A New Concept Toward Asymmetric Synthesis
—Chiral relay in auxiliary and catalyst design

Gang Hu

Department of Chemistry
Michigan State University

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Conventional Strategies for Asymmetric Induction

1. Substrate Control

$$S^* \xrightarrow{R} P^*$$

2. Auxiliary control

$$S{+}A^* \xrightarrow{R} P\text{-}A^* \xrightarrow{-A^*} P^*$$

3. Reagent control

$$S \xrightarrow{R^*} P^*$$

$$S^* \xrightarrow{R^*} P^*$$

4. Catalyst control

$$S \xrightarrow{Cat^*} P^*$$

$$S \xrightarrow{Cat/L^*} P^*$$

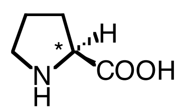
Ling, G.; Cheng, Y.; Cheng, X.; Li, Y. *Asymmetric synthesis---Enantioselective reactions and their applications*. Science Publishing, Beijing, **2000**

Can achiral auxiliary or ligand induce asymmetry?

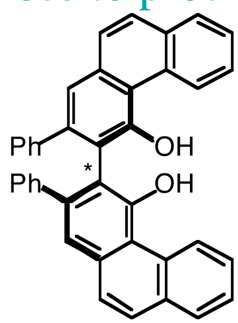
Conventional Model:

(1) Rigid, conformationally constricted auxiliary or ligand is usually required

(2) Stereogenic center would better be close to prochiral reactive site

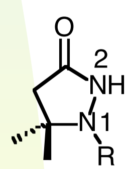


L-Proline

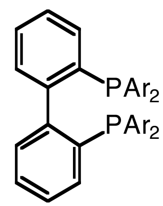


(R)-VAPOL

Conformationally flexible species:



Pyrazolidinone



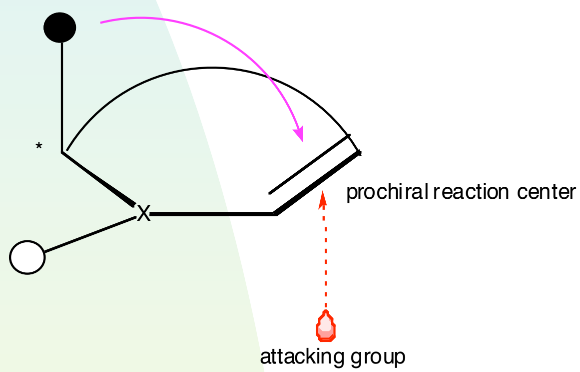
BIPHEP

Seyden-Penne, J. *Chiral Auxiliary and Ligands in Asymmetric Catalysis*; Wiley: New York, **1995**

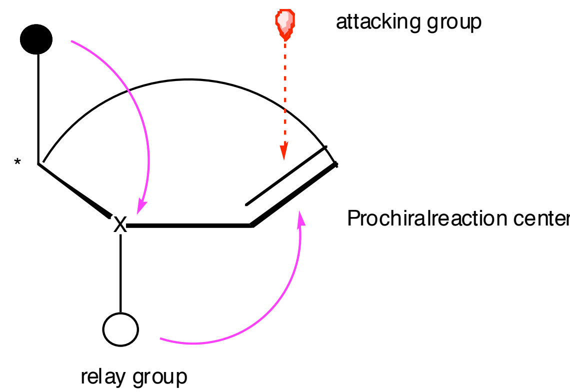
The Concept of Chiral Relay

First explicitly proposed by Davies in 1998 as follows:

"an achiral conformationally flexible group is inserted between the stereogenic center and the prochiral reaction center……In ideal circumstances, the conformationally flexible group should serve to both relay, and amplify the stereochemical information of the existing stereogenic center, thus enabling efficient control of diastereoselectivity"



Conventional remote asymmetric induction



chiral relay involved asymmetric induction

***A group of sloppy lazy men are trained into aggressive Spartans with iron will by a strict commander.**

Bull, S. D.; Davis, S. G.; Fox, D. J.; Garner, A. C.; Sellers, T. G. R. *Pure Appl. Chem.* **1998,** 70, 1501

Two principal kinds of chiral relay

1. Chiral relay in auxiliary

   a. Stereogenic center fixed on the auxiliary

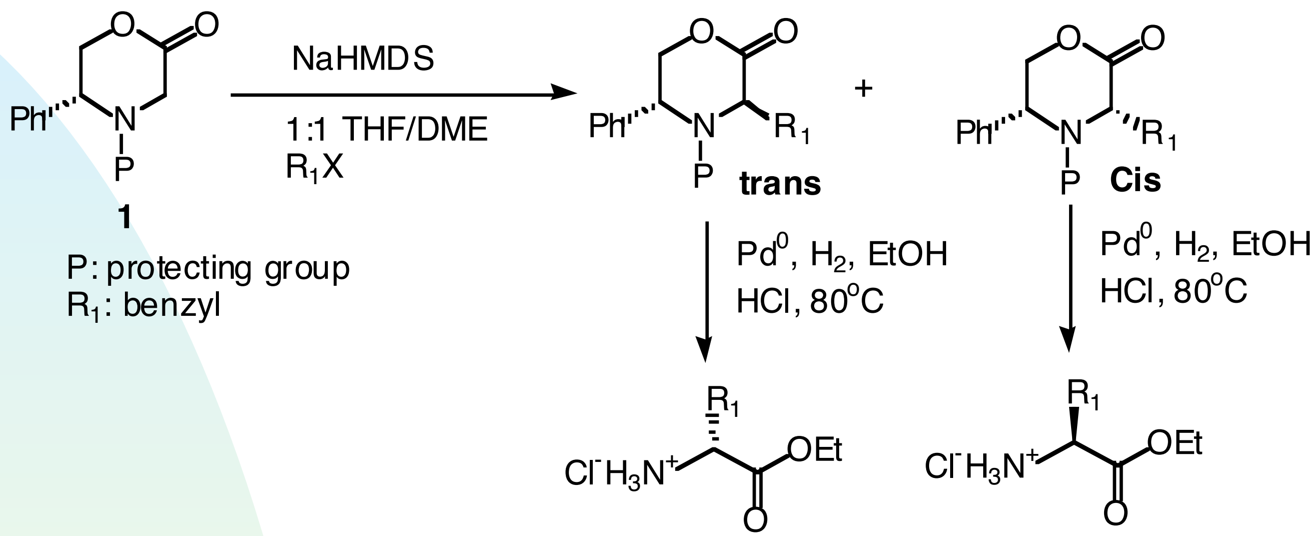
   b. Lewis acid mediated chiral relay

2. Chiral relay in catalyst

   a. Cooperative functions of flexible ligand and chiral ligand

   b. Independent function of flexible ligand

Chiral Relay in Auxiliary



Entry	Protecting group	X	Trans:Cis	Yield
1	Boc (-OCO-^{t}Bu)	Br	200:1	78%
2	Cbz (-COOCH$_2$Ph)	I	200:1	85%
3	Bn (-CH$_2$Ph)	Br	1:17	83%
4	Me	Br	1:18	

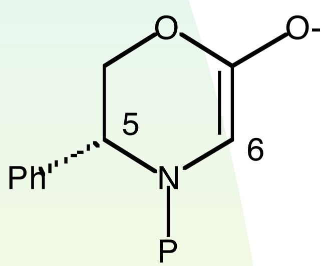
Sugg, E. E.; Griffin, J. F.; Portoghese, P. S. *J. Org. Chem.* **1985,** 50, 5032-5037

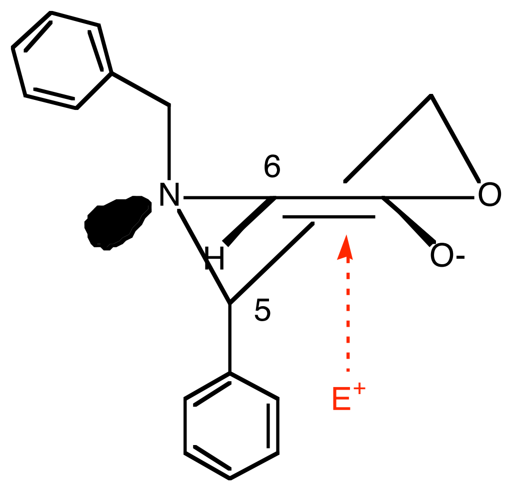
Chiral Relay in Auxiliary

Effects being considered for the conformational preference:

1. Electronic effect

2. Steric effect

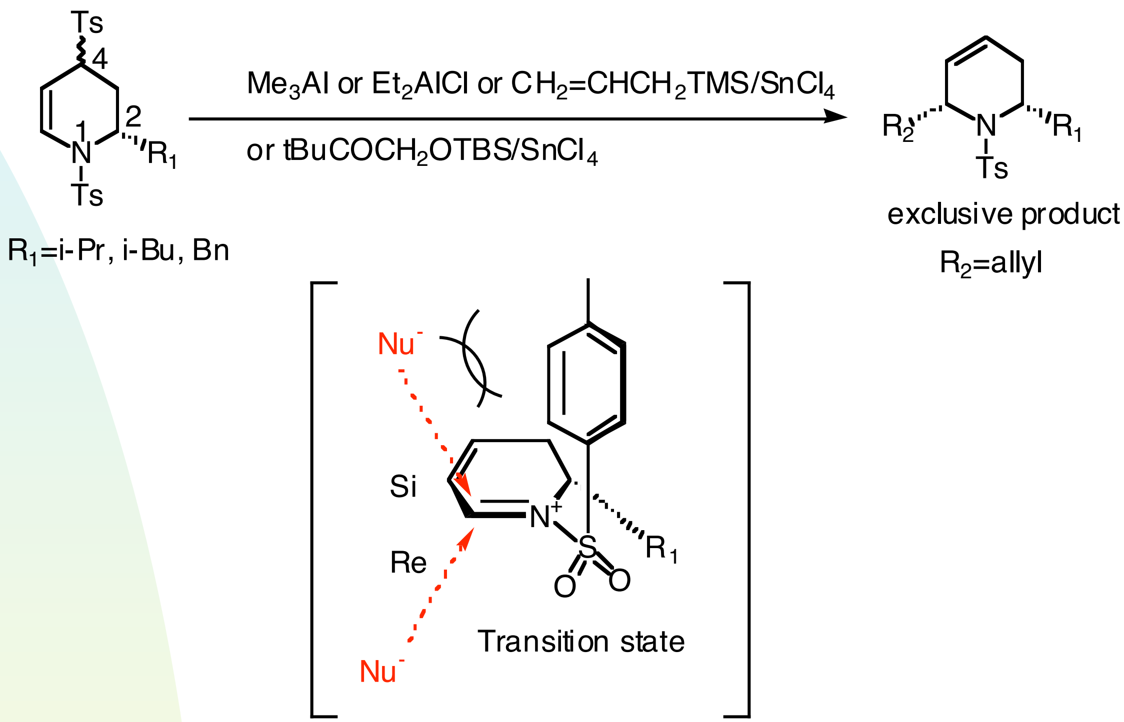




preferred half-chair conformation of the enolate

Sugg, E. E.; Griffin, J. F.; Portoghese, P. S. *J. Org. Chem.* **1985,** 50, 5032-5037

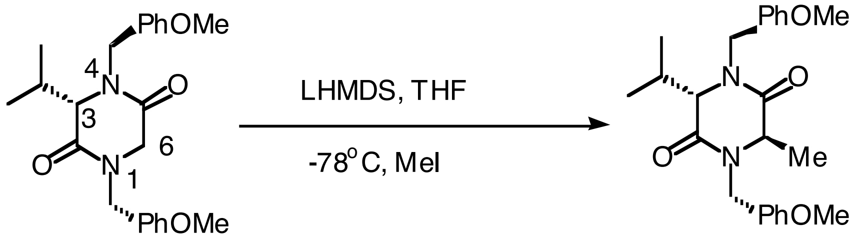
Chiral Relay in Auxiliary



Craig, D.; McCague, R.; Potter, G. A.; Williams, M. R. V. *Synlett*, **1998**, 55

Chiral Relay in Auxiliary

Relay network

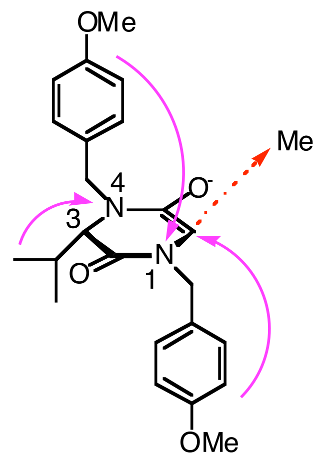


2
Diketopiperazine (DKP)

d.e=93%

When N-protecting groups replaced by methyl d.e=33%

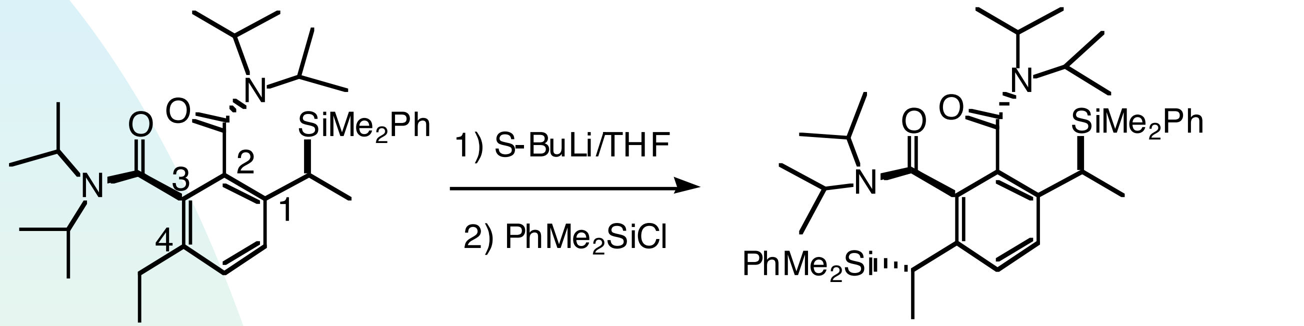
Transition State



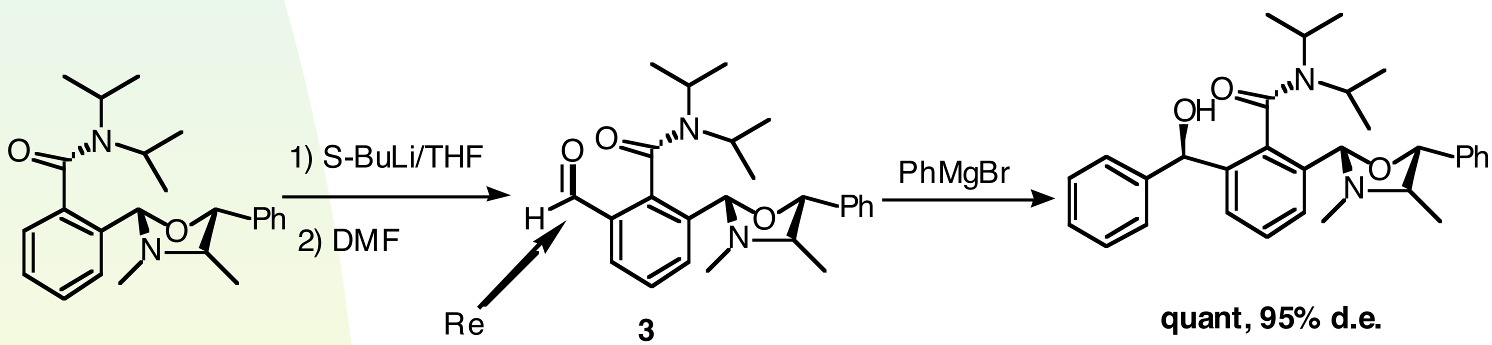
Bull, S. D.; Davies, S. G.; Epstein, S. W. Ouzman, J. V. A. *J. Chem. Soc., Chem. Commun.* **1998,** 659

Chiral Relay in Auxiliary

Tertiary amide as relay group



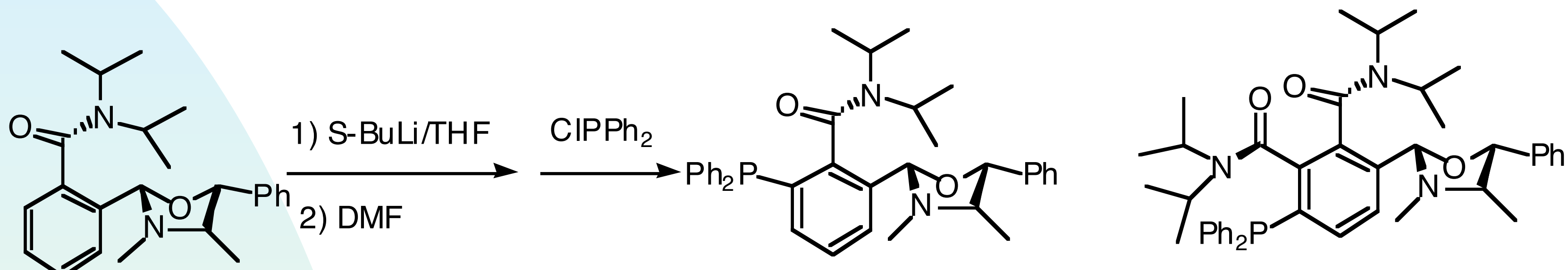
77% yield, only one diastereomer



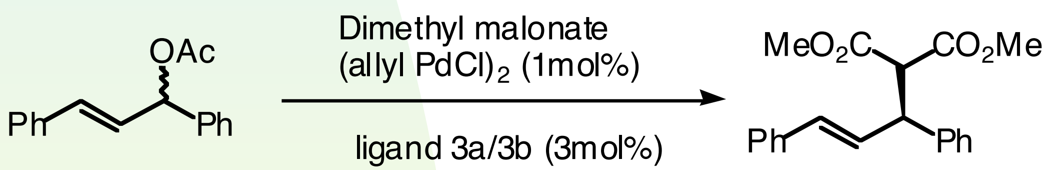
Clayden, J.; Pink, J. H.; Yasin, S. A. *Tet. Lett.* **1998,** 39, 105

Clayden, J.; Lai, L. W.; Helliwell, M. *Tet. Asymmetry* **2001,** 12, 695-698

Chiral Relay in Auxiliary



Ligand 3a **Ligand 3b**



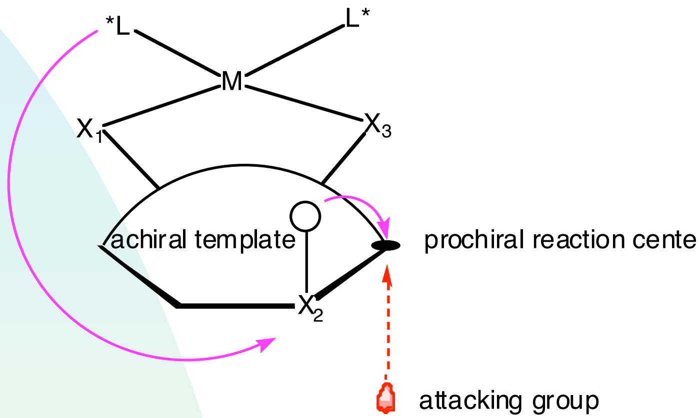
Ligand 3a: (S)-(-), 82%ee, 93% yield
Ligand 3b: (R)-(+), 53%ee, 85% yield

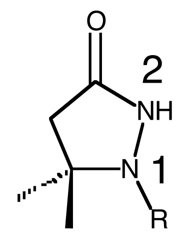
Clayden, J.; Lai, L. W.; Helliwell, M. *Tet. Asymmetry* **2001**, 12, 695-698

For review of asymmetric allylic alkylation, see Trost. B. M. *Chem. Rew.* **1996**, 96, 395-422

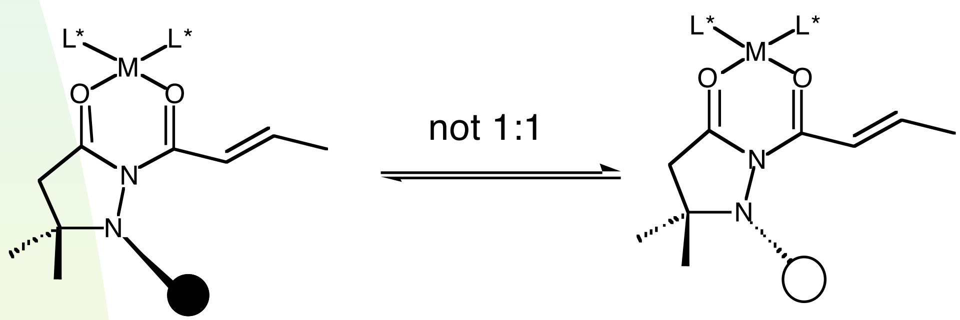
Lewis acid mediated chiral relay

Chiral relay controlled by labile group





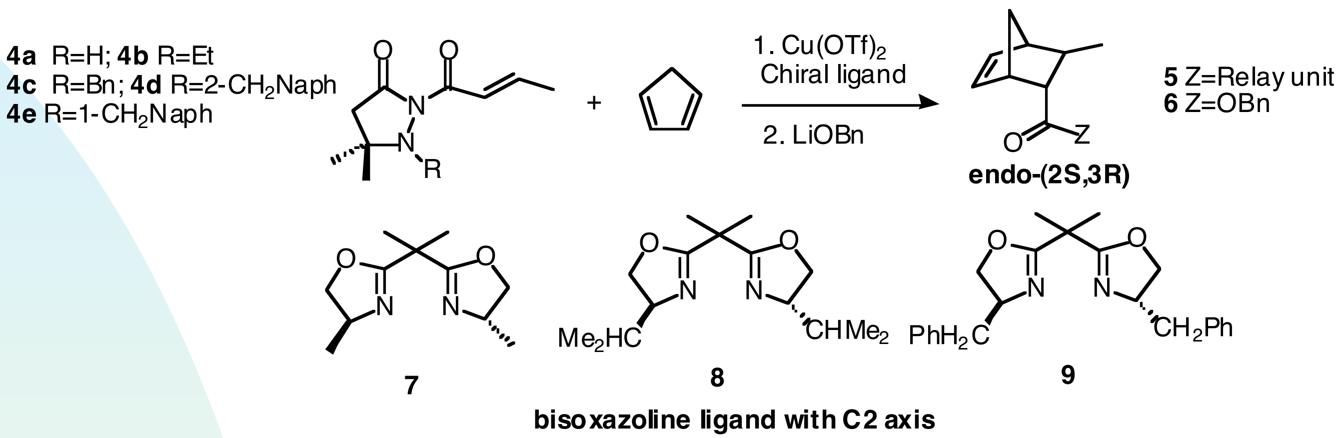
Pyrazolidinone



Interconversion of Pyrazolidinone complex

Sibi, M. P.; Venkatraman, L.; Liu, M.; Jaspere, C. P. *J. Am. Chem. Soc.* **2001**, 123, 8444-8445

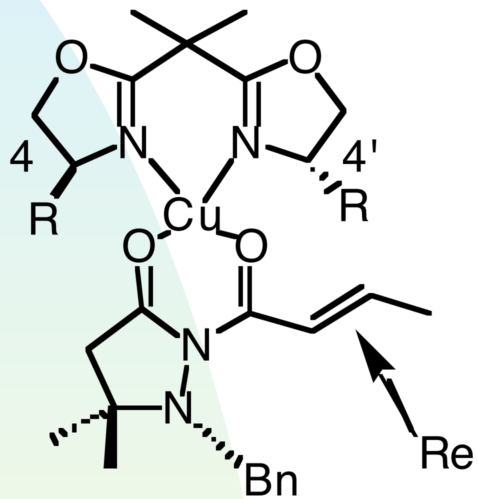
Lewis acid mediated chiral relay



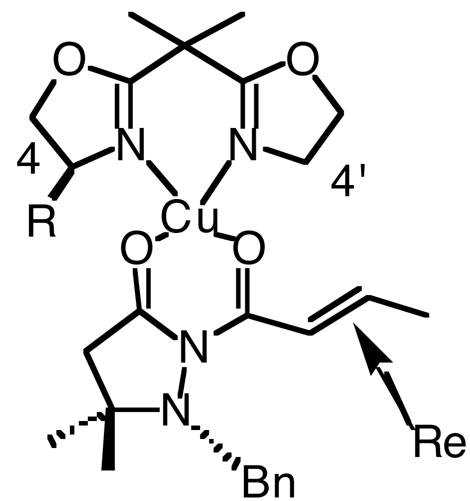
Run	Substrate	7 ee(endo)	8 ee(endo)	9 ee(endo)
1	4a R=H	29%	08%	03%
2	4b R=Et	64%	56%	55%
3	4c R=Bn	71%	71%	71%
4	4d R=2-CH_2Naph	79%	65%	69%
5	4e R=1-CH_2Naph	86%	92%	85%

Sibi, M. P.; Venkatraman, L.; Liu, M.; Jaspere, C. P. *J. Am. Chem. Soc.* **2001**, 123, 8444-8445

Lewis acid mediated chiral relay



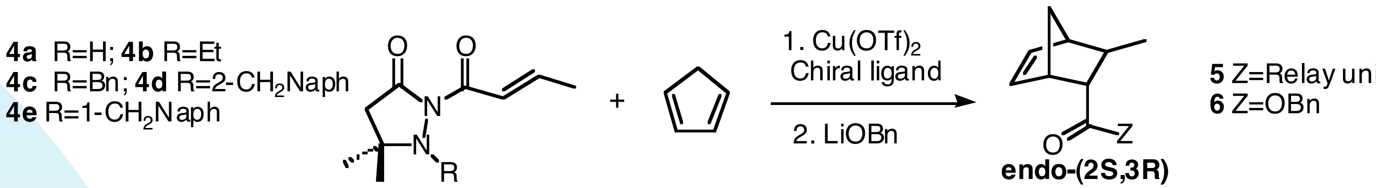
Complex with C2 ligand

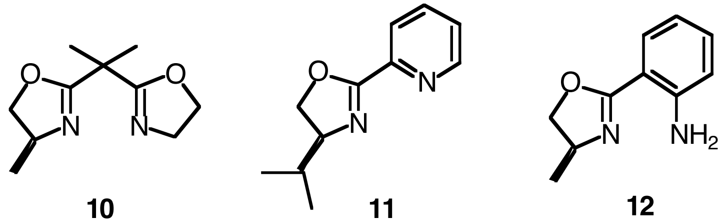


Complex with C1 ligand

Evans, D. A.; Miller, S. J.; Lectka, T.; Matt, P. V. *J. Am. Chem. Soc.* **1999**, 121, 7559-7573

Lewis acid mediated chiral relay





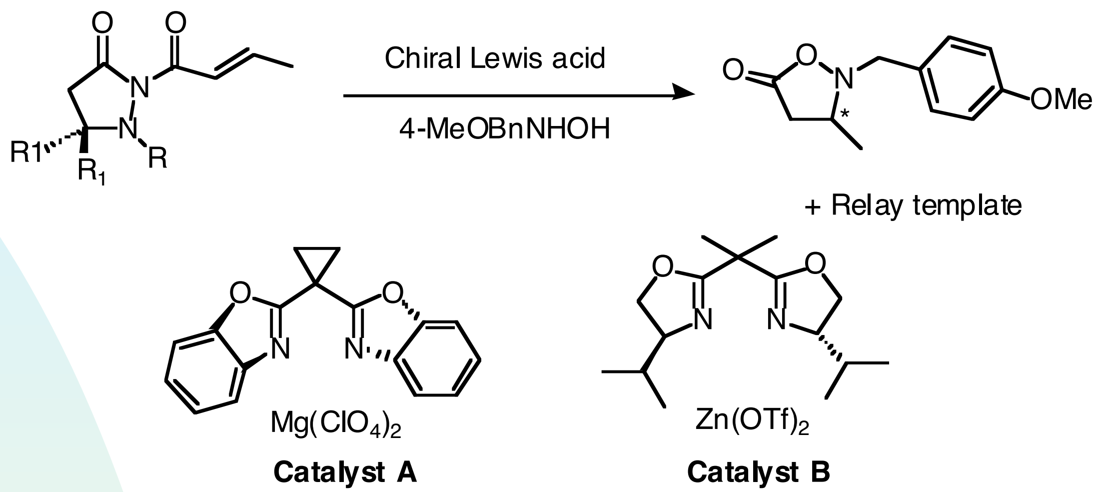
10 11 12

C1 ligand

Run	Substrate	10 *ee(endo)*	11 *ee(endo)*	12 *ee(endo)*
1	4a R=H	04%	01%	01%
2	4b R=Et	29%	12%	26%
3	4c R=Bn	47%	38%	51%
4	4d R=2-CH_2Naph	56%	59%	58%
5	4e R=1-CH_2Naph	69%	66%	71%

Sibi, M. P.; Venkatraman, L.; Liu, M.; Jaspere, C. P. *J. Am. Chem. Soc.* **2001**, 123, 8444-8445

Lewis acid mediated chiral relay



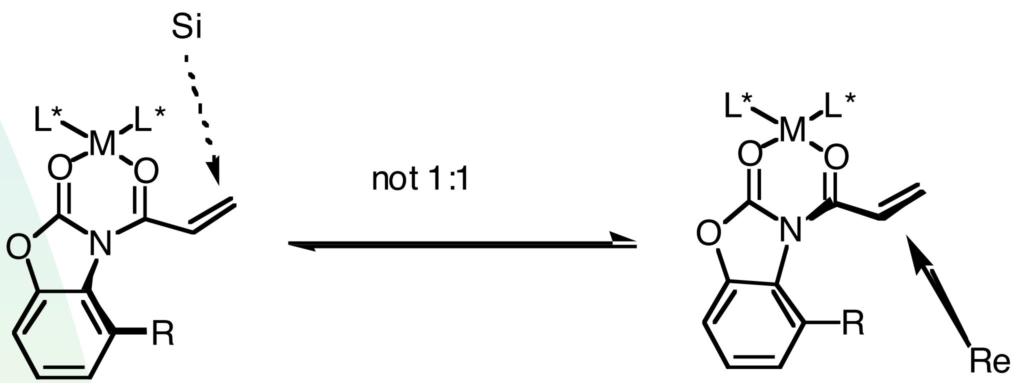
run	Substrate	Catalyst A Yield	Catalyst A ee%	Catalyst B Yield	Catalyst B ee%
1	R_1=Me, R=H	75%	76(R)*	74%	28(S)
2	R_1=Me, R=Et	70%	52(R)	74%	49(S)
3	R_1=Me, R=Bn	67%	78(R)	71%	68(S)
4	R_1=Me, R=2-CH_2Naph	75%	78(R)	73%	70(S)
5	R_1=Me, R=1-CH_2Naph	77%	81(R)	75%	75(S)

Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, 3, 4181-4184

* The unusually high ee is presumably attributed to a very different chelation pattern

Lewis acid mediated chiral relay

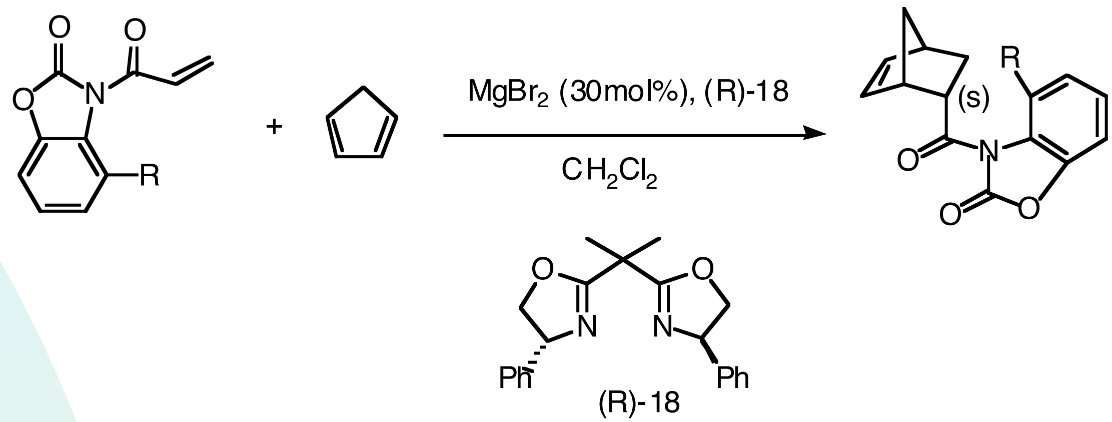
Chiral relay controlled by axis



Benzoxazol acrylamide

Quaranta, L.; Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002,** 4, 39-42

Lewis acid mediated chiral relay

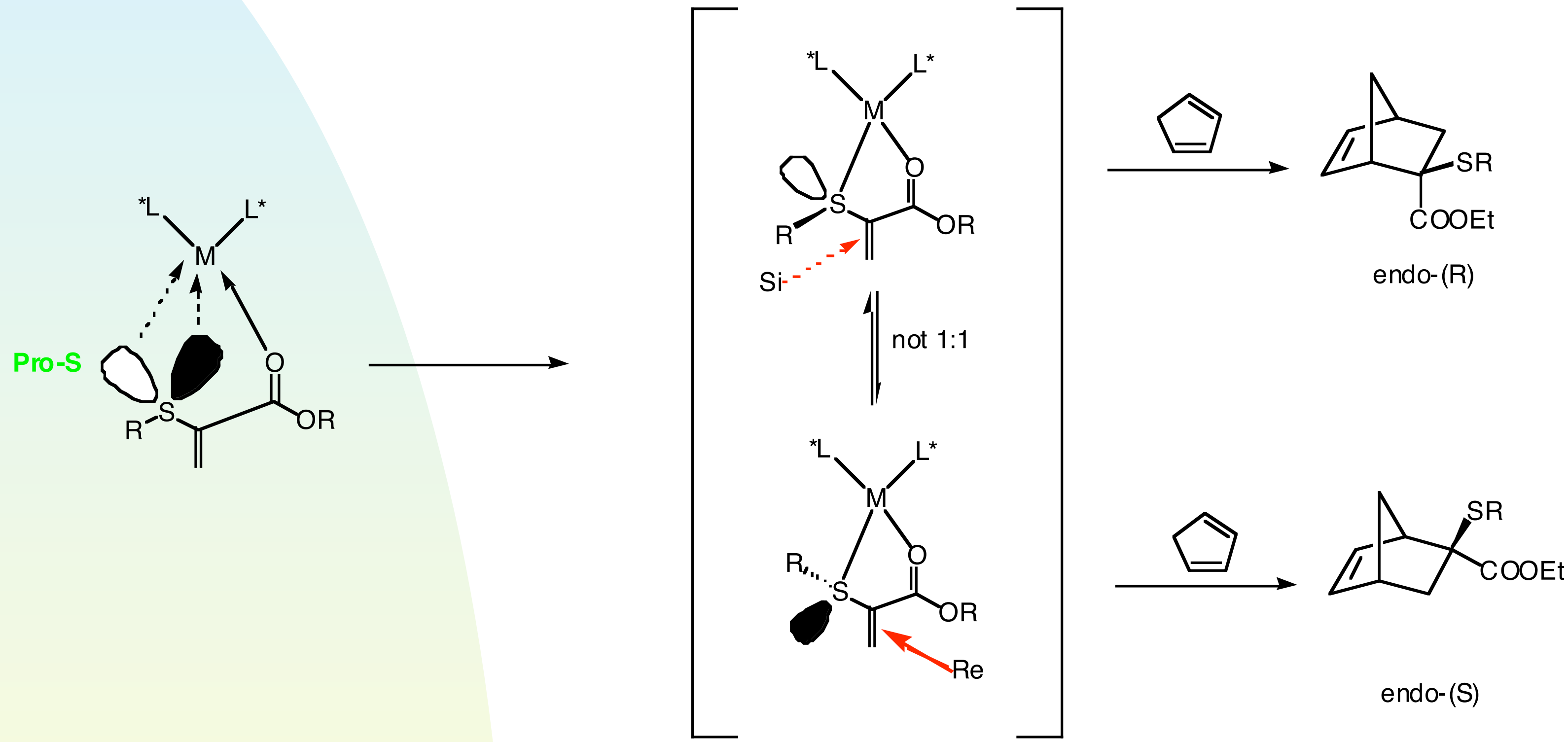


Run	R	Yield (endo/exo)	ee (endo)
1	H	98%(22:1)	14%(s)
2	Me	97%(32:1)	74%(s)
3	Et	97%(33:1)	76%(s)
4	Bn	97%(11:1)	86%(s)
5	PMB	98%(16:1)	88%(s)
6	CH_2t-Bu	98%(20:1)	10%(s)
7	$CH(Ph)_2$	97%(17:1)	72%(s)
8	$SiMe_3$	95%(40:1)	40%(s)

Quaranta, L.; Corminboeuf, O.; Renaud, P. *Org. Lett.* **2002,** 4, 39-42

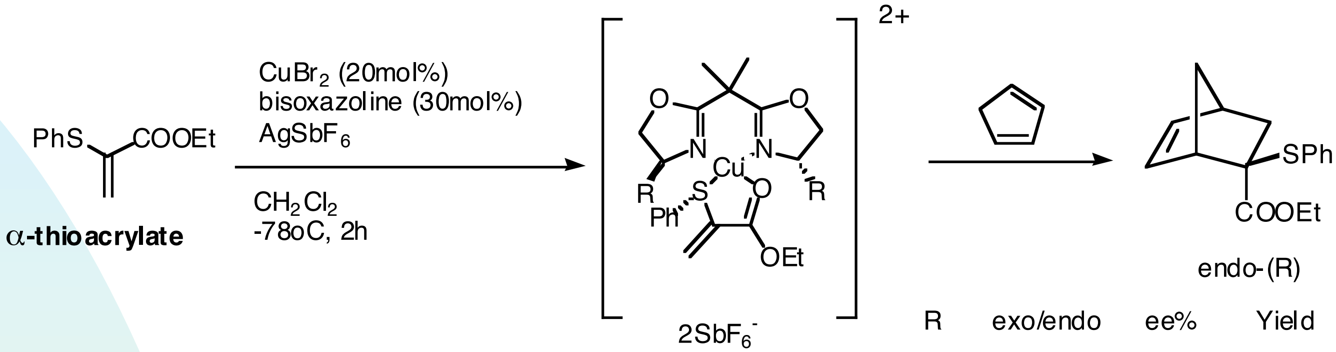
Lewis acid mediated chiral relay

Chiral relay controlled by selectively binding to lone pair

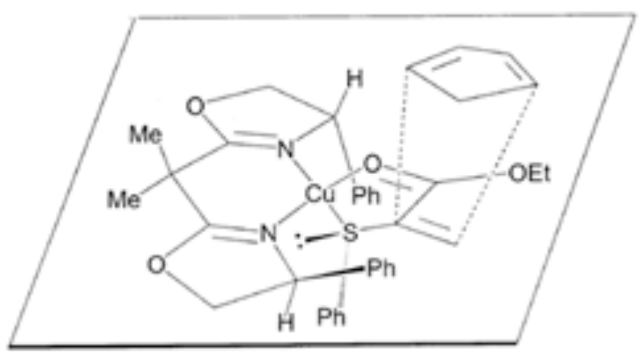


Aggarwal, V. K.; Jones, D. E.; Martin-Castro, A. M. *Eur. J. Org. Chem.* **2000**, 2939-2945

Lewis acid mediated chiral relay



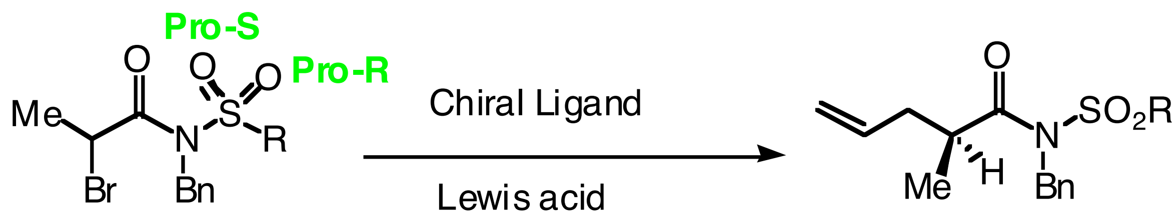
R	exo/endo	ee%	Yield
Ph	1:15	>95%	92%
^{t}Bu	1:5.6	78%	64%



Proposed transition state

Aggarwal, V. K.; Jones, D. E.; Martin-Castro, A. M. *Eur. J. Org. Chem.* **2000**, 2939-2945

Lewis acid mediated chiral relay

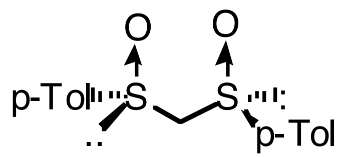


Lewis acid
Allyl (tri-n-butyl) Stannane

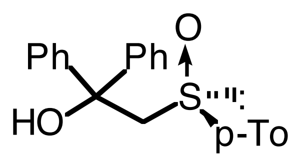
1a R=Me
1b R=Tol

(S)-2a R=Me
(S)-2b R=p-Tol

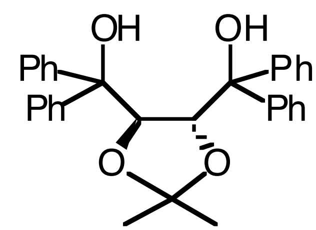
Chiral Ligand:



3a



3b

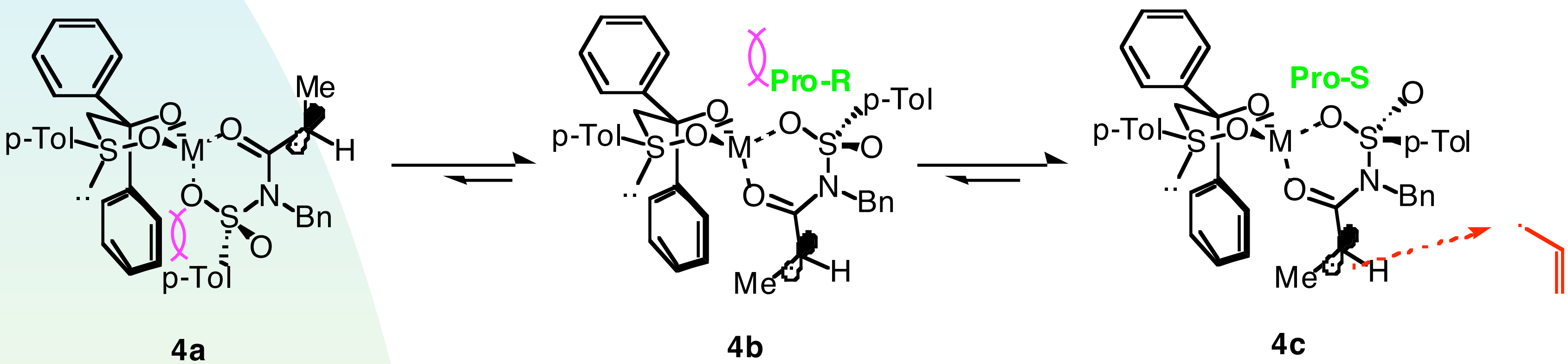


3c

Entry	R	Chiral ligand	Lewsi acid	Yield	*ee*
1	p-Tol	3a	$Mg(OTf)_2$	65%	52%
2	p-Tol	3b	$Mg(OTf)_2$	41%	83%
3	p-Tol	3c	$Ti(O\text{-}ipr)_4$	44%	50%
4	methyl	3c	$Ti(O\text{-}ipr)_4$	33%	5%

Hiroi, K.; Ishii, M. *Tet. Lett.* **2000**, 41, 7071-7074

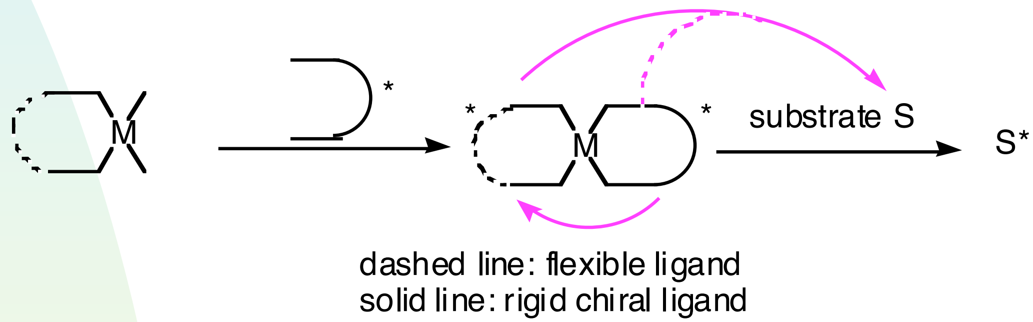
Lewis acid mediated chiral relay



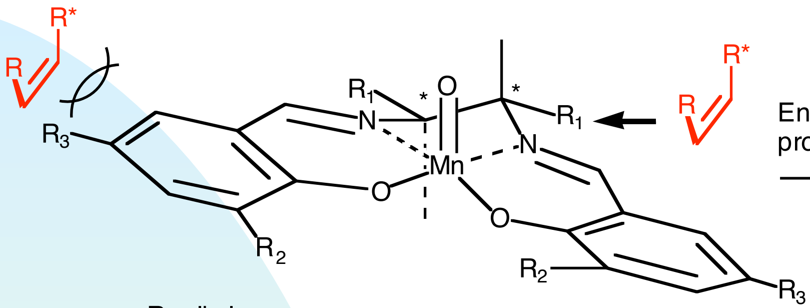
Hiroi, K.; Ishii, M. *Tet. Lett.* **2000**, 41, 7071-7074

Chiral Relay in Catalyst

Illustration of the chiral relay in catalyst with the original stereogenic center

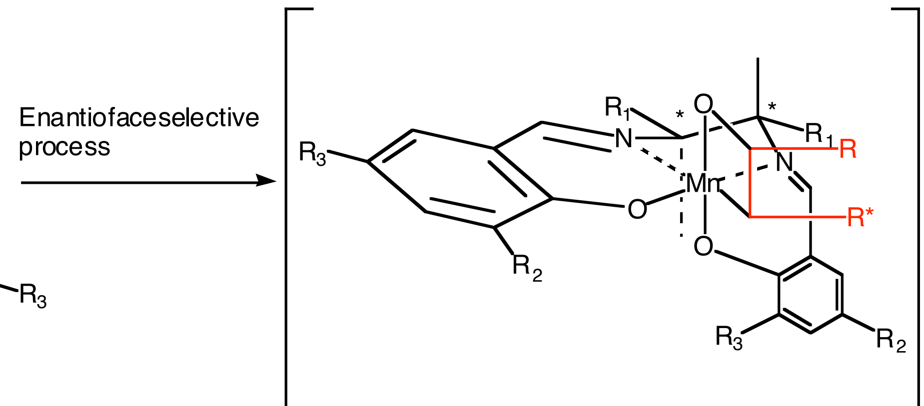


Chiral Relay in Catalyst



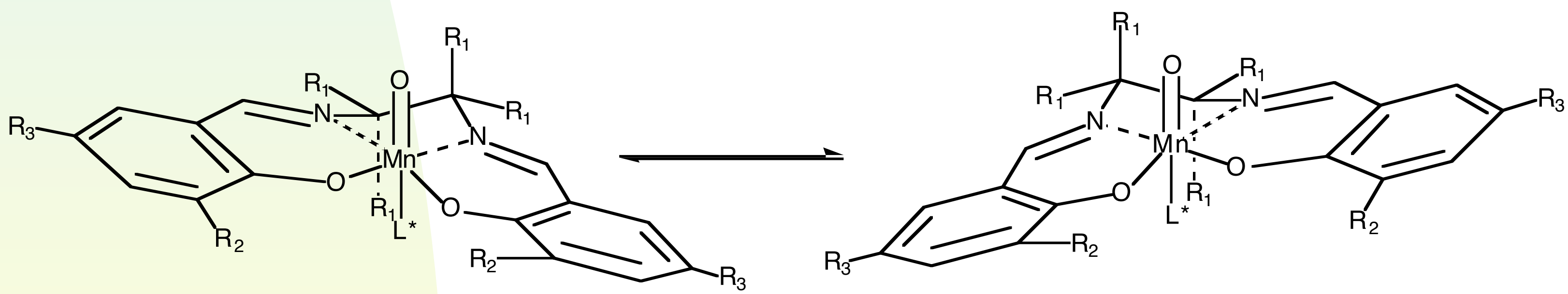
R=alkyl group
R*=pi-electron rich and radicalstabilizing group:
aryl, alkenyl, and alkyl groups

Oxo Mn-Salen Complex



Major metallaoxetane

(major enantiomer)

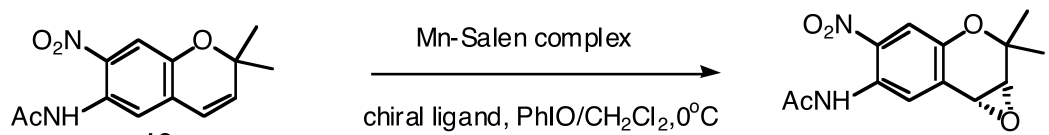


19 **ent-19**

Hashihayata, T; Ito, Y.; Katsuki, T. *Synlett* **1996**, 1079-1081

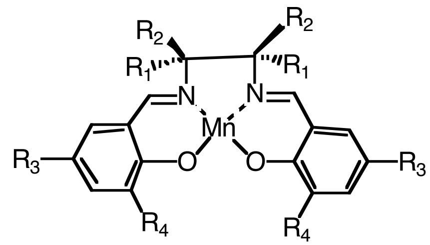
Hashihayata, T.; Ito, Y.; Katsuki, T. *Tetrahedron,* **1997**, 53, 9541

Chiral Relay in Catalyst



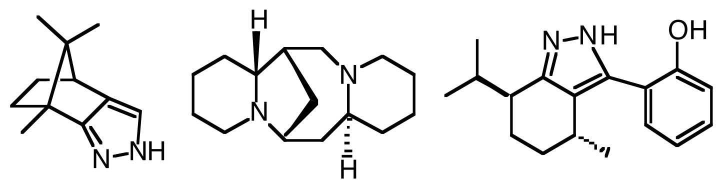
13

(3R, 4R)



14

meso Mn-Salen complex

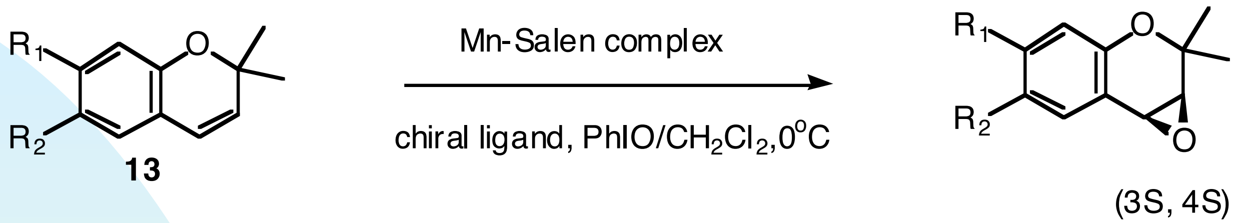


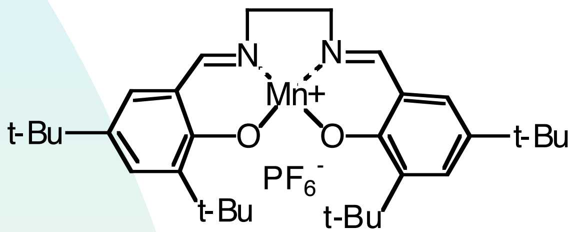
15 16 17

chiral ligand

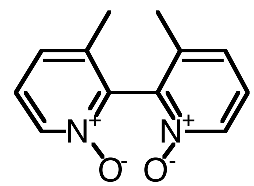
Entry	Mn-Salen complex	Ligand	ee
1	$Mn(OAc)_2$ or $Mn(OAc)_3$	16	0%
2	14a: R_1=R_2=R_3=R_4=t-Bu, X=PF_6	15	3%
3	14b: R_1=R_2=H, R_3=R_4=t-Bu, X=OAc	15	6%
4	14c: n=R_1=R_2=H, R_3=R_4=t-Bu, X=OAc	16	18%
5	14f: R_1=R_2=Me, R_3=R_4=t-Bu, X=PF_6	16	60%
6	14i: R_1=R_2=Me, R_3=OSi(Pr-i)$_3$, R_4=t-Bu, X=PF_6	16	52%

Chiral Relay in Catalyst





meso Mn-Salen complex

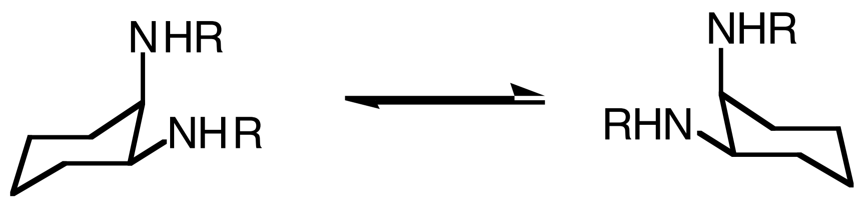


(+)3,3'-dimethyl-2,2'-bipyridine N,N'-dioxide
Chiral Ligand

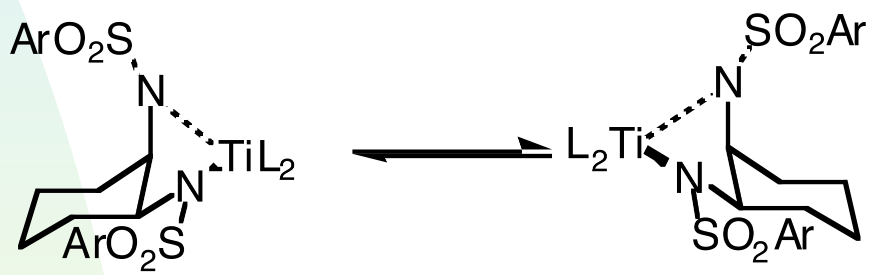
Entry	R_1	R_2	Yield	ee	Config.
1	NO_2	AcHN	65%	82%	3S,4S
2	H	NC	59%	77%	3S,4S
3	=N(O)-O-N=		90%	78%	3S,4S

Miura, K.; Katsuki, T. *Synlett* **1999**, 6, 783-785

Chiral Relay in Catalyst



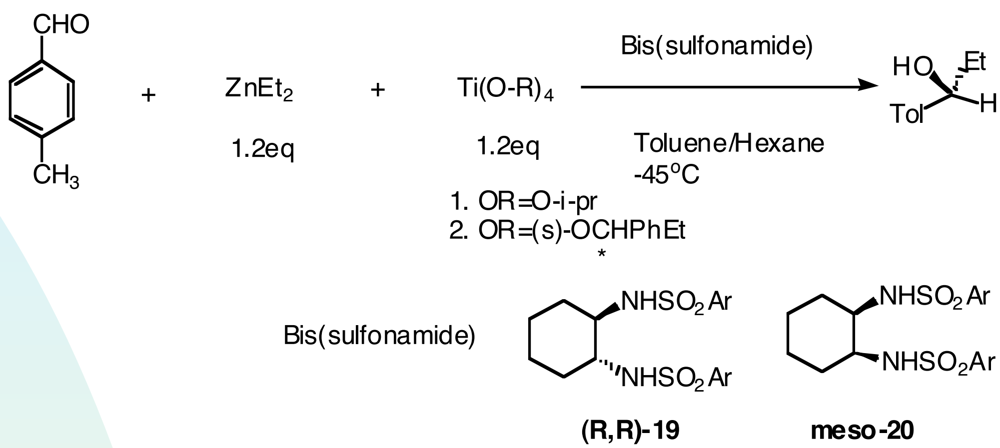
interconversion of diaminocyclohexane



desymmetrization when chelate to chiral LA

Bassells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, 122, 1802-1803

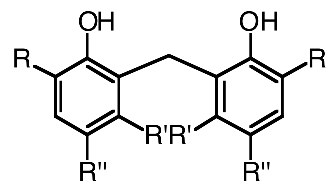
Chiral Relay in Catalyst



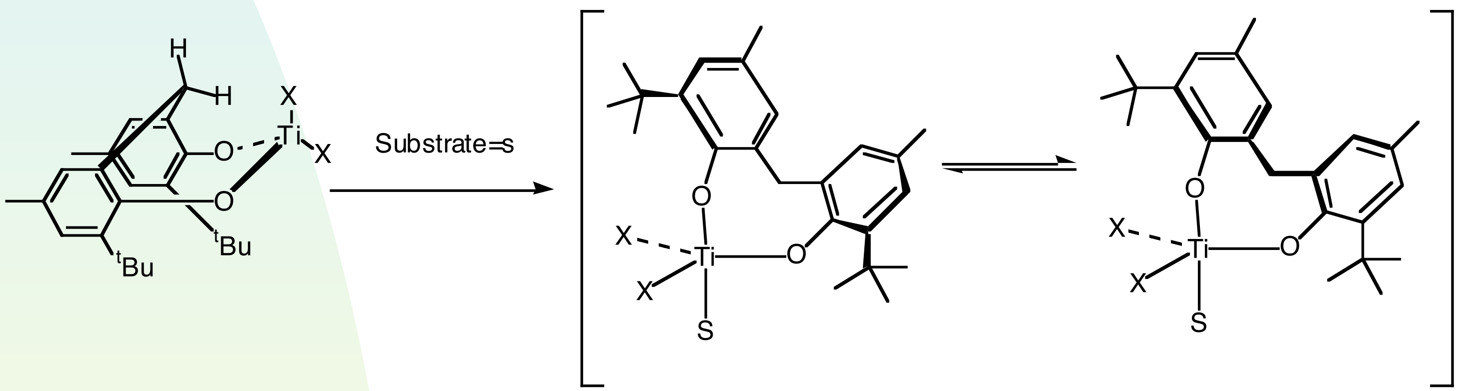
run	R	Ligand	Ar	ee
1	i-pr	(R,R)-19	2,4-C_6H_3-Me_2	79%(S)
2	s-CHPhEt	(R,R)-19	2,4-C_6H_3-Me_2	84%(S)
3	s-CHPhEt	(S,S)-19	2,4-C_6H_3-Me_2	81%(R)
4	s-CHPhEt	---	---	42%(S)
5	s-CHPhEt	20a	4-C_6H_4-CMe_3	84%(R)
6	s-CHPhEt	20b	4-C_6H_3-OMe	78%(R)

Bassells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, 122, 1802-1803

Chiral Relay in Catalyst

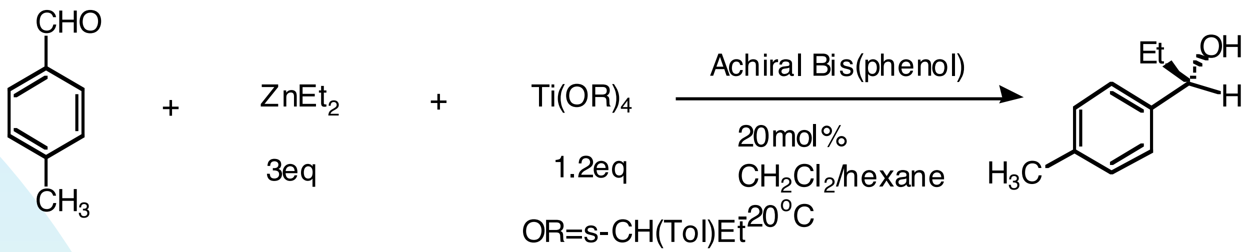


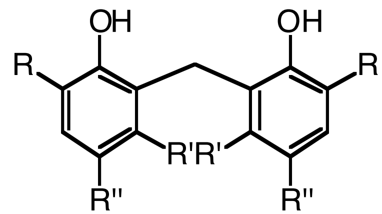
2,2'-methylene-Bisphenol (MBP)



Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, 3, 2161

Chiral Relay in Catalyst



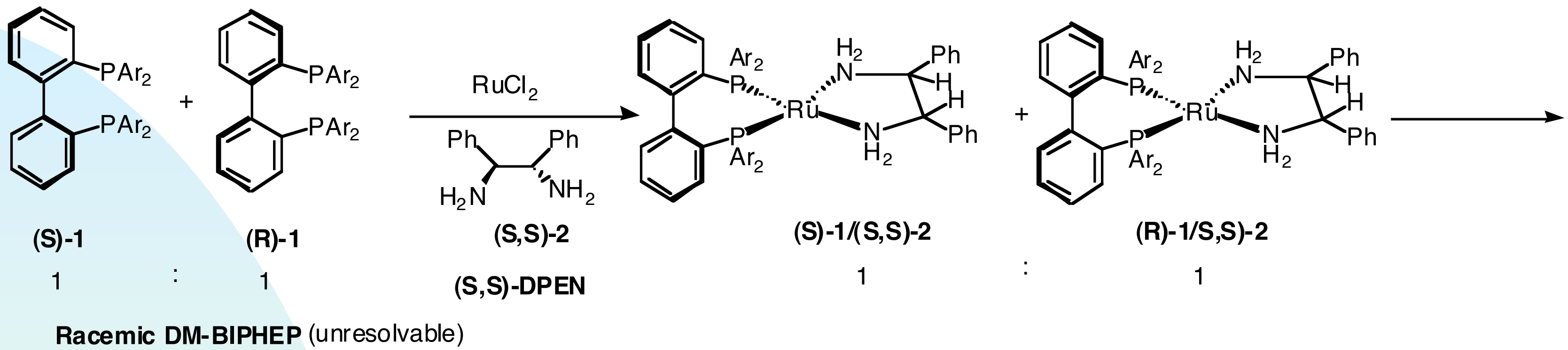


MBP

Entry	Ligand	R	R’	R’’	ee%
1	No MBP				39(S)
2	1a	H	H	H	1(S)
3	1c	Cl	Cl	Cl	24(S)
4	1d	Me	H	Me	16(S)
5	1e	Ph	H	H	36(S)
6	1f	t-Bu	H	t-Bu	68(S)
7	1g	t-Bu	H	Me	79(S)
8	1h	t-Bu	H	H	73(S)
9	li	Adamantyl	H	Me	83(S)

Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, 3, 2161

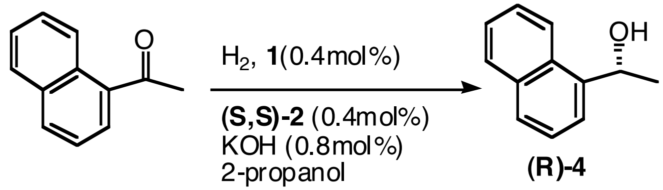
Chiral Relay in Catalyst



[D_8]2-propanol → (S)-1/(S,S)-2 + (R)-1/(S,S)-2

rt. for 3hr or 80°C for 30min

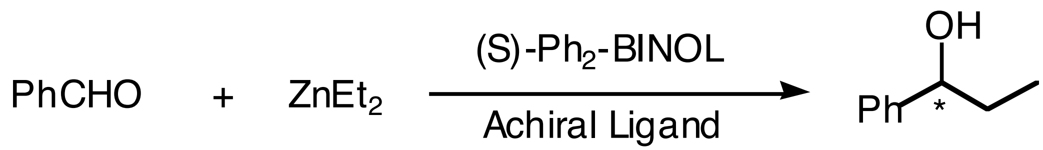
3 : 1

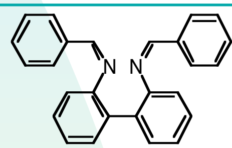
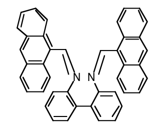
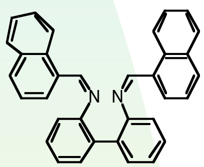
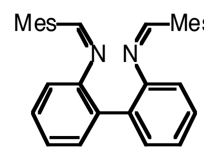
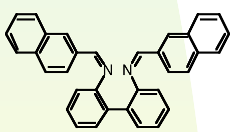
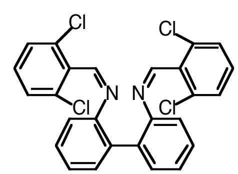


Entry	Phosphane	(S)/(S,S):(R)/(S,S)	*ee*	Yield
1	DM-BIPHEP	1:1	63%	99%
2	DM-BIPHEP	2:1	73%	99%
3	DM-BIPHEP	3:1	84%	99%
4*	DM-BIPHEP	3:1	92%	99%

Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem. Int. Ed.* **1999**, 38, 495-497 * The experiment was performed under -35°C instead of 28°C as in other entries

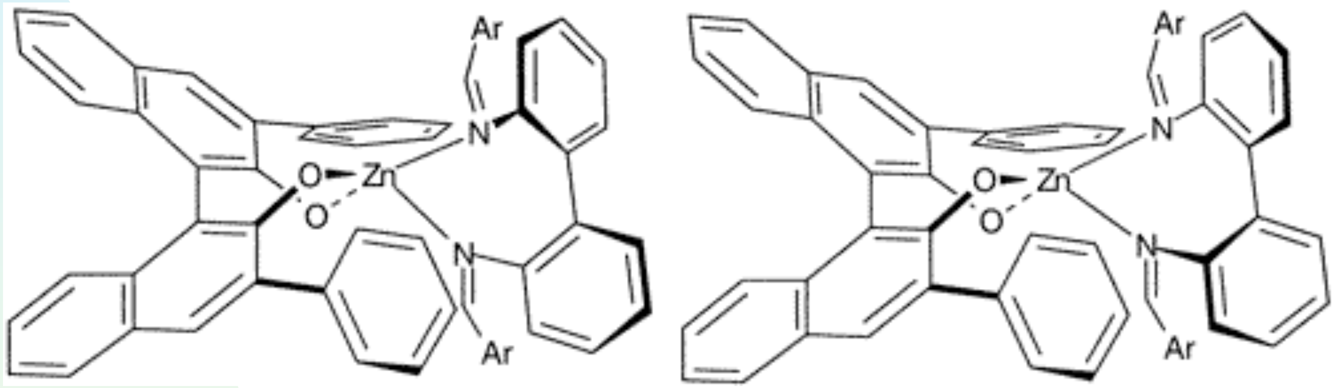
Chiral Relay in Catalyst



Entry	Achiral Ligand	ee/ 0ºC(config.)	Entry	Achiral Ligand	ee/ 0ºC(config.)
1		38%(S)	4		54%(R)
2		25%(R)	5		38%(S)
3		27%(S)	6		89%(R)

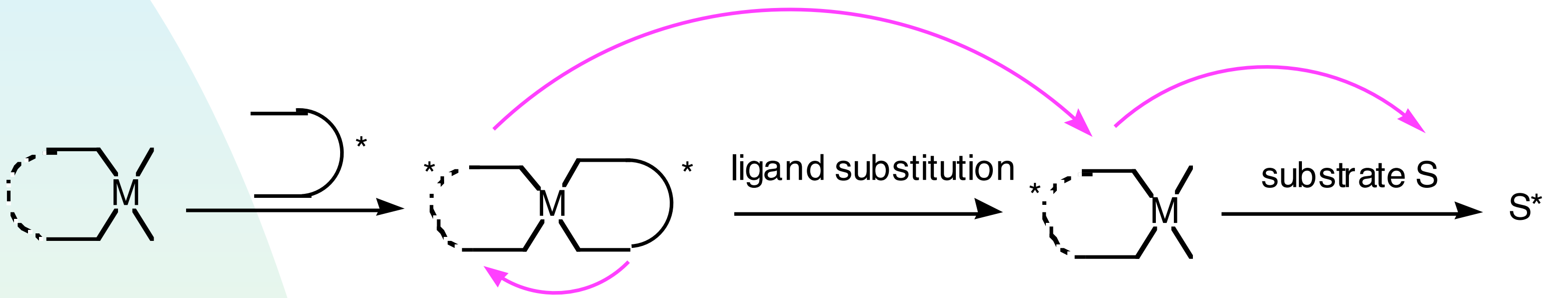
Costa, A. M.; Jimeno, C.; Gavenonis, J.; Carroll, P. J. Walsh, P. J. *J. Am. Chem. Soc.* **2002**, 124, 6929-6941

Chiral Relay in Catalyst



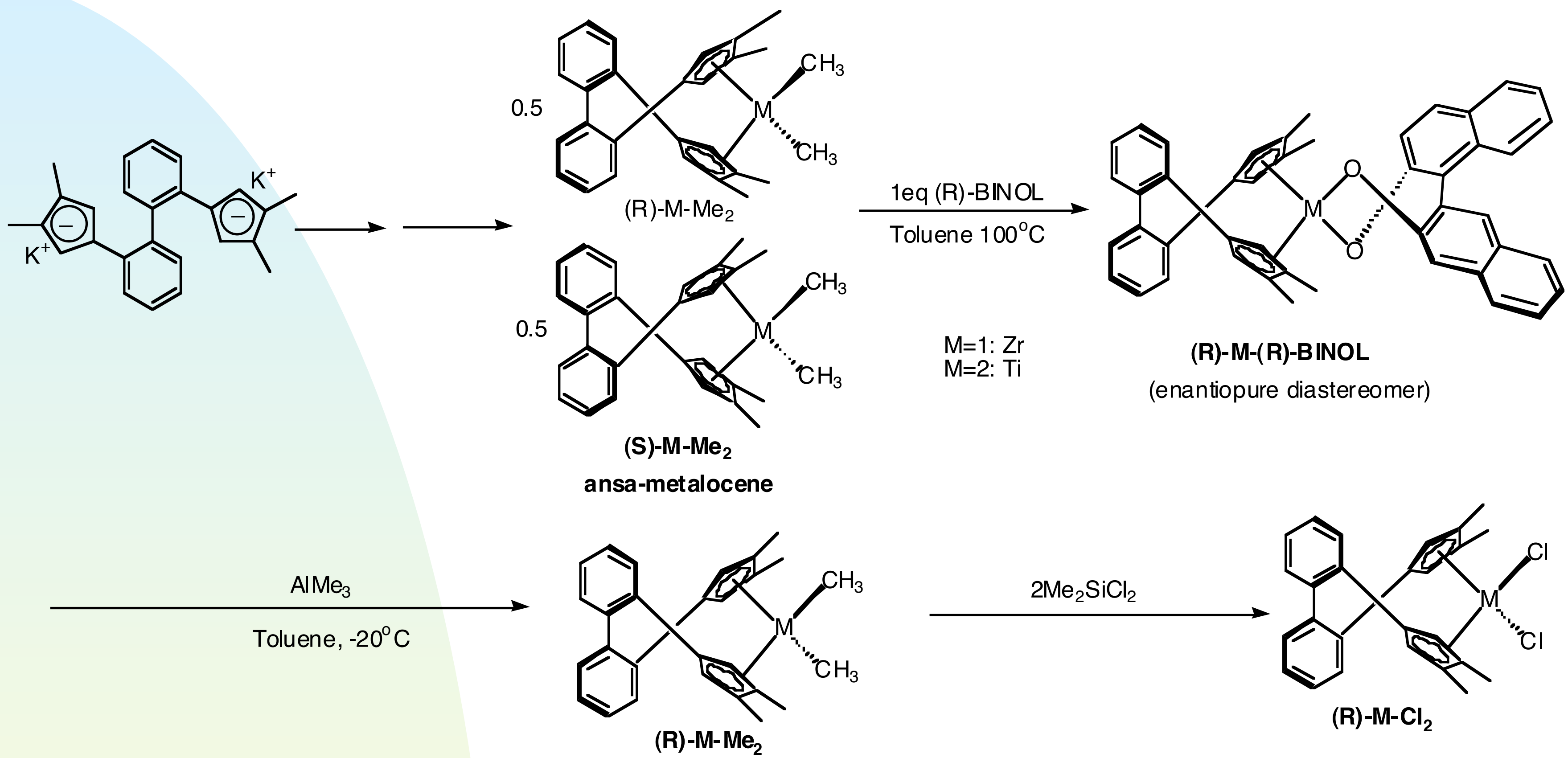
Costa, A. M.; Jimeno, C.; Gavenonis, J.; Carroll, P. J. Walsh, P. J. *J. Am. Chem. Soc.* **2002**, 124, 6929-6941

Chiral Relay in Catalyst



dashed line: flexible ligand
solide line: rigid chiral ligand

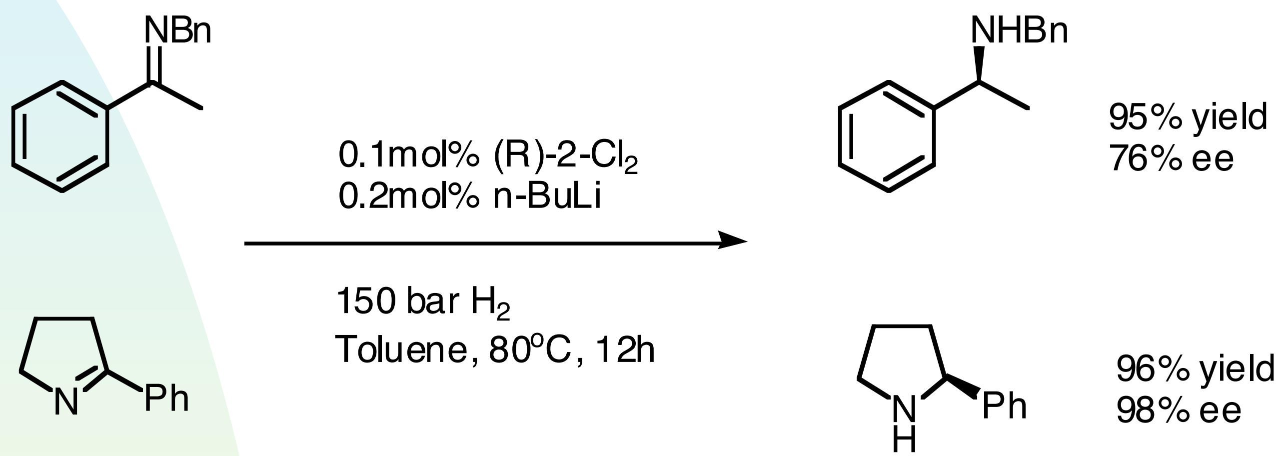
Chiral Relay in Catalyst



Huttenloch, M. E.; Dorer, B.; Rief, U.; Prosenc, M-H.; Schmidt, K.; Bringtzinger, H. H.; *J. Organomet. Chem.* **1997**, 541, 219

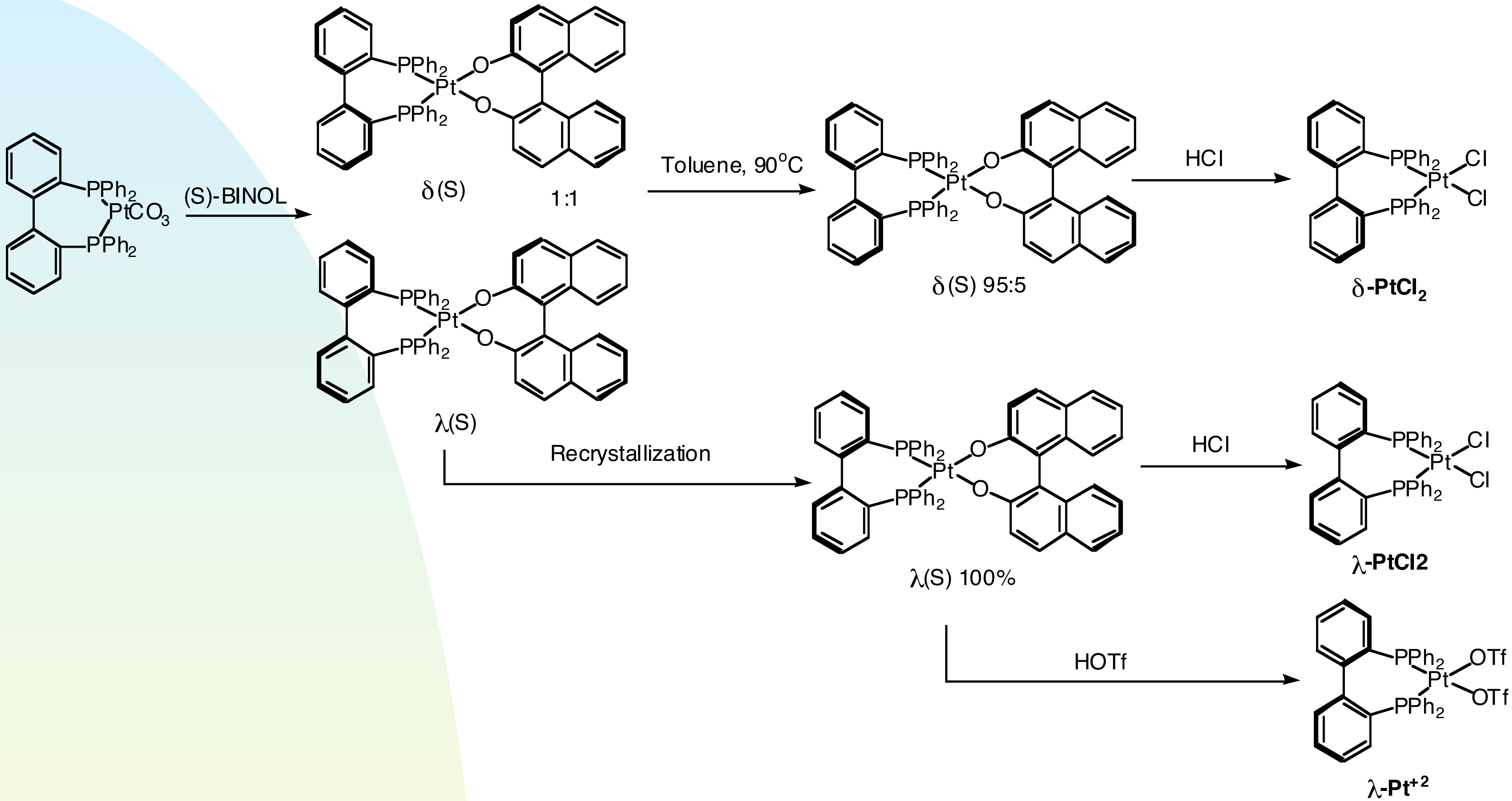
Ringwald, M.; Sturmer, R.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1999**, 121, 1524-1527

Chiral Relay in Catalyst



Ringwald, M.; Sturmer, R.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1999**, 121, 1524-1527

Chiral Relay in Catalyst

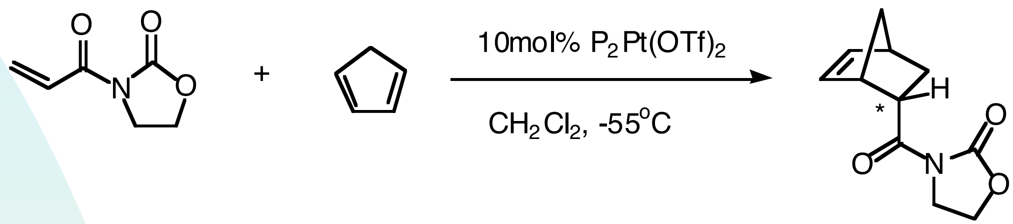


* (λ/δ) are arbitrarily assigned to the biphep stereochemistry in terms of its skew conformation

Tudor, M. D.; Becker, J. J; White, P. S.; Gagne, M. R. *Organometallics* **2000**, 19, 4376

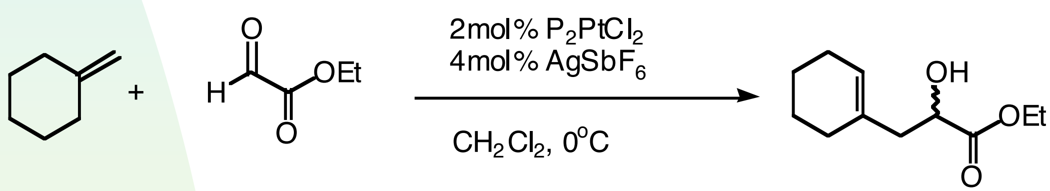
Becker, J. J.; White, P. S.; Gagne, M. R. *J. Am. Chem. Soc.* **2001**, 123, 9478-9479

Chiral Relay in Catalyst



20

λ-Pt^{+2}: **(S)-20**, 92-94% ee, 93:7 endo/exo
δ-Pt^{+2} : **(R)-20**, 92-94% ee, 94:6 endo/exo



21

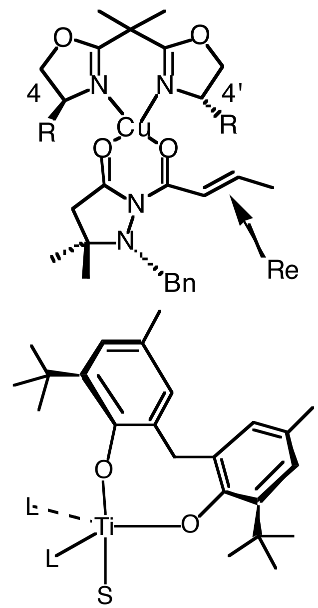
λ-$PtCl_2$: **(S)-21**, 71%ee
δ-$PtCl_2$: **(R)-21**, 70%ee

Tudor, M. D.; Becker, J. J; White, P. S.; Gagne, M. R. *Organometallics* **2000**, 19, 4376

Becker, J. J.; White, P. S.; Gagne, M. R. *J. Am. Chem. Soc.* **2001**, 123, 9478-9479

Problems in this model

(1) Straightforward experimental evidence is inadequate to support the relay mechanism. Stereochemical outcome is still not predictable in a majority of reactions.



(2) The role of relay ligand has not been well decoupled with chiral ligand. It's still hard to determine which one plays a major part in catalyst.

(3) Some other concepts describing the similar events in catalysts have been proposed, such as achiral additives,[24] ligand acceleration,[18] asymmetric activation,[25] and asymmetric poisoning,[26] It is difficulty to conclude which one is closer to the real picture at least by now.

For review, Vogel, E. M.; Groger, H; Shibasaki, M. *Angew. Chem. Int. Ed.* **1999**, 38, 1570-1577

Long, J; Ding, K. *Angew. Chem. Int. Ed.* **2001**, 40, 452-457

Faller, J. W.; Lavorie, A. R.; Grimmond, B. J. *Organometallics* **2002**, 21, 1662-1666

Future Work

(1) Mechanism elucidation

(2) Experimental evidence for the relay process

(3) Kinetic study for decoupling different pathways

(4) Efficient design of relay template and ligand

(5) Theoretic modeling may provide insight for relay process

Conclusion

1. Chiral relay is a conceptually novel idea and has been successfully applied in many reaction systems.

2. The mechanism of chiral relay is not very clear and problems still exist.

3. Future work should be done to elucidate the mechanism and direct the design of novel chiral relay groups.

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Yu, Chunrui, Jie, Yiqian,

Andreiv, Shi Feng,

Yang Jian, Yana