Scandium-Catalyzed Asymmetric Reactions

Jimmy Wu

Evans Group Seminar
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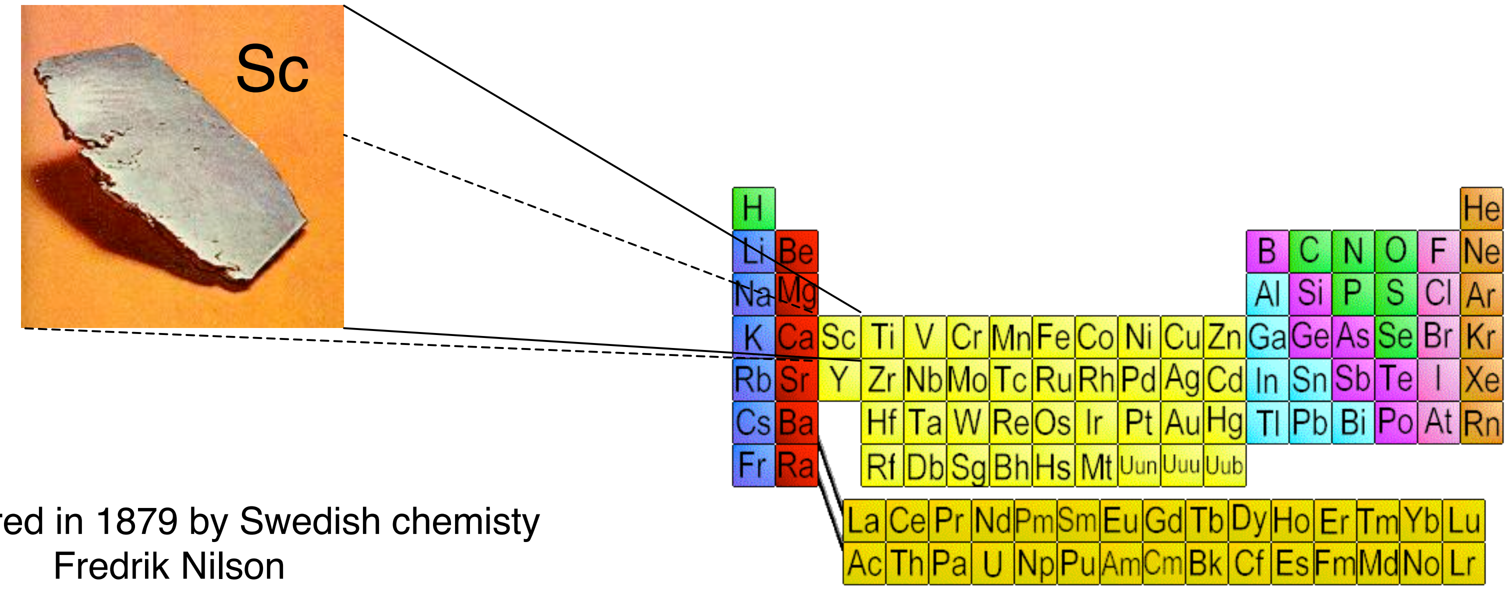
Leading References:

Aspinall, H. C. "Chiral Lanthanide Complexes: Coordination Chemistry and Applications" *Chem. Rev.* **2002**, 1807

Mikami, K.; Terada, M.; Matsuzawa, H. "Asymmetric Catalysis by Lanthanide Complexes" *Angew. Chemie., Int. Ed.* **2002**, 3554.

Interesting Tidbits



• Discovered in 1879 by Swedish chemisty Lars Fredrik Nilson

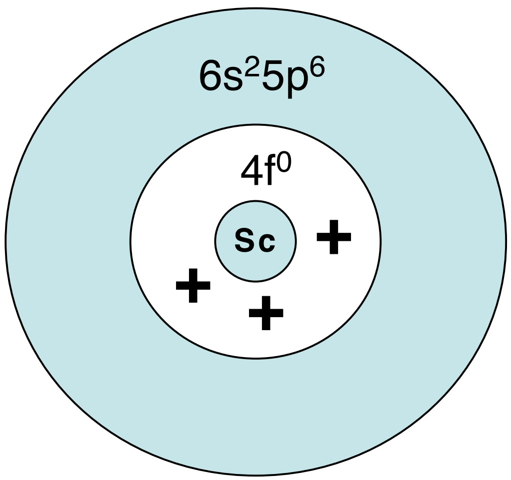
• Silvery-white metal found more abundantly on the sun than on earth

• Thortveitite contains 35-40% Sc_2O_3 while by-products of uranium ore processing contain 0.02% Sc_2O_3

• 1st pound of scandium not produced until 1960

• Shu Kobayashi was 1st to prepare $Sc(OTf)_3$

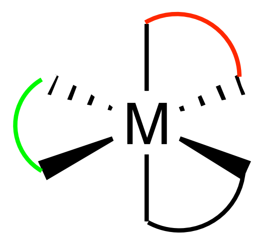
Atomic Structure



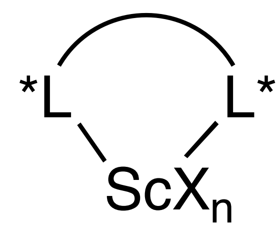
Atomic radii:

Sc(III) – 0.754 Å
La(III) – 1.032 Å
Lu(III) – 0.861 Å

- Coordination number 6 – 12
- Metal/Ligand Interactions mostly electrostatic in nature
- No orbital restrictions
- Ligands are extremely labile

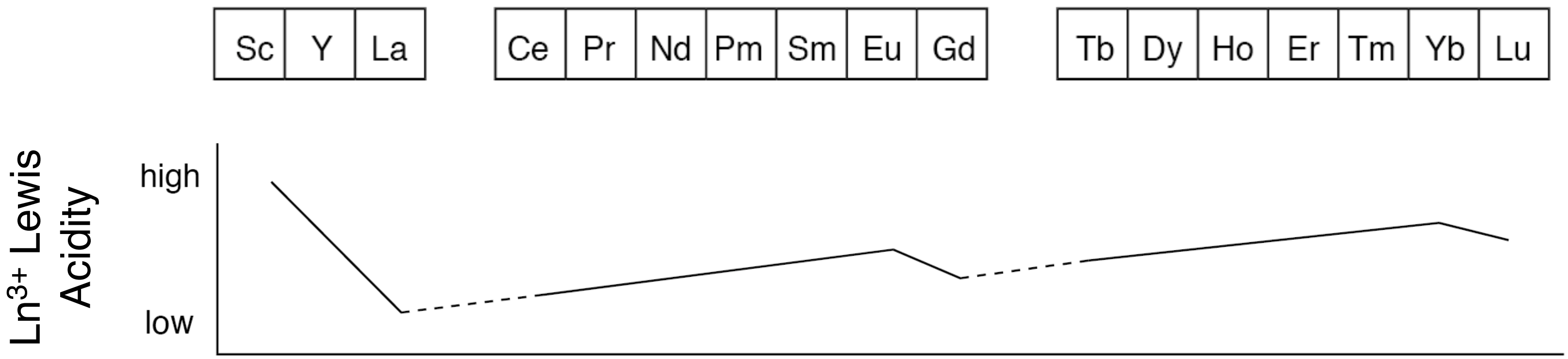


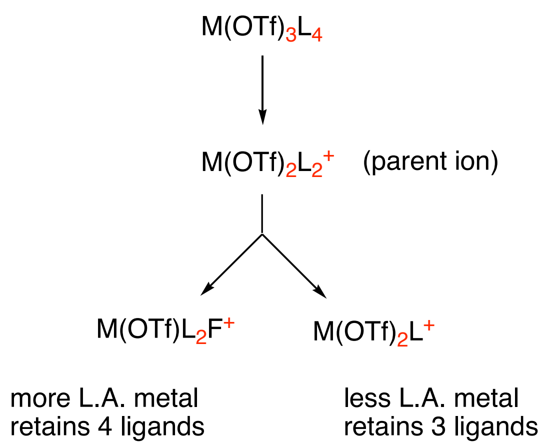
"classic chirality"
M(bidentate)$_3$

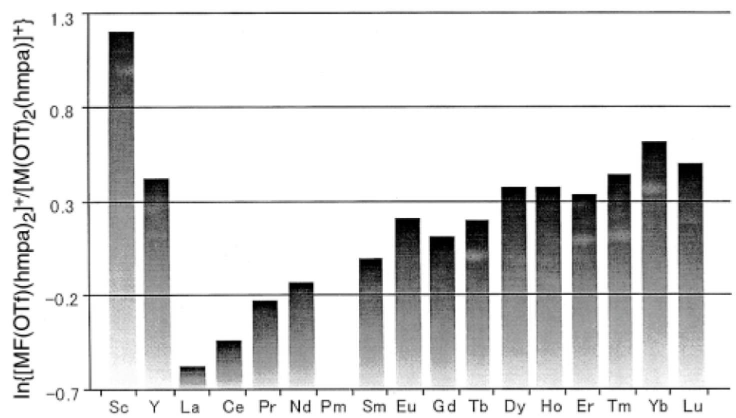


Chirality must reside on the ligand

A Measure of Lewis Acidity



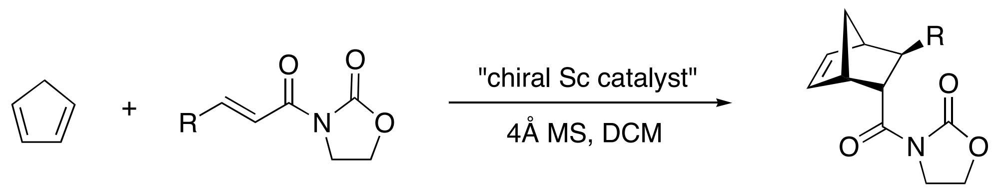




Tandem Mass Spectrometry

Imamoto, T. *Chem. Comm.* **1999**, 1703

Neutral BINOL Ligands: Kobayashi's Catalyst

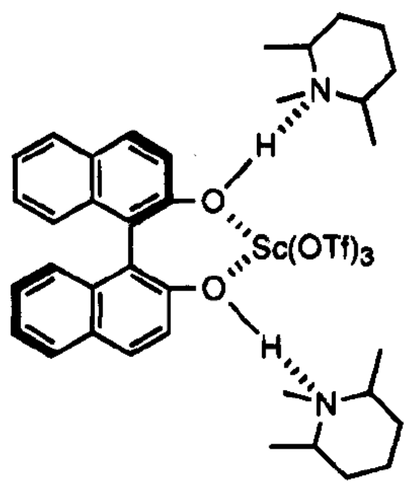


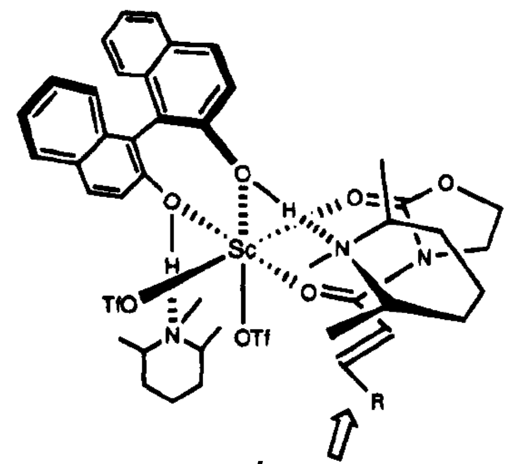
entry	R	cat.	yield (%)	*endo/exo*	ee (%)
1	Me	20	94	89:11	92
2		10	84	86:14	96
3		5	84	87:13	93
4		3	83	87:13	92
5	Ph	20	99	89:11	93
6		10	96	90:10	97
7	*n*-Pr	20	95	78:22	74
8		10	85	78:22	75

"chiral Sc catalyst" = $Sc(OTf)_3$, (*R*)-BINOL, 1,2,6-trimethylpiperidine

Kobayashi, S. *JOC* **1994**, 3758

Neutral BINOL Ligands: Catalyst Structure and TS‡





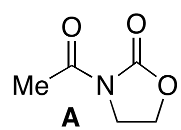
Proposed TS‡

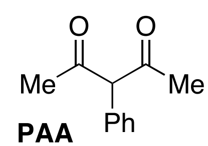
conditions	wavenumber (cm^{-1})
tetramethylpiperidine (TMP)	947
TMP + (*R*)-BINOL	989, 947
TMP + $Sc(OTf)_3$	947
TMP + $Sc(OTf)_3$ + (*R*)-BINOL	997, 956

Fritsch, J. *J. Phys. Chem*. **1981**, 556

Neutral BINOL Ligands: Turnover in Enantioselection

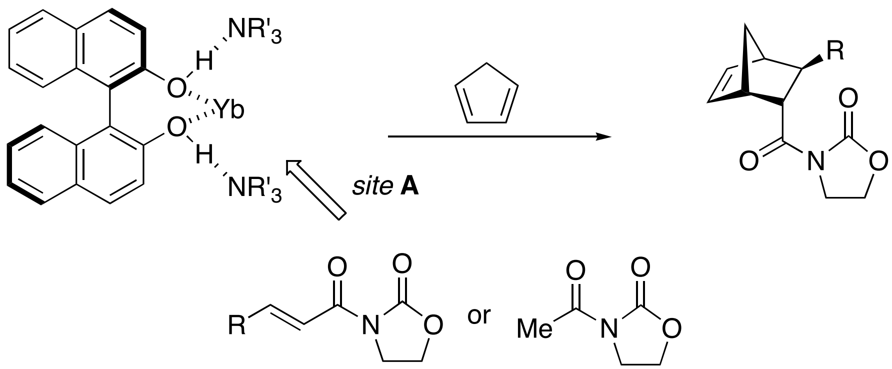
Metal	Conditions	Additive	Yield	*endo/exo*	ee (%)
Yb	0 °C, 0.5 h	–	77	89/11	93
	0 °C, 5.5 h	–	61	87/13	78
	0 °C, 0.5 h; 23 °C, 5 h	–	77	86/14	65
	0 °C, 5.5 h	A	77	89/11	83
	0 °C, 5.5 h	acac	87	85/15	–55
	40 °C, 3h	PAA	83	93/7	–81
Sc	0 °C, 0.5 h	–	97	84/16	84
	0 °C, 0.5 h; 23 °C, 3 h	–	87	80/20	–7
	0 °C, 0.5 h; 23 °C, 3 h	A	92	83/17	78
	0 °C, 0.5 h; 23 °C, 3 h	acac	90	90/10	–5
	-78 °C, 0.5 h	–	94	89/11	92





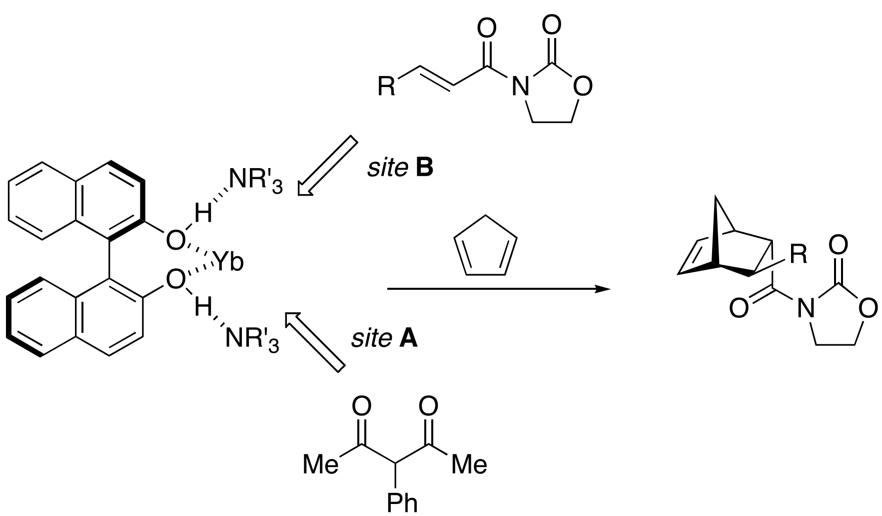
Kobayashi, S. *TL* **1994**, 6325

Neutral BINOL Ligands: Rationalizing Turnover



• Both oxazolidinones are in rapid equilibrium at site A

• CP attacks from *si* face



• Site A is occupied by PAA

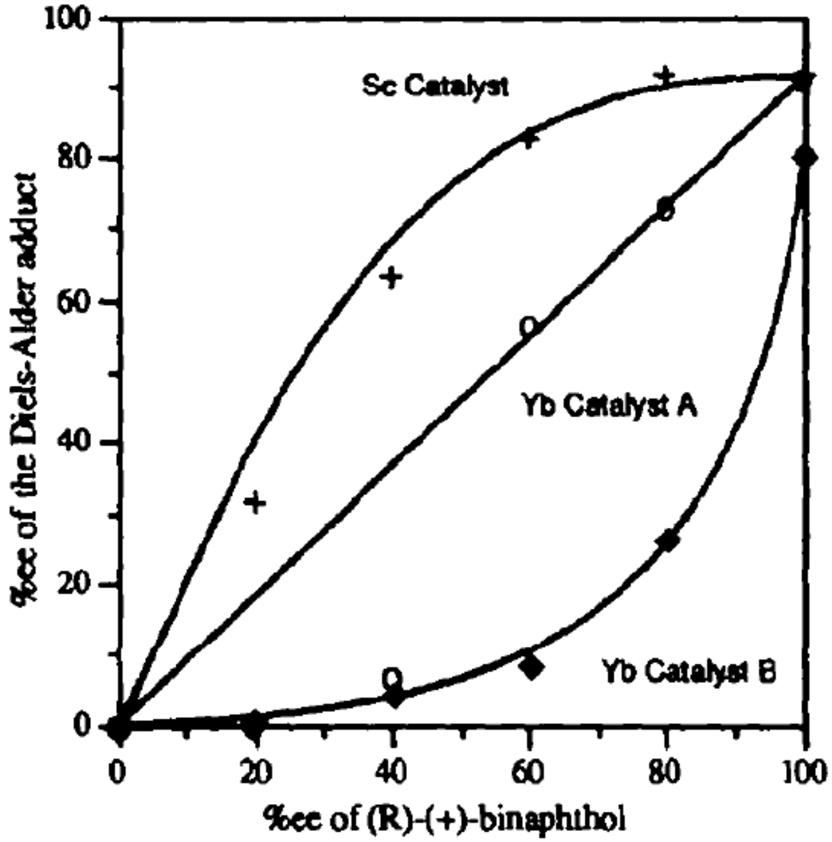
• Oxazolidinone binds site B

• CP attacks from *re* face

• Sc(OTf) prefers coordination number 7

Kobayashi, S. *JACS* **1994**, 4083

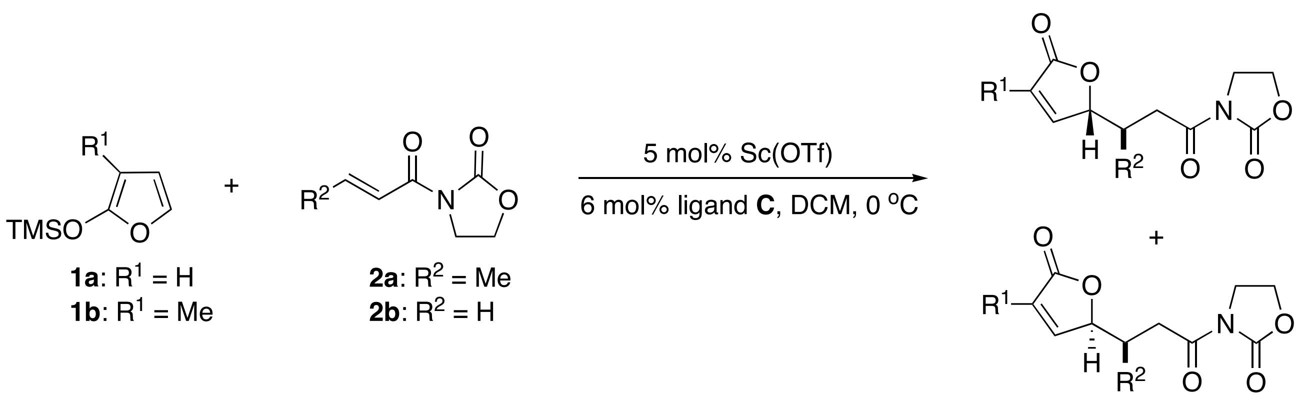
Neutral BINOL Ligands: Nonlinear Effects

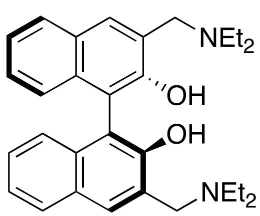


Yb Catalyst A : $Yb(OTf)_3$ + (R)-(+)-binaphthol + TMP + 1
Yb Catalyst B : $Yb(OTf)_3$ + (R)-(+)-binaphthol + TMP + PAA
Sc Catalyst : $Sc(OTf)_3$ + (R)-(+)-binaphthol + TMP

Kobayashi, S. *TL* **1994**, 6325

Neutral BINOL Ligands: Mukaiyama Michael Addition





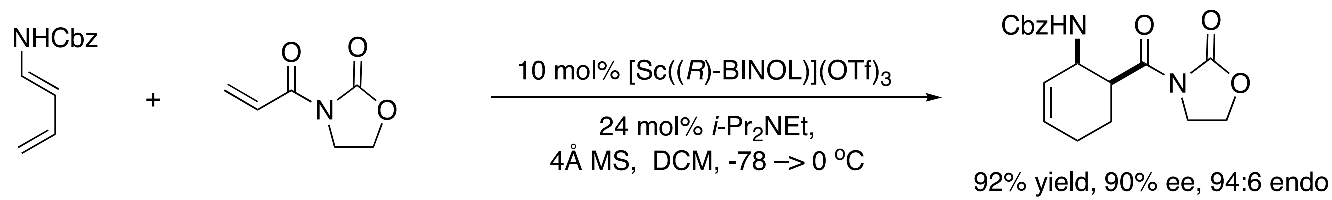
C

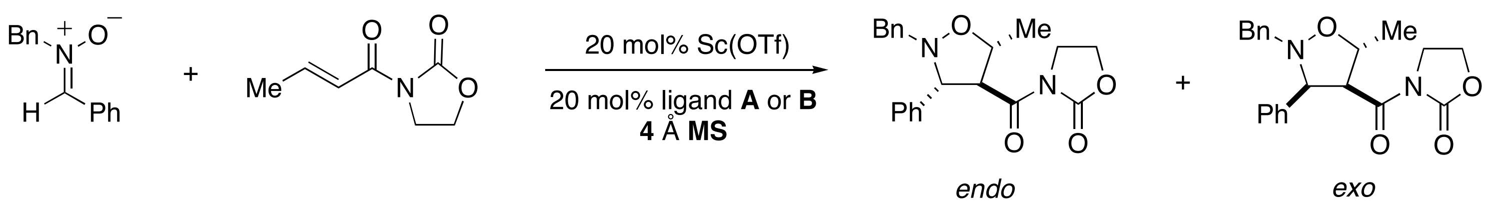
entry	substrate	yield (%)	*anti*:*syn*	ee (%)
1	**1a** + **2a**	44	>50:1	73
2[a]	**1a** + **2a**	45	>50:1	37
3	**1b** + **2a**	64	41:1	60
4	**1a** + **2b**	59	–	41

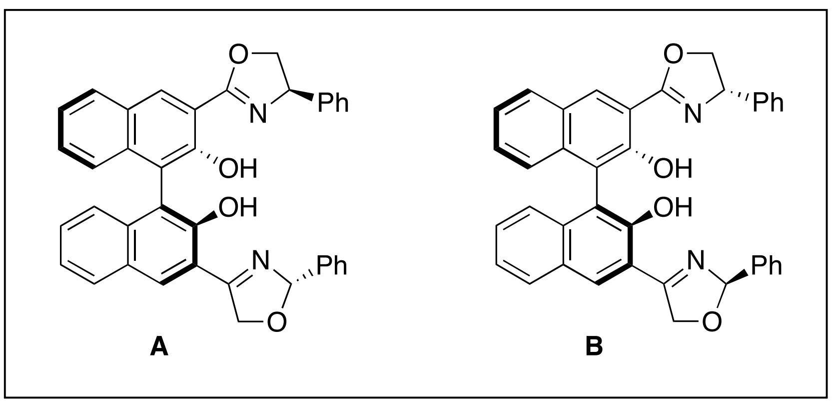
[a] Reaction run without molecular seives

Katsuki, T. *Tetrahedron* **1997**, 17015

Neutral BINOL Ligands: More Useful Transformations





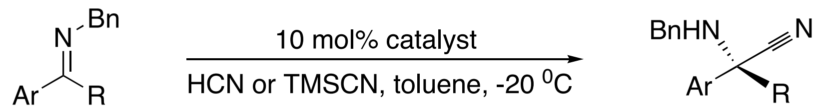


Ligand **A**; 92:8 endo, 83% ee (*R,S,R*)

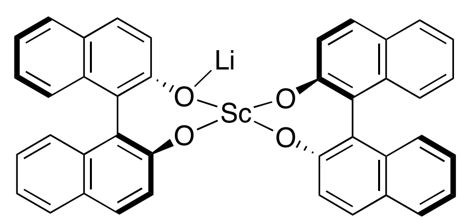
Ligand **B**; 97:3 endo, 31% ee (*R,S,R*)

Wipf, P. *TL* **2000**, 8747
Ohta, T. *JOMC* **2000**, *603*, 6

Anionic BINOL Ligands: Asymmetric Strecker



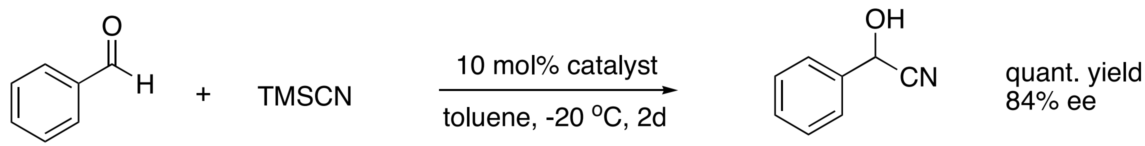
entry	substrate	yield (%)	XCN	ee (%)
1	Ar = Ph; R = Me	80	TMSCN	91
2	Ar = Ph; R = Me	95	HCN	81
3	Ar = β-Naphthyl; R = H	45	TMSCN	65
4	Ar = β-Naphthyl; R = H	80	HCN	86
5	Ar = Ph; R = H	70	TMSCN	45

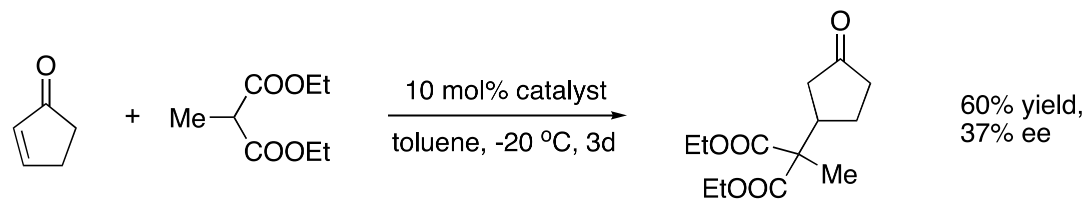


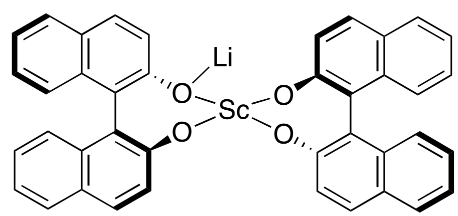
Sc[(*R*)-BINOL$)_2$]Li

Vallée, Y. *Tetrahedron*: *Asymm*. **2001**, 1147

Anionic BINOL Ligands: Other Applications



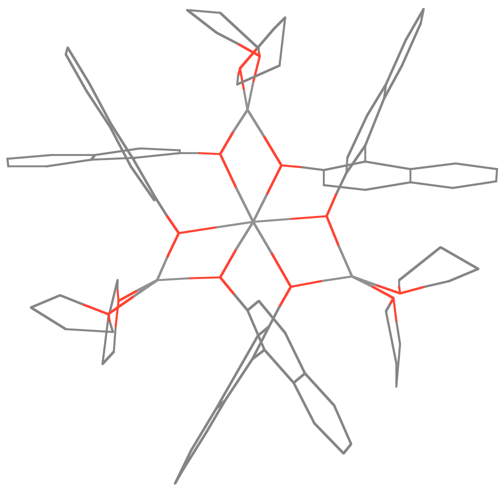




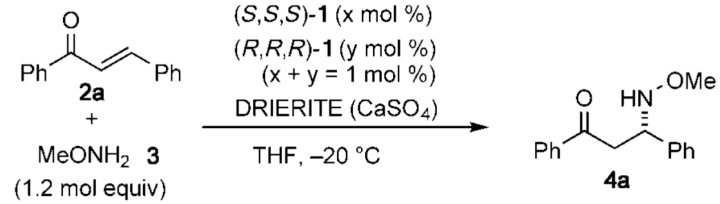
Sc[(*R*)-BINOL)$_2$]Li

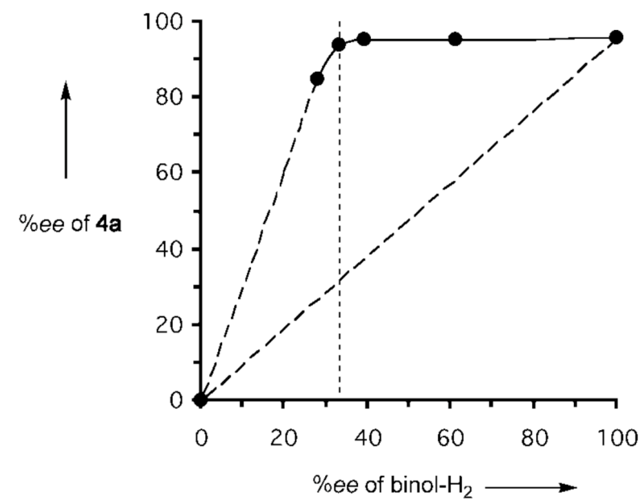
Vallée, Y. *Tetrahedron*: *Asymm*. **2001**, 1147

Anionic BINOL Ligands: Y[(R,R,R)-BINOL$_3$)]Li$_3$thf$_6$



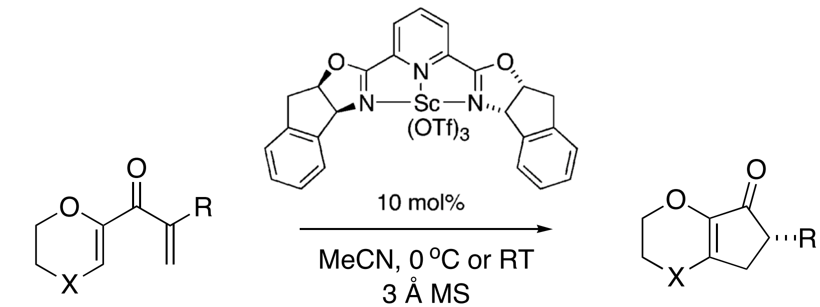
1: Y[(*R,R,R*)-BINOL$_3$)] Li$_3$thf$_6$





Shibasaki, M. *ACIEE* **2004**, 4493

Pybox Ligands: Nazarov Reaction

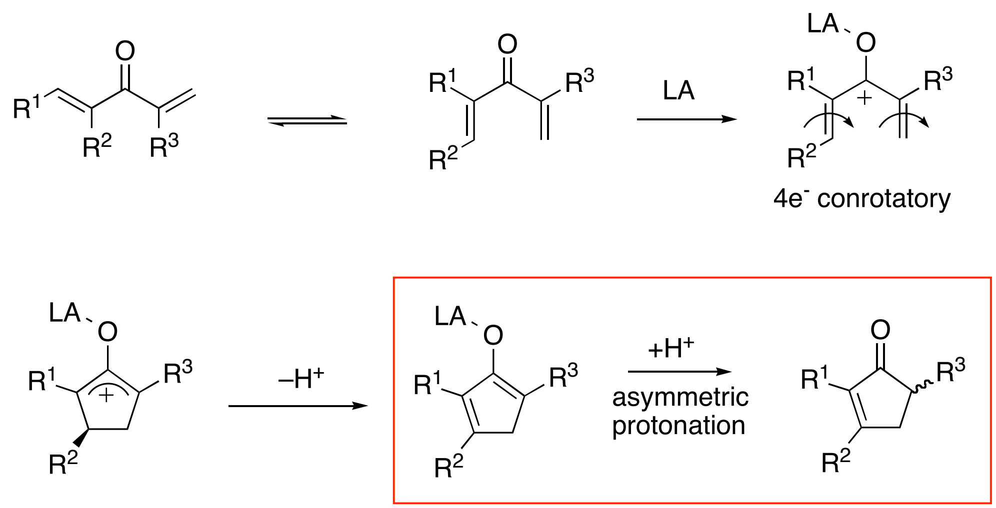


entry	X	R	yield[a] (%)	ee (%)
a	CH_2	Me	65	85
b	CH_2	Et	75	92
c	CH_2	*n*-Pr	70	93
d	CH_2	*n*-Bu	70	94
e[b]	CH_2	*i*-Pr	88	95
f	CH_2	*t*-Bu	94	97
g	CH_2	Cy	76	76
h	CH_2	Ph	65	87
j[b]	O	*i*-Pr	65	72
k	O	*t*-Bu	80	91

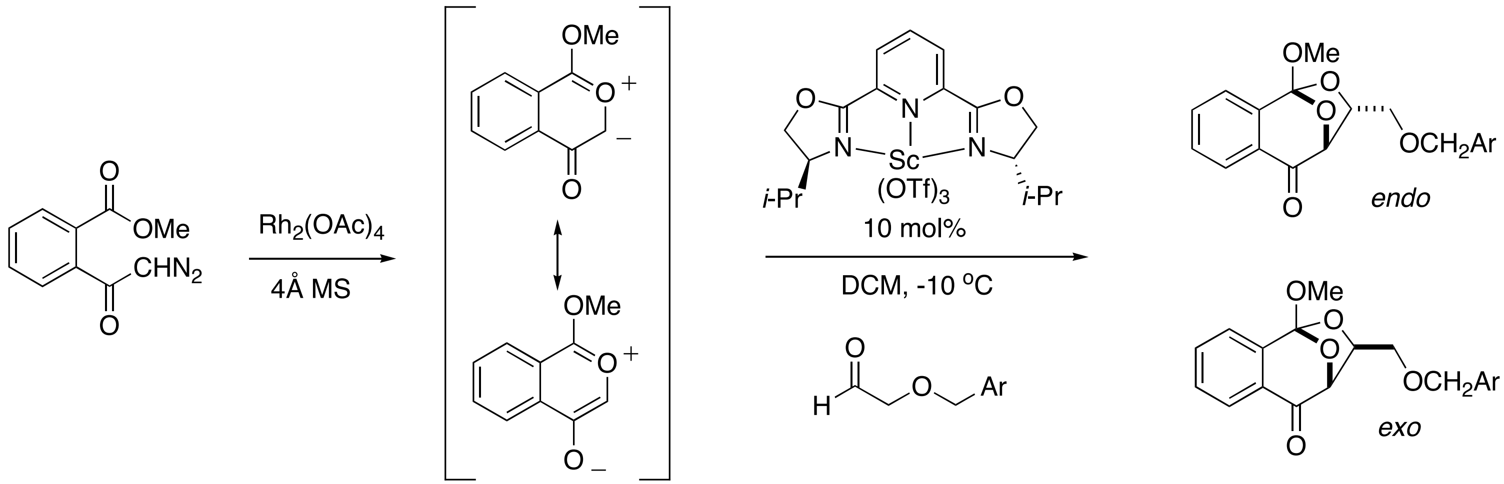
[a] Isolated yield after silica gel column chromatography. [b] Reaction performed at 0 °C (3 h).

Trauner, D. *JACS* **2004**, 9544

Pybox Ligands: Nazarov Mechanism – Asymmetric Protonation



Pybox Ligands: 1,3-Dipolar Cycloaddition

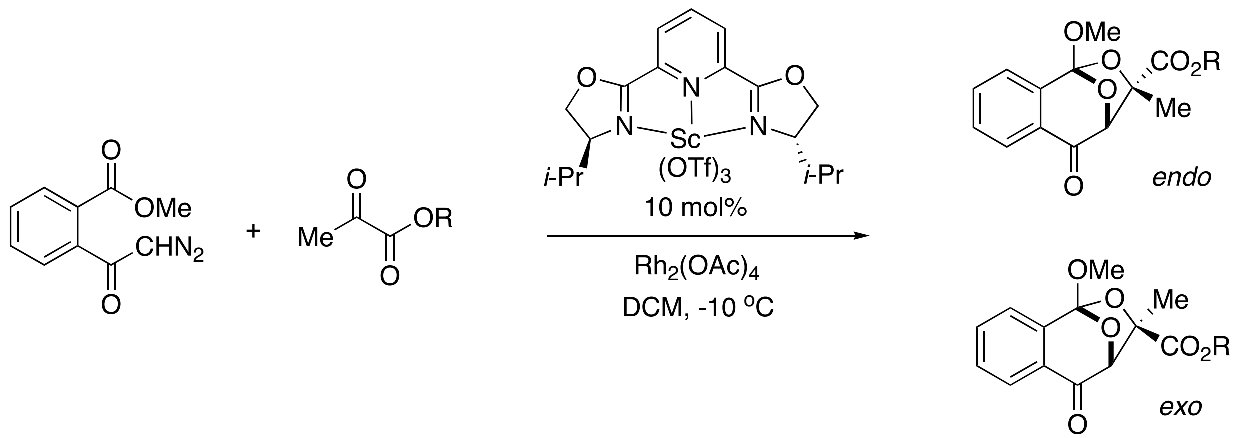


entry	–Ar	yield	*endo/exo*	ee (%)
1	Ph	96	88:12	91
2[a]	Ph	91	55:45	85
3	2-MeO-Ph	82	85:15	82
4	4-MeO-Ph	53	91:9	89
5	4-F-Ph	97	82:18	93
6	4-Cl-Ph	84	73:27	86
7	4-Br-Ph	77	67:37	83

[a] no molecular seives used

Suga, H. *JACS* **2002**, 14836

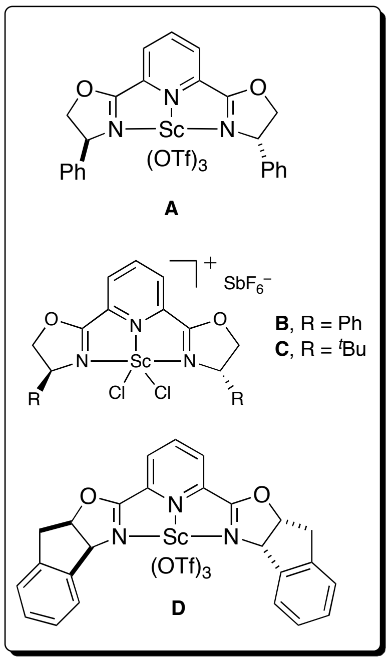
Pybox Ligands: 1,3-Dipolar Cycloadditions – Pyruvates

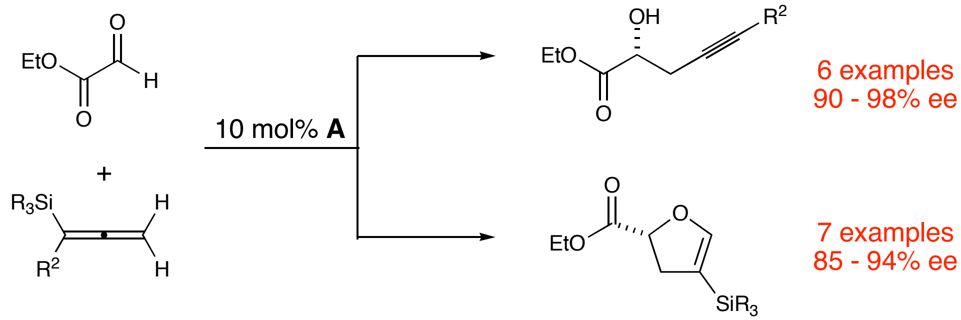


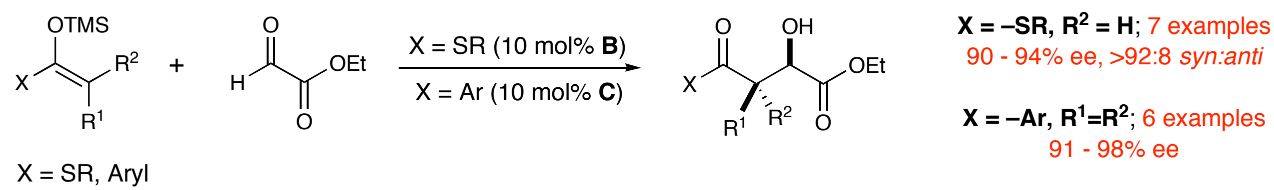
entry	–R	additive	yield (%)	*endo/exo*	ee (%)
1	Me	no	84	12:88	45
2	Me	pyruvic acid	88	4:96	78
3	Bn	no	82	18:82	11
4	Bn	pyruvic acid	88	7:97	87

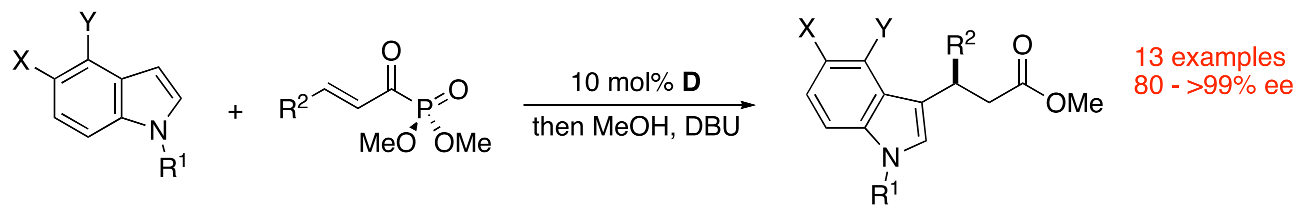
Suga, H. *JACS* **2002**, 14836

Pybox Ligands: Evans Group Methodology







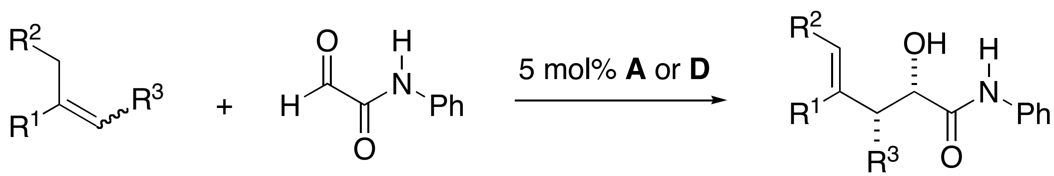


Evans, D. A. *JACS* **2001**, 12095

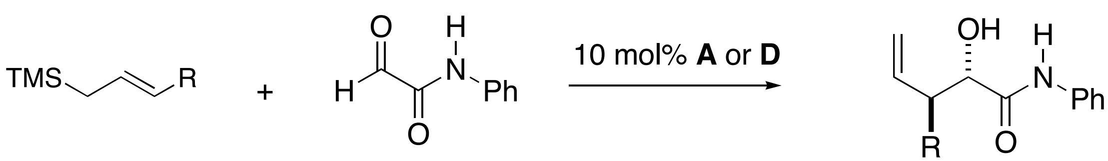
Evans, D. A. *OL* **2002**, 3375

Evans, D. A. *JACS* **2003**, 10780

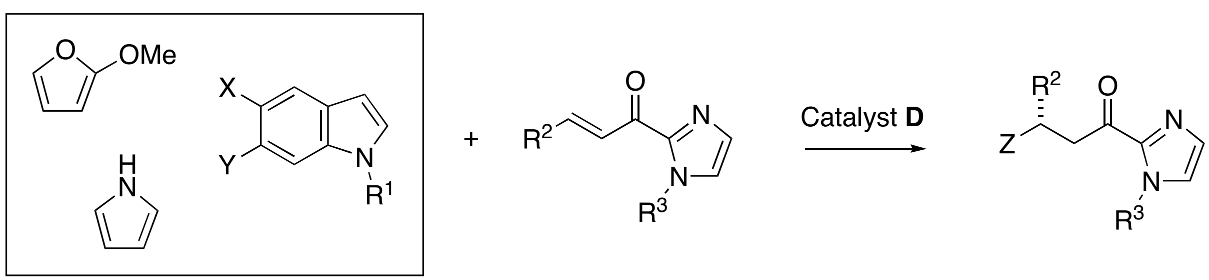
Pybox Ligands: Evans Group Method. – Unpublished Results



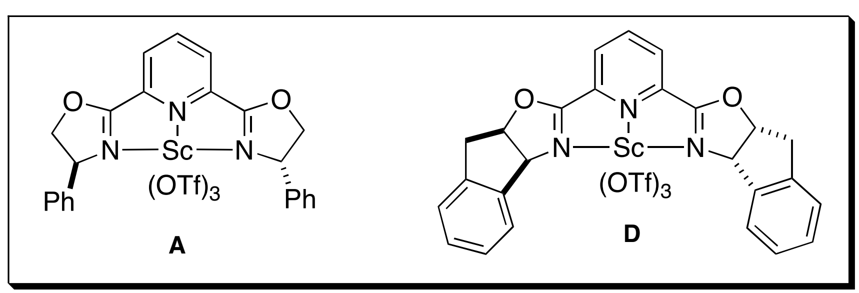
14 examples
92 – 99% ee
9 – 24:1 *syn/anti*



8 examples
93 – 99% ee
10 – 99:1 *anti/syn*

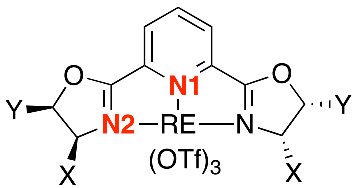


20 examples
90 – 98% ee



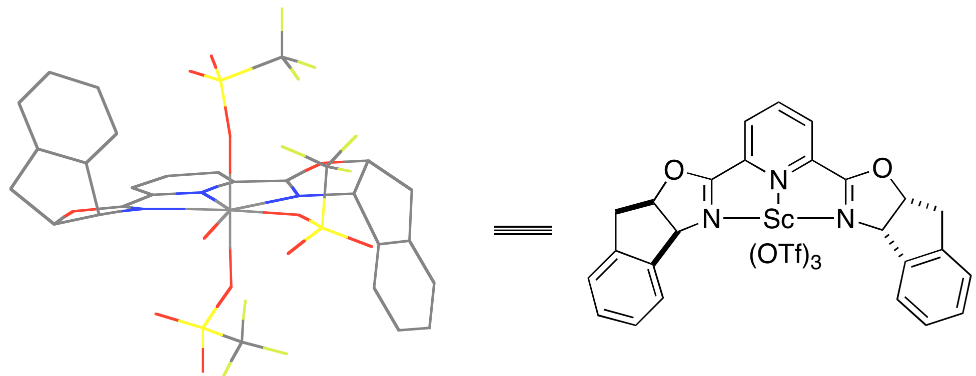
Unpublished results

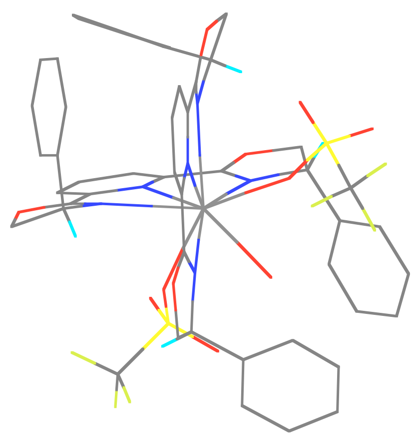
Pybox Ligands: X-Ray Cystallography



RE	Pybox	N1-RE-N2 (º)	N1-RE (Å)
La	*i*-Pr	60.8	2.711
La*	Bn	61.1	2.678
Sm*	Ph	63.0	2.614
Eu	*i*-Pr	62.0	2.579
Yb	*i*-Pr	65.0	2.433
Yb*	Norephedrine	65.2	2.475
Sc*	Ph	68.2	2.333
Sc*	Inda	68.1	2.346

*Crystals solved by Evans group



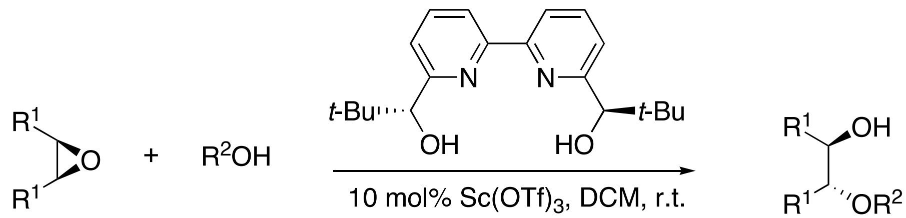


RE[(*S,S*)-Pybox]$(OTf)_3$

RE = La, Sm, Eu, Yb
Pybox = Ph, Bn, *i*-Pr, Inda, Norephedrine

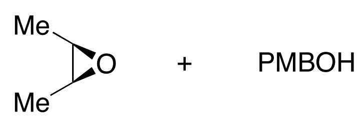
Aspinall, H. C. *JOMC* **2002**, 151
Evans, D. A. *JACS* **2001**, 12095
Evans, D. A. *JACS* **2003**, 10780
Evans, D. A. *unpublished results*

Bipyridine Ligands: Epoxide Openings by Alcohols



entry	R^1	R^2	yield (%)	ee (%)
1	Ph	Me	92	81
2	Ph	Et	96	75
3	Ph	*n*Bu	94	80
4	Ph	allyl	95	78
5	Ph	PMB	97	82
6	β-Naphthyl	MeOH	98	83
7	2-tolyl	MeOH	96	75

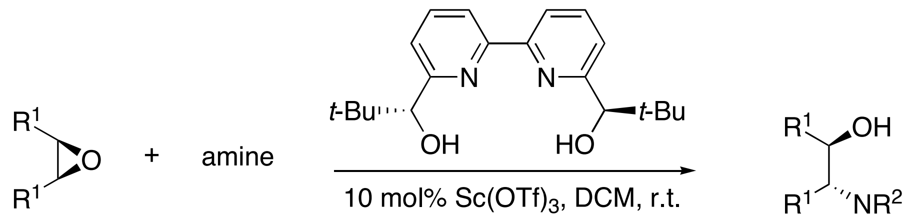
90% yield, 54% ee



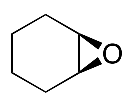
93% yield, 49% ee

Schneider, C. *ACIEE* **2004**, 5691

Bipyridine Ligands: Epoxide Openings by Amines

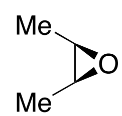


entry	R^1	amine	yield (%)	ee (%)
1	Ph	$PhNH_2$	95	93
2	Ph	$PhNHCH_3$	85	97
3	Ph	*p*-anisidine	87	82
4	Ph	BnO-NH_2	85	86
5	β-Naphthyl	$PhNH_2$	76	82
6	2-tolyl	$PhNH_2$	93	91



\+ PhNH2

96% yield, 54% ee

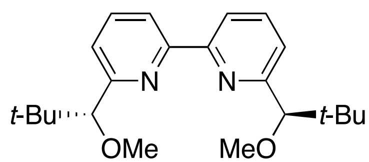


\+ $PhNH_2$

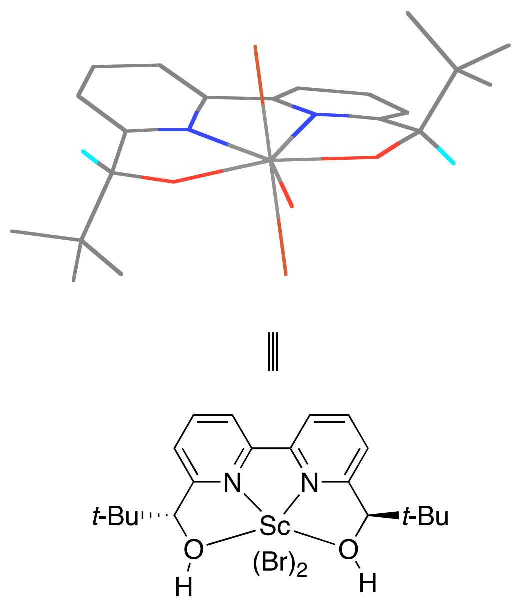
92% yield, 60% ee

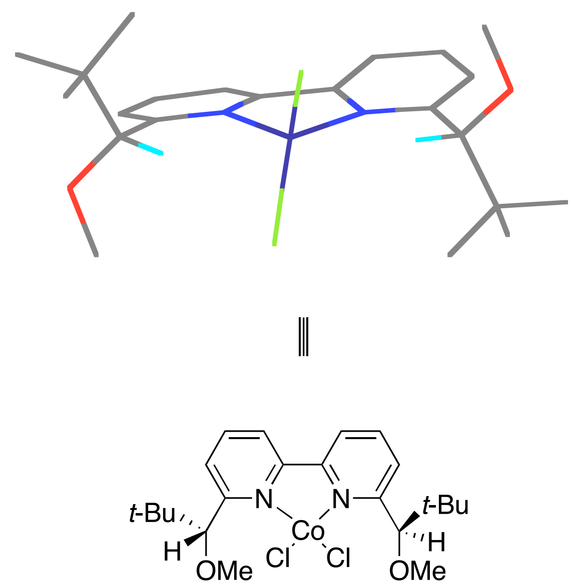
Schneider, C. *ACIEE* **2004**, 5691

Bipyridine Ligands: X-Ray Structures



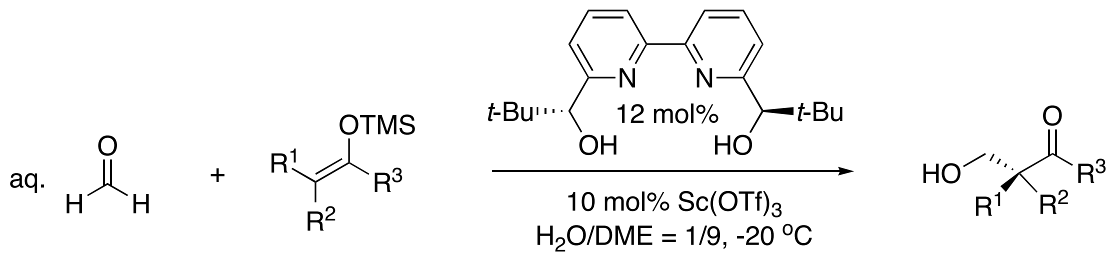
- Complete loss of enantioselectivity
- Free hydroxyl groups are essential

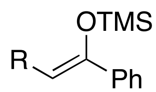




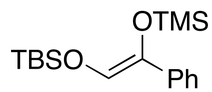
Kobayashi, S. *JACS* **2004**, 12236
Bolm, C. *ACIEE* **1990**, 205

Bipyridine Ligands: Hydroxymethylation

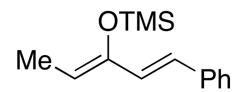




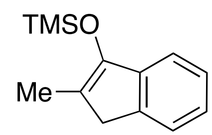
R = Me; 80%yield, 90% ee
R = Et; 66% yield, 88% ee



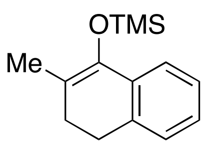
53% yield, 80% ee



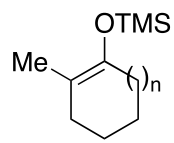
73% yield, 92% ee



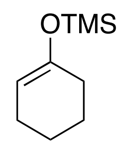
90% yield, 90% ee



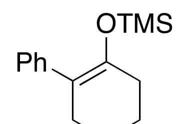
84% yield, 94% ee



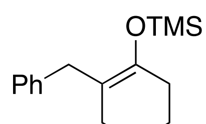
n = 0; 50% yield, 85% ee
n = 1; 68% yield, 91% ee
n = 2; 62% yield; 90% ee



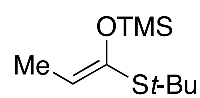
26% yield, 78% ee



63% yield, 60% ee



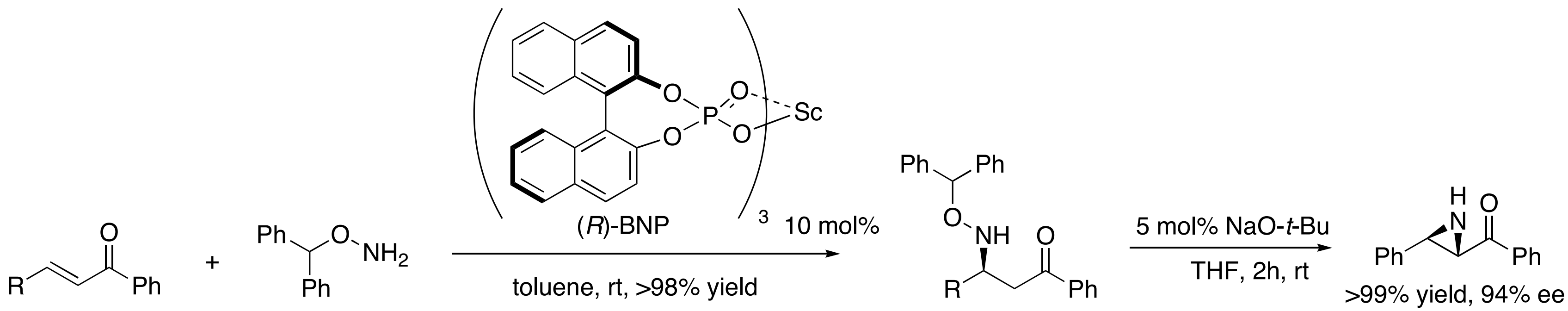
59% yield, 80% ee

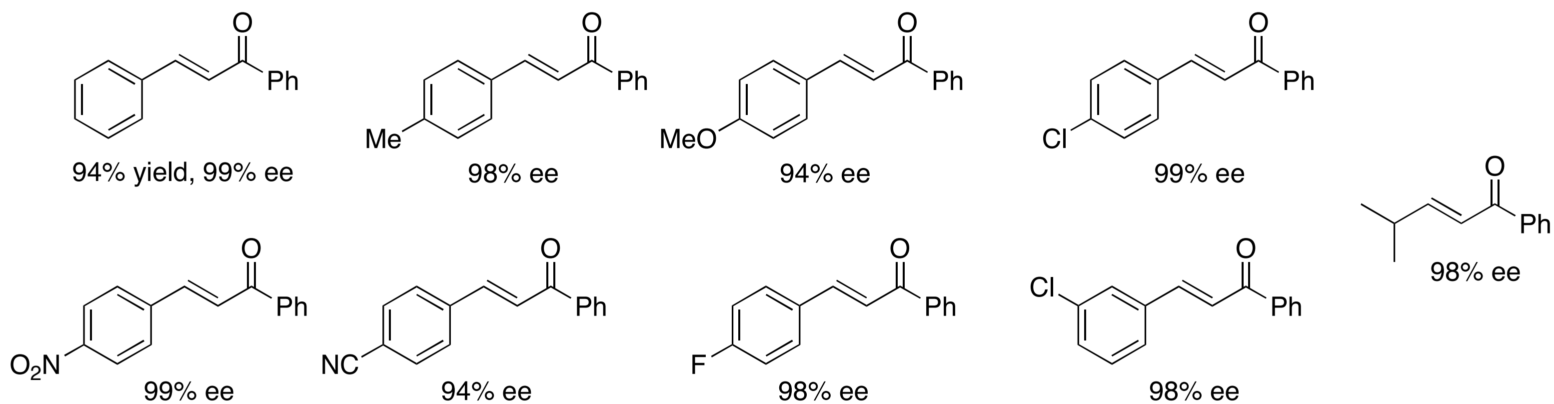


24% yield, 94% ee

Kobayashi, S. *JACS* **2004**, 12236

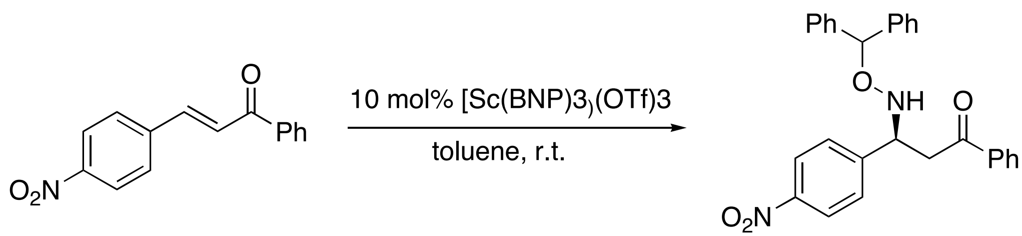
Organophosphate Ligands: Heteroconjugate Additions

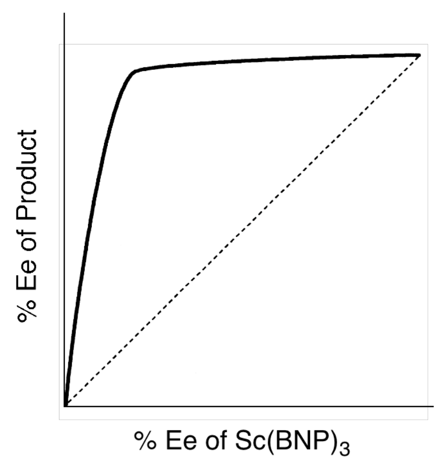




Inanaga, J. *Tetrahedron* **2002**, 8321

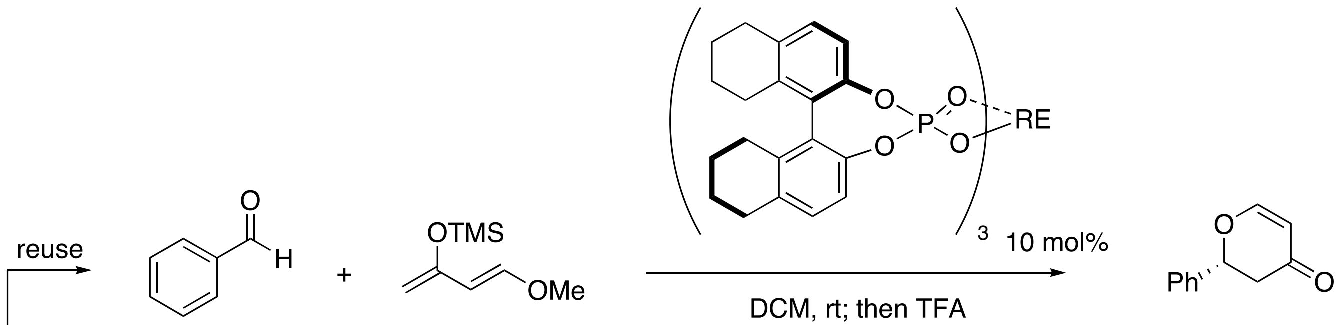
Organophosphate Ligands: Heteroconjugate Addition II

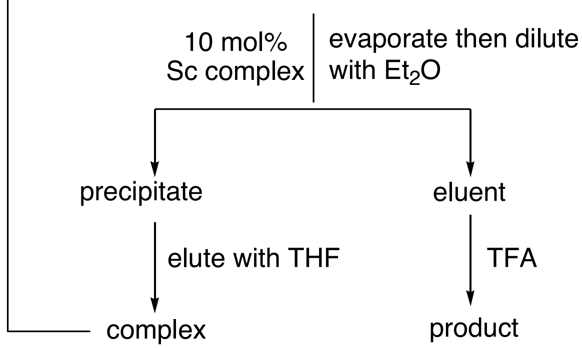




Inanaga, J. *Tetrahedron* **2002**, 8321

Organophosphate Ligands: Hetero-D.A. & Catalyst Recovery



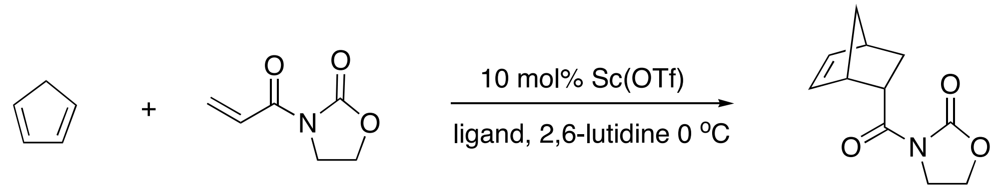


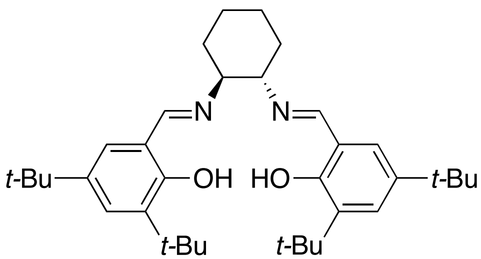
run	yield (%)	ee (%)
1	99	93
2	99	89
3	95	87

entry	metal	yield (%)	ee (%)
1	Sc	99	94
2	Yb	73	98
3	Er	76	98
4	Y	81	99
5	Dy	58	91
6	Sm	79	93
7	La	68	92

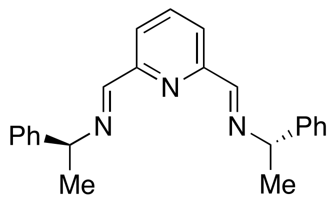
Inanaga, J. *Tetrahedron* **2003**, 10509

Bisimine/Diol Ligands: Diels-Alder

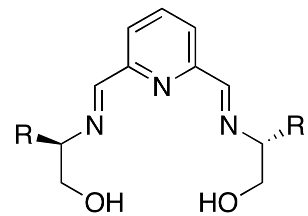




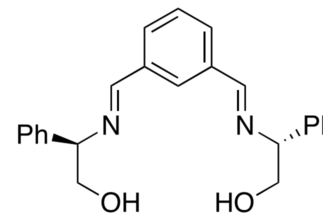
89:11 *endo/exo*, 81% yield, 85% ee
without lutidine: 45% ee



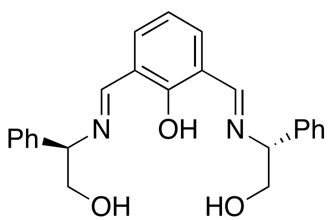
82:18, 71% yield, 34% ee
without lutidine: 29% ee



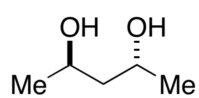
R = Ph; 86:14, 71% yield, 69% ee
without lutidine: 23% ee
R = *i*-Pr; 81:19, 82% yield, 9% ee



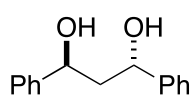
75:25, 69% yield, 3% ee



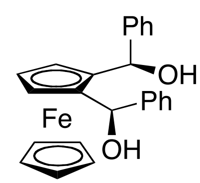
R = Ph; 90:10, 80% yield, 68% ee
R = *i*-Pr; 91:9, 86% yield, 71% ee



86:14, 65% yield, 83% ee
without lutidine: 14% ee



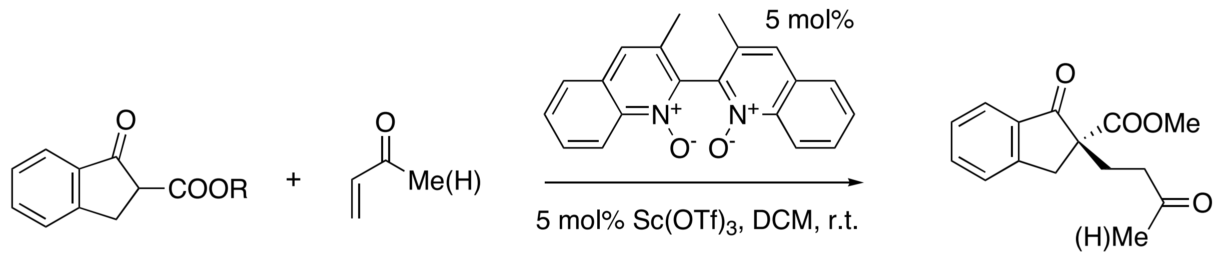
80:20, 84% yield, 29% ee



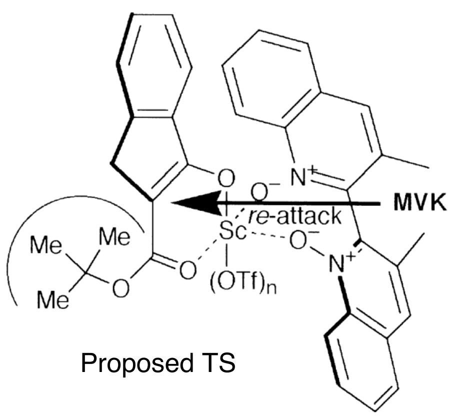
90:10, 99% yield, 91% ee
without lutidine: 19% ee

Fukuzawa, S. *TL* **2003**, 3671
Fukuzawa, S. *OL* **2002**, 707

N-Oxide Ligands: Michael Addition



entry	R	Acceptor	Yield (%)	ee (%)
1	Me	MVK	98	39
2	CH_2Ph	MVK	85	38
3	*i*-Pr	MVK	94	47
4	*i*-Bu	MVK	98	69
5	*t*-Bu	MVK	89	84
6	*t*-Bu	acrolein	73	75



Proposed TS

Nakajima, M. *Tetrahedron* **2003**, 7307

Summary

- Compared to main group TM catalysis, asymmetric Sc mediated transformations is relatively new
- BINOL and Pybox ligands are most widely used in asymmetric scandium catalysis
- Tertiary amines form H-bonds to Sc-BINOL complexes
- Molecular sieves often influence selectivities in unpredictable ways