

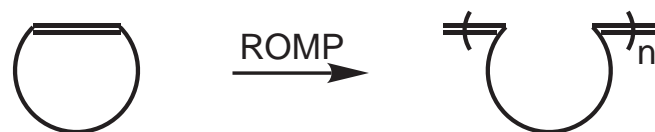
## Reviews:

Fürstner, A. *Angew. Chem., Int. Ed. Engl.* **2000**, 39, 3013-3043.

Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, 54, 4413-4450.

Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371-388.

## Ring-Opening Metathesis Polymerization (ROMP):



- ROMP is thermodynamically favored for strained ring systems, such as 3-, 4-, 8- and larger-membered compounds.
- When bridging groups are present (bicyclic olefins) the  $\Delta G$  of polymerization is typically more negative as a result of increased strain energy in the monomer.
- Block copolymers can be made by sequential addition of different monomers (a consequence of the "living" nature of the polymerization).

## Ring-Closing Metathesis (RCM):



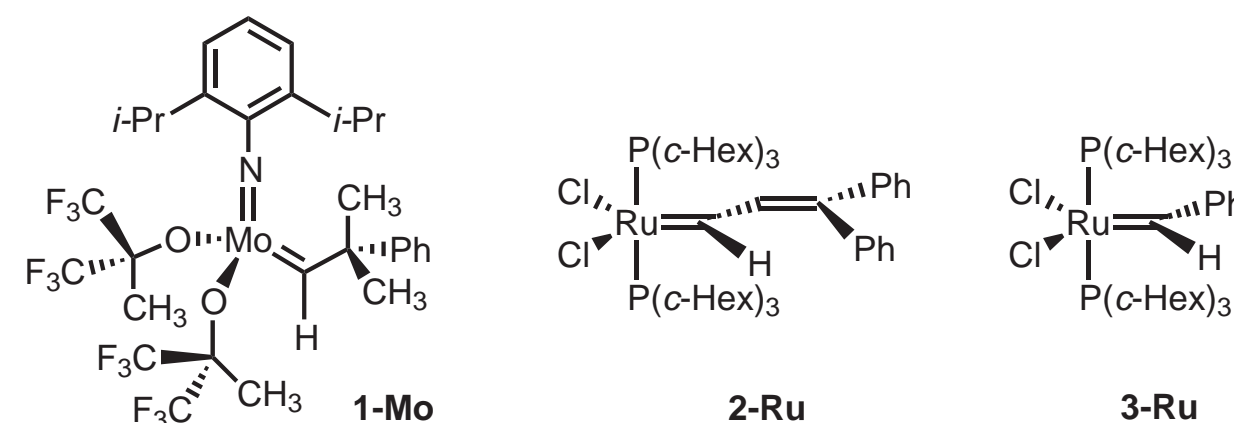
- The reaction can be driven to the right by the loss of ethylene.
- The development of well-defined metathesis catalysts that are tolerant of many functional groups yet reactive toward a diverse array of olefinic substrates has led to the rapid acceptance of the RCM reaction as a powerful method for forming carbon-carbon double bonds and for macrocyclizations.
- Where the thermodynamics of the closure reaction are unfavorable, polymerization of the substrate can occur. This partitioning is sensitive to substrate, catalyst, and reaction conditions.

## Acyclic Diolefin Metathesis (ADMET):

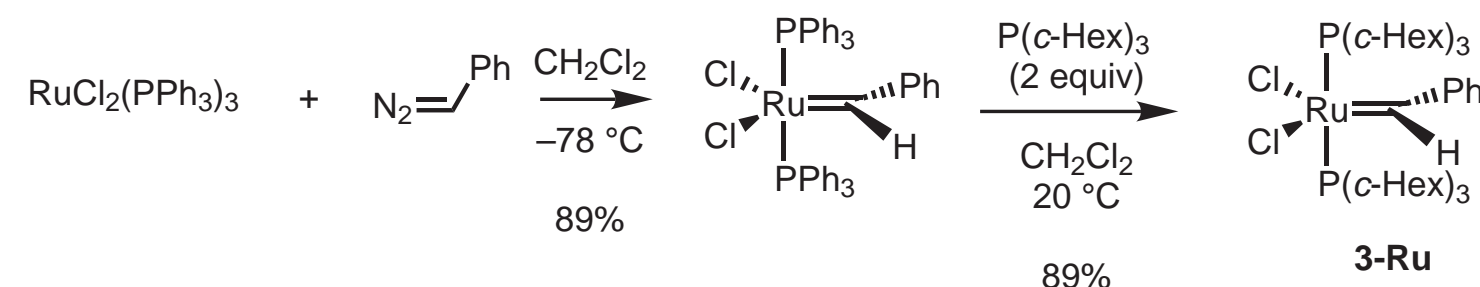


- Self-dimerization reactions of the more valuable alkene may be minimized by the use of an excess of the more readily available alkene.

## Catalysts



- The Well-defined catalysts **1-Mo**, **2-** and **3-Ru** have been used widely for the olefin metathesis reaction. Titanium- and tungsten-based catalysts have also been developed but are less used.
- Schrock's alkoxy imidomolybdenum complex **1-Mo** is highly reactive toward a broad range of substrates; however, this Mo-based catalyst has moderate to poor functional group tolerance, high sensitivity to air, moisture or even to trace impurities present in solvents, and exhibits thermal instability.



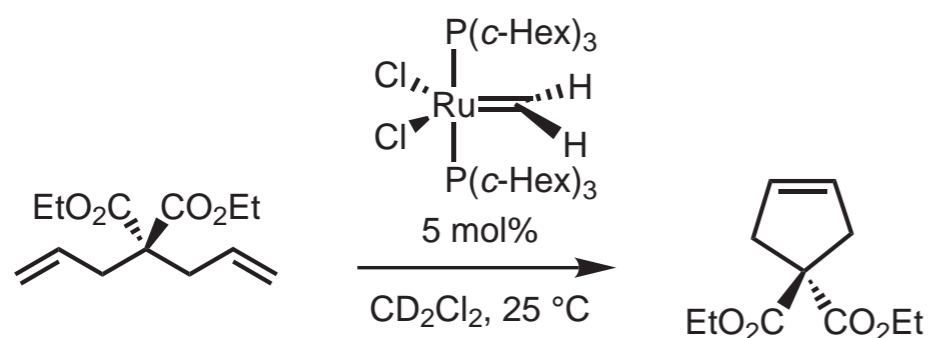
- Grubbs' Ru-based catalysts exhibit high reactivity in a variety of ROMP, RCM, and ADMET processes and show remarkable tolerance toward many different organic functional groups.
- Alkyldiene complexes **2-** and **3-Ru** can be easily prepared. Polymer-supported and water-soluble versions have been described.
- The  $d^6$  Ru(II) metal center in alkyldienes **2-** and **3-Ru** requires electron-rich ancillary ligands for increased metathesis activity; the exchange of triphenylphosphine for tricyclohexylphosphine results in a superior catalyst.
- Ru-based catalysts show little sensitivity to air, moisture or minor impurities in solvents. These catalysts can be conveniently stored in the air for several weeks without decomposition.
- Although the Ru-based catalysts often show lower propagation rates when compared to the catalyst **1-Mo**, their availability and ease of use make them the catalyst of choice for all but the most difficult substrates.

Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed Engl.* **1995**, 34, 2039-2041.

Nguyen, S.-B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, 115, 9858-9859.

## Mechanism:

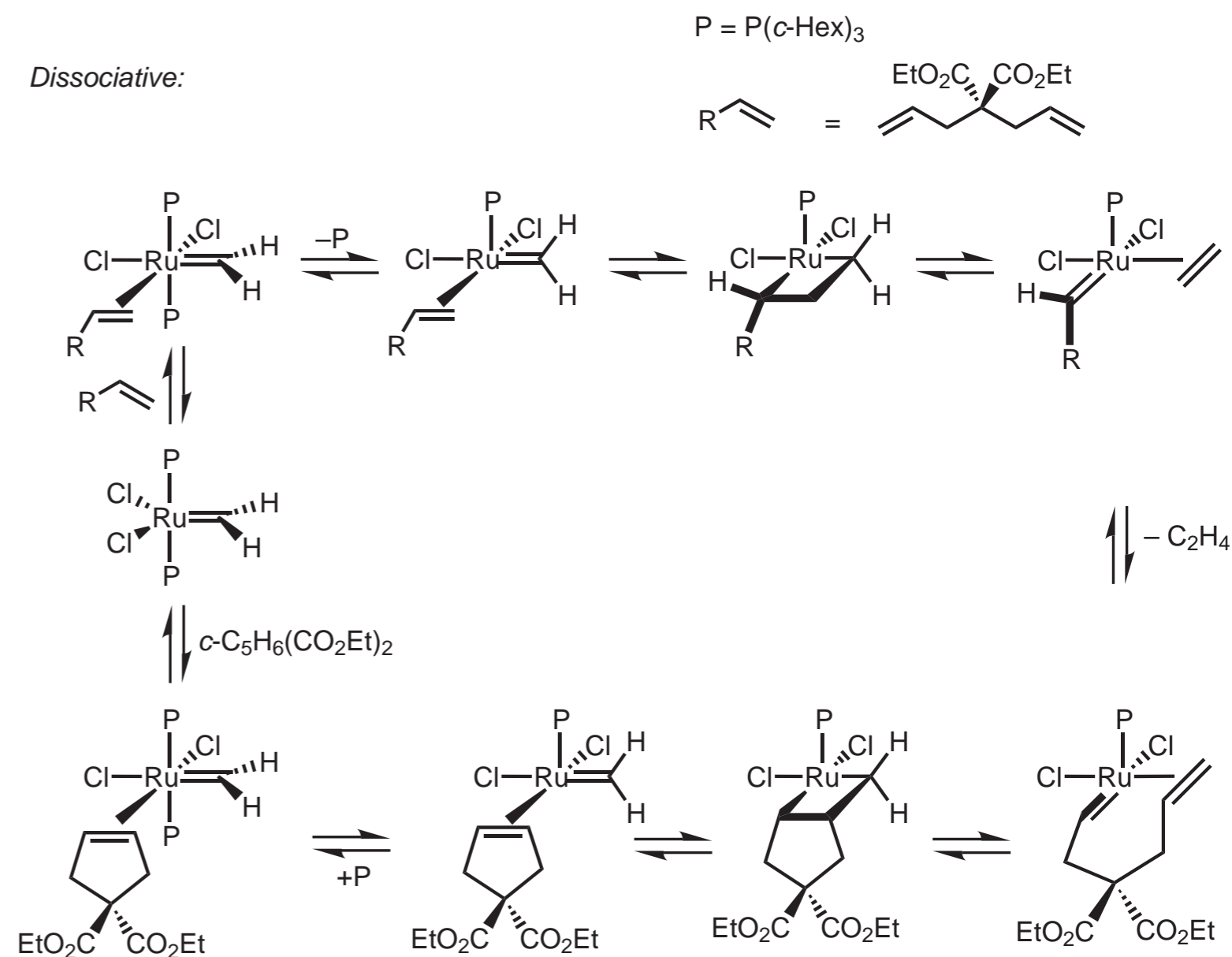
- The olefin metathesis reaction was reported as early as 1955 in a Ti(II)-catalyzed polymerization of norbornene: Anderson, A. W.; Merckling, M. G. *Chem. Abstr.* **1955**, 50, 3008i.
- 15 years later, Chauvin first proposed that olefin metathesis proceeds via metallacyclobutanes: Herisson, P. J.-L.; Chauvin, Y. *Makromol. Chem.* **1970**, 141, 161-176.
- It is now generally accepted that both cyclic and acyclic olefin metathesis reactions proceed via metallacyclobutane and metal-carbene intermediates: Grubbs, R. H.; Burk, P. L.; Carr, D. D. *J. Am. Chem. Soc.* **1975**, 97, 3265-3266.



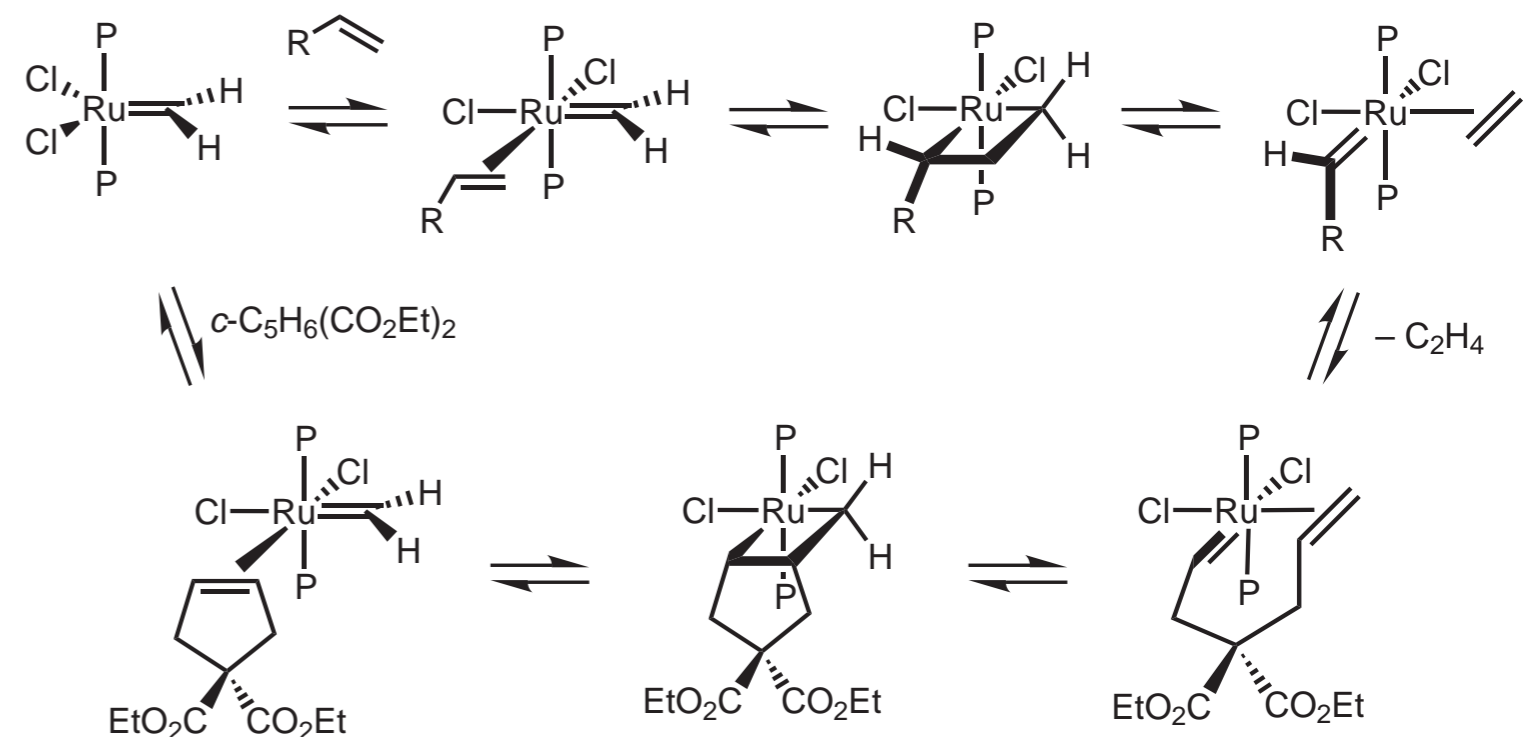
- A kinetic study of the RCM of diethyl diallylmalonate using a Ru-methylidene describes two possible mechanisms for olefin metathesis:
- The "dissociative" mechanism assumes that upon binding of the olefin a phosphine is displaced from the metal center to form a 16-electron olefin complex, which undergoes metathesis to form the cyclized product, regenerating the catalyst upon recoordination of the phosphine.
- The "associative" mechanism assumes that an 18-electron olefin complex is formed which undergoes metathesis to form the cyclized product.
- Addition of 1 equivalent of phosphine (with respect to catalyst) decreases the rate of the reaction by as much 20 times, supporting the dissociative mechanism.
- It was concluded in this study that the "dissociative" pathway is the dominant reaction manifold (>95%).

Dias, E. L.; Nguyen, S.-B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, 119, 3887-3897.

## Dissociative:



## Associative:

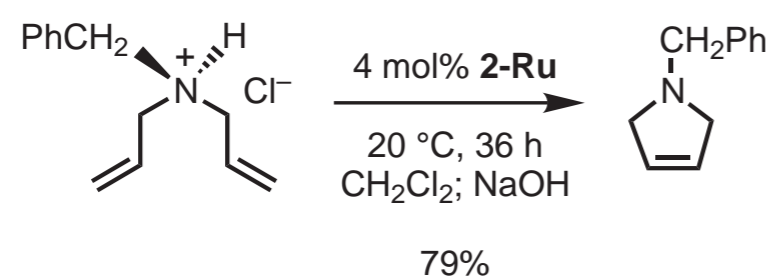


## Catalytic RCM of Dienes:

substrate	product	time (h)	yield (%) <sup>a</sup>
		1	93
X = CF <sub>3</sub>		1	91
X = O <i>t</i> -Bu			
		2	84
		5	86
		8	72
		1	87
		1	87
		1	88
		1	82

<sup>a</sup>2-4 mol% **2-Ru**, C<sub>6</sub>H<sub>6</sub>, 20 °C.

- Five-, six-, and seven-membered oxygen and nitrogen heterocycles and cycloalkanes are formed efficiently.
- Catalyst **2-Ru** can be used in the air, in reagent-grade solvents (C<sub>6</sub>H<sub>6</sub>, CH<sub>2</sub>Cl<sub>2</sub>, THF, *t*-BuOH).
- In contrast to the molybdenum catalyst **1-Mo**, which is known to react with acids, alcohols, and aldehydes, the ruthenium catalyst **2-Ru** is stable to these functionalities.
- Free amines are not tolerated by the ruthenium catalyst; the corresponding hydrochloride salts undergo efficient RCM with catalyst **2-Ru**.



Fu, G. C.; Nguyen, S.-B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856-9857.

## Synthesis of Tri- and Tetrasubstituted Cyclic Olefins via RCM

substrate <sup>a</sup>	product	yield with <b>3-Ru</b> (%) <sup>b</sup>	yield with <b>1-Mo</b> (%) <sup>c</sup>
		93	100
R = CH <sub>3</sub>		98	100
<i>i</i> -Pr		NR	96
<i>t</i> -Bu		25	97
Ph		NR	NR
Br		98	decomp
CH <sub>2</sub> OH			
		97	100
		96	100
	—	No RCM <sup>d</sup>	No RCM <sup>d</sup>
		NR	93
		NR	61
		96 <sup>e</sup>	100 <sup>e</sup>

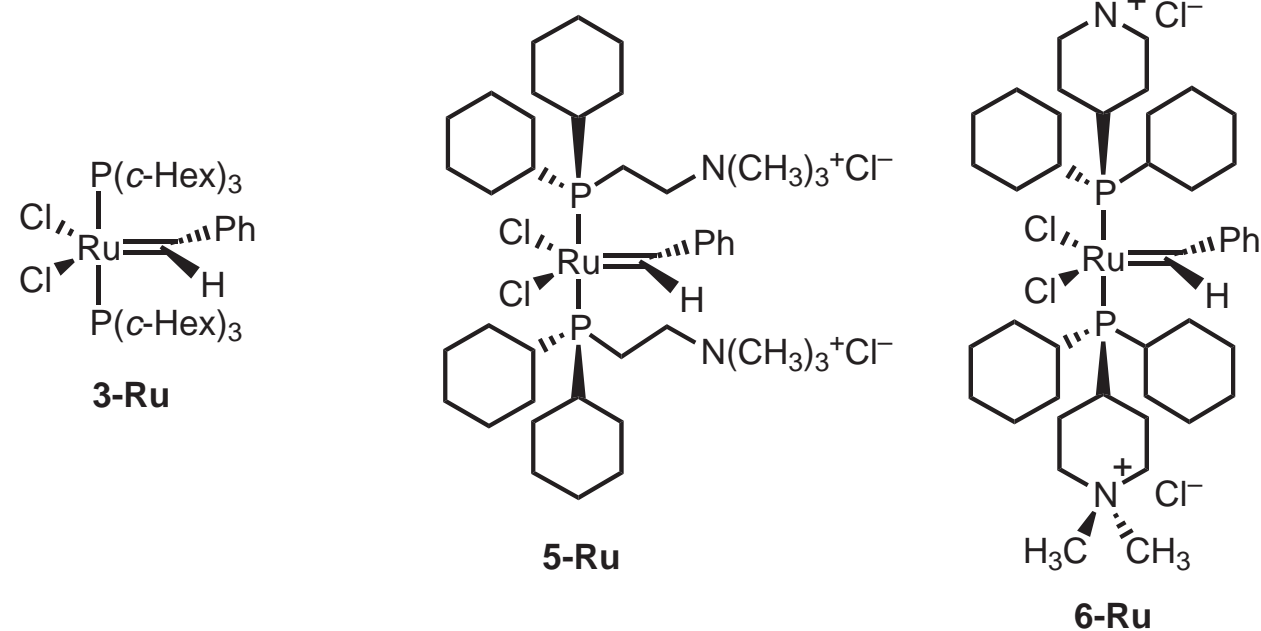
<sup>a</sup>E = CO<sub>2</sub>Et. <sup>b</sup>0.01 M, CH<sub>2</sub>Cl<sub>2</sub>, 5 mol%. <sup>c</sup>0.1 M, C<sub>6</sub>H<sub>6</sub>, 5 mol%. <sup>d</sup>Only recovered starting material and an acyclic dimer were observed. <sup>e</sup>The isomeric cyclopentene product is not observed.

- Functional group compatibility permitting, the Mo-alkylidene catalyst is typically more effective for RCM of substituted olefins.

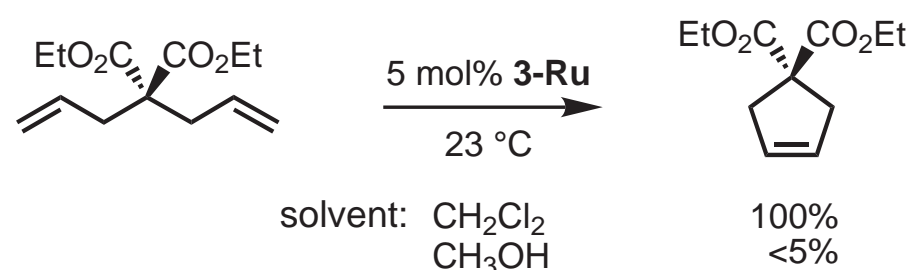
Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310-7318.



## RCM in Methanol and Water

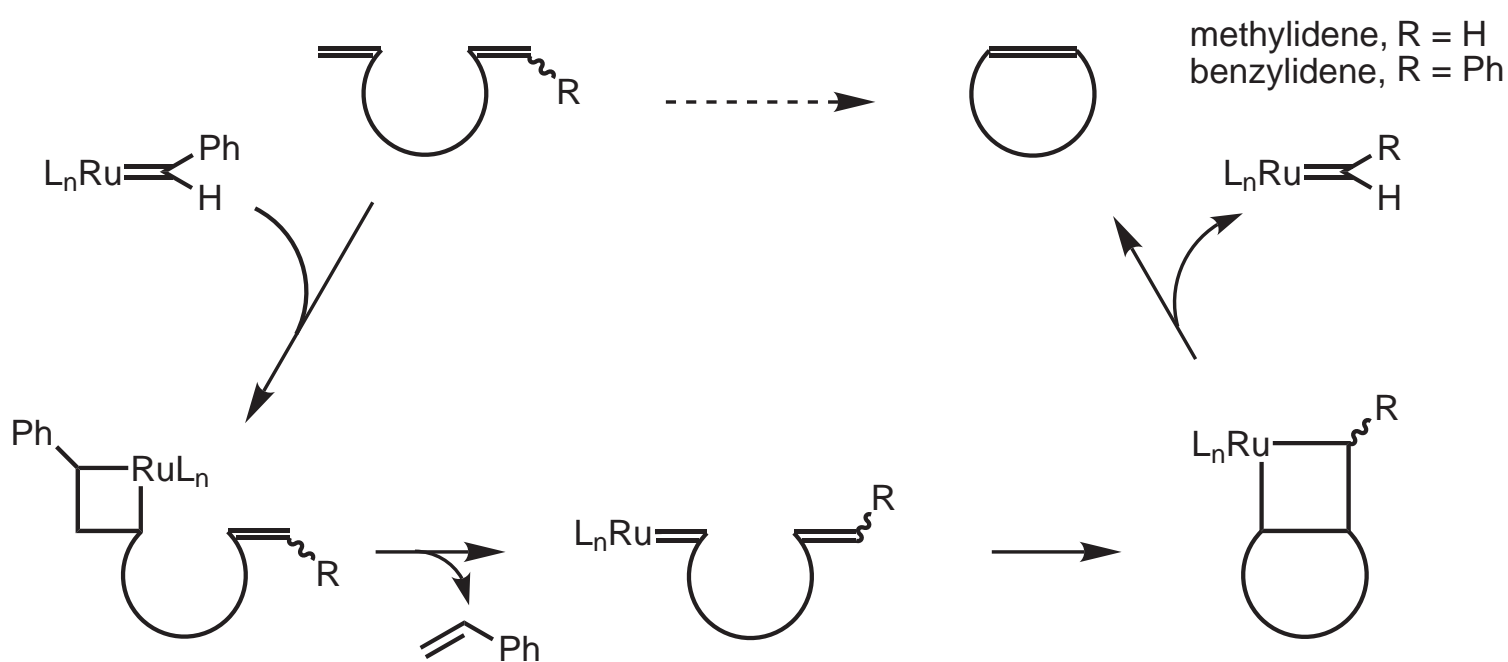


- Alkylidenes **5-Ru** and **6-Ru** are well-defined, water-soluble Ru-based metathesis catalysts that are stable for days in methanol or water at 45 °C.
- Although benzylidene **3-Ru** is highly active in RCM of dienes in organic solvents, it has no catalytic activity in protic media.



## Stabilization of Ru-Carbene Intermediates by Phenyl Substitution

- first turnover step of RCM:

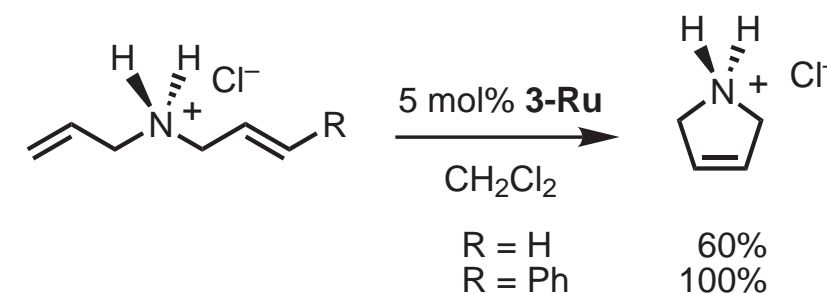


- Substitution of one of the two terminal olefins of the substrate with a phenyl group leads to regeneration of benzylidene catalyst, which is far more stable than the corresponding methylidene catalyst in methanol.

substrate <sup>a</sup>	product <sup>b</sup>	solvent	catalyst	conversion <sup>c</sup>
		methanol	<b>5-Ru</b>	80
		methanol	<b>6-Ru</b>	95
		methanol	<b>5-Ru</b>	45 <sup>d</sup>
		methanol	<b>6-Ru</b>	55 <sup>d</sup>
		methanol	<b>6-Ru</b>	>95
		methanol	<b>5-Ru</b>	40
		methanol	<b>6-Ru</b>	90 <sup>e</sup>
		methanol	<b>5-Ru</b>	30
		methanol	<b>6-Ru</b>	>95 <sup>f</sup>
		methanol	<b>6-Ru</b>	90
		water	<b>6-Ru</b>	60
		water	<b>6-Ru</b>	90 <sup>g</sup>

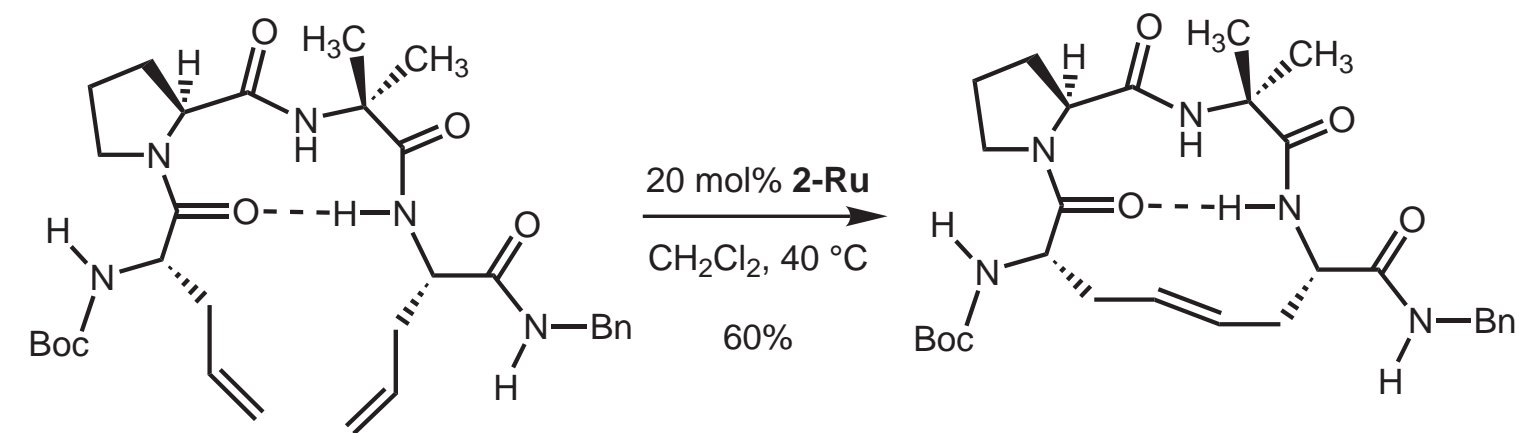
<sup>a</sup>E = CO<sub>2</sub>Et. <sup>b</sup>5 mol% catalyst (**5-Ru** or **6-Ru**), 0.37 M substrate, 45 °C. <sup>c</sup>Conversions were determined by <sup>1</sup>H NMR. <sup>d</sup>Substrate conc. = 0.1 M. <sup>e</sup>30 h. <sup>f</sup>2 h. <sup>g</sup>10 mol% **6-Ru** used.

- Alkylidene **6-Ru** is a significantly more active catalyst than alkylidene **5-Ru** in these cyclizations; this higher reactivity is attributed to the more electron-rich phosphines in **6-Ru**.
- Cis*-olefins are more reactive in RCM than the corresponding *trans*-olefins.
- Phenyl substitution within the starting material can also greatly increase the yield of RCM in organic solvents.



Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, 63, 9904-9909.

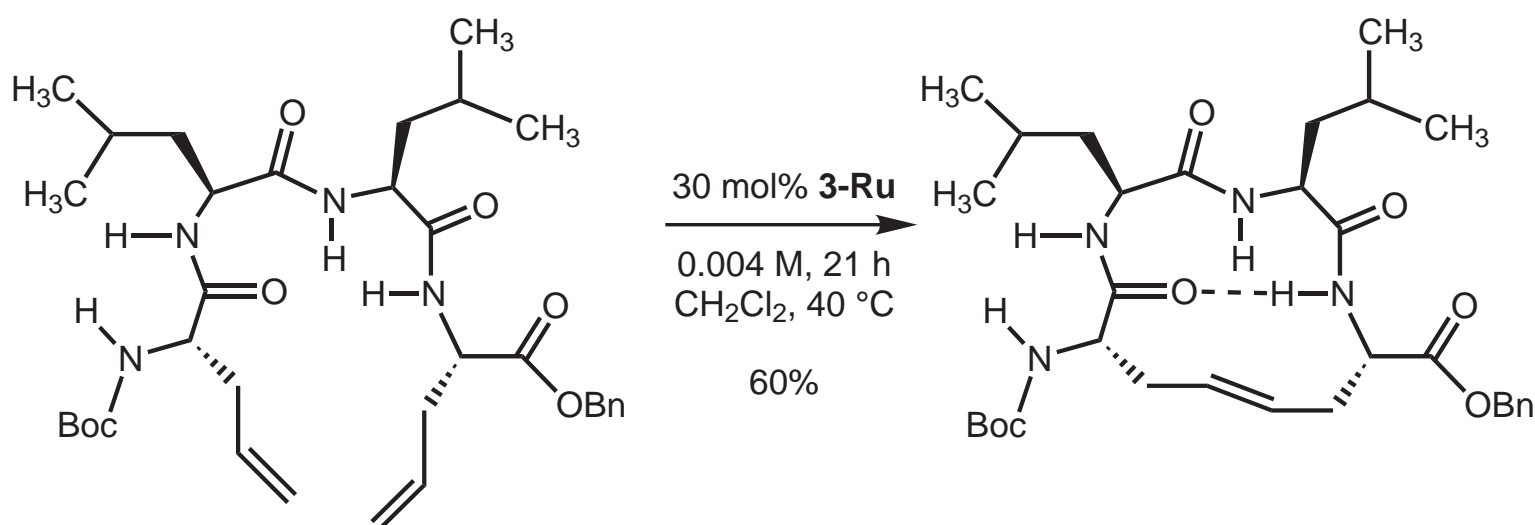
## Synthesis of Cyclic $\beta$ -Turn Analogs by RCM



- The presence of the Pro-Aib sequence in the tetrapeptide induces a  $\beta$ -turn conformation which was covalently captured by RCM, yielding a 14-membered macrocycle.
- The conformational sensitivity in RCM was highlighted when a mixture all four diastereomers of the tetrapeptide above, containing all combinations of (*R*)- and (*S*)-allylglycine, were subjected to identical reaction conditions; a single product (shown) was isolated along with unreacted diastereomers of the acyclic tetrapeptide.

Miller, S. J.; Kim, S. H.; Chen, Z. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108-2109.

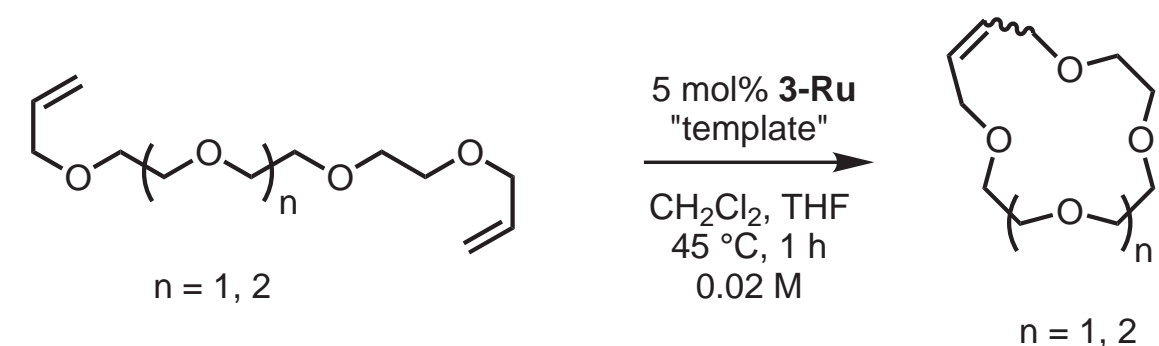
Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855-5856.



- Although interactions that increase the rigidity of the substrate and reduce the entropic cost of cyclization can be beneficial in RCM, it is not a strict requirement for macrocyclization by RCM.

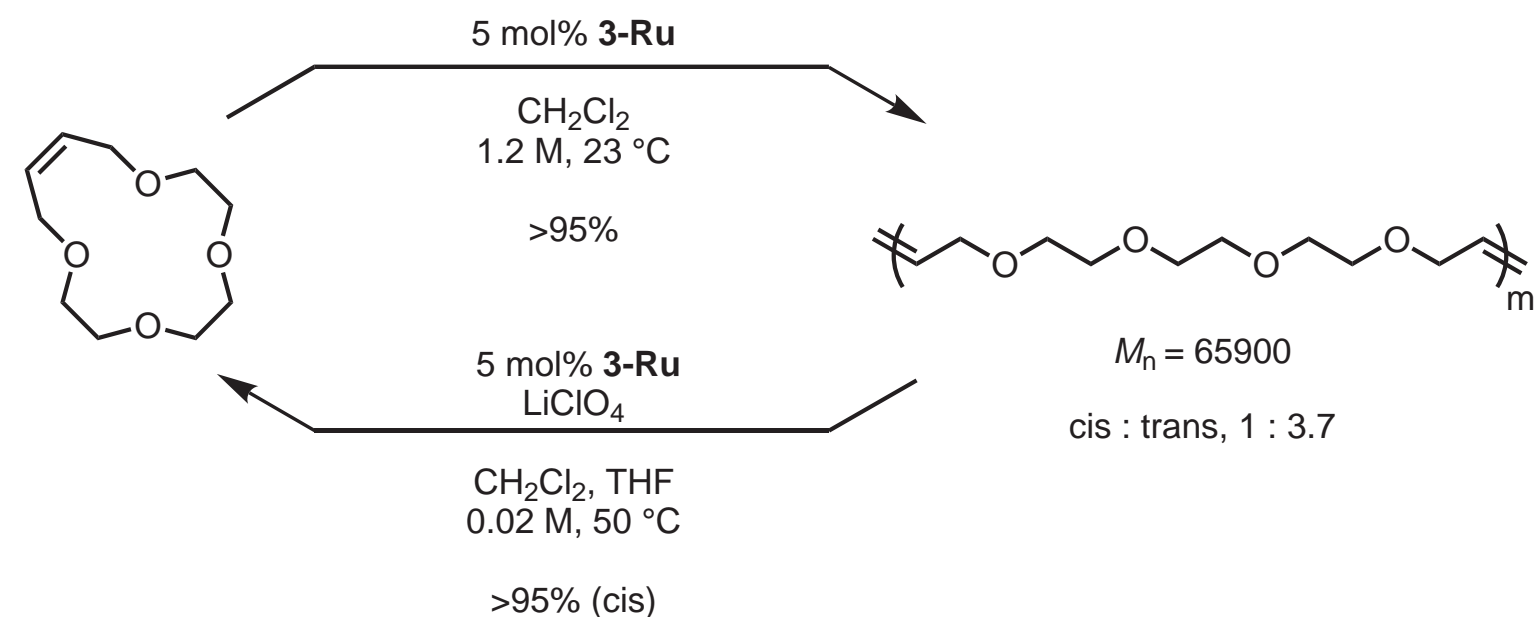
Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606-9614.

## Template-Directed RCM



substrate (n)	"template" (equiv)	yield (%)	cis:trans
1	none	39	38:62
1	LiClO <sub>4</sub> (5)	>95	100:0
1	NaClO <sub>4</sub> (5)	42	62:38
2	none	57	26:74
2	LiClO <sub>4</sub> (5)	89	61:39

- Preorganization of the linear polyether about a complementary metal ion can enhance RCM.
- In general, ions that function best as templates also favor the formation of the cis isomer.

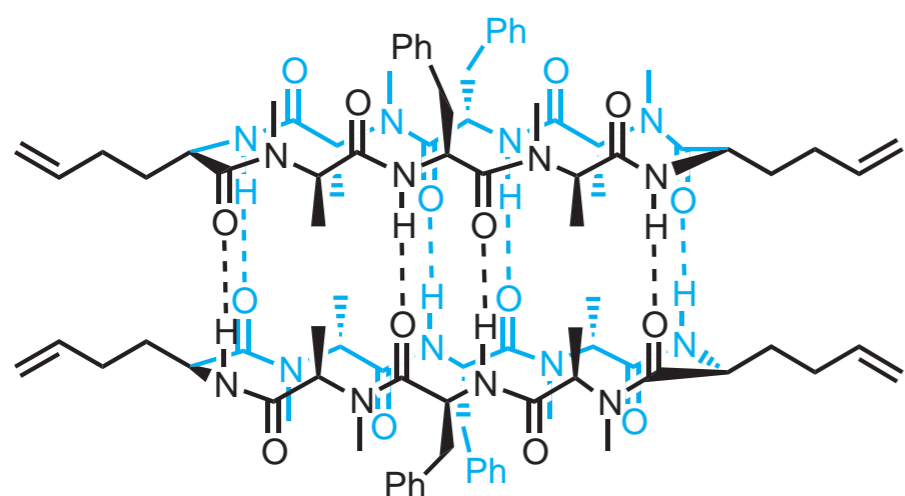


- Polymer degradation in the absence of a Li<sup>+</sup> template produced the corresponding crown ether as a mixture of *cis*- and *trans*-olefins (20% combined yield) along with other low molecular weight polymers.

Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101-1103.

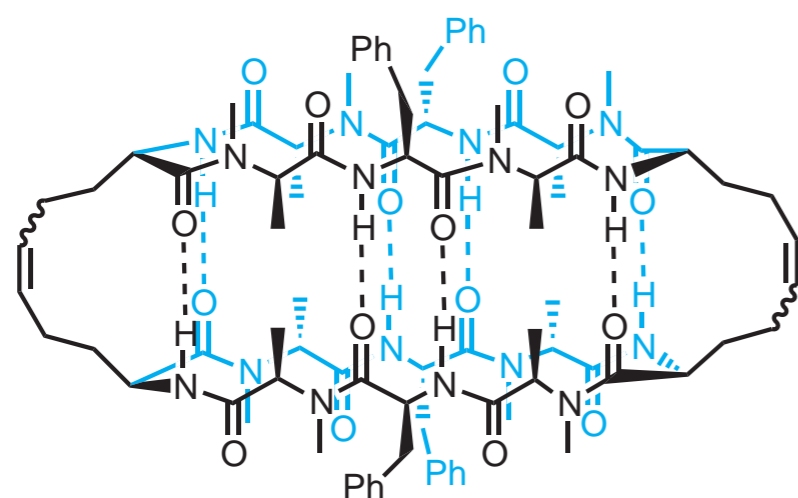
## RCM Mediated Covalent Capture

- The eight-residue cyclic peptide cyclo[-(L-Phe-D-MeN-Ala-L-HomoallylGly-D-MeN-Ala)<sub>2</sub>-] self-assembles to form two slow-exchanging antiparallel β-sheet-like hydrogen bonded cylinders ( $K_a(\text{CDCl}_3) = 99 \text{ M}^{-1}$ , only the reactive isomer is shown).



20-25 mol% **2-Ru**  
 $\text{CDCl}_3$ , 23 °C, 48 h

65%

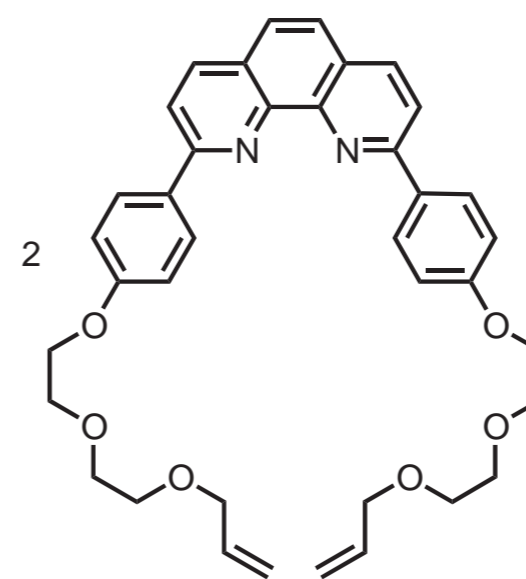


- The hydrogen-bonded ensemble positions the terminal olefins of the four L-homoallylglycine residues in sufficiently close proximity that each pair undergoes RCM in the presence of alkylidene **2-Ru** to give a tricyclic cylindrical product containing a 38-membered ring as a mixture of three (cis-cis, cis-trans, trans-trans) olefin isomers.

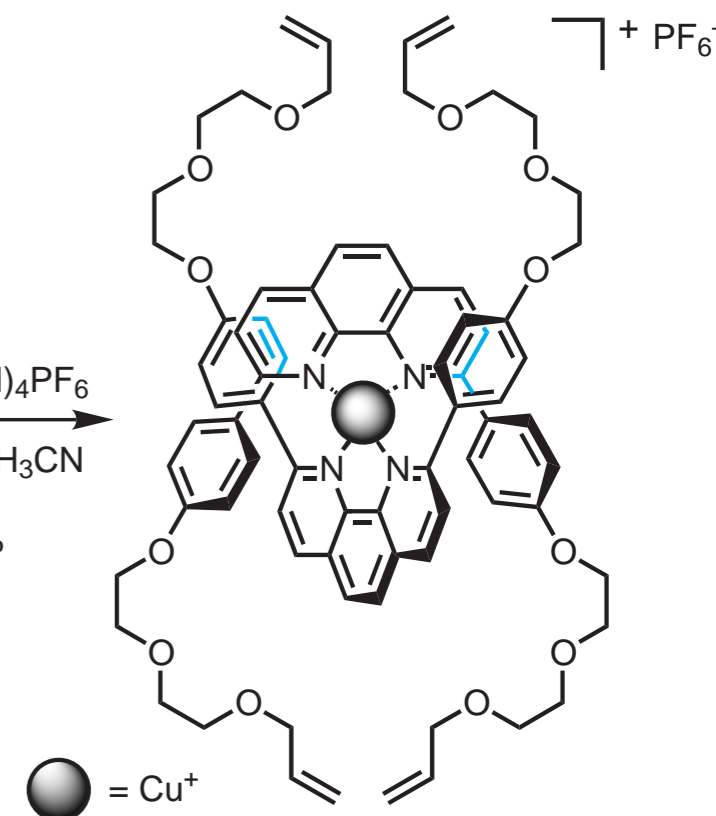
- This covalent capture strategy may be useful in stabilizing kinetically labile α-helical and β-sheet peptide secondary structures.

Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364-12365.

## Synthesis of Catenanes

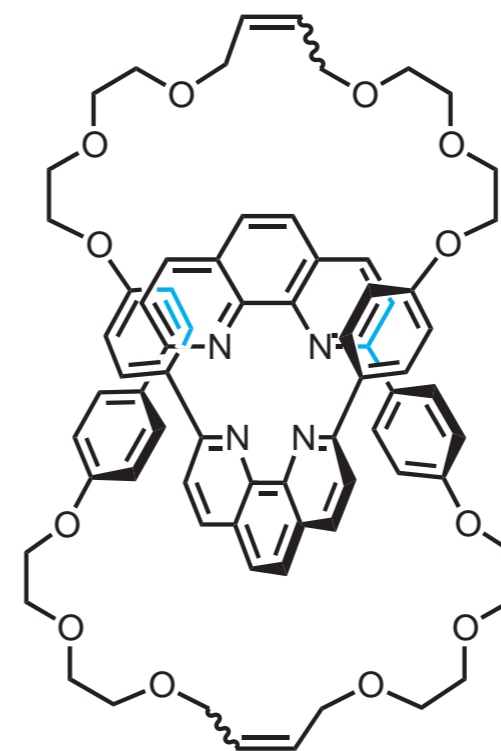


$\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6$   
 $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_3\text{CN}$   
 100%



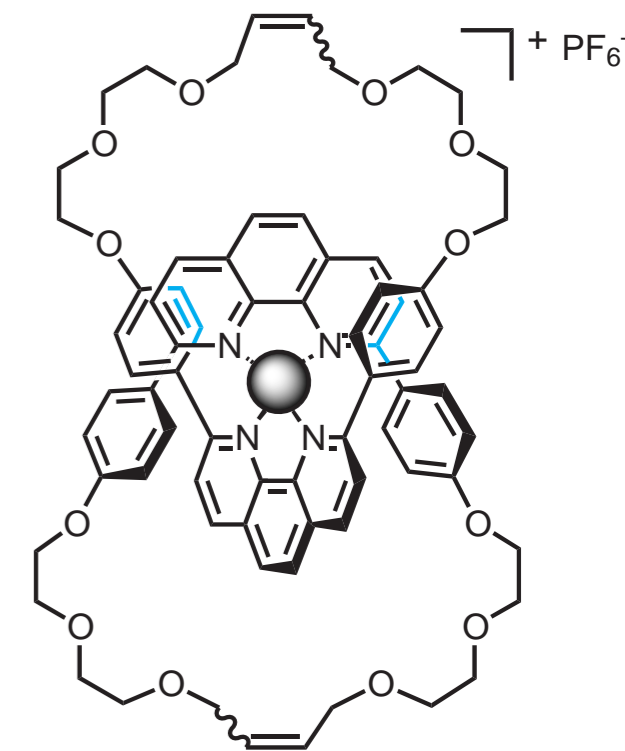
5 mol% **3-Ru**  
 23 °C, 6 h  
 0.01 M,  $\text{CH}_2\text{Cl}_2$

92%



32-membered catenane

$\text{KCN}$ ,  $\text{H}_2\text{O}$   
 $\text{CH}_3\text{CN}$   
 ~100%

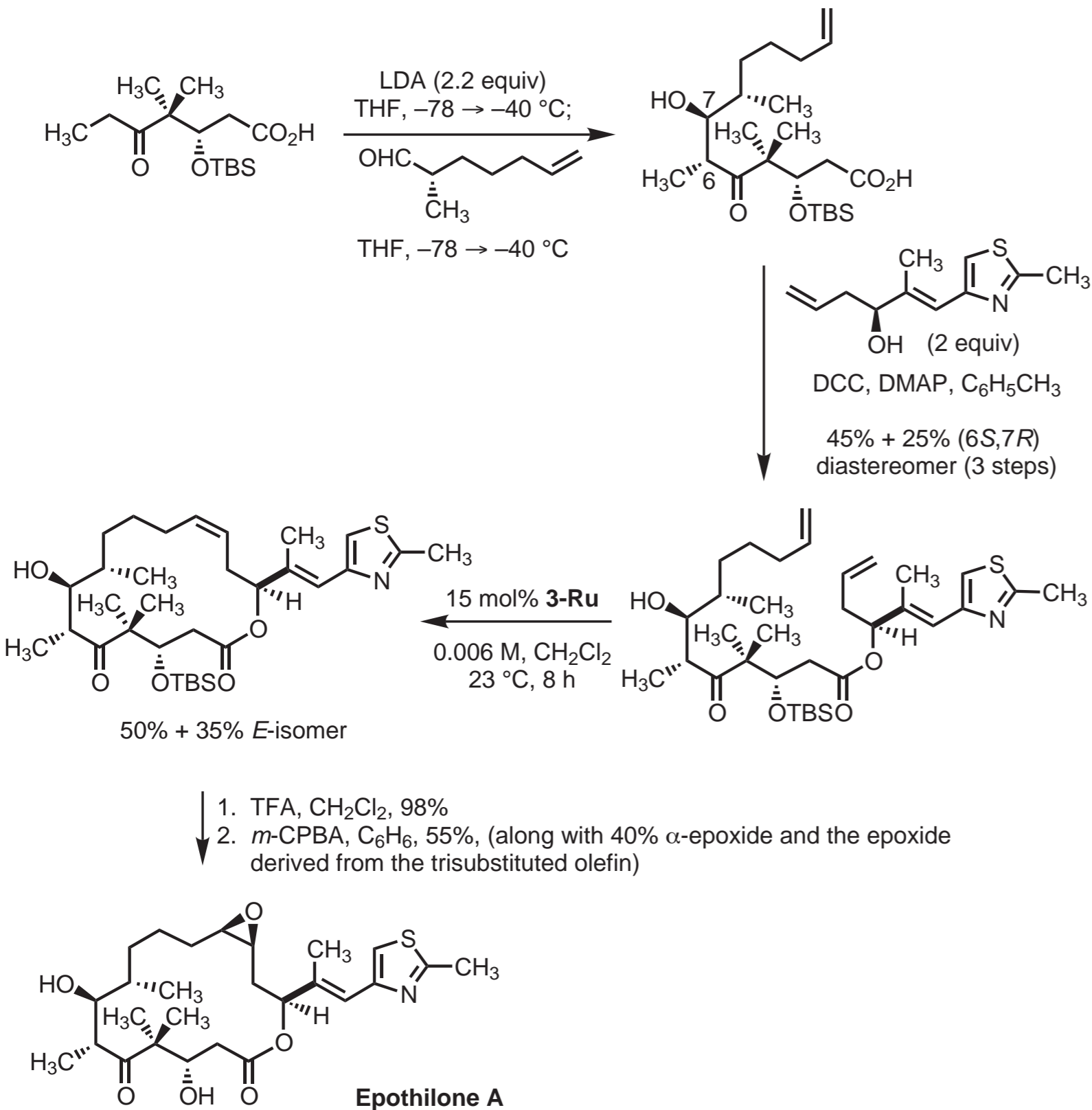


trans:cis, 98:2

- The remarkable efficiency of this RCM is proposed to be due to preorganization of the substrate.

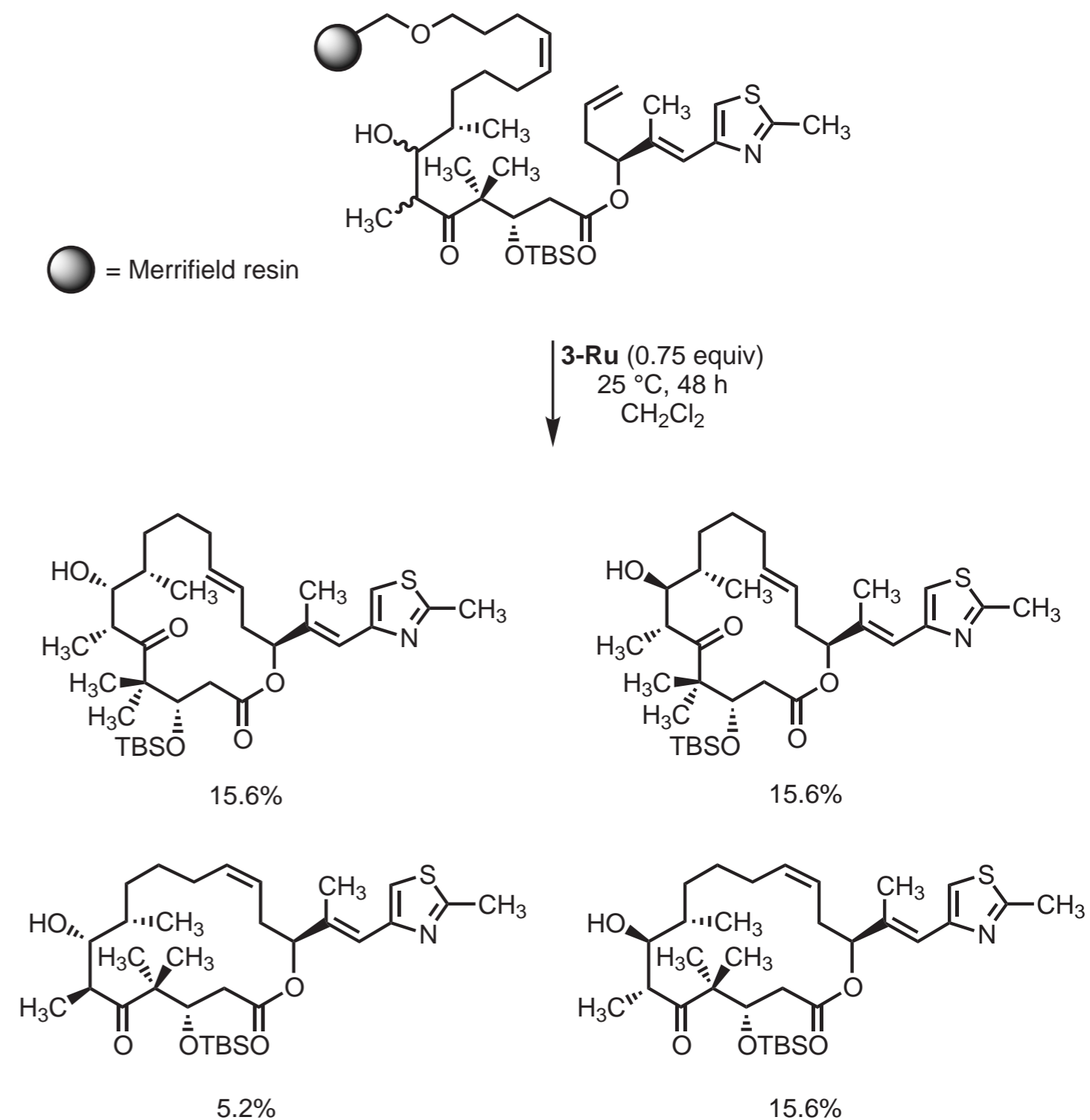
Mohr, B.; Weck, M.; Sauvage, J.-P.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1308-1310.

### Application of RCM to Epothilone A:



Yang, A.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166-168.

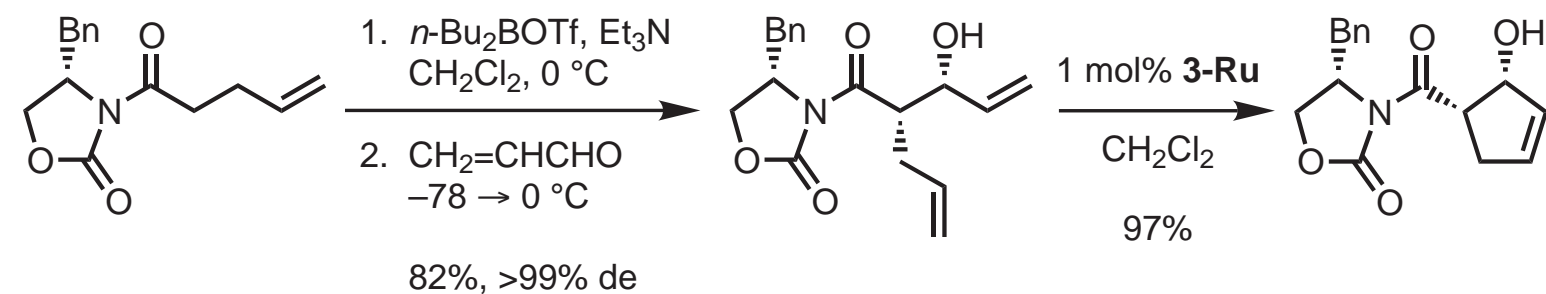
### Solid-Phase Synthesis of Epothilone A:



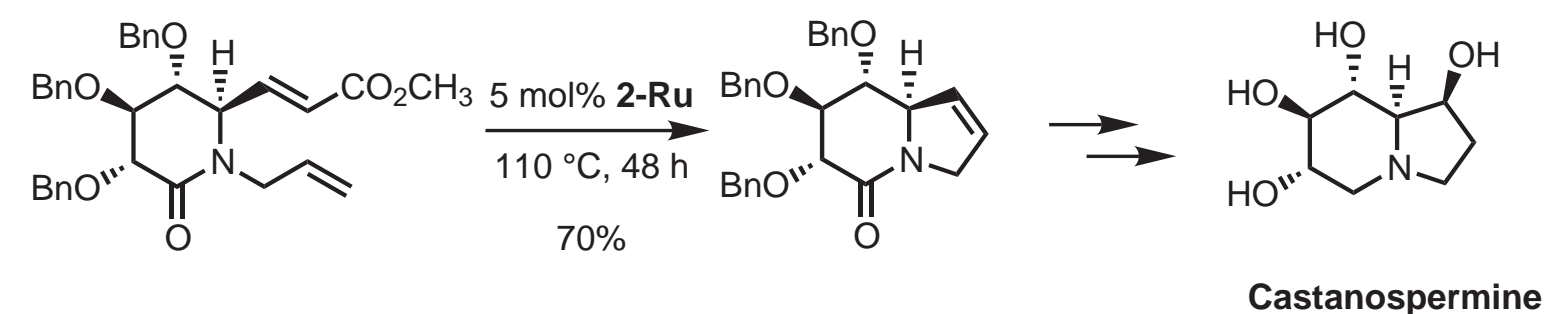
- The amount of alkylidene **3-Ru** (75%) used was greater than the total yield of product (52%), perhaps reflecting the generation of a resin-bound Ru intermediate.
- Addition of *n*-octene or ethylene has been documented to provide a catalytic cycle; see: Maarseveen, J. H.; Hartog, J. A. J.; Engelen, V.; Finner, E.; Visser, G.; Kruse, C. G. *Tetrahedron Lett.* **1996**, *37*, 8249.

Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268-272.

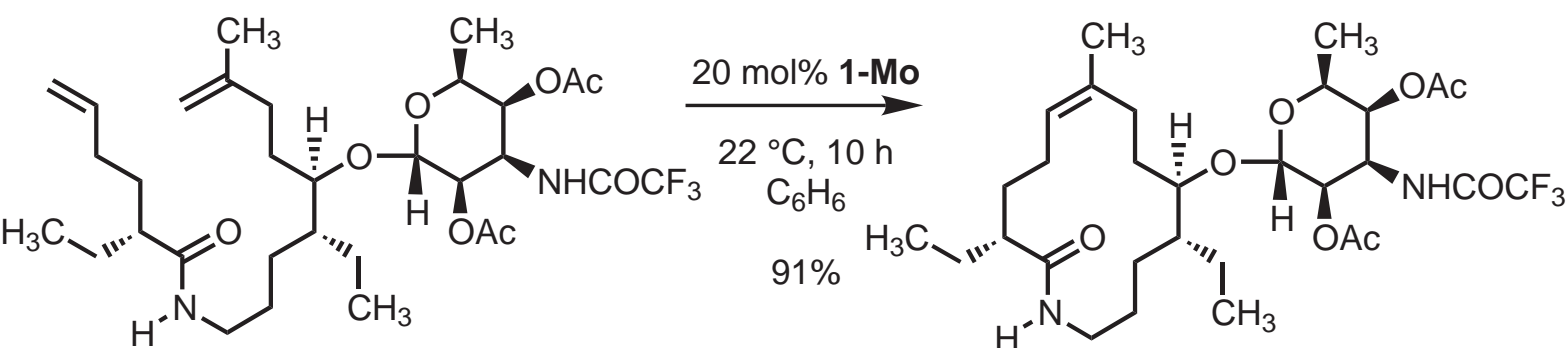
## Other RCM Applications in Synthesis:



Crimmins, M. T.; King, B. W. *J. Org. Chem.* **1996**, *61*, 4192-4193.

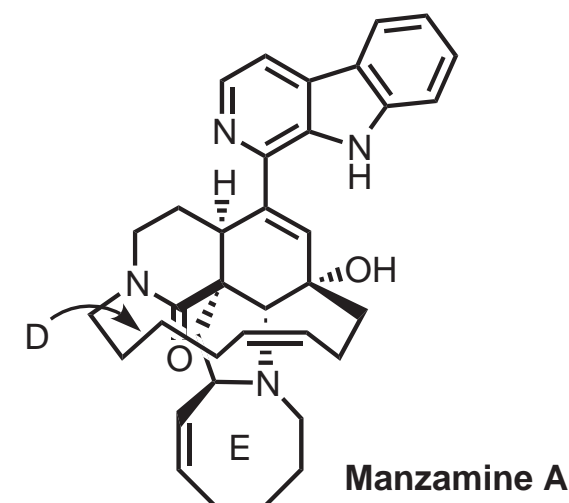


Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547-550.

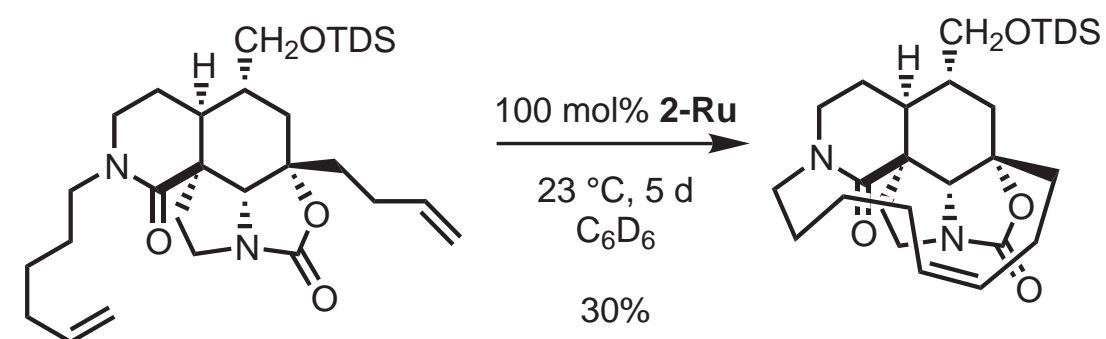


- Due to the greater sensitivity of the Ru-alkylidene catalysts to olefin substitution (steric hindrance) than the Mo-catalyst, the alkylidene **1-Mo** is generally more useful for the closure of macrocyclic trisubstituted olefins.

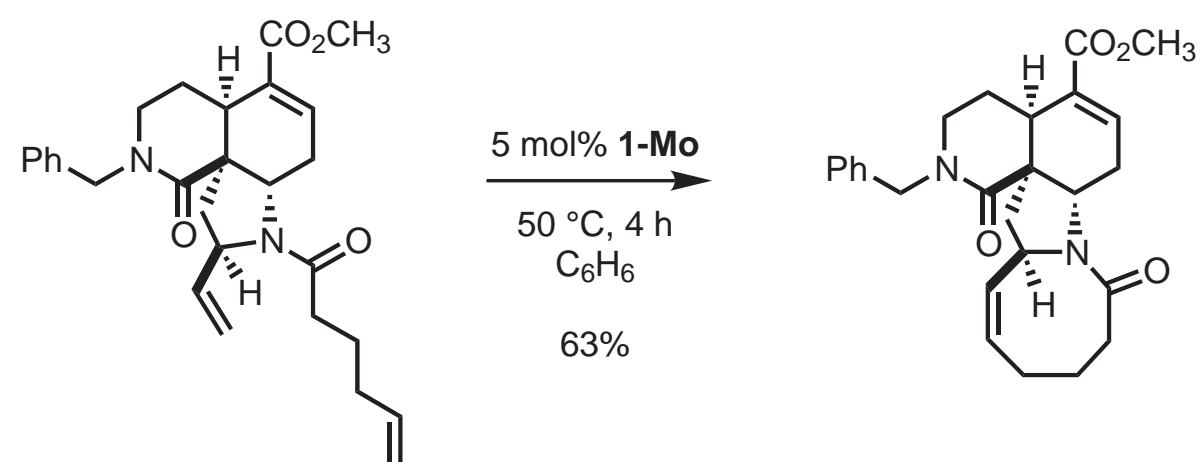
Zhongmin, X.; Johannes, C. W.; Houry, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 10302-10316.



- The use of RCM in construction of both the D and the E rings of Manzamine A has been reported:

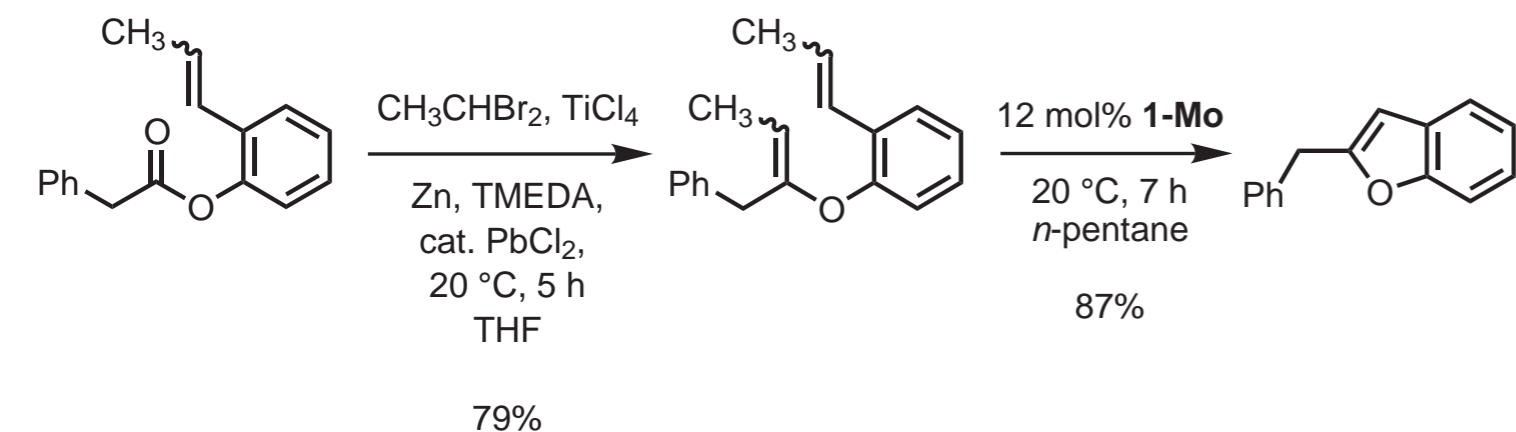
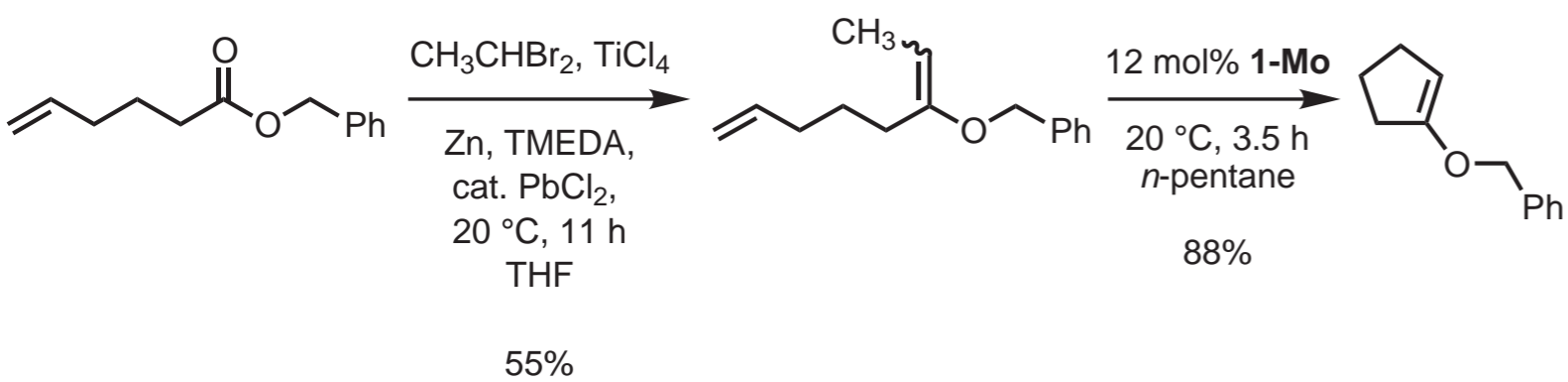


Borer, B. C.; Deerenberg, S.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191-3194.



Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691-694.

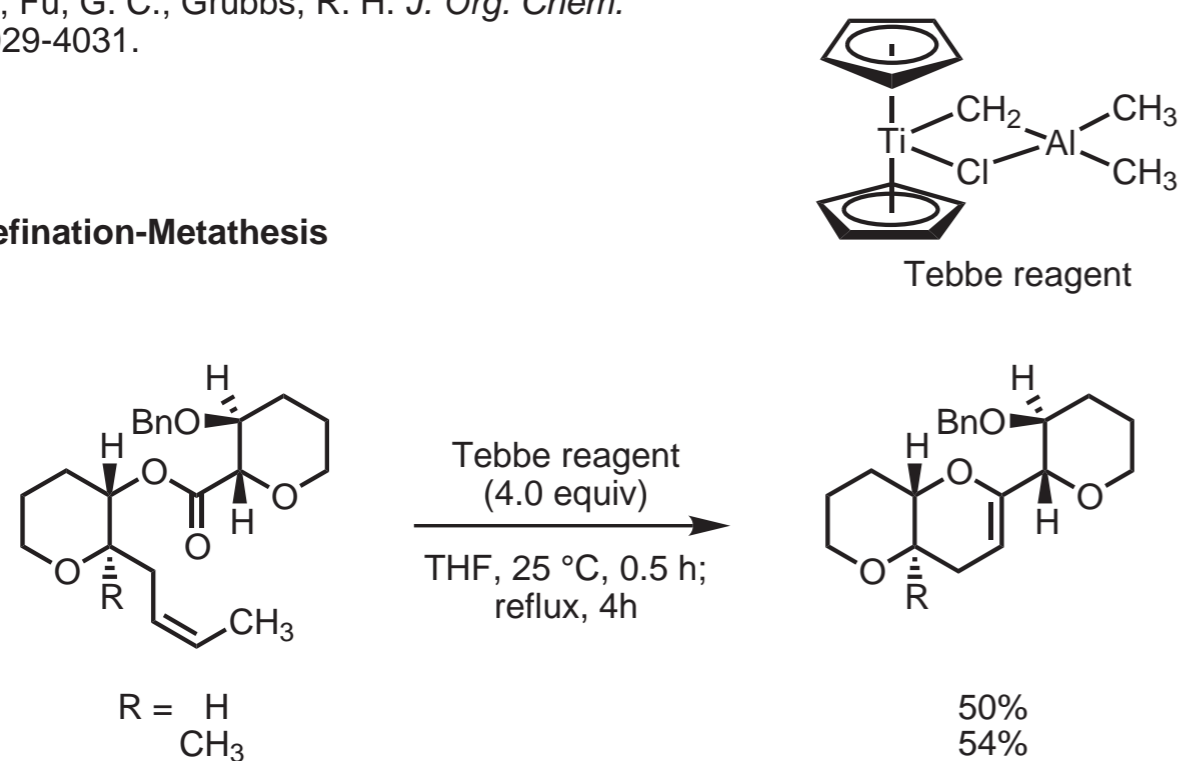
## Catalytic RCM of Olefinic Enol Ethers:



- Only catalyst **1-Mo** is effective for RCM of these substrates.

Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029-4031.

## Tandem Olefination-Metathesis

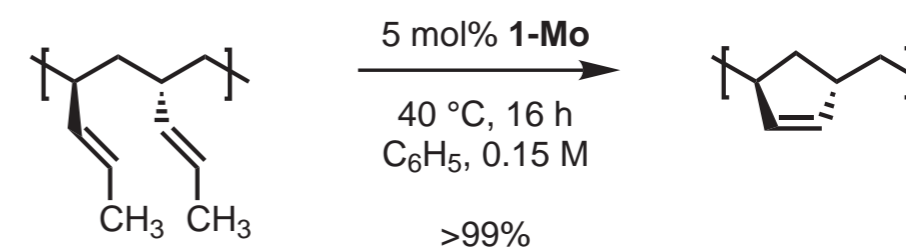
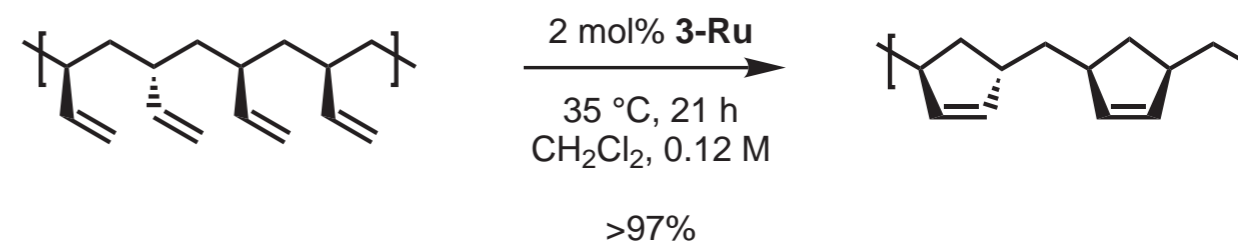


- Here, a Ti-alkylidene is used in RCM.

Nilolaou, K. C.; Postema, M. H. D.; Yue, E. W.; Nadin, A. *J. Am. Chem. Soc.* **1996**, *118*, 10335-10336.

## RCM of Polyolefins

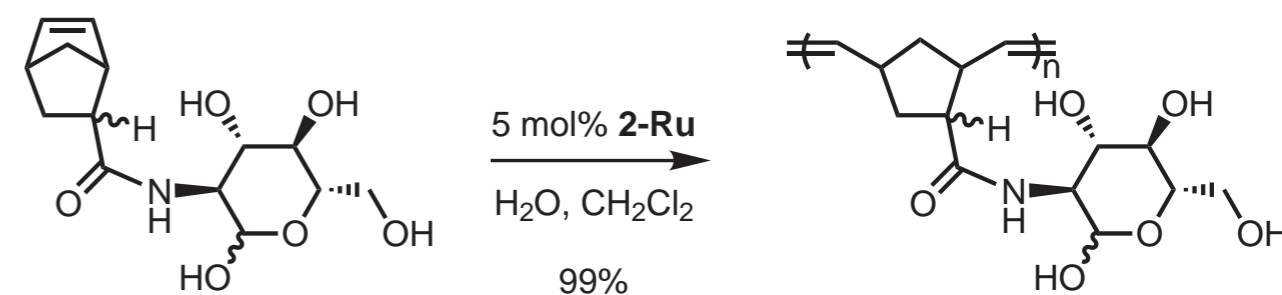
- RCM can be used within polymers containing suitably-spaced olefins (postpolymerization modification).



- Kinetic profiles suggest random site RCM leaving isolated olefins on the chain followed by catalyst migration up and down the chain until all olefins are cyclized.

Coates, G. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 229-230.

## Use of Functionalized Monomers in ROMP with Ru-Alkylidene 2



- The remarkable stability of the alkylidene **2-Ru** allows the ROMP of unprotected, sugar-substituted norbornene derivatives in an aqueous two-phase system.

Fraser, C.; Grubbs, R. H. *Macromolecules* **1995**, *28*, 7248-7255.

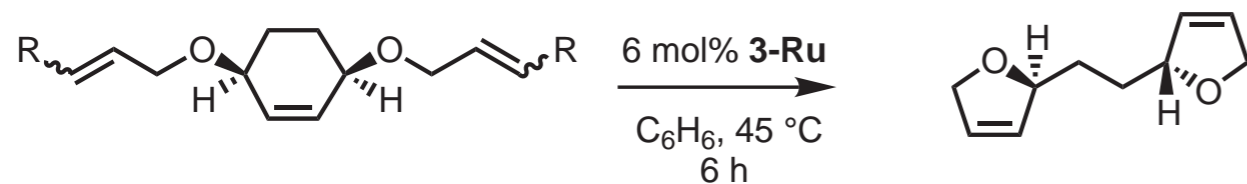
For leading references on applications of metathesis to polymerization see: Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036-2056 and references therein.

# Tandem Ring Opening-Ring Closing Metathesis of Cyclic Olefins

substrate	product	yield (%)	catalyst <b>3-Ru</b> (mol %)	conc. (M)	time (h)	temp. (°C)
		82	3	0.1	1.5	45
		90	5	0.1	2	60
		70	3	0.07	6	45
		68	6	0.04	2	45
		92	5	0.04	3	60

• Without sufficient ring strain in the starting cyclic olefin, competing oligomerization (via ADMET) can occur.

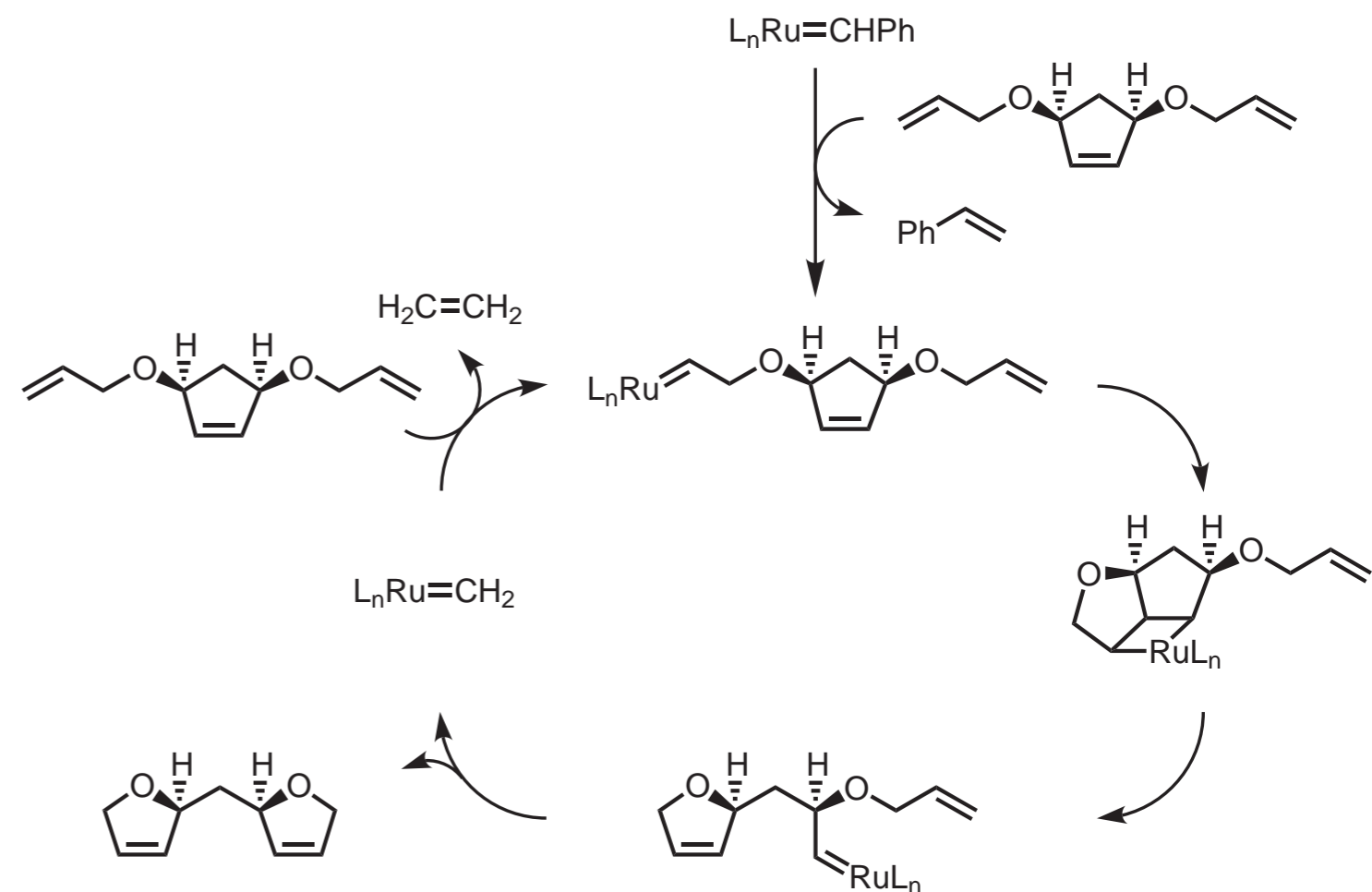
• Higher dilution favors intramolecular reaction:



R = H	0.12 M	16%
H	0.008 M	73%
CH <sub>3</sub>	0.2 M	42%

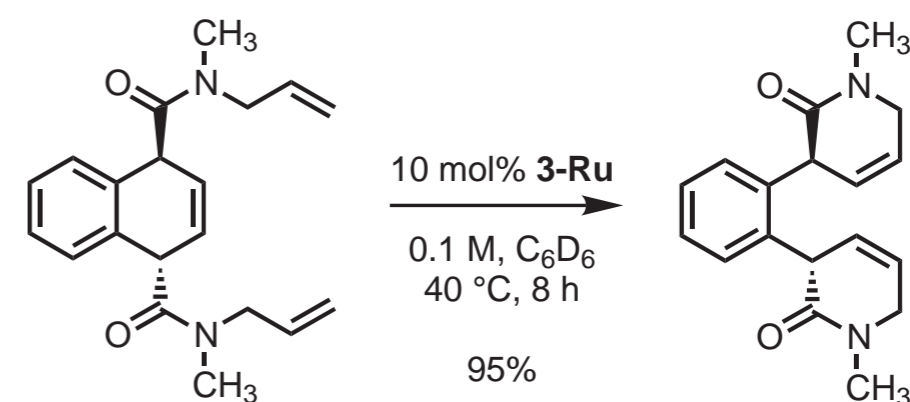
• The relative rate of intramolecular metathesis versus ADMET may be further increased by substitution of the acyclic olefin.

# Proposed Mechanism for Ring Opening-Ring Closing Metathesis:

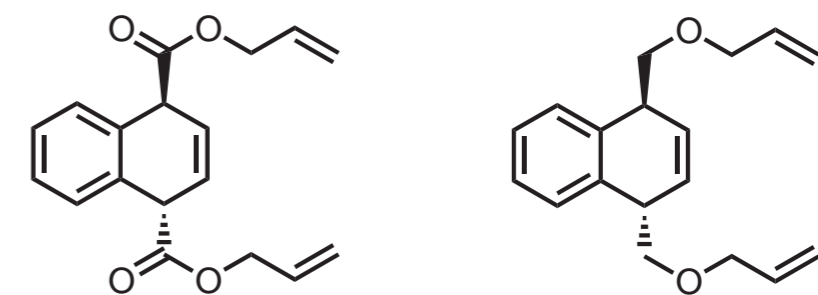


• Initial metathesis of the acyclic olefin is supported by the fact that substitution of this olefin decreases the rate of metathesis and by the beneficial effects of dilution upon the intramolecular manifold.

• Subtle conformational preferences within the substrate are key to the success of these transformations; as shown, *trans*-1,4-dihydronaphthalene diamide undergoes efficient ring opening-ring closing metathesis while the corresponding diester and diether derivatives do not.

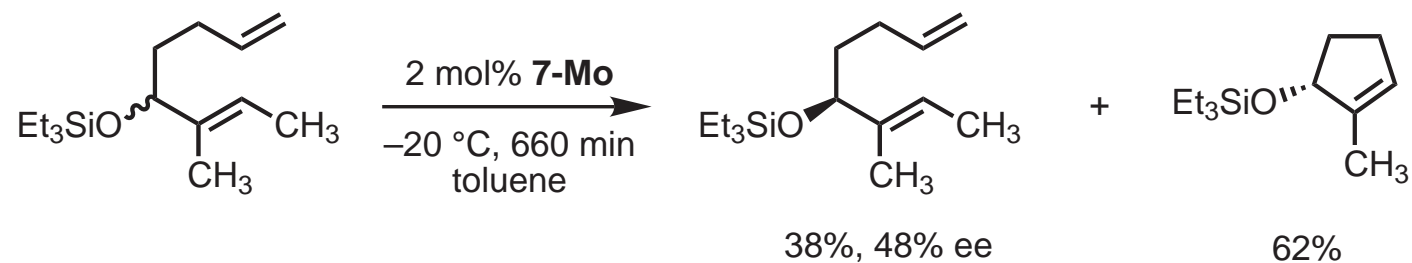
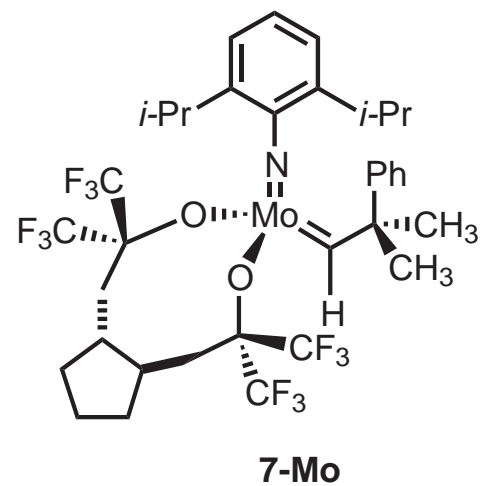


unreactive substrates:



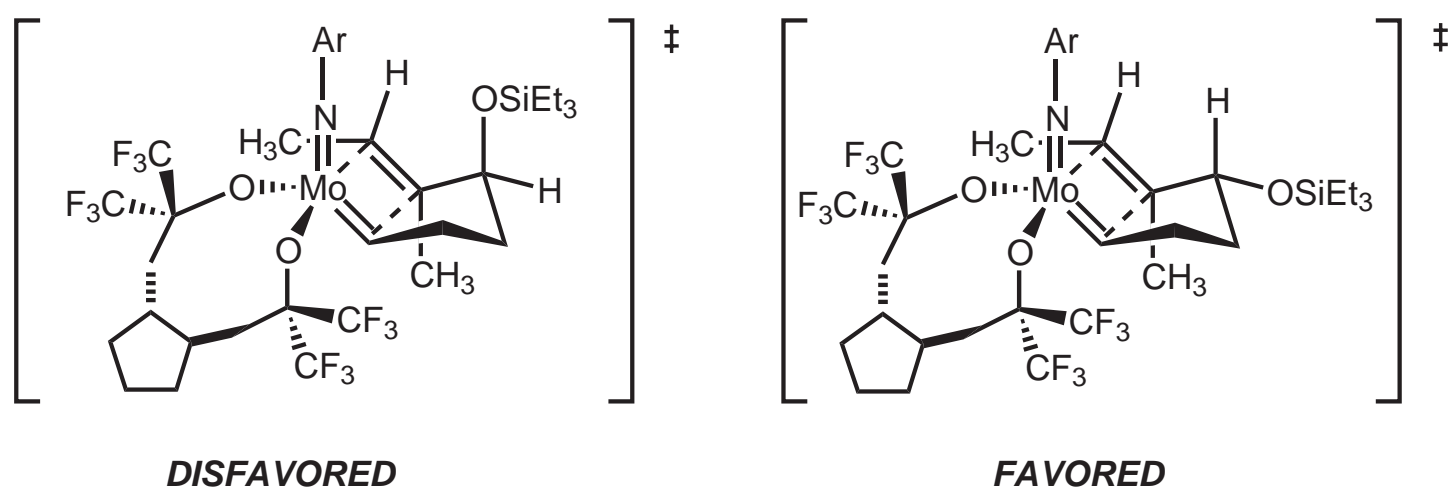
Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634-6640.

## Kinetic Resolution via Asymmetric RCM



- The first catalytic, asymmetric kinetic resolution via RCM was achieved, with low selectivity, using the chiral alkylidene **7-Mo**.

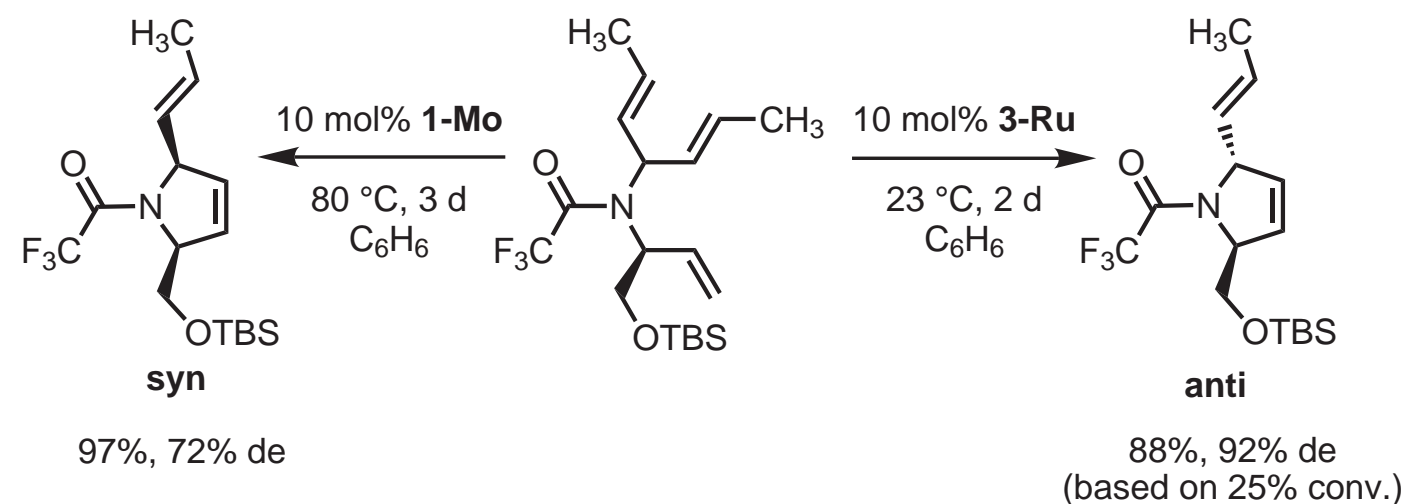
## Proposed Transition State Models for the Observed Selectivity



Ar = 2,6-(*i*-Pr)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>

Fujimura, O.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 824-832.  
Fujimura, O.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 2499-2500.

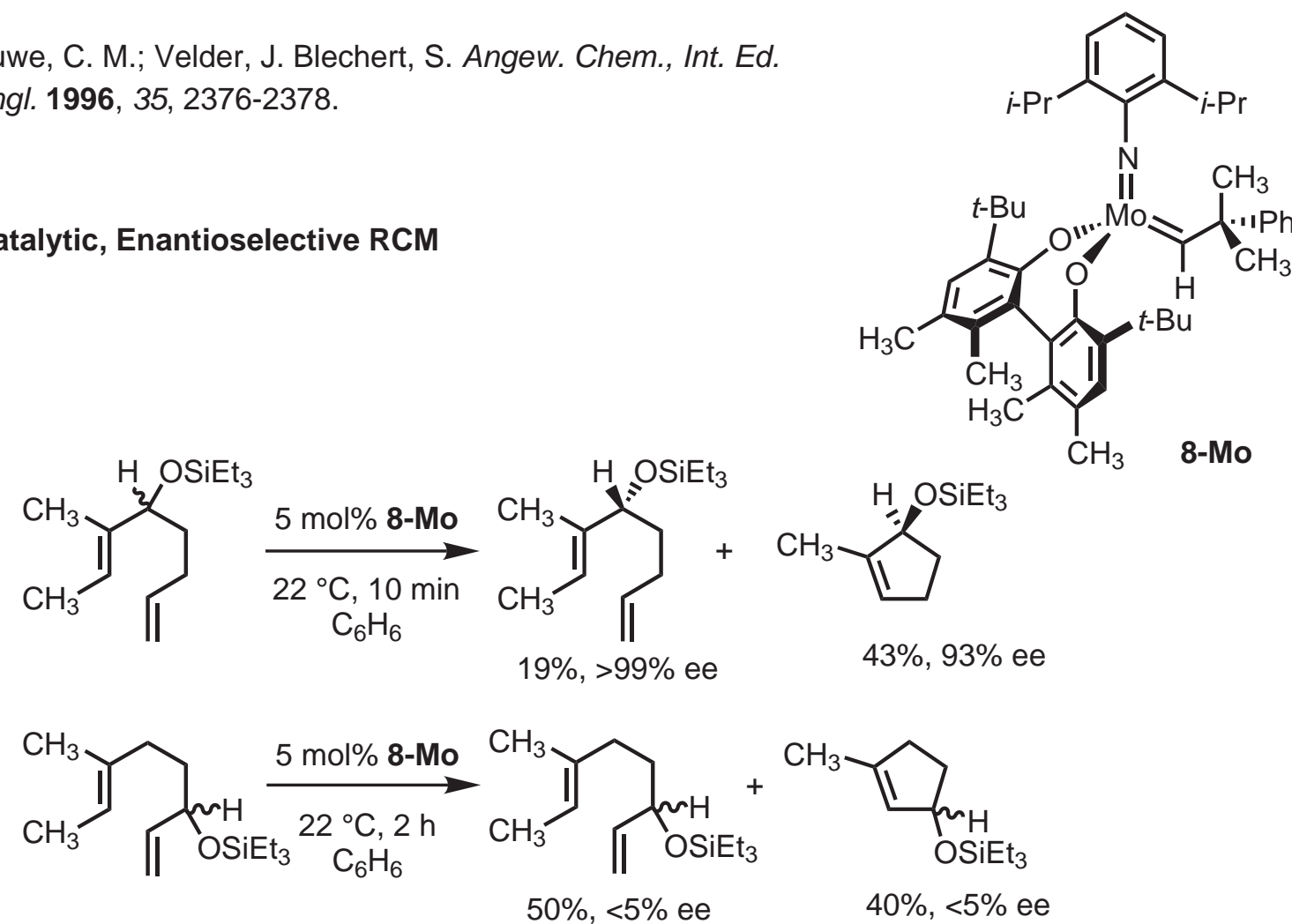
## RCM with Chiral Substrates



- The diastereoselectivity of the ring closure is maximized by ensuring initial metathesis of the olefin nearer the stereogenic center; this selectivity is achieved by substitution of the prochiral olefins.

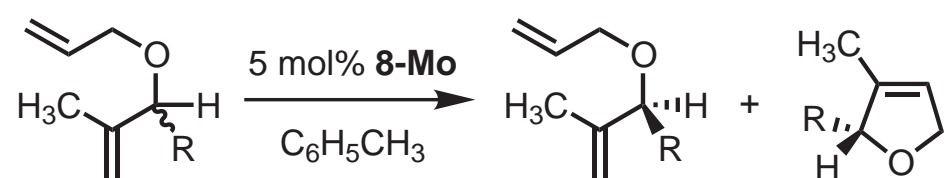
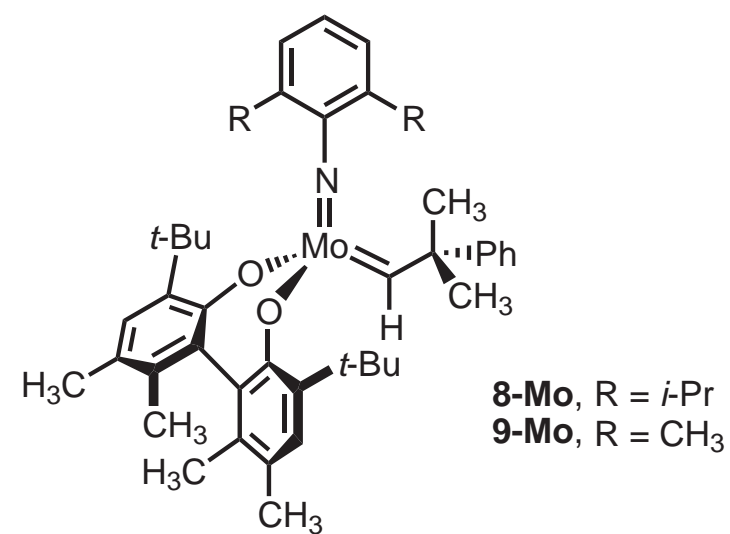
Huwe, C. M.; Velder, J. Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2376-2378.

## Catalytic, Enantioselective RCM



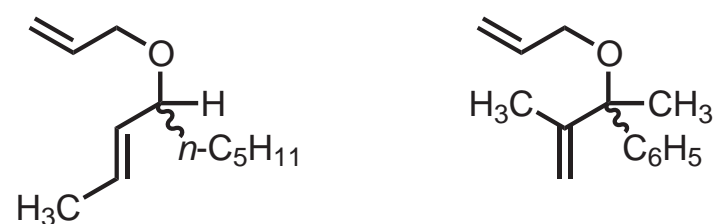
- Diastereodifferentiation occurs during formation or breakdown of the metallabicyclobutane intermediates and not during the initial metathesis step.

Alexander, J. B.; La, D. S.; Cefalo, D. R. Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041-4042.



R	temp. (°C)	time (h)	conv. (%)	SM ee (%)	<i>k</i> <sub>rel</sub>
<i>n</i> -C <sub>5</sub> H <sub>11</sub>	-25	6	63	92	10
<i>i</i> -C <sub>4</sub> H <sub>9</sub>	-25	10	56	95	23
<i>c</i> -C <sub>6</sub> H <sub>11</sub>	-25	7	62	98	17
<i>c</i> -C <sub>6</sub> H <sub>11</sub>	22	0.1	64	97	13
C <sub>6</sub> H <sub>5</sub>	-25	6	56	75	8

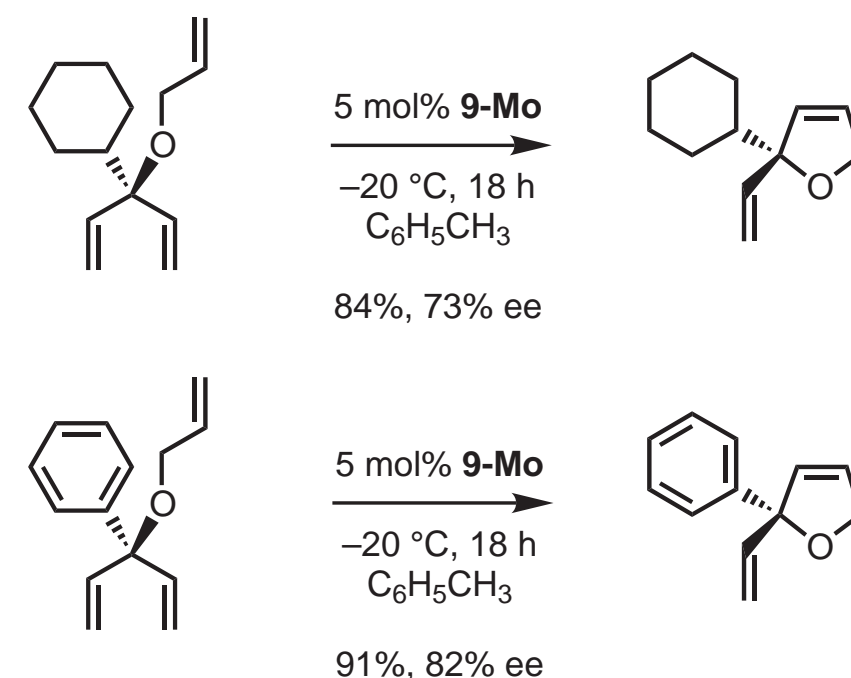
- Increasing the size of the  $\alpha$ -substituent can lead to greater selectivity.
- 1,2-disubstituted alkenes and tertiary ethers are not effectively resolved by either alkylidene **8-Mo** or **9-Mo**.



- The alkylidene catalysts **8-Mo** and **9-Mo** are very effective in catalytic, enantioselective desymmetrization processes, especially in the case of secondary allylic ethers.



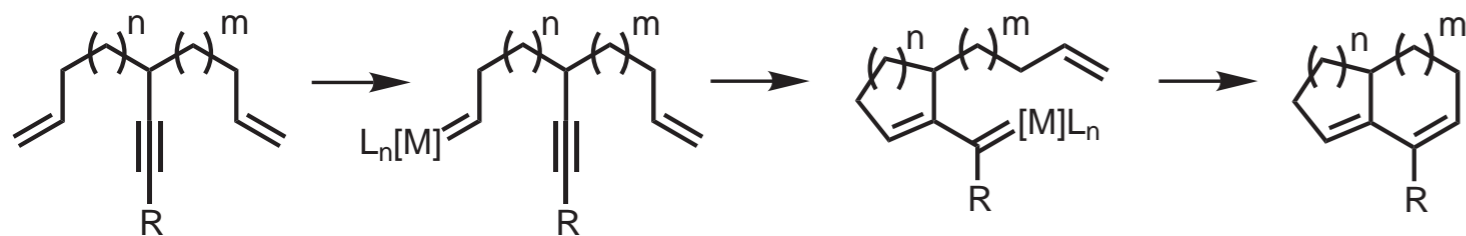
- Remarkably, this catalytic, asymmetric RCM can be carried out in the absence of solvent, with <5% dimer formation.
- The catalytic, enantioselective desymmetrization of tertiary allylic ethers requires the use of alkylidene **9-Mo**.



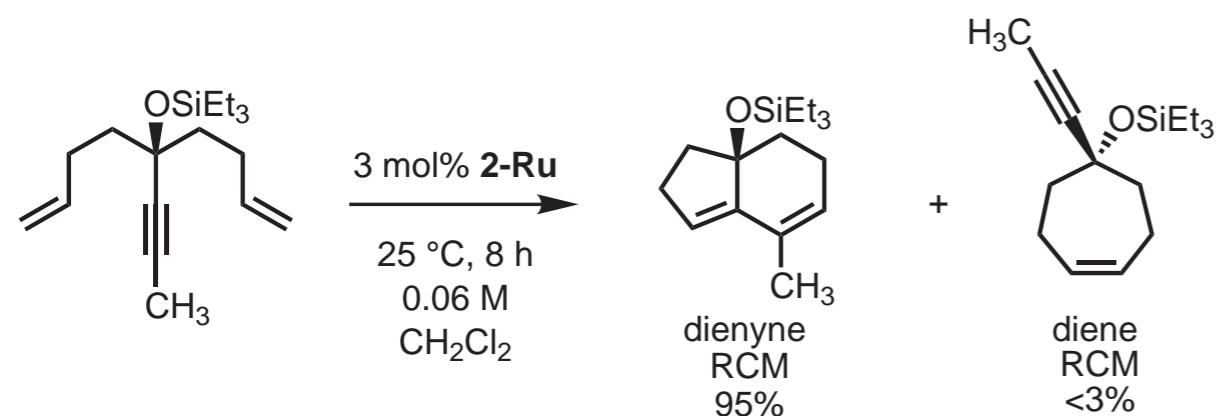
- It is believed that the stereodifferentiating step is the formation of the metallabicyclobutane intermediate; see: Alexander, J. B.; La, D. S.; Cefalo, D. R. Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4141-4042.

La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720-9721.

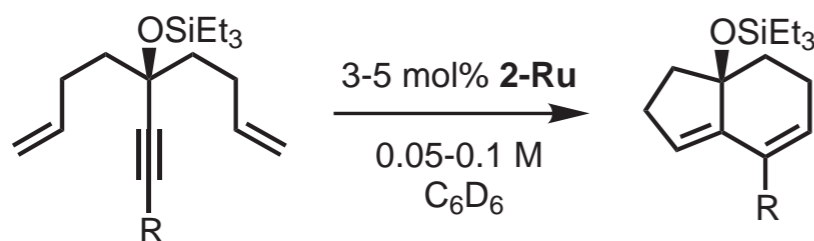
## Catalytic RCM of Dienynes: Construction of Fused Bicyclic Rings



- Fused [5.6.0], [5.7.0], [6.6.0], and [6.7.0] bicyclic rings have been successfully constructed by RCM of dienynes.



- The dienyne RCM is largely favored over the competing diene RCM.

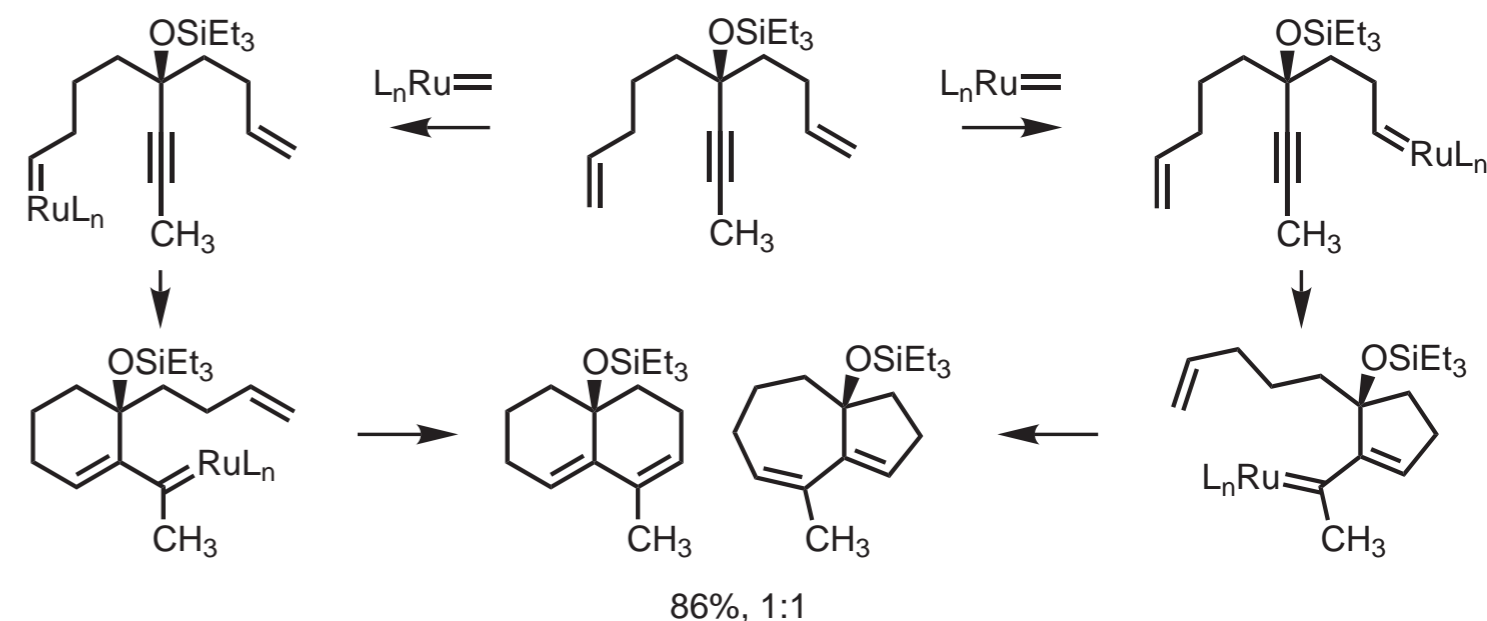


R	yield (%)	conditions
H	>98	23 °C, 15 min
CH <sub>3</sub>	95	23 °C, 8 h
<i>i</i> -Pr	78	60 °C, 4 h
<i>t</i> -Bu	NR	
Ph	96	60 °C, 3 h
CO <sub>2</sub> CH <sub>3</sub>	82	60 °C, 4 h
Si(CH <sub>3</sub> ) <sub>3</sub>	NR	
Sn( <i>n</i> -Bu) <sub>3</sub>	NR	
Cl, Br, I	NR	

- Mo-, W- or Ti-based catalysts are not effective for the above transformations.
- Reaction rates decrease as the size of the acetylene substituent increases.
- Substrates containing heteroatoms directly attached to the acetylene do not cyclize.

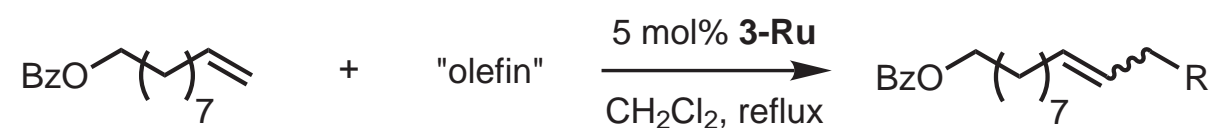
substrate	product	yield (%)	mol% 2-Ru	time (h)	conc. (M)	temp. (°C)
		88	6	8	0.06	65
		83	3	6	0.03	65
		78	15	1.5	0.01	100
		89	15	12	0.05	65
		88	3	6	0.05	65

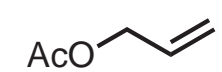
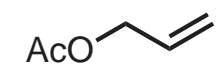



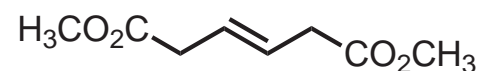
- Regiochemical control within unsymmetrical substrates is achieved by substitution of the olefin required to undergo metathesis last.
- Unsymmetrical substrates containing equally reactive olefins produce a mixture of bicyclic products:



Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073-1081.

## Cross-Metathesis Reactions



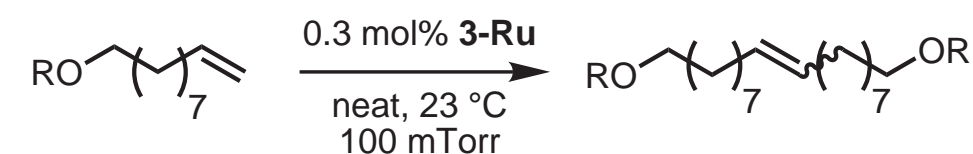
"olefin"	R	equiv	yield (%)	<i>E:Z</i>
	OAc	1	59	5.7:1
	OAc	4	81	3:1
	OAc	2	89	4.7:1
	O <i>t</i> -Bu	2	90	7:1
	NHBoc	4	71	3:1
	CO <sub>2</sub> CH <sub>3</sub>	2	74	3.3:1

• The use of two equivalents of *cis*-2-butene-1,4-diol diacetate was found to be more efficient than simply using one, two, or four equivalents of allyl acetate.

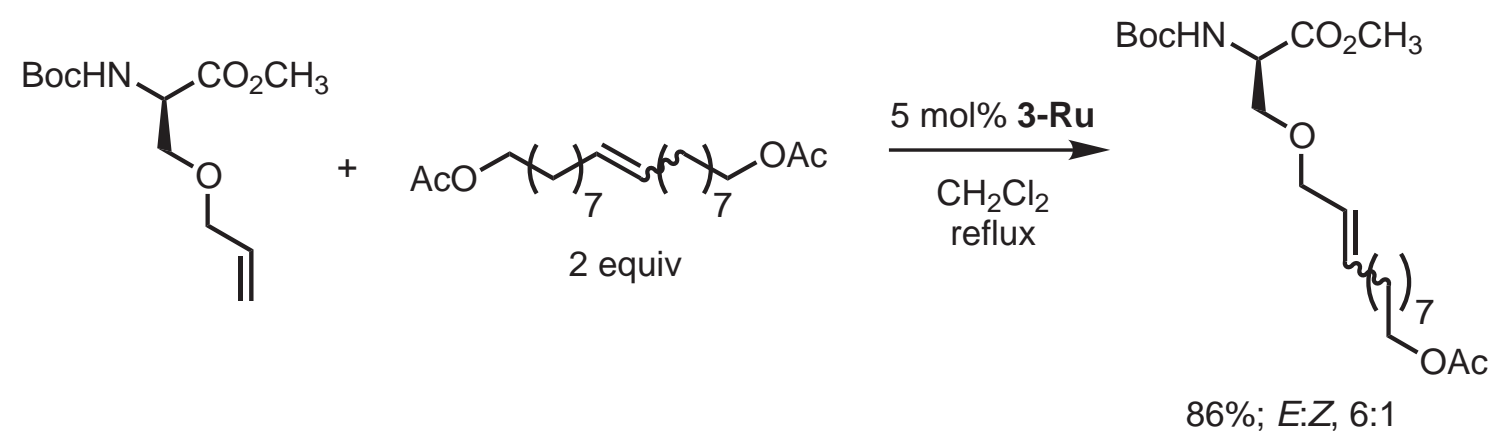
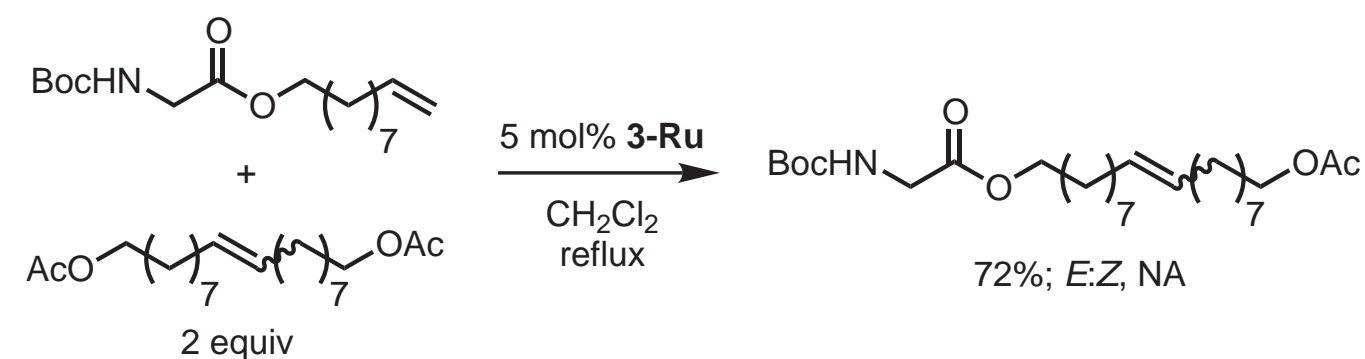
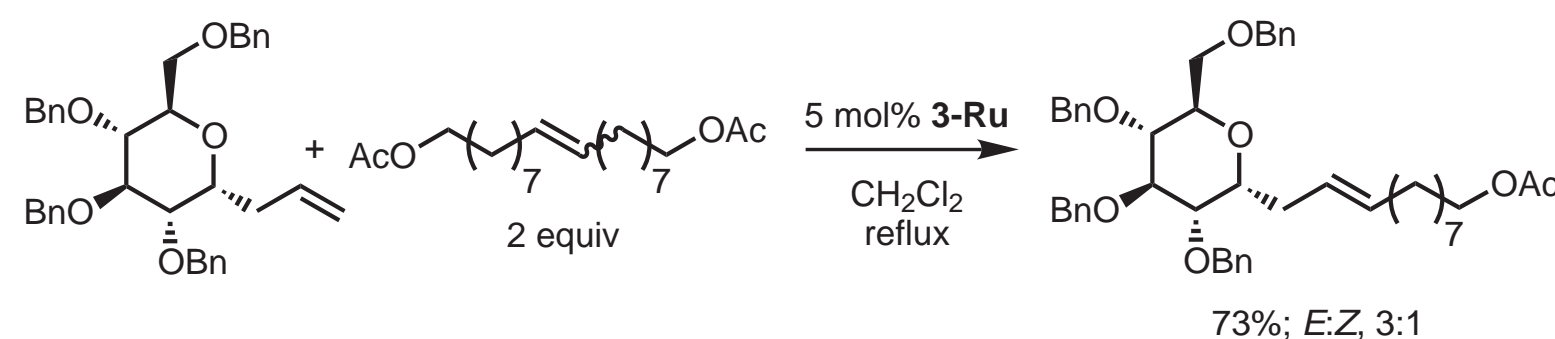
• The use of disubstituted olefins in cross-metathesis reactions minimizes the formation of a methylidene intermediate (L<sub>4</sub>Ru=CH<sub>2</sub>), which is a less stable catalyst.

• The disubstituted alkene may be used as solvent to increase the yield of cross metathesis.

- An efficient two-step procedure for cross metathesis of terminal olefins involves initial homodimerization of the more readily available terminal olefin, followed by use of 2 equivalents of this homodimer in cross metathesis with the more valuable terminal olefin.

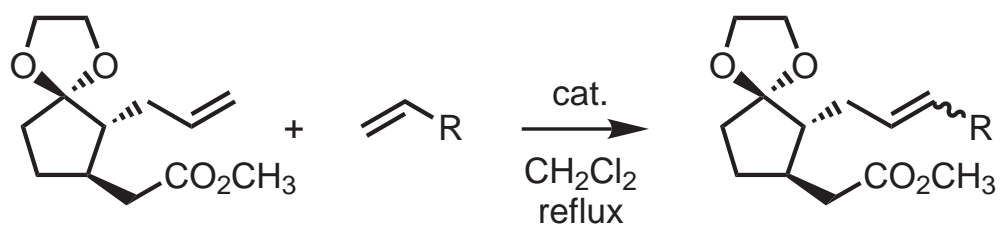


R	yield (%)	<i>E:Z</i>
Bz	94	4:1
Ac	95	4:1
<i>N</i> -Boc-Gly	93	4:1



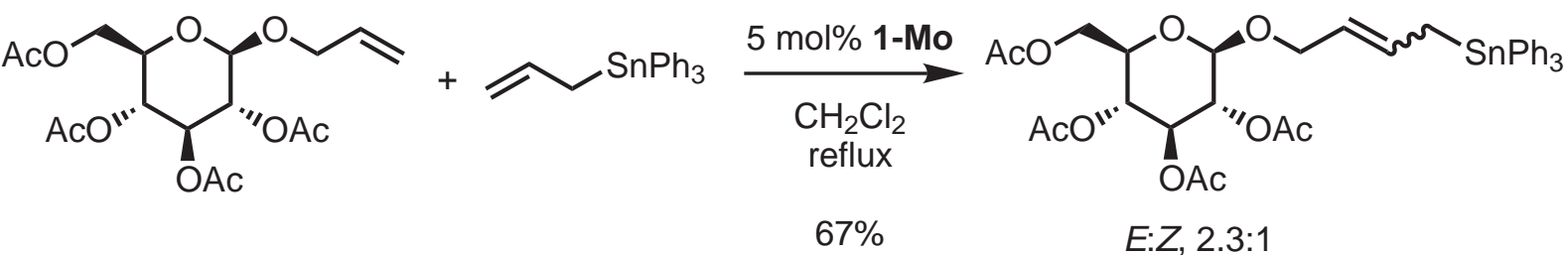
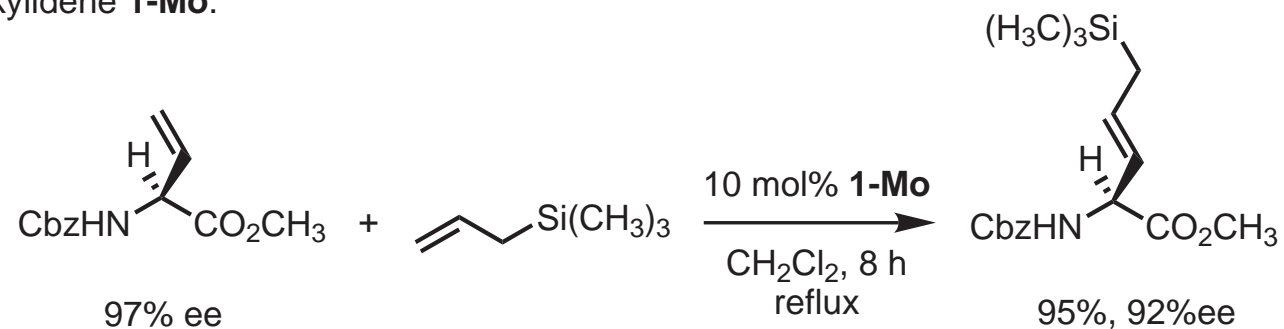
O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 7427-7430.

Other Cross-Metathesis Examples:



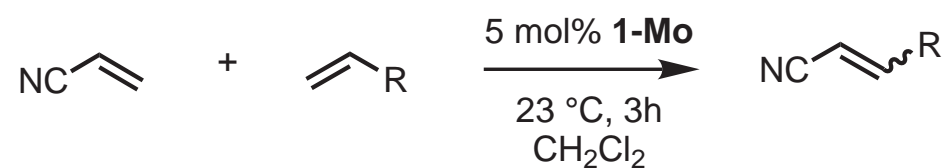
R	equiv	cat.	mol% cat.	time (h)	yield (%)	E:Z
CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	1.5	<b>1-Mo</b>	5	5	83	2:1
CH <sub>2</sub> OAc	2.0	<b>3-Ru</b>	5	20	73	2:1
CH <sub>2</sub> CH <sub>2</sub> OH	1.5	<b>3-Ru</b>	8	8	70	6:1
CN	2.0	<b>1-Mo</b>	5	2	92	<b>0:100</b>
CH <sub>2</sub> <i>t</i> -Bu	1.5	<b>1-Mo</b>	5	3	65	4:1

- Cross-coupling reactions with allyl acetate and homoallylic alcohol only proceed with alkylidene **3-Ru**, whereas cross-coupling with acrylonitrile was only successful with alkylidene **1-Mo**.



Brümmer, O.; Rückert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441-446.

Feng, J.; Schuster, M.; Blechert, S. *Synlett* **1997**, 129-130.

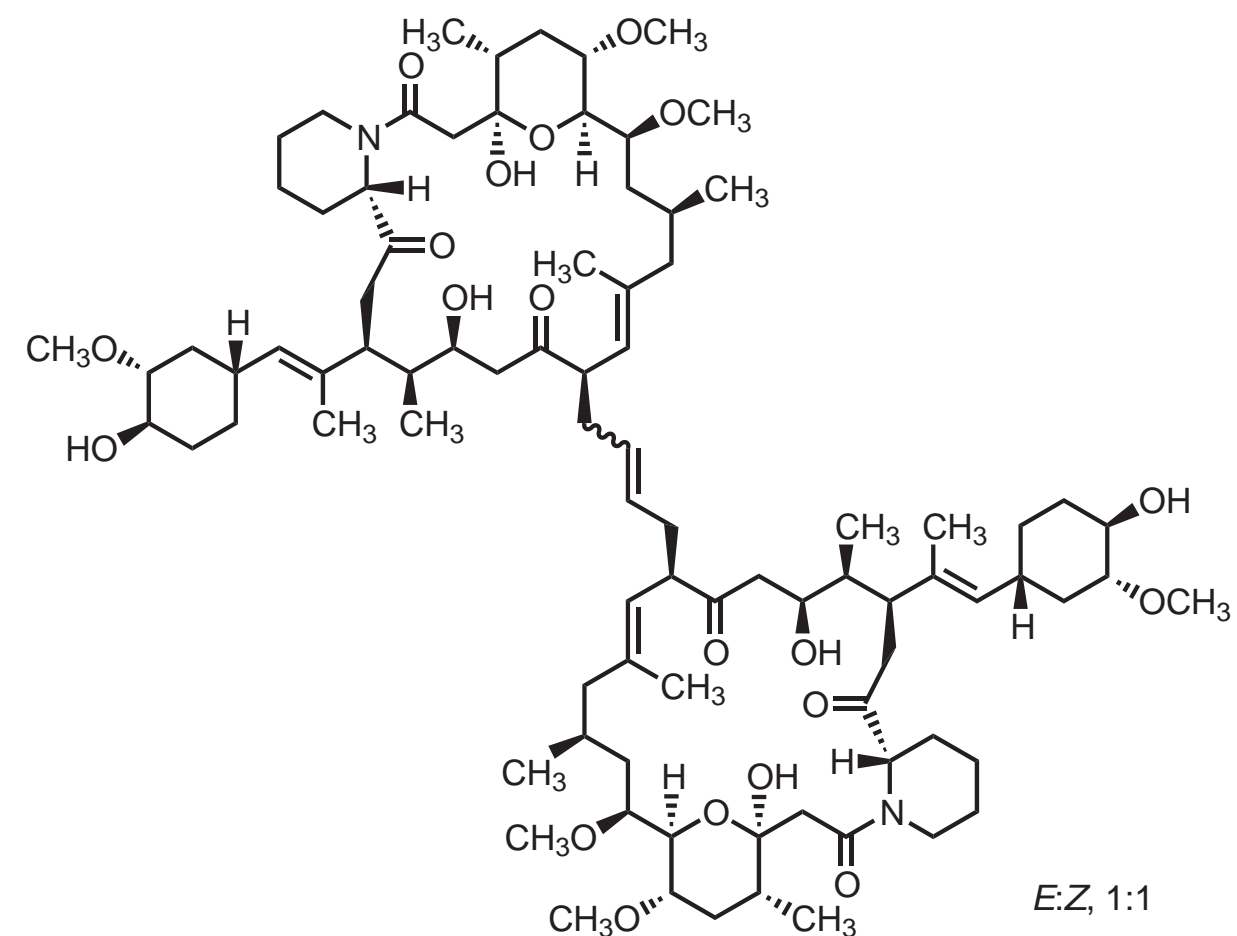
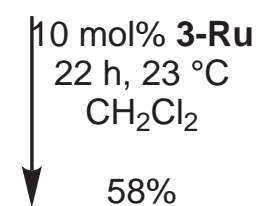
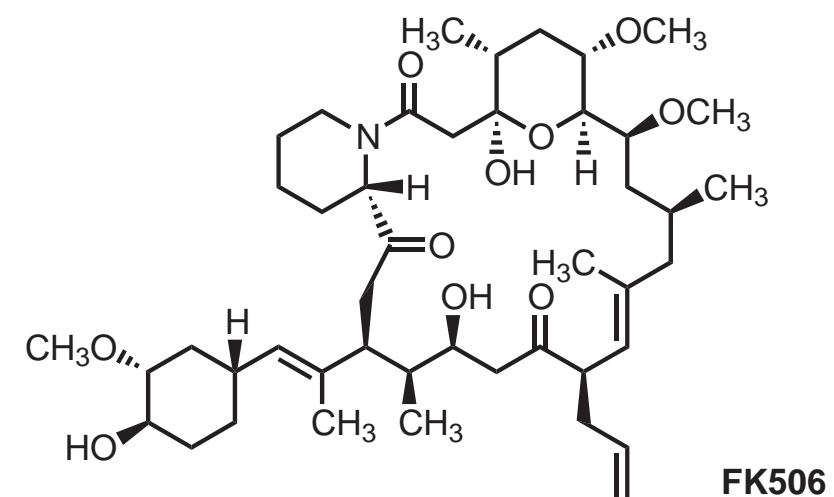


R	yield (%)	E:Z
CH <sub>2</sub> Si(CH <sub>3</sub> ) <sub>3</sub>	76	1:3
(CH <sub>2</sub> ) <sub>3</sub> OBn	60	1:7.6
(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> Bn	44	1:5.6

- A clear rationale for the unique and high *cis*-selectivity of acrylonitrile is not available.

Crowe, W. E.; Goldberg, D. R. *J. Am. Chem. Soc.* **1995**, *117*, 5162-5163.

Dimerization of FK506



Diver, S. T.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 5106-5109.

## Ring Opening Cross-Metathesis:

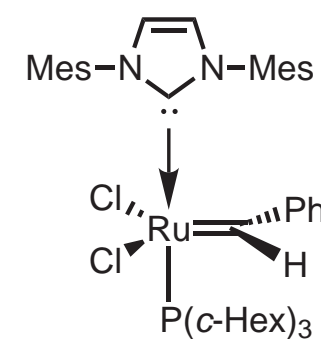
substrate	product	alkene <sup>a</sup>	solvent	mol % cat. <sup>b</sup>	time	yield	<i>E,E:E,Z</i>
		A	C <sub>6</sub> H <sub>6</sub>	6	96	94	2:1
		B	C <sub>6</sub> H <sub>6</sub>	2	14	85	2:1
		C	CH <sub>2</sub> Cl <sub>2</sub>	8 <sup>c</sup>	3	73	1.5:1
		A	CH <sub>2</sub> Cl <sub>2</sub>	2	89	15	NA

<sup>a</sup>25 °C; 1.5 Equivalents of alkene used: A = *trans*-1,4-dimethoxybut-2-ene; B = *trans*-hex-3-ene; C = *cis*-hex-3-ene. <sup>b</sup>Cat. = **2-Ru**. <sup>c</sup>Cat. = **3-Ru**.

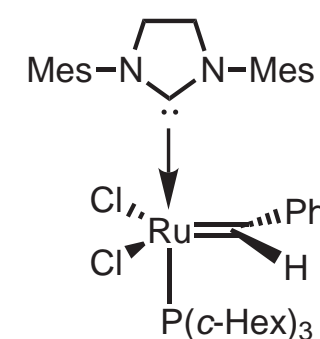
- In these cases a preference for the *E*-olefin geometry is observed in ring opening metathesis.
- Higher yields were achieved by the slow addition of the cyclic alkene to a solution of the 1,2-disubstituted alkene.
- Faster and more efficient ring opening cross metathesis was observed using *cis*-hex-3-ene vs. *trans*-hex-3-ene.

Schneider, M. F.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 411-412.

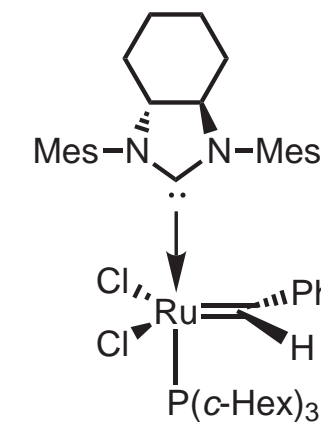
## New Ru-Based Catalysts:



**10-Ru**



**11-Ru**



**12-Ru**

substrate <sup>a</sup>	product	time (h)	yield of product (%) using catalyst: <sup>b</sup>				
			<b>1-Mo</b>	<b>3-Ru</b>	<b>10-Ru</b>	<b>11-Ru</b>	<b>12-Ru</b>
		1	37	0	100	100	100
		24	93	0	40 <sup>c</sup>	31	55
		1.5	52	0	95	90	87
		0.2	0	0	NA	100	100

<sup>a</sup>E = CO<sub>2</sub>Et. <sup>b</sup>5 mol% of catalyst, CD<sub>2</sub>Cl<sub>2</sub>, reflux. <sup>c</sup>1.5 h.

- Alkylidenes **11-** and **12-Ru** are the most reactive Ru-based catalysts.
- In the case of **11-** and **12-Ru** as little as 0.05 mol% is required for efficient RCM.

Scholl, M.; Ding, S.; Lee, C.-W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956.

Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247-2250.

For the first Ru-based metathesis catalyst employing the Arduengo carbene ligand, see:  
Weskamp, T.; Schattenmann, W. C.; Spiegler, M.; Herrmann, W. A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2490-2493.

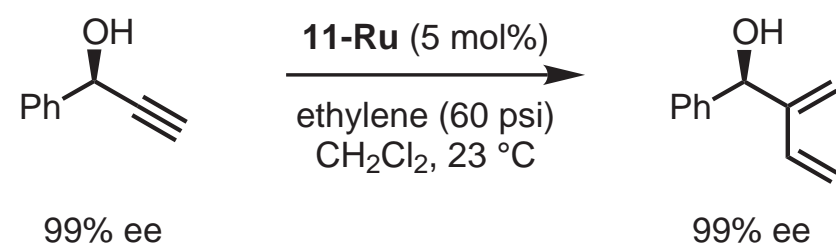
## Ethylene-Alkyne Cross-Metathesis

- **11-Ru** outperforms **3-Ru** in both rate and overall conversion in the cross-metathesis of ethylene and alkynes.

substrate	product	time (h)	yield (%)
		R = H 2.0 R = Ac 2.0 R = TBS 8.5	73 92 91
		16	77
		4.0	69
		4.0	91
		6.0	72

<sup>a</sup>Reactions conducted in CH<sub>2</sub>Cl<sub>2</sub> at 23 °C using 5 mol% of **11-Ru** at 60 psi of ethylene pressure.

- Reactions conducted at 1 atm of ethylene pressure typically gave low conversions even after extended reaction times.
- The more reactive imidazolylidene **11-Ru** can tolerate free hydroxyl groups and coordinating functionality at the propargylic and homopropargylic positions.
- Chiral propargylic alcohols afford chiral diene products without loss of optical purity:



Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, 2, 2271-2274.

## Enyne Metathesis Reactions Catalyzed by PtCl<sub>2</sub>

substrate	product	yield
		96%
		70%
		54%
		80%

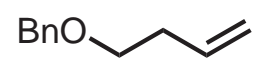
<sup>a</sup>Reactions conducted in toluene at 80 °C using 4-10 mol% of PtCl<sub>2</sub>

- In most cases commercial PtCl<sub>2</sub> was used as received.
- A cationic reaction pathway, involving the complexation of cationic Pt(II) with the alkyne, has been proposed.
- Remote alkenes are unaffected.

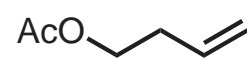
Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, 122, 6785-6786.

## Synthesis of Functionalized Olefins by Cross Metathesis and Ring-Closing Metathesis

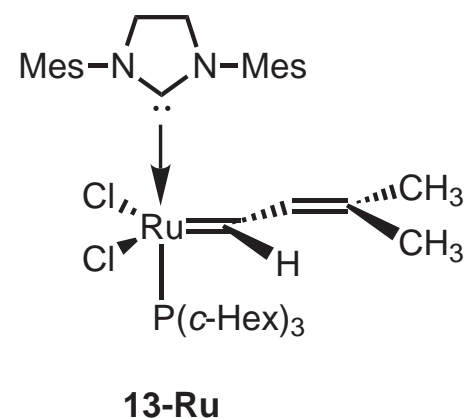
- Cross-metathesis reaction with  $\alpha$ -functionalized olefins:



**A**



**B**



$\alpha$ -functionalized olefin (equiv)	alkene	product <sup>a</sup>	yield (%)	<i>E</i> : <i>Z</i>
(2.0)	<b>A</b>		91	4.5:1
(0.5)	<b>B</b>		92	>20:1
(2.0)	<b>B</b>		62	1.1:1
(2.0)	<b>B</b>		95	>20:1
(4.0)	<b>B</b>		55	5:1
(2.0)	<b>B</b>		81	11:1

<sup>a</sup>Reactions conducted with 5 mol% **13-Ru**.

- Vinyl halides, phthalimides, sulfones, acetates, ethers, alkyltins, and acrylonitriles are not reactive in cross-metathesis reactions using **13-Ru**, perhaps due to the formation of a Fischer carbene complex which either rapidly decomposes or fails to react further.

## RCM of functionalized dienes

diene	product	yield (%)
		49
		0
		97
		86
		93

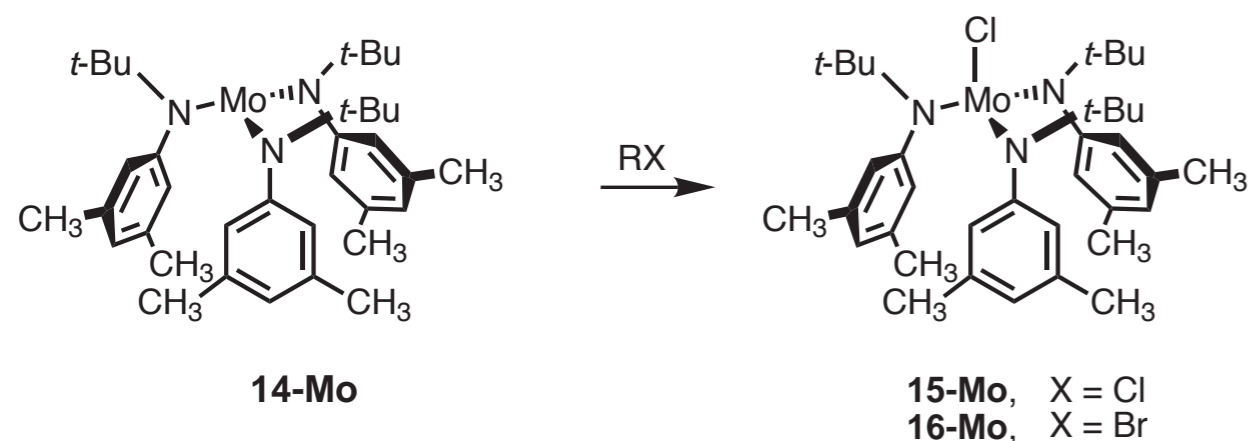
<sup>a</sup>Reactions conducted with 5 mol% **13-Ru**.

- Substrates containing both allyl and vinyl ethers provide RCM products while no RCM products are observed if vinyl ethers alone are present.
- $\alpha,\beta$ -Unsaturated lactones and enones of various ring sizes are produced in good to excellent yields.

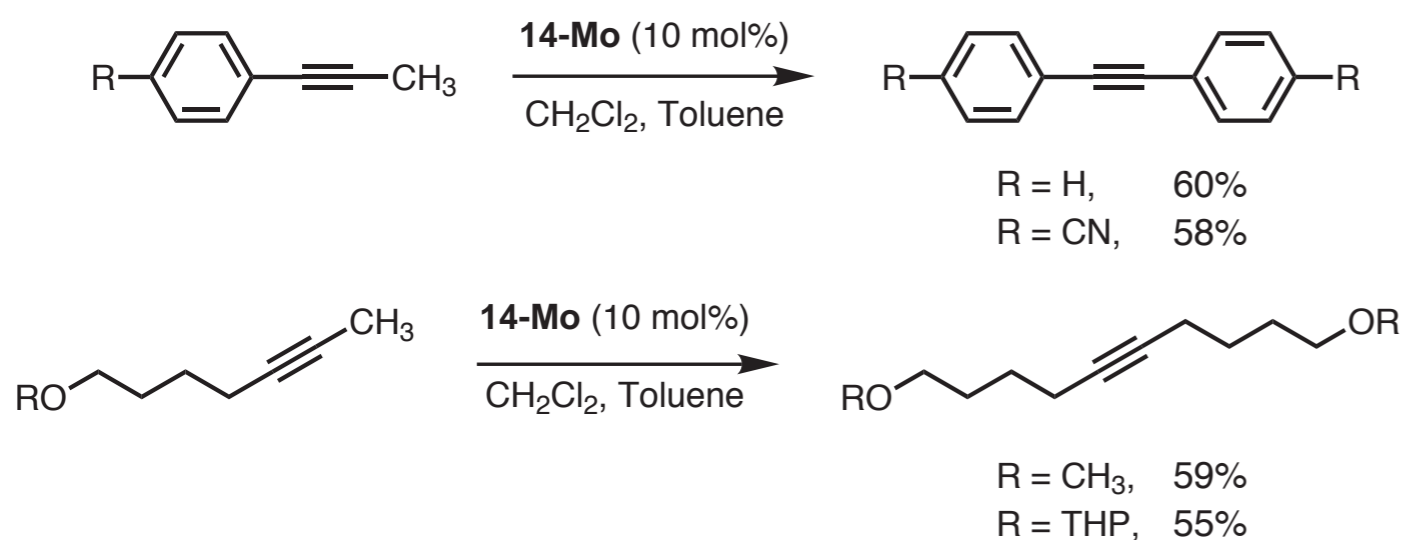
Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784.

## Metathesis of Alkynes and Diynes

- Inspired by the activation of the triple bond of molecular nitrogen with molybdenum complexes of the general type  $\text{Mo}[\text{N}(\text{t-Bu})\text{Ar}]_3$  (see: Laplaza, C. E.; Cummins, C. C. *Science*, **1995**, 268, 861), the reactivity of this class of molybdenum catalysts toward alkynes was explored.



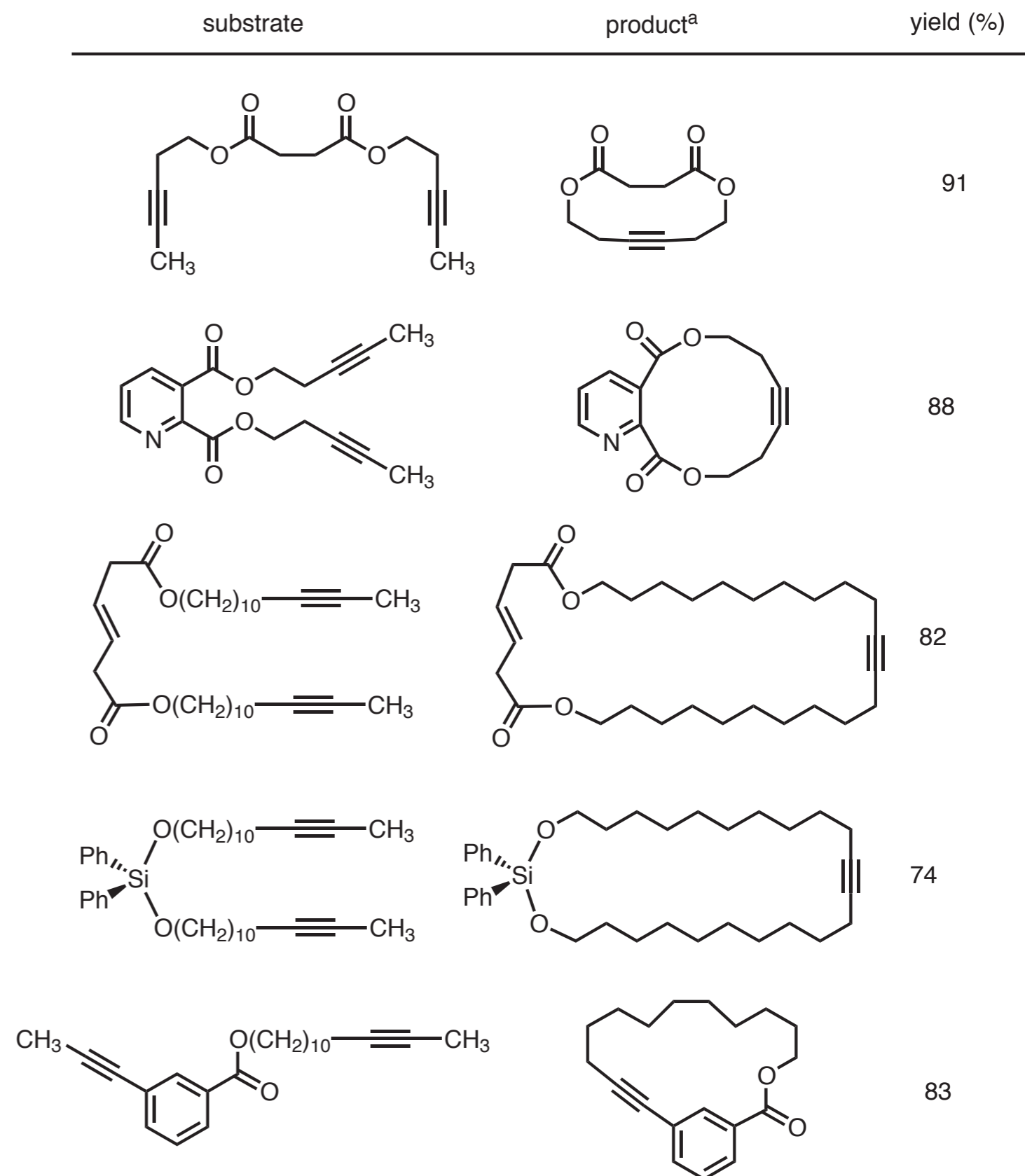
- Oxidation of the Mo(III)-precatalyst **14-Mo** occurs in situ upon addition of ~25 equivalents of additives such as  $\text{CH}_2\text{Cl}_2$ ,  $\text{CH}_2\text{Br}_2$ ,  $\text{CH}_2\text{I}_2$ , and  $\text{BnCl}$ .
- Alkyne metathesis may be achieved with equal efficiency either by in situ oxidation of precatalyst **14-Mo** or by use of pure Mo(IV)-catalysts **15-Mo** and **16-Mo**.



- Catalyst **15-Mo** is sensitive to acidic protons such as those of secondary amides.
- Use of  $\text{CH}_2\text{Cl}_2$  as the reaction solvent or the addition of ~25 equivalents of  $\text{CH}_2\text{Cl}_2$  per mol of **14-Mo** in toluene are equally effective.
- Catalysts **15-Mo** and **16-Mo** tolerate functional groups such as esters, amides, thioethers, basic nitrogen atoms, and polyether chains, many of which are incompatible with the tungsten alkylidyne catalysts previously used.

## RCM of Diynes

- Efficient synthesis of  $\geq 12$ -membered rings containing internal alkynes can be achieved with **15-Mo**.



<sup>a</sup>Reactions conducted in toluene at 80 °C for 20-48h; **15-Mo** was generated in situ from **14-Mo** and  $\text{CH}_2\text{Cl}_2$  (~25 equiv).

Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, 121, 9453-9454.