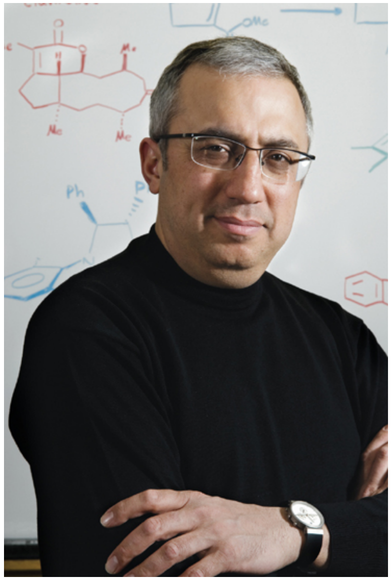
THE CAREER PATH OF AMIR H. HOVEYDA



WENJUN ZHAO

DEPARTMENT OF CHEMISTRY
MICHIGAN STATE UNIVERSITY

11-1-2013

BIOGRAPHY OF AMIR H. HOVEYDA

PERSONAL:
Date of Birth: April 5, 1959; Iranian

EDUCATION:
1981, B. A., Columbia University

1986, Ph. D., Yale University
Thesis Advisor: **Professor Stuart L. Schreiber**

1986-1987 & 1988-1990, Postdoctoral Fellow, Harvard University
Research Advisor: **Professor David A. Evans**

1987/11-1988/05, Pfizer Central Research, Cancer Group

EMPLOYMENT:
1990/06–1994/08, Assistant Professor, Boston College

1994/09–1998/08, Professor, Boston College,

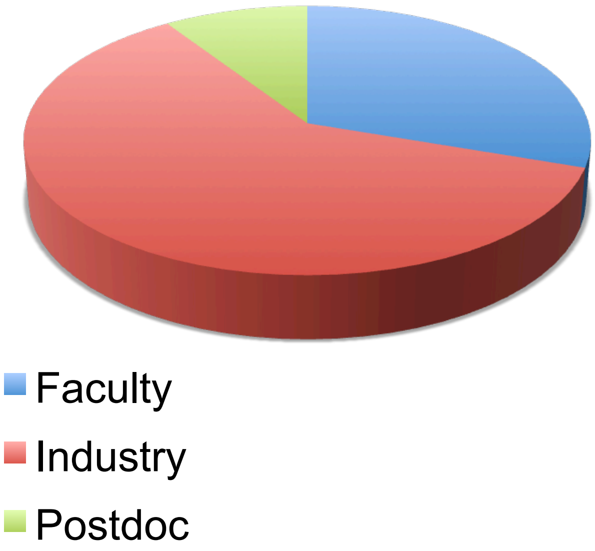
1998/09-present, Vanderslice Millennium Professor

HOVEYDA'S GROUP

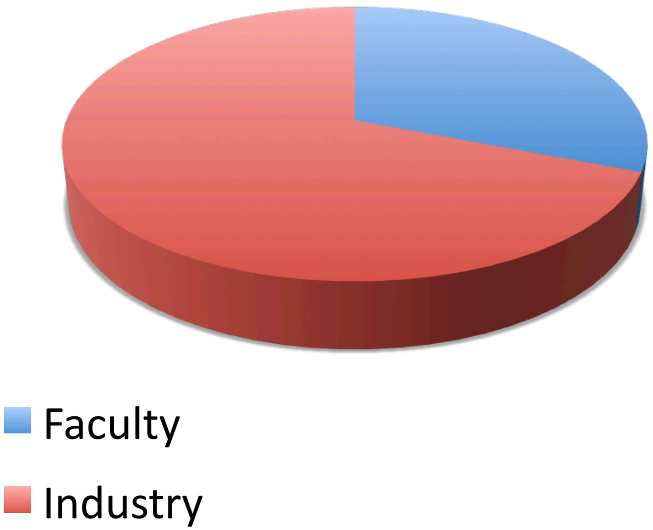
Current members: 15 graduate students; 4 postdocs

Former members: 43 graduate students and 45 postdocs

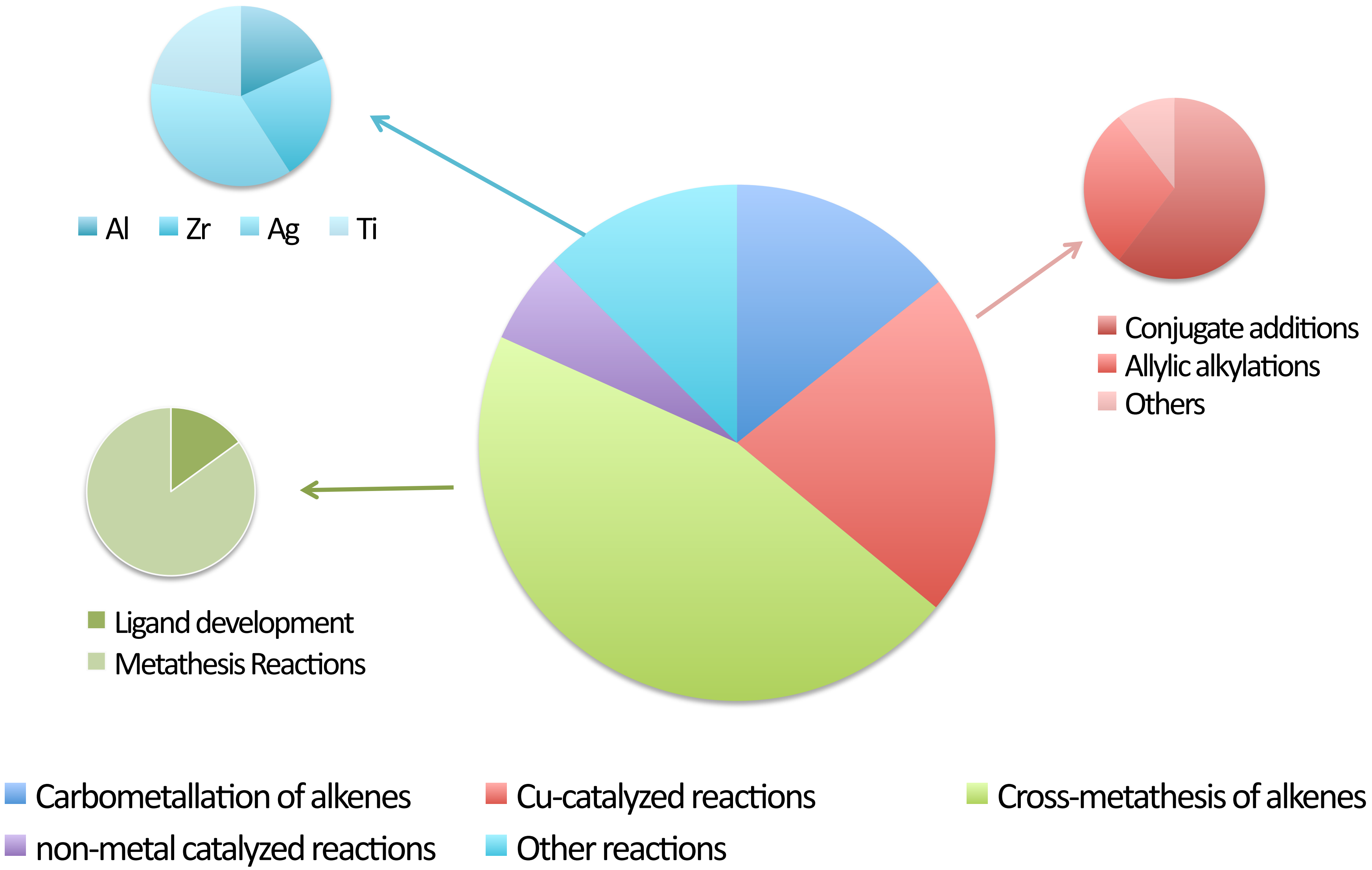
Students' current positions
(43 in total)



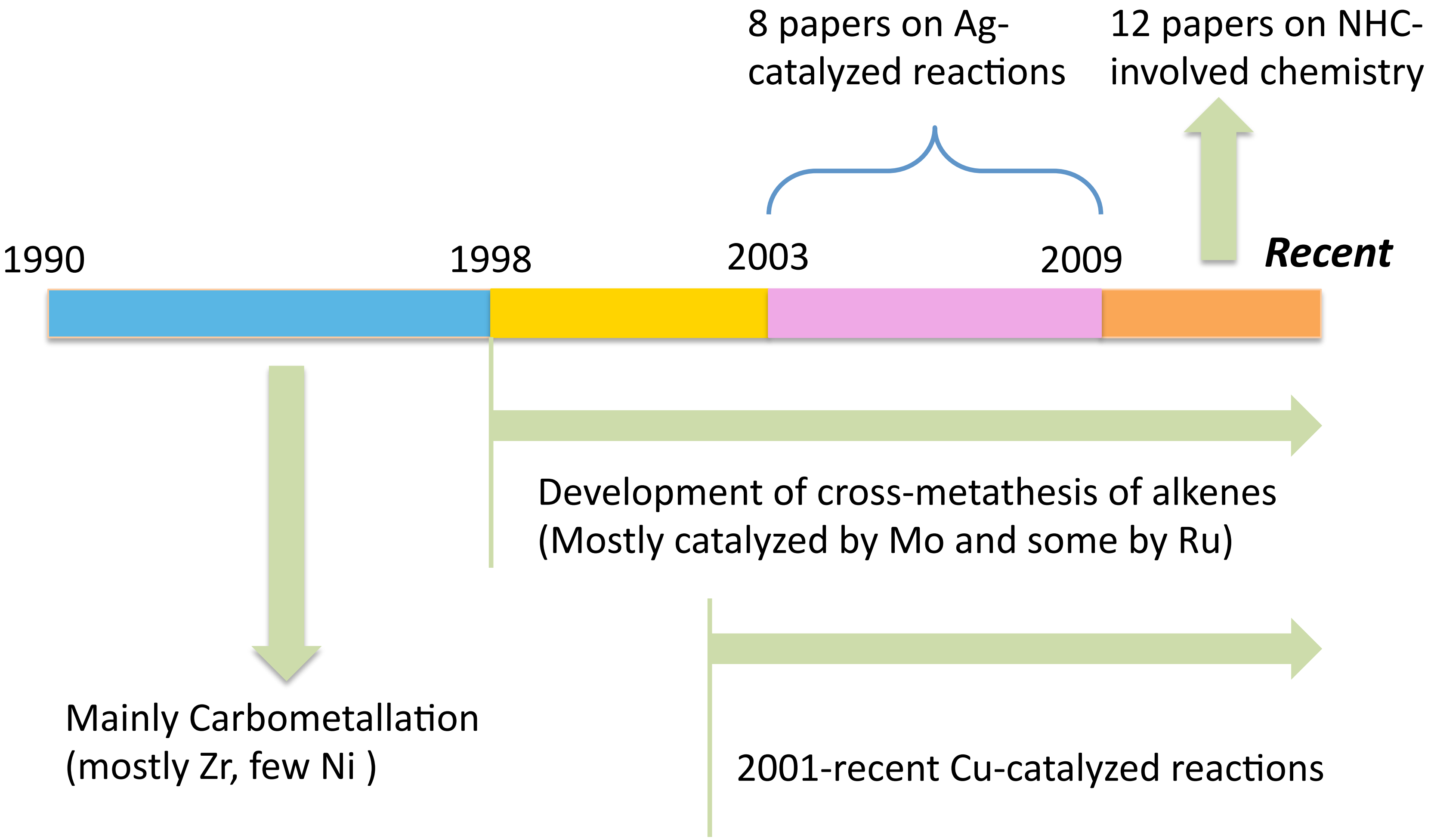
Postdocs' current positions
(45 in total)



PUBLICATIONS BY RESEARCH AREAS
(195 RESEARCH PUBLICATIONS)



PUBLICATIONS BY RESEARCH AREAS (195 RESEARCH PUBLICATIONS)



8 papers on Ag-catalyzed reactions

12 papers on NHC-involved chemistry

1990

1998

2003

2009

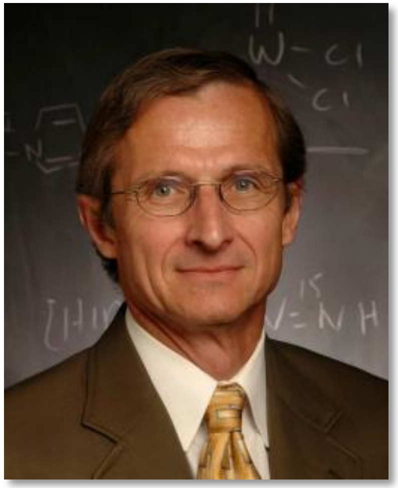
Recent

Development of cross-metathesis of alkenes
(Mostly catalyzed by Mo and some by Ru)

Mainly Carbometallation
(mostly Zr, few Ni)

2001-recent Cu-catalyzed reactions

COLLABORATION



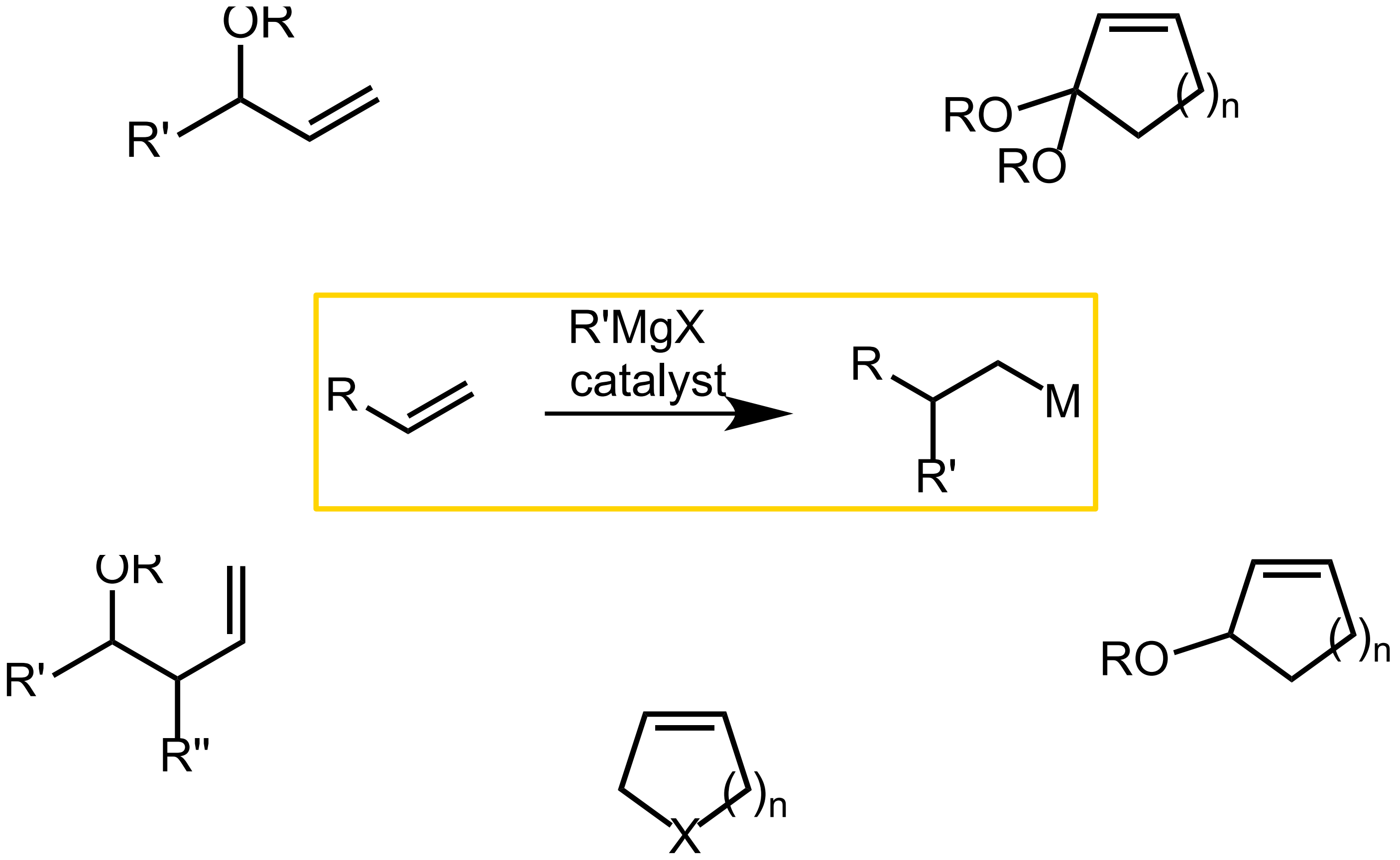
Richard R. Schrock
Department of Chemistry
MIT
2005 Nobel laureate

Marc L. Snapper
Department of Chemistry
Boston college

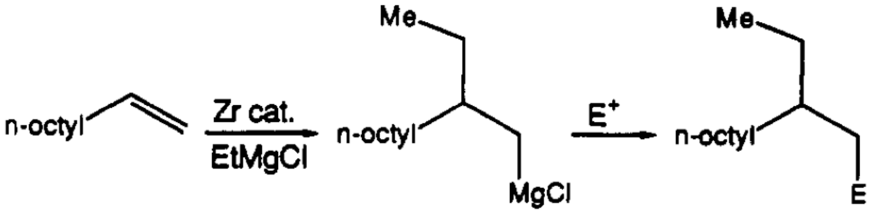
60 research papers
& 5 review articles
since 1998

32 research papers
& 5 review articles
since 1996

DIFFERENT SUBSTRATES IN CARBOMETALATIONS



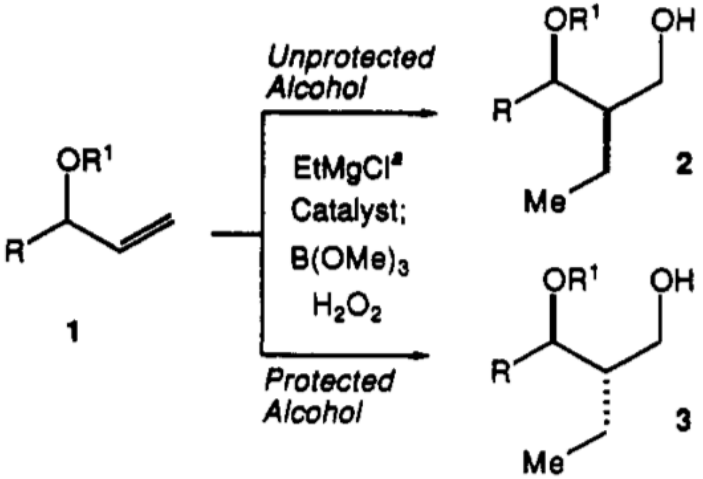
CARBOMETALATIONS OF ALKENES BY EtMgCl



Electrophile	E	Yield
CH_3CHO	$CH(OH)CH_3$	55%
$B(OCH_3)_3$; H_2O_2	OH	60%
NBS	Br	60%
I_2	I	65%

Zr catalyst = Cp_2ZrCl_2, Cp_2ZrBu_2, or Cp_2ZrEt_2

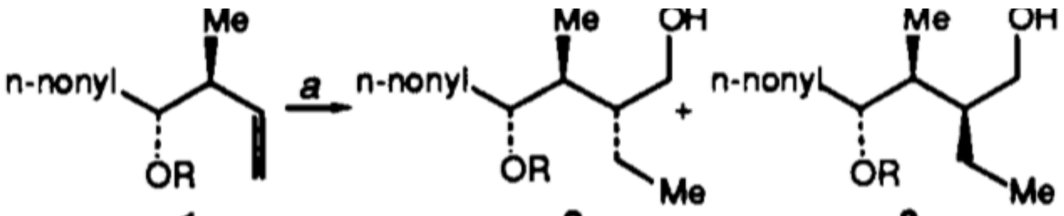
Regioselectivity > 99:1



Stereoselectivity suffers severely when THF is employed as cosolvent. (Et_2O is the solvent for this reaction.)

A. H. Hoveyda, Z. Xu *J. Am. Chem. Soc.* **1991**, *113*, 5079
A. F. Houri, M. T. Didiuk, Z. Xu, N. R. Horan, A. H. Hoveyda *J. Am. Chem. Soc.* **1993**, *115*, 6614

CARBOMETALATIONS OF ALKENES BY EtMgCl



1 2 3

substrate	R	solvent	anti:syn (2:3)[b]	yield,[c] %
1a	H	Et_2O	>99:1	75
		THF	99:1	75
1b	Me	Et_2O	97:3	65
		50% Et_2O/THF	97:3	35
		THF	–	5
1c	MEM	Et_2O	92:8	50
		50% Et_2O/THF	87:13	26
		THF	–	0

[a] Conditions: 3–4 equiv of EtMgCl, 5 mol % Cp_2ZrCl_2, 12 h; $B(OMe)_3$; H_2O_2. [b] Ratios determined by GLC analysis of lactones. [c] Isolated yields of purified products; mass balance ≥95% in all reactions.

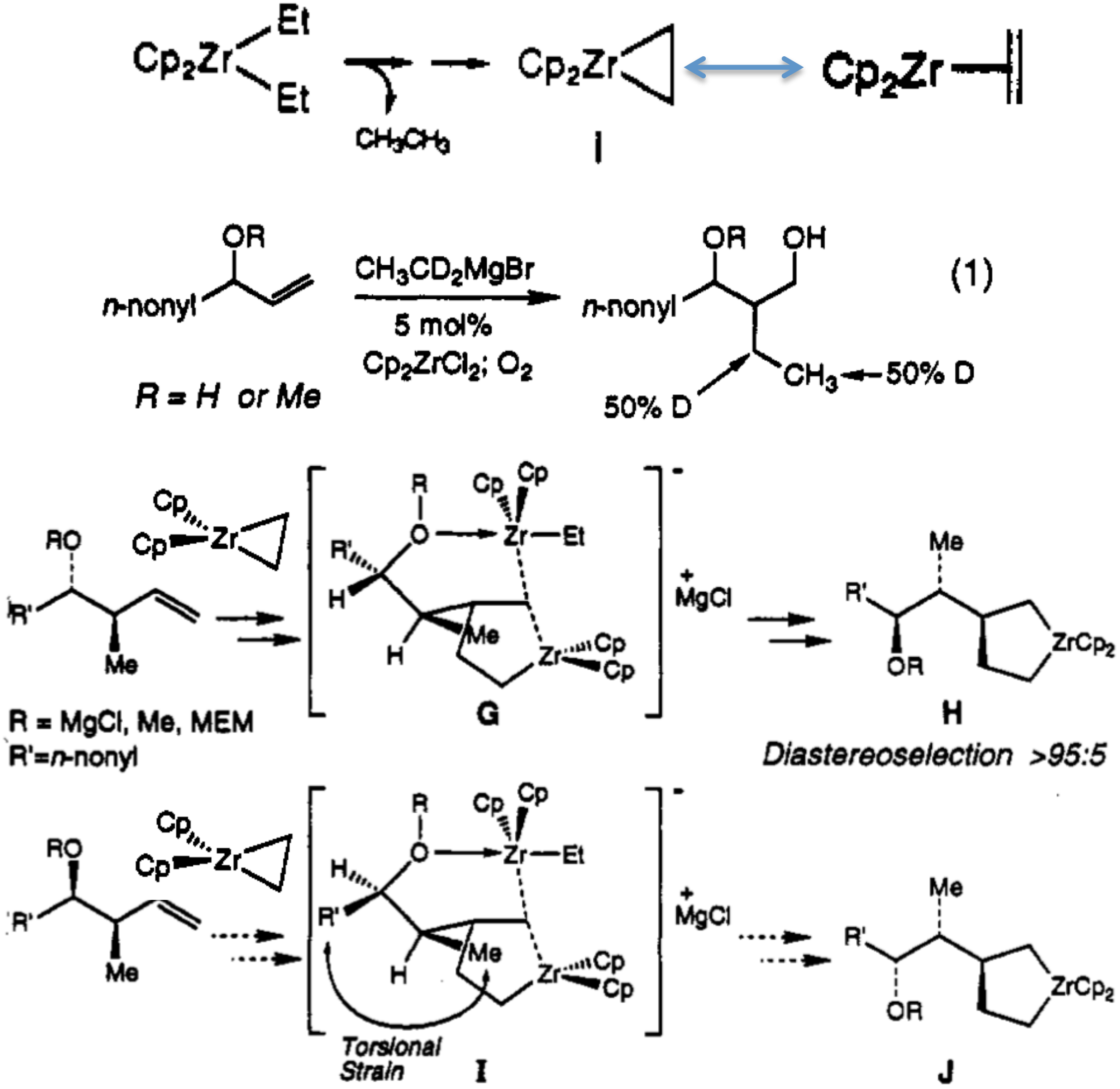
No selectivity

Syn-homoallylic alkenes give the same, but lower selectivity.

Both –OR and α-methyl are crucial to the diastereoselectivity.

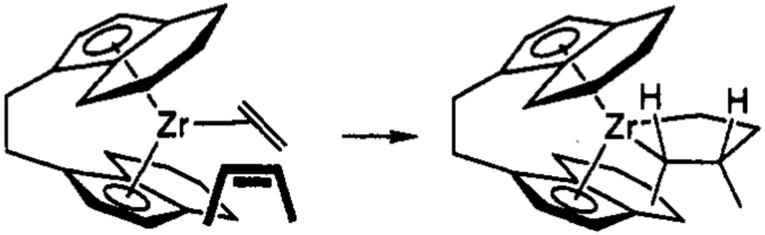
A. H. Hoveyda, Z. Xu, J. P. Morken, A. F. Houri *J. Am. Chem. Soc.* **1991**, *113*, 8950

CARBOMETALATIONS OF ALKENES BY EtMgCl — Mechanistic Study

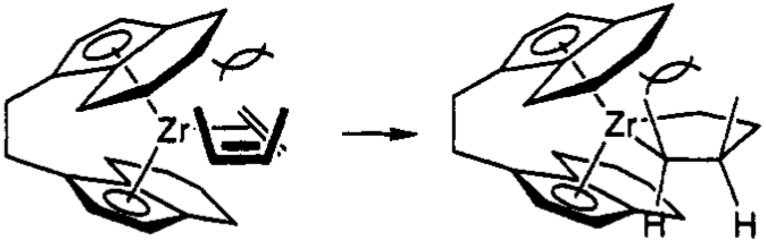


A. F. Houri, M. T. Didiuk, Z. Xu, N. R. Horan, A. H. Hoveyda *J. Am. Chem. Soc.* **1993**, *115*, 6614

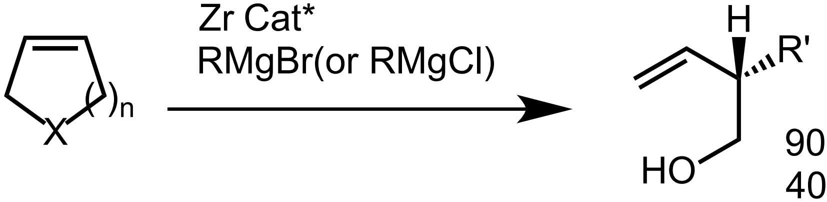
ASYMMETRIC CARBOMETALATIONS OF ALKENES



I



II



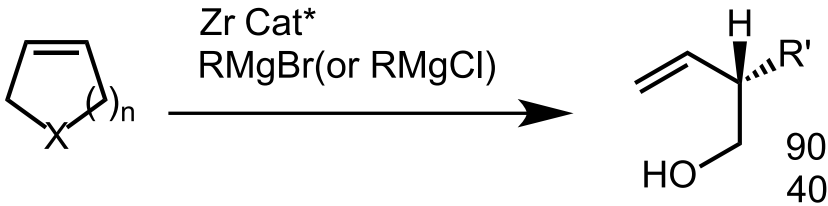
90-98% *ee*
40-75% yield

X = O, n = 1,2
N(n-nonyl), n = 1
NTs, n = 2, 3, 4

J. P. Morken, M. T. Didiuk, A. H. Hoveyda *J. Am. Chem. Soc.* **1993**, *115*, 6997.

M. S. Visser, N. M. Heron, M. T. Didiuk, J. F. Sagal, A. H. Hoveyda *J. Am. Chem. Soc.* **1996**, *118*, 4291

ASYMMETRIC CARBOMETALATIONS OF ALKENES



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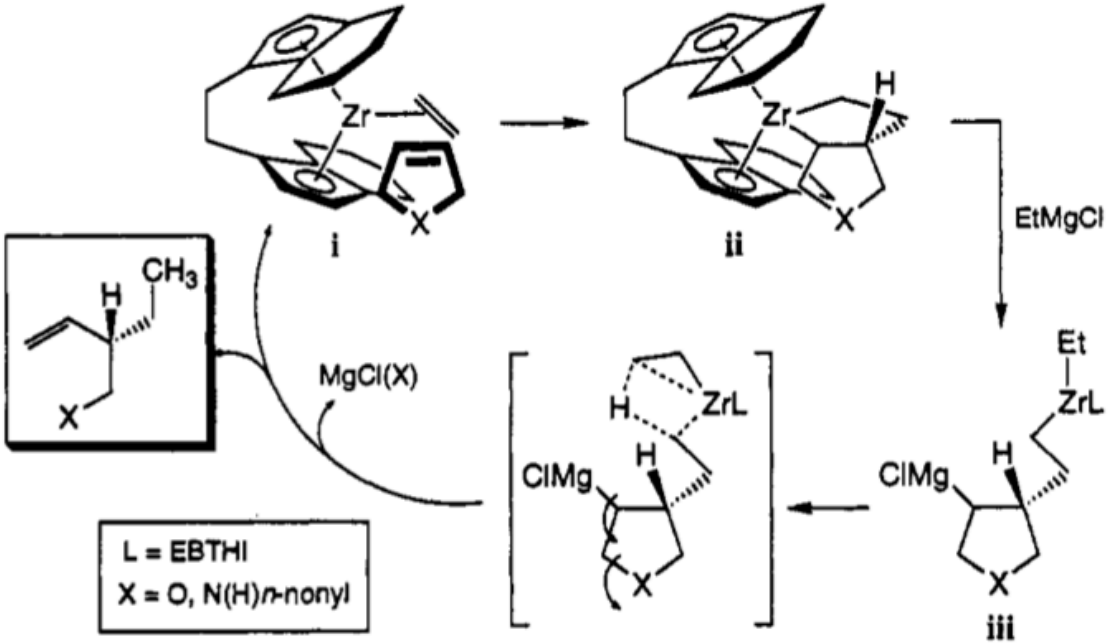


J. P. Morken, M. T. Didiuk, A. H. Hoveyda *J. Am. Chem. Soc.* **1993**, *115*, 6997.

M. S. Visser, N. M. Heron, M. T. Didiuk, J. F. Sagal, A. H. Hoveyda *J. Am. Chem. Soc.* **1996**, *118*, 4291

KINETIC RESOLUTION OF UNSATURATED HETEROCYCLES BY CARBOMETALATIONS

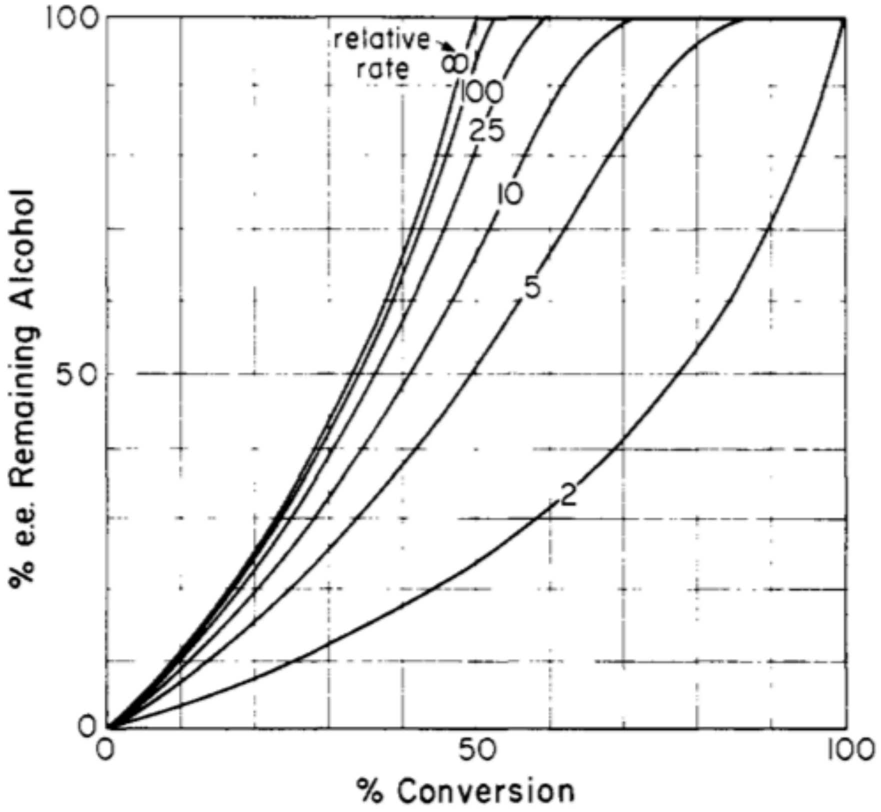
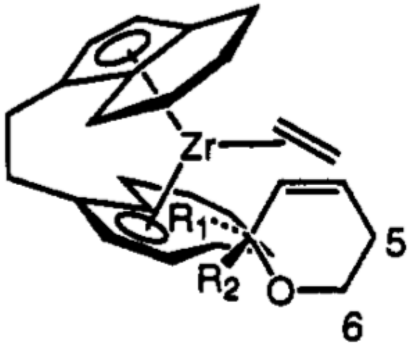


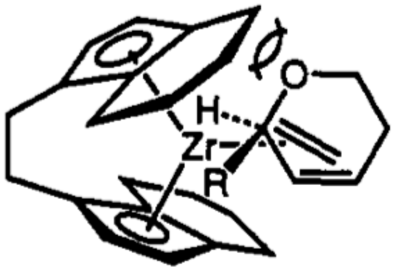
Figure 1. Dependence of enantiomeric excess on relative rate.

$$s = \frac{\text{rate of fast-reacting enantiomer}}{\text{rate of slow-reacting enantiomer}}$$

Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B.*J. Am. Chem. Soc.* **1981**, *103*, 6237

KINETIC RESOLUTION OF UNSATURATED HETEROCYCLES BY CARBOMETALATIONS

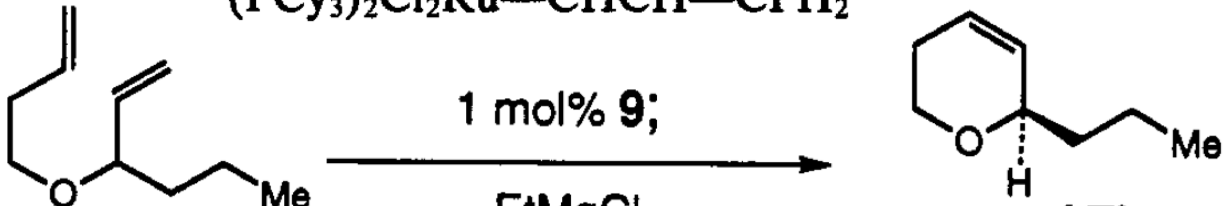




I $R_1 = H, R_2 = alkyl$

II $R_1 = alkyl, R_2 = H$

III $R = alkyl$



$(PCy_3)_2Cl_2Ru{=}CHCH{=}CPH_2$

1 mol% **9**;

EtMgCl,

10 mol% (*R*)-EBTHIZrCl$_2$

THF, 25→70 °C

8

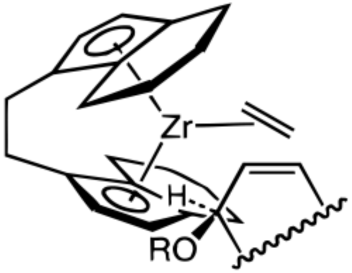
(*R*)-1

>99% ee at 60% conversion

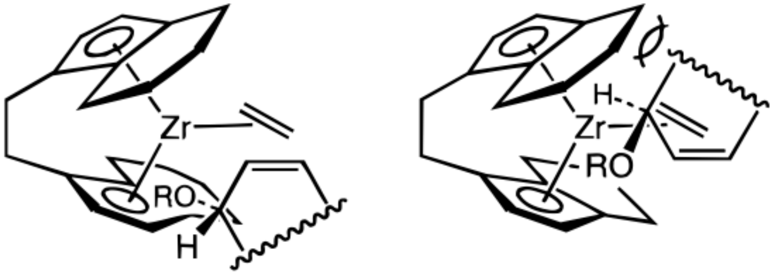
(1)

J. P. Morken, M. T. Didiuk, M. S. Visser, A. H. Hoveyda *J. Am. Chem. Soc.* **1994**, *116*, 3123

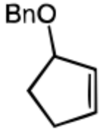
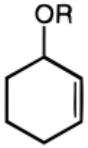
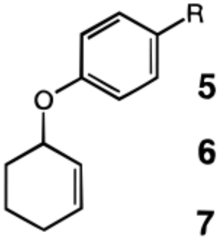
KINETIC RESOLUTION OF CYCLIC ALLYLIC ETHERS BY CARBOMETALATIONS



Addition pathway available to the faster-reacting enantiomer

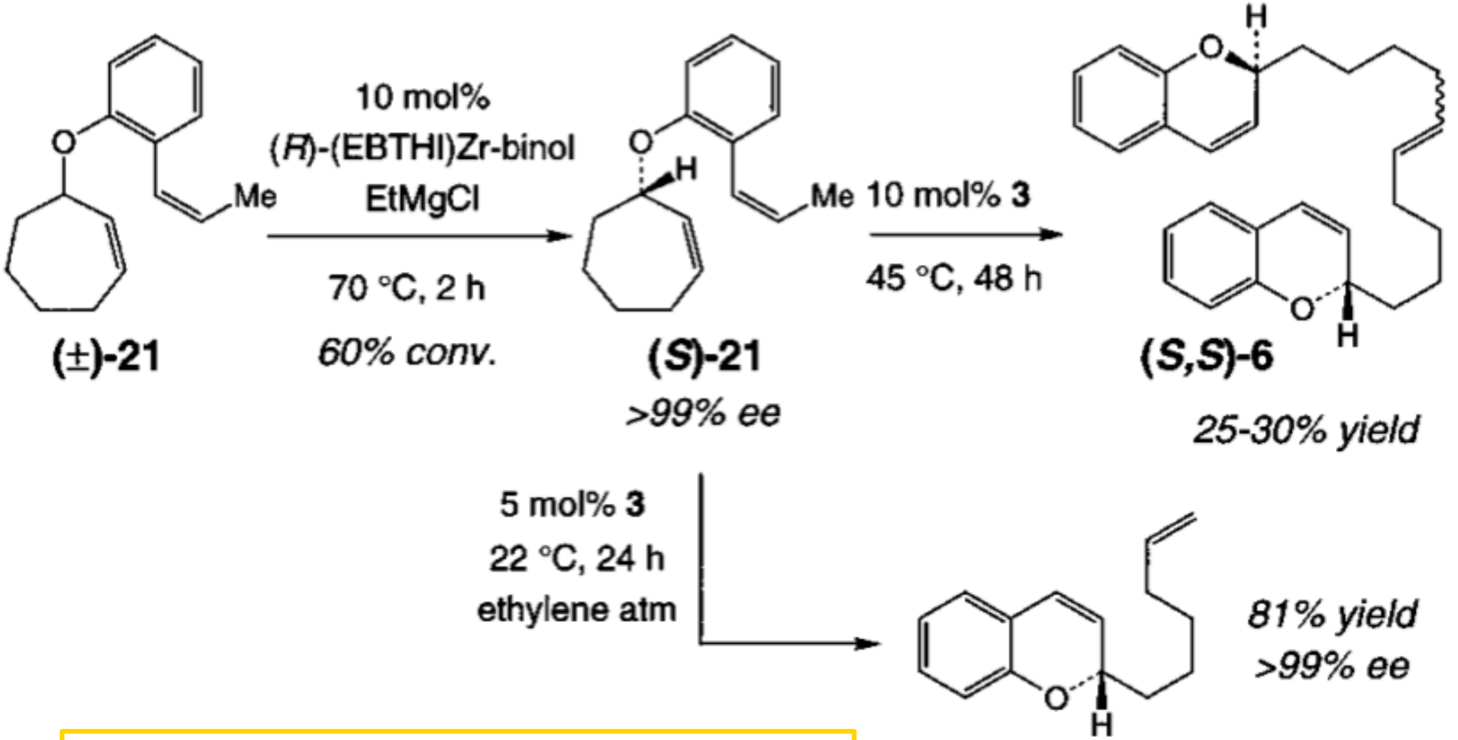


Addition pathways available to the slower-reacting enantiomer

entry	substrate			time (h)	conv.^{b} (%)	recovered start. material config.; ee (%)^c	k_{fast}/k_{slow}
1		**1**		3	65	*S*; 52	2.8
2		**2**	R = OMEM	4-5	63	*S*; 50	2.8
3		**3**	R = *n*-Bu	9-10	63	*S*; 79	6.2
4		**4**	R = Bn	2.5-3	60	*S*; 81	7.8
5		**5**	R = H	2	60	*S*; 97	>20
6		**6**	R = OMe	1.5-2	60	*S*; 93	15.4
7		**7**	R = F	2	60	*S*; 95	15.6

M. S. Visser, J. P. A. Harrity, A. H. Hoveyda *J. Am. Chem. Soc.* **1996**, *118*, 3779

COUPLED CARBOMETALATIONS AND RING-CLOSING METATHESES



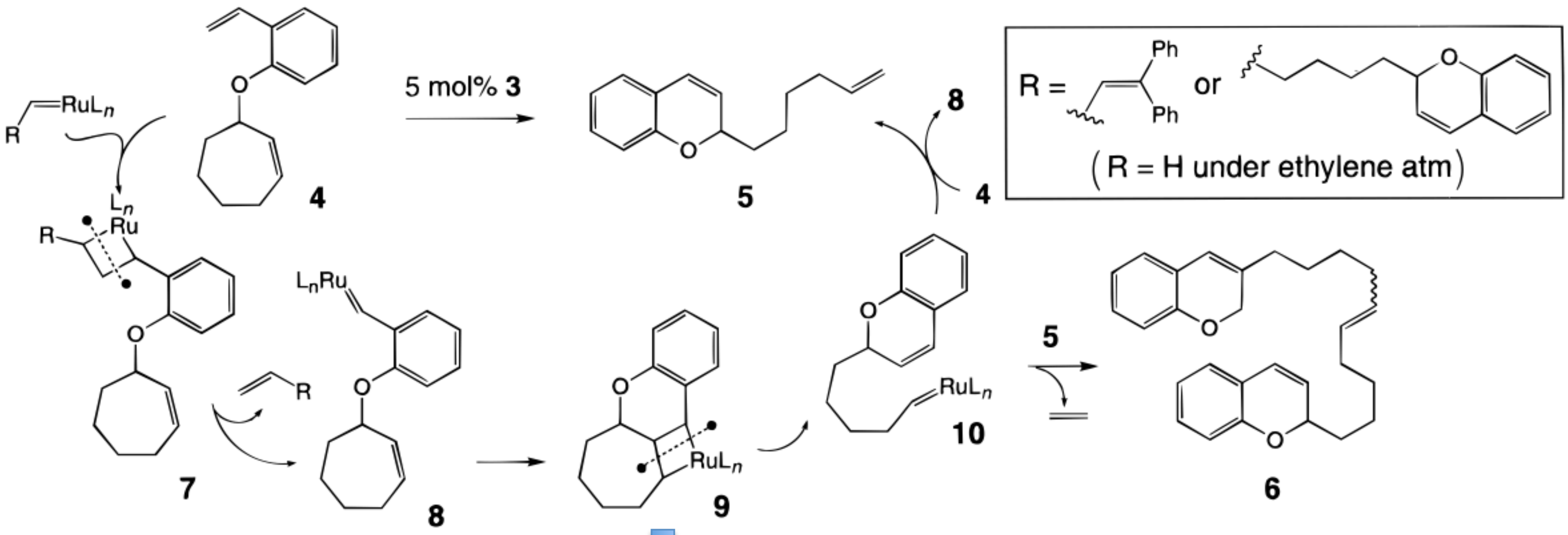
Cat 3 : $(PCy_3)_2Cl_2Ru=CHCH=CPh_2$

No reaction with 5-membered ring cyclic allylic ethers.
Low yield with 6-membered ring system.

J. P. A. Harrity, M. S. Visser, J. D. Gleason, A. H. Hoveyda *J. Am. Chem. Soc.* **1997**, *119*, 1488

COUPLED CARBOMETALATIONS AND RING-CLOSING METATHESES

Cat 3 : $(PCy_3)_2Cl_2Ru{=}CHCH{=}CPh_2$

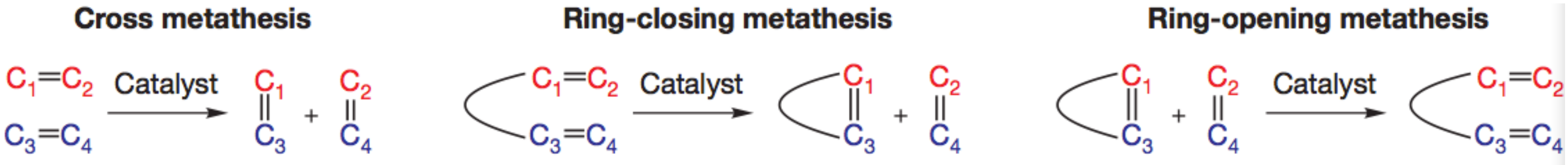


Angle strain

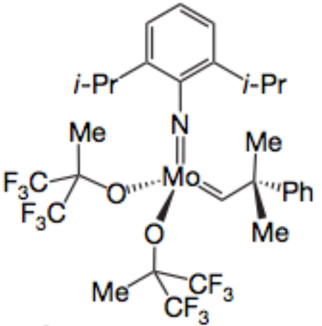
No reaction with 5-membered ring cyclic allylic ethers.
Low yield with 6-membered ring system.

J. P. A. Harrity, M. S. Visser, J. D. Gleason, A. H. Hoveyda *J. Am. Chem. Soc.* **1997**, *119*, 1488

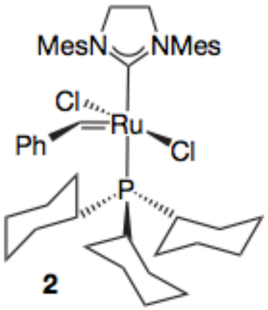
CROSS METATHESIS OF ALKENES



Achiral olefin metathesis catalysts



1



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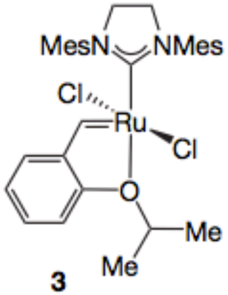

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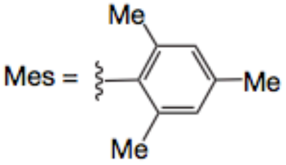
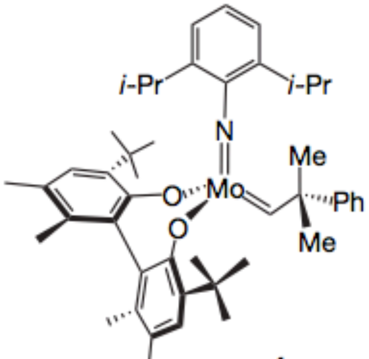


Chiral olefin metathesis catalysts



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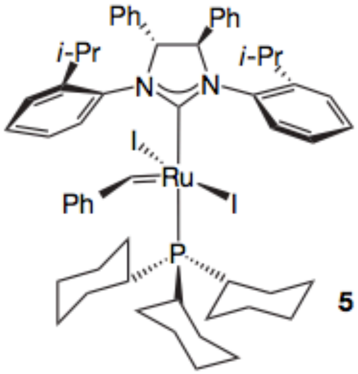

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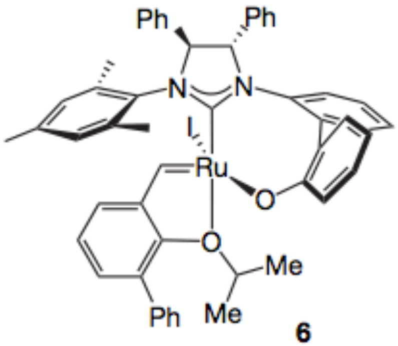
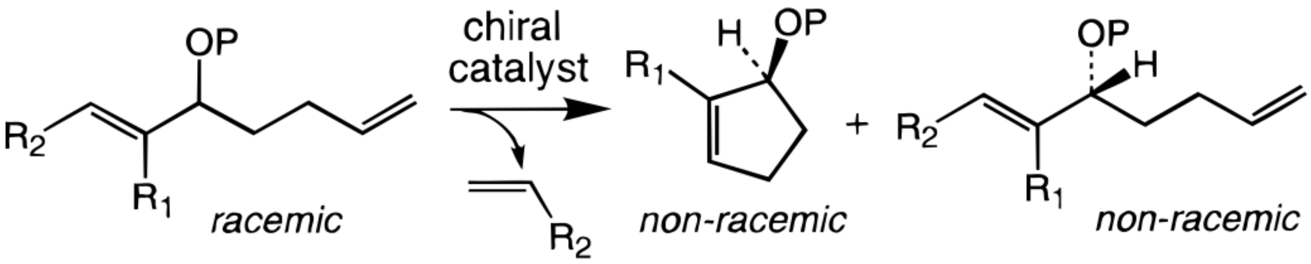
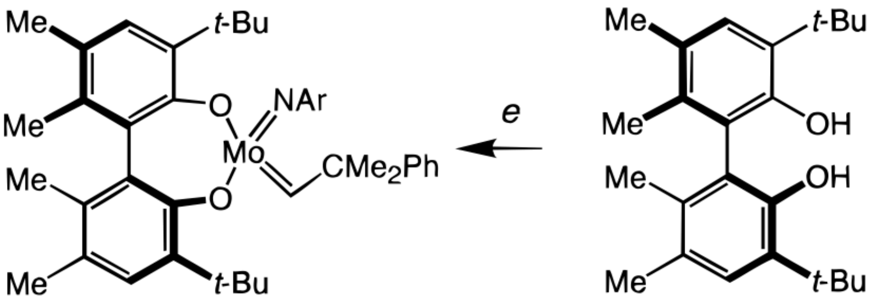


6

A. H. Hoveyda, A. R. Zhugralin *Nature* **2007**, *450*, 243

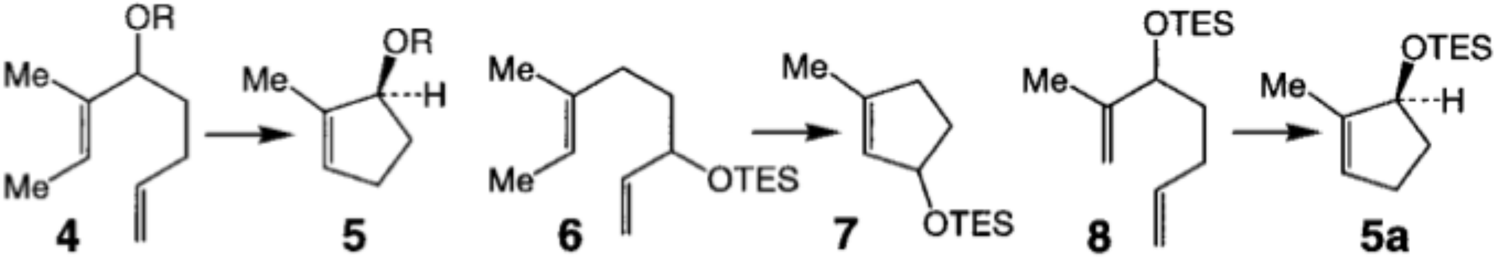
RING-CLOSING METATHESIS — KINETIC RESOLUSION





1 Ar=2,5-(*iso*-Pr)$_2$C$_6$H$_3$

(*S*)-**2**



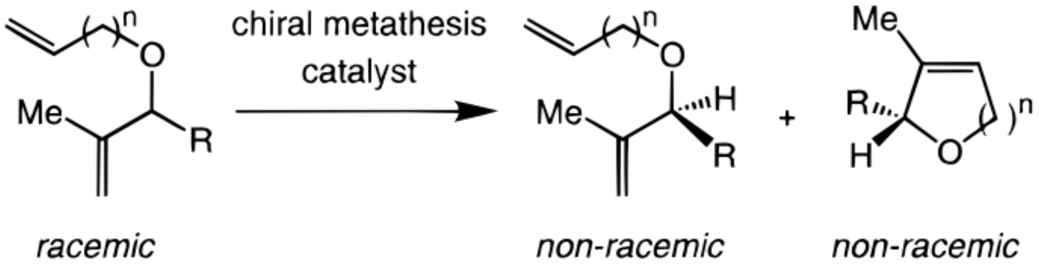
93% ee for pdt
>99% ee for SM

65% ee for pdt
97% ee for SM

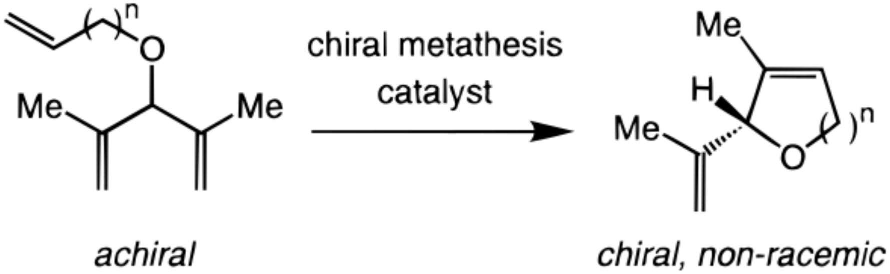
J. B. Alexander, D. S. La, D. R. Cefalo, A. H. Hoveyda, R. R. Schrock *J. Am. Chem. Soc.* **1998**, *120*, 4041

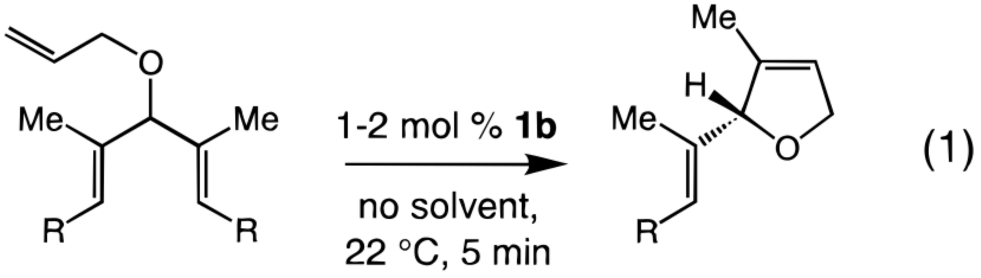
RING-CLOSING METATHESIS — KINETIC RESOLUSION

■ Catalytic Kinetic Resolution



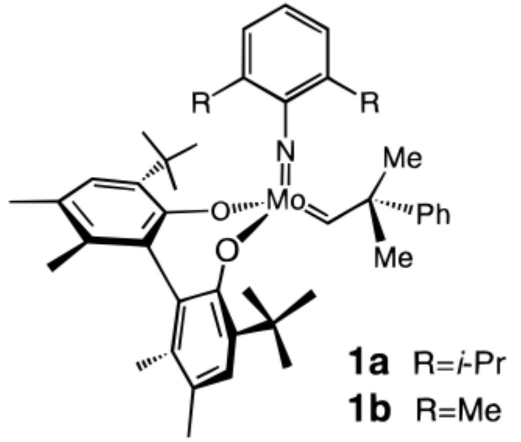
■ Catalytic Enantioselective Desymmetrization





6 R=H (1 mol % **1b**) (*R*)-**7** *93% ee, 85% yield*

8 R=Me (2 mol % **1b**) (*R*)-**9** *99% ee, 93% yield*

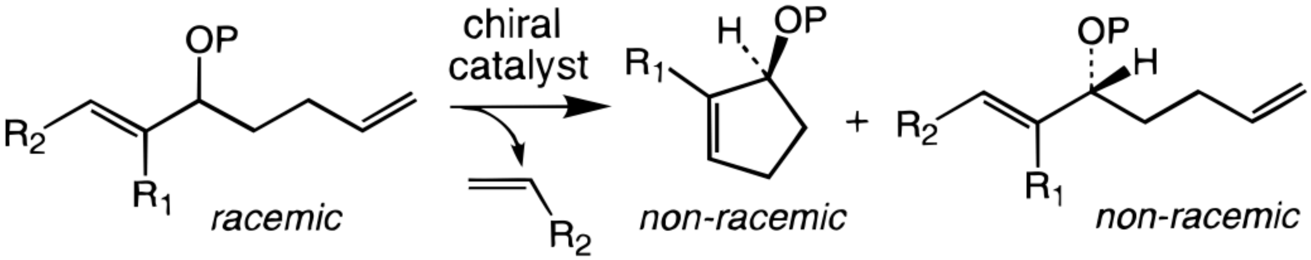


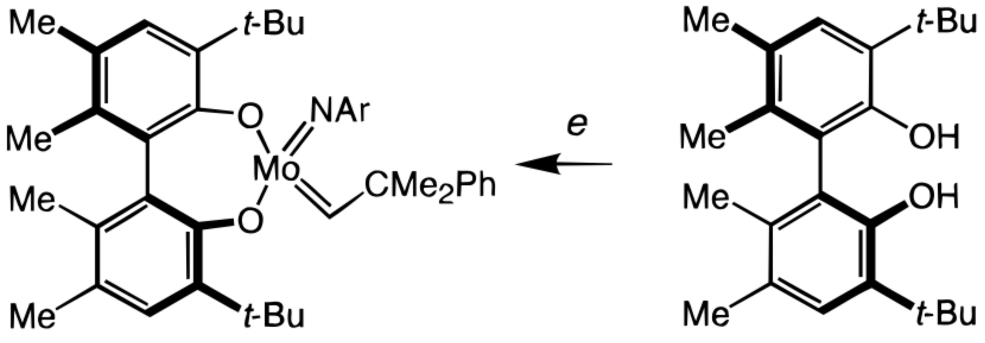
1a R=*i*-Pr

1b R=Me

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

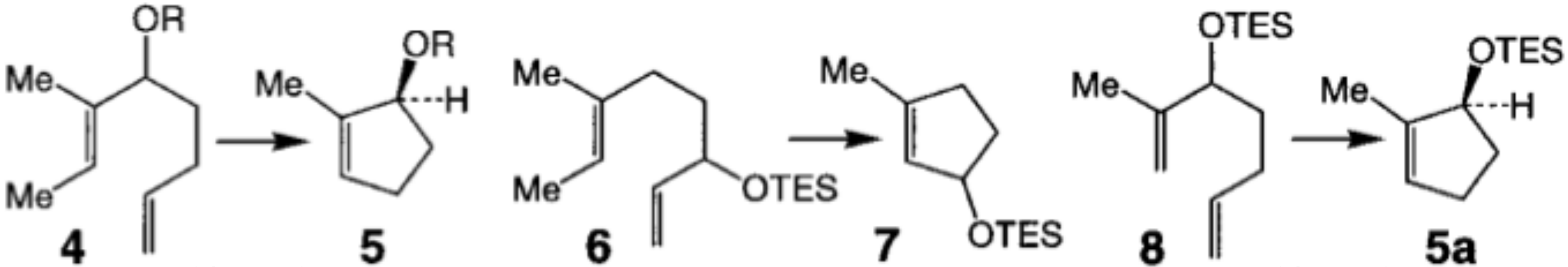
RING-CLOSING METATHESIS — KINETIC RESOLUSION





1 Ar=2,5-(*iso*-Pr)$_2$C$_6$H$_3$

(*S*)-**2**

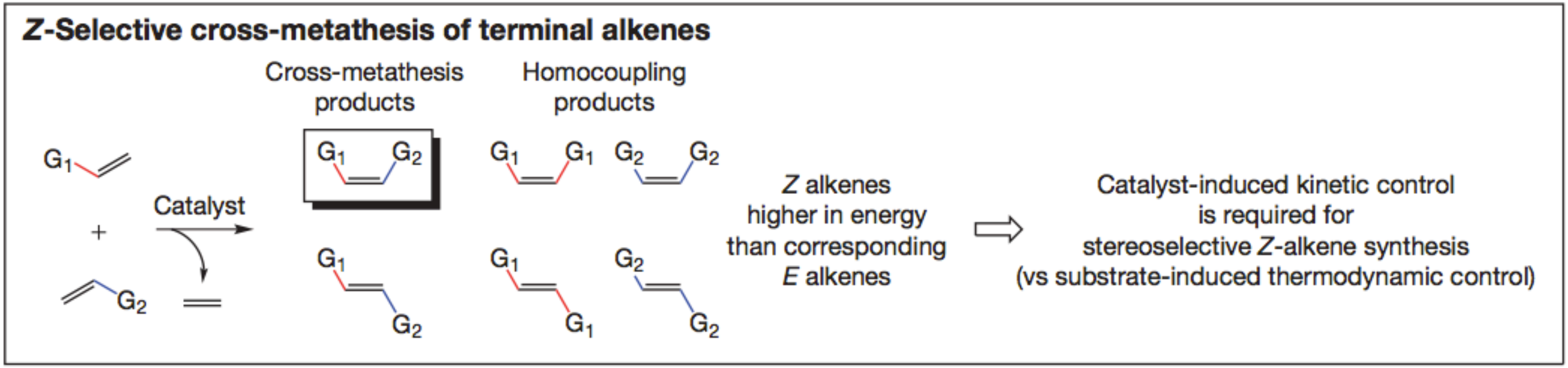


93% ee for pdt
>99% ee for SM

65% ee for pdt
97% ee for SM

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

Z-SELECTIVE OLEFIN CROSS-METATHESIS



Z-Selective cross-metathesis of terminal alkenes

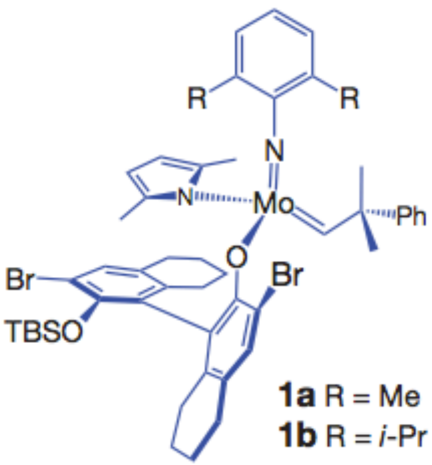
Cross-metathesis products

Homocoupling products

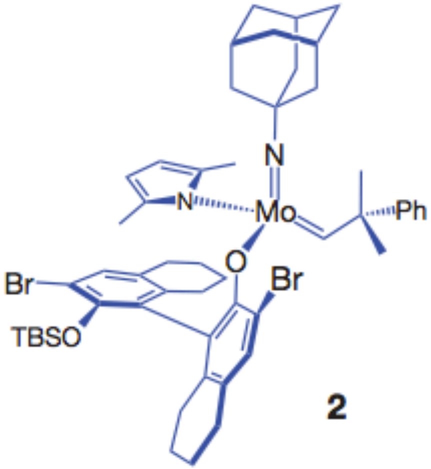
Catalyst

Z alkenes higher in energy than corresponding *E* alkenes

Catalyst-induced kinetic control is required for stereoselective *Z*-alkene synthesis (vs substrate-induced thermodynamic control)



1a R = Me
1b R = *i*-Pr



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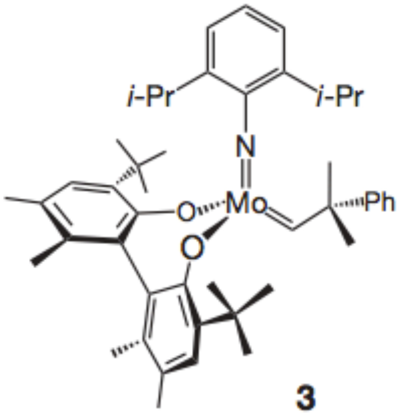

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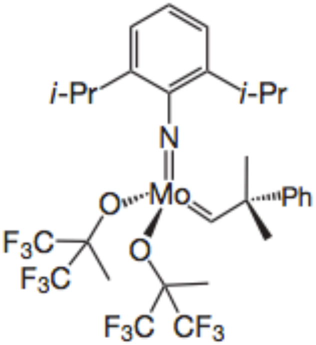

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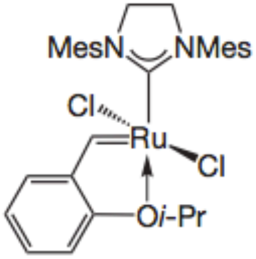
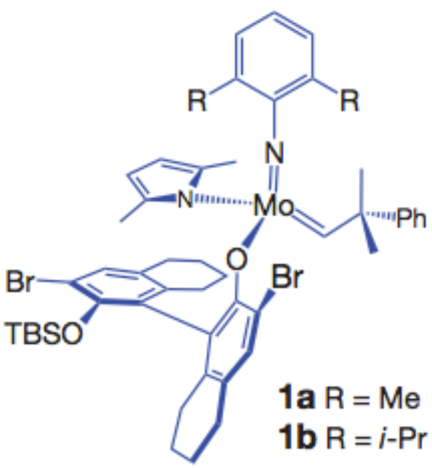


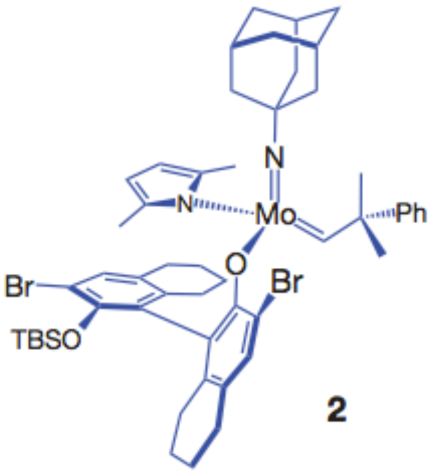
5

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

Z-SELECTIVE OLEFIN CROSS-METATHESIS



1a R = Me
1b R = *i*-Pr



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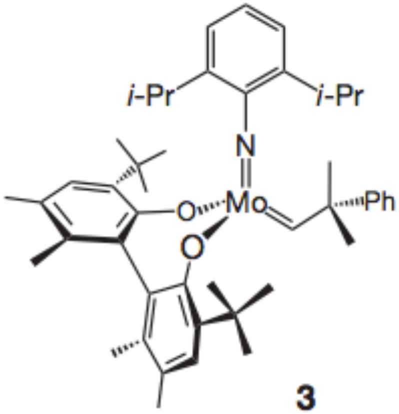

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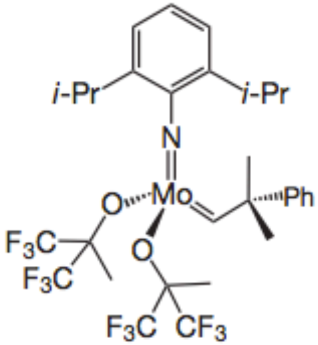

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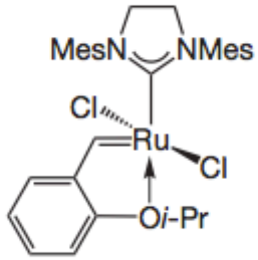

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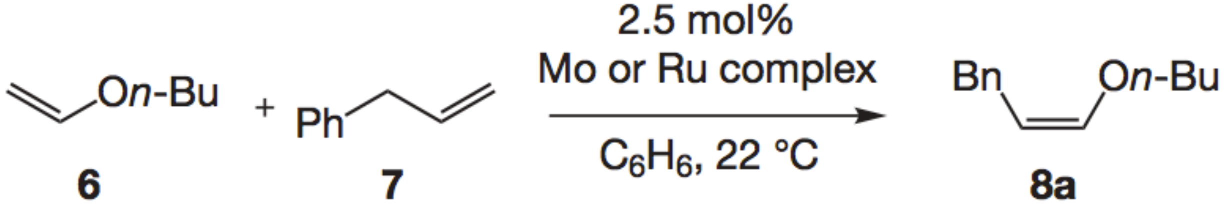


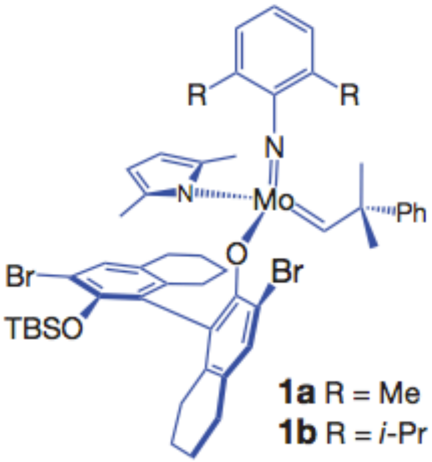
6 + **7** → **8a**

2.5 mol%
Mo or Ru complex
C_6H_6, 22 °C

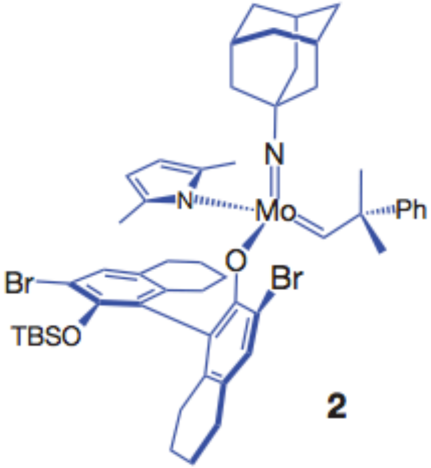
Entry no.	Complex	Time	Conv. (%)*	Yield (%)†	*Z*:*E**
1	**1a**	2 h	85	73	98:2
2	**1b**	2 h	47	ND	>98:2
3	**2**	2 h	37	ND	>98:2
4	**3**	2 h	<2	NA	NA
5	**4**	10 min	80	ND	47.5:52.5
6	**5**	24 h	<2	NA	NA

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

Z-SELECTIVE OLEFIN CROSS-METATHESIS



1a R = Me
1b R = *i*-Pr



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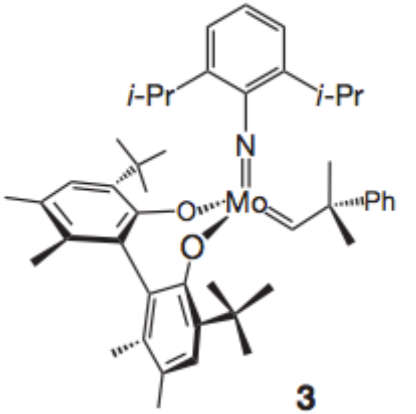

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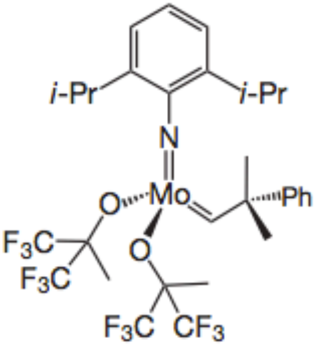

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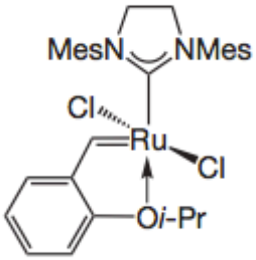

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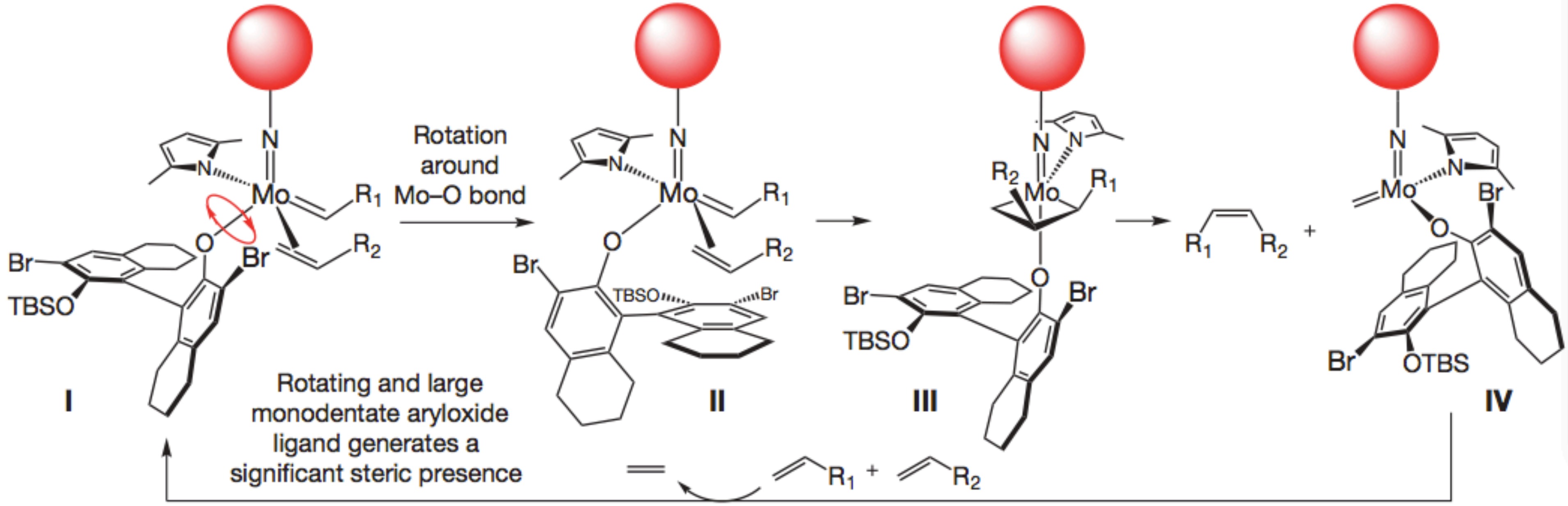
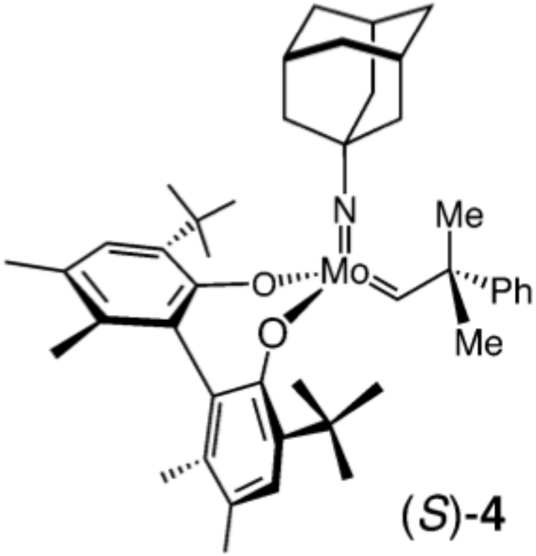


Rotation around Mo–O bond

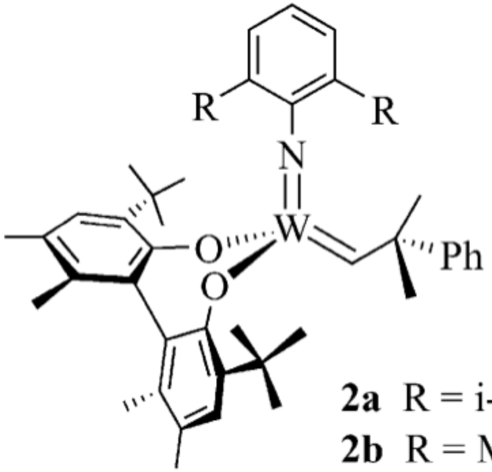
Rotating and large monodentate aryloxide ligand generates a significant steric presence

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

OTHER CATALYSTS SYNTHESIZED FOR OLEFIN CROSS-METATHESIS



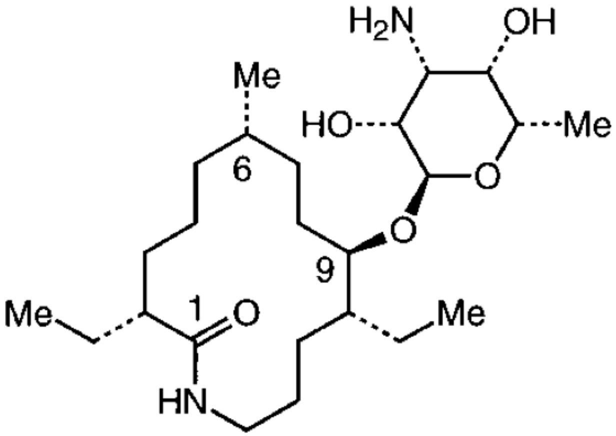
(*S*)-**4**



2a R = i-Pr
2b R = Me

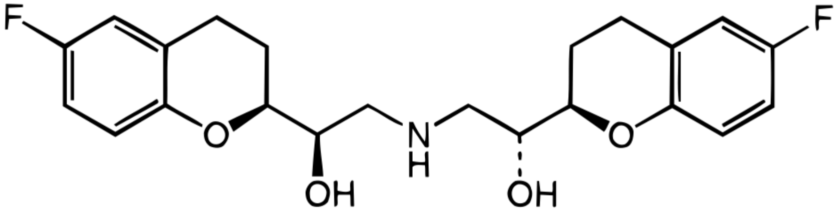
W. C. P. Tsang, K. C. Hultzsch, J. B. Alexander, P. J. Bonitatebus, Jr., R. R. Schrock, A. H. Hoveyda
J. Am. Chem. Soc. **2003**, *125*, 2652
W. C. P. Tsang, J. A. Jernelius, G. A. Cortez, G. S. Weatherhead, R. R. Schrock, A. H. Hoveyda
J. Am. Chem. Soc. **2003**, *125*, 2591

APPLICATION OF CARBOMETALATIONS AND CROSS METATHESIS OF ALKENES IN TOTAL SYNTHESIS



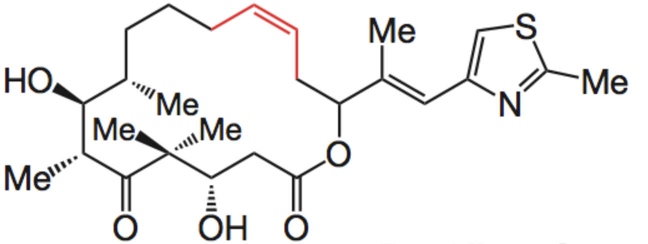
Sch 38516 **1**
(fluvirucin B$_1$)

J. Am. Chem. Soc. **1997**, *119*, 10302
J. Am. Chem. Soc. **1995**, *117*, 2943
J. Am. Chem. Soc. **1996**, *118*, 10926

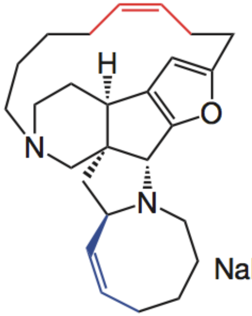


(*S*,*R*,*R*,*R*)-nebivolol **3**

J. Am. Chem. Soc. **1998**, *120*, 8340



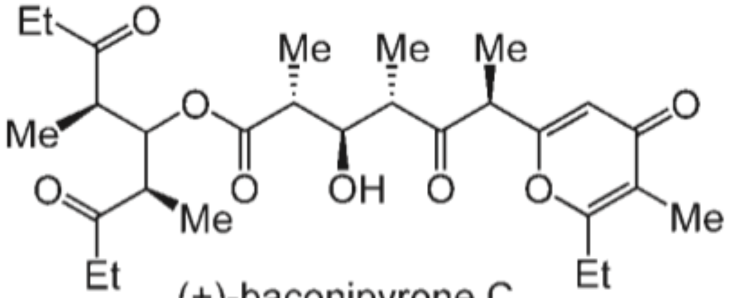
Epothilone C



Nakadomarin A

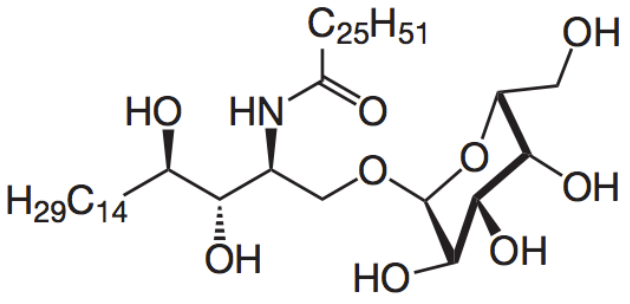
Nature **2011**, *479*, 88

APPLICATION OF CARBOMETALATIONS AND CROSS METATHESIS OF ALKENES IN TOTAL SYNTHESIS

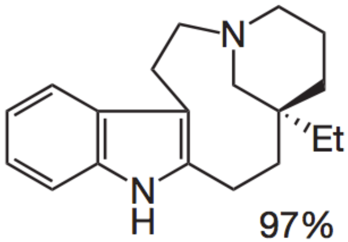


(+)-baconipyrone C

Angew. Chem., Int. Ed. **2007**, *46*, 3860

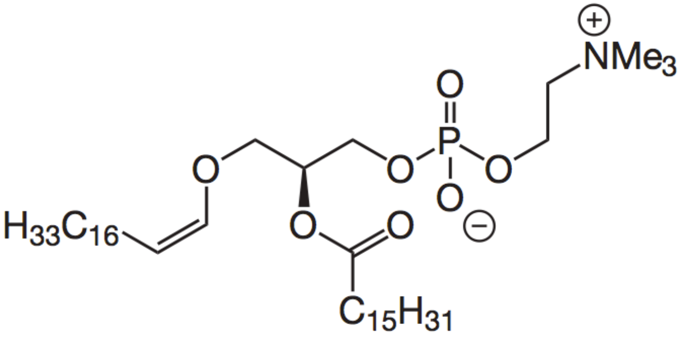


KRN7000



(+)-quebrachamine

Nature **2008**, *456*, 933

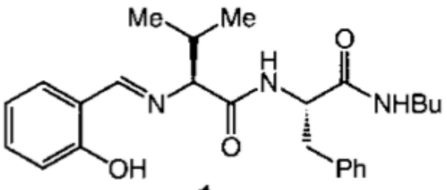


C18 (plasm)-16:0 (PC)

Nature **2011**, *471*, 461

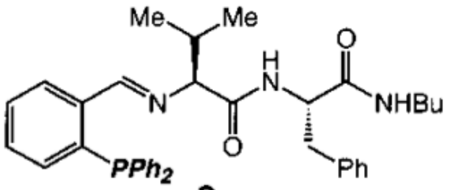
CU-CATALYZED CONJUGATE ADDITIONS

chiral ligand for early transition metals



1

chiral ligand for ***late*** *transition metals*



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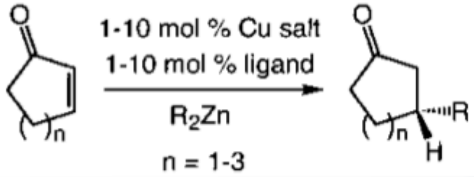
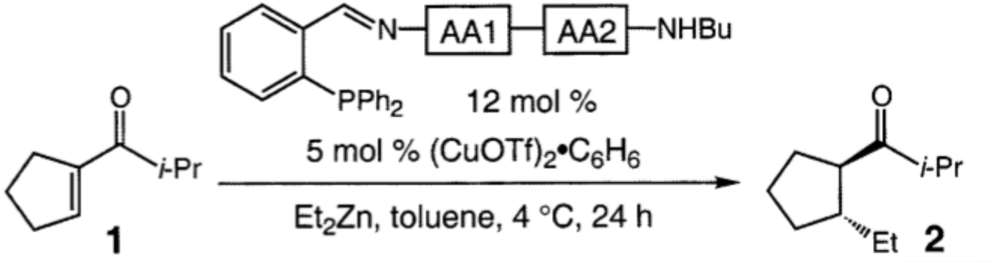
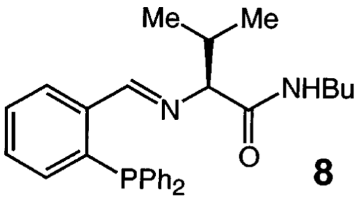


62->98% *ee*

Peptide-based Schiff bases as chiral ligands





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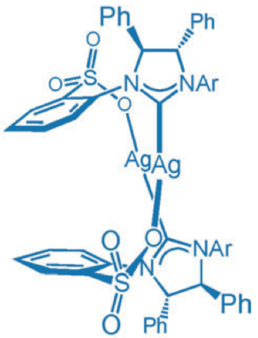
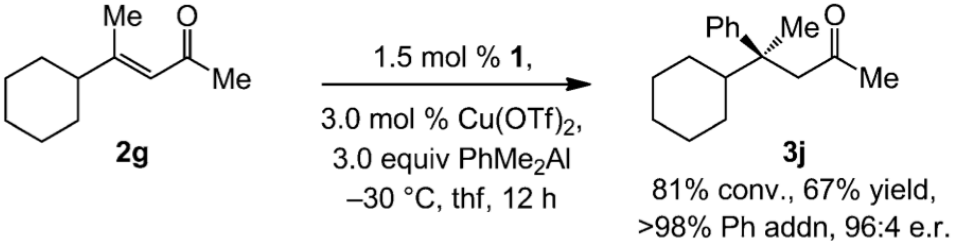


1



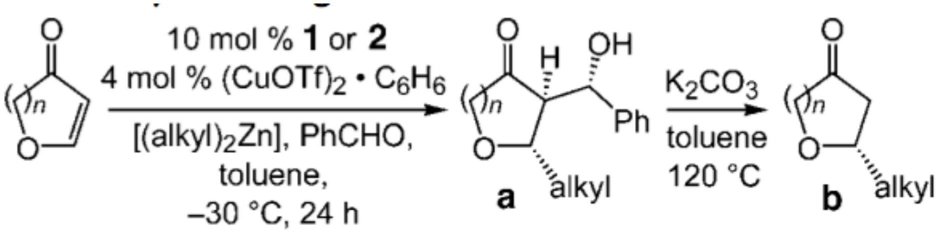
NHC-carbenes as chiral ligands

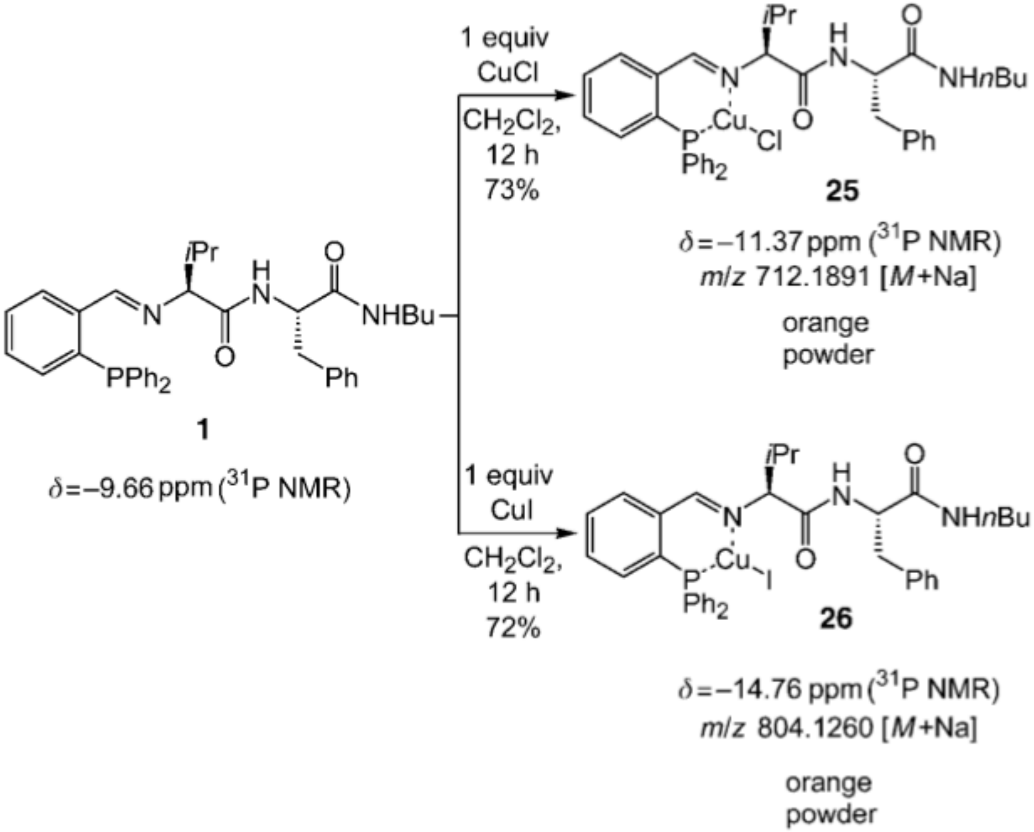
S. J. Degrado, H. Mizutani, A. H. Hoveyda [*J. Am. Chem. Soc.* **2002**, *124*, 13362]

S. J. Degrado, H. Mizutani, A. H. Hoveyda [*J. Am. Chem. Soc.* **2001**, *123*, 755.]

J. A. Dabrowski, M. T. Villaume, A. H. Hoveyda [*Angew. Chem., Int. Ed.* **2013**, *52*, 8156]

CU-CATALYZED CONJUGATE ADDITIONS





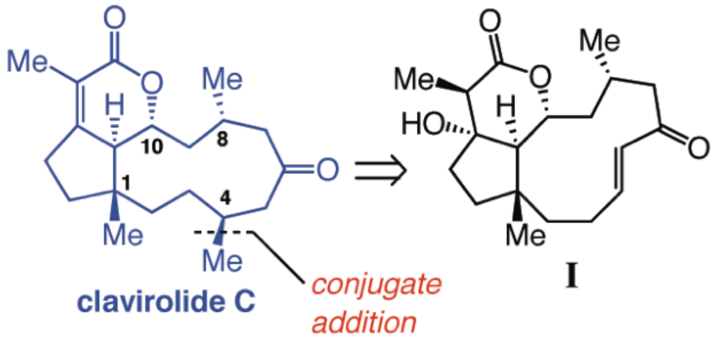
$\delta = -9.66$ ppm (^{31}P NMR)

$\delta = -11.37$ ppm (^{31}P NMR)
m/z 712.1891 [M+Na]
orange powder

$\delta = -14.76$ ppm (^{31}P NMR)
m/z 804.1260 [M+Na]
orange powder

M. K. Brown, S. J. Degrado, A. H. Hoveyda *Angew. Chem., Int. Ed.* **2005**, *44*, 5306

APPLICATION OF CONJUGATE ADDITION IN TOTAL SYNTHESIS

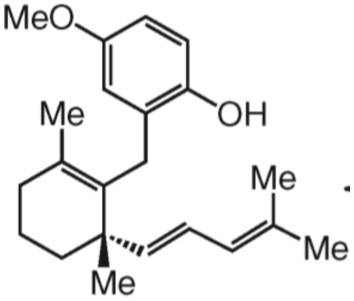


clavirolide C

conjugate addition

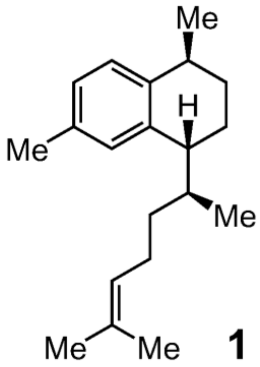
I

J. Am. Chem. Soc. **2008**, *130*, 12904



riccardiphenol B

J. Am. Chem. Soc. **2011**, *133*, 736

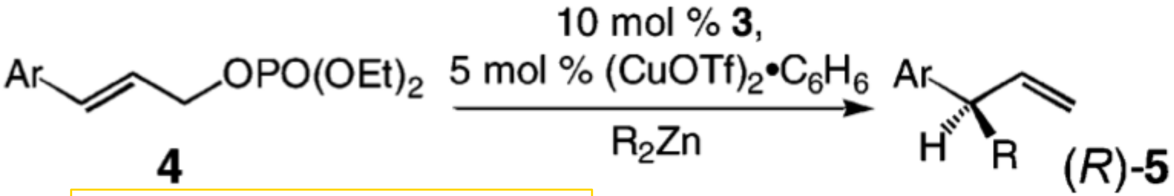


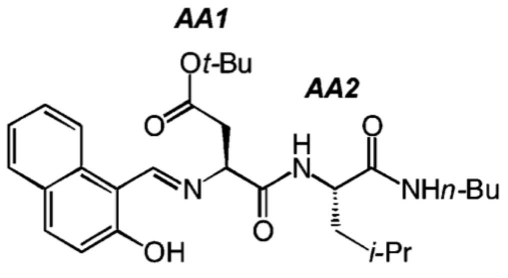
1

erogorgiaene

J. Am. Chem. Soc. **2004**, *126*, 96

ALLYLIC SUBSTITUTION





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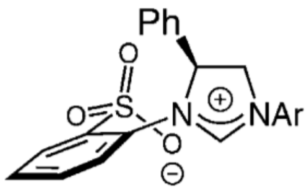
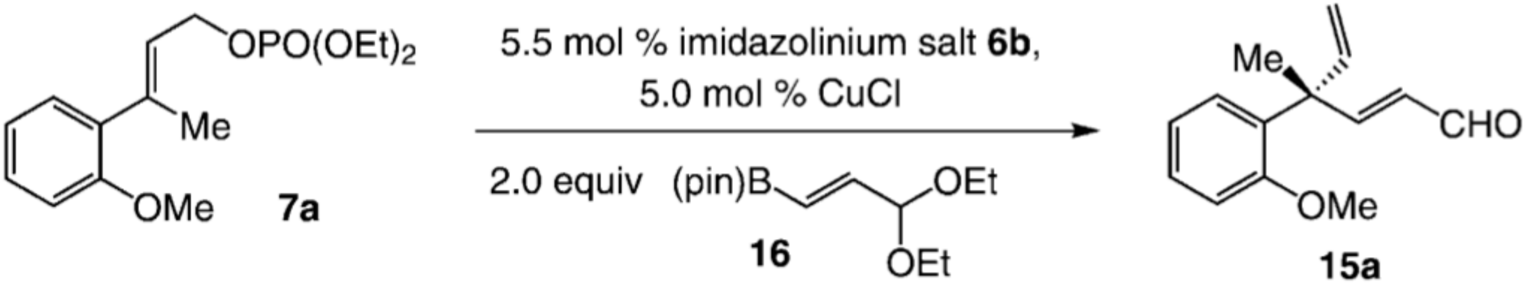


6a Ar = 2,4,6-$(Me)_3C_6H_2$ (Mes)
6b Ar = 2,6-$(iPr)_2C_6H_3$
6c Ar = 2,4,6-$(iPr)_3C_6H_2$



2.0 equiv NaOMe, thf, 60 °C, 24 h;
silica gel, Et_2O, 22 °C, 1.0 h

90% conv., 88% yield,
>98% S_N2', >98:2 e.r.

M. A. Kacprzynski, A. H. Hoveyda *J. Am. Chem. Soc.* **2004**, *126*, 10676
F. Gao, J. L. Carr, A. H. Hoveyda *Angew. Chem., Int. Ed.* **2012**, *51*, 6613

THANKS!