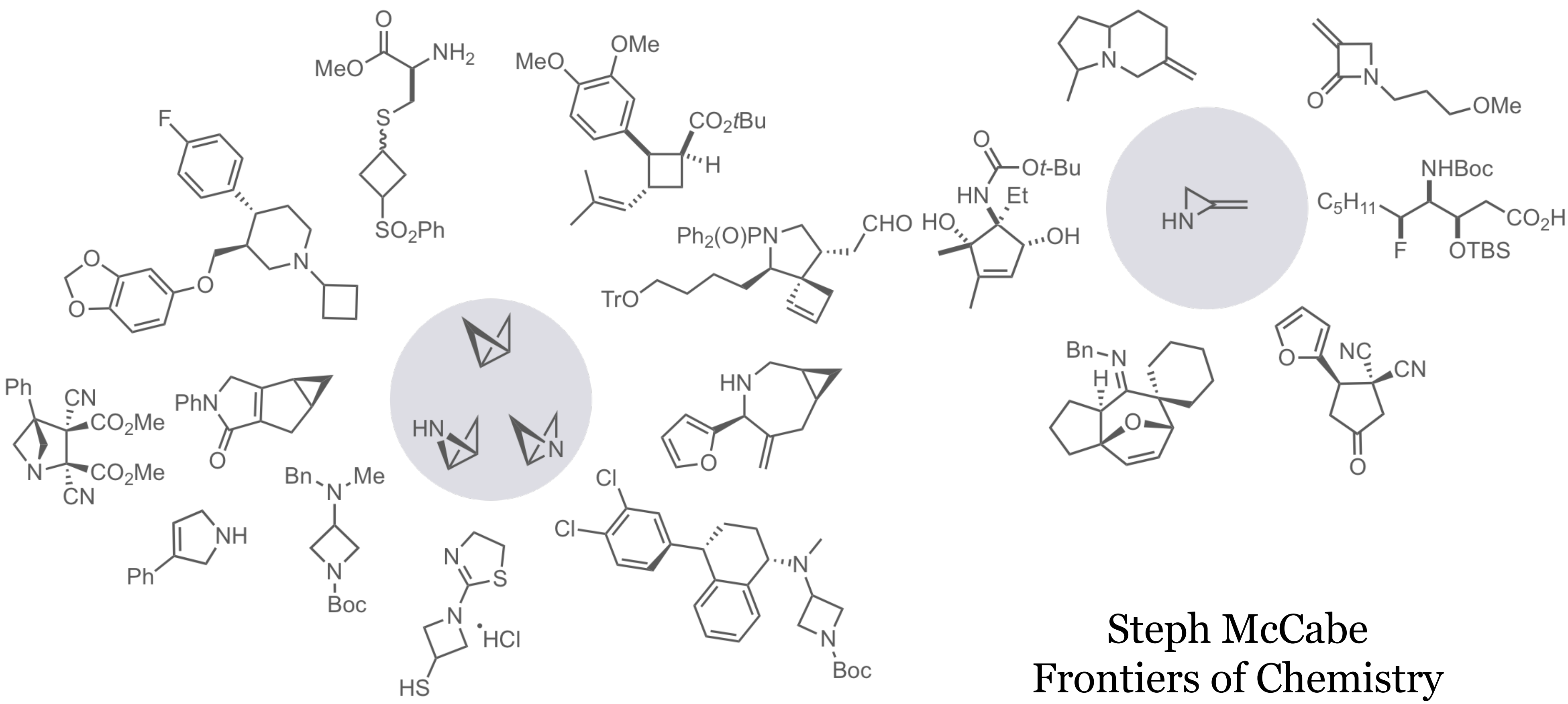
Strain-Promoted Reactivity in Organic Synthesis

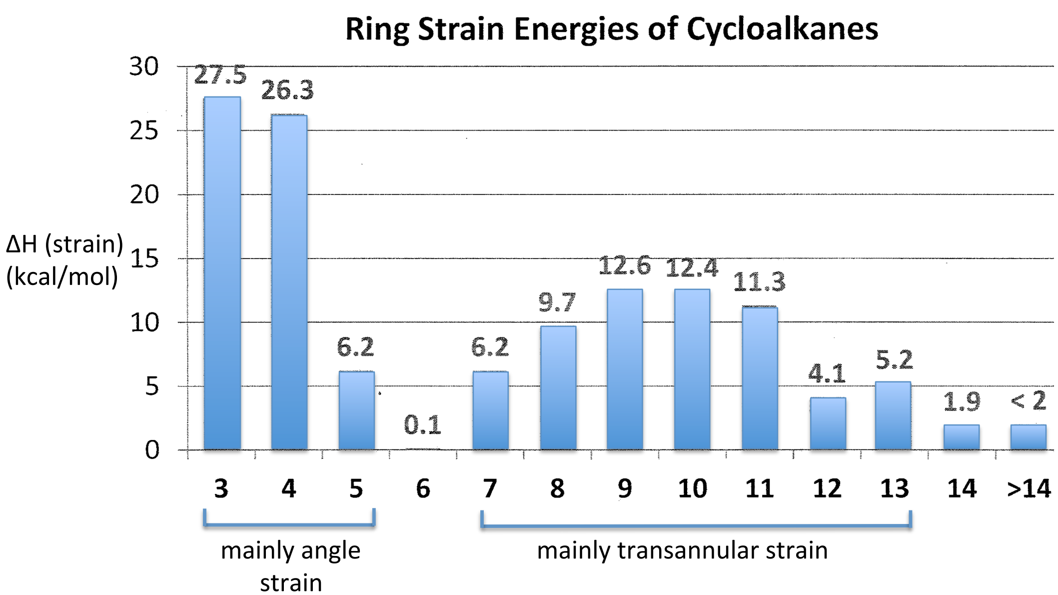


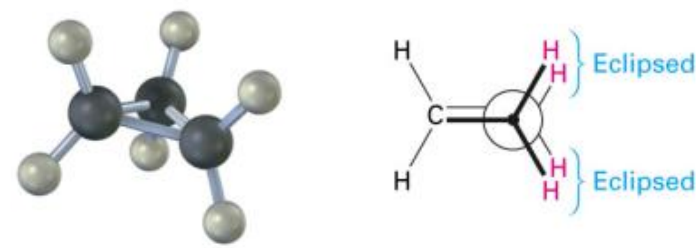
Steph McCabe
Frontiers of Chemistry
08/19/2017 Wipf Group

What is Ring Strain?

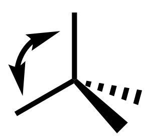
Ring Strain Theory: Adolf von Baeyer (Nobel Prize in Chemistry 1905)

1. **Angle Strain:** Expansion/compression of ideal (tetrahedral) bond angle
2. **Torsional Strain:** Rotational strain e.g. eclipsing bonds on neighboring atoms vs staggered
3. **Steric Strain:** Repulsive interaction when atoms approach each other too closely

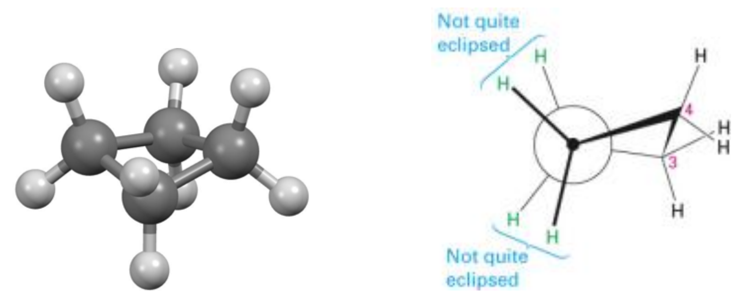




Ring strain: 27.5 kcal/mol
C–C–C ∠60°
C-C bond: 61 kcal/mol (vs 85 kcal/mol in propane)



C–C–C ∠109.5°

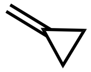


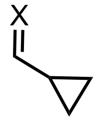
Ring Strain: 26.4 kcal/mol
C–C–C ∠~88°
C-C bond: 63 kcal/mol (vs 85 kcal/mol in butane)

Small Strained Aza- and Carbocycles

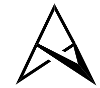

cyclopropane

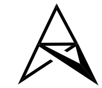

cyclopropene


methylenecyclopropane

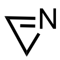

vinylcyclopropane

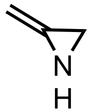

bicyclo[1.1.0]butane

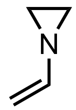

bicyclo[1.1.1] pentane

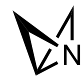

[1.1.1]propellane


aziridine

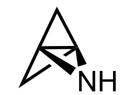

2*H*-azirine


methylene aziridine

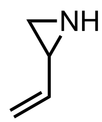

N-vinylaziridine


1-azabicyclo[1.1.0]butane


1-azabicyclo[1.1.1]pentane


2-aza[1.1.1]propellane
**unknown*


1*H*-azirine


2-vinylaziridine


2-azabicyclo[1.1.0]butane
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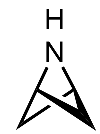
2-azabicyclo[1.1.1]pentane
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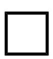
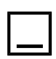
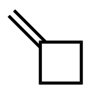
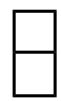
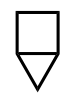
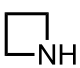

cyclobutane


cyclobutene

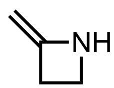

methylenecyclobutane

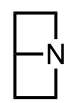

bicyclo[2.2.0]hexane

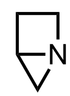

bicyclo[2.1.0]pentane
'housane'

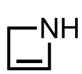

azetidine

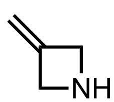

1-azetine

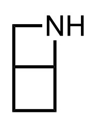

2-methyleneazetidine

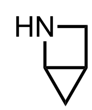

1-azabicyclo[2.2.0]hexane
**unknown*

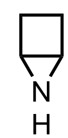

1-azabicyclo[2.1.0]pentane


2-azetine


3-methyleneazetidine


2-azabicyclo[2.2.0]hexane


2-azabicyclo[2.1.0]pentane

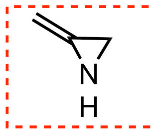

5-azabicyclo[2.1.0]pentane

- Cyclopropane (~27 000 hits in scifinder) vs bicyclobutane (831), methyleneaziridine (89), azabicyclobutane (56)

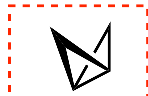
Scope/Brief History

Scope of Presentation:

1. Reactivity/applications of underrepresented carbo- and azacycles containing a 3-membered ring
2. Proposal Section – Gaps in the synthesis and reactivity profile of strained ring systems and applications in total synthesis



methylene aziridine
(MA)



bicyclo[1.1.0]butane
(BCB)

1-azabicyclo[1.1.0]butane
(ABB)

1950s – 1990s
Theoretical/Synthetic Research

- Useful models to study ring strain in organic compounds
- Synthesis:

MA (1951, Pollard)
BCB (1959, Wiberg)
ABB (1969 Funke)

2001-2017
General reactivity

- Methods to form small-medium sized rings and novel scaffolds

2008-2017
Applications

- Total synthesis
- Chiral Ligands for asymmetric catalysis
- Medicinal chemistry

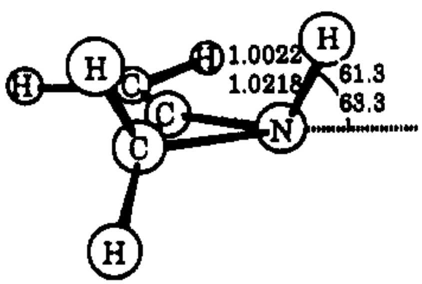
unnatural amino acids, peptide labeling

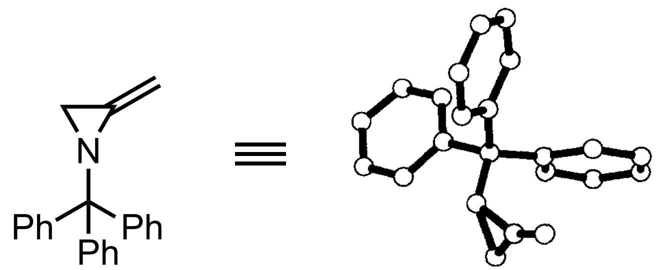
Methyleneaziridines: Properties

- Ring strain ~43 kcal/mol

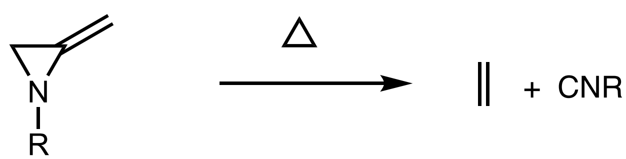
29.71 kcal/mol   42.55 kcal/mol   28.75 kcal/mol   40.03 kcal/mol

- Very little enamine character (Nitrogen lone pair is pyramidal)





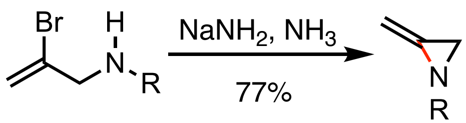
- Thermal decomposition to olefin and isonitrile (slow T>120 °C, fast T>190 °C)



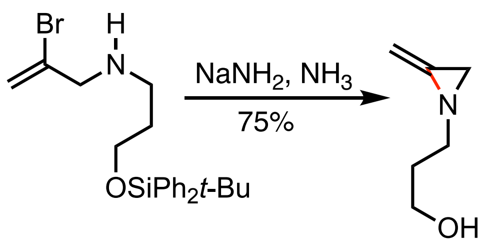
Calculated ring strain energy (HF/6-31G*) Bachrach *J. Phys. Chem.* 1993, *97*, 4996; Shipman *Tetrahedron*, 1996, *52*, 7037

Methyleneaziridine Synthesis

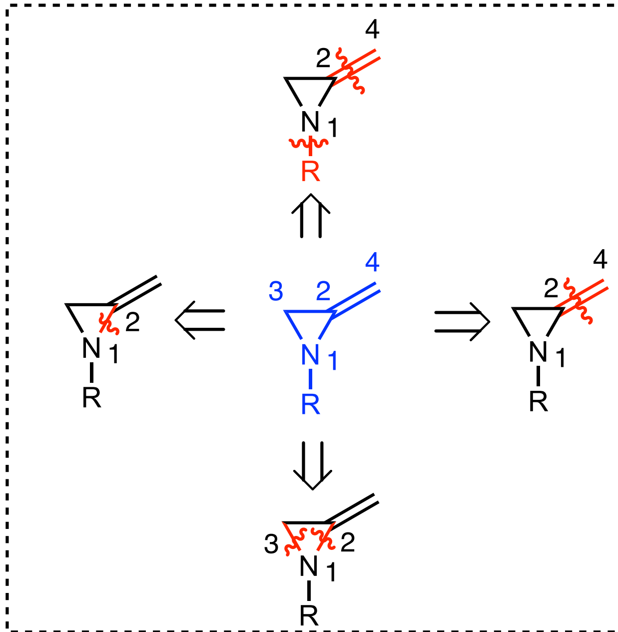
**most general route*

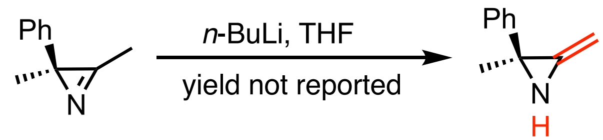


Olsen *J. Org. Chem.* 1963, *28*, 3241

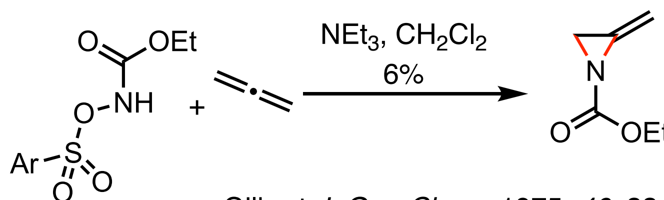


Shipman *Org. Lett.* 2005, 22, 4987

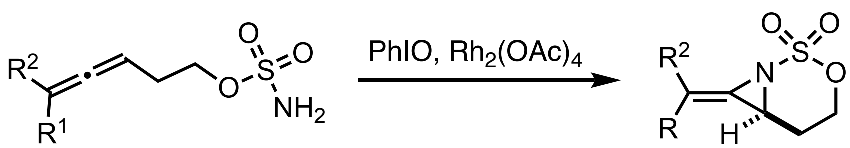




Mison *Tetrahedron Lett.* 1985, *26*, 2637

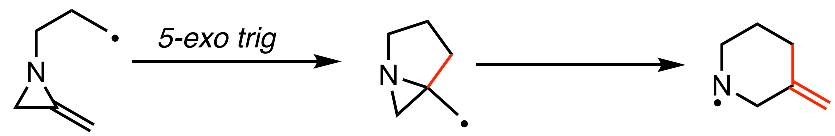


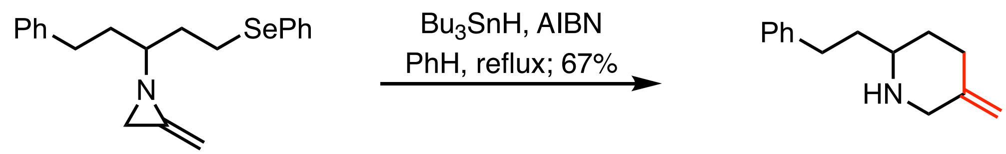
Gilbert *J. Org. Chem.* 1975, *40*, 224

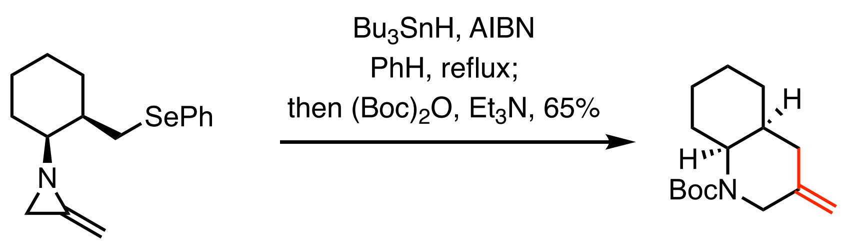


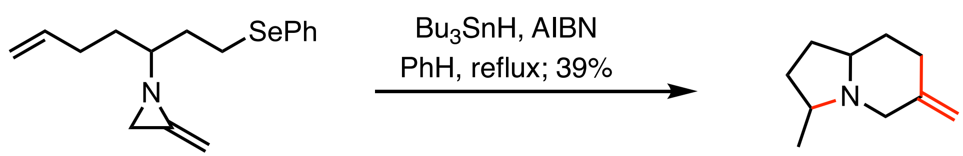
Schomaker *Org. Lett.* 2017, *19*, 3239

Heterocycle Synthesis: Radical cyclization



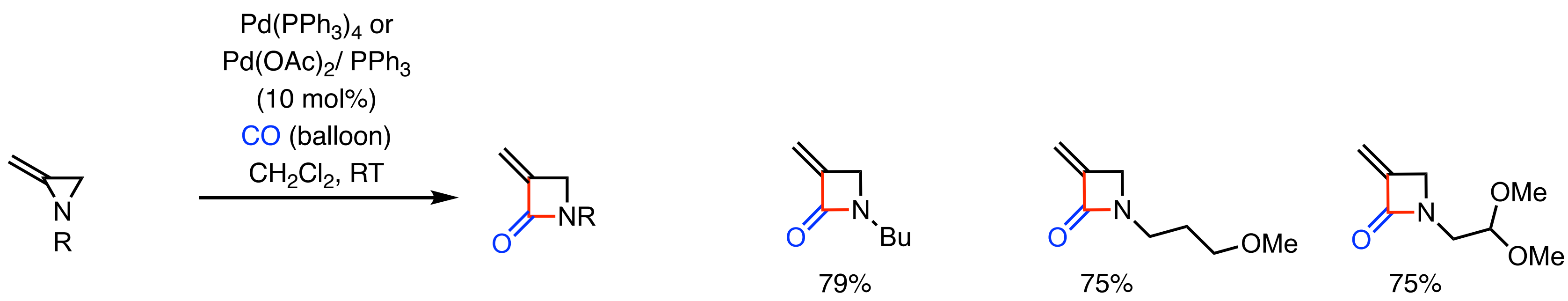


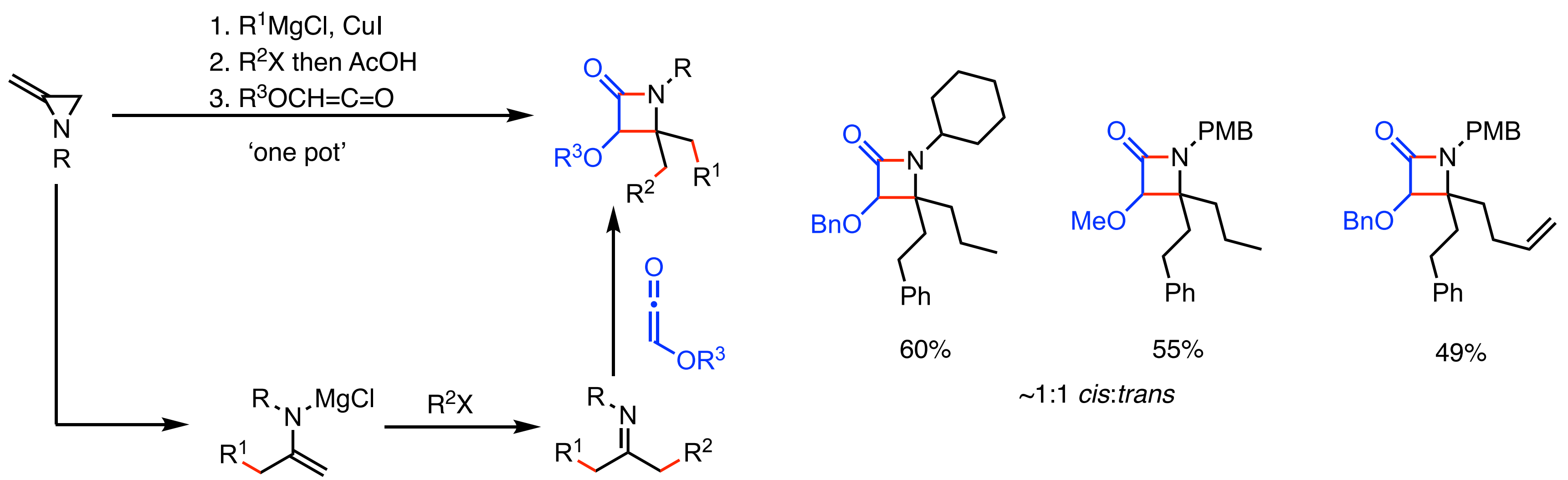




Shipman *Org. Lett.* 2001, *3*, 2383

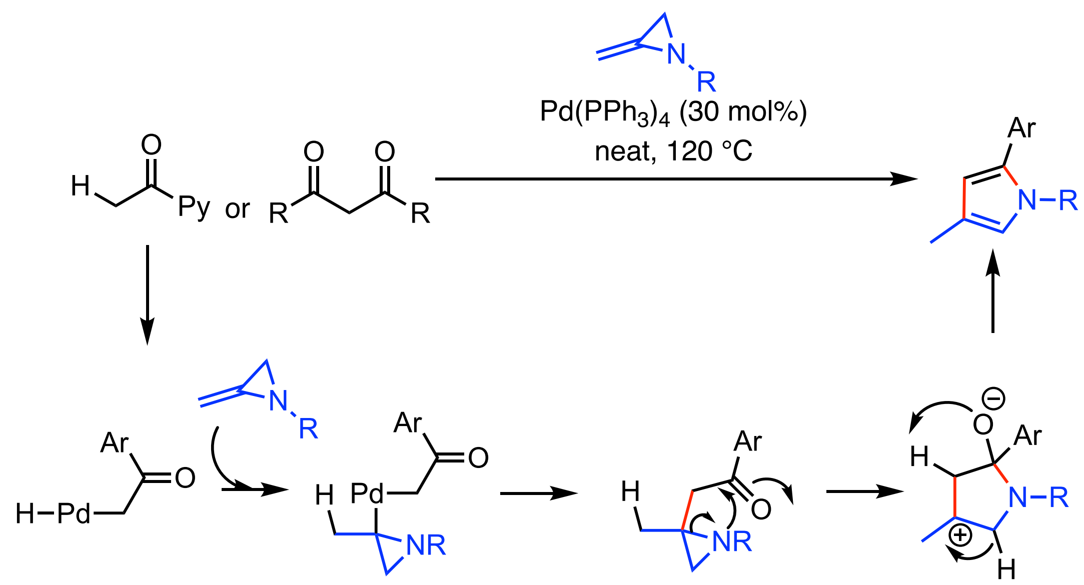
Transition Metal Catalyzed Ring-Expansion to β-lactams

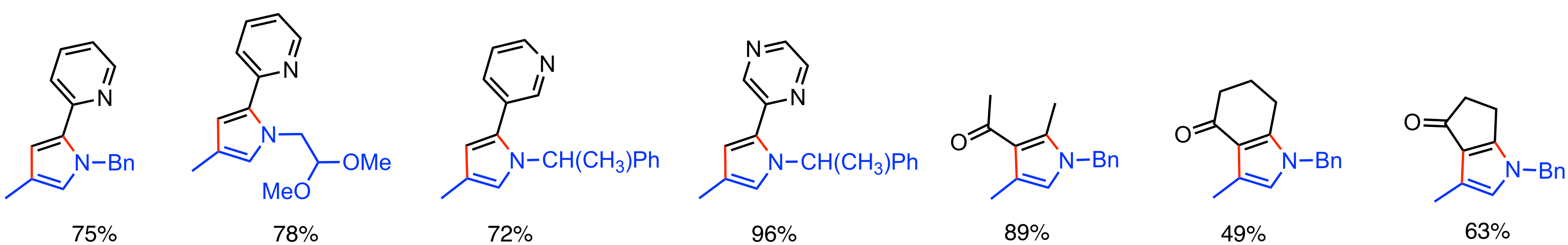




Alper *Tetrahedron Lett.*, 1987, *28*, 3237; Shipman *J. Org. Chem.*, 2008, 73, 9762

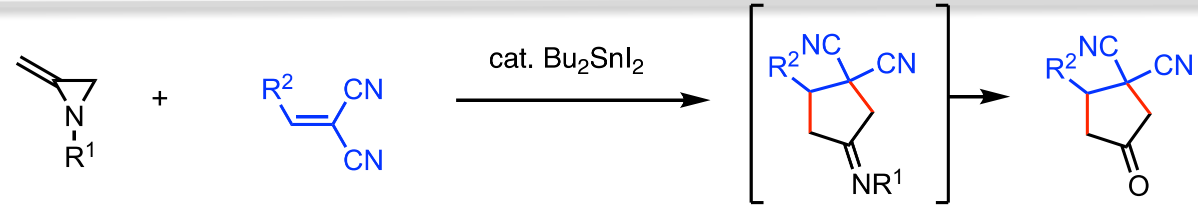
Heterocycle Synthesis: 3-Me-Pyrroles

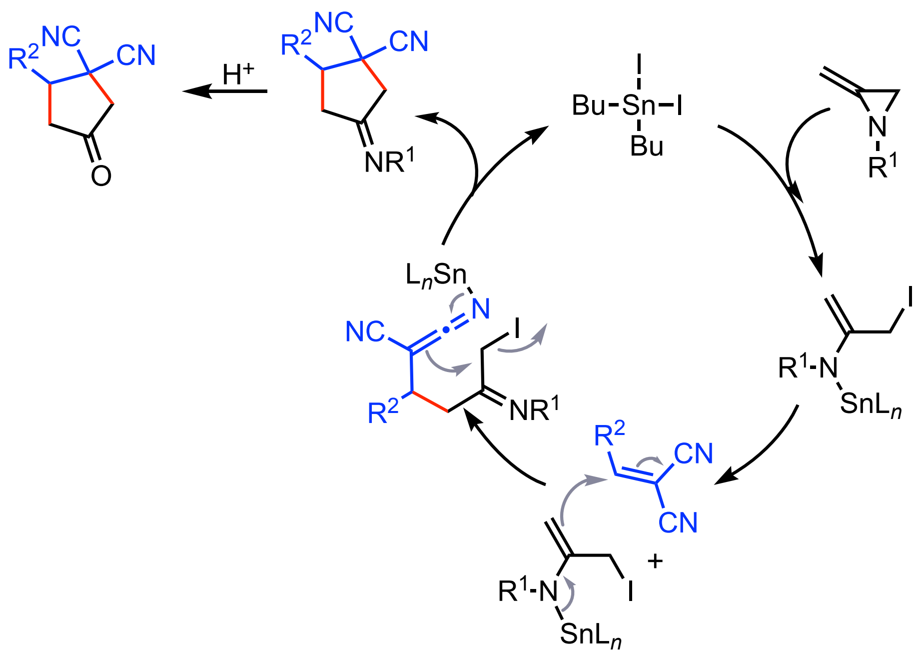


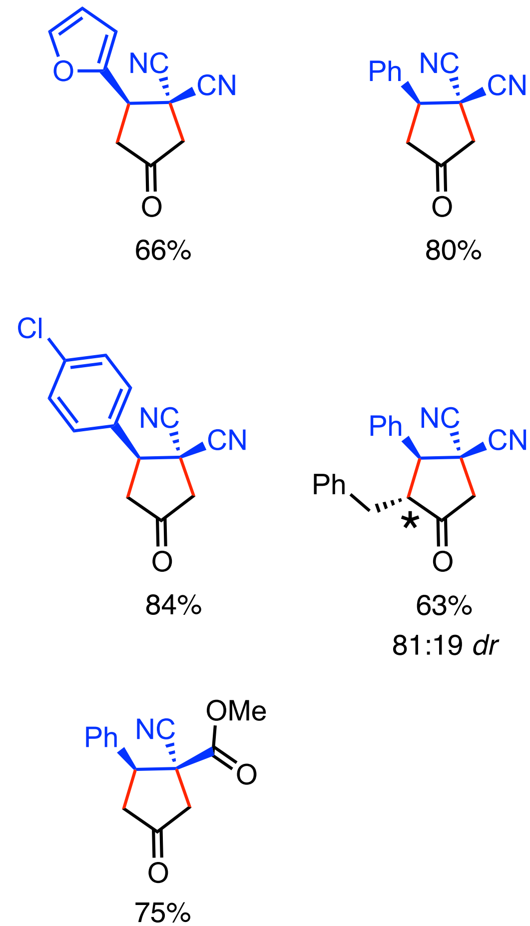


Yamamoto *J. Am. Chem. Soc.*, 2004, *126*, 13898; Yamamoto *Tetrahedron Lett.* 2007, *48*, 2267; Wan *Chem. Commun.*, 2013, *49*, 5073

Lewis Acid Catalyzed [3+2]Cycloaddition

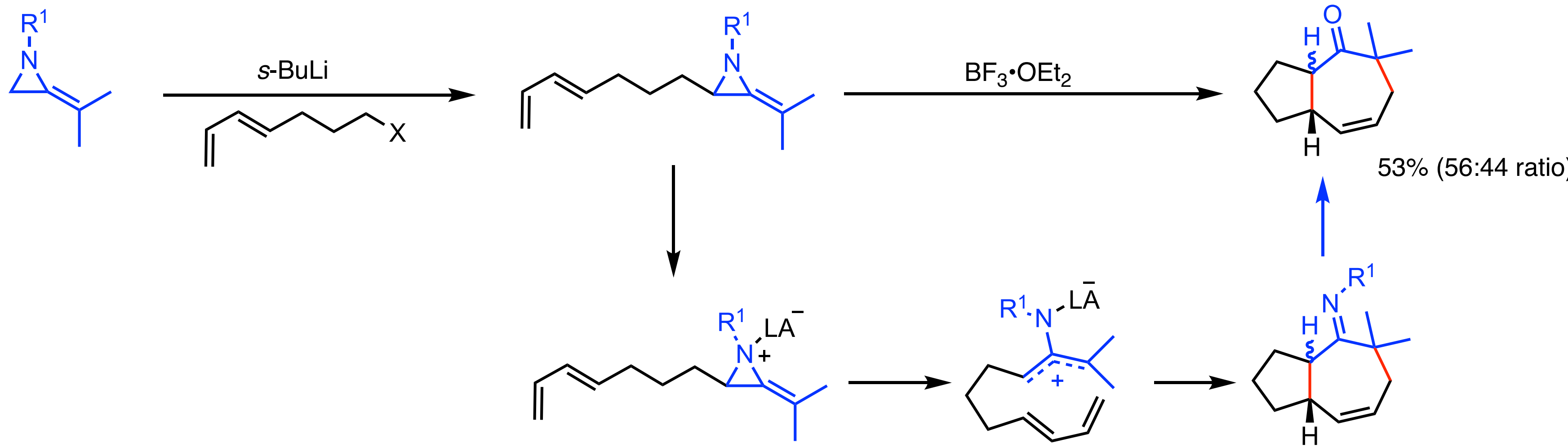


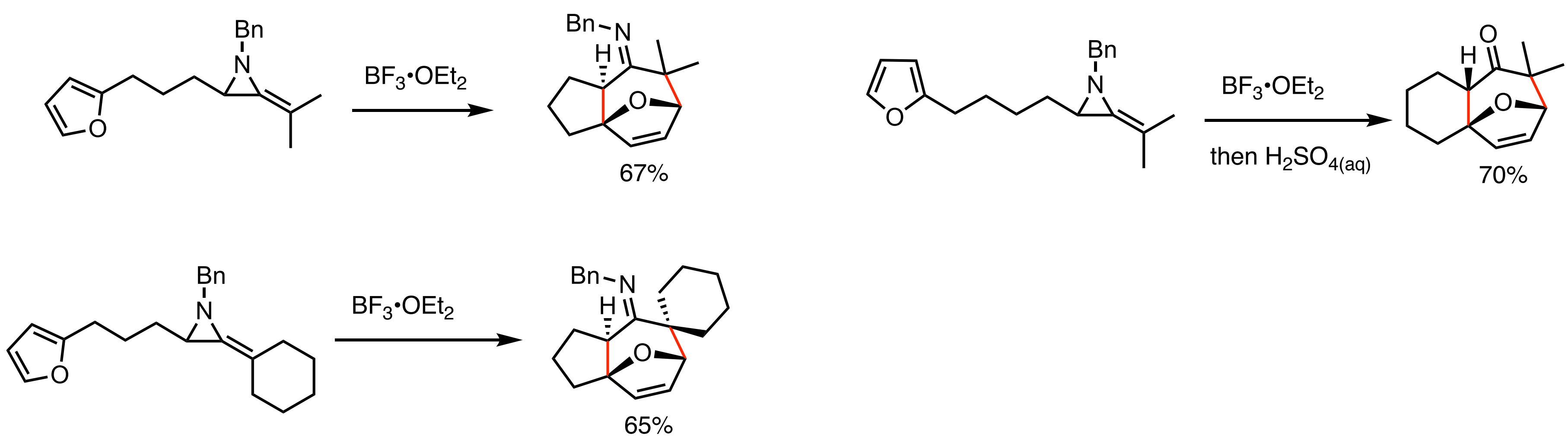




Shibata *Org. Lett.*, 2014, *16*, 1192

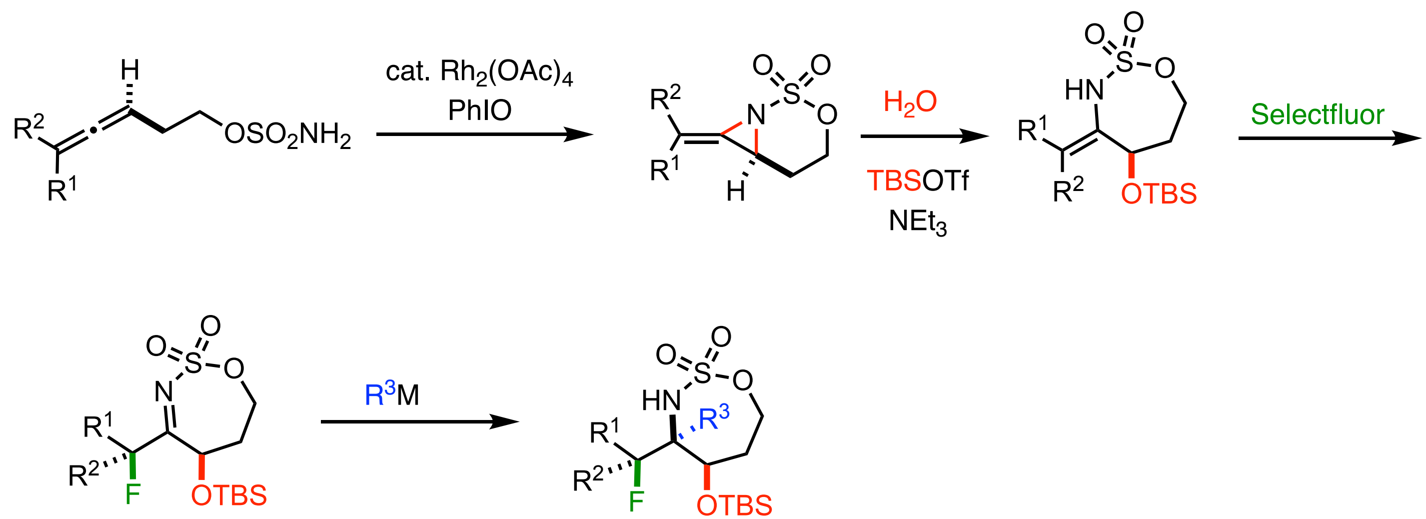
Lewis Acid Catalyzed [4+3] Cycloaddition of 2-Amino-Allyl Cations

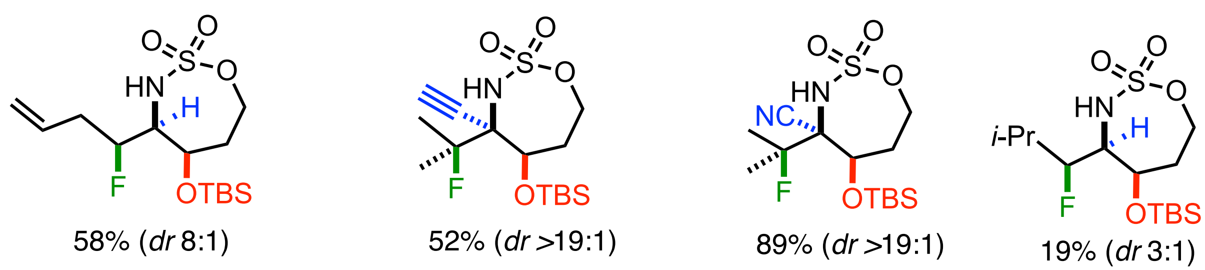




Shipman *Angew. Chem. Int. Ed.* 2004, *43*, 6517

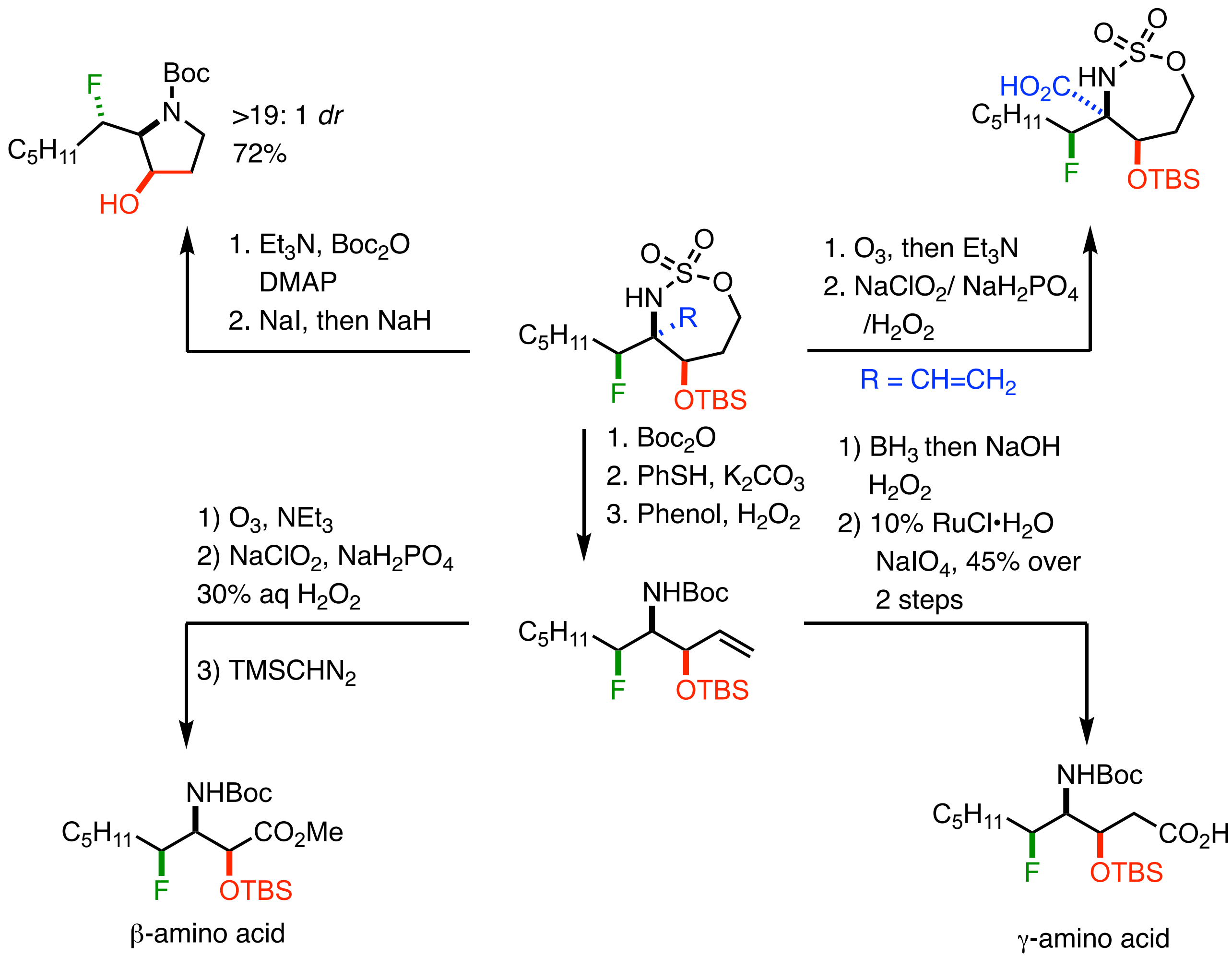
C–F/C–N/C–O Stereotriads





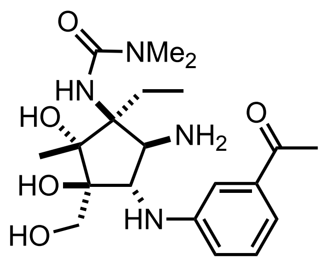
Schomaker *Org. Lett.* 2017, *19*, 3239−3242

C–F/C–N/C–O Stereotriads



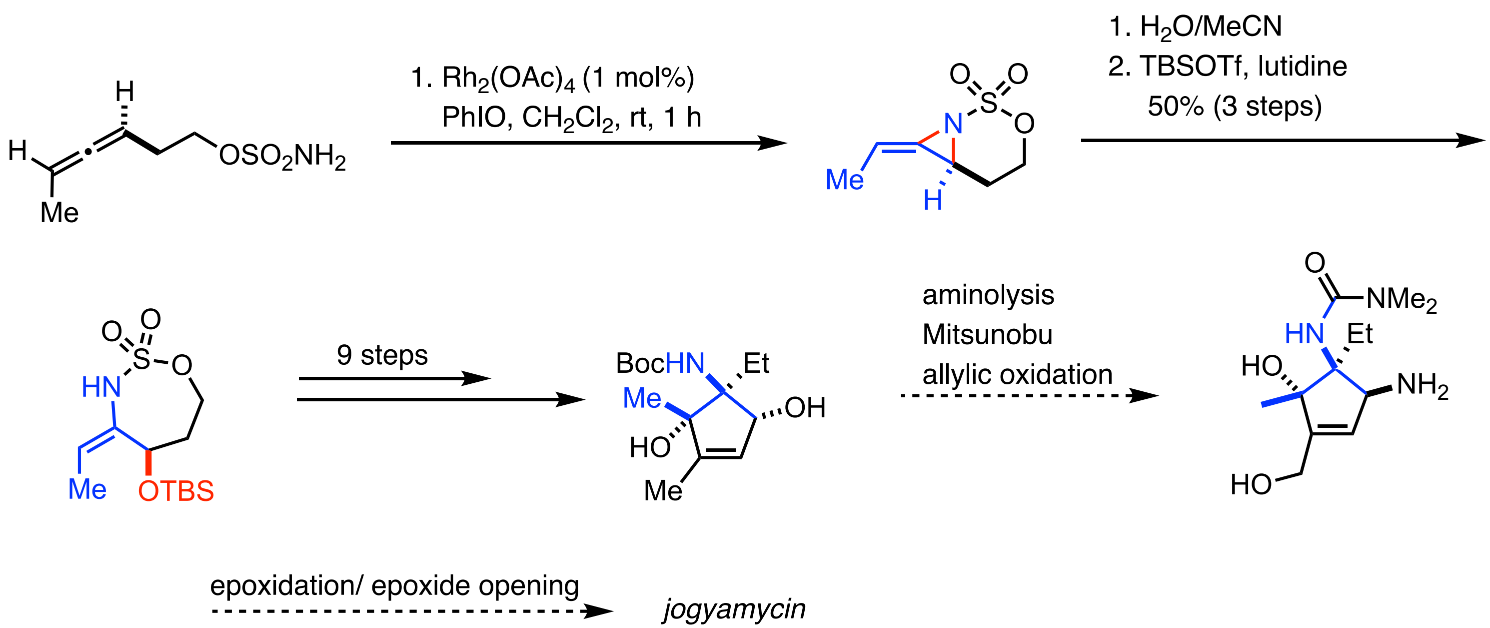
Schomaker *Org. Lett.* 2017, *19*, 3239–3242

Synthesis of the Aminocyclopentitol Core of Jogyamycin using an Allene Aziridination Strategy



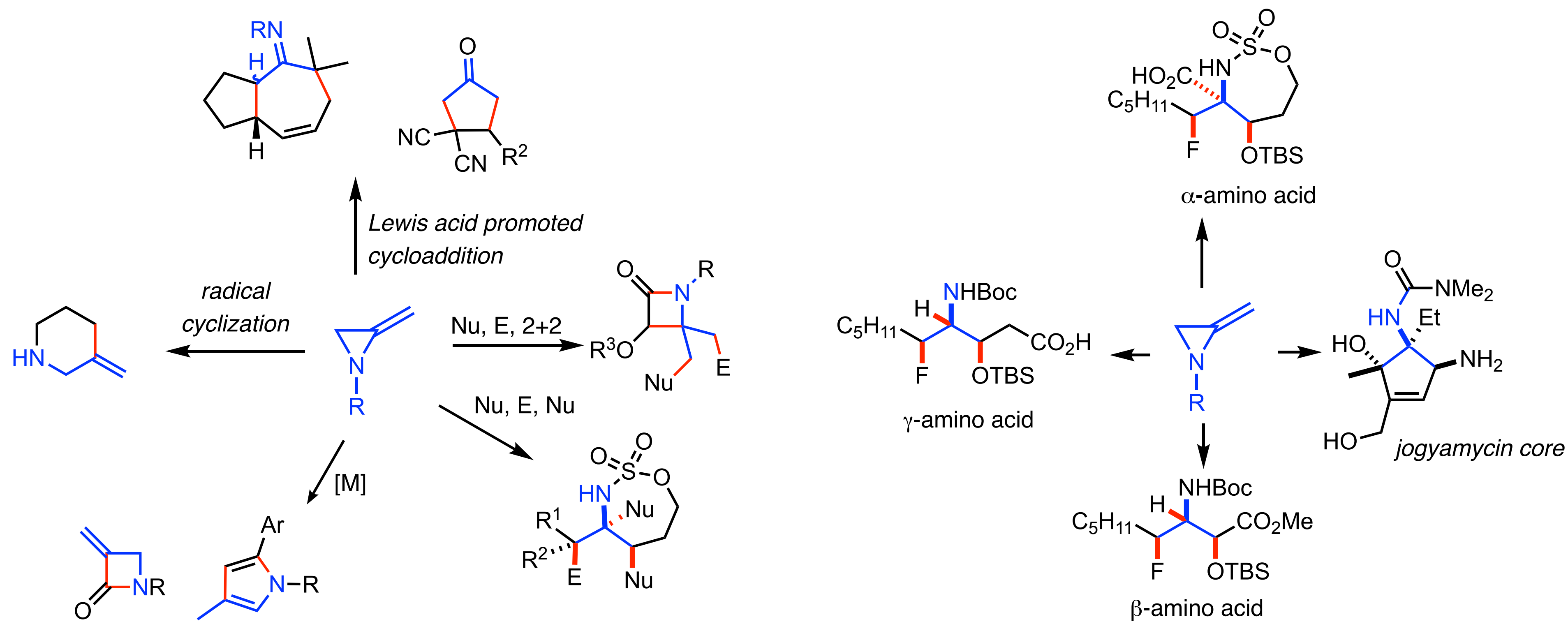
jogyamycin

- Antimalarial/ African sleeping sickness treatment
- IC_{50} = 1.5 nM *Plasmodium falciparum* K1 strain (drug resistant)
- IC_{50} = 12.3 nM *Trypanosoma brucei brucei* strain GUTat 3



Schomaker, *Org. Lett.* 2016, *18*, 284–287

Summary Methyleneaziridines



REACTIONS

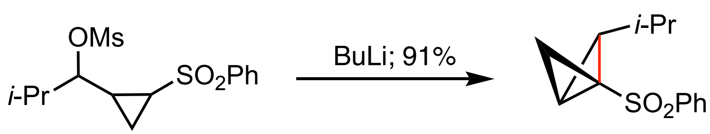
- Lewis Acid promoted cycloadditions
- Radical/TM-catalyzed heterocycle synthesis
- Sequential functionalization's to stereotriads/ β-lactams

APPLICATIONS

- α, β and γ amino acids synthesis
- total synthesis applications

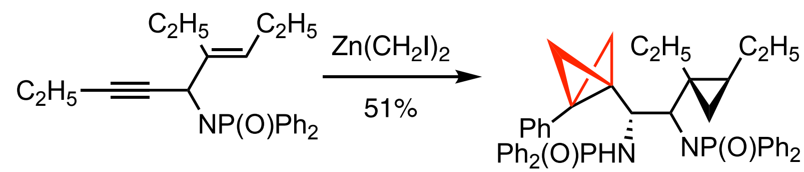
Bicyclobutane Synthesis

Intramolecular displacement of a leaving group by a cyclopropyl anion



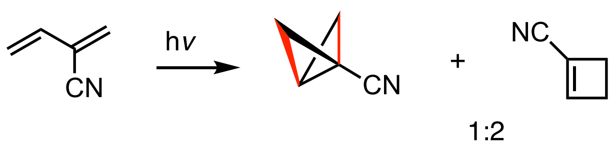
Gaoni *Tetrahedron Lett.*, 1981, 4339

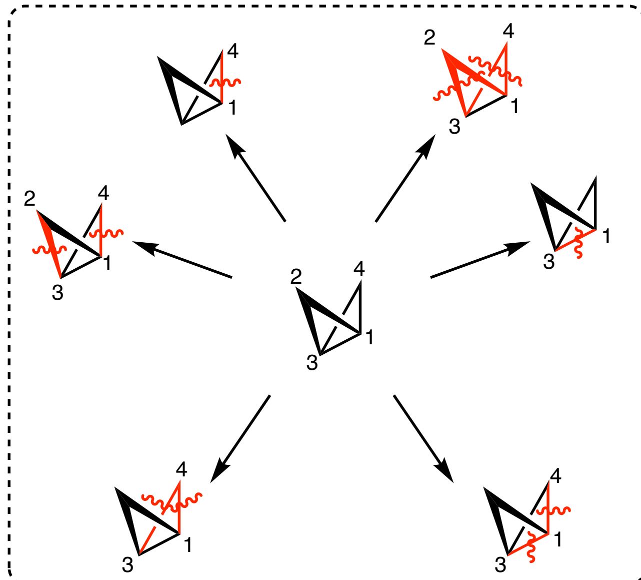
Intermolecular cyclopropanation (2x) of an alkyne



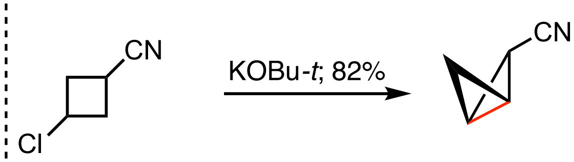
Wipf *J. Am. Chem. Soc.* 2003, *125*, 14694–14695.

Photochemical activation of butadiene



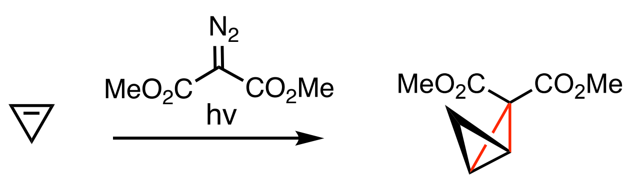


Intramolecular displacement of a leaving group across a cyclobutane



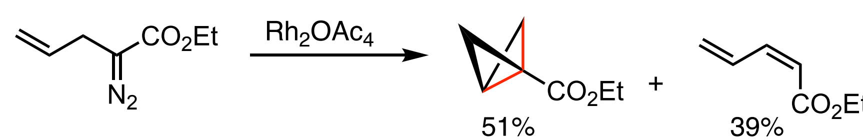
Sheppard *J. Am. Chem. Soc.*, 1971, *93*, 110

Intermolecular cyclopropanation



Maier, G.; Wolf, B. *Synthesis* 1985, *1985*, 871

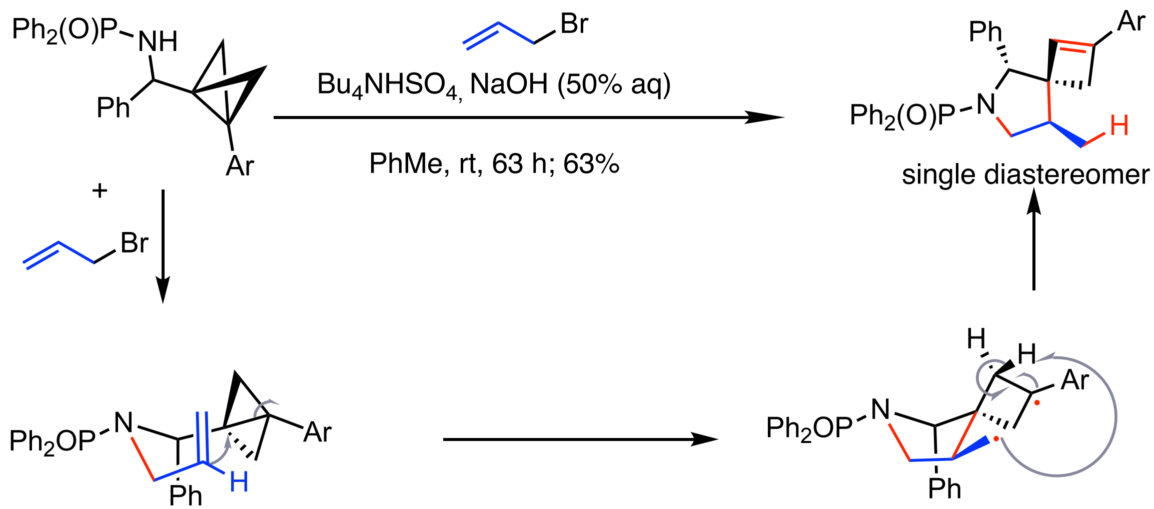
Intramolecular cyclopropanation

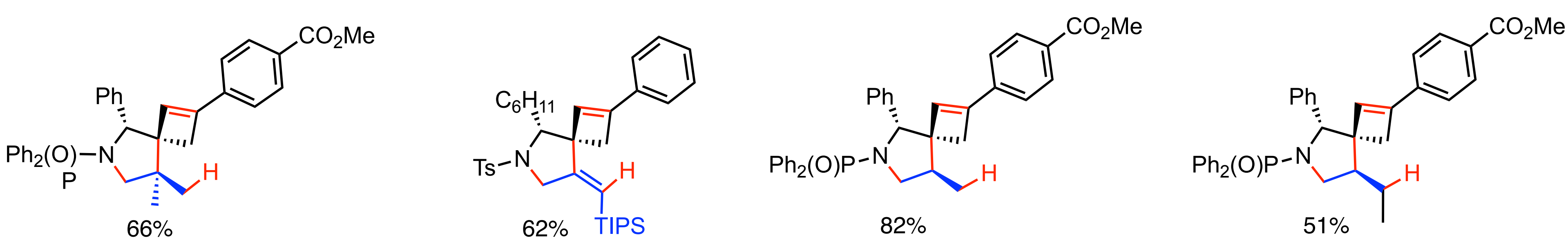


Ganem *Tetrahedron Lett.*, 1981, *22*, 4163

Thermal Reactions

Formal Alder-Ene

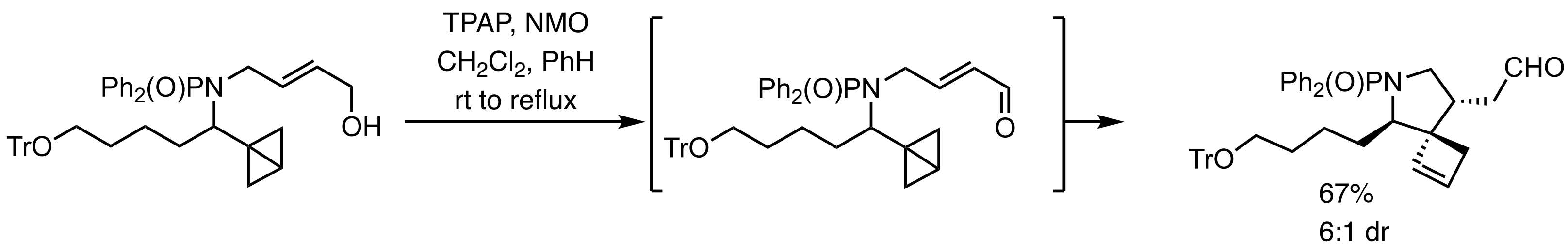


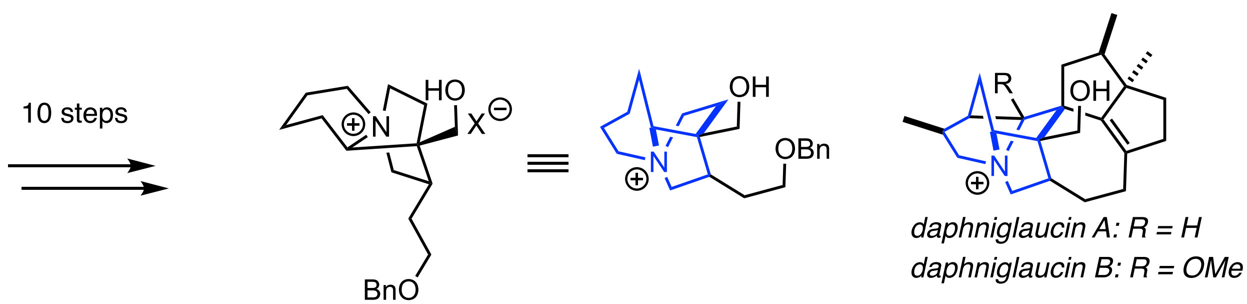


Wipf *et al. Acc. Chem. Res.*, 2015, *48*, 1149; Wipf and Walczak *Angew. Chem. Int. Ed.*, 2006, *45*, 4172

Thermal Reactions

Formal Alder-Ene

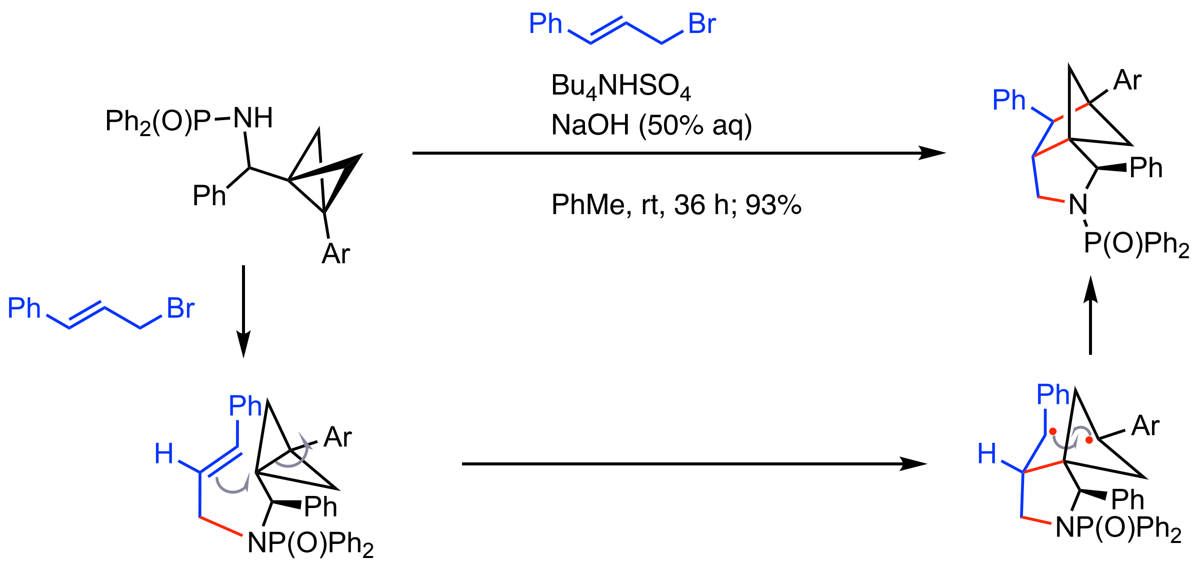


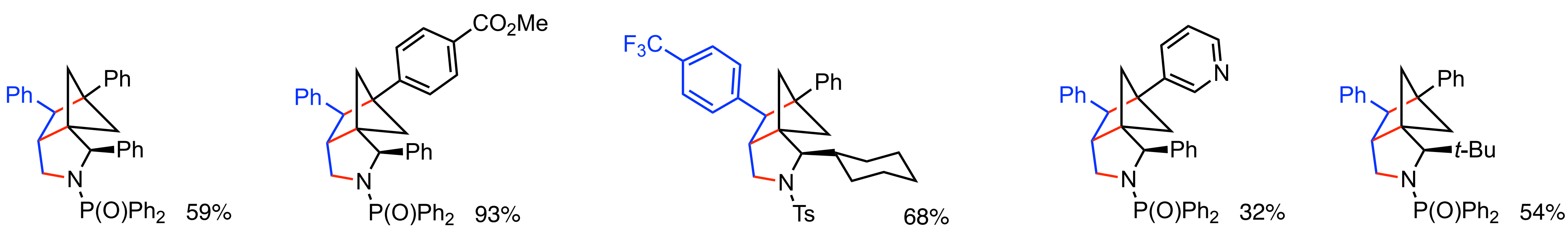


Wipf *et al.* Tetrahedron Lett. 2008, *49*, 5989

Thermal Reactions

[2+2] Cycloaddition

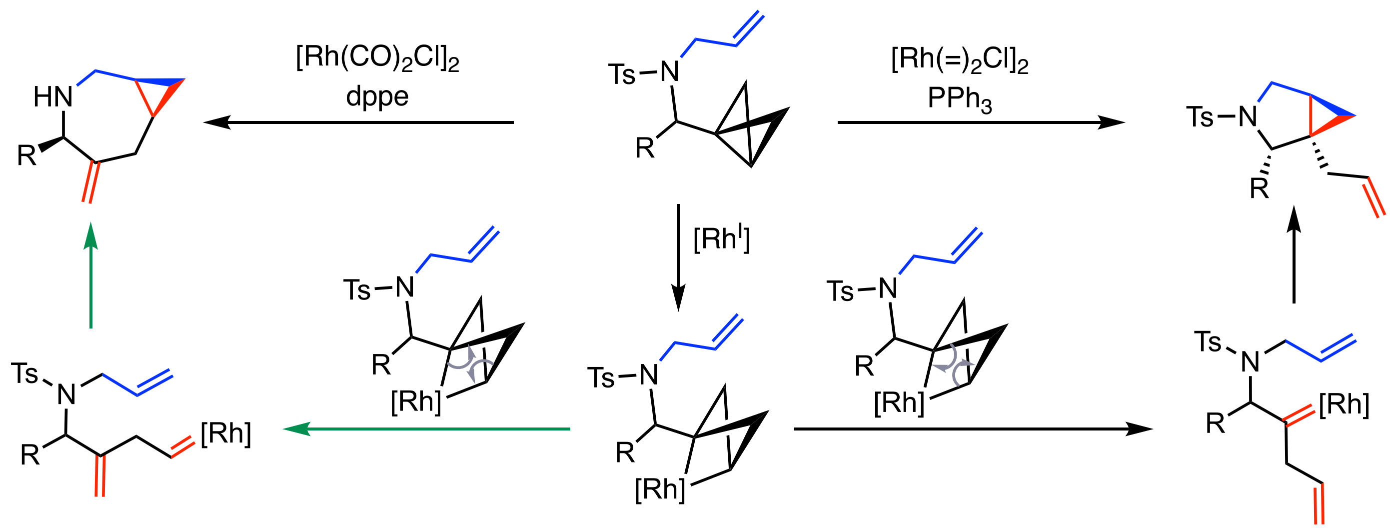


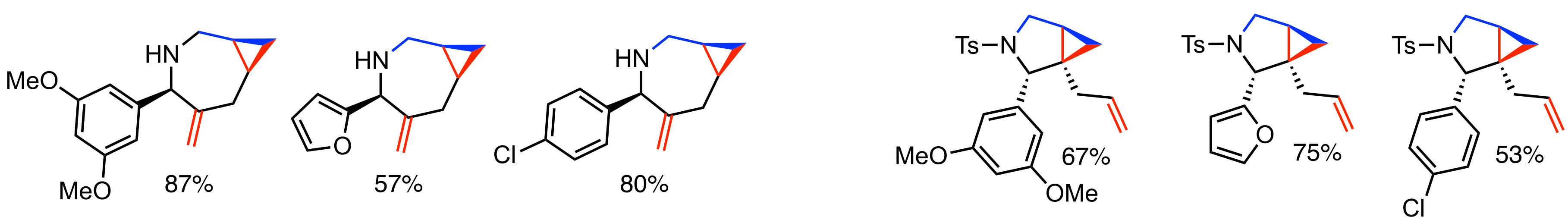


Wipf *et al. Acc. Chem. Res.*, 2015, *48*, 1149; Wipf and Walczak *Angew. Chem. Int. Ed.*, 2006, *45*, 4172

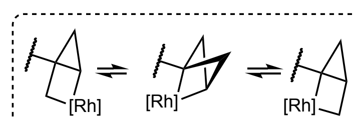
Metal-Catalyzed Reactions

Rh(I) Cycloisomerizations

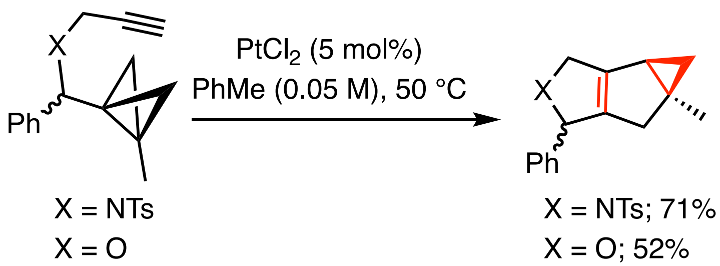


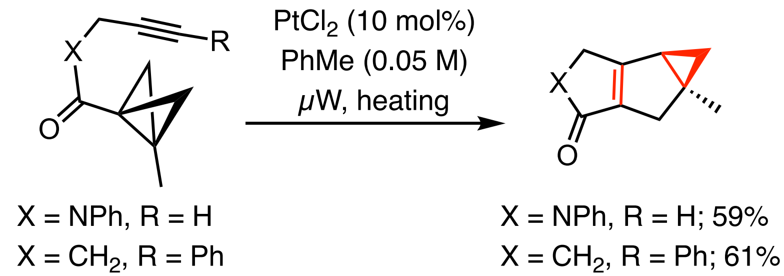


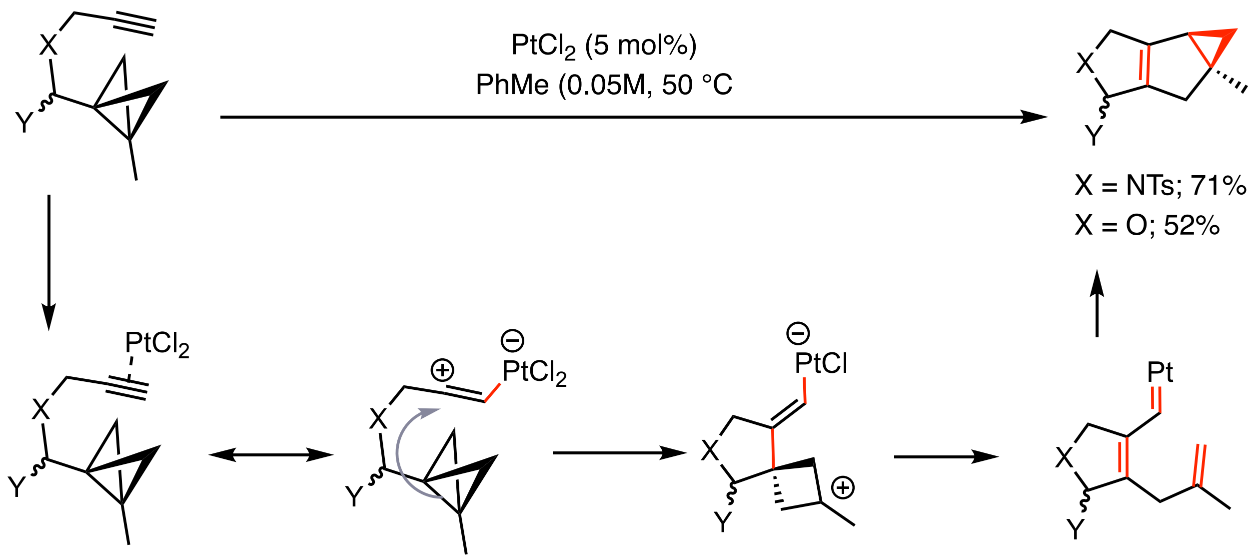
Wipf *et al.* *Acc. Chem. Res.*, 2015, *48*, 1149; Wipf and Walczak *J. Am. Chem. Soc.* 2008, *130*, 6924



Pt^{II} Cycloisomerizations







Wipf *et al. Acc. Chem. Res.*, 2015, *48*, 1149

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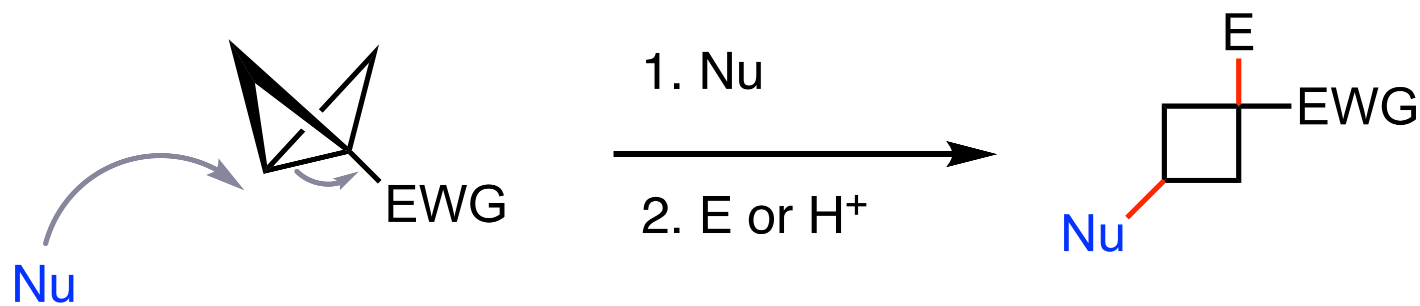
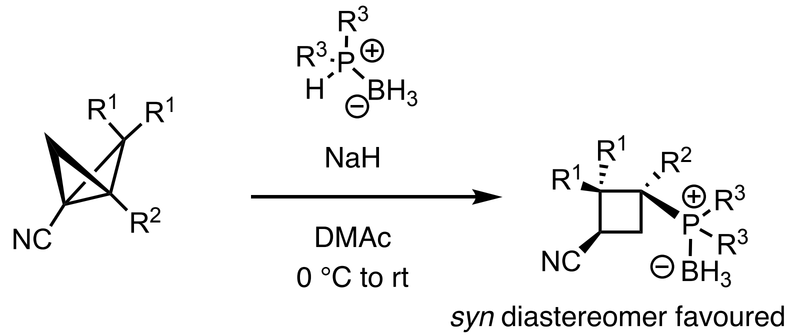
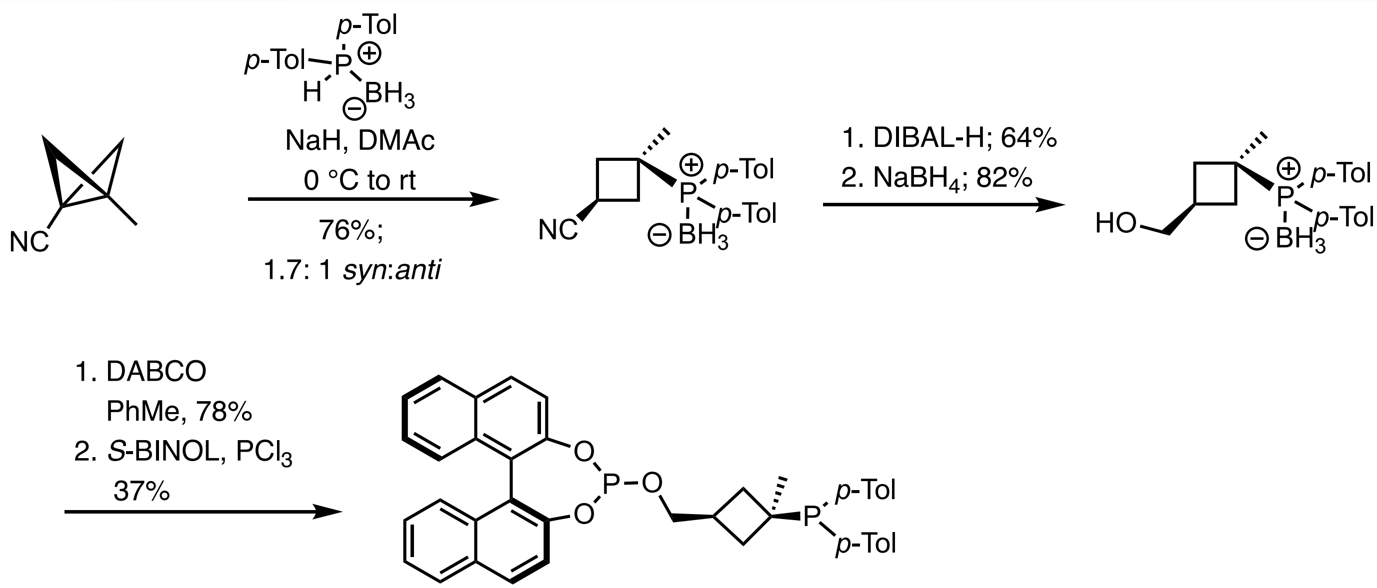
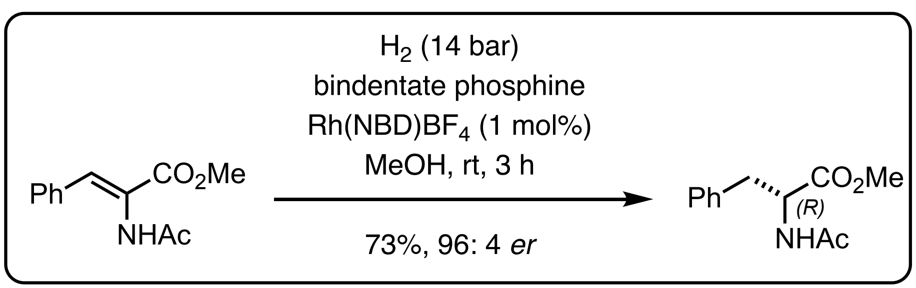
Applications: C–C Bond Functionalization



Strain-Release Hydrophosphination

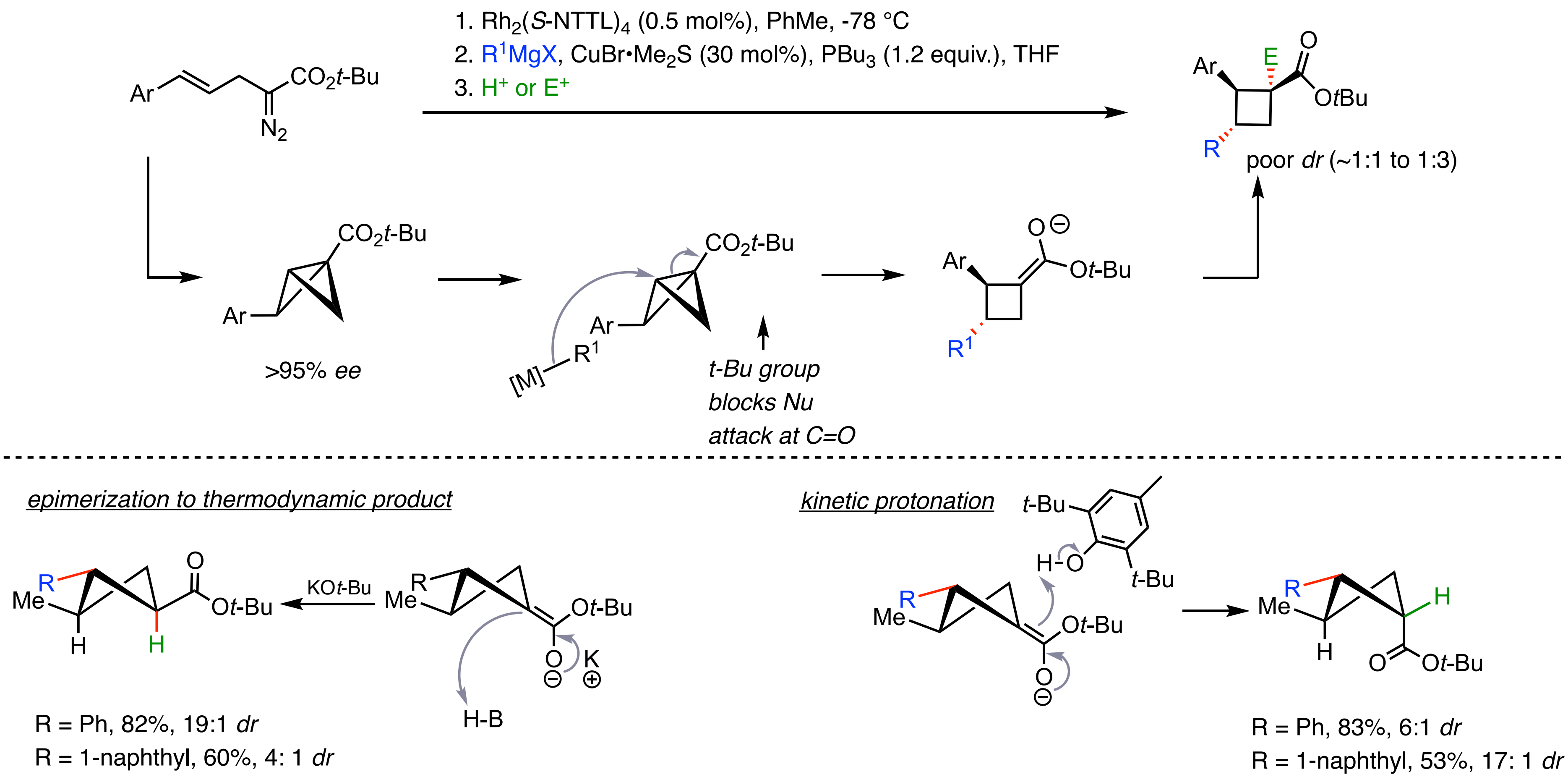






Wipf, Milligan et al *Org. Lett.* 2016, *18*, 4300

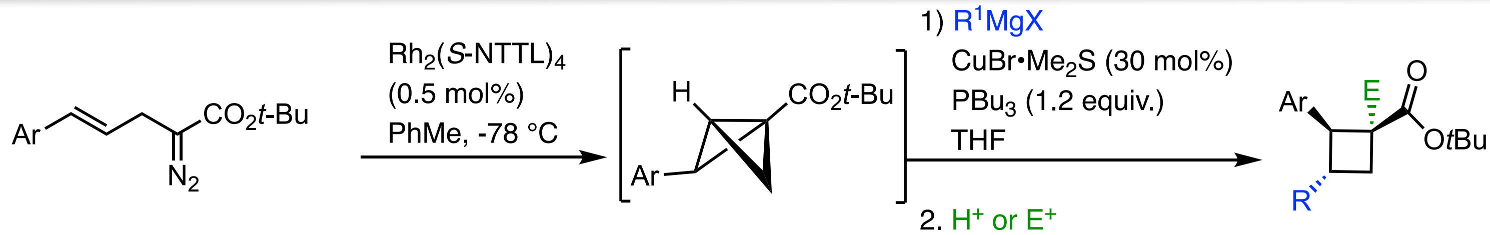
Chiral Cyclobutanes *via* Homoconjugate Addition

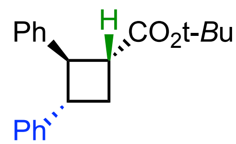


- One pot procedure (no β-H elimination to diene)
- High *ee* (> 95%) in bicyclobutanation
- *d.r.* upgraded by epimerization/ reversal od *dr* by kinetic protonation

Fox *J. Am. Chem.Soc*, 2013, *135*, 9283

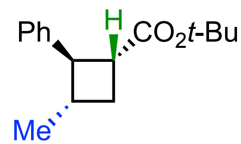
Chiral Cyclobutanes *via* Homoconjugate Addition





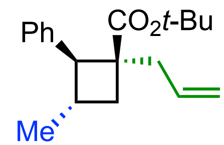
80%; E = $HCl_{(aq)}$

1.1: 1 *dr* (21:1 *dr* epim.)



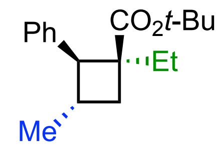
82%; E = $HCl_{(aq)}$

1.3: 1 *dr* (19:1 *dr* epim.)



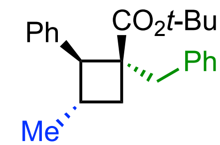
81%; E = AllylI

8: 1 *dr*

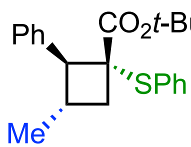


62%; E = EtI

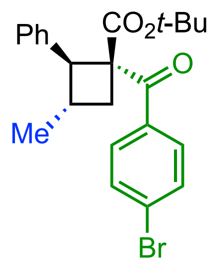
7: 1 *dr*



72%; E = BnBr

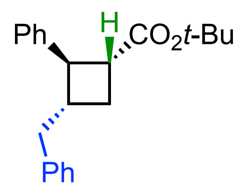


77% E = $(SPh)_2$



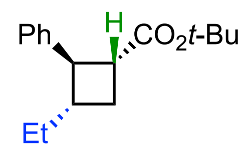
63%; E = *p*-Br(C_6H_4)COCl

14:1 *dr*, **X-ray**



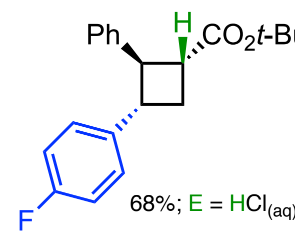
76%; E = $HCl_{(aq)}$

1:1.4 *dr* (21:1 *dr* epim.)



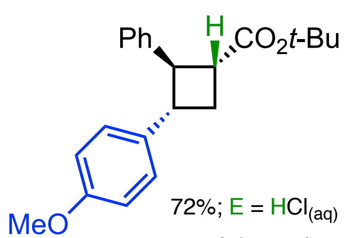
73%; E = $HCl_{(aq)}$

1:1.2 *dr* (17:1 *dr* epim.)



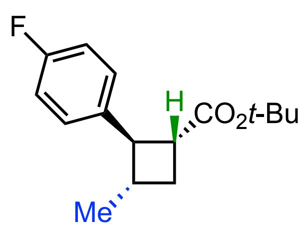
68%; E = $HCl_{(aq)}$

1:1 *dr* (21:1 *dr* epim.)



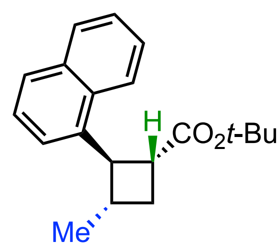
72%; E = $HCl_{(aq)}$

1:1 *dr* (30:1 *dr* epim.)



74%; E = $HCl_{(aq)}$

1.4:1 *dr* (19:1 *dr* epim.)



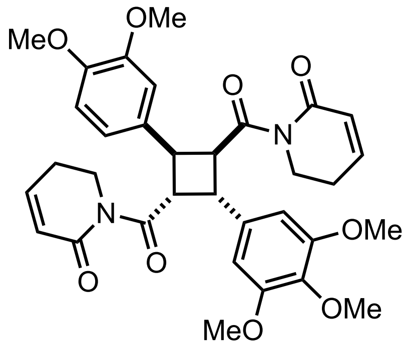
72%; E = $HCl_{(aq)}$

1:3 *dr* (4:1 *dr* epim.)

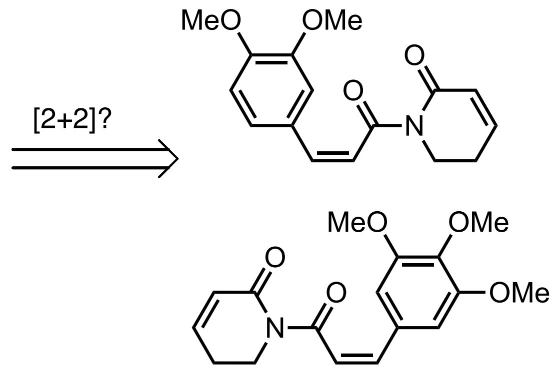
- All other methods to form 1,3 functionalized cyclobutanes require prior functionalization of cyclobutane

Fox *J. Am. Chem. Soc.* 2013, *135*, 9283

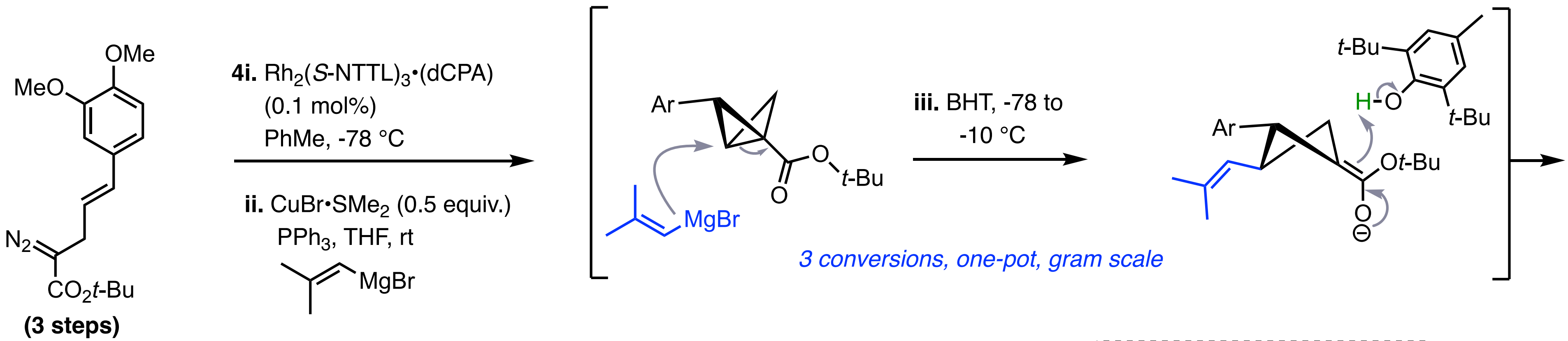
Enantioselective Total Synthesis of Piperarborenine B

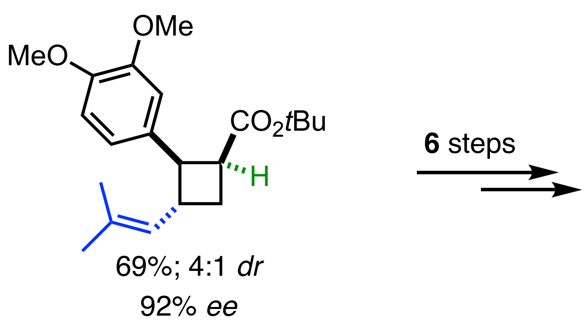


- Pseudo-symmetric
- Anti-cancer properties



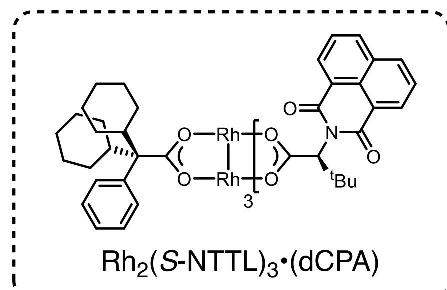
- Homodimerization
- Orientation (head-head vs head-tail)
- *E*/*Z* isomerization





piperarborenine B

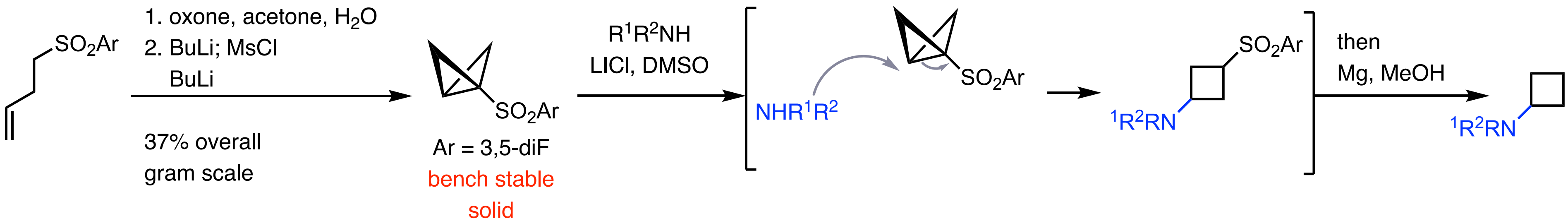
10-steps/ 8% overall yield
>400 mg prepared

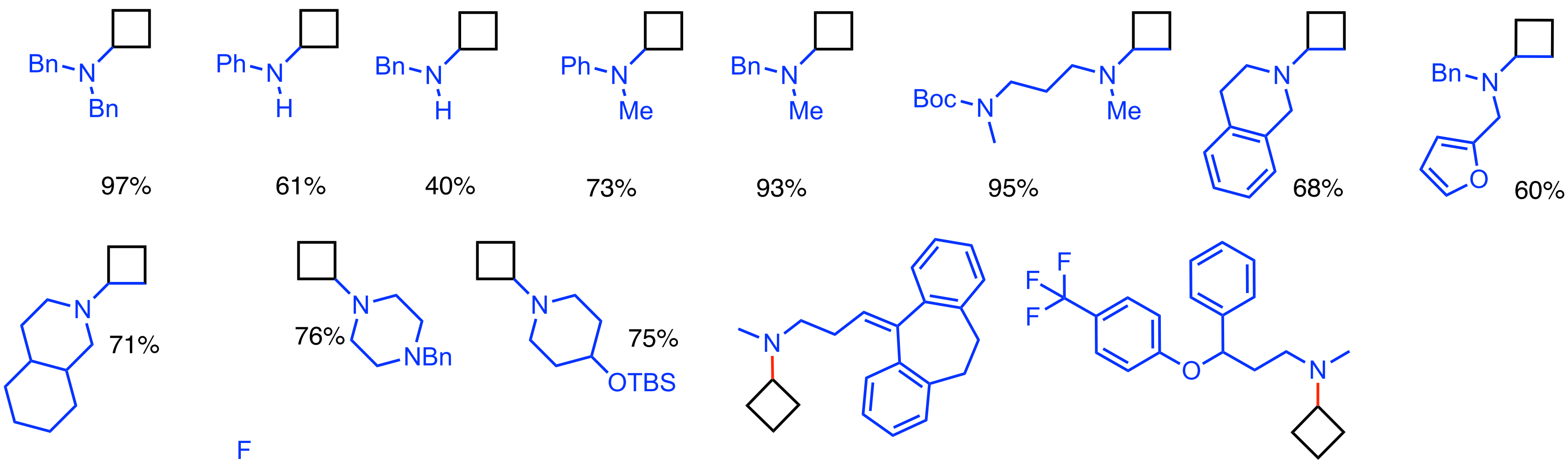


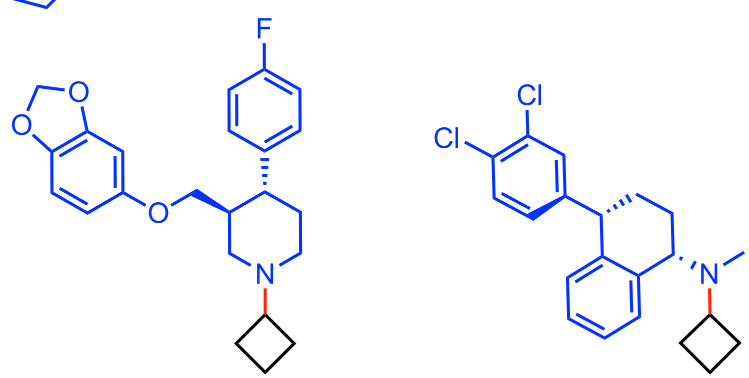
Rh$_2$(*S*-NTTL)$_3$•(dCPA)

Fox *Angew. Chem. Int. Ed.*, 2016, *55*, 4983

Strain-Release Amination







- 15 structurally diverse cyclic, acylic , 1° and 2° amines or anilines
- four late stage pharmaceuticals.

Baran *JACS*, 2017, *139*, 3209

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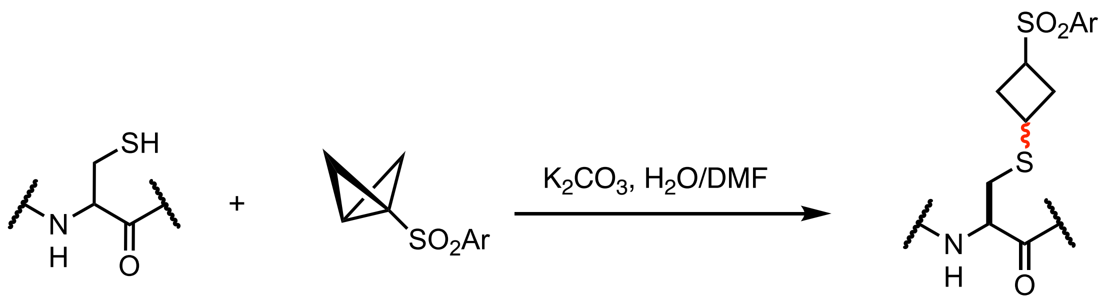
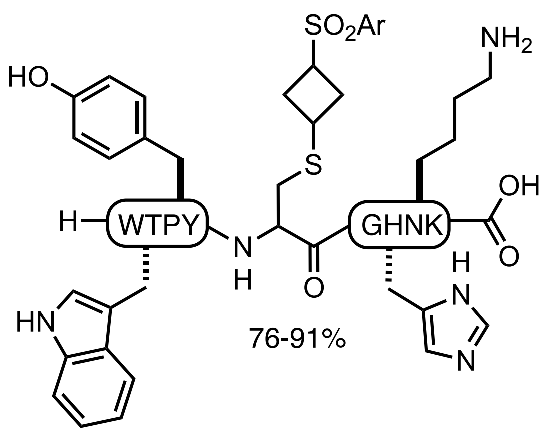
Peptide Labeling

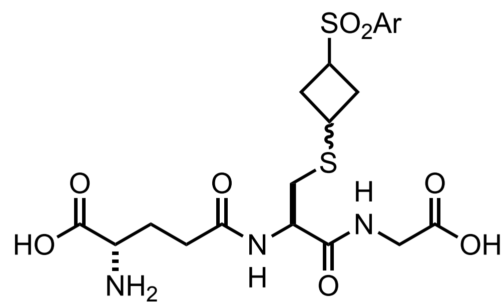


AA	Yield*
Tyr	NR
Trp	NR
Lys	NR
Ser	NR
His	NR
Cys	45%

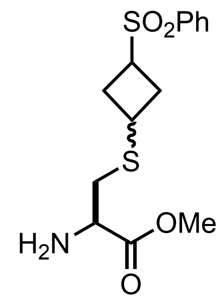
*isolated yields



76-91%



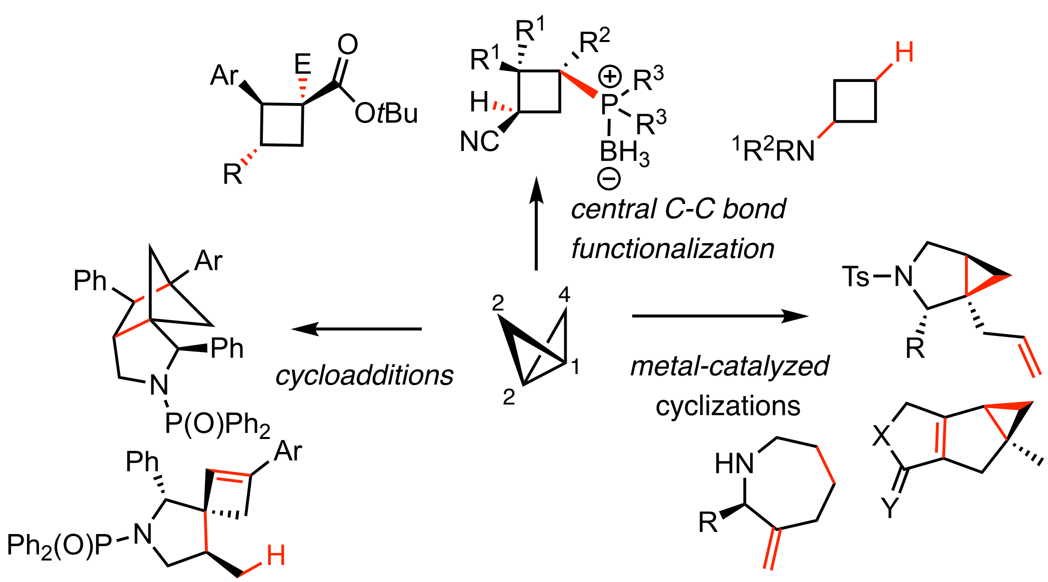
81-89%

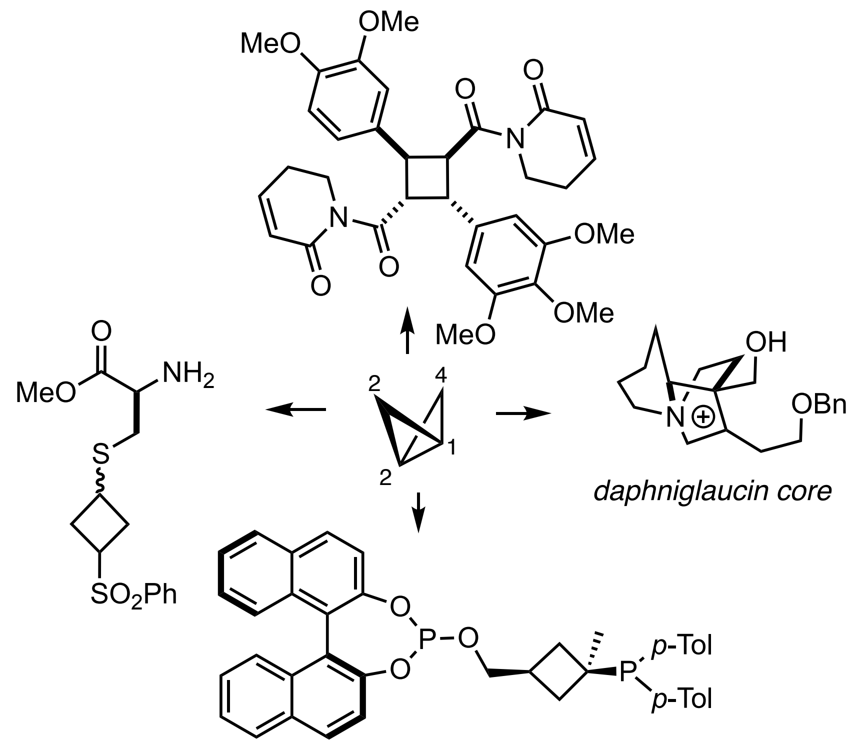


88%

Baran *JACS*, 2017, *139*, 3209

Summary BCB





REACTIONS
- Thermal cycloadditions
- TM-catalyzed heterocycle synthesis
- C-C bond Difunctionalization

APPLICATIONS
- Total synthesis
- Peptide labeling
- Chiral ligand synthesis

Thank you!

- Dr Peter Wipf
- Wipf group members past and present