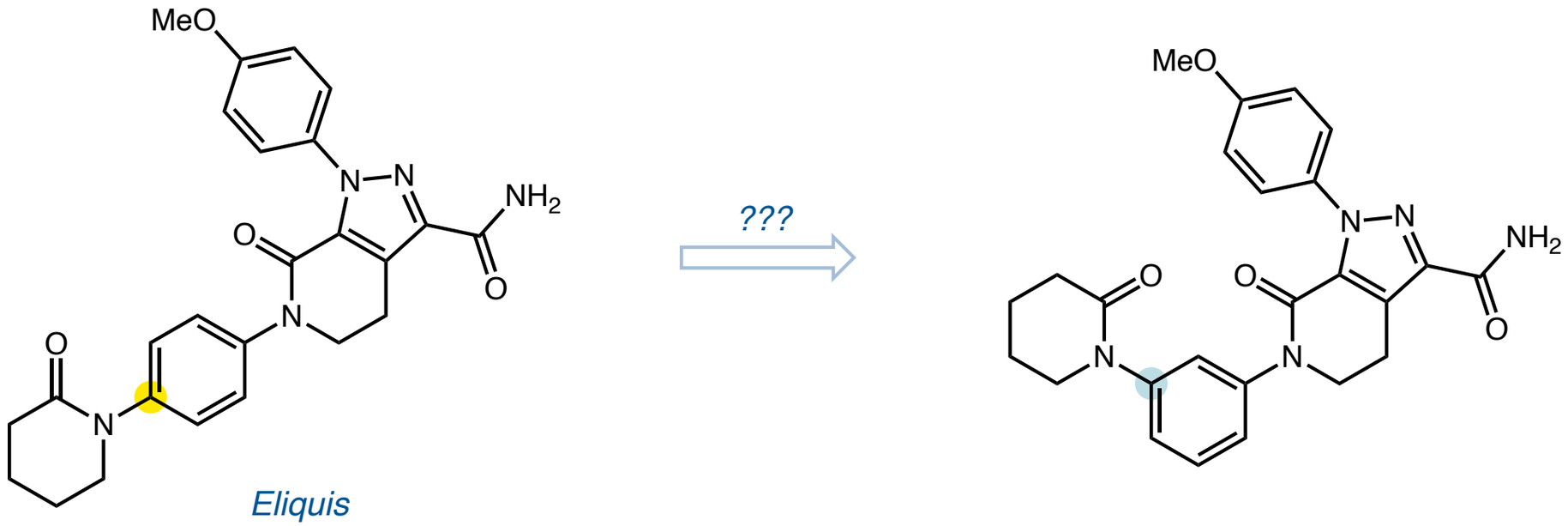
Migratory Functional-Group Modification



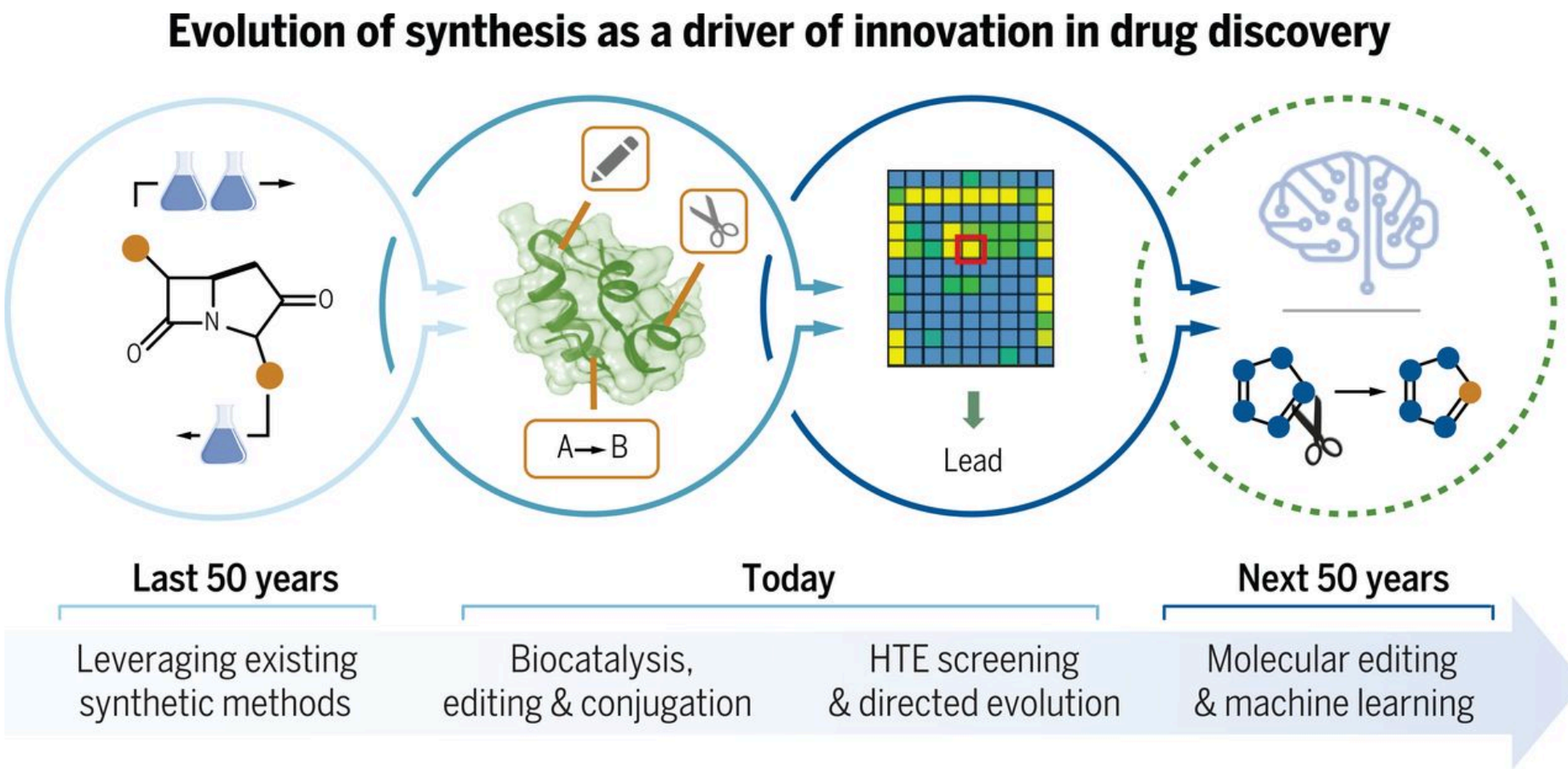
Eliquis

Yufan Liang

MacMillan Literature Group Meeting

January 6, 2021

Molecular Editing



Molecular Editing

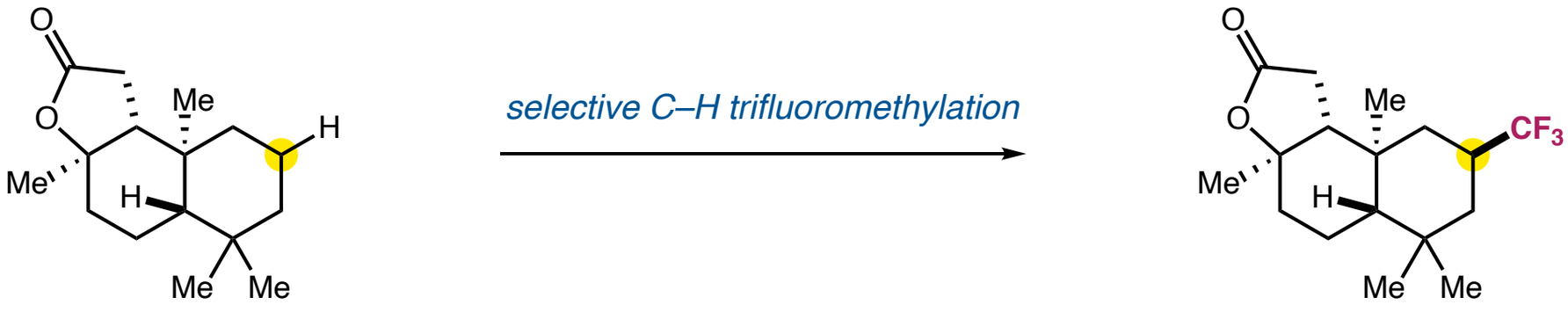
Modification and functionalization any molecules at molecular level, specifically, it includes but not limited to the insertion, deletion, exchange, positional rearrangement of atoms and functional groups at will and in highly specific and flexible fashion

Campos, K. R.; Coleman, P. J. *et. al. Science* **2019**, *363*, eaat0805

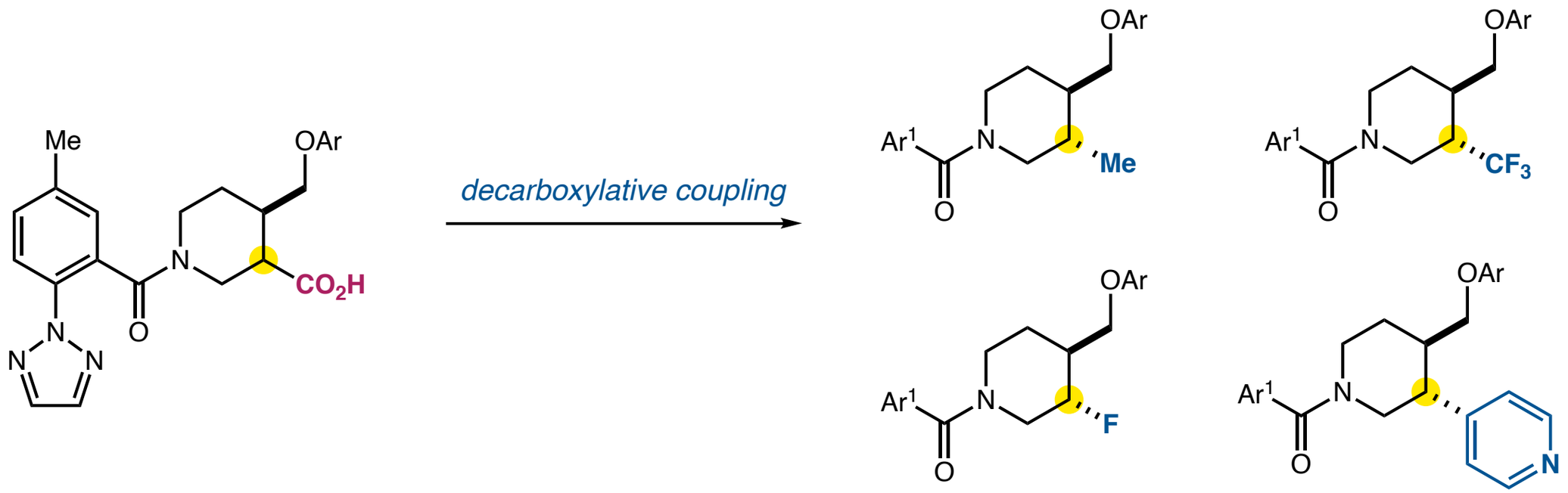
*What is the difference between **late-stage functionalization** and **late-stage molecular editing**?*

Two Major Strategies for Late-Stage Functionalization

Late-stage C–H functionalization

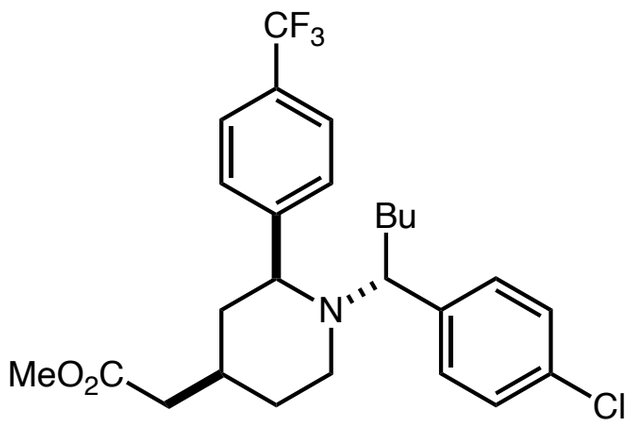


Late-stage functional group transformation

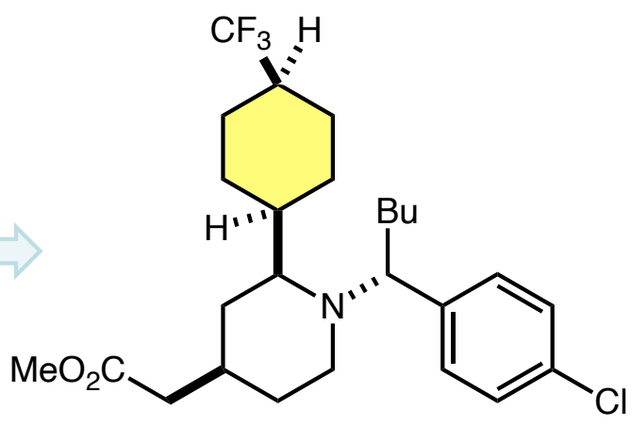


Sarver, P. J.; Bacauanu, V.; Schultz, D. M.; Dirocco, D. A.; Lam, Y.-h.; Sherer, E. C.; MacMillan, D. W. C. *Nat. Chem.* **2020**, *12*, 459

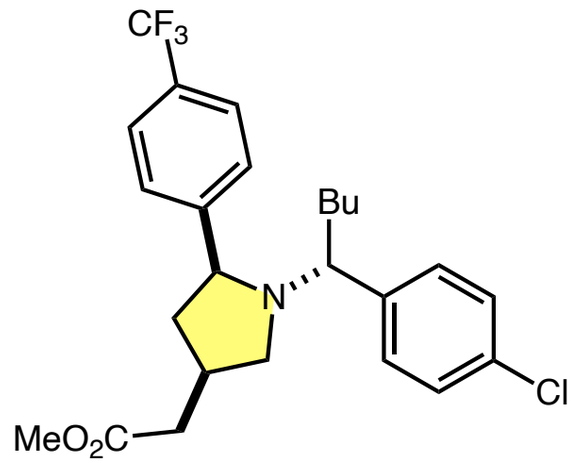
Late-Stage Molecular Editing for Drug Molecule Functionalization



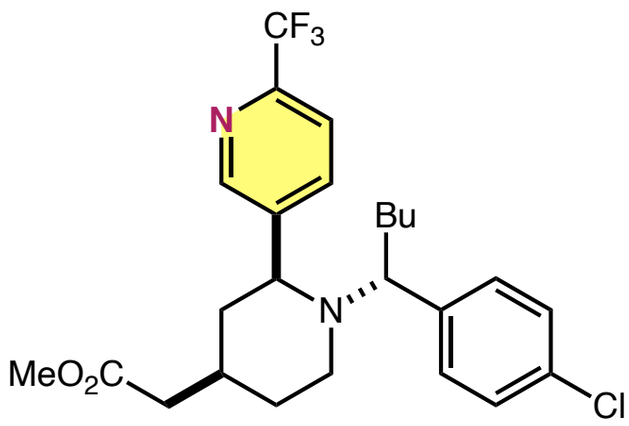
advanced intermediate



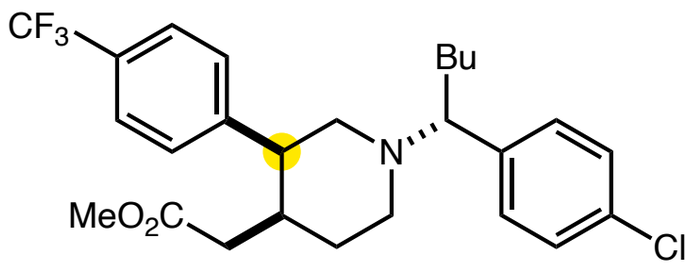
aromatic ring saturation



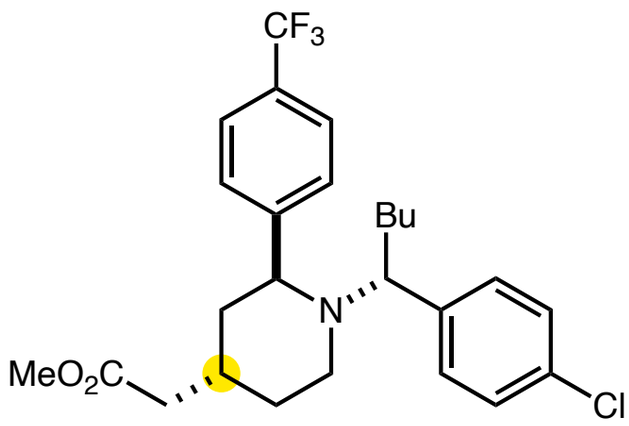
ring contraction



atom swap

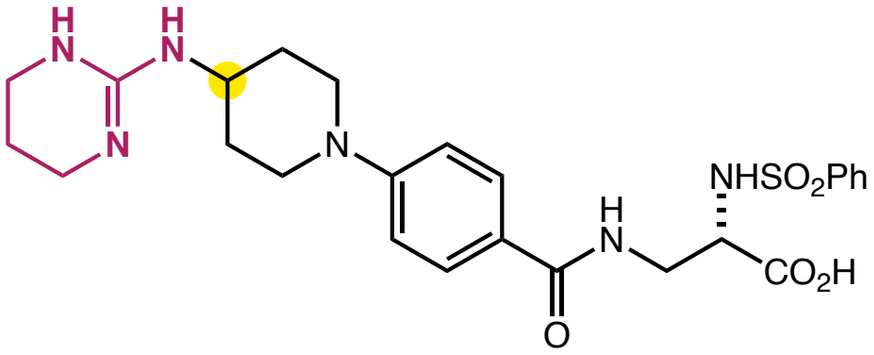


migratory functional-group modification

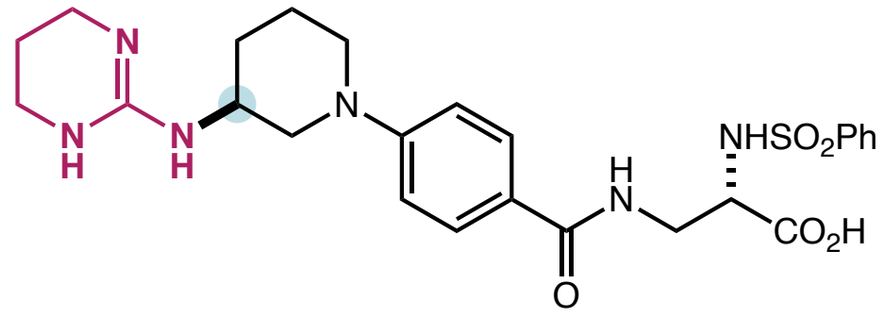


stereocenter flip

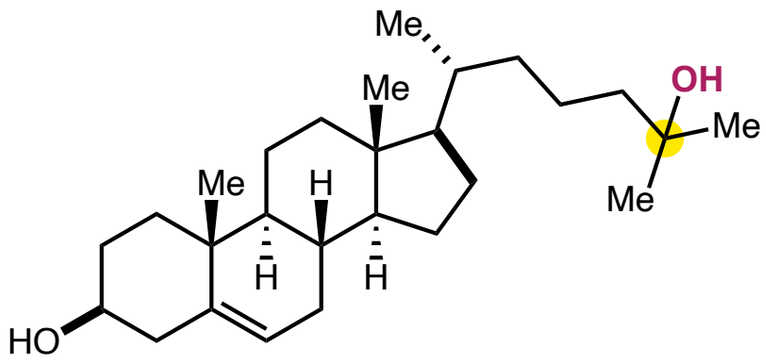
Regioisomers in Drug Discovery



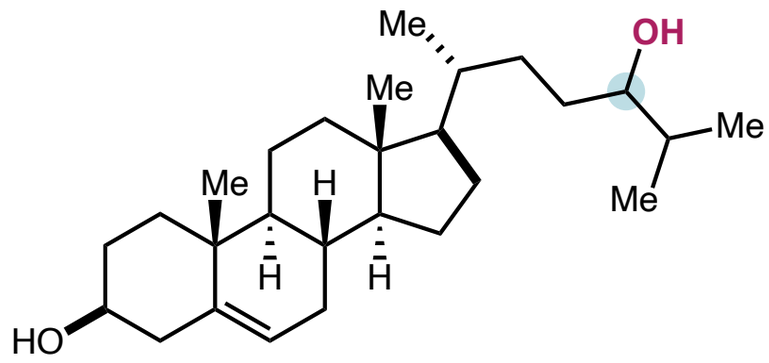
[IC_{50} $\alpha_v\beta_3$] 1.3 nM
solubility: <0.1 mg/mL



[IC_{50} $\alpha_v\beta_3$] 0.48 nM
solubility: 3.5 mg/mL



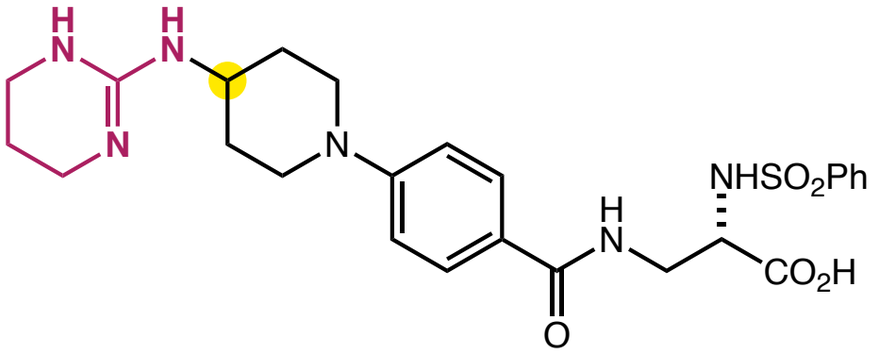
[EC_{50}, GluN2A] >10000 nM



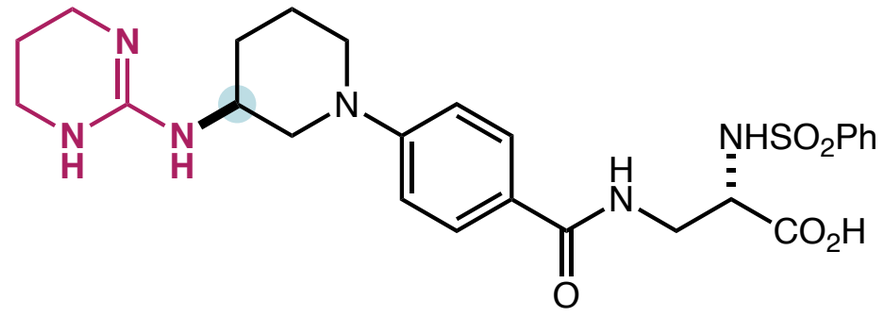
(*S*) isomer: [EC_{50}, GluN2A] 150 nM
(*R*) isomer: [EC_{50}, GluN2A] 37 nM

Ishikawa, M. *et. al., Bioorg. Med. Chem.* **2006**, *14*, 2131
La, D. S. *et. al., J. Med. Chem.* **2019**, *62*, 7526

Rapid Generation of Regioisomers via Migratory FG Modification



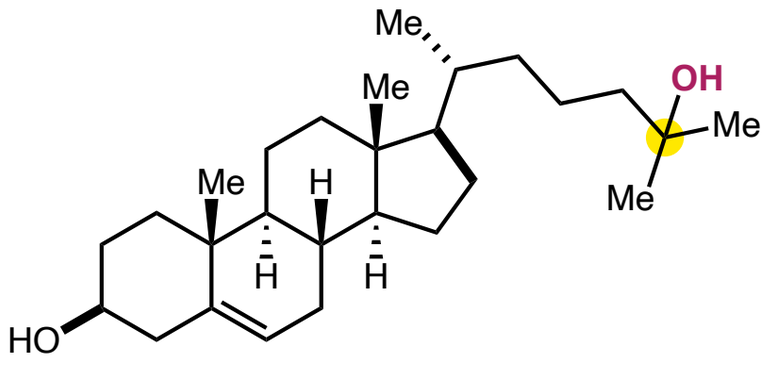
[IC_{50} $\alpha_v\beta_3$] 1.3 nM
solubility: <0.1 mg/mL



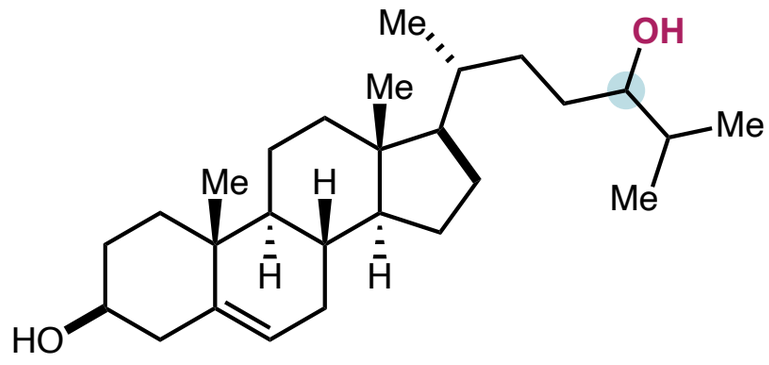
[IC_{50} $\alpha_v\beta_3$] 0.48 nM
solubility: 3.5 mg/mL

???

???



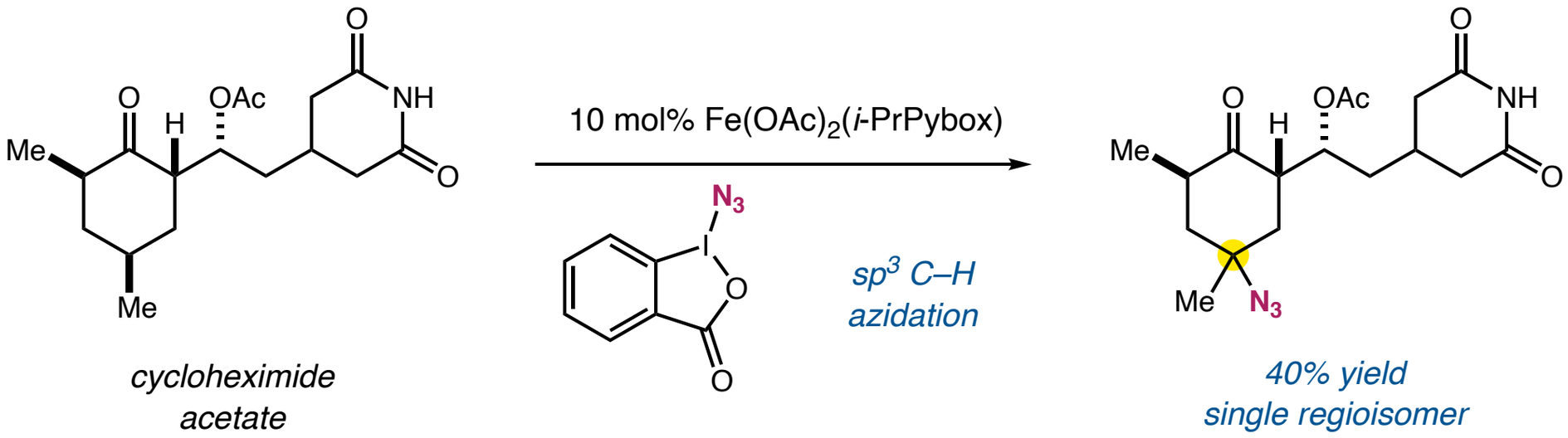
[EC_{50}, GluN2A] >10000 nM

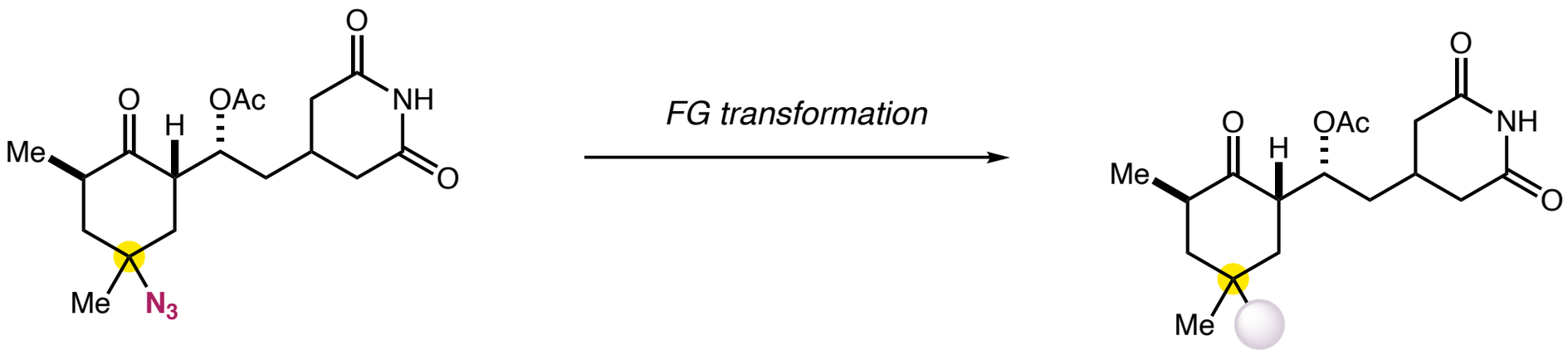


(*S*) isomer: [EC_{50}, GluN2A] 150 nM
(*R*) isomer: [EC_{50}, GluN2A] 37 nM

Ishikawa, M. *et. al., Bioorg. Med. Chem.* **2006**, *14*, 2131
La, D. S. *et. al., J. Med. Chem.* **2019**, *62*, 7526

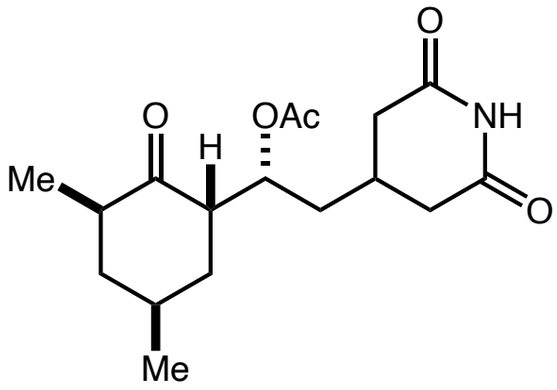
Exploration of Unaccesible C–H Chemical Space





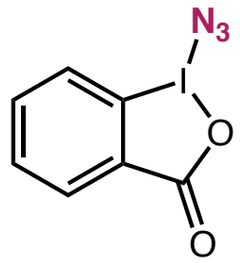
Karimov, R. R.; Sharma, A.; Hartwig, J. F. *ACS Cent. Sci.* **2016**, *2*, 715

Exploration of Unaccesible C–H Chemical Space

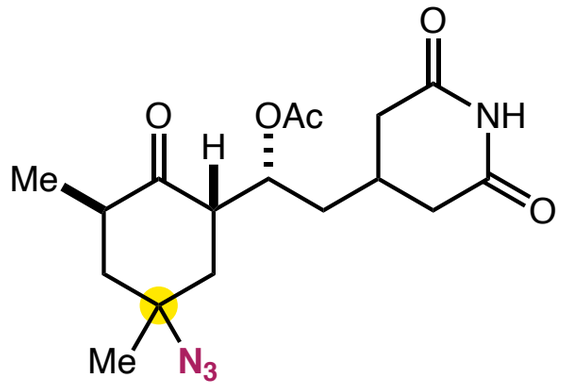


cycloheximide acetate

10 mol% $Fe(OAc)_2$(*i*-PrPybox)



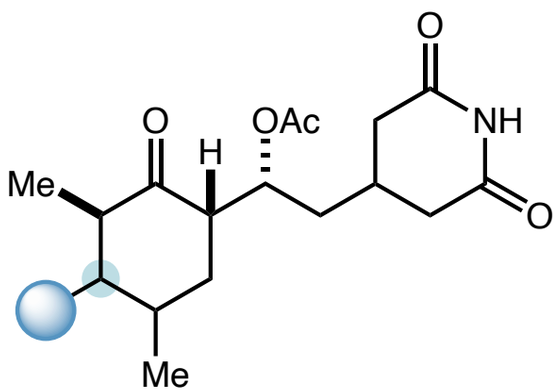
sp^3 C–H azidation



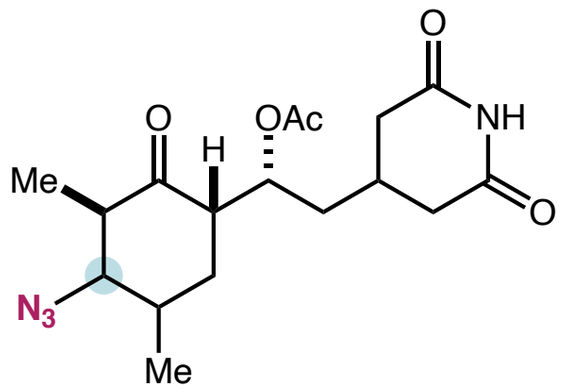
40% yield
single regioisomer

direct C–H functionalization might be nontrivial

Migratory FG Modification

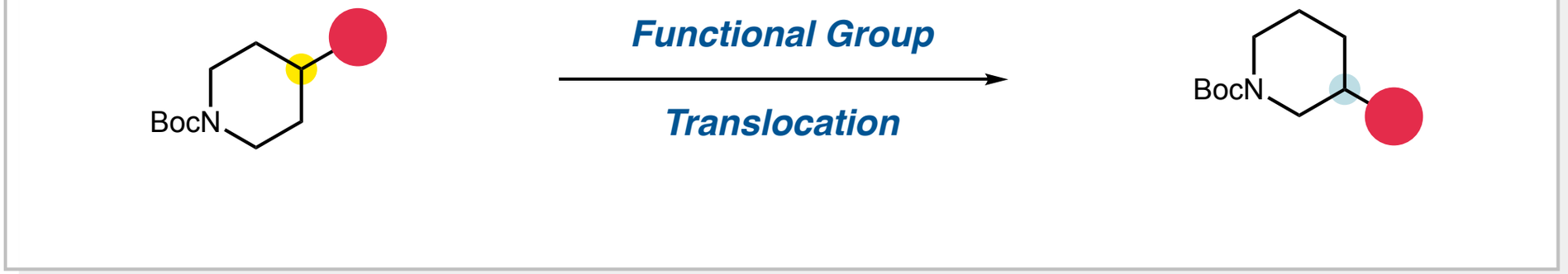


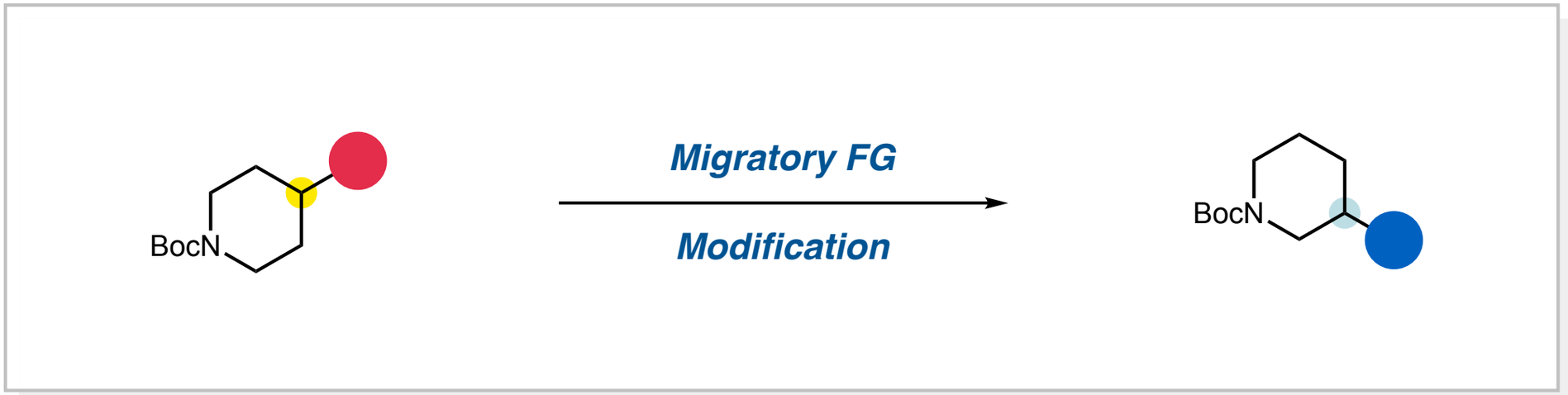
FG transformation



Karimov, R. R.; Sharma, A.; Hartwig, J. F. *ACS Cent. Sci.* **2016**, *2*, 715

Two Related-Concepts



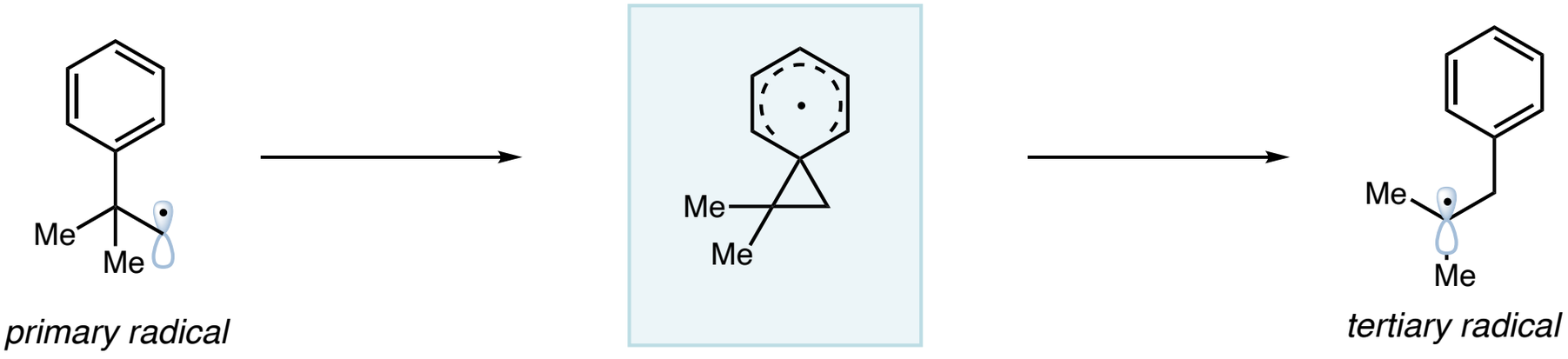


Outline

- Migratory FG modification via radical intermediates
- Migratory FG modification via non-radical intermediates
- Migratory FG modification via enzymatic catalysis

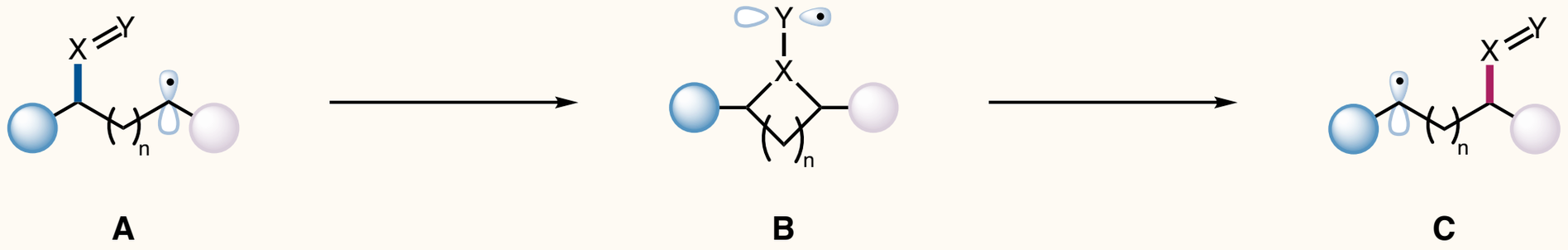
Migratory FG Modification via Radical Intermediates

- Neophyl rearrangement



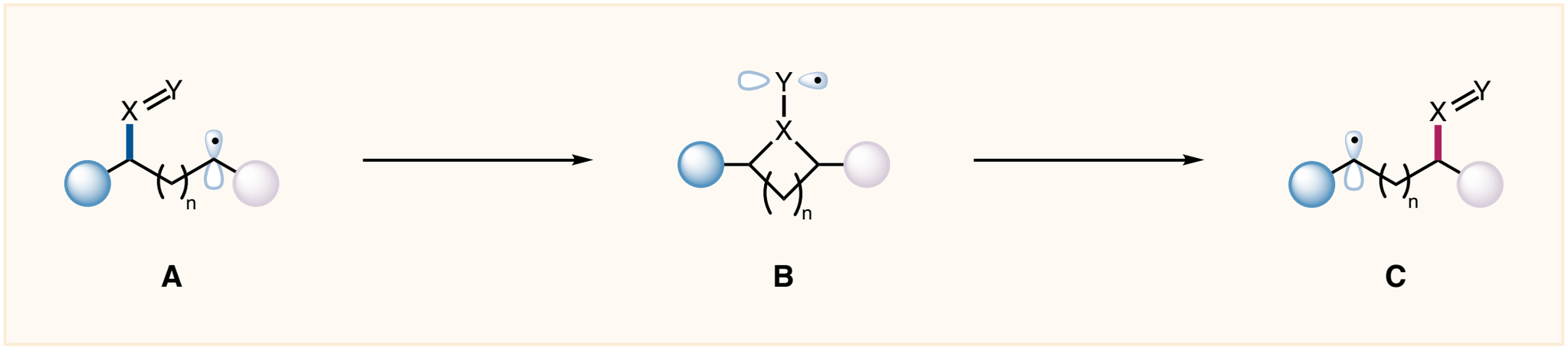
primary radical

tertiary radical



A **B** **C**

Migratory FG Modification via Radical Intermediates



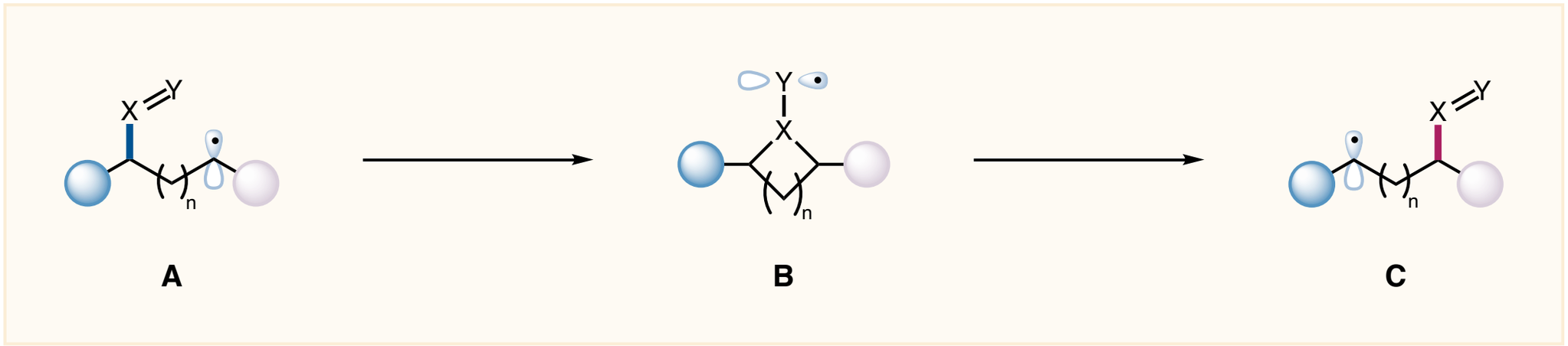
- Driving force: formation of more stable radicals (**C** vs. **A**); an ***irreversible*** downstream reaction from **C**

- Spatial requirement (aka, parameter **n**)

n = 0	*n* = 1	*n* = 2	*n* = 3	*n* > 3
1,2-migration	*1,3-migration*	*1,4-migration*	*1,5-migration*	*1,n-migration*
cyclopropyl intermedicate	cyclobutyl intermedicate	cyclopentyl intermedicate	cyclohexyl intermedicate	>6-memeberd ring intermedicate
favored	**disfavored**	**favored**	**favored**	**disfavored**

1,4- and 1,5-migrations are the most common ones.

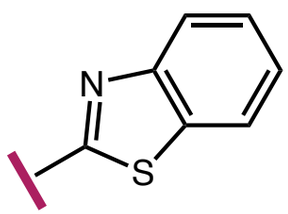
Migratory FG Modification via Radical Intermediates



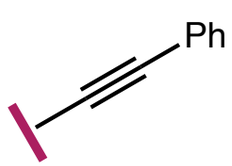
- Driving force: formation of more stable radicals (**C** vs. **A**); an ***irreversible*** downstream reaction from **C**

- Spatial requirement (aka, parameter **n**): 1,2-, 1,4-, and 1,5-migration

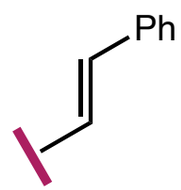
- FGs that can undergo radical migration



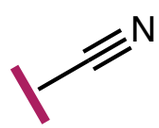
(hetero)arene



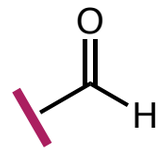
alkyne



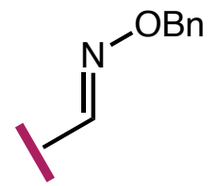
alkene



cyano



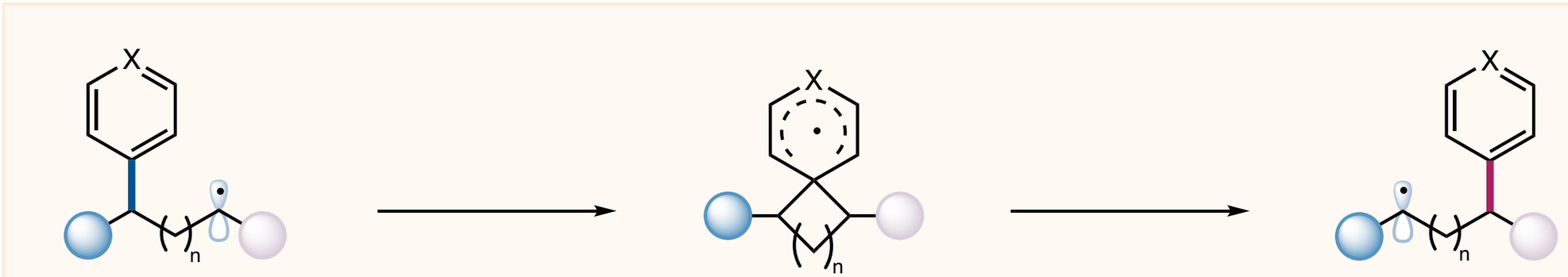
formyl



imino

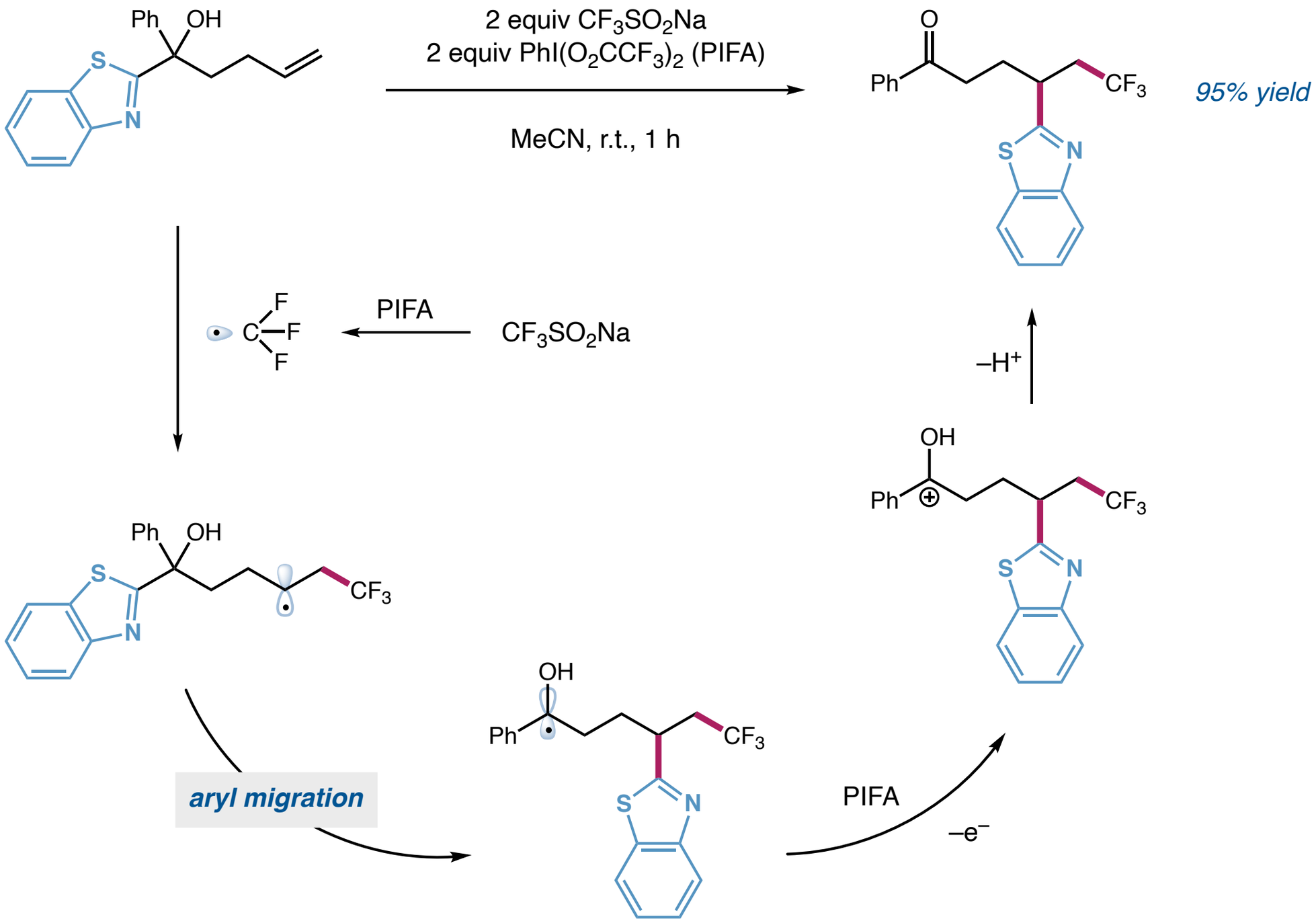
Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649
Li, W.; Xu, W.; Xie, J.; Yu, S.; Zhu, C. *Chem. Soc. Rev.* **2018**, *47*, 654

(Hetero)arene Migration: From Carbon to Carbon



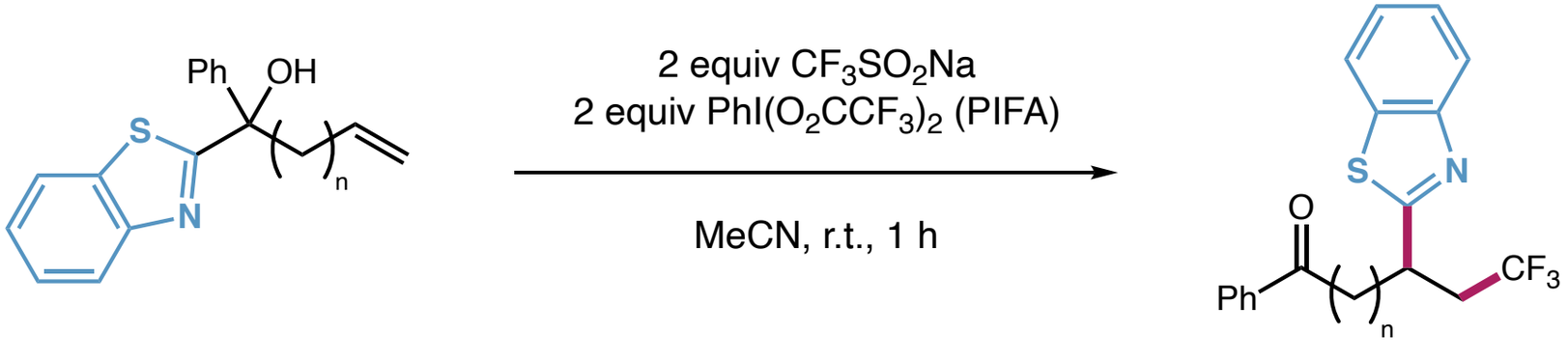
carbon-centered radical ***carbon-centered radical***

(Hetero)arene Migration: From Carbon to Carbon



Wu, Z.; Wang, D.; Liu, Y.; Huan, L.; Zhu, C. *J. Am. Chem. Soc.* **2017**, *139*, 1388

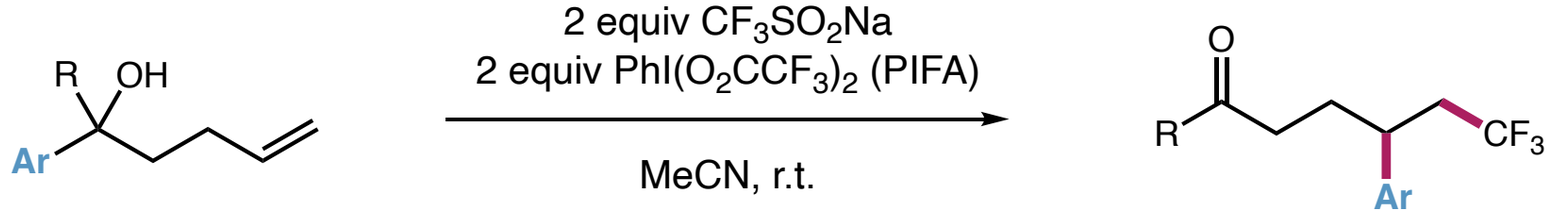
(Hetero)arene Migration: From Carbon to Carbon

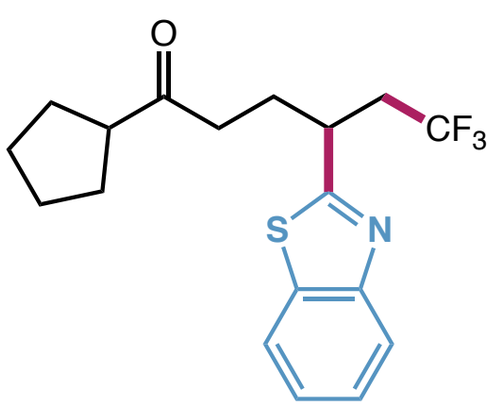


n = 0	*1,2-migration*	*77% yield*
n = 1	*1,3-migration*	*trace*
n = 2	*1,4-migration*	*95% yield*
n = 3	*1,5-migration*	*61% yield*
n = 4	*1,6-migration*	*trace*

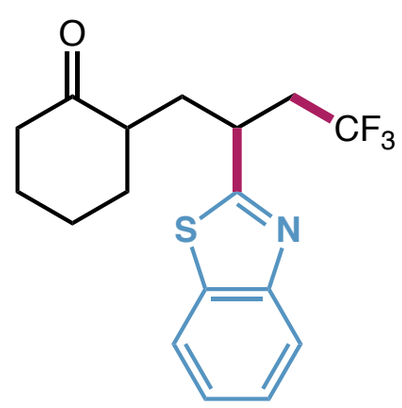
Wu, Z.; Wang, D.; Liu, Y.; Huan, L.; Zhu, C. *J. Am. Chem. Soc.* **2017**, *139*, 1388

(Hetero)arene Migration: From Carbon to Carbon

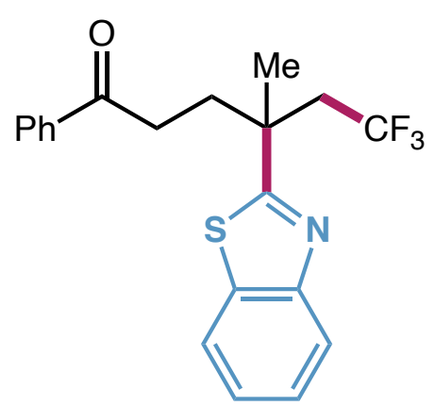




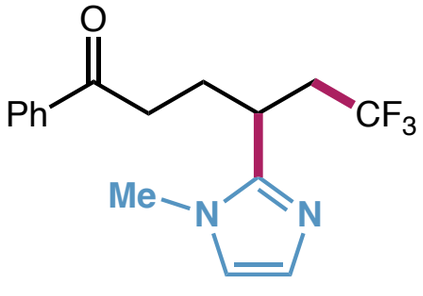
83% yield



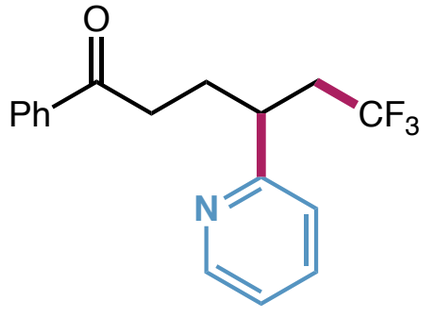
65% yield



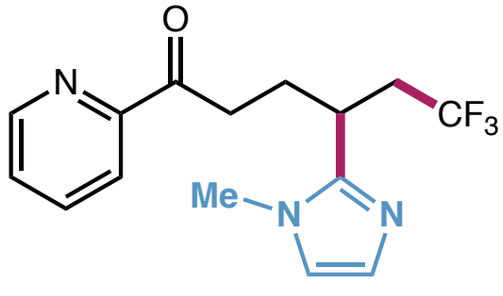
65% yield



75% yield



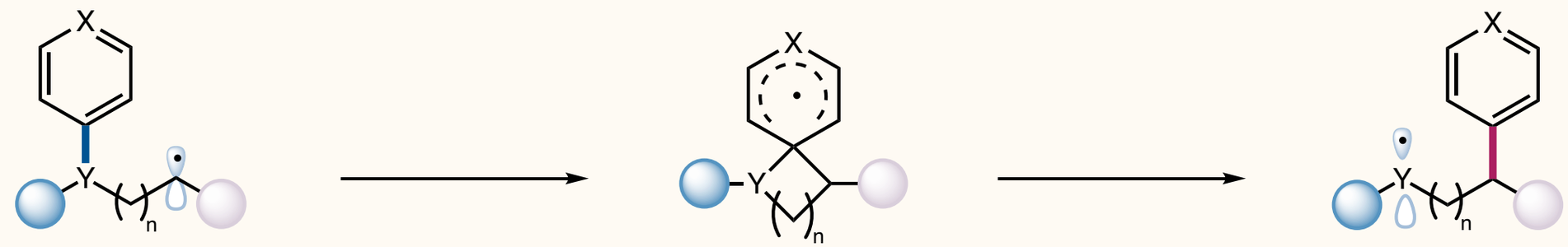
60% yield



51% yield

Wu, Z.; Wang, D.; Liu, Y.; Huan, L.; Zhu, C. *J. Am. Chem. Soc.* **2017**, *139*, 1388

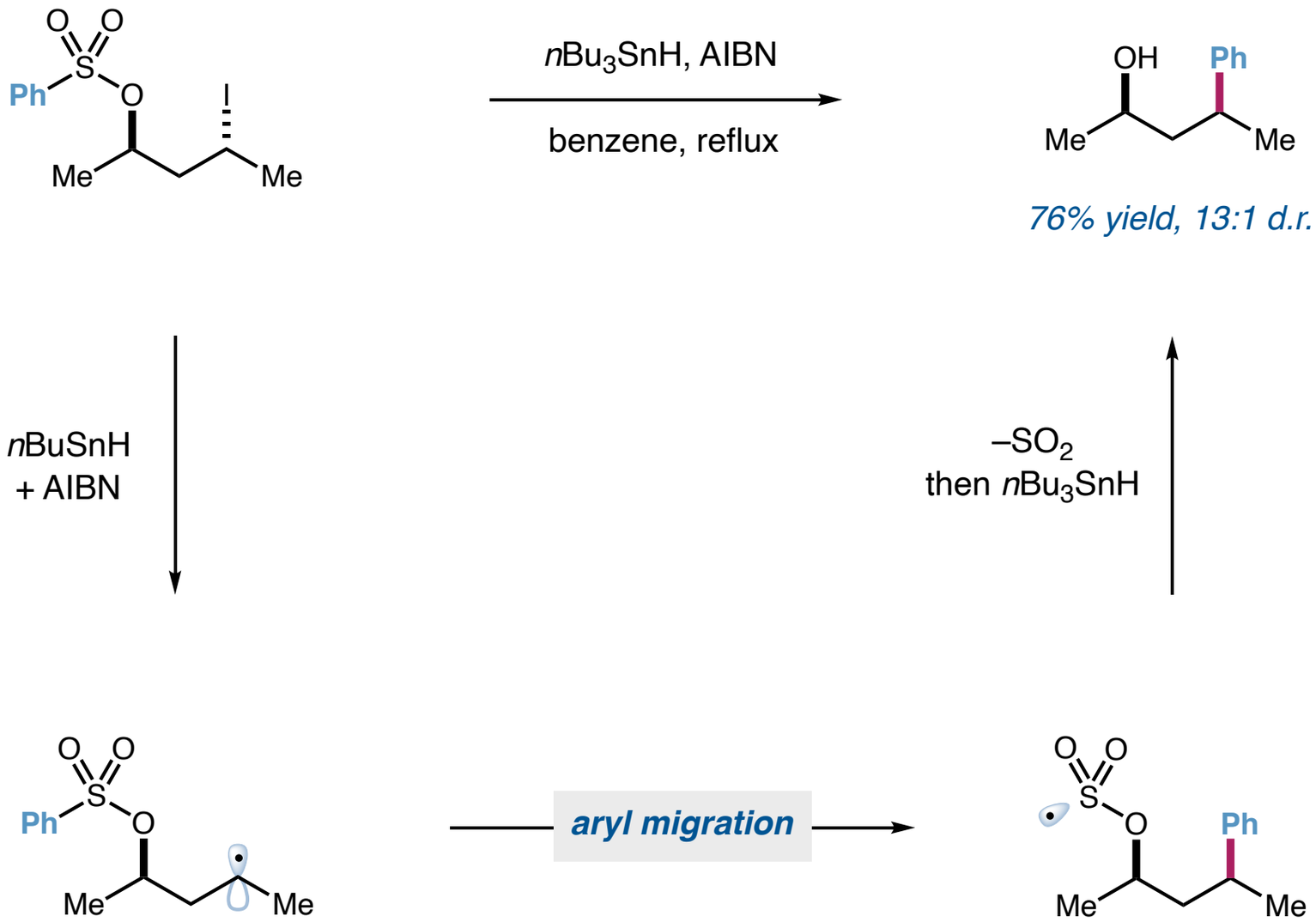
(Hetero)arene Migration: From Carbon Radical to Heteroatom Radical



carbon-centered radical

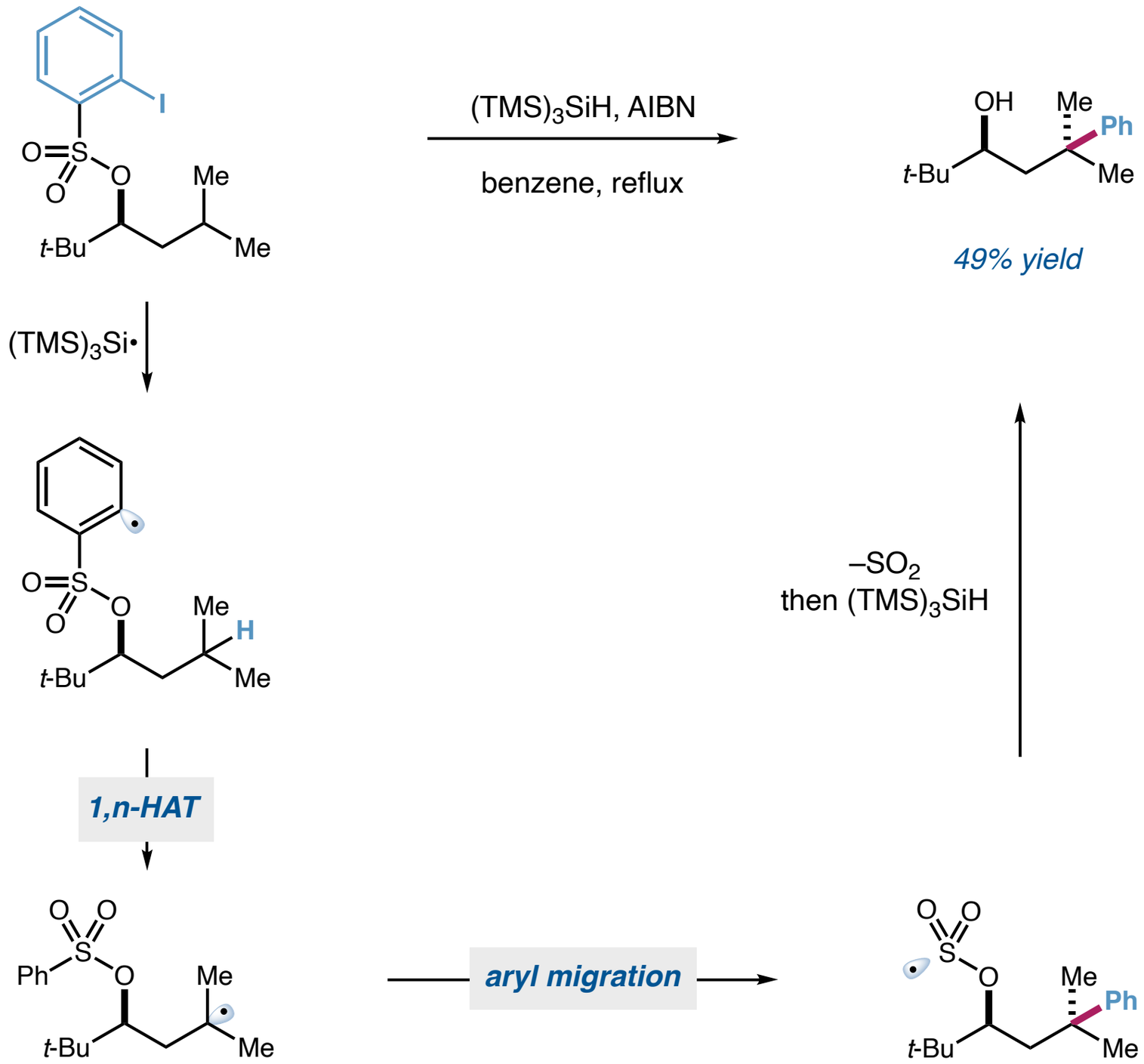
Heteroatom-centered radical

(Hetero)arene Migration: From Carbon Radical to Sulfur Radical



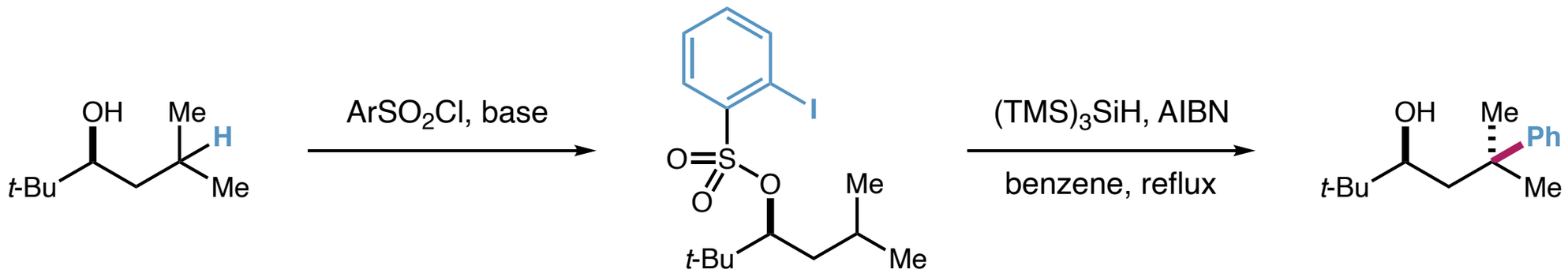
Studer, A.; Bossart, M. *Chem. Commun.* **1998**, 2127.
Bossart, M.; Fassler, R.; Schoenberger, J.; Studer, A. *Eur. J. Org. Chem.* **2002**, 2742

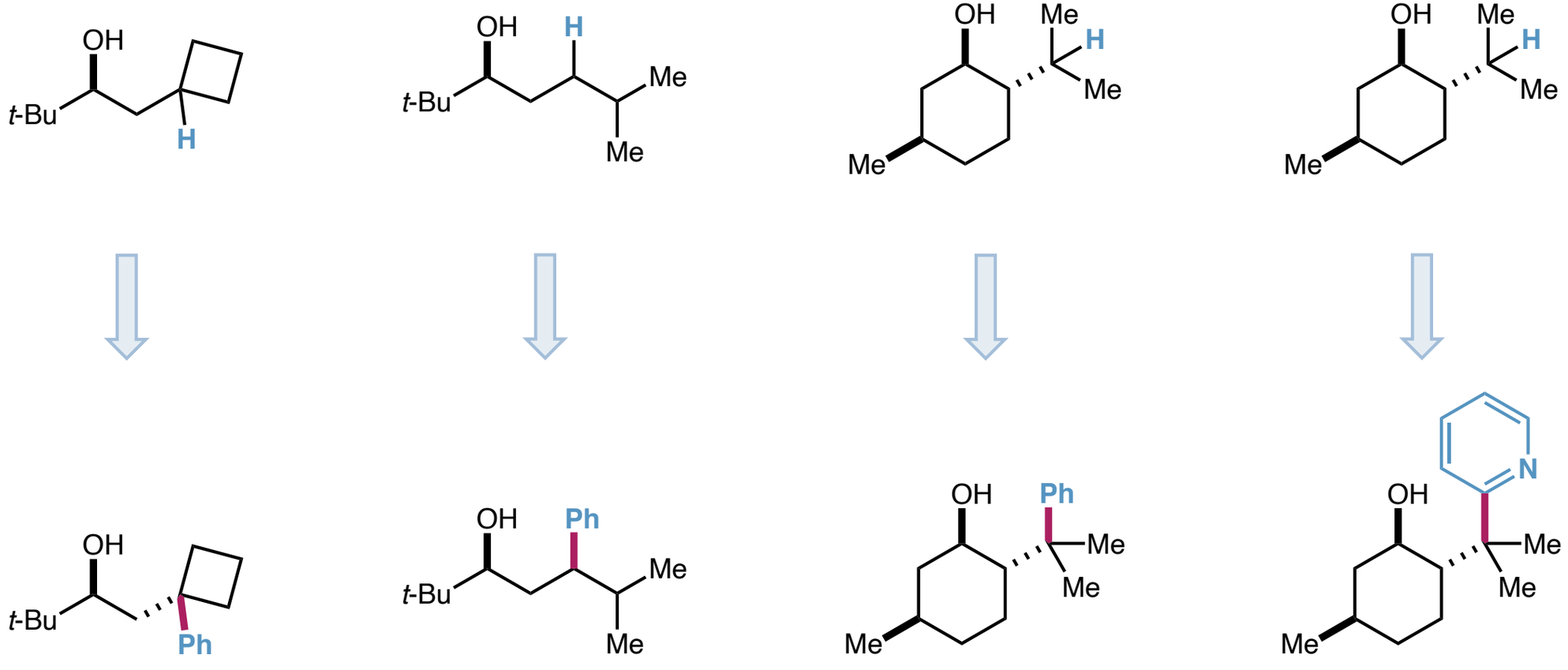
(Hetero)arene Migration: From Carbon Radical to Sulfur Radical



Friese, F. W.; Muck-Lichtenfeld, C.; Studer, A. *Nat. Commun.* **2018**, *9*, 2808

(Hetero)arene Migration: From Carbon Radical to Sulfur Radical





62% yield

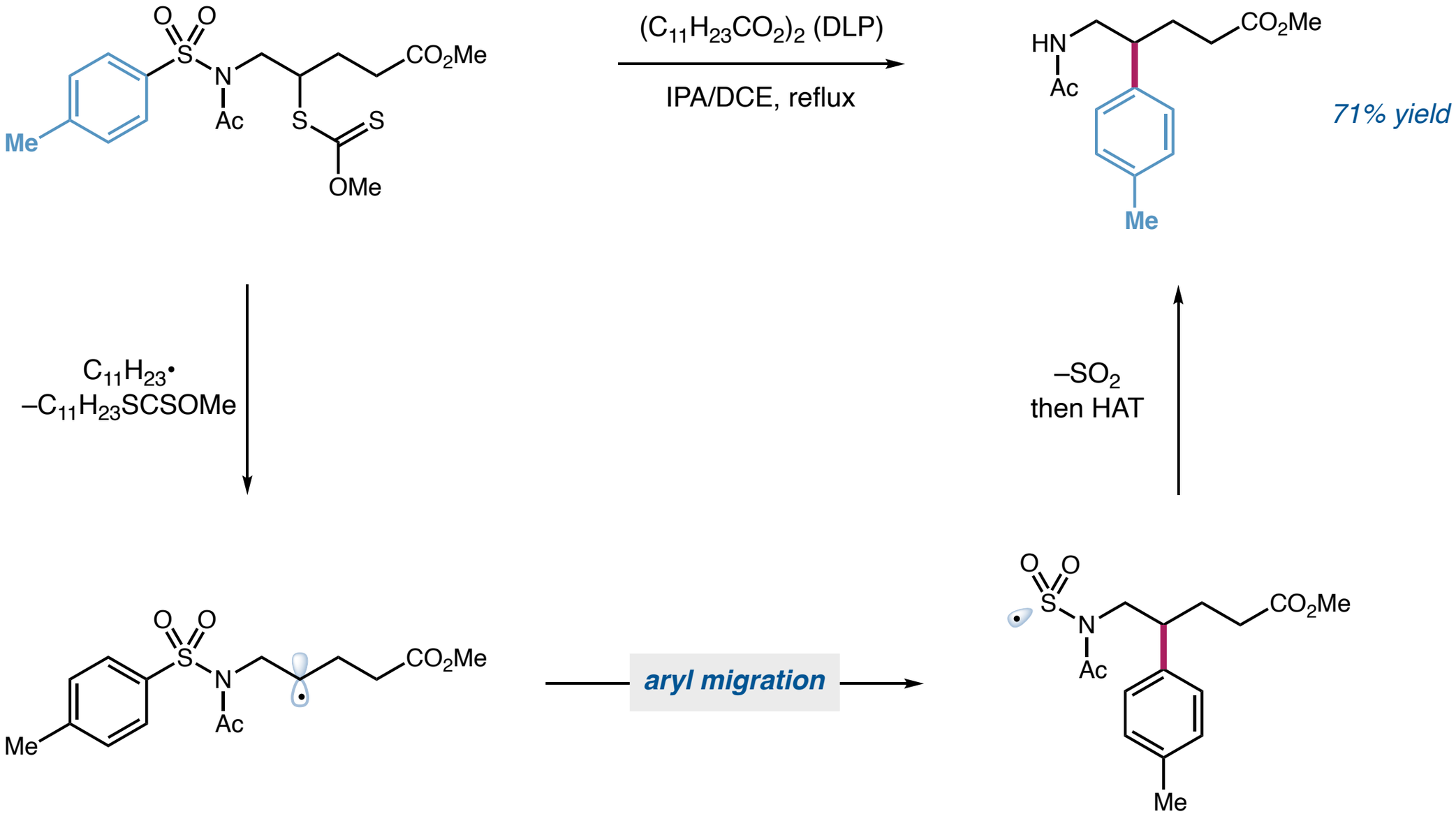
43% yield, d.r. = 10:1

65% yield

46% yield

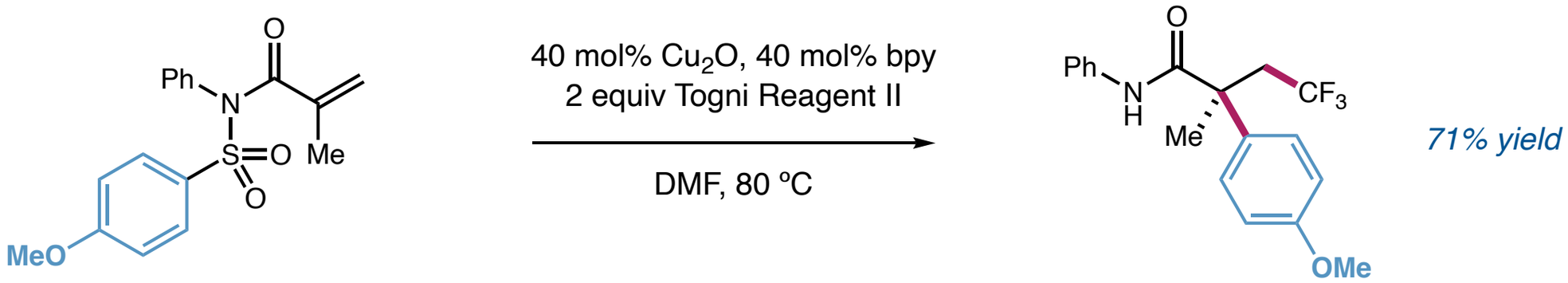
Friese, F. W.; Muck-Lichtenfeld, C.; Studer, A. *Nat. Commun.* **2018**, *9*, 2808

(Hetero)arene Migration: From Carbon Radical to Sulfur Radical



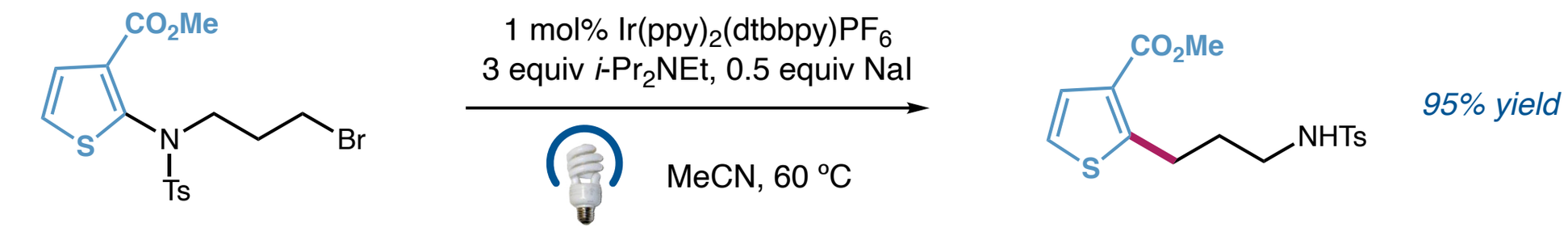
Gheorghe, A.; Quiclet-Sire, B.; Vila, X.; Zard, S. Z. *Org. Lett.* **2005**, *7*, 1653

(Hetero)arene Migration: From Carbon Radical to Sulfur Radical



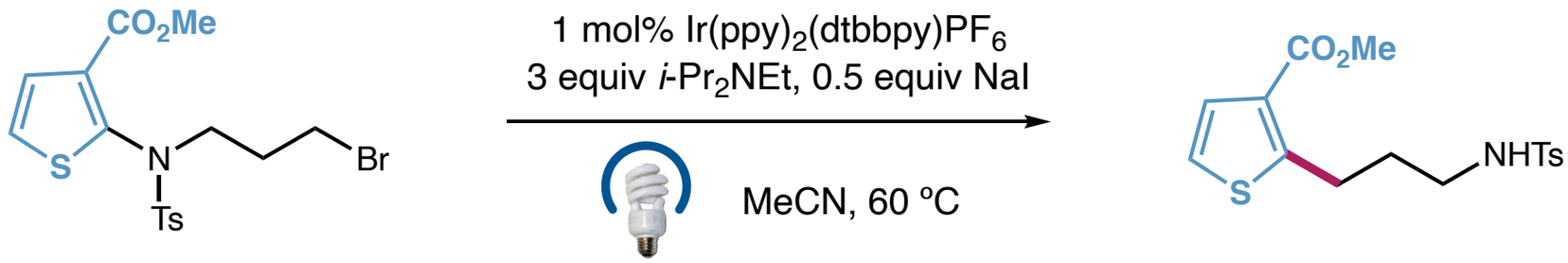
Kong, W.; Casimiro, M.; Merino, E.; Nevado, C. *J. Am. Chem. Soc.* **2013**, *135*, 14480

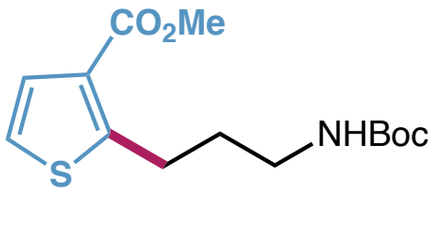
(Hetero)arene Migration: From Carbon Radical to Nitrogen Radical



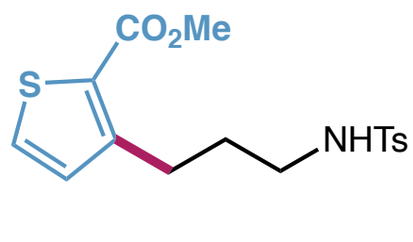
Alpers, D.; Cole, K. P.; Stephenson, C. R. J. *Angew. Chem. Int. Ed.* **2018**, *57*, 12167

(Hetero)arene Migration: From Carbon Radical to Nitrogen Radical

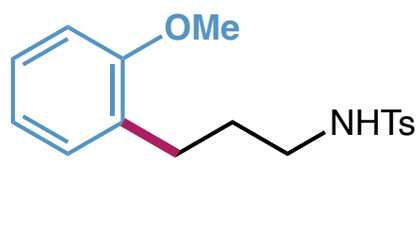




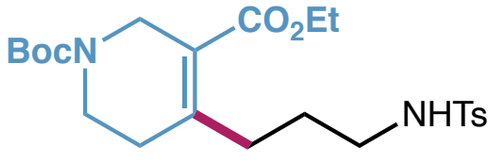
67% yield



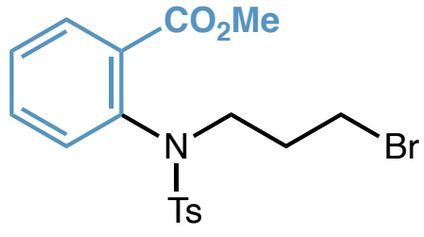
76% yield



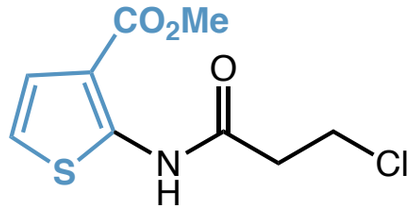
45% yield



69% yield



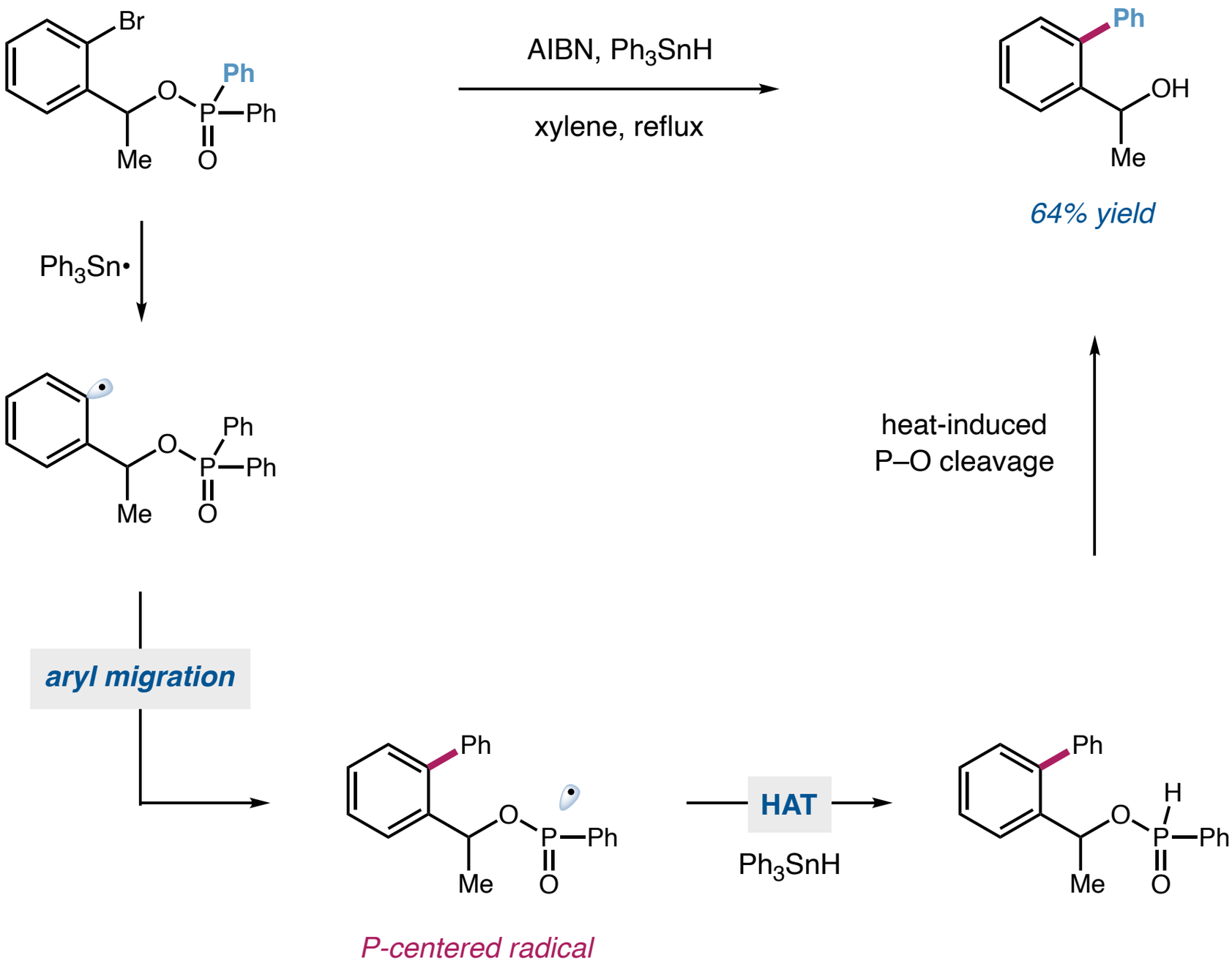
no product



no product

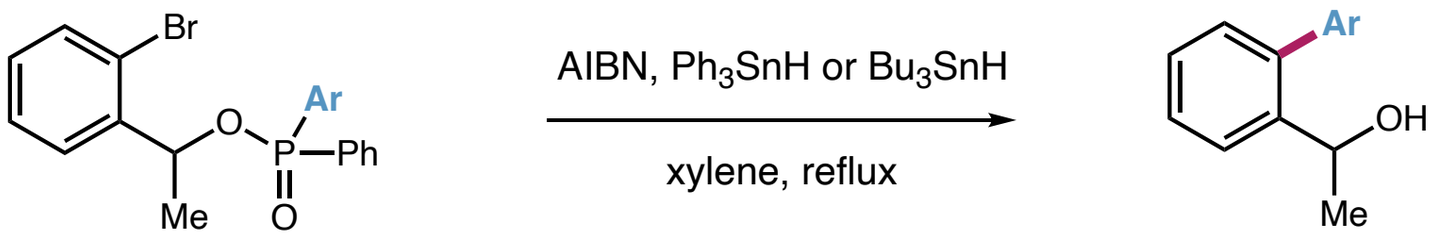
Alpers, D.; Cole, K. P.; Stephenson, C. R. J. *Angew. Chem. Int. Ed.* **2018**, *57*, 12167

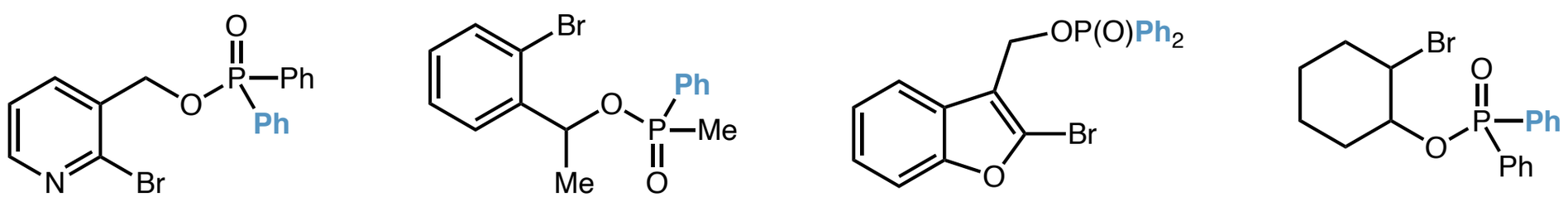
(Hetero)arene Migration: From Carbon Radical to P-Centered Radical

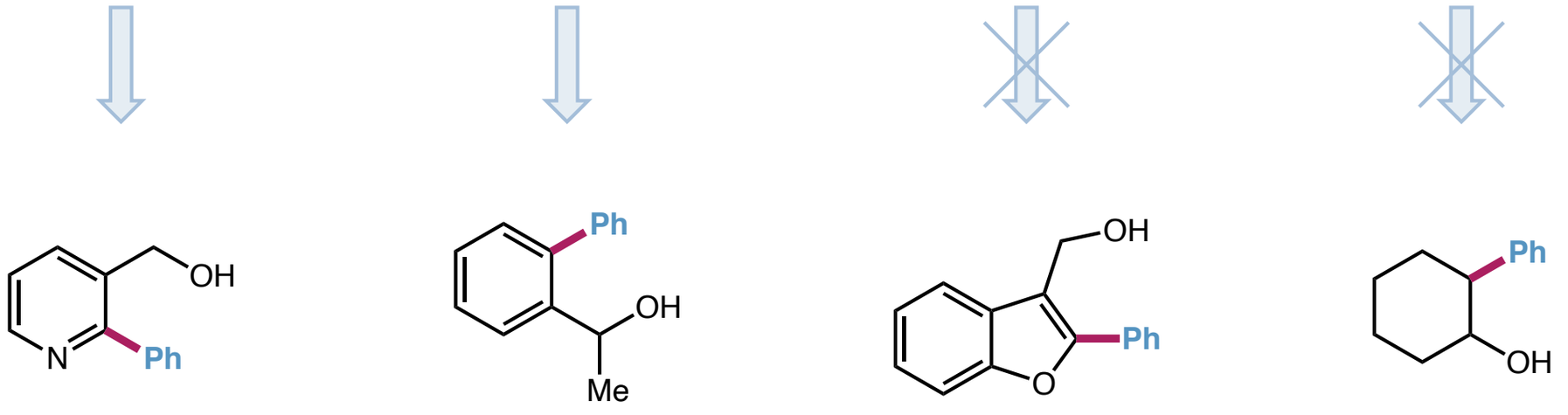


Clive, D. L. J.; Kang, S. *Tetrahedron Lett.* **2000**, *41*, 1315
Clive, D. L. J.; Kang, S. *J. Org. Chem.* **2001**, *66*, 6083

(Hetero)arene Migration: From Carbon Radical to P-Centered Radical



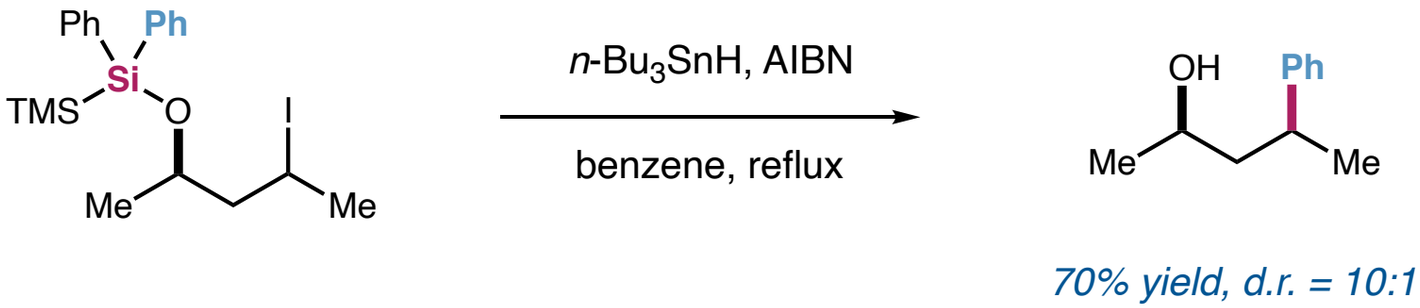




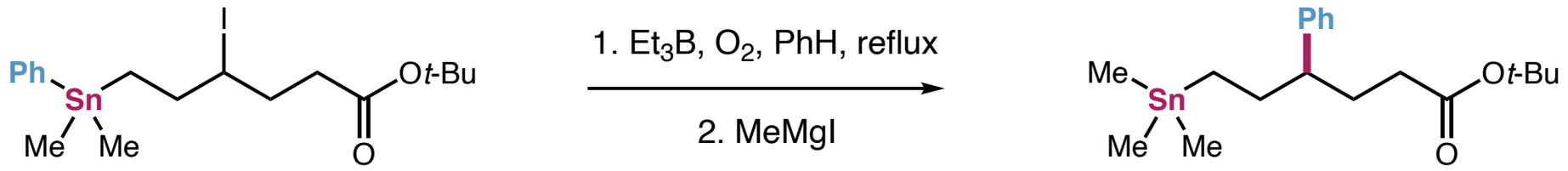
41% yield *73% yield* *not observed* *not observed*

Clive, D. L. J.; Kang, S. *Tetrahedron Lett.* **2000**, *41*, 1315
Clive, D. L. J.; Kang, S. *J. Org. Chem.* **2001**, *66*, 6083

(Hetero)arene Migration: From Carbon Radical to Si or Sn-Centered Radical



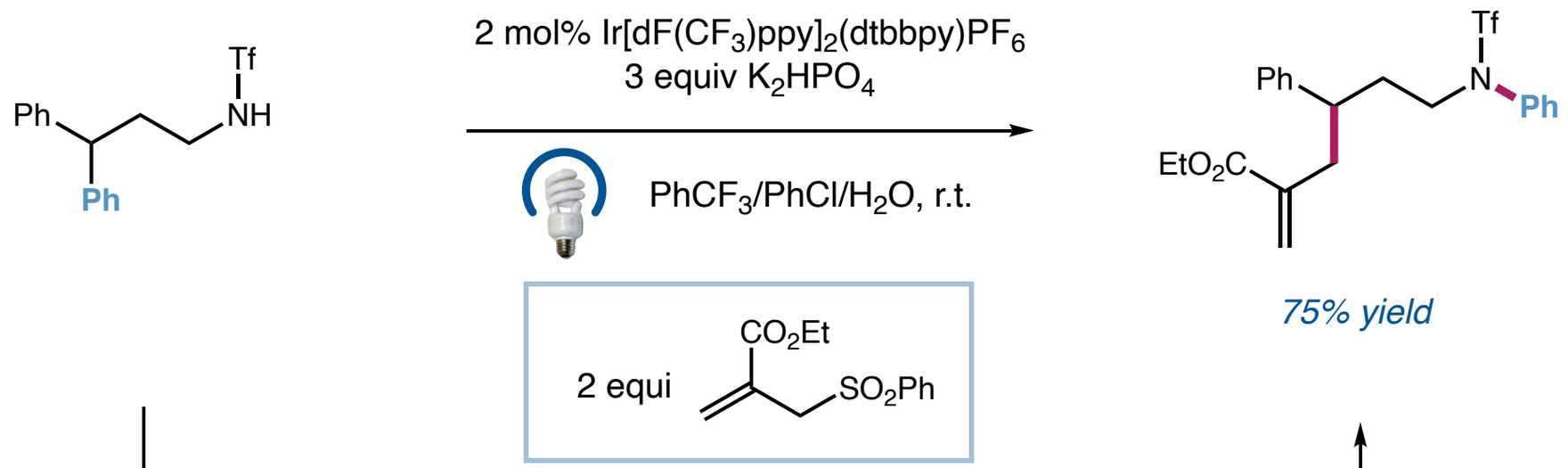
70% yield, d.r. = 10:1



53% yield

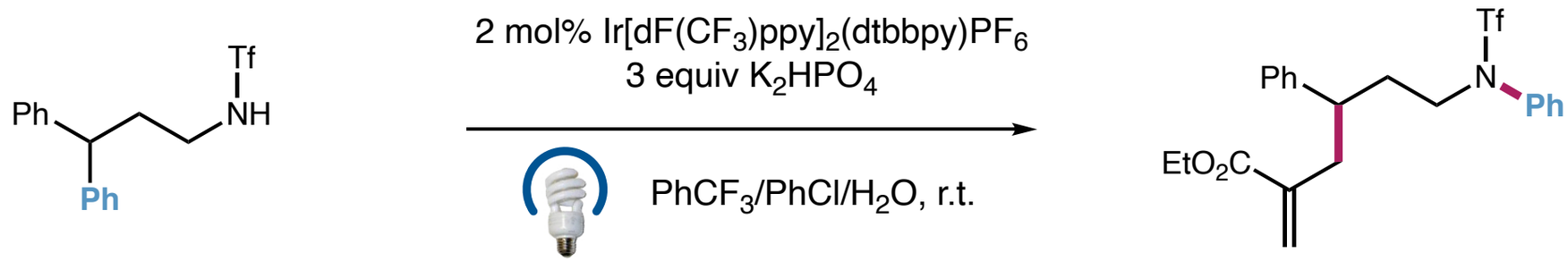
Amrein, S.; Bossart, M.; Vasella, T.; Studer, A. *J. Org. Chem.* **2000**, *65*, 4281
Wakabayashi, K.; Yorimitsu, H.; Shinoubu, H.; Oshima, K. *Org. Lett.* **2000**, *2*, 1899

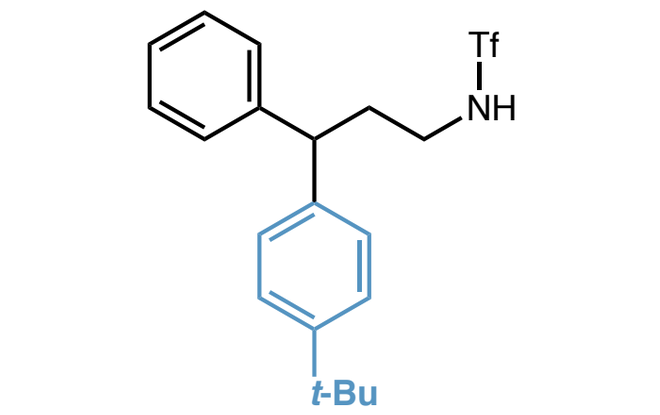
(Hetero)arene Migration: Other Types (N-radical to C-radical)

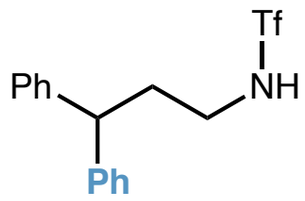


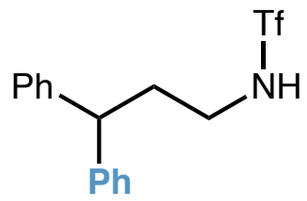
Shu, W.; Genoux, A.; Li, Z.; Nevado, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 10521

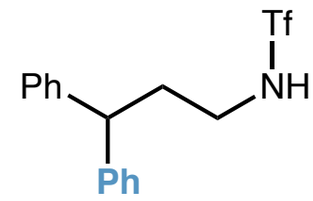
(Hetero)arene Migration: Other Types (N-radical to C-radical)

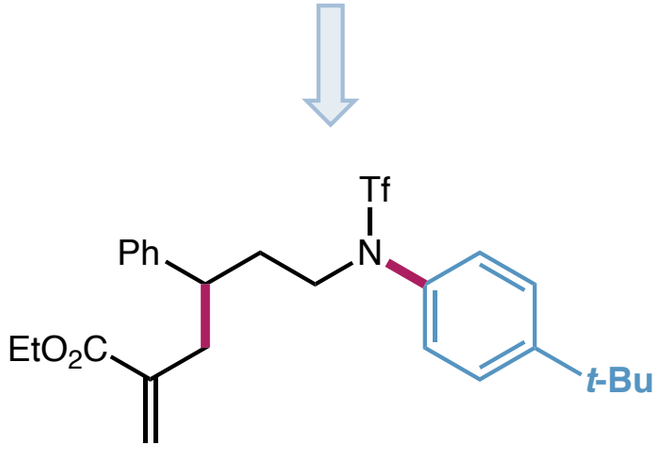




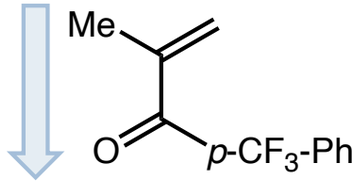


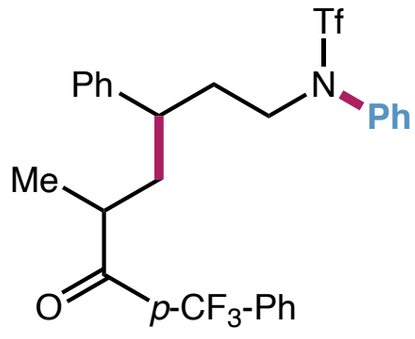




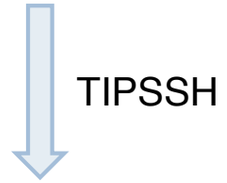


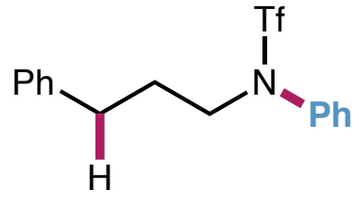
73% yield, 8:1 selectivity



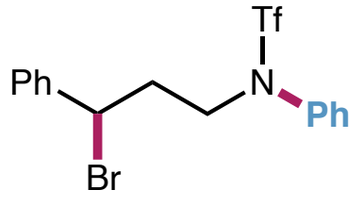


68% yield





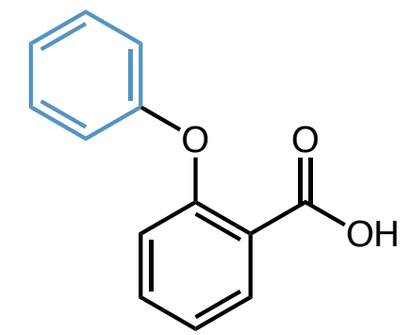
74% yield



53% yield

Shu, W.; Genoux, A.; Li, Z.; Nevado, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 10521

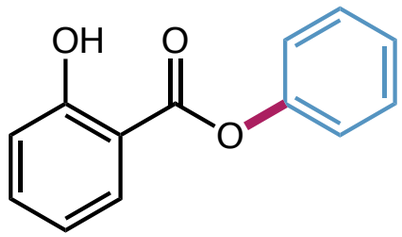
(Hetero)arene Migration: Other Types (O-radical to O-radical)



C–O BDE: ~79 kcal/mol

1 mol% Mes-Acr (ClO_4)
10 mol% K_2HPO_4

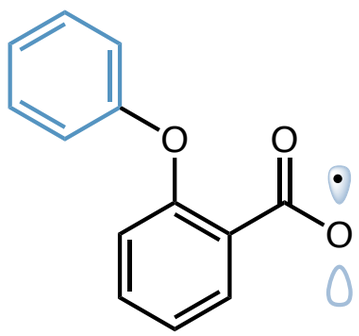
MeCN, r.t.



92% yield

C–O BDE: ~90 kcal/mol

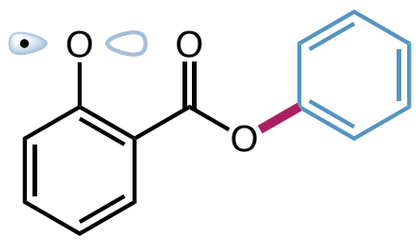
PCET



O-centered radical

aryl migration

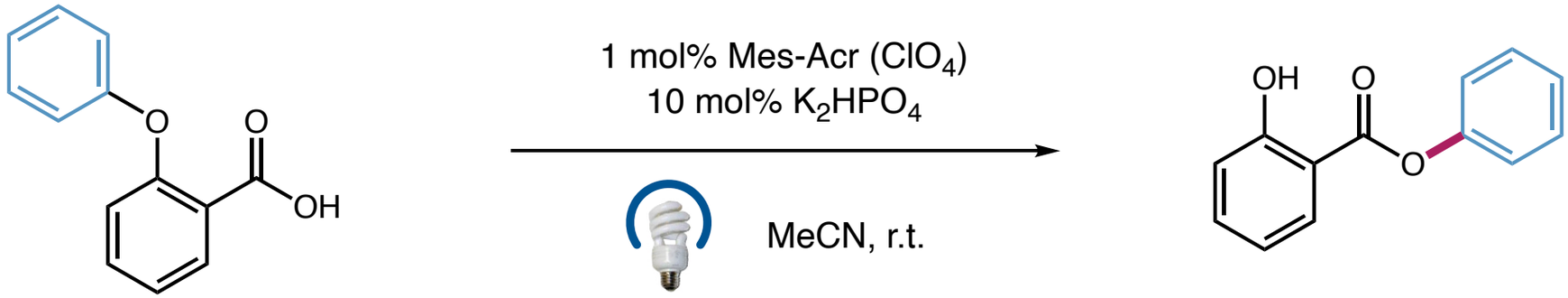
SET $+H^+$

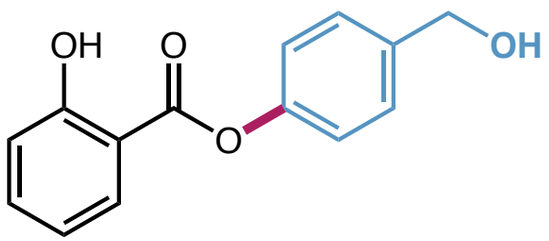


O-centered radical

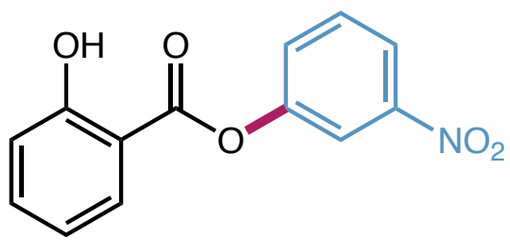
Wang, S.-F.; Cao, X.-P.; Li, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 13809

(Hetero)arene Migration: Other Types (O-radical to O-radical)

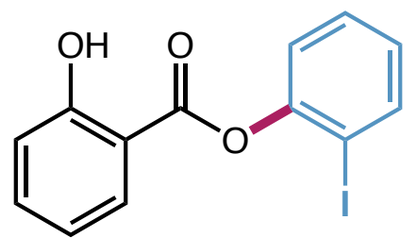




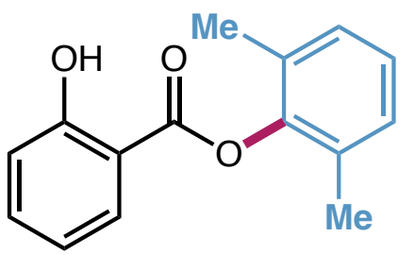
82% yield



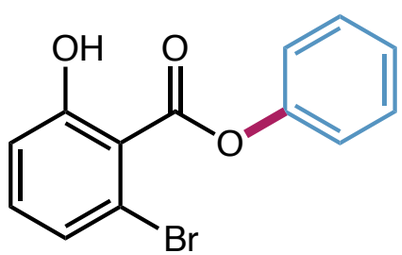
76% yield



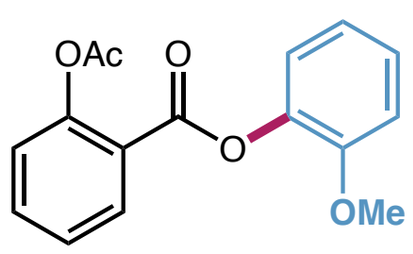
78% yield



80% yield



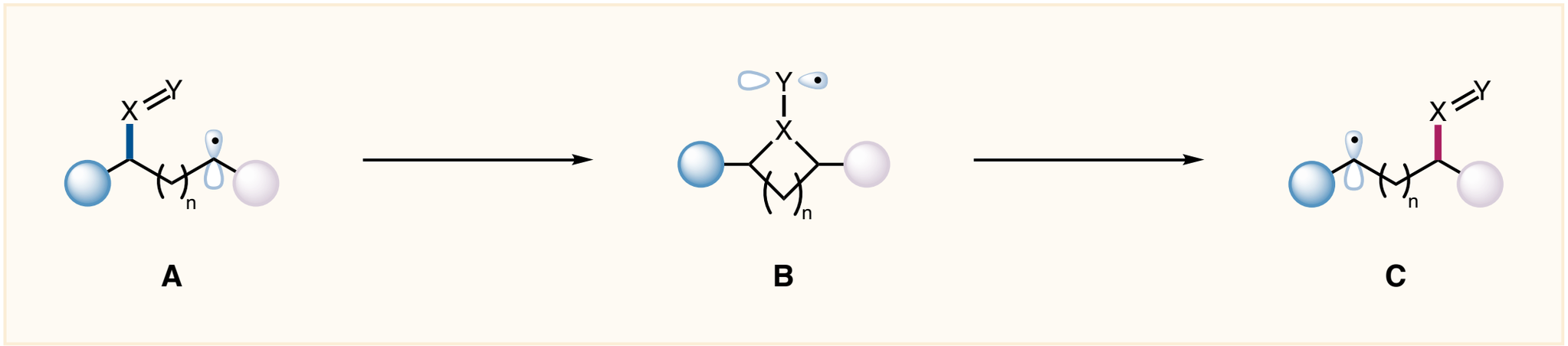
51% yield



Guacetisal
92% yield (2 steps, >1 g)

Wang, S.-F.; Cao, X.-P.; Li, Y. *Angew. Chem. Int. Ed.* **2017**, *56*, 13809

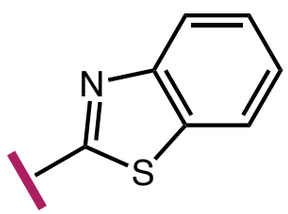
Migratory FG Modification via Radical Intermediates



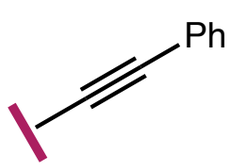
- Driving force: formation of more stable radicals (**C** vs. **A**); an ***irreversible*** downstream reaction from **C**

- Spatial requirement (aka, parameter **n**): 1,2-, 1,4-, and 1,5-migration

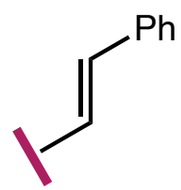
- FGs that can undergo radical migration



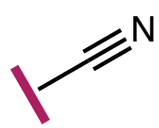
(hetero)arene



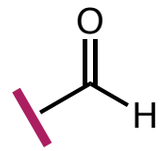
alkyne



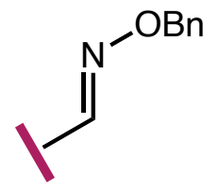
alkene



cyano



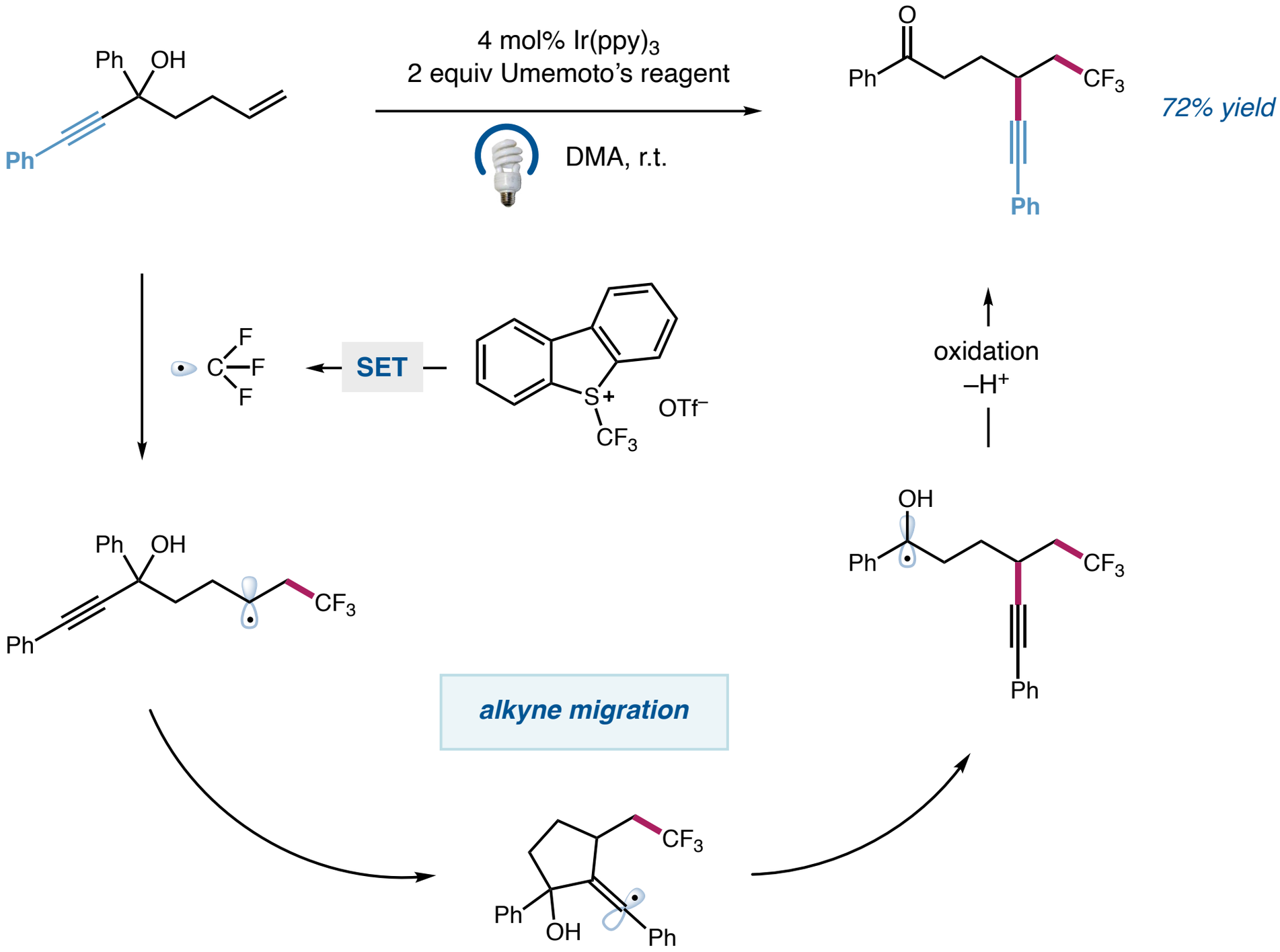
formyl



imino

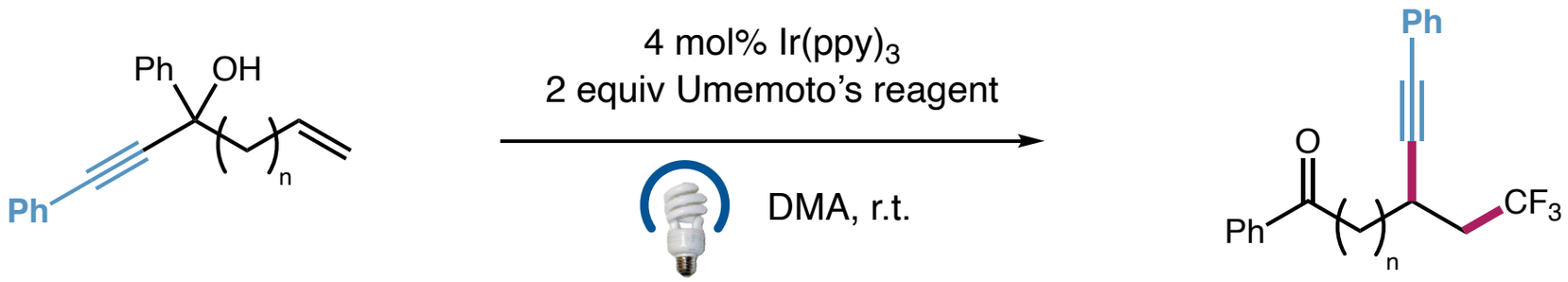
Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649
Li, W.; Xu, W.; Xie, J.; Yu, S.; Zhu, C. *Chem. Soc. Rev.* **2018**, *47*, 654

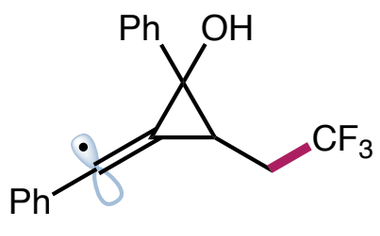
Alkyne Migration



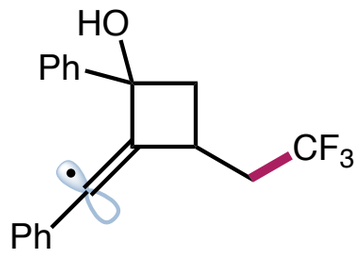
Xu, Y.; Wu, Z.; Jiang, J.; Ke, Z.; Zhu, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 4545

Alkyne Migration: Length of the Linker

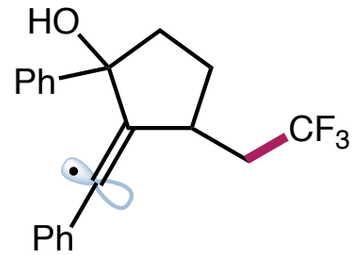




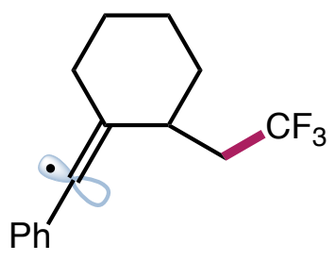
n = 0
<1% yield



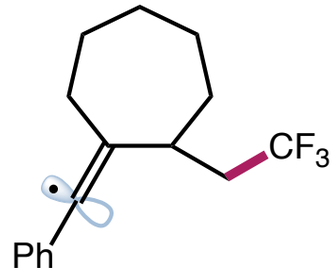
n = 1
<1% yield



n = 2
72% yield



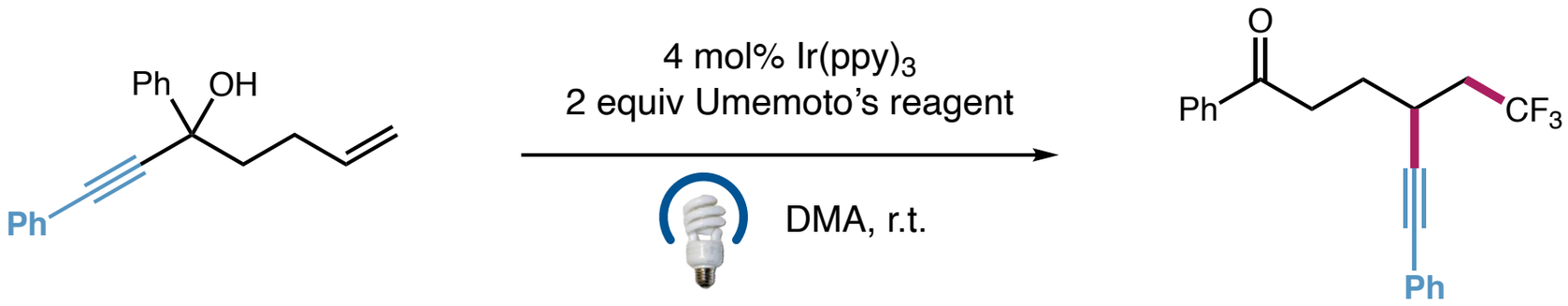
n = 3
61% yield

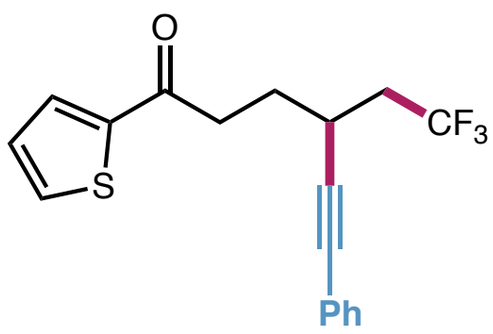


n = 4
<1% yield

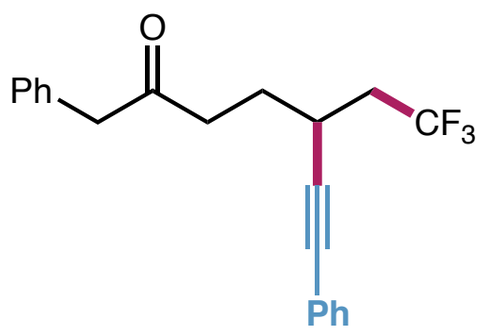
Xu, Y.; Wu, Z.; Jiang, J.; Ke, Z.; Zhu, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 4545

Alkyne Migration: Scope

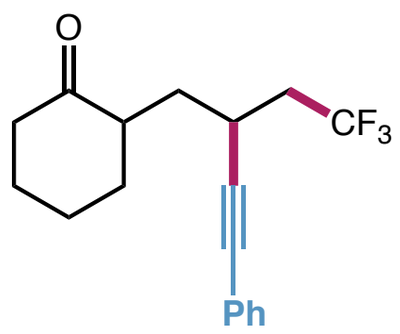




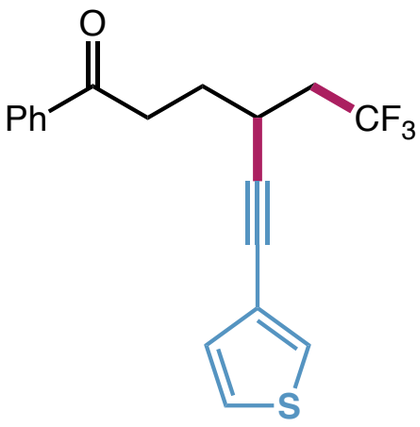
66% yield



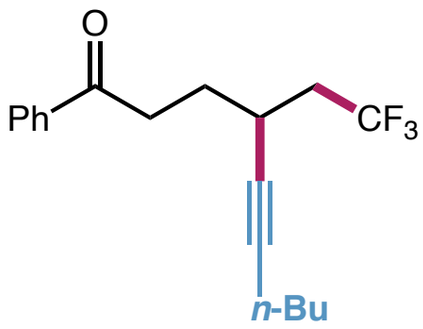
70% yield



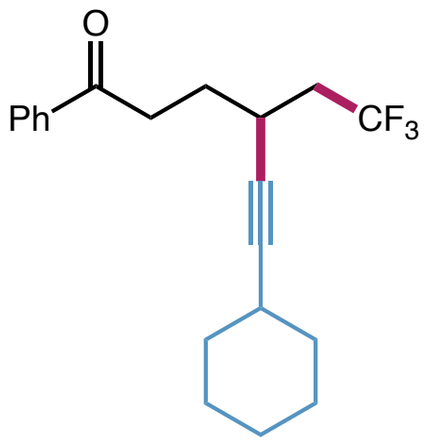
70% yield



50% yield



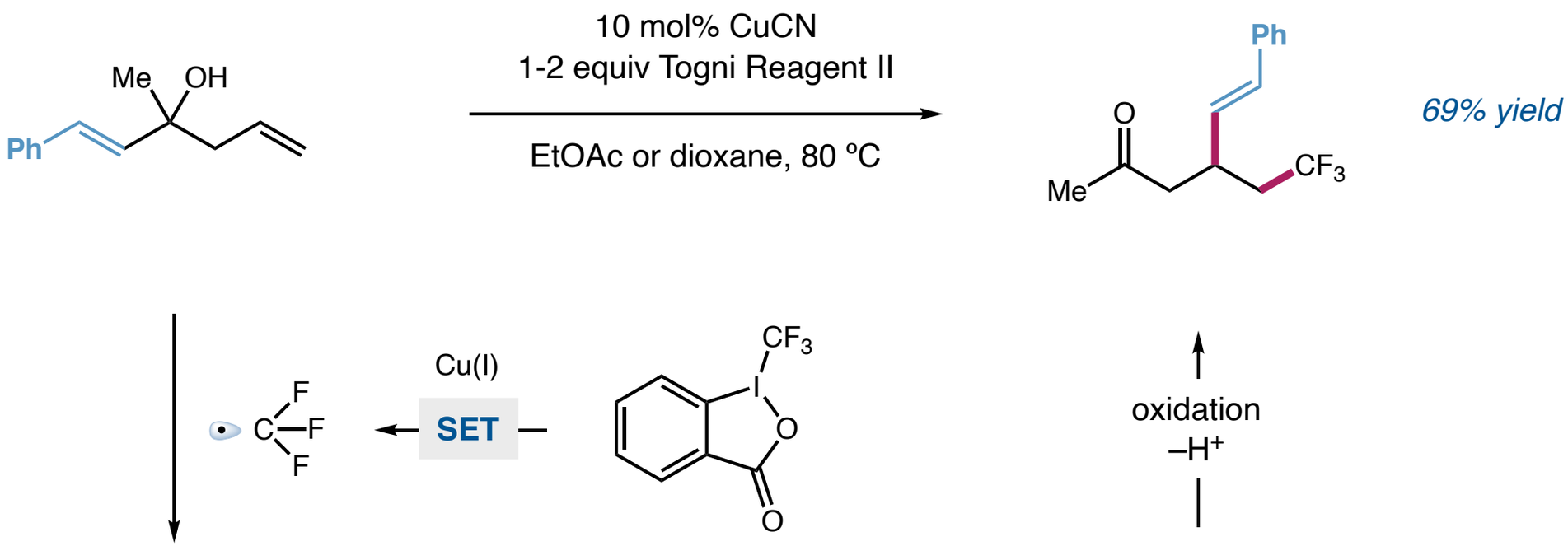
47% yield

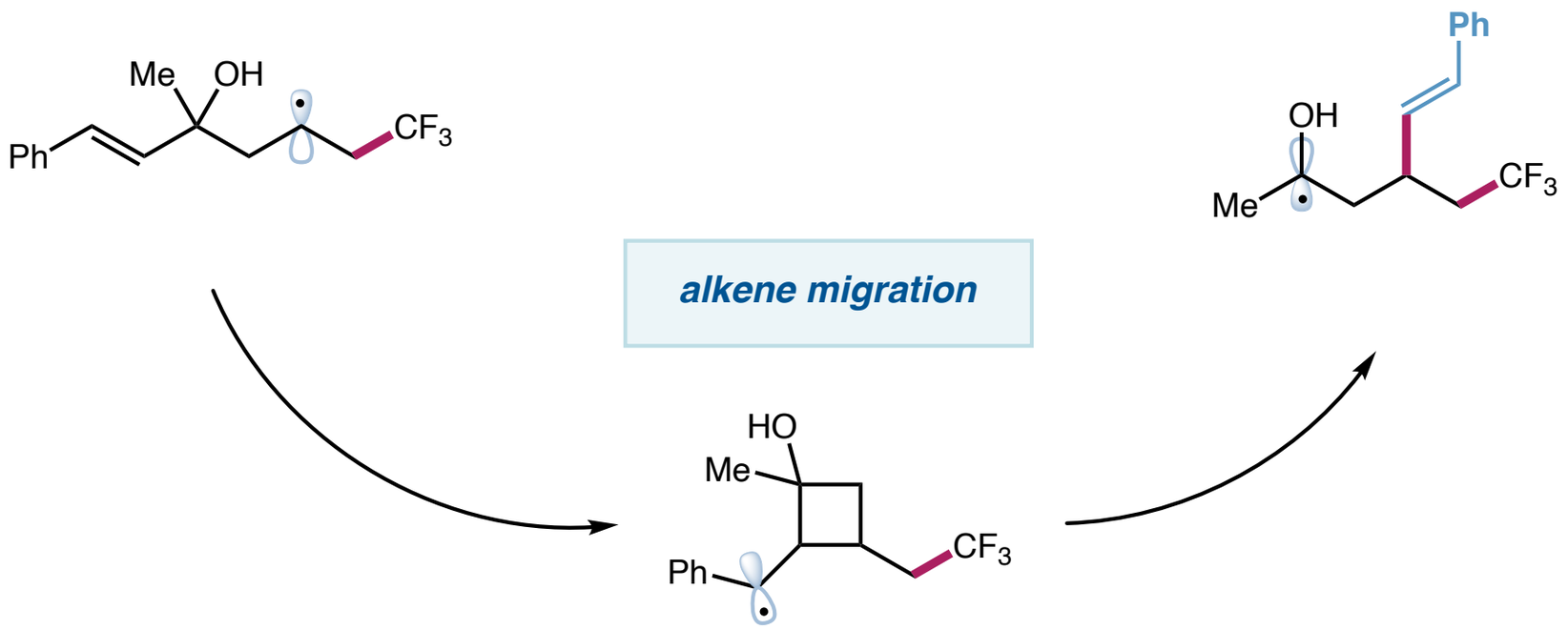


40% yield

Xu, Y.; Wu, Z.; Jiang, J.; Ke, Z.; Zhu, C. *Angew. Chem. Int. Ed.* **2017**, *56*, 4545

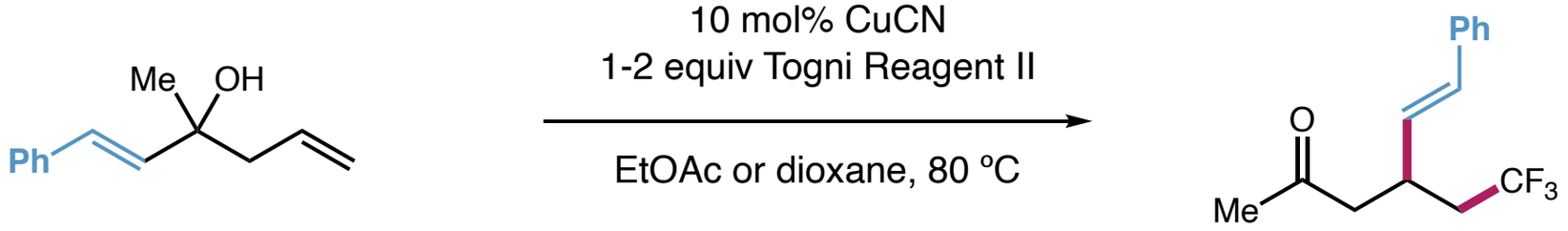
Alkene Migration

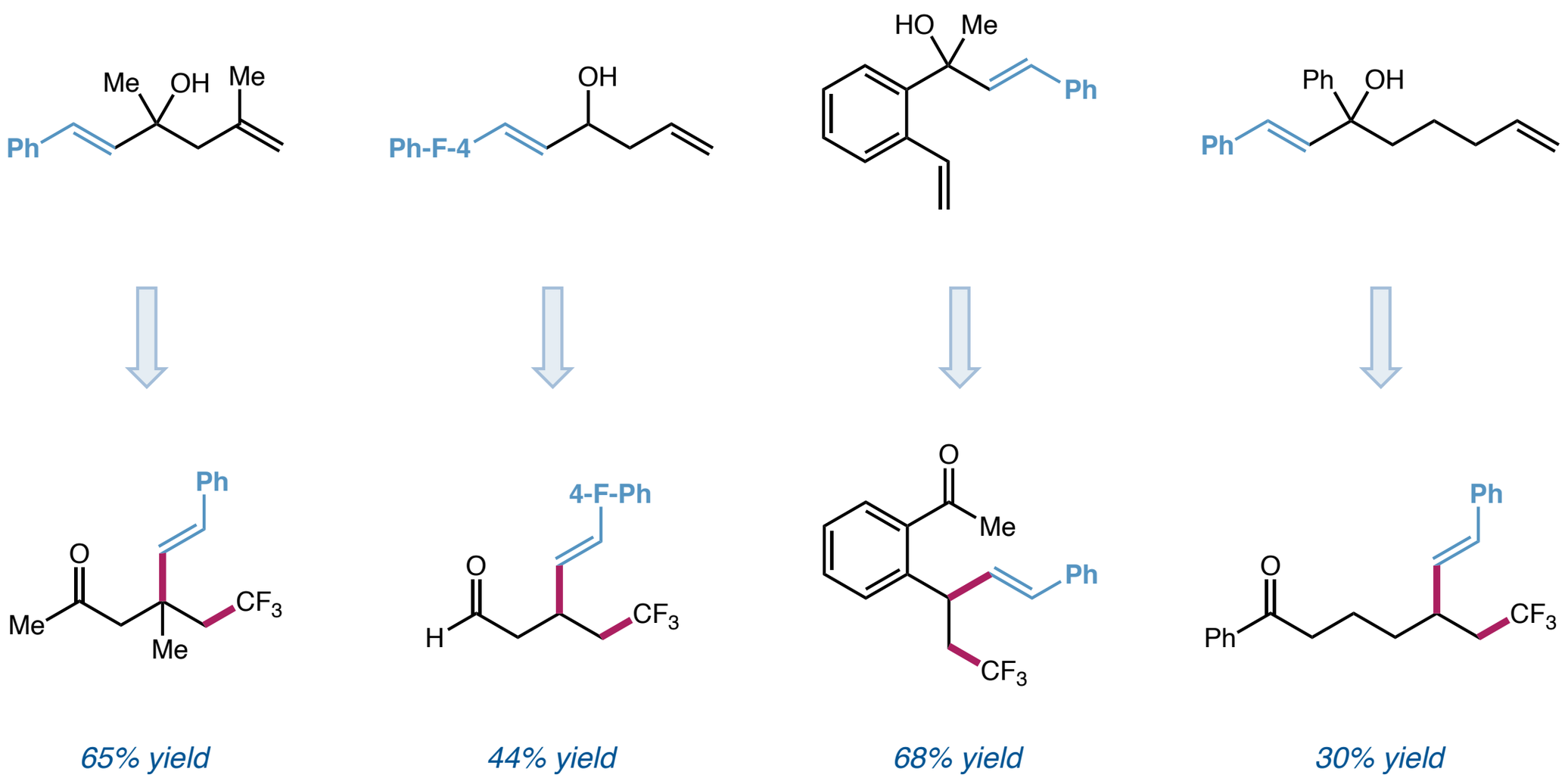




Li, L.; Li, Z.-L.; Gu, Q.-S.; Wang, N.; Liu, X.-Y. *Sci. Adv.* **2017**, *3*, e1701487

Alkene Migration: Scope, Part 1

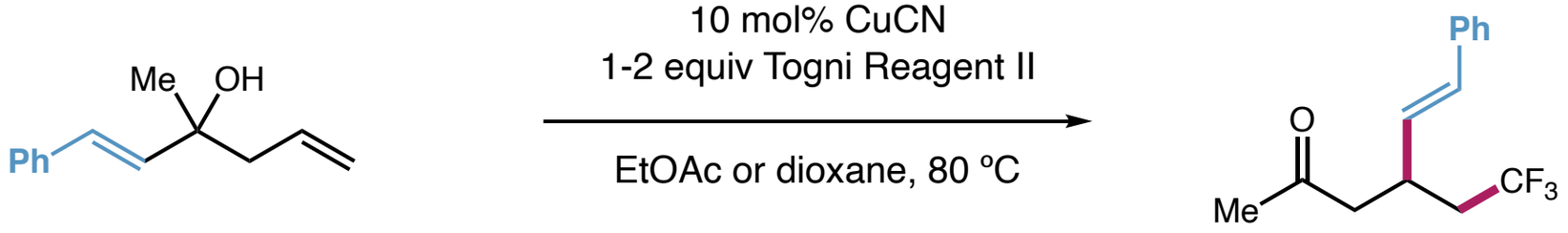


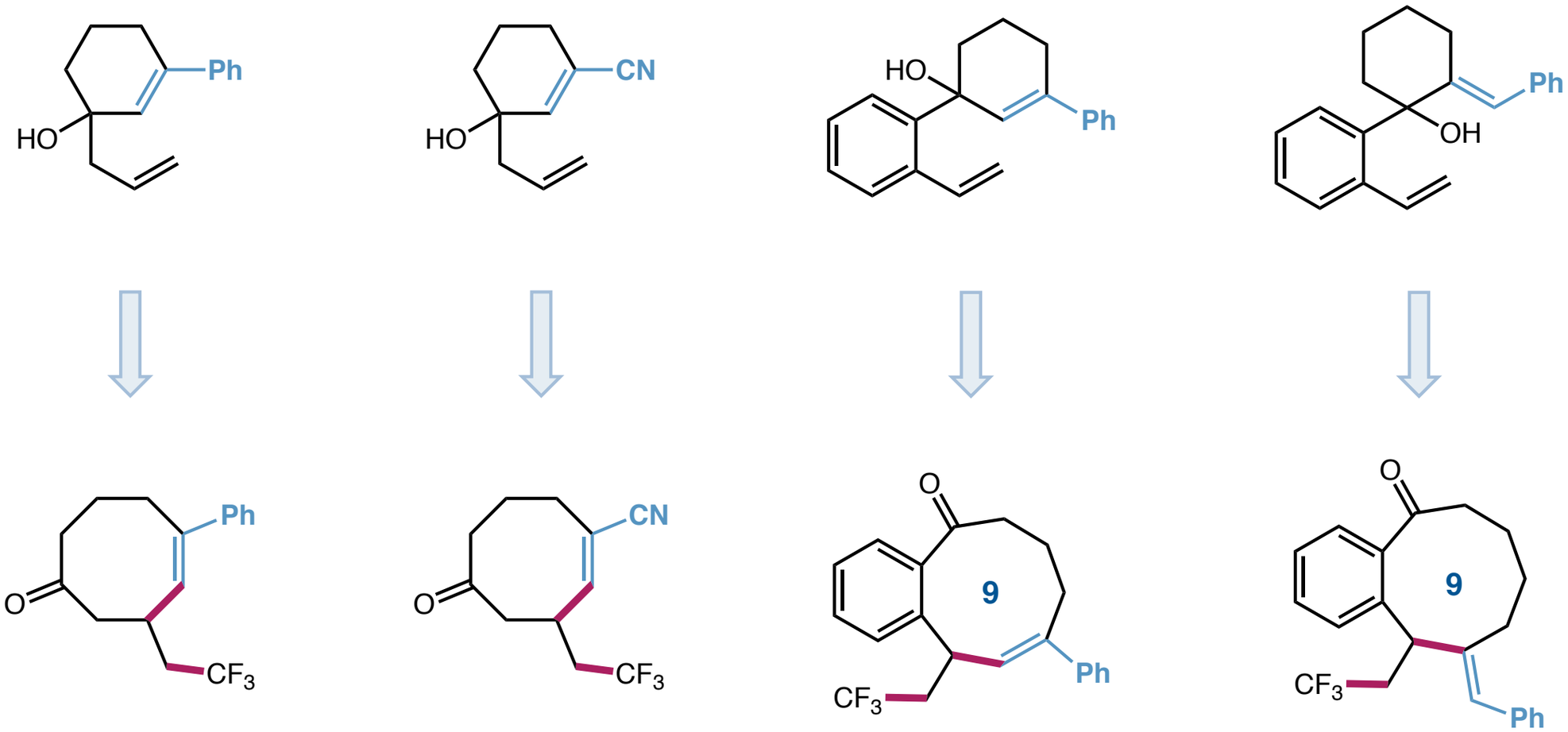


65% yield *44% yield* *68% yield* *30% yield*

Li, L.; Li, Z.-L.; Gu, Q.-S.; Wang, N.; Liu, X.-Y. *Sci. Adv.* **2017**, *3*, e1701487

Alkene Migration: Scope, Part 2

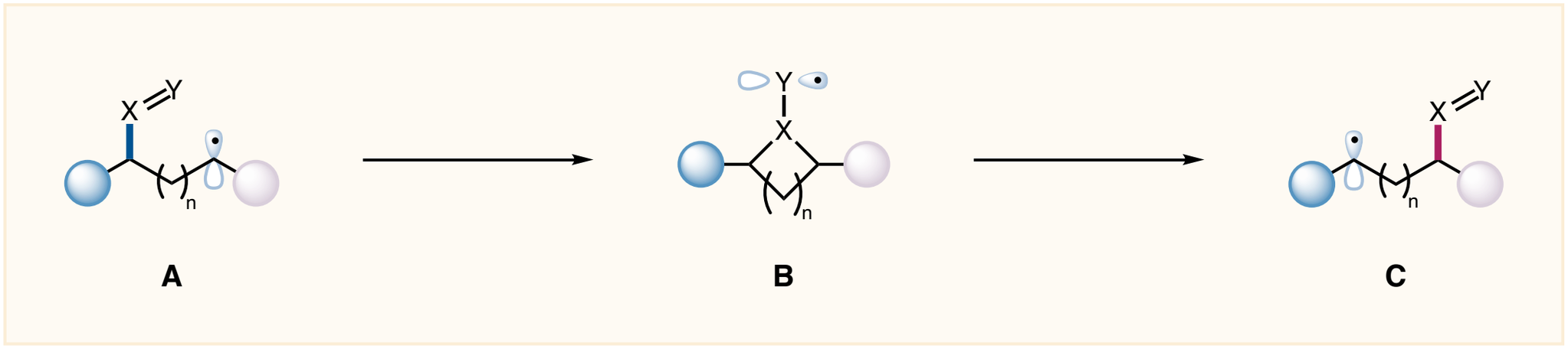




65% yield *58% yield* *46% yield* *60% yield, 5:1 E/Z*

Li, L.; Li, Z.-L.; Gu, Q.-S.; Wang, N.; Liu, X.-Y. *Sci. Adv.* **2017**, *3*, e1701487

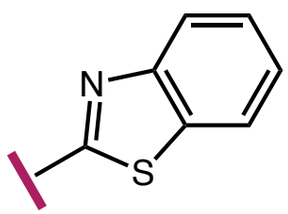
Migratory FG Modification via Radical Intermediates



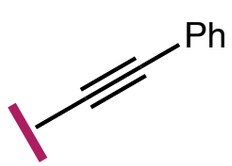
- Driving force: formation of more stable radicals (**C** vs. **A**); an ***irreversible*** downstream reaction from **C**

- Spatial requirement (aka, parameter **n**): 1,2-, 1,4-, and 1,5-migration

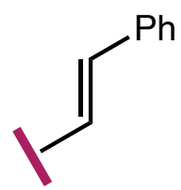
- FGs that can undergo radical migration



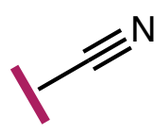
(hetero)arene



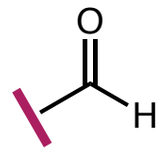
alkyne



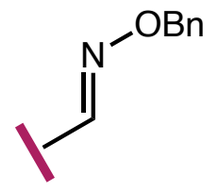
alkene



cyano



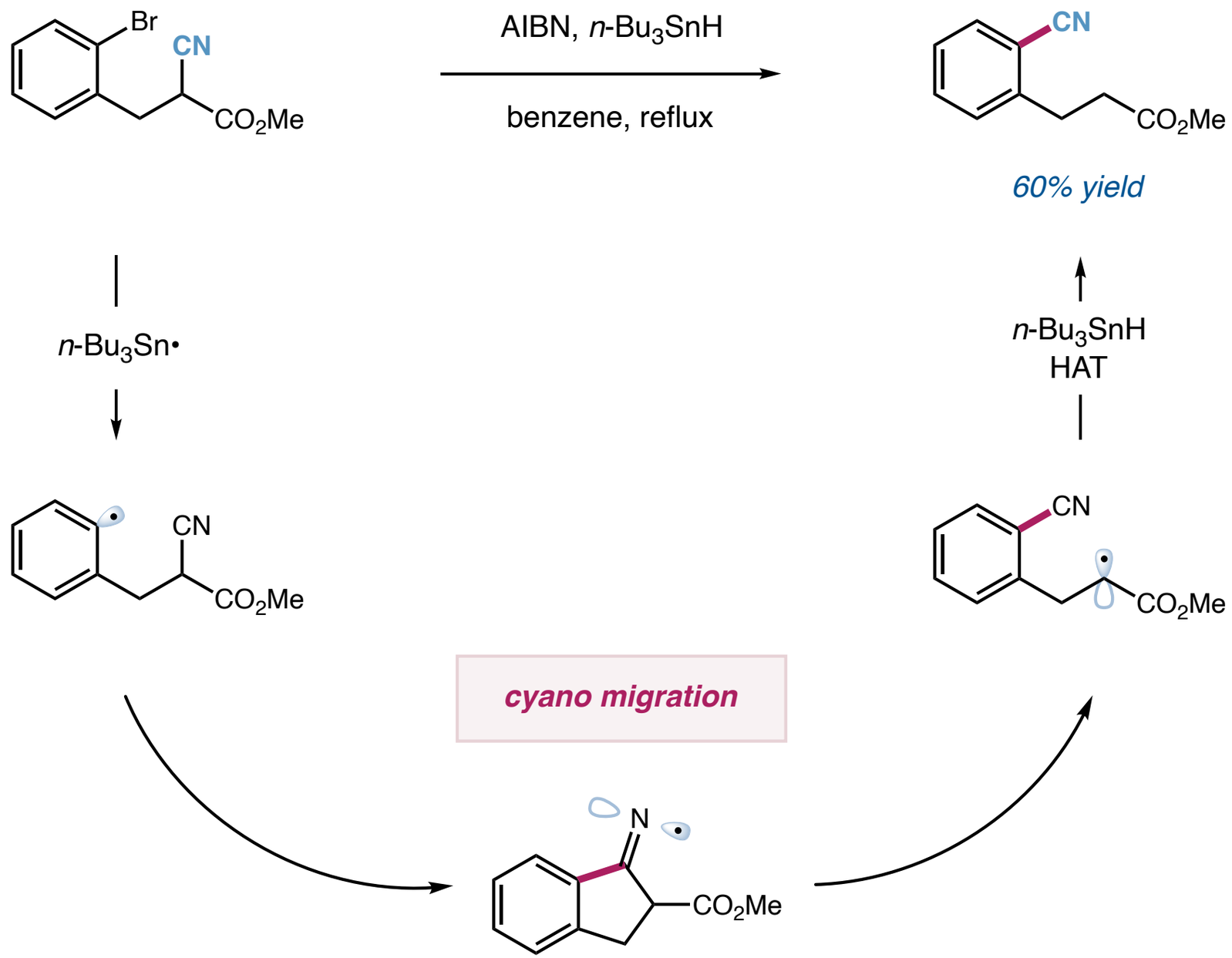
formyl



imino

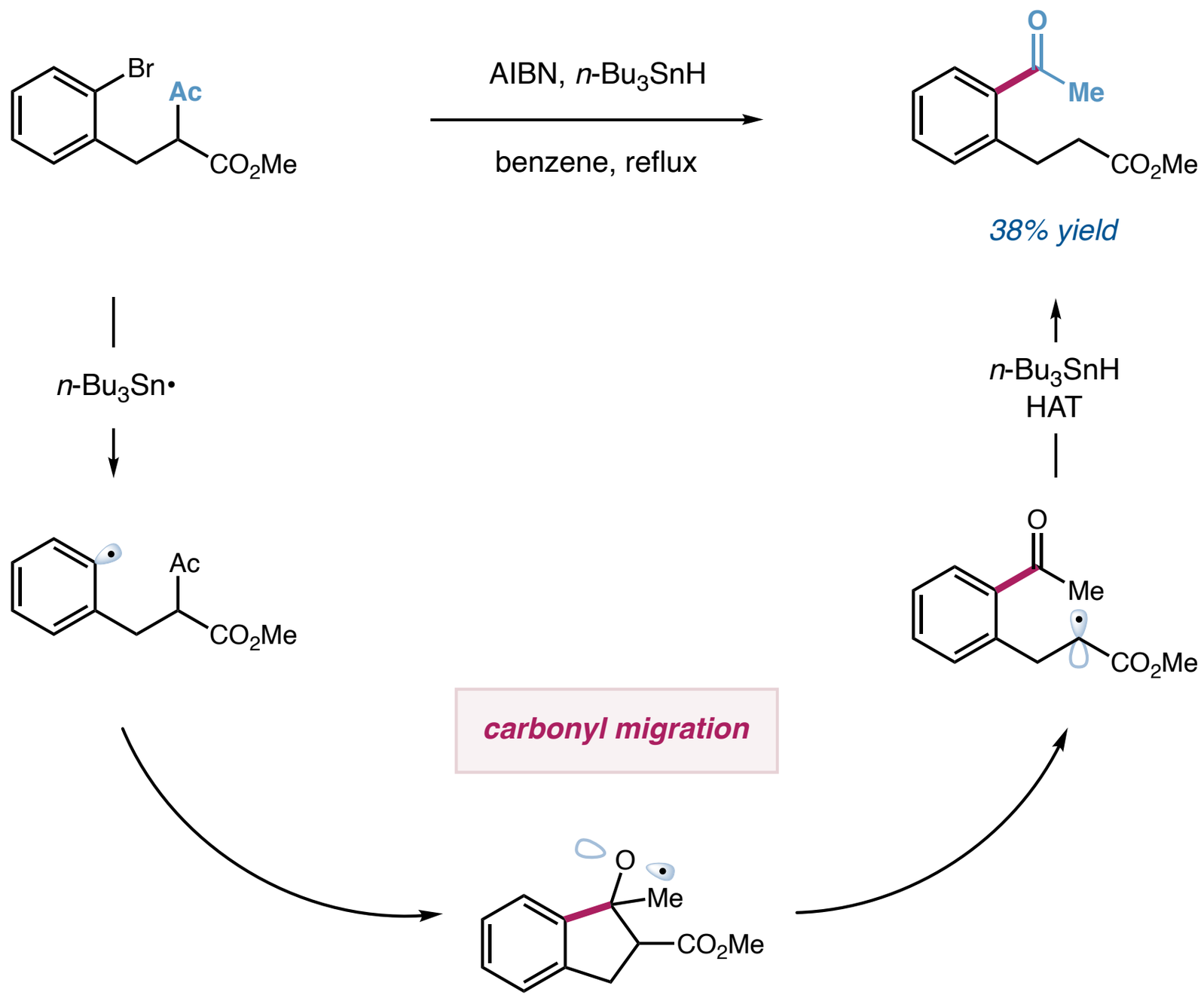
Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649
Li, W.; Xu, W.; Xie, J.; Yu, S.; Zhu, C. *Chem. Soc. Rev.* **2018**, *47*, 654

Migration of Cyano, Carbonyl, and Imino Groups: Early Studies



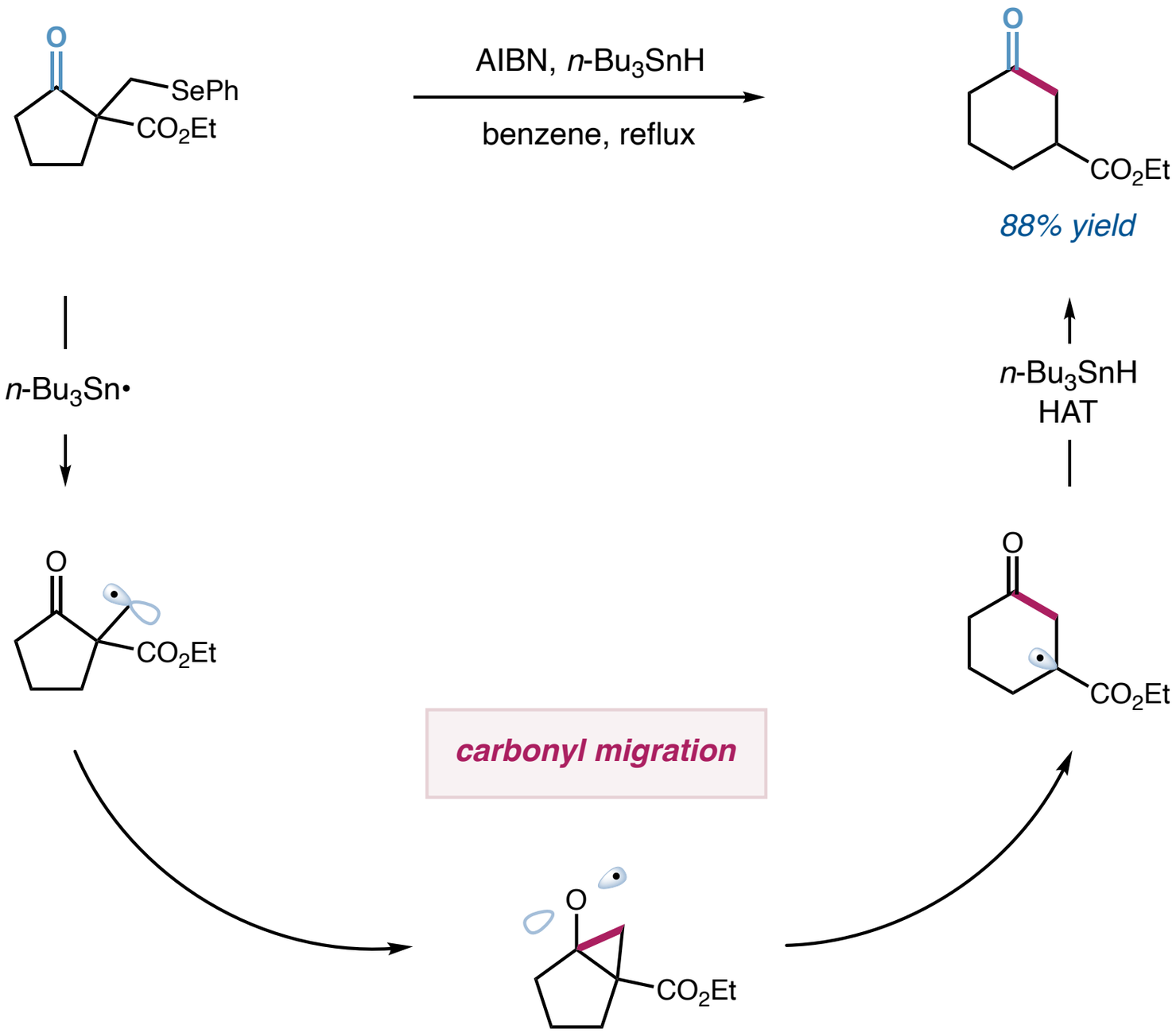
Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc. Chem. Commun.* **1987**, 666
Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565

Migration of Cyano, Carbonyl, and Imino Groups: Early Studies



Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc. Chem. Commun.* **1987**, 666
Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565

Migration of Cyano, Carbonyl, and Imino Groups: Early Studies

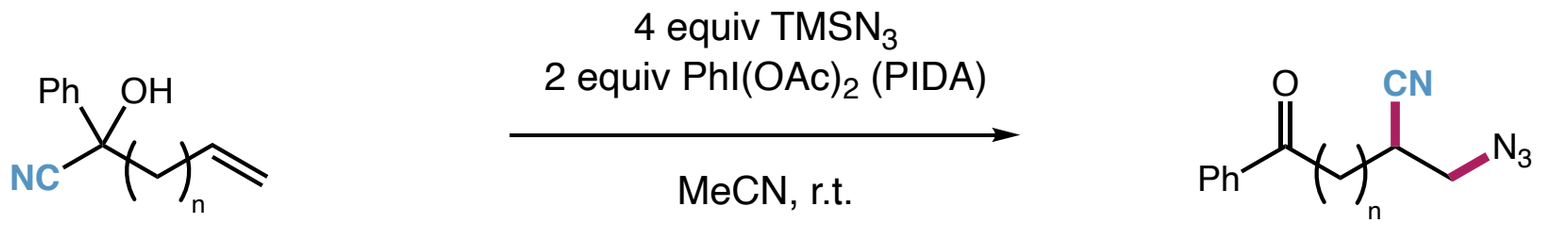


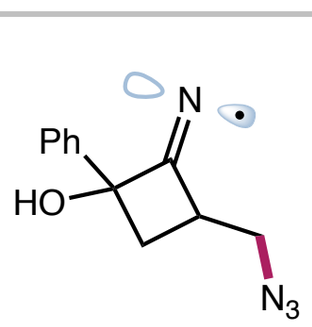
Beckwith, A. L. J.; O'Shea, D. M.; Gerba, S.; Westwood, S. W. *J. Chem. Soc. Chem. Commun.* **1987**, 666
Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565

Migration of Cyano Group

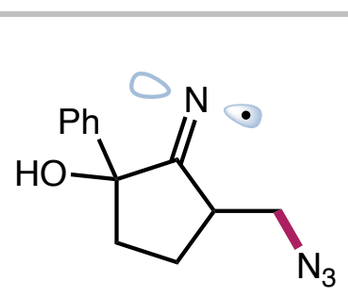
Wu,Z.; Ren, R.; Zhu, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 10821

Migration of Cyano Group: Length of the Linker

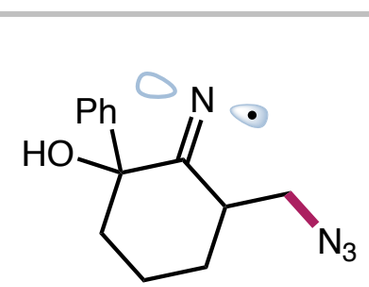




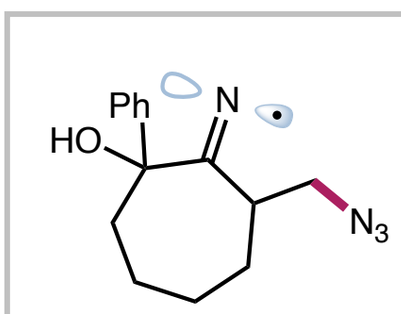
n = 1
23% yield



n = 2
85% yield



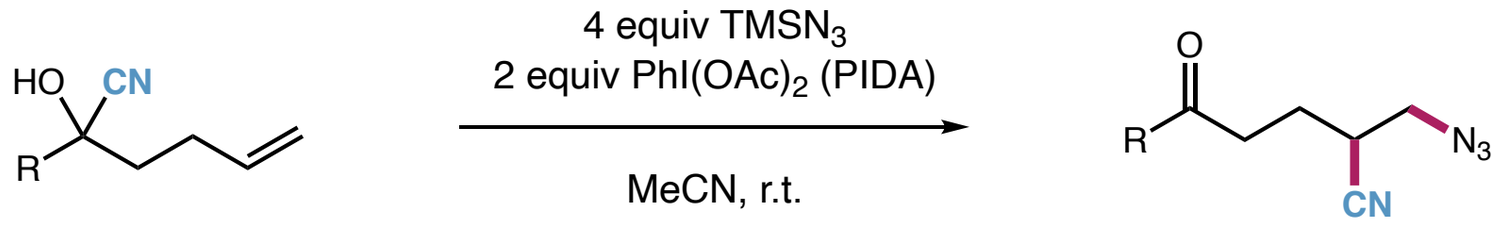
n = 3
66% yield

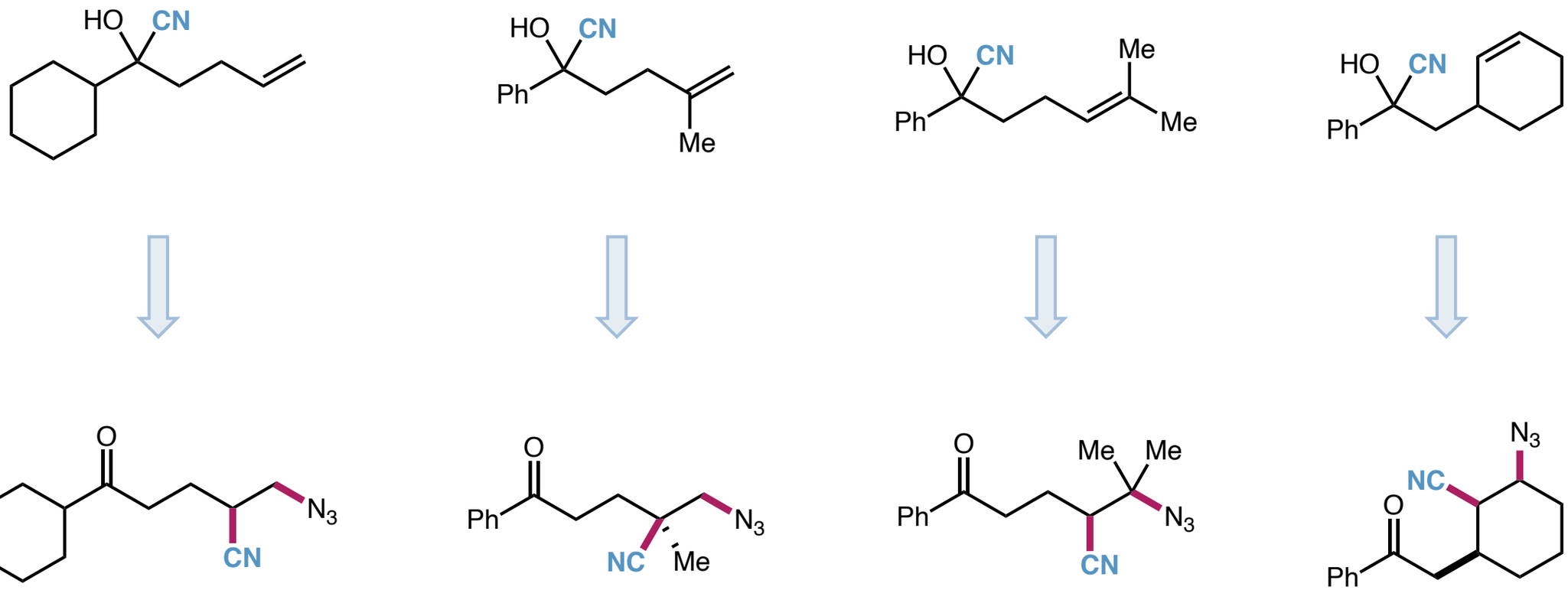


n = 4
<5% yield

Wu,Z.; Ren, R.; Zhu, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 10821

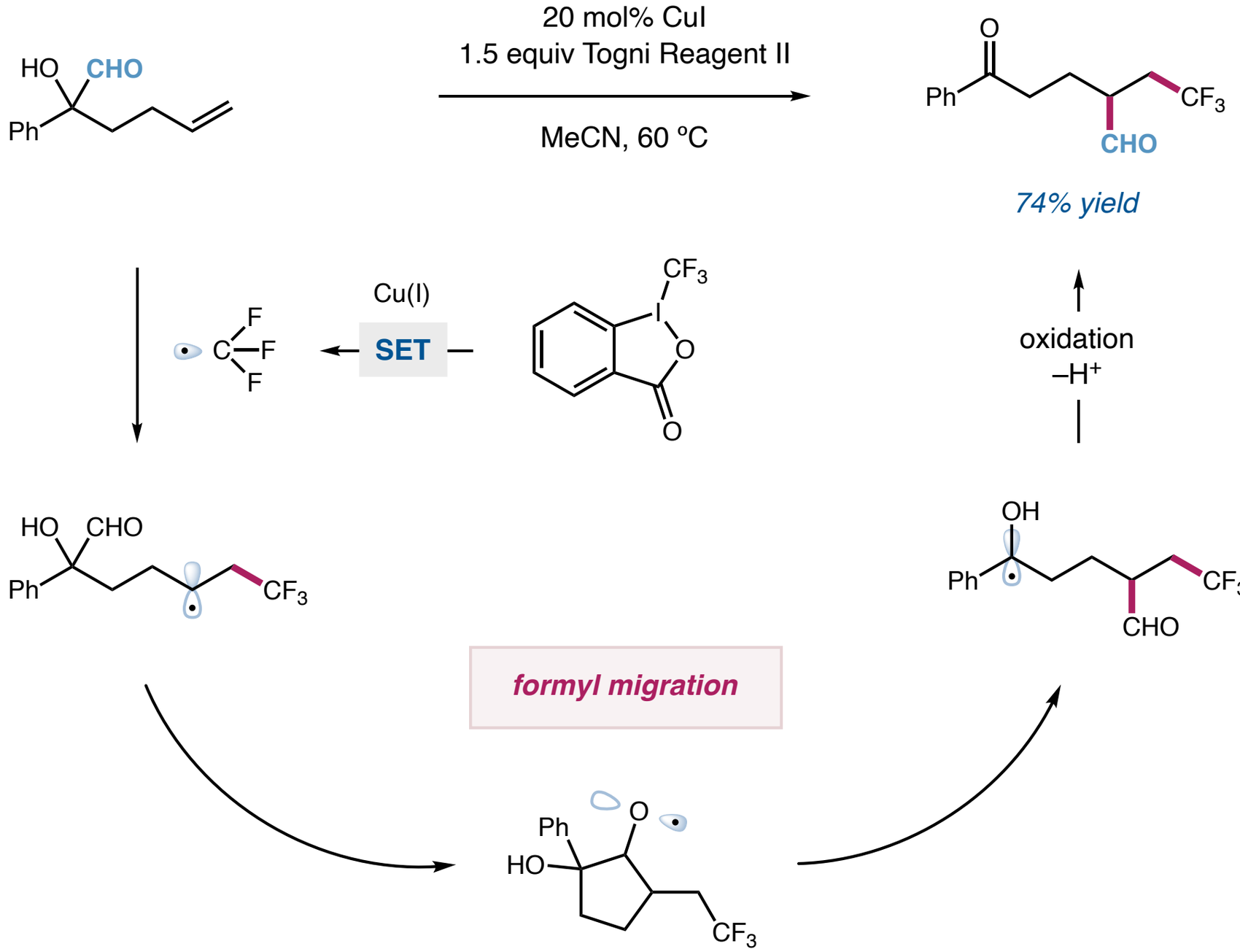
Migration of Cyano Group: Scope





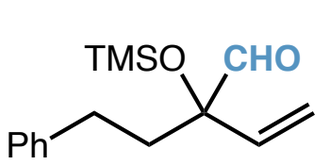
Wu,Z.; Ren, R.; Zhu, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 10821

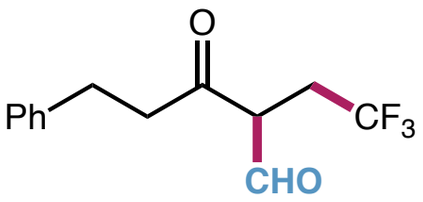
Migration of Formyl Group



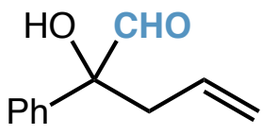
Li, Z.-L.; Li, X.-H.; Wang, N.; Yang, N.-Y.; Liu, X.-Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 15100

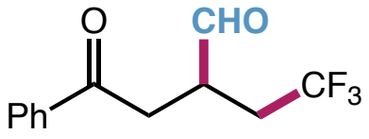
Migration of Formyl Group: Length of the Linker



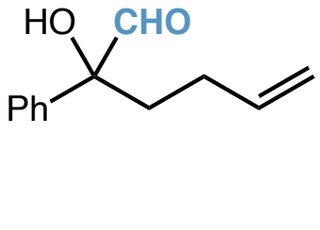


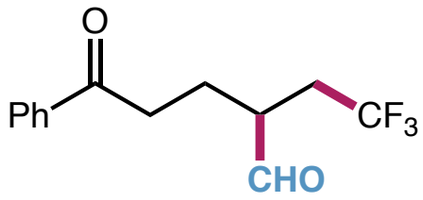
1,2-migration
84% yield



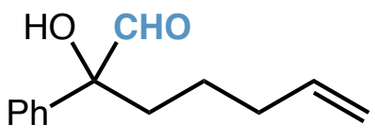


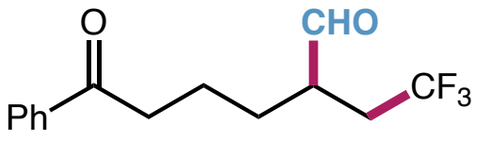
1,3-migration
<5% yield



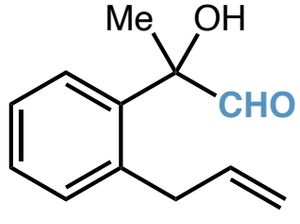


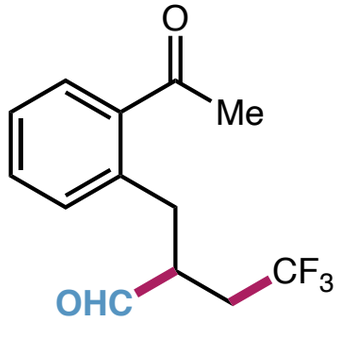
1,4-migration
74% yield





1,5-migration
73% yield

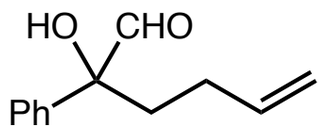


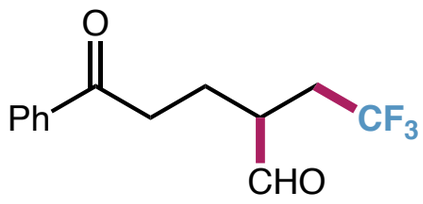


1,5-migration
56% yield

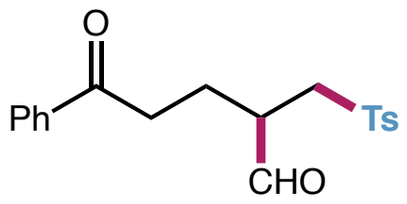
Li, Z.-L.; Li, X.-H.; Wang, N.; Yang, N.-Y.; Liu, X.-Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 15100

Migration of Formyl Group: Scope

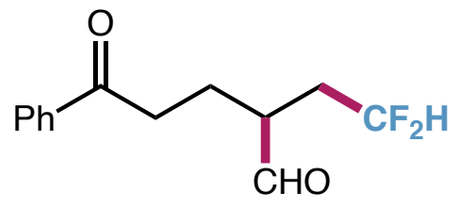




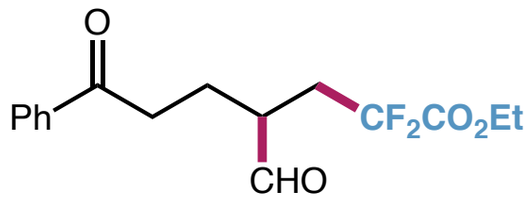
74% yield
with Togni II



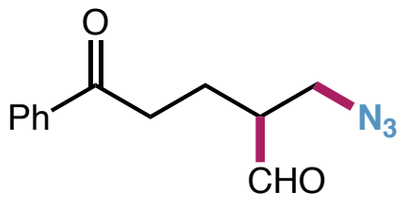
71% yield
with TsCl



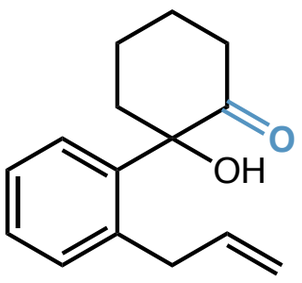
54% yield
with CF_2HSO_2Cl

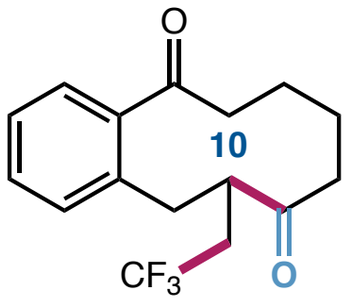


43% yield
with $BrCF_2CO_2Et$

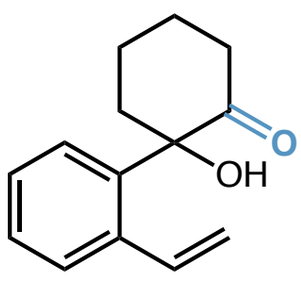


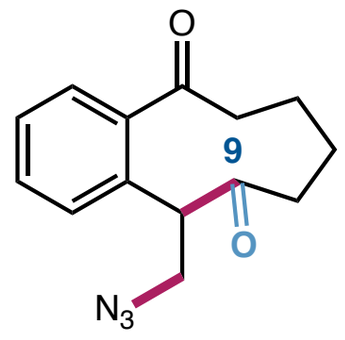
30% yield
with I(III)–N_3 reagent





70% yield

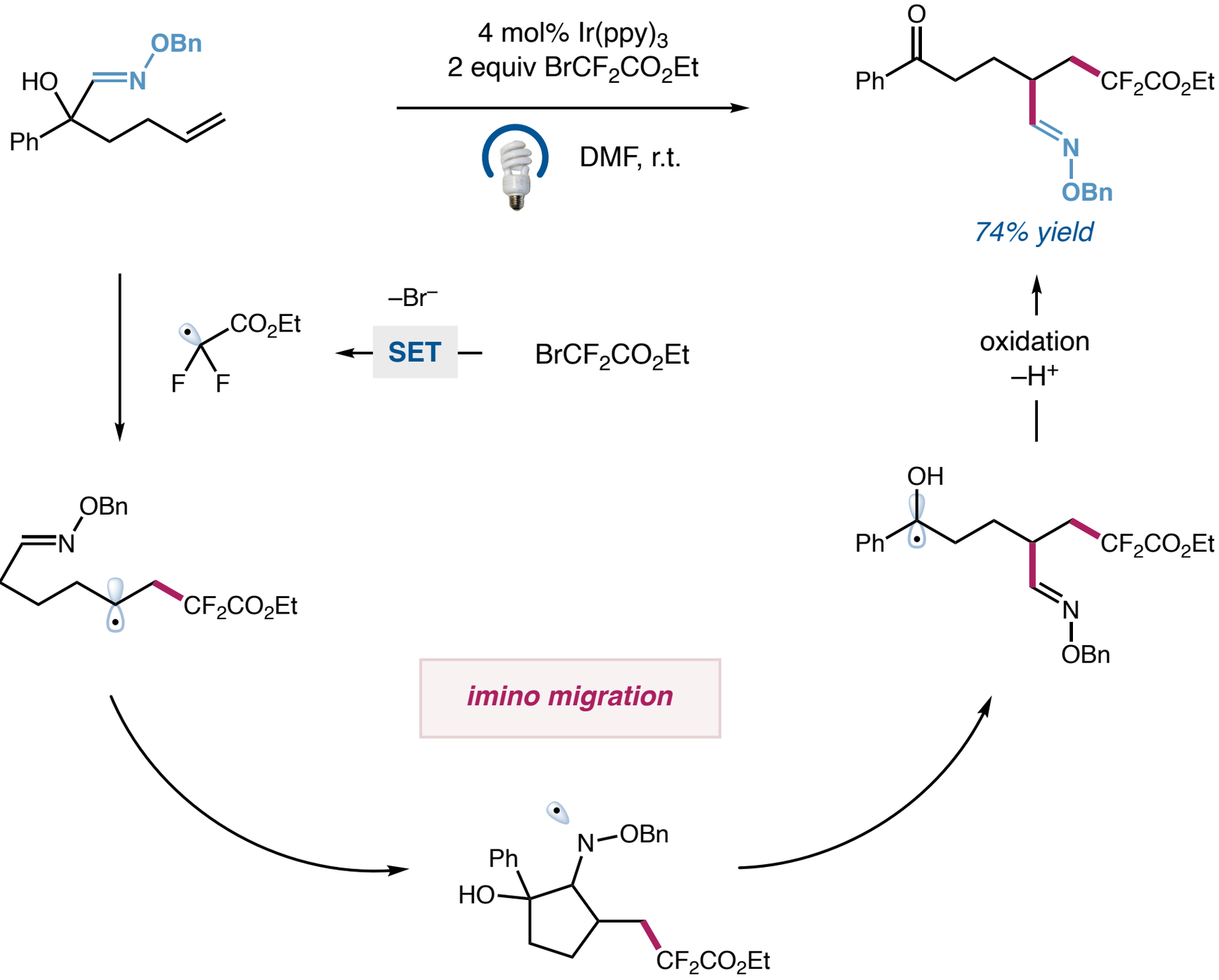




65% yield

Li, Z.-L.; Li, X.-H.; Wang, N.; Yang, N.-Y.; Liu, X.-Y. *Angew. Chem. Int. Ed.* **2016**, *55*, 15100

Migration of Imino Group



Yu, J.; Wang, D.; Xu, Y.; Wu, Z.; Zhu, C. *Adv. Synth. Catal.* **2018**, *360*, 744

Outline

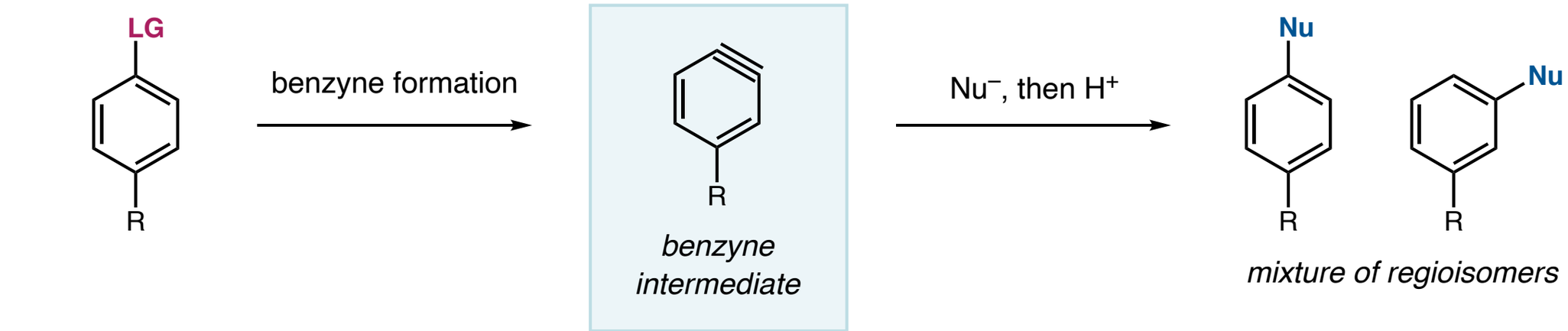
- Migratory FG modification via radical intermediates

- Migratory FG modification via non-radical intermediates (two case studies)
  - Halogen dance reaction
  - Ester dance reaction

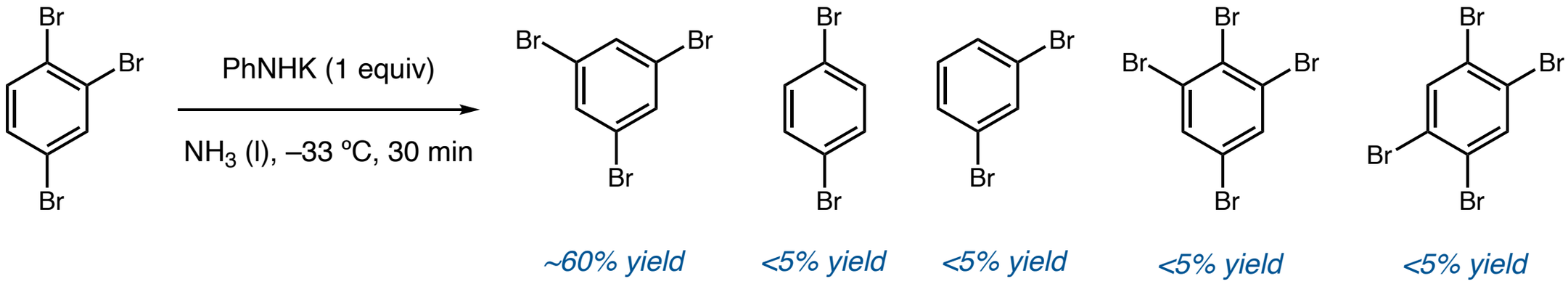
- Migratory FG modification via enzymatic catalysis

Migratory FG Modification for Aromatic Systems: Early Studies

- S_NAr reactions *via* benzyne intermediates

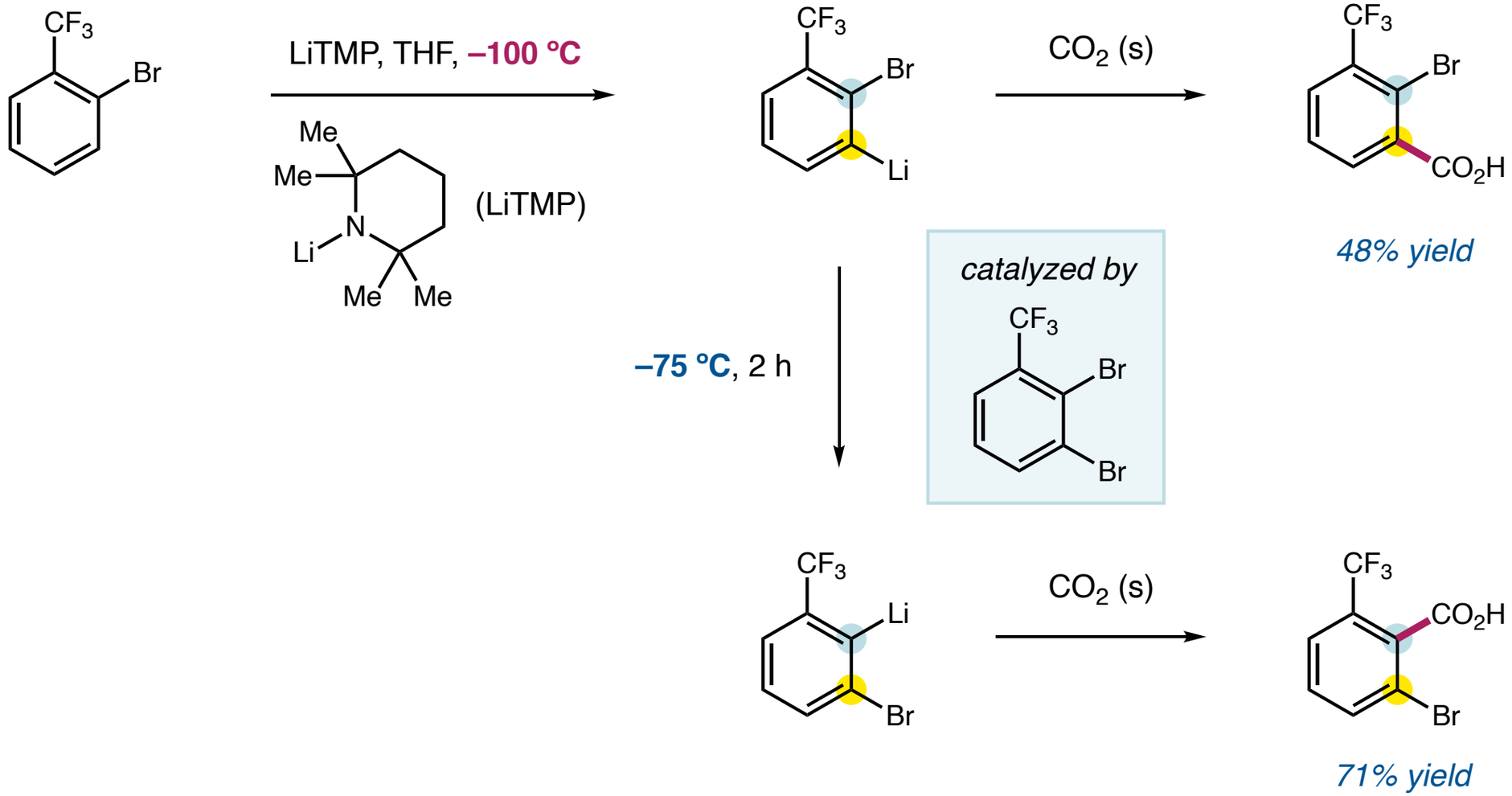


- Halogen dance reaction



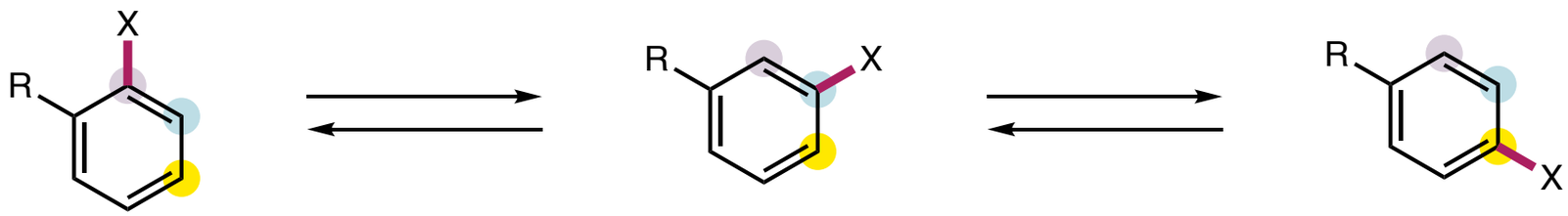
Bunnett, J. F.; Moyer, C. E., Jr. *J. Am. Chem. Soc.* **1971**, *93*, 1183
Bunnett, J. F. *Acc. Chem. Res.* **1971**, *5*, 139

Halogen Dance Reactions: An Early Example



Mongin, F.; Desponds, O.; Schlosser, M. *Tetrahedron Lett.* **1996**, *37*, 2767

Halogen Dance Reactions: Summary of Early Work



1. Stereodivergent synthesis of regioisomers starting from a signle starting material

2. Generating expensive/less available haloarenes from cheap and readily available aryl halides

3. Often requires harsh conditions (e.g., strong base) and cryogenic temperature

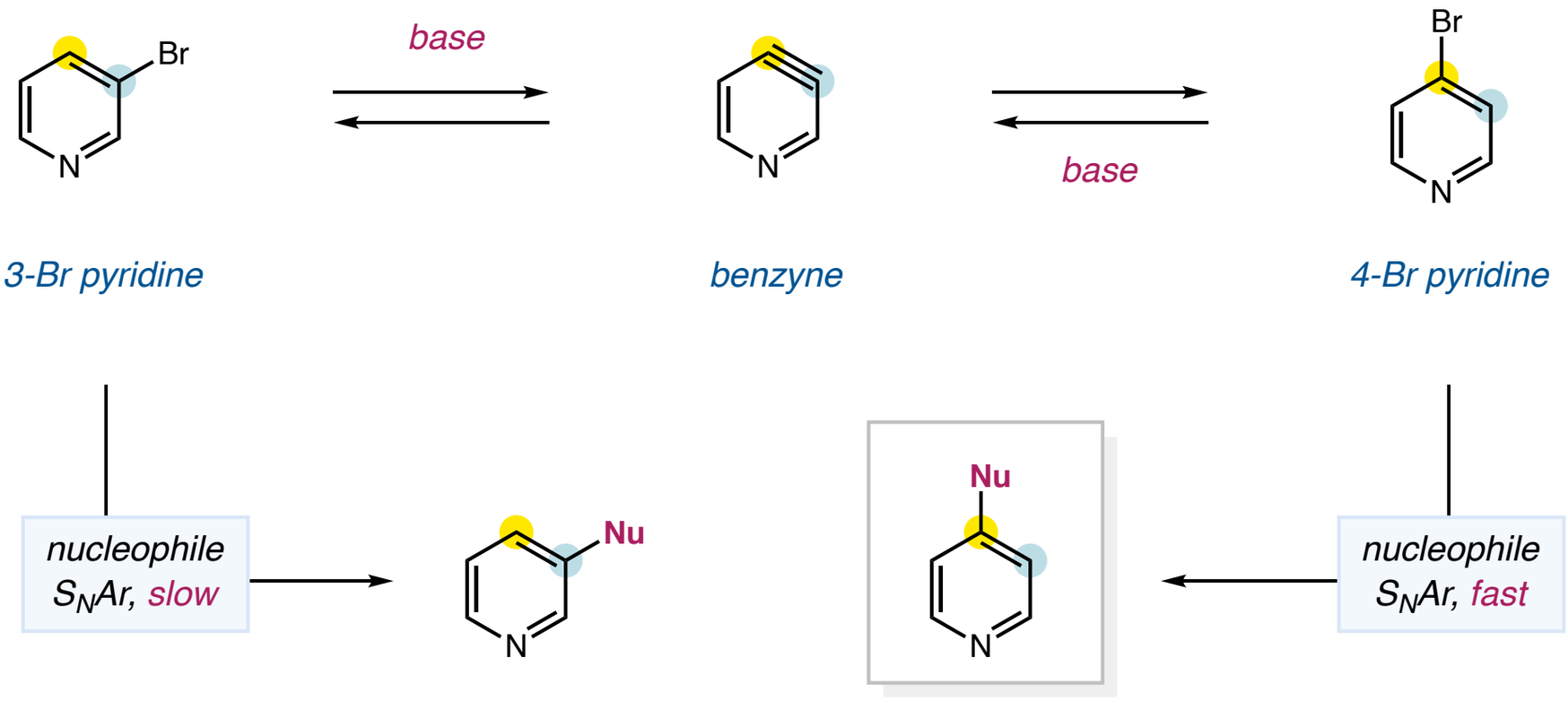
Reviews:

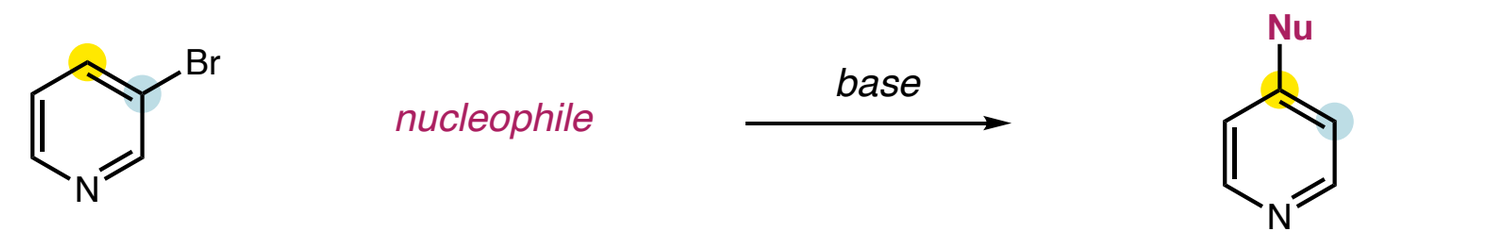
1. Schnurch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046

2. Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376

3. Erb, W.; Mongin, F. *Tetrahedron* **2016**, *72*, 4973

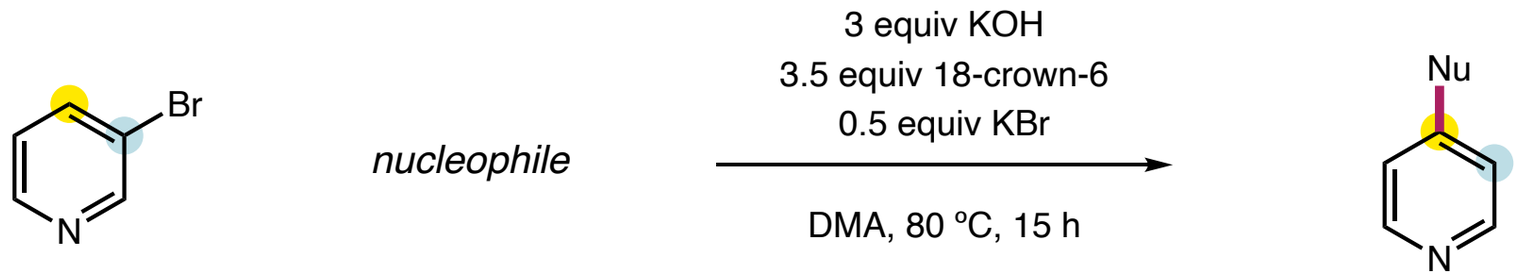
Recent Work #1: 4-Selective Functionalization of 3-Bromopyridines





Puleo, T. R.; Bandar, J. S. *Chem. Sci.* **2020**, *11*, 10517.

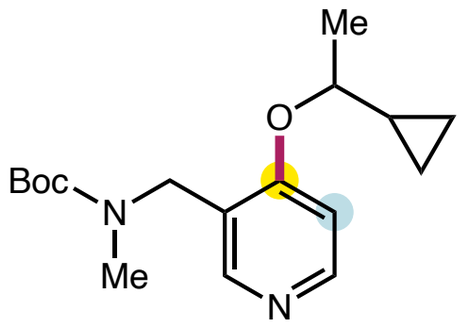
Recent Work #1: 4-Selective Functionalization of 3-Bromopyridines



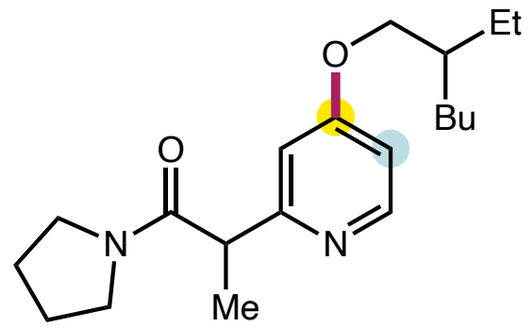
1–1.5 equiv

1 equiv

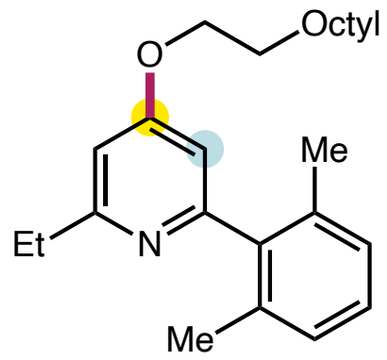
4-substituted pyridine
>10:1 selectivity



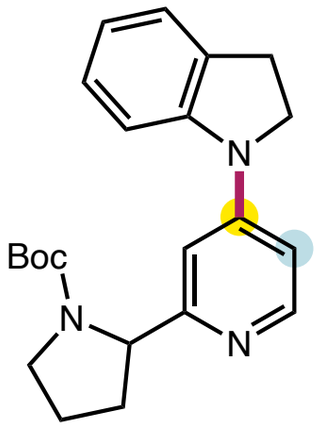
61% yield



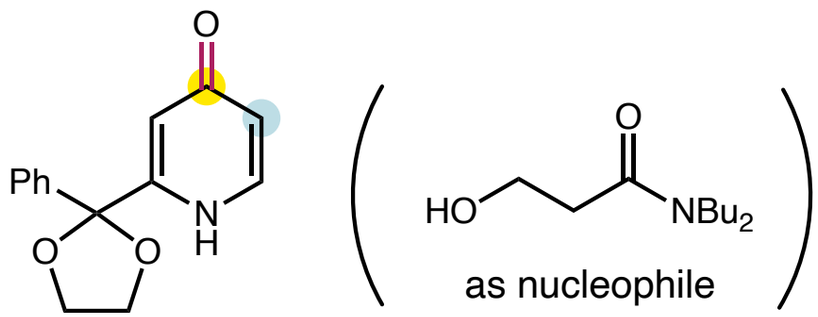
44% yield



57% yield



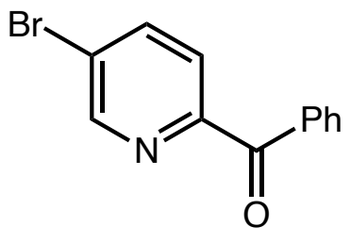
50% yield



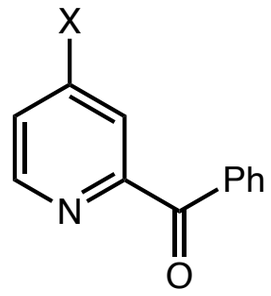
50% yield

Puleo, T. R.; Bandar, J. S. *Chem. Sci.* **2020**, *11*, 10517.

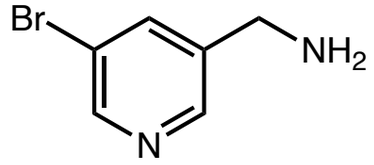
Recent Work #1: 4-Selective Functionalization of 3-Bromopyridines



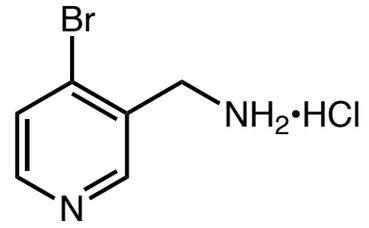
$170 / 1 g



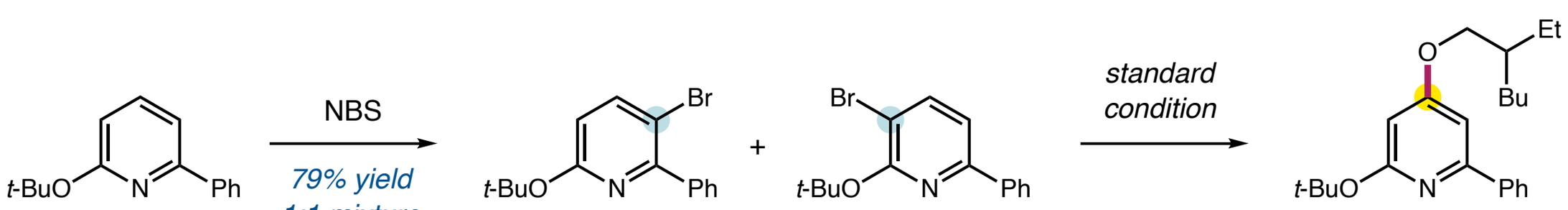
X = F, Cl, Br, I, OH
not commercial



$74 / 1 g

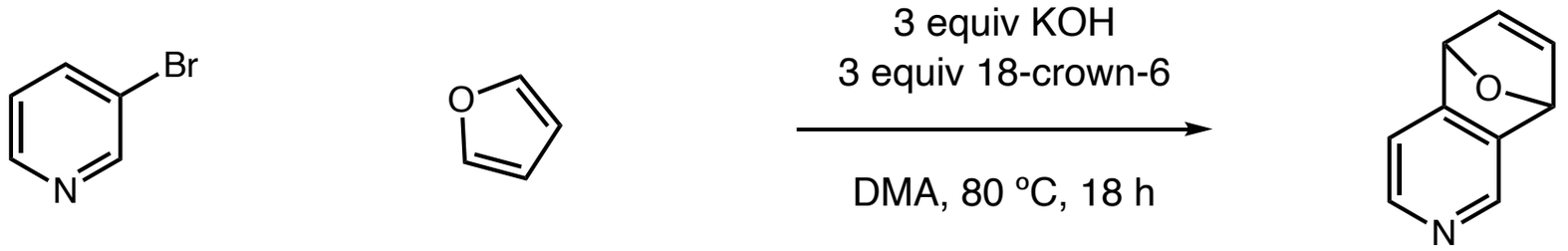


$1001 / 1g



Puleo, T. R.; Bandar, J. S. *Chem. Sci.* **2020**, *11*, 10517.

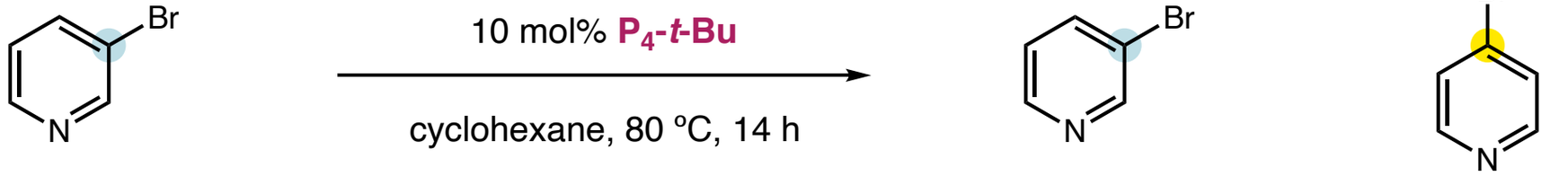
Recent Work #1: 4-Selective Functionalization of 3-Bromopyridines



1 equiv

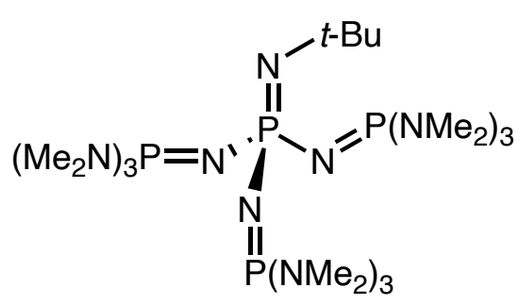
20 equiv

42% yield



72% yield

18% yield

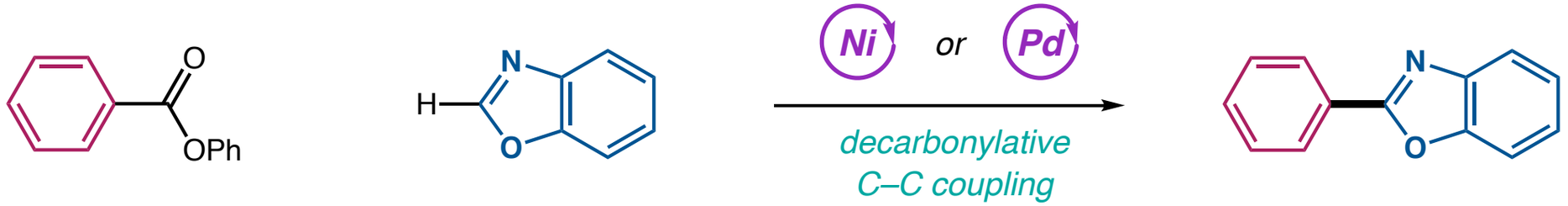


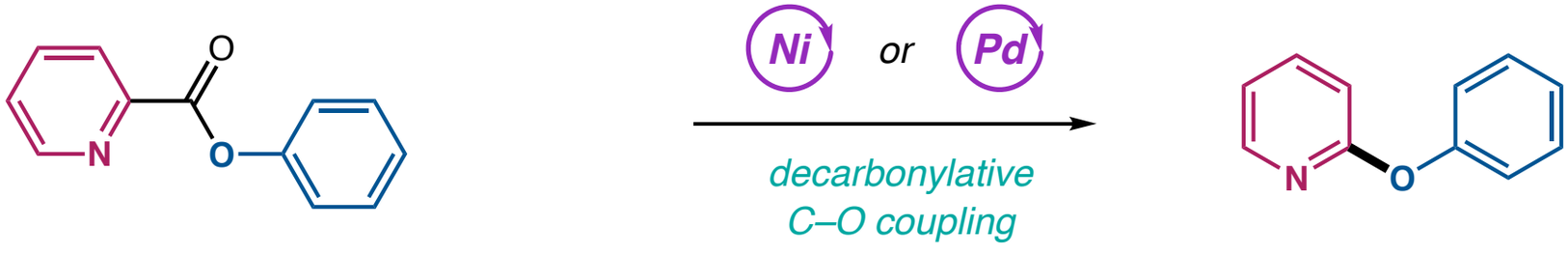
P_4-*t*-Bu

pK_{BH}+ = 30.2 in DMSO

Puleo, T. R.; Bandar, J. S. *Chem. Sci.* **2020**, *11*, 10517.

Recent Work #2: Ester Dance Reactions via Pd-Catalyzed Decarbonylation





Junichiro Yamaguchi, Kenichiro Itami *et al., J. Am. Chem. Soc.* **2012**, *134*, 13573; *Nat. Commun.* **2015**, *6*, 7508; *Org. Lett.* **2016**, *18*, 5106; *J. Am. Chem. Soc.* **2017**, *139*, 3340; *Chem. Asian J.* **2018**, *13*, 2393.
For a recent review: Takise, R.; Muto, K.; **Yamaguchi, J.** *Chem. Soc. Rev.* **2017**, *46*, 5864.

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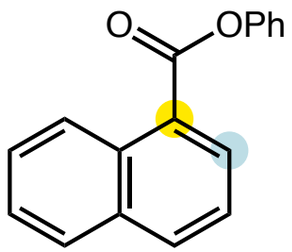
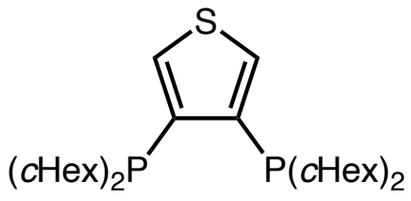
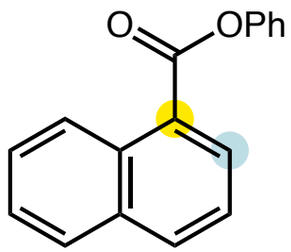


1-naphthoate

10 mol% $PdCl_2$, 20 mol% dcypt
0.5 equiv K_2CO_3, *m*-xylene, 150 °C

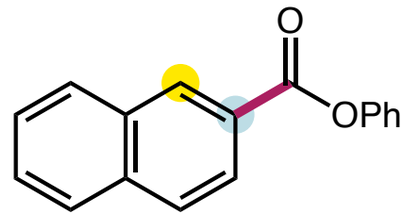


dcypt



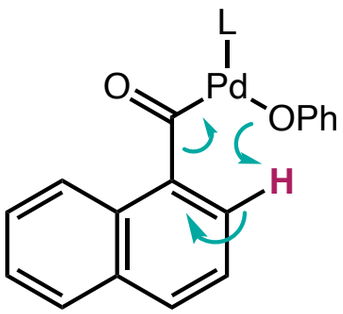
1-naphthoate
7% recovery

+

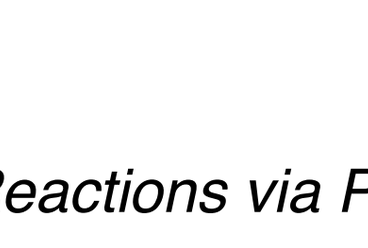


2-naphthoate
85% yield

oxidative addition

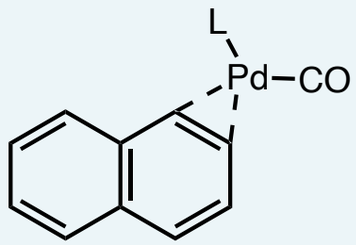


deprotonation decarbonylation



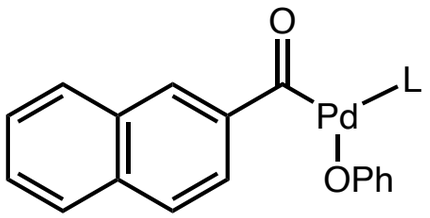
aryne-Pd

or



η²-arene Pd

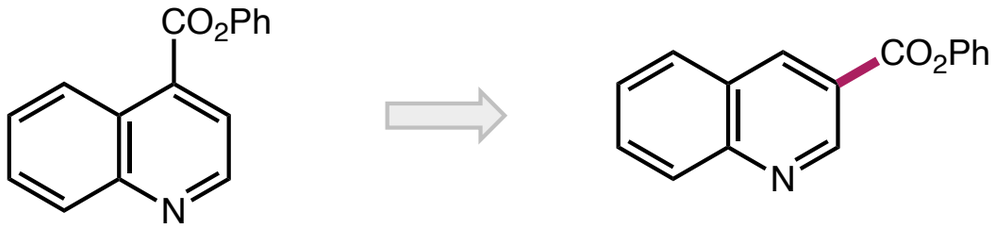
protonation carbonylation



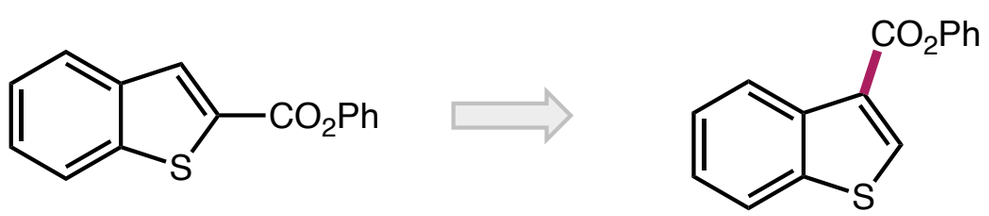
reductive elimination

Matsushita, K.; Takise, R.; Muto, K.; Yamaguchi, J. *Sci. Adv.* **2020**, *6*, eaba7614.

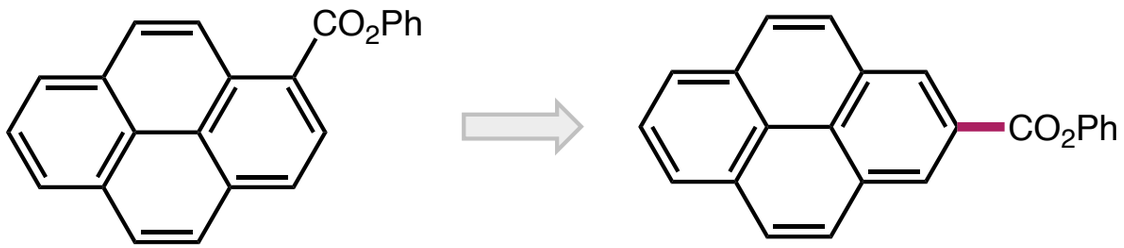
Recent Work #2: Ester Dance Reactions via Pd-Catalyzed Decarbonylation



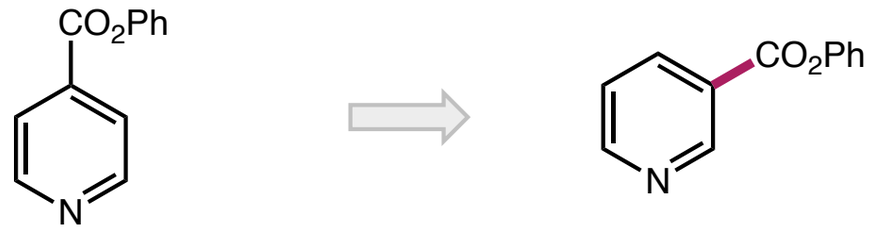
60% yield
(2% SM recovery)



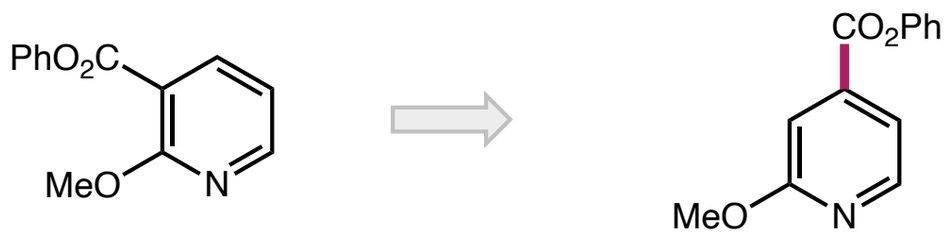
27% yield
(25% SM recovery)



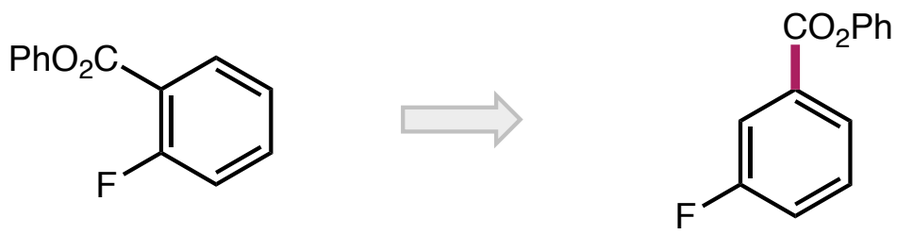
41% yield
(27% SM recovery)



54% yield
(16% SM recovery)



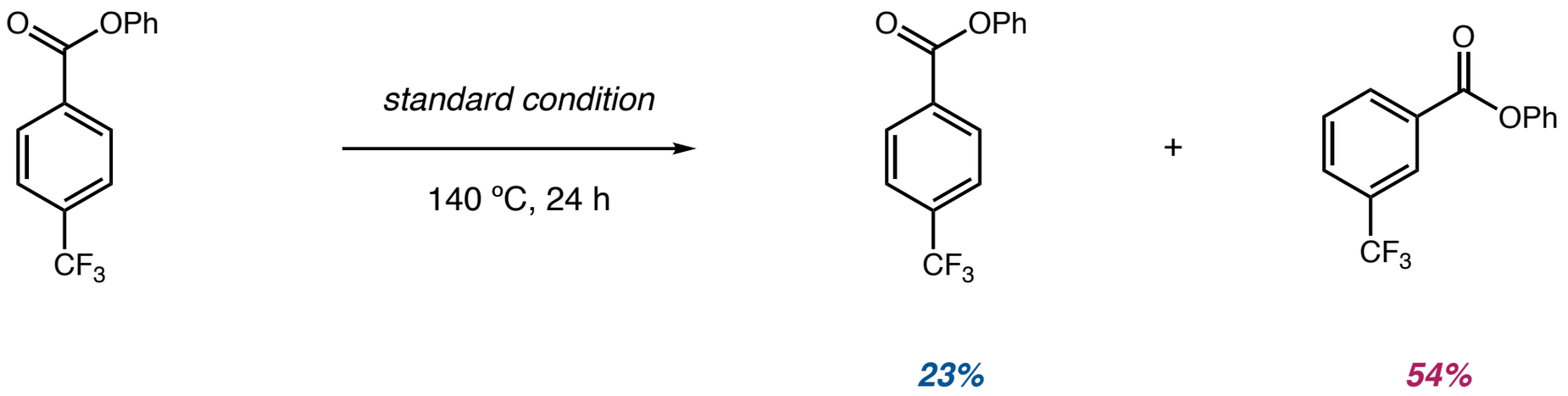
61% yield
(10% SM recovery)

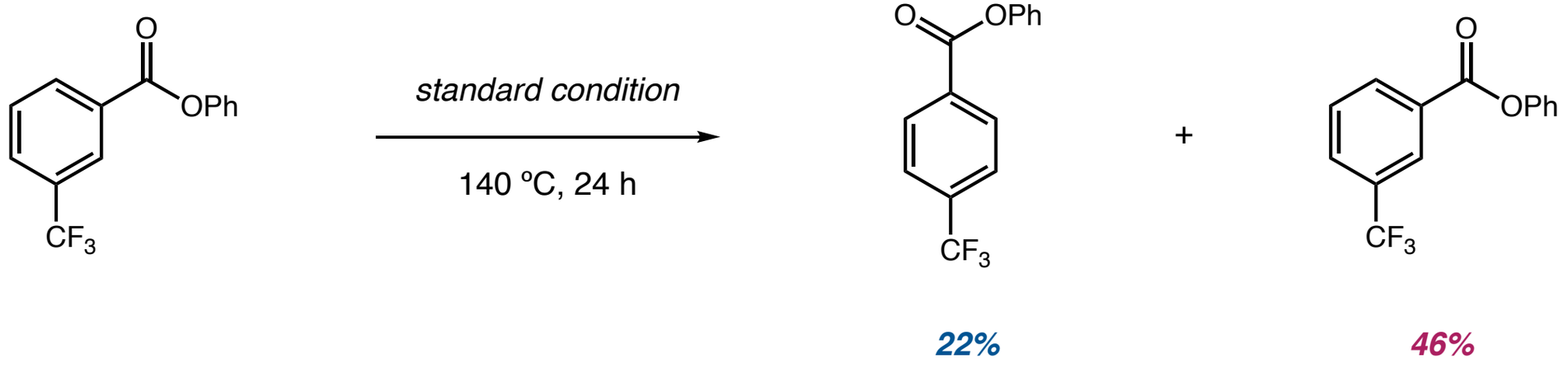


30% yield
(19% SM recovery)

Matsushita, K.; Takise, R.; Muto, K.; Yamaguchi, J. *Sci. Adv.* **2020**, *6*, eaba7614.

Recent Work #2: Ester Dance Reactions via Pd-Catalyzed Decarbonylation





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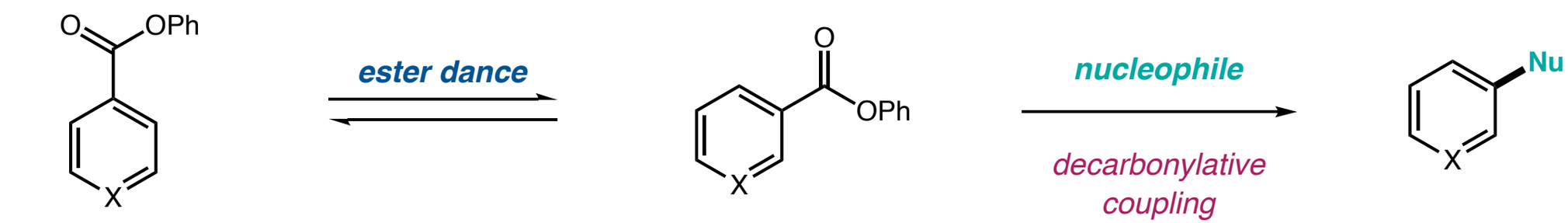

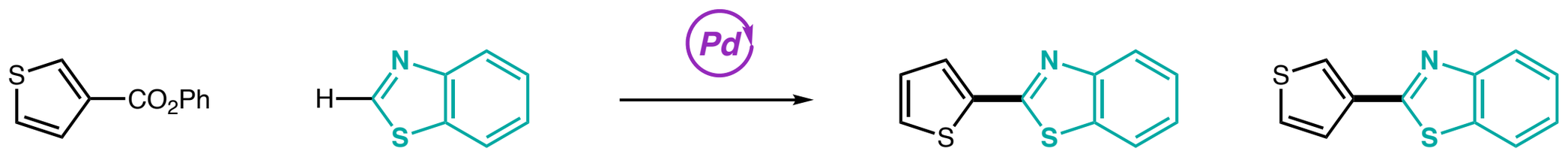

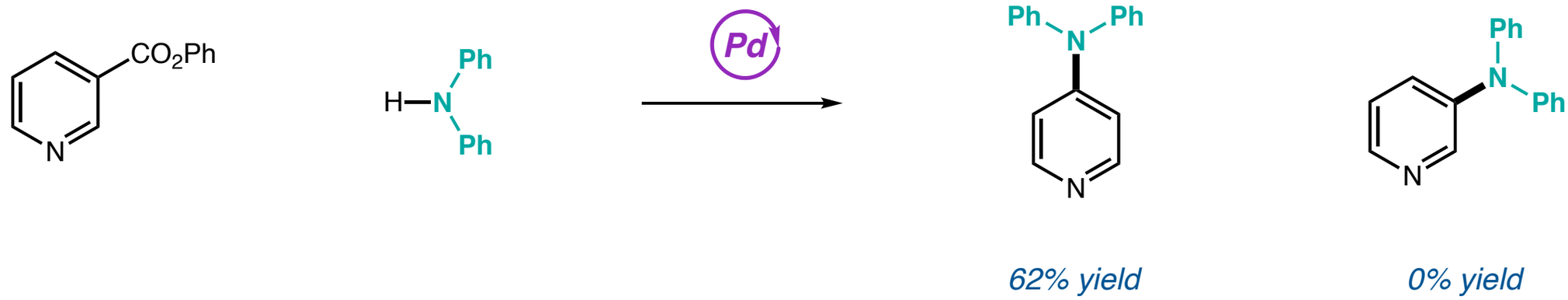

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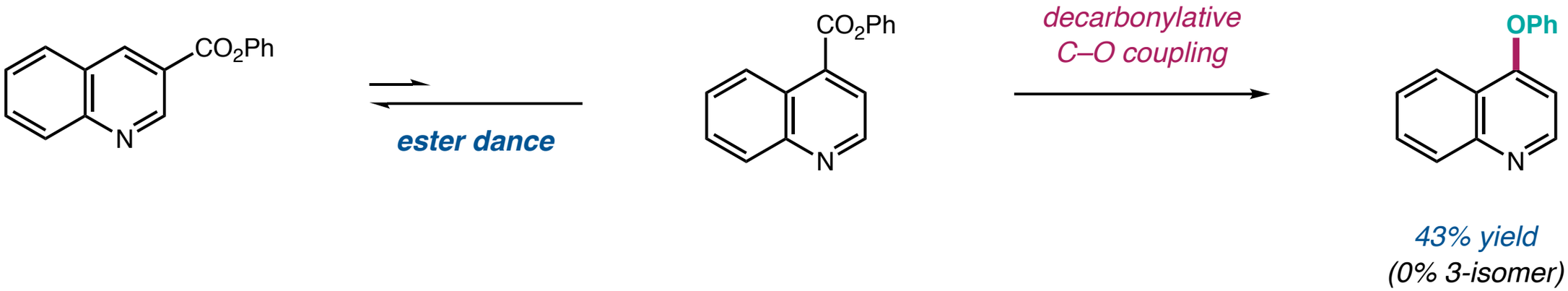
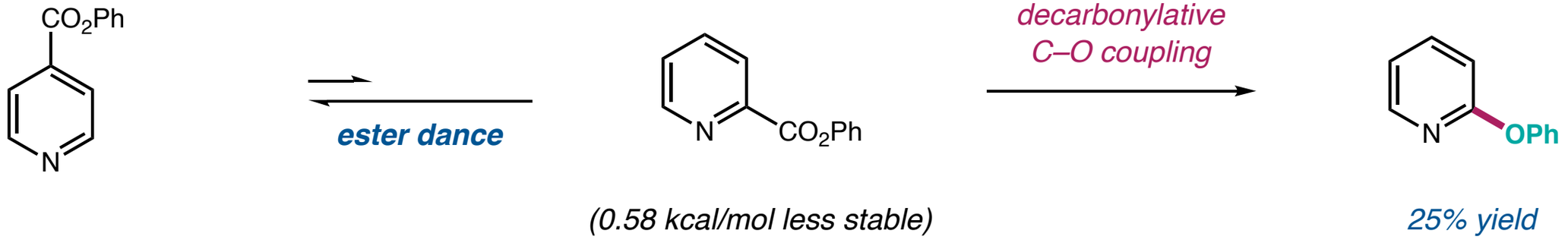




Matsushita, K.; Takise, R.; Muto, K.; Yamaguchi, J. *Sci. Adv.* **2020**, *6*, eaba7614.

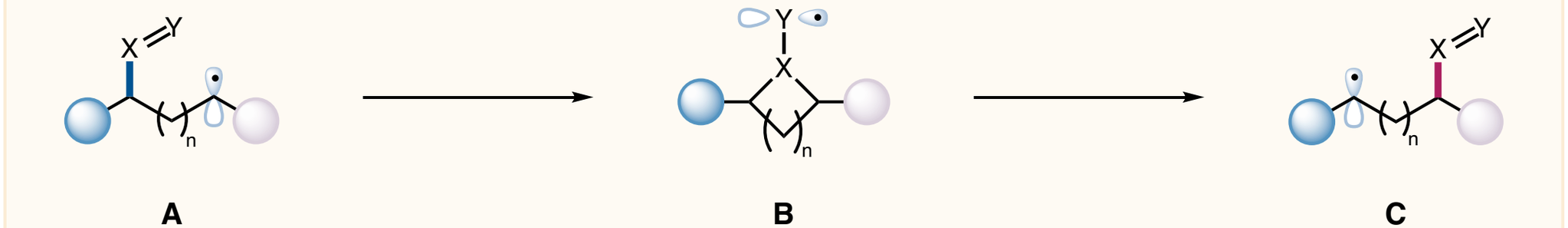
Outline

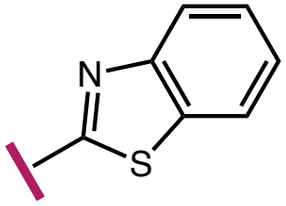
- Migratory FG modification via radical intermediates

- Migratory FG modification via non-radical intermediates (two case studies)
  - Halogen dance reaction
  - Ester dance reaction

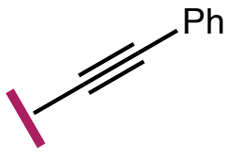
- Migratory FG modification via enzymatic catalysis

Migratory FG Modification via Radical Intermediates

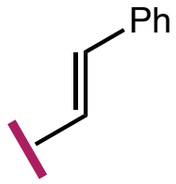




(hetero)arene

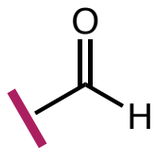


alkyne

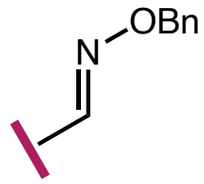


alkene

cyano



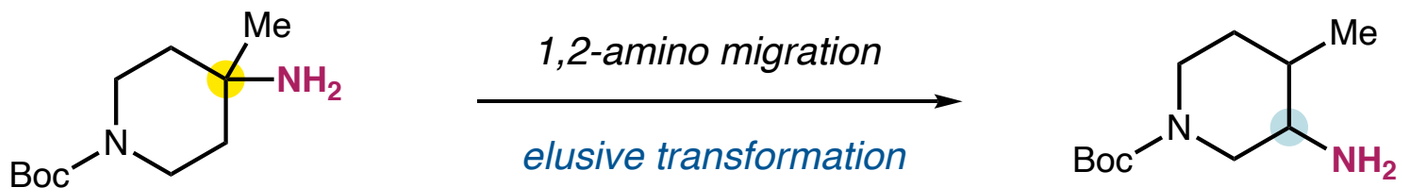
formyl



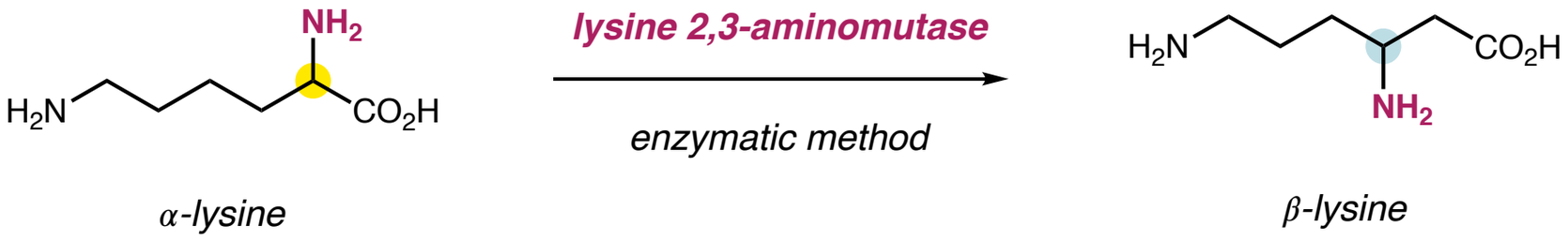
imino

- Usually long-distance migration, e.g., 1,4- and 1,5-migration
- Unsaturation of the functional groups is necessary

Amino Translocation Catalyzed by Enzymes

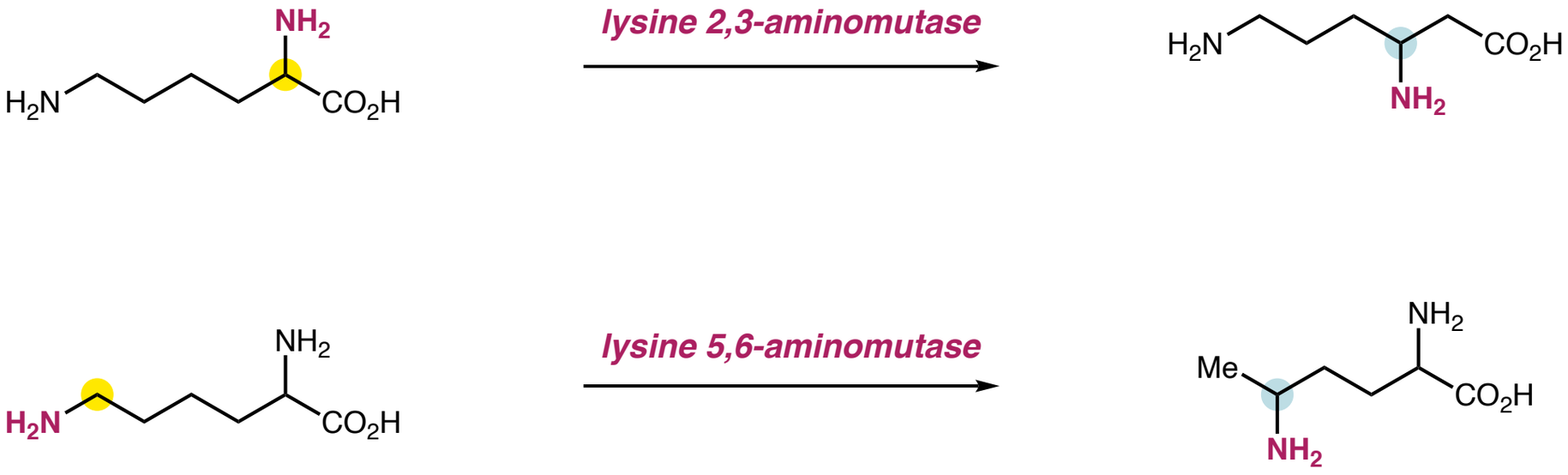


However, 1,2-amino migration is indeed possible in biological systems.



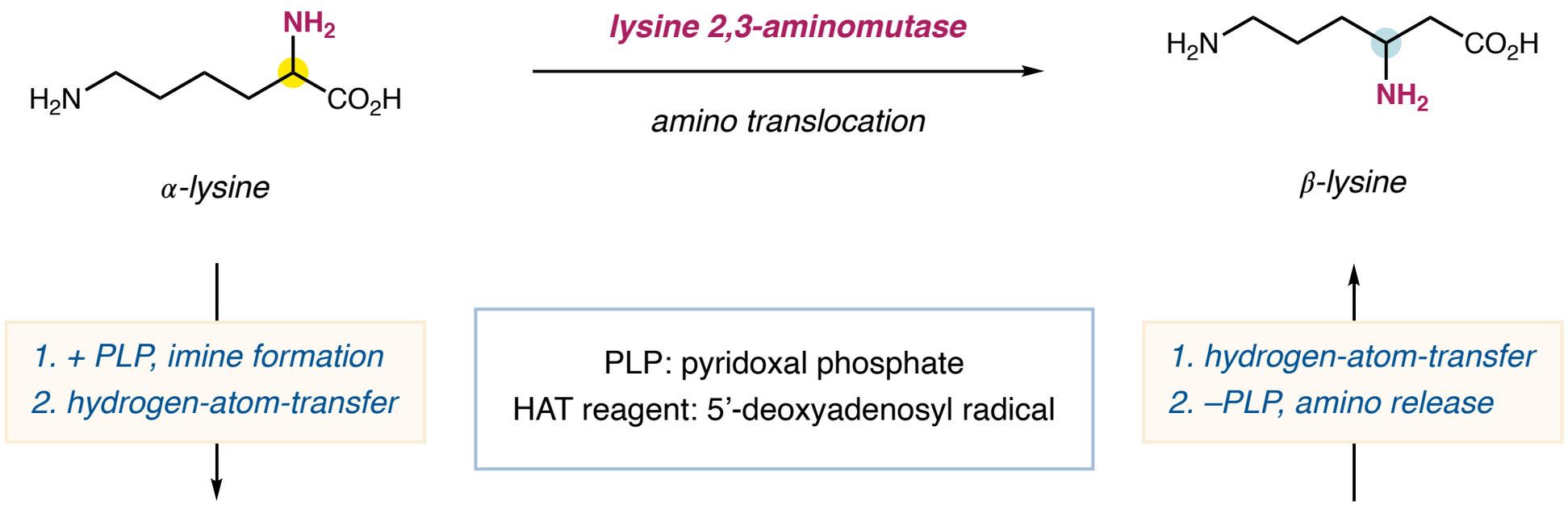
Wu, B.; Szymanski, W.; Heberling, M. M.; Feringa, B. L.; Janssen, D. B. *Trends Biotechnol.* **2011**, *29*, 352

Amino Translocation using Aminomutases



Wu, B.; Szymanski, W.; Heberling, M. M.; Feringa, B. L.; Janssen, D. B. *Trends Biotechnol.* **2011**, *29*, 352

Simplified Mechanism for Lysine 1,2-Amino Translocation



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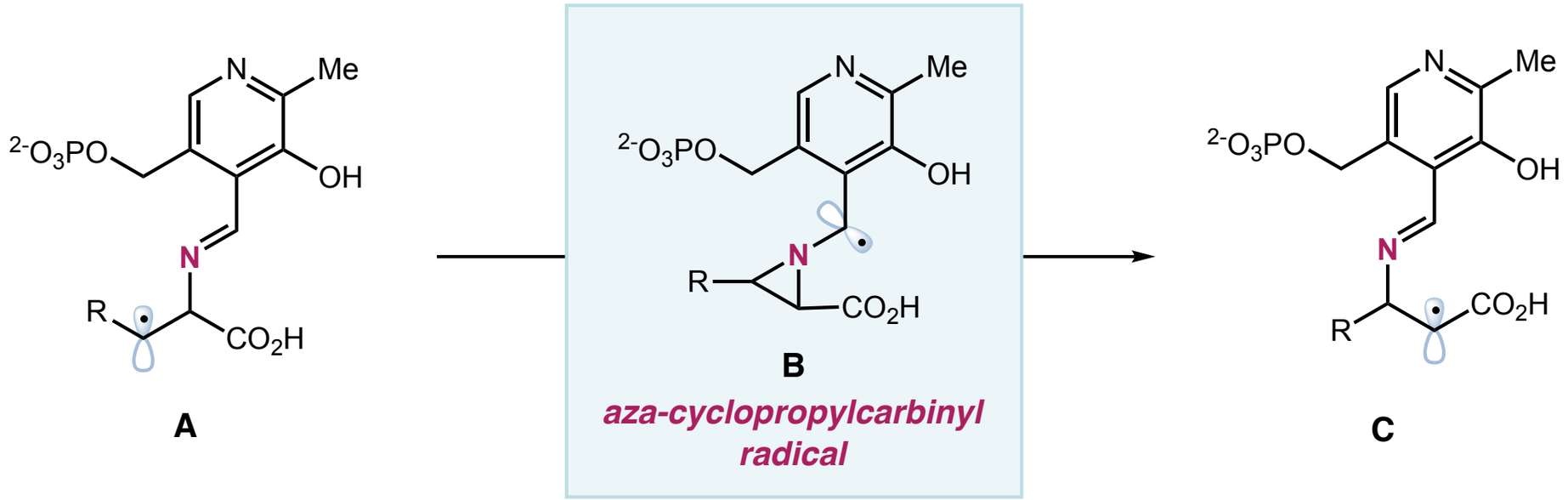
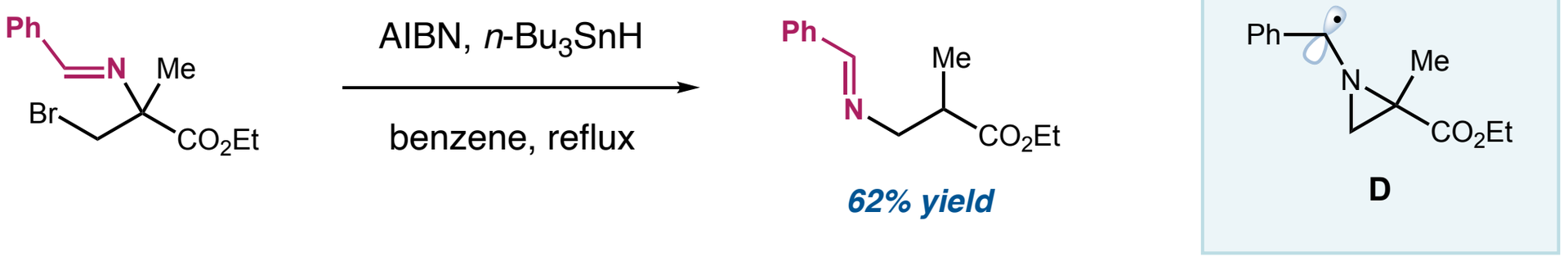
Prove the Chemical Model under Non-Enzymatic Condition





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