

Rhodium Catalyzed [5+2] Cycloaddition

Aaron Bailey
Denmark Group Meeting
March 11, 2008

Outline

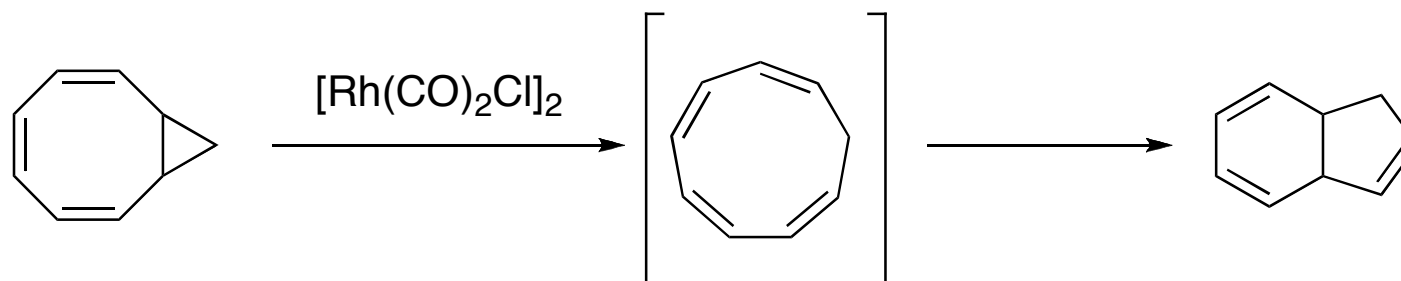
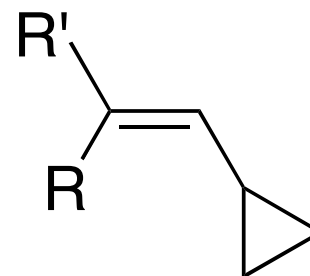
- The early years- discovery & substrate scope
- Catalyst development-expansion of scope
- Stereochemical Studies

Outline

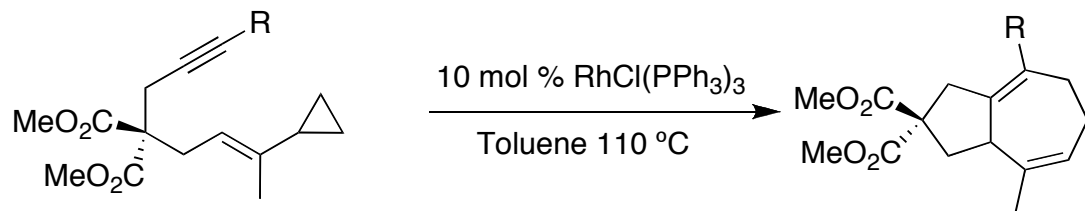
- The early years- discovery & substrate scope
- Catalyst development-expansion of scope
- Stereochemical Studies

Vinylcyclopropanes

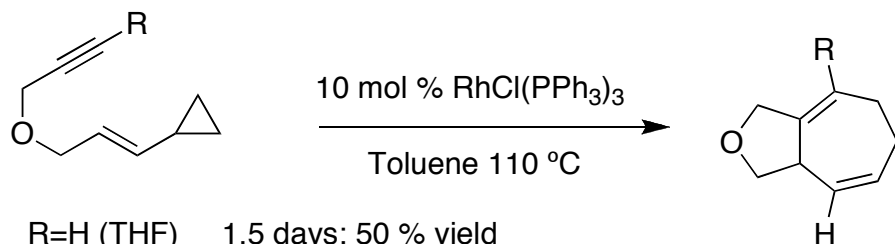
- Due to small ring size carbons obtain high p character
- Undergo rearrangements readily
- Potential substrate for cycloadditions



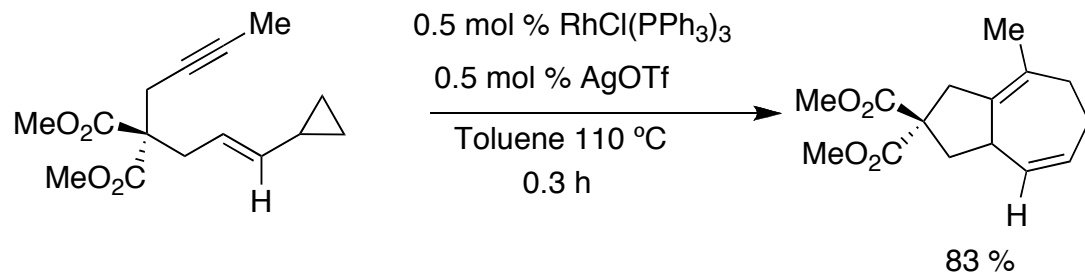
Initial Results



R=H 2 days; 82 % yield
Me 2 days; 89 % yield
CO₂Me 16 h; 81 % yield



R=H (THF) 1.5 days; 50 % yield
Me 1.5 h; 88 % yield
CO₂Me 1.25 h; 74 % yield
TMS 3.5 h; 83 % yield

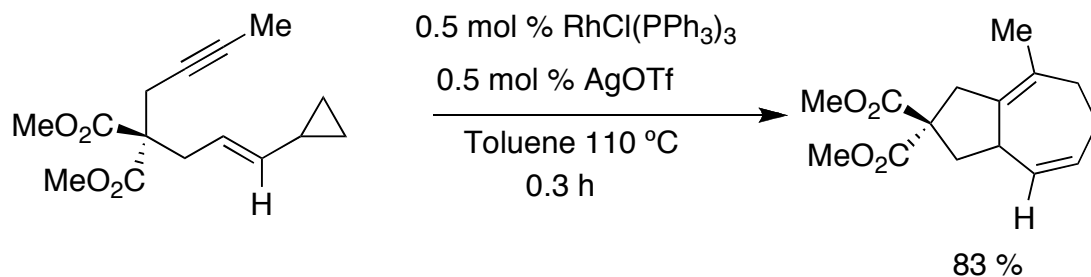
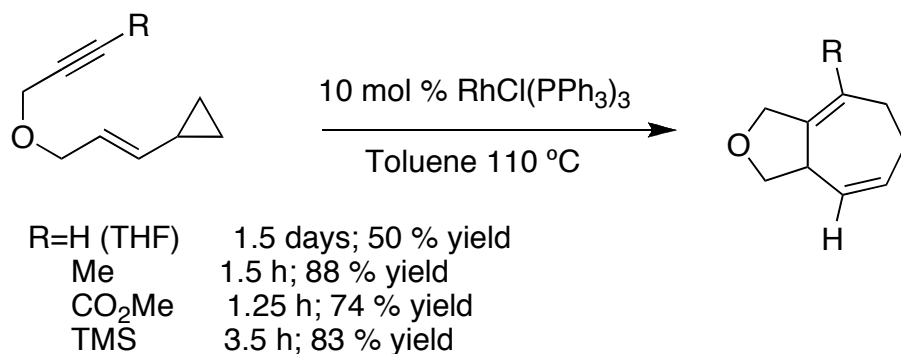
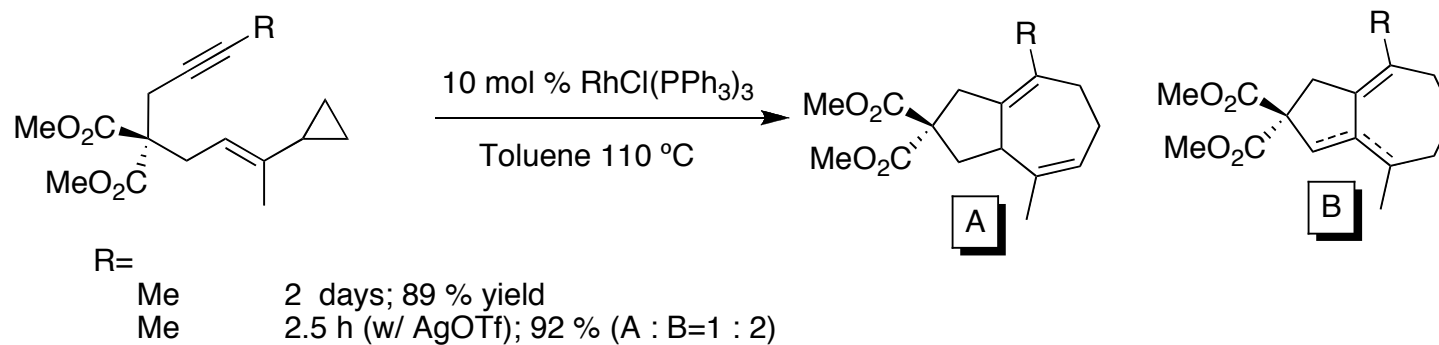


Reaction time=2 days without AgOTf

Wender, P. A.; et al. *J. Am. Chem. Soc.* **1995**, *117*, 4720

Wender, P. A.; et al. *Tetrahedron*, **1998**, *54*, 7203.

Initial Results

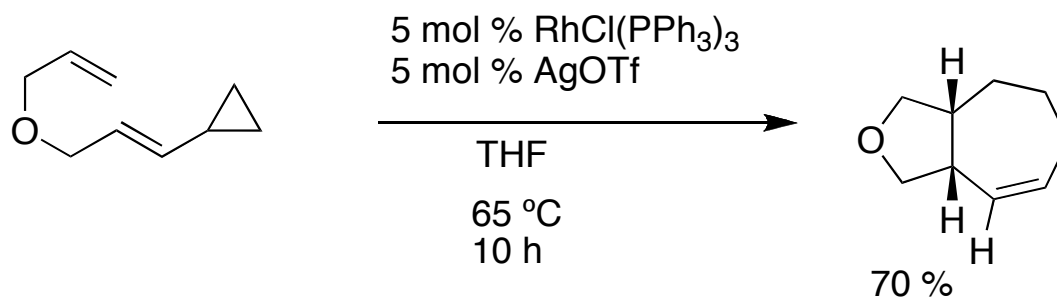
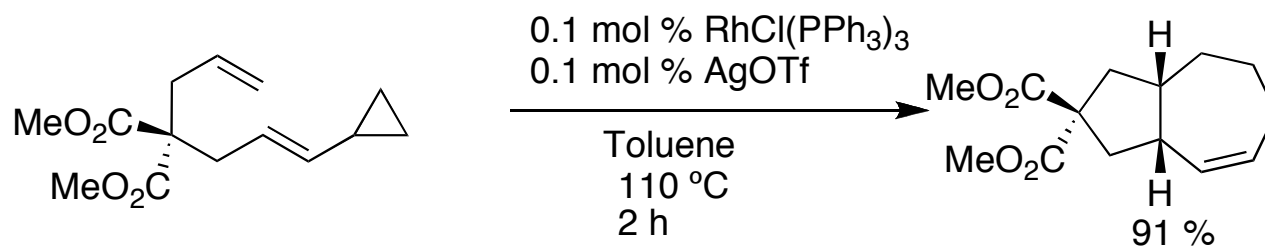


Reaction time=2 days without AgOTf

Wender, P. A.; et al. *J. Am. Chem. Soc.* **1995**, *117*, 4720

Wender, P. A.; et al. *Tetrahedron*, **1998**, *54*, 7203.

Intramolecular Reactions with Alkenes



AgOTf required for clean conversion

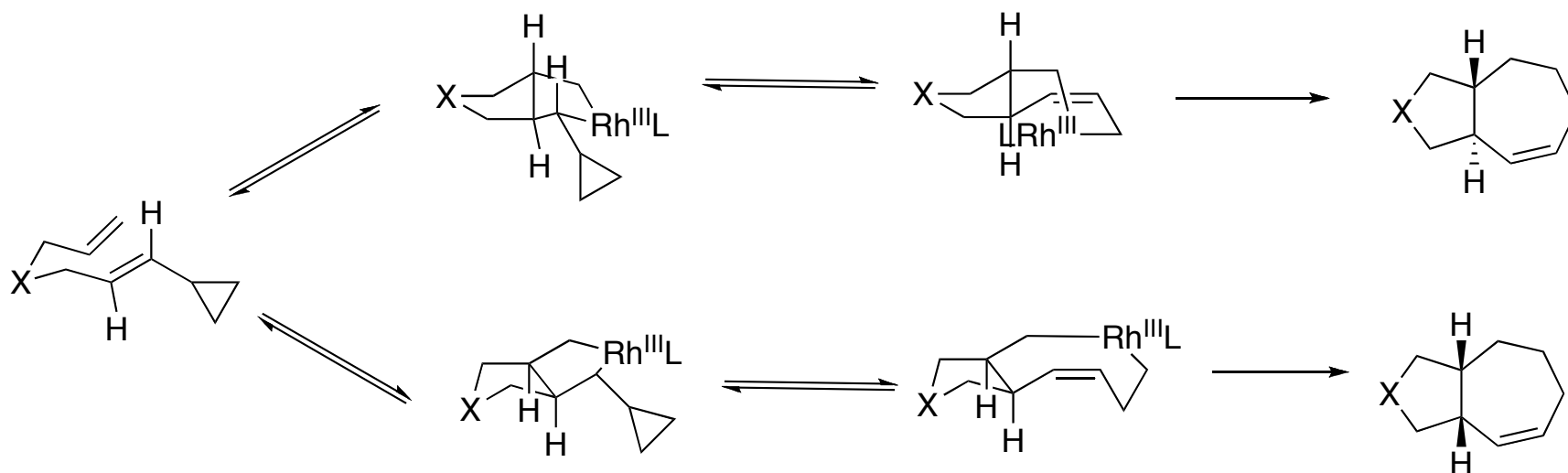
Reaction is successful with a substrate conc. 5M

Only obtain *cis*-fused products

Wender, P. A.; et al. *J. Am. Chem. Soc.* **1998**, *120*, 1940.

Wender, P. A.; et al. *Tetrahedron*, **1998**, *54*, 7203.

Initial Mechanistic Proposal



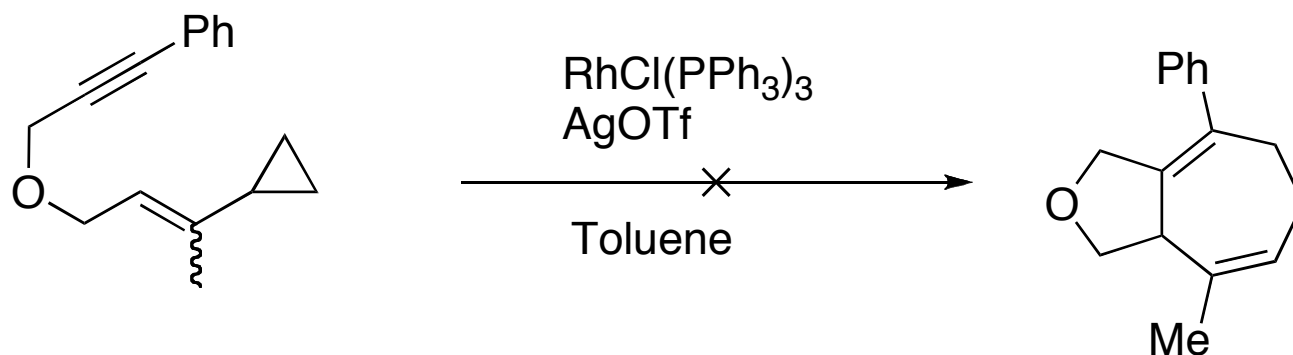
Not clear as to why kinetically more favorable formation of cis product

Outline

- The early years- discovery & substrate scope
- **Catalyst development-expansion of scope**
- Stereochemical Studies

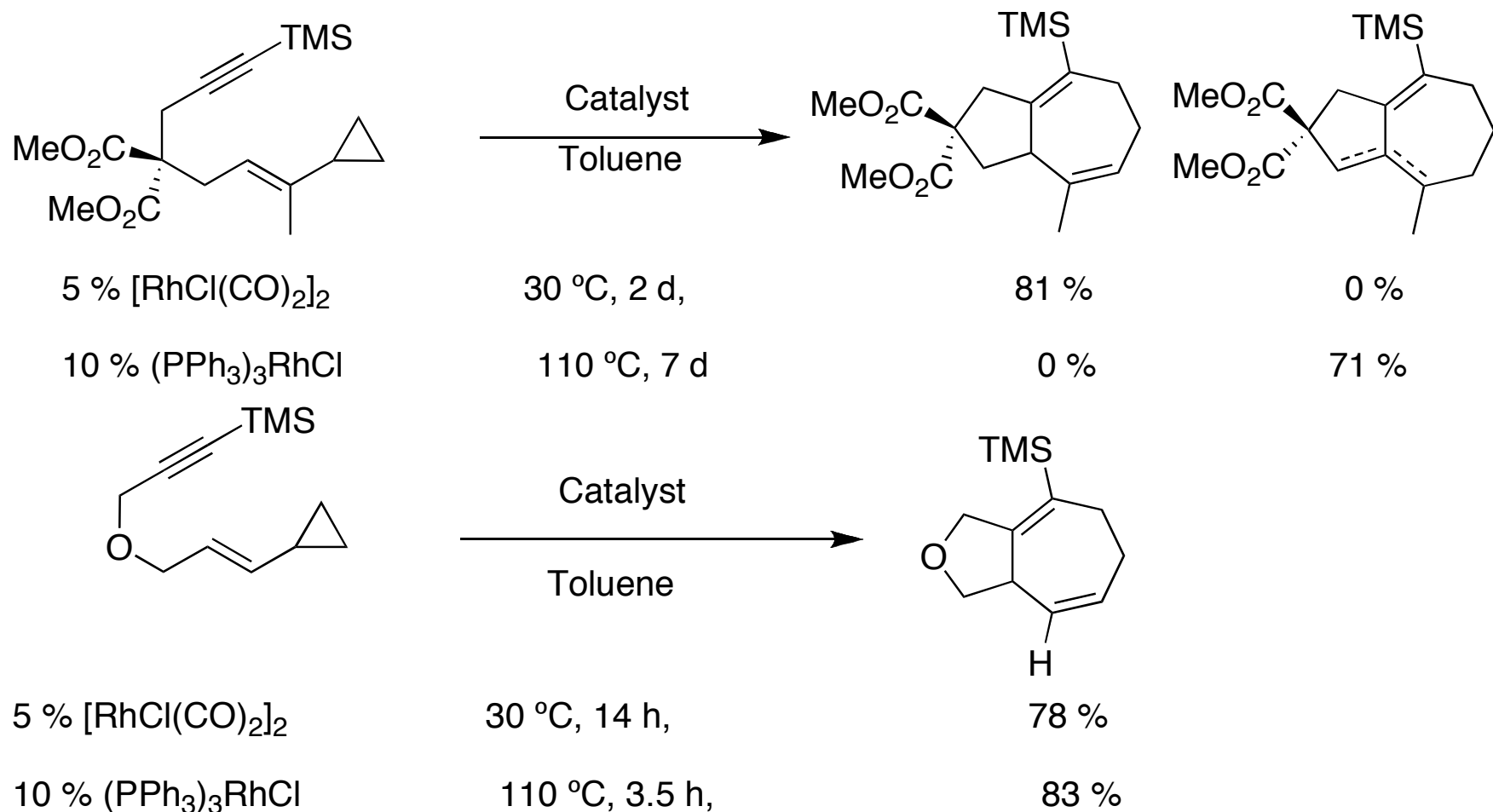
Discovery of Different Rh catalyst

- Not all cases have proven effective for Wilkinson's catalyst



- Investigate $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ based on previous studies

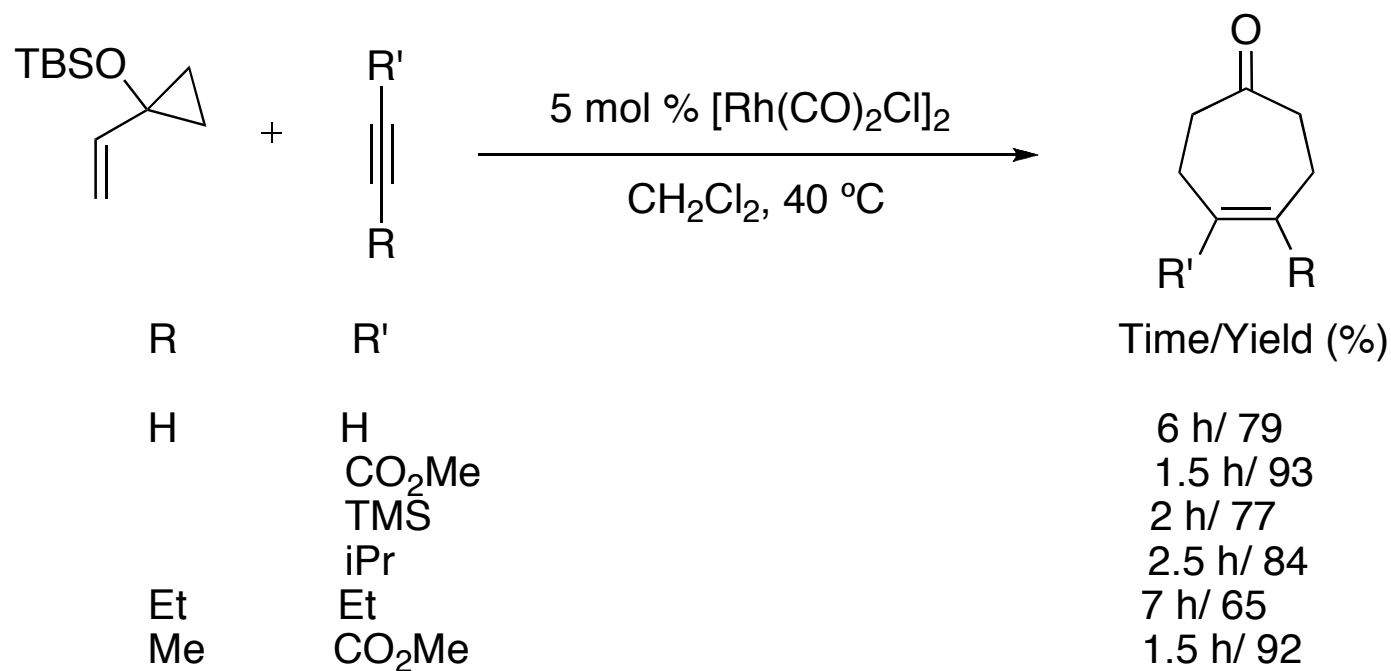
Comparison of Catalytic Systems



Wender, P. A.; et al. *J. Am. Chem. Soc.* **1995**, *117*, 4720.

Wender, P. A.; et al. *J. Org. Chem.* **1998**, *63*, 4164.

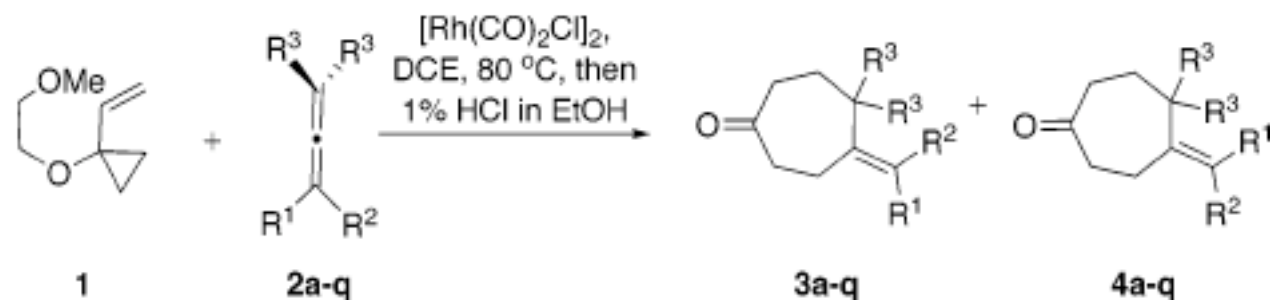
Intermolecular Cycloadditions



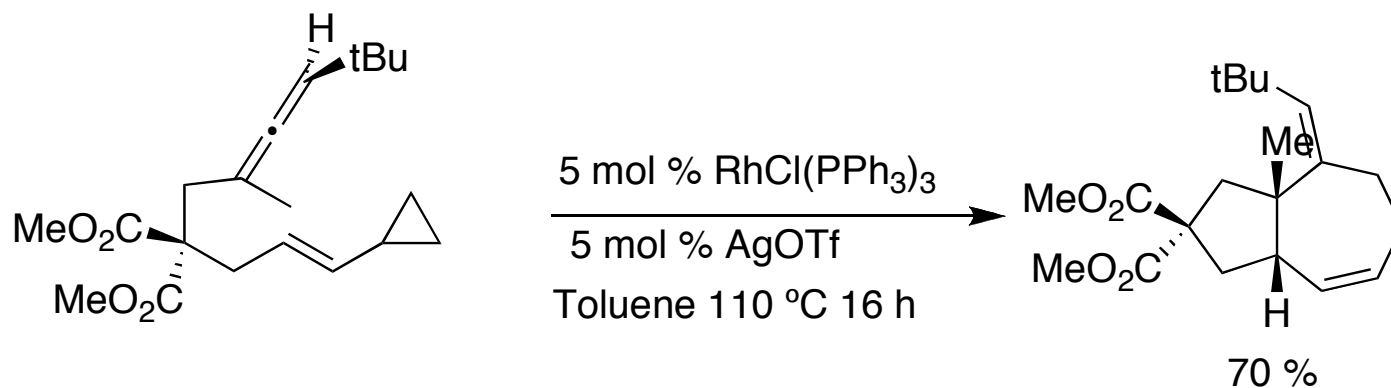
Initial attempts using Wilkinson's catalyst failed

Decomposition of SM/Cyclotrimerization of alkyne

[5+2] Cycloaddition with Allenes



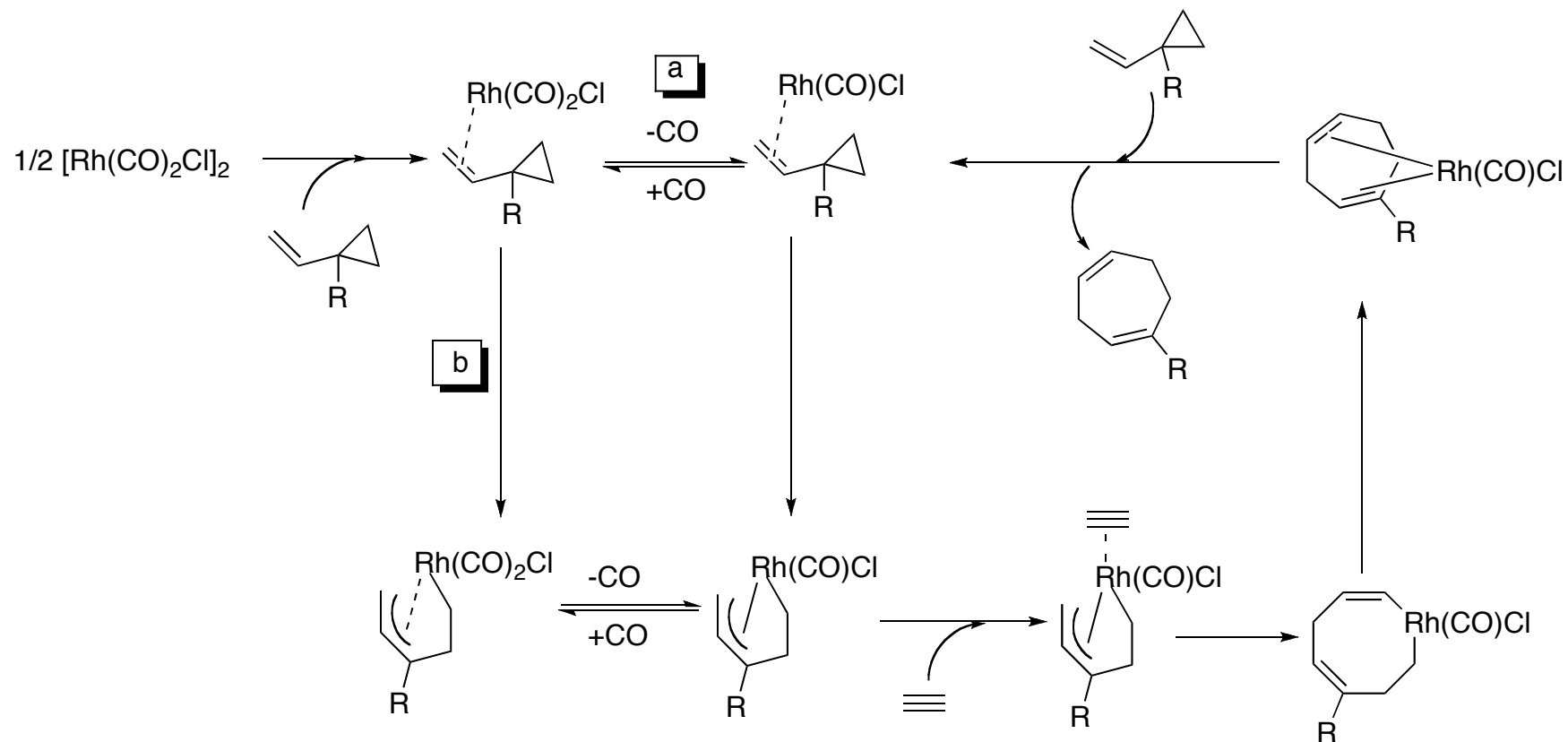
R1	R2	R3	Time	Yield
$\equiv\text{-TMS}$	H	Me	1 h	95 % (1:1.8)
$\equiv\text{-Ph}$	$\text{CH}_2\text{CO}_2\text{Et}$	Me	1 h	92 % (1:2)
CN	H	Me	1 h	99 % (2:3)



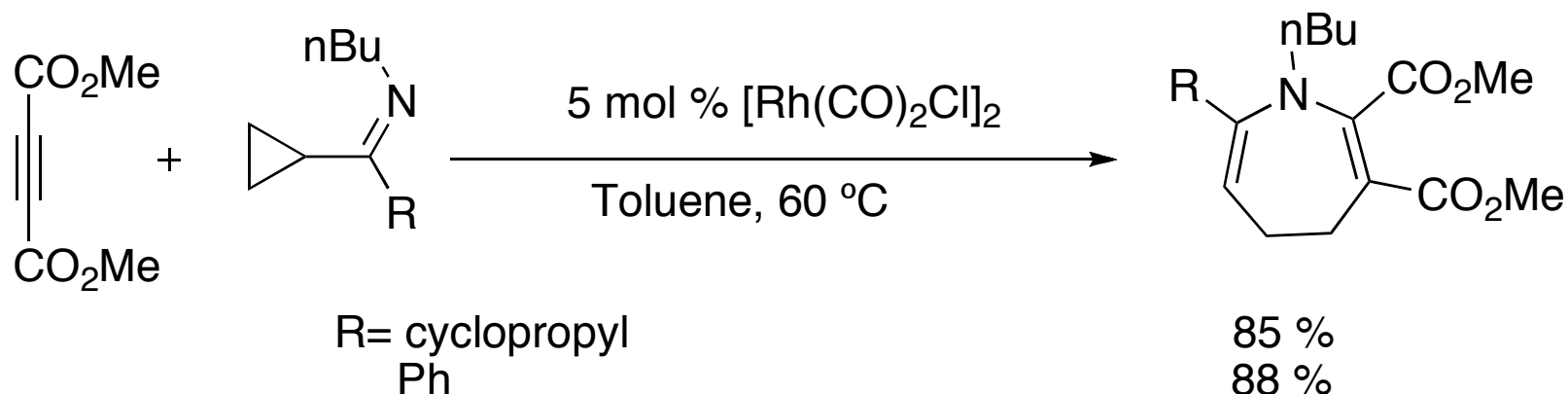
Wender, P. A. et al. *J. Am. Chem. Soc.* **2005**, 127, 6530.

Wender, P. A. et al. *J. Am. Chem. Soc.* **1999**, 121, 5348.

Mechanism Toward Intermolecular Cycloaddition



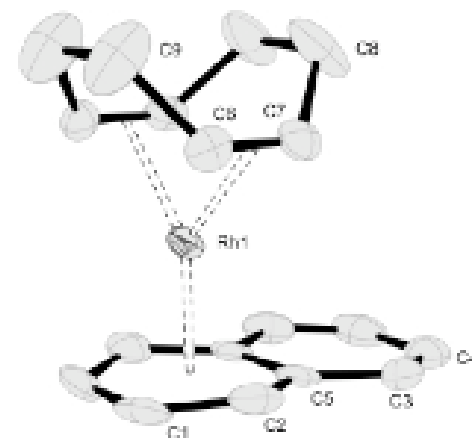
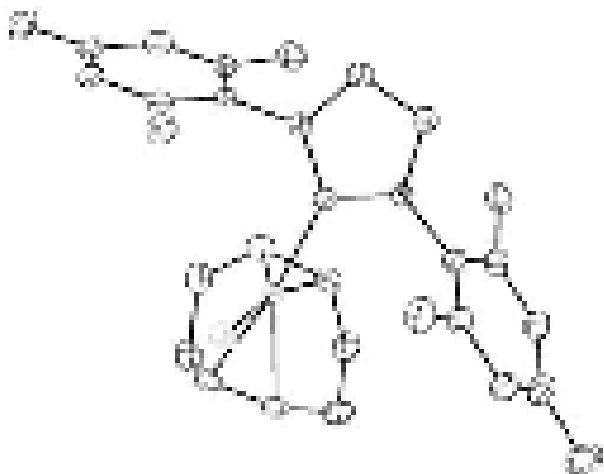
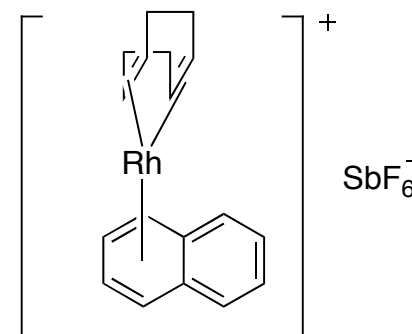
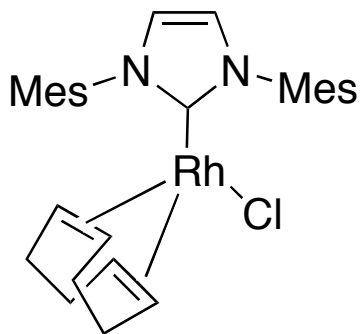
Aza-[5+2] Cycloaddition



- Reactions able to be run on multi-gram scale
- Able to start from aldehyde and do sequential imine formation followed by [5+2]

L_nRhCOD Complexes

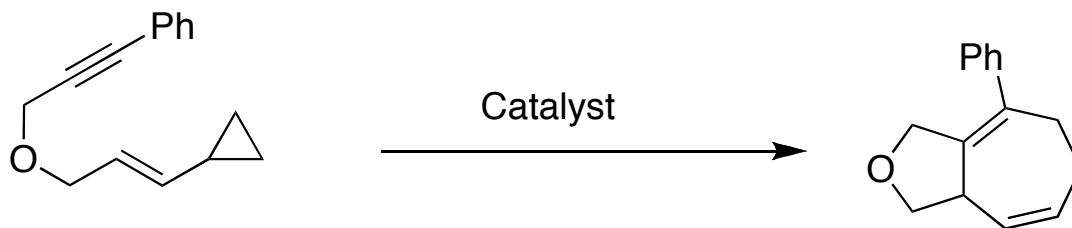
- Work by Chung and Wender showed that RhCOD complexes are efficient catalyst for the cycloaddition



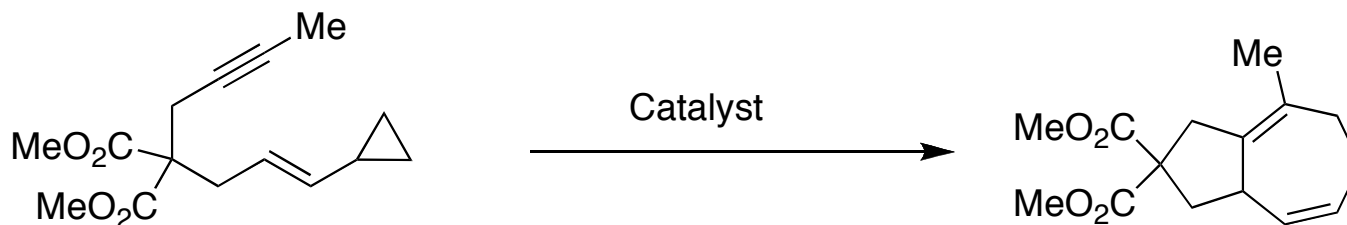
Evans, A. P. et al. *Chem. Commun.* **2005**, 63. Chung, Y. K. et al. *J. Org. Chem.* **2006**, 71, 91.

Wender, P. A. et al. *J. Am. Chem. Soc.* **1998**, 120, 10976

Applications of L_nRhCod



<p>Catalyst $(PPh_3)_3RhCl$ (10 mol %) $[RhCl(CO)_2]_2$ (5 mol %) $[Rh(NHC)Cl(COD)]/AgSbF_6$ (2 mol %)</p>	<p>Solvent/Temp Toluene/ 110 °C Toluene/ 30 °C CH_2Cl_2/ rt</p>	<p>Time/Yield 1.5 h/ 80 % 14 h/ 80 % 10 min/ 96 %</p>
--	---	--



<p>Catalyst $(PPh_3)_3RhCl$ (10 mol %) $[RhCl(CO)_2]_2$ (1 mol %) $[(C_{10}H_8)RhCl(COD)]/AgSbF_6$ (2 mol %)</p>	<p>Solvent/Temp TFE/ 55 °C Toluene/ 110 °C $ClCH_2CH_2Cl$/ rt</p>	<p>Time/Yield 19 h/ 90 % 3 h/ 89 % 15 min/ 99 %</p>
--	---	--

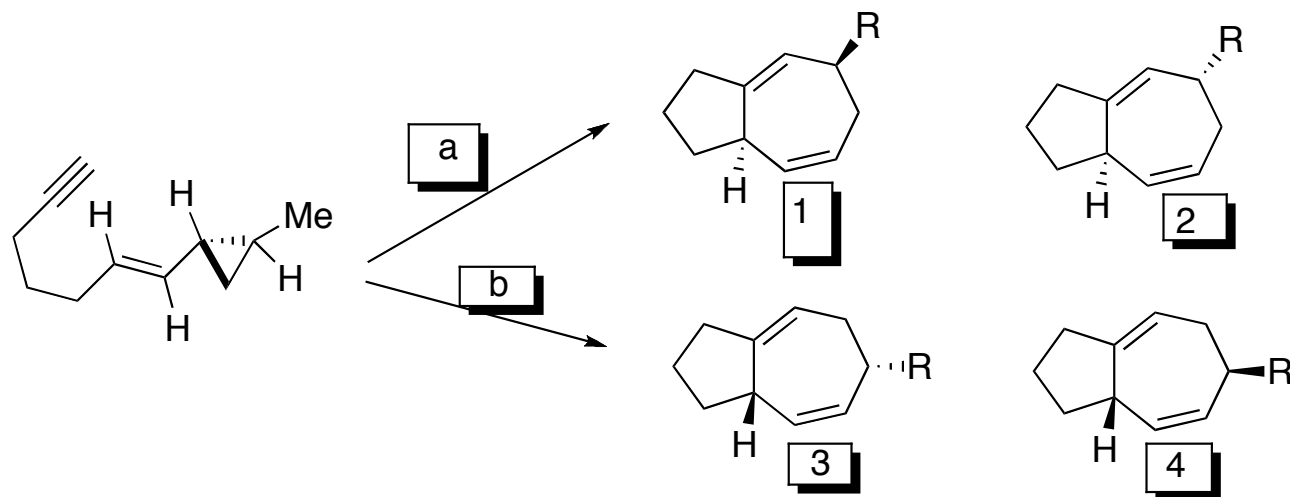
Chung, Y. K. et al. *J. Org. Chem.* **2006**, 71, 91

Wender, P. A. et al. *J. Am. Chem. Soc.* **1998**, 120, 10976

Outline

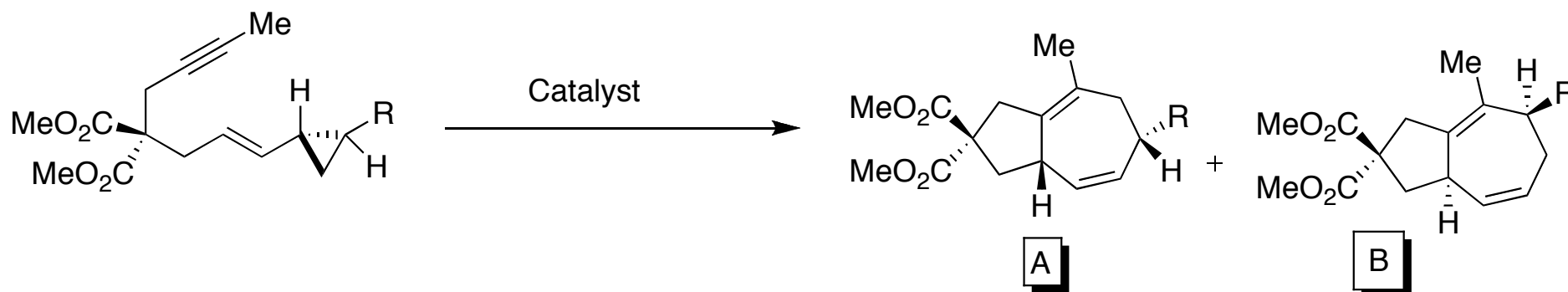
- The early years- discovery & substrate scope
- Catalyst development-expansion of scope
- **Stereochemical Studies**

Regioselectivity of Substituted Cyclopropane



Four potential products arise from 1) site of ring cleavage and 2) retention or loss of starting configuration

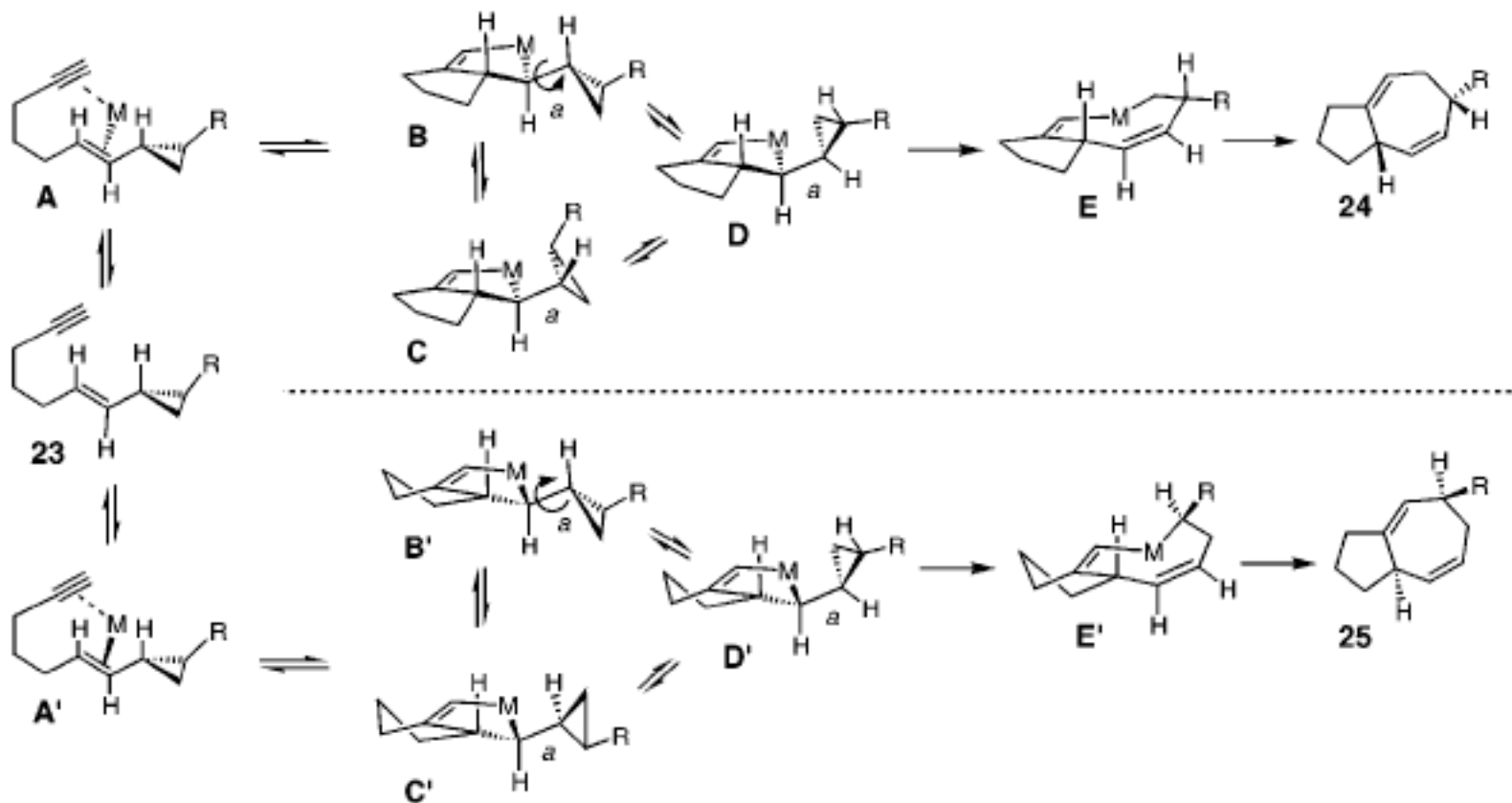
Observed Selectivities



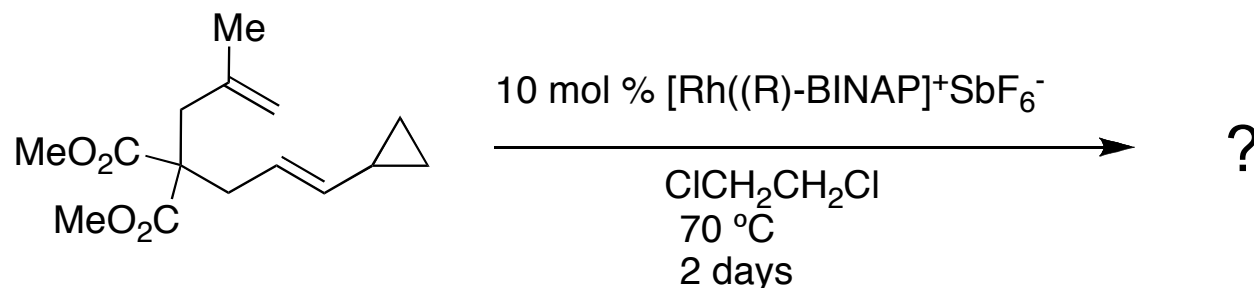
R	Catalyst	Time/Yield	A : B
CH ₂ OH	(PPh ₃) ₃ RhCl/AgOTf [RhCl(CO) ₂] ₂	19 h/ 90 %	1 : 0
		3 h/ 89 %	2.3 : 1
CO ₂ H	(PPh ₃) ₃ RhCl/AgOTf [RhCl(CO) ₂] ₂	2 h/ 69 %	4 : 1
		2 h/ 73 %	1 : 22
CO ₂ Me	(PPh ₃) ₃ RhCl/AgOTf [RhCl(CO) ₂] ₂	1 h/ 81 %	20 : 1
		1 h/ 93 %	1 : 11

Product formation with retention of original cis/trans orientation

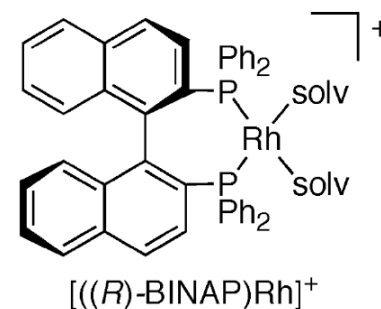
Mechanistic Pathway



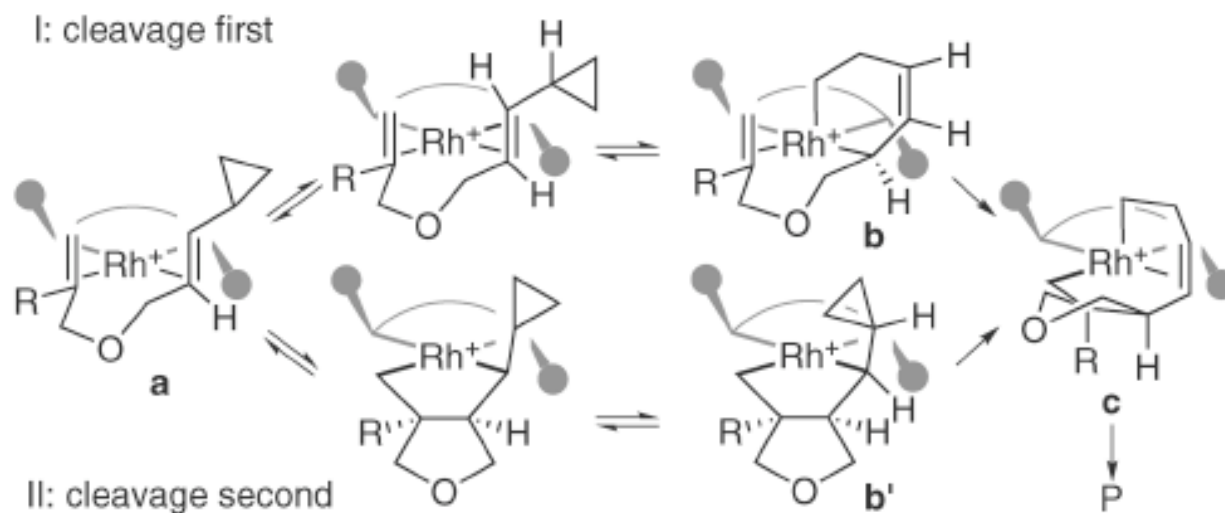
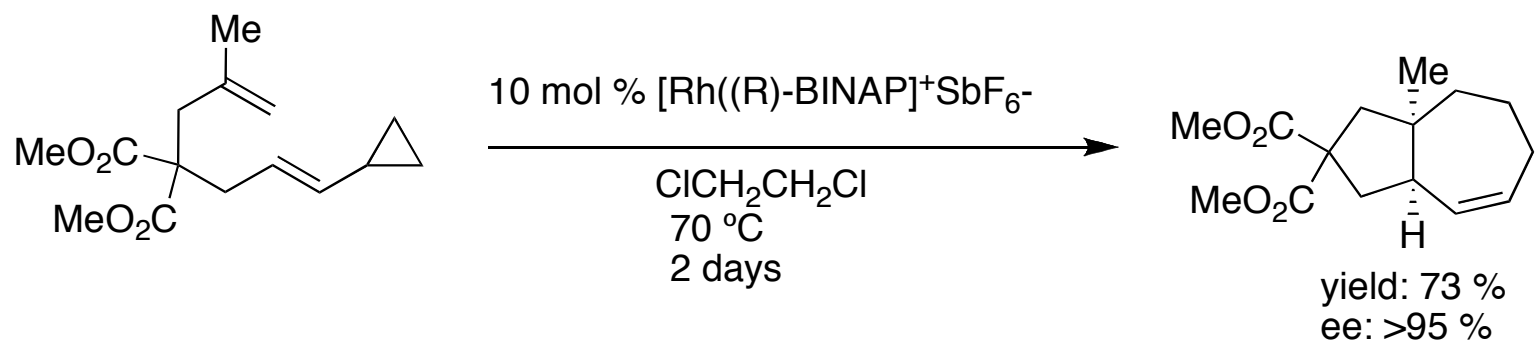
Asymmetric [5+2] Catalysis



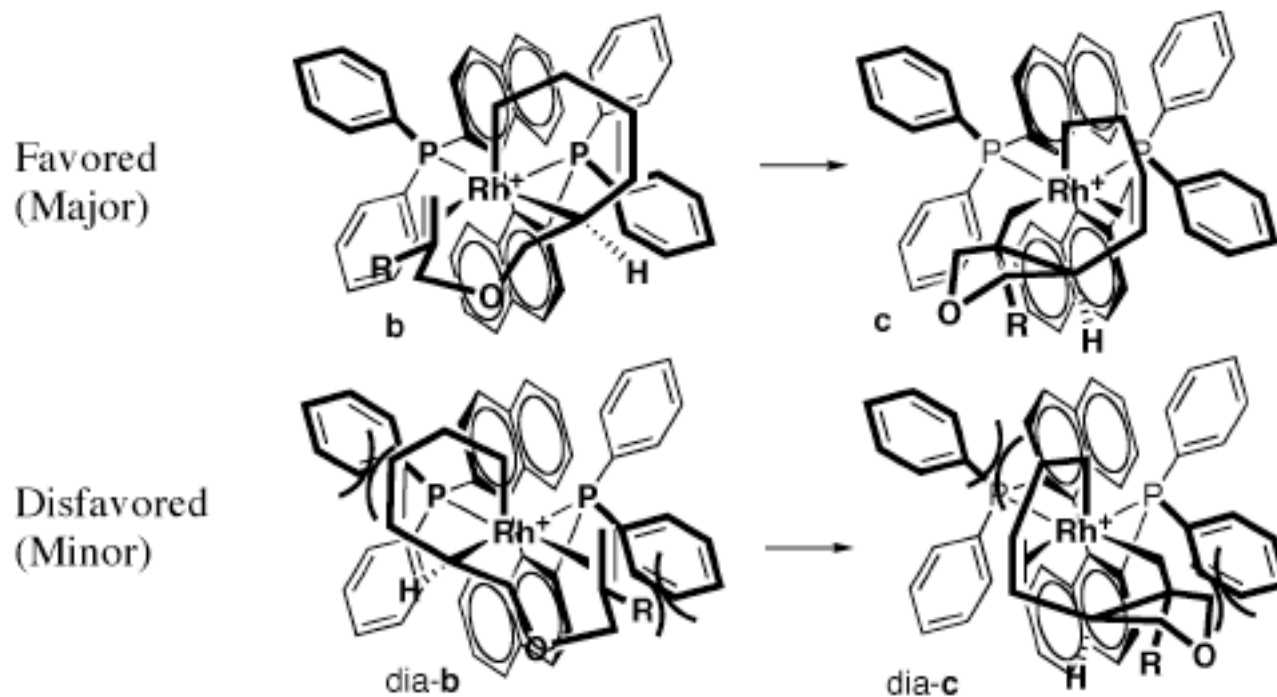
- Discovered cationic Rhodium with chiral ligands catalyze the formation of enantio-enriched cycloadducts
- Based on previous mechanistic insights propose the stereochemically defined product observed and propose the transition state structure that explains the stereochemical outcome



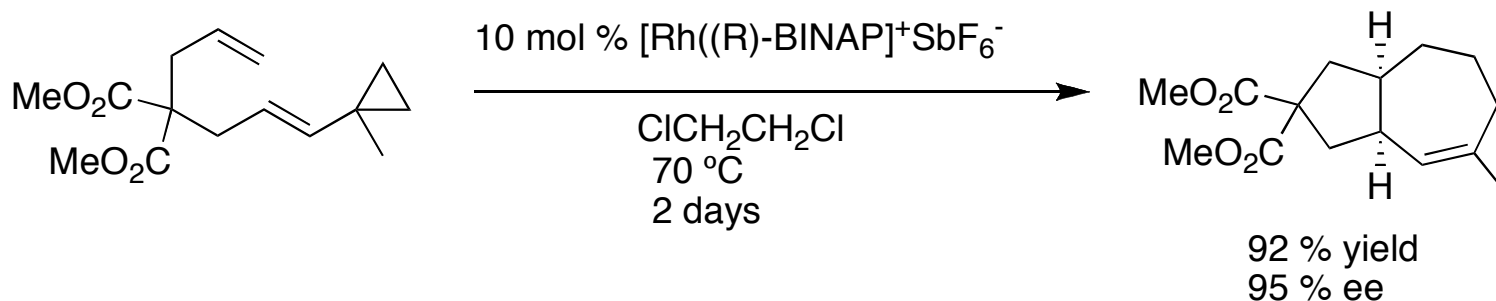
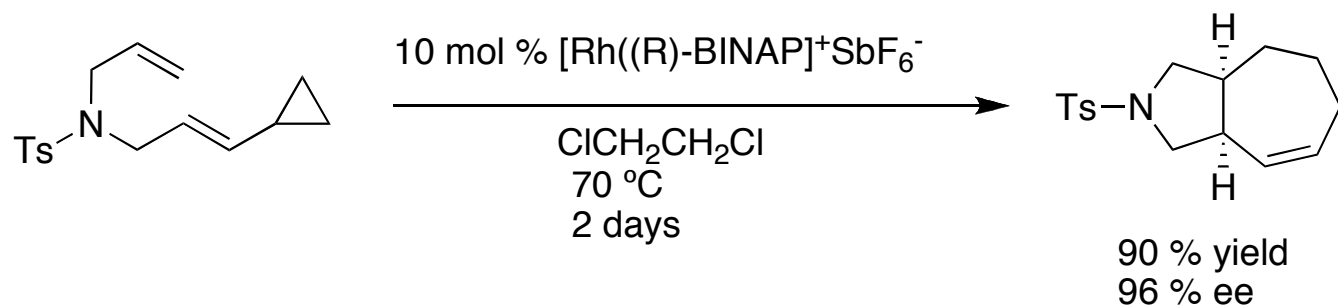
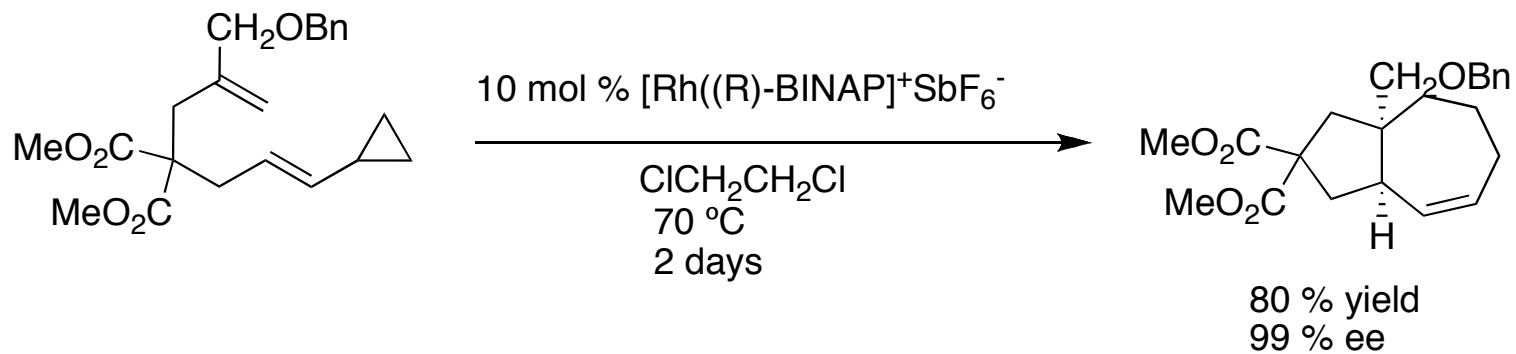
Asymmetric Catalysis



Asymmetric Catalysis



Substrate Scope



Conclusions

- Rh(I) complexes serve as efficient catalysts for [5+2] cycloadditions with vinylcyclopropanes
- Reaction works for both inter- and intramolecular cycloadditions
- Enantiomerically enriched bicyclic compounds can be prepared using chiral ligands