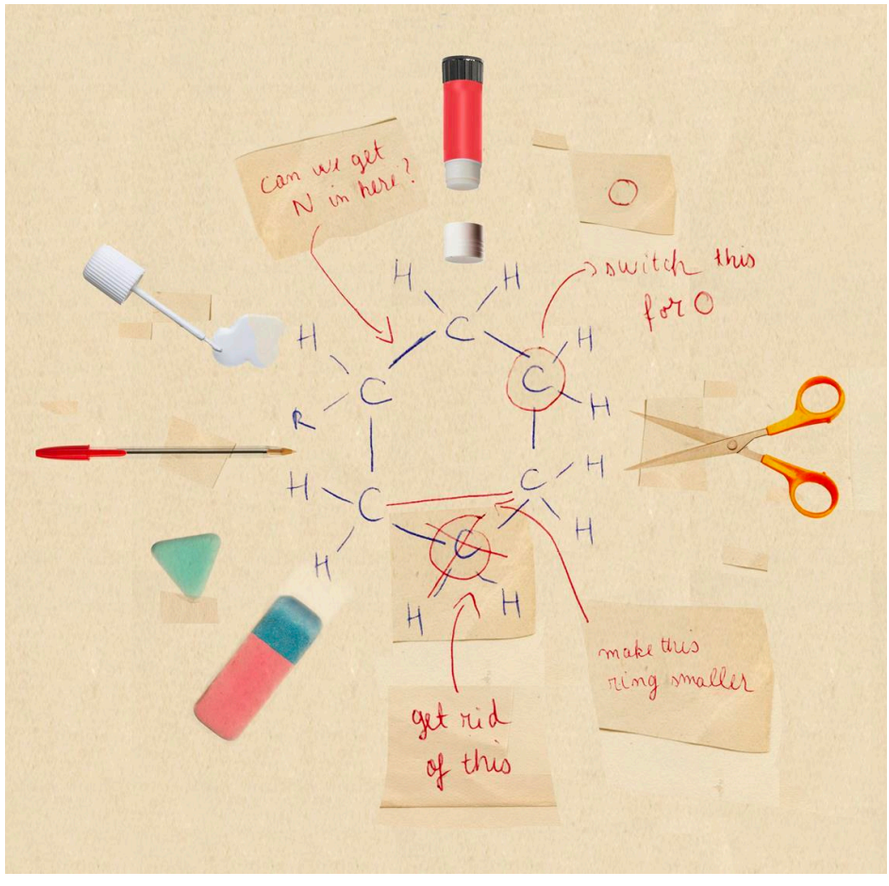
‘Molecular Editing’



William Preston Carson II

What is molecular/skeletal editing?

"[the ability to] rapidly build onto, change, or prune molecules one atom at a time using transformations that are mild and selective enough to be employed at the late stages of a synthetic sequence"

Vague

Questions

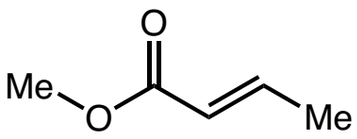
- What constitutes a molecular 'skeleton'?
- What is a single-atom edit?
- What benefits does this offer over other types of transformations?

Jurczyk, J.; Woo, J.; Kim, S. F.; Dherange, B. D.; Sarpong, R.; Levin, M. D. *Nat. Synth.* ***2022***, *1*, 352.

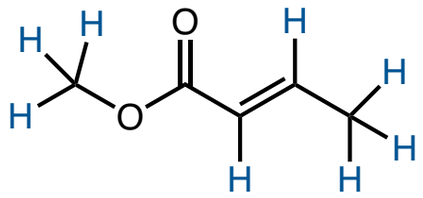
What constitutes a Molecular Skeleton?

Applies to both acyclic and cyclic molecules

acyclic

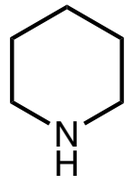


-vs-

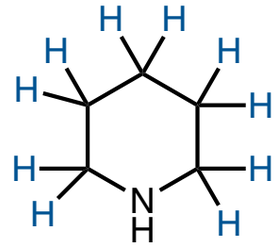


Skeleton is the longest chain (IUPAC rules)

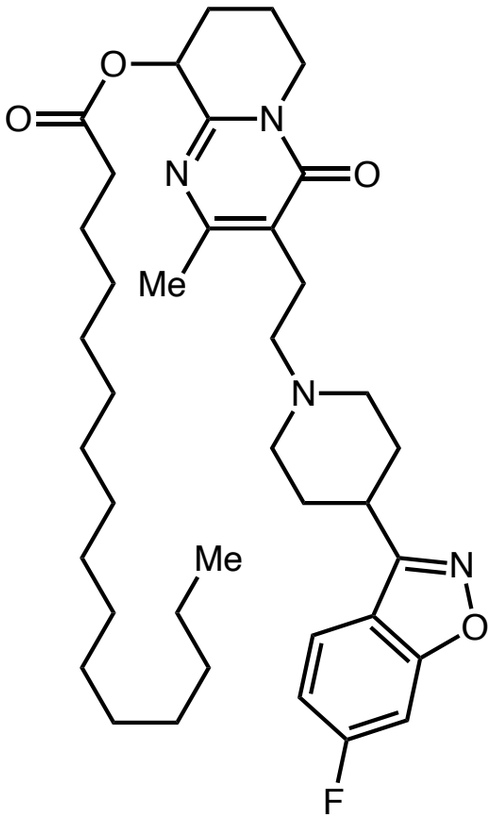
cyclic



-vs-



Skeleton is the atoms that comprise the ring

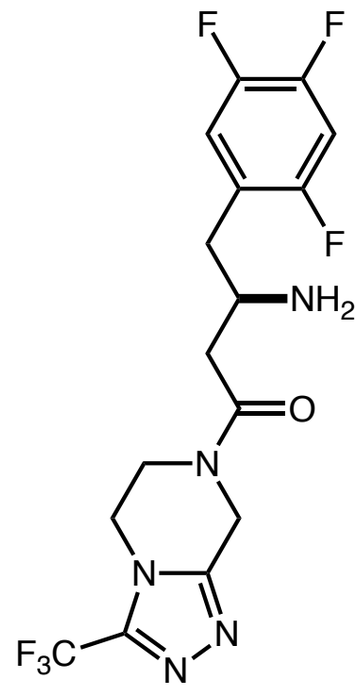


Invega®

hydrogens occupy the molecular 'periphery'

Beyond hydrogen atoms . . .

Where is the skeleton?

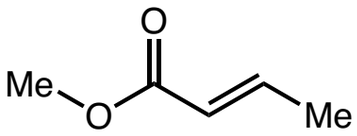


Januvia®

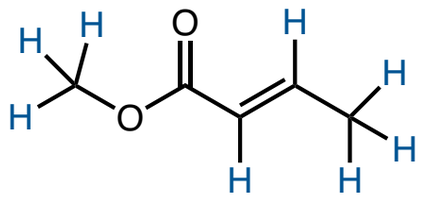
What constitutes a Molecular Skeleton?

Applies to both acyclic and cyclic molecules

acyclic

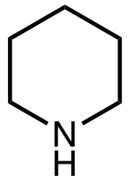


-vs-

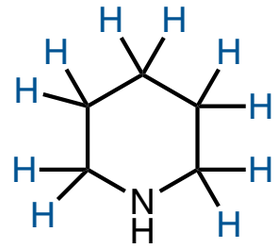


Skeleton is the longest chain (IUPAC rules)

cyclic



-vs-



Skeleton is the atoms that comprise the ring

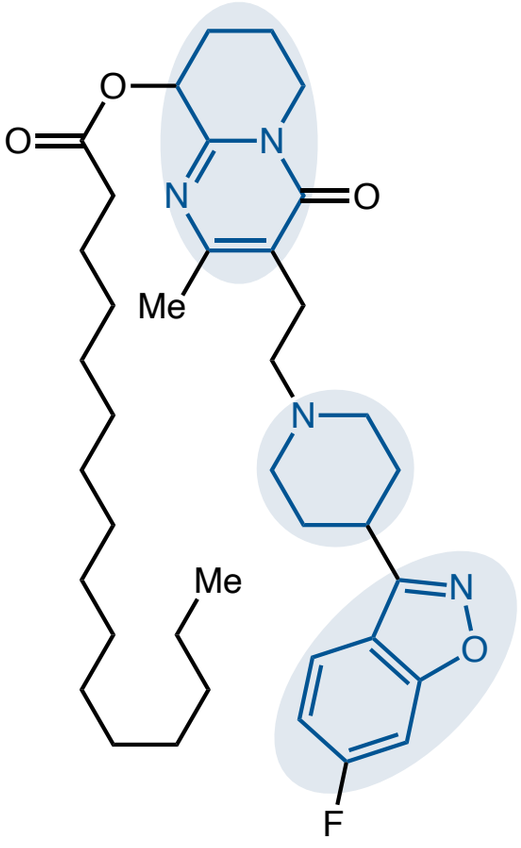
hydrogens occupy the molecular 'periphery'

Beyond hydrogen atoms . . .

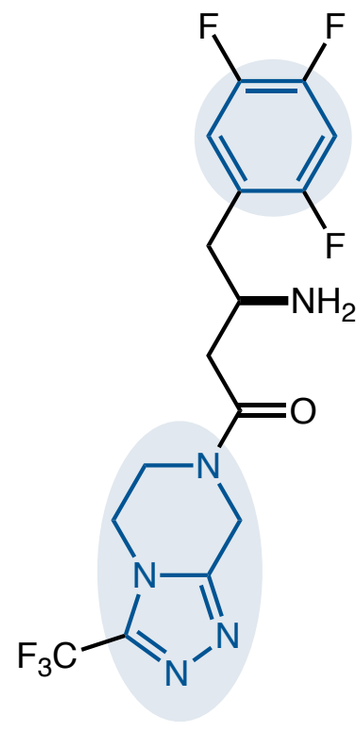
Rings offer a natural dividing line

Blue – skeleton

Black – Periphery



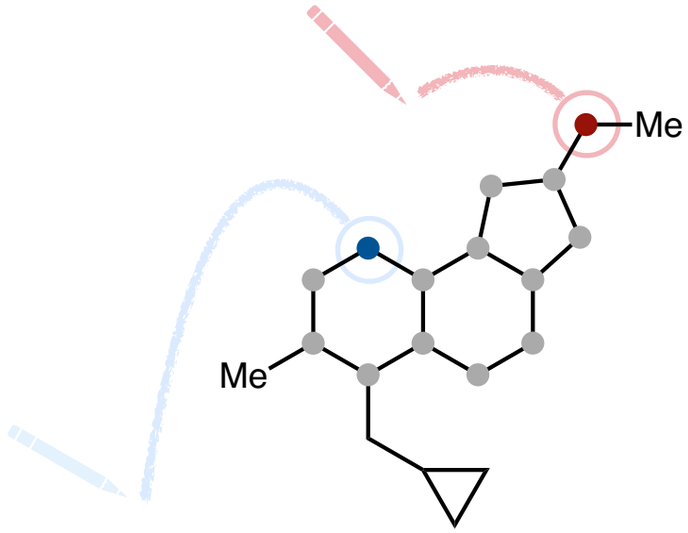
Invega®



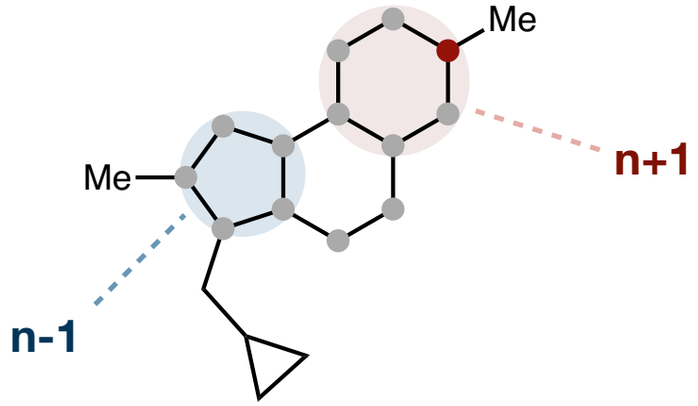
Januvia®

Jurczyk, J.; Woo, J.; Kim, S. F.; Dherange, B. D.; Sarpong, R.; Levin, M. D. *Nat. Synth.* ***2022***, *1*, 352.

What is a Single-Atom Edit?

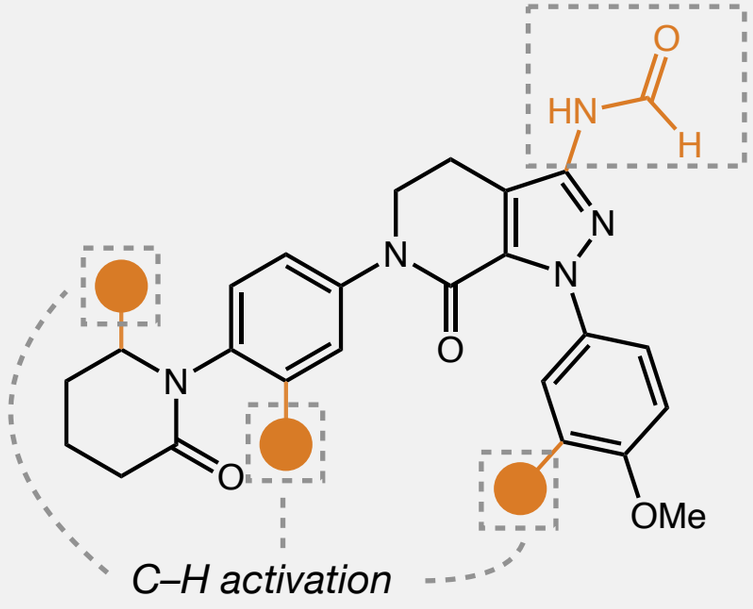


"single-atom editing"



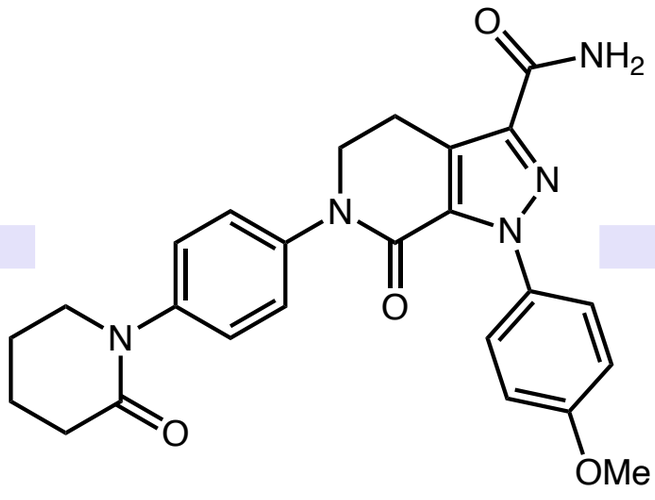
Lead Scaffold Diversification

rearrangement



C–H activation

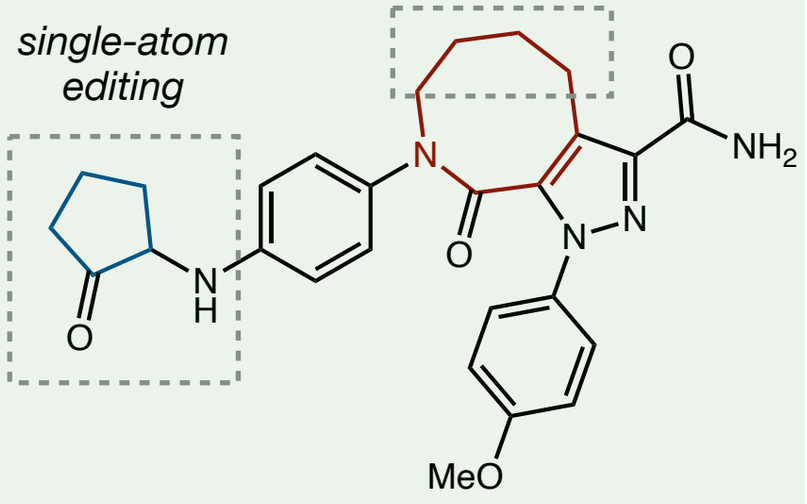
Peripheral editing



Apixaban
hypertension

multi-atom editing

single-atom editing



'Skeletal editing'

Jurczyk, J.; Woo, J.; Kim, S. F.; Dherange, B. D.; Sarpong, R.; Levin, M. D. *Nat. Synth.* ***2022***, *1*, 352.

Benefits that Skeletal Editing can Offer

This single-atom editing is a <u>deliberate</u> and <u>beneficial</u> synthetic logic because . . .

‘Editing’ evokes precision

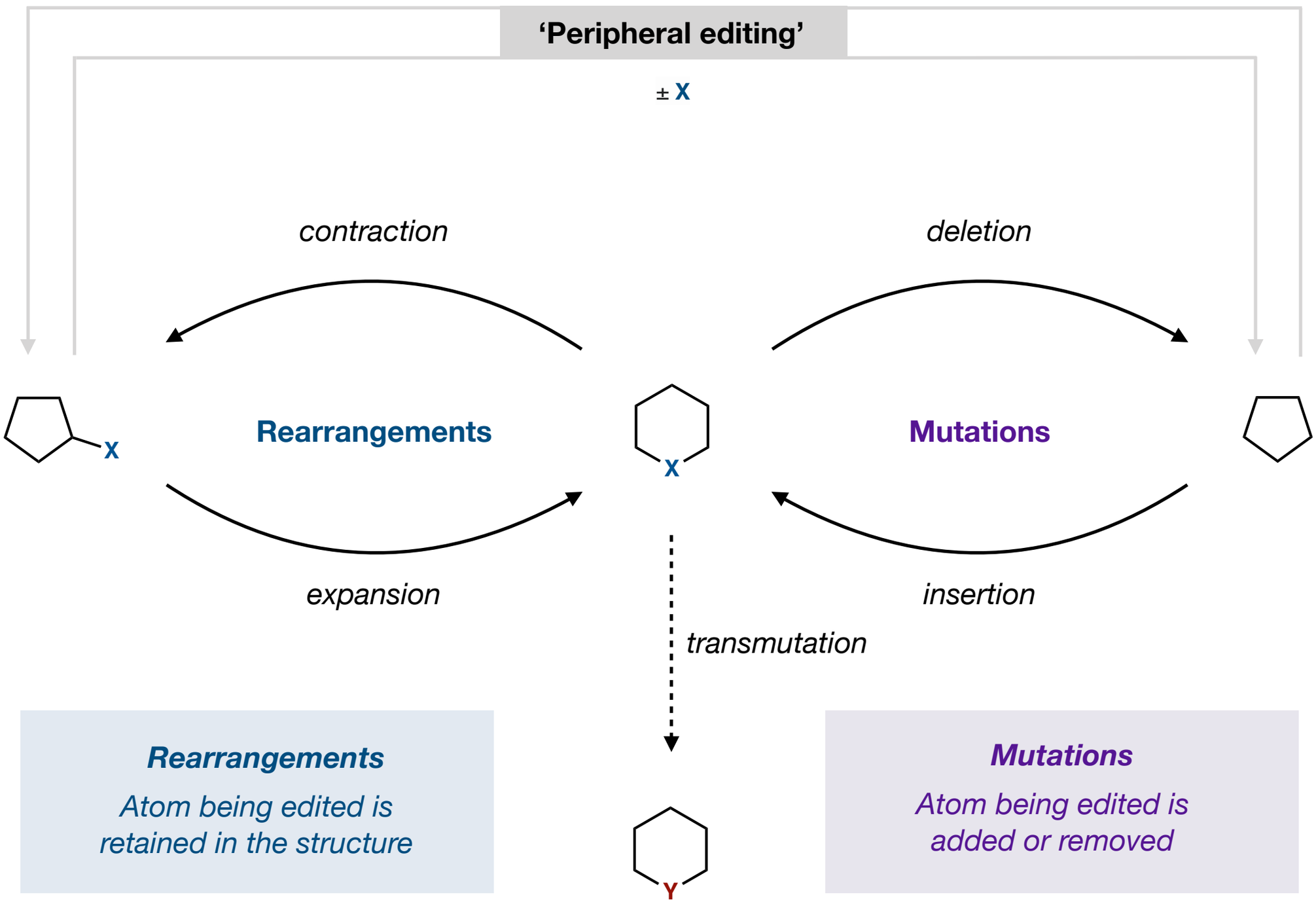
- most elementary of possible changes to a molecular skeleton
- more complex changes are possible as combinations of multiple single-atom edits

Retrosynthetic simplicity

rearrangements | *Single-atom editing*

Jurczyk, J.; Woo, J.; Kim, S. F.; Dherange, B. D.; Sarpong, R.; Levin, M. D. *Nat. Synth.* ***2022***, *1*, 352.

A Classification Scheme

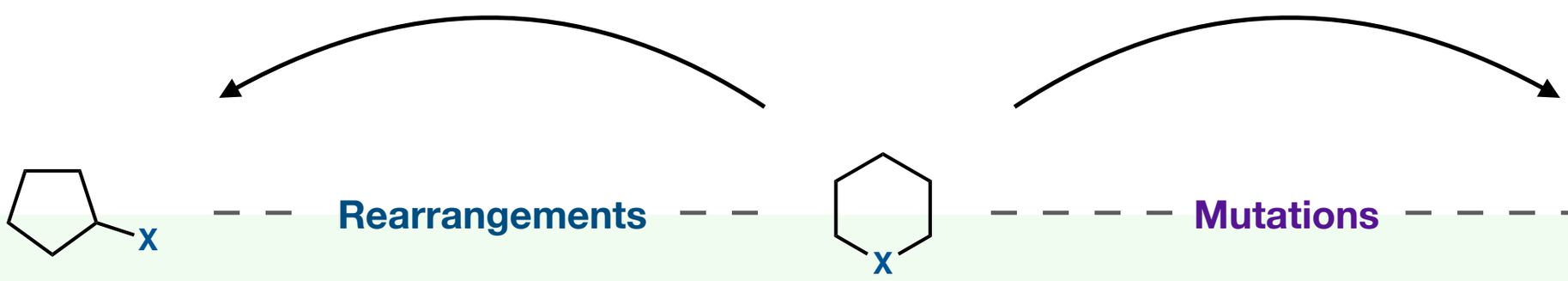


Jurczyk, J.; Woo, J.; Kim, S. F.; Dherange, B. D.; Sarpong, R.; Levin, M. D. *Nat. Synth.* ***2022***, *1*, 352.

A Classification Scheme

contraction

deletion



expansion

insertion

The ring size is increased by one atom

n + 1 single-atom edit

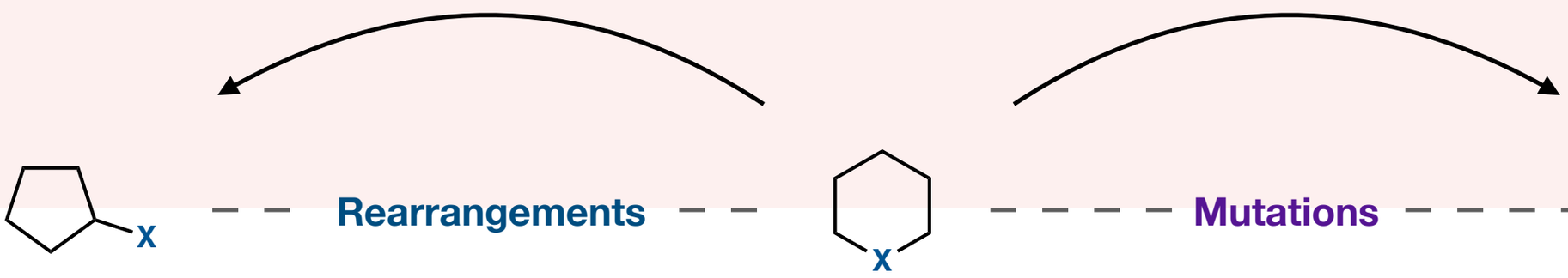
A Classification Scheme

n – 1 single-atom edit

The ring size is decreased by one atom

contraction

deletion



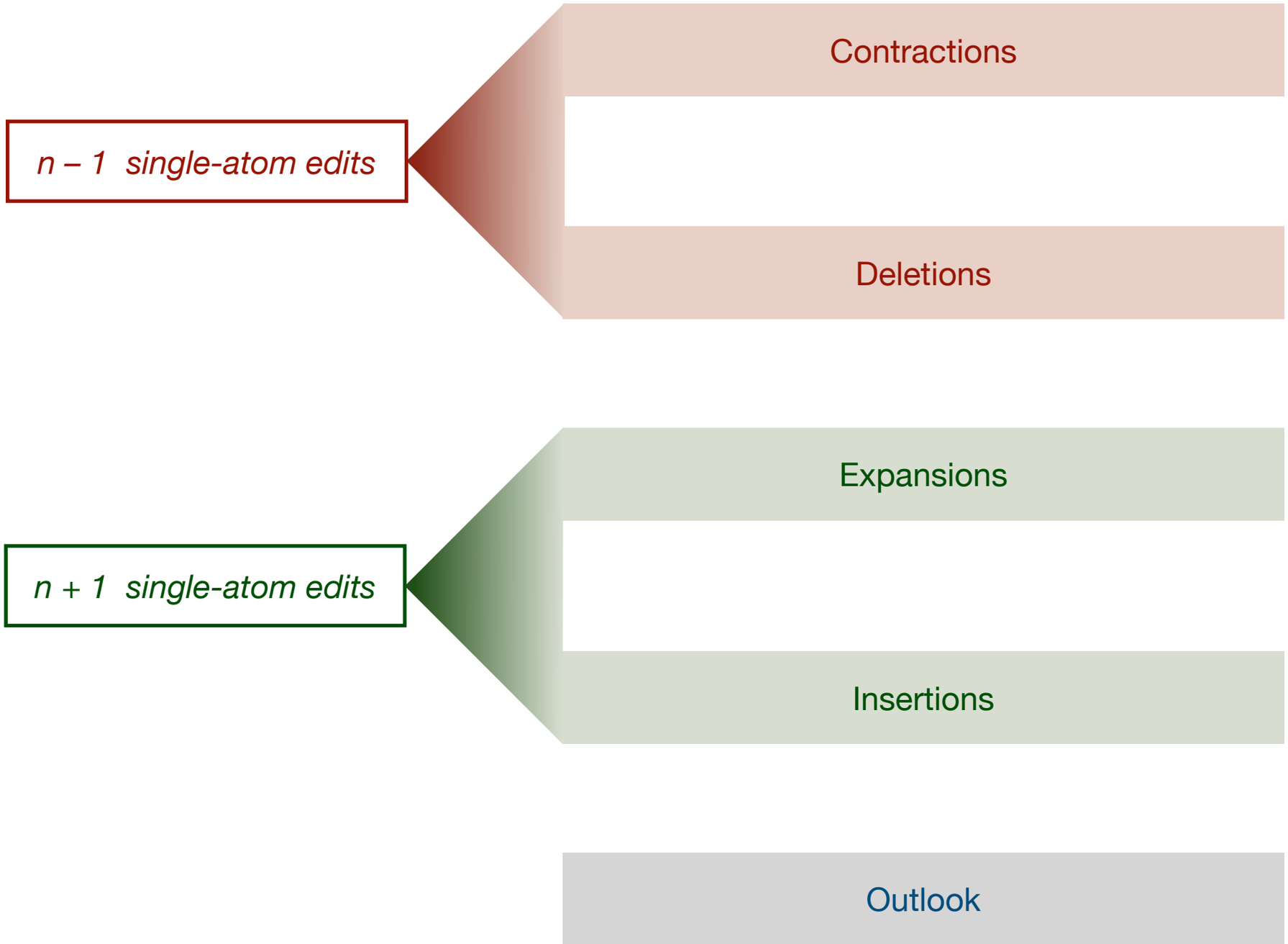
Rearrangements

Mutations

expansion

insertion

Overview


n – 1 single-atom edits
Contractions
Deletions
n + 1 single-atom edits
Expansions
Insertions
Outlook

Overview

n – 1 single-atom edits

Contractions

Deletions

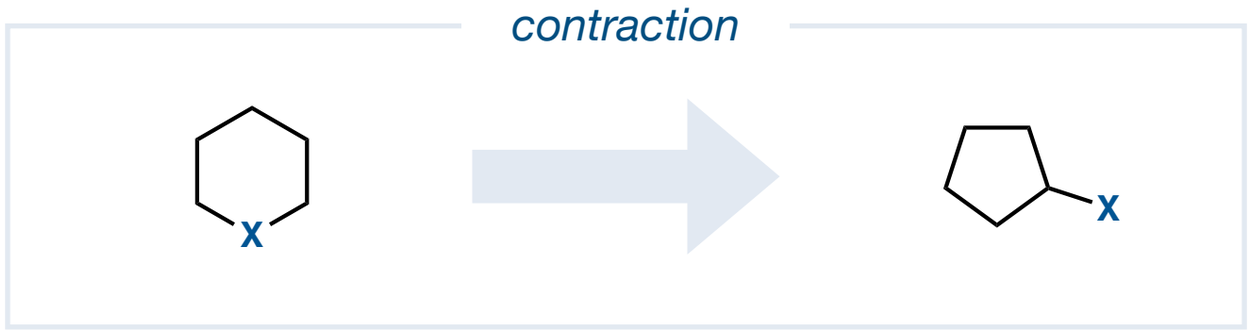
n + 1 single-atom edits

Expansions

Insertions

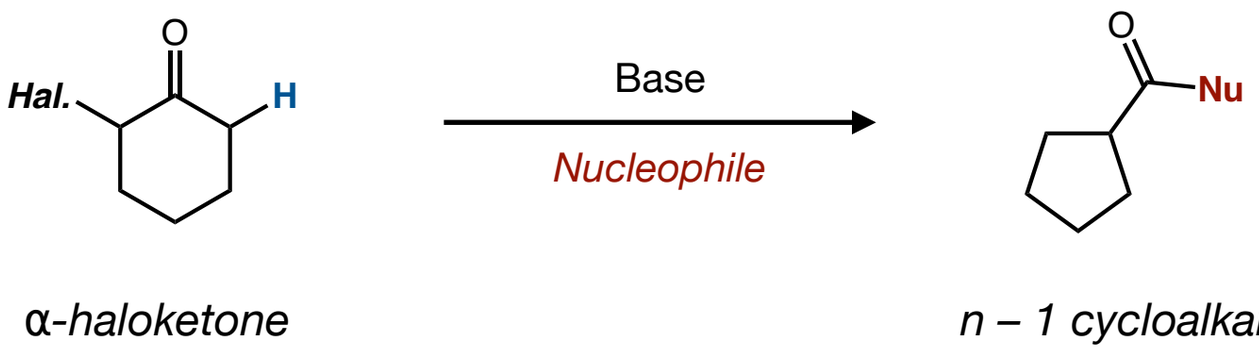
Outlook

Contractions



Contractions are when the <u>ring-size is decreased</u> and a previously-endocylic substituent moves to an exocyclic position

Favorskii Rearrangement

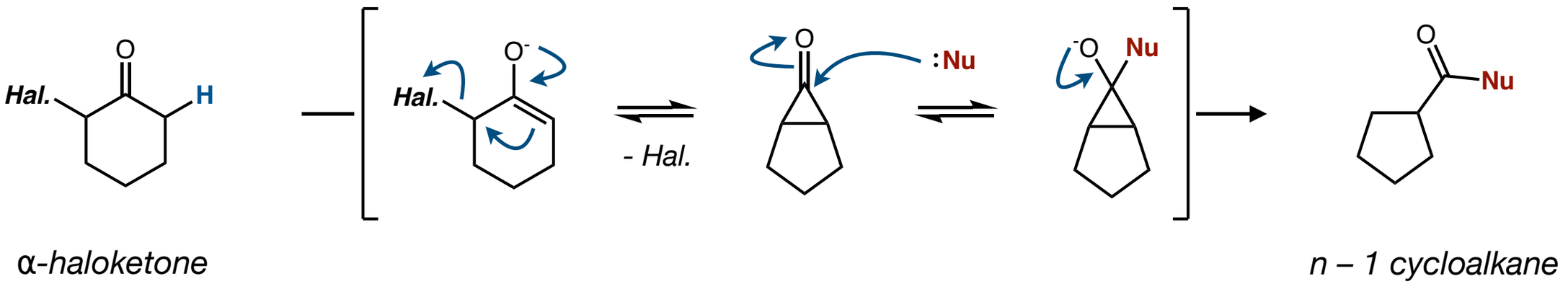


Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, ***1989***, 1111–1114.

Contractions

Contractions are when the <u>ring-size is decreased</u> and a previously-endocylic substituent moves to an exocyclic position

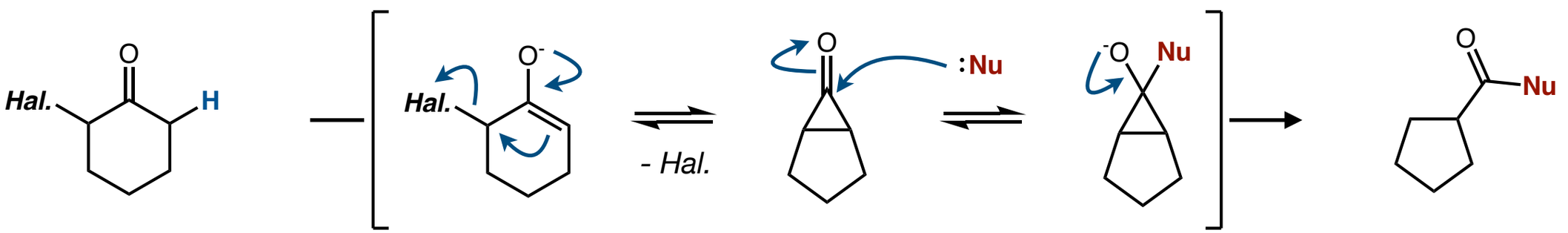
Favorskii Rearrangement



Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, ***1989***, 1111–1114.

Contractions – Favorskii Rearrangement

Favorskii Rearrangement

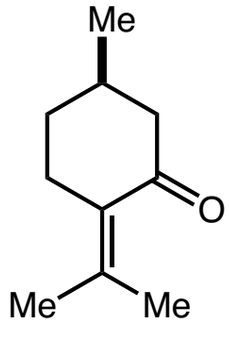


α-*haloketone*

n – 1 cycloalkane

Rapid diversification of (+)-Pulegone

n = 6



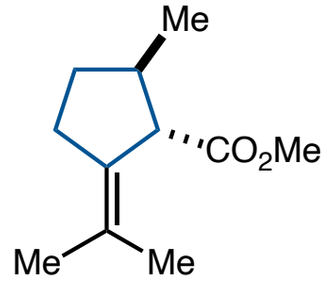
(+)-Pulegone

$7/g (sigma)

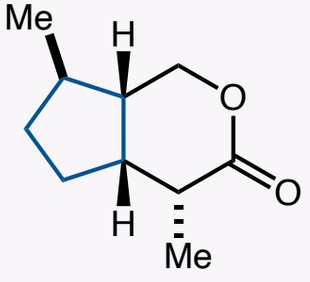
i) Br_2, Et_2O

ii) NaOMe, MeOH

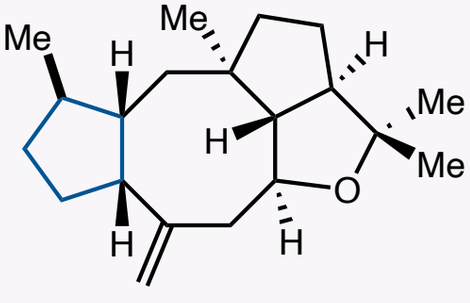
n = 5



Versatile intermediate



(–)-Iridomyrmecin



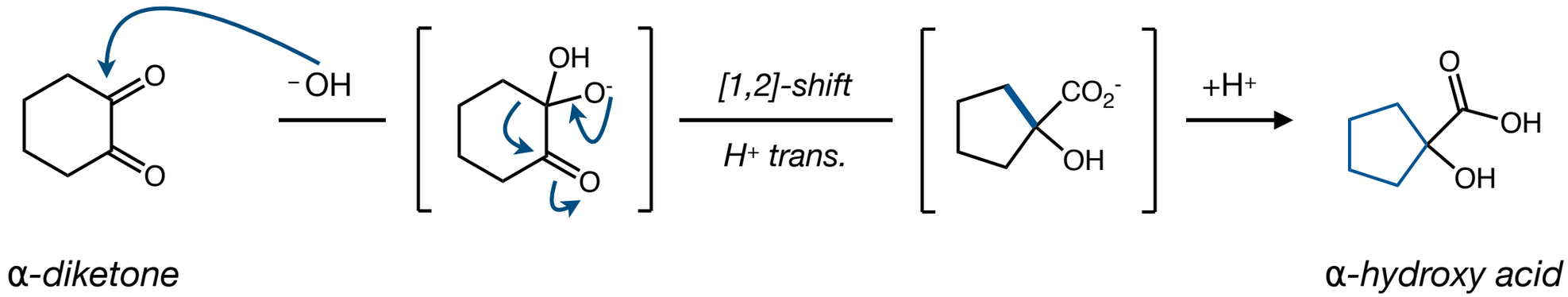
(+)-Epoxydictymene

Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* ***1997***, *119*, 4353.

Wolinsky, J.; Gibson, T.; Chan, D.; Wolf, H. *Tetrahedron*. ***1965***, *21*, 1247.

Benzilic Acid Rearrangement

Benzilic Acid Rearrangement



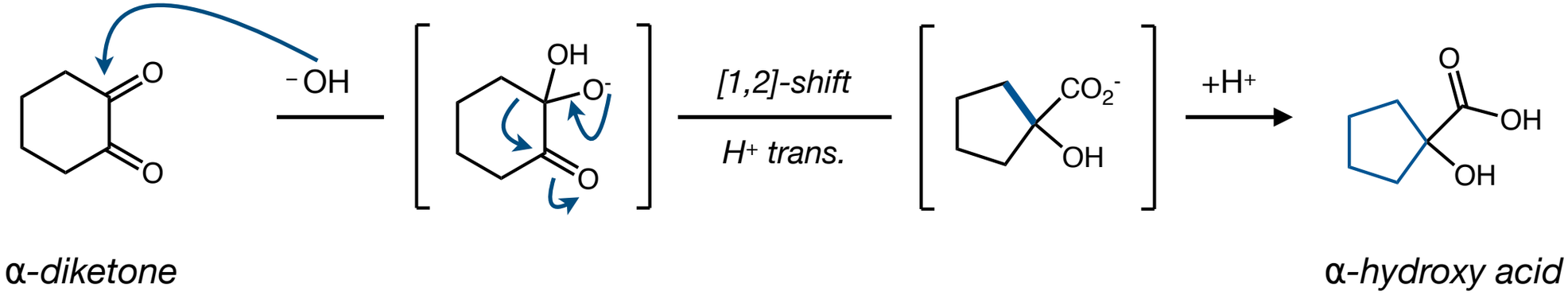
α-*diketone*

α-*hydroxy acid*

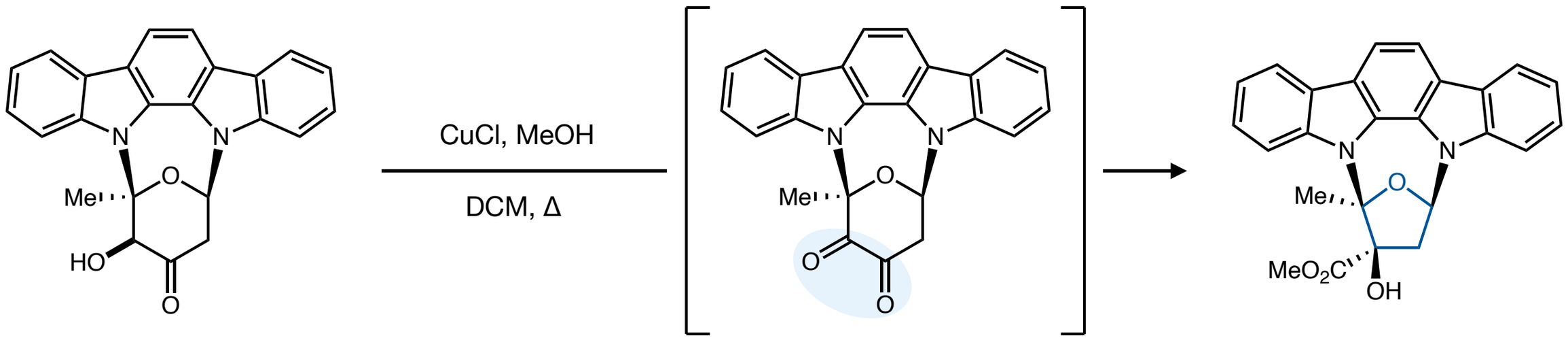
Stoltz, B. M.; Wood, J. L. *Tet. Lett.* **1996**, *37*, 3929.

Benzilic Acid Rearrangement

Benzilic Acid Rearrangement

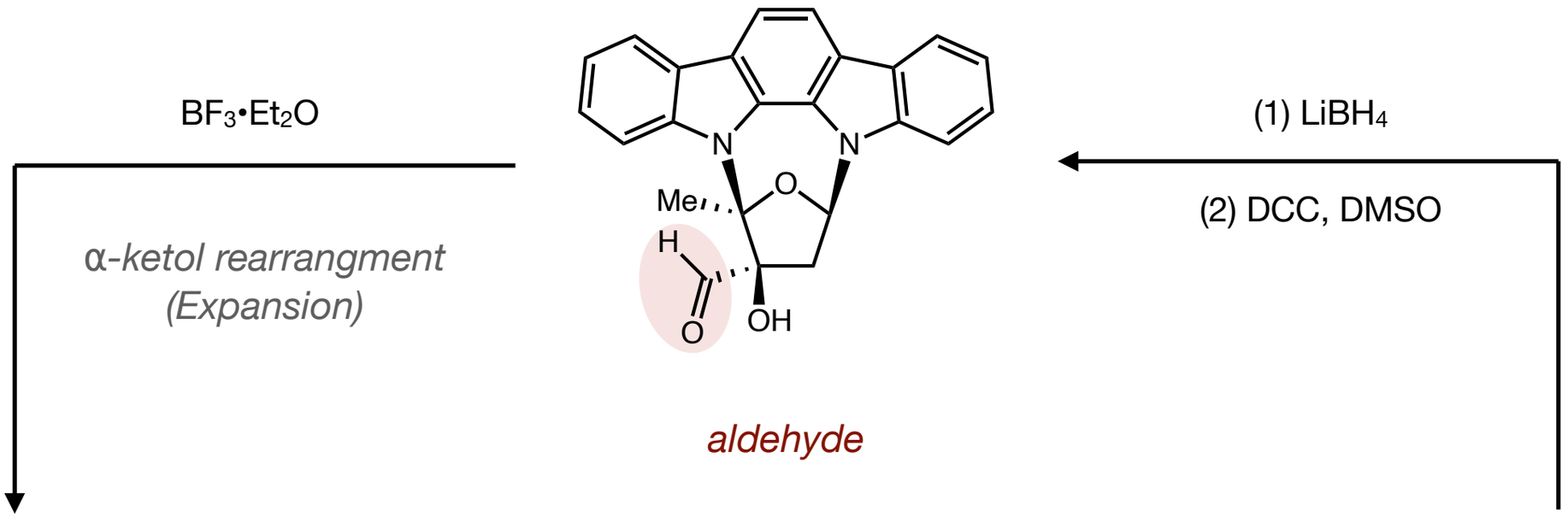


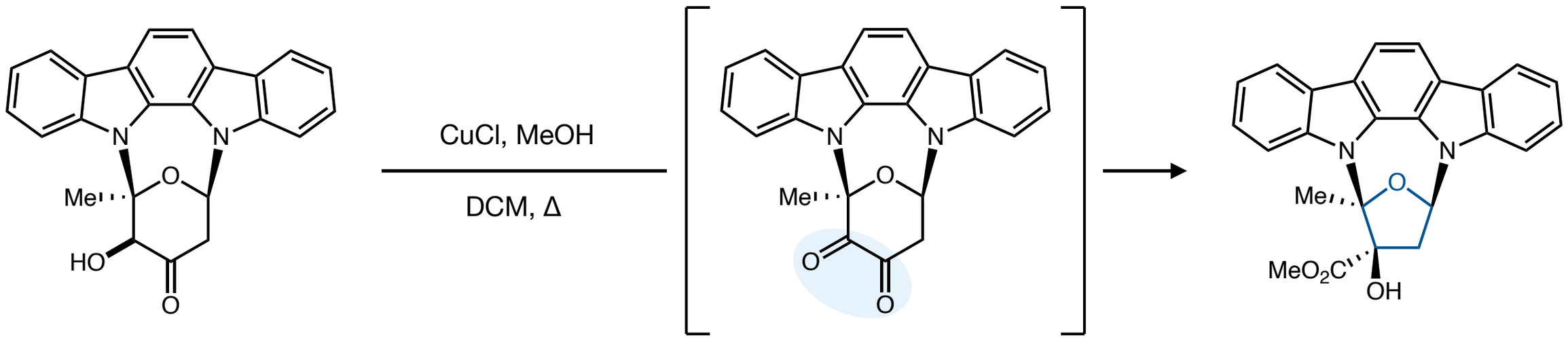
Total synthesis applications



Stoltz, B. M.; Wood, J. L. *Tet. Lett.* **1996**, *37*, 3929.

Benzilic Acid Rearrangement

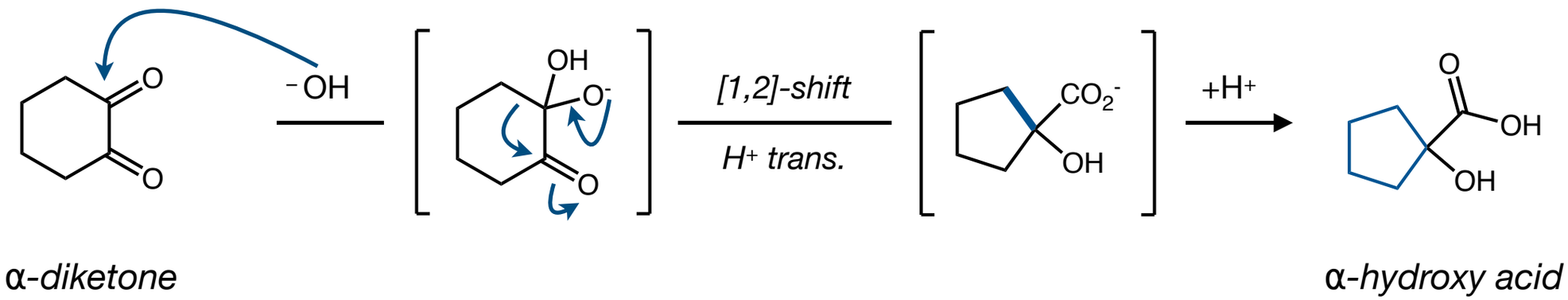




Stoltz, B. M.; Wood, J. L. *Tet. Lett.* **1996**, *37*, 3929.

Benzilic Acid Rearrangement

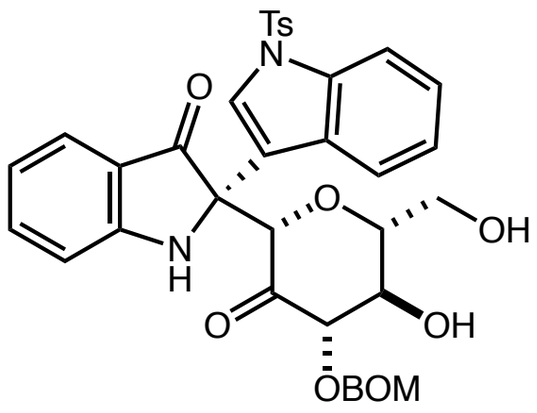
Benzilic Acid Rearrangement



α-*diketone*

α-*hydroxy acid*

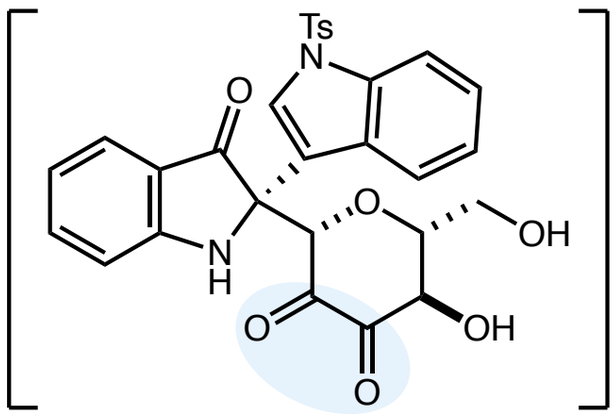
Total synthesis applications



BOM-α-hydroxyketone

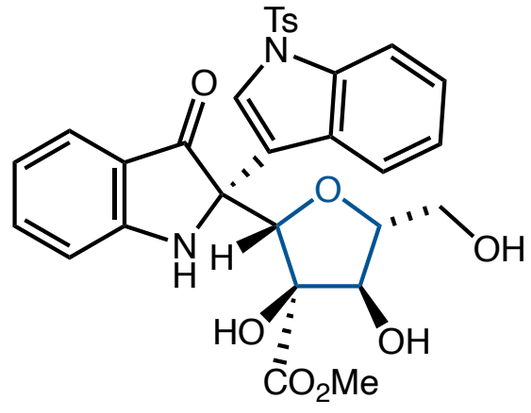
(1) $Pd(OH)_2/C$
MeOH

(2) CuCl, MeOH
DCM, Δ



α-diketone
not isolated

Densely functionalized indole furanoside

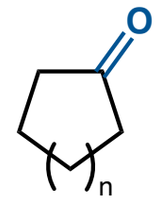


27% yield
(over 2 steps)
towards (–)-isatisine A

Xiao, M. *et al*. *Tetrahedron*. **2015**, *71*, 3705.

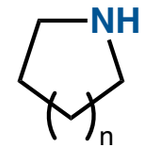
Non-Carbonyl-Containing Ring Contractions

carbonyl-containing starting materials

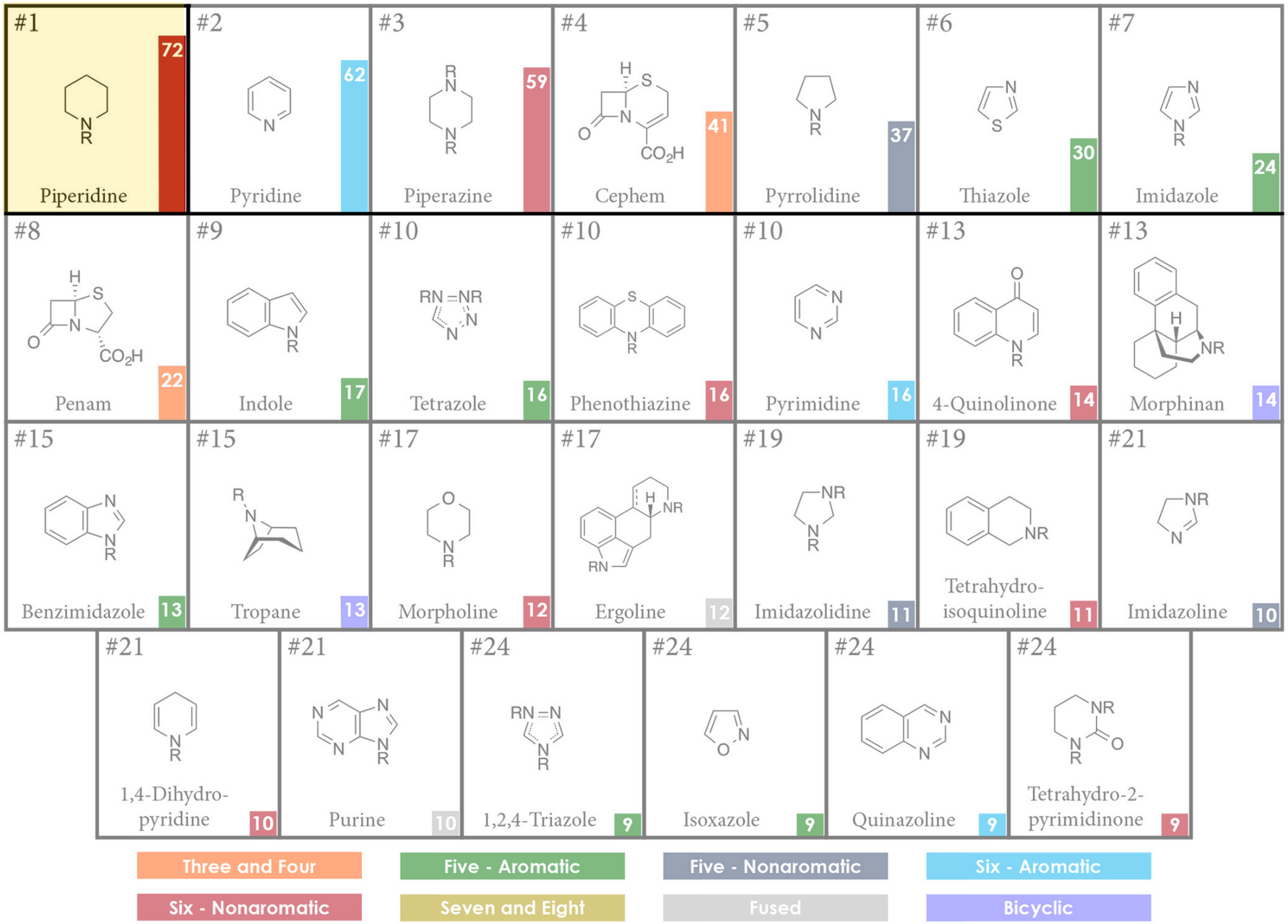


?

non-carbonyl-containing starting materials

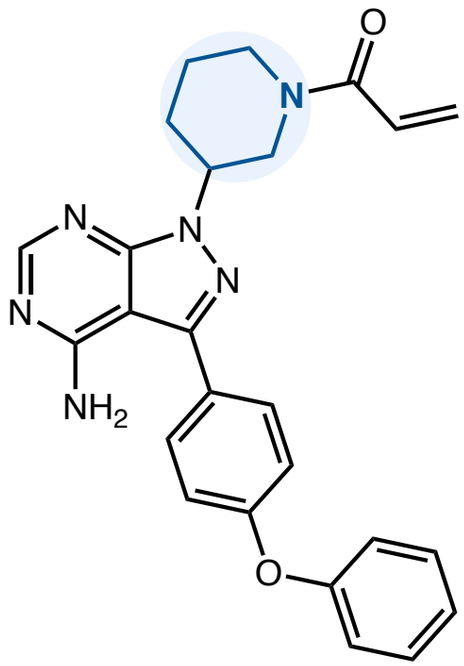


Drugs Have Lots of Saturated Heterocycles

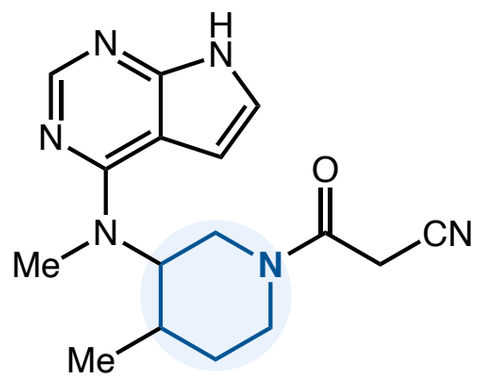


Vitaku, E.; Smith, D. T.; Njardarson, J. T.. *J. Med. Chem.* **2014**, *57*, 10257.

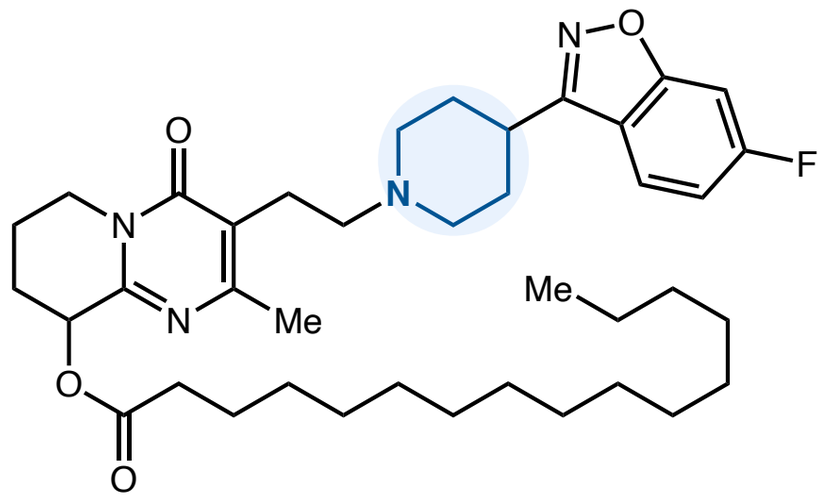
Drugs Containing Piperidine Scaffold



Imbruvica®
AbbVie



Xeljanz®
Pfizer



Invega®
Janssen

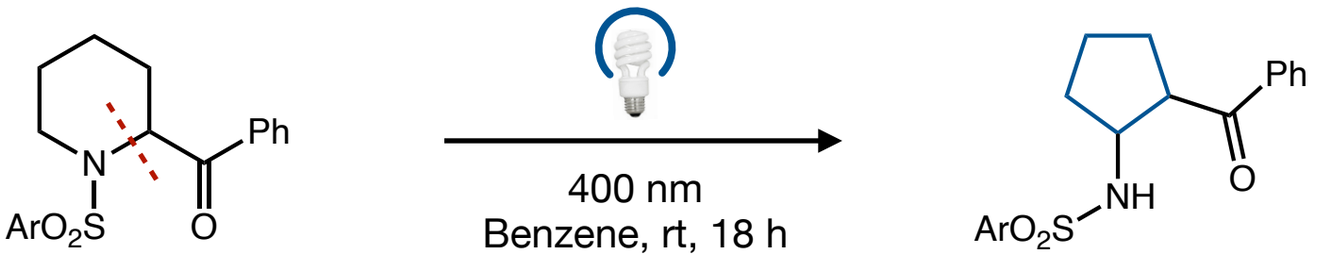
piperidine is the most abundant heterocycle in approved pharmaceuticals

> $16 billion in sales in 2021

Drugs ranging from anticancer, antipsychotic, immunology, etc…

McGrath, N. A.; Brichacek, M.; Njardarson, J. T. *J. Chem. Ed.* **2010**, *87*, 1348.

Photochemical Ring Contractions



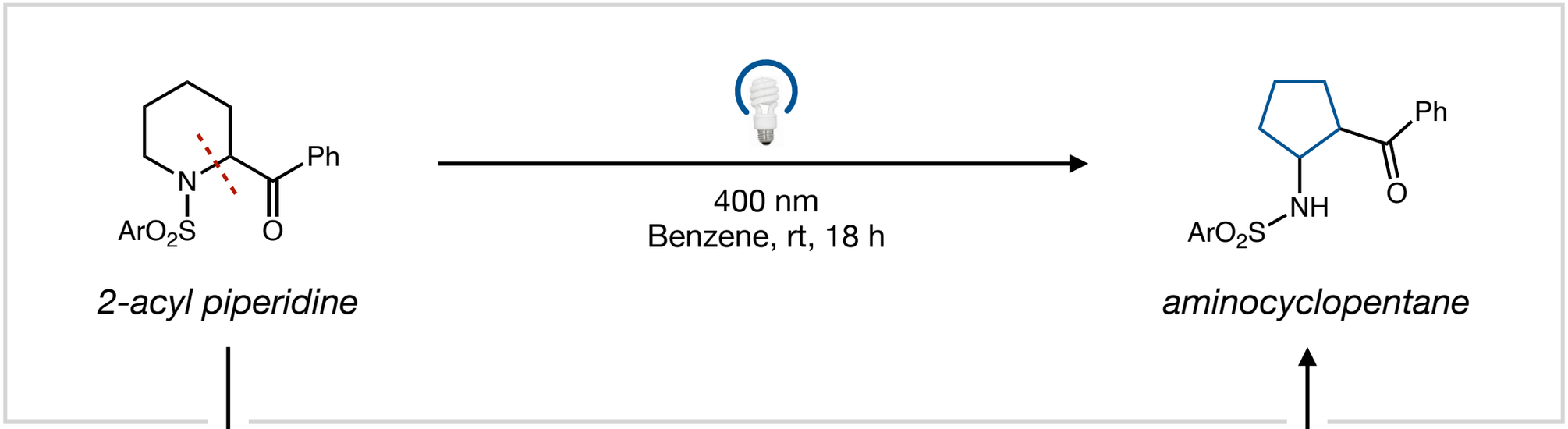
2-acyl piperidine *aminocyclopentane*

"Shuffling nitrogen with a light push"

Richmond Sarpong
UC Berkeley

Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science*. **2021**, *373*, 1004.

Photochemical Ring Contractions



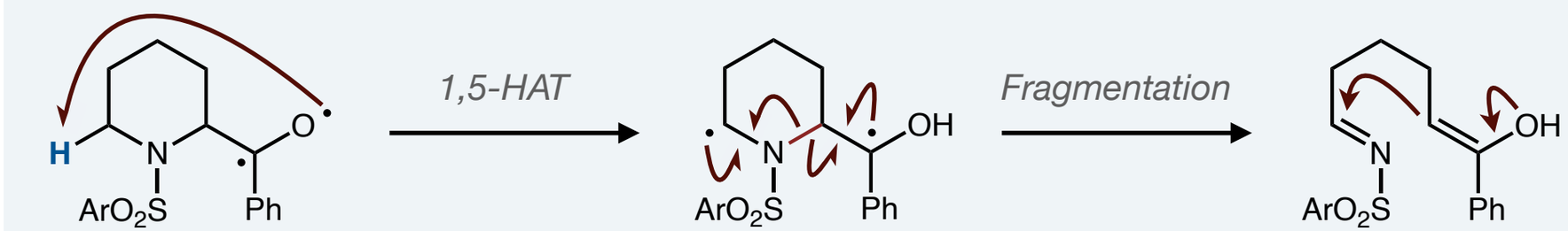
2-acyl piperidine

aminocyclopentane

Excitation

Simple, one-pot, and mild protocol

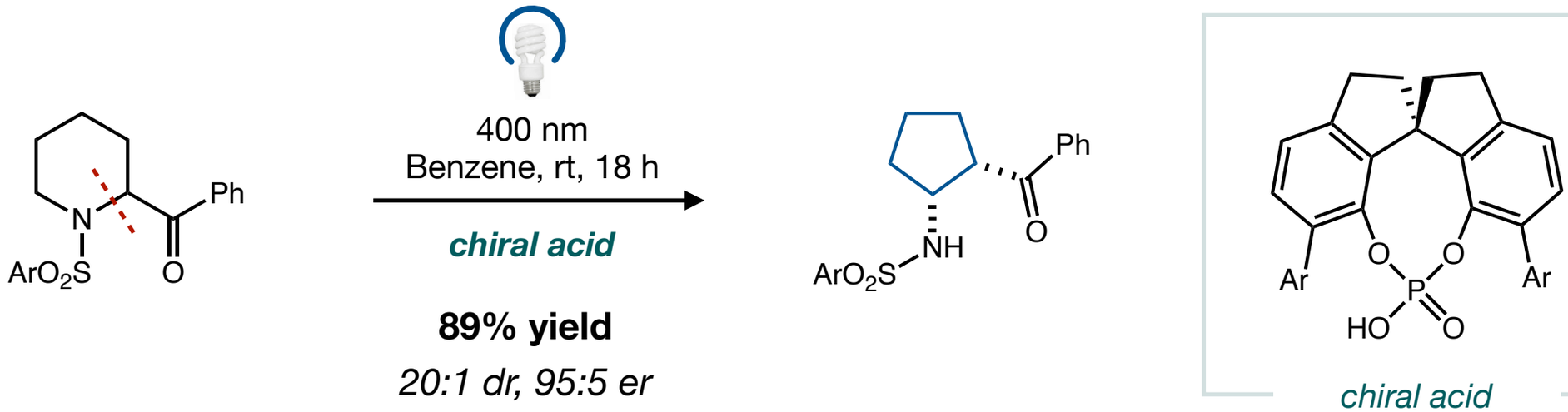
Intramolecular Mannich



Norrish type II Reaction

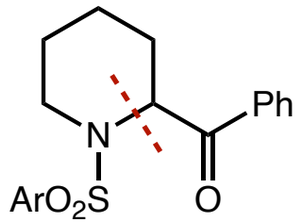
Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science*. **2021**, *373*, 1004.

Photochemical Ring Contractions



Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science*. **2021**, *373*, 1004.

Photochemical Ring Contractions

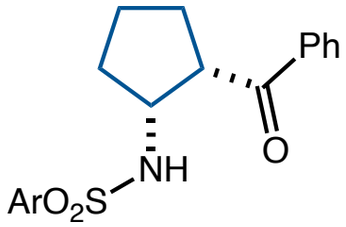


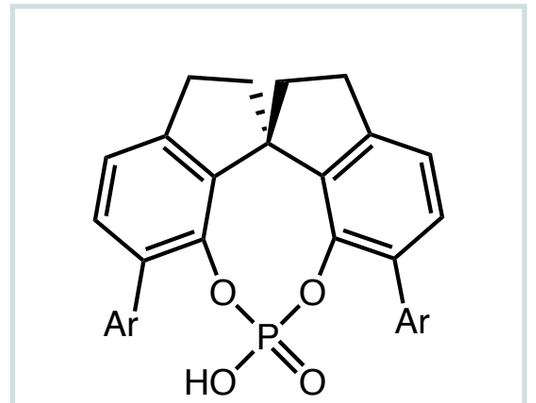
400 nm
Benzene, rt, 18 h

chiral acid

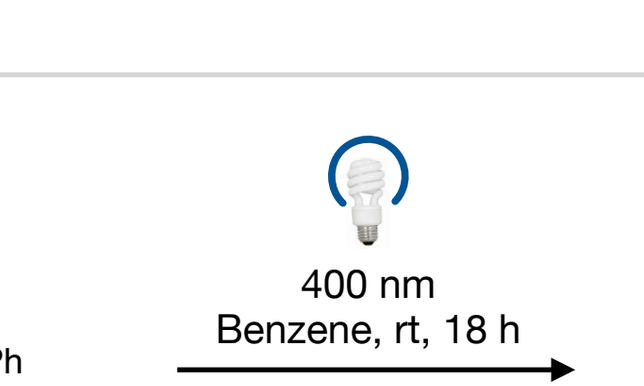
89% yield

20:1 dr, 95:5 er



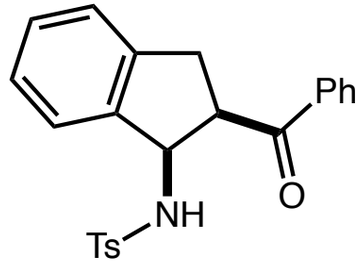


chiral acid



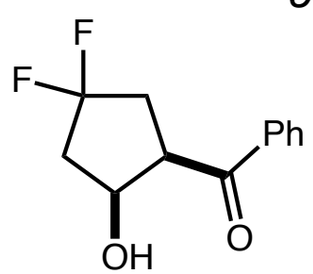
transition state

Strong H-bonding and ion pairing



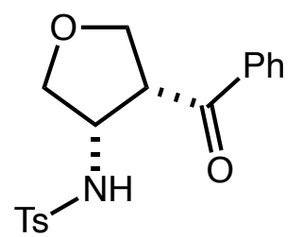
53% yield

9:1 dr, 65:35 er



90% yield

20:1 dr, 83:17 er

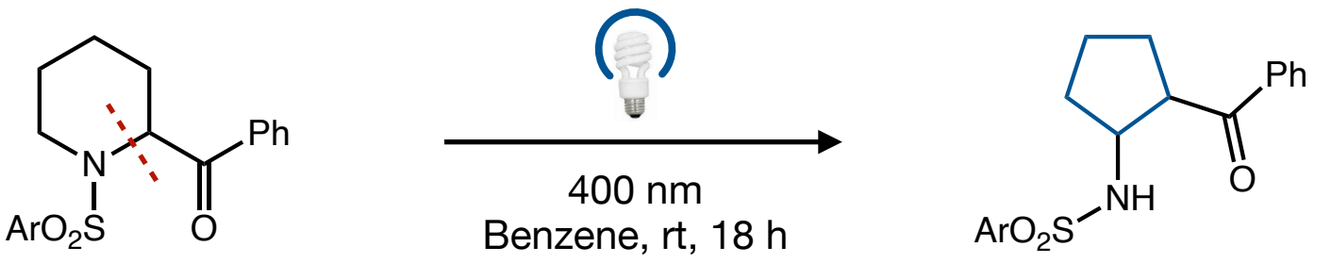


83% yield

20:1 dr, 92:8 er

Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science*. **2021**, *373*, 1004.

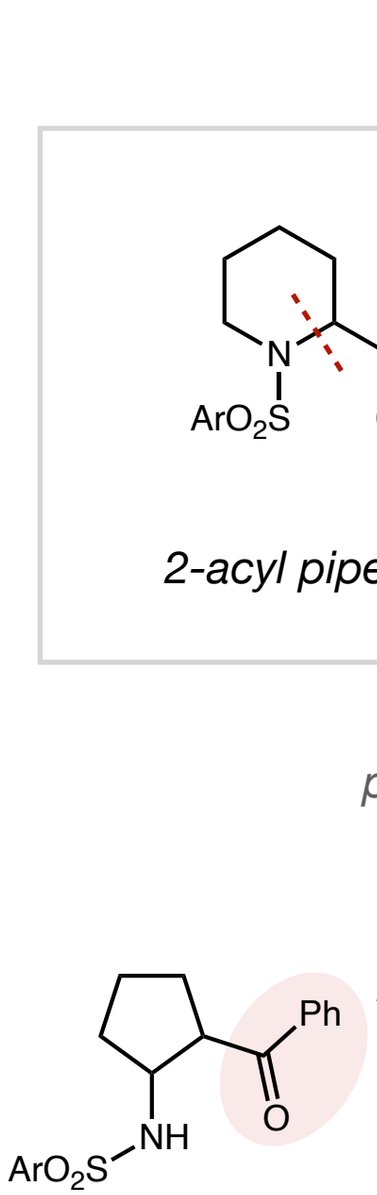
Why isn't Product Degraded?



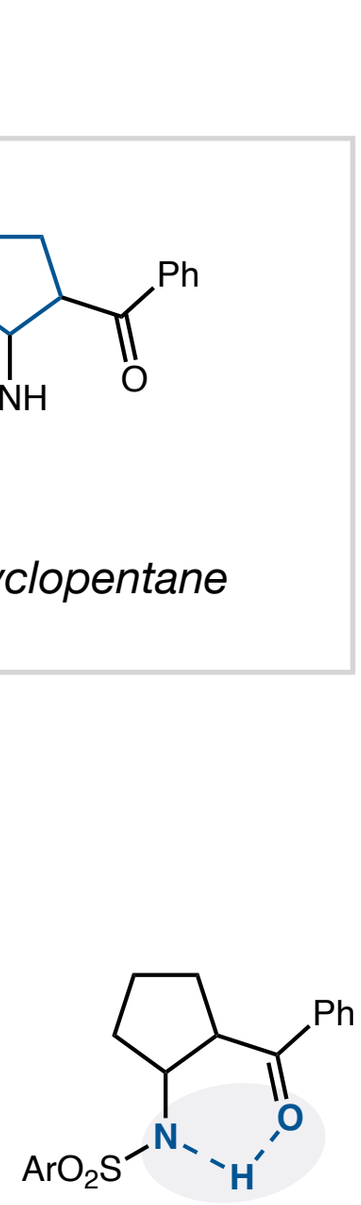
2-acyl piperidine

aminocyclopentane

product contains aryl ketone



Hydrogen bonding



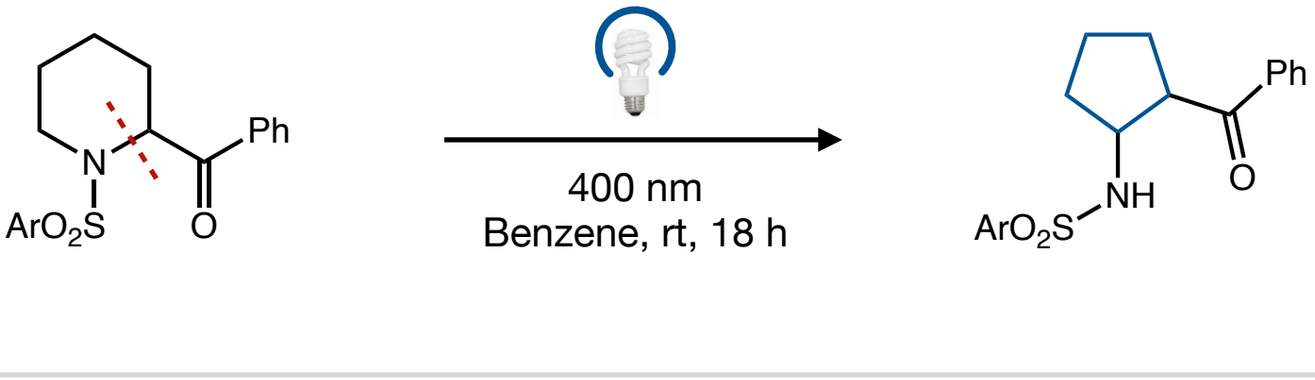
Why doesn't product react further?

Intramolecular H–bonding

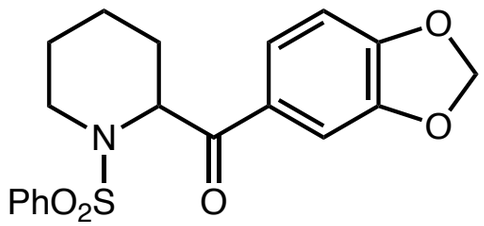
Hypsochromic blue shift in λ_{max}

Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science*. **2021**, *373*, 1004.

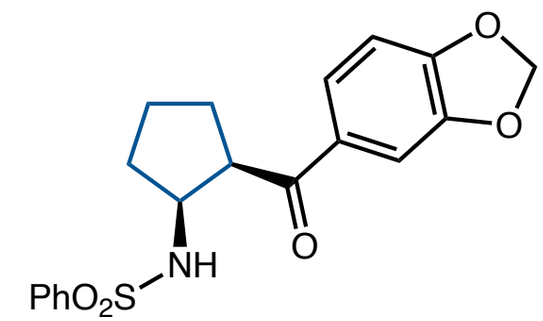
Photochemical Ring Contractions – Drug-like Examples



Drug Editing

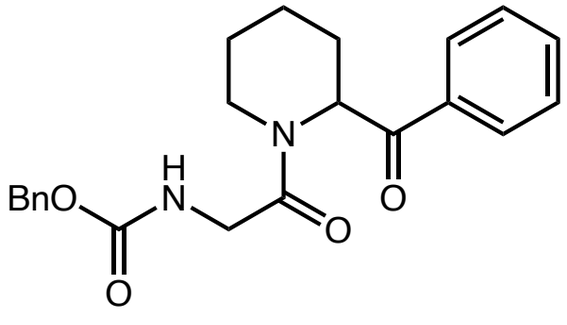


Cyclic MDMC Derivative

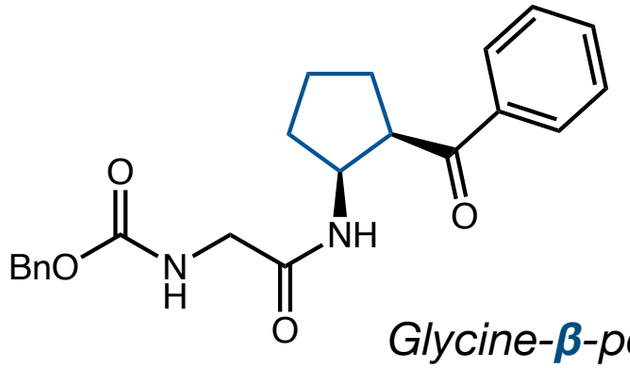


39% yield *(3.2:1 dr)*

Peptide Editing



Glycine-α-peptide

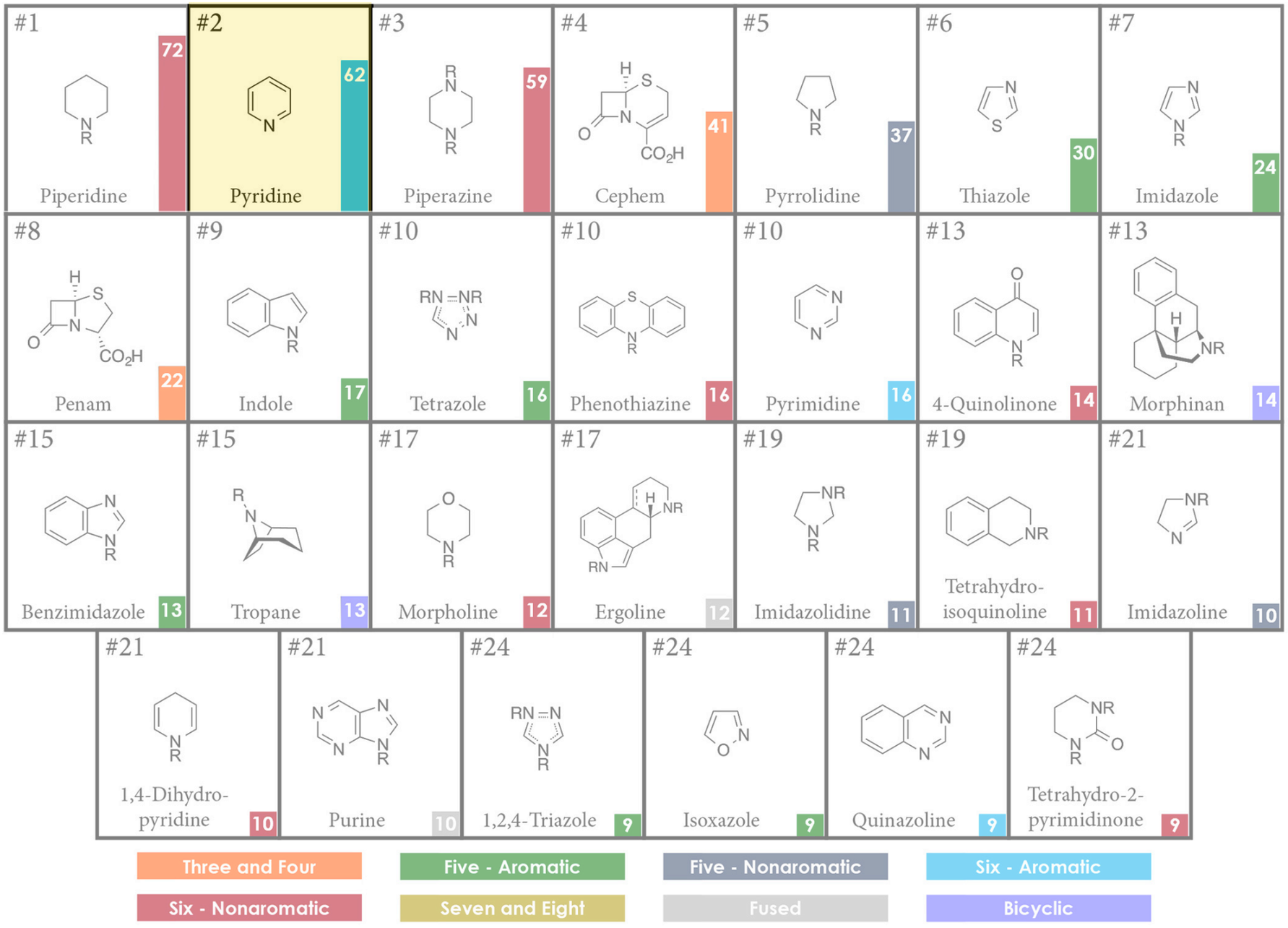


*Glycine-**β**-peptide*

24% yield *(3.1:1 dr)*

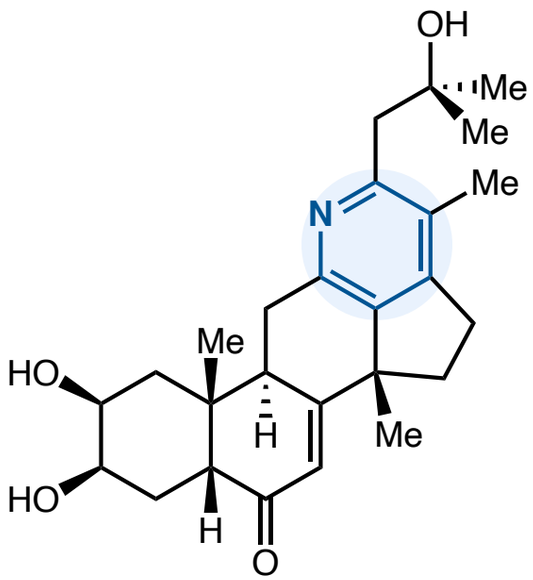
Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-H.; Yeung, C. S.; Sarpong, R. *Science*. **2021**, *373*, 1004.

Drugs Have Lots of Pyridines



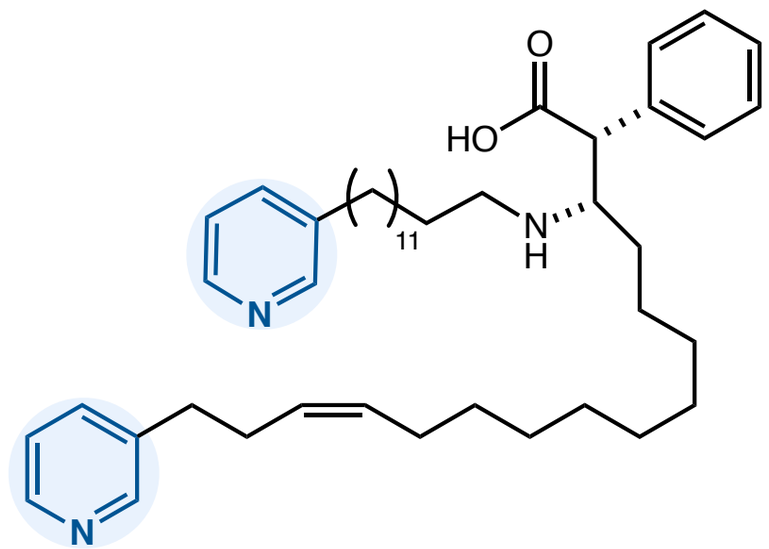
Vitaku, E.; Smith, D. T.; Njardarson, J. T.. *J. Med. Chem.* ***2014***, *57*, 10257.

Pyridines in Drugs & Natural Products



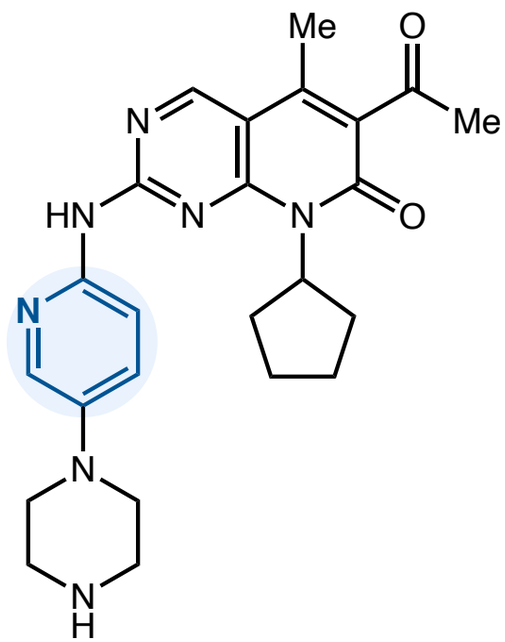
Diploclidine

antihistamine



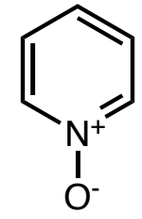
Nakinadine A

interesting cytotoxicity



Ibrance®

anticancer

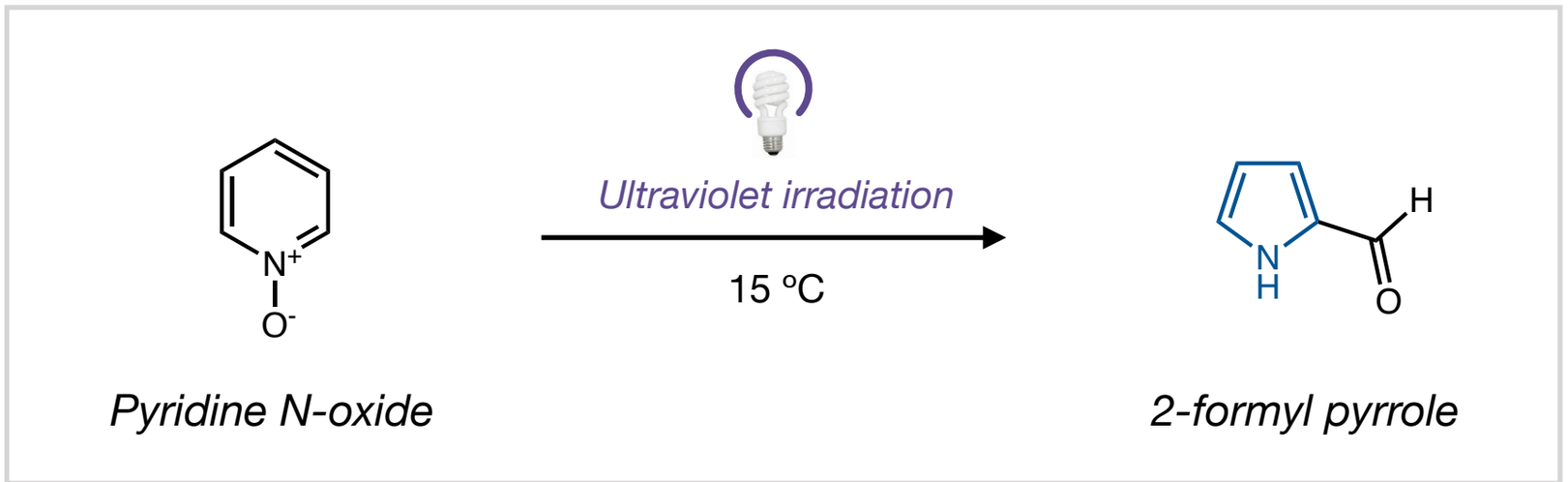


Pyridine N-oxide

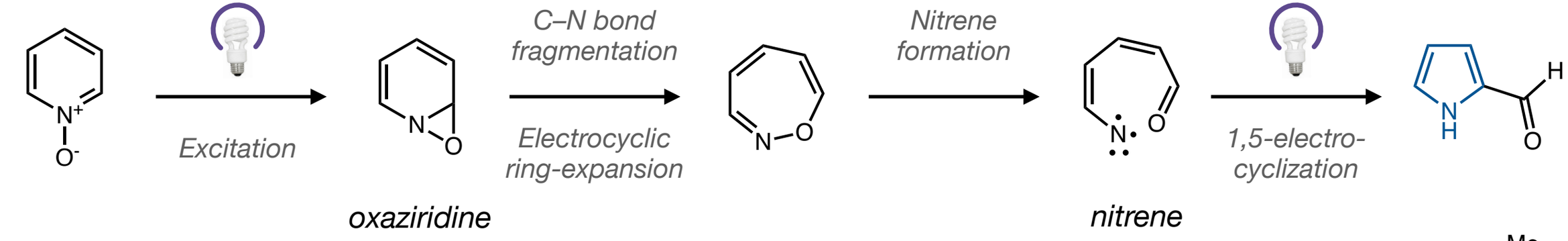
- > 19,000 1-step reactions on SciFinder, not including patents
- many drugs contain N-oxides
- PNO is more nucleophilic and more electrophilic

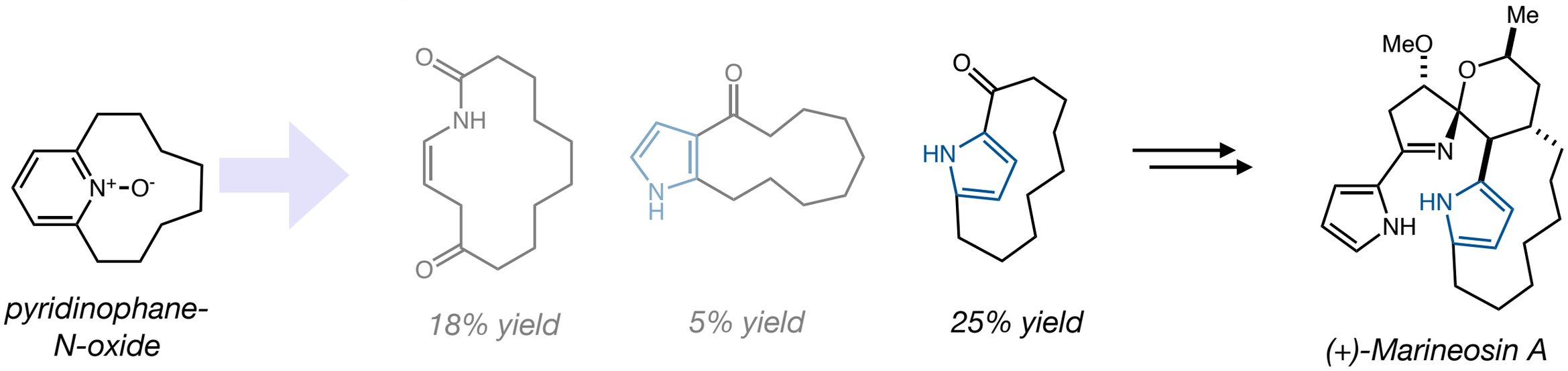
De, S.; Kumar, A. S. S.; Shah, S. K.; Kazi, S.; Sarkar, N.; Banerjee, S.; Dey, S. *RSC Adv.* ***2022***, *12*, 15385.

(Hetero)Aromatic Ring Contractions



Mechanism





Bellamy, F.; Martz, P.; Streith, L. *Heterocycles*. **1975**, *3*, 395.

Overview

n – 1 single-atom edits

Contractions

Deletions

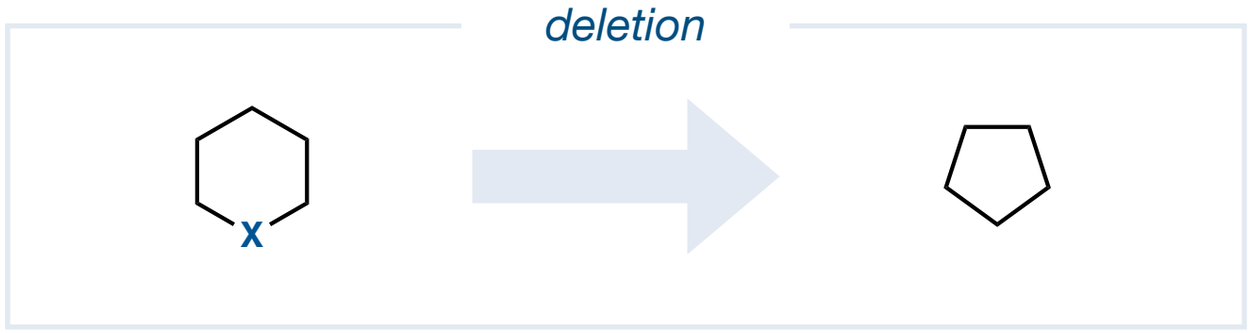
n + 1 single-atom edits

Expansions

Insertions

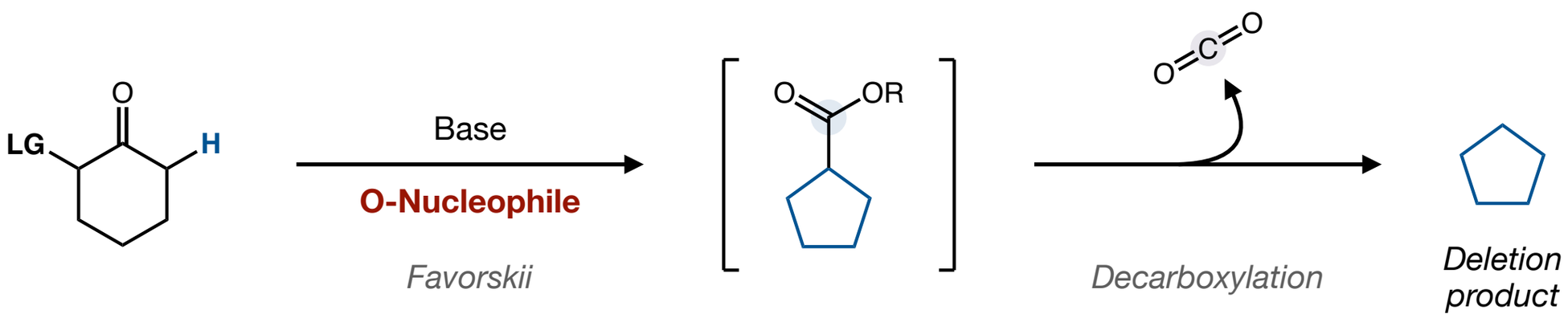
Outlook

Deletions



Deletions are when the ring-size is decreased and the previously-endocyclic atom is **removed entirely from the molecule**

Favorskii Rearrangement (again?!)



Decarboxylative Favorskii is formally a **deletion**

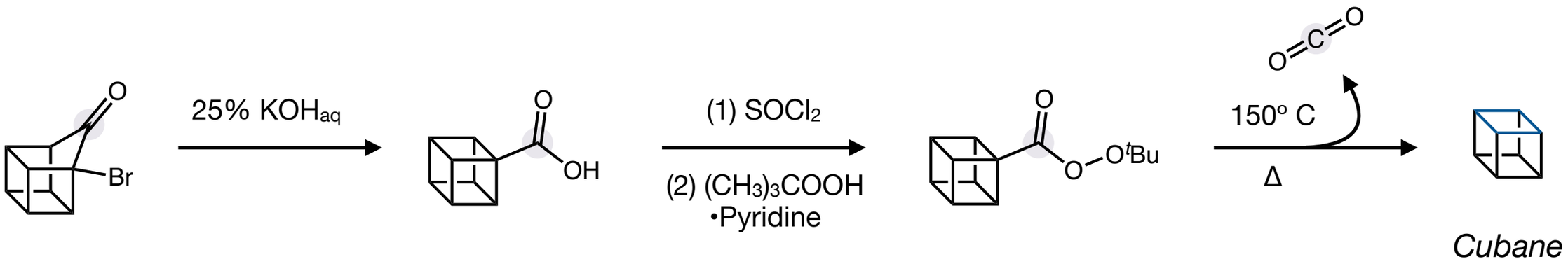
Carbonyl-Related Deletions: First Cubane Synthesis

Cubane

- Reduces C(sp^2)-character in molecules
- Improved solubility and metabolic stability
- Suitable as a phenyl ring bioisostere

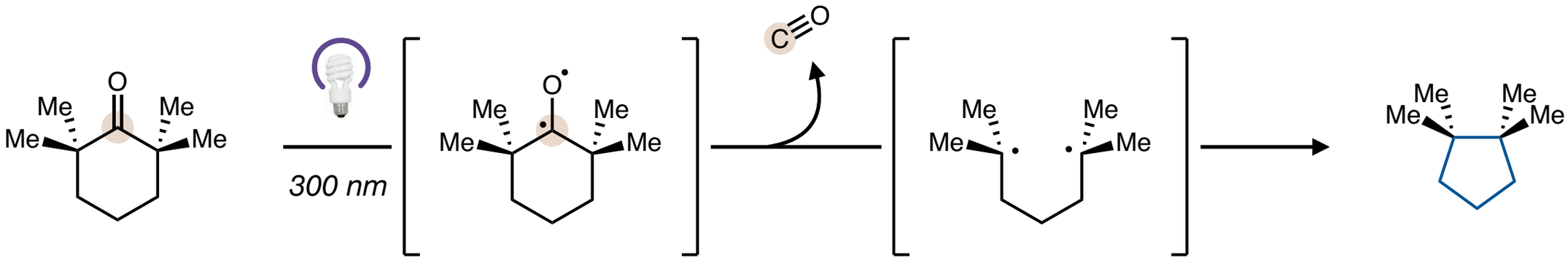
Incorporation into pharmaceuticals

1964 *– First synthesis of cubane – Eaton & Cole*



Eaton, P. E.; Cole, T. W. *J. Am. Chem. Soc.* **1964**, *86*, 962.

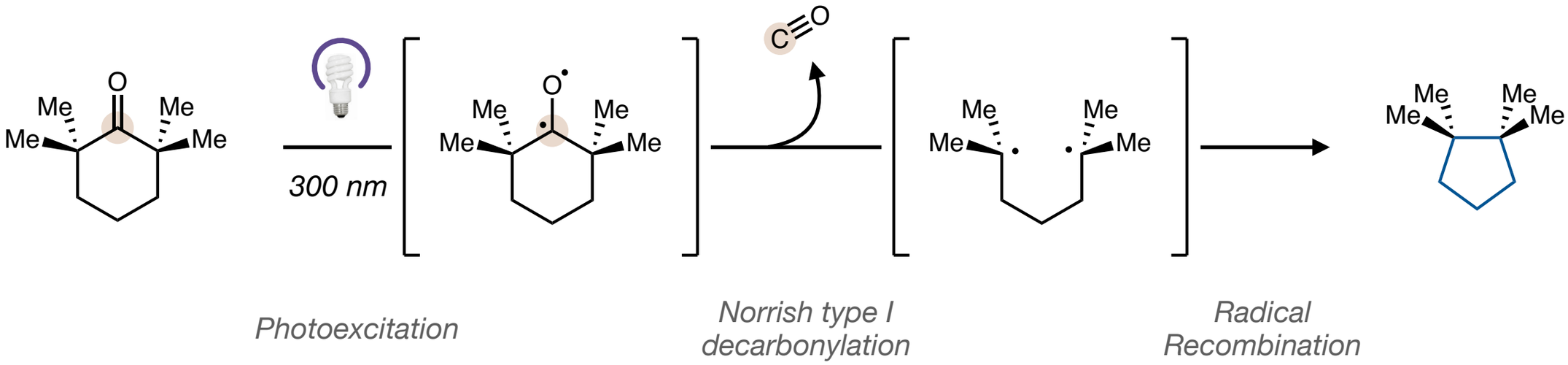
Photodecarbonylation: Formal CO Deletion



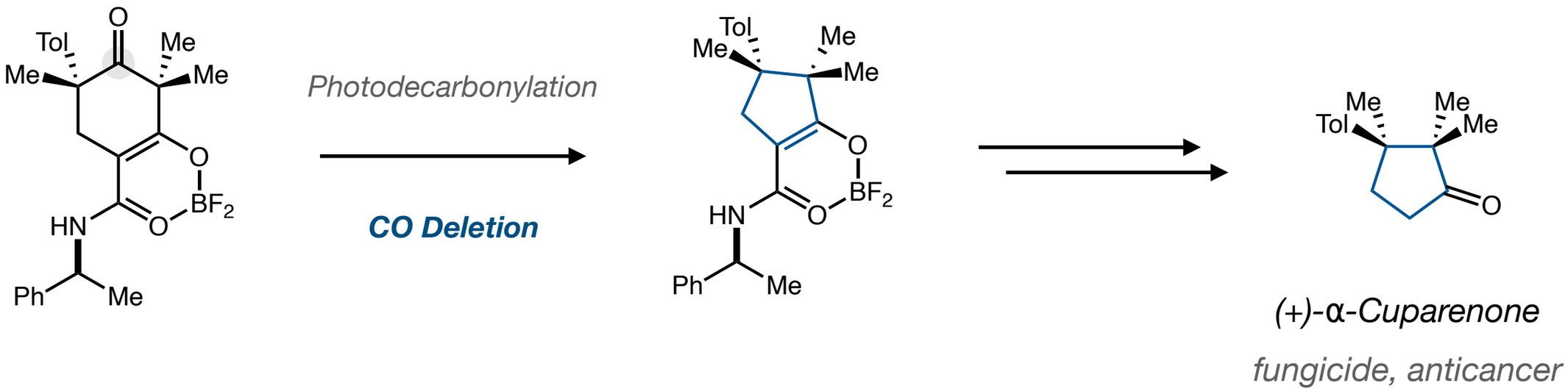
- Simple and ‘green’ approach (few steps, and higher yields)
- Easy to scale-up
- Can stereoselectively forge contiguous all-carbon quaternary centers

Natarajan, A.; Ng, D.; Yang, Z.; Garcia-Garibay, M.A. *Angew. Chem. Int. Ed*. **2007**, *46*, 6485.

Photodecarbonylation: Formal CO Deletion

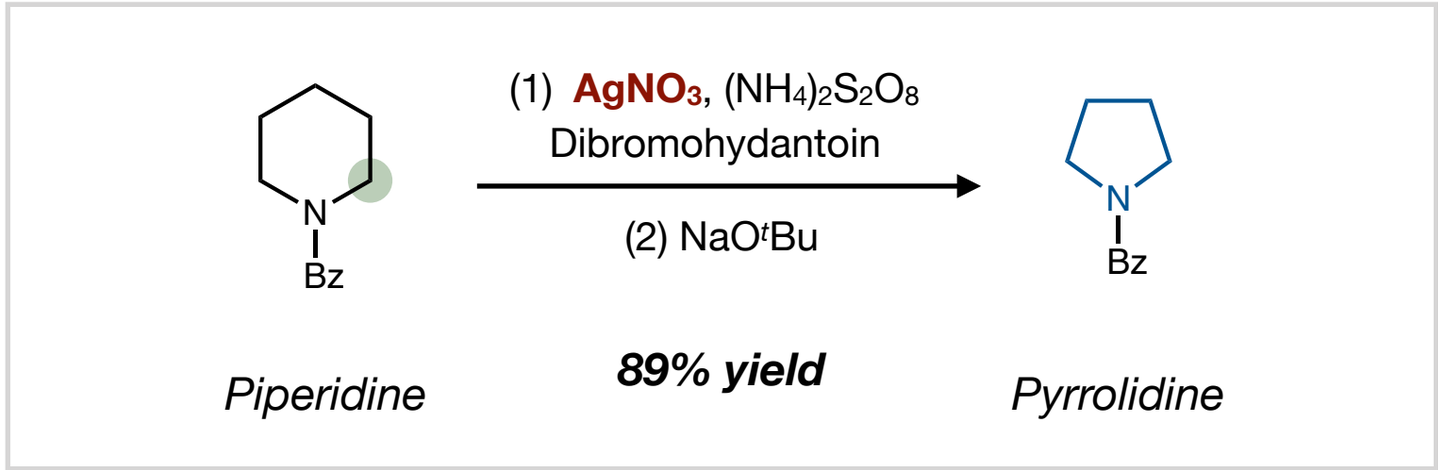


Garcia-Garibary – Synthesis of (+)-α-Cuparenone



Natarajan, A.; Ng, D.; Yang, Z.; Garcia-Garibay, M.A. *Angew. Chem. Int. Ed*. **2007**, *46*, 6485.

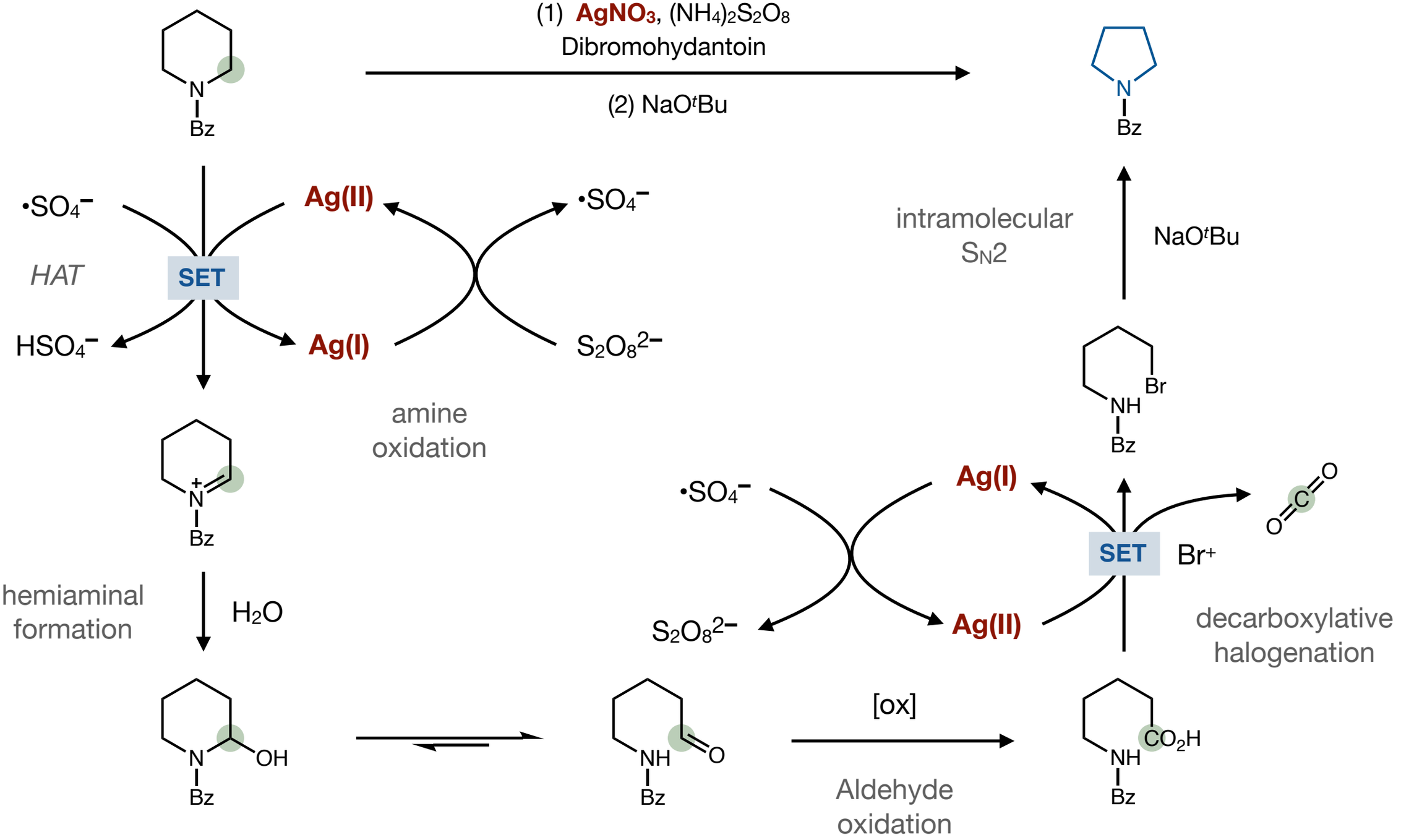
Deconstructive Diversification of Cyclic Amines



Jose Roque
UC Berkeley

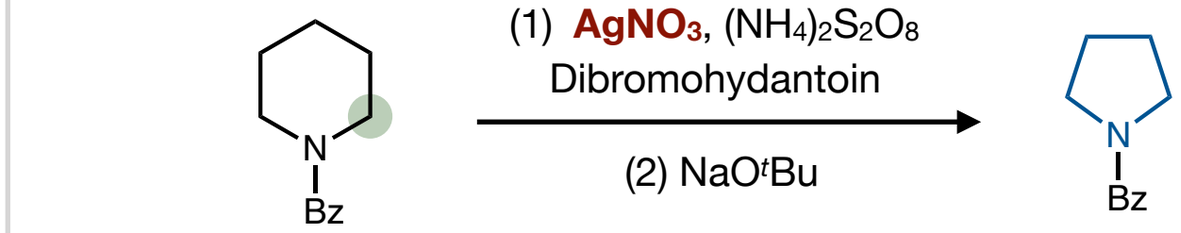
Roque, J. B.; Kuroda, Y.; Gottemann, L. T.; Sarpong, R. *Nature*. **2018**, *564*, 244.

Deconstructive Diversification of Cyclic Amines – Mechanism



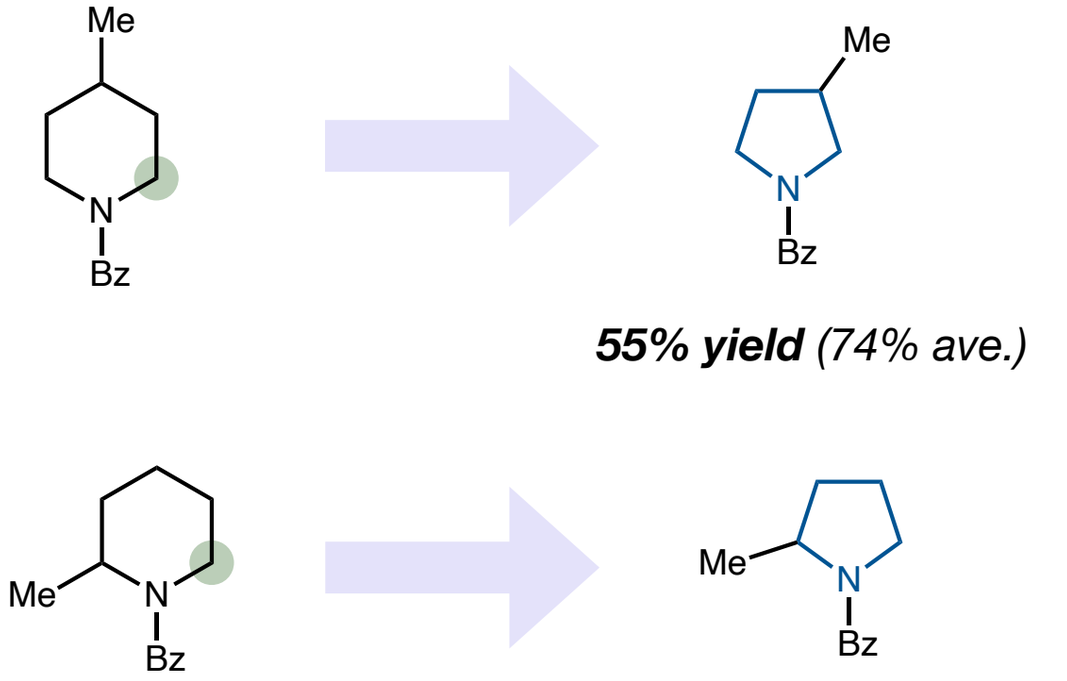
Roque, J. B.; Kuroda, Y.; Gottemann, L. T.; Sarpong, R. *Nature*. **2018**, *564*, 244.

Deconstructive Diversification of Cyclic Amines – Scope



sat. heterocycle *C-deletion product*

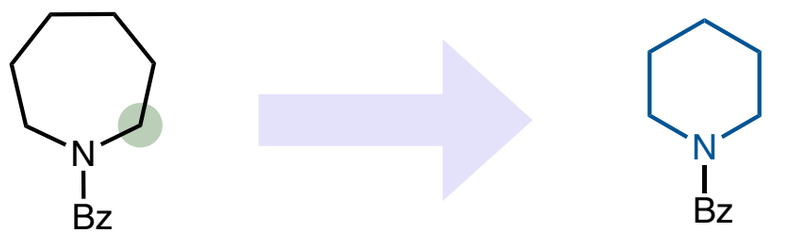
Substituted piperidine editing



55% yield *(74% ave.)*

60% yield *(77% ave.)*

7-membered ring modification

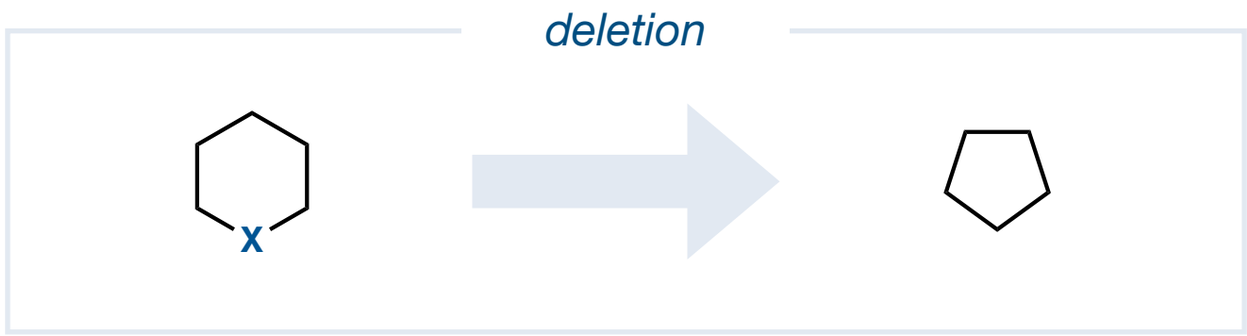


azepane *piperidine*

35% yield *(59% ave.)*

Roque, J. B.; Kuroda, Y.; Gottemann, L. T.; Sarpong, R. *Nature*. **2018**, *564*, 244.

Non-Carbonyl Deletions: Nitrogen Deletion of Secondary Amines



What about deletion of a heteroatom?

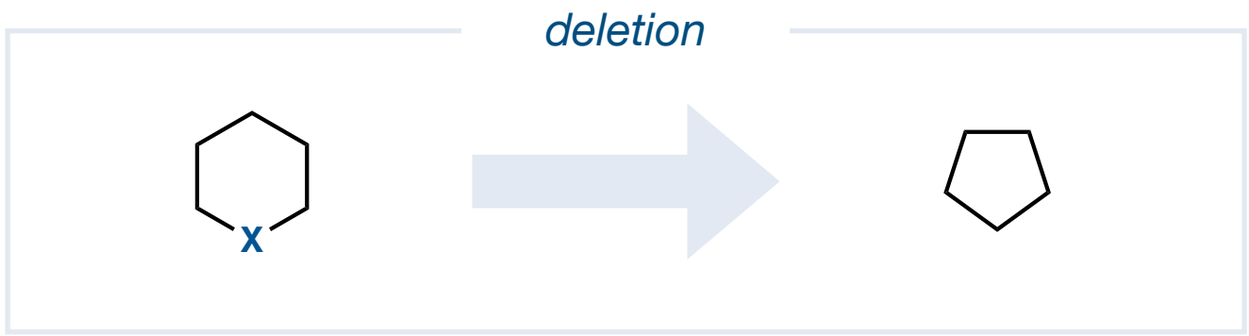
Extrusion of dinitrogen

$\Delta G << 0$

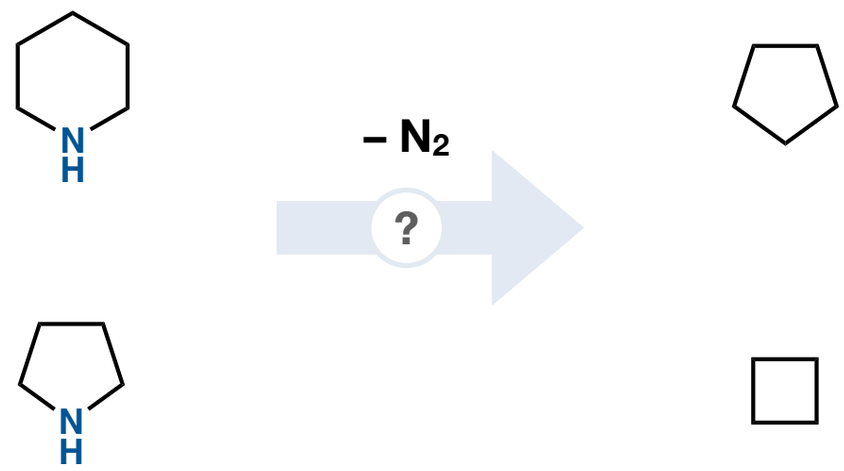
Mark Levin
Univ. of Chicago

Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature*. **2021**, *593*, 223.

Non-Carbonyl Deletions: Nitrogen Deletion of Secondary Amines



What about deletion of a heteroatom?



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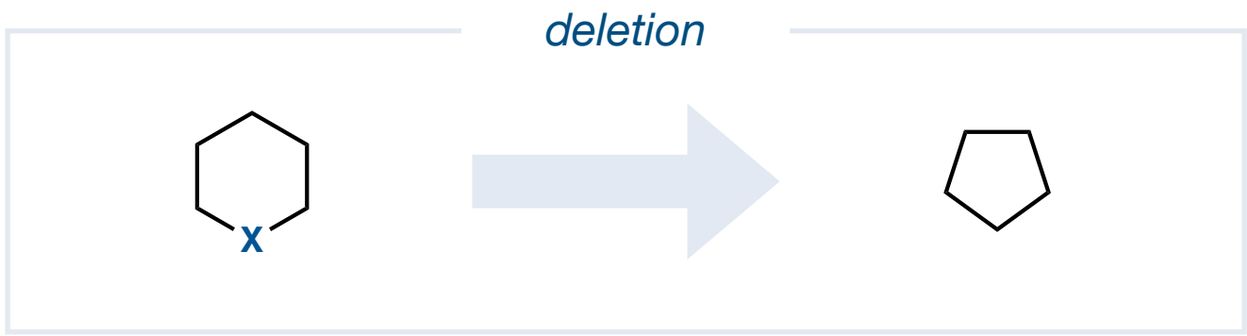
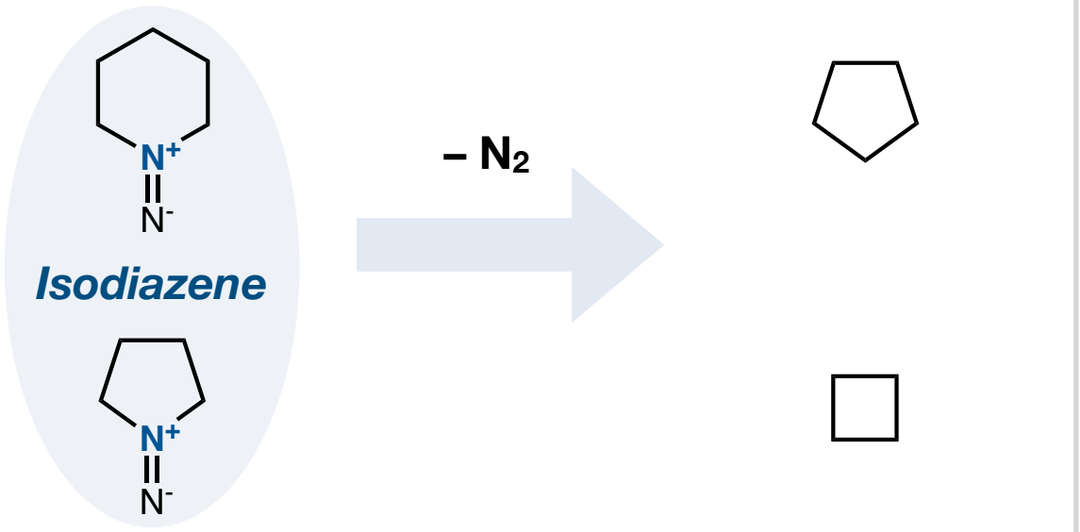
Univ. of Chicago

Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature*. **2021**, *593*, 223.

Non-Carbonyl Deletions: Nitrogen Deletion of Secondary Amines



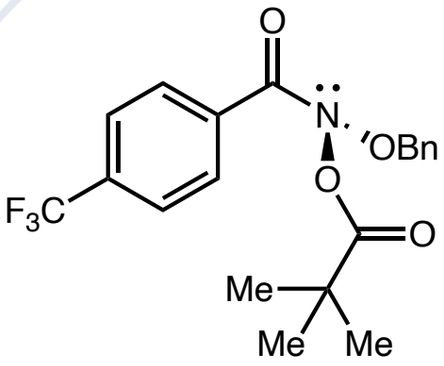
What about deletion of a heteroatom?



Mark Levin
Univ. of Chicago

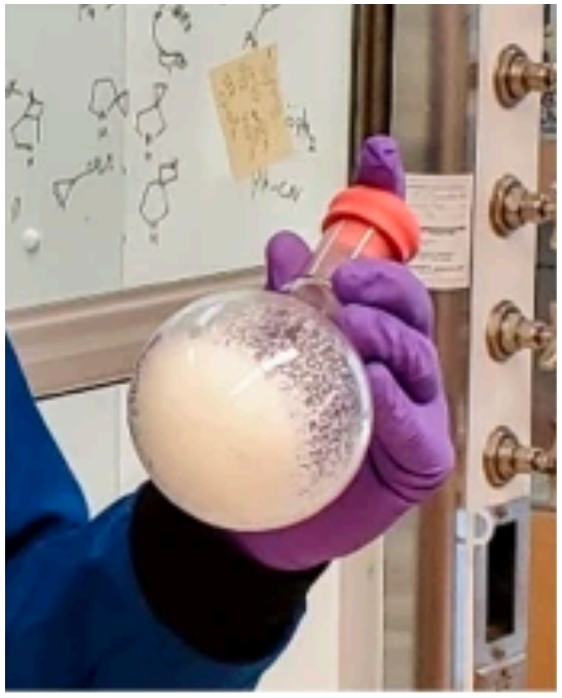
Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature*. **2021**, *593*, 223.

Non-Carbonyl Deletions: Nitrogen Deletion of Secondary Amines



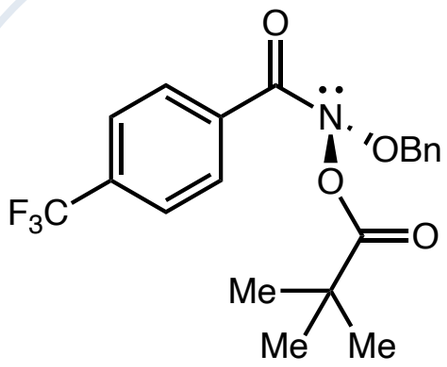
Anomeric amide

- Straightforward to prepare on a multigrain scale
- 78% yield over 3 steps
- No chromatographic methods necessary to purify



Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature*. **2021**, *593*, 223.

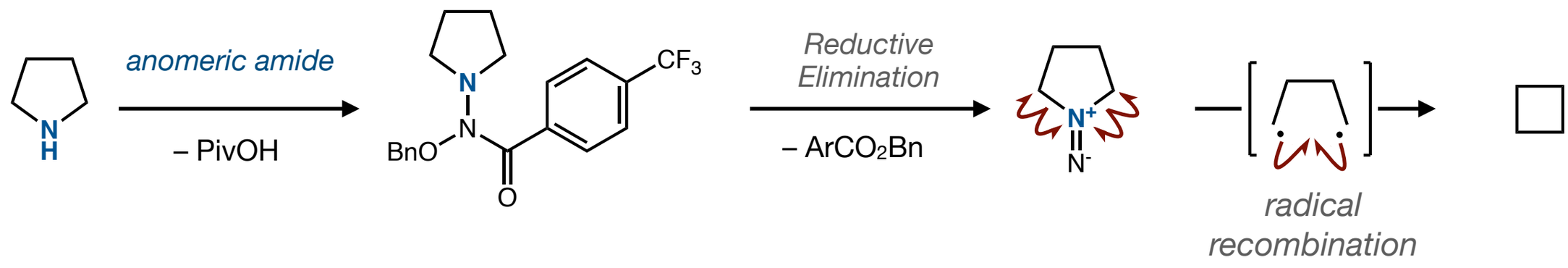
Non-Carbonyl Deletions: Nitrogen Deletion of Secondary Amines



Anomeric amide

- Straightforward to prepare on a multigrain scale
- 78% yield over 3 steps
- No chromatographic methods necessary to purify

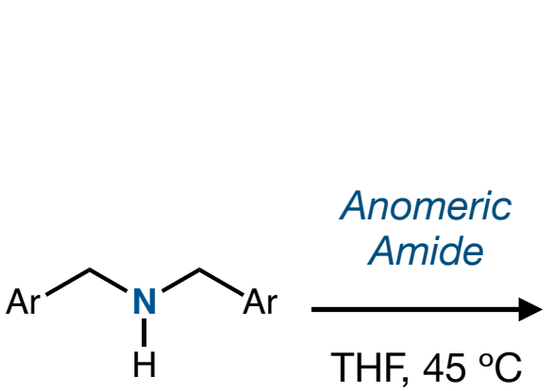
Activation of secondary amines

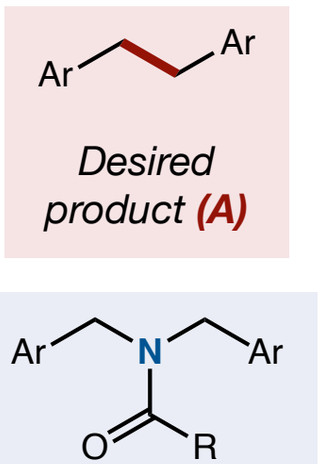


amine *activated amine* *isodiazene*

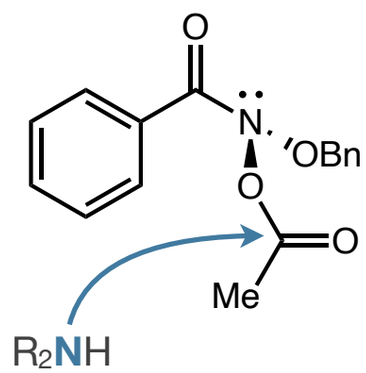
Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature*. **2021**, *593*, 223.

Nitrogen Deletion of Secondary Amines – Anomeric Amide Optimization

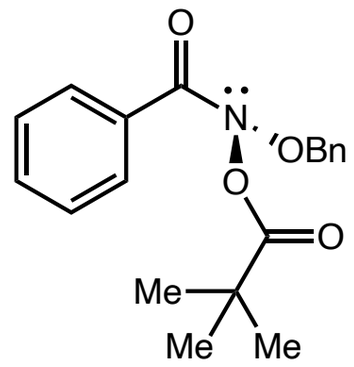




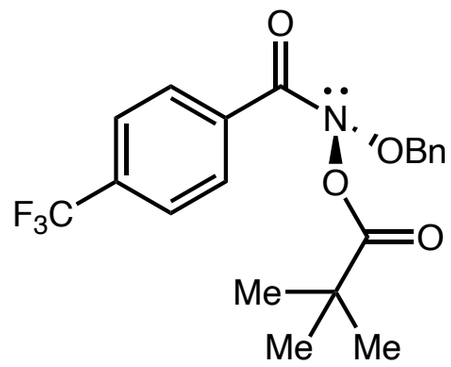
Anomeric Amide Library



35% yield
2:1 (**A**:**B**)

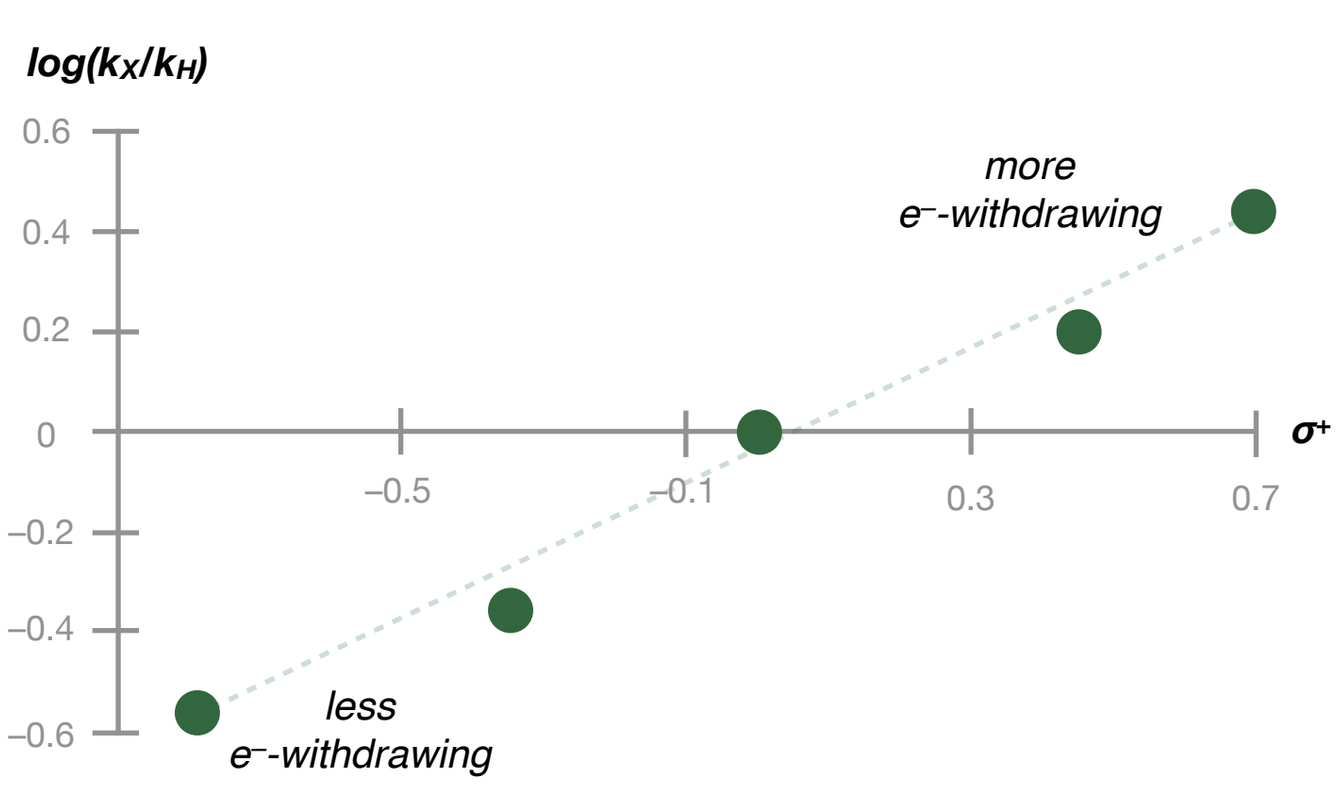


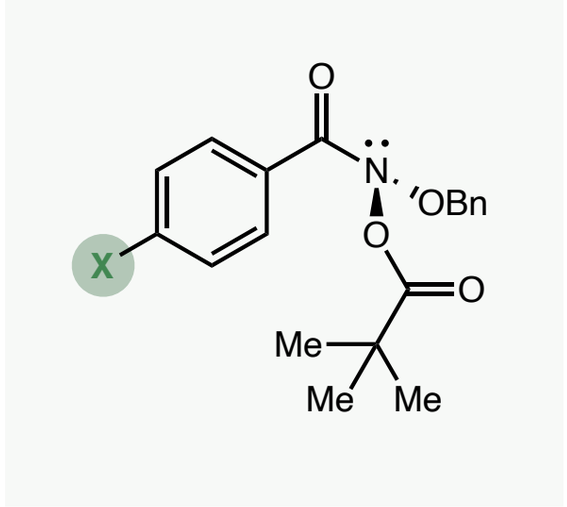
57% yield
>20:1 (**A**:**B**)



74% yield
>20:1 (**A**:**B**)

Competition Hammett Study





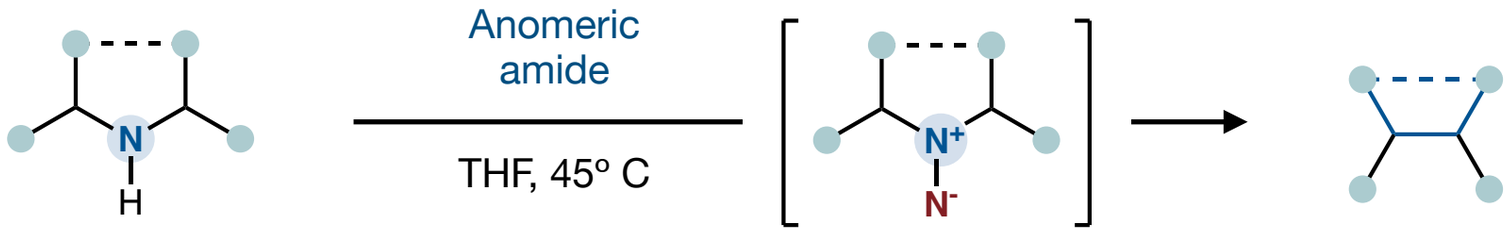
ρ = +0.60
(R^2 = 0.94)

Negative charge buildup

Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature*. **2021**, *593*, 223.

Nitrogen Deletion of Secondary Amines – Scope

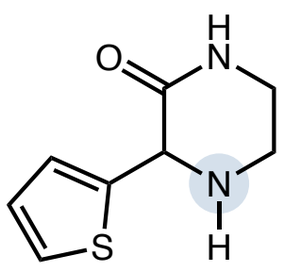
Levin – N-deletion



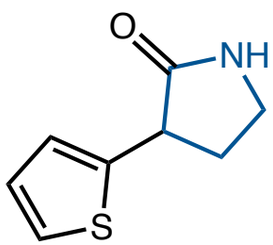
2° amine | *isodiazene* | *N-deleted product*

zinger scope

Skeletal editing of bioactive compounds

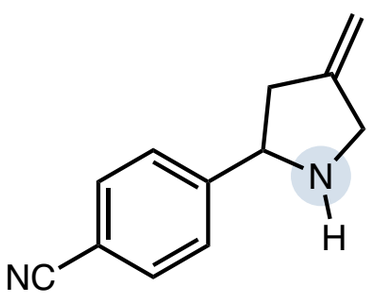


tenilsetam
AGE inhibitor

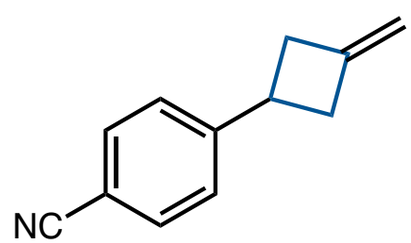


53% yield

Nitrogen linchpin cyclobutane synthesis



from [3+2] cycloaddition

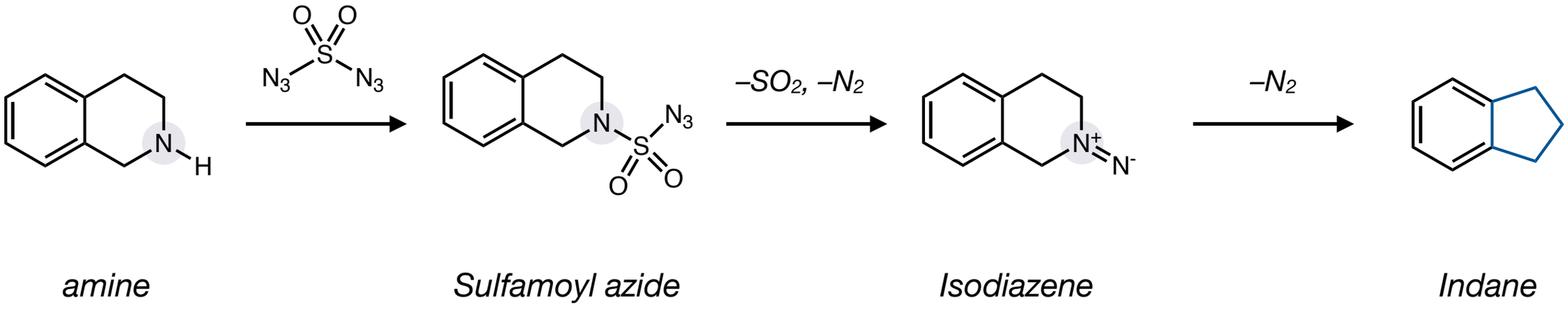


71% yield
Toward synthesis of H_3 receptor modulator

Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. *Nature*. **2021**, *593*, 223.

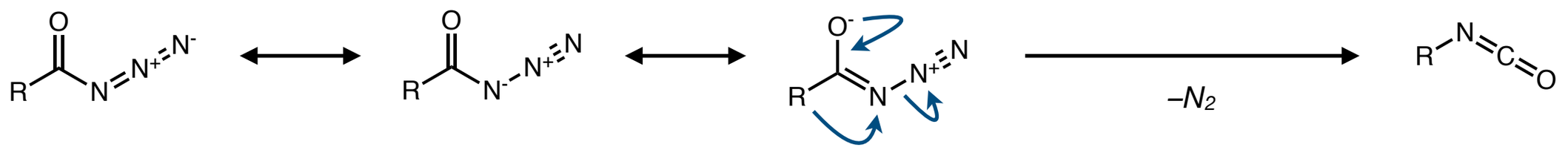
Alternative Nitrogen-Atom Deletion

Lu Group – Nanjing Univ. – 2021



amine *Sulfamoyl azide* *Isodiazene* *Indane*

Curtius-type rearrangement

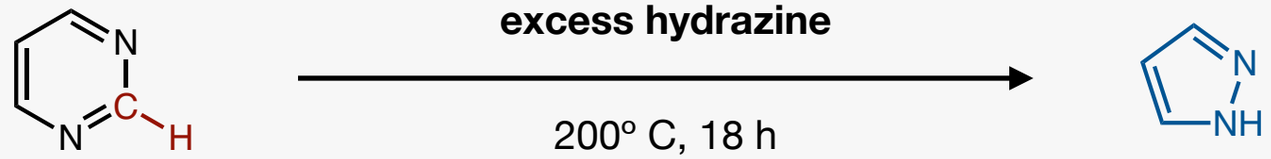


Acyl Azide *Isocyanate*

Qin, H.; Cai, W.; Wang, S.; Guo, T.; Li, G.; Lu, H.. *Angew. Chem. Int. Ed.* **2021**, *60*, 20678.

Non-Carbonyl Deletions: Carbon Deletion of Pyrimidines

***1968:** discovery*

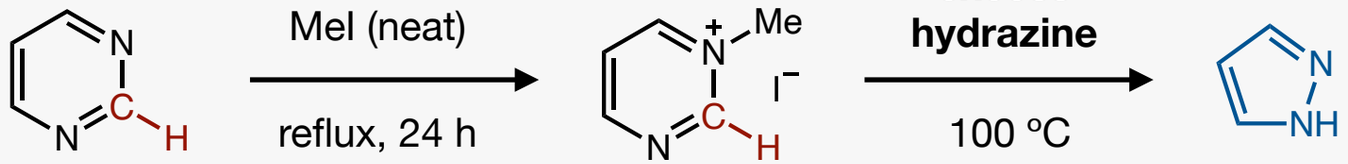


Harsh conditions

Low yields

Extremely limited substrate scope

***1968:** advance*

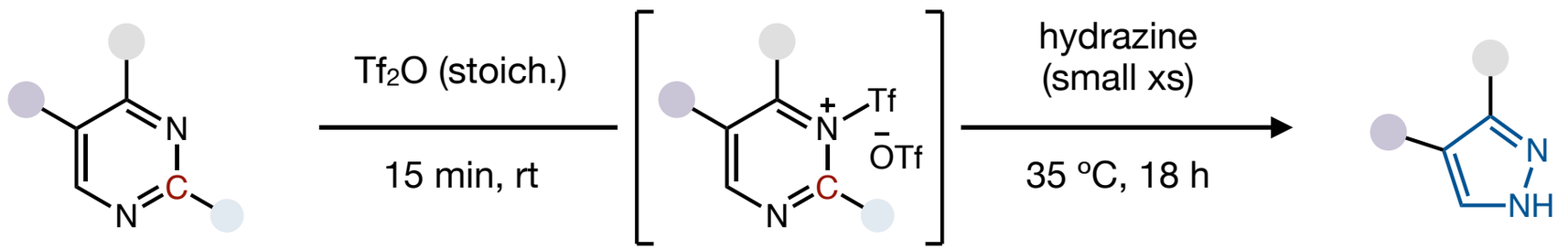


Two-step protocol

Moderate yields

Limited substrate scope

***2022:** Today – Sarpong*

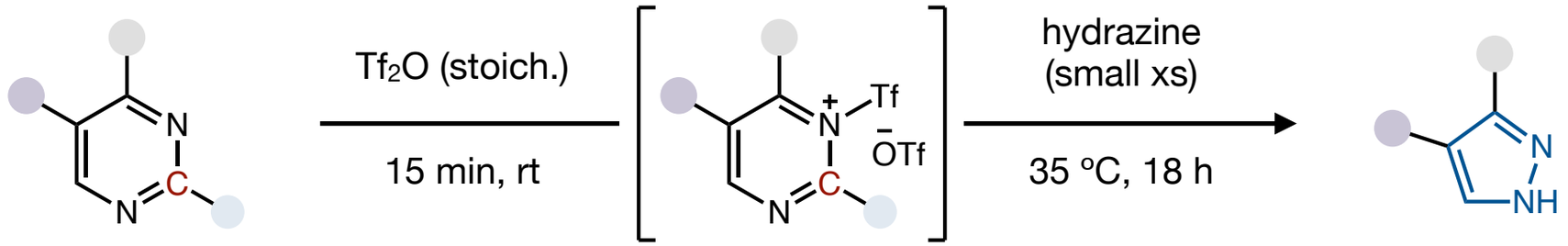


pyrimidine — *Isolable but not isolated* — *pyrazole*

Bartholomew, G. L.; Carpaneto, F.; Sarpong, R. *J. Am. Chem. Soc.* **2022**, *144*, 22309.

Non-Carbonyl Deletions: Carbon Deletion of Pyrimidines

2022: *Today – Sarpong*



pyrimidine *Isolable but not isolated* *pyrazole*

up to 90% yield

over 40 examples

mild conditions

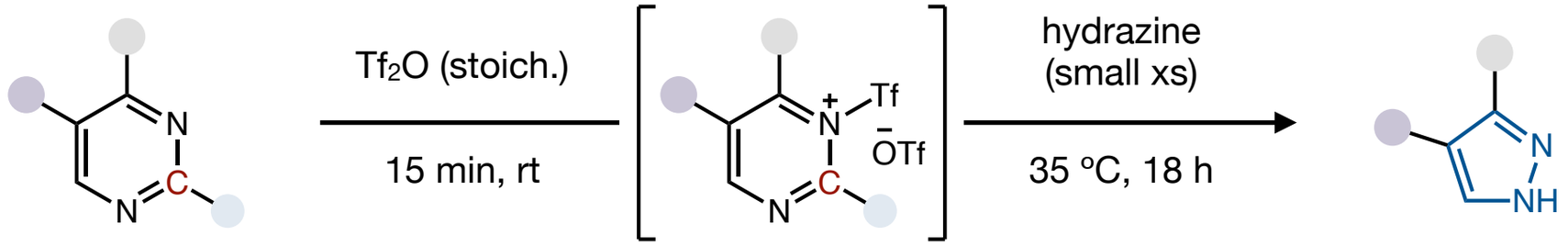
one-pot protocol

complex substrates

Bartholomew, G. L.; Carpaneto, F.; Sarpong, R. *J. Am. Chem. Soc.* **2022**, *144*, 22309.

Non-Carbonyl Deletions: Carbon Deletion of Pyrimidines

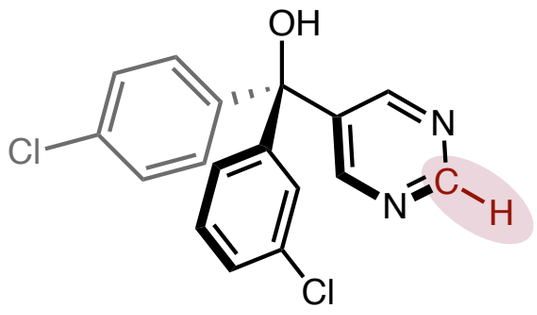
2022: *Today – Sarpong*



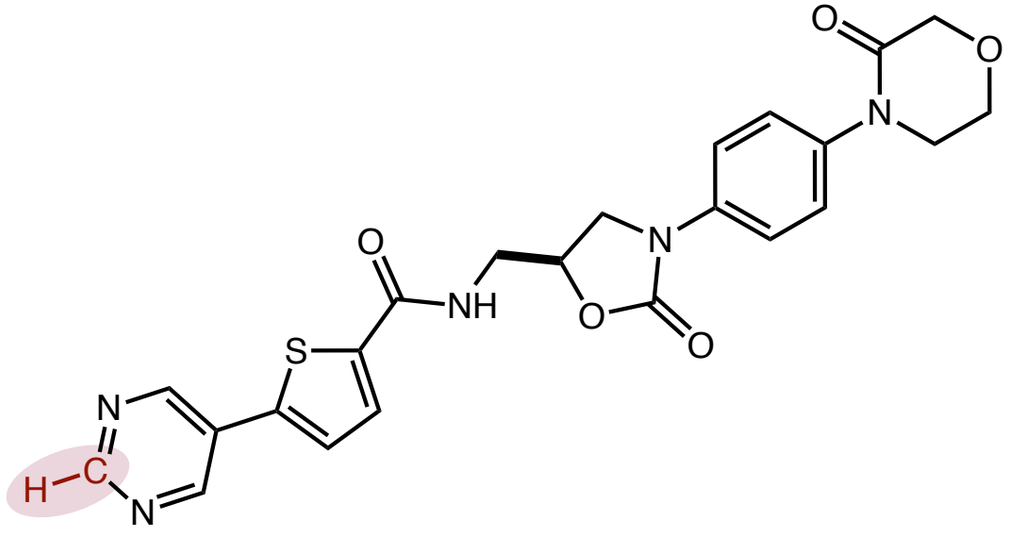
pyrimidine

Isolable but not isolated

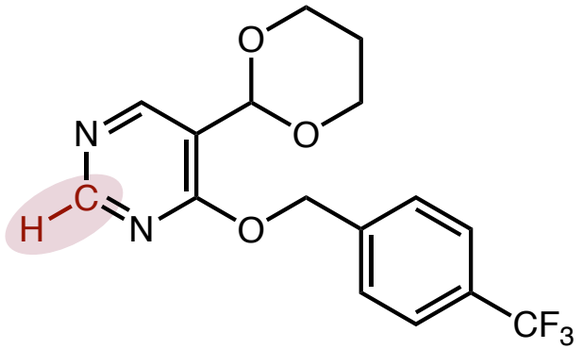
pyrazole



Contraction yield – 20 %
(Benzpyrimoxan®)



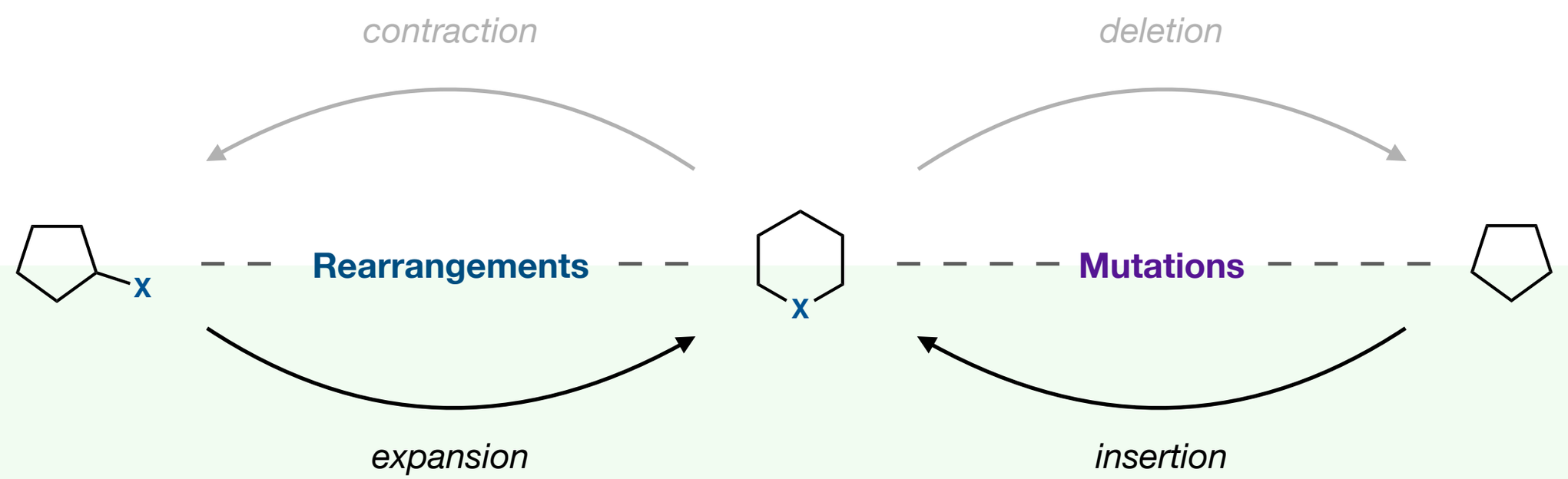
Contraction yield – 17 % *(81% BRSM)*
(Rivaroxaban® derivative)



Contraction yield – 37 %
(Fenarimol®)

Bartholomew, G. L.; Carpaneto, F.; Sarpong, R. *J. Am. Chem. Soc.* **2022**, *144*, 22309.

n + 1 Single-Atom Editing



The ring size is increased by one atom

n + 1 single-atom edit

Overview

n – 1 single-atom edits

Contractions

Deletions

n + 1 single-atom edits

Expansions

Insertions

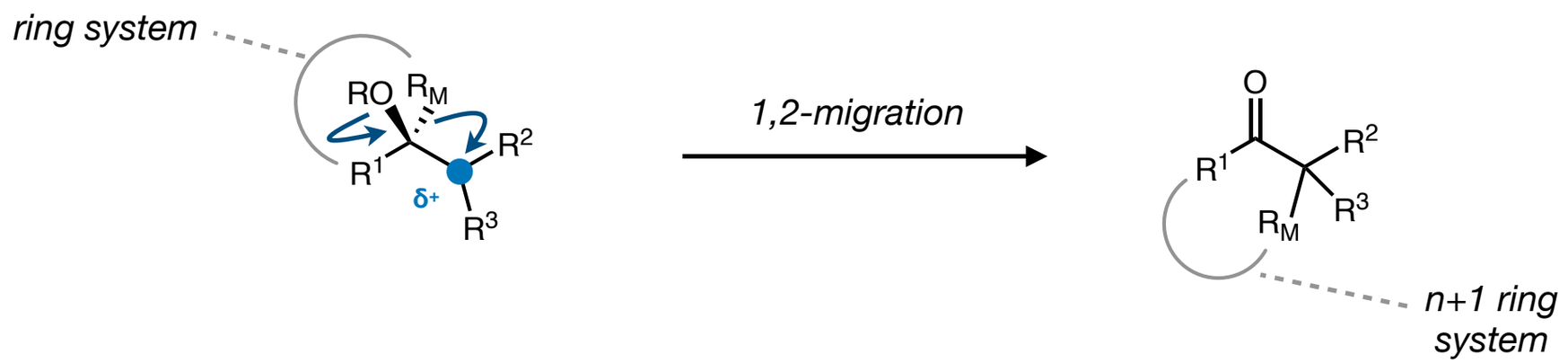
Outlook

Expansions

expansion

n + 1 single-atom edit where the exocyclic substituent is retained within the ring system

semi-pinacol rearrangment



Common reaction pathways involve semi-pinacol-like expansions, wherein cyclic tertiary carbinols bearing exocyclic leaving groups undergo the incorporation of the exocyclic methylene and formation of a carbonyl group

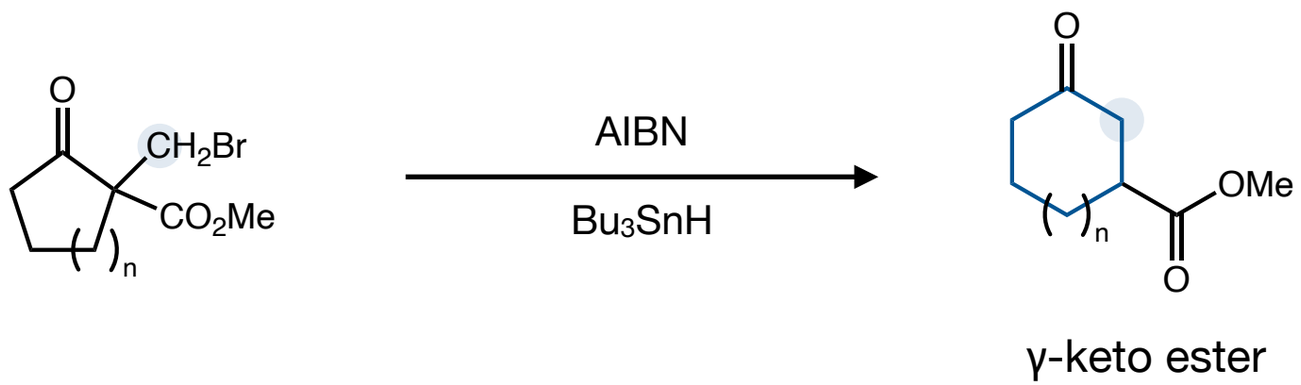
Song, Z.-L.; Fan, C.-A.; Tu, Y.-Q. *Chem. Rev.* **2011**, *111*, 7523.

Expansions

expansion

n + 1 single-atom edit where the exocyclic substituent is retained within the ring system

Dowd-Beckwith ring expansion

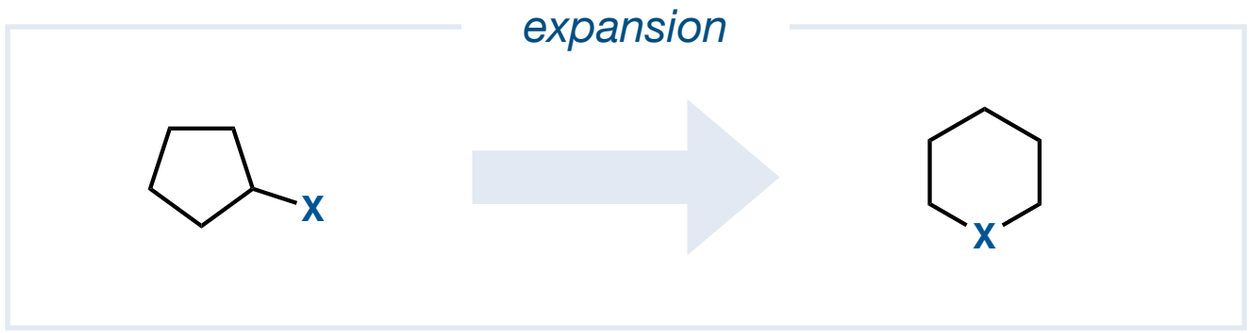


γ-keto ester

Discovered in 1987

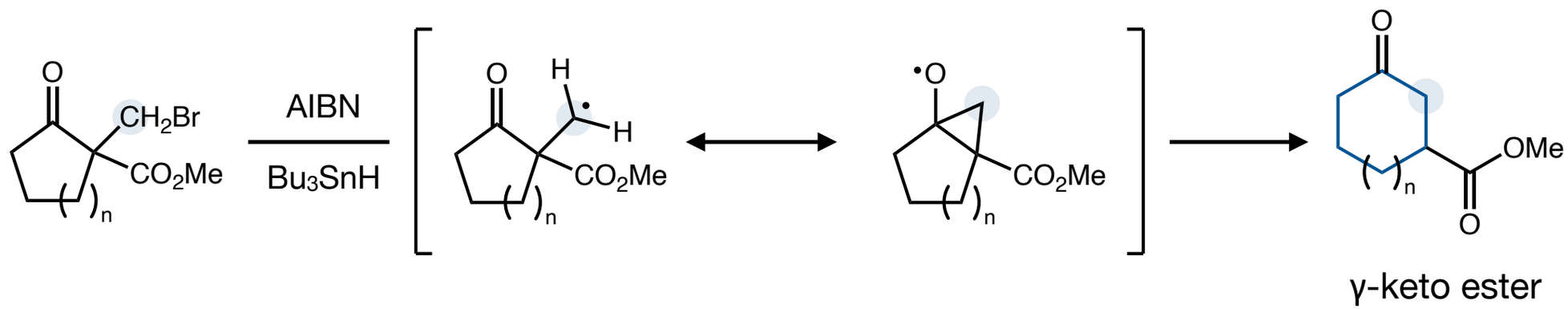
Singha, T.; Mondal, A. R. S.; Midya, S.; Hari, D. P. *Chem. Eur. J.* **2022**, *28*, 61.

Expansions



n + 1 single-atom edit where the exocyclic substituent is retained within the ring system

Dowd-Beckwith ring expansion



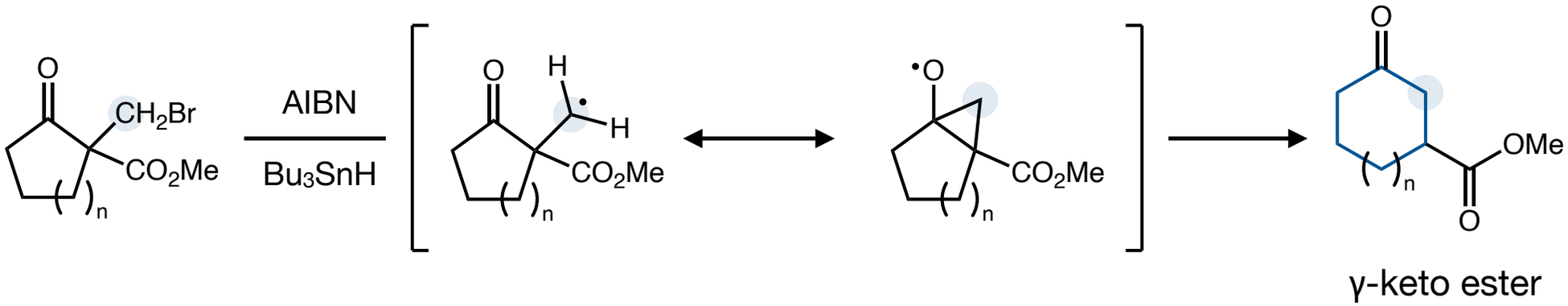
γ-keto ester

Discovered in 1987

Singha, T.; Mondal, A. R. S.; Midya, S.; Hari, D. P. *Chem. Eur. J.* **2022**, *28*, 61.

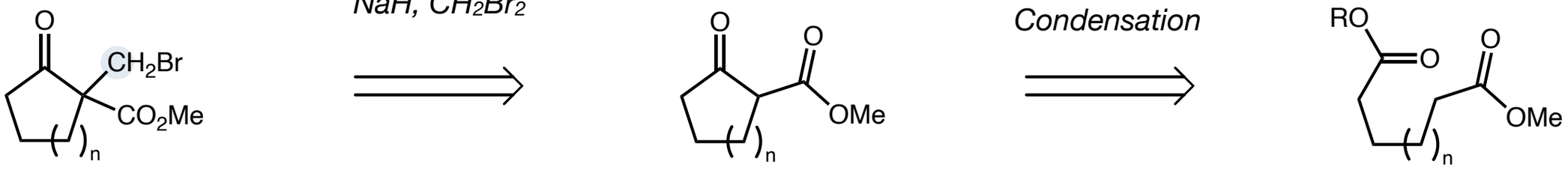
Dowd-Beckwith Ring Expansion

Dowd-Beckwith ring expansion



γ-keto ester

Synthesis of Starting materials



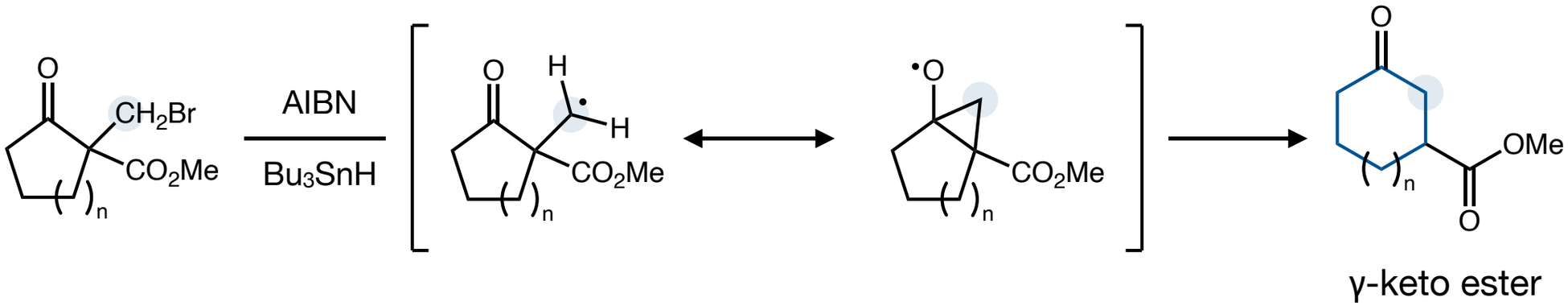
Cyclic β-keto ester

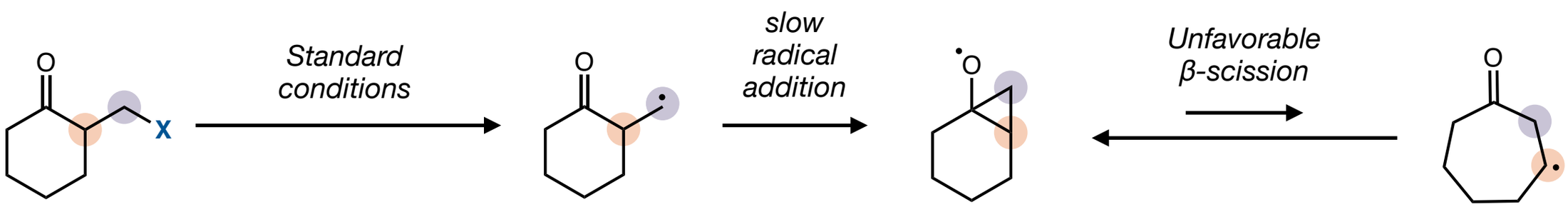
Acyclic diester

Singha, T.; Mondal, A. R. S.; Midya, S.; Hari, D. P. *Chem. Eur. J.* **2022**, *28*, 61.

Dowd-Beckwith Ring Expansion – Importance of Ester Group

Dowd-Beckwith ring expansion



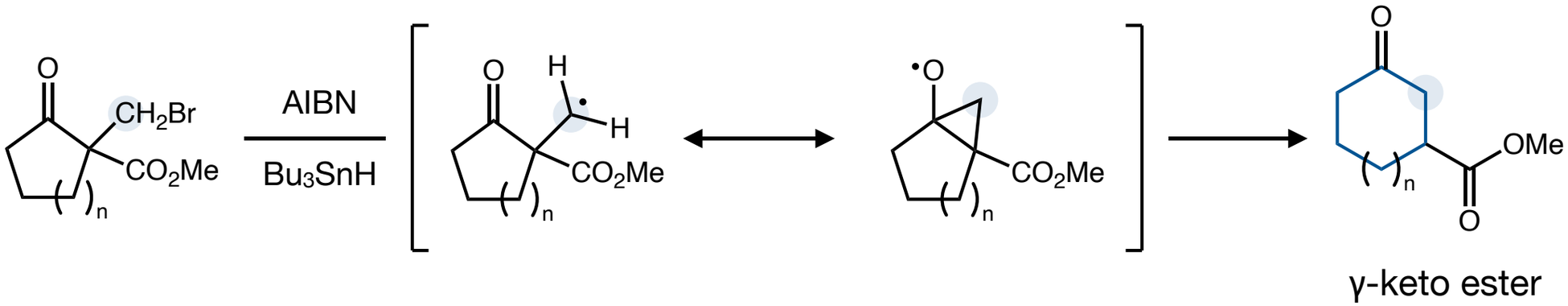


- Activation of ketone towards attack by the nucleophilic carbon radical
- Provides a driving force for the ring expansion

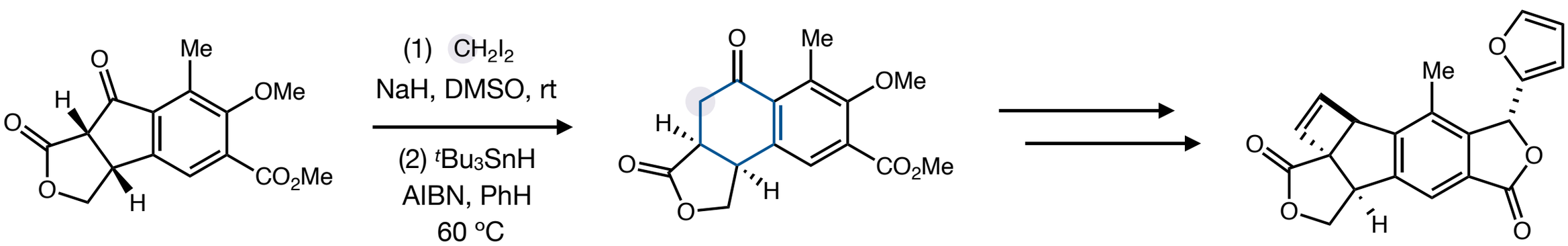
Singha, T.; Mondal, A. R. S.; Midya, S.; Hari, D. P. *Chem. Eur. J.* **2022**, *28*, 61.

Dowd-Beckwith Ring Expansion – Total Synthesis

Dowd-Beckwith ring expansion



Natural product synthesis application



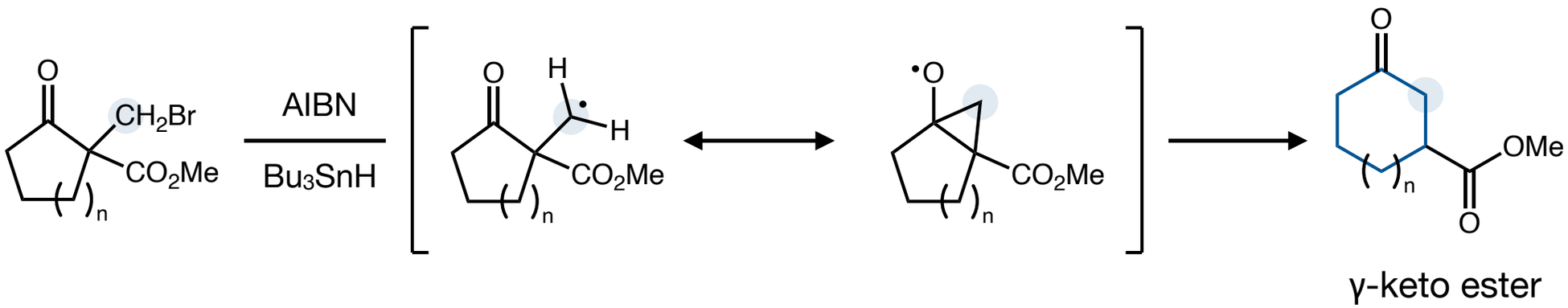
80% yield

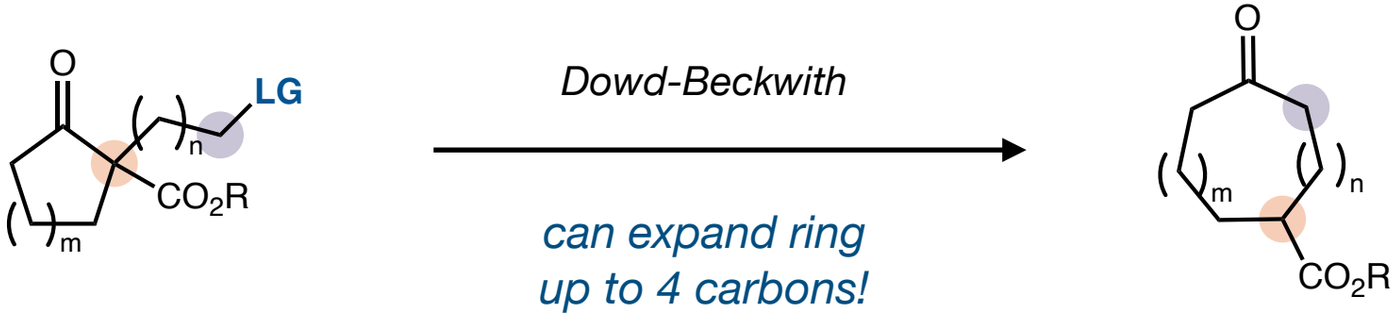
Salvileucalin C

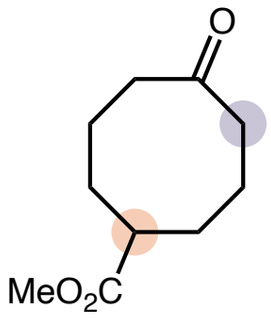
Fu, C. *et al*. *Org. Lett*. **2014**, *16*, 3376.

Dowd-Beckwith Ring Expansion

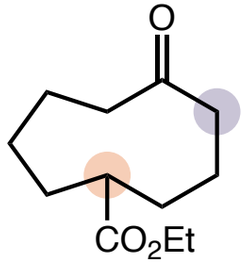
Dowd-Beckwith ring expansion



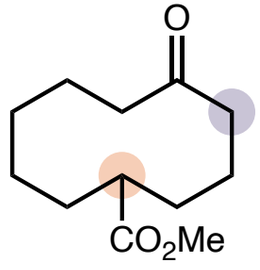




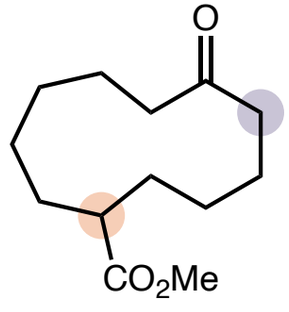
69% yield



75% yield



34% yield

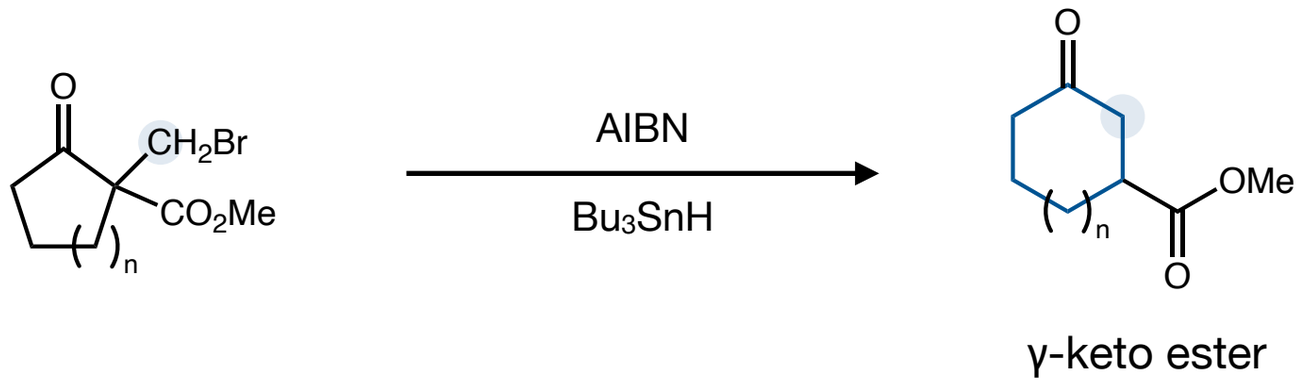


45% yield

Singha, T.; Mondal, A. R. S.; Midya, S.; Hari, D. P. *Chem. Eur. J.* **2022**, *28*, 61.

Dong – Ring Expansion of Cyclobutanones

Dowd-Beckwith ring expansion

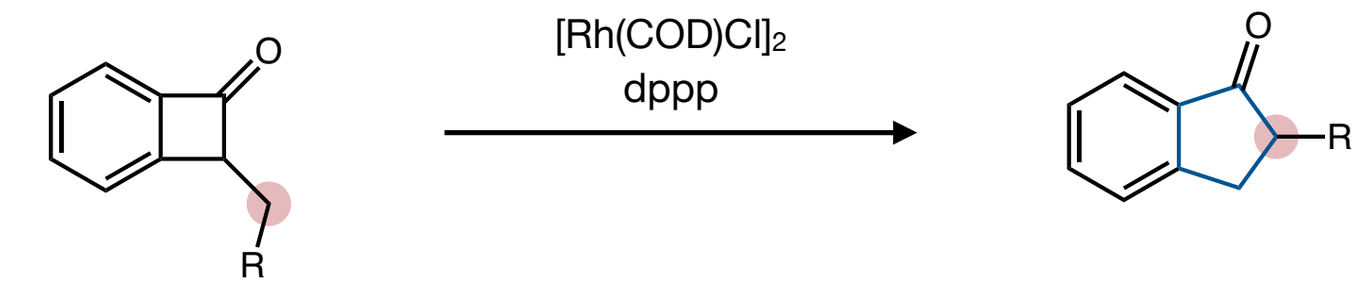


γ-keto ester

Requires a halogen/leaving-group for initiation

Guangbin Dong
Univ. of Chicago

Dong ring expansion



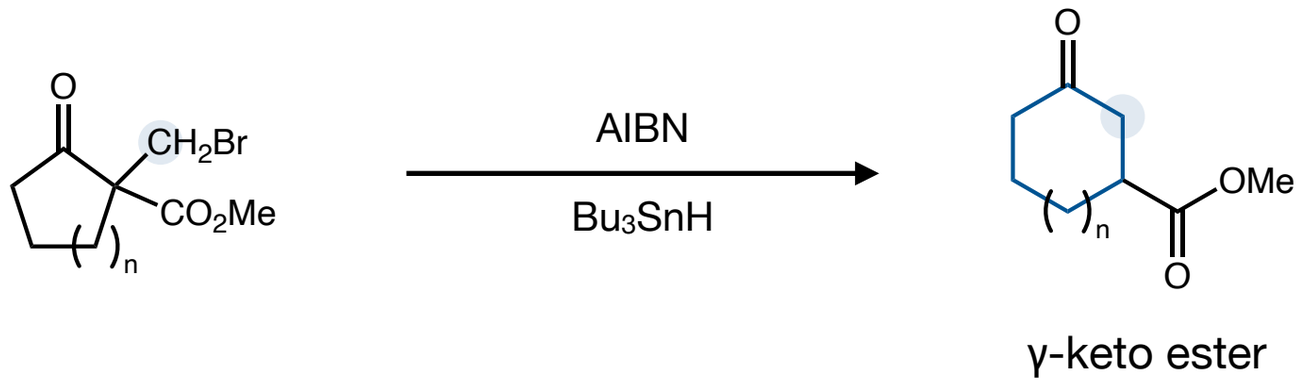
Cyclobutanones

Indanones

Chen, P.; Sieber, J.; Senanayake, C. H.; Dong, G. *Chem. Sci.* **2015**, *6*, 5440.

Dong – Ring Expansion of Cyclobutanones

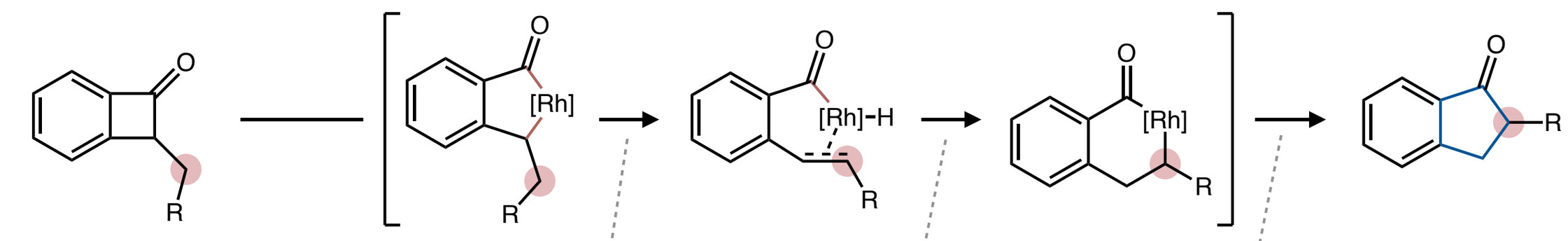
Dowd-Beckwith ring expansion



γ-keto ester

Requires a halogen/leaving-group for initiation

Dong ring expansion



Cyclobutanones

β-hydride elim.

Reinsertion

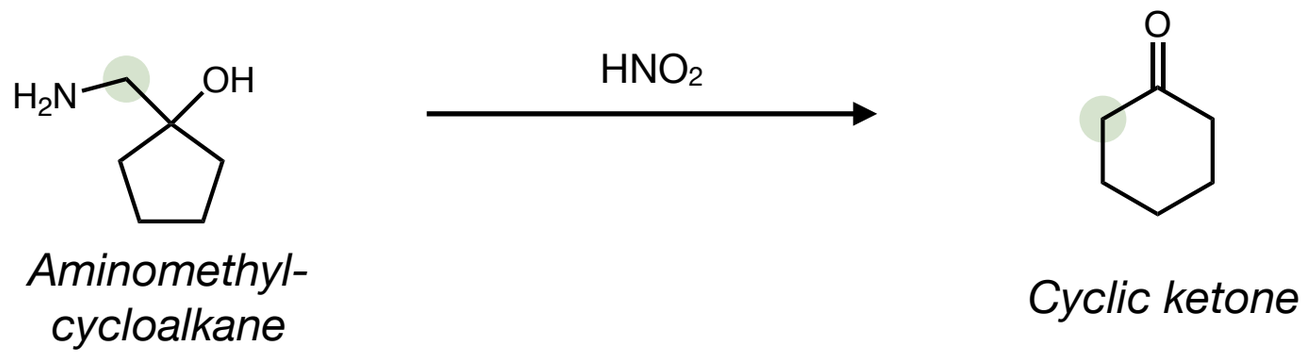
Red. Elim.

Indanones

Chen, P.; Sieber, J.; Senanayake, C. H.; Dong, G. *Chem. Sci.* **2015**, *6*, 5440.

Tiffeneau-Demjanov Rearrangment

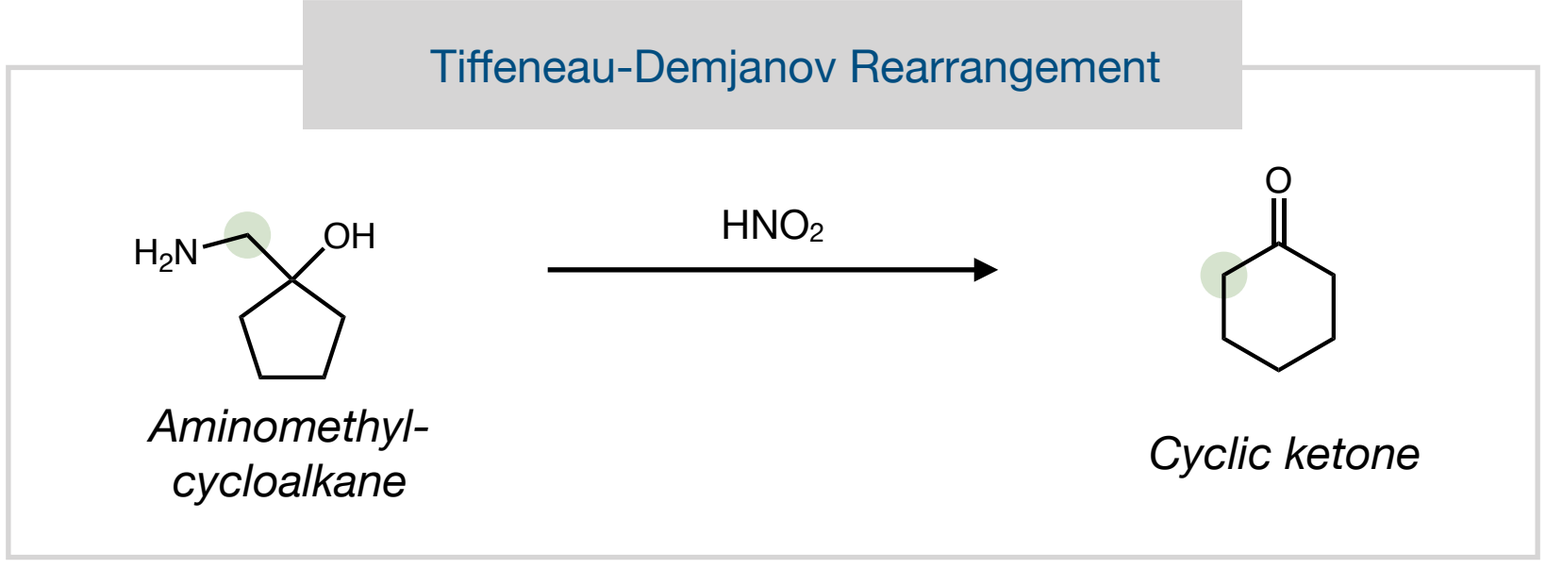
Tiffeneau-Demjanov Rearrangement



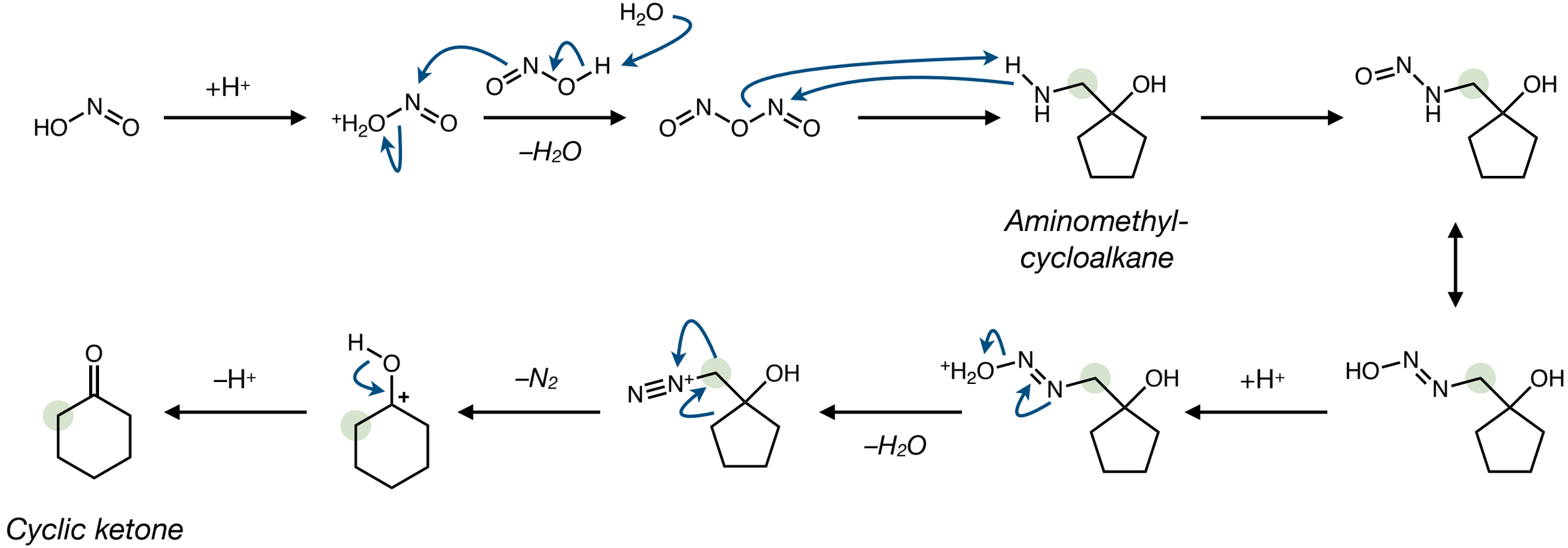
Carbocation rearrangment of β-aminoalcohols via diazotization to afford carbonyl compounds through C–C bond migration

Smith, P. A. S.; Baer, D. R. *Organic Reactions*. **2011**, doi.org/10.1002/0471264180.or011.02.

Tiffeneau-Demjanov Rearrangment

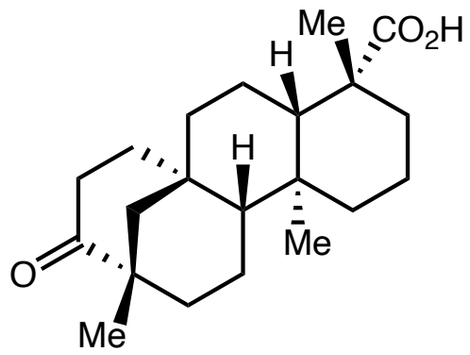


Mechanism



Smith, P. A. S.; Baer, D. R. *Organic Reactions*. **2011**, doi.org/10.1002/0471264180.or011.02.

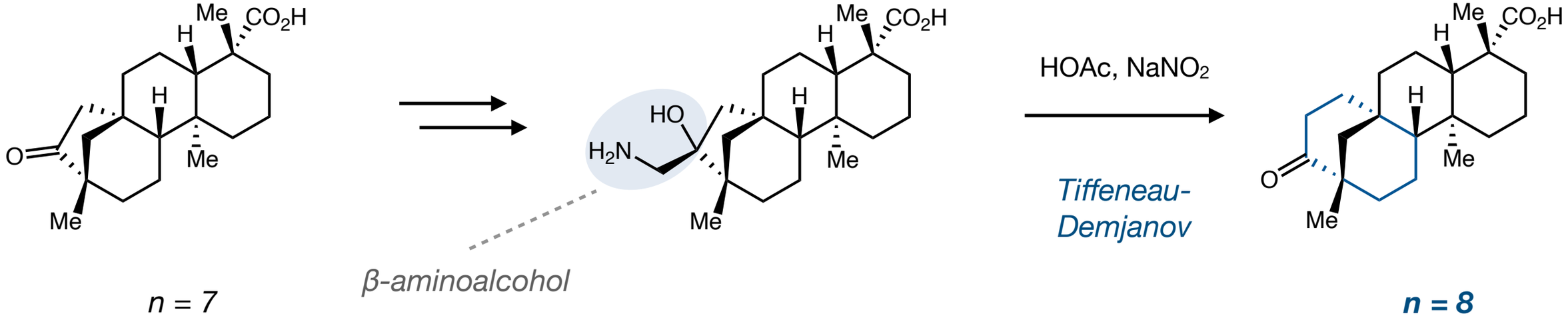
Tiffeneau-Demjanov Rearrangment – Total Synthesis



(–)-isosteviol

Exhibits a wide range of biological activities

Cardioprotective, cytotoxic, antibacterial, sweetener, etc…

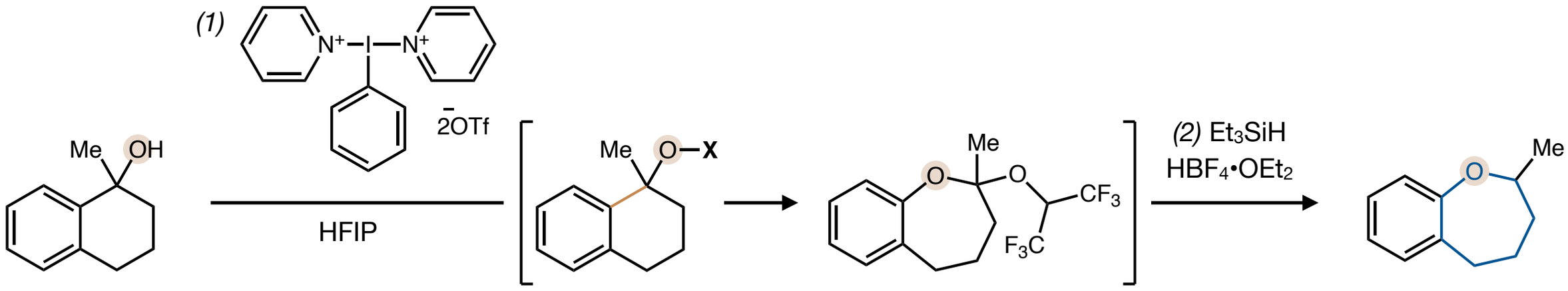


- Unusual TD regioselectivity where steric demand overrides electronic arguments
- 8-step total synthesis with a 16% overall yield

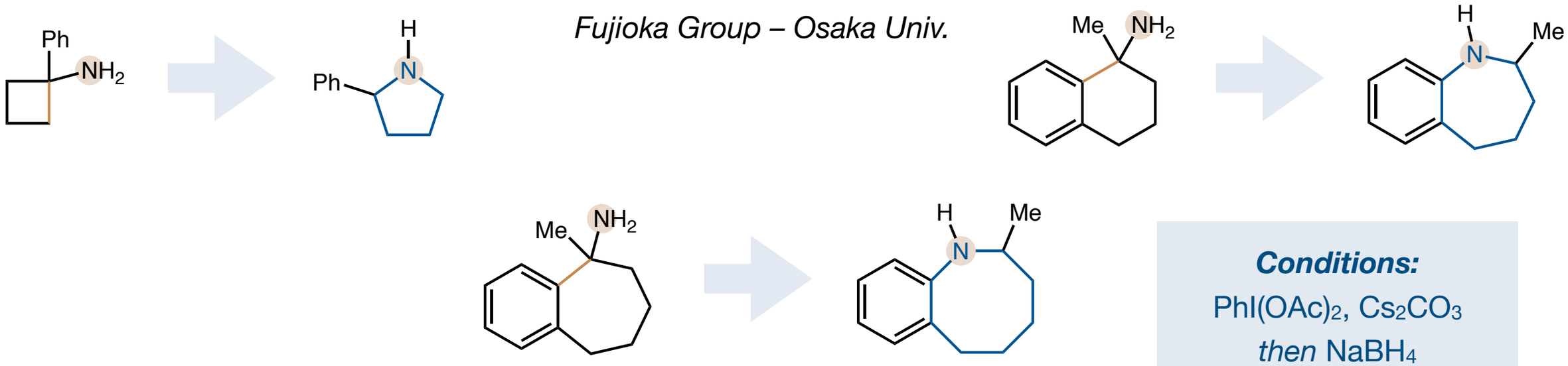
Lohoelter, C.; Schollmeyer D.; Waldvogel, S. R. *Eur. J. Org. Chem.* **2012**, *32*, 6364.

Select Advances in Oxidative Single-Atom Ring Expansion

Wengryniuk Group – Temple Univ.



Fujioka Group – Osaka Univ.

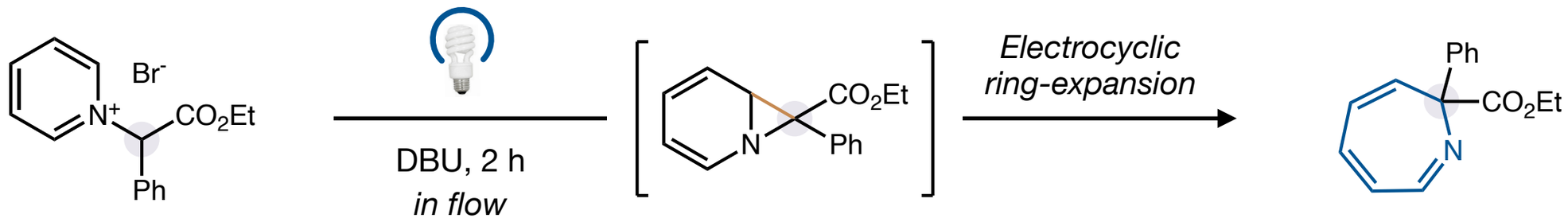


Conditions:
$PhI(OAc)_2$, Cs_2CO_3
then $NaBH_4$

Kelley, B. T.; Walters, J. C.; Wengryniuk, S. E. *Org. Lett.* **2016**, *18*, 1896.

Murai, K.; Komatsu, H.; Nagao, R.; Fujioka, H. *Org. Lett.* **2012**, *14*, 772.

Aromatic Expansions – Synthesis of Azepines



Pyridinium ylide *Azanocaradiene* *Azepine*

- Mild dearomatization enabling the synthesis of valuable azepine derivatives
- Demonstrated on pyridine, isoquinoline, quinoline, and phenanthridine cores

Mailloux, M. J.; Fleming, G. S.; Kumta, S. S.; Beeler, A. B. *Org. Lett.* **2021**, *23*, 525.

Overview

n – 1 single-atom edits

Contractions

Deletions

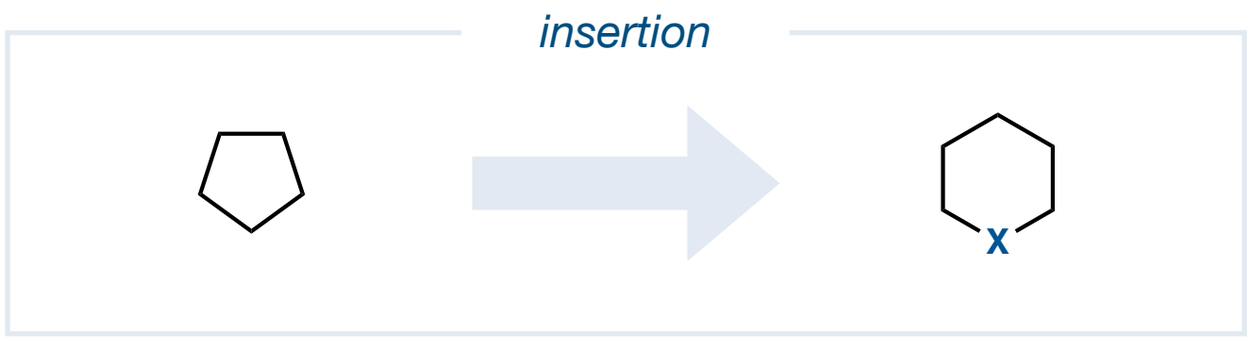
n + 1 single-atom edits

Expansions

Insertions

Outlook

Insertion

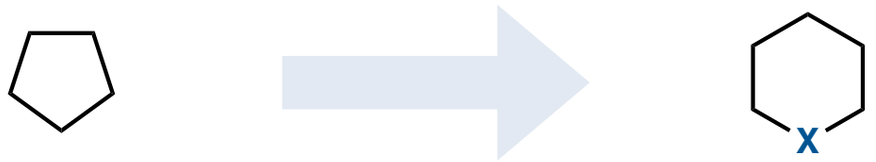


n + 1 single-atom edit where a new atom is added to the ring system

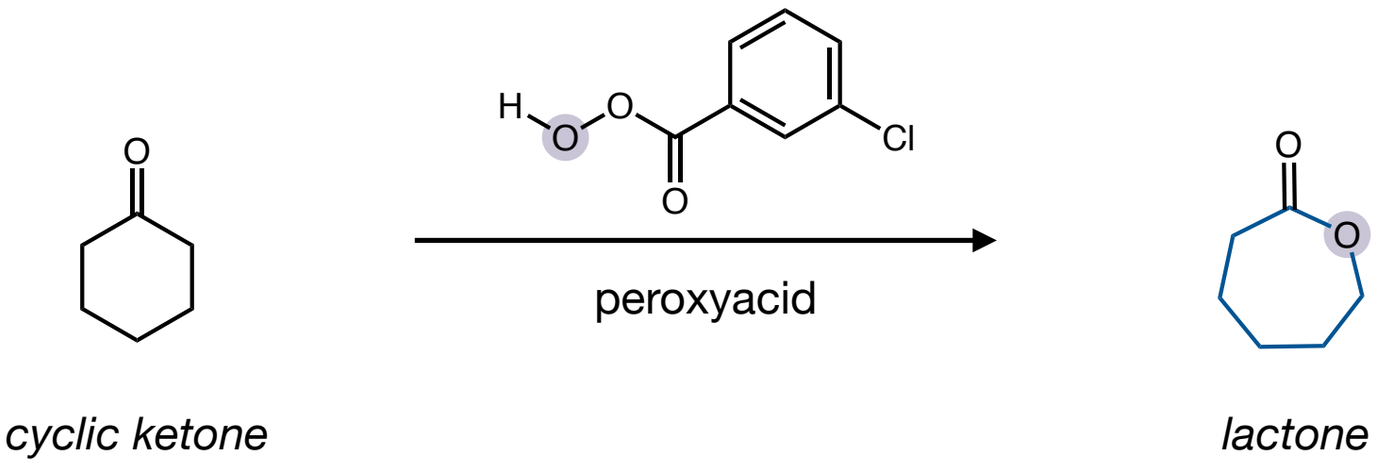
The widest number of classical carbonyl rearrangements falls into this category

Insertion

insertion



Baeyer-Villager Oxidation



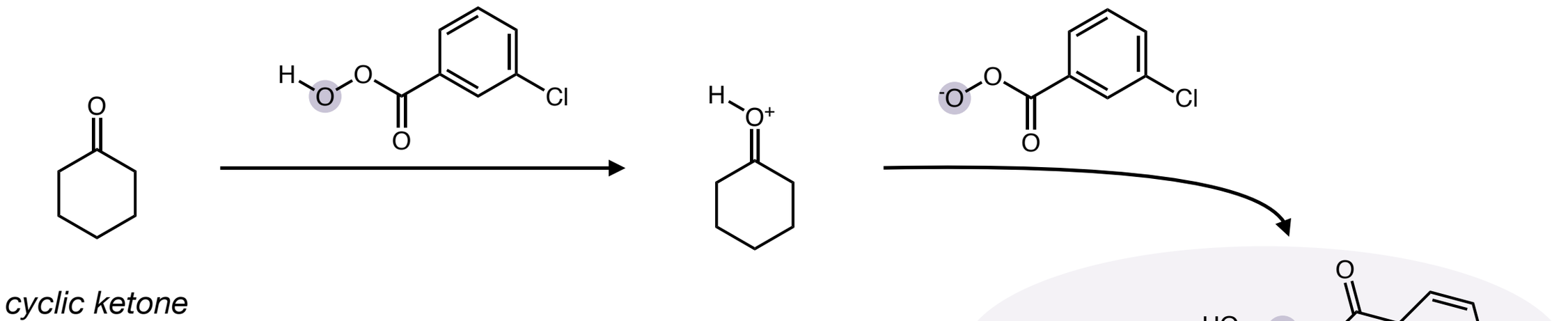
cyclic ketone

lactone

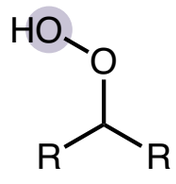
- Discovered in 1899 by Adolf von Baeyer & Victor Villiger
- **Migration preference** – 3° > 2° > Ph > 1° (ability to stabilize positive charge)
- Asymmetric, (bio)catalytic, more selective versions have been developed

Brink, G.-J., Arends, W. C. E.; Sheldon, R. A. *Chem. Rev*. **2004**, *104*, 4105.

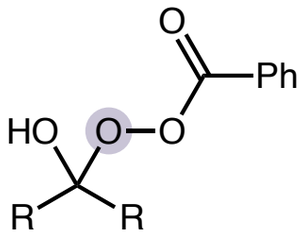
Baeyer Villager Mechanistic Study



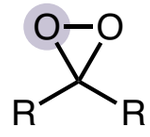
Dorfman & Doering Labelling Experiment



Wittig and Pieper



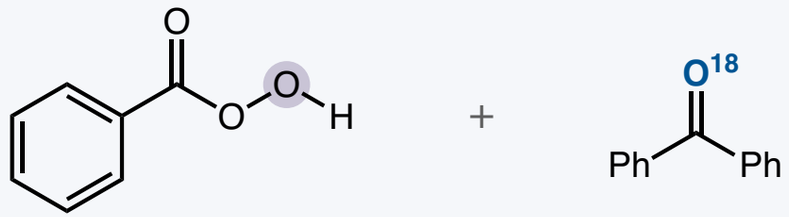
Criegee



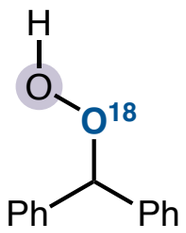
Baeyer & Villiger

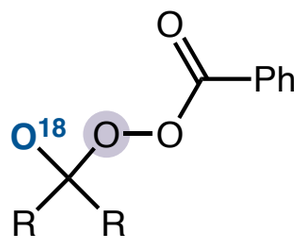
Brink, G.-J., Arends, W. C. E.; Sheldon, R. A. *Chem. Rev*. **2004**, *104*, 4105.

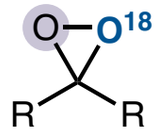
Baeyer Villager Mechanistic Study



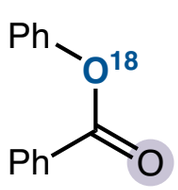
intermediate

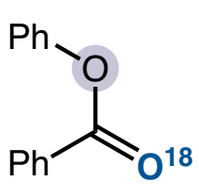


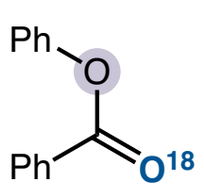




product







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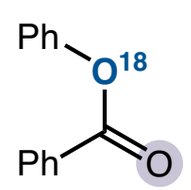
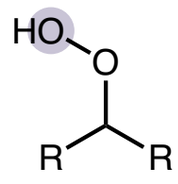


Not Observed

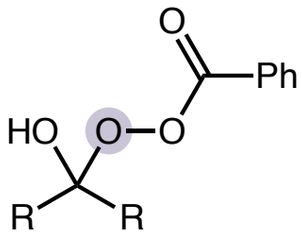
Observed

Not Observed

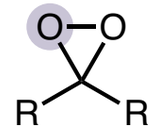
Dorfman & Doering Labelling Experiment



Wittig and Pieper



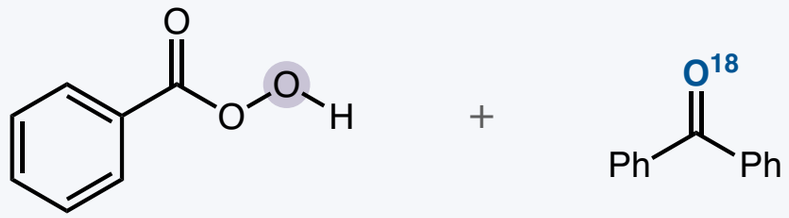
Criegee



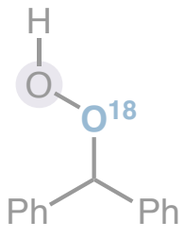
Baeyer & Villiger

Brink, G.-J., Arends, W. C. E.; Sheldon, R. A. *Chem. Rev*. **2004**, *104*, 4105.

Baeyer Villager Mechanistic Study



intermediate



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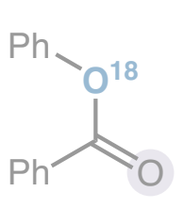

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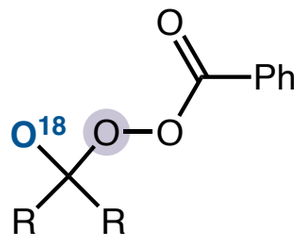
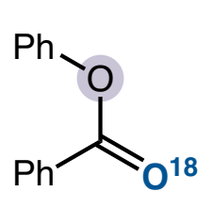
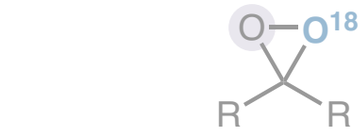




Observed



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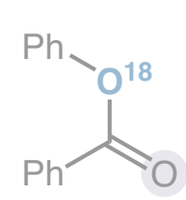
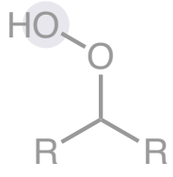
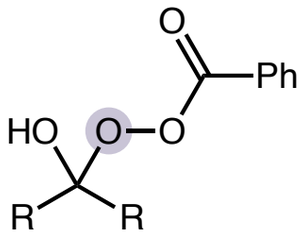


Not Observed

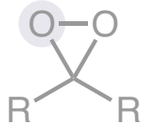
Dorfman & Doering Labelling Experiment



Wittig and Pieper



Criegee



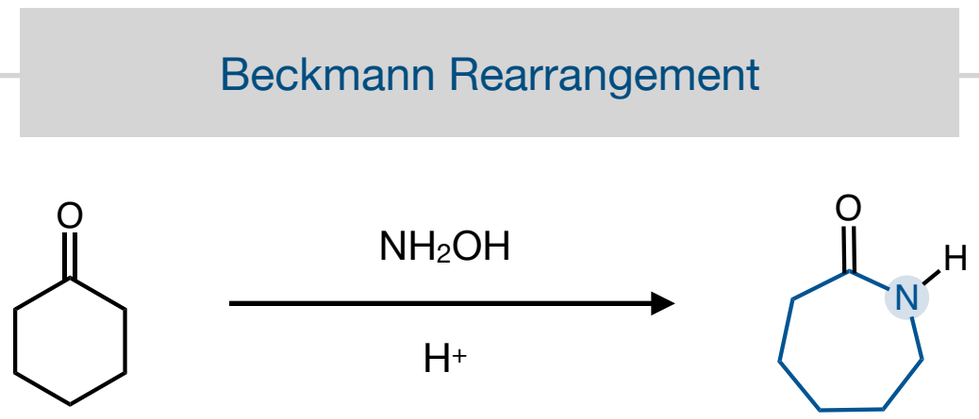
Baeyer & Villiger

Brink, G.-J., Arends, W. C. E.; Sheldon, R. A. *Chem. Rev*. **2004**, *104*, 4105.

Insertion

insertion

Beckmann Rearrangement



- Discovered in 1886 by Ernst Otto Beckmann in Germany
- Often acid-catalyzed, but also works with TsCl, $SOCl_2$, PCl_5 … etc
- Has been applied to haloimines as well as nitrones

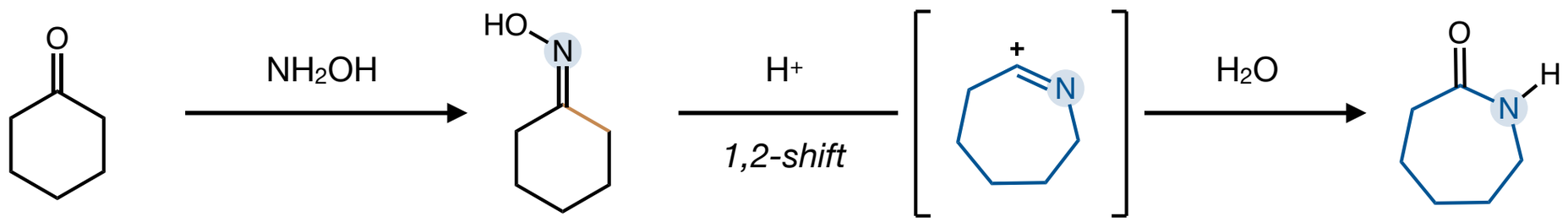
Blatt, A. H. *Chem. Rev*. **1933**, *12*, 215.

Kaur, K.; Srivastava, S. *New J. Chem.* **2020**, *44*, 18530.

Insertion

insertion

Beckmann Rearrangement



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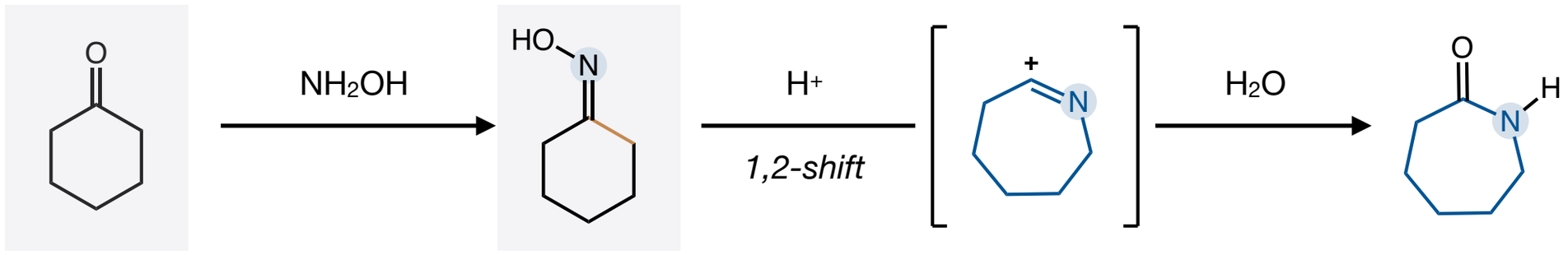
Insertion

insertion

Beckmann Rearrangement



Skeletal editing classification problem:

If cyclic ketone is defined as the start of the transformation… → ***Insertion***

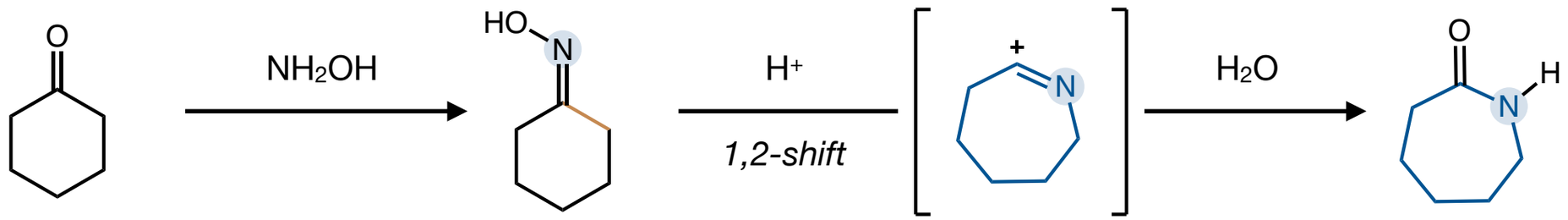
If oxime is isolated and defined as the start of the transformation… → ***Expansion***

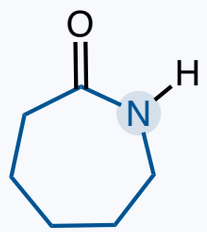
Blatt, A. H. *Chem. Rev.* **1933**, *12*, 215.

Kaur, K.; Srivastava, S. *New J. Chem.* **2020**, *44*, 18530.

Beckmann Rearrangement – Nylon Synthesis

Beckmann Rearrangement

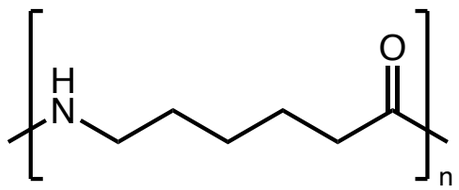




caprolactam

5–10% H_2O

533K , 4–5 h, N_2 (atm)



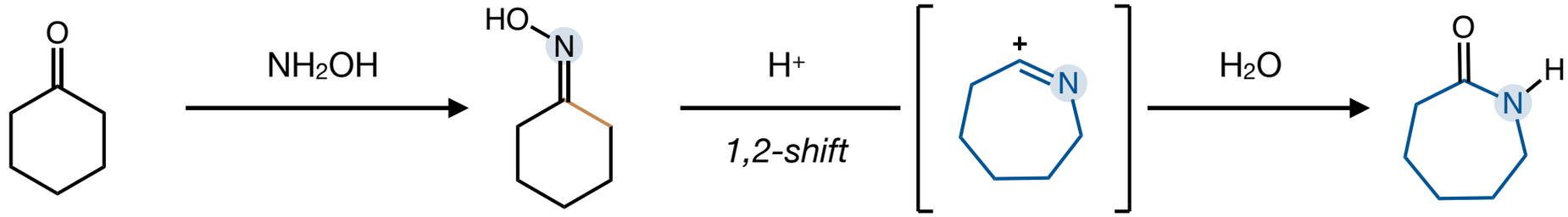
Nylon 6

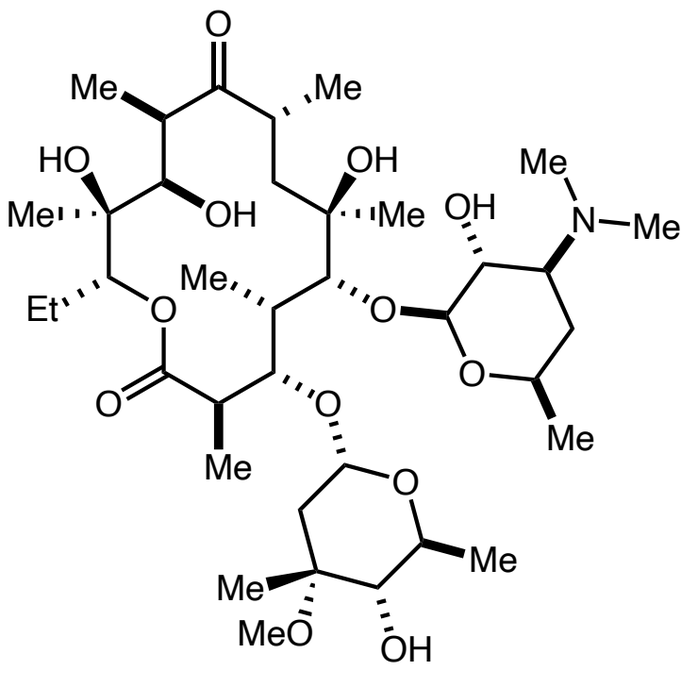
- Employed on a multi ton scale
- Accounts for 90% of the global demand for Nylon
- Clothing, reinforcement, industry parts, plastics

Tinge, J *et al. Ullmann's Encyclopedia of Industrial Chemistry.* **2008**.

Beckmann Rearrangement Applications

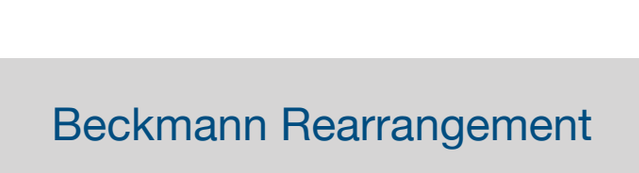
Beckmann Rearrangement

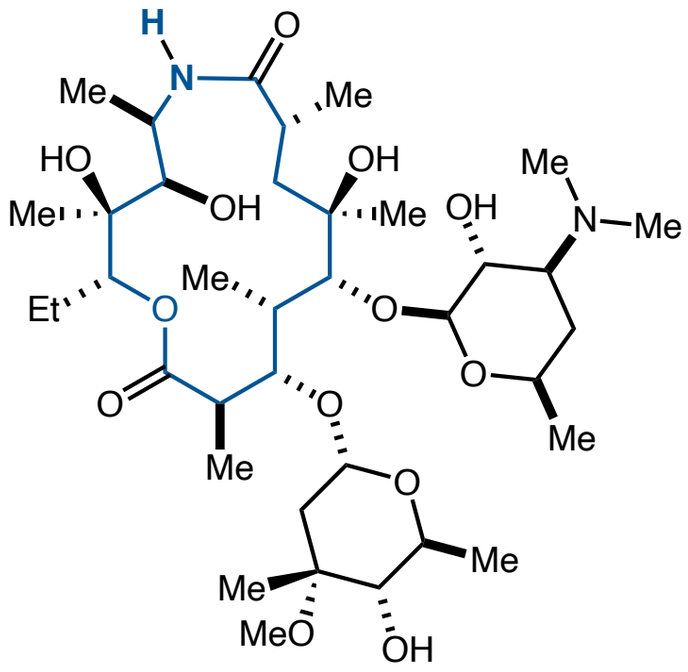




Erythromycin A

Beckmann Rearrangement



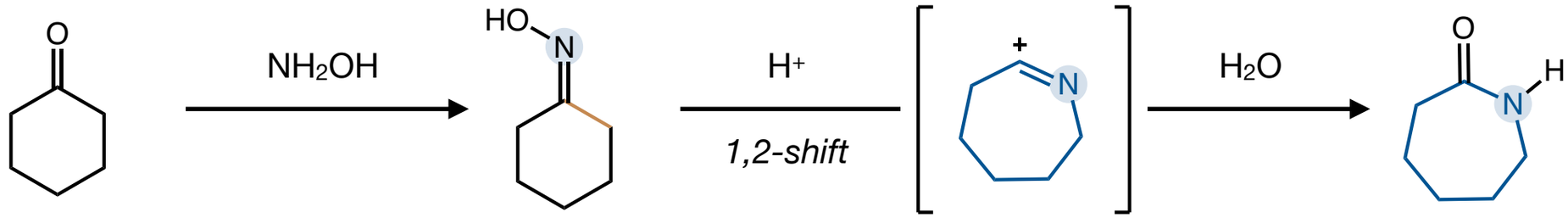


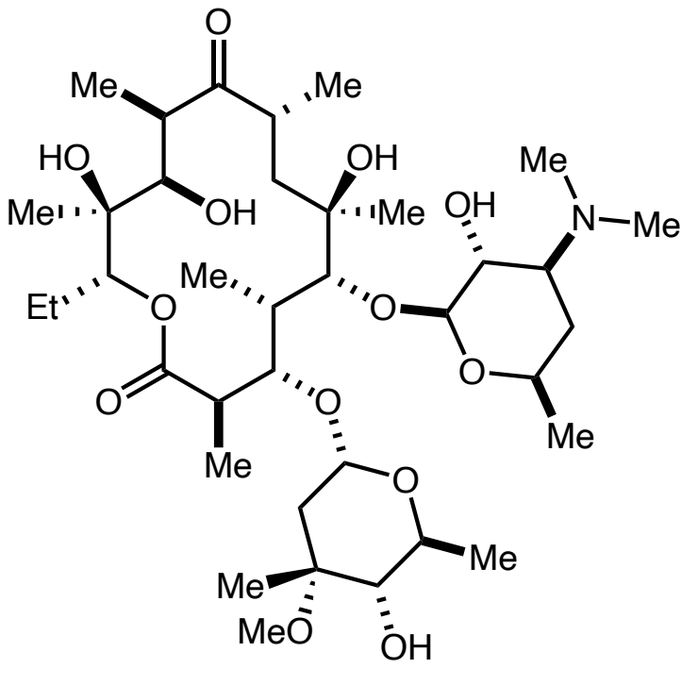
Insertion Product

Banić Tomišić, Z. *Kem. Ind.* **2011**, *60*, 603.

Beckmann Rearrangement Applications

Beckmann Rearrangement





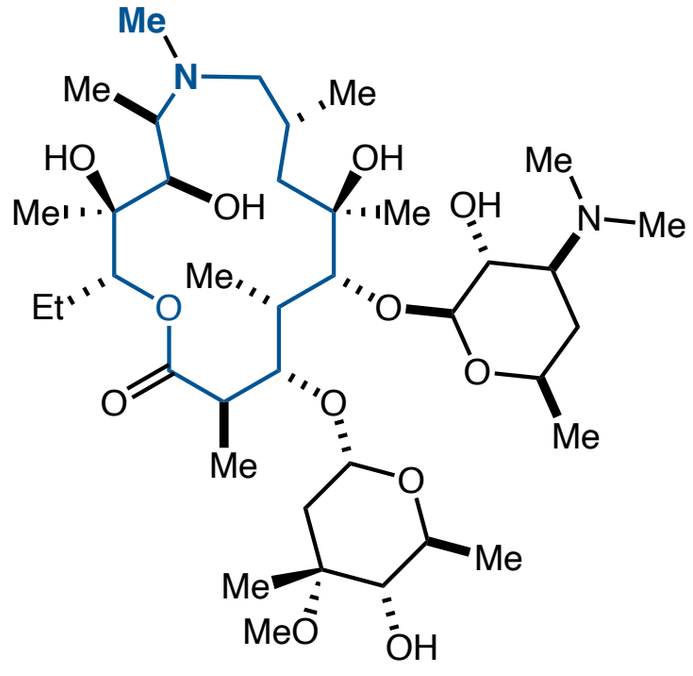
Erythromycin A

Beckmann Rearrangement

Reductive methylation

Reduction

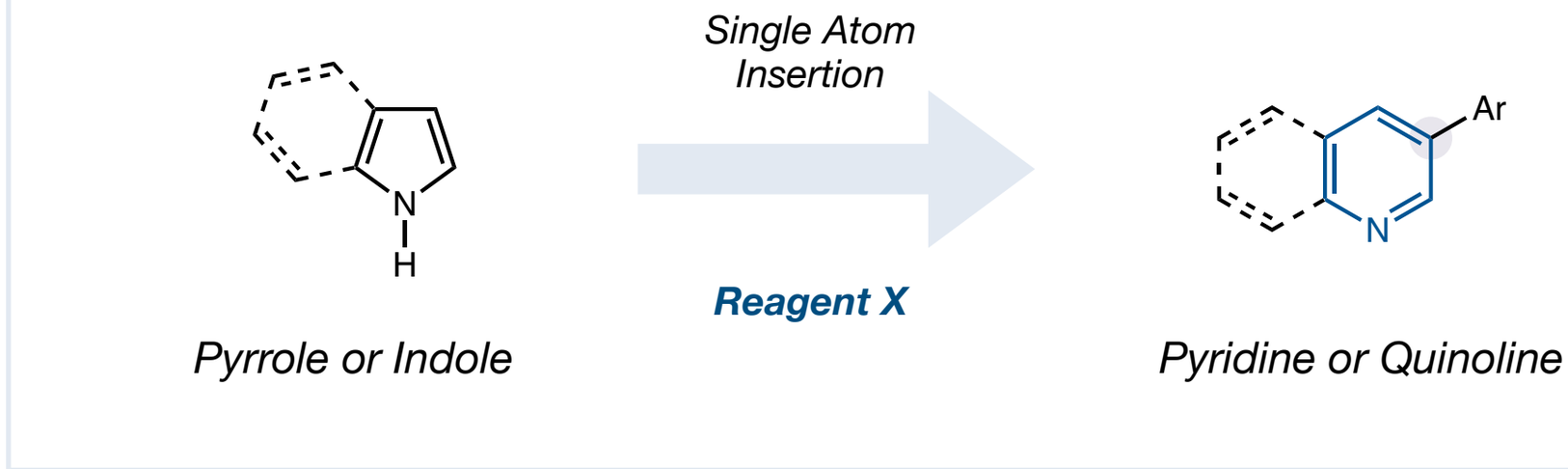
- *Increased potency and half-life*
- *The first 15-membered macrolide antibiotic*



Azithromycin

Banić Tomišić, Z. *Kem. Ind.* **2011**, *60*, 603.

Recent Advances in Single-Atom Insertions into Heterocycles

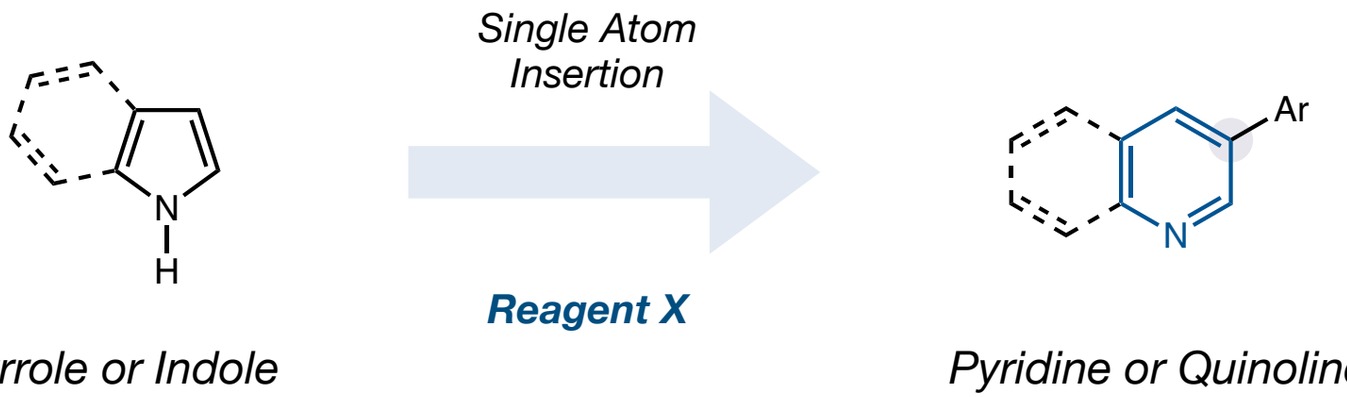


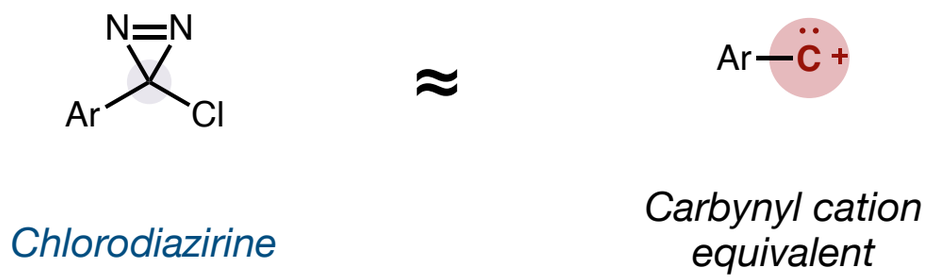
Matthew Sigman
Univ. of Utah

Mark Levin
Univ. of Chicago

Dherange, B. D.; Kelly, P. Q.; Liles, J. P.; Sigman, M. S.; Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 11337.

Recent Advances in Single-Atom Insertions into Heterocycles

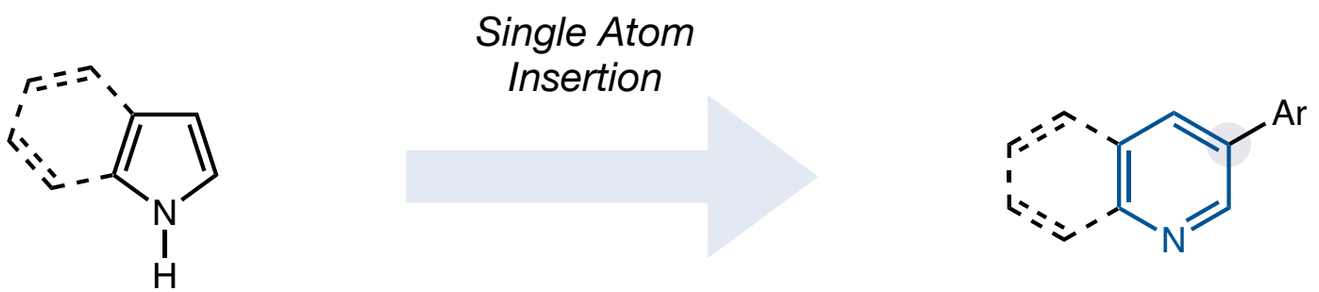




Stable and isolable

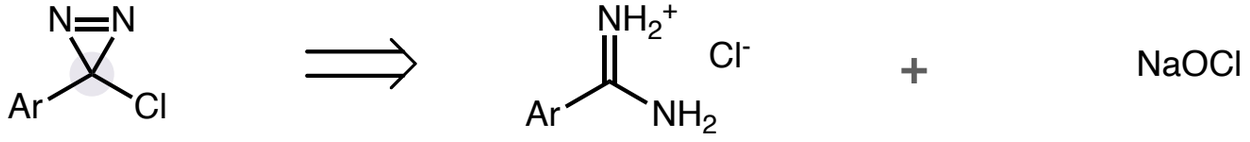
Dherange, B. D.; Kelly, P. Q.; Liles, J. P.; Sigman, M. S.; Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 11337.

Recent Advances in Single-Atom Insertions into Heterocycles

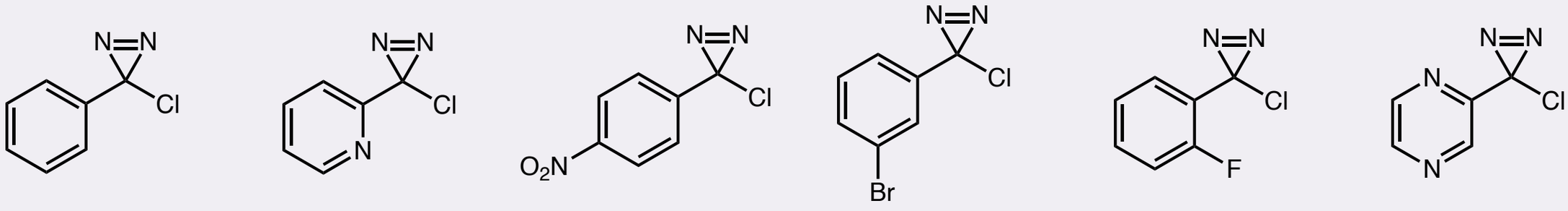


Synthesis of chlorodiazirine

Graham oxidation of amidine precursors

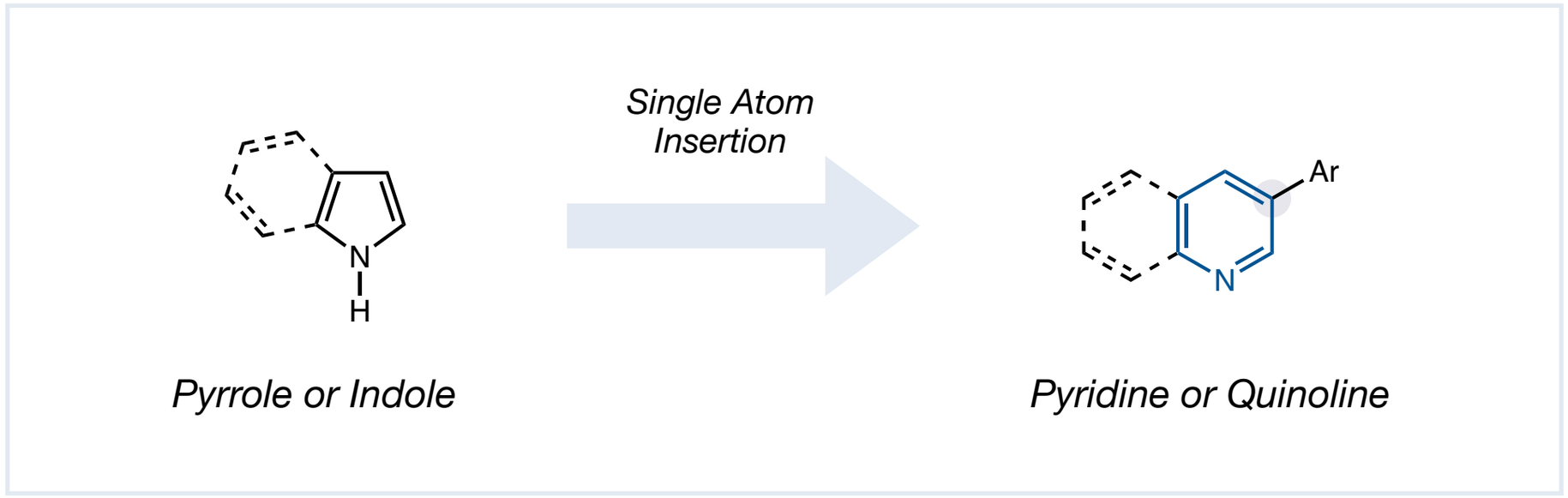


Chlorodiazirine library synthesis



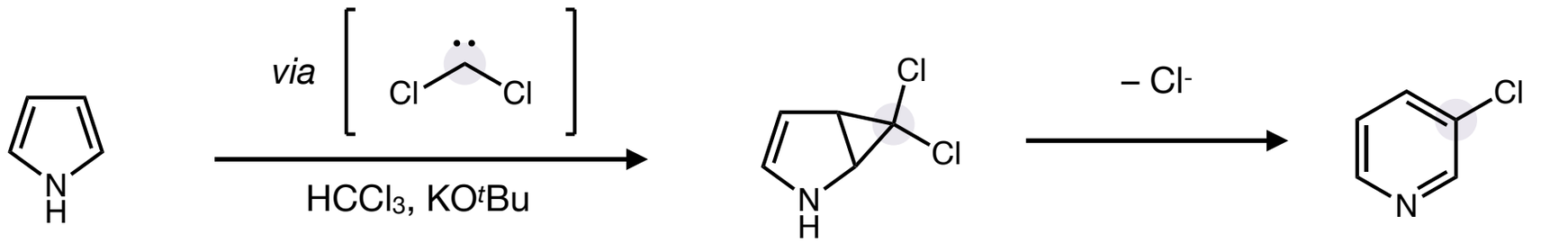
Dherange, B. D.; Kelly, P. Q.; Liles, J. P.; Sigman, M. S.; Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 11337.

Recent Advances in Single-Atom Insertions into Heterocycles



Mechanism

<u>Ciamician-Dennstedt Rearrangement</u>

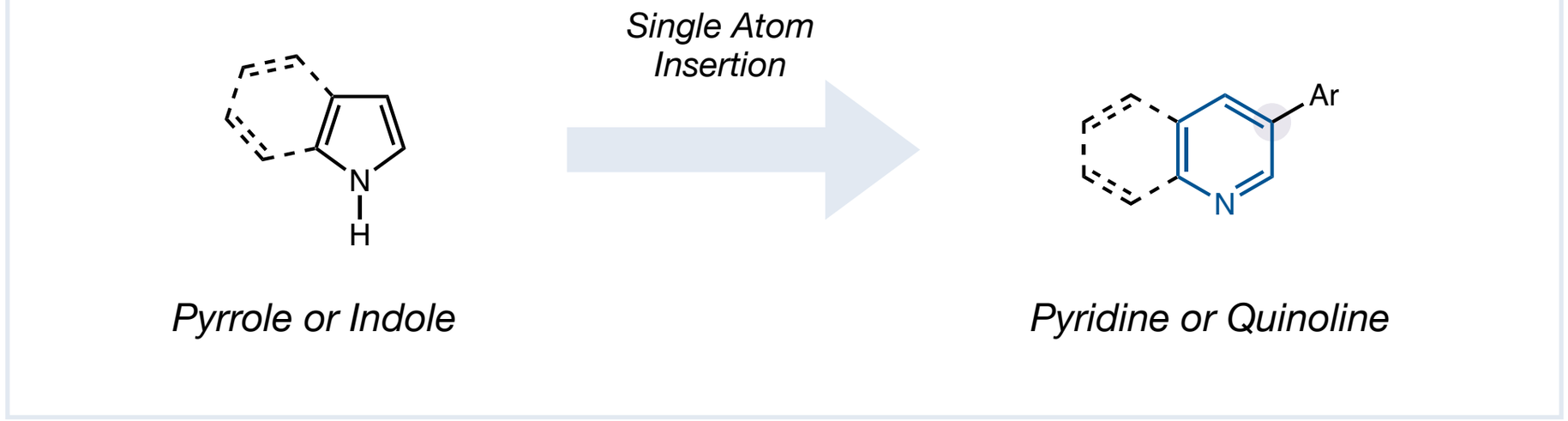


Drawbacks

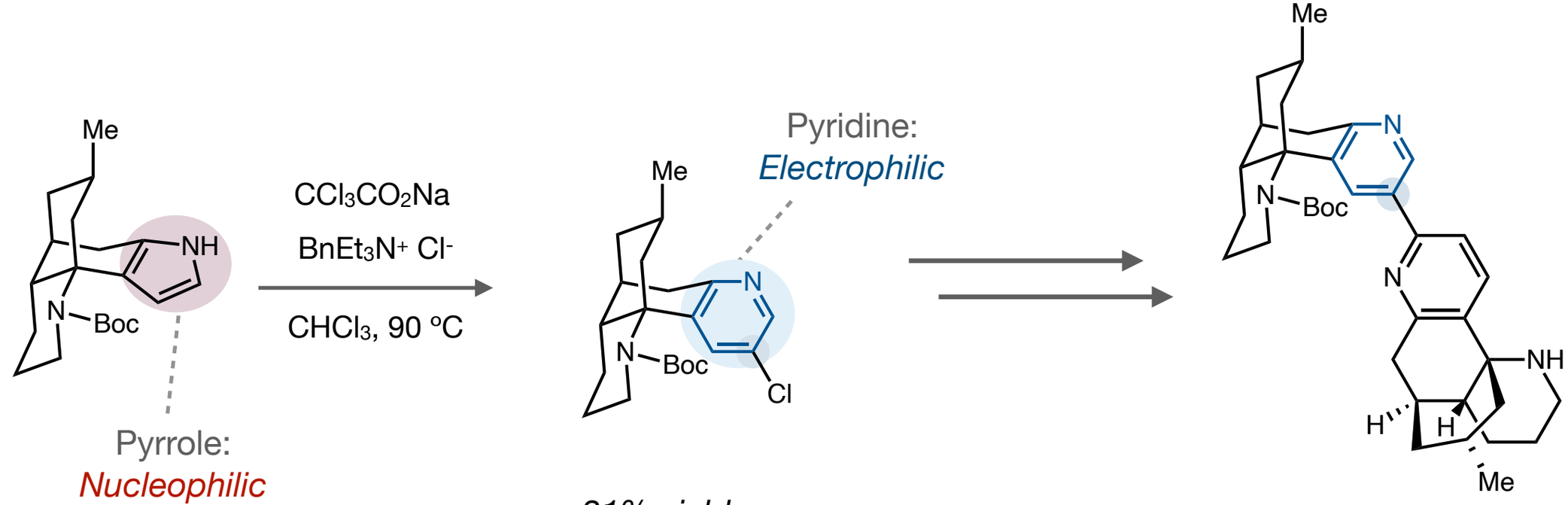
- Limited to 3-halopyridine synthesis
- Harsh conditions and low yielding

Dherange, B. D.; Kelly, P. Q.; Liles, J. P.; Sigman, M. S.; Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 11337.

Recent Advances in Single-Atom Insertions into Heterocycles

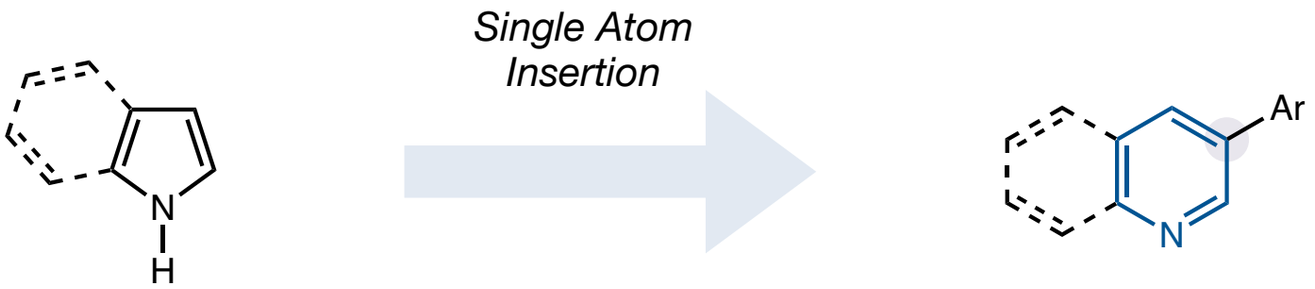


Ciamician-Dennstedt Rearrangement

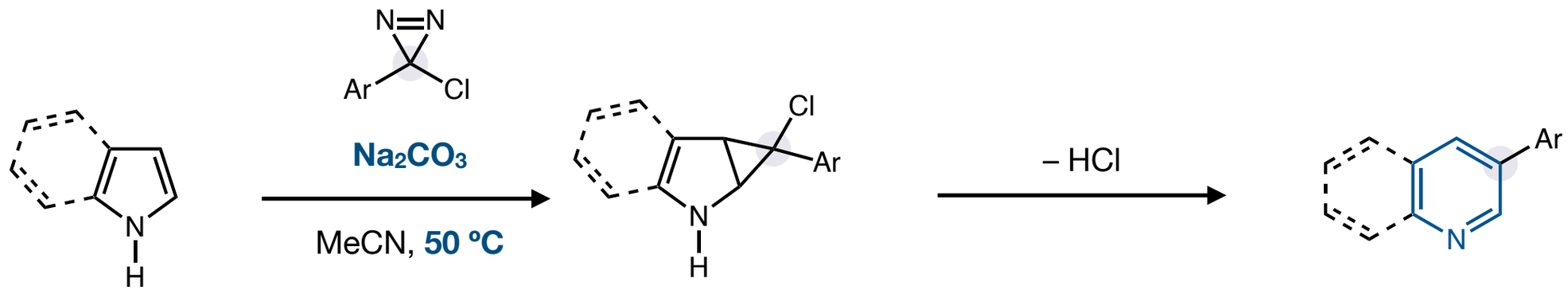


Ma, D.; Martin, B. S.; Gallagher, K. S.; Saito, T.; Dai, M. *J. Am. Chem. Soc.* **2021**, *143*, 16383.

Recent Advances in Single-Atom Insertions into Heterocycles



Mechanism



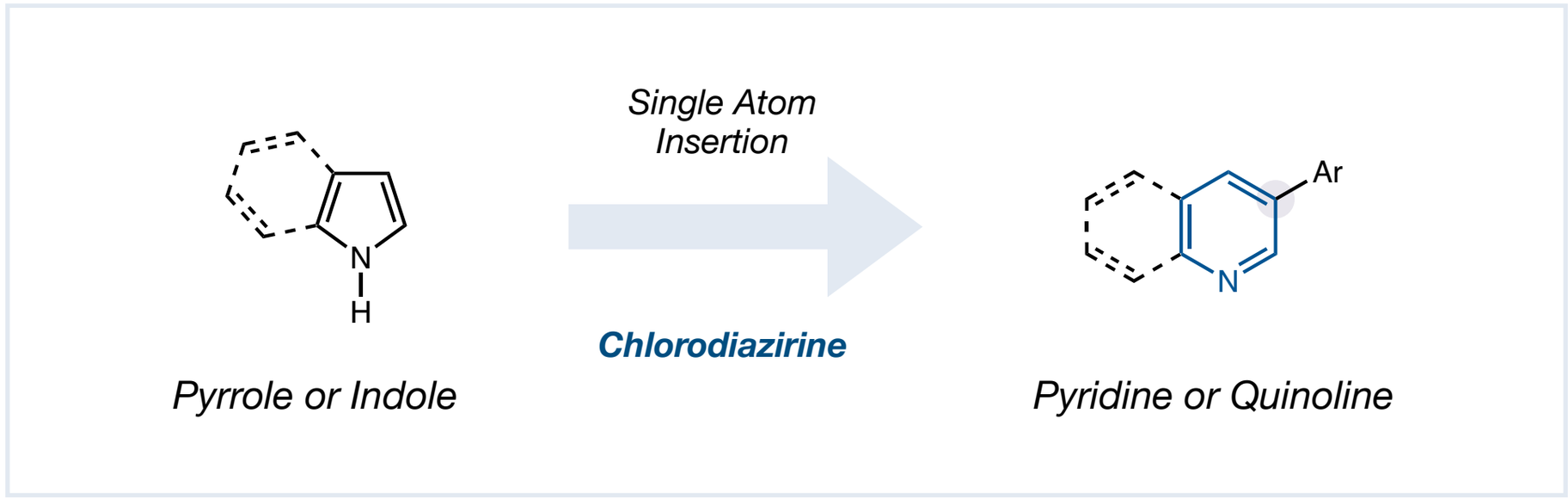
Mild Cyclopropantion

- *Weaker Base (Na_2CO_3 vs KO^tBu/KOH)*
- *Lower Reaction Temperatures*

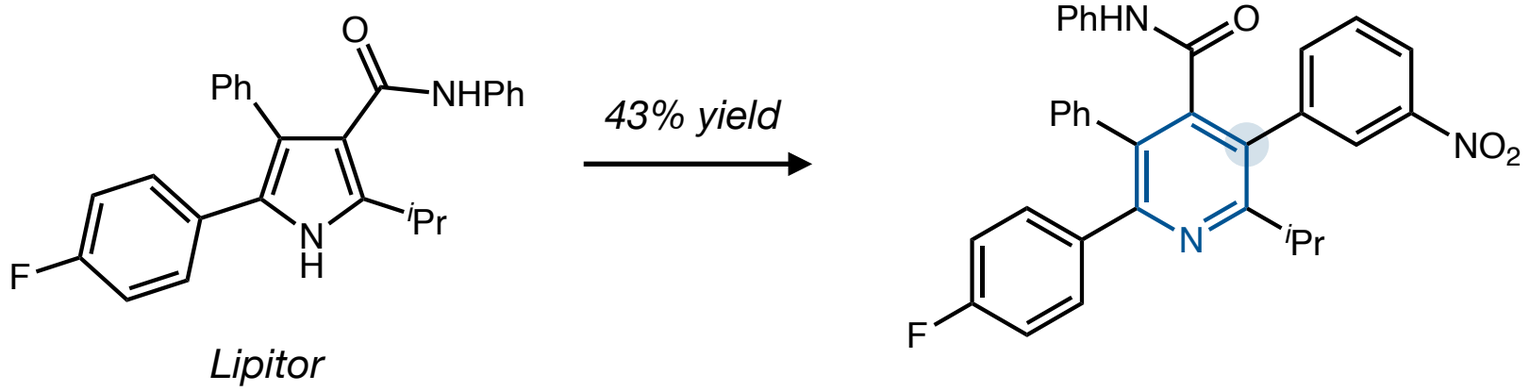
Broader Reaction Scope

Dherange, B. D.; Kelly, P. Q.; Liles, J. P.; Sigman, M. S.; Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 11337.

Recent Advances in Single-Atom Insertions into Heterocycles

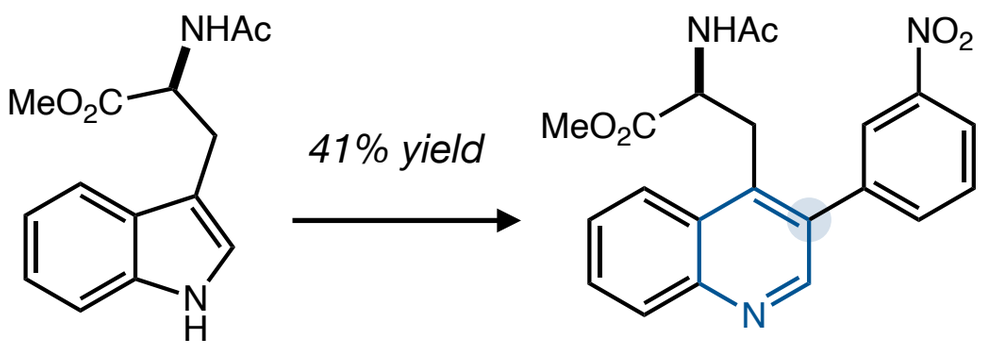


Late Stage Skeletal Editing

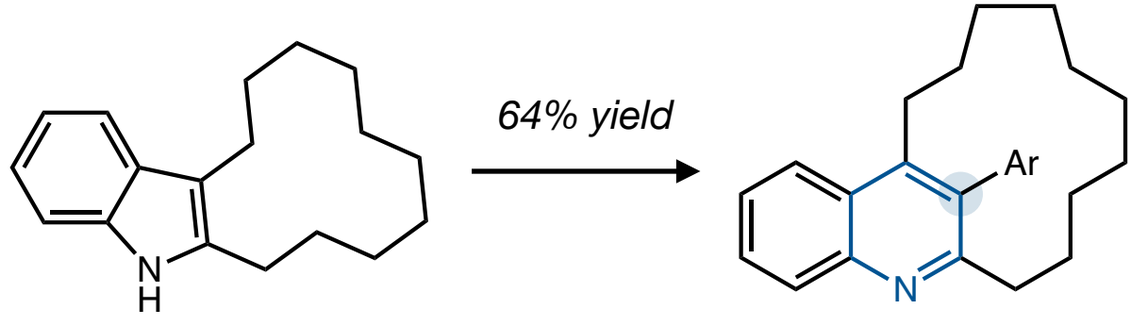


Lipitor

tryptophan editing



cyclophane derivatization



Ar = (p-F)C$_6$H$_4$

Dherange, B. D.; Kelly, P. Q.; Liles, J. P.; Sigman, M. S.; Levin, M. D. *J. Am. Chem. Soc.* **2021**, *143*, 11337.

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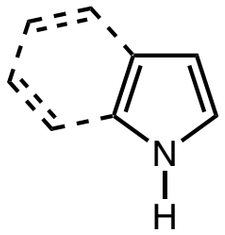
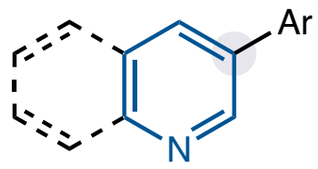
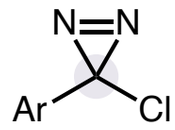


Pyrrole or Indole

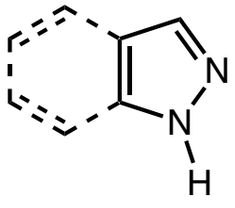


Pyridine or Quinoline

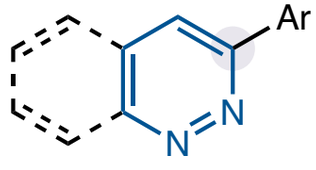
Single C-Atom Insertion



Chlorodiazirine



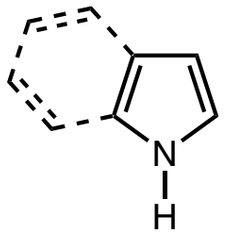
Pyrazole or Indazole



Pyridazine or Cinnoline

Hyland, E. E.; Kelly, P. Q.; McKillop, A. M.; Dherange, B. D.; Levin, M. D. *J. Am. Chem. Soc.* **2022**, *144*, 19258.

Recent Advances in Single-Atom Insertions into Heterocycles



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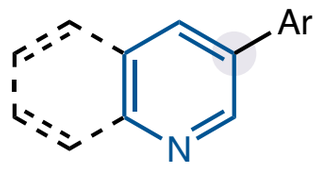

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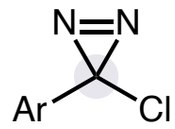

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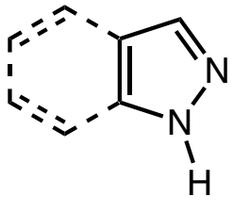

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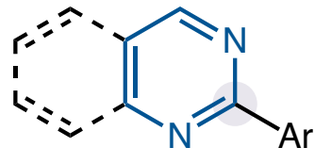
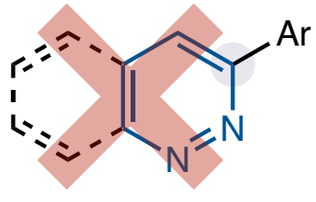


Pyrimidine or Quinazoline

Major product observed



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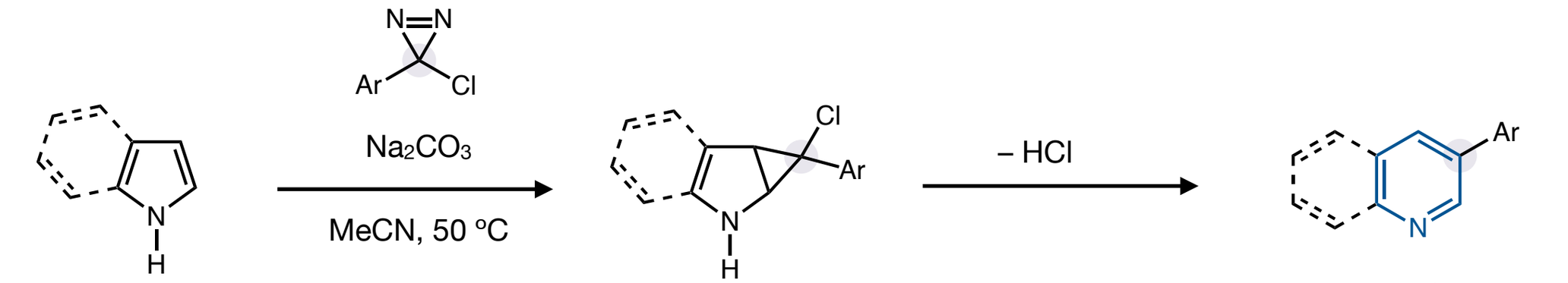
Hyland, E. E.; Kelly, P. Q.; McKillop, A. M.; Dherange, B. D.; Levin, M. D. *J. Am. Chem. Soc.* **2022**, *144*, 19258.

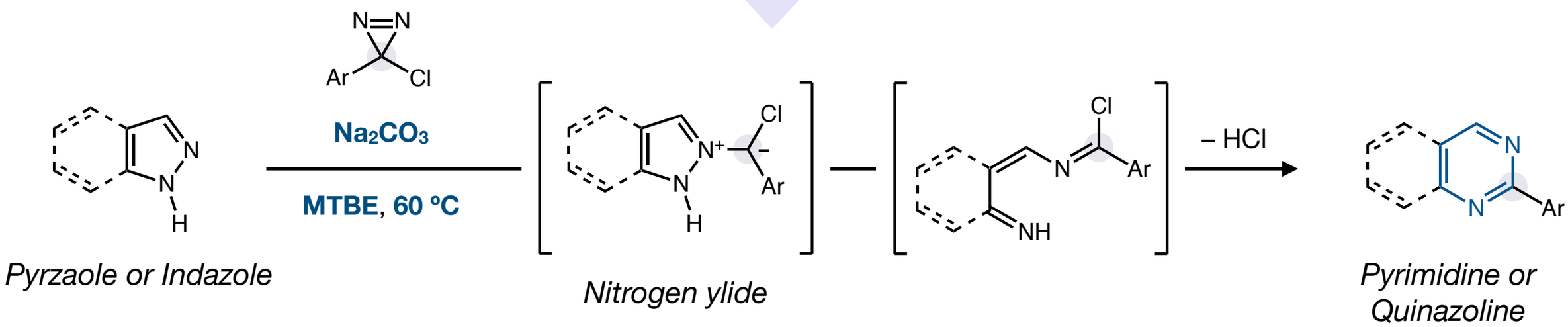
Levin – Unified Access to Pyrimidines and Quinazolines



Pyrrole or Indole

Pyridine or Quinoline

Pyrrole/Indole C-Atom Insertion Mechanism



Pyrzaole or Indazole

Nitrogen ylide

Pyrimidine or Quinazoline

Pyrazole/Indazole C-Atom Insertion Mechanism

Hyland, E. E.; Kelly, P. Q.; McKillop, A. M.; Dherange, B. D.; Levin, M. D. *J. Am. Chem. Soc.* **2022**, *144*, 19258.

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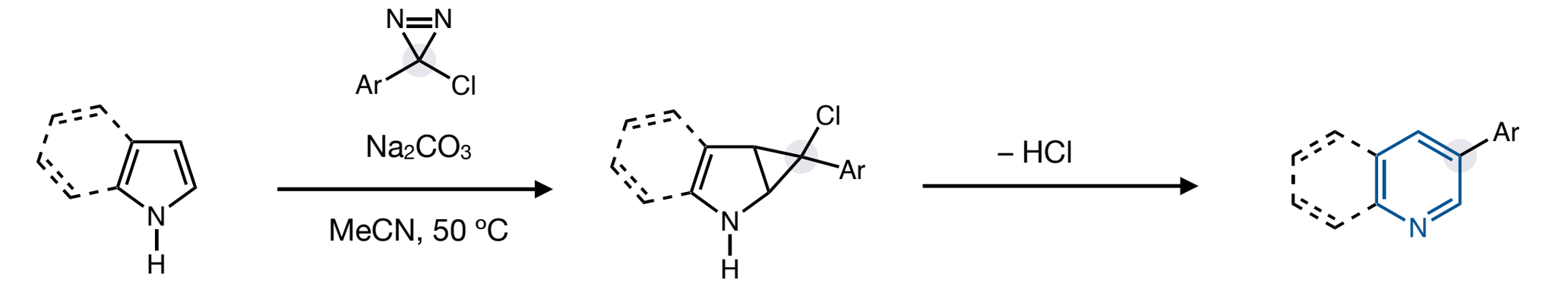

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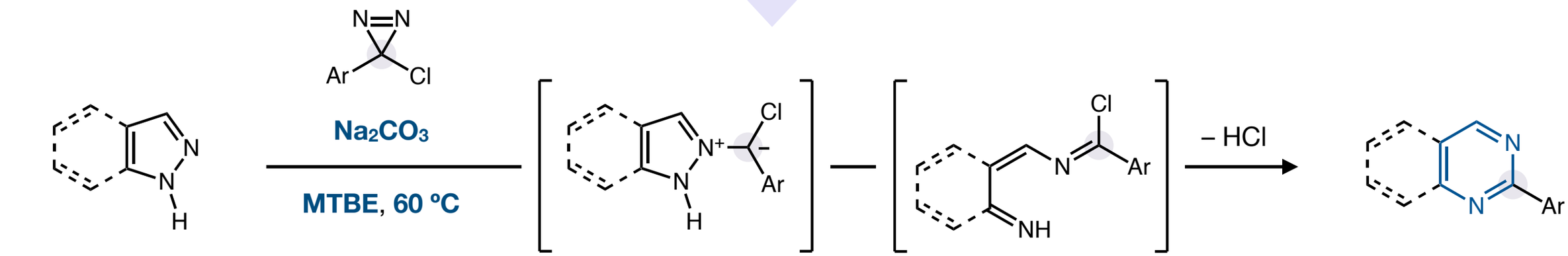
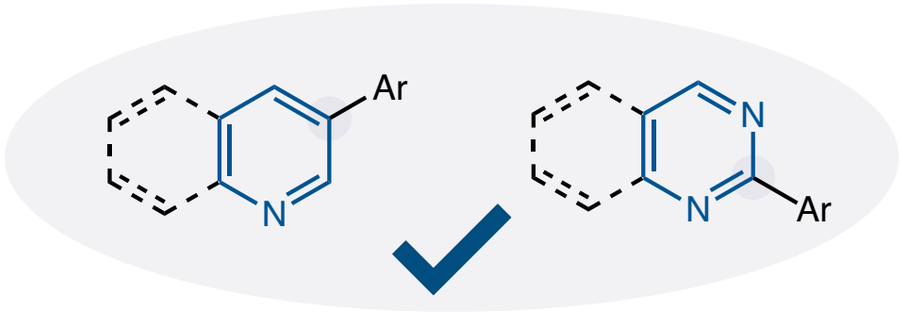


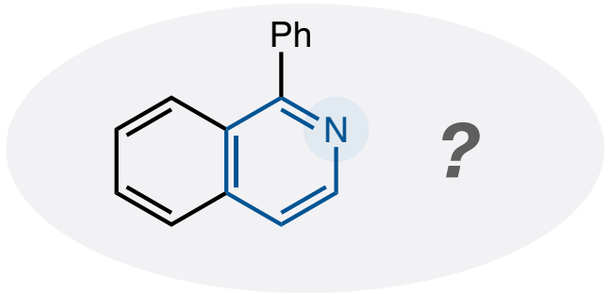
Serendipitous functionalization of the relatively weak N–N bond

Hyland, E. E.; Kelly, P. Q.; McKillop, A. M.; Dherange, B. D.; Levin, M. D. *J. Am. Chem. Soc.* **2022**, *144*, 19258.

Levin – Heteroarene Synthesis via Nitride Insertion

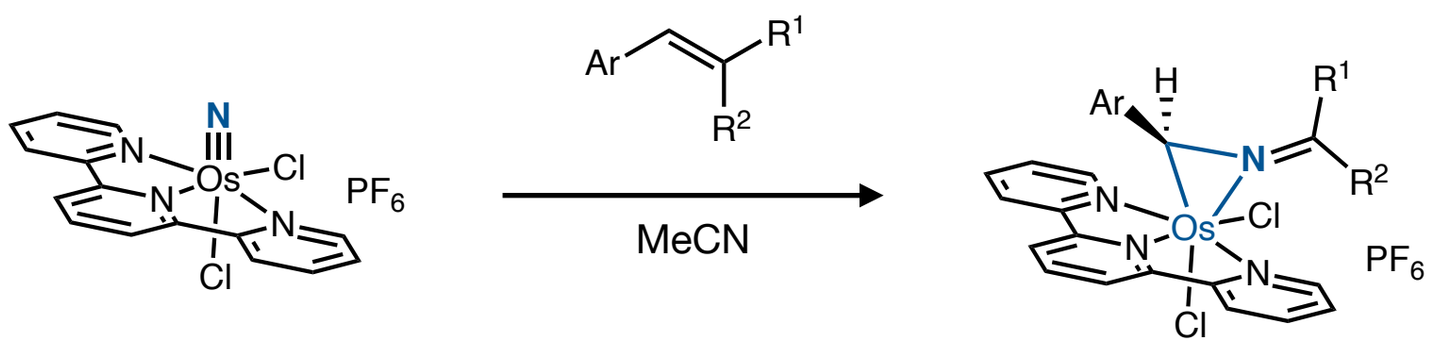


***C-atom insertions** into heteroaromatics well-established*



*Can we develop a **N-atom insertions** into heteroaromatics?*

Key Precedence – Brown 1999



Inspiring reactivity from group 8 metal nitrides

Terminal osmium(VI) nitrido complexes can insert nitrogen into conjugated olefines

Brown, S. N. *J. Am. Chem. Soc.* **1999**, *121*, 9752.

Levin – Heteroarene Synthesis via Nitride Insertion

1) $TsOH•H_2O$, $PhI(OAc)_2$
then NBu_4Cl
2) LiCl, Δ
then NH_4PF_6

48% yield (over 2 steps)

77% yield

Nucleophilic attack

Aziridination

Electrocyclic ring-opening

Rapid Isomerization

74% yield

$NH_4O_2CNH_2$
$PhI(OAc)_2$
then NH_4PF_6
MeOH

Et_3N, MeCN
80 °C, 1 h

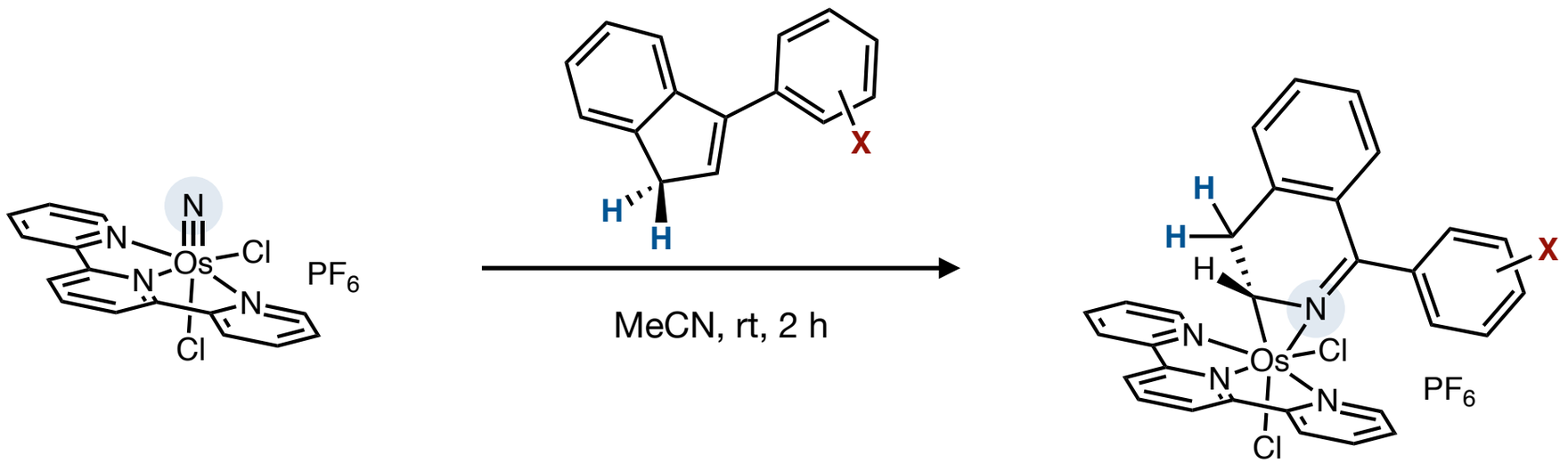
N-Insertion Product

60% yield

DFT: *–20 kcal/mol*

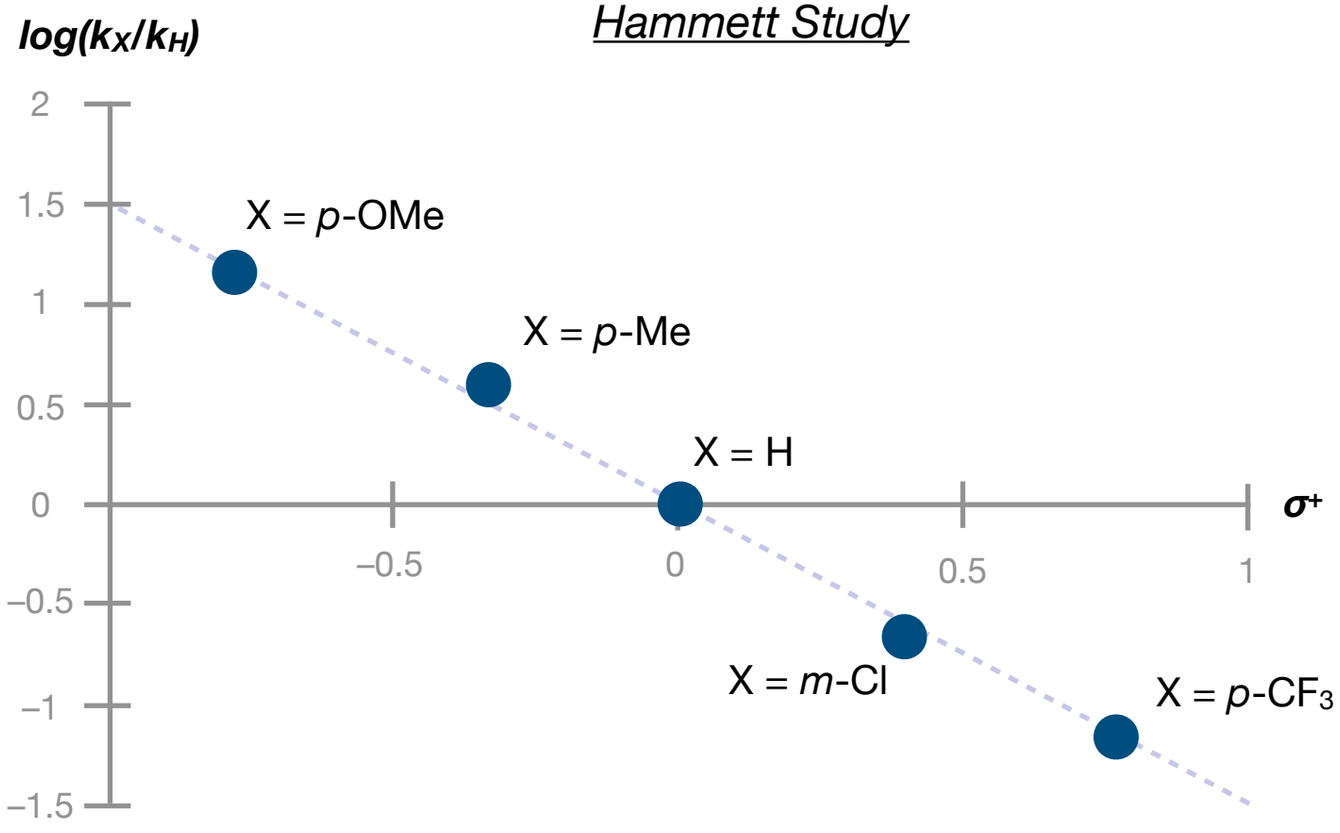
Kelly, P. Q.; Filatov, A. S.; Levin, M. D. *Angew. Chem. Int. Ed.* **2022**, *61*, e202213041.

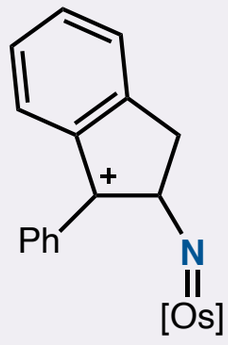
Levin – Heteroarene Synthesis via Nitride Insertion – Hammett Study



Distinctive protons easily monitored by ^{1}H-NMR

Hammett Study





ρ = –1.5 (R^2 = 0.996)

Strong evidence for dibenzylic cation intermediate

Kelly, P. Q.; Filatov, A. S.; Levin, M. D. *Angew. Chem. Int. Ed.* **2022**, *61*, e202213041.

Overview

n – 1 single-atom edits

- Contractions
- Deletions

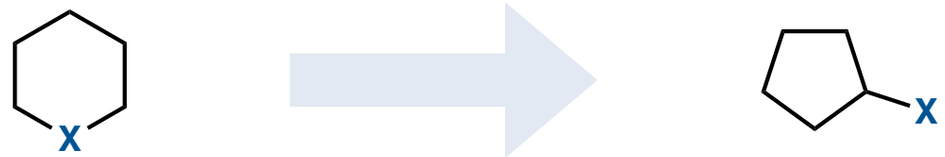
n + 1 single-atom edits

- Expansions
- Insertions

Outlook

Outlook

contraction



deletion

expansion

insertion

Maturity

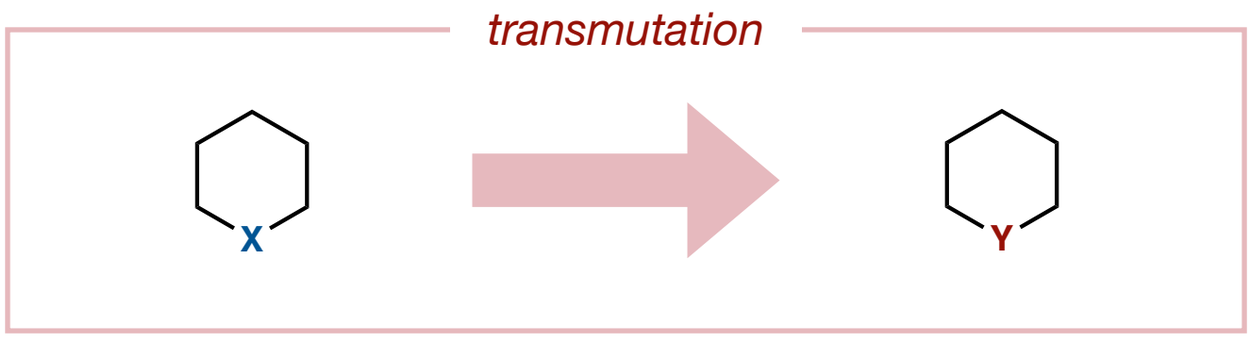
Context-independent deployment

Non-traditional reactivity manifolds

Single-step operations

Moving beyond n±1

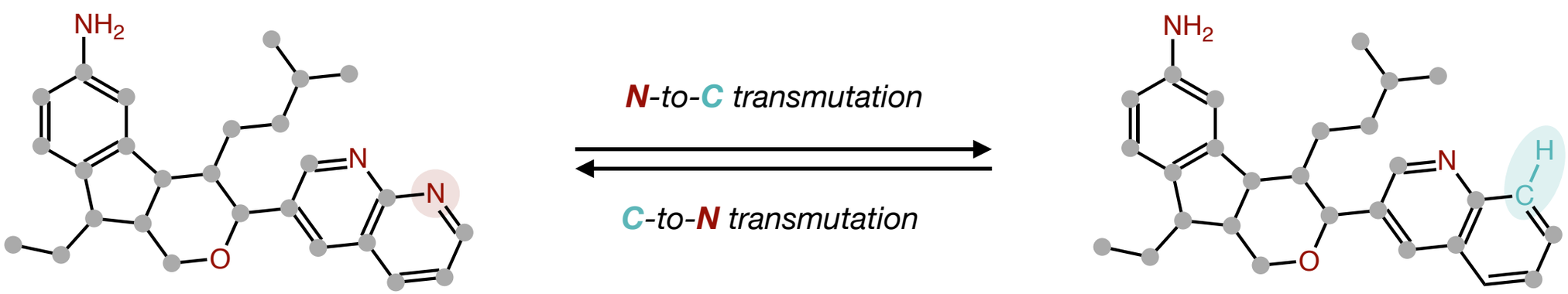
Transmutations



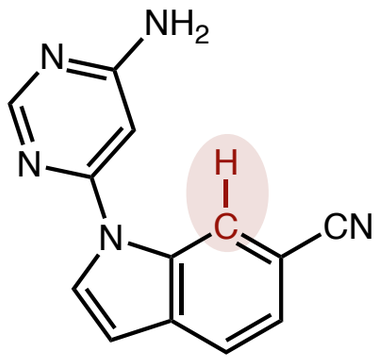
Maintaining the ring size while replacing one atom in a ring system

The ultimate goal of skeletal editing

Such transmutations would enable the direct interrogation of shape-conserving structure-activity relationships in drugs



'Necessary Nitrogen Effect'



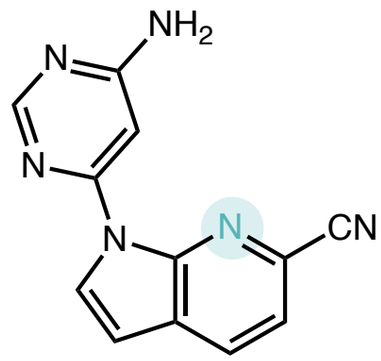
Lead compound

Cdc7 kinase inhibitor

IC_{50} = 2,700 nM

C-to-N editing

300-fold biochemical potency improvement



IC_{50} = 9.0 nM

Cdc – Cell division cycle

IC_{50} – half maximal inhibitory concentration

Pennington, L. D. & Moustakas, D. T. *J. Med. Chem.* **2017**, *60*, 3552.

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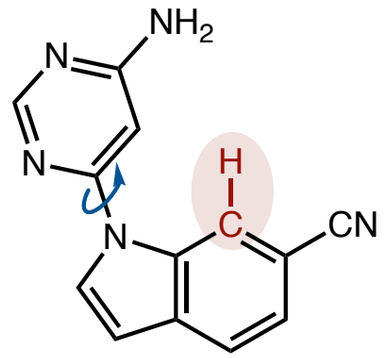
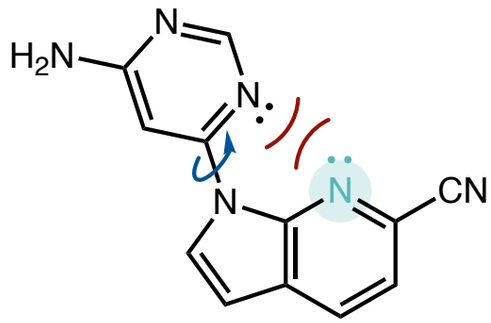


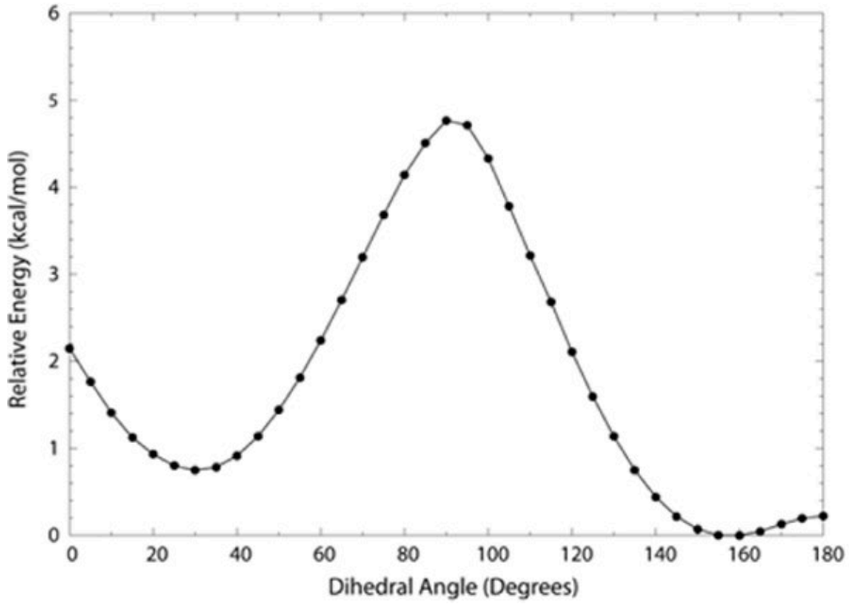
Dihedral angle = 0°

C-to-N editing

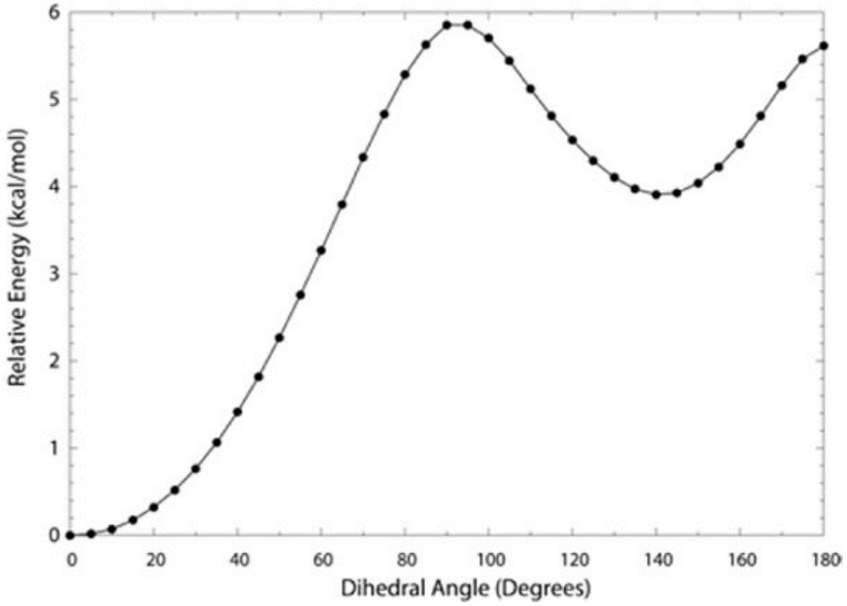
300-fold biochemical potency improvement



Dihedral angle = 180°



Preference for >150° biaryl dihedral angle



Strong preference for 0° biaryl dihedral angle due to **nitrogen lone-pair/lone-pair repulsion**

Pennington, L. D. & Moustakas, D. T. *J. Med. Chem.* **2017**, *60*, 3552.

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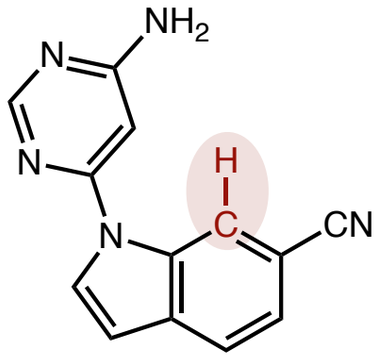

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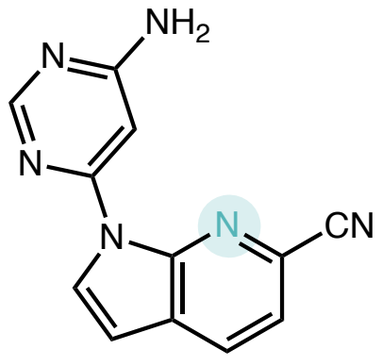

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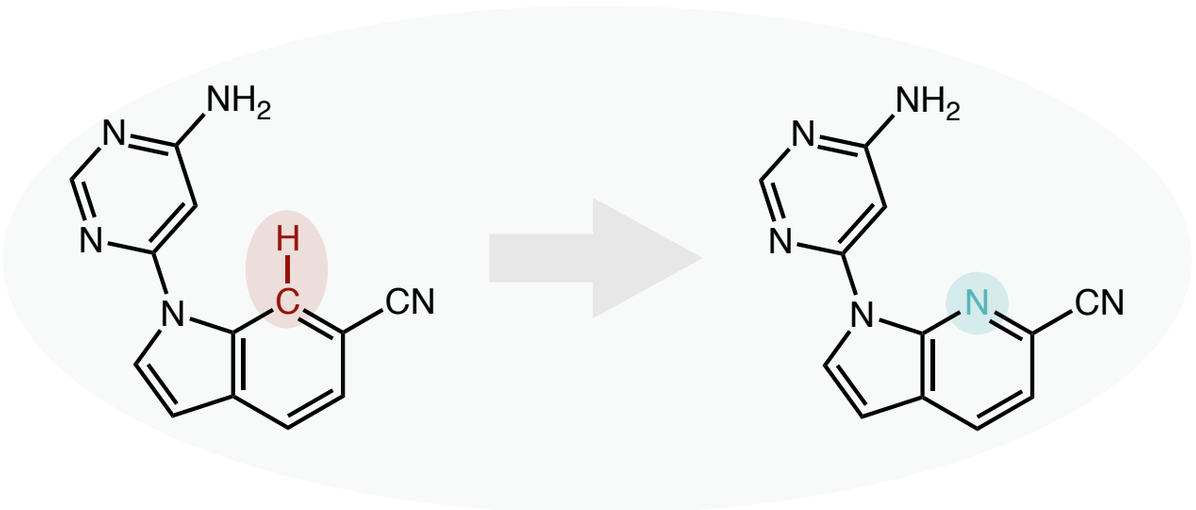

Pharma – 'Nitrogen Scans'

Conventional methods demand lengthy de novo synthesis

Cdc – Cell division cycle

IC_{50} – half maximal inhibitory concentration

Pennington, L. D. & Moustakas, D. T. *J. Med. Chem.* **2017**, *60*, 3552.

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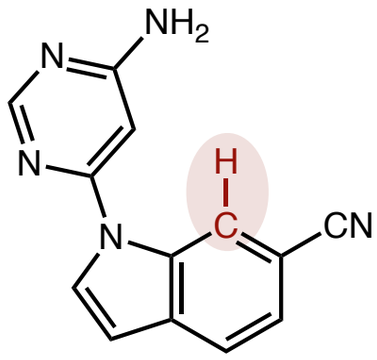

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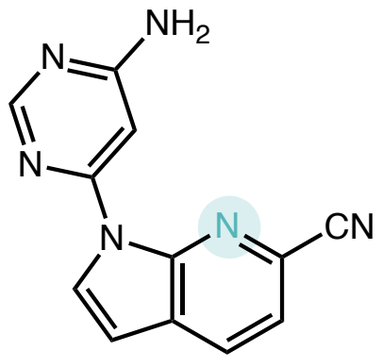

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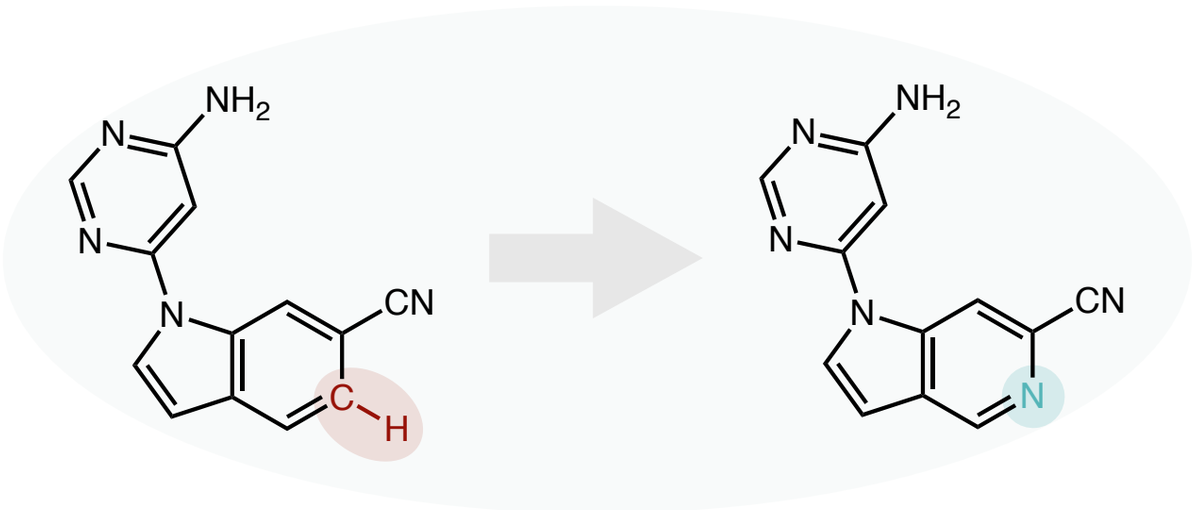

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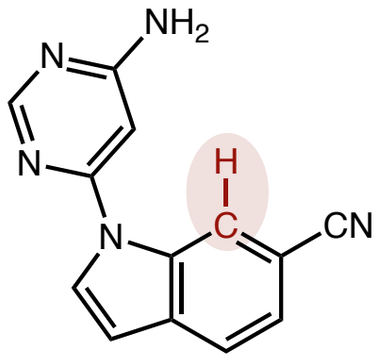

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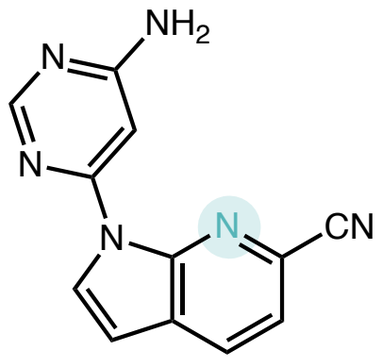

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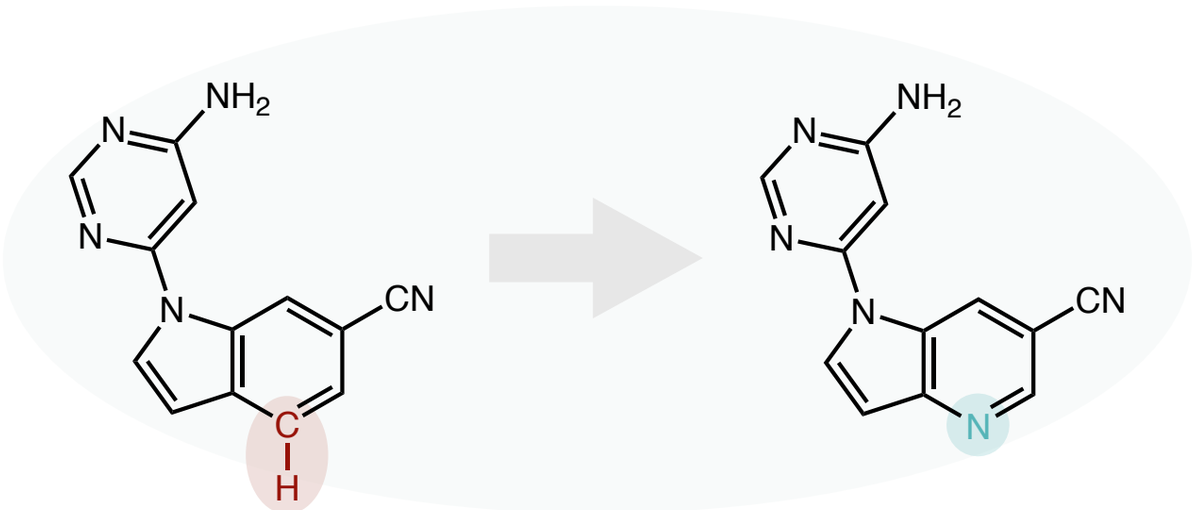

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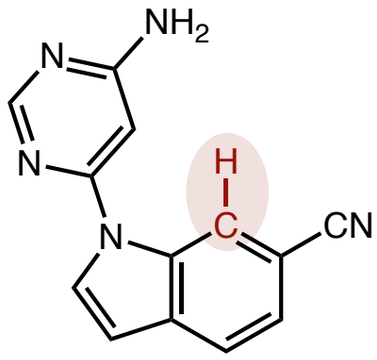

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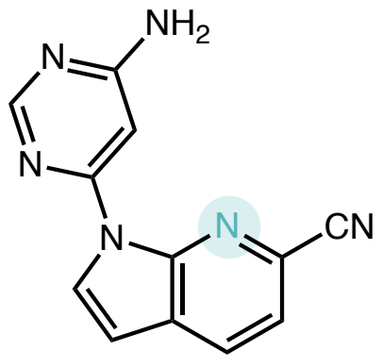

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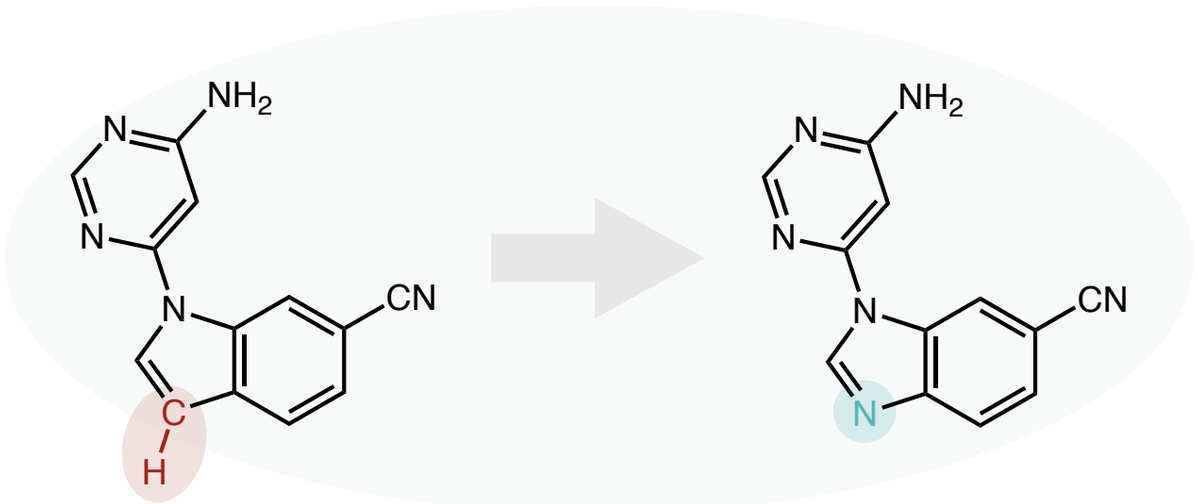

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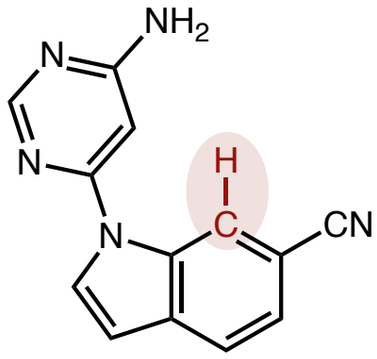
'Necessary Nitrogen Effect'



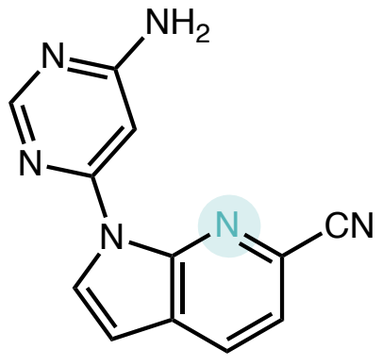
Lead compound

Cdc7 kinase inhibitor

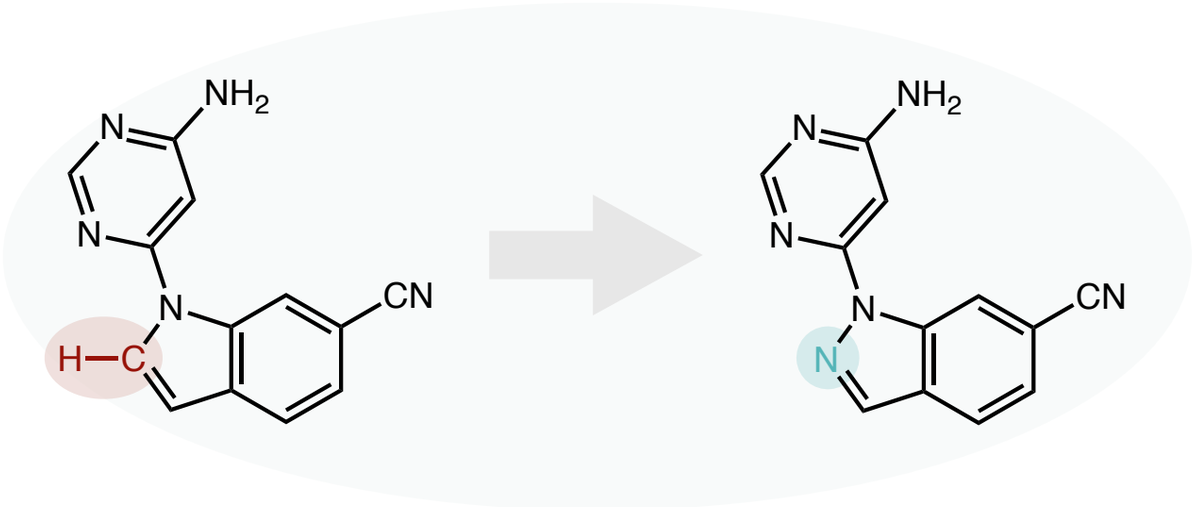
IC_{50} = 2,700 nM

C-to-N editing

300-fold biochemical potency improvement



IC_{50} = 9.0 nM



Pharma – 'Nitrogen Scans'

Conventional methods demand lengthy de novo synthesis

Cdc – Cell division cycle

IC_{50} – half maximal inhibitory concentration

Pennington, L. D. & Moustakas, D. T. *J. Med. Chem.* **2017**, *60*, 3552.

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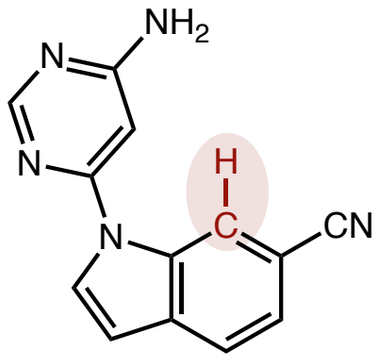

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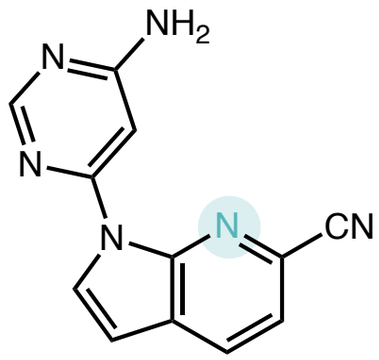

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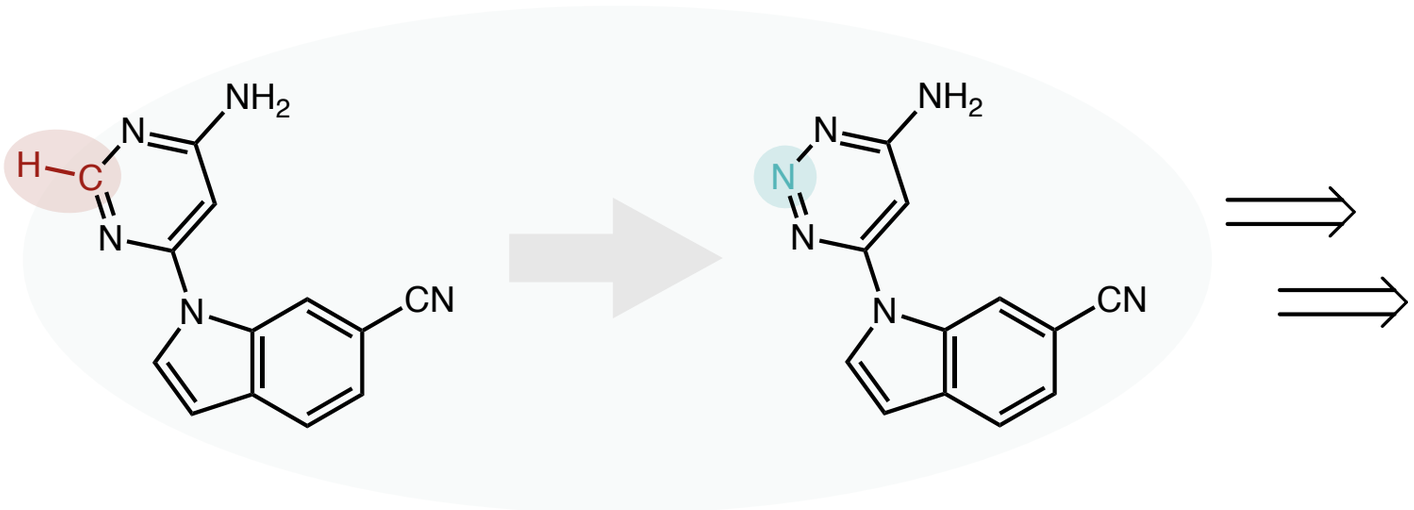

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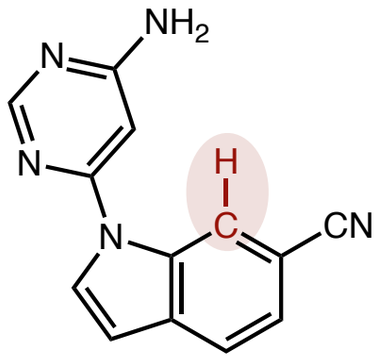

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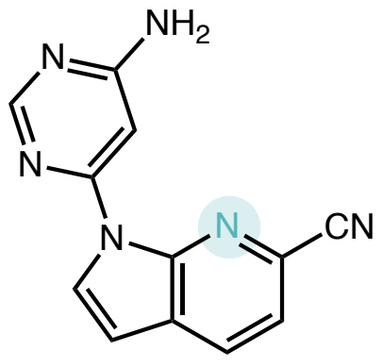

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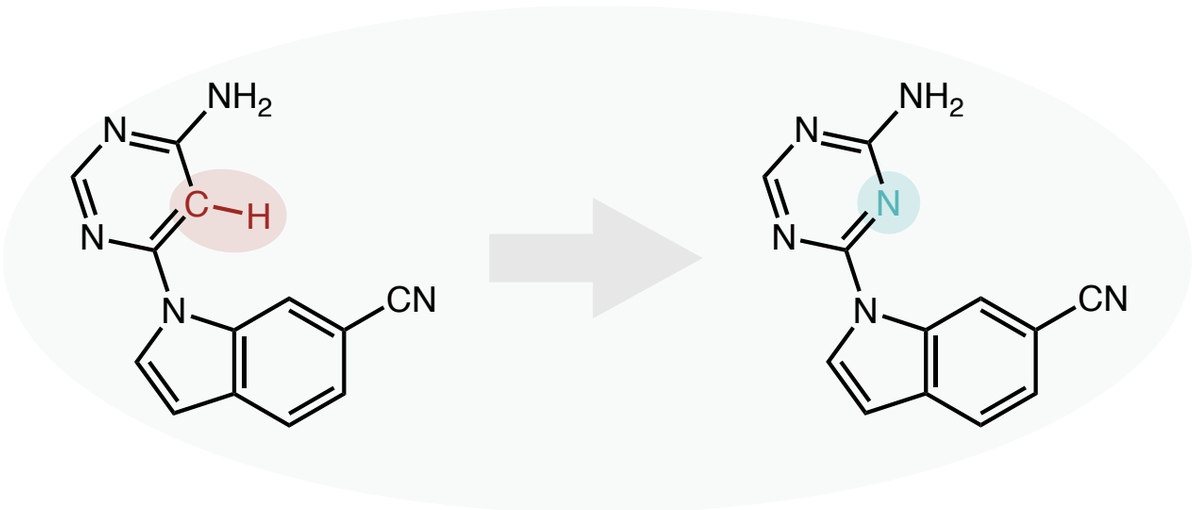

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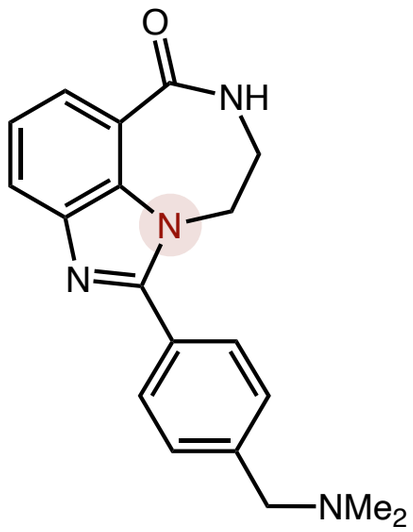
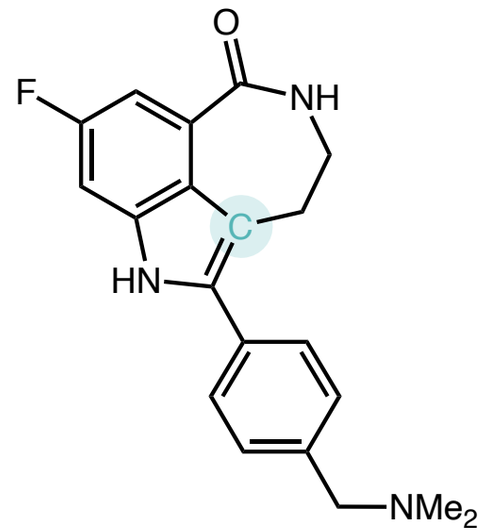


Lead compound

PARP inhibitor

K_i = *5.8 nM*

N-to-C editing



Transmuted product

K_i = *1.4 nM*

Sometimes nitrogen is 'unnecessary'

?

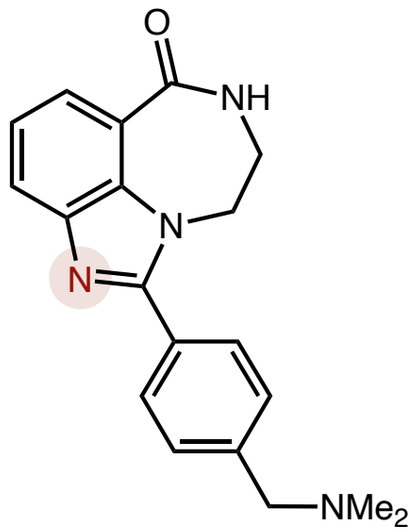
How can we efficiently 'scan' for where nitrogen is needed?

K_i – inhibitory constant

PARP – polyadensosine diphosphate ribose polymerase

Golding, B. T. in *Successful Drug Discovery.* **2019**, John Wiley & Sons, Ltd. 201.

'Necessary Nitrogen Effect'

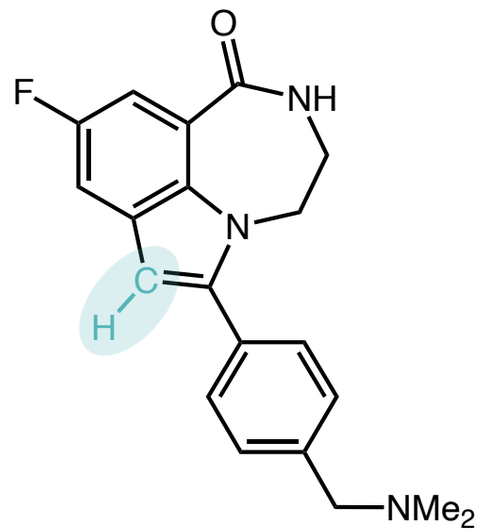


Lead compound

PARP inhibitor

K_i = *5.8 nM*

N-to-C editing



Transmuted product

K_i = *??*

Sometimes nitrogen is '<u>unnecessary</u>'

?

How can we efficiently 'scan' for where nitrogen is needed?

K_i *– inhibitory constant*

PARP – polyadensosine diphosphate ribose polymerase

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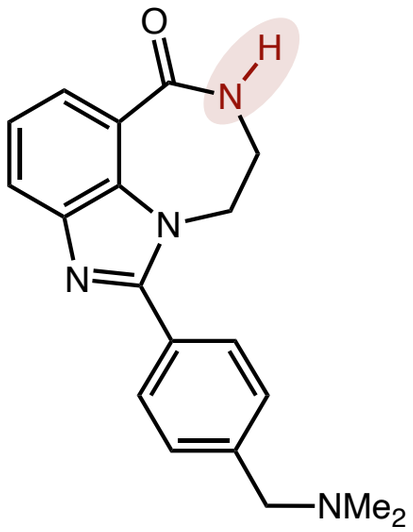
'Necessary Nitrogen Effect'

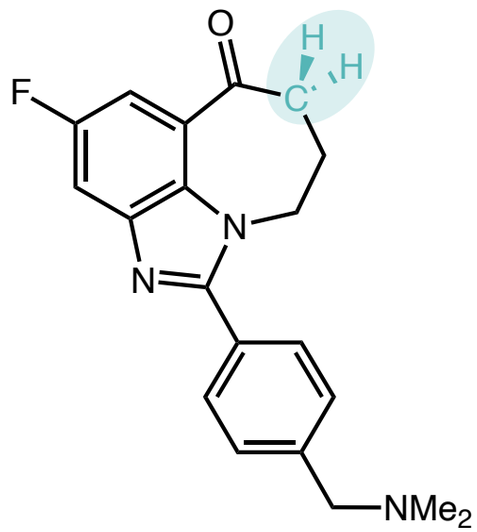


Lead compound

PARP inhibitor

K_i = *5.8 nM*

N-to-C editing



Transmuted product

K_i = *??*

Sometimes nitrogen is 'unnecessary'

?

How can we efficiently 'scan' for where nitrogen is needed?

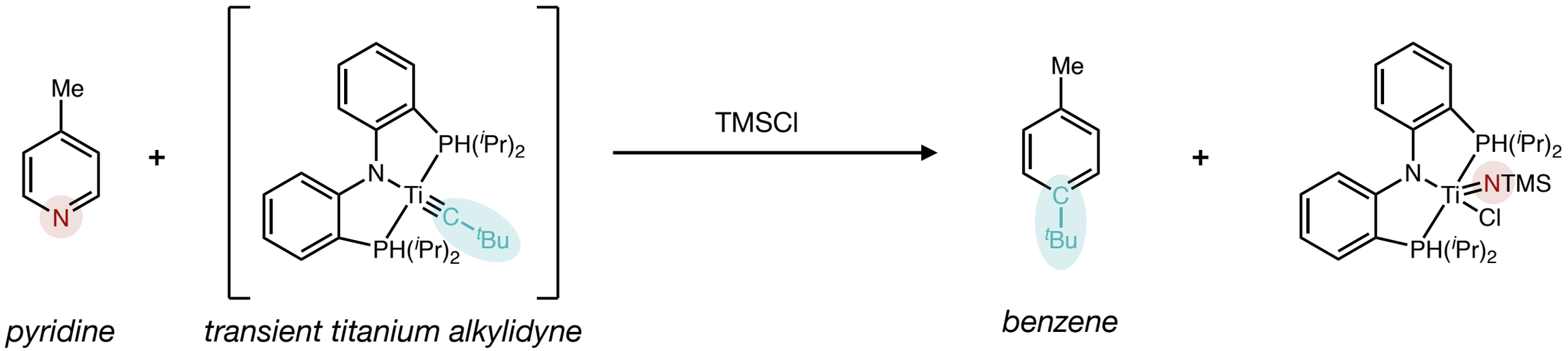
K_i – inhibitory constant

PARP – polyadensosine diphosphate ribose polymerase

Golding, B. T. in *Successful Drug Discovery.* **2019**, John Wiley & Sons, Ltd. 201.

Promising Examples of Formal Carbon-Nitrogen Transmutation

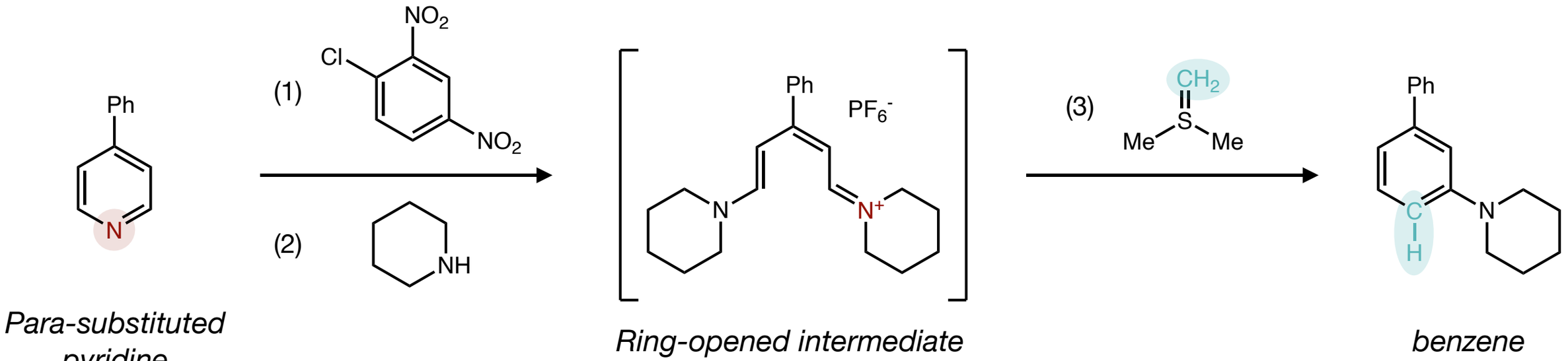
Mindiola Group – Univ. of Pennsylvania



pyridine *transient titanium alkylidyne* *benzene*

require stoichiometric metals or multistep sequences

Kano Group – Gakushuin Univ.



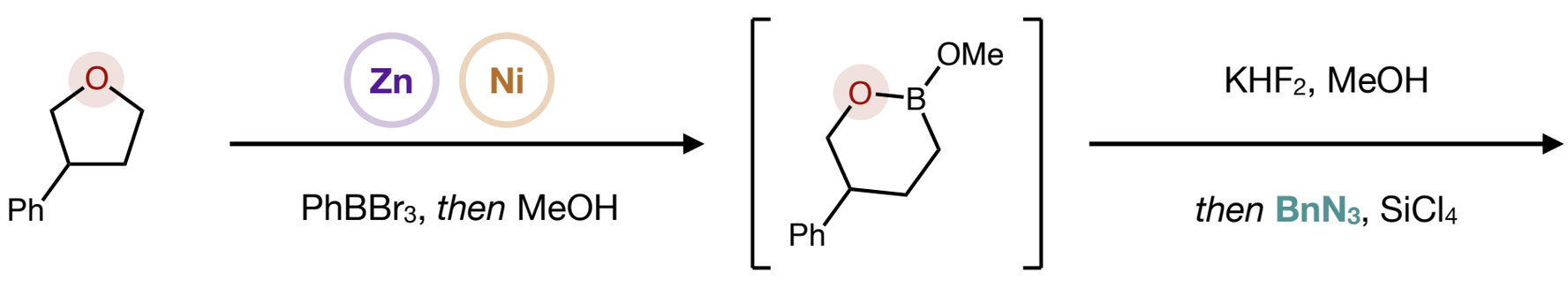
Para-substituted pyridine *Ring-opened intermediate* *benzene*

Fout, A. R.; Bailey, B. C.; Tomaszewski, J.; Mindiola, D.J. *J. Am. Chem. Soc.* **2007**, *129*, 12640.

Morofuji, T.; Inagawa, K.; Kano, N. *Org. Lett.* **2021**, *23*, 6126.

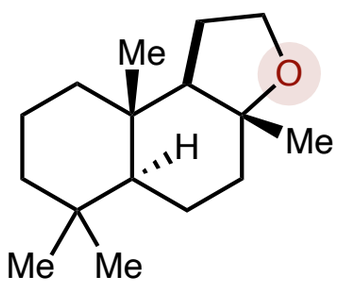
Dong – Formal Transmutation of Other Heteroatoms

Dong Group – Univ. of Chicago



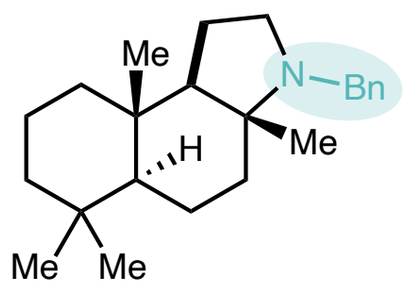
O-to-N transmuted product

only one purification



(–)-Ambroxide

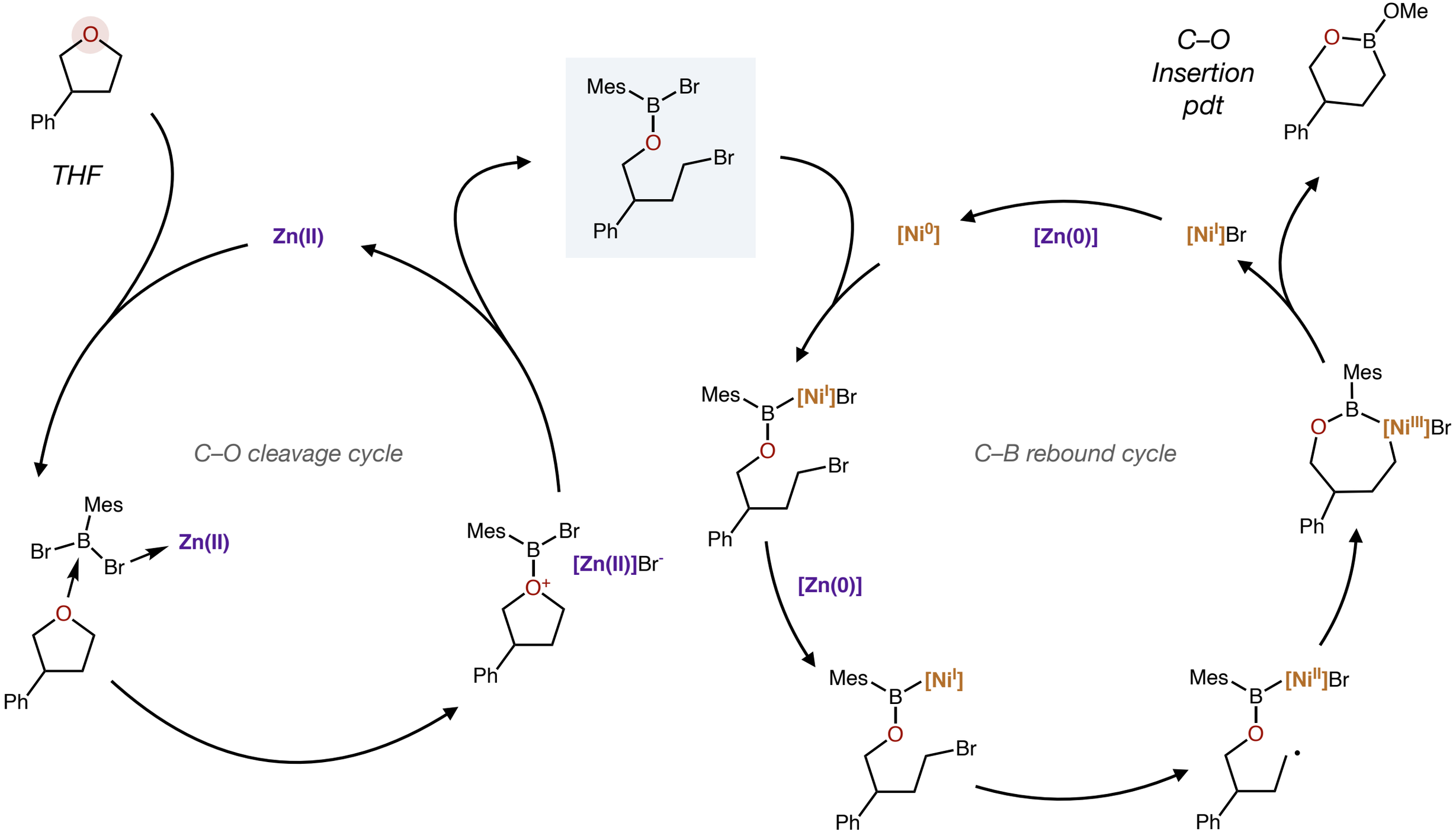
O-to-N editing



24% yield
(over 3 steps)

Lyu, H.; Kevlishvili, I.; Yu, X.; Liu, P.; Dong, G. *Science.* **2021**, *372*, 175.

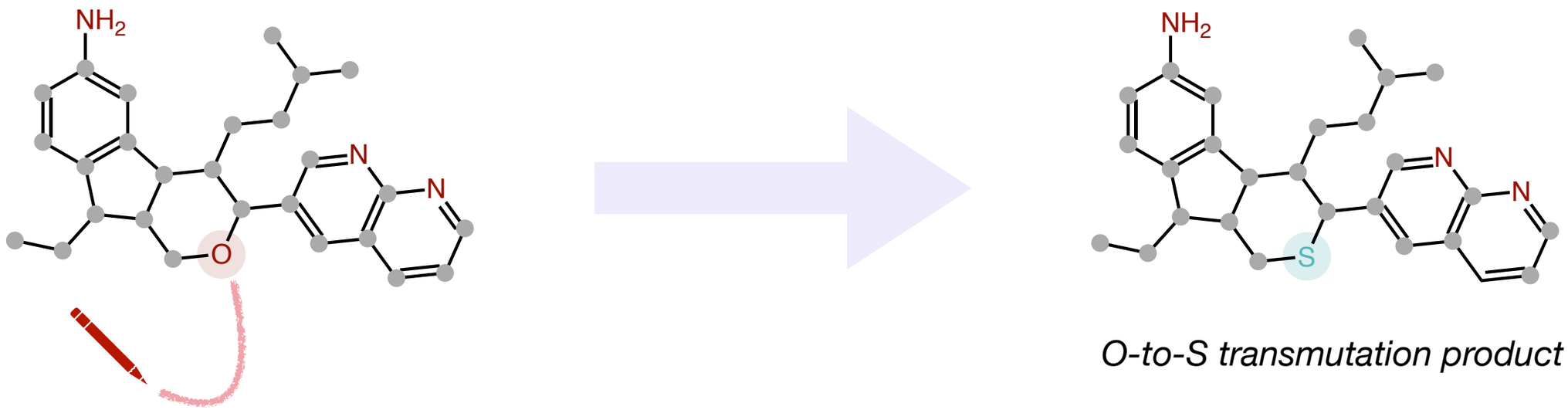
Dong – Formal Transmutation of Other Heteroatoms



Lyu, H.; Kevlishvili, I.; Yu, X.; Liu, P.; Dong, G. *Science.* **2021**, *372*, 175.

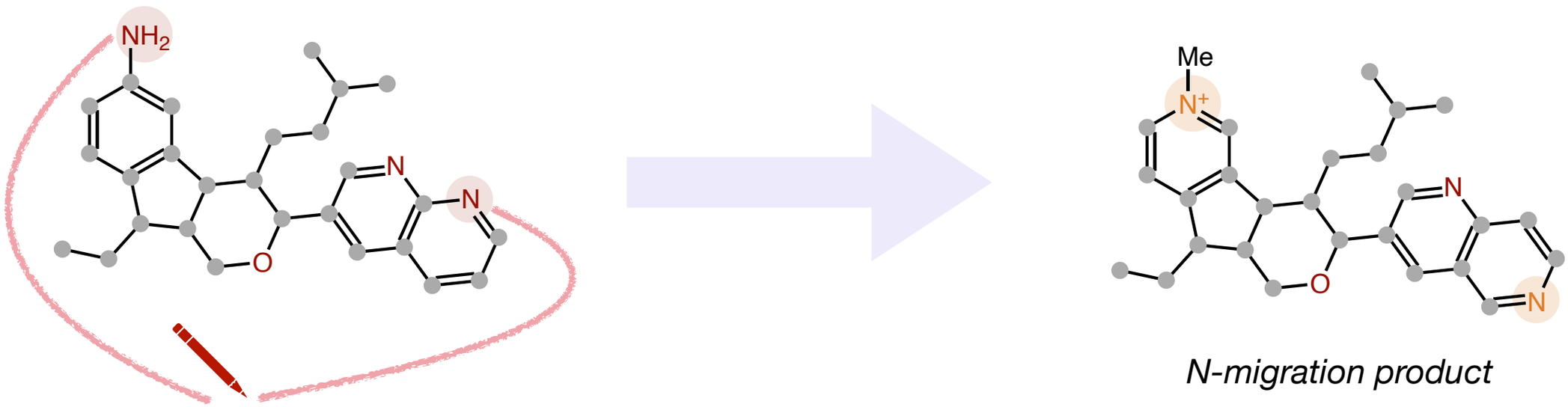
Skeletal Editing Dream Reactions

Heteroatom transmutation



O-to-S transmutation product

Heteroatom migration

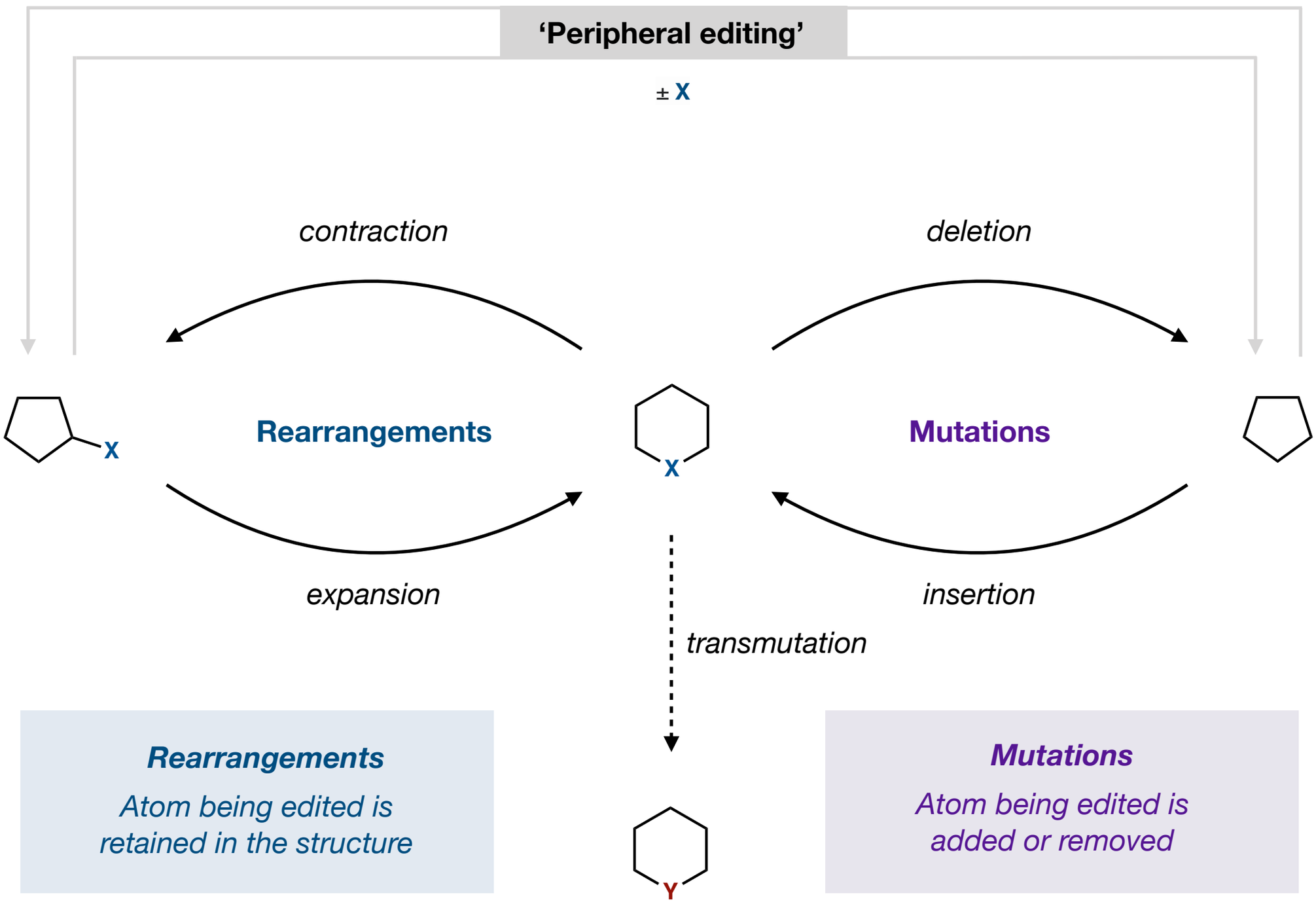


N-migration product

“[Skeletal editing is] … like suddenly discovering while you're driving that there's a new shortcut road that you didn't know about, one that connects two neighborhoods that you've always thought of as being far apart.”

https://www.science.org/content/blog-post/ripping-out-amines

Questions?



Rearrangements

Atom being edited is retained in the structure

Mutations

Atom being edited is added or removed