

Olefin Metathesis in Organic Synthesis

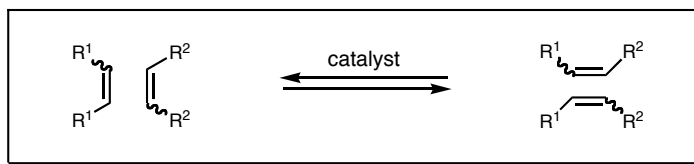
Wendy Jen
MacMillan Group Meeting
January 17, 2001

- I. Well-defined alkene metathesis catalysts
- II. Applications of Olefin Metathesis
 - A. Ring closing metathesis
 - B. Cross metathesis
 - C. Ring opening metathesis

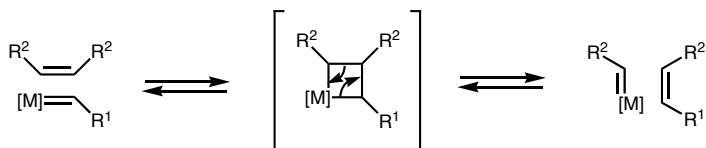
Recent Reviews:

Furstner, A. *Angew. Chem. Int. Ed.* **2000**, 39, 3013.
Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, 54, 4413.
Furstner, A. *Topics in Organometallic Chemistry* **1998**, 1, 1.
Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed.* **1997**, 36, 2036

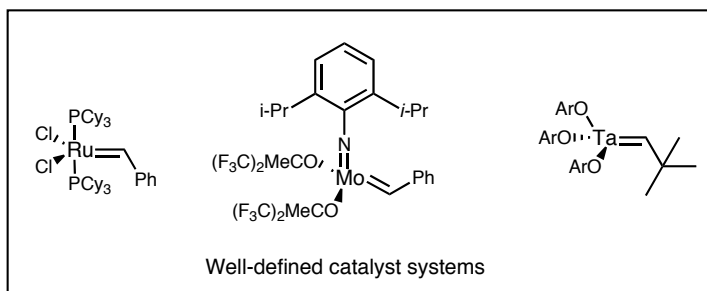
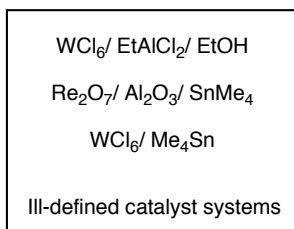
Olefin Metathesis: Introduction



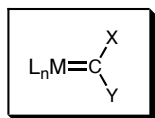
■ Chauvin-type mechanism: model proceeds through a metallacyclobutane intermediate



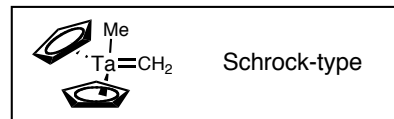
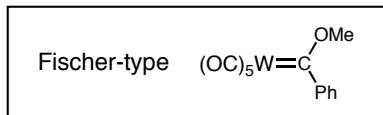
■ Catalyst systems



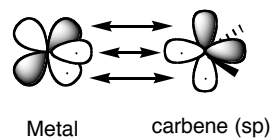
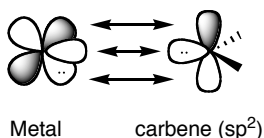
Background: Metal Carbenes



- Definition: Transition metal complex possessing a formal metal to carbon double bond
- X, Y = alkyl, aryl, H, or heteroatom (O, N, S, Halogen)
- Two types of metal carbenes: Fischer-type and Schrock-type

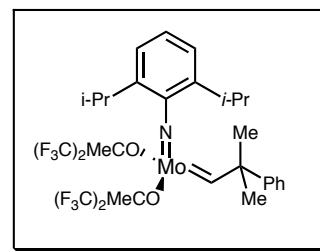


- | | |
|--|---|
| <ul style="list-style-type: none"> ■ low oxidation state middle to late TM ■ Substituents (X & Y): at least one electronegative atom ■ Ligands are generally good π acceptors ■ Electrophilic carbenes: nucleophile attacks at C_{carbene} ■ C_{carbene} is L-type ligand: Metal oxidation state unchanged | <ul style="list-style-type: none"> ■ high oxidation state early TM ■ Substituents (X & Y) are H or alkyl ■ Ligands are generally good σ or π donors ■ Nucleophilic carbenes: electrophile attacks at C_{carbene} ■ C_{carbene} is X_2-type ligand: metal oxidation state changed by +2 |
|--|---|



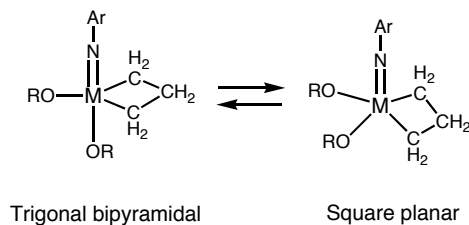
Schrock's Metathesis Catalyst

- Commercially available, as is synthetic precursor $Mo(CHt-Bu)(NAr)(OTf)_2(dme)$
- Must be handled under Ar or N_2 using dry solvents and substrates
- Relatively intolerant of protons on heteroatoms ($RCOOH$, RSH , ROH , etc.) and some functionalities (eg. $RCHO$)
- Tolerant of S, P and nitrile functional groups
- High reactivity



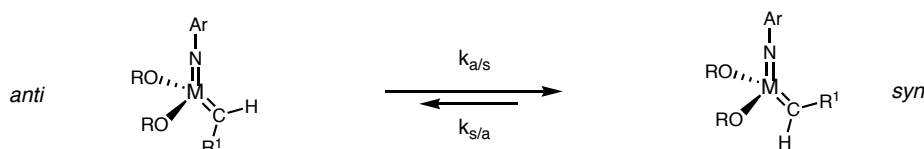
Structural Features

- Electron deficient Mo(VI), 14 electron species
- Pseudo-tetrahedral coordination sphere
- NAr ligand, OR ligands, and initial alkylidene need to be bulky to allow for isolation.
- Electron withdrawing alkoxides increase electrophilicity of metal center, hence increasing reactivity.



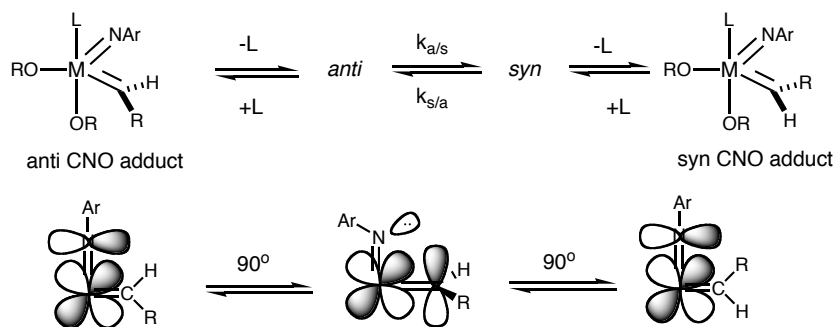
Schrock's Catalyst: Influence of Ligand Set on Reactivity

Two possible rotamers



Generally, *syn* isomer is more stable and *anti* isomer is more reactive

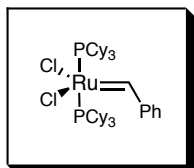
Rate of interconversion between two rotamers is dependant on metal ligands and substrate



electron withdrawing alkoxide substituents and bulky aryl groups decrease $k_{s,a}$

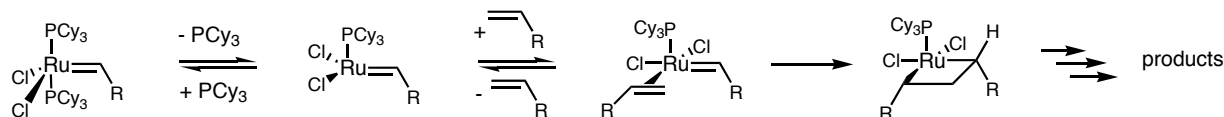
Schrock, R.R. *Tetrahedron* **1999**, *55*, 8141.

Grubbs' Metathesis Catalyst



- Commercially available
- Reasonably stable toward H₂O, O₂, and minor impurities $\Rightarrow$ ease of handling
- Lower reactivity vs. Molybdenum imido alkylidene catalyst
- High functional group tolerance

Mechanism: olefin binds *cis* to carbene and *trans* to Cl; formation of metallacycle believed to be rate determining



Ligand Effect on Catalyst Activity:

Halides: Catalyst activity increases from I < Br < Cl

Trans influence I > Br > Cl $\Rightarrow$ olefin is bound tightest for Cl complex

Cl is smallest $\Rightarrow$ large halogens disfavor olefin binding due to steric crowding

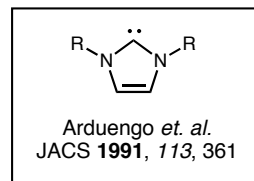
Phosphines: Catalyst activity increases as cone angle and electron donating ability increase

As cone angle increases, dissociation of phosphine more facile for steric reasons

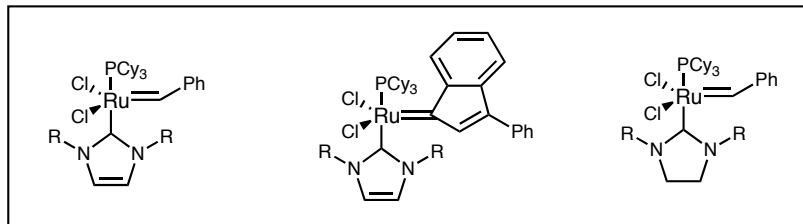
More electron donating ligand labilizes *trans* ligand and stabilizes vacant orbital in 14 e⁻ intermediate

Dias, E. L.; Nguyen, S.T.; Grubbs, R.H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.

Ruthenium Catalysts Containing N-Heterocyclic Carbene (NHC) Ligands



- Sought to find more basic and sterically demanding ligand than PCy₃;
- "Stable" imidazol-2-ylidene ligands (NHC) are such phosphine mimics



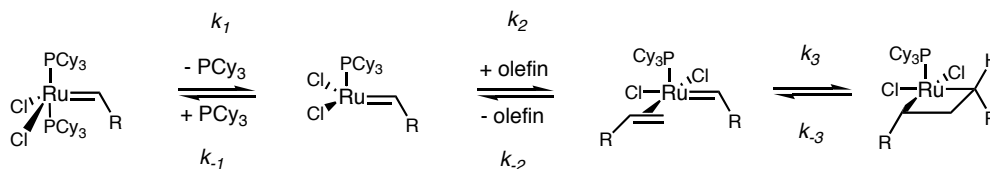
Herrmann *et al.* *Angew. Chem. Int. Ed.* **1999**, 38, 2416.

Grubbs *et al.* *Org. Lett.* **1999**, 1, 953.

Nolan *et al.* *J. Am. Chem. Soc.* **1999**, 121, 2674.

Activity is significantly higher than parent Ru complex

Origin of increased reactivity:

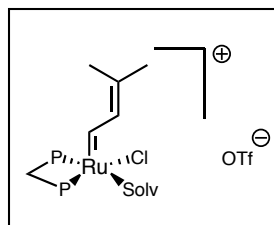


High activity of NHC complex is due to improved selectivity for binding π -acidic olefinic substrates in the presence of σ -donating free phosphine (decreasing k_1/k_2).

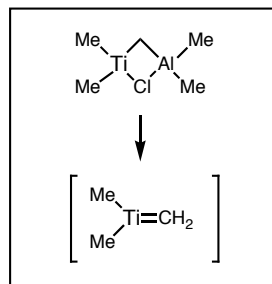
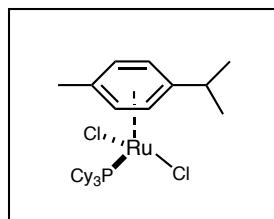
Sanford, M.S.; Ulman, M.; Grubbs, R.H. *J. Am. Chem. Soc.* **2001**, ASAP

Other Metathesis Catalyst Systems

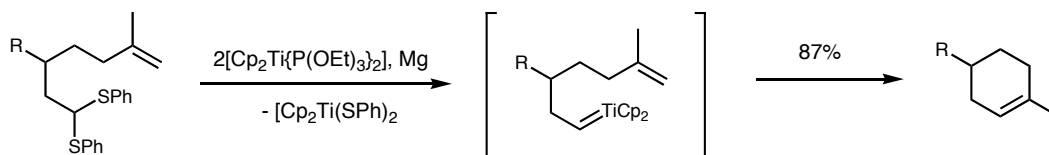
Hansen, S. M.; Rominger, F.; Metz, M.; Hofmann, P. *Angew Chem. Int. Ed.* **1999**, 38, 1273.



Demonceau, A.; Noels, A. F.; Saive, E.; Hubert, A. J. *J. Mol. Catal.* **1992**, 76, 123.

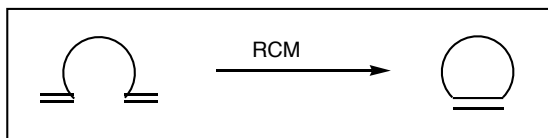


Tebbe, F. N.; Parshall, G.W.; Reddy, G.S. *J. Am. Chem. Soc.* **1978**, 100, 3611



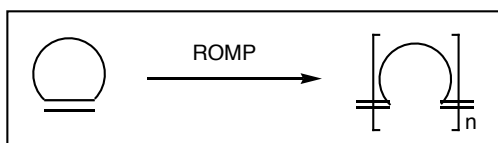
Fujiwara, T.; Takeda, T. *Synlett* **1999**, 354.

Fundamental Olefin Metathesis Reactions



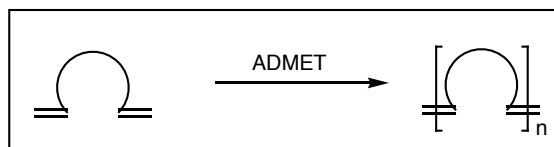
Ring Closing Metathesis (RCM)

Cross Metathesis (CM)



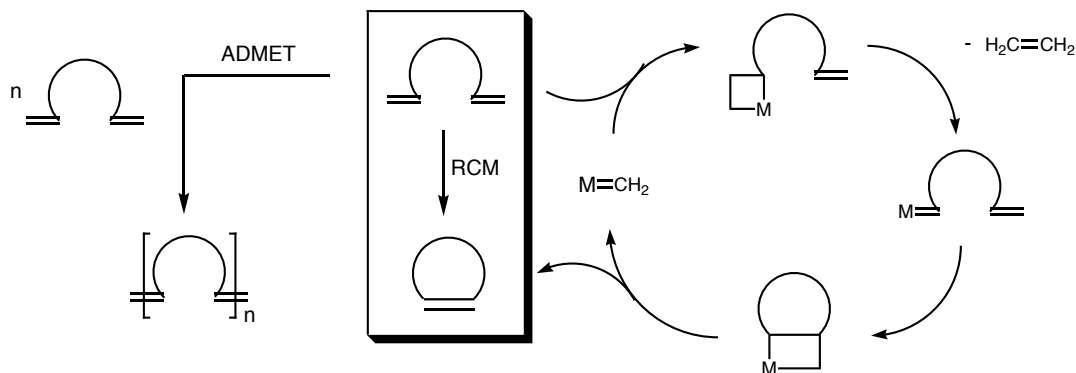
Ring Opening Metathesis Polymerization (ROMP)

Acyclic Diene Metathesis Polymerization (ADMET)



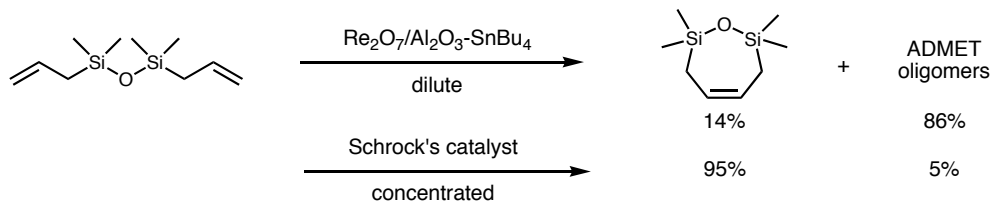
Ring Closing Metathesis (RCM)

- Intramolecular metathesis of a diene to form a cyclic olefin



- Reaction pathway of diene depends on catalyst, dilution, ring size, and substrate (functional groups and sterics)

Catalyst:

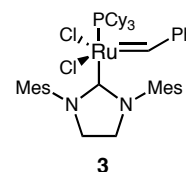
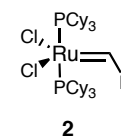
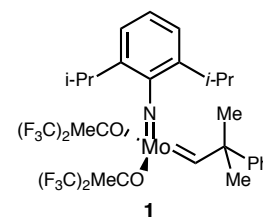


Dilution: Intermolecular ADMET can generally be prevented by applying dilution principle

RCM of Small Rings: Olefin Substitution

- Synthesis of 5-7 membered rings fairly facile; proper selection of catalyst depends on functional groups and steric demands of the substrate
- Typically ruthenium catalysts are preferred over molybdenum catalysts from a synthetic standpoint due to ease of handling and high function group tolerance of Ru catalyst.
- Choice of catalyst depends on olefin substitution of product

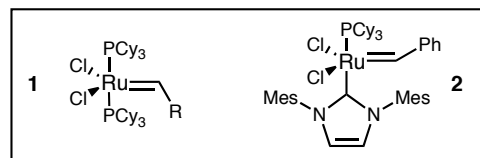
substrate	product	time	Yield (%) using		
			1	2	3
		10 min	quant.	quant.	quant.
		10 min	quant.	20	quant.
		90 min	52	N.P.	90
		24 hrs	93	N.P.	31



Molybdenum and Ruthenium NHC catalysts are more effective for highly substituted olefins

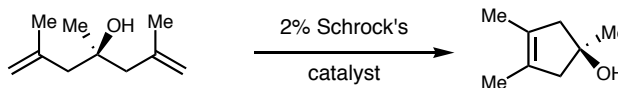
Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R.H. *Org. Lett.* **1999**, 1, 953.

RCM of Small Rings: Alcohols



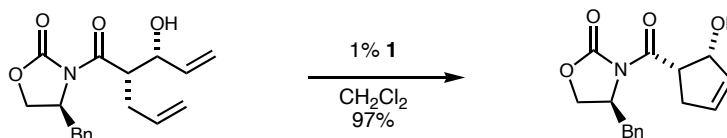
- **Free alcohols:** highly compatible with Ru based catalysts; Mo catalysts have low tolerance for ROH

Exception:



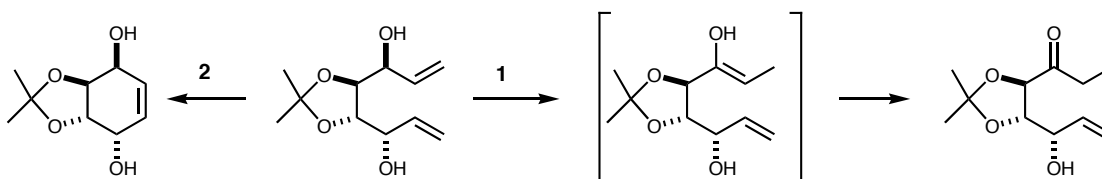
Schrock, R. R. *Top. Organomet. Chem.* **1998**, 1, 1.

- **Allylic Alcohols:** compatible with Ru catalysts



Crimmins, M.T.; King, B. W. *J. Org. Chem.* **1996**, 61, 4192.

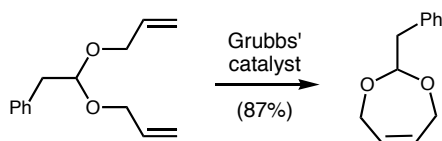
Potential for isomerization of olefin if catalyst is not reactive enough



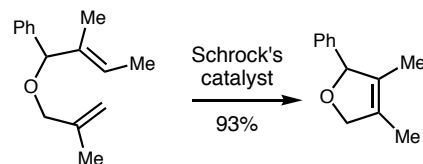
Ackermann, L.; Tom, D. E.; Furstner, A. *Tetrahedron*, **2000**, 56, 2195.

RCM of Small Rings: Ethers

- **Allyl ethers and acetals:** Both Mo and Ru catalysts tolerate these functionalities

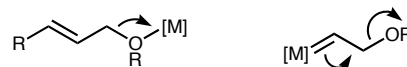


Fu, G.C.; Nguyen, S.T.; Grubbs, R.H. *JACS* **1993**, *115*, 9856.

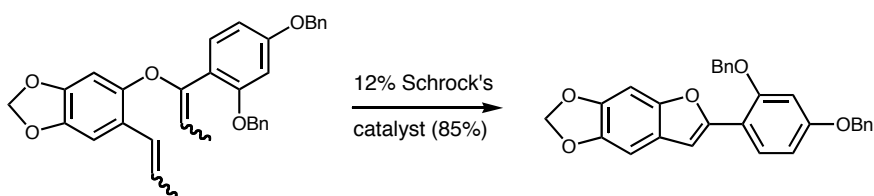


Fu, G.C.; Grubbs, R.H. *JACS* **1992**, *114*, 5426.

Caveat: allylic ethers have potential for decomposition



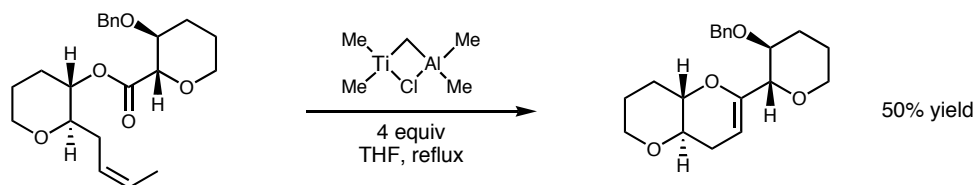
- **Vinyl ethers:** Mo catalyst used for the reaction/ formation of enol ethers; Ru is incompatible because resulting Ru carbene is unreactive



Fujimura, O.; Fu, G.C.; Grubbs, R.H. *J. Org. Chem.* **1994**, *59*, 4029.

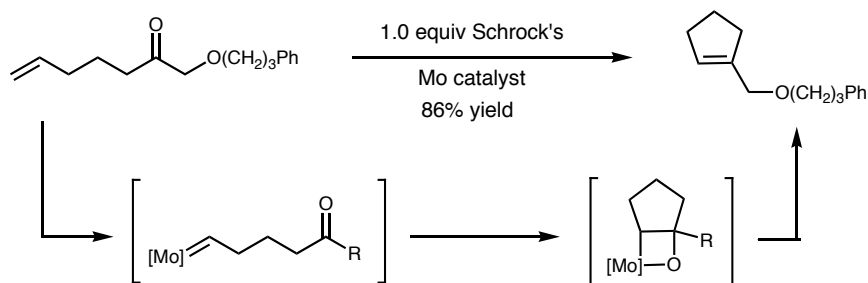
RCM of Small Rings: Vinyl Ethers

- **Tebbe reagent:** carbonyl ester olefination and metathesis to form cyclic enol ether



Nicolaou et al. *J. Am. Chem. Soc.* **1996**, *118*, 10335.

- Schrock's molybdenum and tungsten catalyst can also mediate olefin metathesis/ carbonyl olefination



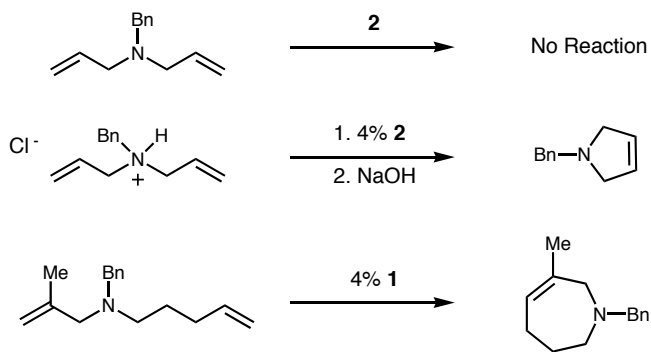
catalyst metathesizes olefins faster than it olefinates ketones

Fu, G.C.; Grubbs, R.H. *JACS* **1993**, *115*, 3800.

RCM of Small Rings: Amines

■ **Primary and secondary amines:** incompatible with Schrock and Grubbs' Catalysts

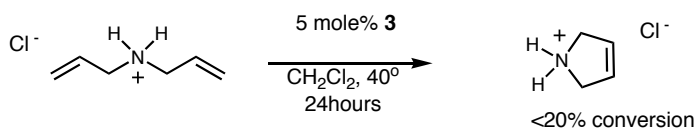
■ **Tertiary amines:** typically tolerated by Mo and Ru catalysts, but they can be problematic



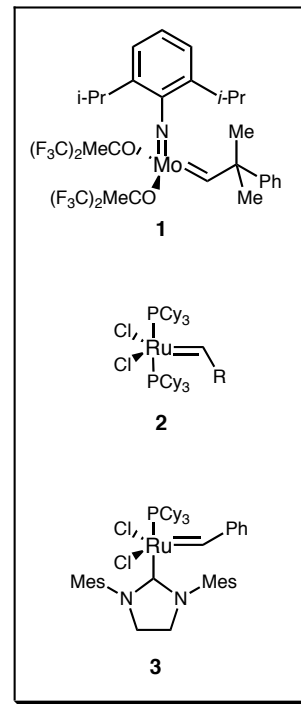
Fu, G.C.; Grubbs, R.H. *JACS* **1992**, 114, 5426.

Fu, G.C.; Nguyen, S.T.; Grubbs, R.H. *JACS* **1993**, 115, 9856.

However newer ruthenium NHC initiators are not as tolerant of amine salts



A. Furstner et al. *J. Org. Chem.* **2000**, 65, 2204.

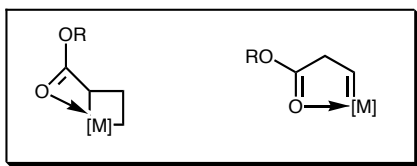


RCM of Small Rings: Carbonyls

■ **Ketones:** inert to ruthenium catalysts; typically tolerated by molybdenum catalysts, but olefination can occur

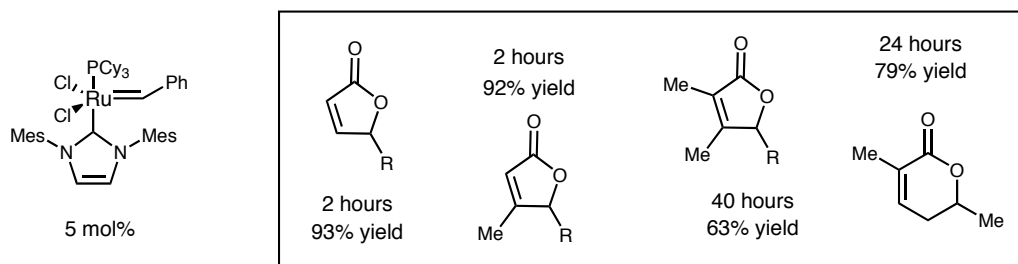
■ **Carboxylic acids and aldehydes:** tolerated by Grubbs' catalyst, but not by Schrock's catalyst

■ **Esters:** compatible with both ruthenium and molybdenum catalysts



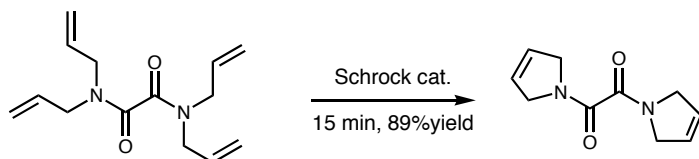
R.R. Schrock et al. *Organometallics*, **1989**, 8, 2260

Synthesis of α, β unsaturated lactones from acrylate esters: Ruthenium NHC catalyst



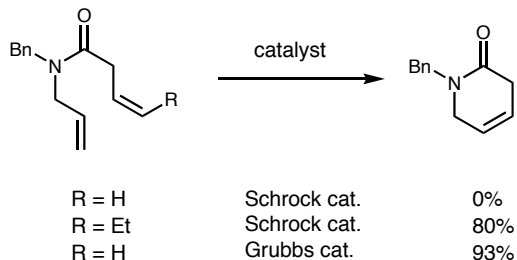
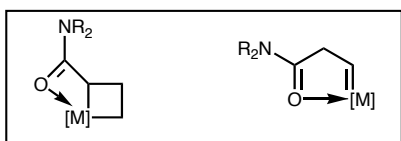
A. Furstner et al. *J. Org. Chem.* **2000**, 65, 2204.

RCM of Small Rings: Amides

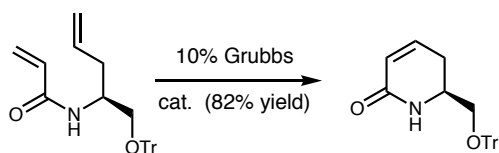


Fu, G.C.; Grubbs, R.H. *JACS* **1992**, 114, 7325.

However chelative effect is also an issue with amides

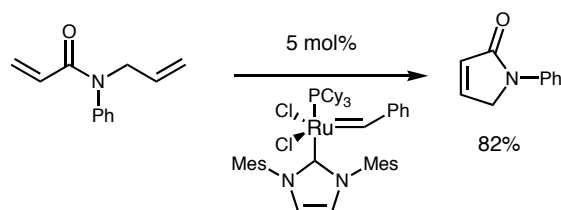


■ Ruthenium catalysts are more general for amides



N-H amides can be used only if sterically protected

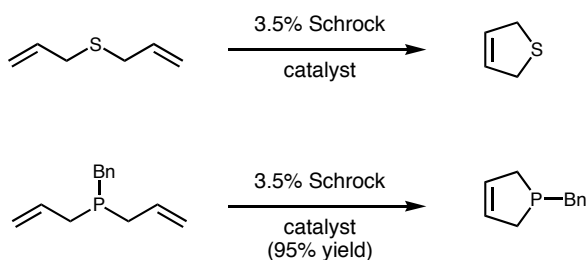
Rutjes, F.P.J.T.; Schoemaker, H. E. *Tet. Lett.* **1997**, 38, 677.



A. Furstner et al. *J. Org. Chem.* **2000**, 65, 2204.

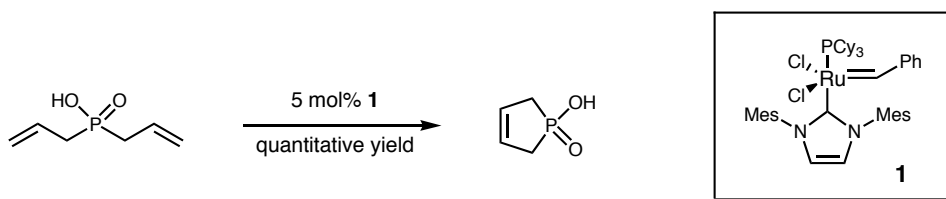
RCM of Small Rings: Sulfur and Phosphorus

■ **Sulfides and Phosphines:** incompatible with ruthenium catalysts; use molybdenum catalyst



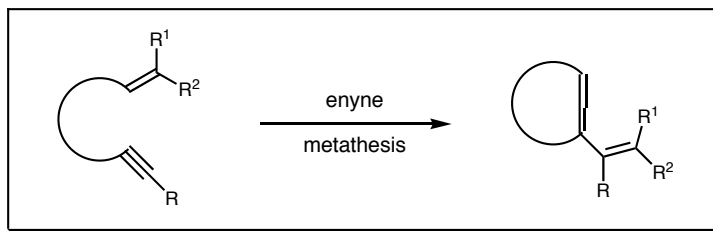
J. M. Basset et al. *J. Chem. Soc. Chem. Comm.* **1995**, 857.

■ Newer Ruthenium NHC catalysts are compatible with phosphinic acids



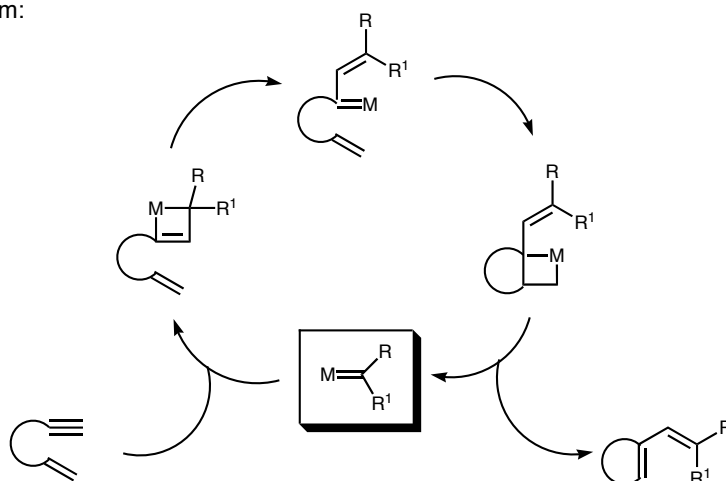
Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, 2, 1517.

RCM of Small Rings: Enyne Metathesis



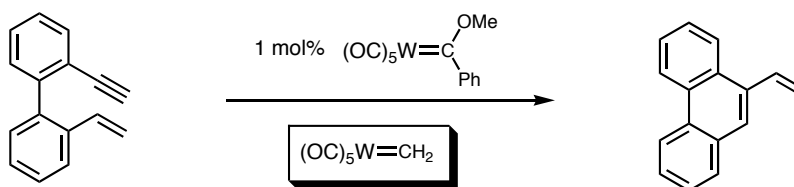
Enyne metathesis: alkylidene migration reaction from the alkene to part to alkyne carbon

Mechanism:

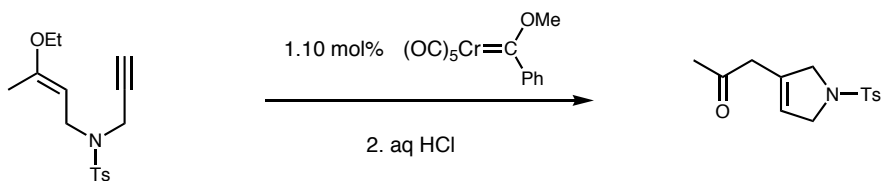


RCM of Small Rings: Enyne Reactions

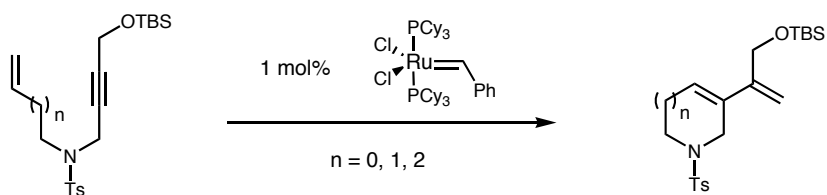
- Fischer carbenes can be used to initiate enyne metathesis reactions



Katz et al. *J. Am. Chem. Soc.* **1985**, 107, 737



- Enyne metathesis can also be initiated by Grubbs and Schrock catalysts

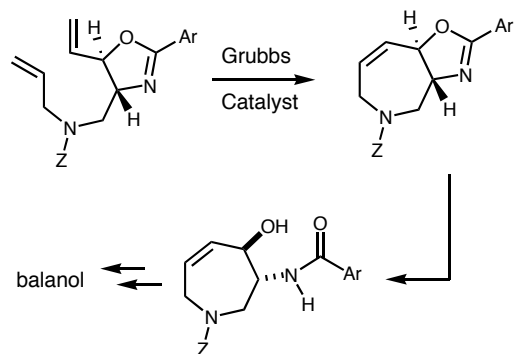
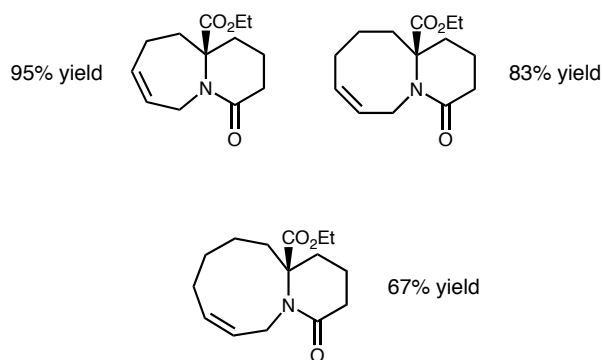


Mori et al. *Synlett* **1994**, 1020

RCM of Medium Rings

- Because of enthalpic and entropic influences, medium sized rings are difficult to prepare; hence substrates are more prone to intermolecular acyclic diene metathesis reactions (ADMET)
- Desired cyclization can be facilitated by providing some sort of conformational constraint.

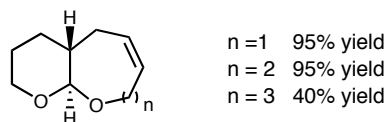
Cyclic Conformational Constraints



Cook et al. *Org. Lett.* **1999**, 1, 615

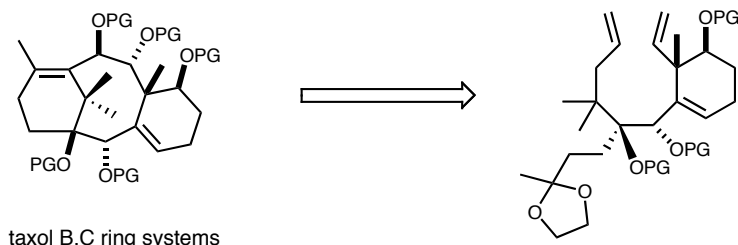
Attachment of olefin side chains to β -lactams

Diedrichs, N.; Westermann, B. *Synlett* **1999**, 1127

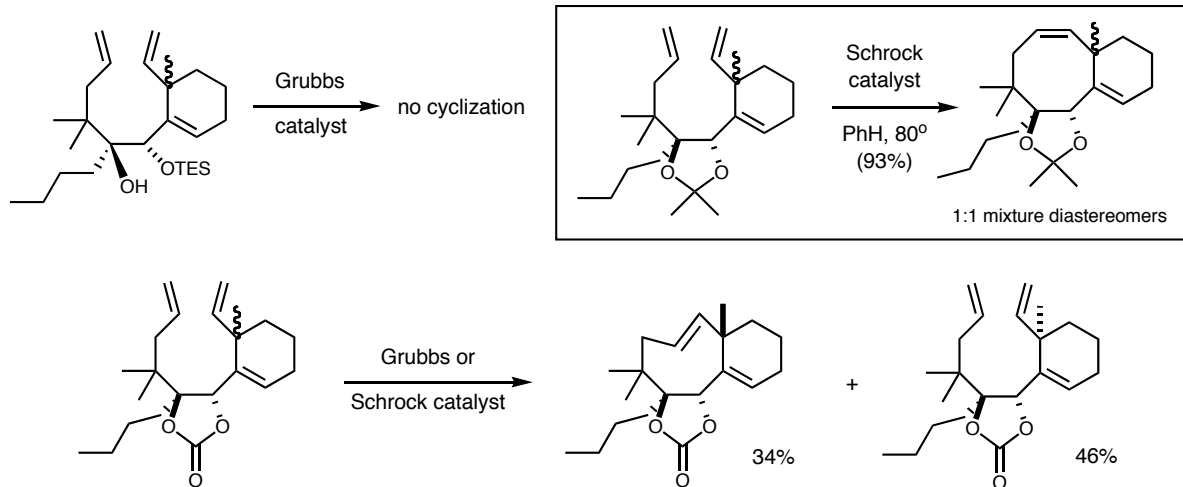


Delgado et al. *J. Org. Chem.* **1999**, 64, 4798

RCM of Medium Rings: Cyclic Conformational Control



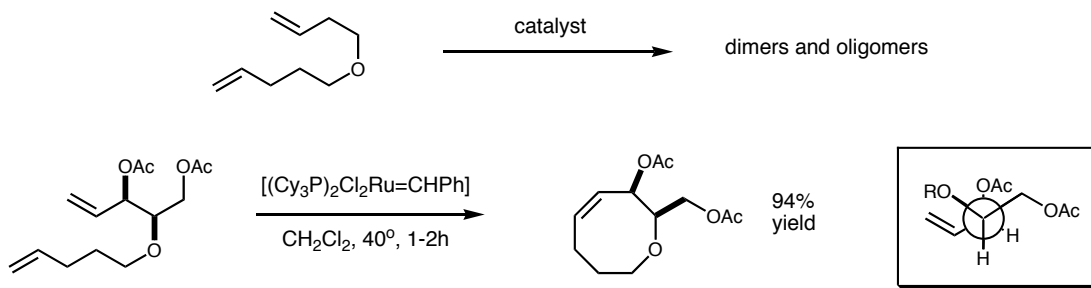
Model Study: Cyclic protecting group facilitates cyclization



Prunet et al. *Angew. Chem. Int. Ed.* **2000**, 39, 726.

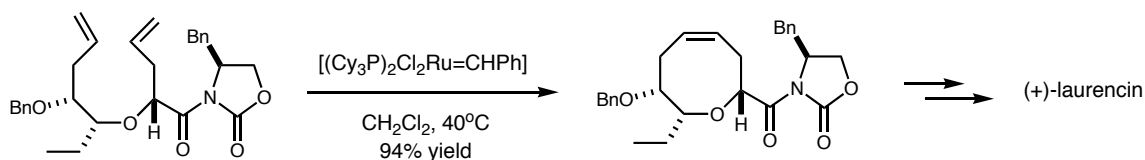
RCM of Medium Rings: Acyclic Conformational Control

- Use of *gauche* effect of 1,2-dioxygen substituents to facilitate ring closure



Crimmins, M.T.; Choy, A.L. *J. Am. Chem. Soc.* **1999**, 121, 5653

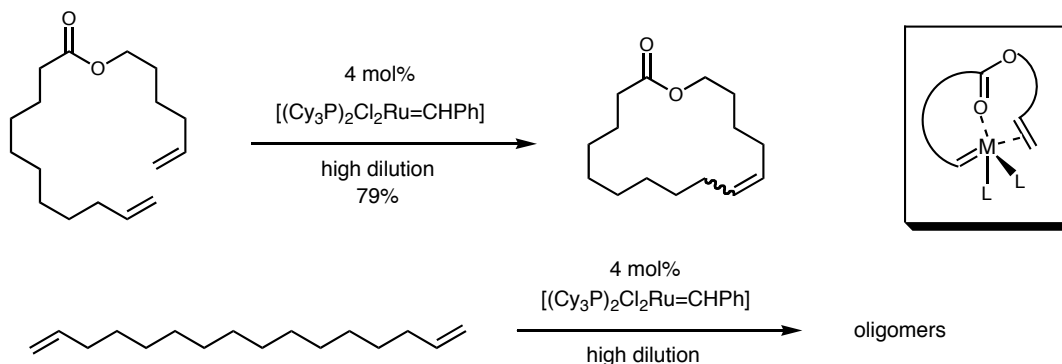
Use of acyclic conformational control: synthesis of laurencin



Crimmins, M.T.; Emmitte, K.A. *Org. Lett.* **1999**, 1, 2029

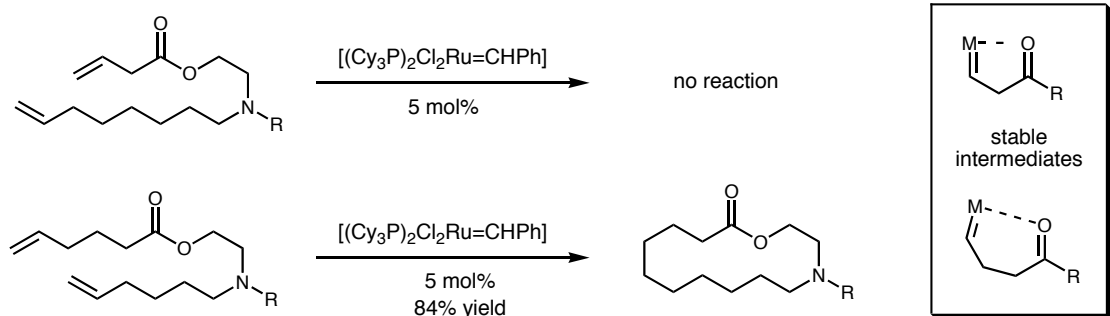
RCM: Macrocyclizations

- Dienes devoid of any conformational predisposition towards ring closure can be good RCM substrates
- Formation of *cis* and *trans* isomers in the formation of large rings
- Experimental Considerations:
 1. Rate of oligimerization can be slowed by diluting the reaction or adding the diene slowly
 2. Higher temperatures generally required
 3. Higher catalyst loadings
- Substrate considerations
 1. Presence of a polar functional group (ester, amide, ketone, ether, sulfonamide, urethane)

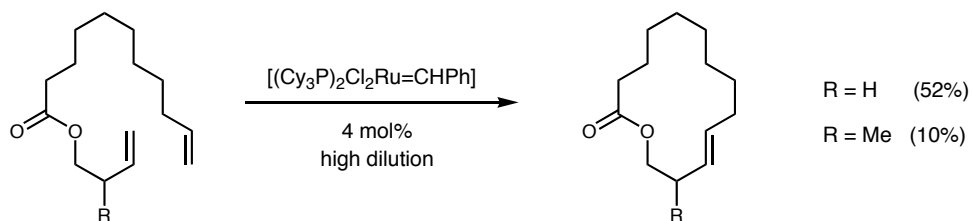


RCM: Macrocyclizations

2. Site of ring close is a key issue



3. Steric Hindrance close to the double bonds significantly lowers yield

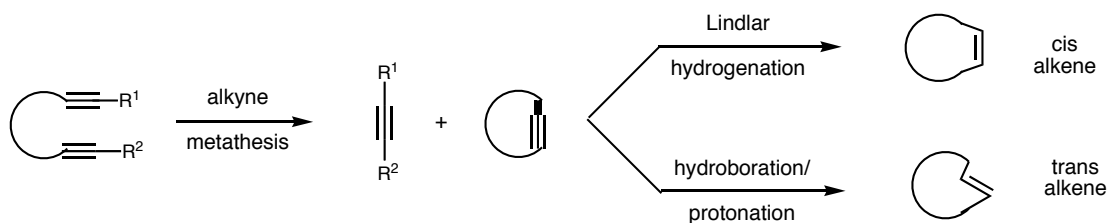


Due to bulky nature of metal ligands, bulky substituents close to olefins to be metathesized will have adverse effect on the cyclization

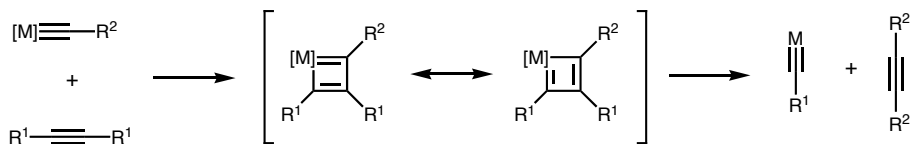
Furstner, A. *Top. Organomet. Chem.* **1998**, 1, 37.

Macrocyclizations using RCM: Alkyne Metathesis

■ Alkyne Metathesis: viable solution to lack of *E/Z* control in alkene RCM macrocyclizations



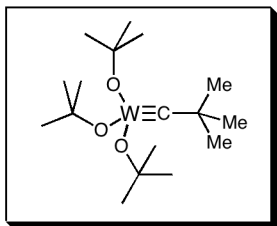
Chauvin-type mechanism:



Katz, J.; McGinnis, J. *J. Am. Chem. Soc.* **1975**, 97, 1592

Macrocyclizations with RCM: Alkyne Metathesis

Schrock's Tungsten alkylidyne complex



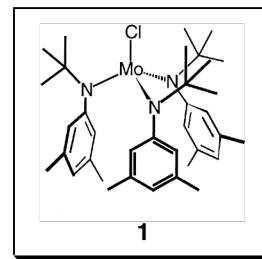
1. Rings with more than 12 atoms readily accessible in good yields
2. Ring Diyne metathesis is faster than RCM of corresponding dienes
3. Reaction tolerates ethers, esters, silyl ethers, amides, urethanes, ketones, enones, sulfones, furans, etc.
4. Catalyst rigorously distinguishes between alkynes and preexisting alkenes in the substrate

R. R. Schrock et al. *Organometallics*, **1982**, 1, 1645.
A. Furstner et al. *J. Am. Chem. Soc.* **1999**, 121, 11108
A. Furstner et al. *Angew. Chem. Int. Ed.* **1998**, 37, 1734

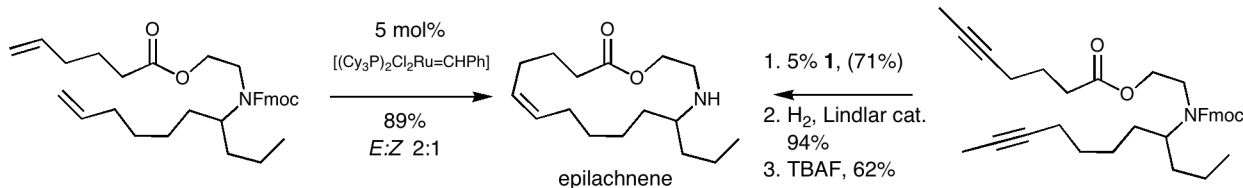
Furstner's trisamido molybdenum alkylidyne complex

1. Generated *in situ* from $\text{Mo}[\text{N}(\text{tBu})(\text{Ar})]_3$ and CH_2Cl_2 . ($\text{Ar} = 3,5$ dimethylphenyl)
2. Mechanism and intermediates still unknown
3. Reaction profile is similar to $(\text{tBuO})_3\text{WCCMe}_3$; also tolerates thioethers, crown ether segments, and pyridine rings, which $(\text{tBuO})_3\text{WCCMe}_3$ does not

Furstner et al. *J. Am. Chem. Soc.* **1999**, 121, 9453

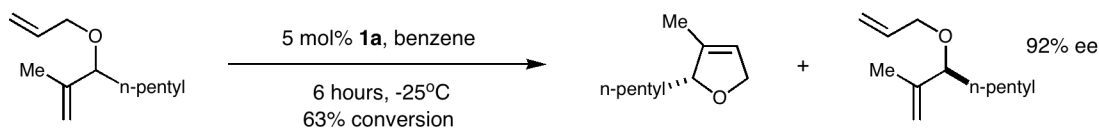
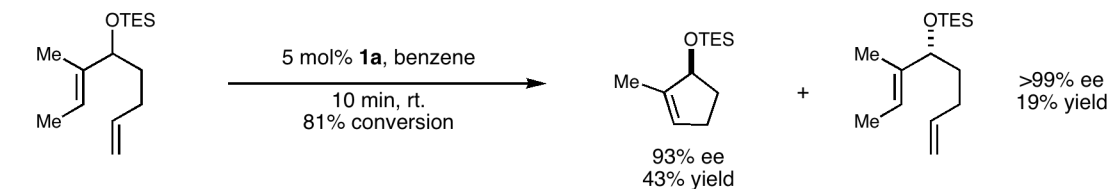
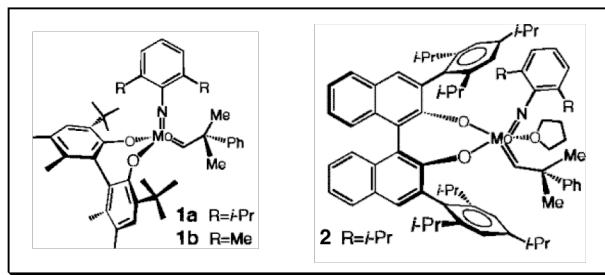


Synthesis of Epilachnene: Furstner et al. *J. Am. Chem. Soc.* **1999**, 121, 11108



Asymmetric Ring Closing Metathesis

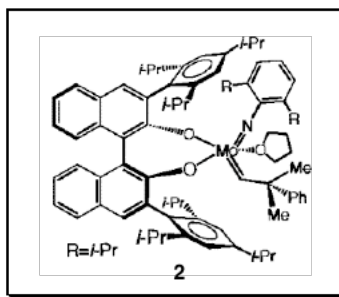
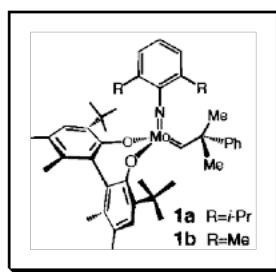
Catalytic kinetic resolution



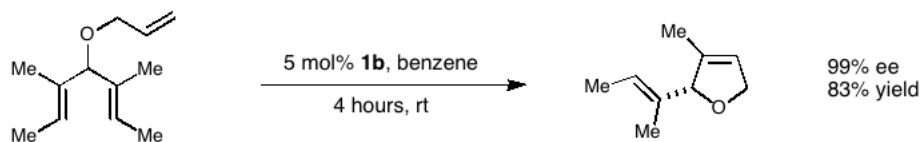
1,2 disubstituted olefin substrates and tertiary ethers are not effectively resolved



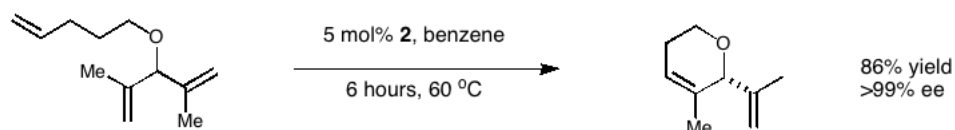
Asymmetric Ring Closing Metathesis



■ Catalytic Enantioselective Desymmetrization of Trienes

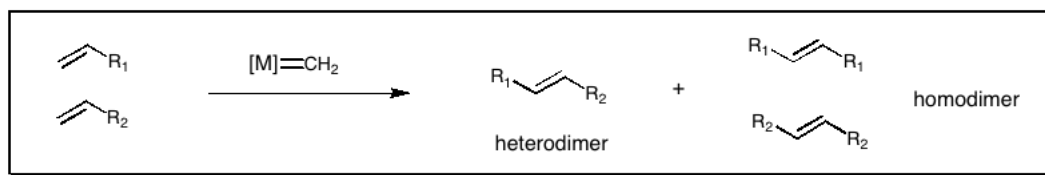


stereochemistry of quaternary carbon stereocenters can be controlled in this manner



Hoveyda and Schrock *et al. J. Am. Chem. Soc.* **1998**, *120*, 9720; **1999**, *121*, 8251

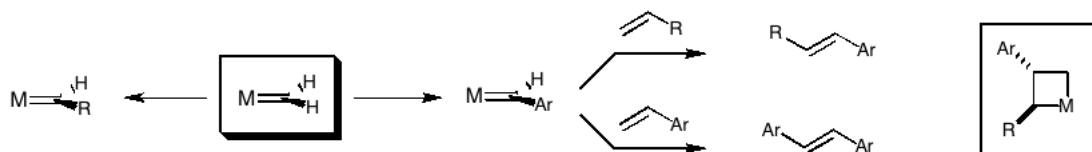
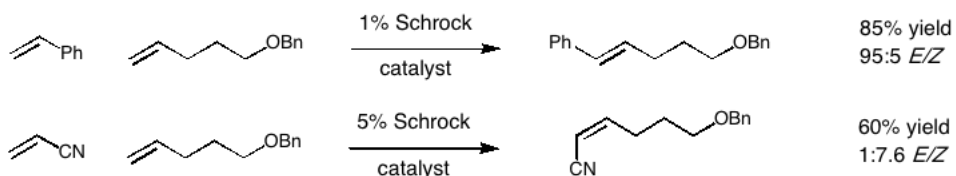
Cross metathesis



■ Two major issues in cross metathesis

1. Must control homodimerization in order to obtain useful yields
2. *E/Z* ratios are hard to control and predict

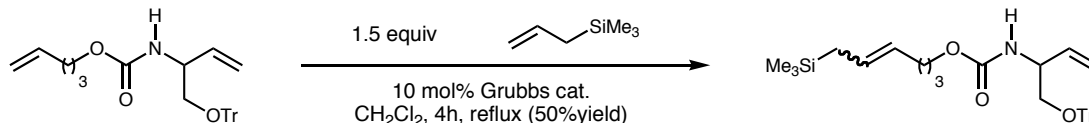
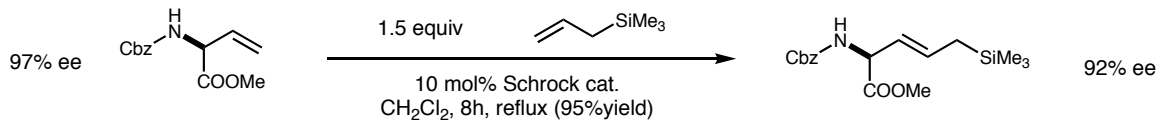
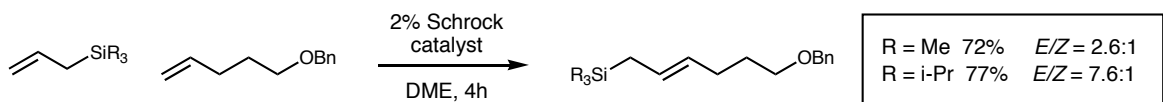
■ Early studies using molybdenum imido alkylidene catalysts involved styrene and acrylonitrile



Crowe *et al. J. Am. Chem. Soc.* **1993**, *115*, 10998; **1995**, *117*, 5162.

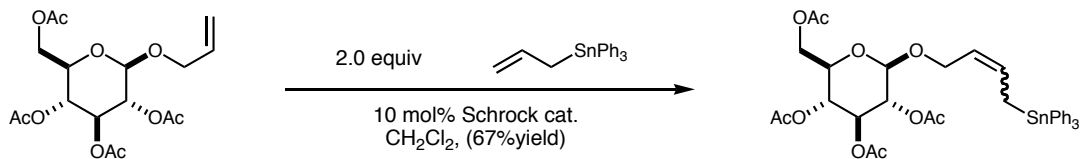
Cross metathesis

- Allyl silanes: stabilization of β -cation (silicon β -effect) enhances nucleophilicity



Blechert et al. *Chem. Eur. J.* **1997**, 3, 441
 Fleming et al. *Org. React.* **1989**, 37, 57
 Schinzer, D. *Synthesis* **1988**, 263.

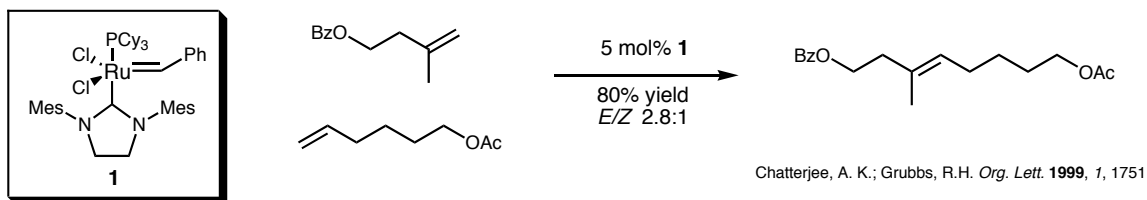
- Allyl stannanes: compatible with Schrock's catalyst, but not with ruthenium catalysts



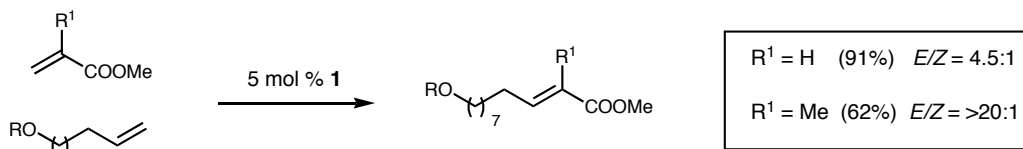
Blechert et al. *Synlett.* **1997**, 129

Cross metathesis

- Trisubstituted Olefins: Ruthenium NHC catalyst

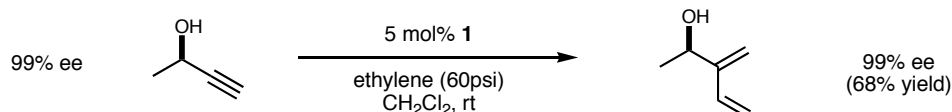


- Cross Metathesis using α,β unsaturated carbonyl substrates: Ruthenium NHC catalyst



Grubbs et al. *J. Am. Chem. Soc.* **2000**, 122, 3783

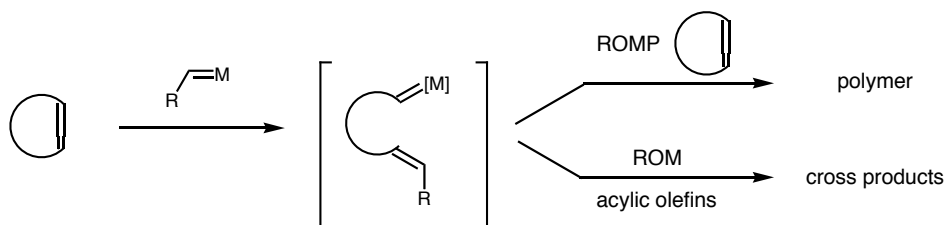
- Enyne cross metathesis



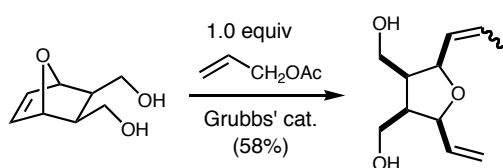
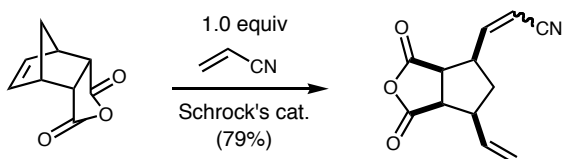
Smulik, J.A.; Diver, S. T. *Org. Lett.* **2000**, 2, 2271

Ring Opening Metathesis

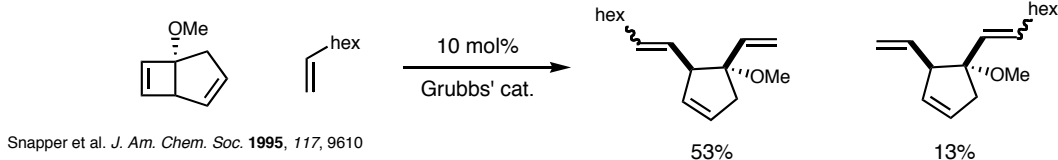
- Ring opening of strained cyclic olefin to give open chain metal carbene provides driving force for ROM



- Selection of catalyst decided by functionality in the substrate
- Use of terminal olefin results in exclusive formation of monosubstituted diene; however *E/Z* ratios are low



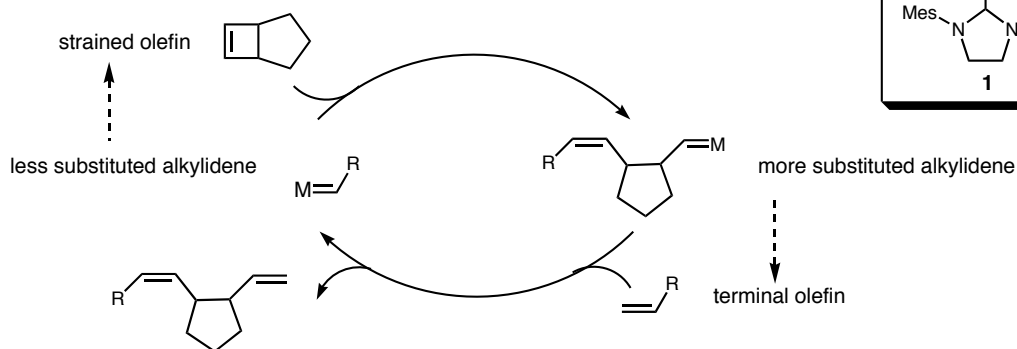
Blechert et al. *Angew. Chem. Int. Ed.* **1997**, 36, 257



Snapper et al. *J. Am. Chem. Soc.* **1995**, 117, 9610

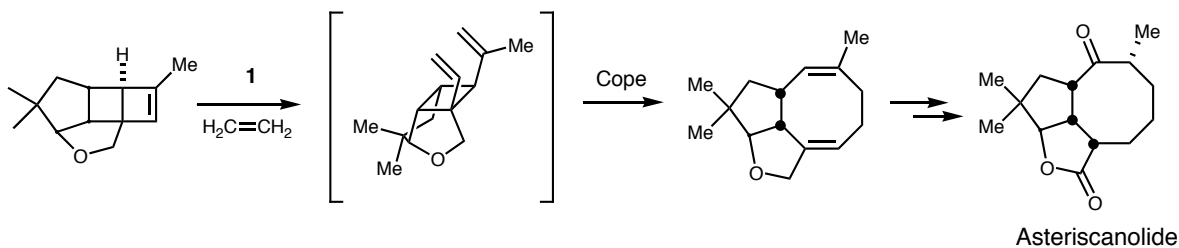
Ring Opening Metathesis

- Cross Metathesis selectivity

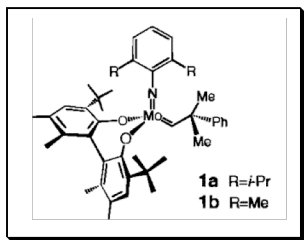


Tallarico, J. A.; Randall, M. L. *Tetrahedron* **1997**, 48, 16511

- Synthetic application of ring opening metathesis: (+) and (-)-Asteriscanolide

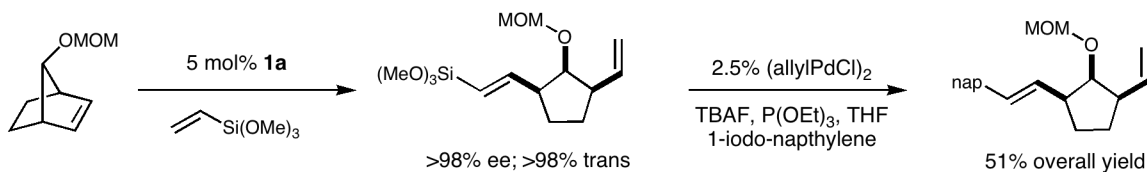


Limanto, J.; Snapper, M.L. *J. Am. Chem.Soc.* **2000**, 122, 8071



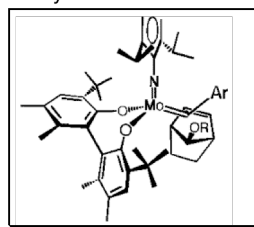
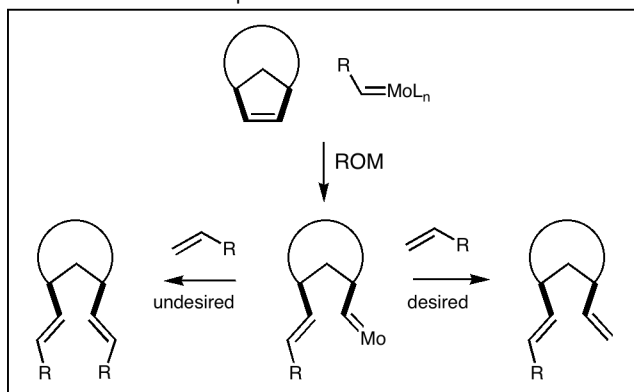
Asymmetric Catalytic Ring Opening Metathesis/ Cross Metathesis

Hoveyda and Schrock *et al. J. Am. Chem. Soc.* **1999**, 121, 11603

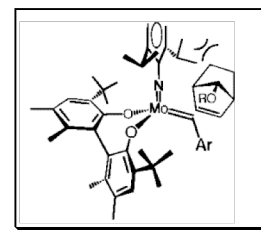


Use of unprotected strained olefins resulted in polymerization

aliphatic olefin substrates lead to diminished efficiency and enantioselectivity



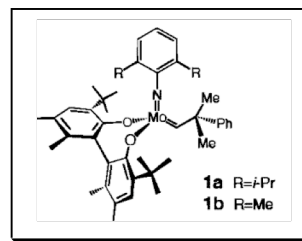
Favored



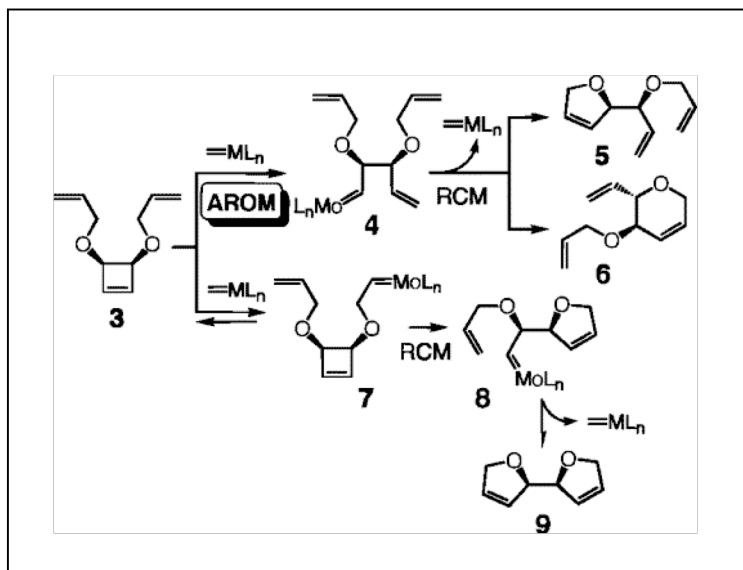
Disfavored

Tandem Catalytic Asymmetric Ring Opening Metathesis/ Ring Closing Metathesis

Hoveyda and Schrock *et al. J. Am. Chem. Soc.* **2000**, 122, 1828



General Strategy



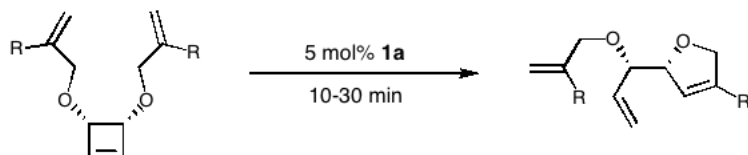
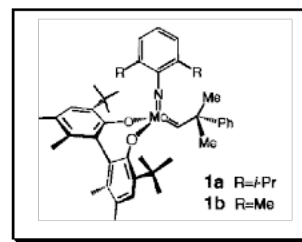
■ Must initiate site selectively and irreversibly at central alkene to give **4**

■ Catalytic rate of AROM (**3** to **5**) must be faster than that of second ring closure to get optically enriched product

■ Which will predominate: **5** or **6**?

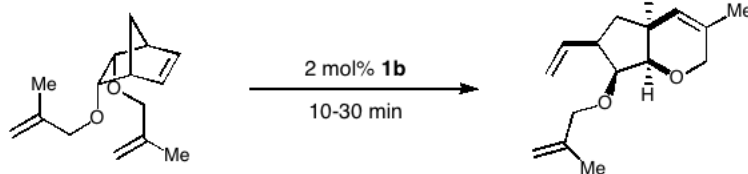
Tandem Catalytic Asymmetric Ring Opening Metathesis/ Ring Closing Metathesis

Hoveyda and Schrock *et al. J. Am. Chem. Soc.* **2000**, *122*, 1828



R = H 83% conv (73% bicycle)
 10% yield, >98% ee

R = Me >98% conv (0% bicycle)
 69% yield, 92% ee



>98% conv (10% bicycle)
84% yield, >98% ee

