# *Group Seminar*

## *Classical Reaction, Eternal Vitality*

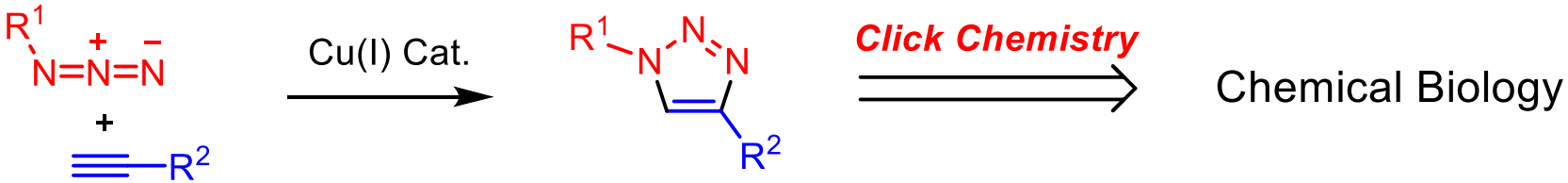
陈丽君

2021.05.27

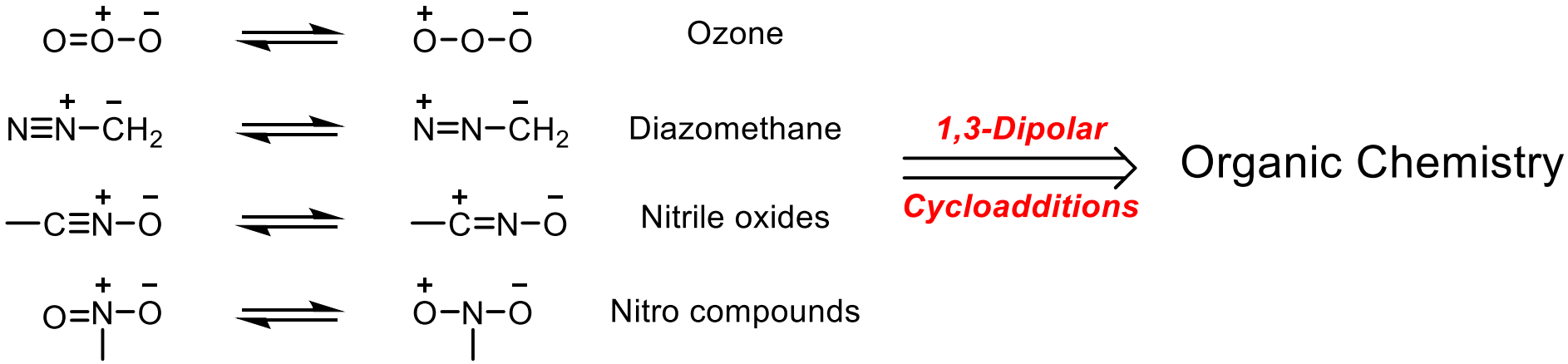
# 1,3-Dipolar Cycloaddition Reactions

Rolf Huisgen
(1920–2020)

## Huisgen Reaction



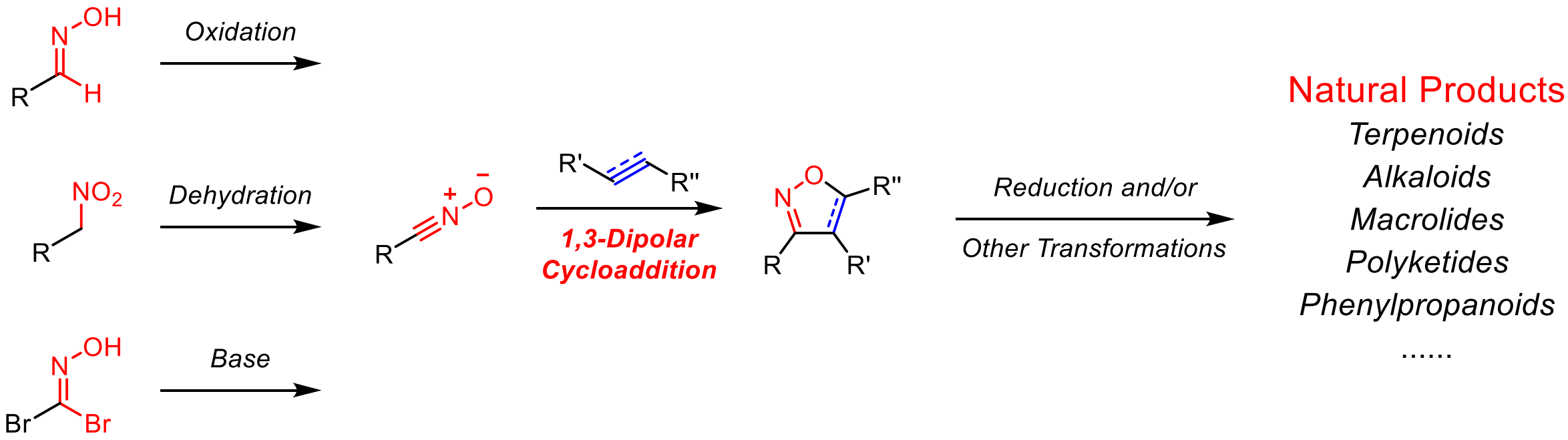

## 1,3-Dipoles




D. Trauner, Rolf Huisgen (1920–2020), *Nat. Chem. Biol.* **2020**, *16*, 711.
R. Huisgen, *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 565-532.

# Nitrile Oxides in the Total Synthesis of Natural Products

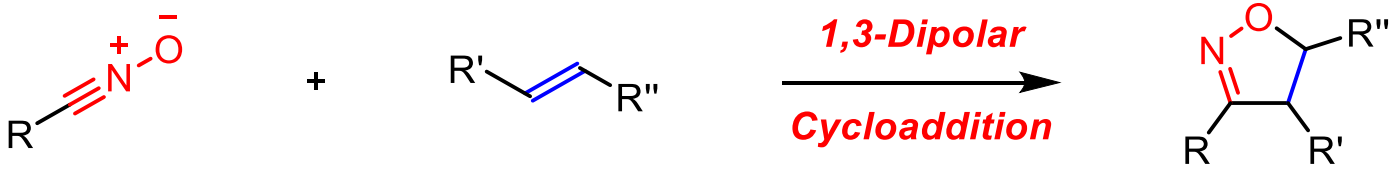
## ——*via 1,3-Dipolar Cycloaddition Reactions*

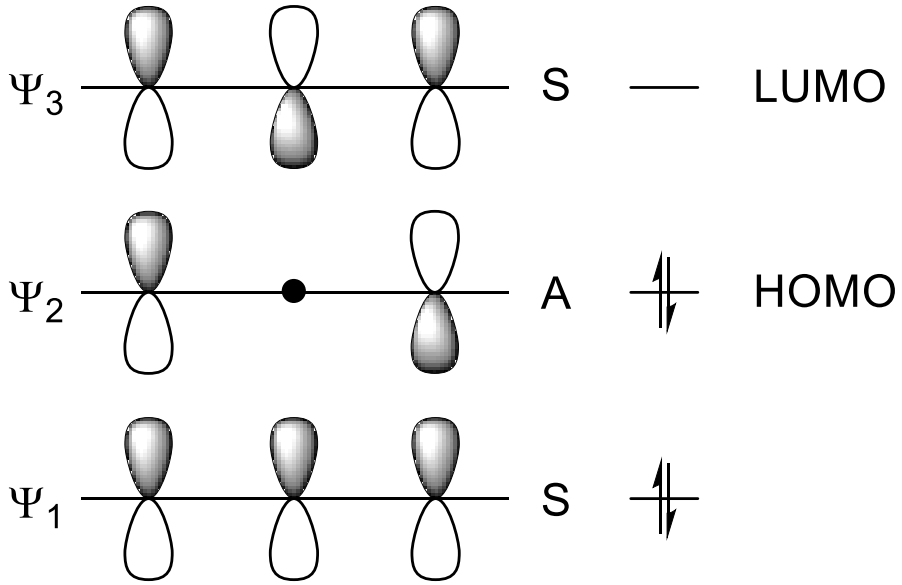


# Contents

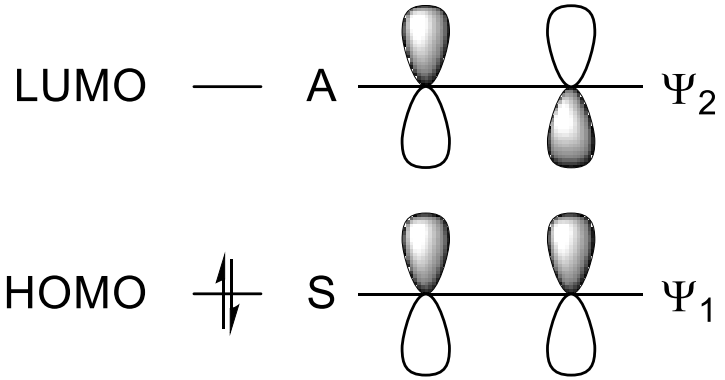
- Reactivity & Stereoselectivity
- Applications in the Total Synthesis of Natural Products
- Mechanism & Supplement

# Reactivity: *Frontier Molecular Orbital*



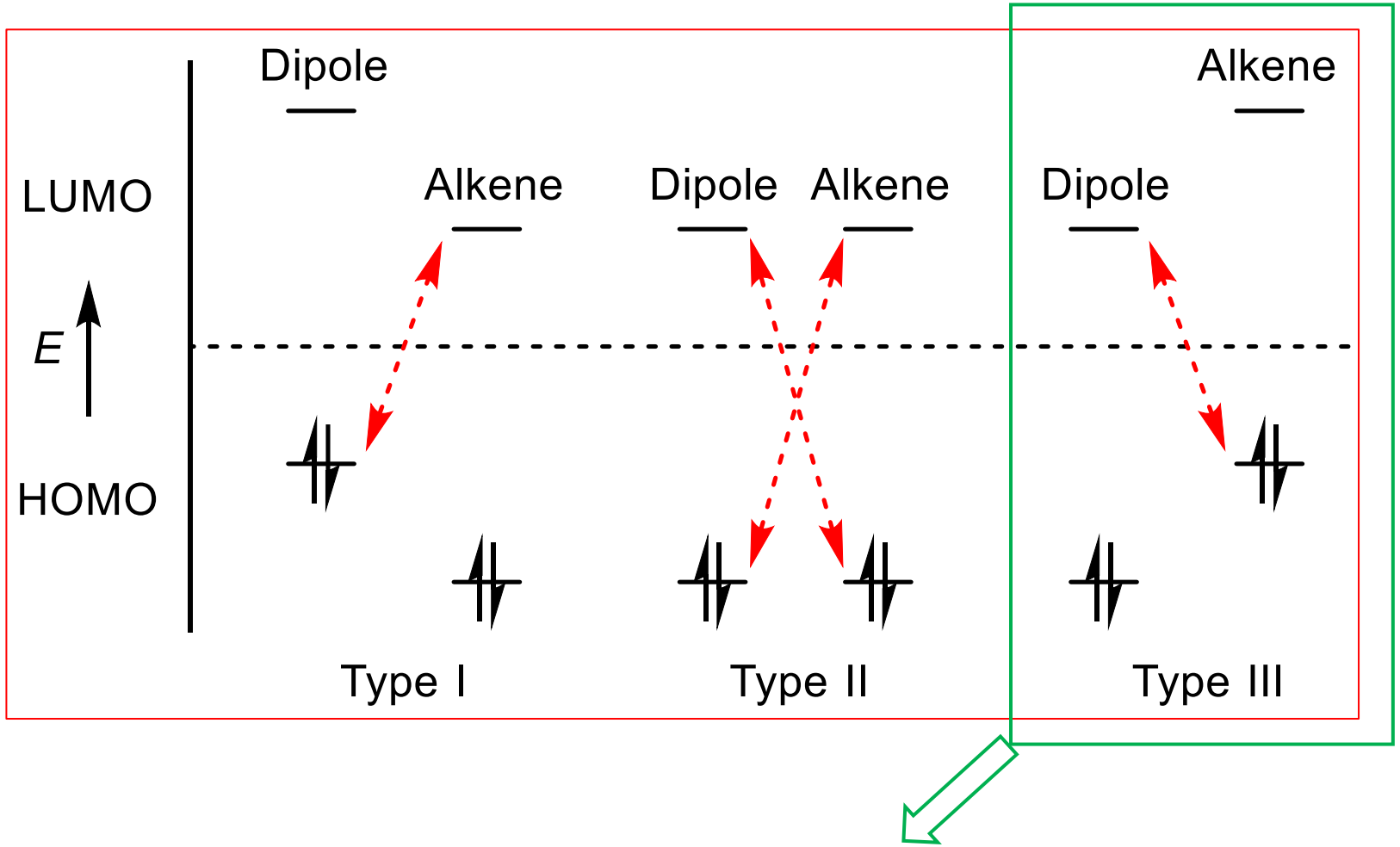




Dipole (Nitrile oxide)




Dipolarophile (Alkene)

# Reactivity: *Sustmann Classification of the 1,3-Dipolar Cycloaddition Reactions*

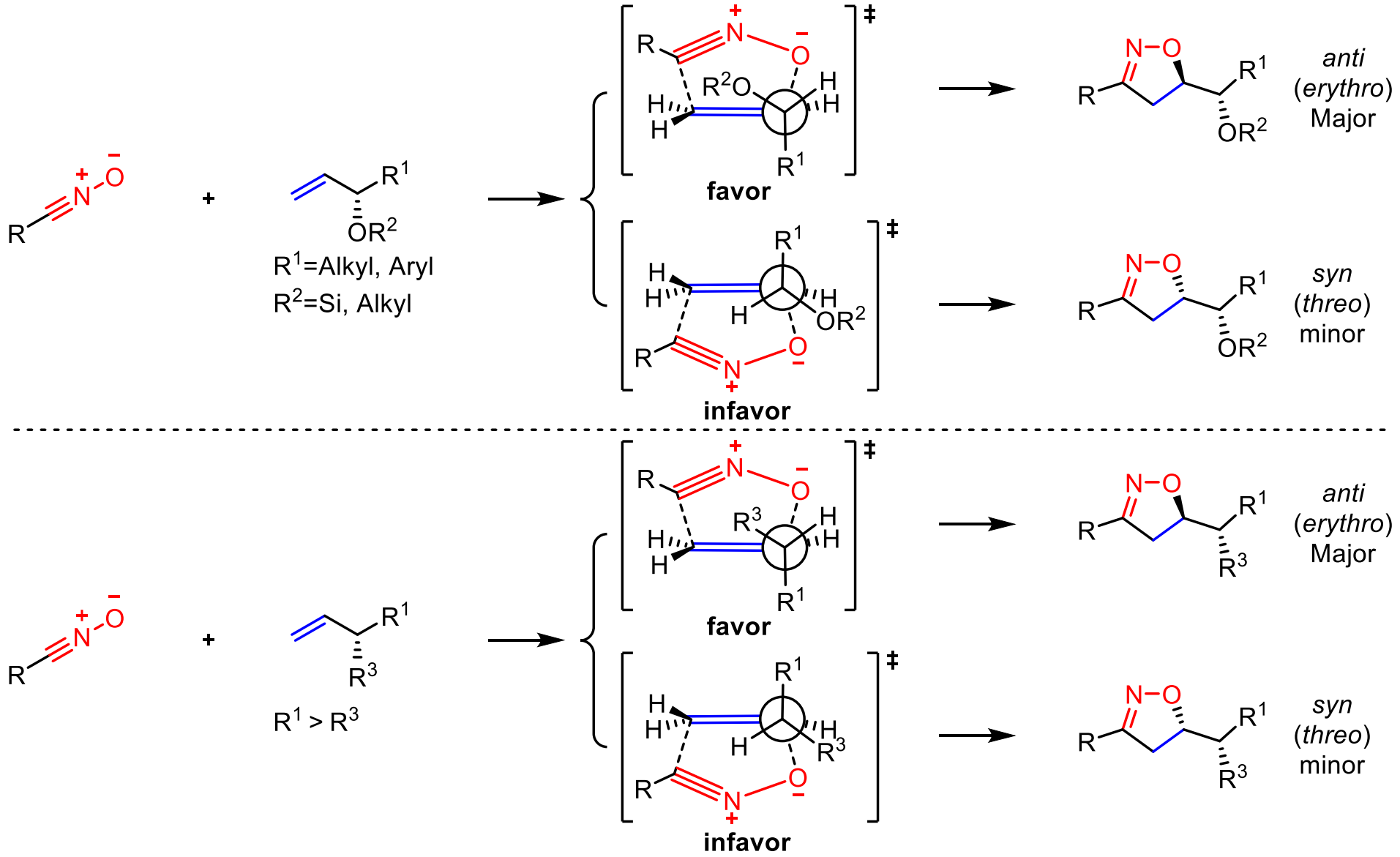



The 1,3-Dipolar Cycloaddition Reactions of Nitrile Oxides

# Reactivity: *Electronic and Steric Effect*

1. Electron-withdrawing substituents on the nitrile oxides increase the reactivity
2. Electron-donating substituents on the olefin increase the reactivity
3. Conjugating substituents raise an olefin's HOMO and lower its LUMO, increasing the reactivity
4. The steric effect of a single alkyl substituent on an alkene decreases reactivity.
5. Trans-disubstituted alkenes are more reactive than the cis-isomers.
6. Trisubstituted alkenes are even less reactive and steric effects dominate.
7. The degree of strain in cyclic olefins and their ease of deformation to form cycloaddition transition states also affect reactivity.

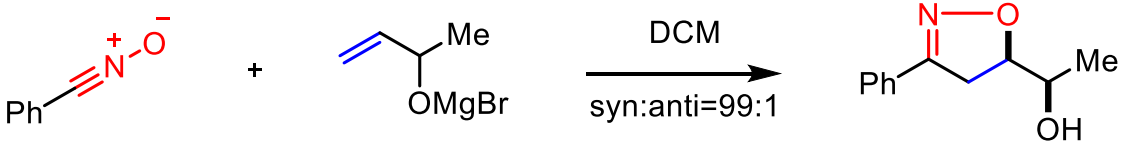
# Stereoselectivity: *The Addition of Nitrile Oxides to Chiral Allyl Ethers*



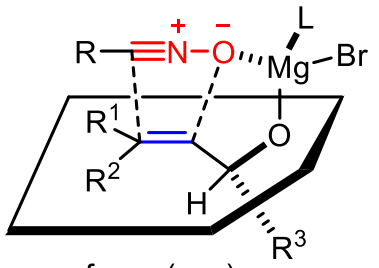

K. N. Houk, et al. *J. Am. Chem. Soc.* **1984**, *106*, 3880-3882; *J. Am. Chem. Soc.* **1984**, *106*, 2754-2755.

# Stereoselectivity: *Metal Coordination Control in 1,3-Dipolar Cycloadditions*

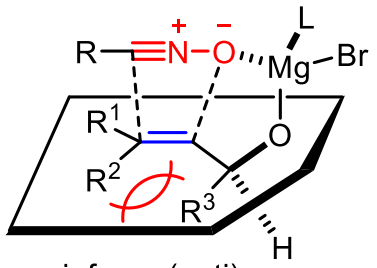
## Kanemasa reaction: $Mg^{II}$-Mediated Cycloadditions of Nitrile Oxides




Shuji Kanemasa, et al. *J. Am. Chem. Soc.* **1994**, *116*, 2324-2339.




favor (syn)




infavor (anti)

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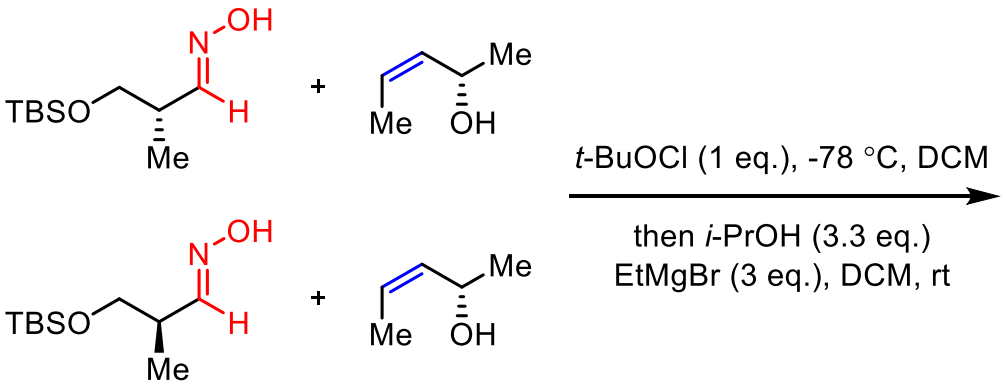
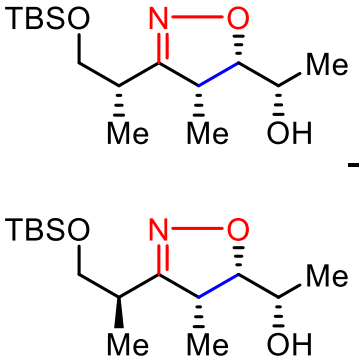
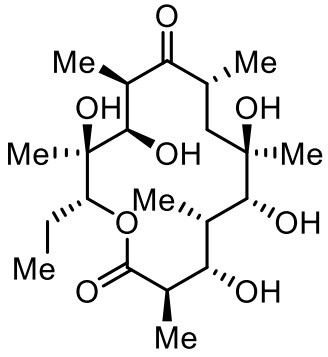
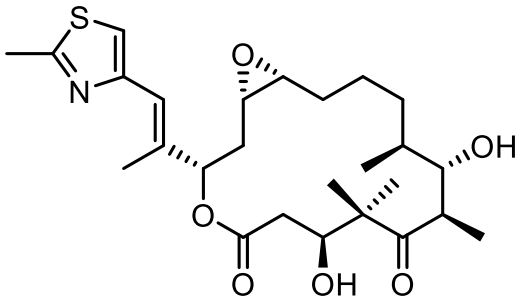


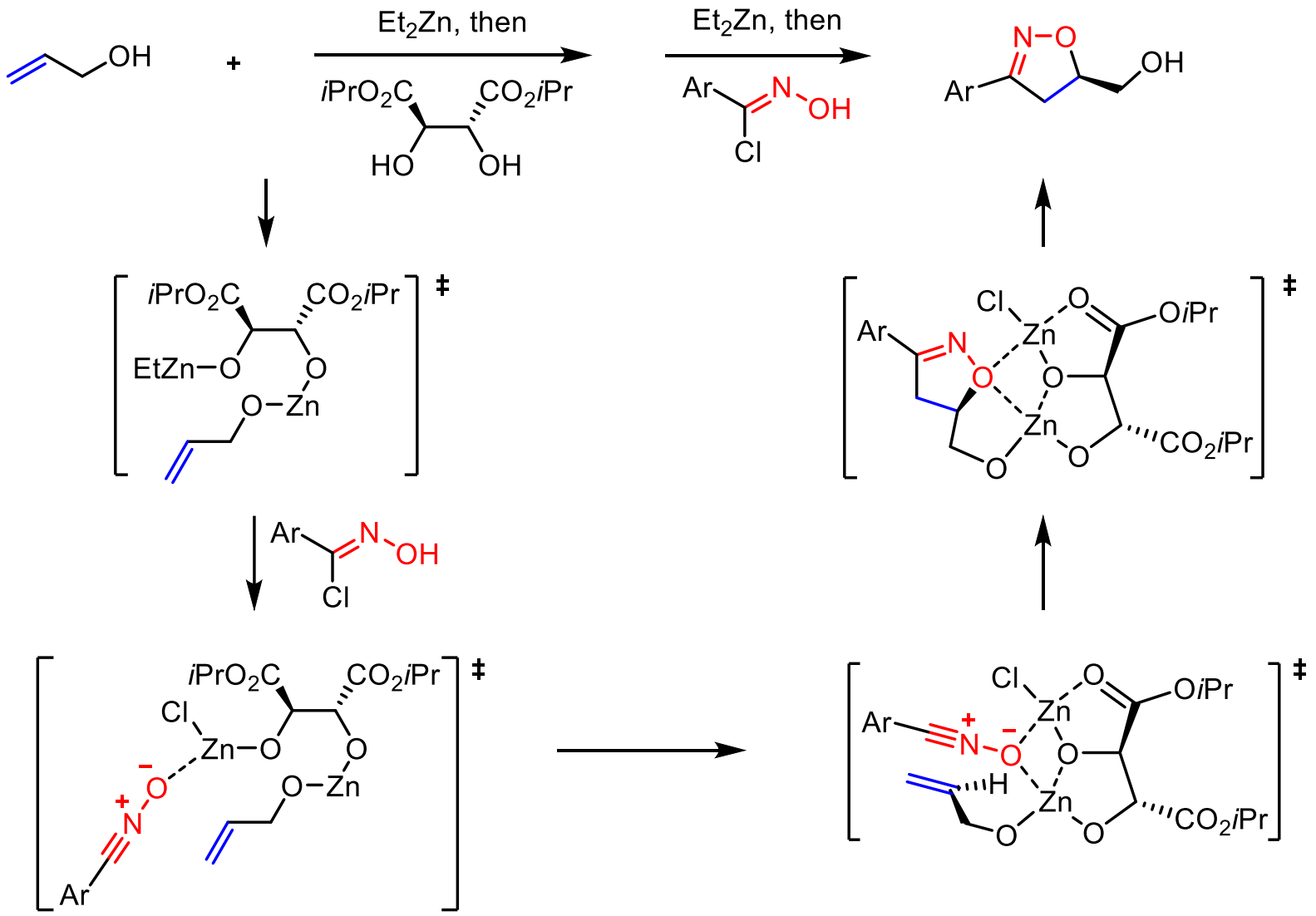

Erythronolide A
*ACIE* **2005**, *44*, 4036
*JOC* **2009**, *74*, 8695




Epothilone A
*JACS* **2001**, *123*, 3611
*JOC* **2001**, *66*, 6410

Erick M. Carreira, et al. *Angew. Chem. Int. Ed.* **2001**, *40*, 2082-2085

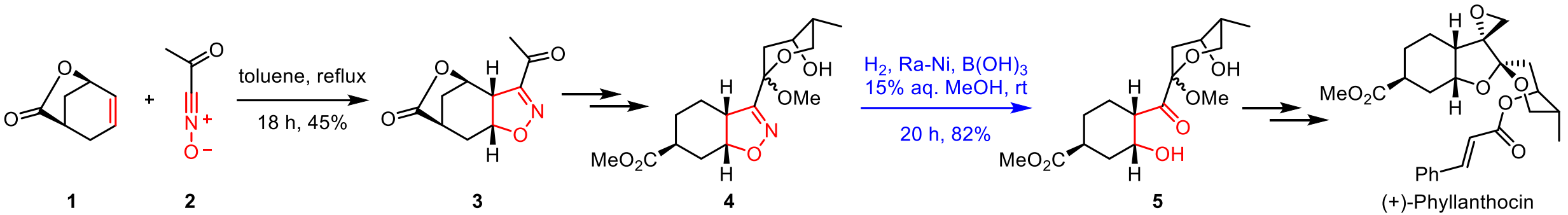
# Stereoselectivity: *Metal Coordination Control in 1,3-Dipolar Cycloadditions*



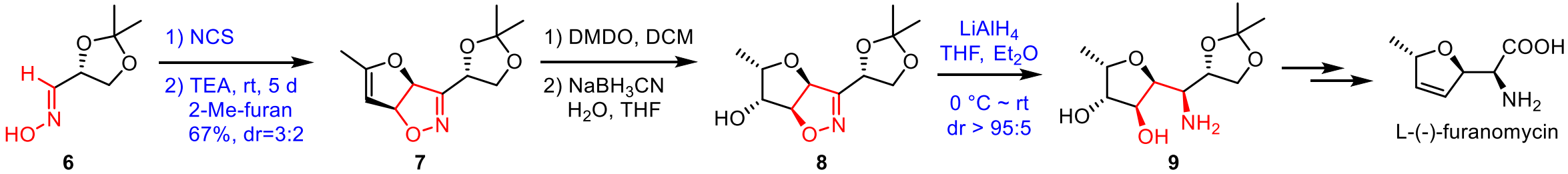

Katsuhiko Inomata, et al. *Chem. Lett.* **1993**, 1847-1850.

*Applications in the Total Synthesis of Natural Products*

# Intermolecular Cycloaddition

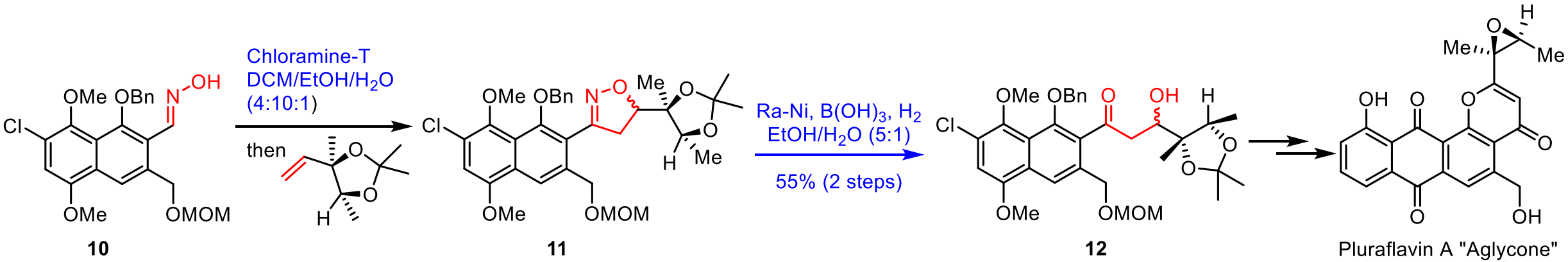



Stephen F. Martin, et al. *J. Org. Chem.* **1987**, *52*, 3706-3708
Stephen F. Martin, et al, *J. Org. Chem.* **1989**, *54*, 2209-2216



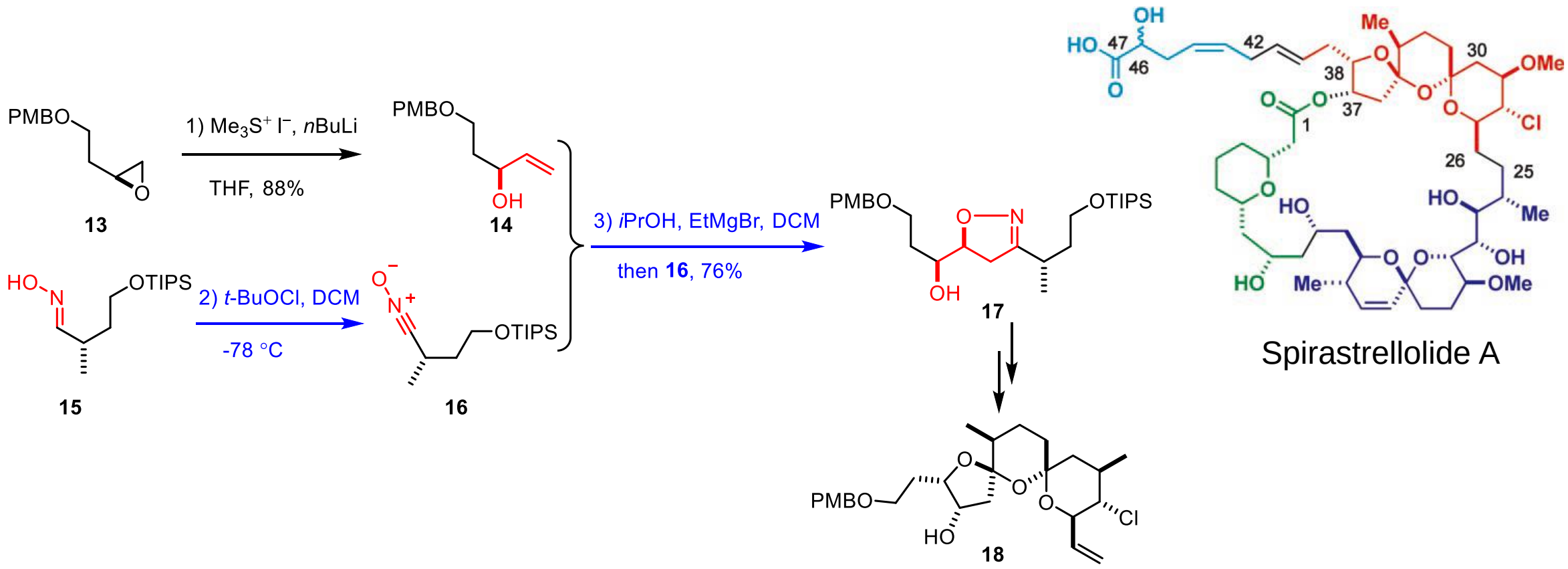

Volker Jäger, et al. *Angew. Chem. Int. Ed.* **2000**, *39*, 910-912

# Intermolecular Cycloaddition



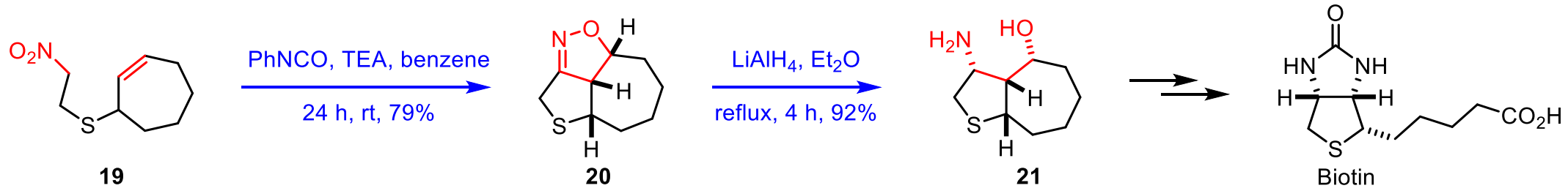

Samuel J. Danishefsky, et al. *J. Am. Chem. Soc.* **2008**, *130*, 16786-16790

# Intermolecular Cycloaddition: *Kanemasa Reaction*

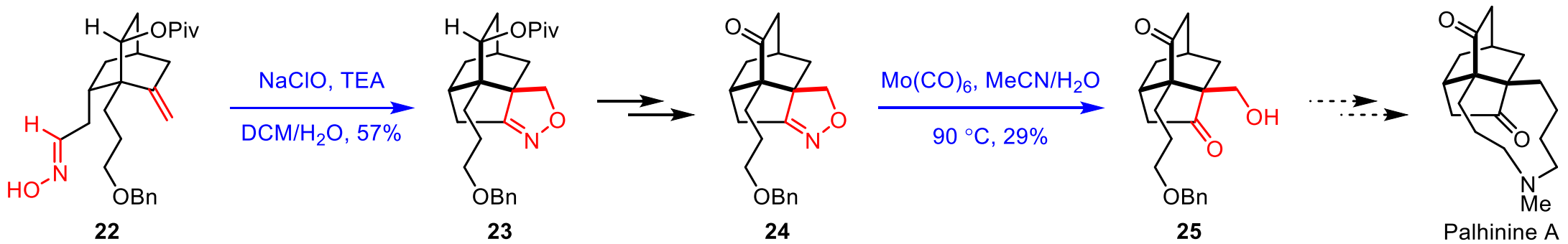



Alois Fürstner, et al. *Angew. Chem. Int. Ed.* **2006**, *45*, 5510-5515
Alois Fürstner, et al. *Chem. Eur. J.* **2013**, *19*, 3596-3608.

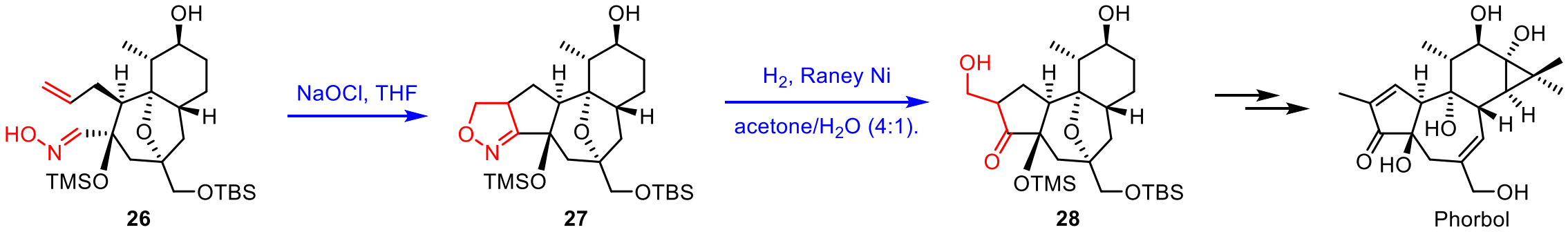
# Intramolecular Cycloaddition: *To Construct the Five-Membered Ring*




Pat N. Confalone, et al. *J. Am. Chem. Soc.* **1980**, *102*, 1954-1960

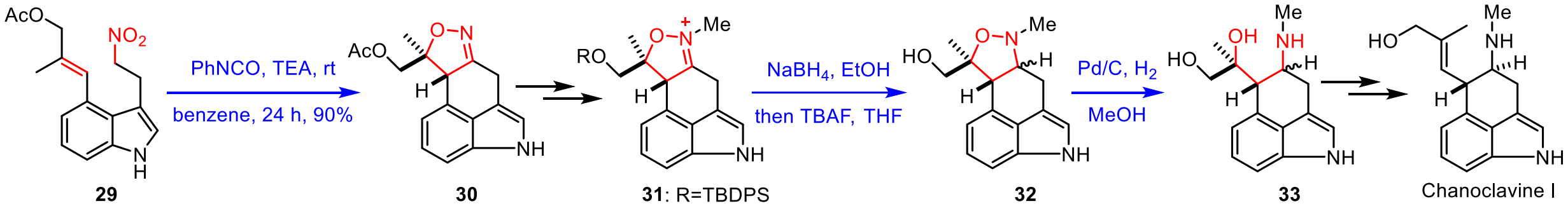



Martin E. Maier, et al. *Eur. J. Org. Chem.* **2021**, 2549-2556



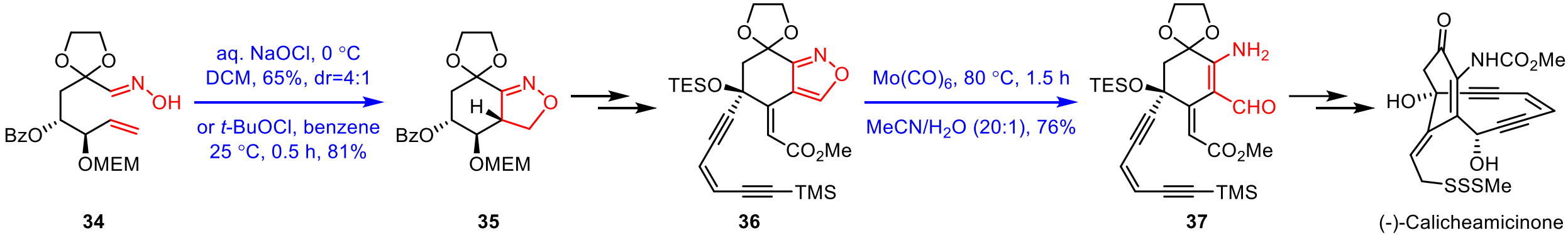

Paul A. Wender, et al. *J. Am. Chem. Soc.* **1989**, *111* , 8954-8957; *J. Am. Chem. Soc.* **1989**, *111* , 8957-8958

# Intramolecular Cycloaddition: *To Construct the Six-Membered Ring*




**29** **30** **31**: R=TBDPS **32** **33** Chanoclavine I

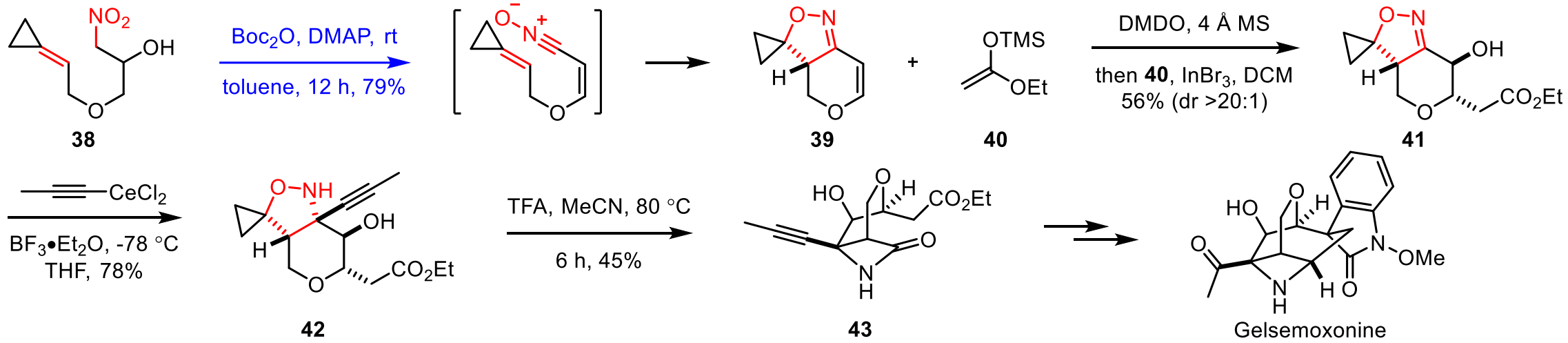
Alan P. Kozikowski, et al. *J. Am. Chem. Soc.* **1980**, *102*, 4265-4267



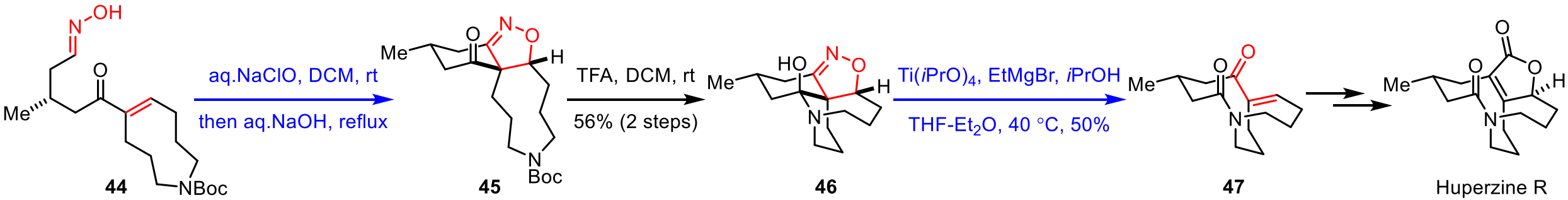

**34** **35** **36** **37** (-)-Calicheamicinone

K. C. Nicolaou, et al. *J. Am. Chem. Soc.* **1992**, *114*, 3134-3136; *J. Am. Chem. Soc.* **2015**, *137*, 8716-8719

# Intramolecular Cycloaddition: *To Construct the Six-Membered Ring*

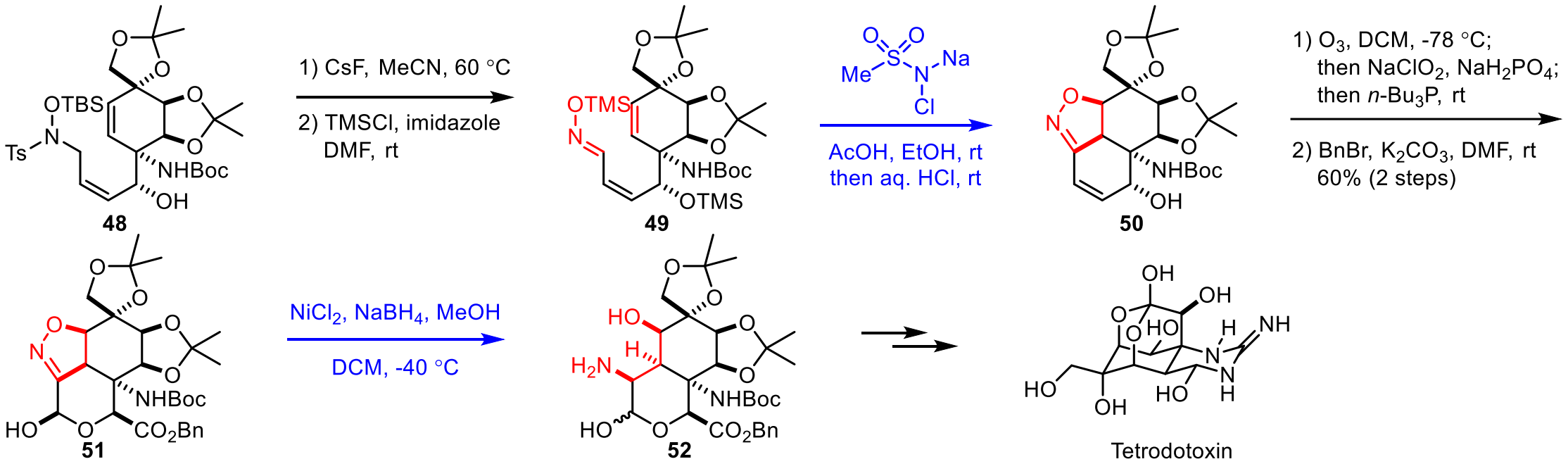



Erick M. Carreira, et al. *J. Am. Chem. Soc.* **2015**, *137*, 6084-6096

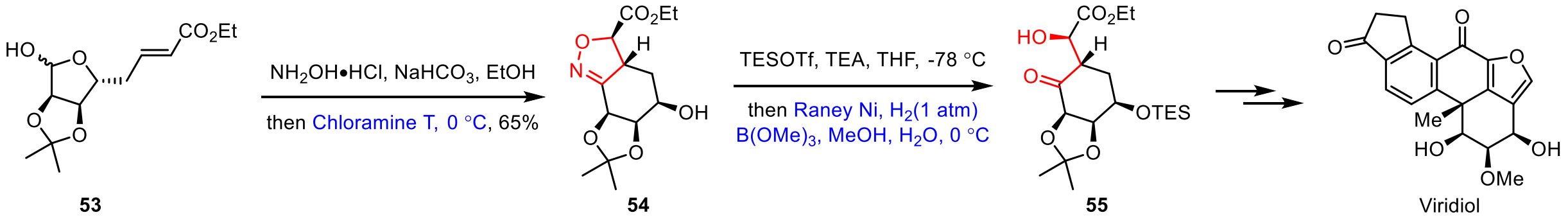



Tohru Fukuyama, et al. *Org. Lett.* **2018**, *20*, 119-121.

# Intramolecular Cycloaddition: *To Construct the Six-Membered Ring*

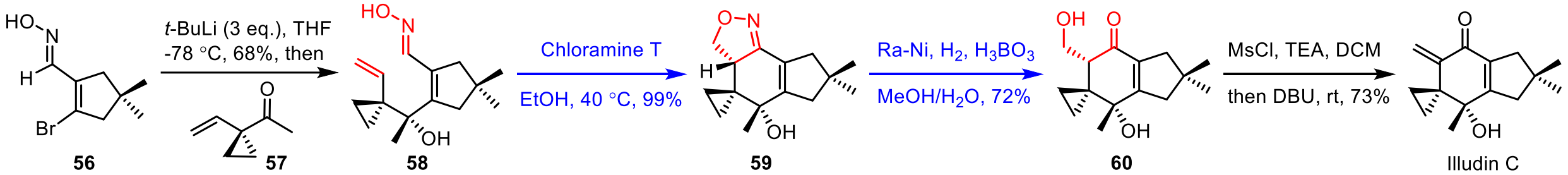



Tohru Fukuyama, et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 1549-1552.

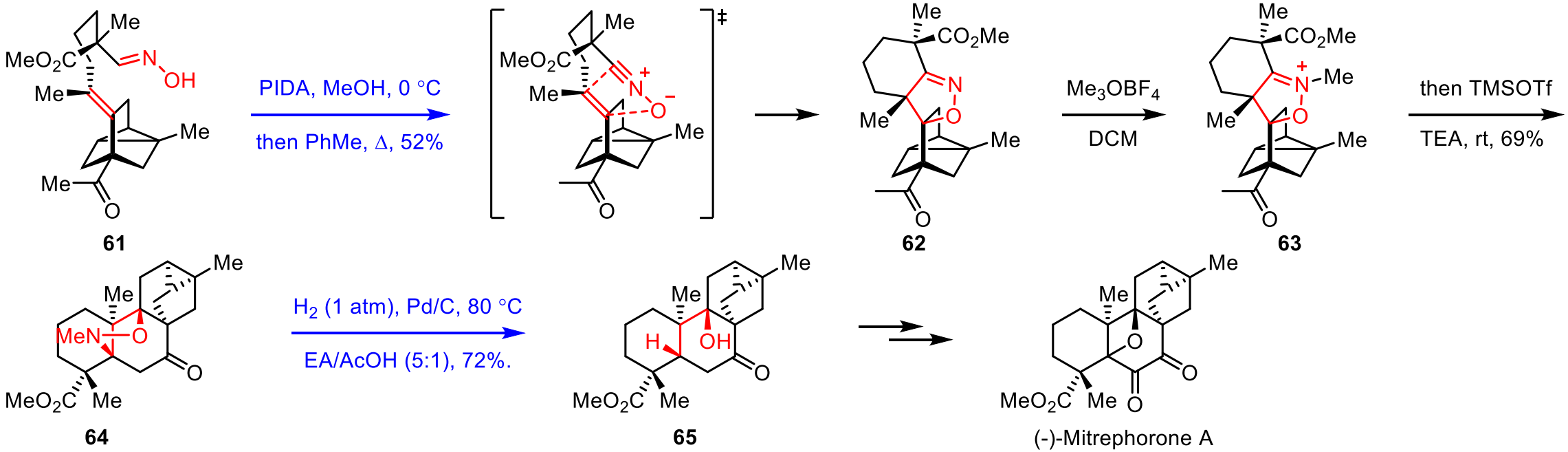



Shuanhu Gao, et al. *J. Am. Chem. Soc.* **2019**, *141*, 16208-16212

# Intramolecular Cycloaddition: *To Construct the Six-Membered Ring*

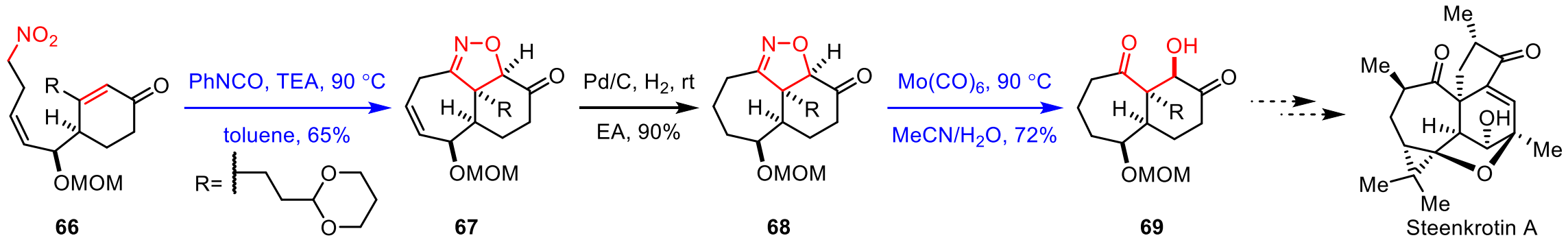



Raymond L. Funk, et al. *Org. Lett.* **2001**, *3*, 2611-2613

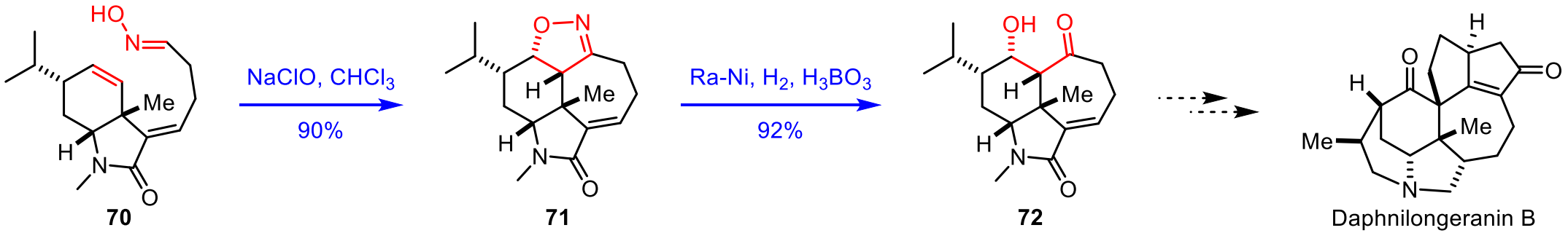



Erick M. Carreira, et al. *J. Am. Chem. Soc.* **2020**, *142*, 17802-17809

# Intramolecular Cycloaddition: *To Construct the Seven-Membered Ring*

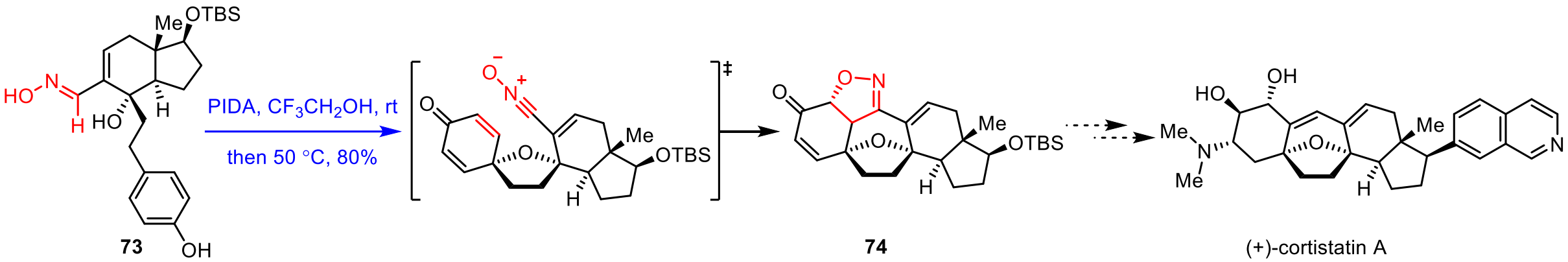



Hanfeng Ding, et al. *Org. Biomol. Chem.* **2015**, *13*, 1643-1646.



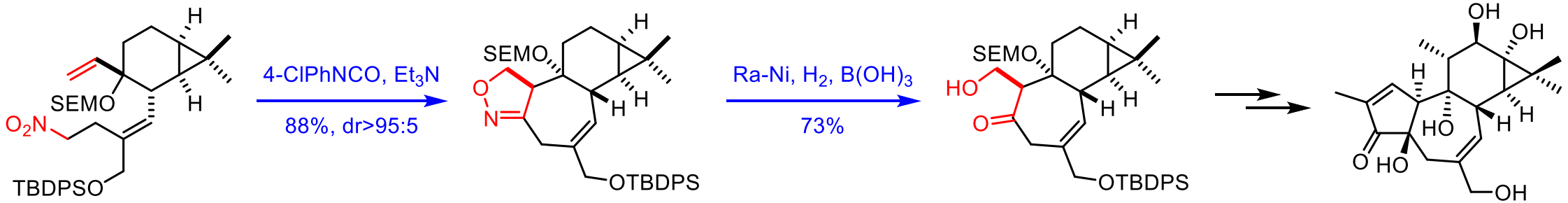

Xiaojiang Hao, et al. *Org. Lett.* **2014**, *16*, 1076-1079

# Intramolecular Cycloaddition: *To Construct the Seven-Membered Ring*




**73** **74** (+)-cortistatin A

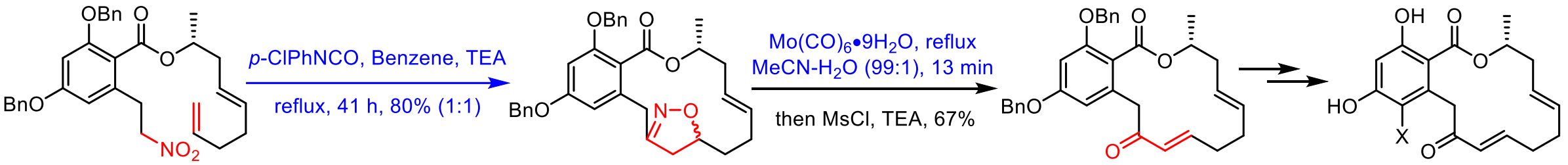
Erik J. Sorensen, et al. *Org. Lett.* **2009**, *11*, 5394-5397




**75** **76** **77** Phorbol

Masakatsu Shibasaki, et al. *Heterocycles*, **1992**, *33*, 161-171; *Tetrahedron Lett*. **1992**, *33*, 4937-4940.

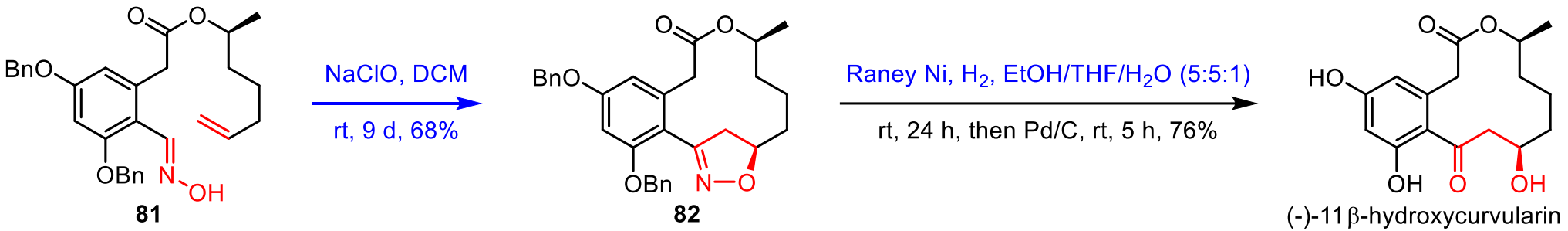
# Intramolecular Cycloaddition: *To Construct the Macrocycle*




**78** **79** **80**

(+)-monocillin II: X=H
(+)-pochonin D: X=Cl

Jongkook Lee, et al. *Org. Lett.* **2017**, *19*, 6004-6007

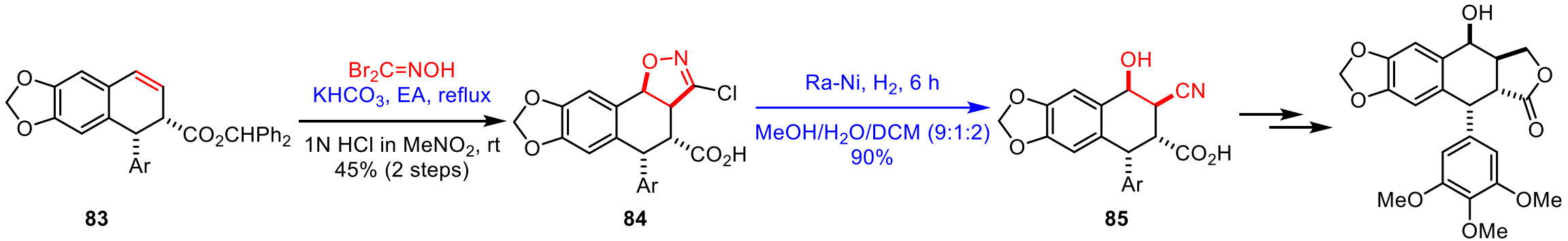



**81** **82**

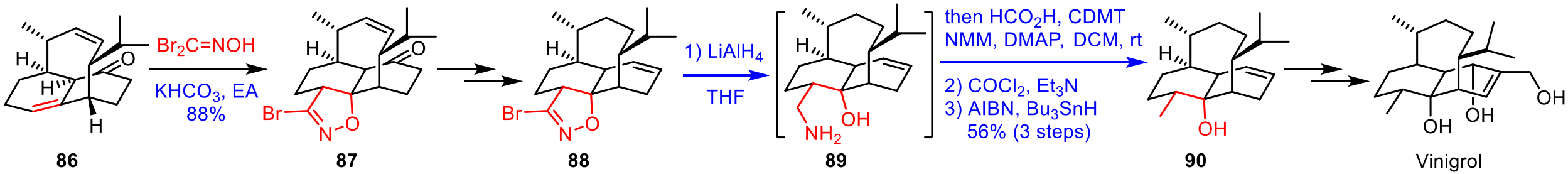
(-)-11β-hydroxycurvularin

Jongkook Lee, et al. *J. Org. Chem.* **2016**, *81*, 2612-2617.

# $Br_2C$=NOH: *Applications in the Total Synthesis*

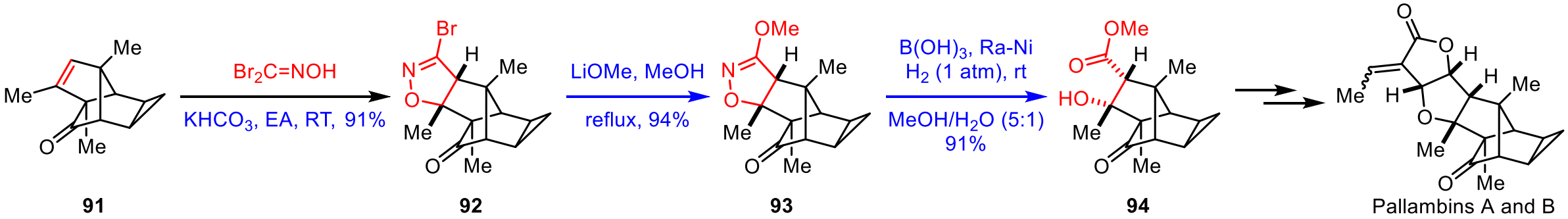



D.M. Vyas, et al. *Tetrahedron Lett.* **1986**, *27*, 3099-3102

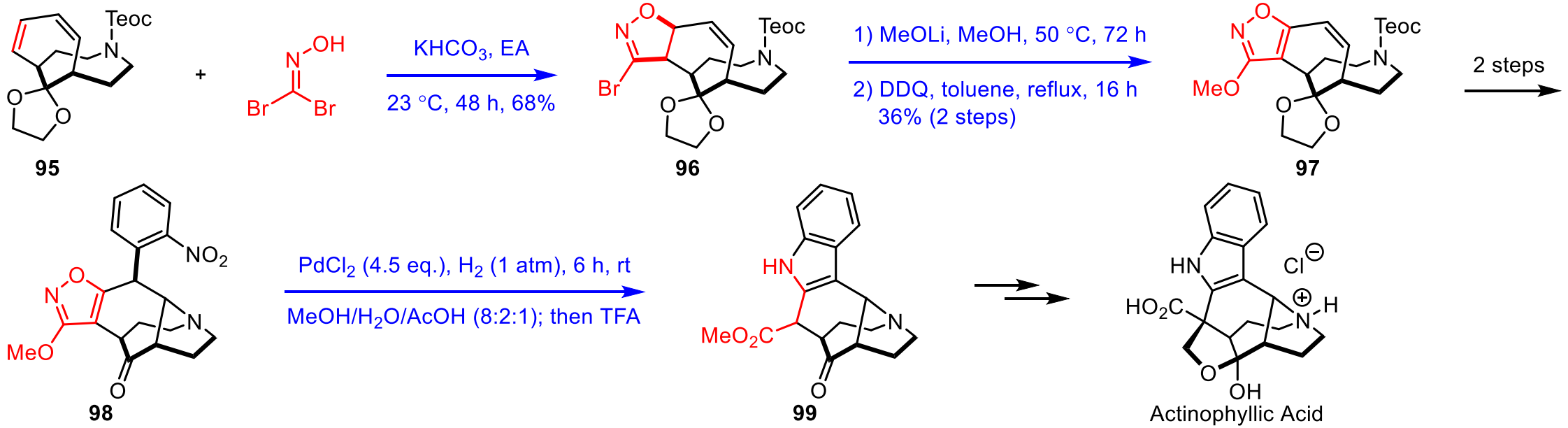



Phil S. Baran, et al. *J. Am. Chem. Soc.* **2009**, *131*, 17066-17067

# $Br_2C$=NOH: *Applications in the Total Synthesis*



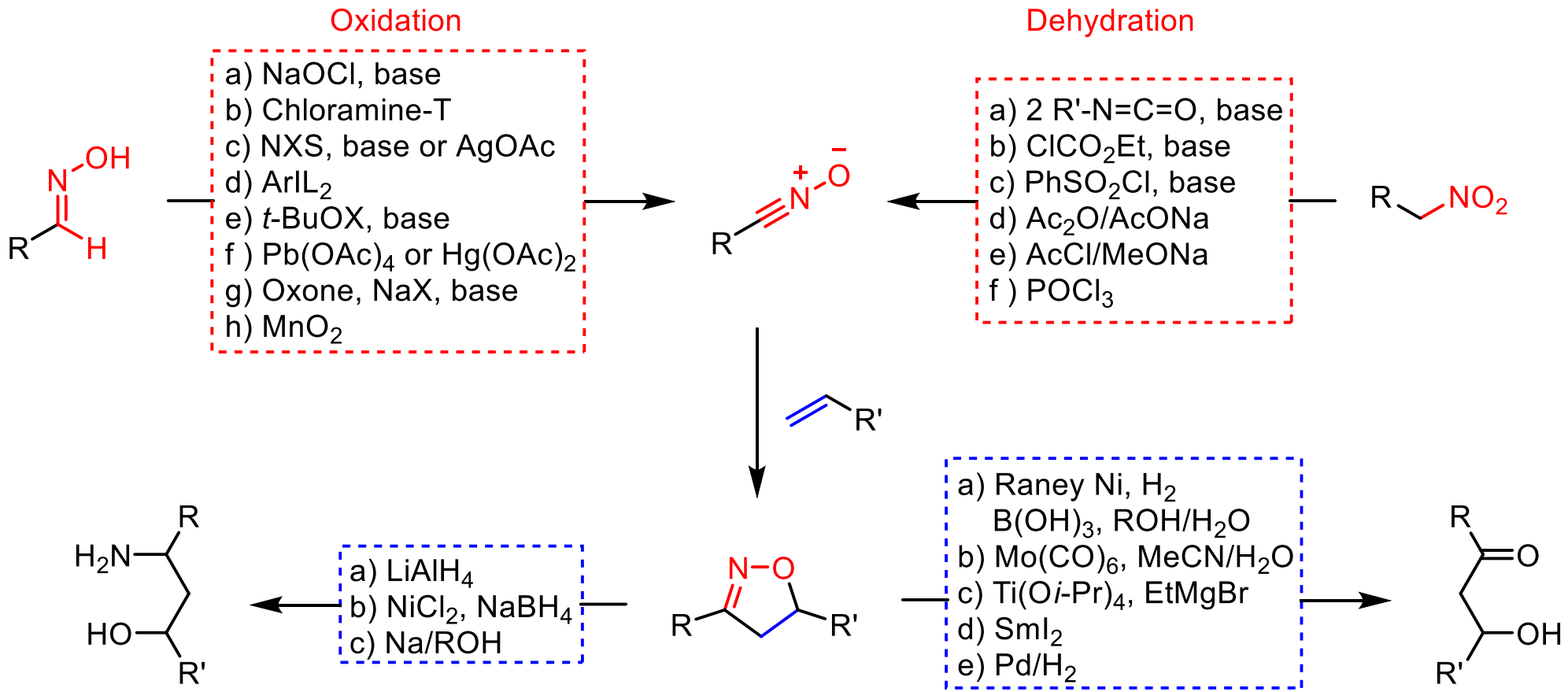

Erick M. Carreira, et al. *Angew. Chem. Int. Ed.* **2015**, *54*, 11227-11230

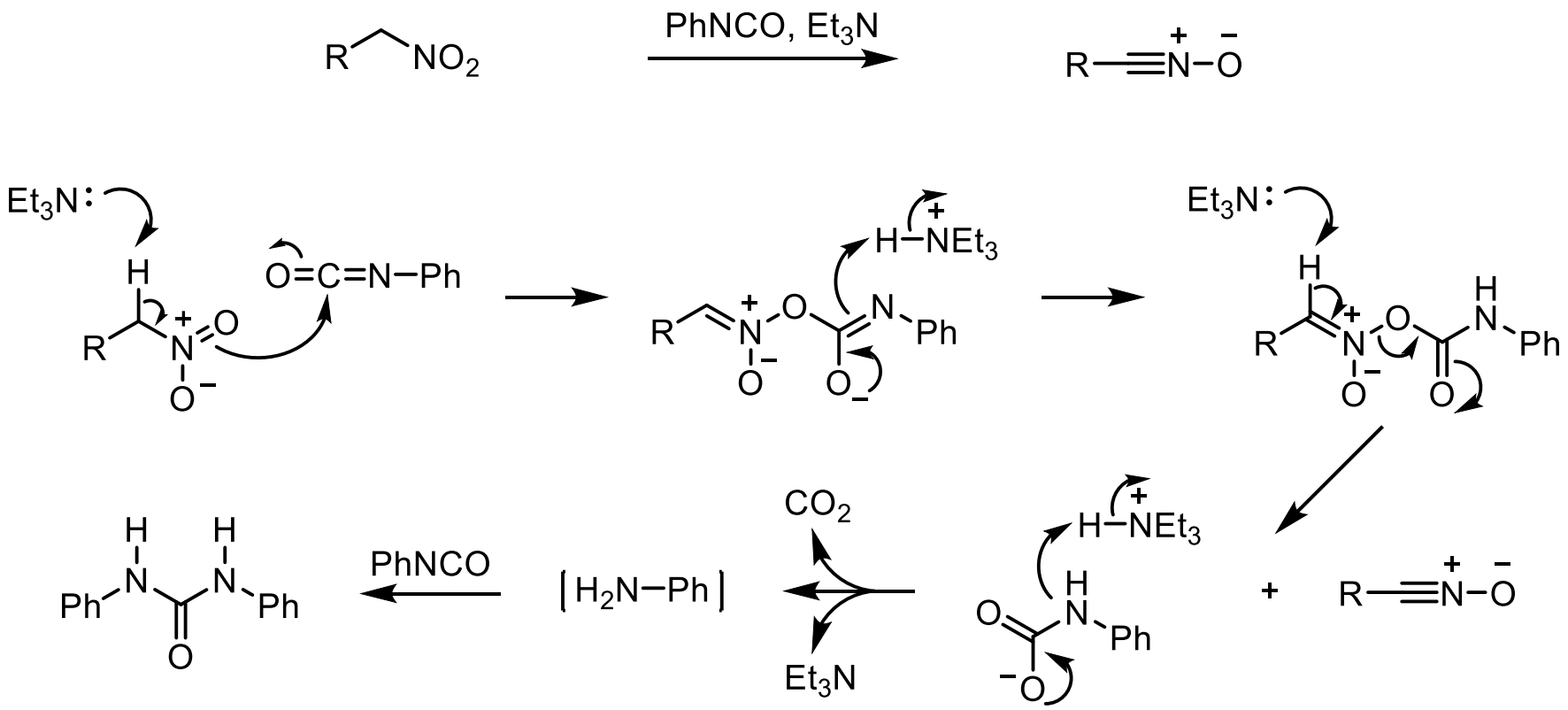



David Y.-K. Chen, et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 12277-12281

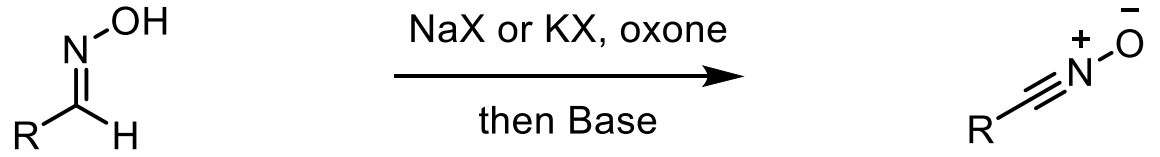
*Mechanism & Supplement*

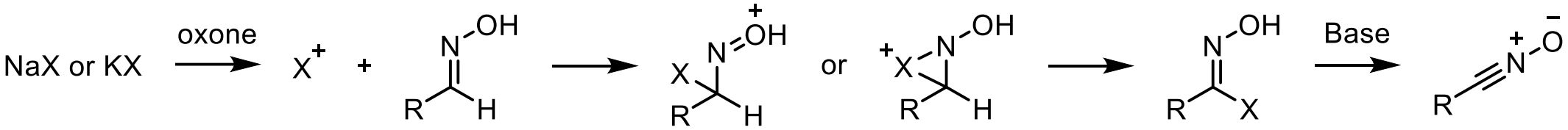
# Summary: *The Tranformations of Nitrile Oxides in 1,3-DPCA*



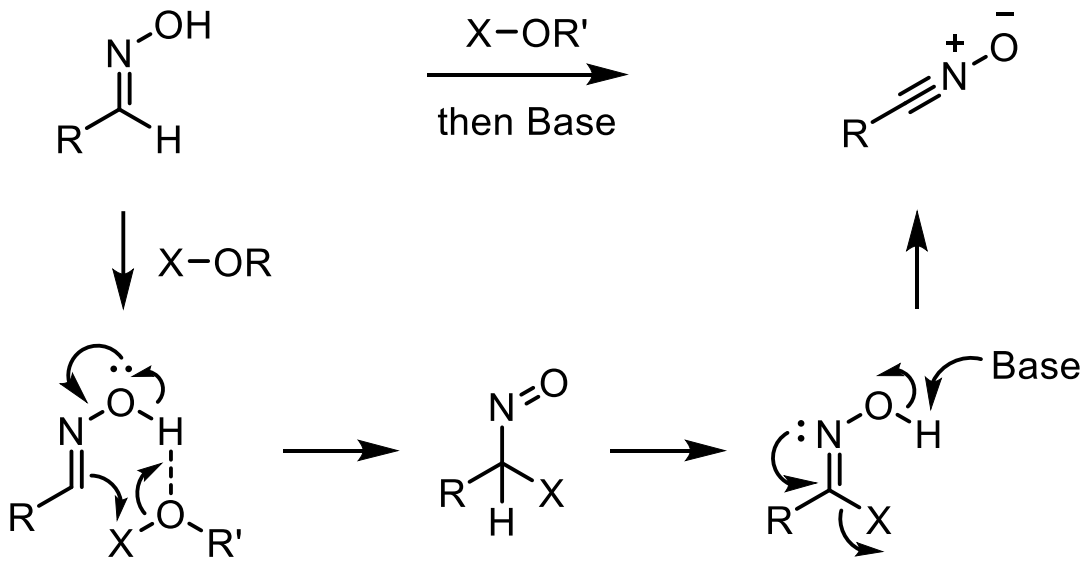



Teruaki Mukaiyama, et al. *J. Am. Chem. Soc.* **1960**, *20*, 5339-5342

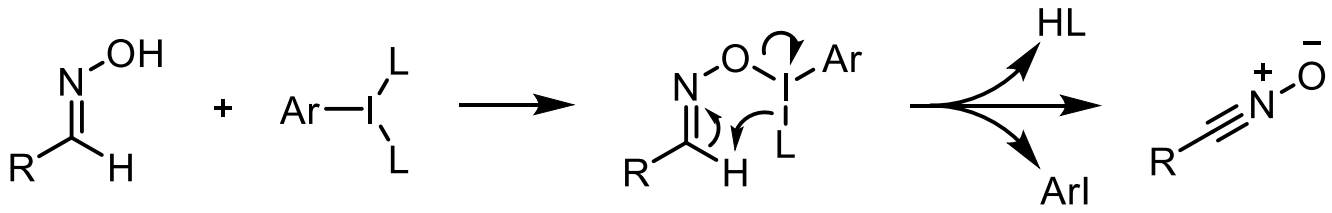



Rongbiao Tong, et al. *Org. Lett.* **2019**, *21*, 315-319




Satoshi Minakata, et al. *Org. Lett.* **2011**, *13*, 2966-2969.

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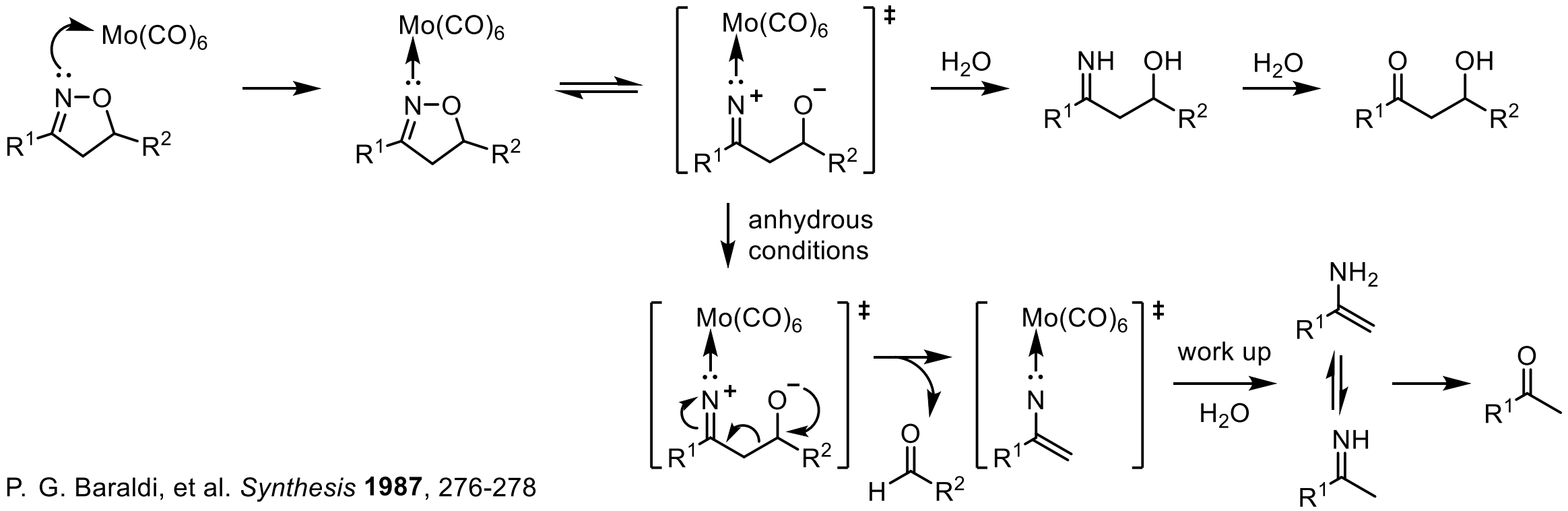


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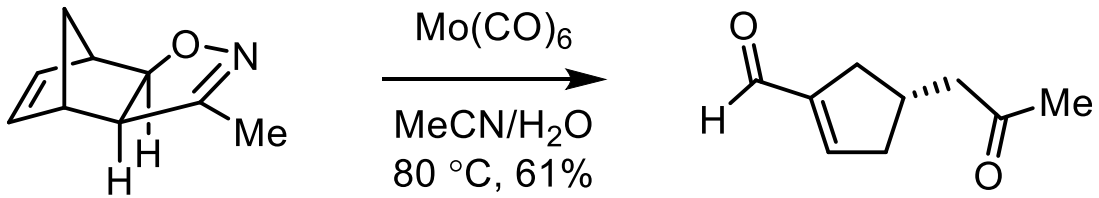
*Example*

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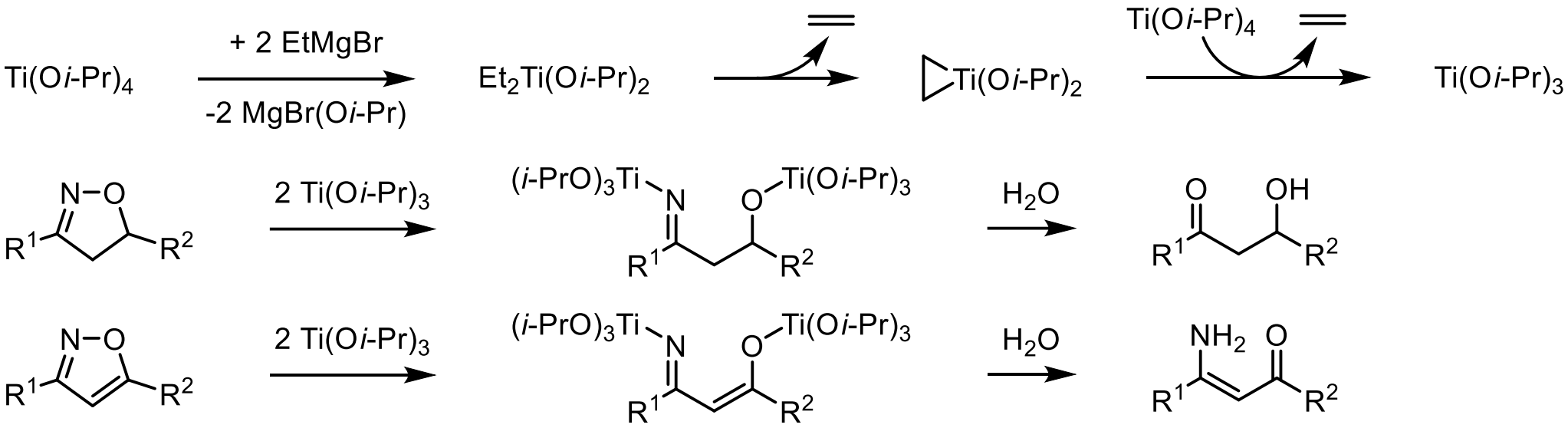


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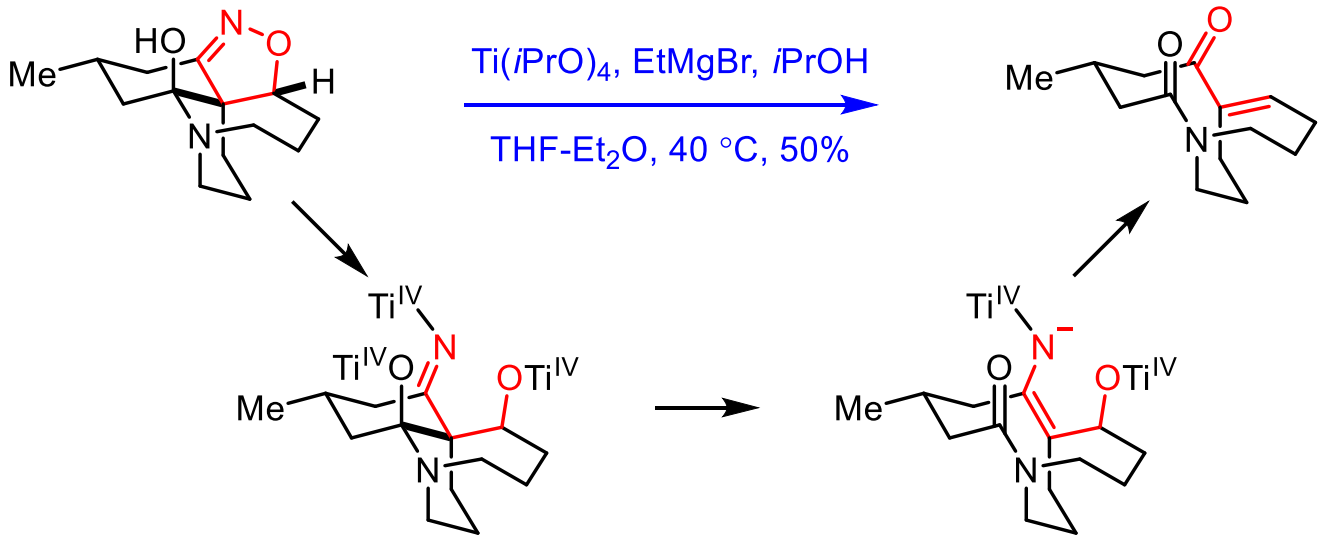

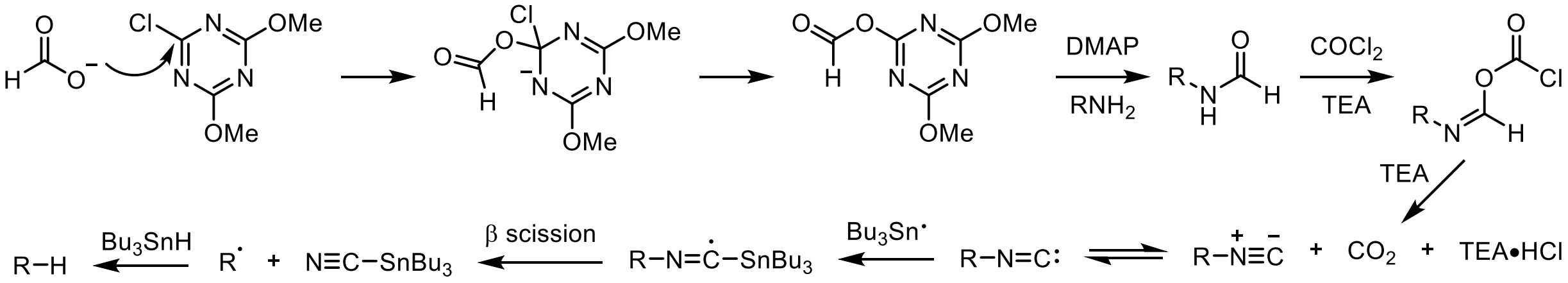


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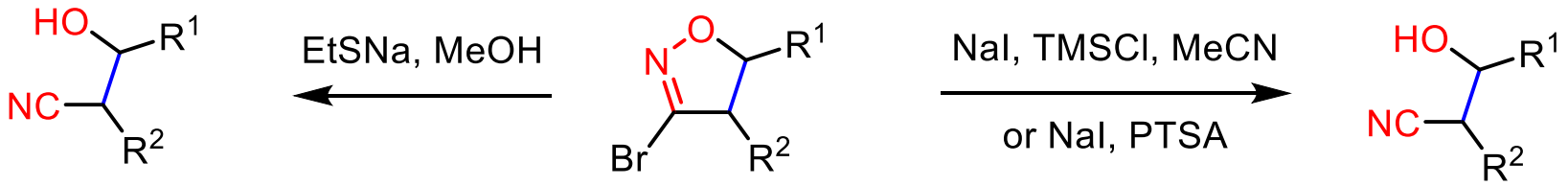


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# *Group Seminar*

*That is all, thanks*

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