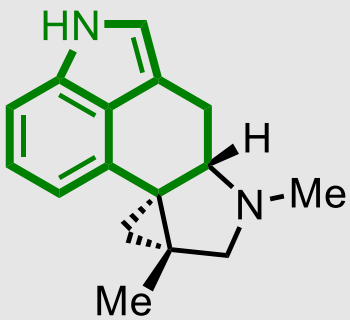
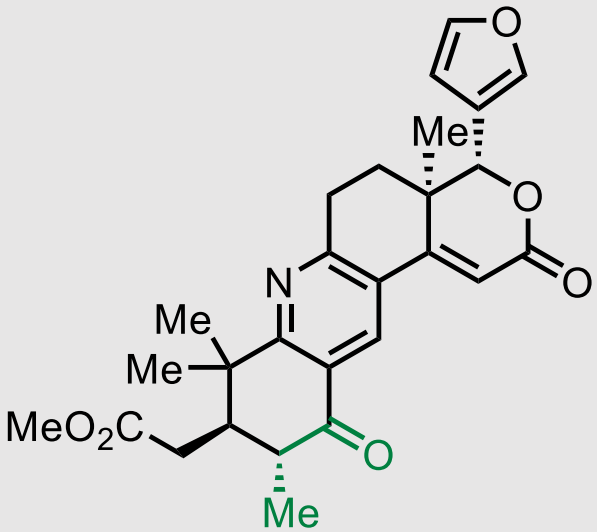
Carbon-Carbon Bond Functionalization Enabled by Transition-Metal Catalysts

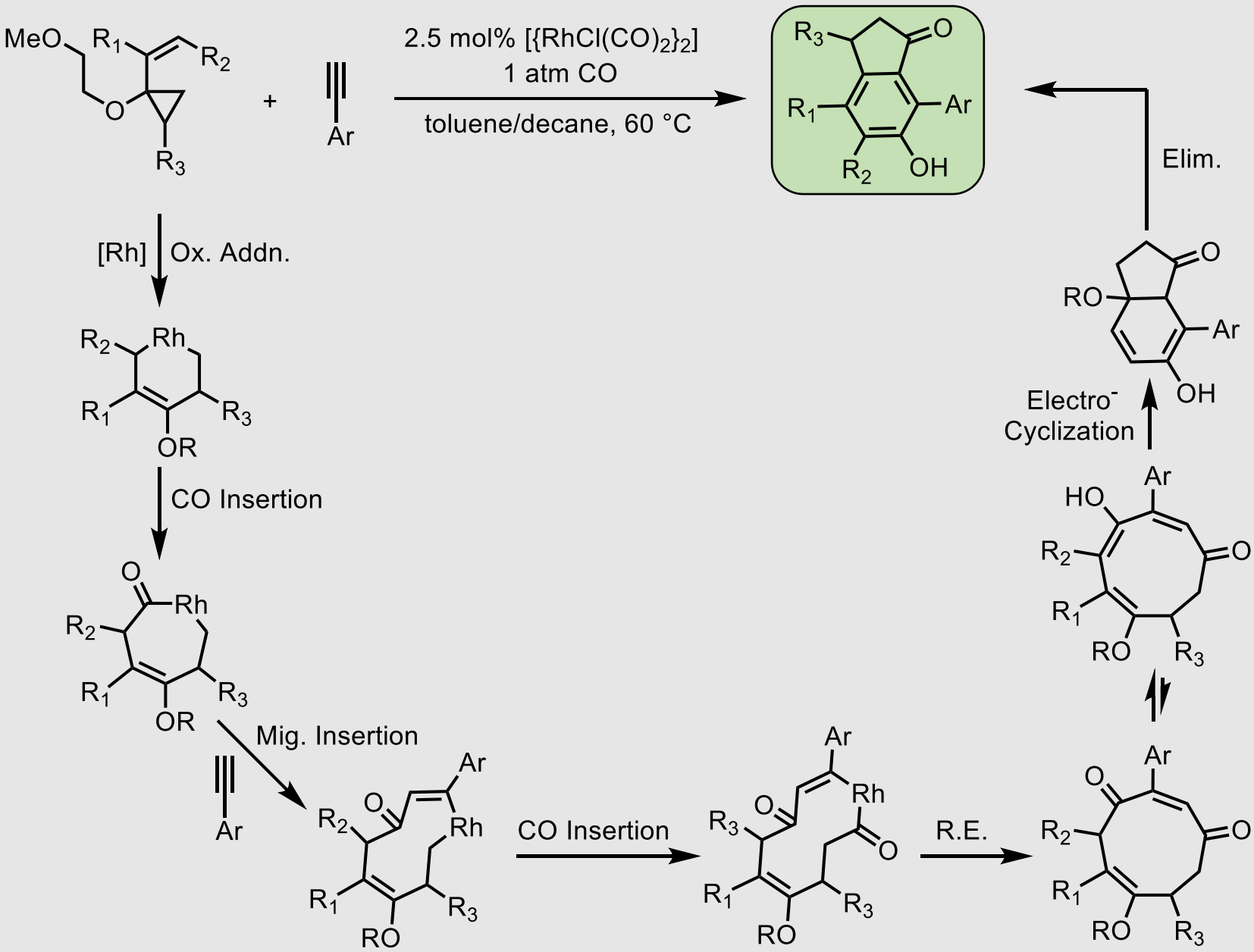




Vincent Kassel

10-26-2021

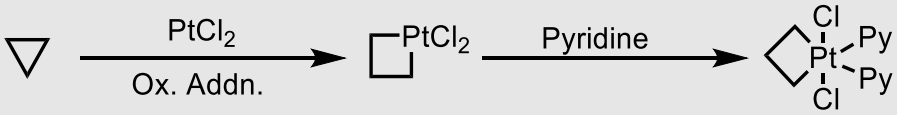
Inspiring Creativity



Wender, P. et al. *J. Am. Chem. Soc.* 2005, 127, 9, 2836−2837

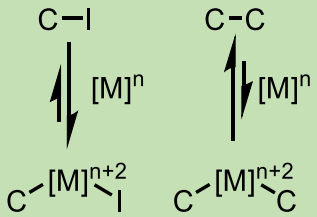
C-C Bond Activation Fundamentals

Isolation of First Metallocyclobutane from Direct C-C Activation



Tipper, C. *J. Chem. Soc.* **1955**, 2043.

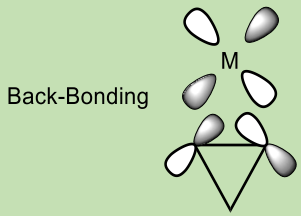
Thermodynamic Challenges With C-C Bond Activation



"Bond energies of C—C σ-bonds are often much larger than those of metal-carbon (M—C) bonds"

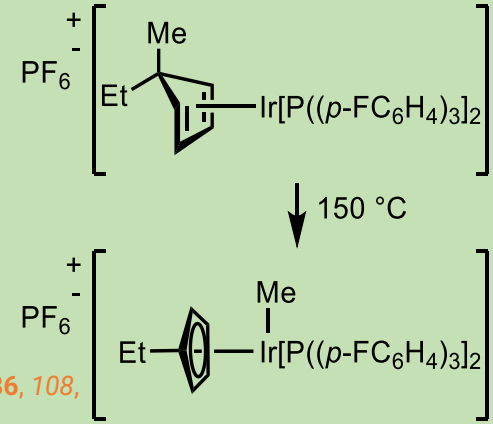
Murakami, M. *J. Am. Chem. Soc.* **2016**, *138*, 13759.

Ring Strain



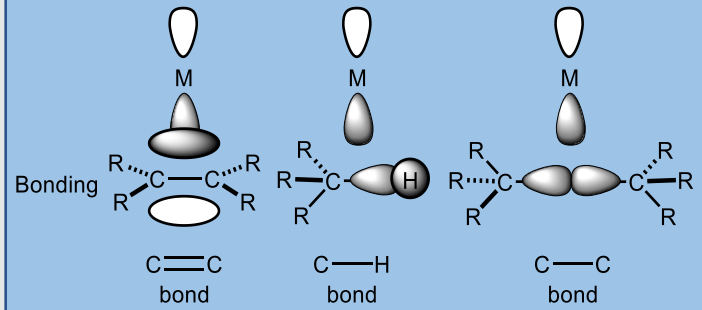
Ring Strain ~29.0 kcal/mol

Aromatization



Crabtree, R. *J. Am. Chem. Soc.* **1986**, *108*, 7222.

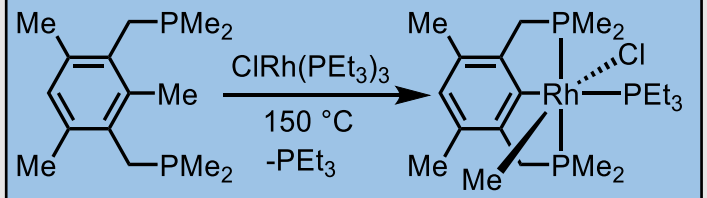
Kinetic Challenges With C-C Bond Activation



"The σ-orbital of a C—C single bond possesses high directionality along the bond axis. Moreover, there are several substituents on both ends, which sterically prevent the approach of metal orbitals."

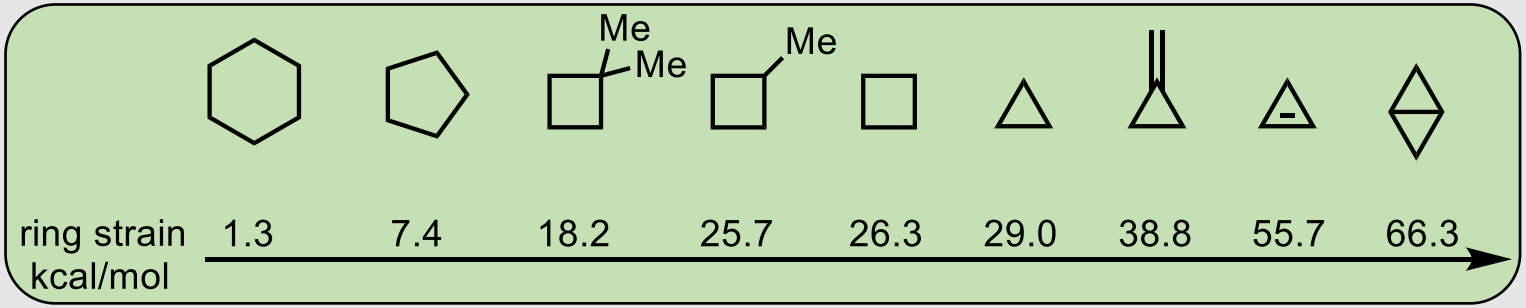
Murakami, M. *Cleavage of C-C Single Bonds by Transition Metals*, **2016**.

Directing Group Phenomena



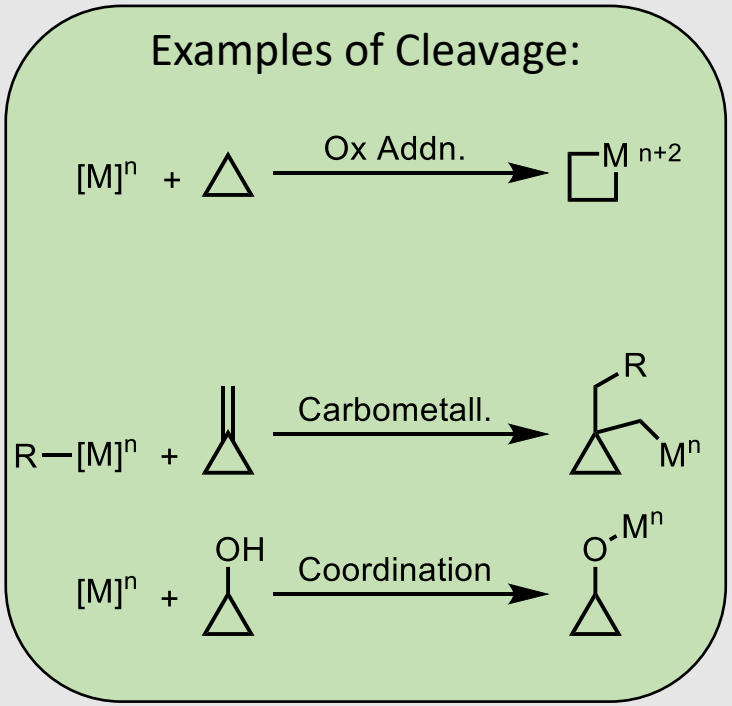
Milstein, D. *J. Am. Chem. Soc.* **1995**, *117*, 9774.

Common Modes of C-C Bond Cleavage

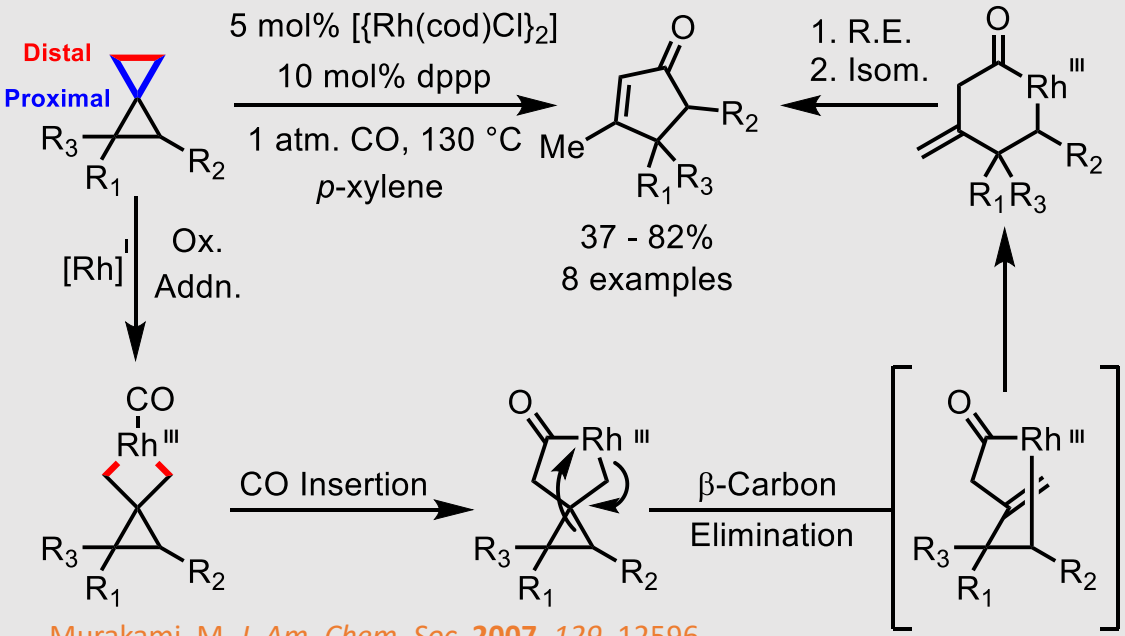


Cramer, N. *Chem. Rev.* **2015**, *115*, 9410.

Examples of Cleavage:

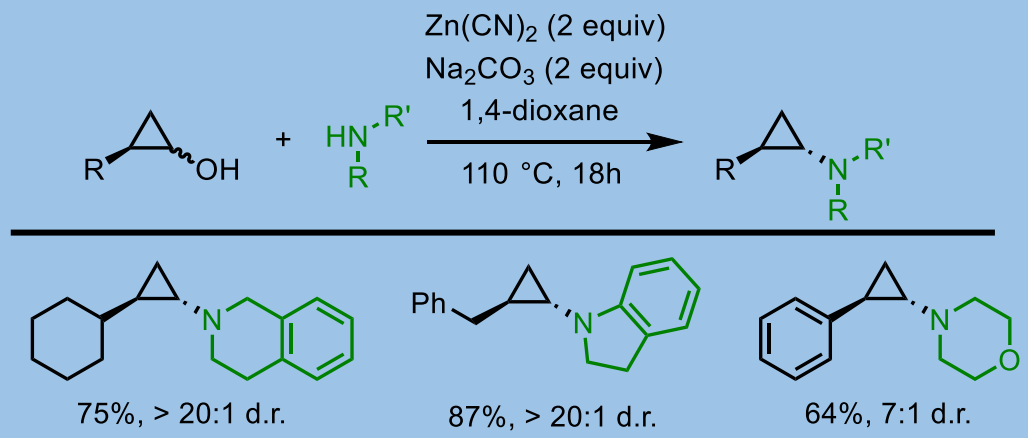


Cramer, N. *Chem. Rev.* **2015**, *115*, 9410.



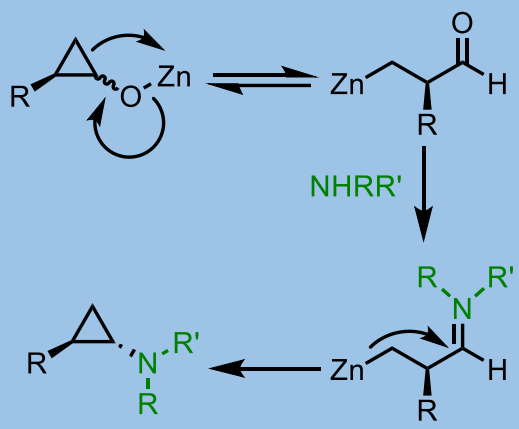
Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12596.
Cramer, N. *Chem. Rev.* **2015**, *115*, 9410.

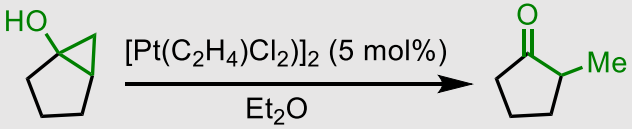
Cyclopropanol C-C Bond Cleavage Examples



Rousseaux, S. et al. *J. Am. Chem. Soc.* **2017**, 139, 9, 11357.

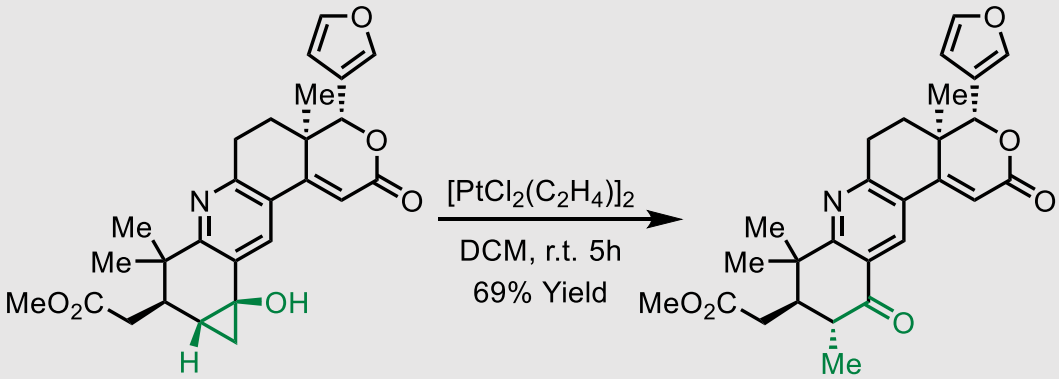
Likely Mechanism





65 - 85%

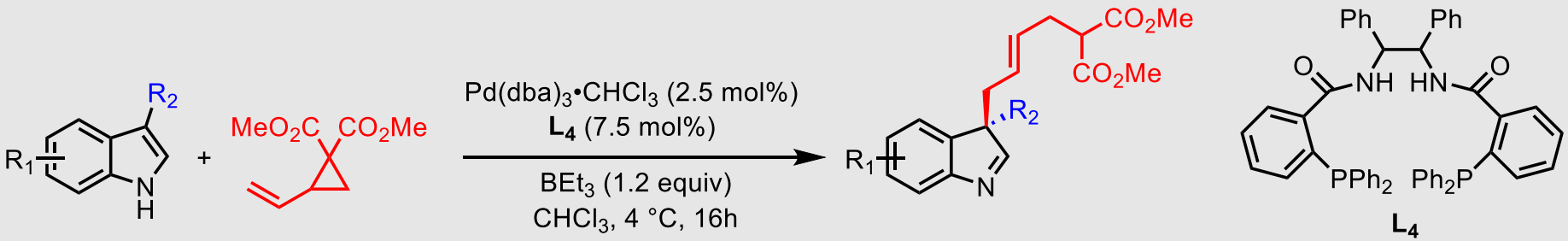
Jennings, P. *Organometallics*, **1996**, *15*, 3902.

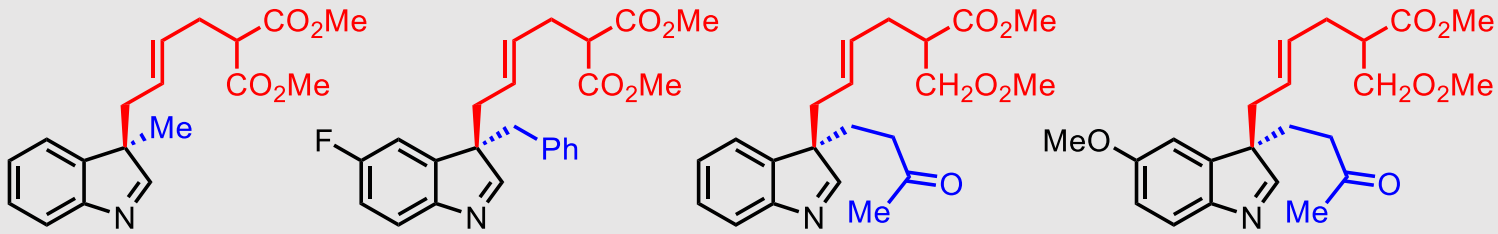


xylogranatopyridine B

Newhouse, T. *J. Am. Chem. Soc.*, **2018**, *140*, 2062.

Vinyl Cyclopropane (VCP) Reactivity



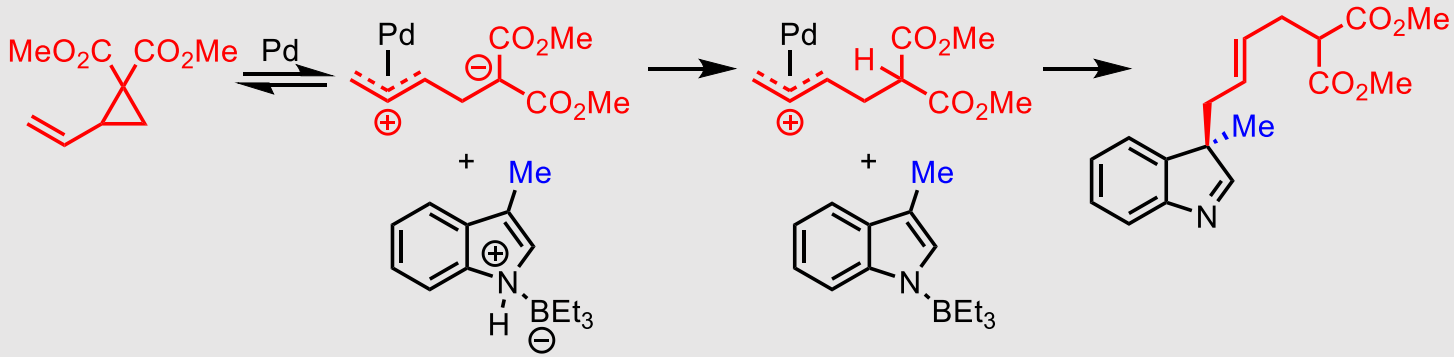


93% Yield
96:4 e.r.

90% Yield
99:1 e.r.

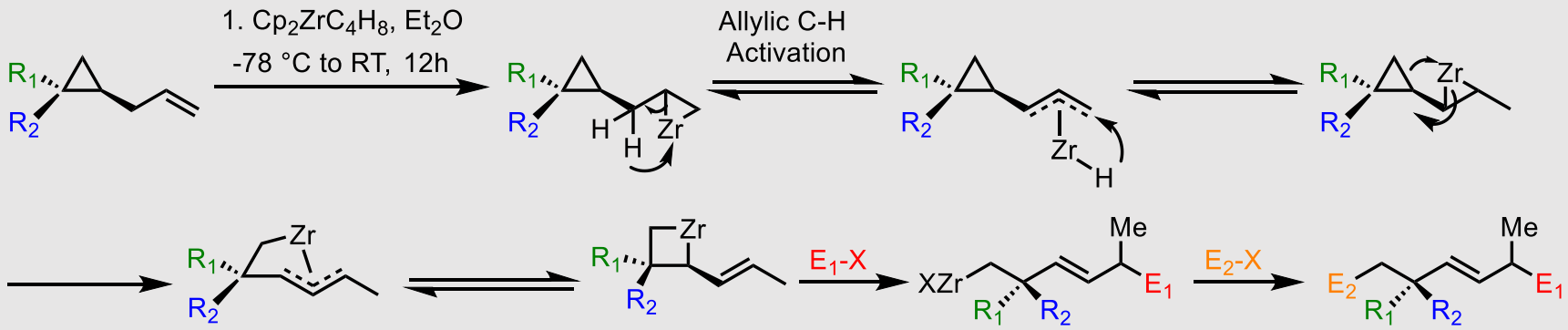
96% Yield
96:4 e.r.

92% Yield
95:5 e.r.

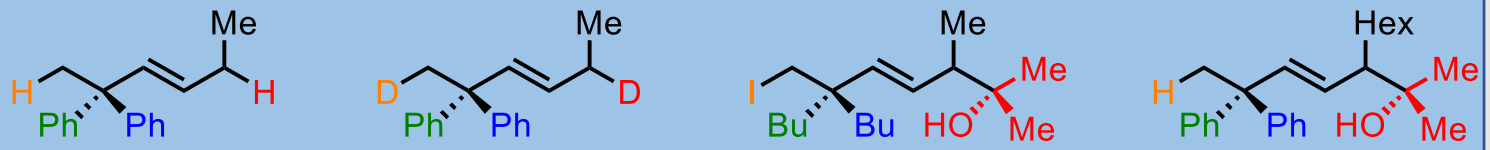


Trost, B. J. Am. Chem. Soc. **2018**, *140*, 6710.

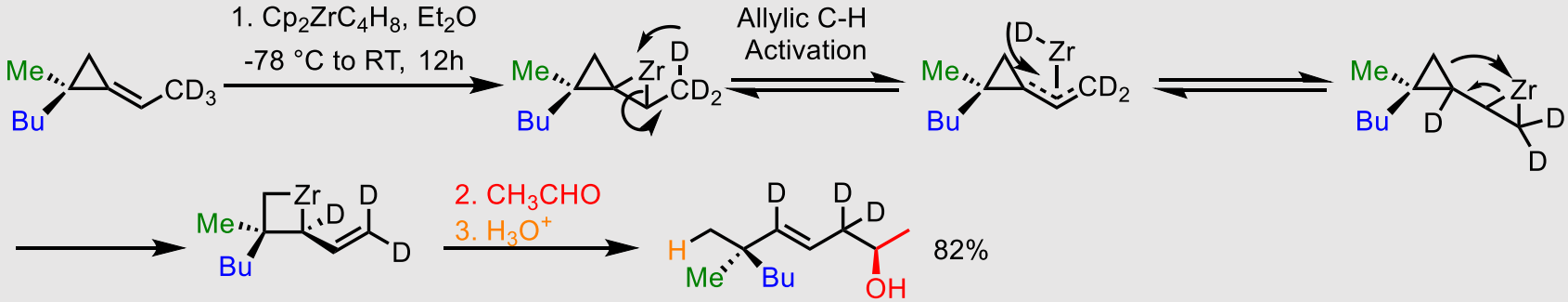
Approaches to Acyclic Quaternary Carbons



Substrate Examples:

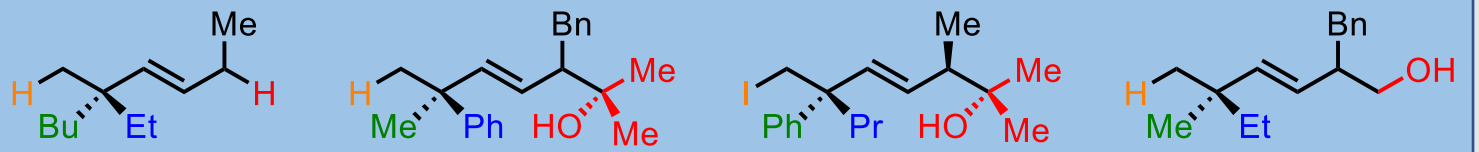


71% 71% 53% 55%



82%

Substrate Examples:

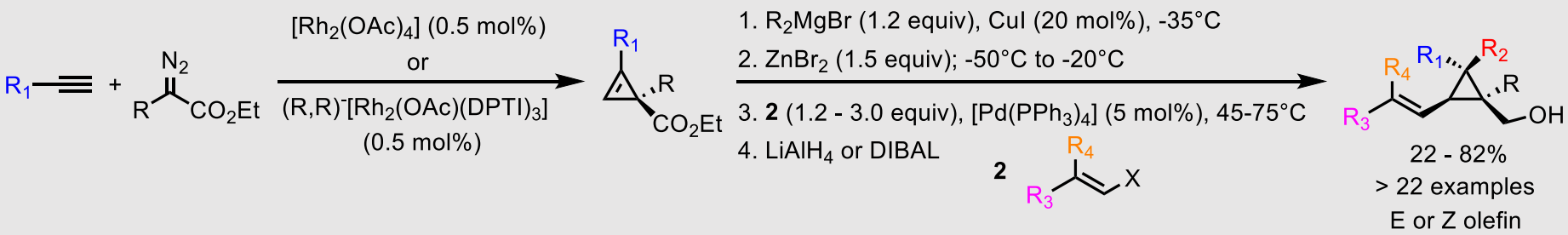


84% 92% 62% 90%

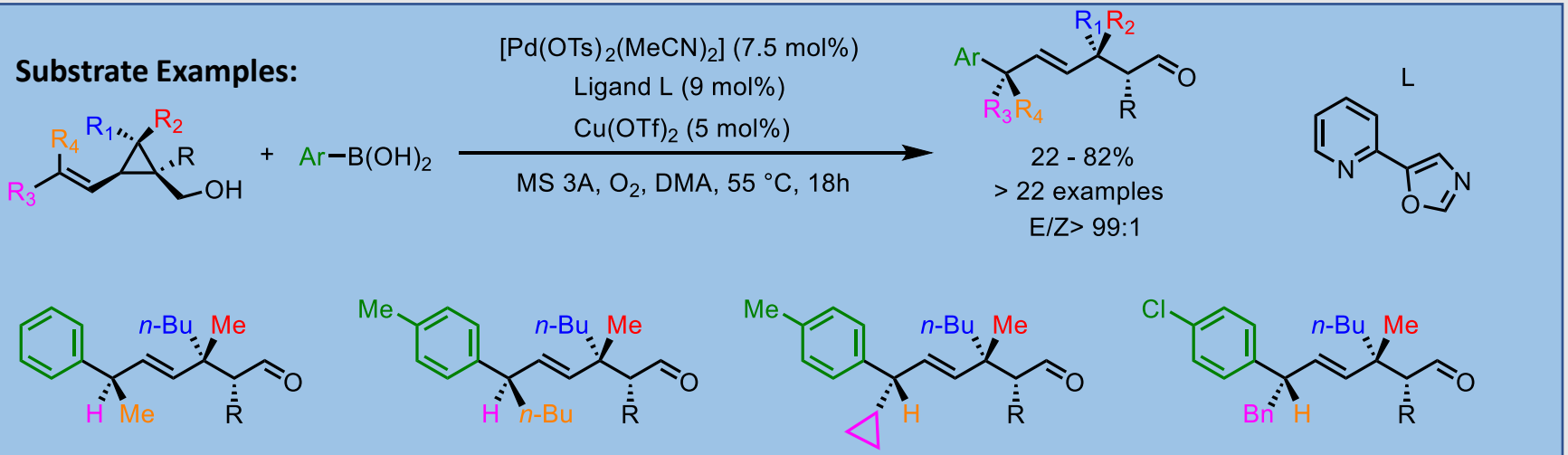
98:2 e.r. 97:3 d.r.

Marek, I. Nature **2014**, *505*, 199.

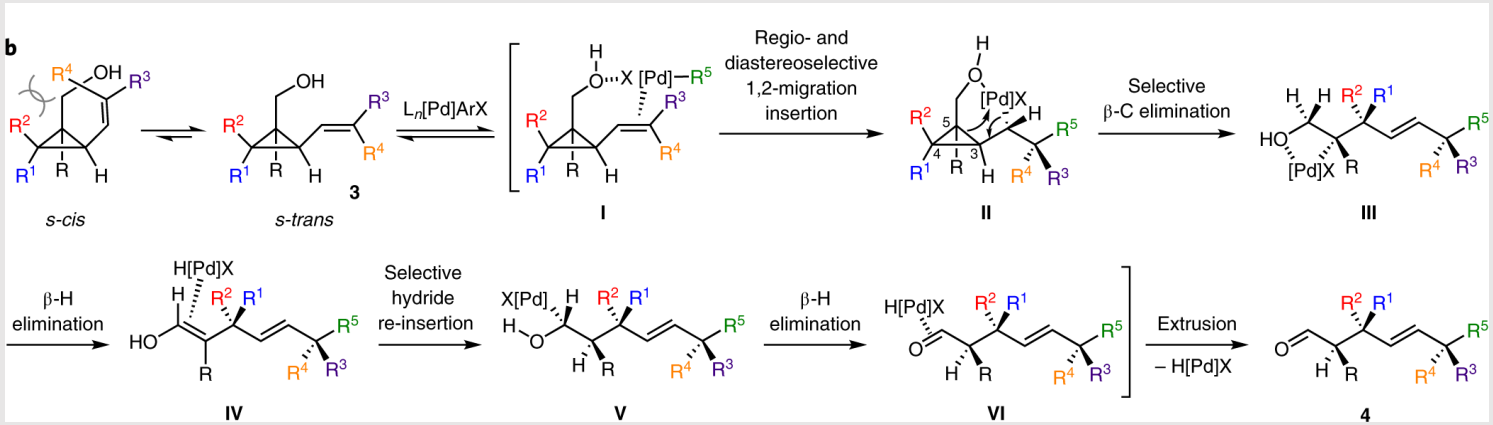
Approaches to Acyclic Quaternary Carbons



Substrate Examples:

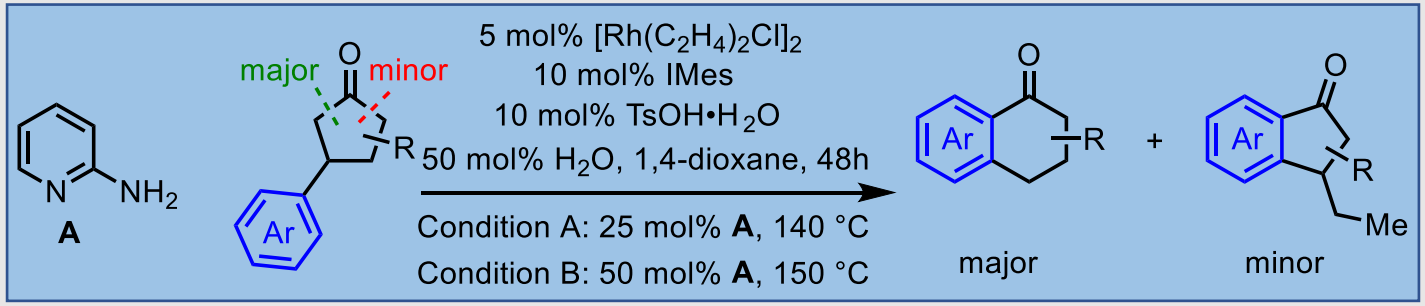


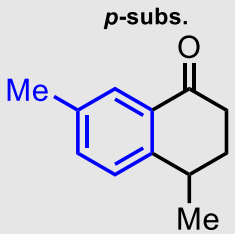
Rationale:

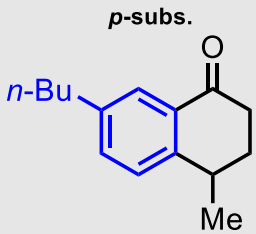


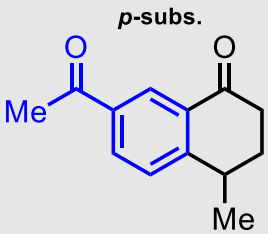
Marek, I. Nat. Chem. **2018**, *10*, 1164.

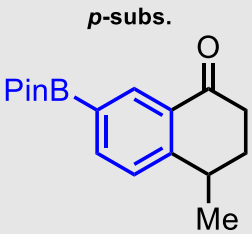
Catalytic Activation of Unstrained Cyclopentanones

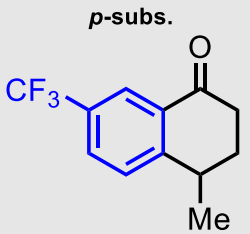


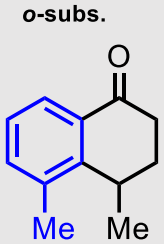


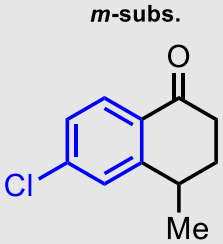


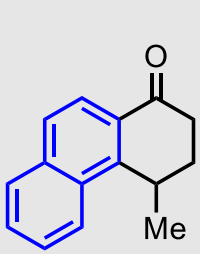


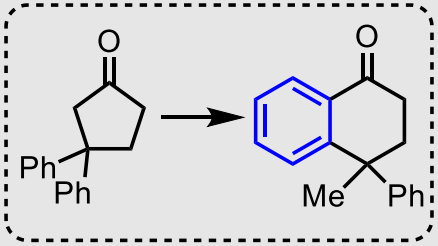


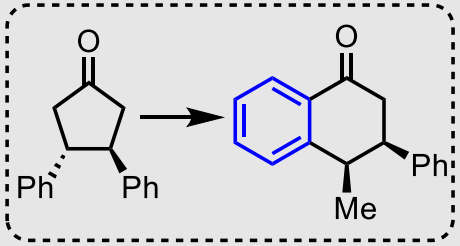


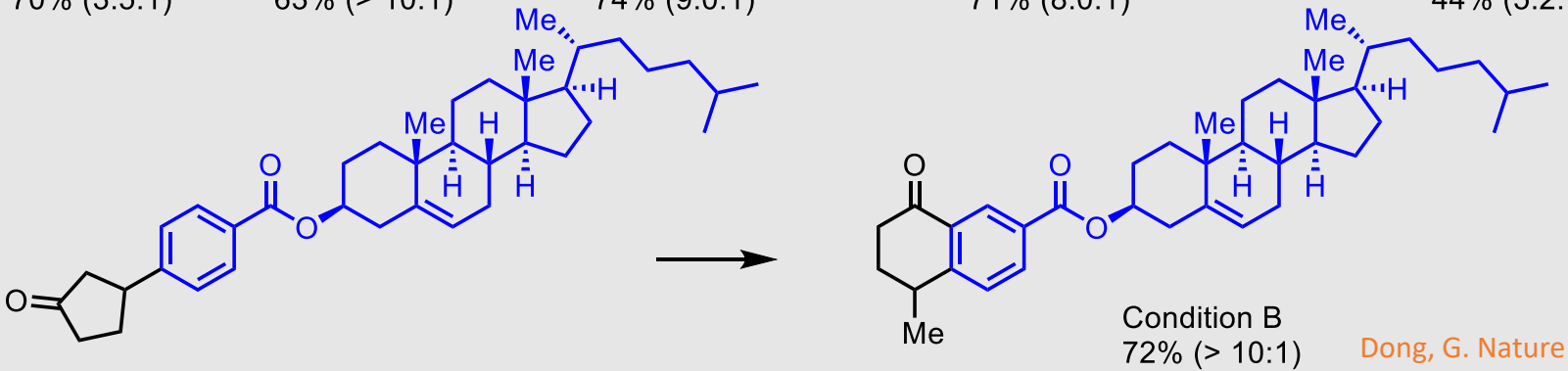






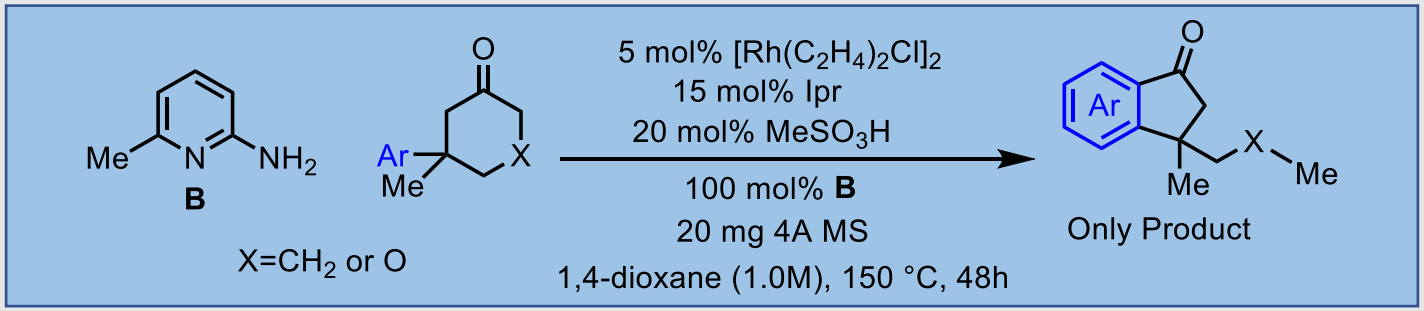


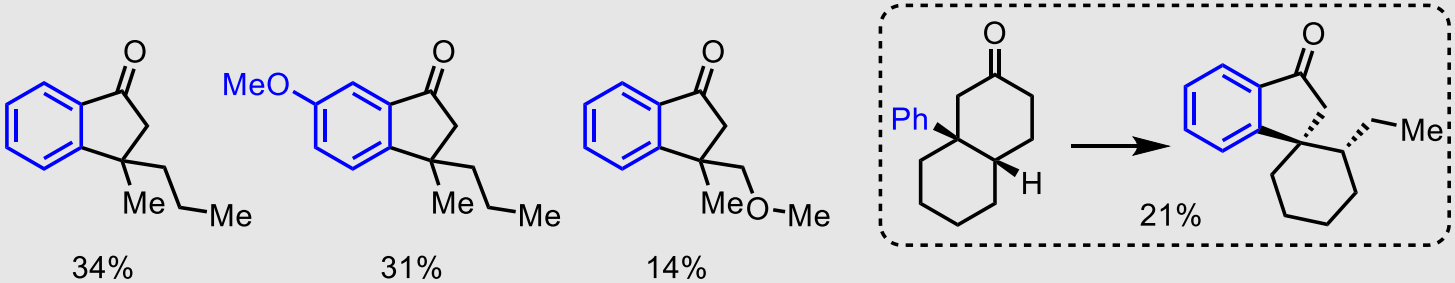


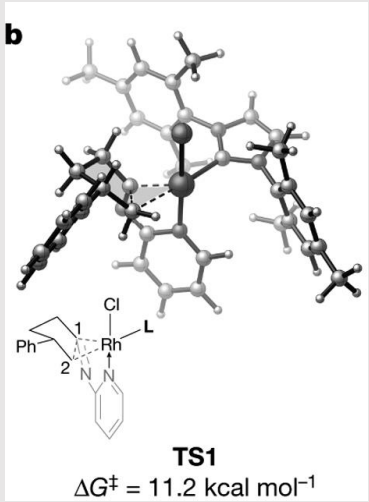


Dong, G. Nature **2016**, *539*, 546.

Catalytic Activation of Unstrained Cyclopentanones







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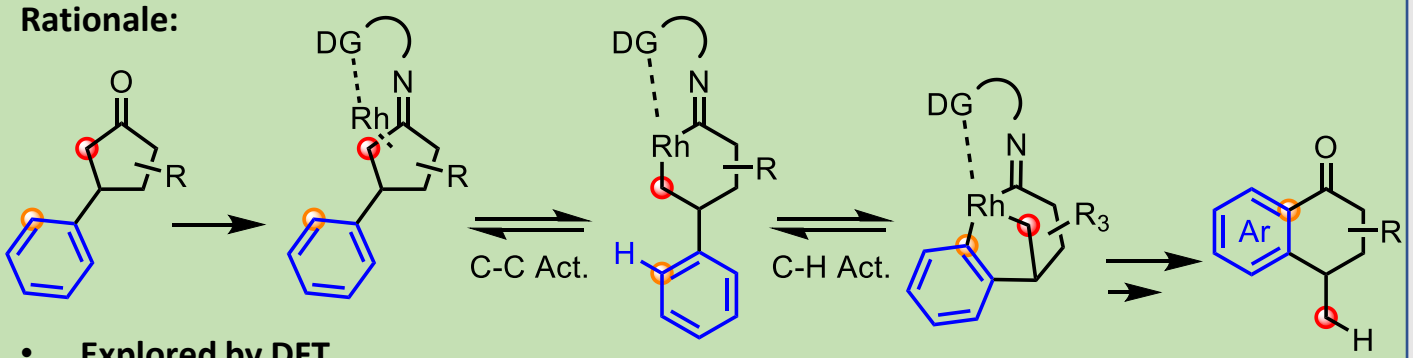
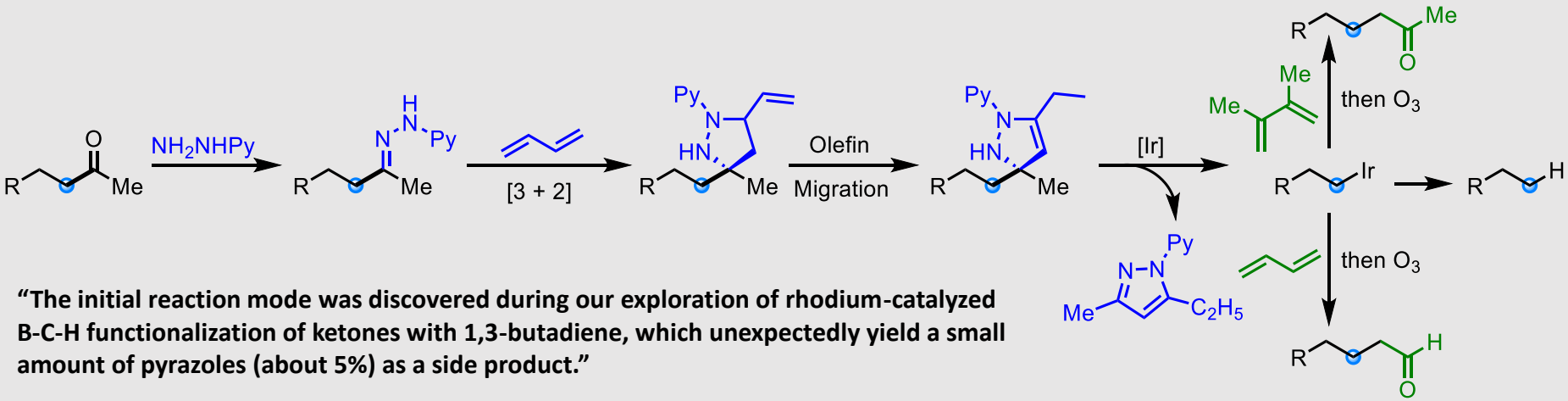


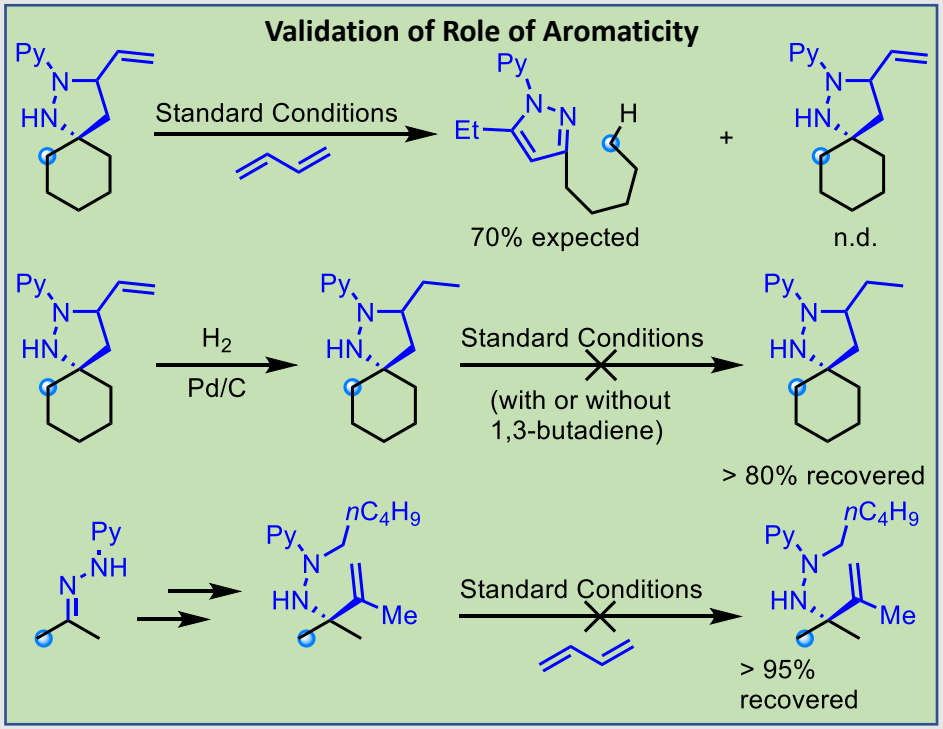
- **Explored by DFT**
- **Alkyl to aryl ketone is ~ ΔG=-6 kcal/mol**
- **Regioselectivity determined by C-H activation**

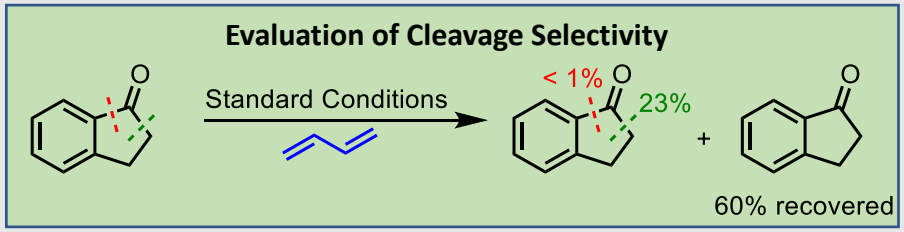
Dong, G. Nature **2016**, *539*, 546.

Deacylative Transformations of Unactivated Ketones



"The initial reaction mode was discovered during our exploration of rhodium-catalyzed B-C-H functionalization of ketones with 1,3-butadiene, which unexpectedly yield a small amount of pyrazoles (about 5%) as a side product."

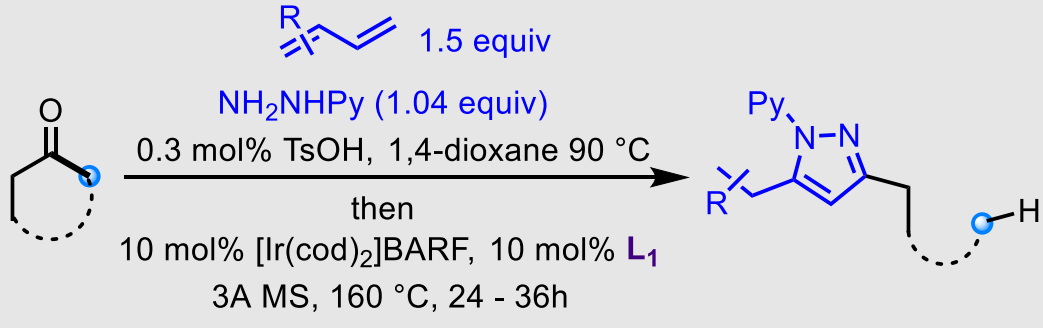


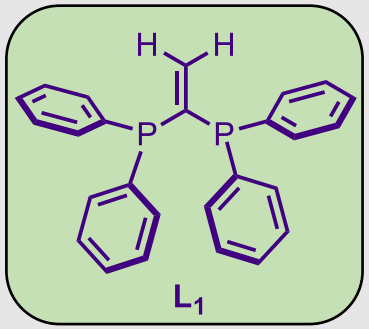


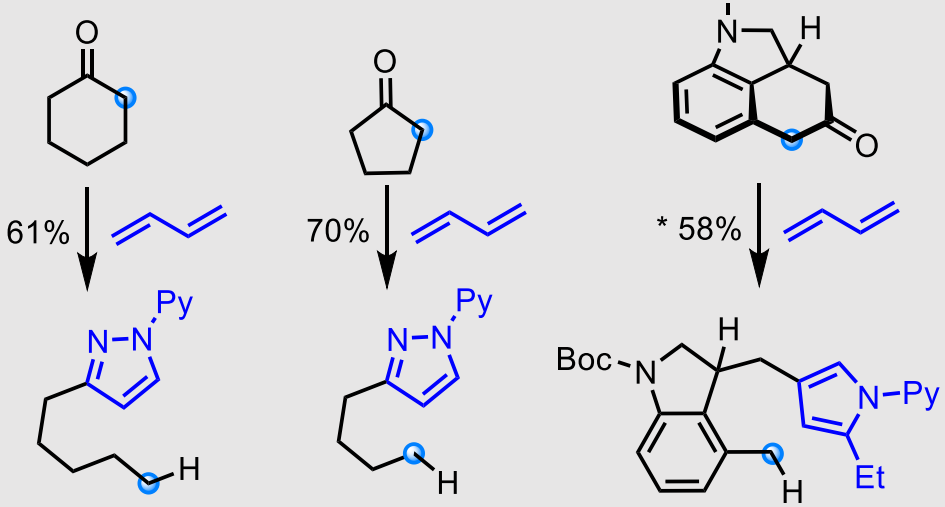
Dong, G. Nature **2019**, *567*, 373.

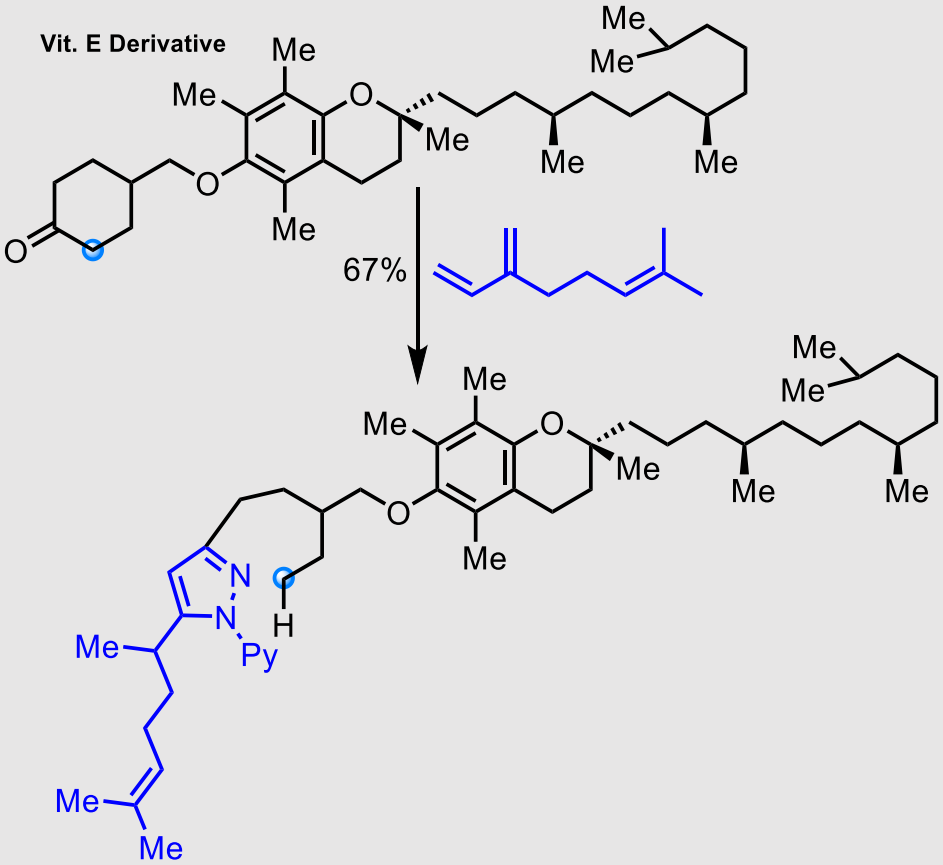
Deacylative Transformations of Unactivated Ketones

Pyrazole Synthesis from Cyclic Ketones

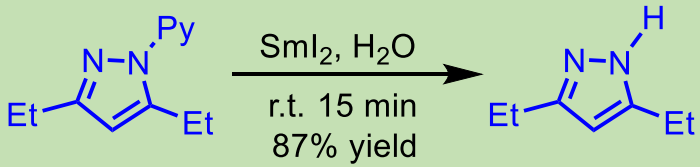






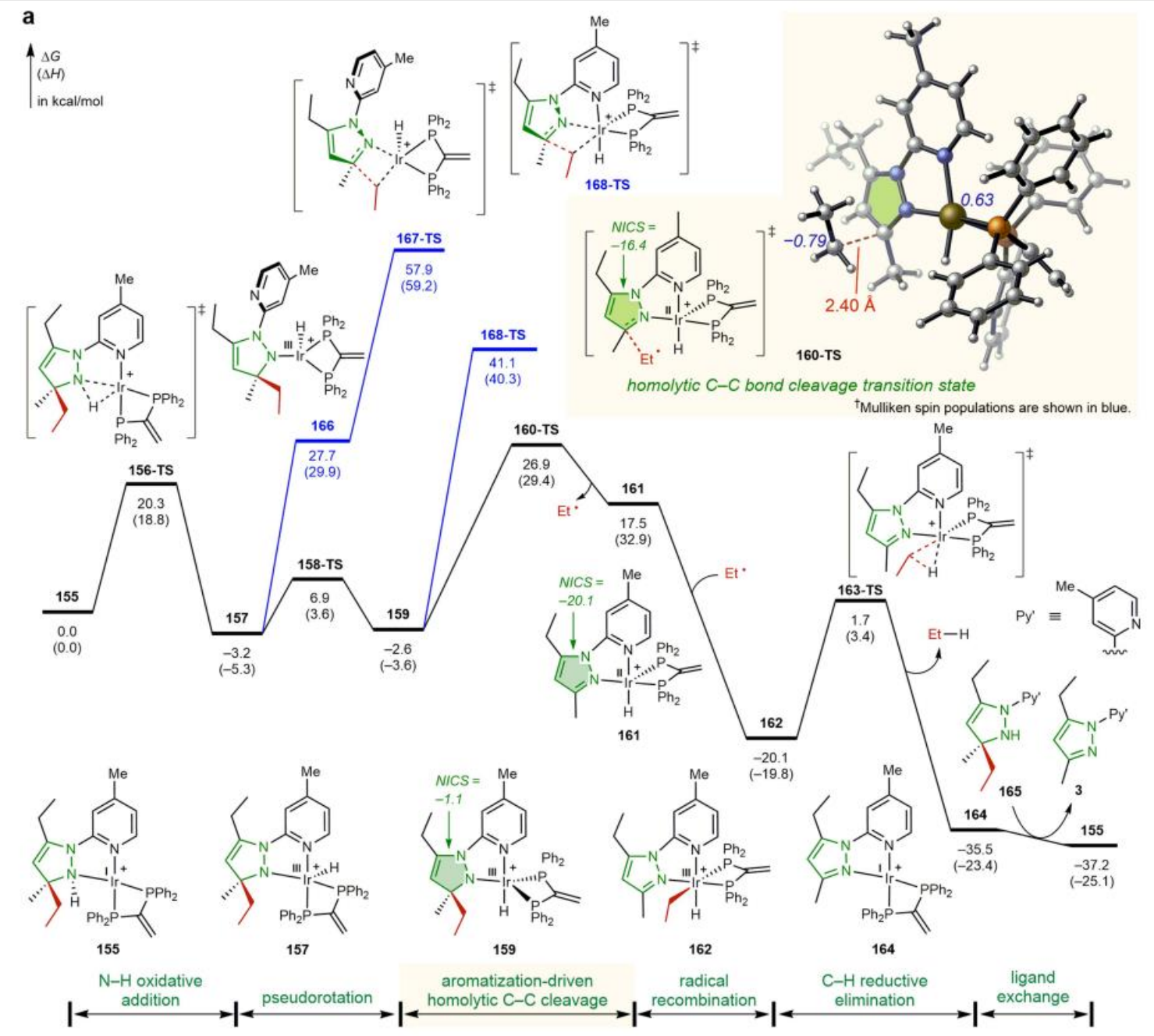


Pyrazole Deprotection



Dong, G. Nature **2019**, *567*, 373.

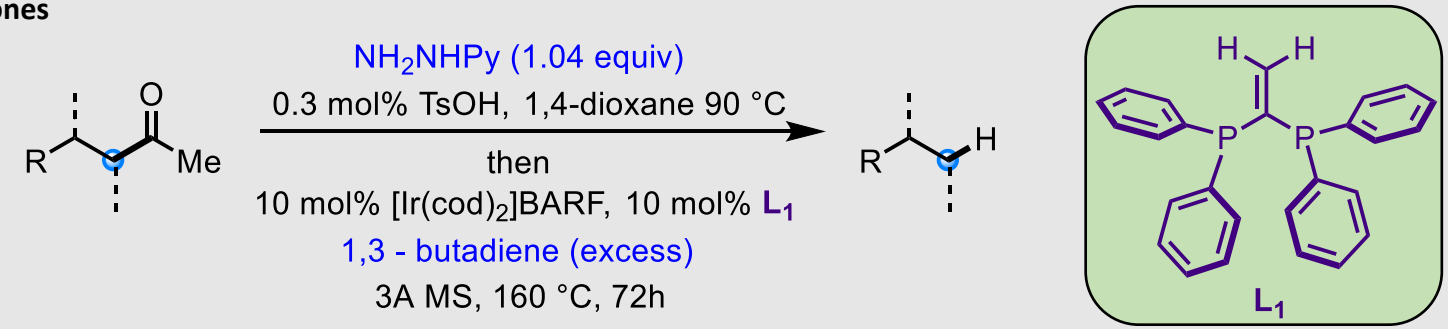
Deacylative Transformations of Unactivated Ketones

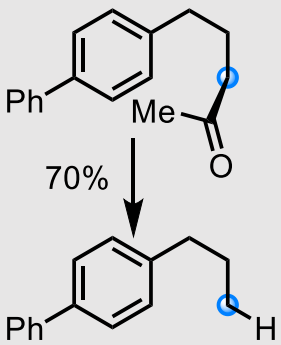


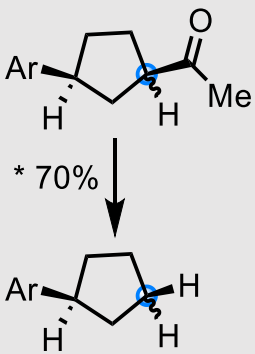
Dong, G. Nature **2019**, *567*, 373.

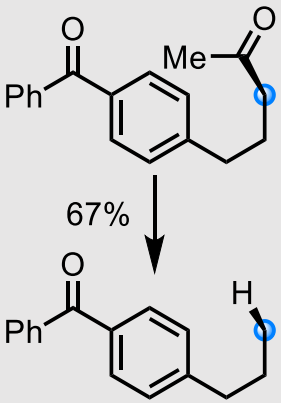
Deacylative Transformations of Unactivated Ketones

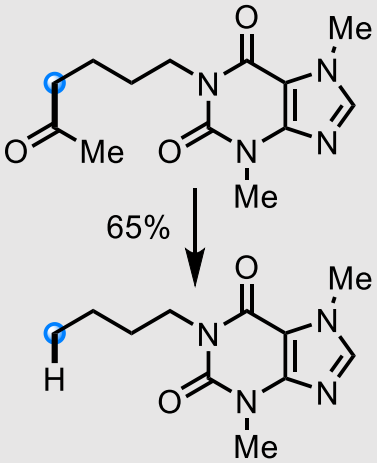
Deacylation of Methyl Ketones

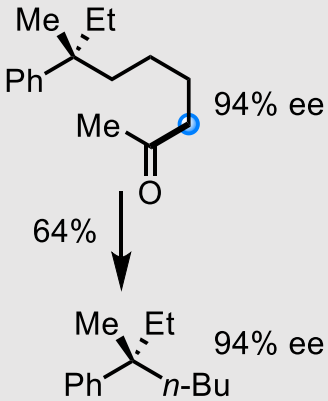


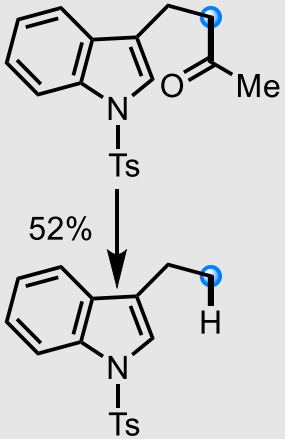








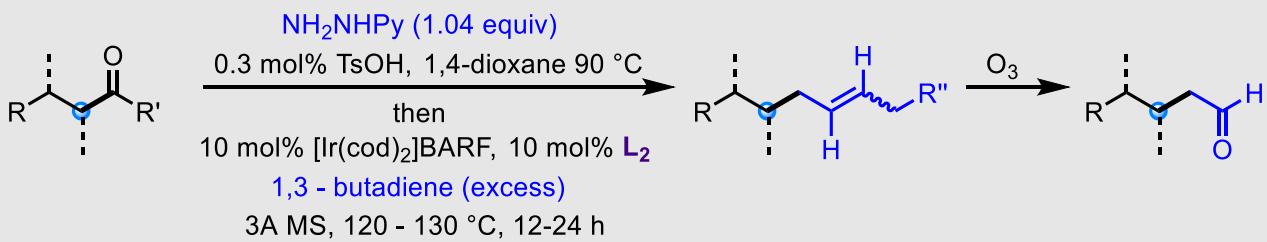


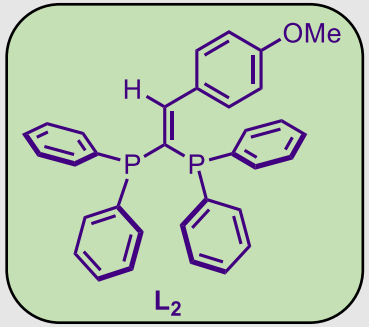


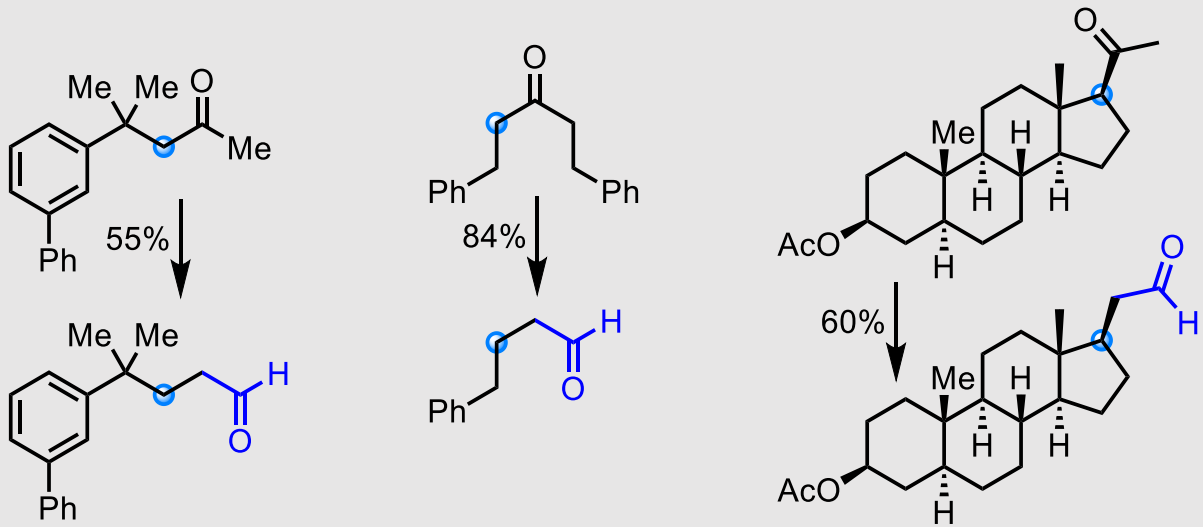
Dong, G. Nature **2019**, *567*, 373.

Deacylative Transformations of Unactivated Ketones

Formal 1,2-Oxo Migration

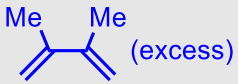


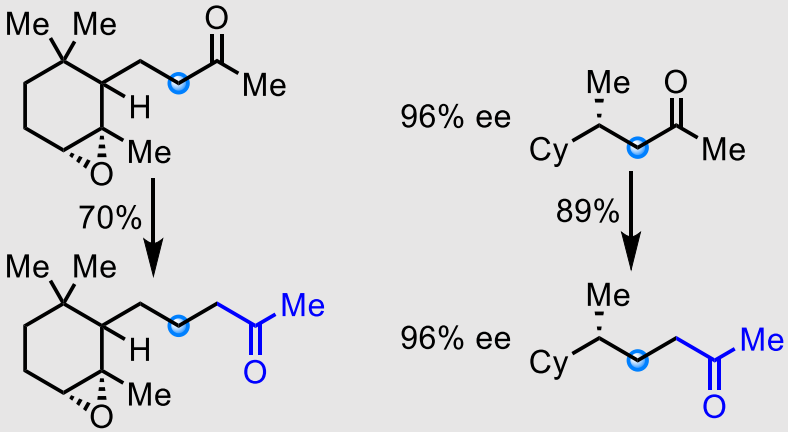




Homologation of Methyl Ketones

From:



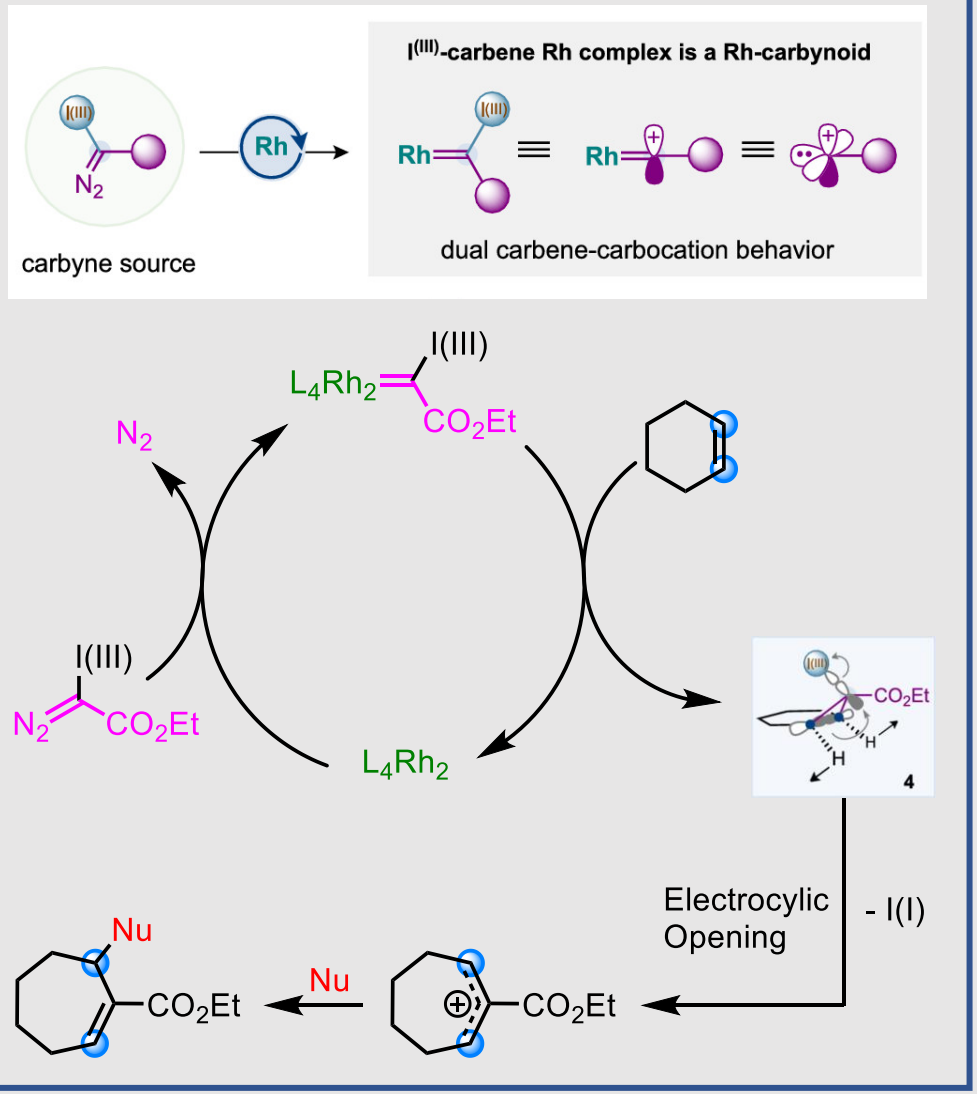


Dong, G. Nature **2019**, *567*, 373.

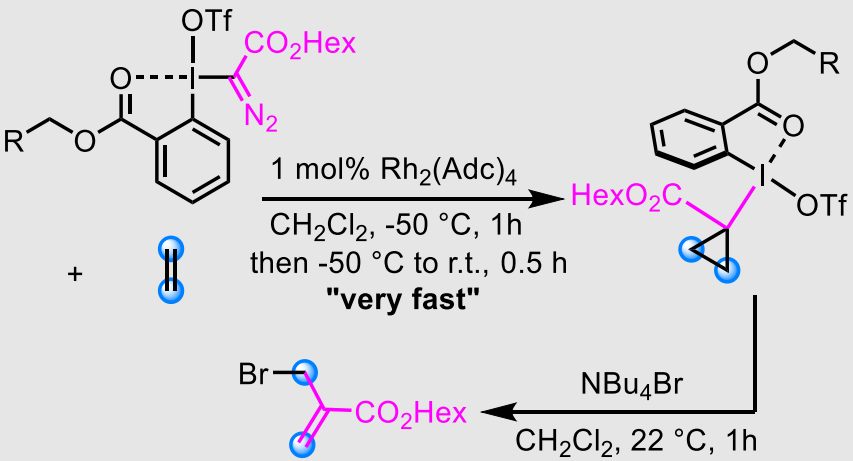
Olefin Activation by Rh Carbynoids

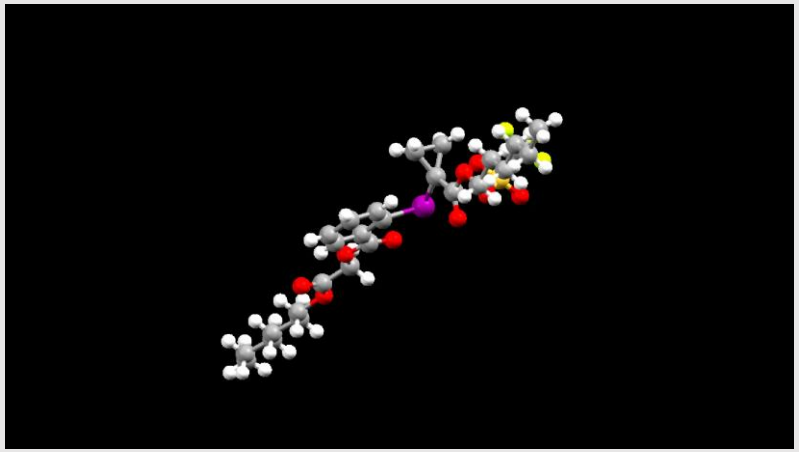
***Not formally TM-promoted cleavage, but fascinating!**

Proposed Activation



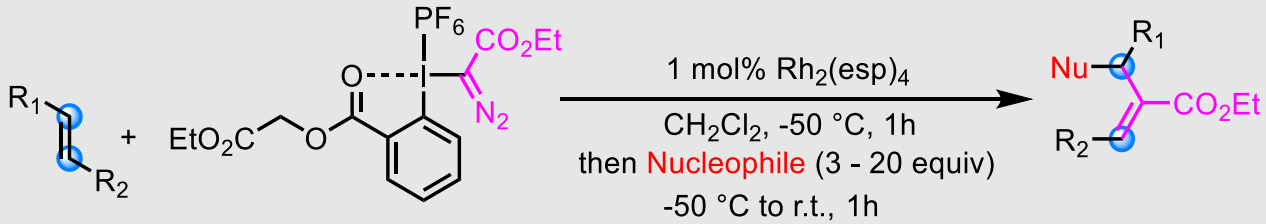
Isolation of Key Intermediate

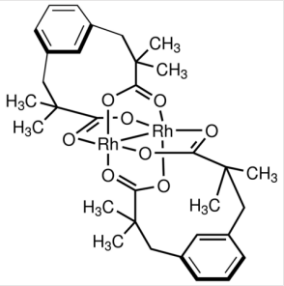




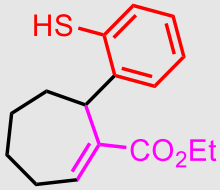
Suero, M. et al. J. Am. Chem. Soc. **2019**, *141*, 15509.

Olefin Activation by Rh Carbynoids

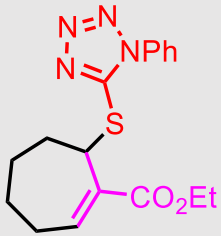




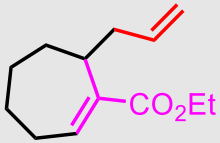
From Cyclohexenes



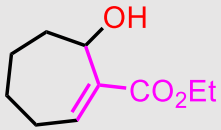
85%
with thiophenol



85%
with tetrazole thiol

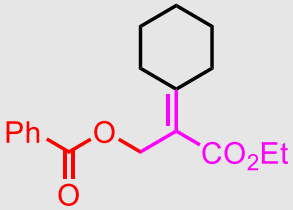


94%
with allyl-$SnBu_3$



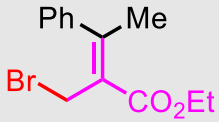
64%
with H_2O

From Methylene-Cyclohexane



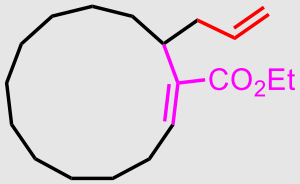
62%, L:B= 4:1
with Bu_4NO_2CPh

From α-Me Styrene

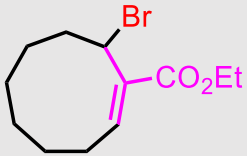


72%, L:B > 20:1
14:1 Z:E
with NBu_4Br

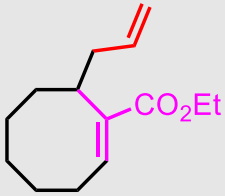
From Larger Cycloalkenes



51%; 1.7:1 Z:E
with allyl-$SnBu_3$

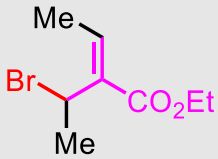


48%
with NBu_4Br



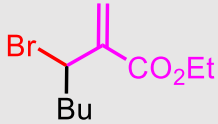
54%
with allyl-$SnBu_3$

From (E)-2-Butene



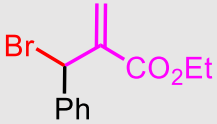
70%, 10:1 Z:E
with NBu_4Br

From 1-Hexene



88%, L:B = 7:1
3:1 Z:E
with NBu_4Br

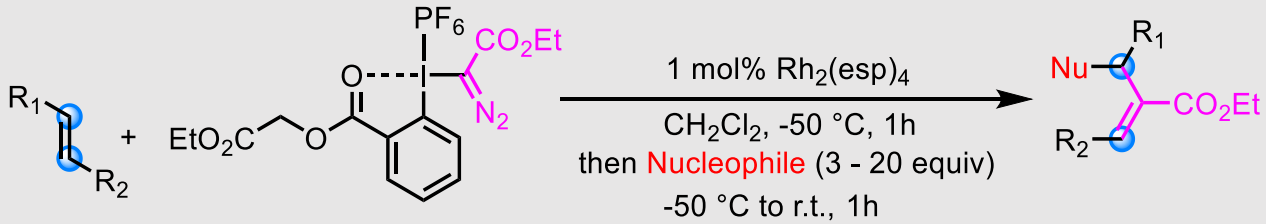
From Styrene

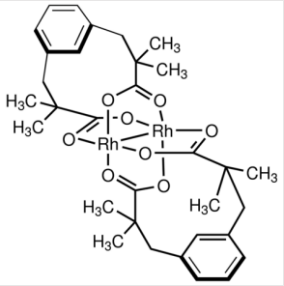


98%, L:B > 20:1
10:1 Z:E
with NBu_4Br

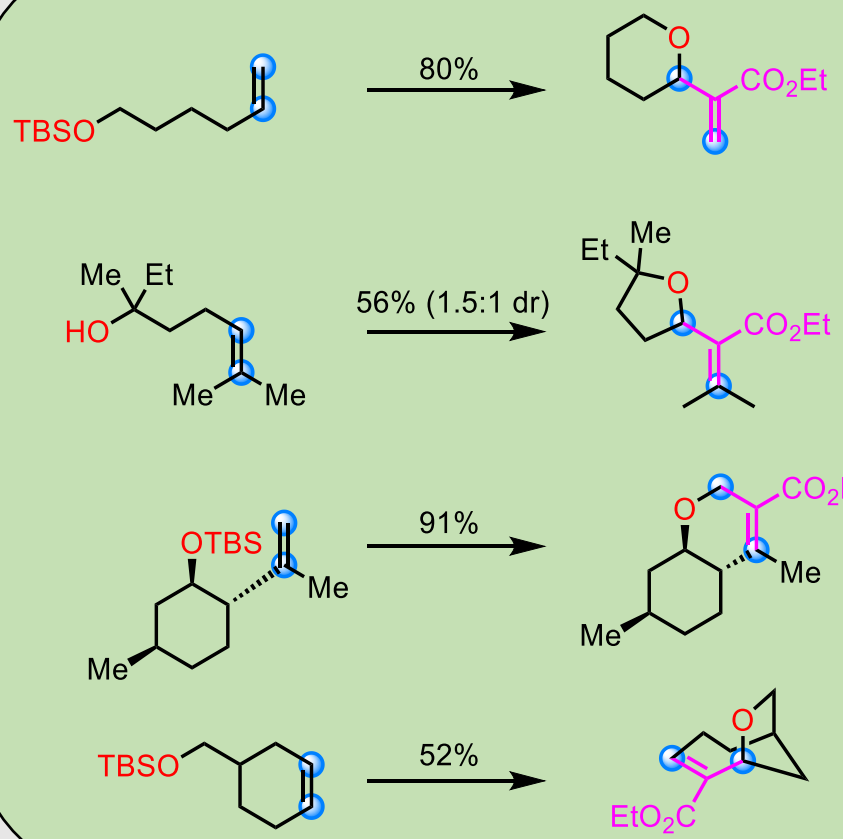
Suero, M. et al. J. Am. Chem. Soc. **2019**, *141*, 15509.

Olefin Activation by Rh Carbynoids

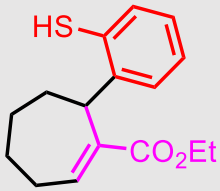




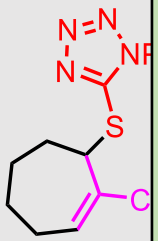
Cyclizations



From Cyclohexenes

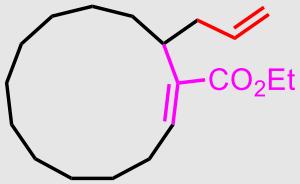


85%
with thiophenol



85%
with tetrazol

From Larger Cycloalkenes



51%; 1.7:1 Z:E
with allyl-$SnBu_3$

48%
with NBu_4Br

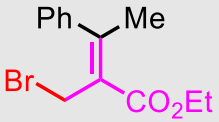
with allyl-$SnBu_3$

yclohexane

$_2$Et

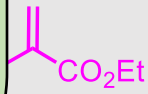
1
CPh

From α-Me Styrene



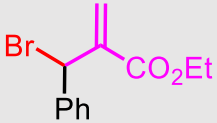
72%, L:B > 20:1
14:1 Z:E
with NBu_4Br

1-Hexene



u
%, L:B = 7:1
3:1 Z:E
with NBu_4Br

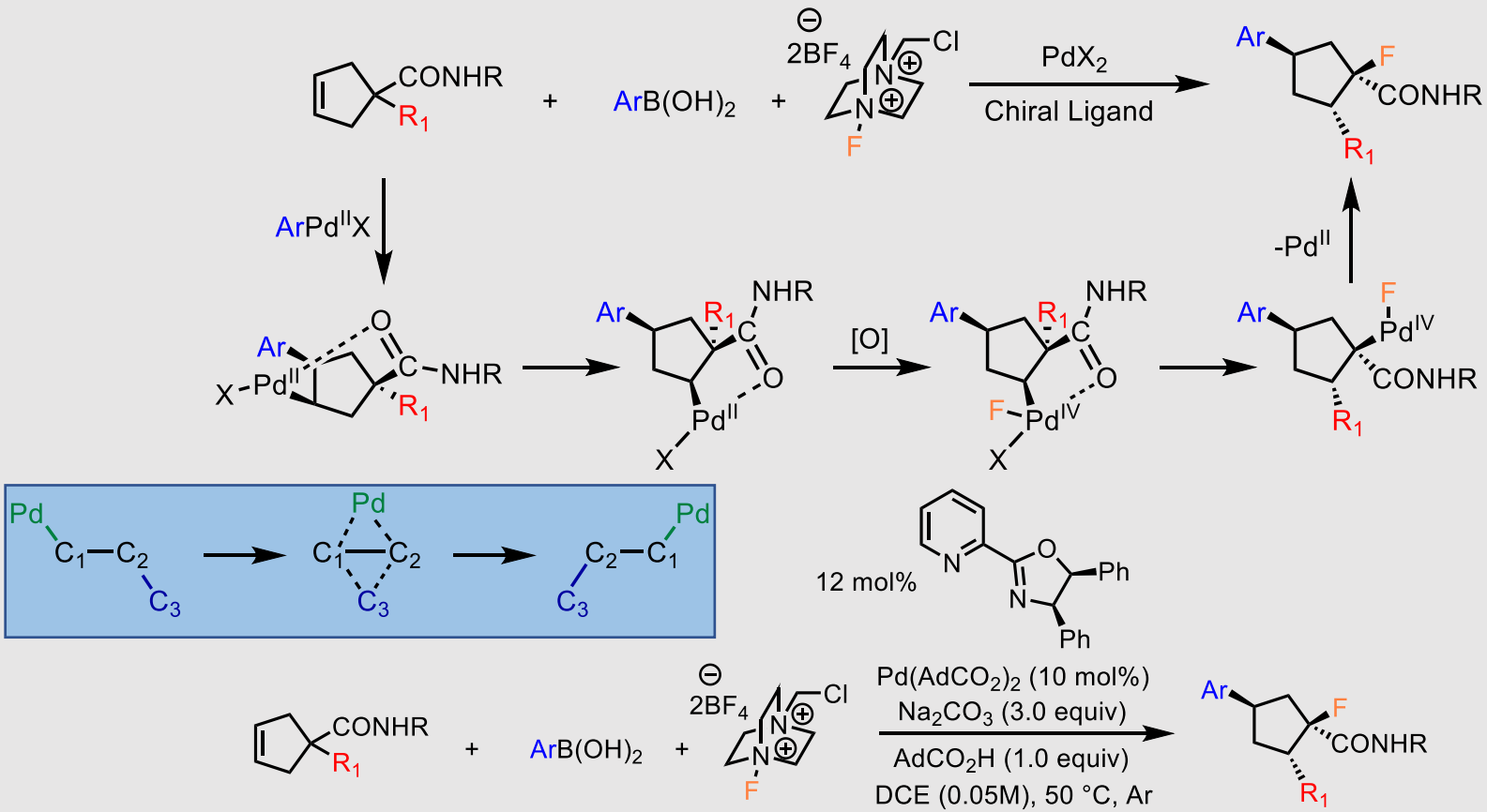
From Styrene

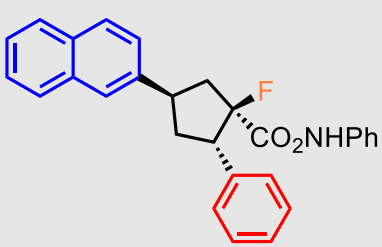


98%, L:B > 20:1
10:1 Z:E
with NBu_4Br

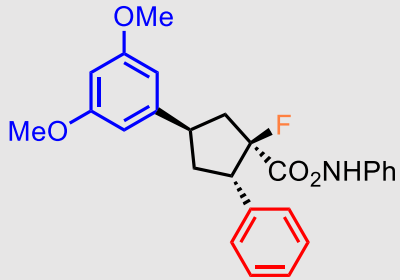
Suero, M. et al. J. Am. Chem. Soc. **2019**, *141*, 15509.

Dyotropic Pd(IV) Rearrangement

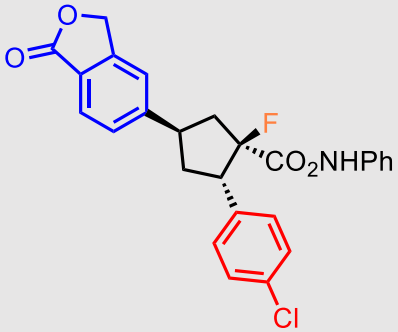




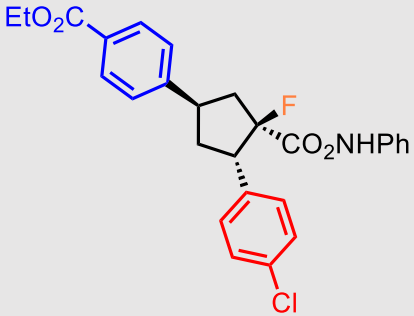
72%, 92% e.e.



76%, 91% e.e.



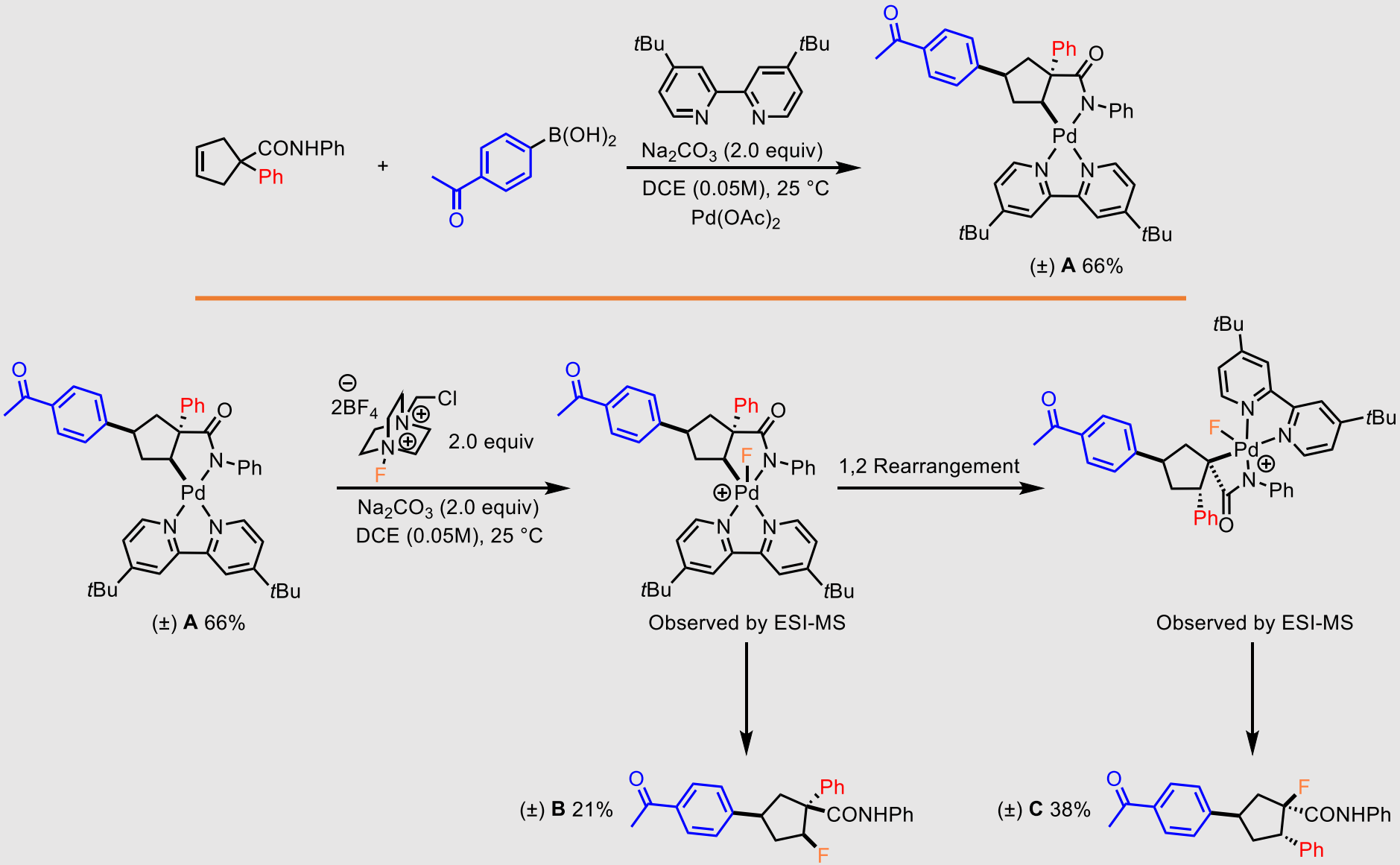
51%, 89% e.e.



52%, 90% e.e.

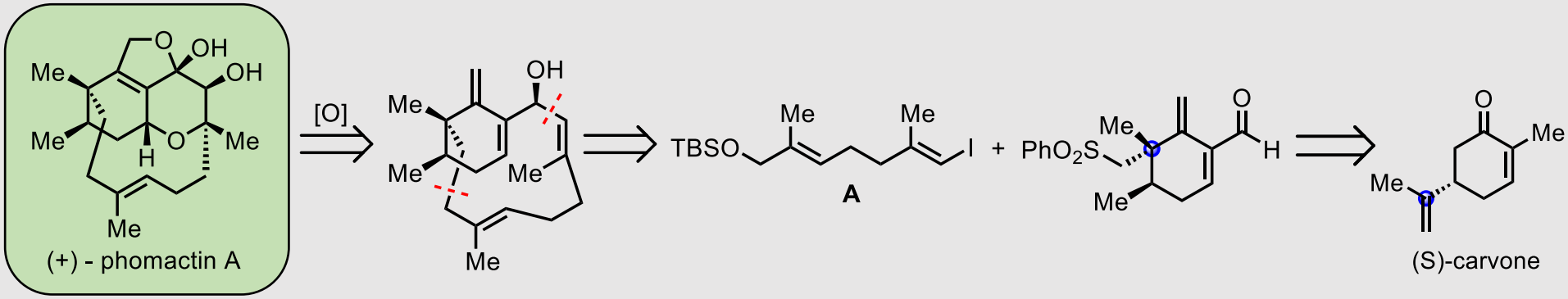
Zhu, J. Nat. Chem. **2021**, *13*, 671.

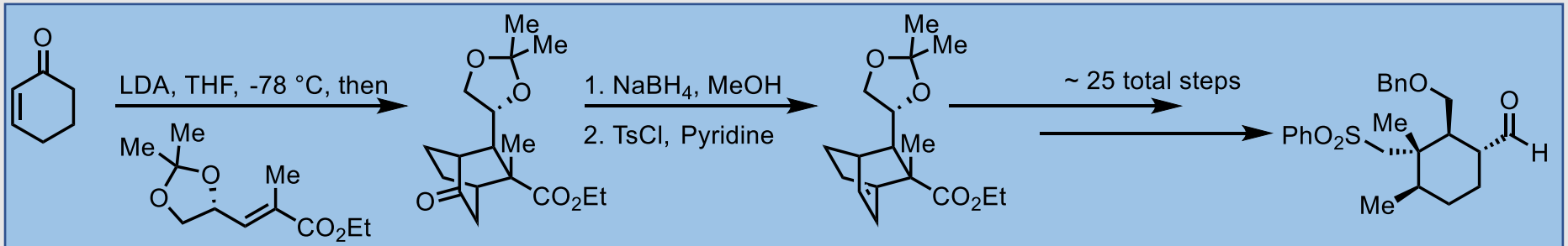
Dyotropic Pd(IV) Rearrangement



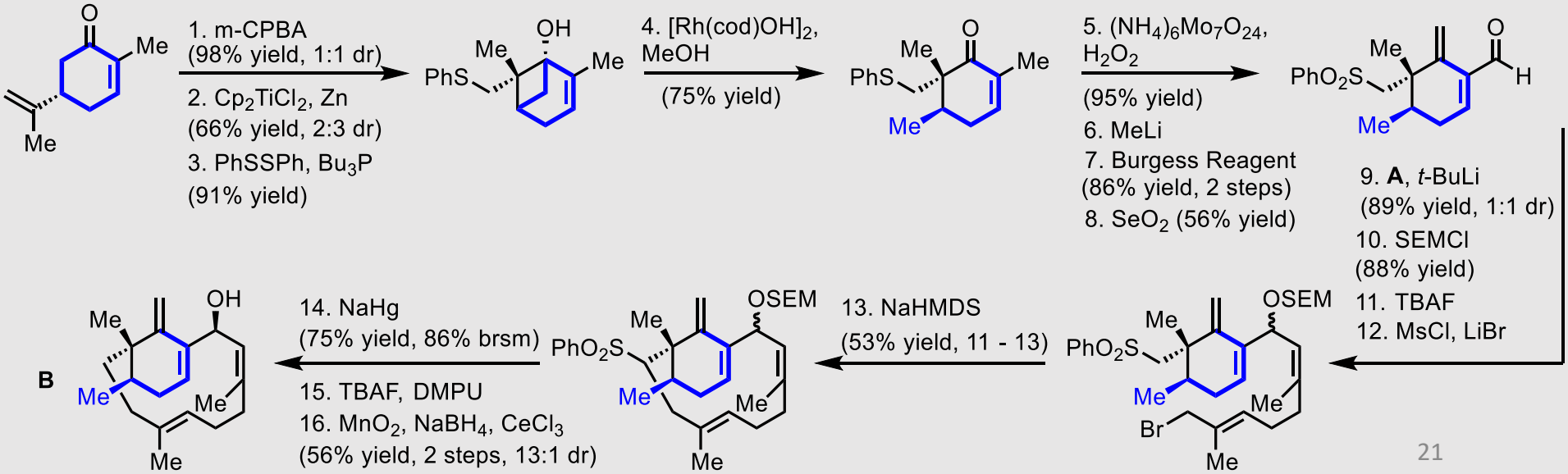
Zhu, J. Nat. Chem. **2021**, *13*, 671.

Phomactin Total Syntheses



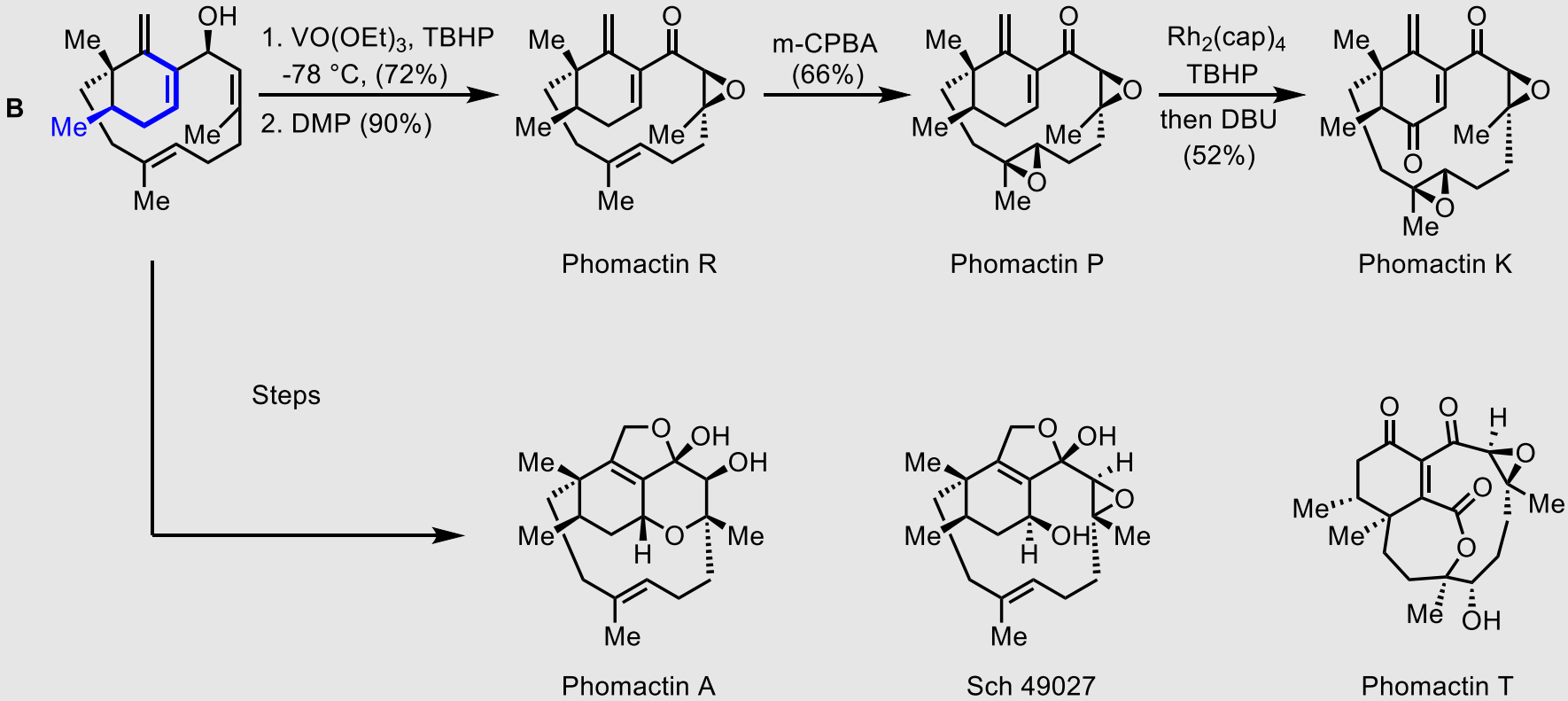


Yamada, Y. *Tetrahedron Lett.* **1996**, *37*, 7107.



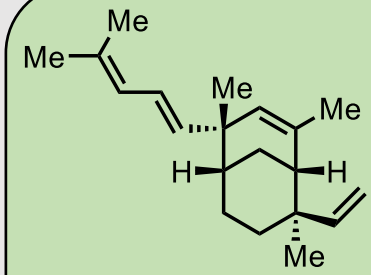
Sarpong R. et al. J. Nat. Chem. **2018**, *10*, 938.

Phomactin Total Syntheses



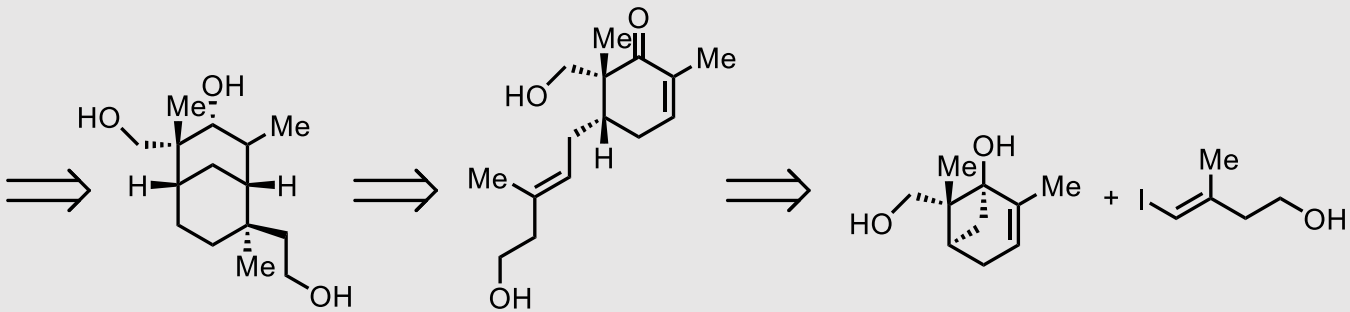
Sarpong R. et al. J. Nat. Chem. **2018**, *10*, 938.

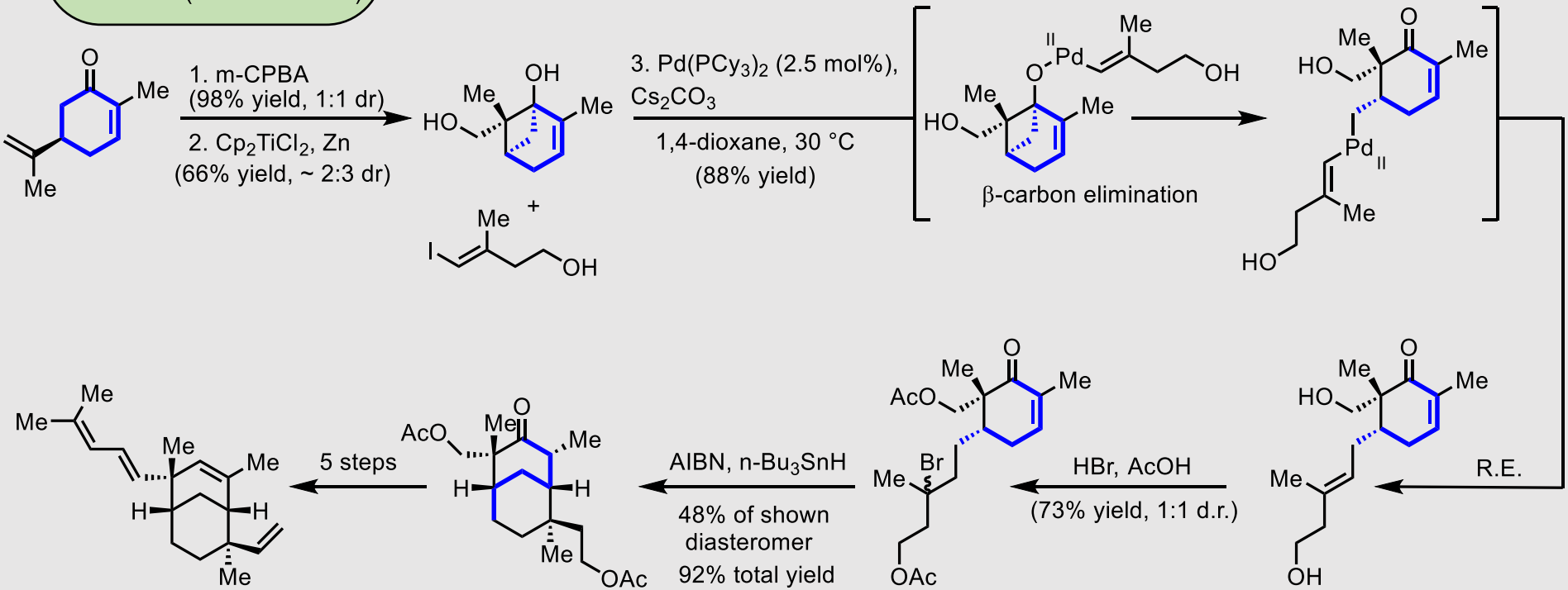
(-) xishacorene B Total Synthesis



(-) - xishacorene B

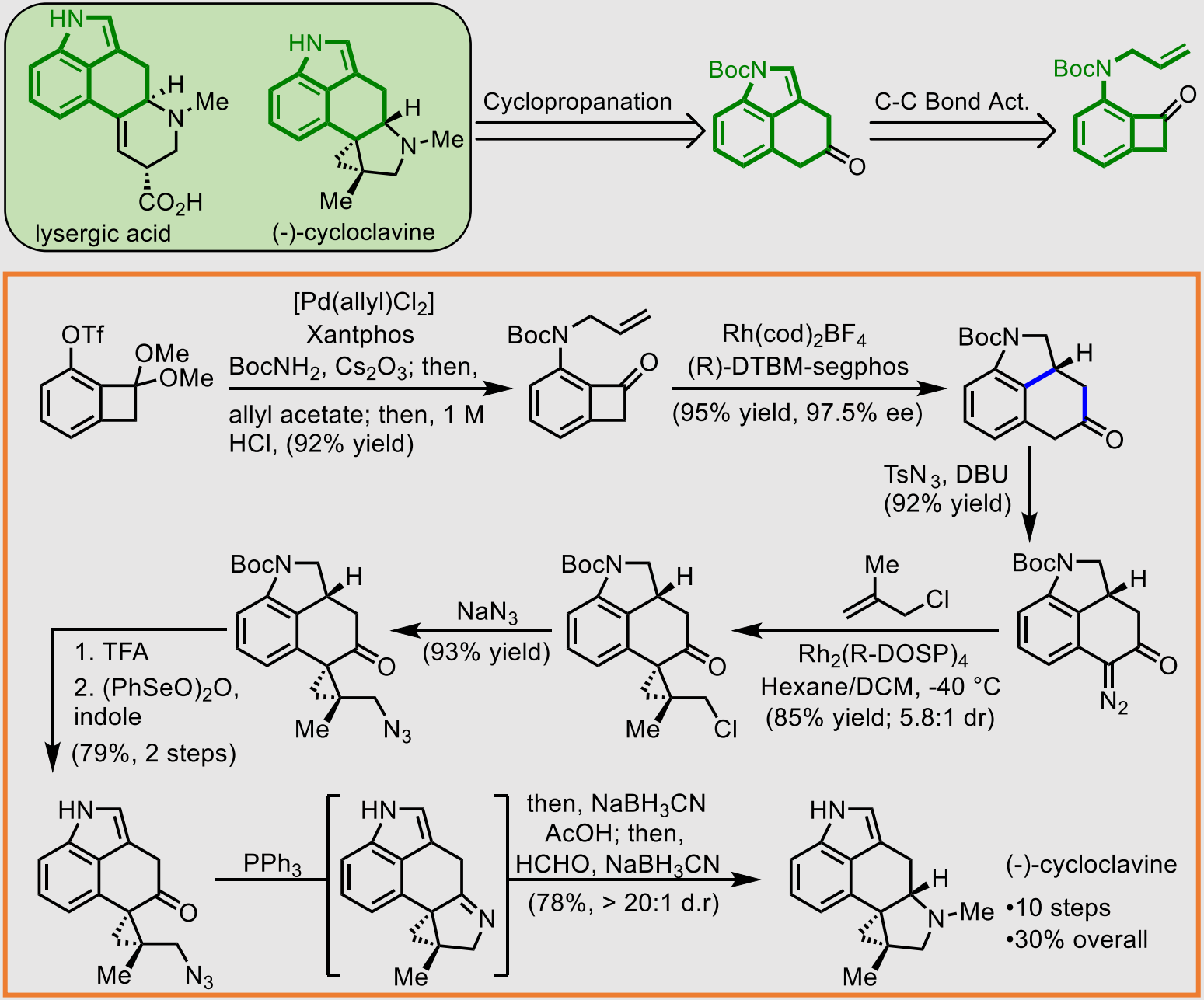
- bicyclo[3.3.1]nonane
- Recently isolated from soft coral (Chinese coast)





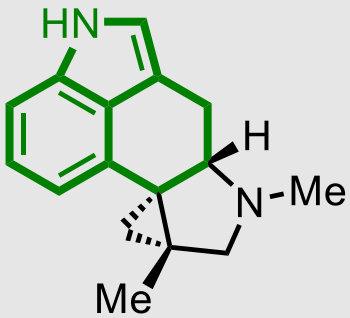
Sarpong R. et al. J. Am. Chem. Soc. **2018**, *140*, 9810.

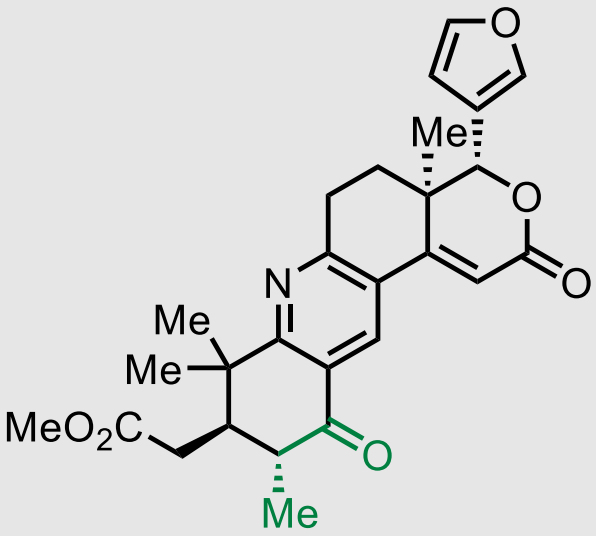
Total Synthesis of (-)-Cycloclavine



Dong, G. et al. *J. Am. Chem. Soc.* **2018**, *140*, 9652. Sarpong, R. et al. *Angew. Chem. Int. Ed.* **2020**, *59*, 18898.

Conclusions





- This would make an excellent Chem 535.
- Would be useful for the deconstruction of complex natural products to discover biological activity in new, topologically complex systems.
- Continued breakthroughs in unstrained C—C bonds will enable further adoption.
- Some advances in base metals (e.g. Ni(0)). The cost of
- rhodium warrants new advances.
- This area will expand rapidly in the coming decades.
- Metal alkylidenes to functionalize olefins?