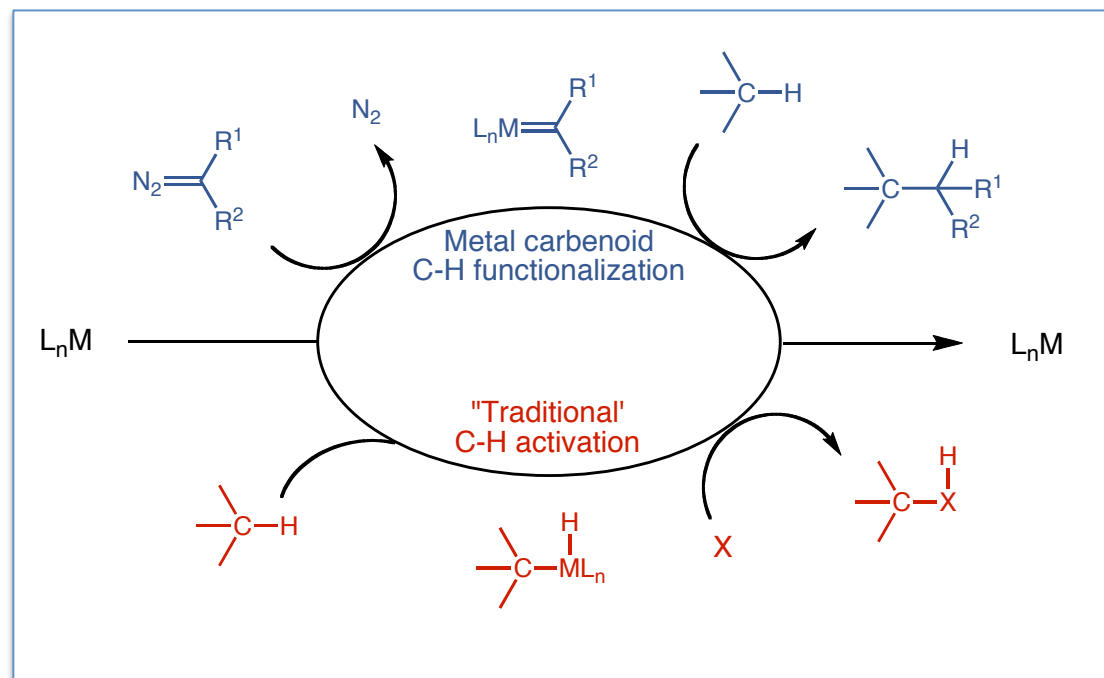


Recent Developments in Rhodium Carbene and Nitrene Chemistry



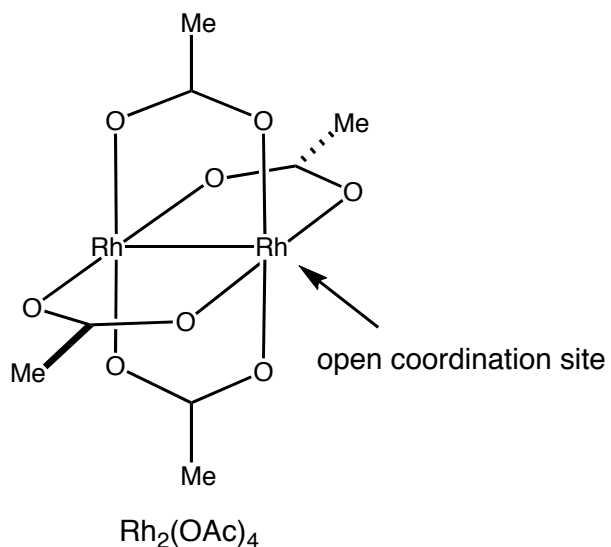
MacMillan Group Meeting

February 3, 2010

Brian Ngo Laforteza

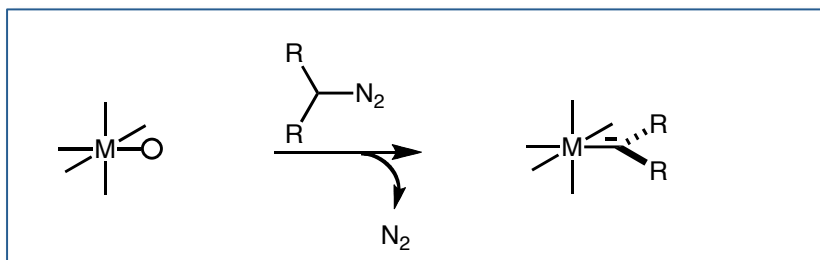
Rhodium Carbene and Nitrene Chemistry Catalysts

- Rhodium(II) acetate – prototypical structure of dirhodium carbene/nitrene catalysts



- "Paddle wheel" catalyst

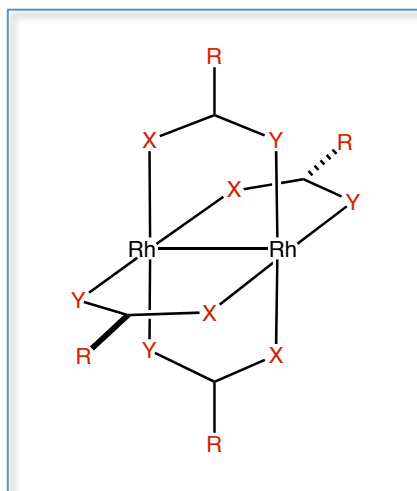
- Only one rhodium center functions as carbene binding site
 - Second acts as electron sink to increase electrophilicity of carbene moiety – additional stabilization



- Catalyst binds carbene through strong σ -acceptor interactions and weak π -back-donation

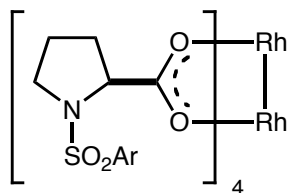
Rhodium Carbene and Nitrene Chemistry Catalysts

- Two widely utilized classes of catalysts



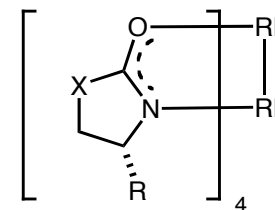
- Symmetry may vary depending on orientation of ligand binding

Rhodium(II) carboxylates



- Very active at decomposing diazo compounds
- Optimal for intermolecular C–H insertion reactions
- Later generations possess rigid bridged structure

Rhodium(II) carboxamidates

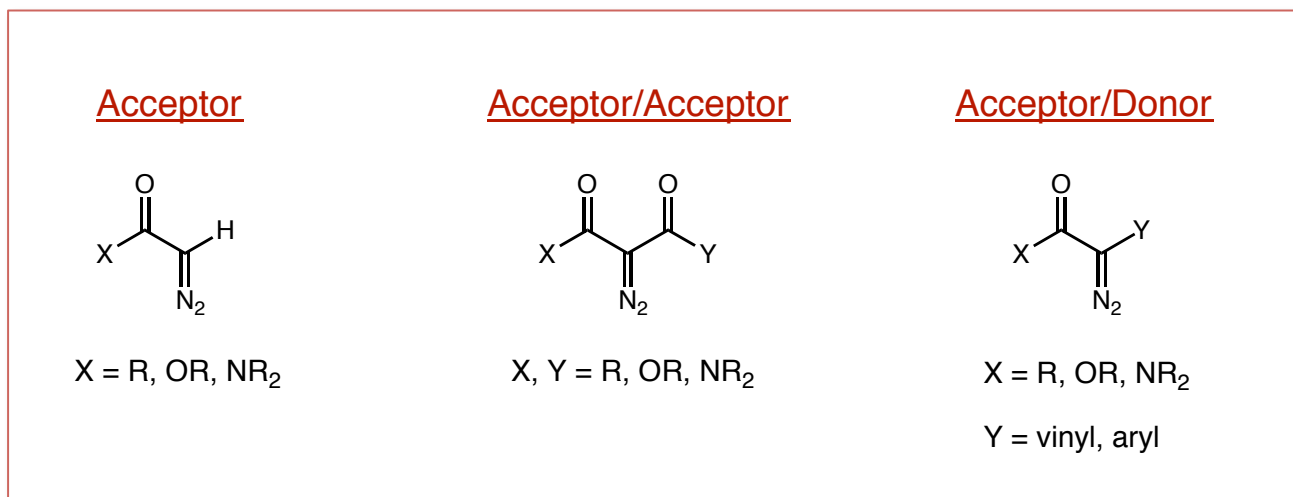


X = O, NCOR

- Generally much more rigid than rhodium carboxylates
- Optimal for enantioselective intramolecular C–H insertion

Rhodium Carbene Chemistry The Metal Carbene

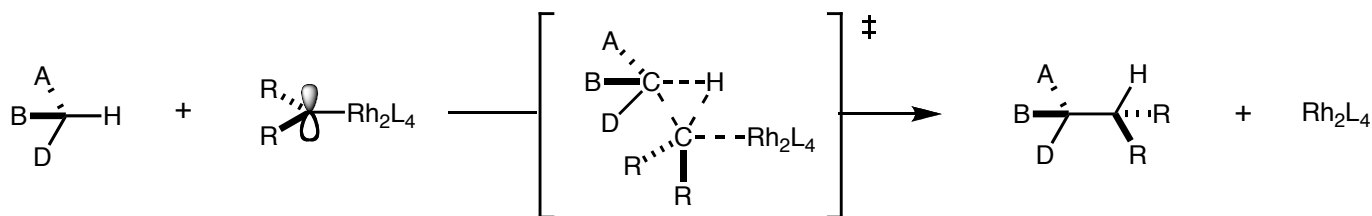
- Control carbene reactivity through substituents - “acceptors” and “donors”



- Acceptor/acceptor and acceptor/donor groups stabilize diazo compound – more active catalyst needed for decomposition
- Carbenoids formed from acceptor/acceptor diazo compounds very electrophilic
- Donor substituent stabilizes carbenoid through resonance

Rhodium Carbene Chemistry Trends in C–H Activation

- Generally believed to occur through concerted (though asynchronous), three-centered transition state



- Build-up of positive charge at carbon undergoing C-H cleavage
- C–H activation occurs preferentially at sites that can stabilize δ^+

α -hetero C–H, allylic C–H, benzylic C–H preferred sites of activation

Reactivity of C–H bonds undergoing insertion

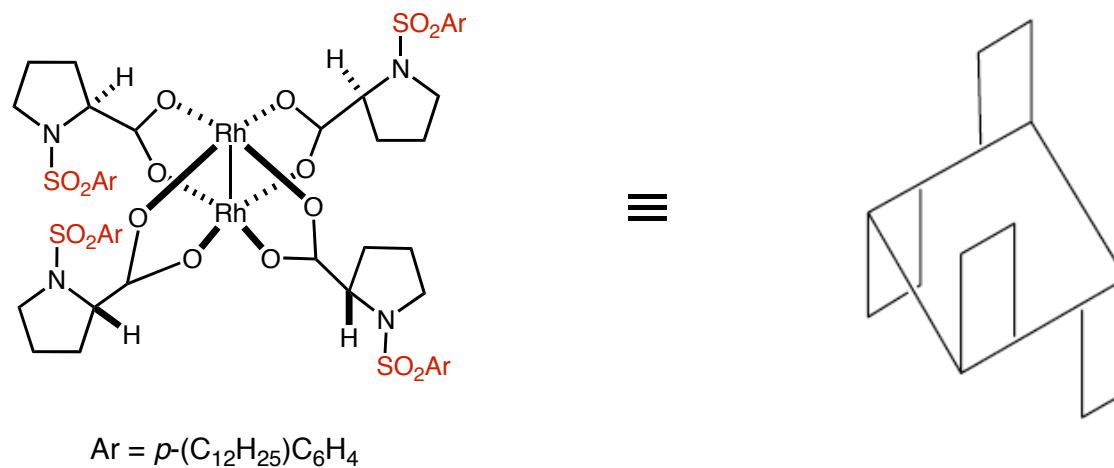
methine > methylene >> methyl

- Steric factors, however, can sometimes override this selectivity

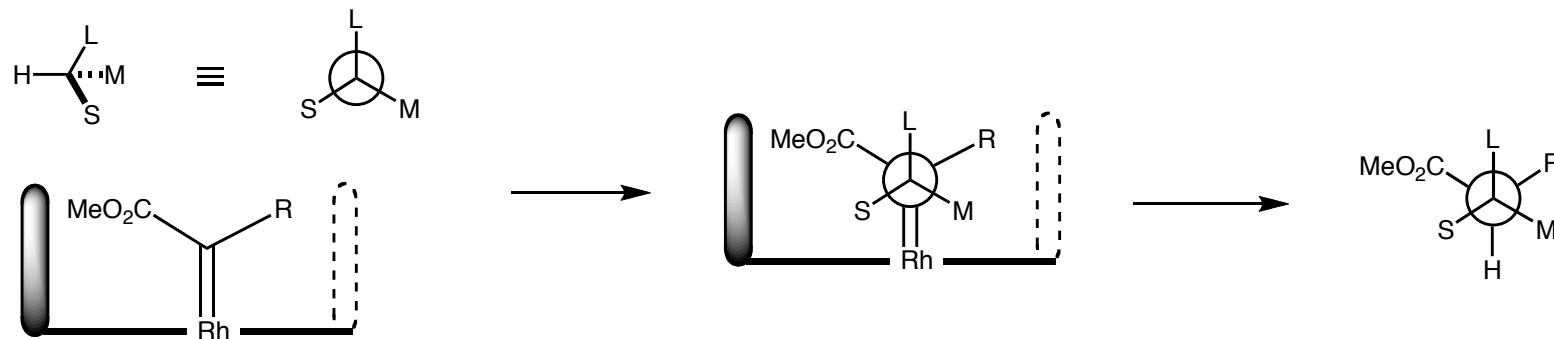
Rhodium Carbene Chemistry

$Rh_2(DOSP)_4$

- Rhodium(II) carboxylate developed and heavily utilized by Huw M. L. Davies (Emory)



- Stereochemical model

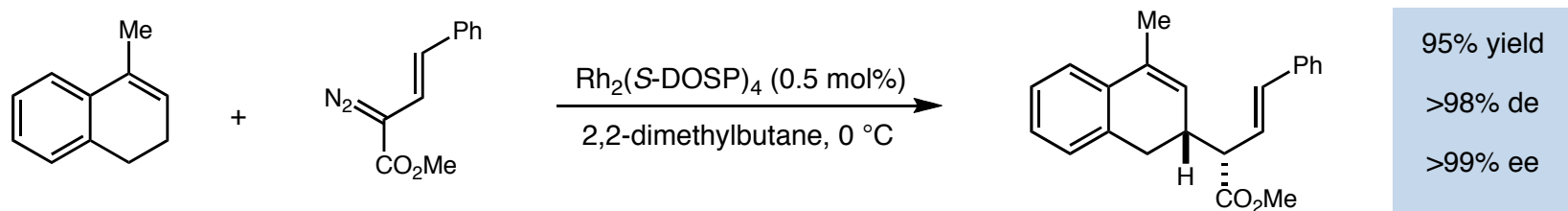


- Esther considered sterically demanding group

Davies et al. *Chem. Rev.* **2003**, *103*, 2861.
 Davies et al. *J. Org. Chem.* **2009**, *74*, 6555.

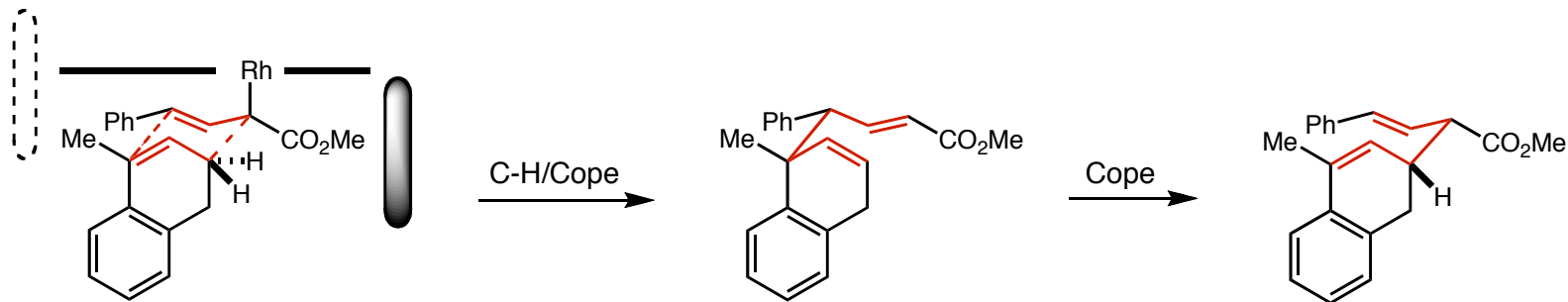
Combined C–H Insertion/Cope Rearrangement Synthesis of 4-Substituted Indoles

- C–H insertion into 4-methyl-1,2-dihydronaphthalene proceeded with high diastereoselectivity



- Selectivity unusually high compared to what is known for C–H insertion into cycloalkenes
- Mechanism more complex than appears?

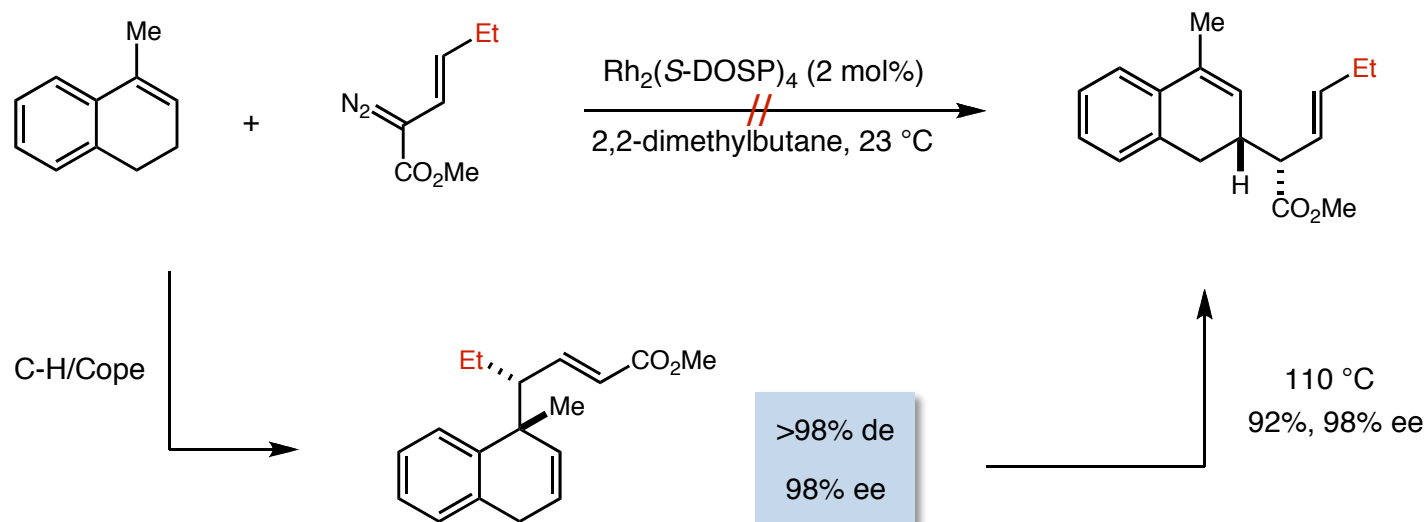
- Proposed combined C–H activation/Cope rearrangement, followed by retro-Cope rearrangement



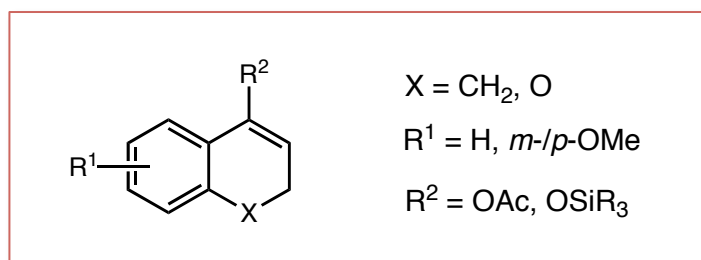
- Fully conjugated product favored

Combined C–H Insertion/Cope Rearrangement Retro-Cope

■ Mechanistic analysis

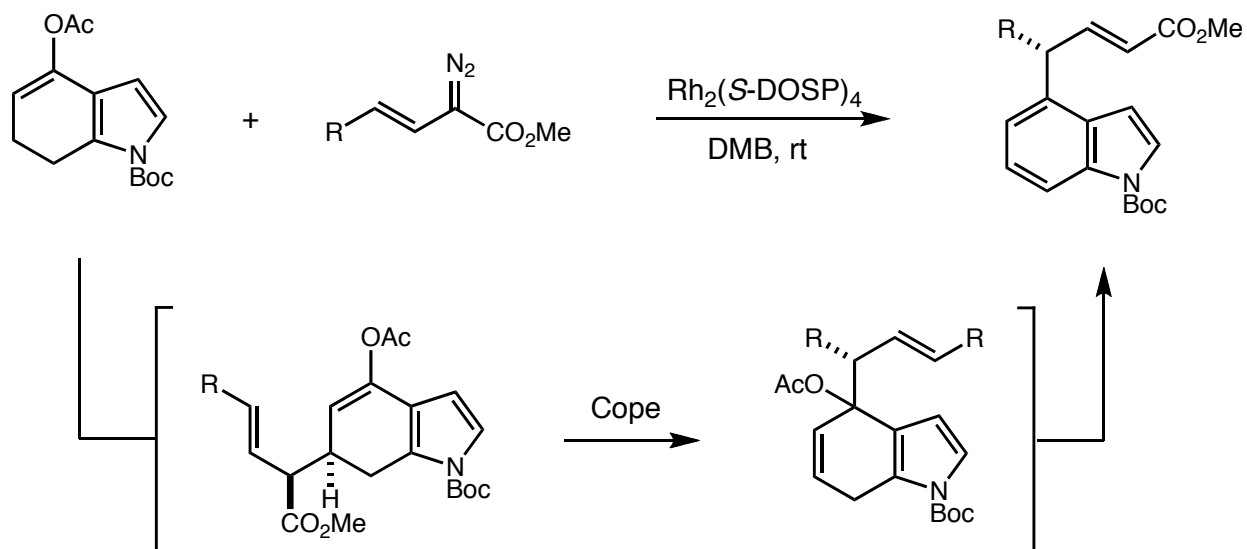


■ Preliminary scope



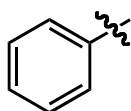
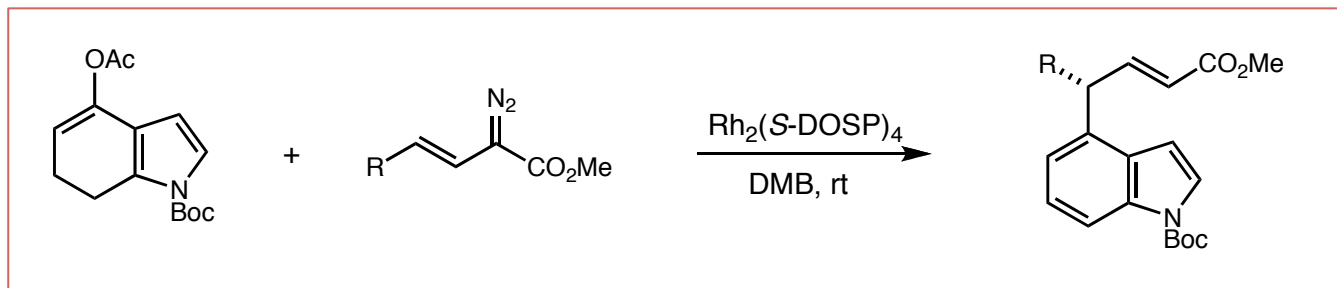
Combined C–H Insertion/Cope Rearrangement Synthesis of 4-Substituted Indoles

- C–H insertion into dihydroindoles followed by Cope rearrangement and aromatization

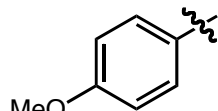


Combined C–H Insertion/Cope Rearrangement Synthesis of 4-Substituted Indoles

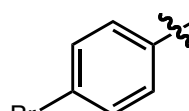
- C–H insertion into dihydroindoles followed by Cope rearrangement and aromatization



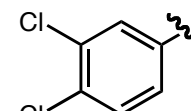
65%, 98% ee



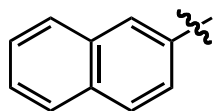
52%, 98% ee



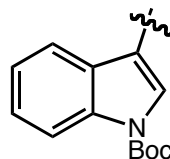
53%, 99% ee



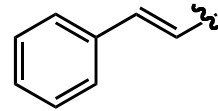
45%, 98% ee



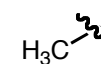
56%, 98% ee



64%, 98% ee



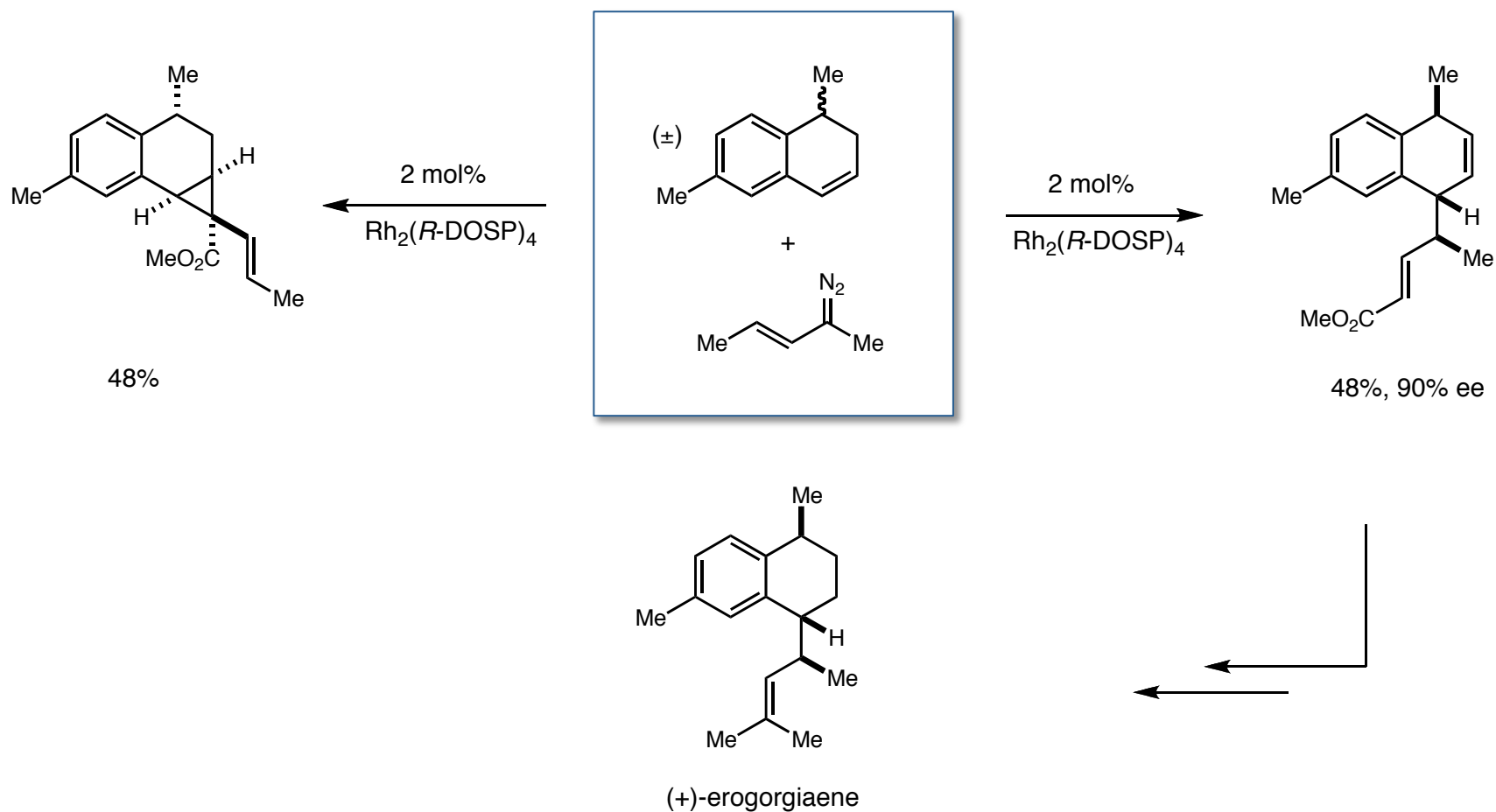
65%, 99% ee



61%, 99% ee

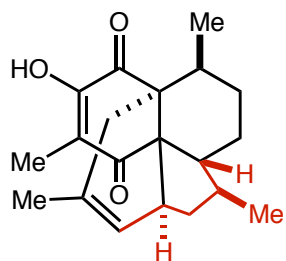
Combined C–H Insertion/Cope Rearrangement Application Towards Natural Product Synthesis

■ (+)-erogorgiaene: kinetic enantiodifferentiation

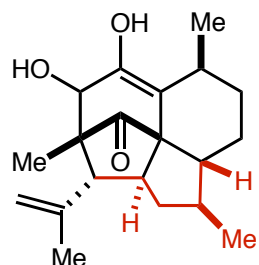


Combined C–H Insertion/Cope Rearrangement Application Towards Natural Product Synthesis

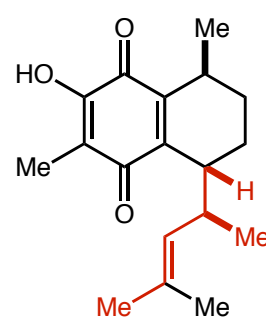
- Similar enantiodifferentiating step used in analogous syntheses



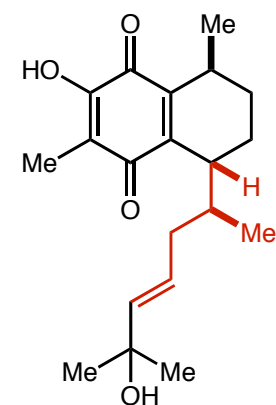
(-)-colombiasin A



(-)-elisapterosin B



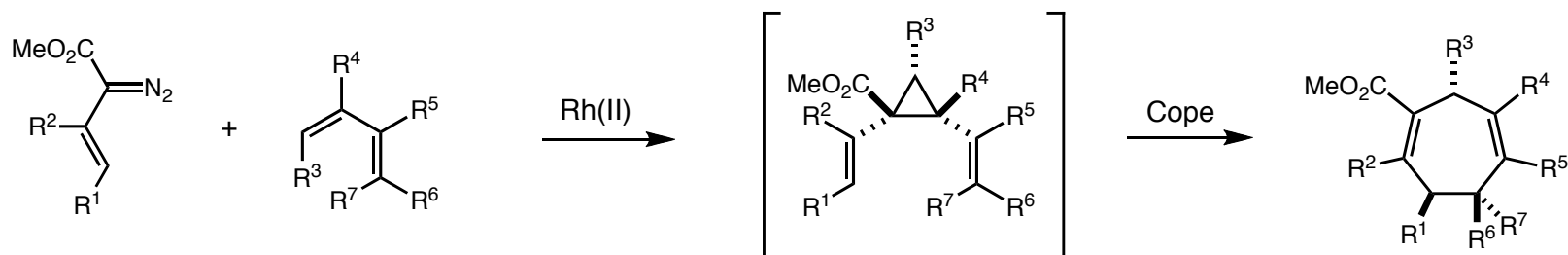
(+)-elisabethadione



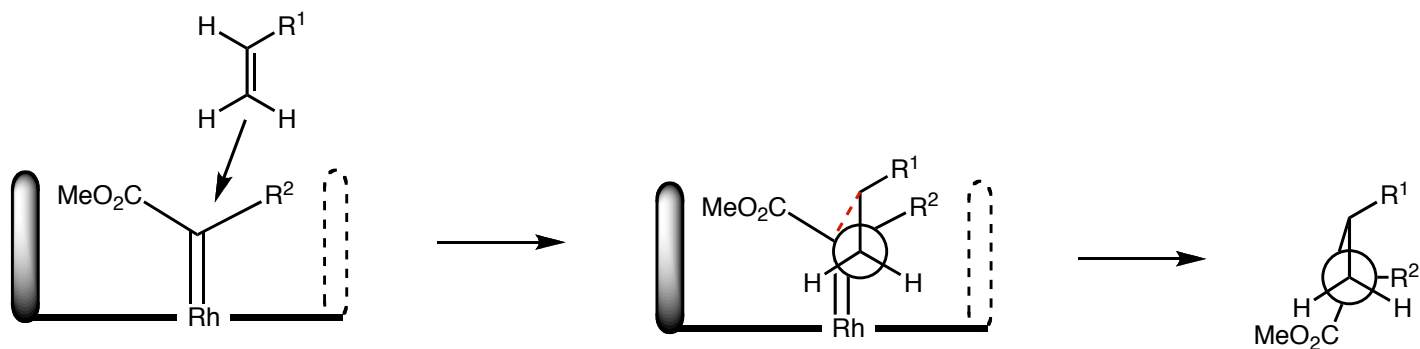
(+)-*p*-benzoquinone

Tandem Cyclopropanation/Cope Rearrangement Formal [4+3] Cycloadditions

■ General idea

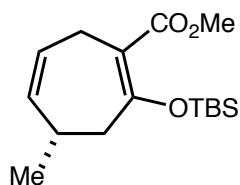
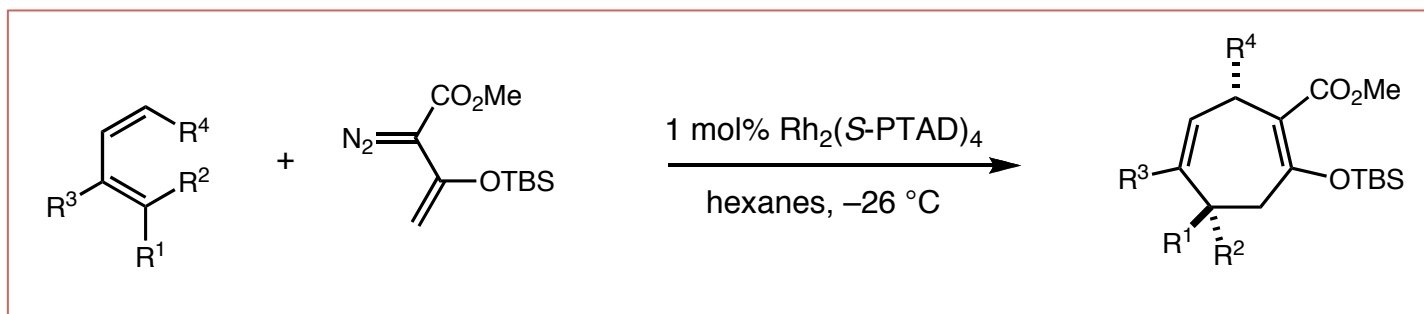


■ Stereochemical model for cyclopropanation: based on “end-on” approach of olefin

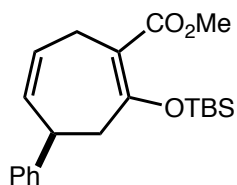


Tandem Cyclopropanation/Cope Rearrangement Formal [4+3] Cycloadditions

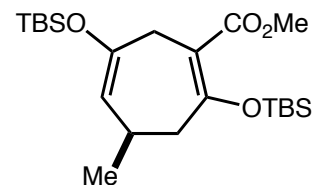
Scope of dienes



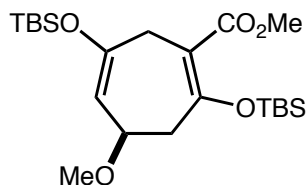
80% yield
87% ee



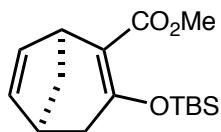
82% yield
95% ee



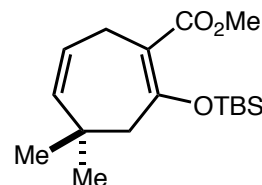
70% yield
99% ee



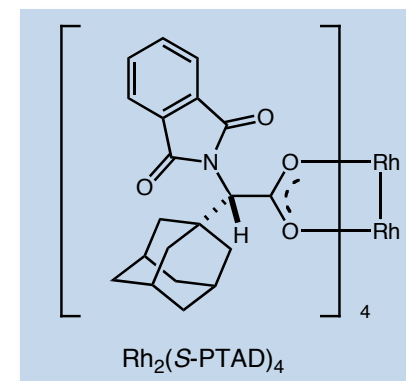
63% yield
95% ee



86% yield
92% ee

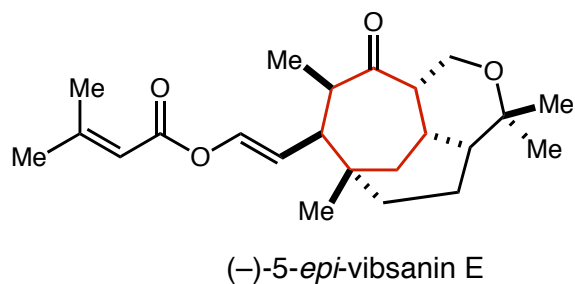
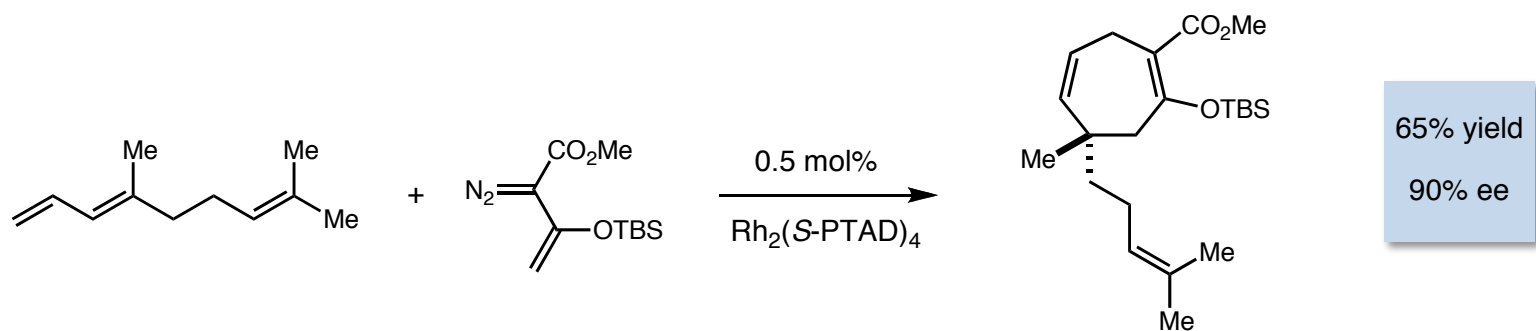
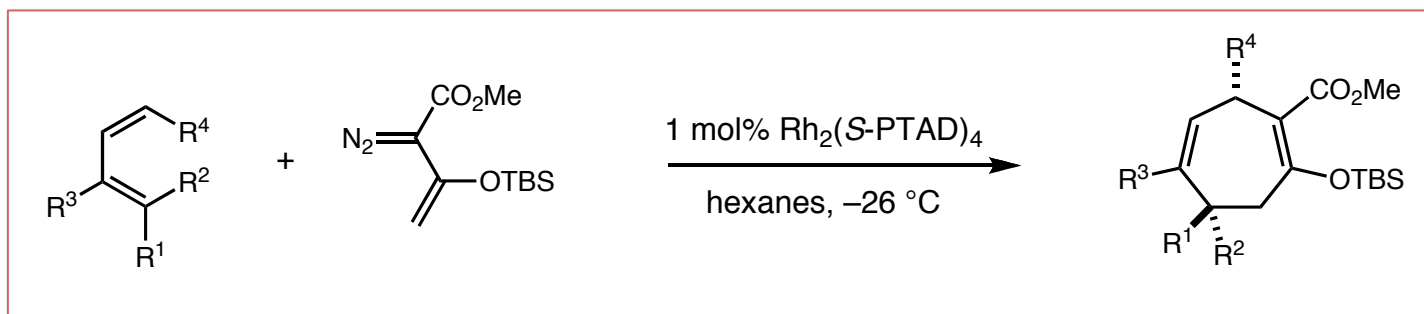


57% yield



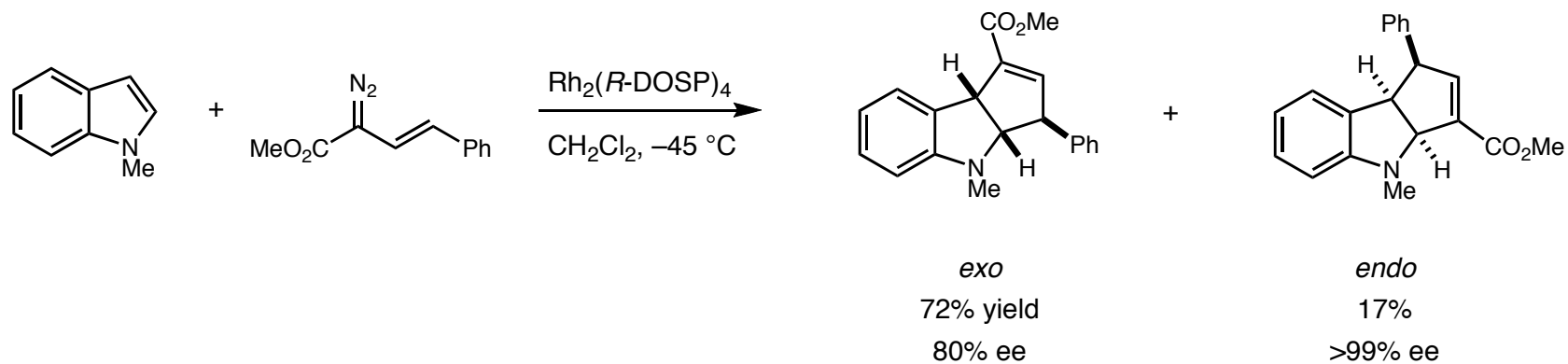
Tandem Cyclopropanation/Cope Rearrangement Formal [4+3] Cycloadditions

■ Total synthesis of (-)-5-*epi*-vibsanin E

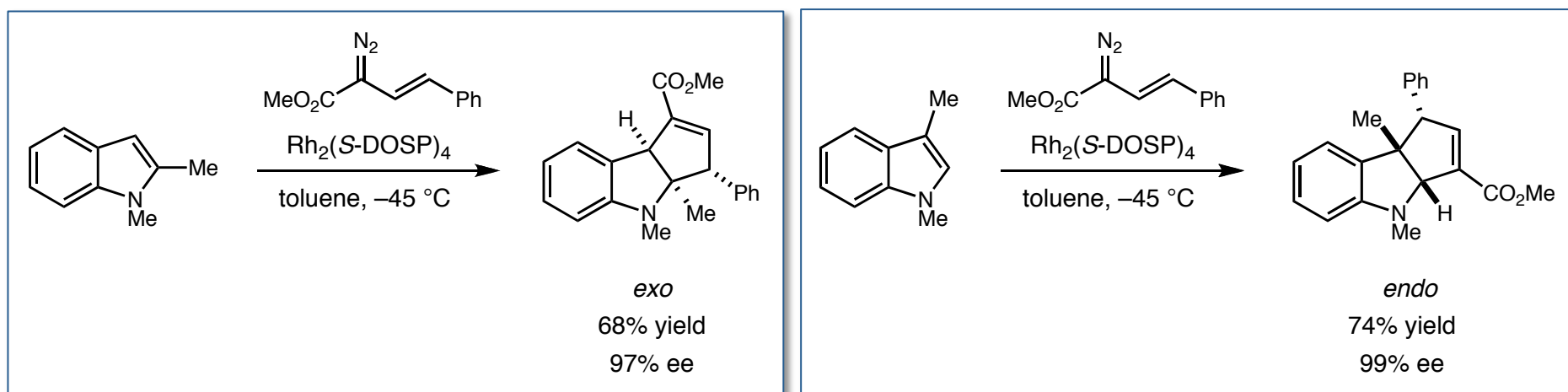


Nucleophilic Attack on Rhodium Carbenes Formal [3+2] Annulation of Indoles

- Two isomers of annulated product initially observed

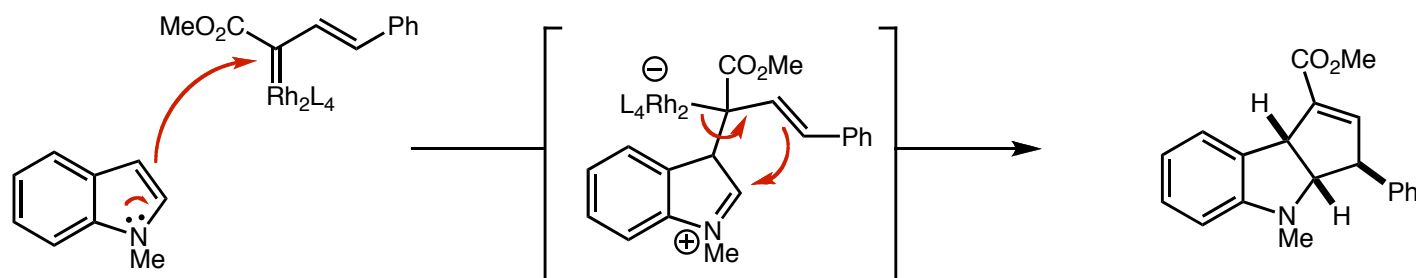


- Competition between C2- and C3-nucleophilic attack?



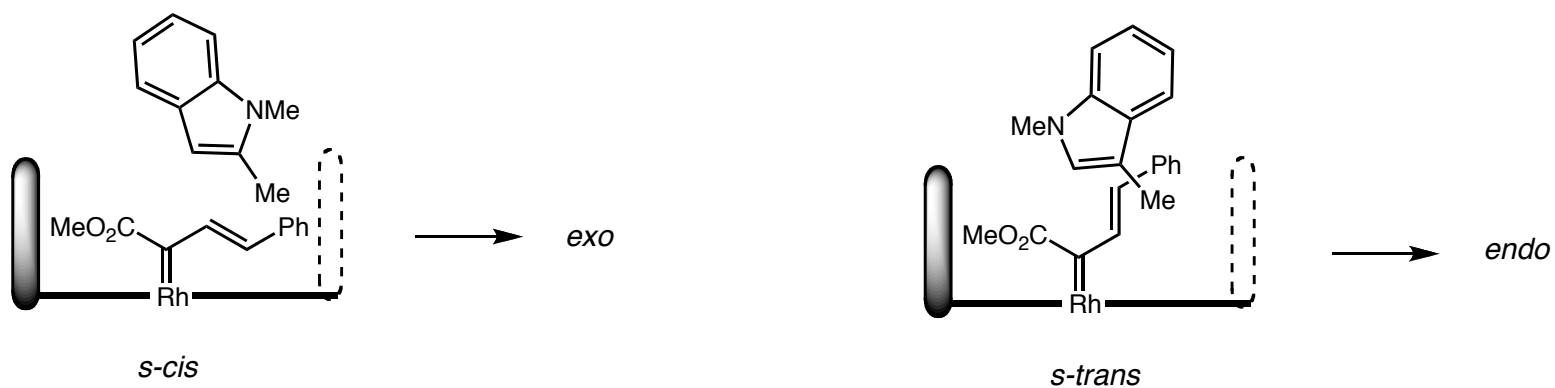
Nucleophilic Attack on Rhodium Carbenes Formal [3+2] Annulation of Indoles

Proposed mechanism



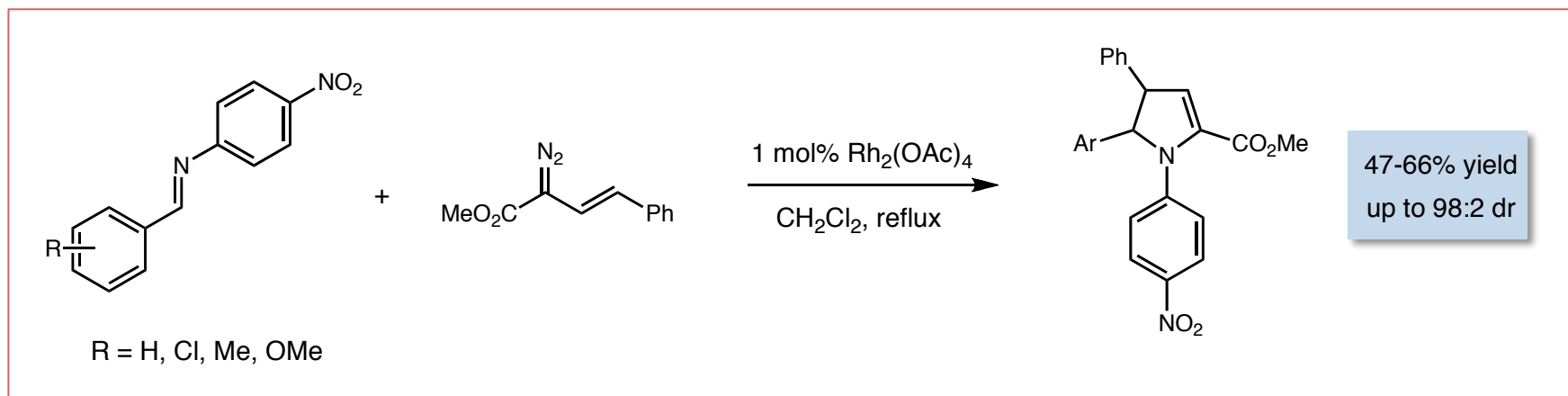
Zwitterionic intermediate

Stereochemical rationale: configuration of carbene and olefin govern diastereoselectivity

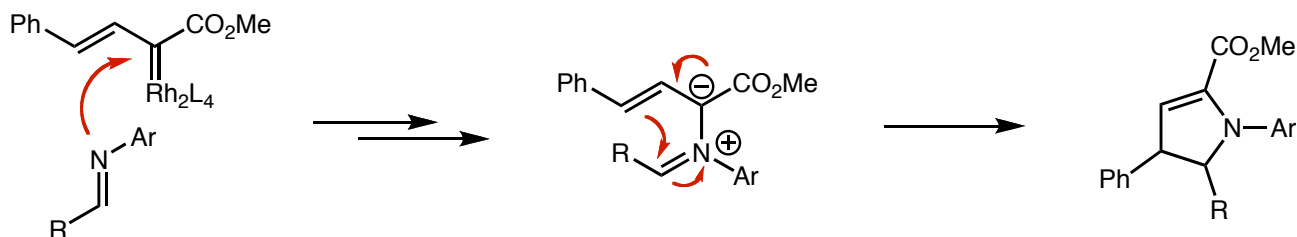


Nucleophilic Attack on Rhodium Carbenes Imines As Nucleophiles

- Bicyclic pyrrolidines are formed when excess diazo compound is used

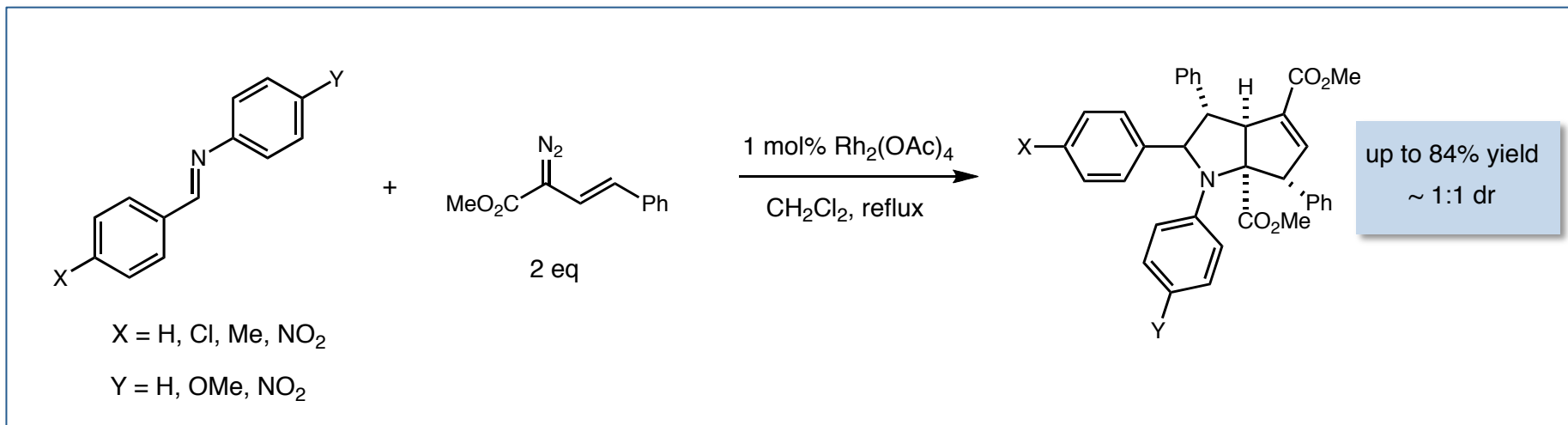


- Proposed mechanism

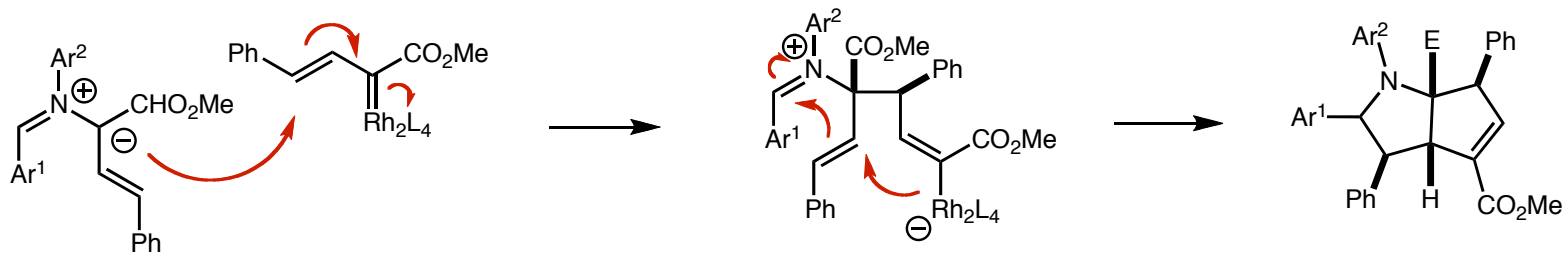


Nucleophilic Attack on Rhodium Carbenes Imines As Nucleophiles

■ Bicyclic pyrrolidines are formed when excess diazo compound is used

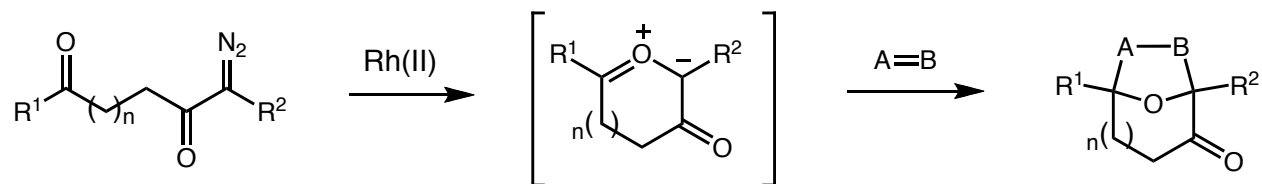


■ Proposed mechanism



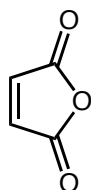
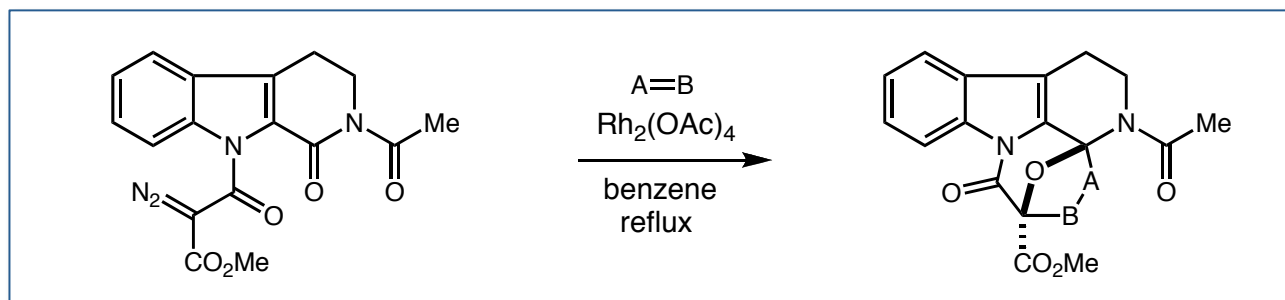
Rhodium(II) Carbenoid Cyclization/Cycloaddition Cascade Cycloadditions with Carbonyl Ylides

- Carbonyl oxygen can also act as nucleophile

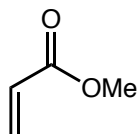


- Carbonyl ylide

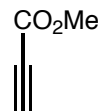
- Albert Padwa (Emory) – amide cyclization followed by [3+2] cycloaddition



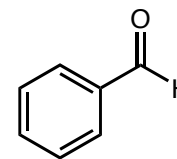
75%



77%



78%

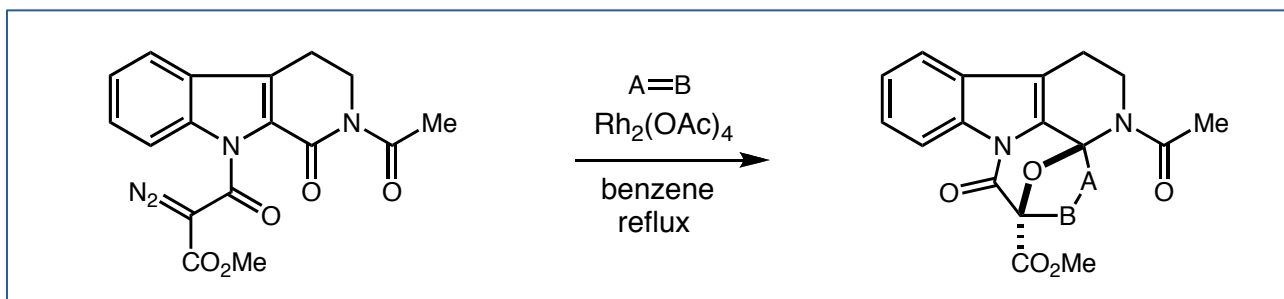


85%

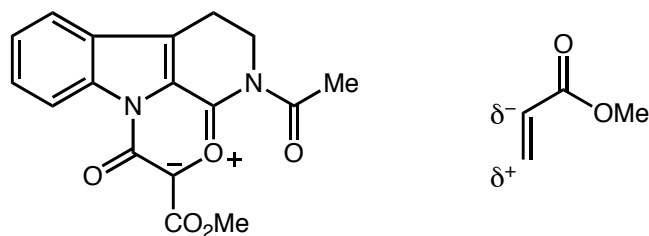
Padwa et al. *Tetrahedron* **2008**, 64, 988.

Rhodium(II) Carbenoid Cyclization/Cycloaddition Cascade Cycloadditions with Carbonyl Ylides

- Reactions highly regio- and stereoselective



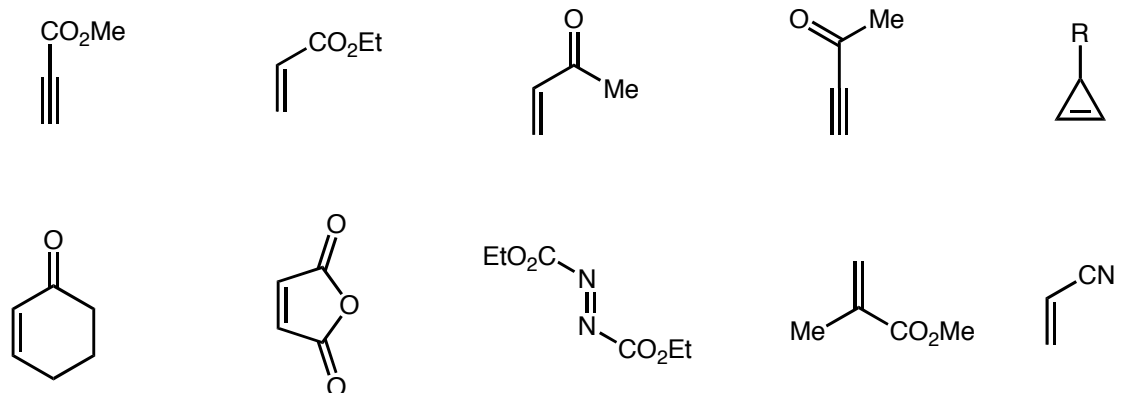
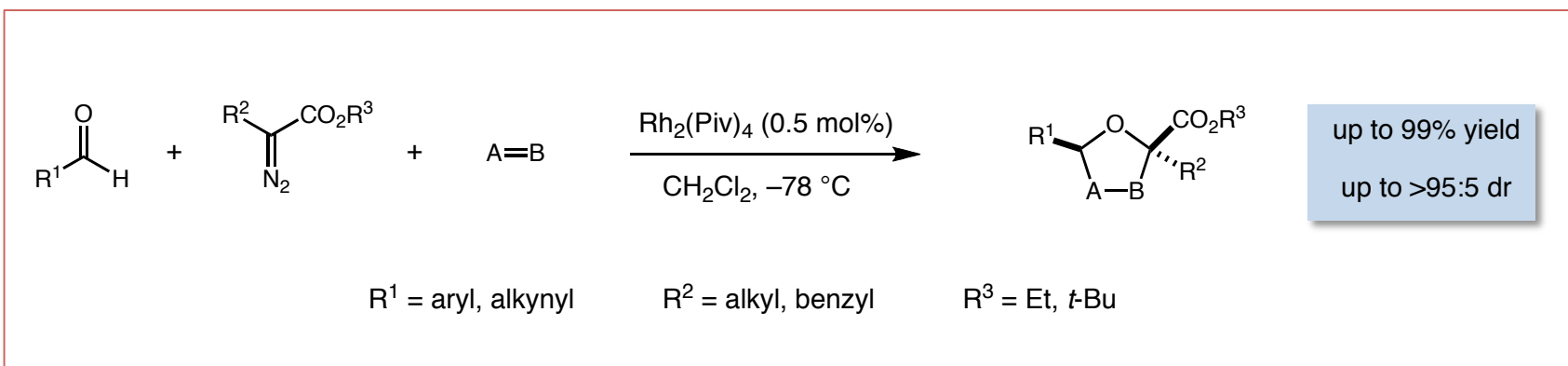
- Regioselectivity governed by FMO interactions – HOMO of carbonyl ylide, LUMO of dipolarophile
- Predominant *exo*-selectivity result of steric interactions



Carbonyl Ylides

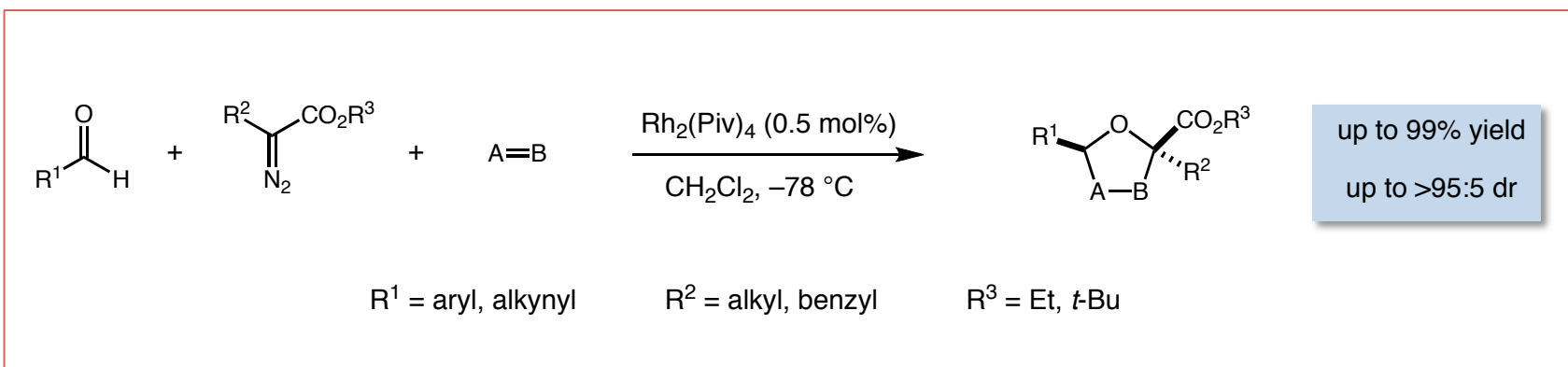
Three-Component Cycloaddition

■ Joe Fox (Delaware): Coupling between aldehydes, diazo compounds, and dipolarophiles

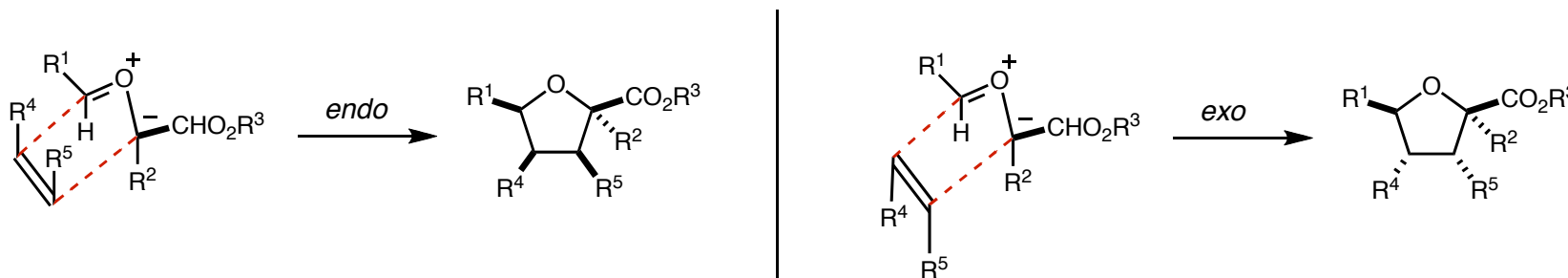


Carbonyl Ylides Three-Component Cycloaddition

- Joe Fox (Delaware): Coupling between aldehydes, diazo compounds, and dipolarophiles

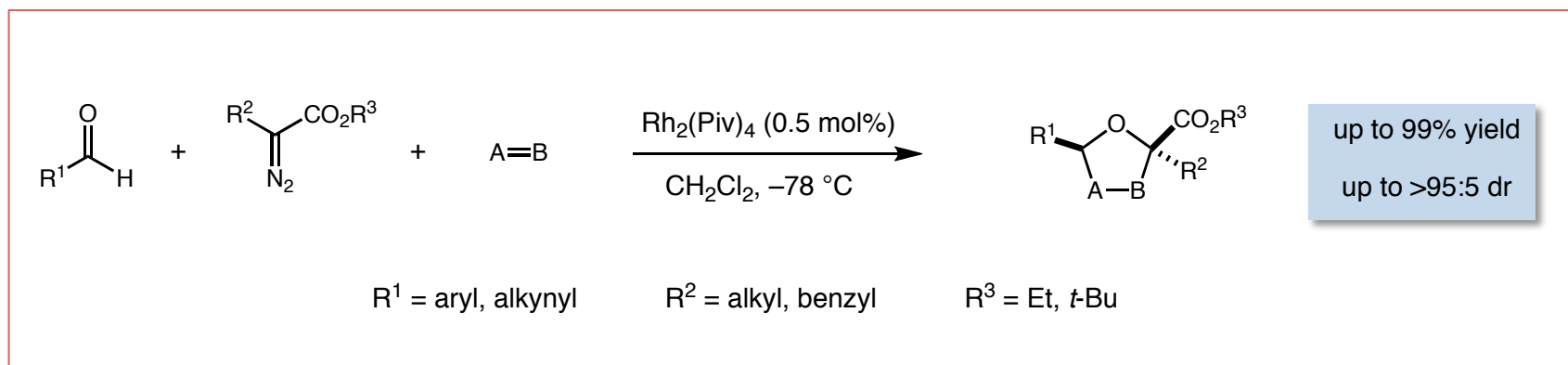


- High diastereoselectivity result of *endo* approach of dipolarophile

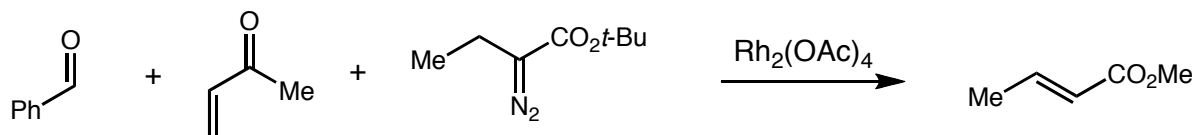


Carbonyl Ylides Three-Component Cycloaddition

- Joe Fox (Delaware): Coupling between aldehydes, diazo compounds, and dipolarophiles

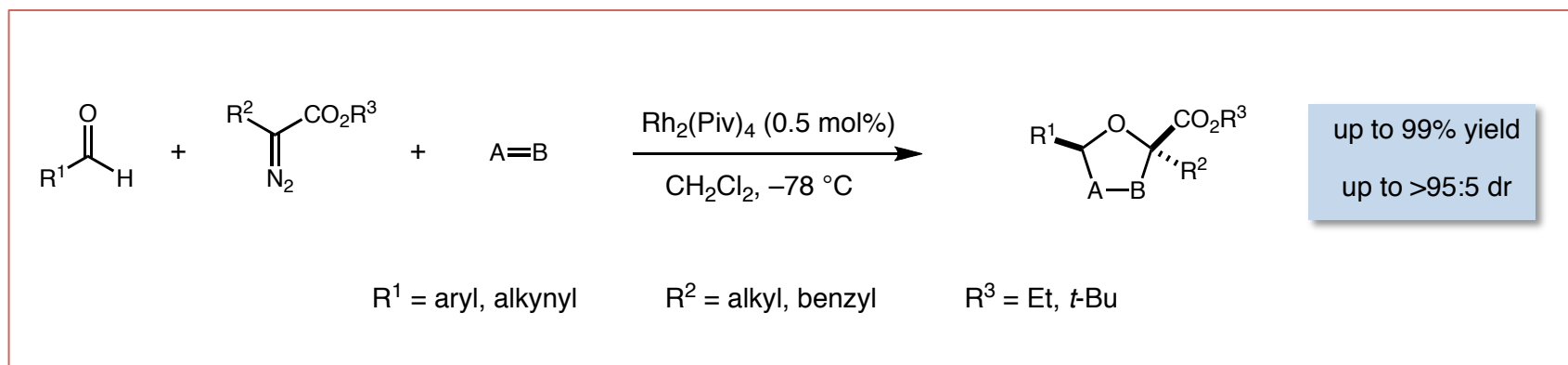


- Suppression of β-hydride elimination of alkyldiazoacetates has been a continuing challenge

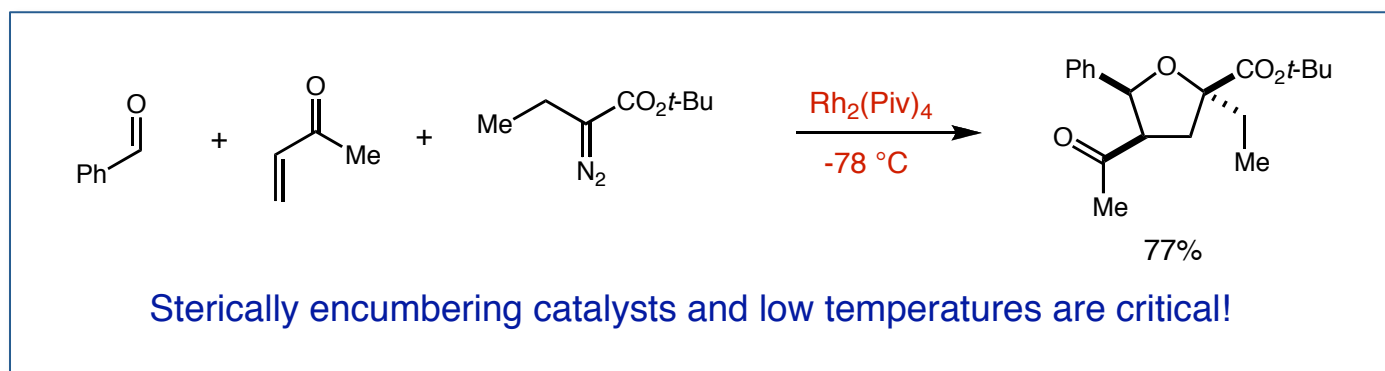


Carbonyl Ylides Three-Component Cycloaddition

- Joe Fox (Delaware): Coupling between aldehydes, diazo compounds, and dipolarophiles

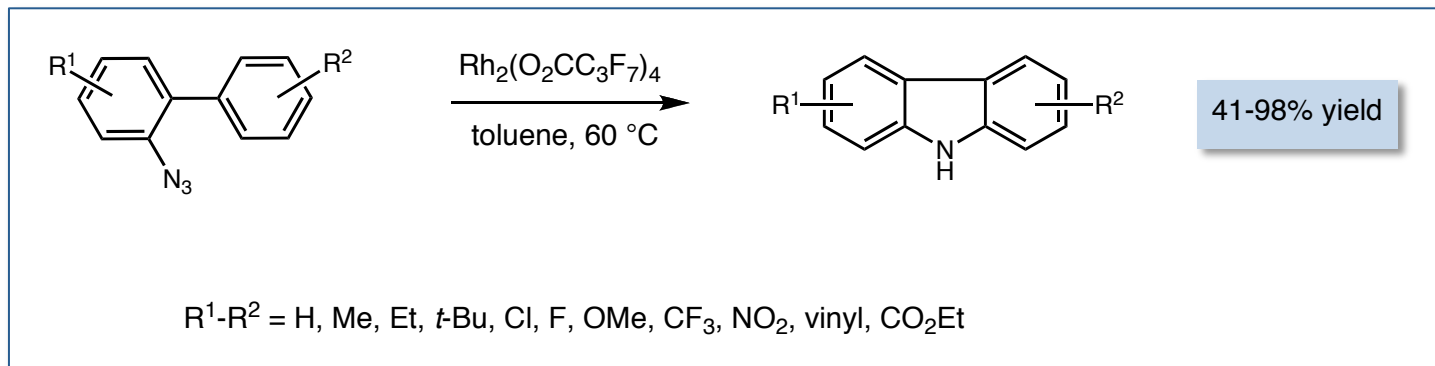


- β-hydride elimination can be completely suppressed through appropriate conditions



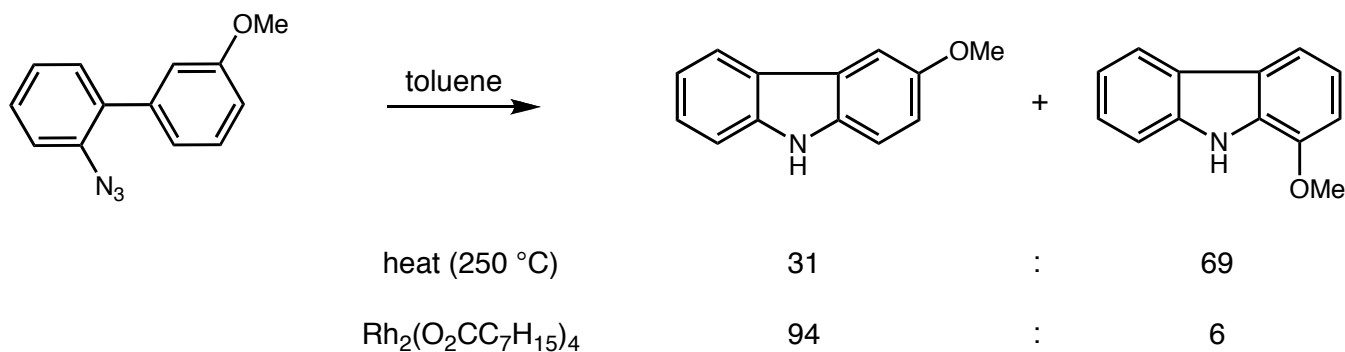
Rhodium(II) Nitrene-Mediated C–H Insertion Azide Precursors to Nitrenes

■ Carbazole synthesis via bisaryl azides



- *m*-substituted pendant arenes lead to mixtures of regioisomers

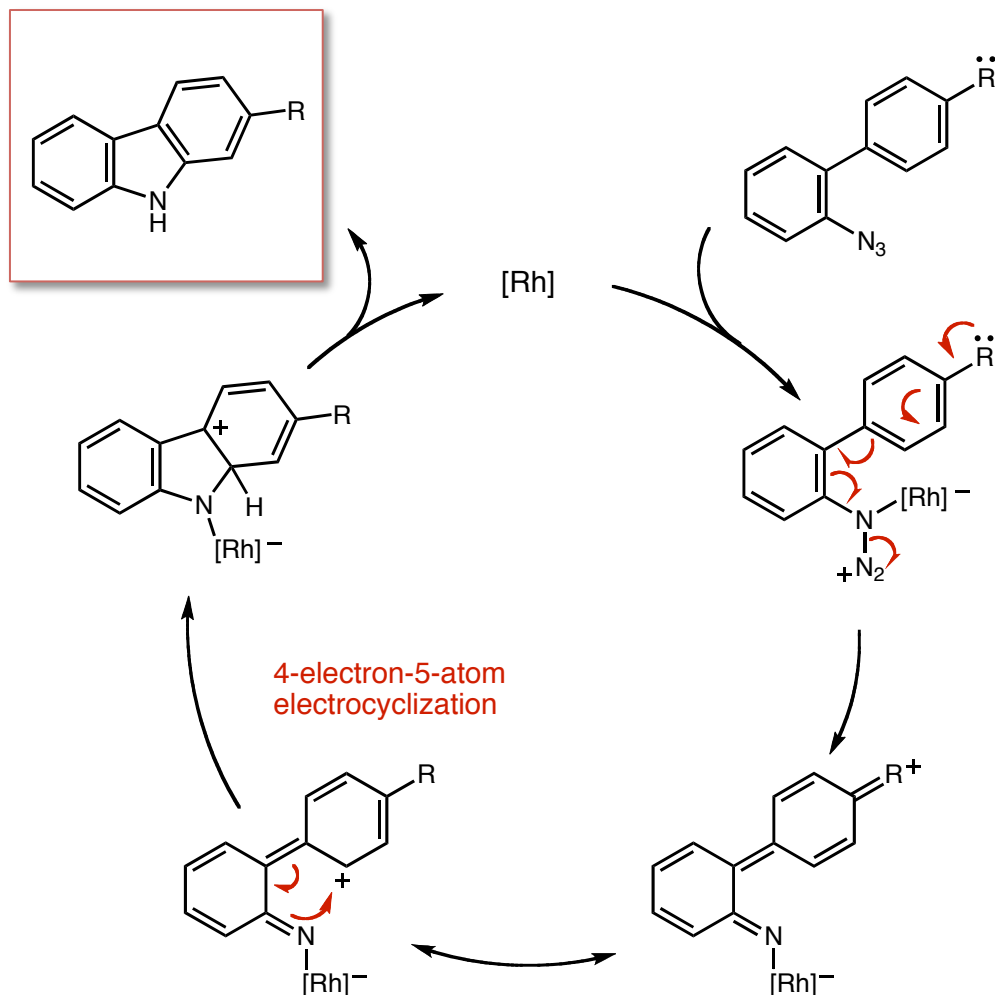
■ Intermediacy of free nitrene, or completely catalyst-mediated?



- reversal in thermal selectivity argues against presence of free nitrene

Rhodium(II) Nitrene-Mediated C–H Insertion Azide Precursors to Nitrenes

Proposed mechanism

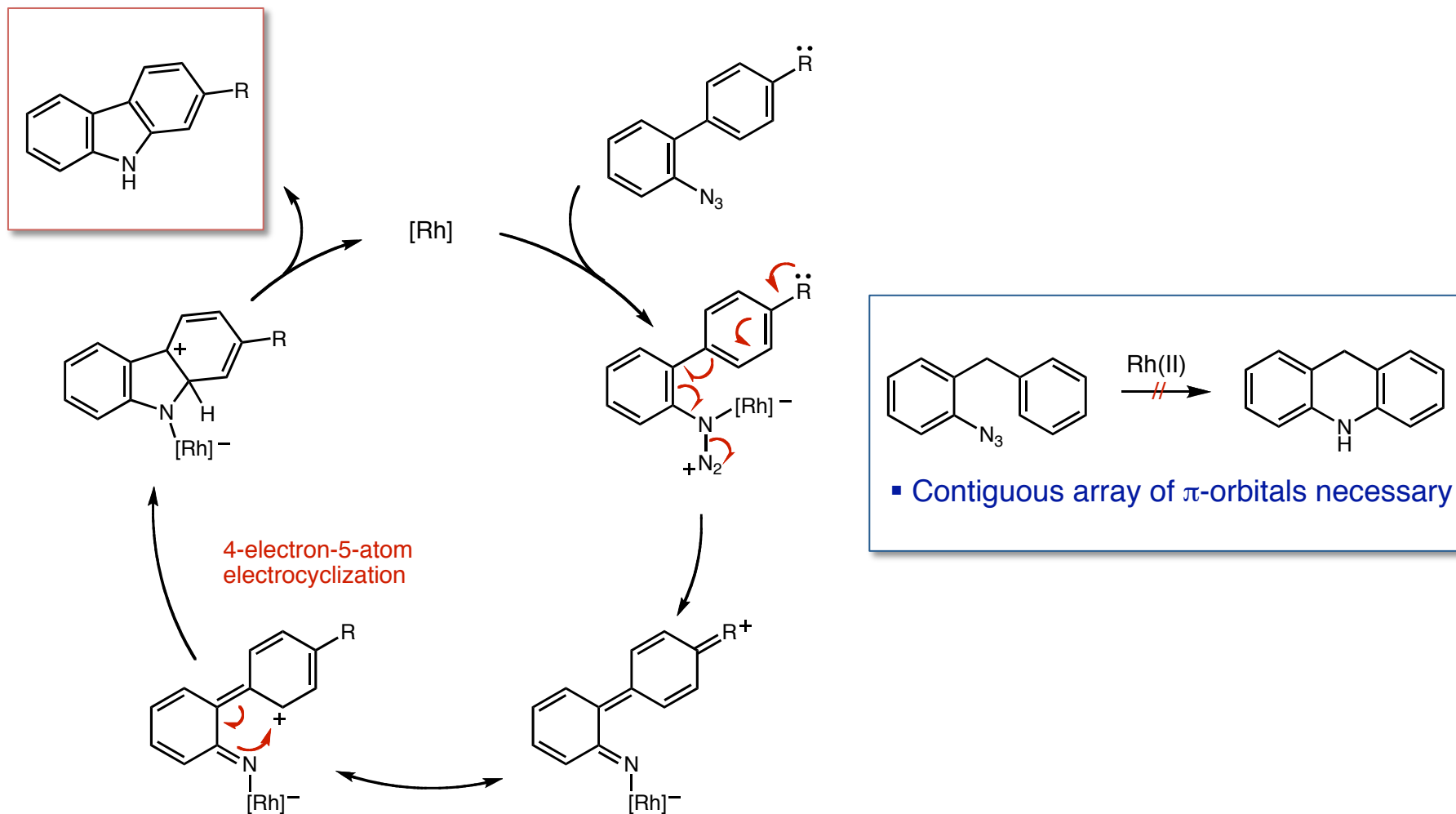


Mechanistic Evidence

- Primary KIE 1.01
- Nonlinear correlation with σ_m Hammett values (not electrophilic aromatic substitution on nitrene)
- Linear correlation with σ_p Hammett values (negative ρ values)

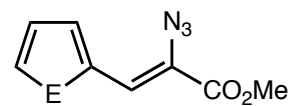
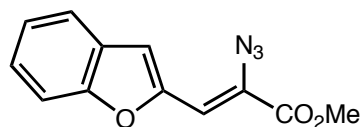
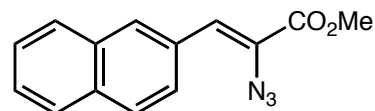
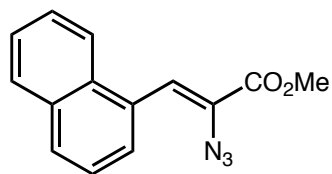
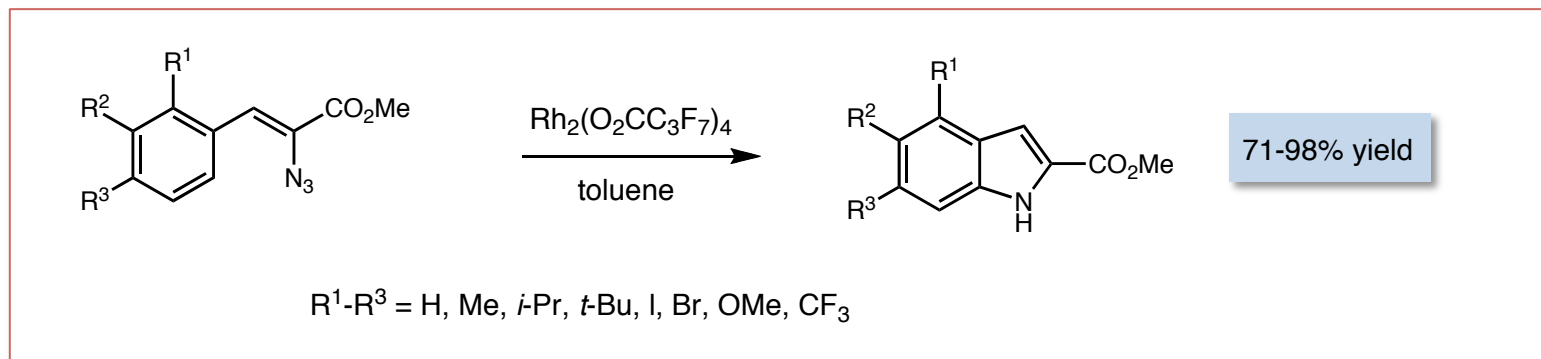
Rhodium(II) Nitrene-Mediated C–H Insertion Azide Precursors to Nitrenes

Proposed mechanism



Rhodium(II) Nitrene-Mediated C–H Insertion Azide Precursors to Nitrenes

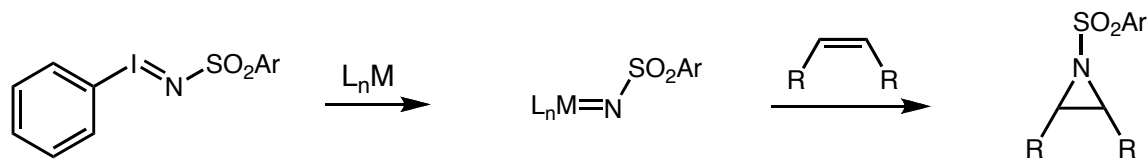
■ Synthesis of indoles and N-heteroarenes via vinyl azides



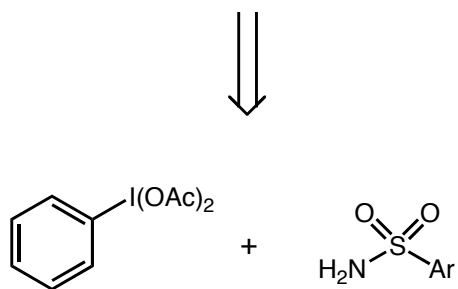
E = O, S, N(PG)

Rhodium(II)-Catalyzed C–H Amination Iminoiodanes

- Traditionally, iminoiodanes were treated with metal complexes to generate nitrenes

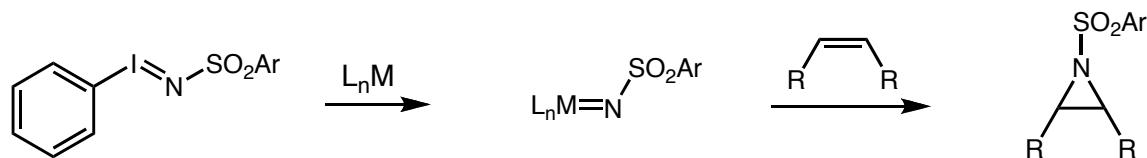


- Isolated material

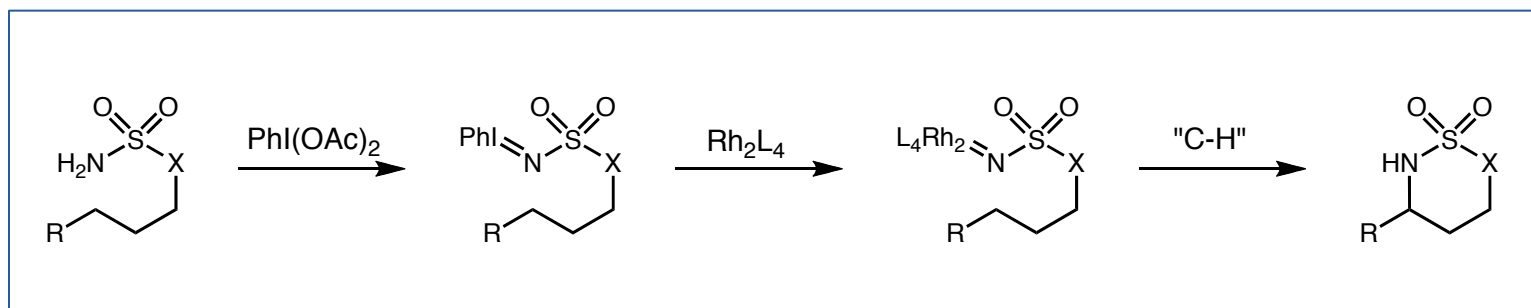


Rhodium(II)-Catalyzed C–H Amination Iminoiodanes

- Traditionally, iminoiodanes were treated with metal complexes to generate nitrenes



- Du Bois (Stanford): generation of iminoiodanes *in situ*

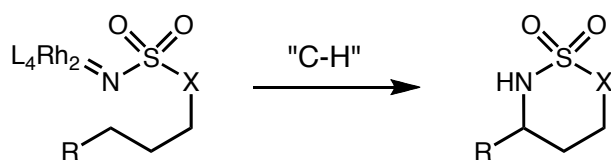


Rhodium(II)-Catalyzed C–H Amination Understanding the Mechanism

- General reactivity trends parallel those of rhodium(II) carbenes

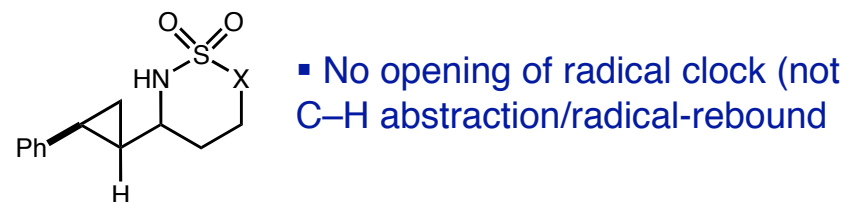
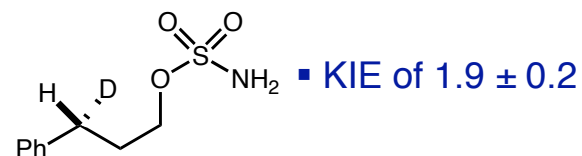
Reactivity of C–H bonds undergoing insertion
methine > ethereal ~ benzylic > methylene >> methyl

- Six-membered oxathiazinanes favored



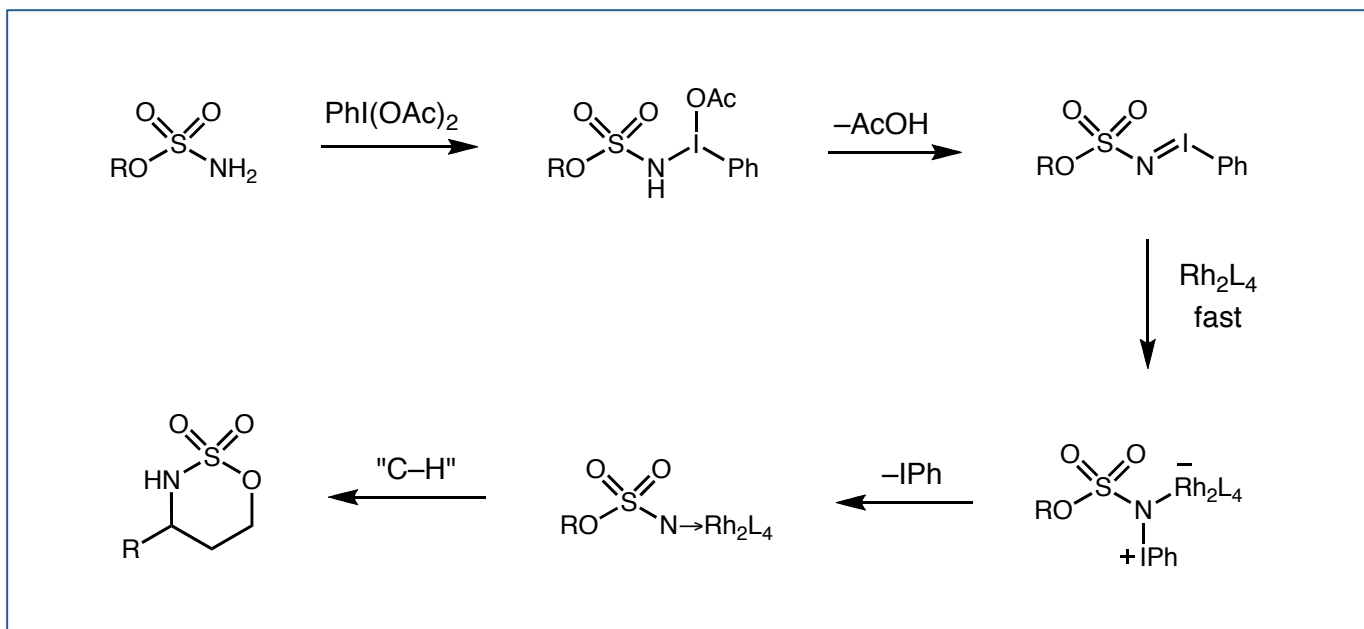
- Elongated S–X, S–N bonds
- Obtuse N–S–X bond angle

- Concerted C–H insertion



Rhodium(II)-Catalyzed C–H Amination Understanding the Mechanism

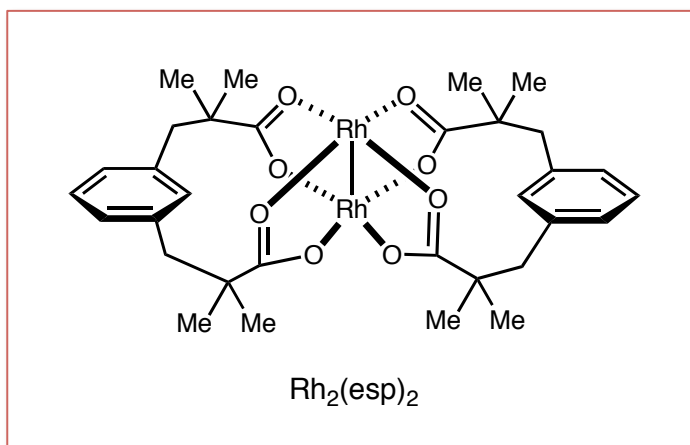
■ Proposed mechanism of rhodium-nitrene formation



- First-order dependence on sulfamate and oxidant
- Zero-order dependence on catalyst (during initial reaction burst)

Rhodium(II)-Catalyzed C–H Amination $Rh_2(esp)_2$

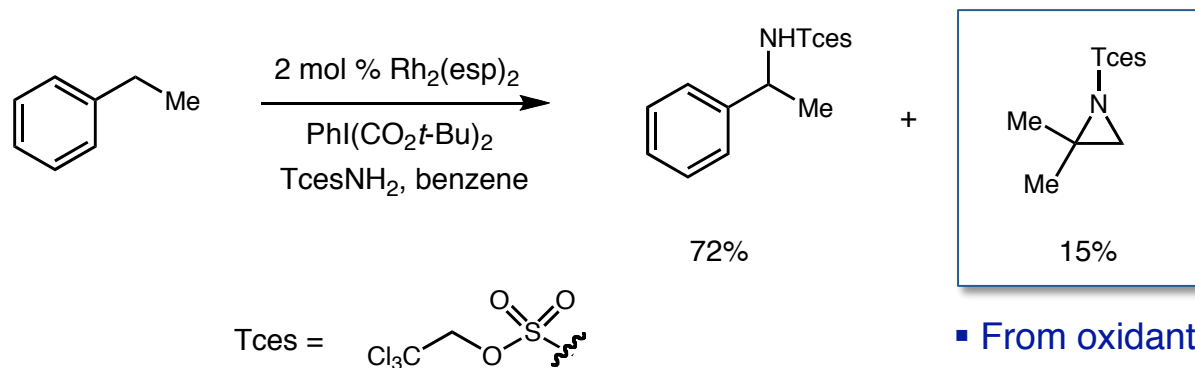
- Very efficient catalyst for C–H aminations



- Dinuclear rhodium catalysts known to undergo structural changes within minutes of initiating the reaction
 - Catalyst degradation believed to proceed through ligand exchange
 - Appropriately spaced linker in (esp) ligand adds stability to dirhodium complex

Rhodium(II)-Catalyzed C–H Amination $Rh_2(esp)_2$

- Interesting results obtained in intermolecular C–H amination experiments



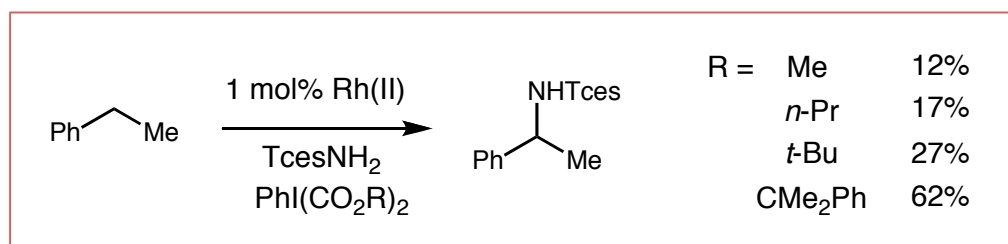
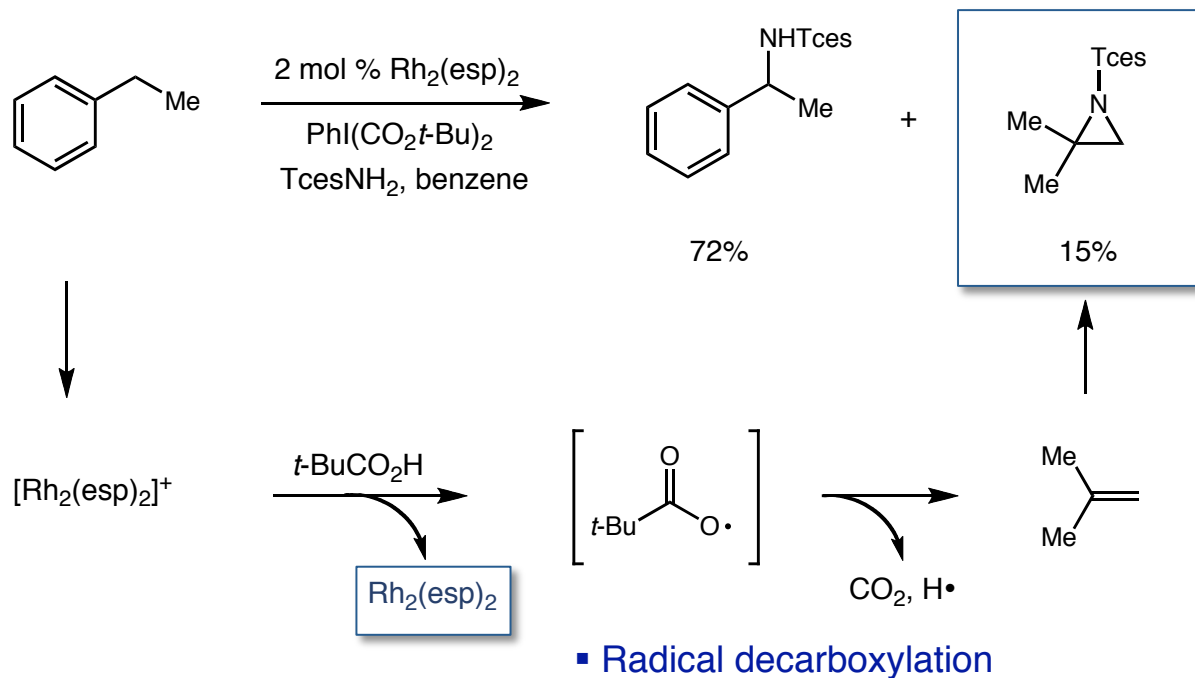
- If C–H bond is slow to intercept reactive Rh-nitrene intermediate, catalyst degradation occurs

■ Formation mixed-valence Rh^{2+}/Rh^{3+} species observed by UV/vis spectroscopy

- Could this mixed-valence dimer interact with oxidant in reaction mixture?

Rhodium(II)-Catalyzed C–H Amination $Rh_2(esp)_2$

- Interesting results obtained in intermolecular C–H amination experiments



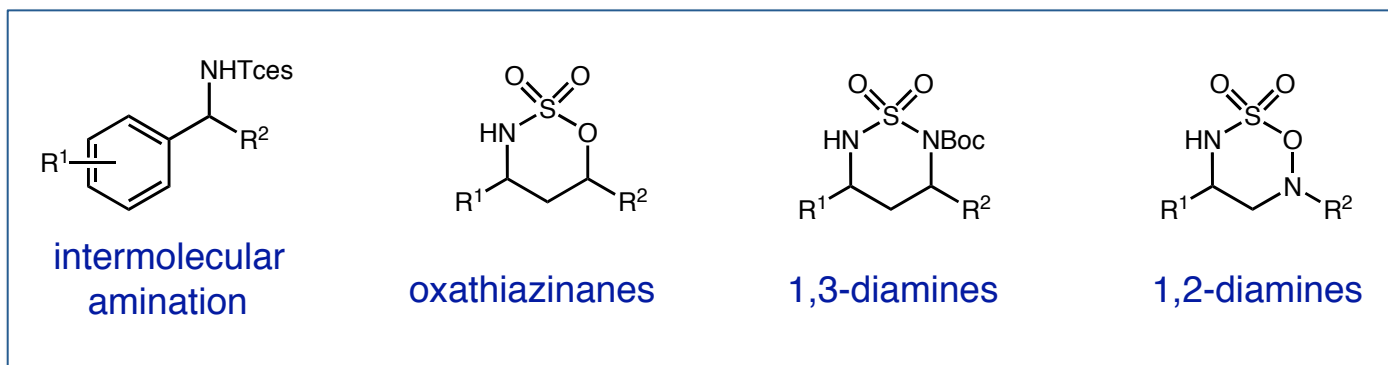
- More reducing carboxylic acid – higher yields
- Evidence that $Rh_2(esp)_2$ is active catalyst

Du Bois et al. *J. Am. Chem. Soc.* **2007**, 129, 562.
Du Bois et al. *J. Am. Chem. Soc.* **2009**, 131, 7558.

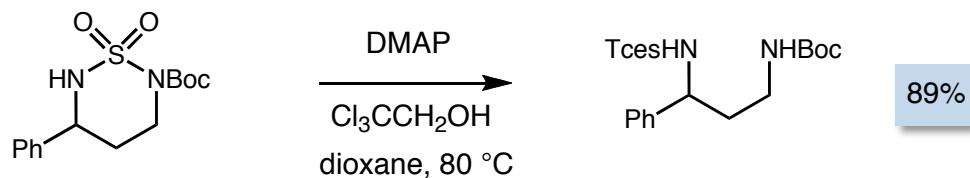
Rhodium(II)-Catalyzed C–H Amination

Justin Du Bois

Rich variety of rhodium-catalyzed aminations



Amines are readily deprotected

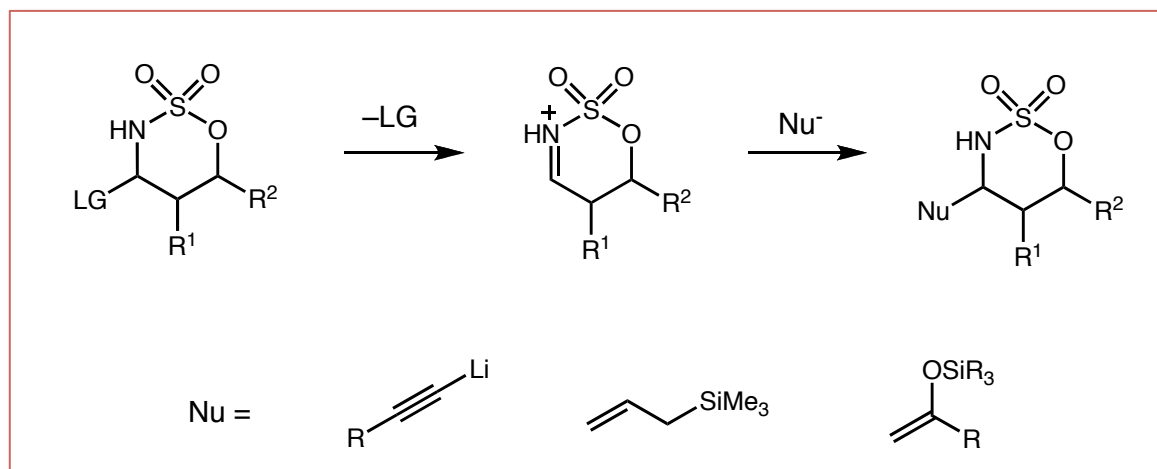


J. Am. Chem. Soc. **2001**, *123*, 6935.
J. Am. Chem. Soc. **2007**, *129*, 562.
J. Am. Chem. Soc. **2008**, *130*, 11248.
Angew. Chem. Int. Ed. **2009**, *48*, 2777.

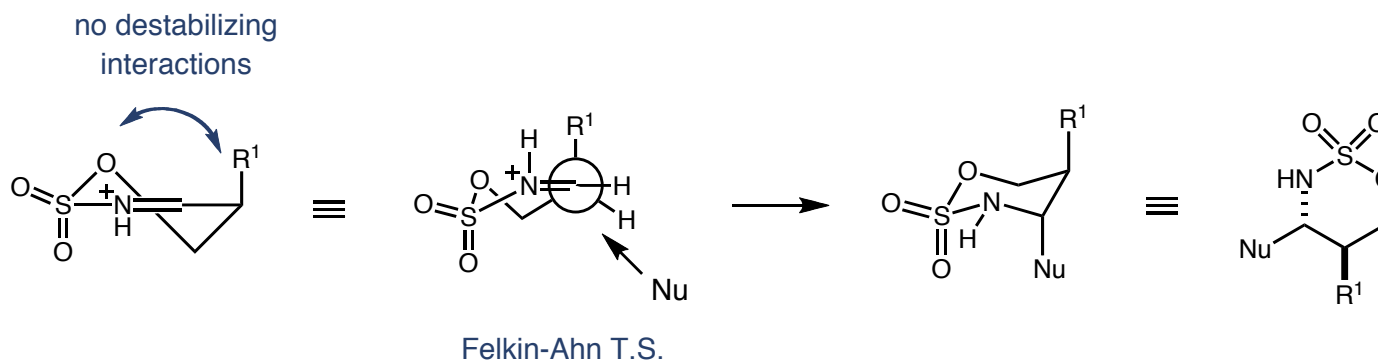
Rhodium(II)-Catalyzed C–H Amination

Justin Du Bois

- Products can act as iminium ion equivalents



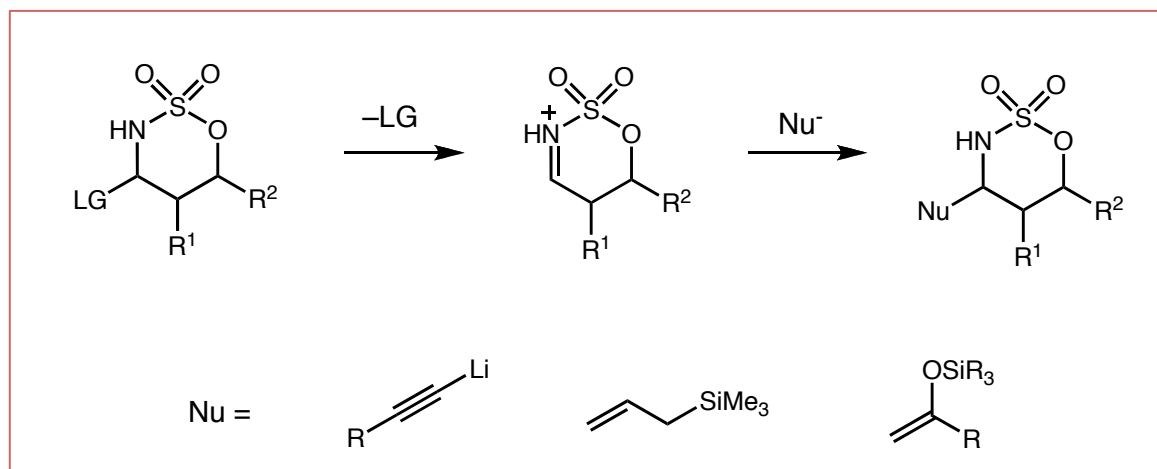
- Diastereoselectivity governed by combination of twist Felkin-Ahn transition state model



Rhodium(II)-Catalyzed C–H Amination

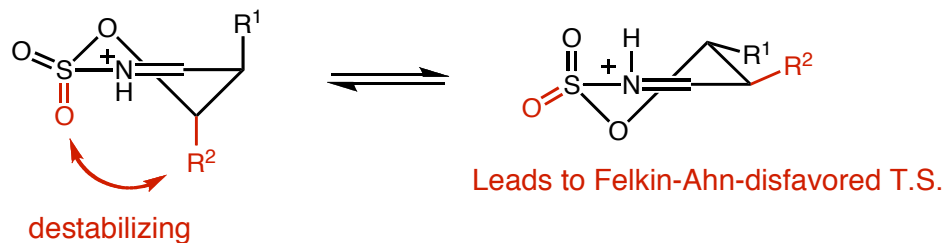
Justin Du Bois

- Products can act as iminium ion equivalents



- Diastereoselectivity governed by combination of twist Felkin-Ahn transition state model

- Introduction of R² can have a dramatic impact on selectivity!

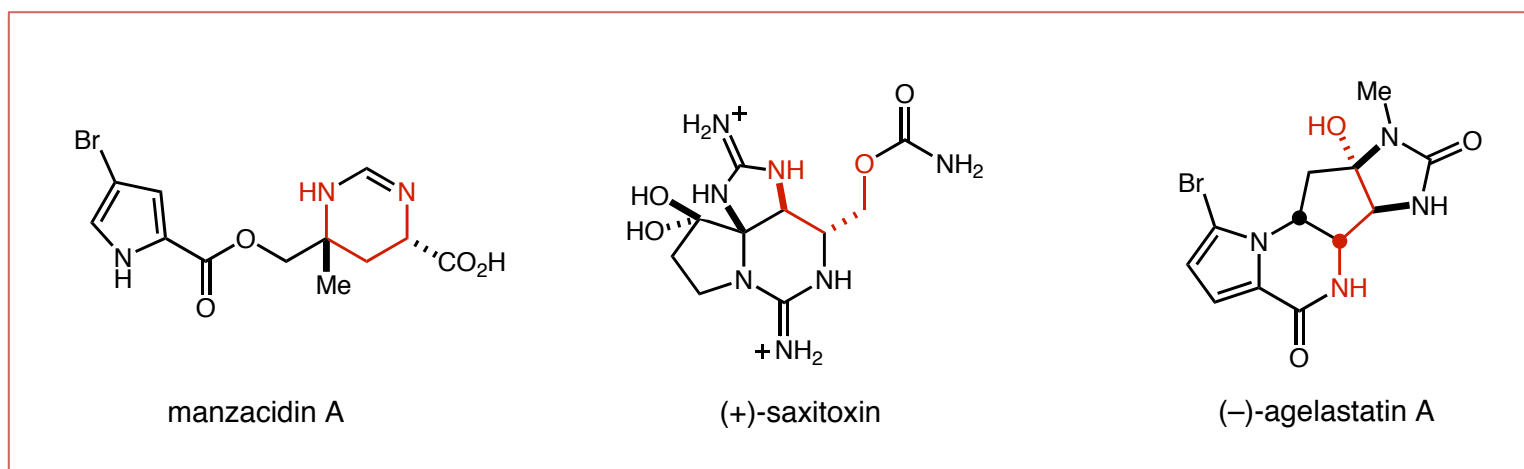


- Erosion of diastereoselectivity

Rhodium(II)-Catalyzed C–H Amination

Justin Du Bois

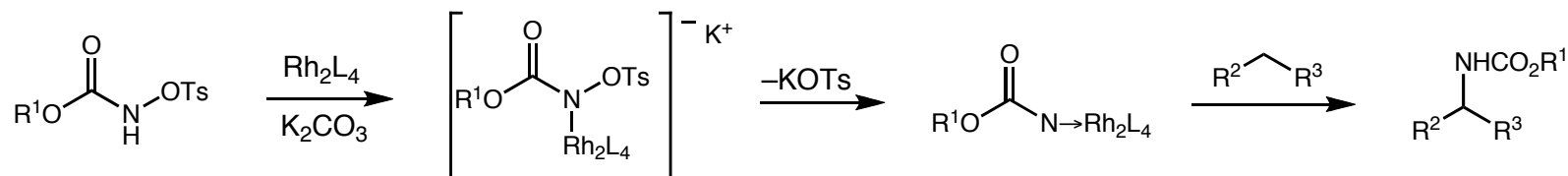
■ Application towards natural product synthesis



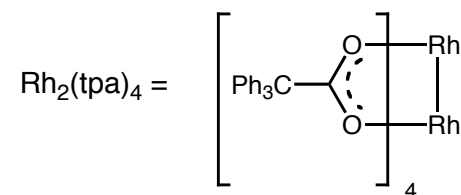
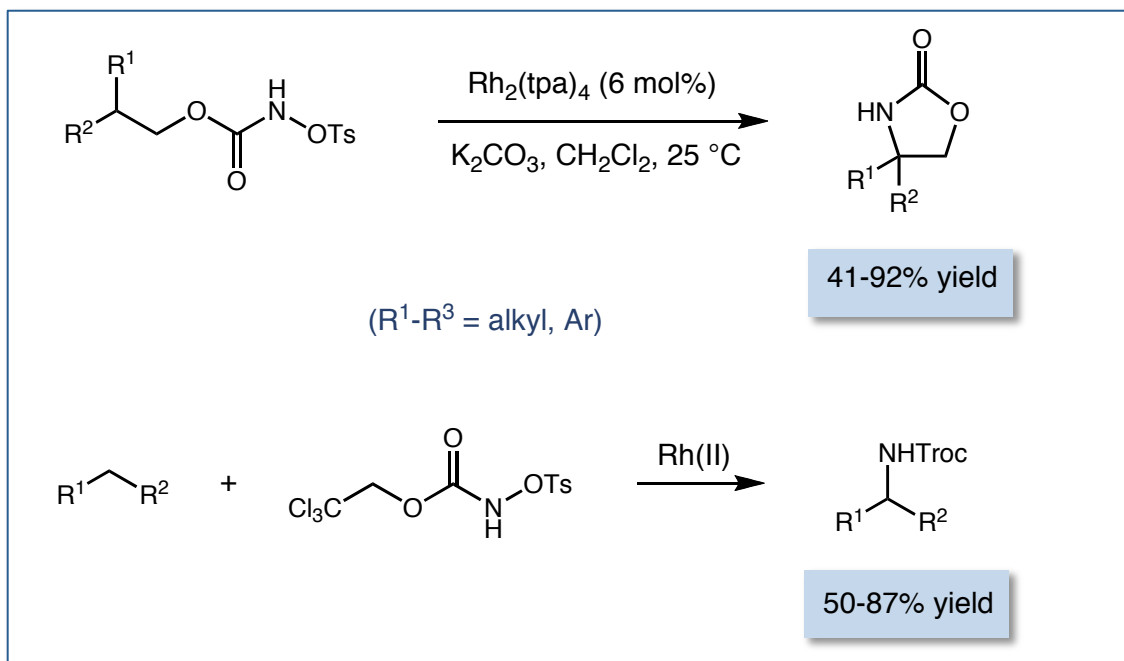
J. Am. Chem. Soc. **2002**, *124*, 12950.
J. Am. Chem. Soc. **2006**, *128*, 3926.
Angew. Chem. Int. Ed. **2009**, *48*, 3802.

C–H Amination with N-Tosylloxycarbamates Rhodium Nitrene Formation without Iminoiodanes

- Substitute *in situ*-generated iminoiodanes with alternative leaving group?



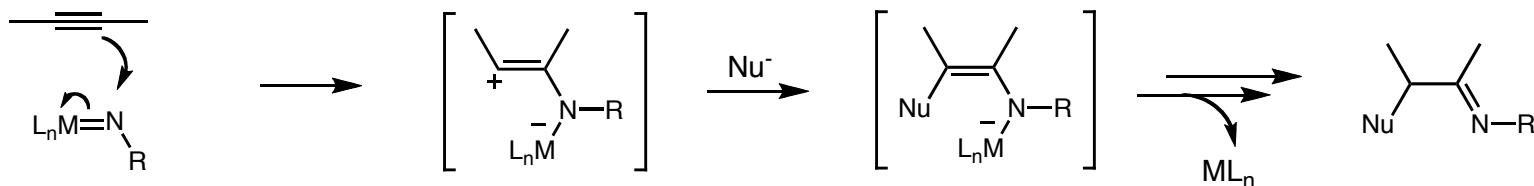
- Lebel (Montréal) utilized the tosyl leaving group



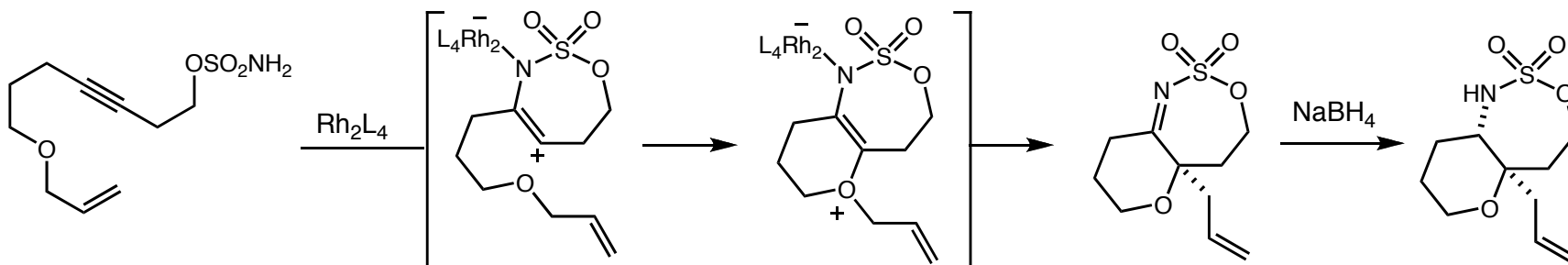
- Up to 15 eq of alkane required (Du Bois requires only 1 eq)

Amination of Alkynes and Allenes π -Nucleophilic Attack onto Rhodium Nitrenes

- Electrophilic rhodium(II) nitrene analogous to rhodium carbenes



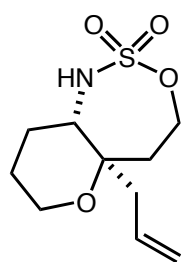
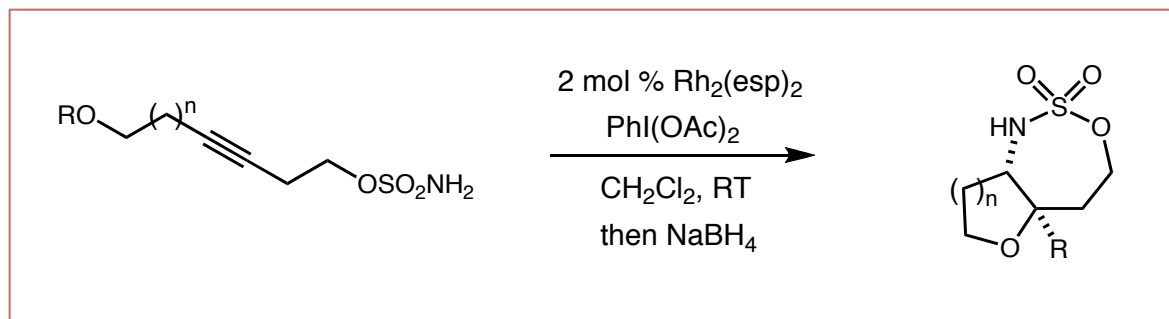
- Blakey (Emory) utilized oxygen for nucleophilic attack onto carbocation



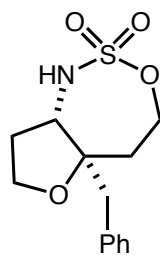
Amination of Alkynes and Allenes

π -Nucleophilic Attack onto Rhodium Nitrenes

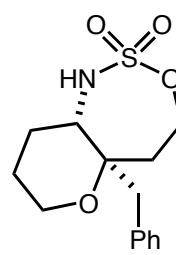
■ Scope



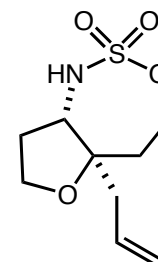
85%



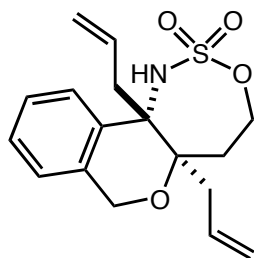
71%



56%

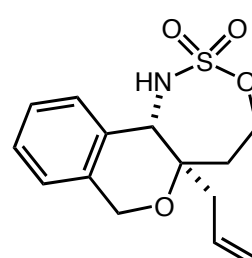


76%

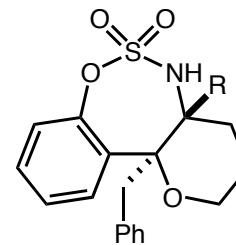


81%

(quenched with allyl-MgBr)



98%

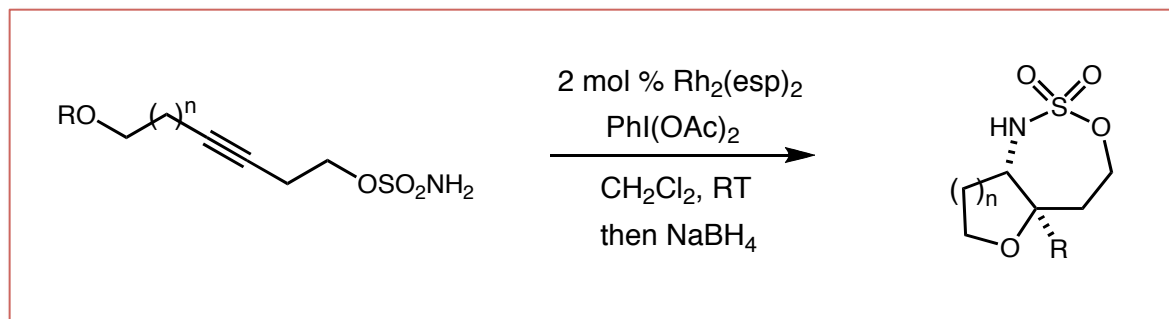


R = H, 55%

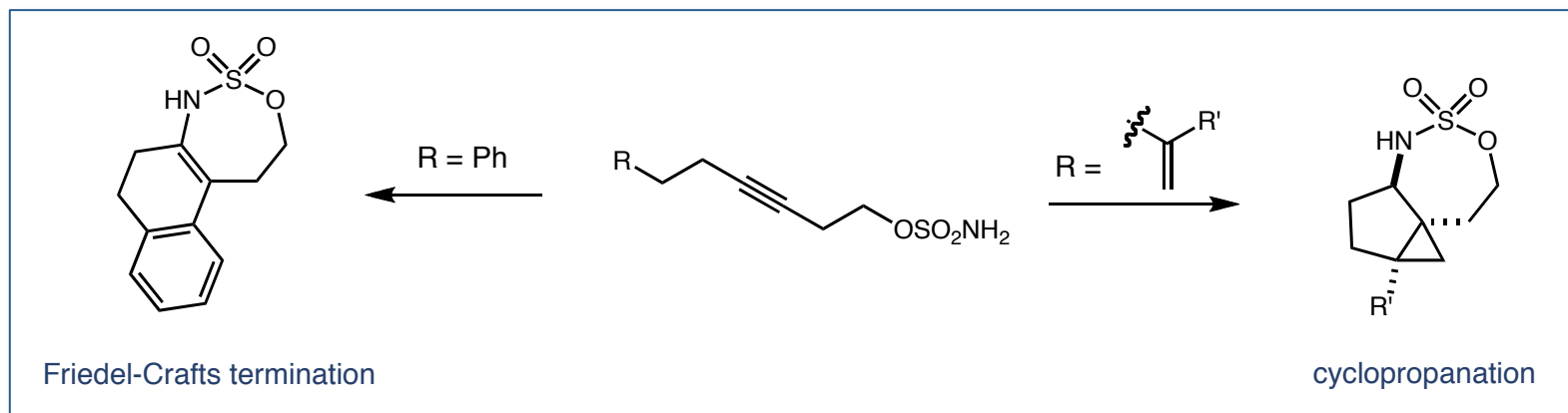
Me, 48%

Amination of Alkynes and Allenes π -Nucleophilic Attack onto Rhodium Nitrenes

■ Scope



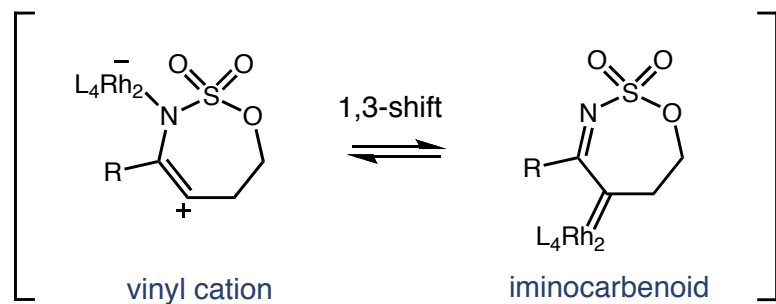
■ Other nucleophilic traps – arenes and olefins



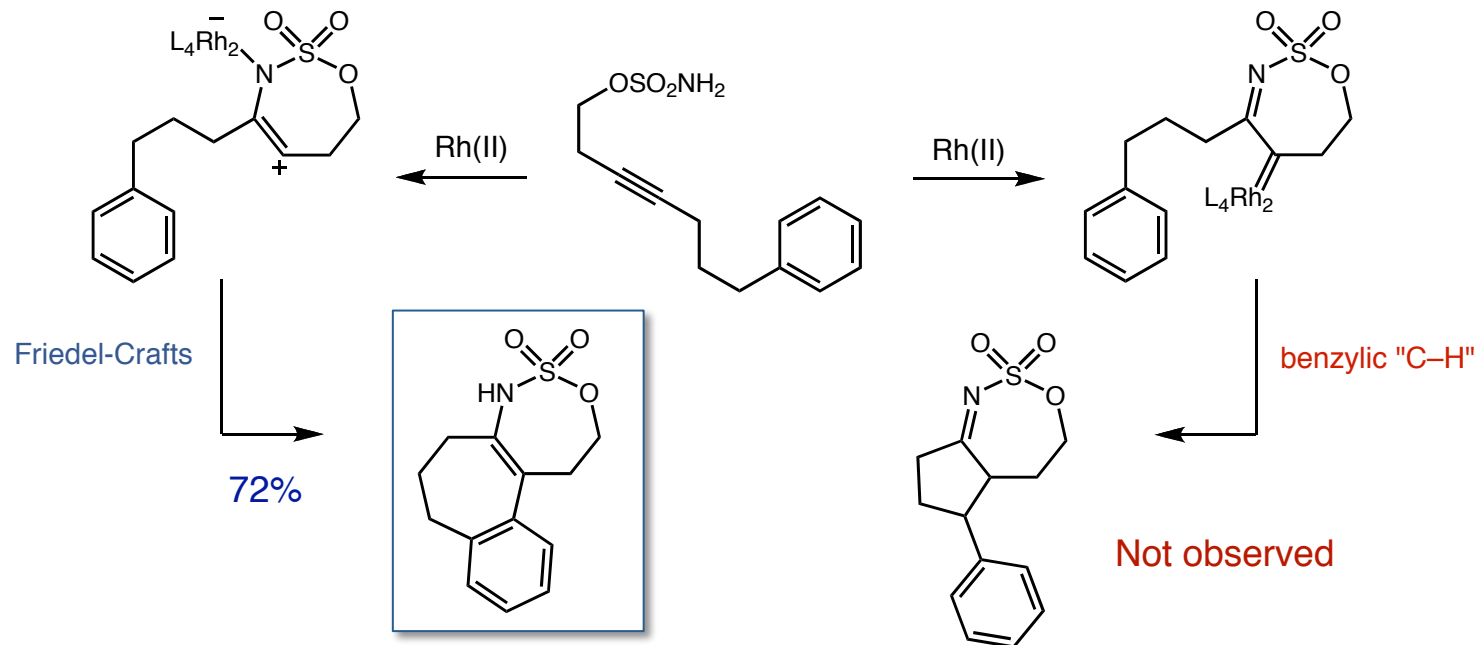
Amination of Alkynes and Allenes

π -Nucleophilic Attack onto Rhodium Nitrenes

Mechanistic insight – what is the active intermediate?



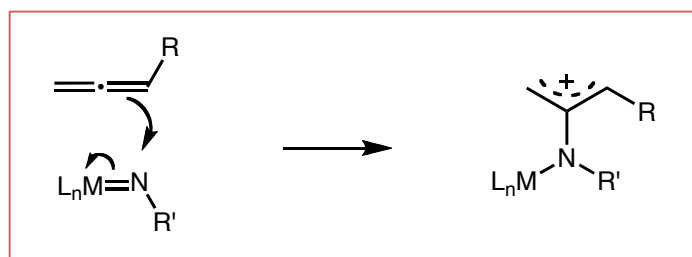
Control experiment



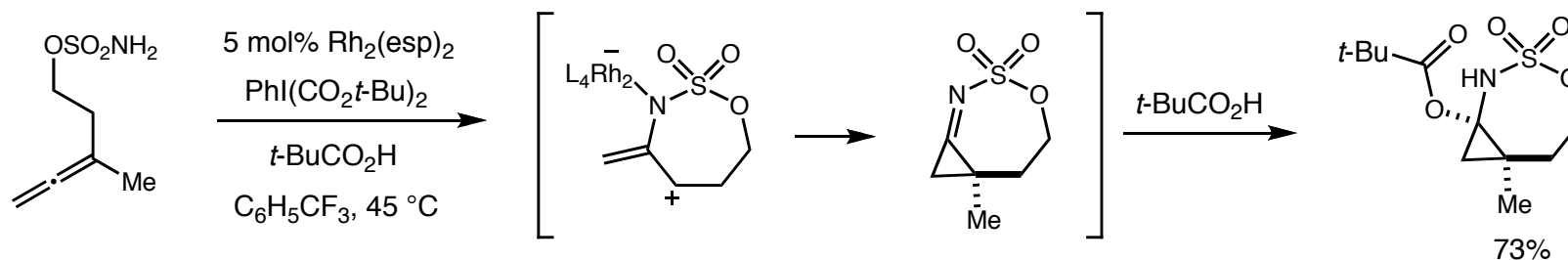
Amination of Alkynes and Allenes

π -Nucleophilic Attack onto Rhodium Nitrenes

■ Allene amination - amidoallylcations



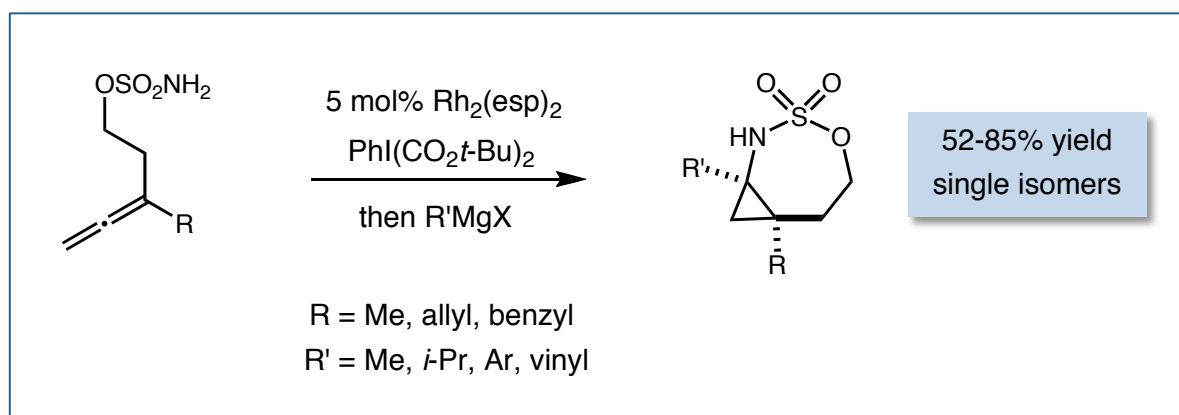
■ Aminocyclopropanes



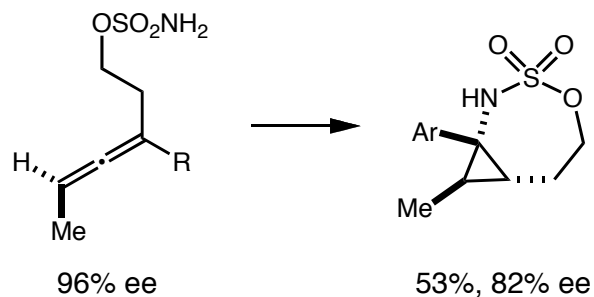
Amination of Alkynes and Allenes

π -Nucleophilic Attack onto Rhodium Nitrenes

■ Allene amination - amidoallylations



■ Chirality transfer



■ Cycloadditions

