N-Atom Deletion in Nitrogen Heterocycles

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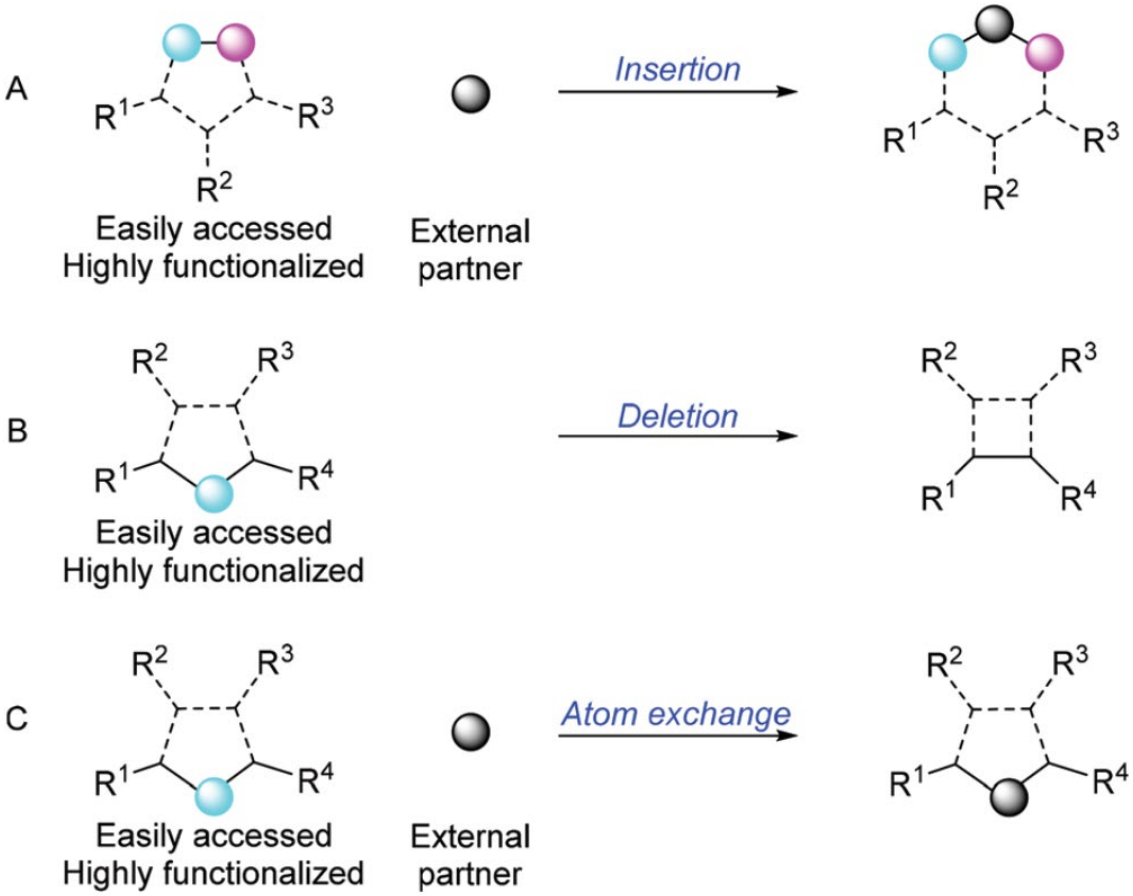
July, 9th, 2022

Outline

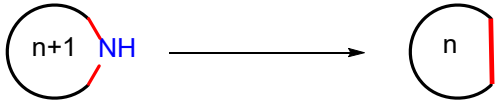
- Introduction
- Mechanism Study
- Applications
- Related Reactions
- Summary & Outlook
- Acknowledgement

Introduction: Molecular Editing

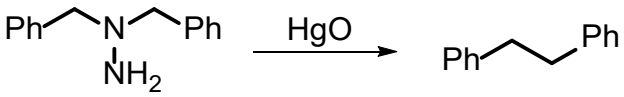


H. Chunngai; W. Zhuo; W. Shiping; X. Chunfa; *Org. Chem. Front*. **2022**, *9*, 1451.

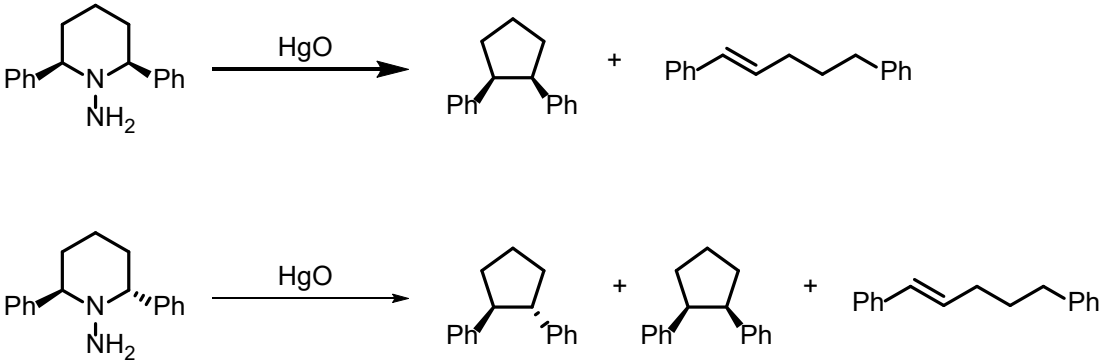
Introduction: Reaction Discovery



First sample in 1900:



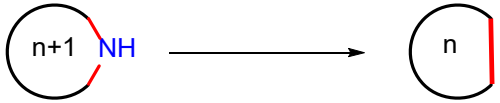
First shrink ring in 1957:



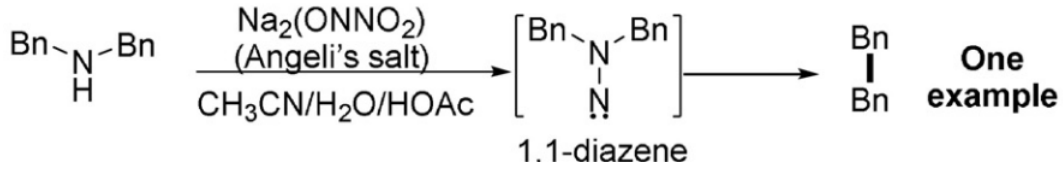
Busch M.; Weiss B. *Ber.* **1900**, *33*, 2701.

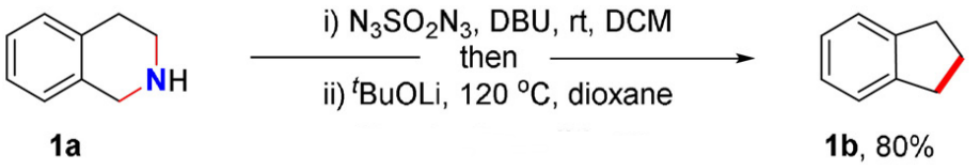
Overberger C. G.; Lombardino J. G.; Hiskey R. *J. Am. Chem. Soc.* 1957, **79**, 6430

Introduction: Reaction Discovery



Initial discovery (Rave, 1965)





1a **1b**, 80%

Lemal D. M.; Rave T. W. *J. Am. Chem. Soc.* **1965**, *87*, 393.

Zou X.; Zou J.; Yang L.; Li G.; Lu H. *J. Org. Chem.* **2017**, *82*, 4677.

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

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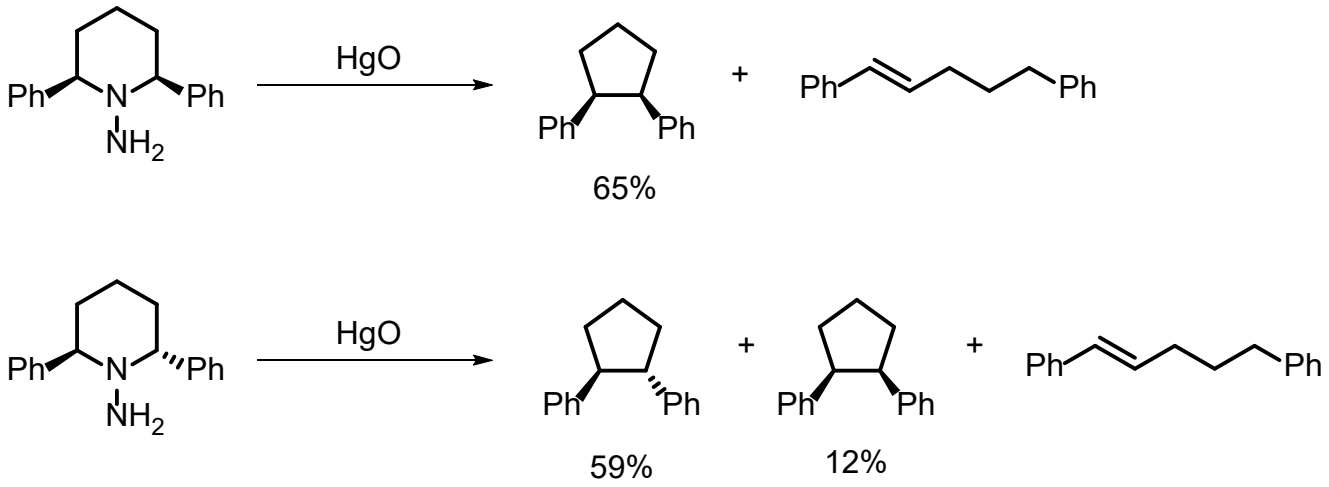
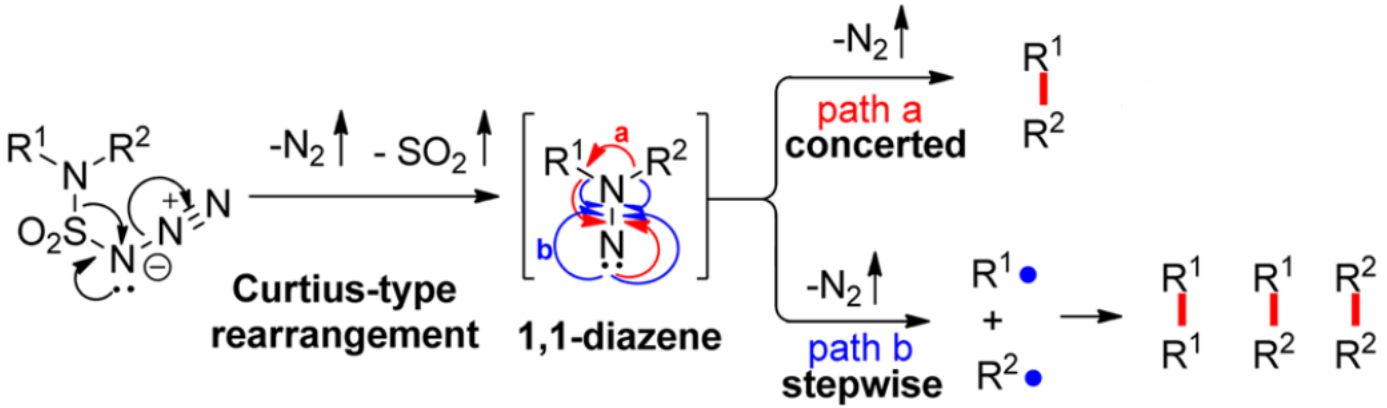
Mechanism Study

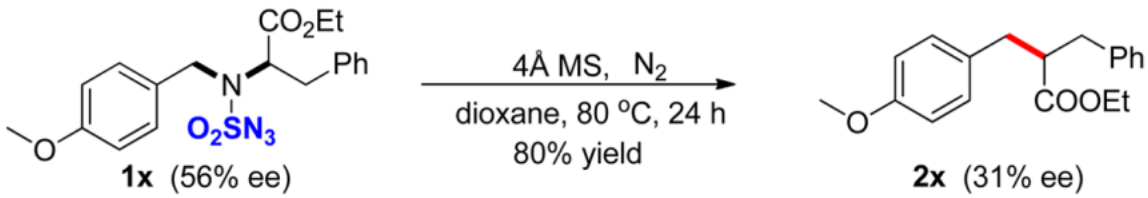


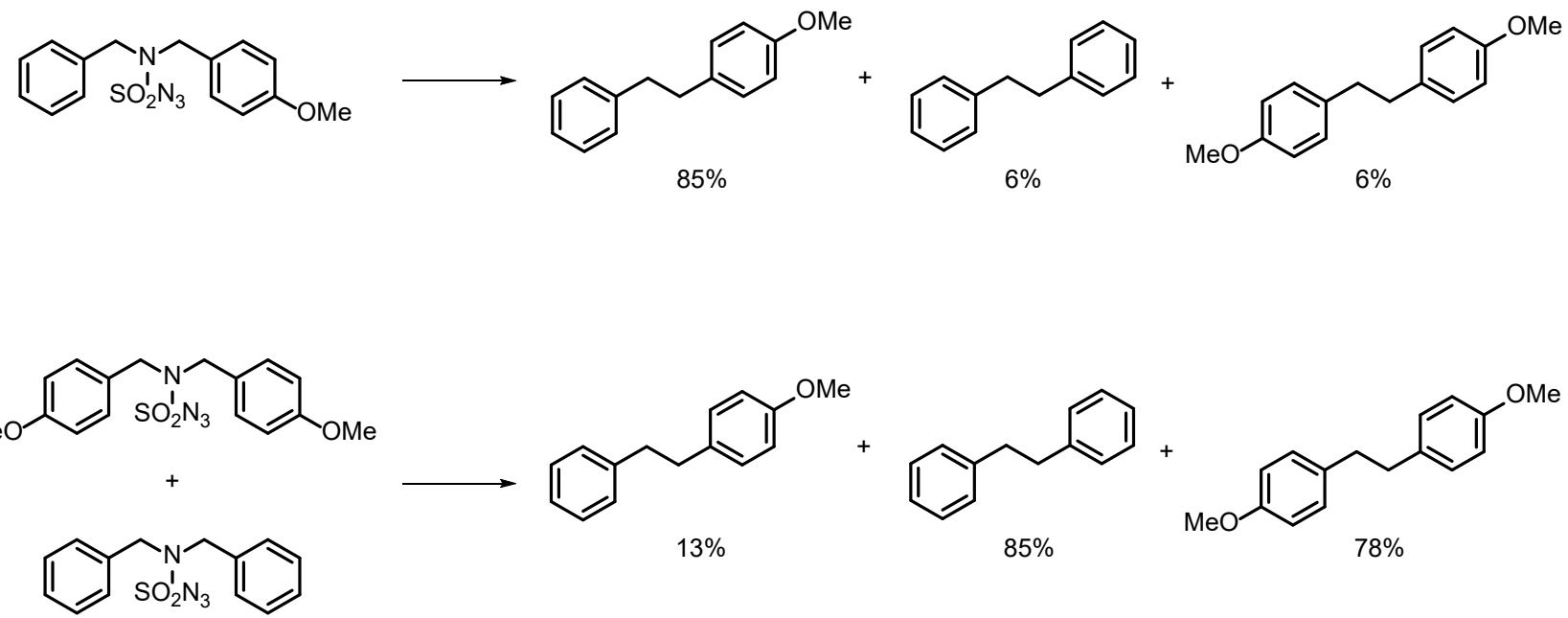
Overberger C. G.; Lombardino J. G.; Hiskey R.; *J. Am. Chem. Soc.* 1957, **79**, 6430



Zou X.; Zou J.; Yang L.; Li G.; Lu H.; *J. Org. Chem.* **2017**, *82*, 4677.

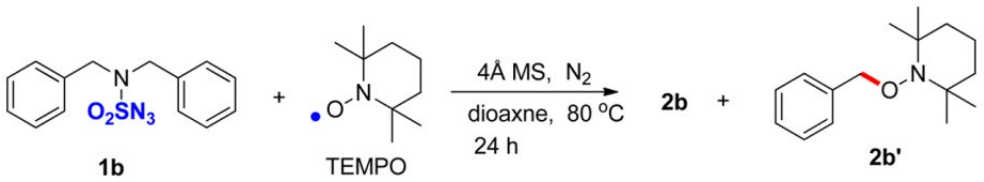
Mechanism Study: Cross-Coupling

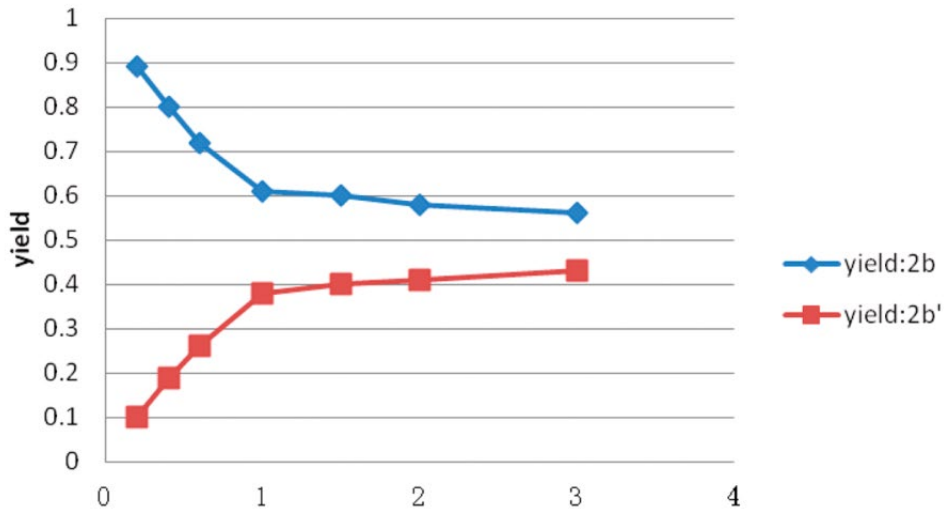




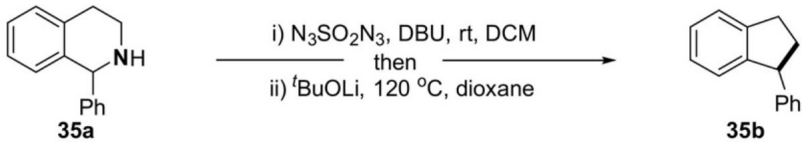
Zou X.; Zou J.; Yang L.; Li G.; Lu H.; *J. Org. Chem.* **2017**, *82*, 4677.

Mechanism Study: Tempo Capture





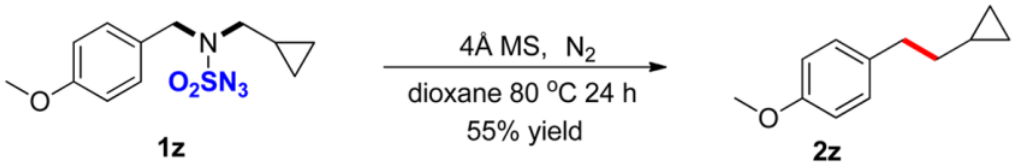
Zou X.; Zou J.; Yang L.; Li G.; Lu H.; *J. Org. Chem.* **2017**, *82*, 4677.

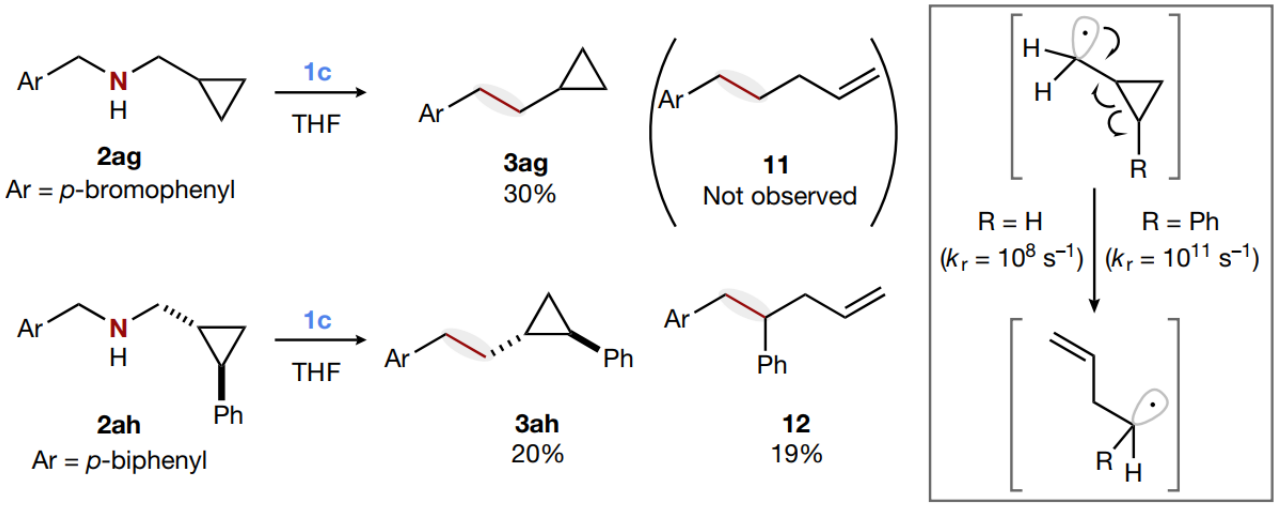


--	85%
TEMPO (1.0 equiv)	72%
BHT (1.0 equiv)	67%

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

Mechanism Study: Radical Clock



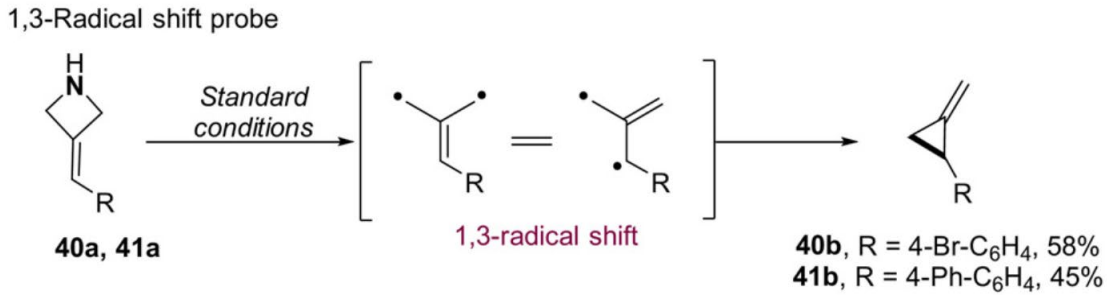


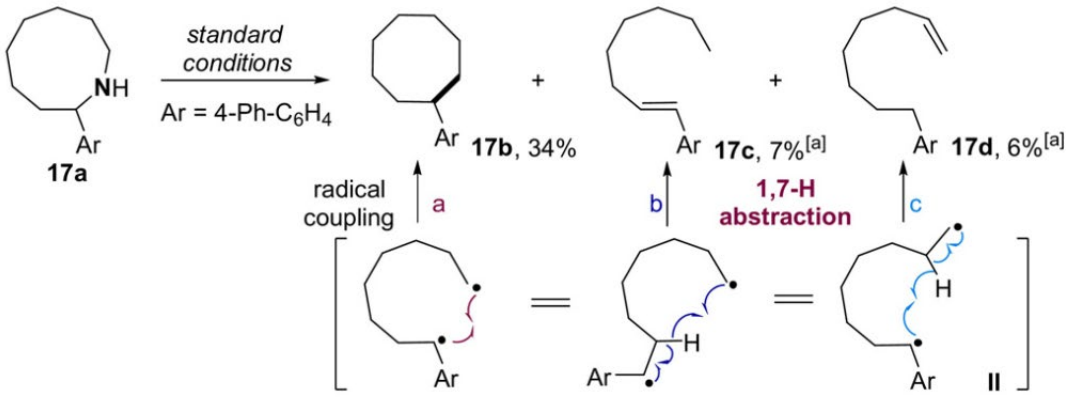
Zou X.; Zou J.; Yang L.; Li G.; Lu H.; *J. Org. Chem.* **2017**, *82*, 4677.

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

Kennedy S.H.; Dherange B.D.; Berger K.J.; Levin M.D. *Nature* **2021**, *3*, 223

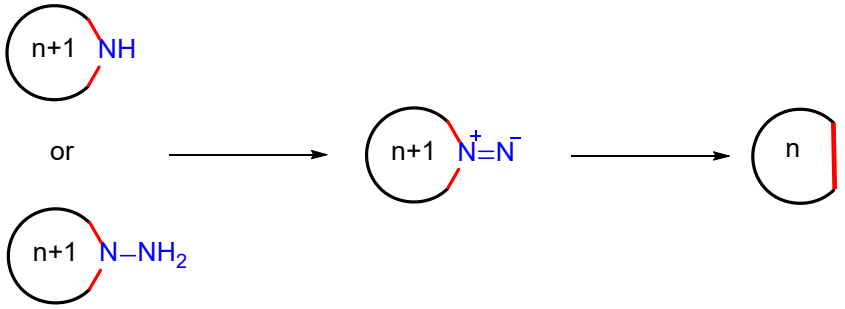
Mechanism Study: Radical Side Reactions

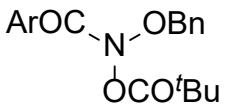
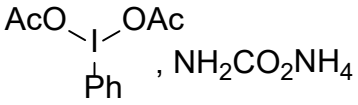




Qin H.; Cai W.; Wang S.; Guo T.; Li G.; Lu H. *Angew. Chem. Int. Ed.* **2021**, *60*, 20678.

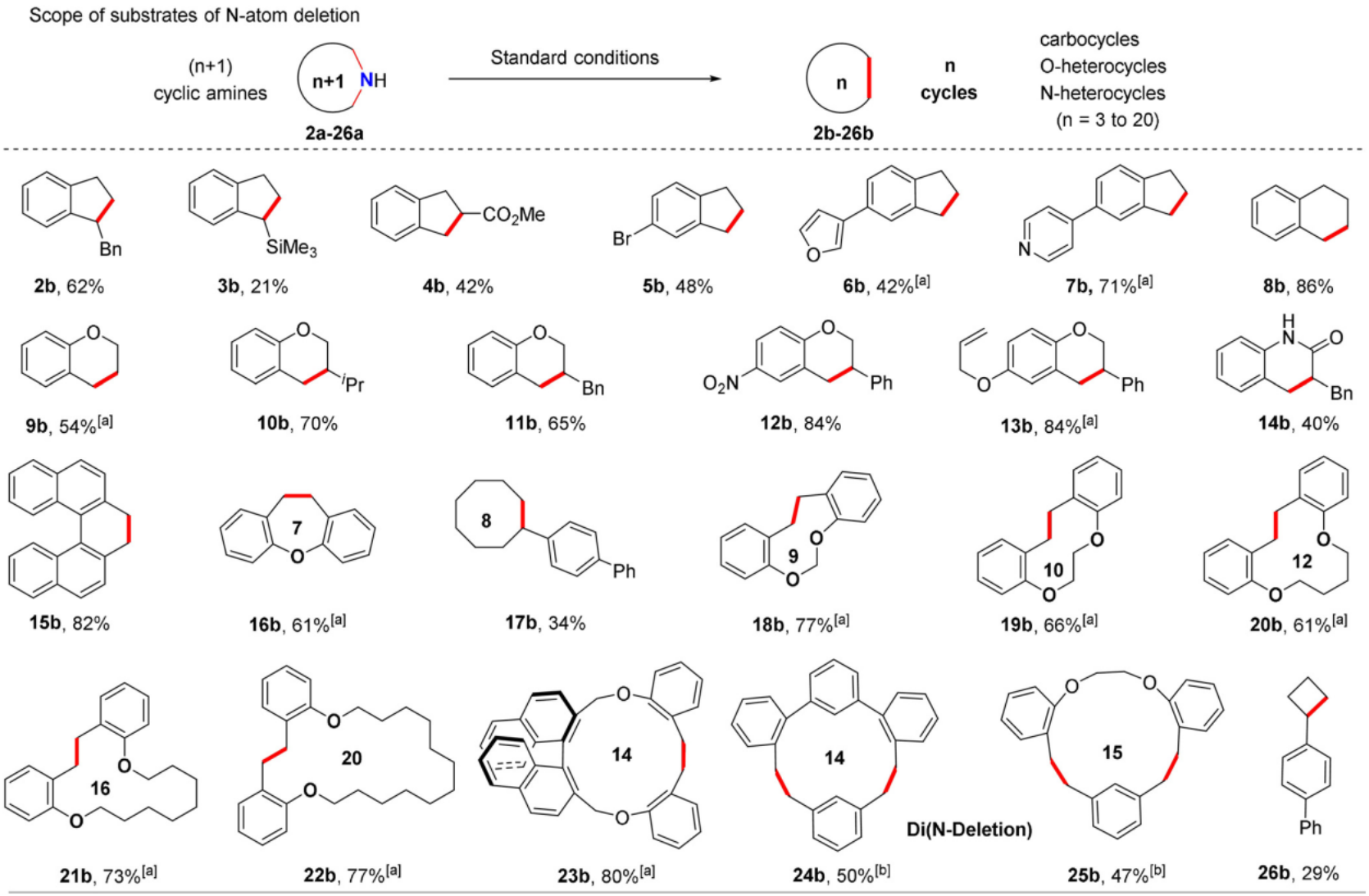
Development of Activation Reagents



HgO	$Na_2(ONNO_2)$	$Pb(OAc)_4$, Me_2SO	$N_3SO_2N_3$		
1900	1965	1984	2017	2021	2021

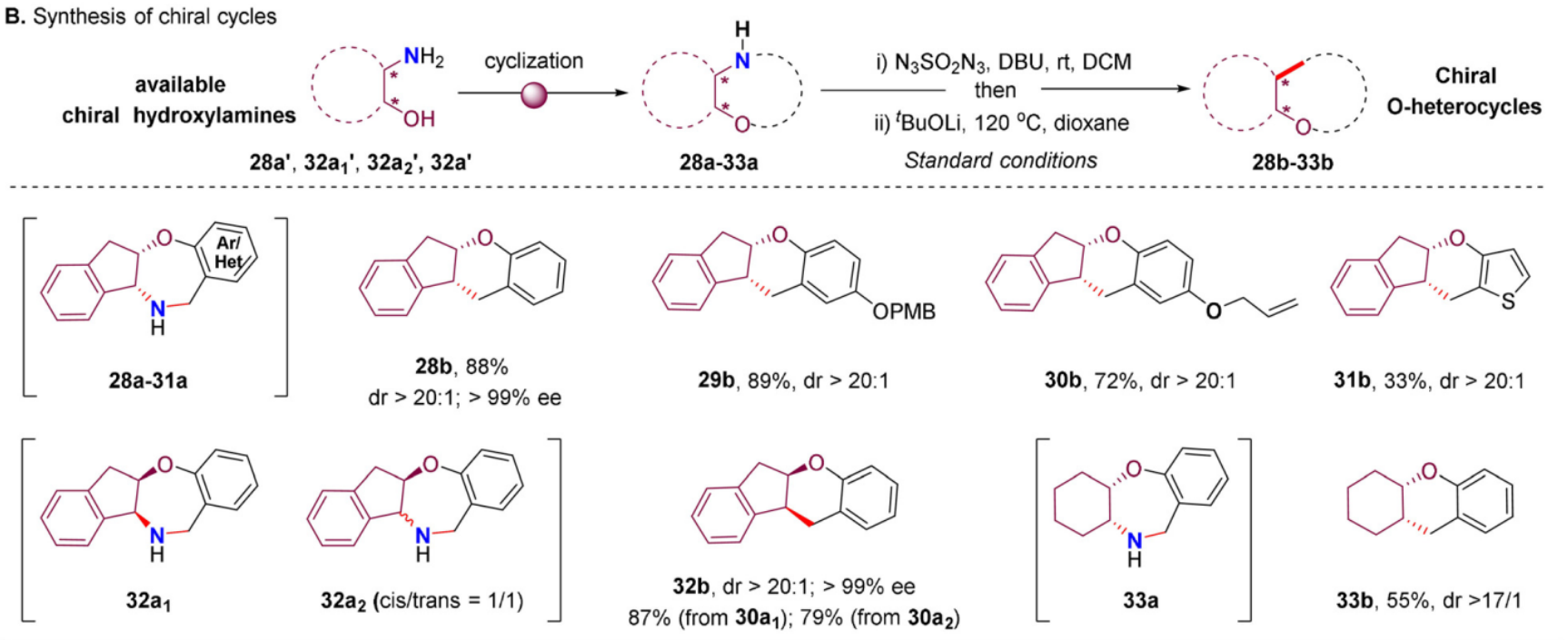
Kennedy, S.H.; Dherange, B.D.; Berger, K.J. et al. *Nature* **2021**, *593*, 223.

Reaction Scope



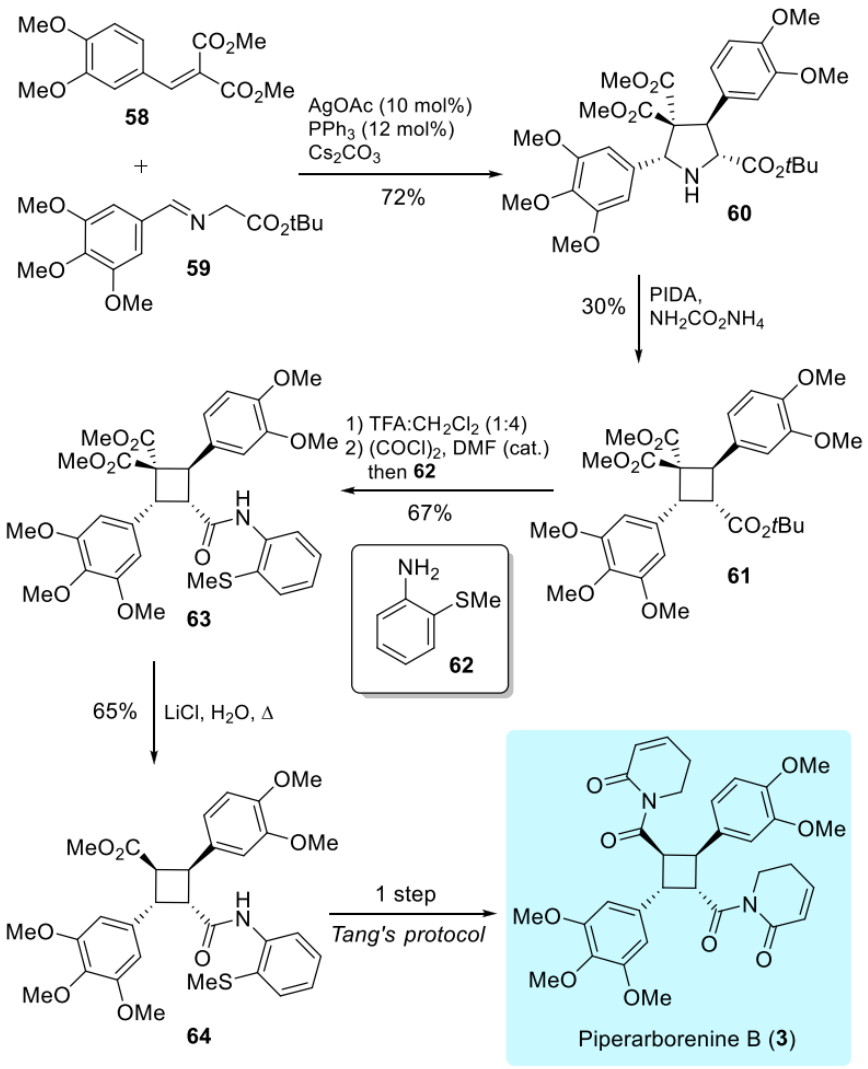
Qin H.; Cai W.; Wang S.; Guo T.; Li G.; Lu H. *Angew. Chem. Int. Ed.* **2021**, *60*, 20678.

Synthetic Applications



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

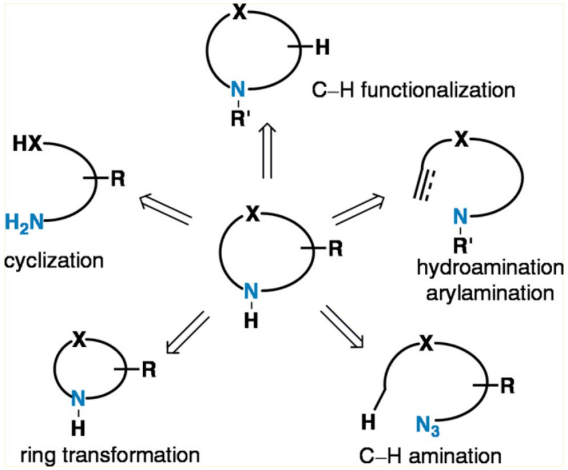
Synthetic Applications



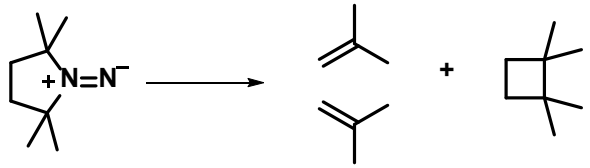
Hui C.; Brieger L.; Strohmann C.; Antonchick A. P.; *J. Am. Chem. Soc.* **2021,** *143,* 18864.

Brief Summary

- Generation of Saturated N-Heterocycles



- Reaction Characteristics



- Formation of strained C-C bond
- Stereoselectivity
- Good functional group tolerance
- Readily accessible pyrrolidine or piperidine
- Applied to natural product synthesis
- Special amine position

0 °C	47%	49%
-10 °C	53%	44%
-20 °C	59%	39%
-78 °C, *hv*	54%	44%

Schultz P. G.; Dervan P. B.; *J. Am. Chem. Soc.* **1982,** *104,* 6660.

Hui C.; Brieger L.; Strohmann C.; Antonchick A. P.; *J. Am. Chem. Soc.* **2021,** *143,* 18864.

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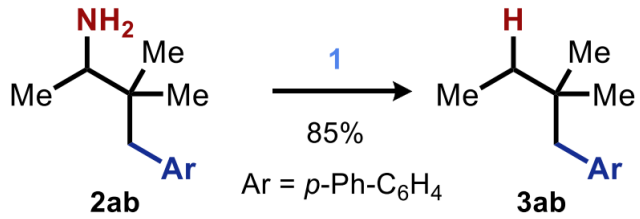
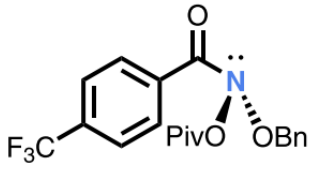
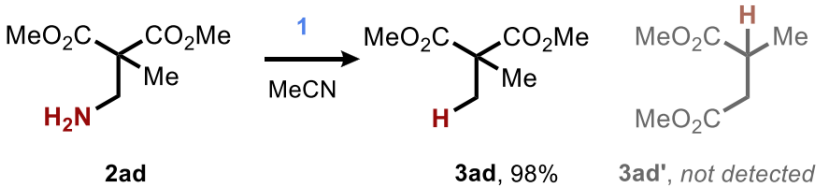
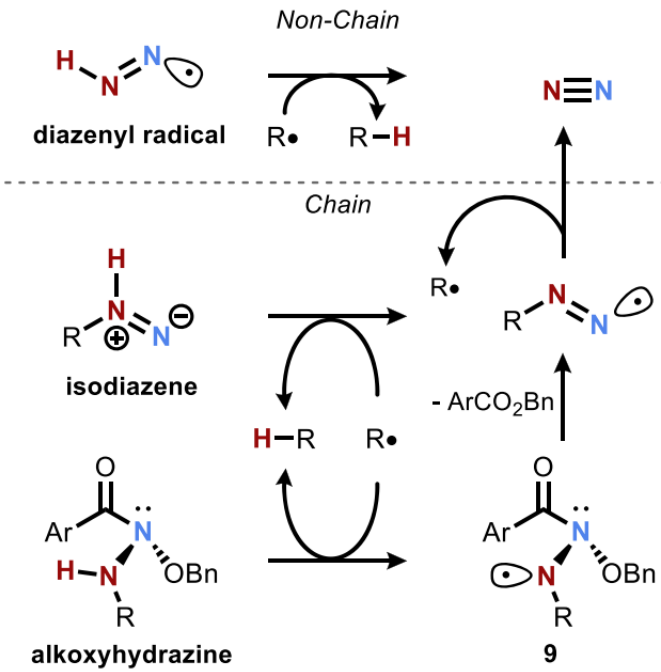
Elimination of Primary Amine





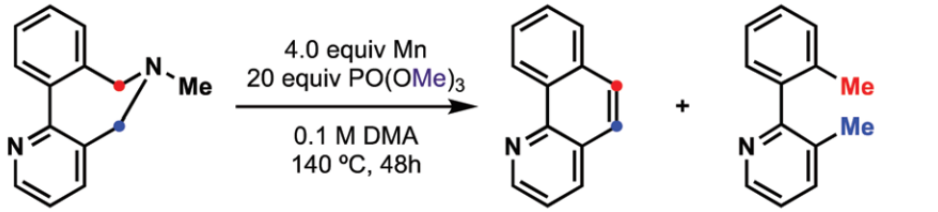
anomeric amide (1)





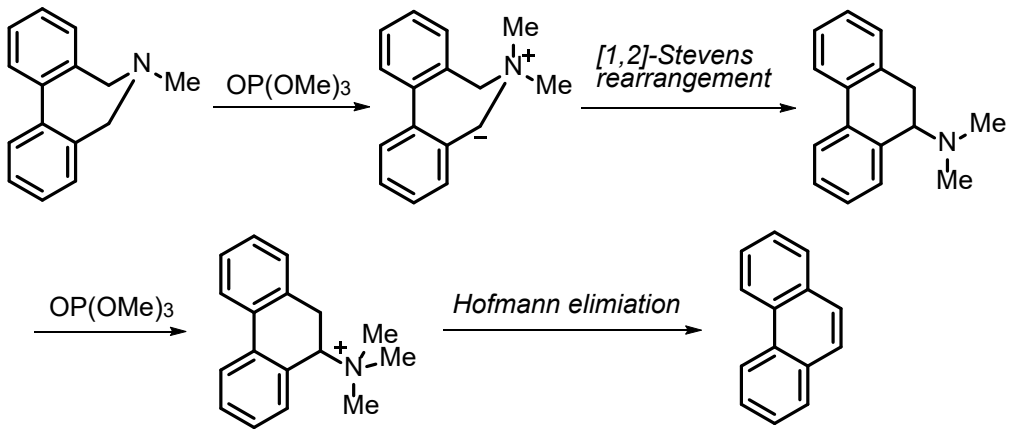
Berger K. J.; Driscoll J. L.; Yuan M.; Dherange B. D.; Gutierrez O.; Levin M. D. *J. Am. Chem. Soc.* **2021**, 143, 17366.

Elimination of Tertiary Amine



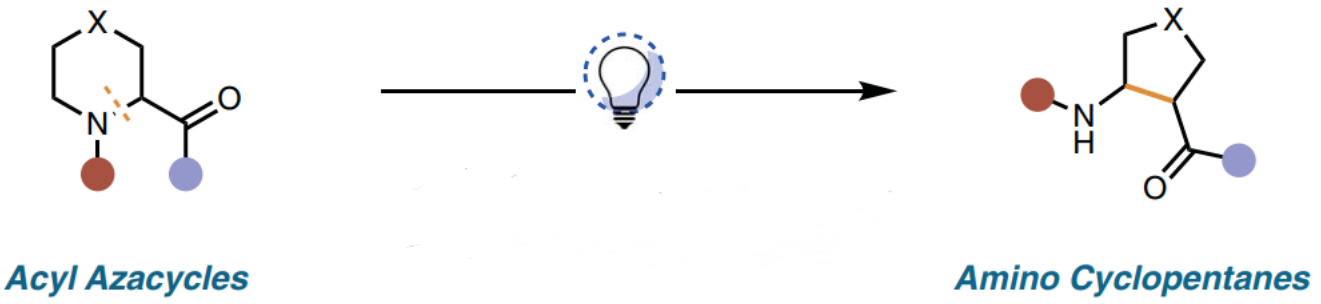
18 **27 (40%)** **28** (*not detected, nd*)

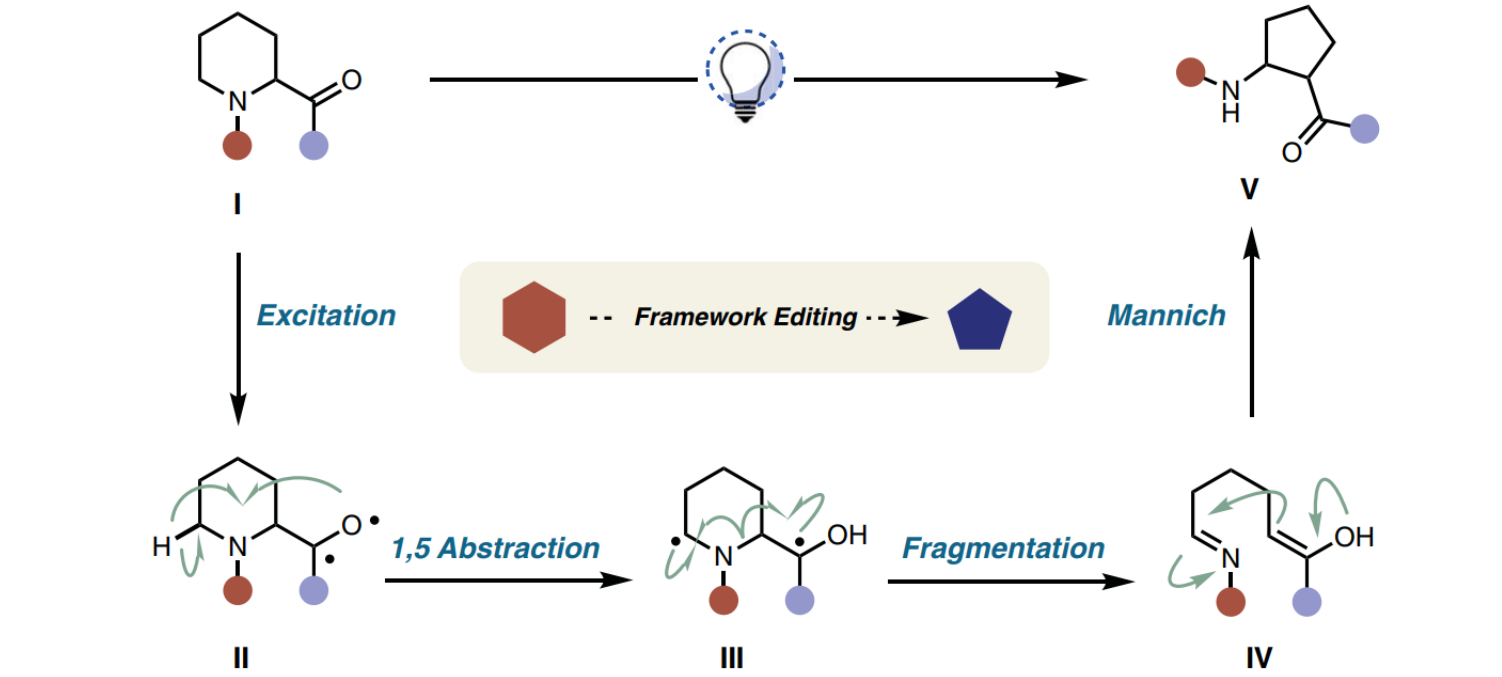
entry	deviation from standard conditions	% of **27**
1	none	40
2	Mn omitted	21
3	Zn instead of Mn	34
4	MeI instead of $PO(OMe)_3$	*nd*
5	+8 equiv KI	*nd*
6	+1 equiv $NaOPO(OMe)_2$	5



McFadden T. P.; Nwachukwu C. I.; Roberts A. G. *Org. Biomol. Chem.*, **2022**, *20*, 1379.

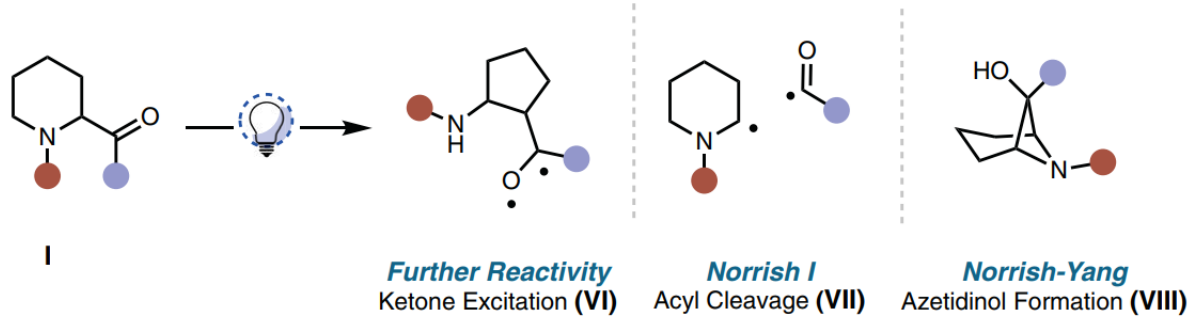
Photomediated Ring Contraction

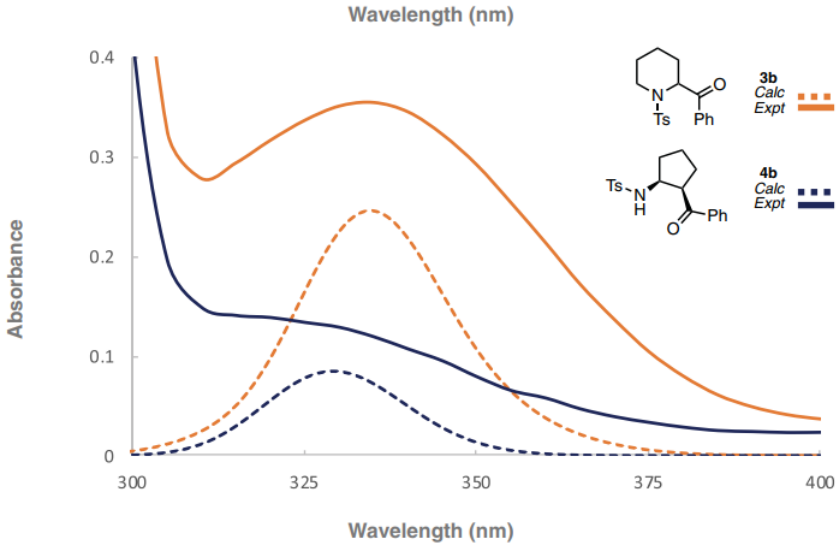




J. Jurczyk; M. C. Lux; D. Adpressa; S. F. Kim; Y. Lam; C. S. Yeung; R. Sarpong *Science* **2021**, *373*, 1004.

Mechanism Study

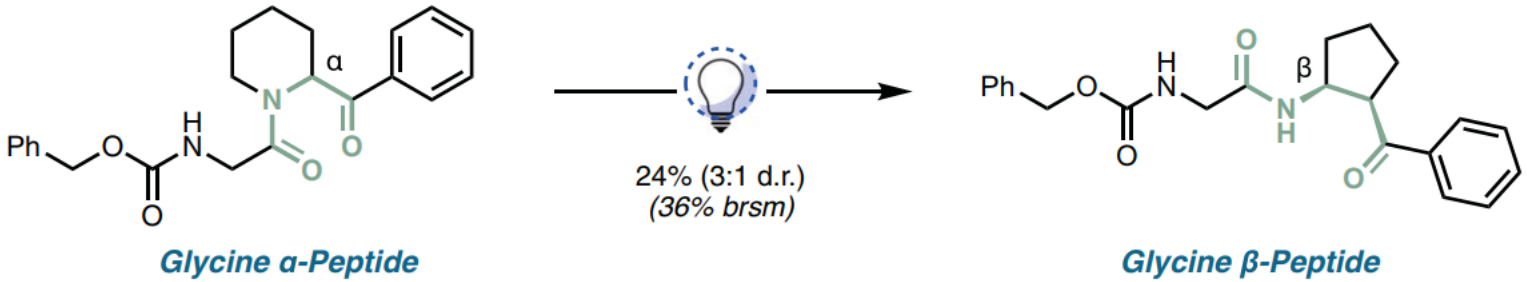


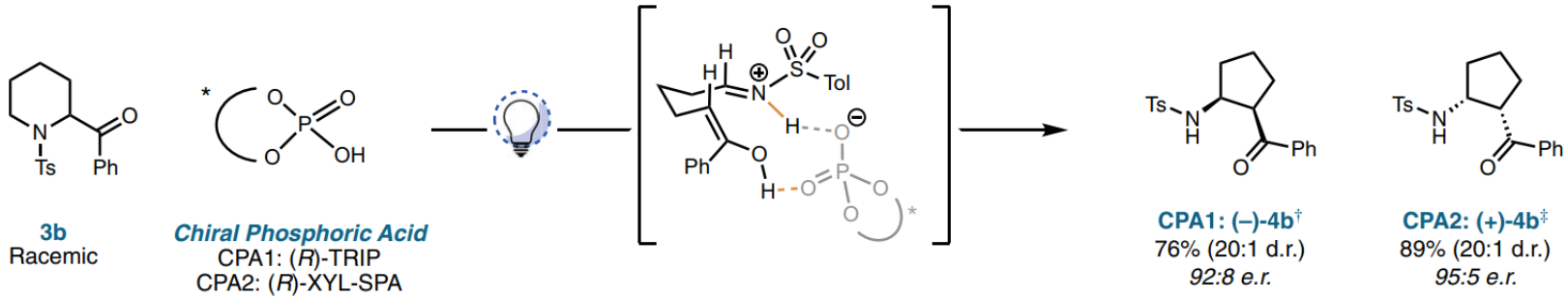


- Low yield if ketone is alkyl C(sp^3)–substituted
- This method is limited to substituents rather than intra-ring heteroatoms

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

Applications

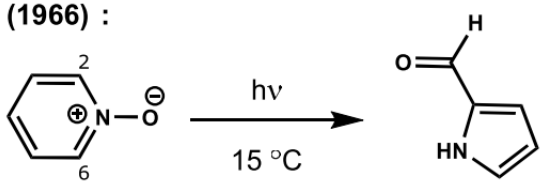




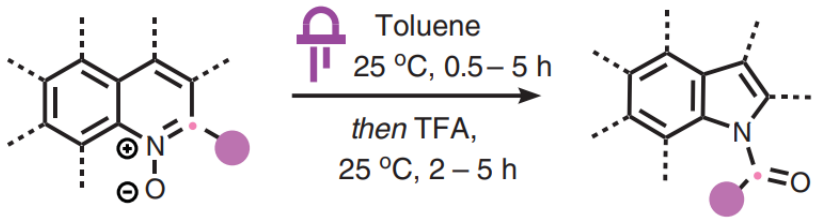
J. Jurczyk; M. C. Lux; D. Adpressa; S. F. Kim; Y. Lam; C. S. Yeung; R. Sarpong *Science* **2021**, *373*, 1004.

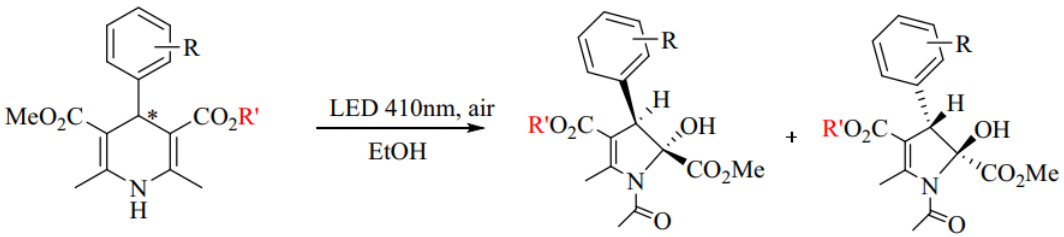
Other Interesting and Related Photoreactions

Streith (1966) :



1 **2**





Hurlow E. E.; Lin J. B.; Dweck M. J.; Nuryyeva S.; Feng Z.; Allred T. K.; Houk K. N.; Harran P. G. *J. Am. Chem. Soc.* **2020**, *142*, 20717.

Wang S.; Wang H.; Tian N.; Yan H. *Tetrahedron Lett.* **2021**, *65*, 152797.

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Summary

- By means of isodiazo intermediates: produce short-lived diradicals that rapidly combine to form new carbon-carbon bonds
- Has a wide range of functional group tolerance: a strategy for ring synthesis
- Although the concept of skeleton editing has been proposed, our current ability to make precise changes to the molecular skeleton itself remains limited.