Nitrogen Atom Insertion to C-C Double Bond

2023.6.10 Literature Seminar

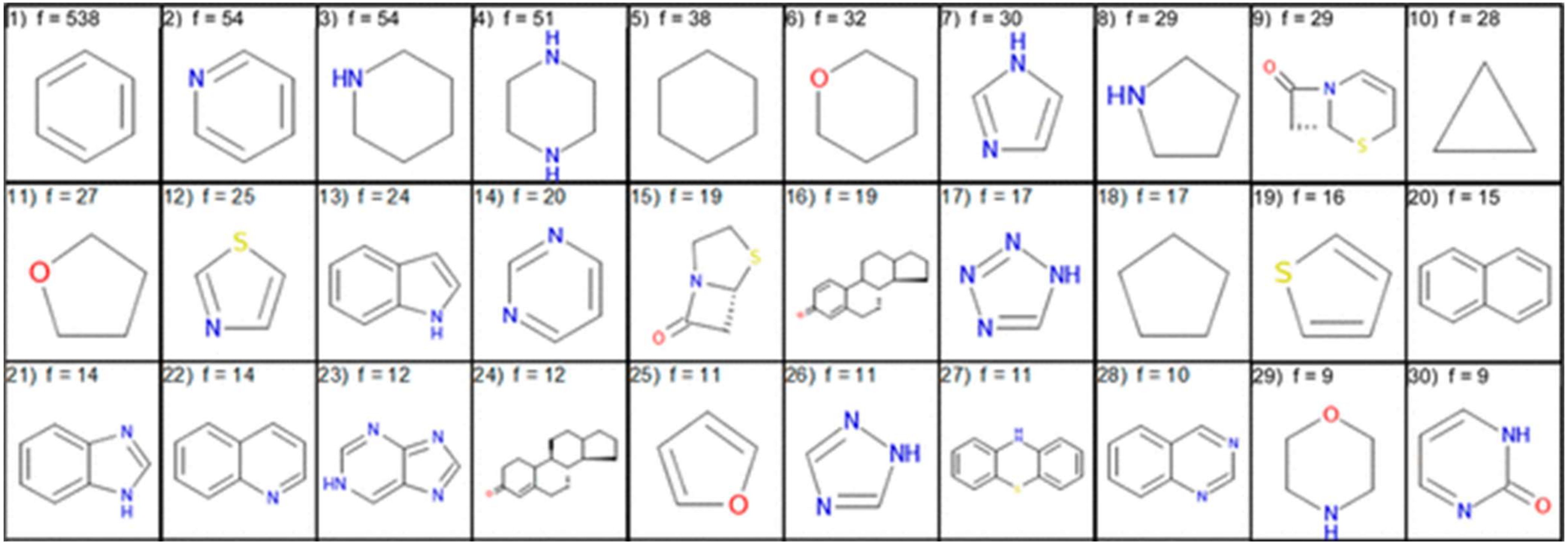
M1 Shuji Toyama

Contents

Contents

N Atom in Drugs

Most Frequently Used Ring Systems from Small Molecule Drugs Listed in the FDA Orange Book (2012)

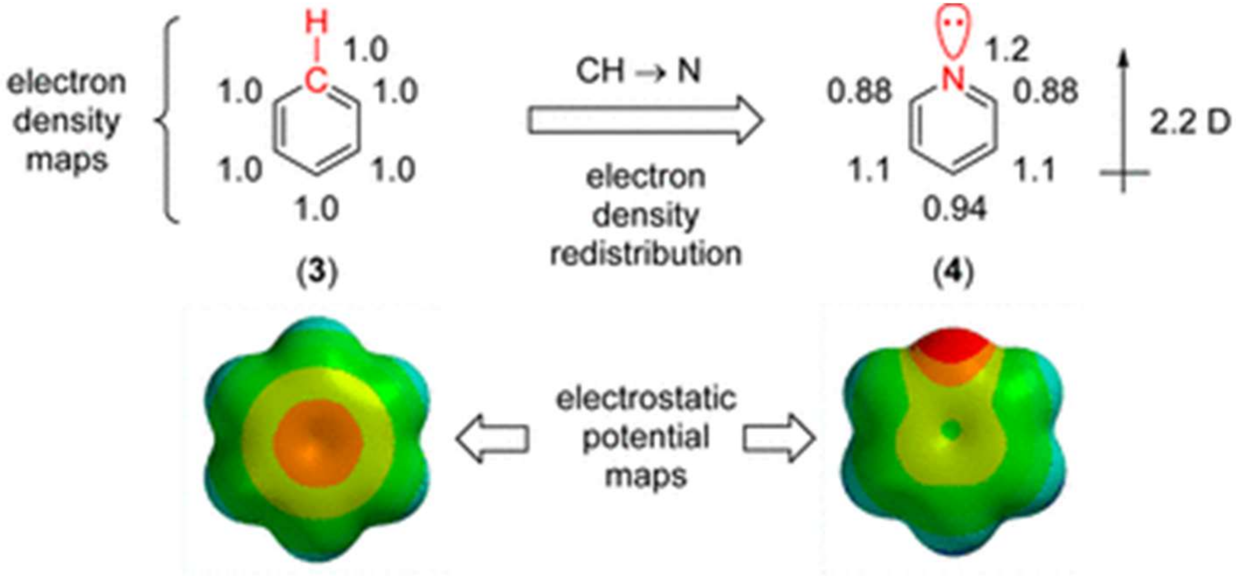


Many nitrogen-containing ring systems, including pyridine, are found in drugs.

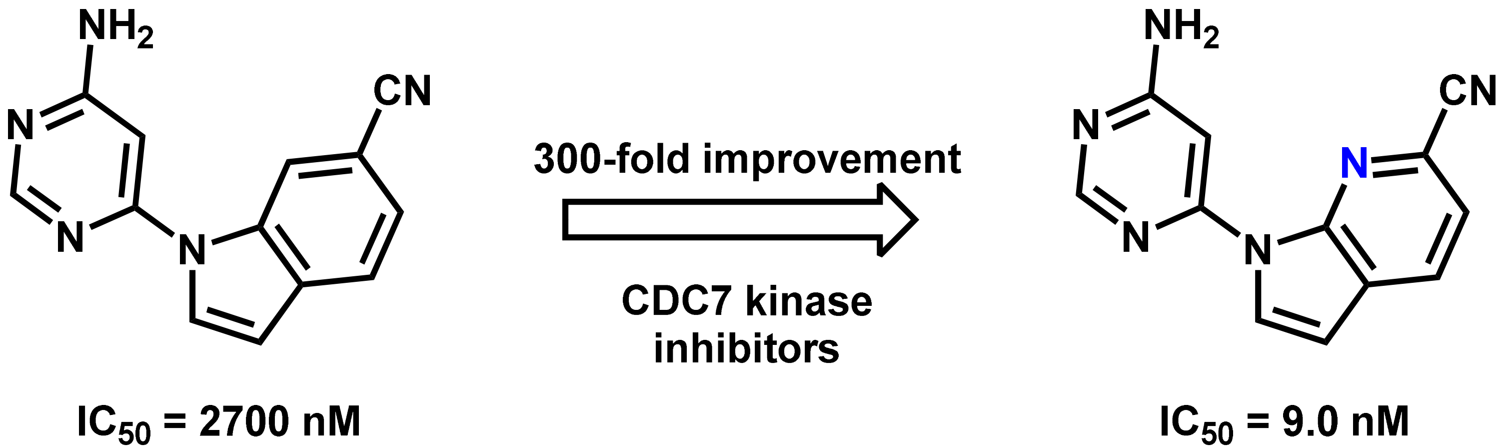
1) Taylor, R. D.; MacCoss, M.; Lawson, A. D. *J. Med. Chem.* **2014**, *57*, 5845.

Potential Effect of N Atom

The presence of nitrogen atom can strongly influence biological and physical properties.

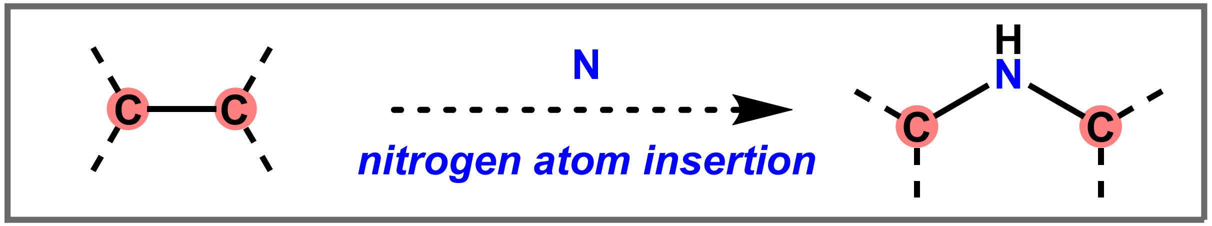


Aqueous solubility
Metabolic stability
Hydrogenbond capability

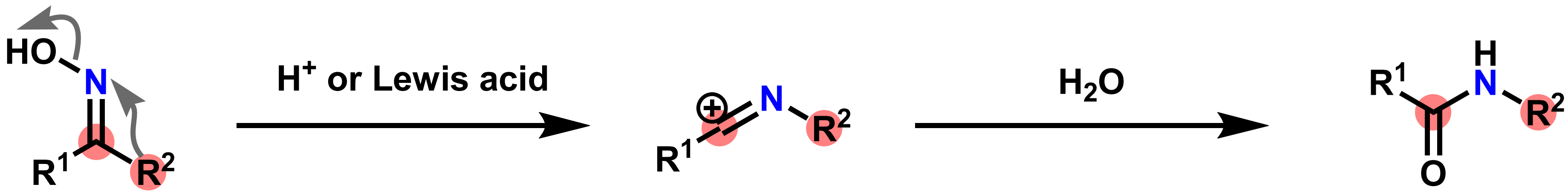


1) Pennington, L. D.; Moustakas, D. T. *J. Med. Chem.* **2017**, *60*, 3552.

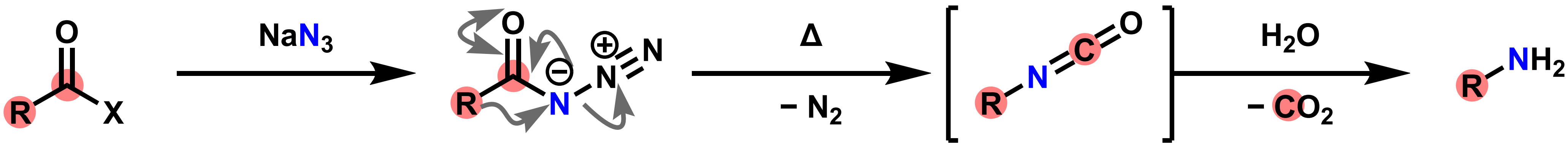
Classic N atom Insertion Reaction



■ Beckmann Rearangement (Beckmann, E. 1886)



■ Curtius Rearangement (Curtius, T. 1890)



1. Beckmann, E. *Ber.* **1886**, *19*, 988.
2. Curtius, T. *Ber.* **1890**, *23*, 3023.

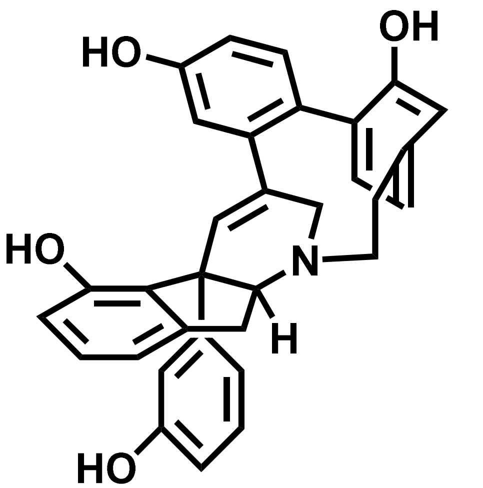
Contents

Associate Prof. Noah Z. Burns

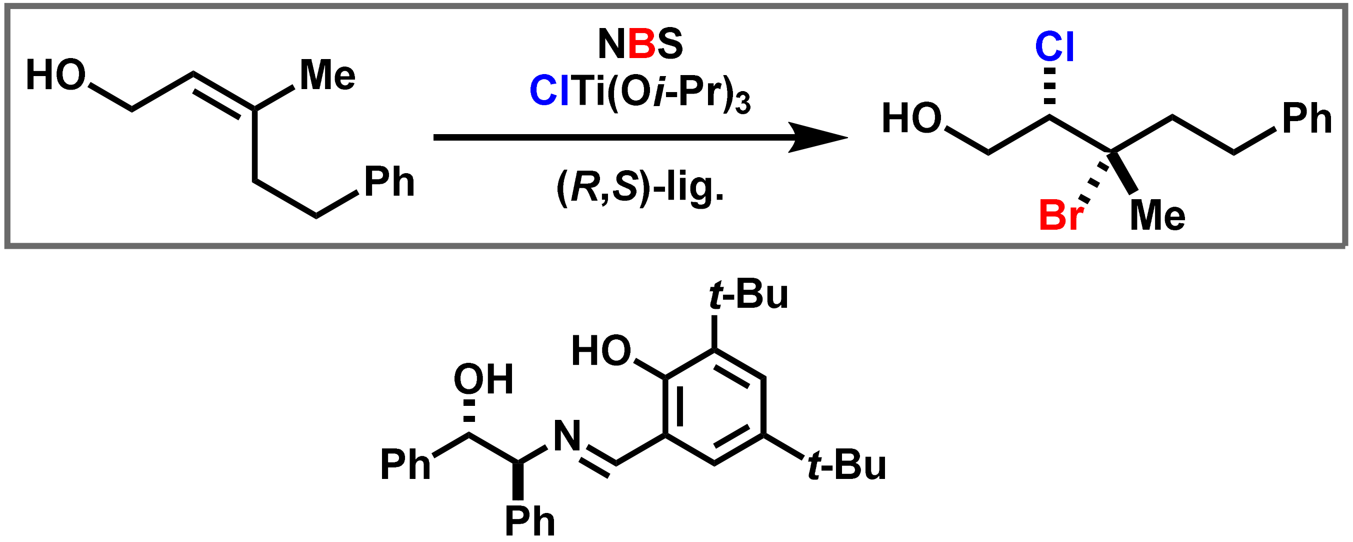
2004 B.S., @ Columbia University
2009 Ph.D., @ The Scripps Research Institute (Prof. Baran P. S.)
2009 NIH postdoctoral fellow @ Harvard University (Prof. Jacobsen E. N.)
2012- Assistant Professor @ Stanford University
2019- Associate Professor @ Stanford University

Research topic: Total synthesis of natural products (unusual lipids, etc.),
Selective halogenation of organic molecules

■ Total Synthesis of (−)-Haouamine A[2)]



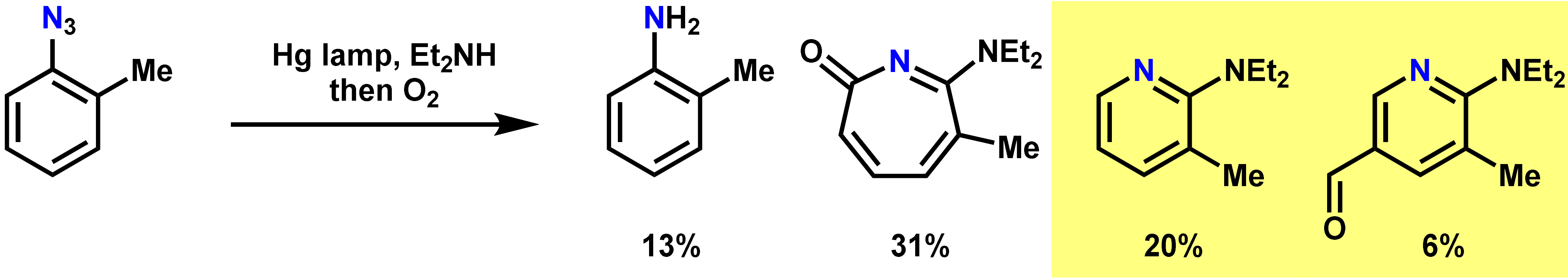
■ Enantioselective Dihalogenation[3)]



1) https://www.chem-station.com/chemist-db/2018/08/noah-z-burns.html
2) Baran, P. S.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3608.
3) Landry, M. L.; Burns, N. Z. *Acc. Chem. Res.* **2018**, *51*, 1260.

Key Precedent and Initial Observation

■ Key Precedent (Sundberg 1972)[1]

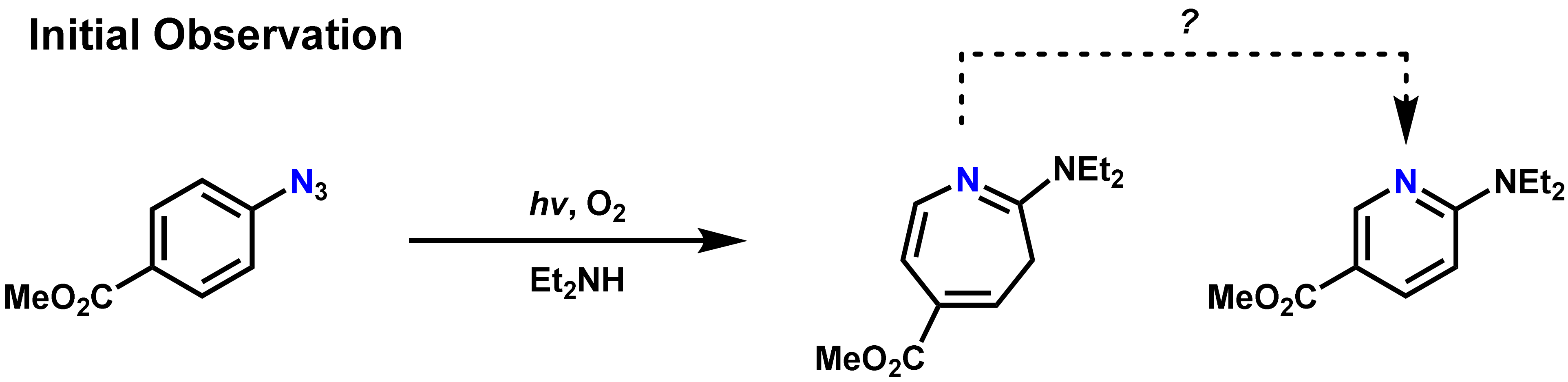


- forming pyridine from benzene

Problem

- low-yield and product mixtures
- harsh condition (Hg light source, solvent amount of Et_2NH)

■ Initial Observation

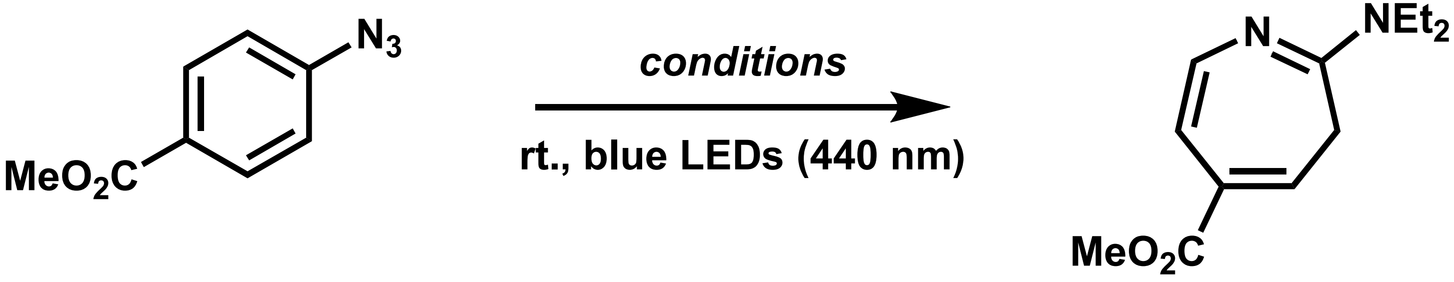


major product
intermediate?

<9%

1. Patel S. C.; Burns. N. Z. *J. Am. Chem. Soc.* **2022**, *144*, 17797.

Optimization of Nitrogen Insertion



Entry	Reagents, Solvent	Atmosphere	Yield[a]
1	acridine orange (20%) MeOH/Et_2NH (9:1)	N_2	80%
2	MeOH/Et_2NH (9:1)	N_2	92%
3	Et_2NH (1.1 eq.), THF	N_2	>99%
4	Et_2NH (1.1 eq.), THF	air	90%

[a]calculated by ^1H NMR (1,4-dinitrobenzene was used as an internal standard.)

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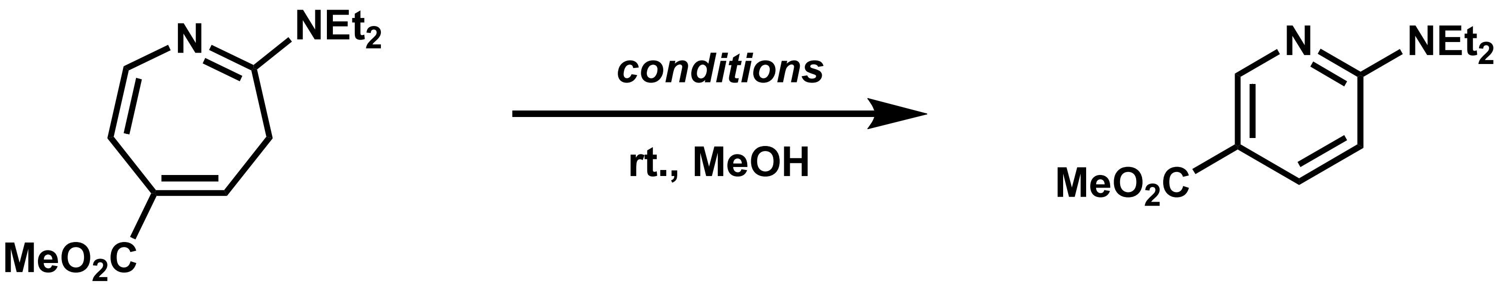
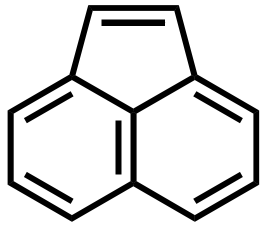
Optimization of Carbon Deletion



Entry	Conditions	Yield[a]
1	O_2	no reaction
2	O_2, TEMPO or $FeCl_3$ or Et_3B	no reaction
3	O_2, blue LEDs	21%
4	O_2, blue LEDs, acenaphthylene (10 %)	54%

[a]calculated by ^1H NMR (1,4-dinitrobenzene was used as an internal standard.)



acenaphthylene
(photosensitizer)

Singlet oxigen rather than triplet one may be invoved in the reaction.

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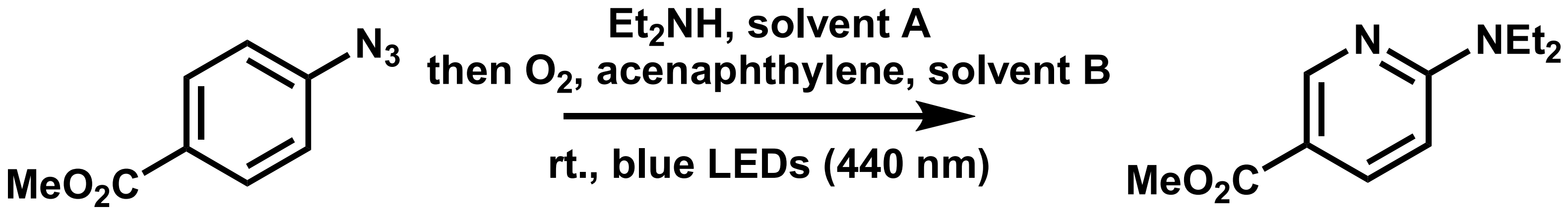
One-Pot Reaction



Entry	Solvent A, B	Acenaphthylene (mol %)	Yield[a]
1	THF, THF	50%	2%
2	MeOH, MeOH	50%	22%
3	THF, MeOH	50%	39%
4	THF, MeOH	10% ×2	57%

= standard cond. (entry 4)

[a]calculated by ^1H NMR (1,4-dinitrobenzene was used as an internal standard.)

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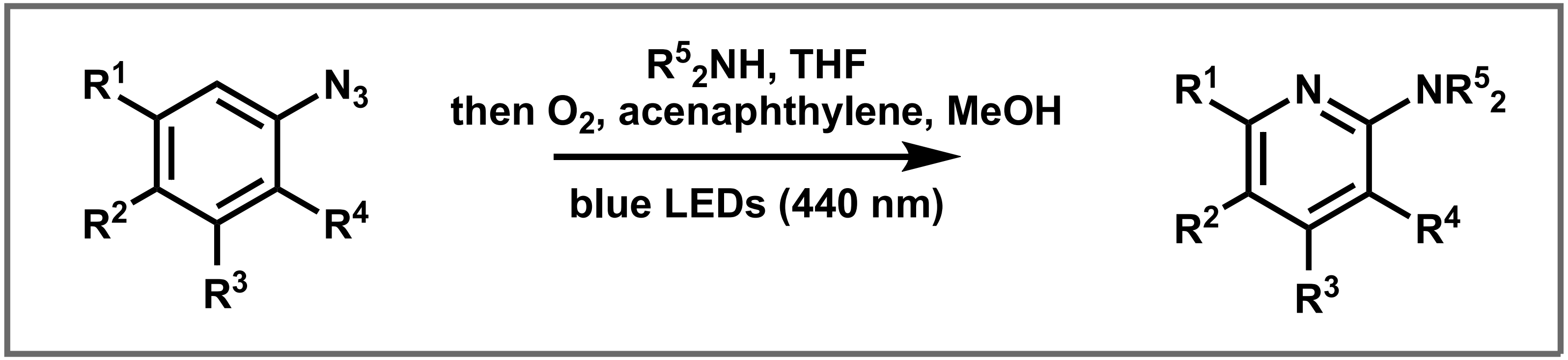
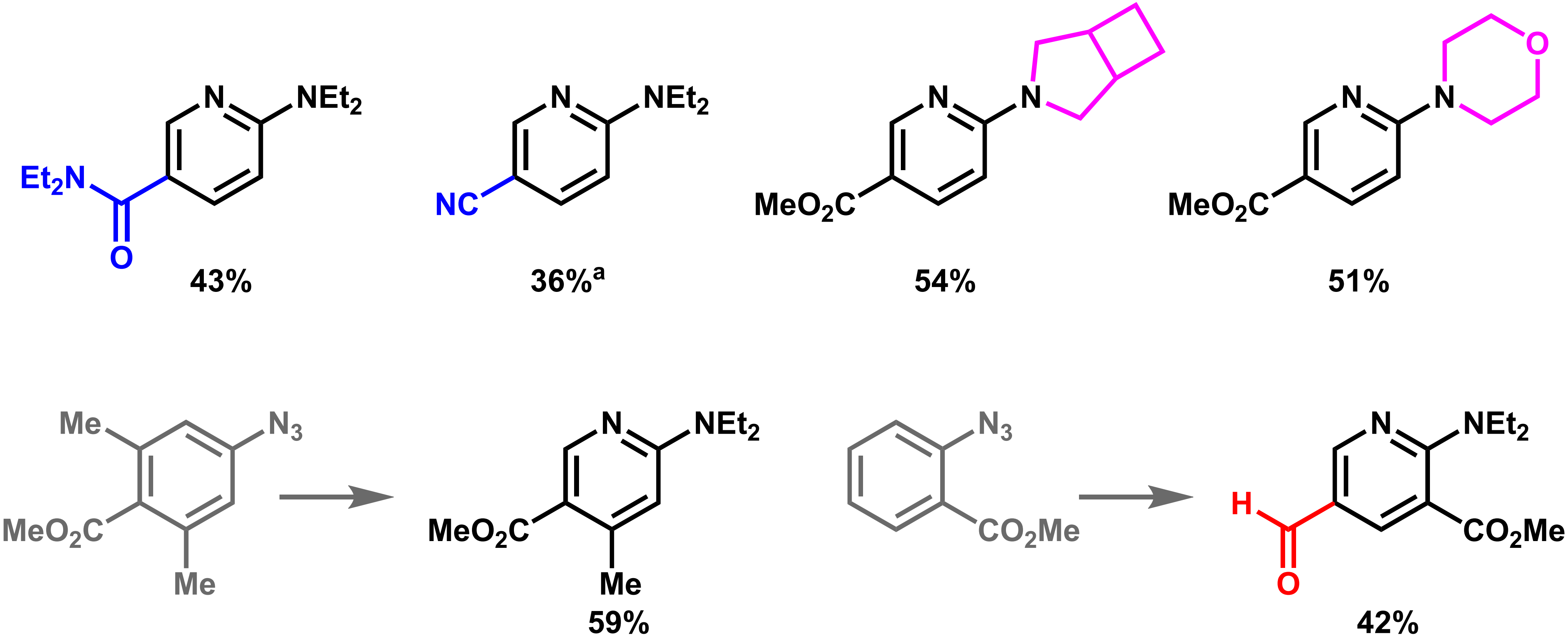
Substrate Scope





[a]30 mol%acenaphthylene added in three portions

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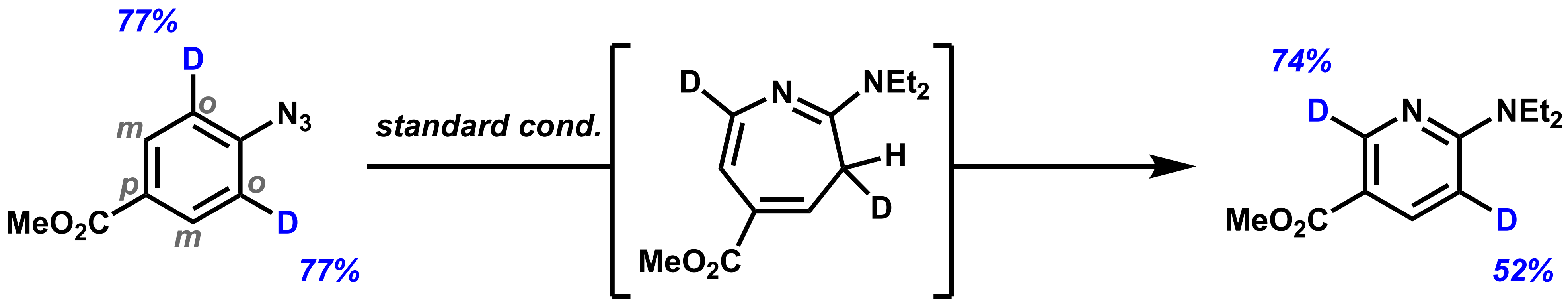
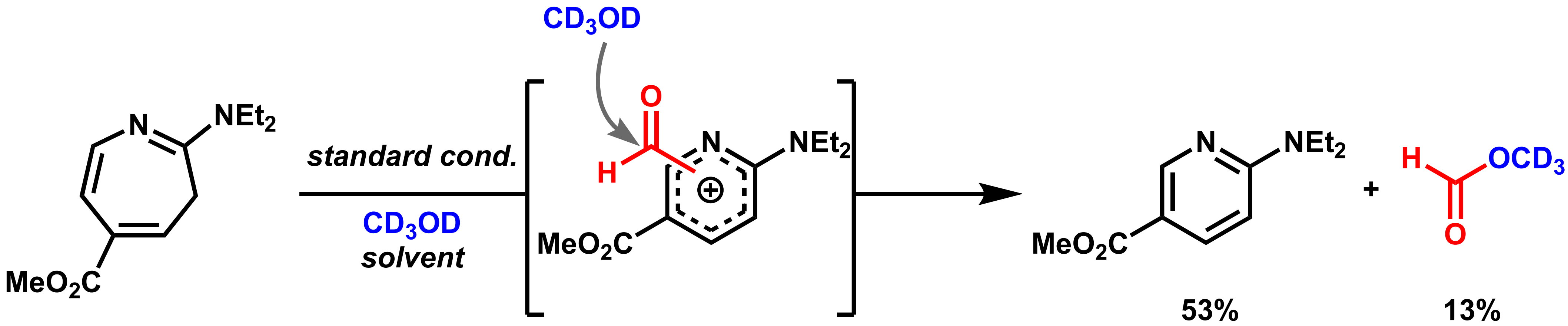
Mechanism Studies



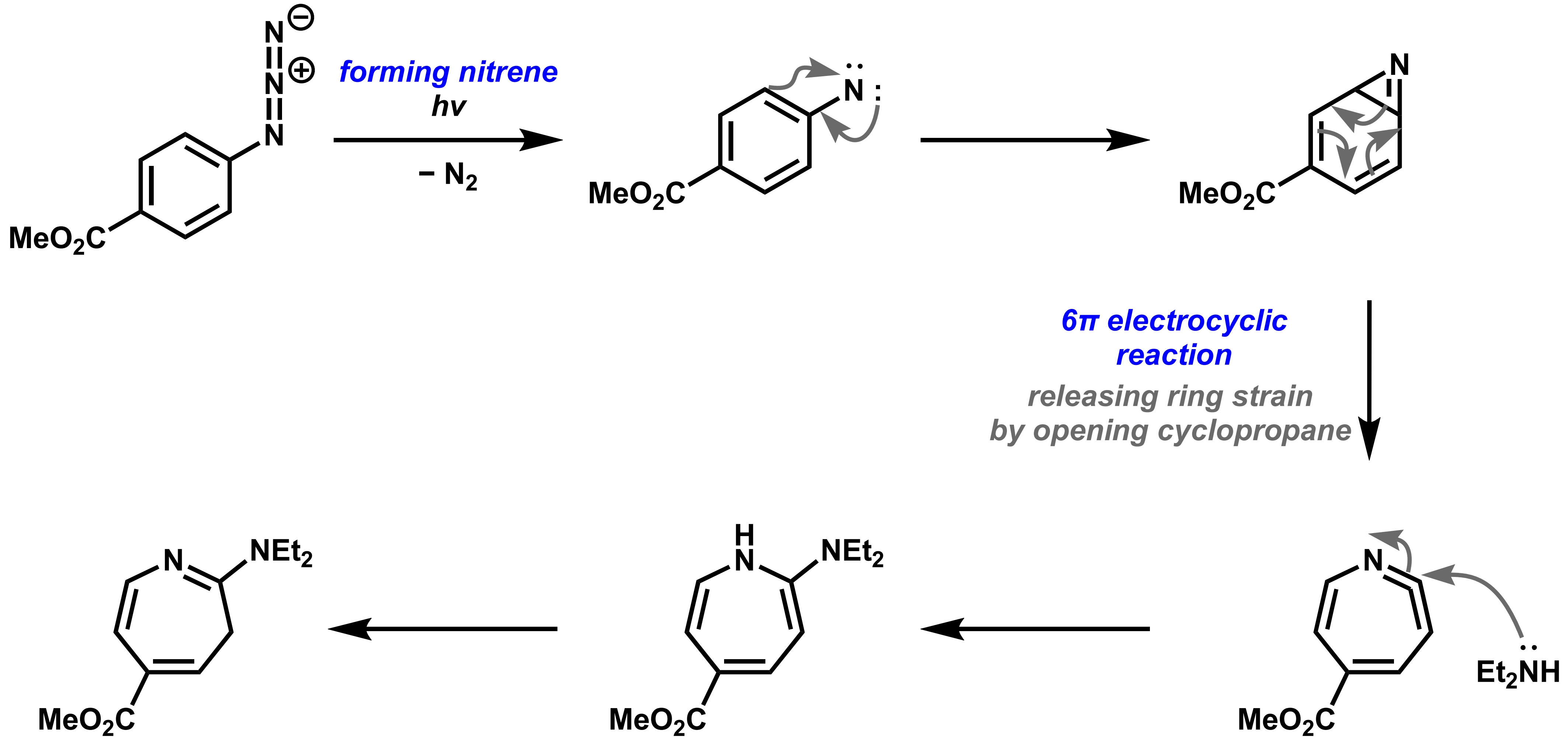
indicating the ortho carbons are not deleted



indicating the reaction proceeds via arenium ion.

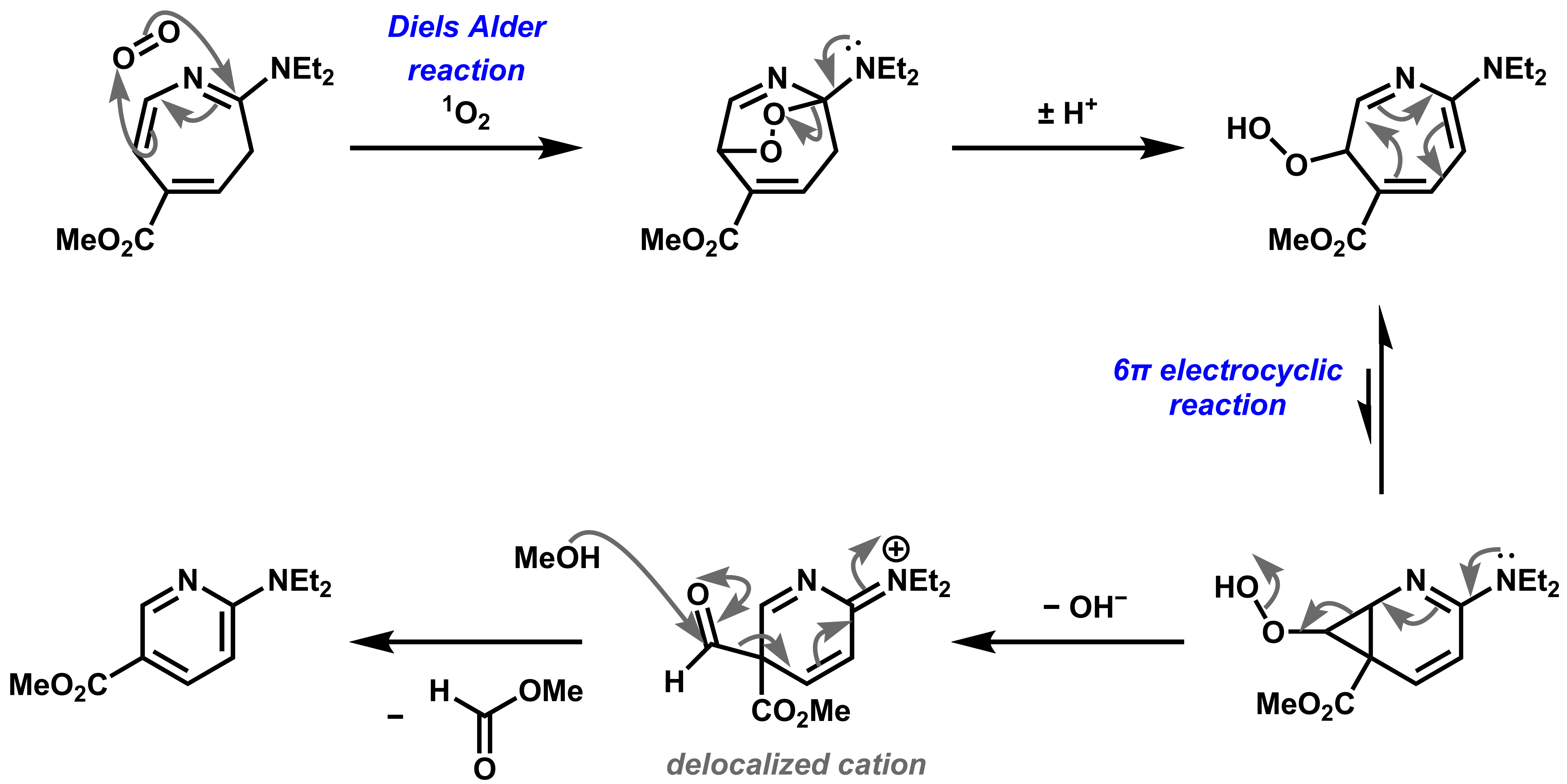
1. Patel S. C.; Burns. N. Z. *J. Am. Chem. Soc.* **2022**, *144*, 17797.

Proposed Reaction Mechanism (1)



1. Patel S. C.; Burns. N. Z. *J. Am. Chem. Soc.* **2022**, *144*, 17797.

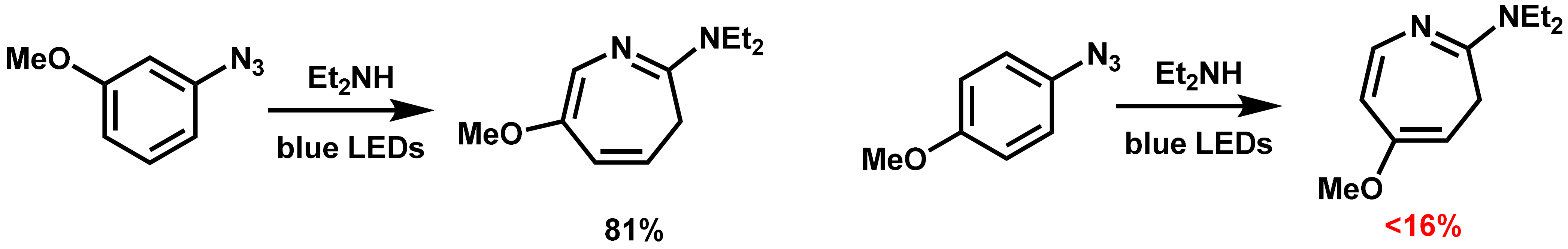
Proposed Reaction Mechanism (2)

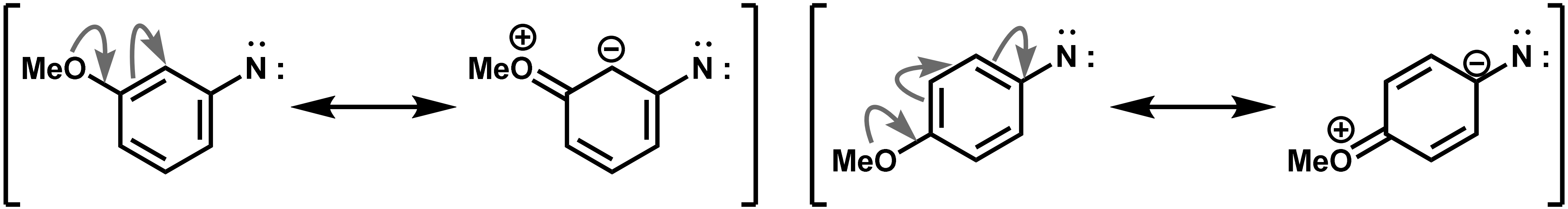


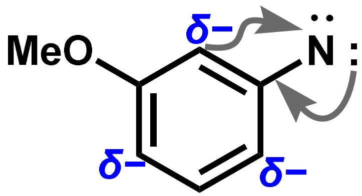
1. Patel S. C.; Burns. N. Z. *J. Am. Chem. Soc.* **2022**, *144*, 17797.

Limitations (1)

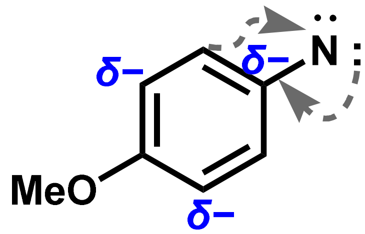
- **Nitrogen insertion step did not go well when electron donating group was substituted at the para position.**







match the electrostatic potential



don't match the electrostatic potential

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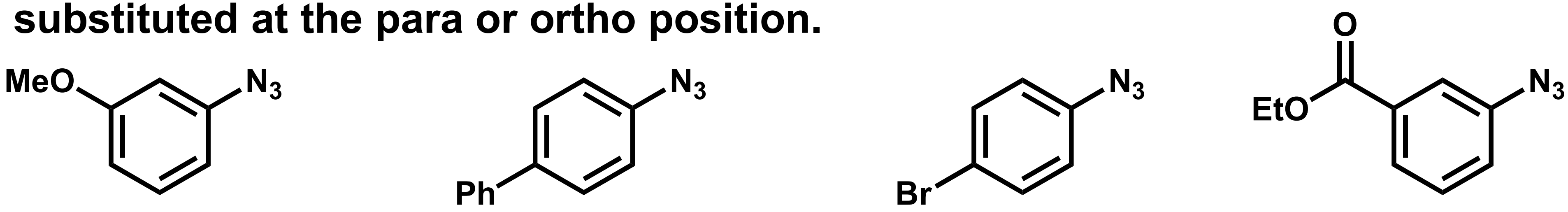
Limitations (2)

- **Carbon deletion step went well only when electron withdrawing group was substituted at the para or ortho position.**

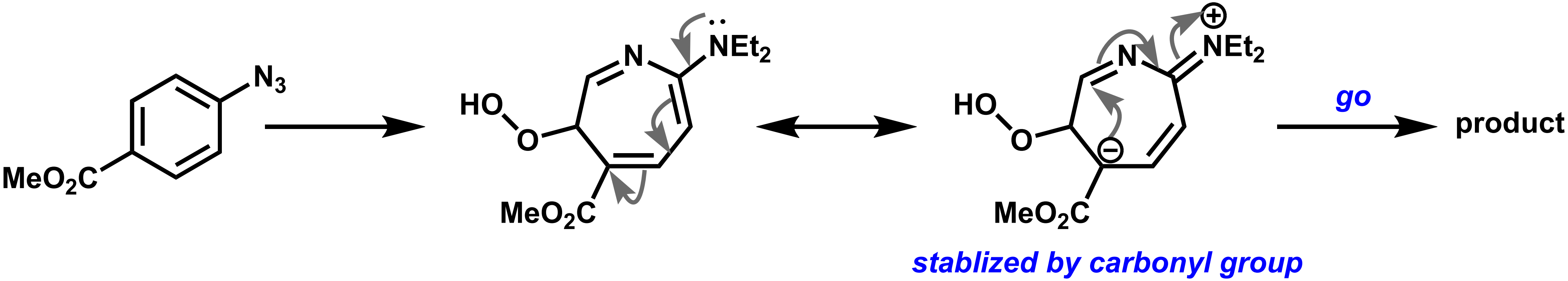


Nitrogen insertion: 81%
Carbon deletion: 9%

Nitrogen insertion: 62%
Carbon deletion: 10%

Nitrogen insertion: 72%
Carbon deletion: <6%

Nitrogen insertion: 66%
Carbon deletion: 0%



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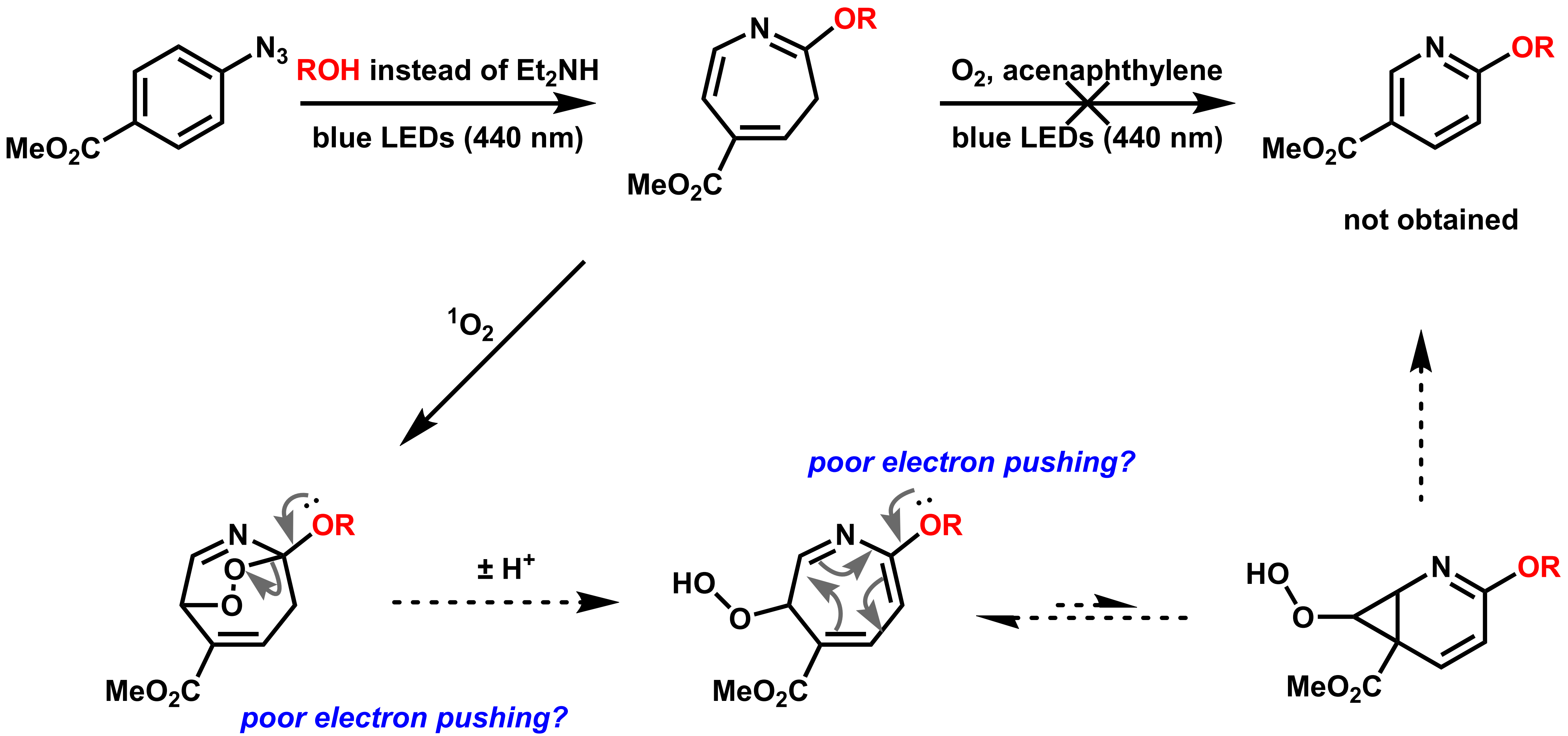
Limitations (3)

- Substitiution of alcohols for nucleophiles was unsuccessful.



1. Patel S. C.; Burns. N. Z. *J. Am. Chem. Soc.* **2022**, *144*, 17797.

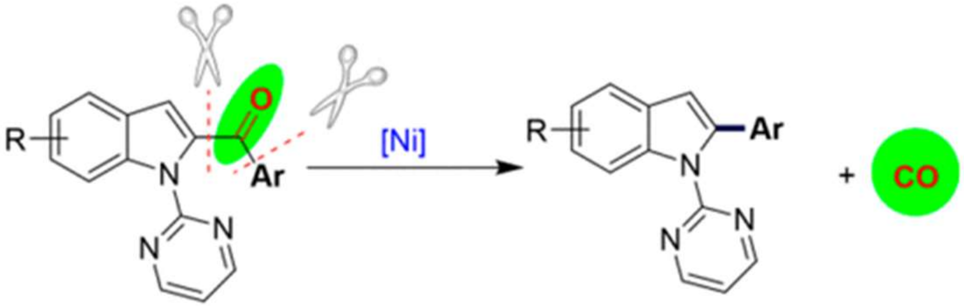
Contents

Professor Hao Wei

2006, B.C. (Science) @ Lanzhou University
2011, Ph.D. (Science) @ Lanzhou University (Prof. Xu P.)
2011- Postdoctoral fellow @ Peking University (Prof. Yang Z.)
2013- Postdoctoral fellow @ University of Idaho (Dr. Shreeve)
2015- Professor @ Northwestern University

Research topic: Synthetic methodology, Total synthesis of natural products, Heterocyclic chemistry

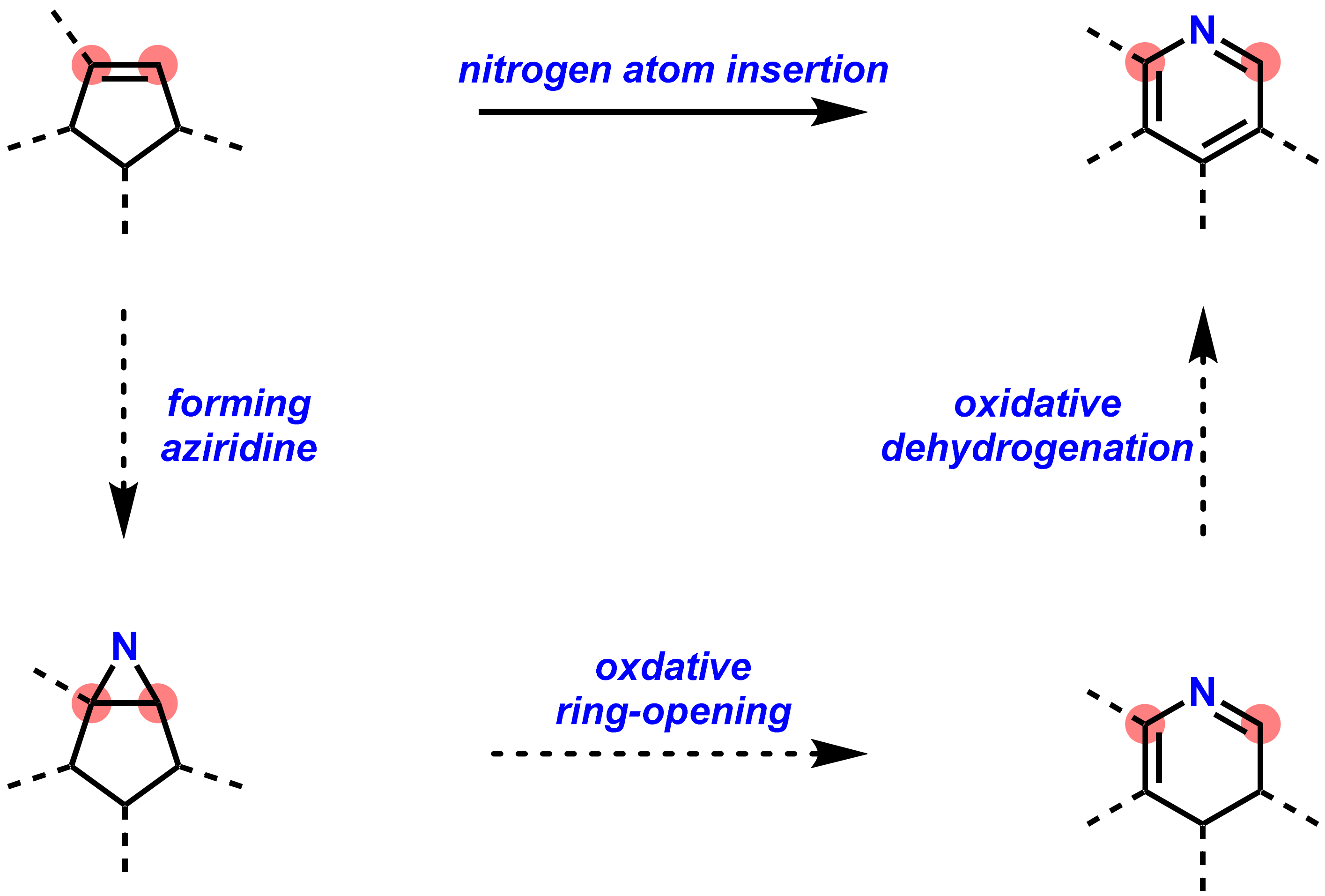
■ Directed Decarbonylation of Unstrained Aryl Ketones[2)]



- *Up to 98% yields*
- *Catalytic Ni complex*
- *Good functional group tolerance*

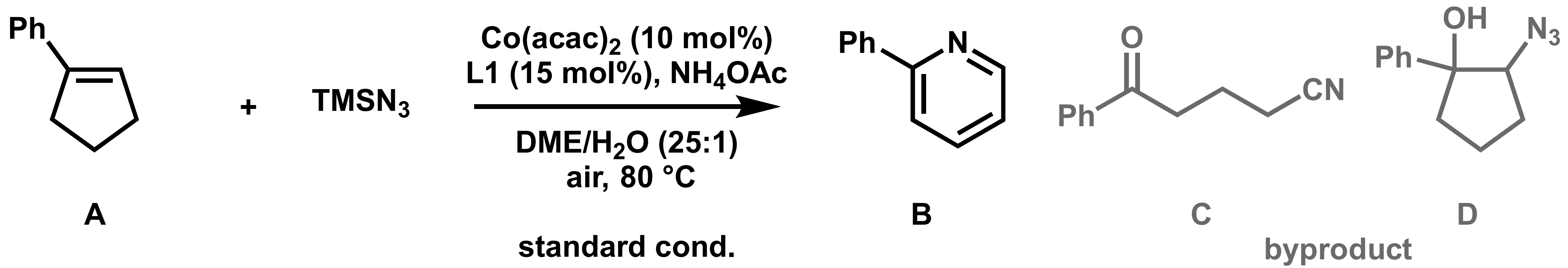
1) http://www.cailiaoquan.com/forum.php?mod=viewthread&tid=16970
2) Zhao, T. T.; Xu, W. H.; Zheng, Z. J.; Xu, P. F.; Wei, H. *J. Am. Chem. Soc.* **2018**, *140*, 586.

Concept of This Paper

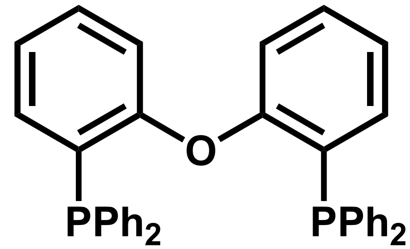


1. Wang, J.; Lu, H.; He, Y.; Jing, C.; Wei, H. *J. Am. Chem. Soc.* **2022**, *144*, 22433.

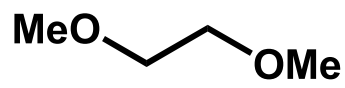
Optimization of the Reaction (1)



Entry	Variation from standard cond.	Toal yield	B:C+D
1	none	92%	10:1
2	$CoCl_2$ instead of $Co(acac)_2$	70%	5:1
3	$Co(OAc)_2$ instead of $Co(acac)_2$	69%	6:1
4	$Pd(OAc)_2$ instead of $Co(acac)_2$	trace	N/A
5	$RhCl(cod)_2$ instead of $Co(acac)_2$	trace	N/A



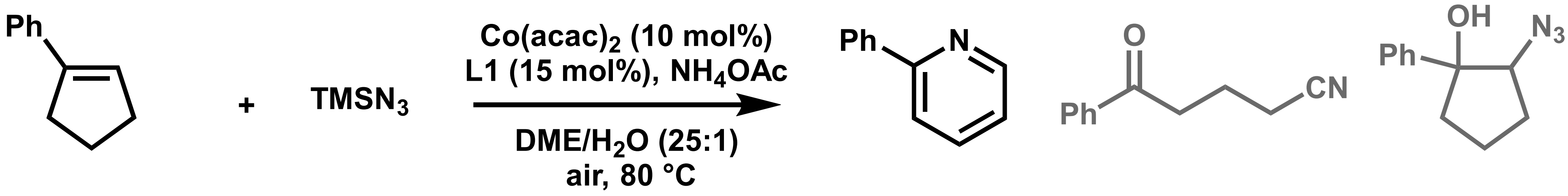
L1



DME

1. Wang, J.; Lu, H.; He, Y.; Jing, C.; Wei, H. *J. Am. Chem. Soc.* **2022**, *144*, 22433.

Optimization of the Reaction (2)

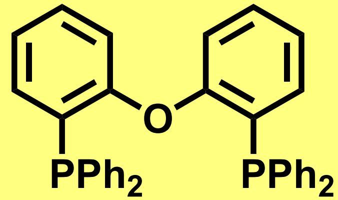


A B C D

standard cond.

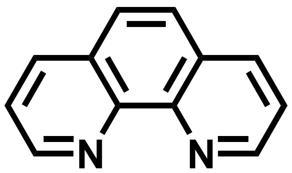
byproduct

Entry	Variation from standard cond.	Toal yield	B:C+D
1	without H_2O	84%	9:1
2	toluene instead of DME	58%	1:2
3	dioxane instead of DME	67%	3:1
4	Ligand instead of L1	below	

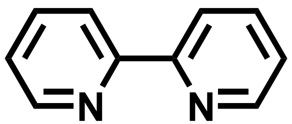


L1
92%, (10:1)

Ligand



trace

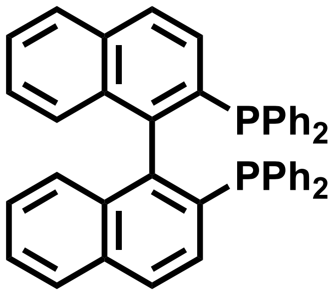


trace

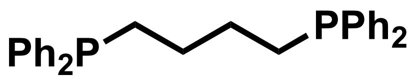
PPh_3

65% (5:1)

63% (6:1)



73% (7:1)



84% (8:1)

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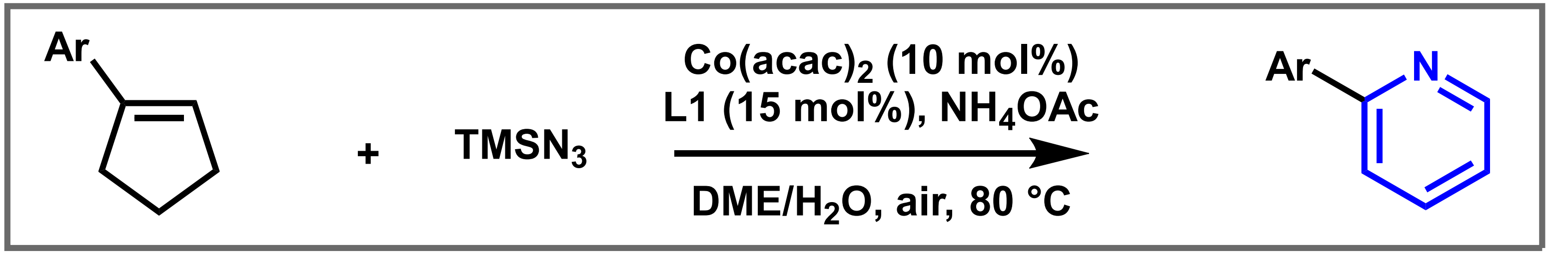
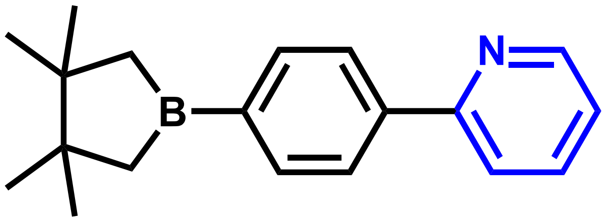
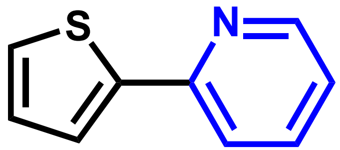
Substrate Scope (1)

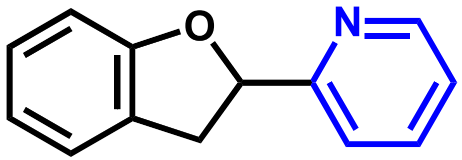




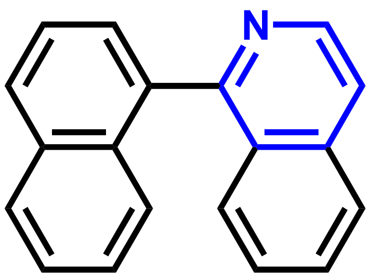
63%



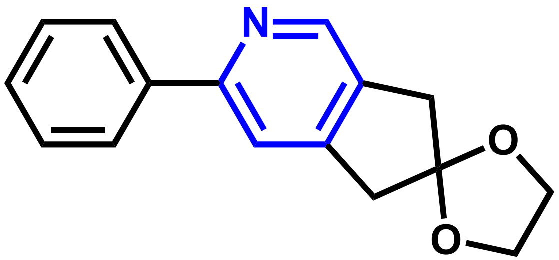
46%



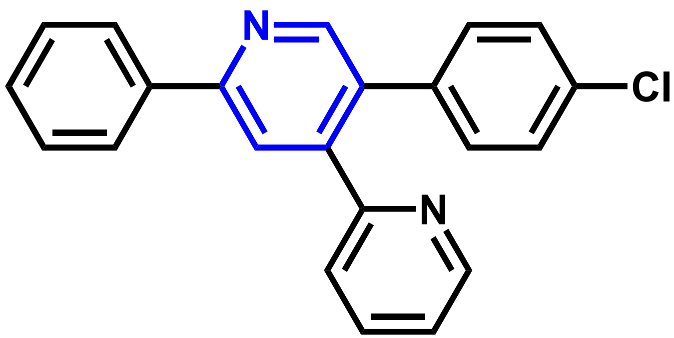
65%



53%



88%

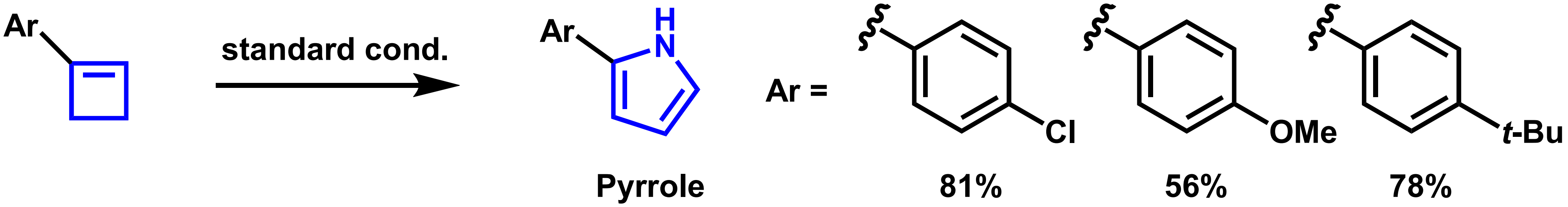


76%

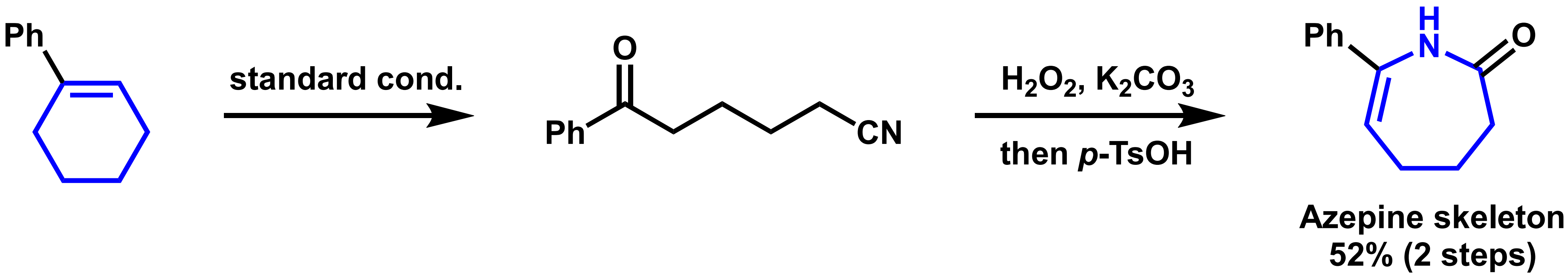
1. Wang, J.; Lu, H.; He, Y.; Jing, C.; Wei, H. *J. Am. Chem. Soc.* **2022**, *144*, 22433.

Substrate Scope (2)

■ Application to arylcyclobutene

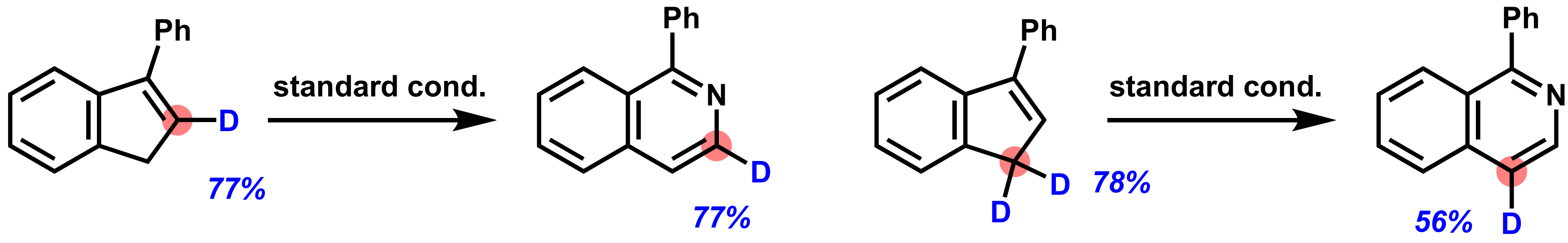


■ Application to arylcyclohexene

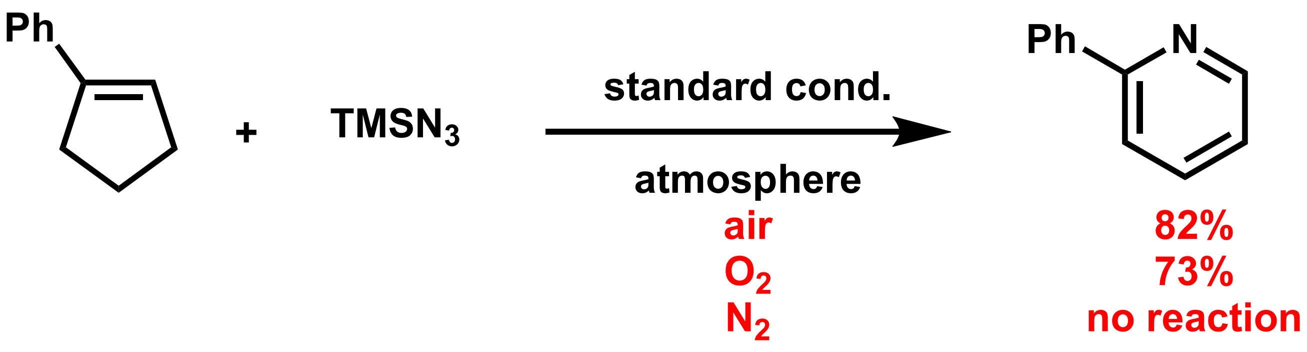


1. Wang, J.; Lu, H.; He, Y.; Jing, C.; Wei, H. *J. Am. Chem. Soc.* **2022**, *144*, 22433.

Mechanism Studies



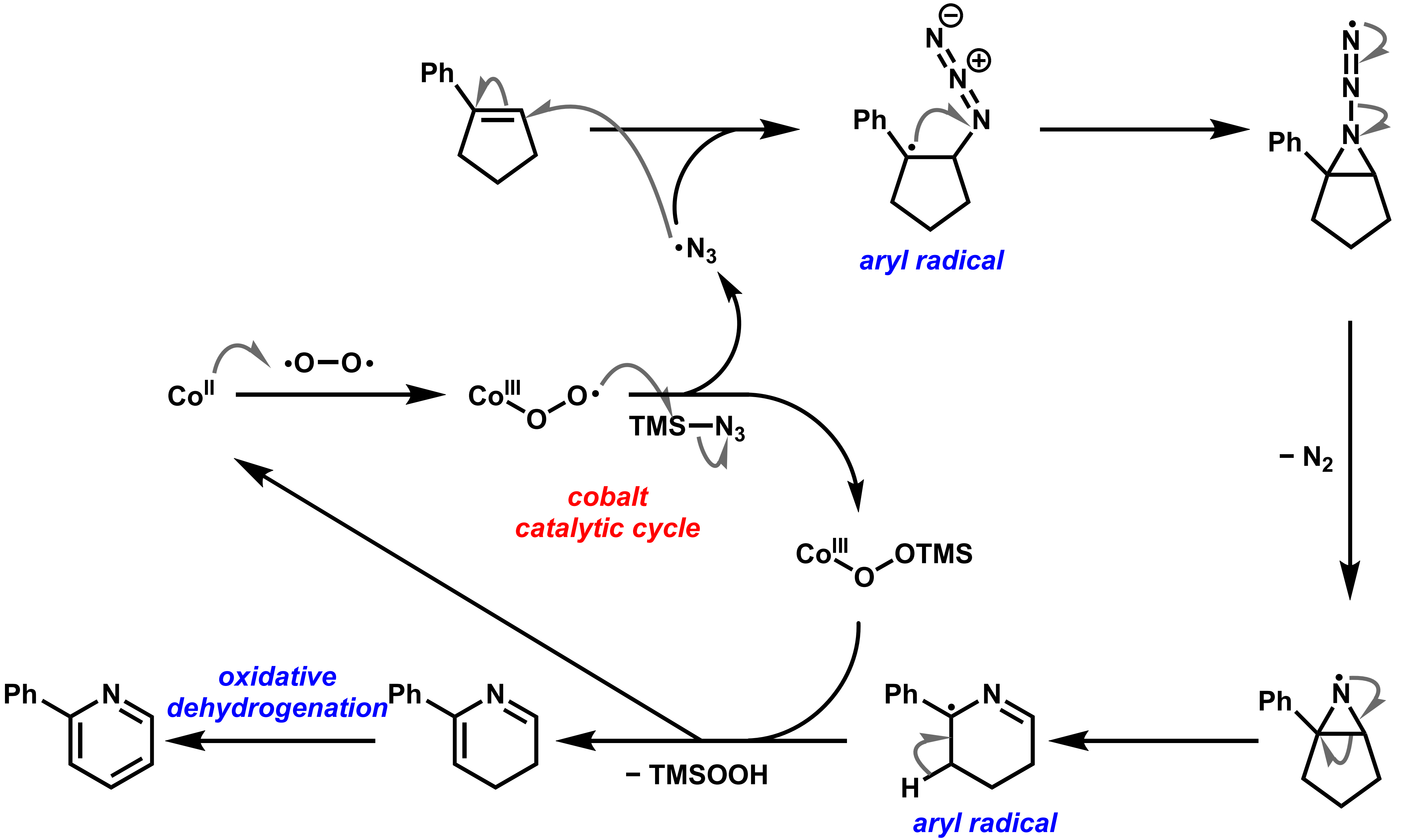
indicating highlighted carbons are retained



indicating O_2 is necessary

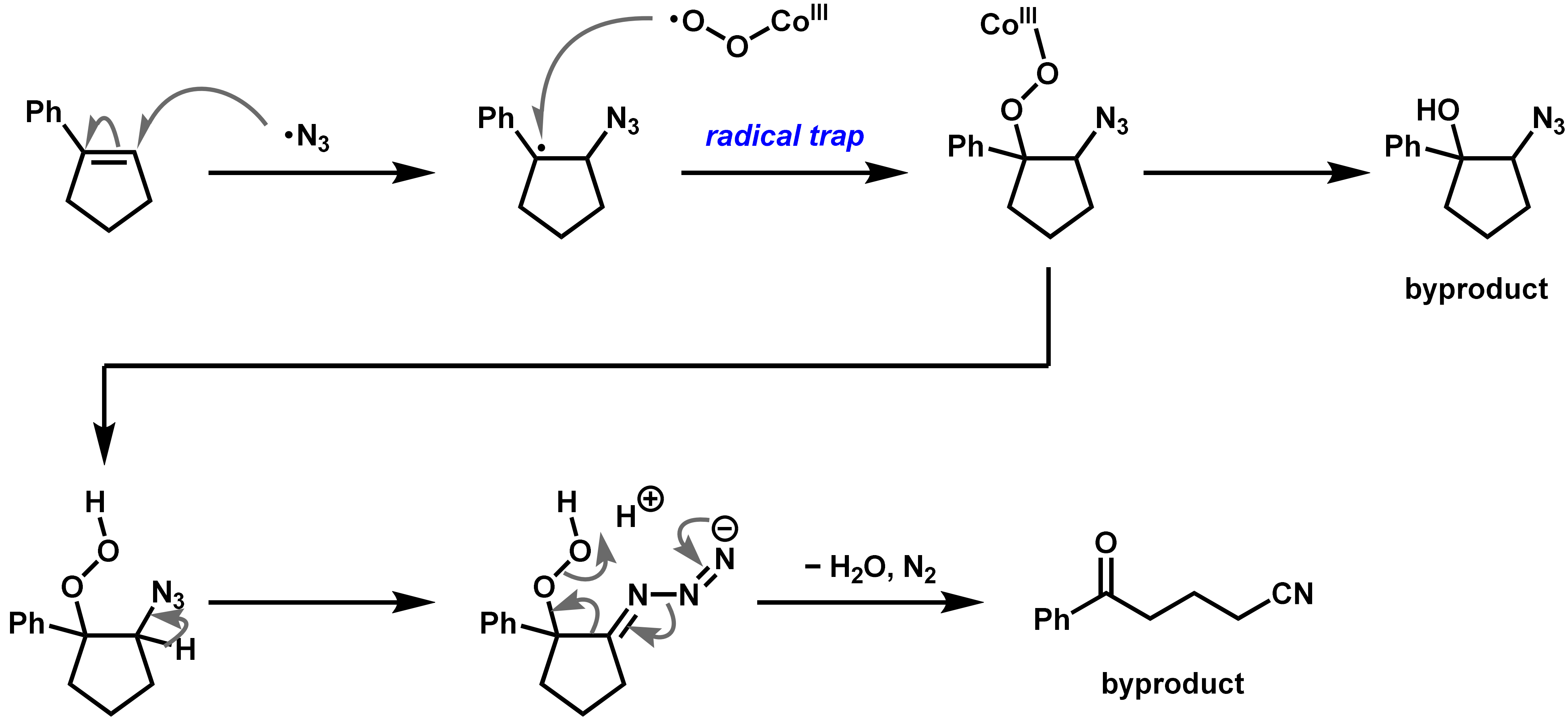
1. Wang, J.; Lu, H.; He, Y.; Jing, C.; Wei, H. *J. Am. Chem. Soc.* **2022**, *144*, 22433.

Proposed Reaction Mechanism



1. Wang, J.; Lu, H.; He, Y.; Jing, C.; Wei, H. *J. Am. Chem. Soc.* **2022**, *144*, 22433.

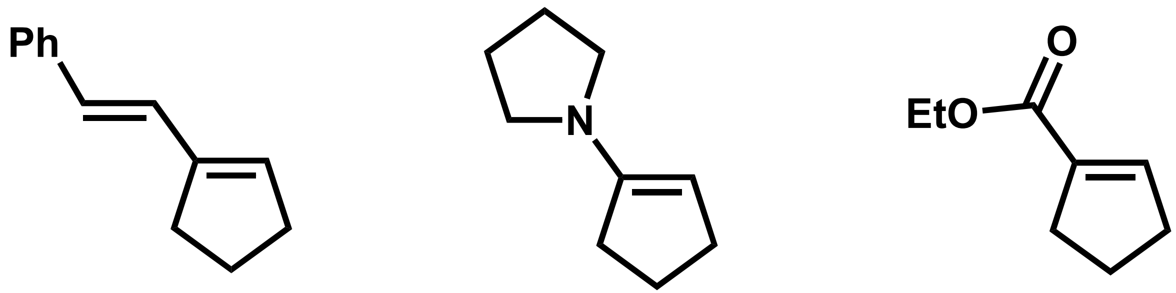
Proposed Mechanism of Side Reaction



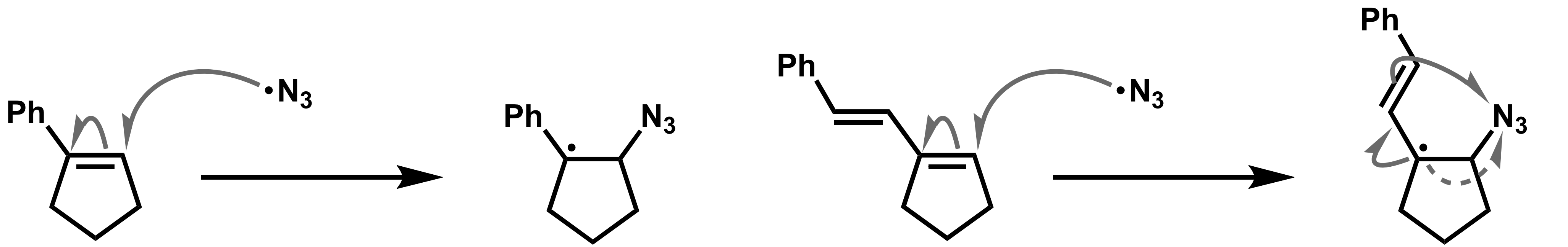
1. Wang, J.; Lu, H.; He, Y.; Jing, C.; Wei, H. *J. Am. Chem. Soc.* **2022**, *144*, 22433.

Limitation

- **Unsuccessful substrate**



Only 'aryl' C-C double bond could be applyed to this N atom insertion reaction.



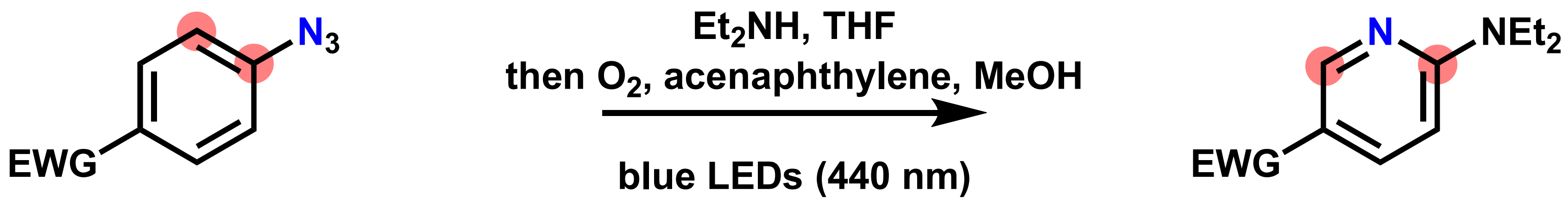
stable benzyl radical

stable allyl radical
but side reaction?

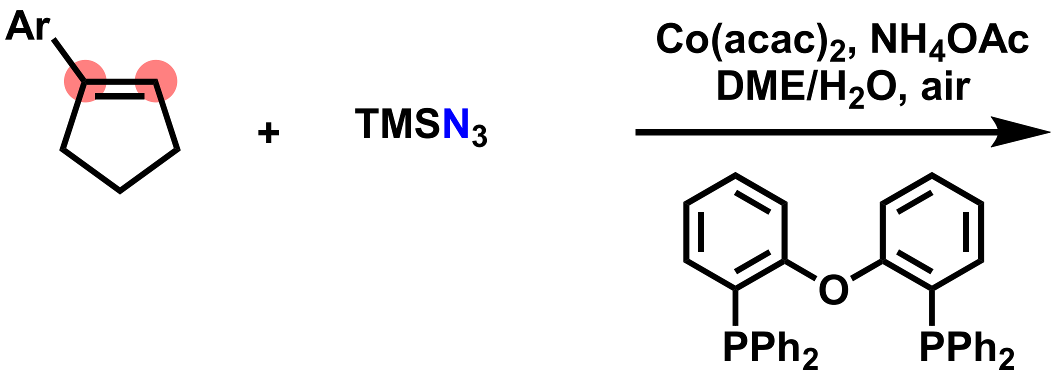
1. Wang, J.; Lu, H.; He, Y.; Jing, C.; Wei, H. *J. Am. Chem. Soc.* **2022**, *144*, 22433.

Accomplishment of N Atom Insertion

■ Noah Z. Burns' group



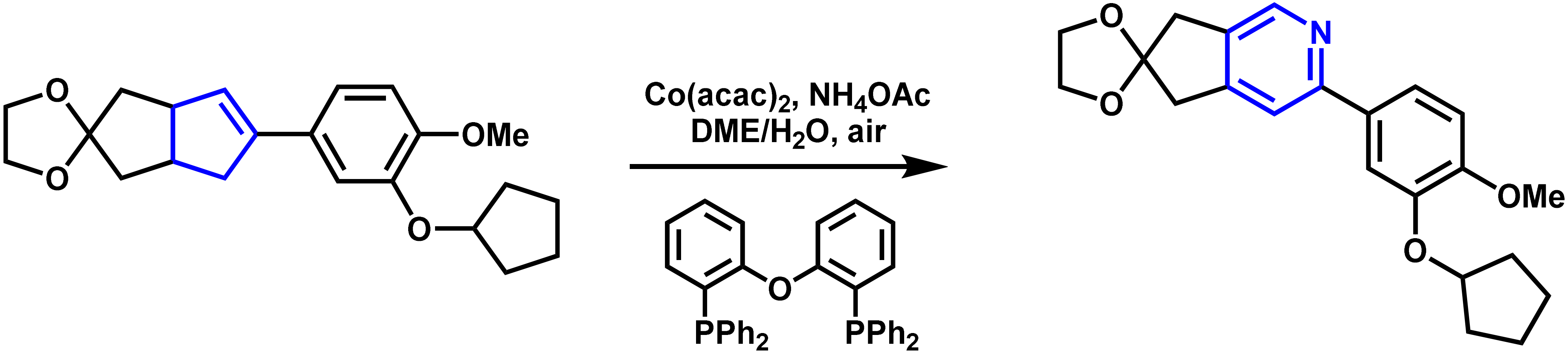
■ Hao Wei's group



1. Patel S. C.; Burns. N. Z. *J. Am. Chem. Soc.* **2022**, *144*, 17797.
2. Wang, J.; Lu, H.; He, Y.; Jing, C.; Wei, H. *J. Am. Chem. Soc.* **2022**, *144*, 22433.

Strong Advantage of N Atom Insertion

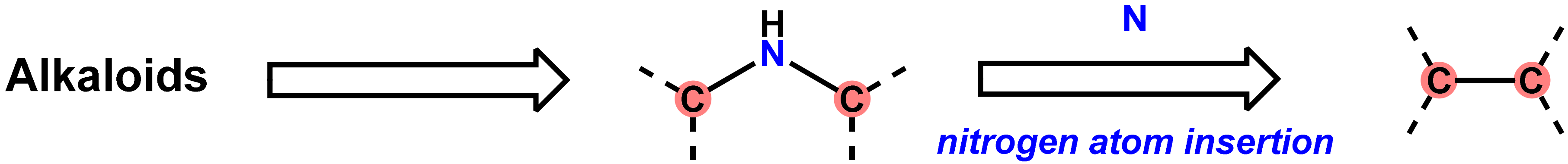
■ **Derivatization of bioactive compounds by direct skeletal modification**



from PDE4 inhibitor[1)]

83%[2)]

■ **New synthetic strategies based on nitrogen atom insertion**



1. Ochiai, H.; Odagaki, Y.; Ohtani, T.; Ishida, A.; Kusumi, K.; Kishikawa, K.; Yamamoto, S.; Takeda, H.; Obata, T.; Kobayashi, K.; Nakai, H.; Toda, M. *Bioorg. Med. Chem.* **2004**, *12*, 5063.
2. Wang, J.; Lu, H.; He, Y.; Jing, C.; Wei, H. *J. Am. Chem. Soc.* **2022**, *144*, 22433.