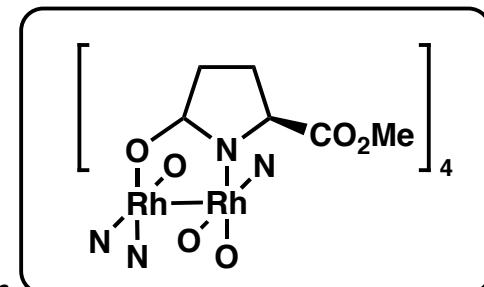
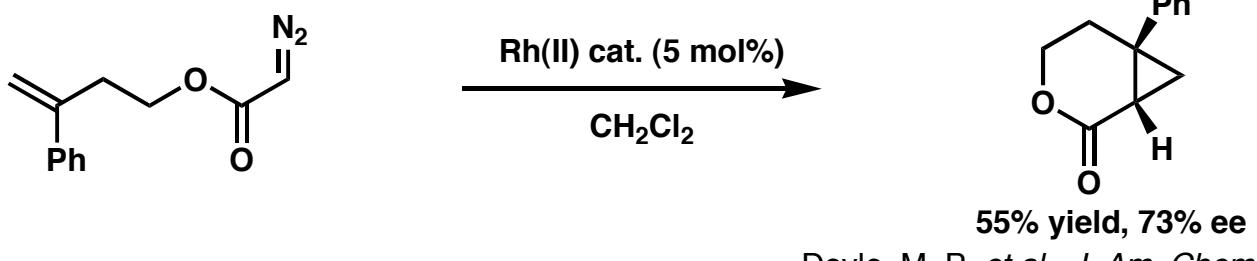
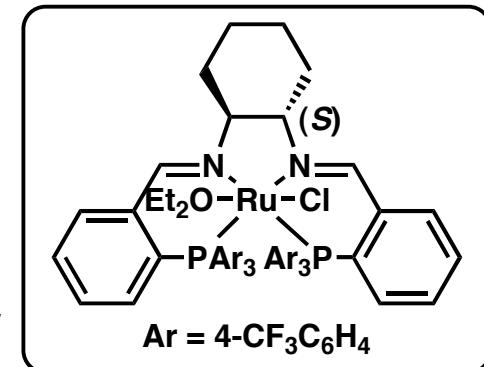
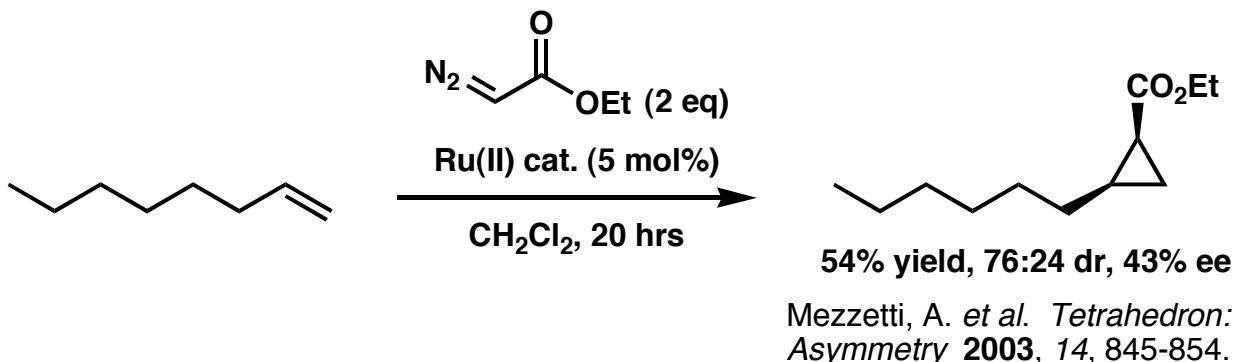


The Quest for Selective Cyclopropanation



Jennifer Roizen
Stoltz Group Literature Presentation
Monday, November 1, 2004
8pm
Noyes 147

The Quest for Selective Cyclopropanations - Outline

Cyclopropanation in General

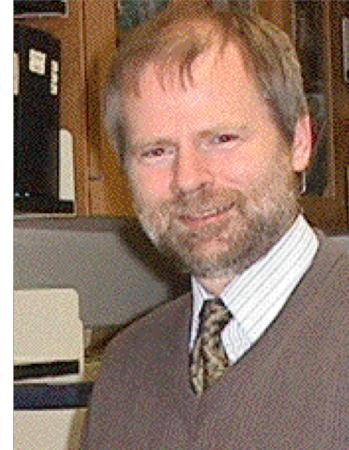
- History and Types

Carbene Addition Across an Alkene

- Mechanisms
- Stereoselectivity
- Challenges
- Influences
 - Carbene Source
 - Alkene Source
 - Ligand Structure
 - Ligand Electronics



Michael P. Doyle
University of Maryland



Huw M. L. Davies
University of Buffalo



André B. Charette
University of Montreal

Recommended Reviews:

- Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis With Diazo Compounds: From Cyclopropanes to Ylides*; John Wiley & Sons, Inc.: New York, 1998.
- Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. Stereoselective Cyclopropanation Reactions. *Chem. Rev.* **2003**, *103*, 977-1050.

Additional Reviews Recommended by Gene:

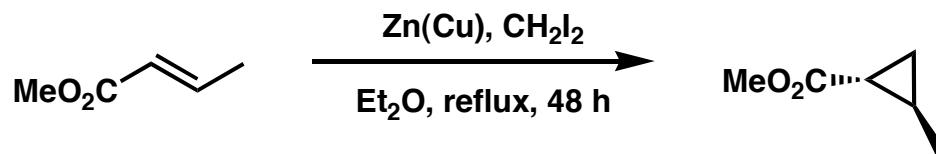
- Davies, *et al.* Intermolecular Metal-Catalyzed Carbenoid Cyclopropanations. *Organic Reactions*; New York, **2001**, *57*, 1-326.
- Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*(2), 911-935.
- Doyle, M. P.; Protopopova, M. N. *Tetrahedron* **1998**, *54*(28), 7919-7946.

Historic Cyclopropanations

• 1884 - 1st Cyclopropane derivative made (William Henry Perkin in lab of Adolf von Baeyer)

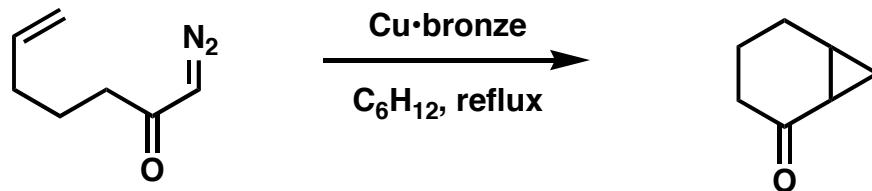
• 1958 - Simmons-Smith Cyclopropanation

Review: S. Denmark; G. Beutner. Enantioselective [2+1] Cycloaddition: Cyclopropanation with Zinc Carbenoids *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim (Germany), 2002, 85-156.



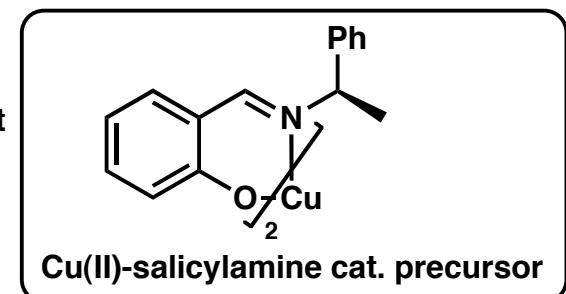
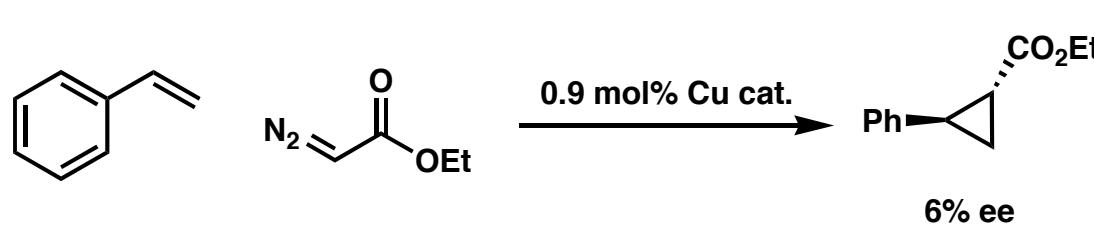
Simmons; Smith. *J. Am. Chem. Soc.* 1958, 80(19), 5323-5324.

• 1961 - 1st Intramolecular Cyclization of An Unsaturated Diazocarbonyl Compound



Stork, G.; Ficini, J. *J. Am. Chem. Soc.* 1961, 83(22), 4678.

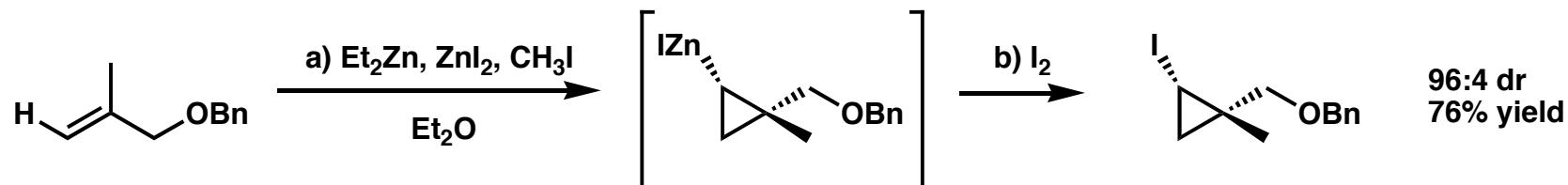
• 1966 - 1st Asymmetric Catalysis with a Transition Metal Complex



Nozaki, et al. *Tetrahedron Letters* 1966, 7, 5239-5244.

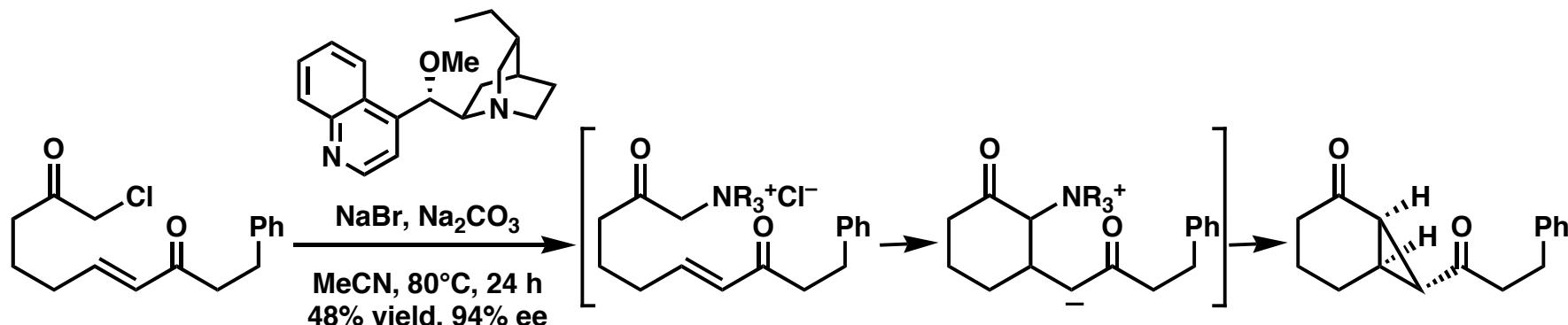
Types of Cyclopropanation

1. Halomethyl Metal-Mediated Cyclopropanation (Zn, Sm, Al)



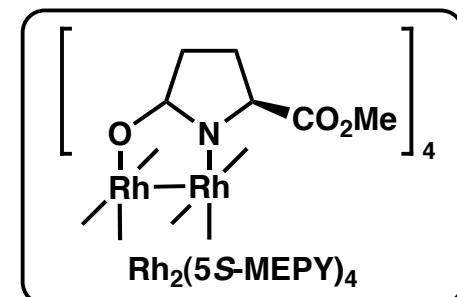
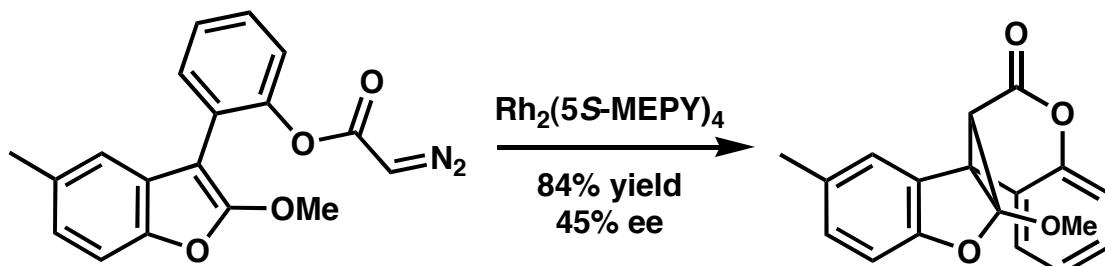
Fournier, J.-F.; Charette, André B. *Eur. J. Org. Chem.* **2004**, 1401-1404.

2. Nucleophilic Addition, Followed by Ring Closure



Ley, S. V. et al. *Angew. Chem. Int. Ed.* **2004**, 43, 2681-2684.

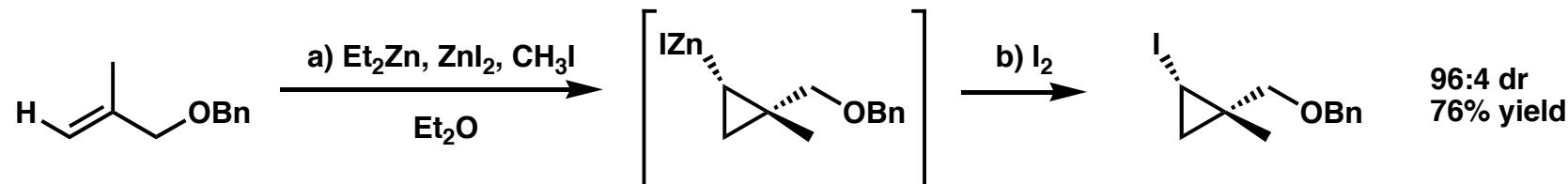
3. Carbene Addition Across an Alkene or Alkyne



Fuerst, D. E.; Stoltz, B. M.; Wood, J. L. *Org. Lett.* **2000**, 2(22), 3521-3523.

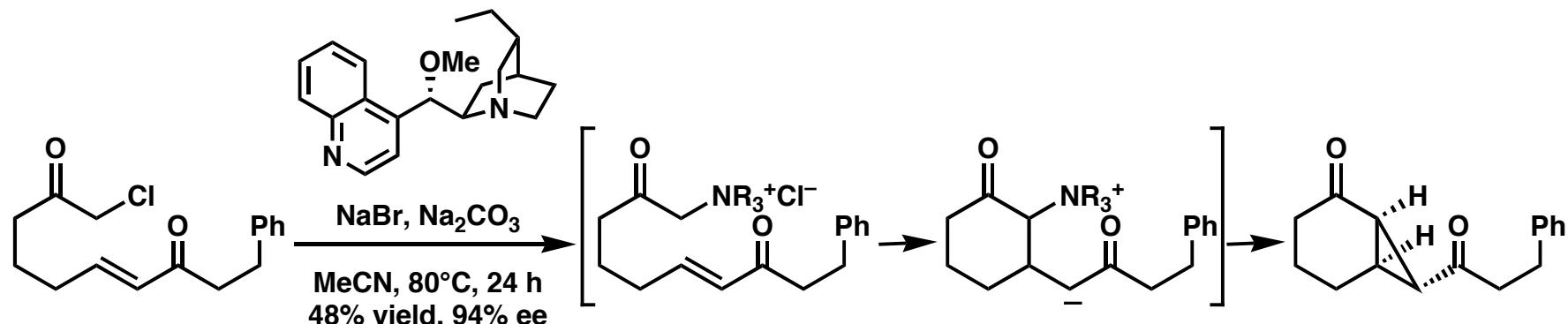
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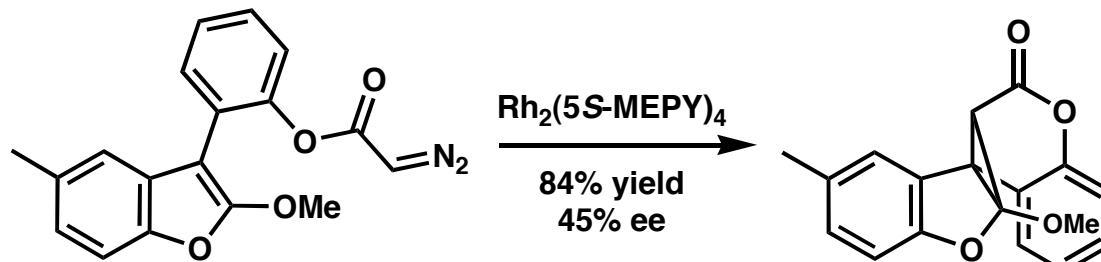
Fournier, J.-F.; Charette, André B. *Eur. J. Org. Chem.* **2004**, 1401-1404.

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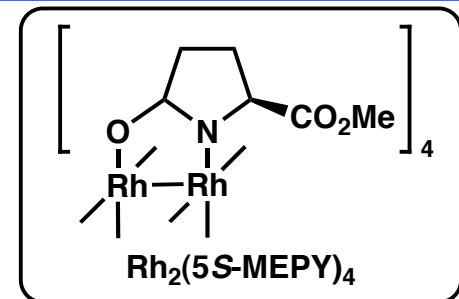


Ley, S. V. et al. *Angew. Chem. Int. Ed.* **2004**, 43, 2681-2684.

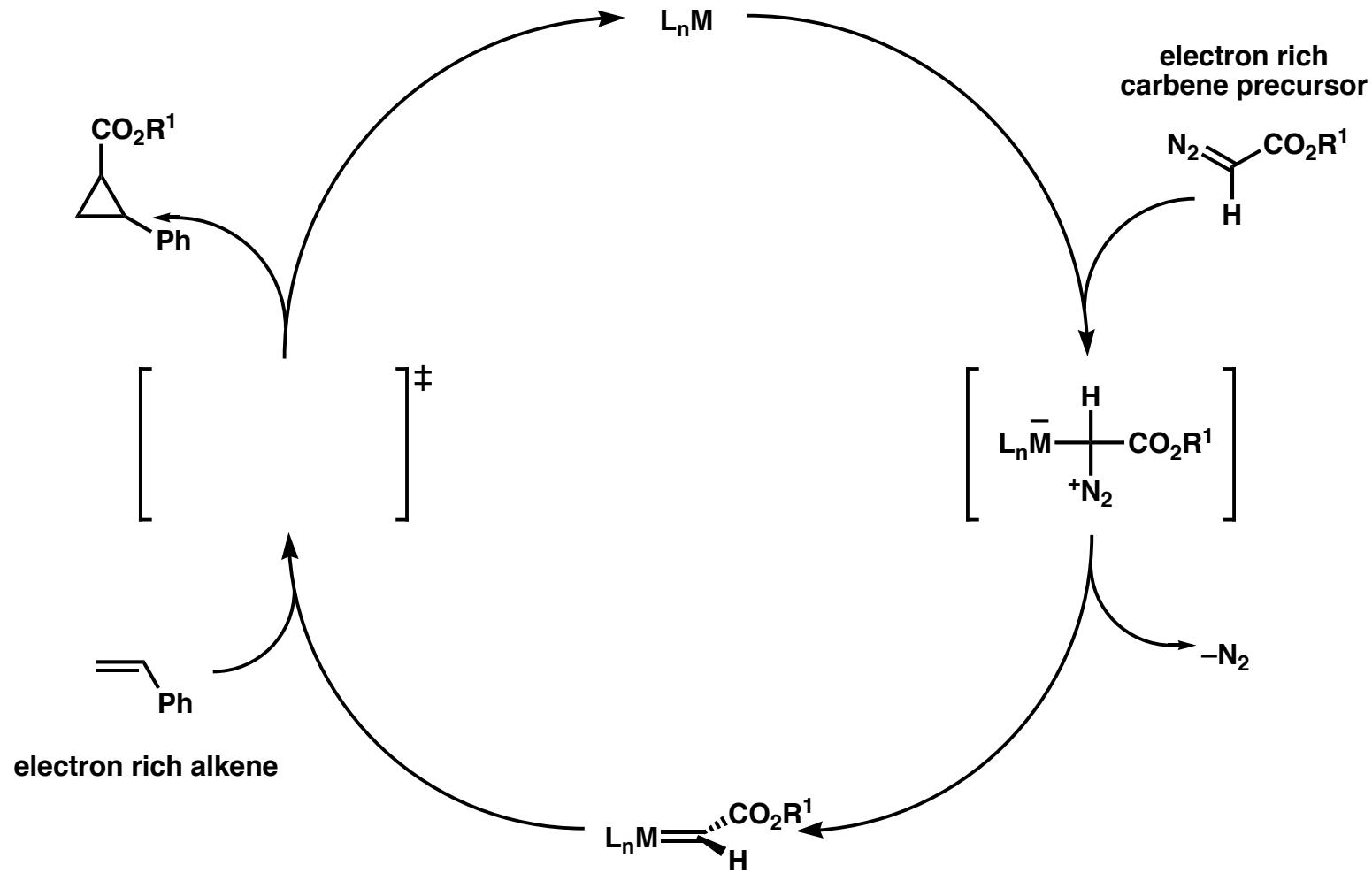
3. Carbene Addition Across an Alkene or Alkyne



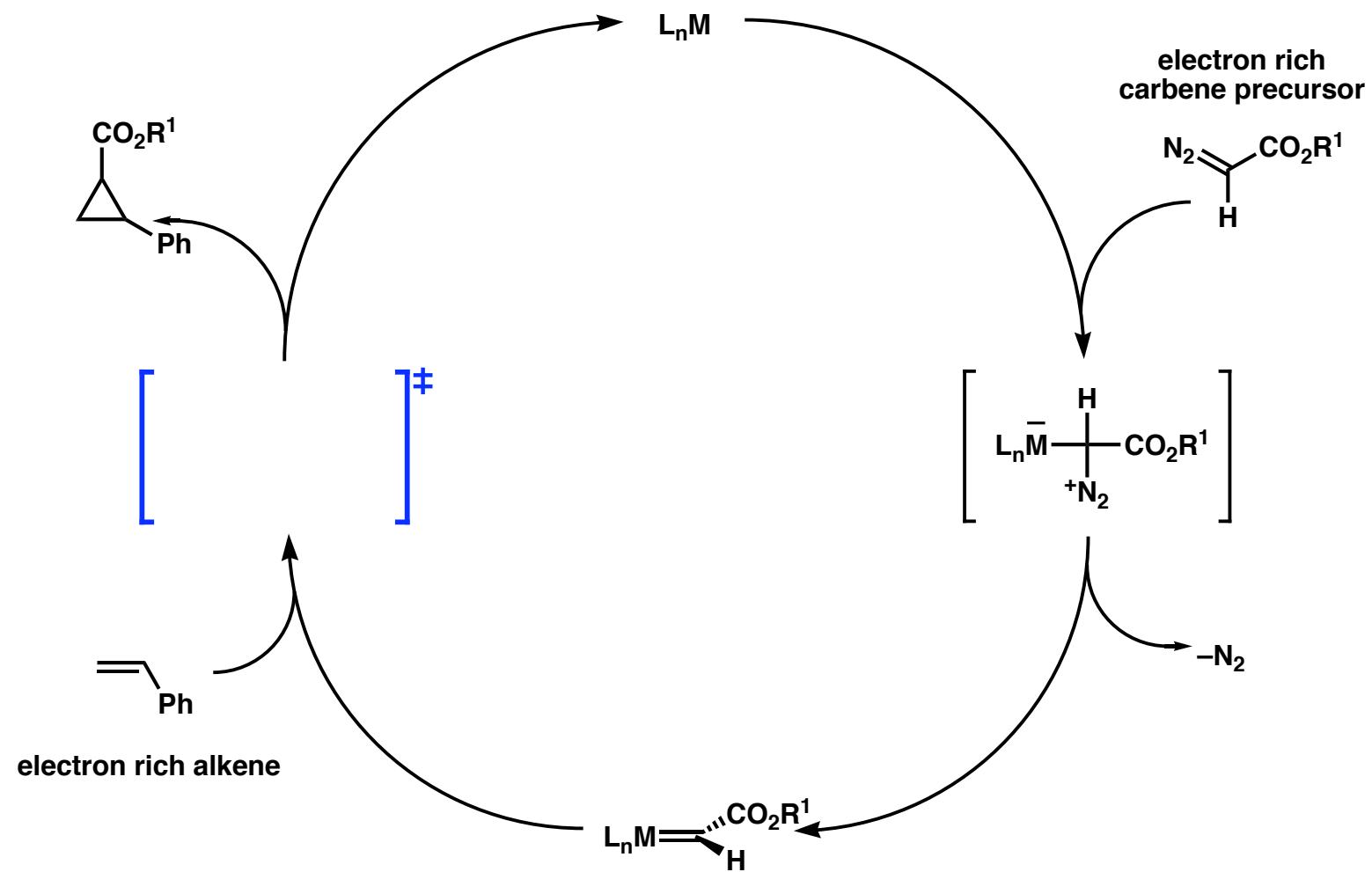
Fuerst, D. E.; Stoltz, B. M.; Wood, J. L. *Org. Lett.* **2000**, 2(22), 3521-3523.



Catalytic Cycle

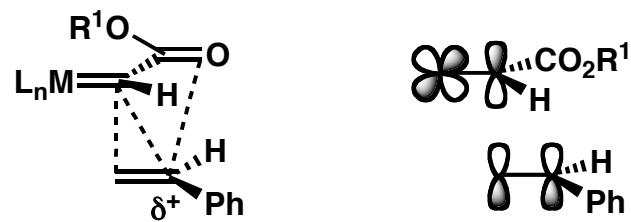


Catalytic Cycle

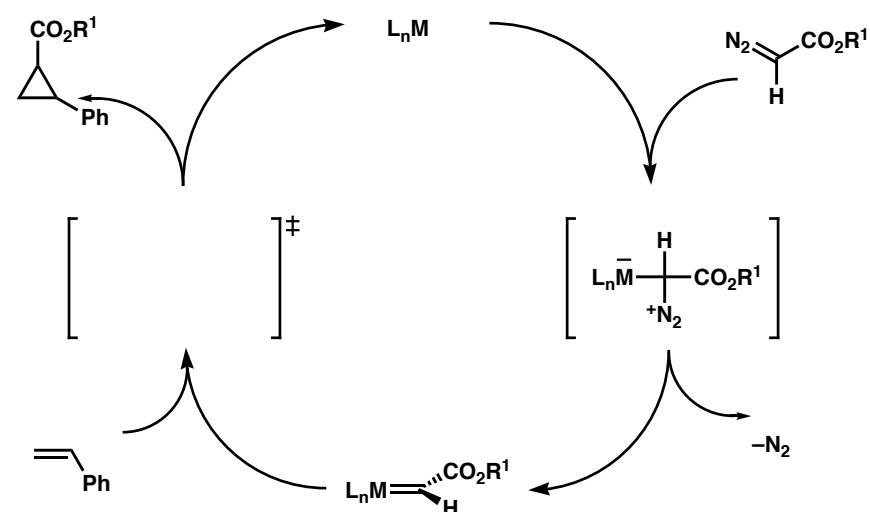


Transition States in Catalytic Cycle

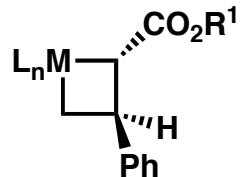
1. Cyclopropane (Doyle)



- Accepted model



2. Metallacyclobutane (Aratani)

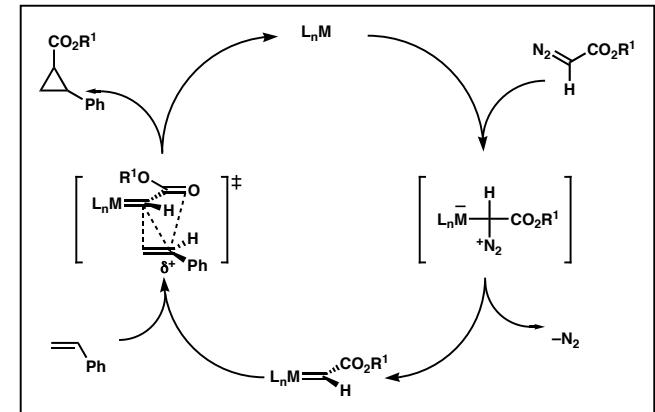


- Intermediate still proposed in stoichiometric cyclopropanations with Cr and other metals
Yamada. *Org. Lett.* 2004, 6(6), 949-952.

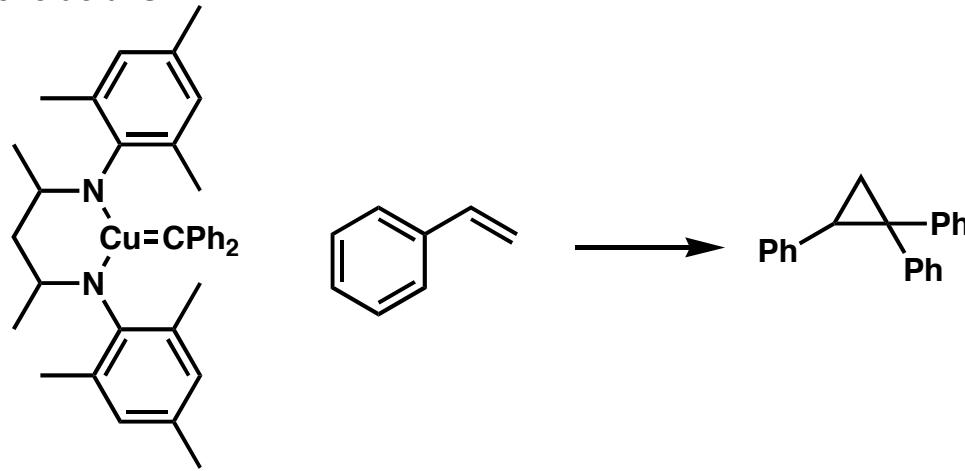
Metals that Employ this Mechanism

Ru(II,III), Rh(II), Cu(I) - early TS
 Os(II) } late TS
 Fe(II)

- isolated carbene complexes
- competent for reaction
- with electron rich alkenes



Cu(I) carbene details



- C₂ dicopper carbene; C_{2v} terminal carbene
- kinetics (after carbene isolation)- 1st order in carbene complex, styrene
- associative
- electron rich styrenes accelerate the reaction

Dai, X.; Warren, T. H. *J. Am. Chem. Soc.* **2004**, 126, 10085-10094.

Not a Universal Mechanism

Metals that promote cyclopropanation

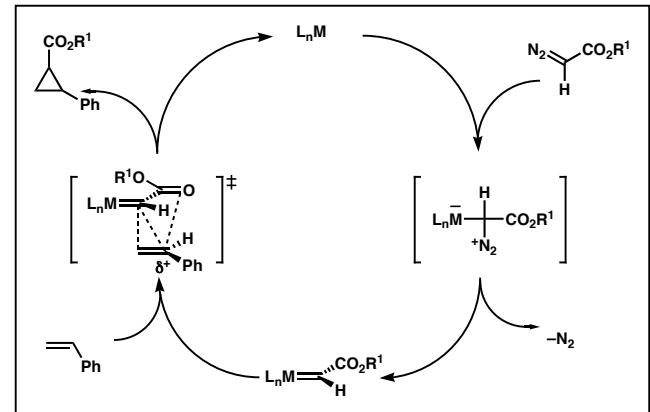
- late transition metals
- lewis acids
- coordinatively unsaturated at the metal center
(base may influence reactivity)

Noted: Ru(II, III), Rh(II), Cu(I), Os(II), Fe(II)

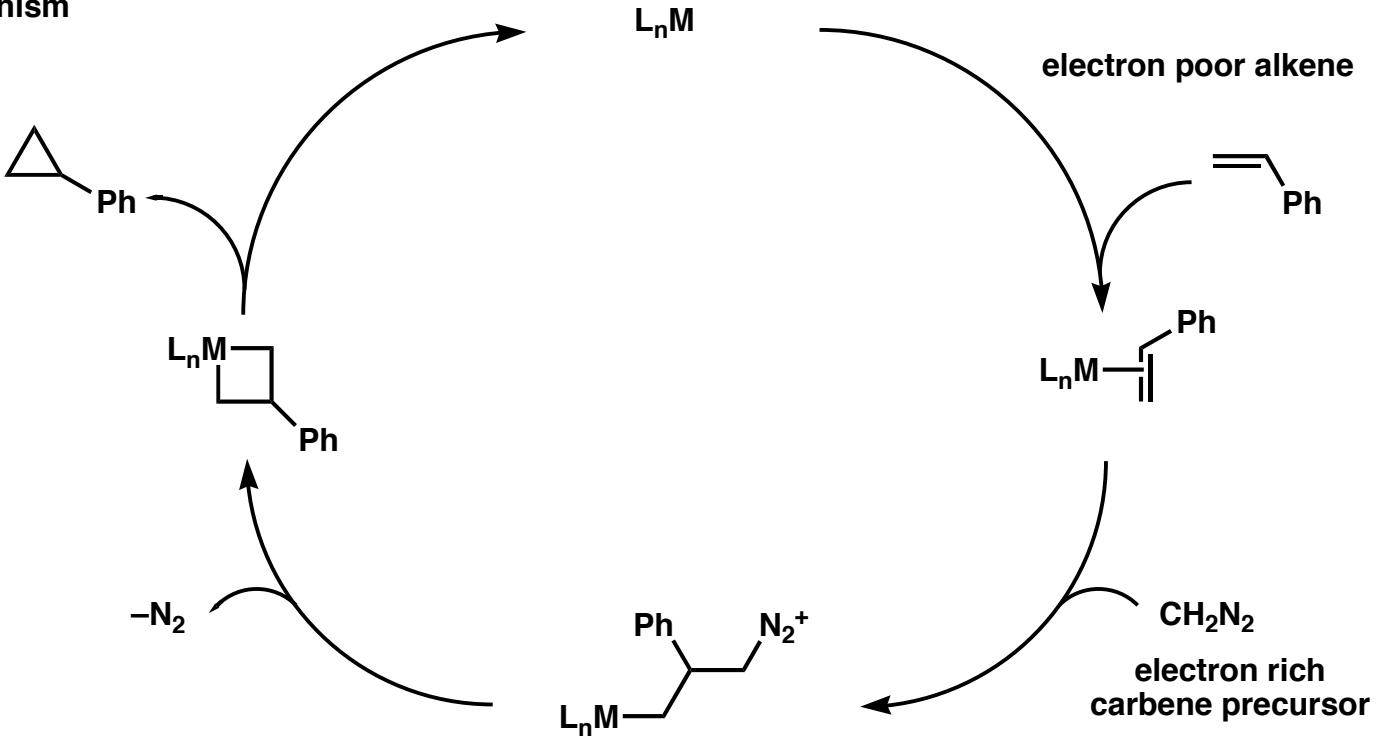
Others: Co(II), Pd(II)

Stoichiometric: Pt(II), Cr(II)

More Others: Ni, Zn, U (with diazomethane as a carbene precursor)



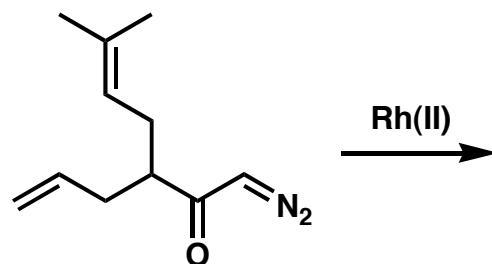
Pd mechanism
- Co?



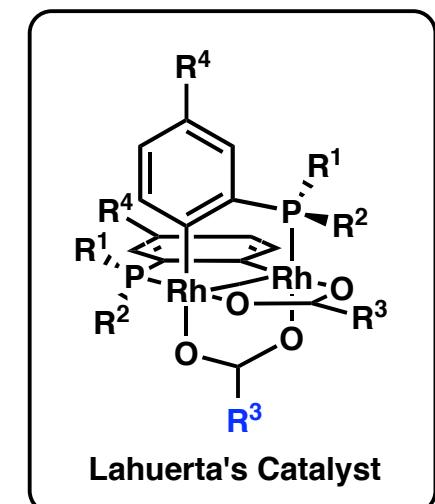
Stereoselectivity

- Chemoselectivity - cyclopropanation, C–H / X–H insertion, ylide formation

- Position selectivity

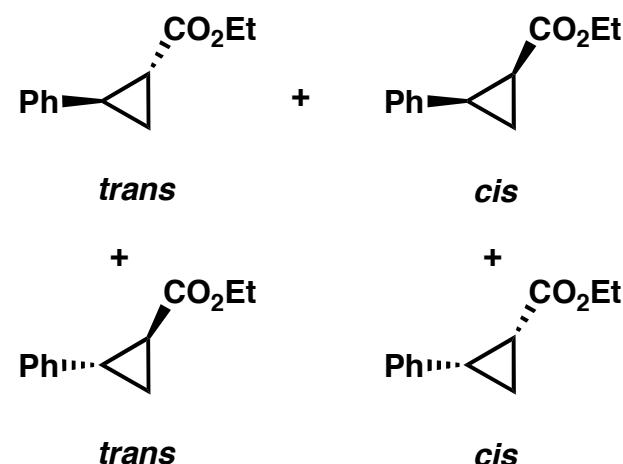
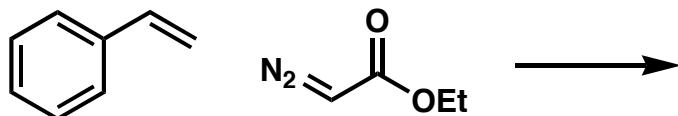


	Total Yield	<i>syn</i>	<i>Relative yields</i>	<i>syn</i>	<i>Relative yields</i>
$R^1=R^2=p\text{-CH}_3C_6H_5$; $R^3=CH_3$; $R^4=CH_3$	90%	74%		26%	
$R^1=R^2=p\text{-CH}_3C_6H_5$; $R^3=C_6F_5$; $R^4=CH_3$	93%	32%		68%	



Lahuerta, et al. *Tetrahedron: Asymmetry* **2003**, *14*, 787-790.

- Diastereoselectivity

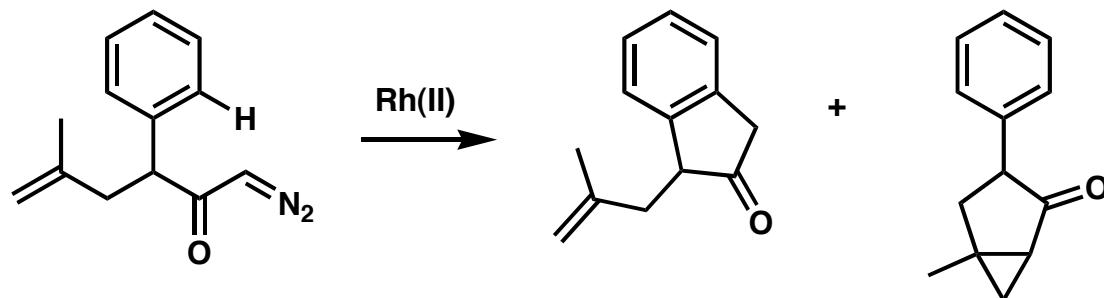


- Enantioselectivity

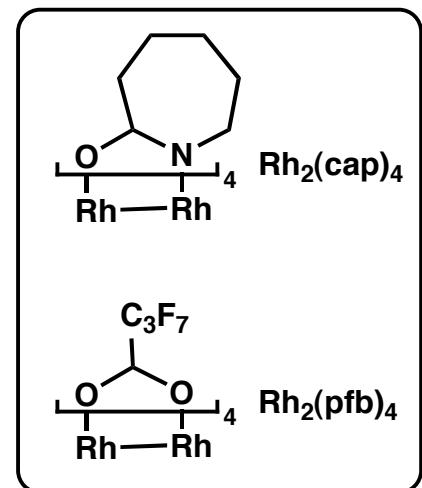
Chemoselectivity

Electronics

- more electrophilic metals --> more reactive carbenoid
- > may favor C–H insertion over cyclopropanation



	Total Yield	C–H insertion	Relative Yields	cyclopropanation	
Least E ⁺	Rh ₂ (cap) ₄	75%	0	:	100
	Rh ₂ (OAc) ₄	99%	67	:	33
Most E ⁺	Rh ₂ (pfb) ₄	86%	100	:	0



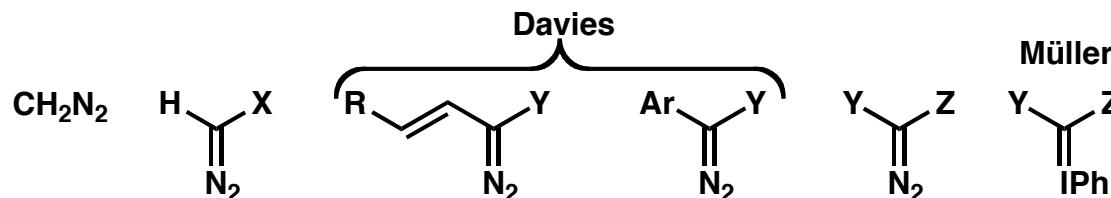
Padwa; Doyle *et al.* *J. Am. Chem. Soc.* **1992**, *114*, 1874-1876.

Sterics

- dimerization of the carbene, and C–H insertion are favored with smaller carbene pocket

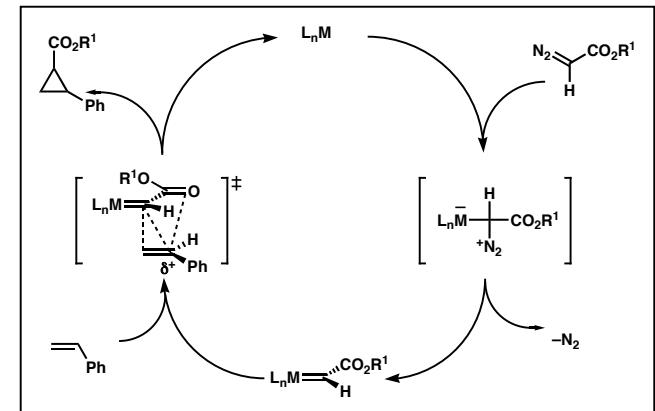
Carbene Source

1. Carbene Formation



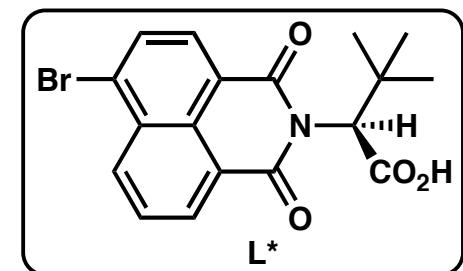
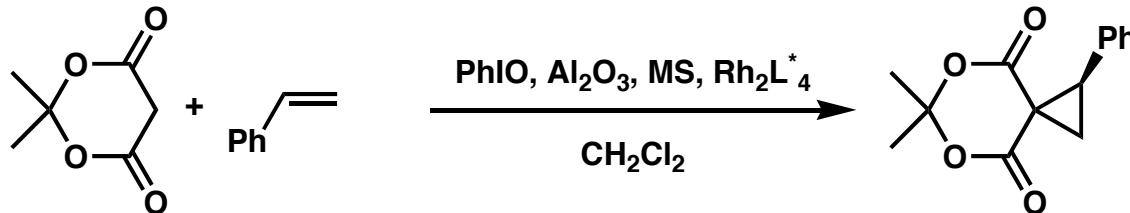
$pK_a \sim 10$

X, Y, Z: CO_2R , COR , CN , $\text{PO}(\text{OR})_2$, SO_2R , NO_2
X: CO_2R , COR ; $pK_a \sim -5$ to -2



Phenyliodonium Ylides - mechanism questioned for the intramolecular case (Cu, Rh)

- when intermolecular reaction, similar dr, ee to corresponding diazo compound
- sometimes react when corresponding diazo compounds may not form carbene

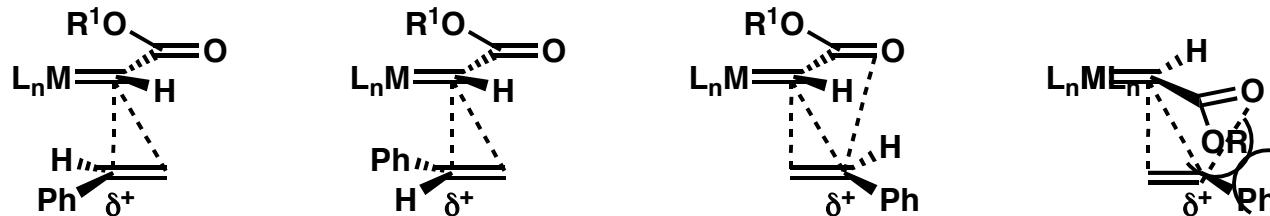


Müller, P.; Gharem, A. *Org. Lett.* 2004, ASAP.

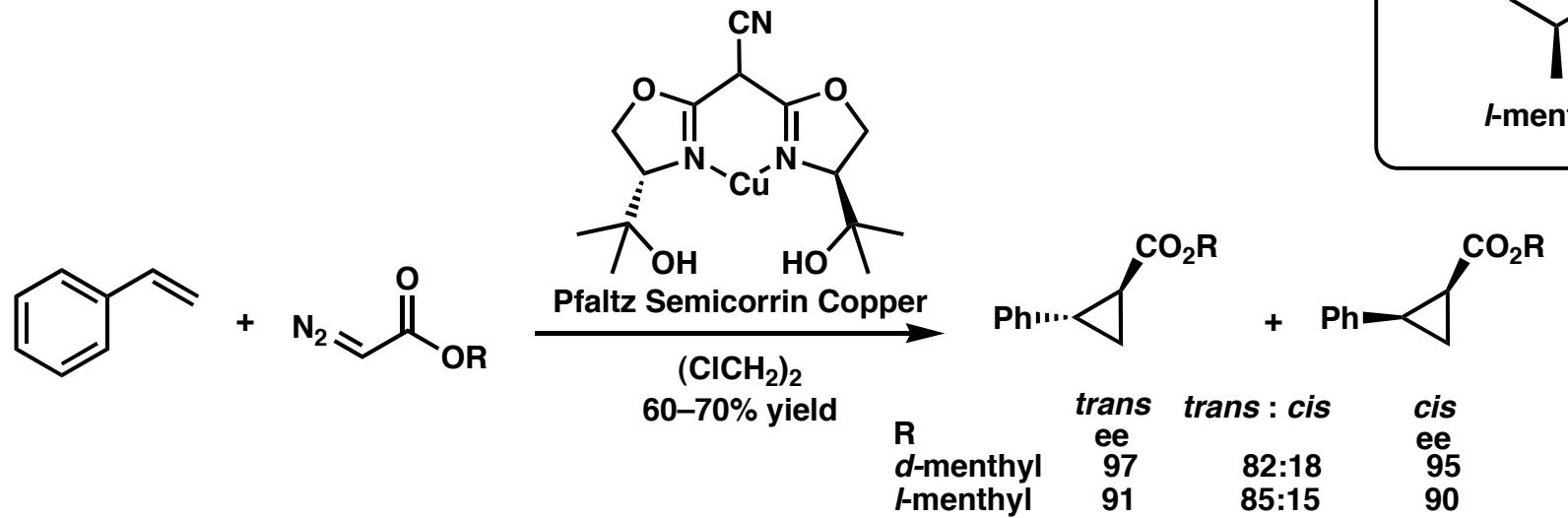
Carbene Source

2. Transition State

- electronic: polar substituent --> transition state geometry (think Diels-Alder)
- steric: ester substituent size - larger substituents favor *trans* geometry



- steric: ester substituent chirality --> dr, ee

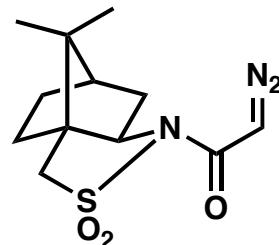
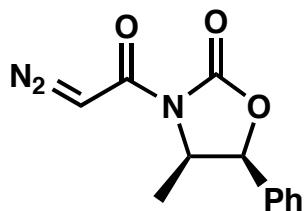
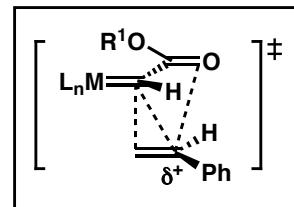


Pfaltz, et al. *Helv. Chim. Acta* 1988,
71, 1553-1565.

Chiral Auxiliaries – Alkene and Carbene

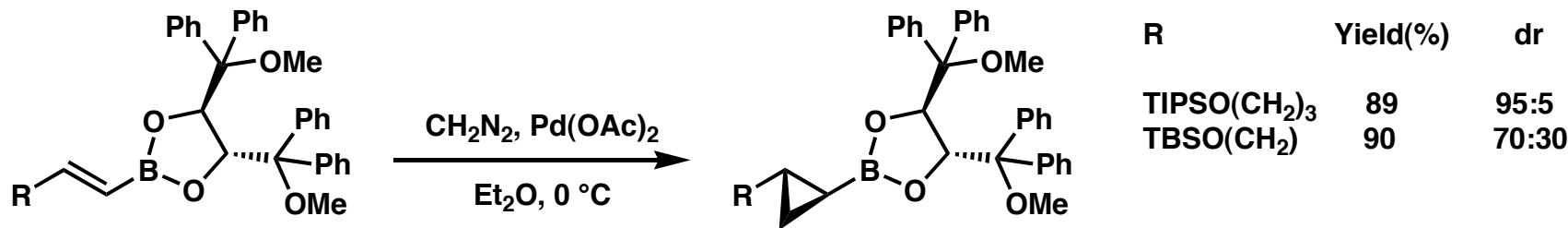
Carbene

- chiral auxiliaries have not worked well with diazoalkanes with an electron withdrawing group



Alkene

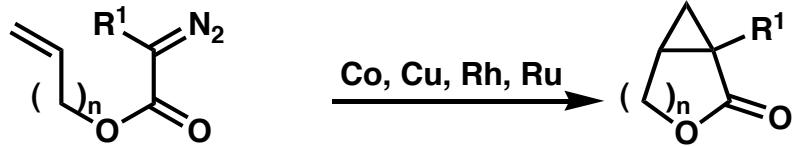
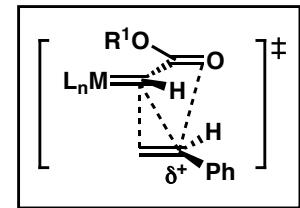
- chiral auxiliaries have worked in *trans*-alkenes with diazomethane



Luithle, J. E. A.; Pietruszka, J. *J. Org. Chem.* **1999**, *64*, 8287-8297.

- dr drops with *cis*-alkene for diazomethane
- chiral auxiliaries have not worked well with diazoalkanes with an electron withdrawing group

Carbene Influence on Intramolecular Reactions

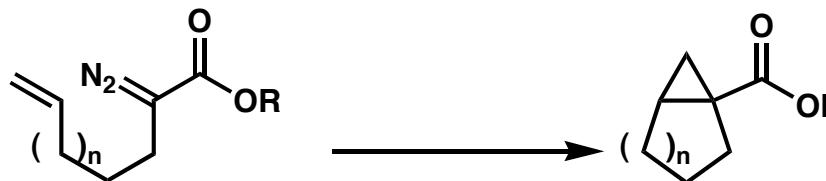


$R^1 = H$

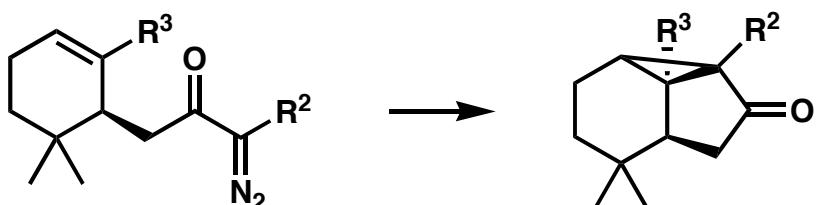
- mono- and disubstituted alkenes
(most without high ee)
 - small fused rings - Rh carboxamidate
 - medium, large ring - Cu bisoxazole
- trisubstituted alkenes
 - 5,6-membered ring - Co, Ru

$R^1 = \text{vinyl, aryl}$

- monosubstituted alkenes - Davies $\text{Rh}_2(\text{DOSP})_4$



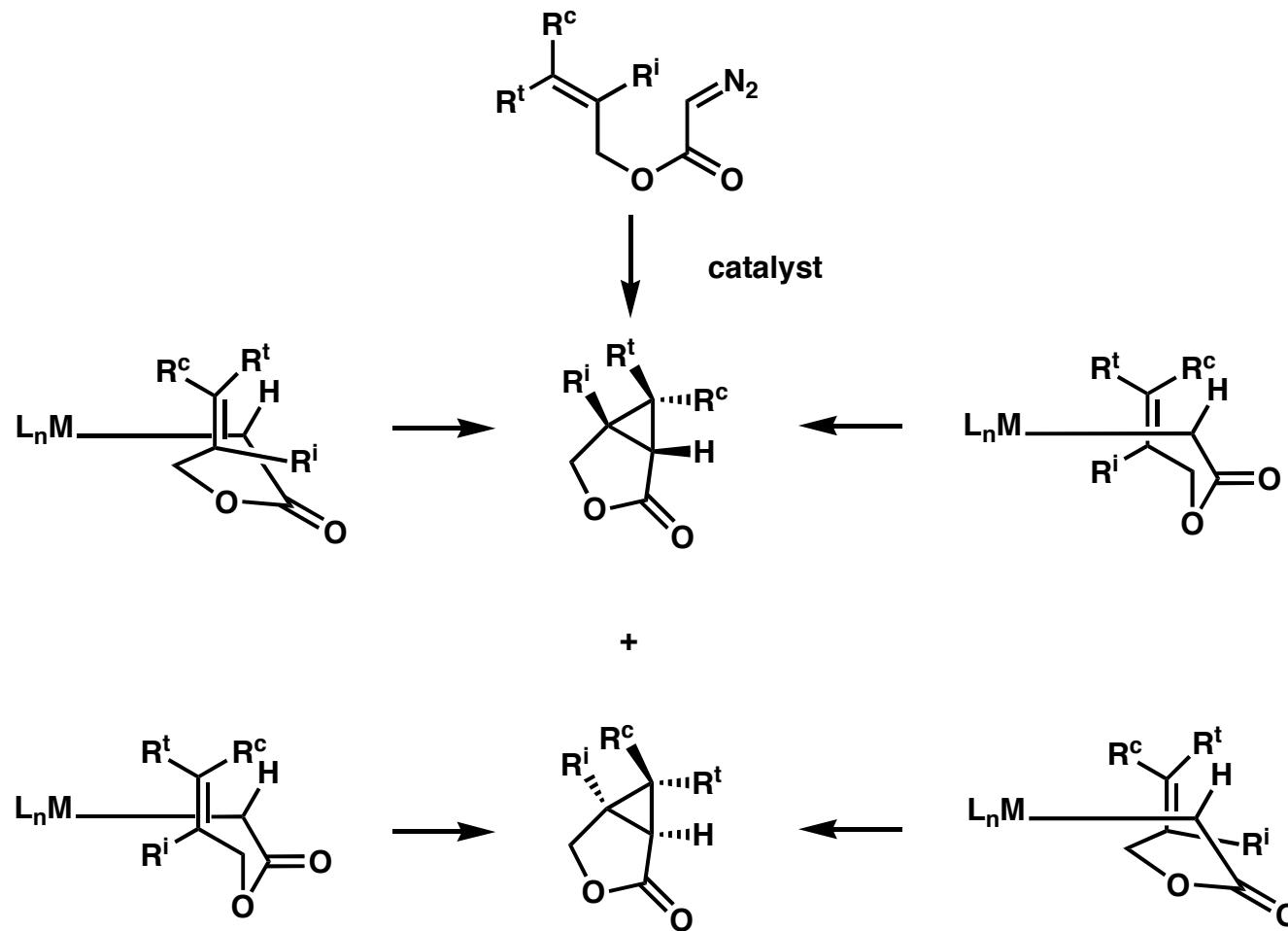
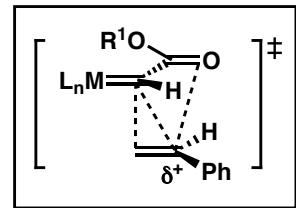
Did not note successful chiral catalysis in literature



$R^2 = \text{furan, } R^1 = \text{Me}$
 $\text{Cu}(\text{OTBS})_2, \text{PhCH}_3, \text{heat} \rightarrow 57\% \text{ yield}$
 $\text{Rh}_2(\text{OAc})_4 \rightarrow \text{carbene dimer}$
 $R^2 = R^3 = H, \text{Rh}_2(\text{OAc})_4 \rightarrow \text{reaction (yield not noted)}$

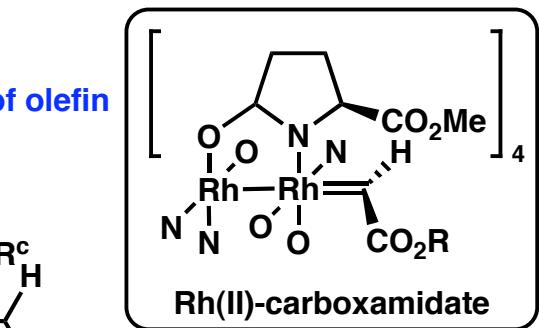
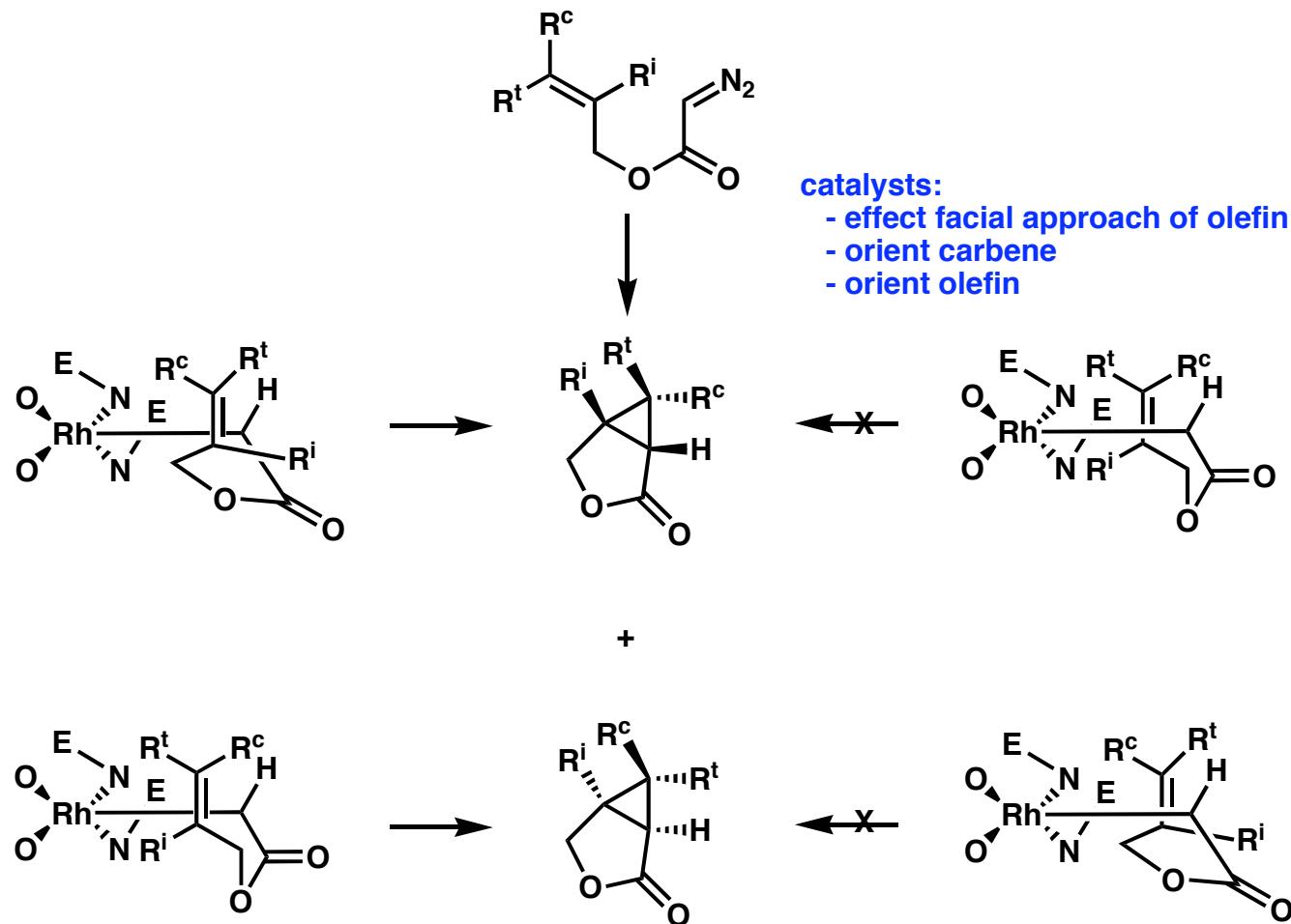
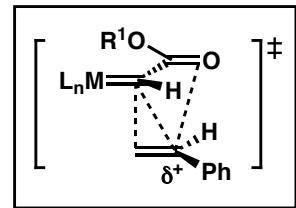
Fernandez Mateos, A.; Lopez Barba, A. M. *J. Org. Chem.* **1995**, *60*, 3580-3585.

Transition States for Intramolecular Reactions – The Alkene



Doyle Review
 Doyle, M. P. et al. *J. Am. Chem. Soc.* 1995, 117(21), 5763-5775.

Transition States for Intramolecular Reactions – The Alkene

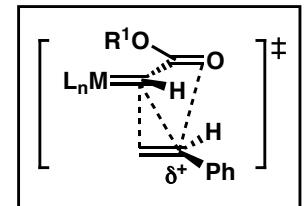


Doyle Review
 Doyle, M. P. et al. *J. Am. Chem. Soc.* 1995, 117(21), 5763-5775.

Alkenes in Intermolecular Reactions

1. General

- Alkenes can coordinate to the metal, decreasing reactivity
(demonstrated with porphyrins)



Tagliatesta, P.; Pastorini, A. *Journal of Molecular Catalysis* **2002**, 185(1-2), 127-133.

- Substitution

- most ligand frameworks developed for cyclopropanation handle monosubstituted olefins though some only handle monosubstituted olefins with aryl substituents
- 1,1-substituted terminal alkenes stabilize charge in the transition state
--> more rapid reaction (neglecting sterics)

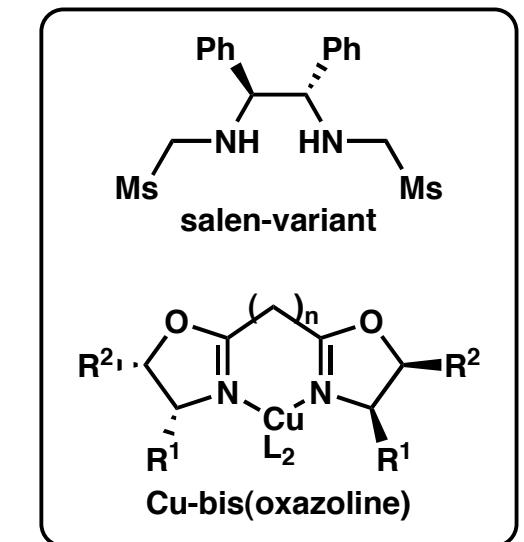
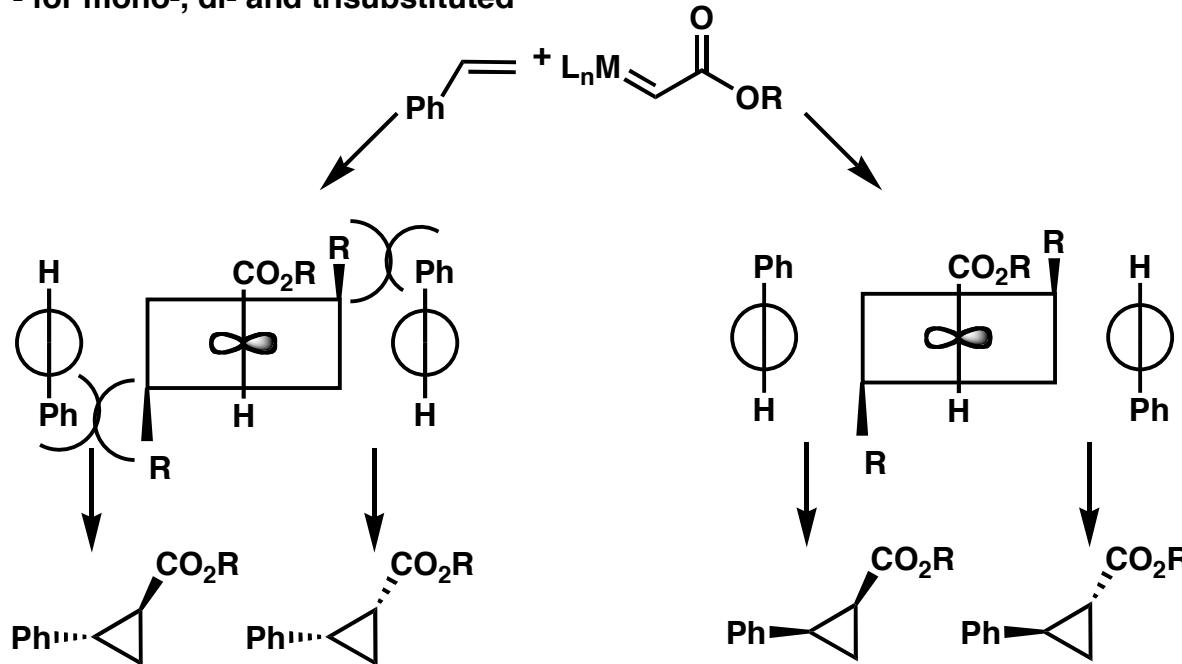
2. Specific

Diazoacetate

trans product (good ee)

Cu-bis(oxazoline) variants and below salen-like ligand

- for mono-, di- and trisubstituted

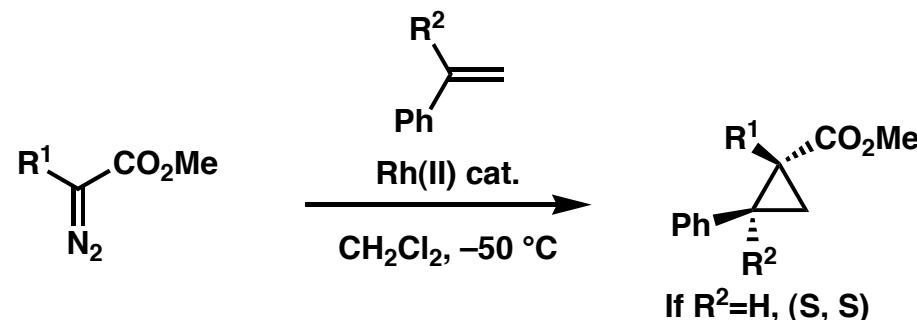
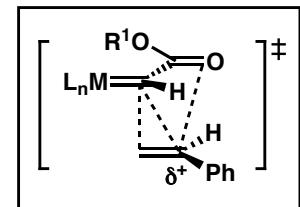


Trans Selection with Alkenes and Vinyl / Aryl Diazoacetates

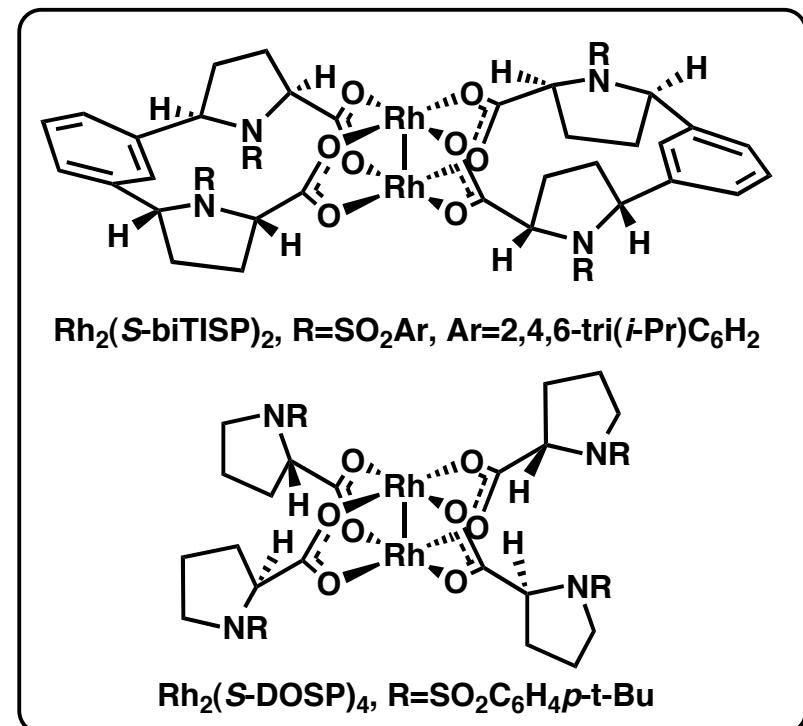
trans product (good ee)

Davies D₂ symmetric Rh catalysts

- for mono- and 1,1-disubstituted alkenes



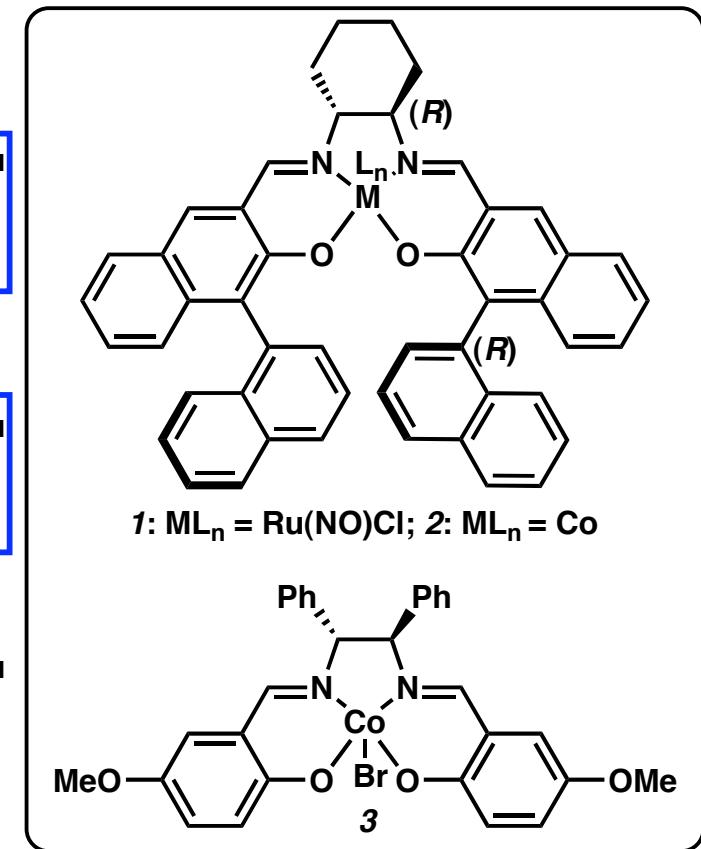
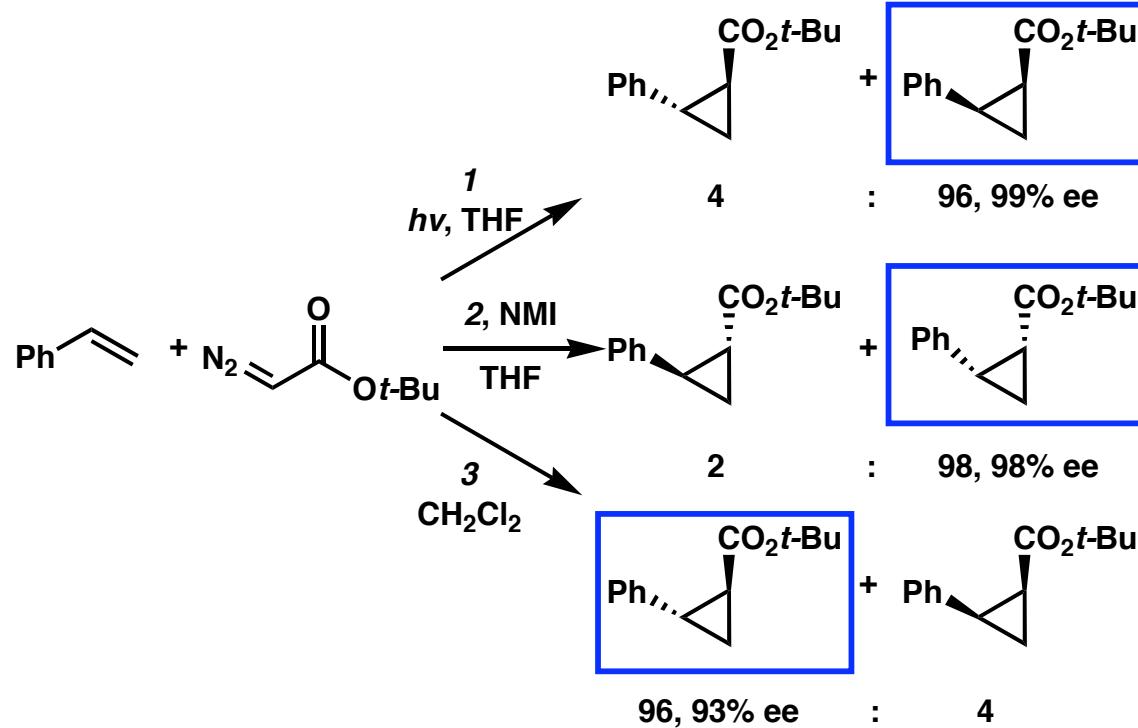
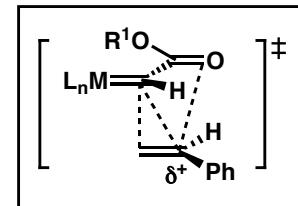
R ¹	R ²	catalyst	ee	yield
CH=CHPh	H	Rh ₂ (S-biTISP) ₂	98 (S,S)	NR
CH=CHPh	H	Rh ₂ (S-DOSP) ₄	88 (R,R)	NR
CH=CHPh	Ph	Rh ₂ (S-biTISP) ₂	>97 (S)	32
Ph	Ph	Rh ₂ (S-biTISP) ₂	>97 (S)	81



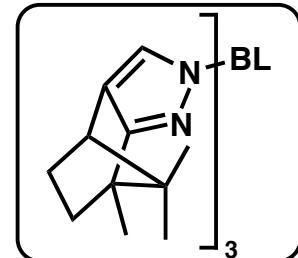
Davies, H. M. L.; Panaro, S. A.
Tetrahedron Lett. 1999, 5287-5290.

Cis Selection with Diazoacetates in Intermolecular Reactions

cis diastereomers less readily available
 Co salen or borate (with diazoacetate carbene precursor)
 - for mono- and 1,1-disubstituted alkenes



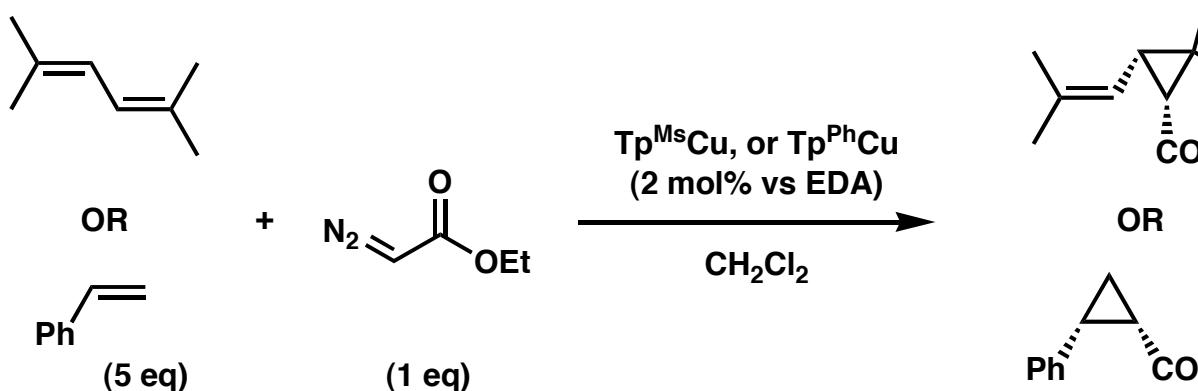
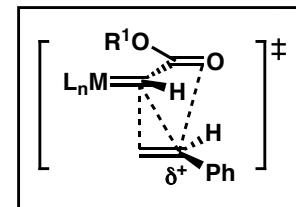
Katsuki, et al. *Tetrahedron: Asymmetry* 2003, 14, 823-836.



Ligand Steric Bulk Enhances C–H Activation, *cis* Selection

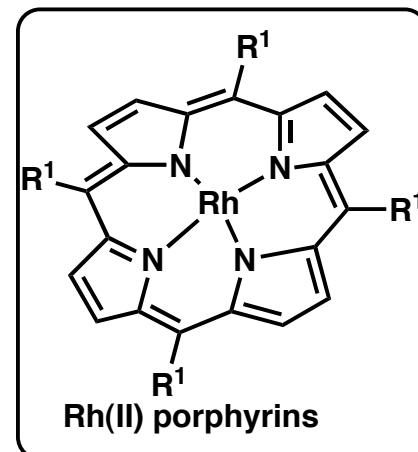
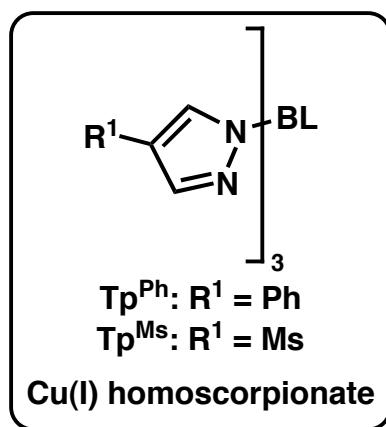
Cu(I) homoscorpionate, Rh(II) porphyrins

- C–H activation yields increase in parallel to *cis* dr
- smallest catalytic pocket enhances both *cis* dr and C–H insertion



Ligand	Yield	<i>cis</i> : <i>trans</i>
Tp^{Ms}	97	78 : 22
Tp^{Ph}	99	42 : 58

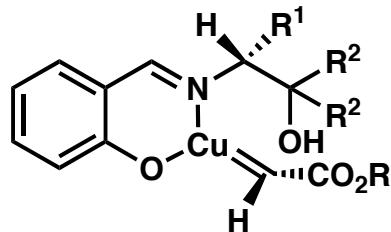
Ligand	Yield	<i>cis</i> : <i>trans</i>
Tp^{Ms}	97	98 : 2
Tp^{Ph}	80	80 : 20



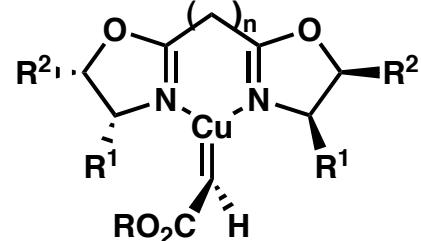
Representative Ligands for Evaluating Sterics

quadrants - C₁, C₂, D₂, D₄

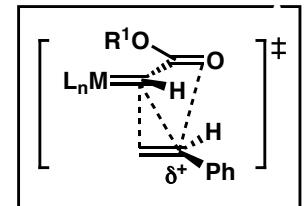
Cu(I) - bidentate



C₁: Cu(I)-salicylaldimide



C₂: Cu-bis(oxazoline)



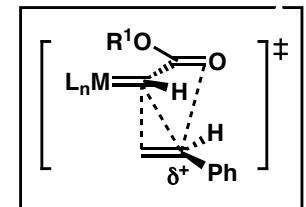
catalysts:

- effect facial approach of olefin
- orient carbene
- orient olefin

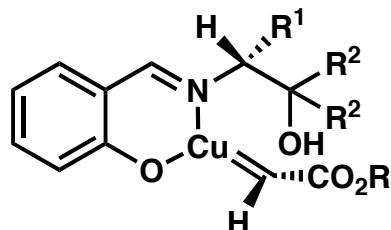
Disclaimer: Depicted carbenes may not accurately represent reality

Representative Ligands for Evaluating Sterics

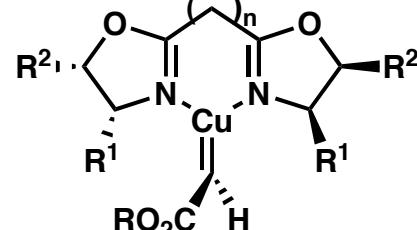
quadrants - C₁, C₂, D₂, D₄



Cu(I) - bidentate

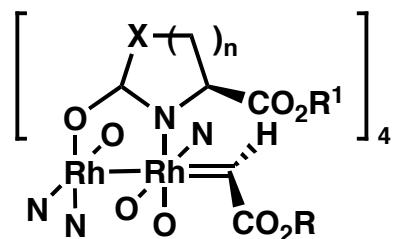


C₁: Cu(I)-salicylaldimide

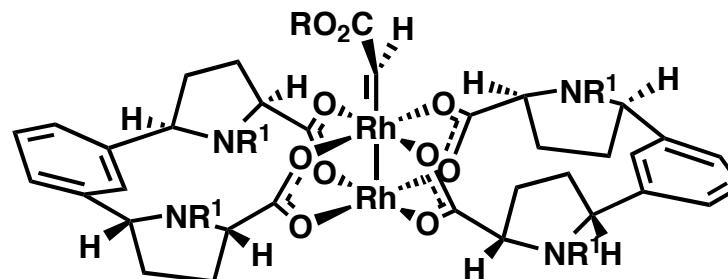


C₂: Cu-bis(oxazoline)

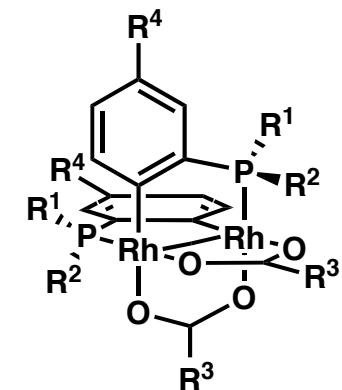
Rh(II) - bridged tetradentate



C₂: Rh(II)-carboxamidate



D₂: Rh(II)-carboxylate (others C₂)



C₂: Lahuerta's Catalyst

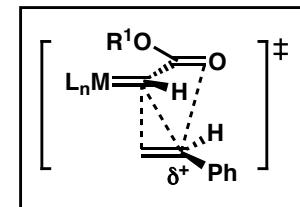
catalysts:

- effect facial approach of olefin
- orient carbene
- orient olefin

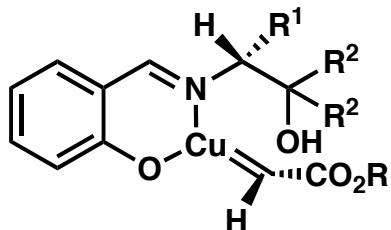
Disclaimer: Depicted carbenes may not accurately represent reality

Representative Ligands for Evaluating Sterics

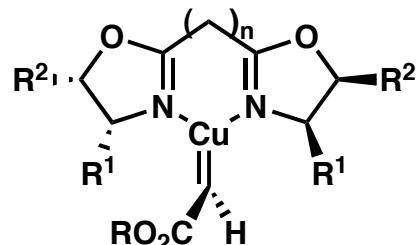
quadrants - C₁, C₂, D₂, D₄



Cu(I) - bidentate



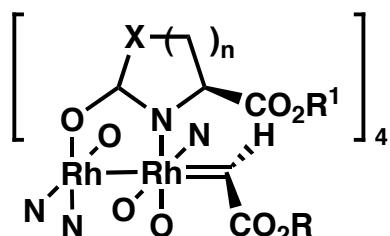
C₁: Cu(I)-salicylaldimide



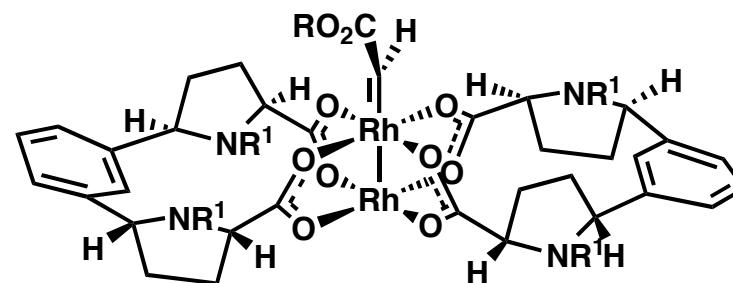
catalysts:

- effect facial approach of olefin
- orient carbene
- orient olefin

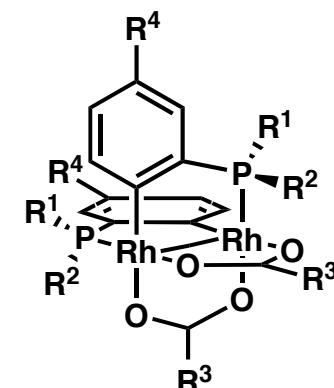
Rh(II) - bridged tetradentate



C₂: Rh(II)-carboxamidate

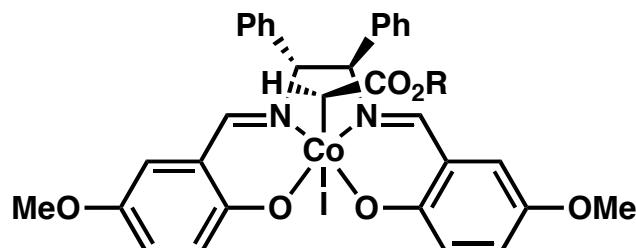


D₂: Rh(II)-carboxylate (others C₂)

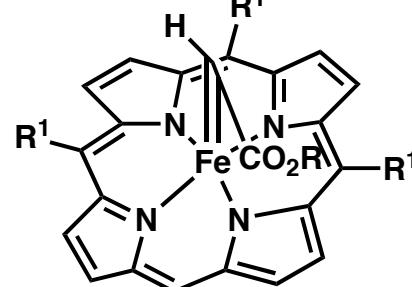


C₂: Lahuerta's Catalyst

Co(II, III), Ru(II, III) - tetradentate



pseudo C₂: Co(III)-salen

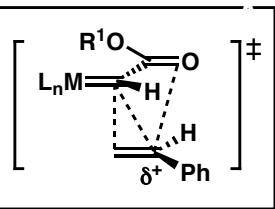


D₄: Fe(II)-porphyrins

Fe(II), Rh(II), Os(II), Ru(II,III) - tetradentate

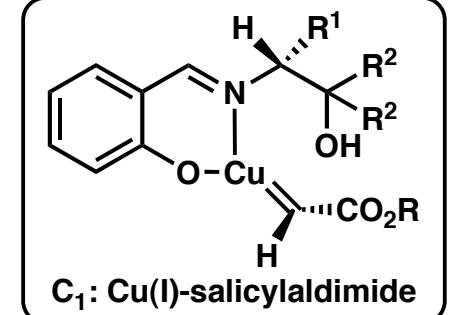
Disclaimer: Depicted carbenes may not accurately represent reality

Representative Ligands for Evaluating Sterics



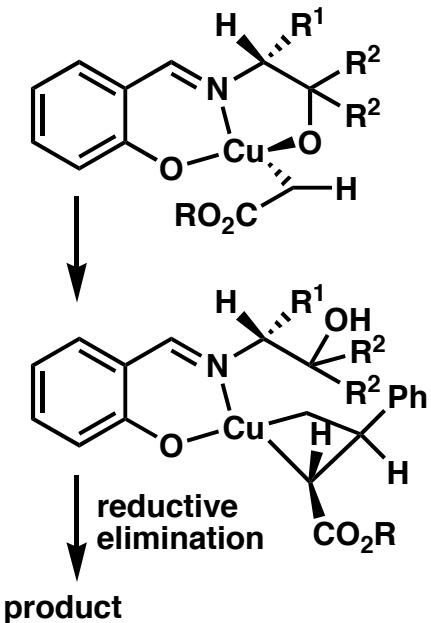
Copper Salicylaldimine

Cu(I) - bidentate C₁



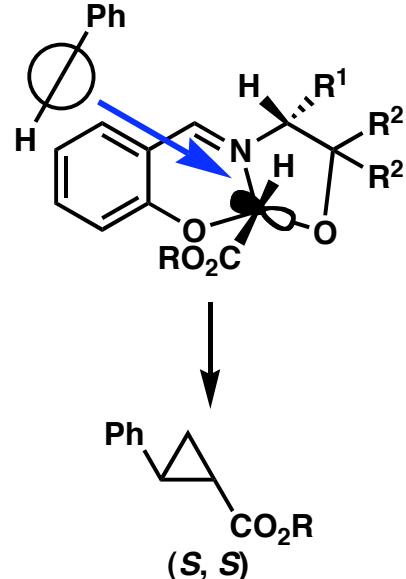
Large R² required for high ee
R¹ - ee: Me > CH₂Ph > i-Pr > i-Bu

Aratani's proposal



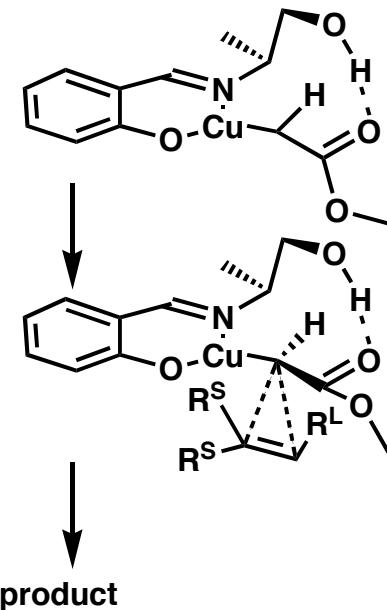
Aratani. *Pure and Appl. Chem.*
1985, 57, 1839-1844.

Doyle's proposal



Doyle Review
(1991)

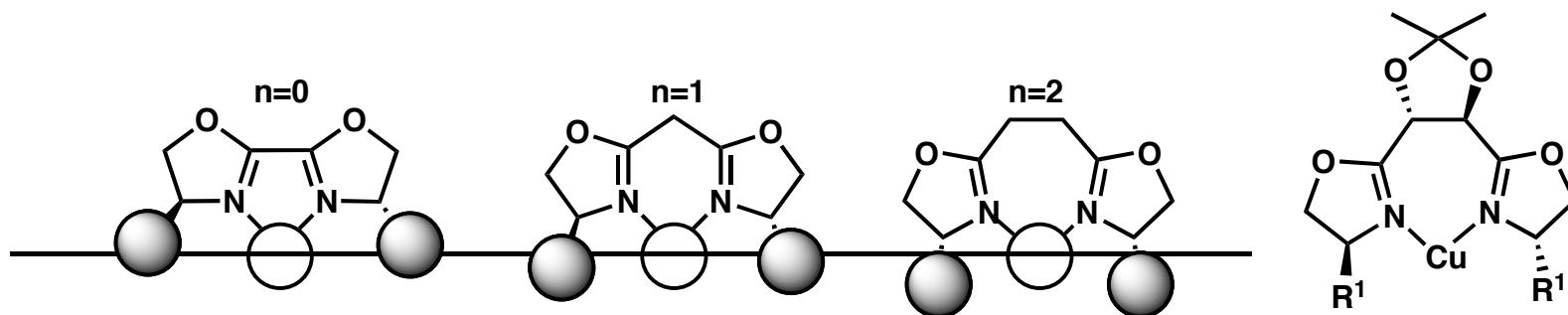
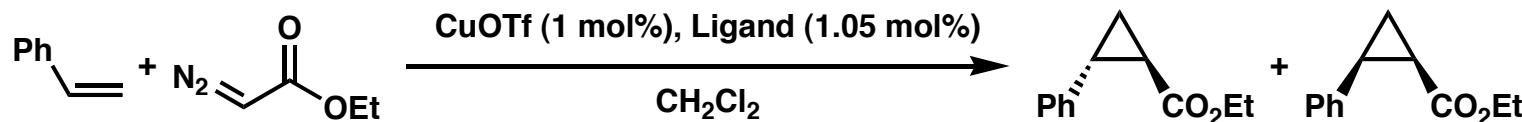
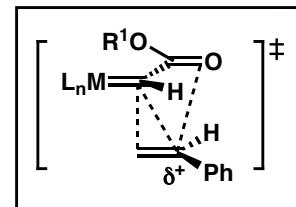
Nakamura's DFT Calculations



Nakamura, et al. *J. Am. Chem. Soc.*
2004, 126, 7271-7280.

Representative Ligands for Evaluating Sterics

Copper Bis(oxazoline) - bidentate



Yield: $n = 1 \sim 2$ (with chiral backbone) $> 2 > 0$

dr: small variations 64:36 - 71:29

ee: 2 (with chiral backbone) $> 2 > 1$ (with substituted backbone) $> 1 > 0$

In the absence of a tartrate backbone, ee: $R^1 = t\text{-Bu} > i\text{-Pr}$

With tartrate backbone, *trans* ee: $i\text{-Pr} > i\text{-Bu} > \text{Bn} > \text{Et} > t\text{-Bu} \dots$ *cis* ee: $i\text{-Bu} > i\text{-Pr} > \text{Bn}$

84	77	50	18	2	70	65	39
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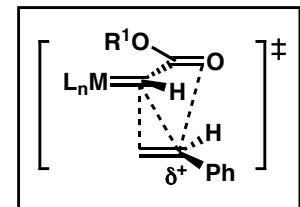
With tartrate backbone, dr:

$i\text{-Bu} > i\text{-Pr} > \text{Bn} > t\text{-Bu} > \text{Et}$
73:27 70:30 68:32 64:36 58:44

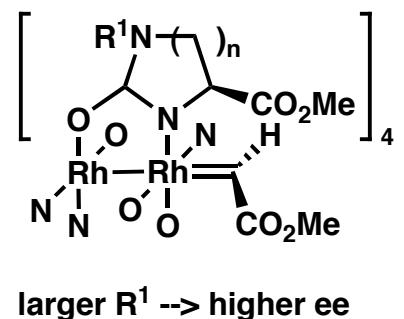
Andersson, et al. *J. Org. Chem.*
1997, 62, 2518-2526.

Representative Ligands for Evaluating Sterics

Rh(II) Carboxamides - bridged tetradentate

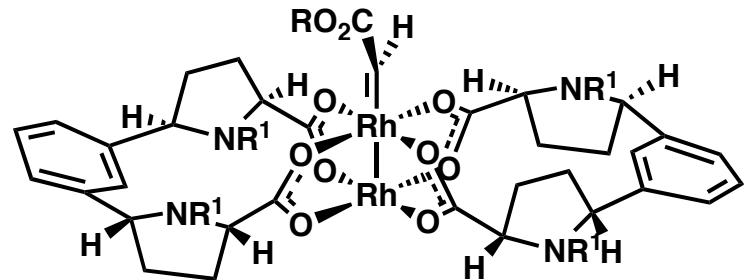


R^1	ee
$C(O)C_6H_4p-t\text{-}Bu$	78
$C(O)C_6H_5$	46

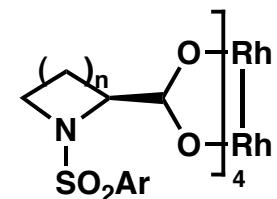


Rh(II) Carboxylates

Higher ee result with larger $R^1 = SO_2Ar$



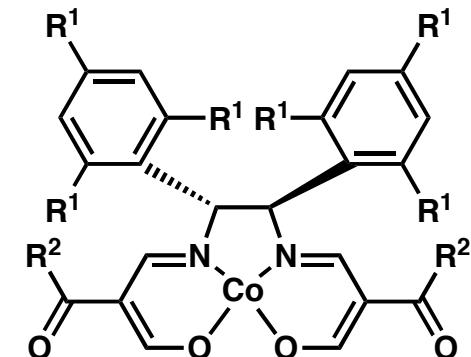
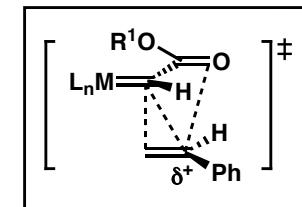
ee decreases, while reactivity increases with longer Rh–Rh bonds
- n=1: good E:Z, elevated reactivity, poor ee (relative to n=2)



Representative Ligands for Evaluating Sterics

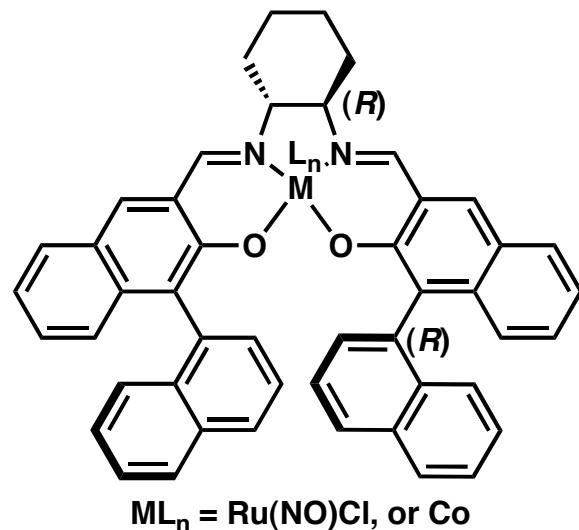
Co(II) salen - tetradentate

				CoL^* (0.5 mol%), NMI (0.1 mol%)	
				THF	
<chem>Ph=</chem>	<chem>[N+](=O)[C@@H](COEt)C=C</chem>				<chem>CC1(C)C[C@H]1[C@@H](CO2Et)Ph</chem>
R^1	R^2	Temp / °C	Reaction time / hr	Yield / %	<i>trans:cis</i>
Me	Me	40	10	80	83:17
Me	<chem>OC5H9</chem>	40	4.5	97	90:10
H	<chem>OC5H9</chem>	25	2	quant.	81:19
					ee (<i>trans</i>) / %
					96
					96
					66



Yamada, T. et al. *Bull. Chem. Soc. Jpn.* 2001, 74(11), 2139-2150.

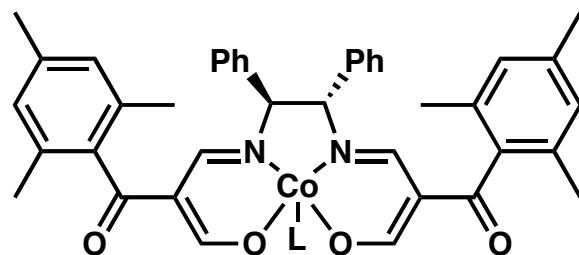
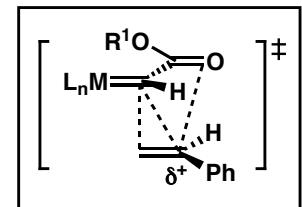
With larger salen complexes, the diamine chirality still dictates the approach of the olefin (intramolecularly)



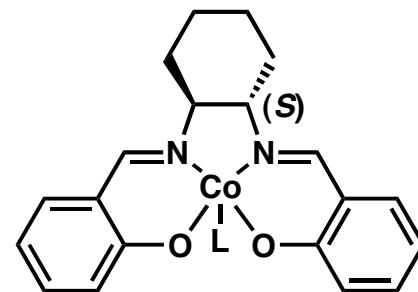
Katsuki, et al. *Chem. Lett.* 2002, 846-847.

Cobalt Carbenes with Single Bond Character

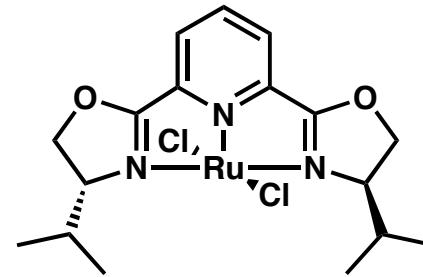
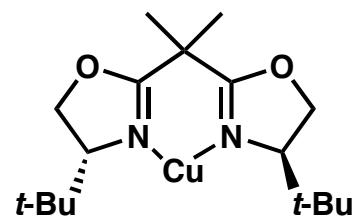
Co carbenes: single bond character



L = *N*-methylimidazole, or Cl

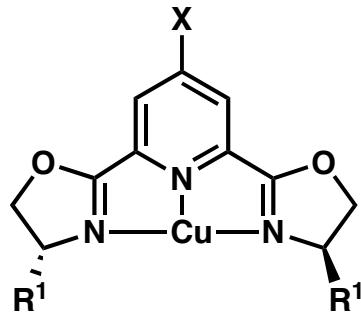


L = *N*-methylimidazole, or I
(L=NMI --> more double bond character)

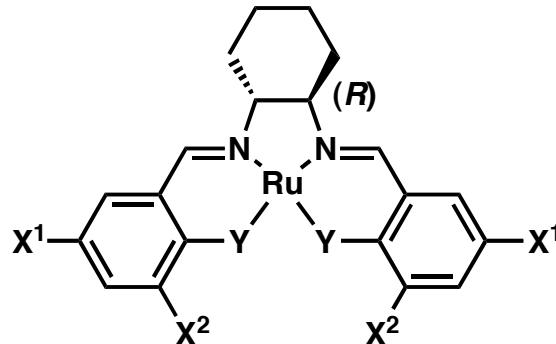


Tuning Ligands: Electronics

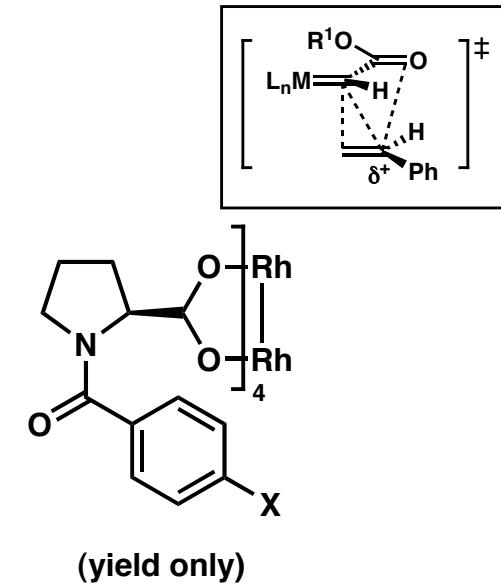
Electron poor ligands increase ee, reactivity in many systems



Nishiyama, et al. *Tetrahedron: Asymmetry* **1995**, 6(10), 2487-2494.

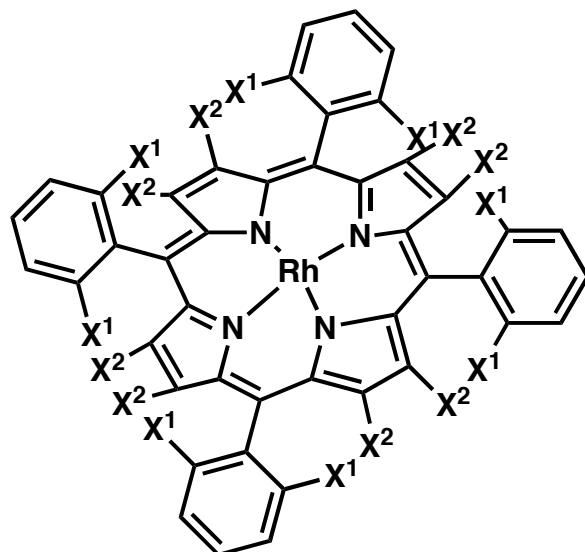


$Y=O$, or $Y=P(ArX^3)_3$ with $X^1=X^2=H$
Mezzetti, A. et al. *Tetrahedron: Asymmetry* **2003**, 845-854.



Ishitani and Achiwa
in Doyle Review

This relationship does not hold for Rh(III) porphyrins

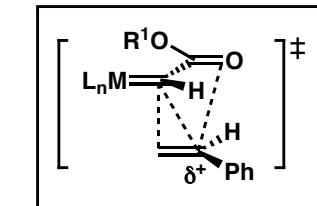


X^1 : *syn : anti* dr increases with ewg (styrene + ethyl diazoacetate)
 X^2 : *syn : anti* dr decreases with Br (styrene + ethyl diazoacetate)
- Trends do not appear with norbornene, or cyclohexene alkenes

Tagliatesta, P.; Pastorini, A. *Journal of Molecular Catalysis* **2002**, 185(1-2), 127-133.

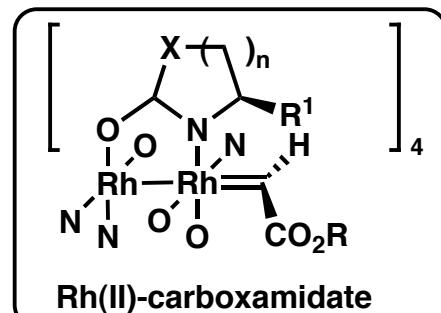
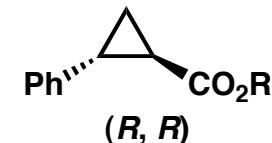
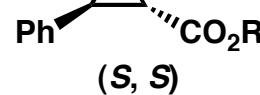
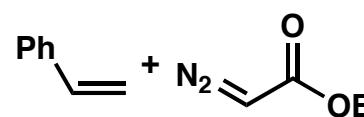
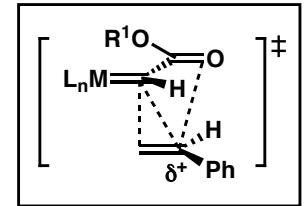
Fe(II), Os(II), Ru(II) porphyrins
- electron poor ligands increase the rate of cyclopropanation

Kodadek; Woo. *J. Am. Chem. Soc.* **1995**, 117(36), 9194-9199.
Berkessel, A. et al. *Chem. Eur. J.* **2003**, 9, 4746-4756.

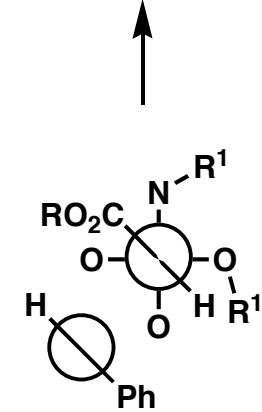
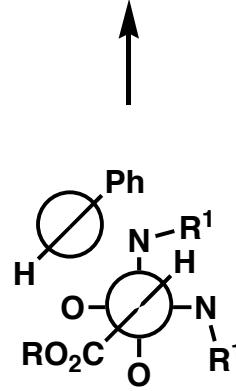


Tuning Ligands: Electronics of TS Populations

Dipole interactions --> transition state carbene populations

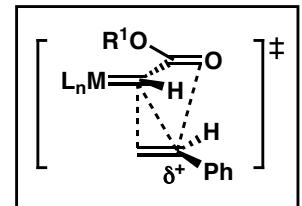


ee: $\text{R}^1 = \text{CO}_2\text{Me} > i\text{-Pr} > \text{CH}_2\text{Ph}$



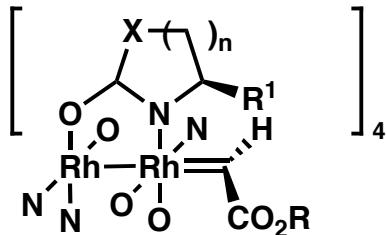
Heteroatom Exchange in Ligands

Heteroatom exchange --> reactivity and ee



oxazolidinone v. pyrrolidinone

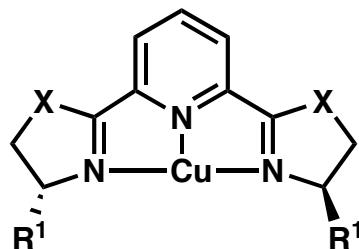
Yield: X = O > CH₂
ee: X = CH₂ > O



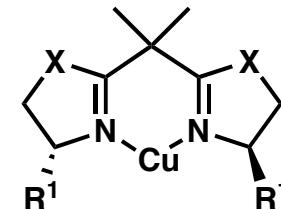
Rh(II)-carboxamidate
Doyle Review

thiazolidine v. pyrrolidine

If R¹ = Et, ee: X = S > O
If R¹ = i-Pr, Bnz, Ph, ee: X = O > S Pd-allylic substitutions (π-allyl)



Masson, S. et al. *Tetrahedron: Asymmetry* 2004, 15, 2569-2573.

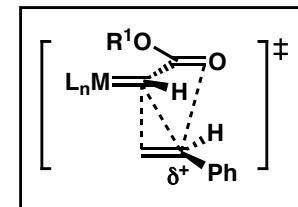


Masson, S. et al. *Tetrahedron* 2004, 60, 9263-9272.

Tuning with Additives: Electronics or Sterics?

Ligands and Additives

- Rh(II) carboxylates - solvent: higher dielectric constants \rightarrow lower ee (early TS?)
- solvent and additive: coordinating ability
 \rightarrow no obvious trend, but clearly influential



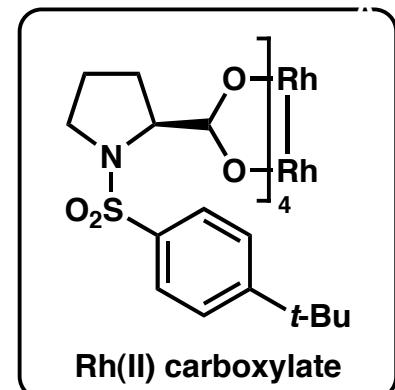
Confusing Examples:

Oxygen-containing additives:

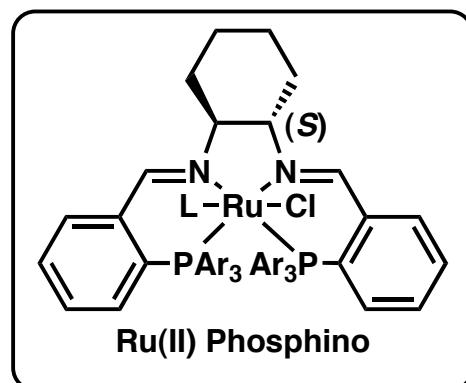
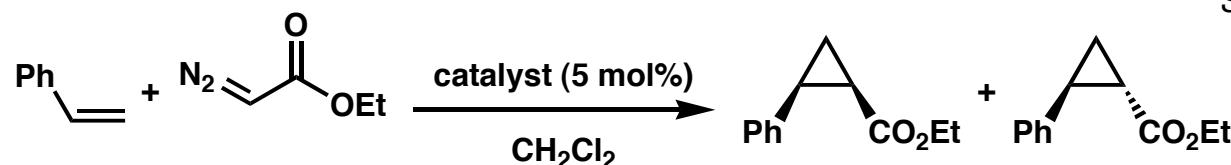
- Ru(II) phosphino complex (vs. 5-coord.)
 - Oxygen donor L (OEt_2) \rightarrow ee decreased
 - Oxygen donor L (H_2O) \rightarrow ee, dr still high; reactivity decreased
- Ru(II) pybox complex
 - $i\text{-PrOH}, \text{H}_2\text{O} \rightarrow$ ee, dr, yield increased (less pronounced with H_2O)

Nitrogen ligands:

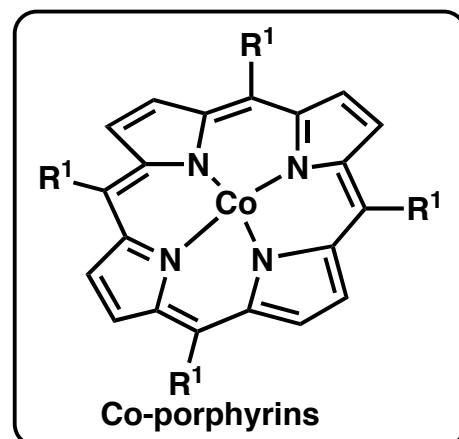
- Co porphyrin L (pyridine, NMO) \rightarrow *trans* dr increased (Zhang, X. Peter)



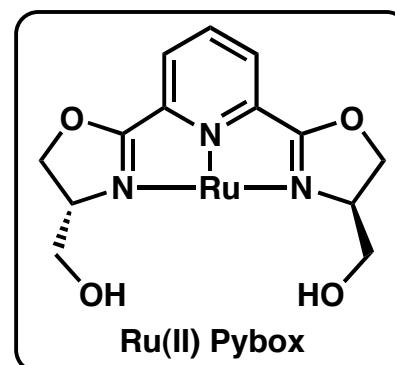
Jessop, P. G. et al. *J. Am. Chem. Soc.* **2000**, 122, 7638-7647.



Mezzetti, et al. *Tetrahedron: Asymmetry* **2003**, 14, 845-854.



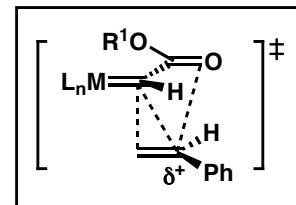
Charette Review



Nishiyama, H. et al. *Tetrahedron: Asymmetry* **2003**, 14, 855-865.

Anions – Electronic Confusion

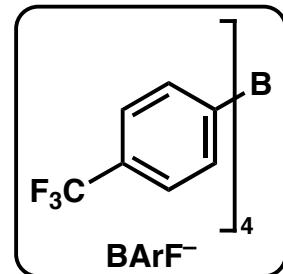
Counterions and ligands



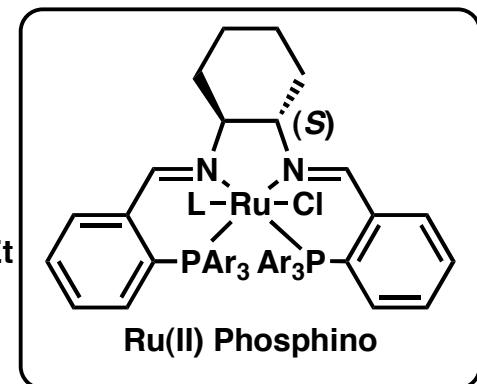
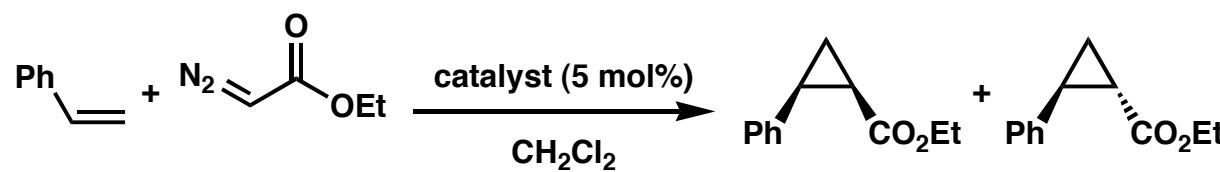
Confusing Examples:

Counter anions:

- Ru(II) phosphino complex counteranions (PF_6^- , BArF^-)



Anion	Ar	L	Yield	<i>cis : trans</i>	ee <i>cis</i>
PF_6^-	C_6H_5	H_2O	28	86 : 14	91
PF_6^-	4-CF ₃ C ₆ H ₄	H_2O	17	93 : 7	89
BArF^-	C_6H_5	H_2O	12	72 : 28	34
BArF^-	4-CF ₃ C ₆ H ₄	H_2O	35	98 : 2	80

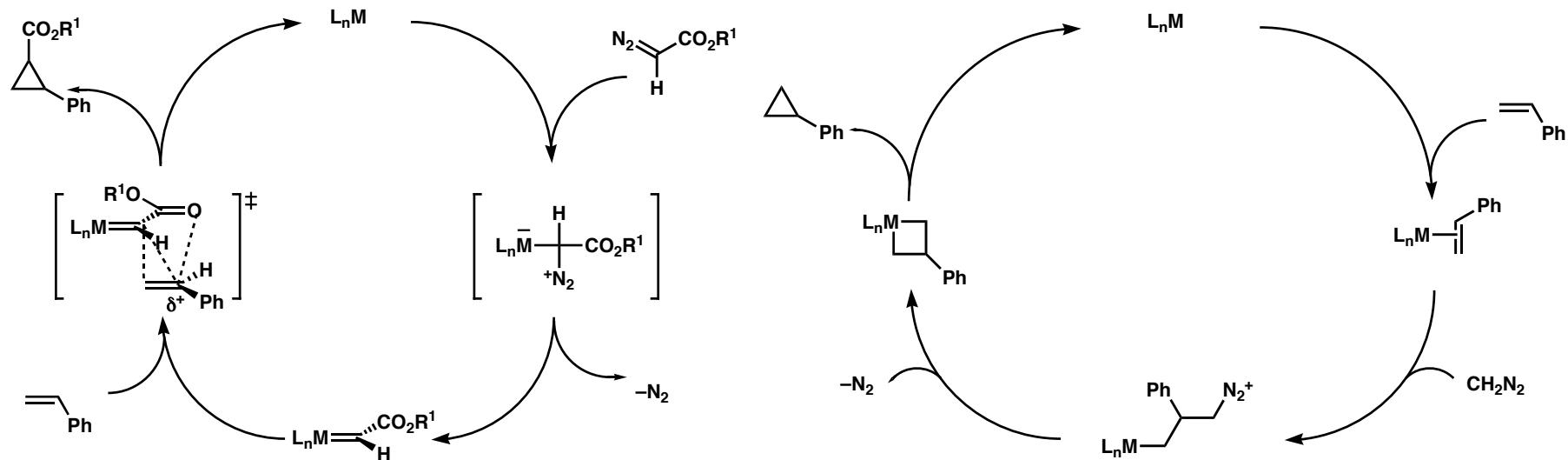


The Quest for Selective Cyclopropanations - Summary

Introduce Challenges and Accomplishments in Cyclopropanation Chemistry

Unique Challenge: Carbene Addition Across an Alkene or Alkyne Engages Chemoselectivity, Position Selectivity, Diastereoselectivity and Enantioselectivity SIMULTANEOUSLY

Questions: Can we exploit variations in mechanism or reaction timing?



Inputs to selectivity: carbene source, alkene source, ligand structure, ligand electronics

