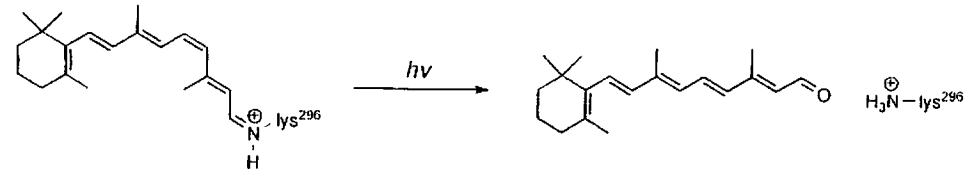
Stereochemistry as Information

Stereochemistry : *syn/anti*, (*R*)/(*S*), etc...
Information : easy to record, copy, amplify, transfer

In Nature, stereochemical information is used effectively.

ex) Rhodopsin



Today, we overview some examples in which stereochemical information is transmitted intra- or intermoleculary.

contents
1. "Memory of Chirality" introduced by Fuji and Kawabata
2. "Chiral Relay" introduced by Sibi and Renaud
3. "Ultra-remote Stereocontrol"

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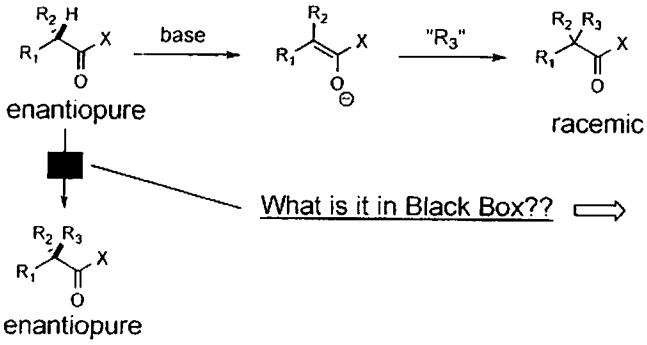
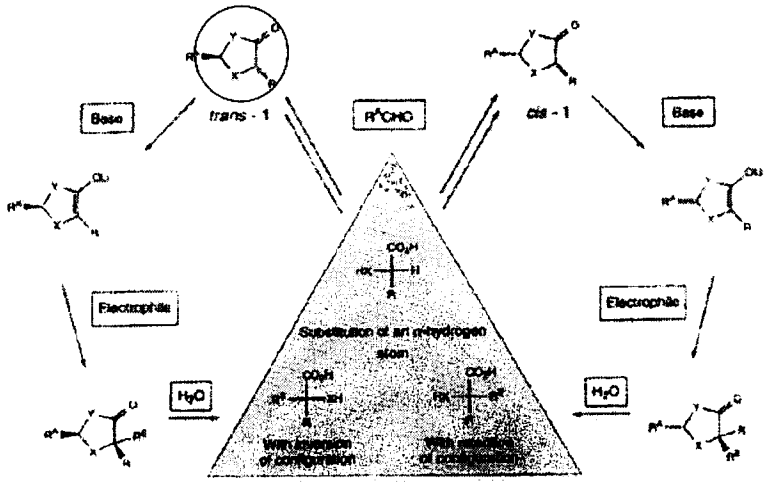
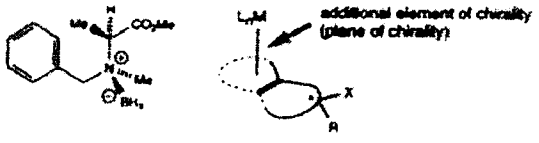
1. Memory of Chirality

1-1. background



Self-Regeneration of Stereocenters (SRS) developed by D. Seebach





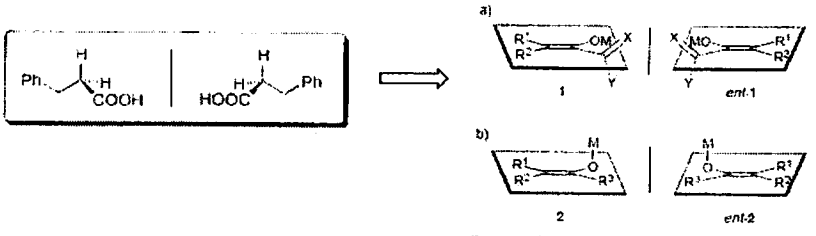
non-covalnet diastereo-complex with BH3, transition-metal complex, and so on

⇒ Pre-complextation and achiral auxiliary are needed.

covalent diastereo-complex (RCHO as achiral auxiliary)

1-2. memory of chirality : proof of concept

consider the "dynamic chirality", one type of conformational chirality



possible to be differentiated from each other (1/ent-1, 2/ent-2) at an extremly low temperature or by the introduction of specific structural constraints into the molecule

Figure 2. Enantiomeric forms of enolates with a) axial chirality (1) and b) planar chirality (2).

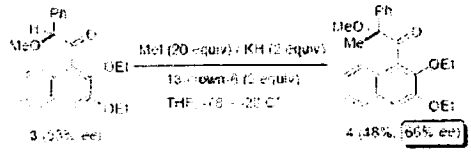
Memory of Chirality: Enantioselective Alkylation Reactions at an Asymmetric Carbon Adjacent to a Carbonyl Group

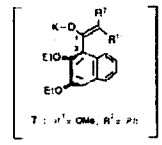
Takeo Kawabata, Kiyoshi Yahiro, and Kaoru Fuji*

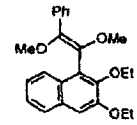
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611, Japan

Received July 17, 1991

JACS **1991**, *113*, 9694.







bypro (>65% ee)

via axially chiral enolate

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definition of memory of chirality

central chirality at a carbon α to a carbonyl group is preserved as transient axial chirality of the intermediate enolate and is then regenerated as central chirality in the reaction product (memory of chirality)

original definition

A "memory of chirality" reaction can be defined as a formal substitution at an sp^3 stereogenic center that proceeds stereospecifically, even though the reaction proceeds by trigonalization of that center, and despite the fact that no other permanently chiral elements are present in the system.

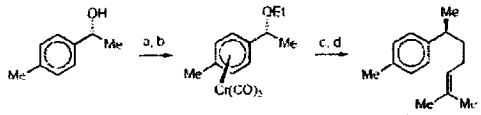
Synthesis **2005**, 1.

but, the term "memory of chirality" is easy to misinterpretation.

Memory of Chirality in Electron Transfer Mediated Benzylic Umpolung Reactions of Arene–Cr(CO)$_3$ Complexes

Hans-Günther Schmalz,* Charles B. de Koning, Dirk Bernicke, Stephan Siegel, and Anja Pfletschinger

ACIE **1999**, *38*, 162

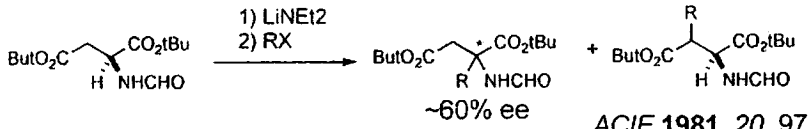


Scheme 5. a) EtBr, NaH, THF, sealed tube, 80 °C, 7 h, 70%; b) Cr(CO)$_6$, Bu$_2$O, THF, 145 °C, 30 h, 36%; c) LiDBB, THF, −78 °C, then 5-iodo-2-methyl-2-pentene, 27%; d) hν, sunlight, 99%.

Although authors insisted this reaction involved a normally notoriously labile radical intermediate, it seems at least to me this reaction is more suitable to be classified into SRS-type reaction.

precedents

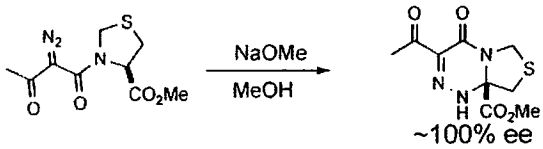
Acutually, a few examples about "memory of chirality" existed before the report by Fuji and Kawabata.



~60% ee

authors proposed two possibilities
1) axially chiral enolate
2) mixed aggregates with chiral SM or β-adduct

ACIE **1981**, *20*, 971.

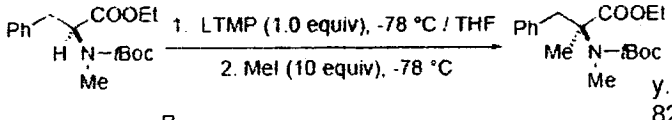


~100% ee

JCS Chem. Commun. **1991**, 924.

1-3. memory of chirality : enolate chemistry (Kawabata's work)

Asymmetric α-alkylation of phenylalanine derivatives



drawbacks
1) low chemical yield
2) low substrate generality
3) removal of *N*-Me group

improvement

JACS **1994**, *116*, 10809.

<u>substrates generality</u>

ACIE **2000**, *39*, 2155.
OL **2000**, *2*, 3883.

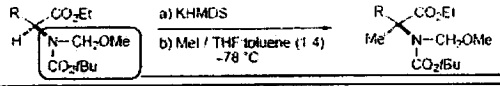
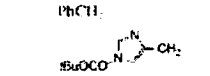
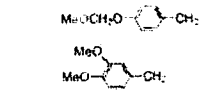
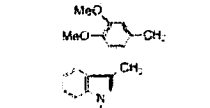
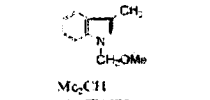


Table 1. Asymmetric α-methylation of α-amino acid derivatives[a]

Entry	R	Substrate[b]	Product	Yield [%]	ee [%] [c]	$[\alpha]_D^{20}$ (c in $CHCl_3$)	Configuration[d]
1	PhCH$_2$	3	4	96	81	−89 (1.2)	*S*
2		5	6	83	95	43 (1.1)	[e]
3		7	8	94	70	−81 (1.0)	*S*
4		9	10	95	80	−96 (1.0)	*S*
5		11	12	88	76	−64 (0.9)	[e]
6	Me$_2$CH	13	14[f]	81	87	+8.5 (1.2)[g]	*S*
7	Me$_2$CHCH$_2$	15	16[f]	78	78	+20 (0.5)[g]	*S*

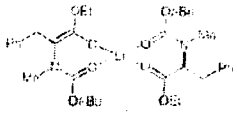
[a] The substrate was treated with 1.1 equiv of KHMDS at −78 °C for 30 min (for 3, 5, 7, 9, and 11) or 60 min (for 13 and 15) followed by 10 equiv of methyl iodide for 16–17 h at −78 °C. See the Supporting Information for the experimental procedure and physical data. [b] The *ee* value of each substrate is >99%. [c] Determined by HPLC using columns with chiral stationary phases: 4: Chiralpack AD, 2% *i*PrOH in hexane; 6, 8: Chiralpack AD, 5% EtOH in hexane; 10, 12: Chiralpack AD 5% *i*PrOH in hexane; 14 (benzoate): Chiralpack AS, 3% *i*PrOH in hexane; 16 (benzoate): Chiralpack AD, 1% *i*PrOH in hexane. [d] Absolute configuration of the corresponding α-methyl-α-amino acid. [e] Not determined. [f] Obtained as an inseparable mixture with the substrate. The yield was determined on the basis of the ratio of signals observed in the 400 MHz ^{1}H NMR spectra. Complete separation was achieved with the corresponding *N*-benzoyl derivative. [g] Optical rotation of the corresponding *N*-benzoyl derivative.

N-Boc : essential to realize MoC
N-MOM : easy to remove (treatment of 6N HCl)

mechanistic insights

#mixed aggregates as intermediate??

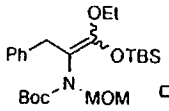
⇨ denied by crossover experiment



~~asymmetric induction~~. This was eliminated by a crossover experiment between 3 and 7: A 1:1 mixture of racemic 3 and (*S*)-7 (≥99% *ee*) was α-methylated according to the procedure in Table 1 and afforded racemic 4 (79% yield) and (*S*)-8 (74% *ee*, 79% yield), respectively.

3 : R = $PhCH_2$-
7 : R = *p*MOMO-C_6H_4-CH_2-

#trapping by TBSOTf



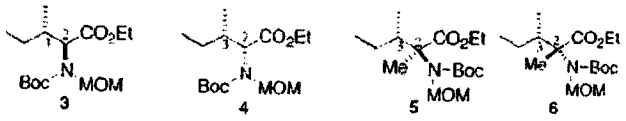
In ^{1}H NMR spectra, MOM group appeared as AB quartets.

⟹ rotational barrier of C-N bond

(Z) / (E) = 2/1 : 16.8 kcal/mol determined by NMR for Z isomer

$t_{1/2}$ ~ 7 d at -78 C

#chirality at C3 position

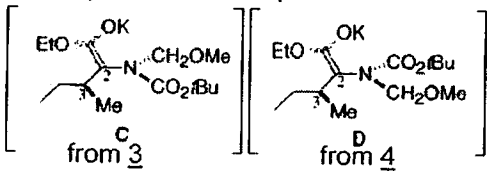


3 4 5 6

⇨ If 3 and 4 gave the same ratio of 5/6, chirality at C2 was not preserved.

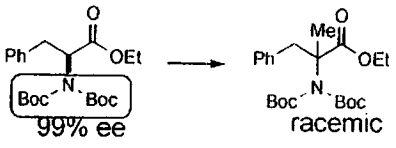
3 : y.93% dr(**5/6** : 93/7)

4 : y.91% dr(**5/6** : 14/86)



C from 3 D from 4

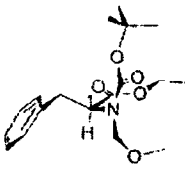
diBoc substrate



99% ee racemic

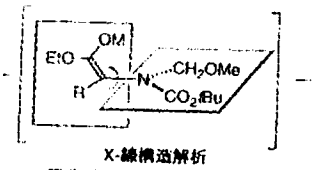
impossible to preserve chirality on N

explanation of kinetic deprotonation



; then attack from less hindered MOM face

X-ray of enolate (unpublished yet)



X-線構造解析

発生時の光学純度 ≥99%ee

$\Delta G^{\ddagger}_{rac}$ = 16.0 kcal / mol, (R=CH_2Ph, M=K)

life time of enolate

at -78 C for 24 h : 84%, 36% ee

at -78 C for 30min + -40 C for 30 min : 88%, 5% ee

⟹ racemization shoud occur

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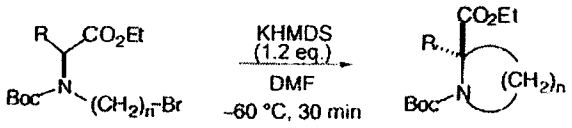
other applications

Asymmetric Cyclization via Memory of Chirality: A Concise Access to Cyclic Amino Acids with a Quaternary Stereocenter

Takeo Kawabata,* Shimpei Kawakami, and Swapan Majumdar

Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan

JACS **2003**, *125*, 13012.

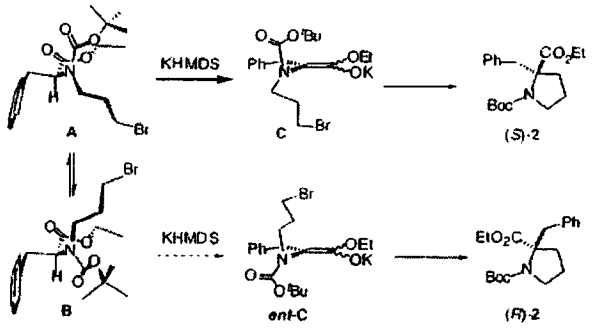


KHMDS (1.2 eq.), DMF, −60 °C, 30 min

entry	substrate	*n*	R	product	yield (%)	ee (%)[b]
1	1[c]	3	$PhCH_2$	2	94	98 (*S*)
2	3	3	4-EtO-C_6H_4-CH_2	4	95	97
3	5	3	$MeSCH_2CH_2$	6	92	97
4	7	3	Me_2CH	8	78	94
5	9	3	CH_3	10	91	95 (*R*)
6	11	2	$PhCH_2$	12	61	95
7	13[c]	4	$PhCH_2$	14	84	97
8	15[c]	5	$PhCH_2$	16	31[e]	83 (*S*)
9[d]	15[c]	5	$PhCH_2$	16	61[f]	72 (*S*)

[a] A solution of substrate (0.25 mmol) in dry DMF (2.4 mL) was treated with 1.2 mol equiv of KHMDS (0.50 M in THF) for 30 min at −60 °C, unless otherwise mentioned. [b] The ee was determined by HPLC analysis. The letter in the parentheses indicates the absolute configuration. See the Supporting Information. [c] >99% ee. [d] The reaction was run for 2 h. [e] 15 (70% ee) was recovered in 52% yield. [f] 15 (54% ee) was recovered in 17% yield.

Stereoselectivity is also explained by the simillar model as intermolecular alkylation.



A : 0.1 kcal/mol stable than B (calculation)

cf) racemization barrier and half-life time

Racemization barrier $\Delta G^{\ddagger}$ (kcal/mol)	Racemization $t_{1/2}$ at −78 °C[a]	Racemization $t_{1/2}$ at 25 °C[a]
12	2.4 s	3.5×10^{-5} s
14	7 min	1.0×10^{-3} s
16	20 h	3.0×10^{-2} s
18	148 d	0.9 s
20	70 years	26 s

[a] Racemization $t_{1/2} = \ln 2/k_{rac}$, where $k_{rac} = 2 \cdot (kT/h) \cdot \exp(-\Delta G^{\ddagger}/RT)$.

Stereochemical Diversity in Asymmetric Cyclization via Memory of Chirality

Tetsuo Kamashata,* Seiji Matsuda, Shunpei Kawakami, Daiki Moriguchi, and Katsuhiko Moriyama

JACS **2006**, *128*, 15394.

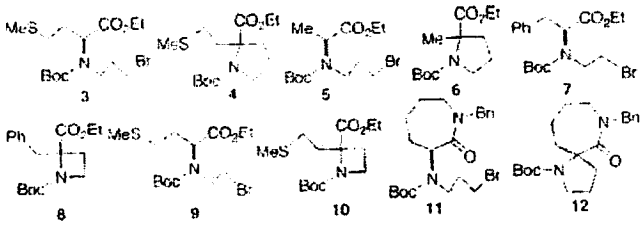
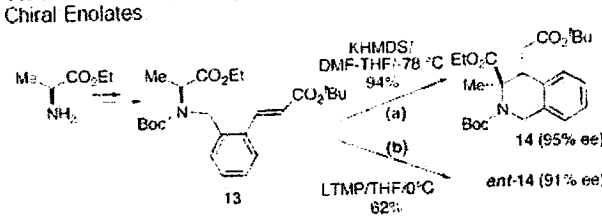


Table 2. Enantiodivergent Asymmetric Cyclization[a]

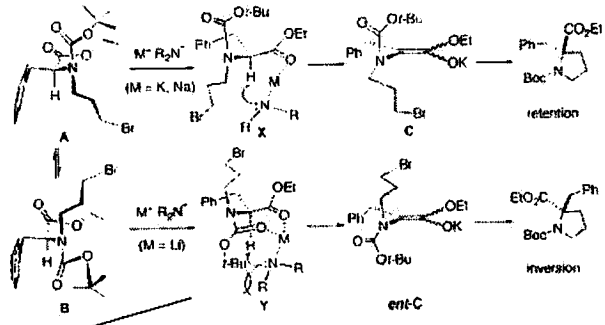
entry	substrate	base, solvent, temp	product	yield (%)	ee (%)[b]
1[c]	1	KHMDS, DMF, −60 °C	2	94	98 (*S*)
2	1	LTMP, THF, 20 °C	2	93	91 (*R*)
3[c]	3	KHMDS, DMF, −60 °C	4	92	97 (*S*)
4	3	LTMP, THF, −20 °C	4	92	81 (*R*)
5[c]	5	KHMDS, DMF, −60 °C	6	91	95 (*R*)
6	5	LTMP, THF, 20 °C	6	91	87 (*S*)
7[c]	7	KHMDS, DMF, −60 °C	8	61	95 (*R*)
8	7	LTMP, THF, −20 °C	8	69	90 (*S*)
9	9	KHMDS, DMF, −60 °C	10	98	97 (*S*)
10	9	LTMP, THF, 0 °C	10	66	83 (*R*)
11	11	NaHMDS, THF, 20 °C	12	72	99 (*R*)[d]
12	11	LHMDS, toluene, 0 °C	12	66	94 (*S*)[d]

remarkable temp. effect : ?????

Scheme 3. Enantiodivergent Intramolecular Conjugate Addition of Chiral Enolates



Scheme 2. A Hypothetical Scheme for Stereochemical Course of Asymmetric Cyclization

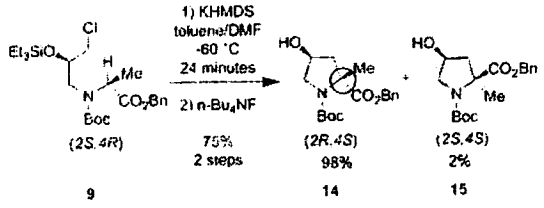


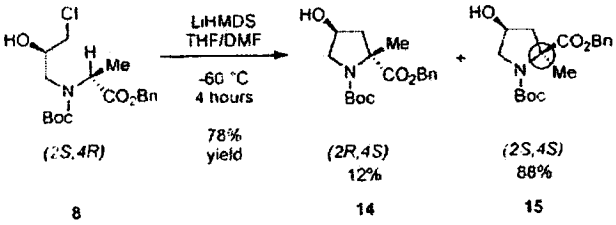
Recently simillar chelation based stereo-inversion was observed.

A Memory of Chirality Approach to the Stereoselective Synthesis of 4-Hydroxy-α-methylprolines

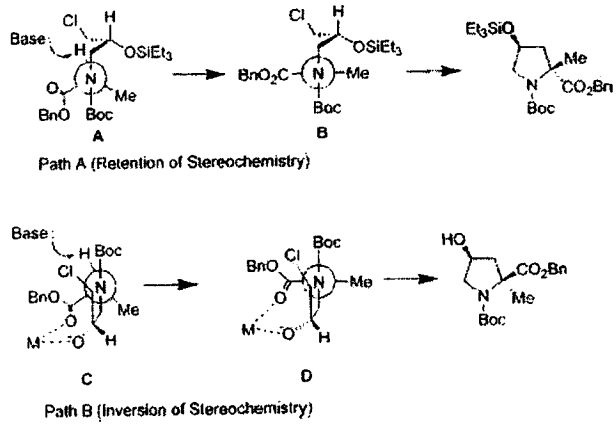
Lawrence Kotaczkowski* and David M. Barnes

OL ASAP (published on web 070712)





Scheme 4. Possible Mechanism for Stereoselective Cyclizations



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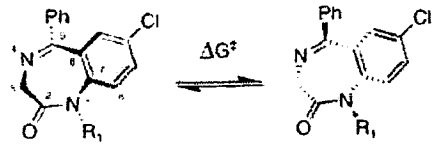
reports from other groups

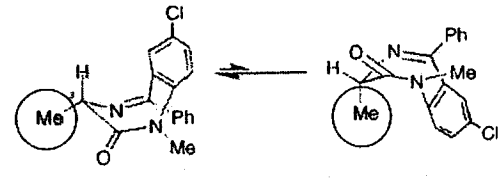
reaction of 1,4-benzodiazepin-2-one

JACS **2003**, *125*, 11482.
JOC **2005**, *70*, 1530.
OL **2005**, *7*, 5305.



		$\Delta G^{\ddagger}$ (kcal/mol)	$t_{1/2}$(rt)
(*M*)-**1a**: R_1 = H	(*P*)-**1a**	12.3 (ref. 4)	60 *us*
(*M*)-**1b**: R_1 = Me	(*P*)-**1b**	18.0	0.9 s
(*M*)-**1c**: R_1 = *i*-Pr	(*P*)-**1c**	21.1	2.8 min
(*M*)-**1d**: R_1 = *t*-Bu	(*P*)-**1d**	>24 (ref. 8)	

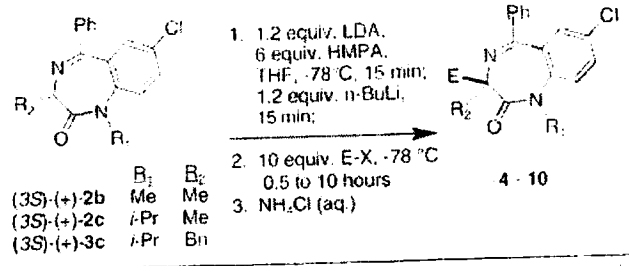
dynamic chirality



pseudoequatorial methyl in (*M*)-conformer of (*3S*)-**2b**

pseudoaxial methyl in (*P*)-conformer of (*3S*)-**2b**

confomational bias => chance to memory of chirality



	R_1	R_2
(3*S*)-(+)-2b	Me	Me
(3*S*)-(+)-2c	*i*-Pr	Me
(3*S*)-(+)-3c	*i*-Pr	Bn

entry	R_1	R_2	E[a]	product	% yield	% ee[b]
1	Me	Me	Bn	(±)-4	72	0[c]
2	*i*-Pr	Me	Bn	(+)-5	74	97 (3*R*)
3	*i*-Pr	Me	4-$MeC_6H_4CH_2$	(+)-6	68	95 (3*R*)
4	*i*-Pr	Me	2-$PhC_6H_4CH_2$	(+)-7	70	99
5	*i*-Pr	Me	allyl	(+)-8	76	94
6	*i*-Pr	Me	D	(+)-9	85[d]	99 (3*S*)
7	*i*-Pr	Bn	Me	(−)-5	64	95 (3*S*)
8	*i*-Pr	Bn	allyl	(+)-10	57	86

[a] Electrophiles used: BnBr, 4-$MeC_6H_4CH_2Br$, 2-$PhC_6H_4CH_2Br$, allyl bromide, D-OTFA, MeI. [b] % ee measured by chiral stationary phase HPLC (Chiralcel OD, AD). [c] Racemic 4 is also obtained if BnBr is added only 10 s after deprotonation by LDA. [d] The extent of deuteration is 96%.

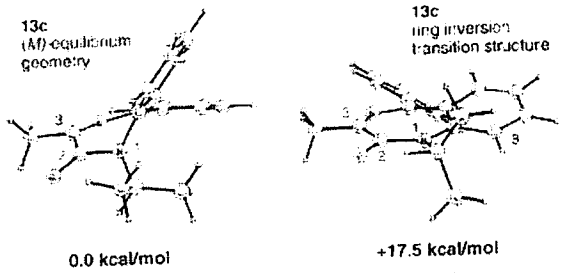


Figure 1. B3LYP/6-31G* equilibrium geometry and ring inversion transition structure of *N*-*i*-Pr enolate anion 13c (relative free energies at B3LYP/6-31+G*//B3LYP/6-31G*)

N-Me : 12.4 kcal/mol : $t_{1/2}$ = 0.11 min @-78 C
N-iPr : 17.5 kcal/mol : $t_{1/2}$ = 970 h @-78 C
good agreement
In N-iPr, 92% ee after 8 h deprotonation (vs entry2)

1-4. memory of chirality : radical chemistry

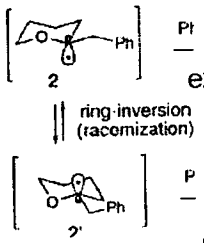
Conformational Memory in Enantioselective Radical Reductions and a New Radical Clock Reaction

Alexandre J. Buckmelter, Angie I. Kim, and Scott D. Rychnovsky*

Contribution from the Department of Chemistry, University of California, Irvine, California 92697-2025

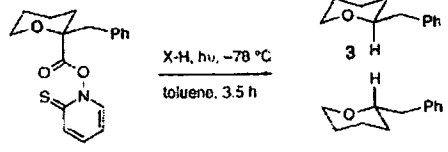
JACS **2000**, *122*, 9386.

concept : use of tetrahydropyranyl radical



expected: 5-10 kcal/mol barrier

decarboxylative rxn

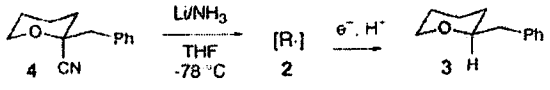


by resolution

donor	[X-H] (M)	% yield	ratio 3:3'	% ee
PhSH	1.0	92	93.2:6.8	86.5
PhSH	0.05	58	61.5:38.5	23.0

sensitive to conc. => easy racemize even under -78 C
at >-78 C => ee greatly drop down

other substrate



Li (6.4 M)/NH_3, −78 °C[d] 90% ee

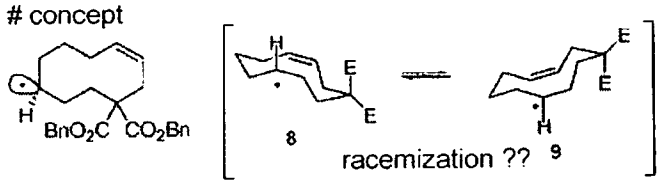
also need high concentration
Li better than Na : why??

Memory of Chirality in the Transannular Cyclization of Cyclodecenyl Radicals

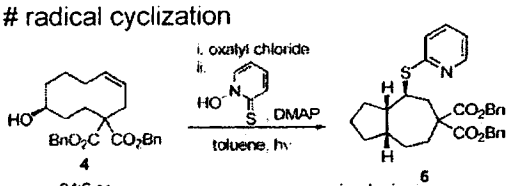
Jackline E. Dalgard and Scott D. Rychnovsky*

OL **2004**, *6*, 2713.

concept



radical cyclization



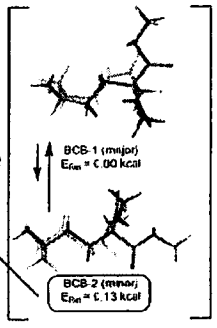
entry[a]	temp (°C)	yield (%)	er[b]
1	23	88	63:37
2	0	67	79:21
3	−15	51	84:16
4	−35	43	84:16

[a] Reaction mixtures were photolyzed with a 500-W tungsten lamp. [b] Enantiomeric ratio determined by chiral HPLC analysis (Diacel OD-H column), 90:10 hexanes/IPA, 0.9 mL/min.

conformational isomer of 4

15.5 kcal/mol by variable-temp. NMR

big difference

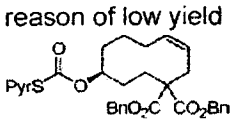


trans-fused adduct (not observed)

by MM2 calculation

cis-fused adduct

reason of low yield



Reaction seems to be obeyed "Curtin-Hammett principle" and it attributes low ee ??

2. Chiral Relay

2-1. background

design of superior ligand

development of efficient chiral Lewis acid catalyst

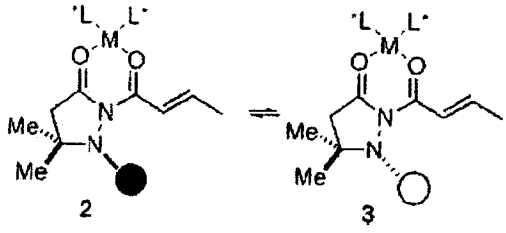
other strategies not to rely on ligand tuning
- autocatalysis / autoinduction
- chiral poisoning
- enantiomer-selective activation (use of racemic ligand)
- chiral environment amplification (use of achiral, meso ligand)
- etc...

$\Longrightarrow$ strategy to forcus on the tuning of metal-ligand complex
How about metal-substrate complex?

A New Approach to Enantiocontrol and Enantioselectivity Amplification: Chiral Relay in Diels–Alder Reactions

Mukund P. Sibi,* Lakshmanan Venkatraman, Mei Liu, and Craig P. Jasperse

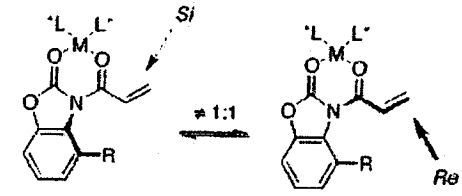
JACS **2001**, *123*, 8444.



Chiral Relay Effect: 4-Substituted 1,3-Benzoxazol-2-(3*H*)-ones as Achiral Templates for Enantioselective Diels–Alder Reactions

Laura Quaranta, Olivier Corminboeuf, and Philippe Renaud*

OL **2002**, *4*, 39.

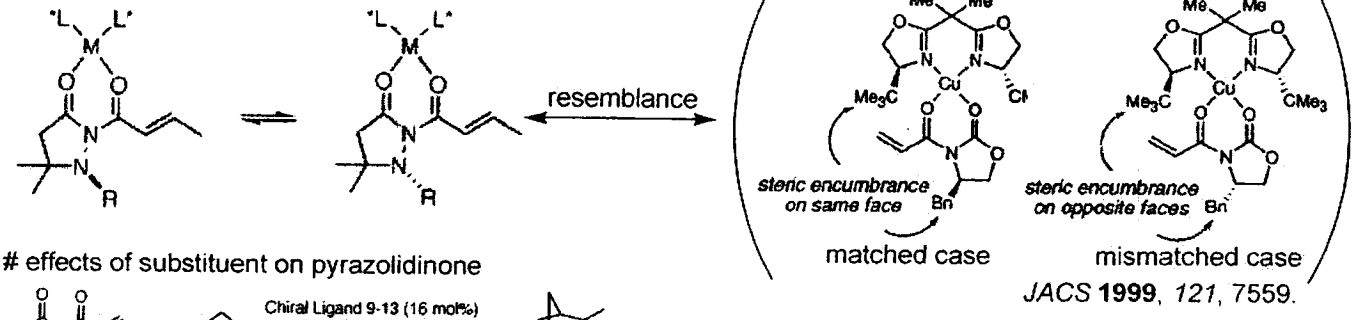


Sibi and Renaud had indipendently reported the simillar concept using fluxional chirality.
In both systems, existence of dynamic chirality show the positive effect on ee.

2-2. Sibi's system : application for Diels-Alder Reaction

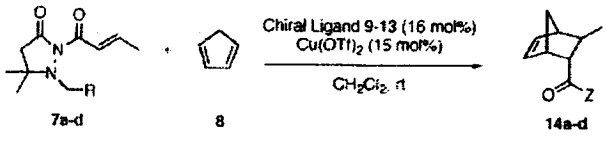
JACS **2001**, *123*, 8444.
JACS **2007**, *129*, 395.

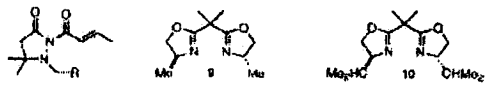
\# two possibilities of complex

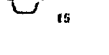


JACS **1999**, *121*, 7559.

\# effects of substituent on pyrazolidinone

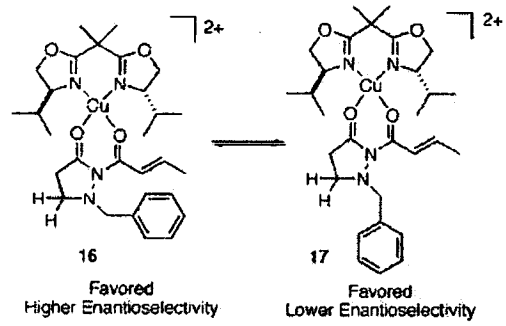




Entry	Substrate	%ee	endo/ exo	%ee	endo/ exo
1	 15	38	88:12	23	87:13
2	7a R = Me	64	91:09	56	96:04
3	7b R = Ph	71	93:07	84	92:08
4	7c R = 2-Naphthyl	79	93:07	65	91:09
5	7d R = 1-Naphthyl	86	90:10	95	93:07

\$ more bulky, better ee
\$ *maybe through* matched-type complex

\# role of C5 substituent effect

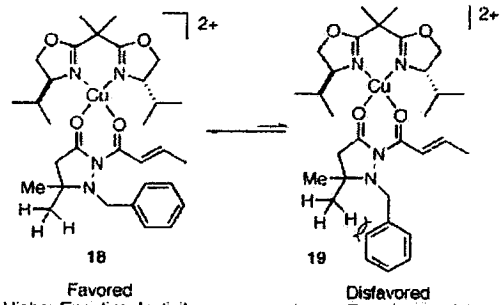


Favored
Higher Enantioselectivity

Favored
Lower Enantioselectivity

H, H : 65% ee
Me, Me : 84% ee

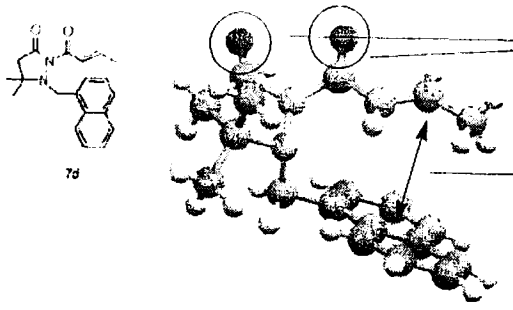
gem-alkyl group
$\Longrightarrow$ beneficial



Favored
Higher Enantioselectivity

Disfavored
Lower Enantioselectivity

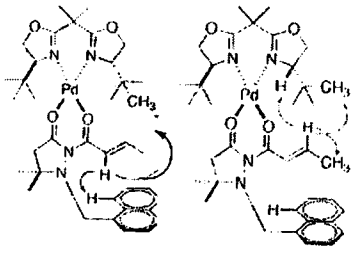
crystal structure of 7d



carbonyl group : *syn* alignment

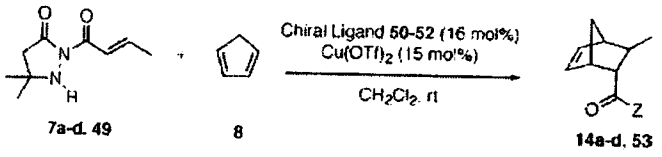
possibility of pi-pi interaction
⇒ no positive effects are observed
by electronic substituent study

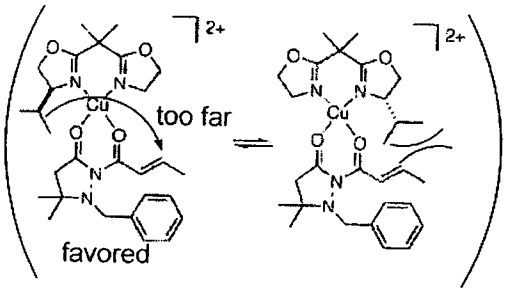
nOe study : $Pd(OTf)_2$ + tBu-BOX + substrate complex

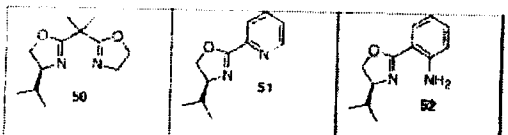


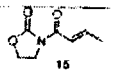
Although correlation is not strong, it suggest the fluxional group locates near the olefin.

reactions using non-C_2 symmetric ligands







Entry	Substrate	ee (%)	endo/exo	ee (%)	endo/exo	ee (%)	endo/exo
1	 15	06	85:15	03	84:16	00	83:17
2	R = H (49)	04	86:14	01	88:12	01	87:13
3	R = Et (7a)	29	85:15	12	86:14	26	84:16
4	R = Bu (7b)	47	88:12	21	87:13	51	84:16
5	R = 2-CH_2Naph (7c)	56	88:12	38	88:12	58	84:16
6	R = 1-CH_2Naph (7d)	69	85:15	59	88:12	71	83:17

conclusion

Sibi et al. showed usefulness of pyrazolidinone template, but still there is only circumstantial evidence.
For example, we can't deny the posibility that this template just works as strong Lewis base and then make ligand and substrate closer due to its bulkyness.

ひとつの妄想
low-temp. NMR : inversion barrier of N
Reaction at such a low temp. should give lower ee due to the impossibility of inversion

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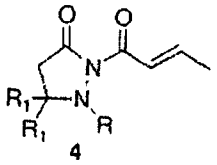
other application

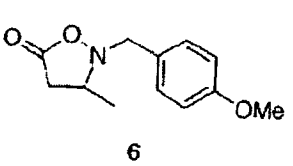
Enantioselective Conjugate Addition of Hydroxylamines to Pyrazolidinone Acrylamides

Mukund P. Sibi* and Mei Liu

OL **2001**, *3*, 4181.

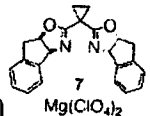

4

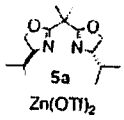
chiral Lewis acid
4-MeOBnNHOH



6

entry	substrate	catalyst A yield[b] (%)	catalyst A ee[c] (%)	catalyst B yield[b] (%)	catalyst B ee (%)[c]
1	4a R_1 = Me, R = H	75	76 (*R*)[11]	74	28 (*S*)
2	4b R_1 = Me, R = ethyl	70	52 (*R*)	74	49 (*S*)
3	4c R_1 = Me, R = benzyl	67	78 (*R*)	71	68 (*S*)
4	4d R_1 = Me, R = 2-CH_2naphthyl	75	78 (*R*)	73	70 (*S*)
5	4e R_1 = Me, R = 1-CH_2naphthyl	77	81 (*R*)	75	75 (*S*)
6	4f R_1 = H, R = $CH(Ph)_2$	71	84 (*R*)	72	57 (*S*)


7
$Mg(ClO_4)_2$
Catalyst A

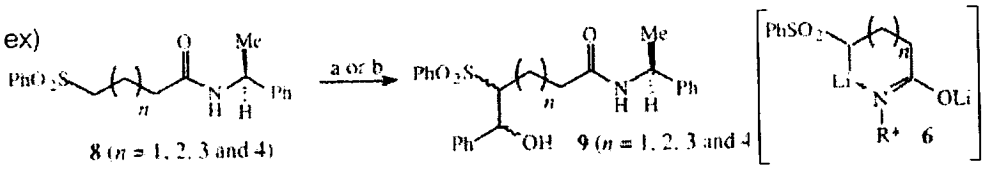

5a
$Zn(OTf)_2$
Catalyst B

3. Remote stereocontrol

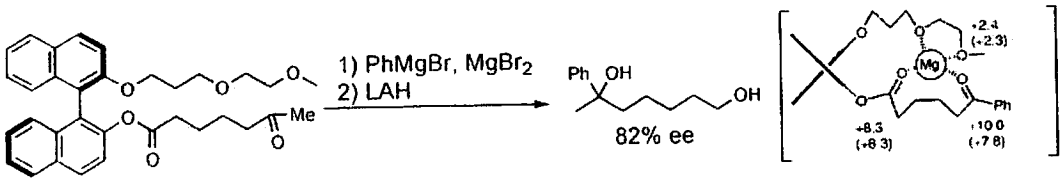
3-1. meaning of "remote"

Usually more than 1,5-stereoinduction is called as "remote stereocontrol" or "remote asymmetric induction."
In many examples, however, actual reaction site is fixed into temporary proximity.

ex)



Nature **1997**, *385*, 799.



JCS Perkin Trans. 1 **2001**, 645.

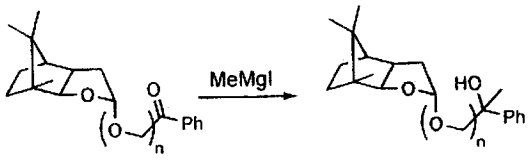
In order to achieve real remote stereoselection, a use of thermodynamically rigid conformation seems better.

3-2. remote stereocontrol based on rigid structure

Paraformaldehyde as Possible Chirality Amplifier**

By *Christian R. Noe.* Max Knollmüller,* and *Peter Ettmayer*

ACIE **1988**, *27*, 1379.



polyoxymethylene : helical conformation
Selectivity gradually decreased in accordance with increasing *n*(1-4).

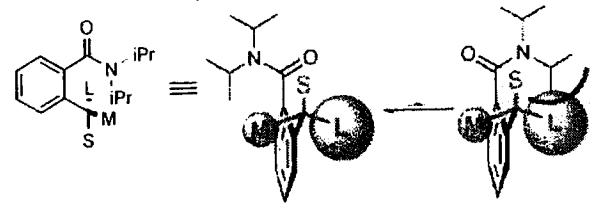
Ultra-remote stereocontrol by conformational communication of information along a carbon chain

Jonathan Clayden, Andrew Lund, Lluis Vallverdú & Madeleine Helliwell

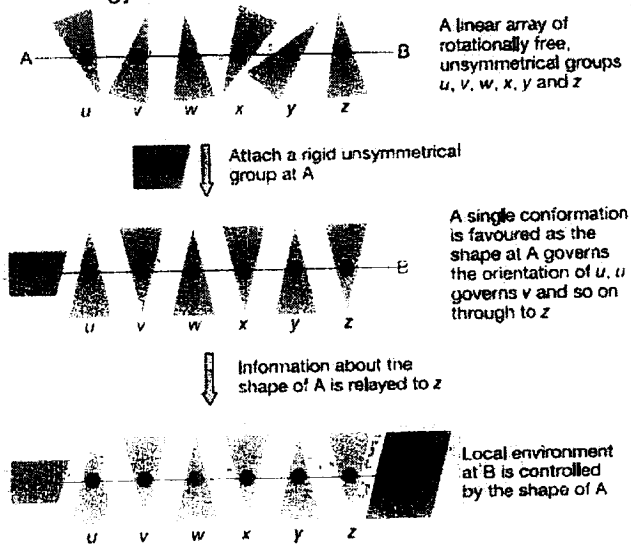
Department of Chemistry, University of Manchester, Oxford Road, Manchester M13 9PL, UK

Nature **2004**, *431*, 966.

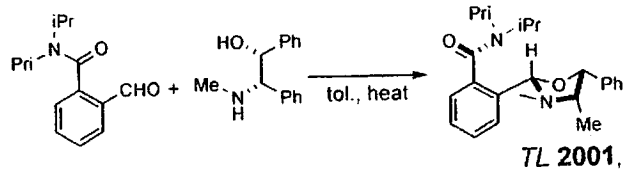
choice of tertiary benzamide as building block



strategy for remote stereocontrol



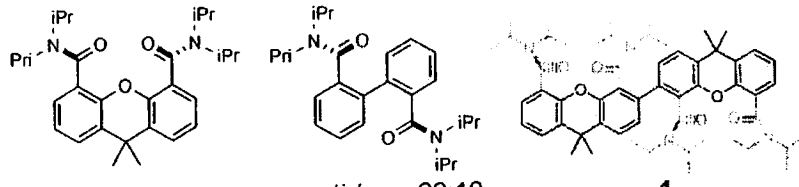
chiral auxiliary induced conformation (A to *u*)



single isomer confirmed by X-ray

TL **2001**, *42*, 3163.

conformational preference of bisamide (*u* to *v*, *v* to *w*, etc.)

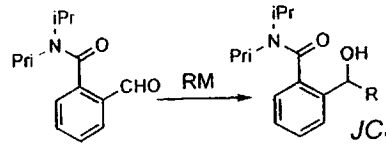


anti / syn >95:5
TL **2000**, *41*, 5171.

anti / syn 90:10
OL **2001**, *3*, 4133.

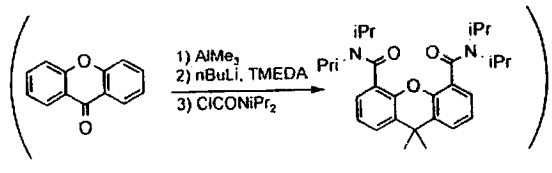
4
anti,anti,anti >95%
combined

atropselective attack of nucleophiles (*z* to B)



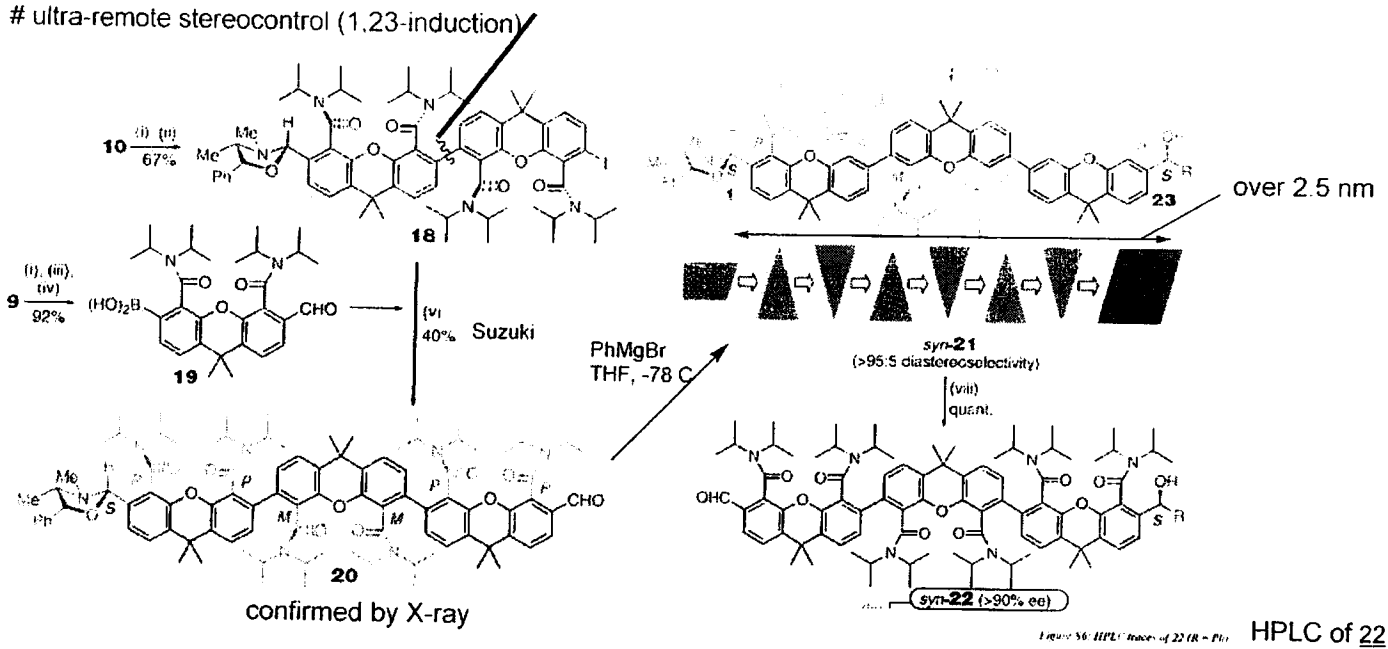
RMgX : syn selective through chelation
RLi, RLi-AlR_3, $RTi(OiPr_3)$: anti selective

JCS Perkin Trans 1 **2000**, 1363.

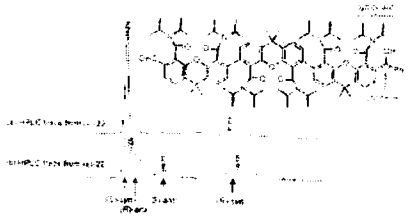


Suzuki coupling
(Buchwald modified)

ultra-remote stereocontrol (1,23-induction)



HPLC of 22



Authors described *" the length over which stereochemical information can be communicated is limited by the efficiency of the synthesis of the substrates, rather than by the reliability of each stage in the information relay. ..... .but we were unable to synthesize a tetraxanthene by any reasonable coupling."*

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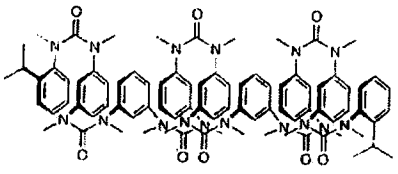
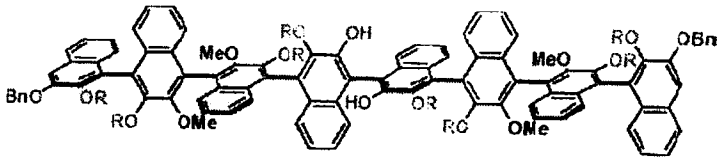
perspective

several out-put variations : other conformational framework

Frameworks which are recently constructed in bottom-up manner.

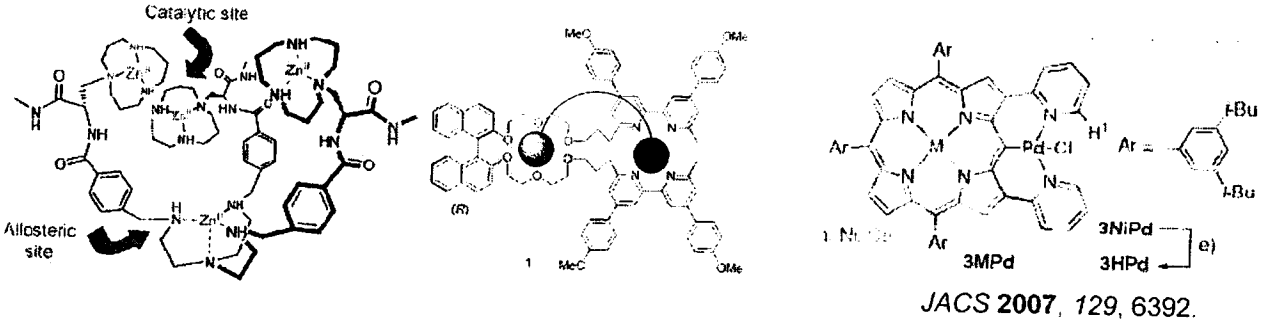


JOC **2007**, *72*, 2302.



JOC **2006**, *71*, 6579.

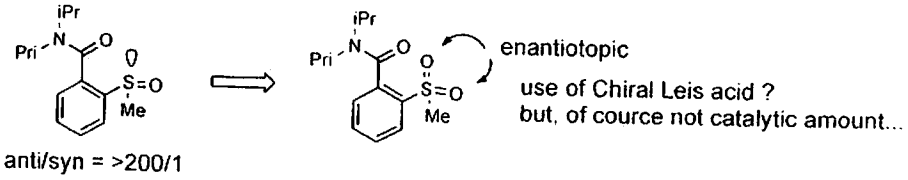
several in-put variations : metal ion induced conformational change



JACS **2007**, *129*, 6392.

much more examples in supramolecular chemistry

妄想



anti/syn = >200/1

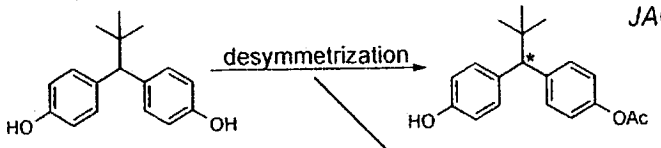
3-3. long range desymmetrization catalyzed by small molecule

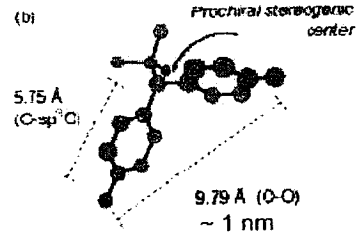
Remote Desymmetrization at Near-Nanometer Group Separation Catalyzed by a Miniaturized Enzyme Mimic

Chad A. Lewis,[†‡] Anna Chiu,[§] Michele Kubryk,[§] Jaume Balsells,[§] David Pollard,[§] Craig K. Esser,[§] Jerry Murry,[§] Robert A. Reamer,[§] Karl B. Hansen,[*,§] and Scott J. Miller[*,†]

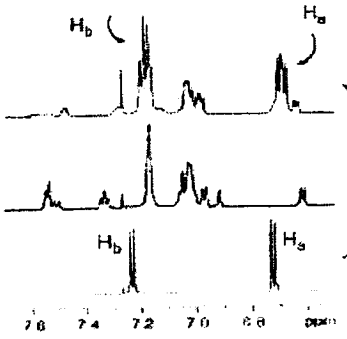
Department of Chemistry, Yale University, New Haven, Connecticut 06520, Department of Chemistry, Boston College, Chestnut Hill, Massachusetts 02467, and Merck Research Laboratories, Rahway, New Jersey 07065

JACS **2006**, *128*, 16454.



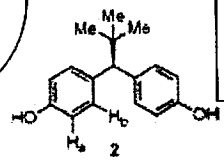


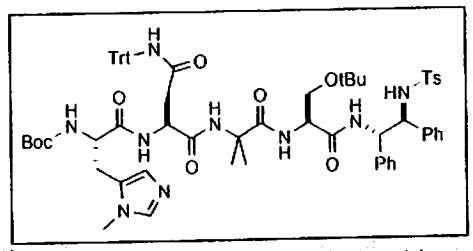
among enzymes, peptide library screening, hexameric peptide was found to be optimal.



2 + Catalyst 14 (H_a and H_b lose degeneracy)

Catalyst 14





Although tetrapeptide is rather big as to cat., smaller tripeptide gave moderate result. (~55% ee)

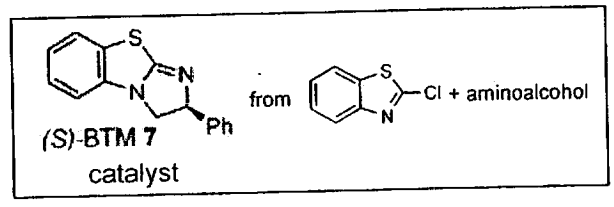
⇓ further optimization

optimized condition
2.1 eq. Ac_2O, 5 mol% peptide
$CHCl_3$, y.93%, 95% ee

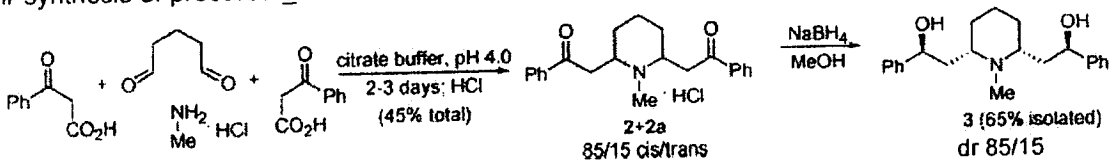
Enantioselective Synthesis of Lobeline via Nonenzymatic Desymmetrization

Vladimir B. Birman,* Hui Jiang, and Ximin Li

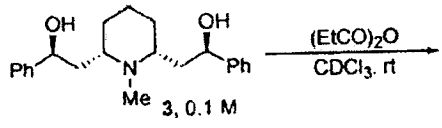
OL ASAP
(published on Web 070720)



synthesis of precursor3



desymmetrization study

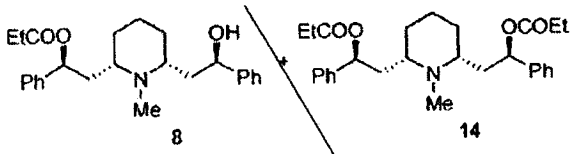


entry	catalyst loading (mol %)	condn[a]	time	% 3[b]	% 8[b] (% ee)	% 14[b]
1		A	60 min	57	42	1
2	10	A	60 min	38	58 (89)	4
3	20	A	60 min	26	71 (>99)	3
4	20	B	60 min	21	76 (>99)	3
5	20	C	2 d	ND[c]	92[d] (>99)	8[d]
6[e]	20	D	2 d	8[d]	88[d] (>99)	≤4
7		A	1 min	99	1	ND[c]
8	20	A	1 min	85	15 (91)	ND[c]

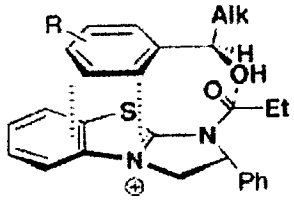
[a] Conditions: (A) 1.0 equiv of $(EtCO)_2O$, 1.0 equiv of *i*-Pr_2NEt, (B) 1.0 equiv of $(EtCO)_2O$, no base added; (C) 1.1 equiv of $(EtCO)_2O$, no base added. (D) 1.0 equiv of $(EtCO)_2O$, 1.0 equiv of *i*-Pr_2NEt. [b] Yields were estimated by ^1H NMR unless stated otherwise. [c] Not detected. [d] Isolated yields are given. [e] (*R*)-BTM was used resulting in the opposite enantiomer of 8a

ee increase!

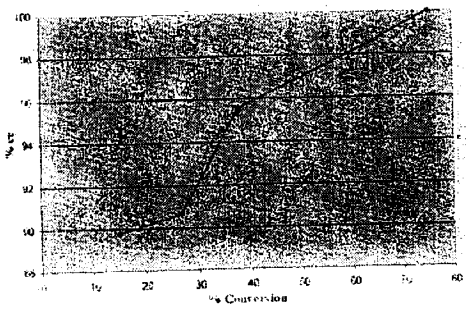
slow background



proposed TS



X-ray structure showed one of the oxygen atoms forms an intramolecular hydrogen bond with N.



Unmatched background product might be converted into diester14 selectivly.

completion