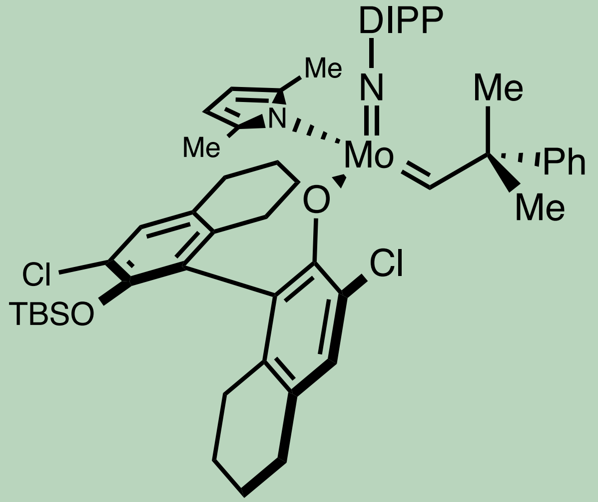
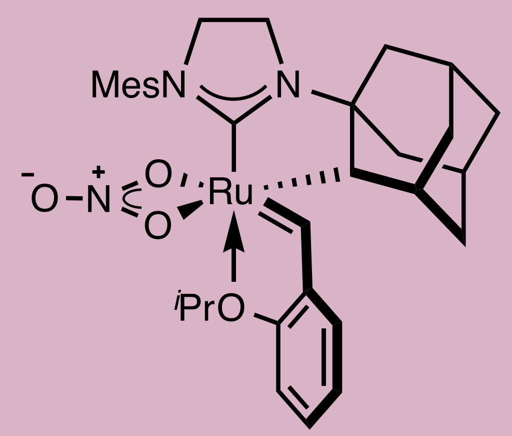
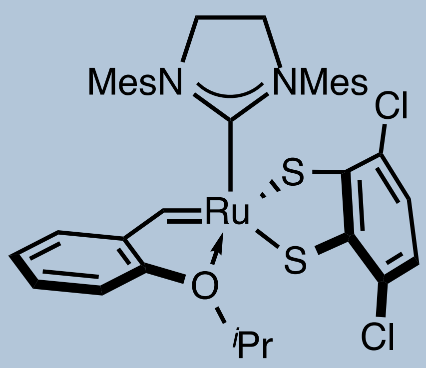
Recent Advances in Selective Olefin Metathesis Reactions





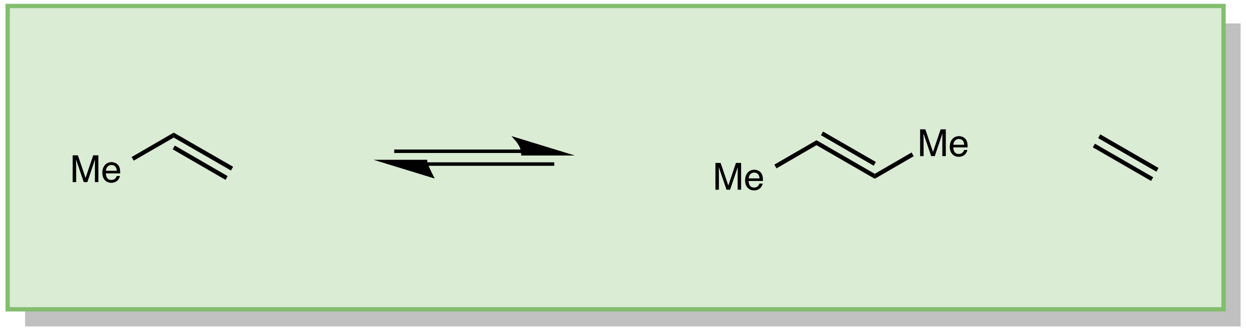


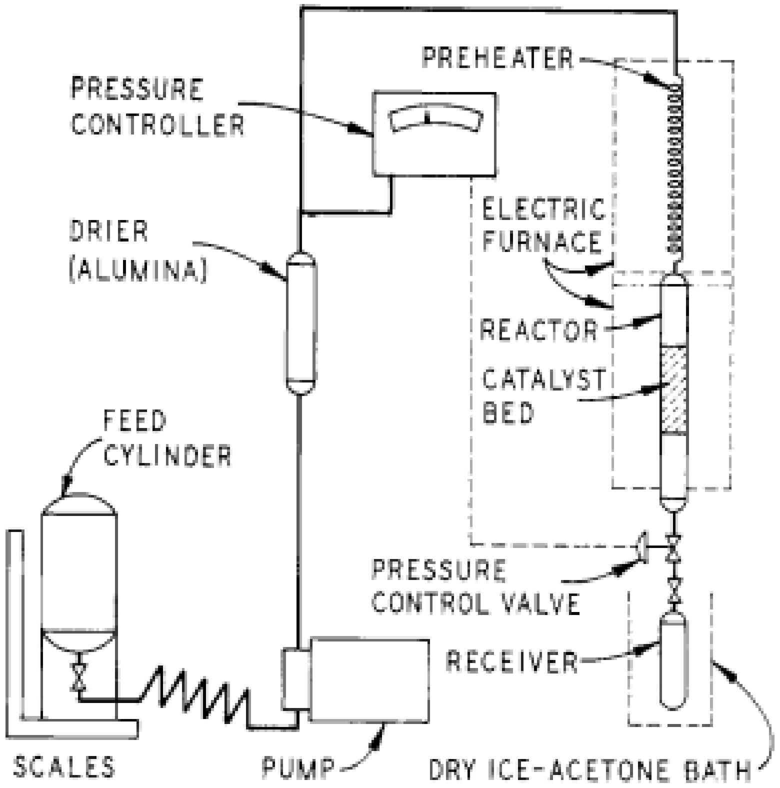
Jeffrey Lipshultz
Group Meeting
MacMillan Group
January 22, 2015

Olefin Metathesis

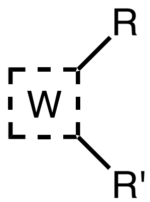
Initial Discoveries

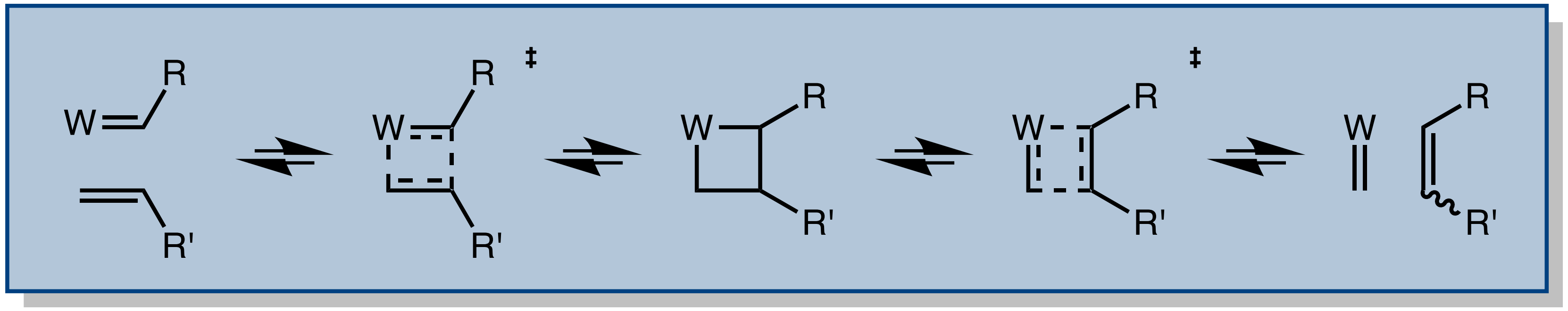
- Phillips Triolefin Process (1964)
  - $Mo(CO)_6 \bullet AlO_2$, $WO_3 \bullet SiO_2$





- Chauvin first proposed metallacyclobutane intermediate (1971)
  - Previously, coordinated *quasicyclobutane* was widely accepted intermediate





Calderon, N.; Chen, H.Y.; Scott, K.W. *Tetrahedron Lett.* **1967**, *34*, 3327.

Herisson, P.J.-L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161.

Heckelsberg, L.F.; Banks, R.L.; Bailey, G.C. *Ind. Eng. Chem. Prod. Red. Dev.* **1968**, *7*, 29.

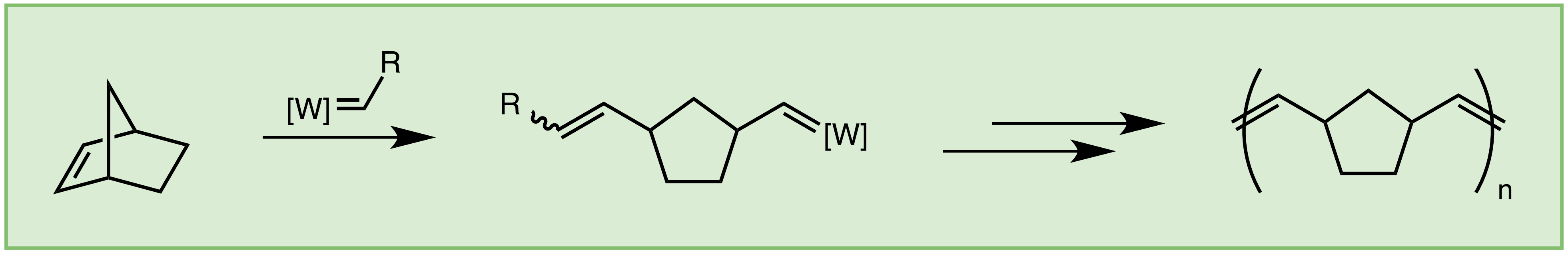
Banks, R.L.; Bailey, G.C. *Ind. Eng. Chem. Prod. Res. Dev.* **1964**, *3*, 170.

Olefin Metathesis

Practical Developments

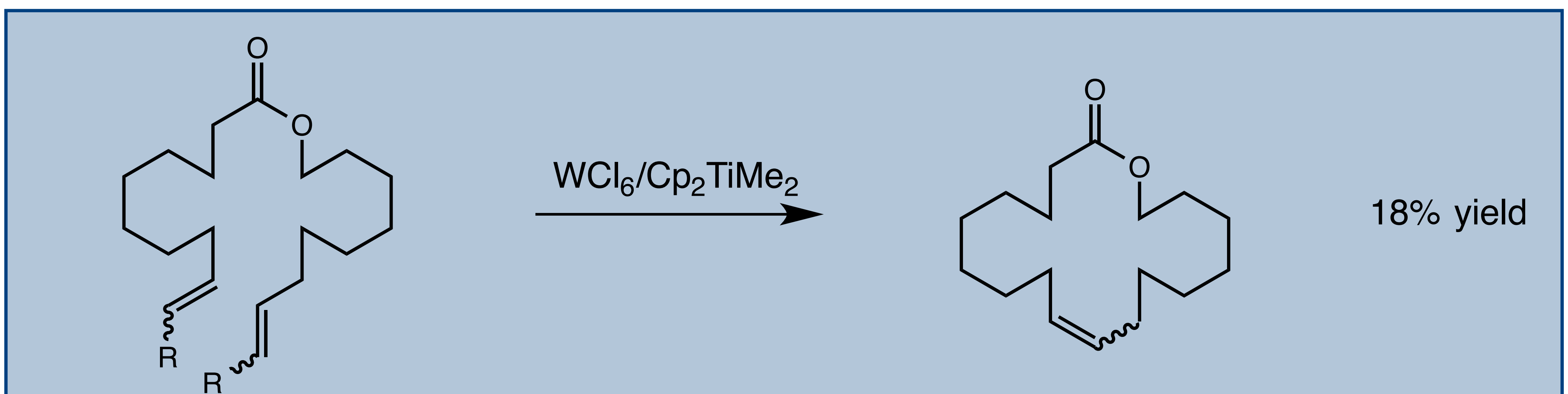
Ring-opening Metathesis Polymerization (ROMP)

Norsorex Process for polynorbornene (1980)



Ring-closing Metathesis (RCM)

First applied with *in situ* prepared W/Ti mixed catalysts



Tsuji, J.; Hashiguchi, S. *Tetrahedron Lett.* **1980**, *21*, 2955.

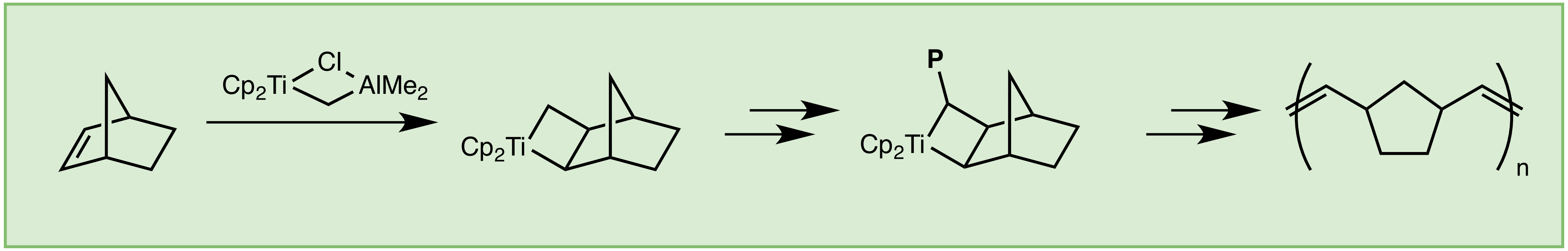
Ohm, R.F. *Chemtech* **1980**, 198.

Olefin Metathesis

Well-defined Catalysts

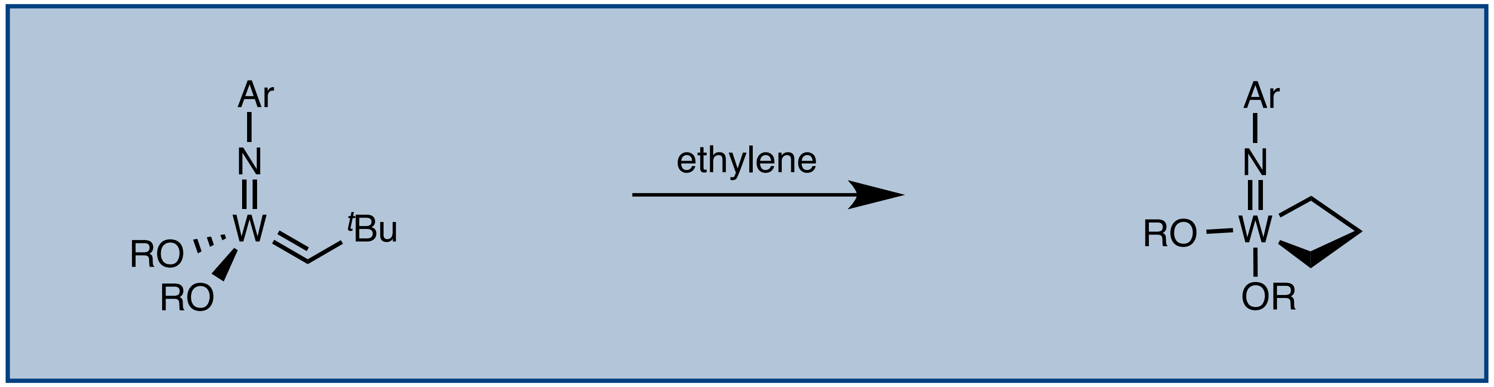
■ Ring-opening Metathesis Polymerization with Tebbe's Reagent (1986)

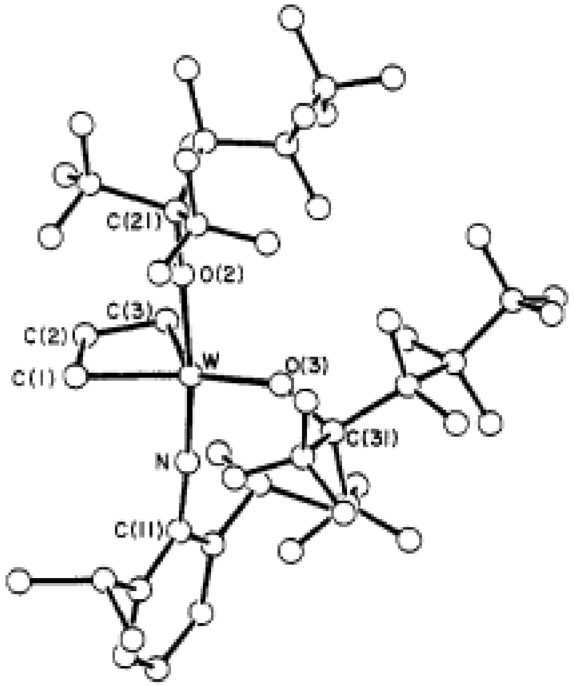
■ *Living Polymerization*



■ First well-defined Tungsten alkylidene catalysts (1988)

■ Set the stage for detailed studies on structure and mechanism





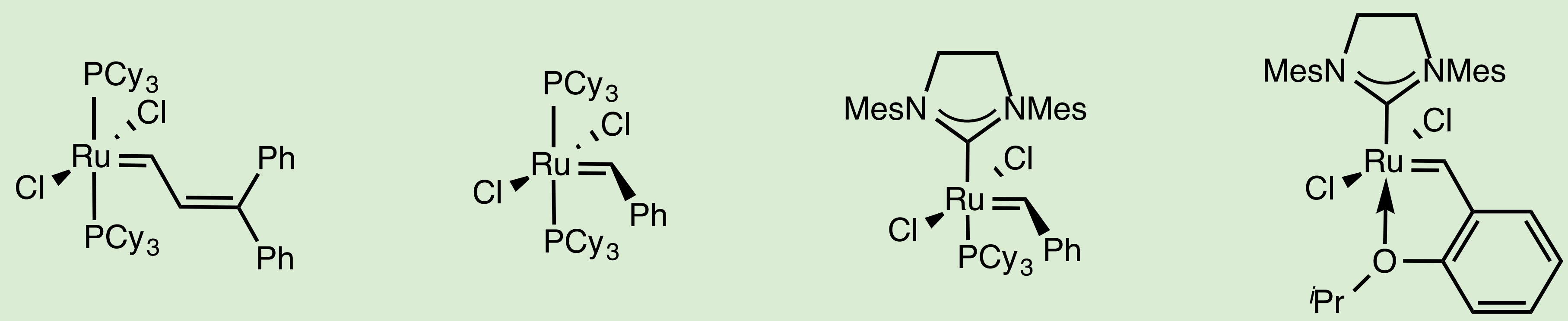
Gillion, L.R.; Grubbs, R.H. *J. Am. Chem. Soc.* **1986**, *108*, 733.

Schrock, R.R.; DePue, R.T.; Feldman, J.; Chaverien, C.J.; Dewan, J.C.; Liu, A.H. *J. Am. Chem. Soc.* **1988**, *110*, 1423.

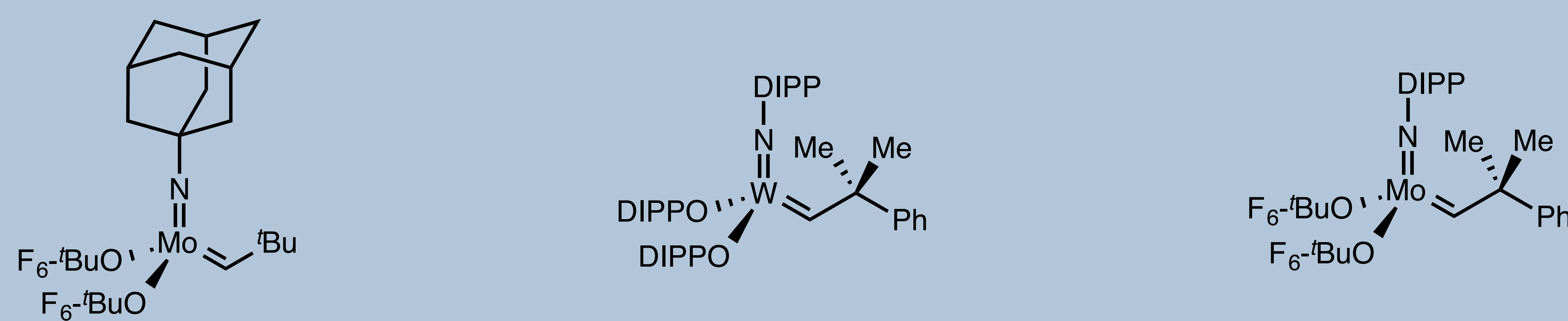
Olefin Metathesis

Nobel-Prize Winning Catalysts

■ Development of stable Ru-carbene complexes (Grubbs)



■ Molybdenum and Tungsten alkylidenes (Schrock, Hoveyda)



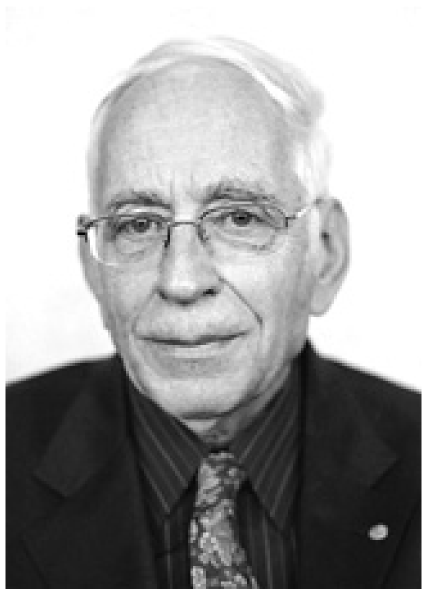
Grubbs, R.H. *Tetrahedron* **2004**, *60*, 7117.

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

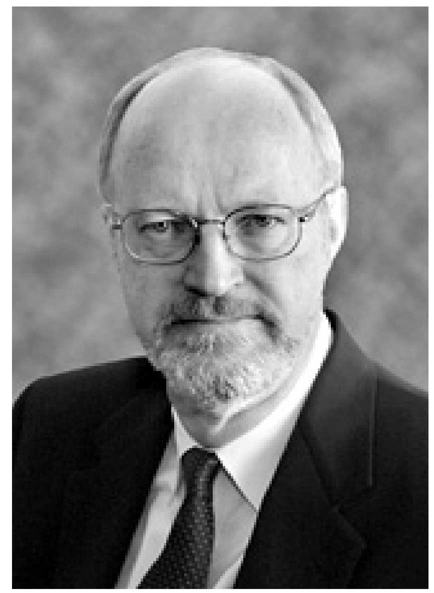
Olefin Metathesis

Nobel-Prize Winning Catalysts

- Nobel Prize in Chemistry award jointly in 2005



Prof. Yves Chauvin



Prof. Robert Grubbs

Prof. Richard Schrock

"for the development of the metathesis method in organic synthesis"

Olefin Metathesis

Talk Breakdown

- Part 1: Enantioselective (desymmetrizing) olefin metathesis
  - Early asymmetric catalysts utilizing chiral ligands (pre-2008)
  - Recent mechanistic understanding
  - Chiral-at-metal catalysts achieve new success (post-2008)

- Part 2: *Z*-selective olefin metathesis
  - Early successes with MAP catalysts
  - The rise of carbometalated Ru catalysts
  - Bidentate anionic ligands unlock full potential of Ru catalysts

Olefin Metathesis

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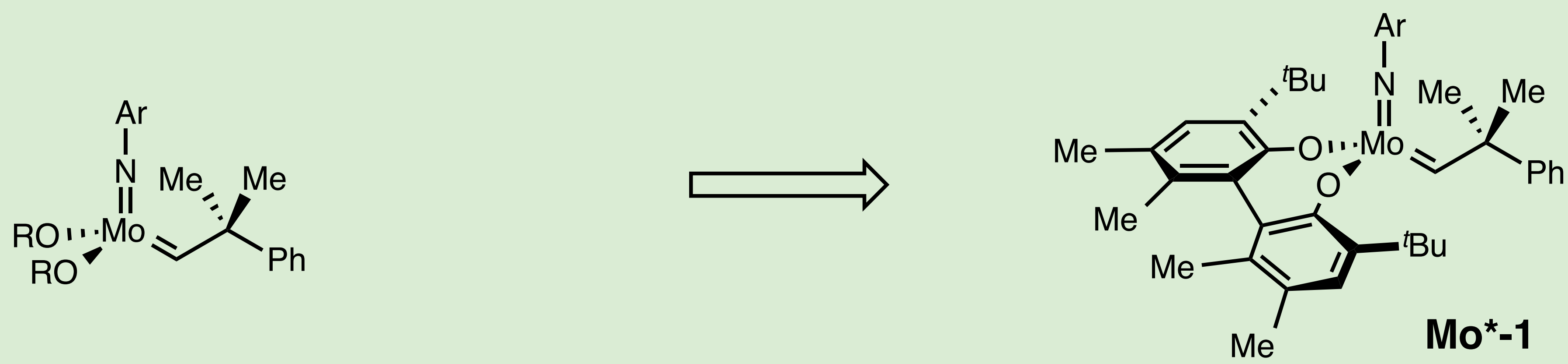
Olefin Metathesis

Early Asymmetric Catalyst Systems

■ Simple modification of the alcohol ligands on an Mo-catalyst generate chiral catalysts



Mo*-1

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

Olefin Metathesis

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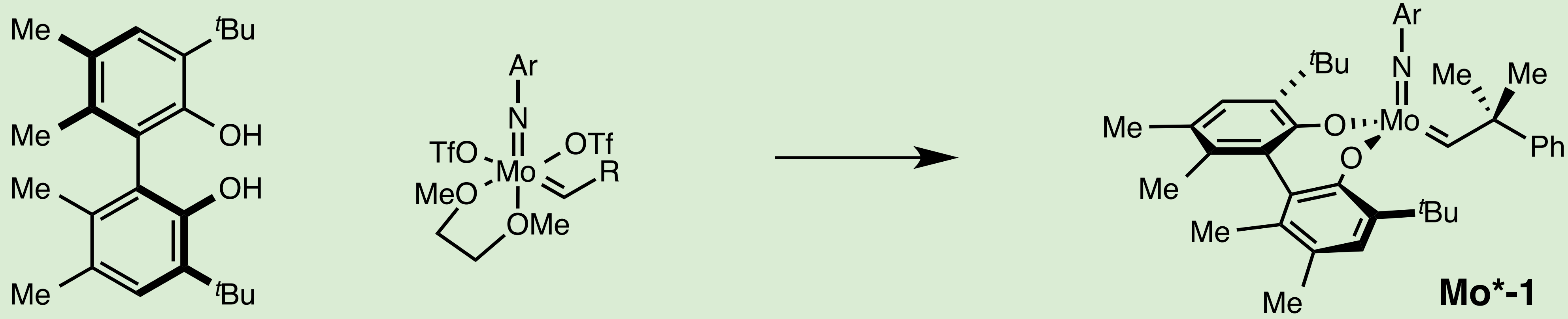
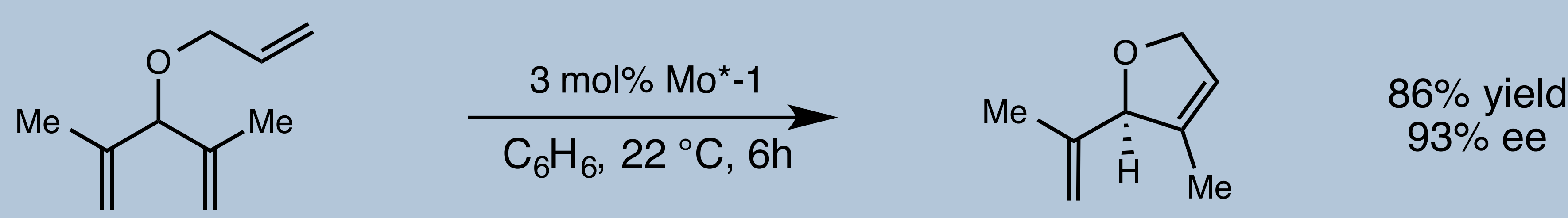


Mo*-1

■ Excellent stereochemical transfer to certain substrates

■ Kinetic resolutions and desymmetrizations



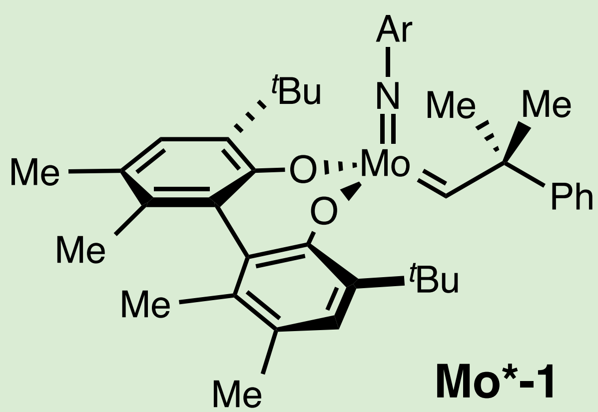
Alexander, J.B.; La, D.S.; Cefalo, D.R.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc.* **1998**, *120*, 4041.

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.

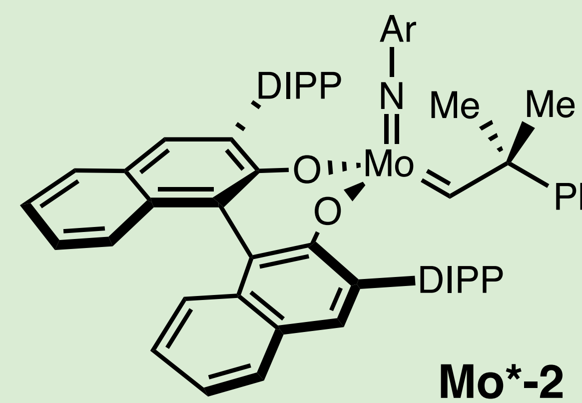
Olefin Metathesis

Early Asymmetric Catalyst Systems

- Other chiral diols could be utilized

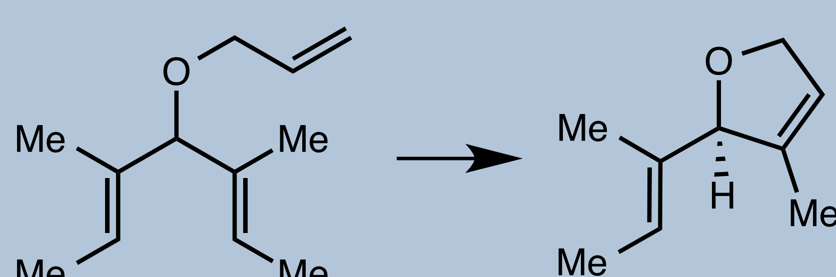


Mo*-1

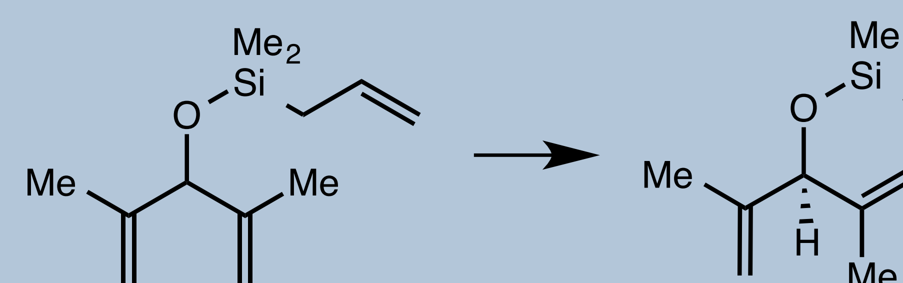


Mo*-2

- Different chiral diols were optimal for different substrate classes
  - For example, 5 vs. 6 membered rings



Mo*-1	Mo*-2
83% yield	77% yield
99% ee	89% ee



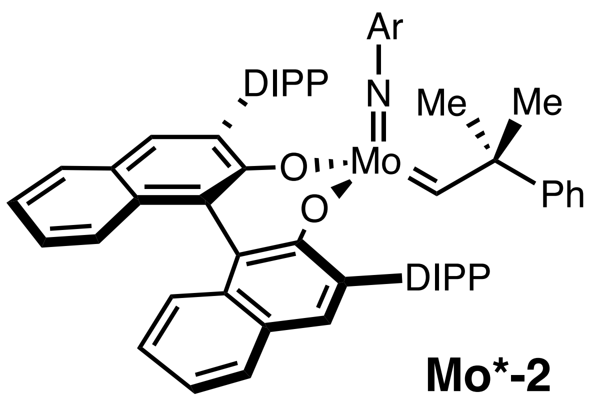
Mo*-1	Mo*-2
17% yield	98% yield
65% ee	>99% ee

Zhu, S.S.; Cefalo, D.R.; La, D.S.; Jamieson, J.Y.; Davis, W.M.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc.* **1999**, *110*, 8251.

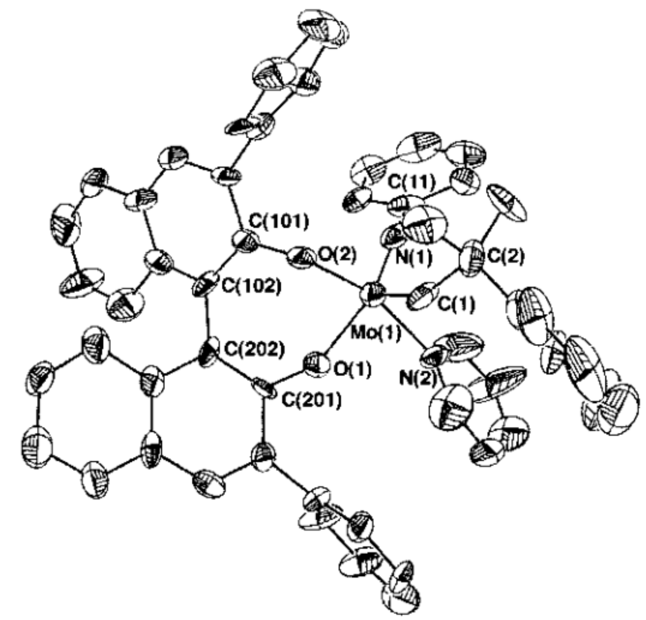
Olefin Metathesis

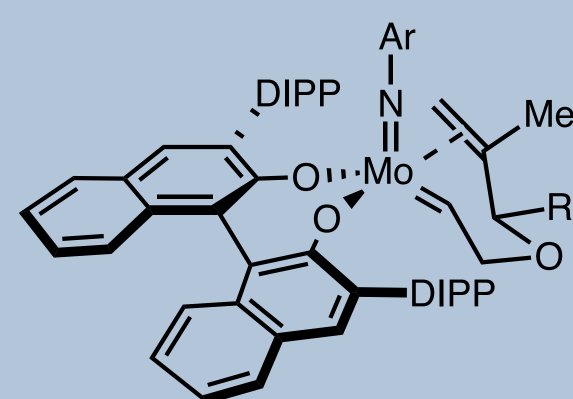
Early Asymmetric Catalyst Systems

Simple proposed model



Mo*-2





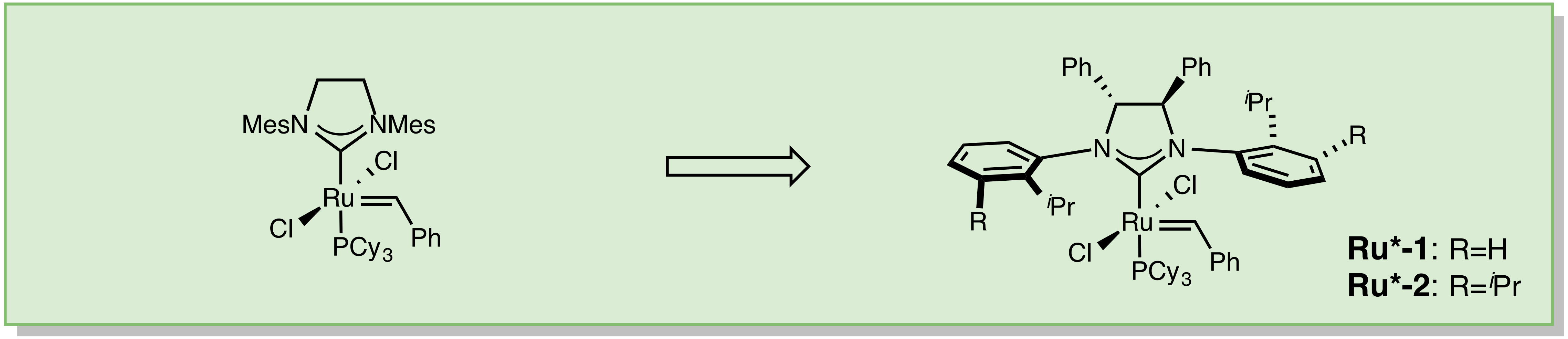
"The reason for the inefficiency of 1a in promoting the asymmetric formation of 7... is unclear."

Weatherhead, G.S.; Houser, J.H.; Ford, J.G.; Jamieson, J.Y.; Schrock, R.R.; Hoveyda, A.H. *Tetrahedron Lett.* **2000**, *41*, 9553.
Zhu, S.S.; Cefalo, D.R.; La, D.S.; Jamieson, J.Y.; Davis, W.M.; Hoveyda, A.H.; Schrock, R.R. *J. Am. Chem. Soc.* **1999**, *110*, 8251.

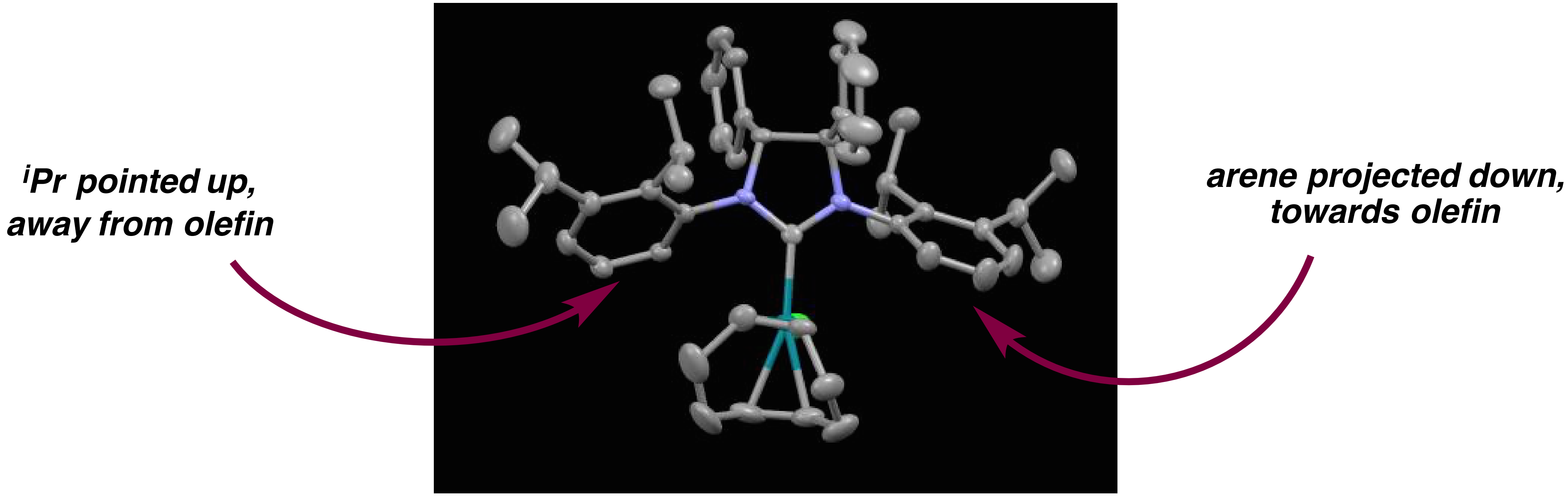
Olefin Metathesis

Early Asymmetric Catalyst Systems

■ Chiral NHCs allow for asymmetric Ru catalysts



■ N-arenes are twisted, enforcing an open/closed geometry



Seiders, T.J.; Ward, D.W.; Grubbs, R.H. *Org. Lett.* **2001**, *3*, 3225.

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

Olefin Metathesis

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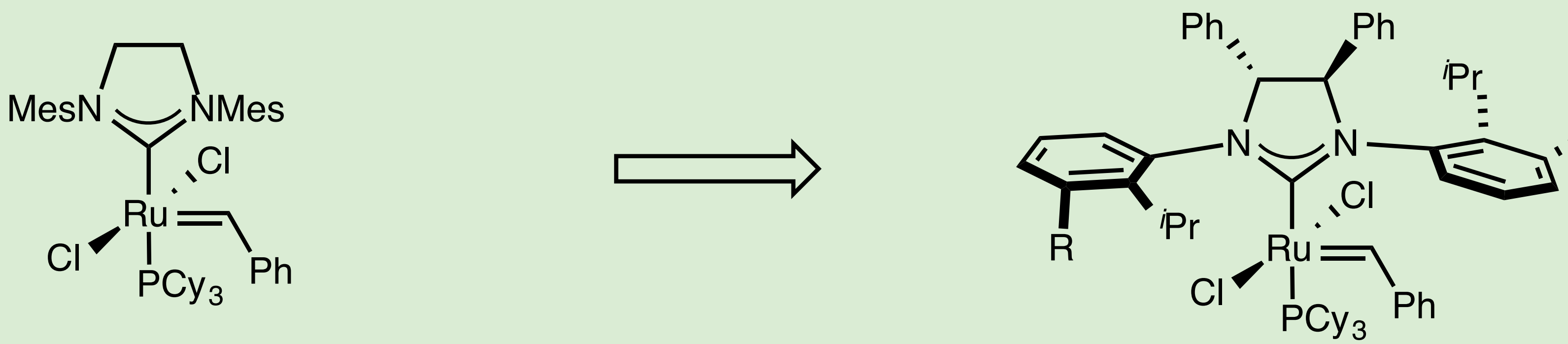
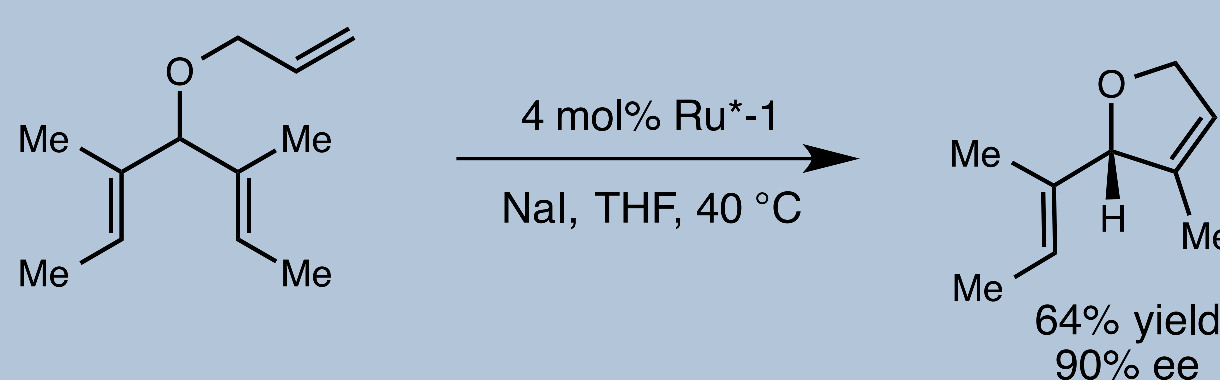
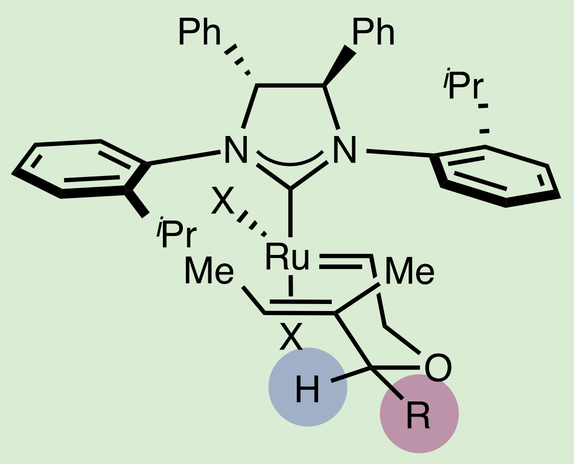


Ru*-1: R=H
Ru*-2: R=^{i}Pr

- Ru catalysts have similar limited substrate scope but increased tolerance
    - Projecting aryl group and axial ligand combine to enforce geometry





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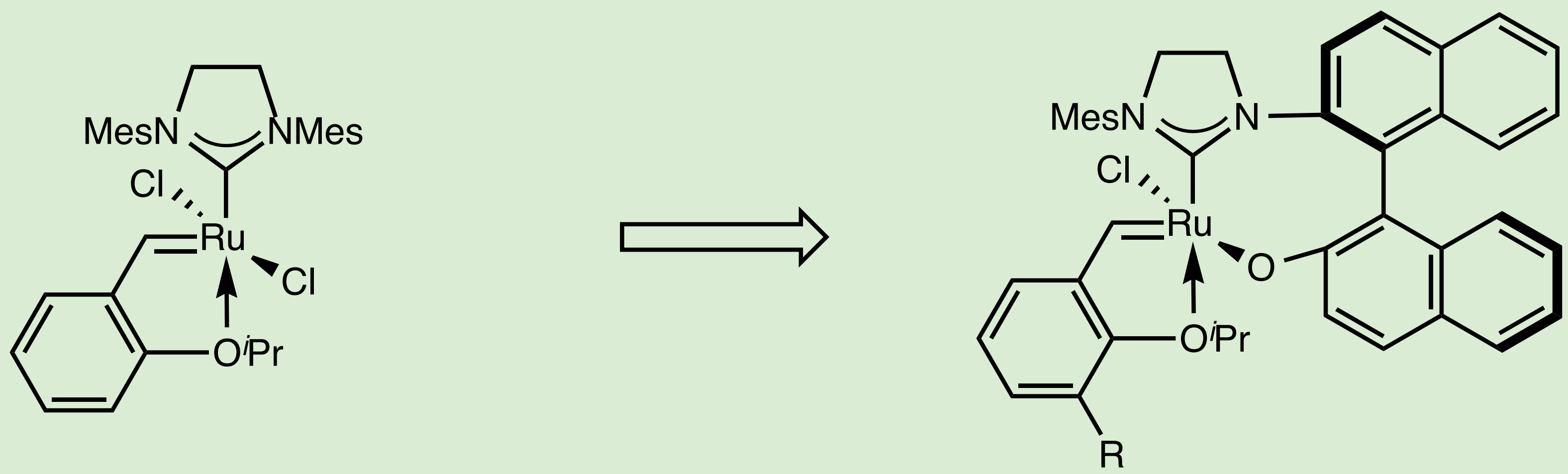
Funk, T.W.; Berlin, J.M.; Grubbs, R.H. *J. Am. Chem. Soc.* **2006**, *128*, 1840.

Olefin Metathesis

Early Asymmetric Catalyst Systems

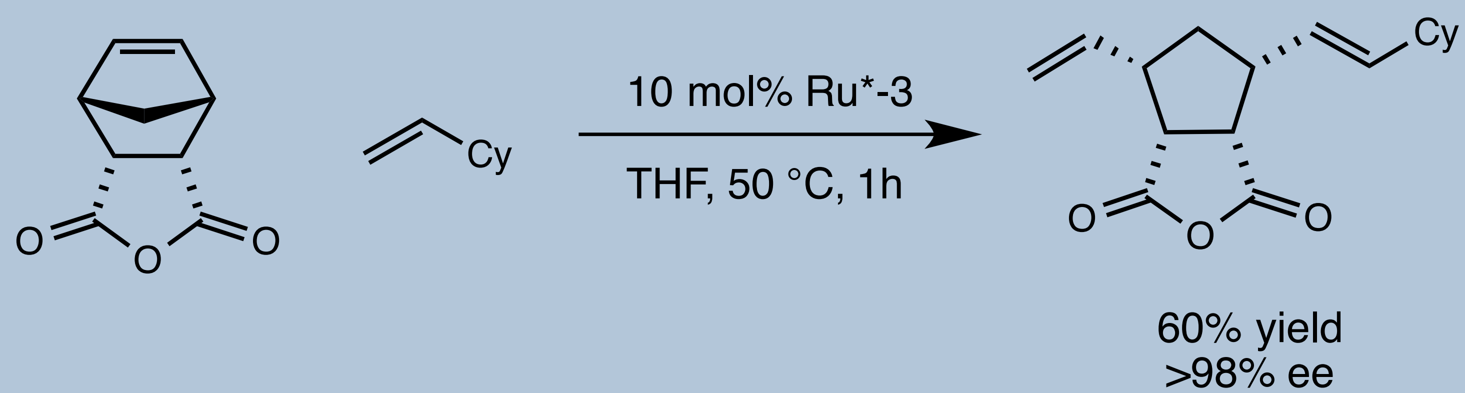
■ Hoveyda explored BINOL-derived bidentate NHC ligands

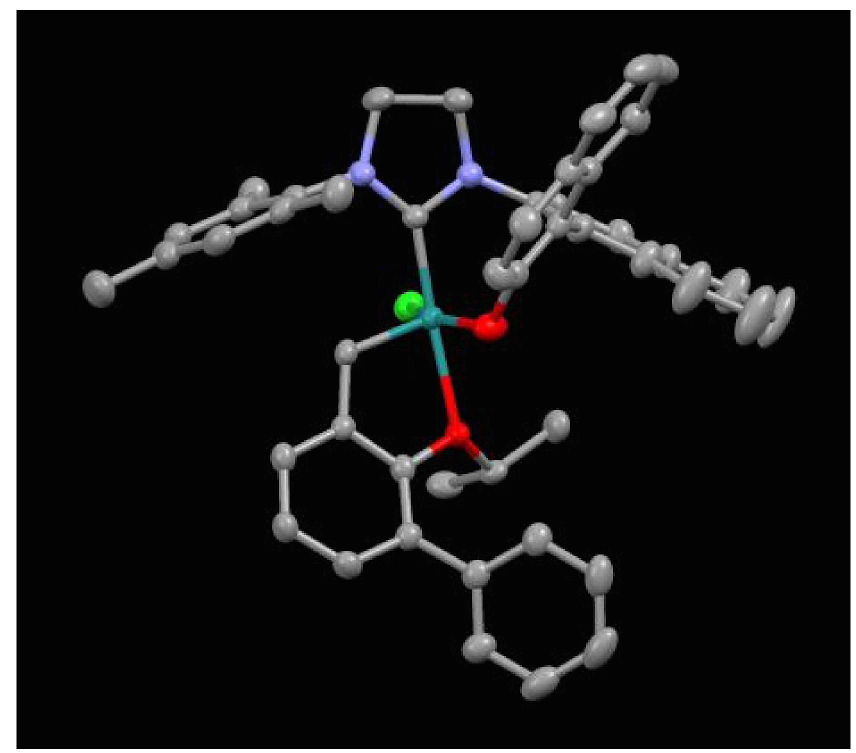


Ru*-3: R=H
Ru*-4: R=Ph

■ Bidentate catalysts capable of ROCM, mild success with RCM

■ Additionally, catalyst is recoverable by chromatography (up to 98%)



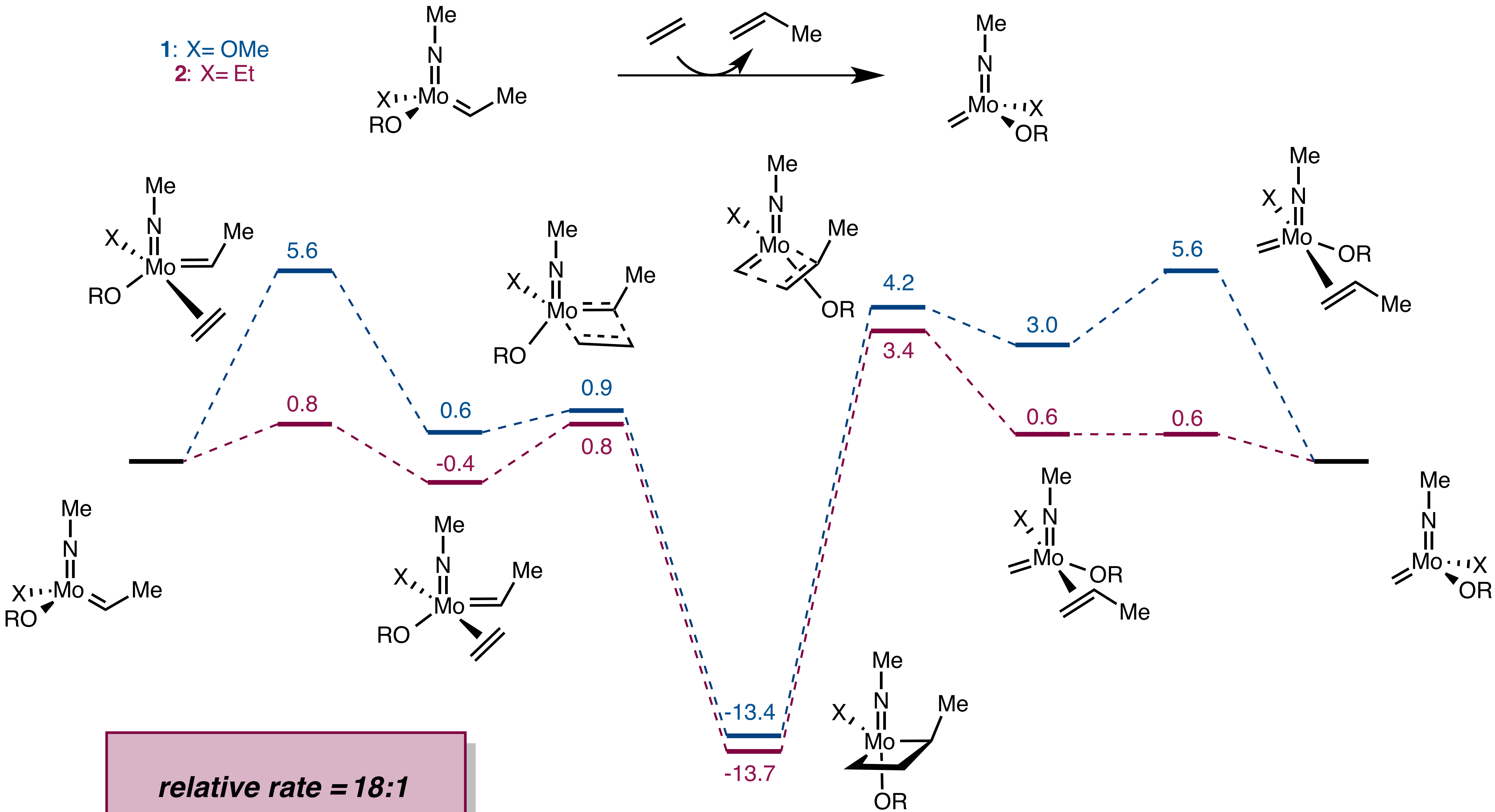


Van Veldhuizen, J.J.; Garber, S.B.; Kingsbury, J.S.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2002**, *124*, 4954.
Van Veldhuizen, J.J.; Gillingham, D.G.; Garbder, S.B.; Kataoka, O.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2003**, *125*, 12502.

Olefin Metathesis

Theory Informs Synthethis

- Theoretical studies identify desired reactivity could be achieved thru asymmetrically bound metal



relative rate = 18:1

Monfort-Solans, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2005**, *127*, 14015.
Poater, A.; Monfort-Solans, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2007**, *129*, 8207.

Olefin Metathesis

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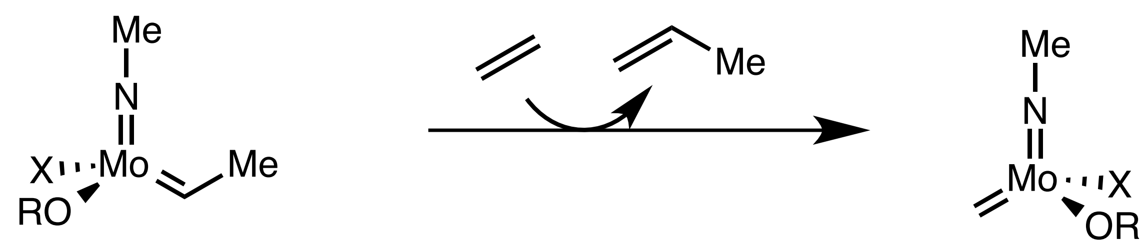
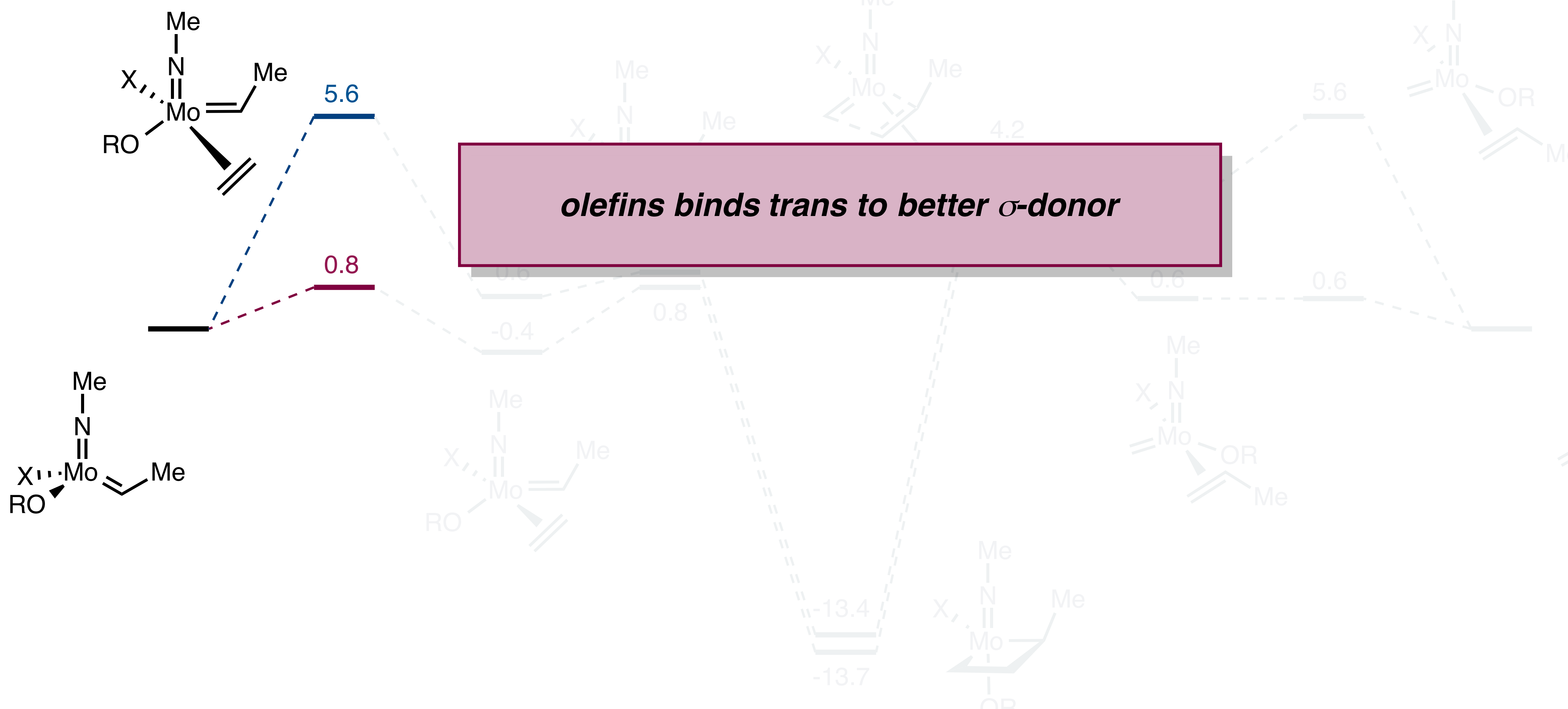
1: X= OMe
2: X= Et





olefins binds trans to better σ-donor

Monfort-Solans, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2005**, *127*, 14015.
Poater, A.; Monfort-Solans, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2007**, *129*, 8207.

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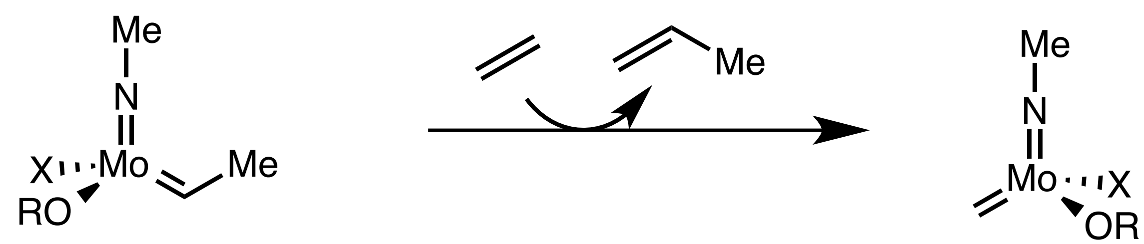
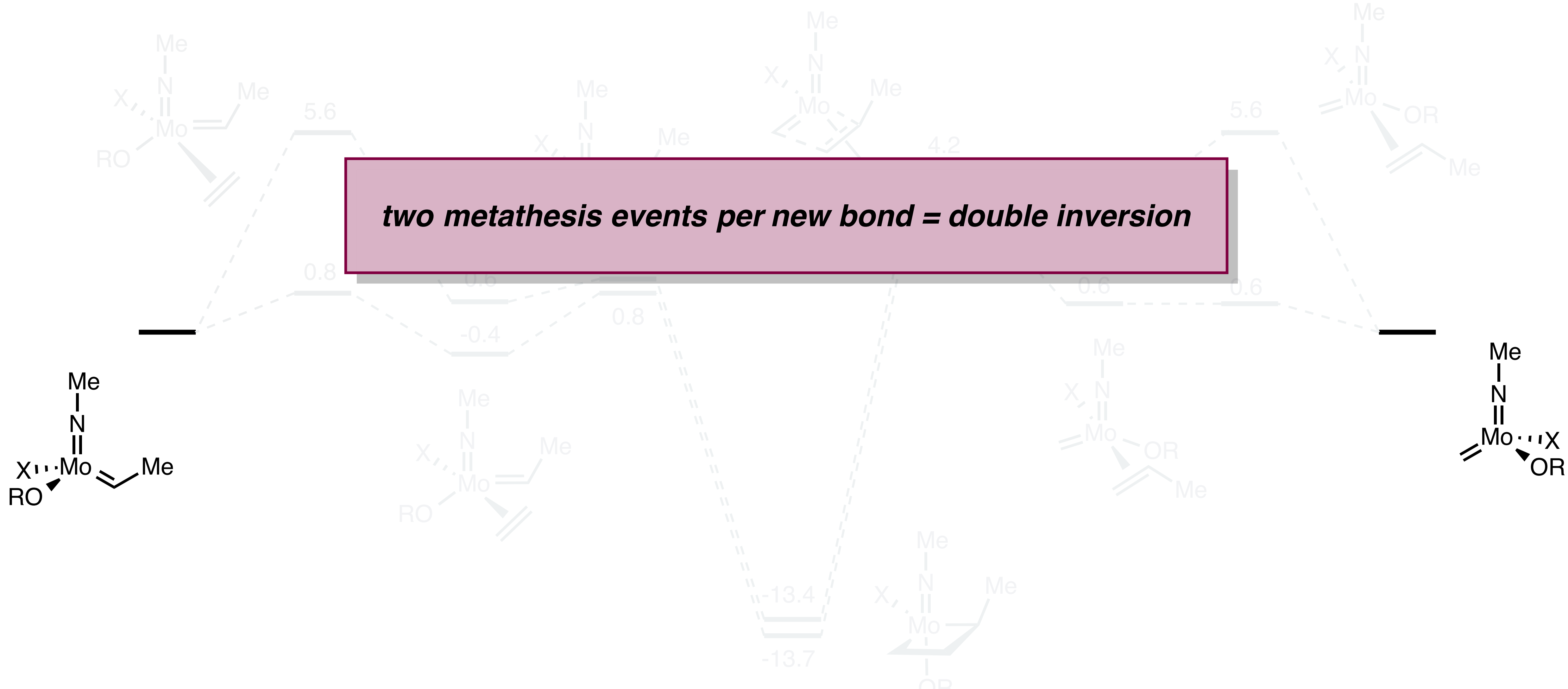




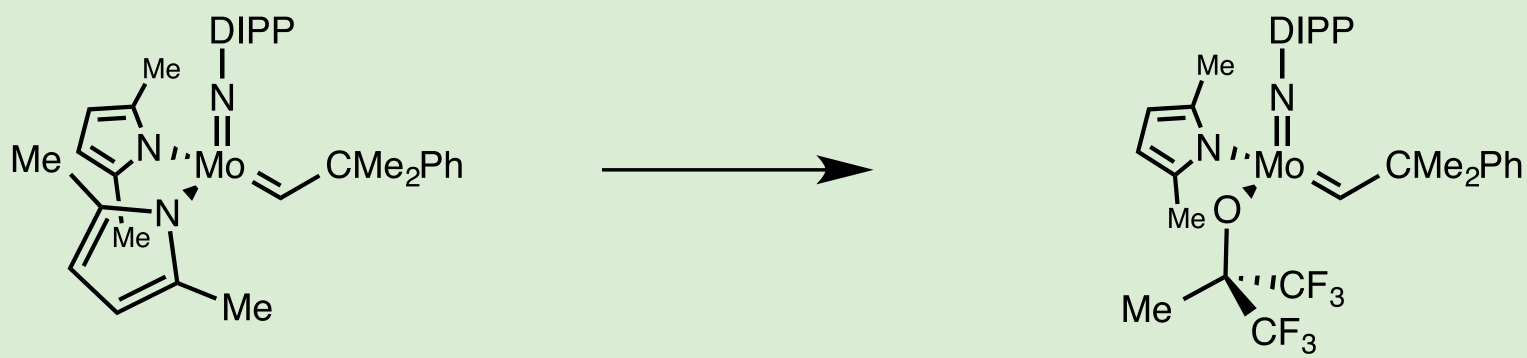
two metathesis events per new bond = double inversion

Monfort-Solans, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2005**, *127*, 14015.
Poater, A.; Monfort-Solans, X.; Clot, E.; Copéret, C.; Eisenstein, O. *J. Am. Chem. Soc.* **2007**, *129*, 8207.

Olefin Metathesis

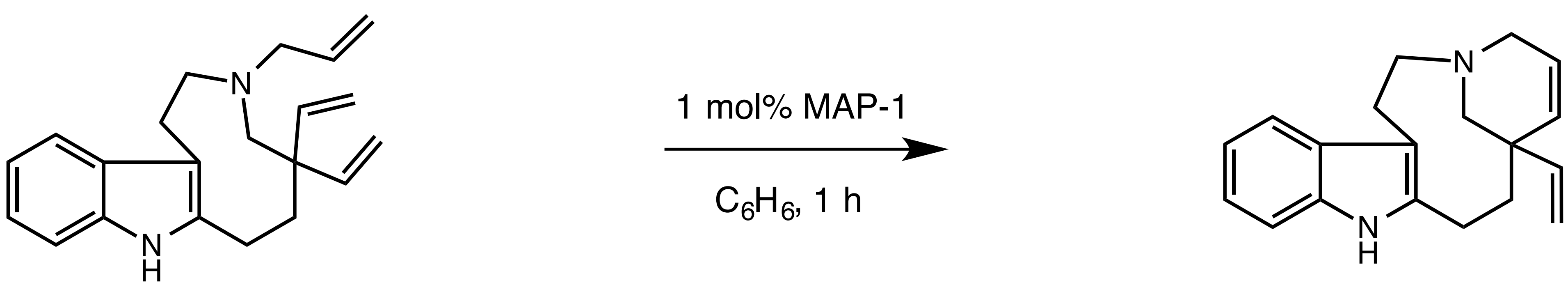
State of the Art Chiral Catalysts

■ MonoAlkoxidePyrrolide (MAP) catalysts exhibit enhanced reactivity



MAP-1

■ Capable of previously inefficient reactions



79% yield

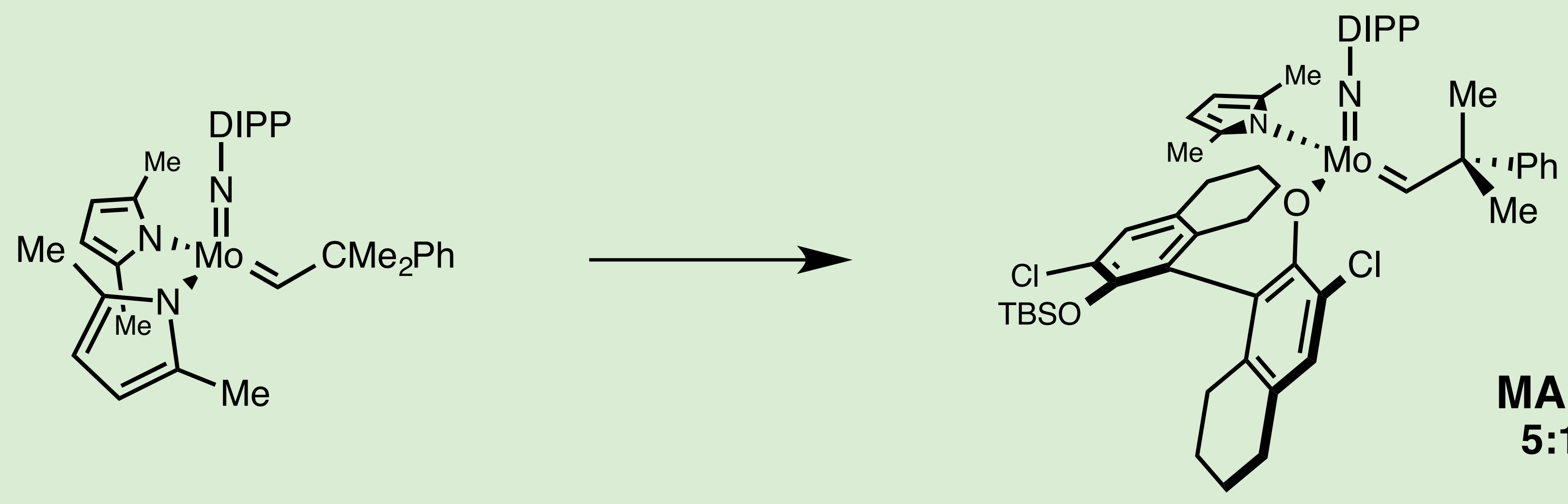
previous best: 61% yield, 6h

Malcolmson, S.J.; Meek, S.J.; Sattely, E.S.; Schrock, R.R.; Hoveyda, A.H. *Nature* **2008**, *456*, 933.
Sattely, E.S.; Meek, S.J.; Malcolmson, S.J.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2009**, *131*, 943.

Olefin Metathesis

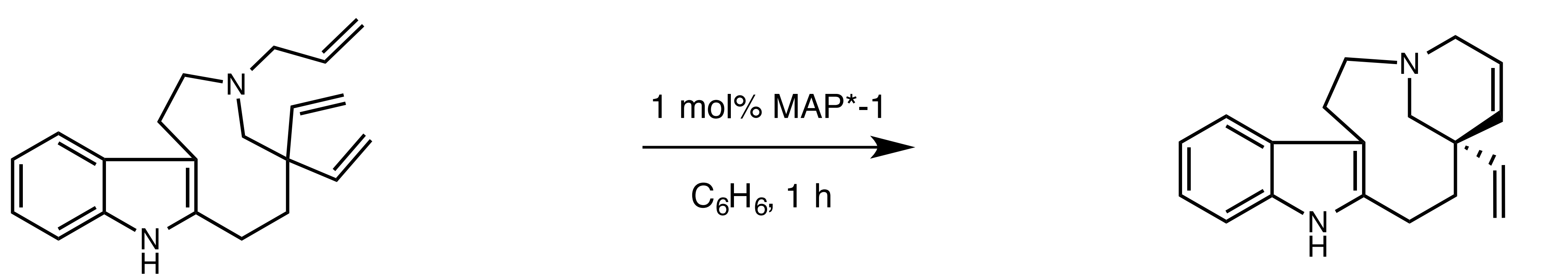
State of the Art Chiral Catalysts

■ Utilizing an enantiopure monodentate alkoxide ligand generates chiral, diastereomeric catalyst



MAP*-1
5:1 dr

■ Enantioselective total synthesis of (+)-quebrachamine



10 steps

84% yield, 96% ee

1 step to quebrachamine

Malcolmson, S.J.; Meek, S.J.; Sattely, E.S.; Schrock, R.R.; Hoveyda, A.H. *Nature* **2008**, *456*, 933.
Sattely, E.S.; Meek, S.J.; Malcolmson, S.J.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2009**, *131*, 943.

Olefin Metathesis

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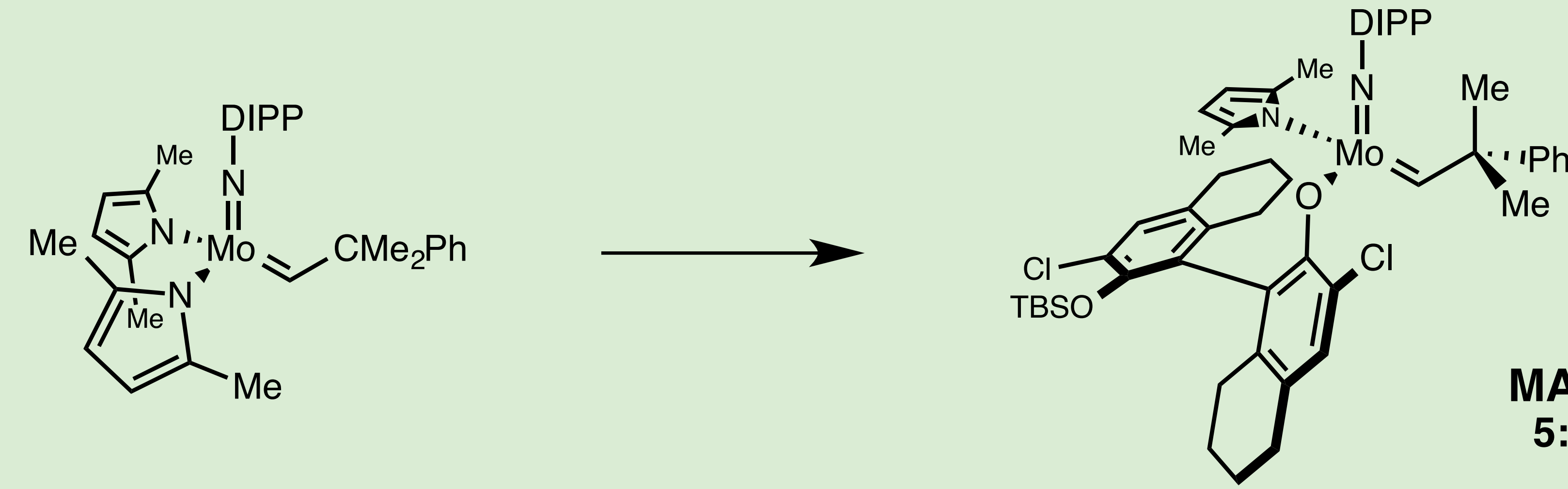
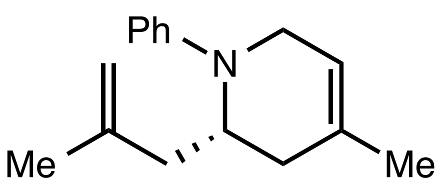
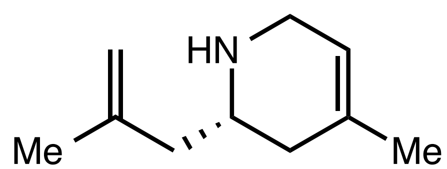


MAP*-1
5:1 dr

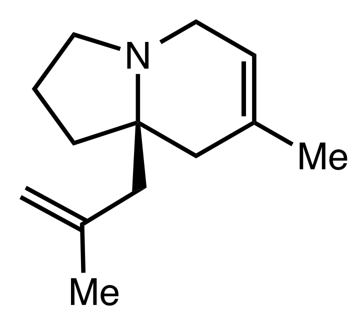
■ Very limited scope



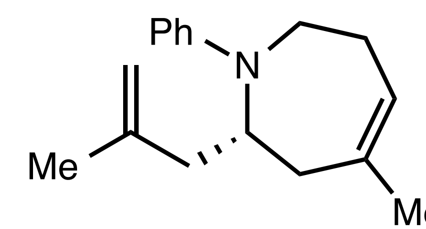
91% yield, 93% ee



89% yield, 67% ee



98% yield, 92% ee



86% yield, 93% ee

7 years later, this remains state of the art

Malcolmson, S.J.; Meek, S.J.; Sattely, E.S.; Schrock, R.R.; Hoveyda, A.H. *Nature* **2008**, *456*, 933.
Sattely, E.S.; Meek, S.J.; Malcolmson, S.J.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2009**, *131*, 943.

Olefin Metathesis

Talk Breakdown

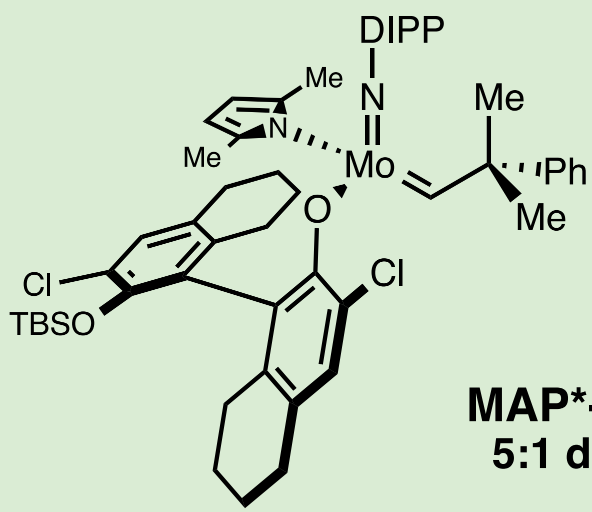
- Part 1: Enantioselective (desymmetrizing) olefin metathesis
  - Early asymmetric catalysts utilizing chiral ligands (pre-2008)
  - Recent mechanistic understanding
  - Chiral-at-metal catalysts achieve new success (post-2008)

- Part 2: *Z*-selective olefin metathesis
  - Early successes with MAP catalysts
  - The rise of carbometalated Ru catalysts
  - Bidentate anionic ligands unlock full potential of Ru catalysts

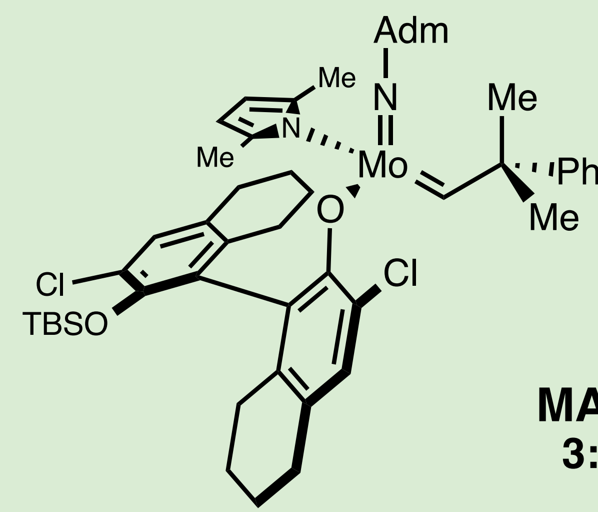
Olefin Metathesis

First Z-selective Catalysts

■ Bulky aryloxide ligand of MAP complexes imparts excellent steric control

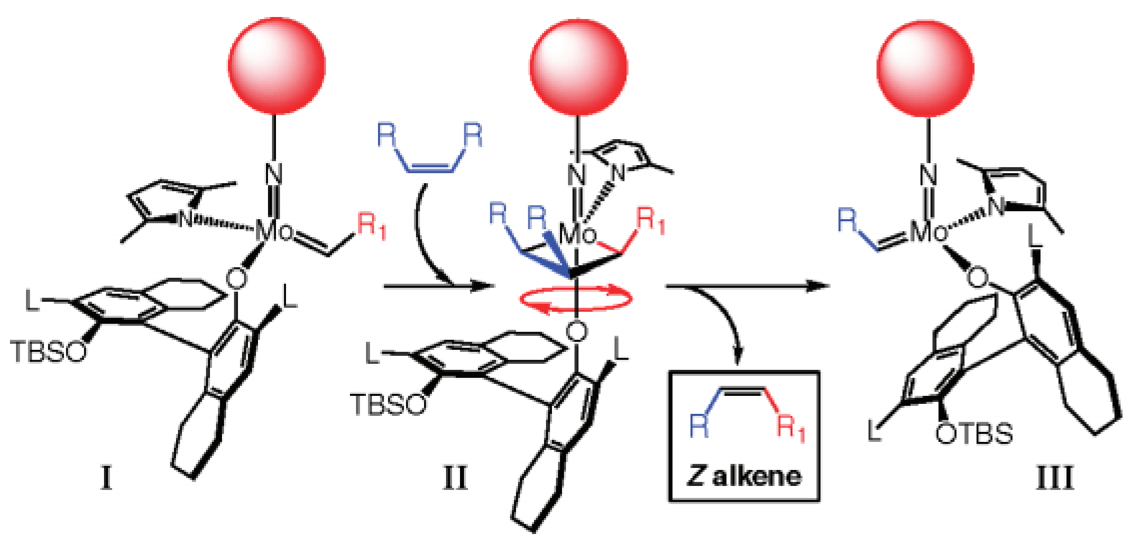


MAP*-1
5:1 dr



MAP*-2
3:1 dr

■ Size differential between aryloxide and imido substituent key factor



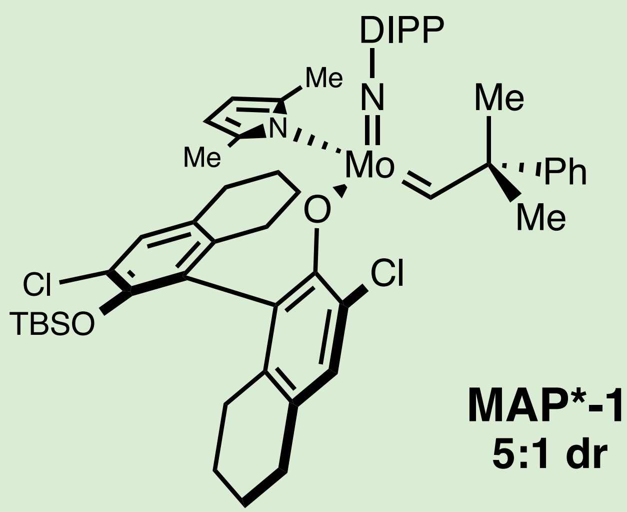
Adm<DIPP → better kinetic control

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

Olefin Metathesis

First Z-selective Catalysts

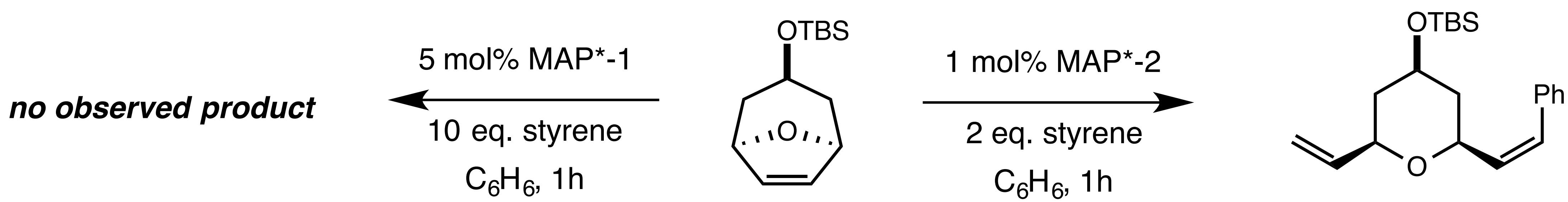
■ Bulky aryloxide ligand of MAP complexes imparts excellent steric control



MAP*-1
5:1 dr

MAP*-2
3:1 dr

■ Size differential between aryloxide and imido substituent key factor



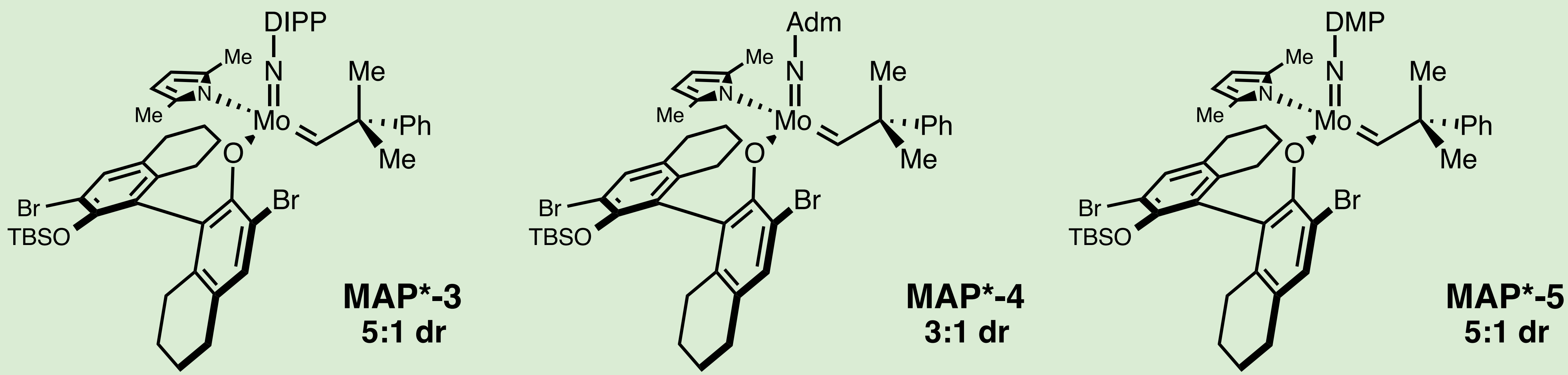
80% yield, 90% ee
> 98% Z

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

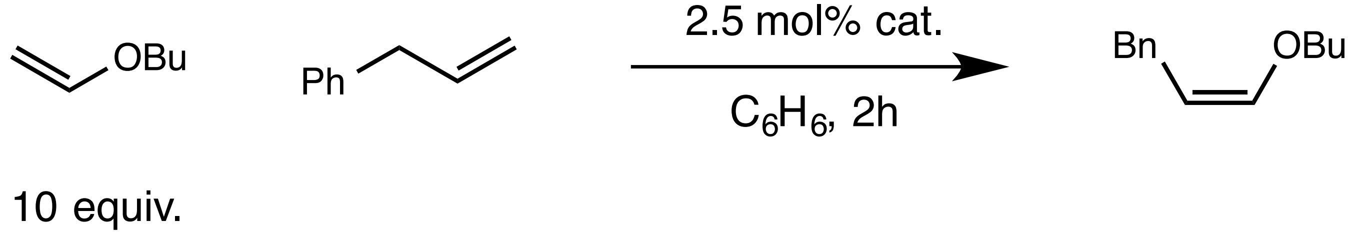
Olefin Metathesis

First Z-selective Catalysts

■ Modifiable monodentate alkoxide and N-substituent allow for substantial catalyst diversity



■ Extension of ROCM chemistry to CM, including with enol ethers



cat	conv	*Z* %
MAP*-3	47	>98
MAP*-4	37	>98
MAP*-5	85	98

73% yield

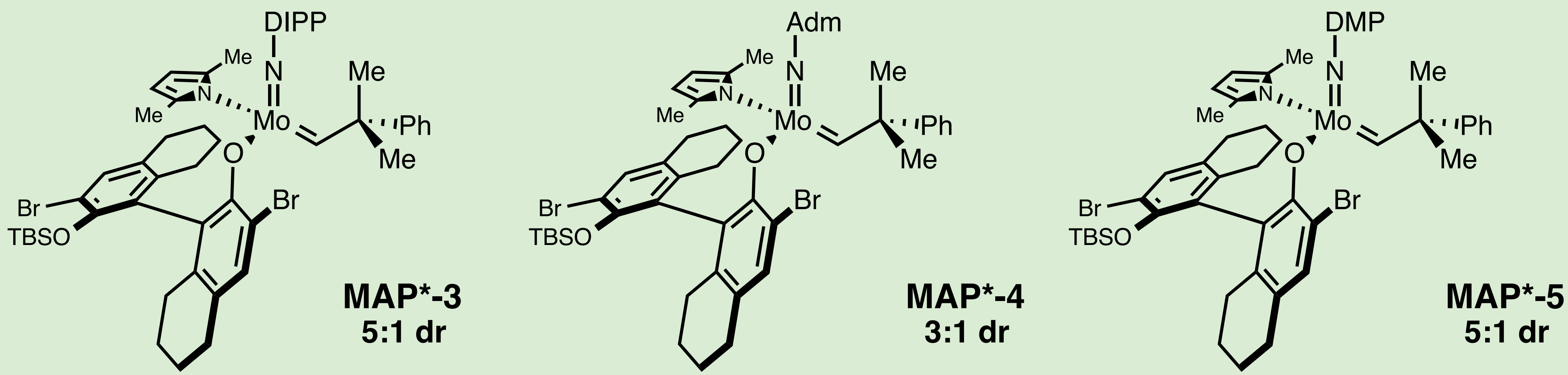
substantial enol ether and α-olefin scope

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

Olefin Metathesis

First Z-selective Catalysts

■ Modifiable monodentate alkoxide and N-substituent allow for substantial catalyst diversity

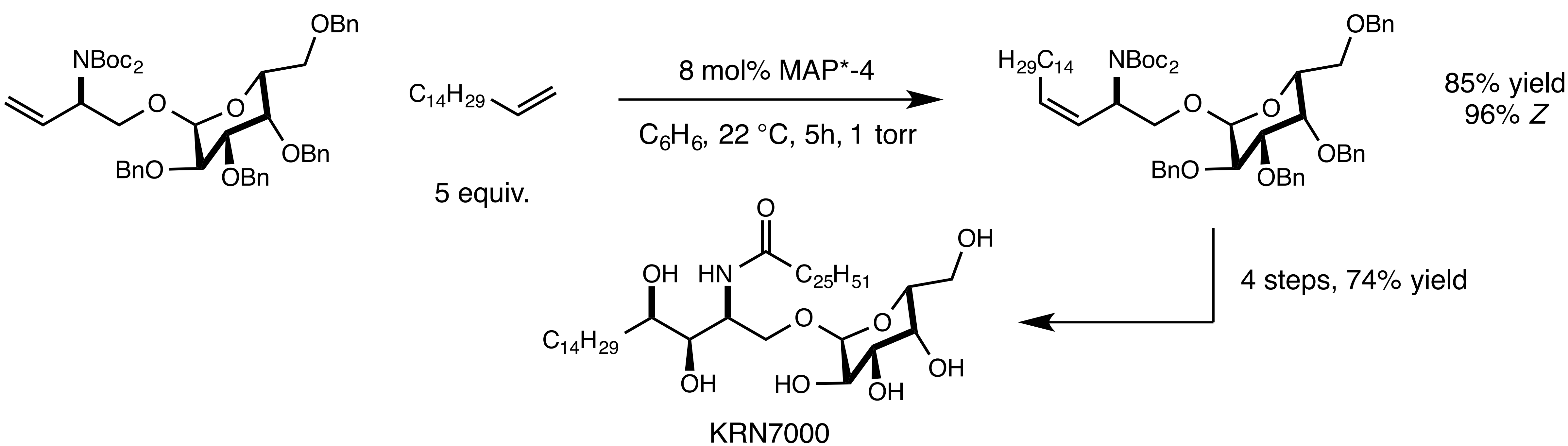


MAP*-3
5:1 dr

MAP*-4
3:1 dr

MAP*-5
5:1 dr

■ Extension of ROCM chemistry to CM, including with protected allylic amines

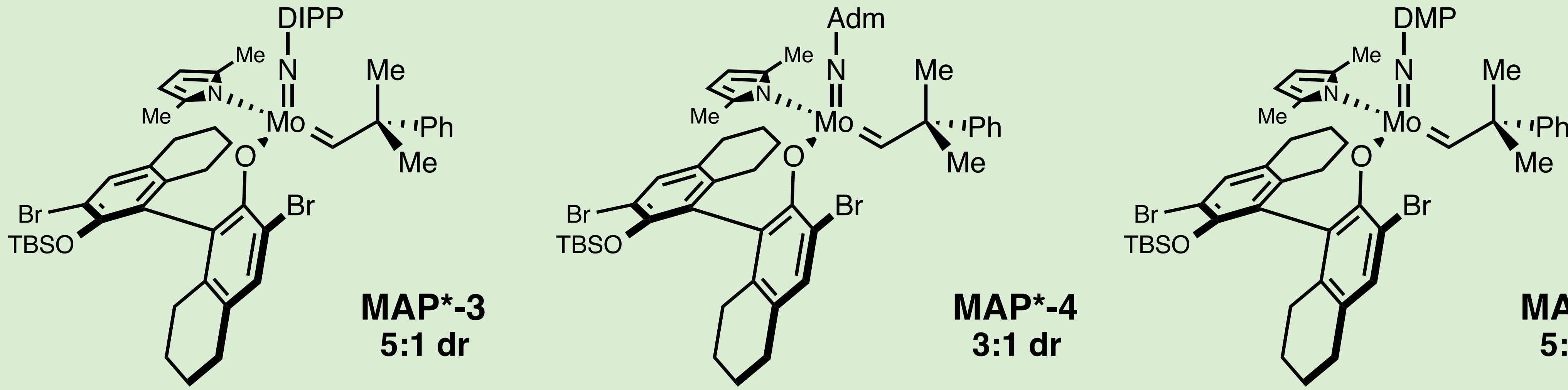


Meek, S.J.; O'Brien, R.V.; Llaveria, J.; Schrock, R.R.; Hoveyda, A.H. *Nature* **2011**, *471*, 461.

Olefin Metathesis

First Z-selective Catalysts

■ BINOL-derived catalysts still find use for selective formation of *Z*-vinyl boronates via CM

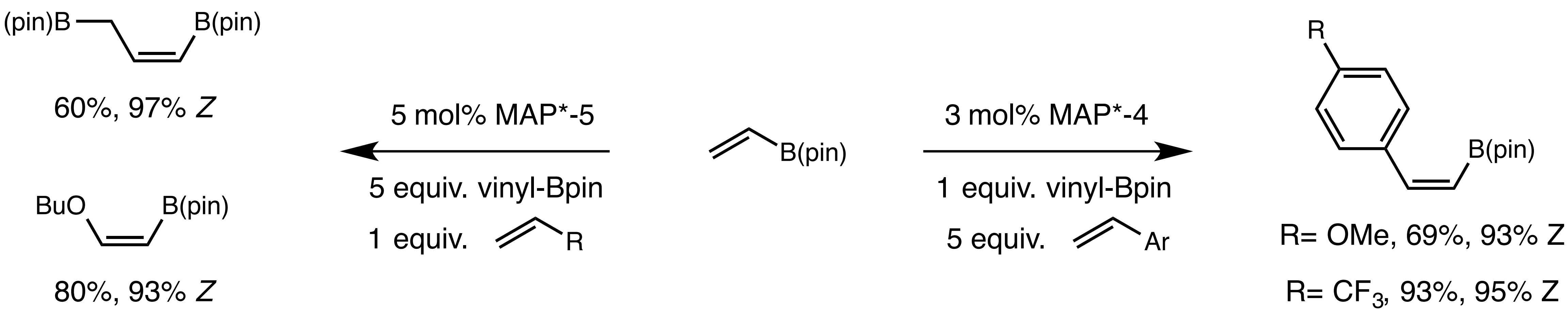


MAP*-3
5:1 dr

MAP*-4
3:1 dr

MAP*-5
5:1 dr

■ Different *N*-substituent for diffent α-olefin coupling partners

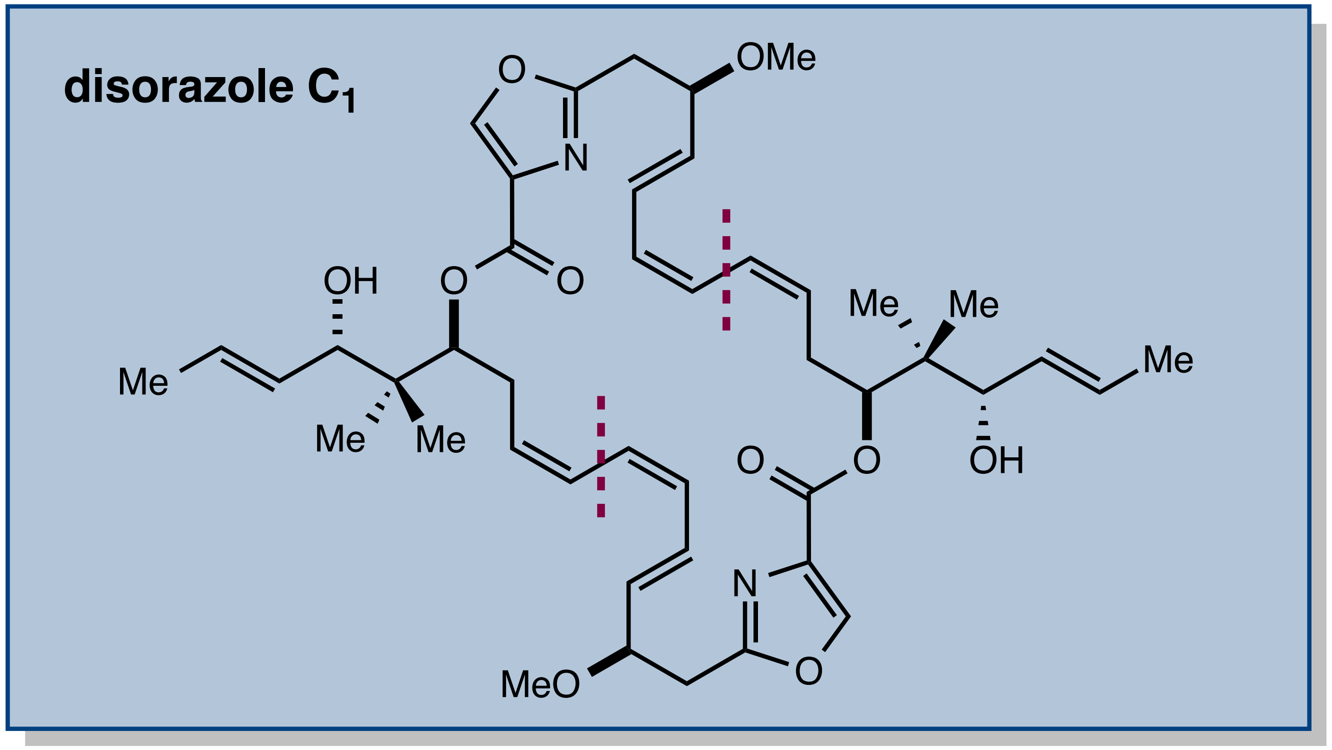


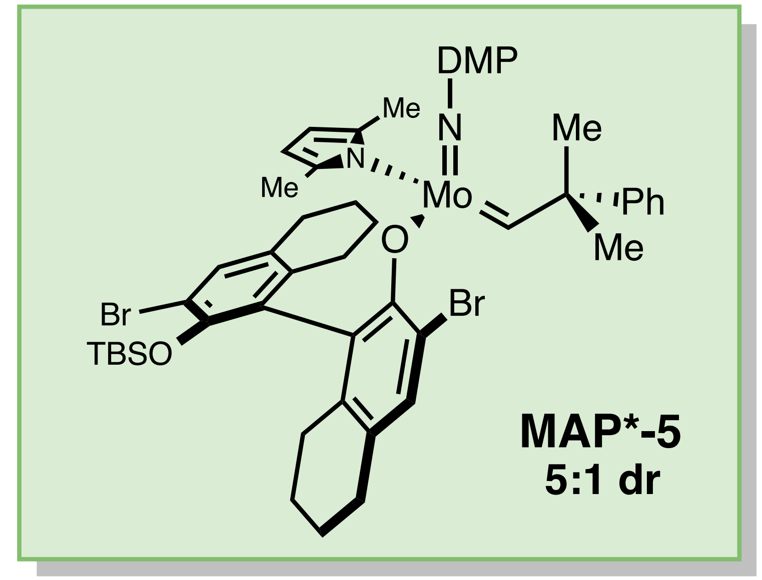
Kiesewetter, E.T.; O'Brien, R.V.; Yu, E.C.; Meek, S.J.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2013**, *135*, 6026.

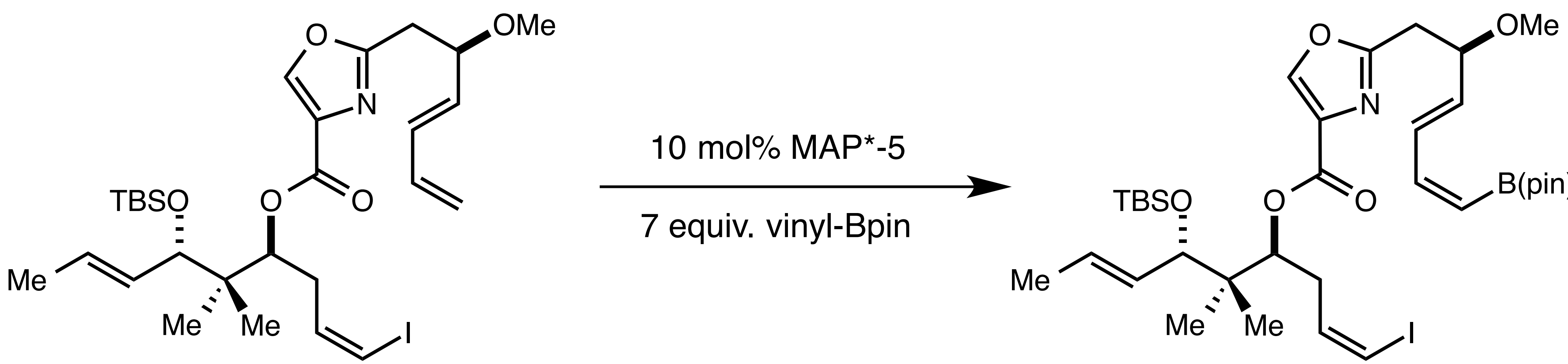
Olefin Metathesis

First Z-selective Catalysts

■ Catalytic generation of *Z*-alkenyl boronate esters to enable a total synthesis





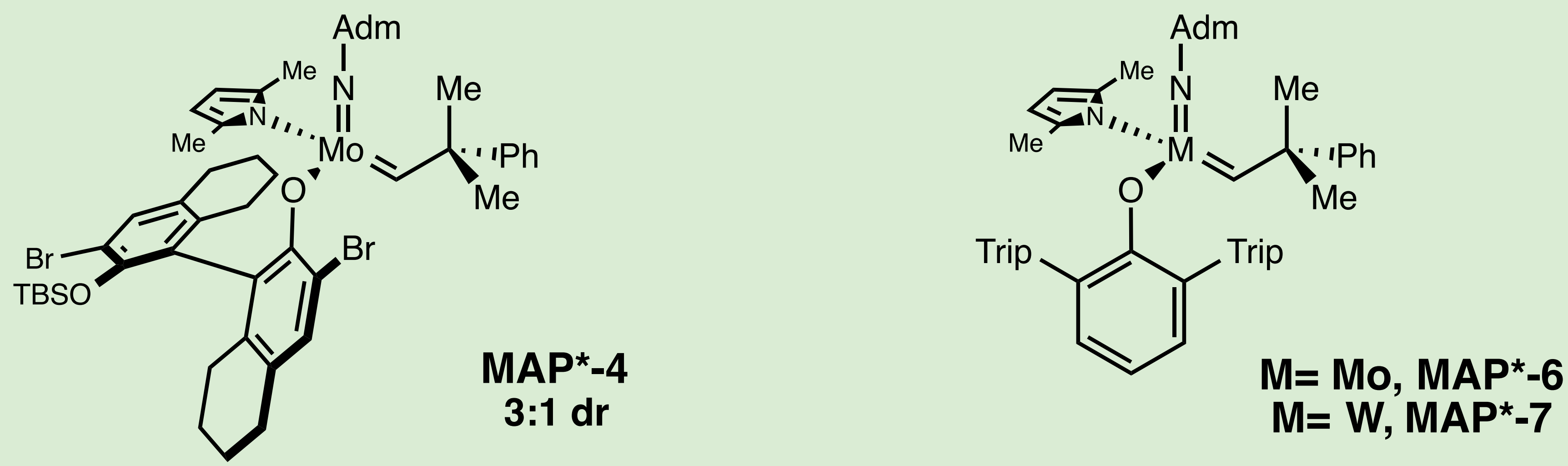


Speed, A.W.H.; Mann, T.J.; O'Brien, R.V.; Schrock, R.R.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2014**, *136*, 16136.

Olefin Metathesis

Simpler MAP Catalysts

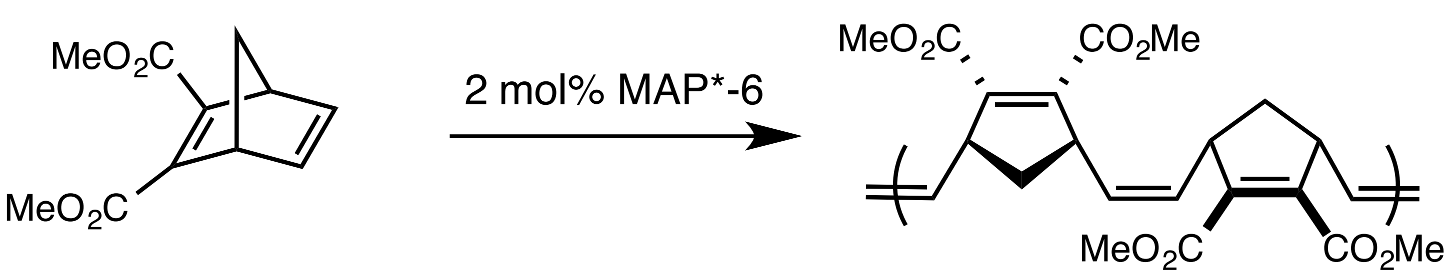
- If sterics of the alkoxide vs. imide are determining factor, why use chiral alcohols?



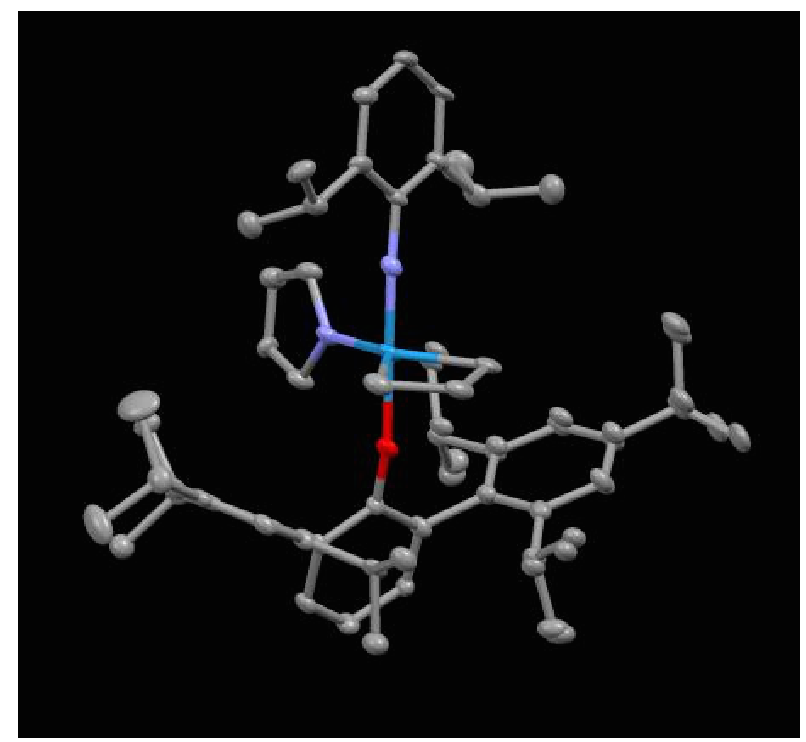
MAP*-4
3:1 dr

M= Mo, MAP*-6
M= W, MAP*-7

- Steric bulk of 2,6-Trip phenoxide ligand is sufficient for *Z* control

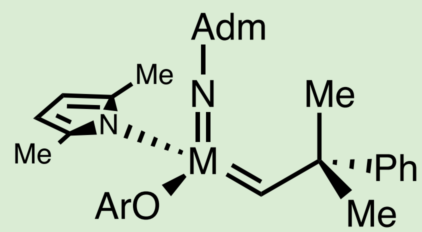


>99% *Z*, >99% syndiotactic

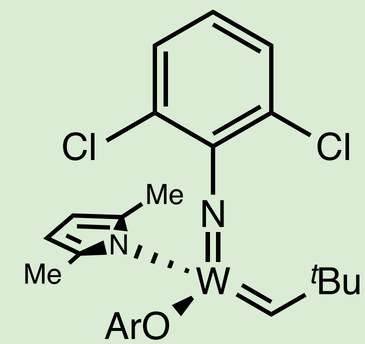


Flook, M.M.; Jiang, A.J.; Schrock, R.R.; Müller, P.; Hoeyda, A.H. *J. Am. Chem. Soc.* **2009**, *131*, 7962.

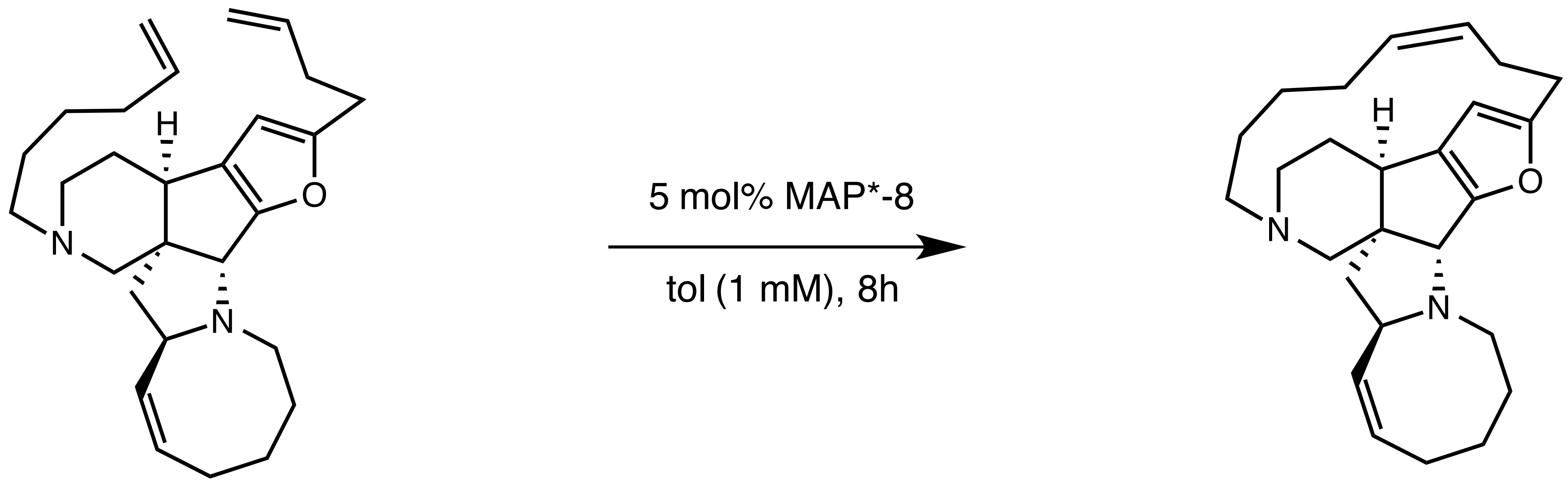
Application towards the total synthesis of nakadomarin A by *Z*-selective RCM



M= Mo, MAP*-6
M= W, MAP*-7



MAP*-8



nakadomarin A

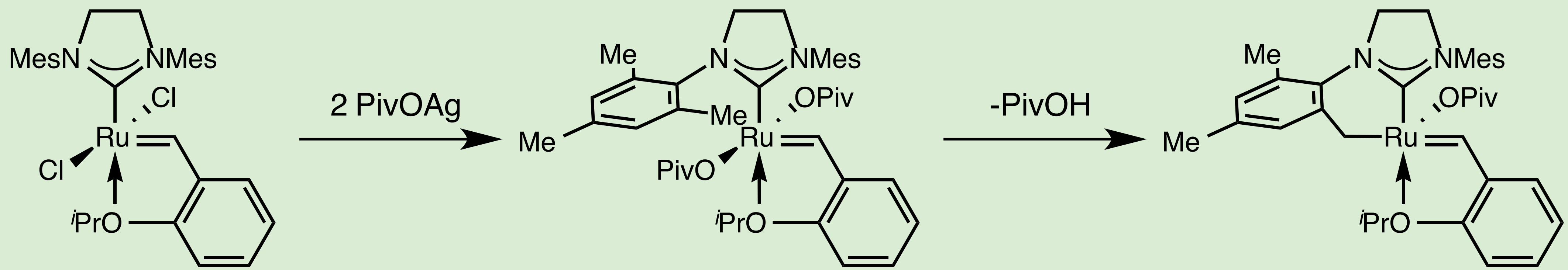
63% yield, 94% *Z*

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

Olefin Metathesis

Cyclometalated Ru Catalysts

- CH activation leads to a surprisingly active and selective class of catalysts



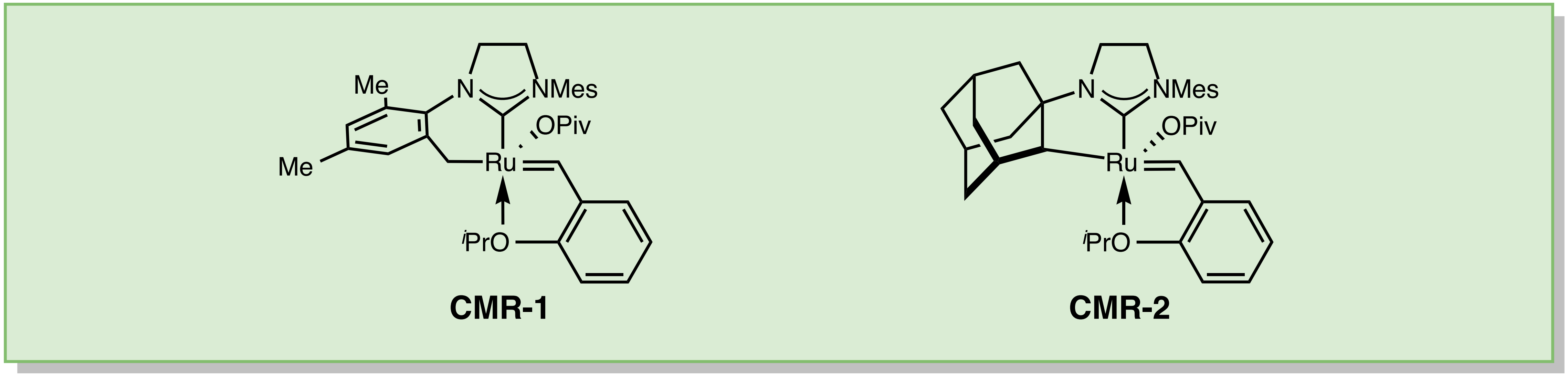
CMR-1

Endo, K.; Grubbs, R.H. *J. Am. Chem. Soc.* **2011**, *133*, 8525.

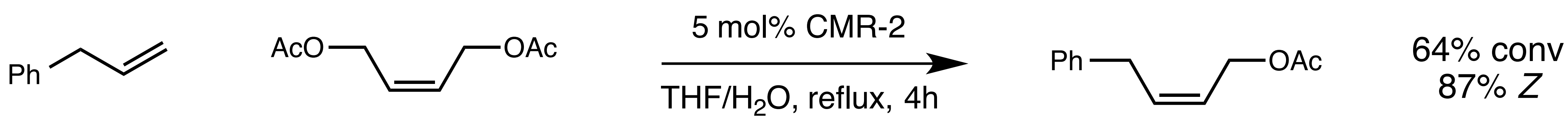
Olefin Metathesis

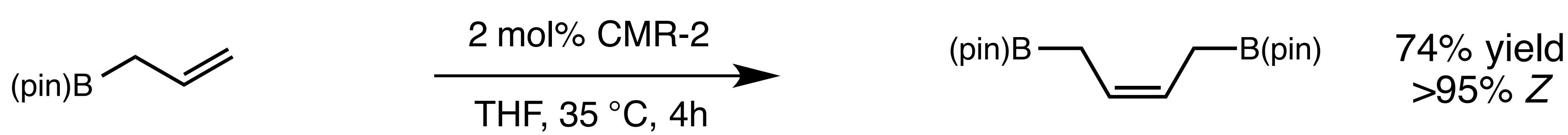
Cyclometalated Ru Catalysts

■ CH activation leads to a surprisingly active and somewhat selective class of catalysts



■ Highly promising levels of *Z* selectivity in CM and homodimerization





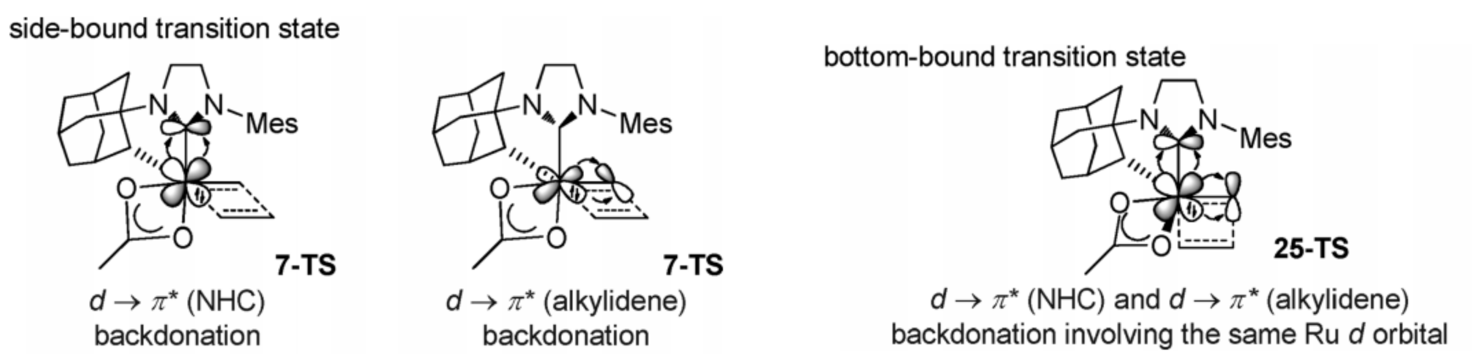
Endo, K.; Grubbs, R.H. *J. Am. Chem. Soc.* **2011**, *133*, 8525.

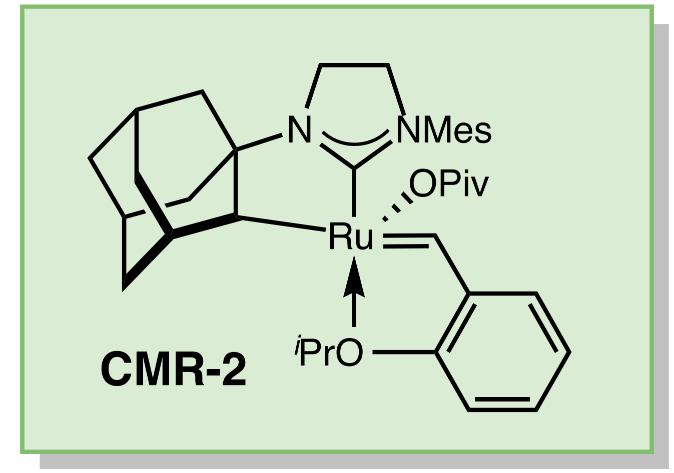
Keitz, B.K.; Endo, K.; Herbert, M.B.; Grubbs, R.H. *J. Am. Chem. Soc.* **2011**, *133*, 9686.

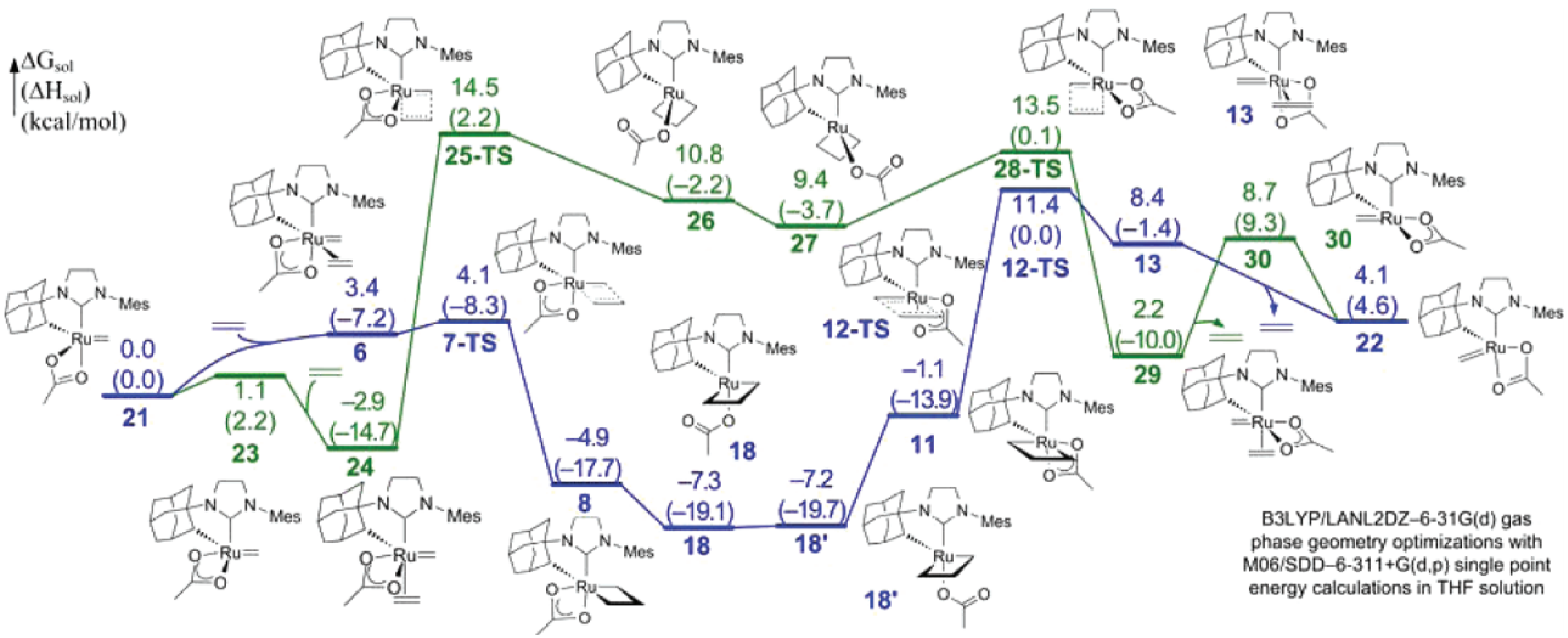
Olefin Metathesis

Cyclometalated Ru Catalysts

- Computational and mechanistic understanding elucidates important aspects of *Z* selective Ru catalysts





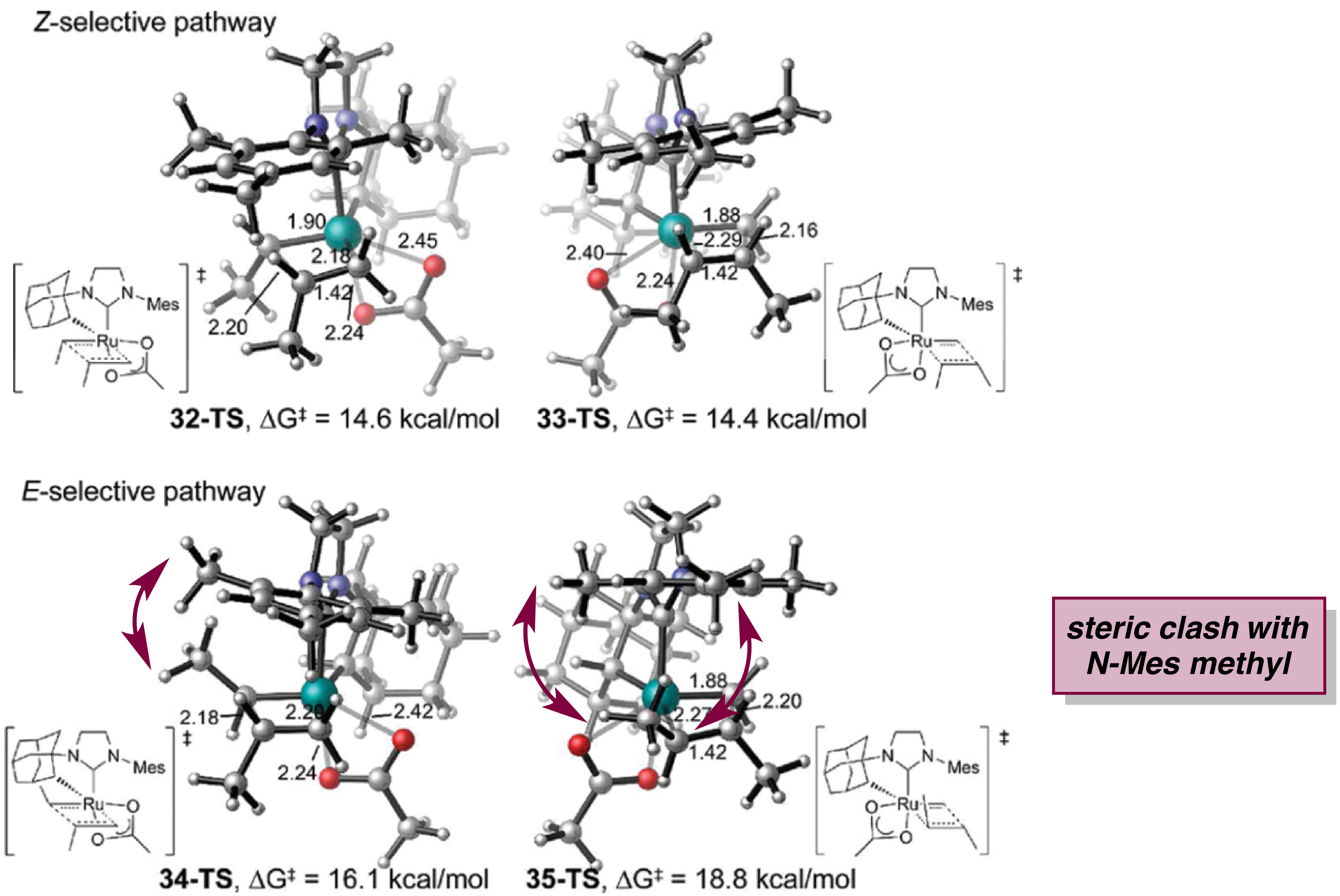


Liu, P.; Xu, X.; Dong, X.; Keitz, B.K.; Herbert, M.B.; Grubbs, R.H.; Houk, K.N. *J. Am. Chem. Soc.* **2012**, *134*, 1464.

Olefin Metathesis

Cyclometalated Ru Catalysts

- Side-bound transition state favors *Z* geometry over *E* geometry

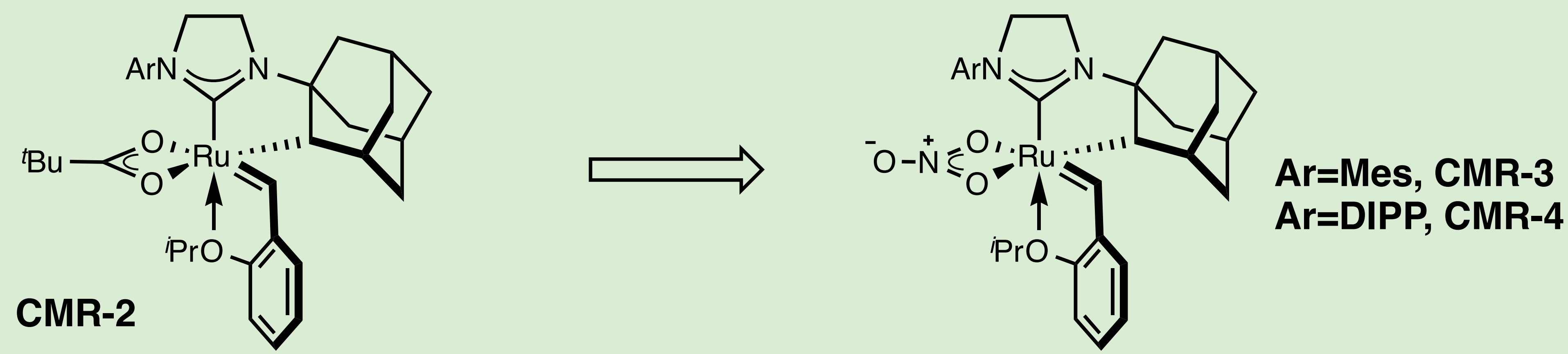


Liu, P.; Xu, X.; Dong, X.; Keitz, B.K.; Herbert, M.B.; Grubbs, R.H.; Houk, K.N. *J. Am. Chem. Soc.* **2012**, *134*, 1464.

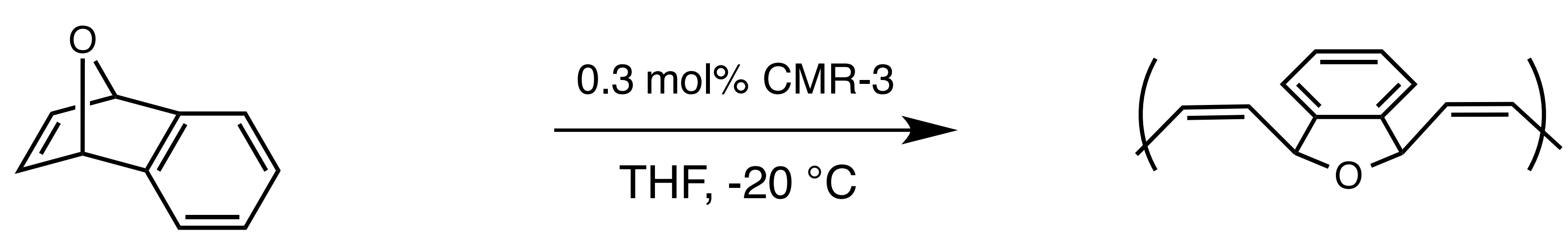
Olefin Metathesis

Optimized Cyclometalated Ru Catalysts

- Swapping bidentate X ligands and varying arenes on NHC yielded ideal catalyst



- Nitrate ligand proved to be key to unlocking full potential
  - *Z*-selective ROMP



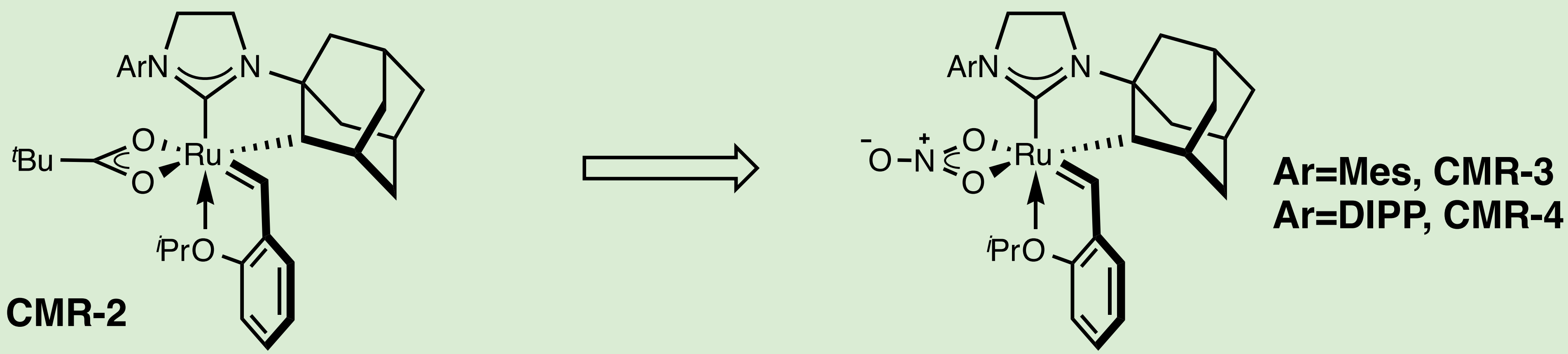
80% yield, 91% *Z*

Rosenbrugh, L.E.; Herbert, M.B.; Marx, V.M.; Keitz, B.K.; Grubbs, R.H. *J. Am. Chem. Soc.* **2013**, *135*, 1276.
Marx, V.M.; Herbert, M.B.; Keitz, B.K.; Grubbs, R.H. *J. Am. Chem. Soc.* **2013**, *135*, 94.
Keitz, B.K.; Fedorov, A.; Grubbs, R.H. *J. Am. Chem. Soc.* **2012**, *134*, 2040.
Keitz, B.K.; Endo, K.; Patel, P.R.; Herbert, M.B.; Grubbs, R.H. *J. Am. Chem. Soc.* **2012**, *134*, 693.

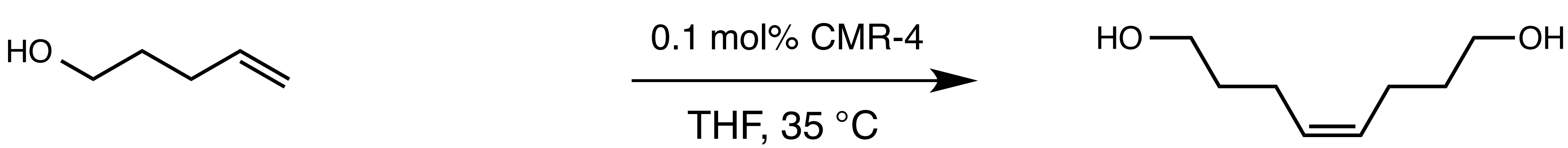
Olefin Metathesis

Optimized Cyclometalated Ru Catalysts

- Swapping bidentate X ligands and varying arenes on NHC yielded ideal catalyst



- Nitrate ligand proved to be key to unlocking full potential
  - *Z*-selective homodimerization



77% yield, >95% *Z*

Rosenbrugh, L.E.; Herbert, M.B.; Marx, V.M.; Keitz, B.K.; Grubbs, R.H. *J. Am. Chem. Soc.* **2013**, *135*, 1276.

Marx, V.M.; Herbert, M.B.; Keitz, B.K.; Grubbs, R.H. *J. Am. Chem. Soc.* **2013**, *135*, 94.

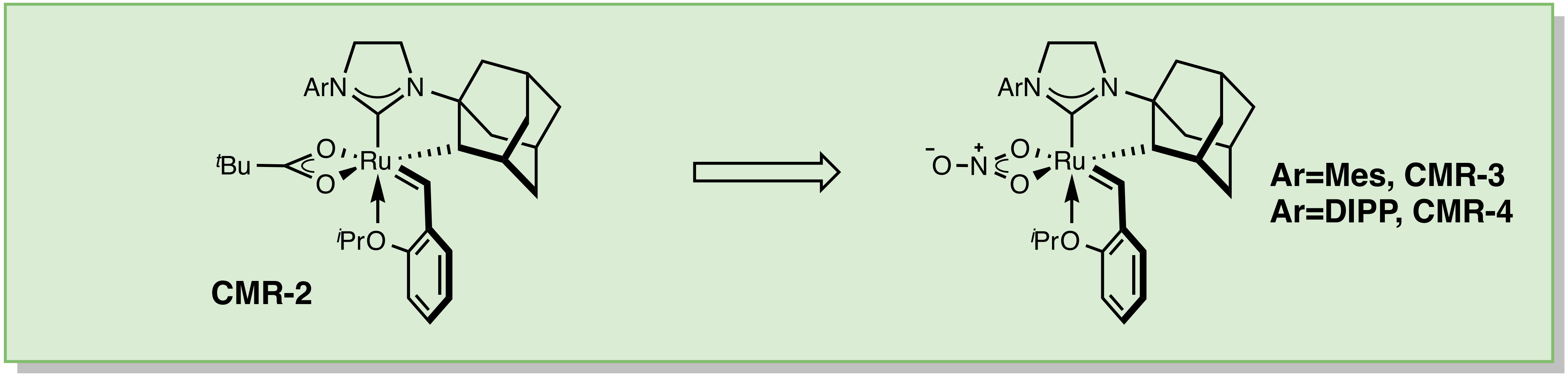
Keitz, B.K.; Fedorov, A.; Grubbs, R.H. *J. Am. Chem. Soc.* **2012**, *134*, 2040.

Keitz, B.K.; Endo, K.; Patel, P.R.; Herbert, M.B.; Grubbs, R.H. *J. Am. Chem. Soc.* **2012**, *134*, 693.

Olefin Metathesis

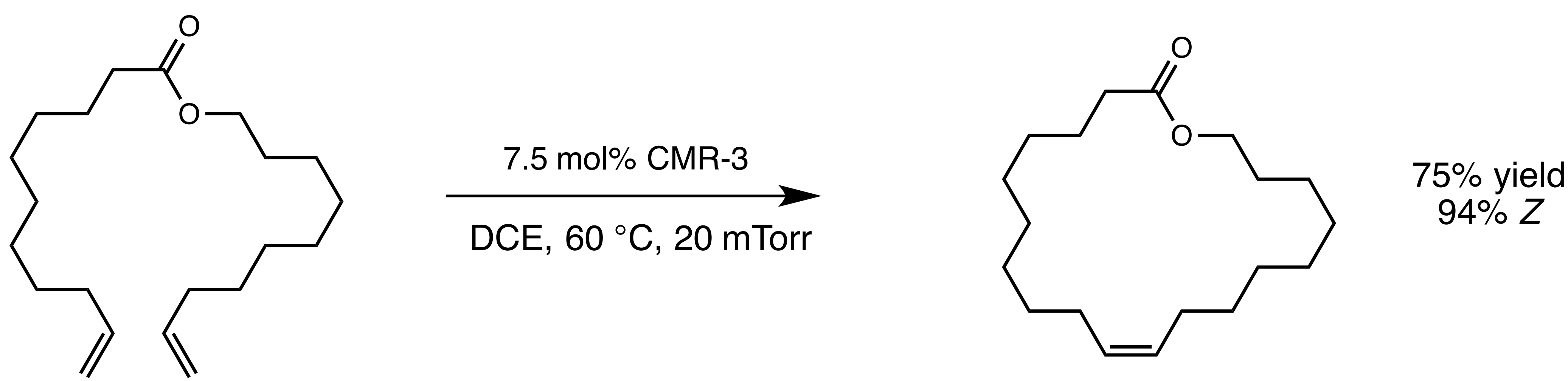
Optimized Cyclometalated Ru Catalysts

■ Swapping bidentate X ligands and varying arenes on NHC yielded ideal catalyst



■ Nitrate ligand proved to be key to unlocking full potential

■ *Z*-selective macrocyclic RCM



Rosenbrugh, L.E.; Herbert, M.B.; Marx, V.M.; Keitz, B.K.; Grubbs, R.H. *J. Am. Chem. Soc.* **2013**, *135*, 1276.

Marx, V.M.; Herbert, M.B.; Keitz, B.K.; Grubbs, R.H. *J. Am. Chem. Soc.* **2013**, *135*, 94.

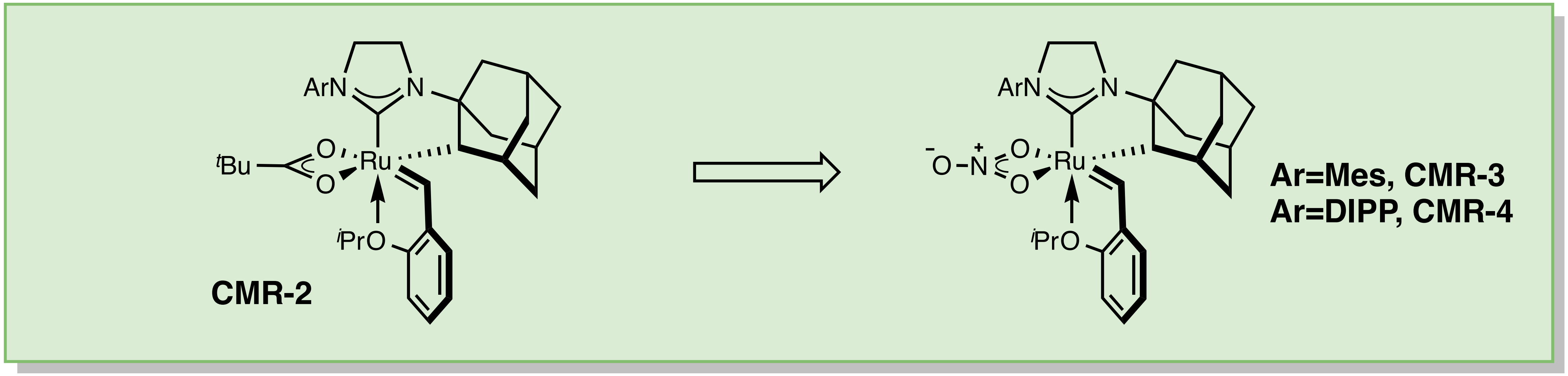
Keitz, B.K.; Fedorov, A.; Grubbs, R.H. *J. Am. Chem. Soc.* **2012**, *134*, 2040.

Keitz, B.K.; Endo, K.; Patel, P.R.; Herbert, M.B.; Grubbs, R.H. *J. Am. Chem. Soc.* **2012**, *134*, 693.

Olefin Metathesis

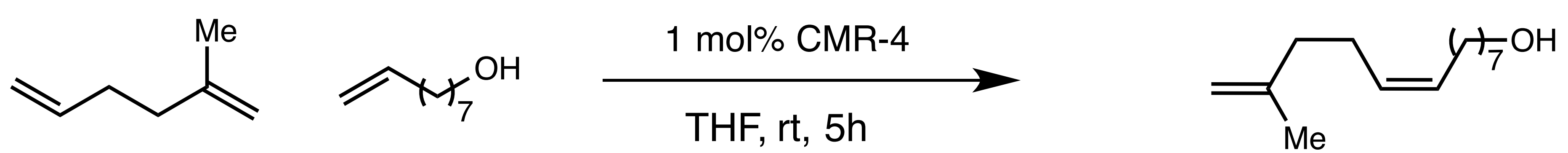
Optimized Cyclometalated Ru Catalysts

■ Swapping bidentate X ligands and varying arenes on NHC yielded ideal catalyst



■ Nitrate ligand proved to be key to unlocking full potential

■ *Z*-selective **and** chemoselective cross metathesis



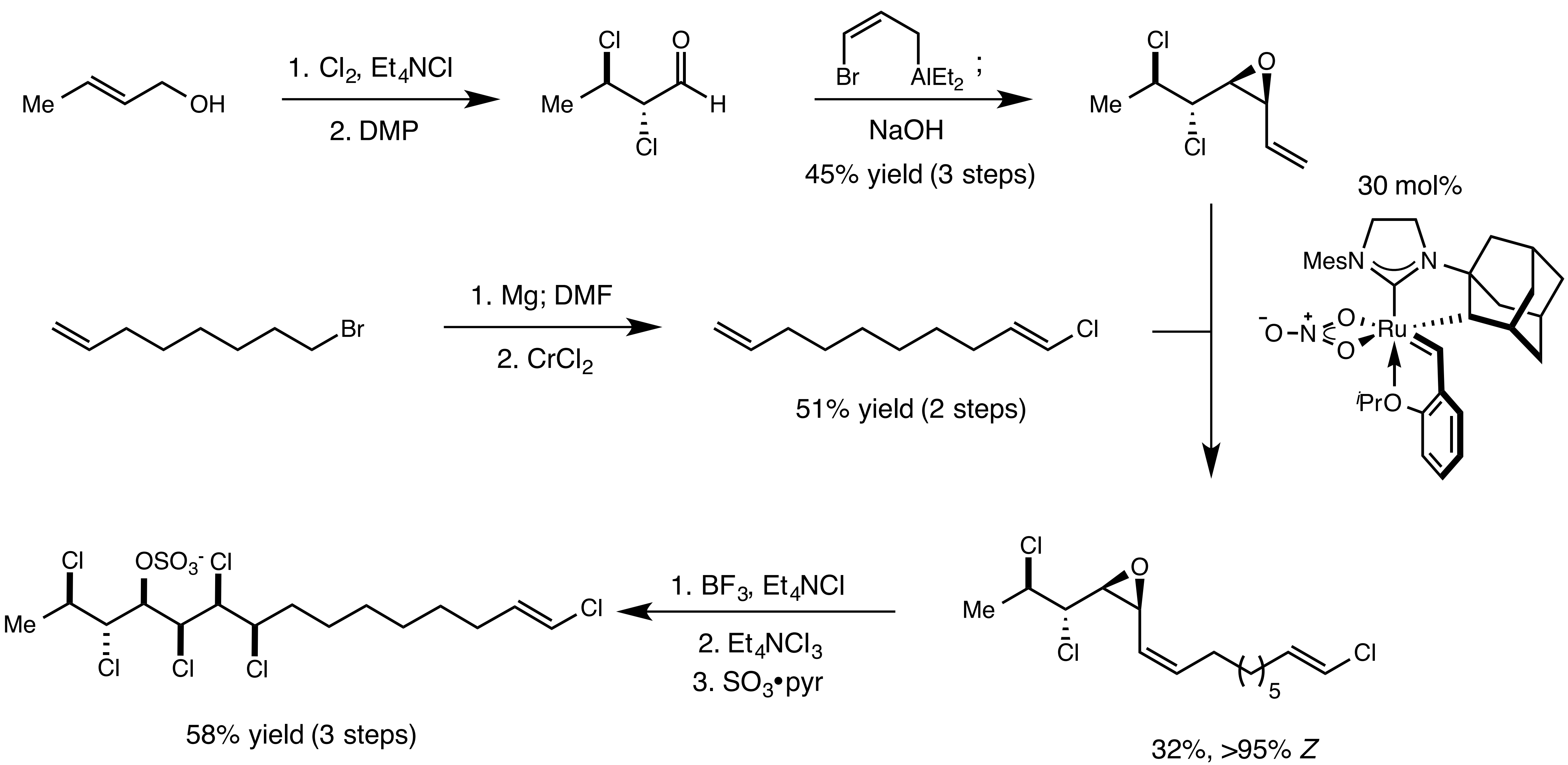
1 equiv.	5 equiv.	45% yield, >95% *Z*
7 equiv.	1 equiv.	66% yield, >95% *Z*

Cannon, J.S.; Grubbs, R.H. *Angew. Chem. Int. Ed.* **2013**, *52*, 9001.

Olefin Metathesis

Optimized Cyclometalated Ru Catalysts

- Highly enabling technology for total synthesis of complex molecules
  - Vanderwal's synthesis of myltilipin A in 7 steps

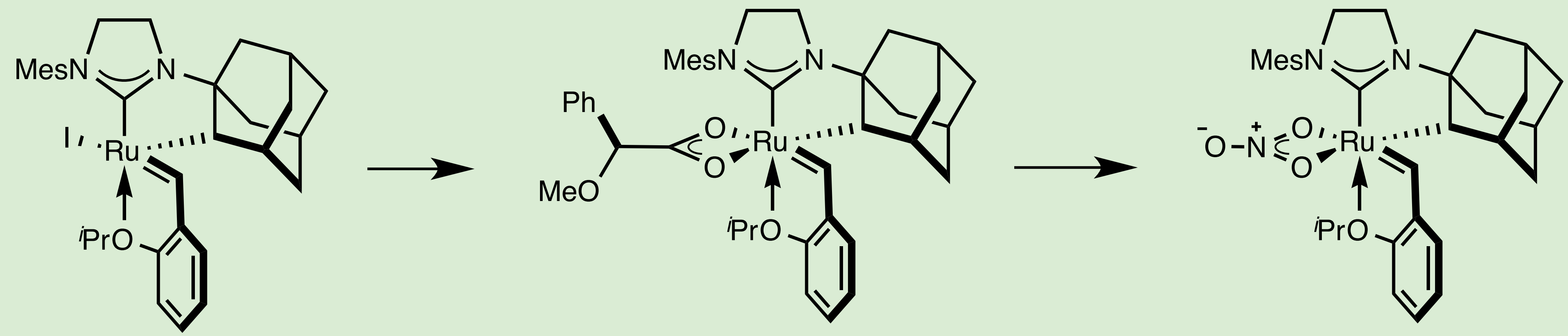


Chung, W.; Carlson, J.S.; Bedke, D.K.; Vanderwal, C.D. *Angew. Chem. Int. Ed.* **2013**, *52*, 10052.

Olefin Metathesis

Enantiopure Carbometalated Ru Catalysts

■ Chirality at Ru center can be resolved by classical resolution

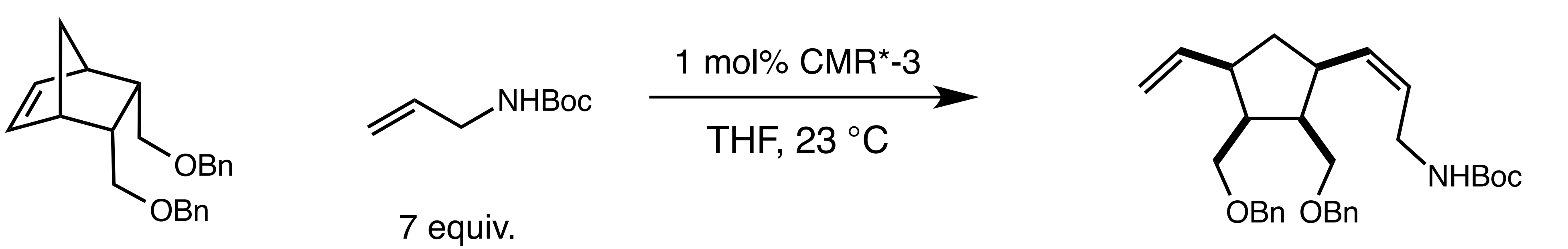


separation of diastereomers

CMR*-3

■ Chiral-at-Ru CMR catalysts can provide excellent asymmetric induction

■ *Z*-selective enantioselective ROCM



41% yield, 95% *Z*, 94% ee

brand new technology, still developing

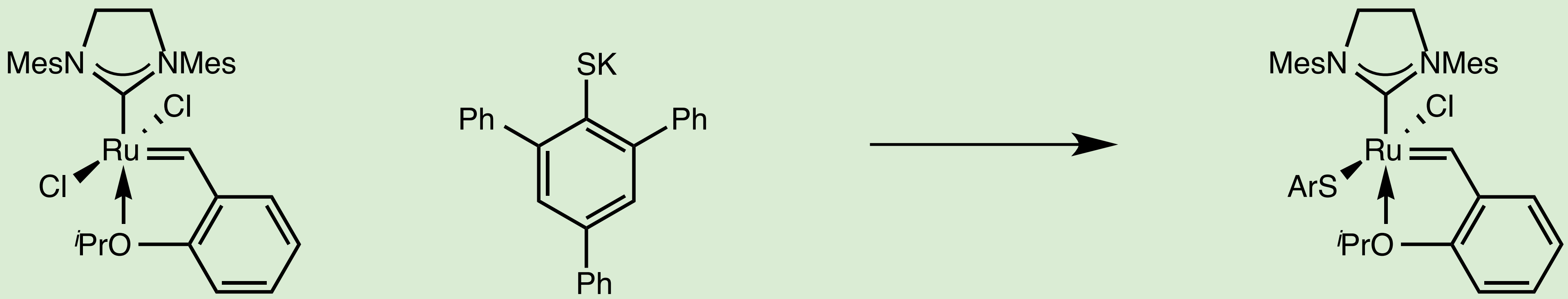
Hartung, J.; Grubbs, R.H. *J. Am. Chem. Soc.* **2013**, *135*, 10183.

Hartung, J.; Dornan, P.K.; Grubbs, R.H. *J. Am. Chem. Soc.* **2014**, *136*, 13029.

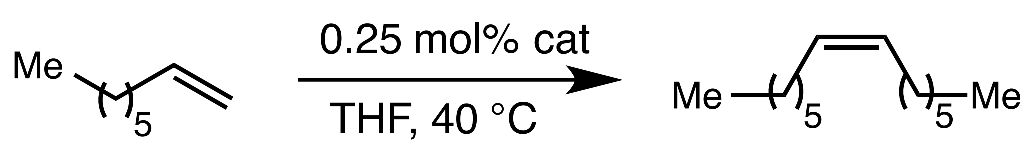
Olefin Metathesis

Bidentate Anionic LIgands

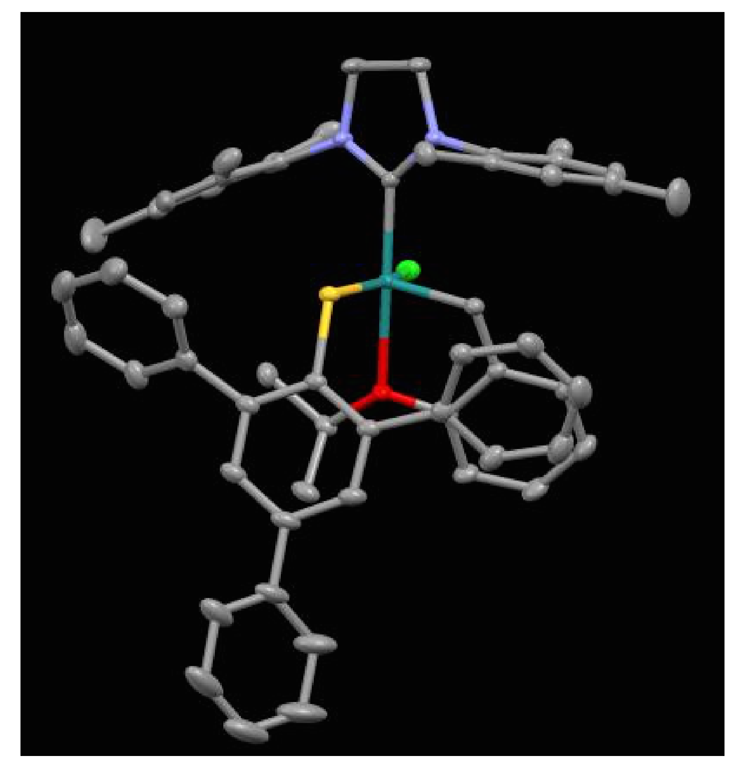
■ Ruthenium catalysts with aryl thiolate ligand show promise for *Z*-selective CM



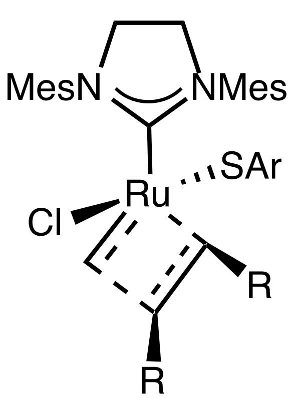
■ Very mild *Z*-selectivities, and only at low conversion

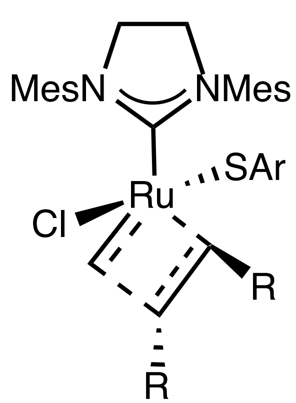


17% conv, 86% *Z*
45% conv, 81% *Z*
64% conv, 75% *Z*



■ Rate-limiting cyclobutane reversion, favors *cis* by ~1.2 kcal/mol



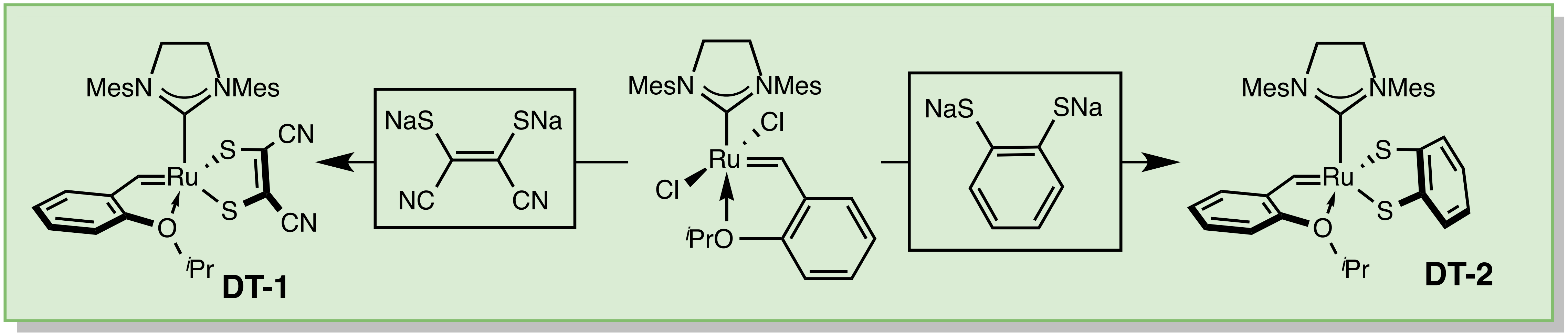


Occhipinti, G.; Hansen, F.R.; Tornroos, K.W.; Jensen, V.R. *J. Am. Chem. Soc.* **2013**, *135*, 3331.
Occhipinti, G.; Koudriavtsev, V..; Tornroos, K.W.; Jensen, V.R. *Dalton Trans.* **2014**, *43*, 11106.
Nelson, J.W.; Grundy, L.M.; Dang, Y.; Wang, Z.-X.; Wang, X. *Organometallics* **2014**, *33*, 4290.

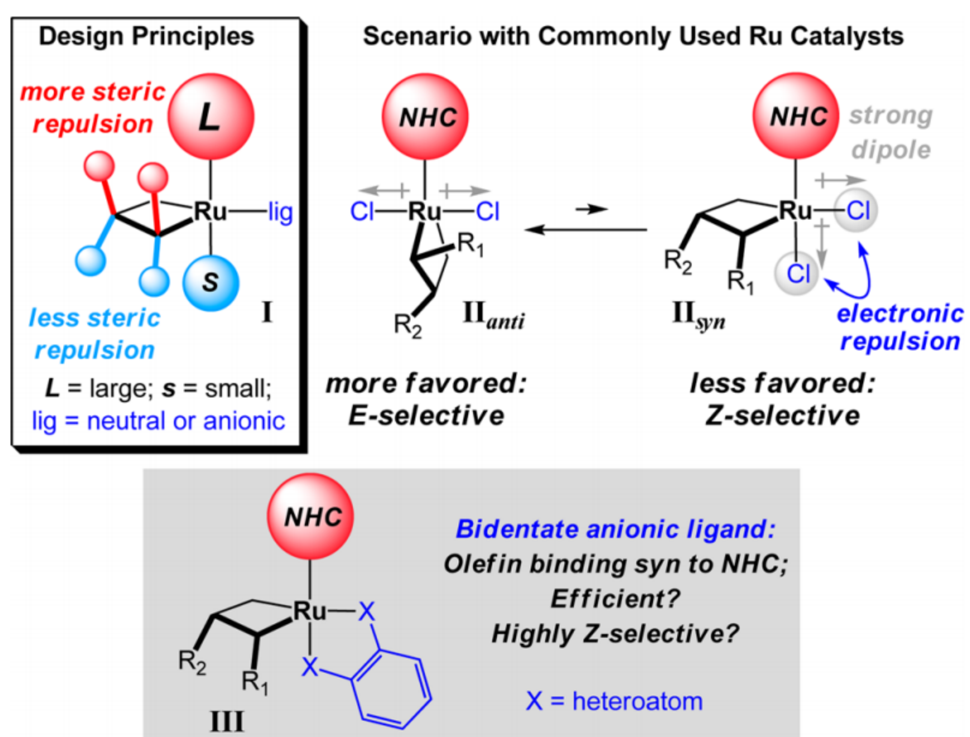
Olefin Metathesis

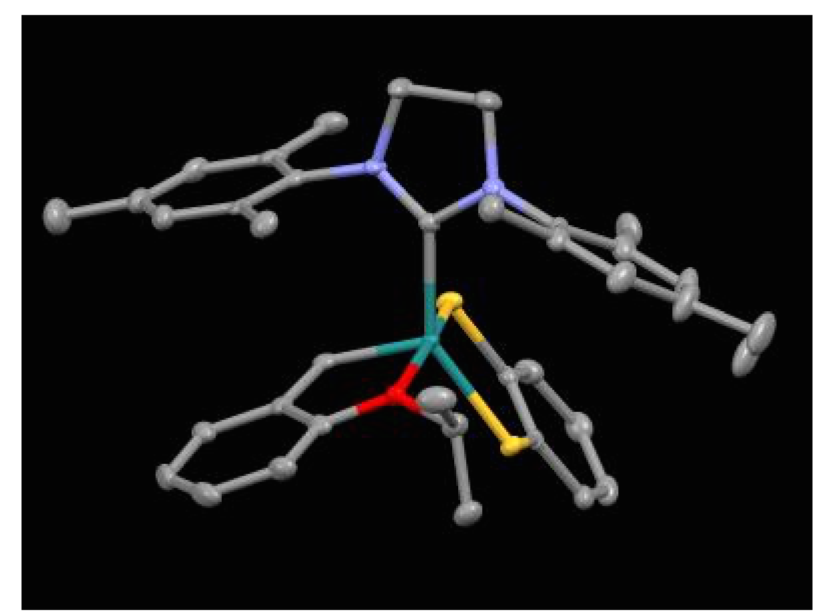
Bidentate Anionic LIgands

- Utilizing dithiolate (bidentate) ligands proves to be key for control



- Design principle: tie back small anionic ligands, allow for bulky NHC to control





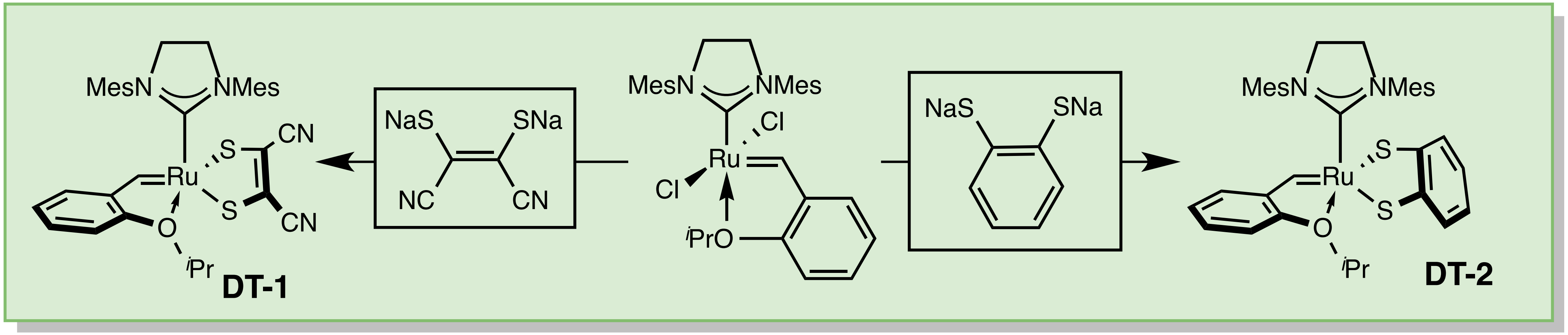
DT-2

Khan, R.K.M.; Torker, S.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2013**, *135*, 10258.

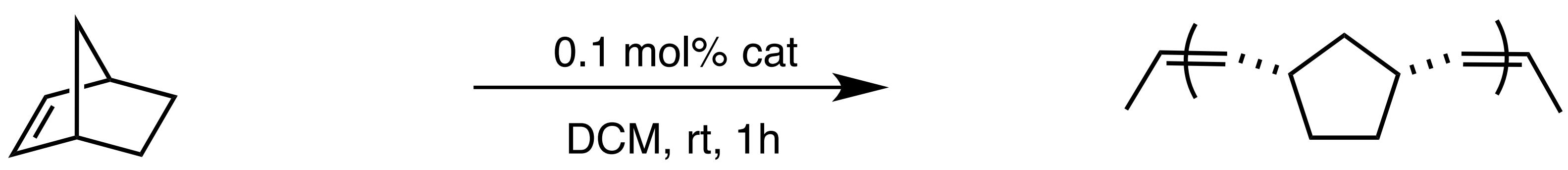
Olefin Metathesis

Bidentate Anionic LIgands

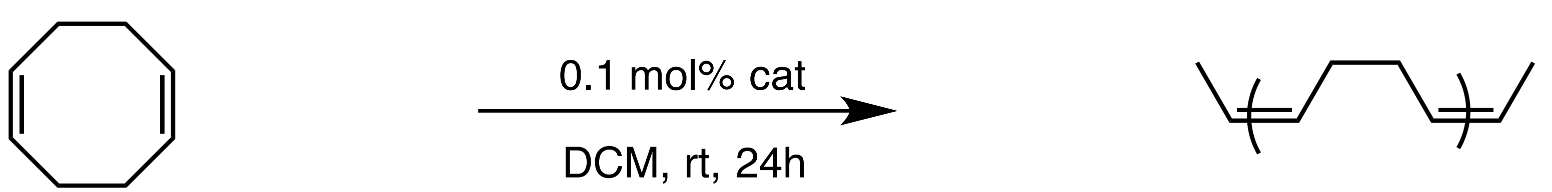
■ Utilizing dithiolate (bidentate) ligands proves to be key for control



■ Excellent reactivity and perfect selectivity for ROMP



DT-1: 90% yield, >98% *Z*
DT-2 : 93% yield, >98% *Z*



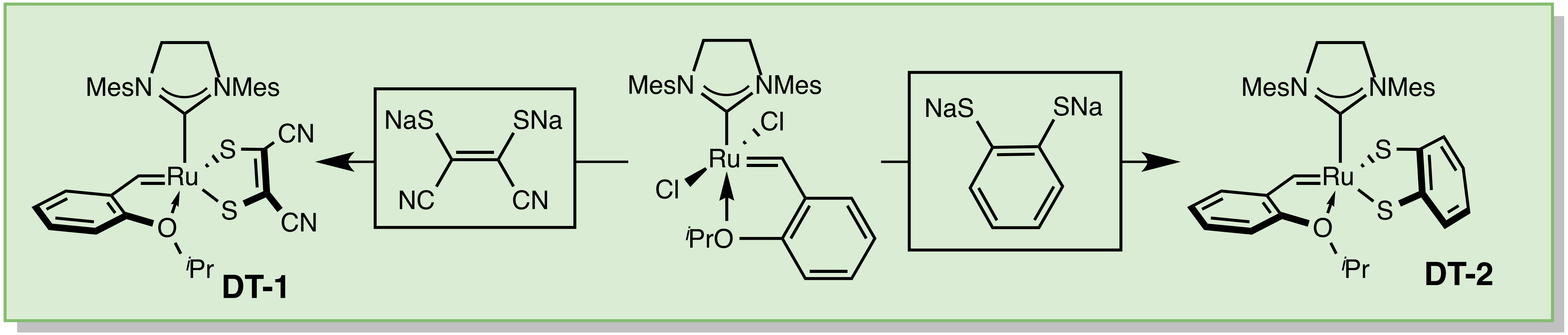
DT-1: 75% yield, >98% *Z*
DT-2: 75% yield, >98% *Z*

Khan, R.K.M.; Torker, S.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2013**, *135*, 10258.

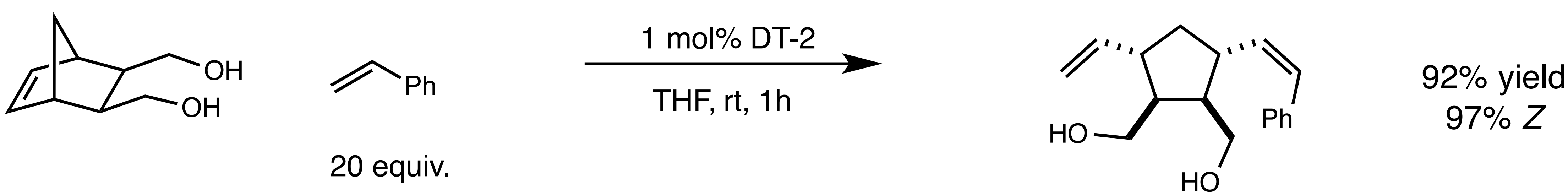
Olefin Metathesis

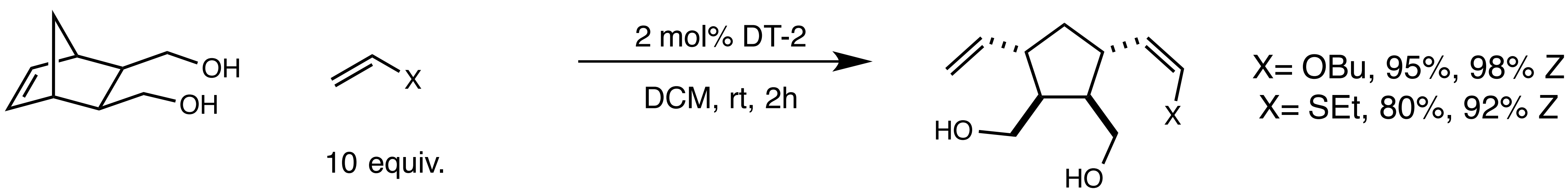
Bidentate Anionic LIgands

■ Utilizing dithiolate (bidentate) ligands proves to be key for control



■ *Z*-selective ROCM are also highly efficient



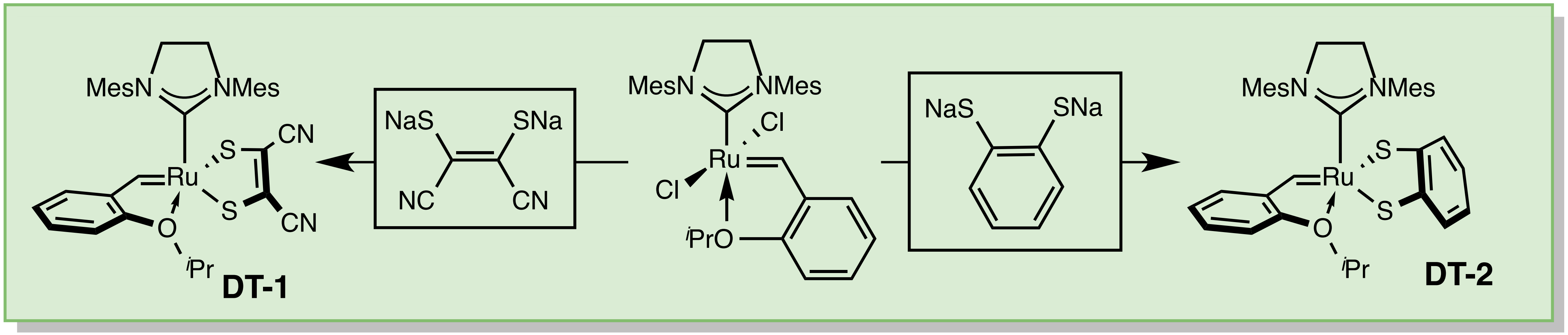


Koh, M.J.; Khan, R.K.M.; Torker, S.; Hoveyda, A.H. *Angew. Chem. Int. Ed.* **2014**, *126*, 1999.
Khan, R.K.M.; Torker, S.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2013**, *135*, 10258.

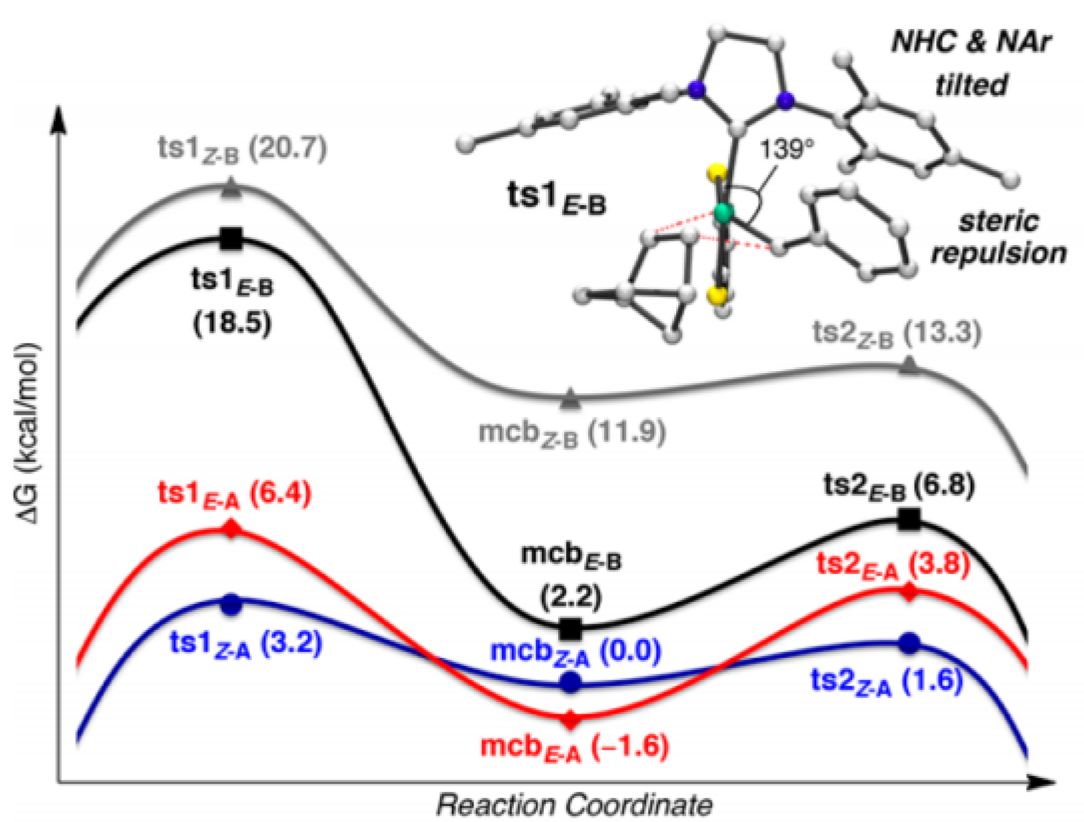
Olefin Metathesis

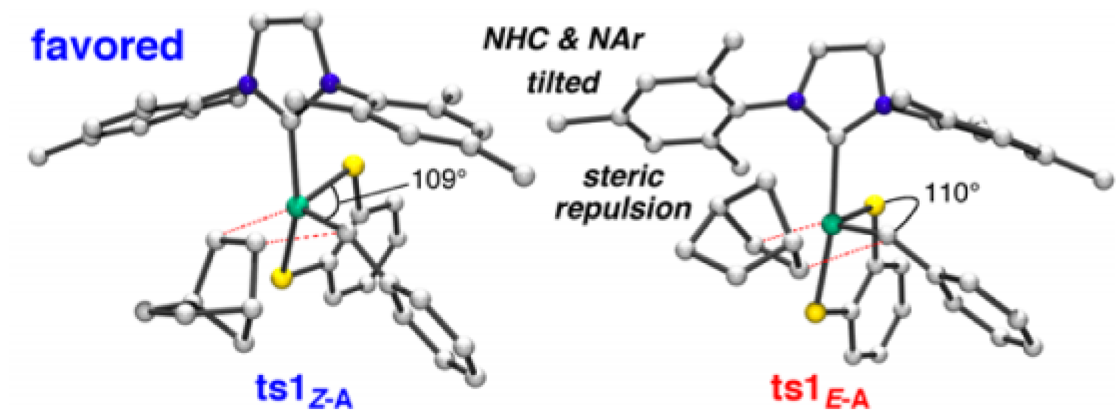
Bidentate Anionic LIgands

- Utilizing dithiolate (bidentate) ligands proves to be key for control



- Computational support for simple stereochemical model





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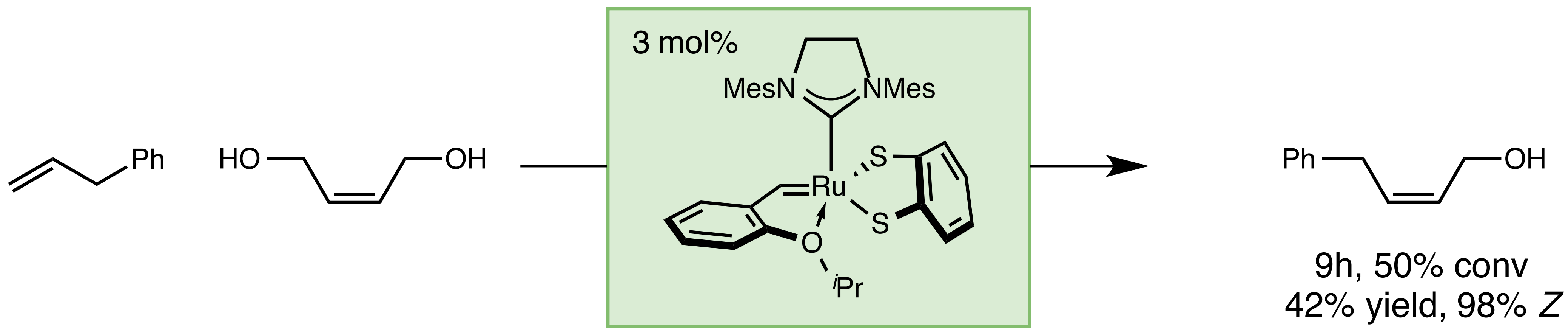
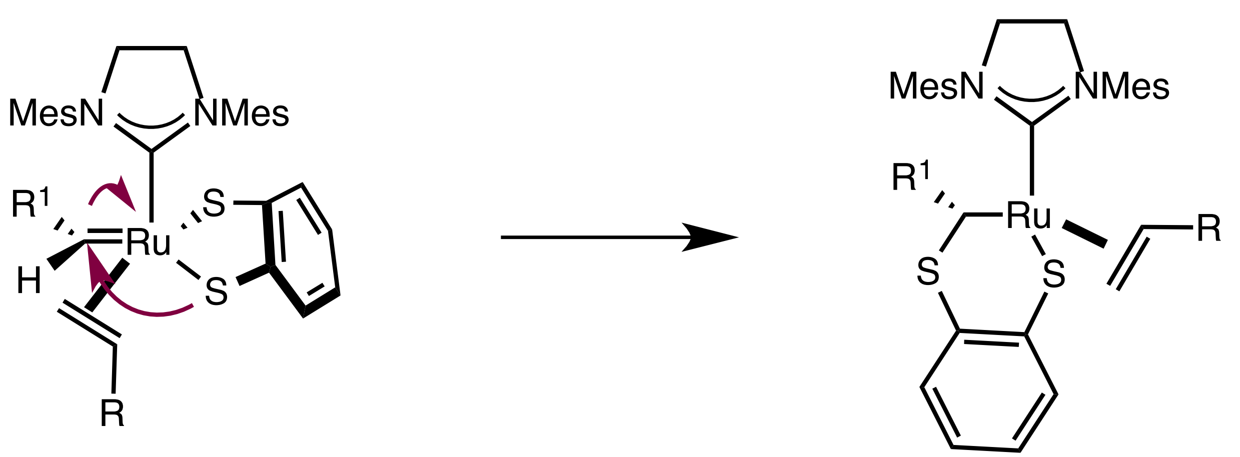
Olefin Metathesis

Bidentate Anionic LIgands

■ Limited in ability to perform CM with allyl alcohols - only can do ROCM efficiently



■ No further conversion implies decomposition of catalyst...



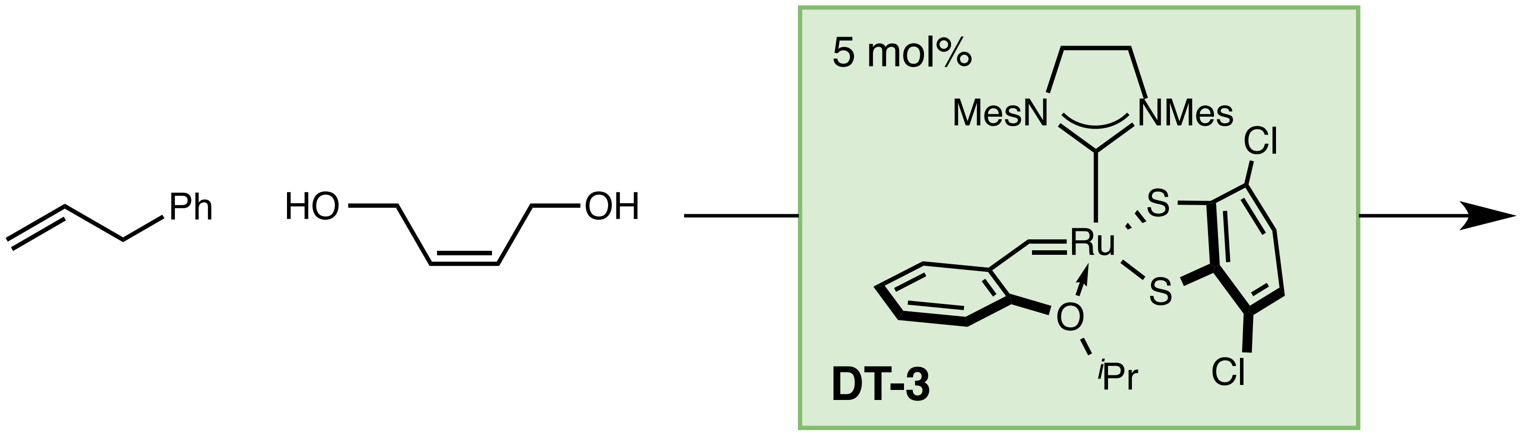
- ***1,2 shift likely deactivates catalyst***
- ***strong σ-donor (NHC) = large trans inf***
- ***large trans inf = electron rich apical S***
- ***electron deficient groups on S-arene?***

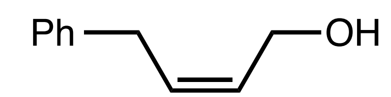
Koh, M.J.; Khan, R.K.M.; Torker, S.; Yu, M.; Mikus, M.S.; Hoveyda, A.H. *Nature* **2015**, 10.1038/nature14061.

Olefin Metathesis

Bidentate Anionic LIgands

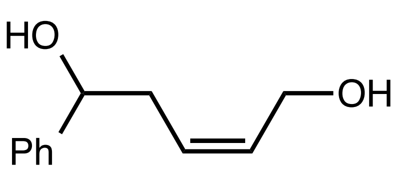
■ More stable dithiolate catalysts allow for broader substrate scope



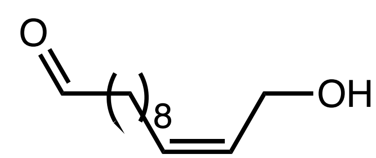


9h, 84% conv
71% yield, 96% *Z*

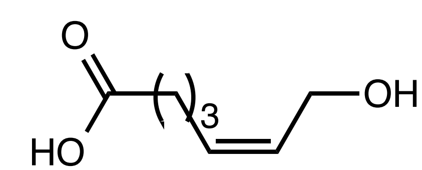
■ Excellent scope - extremely broad functional group tolerance



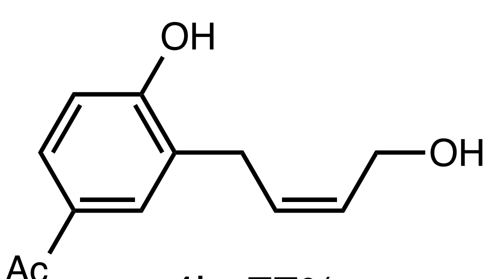
4h, 72% conv
64% yield, 96% *Z*



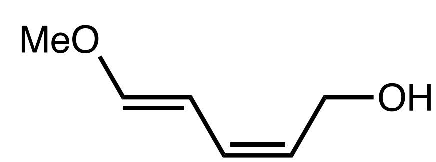
4h, 86% conv
80% yield, 94% *Z*



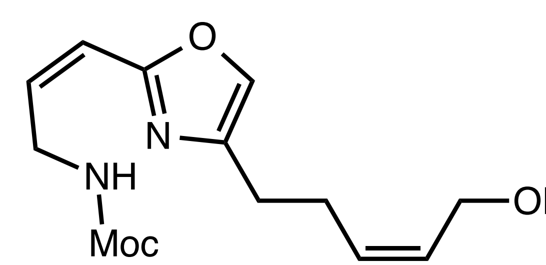
4h, 85% conv
70% yield, 96% *Z*



4h, 77% conv
68% yield, 98% *Z*



8h, 72% conv
63% yield, 92% *Z*



12h, 85% conv
70% yield, 98% *Z*

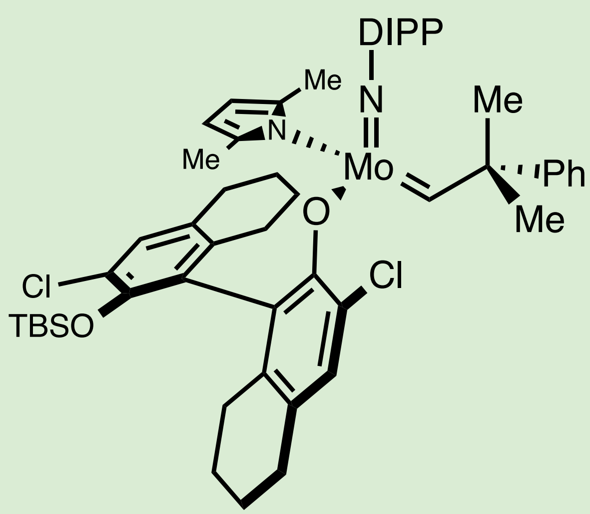
Koh, M.J.; Khan, R.K.M.; Torker, S.; Yu, M.; Mikus, M.S.; Hoveyda, A.H. *Nature* **2015**, 10.1038/nature14061.

Olefin Metathesis

What's Next?

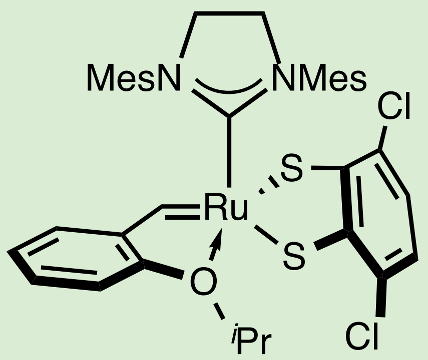
Current State-of-the-Art:

enantioselective



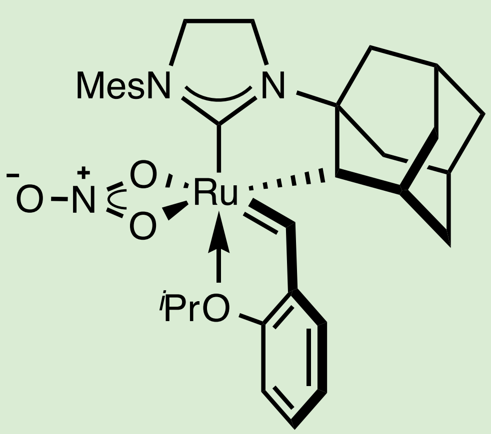
very poor generality

Z-selective



decomposes readily

What's coming in the next 5 years?



broader scope for ee?

Is kinetic E-selecitivity possible?

Olefin Metathesis

Useful references

- Marx, V.M.; Rosebrugh, L.E.; Herbert, M.B.; Grubbs, R.H. *Top. Organomet. Chem.* **2014**, *48*, 1.
- Hoveyda, A.H. *J. Org. Chem.* **2014**, *79*, 4763.
- Fürstner, A. *Science*, **2013,** 10.1126/science.1229713.