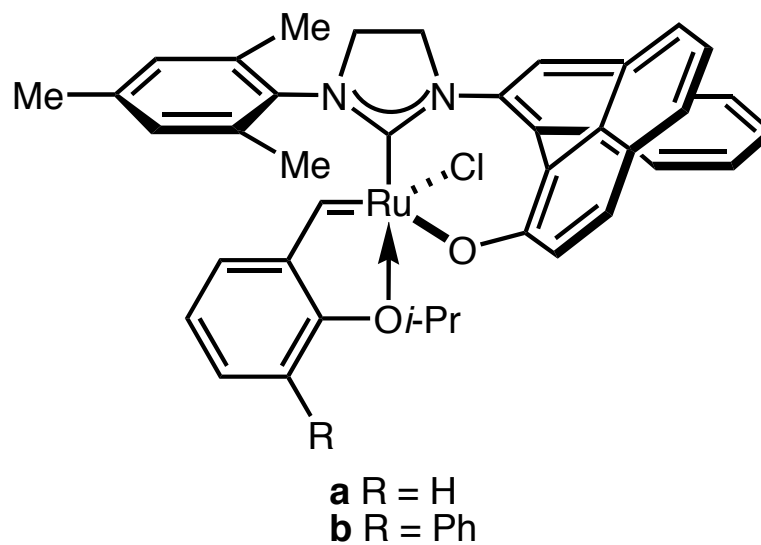
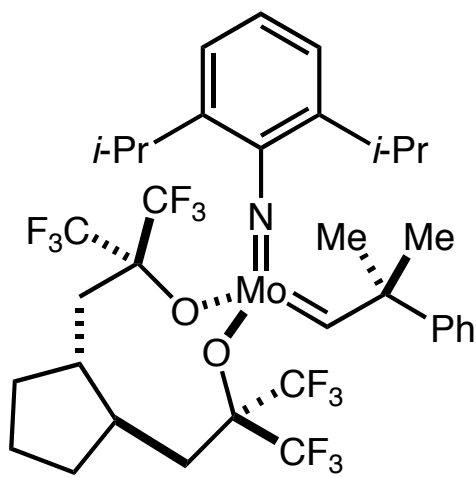


Enantioselective Metathesis Catalysts: Synthesis, Application, and Mechanism



Joe Young
Evans Group Seminar
November 19, 2004

Outline

Brief Introduction

Molybdenum catalysis

- Grubbs' work
- Schrock and Hoveyda's work

Ruthenium catalysis

- Grubbs' work
- Cavallo's mechanistic investigations
- Hoveyda's work

Synthetic applications

- Burke
- Hoveyda

Leading Reviews

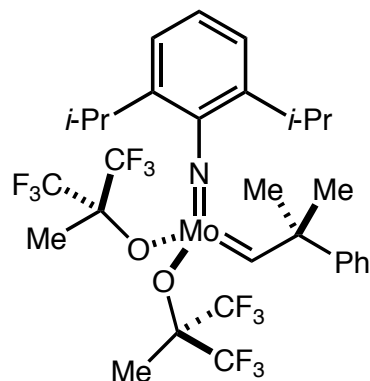
Hoveyda, A. H, Schrock, R. R. *Chem Eur J*, **2001**, 7, 945-950

Covers the early asymmetric work with molybdenum

Hoveyda, A. H. *et al Org Biomol Chem*, **2004**, 2, 8-23

Covers the Hoveyda work on Ru metathesis

A Brief Introduction to Olefin Metathesis

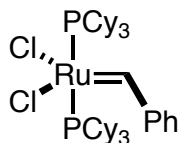


I

Complex I was developed by Schrock in the 80's.

Ligands can be tuned to specific substrates.

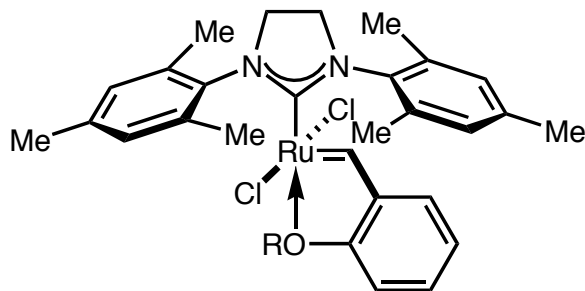
When biphenyl ligands are used for ROMP, the polymers generated have high stereoregularity.



II

Complex II was developed by Grubbs in the early 90's.

First catalyst widely used by the synthetic community.



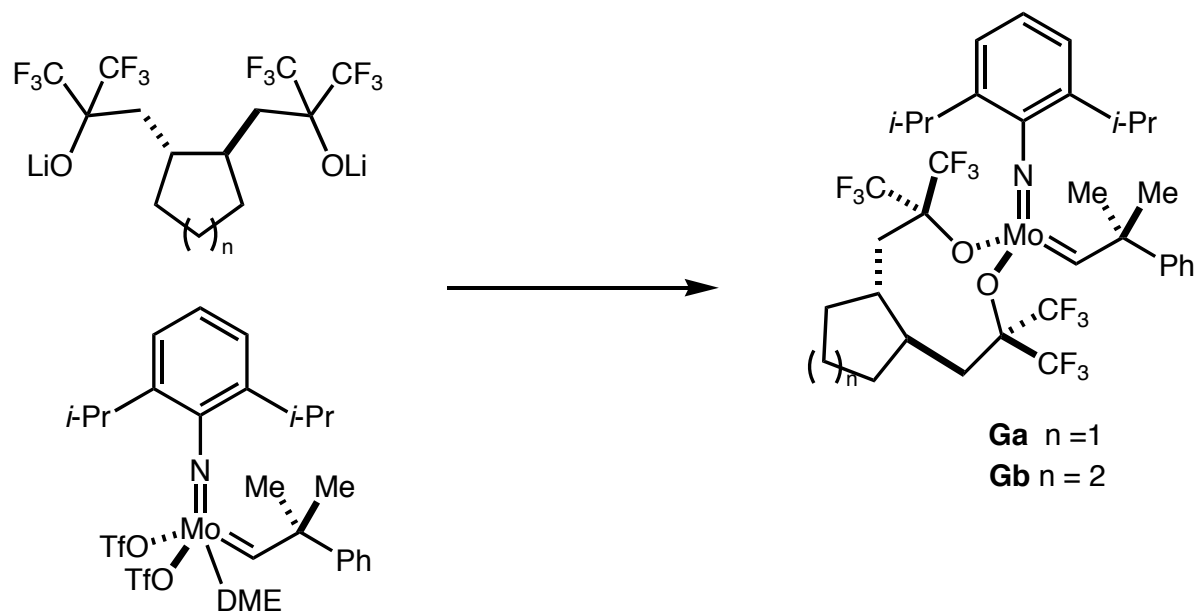
III

Complex III was designed to be a more active, robust version of II.

N-heterocyclic carbenes significantly increase the lifetime of the active catalyst.

Chelating alkylidene increases the activity of the catalyst.

Grubbs' Asymmetric Molybdenum Catalysts



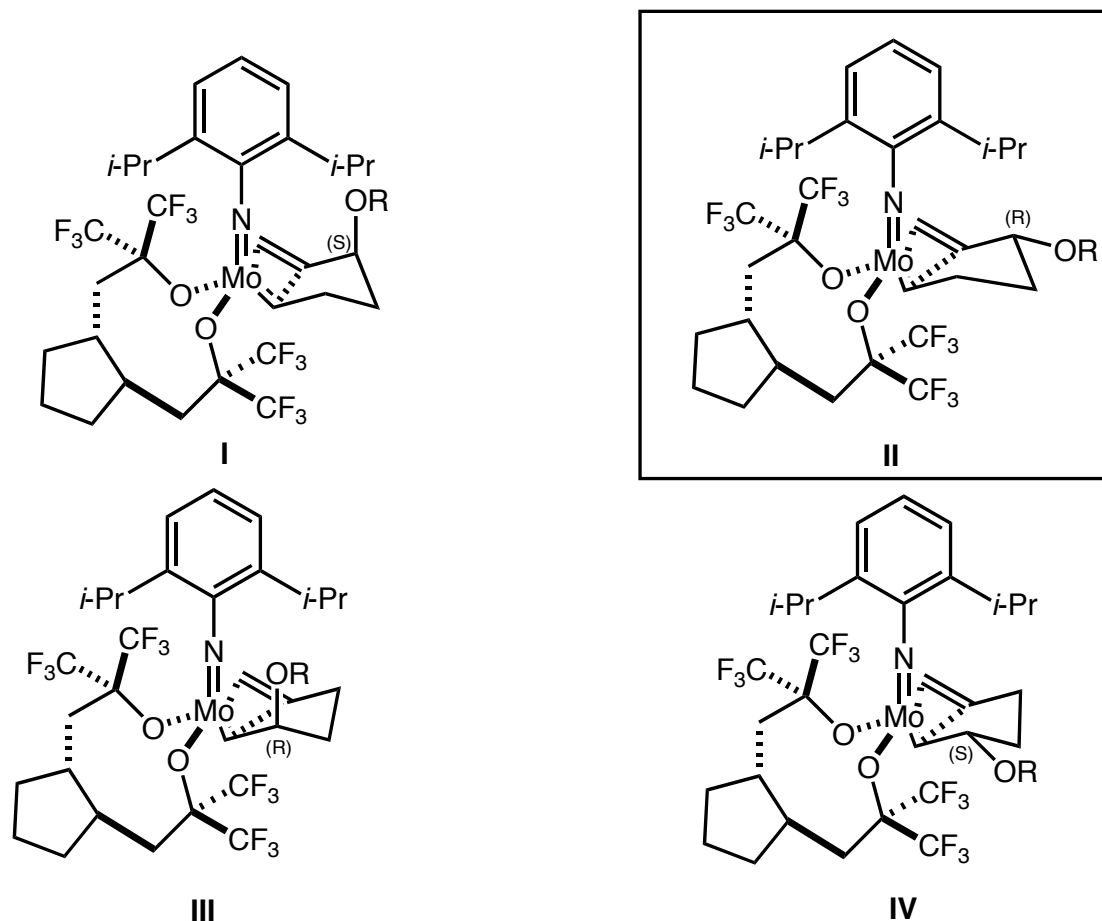
Diol ligands were prepared in 5 steps and poor overall yield from the appropriate cyclic diacid.

Grubbs Mo Catalyst: Kinetic Resolution of Racemic Dienes

substrate	products	catalyst	temp (°C)/ time(min)	conv. (%)	Unreact. subst. ee (%)
		Ga Gb	0 / 90	62	40
		Ga	-20 / 660	72	48
		Ga	0 / 20	46	22
		Ga	0 / 120	64	26

2.0 mol % catalyst was used in all cases. Mass balance (yield of cyclic product + recovery of substrate), > 90%

Grubbs Mo Catalyst: Explanation of Induction

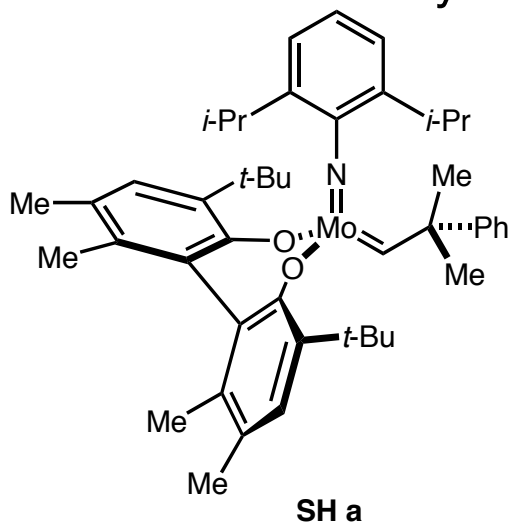


Grubbs believes that resolution occurs during the ring closing step.

Di- and trisubstituted olefins are required to slow down ring closing step in order to establish a dynamic equilibrium between **I** and **II**.

Di- and trisubstituted olefins also minimize the formation of **III** and **IV**.

The Shrock/Hoveyda Molybdenum Asymmetric Metathesis Catalysts



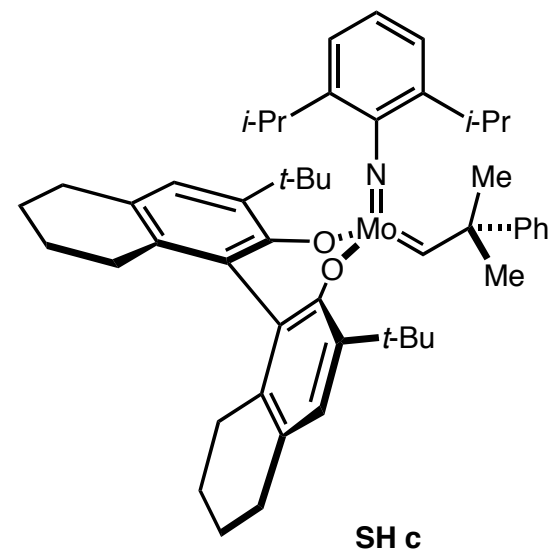
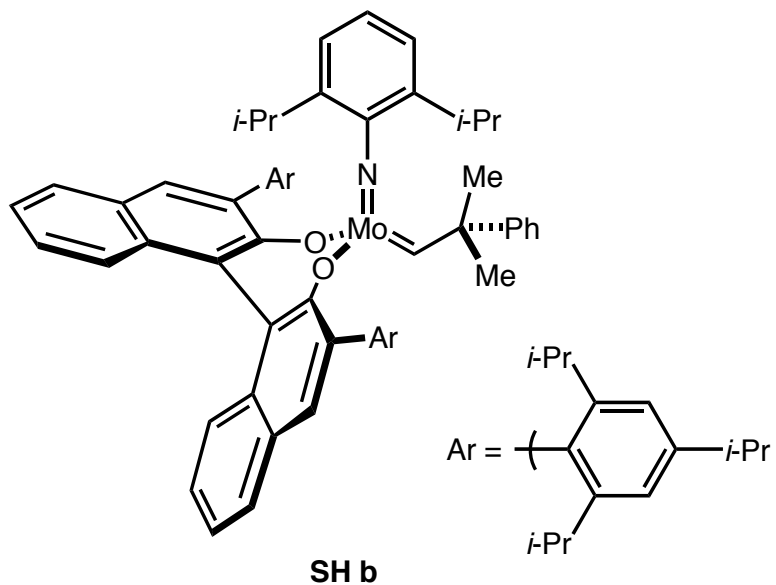
O-Mo-O bond angles:

SH a: 127.0°

SH b: 87.8° **

SH c: 119.9°

** -THF adduct



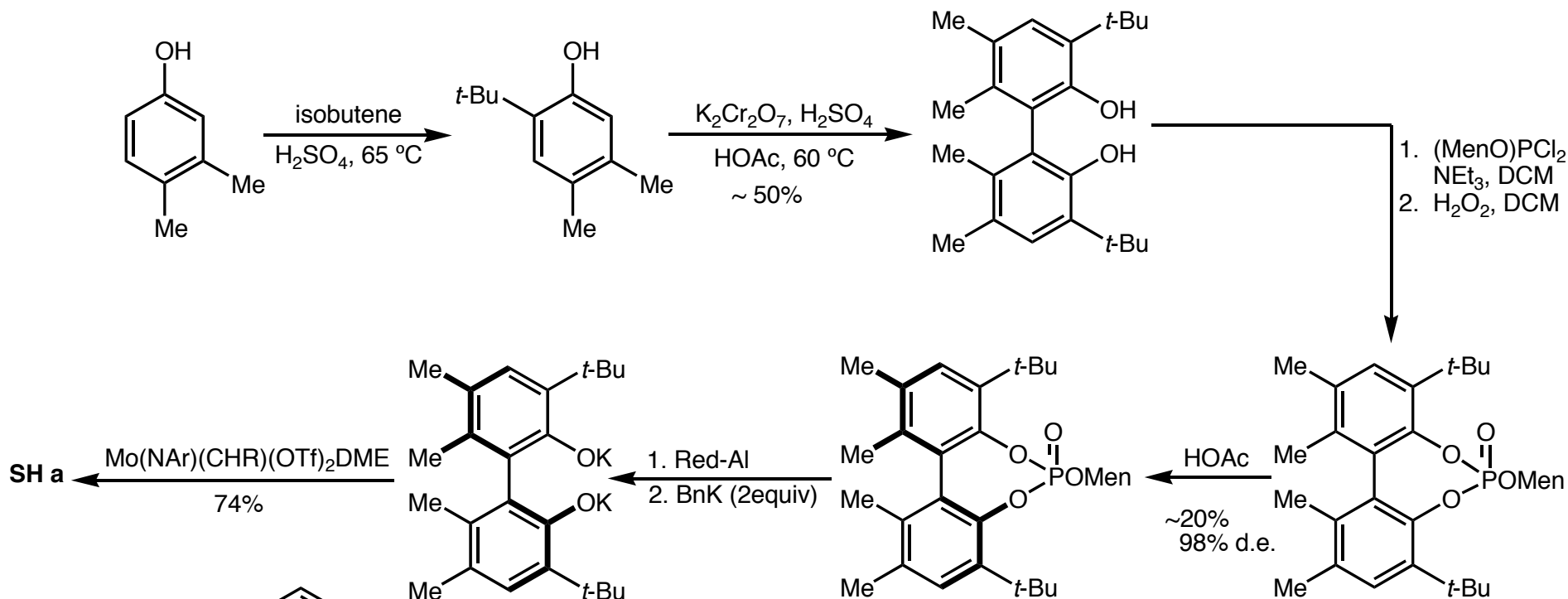
Changing substituents on the biaryl ligand changes the dihedral angle around the biaryl bond. This alters the O-Mo-O angle and the amount of steric bulk on either side of the molybdenum.

Alexander *et al* *J. Am. Chem. Soc.* **1998**, *120*, 4041

Zhu *et al* *J. Am. Chem. Soc.* **1999**, *121*, 8251

Aeilts *et al* *Angew. Chem. Int. Ed.* **2001**, *40*, 1452

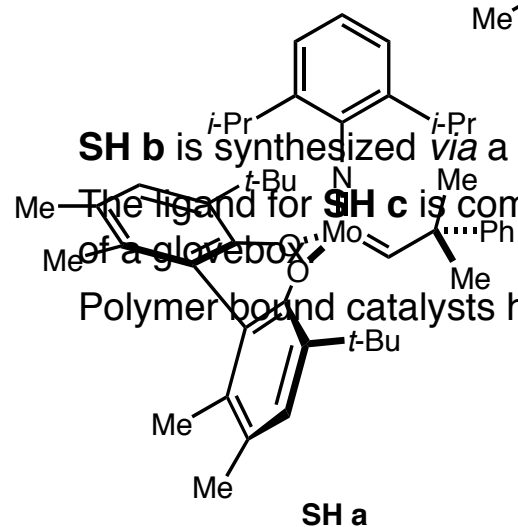
Schrock/ Hoveyda Mo Catalyst: A Sample Synthesis



SH b is synthesized *via* a similar route.

The ligand for **SH c** is commercially available, and this catalyst can be generated *in situ* outside of a glovebox.

Polymer bound catalysts have also been developed, although their recyclability is moderate at best.



Alexander *et al* *J. Am. Chem. Soc.* **1998**, *120*, 4041

SH c: Aeilts *et al* *Angew. Chem. Int. Ed.* **2001**, *40*, 1452

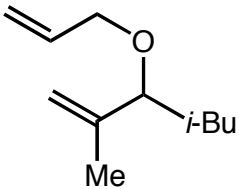
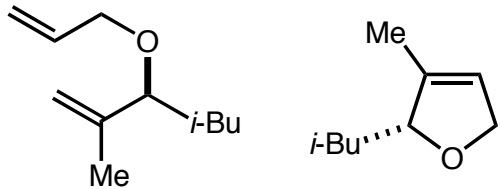
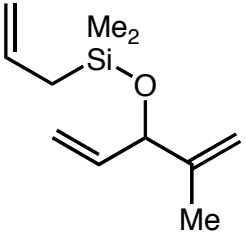
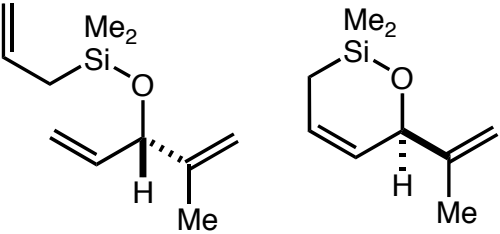
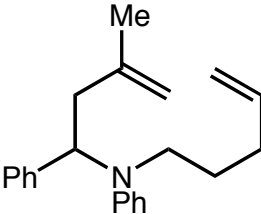
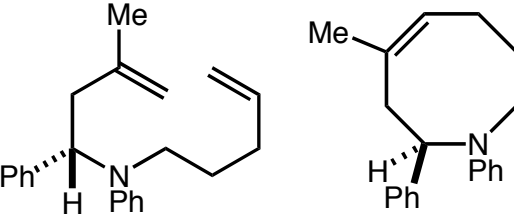
Polymer: Hultsch *et al* *Angew. Chem. Int. Ed.* **2002**, *41*, 589

Schrock/ Hoveyda Mo Catalyst: Kinetic Resolution of Racemic Dienes

substrate	products	catalyst	temp (°C)/ time(min)	conv. (%)/ dimer (%)	unreact. subst. ee (%)	react. ee (%)	k_{rel}
		SH a	22/ 10	81/ 38	>99 (R)	93 (S)	58
		SH b	--/--	--	--	--	7
		SH a	22/ 120	60/ 20	< 5	< 5	--
		SH a	22 / 30	58/ 11	57 (R)	45 (S)	4
		SH b	65 / 40	77/ 27	--	--	24

Production of dimer implies poor transfer of catalyst between substrate molecules.
Results indicate that choice of catalyst is substrate specific.

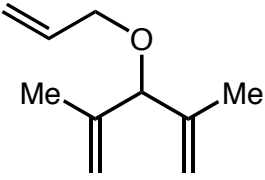
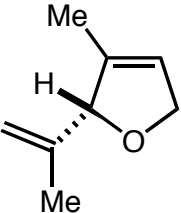
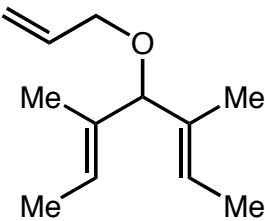
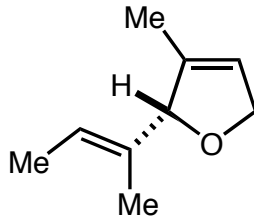
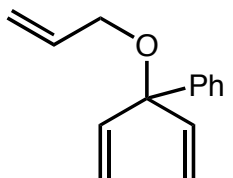
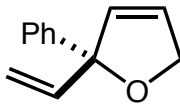
Schrock/ Hoveyda Mo Catalyst: Kinetic Resolution of Racemic Dienes

substrate	products	catalyst	temp (°C)/ time	conv. (%)/ dimer (%)	unreact. subst. ee (%)	k_{rel}
		SH a	-22/ 10 h	56 / < 2	95	23
		SH b	22 / 6 h	44 / < 2	--	< 2.0
		SH c	22 / 1 h	58 / < 2	--	23
		SH a	22 / 5 min	51 / < 2	--	2
		SH b	22 / 30 min	41 / < 2	--	5
		SH c	22 / 5 min	42 / 18	--	20
		SH a	22 / 6 h	41 / < 2	--	> 50

The "best" catalyst for the top two cases changes based on the R group on the ethereal stereocenter. Screening is required to determine which catalyst should be used in each case.

The amino substrates can be run neat with no reduction in selectivity or conversion. Additives (diallyl ether or ethylene) are required to achieve good selectivity for smaller ring sizes.

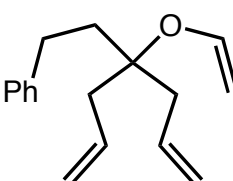
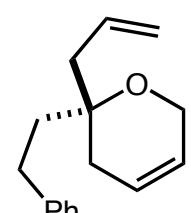
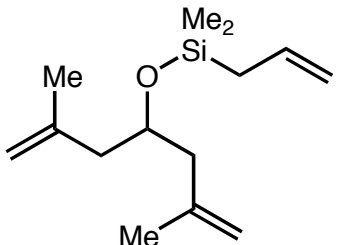
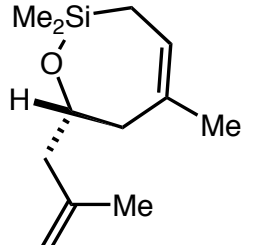
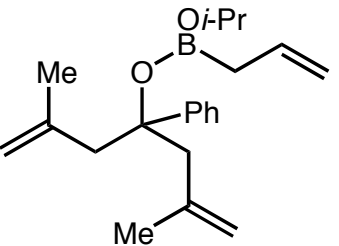
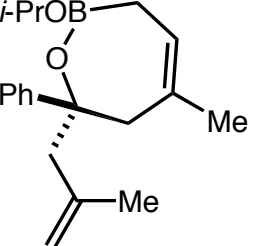
Schrock/ Hoveyda Mo Catalyst: Desymmetrization of Achiral Trienes by ARCM

substrate	product	catalyst	temp (°C) / time (h)	conv. (%) / dimer (%)	yield (%)	ee (%)
		SH a	22 / 6	52 / < 2	86	93
		SH b	22 / 1	63 / < 2	72	90
		SH c	22 / 1	58 / 7	81	92
		SH a	22 / 9	32 / < 2	--	94
		SH b	22 / 18	< 5 / --	--	--
		SH a	22 / 18	36 / --	34	16

Better yields and ee's can be attained by altering the imido ligand on **SH a**.

~30 variants of **SH a** have been prepared, and exhibit different results for any given substrate.

Schrock/ Hoveyda Mo Catalyst: Expansion of ARCM Scope

substrate	product	catalyst	temp (°C) / time (h)	conv. (%) / dimer (%)	yield (%)	ee (%)
		SH b	50 / 3	> 98 / --	--	35
		SH b	80 / 3	-- / --	93	74
		SH a	22 / 12	95 / < 2	89	86
		SH c'	22 / 24	80 / --	38 + 40 % cyclo- pentene	> 98
		SH c' : imido = <i>o</i> -CF ₃				

Schrock/ Hoveyda Mo Catalyst: Expansion of ARCM Scope

substrate	product	catalyst	temp (°C) /time	conv. (%) / dimer (%)	yield (%)	ee (%)
		SH a	22 / 15 min	> 99 + 20 % bicycle	72	> 98
		SH c	22 / 12 h	> 98 / --	66	82
		SH a	22 / 20 min	97 / < 2	81	97
		SH b	22 / NA	40 + 47 % cyclo- pentene	--	50

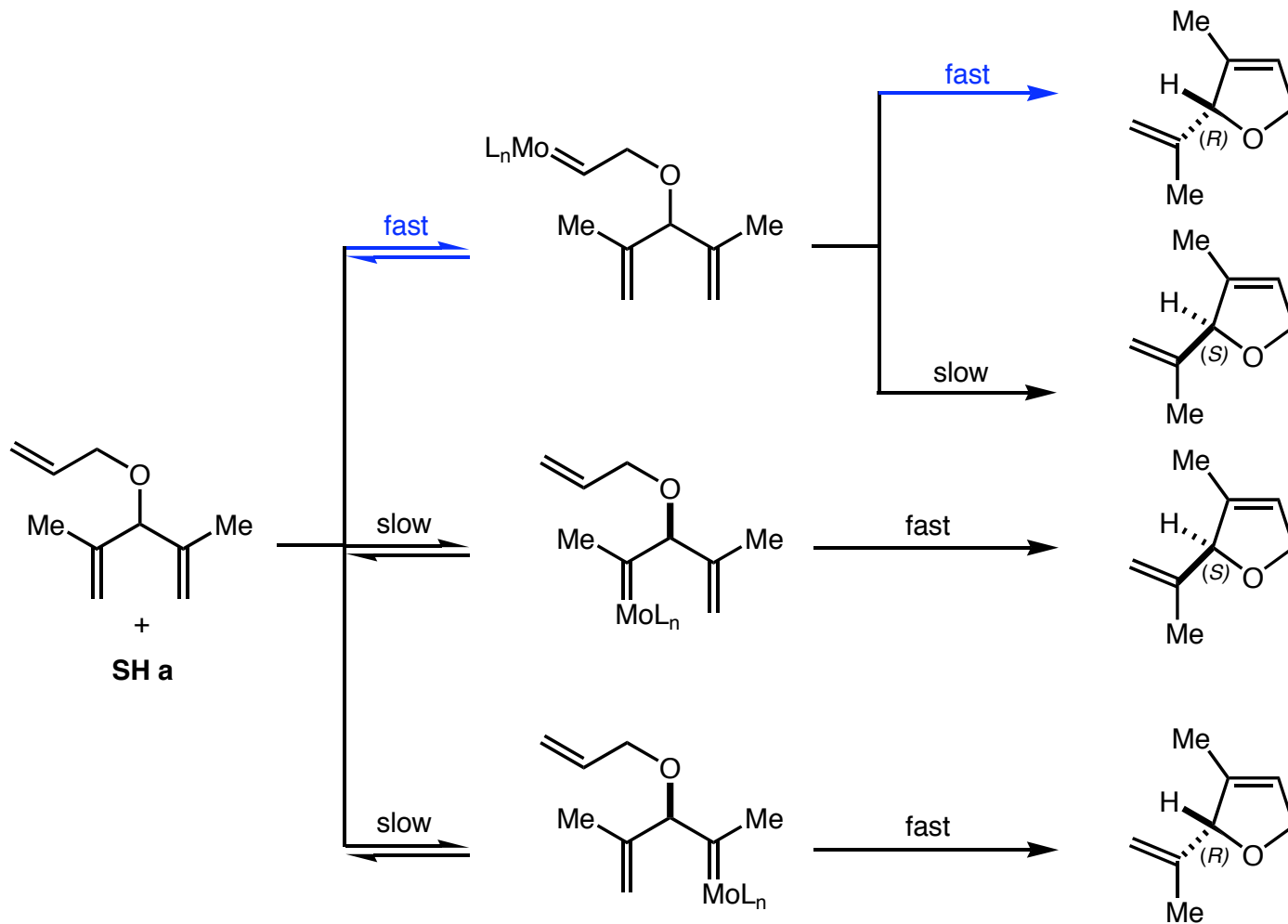
Ar = *p*-MeOPh

Altering olefin substitution or ring size affects choice of catalyst.

The aryl protecting group does not seem to affect selectivity.

Weatherhead *et al Tetrahedron Lett.* **2000**, 41, 9553
Dolman *et al J. Am. Chem. Soc.* **2002**, 124, 6991

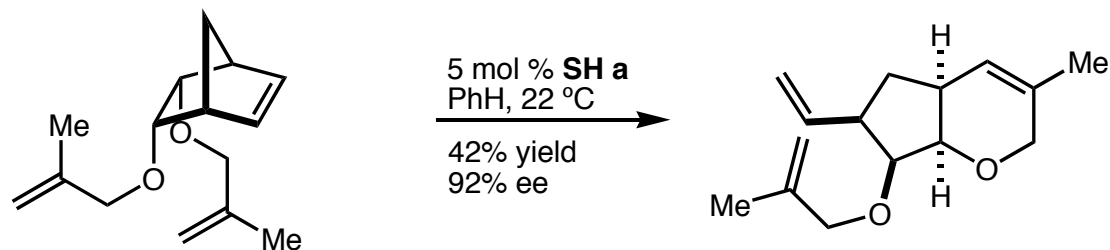
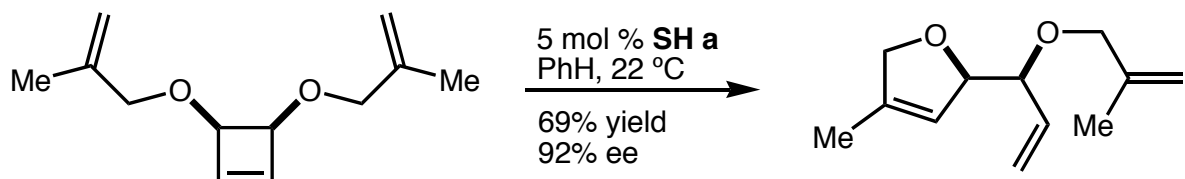
Schrock/ Hoveyda Mo Catalyst: Kinetics of ARCM



Olefin substitution alters both the absolute and relative rates of each step. This can affect the choice of catalyst.

With elevated temperatures, the second step is reversible, and this can affect the selectivity of the reaction.

Schrock/ Hoveyda Mo Catalyst: Desymmeterization *via* Tandem AROM/ ARCM



Catalyst **SH b** was also tested, but is generally less effective than **SH a**.

Unsubstituted terminal olefins gave poor ee's and significant amounts of overcyclization.

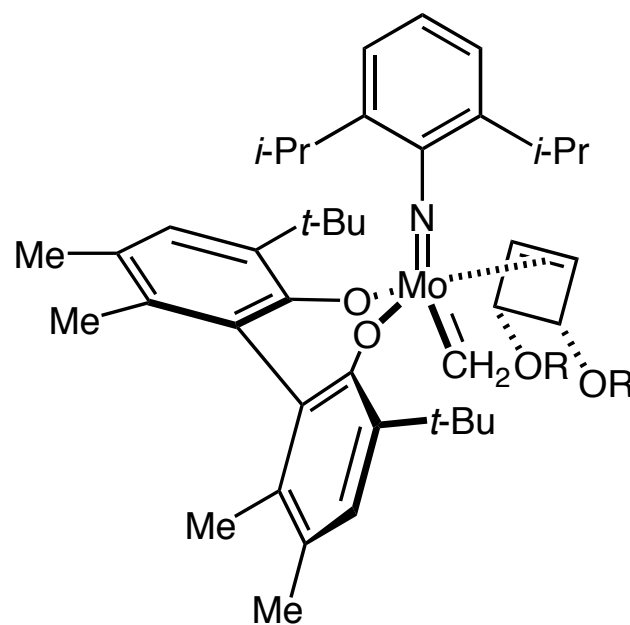
Schrock/ Hoveyda Mo Catalyst: Explanation of Induction

Ring opening is proposed to be the chirality inducing step.

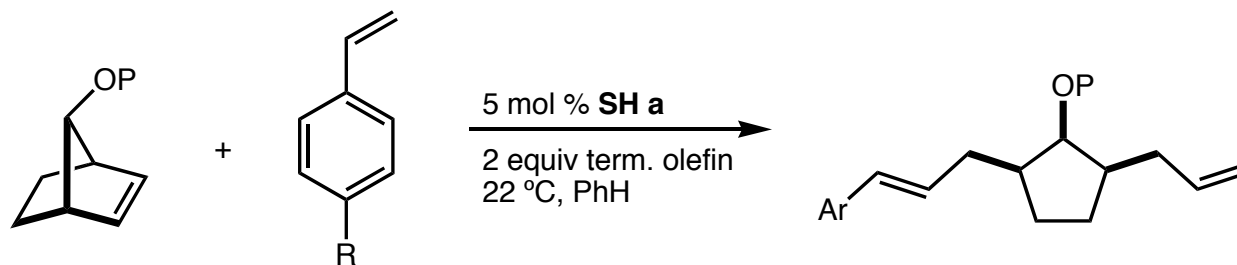
Strained cycloalkene is more reactive than terminal olefin.

Substituents are directed away from ligands.

The cycloalkene attacks the least hindered LUMO.



Schrock/ Hoveyda Mo Catalyst: Tandem Asymmetric Ring Opening Metathesis/ Asymmetric Cross Metathesis

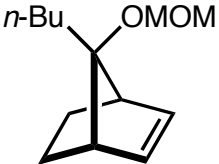
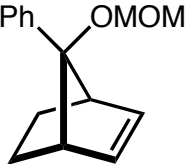
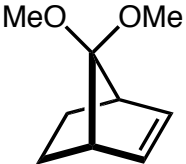



P	R	time (h)	yield (%)	ee(%)
TBS	H	7	57	96
TMS	H	1	85	>98
MOM	H	0.3	96	>98
	OMe	0.1	88	>98
	CF ₃	0.4	80	>98

SH a was selected based on a screen against P = TBS and R = H.
Other catalysts may give better ee's and yields for other substituents

Schrock/ Hoveyda Mo Catalyst: AROM/ ACM

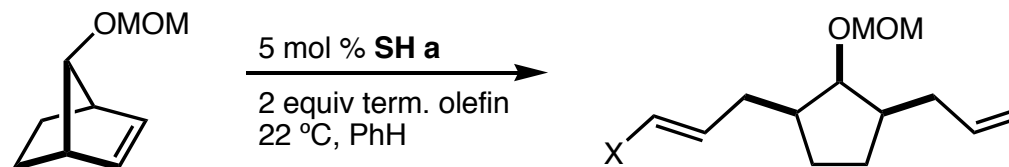
The AROM/ ACM works with a variety of norbornenes:

				
yield (%)	85	84	84	32
% ee	> 98	98	> 98	> 98

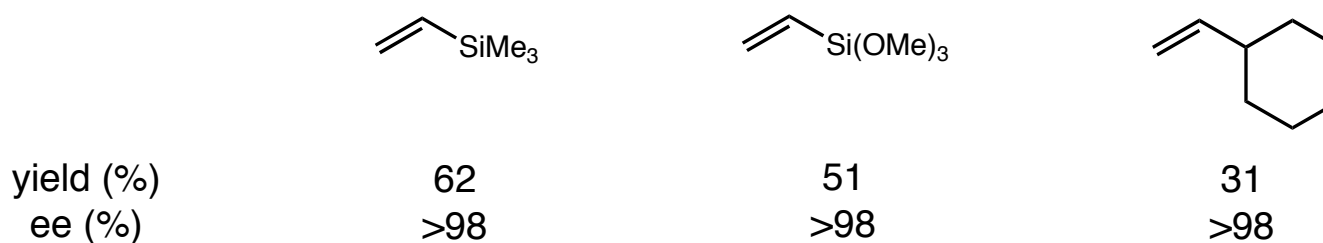
All reactions were performed with styrene and **SH a**

Schrock and Hoveyda posit that either a heteroatom must be proximal to the reacting olefin or the substituents must be sterically unencumbering.

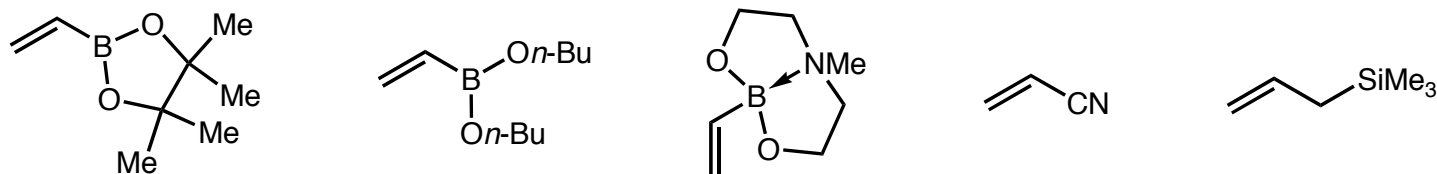
Schrock/ Hoveyda Mo Catalyst: AROM/ ACM



A series of terminal olefin partners were screened with mixed success:



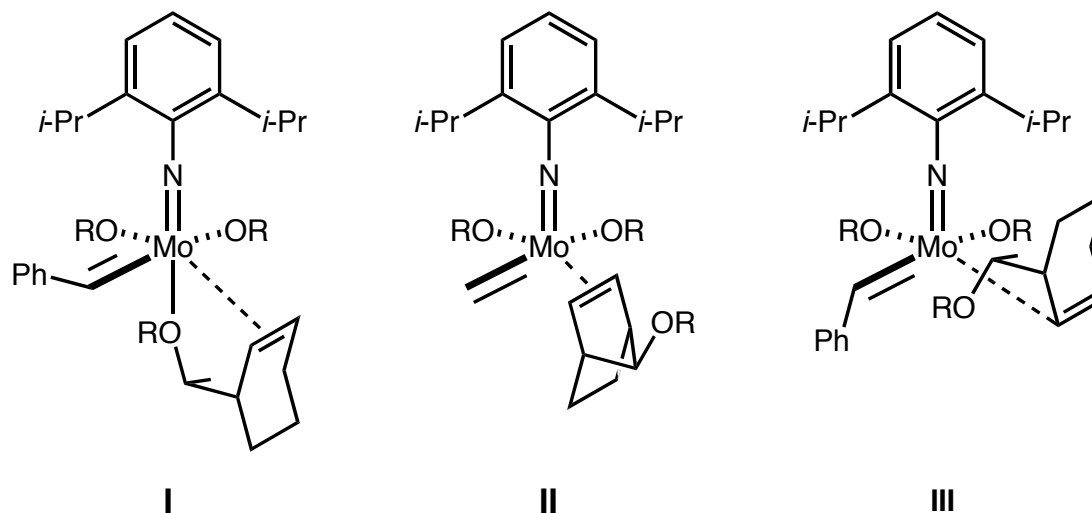
No reaction was observed with the following olefins:



Schrock and Hoveyda posit that the substituents stabilize the alkylidene too much for it to be reactive.

Schrock/ Hoveyda Mo Catalyst: A Model for AROM/ ACM

There are three possible explanations for the stereochemical induction observed:

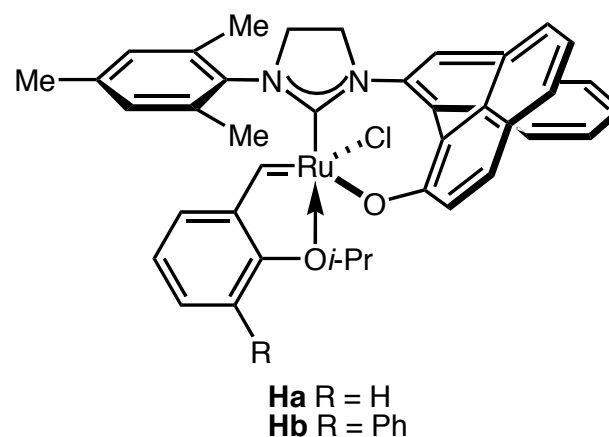
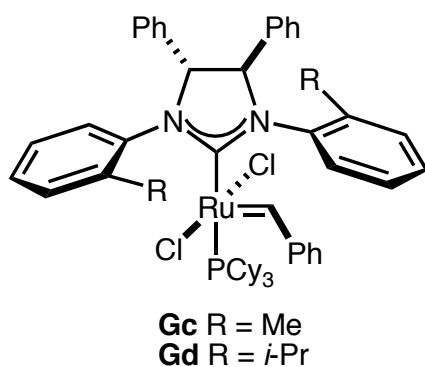


Schrock and Hoveyda prefer model I:

Bases on NMR studies, the aryl alkylidene is believed to be the active species.

The imido group should block the approach of the norbornene in III.

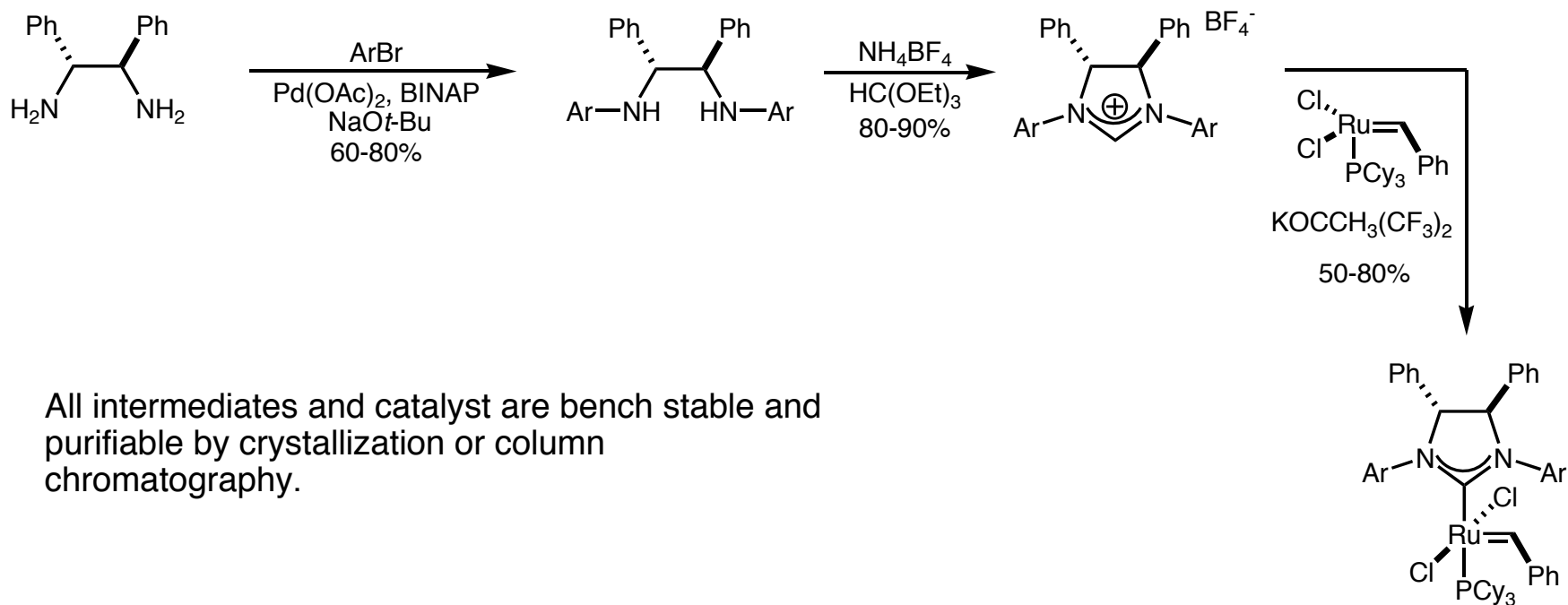
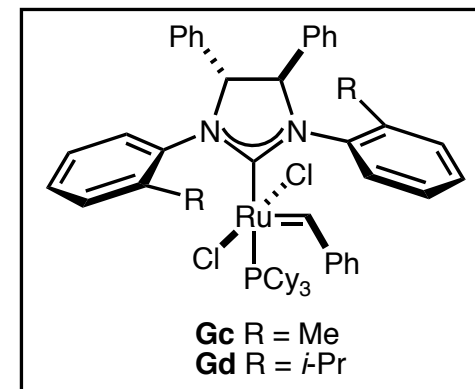
Chiral Ru-based Catalysts: Making AROM and ARCM More Practical



Ru based catalysts are bench stable in contrast to the air- and water-sensitive Mo catalysts

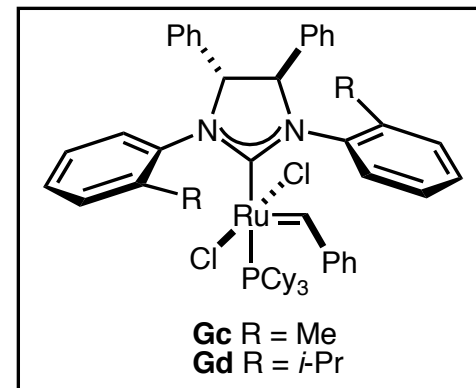
Reactions with **Ha** can be run in wet THF at ambient temperature under an air atmosphere without loss of enantioselectivity but in slightly lower yields.

Grubbs' Asymmetric Ru Catalyst: Synthesis



All intermediates and catalyst are bench stable and purifiable by crystallization or column chromatography.

Grubbs Ru Catalyst: Desymmetrizations of Racemic Trienes

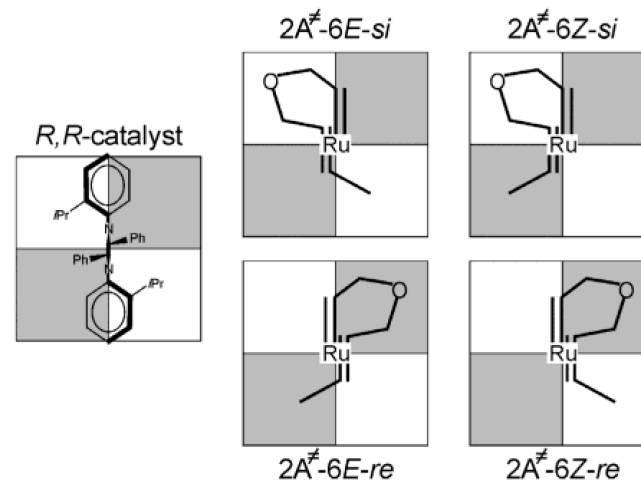
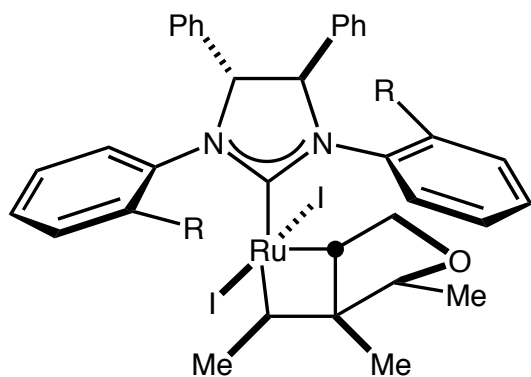
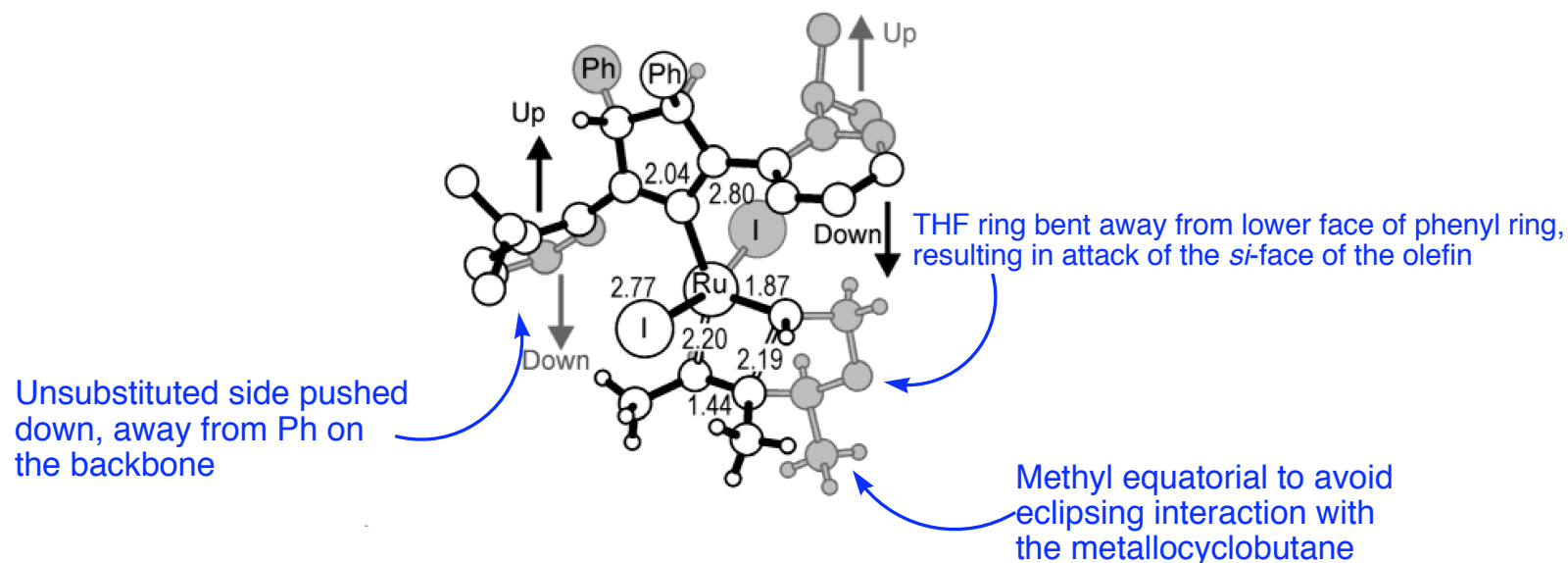


substrate	catalyst	product	ee(%)	conver.(%)
	Gc		23	95
	Gd		23	96
	Gc + NaI		38	18
	Gd + NaI		39	20
	Gc + NaI		27	78
	Gd + NaI		35	90
	Gc + LiBr		63	90
	Gd + LiBr		69	90
	Gc + NaI		85	91
	Gd + NaI		90	82

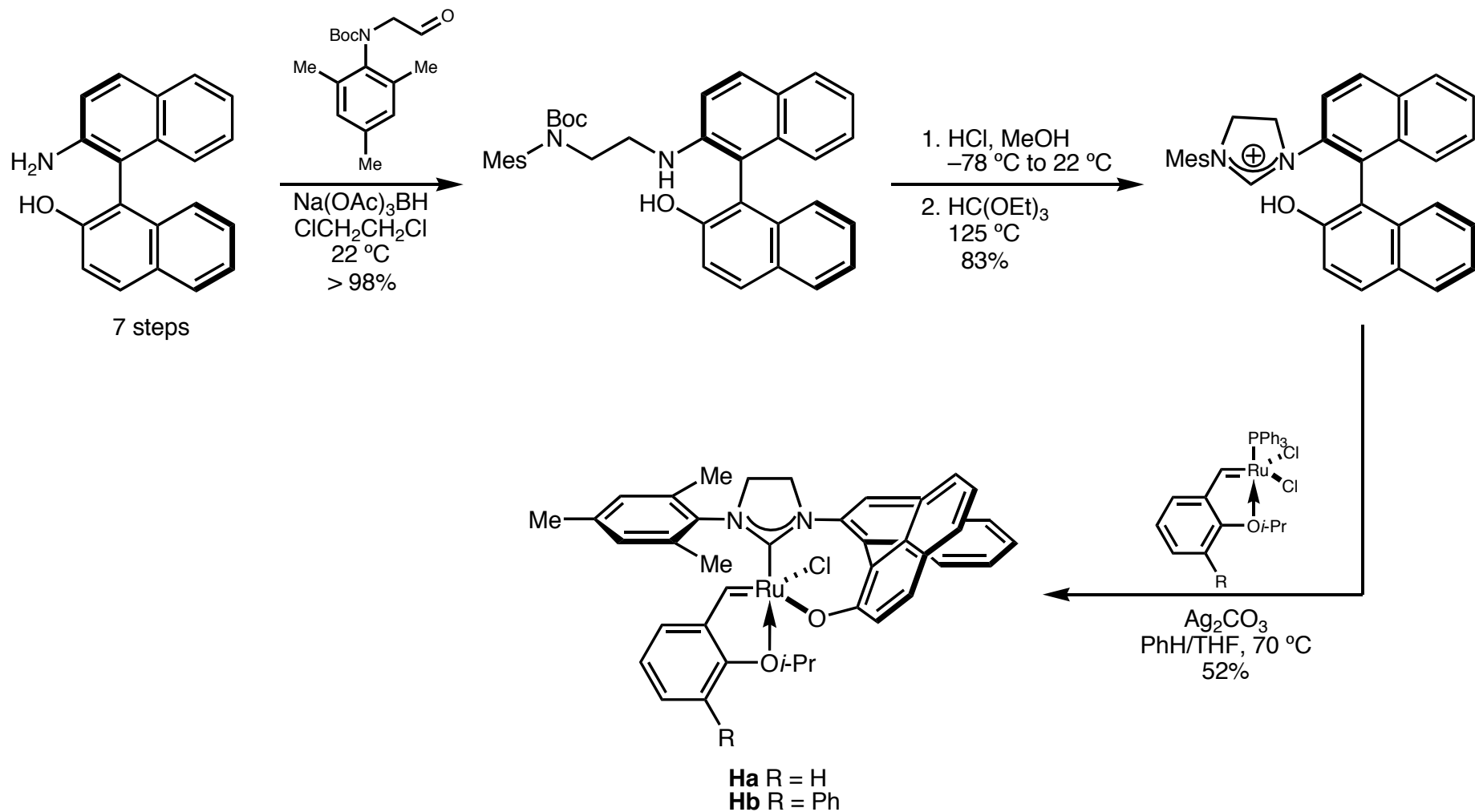
Conditions: 2.5 mol % catalyst, 55 nM substrate in DCM, 38 °C.

When halide salt is added: 5 mol % catalyst, 100 mol % of halide salt, 55 nM in THF, 38 °C

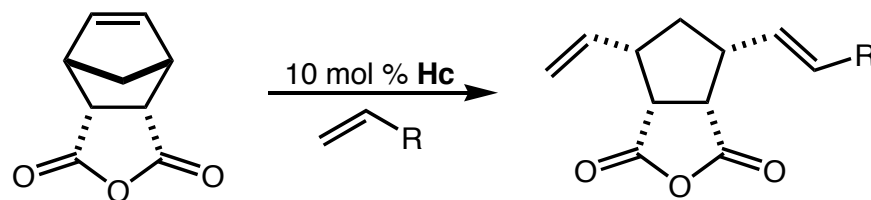
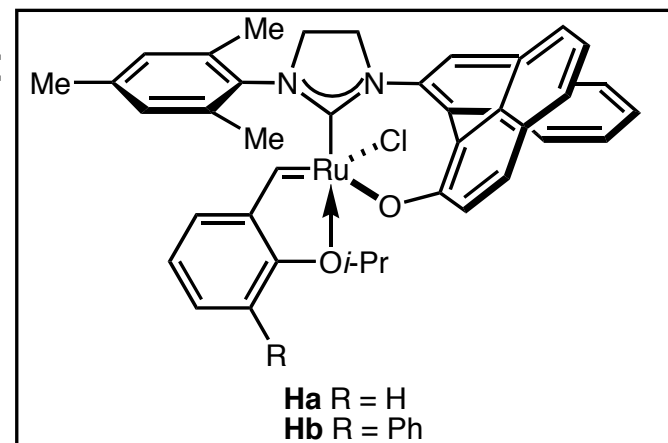
Grubbs Ru Catalyst: Molecular Modeling Studies



Hoveyda's Ru Catalyst: Synthesis



Hoveyda Ru Catalyst: Initial Results

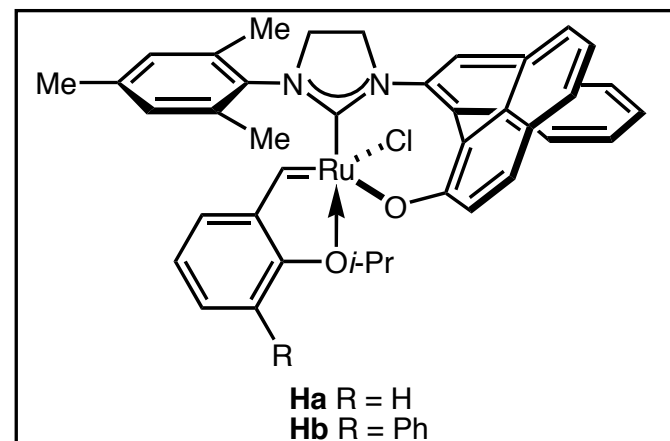
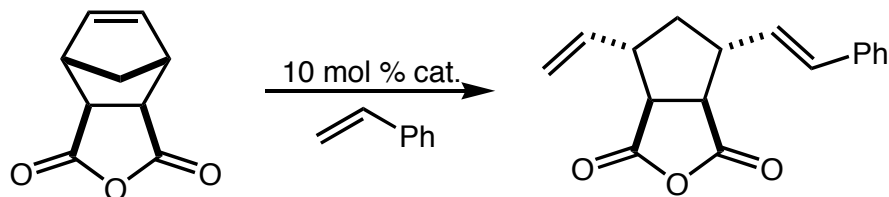


R	temp (°C)/ time (h)	conv (%)/ yield (%)	recov. cat. (%)	trans:cis	ee (%)
Ph	50/ 1.0	> 98/ 71	96	> 98: 2	80
<i>n</i> -C ₅ H ₁₁	50/ 1.5	> 98/ 57	92	> 98: 2	> 98
Cy	50/ 1.0	> 98/ 60	88	> 98: 2	> 98

This catalyst is less active than the achiral parent catalyst.

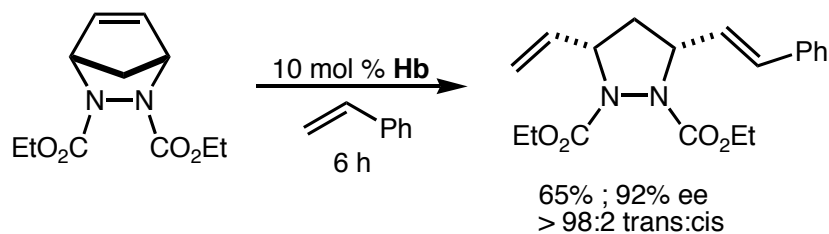
Higher reaction temperatures and longer reaction times are required.

Hoveyda Ru Catalyst: Ligand Modification



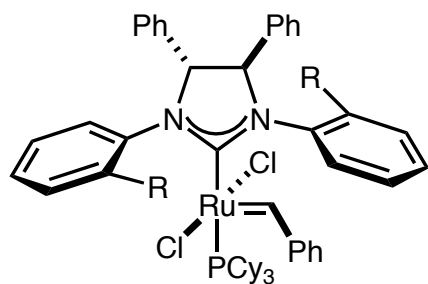
catalyst	temp (°C)/ time (h)	conv (%)/ yield (%)	recov. cat. (%)	trans:cis	ee (%)
Ha	22/ 1.0	> 98/ 63	98	92:8	70
Hb	22/ 0.25	> 98/ 60	50	95:5	70

Other norbornene systems show similar results.

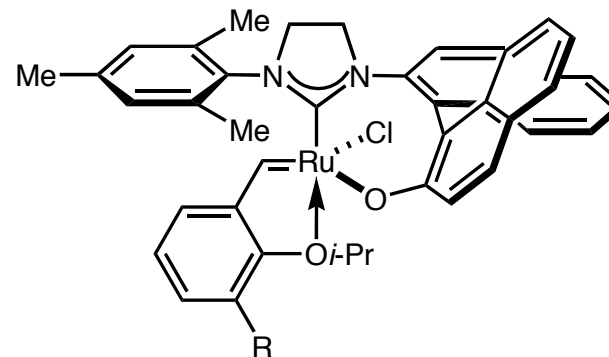


No reaction was observed
when **Ha** was used.

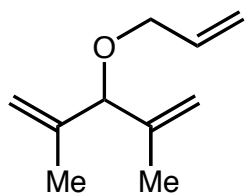
Asymmetric Ru Metathesis: A Comparison of the Catalysts



Gc R = Me
Gd R = *i*-Pr

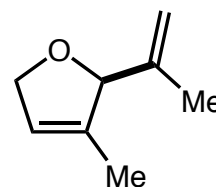


Ha R = H
Hb R = Ph



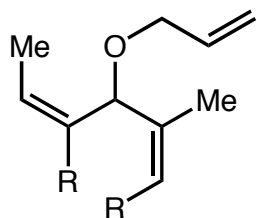
A. 5 mol % **Gd**, 100 mol % NaI
38 °C, DCM

B. 5 mol % **Hb**, 60 °C
toluene



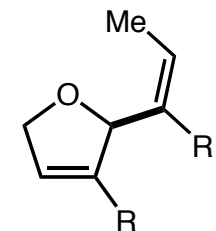
A. 20% conversion, 39% ee

B. 58% yield, 68% ee



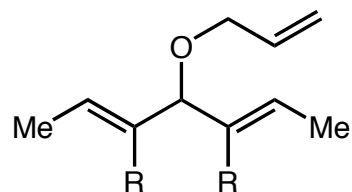
A. 5 mol % **Gd**, 100 mol % NaI
38 °C, DCM, R = Me

B. 5 mol % **Hb**, 60 °C
toluene, R = H



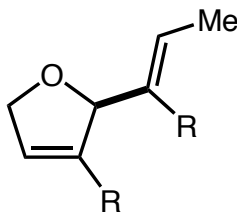
A. 90% conversion, 35% ee

B. > 98% conversion, 72% ee



A. 5 mol % **Gd**, 100 mol % NaI
38 °C, DCM, R = Me

B. 5 mol % **Hb**, 60 °C
toluene, R = H



A. 82% conversion, 90% ee

B. < 5% desired product

Conclusions About the Available Catalysts

Molybdenum based catalysts:

can be applied to a large number of different desymmetrizations (ARCM, AROM/ACM, AROM/ARCM)

can be tuned to work well for a wide variety of substrates

poorly understood connection between ligands and substrate specificity

highly sensitive to air and moisture

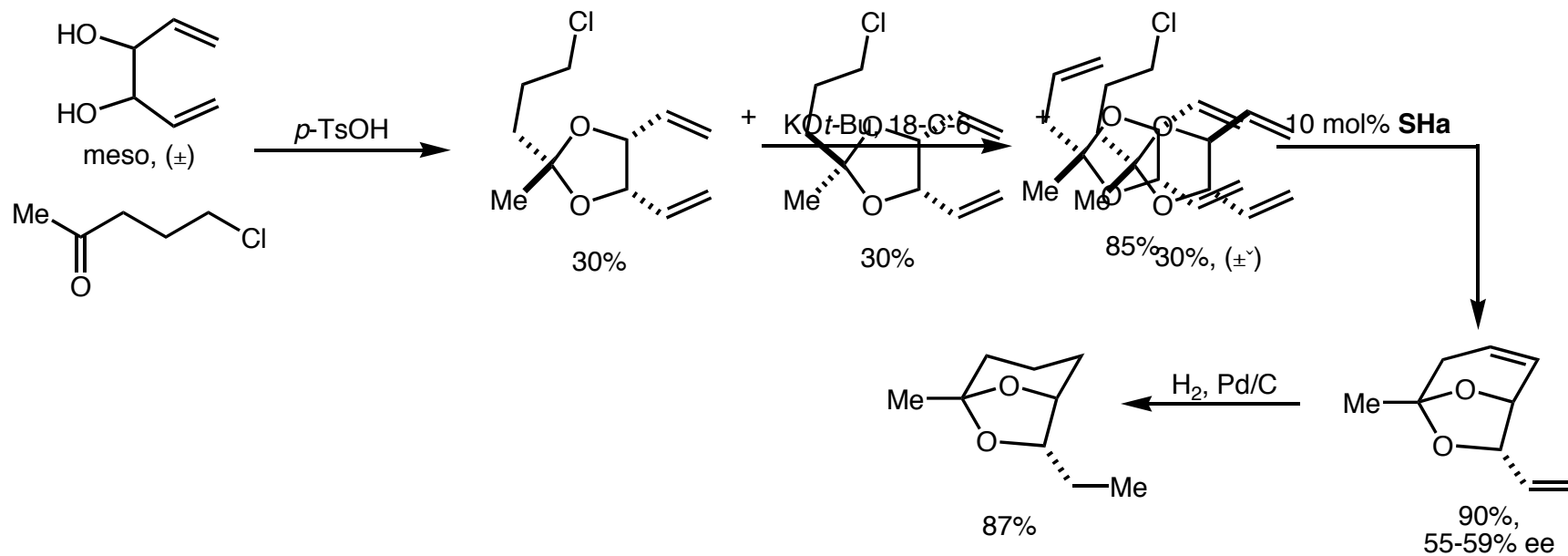
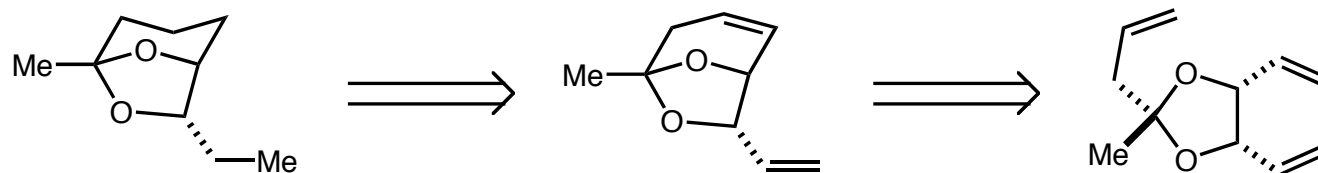
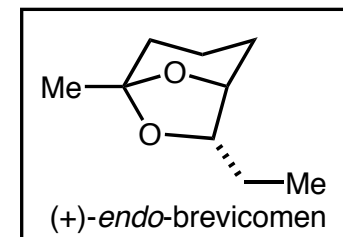
Ruthenium based catalysts:

well understood transition states

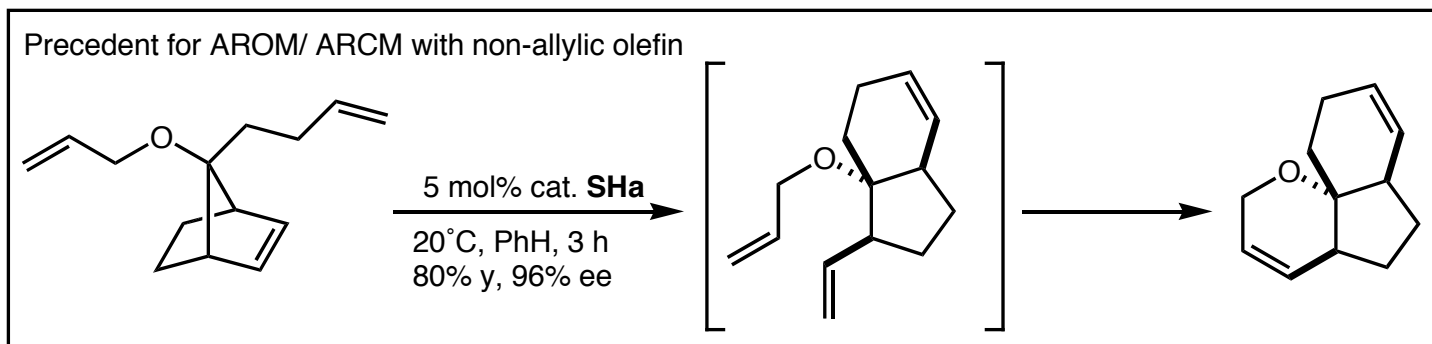
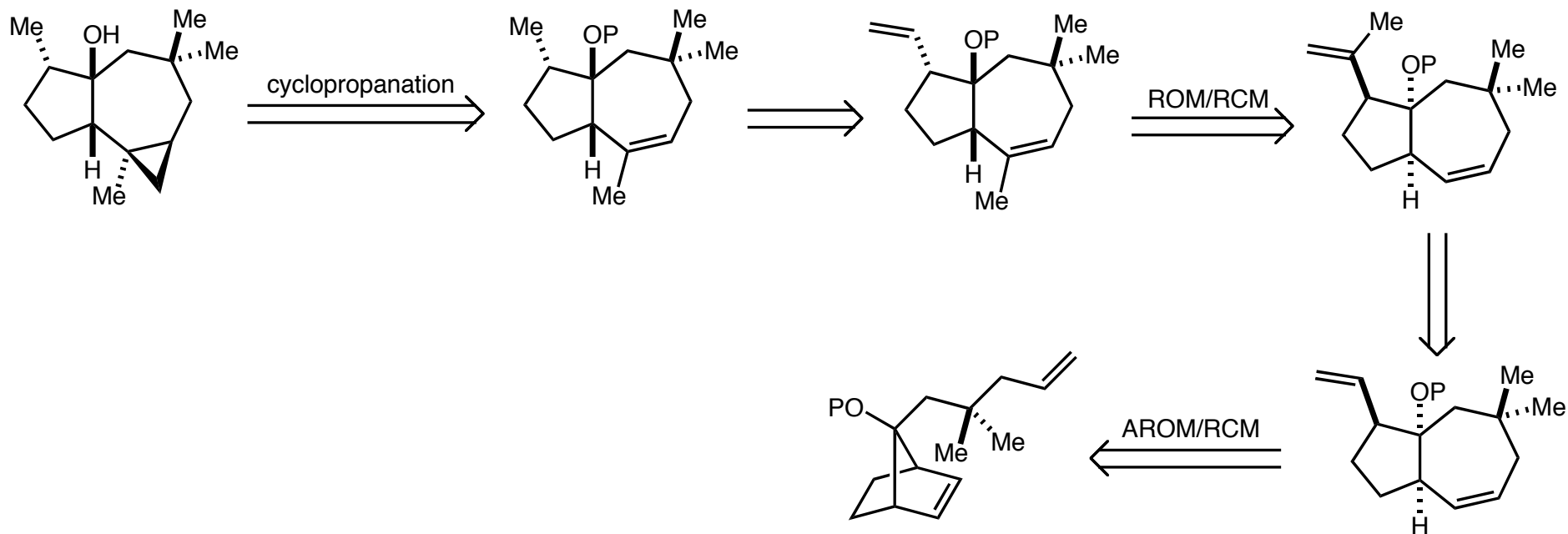
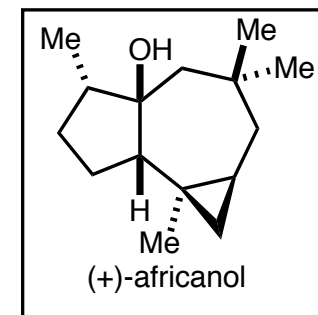
higher tolerance air and moisture than the Mo catalysts

only a small number have substrates have been tested

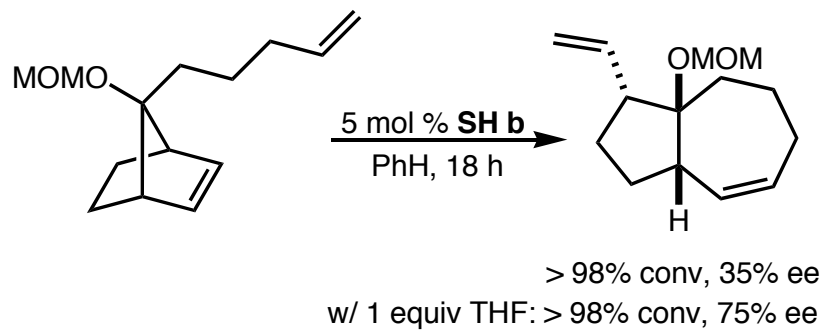
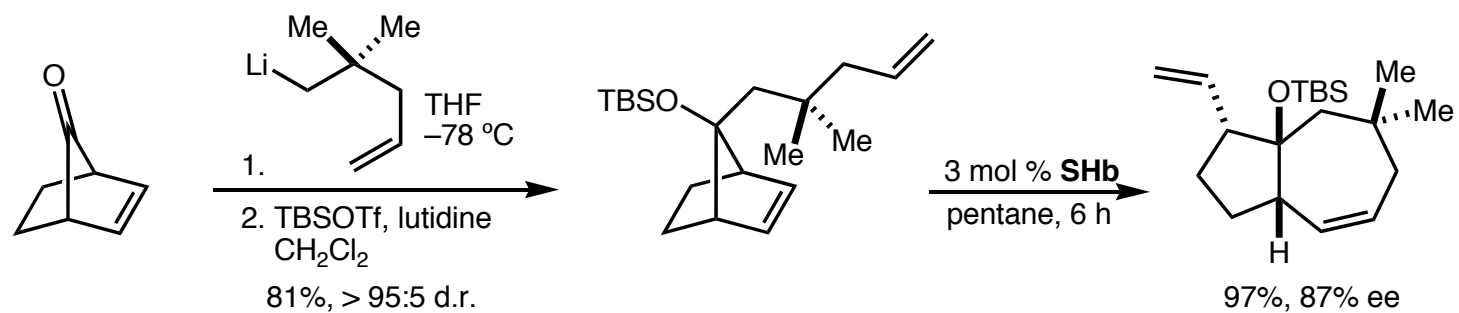
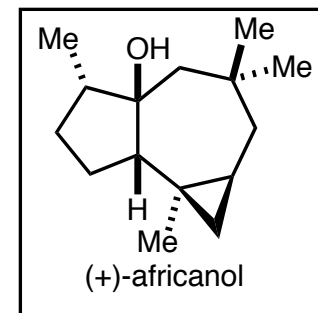
Total Synthesis of Enantio-enriched (+)-*endo*-Brevicomene



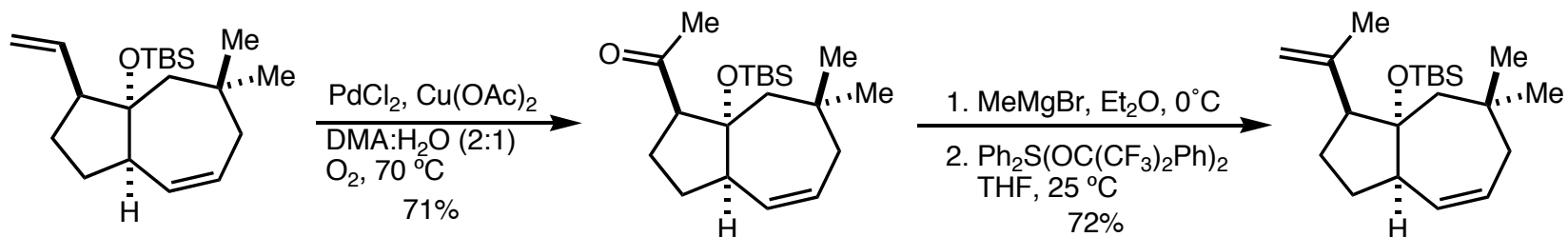
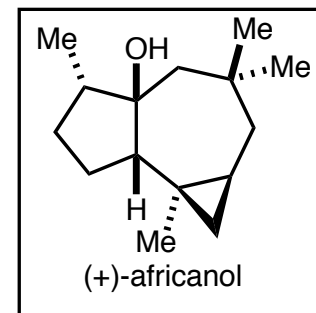
A Formal Synthesis of (+)-Africanol: Retrosynthesis



(+)-Africanol: Synthesis of the Bicyclic Core



(+)-Africanol: ROM/RCM Rearrangement



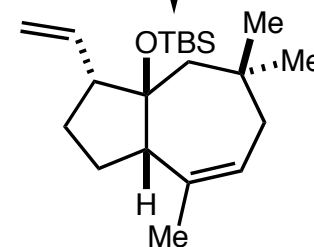
Various Mo and Ru Catalysts

< 2% conv.

Poor conversion may be due to:

resistance of cycloalkene toward ROM

ROM may occur with the incorrect regioselectivity



(+)-Africanol: A New Route

