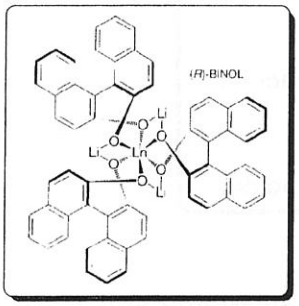
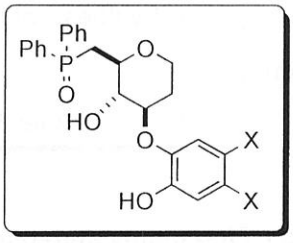
“研究の流れを創ろう”

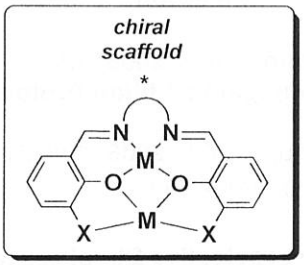
Chen Zhihua (D2)
2009/4/4

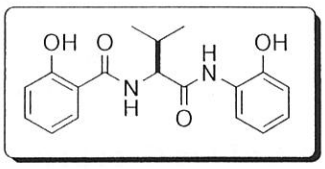
Why this topic?

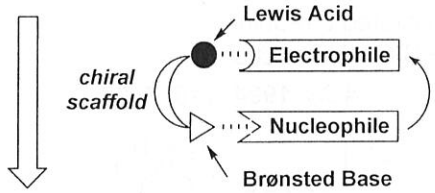
Original concept of our lab: Multi-metal center catalysts











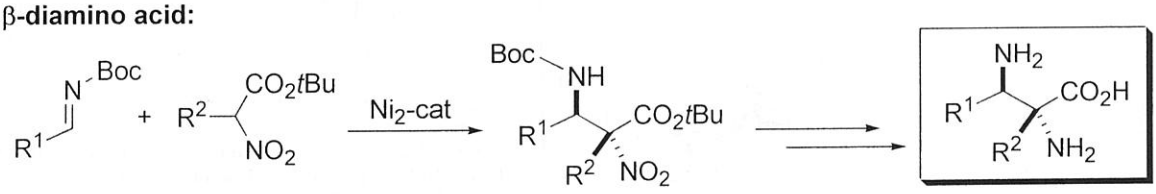
Bifunction

Target:

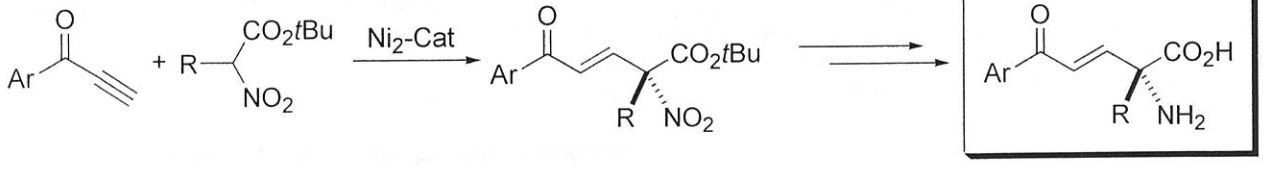
- New catalysts.
- New catalytic asymmetric reaction.
- Useful chiral building block.
- New synthesis methods of bioactive compounds

Why Manzacidin: To apply my research results:

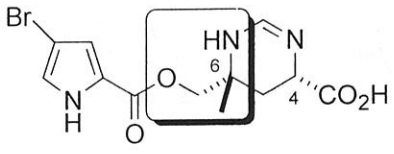
i α,β-diamino acid:



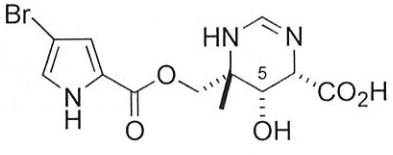
ii α,α-disubtituted amino acid



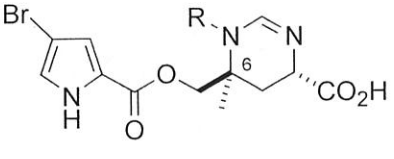
One of Nature compounds contant α,α-disubtituted amino acid: Manzacidin



Manzacidin A



Manzacidin B



Manzacidin C: R = H

Manzacidin D: R = Me

Isolation: Isolated from the Okinawan sponge *Hymeniacidon* sp. (Kobayashi et al. *JOC.* 1991, *56*, 4574.)
Bioactivity: α-adrenoceptor blocks, actomyosin ATPase activators
Structure: C4, 6-tertiary-quarternary carbon center

Typical total synthesis of Manzacidin:

1 Ohfune Group: *JACS*. **2000**, *122*, 10708.
(Diastereoselective Strecker reaction
First highly stereoselective synthesis)

2 **Du Bois Group**: *JACS*. **2002**, *124*, 12950.
(**Oxidative C- H insertion**)

3 **Li Deng Group**: *JACS*. **2006**, *128*, 3928.
(**Tandem conjugate addition-Protonation**)

4 Maruoka Group: *JACS*. **2006**, *128*, 2174.
(1,3 Dipolar cycloaddition)

Before **Manzacidin**
⇩
Synthesis of **Manzacidin**
⇩
After **Manzacidin**

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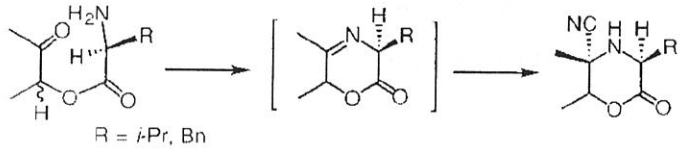
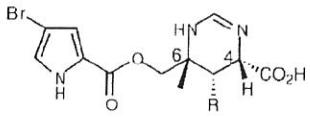
1 Ohfune Group: (Diastereoselective Strecker reaction, First highly stereoselective synthesis)

Concept: Synthesis of α-substituted threonine:
Diastereoselective Strecker reaction

JACS. **1994**, *116*, 7405.



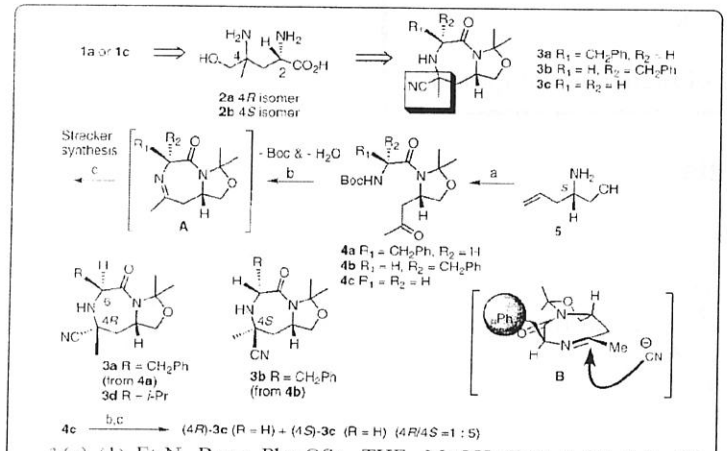
Scheme 1 Diastereoselective Strecker reaction



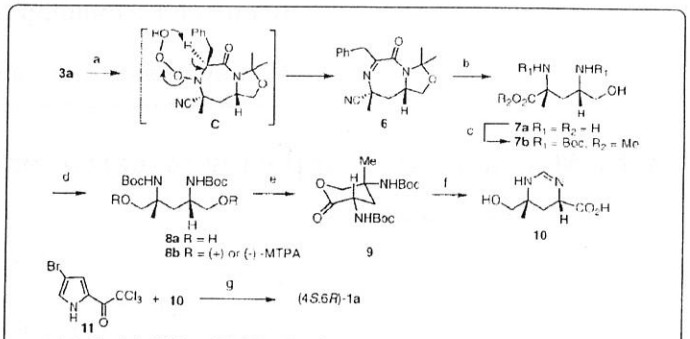
1a Manzacidin A (R = H)
1b B (R = OH)
1c 6*S* isomer of **1a**

JACS. **2000**, *122*, 10708.

Scheme 2 Total synthesis

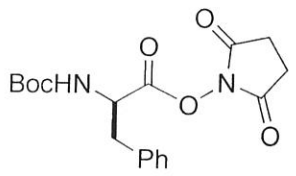


[a] (a) (1) Et_3N, Boc-L-Phe-OSu, THF−MeOH (7:1), 0 °C, 2 h; (2 *p*-TsOH, 2,2-dimethoxypropane, toluene, reflux, 2 h; (3) 0.1 equiv $PdCl_2$ 1 equiv CuCl, O_2, DMF−H_2O (7:1), rt, 12 h (66% from **5**). (b) TMSOTf 2,6-lutidine, CH_2Cl_2, rt, 30 min. (c) TMSCN, $ZnCl_2$, 2-PrOH, rt, 18 h (81% from **3a**, 87% from **3b**, and 48% from **3c**).

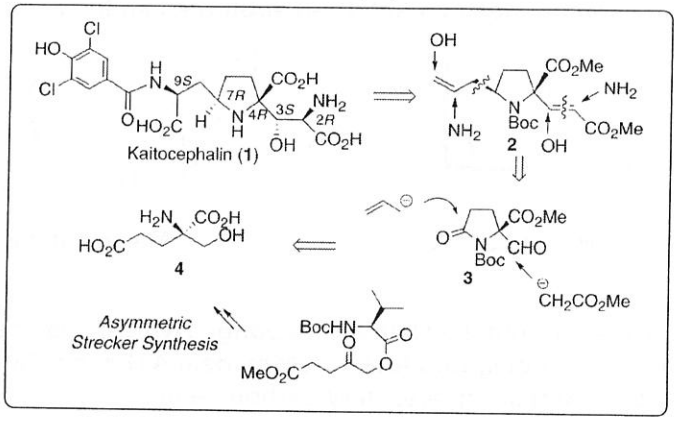


[a] (a) O_3, MeOH, −78 °C, 20 min (94%). (b) concd HCl, 0 °C, 8 h, rt, 15 h, and 100 °C, 18 h. (c) (1) Boc_2O, $NaHCO_3$, dioxane−H_2O (1:1), rt, 12 h; (2) $Me_4NOH{-}5H_2O$, Boc_2O, CH_3CN, rt, 15 h; (3) CH_2N_2, Et_2O (70% from **6**). (d) $LiAlH_4$, Et_2O, 0 °C, 2 h (81%). (e) PDC, CH_2Cl_2, rt, 15 h (55%). (f) TFA, CH_2Cl_2, rt, 30 min, then $CH(OMe)_3$, catalytic amount of concd HCl, reflux, 4 h (91%). (g) 2 equiv NaH, DMF, rt, 4 h (100%).

Boc-L-Phe-OSu:



Scheme 3 Total synthesis of Kaitocephalin
JOC. **2005**, *7*, 4165.



2 Du Bois Group

i Before Manzacidin

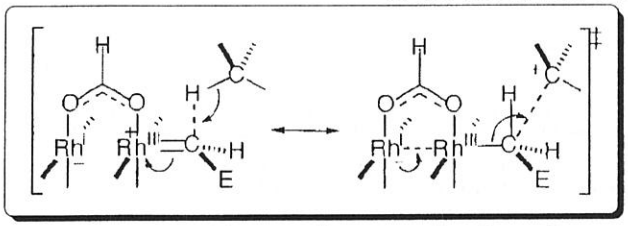
a Background of C- H activation around 2001:

Chem. Rew. **1998**, *98*, 911.

Journal of Organo Metallic Chemistry **2001**, *618*, 47.

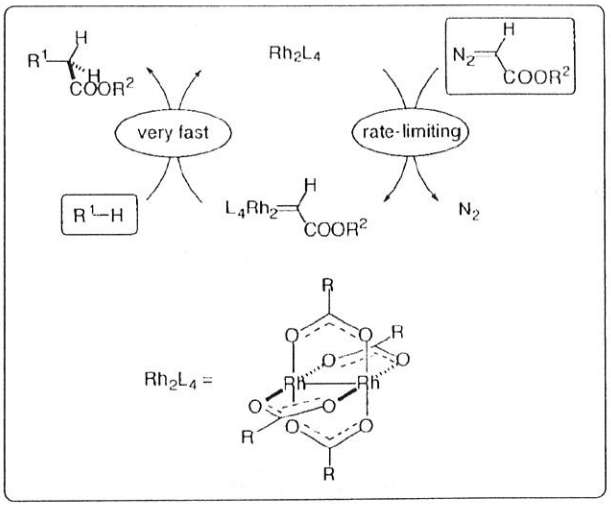
Scheme 5 Carbene C-H insertion mechanism speculated by Nakamura group

JACS **2002**, *124*, 7181.



Also see literature Seminar of Yamaguchi(2006) and Tanaka (2007)

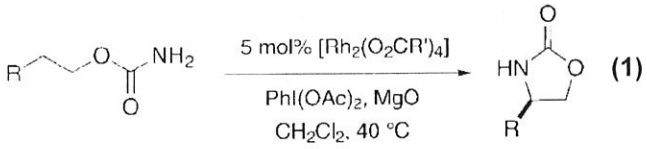
Scheme 4 Rhodium Tetracarboxylate-catalyzed C-H bond activation/C-C bond forming reaction of an α-diazoacetate with an Alkane



b A Rh-Catalyzed C–H Insertion Reaction for the Oxidative Conversion of Carbamates to Oxazolidinones**

Angew **2001**, *40*, 598.

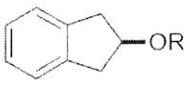
Concept:
New convenient way: in-situ generate L_4Rh_2=NHR



(1)

Benefit:

1 SM is easy to symthesis.



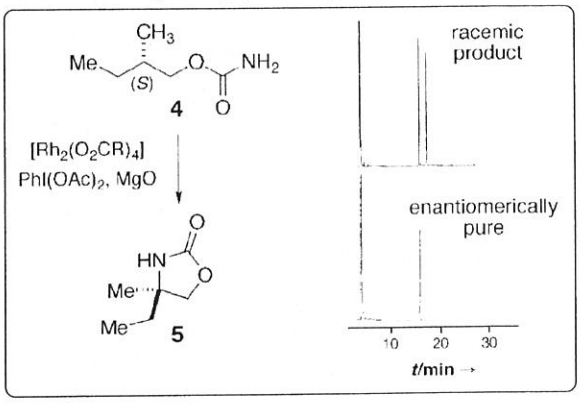
a 1: R = H; 2: R = $CONH_2$

a) $CCl_3C(O)NCO$; K_2CO_3/MeOH;

2 Commercial oxidant: $PhI(OAc)_2$

3 Nitrogen can be introduce to unactived C-H bond.

Scheme 6 Optically pure carbamate



c Synthesis of 1,3-Difunctionalized Amine Derivatives through Selective C–H Bond Oxidation

JACS **2001**, *123*, 6935.

Concept:

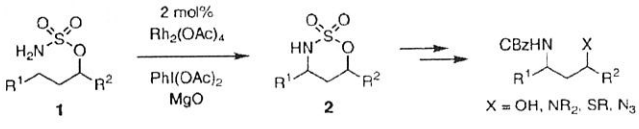
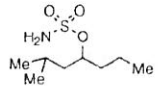
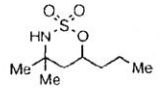
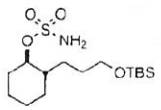
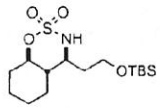
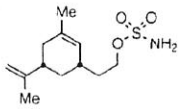
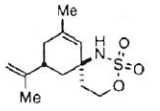
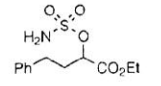
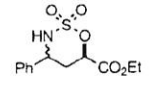
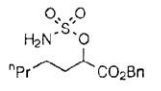
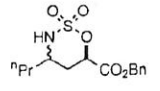
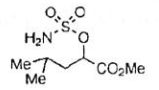
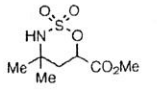
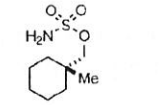
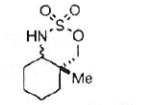
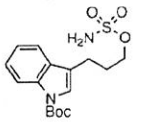
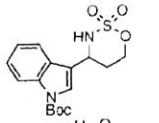
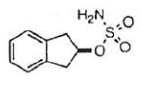
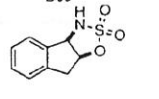


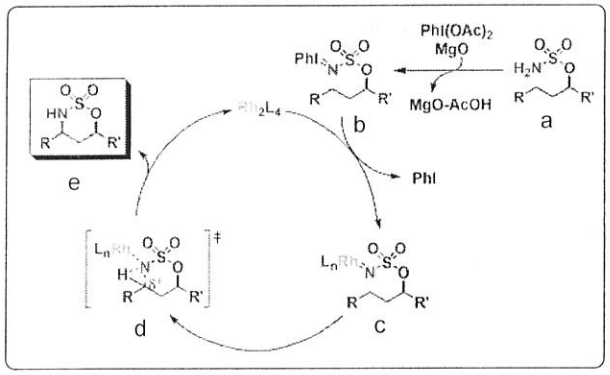
Table 1

Entry	Substrate	Product	Catalyst[a]	Yield[b]
1			A	90[c]
2			B	75[d]
3			A	80[c]
4			B	91[e]
5			B	78[f]
6			A	86
7			A	85[g]
8			A	78[h]
9			A	60[h]

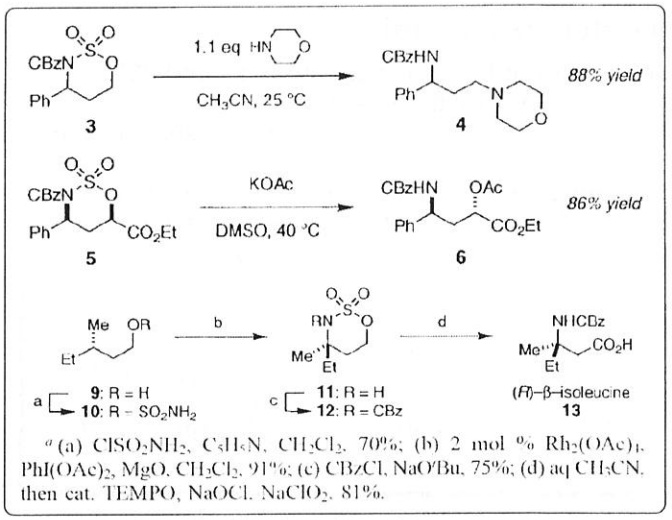
[a] (a) Catalyst: A = $Rh_2(OAc)_4$, B = $Rh_2(oct)_4$. (b) Reactions

(Rhodium octanoate)

Scheme 7 Mechanism



Scheme 8 Conversion reaction



[a] (a) $ClSO_2NH_2$, C_5H_5N, CH_2Cl_2, 70%; (b) 2 mol % $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 91%; (c) CBzCl, NaO^{t}Bu, 75%; (d) aq CH_3CN, then cat. TEMPO, NaOCl, $NaClO_2$, 81%.

ii Synthesis of Manzacidin

Enantioselective Synthesis of the Bromopyrrole Alkaloids Manzacidin A and C by Stereospecific C–H Bond Oxidation

JACS. **2002**, *124*, 12950.

Scheme 9 Retro-synthesis

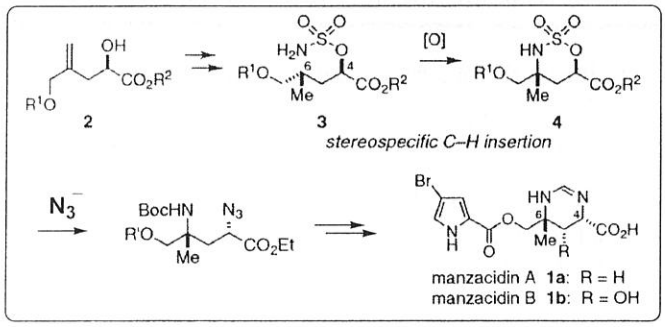
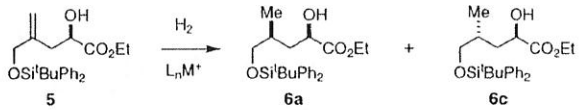
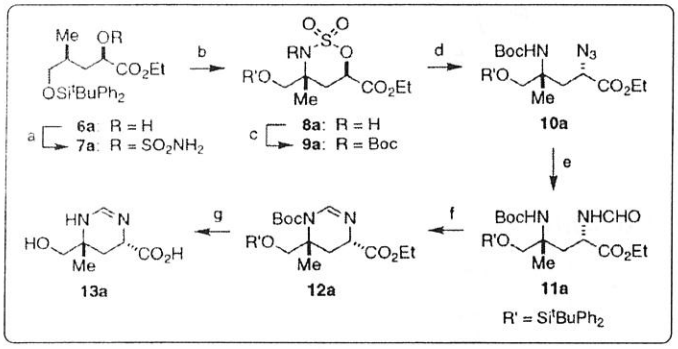


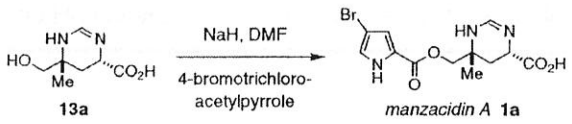
Table 2 Hydrogenation Reactioin



entry	catalyst[a]	ligand	6a/6c[b]
1	5% Pt-C	none	50:50
2	$(Ph_3P)_3RhCl$	none	50:50
3	$Ir[(cod)(pyr)(PCy_3)]PF_6$	none	65:35
4	**$Rh(cod)_2OTf$**	**(*R*)-PHANEPHOS[c]**	**75:25**
5	$Rh(nbd)_2BF_4$	dppb	40:60
6	$Rh(nbd)_2BF_4$	(*R*)-BINAP	20:80
7	**Rh[(*S,S*)-Et-DUPHOS)(cod)]OTf**	none	**>5:95**

Scheme 10 Total synthesis





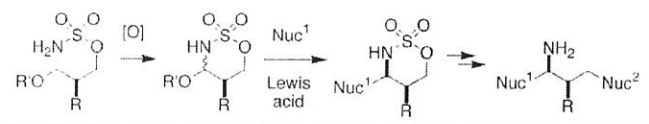
[a] Conditions: (a) $ClSO_2NCO$, HCO_2H, 87% (3:1 mixture of C6 epimers); (b) 2 mol % $Rh_2(OAc)_4$, $PhI(OAc)_2$, MgO, CH_2Cl_2, 85%; (c) Boc_2O, C_5H_5N; (d) NaN_3, DMF, 92%, two steps; (e) H_2, Pd–C, then *N*-formylbenzotriazole; (f) $POCl_3$, 2,6-^{t}Bu$_2$-4-MeC_5H_2N, 73%, two steps; (g) 8 M HCl, DME, 60 °C, $NaHCO_3$, 60 °C, 99%.

iii After Manzacidin

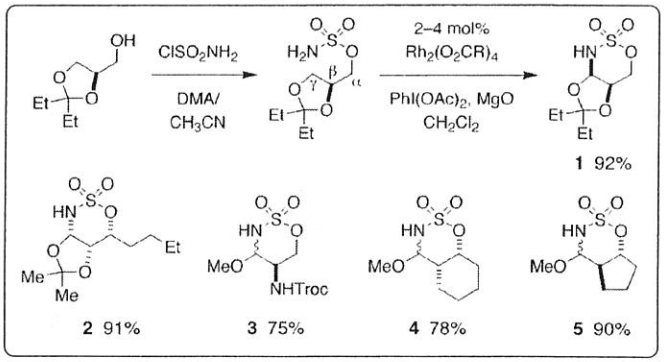
a Novel Iminium Ion Equivalents Prepared through C–H Oxidation for the Stereocontrolled Synthesis of Functionalized Propargylic Amine Derivatives

JACS. **2003**, *125*, 2028

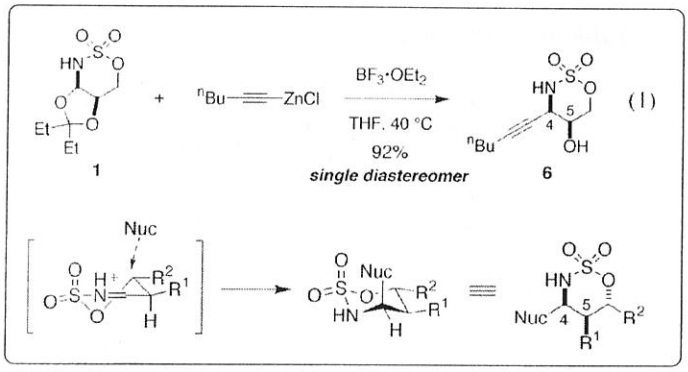
Concept: N,O-acetal oxathiazinanae heteroxycles as reactive iminium ion equivalents



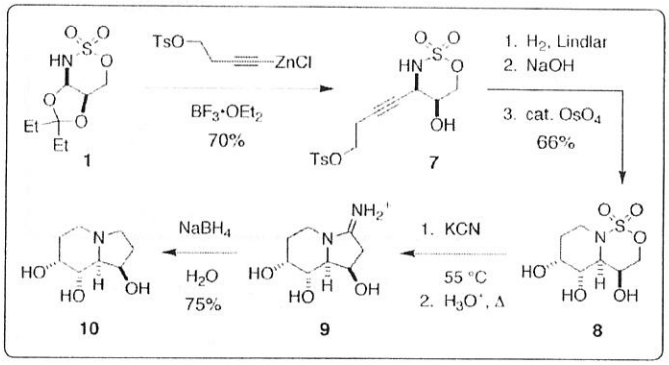
Scheme 11 Rh-catalyzed C - H insertion furnishes *N,O*-acetal substrates



Scheme 12

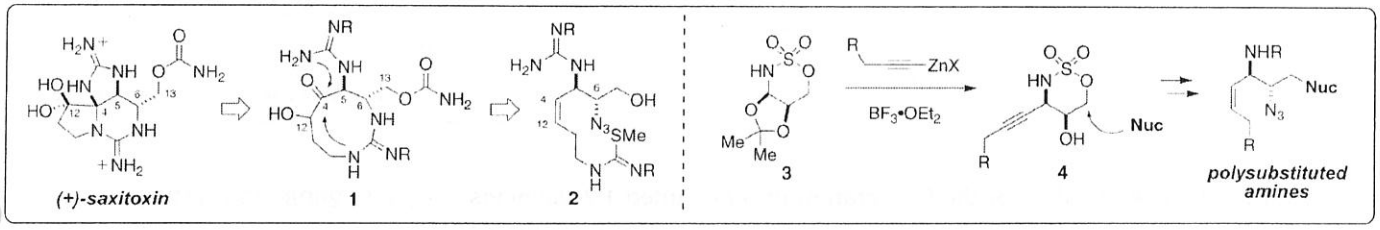


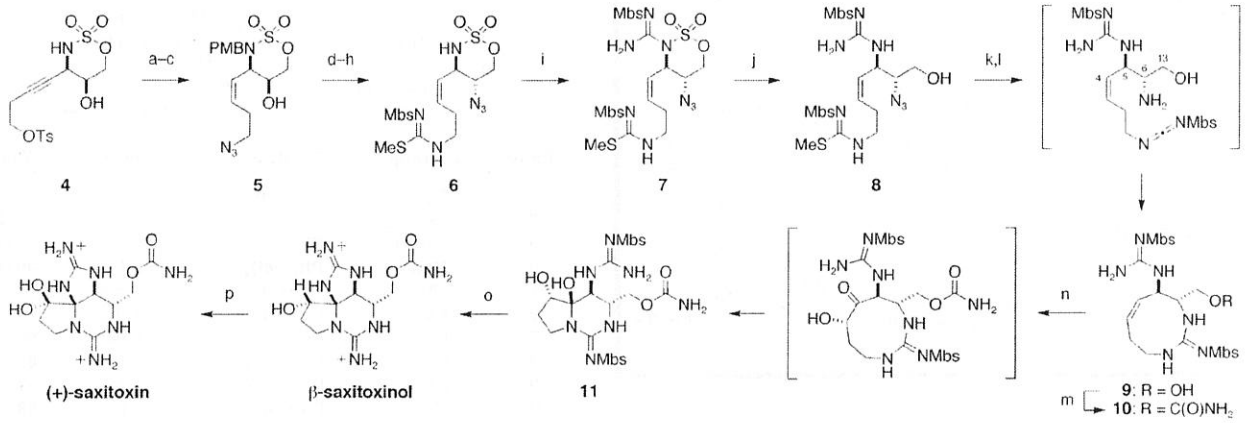
Scheme 13 Application



b A Synthesis of (+)-Saxitoxin *JACS.* **2006**, *128*, 3926.

Scheme 14 Retro-synthesis

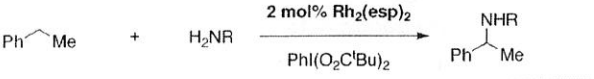


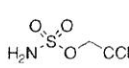
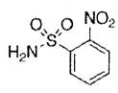
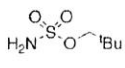
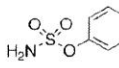
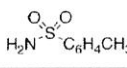


[a] Conditions: (a) H_2, Pd/$CaCO_3$/Pb, THF; (b) NaN_3, $^nBu_4NI$, DMF, 90% (2 steps); (c) *p*-$MeOC_6H_4CH_2Cl$, $^nBu_4NI$, K_2CO_3, CH_3CN, 85%; (d) Me_3P, THF/H_2O; (e) MeS(Cl)C=NMbs, $^iPr_2NEt$, CH_3CN, 72% (2 steps); (f) Tf_2O, C_5H_5N, DMAP, CH_2Cl_2; (g) NaN_3, DMF, −15 °C, 70% (2 steps); (h) $(NH_4)_2Ce(NO_3)_6$, $^tBuOH/CH_2Cl_2$, 74%; (i) KO^{t}Bu, Cl_2C=NMbs; then $(Me_3Si)_2NH$, 70% (+20% of **6**); (j) aq. CH_3CN, 70 °C, 95%; (k) Me_3P, THF/H_2O; (l) $AgNO_3$, Et_3N, CH_3CN, 65% (2 steps); (m) $Cl_3CC(O)NCO$, THF/CH_3CN, −78 °C; then K_2CO_3, MeOH, 82%; (n) 10 mol % of $OsCl_3$, Oxone, Na_2CO_3, $EtOAc/CH_3CN/H_2O$, 57%; (o) $B(O_2CCF_3)_3$, CF_3CO_2H, 82%; (p) DCC, $C_5H_5N{\cdot}HO_2CCF_3$, DMSO, 70%. Mbs = *p*-$MeOC_6H_4SO_2$.

c Catalytic Intermolecular Amination of C−H Bonds *JACS.* **2007**, *129*, 562

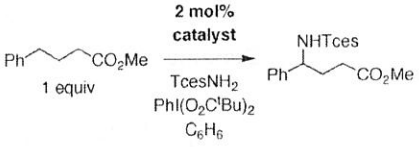
Table 3 Varying the influenece of the nitren precursor



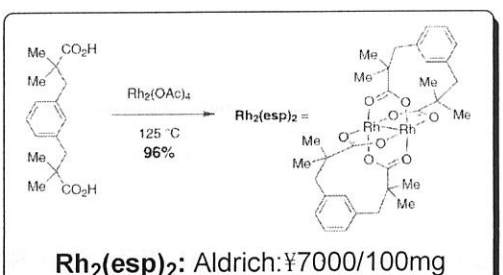
Entry	H_2NR	Yield[a,b]	Entry	H_2NR	Yield[a,b]
1		72	5		29
2		47	6	$H_2NSO_2CH_3$	20
3		20	7	$H_2NSO_2CF_3$	35
4		< 5	8	H_2NCOCF_3	< 5

Temp:rt, Sol:C_6H_6

Table 4 Comparsion of rodium catalyst



catalyst	%conv.[a]
$Rh_2(O_2C^tBu)_4$	< 5
$Rh_2(O_2CCPh_3)_4$	10
$Rh_2(NHCOCF_3)_4$	35
Rh_2(*S*-TCPTAD)$_4$	15
Rh_2(*S*-biTISP)$_2$	0
$Rh_2(esp)_2$	**75 (70)**[b]



$Rh_2(esp)_2$: Aldrich:¥7000/100mg

d A Chiral Rhodium Carboxamidate Catalyst for Enantioselective C–H Amination

JACS. **2008**, *130*, 9220

Concept

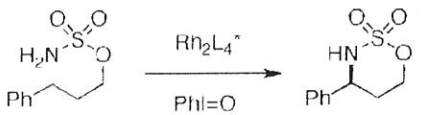
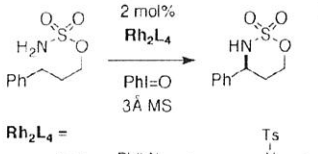


Table 5 Chiral rhodium carboxamidate catalyst



Rh_2L_4	$E_{ox}^{(II/II\rightarrow II/III)}$	% yield	% ee
1	11 mV	< 5	–
2	120 mV	22	54
3	242 mV	< 5	nd
4	**330 mV**	**85**	**92**
5	**742mv**	**<10**	nd

Rh_2L_4 =

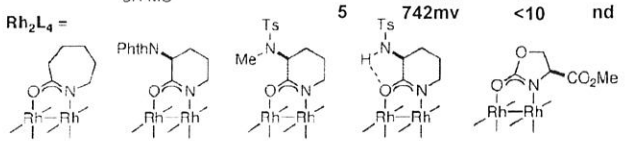
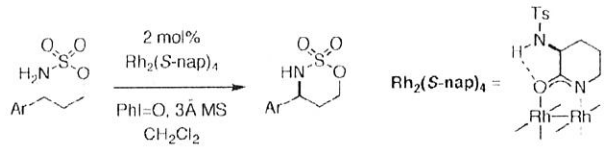
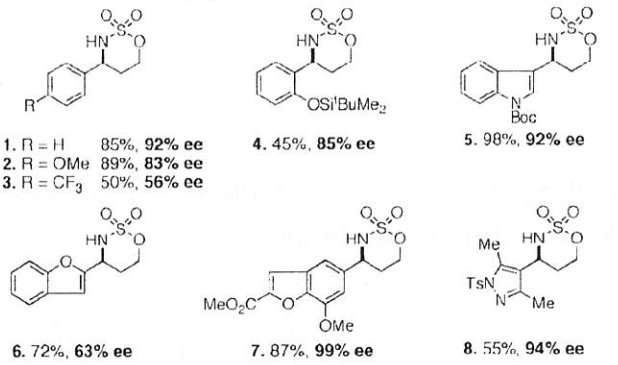


Table 6 Substrant scope





e Catalytic C–H Amination for the Preparation of Substituted 1,2-Diamines

JACS. **2008**, *130*, 11248

Concept

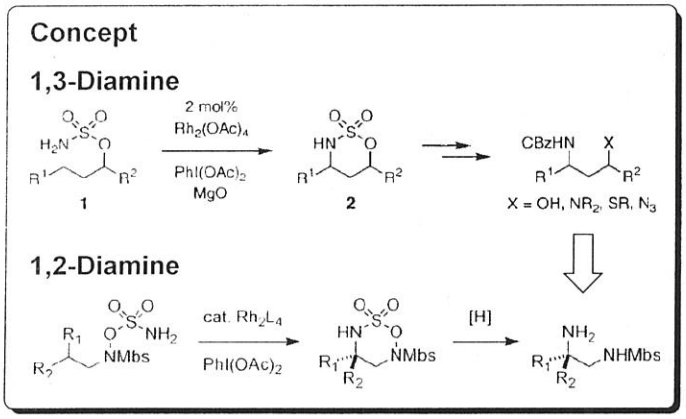
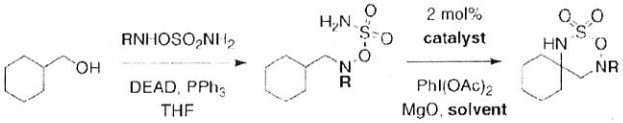


Table 7 Modification

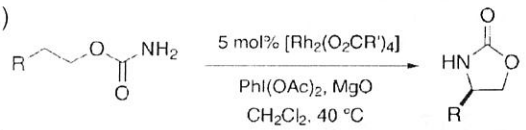


Entry[a]	R Group	Catalyst	Solvent	Yield[b]
1	Boc	$Rh_2(oct)_4$	C_6H_6	– (29)
2	CHO	$Rh_2(oct)_4$	C_6H_6	– (23)
3	$MeSO_2$	$Rh_2(oct)_4$	C_6H_6	– (100)
4	**Mbs**	**$Rh_2(oct)_4$**	C_6H_6	**99 (100)**
5	Mbs	$Rh_2(oct)_4$	toluene	**77**
6	Mbs	$Rh_2(oct)_4$	CH_2Cl_2	**74**
7	Mbs	$Rh_2(oct)_4$	EtOAc	**90**
8	Mbs	$Rh_2(OAc)_4$	C_6H_6	**87**
9	Mbs	$Rh_2(O_2CCPh_3)_4$	C_6H_6	**43**
10	Mbs	$Rh_2(esp)_2$	C_6H_6	**98**

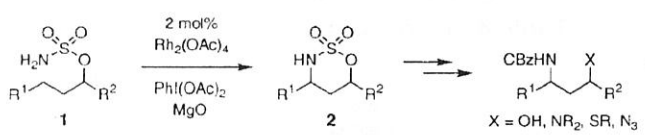
[a] Reactions were performed with 2 mol % of catalyst, 2.3 equiv of MgO, and 1.1 equiv of $PhI(OAc)_2$. [b] Isolated yields; values in parentheses denote percent conversions based on integration of the unpurified ^1H NMR spectrum.

Summary of "Rh_2L_4, $PhI(OR)_2$, MgO" system

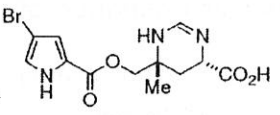
1)



2)

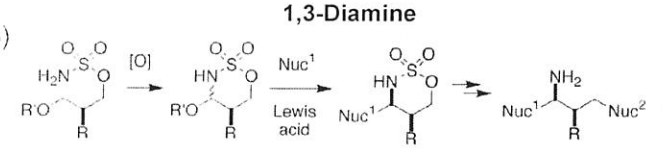


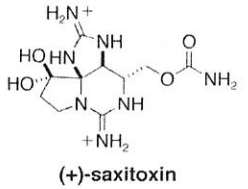
1,3-Diamine



manzacidin A **1a**

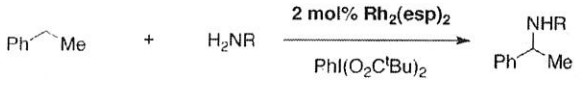
3)



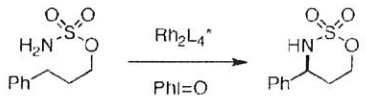


(+)-saxitoxin

4)



5)



One catalytic system, but different SM to get different useful building block!

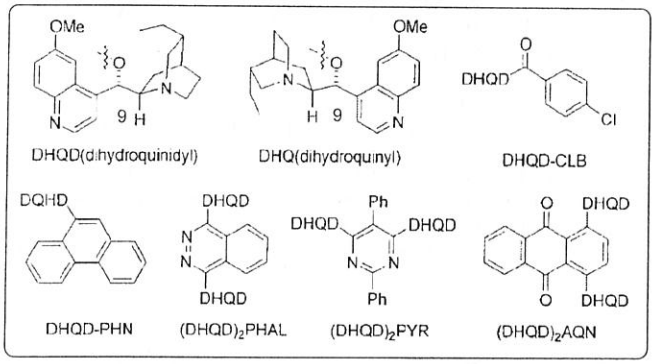
3 Li Deng group:

i Before Manzacidin

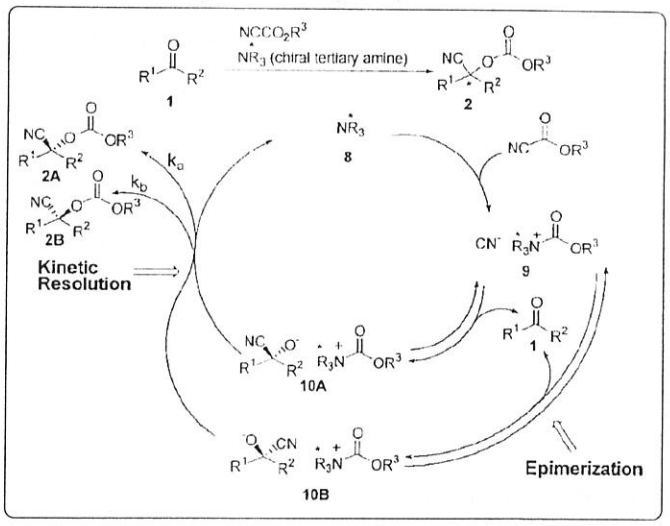
a A Highly Enantioselective Chiral Lewis Base-Catalyzed Asymmetric Cyanation of Ketones

JACS **2001**, *123*, 6195.

Fig 1 Structures of modified cinchona alkaloids

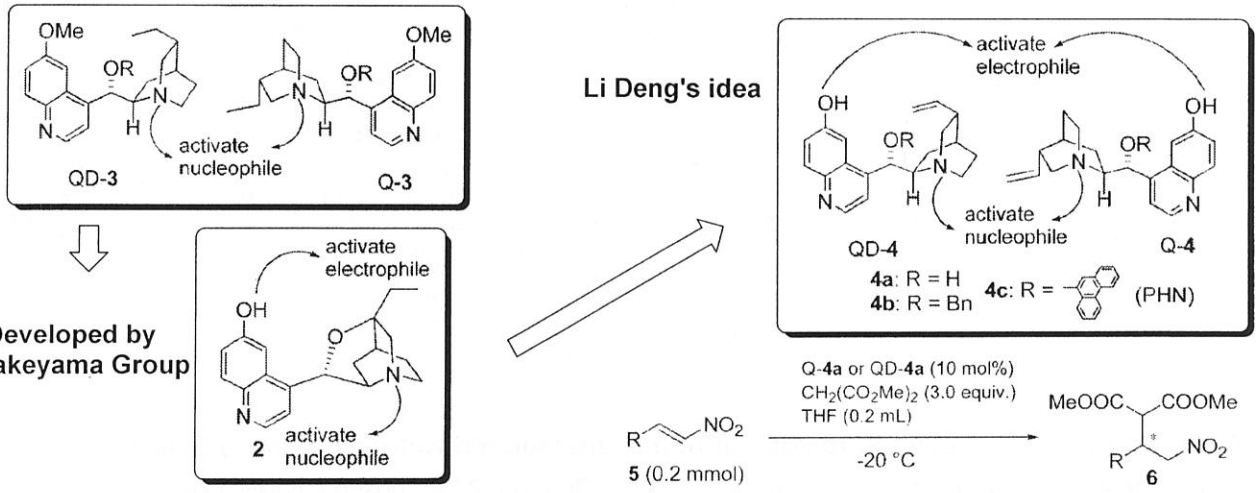


Scheme 15 Proposed catalytic cycle



b Highly Enantioselective Conjugate Addition of Malonate and β-Ketoester to Nitroalkenes: Asymmetric C–C Bond Formation with New Bifunctional Organic Catalysts Based on Cinchona Alkaloids

JACS **2004**, *126*, 9906.

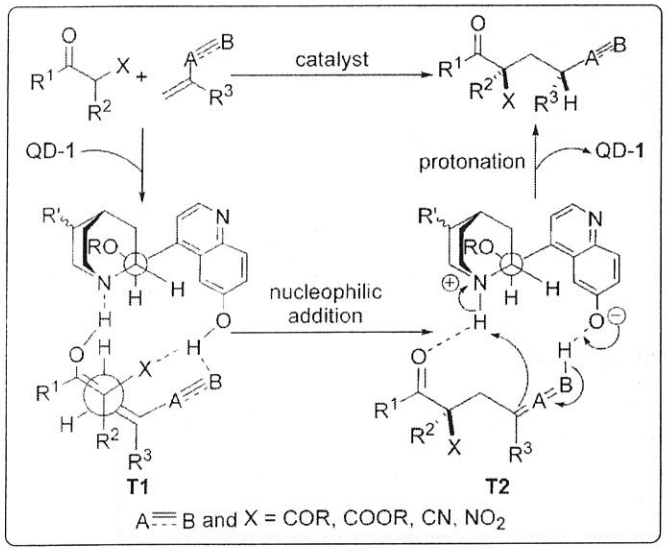


ii Synthesis of Manzacidin

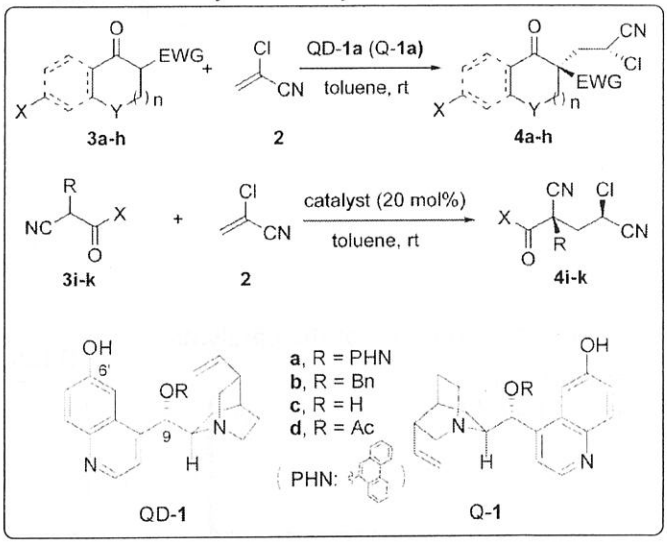
Dual-Function Cinchona Alkaloid Catalysis: Catalytic Asymmetric Tandem Conjugate Addition–Protonation for the Direct Creation of Nonadjacent Stereocenters

JACS **2006**, *128*, 3928.

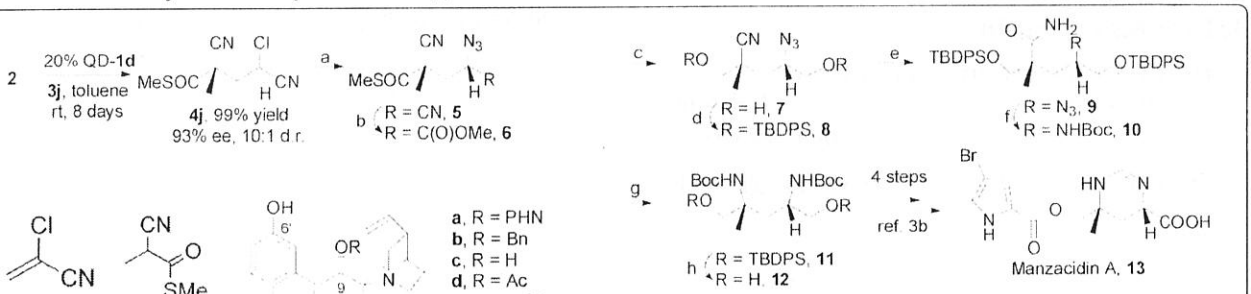
Scheme 16 Proposed model for Tandem conjugate addition-Protonation



Scheme 17 Cycli and acyclic Michael Donors



Scheme 18 Asymmetric synthesis of (-)-Manzacidin A



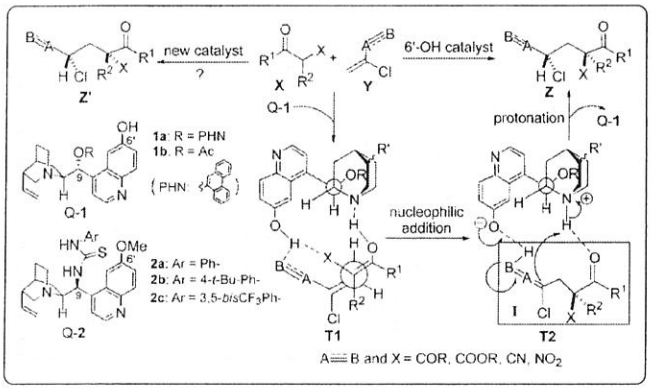
[a] Reagents and conditions: (a) NaN_3, DMSO, rt, 56%, 10:1 dr. (b) TMSCl, MeOH, 0 °C, 95%, 10:1 dr. (c) $NaBH_4$, $Hg(OAc)_2$, EtOH, 0 °C, 83%, 9:1 dr. (d) TBDPSCl, imidazole, DMF, rt, 91%, 10:1 dr. (e) $[PtH(PMe_2OH)(PMe_2O)_2H]$, EtOH, H_2O, 80 °C, 97%, 93% ee, 10:1 dr. (f) Pd/C, Boc_2O, EtOH, H_2, rt, 68%, 91% ee, nd, dr. (g) $Pb(OAc)_4$, ^{t}BuOH, reflux, 83%, 11:1 dr. (h) TBAF, THF, rt, 70%, 92% ee, single diastereomer. TBDPS = *tert*-butylchlorodiphenylsilane.

iii After Manzacidin

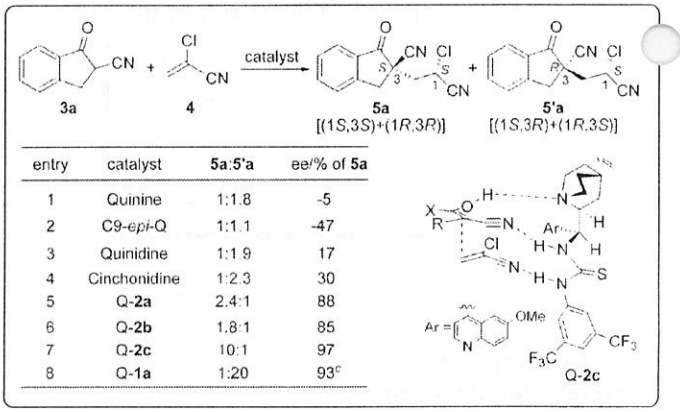
a Control of Diastereoselectivity in Tandem Asymmetric Reactions Generating Nonadjacent Stereocenters with Bifunctional Catalysis by Cinchona Alkaloids

JACS **2007**, *129*, 768.

Scheme 19 Proposed model



Scheme 20 Reaction using **Q-2**

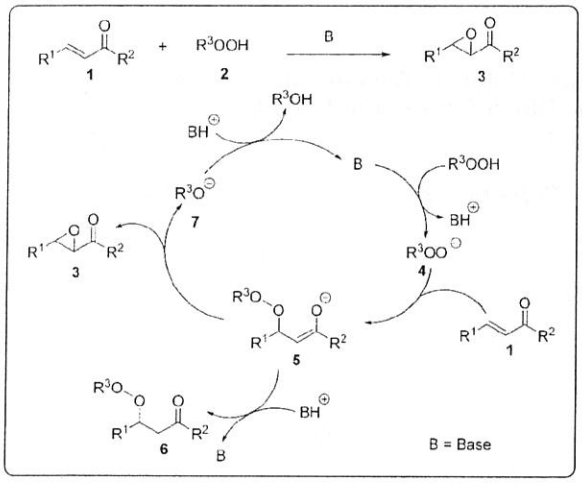


entry	catalyst	5a:5'a	ee/% of 5a
1	Quinine	1:1.8	-5
2	C9-*epi*-Q	1:1.1	-47
3	Quinidine	1:1.9	17
4	Cinchonidine	1:2.3	30
5	Q-**2a**	2.4:1	88
6	Q-**2b**	1.8:1	85
7	Q-**2c**	10:1	97
8	Q-**1a**	1:20	93[c]

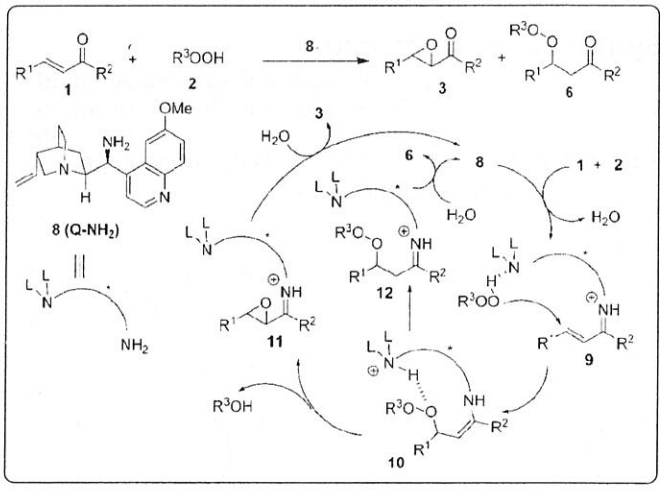
b Catalytic Enantioselective Peroxidation of α,β-Unsaturated Ketones

JACS **2008**, *130*, 8134.

Scheme 21 Mechanism of epoxidation

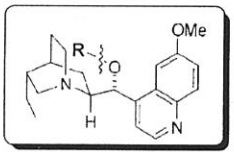


Scheme 22 Proposed catalytic cycle

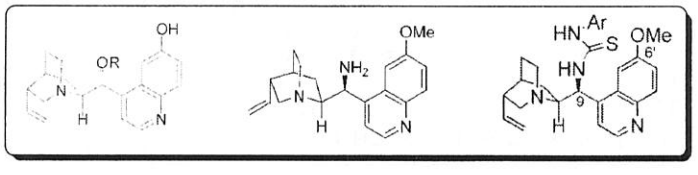


Summary: Development of the catalysts

Chiral Lewis Base Catalysts:



Bifunctional Catalysts



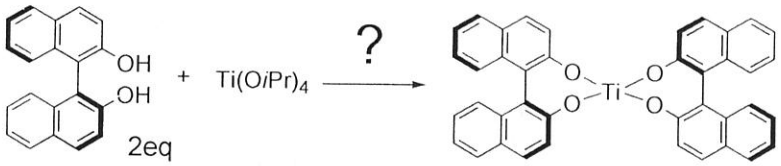
4 Maruoka group

i Before Manzacidin

a **Bis(((*S*)-binaphthoxy)(isopropoxy)titanium) Oxide as a μ-Oxo-Type Chiral Lewis Acid: Application to Catalytic Asymmetric Allylation of Aldehydes** *JACS* **2003**, *125*, 1708.

Background: Keck et al.

JACS **1993**, *115*, 8467.



Maruoka group: Ti-O-Ti

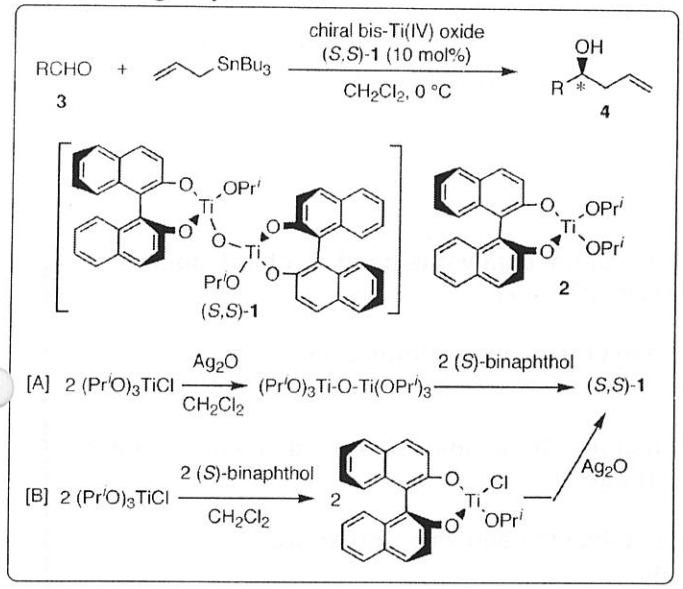
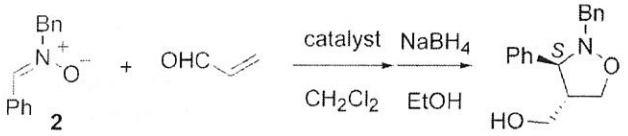


Table 8

entry	aldehyde	Ti catalyst (mol %)	time (h)	% yield[b]	% ee[c] (config)[d]
1	$PhCH_2CH_2CHO$	**1** (10)	4	84	99 (*R*)
2		**1** (10)[e]	16	82	98 (*R*)
3		**1** (5)	12 [7][f]	77 [95]	98 [98] (*R*)
4	$CH_3(CH_2)_6CHO$	**1** (10)	12	85	99 (*R*)[g]
5		**2** (20)	12	14	81 (*R*)[g]
6		**1** (5)	24 [12][f]	86 [92]	99 [98] (*R*)[g]
7	$(CH_3)_2CHCHO$	**1** (10)	28 [18][f]	71 [91]	>99 [99] (*S*)[h]
8		**2** (20)	28	7	85 (*S*)[h]
9	PhCH=CHCHO	**1** (10)	15	70	95 (*S*)
10	PhCHO	**1** (10)	7	90	96 (*S*)
11		**1** (10)[e]	24	81	96 (*S*)
12		**1** (5)	[9][f]	[94]	[97] (*S*)
13	*p*-bromobenzaldehyde	**1** (10)	15	85	98 (*S*)
14	furfural	**1** (10)	18	96	97 (*S*)

b **Asymmetric 1,3-Dipolar Cycloaddition Reaction of Nitrones and Acrolein with a Bis-Titanium Catalyst as Chiral Lewis Acid** *JACS* **2005**, *127*, 11927.

Table 9 Ti catalyst for 1,3 dipolar cycloaddition



entry	catalyst	(mol %)	conditions (°C, h)	yield (%)[b,c]	ee (%)[d] [config][e]
1	(*S,S*)-**1**	10	0, 2	78	89 [*S*]
2	$Ti(O\textit{i}\text{-}Pr)_4$ (*S*)-BINOL	20	0, 2	40	60 [*S*]
3	$ClTi(O\textit{i}\text{-}Pr)_3$ (*S*)-BINOL	20	0, 2	36	60 [*S*]
4	(*S,S*)-**1**	10	−20, 17	90	91 [*S*]
5	(*S,S*)-**1**	10	−40, 24	94	93 [*S*]

ii Synthesis of Manzacidin A: The most efficient route. *JACS* **2006**, *128*, 2174.

Enantioselective 1,3-Dipolar Cycloaddition Reaction between Diazoacetates and α-Substituted Acroleins: Total Synthesis of Manzacidin A

Scheme 23 Retro-synthesis

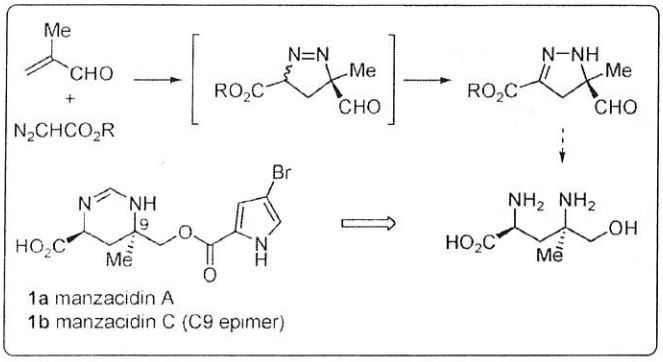
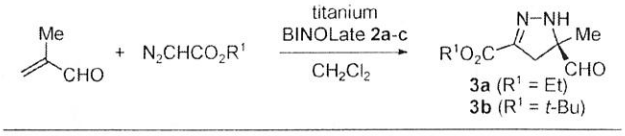


Table 10 Titanium BINOLates



entry	R^1	catalyst (mol %)	conditions (°C, h)	yield (%)[b]	ee (%)[c]
1	Et	–	rt, 40	16	
2	Et	**2a** (10)	0, 1	–	
3	Et	**2a** (10)	−40, 4	42	88
4	Et	**2b** (10)	−40, 2	54	90
5	Et	**2c** (5)	−40, 3	52	95
6	*t*-Bu	**2b** (10)	−40, 1	52	91
7	*t*-Bu	**2c** (5)	−40, 1	43	94

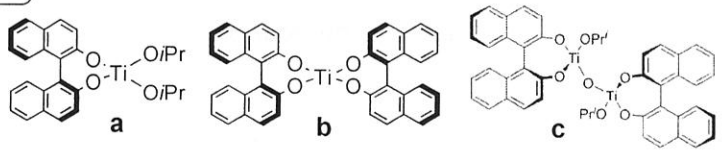
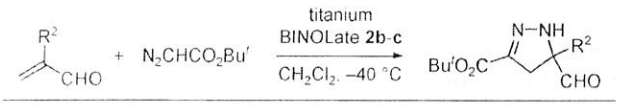
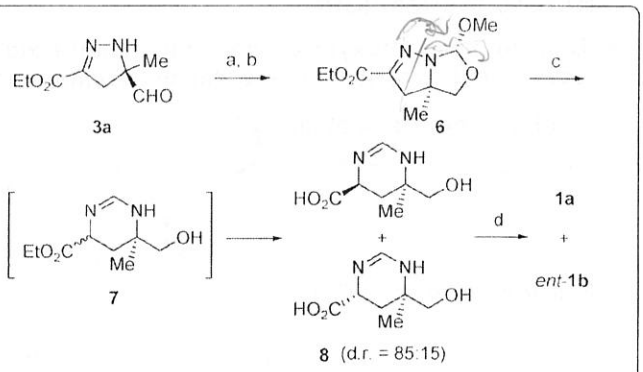


Table 11 Substrant scope



entry	R^2	catalyst (mol %)	time (h)	yield (%)[e]	ee (%)[c]
1	Me	**2b** (10)	1	52	91[d]
2	Me	**2c** (5)	1	43	94[d]
3	Et	**2b** (10)	3	63	83
4	Et	**2c** (5)	3	48	84
5	$BnOCH_2CH_2$	**2b** (10)	1	81	80
6	$PhCH_2CH_2$	**2b** (10)	4	63	82
7	*i*-Pr	**2b** (10)	3	82	92
8	Cy	**2b** (10)	5	77	94
9	Cy	**2c** (5)	5	75	94

Scheme 24 Total synthesis



[e] Conditions: (a) $NaBH_4$, EtOAc, 73%; (b) PPTS, $HC(OMe)_3$, 89%; (c) Raney-Ni, H_2, $^iPrOH/H_2O$; (d) 4-bromo-2-trichloroacetylpyrrole, NaH, DMF, 50% (two steps).

Summary of total synthesis of Manzacidin A

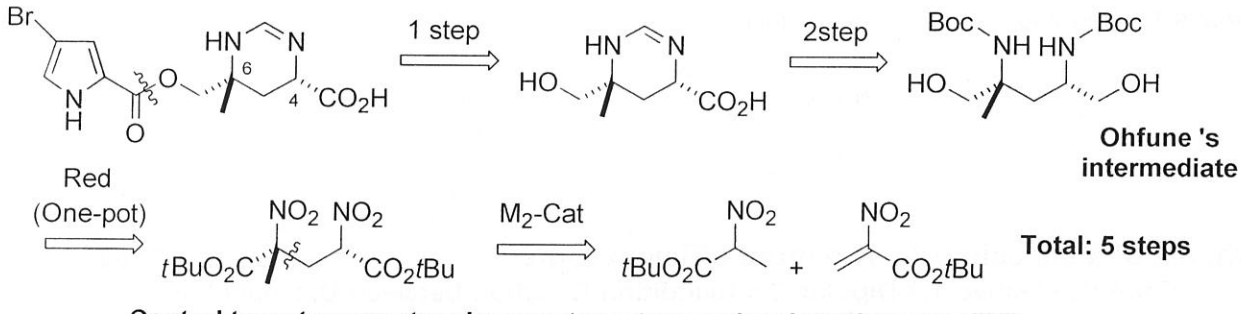
1 Ohfune Group: Diastereoselective Strecker reaction, Chiral catalyst is used as chiral source, First highly stereoselective synthesis. (Page 2)

2 Du Bois Group: Oxidative C- H insertion, Chiral catalyst is used as chiral source, New synthesis method. (Page 4)

3 Li Deng Group: Tandem conjugate addition-Protonation, Chiral catalyst is used as chiral source, Stereoselective efficient method. (Page 8)

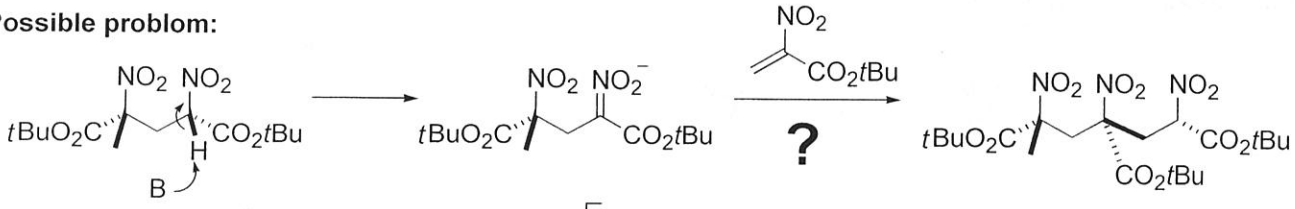
4 Maruoka Group: 1,3 Dipolar cycloaddition, Chiral catalyst is used as chiral source, The most efficient route. (Page 10)

My synthesis plan:

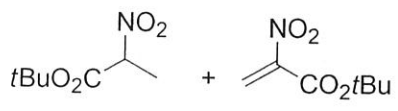


Control two stereocenters in one step, at same time introduce two "N".

Possible problom:



Solution a



Solution b: Other Electrophiles