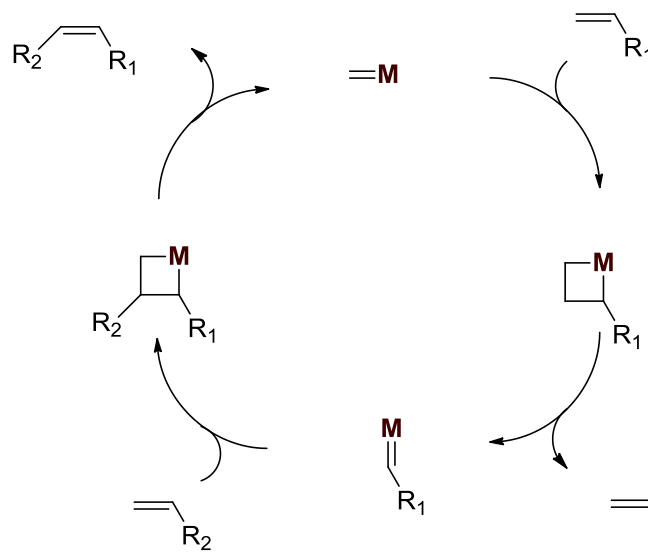
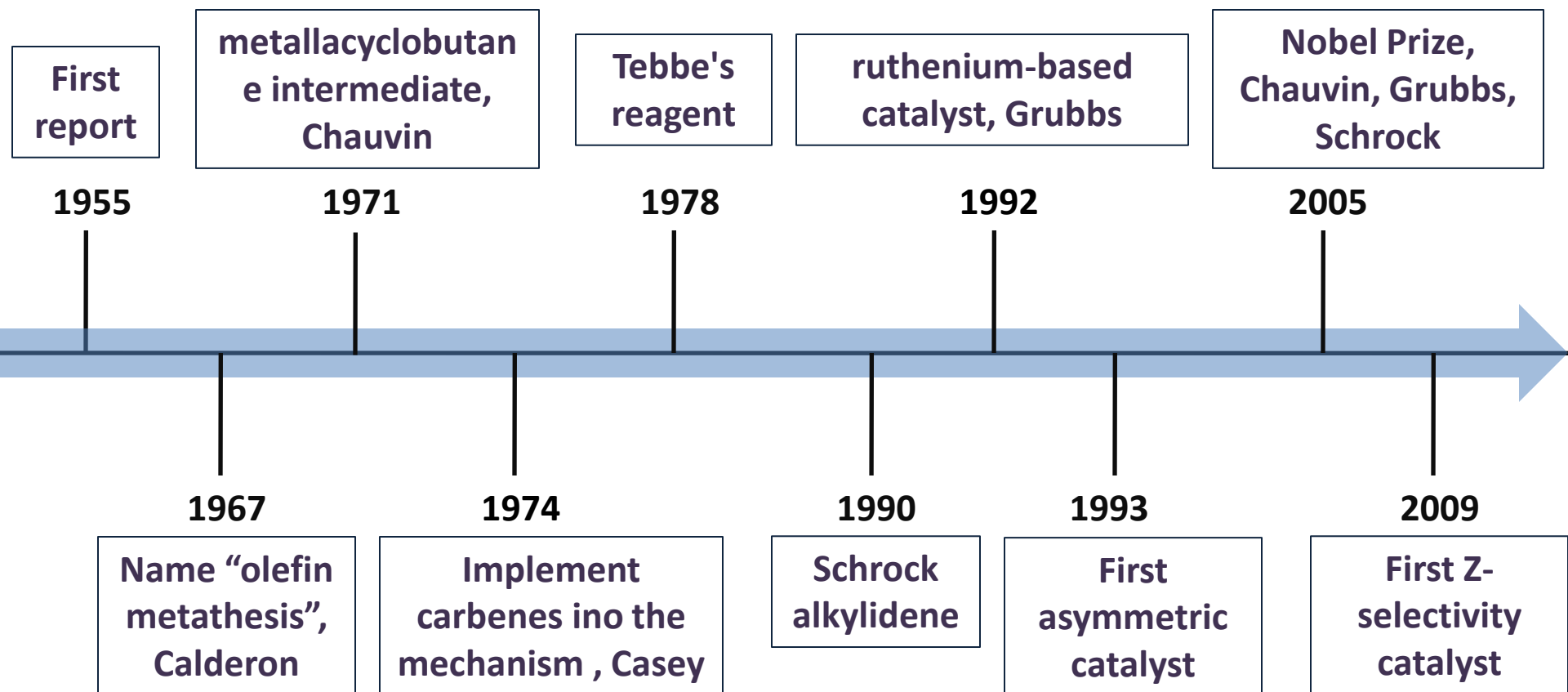


Recent Advances in Z-Selective Olefin Metathesis



Min Zhou
2015.05.05
Hu Group, SIOC

History of Olefin Metathesis



Z-Selective catalysts

1

**MAP(monoaryloxy
pyrrolide) catalysts**

2

**Chelated Ruthenium
Catalysts**

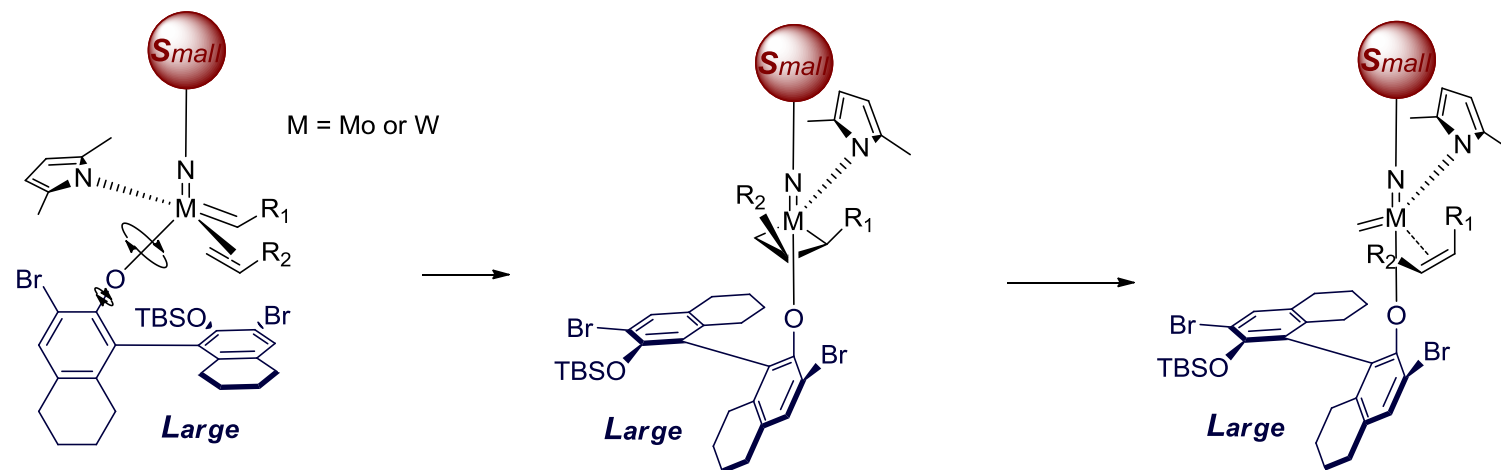
3

**Other Ruthenium
Catalysts**

MAP(monoaryloxo pyrrolide) catalysts

● First Z-selective Catalysts

● Basis design of Z-selective catalysts

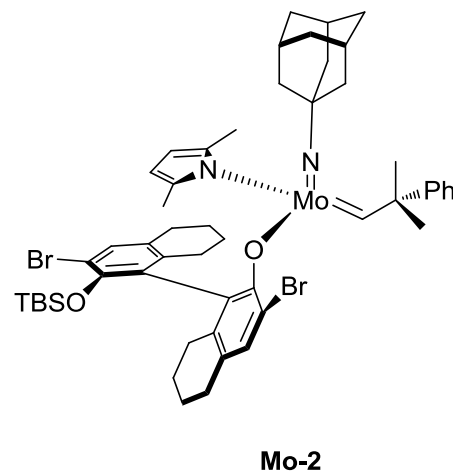
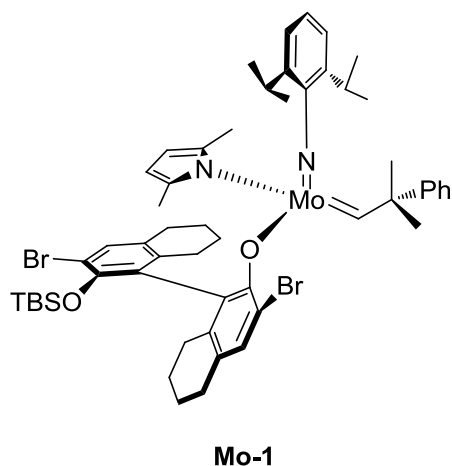


Central Design Principle:

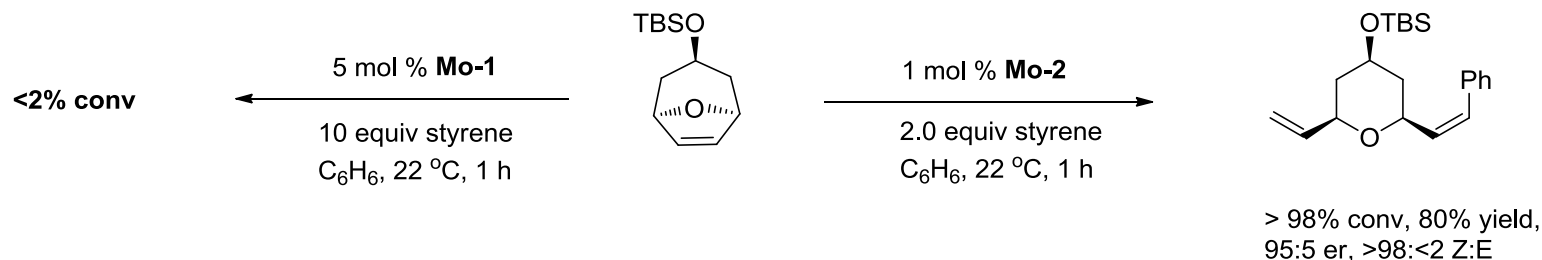
Size differential between rotating large monodentate aryloxo ligand and smaller imido group leads to high kinetic of Z-selective

MAP(monoaryloxide pyrrolide) catalysts

● First Z-selective Catalysts

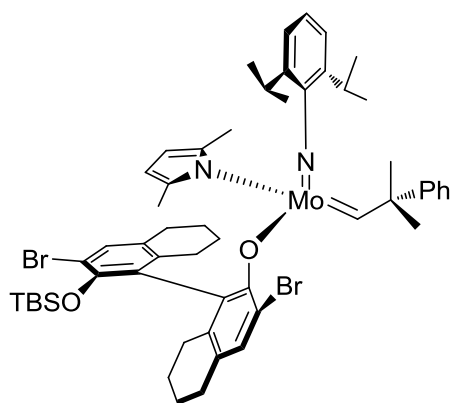


● Z-selective ROCM(ring-opening /cross-metathesis)

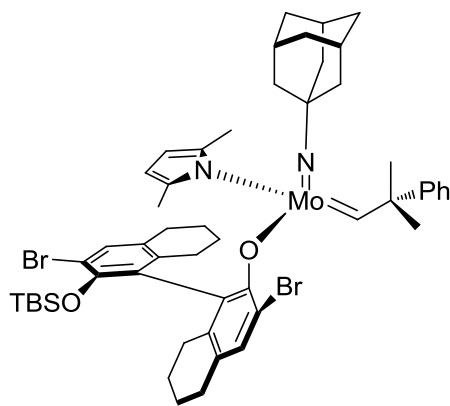


MAP(monoaryloxy pyrrolide) catalysts

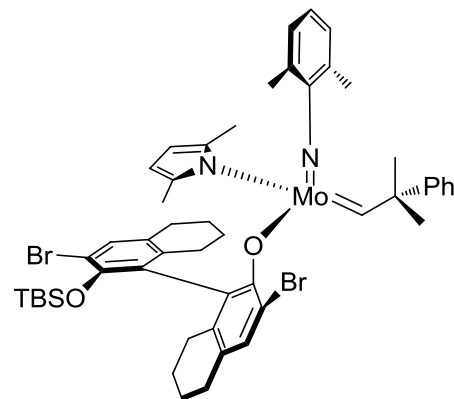
● Z-selective CM(cross-metathesis) reaction



Mo-1

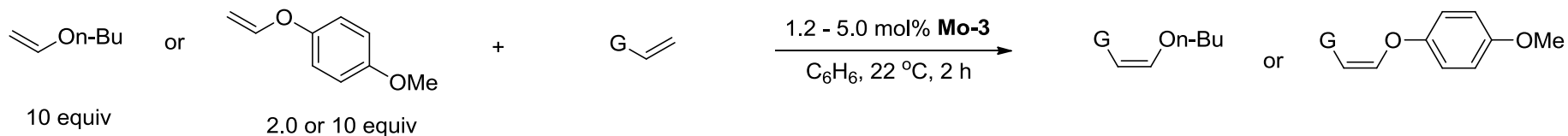


Mo-2



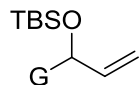
Mo-3

● Z-selective CM of enol ethers with terminal alkenes

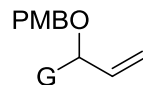


MAP(monoaryloxyde pyrrolide) catalysts

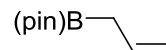
● Z-selective CM of different α -olefin coupling partners



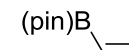
silyl-protected allylic ether



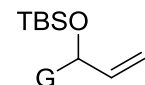
benzyl-protected allylic ether



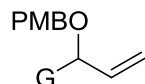
(pinacolato)allylboron



(pinacolato)alkenylboron



or



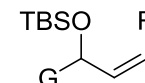
+



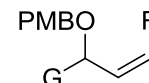
(2.0-3.0 equiv)

Mo-3 (3.0 mol%)

7.0 torr, C₆H₆, 22 °C, 8.0 h



or

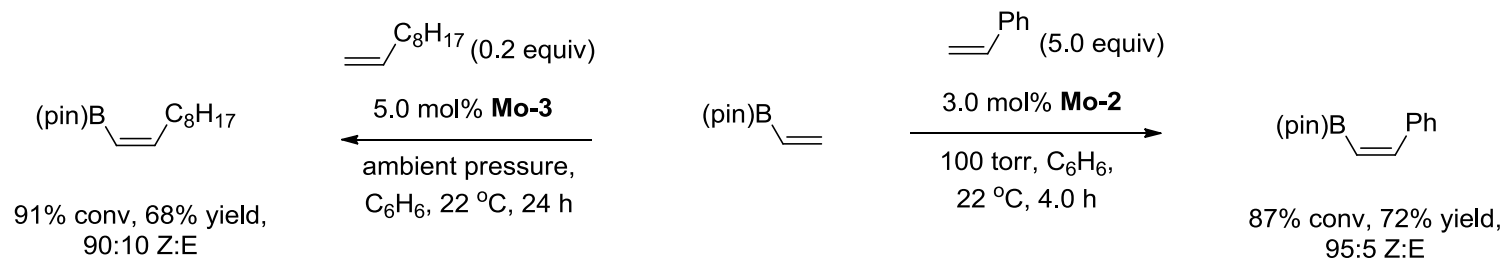
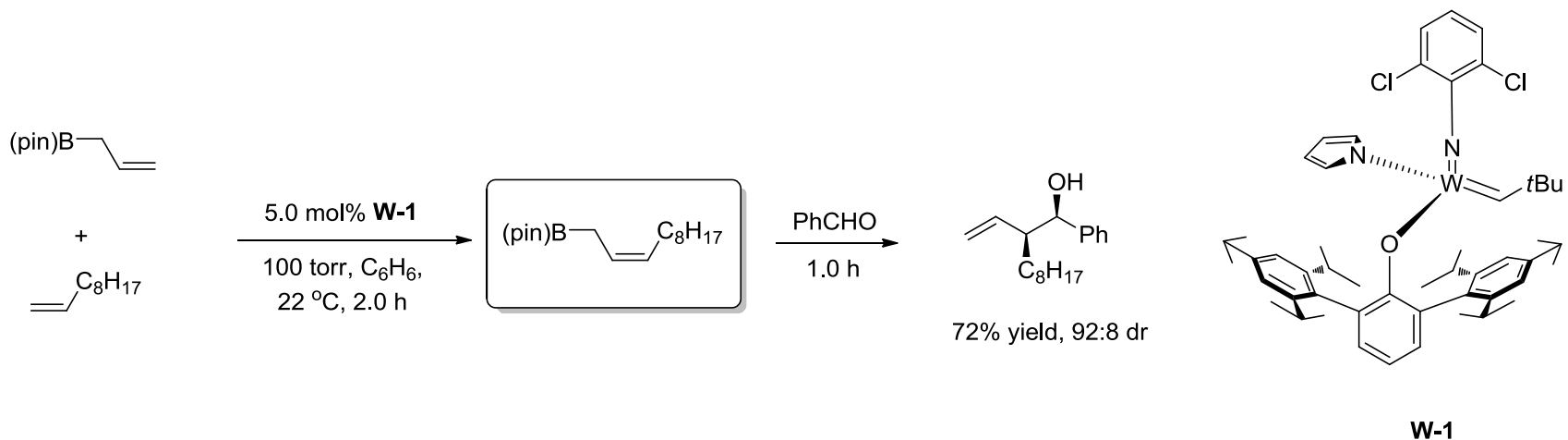


43-89% conv, 37-86% yield
(78:22) to (95:5) Z:E

43-93% conv, 39-87% yield
(90:10) to (>98:2) Z:E

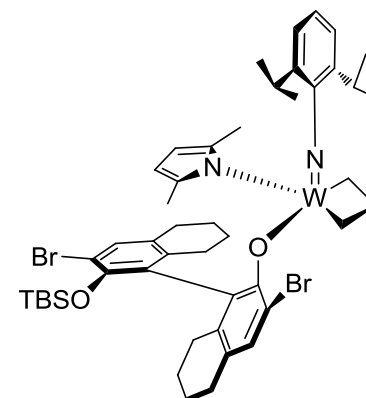
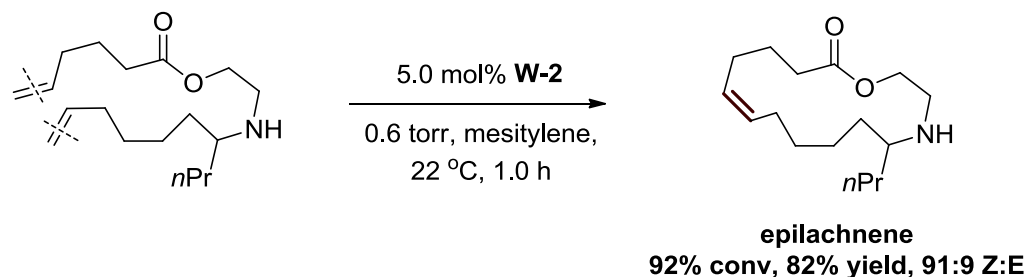
MAP(monoaryloxyde pyrrolide) catalysts

● Z-selective CM of different α -olefin coupling partners

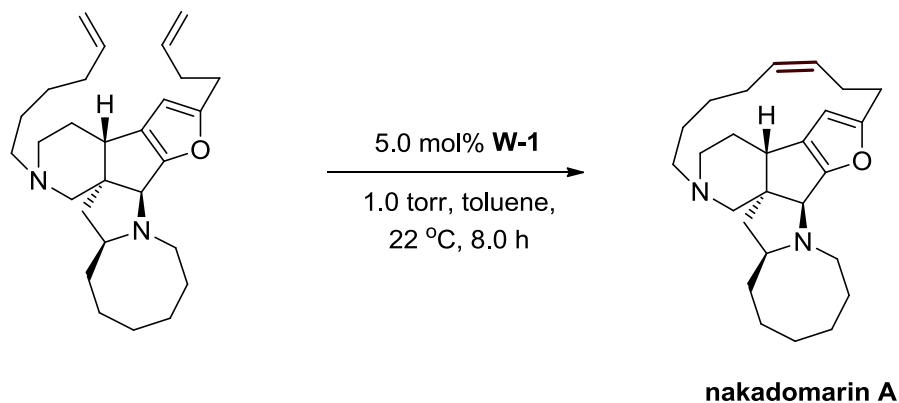


MAP(monoaryloxide pyrrolide) catalysts

● Z-selective RCM(ring-close metathesis)



W-2

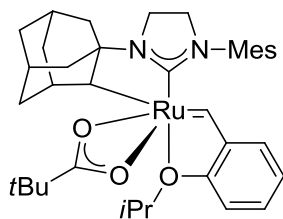


>98% conv, 63% yield, 94:6 Z:E

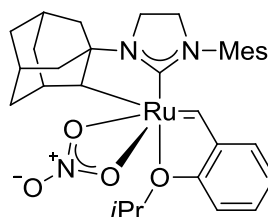
nakadomarin A

Chelated Ruthenium Catalysts

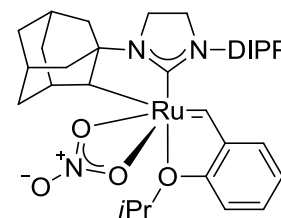
● Z-Selective Terminal Olefin Homocoupling



Ru-1

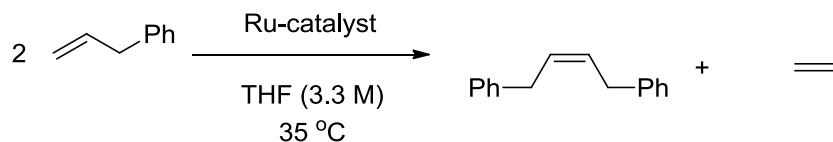


Ru-2



Ru-3

● Improved activity of Ru catalysts by altering the structure



cat	loading	conv	yield	Z%	
Ru-1	2.0 mol%	>95	81	92	
Ru-2	0.1 mol%	-	91	92	TON: up to 1000
Ru-3	0.1 mol%	>95	-	>95	
Ru-3	0.01 mol%	-	-	>95	rt, TON 7400

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.

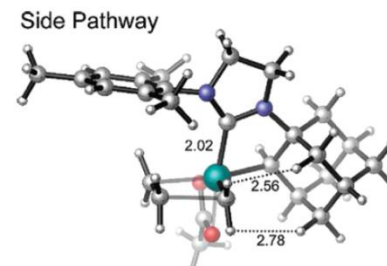
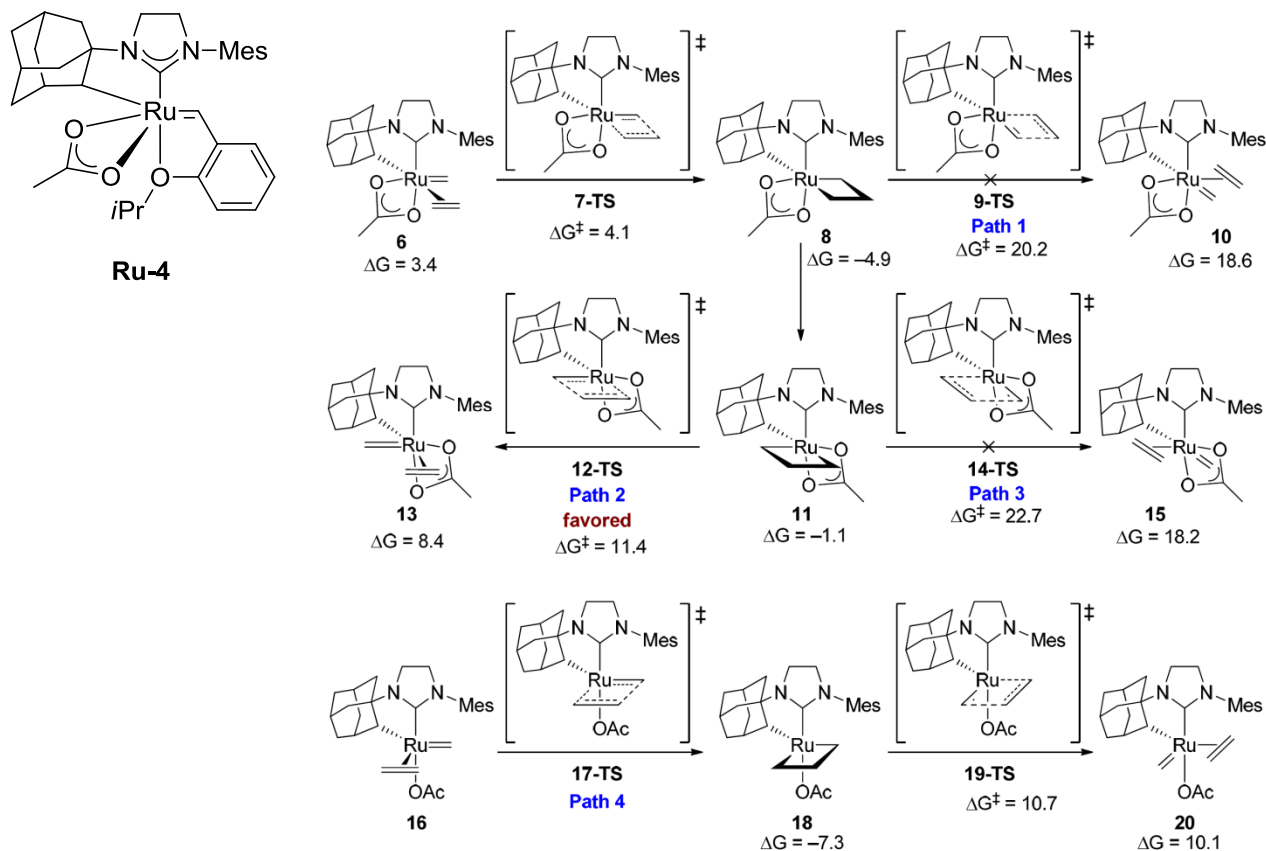
Hu Group, SIOC B. K. Keitz, K. Endo, P. R. Patel, M. B. Herbert, R. H. Grubbs, *J. Am. Chem. Soc.* **2012**, *134*, 693.

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

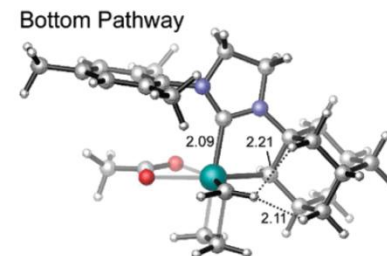
Chelated Ruthenium Catalysts

● Computational Studies show the mechanism and origins of Z-selectivity

side-bound vs bottom-bound (steric and electronic effects)



7-TS, $\Delta G^\ddagger = 4.1$ kcal/mol



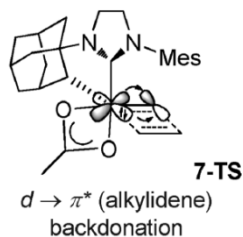
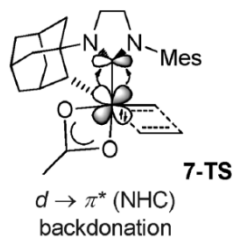
25-TS, $\Delta G^\ddagger = 14.5$ kcal/mol

Barrier: bottom-bound over
side-bound ~ 3.1 kcal/mol higher

4 pathways in side-bound

Chelated Ruthenium Catalysts

side-bound transition state



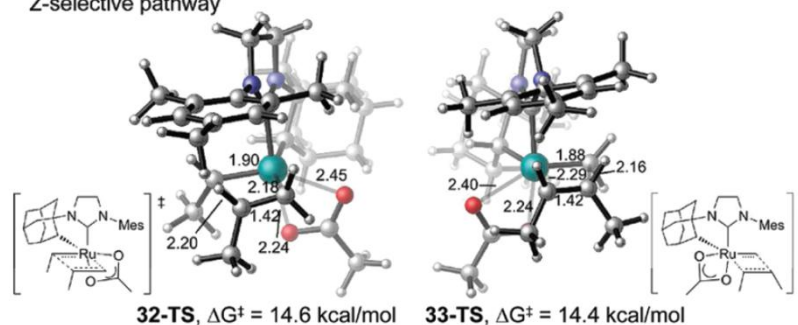
bottom-bound transition state



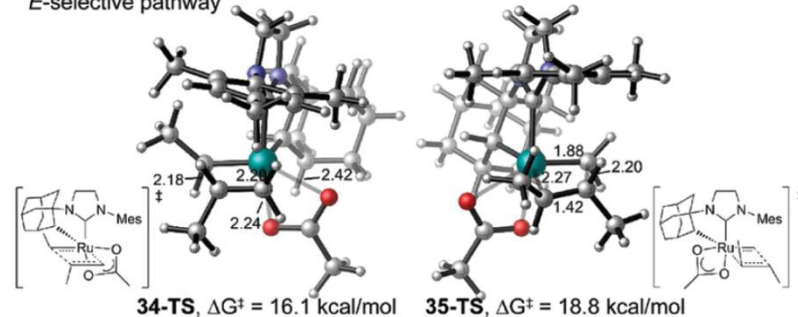
$d \rightarrow \pi^*$ (NHC) and $d \rightarrow \pi^*$ (alkylidene)
 backdonation involving the same Ru d orbital

Z-selectivity vs E-selectivity

Z-selective pathway

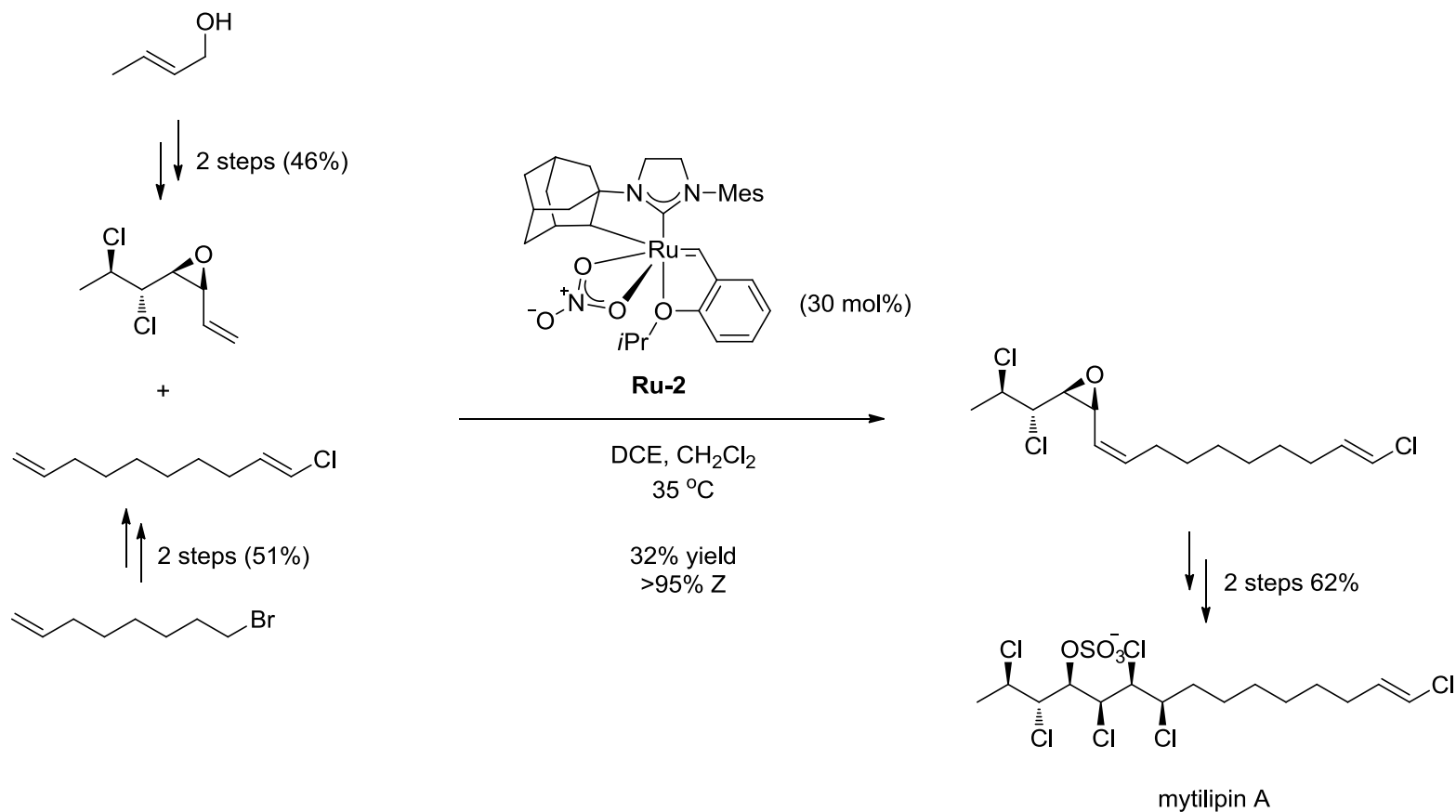


E-selective pathway



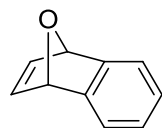
Chelated Ruthenium Catalysts

● Synthesis of mytilipin A via a seven-step longest linear sequence

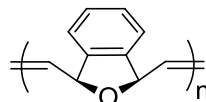
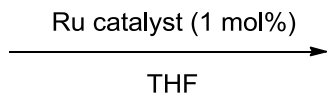


Chelated Ruthenium Catalysts

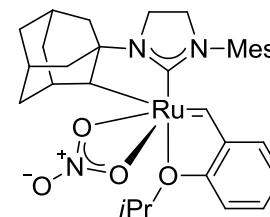
● cis-selective ROM polymerization



Ru-5, rt, >95% yield, 67% Z

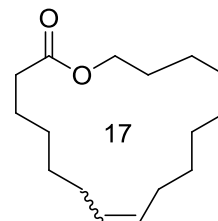
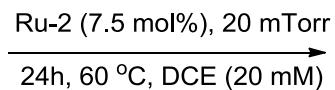
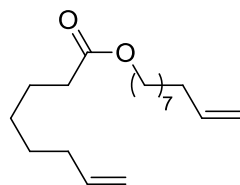


Ru-2, -20 °C, 80% yield, 91% Z

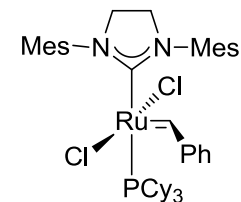


Ru-2

● Z-selective RCM



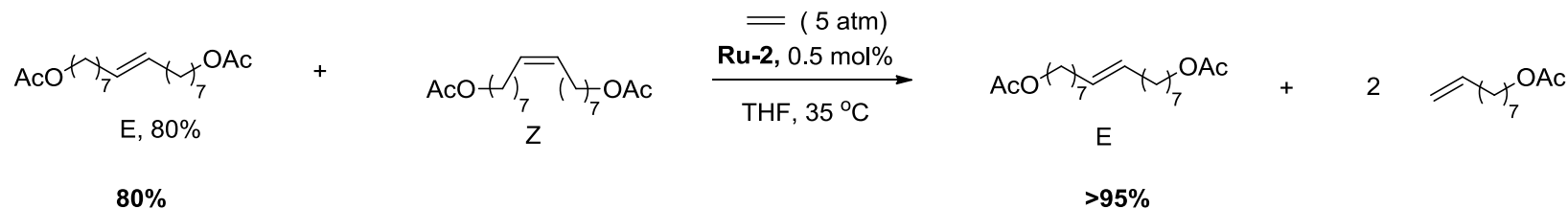
71% yield, 89% Z



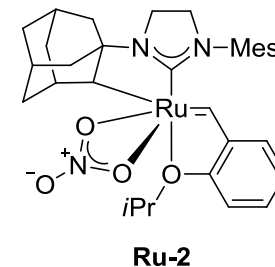
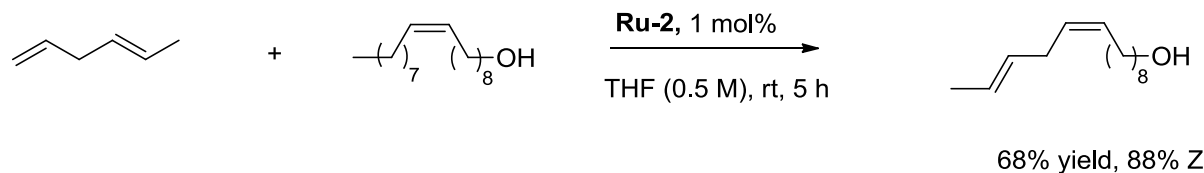
Ru-5

Chelated Ruthenium Catalysts

● Z-Selective Ethenolysis

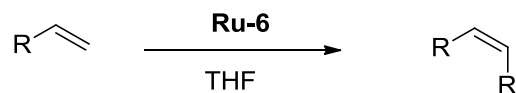
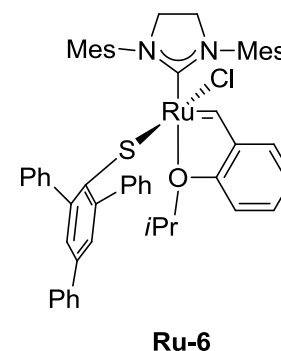
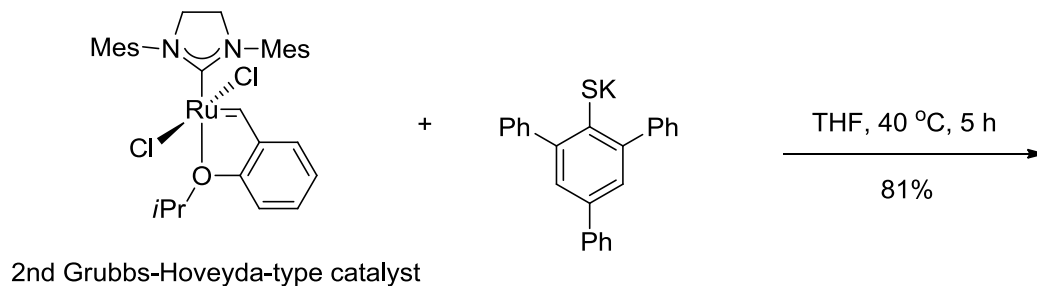


● chemoselective cross metathesis

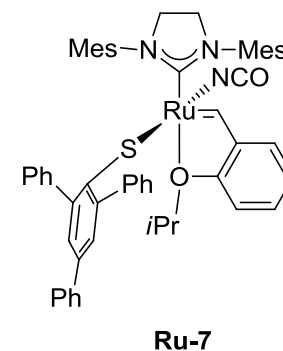


Other Ruthenium Catalysts

● Simple and Highly Z-Selective Ruthenium Catalyst

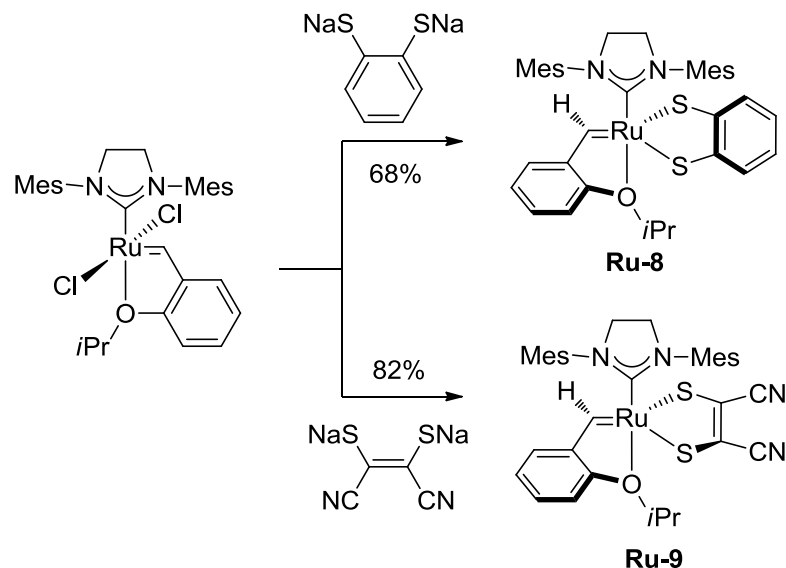
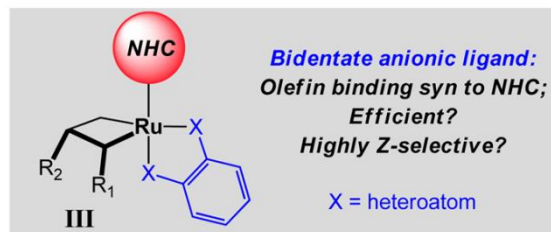
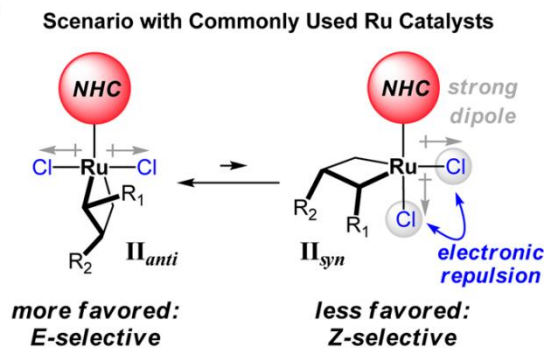
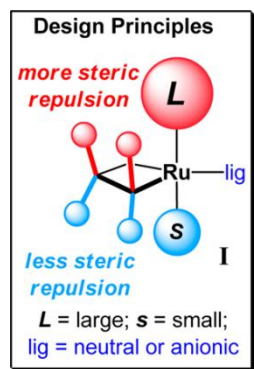


R = hexyl, 55% yield, 85% Z, 10^{-5} bar
R = CH_2SiMe_3 , 11% yield, 95% Z, 1 bar
R = CH_2OAc , 100% yield(NMR), 81% Z, 1 bar



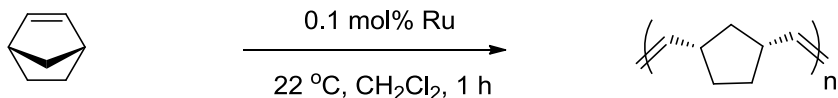
Other Ruthenium Catalysts

● Rationally designed Ru-based catalysts for efficient Z-selective



Other Ruthenium Catalysts

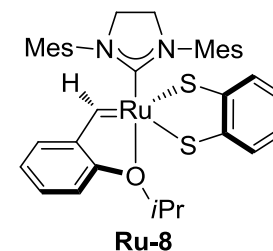
● excellent reactivity and perfect selectivity for ROMP



Ru-8, 93% yield, >98% Z, 930 TON

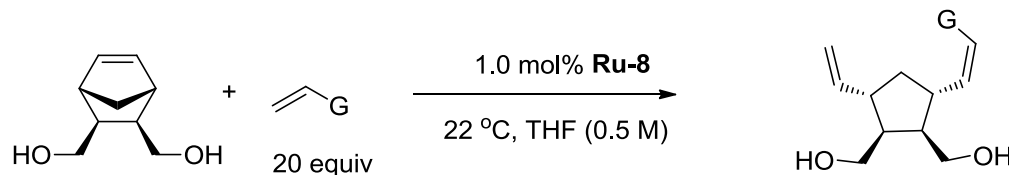
Ru-9, 90% yield, >98% Z, 900 TON

Ru-9 (0.002 mol%), 86% yield, >98% Z, 43000 TON



Ru-8

● excellent Z-selective ROCM

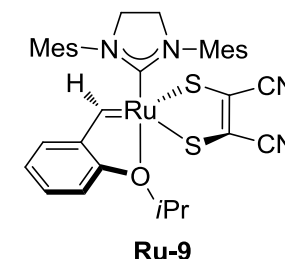


G = C₆H₅, >98% conv, 92% yield, 97% Z

G = m-FC₆H₄, >98% conv, 93% yield, 96% Z

G = p-MeOC₆H₄, >98% conv, 82% yield, 98% Z

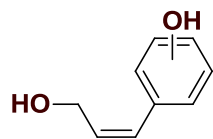
G = Cy, 88% conv, 61% yield, >98% Z



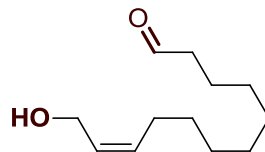
Ru-9

Other Ruthenium Catalysts

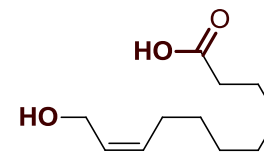
- Issues unaddressed by state-of-the-art catalytic olefin metathesis regarding several critical functional units



Alcohols or phenols?

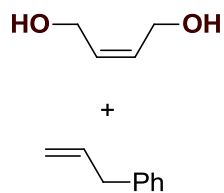


aldehydes?



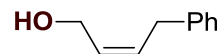
carboxylic acids?

● Initial observations



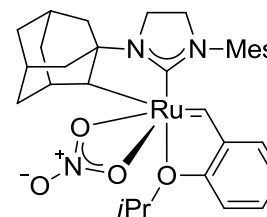
3.0 mol% Ru complex

THF, 22 °C, 9 h

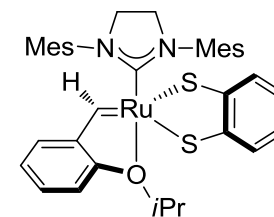


with **Ru-2**: 70% conv, 50% yield, 91% Z

with **Ru-8**: 50% conv, 42% yield, 98% Z



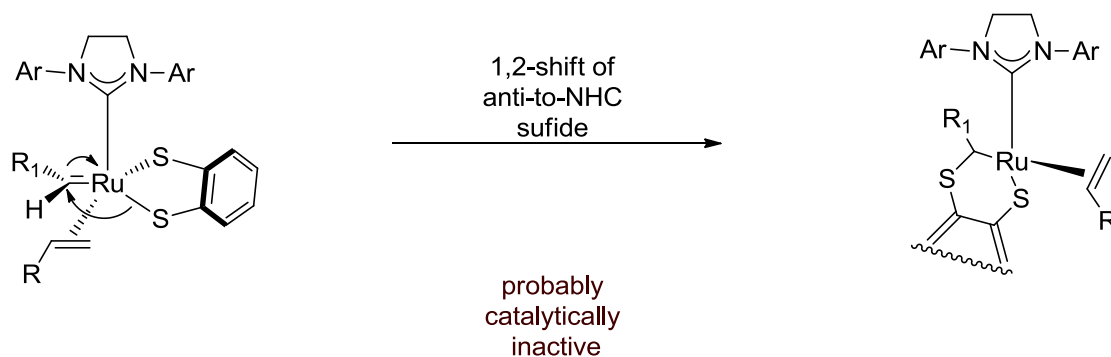
Ru-2



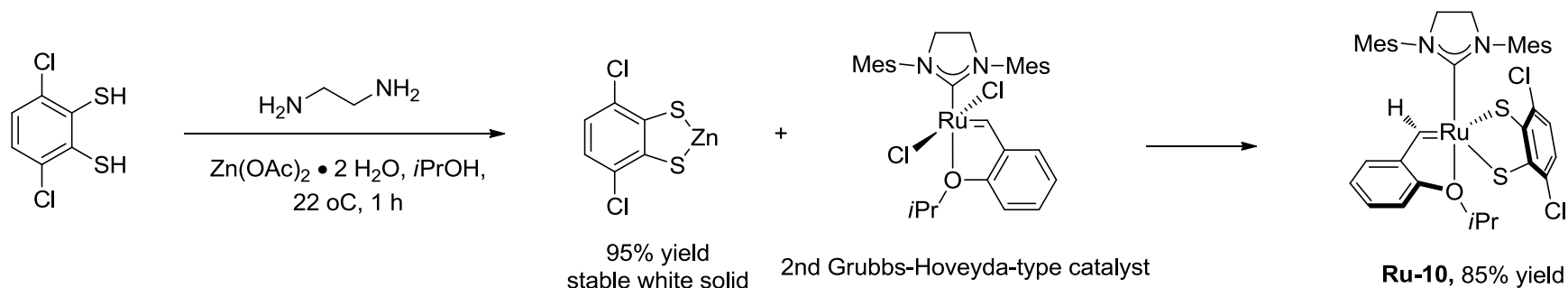
Ru-8

Other Ruthenium Catalysts

● Possible pathway for catalyst decomposition

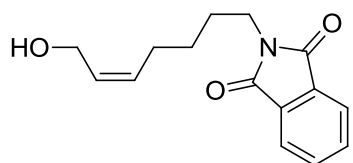
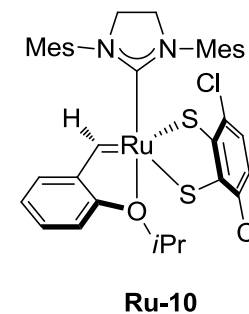
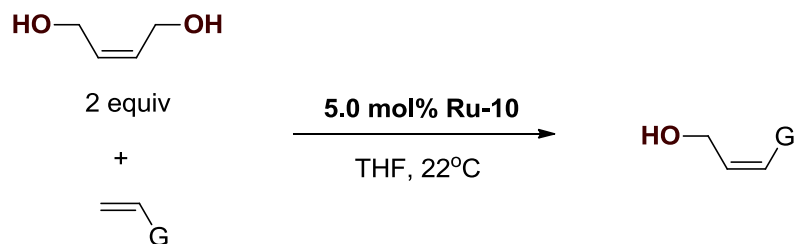


● Modified complexes Ru-8

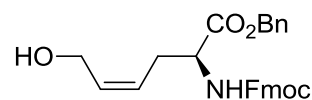


Other Ruthenium Catalysts

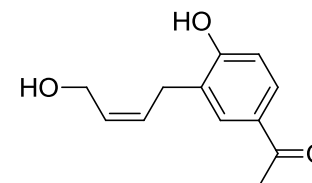
- Excellent scope—extremely broad functional group tolerance with catalyst Ru-10



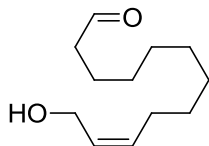
73% conv (4 h), 64% yield
98% Z



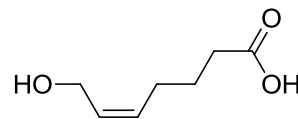
83% conv (4 h), 73% yield
98% Z



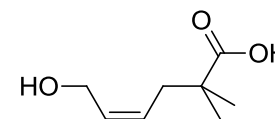
77% conv (4 h), 68% yield
98% Z



86% conv (4 h), 80% yield
94% Z



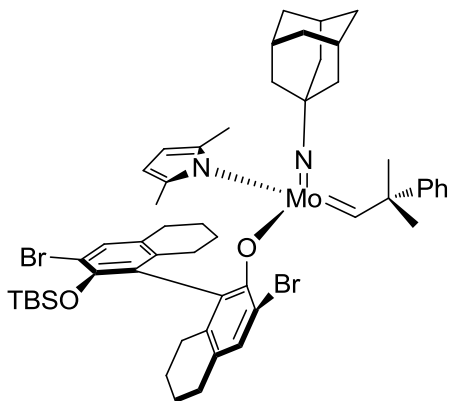
86% conv (4 h), 70% yield
96% Z



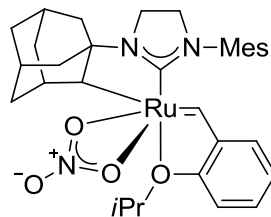
66% conv (4 h), 61% yield
96% Z

Conclusion and Outlook

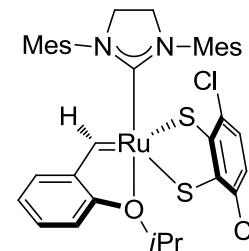
● Conclusion--current state-of-the-art



Mo, Hoveyda



Ru, Grubbs



Ru, Hoveyda

● Outlook--next generation catalysts

**E-selectivity?
Z- and enantioselectivity?**

Thank you!

