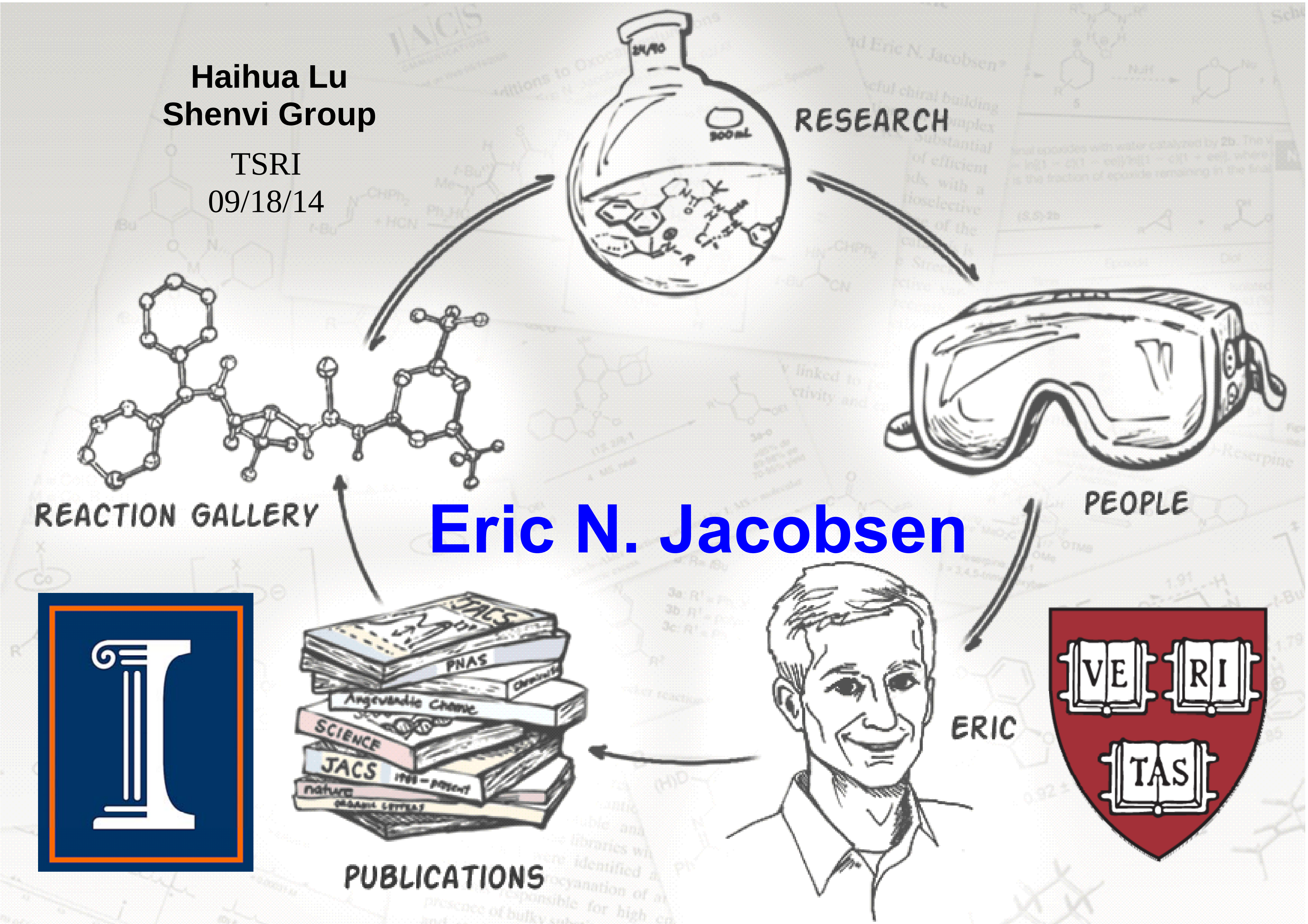
Haihua Lu
Shenvi Group

TSRI
09/18/14

Eric N. Jacobsen



http://www.people.fas.harvard.edu/~enjacobs/

Eric N. Jacobsen

Biography

- ☐ Born: February 22, 1960 in Manhattan, raised in New York city
- ☐ BS, 1982: New York University, Yorke Rhodes
- ☐ PhD, 1986: UC Berkeley, Robert Bergman
- ☐ NIH Postdoc, 1988: MIT, Karl Barry Sharpless

Independent Career

- ☐ University of Illinois: 1988-1993
- ☐ Harvard University: 1993 (full prof.)-now
  Sheldon Emory Professor & Chair

  Also a consultant at Merck, Amgen, Cubist, Firmenich, and PTC Pharmaceuticals.

Current Group: 12 graduate stuedents + 11 postdocs

128 former students and postdocs and 43 in academia

website: http://www.people.fas.harvard.edu/~enjacobs/

Awards

1. 1990: NSF Presidential Young Investigator Award
2. 1991: the Packard Fellowship
3. 1992: the Camille and Henry Dreyfus Teacher-Scholar Award
   the Alfred P. Sloan Foundation Fellowship
4. 1993: the ACS Cope Scholar Award
5. 1994: the Fluka "Reagent of the Year" Prize
6. 1996: the Thieme-IUPAC Prize in Synthetic Organic Chemistry
7. 1999: the Baekeland Medal
8. 2001: the ACS Award for Creativity in Synthetic Organic Chemistry
9. 2002: the NIH Merit Award
10. 2004: election to the American Academy of Arts & Sciences
11. 2005: the Mitsui Catalysis Science Award
12. 2008: the ACS H.C. Brown Award for Synthetic Methods
    election to the National Academy of Sciences
13. 2010: the Janssen Prize
14. 2011: the Noyori Prize
    the Nagoya Gold Medal Prize
15. 2012: the Chirality Medal
16. 2013: the Remsen Award

Eric N. Jacobsen

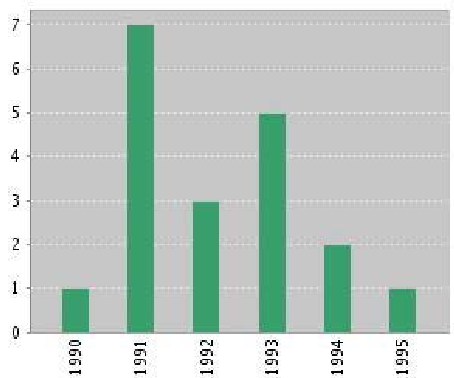
Research Impact

(from *web of science*)

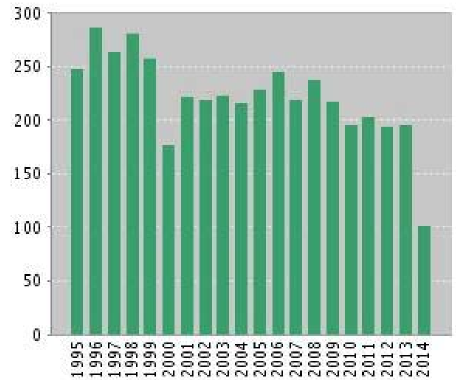
☐ **Illinois**: 19 publications

Times Cited: 4987
Average citations per year: 199.48

Published Items in Each Year



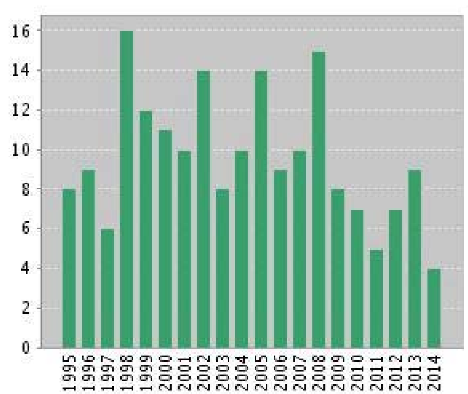
Citations in Each Year



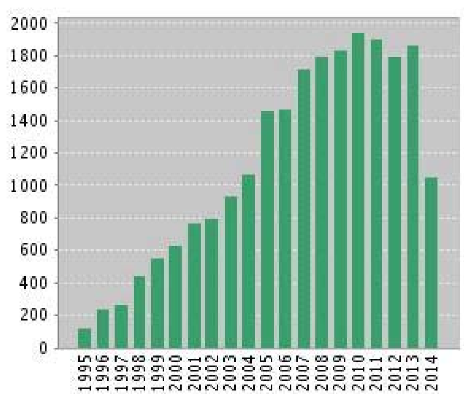
☐ **Harvard:** 204 publications

Times Cited: 22725
Average citations per year: 1082.14

Published Items in Each Year

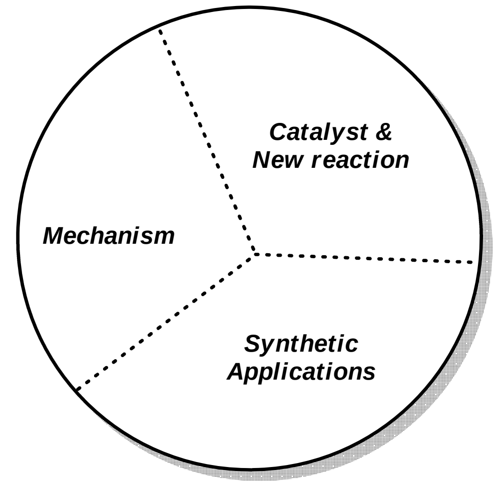


Citations in Each Year



The latest 20 years are displayed.

Research Overview



Top 3 work

Enantioselective epoxidation of unfunctionalized olefins catalyzed by salen manganese complexes
By: ZHANG, W; LOEBACH, JL; WILSON, SR; et al.
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY Volume: 112 Issue: 7
Pages: 2801-2803 Published: MAR 28 1990
Total citations: 1262

Asymmetric catalysis with water: Efficient kinetic resolution of terminal epoxides by means of catalytic hydrolysis
By: Tokunaga, M; Larrow, JF; Kakiuchi, F; et al.
SCIENCE Volume: 277 Issue: 5328
Pages: 936-938 Published: AUG 15 1997
Total citations: 915

Highly enantioselective epoxidation catalysts derived from 1,2-diamino-cyclohexane
By: JACOBSEN, EN; ZHANG, W; MUCI, AR; et al.
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY Volume: 113 Issue: 18
Pages: 7063-7064 Published: AUG 28 1991
Total citations: 826

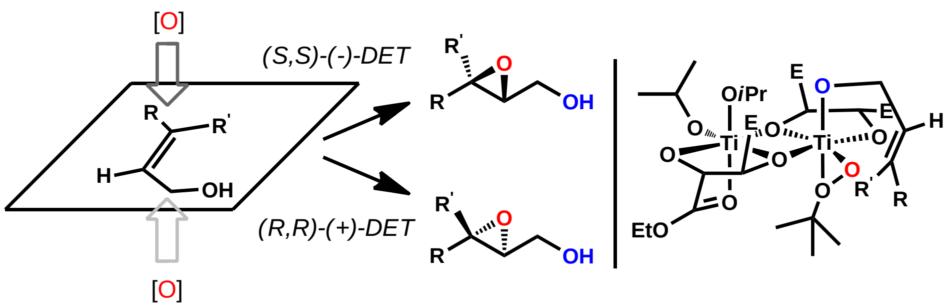
Top 100 Chemists, 2000-2010

			Papers	Citations	Impact
Top 100 Chemists, 2000-2010	14	Eric N. JACOBSEN Harvard University	81	7,985	98.58

Schiff Base in Metal Catalysis

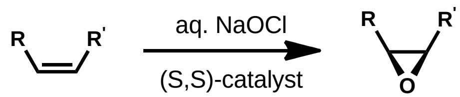
□ Jacobsen(-Katsuki) epoxidation

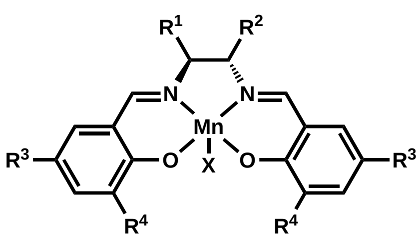
Functionalized alkenes: e.g. Sharpless epoxidation of allylic alcohol



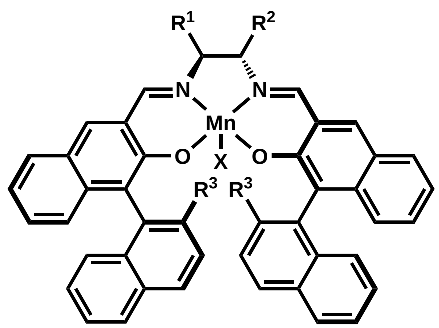
Katsuki, T.; Sharpless, K. B. *JACS*, **1980**, *102*, 5974

Unfunctionalized alkenes:



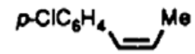
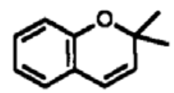
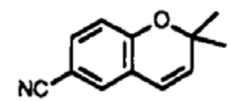
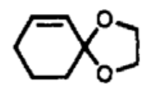
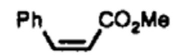


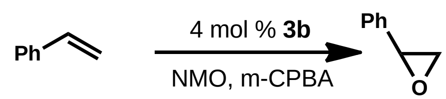
Jacobsen (3)

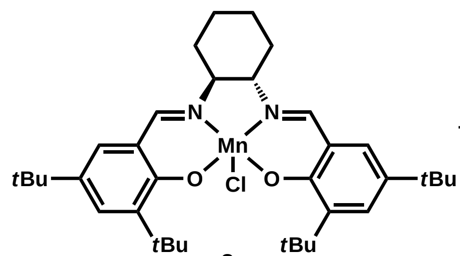


Katsuki (4)

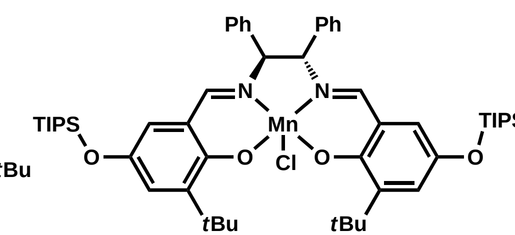
Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *JACS* **1990**, *112*, 2801
Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *TL*, **1990**, *31*, 7345

entry	olefin	epoxide yield,[b] %	ee,[c] %	equiv of 3a required for complete reactn
1		84	92	0.04
2		67	92	0.04
3		72	98	0.02
4		96	97	0.03
5		63	94	0.15
6[d]		65[e]	89	0.10





3a



3b

Jacobsen, E. N. et al. *JACS* **1991**, *112*, 7063
JACS **1994**, *116*, 9333

***trans*-alkenes are not good subtrates!**

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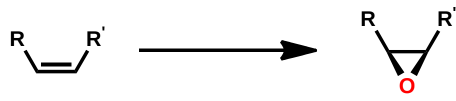
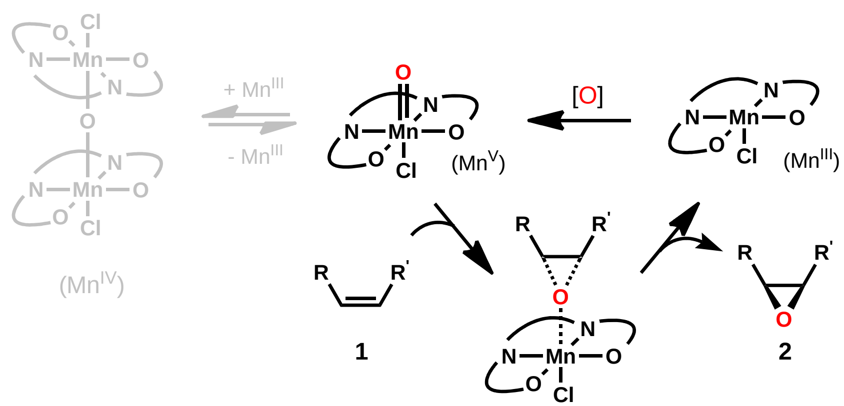
The Mechanism



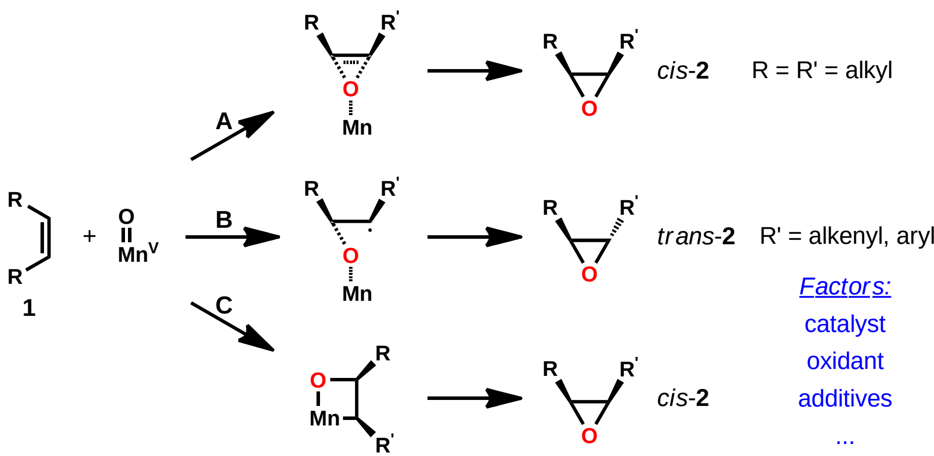
1 2

General catalytic cycle

Linker, T. *ACIEE*, **1997**, *36*, 2060



The controversy over oxygen transfer



Norrby, P. et al. *JACS*, **1995**, *117*, 11035

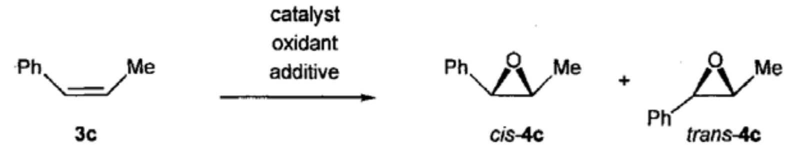
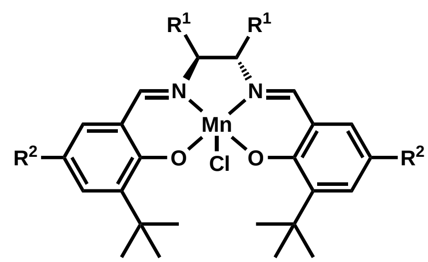


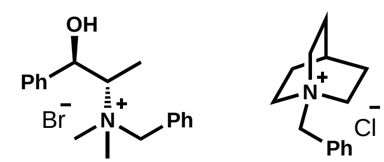
Table 1. Epoxidation of *cis-β*-methylstyrene (**3c**) with 0.04 equiv catalyst.

Entry [ref.]	Cat.	Oxidant [a]	Additive	Yield [%]	*cis*:*trans*	ee_{fac} [%] [e]
1 [8]	**1d**	NaOCl	4-PPNO [b]	98	95:5	81
2 [8]	**1d**	MCPBA	NMO [c]	91	94:6	82
3 [9]	**1a**	NaOCl	–	86	92:8	81
4 [2d]	**1e**	PhIO	4-PPNO [b]	48	77:23	88
5 [8]	**1d**	PhIO	4-PPNO [b]	76	75:25	72
6 [9]	**1c**	NaOCl	–	86	71:29	81
7 [9]	**1c**	NaOCl	**QAS** [d]	86	5:95	81

[a] NaOCl: in phosphate buffer/chlorobenzene; *m*-chloroperbenzoic acid (MCPBA): in dichloromethane; iodosobenzene (PhIO): in acetonitrile. [b] 0.2–0.4 equiv 4-phenylpyridine *N*-oxide (4-PPNO). [c] 10.0 equiv *N*-methylmorpholine *N*-oxide (NMO). [d] 0.2 equiv of a quaternary quinine ammonium salt (QAS). [e] $ee_{fac} = \% cis \times ee_{cis} + \% trans \times ee_{trans}$.



1a: R^1,R^1 = -$(CH_2)_4$-, R^2 = *t*Bu
1b: R^1,R^1 = -$(CH_2)_4$-, R^2 = OMe
1c: R^1,R^1 = -$(CH_2)_4$-, R^2 = OTIPS
1d: R^1 = Ph, R^2 = Br



same effect as QAS *neglibile*

no explanation yet!

Jacobsen, E. N. et al. *JACS* **1994**, *116*, 6937

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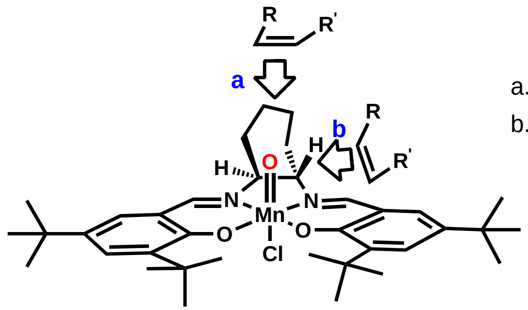
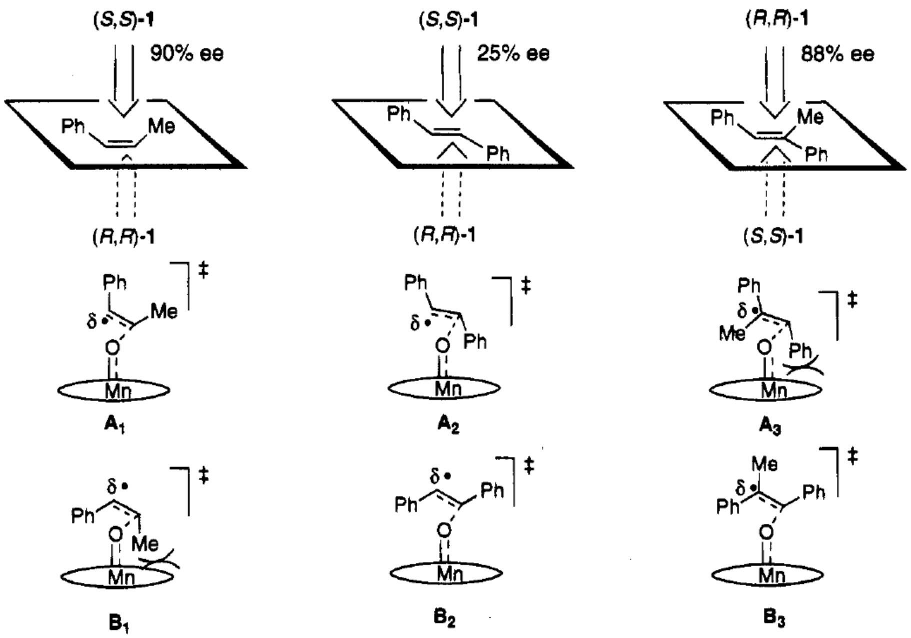
Enantioslective outcome rationale



a. Jacobsen
b. Katsuki

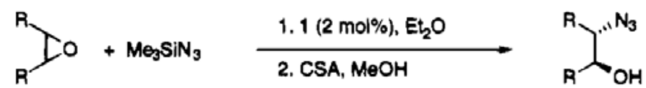


T **1994**, *50*, 4323
JOC, **1994**, *59*, 4378

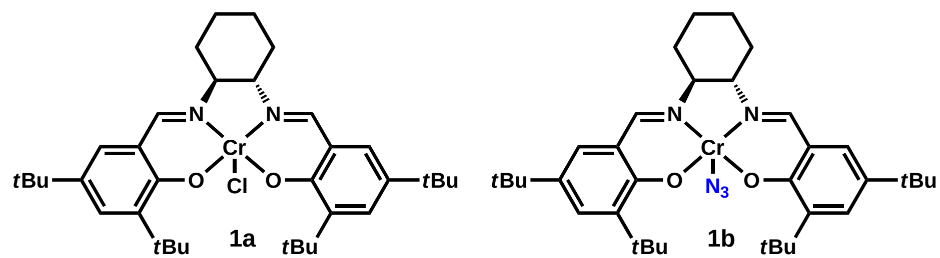
☐ Tetradentate Salen in LA catalysis

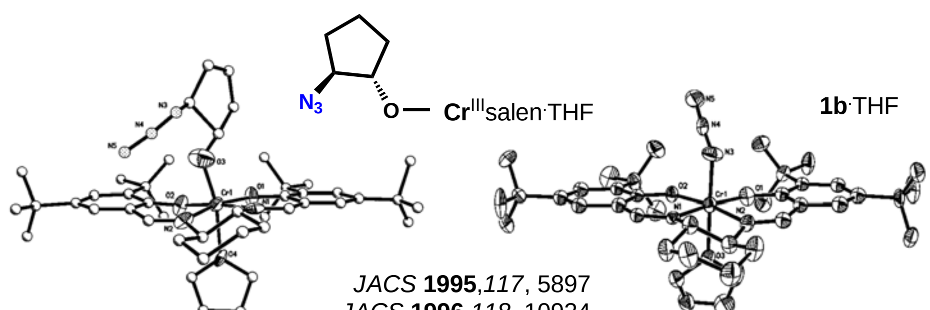
1. Ring-opening Reactions

Table 1. Enantioselective Opening of Meso Epoxides with (*R*,*R*)-**1**[a]



	3	7	8	9	10	11	12
Time (h)	18	28	18	36	16	46	30
Yield (%)[b]	80	80	80	80	90	72	65[d]
ee (%)[c]	88	94	98	95	95	81	82





JACS **1995**,*117*, 5897
JACS **1996**,*118*, 10924

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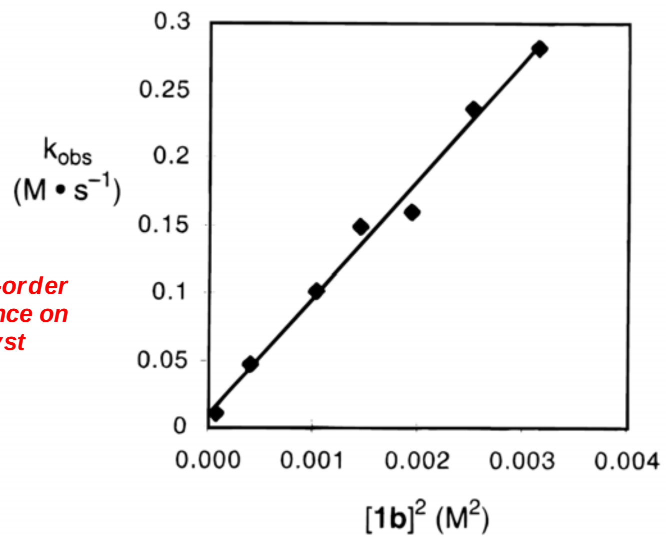
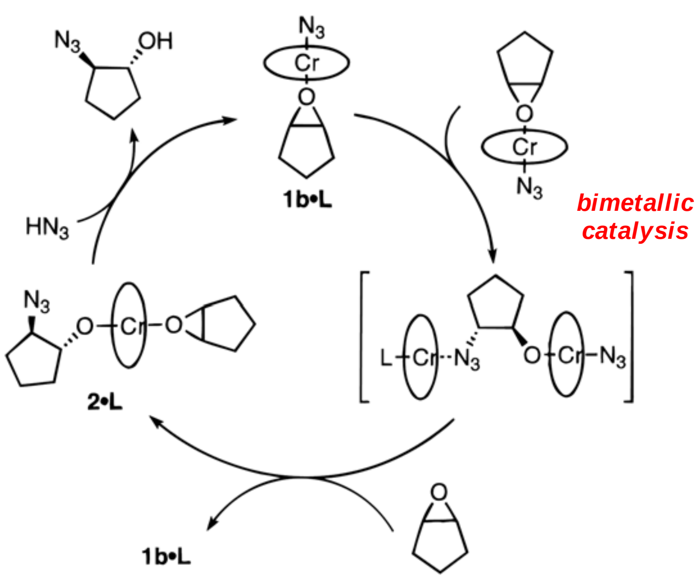
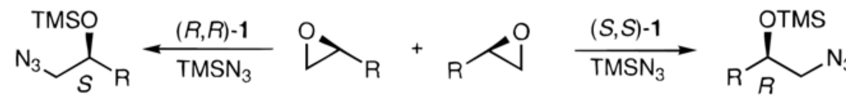


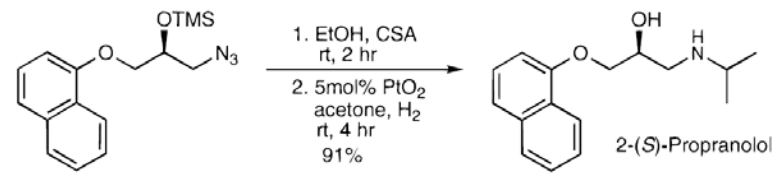
a second-order dependence on catalyst

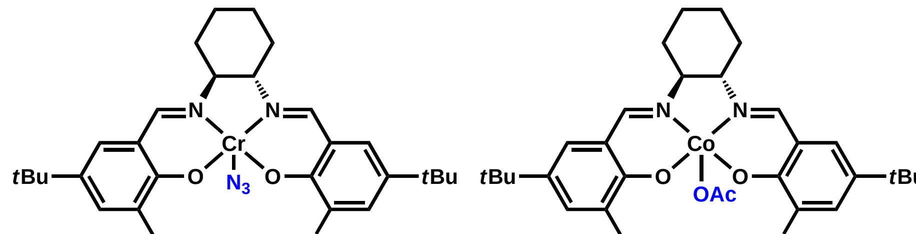
proposed mechanism



Kinetic resolution of terminal epoxides

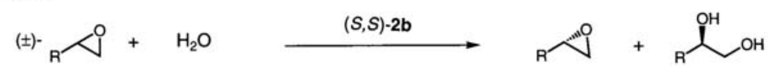






1 — *JACS* **1996**, *118*, 7420 **2b** — *Science* **1997**, *277*, 936

Table 1. Hydrolytic kinetic resolution of terminal epoxides with water catalyzed by **2b**. The values for k_{rel} were calculated using the equation $k_{rel} = \ln[(1 - c)(1 - ee)]/\ln[(1 - c)(1 + ee)]$, where ee is the enantiomeric excess of the epoxide and c is the fraction of epoxide remaining in the final reaction mixture (*4*).



Entry	R	Concentration: 2b (mol %)	Concentration: Water (equiv)	Time (hours)	Epoxide: ee (%)	Epoxide: Isolated yield (%)	Diol: ee (%)	Diol: Isolated yield (%)	k_{rel}
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.

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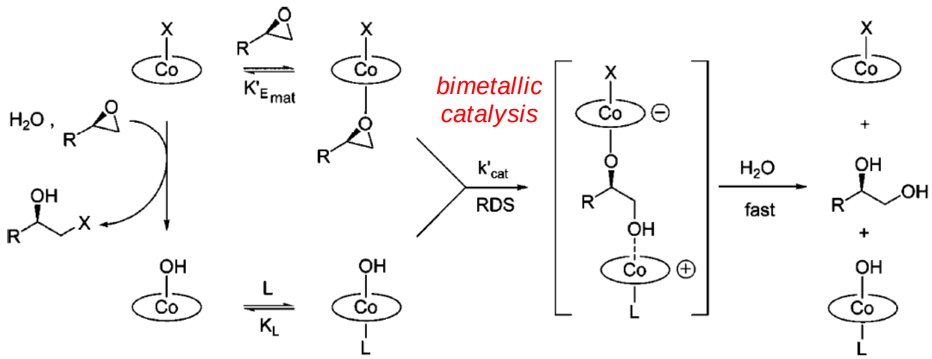
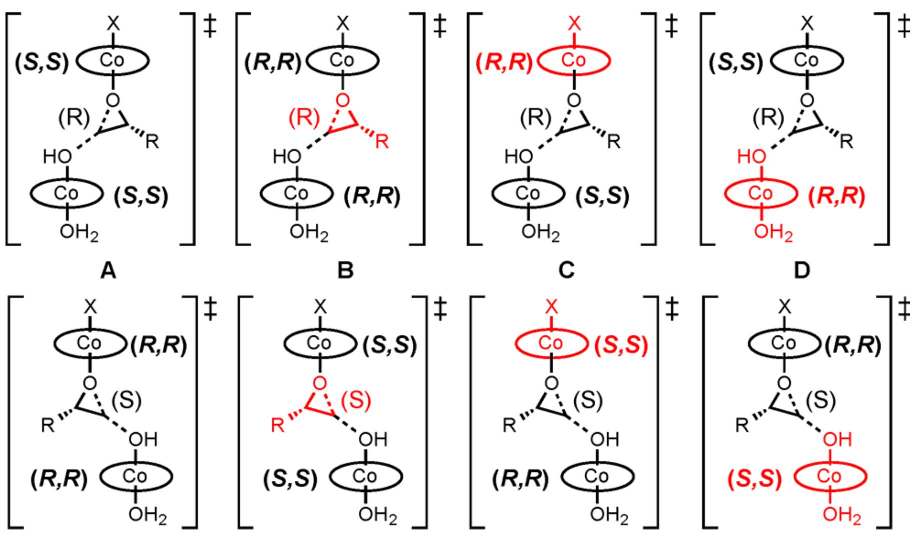
proposed mechanism

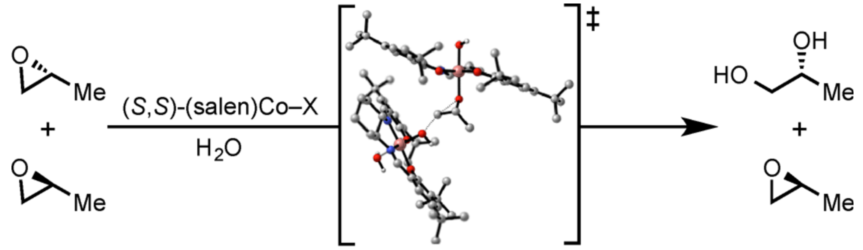


JACS **2004**, *126*, 1360
JOC **2012**, *77*, 2486

8 possible stereochemically distinct pathways

all matched	*mismatched epoxide*	*mismatched Lewis acid*	*mismatched nucleophile*

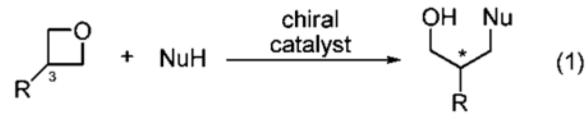




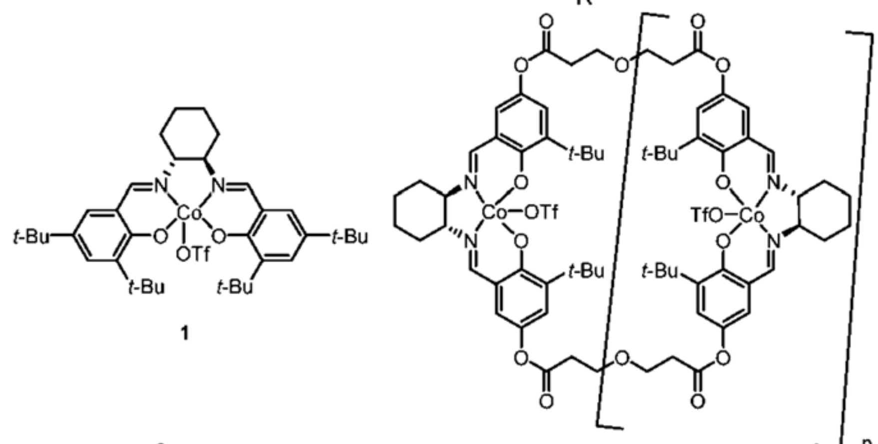
stereoselectivity is achieved through the cooperative action of both catalyst molecules

JACS **2013**, *135*, 15595

Extended to ring-opening of oxetanes

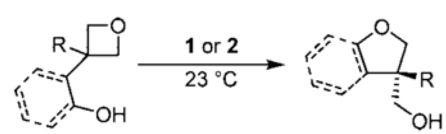


(1)



1

2 (n = 1-4)

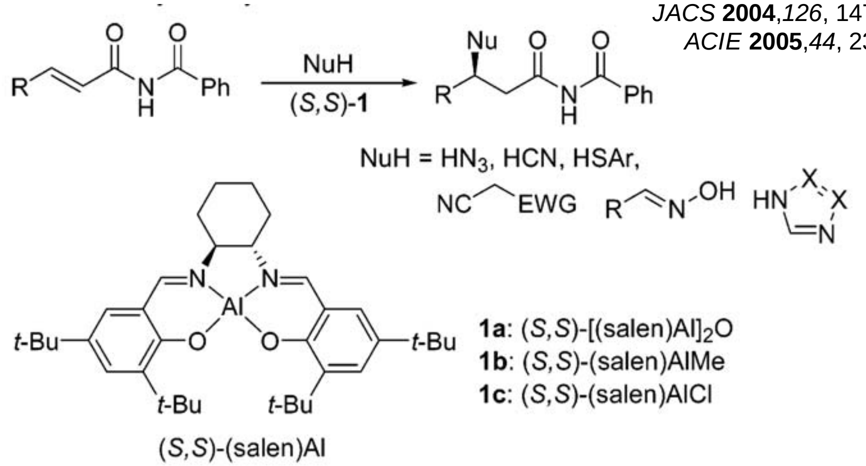


84-99% ee

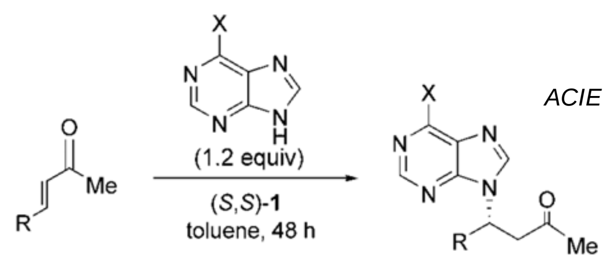
JACS **2013**, *135*, 15595

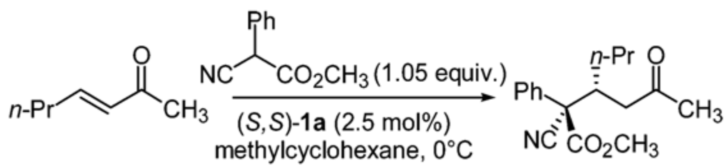
2. Asymmetric conjugate additions

JACS **1999**,*121*, 8959
JACS **2003**,*125*, 4442
JACS **2003**,*125*, 11204
JACS **2004**,*126*, 14724
ACIE **2005**,*44*, 2393



ACIE **2005**,*44*, 2393



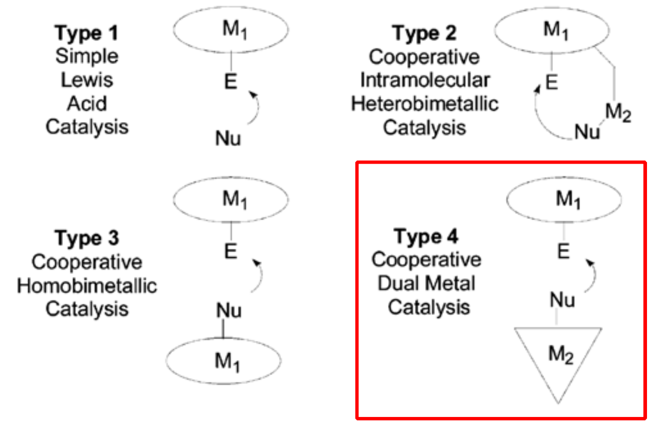


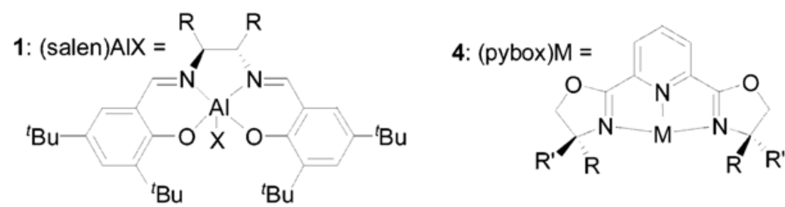
2j
88% yield
>30:1 d.r.
89% *ee*

JACS **2005**,*44*, 1313

Cooperative dual catalysis

JACS **2004**,*126*, 9928

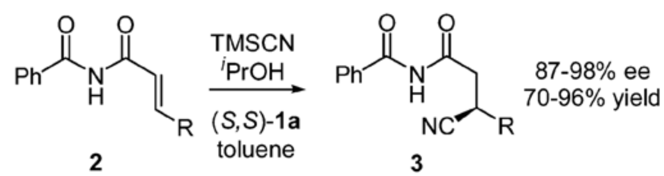




1a: (salen)AlCl:
(R= -$(CH_2)_4$-; X=Cl)
1b: $[(salen)Al]_2O$:
(R= -$(CH_2)_4$-; X=OAl(salen))
1c: achiral $[(salen)Al]_2O$:
(R=H; X=OAl(salen))

(*S*,*S*)-**4a**: R=H; R'=^{i}Pr; M=$YbCl_3$
(*S*,*S*)-**4b**: R=H; R'=^{i}Pr; M=$ErCl_3$
4c: R, R'=Me; M=$ErCl_3$

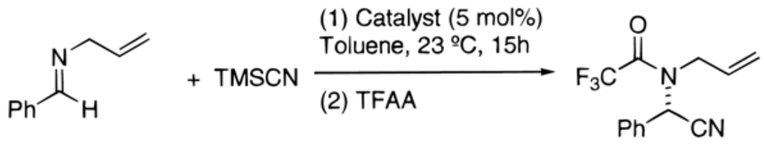
time: 26-48 to 8-24 h
TMSCN: 2.5-4.0 to 2.0 equiv.
cat: 10-15 mol % to 7 mol %
ee: similar or better



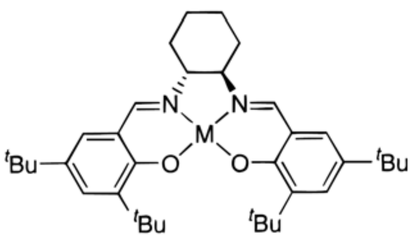
87-98% ee
70-96% yield
(1)

3. Asymmetric 1,2-additions

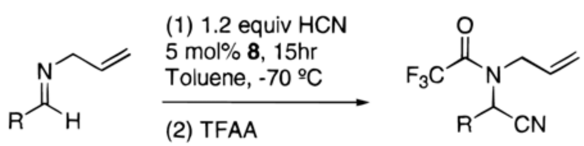
Sigman, M. S.; Jacobsen, E. N.
JACS **1998**, *120*, 5315



9a **10a**



M	ee	% Conv.
1: M = H, H		
2: M = Ti(IV)Cl_2	24	19
3: M = Cr(III)Cl	0	83
4: M = Mn(III)Cl	20	80
5: M = Ru(III)(NO)Cl	6	93
6: M = Co(II)	0	43
7: M = Co(III)OAc	6	65
8: M = Al(III)Cl	45	100



9a-i **10a-i**

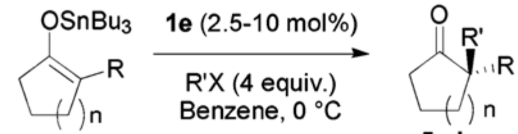
Entry		R	%yield[a]	%ee[b]
a	**9a**	Ph	91	95
b	**9b**	*p*-$CH_3OC_6H_4$	93	91
c	**9c**	*p*-$CH_3C_6H_4$	99	94
d	**9d**	*p*-ClC_6H_4	92	81
e	**9e**	*p*-BrC_6H_4	93	79
f	**9f**	1-Napthyl	95	93
g	**9g**	2-Napthyl	93(55)[c]	93(>99)[c]
h	**9h**	Cyclohexyl	77	57
i	**9i**	*t*-Butyl	69	37

☐ Miscellaneous reactions with Salen complexes

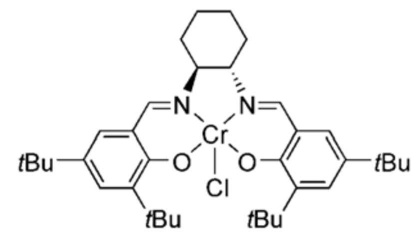
e.g. 1: Asymmetric alkylations of Tin enolates

JACS **2005**, *127*, 62
ACIE **2007**, *46*, 3701

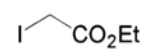
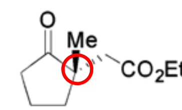
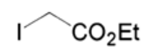
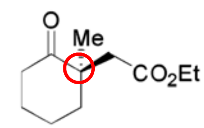
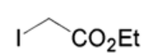
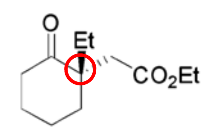
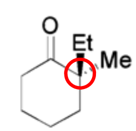
4a: n = 1, R = Me
4b: n = 2, R = Me
4c: n = 2, R = Et
4d: n = 3, R = Me



5a-i

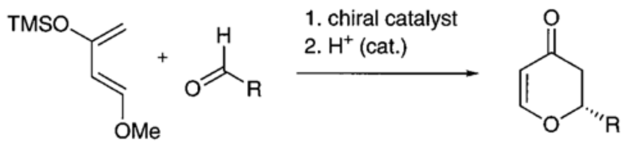


1a

4a[f]		*R,R*	 **5c**	73	96
4b[f]		*R,R*	 **5e**	67	95
4c[g]		*S,S*	 **5g**	72	89
4c[f]	CH_3I	*S,S*	 **5h**	43	90

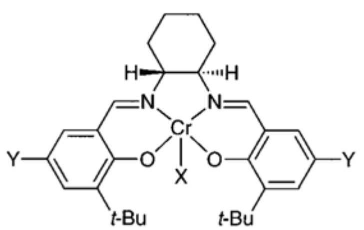
Hetero-Diels-Alder Reaction

JOC **1998**, *63*, 403



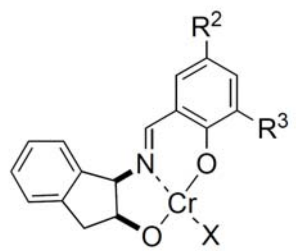
1 2

entry	R	temp (°C)	cat. 6a ee (%)[b]	cat. 6a yield (%)[c]	cat. 6b ee (%)[b]	cat. 6b yield (%)[c]
a	Ph	−30	87	85	65	98
b	C_6H_{11}	−20	93	71	85	76
c	*n*-C_5H_{11}	−40	83	86	62	85
d	2-furyl	−10	76 (99)	89 (63)	68	80
e	(*E*)-PhCH=CH	0	70	65	73 (99)	96 (64)
f	*p*-$BrC_6H_4CH_2OCH_2$	−30	79	67	84 (99)[d]	94 (70)[d]
g	*o*-$ClC_6H_4CO_2CH_2$	−20	83 (99)[d]	92 (67)[d]	72	86



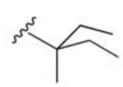
(*R*,*R*) - **3**: X = Cl, Y = *t*-Bu
4: X = N_3, Y = *t*-Bu
5: X = F, Y = *t*-Bu
6: X = BF_4 **a**: Y = *t*-Bu
b: Y = OMe

☐ **Tridentate Schiff base complexes**

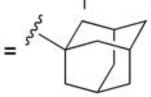


(1*R*,2*S*)-**1a,b** R^2 = *t*Bu R^3 = *t*Bu

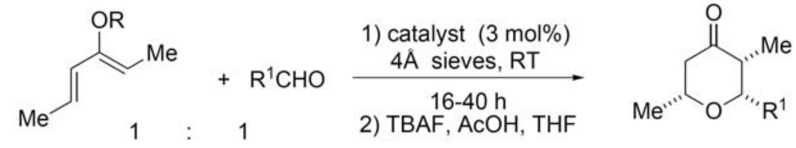
(1*R*,2*S*)-**2a,b** R^2 = H R^3 =



(1*R*,2*S*)-**3a,b** R^2 = Me R^3 =



a : X = Cl **b** : X = SbF_6



4a: R = $SiMe_3$ (TMS)
b: R = $SiEt_3$ (TES)
c: R = Si(*t*Bu)Me_2 (TBS)
d: R = Si(*i*Pr)$_3$ (TIPS)

5a: R^1 = Ph
b: R^1 = CH_2OTBS
c: R^1 = CH_2OBn
d: R^1 = *n*-C_5H_{11}
e: R^1 = $(CH_2)_4CH=CH_2$
f: R^1 = CH_2CH_2Ph
g: R^1 = CH_2CH_2NHBoc
h: R^1 = 2-furyl

6a-h
>95% *de* (all *cis*)

6a: 70-82% ee
6b: 24-40% ee
tetradentate (salen)CrIII complexes

Entry	Diene	Aldehyde	Conditions[b]	Catalyst	Yield [%][c]	ee [%][d]
3	**4b**	**5b**	A	**2b**	n.d.	85
4	**4b**	**5b**	A	**3a**	88	98
5	**4b**	**5b**	A	**3b**	93	98
6	**4b**	**5a**	A	**3a**	n.d.	65
7	**4b**	**5a**	A	**3b**	n.d.	81
8	**4b** +	**5a** → **6a**	B	**3b**	72 (80)[e]	90
9	**4b** +	**5b** → **6b**	B	**3a**	90	99
10	**4b**	**5b**	B	**3b**	97	> 99
11	**4b**	**5c**	B	**3b**	89	94
12	**4b**	**5d**	A	**3b**	85	98
13	**4b**	**5e**	A	**3b**	78	98
14	**4b**	**5f**[f]	B	**3b**	78 (84)[e]	98
15	**4b**	**5g**	B	**3b**	28 (31)[e]	96
16	**4b**	**5h**	B	**3b**	77 (86)[e]	95
17	**4a**	**5d**	A	**3b**	81	98
18	**4c**	**5d**	A	**3b**	93	96
19	**4b**	**5d**	A	**3b**	77	94

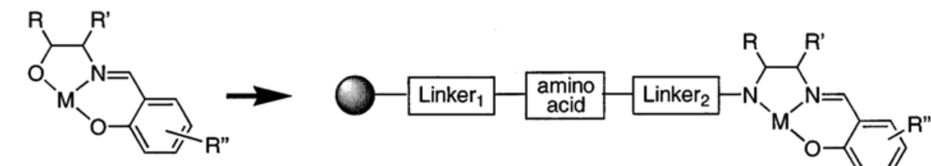
ACIE **1999**,*38*, 2398

Eric N. Jacobsen

H-Bonding Catalysis

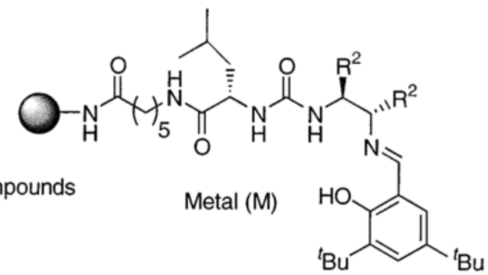
☐ Sigman, M. S.; Jacobsen, E. N. *JACS* **1998**, *120*, 4901

Development of Schiff base catalysts
***Break into** a new area and can't stop...*



tridentate Schiff base complex

Library 1



Library Size : 12 Compounds

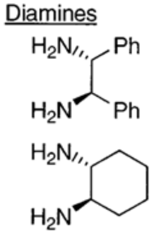
M	None	Ti	Mn	Fe	Ru	Co	Cu	Zn	Gd	Nd	Yb	Eu
e (%)	19	4	5	10	13	0	9	1	2	3	0	5
conv.(%)	59	30	61	69	63	68	55	91	95	84	94	34

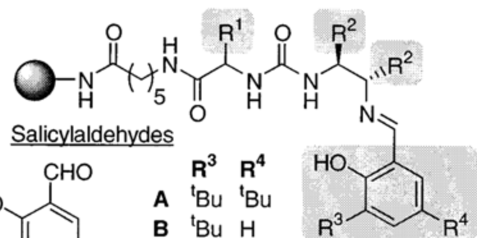
Library 2

<u>Amino Acid</u>
Leu, **D-Leu**, **His**
Phg (Phenylglycine)

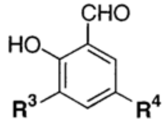
<u>Diamines</u>

DP
CH





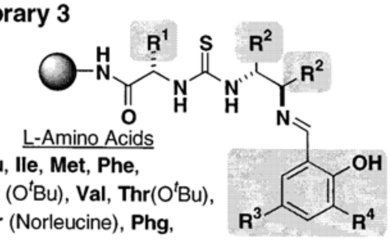
<u>Salicylaldehydes</u>



	R^3	R^4
A	^{t}Bu	^{t}Bu
B	^{t}Bu	H
C	H	^{t}Bu
D	^{t}Bu	OMe
E	Br	Br
F	^{t}Bu	NO_2

<u>Library Size: 48 Compounds</u>

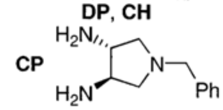
Library 3



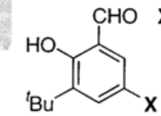
<u>L-Amino Acids</u>
Leu, **Ile**, **Met**, **Phe**,
Tyr (O^{t}Bu), **Val**, **Thr**(O^{t}Bu),
Nor (Norleucine), **Phg**,
Chg (Cyclohexylglycine),
***t*-Leu** (*tert*-Leucine)

<u>(*R, R*)-Diamines</u>
DP, CH

CP

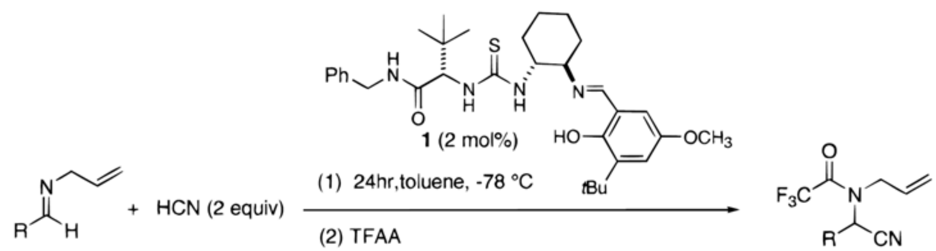


<u>Salicylaldehydes</u>



X = OMe, H, ^{t}Bu, Br

<u>Library Size: 132 Compounds</u>



entry	R	yield[a] (%)	ee[b] (%)
a	Ph	78	91
b	*p*-$OCH_3C_6H_4$	92	70
c	*p*-BrC_6H_4	65	86
d	2-napthyl	88	88
e	*tert*-butyl	70	85
f	cyclohexyl	77	83

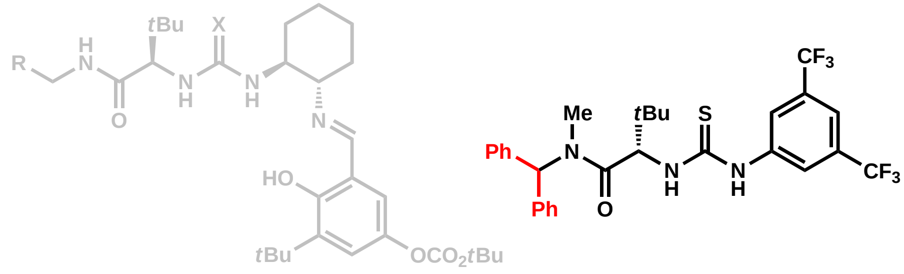
ACIE **2000**, *39*, 1279
JACS **2002**, *124*, 10012
JACS **2005**, *127*, 8946
Nature **2009**, *461*, 968

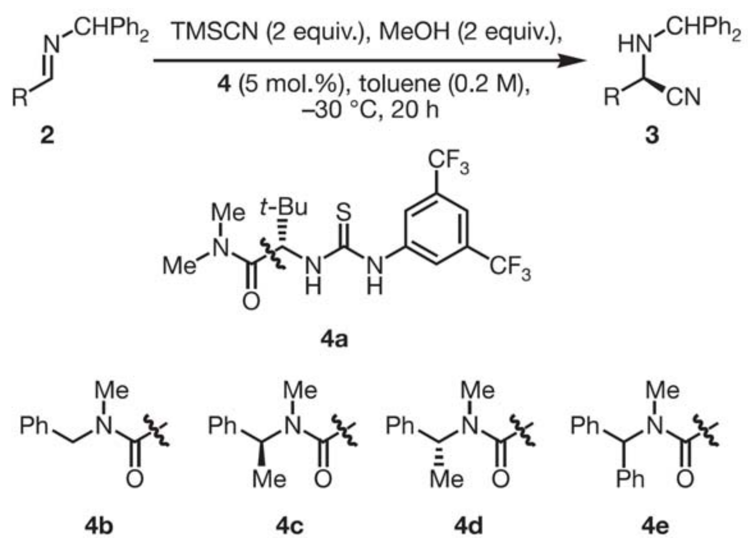
⋮

Reviews: *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543; *Chem. Rev.* **2007**, *107*, 5713–5743; *Angew. Chem., Int. Ed.* **2013**, *52*, 534–561.

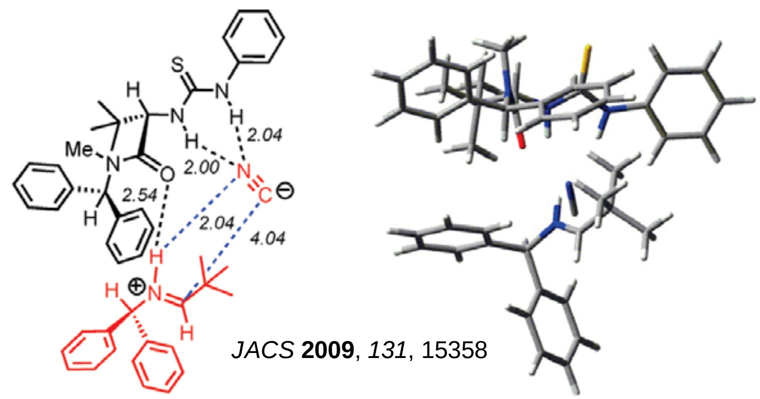
Scaleable Strecker syntheses of unnatural α-amino acids

Nature **2009**, *461*, 968

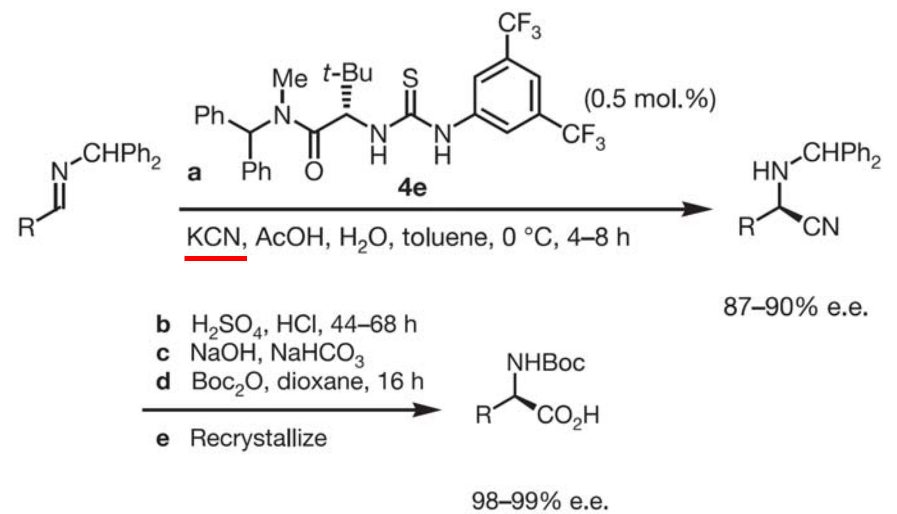


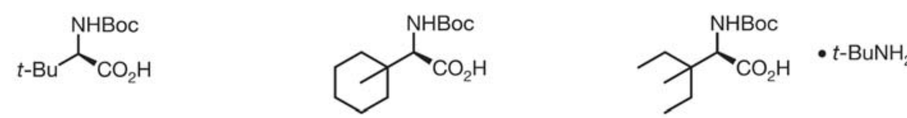


Entry	Catalyst	Enantiomeric excess (%), *R* = *tert*-Bu	Enantiomeric excess (%), *R* = C_6H_5
1	**4a**	−14	41
2	**4b**	30	86
3	**4c**	58	90
4	**4d**	77	97
5	**4e**	93	98



JACS **2009**, *131*, 15358





5a: 62–65% yield, 6 to 14-g scale

5b: 50–51% yield, 3.5-g scale

5d: 48–51% yield, 4-g scale

Reviews: *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543; *Chem. Rev.* **2007**, *107*, 5713–5743; *Angew. Chem., Int. Ed.* **2013**, *52*, 534–561.

Eric N. Jacobsen

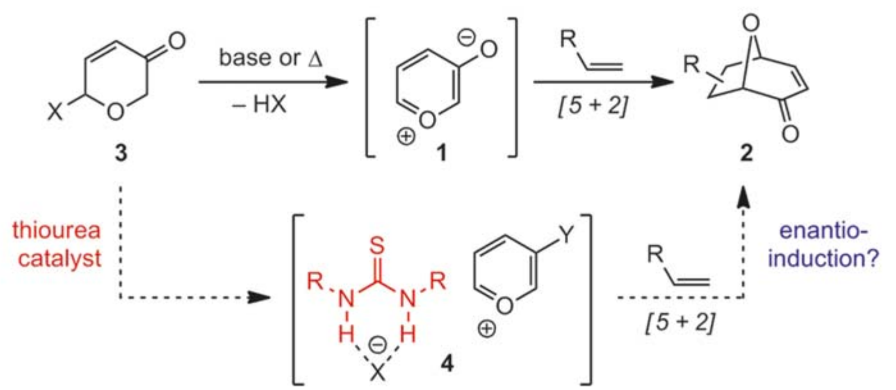
Pictet-Spengler Reaction
Mannich Reaction
Claisen Rearrangement
Cationic Polycyclization
⋮

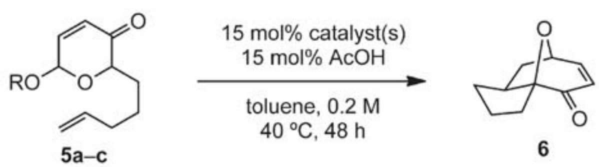
⇒ **Numerous publications**

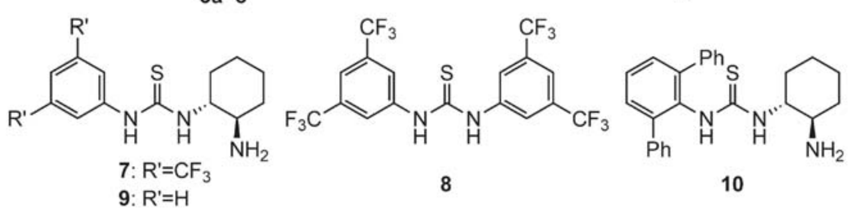
Anyon-binding catalysis

Oxidopyrylium-Based [5 + 2] Cycloadditions

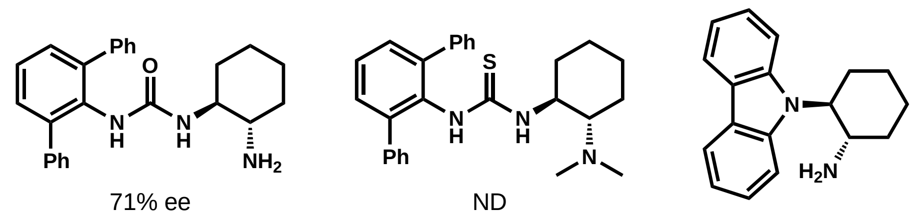
JACS **2011**, *133*, 14578
ACIE **2014**. *53*. 5912

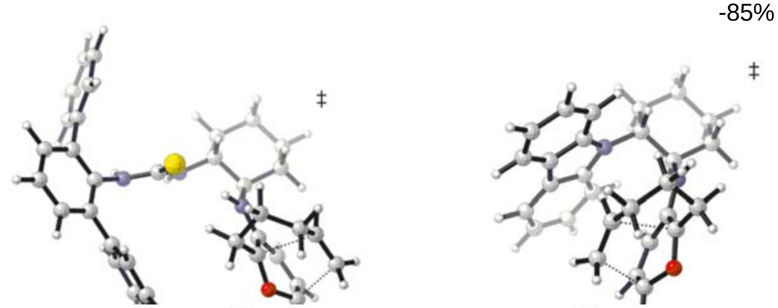


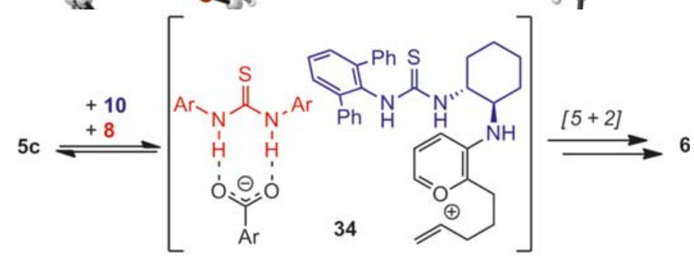




entry	substrate (R)	catalyst(s)	yield (%)[b]	ee (%)[c]
1[d]	**5a** (Ac)	**7**	37	21
2[d]	**5a** (Ac)	**7** + **8**	44	67
3	**5a** (Ac)	**7** + **8**	53	67
4	**5a** (Ac)	**9** + **8**	41	66
5	**5a** (Ac)	**10** + **8**	30	88
6	**5b** (Bz)	**10** + **8**	56	91
7	**5c** (*p*-MeSBz)	**10** + **8**	72	91
8[e]	**5c** (*p*-MeSBz)	**10** + **8**	76	91







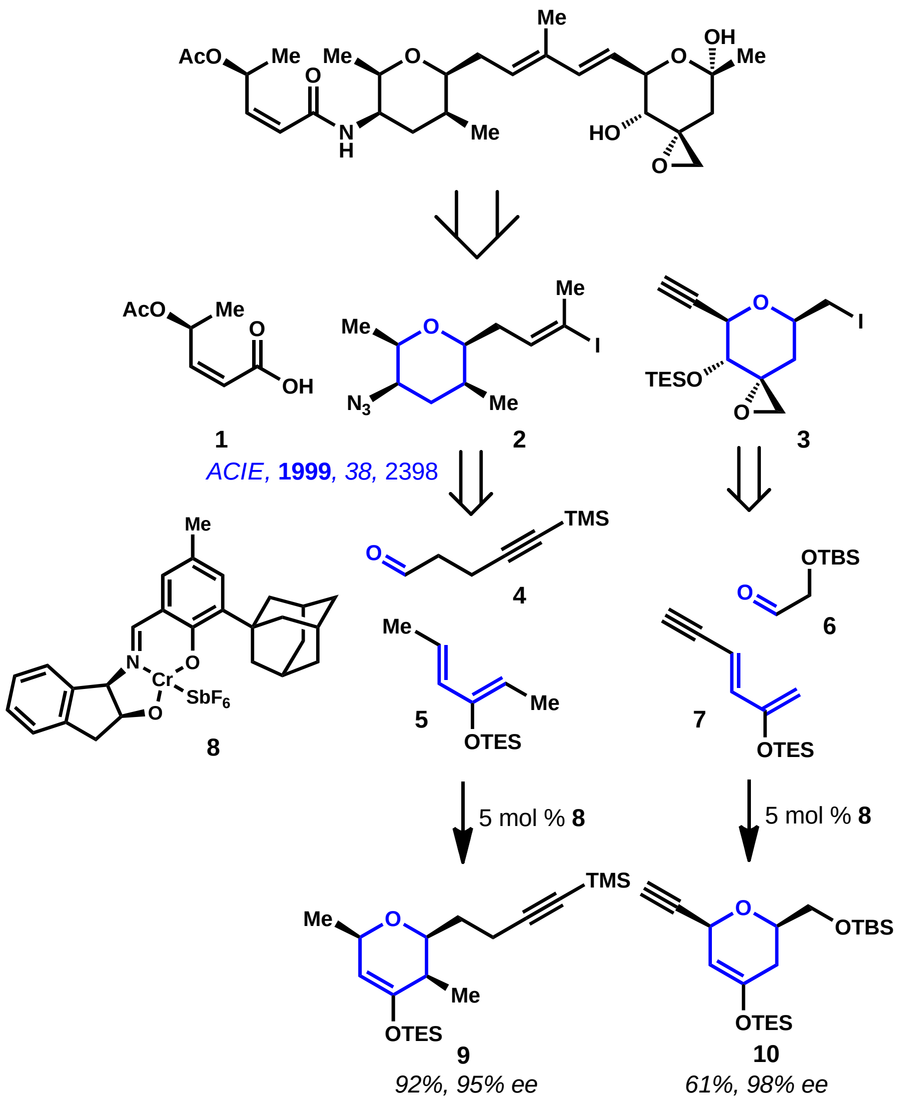
Review: "Asymmetric Ion-Pairing Catalysis" Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534–561.

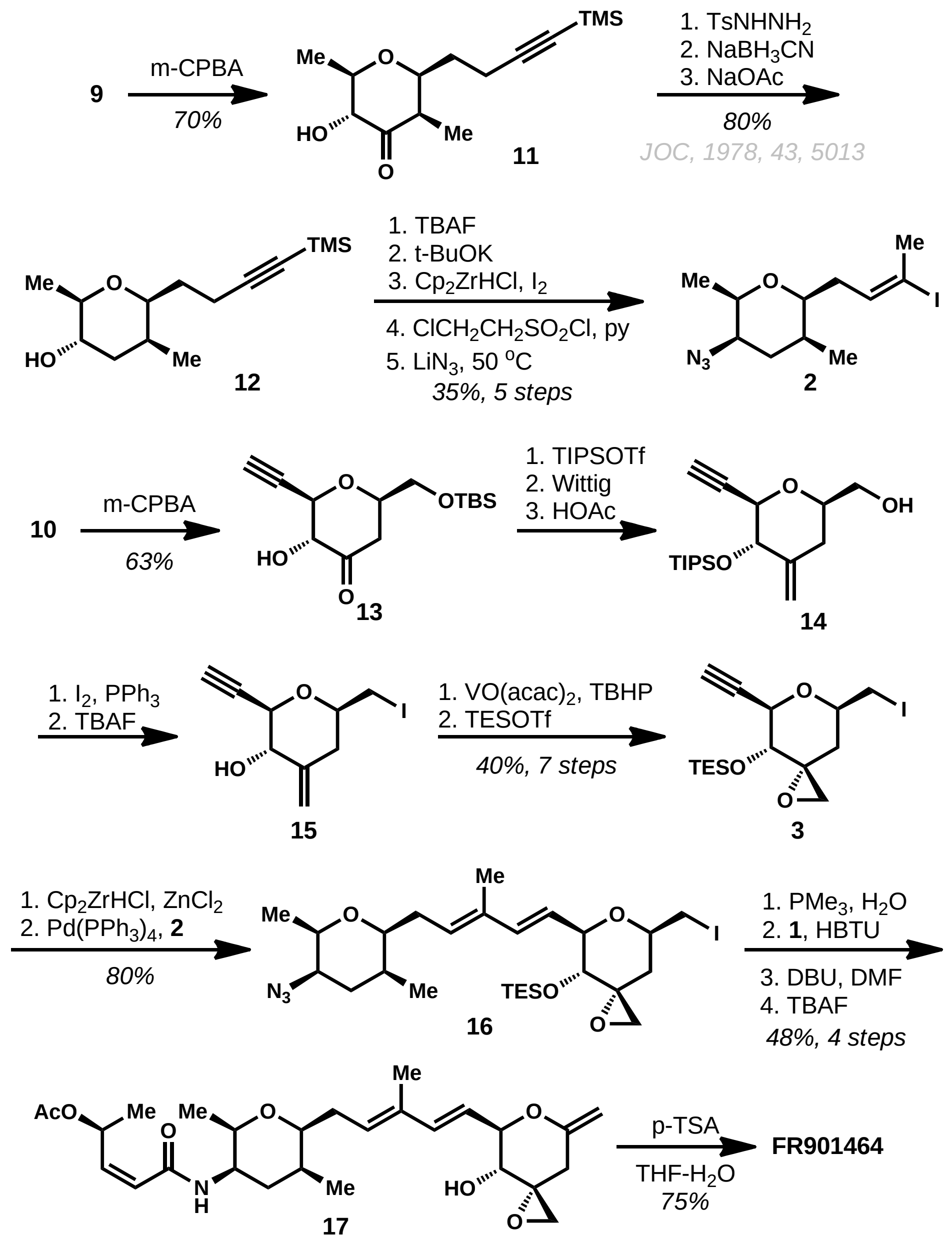
Total Synthesis

1. FR901464

antitumor antibiotic

JACS **2000**, *122*, 10482
JACS **2001**, *123*, 9974



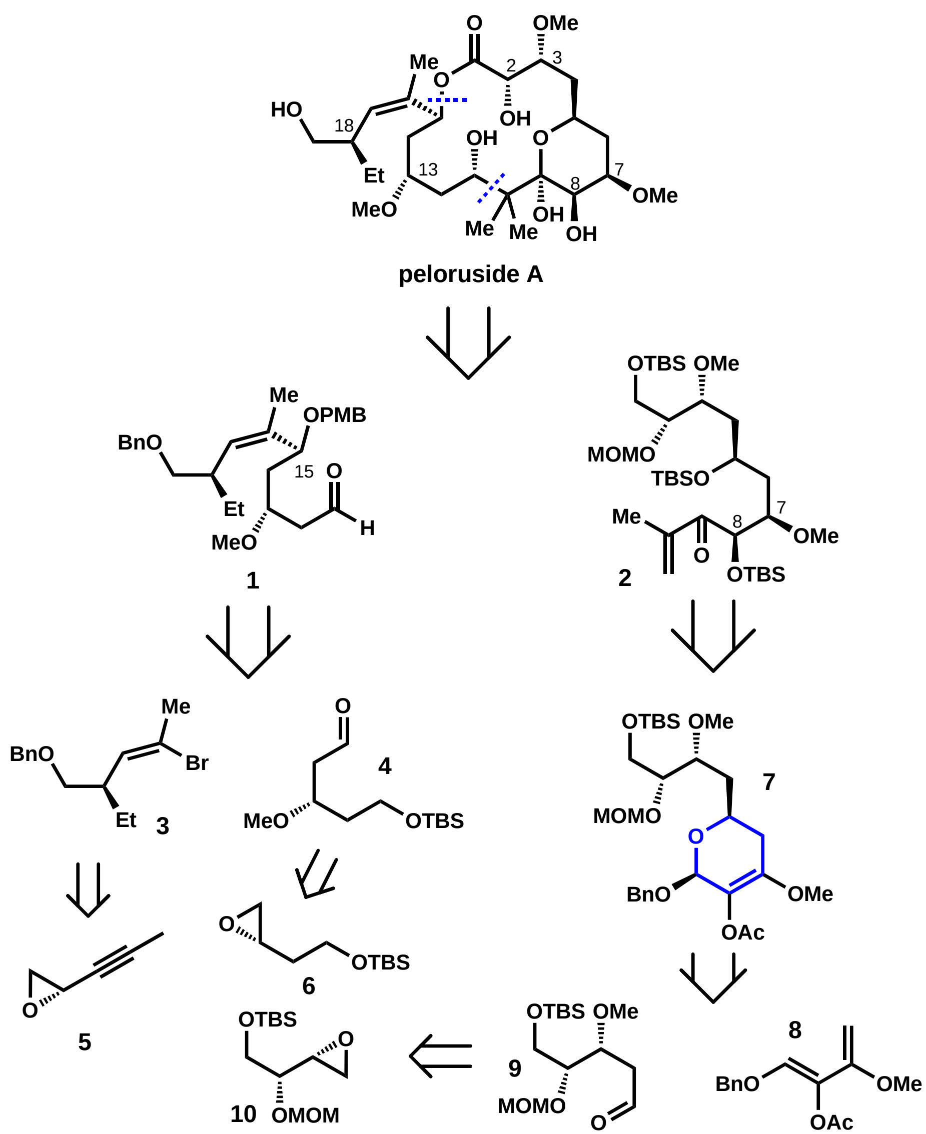


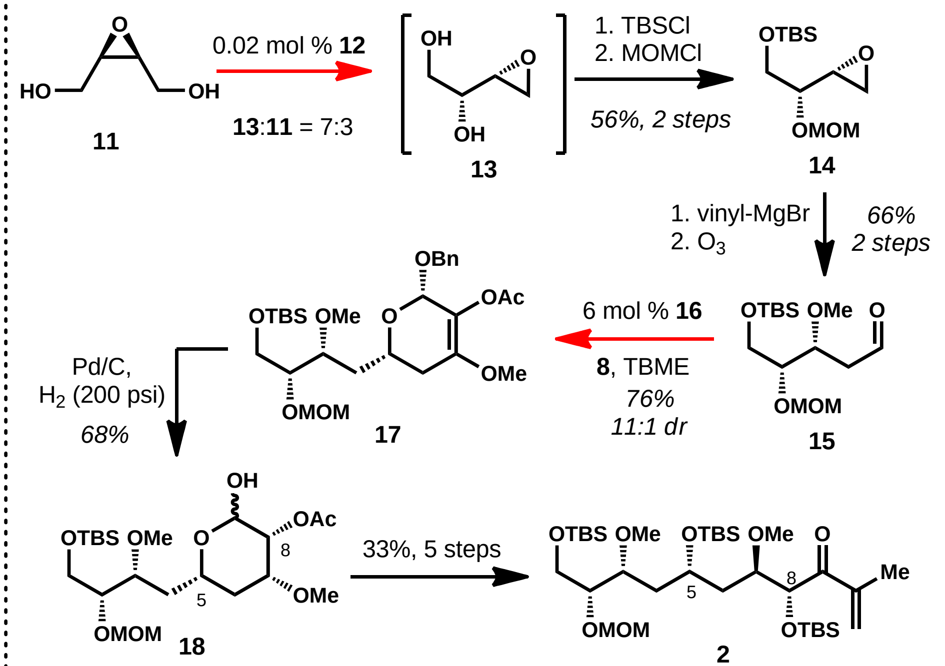
Eric N. Jacobsen

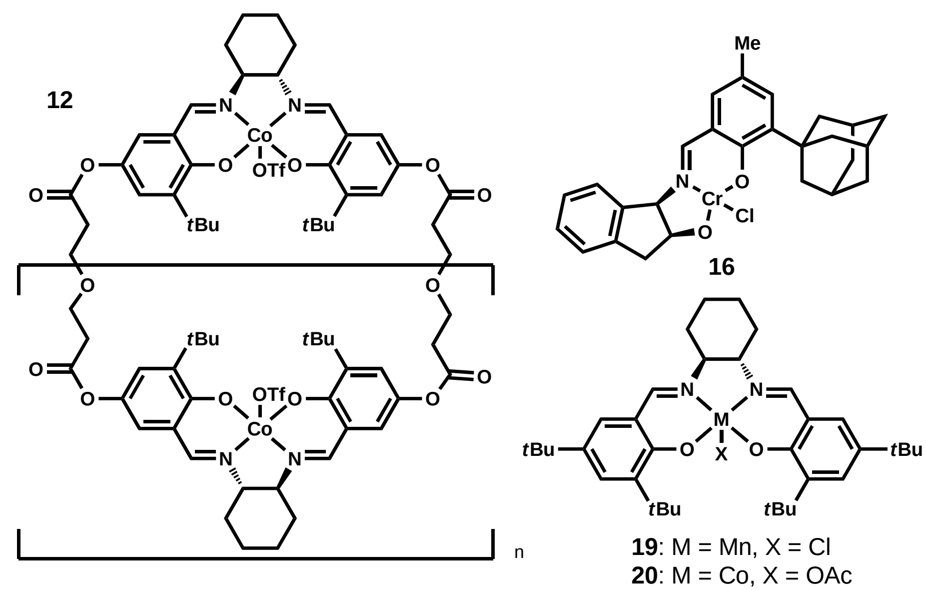
2. (+)-Peloruside A

a potent microtubule stabilizer

ACIE **2010**, *49*, 6147







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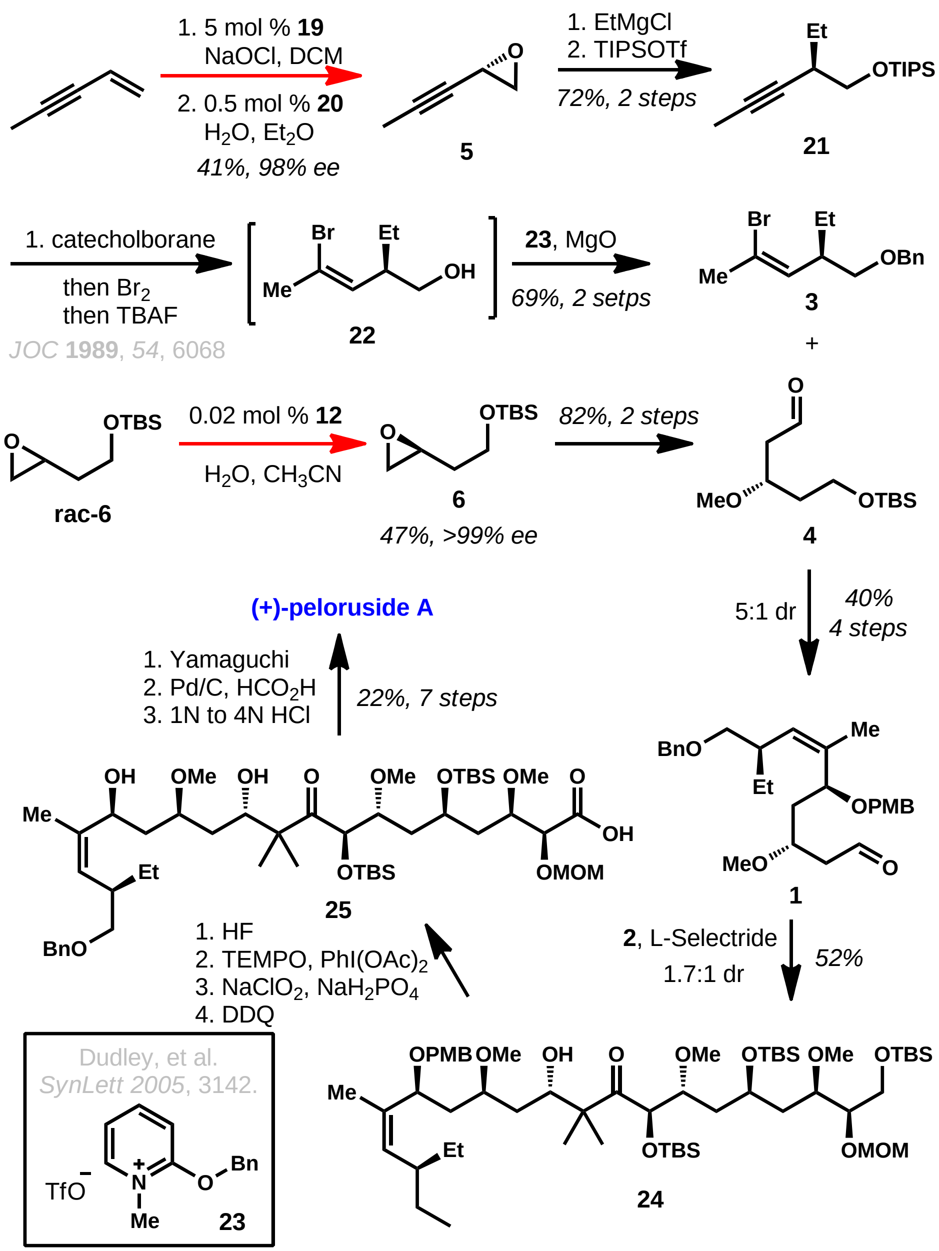
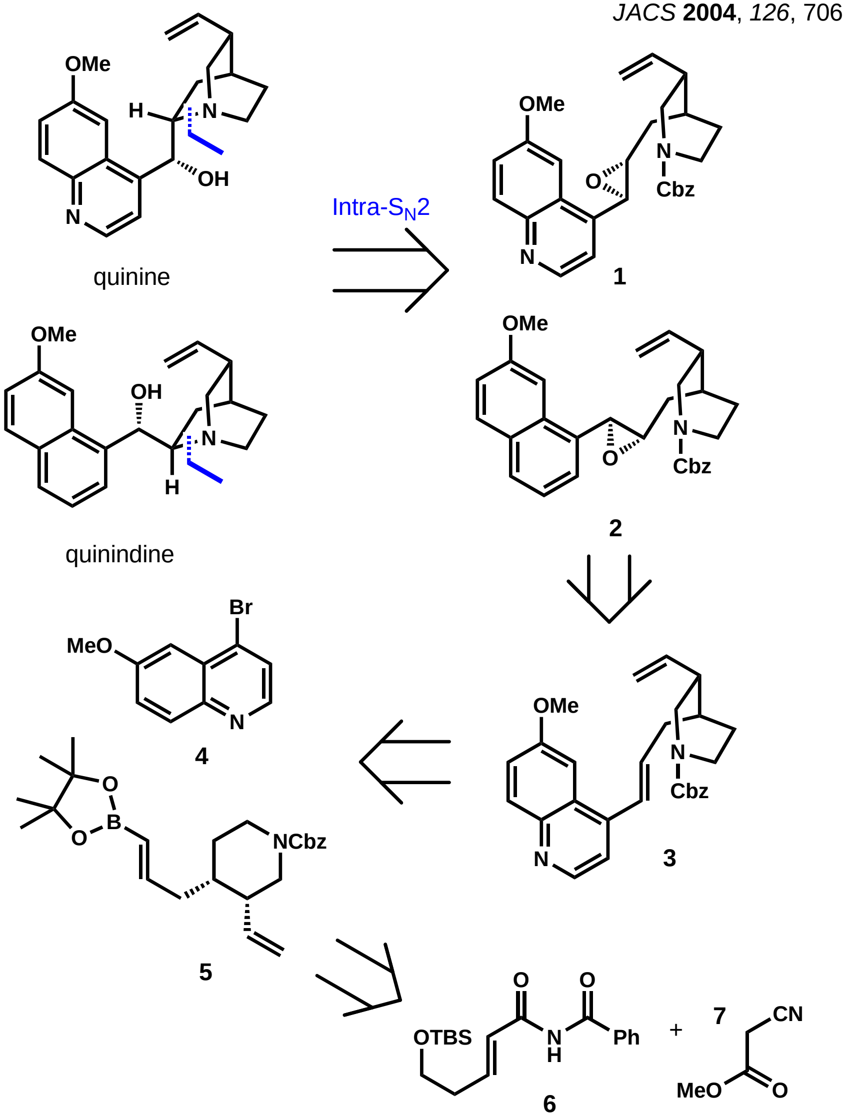


3. Quinine and Quinidine

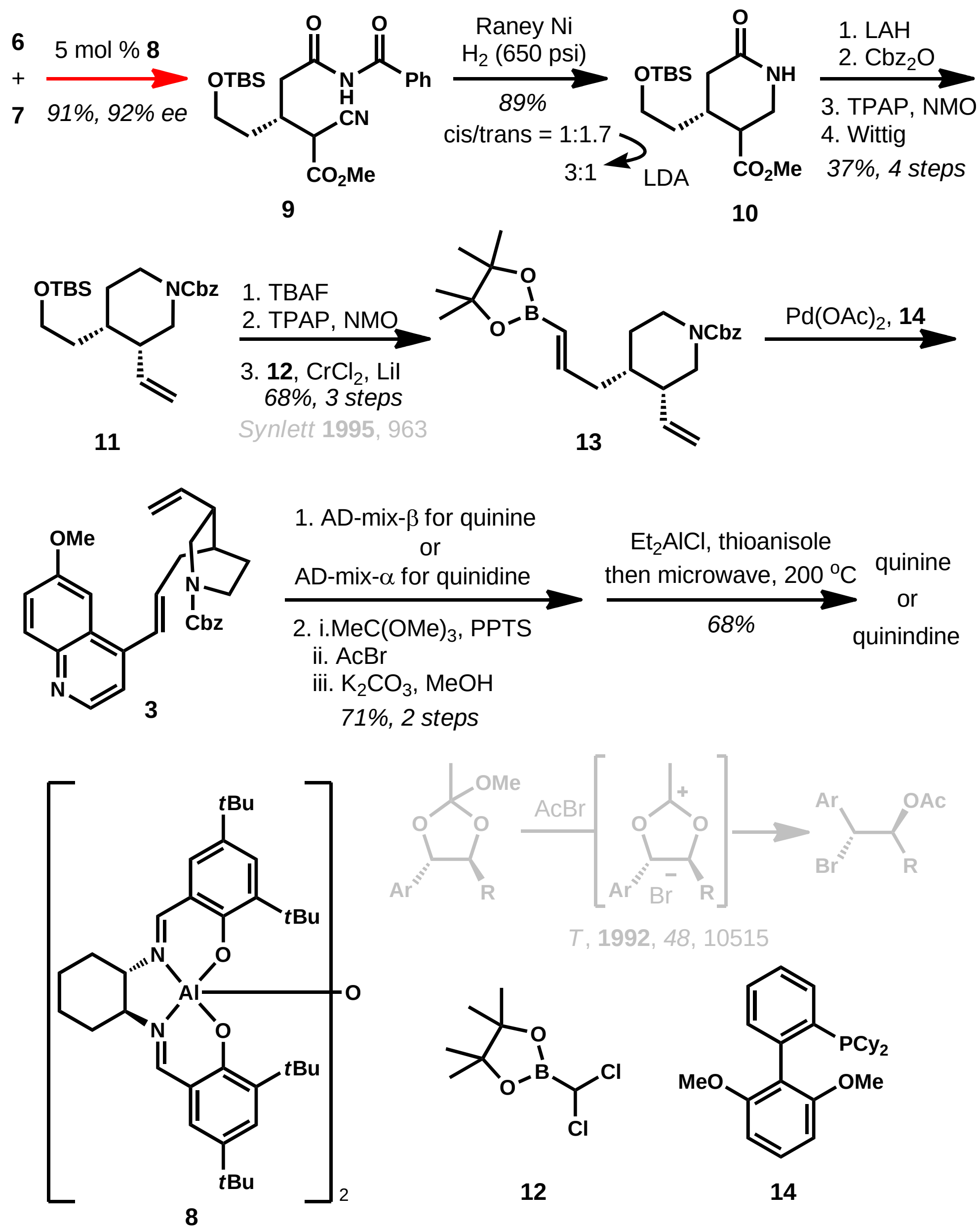
antipyretic, antimalarial, analgesic, and anti-inflammatory; ligand, catalyst, ...

JACS **2004**, *126*, 706

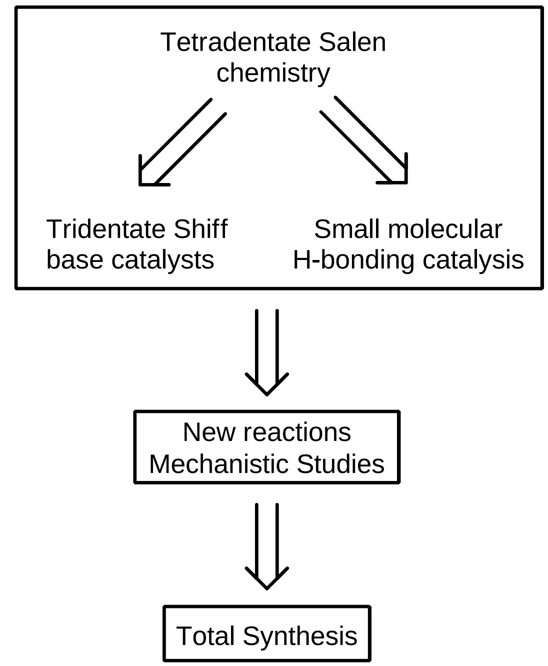


Haihua Lu
09/18/2014

Eric N. Jacobsen



Summary



His way to be a top chemist

remarkable insight to identify and ability to solve highly important unsolved problems