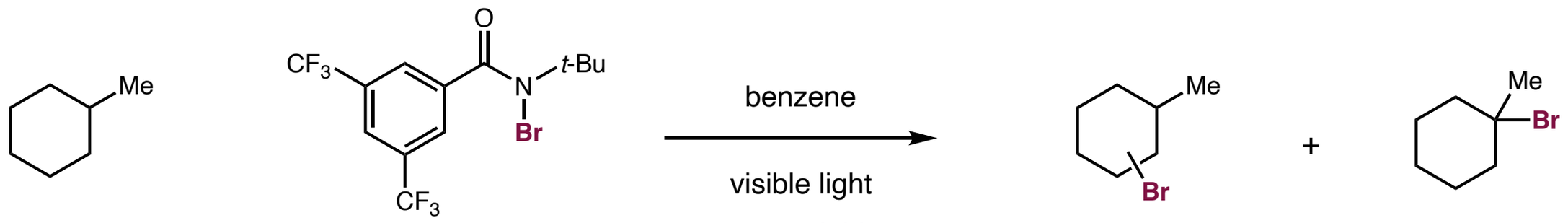
69% yield

Choi, G, J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. *Nature* **2016**, *539*, 268.

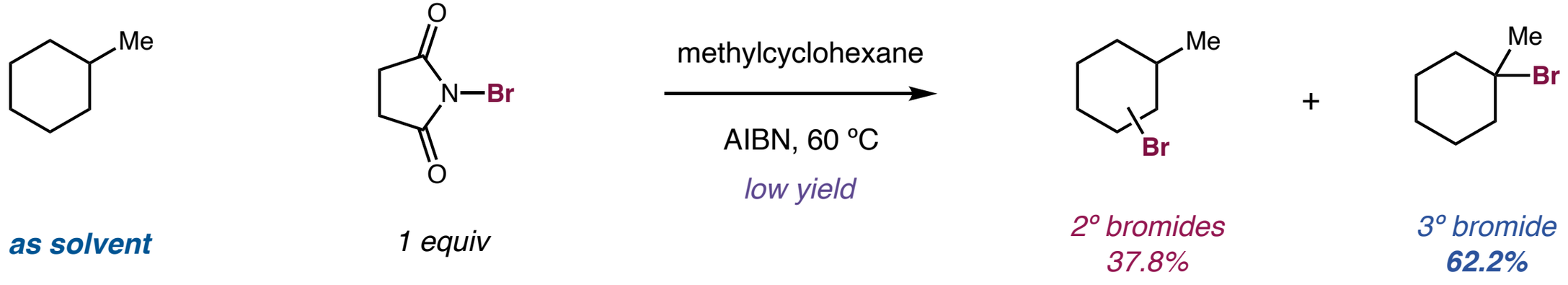
Amidyl Radical as HAT Reagent: C–H Bromination



1 equiv *1 equiv* *70% yield*



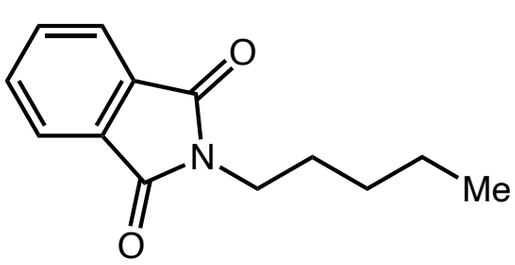
1 equiv *1 equiv* *75% yield* *2° bromides* ***98.5%*** *3° bromide* *1.5%*



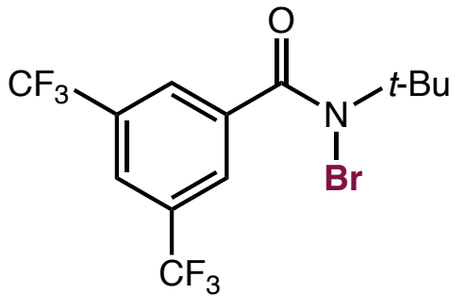
as solvent *1 equiv* *low yield* *2° bromides* *37.8%* *3° bromide* ***62.2%***

Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 14389.

Amidyl Radical as HAT Reagent: C–H Bromination



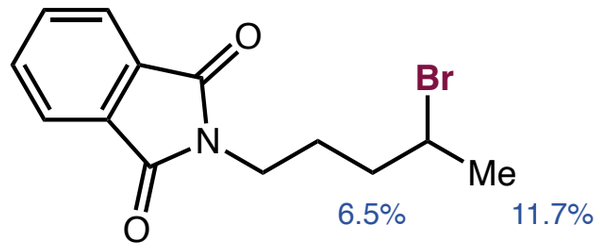
1 equiv



2 equiv

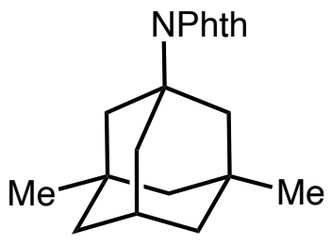
benzene

visible light



56% yield

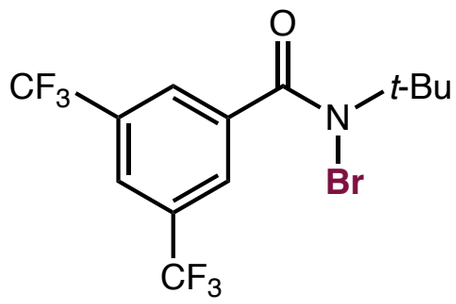
(81.8% selectivity for δ position)



1 equiv

Namenda

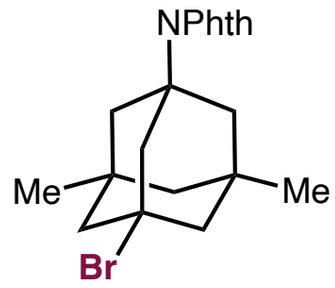
anti-Alzheimer



3 equiv

benzene

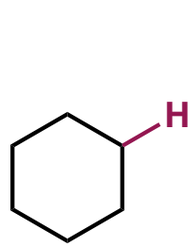
visible light



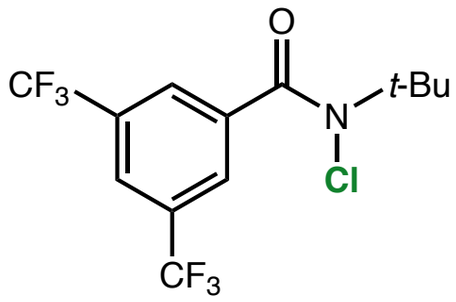
70% yield

Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 14389.

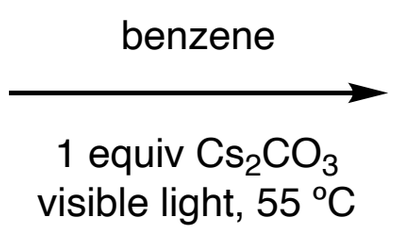
Amidyl Radical as HAT Reagent: C–H Chlorination



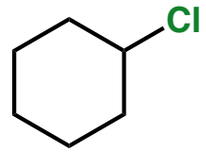
1 equiv



1 equiv

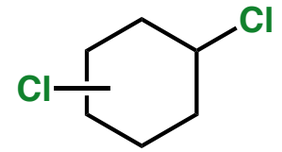


72% yield

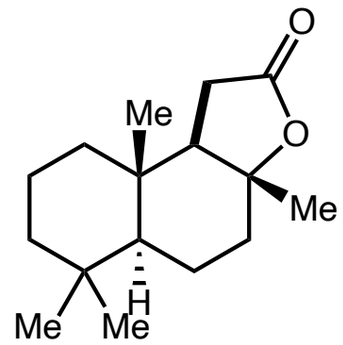


96.9% monochloride

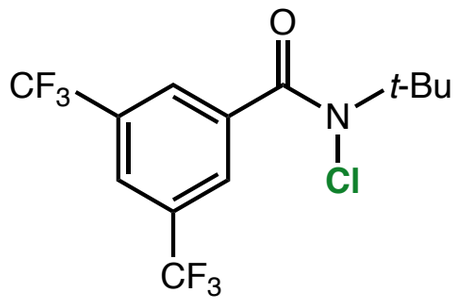
+



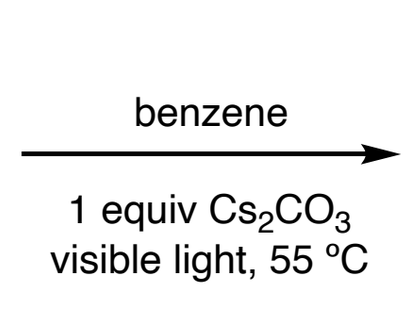
3.1% dichloride

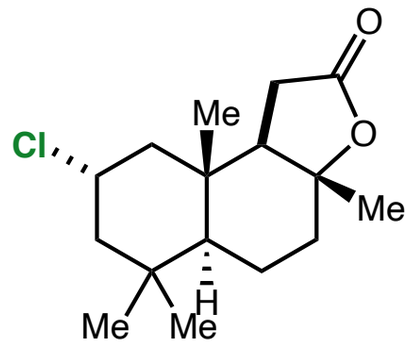


sclareolide, ***1 equiv***



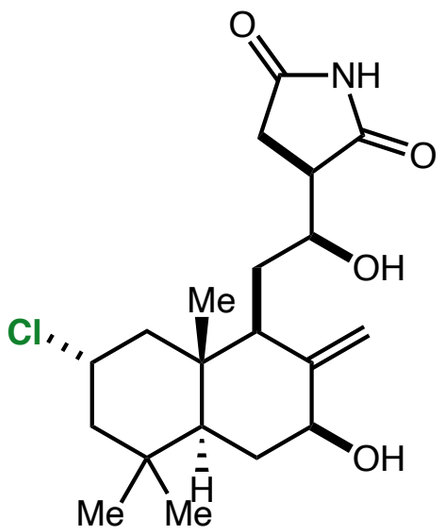
2 equiv





82% yield

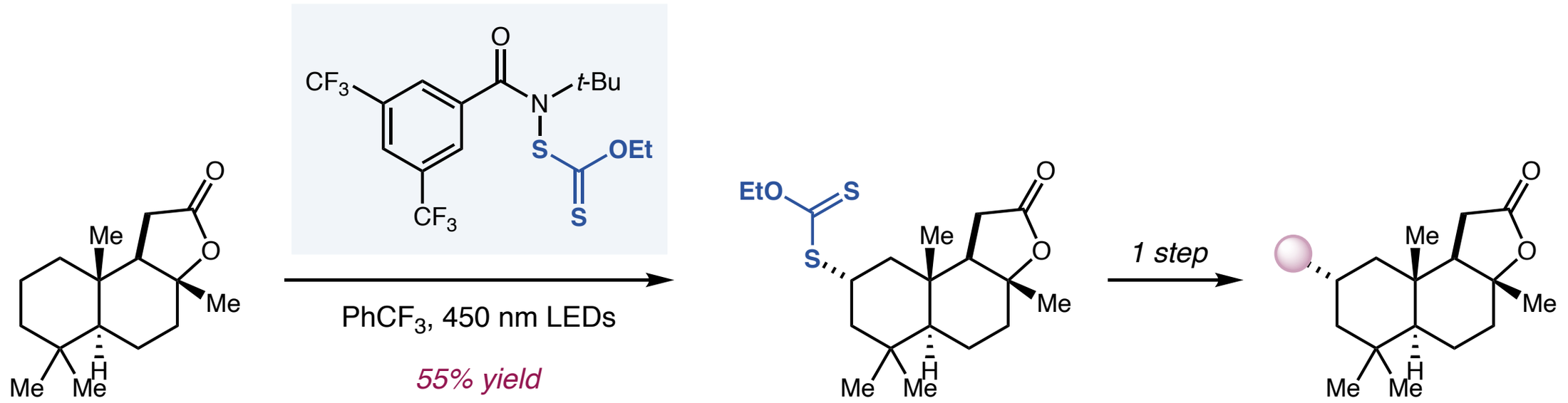
chlorolissoclimide
8–14% overall yield



8 steps

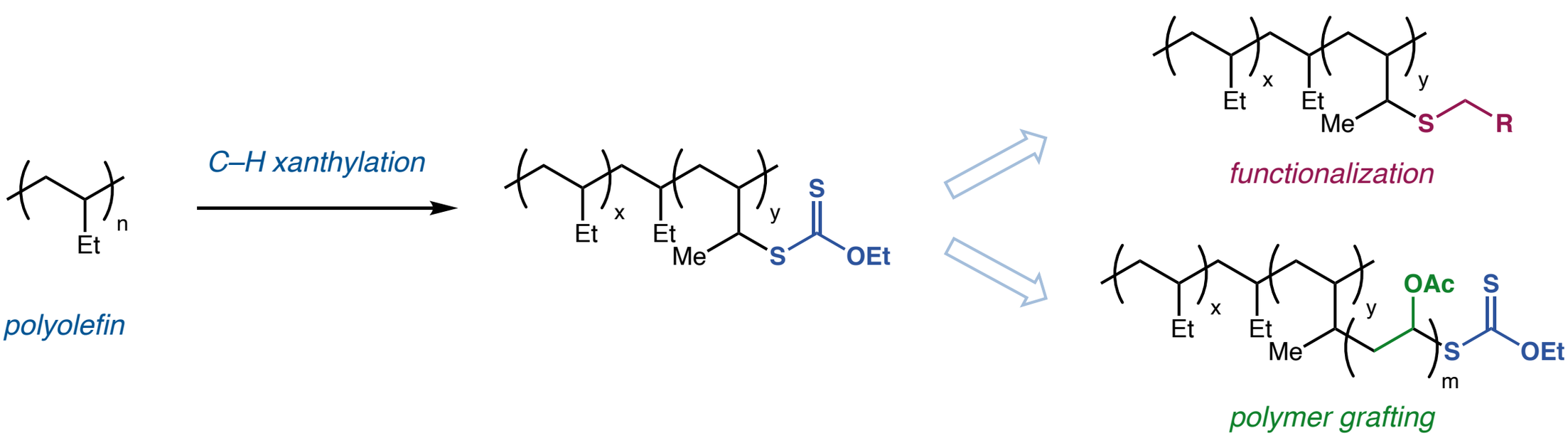
Quinn, R. K. *et al., J. Am. Chem. Soc.* **2016**, *138*, 696.

Amidyl Radical as HAT Reagent: C–H Xanthylation



sclareolide, ***1 equiv***

versatile building block



polyolefin

Czaplyski, W. L.; Na, C. G.; Alexanian, E. J. *J. Am. Chem. Soc.* **2016**, *138*, 13854.

Williamson, J. B.; Czaplyski, W. L.; Alexanian, E. J.; Leibfarth, F. A. *Angew. Chem. Int. Ed.* **2018**, *57*, 6261.

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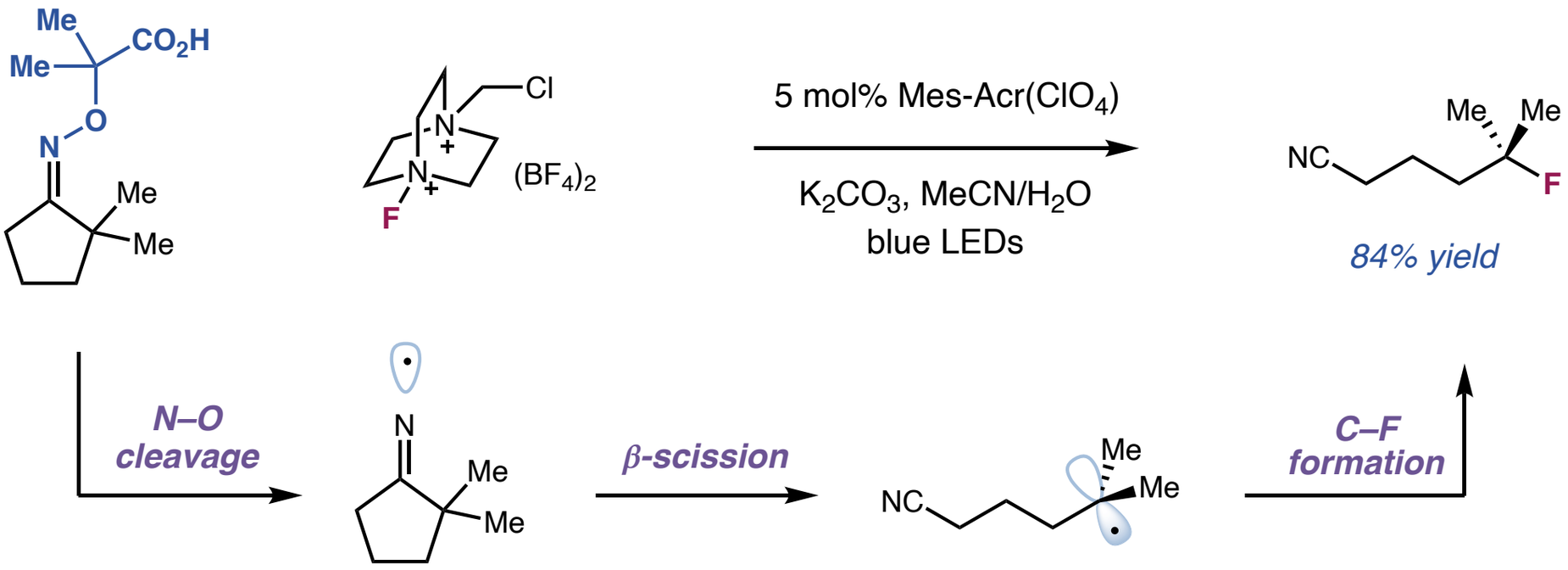
B. Formation of sp^3 C–N bonds: addition to olefins

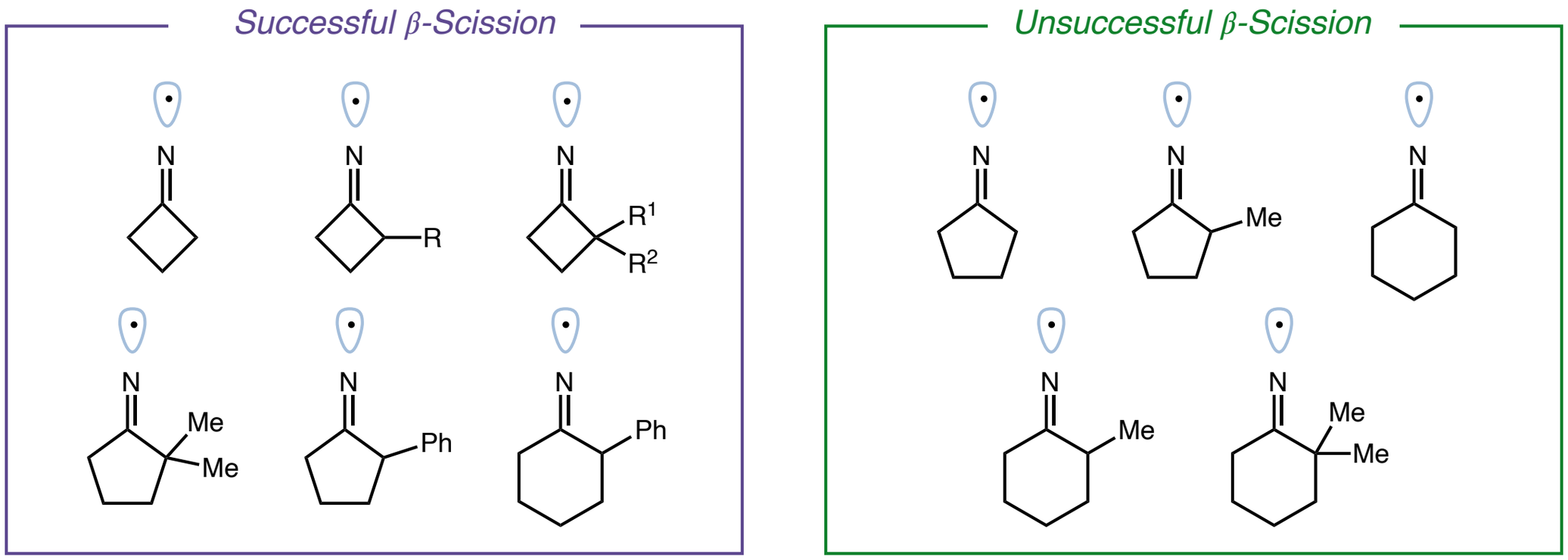
C. Formation fo sp^2 C–N bonds: addition to aromatic compounds

D. *N*-centered radicals-mediated HAT of sp^3 C–H bonds

E. Fragmentation of *N*-centered radicals

Fragmentation of N-Radicals: β-Scission of Iminyl Radical





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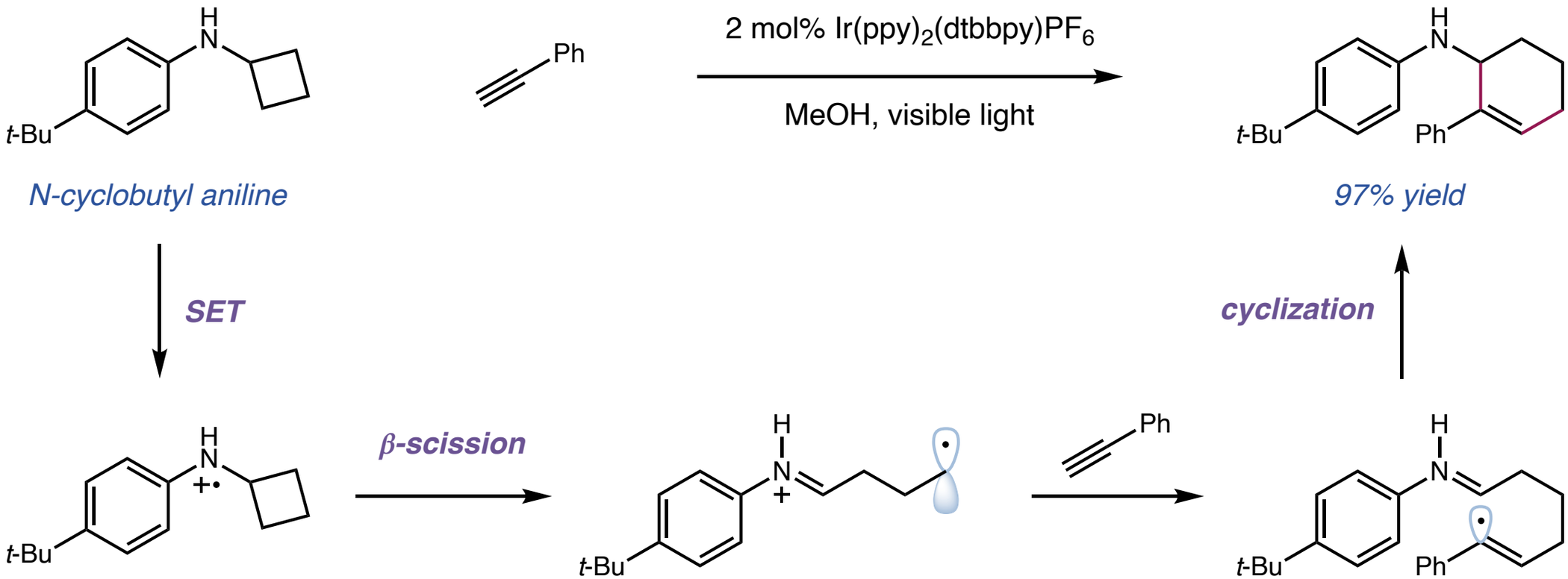
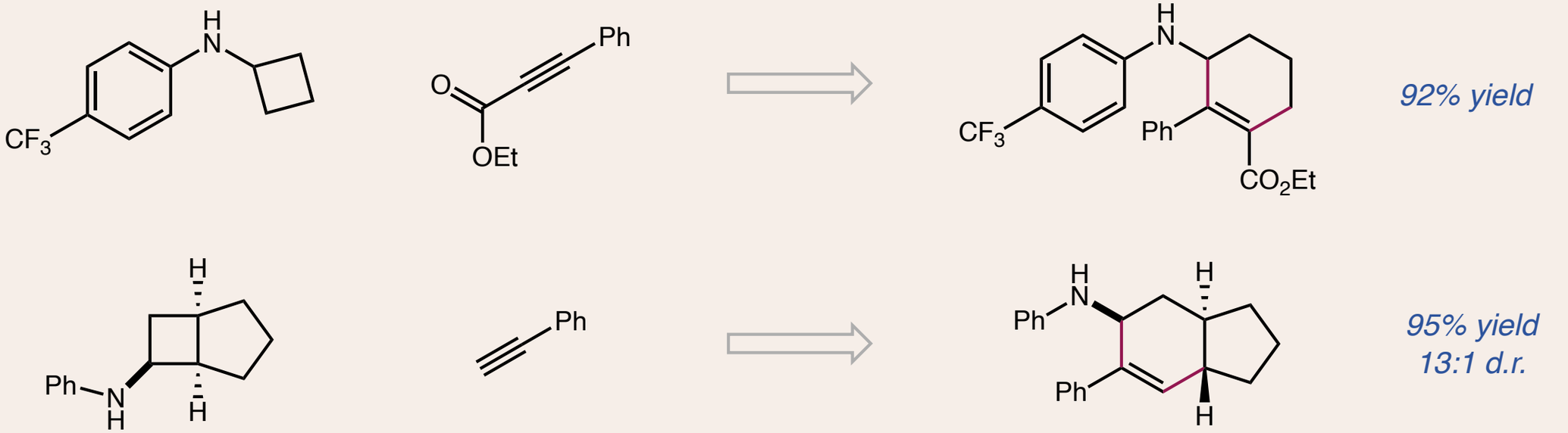
Fragmentation of N-Radicals: β-Scission of Aminyl Radical Cation





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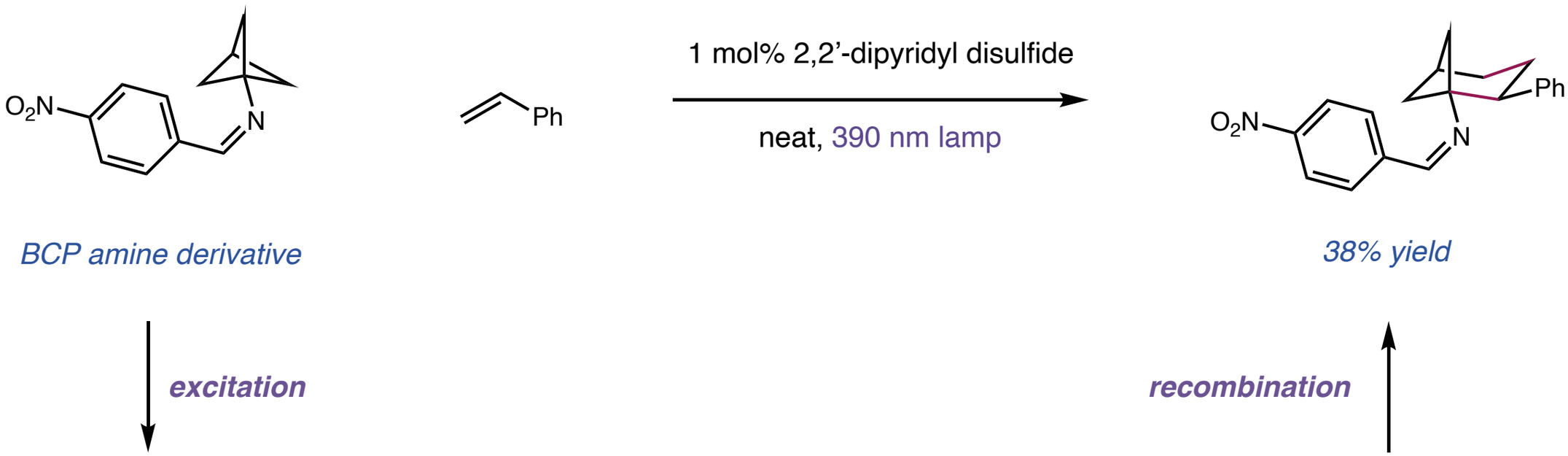
Fragmentation of N-Radicals: β-Scission of Aminyl Radical Cation



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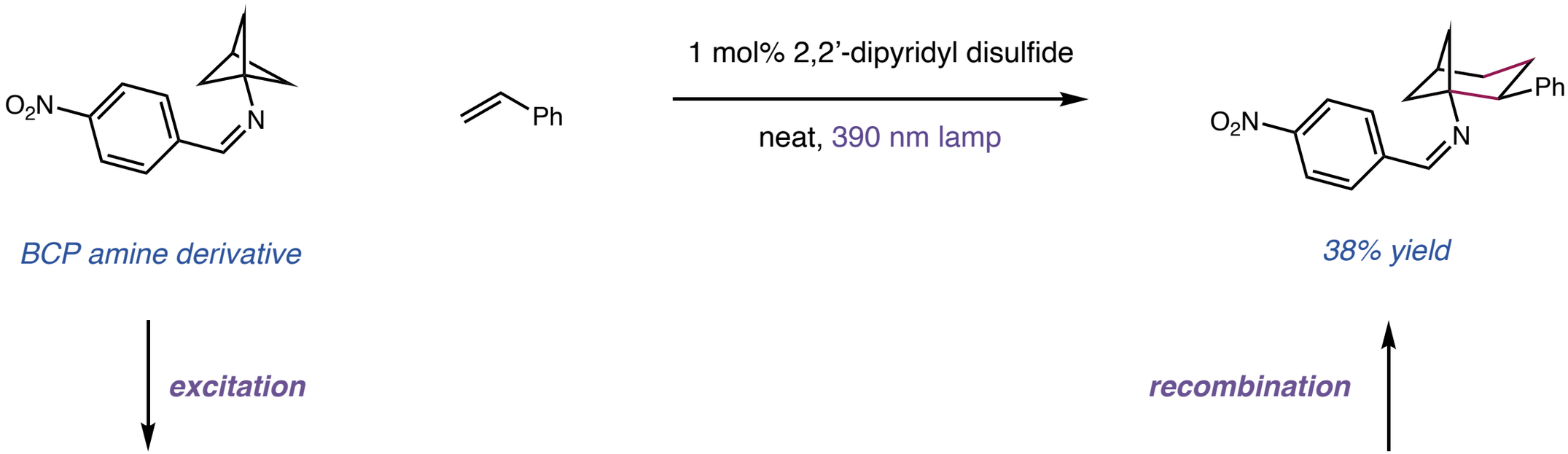
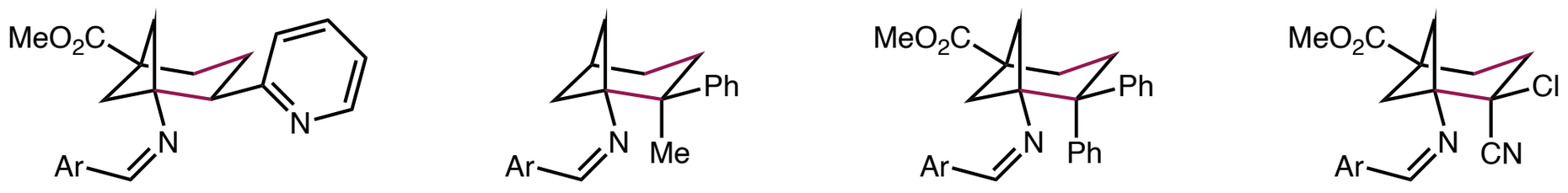
Fragmentation of N-Radicals: β-Scission of Aminyl Radical Cation





65% yield *30% yield* *31% yield* *73% yield*

Harmata, A. S.; Sowden, M. J.; Stephenson, C. R. J. *ChemRxiv.* doi: 10/26434/chemrxiv.13118528.v1

Summary

A. Formation of sp^3 C–N bonds: intramolecular cyclization

B. Formation of sp^3 C–N bonds: addition to olefins

C. Formation fo sp^2 C–N bonds: addition to aromatic compounds

D. *N*-centered radicals-mediated HAT of sp^3 C–H bonds

E. Fragmentation of *N*-centered radicals

Seminal reviews:

• “**Photocatalytic Generation of Aminium Radical Cations for C–N Bond Formation”** Ganley, J. M.; Murray, P. R. D.; Knowles, R. R. *ACS Catal.* **2020**, *10*, 11712–11738.

• “**Recent advances in visible-light photoredox-catalyzed nitrogen radical cyclization**” Wang, P.; Zhang, Q.; Xiao, W.; Chen, J. *Green Synthesis and Catalysis* **2020**, *1*, 42–51.

• “**Chemistry with *N*-Centered Radicals Generated by Single-Electron Transfer-Oxidation Using Photoredox Catalysis**” Jiang, H.; Studer, A. *CCS Chem.* **2019**, *1*, 38–49.

• “**Hydroxylamine Derivatives as Nitrogen-Radical Precursors in Visible-Light Photochemistry**” Davies, J.; Morcillo, S. P.; Douglas, J. J.; Leonori, D. *Chem. Eur. J.* **2018**, *24*, 12154–12163.

• “**Photochemical Generation of Nitrogen-Centered Amidyl, Hydrazonyl, and Imidyl Radicals: Methodology Developments and Catalytic Applications**” Kärkäs, M. D. *ACS Catal.* **2017**, *7*, 4999–5002.