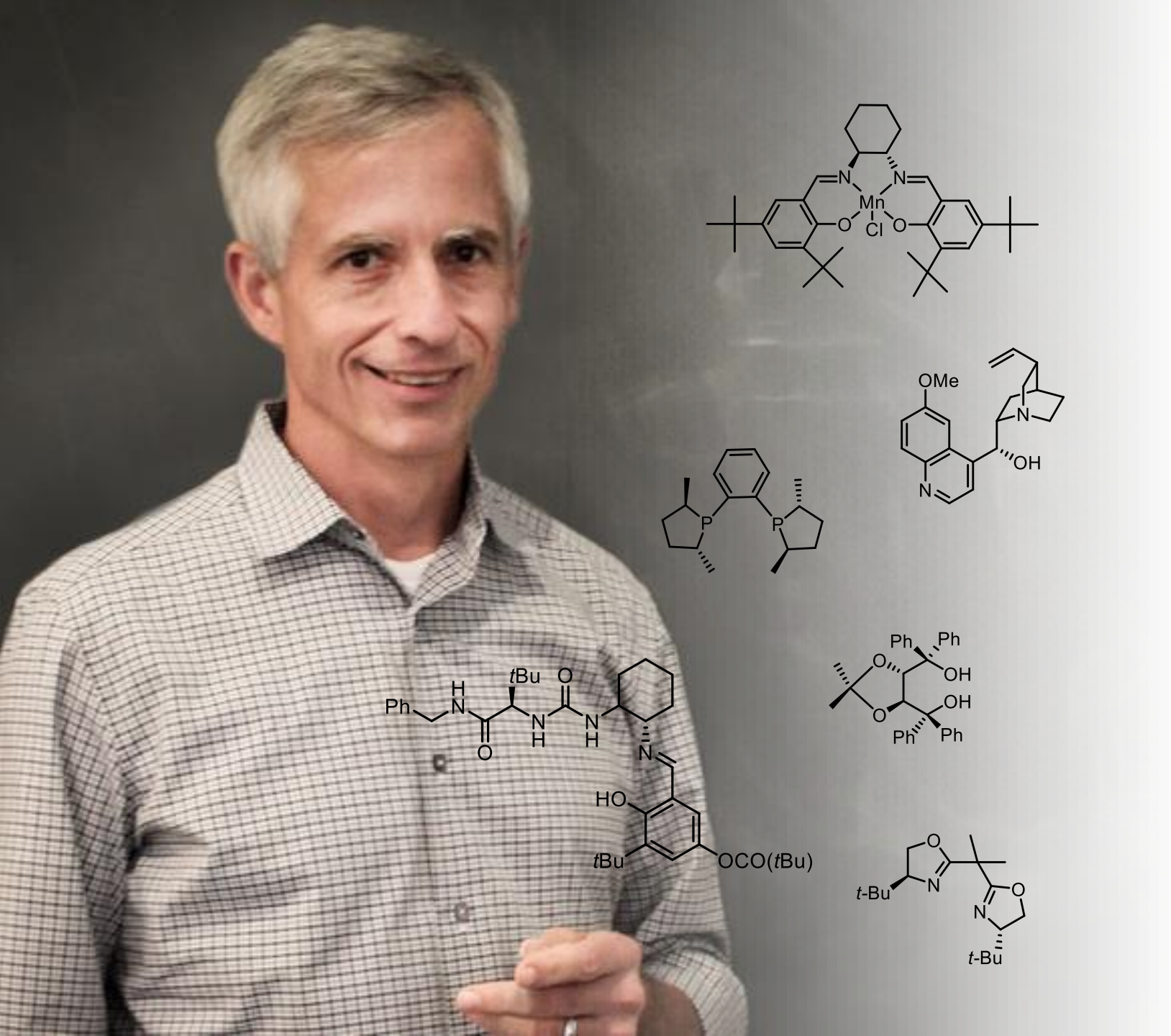


Career Summary of Prof. Eric N. Jacobsen

Jisoo Woo

Levin Group Meeting

8/5/2020

A Life Dedicated To Asymmetric Synthesis

- **February 22, 1960**: Born in New York, NY
- **1978-1982:** B.S. in Chemistry from NYU

  Advisor: *Prof. Yorke E. Rhodes*
- **1982-1986:** Ph.D. from UC Berkeley

  Advisor: *Prof. Robert G. Bergman*
- **1986-1988:** NIH Postdoctoral Fellow at MIT

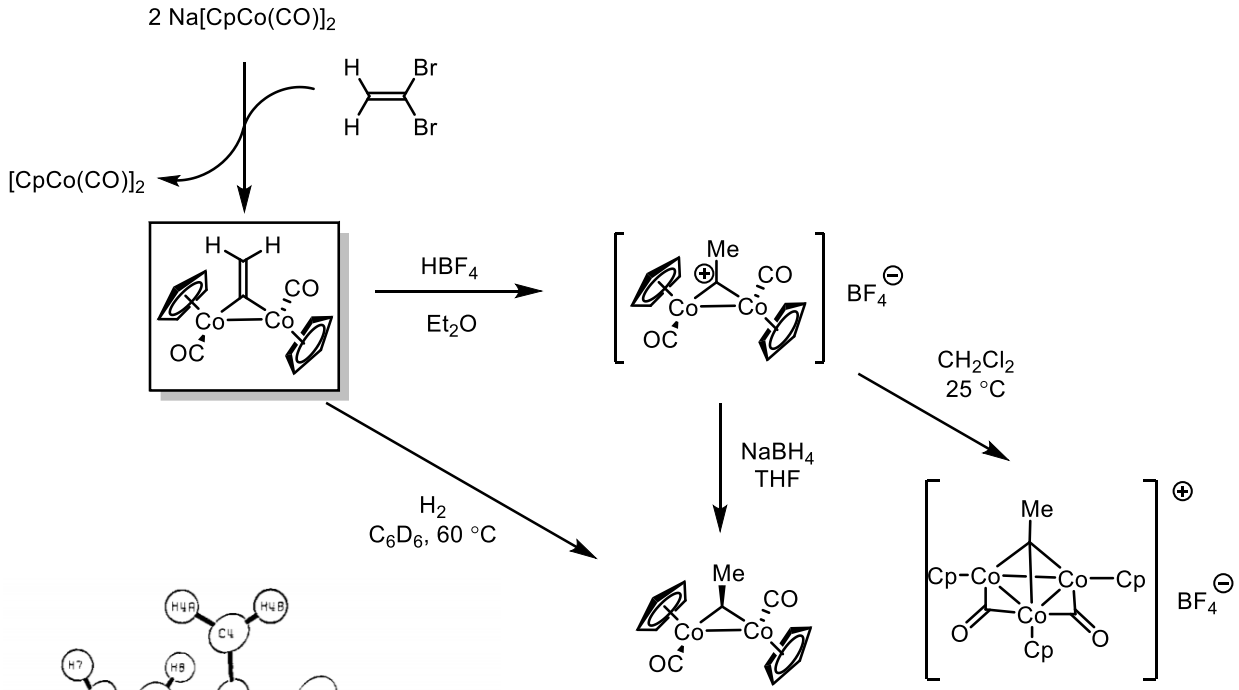
  Advisor: *Prof. K. Barry Sharpless*
- **1988-1993:** Assistant & Associate Professor at UIUC
- **1933-present:** Professor at Harvard University

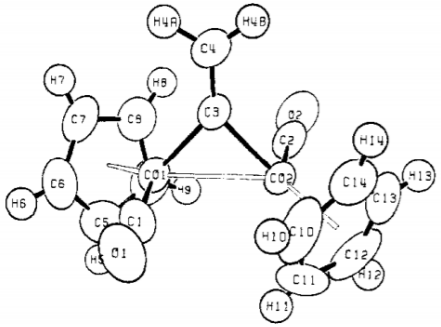
Prof. Jacobsen and his daughter, Emilia, at a reunion of the Bergman Group

Bergman, R. G. *Adv. Synth. Catal.* **2020,** *362,* 279-280.

Ph.D. Work: Bridging Vinylidenecobalt Complex

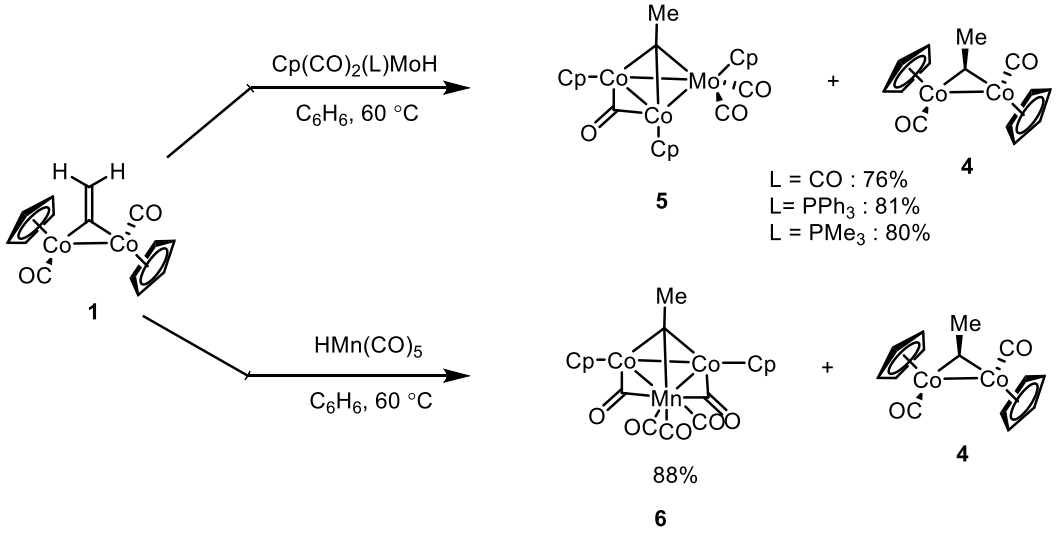
- **Synthesis & Reactivity**

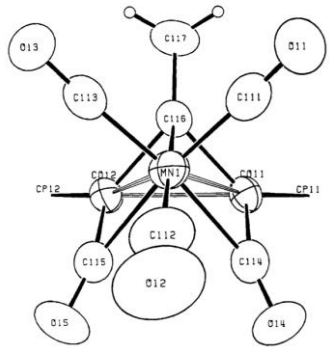




Jacobsen, E. N.; Bergman, R. G. *Organometallics* **1984**, *3*, 329.
Jacobsen, E. N.; Bergman, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 2023.

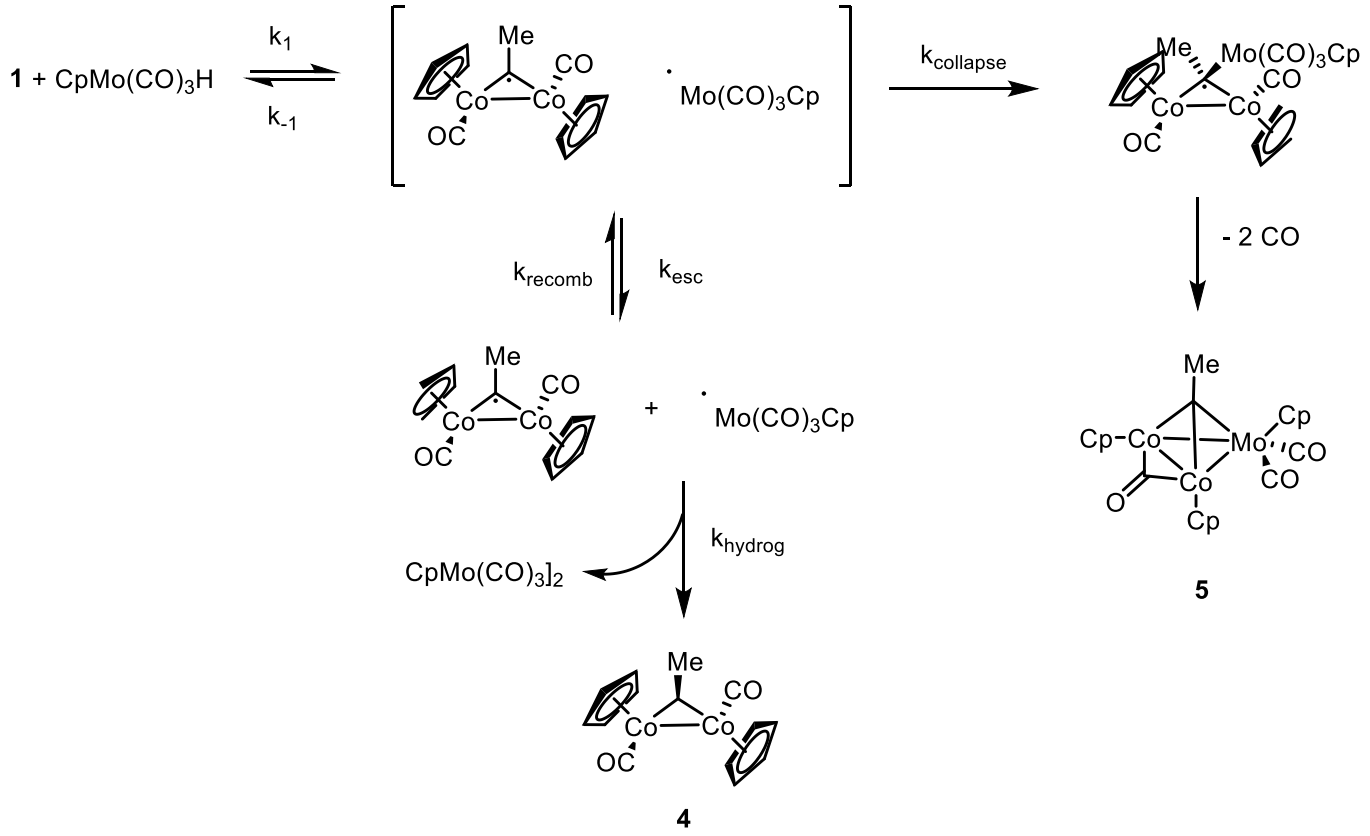
- **Heteronuclear Co/Mo Cluster**





Ph.D. Work: Bridging Vinylidenecobalt Complex

- **Mechanistic Study of Cluster-forming Reactions**



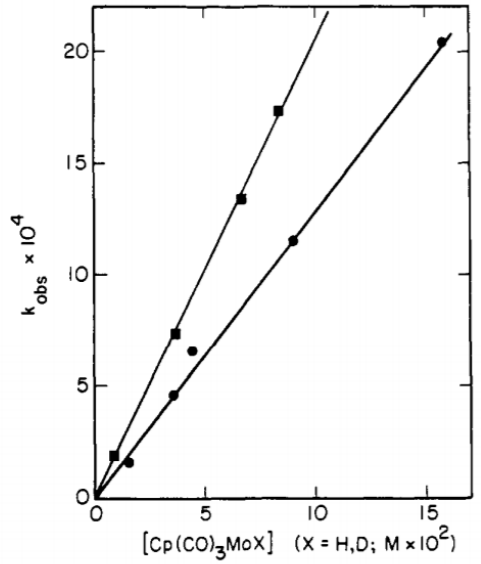


Figure 4. k_{obsd} vs. concentration plot, for the reaction of **1** with $CpMo(CO)_3X$ (X = H, D) at 60 °C, (●) X = H, (■) X = D.

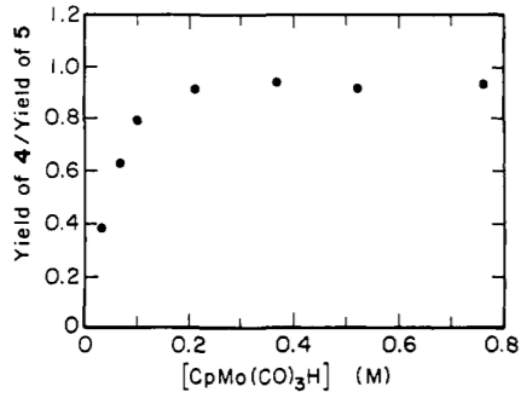
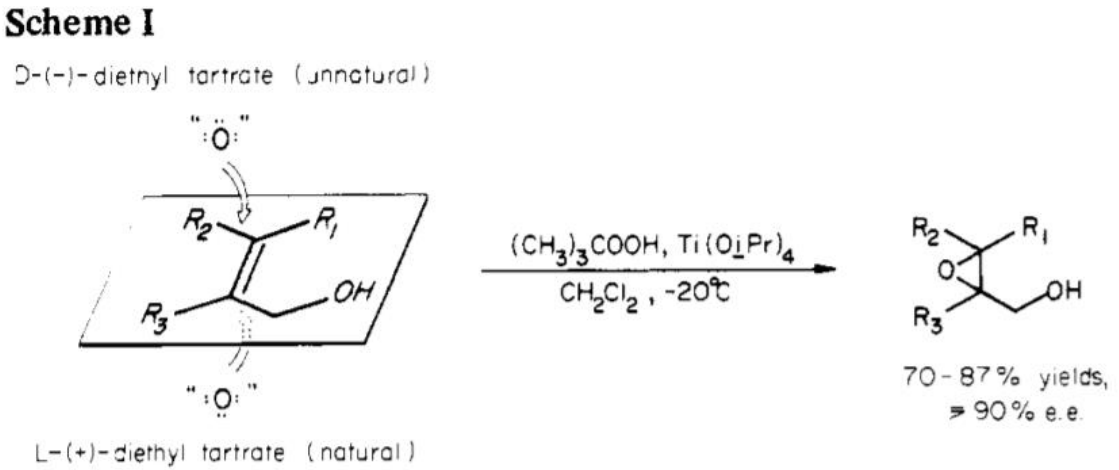


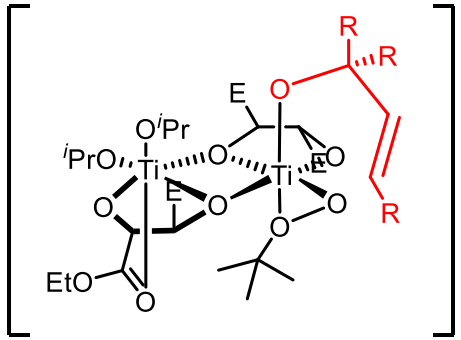
Figure 5. Plot of the yield ratio of **4**/**5** vs. $CpMo(CO)_3H$ in the reaction of **1** with varying concentrations of $CpMo(CO)_3H$ at 20 °C.

Jacobsen, E. N.; Bergman, R. G. *Organometallics* **1984**, *3*, 329.
Jacobsen, E. N.; Bergman, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 2023.

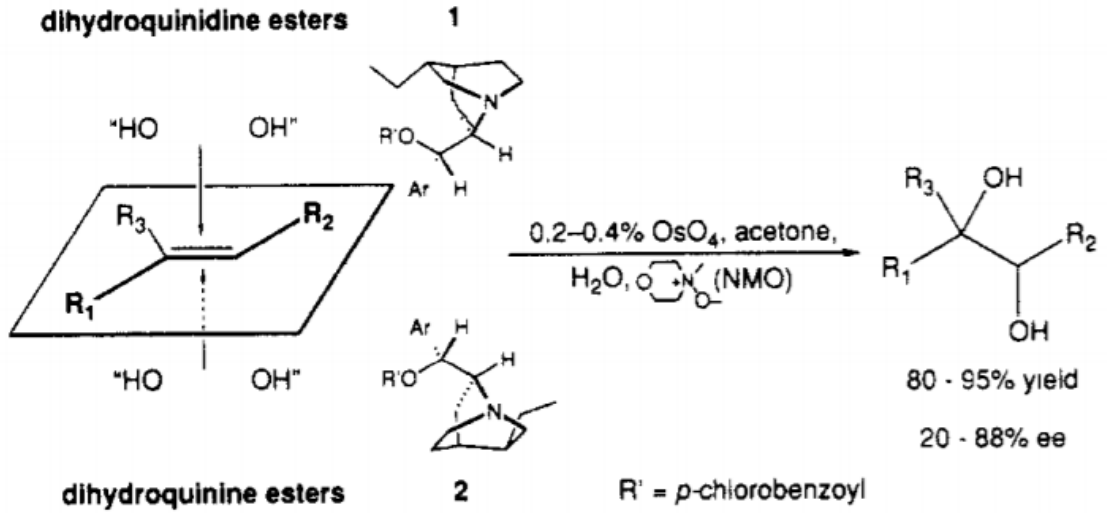
Postdoctoral Works: Asymmetric Dihydroxylation

- **Sharpless Epoxidation**





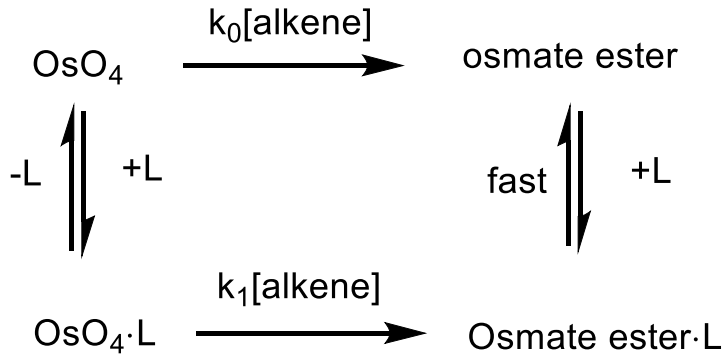
- **Dihydroxylation**



- The ligand-acceleration phenomenon with *Cinchona* alkaloid ligands

Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, 102, 18, 5974–5976
Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968.

Postdoctoral Works: Asymmetric Dihydroxylation



L = amine

$$\Delta k = k_2 - k_0 = \frac{(k_1 - k_0)K_{eq}[amine]}{K_{eq}[amine] + 1}$$

$$ee = \frac{(k_f - k_s)K_{eq}[amine]}{k_1 K_{eq}[amine] + k_0}$$

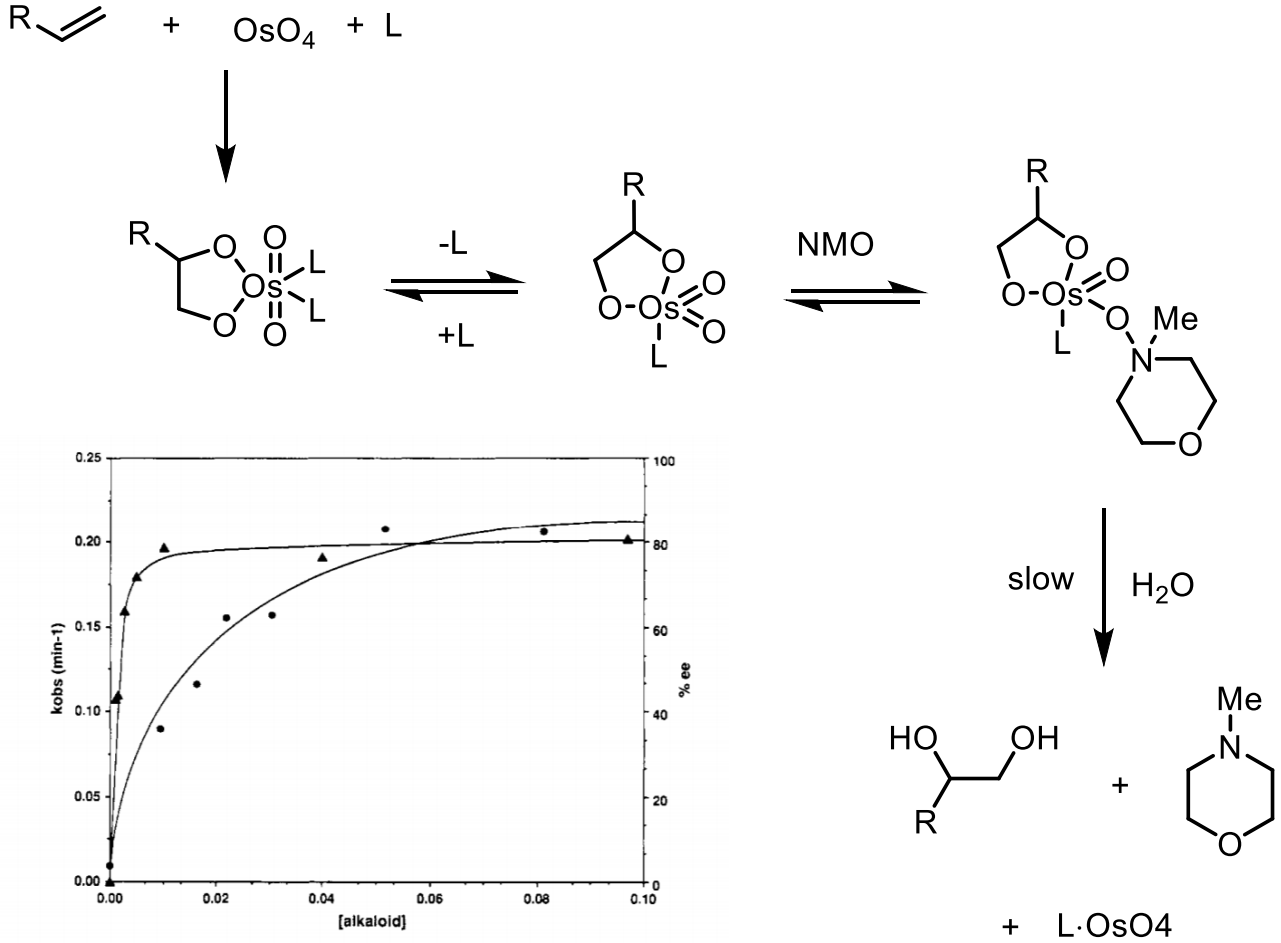


Figure 1. Plot of the concentration of alkaloid ligand **1** vs observed rate constant k_{obsd} (●) and % ee (▲) for the catalytic dihydroxylation of *trans*-stilbene. Conditions: 25 °C, $[OsO_4]_0 = 3.8 \times 10^{-4}$ M, $[NMO]_0 = 0.2$ M, $[stilbene]_0 = 0.1$ M.

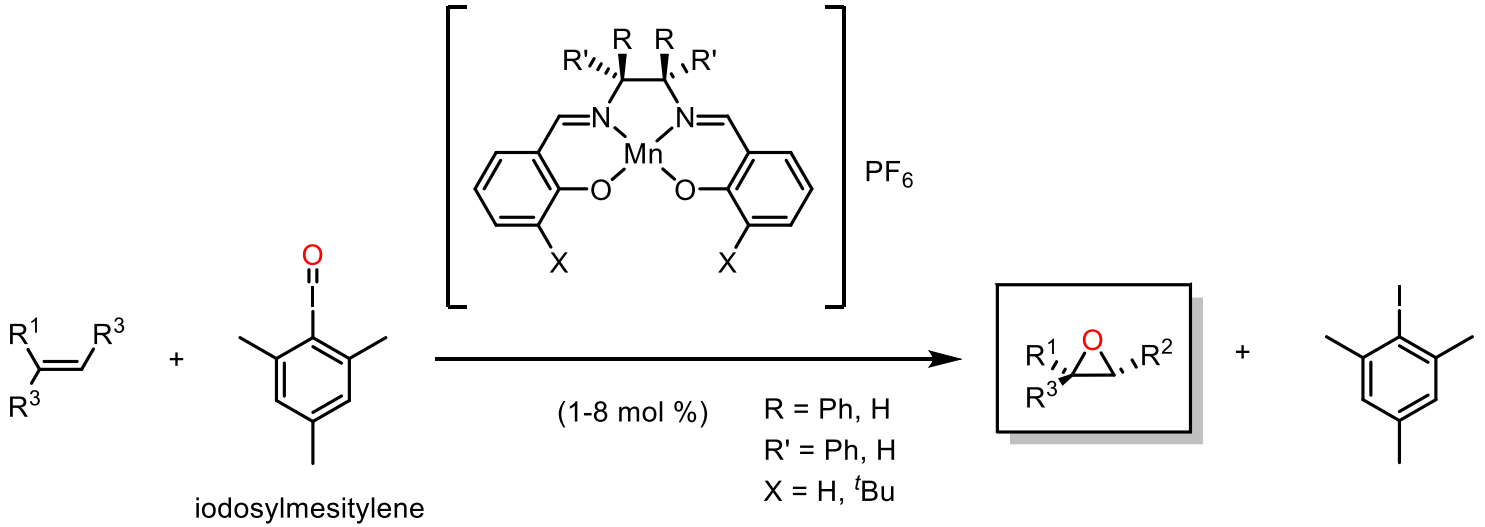
Jacobsen, E. N.; Markó, I. E.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737.

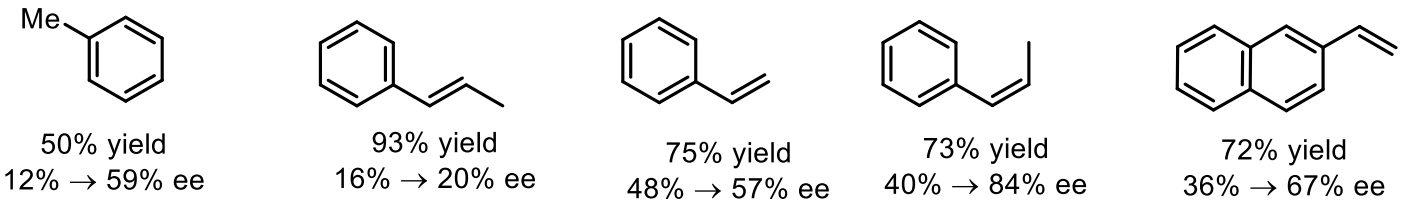
Selected Independent Career Research

- Asymmetric Epoxidation
- Epoxide Ring Opening
- Hydrolytic Kinetic Resolution (HKR)
- Asymmetric Michael Additions
- Asymmetric Strecker Reaction
- H-Bond Donor Catalysis
- Hypervalent Iodine

"Substrate Generality & Reaction Generality"

Epoxidation



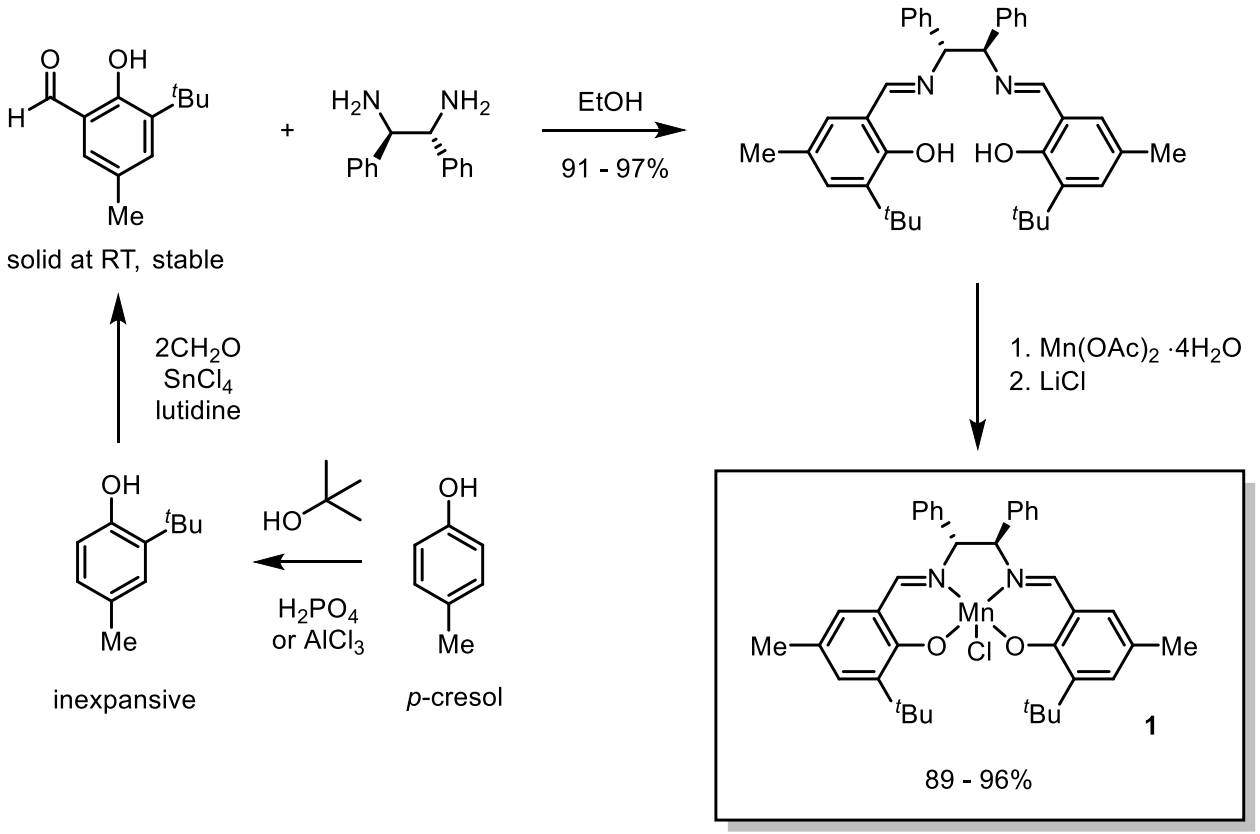


- The first report of UNDIRECTED asymmetric epoxidation of UNFUNCTIONALIZED olefin substrates
  - Stereoselectivity relies solely on nonbonded interactions
- "[…]the pool of potential substrates could in principle be unlimited"
- Difficult catalyst synthesis
- Iodosylarene as stoichiometric oxidants

Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801–2803.

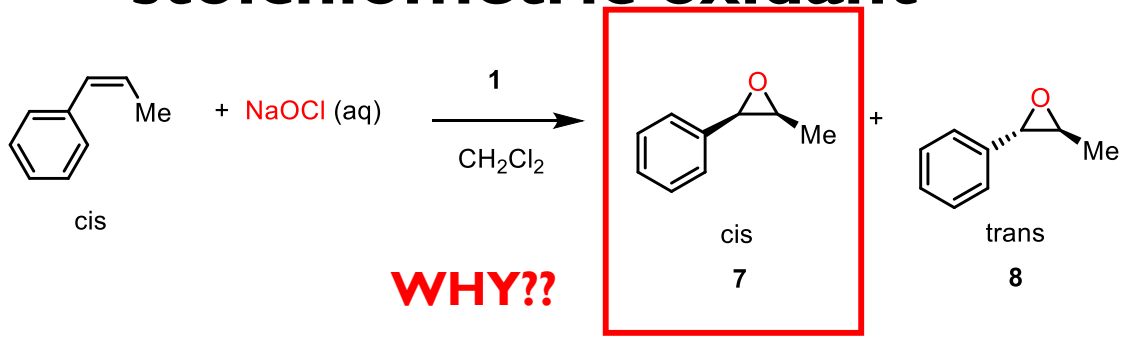
Epoxidation

- **Improved Synthesis**



Thermally stable, indefinately in the solid state despite light, air, or moisture

- **NaOCl as stoichiometric oxidant**

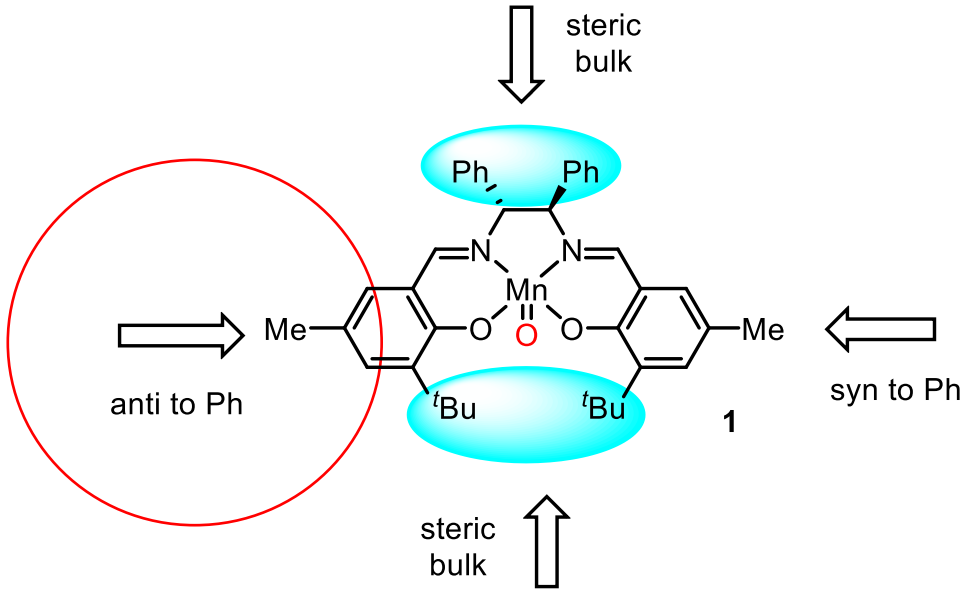


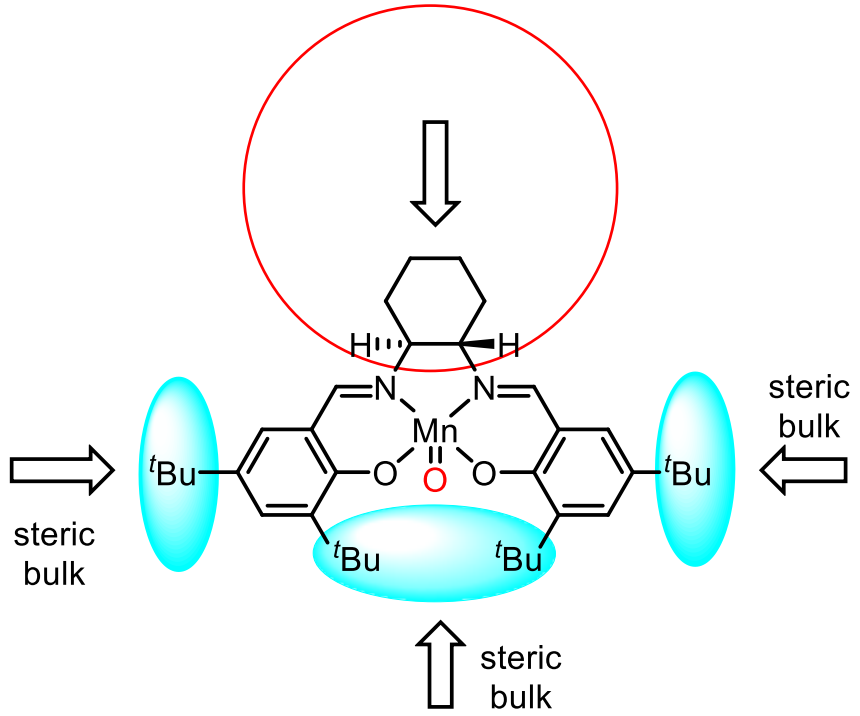
pH[b]	yield of 7[c]	% ee of 7	yield 7/ yield 8	total catalyst turnovers	initial rate[d] (turnovers/ min)
9.5	56	80	7.4	37	7.3
10	74	79	11.5	35	5.8
10.5	81	81	15	37	3.0
11	86	81	15	37	2.9
11.5	87	82	14	35	2.2

Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064.
Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296–2298.

Epoxidation

- **Jacobsen's Catalyst: Ligand modification using 1,2-diaminocyclohexane**





- Maximized stereochemical communication
- Limitation of competing substrate approach
- No directing affect by pi stacking
- Low selectivity for trans olefins

Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064.
Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296–2298.

Epoxidation

- **Epoxidation of conjugated dienes and enynes**

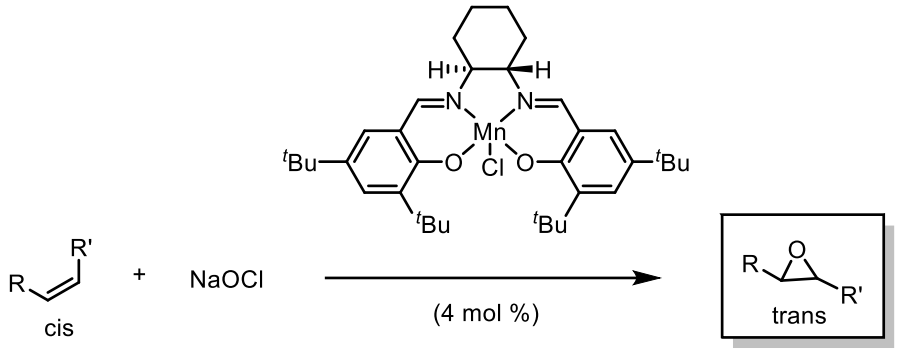
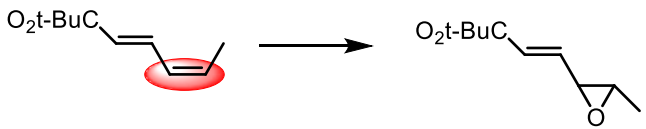
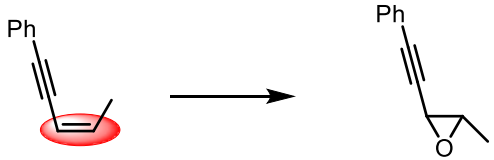


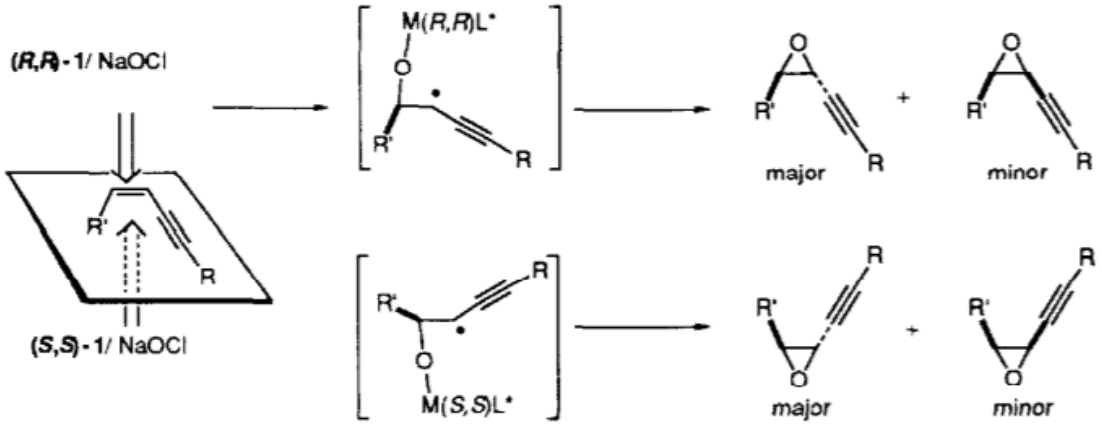
Figure 1



(trans:cis = 7:1)
trans: 66% ee
cis: 14% ee



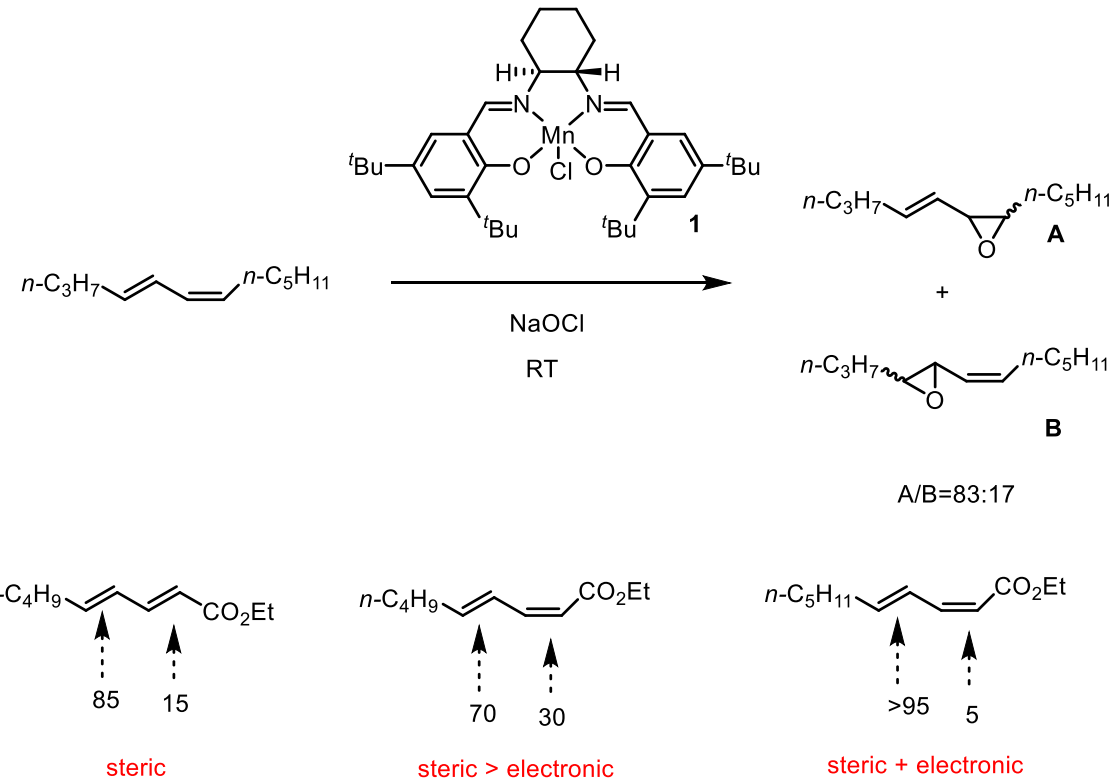
(trans:cis = 2:1)
trans: 93% ee
cis: 58% ee



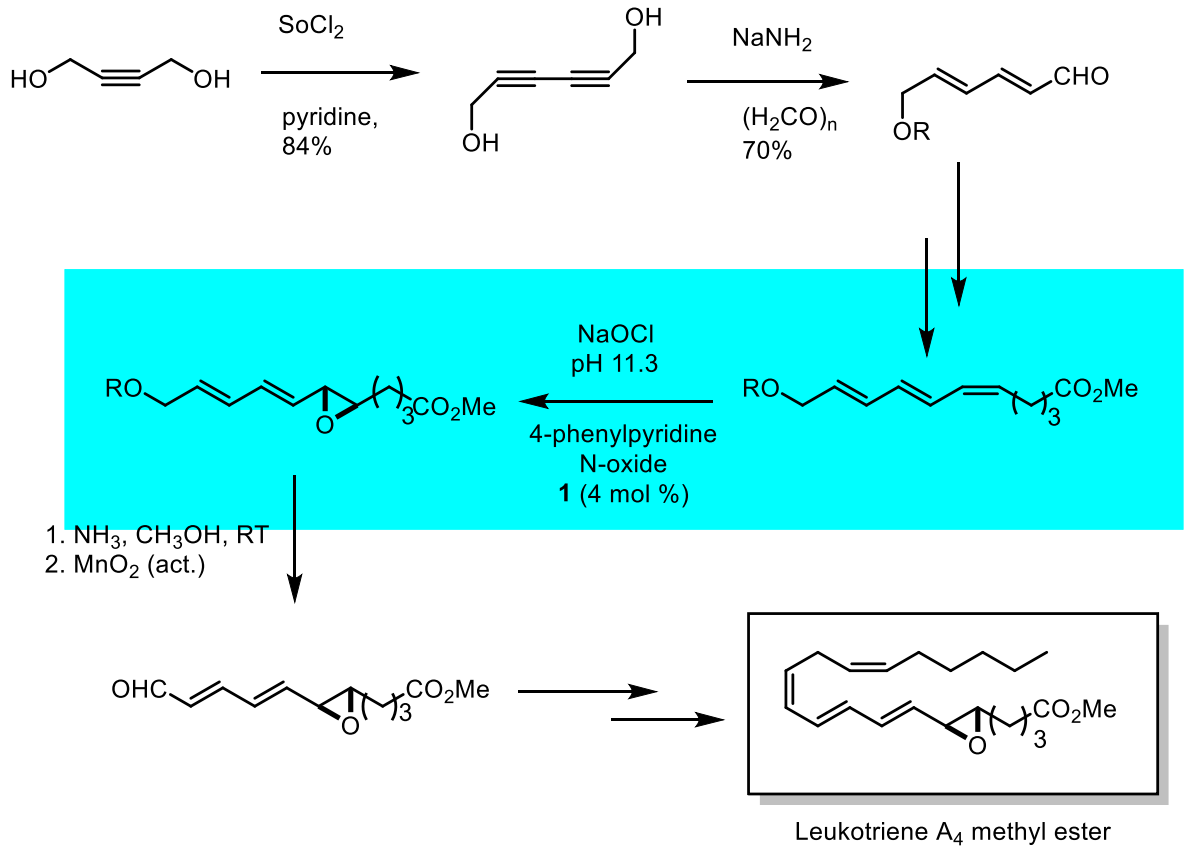
Lee, N. H.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 6533–6536.

Epoxidation

- **More on regioselectivity: Epoxidation of conjugated polyenes**



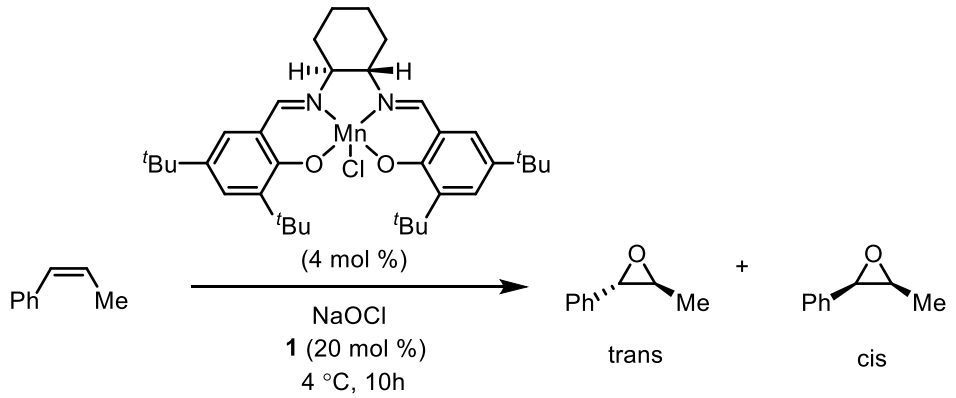
- **Synthesis of LTA4 Methyl Ester**

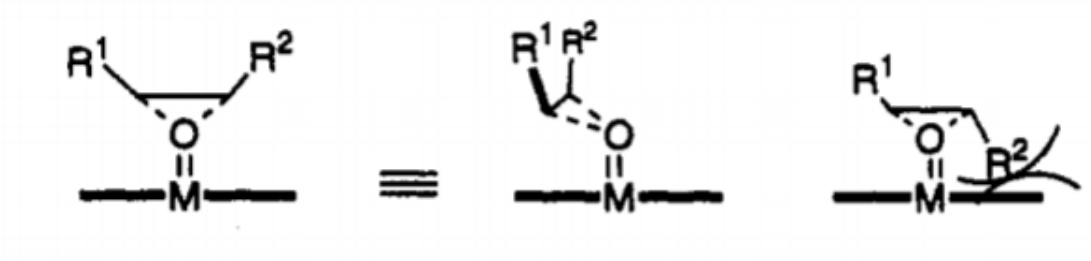


Chang, S.; Lee, N. H.; Jacobsen, E. N. *J. Org. Chem.* **1993**, *58*, 6939–6941.

Epoxidation

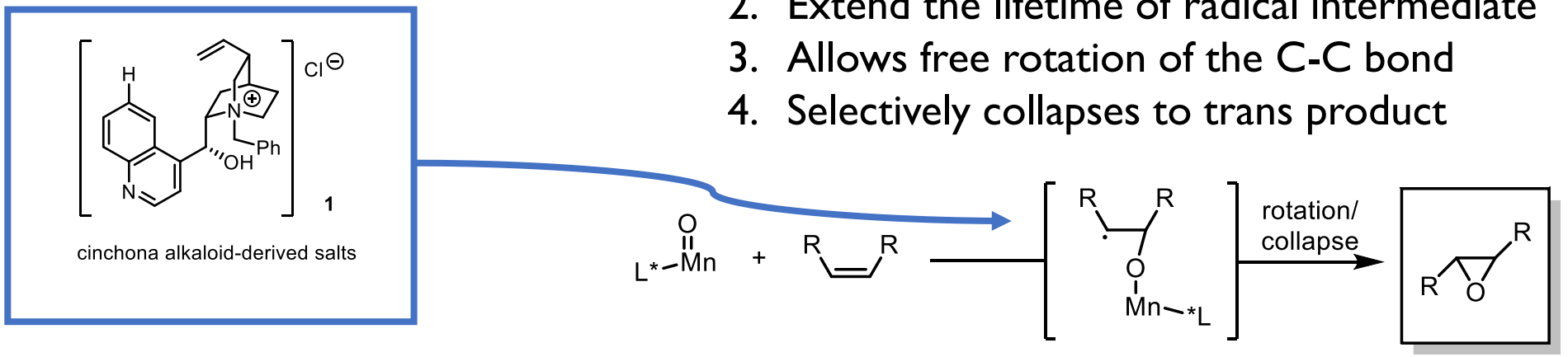
- **Reversing diastereoselectivity with chiral quaternary ammonium salts**





- **Possible Mechanism:**

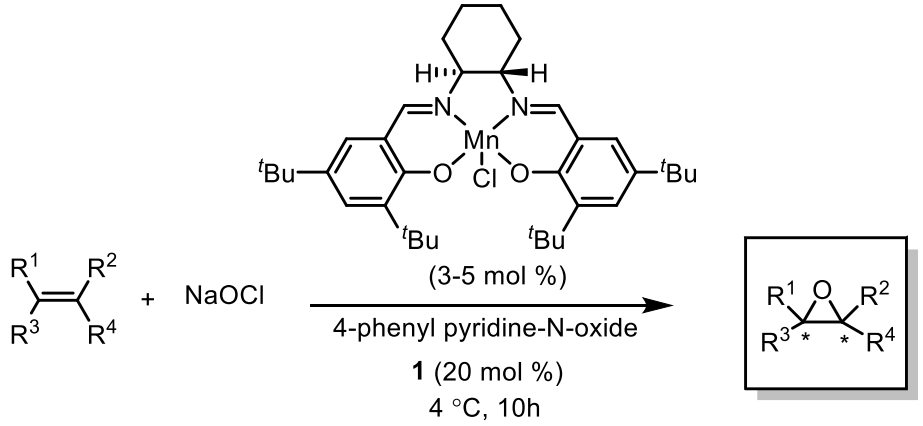
1. ammonium salts interact with **1**
2. Extend the lifetime of radical intermediate
3. Allows free rotation of the C-C bond
4. Selectively collapses to trans product

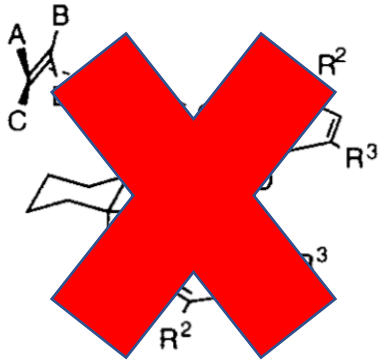


Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937–6938.

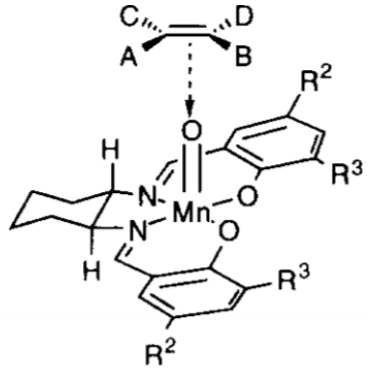
Epoxidation

- **Epoxidation of tetrasubstituted olefins**





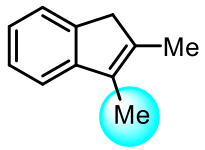
Side-on approach



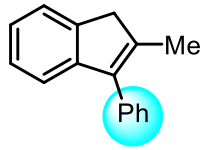
Top-on approach

???

indene derivatives:

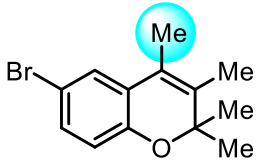


32% ee

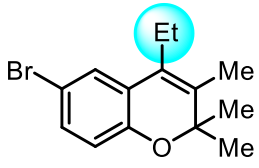


77% ee

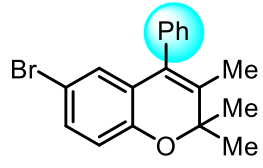
choromene dereivatives:



94% ee



97% ee



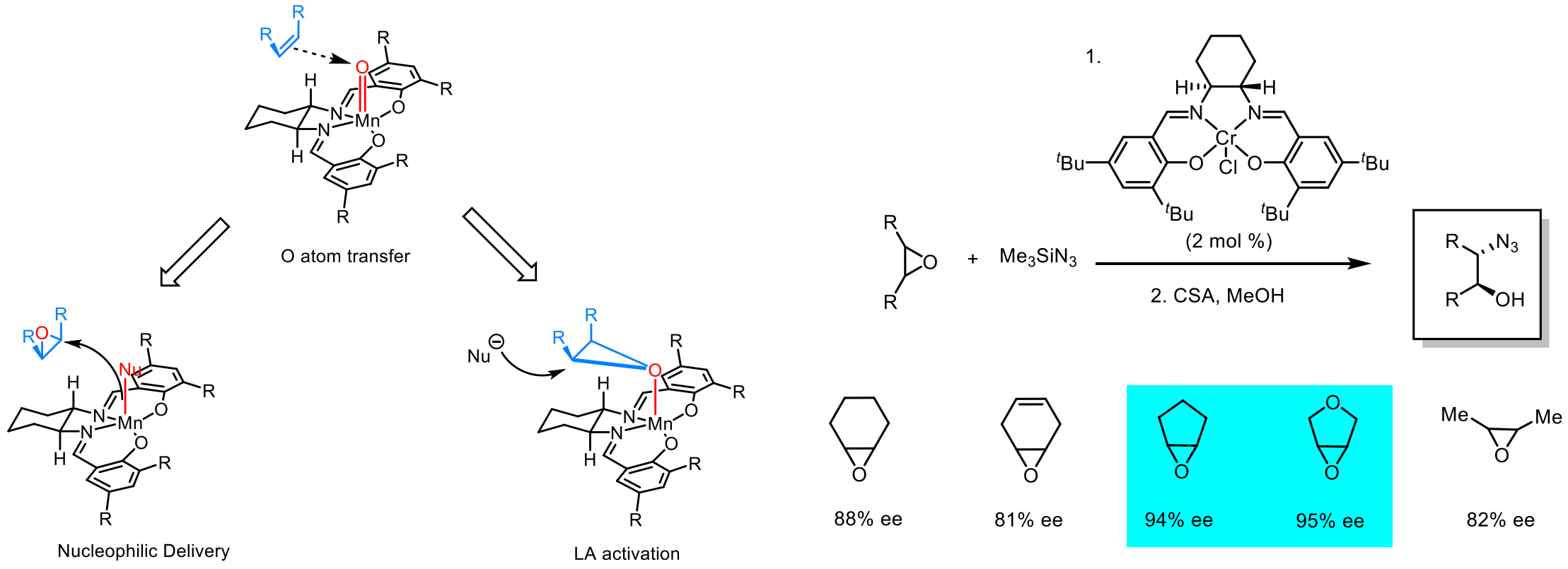
1% ee

"Clearly, there exists subtleties to the chiral recognition […] that defy straightforward interpretations"

Brandes, B. D.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5123–5126.

Epoxide Ring Opening

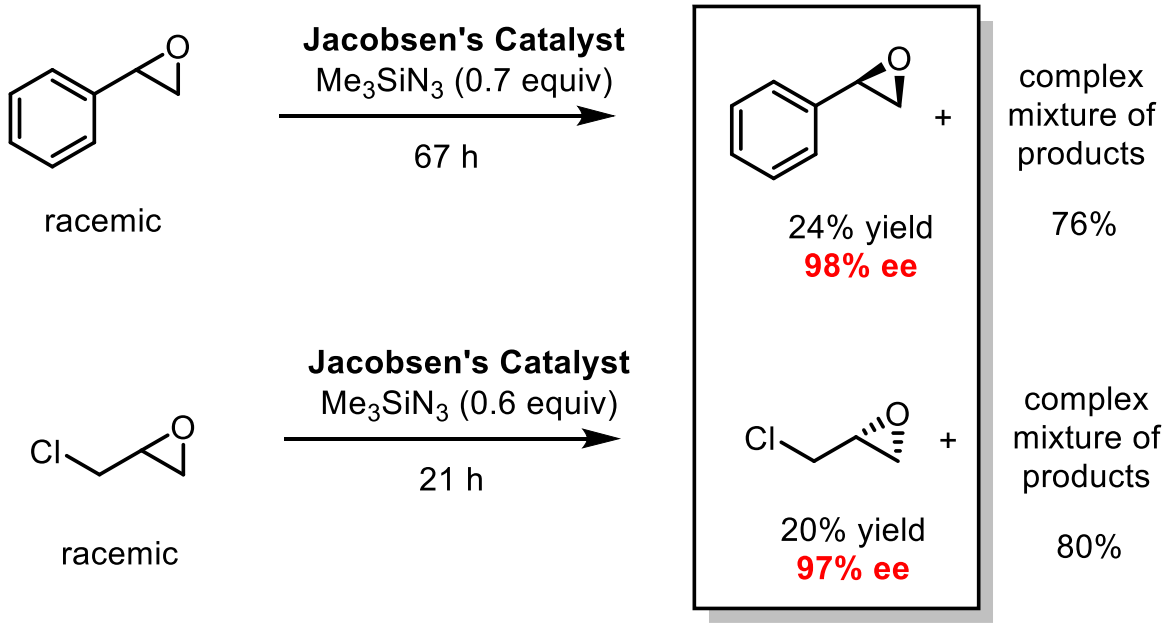
- **Going beyond substrate generality:**



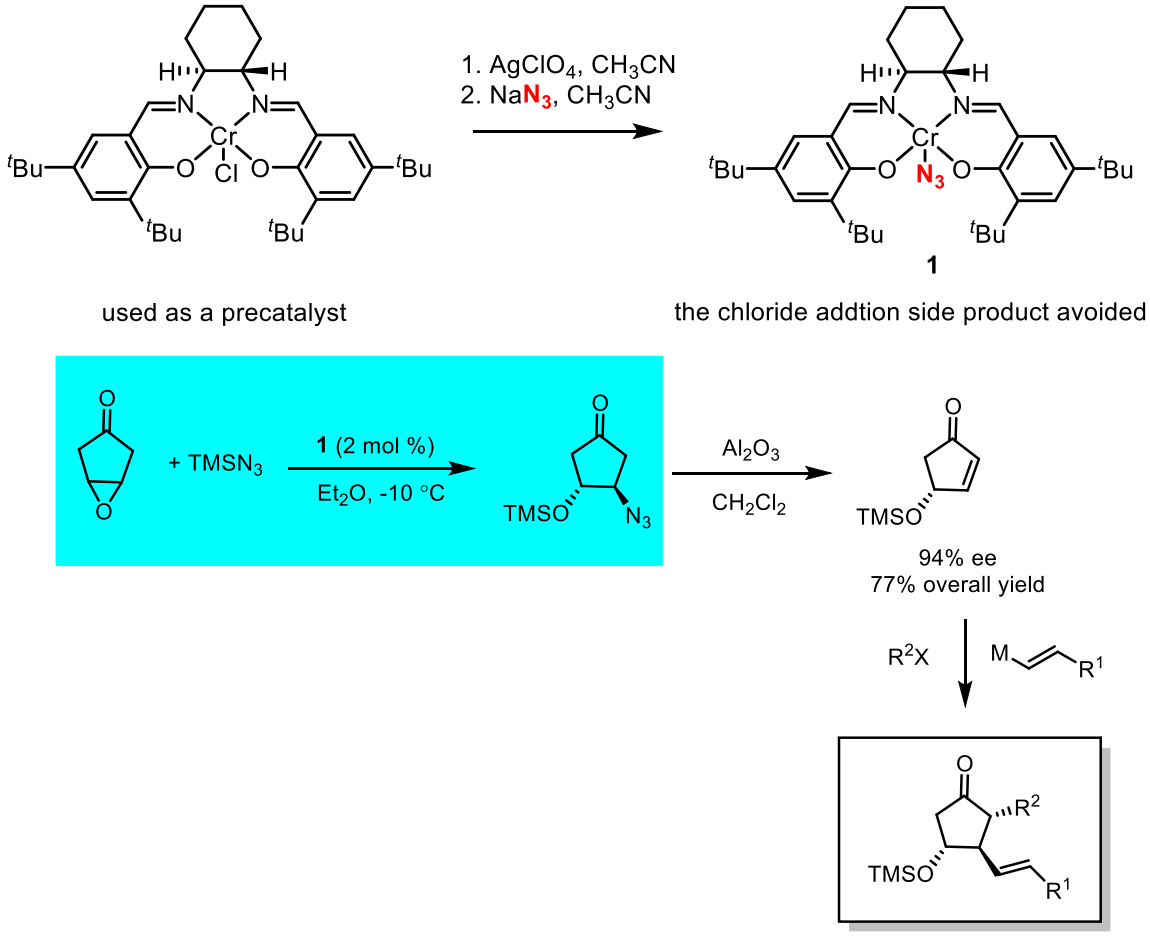
Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897–5898.
Leighton, J. L.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 389–390.

Epoxide Ring Opening

- **Kinetic Resolution**



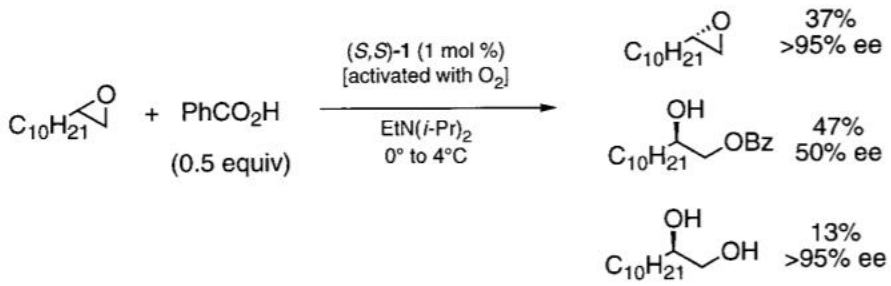
- **Synthetic Application**

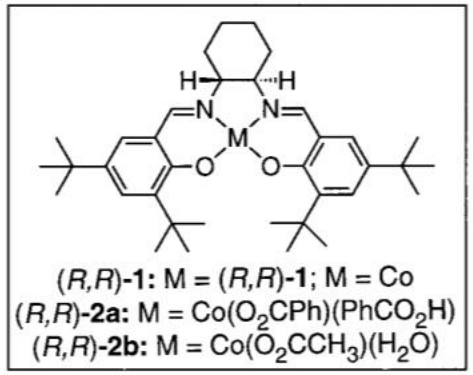


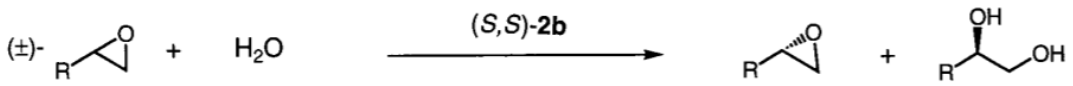
Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.
Leighton, J. L.; Jacobsen, E. N. *J. Org. Chem.* **1996**, *61*, 389–390.

Hydrolytic Kinetic Resolution

- **Unexpected Discovery**







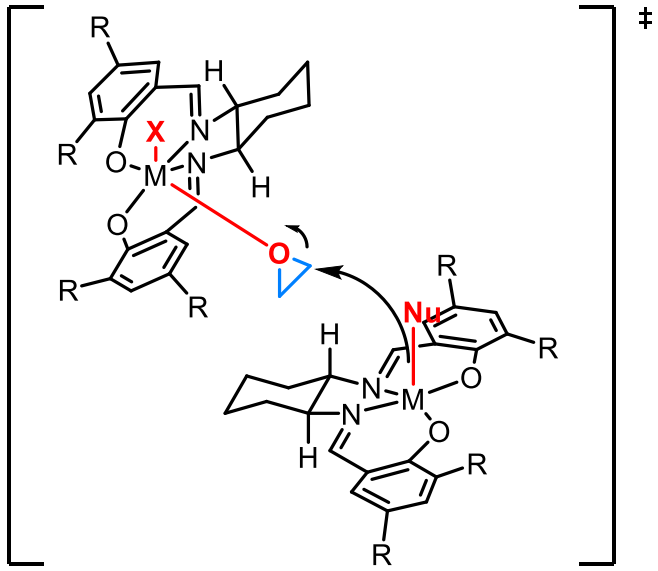
Entry	R	Concentration		Time (hours)	Epoxide		Diol		k_{rel}
		2b (mol %)	Water (equiv)		ee (%)	Isolated yield (%)	ee (%)	Isolated yield (%)	
1	CH_3	0.2	0.55	12	>98	44	98	50	>400
2	CH_2Cl	0.3	0.55	8	98	44	86	38	50
3	$(CH_2)_3CH_3$	0.42	0.55	5	98	46	98	48	290
4	$(CH_2)_5CH_3$	0.42	0.55	6	99	45	97	47	260
5	Ph	0.8	0.70	44	98	38	98*	39*	20
6	$CH{=}CH_2$	0.64	0.50	20	84	44	94	49	30
7	$CH{=}CH_2$	0.85	0.70	68	99	29	88	64	30

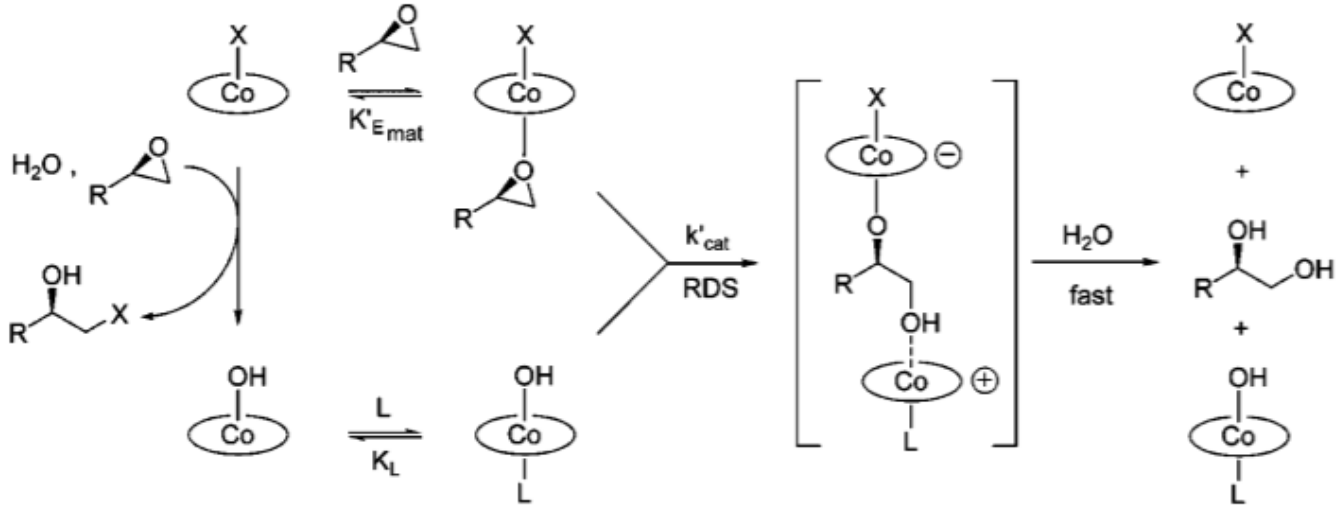
*After recrystallization.

Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 7420–7421.

Hydrolytic Kinetic Resolution

- **Mechanistic study for HKR**



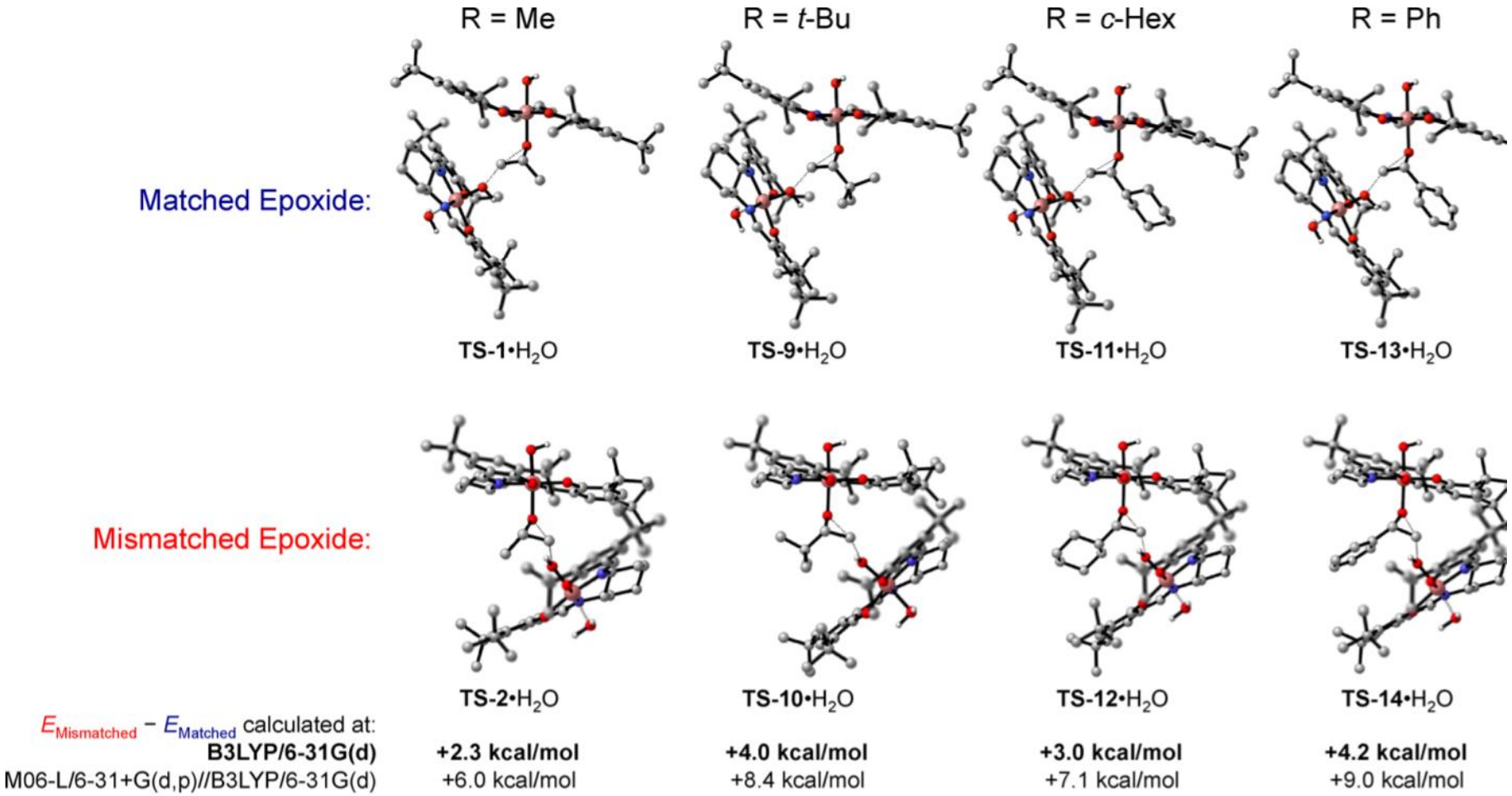


How can HKR be general and selective at the same time?

Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936–938.
Nielsen, L. C. P.; Stevenson, C. P.; Blackmond, D.G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360–1362.

Hydrolytic Kinetic Resolution

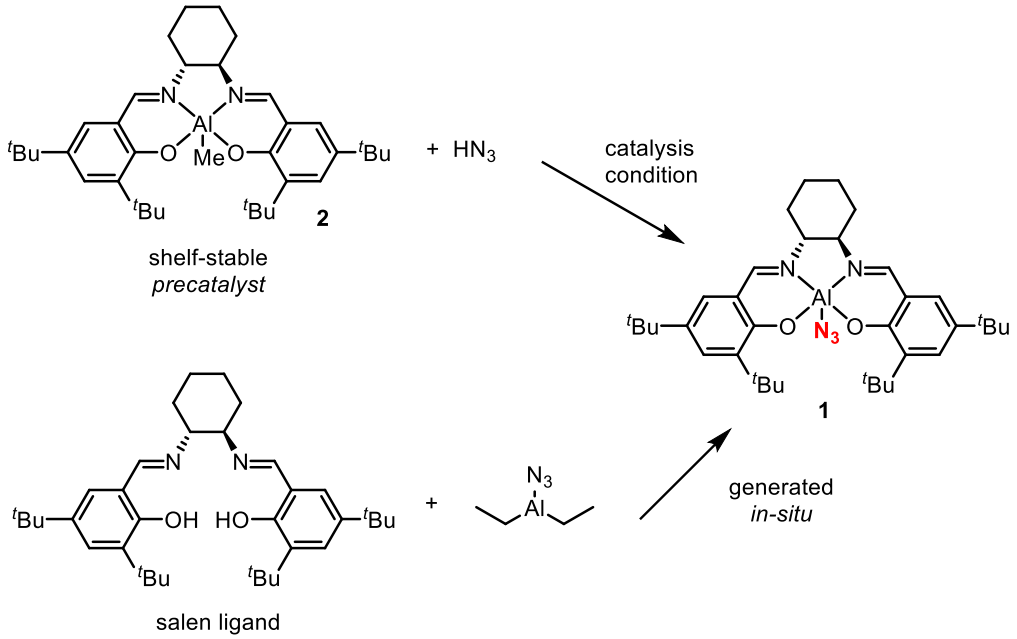
- **The Selectivity and Generality of HKR**

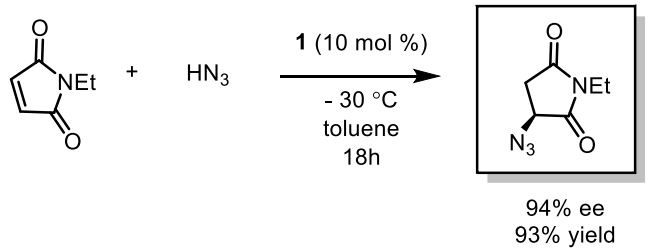


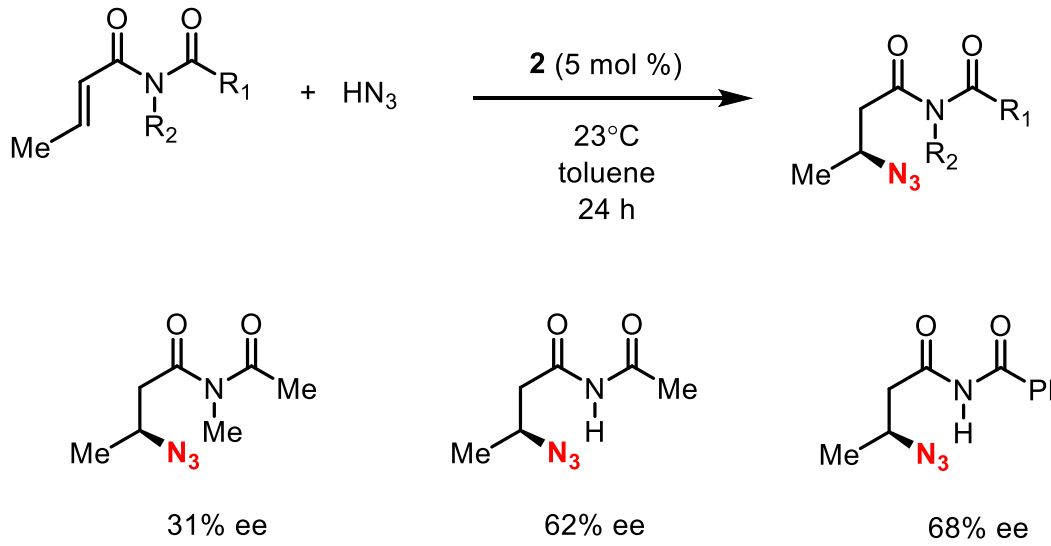
Ford, D. D.; Nielsen, L. P. C.; Zuend, S. J.; Musgrave, C. B.; Jacobsen, E. N. *J. Am. Chem. Soc*. **2013**, *135*, 15595–15608

Asymmetric Michael Addition

- **Conjugate Addition of Hydrazoic Acid**



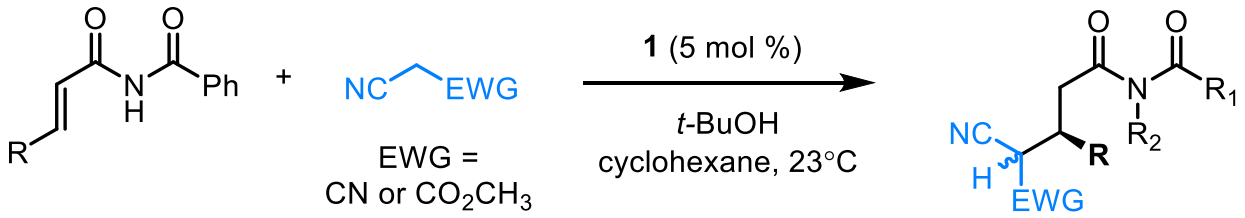


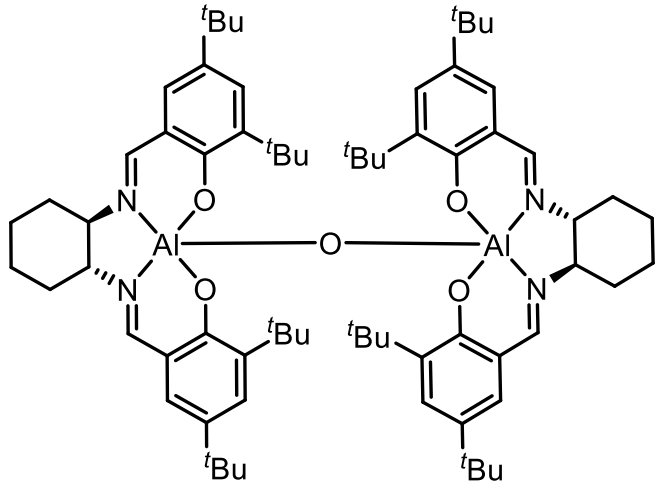


Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959–8960.

Asymmetric Michael Addition

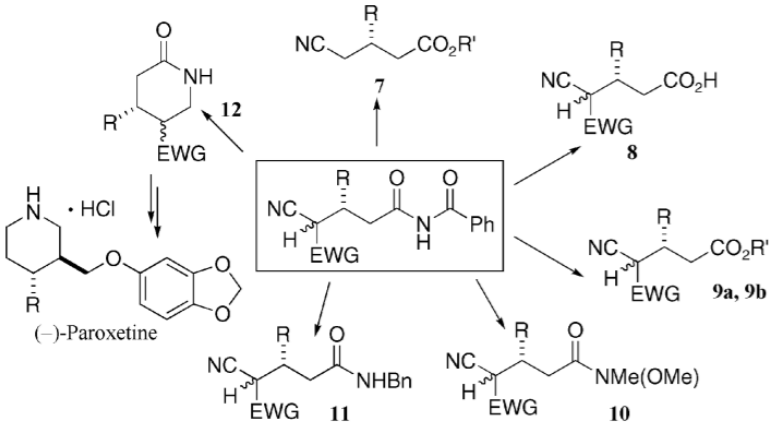
- **Conjugate Addition of Malononitrile and Methyl Cyanoacetate**





μ-oxo dimer **1**

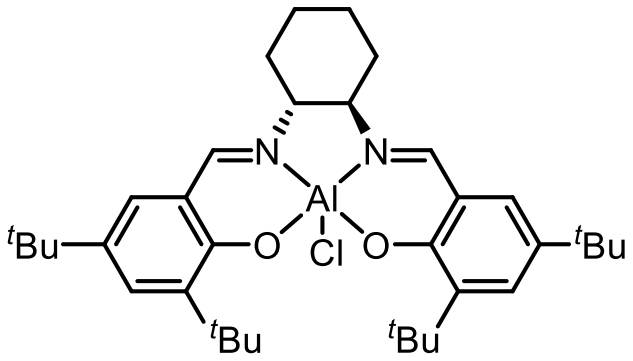
product	R	EWG	time	yield (%)[a]	ee (%)[b]
3a	Ph[c]	CN	28 h	87	90
3b	*p*-FC_6H_4[c,j]	CN	36 h	88	93
3c	*p*-ClC_6H_4[c]	CN	38 h	99	92
3d	Me[c,d]	CN	20 h	89	96
3e	*n*-Pr[c,d]	CN	20 h	95	97
3f	*i*-Pr[c]	CN	36 h	91	96
3g	*t*-Bu[c]	CN	48 h	88	97
4a	Ph[e]	CO_2CH_3	40 h	98	88[f]
4b	*p*-FC_6H_4[e,g,k]	CO_2CH_3	54 h	94	89[f]
4c	*p*-ClC_6H_4[e]	CO_2CH_3	56 h	99	89[f]
4d	Me[e]	CO_2CH_3	48 h	96	86[f,h]
4e	*n*-Pr[e]	CO_2CH_3	40 h	88	90[f]
4f	*i*-Pr[i]	CO_2CH_3	6 d	89	95[f]



Sammis, G. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 4442–4443.

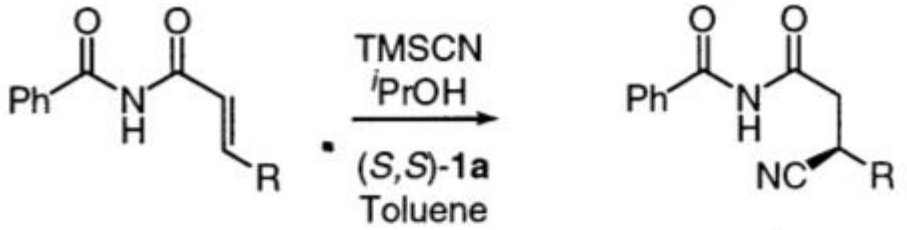
Asymmetric Michael Addition

- **Conjugate Addition of Cyanide**



1a

Btw, cyanide & imine (or imide) reminds me of…



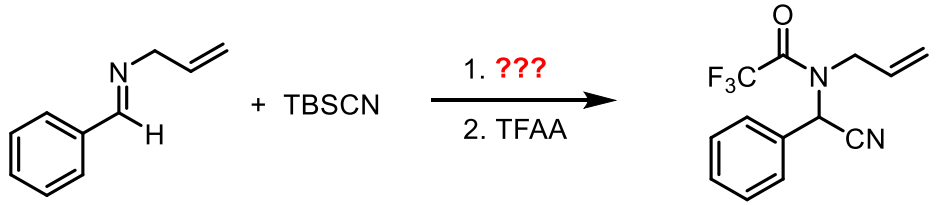
2a-h **3a-h**

product	R	method[a]	time (h)	isolated yield (%)	ee[b] (%)
3a	Me	A	26	92	98[c]
3b	Et	A	26	95	97
3c	^{n}Pr	A	26	90	97
3d	^{i}Pr	A	26	91	94
3e	^{i}Bu	A	26	93	96
3f	$(CH_2)_3CHCH_2$	A	48	96	95
3g	^{t}Bu	B	48	90	97
3h	CH_2OBn	B	48	70	87

Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2003**, *125*, 11204–11205.

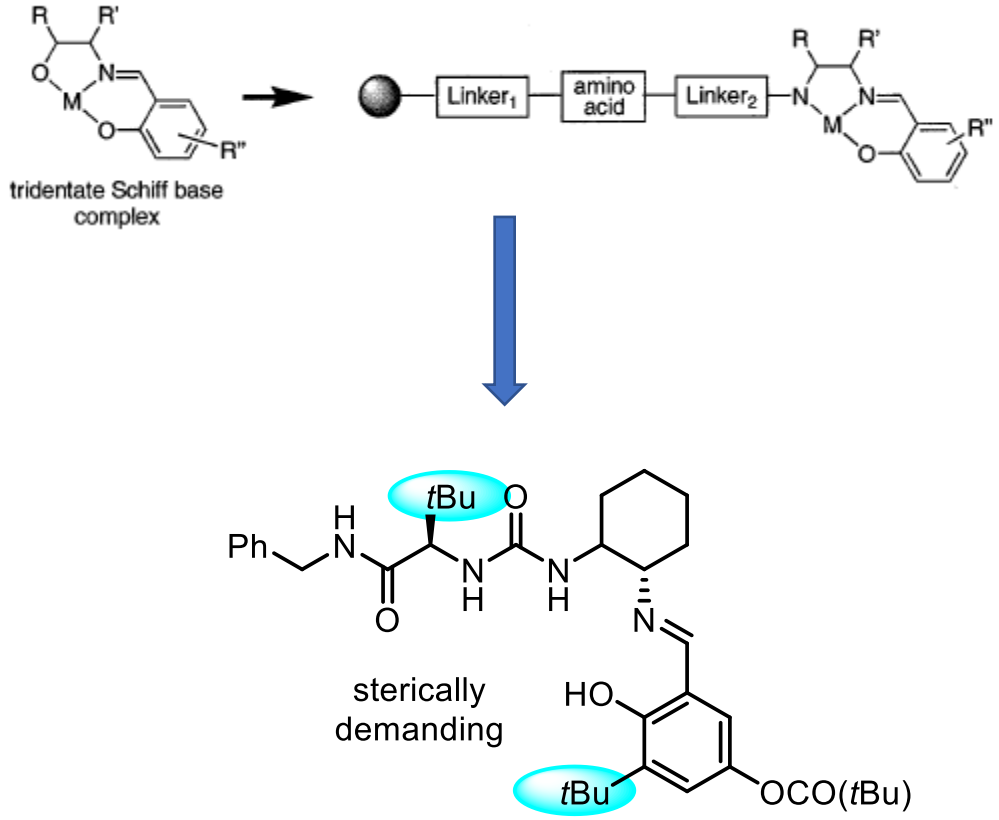
Asymmetric Strecker Reaction

- **Catalyst Design**



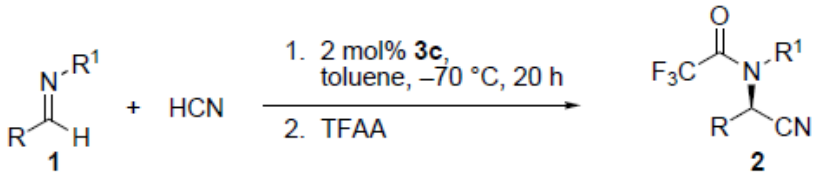
  - **The parallel library approach:** the basic features of the target structures have already been established
  - **The selection of potential catalyst system:**
    - Amenable to solid-phase synthesis
    - Systematic structural variation
    - A selective system for chirality transfer

Tridentate Schiff base!!

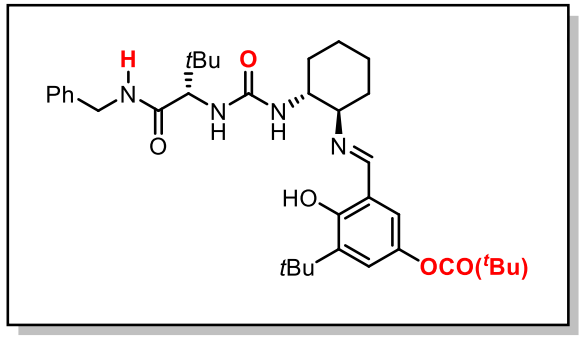


Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.
M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315–5316.

Asymmetric Strecker Reaction



Entry		Imine **1** R	Imine **1** R^1	Yield [%]	*ee* [%][a]
1	**a**	C_6H_5	allyl	74	95
2	**b**	*tert*-butyl	allyl	75	95 (91)
3	**c**	*p*-$OCH_3C_6H_4$	allyl	98	95
4	**d**	*m*-$OCH_3C_6H_4$	allyl	99	93
5	**e**	*o*-$OCH_3C_6H_4$	allyl	93	77
6	**f**	*p*-$CH_3C_6H_4$	allyl	99	95
7	**g**	*m*-$CH_3C_6H_4$	allyl	97	96
8	**h**	*o*-$CH_3C_6H_4$	allyl	96	95
9	**i**	*p*-BrC_6H_4	allyl	89	89
10	**j**	*m*-BrC_6H_4	allyl	87	90
11	**k**	*o*-BrC_6H_4	allyl	88[b]	95
12	**l**	*p*-$(CH_3)_3CC_6H_4$	allyl	89	97
13	**m**	*tert*-butyl	benzyl	88	96 (93)
14	**n**	cyclohexyl	benzyl	85	87
15	**o**	cyclohexyl	allyl	88	86
16	**p**	1-cyclohexenyl	benzyl	90	91 (87)
17	**q**	$(CH_3)_3CCH_2$	benzyl	85	90 (87)
18	**r**	$CH_3(CH_2)_4$	benzyl	69	78
19	**s**	$(CH_3)_2CH$	benzyl	74	79
20	**t**	cyclopropyl	benzyl	89	91
21	**u**	cyclooctyl	allyl	65	90



3c

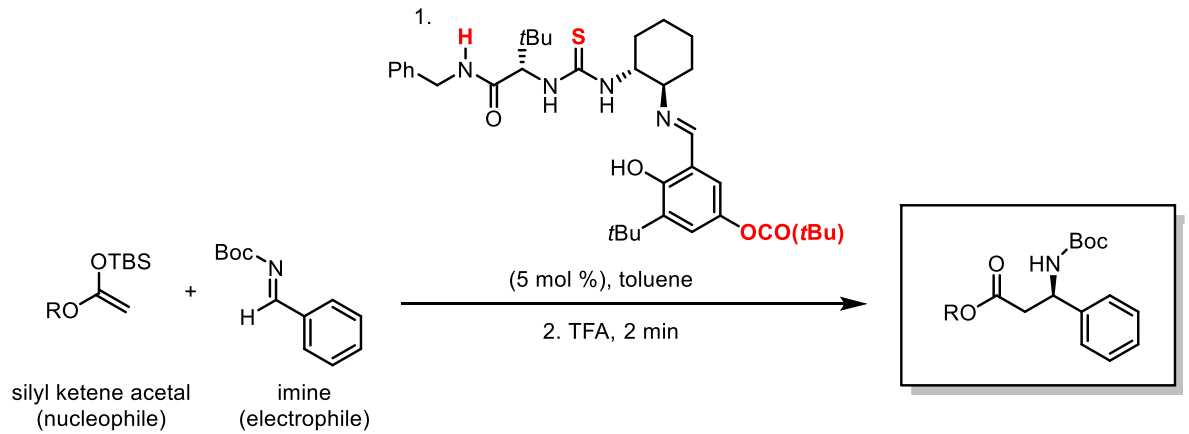
Remarkably general substrate scope!

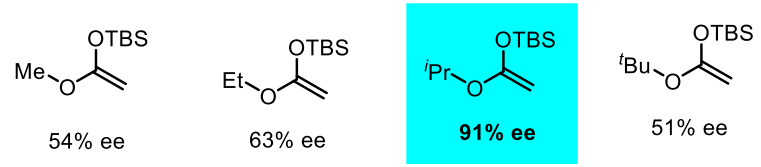
Can this new catalyst be also general for other types of reactions?

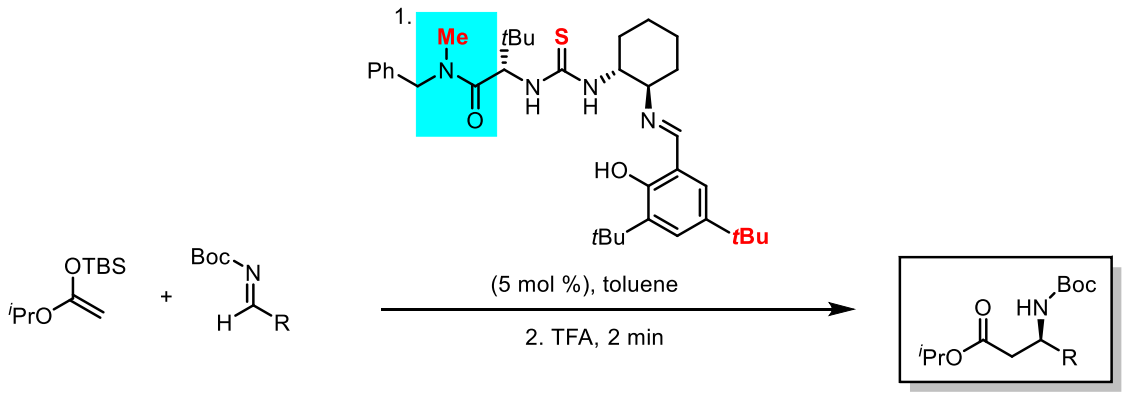
Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.
M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 5315–5316.

H-Bond Donor Catalysis

- **Asymmetric Mannich Reaction**





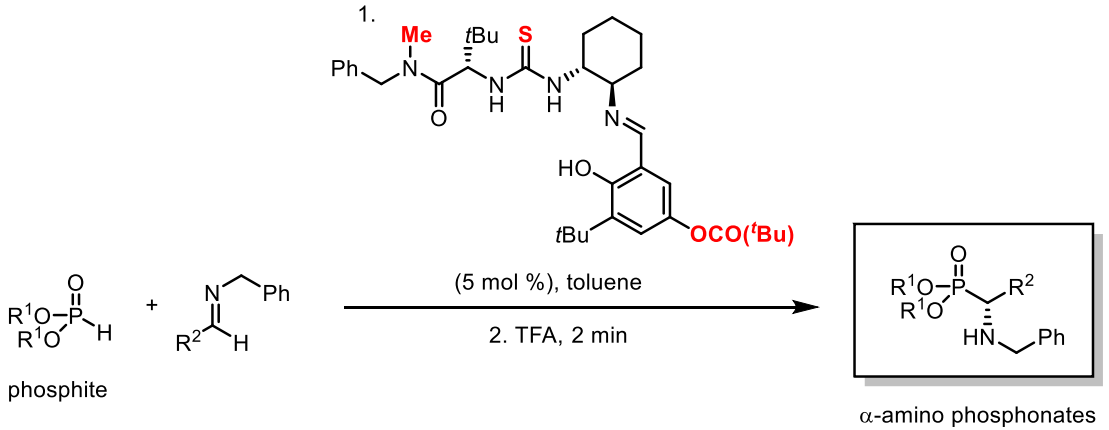


entry	imine	R	temp (°C)	yield (%)[a]	ee (%)[b]
1	**3a**	Ph	−40	95	97
2	**3b**	*o*-$CH_3C_6H_4$	−30	88	91
3	**3c**	*m*-$CH_3C_6H_4$	−30	98	94
4	**3d**	*p*-$CH_3C_6H_4$	−30	87	96
5	**3e**	*p*-$OMeC_6H_4$	4	91	86
6	**3f**	*p*-FC_6H_4	−30	88	93
7	**3g**	*m*-BrC_6H_4	−30	96	92
8	**3h**	*p*-BrC_6H_4	−30	93	94
9	**3i**	1-naphthyl	−30	93	87
10	**3j**	2-naphthyl	−30	88	96
11	**3k**	2-furyl	−40	84	91
12	**3l**	2-thienyl	−30	95	92
13	**3m**	3-quinolinyl	−30	99	96
14	**3n**	3-pyridyl	−30	99	98

Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965.

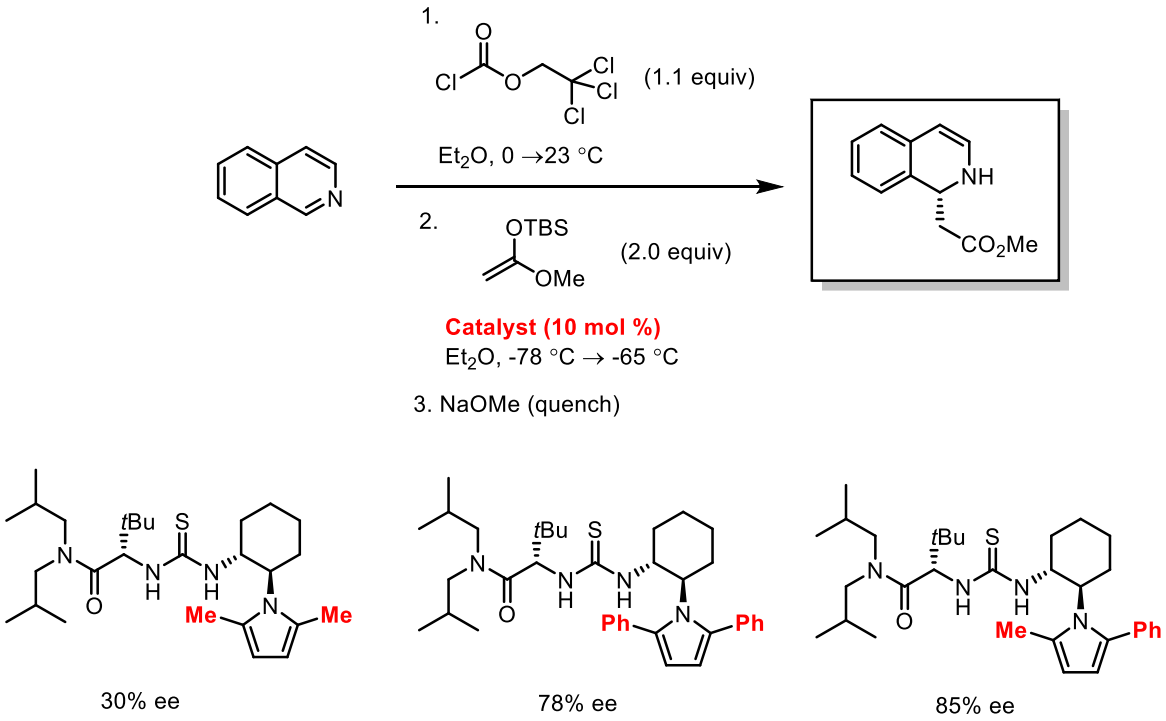
H-Bond Donor Catalysis

- **Hydrophosphonylation of Imines**



Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103.

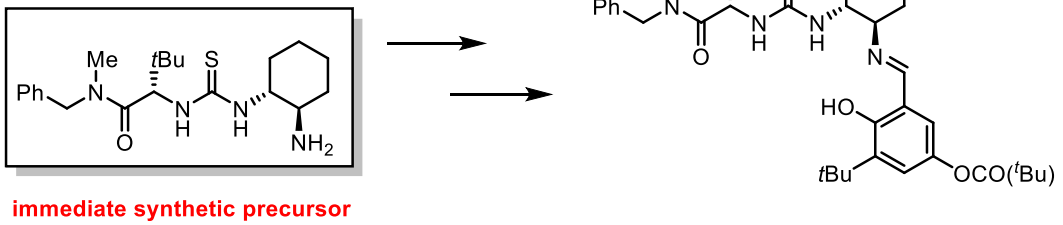
- **Acyl-Mannich Reactions of Isoquinolines**

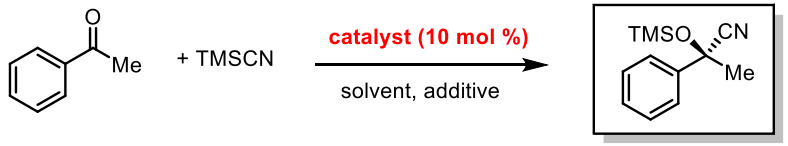


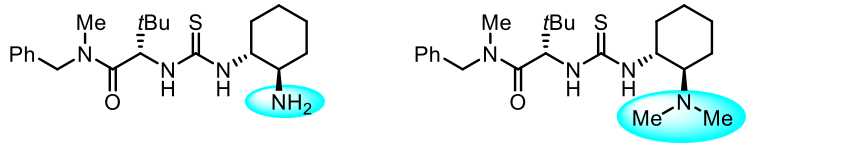
Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700–6704

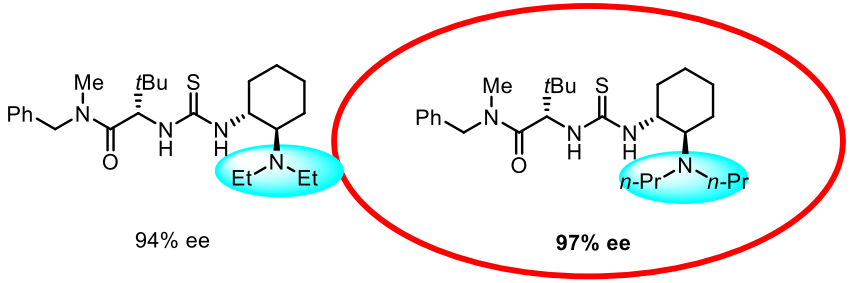
H-Bond Donor Catalysis

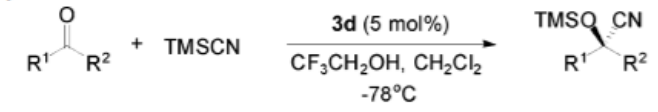
- **Cyanosilylation of Ketones**









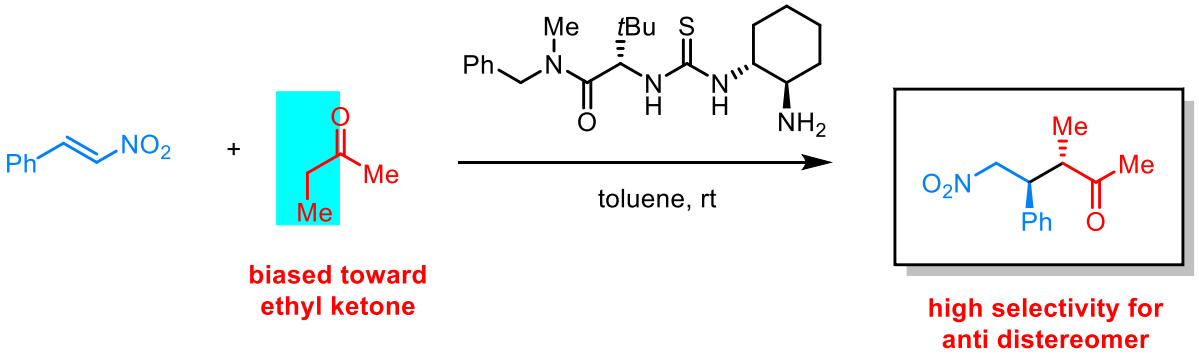


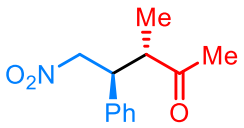
entry	ketone	time (h)	yield (%)[b]	ee (%)[c]
1	R = Me	24	96	97
2	R = Et	24	95	95
3	R = *i*-Pr	24	97	86
4[d]	R = *o*-Me	36	96	98
5	R = *p*-Me	36	97	96
6[e]	R = *m*-OMe	12	97	97
7	R = *p*-OMe	48	93	95
8	R = *p*-Br	12	94	93
9		36	91	95
10		12	98	97
11[e]		48	81	97
12[e,f]		48	88	98
13[e]		48	87	97
14	R = Me	12	94	96
15	R = *n*-Bu	12	97	93
16		48	95	89
17		12	95	97
18[e]		48	97	91

Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965.

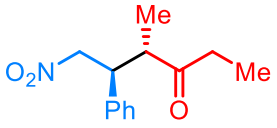
H-Bond Donor Catalysis

- **Conjugate Addition to Ketones**

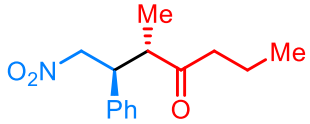




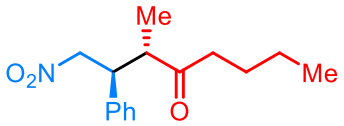
97% ee
15:1 dr



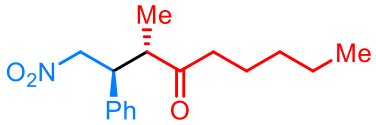
99% ee
20:1 dr



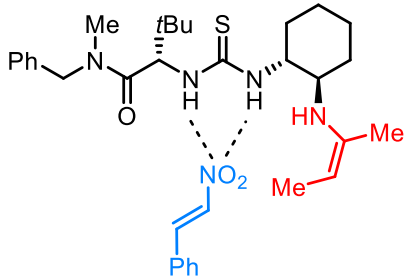
99% ee
11:1 dr



99% ee
15:1 dr



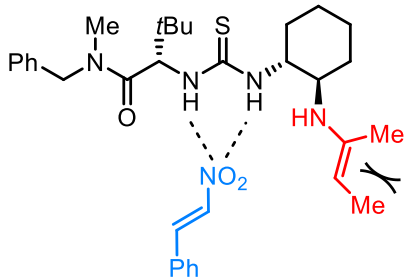
99% ee
20:1 dr



Z-enamine

anti
diastereomer

v.



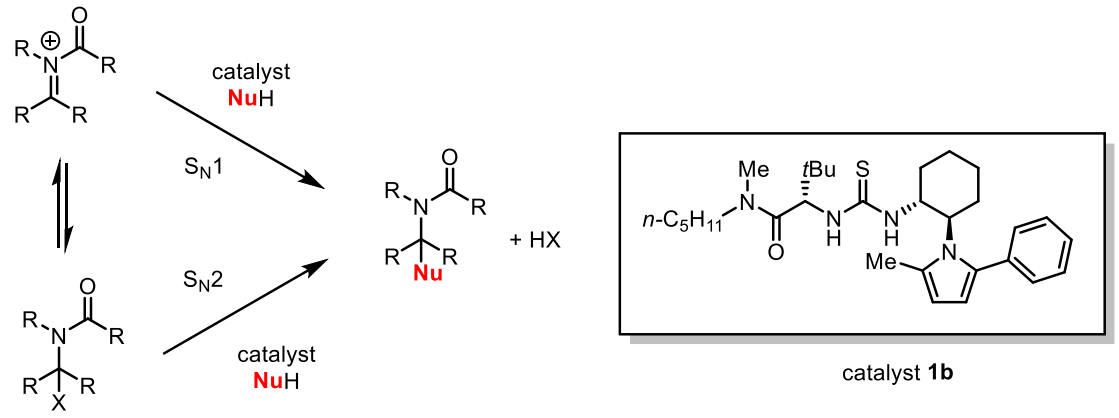
E-enamine

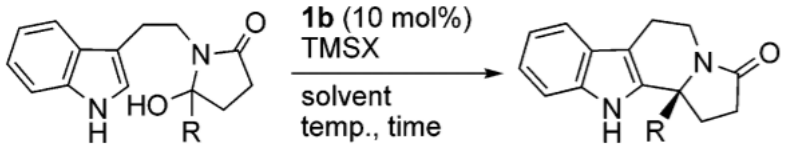
syn
diastereomer

Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170–7171.

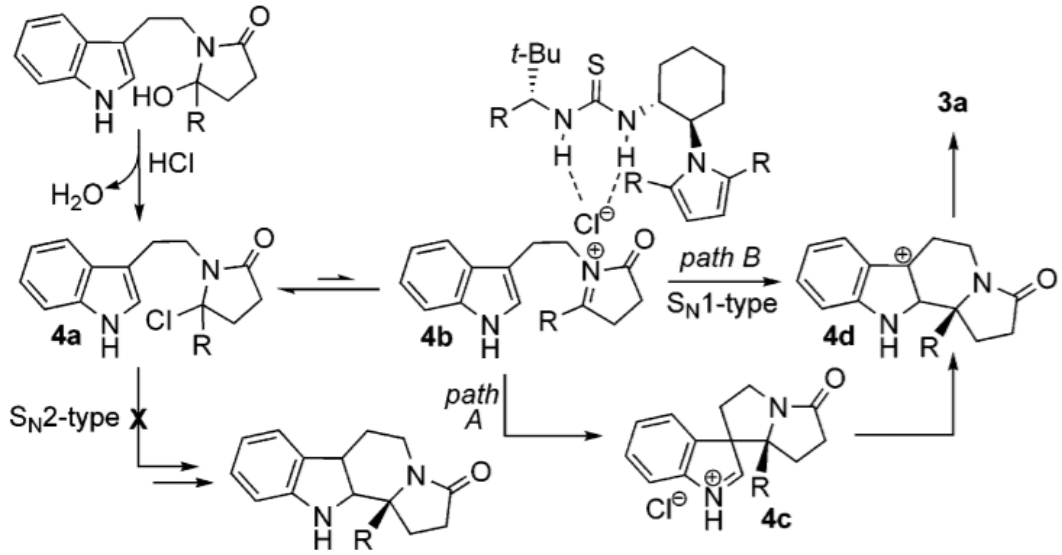
H-Bond Donor Catalysis

- **Anion Binding: Pictet-Spengler-Type Cyclization**



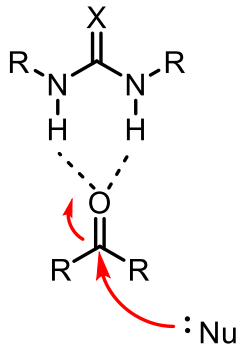


entry	solvent	X	R	temp (°C)	time (h)	conv[a] (%)	ee[b] (%)
1	TBME	Cl	H	−78	8	12	99
2	TBME	Cl	CH_3	−78	8	94	96
3	TBME	Cl	H	−55	23	80	97
4	TBME	Br	H	−55	23	82	68
5	TBME	I	H	−55	23	75	<5
6	TBME	Cl	H	−55	8	65	97
7	THF	Cl	H	−55	8	>95	34
8	CH_2Cl_2	Cl	H	−55	8	>95	<5



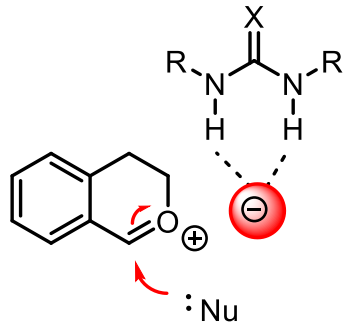
Raheem, I. T.; Thiara, P. V.; ; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404–13405

H-Bond Donor Catalysis



Direct Electrophile Activation

LUMO-lowering effect on Lewis basic electrophile



Anion-binding Activation

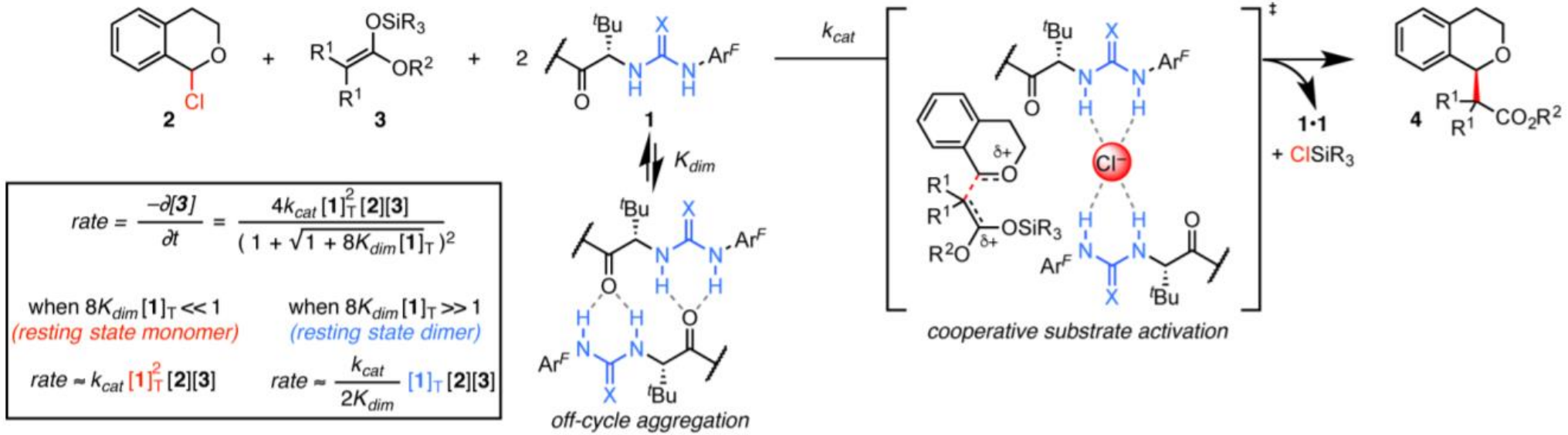
Chiral ion pairs promotes enantioselective addtion to a reactive cationic intermediate

- **Limitations: low catalytic efficiency**
  - Requires high catalyst loadings (5-20 mol %)
  - Long reaction time (>24 h)
  - Most effective under dilute reaction conditions (<0.1 M)
  - **WHY??**

Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198–7199.
Ford, D.D.; Lehnherr, D.; Kennedy, C.R.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2016**, *138*, 7860-7863.

H-Bond Donor Catalysis

- **On- and Off- Cycle**

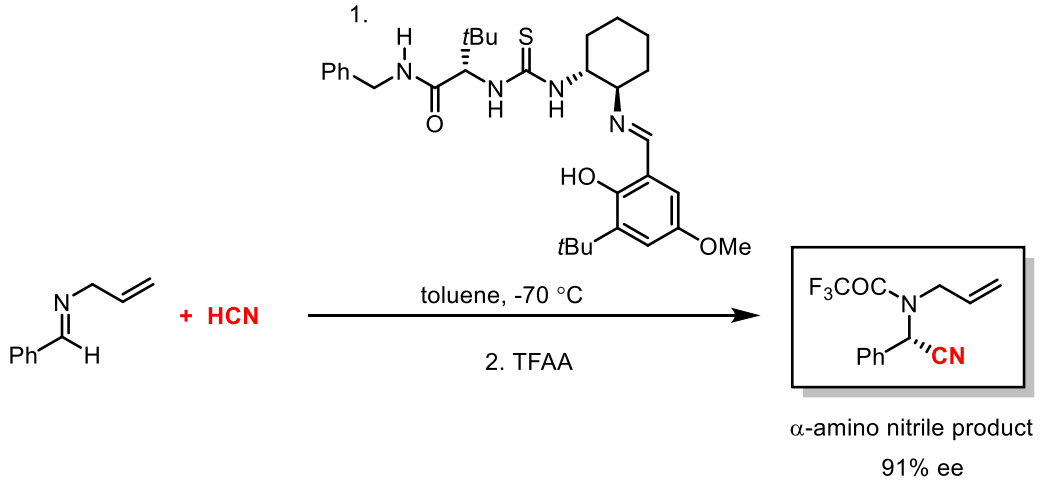


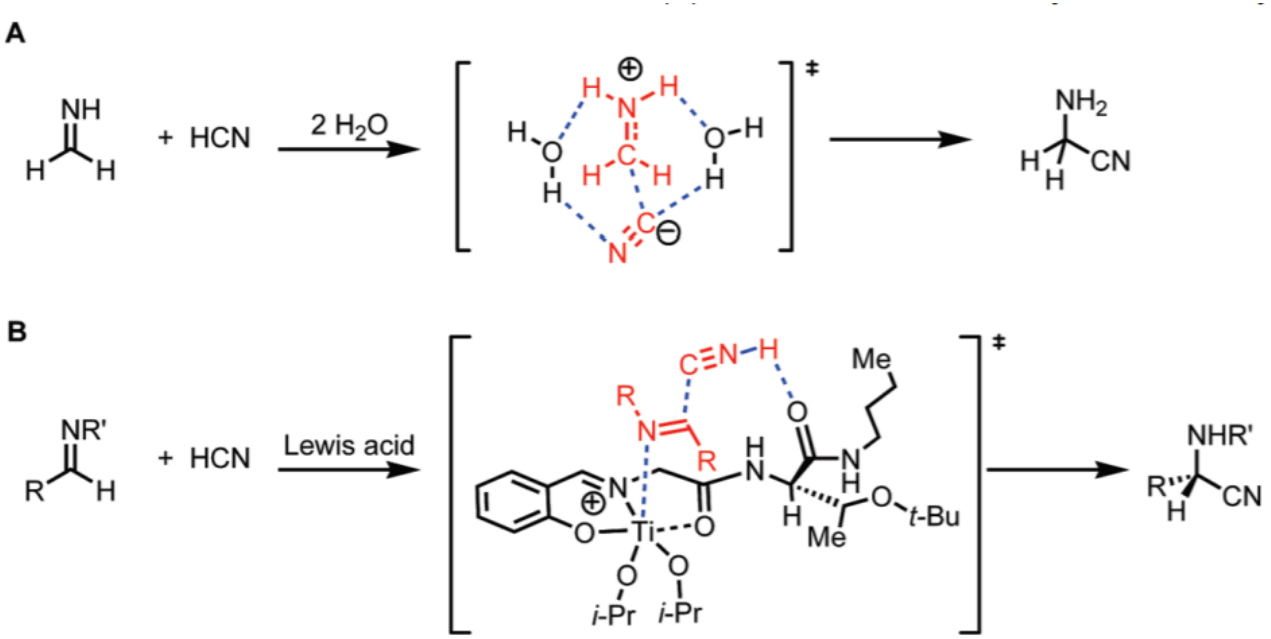
- **How to improve this?**
  - Favor cooperative substrate activation
  - Avoid nonproductive aggregation
  - *Link the dimeric catalysts*

Ford, D.D.; Lehnherr, D.; Kennedy, C.R.; Jacobsen, E.N. *J. Am. Chem. Soc.* **2016**, *138*, 7860-7863.

H-Bond Donor Catalysis

- **Transition State Stabilization: Hydrocyanation of Imines**





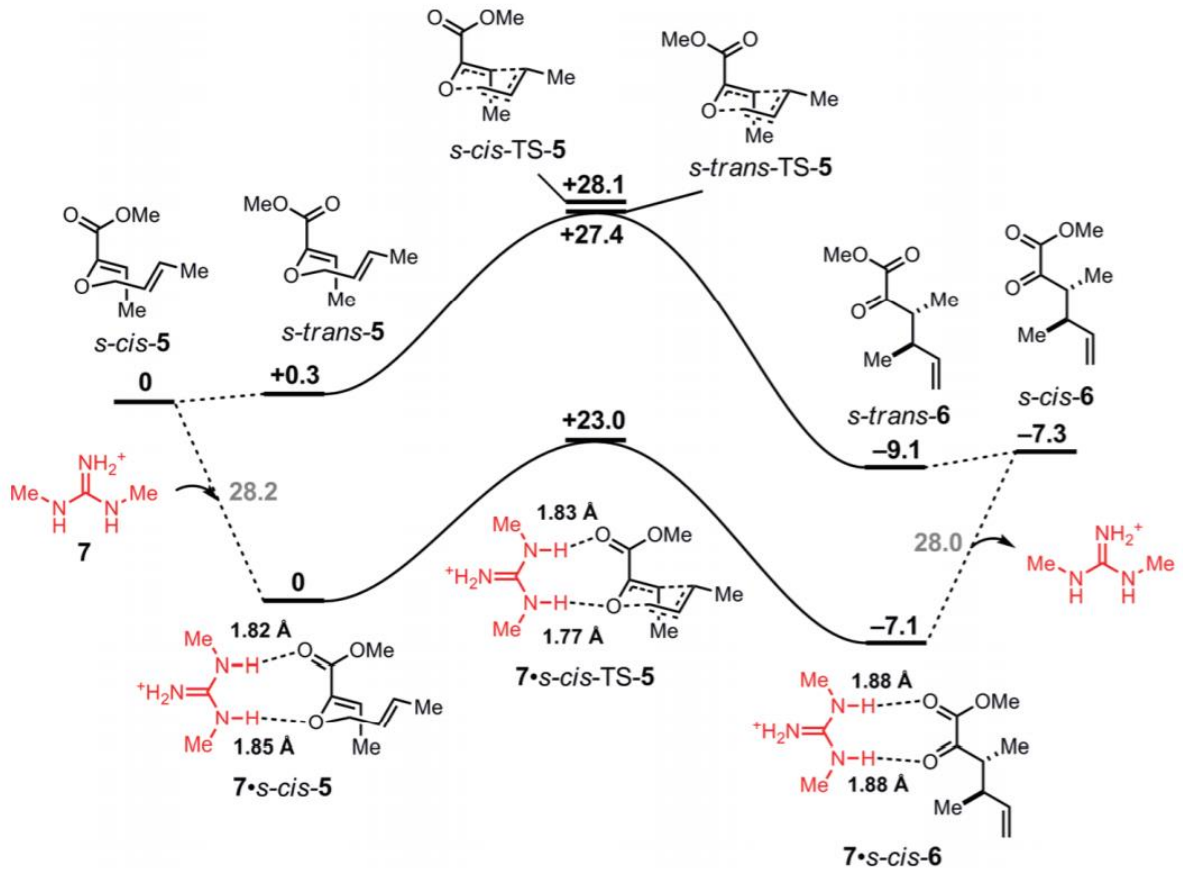
- **Nonasymmetric Imine Hydrocyanation**:
  - Promoted by polar, protic solvents
  - Charge separation and proton transfer
  - Formation of iminium/cyanide ion pair

But LA only works in nonpolar, aprotic solvents

Zuend, S. J., Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358–15374.

H-Bond Donor Catalysis

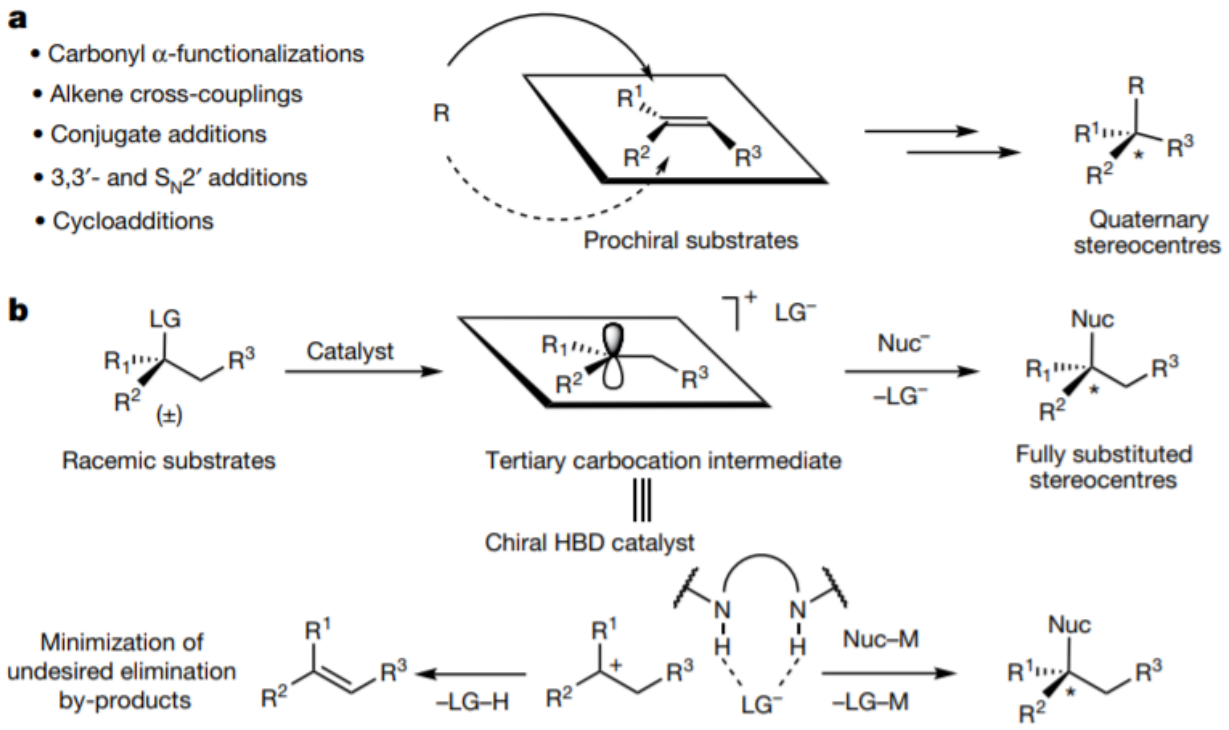
- **Transition State Stabilization: Claisen Rearrangement**

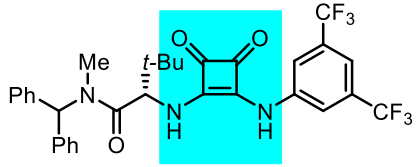


Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062–5075.

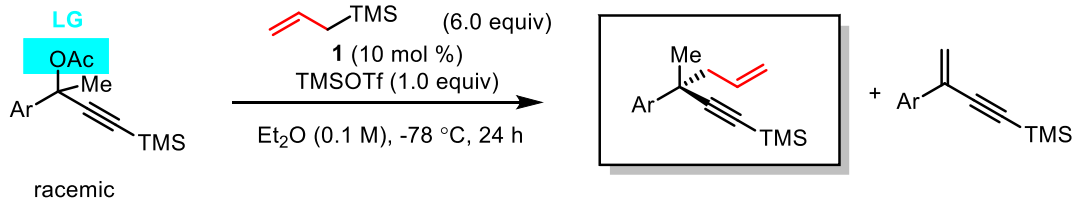
H-Bond Donor Catalysis

- **Quaternary Stereocenters**

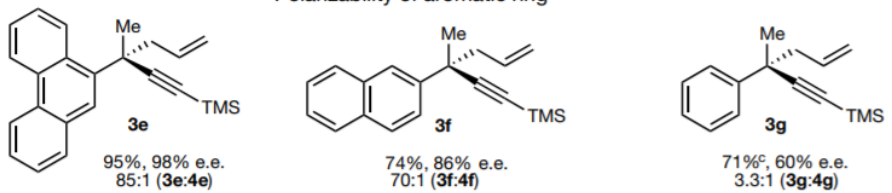


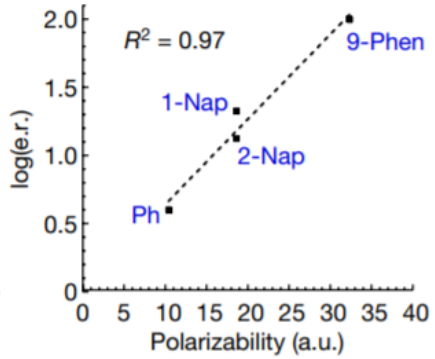


1 optimized HBD catalyst



Polarizability of aromatic ring

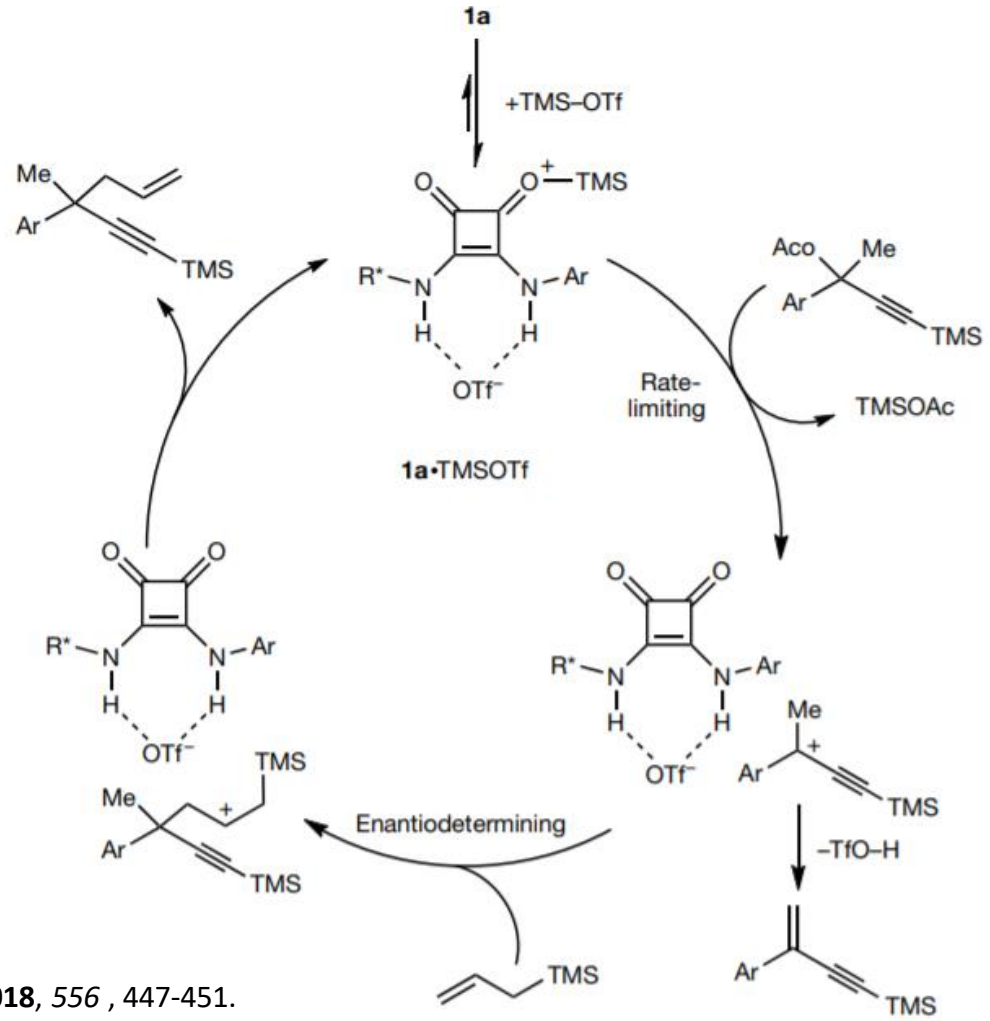




Wendlandt, A.E.; Vangal, P.; Jacobsen, E.N. *Nature* **2018**, *556* , 447-451.

H-Bond Donor Catalysis

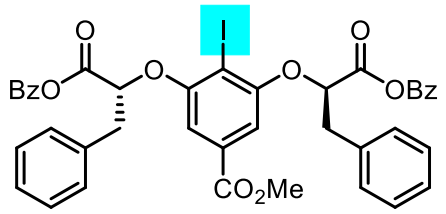
- **Quaternary Stereocenters**



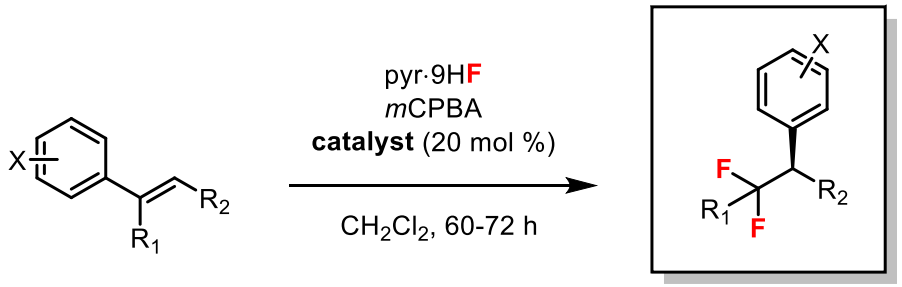
Wendlandt, A.E.; Vangal, P.; Jacobsen, E.N. *Nature* **2018**, *556* , 447-451.

Hypervalent Iodine

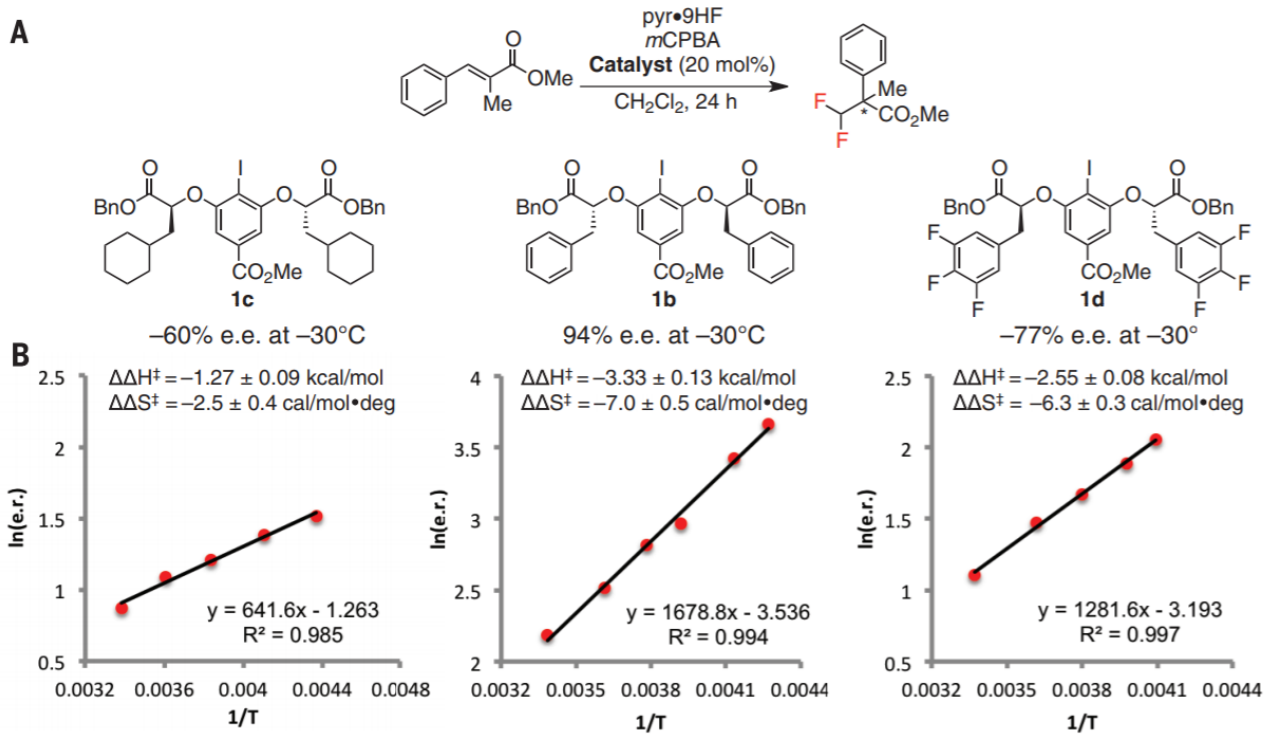
- **Asymmetric Difluorination**



optimized aryl iodide catalyst



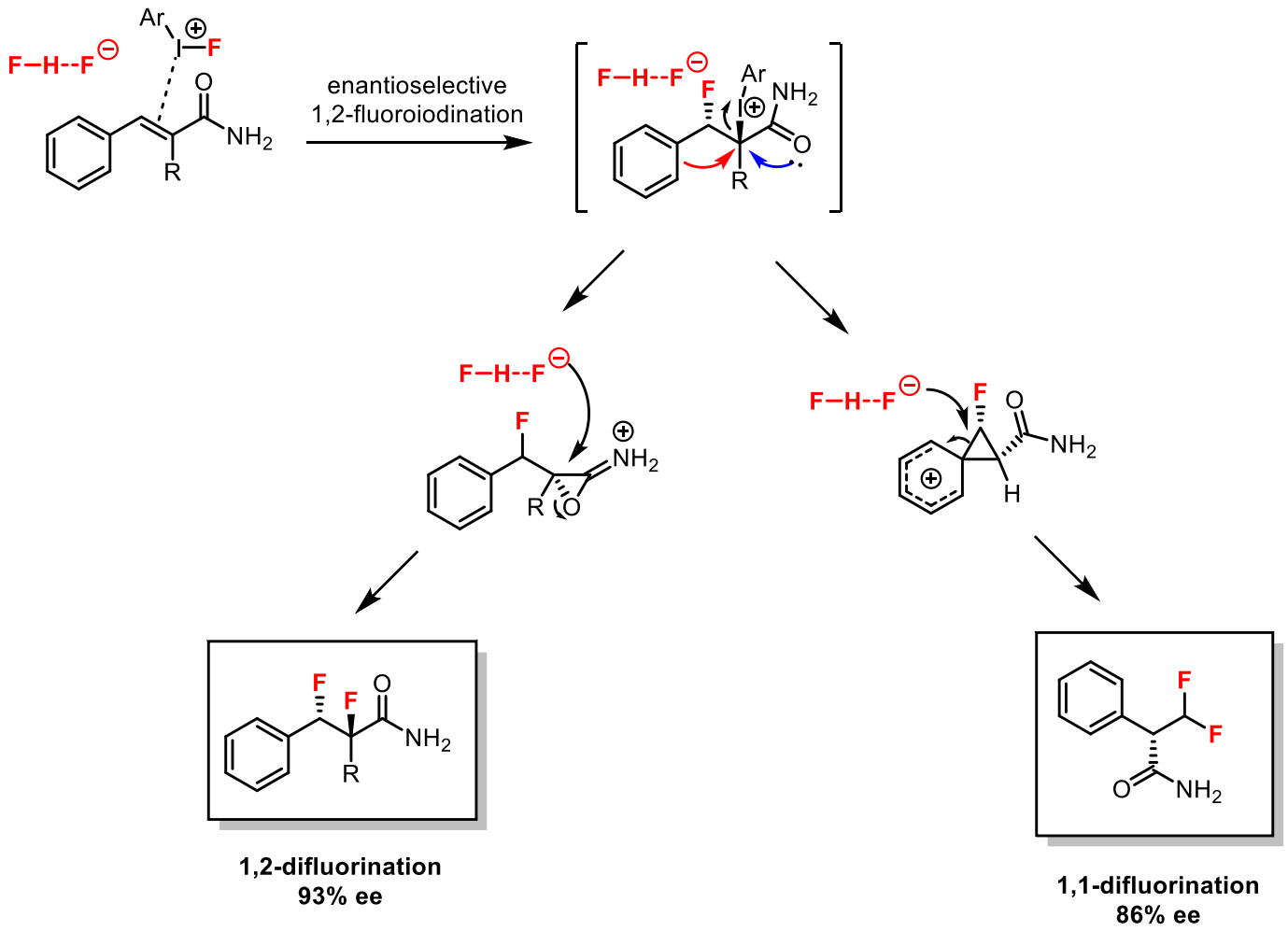
- **Primary, secondary, and tertiary cinnamamides**: all highly enantioselective
- **Substrate with no conjugation to C=O**: good reactivity with modest selectivity



Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *Science,* **2016,** *353,* 6294

Hypervalent Iodine

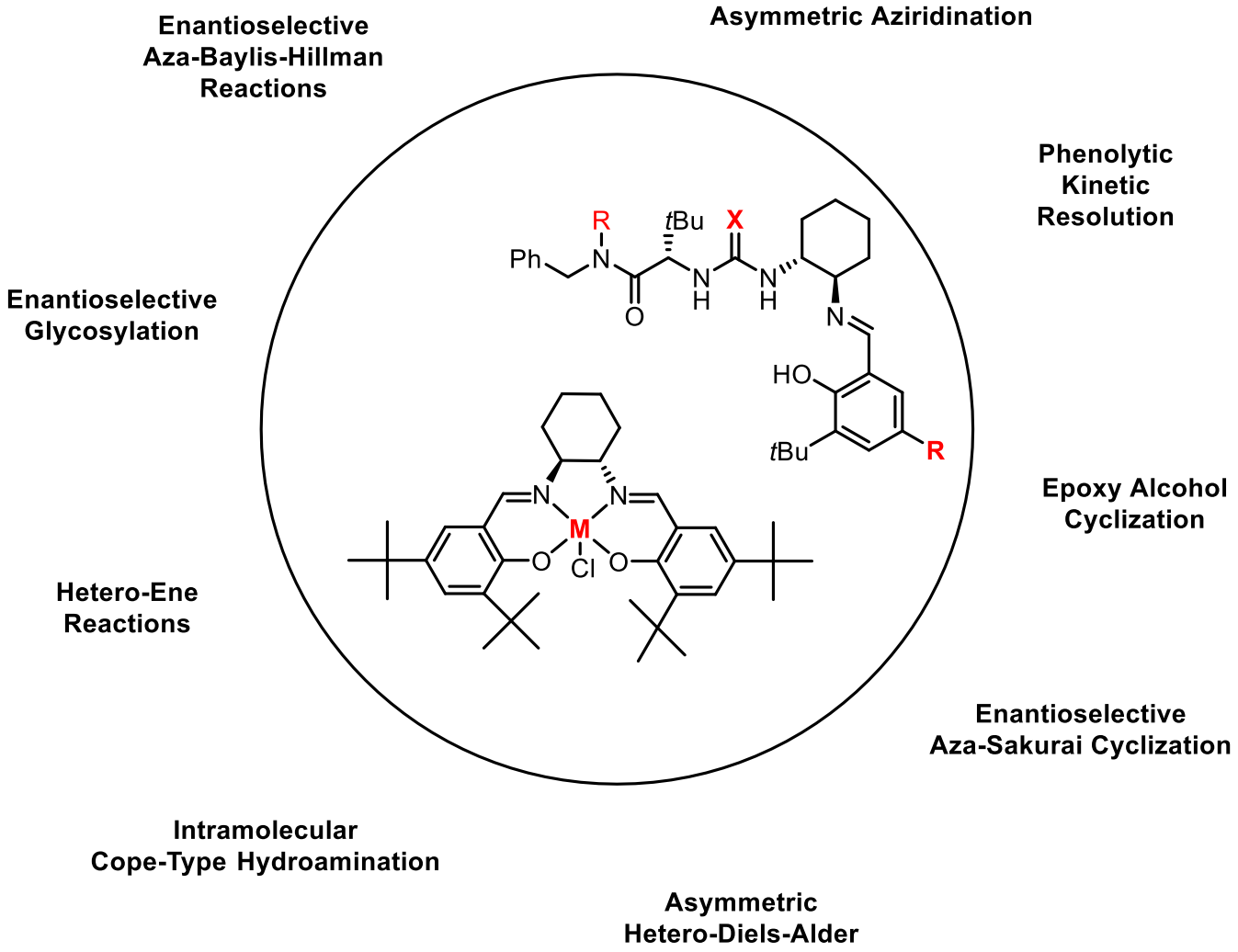
- **Mechanistic Insight**



Banik, S. M.; Medley, J. W.; Jacobsen, E. N. *Science,* **2016,** *353,* 6294

…And Many More!

- **"Privileged" Ligands**



"If you have a [asymmetric] reaction you wanna develop, try these [general] ligands and look for a hit or leads, and optimize from those leads"

"[privileged chiral ligands] Took asymmetric catalysis out of the realm of specialists to the realm of just synthetic chemistry"

-Prof. Jacobsen