Thomas Group

TEXAS A&M UNIVERSITY

Metal Stereogenicity in Asymmetric Transition Metal Catalysis

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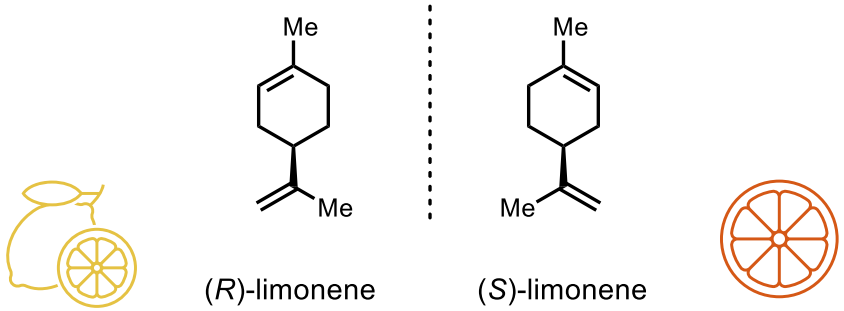
Texas A&M University

04.11.2023

Introduction

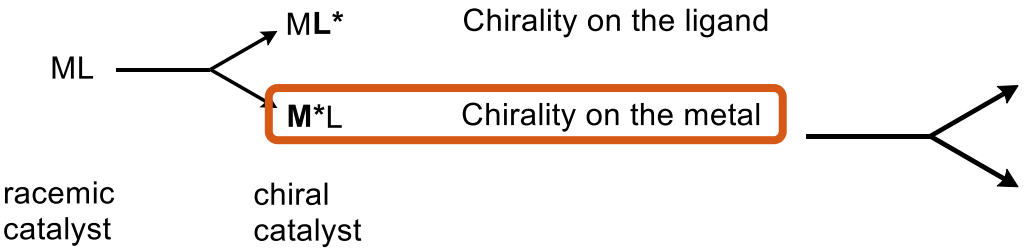
- Stereochemistry matters!



(*R*)-limonene (*S*)-limonene

- Metal-assisted enantioselective catalytic reactions
  - Ability to catalyze a given reaction
  - Potential for asymmetric induction

- Preparation of stereogenic catalysts



chiral ligands

achiral ligands

The Nobel Prize in Chemistry 2001

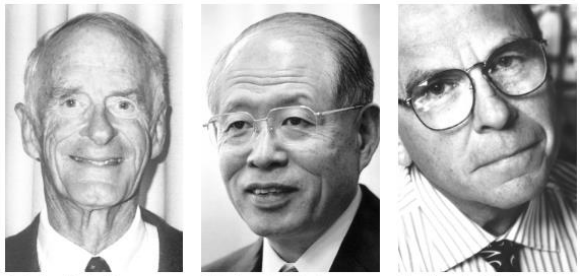


Photo from the Nobel Foundation archive. William S. Knowles

Photo from the Nobel Foundation archive. Ryoji Noyori

Photo from the Nobel Foundation archive. K. Barry Sharpless

Chiral transition-metal complexes

The Nobel Prize in Chemistry 2001

Fontecave, M.; Hamelin, O.; Ménage, S. *Top. Organomet. Chem.* **2005**, *15*, 271–288

Outline

I. Introduction

II. Organometallic refresher

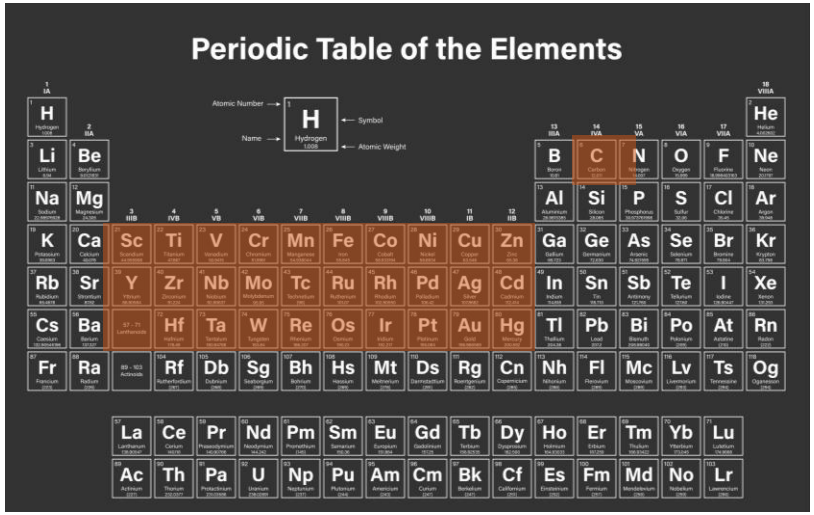
III. Stereogenic-at-Metal Catalysts from *Chiral* Ligands
- Half-sandwich geometry
- Tetracoordinated
- Pentacoordinated
- Hexacoordinated

IV. Stereogenic-at-Metal Catalyst from *Achiral* Ligands
- Tetracoordinated
- Hexacoordinated

V. Conclusion

Organometallic Refresher

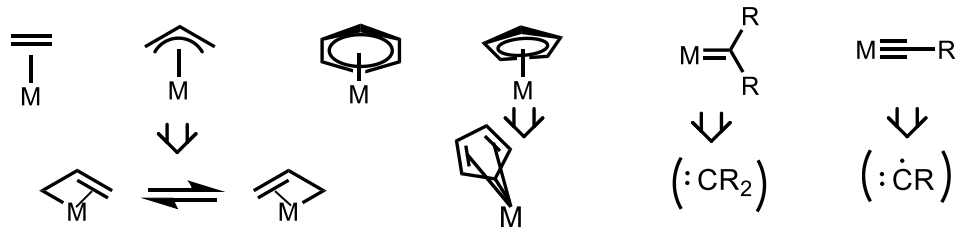
- Organo-transition metal chemistry



- Standard geometries

Octahedral | Tetrahedral | Square planar | Trigonal bipyramidal | Square pyrimidal

- Metal Ligands



π allyl | Cyclopentadienyl (Cp) | alkylidene | alkylidyne

Anslyn, E. V.; Dougherty, D.A. Modern Physical Organic Chemistry University Science Books: Mill Valley, CA, 2006

Outline

I. Introduction

II. Organometallic refresher

III. Stereogenic-at-Metal Catalysts from *Chiral* Ligands

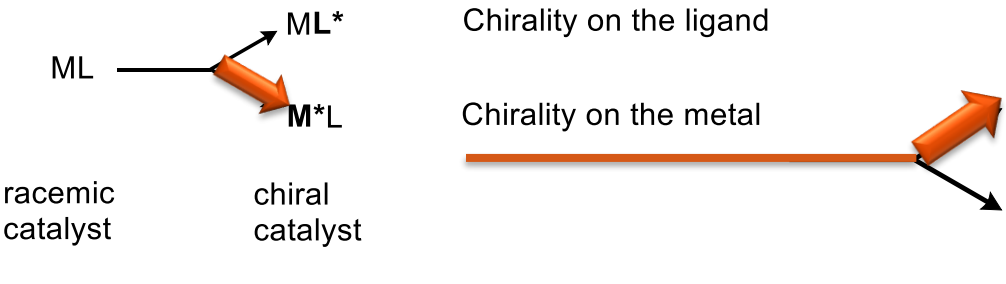
- **Half-sandwich geometry**
- **Tetracoordinated**
- **Pentacoordinated**
- **Hexacoordinated**

IV. Stereogenic-at-Metal Catalyst from *Achiral* Ligands

- Tetracoordinated
- Hexacoordinated

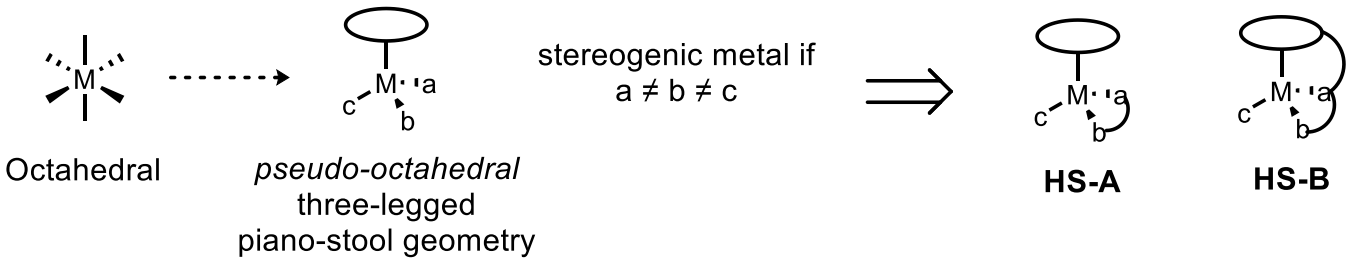
V. Conclusion

*Stereogenic-at-Metal Catalyst from **Chiral** Ligands*



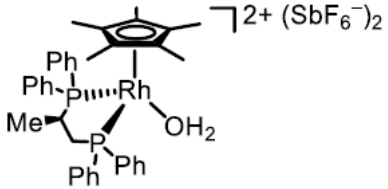
- Half-sandwich
- Tetracoordinated
- Pentacoordinated
- Hexacoordinated

- **Half-sandwich** stereogenic-at-metal catalyst

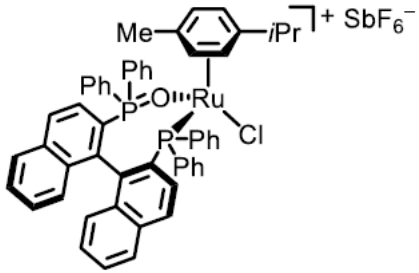


Octahedral

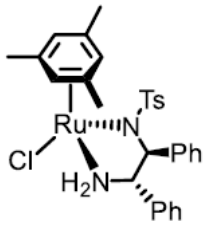
pseudo-octahedral three-legged piano-stool geometry



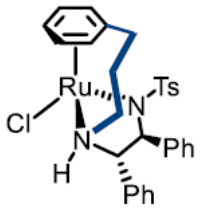
(S_{Rh},*R*)-**M1**



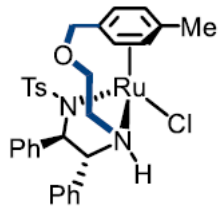
(R_{Ru},a*S*)-**M3**



(R_{Ru},*S*,*S*)-**M4**



(R_{Ru},*S*,*S*)-**M5**

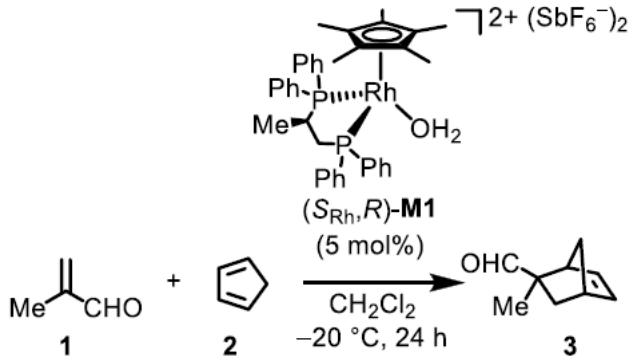


(S_{Ru},*R*,*R*)-**M6**

Steinlandt, P.S.; Zhang, L.; Meggers, E. *Chem. Rev.* **2023**, *123*, 4764−4794

Half-sandwich Stereogenic-at-Metal Catal from Chiral Ligands

- 1996, **Carmona** - Enantioselective Diels-Alder reaction

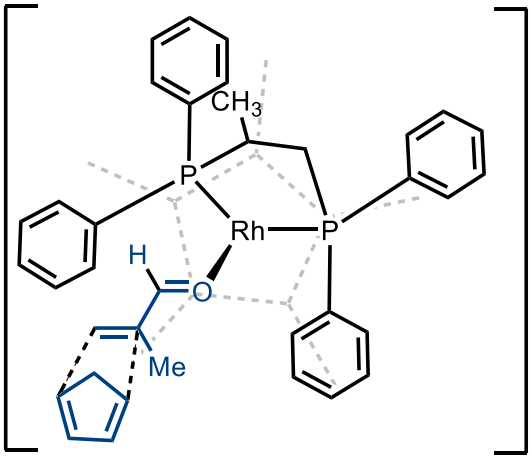


methacrolein cyclopentadiene

Entry	Catalyst (molar ratio)	H/C_5H_5 Metha-crolein	T/°C[a]	t/h	Yield (%)	Isomer ratio (*exo* : *endo*)	Ee[b] (%)
1	—	—	RT	1	0.5	—	—
2	**1** (1%)	1/1	RT	1.5	81	82 : 18	—
3	**1** (1%)	6/1	RT	0.83	99	83 : 17	5 (*R*)
4	**1** (5%)	1/1	RT	3	78	85 : 15	9 (*R*)
5	**1** (5%)	6/1	RT	0.83	97	85 : 15	10 (*R*)
6	**1** (5%)	6/1	−20	144	65	94.5 : 5.5	28 (*R*)
7	**1** (5%)	20/1	−20	48	88	93 : 7	27 (*R*)
8	**1** (10%)	6/1	−20	72	77	95 : 5	46 (*R*)
9	**1** (10%)	6/1	−50	168	49	98 : 2	52 (*R*)
10	**2** (5%)	6/1	−20	24	87	97.5 : 2.5	62 (*R*)
11	**2** (10%)	6/1	−20	3	65	97 : 3	60 (*R*)
12	**2** (10%)	6/1	−50	27	73	98 : 2	71 (*R*)

[a] RT = room temp. [b] Absolute configuration at C_2.

Model of the transition state



Initial selectivity

Increase on catalyst loading

Change in temperature

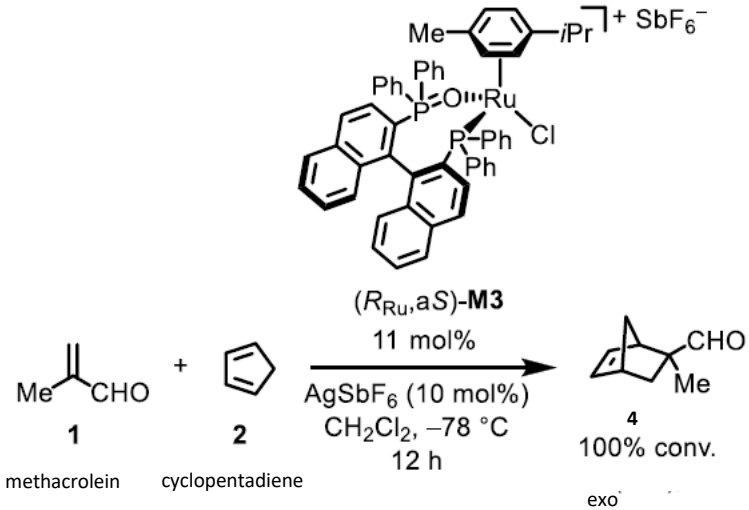
Change SbF_6^- derivative instead of BF_4^-

A = BF4 **(I)**, SbF6 **(2)]**

Carmona, D.; Cativiela, C.; García-Correas, R.; Lahoz, F. J.; Lamata, M. P.; López, J. A. Lopez-Ram De Víu, M. P.; Oro, L. A.; José, E. S.; Viguri, F. *Chem. Commun.* **1996**, 1247−1248.

Half-sandwich Stereogenic-at-Metal Catal from Chiral Ligands

- 2001, **Faller** - Enantioselective Diels-Alder reaction

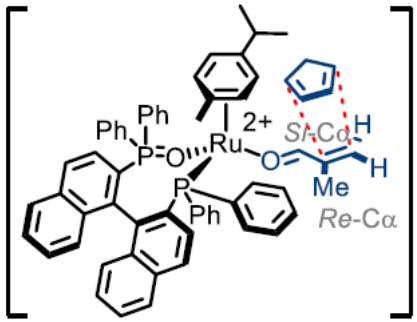


entry (R)	catalyst[a] loading (%)	temp (°C)	product	conversion (%)	de (%)	ee (%) [config]	
1 (Me)	10	-78	**4**	100	93	99 [*S*-(+)]	2h
2 (Me)	1	-78	**4**	100	91	92 [*S*-(+)]	12h
3 (Me)	10	-24	**4**	100	99	94 [S−(+)]	
4 (Me)	1	-24	**4**	100	95	85 [*S*-(+)]	

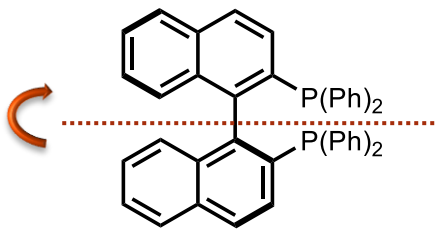
Ru center was on longer stereogenic

entry (ligand)[a]	temp (°C)	product	conversion (%)	de (%)	ee (%) [config]
1 (BINAP)	−24	**4**	100	93	50 [*R*-(−)]
2 (BINAP)	−78	**4**	100	82	19 [*R*-(−)]
3 (TolBINAP)	−24	**4**	19	99	26 [*R*-(−)]
4 (TolBINAP)	−78	**4**	15	99	24 [*R*-(−)]

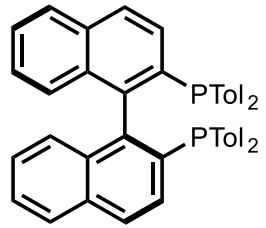
Model of the transition state



BINAP



TolBINAP

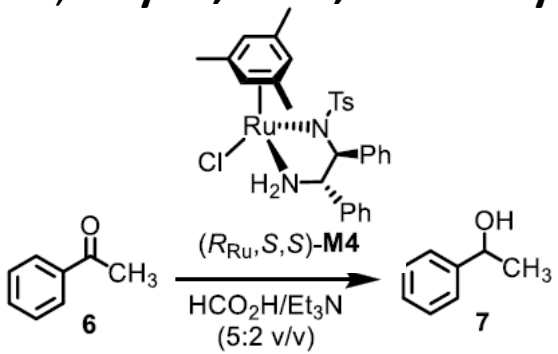


C_2 symmetry

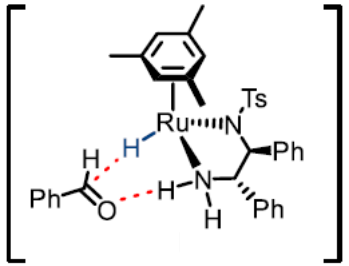
Faller, J. W.; Grimmond, B. J.; D'Alliessi, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 2525-2529

Half-sandwich Stereogenic-at-Metal Catal from Chiral Ligands

- 1995, **Noyori, Wills, and Ikariya** - Asymmetric Hydrogenation

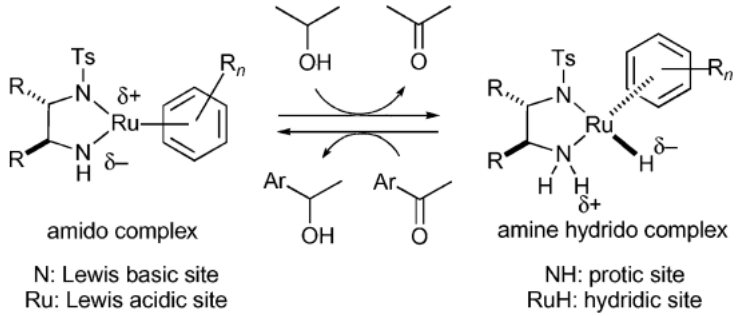


Model of the transition state

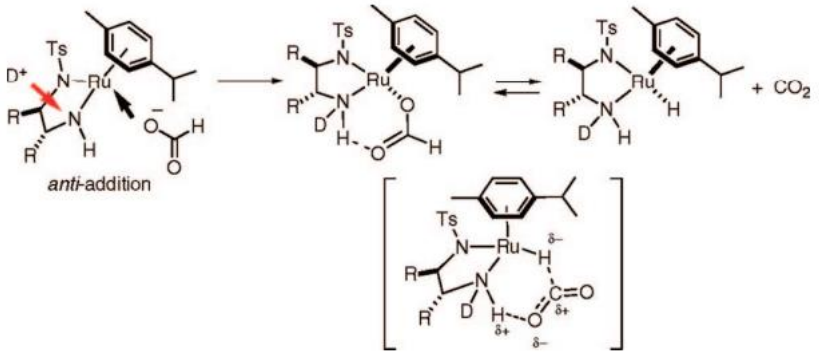


- TsDPEN = 1,2-diphenyl ethylene amine
- Bifunctional catalysis: H-donor and H+ donor
- Stereogenic carbons of ligand are secluded

- Asymmetric Hydrogenation



- Possible Mechanism with Formic Acid



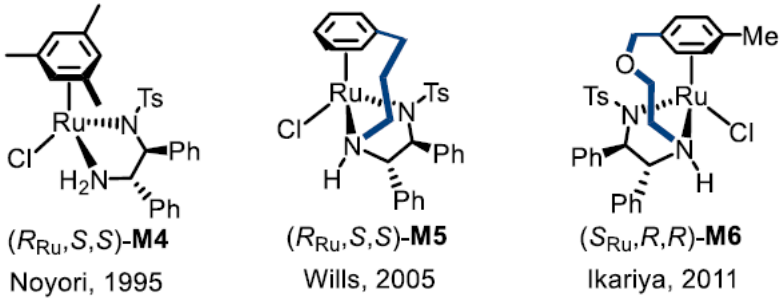
Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522

Ikariya, T.; Murata, K.; Noyori, R. *Org. Biomol. Chem.* **2006**, *4*, 393−406

Ikariya, T.; Blacker, A. J. *Acc. Chem. Res.* **2007**, *40*, 1300–1308

Half-sandwich Stereogenic-at-Metal Catal from Chiral Ligands

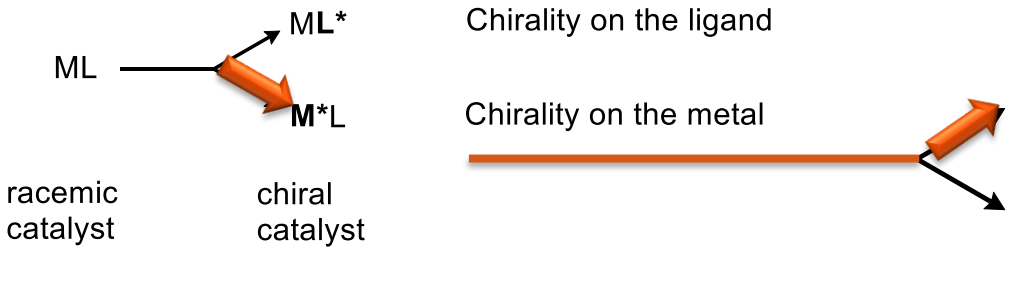
- 1995, **Noyori, Wills, and Ikariya** - Asymmetric Hydrogenation



M4: 0.5 mol% cat, 28 °C, 20 h, >99% yield, 98% ee (*S*)
M5: 0.01 mol% cat, 40 °C, 79 h, 98% conv., 96% ee (*S*)
M6: 0.0033 mol% cat, 60 °C, 96 h, 95% yield, 97% ee (*R*)

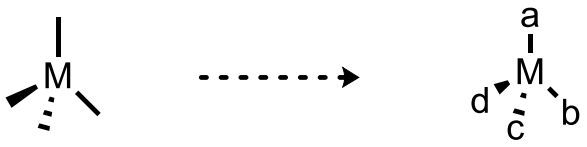
Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521−2522
Hannedouche, J.; Clarkson, G. J.; Wills, M. *J. Am. Chem. Soc.* **2004**, *126*, 986−987
Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* **2011**, *133*, 14960−14963

Stereogenic-at-Metal Catalyst from **Chiral** Ligands



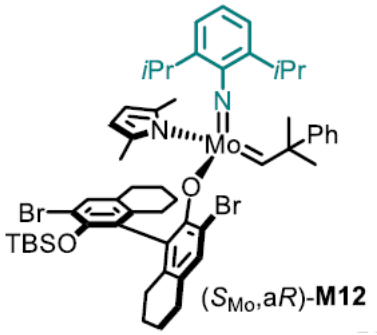
- Half-sandwich
- Tetracoordinated
- Pentacoordinated
- Hexacoordinated

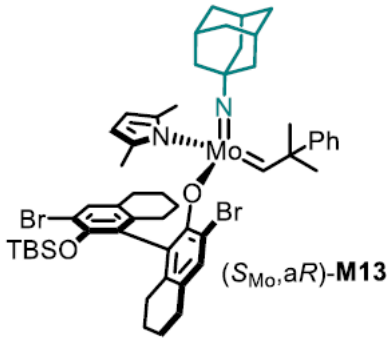
- **Tetracoordinated** stereogenic-at-metal catalyst



Tetrahedral

stereogenic metal if
a ≠ b ≠ c ≠ d

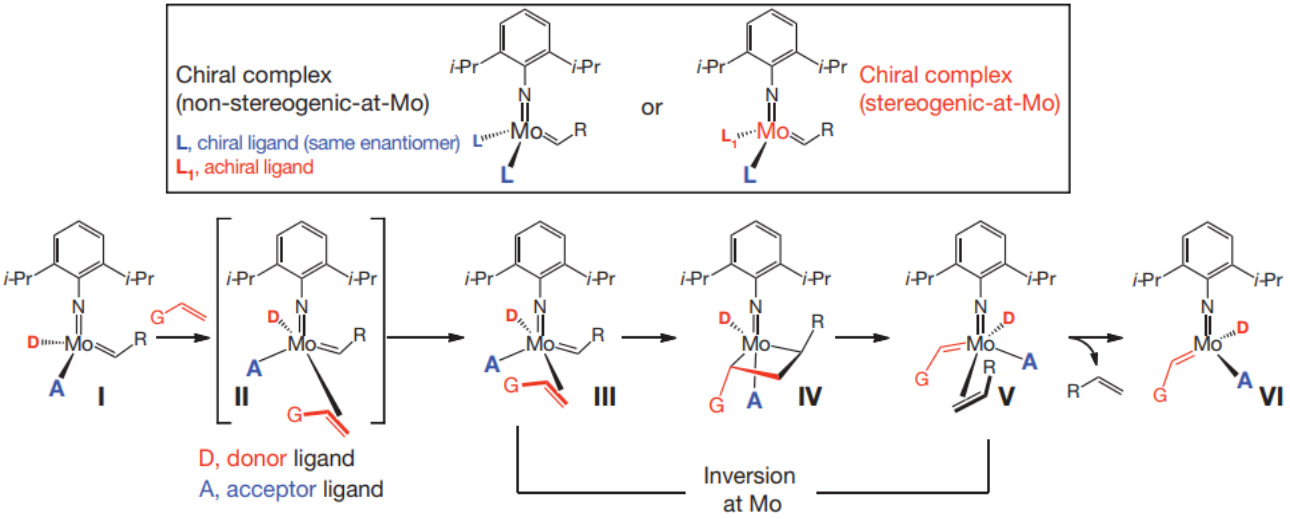




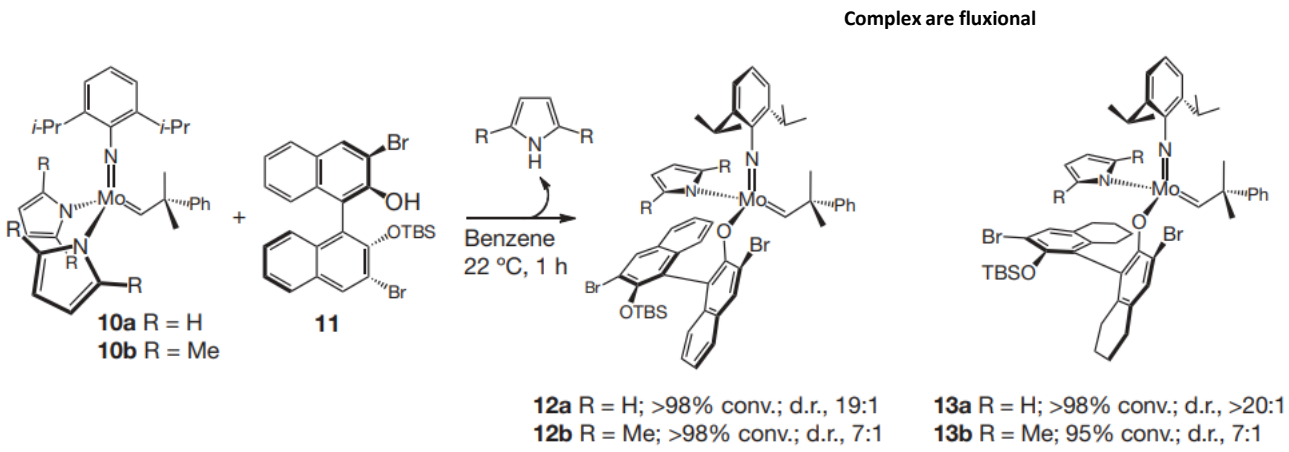
Steinlandt, P.S.; Zhang, L.; Meggers, E. *Chem. Rev.* **2023**, *123*, 4764−4794

Tetracoordinated Stereogenic-at-Metal Catal - Chiral Ligands

- Rational ligand design rational



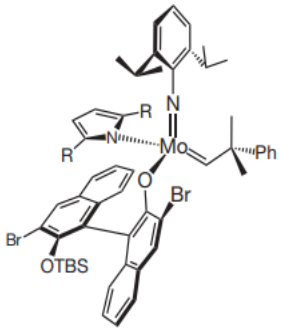
- Diastereoselective synthesis of stereogenic-at-Mo complex



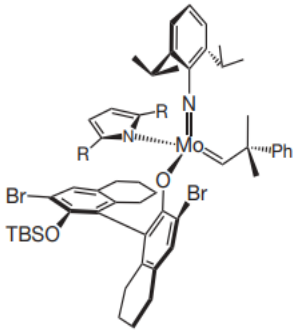
Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933–937

Tetracoordinated Stereogenic-at-Metal Catal - Chiral Ligands

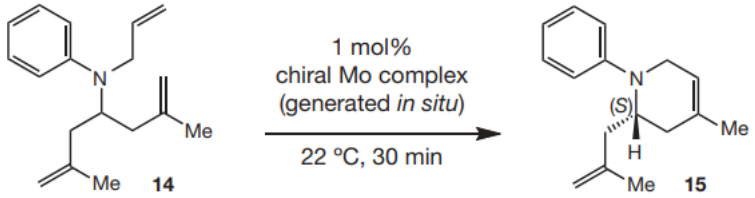
- Initial examination for Ring Closing Metathesis



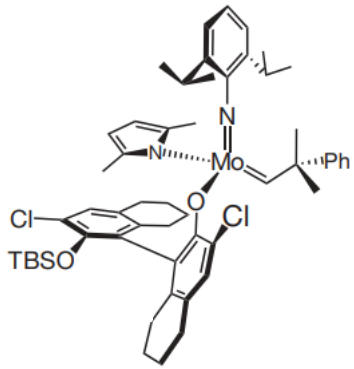
12a R = H; >98% conv.; d.r., 19:1
12b R = Me; >98% conv.; d.r., 7:1



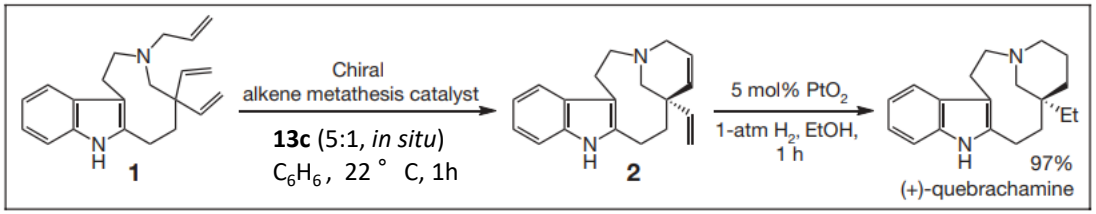
13a R = H; >98% conv.; d.r., >20:1
13b R = Me; 95% conv.; d.r., 7:1



Entry no.	Chiral complex	Conv. (%)*; Yield (%)†	e.r.‡	e.e. (%)§; Config.‖	
1	**12a**	50; ND	41:59	18; (*R*)	
2	**12b**	>98; 91	75:25	50; (*S*)	Complete conversion
3	**13a**	54; ND	43.5:56.5	13; (*R*)	
4	**13b**	>98; 91	96.5:3.5	93; (*S*)	Complete conversion



13c



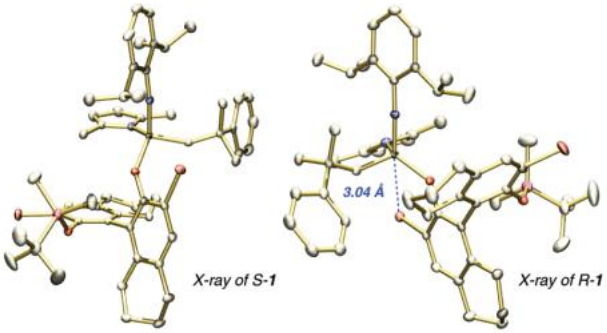
98% conv., 84% yield
96% e.e. (e.r., 98:2)

adrenergic blocker
high block pressure

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

Tetracoordinated Stereogenic-at-Metal Catal - Chiral Ligands

- X-ray crystal structure

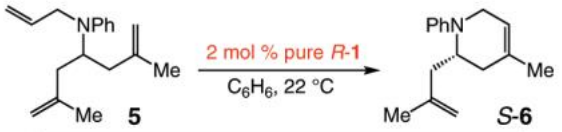


SMo ***R***Mo

Approach of an alkene

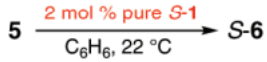
- S-1 trans to the pyrrolide7 is hindered by a Br
- R-1 blocked by the larger tetrahydronaphthyl ring of the aryloxide
- Mo-Br interaction

- Time Dependence of Conversion and Selectivity in Catalytic RCM



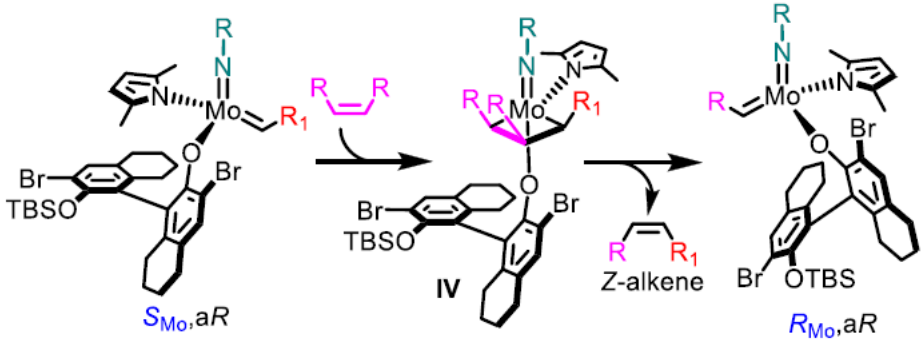
entry	time (min)	conv (%)[b]	er (*S*:*R*)[c]
1	30	5	85.5:14.5
2	45	15	94:6
3	60	23	95:5
4	180	>98	96:4

lower rate
Same enantiomer



entry	time (min)	conv (%)[b]	er (*S*:*R*)[c]
1	2	4	76:24
2	2.5	7	87.5:12.5
3	3	13	93.5:6.5
4	20	>98	96.5:3.5

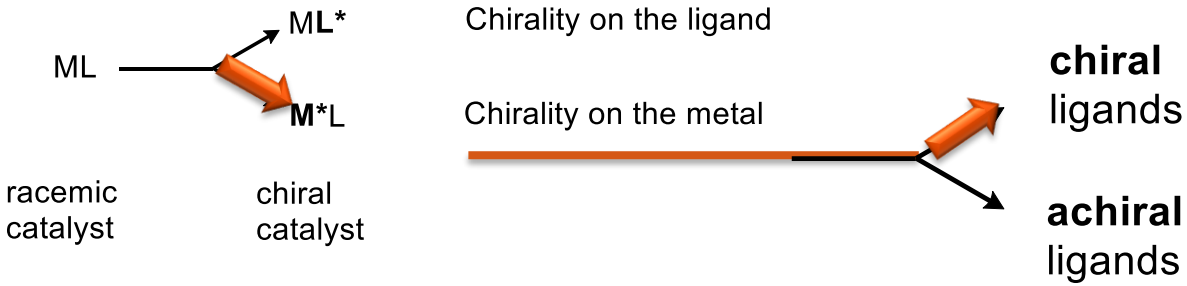
- Inversion of Mo stereocenter promoted by metathesis reaction



- Isomerization is faster than ring closure

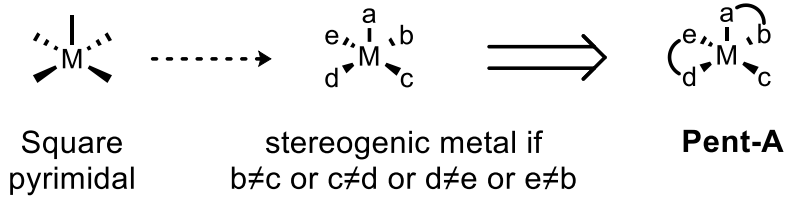
Meek, S. J.; Malcolmson, S. J.; Li, B.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16407−16409

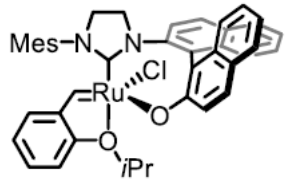
*Stereogenic-at-Metal Catalyst from **Chiral** Ligands*

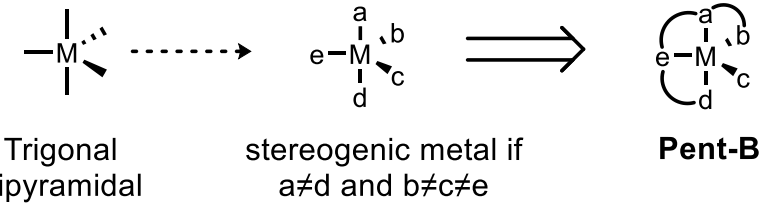


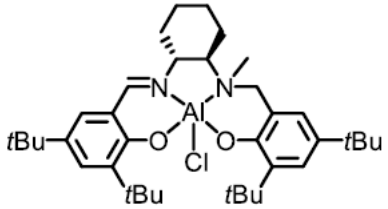
- Half-sandwich
- Tetracoordinated
- Pentacoordinated
- Hexacoordinated

- **Pentacoordinated** stereogenic-at-metal catalyst





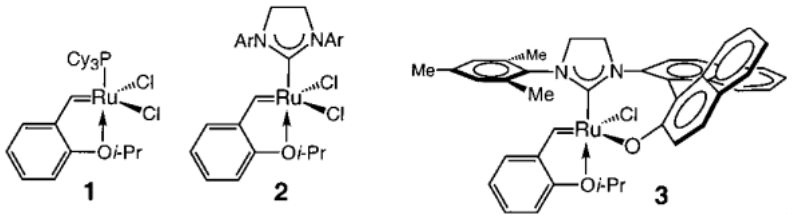




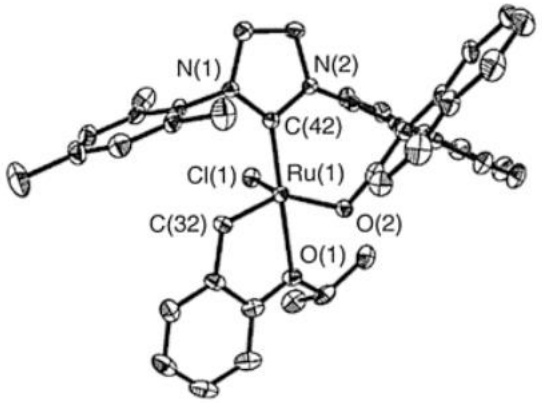
Steinlandt, P.S.; Zhang, L.; Meggers, E. *Chem. Rev.* **2023**, *123*, 4764−4794

Pentacoordinated Stereogenic-at-Metal Catal - Chiral Ligands

- Asymmetric Ring-Opening Metathesis/ Cross-Metathesis

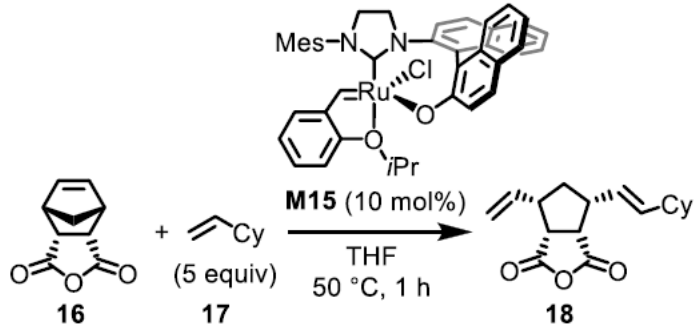


ORTEP diagram of complex 3



- Distorted square pyramidal coordination geometry
- Stereogenic at Ru-center

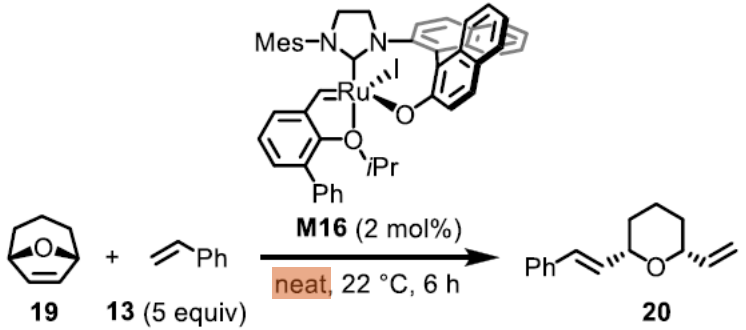
a.) Asymmetric ROCM with tricyclic norbornene



Tricycli nornornene

entry	R		temp (°C); time (h)	conv (%)[b]; yield (%)[c]	recov. cat. (%)[c]	trans:cis[b]	ee (%)[d]
1	Ph	**a**	50; 1.0	>98; 71	96	>98: 2	80
2	*n*-C_5H_{11}	**b**	50; 1.5	>98; 57	92	>98: 2	>98
3	Cy	**c**	50; 1.0	>98; 60	88	>98: 2	>98

b.) Asymmetric ROCM with oxabicyclic olefin



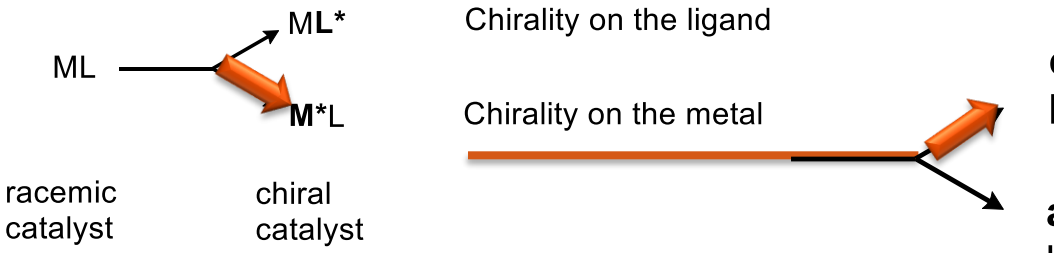
Cl >98% conv., 68% yield, 98% ee

I >98% conv., 72% yield, 93% ee

J Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954−4955

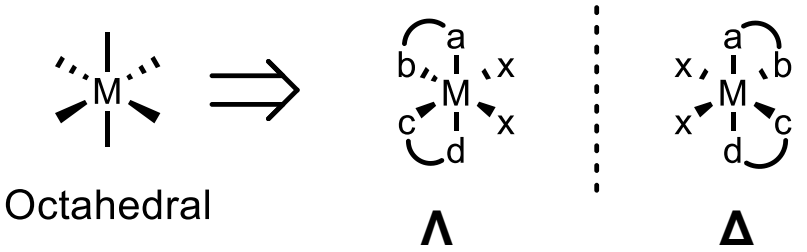
Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288−12290

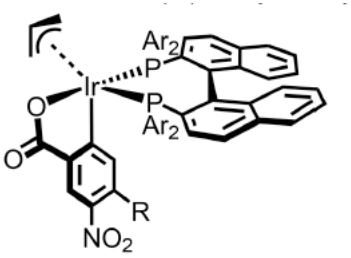
*Stereogenic-at-Metal Catalyst from **Chiral** Ligands*

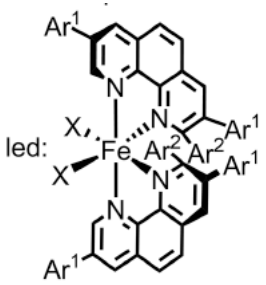


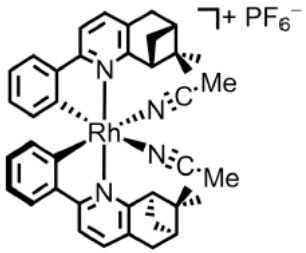
- Half-sandwich
- Tetracoordinated
- Pentacoordinated
- Hexacoordinated

- **Hexacoordinated** stereogenic-at-metal catalyst
  Helical arrangement of bidentate ligands





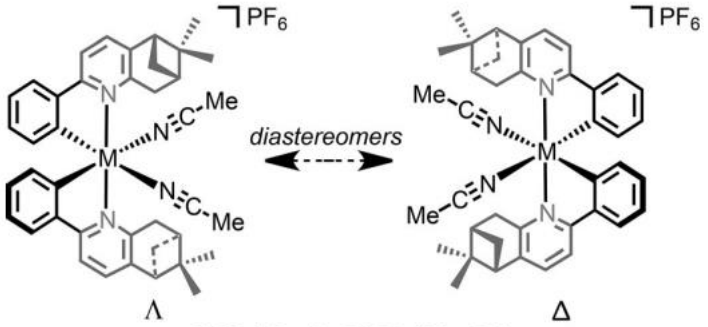




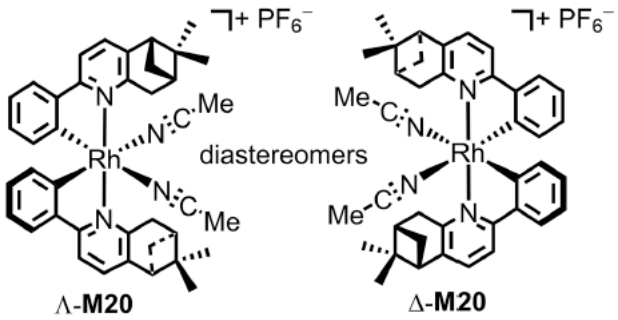
Steinlandt, P.S.; Zhang, L.; Meggers, E. *Chem. Rev.* **2023**, *123*, 4764−4794

Hexacoordinated Stereogenic-at-Metal Catal - Chiral Ligands

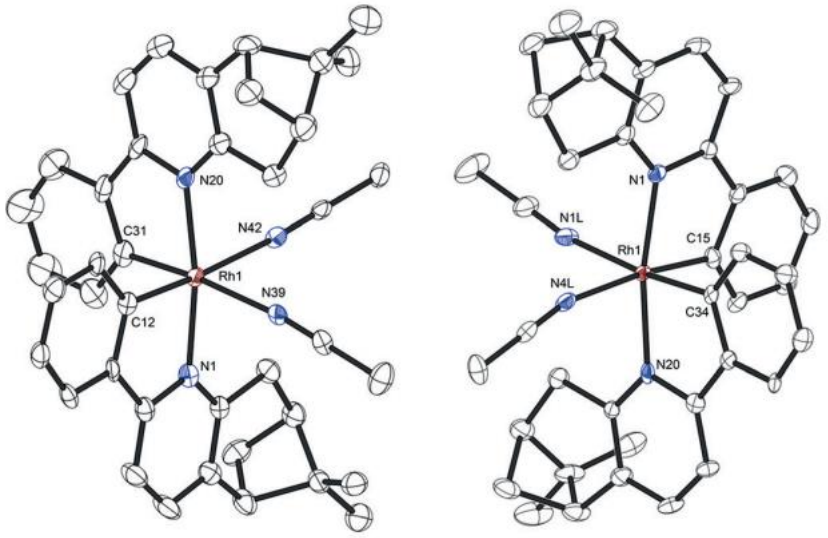
- Meggers' pinene-based bis-cyclometalated Rh(II) catalyst



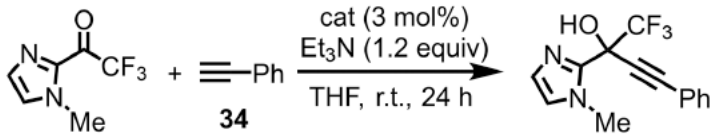
IrPP (M = Ir), **RhPP** (M = Rh)



Λ-**M20** Δ-**M20**



Λ-**RhPP** Δ-**RhPP**

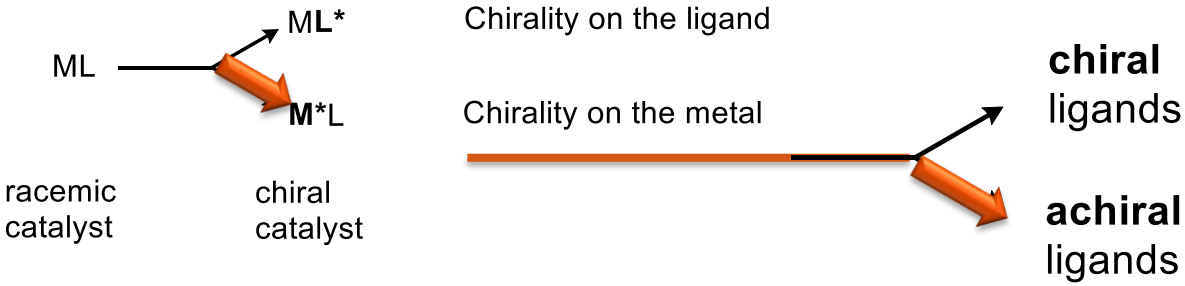


Δ-**M20**: 92% yield, >99% ee (*R*)
Λ-**M20**: 90% yield, >99% ee (*S*)

- Asymmetric induction is controlled by:
  - Metal-centered configuration
  - Overall topology of metal complex

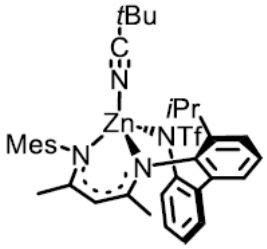
Zheng, Y.; Harms, K.; Zhang, L.; Meggers, E. *Chem. Eur. J.* **2016**, *22*, 11977−11981

*Stereogenic-at-Metal Catalyst from **Achiral** Ligands*

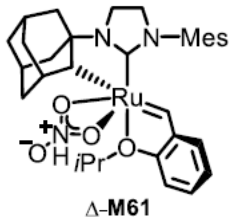


- **Chiral-at-metal**
  - Tetracoordinated
  - Hexacoordinated

- Tetracoordinated chiral-at-metal catalyst



- Hexacoordinated chiral-at-metal catalyst

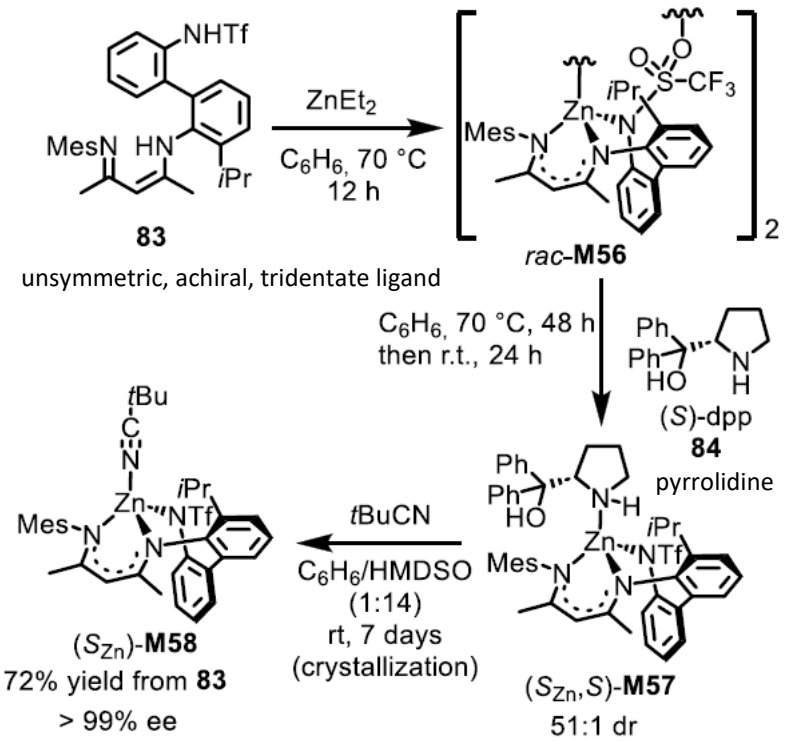


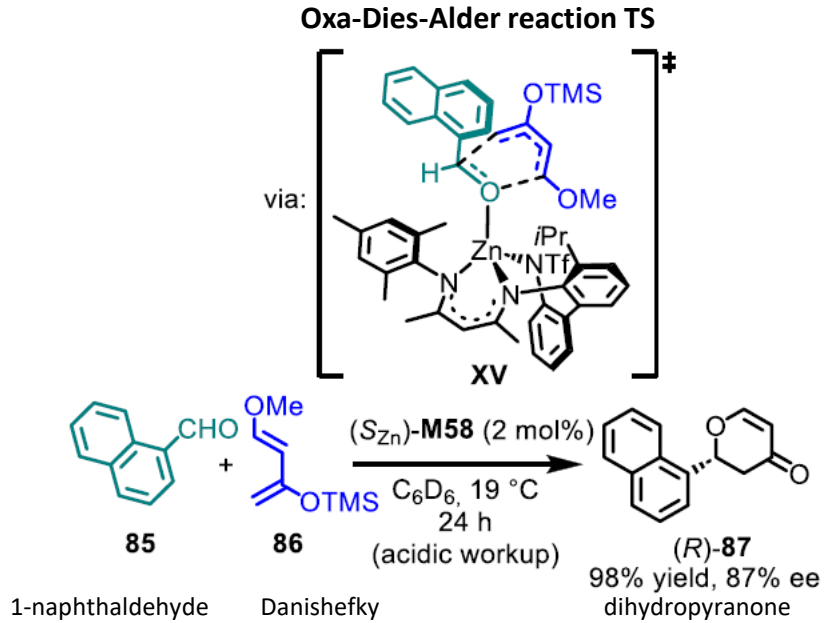
Δ-**M61**

Steinlandt, P.S.; Zhang, L.; Meggers, E. *Chem. Rev.* **2023**, *123*, 4764−4794

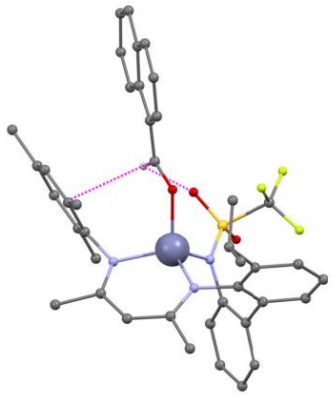
*Tetracoordinated Chiral-at-Metal Catal from **Achiral** Ligands*

- Auxiliary-mediated synthesis of chiral-at-zinc





- Single crystal X-ray structure of R_{Zn}

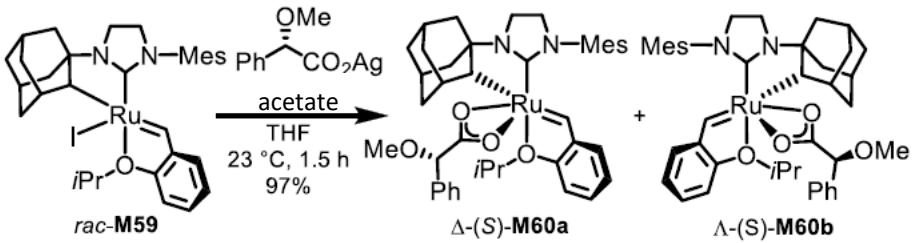


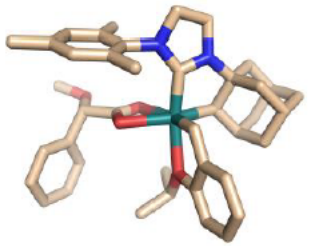
- Single enantiomer
- Stereogeninc Zn center
- Four different coordinating groups
- Biphenyl backbone – axial chirality

Endo, K.; Liu, Y.; Ube, H.; Nagata, K.; Shionoya, M. *Nat. Commun.* **2020**, *11*, 6263
Steinlandt, P.S.; Zhang, L.; Meggers, E. *Chem. Rev.* **2023**, *123*, 4764−4794

*Hexacoordinated Chiral-at-Metal Catal from **Achiral** Ligands*

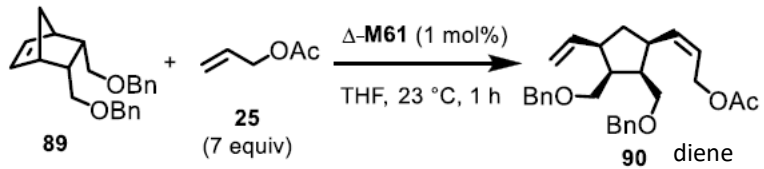
- Synthesis of cyclometalated chiral-at-Ru complex





X-ray structure of Δ-(*S*)-**M60a**

- Ring Opening Metathesis

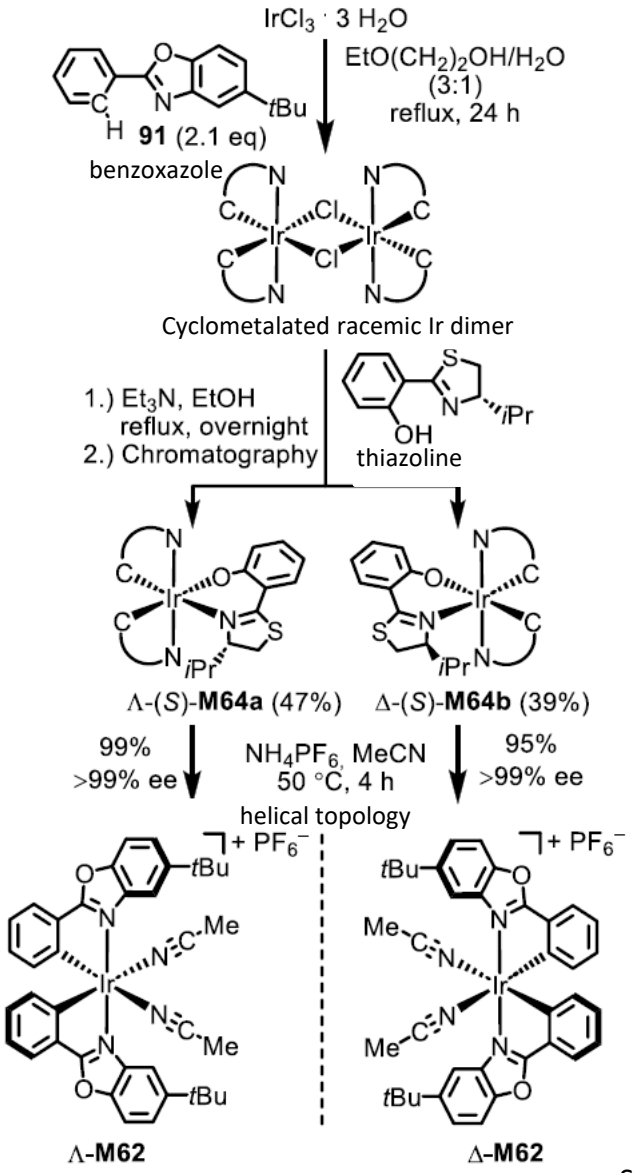


Hartung, J.; Grubbs, R. H. *J. Am. Chem. Soc.* **2013**, *135*, 10183−10185

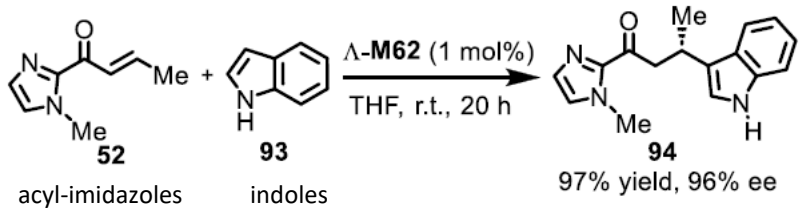
Steinlandt, P.S.; Zhang, L.; Meggers, E. *Chem. Rev.* **2023**, *123*, 4764−4794

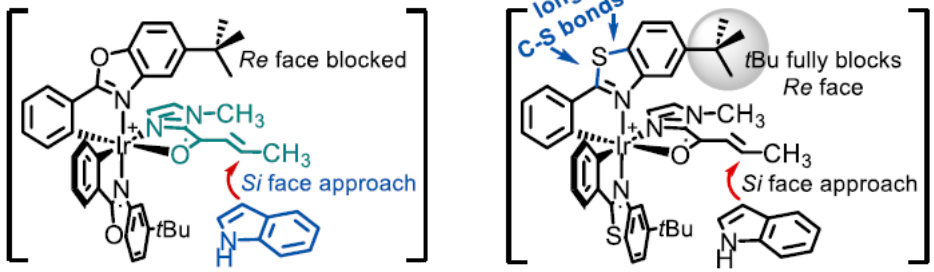
*Hexacoordinated Chiral-at-Metal Catal from **Achiral** Ligands*

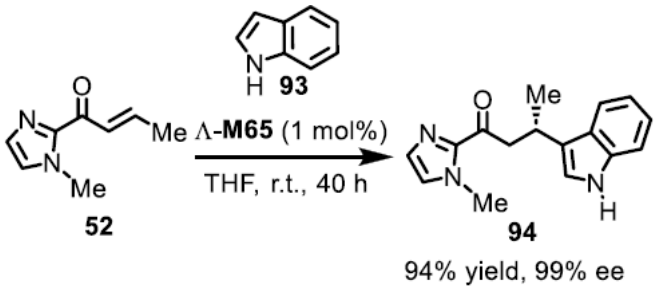
- Chiral auxiliary-mediated synthesis



- Enantioselective conjugate addition





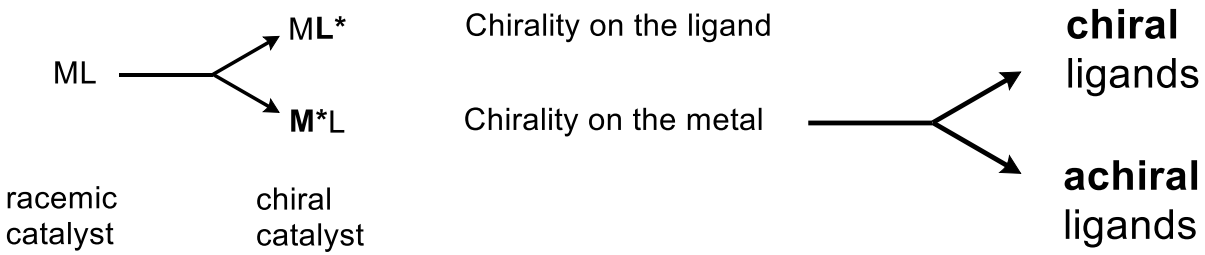


Huo, H.; Fu, C.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.* **2014**, *136*, 2990−2993

Shen,X.; Huo, H.; Wang, C.; Zhang,B.; Harms,K.; Meggers, E. *Chem.Eur. J.* **2015**, *21*, 9720−9726

Conclusion

- Preparation of metal stereogenicity



Thank you for your attention!

Thoughts or questions?