Reviews:

Hoveyda, A. H.; Khan, R. K. M.; Torker, S.; Malcolmson, S. J. **2013** (We gratefully acknowledge Professor Hoveyda and co-workers for making this review available to us ahead of print).

Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 4490–4527.

Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117–7140.

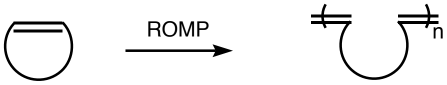
Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633.

Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 1900–1923.

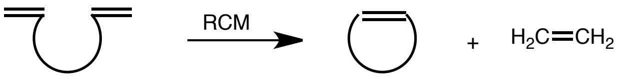
Fürstner, A. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3012–3043.

Ring-Opening Metathesis Polymerization (ROMP):



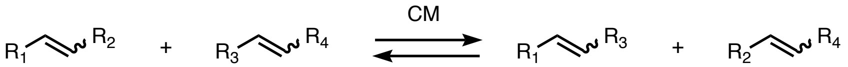
- ROMP is thermodynamically favored for strained ring systems, such as 3-, 4-, 8- and larger-membered compounds.
- When bridging groups are present (bicyclic olefins) the ΔG of polymerization is typically more negative as a result of increased strain energy in the monomer.
- Block copolymers can be made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

Ring-Closing Metathesis (RCM):



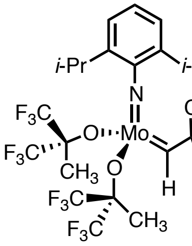
- The reaction can be driven to the right by the loss of ethylene.
- The development of well-defined metathesis catalysts that are tolerant of many functional groups yet reactive toward a diverse array of olefinic substrates has led to the rapid acceptance of the RCM reaction as a powerful method for 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.

Cross Metathesis (CM):

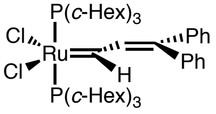


- Self-dimerization reactions of the more valuable alkene may be minimized by the use of an excess of the more readily available alkene.

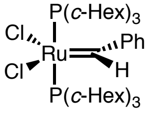
Catalysts



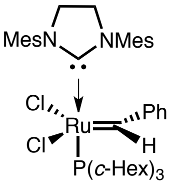
1-Mo



2-Ru



3-Ru
(Grubbs' 1st Generation Catalyst)



4-Ru
(Grubbs' 2nd Generation Catalyst)

- The well-defined catalysts shown above 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 CM processes and show remarkable tolerance toward many different organic functional groups.
- The electron-rich tricyclohexyl phosphine ligands of the d^6 Ru(II) metal center in alkylidenes **2-Ru** and **3-Ru** leads to increased metathesis activity. The NHC ligand in **4-Ru** is a strong σ-donor and a poor π-acceptor and stabilizes a 14 e^- Ru intermediate in the catalytic cycle, making this catalyst more effective than **2-Ru** or **3-Ru**.
- 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. All of the catalysts above are commercially available, but **1-Mo** is significantly more expensive.

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

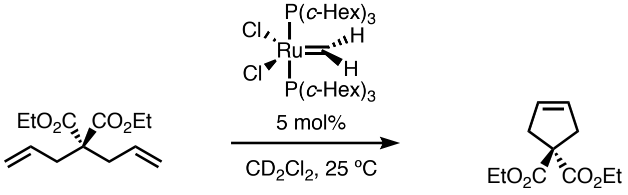
M. Movassaghi, L. Blasdel

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.

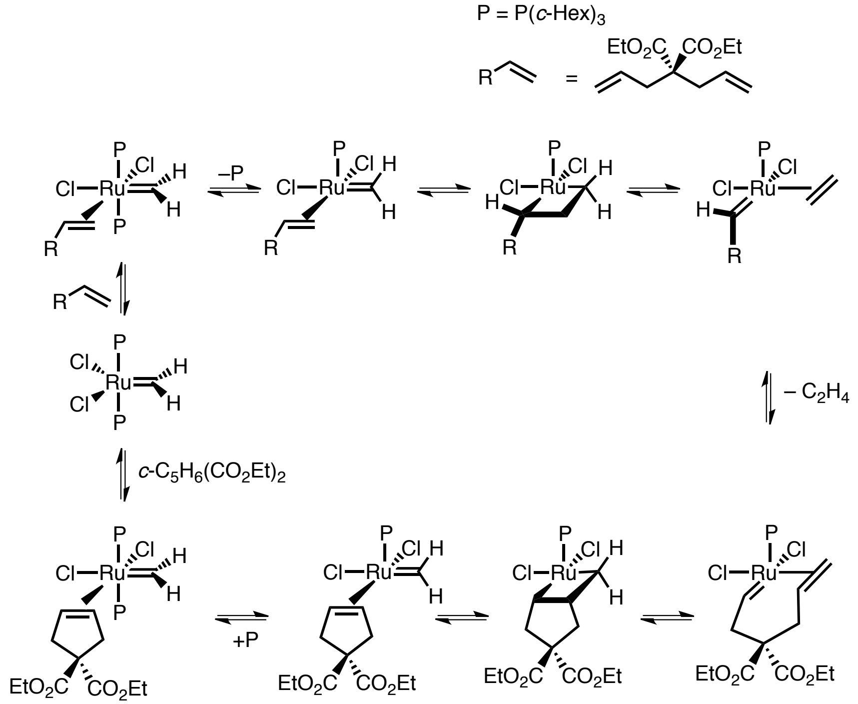
- The "associative" mechanism assumes that an 18-electron olefin complex is formed which undergoes metathesis to form the cyclized product.

- Addition of 1 equivalent of phosphine (with respect to catalyst) decreases the rate of the reaction by as much as 20 times, supporting the dissociative mechanism.

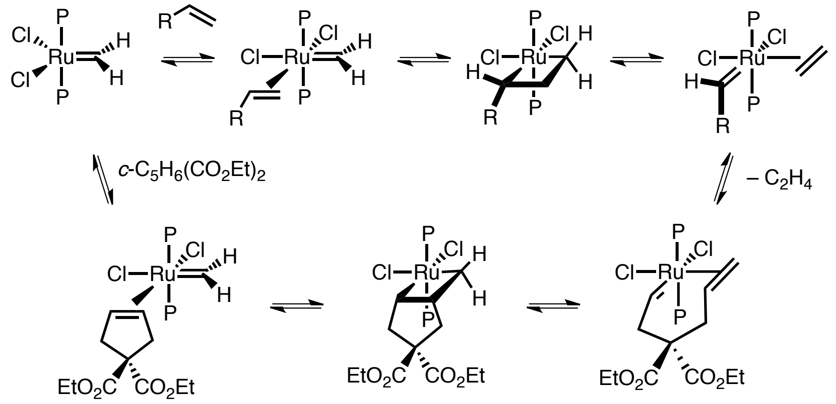
- It was concluded in this study that the "dissociative" pathway is the dominant reaction manifold (>95%).

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

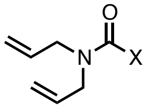
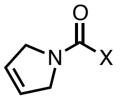
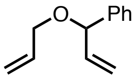
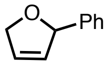
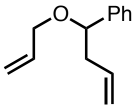
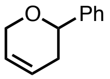
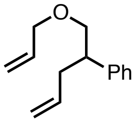
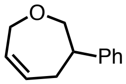
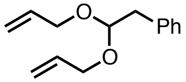
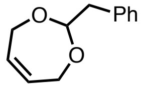
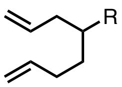
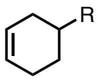
Dissociative:



Associative:

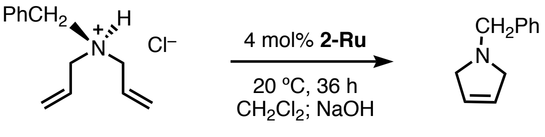


Catalytic RCM of Dienes:

substrate		product	time (h)	yield (%)[a]
	X = CF_3		1	93
	X = O *t*-Bu		1	91
			2	84
			5	86
			8	72
			1	87
	R = CO_2H		1	87
	CH_2OH		1	88
	CHO		1	82

[a] 2-4 mol% **2-Ru**, C_6H_6, 20 °C

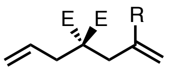
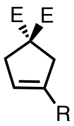
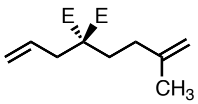
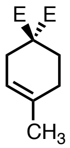
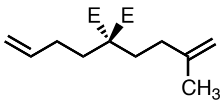
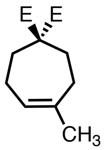
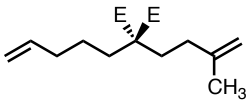
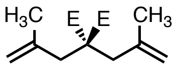
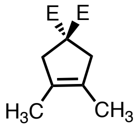
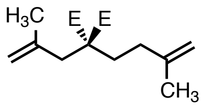
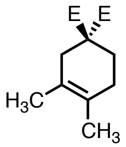
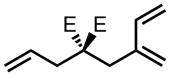
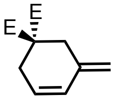
- Five-, six-, and seven-membered oxygen and nitrogen heterocycles and cycloalkanes are formed efficiently.
- Catalyst **2-Ru** can be used in the air, in reagent-grade solvents (C_6H_6, CH_2Cl_2, THF, *t*-BuOH).
- In contrast to the molybdenum catalyst **1-Mo**, which is known to react with acids, alcohols, 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**.



79%

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

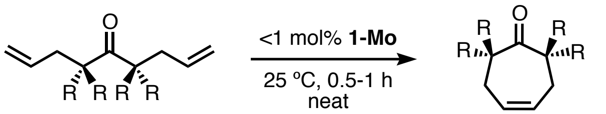
substrate[a]		product	yield with **3-Ru** (%)[b]	yield with **1-Mo** (%)[c]
	R = CH_3		93	100
	i-Pr		98	100
	t-Bu		NR	96
	Ph		25	97
	Br		NR	NR
	CH_2OH		98	decomp
			97	100
			96	100
		–	No RCM[d]	No RCM[d]
			NR	93
			NR	61
			96[e]	100[e]

[a] E = CO_2Et. [b] 0.01 M, CH_2Cl_2, 5 mol%. [c] 0.1 M, C_6H_6, 5 mol%. [d] Only recovered starting material and an acyclic dimer were observed. [e] 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.

Geminal Substitution



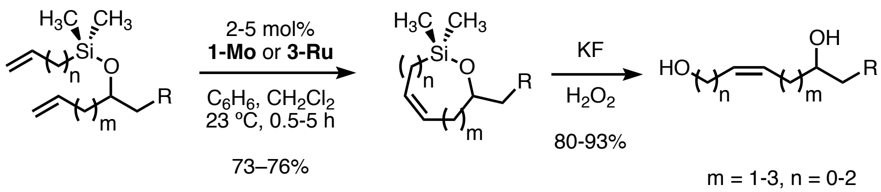
R = H 0%; (polymerization)

CH_3 95%

- Standard "Thorpe-Ingold" effects favor cyclization with gem-disubstituted substrates.

Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W.; Schulz, G. R., Jr.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978-10980.

RCM of Temporarily Connected Dienes

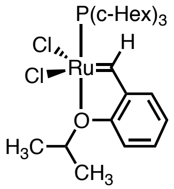


- RCM of allyl- or 3-butenylsilyloxy dienes (n≥1) proceeded efficiently with alkylidene **3-Ru**, while the more sterically hindered vinylsilyl substrates (n=0) required the use of alkylidene **1-Mo**.

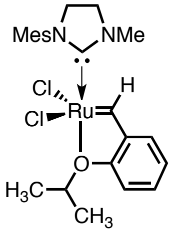
- RCM of silicon-tethered alkenes is very efficient even at higher concentrations (0.15 M with catalyst **3-Ru**).

Chang. S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757–4760.

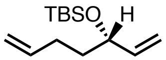
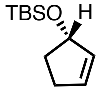
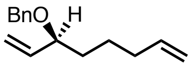
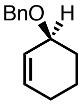
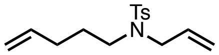
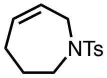
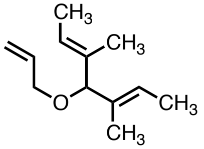
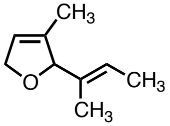
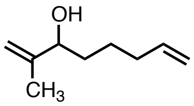
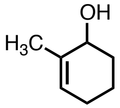
Recyclable Ru-Based Metathesis Catalysts



5a-Ru



5b-Ru

substrate[a]	product	cat	time (h)	temp (ºC)	yield (%)[b]	recovered catalyst (%)[b]
		**5a-Ru**	0.5	22	99	75
		**5a-Ru**	2.0	22	95	89
		**5a-Ru**	1.0	40	99	88
		**5b-Ru**[c]	0.3	22	87	98
		**5b-Ru**	2	22	75	95

[a] 5 mol% catalyst, CH_2Cl_2. [b] Isolated yield after silica gel chromatography. [c] 1 mol% of **5b-Ru** was used.

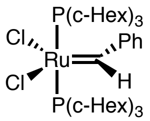
- Catalysts **5a-Ru** and **5b-Ru** offer excellent stability to air and moisture and can be recycled in high yield by chromatography on silica gel. **5a-Ru** is effective for metathesis of terminal alkenes while **5b-Ru** offers enhanced catalytic activity toward substituted alkenes.

Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.

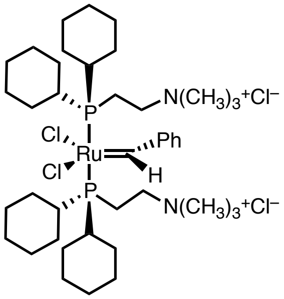
Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

M. Movassaghi, Fan Liu

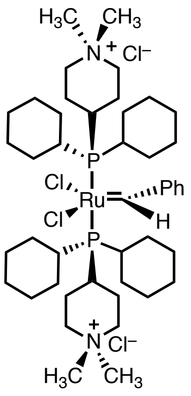
RCM in Methanol and Water



3-Ru

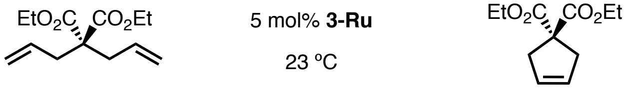


6-Ru



7-Ru

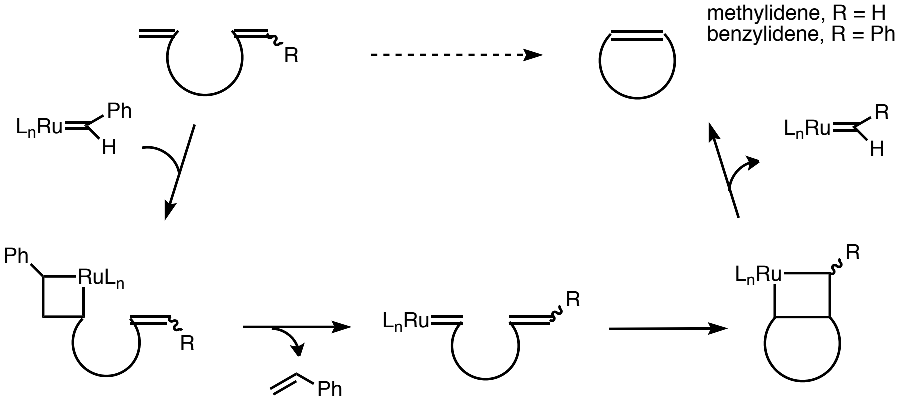
- Alkylidenes **5-Ru** and **6-Ru** are well-defined, water-soluble Ru-based metathesis catalysts that are stable for days in methanol or water at 45 °C.
- Although benzylidene **3-Ru** is highly active in RCM of dienes in organic solvents, it has no catalytic acitivity in protic media.



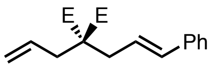
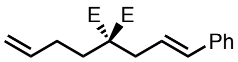
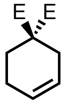
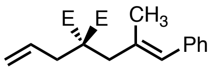
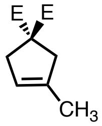
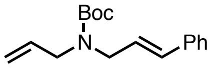
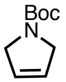
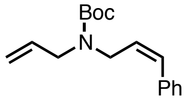
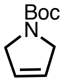
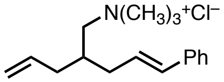
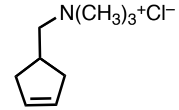
solvent:		
	CH_2Cl_2	100%
	CH_3OH	<5%

Stabilization of Ru-Carbene Intermediates by Phenyl Substitution

- first turnover step of RCM:

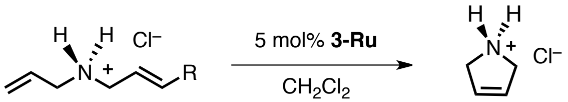


- Substitution of one of the two terminal olefins of the substrate with a phenyl group leads to regeneration of benzylidene catalyst, which is far more stable than the corresponding methylidene catalyst in methanol.

substrate[a]	product[b]	solvent	catalyst	conversion[c]
		methanol	**6-Ru** **7-Ru**	80 95
		methanol	**6-Ru** **7-Ru**	45[d] 55[d]
		methanol	**7-Ru**	>95
		methanol	**6-Ru** **7-Ru**	40 90[e]
		methanol	**6-Ru** **7-Ru**	30 >95[f]
		methanol water water	**7-Ru** **7-Ru** **7-Ru**	90 60 90[g]

[a] E = CO_2Et. [b] 5 mol% catalyst (**5-** or **6-Ru**), 0.37 M substrate, 45 °C. [c] Conversions were determined by 1H NMR. [d] Substrate conc. = 0.1 M. [e] 30 h. [f] 2 h. [g] 10 mol% **6-Ru** used.

- Alkylidene **7-Ru** is a significantly more active catalyst than alkylidene **6-Ru** in these cyclizations; this higher reactivity is attributed to the more electron-rich phosphines in **7-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.

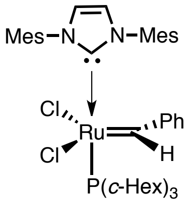


R = H	60%
R = Ph	100%

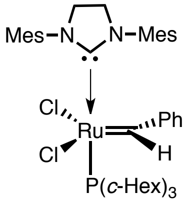
Kirkland, T. A.; Lynn, D. M.; Grubbs, R. H. *J. Org. Chem.* **1998**, *63*, 9904–9909.

M. Movassaghi

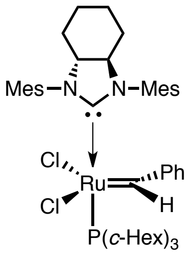
NHC Ruthenium Catalysts:



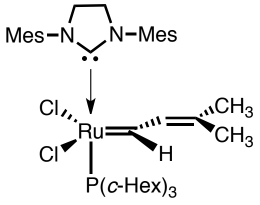
8-Ru



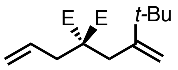
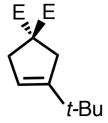
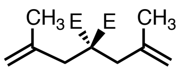
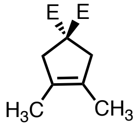
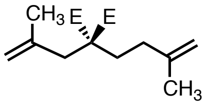
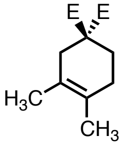
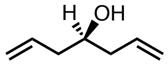
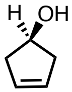
4-Ru



9-Ru



10-Ru

substrate[a]	product	time (h)	yield of product (%) using catalyst:[b] 1-Mo	3-Ru	8-Ru	4-Ru	9-Ru
		1	37	0	100	100	100
		24	93	0	40[c]	31	55
		1.5	52	0	1.5	90	87
		0.2	0	0	0.2	100	100

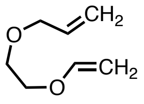
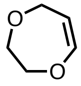
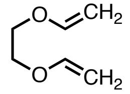
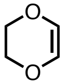
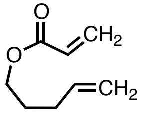
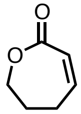
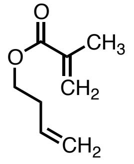
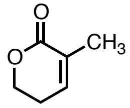
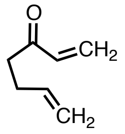
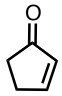
[a] E = CO_2Et. [b] 5 mol% of catalyst, CD_2Cl_2, reflux. [c] 1.5 h.

- Alkylidenes **4-** and **9-Ru** are the most reactive Ru-based catalysts.
- In the case of **4-** and **9-Ru** as little as 0.05 mol% is sufficient 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.

RCM of functionalized dienes

substrate[a]	product	yield (%)
		49
		0
		97
		86
		93

[a] Reactions conducted with 5 mol% **10-Ru**.

- Substrates containing both allyl and vinyl ethers provide RCM products while no RCM products are observed if vinyl ethers alone are present.
- α,β-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.

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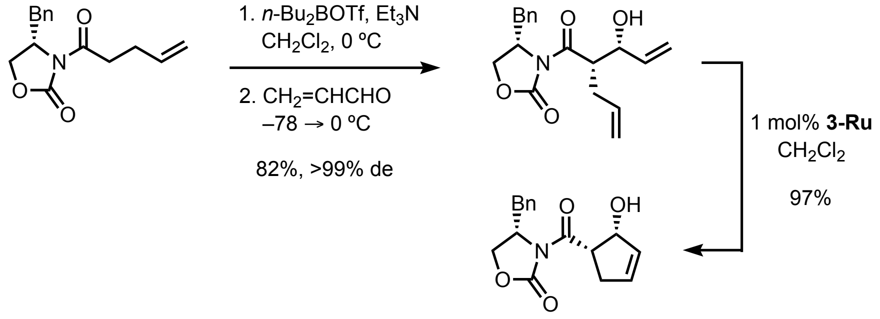
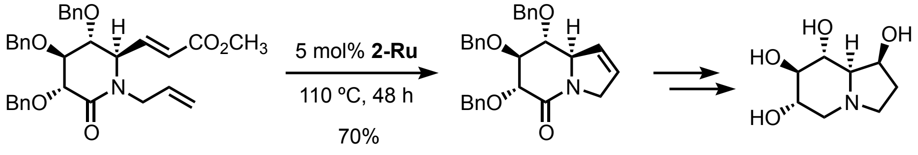
RCM Applications in Synthesis:



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

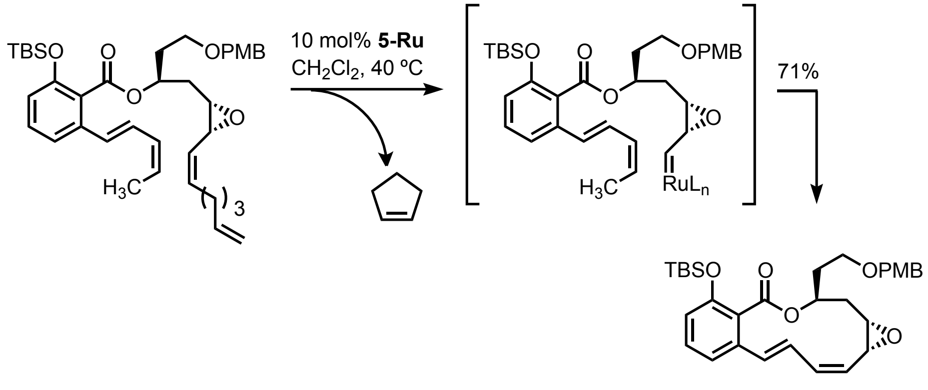


Castanospermine

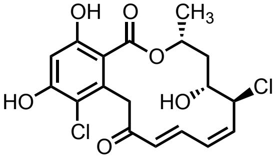
Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547–550.

- Particularly difficult cyclizations (due to steric congestion or electronic deactivation) can be achieved by **relay ring closing metathesis**, which initiates catalysis at an isolated terminal olefin. The reaction is driven by release of cyclopentene.

Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211.

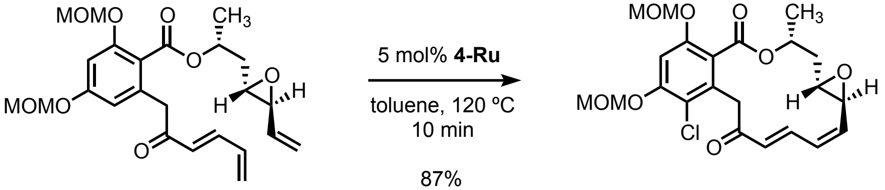


Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *Angew. Chem. Int. Ed.* **2004**, *43*, 3601–3605.

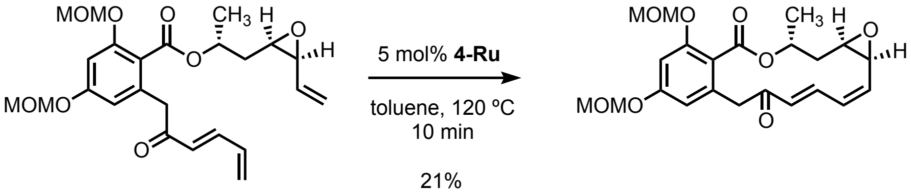


Pochonin C

trans epoxide



cis epoxide



- Pre-organization of the substrate can have a dramatic effect upon the reaction efficiency.
- Both epoxide substrates produce macrocycles with good regioselectivity (i.e., the 14-membered ring rather than the 12-membered ring) and *E*/*Z* selectivity. However, the *trans* epoxide macrocycle is formed in a much higher yield.

Barluenga, S.; Lopez, P.; Moulin, E.; Winssinger, N. *Angew. Chem. Int. Ed.* **2004**, *43*, 2367–2370.

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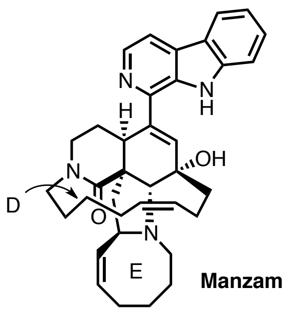
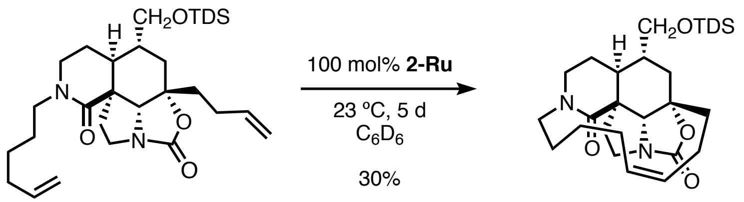


Manzamine A

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



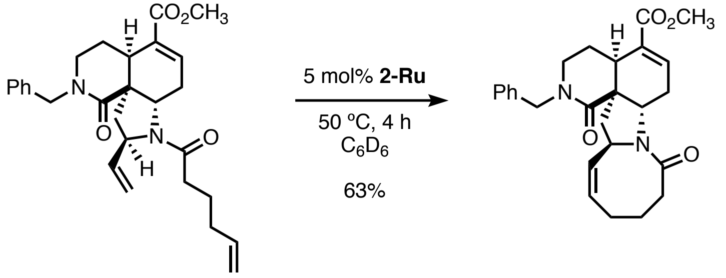
100 mol% **2-Ru**

23 ºC, 5 d

C_6D_6

30%

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



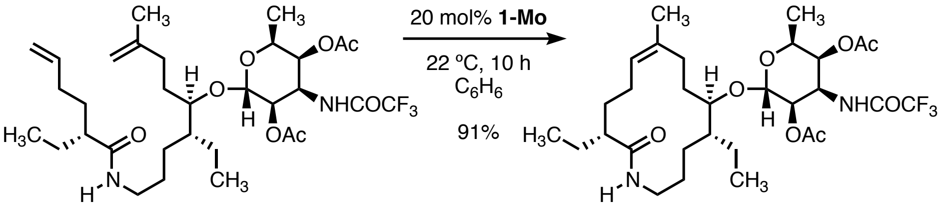
5 mol% **2-Ru**

50 ºC, 4 h

C_6D_6

63%

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



20 mol% **1-Mo**

22 ºC, 10 h

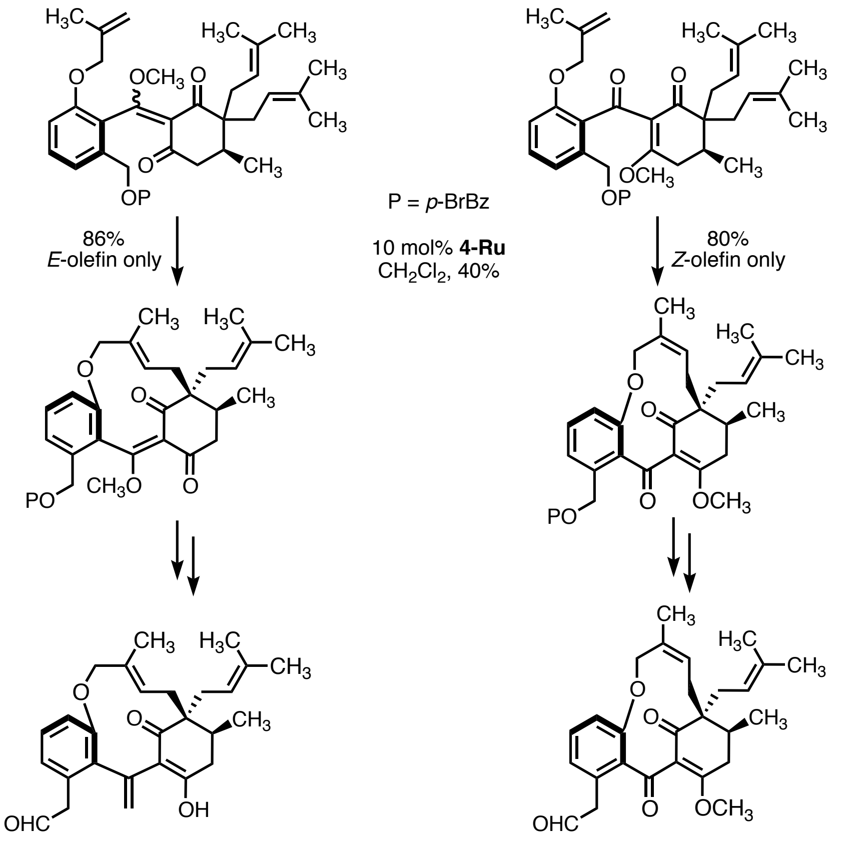
C_6H_6

91%

- Before the advent of NHC ligands, **1-Mo** was used more frequently than the Ru catalysts for macrocyclization of trisubstituted olefins. The latter catalysts are typically less reactive with sterically hindered substrates.

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

Slight changes in substrate structure can control whether the *E*- or *Z*-olefin is formed:



86%
E-olefin only

P = *p*-BrBz

10 mol% **4-Ru**
CH_2Cl_2, 40%

80%
Z-olefin only

Coleophomone B

Coleophomone C

Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N. *J. Am. Chem. Soc.* **2005**, 127, 8872–8888.

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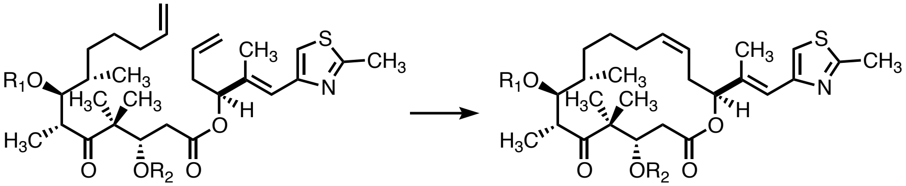
Synthesis of Epothilone C:

- Small changes can drastically affect reaction outcome. In the example below, TBS protective groups changes the E/Z selectivity.



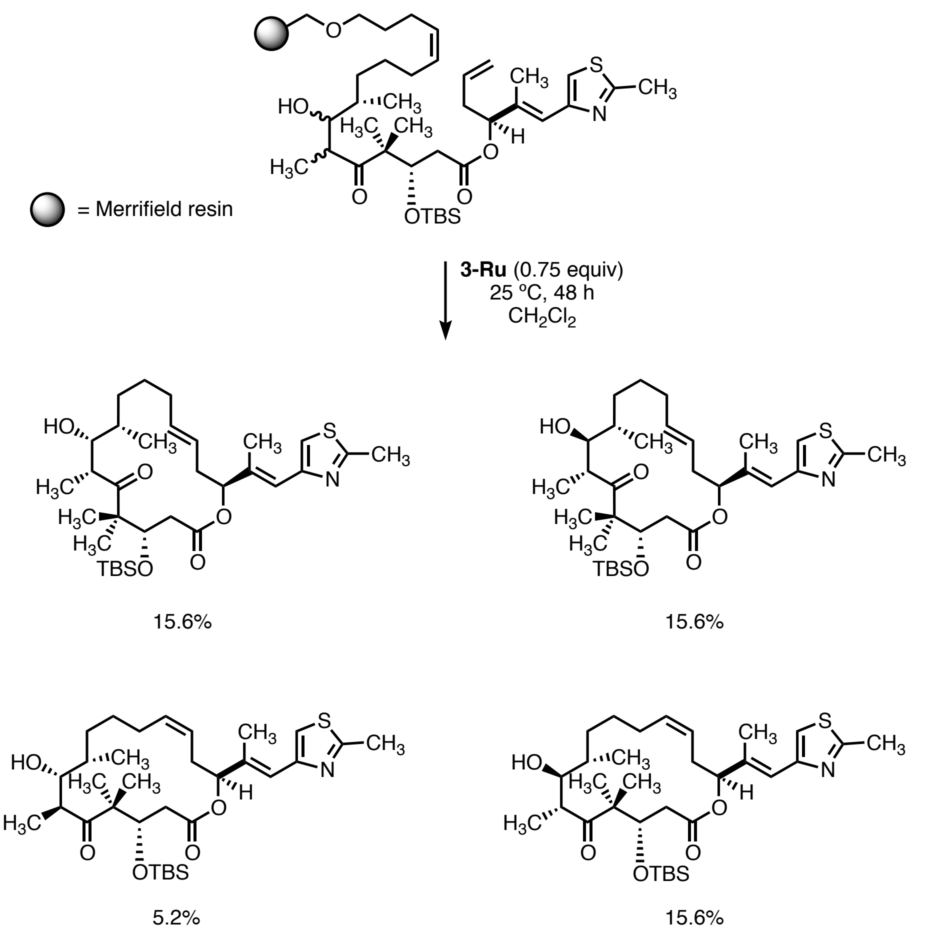
R_1	R_2	Catalyst	Conditions	Yield	E/Z
H	H	**1-Mo**	50 mol%, PhH, 55 ºC	65%	2 : 1
H	TBS	**3-Ru**	10 mol%, CH2Cl2, 25 ºC	85%	1 : 1.2
TBS	TBS	**8-Ru**	6 mol%, CH2Cl2, 25 ºC	94%	1 : 1.7
TBS	TBS	**4-Ru**	50 mol%, PhH, 55 ºC	86%	1 : 1.7

Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Roschangar, F.; Sarabia, F.; Ninkovic, S.; Yang, Z.; Trujillo, J. I. *J. Am. Chem. Soc.* **1997**, *119*, 7960–7973.

Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1997**, *119*, 11073–11092.

Schinzer, D.; Bauer, A.; Bohm, O. M.; Limberg, A.; Cordes, M. *Chem. Eur. J.* **1999**, *5*, 2483–2491.

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.

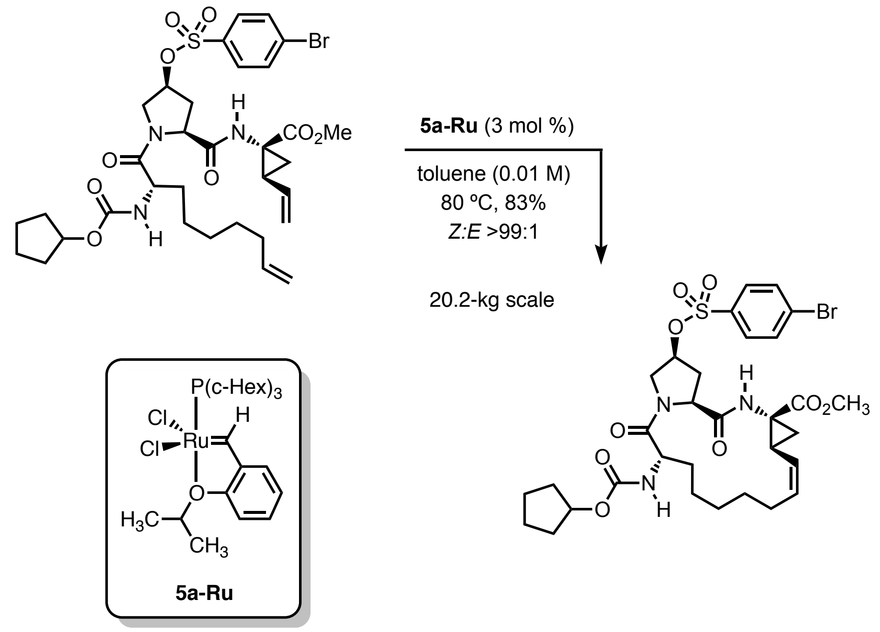
Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268–272.

M. Movassaghi and L. Blasdel

Applications of Olefin Metathesis in Industry

- BILN 2061 ZW was investigated as a potential medication for the treatment of hepatitis C:

- First-generation route:



5a-Ru

- 400 kg of the RCM product has been prepared using the first-generation route.

- During the reaction, nitrogen was bubbled through the reaction solution to remove ethylene.

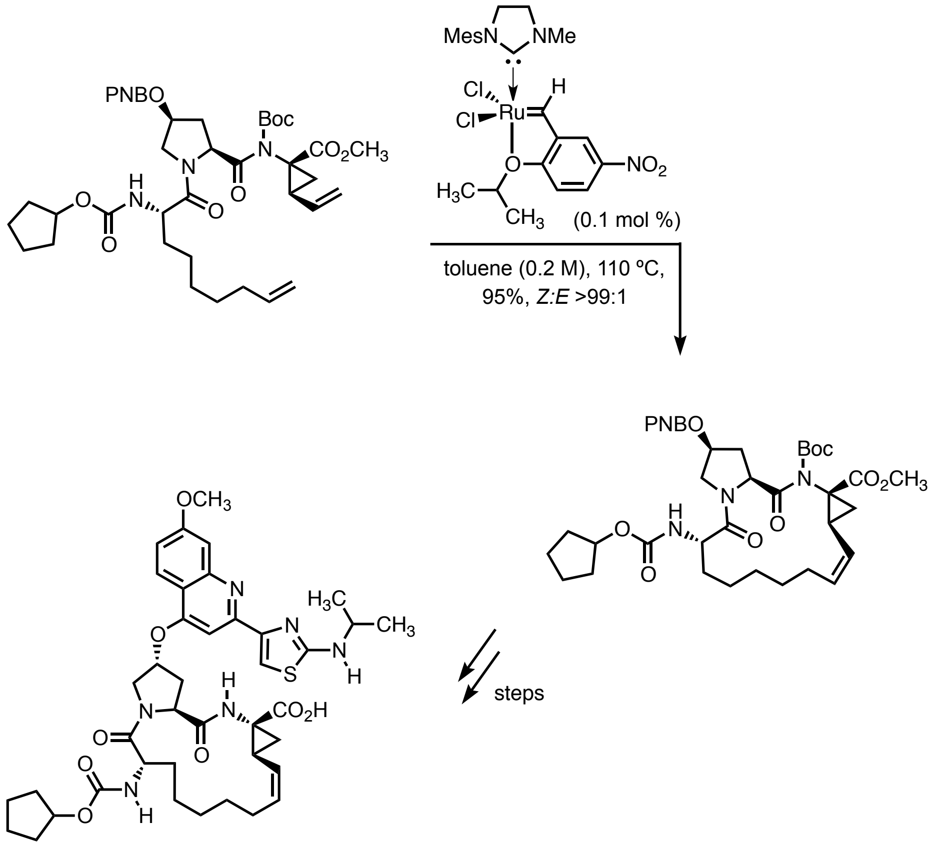
- **5-Ru** was not stable at 80 ºC for the duration of the reaction so the catalyst was added in several portions over 2 h.

- A dilute concentration (0.01 M) was used to minimize dimerization.

- Because traces of morpholine in the toluene led to catalyst inhibition, all toluene used was washed with HCl prior to use.

Nicola,T.; Brenner, M.; Donsbach, K.; Kreye, P. *Org. Process Res. Dev.* **2005**, *9*, 513–515.
Yee, N. K.; et al. *J. Org. Chem.* **2006**, *71*, 7133–7145.
Farina, V.; Shu, C.; Zeng, X.; Wei, X.; Han, Z.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2009**, *13*, 250–254.

- A second-generation route was developed, which permitted higher reaction concentrations and lower catalyst loading:

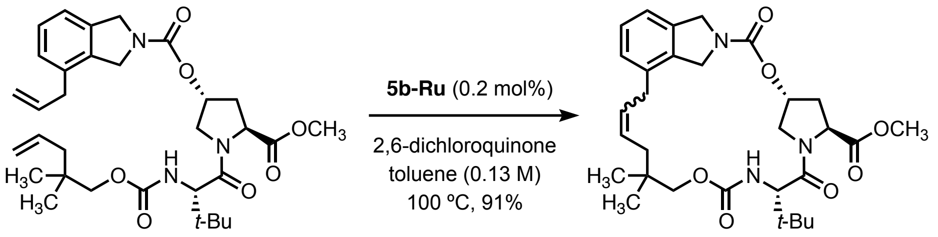


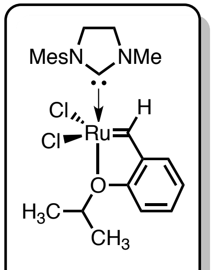
BILN 2061 ZW

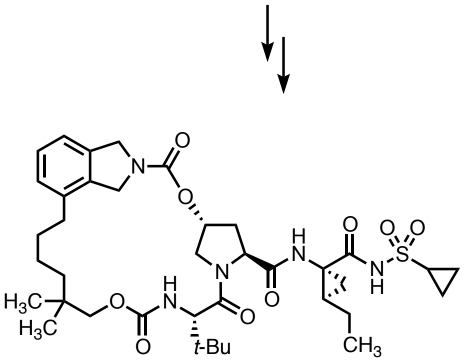
Farina, V.; Shu, C.; Zeng, X.; Wei, X.; Han, Z.; Yee, N. K.; Senanayake, C. H. *Org. Process Res. Dev.* **2009**, *13*, 250–254.

David W. Lin, Fan Liu

- Synthesis of MK-7009 (vaneprevir), now in clinical trials for the treatment of hepatitis C:



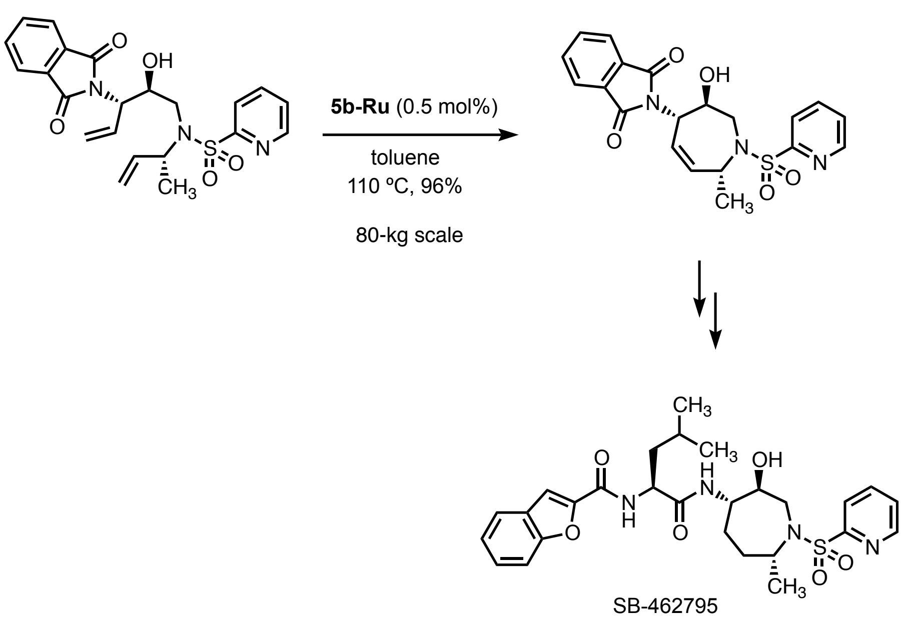

5b-Ru


vaneprevir (MK-7009)

- The catalyst was added over 1h to minimize decomposition and mimic high dilution, which allows the reaction to be run at higher concentrations.
- The reaction yield increased when nitrogen was bubbled through the reaction solution to remove ethylene and adventitious oxygen.
- Trace Ru–H intermediates were trapped using 2,6-dichloroquinone, which also allowed the catalyst loading to be lowered.
- It was necessary to recrystallize the starting material to avoid poisoning the catalyst with trace impurities.

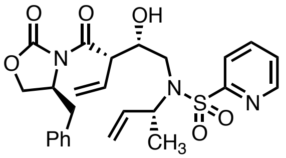
Kong, J.; Chen, C.-y.; Balsells-Padros, J.; Cao, Y.; Dunn, R. F.; Dolman, S. J.; Janey, J.; Li, H.; Zacuto, M. J. *J. Org. Chem.* **2012**, *77*, 3820–3828.

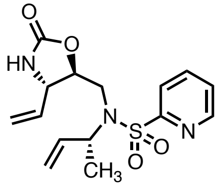
- SB-462795 is under development as a cathepsin K inhibitor for the treatment of osteoporosis:



SB-462795

- The choice of RCM substrate was crucial. Alternative substrates required higher catalyst loadings:


5b-Ru (10 mol%): 100%
5b-Ru (5 mol%): 60%

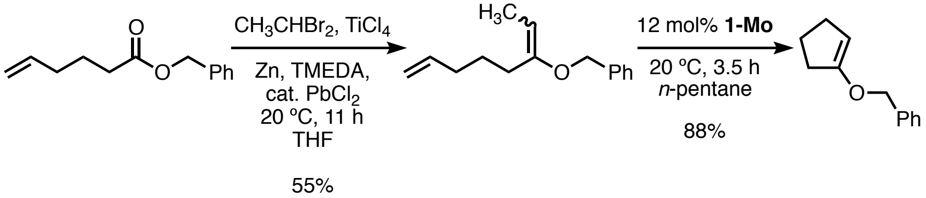

5b-Ru (11 mol%): 90%

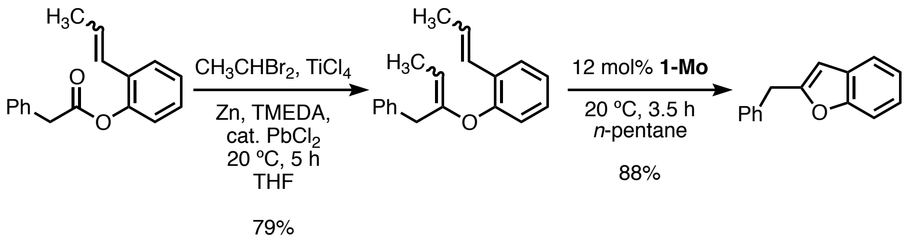
- The diene substrate was required to be of high purity in order to achieve full conversion. Minor urea or amide contaminants inhibited RCM.

Wang, H.; Goodman, S. N.; Dai, Q.; Stockdale, G. W.; Clark, W. M., Jr. *Org. Process Res. Dev.* **2008**, *12*, 226–234.
Wang, H.; Matsuhashi, H.; Doan, B. D.; Goodman, S. N.; Ouyang, X.; Clark, W. M., Jr. *Tetrahedron* **2009**, *65*, 6291–6303.

David W. Lin, Fan Liu

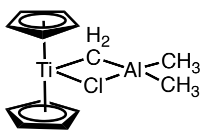
Catalytic RCM of Olefinic Enol Ethers:





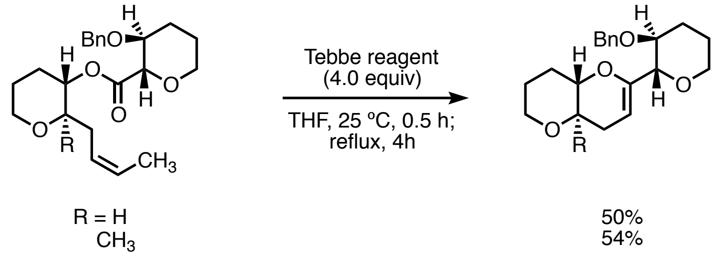
- Only catalyst **1-Mo** is effective for RCM of these substrates.

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



Tebbe reagent

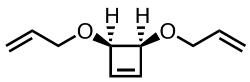
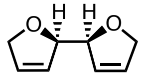
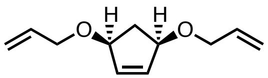
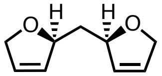
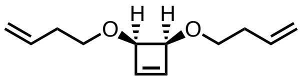
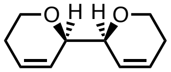
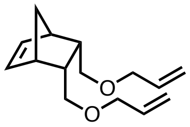
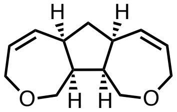
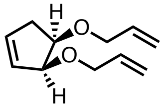
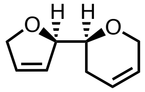
Tandem Olefination-Metathesis



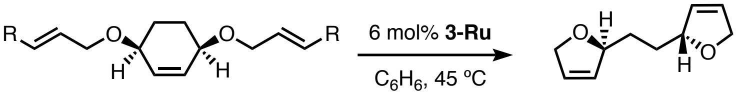
- Here, a Ti-alkylidene is used in RCM.

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

Tandem Ring Opening-Ring Closing Metathesis of Cyclic Olefins:

substrate	product	yield (%)	catalyst **3-Ru** (mol%)	conc. (M)	time (h)	temp. (ºC)
		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 CM) can occur.
- Higher dilution favors intramolecular reaction:



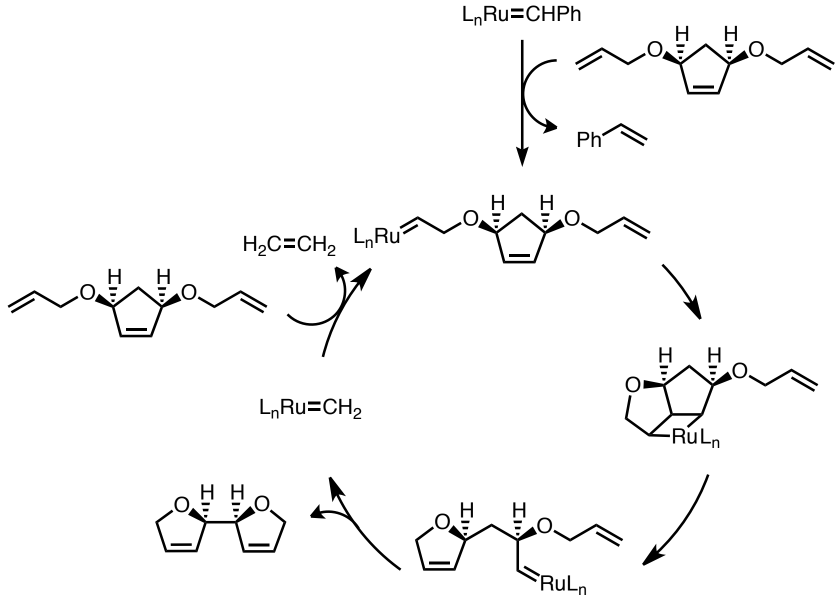
mixture of *E*/*Z* isomers

R = H	0.12 M	16%
H	0.008 M	73%
CH_3	0.2 M	42%

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

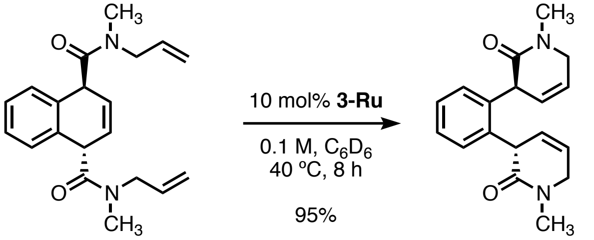
M. Movassaghi

Proposed Mechanism for Ring Opening-Ring Closing Metathesis

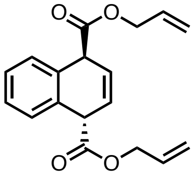


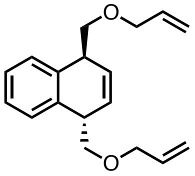
- Initial metathesis of the acyclic olefin is supported by the fact that substitution of this olefin decreases the rate of metathesis.

- 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.



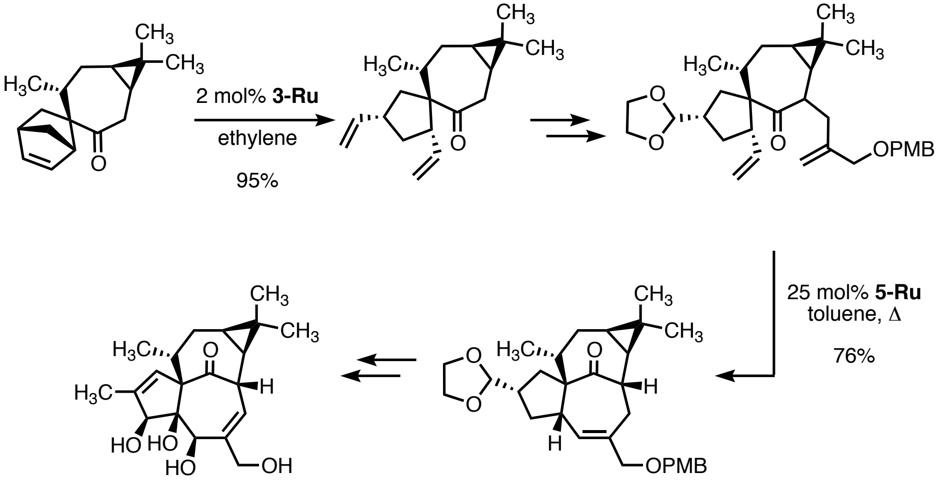
unreactive substrates:





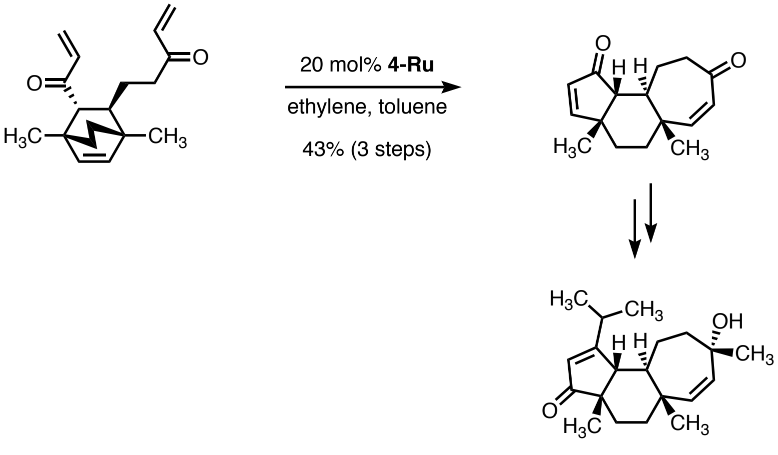
Zuercher, W. J.; Hashimoto, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 6634–6640.

Examples in Complex Synthesis:



Ingenol

Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300–16301.

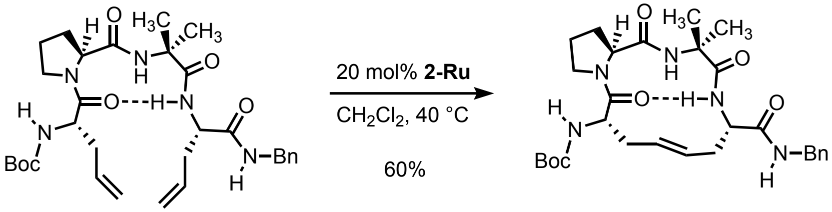


Cyanthiwigin U

Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, *127*, 5334–5335.

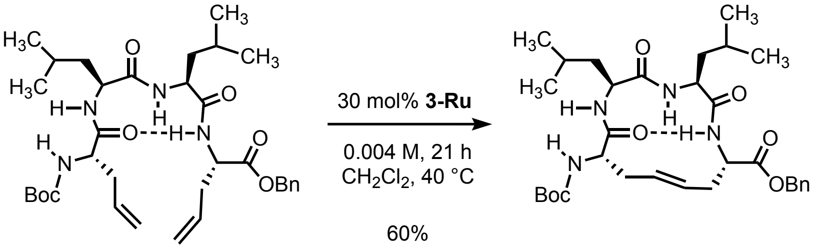
M. Movassaghi and L. Blasdel

Synthesis of Cyclic β-Turn Analogs by RCM



- The presence of the Pro-Aib sequence in the tetrapeptide induces a ß-turn conformation which was covalently captured by RCM, yielding a 14-membered macrocycle.

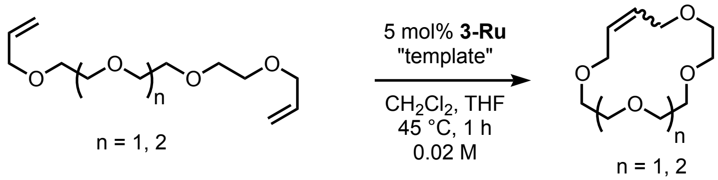
Miller, S. J.; Kim, S. H.; Chen, Z. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109.
Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855-5856.



- 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.

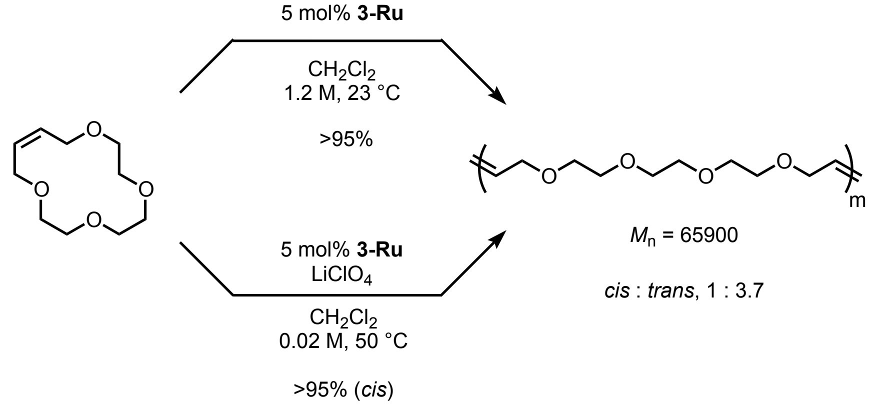
Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606–9614.

Template-Directed RCM



substrate (n)	"template" (equiv)	yield (%)	cis:trans
1	none	39	38 : 62
1	$LiClO_4$ (5)	>95	100 : 0
1	$NaClO_4$ (5)	42	62 : 38
2	none	57	26 : 74
2	$LiClO_4$ (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.



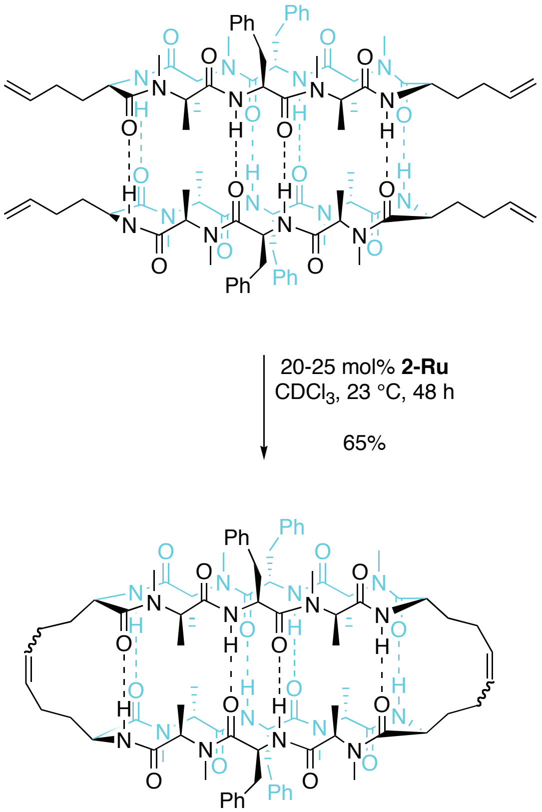
- Polymer degradation in the absence of a Li^+ template produced the corresponding crown ether as a mixture of cis- and trans-olefins (20% combined yield) along with other low molecular weight polymers.

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

M. Movassaghi

RCM-Mediated Covalent Capture

- The eight-residue cyclic peptide cyclo[-(L-Phe-D-^{Me}*N*-Ala-L-HomoallylGly-D-^{Me}*N*-Ala)$_2$-] self-assembles to form two slow-exchanging antiparallel β-sheet-like hydrogen bonded cylinders (K_a(CDCl$_3$) = 99 M^{-1}, only the reactive isomer is shown).



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

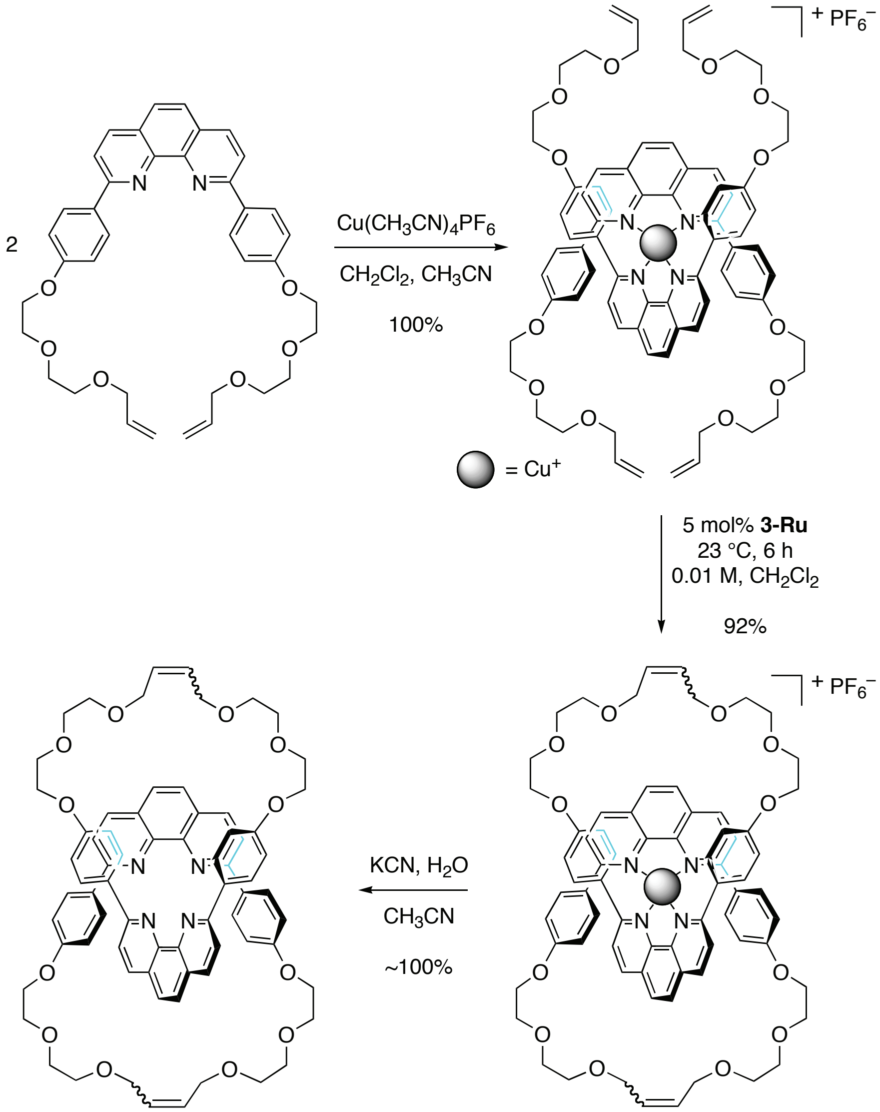
65%

- 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



Cu(CH$_3$CN)$_4$PF$_6$
CH$_2$Cl$_2$, CH$_3$CN
100%

5 mol% **3-Ru**
23 °C, 6 h
0.01 M, CH$_2$Cl$_2$
92%

KCN, H$_2$O
CH$_3$CN
~100%

32-membered catenane

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.

Cross Metathesis

Olefin categorization and rules for selectivity

Type I – Rapid homodimerization, homodimers reactive

Type II – Slow homodimerization, homodimers largely unreactive

Type III – No homodimerization

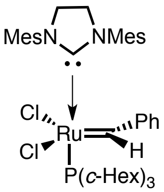
Type IV – Olefins inert to CM, but do not deactivate catalyst (spectator)

Reaction between two olefins of Type I.................................. Statistical CM

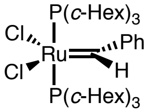
Reaction between two olefins of same type (non-Type I)........ Non-selective CM

Reaction beween olefins of two different types...................... Selective CM

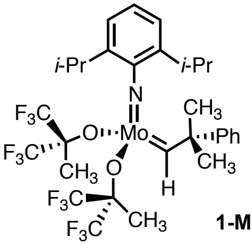
Selective Cross-Metathesis Reactions as a Function of Catalyst Structure:



4-Ru



3-Ru

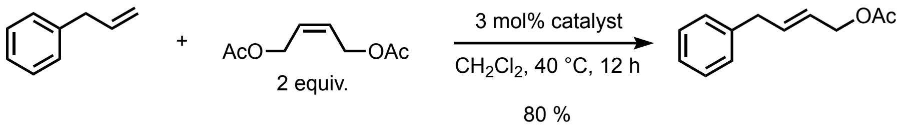


1-Mo

Olefin type	4-Ru	3-Ru	1-Mo
Type I (fast homodimerization)	terminal olefins, 1° allylic alcohols, esters, allyl boronate esters, allyl halides, styrenes (no large ortho substit.), allyl phosphonates, allyl silanes, allyl phosphine oxides, allyl sulfides, protected allyl amines	terminal olefins, allyl silanes, 1° allylic alcohols, ethers, esters, allyl boronate esters, allyl halides	terminal olefins, allyl silanes
Type II (slow homodimerization)	styrenes (large ortho substit.), acrylates, acrylamides, acrylic acid, acrolein, vinyl ketones, unprotected 3° allylic alcohols, vinyl epoxides, 2° allylic alcohols, perfluoalkyl substituted olefins	styrene, 2° allylic alcohols, vinyl dioxolanes, vinyl boronate	styrene, allyl stannanes
Type III (no homodimerization)	1,1-disubstituted olefins, non-bulky trisub. olefins, vinyl phosphonates, phenyl vinyl sulfone, 4° allylic carbons (all alkyl substituents), 3° allylic alcohols (protected)	vinyl siloxanes	3° allyl amines, acrylonitrile
Type IV (spectators to CM)	vinyl nitro olefins, trisubstituted allyl alcohols (protected)	1,1-disubstituted olefins, disub a,b-unsaturated carbonyls, 4° allylic carbon-containing olefins, perfluorinated alkane olefins, 3° allyl amines (protected)	1,1-disubstituted olefins

Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

Non-selective Cross Metathesis: Two Type I Olefins

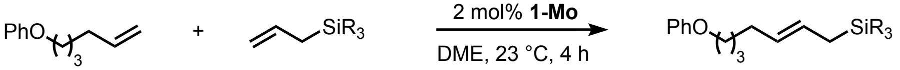


catalyst	*E/Z*
3-Ru	3.2 : 1
4-Ru	7 : 1

- The difference in *E/Z* ratios reflects the enhanced activity of **4-Ru** relative to **3-Ru.** Because it is more active, **4-Ru** can catalyze secondary metathesis of the product, allowing equilibration of the olefin to the more thermodynamically stable trans isomer.

Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

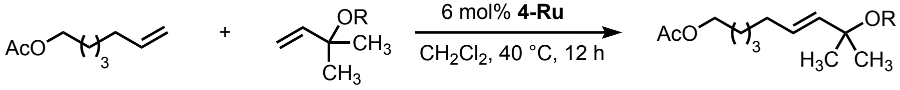
- Selectivity for the *trans* olefin can also be enhanced using sterically hindered substrates:



R	Yield	*E/Z*
CH_3	72%	2.6 : 1
Ph	77%	7.6 : 1

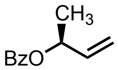
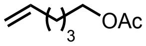
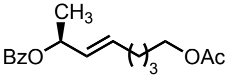
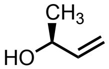
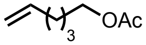
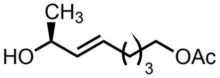
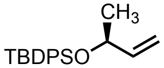
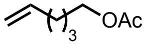
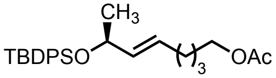
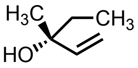
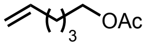
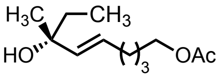
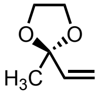
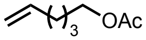
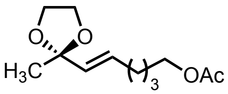
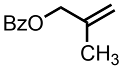
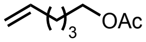
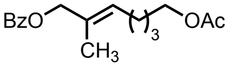
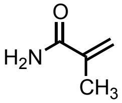
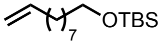
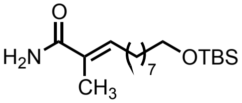
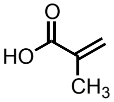
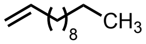
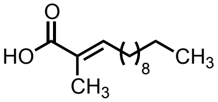
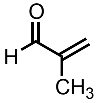
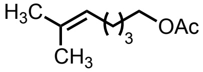
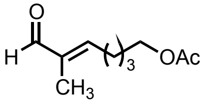
Crowe, W. E.; Goldberg, D. R.; Zhang, Z. J. *Tetrahedron Lett.* **1996**, *37*, 2117–2120.

- In addition, steric bulk can assist in favoring the cross metathesis reaction over homodimerization pathways.
- The lower yield obtained with the unprotected alcohol is a result of homodimerization of the tertiary allylic alcohol. Subjecting this dimer to the reaction conditions results in no CM product, indicating that the dimer cannot undergo a secondary metathesis reaction.



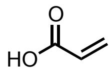
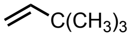
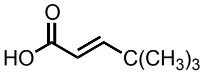
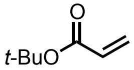
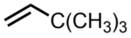
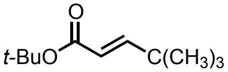
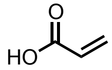
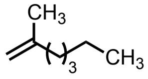
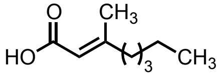
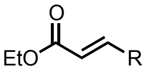
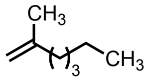
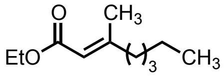
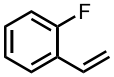
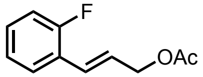
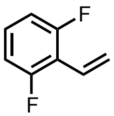
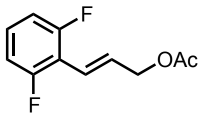
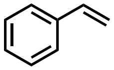
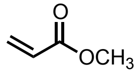
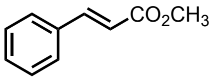
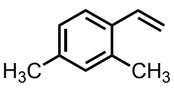
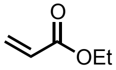
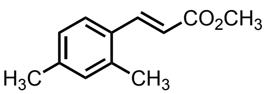
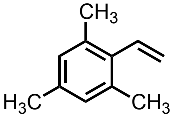
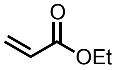
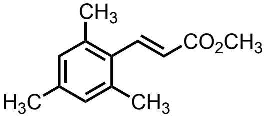
R = H 58% yield
R = TBS 97% yield

Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

Olefin 1	Olefin 2	product[a,b]	Isolated Yield (%)	*E/Z*
Secondary allylic alcohols (Type II with Type I)				
	 2 equiv.		82	10 : 1
	 1 equiv.		50[c] (62)[d]	14 : 1
	 2 equiv.		53	6.7 : 1
Quaternary allylic olefins (Type III with Type I)				
 2 equiv.			93	>20 : 1
 1 equiv.			91	>20 : 1
1,1-Disubstituted olefins (Type III with Type I)				
	 2 equiv.		80	4 : 1
	 1.2 equiv.		71	>20 : 1
	 1.1 equiv.		23	4 : 1
	 1.0 equiv.		97	>20 : 1

[a] 3–5 mol% **4-Ru**, CH_2Cl_2, 40 °C. [b] See last reference on left half of this page.
[c] With 2 equiv Olefin 2, the yield was 92%. [d] Reaction was performed at 23 °C

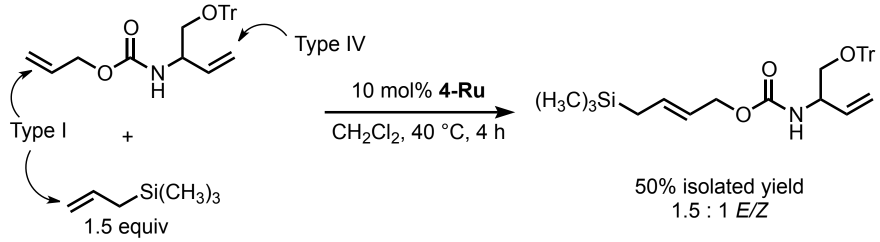
L. Blasdel

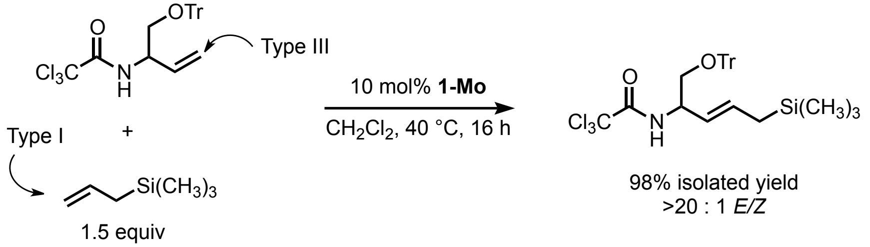
Olefin 1	Olefin 2	product[a,b]	Isolated Yield (%)	*E/Z*
Type II and Type III				
	 neat		73	
	 neat		73	
	 4.0 equiv.		83	2 : 1
	 4.0 equiv.		55 R = H 83 R = CH_3	2 : 1 2 : 1
	 2.0 equiv.		98	>20 : 1
	 2.0 equiv.		50	>20 : 1
	 1.5–2.0 equiv.		92	>20 : 1
	 1.5–2.0 equiv.		87	>20 : 1
	 1.5–2.0 equiv.		5	>20 : 1

[a] 1–5 mol% **4-Ru**, CH_2Cl_2, 40 °C.

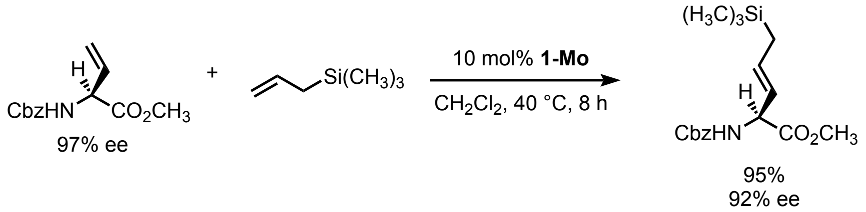
Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

Selective Cross-Metathesis Reactions:

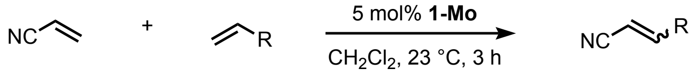




Brümmer, O; Rückert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3*, 441–446



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



R	yield (%)	*E/Z*
$CH_2Si(CH_3)_3$	76	1 : 3
$(CH_3)_3OBn$	60	1 : 7.6
$(CH_2)_2CO_2Bn$	44	1 : 5.6

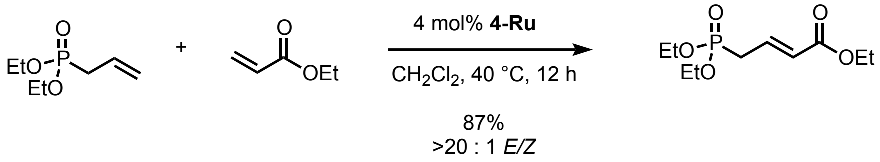
- The basis for the high cis-selectivity with acrylonitrile as substrate is not known.

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

L. Blasdel and M. Movassaghi

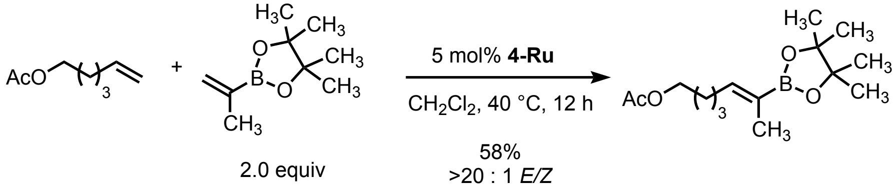
Reagent preparation

A Horner-Wadsworth-Emmons reagent:



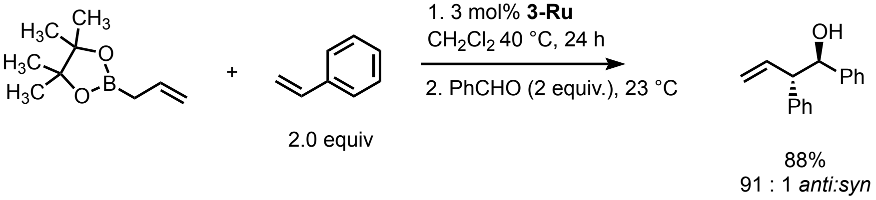
Toste, F. D.; Chatterjee, A. K.; Grubbs, R. H. *Pure Appl. Chem.* **2002**, *74*, 7–10.

A Suzuki reagent:



Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733–7736.

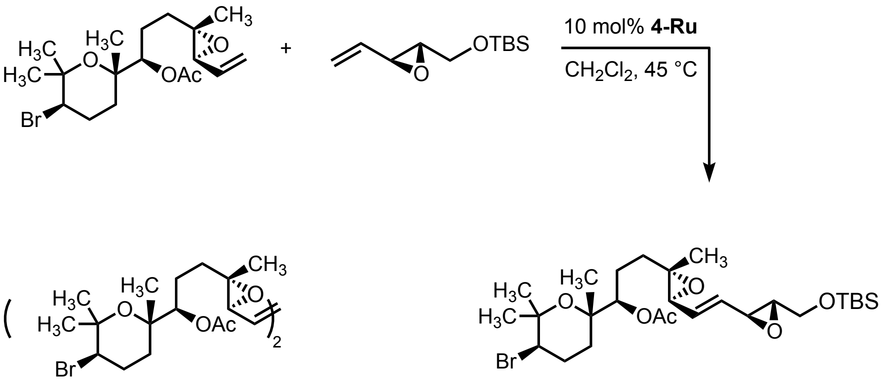
One-pot CM and allylboration reactions:



Yamamoto, Y.; Takahashi, M.; Miyaura, N. *Synlett* **2002**, 128–130.

Examples in synthesis

- En route to the ABS ring fragment of thyrsiferol:

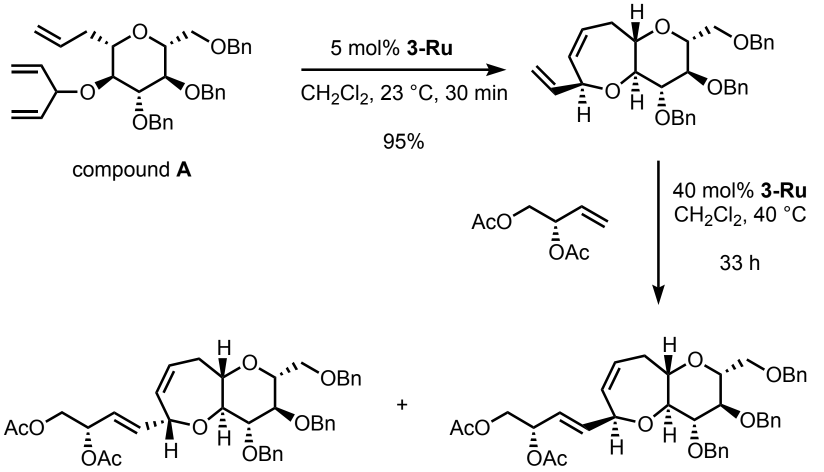


starting material homodimer

44% *E*-isomer
64% after recycling the homodimer

McDonald, F. E.; Wei, X. *Org. Lett.* **2002**, *4*, 593–595.

- CM can be difficult in the presence of strained olefins, as was found in the preparation of the AB ring fragment of ciguatoxin:



compound **A**

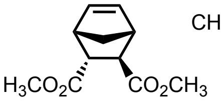
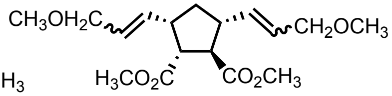
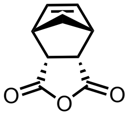
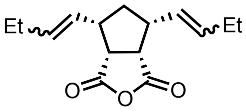
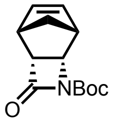
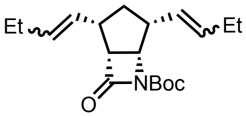
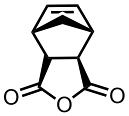
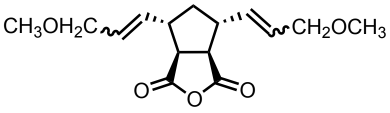
19%
via ring opening to compound **A**

8%
AB ring fragment of ciguatoxin

Oguri, H.; Sasaki, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 5405–5408

L. Blasdel

Ring Opening Cross-Metathesis

substrate	product	alkene[a]	mol% cat.[b]	time	yield	*E,E;E,Z*
		A	6	96	94	2 : 1
		B	2	14	85	2 : 1
		C	8[c]	3	73	1.5 :1
		A	2	89	15	NA

[a]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. Solvent: C_6H_6 (entries 1 and 2) or CH_2Cl_2 (entries 3 and 4). [b]Cat. = **2-Ru**. [c]Cat. = **3-Ru**.

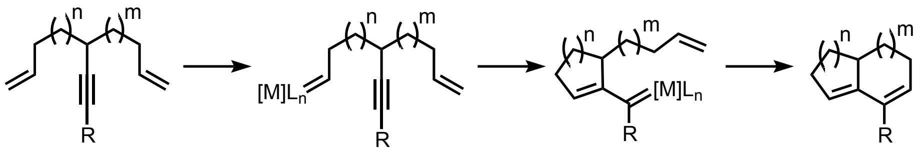
- In these cases a preference for the E-olefin geometry is observed in ring opening metathesis.
- Higher yields were achieved by slow addition of the cyclic alkene to a solution of the 1,2-disubstituted alkene.
- Faster and more efficient ring opening cross metathesis was observed using *cis*-hex-3-ene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

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

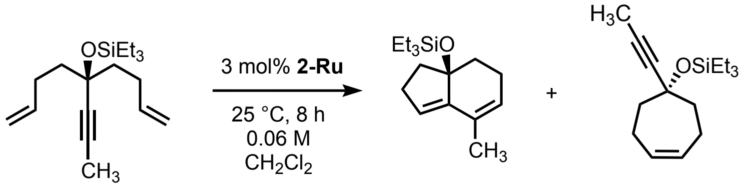
Enantioselective ROM–CM reactions have been described: La, D. S.; Ford, J. F.; Sattely, E. S.; Bonitatebus, P. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 11603–11604.

Metathesis of Enyne Substrates

Catalytic RCM of Dienynes: Construction of Fused Bicyclic Rings



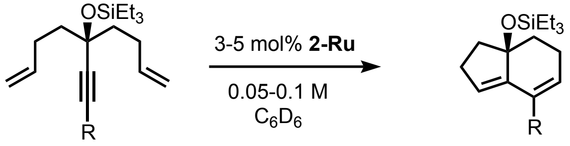
- Fused [5.6.0], [5.7.0], [6.6.0], and [6.7.0] bicyclic rings have been successfully constructed by RCM of dienynes.



dienyne RCM 95%

diene RCM <3%

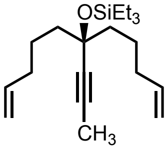
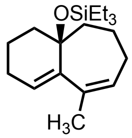
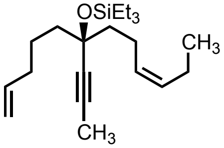
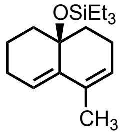
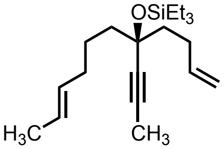
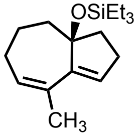
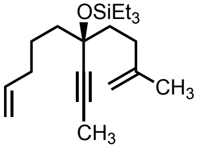
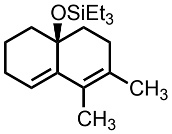
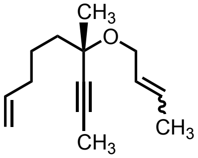
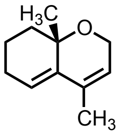
- The dienyne RCM is largely favored over the competing diene RCM.



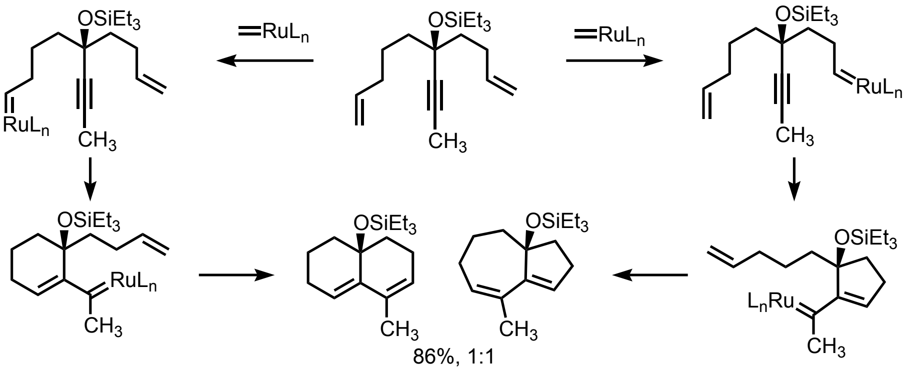
R	yield (%)	conditions
H	>98	23 °C, 15 min
CH_3	95	23 °C, 8 h
i-Pr	78	60 °C, 4 h
t-Bu	NR	
Ph	96	60 °C, 3 h
CO_2CH_3	82	60 °C, 4h
$Si(CH_3)_3$	NR	
Sn(*n*-Bu)$_3$	NR	
Cl, Br, I	NR	

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

M. Movassaghi

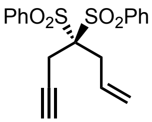
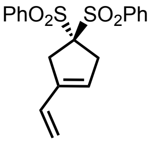
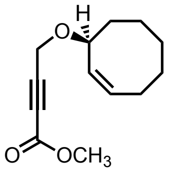
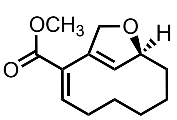
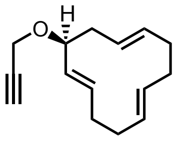
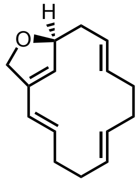
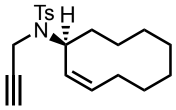
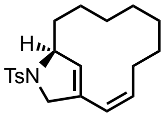
substrate	product	yield (%)	mol% **2-Ru**	time (h)	conc. (M)	temp (°C)
		88	6	8	0.06	65
		83	3	6	0.03	65
		78	15	1.5	0.01	100
		89	15	12	0.05	65
		88	3	6	0.05	65

- 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.

Enyne Metathesis Reactions Catalyzed by $PtCl_2$

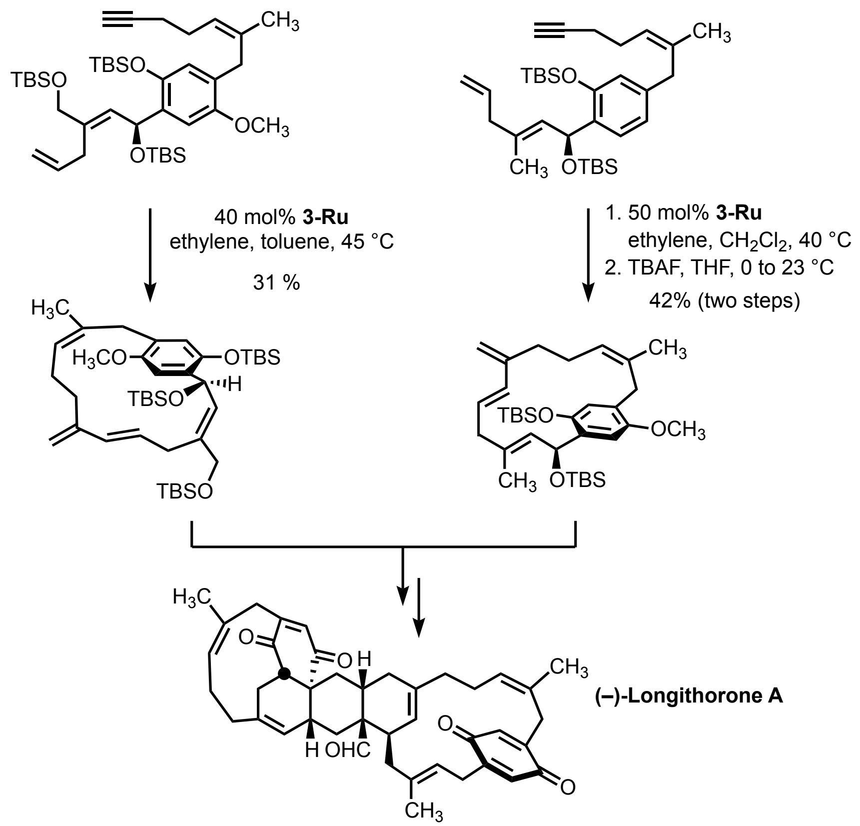
substrate	product	yield
		96%
		70%
		54%
		80%

[a]Reactions conducted in toluene at 80 °C using 4-10 mol% of $PtCl_2$

- In most cases commercial $PtCl_2$ was used as received.
- A pathway involving 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.

Enyne Metathesis in Synthesis

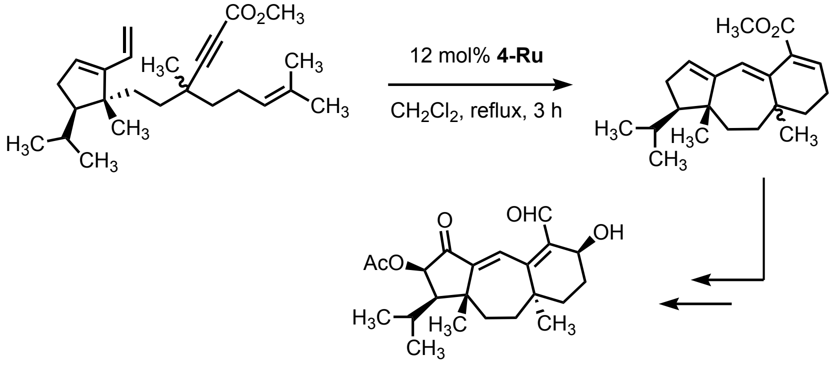


40 mol% **3-Ru**
ethylene, toluene, 45 °C
31 %

1. 50 mol% **3-Ru**
ethylene, CH_2Cl_2, 40 °C
2. TBAF, THF, 0 to 23 °C
42% (two steps)

(–)-Longithorone A

Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773–775.



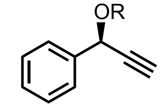
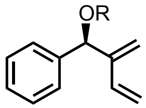
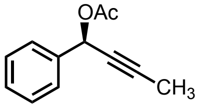
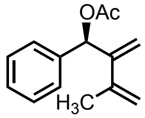
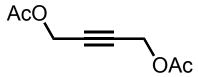
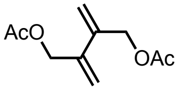
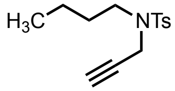
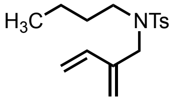
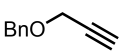
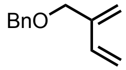
12 mol% **4-Ru**
CH_2Cl_2, reflux, 3 h

Guanacastepene A

Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2004**, *6*, 1817–1820.

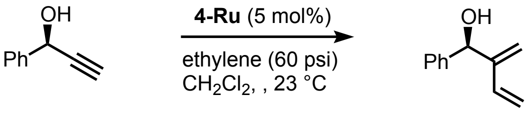
Enyne Cross-Metathesis

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

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

[a] Reactions conducted in CH_2Cl_2 at 23 °C using 5 mol% of **4-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 **4-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:



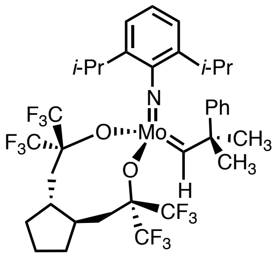
4-Ru (5 mol%)
ethylene (60 psi)
CH_2Cl_2, , 23 °C

99% ee 99% ee

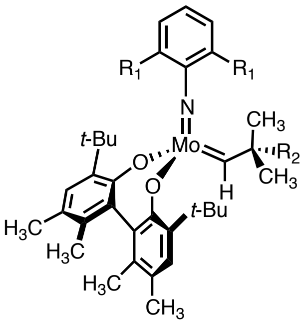
Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271–2274

L. Blasdel and M. Movassaghi

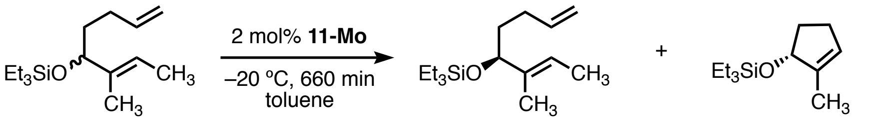
Kinetic Resolution via Asymmetric RCM



11-Mo



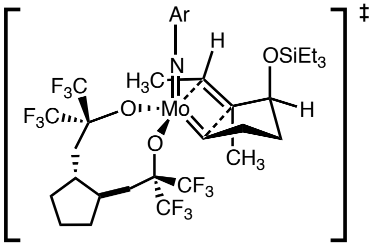
12-Mo: R_1 = i-Pr R_2 = Ph
13-Mo: R_1 = CH_3 R_2 = Ph
14-Mo: R_1 = Cl R_2 = Ph
15-Mo: R_1 = Cl R_2 = CH_3



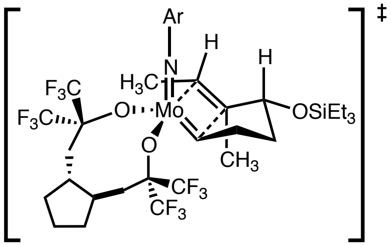
38%, 48% ee 62%

- The first catalytic, asymmetric kinetic resolution via RCM was achieved, with low selectivity, using the chiral alkylidene **11-Mo**.

Proposed Transition State Models for the Observed Selectivity



DISFAVORED

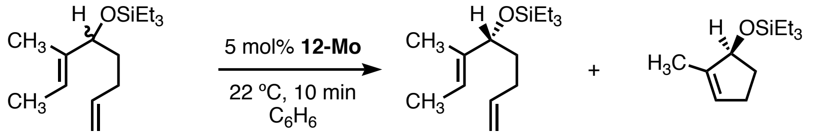


DISFAVORED

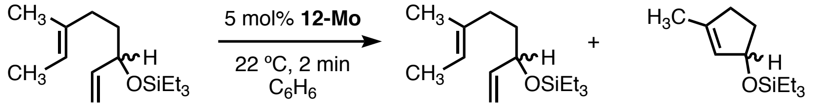
Ar = 2,6-(i-Pr)$_2$C$_6$H$_3$

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.

Catalytic, Enantioselective RCM



19%, >99% ee 43%, 93% ee

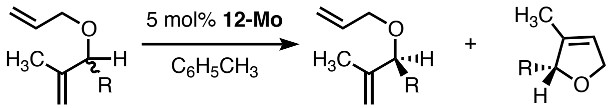


50%, <5% ee 40%, <5% ee

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

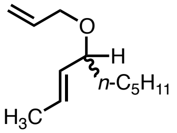
Alexander, J. B.; La, D. S.; Cefalo, D. R. Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041–4042.

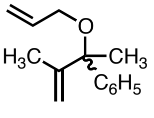
Mo-alkylidene Catalyzed Kinetic Resolution and Enantioselective Desymmetrization via RCM



R	temp. (°C)	time (h)	conv. (%)	recovered SM ee (%)	k_{rel}
n-C_5H_{11}	–25	6	63	92	10
i-C_4H_9	–25	10	56	95	23
c-C_6H_{11}	–25	7	62	98	17
c-C_6H_{11}	22	0.1	64	97	13
C_6H_5	–25	6	56	75	8

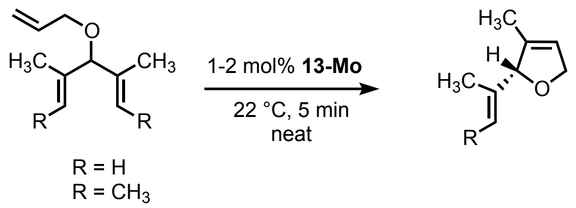
- Increasing the size of the α-substituent can lead to greater selectivity.
- 1,2-disubstituted alkenes and tertiary ethers are not effectively resolved by either alkylidene **12-Mo** or **13-Mo**.



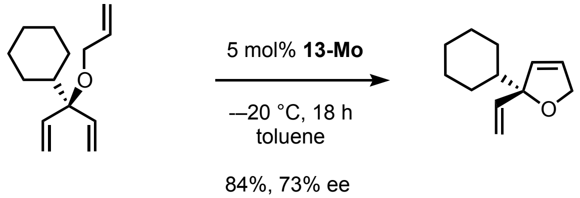


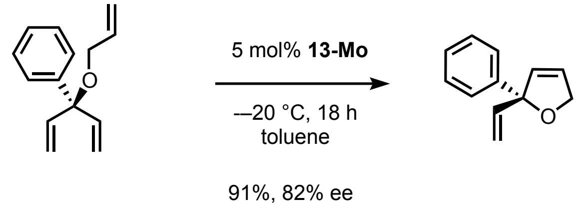
M. Movassaghi

- The alkylidene catalysts **12-Mo** and **13-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 **13-Mo.**

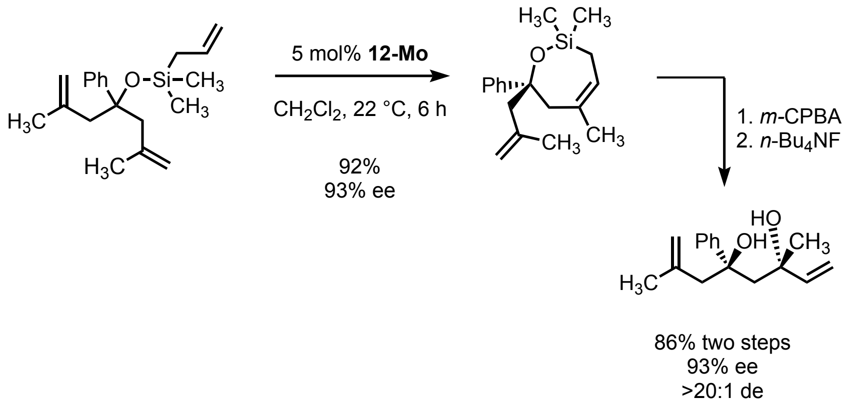




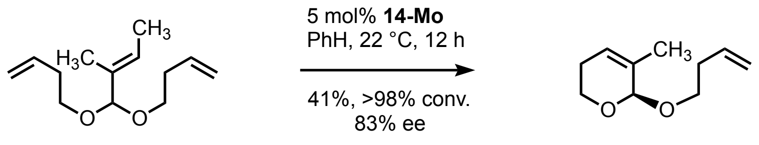
- It is believed that the stereodifferentiating step is the formation of the metallabicyclobutane intermediate; see: Alexander, J. B.; La, D. S.; Cefalo, D. R. Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 4041–4042.

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.

- Desymmetrization metathesis reactions have been used to make a variety of heteroatom-containing products:

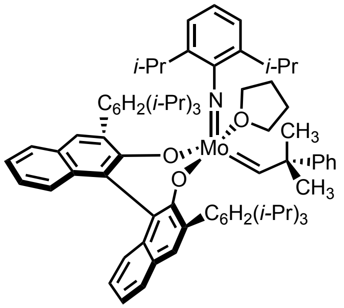


Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 2868.

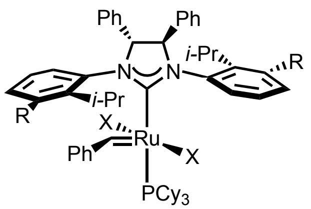


- Only 29% ee was observed using **12-Mo. 14-Mo** is the catalyst of choice for synthesizing non-racemic acetals.

Weatherhead, G. S.; Houser, J. H.; Ford, J. G.; Jamieson, J. Y.; Schrock, R. R.; Hoveyda, A. H. *Tetrahedron Lett.* **2000**, *41*, 9553–9559.

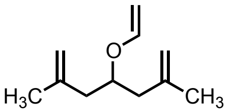
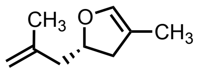
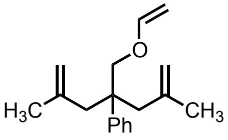
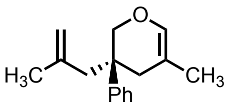
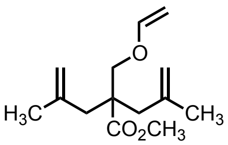
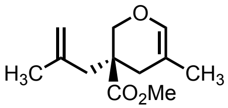


16-Mo



17-Ru: R = H, X = I
18-Ru: R = i-Pr, X = Cl

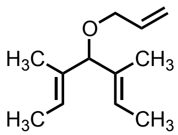
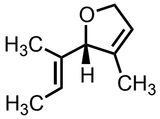
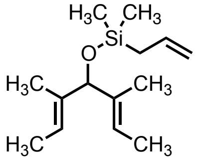
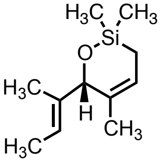
- Catalyst **16-Mo** was found to be effecive for the synthesis of cyclic enol ethers by an enantioselective desymmetrizing RCM:

substrate	product	yield (%)	**16-Mo** (mol%)	time (h)	temp (ºC)	ee (%)
		70	10	6	22	90
		96	15	20	22	87
		94	15	17	22	94

*The absolute stereochemistry of the RCM products was not reported.

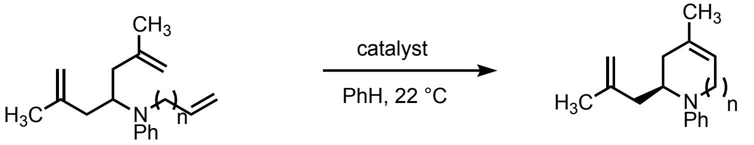
Lee, A.-L.; Malcolmson, S. J.; Puglisi, A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 5153–5157.

- Ruthenium based catalysts can also be used for enantioselective desymmetrizing RCM for the preparation of allyl ethers:

substrate	product	yield (%)	**catalyst** (mol%)	temp (ºC)	ee (%)
		64	**17-Ru** (4)	40	90
		77	**18-Ru** (0.8)	40	92

Funk, T. W.; Berlin, J. M.; Grubbs, R. H. J. *Am. Chem. Soc.* **2006**, *128*, 1840–1846.

- **Synthesis of azaheterocycles**
- Arylamines are compatible with Mo catalysts:



n	catalyst	%mol catalyst	time	yield	ee
1	**12-Mo**	5	20 min	78%	98%
2	**12-Mo**	2	7 h	90%	95%
3	**15-Mo**	5	20 min	93%	>98%

*The absolute stereochemistry of the RCM products was not reported.

Dolman, S. J.; Sattely, E. S.; Hoveyda, A. H.; Schrock, R. R. *J Am. Chem. Soc.* **2002**, *124*, 6991–6997.

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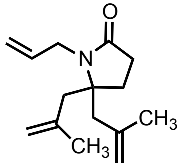
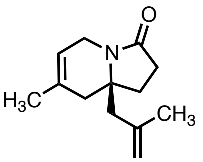
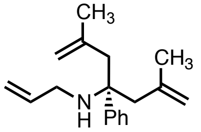
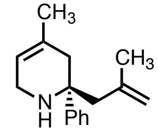
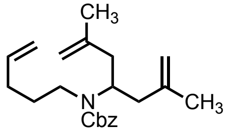
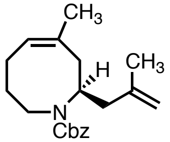
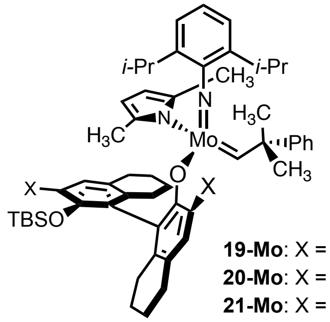
- Mo catalysts can be used for the synthesis of cyclic amides and amines, although a high catalyst loading is often required. Free secondary amines are tolerated but only when the amine contains a fully substituted α-carbon center.

substrate	product	yield (%)	**catalyst** (mol%)	time (h)	temp (ºC)	ee (%)
		91	**16-Mo** (10)	48	22	>98
		95	**15-Mo** (5)	24	22	71
		94	**13-Mo** (5)	24	22	97

*The absolute stereochemistry of the RCM products was not reported.

Sattely, E. S.; Cortez, G. A.; Moebius, D. C.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 8526–8533.

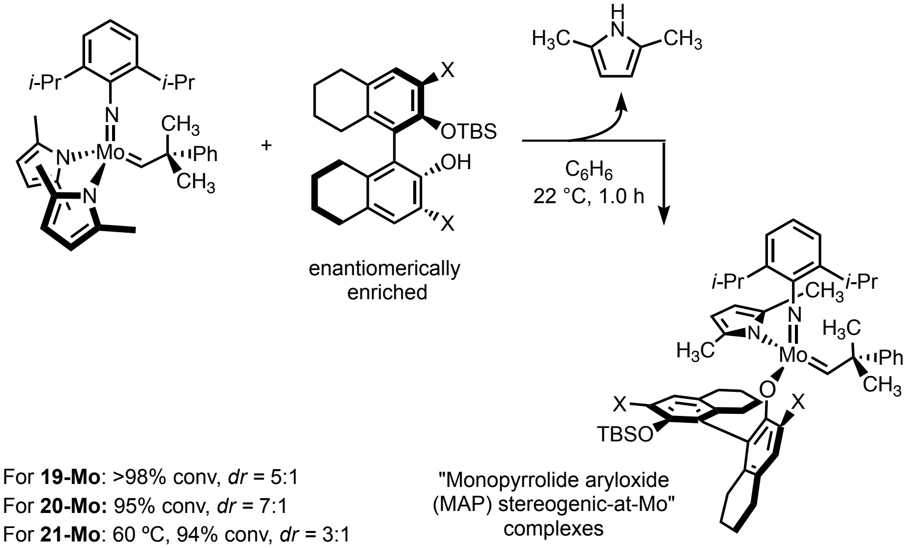
- Monopyrrolide aryloxide (MAP) complexes **19–21** exhibit improved catalytic activity in enantioselective RCM desymmetrization reactions:



19-Mo: X = Cl
20-Mo: X = Br
21-Mo: X = I

Monopyrrolide aryloxide (MAP) complexes

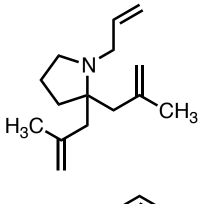
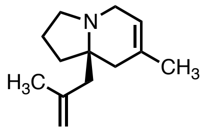
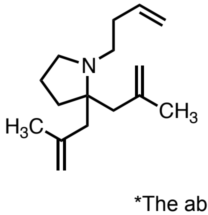
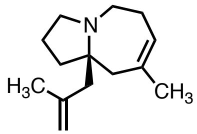
- Chiral MAP complexes are prepared from enantiomerically enriched monoprotected diols. They are sensitive to air and moisture and must be handled in the glovebox.
- These complexes are isolated as diastereomeric mixtures:



For **19-Mo**: >98% conv, *dr* = 5:1
For **20-Mo:** 95% conv, *dr* = 7:1
For **21-Mo**: 60 ºC, 94% conv, *dr* = 3:1

"Monopyrrolide aryloxide (MAP) stereogenic-at-Mo" complexes

- Kinetic studies indicate that Curtin-Hammett kinetics are operating under the reaction conditions: these diastereomeric complexes rapidly equilibrate, and one diastereomer catalyzes RCM at a faster rate.

substrate	product	**catalyst** (mol%)	yield (%)	ee (%)	**catalyst** (mol%)	yield (%)	ee (%)
		**20-Mo** (1)	>98	92	**13-Mo** (15)	<75	30
		**19-Mo** (3)	86	81	**13-Mo** (5)	ND	40

*The absolute stereochemistry of the RCM products was not reported.

Malcolmson, S. J.; Meek, S. J.; E. S. Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933–937.

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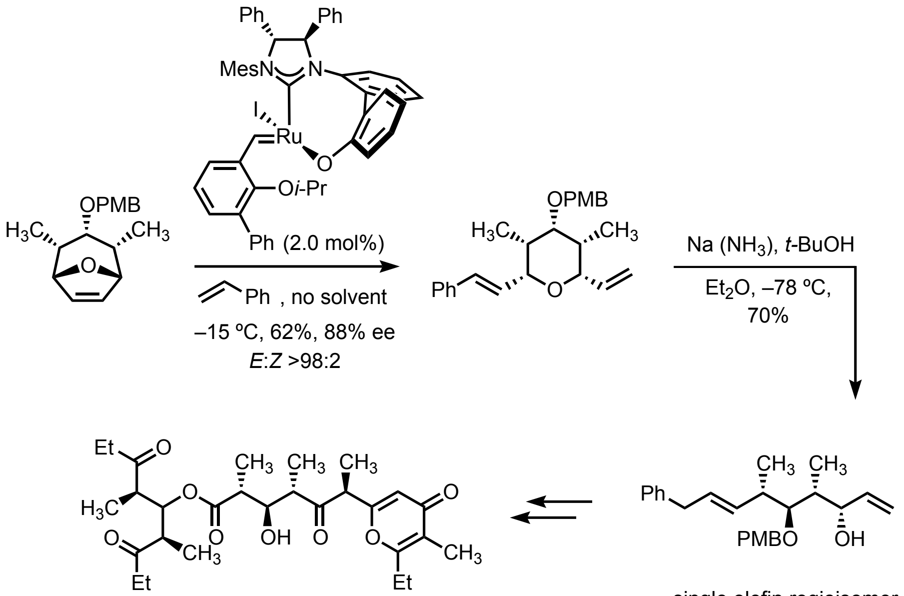
Examples of Enantioselective Olefin Metathesis in Synthesis

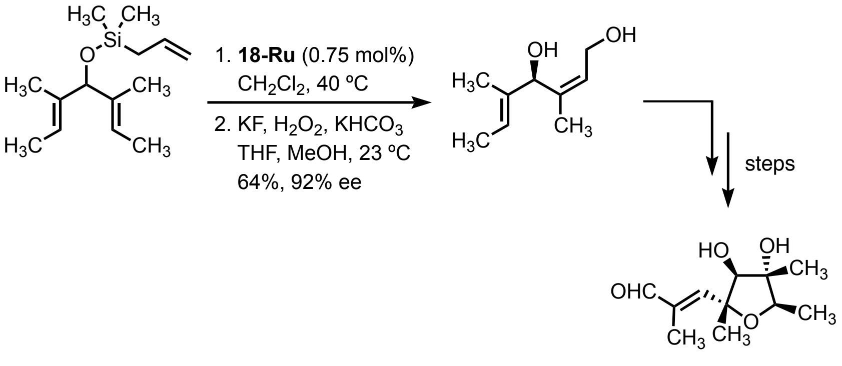
- An enantioselective ring-opening-cross-metathesis (ROCM) reaction:



baconipyrone C

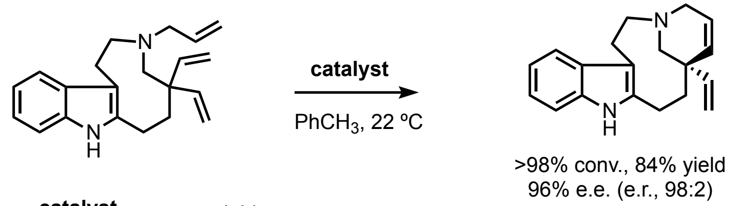
single olefin regioisomer

Gillingham D. G., Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007,** *46,* 3860–3864.

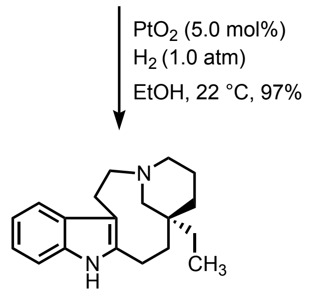


5-*epi*-citreoviral

Funk, T. W. *Org. Lett.* **2009**, *11,* 4998–5001.

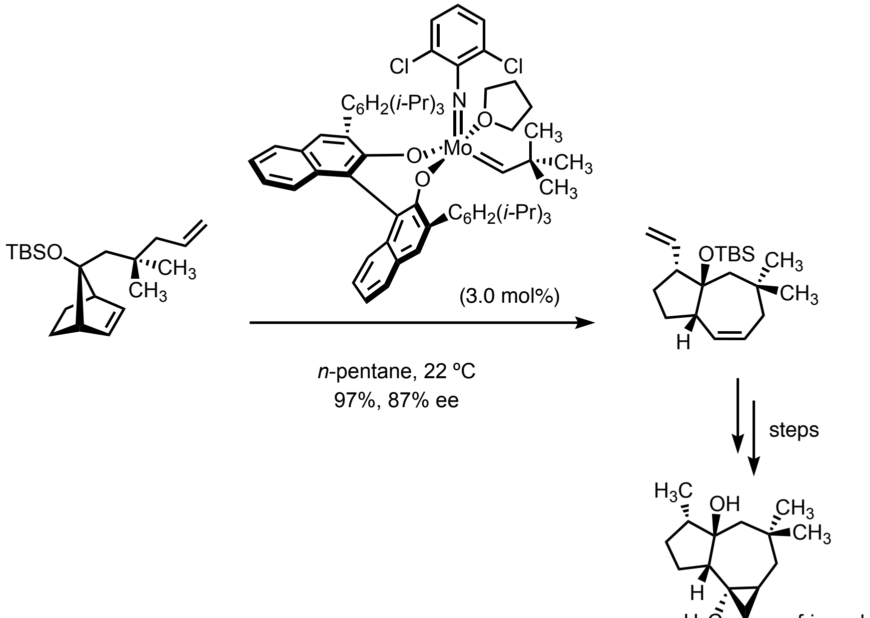


catalyst (mol%)	yield (%)	ee (%)
19-Mo (1 mol%)	84	96
20-Mo (1 mol%)	83	95
21-Mo (1 mol%)	93	93
Other Mo catalysts	<5	–



(+)-quebrachamine

Malcolmson, S. J.; Meek, S. J; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008,** *456,* 933–937.

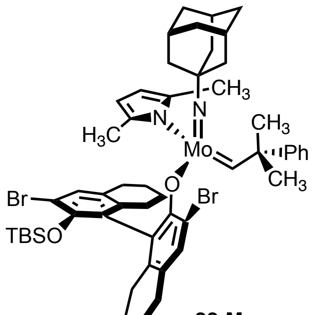


africanol

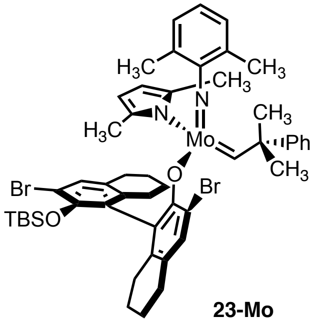
Weatherhead, G. S.; Cortez, G. A.; Schrock, R. R.; Hoveyda, A. H. *Proc. Natl. Acad. Sci., U.S.A.* **2004,** *101,* 5805–5809.

Z-Selective Olefin Metathesis

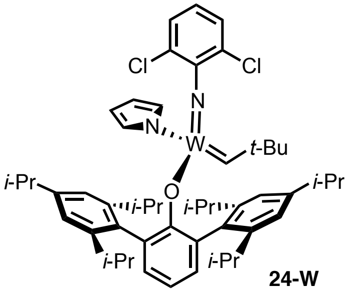
Soon-to-be-Published Review: Hoveyda, A. H.; Khan, R. K. M.; Torker, S.; Malcolmson, S. J. **2013** (We gratefully acknowledge Professor Hoveyda and co-workers for making this review available to us ahead of print).



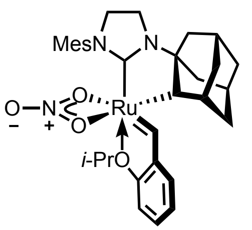
22-Mo



23-Mo

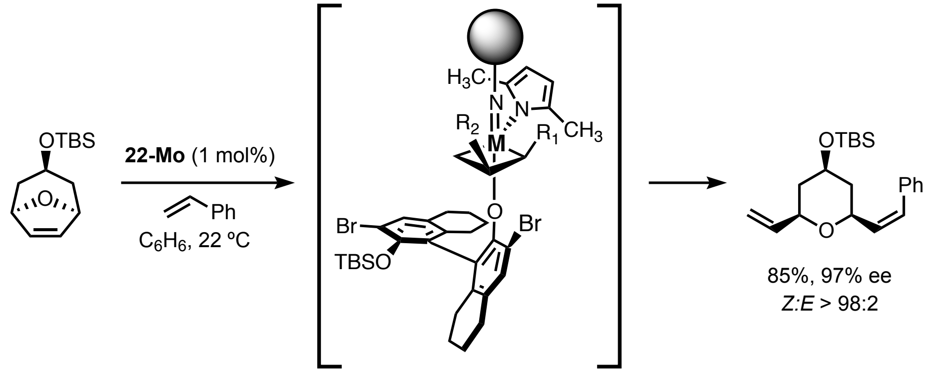


24-W



25-Ru

- Because olefin metathesis is a reversible process, metathesis catalysts typically afford the thermodynamically more stable *trans* olefin isomer.
- In 2009, a *Z*-selective Ring Opening Cross Metathesis reaction was reported, the first example of *Z*-selective olefin metathesis: The bulky, freely rotating phenoxide ligand forces the alkene substituents to be *cis* in the metallocyclobutane intermediate:



22-Mo (1 mol%)

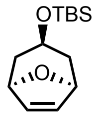
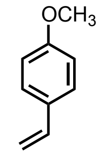
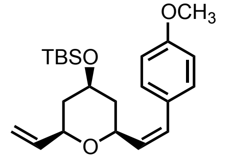
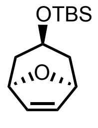
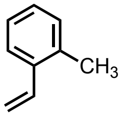
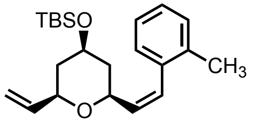
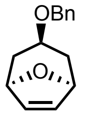
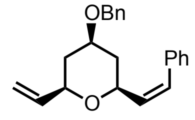
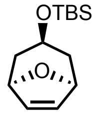
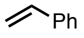
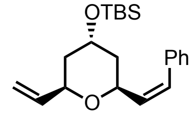
Ph

C_6H_6, 22 ºC

85%, 97% ee

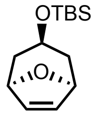
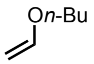
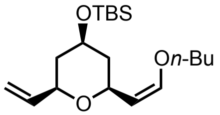
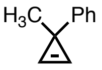
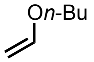
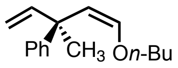
Z:*E* > 98:2

Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.

substrate	Olefin	product	yield (%)	**22-Mo** (mol%)	time (h)	temp (ºC)	ee (%)	*Z*:*E*
			80	1	0.5	22	94	95:5
			54	2	1	22	99	88:12
			75	5	1	60	84	95:5
			83	2	1	22	94	96:4

Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.

- Enol ethers can also be used:

substrate	Olefin	product	yield (%)	**22-Mo** (mol%)	time (h)	temp (ºC)	ee (%)	*Z*:*E*
			80	0.6	0.5	22	89	>98:2
			79	3	0.5	22	89	>98:2

Yu, M.; Ibrahem, I.; Hasegawa, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2012**, *134*, 2788–2799.

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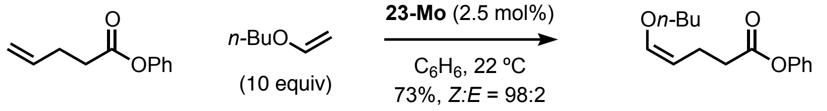
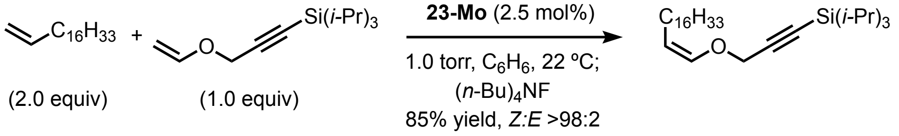
- ***Z*-Selective Cross Metathesis**
- Mo-based catalysts have been developed for *Z*-selective cross metathesis of several substrate classes.
- Enol ethers

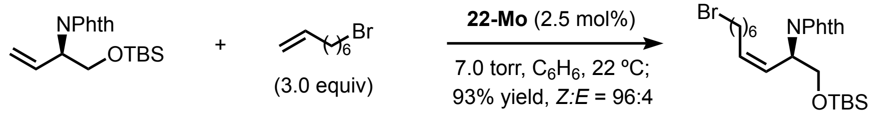


- By decreasing the reaction pressure, the stoichiometry of the reaction can be improved: lowering the pressure removes ethylene, which competitively reacts with the catalyst to form a highly reactive metal alkylidene complex that can potentially catalyze unwanted *Z*- to *E*-isomerization.

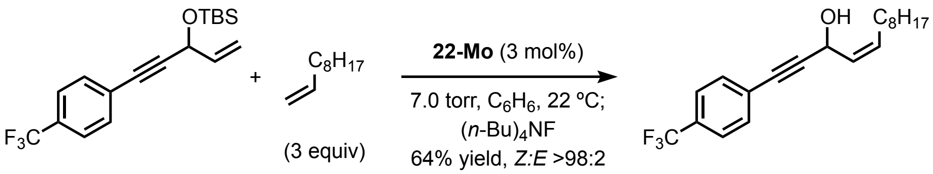


Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461–466.

- Allylic amides and ethers

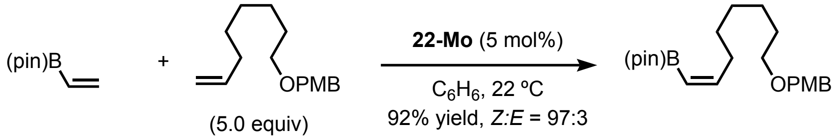


Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461–466.

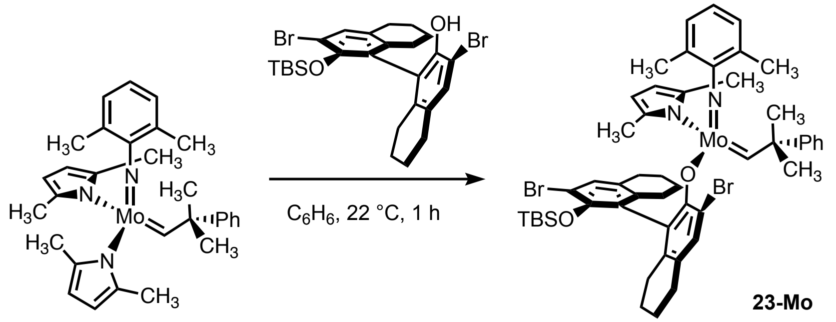


Mann, T. J.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 8395–8400.

- Z-allyl- and Z-alkenylboron compounds



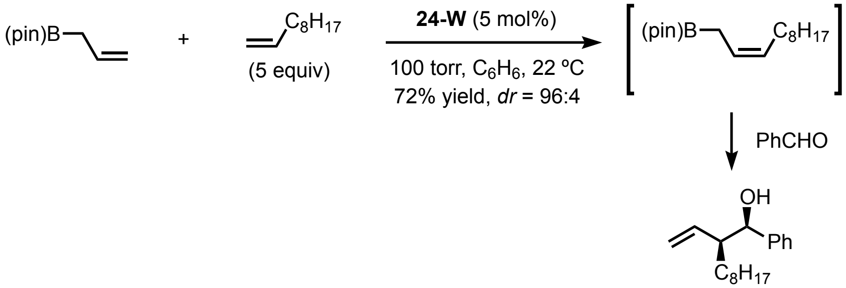
- Mo-based catalysts are sensitive to air and moisture and must be prepared *in situ* and handled in the glovebox:



23-Mo

Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.
Hock, A. S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 16373–16375.

- Tungsten-based catalysts are less reactive but more stable than Mo-based catalysts and can be handled in air. **24-W** can be used for the synthesis of *Z*-allylboron compounds. Sensitive to isolation, *Z*-allylboron compounds were prepared *in situ* and used directly in subsequent reactions:



Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026–6029.

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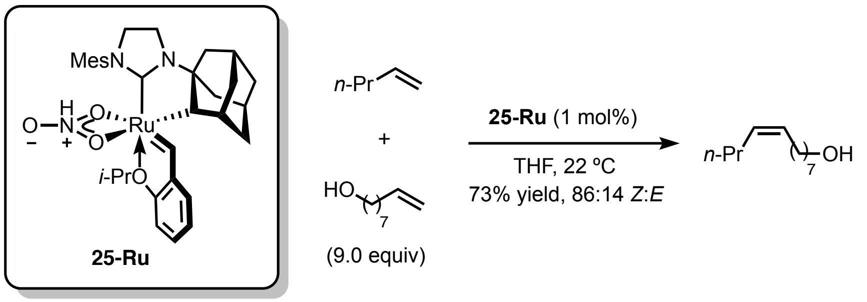
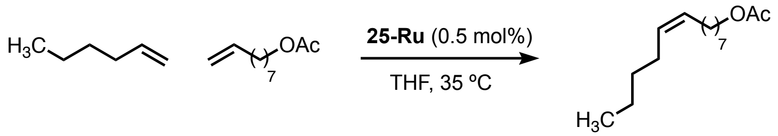
- Ruthenium-based catalysts have also been developed for *Z*-selective cross-metathesis.
- Ru catalysts exhibit better functional group tolerance compared to Mo catalysts. In the example below, free hydroxyl groups are tolerated:

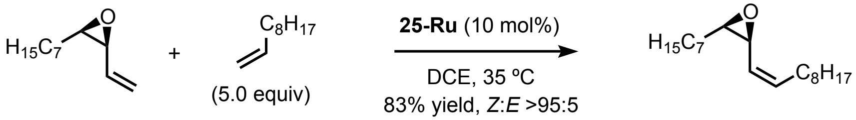


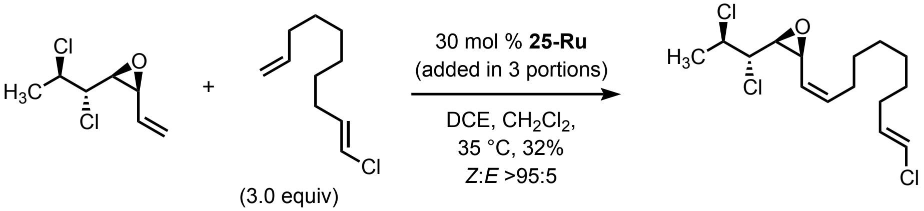
Herbert, M. B.; Marx, V. M.; Pederson, R. L.; and Grubbs, R. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 310–314.



Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **2011**, *134*, 693–699.

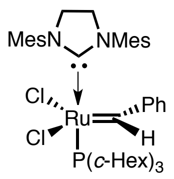
- This methodology was recently employed en route to a total synthesis of the chlorosulfolipid mytilipin A :



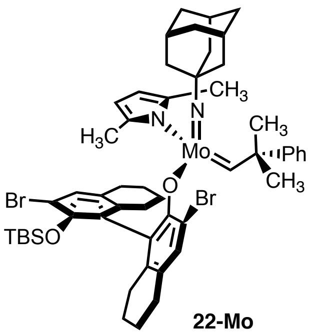


Chung, W.-j.; Carlson, J. S.; Bedke, D. K.; Vanderwal, C. D. *Angew. Chem. Int. Ed.* **2013**, *52*, 10052–10055.

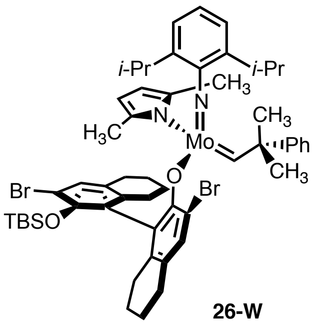
- **Z-selective Ring-Closing Metathesis (RCM)**
- Both Mo and W catalysts have been found to be effective for *Z*-selective ring-closing metathesis:



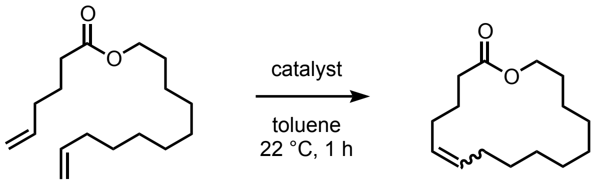
4-Ru



22-Mo



26-W



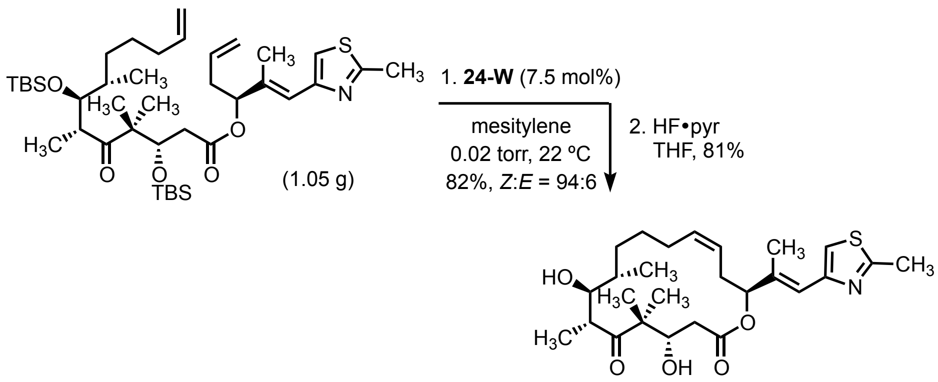
DFT calculations:
E isomer is favored
by 1.2 kcal/mol,
88:12 E/Z
thermodynamic
ratio expected

catalyst (mol%)	pressure (torr)	yield (%)	*Z:E*
4-Ru (5.0)	760	61	21:79
22-Mo (3.0)	7	62	85:15
22-Mo (1.2)	7	56	92:8
26-W (5.0)	7	62	91:9

Kiesewetter, E. T.; O'Brien, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2013**, *135*, 6026–6029.

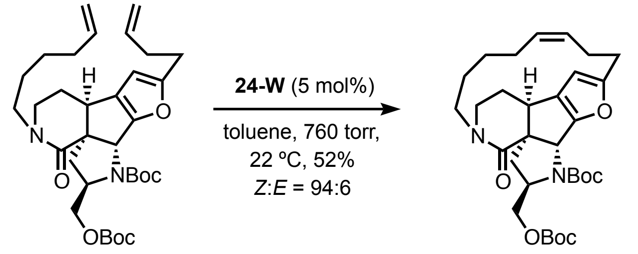
David W. Lin, Fan Liu

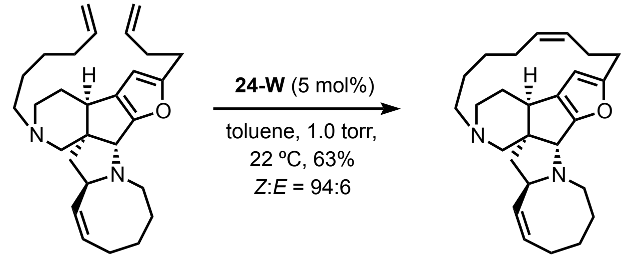
- Air-stable **24-W** was found to be optimal for the ring-closing metathesis reaction in the synthesis of epothilone C and nakadomarin A:



Epothilone C

- In the example above, Mo catalysts led to lower selectivities. The authors propose that the less reactive tungsten catalyst **24-W** possesses the right level of activity to promote RCM without olefin isomerization.

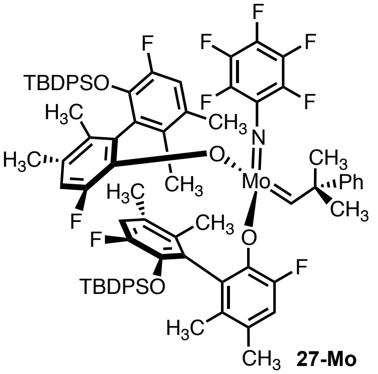




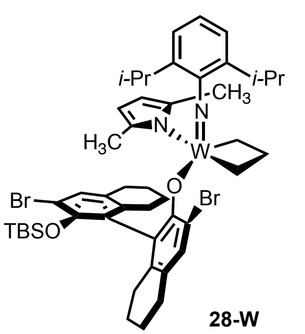
nakadomarin A

- In all cases above, a mixture of *E/Z* olefin isomers was obtained when traditional Ru catalysts were used.

Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *479*, 88–93.

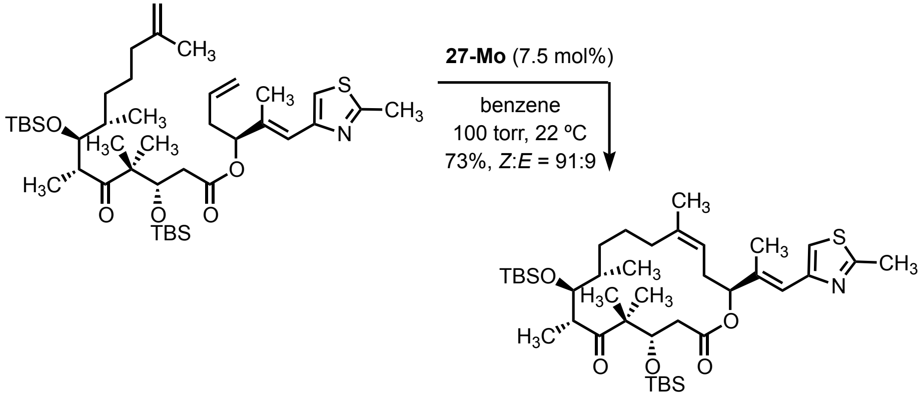


27-Mo



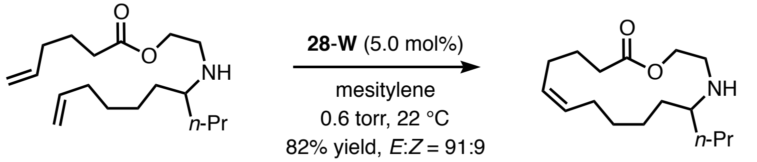
28-W

- Tri-substituted alkenes can be prepared:



Wang, C.; Haeffner, F; Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2013**, *52*, 1939–1943.

- **28-W** can be handled in air under up to 80% humidity and can catalyze metathesis in the presence of free amines:



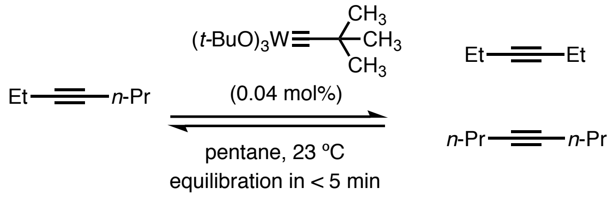
epilachnene

C. Wang, C.; M. Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 2726–2740.

Metathesis of Alkynes and Diynes

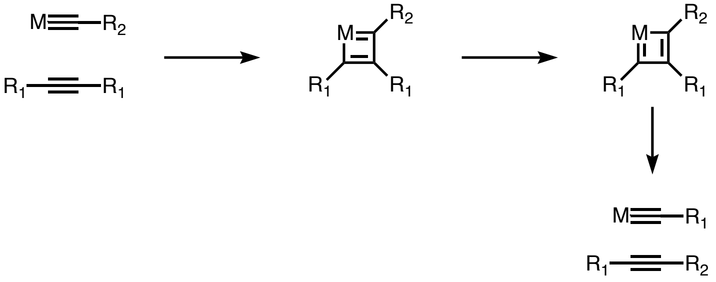
Review:
Fürstner, A.; Davies, P. W. *Chem. Commun.* **2005**, 2307–2320.
Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, *52*, 2794–2819.

- The first well-defined pre-catalyst for alkyne metathesis was reported in 1981:



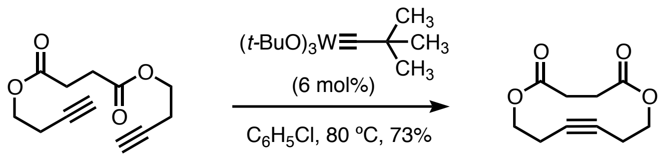
Wengrovius, J. H.; Sancho, J.; Schrock, R. R. *J. Am. Chem. Soc.* **1981**, *103*, 3932–3934.

- **Mechanism**: the mechanism of alkyne metathesis parallels that of alkene metathesis.



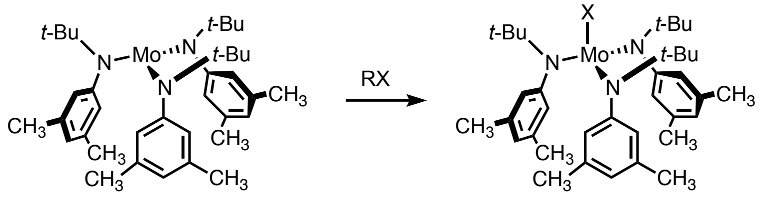
Proposal: Katz, T. J.; McGinnis, J. *J. Am. Chem. Soc.* **1975**, *97*, 1592–1594.
Experimental verification: Churchill, M. R.; Ziller, J. W.; Freudenberger, J. H.; Schrock, R. R. *Organometallics* **1984**, *3*, 1554–1562.

- This tungsten catalyst was shown to be effective for alkyne ring-closing metathesis, but with limited functional group compatibility (Lewis-basic functional groups such as basic nitrogens, polyethers, and many heterocycles are not tolerated):



Fürstner, A.; Seidel, G. *Angew. Chem. Int. Ed.* **1998**, *37*, 1734–1736. .

- Inspired by the activation of the triple bond of molecular nitrogen with molybdenum complexes of the general type Mo[N(t-Bu)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.

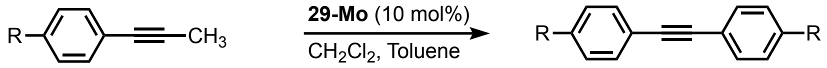


29-Mo

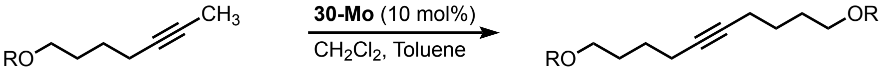
30-Mo, X = Cl
31-Mo, X = Br

- Oxidation of the Mo(III)-precatalyst **29-Mo** occurs *in situ* upon addition of ~25 equivalents of additives such as CH_2Cl_2, CH_2Br_2, CH_2I_2, and BnCl.

- Alkyne metathesis may be achieved with equal efficiency either by *in situ* oxidation of precatalyst **29-Mo** or by use of pure Mo(IV)-catalysts **30-Mo** and **31-Mo**.



R = H 60%
R = CN 58%



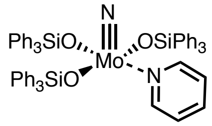
R = CH_3 59%
R = THP 55%

- Catalyst **30-Mo** is sensitive to acidic protons such as those of secondary amides.
- Terminal alkynes are incompatible with the catalysts.
- Use of CH_2Cl_2 as the reaction solvent or the addition of ~25 equivalents of CH_2Cl_2 per mol of **29-Mo** in toluene are equally effective.
- Catalysts **30-Mo** and **31-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. However, because they react with dinitrogen, they must be handled under an argon atomsphere.

Fan Liu

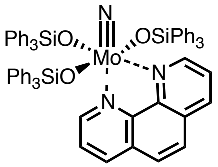
Other Alkyne Metathesis Catalysts

- Since the initial reports, newer alkyne metathesis pre-catalysts have been developed that show improved stability and functional group compatibilities:



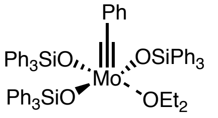
32-Mo

- can be weighed in air but must be stored under an inert atomsphere.
- not compatible with epoxides, aldehydes, and acid chlorides



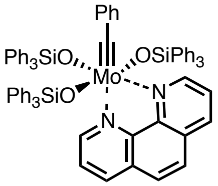
33-Mo

- can be stored indefinitely on the benchtop.
- The catalyst is activated by treatment with $MnCl_2$ and metathesis takes place at 80 ºC.



34-Mo

- air and moisture sensitive
- more reactive than other Mo catalysts; one of the most reactive metathesis catalysts known.



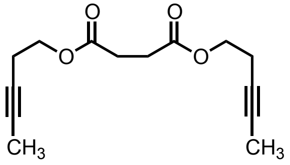
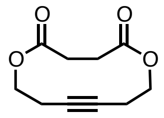
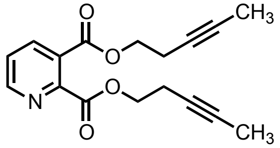
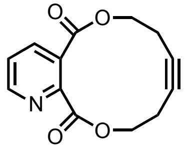
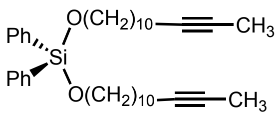
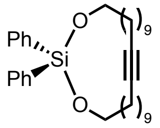
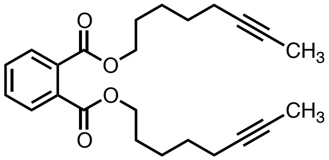
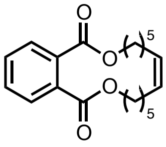
35-Mo

- can be weighed in air but must be stored under an inert atomsphere.
- The catalyst is activated by treatment with $MnCl_2$ and heating at 80 ºC. Subsequent RCM can take place at room temperature.
- Excellent functional group compatibility: epoxides, acetals, primary tosylates and heterocycles are all tolerated.

- 5Å MS is often used in alkyne metathesis reactions to absorb 2-butyne and drive the reaction to completion.

Bindl, M.; Stade, R.; Heilmann, E. K.; Picot, A.; Goddard, R.; Fürstner, A. *J. Am. Chem. Soc.* **2009**, *131*, 9468–9470.
Heppekausen, J.; Stade, R.; Goddard, R.; Fürstner. *J. Am. Chem. Soc.* **2010**, *132*, 11045–11057.

RCM of Diynes

		yield of product (%) using catalyst			
substrate	product	**30-Mo**[a] (10 mol%)	**33-Mo**[b] (10 mol%)	**34-Mo**[c] (2 mol%)	**35-Mo**[d] (5 mol%)
		91	91	73	78
		88	–	–	–
		74	–	–	–
		–	70	97	94

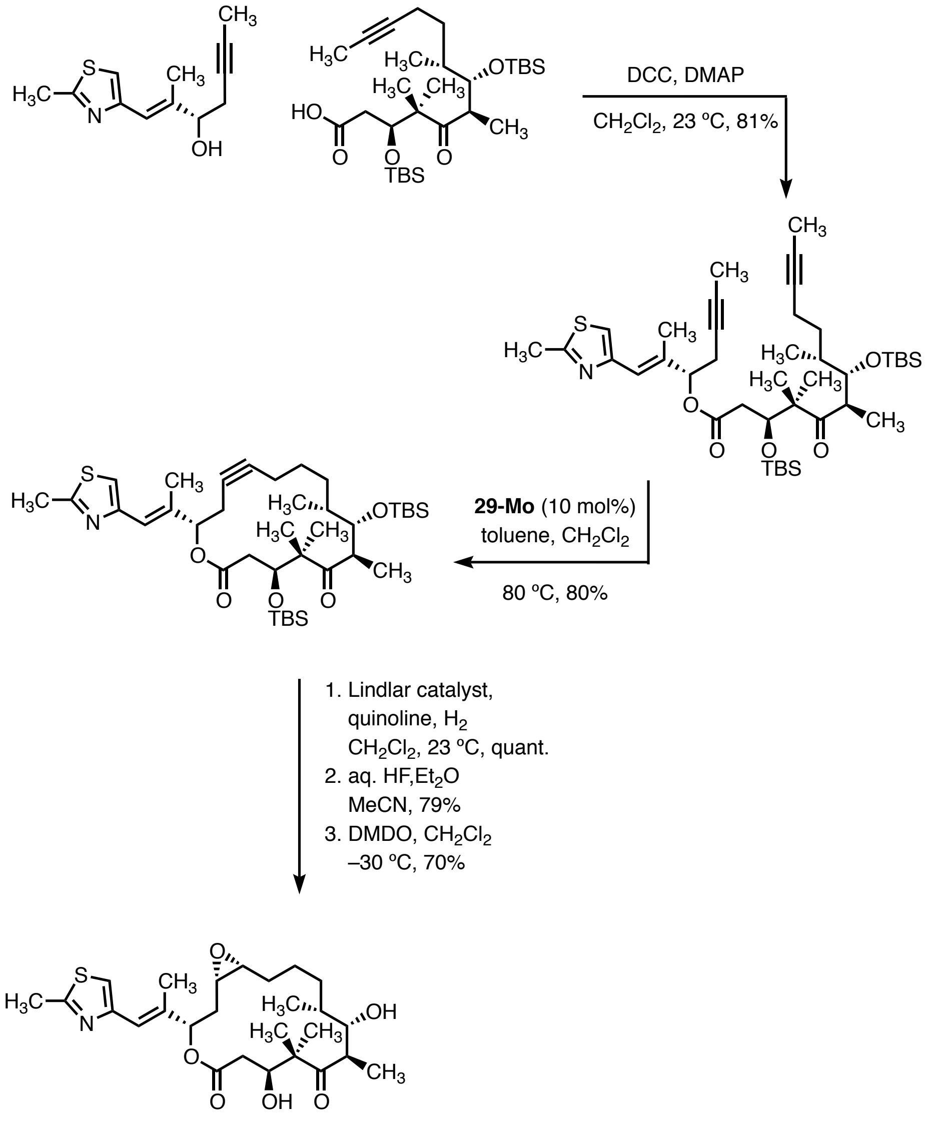
[a]Reactions conducted in toluene at 80 °C for 20-48 h; **30-Mo** was generated *in situ* from **29-Mo** and CH_2Cl_2 (~25 equiv).
[b]$MnCl_2$ (10 mol%), toluene, 80 ºC.
[c]toluene, 23 ºC, 5Å MS.
[d]$MnCl_2$ (5 mol%), toluene, 80 ºC; then addition of substrate, 5Å MS, 23 ºC

Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453–9454
Bindl, M.; Stade, R.; Heilmann, E. K.; Picot, A.; Goddard, R.; Fürstner, A. *J. Am. Chem. Soc.* **2009**, *131*, 9468–9470.
Heppekausen, J.; Stade, R.; Goddard, R.; Fürstner. *J. Am. Chem. Soc.* **2010**, *132*, 11045–11057.

Fan Liu, M. Movassaghi

Alkyne Metathesis in Synthesis

- Synthesis of Epothilone:



DCC, DMAP

CH_2Cl_2, 23 ºC, 81%

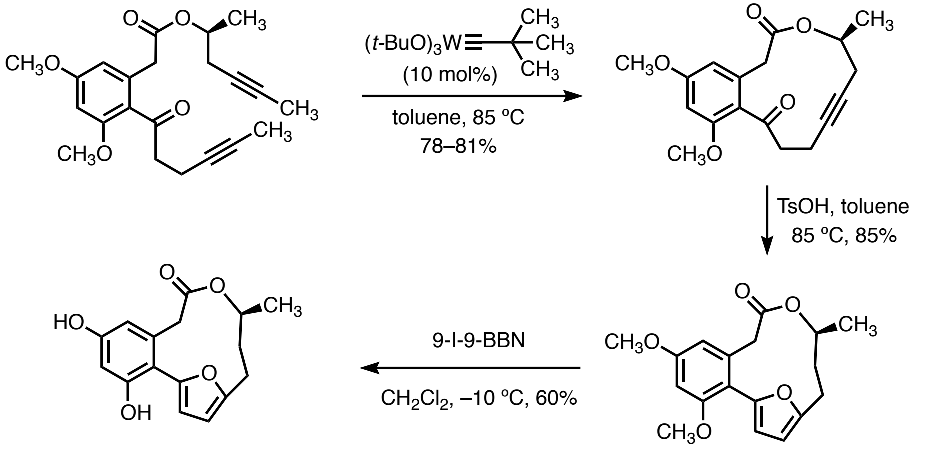
29-Mo (10 mol%)
toluene, CH_2Cl_2
80 ºC, 80%

1. Lindlar catalyst, quinoline, H_2 CH_2Cl_2, 23 ºC, quant.
2. aq. HF,Et_2O MeCN, 79%
3. DMDO, CH_2Cl_2 –30 ºC, 70%

epothilone A

Fürstner, A.; Mathes, C.; Lehmann, C. W. Chem. Eur. J. 2001, 7, 5299–5317.
Fürstner, A.; Mathes, C. Grela, K. Chem. Commun. 2001, 1057–1059.

- Furan Synthesis:



$(t\text{-BuO})_3W\equiv C\text{-}C(CH_3)_3$ (10 mol%)
toluene, 85 ºC
78–81%

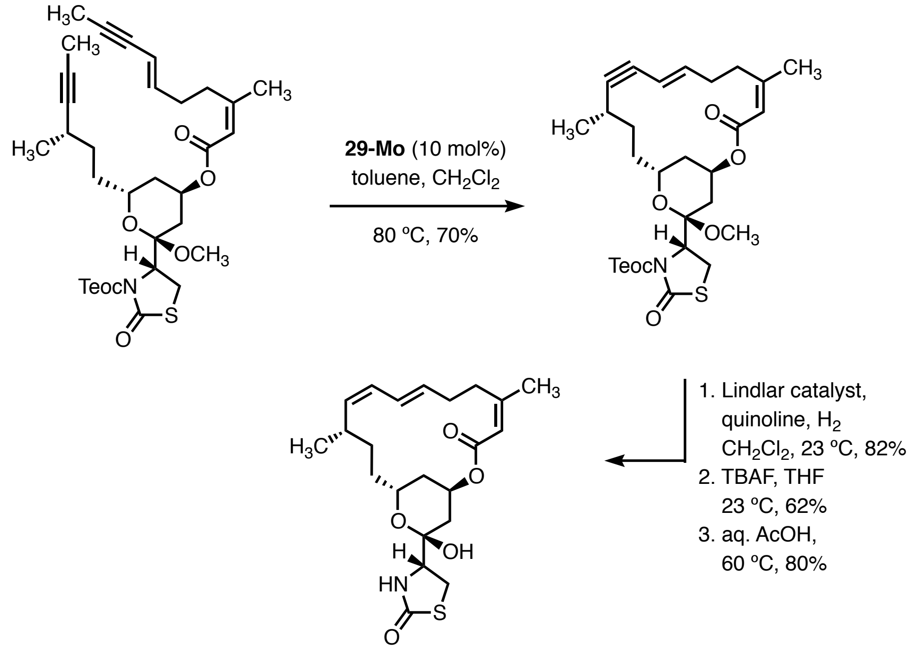
TsOH, toluene
85 ºC, 85%

9-I-9-BBN
CH_2Cl_2, –10 ºC, 60%

citreofuran

Fürstner, A.; Castanet, A. S.; Radkowski, K.; Lehmann, C. W. *J. Org. Chem.* **2003**, *68*, 1521–1528.

- *Z,E*-diene synthesis:



29-Mo (10 mol%)
toluene, CH_2Cl_2
80 ºC, 70%

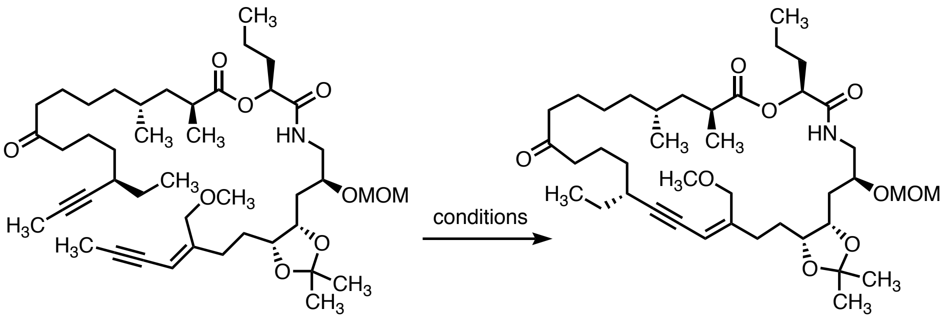
1. Lindlar catalyst, quinoline, H_2 CH_2Cl_2, 23 ºC, 82%
2. TBAF, THF 23 ºC, 62%
3. aq. AcOH, 60 ºC, 80%

latrunculin A

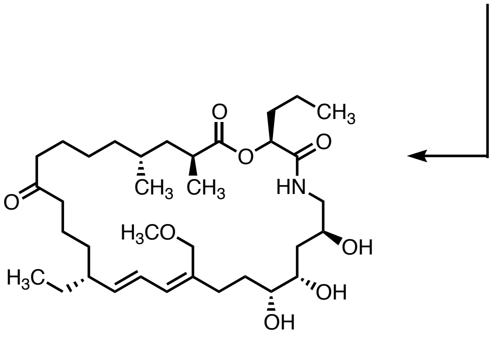
Fürstner, A.; Laurent, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 3462–2466.

Fan Liu

- *E,E*-diene synthesis (In the example below, 5Å MS is used to absorb 2-butyne to drive the reaction to completion):



conditions	yield
29-Mo (40–50 mol%) toluene, CH_2Cl_2, 80 ºC	79%
34-Mo (2 mol%) toluene, 5Å MS, 23 ºC,	79%

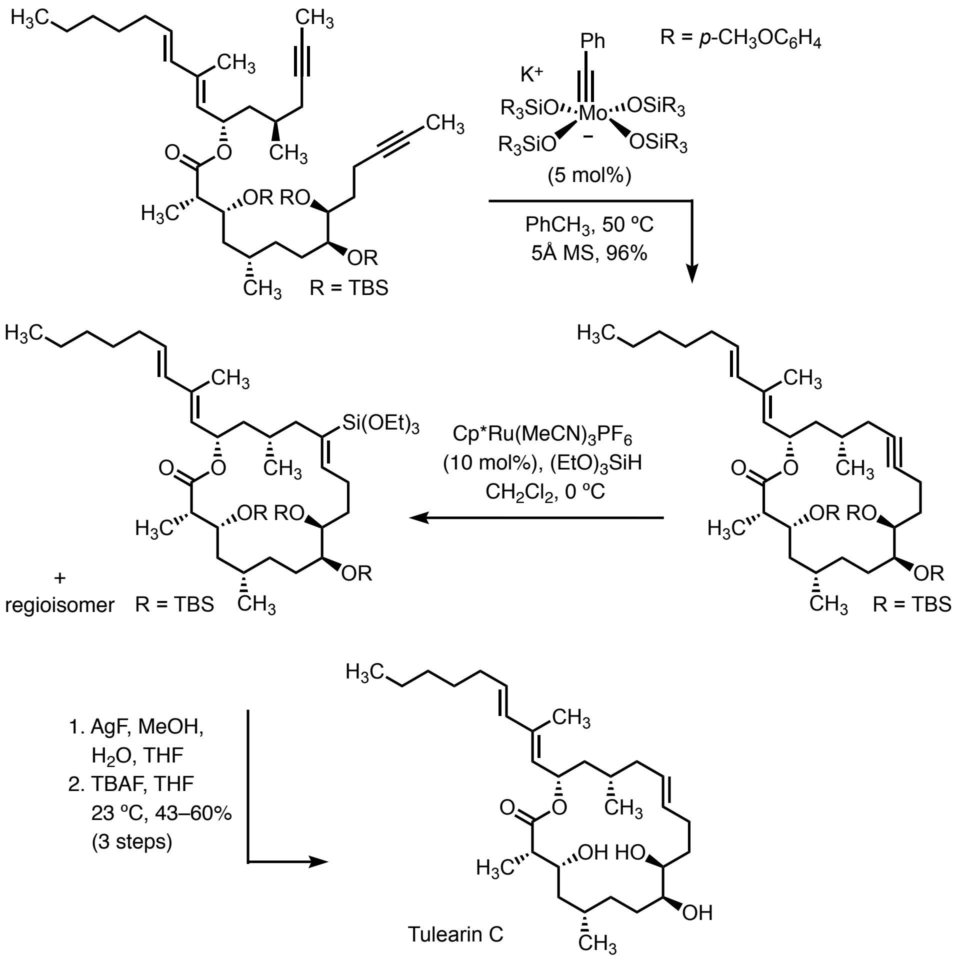


1. $Cp^*Ru(MeCN)_3PF_6$ (30 mol%), $(EtO)_3SiH$, toluene, 23 ºC 68%, *E/Z* > 4:1
2. AgF, MeOH, H_2O THF, 94%
3. $HClO_4$, 38–52%

myxovirescin A_1

Fürstner, A.; Bonnekessel, M.; Blank, J. T.; Radkowski, K.; Seidel, G.; Lacombe, F.; Gabor, B.; Mynott, R. *Chem. Eur. J.* **2007**, *13*, 8762–8783.
Heppekausen, J.; Stade, R.; Goddard, R.; Fürstner. *J. Am. Chem. Soc.* **2010**, *132*, 11045–11057.
Fürstner, A.; Radkwoski, K. *Chem. Commun.* **2002**, 2182–2183.
Lacombe, F.; Radkowski, K. Seidel, G.; Fürstner, A. *Tetrahedron*, **2004***, 60,* 7315–7324.

For an alternative method of alkyne reduction to the *E* alkene, see: Sundararaju, B.; Fürstner, A. *Angew. Chem. Int. Ed.* **2013**, DOI: 10.1002/anie.201307584.



(5 mol%)

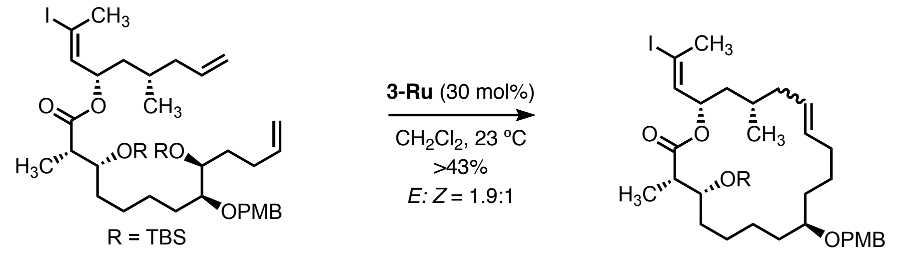
$PhCH_3$, 50 ºC
5Å MS, 96%

$Cp^*Ru(MeCN)_3PF_6$ (10 mol%), $(EtO)_3SiH$ CH_2Cl_2, 0 ºC

1. AgF, MeOH, H_2O, THF
2. TBAF, THF 23 ºC, 43–60% (3 steps)

Lehr, K.; Mariz, R.; Leseurre, L.; Gabor, B.; Fürstner, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 11373–11377.

- For comparison:



3-Ru (30 mol%)

CH_2Cl_2, 23 ºC
>43%
E: Z = 1.9:1

Mandel, A. L.; Bellosta, V.; Curran, D. P.; Cossy, J. *Org. Lett.* **2009**, *11*, 3282–3285.

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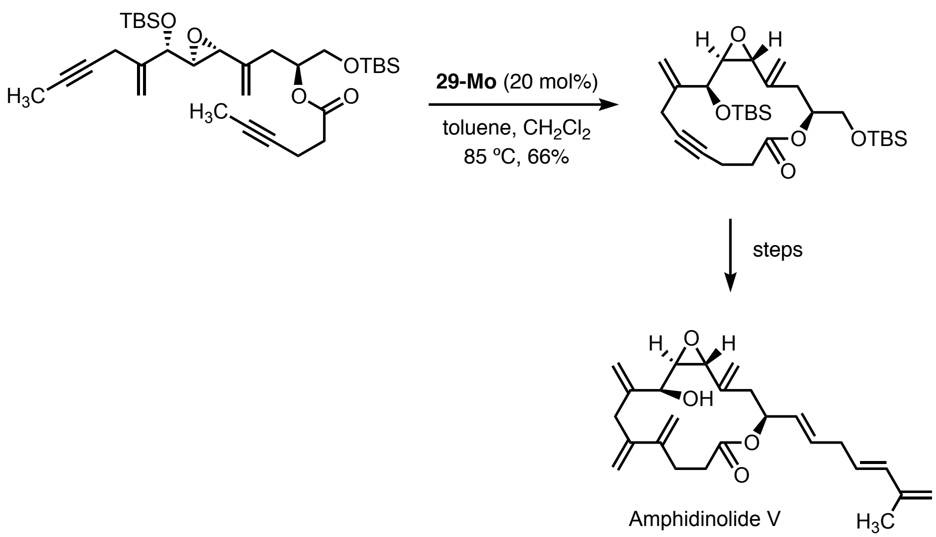
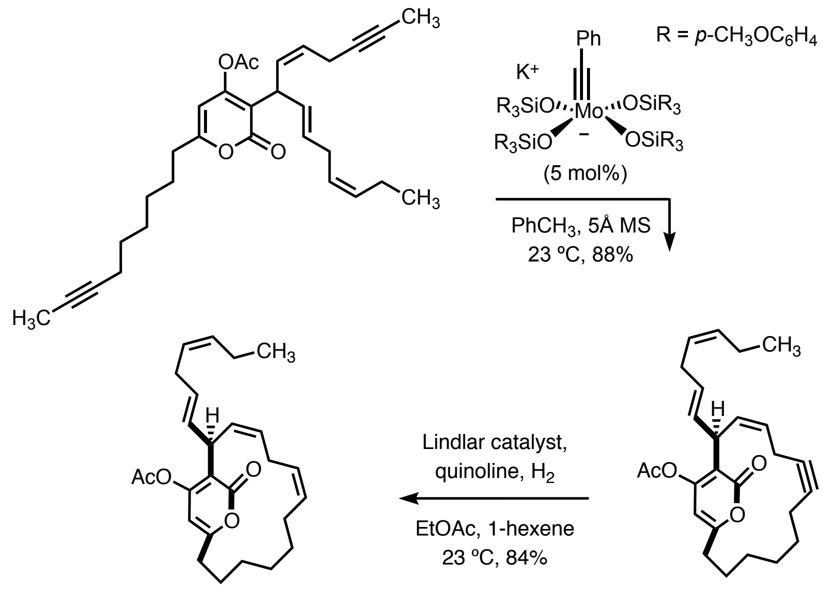
- Synthesis of amphidinolide V:



Amphidinolide V

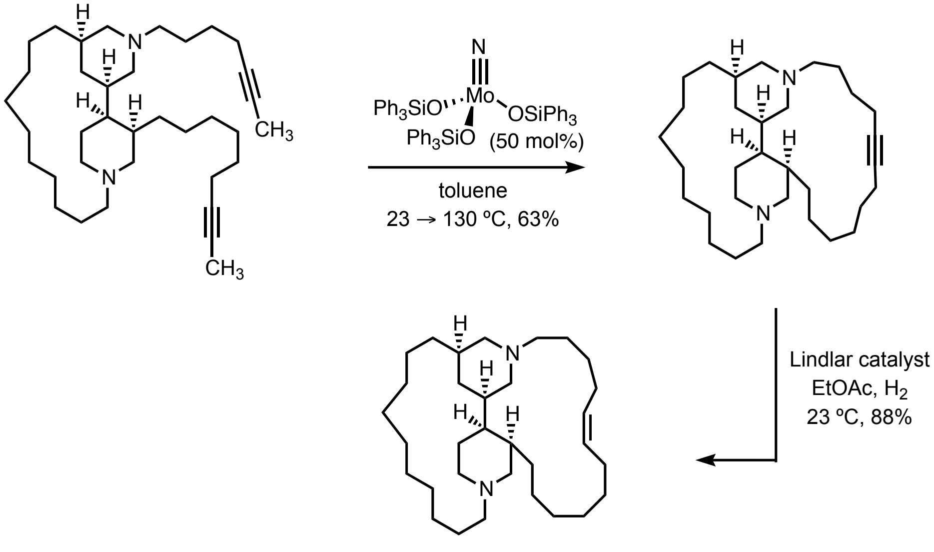
Furstner, A.; Larionov, O.; Flugge, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 5545–5548.

- Olefins are inert in macrocyclic alkyne metathesis:



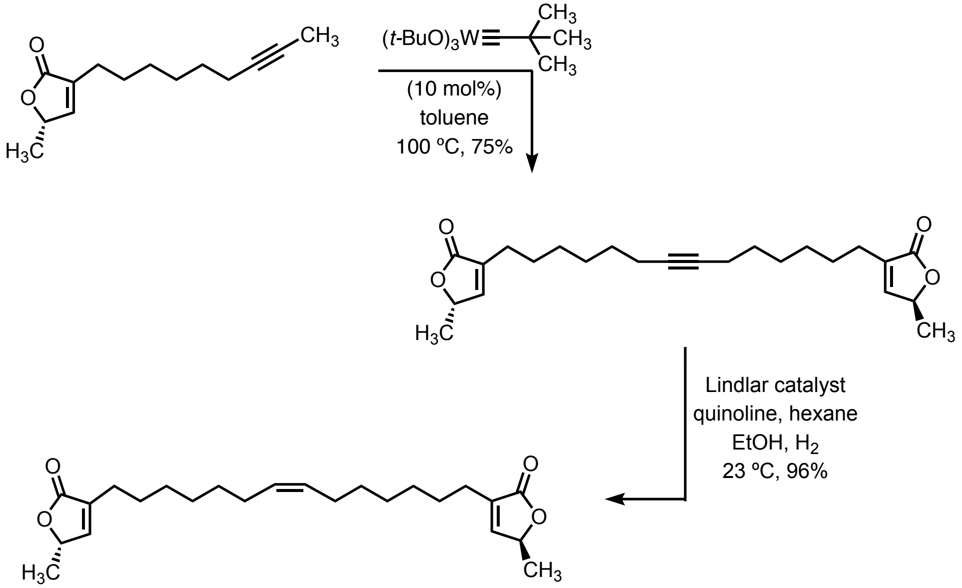
(±)-Neurymenolide A Acetate (±)

Chaladaj, W.; Corbet, M.; Furstner, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 6929–6933.



haliclonacyclamine C

Smith, B. J.; Sulikowski, G. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 1599–1602.

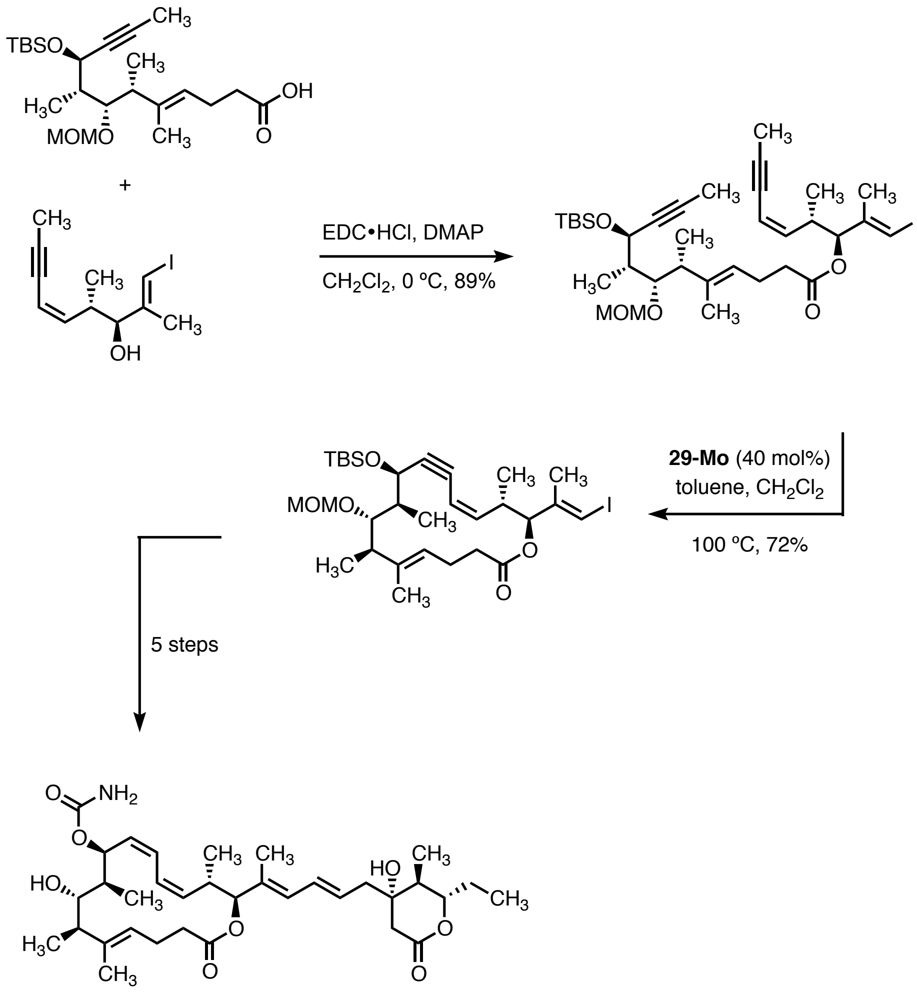


(*S*,*S*)-Dehydrohomoancepsenolidea

Fürstner, A.; Dierkes, T. *Org. Lett.* **2000**, *2*, 2463–2465.

Alpay Dermenci, Fan Liu

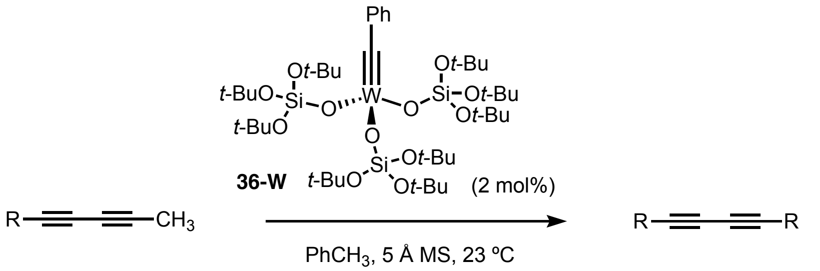
- Synthesis of leiodermatolide:

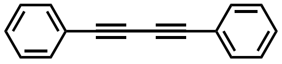
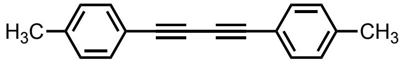
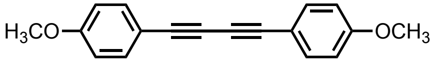
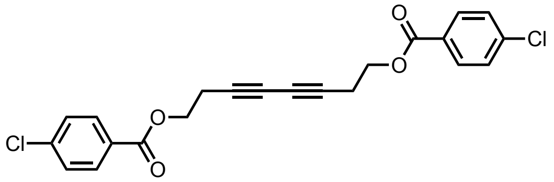
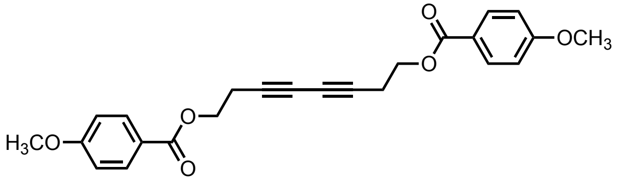


leiodermatolide

Willwacher, J.; Kausch-Busies, N.; Fürstner, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 12041–12046.

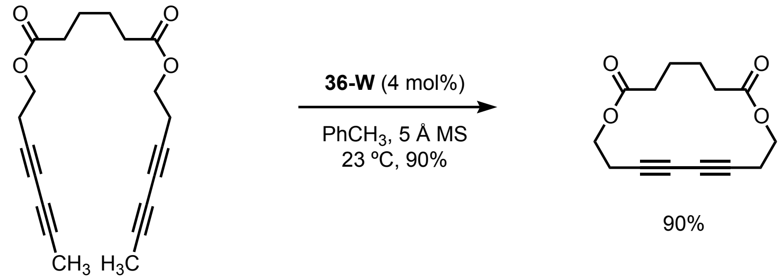
- **Diyne Metathesis**
- Tungsten catalyst **36-W** was found to be effective for diyne metathesis:

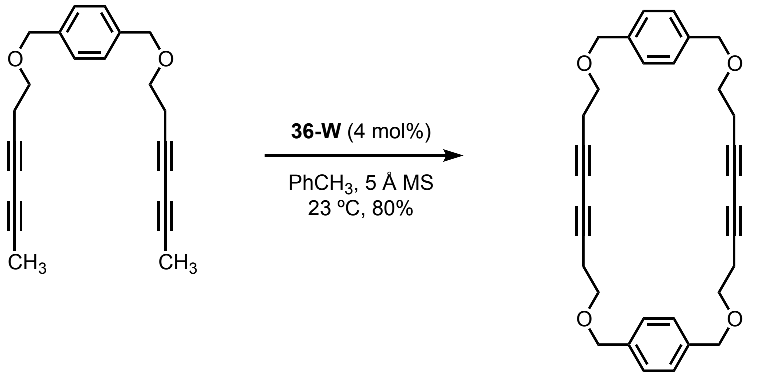


Product	Yield
	97
	95
	97
	95
	96
$Me_3Si-C\equiv C-C\equiv C-SiMe_3$	80

Lysenko, S.; Volbeda, J.; Jones, P. G.; Tamm, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 6757–6761.

- Diyne ring-closing metathesis:





Lysenko, S.; Volbeda, J.; Jones, P. G.; Tamm, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 6757–6761.