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学 位 論 文

Asymmetric Synthesis Using Novel Cationic Diether-Coordinated Lewis Acids and Stereoselective Synthesis of Piperidones and 1,2-Amino Alcohols

平成9年1月

石丸　香緒里

Novel Cationic Diether-Coordinated Lewis Acids, and Stereoselective Synthesis of Chiral Piperidones and 1,2-Amino Alcohols by the Reaction of α-Silyloxyimines

Thesis submitted to Hiroshima University
for the Degree of Doctor of Science

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Asymmetric Synthesis Using Novel Cationic Diether-Coordinated Lewis Acids and Stereoselective Synthesis of Piperidones and 1,2-Amino Alcohols

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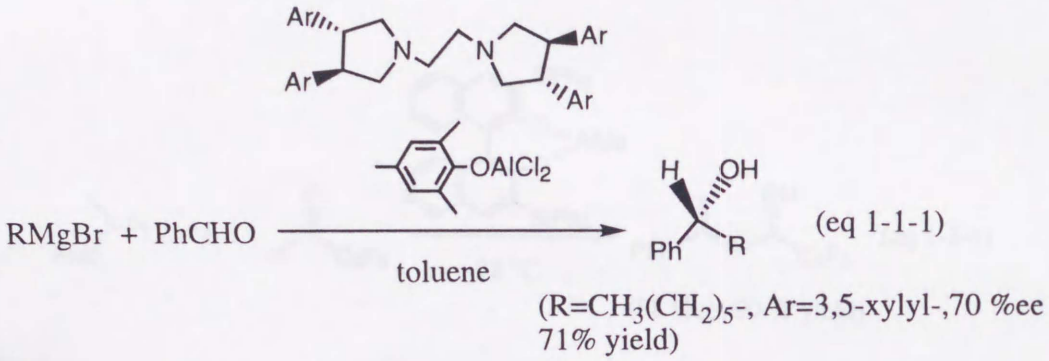
Chapter 1.

Asymmetric Synthesis Using Novel Cationic Diether-Coordinated Lewis Acids

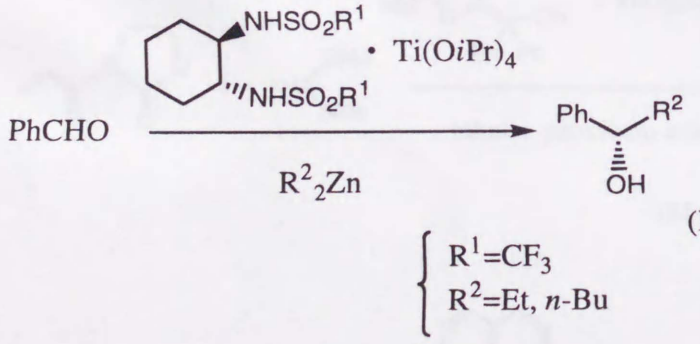
1-1. Introduction

Various Lewis acids with chiral ligands have been utilized for many asymmetric inductions.[1-2] For example, metal halides and alkoxides bearing chiral diamines (eq 1-1),[3] amino alcohols (eq 1-2),[4] and diols (eq 1-3)[5] have been found to be useful as catalysts. In these cases, the Lewis acidity of the complexes are not so strong but stereochemically stable chiral centers at carbon atoms in the ligands control the stereoselectivity of the reactions.



(eq 1-1-1)

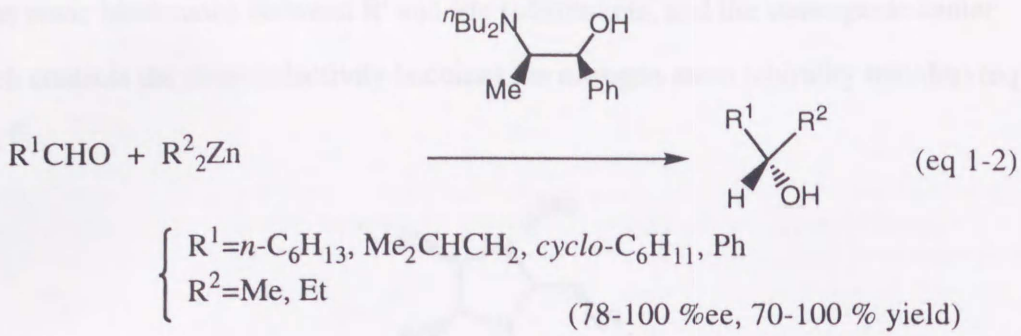
(R=$CH_3(CH_2)_5$-, Ar=3,5-xylyl-,70 %ee
71% yield)



(eq 1-1-2)

(R^2=Et, 98 %ee, 99 % yield)

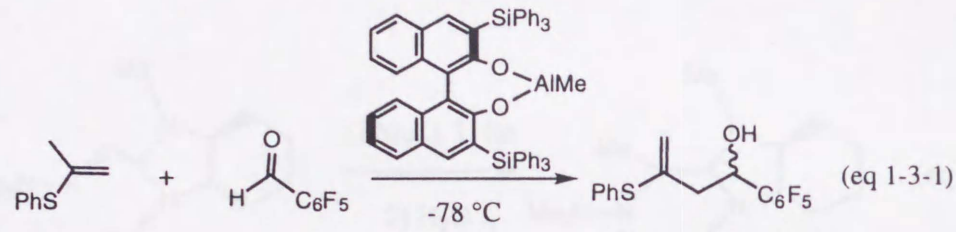
R^1=CF_3
R^2=Et, *n*-Bu



(eq 1-2)

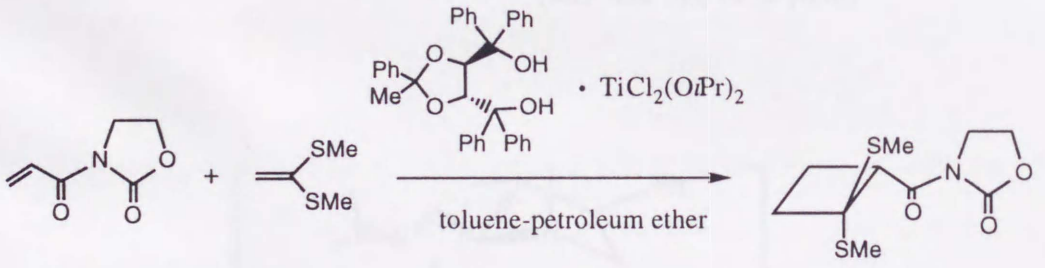
R^1=*n*-C_6H_{13}, Me_2CHCH_2, *cyclo*-C_6H_{11}, Ph
R^2=Me, Et

(78-100 %ee, 70-100 % yield)



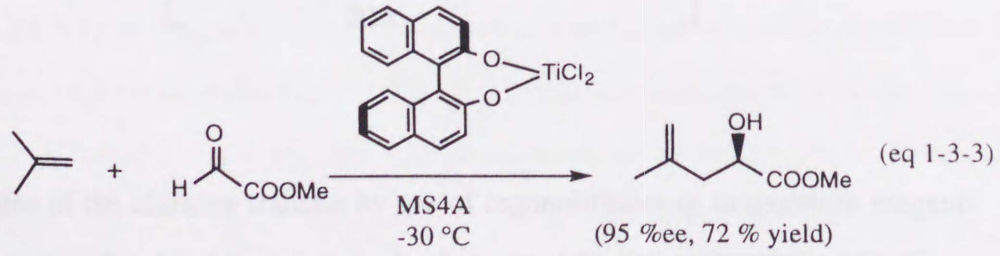
(eq 1-3-1)

(88 %ee, 90 % yield)



(88 %ee, 74 % yield)

(eq 1-3-2)

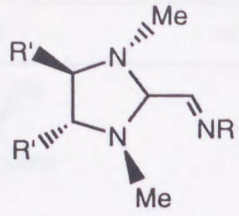


(eq 1-3-3)

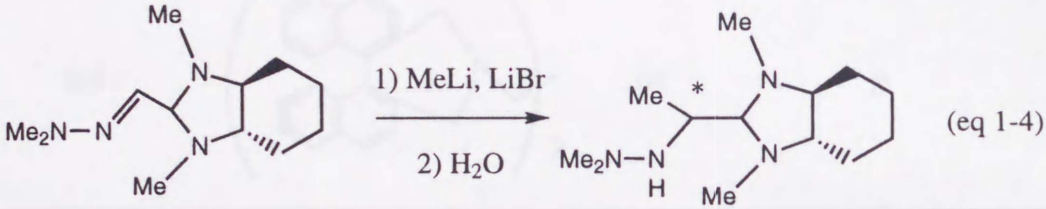
(95 %ee, 72 % yield)

Recently, Alexakis reported novel systems such as **1** derived from *N*-substituted chiral diamines based on the conception that the methyl substituent on the nitrogen should be oriented *trans* to the substituent R' on the neighboring ring carbon because

of the steric hinderance between R' and Me substituents, and the stereogenic center which controls the stereoselectivity becomes the nitrogen atom (chirality transfer) (eq 1-4).[6]

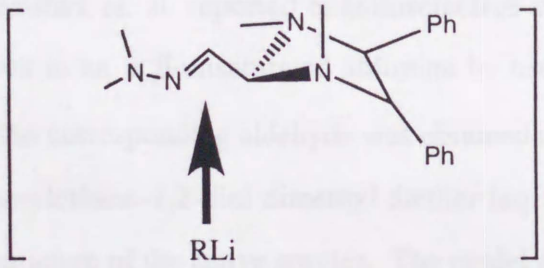


1

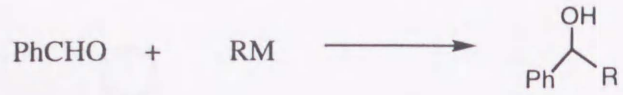


(eq 1-4)

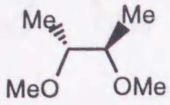
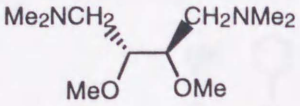
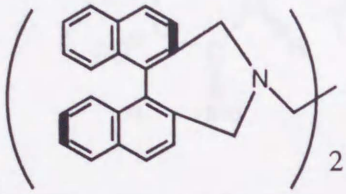
(>99 %ee (S), 74 % yield)



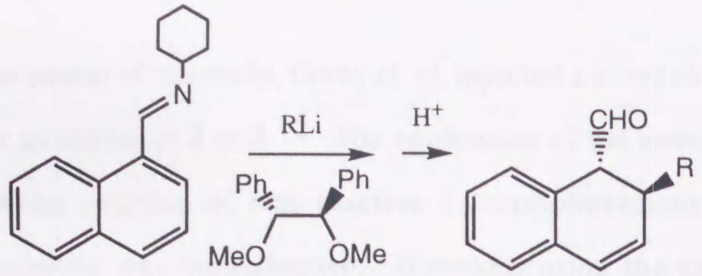
The idea of the chirality transfer by use of organolithium or magnesium reagents coordinating to the chiral ligands has also been used for the nucleophilic addition to aldehydes (eq 1-5),[7-10] but a few examples have been reported thus far as shown below.



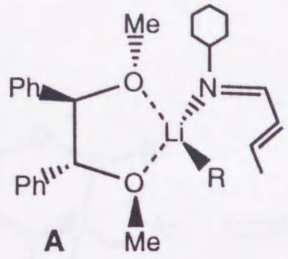
(eq 1-5)

RM	ligand	ee(%)	configuration	ref.
Me_2Mg		20	*S*	7,8
BuLi		40	*R*	9
BuLi		95	*R*	10

More recently, Tomioka et. al. reported enantioselective conjugate addition of organolithium reagents to an α,β-unsaturated aldimine by use of a C_2 symmetric chiral diether,[11] and the corresponding aldehyde was obtained in 94 % ee (R=Ph) by using (*R*,*R*)-1,2-diphenylethane-1,2-diol dimethyl diether (eq 1-6). They proposed the model **A** for the structure of the active species. The model shows that the diether forms a five-membered chelate complex with the organolithium reagent and the lone pair of the nitrogen atom of the aldimine coordinates to the lithium atom. It was assumed that four substituents of the ligand would take an all-*trans* arrangement because of the steric factors which would lead chirality transfer from chirality of the carbon atoms on the backbone to the oxygen atoms.

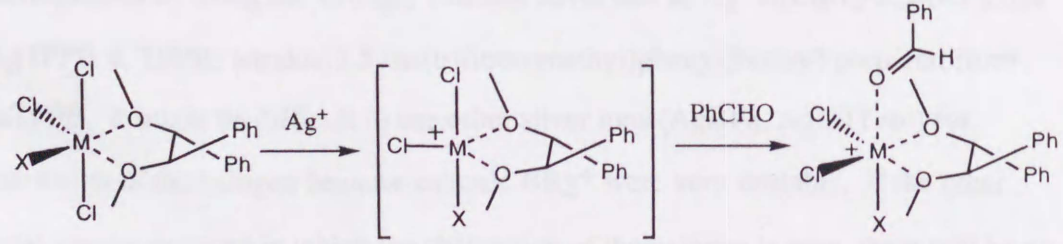


(eq 1-6)



A

In spite of these interests, stronger Lewis acids with chiral diether ligands have not been reported yet. In this Chapter, the author wishes to describe the generation of cationic Lewis acids **16** as shown in Scheme 1-1 hoping that these will be reactive enough to employ unactivated substrates or reactants. In the Lewis acids, the coordinating diether as shown in **16** suppresses polymerization of the cationic species and coordination site for the substrate in octahedral geometry should be available by abstraction of a chloride ion from **14** or **15** with silver ion. As described above, the four substituents of the diether ligand would take an *all-trans* arrangement.

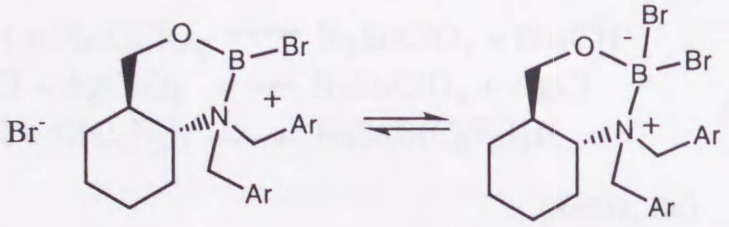


14: X=Cl
15: X=Oalkyl

16 **17**

Scheme 1-1.

In the course of our study, Corey et. al. reported a novel chiral super-Lewis acidic catalyst as shown in **2** or **3**.[12] The application of the oxazaborinane system **2** to Diels-Alder reaction of less reactive 1,3-cyclohexadiene or isoprene with 2-bromoacrolein was unproductive. However, using the catalyst **3**, the reaction proceeded to give products in excellent yield. The results strongly suggest that these cationic metal species should have applicability as Lewis acids.



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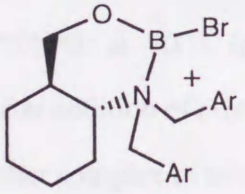


$B[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_4^-$

3

In the Corey's Lewis acid, abstraction of a bromide (or halogen) was accomplished by using the strongly cationic silver salt as $Ag^+B[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_4^-$ (AgTFPB **4**, TFPB: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) prepared from NaTFPB. It might be difficult to use other silver ions ($AgBF_4$, AgOTf etc) for abstraction of the halogen because cationic BR_2^+ were very unstable. If the other metal species are used in which the abstraction of the halogen is easy, there will be no need to use AgTFPB which is difficult to prepare. In addition, the author thought the amine substituent in the Lewis acid might make the strong Lewis acidity weaker so as

not to polymerize cationic species or not to decompose reactants. The results should show the possibility that even weaker neutral Lewis acid would become stronger Lewis acid by the abstraction of the halide anion. The novel idea will widen the chemistry of Lewis acids.

In the coordination chemistry of the cationic species which would have the possibility to be Lewis acids, Lambert et. al. reported rather stable $R_3Sn^+X^-$ species (R=Me, Bu, Ph, X=ClO_4, $B(C_6F_5)_3H$) in 1992.[13] They prepared tin cations as shown in eq 1-7.

$$R_3SnH + Ph_3CClO_4 \longrightarrow R_3SnClO_4 + Ph_3CH$$
$$R_3SnCl + AgClO_4 \longrightarrow R_3SnClO_4 + AgCl \qquad \text{(eq 1-7)}$$
$$R_3SnH + B(C_6F_5)_3 \longrightarrow R_3SnB(C_6F_5)_3H$$

(R=Me, Bu)

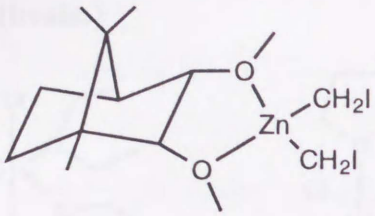
In 1994, Sakurai et. al. reported the $Bu_3Sn^+TFPB^-$ **5** (TFPB: tetrakis[3,5-bis(trifluoromethyl)phenyl]borate), and when a small amount of ether was added to the solution of the $Bu_3Sn^+TFPB^-$ at -70 °C (eq 1-8), ^{119}Sn signal shifted to higher field (**5**; δ 356 at -20 °C, after addition of ether, **6**; δ 165 at -20 °C).[14] The result showed the formation of ether complex of tributyltin cation, and ether-coordination is possible by formation of cationic species.

$$Bu_3SnH + Ph_3CTFPB \xrightarrow[-70°C]{CD_2Cl_2/Et_2O} [Bu_3Sn\text{-}OEt_2]^+TFPB^- + Ph_3CH \qquad \text{(eq 1-8)}$$

6

In the case of neutral metal species coordinating ether, Denmark reported that Et_2Zn or $(XCH_2)_2Zn$ (X: iodide, chloride) coordinating 1,2-dimethoxyethane was observed by ^1H and ^{13}C NMR spectra in benzene-d_6 and **7** could be isolated to determine the structure by X-ray analysis.[15] They also prepared the complexes **8** and

9 in solution but the corresponding diether complexes with $Zn(CH_2Cl)_2$ could not be prepared.



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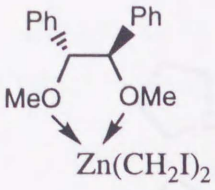

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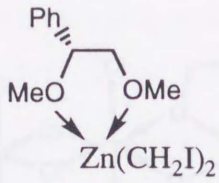
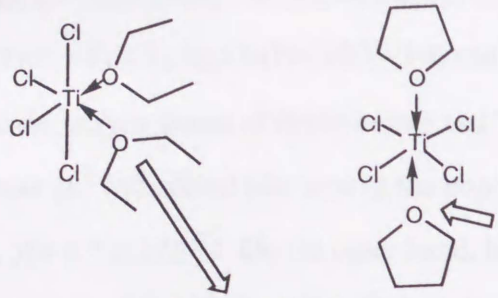


9

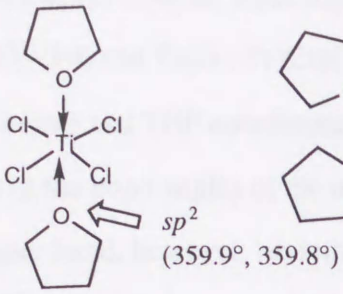
In the case of titanium (IV) or Sn (IV) compounds which are well-known Lewis acids, some of diether-coordinated complexes have been reported. Examples are shown below.

Examples of Diether-Coordinated Ti(IV) or Sn(IV) Complexes (Sum of the bond angles around the indicated oxygen atom is shown in parenthesis.)



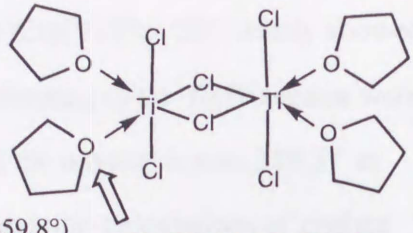
sp^2 (358.3°, 359.4°)

18a[16]



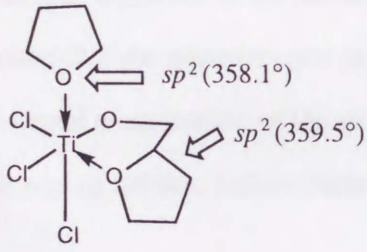
sp^2 (359.9°, 359.8°)

18b[17]



sp^2 (359.8°, 359.8°and 358.3°, 358.3°)

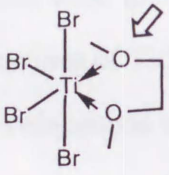
18c[18]



sp^2 (358.1°)

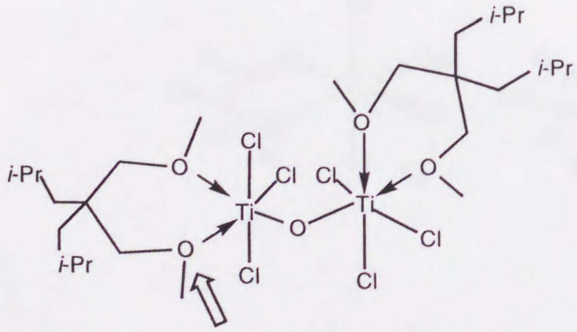
sp^2 (359.5°)

18d[19]



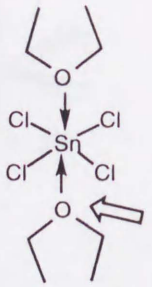
sp^3 (347.1°, 341.5°)

18e[20]



sp^3-sp^2 (351.4°, 359.9° and 355.9°, 360.1°)

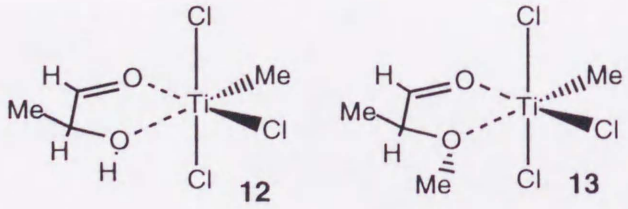
18f[21]



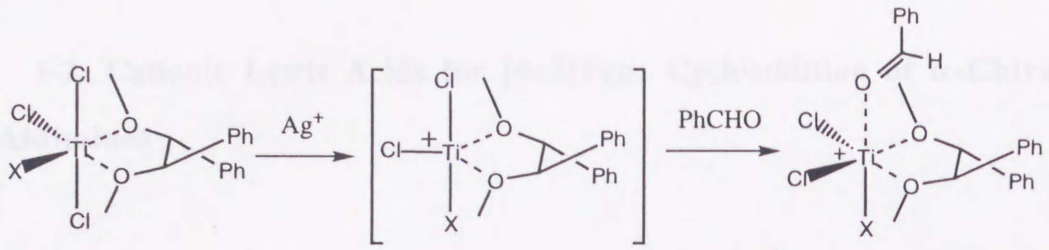
sp^2 (360.0°)

18g[22]

From these X-ray structures, chelation of the ether oxygen to Lewis acidic central atoms such as Ti(IV) usually renders the hybridization of the oxygen to an sp^2 mode from sp^3, thus losing the chirality at the oxygen. Recently reported X-ray structures of Ti(O-*i*-Pr)Cl_3(Et_2O)(PhCHO) (**10**) and Ti(O-*i*-Pr)Cl_3($THF)_2$ (**11**) clearly showed that the oxygen atoms of diethyl ether and THF coordinating to the Ti(IV) center were almost sp^2 hybridized (the sum of the bond angles of the oxygen atoms: 359.3 ° in **10**, 359.8 ° in **11**).[23] On the other hand, however, *ab initio* calculations of chelate complexes of CH_3TiCl_3 with (*S*)-2-hydroxypropionaldehyde (**12**) and (*S*)-2-methoxypropionaldehyde (**13**) showed the oxygen atom of the hydroxy group in **12** was practically sp^2 hybridized whereas some chiral induction on the oxygen atom from the carbon center was observed in **13** (Scheme 1-2).[24] To design the chirality transfer, it was necessary that the ether oxygen atoms were sp^3 hybridized or nearly sp^3. Thus the experimental examination of the structures of Ti(IV) chiral diether complexes (**14** or **15**) was of interest before these compounds were utilized as chiral Lewis acids.



Scheme 1-2.



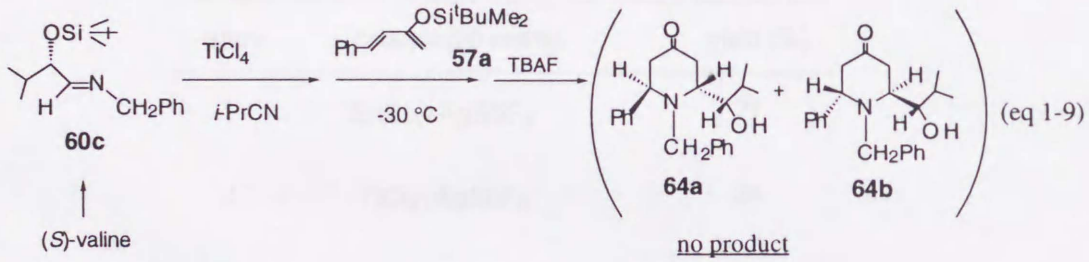
14: X=Cl
15: X=O-alkyl

16 **17**

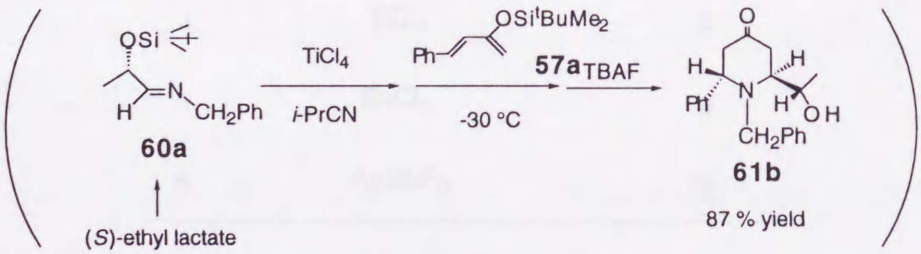
In addition, the applicability of the cationic Lewis acids for some reactions is also quite important. In this Chapter the author wishes to report on the development of the novel cationic Lewis acids bearing diethers derived from (*R*,*R*)-1,2-diphenylethane-1,2-diol. At the beginning of the Chapter, the development of the cationic Lewis acids without the ligands is described. Application for aldol reactions by using the novel cationic Lewis acids and X-ray structures of six-coordinate titanium complexes **14c** and **15a** are also described.

1-2. Cationic Lewis Acids for [4+2]Type Cycloaddition of α-Chiral Aldimines

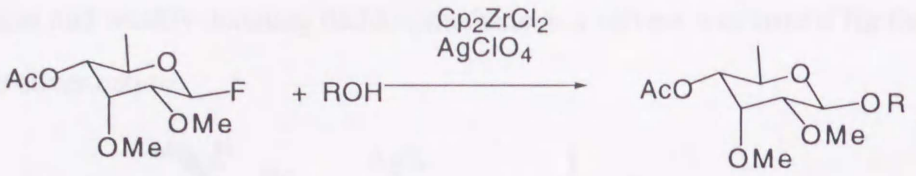
At the beginning of the study, cationic Lewis acids without ligands were investigated. The author selected the [4+2]type cycloaddition of an α-chiral aldimine **60c** derived from (*S*)-valine with a 2-silyloxy-1,3-butadiene **57a** because no product was obtained when $TiCl_4$ was used as a Lewis acid at -30 °C in *i*-PrCN as shown in eq 1-9 although the reaction of the aldimine **60a** derived from (*S*)-ethyl lactate proceeded under the reaction conditions (see Chapter 2).



(eq 1-9)

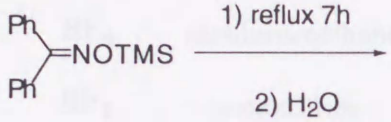


To circumvent the problem, the activated Lewis acids such as the cationic titanium compounds were the candidates for the reaction. Recently, Suzuki et. al. reported new glycosidation by use of Cp_2ZrCl_2-$AgClO_4$ (eq 1-10).[25] They succeeded in highly β-selective glycoside formation.



(eq 1-10)

Mukaiyama et. al. reported the activated Lewis acids for the Beckmann rearrangement of benzophenone oxime derivatives as shown in eq 1-11.[26] They have been using these Lewis acids for other systems until now.

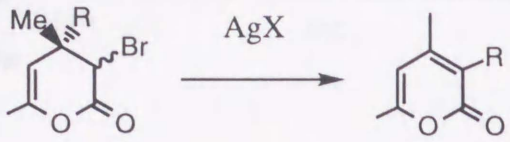


(eq 1-11)

entry	catalyst (20 mol%)	yield (%)
1	$SnCl_4$+$AgSbF_6$	71
2	$TiCl_4$+$AgSbF_6$	24
3	$SbCl_5$+$AgSbF_6$	78
4	$TiCl_4$	2
5	$SnCl_4$	0
6	$AgSbF_6$	19

Akiba et. al. reported the effects of counter ion and solvent on the rate of the silver ion promoted-rearrangement of 4-aryl- or 4-alkenyl-3-bromo-3,4-dihydro-2-pyrones as shown in eq 1-12.[27] The rearrangement with $AgSbF_6$ in dichloromethane proceeded smoothly at room temperature and completed within 15 min to afford the product in high yield. The combination of weakly coordinating hexafluoroantimonate as a counter

anion and weakly donating dichloromethane as a solvent was crucial for the activity of the silver cation.

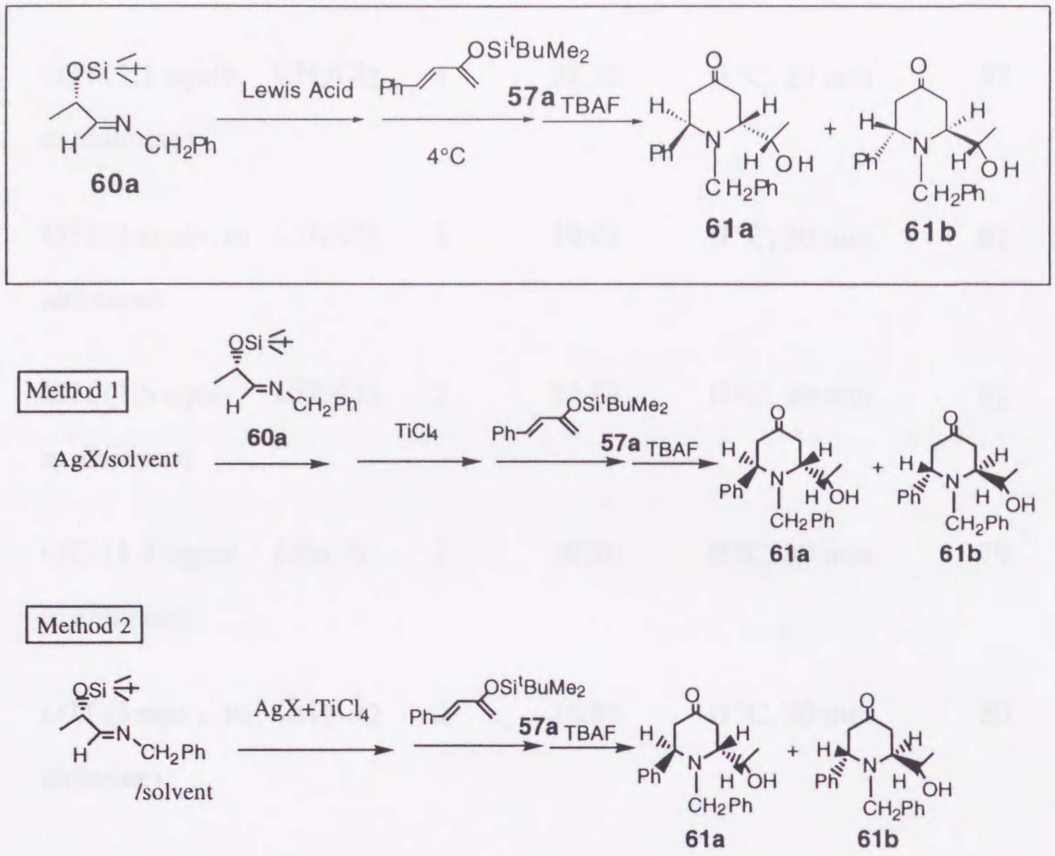


(eq 1-12)

R	X	solvent	conditions	conversion (%)
p-tolyl	SbF_6	dichloromethane	r.t., 15 min	100
p-tolyl	SbF_6	acetonitrile	r.t., 24 h	84
p-tolyl	BF_4	dichloromethane	r.t., 24 h	71
p-tolyl	BF_4	acetonitrile	reflux, 12 h	79
1-propenyl	SbF_6	dichloromethane	r.t., 15 min	100
1-propenyl	BF_4	acetonitrile	reflux, 7 h	81

It seems that the selection of neutral Lewis acids and silver ions for cationic Lewis acid-promoted reactions might be difficult if the substrate is easy to decompose by strongly activated cationic species. In the [4+2]type cycloaddition, the α-silyloxyaldimines were easily to polymerize under some conditions so that careful selection was necessary.

As a model reaction of eq 1-9, the α-silyloxyaldimine derived from (S)-ethyl lactate was selected in the reaction. The methods and results are shown in Scheme 1-3 and Table 1.



Scheme 1-3.

Table 1-1. [4+2]Type Cycloaddition of an α-Silyloxyaldimine 60a Derived from (S)-Ethyl Lactate.

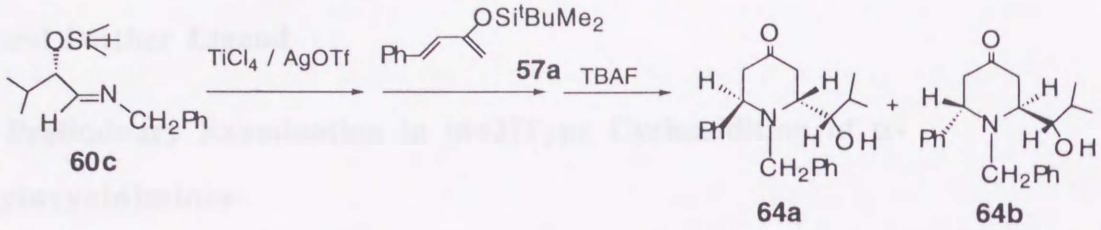
entry	X	solvent	method	**61a:61b**	conditions	yield (%)
1	BF_4	CH_2Cl_2	1	5:95	0 °C, 20 min	27
2	$OCOCF_3$	CH_2Cl_2	1	-	0 °C, overnight	0
3	ClO_4	CH_2Cl_2	1	13:87	0 °C, 20 min	93
4	OTf (0.8 equiv. to aldimine)	CH_2Cl_2	1	36:64	0 °C, 20 min	64

5	OTf (1.1 equiv. to aldimine)	CH_2Cl_2	1	28:72	0 °C, 20 min	57
6	OTf (3 equiv. to aldimine)	CH_2Cl_2	1	19:81	0 °C, 20 min	61
7	OTf (1.5 equiv. to aldimine)	CH_2Cl_2	2	34:66	0 °C, 20 min	82
8	OTf (1.5 equiv. to aldimine)	*i*-PrCN	2	10:90	0 °C, 30 min	79
9	OTf (3 equiv. to aldimine)	CH_2Cl_2	2	15:85	0 °C, 20 min	80
10	SbF_6 (2 equiv. to aldimine)	CH_2Cl_2	2	4:96	0 °C, 20 min	33
11	SbF_6	CH_2Cl_2*a	2	15:85	0 °C, 20 min	58

The ratios of **61a**:**61b** were determined by ^1H NMR spectra.

*a Five times amount of the solvent was used compared with that in other entries.

The product **61b** might be obtained by way of chelation pathway in the case of $TiCl_4$ (Chapter 2), so higher selectivity of **61b** might suggest that more active Lewis acids were formed. $ZnCl_2$-$AgSbF_6$ and $ZnBr_2$-$AgSbF_6$ were also investigated but no selectivity was observed (31 % yield). In Table 1-1, using $AgSbF_6$ gave high selectivity as in entry 10 but in low yield. Higher **61b** selectivities seem to be observed by using more cationic silver ions, but the resulting highly cationic titanium ion might also decompose the aldimine. The reactions did not appear to require the super-cationic Lewis acids. Method 2 was better way to obtain products than the method 1 (61 % yield in entry 6, and 80 % yield in entry 9).

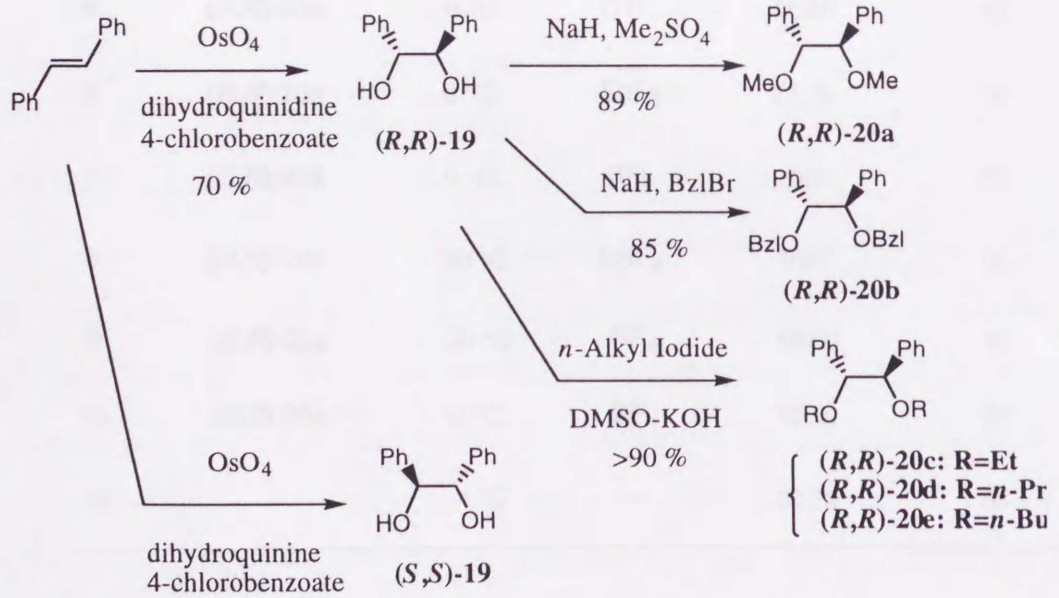


The results were applied for the [4+2]type cycloaddition of an α-chiral aldimine derived from (S)-valine with a 2-silyloxy-1,3-butadiene. The addition of 1 equiv of AgOTf to the mixture was quite effective in activating $TiCl_4$ and only **64b** was obtained in 49 % yield (**64a**:**64b**=<2:>98) at -30 °C in *i*-PrCN. It is unclear what is the activated species, but $TiCl_3^+$-$TiCl_4$ polymer might be the Lewis acid in this system.

1-3. Development of Novel Cationic Lewis Acids Coordinated by a Chiral Diether Ligand

A. Preliminary Examination in [4+2]Type Cycloaddition of α-Silyloxyaldimines

The chiral diether ligands were prepared as shown in Scheme 1-4. Osmium oxidation of *trans*-stilbene by use of dihydroquinidine 4-chlorobenzoate afforded (*R,R*)-1,2-diphenylethane-1,2-diol (***R,R*)-19**.[28] The optical pure compound was obtained after recrystallization of the crude products from EtOH. (*S,S*)-1,2-Diphenylethane-1,2-diol (***S,S*)-19** was prepared by using dihydroquinine 4-chlorobenzoate and OsO_4.[28] The resulting diol (***R,R*)-19** was treated with NaH and Me_2SO_4 to give (*R,R*)-1,2-diphenylethane-1,2-diol dimethyl diether (***R,R*)-20a**,[11] and dibenzyl diether (***R,R*)-20b** could be prepared by using NaH and BzlBr. Other dialkyl diethers could not be obtained by the similar methods, so the (*R,R*)-1,2-diphenylethane-1,2-diol (***R,R*)-19** was treated with KOH-DMSO followed by alkyl iodide at room temperature to give dialkyl diethers in excellent yields.[29]



Scheme 1-4.

As a part of the ongoing project, [4+2]type cycloaddition of an aldimine **60a** with 2-silyloxy-1,3-butadiene **57a** was carried out to test the cationic Lewis acids which were prepared *in situ* (Table 1-2). Based on the results in Section 1-2, the best method to prepare the cationic Lewis acids was decided as shown in eq 1-13.

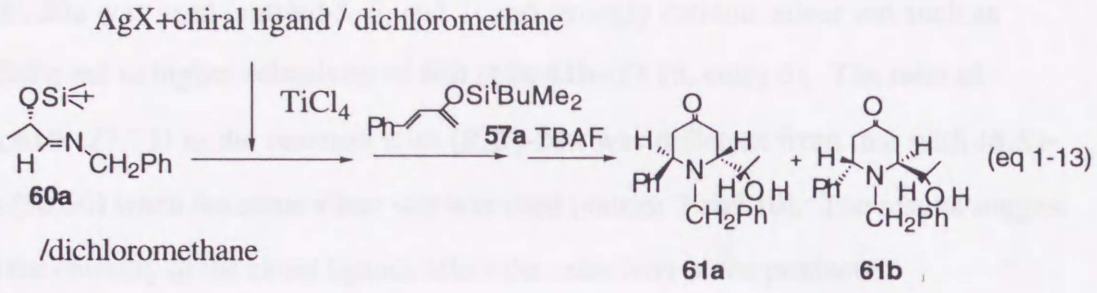


Table 1-2.

entry	chiral ligand	temperature	X	**61a : 61 b**	yield (%)
1	**(*R*,*R*)-20a**	0 °C	-	87:13	70
2	**(*R*,*R*)-20a**	-30 °C	-	76:24	74
3	**(*S*,*S*)-20a**	0 °C	-	87:13	76
4	**(*R*,*R*)-19**	0 °C	BF_4	-	0
5	**(*R*,*R*)-20a**	0 °C	OTf	50:50	40
6	**(*R*,*R*)-20a**	0 °C	SbF_6	27:73	36
7	**(*R*,*R*)-20a**	0 °C	BF_4	29:71	55
8	**(*R*,*R*)-20a**	-30 °C	SbF_6	9:91	35
9	**(*R*,*R*)-20a**	-30 °C	BF_4	50:50	76
10	**(*S*,*S*)-20a**	0 °C	BF_4	50:50	52
11	-	4 °C	-	30:70	86

In Table 1-2, the selectivity by using (***R,R***)-**20a**-$TiCl_4$ without silver ions was the same as that with (***S,S***)-**20a**-$TiCl_4$ (entries 1 and 3). The use of chiral diol ligand (***R,R***)-**19**-$AgBF_4$-$TiCl_4$ gave no product (entry 4). The large effect of the counter anion of the silver salts on the selectivity was observed when the chiral diether ligand (***R,R***)-**20a** was used (entried 5, 6, and 7) and strongly cationic silver ion such as $AgSbF_6$ led to higher selectivity of **61b** (**61a**:**61b**=27:73, entry 6). The ratio of **61a**:**61b** (27:73) in the reaction with (***R,R***)-**20a** was different from that with (***S,S***)-**20a** (50:50) when the same silver salt was used (entries 7 and 10). The results suggest that the chirality of the chiral ligands affect the selectivity of the products.

Table 1-3. Effect of the Aging Time on the Stereoselectivity.

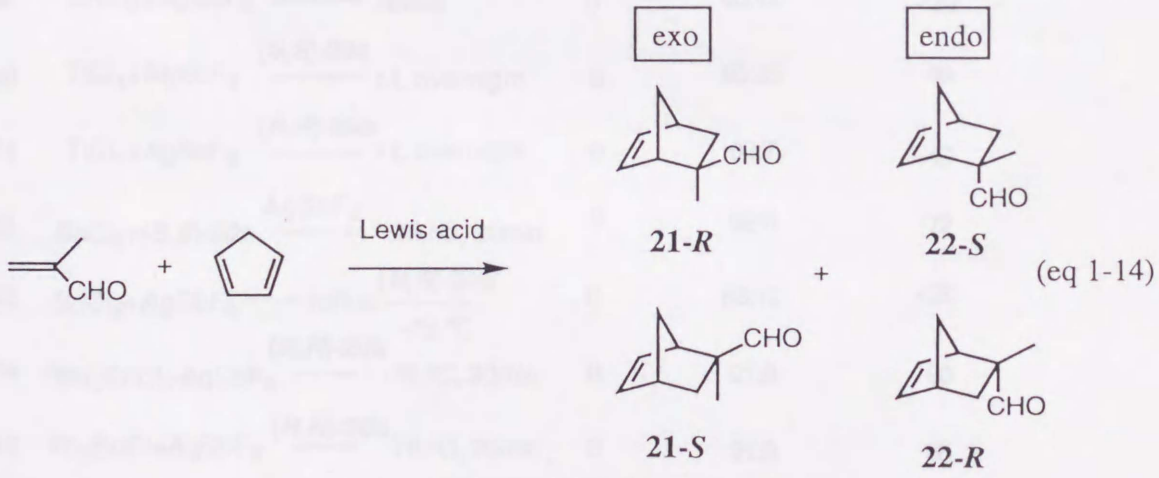
entry	chiral ligand	temperature	X	aging time	**61a : 61 b**	yield (%)
1	(***S,S***)-**20a**	0 °C	BF_4	<10 sec.	<2:>98	trace
2	(***S,S***)-**20a**	0 °C	BF_4	10 min	36:65	72
3	(***S,S***)-**20a**	0 °C	BF_4	1 h	65:35	66

In the reaction as in Table 1-2, to a stirred solution of the chiral ligand and silver salt was added $TiCl_4$ and the mixture was stirred for 1 min. Then **60a** and **57a** was added to the mixture successively. However, the reaction time of the chiral ligand, silver salt and $TiCl_4$ (aging time, 1 min in Table 1-2) might be important for the generation of the cationic Lewis acids. The effect of the aging time in the reaction with (***S,S***)-**20a**-$AgBF_4$-$TiCl_4$ on the selectivity was examined and the results are shown in Table 1-3. As shown in Table 1-3, the author found that the aging time significantly affected the diastereoselectivity. Longer aging time produced **61a** with higher selectivity in the case of (***S,S***)-**20a**-$AgBF_4$-$TiCl_4$. The origin of the selectivities is unclear and should be quite complicated because of the chiral induction from the chirality of the aldimine at the

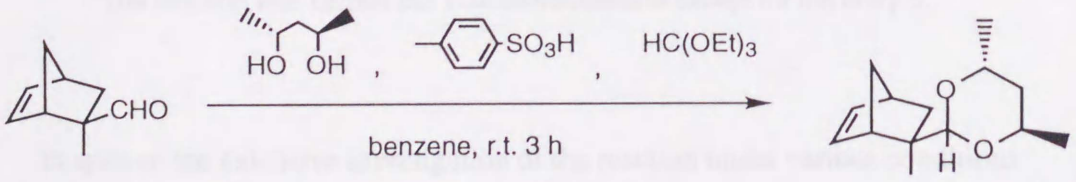
α-position. However, the results show the large possibility for utilizing the novel cationic Lewis acids. In the next section, other reactions by using the novel cationic Lewis acids are described.

B. Examination in Diels-Alder Reaction

The author selected Diels-Alder reaction of methacrolein with cyclopentadiene to examine the enantioselectivity induced by the chirality of the chiral ligand in the Lewis acids (eq 1-14, Table 1-4). The reaction was carried out according to the literature[30] except for the preparation of novel Lewis acids. To determine the enantiomeric excess of the exo products, the cycloadducts were converted to the acetals such as **23** (eq 1-15). In addition to the study of $TiCl_4$-Ag^+ system, other Lewis acids were examined for the reaction.



(eq 1-14)



23

(eq 1-15)

Table 1-4.

entry	aging conditions	ee (%)	exo:endo	yield (%)
1	$ZnBr_2$	0	88:12	96
2	$ZnCl_2$+(*S,S*)-**20a** $\xrightarrow{AgBF_4}$ r.t. 0 min	0	87:13	69
3	r.t. 30 min	0	89:11	75
4	r.t. 1 h	0	89:11	73
5	r.t. 2 h	0	90:10	79
6	$ZnBr_2$+$AgBF_4$ $\xrightarrow{(S,S)\text{-}20a}$ r.t. overnight	0	90:10	83
7	$ZnBr_2$+$AgSbF_6$ $\xrightarrow{(S,S)\text{-}20a}$ r.t. overnight	0	94:6	65
8	$ZnBr_2$+$AgSbF_6$ $\xrightarrow{(S,S)\text{-}20a}$ $ClCH_2CH_2Cl$	0	81:19	<20
9	$SnCl_2$+$AgSbF_6$ $\xrightarrow{(S,S)\text{-}20a}$ reflux	0	88:12	<20
10	$TiCl_4$+$AgSbF_6$ $\xrightarrow{(S,S)\text{-}20a}$ r.t. overnight	0	65:35	40
11	$TiCl_4$+$AgSbF_6$ $\xrightarrow{(R,R)\text{-}20b}$ r.t. overnight	0	93:7	40
12	$SnCl_2$+(*S,S*)-**20a** $\xrightarrow{AgSbF_6}$ -78 °C, 20min	0	92:8	72
13	$SnCl_2$+$AgSbF_6$ $\longrightarrow$ reflux $\xrightarrow[-78\ °C]{(R,R)\text{-}20b}$	0	88:12	<20
14	$^nBu_3SnCl$+$AgSbF_6$ $\xrightarrow{(R,R)\text{-}20b}$ -78 °C, 20min	0	91:9	90
15	Ph_3SnCl+$AgSbF_6$ $\xrightarrow{(R,R)\text{-}20b}$ -78 °C, 20min	0	91:9	85

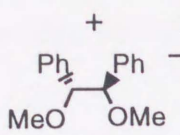
*The reaction was carried out in dichloromethane except for the entry 8.

In spite of the extensive investigation of the reaction under various conditions besides the conditions cited in Table 1-4, enantioselectivity of the exo compounds in the reaction was not observed. The change of the aging time in the reaction of $ZnCl_2$-(*S,S*)-**20a**-$AgBF_4$ resulted in no change of the enantioselectivities (entries 2-5). In

addition, no effect of the counter anion of the silver salt in the reaction of $ZnBr_2$-(***S,S***)-**20a**-$AgBF_4$ was observed (entries 6 and 7). Although formation of precipitates which could be AgX (X=Cl or Br) was noticed after addition of the silver salt in many reactions, the author suspected that the cationic species were not formed . To overcome the problem, the reactions of $ZnBr_2$-(***S,S***)-**20a**-$AgSbF_6$, $SnCl_2$-(***S,S***)-**20a**-$AgSbF_6$, and $SnCl_2$-(***R,R***)-**20b**-$AgSbF_6$ were carried out under reflux conditions (CH_2Cl_2 or $ClCH_2CH_2Cl$) but the decomposition of the chiral ligands occurred (entries 8, 9, and 13). In addition, stronger Lewis acidic $TiCl_4$-(***S,S***)-**20a**-$AgSbF_6$ system which was prepared at r.t. decomposed the chiral diethers (entries 10 and 11). Other Lewis acids such as Et_2AlCl, Ti(O-*i*-Pr)$_3$Cl were tried under various conditions but stereoselectivity was not observed.

To determine the reaction conditions for preparation of the Lewis acids, the amounts of AgCl and the recovered chiral ligands were examined (eq 1-16 and eq 1-17). It is difficult to identify the metal cation directly but the presence of the metal cation might be supported if the resultant AgCl was identified and the quantity was determined. In the reaction of $SnCl_2$ with $AgSbF_6$, the precipitates were observed even at -78 °C, and these were identified as AgCl by powder X-ray diffraction (Fig 1-1). The AgCl was recovered in 75 % yield when (***R,R***)-**20a** was used as a chiral ligand (eq 1-16). After the abstraction of the chloride ion from $SnCl_2$, the mixture was treated with H_2O and was extracted with dichloromethane. The solvent was evaporated and ^1H NMR of the recovered ligand was examined. In the case of (***R,R***)-**20a**, the chiral ligand did not decompose at all, but when (***R,R***)-**20b** was used, the peaks in the ^1H NMR spectrum were quite complex after formation of the cationic Lewis acid. The result shows the chiral dibenzyl diether ligand (***R,R***)-**20b** is unstable under the reaction conditions.

$SnCl_2$ (0.4 mmol)

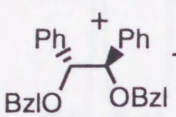


(*R*,*R*)-20a

+ $AgSbF_6$ (0.4 mmol) → AgCl (75 %) (eq 1-16)

CH_2Cl_2, -78 °C

$SnCl_2$ (0.4 mmol)



(*R*,*R*)-20b

+ $AgSbF_6$ (0.4 mmol) → AgCl (15 %) (eq 1-17)

CH_2Cl_2, -78 °C

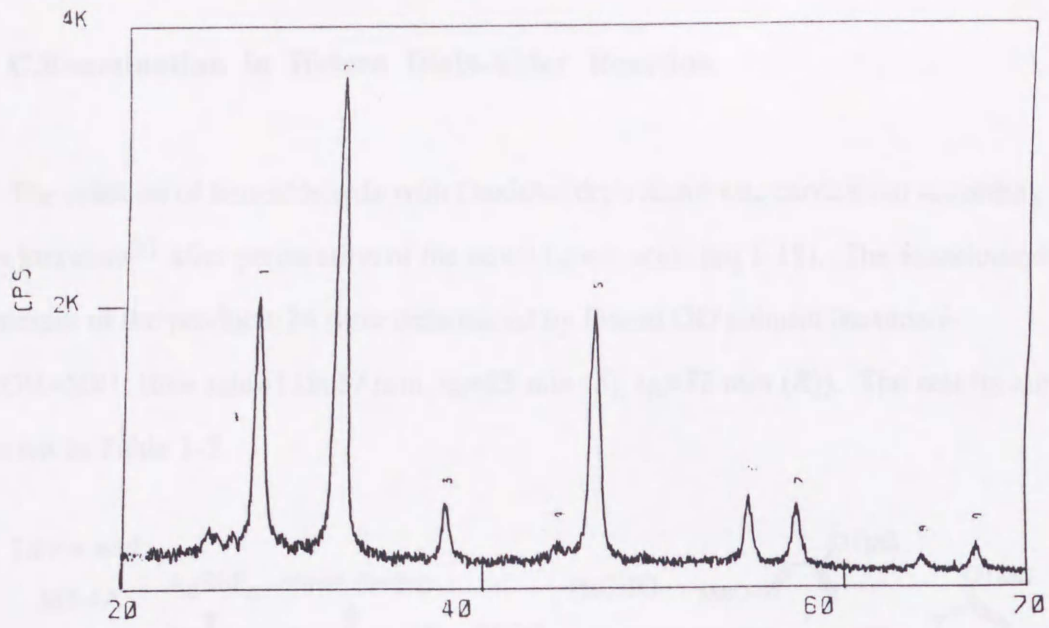
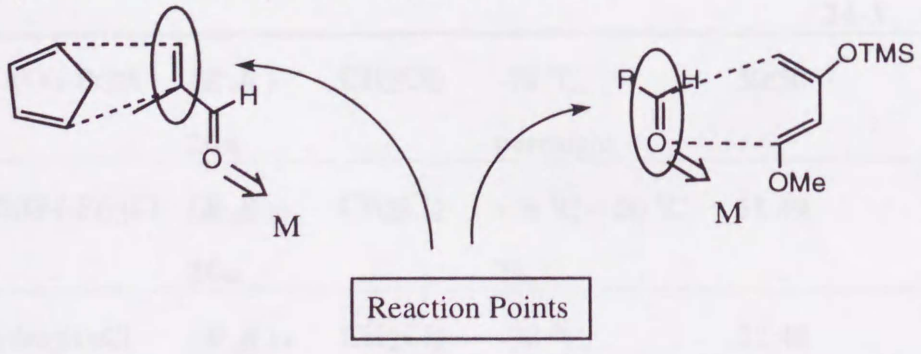


Fig. 1-1. Powder X-ray Diffraction of AgCl formed in the Reaction of Eq 1-16.

Based on the results in Table 1-4, it seemed better to select other reactions because reaction points in the Diels-Alder reaction were far away from the carbonyl oxygen-metal coordinating bond compared to the case in hetero Diels-Alder reactions (Scheme 1-5). To lay groundwork for the novel cationic Lewis acids, closer reaction points should be necessary. The author examined the hetero Diels-Alder reaction of benzaldehyde and Danishefsky's diene in the next section.



Scheme 1-5.

C.Examination in Hetero Diels-Alder Reaction

The reaction of benzaldehyde with Danishefsky's diene was carried out according to the literature[31] after preparation of the novel Lewis acids (eq 1-18). The enantiomeric excesses of the products **24** were determined by Daicel OD column (hexane/*i*-PrOH=50/1, flow rate=1.0ml / min, t_R=25 min (*S*), t_R=32 min (*R*)). The results are shown in Table 1-5.

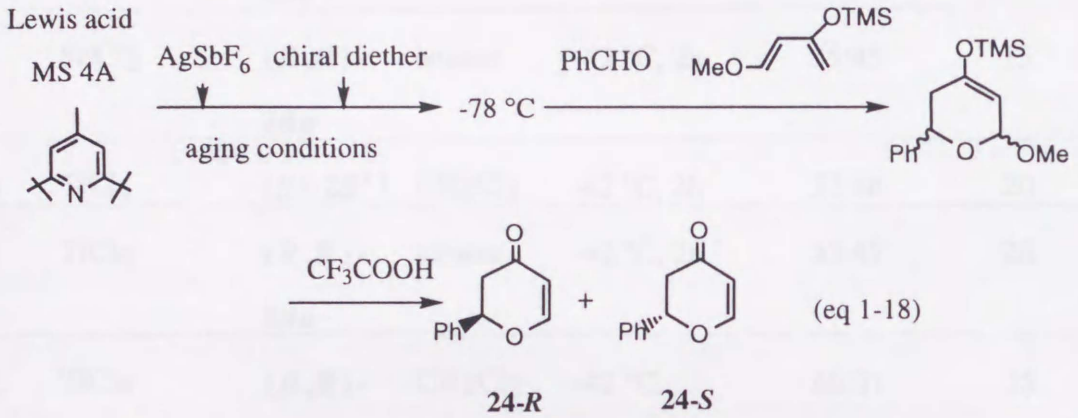


Table 1-5.

entry	Lewis acid	ligand	solvent	aging conditions	**24-*R*** : **24-*S***	yield (%)
1	Ti(O-*i*-Pr)3Cl	(***R*,*R***)-**20a**	CH_2Cl_2	-78 °C, overnight	50:50	35
2	Ti(O-*i*-Pr)3Cl	(***R*,*R***)-**20a**	CH_2Cl_2	-78 °C - -50 °C, 2h	51:49	20
3	*n*-Bu3SnCl	(***R*,*R***)-**20a**	CH_2Cl_2	-78 °C, overnight	52:48	33
4	Ph3SnCl	(***R*,*R***)-**20a**	CH_2Cl_2	-78 °C, overnight	51:49	61

5	Cp_2TiCl	**(*R*,*R*)-20a**	CH_2Cl_2	-78 °C, overnight	51:49	40
6	Ti(O-*i*-Pr)3Cl	**(*R*,*R*)-20a**	hexane	-78 °C, 2h	50:50	10
7	Ti(O-*i*-Pr)3Cl	**(*R*,*R*)-20a**	hexane	-42 °C, 2h	52:48	15
8	$TiCl_4$	**(*R*,*R*)-20a**	CH_2Cl_2	-42 °C, 2h	55:45	30
9	$SnCl_2$	**(*R*,*R*)-20a**	hexane	-42 °C, 2h	55:45	15
10	$TiCl_4$	**(*S*)-25**[*1]	CH_2Cl_2	-42 °C, 2h	52:48	20
11	$TiCl_4$	**(*R*,*R*)-20a**	toluene	-42 °C, 2h	53:47	28
12	$TiCl_4$	**(*R*,*R*)-20a**	CH_2Cl_2	-42 °C, overnight	69:31	35
13	$SbCl_5$	**(*R*,*R*)-20a**	CH_2Cl_2	-42 °C, overnight	60:40	20
14	$TiCl_4$	**(*R*,*R*)-20a**	CH_2Cl_2	-23 °C, 1h	64:36	45
15[*5]	$TiCl_4$	**(*R*,*R*)-20a**	CH_2Cl_2	-23 °C, 1h	60:40	40
16	$ZnCl_2$	**(*R*,*R*)-20a**	CH_2Cl_2	-23 °C, 5h	58:42	69
17	$TiCl_4$	**(*R*,*R*)-20a**[*4]	CH_2Cl_2	-42 °C, overnight	72:28	50
18	$TiCl_4$	**2(*R*,*R*)-20c**[*2,3,4]	CH_2Cl_2	-42 °C, overnight	70:30	55

19	$TiCl_3(OTf)$	**2(*R*,*R*)-20a***3,4	CH_2Cl_2	-42 °C, overnight	60:40	40
20	$TiCl_2(OTf)_2$	**2(*R*,*R*)-20a***3,4	CH_2Cl_2	-42 °C, overnight	50:50	40

*1. **(*S*)-25**: (*S*)-binaphthol dimethyl diether

*2. **(*R*,*R*)-20c** : (*R*,*R*)-hydrobenzoin diethyl diether

*3. 2 equiv. of chiral diether to Lewis acid was used

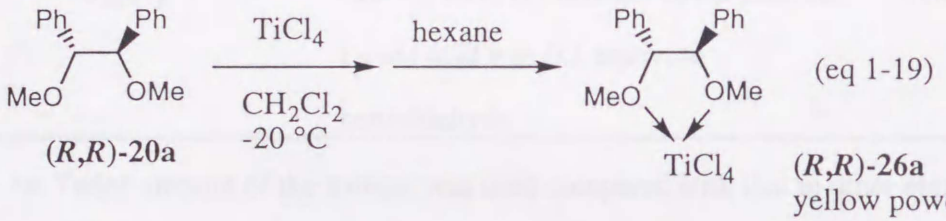
*4. 2 equiv. of $AgSbF_6$ to Lewis acid was used

*5. no molecular sieves 4A

To avoid accidental H_2O in the reaction, molecular sieves 4A was added except for entry 15. Small effect of the molecular sieves 4A on the selectivity was observed as in entry 14 (64:36) compared with entry 15 (60:40). One drop of 2,6-di-*tert*-butyl-4-methylpyridine was used to avoid the small amount of strong H^+. After some experiments, the author found that excess 2,6-di-*tert*-butyl-4-methylpyridine led to lower selectivities. Surprisingly, when large amount of 2,6-di-*tert*-butyl-4-methylpyridine in dichloromethane was added to the $AgSbF_6$ in dichloromethane at r.t., AgCl was precipitated. The abstraction of chloride ion of dichloromethane might have occurred. In entries 1-7, no selectivities were observed when relatively weak Lewis acids such as $Ti(O\text{-}i\text{-}Pr)_3Cl$, $n\text{-}Bu_3SnCl$, Ph_3SnCl, and Cp_2TiCl were used. However, when $TiCl_4$ or $SnCl_2$ was used as a Lewis acid with **(*R*,*R*)-20a**, low selectivities were observed (entries 8, 9, and 11). Chiral binaphthol dimethyl diether **(*S*)-25** in the place of **(*R*,*R*)-20a** did not give better result (entry 10). In order to optimize the reaction conditions, we chose CH_2Cl_2 as a solvent and $TiCl_4$ as a Lewis acid because the reaction with $TiCl_4$ in CH_2Cl_2 gave slightly better result than that in toluene (entries 8 and 11). Longer aging time was effective to obtain **24-*R*** selectively (55:45 in entry 8 vs. 69:31 in entry 12), although the yield was still unsatisfactory. The aging reaction at higher temperature (-23 °C) for 1 h gave fairly good results (entry 14,

64:36, 45 % yield). The best result was obtained as a ratio of 77:28 in 50 % yield when 2 equiv. of $AgSbF_6$ to $TiCl_4$ was used with the long aging time (entry 17). Under similar conditions, $SbCl_5$, $ZnCl_2$, $TiCl_3(OTf)$, and $TiCl_2(OTf)_2$ did not give better results than $TiCl_4$ (entries 13, 16, 19, and 20). $TiBr_4$ and TiI_4 were also tried but no selectivity was observed.

Based on these results, it seems that $TiCl_4$ is the best candidate as a Lewis acid and the conditions of generation of the cationic species are crucial for the selectivity. Thus, the author tried to isolate $TiCl_4$-chiral diether complexes. The stability of these complexes had not been estimated, but these were prepared under the conditions as in eq 1-19 and identified by ^1H NMR in dry $CDCl_3$.



(*R*,*R*)-20a

(eq 1-19)

(*R*,*R*)-26a
yellow powder

After trying to obtain the complex as a solid under various conditions, the following procedure was the method of choice: To a stirred solution of **(*R*,*R*)-20a** in dichloromethane at -20 °C was added $TiCl_4$ very slowly. Then dry *n*-hexane was added to the mixture to give yellow precipitates which were washed with dry *n*-hexane after filtration. The complex was quite moisture sensitive, so the manipulations were conducted under Ar atmosphere. Using the complex **(*R*,*R*)-26a**, the hetero Diels-Alder reaction of benzaldehyde with Danishefsky's diene was carried out and the results are shown in Table 1-6.

Table 1-6. Hetero Diels-Alder Reaction by Use of the Complex (*R*,*R*)-26a.

entry	solvent	aging conditions	**24-*R*** : **24-*S***	yield (%)
1	CH_2Cl_2	-20 °C, overnight, 1.5 equiv. of $AgSbF_6$ to the complex	74:26	49
2	2x(CH_2Cl_2-hexane)*a	-20 °C, 1 day	50:50	55
3	CH_2Cl_2-hexane	-20 °C, 4 h	57.5:42.5	34
4	CH_2Cl_2	-20 °C, 10 h, the amount of the cationic Lewis acid was 0.1 equiv. to benzaldehyde	56.5:43.5	45

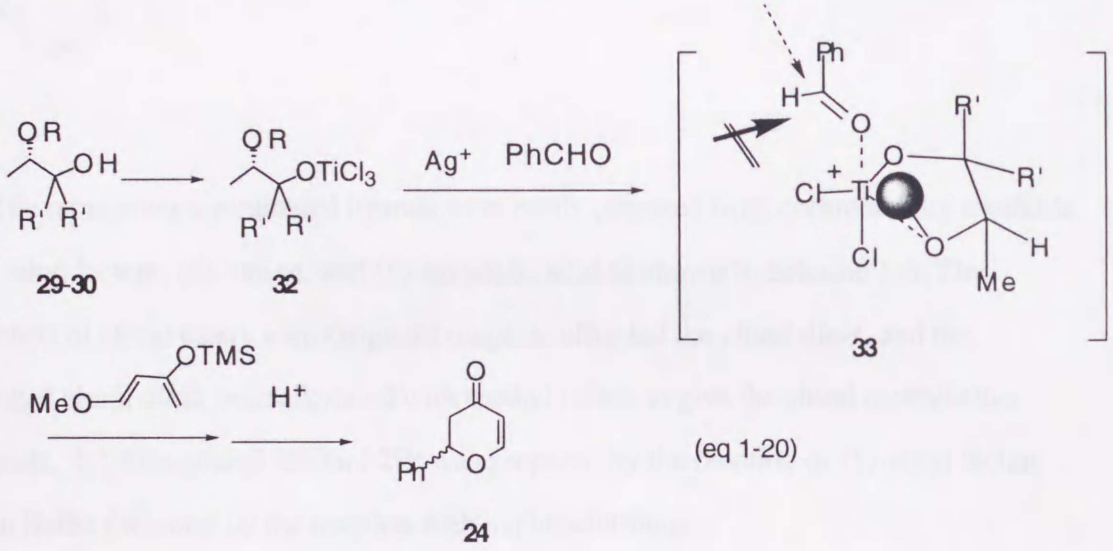
*a: Twice amount of the solvent was used compared with that in other entries.

24-*R* was obtained in a ratio of 74:26 in 49 % yield (entry 1) when 1.5 equiv. of $AgSbF_6$ was reacted with the complex (***R*,*R*)-26a** at -20 °C overnight. The result was almost comparable but slightly better than that without isolation (entry 17 in Table 1-5). The reaction under the diluted conditions did not afford **24-*R*** selectively (entry 2).

In section 1-5, the author applied the novel cationic Lewis acids for the aldol reaction of benzaldehyde and silyl enol ether. Searching for the utility of these Lewis acids is very important. Before the application, the author also tried to examine monoether-coordinated $TiCl_4$ system in the next section.

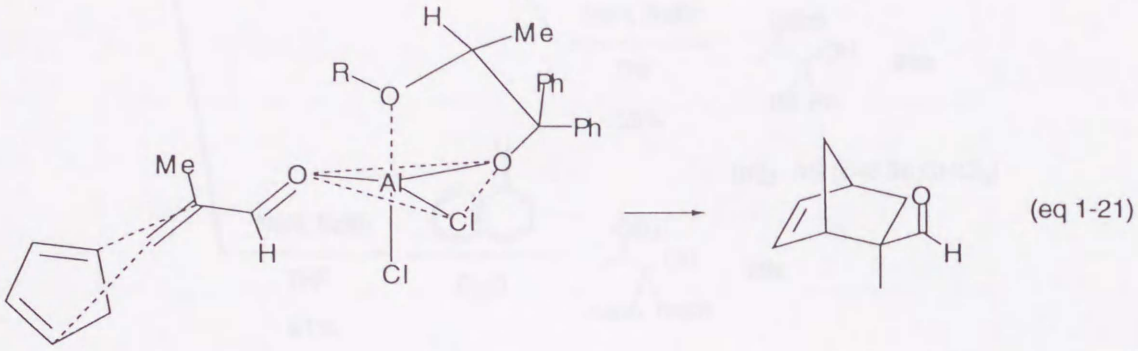
1-4. Attempt to Develop Novel Lewis Acids Bearing a Monoether-Coordinated Ligand

The monoether-coordinated novel cationic Lewis acids are shown in eq 1-20 which is exemplified by the hetero Diels-Alder reaction of benzaldehyde with Danishefsky's diene. The ether moiety in **32** could strongly coordinate to the Ti atom by abstraction of the chloride anion with the silver cation. Addition of benzaldehyde to the cationic Lewis acid would lead the transition state as in **33** in which the chirality transfer from the carbon chiral center in the backbone to the ether oxygen would occur.



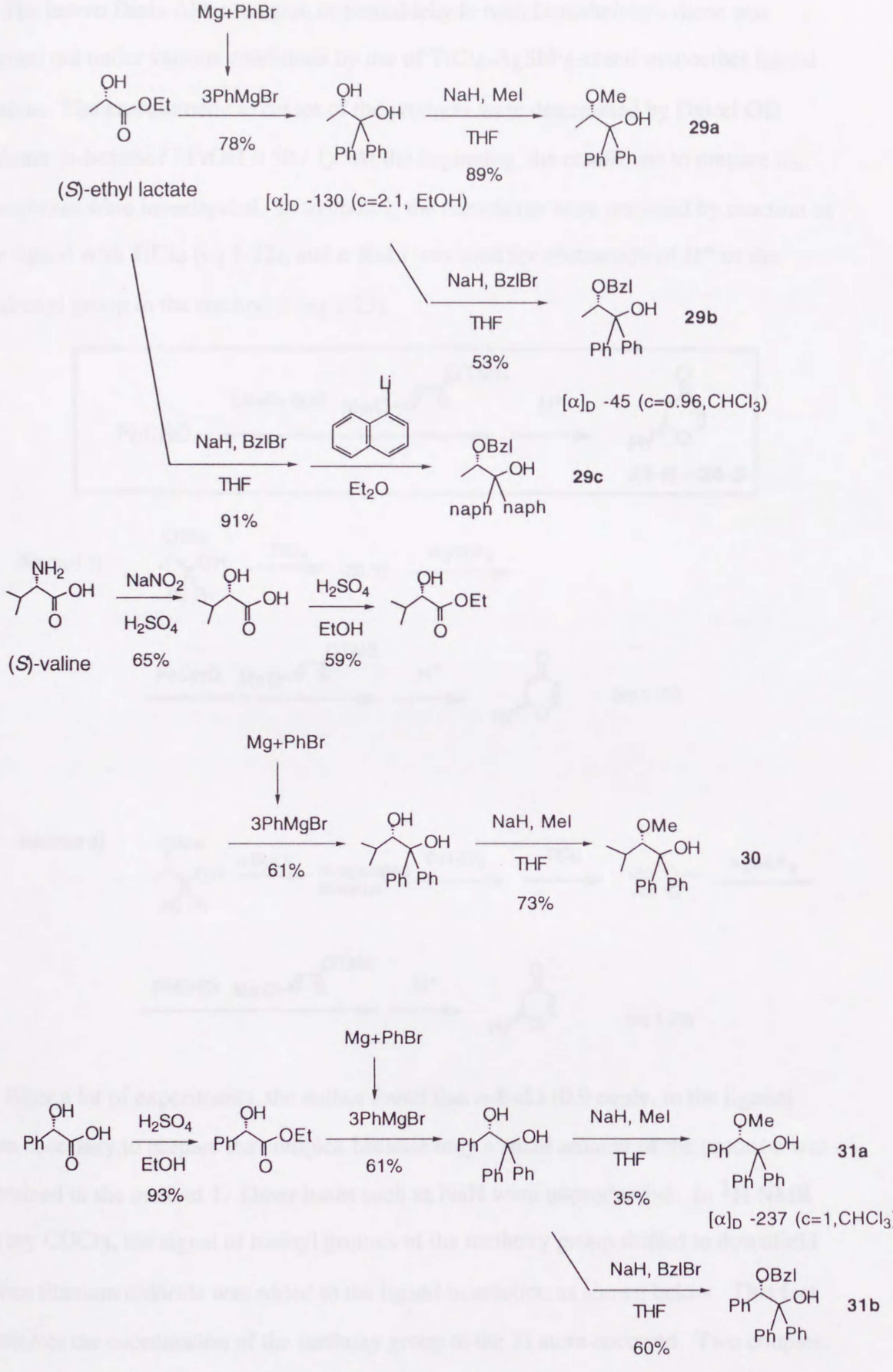
Recently, Rebieve et. al. reported Diels-Alder reaction of methacrolein with cyclopentadiene as shown in eq 1-21, and they succeeded to obtain products with high selectivity by using dialkoxy ligands (R=H in eq 1-21, 73 %ee (-), 90 % yield) but the stereoselectivity was much lower when monoether ligands were used (for example, R=Me in eq 1-21, 20 %ee (+), 90 % yield).[32] They reasoned that the replacement of the hydroxy group in the Lewis acid by an OMe moiety prevented the chelate formation because of steric interference with the vicinal phenyl group. However, the author thought the another possibility that the selectivities in the reaction by using the

monoether chiral ligands might result from poor Lewis acidity of the neutral central atom and coordination of the ether to the metal might be difficult. The author hoped that the novel strongly activated cationic Lewis acids as shown in eq 1-20 would circumvent the problem of the chelation.



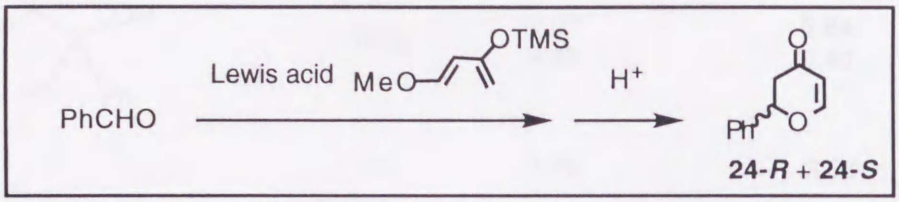
(eq 1-21)

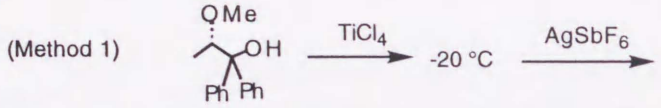
The monoether-coordinated ligands were easily prepared from commercially available (*S*)-ethyl lactate, (*S*)-valine, and (*S*)-mandelic acid as shown in Scheme 1-6. The reaction of chiral esters with Grignard reagents afforded the chiral diols, and the resulted chiral diols were alkylated with methyl iodide to give the chiral methyl ether ligands. 1,1-Dinaphthyl alcohol **29c** was prepared by the reaction of (*S*)-ethyl lactate with BzlBr followed by the reaction with naphthyllithium.

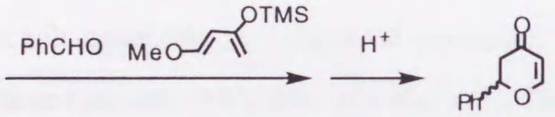

Mg+PhBr
3PhMgBr
78%
NaH, MeI
THF
89%
29a
(S)-ethyl lactate
[α]D -130 (c=2.1, EtOH)
NaH, BzlBr
THF
53%
29b
[α]D -45 (c=0.96,CHCl3)
NaH, BzlBr
THF
91%
Et2O
29c
NaNO2
H2SO4
65%
H2SO4
EtOH
59%
(S)-valine
Mg+PhBr
3PhMgBr
61%
NaH, MeI
THF
73%
30
Mg+PhBr
H2SO4
EtOH
93%
3PhMgBr
61%
NaH, MeI
THF
35%
31a
[α]D -237 (c=1,CHCl3)
NaH, BzlBr
THF
60%
31b

Scheme 1-6.

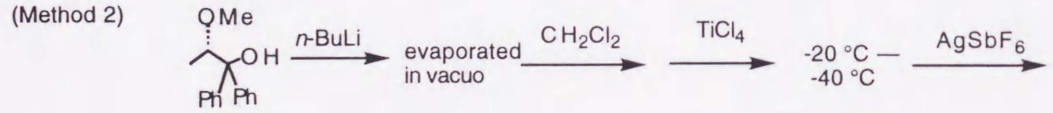
The hetero Diels-Alder reaction of benzaldehyde with Danishefsky's diene was carried out under various conditions by use of $TiCl_4$-$AgSbF_6$-chiral monoether ligand system. The enantiomeric excesses of the products were determined by Daicel OD column (*n*-hexane / *i*-PrOH = 50 / 1). At the beginning, the conditions to prepare the complexes were investigated. In method 1, the complexes were prepared by reaction of the ligand with $TiCl_4$ (eq 1-22), and *n*-BuLi was used for abstraction of H^+ of the hydroxyl group in the method 2 (eq 1-23).

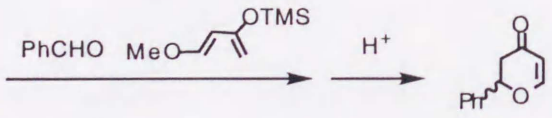






(eq 1-22)



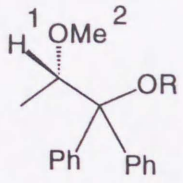


(eq 1-23)

After a lot of experiments, the author found that *n*-BuLi (0.9 equiv. to the ligand) was necessary to prepare the complex because only a small amount of the products was obtained in the method 1. Other bases such as NaH were unproductive. In ^1H NMR in dry $CDCl_3$, the signal of methyl protons of the methoxy group shifted to downfield when titanium chloride was added to the ligand in solution as shown below. This fact indicates the coordination of the methoxy group to the Ti atom occurred. Two couples of the peaks were observed in the complex and the author reasoned that polymer

complexes might exist. Attempt to isolate the Ti complex as solids failed because it was an oil.

^{1}H NMR in dry $CDCl_3$



R	proton 1 (ppm)	proton 2 (ppm)
-$TiCl_3$	5.27 4.90	3.84 3.40
-H	4.29	3.38

In order to optimize the reaction conditions, the effect of Lewis acids, the counter anion of the silver salt, aging time, and the chiral monoether ligand were examined (Table 1-7). In these reactions, 0.9 equiv. of *n*-BuLi and $TiCl_4$ were used as described above to avoid the generation of cationic species other than **33** except for entry 6.

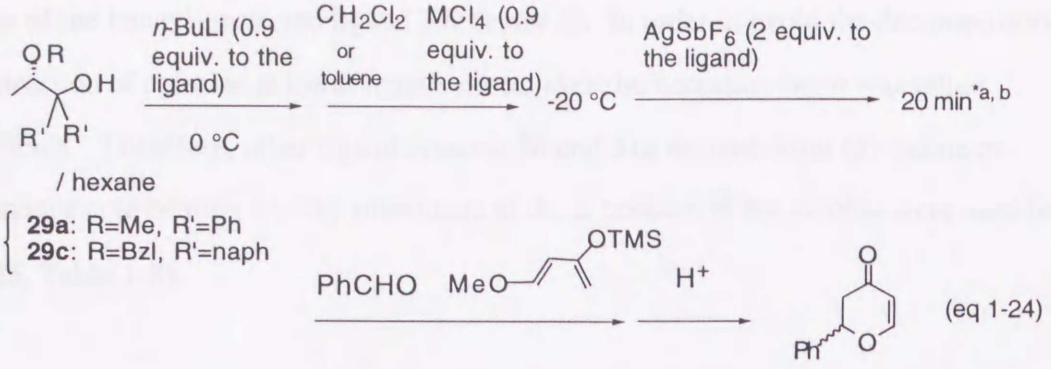


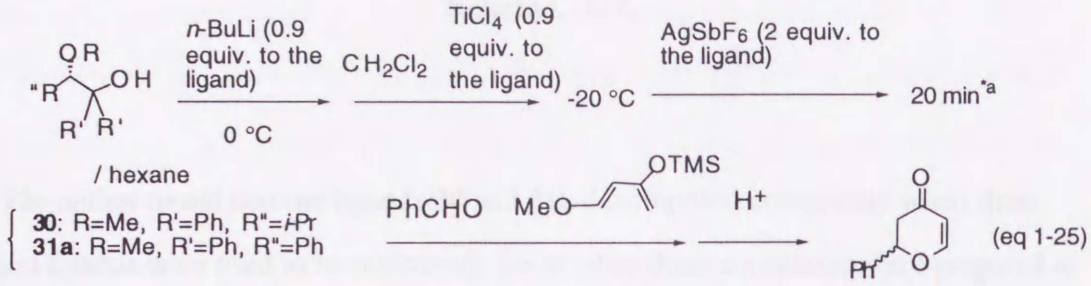
Table 1-7.

entry	catalyst	chiral ligand	solvent	**24-*R*:24-*S***	yield (%)
1	$TiCl_4$+$AgSbF_6$	**29a**	hexane-CH_2Cl_2	65:35	48
2	$TiCl_4$+$AgSbF_6$	**29c**	hexane-CH_2Cl_2	54.5:45.5	48
3	$SnCl_4$+$AgSbF_6$	**29a**	hexane-CH_2Cl_2	52:48	55
4	$TiCl_4$+$AgClO_4$	**29a**	hexane-CH_2Cl_2	53.5:46.5	69*a
5	$TiCl_4$+AgOTf	**29a**	hexane-CH_2Cl_2	51:49	58*a
6	2($TiCl_4$+$AgSbF_6$)	**29a**	hexane-CH_2Cl_2	50:50	50*c
7	$TiCl_4$+$AgSbF_6$	**29a**	hexane-toluene	50:50	47
8	$TiCl_4$+$AgSbF_6$	**29a**	hexane-CH_2Cl_2	54:46	47*b

a. stirred for 1h b. stirred for 10 min
*c. Twice amount of $TiCl_4$ and $AgSbF_6$ compared to the general method was used.

The use of silver hexafluoroantimonate underwent the reactions with higher selectivity (entry 1) in comparison with the use of other silver salts (entries 4 and 5). Excess use of cationic species resulted in no stereoselectivity (entry 6). By the use of hexane-toluene as a solvent, the selectivity was not observed (entry 7). The use of $SnCl_4$ instead of $TiCl_4$ resulted in low selectivity (entry 3). The products in 30 %ee were obtained in entry 1, but partial decomposition of the chiral ligand was also observed. In addition, extensive decomposition of the chiral ligand was observed in the

case of the benzyl-protected ligand **29c** (entry 2). In order to avoid the decomposition, abstraction of chloride at lower temperatures might be necessary but it was rather difficult. Therefore, other ligand systems **30** and **31a** derived from (*S*)-valine or mandelic acid bearing a bulky substituent at the α-position of the alcohol were used (eq 1-25, Table 1-8).



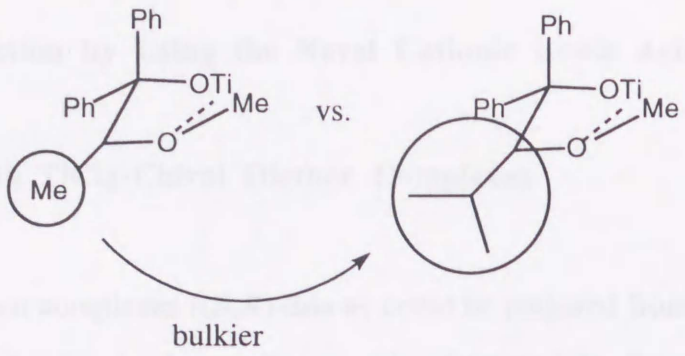
(eq 1-25)

Table 1-8.

entry	catalyst (20 mol%)	ligand	solvent	**24-*R*:24-*S***	yield (%)
1	$TiCl_4$+$AgSbF_6$	**30**	hexane-CH_2Cl_2	50:50	57
2	$TiCl_4$+$AgSbF_6$	**31a**	hexane-CH_2Cl_2	50:50	45 *a
3	$TiCl_4$+$AgSbF_6$	**31a**	hexane-CH_2Cl_2	50:50	51

*a. stirred for 1h

When the ligands **30** and **31a** were used in the reaction, no selectivity was observed (entries 1-3, Table 1-8). This was unexpected results for the author because the chiral transfer would be easier than the case of **29a** because of the bulkiness of the α-substituent (Scheme 1-7).



Scheme 1-7.

The author found that the ligands **30** and **31a** decomposed completely when these chiral ligands were tried to be recovered. Even when these complexes were prepared at low temperature (-78 °C), total decomposition of the chiral ligands was observed. The cationic complexes must be very unstable under the reaction conditions.

In summary, the stereoselectivities up to 30 % ee were observed in hetero Diels-Alder reaction of benzaldehyde with Danishefsky's diene by use of the novel cationic chiral monoether-$TiCl_4$-$AgSbF_6$ system (entry 1 in Table 1-7). However, the instability of the chiral ligands under the conditions to generate cationic species prevented further elaboration of the system.

1-5. Aldol Reaction by Using the Novel Cationic Lewis Acids

A. Reaction with $TiCl_4$-Chiral Diether Complexes

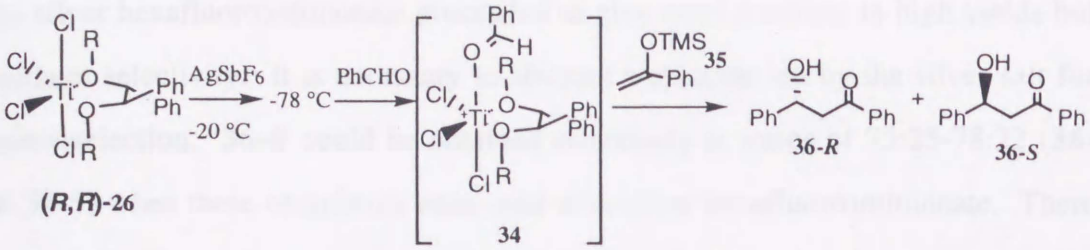
Various titanium complexes ((***R,R***)-**26a-e**) could be prepared from (***R,R***)-**20** with $TiCl_4$ and isolated under Ar as yellow powder (Scheme 1-8). Preparation of these complexes needs careful experimental manipulation as mentioned before. The $TiCl_4$-chiral diether complexes are thermally unstable and should be stored at -20 °C. The complexes bearing longer alkyl chains as ether substituents such as *n*-hexyl could not be isolated as solids.

(***R,R***)-**20a**: R=Me
(***R,R***)-**20b**: R=Bzl
(***R,R***)-**20c**: R=Et
(***R,R***)-**20d**: R=*n*-Pr
(***R,R***)-**20e**: R=*n*-Bu

(***R,R***)-**26a**: R=Me
(***R,R***)-**26b**: R=Bzl
(***R,R***)-**26c**: R=Et
(***R,R***)-**26d**: R=*n*-Pr
(***R,R***)-**26e**: R=*n*-Bu

Scheme 1-8.

The aldol reaction of benzaldehyde and silyl enol ether **35** was carried out (Scheme 1-9)[33] and the enantiomeric excesses of the products were determined by Daicel AS column. After a lot of examinations concerning the aging time, the best result was obtained when the aging time was ca.15-20 min at -20 °C. The results are shown in Table 1-9.



Scheme 1-9.

Table 1-9. Aldol Reaction of Benzaldehyde and Silyl Enol Ether (35) By Using Titanium Tetrachloride-Diether Complexes ((*R*,*R*)-26).

entry	R	**36-*R*:36-*S*** [b]	yield (%)
1 [a]	Et	75:25	81
2 [a]	*n*-Pr	76.5:23.5	76
3	Me	76.5:23.5	80
4	Et	77:23	86
5	*n*-Pr	78:22	82

a The complexes were prepared *in situ*.

b Enantioselectivity was determined by HPLC analysis (Daicel AS column, *i*-PrOH:*n*-hexane=5:95).

The reactions using the complexes (***R,R*)-26** without abstraction of a chloride ion by silver hexafluoroantimonate proceeded to give aldol products in high yields but without selectivity. It is necessary to abstract a chloride ion by the silver salt for stereoselection. **36-*R*** could be obtained selectively in ratios of 75:25-78:22 (**36-*R*:36-*S***) when these complexes were used with silver hexafluoroantimonate. There were little effects of the diether substituents on the selectivity, but the author reasoned the chain-like ether substituents (*n*-alkyl substituents) extended toward the quasi-equatorial direction in the coordinated conformation and did not affect the chiral environments. To overcome the problem, bulkier dibenzyl diether was used but its $TiCl_4$ complex was very unstable and decomposition occurred even at -20 °C. In addition to the reactions with the isolated complexes, the author also investigated the reactions with the complexes prepared *in situ* (entries 1 and 2) and found that there was no change of the selectivity compared with the case of the isolated complexes. The fact suggests the reaction will proceed selectively by the use of the complexes prepared *in situ* without isolation of the complexes.

B. Reaction with $TiCl_3(OR)$-Chiral Diether Complexes

$TiCl_3(OR)$-chiral diether complexes (***R,R*)-37** were also prepared from (***R,R*)-20** with $TiCl_3(OR)$ (eq 1-26, eq 1-27, and Scheme 1-10) and the aldol reaction was carried out by using the complexes. $Ti(OR)_4$ could be prepared from $Ti(O\text{-}i\text{-}Pr)_4$ and ROH at 130 °C while the resulting isopropanol was distilled out (eq 1-26).[34] $TiCl_3(OR)$ was prepared by disproportionation of titanium tetraalkoxide and titanium tetrachloride at low temperatures. Attempt to prepare $TiCl_3(OR)$ at higher temperatures underwent polymerization of titanium compounds which could not be dissolved in the solvent. The appropriate temperature to prepare these $TiCl_3(OR)$ strongly depended on the substituents R (eq 1-27). These $Ti(OR)_4$ and $TiCl_3(OR)$ were prepared and used under Ar. The chiral diether complexes (***R,R*)-37** could be prepared by the similar method of $TiCl_4$ complexes. However, $TiCl_3$(O-amyl)-chiral

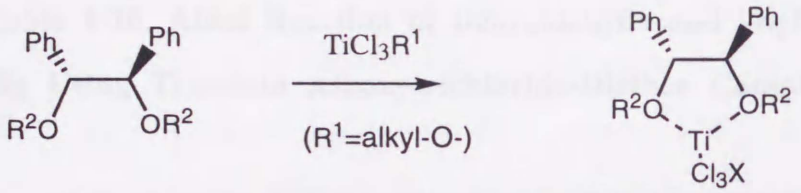
diether complexes could not be prepared probably because of the steric hinderance of the amyl substituent. $TiCl_3(OBzl)$ was tried to prepare, but decomposition occurred even at -78 °C.

$$Ti(O\text{-}i\text{-}Pr)_4 + 4ROH \longrightarrow Ti(OR)_4 + 4i\text{-}PrOH$$

(R=neopentyl, cyclohexyl, diisopropylmethyl)

(eq 1-26)

$$Ti(OR)_4 + 3TiCl_4 \longrightarrow 4TiCl_3(OR) \qquad \text{(eq 1-27)}$$



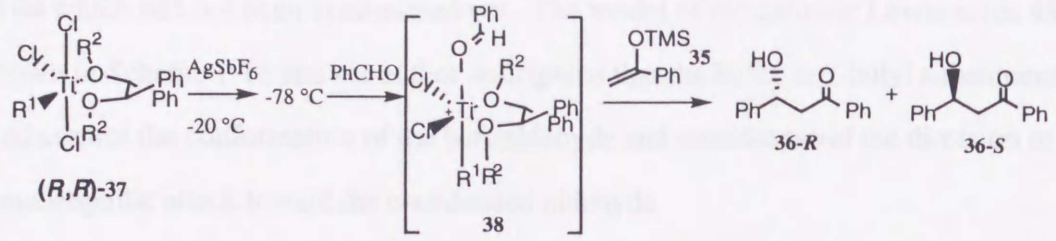
(*R*,*R*)-20a: R^2=Me
(*R*,*R*)-20b: R^2=Bzl
(*R*,*R*)-20c: R^2=Et
(*R*,*R*)-20d: R^2=*n*-Pr
(*R*,*R*)-20e: R^2=*n*-Bu

(*R*,*R*)-37a: R^2=Me, R^1=*i*-PrO
(*R*,*R*)-37b: R^2=Et, R^1=*i*-PrO
(*R*,*R*)-37c: R^2=Et, R^1=EtO
(*R*,*R*)-37d: R^2=Et, R^1=cyclohexyloxy
(*R*,*R*)-37e: R^2=Et, R^1=neopentyloxy
(*R*,*R*)-37f : R^2=Me,R^1=diisopropylmethyloxy

Scheme 1-10.

The aldol reaction by using these complexes proceeded smoothly to give products in excellent yields as shown in Table 1-10. In addition, **36-*R*** was the major product in all cases. The substituent R^1 was smaller, the selectivity of **36-*R*** was higher. Judging from the selectivities, the author proposes the reaction intermediate **38** in the reaction with **(*R*,*R*)-37** (Scheme 1-11). In **38**, strongly coordinating R^1 group prefer to occupy the trans site to the weakly coordinating benzaldehyde. The strong electron-donating property of the R^1 group weakens the coordination of the benzaldehyde resulting in the lower selectivity in the aldol reaction in comparison with the

corresponding $TiCl_4$-chiral diether system. The modification of the chiral ligand system will give higher selectivities, but still the novel cationic system is found to have utility for some reactions.



Scheme 1-11.

Table 1-10. Aldol Reaction of Benzaldehyde and Silyl Enol Ether (35) By Using Titanium Alkoxytrichloride-Diether Complexes ((*R*,*R*)-37).

entry	R^1	R^2	**36-*R*:36-*S*** [b]	yield (%)
1	O-*i*-Pr	Me	57.5:42.5	96
2	O-*i*-Pr	Et	61:39	95
3	O-cyclohexyl	Et	54:46	82
4	O-neopentyl	Et	57:43	88
5[a]	O-neopentyl	Et	55:45	81
6	O-diisopropylmethyl	Me	52:48	91
7	O-ethyl	Et	61:39	93

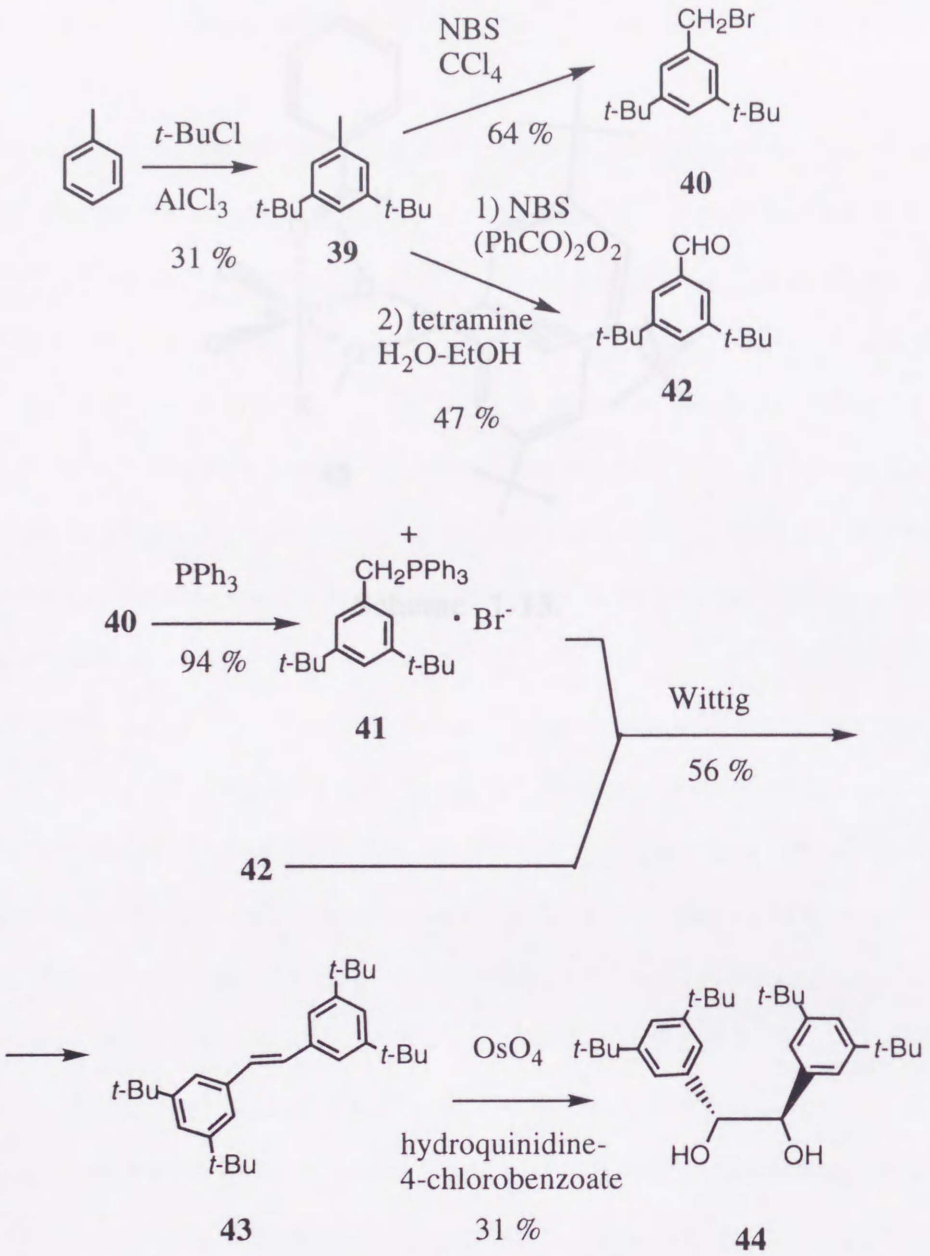
a Reaction was carried out in dichloromethane-isobutyronitrile.

b Enantioselectivity was determined by HPLC analysis (Daicel AS column, *i*-PrOH:*n*-hexane=5:95).

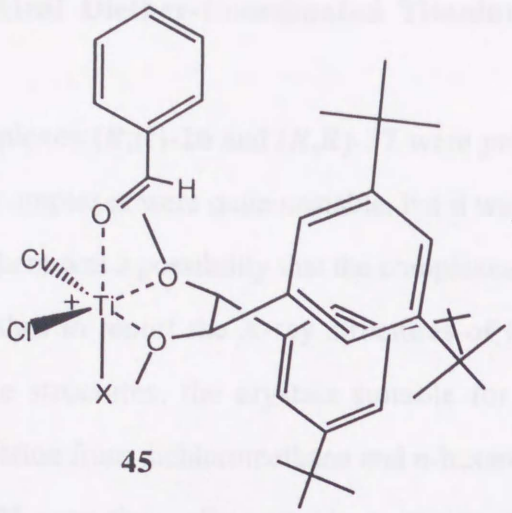
1-6. Synthesis of the Modified Chiral Ligands

The author also synthesized the modified chiral hydrobenzoin for the chirality transfer system. The author selected (*R*,*R*)-1,2-bis(3,5-di-*tert*-butylphenyl)ethane-1,2-diol **44** which had not been synthesized yet. The model of the cationic Lewis acids **45** is shown in Scheme 1-13 and the author anticipated that the bulky *tert*-butyl substituents would control the conformation of the benzaldehyde and would control the direction of the nucleophilic attack toward the coordinated aldehyde.

The chiral diol **44** was prepared as follows: Friedel-Crafts alkylation of toluene with *t*-BuCl in the presence of $AlCl_3$ afforded 1,3-di-*tert*-butyl-5-methylbenzene **39**[35] and the resulting **39** was reacted with NBS to give **40**[36] in 64 % yield. **39** was oxidized to aldehyde **42**[37] and the Wittig reaction of phosphonium bromide **41** and **42** afforded **43**[38] which was obtained as a *cis-trans* mixture in a ratio of 1:25 in 56 % yield. Some isomerization procedures were tried but yields were not good. The author decided to conduct the next procedure without isomerization. Osmium oxidation of **43** by Sharpless method[28] was the best way to obtain the diol **44**. Other reaction conditions were tried but the products could be obtained in quite low yields. The optical purity of the diol **44** was determined by Daicel column OD and it was 45 %ee (*R*). The optical resolution is possible by use of the column. The new chiral diol will widen the utility as a chiral ligand not only for the novel cationic Lewis acid system but also for the Lewis acid system bearing the chiral diol.


NBS
CCl_4
64 %
CH_2Br
t-Bu
t-Bu
40
t-BuCl
$AlCl_3$
31 %
39
1) NBS
$(PhCO)_2O_2$
2) tetramine
H_2O-EtOH
47 %
CHO
42
PPh_3
40
94 %
CH_2PPh_3
Br^-
41
Wittig
56 %
42
OsO_4
hydroquinidine-
4-chlorobenzoate
31 %
HO
OH
43
44

Scheme 1-12.



45

Scheme 1-13.

1-7. Structure of Chiral Diether-Coordinated Titanium Complexes

The titanium complexes (*R*,*R*)-**26** and (*R*,*R*)-**37** were prepared and isolated as mentioned above. The complexes were quite unstable, but it was of interest to confirm the structures because there was a possibility that the complexes were polymer. In this section, the author wishes to report the X-ray structures of (*R*,*R*)-**26d** and (*R*,*R*)-**37a**. To confirm these structures, the crystals suitable for X-ray analysis were prepared by recrystallization from dichloromethane and *n*-hexane in a freezer (-20 °C). The crystals of (*R*,*R*)-**26** were thermally unstable as mentioned above but could be handled under an Ar atmosphere in a glove bag at room temperature for a short period. A single crystal of (*R*,*R*)-**26d** in a sealed capillary was used for X-ray diffraction measurements at ca. -5 °C, but even at this low temperature significant decomposition took place during the measurement. Thus, the obtained data were not quite good (*R*=9.5%) but the position of the atoms could be determined. In contrast, crystals of (*R*,*R*)-**37a** were stable at room temperature and X-ray diffraction of a single crystal of (*R*,*R*)-**37a** could be measured at room temperature in a sealed capillary without any problems. The obtained data showed very good quality (*R*=3.8 %). The ORTEP drawings of (*R*,*R*)-**26d** and (*R*,*R*)-**37a** are shown in Figures 1-2 and 1-3, and the selected bond distances and angles are listed in Table 1-11. These structures show six-coordinate geometry around the titanium center. To our delight the substituents (*n*-propyl in (*R*,*R*)-**26d** and methyl in (*R*,*R*)-**37a**) on the ether oxygen atoms are oriented *trans* to the phenyl group on the neighboring carbon although these oxygen atoms are not completely sp^3 hybridized (the sum of the bond angles around the oxygen atoms are 347.4° and 355.6° in (*R*,*R*)-**26d**, and 345.7° and 347.1° in (*R*,*R*)-**37a**).

The structure of (*R*,*R*)-**37a** is consistent with the reported principle that the strongest ligand (Ti-O-*i*-Pr in (*R*,*R*)-**37a**) prefers a *trans* position to the weakest ligand (Ti-O(ether)). The bond distance of Ti-O(isopropoxide) (1.707(5) Å, **d** in Table 1-11) is comparable to the reported distances 1.742(6) Å in $[Ti(O\textit{i}\text{-Pr})Cl_5]^{2-}$,

1.726(4) Å in Ti(O-*i*-Pr)$Cl_3(THF)_2$, 1.721(2) Å in Ti(O-*i*-Pr)$Cl_3(Et_2O)$(PhCHO), and 1.702(4) Å in [Ti(O-*i*-Pr)Cl_2(μ-Cl)(OC(OMe)C_6H_5)]$_2$.[39] The distance between Ti and the ether oxygen (2.226(5) Å, **a** in Table 1-11) *trans* to the isopropoxide was longer than that between Ti and the *cis* ether oxygen (2.138(4) Å, **b** in Table 1-11). The strong *trans* influence of the isopropoxide ligand has also been pointed out in Ti(O-*i*-Pr)$Cl_3(Et_2O)$(PhCHO) **10** and Ti(O-*i*-Pr)$Cl_3(THF)_2$ **11**.[23]

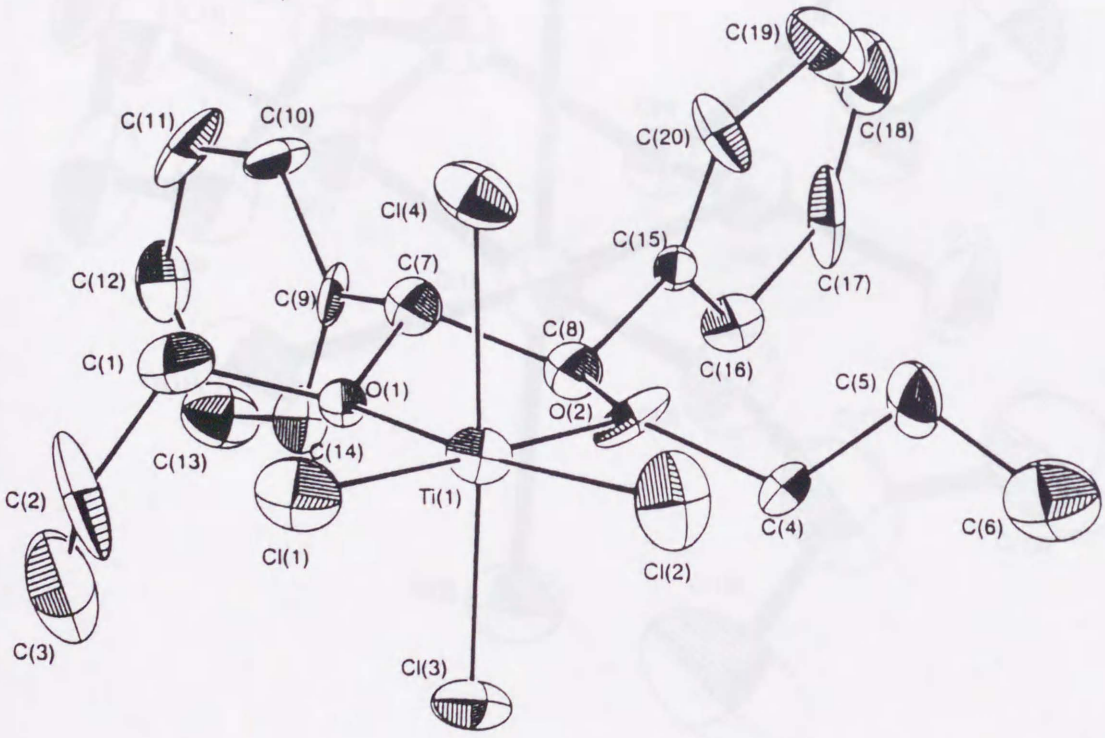


Figure 1-2. ORTEP drawing of (*R*,*R*)-26d showing the thermal ellipsoids at the 30% probability level.

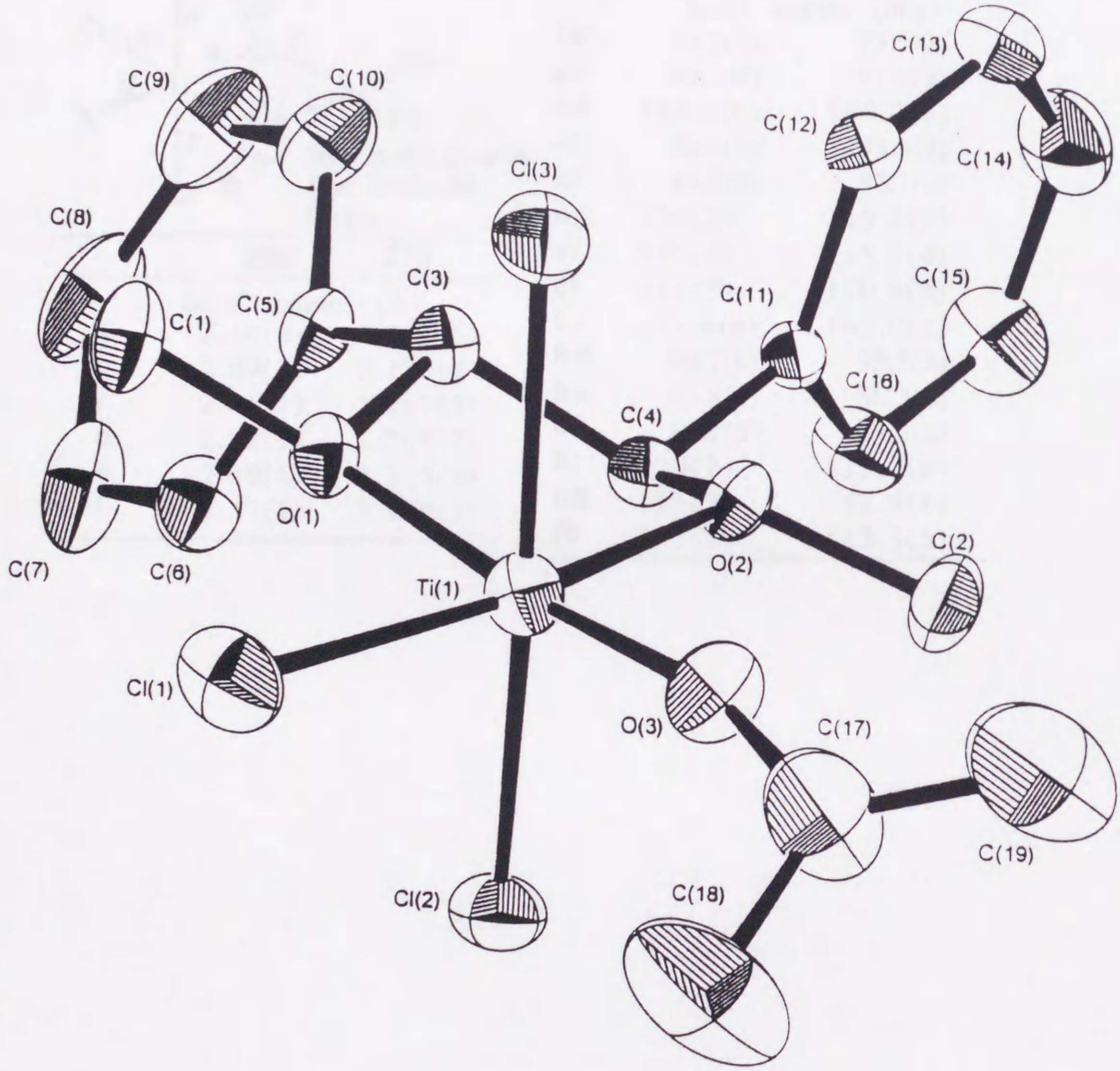
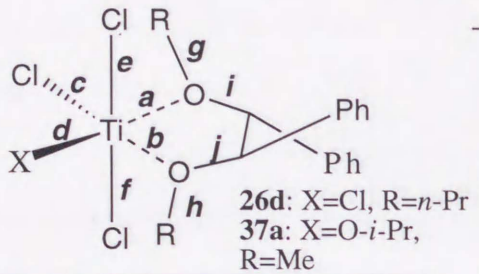


Figure 1-3. ORTEP drawing of (*R*,*R*)-37a showing the thermal ellipsoids at the 30% probability level.

Table 1-11. Selected Bond Lengths and Bond Angles for (*R*,*R*)-26d and (*R*,*R*)-37a.



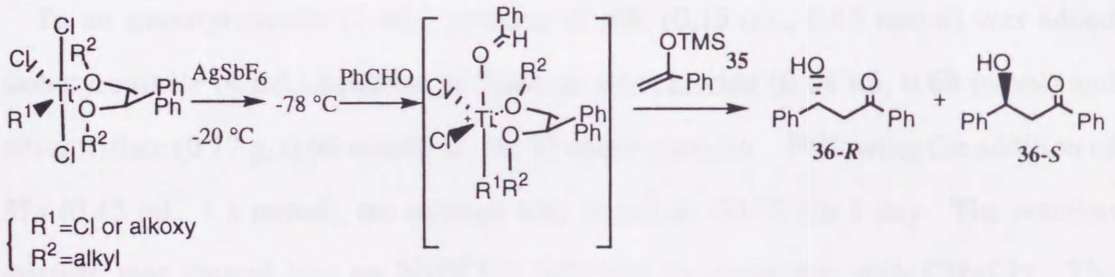
26d: X=Cl, R=*n*-Pr
37a: X=O-*i*-Pr, R=Me

	26d	37a
	bond lengths (Å)	
a	2.14(2)	2.226(5)
b	2.09(2)	2.138(4)
c	2.21(1)	2.267(3)
d	2.22(1)	1.707(5)
e	2.30(1)	2.315(3)
f	2.27(1)	2.339(3)

	26d	37a
	bond angles (deg)	
ab	74.2(7)	73.6(2)
ac	99.2(6)	91.8(2)
ad	164.9(6)	169.0(2)
ae	84.6(5)	83.3(2)
af	84.8(5)	83.7(2)
ag	120(2)	119.8(4)
ai	117(1)	115.3(4)
gi	111(2)	110.6(5)
bc	173.4(6)	165.0(2)
bd	90.7(6)	95.5(2)
be	87.8(6)	86.3(2)
bf	85.1(6)	83.3(2)
bj	120(1)	115.6(4)
bh	125(2)	117.9(4)
jh	111(2)	113.6(5)

1-8. Summary

The exploitation of novel cationic Lewis acids was performed. From the experiments as described above, the author found that titanium(IV) chloride and titanium(IV) alkoxytrichloride were suitable for the asymmetric aldol reaction. In addition, the titanium complexes (***R*,*R*)-26d** and (***R*,*R*)-37a** were isolated and the structures were determined by X-ray analysis. These results will widen the chemistry of Lewis acids because the novel cationic Lewis acids will develop the potential for the reaction of unactivated substrates or reactants.



1-9. Experimental Section

General.

^{1}H NMR spectra were recorded at 400 MHz (JEOL EX400) in $CDCl_3$. Chemical shifts (δ) are reported in ppm downfield from internal tetramethylsilane or from residual chloroform (δ=7.26). The preparation of aldimines are described in Chapter 2. Monoether chiral ligands were prepared according to the literature[32] and $[\alpha]_D$ were consistent with the data in the literature. All reactions were conducted under Ar except for the OsO_4 oxidation procedures.

[4+2]Type Cycloaddition of Aldimine 60c with 2-Silyloxy-1,3-butadiene 57a by Use of Cationic Lewis Acid.

To an isobutyronitrile (2 mL) solution of **60c** (0.15 mL, 0.45 mmol) was added isobutyronitrile (4 mL) solution of titanium tetrachloride (0.08 ml, 0.68 mmol) and silver triflate (0.17 g, 0.69 mmol) at -30 °C under nitrogen. Following the addition of **57a** (0.45 mL, 1.8 mmol), the mixture was stirred at -30 °C for 1 day. The reaction mixture was poured into aq $NaHCO_3$ followed by extraction with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The residue was dissolved in THF and 1.8 mmol of TBAF (in THF solution) was added to the solution. The reaction mixture was stirred for 10 h, quenched with water, extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$. After the solvent was removed in vacuo, the crude product was separated by recycle HPLC (JAI LC 908, JAIGEL-1H and 2H, 1,2-dichloroethane). 74 mg, (49 %)

64b: colorless oil . ^{1}H NMR ($CDCl_3$): δ 0.60 (d, J = 6.3 Hz, 3H), 1.06 (d, J = 6.3 Hz, 3H), 1.70-1.85 (m, 1H), 2.36-2.45 (m, 1H), 2.70-2.85 (m, 2H), 2.98-3.10 (m, 1H), 3.20-3.25 (m, 1H), 3.62 (d, J = 14.0 Hz, 1H), 3.58-3.63 (m, 1H), 3.90 (d, J = 14.0 Hz, 1H), 4.63-4.70 (m, 1H), 7.20-7.75 (m, 10H).

General Procedures for Diels-Alder Reaction of Methacrolein with Cyclopentadiene.

To a stirred solution of the cationic Lewis acid (Lewis acid: $AgSbF_6$: chiral diether=1:0.8:1, aging conditions are described in 1-3-B) was added methacrolein (1 equiv. to the chiral diether) and cyclopentadiene (3 equiv. to the chiral diether) at -78 °C and stirred for ca. 6 h. After usual work-up, the ratio of exo:endo was determined by ^{1}H NMR. The product was acetalized according to the literature.[30]

Diels-Alder adduct 21 (exo).

^{1}H NMR 0.68 (d, 1 H, J = 12.2 Hz), 0.94 (s, 3 H), 1.20-1.62 (m, 2 H), 2.75-2.82 (m, 2 H), 3.17 (dd, 1 H, J = 11.7, 4.0 Hz), 6.02-6.05 (m, 1 H), 6.21-6.24 (m, 1 H), 9.60 (s, 1H).

The peak of aldehyde proton of endo compound **22** is δ 9.32 ppm.

Acetal 23-exo-1

^{1}H NMR 0.71 (dd, 1 H, J = 12.2, 2.6 Hz), 0.82 (s, 3 H), 1.14 (d, 3 H, J = 6.5 Hz), 1.29 (d, 3 H, J = 6.5 Hz), 1.13-1.49 (m, 2 H), 1.15 (d, 3 H, J = 8.8 Hz), 1.70-1.79 (m, 2 H), 2.63 (s, 1 H), 2.70 (s, 1 H), 3.87-3.92 (m, 1 H), 4.19-4.30 (m, 1H), 4.64 (s, 1 H), 6.02-6.10 (m, 2 H),.

Acetal 23-exo-2

^{1}H NMR 0.71 (dd, 1 H, J = 11.7, 2.4 Hz), 0.84 (s, 3 H), 1.10-1.15 (m, 2 H), 1.17 (d, 3 H, J = 6.3 Hz), 1.33 (d, 3 H, J = 6.3 Hz), 1.57 (d, 1 H, J = 8.3 Hz), 1.64 (dd, 1 H, J = 12.2, 3.4 Hz), 1.76 (dt, 1 H, J = 12.2, 6.3 Hz), 2.72 (s, 2 H), 3.82-3.92 (m, 1 H), 4.22-4.32 (m, 1H), 4.68 (s, 1 H), 6.07-6.10 (m, 2 H),.

General Procedures for Hetero Diels-Alder Reaction of Benzaldehyde with Danishefsky's Diene by Using Monoether-Coordinated Titanium Complex.

To a stirred solution of **29a** (0.24 g, 1 mmol) in hexane (3 mL) was added *n*-BuLi (0.57 mL, 0.9 mmol) at 0 °C and the mixture was stirred for 15 min. CH_2Cl_2 (10 mL) and $TiCl_4$ (0.1 mL, 0.9 mmol) was added to the solution and the temperature was cooled to -20 °C. After stirring for 10 min, $AgSbF_6$ (0.69 g, 2 mmol) in CH_2Cl_2 was added to the mixture and stirred for 20 min. Benzaldehyde (0.1 mL, 1 mmol) and Danishefsky's diene (0.39 mL, 2 mmol) was added successively to the mixture and stirred for several hours. The work-up procedure was the same as that in the literature.[31] The crude products were purified by column chromatography (hexane / CH_3COOEt = 3 / 2), and the enantiomeric excesses were determined by Daicel OD column (*n*-hexane / *i*-PrOH = 50 / 1).

General Procedure for the Preparation of Chiral Diethers.

(*R*,*R*)-1,2-diphenylethane-1,2-diol[28] and (*R*,*R*)-1,2-diphenylethane-1,2-diol dimethyl ether[3] were prepared according to the literatures. Other diethers were prepared by modified Johnstone's method[29] as follows; To DMSO (100 mL) was added powdered KOH (22 g) at r.t.. After stirring for ca. 5 min, (*R*,*R*)-1,2-diphenylethane-1,2-diol 10.6 g (50 mmol) in DMSO (50 mL) and alkyl halide (199 mmol) were added to the solution successively (alkyl halide was added very slowly because of the exothermic reaction). The reaction mixture was stirred for 1 day at r.t. and was treated with H_2O. The mixture was extracted with dichloromethane, and the combined organics were washed with water. After the solvents were evaporated, the crude products were purified by column chromatography (Merck silica gel 7734: ether / *n*-hexane = 1 / 5).

(*R*,*R*)-1,2-Diphenylethane-1,2-diol Dimethyl Diether (*R*,*R*)-20a.

^1H NMR 3.34 (s, 6 H), 4.70 (s, 2 H), 7.13-7.27 (m, 10 H).

(*R*,*R*)-1,2-Diphenylethane-1,2-diol Dibenzyl Diether (*R*,*R*)-20b.

^{1}H NMR 4.38 (d, 2 H, J = 12.0 Hz), 4.58 (d, 2 H, J = 12.0 Hz), 4.59 (s, 2 H), 7.10-7.35 (m, 10 H).

(*R*,*R*)-1,2-Diphenylethane-1,2-diol Diethyl Diether (*R*,*R*)-20c.

^{1}H NMR 1.26 (t, 6 H, J = 6.8 Hz), 3.50-3.59 (m, 4 H), 4.55 (s, 2 H), 7.17-7.40 (m, 10 H).

(*R*,*R*)-1,2-Diphenylethane-1,2-diol Di-*n*-propyl Diether (*R*,*R*)-20d.

^{1}H NMR 0.99 (t, 6 H, J = 7.2 Hz), 1.65-1.72 (m, 4 H), 3.39-3.49 (m, 4 H), 4.53 (s, 2 H), 7.16-7.50 (m, 10 H).

General Procedures for the Preparation of $TiCl_4$-Diether Complexes.

To a stirred solution of diether (19 mmol) in dry dichloromethane (15 mL) was added $TiCl_4$ (12.7 mmol) very slowly at -20°C. After stirring for a few minutes, dry *n*-hexane (ca. 50-100 mL) was added to the solution. The yellow precipitates were filtered by using glass wool and washed with dry *n*-hexane. The (*R*,*R*)-1,2-diphenylethane-1,2-diol dialkyl diether (yellow powder) was collected under argon and was dried in vacuo (The powder was unstable at r.t. and moisture sensitive so that rapid manipulation was necessary!).

$TiCl_4$-(*R*,*R*)-1,2-Diphenylethane-1,2-diol Dimethyl Diether Complex (*R*,*R*)-26a.

^{1}H NMR 3.81 (s, 6 H), 5.20 (s, 2 H), 7.20-7.40 (m, 10 H).

$TiCl_4$-(*R*,*R*)-1,2-Diphenylethane-1,2-diol Diethyl Diether Complex (*R*,*R*)-26c.

^{1}H NMR 0.87 (t, 6 H, J = 6.6 Hz), 4.12-4.16 (m, 2 H), 4.61-4.64 (m, 2 H), 5.46 (s, 2 H), 7.25-7.40 (m, 10 H).

$TiCl_4$-(*R*,*R*)-1,2-Diphenylethane-1,2-diol Di-*n*-propyl Diether Complex (*R*,*R*)-26d.

^{1}H NMR 0.56 (t, 6 H, J = 7.4 Hz), 1.88-1.91 (m, 2 H), 1.43-1.51 (m, 2 H), 3.81-3.89 (m, 2 H), 4.42-4.48 (m, 2 H), 5.42 (s, 2 H), 7.18-7.31 (m, 10 H).

$TiCl_4$-(*R*,*R*)-1,2-Diphenylethane-1,2-diol Di-*n*-butyl Diether Complex (*R*,*R*)-26e.

^{1}H NMR 0.59 (t, 6 H, J = 7.3 Hz), 0.76-1.19 (m, 4 H), 1.34-1.45 (m, 2 H), 1.74-1.88 (m, 2 H), 3.88 (dt, 2 H, J = 4.9, 11.7 Hz), 4.45 (dt, 2 H, J = 4.9, 11.7 Hz), 5.40 (s, 2 H), 7.20-7.28 (m, 10 H).

General Procedures for the Preparation of $Ti(OR)_4$.

$Ti(OR)_4$ were prepared according to the literature[34] except for $Ti(OEt)_4$.

$TiCl_3$(O-*i*-propyl)

^{1}H NMR 1.55 (d, 6 H, J = 5.8 Hz), 5.16-5.20 (m, 1 H).

$TiCl_3$(OEt)

^{1}H NMR 1.64 (t, 3 H, J = 7.0 Hz), 4.90-4.95 (m, 2 H).

$TiCl_3$(O-cyclohexyl)

^{1}H NMR 1.41-1.54 (m, 4 H), 1.86-1.94 (m, 4 H), 2.00-2.11 (m, 2 H), 4.95-5.05 (m, 1 H).

$TiCl_3$(O-neopentyl)

^{1}H NMR 1.10 (s, 9 H), 3.85-3.91 (m, 2 H).

$TiCl_3$(O-diisopropylmethyl)

^{1}H NMR 1.08 (d, 6 H, J = 6.5 Hz), 1.17 (d, 6 H, J = 6.5 Hz), 2.07-2.16 (m, 2 H), 4.50 (t, 1 H, J = 5.8 Hz).

General procedures for the preparation of $TiCl_3(OR)$-diether complexes were similar to those for $TiCl_4$-diether complexes.

$TiCl_3$(O-*i*-Pr)-(*R*,*R*)-1,2-Diphenylethane-1,2-diol Dimethyl Diether Complex (*R*,*R*)-37a.

^1H NMR 1.56 (d, 3 H, J = 5.8 Hz), 1.59 (d, 3 H, J = 5.8 Hz), 3.56 (s, 3 H), 3.79 (s, 3 H), 5.01 (d, 1 H, J = 9.9 Hz), 5.10 (d, 1 H, J = 9.9 Hz), 5.38-5.45 (m, 1 H), 7.09-7.24 (m, 10 H).

$TiCl_3$(O-*i*-Pr)-(*R*,*R*)-1,2-Diphenylethane-1,2-diol Diethyl Diether Complex (*R*,*R*)-37b.

^1H NMR 1.03-1.11 (m, 6 H), 1.47 (d, 3 H, J = 6.4 Hz), 1.49 (d, 3 H, J = 6.4 Hz), 3.65-3.80 (m, 1 H), 3.95-4.05 (m, 1 H), 4.15-4.25 (m, 1 H), 4.40-4.50 (m, 1 H), 5.12 (d, 1 H, J = 8.0 Hz), 5.26 (d, 1 H, J = 8.0 Hz), 5.29-5.33 (m, 1 H), 7.00-7.20 (m, 10 H).

$TiCl_3$(OEt)-(*R*,*R*)-1,2-Diphenylethane-1,2-diol Diethyl Diether Complex (*R*,*R*)-37c.

^1H NMR 1.20-1.28 (m, 6 H), 1.64 (t, 3 H, J = 6.8 Hz), 3.81-3.85 (m, 1 H), 4.15-4.19 (m, 1 H), 4.39-4.43 (m, 1 H), 4.61-4.66 (m, 1 H), 5.15 (q, 2 H, J = 6.8 Hz), 5.29 (d, 1 H, J = 10.3 Hz), 5.39 (d, 1 H, J = 10.3 Hz), 7.10-7.40 (m, 10 H).

$TiCl_3$(O-cyclohexyl)-(*R*,*R*)-1,2-Diphenylethane-1,2-diol Diethyl Diether Complex (*R*,*R*)-37d.

^1H NMR 1.20-1.50 (m, 10 H), 1.70-2.05 (m, 4 H), 2.25-2.33 (m, 2 H), 3.85-3.93 (m, 1 H), 4.15-4.26 (m, 1 H), 4.37-4.50 (m, 1 H), 4.60-4.72 (m, 1 H), 5.23 (d, 1 H, J = 8.0 Hz), 5.30-5.40 (m, 1 H), 5.42 (d, 1 H, J = 8.0 Hz), 6.95-7.60 (m, 10 H).

$TiCl_3$(O-neopentyl)-(*R*,*R*)-1,2-Diphenylethane-1,2-diol Diethyl Diether Complex (*R*,*R*)-37e.

^1H NMR 1.15 (s, 9 H), 1.25-1.35 (m, 6 H), 3.83-3.88 (m, 1 H), 4.18-4.22 (m, 1 H), 4.36-4.41 (m, 1 H), 4.62-4.67 (m, 1 H), 4.88 (s, 2 H), 5.33 (d, 1 H, J = 9.8 Hz), 5.40 (d, 1 H, J = 9.8 Hz), 7.05-7.35 (m, 10 H).

$TiCl_3$(O-diisopropylmethyl)-(*R*,*R*)-1,2-Diphenylethane-1,2-diol Dimethyl Diether Complex (*R*,*R*)-37f.

^1H NMR 1.16 (d, 3 H, J = 6.8 Hz), 1.23 (d, 3 H, J = 7.3 Hz), 1.35 (d, 3 H, J = 6.8 Hz), 1.40 (d, 3 H, J = 6.8 Hz), 2.22-2.29 (m, 2 H), 3.59 (s, 3 H), 3.83 (s, 3 H), 4.60 (t, 1 H, J = 5.3 Hz), 5.03-5.06 (bm, 1 H), 5.20-5.22 (bm, 1 H), 7.10-7.40 (m, 10 H).

General Procedures for Aldol Reactions of Benzaldehyde with Silyl Enol Ether by Using Titanium Complex.

To a stirred solution of the titanium complex (1.3 mmol), molecular sieves 4A (30 mg), and 2,6-di-*tert*-butyl-4-methylpyridine (1 drop) in dry CH_2Cl_2 (3 mL) was added silver hexafluoroantimonate (1.9 mmol) in dry CH_2Cl_2 (2 mL) at -20 °C. After stirring for 15 min, the temperature was cooled to -78 °C and the mixture was stirred for 20 min. Benzaldehyde (1.3 mmol) and silyl enol ether (2.5 mmol) were added to the solution successively and the mixture was stirred overnight at the same temperature. The reaction mixture was quenched with 1M HCl, and the mixture was extracted with ether. The organics were dried over Na_2SO_4, and the solvents were evaporarted to give crude aldol products. The products were purified by column chromatography (Merck silica gel 7734: gradient elution, CH_3COOEt / *n*-hexane = 1 / 5 -100 / 0). The products were identified according to the literature.[10] The enantioselectivity was determined by HPLC (Daicel Chiralcel AS, *i*-PrOH:*n*-hexane = 5:95).

General Procedure for Aldol Reaction of Benzaldehyde with Silyl Enol Ether by Using Titanium Complex Prepared *in situ*.

To a stirrded solution of diether (1.5 mmol), molecular sieves 4A (30 mg), and 2,6-di-*tert*-butyl-4-methylpyridine (1 drop) in dry CH_2Cl_2 (3 mL) was added 1 mmol of titanium tetrachloride at -20 °C. After stirring for 2 min, silver hexafluoroantimonate

(1.5 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise to the solution at -20 °C. After the mixture was stirred for 15 min, the temperature was cooled to -78 °C and the reaction mixture was stirred for 20 min. The procedures of the aldol reaction were the same as above.

Synthesis of (*R*,*R*)-1,2-Bis(3,5-di-*tert*-butylphenyl)ethane-1,2-diol 44.

Preparation of 1,3-Di-*tert*-butyl-5-methylbenzene 39.

To a stirred solution of toluene 96 mL (0.9 mol) and *t*-BuCl 196 mL (1.8 mol) was added dropwise $AlCl_3$ 4.7 g (0.035 mol) over half day and the reaction mixture was stirred for 1 day. The mixture was poured into ice-HCl aq. slowly and the organics were evaporated. The crude product was purified by vacuum distillation (78-80 °C / 1.4 mmHg). colorless oil, 170.3 g (31%)

^{1}H NMR 1.40 (s, 18 H), 2.40 (s, 3 H), 7.08 (s, 2 H), 7.30 (s, 1 H).

Preparation of 1-(Bromomethyl)-3,5-di-*tert*-butylbenzene 40.

A mixture of 147 g (0.7 mol) of 1,3-di-*tert*-butyl-5-methylbenzene **39**, 128 g (0.7 mol) of *N*-bromosuccinimide, and 200 mL of CCl_4 was heated under reflux for 18 h. The mixture was allowed to cool to r.t. and was filtered through Celite. The filtrate was concentrated and the residual oil was distilled through a Vigreux column (120-125 °C / 6 mmHg). colorless oil, 128 g (64 %)

^{1}H NMR 1.40 (s, 18 H), 4.55 (s, 2 H), 7.30 (s, 2 H), 7.45 (s, 1 H).

Preparation of 3,5-Di-*tert*-butylbenzyl Phosphonium Bromide 41.

A mixture of PPh_3 (122 g, 0.47 mol) and 1-(bromomethyl)-3,5-di-*tert*-butylbenzene **40** (128 g, 0.47 mol) in toluene (1 L) was heated at 80 °C for 2 h and cooled to r.t.. The mixture was concentrated and the residual solid was washed with ether. The white solid was dried in vacuo to give the product. white powder, 237 g (94 %)

^{1}H NMR 1.36 (s, 18 H), 7.70-7.73 (m, 3 H), 10.00 (s, 1 H).

Preparation of 3,5-Di-*tert*-butylbenzaldehyde 42.

A solution of 131 g (0.64 mol) of **39**, 171 g (0.96 mol) of *N*-bromosuccinimide, and 0.57 g of benzoyl peroxide in 400 mL of CCl_4 was heated to reflux for 4 h. After filtration, the solvent was evaporated. The residue was added to a solution of 246 g (1.8 mol) of tetramine in H_2O (170 mL) and EtOH (170 mL), and the solution was heated to reflux for 4 h. Then 114 mL of concentrated HCl was added to the mixture and refluxing was continued for 30 min. The organic product was isolated as usual to yield a residue which was recrystallized from petroleum ether to give the aldehyde **42**. colorless crystals, 66 g (47 %)

^{1}H NMR 0.75 (s, 18 H), 4.88 (d, 2 H, J = 14.2 Hz), 6.50 (s, 2 H), 6.95 (s, 1 H), 7.31-7.46 (m, 15 H).

Preparation of (E)-1,2-Bis(3,5-di-*tert*-butylphenyl)ethene 43.

A vigorously stirred suspension of the phosphonium salt **41** (0.44 mol) in THF (1L) was added dropwise *n*-BuLi (265 mL, 0.44 mol) at 0 °C. The dark-red solution was stirred for 10 min, the aldehyde **42** (97 g, 0.44 mol) in THF solution (ca. 1 L) was added to the solution at -10 °C. The mixture was allowed to warm to room temperature over 0.5 h, and stirred for a further 0.5 h. The mixture was concentrated, treated with ether, and the resulting suspension was filtered through a short column (silica gel). Evaporation of the elute gave a crude product which was purified by column chromatography. white powder, 100 g (56 %)

^{1}H NMR 1.37 (s, 36 H), 7.12 (brm, 1 H), 7.25 (brm, 1 H), 7.30-7.38 (m, 6 H).

Preparation of (*R*,*R*)-1,2-Bis(3,5-di-*tert*-butylphenyl)ethane-1,2-diol 44.

To a stirred solution of **43** (0.84 g, 2.1 mmol), *N*-methylmorpholine-*N*-oxide in H_2O solution (0.72 g, 3.1 mmol), hydroquinidine-4-chlorobenzoate (47 mg, 0.10 mmol) in acetone was added OsO_4 (ca. 2.5 mg) at 0 °C. The mixture was stirred for 4 °C for 33 h and usual work-up gave the crude product. The crude product was purified

by recrystallization (EtOH). white powder, 0.38 g (33 %), $[\alpha]_D$=+2.4. When the 38 g of **43** was used, the $[\alpha]_D$ was changed and 45 % ee of **44** was obtained (Daicel OD column).

^{1}H NMR 1.18 (s, 36 H), 4.66 (s, 2 H), 7.18 (s, 4 H), 7.26 (s, 2 H).

X-ray Structure Determination of 26d and 37a.

Crystal data and numeric details of the structure determinations are given in Table 4. Crystals in sealed capillaries suitable for X-ray structure determination were mounted on a Mac Science MXC3 diffractometer and irradiated with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) for data collection. Lattice parameters were determined by least-squares fitting of 31 reflections with 44° < 2θ < 50° and 40° < 2θ < 50° for **26d** and **37a**, respectively. Data were collected with the 2θ/ω-scan mode. All data were corrected for absorption.[39] The structures were solved by a direct method with the SIR 92 program[40] in the Crystan-GM package. Refinement on F was carried out by full-matrix least squares. All non-hydrogen atoms were refined with anisotropic thermal parameters except for C(7) and C(8) in **26d**. These carbon atoms were refined with isotropic thermal parameters. All hydrogen atoms in **26d** and **37a** were included in the refinement on calculated positions (C-H = 1.0 Å) riding on their carrier atoms with isotropic thermal parameters. All the computations were carried out on a Indigo 2 computer. Crystallographic data, bond distances and angles, and atomic coordinates are shown in Table 1-12 (**26d** and **37a**), 1-13, 1-14, 1-15 (**26d**), 1-16, 1-17, 1-18 (**37a**).

Table 1-12. Selected Crystallographic Data for 26d and 37a.

No	**26d**	**37a**
formula	$C_{20}H_{26}O_2Cl_4Ti$	$C_{19}H_{25}O_3Cl_3Ti$
mol wt	488.1	455.7
cryst syst	orthorhombic	orthorhombic
space group	$P2_12_12_1$	$P2_12_12_1$
cryst dimens, mm	0.85 x 0.55 x 0.25	0.55 x 0.50 x 0.35
a, Å	13.42 (1)	13.656 (2)
b, Å	15.84 (1)	14.748 (3)
c, Å	10.982 (9)	11.047 (2)
α, deg	90	90
β, deg	90	90
γ, deg	90	90
V, Å^3	2334 (3)	2225 (7)
Z	4	4
D_{calc}, g cm^{-3}	1.39	1.36
abs coeff, cm^{-1}	75.58	68.105

$F(000)$	1008	944
radiation; λ, Å	Cu Kα, 1.54178	Cu Kα, 1.54178
temp, °C	-5±1	23±1
2θ max, deg	130	130
scan rate, deg/min	2.5	1.0
linear decay,%	10	-
data collected	$+h,+k,+l$	$+h,-k,+l$
total data collcd, obsd	2219, 1138 (I>3σ(I))	2177, 1662 (I>3σ(I))
R int	0.189	0.023
no of params refined	234	260
R, R_w, S^a	0.095, 0.107, 4.356	0.038, 0.039, 1.230
max shift in final cycle	0.4495	0.975
final diff map, max, e/Å^3	0.81	0.36

[a] Function minimized was sum $[w(|Fo|^2-|Fc|^2)^2]$ which $w=1.0/[(\sigma|Fo|^2+0.0003|Fo|^2]$. $R=\Sigma[(||Fo|-|Fc||)/\Sigma|Fo|$. $Rw=[\Sigma w(|Fo|-|Fc|)^2/\Sigma|Fo|^2]^{1/2}$.

Table 1-13. Bond Distances of 26d.

Intramolecular Distances (A) with e.s.d. in parentheses

atom	atom	distance
Ti1	Cl4	2.297 (9)
Ti1	Cl3	2.274 (9)
Ti1	Cl1	2.211 (9)
Ti1	Cl2	2.223 (10)
Ti1	O2	2.087 (18)
Ti1	O1	2.140 (16)
O2	C8	1.45 (4)
O2	C4	1.48 (4)
O1	C7	1.49 (3)
O1	C8	2.37 (3)
O1	C1	1.51 (4)
C9	C14	1.37 (4)
C9	C10	1.33 (4)
C9	C7	1.47 (4)
C9	C11	2.35 (4)
C15	C20	1.36 (4)
C15	C16	1.44 (4)
C15	C8	1.50 (4)
C15	C19	2.36 (5)
C15	C17	2.40 (4)
C14	C10	2.31 (4)
C14	C12	2.27 (5)
C14	C13	1.37 (5)
C10	C12	2.37 (5)
C10	C11	1.38 (5)
C20	C19	1.40 (5)
C20	C18	2.33 (6)
C16	C17	1.41 (5)
C7	C8	1.53 (4)
C12	C11	1.39 (6)
C12	C13	1.32 (5)
C4	C5	1.50 (5)
C11	C13	2.39 (5)
C19	C18	1.23 (6)
C19	C17	2.31 (6)
C18	C17	1.44 (6)
C1	C2	1.43 (5)
C1	C3	2.36 (6)
C5	C6	1.50 (6)
C2	C3	1.31 (6)

Table 1-14. Bond Angles of 26d.

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom	atom	atom	angle
Cl4	Ti1	Cl3	168.5 (4)
Cl4	Ti1	Cl1	92.4 (4)
Cl4	Ti1	Cl2	94.8 (4)
Cl4	Ti1	O2	87.8 (6)
Cl4	Ti1	O1	84.6 (5)
Cl3	Ti1	Cl1	93.6 (4)
Cl3	Ti1	Cl2	94.3 (4)
Cl3	Ti1	O2	85.1 (6)
Cl3	Ti1	O1	84.8 (5)
Cl1	Ti1	Cl2	95.9 (4)
Cl1	Ti1	O2	173.4 (6)
Cl1	Ti1	O1	99.2 (6)
Cl2	Ti1	O2	90.7 (6)
Cl2	Ti1	O1	164.9 (6)
O2	Ti1	O1	74.2 (7)
Ti1	O2	C8	120.0 (14)
Ti1	O2	C4	125.1 (16)
C8	O2	C4	110.5 (20)
Ti1	O1	C7	116.6 (13)
Ti1	O1	C8	86.0 (9)
Ti1	O1	C1	119.7 (17)
C7	O1	C8	38.8 (13)
C7	O1	C1	111.1 (19)
C8	O1	C1	149.8 (17)
C14	C9	C10	118.1 (24)
C14	C9	C7	122.2 (23)
C14	C9	C11	87.8 (19)
C10	C9	C7	119.4 (24)
C10	C9	C11	30.3 (17)
C7	C9	C11	149.5 (21)
C20	C15	C16	122.3 (25)
C20	C15	C8	118.4 (25)
C20	C15	C19	31.9 (18)
C20	C15	C17	89.9 (20)
C16	C15	C8	119.0 (21)
C16	C15	C19	90.4 (19)
C16	C15	C17	32.5 (15)
C8	C15	C19	150.0 (21)
C8	C15	C17	151.5 (20)
C19	C15	C17	58.1 (15)
C9	C14	C10	30.5 (14)
C9	C14	C12	92.9 (19)
C9	C14	C13	124.6 (26)
C10	C14	C12	62.4 (13)
C10	C14	C13	94.2 (20)
C12	C14	C13	31.9 (17)
C9	C10	C14	31.4 (15)
C9	C10	C12	89.4 (19)
C9	C10	C11	120.4 (28)
C14	C10	C12	58.0 (12)

C14	--- C10 ---	C11	89.0 (22)
C12	--- C10 ---	C11	31.0 (19)
C15	--- C20 ---	C19	117.2 (29)

Intramolecular Angles (degrees) with e.s.d. in parentheses (contd)

atom	atom	atom	angle
C15	--- C20 ---	C18	91.9 (22)
C19	--- C20 ---	C18	25.5 (20)
C15	--- C16 ---	C17	114.1 (24)
O1	--- C7 ---	C9	117.2 (20)
O1	--- C7 ---	C8	103.7 (19)
C9	--- C7 ---	C8	114.0 (21)
C14	--- C12 ---	C10	59.6 (13)
C14	--- C12 ---	C11	90.3 (21)
C14	--- C12 ---	C13	33.3 (17)
C10	--- C12 ---	C11	30.7 (16)
C10	--- C12 ---	C13	92.9 (22)
C11	--- C12 ---	C13	123.5 (30)
O2	--- C8 ---	O1	79.7 (14)
O2	--- C8 ---	C15	116.8 (20)
O2	--- C8 ---	C7	110.7 (20)
O1	--- C8 ---	C15	148.0 (19)
O1	--- C8 ---	C7	37.5 (12)
C15	--- C8 ---	C7	111.8 (22)
O2	--- C4 ---	C5	115.9 (24)
C9	--- C11 ---	C10	29.2 (16)
C9	--- C11 ---	C12	89.0 (21)
C9	--- C11 ---	C13	61.6 (13)
C10	--- C11 ---	C12	118.3 (29)
C10	--- C11 ---	C13	90.8 (22)
C12	--- C11 ---	C13	27.5 (17)
C15	--- C19 ---	C20	30.9 (16)
C15	--- C19 ---	C18	94.3 (29)
C15	--- C19 ---	C17	61.9 (14)
C20	--- C19 ---	C18	125.0 (35)
C20	--- C19 ---	C17	92.8 (22)
C18	--- C19 ---	C17	32.8 (25)
C14	--- C13 ---	C12	114.9 (27)
C14	--- C13 ---	C11	85.9 (19)
C12	--- C13 ---	C11	29.0 (18)
C20	--- C18 ---	C19	29.5 (21)
C20	--- C18 ---	C17	90.8 (25)
C19	--- C18 ---	C17	119.8 (38)
O1	--- C1 ---	C2	112.6 (28)
O1	--- C1 ---	C3	100.1 (21)
C2	--- C1 ---	C3	28.9 (21)
C15	--- C17 ---	C16	33.4 (15)
C15	--- C17 ---	C19	60.1 (13)
C15	--- C17 ---	C18	87.3 (22)
C16	--- C17 ---	C19	93.3 (21)
C16	--- C17 ---	C18	120.6 (29)
C19	--- C17 ---	C18	27.4 (21)
C4	--- C5 ---	C6	112.5 (28)
C1	--- C2 ---	C3	119.0 (37)

C1 --- C3 --- C2 32.1 (22)

Table 1-15. Atomic Coordinates of 26d.

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	U(eq)
Ti1	1.0697 (3)	-0.0179 (3)	0.2794 (4)	0.047 (3)
C14	0.9237 (5)	0.0526 (6)	0.2393 (6)	0.073 (5)
C13	1.2185 (5)	-0.0676 (5)	0.3479 (8)	0.066 (5)
C11	1.1243 (6)	-0.0002 (6)	0.0911 (7)	0.077 (6)
C12	1.0055 (7)	-0.1456 (5)	0.2487 (9)	0.087 (6)
O2	1.0267 (13)	-0.0217 (9)	0.4619 (15)	0.05 (1)
O1	1.1171 (11)	0.0996 (9)	0.3562 (15)	0.03 (1)
C9	1.1028 (18)	0.2018 (15)	0.5314 (23)	0.04 (2)
C15	0.9694 (16)	0.0660 (16)	0.6395 (25)	0.04 (2)
C14	1.195 (2)	0.198 (2)	0.584 (2)	0.04 (2)
C10	1.055 (2)	0.276 (2)	0.533 (3)	0.06 (2)
C20	0.8715 (18)	0.0730 (22)	0.6093 (28)	0.07 (2)
C16	1.0027 (18)	0.0627 (18)	0.7645 (27)	0.05 (2)
C7	1.0601 (19)	0.1308 (16)	0.4632 (23)	0.045 (7)
C12	1.191 (2)	0.336 (2)	0.641 (3)	0.06 (2)
C8	1.0434 (17)	0.0513 (17)	0.5398 (23)	0.044 (7)
C4	1.017 (2)	-0.100 (2)	0.536 (3)	0.07 (2)
C11	1.098 (3)	0.345 (2)	0.587 (3)	0.08 (2)
C19	0.803 (2)	0.080 (3)	0.705 (4)	0.09 (3)
C13	1.240 (2)	0.263 (2)	0.644 (3)	0.07 (2)
C18	0.825 (3)	0.089 (3)	0.812 (4)	0.09 (3)
C1	1.146 (2)	0.171 (2)	0.273 (3)	0.07 (2)
C17	0.927 (3)	0.077 (2)	0.851 (3)	0.07 (3)
C5	0.916 (2)	-0.140 (2)	0.537 (3)	0.07 (2)
C2	1.247 (3)	0.164 (3)	0.230 (3)	0.11 (3)
C6	0.919 (3)	-0.231 (3)	0.575 (3)	0.10 (3)
C3	1.320 (3)	0.173 (3)	0.307 (5)	0.13 (4)

Table 1-16.Bond Distances of 37a.

Intramolecular Distances (A) with e.s.d. in parentheses

atom	atom	distance
Cl1	Ti1	2.267 (3)
Cl2	Ti1	2.339 (3)
Cl3	Ti1	2.315 (3)
O1	Ti1	2.226 (5)
O2	Ti1	2.138 (4)
O3	Ti1	1.707 (5)
C1	O1	1.471 (8)
C2	O2	1.455 (8)
C3	C4	1.495 (9)
C3	C5	1.513 (9)
C3	O1	1.464 (8)
C3	O2	2.382 (8)
C4	C11	1.524 (9)
C4	O1	2.355 (7)
C4	O2	1.455 (8)
C5	C6	1.382 (10)
C5	C9	2.388 (12)
C5	C10	1.382 (10)
C6	C7	1.412 (12)
C7	C8	1.378 (15)
C7	C9	2.386 (14)
C8	C9	1.364 (15)
C8	C10	2.389 (14)
C9	C10	1.384 (14)
C11	C12	1.372 (9)
C11	C13	2.382 (10)
C11	C15	2.393 (10)
C11	C16	1.372 (9)
C12	C13	1.363 (10)
C12	C14	2.375 (10)
C12	C16	2.359 (10)
C13	C14	1.387 (12)
C13	C15	2.373 (12)
C14	C15	1.350 (12)
C14	C16	2.361 (11)
C15	C16	1.378 (11)
C17	C18	1.408 (19)
C17	C19	1.39 (3)
C17	O3	1.414 (14)
C18	O3	2.352 (16)
C19	O3	2.40 (3)

Table 1-17. Bond Angles of 37a.

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom	atom	atom	angle
C4	C3	C5	111.7 (5)
C4	C3	O1	105.4 (5)
C4	C3	O2	35.6 (3)
C5	C3	O1	112.2 (5)
C5	C3	O2	146.8 (5)
O1	C3	O2	81.9 (4)
C3	C4	C11	110.6 (5)
C3	C4	O1	36.8 (3)
C3	C4	O2	107.7 (5)
C11	C4	O1	146.9 (5)
C11	C4	O2	111.6 (5)
O1	C4	O2	83.0 (4)
C3	C5	C6	120.3 (6)
C3	C5	C9	149.4 (6)
C3	C5	C10	119.0 (7)
C6	C5	C9	90.3 (6)
C6	C5	C10	120.6 (7)
C9	C5	C10	30.4 (5)
C5	C6	C7	119.4 (8)
C6	C7	C8	119.0 (8)
C6	C7	C9	89.7 (6)
C8	C7	C9	29.4 (6)
C7	C8	C9	120.9 (10)
C7	C8	C10	91.0 (7)
C9	C8	C10	29.9 (6)
C5	C9	C7	60.7 (4)
C5	C9	C8	90.4 (7)
C5	C9	C10	30.3 (5)
C7	C9	C8	29.7 (6)
C7	C9	C10	91.0 (6)
C8	C9	C10	120.7 (9)
C5	C10	C8	89.9 (6)
C5	C10	C9	119.3 (8)
C8	C10	C9	29.4 (6)
C4	C11	C12	120.3 (6)
C4	C11	C13	149.6 (5)
C4	C11	C15	150.8 (5)
C4	C11	C16	121.2 (6)
C12	C11	C13	29.3 (4)
C12	C11	C15	88.9 (5)
C12	C11	C16	118.5 (6)
C13	C11	C15	59.6 (3)
C13	C11	C16	89.2 (5)
C15	C11	C16	29.6 (4)
C11	C12	C13	121.1 (7)
C11	C12	C14	90.5 (5)
C11	C12	C16	30.7 (4)
C13	C12	C14	30.6 (5)
C13	C12	C16	90.4 (5)
C14	C12	C16	59.8 (4)
C11	C13	C12	29.5 (4)
C11	C13	C14	89.9 (6)
C11	C13	C15	60.4 (3)
C12	C13	C14	119.4 (7)
C12	C13	C15	90.0 (6)

C14 --- C13 --- C15	29.5 (5)

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom	atom	atom	angle
C12	C14	C13	30.0 (4)
C12	C14	C15	90.2 (6)
C12	C14	C16	59.7 (3)
C13	C14	C15	120.2 (7)
C13	C14	C16	89.7 (5)
C15	C14	C16	30.4 (5)
C11	C15	C13	60.0 (3)
C11	C15	C14	90.3 (6)
C11	C15	C16	29.5 (4)
C13	C15	C14	30.4 (5)
C13	C15	C16	89.4 (6)
C14	C15	C16	119.8 (8)
C11	C16	C12	30.7 (4)
C11	C16	C14	91.2 (5)
C11	C16	C15	120.9 (7)
C12	C16	C14	60.4 (4)
C12	C16	C15	90.2 (5)
C14	C16	C15	29.8 (5)
C18	C17	C19	127.9 (16)
C18	C17	O3	112.9 (13)
C19	C17	O3	117.6 (11)
C17	C18	O3	33.6 (8)
C17	C19	O3	31.5 (7)
C1	O1	C3	110.6 (5)
C1	O1	C4	148.2 (5)
C1	O1	Ti1	119.8 (4)
C3	O1	C4	37.7 (3)
C3	O1	Ti1	115.3 (4)
C4	O1	Ti1	83.9 (2)
C2	O2	C3	150.0 (5)
C2	O2	C4	113.6 (5)
C2	O2	Ti1	117.9 (4)
C3	O2	C4	36.7 (3)
C3	O2	Ti1	88.0 (3)
C4	O2	Ti1	115.6 (4)
C17	O3	C18	33.5 (8)
C17	O3	C19	30.9 (7)
C17	O3	Ti1	162.9 (7)
C18	O3	C19	63.9 (7)
C18	O3	Ti1	129.6 (6)
C19	O3	Ti1	166.2 (5)
Cl1	Ti1	Cl2	92.0 (1)
Cl1	Ti1	Cl3	95.4 (1)
Cl1	Ti1	O1	91.8 (2)
Cl1	Ti1	O2	165.0 (2)
Cl1	Ti1	O3	99.1 (2)
Cl2	Ti1	Cl3	165.2 (1)
Cl2	Ti1	O1	83.7 (2)
Cl2	Ti1	O2	83.3 (2)
Cl2	Ti1	O3	94.7 (2)
Cl3	Ti1	O1	83.3 (2)
Cl3	Ti1	O2	86.3 (2)
Cl3	Ti1	O3	96.8 (2)
O1	Ti1	O2	73.6 (2)
O1	Ti1	O3	169.0 (2)

O2	--- Ti1 ---	O3	95.5 (2)

Table 1-18. Atomic Coordinates of 37a.

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	U(eq)
Ti1	0.53285 (8)	0.13993 (7)	0.59754 (10)	0.0426 (7)
O1	0.4254 (3)	0.2142 (3)	0.7121 (4)	0.042 (2)
O2	0.3995 (3)	0.0643 (3)	0.5901 (4)	0.039 (2)
O3	0.5975 (3)	0.0683 (3)	0.5063 (4)	0.060 (3)
C1	0.4298 (6)	0.3137 (4)	0.7197 (8)	0.063 (5)
C2	0.4053 (6)	-0.0311 (5)	0.5572 (8)	0.056 (4)
C3	0.3238 (4)	0.1835 (4)	0.7016 (6)	0.038 (3)
C4	0.3295 (5)	0.0829 (4)	0.6863 (6)	0.038 (3)
C5	0.2631 (5)	0.2095 (4)	0.8106 (6)	0.044 (3)
C6	0.3016 (6)	0.2022 (5)	0.9258 (6)	0.055 (4)
C7	0.2436 (8)	0.2265 (5)	1.0264 (7)	0.074 (6)
C8	0.1493 (8)	0.2565 (6)	1.0072 (9)	0.082 (6)
C9	0.1114 (7)	0.2614 (6)	0.8931 (10)	0.083 (6)
C10	0.1675 (6)	0.2377 (5)	0.7936 (8)	0.065 (5)
C11	0.2289 (4)	0.0438 (3)	0.6576 (5)	0.032 (3)
C12	0.1792 (5)	0.0714 (4)	0.5562 (6)	0.046 (4)
C13	0.0887 (5)	0.0379 (5)	0.5296 (7)	0.059 (4)
C14	0.0461 (5)	-0.0252 (5)	0.6065 (8)	0.068 (5)
C15	0.0940 (6)	-0.0530 (6)	0.7067 (7)	0.065 (5)
C16	0.1859 (5)	-0.0192 (5)	0.7319 (6)	0.055 (4)
C17	0.6744 (8)	0.0182 (11)	0.4524 (12)	0.128 (9)
C18	0.7624 (10)	0.0229 (19)	0.5186 (16)	0.17 (1)
C19	0.6500 (12)	-0.0423 (15)	0.3609 (15)	0.17 (1)
Cl1	0.65406 (14)	0.23849 (15)	0.64592 (18)	0.071 (1)
Cl2	0.55908 (12)	0.05533 (12)	0.77370 (16)	0.056 (1)
Cl3	0.46717 (15)	0.22832 (12)	0.44462 (14)	0.062 (1)

1-10. References

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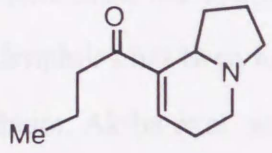
Chapter 2.

Stereocontrol in [4+2]Type Cycloaddition of Imines Bearing α-Hydrogens with 2-Silyloxy-1,3-butadienes

2-1. Introduction

Nucleophilic addition reactions to aldimines have found widespread application in the synthesis of nitrogen-containing natural products.[1-3] These are seen in various alkaloids, and the examples are Elaeocarpus alkaloids elaeokanine A (**46**), B (**47**), the fungal neurotoxin slaframine (**48**), lupinine (**49**), lysergic acid (**50**), palustrine (**51**), anhydrocannabisativene (**52**)[1], ipalbidine (**53**)[2b], and (S)-anabasin (tobacco alkaloid, **54**)[3] as shown below.



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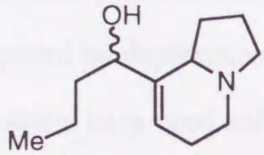

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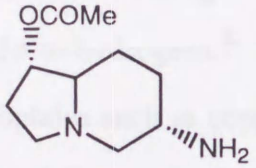

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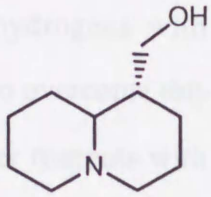

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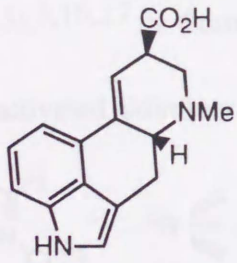

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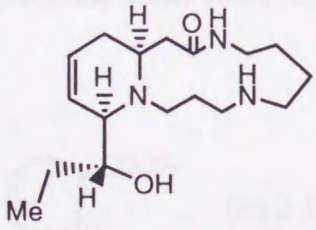

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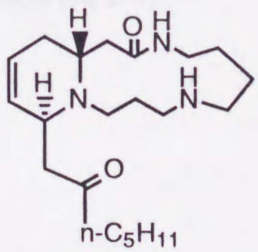

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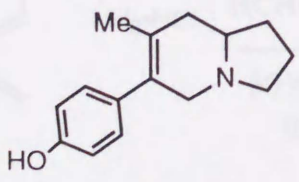

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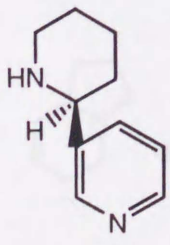
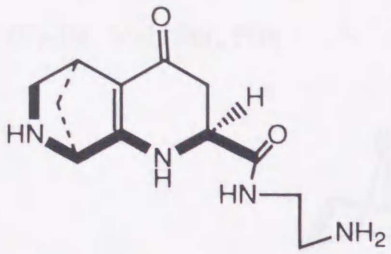
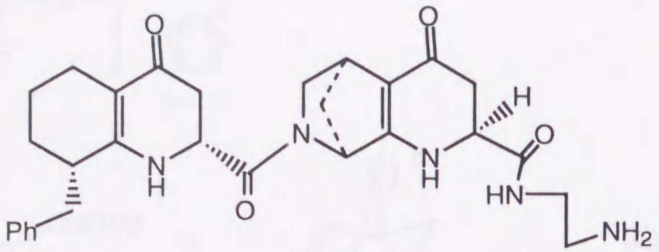


54

In addition, dipeptide mimics of CD4, the cellular receptor of HIV-1 has been synthesized recently.[4]



mimicry of the Thr45-Lys46 segment of CD4



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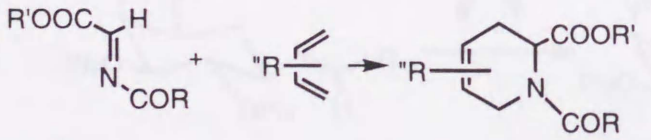
mimicry of the Phe43-Lys46 segment of CD4

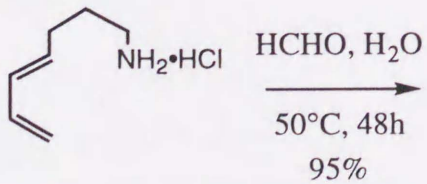
However, the synthetic utility of reactions of aldimines bearing α–hydrogens with nucleophiles has been hampered by deprotonation of the α–hydrogens.[5] To overcome this problem, Akiba et.al. and others have used soft nucleophiles such as copper reagents with Lewis acids as shown in Chapter 3.[6,7] As the approach for synthesizing piperidones or piperidines, some workers have reported on reactions with activated aldimines (eq 2-1),[1,8-11] highly nucleophilic Danishefsky's diene (eq 2-2),[2,12-15] catalytic activation by Lewis acids (eq 2-3),[3,16,17] or thermal intramolecular imino Diels-Alder reaction (eq 2-4).[1b]

i) with activated aldimines

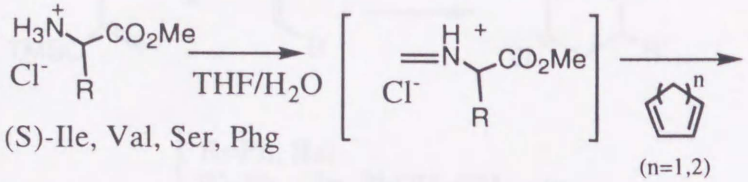


(eq 2-1-1)[8]

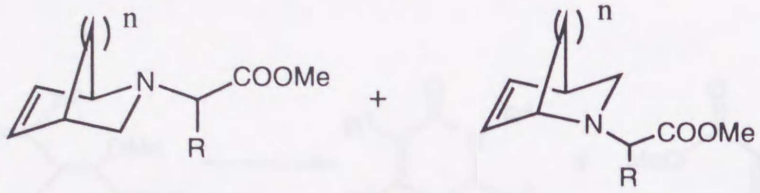
R=Me, O*t*-Bu, OBzl, OCH_2CCl_3
R'=Me, Et
R"=MeO, TMSO, SPh



(eq 2-1-2)[10a,10b]

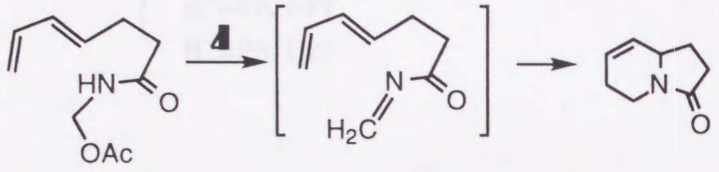


(S)-Ile, Val, Ser, Phg

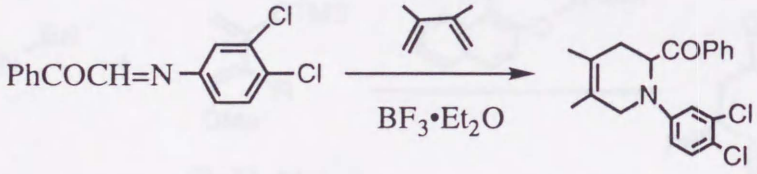


(eq 2-1-3)[11]

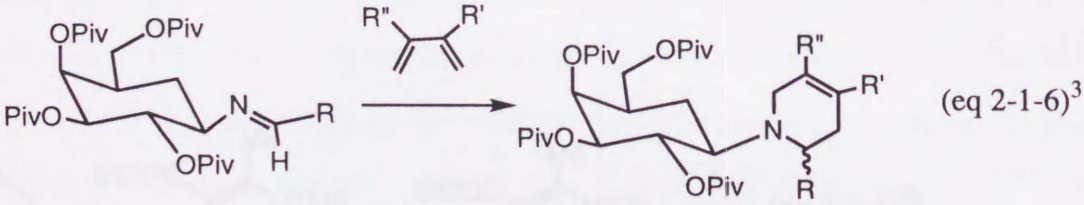
(diastereomeric ratio 93:7-12:88, 35-90% yield)



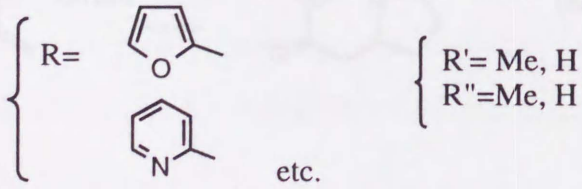
(eq 2-1-4)[1b]



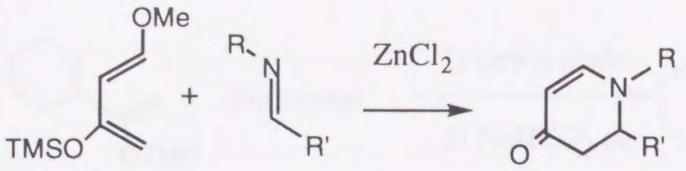
(eq 2-1-5)[1b]



(eq 2-1-6)[3]

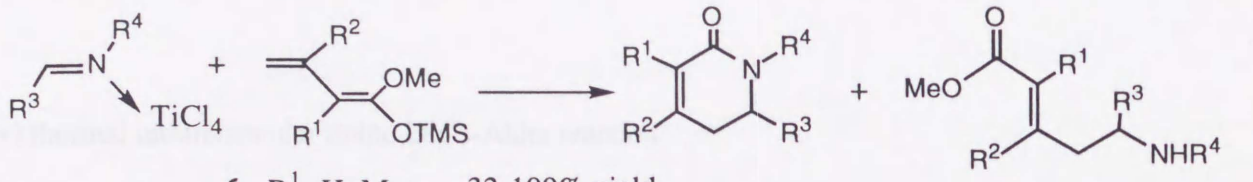


ii) with highly nucleophilic Danishefsky's diene



(eq 2-2-1)[12b]

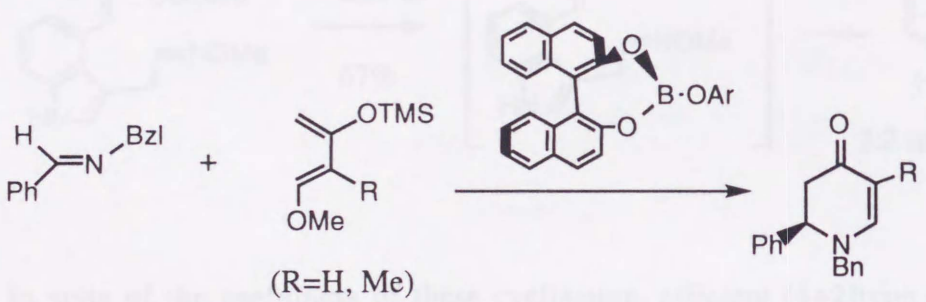
R=Ph, Bzl
R'=Ph, *i*-Pr, PhCH=CH- etc.



R^1=H, Me
R^2=H, Me
R^3=Ph, *i*-Pr
R^4=Ph, Bzl

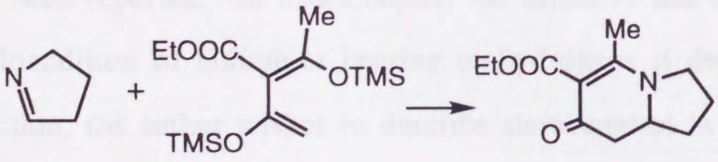
32-100% yield

(eq 2-2-2)[13]



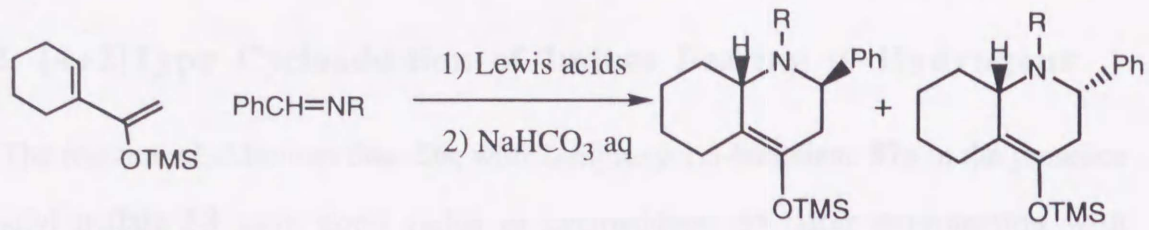
(R=H, Me)

(eq 2-2-3)[15a]



(eq 2-2-4)[2b]

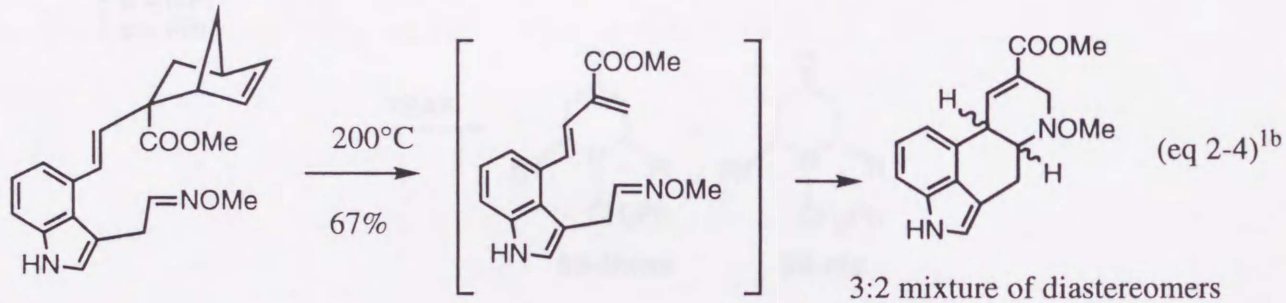
iii) catalytic activation by Lewis acid



(Lewis acid=BF_3•Et_2O, $AlCl_3$, Et_2AlCl, $ZrCl_4$, $TiCl_4$)

(eq 2-3)[17c]

iv) thermal intramolecular imino Diels-Alder reaction



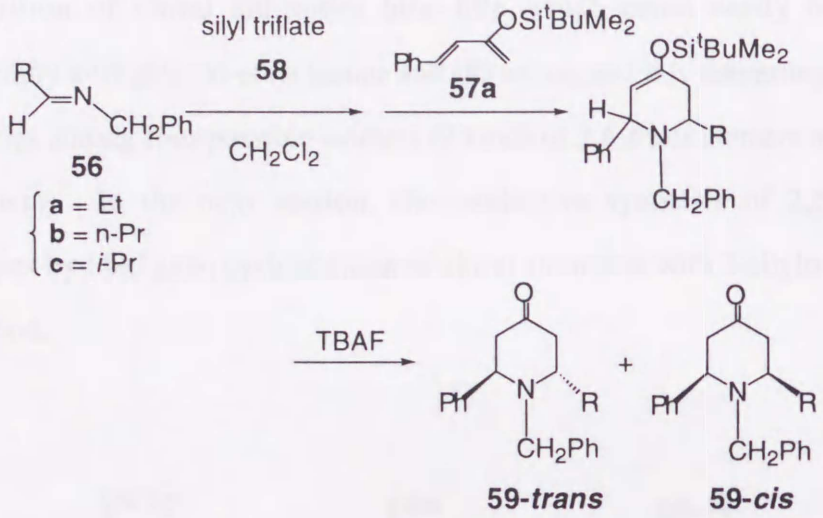
(eq 2-4)[1b]

3:2 mixture of diastereomers

In spite of the usefulness of these cyclization, efficient [4+2]type cycloaddition of unactivated 2-silyloxy-1,3-butadienes with unactivated aldimines bearing α–hydrogens has not been reported. In this Chapter, the effective use of trimethylsilyl triflate for the cycloaddition of aldimines bearing α–hydrogens is described at the beginning.[18] In addition, the author wishes to describe stereocontrol in [4+2]type cycloaddition of α–silyloxyaldimines bearing an α–hydrogen with 2-silyloxy-1,3-butadienes.

2-2. [4+2]Type Cycloaddition of Imines Bearing α–Hydrogens

The reaction of aldimines **56a–56c** with 2-silyloxy-1,3-butadiene **57a** in the presence of silyl triflate **58** gave good yields of cycloadducts **59** after deprotection with tetrabutylammonium fluoride (TBAF) (Scheme 2-1, Table 2-1).



Scheme 2-1

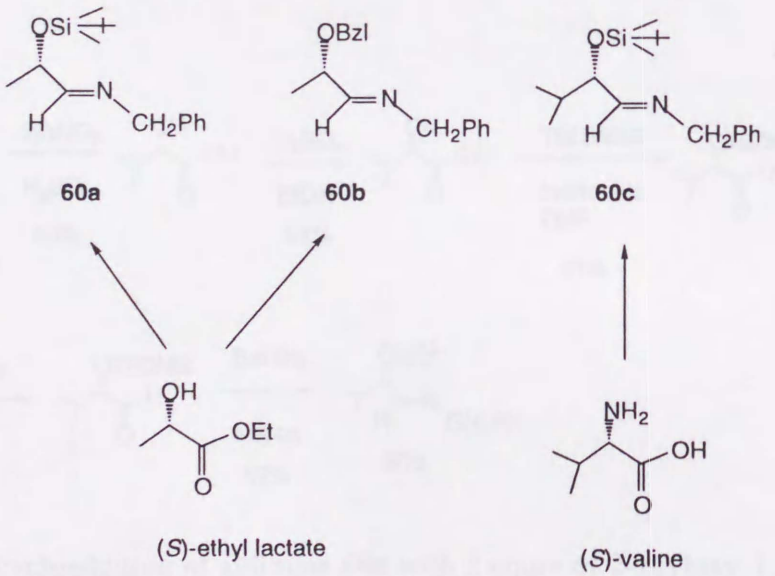
Table 2-1. Diastereoselectivity in [4+2]Type Cycloaddition of Aldimine (56).

entry	R	silyl triflate	*trans*:*cis*	yield(%)
1	Et	TMSOTf	89:11	49
2	n-Pr	TMSOTf	87:13	52
3	i-Pr	TMSOTf	98:2	75
4	n-Pr	TBDMSOTf	88:12	58
5	n-Pr	TIPSOTf	90:10	60

The relative stereochemistry between C(2) and C(6) substituents of these diastereomers was determined by NOESY spectrum after assignment by 2D-COSY spectrum. Higher *trans* selectivity was observed by increasing the bulkiness of the α–substituents of the

aldimine (**58a** (R^1=Et), **58b** (R^1=*n*-Pr), and **58c** (R^1=*i*-Pr); the diastereomeric excess was 78 % (entry 1, 49 % isolated yield), 74 % (entry 2, 52 % isolated yield), and 96 % (entry 3, 75 % isolated yield), respectively). Other silyl triflates were also tried to obtain *trans* isomers selectively, but there was a little change in the ratio and less selective (entries 4 and 5).

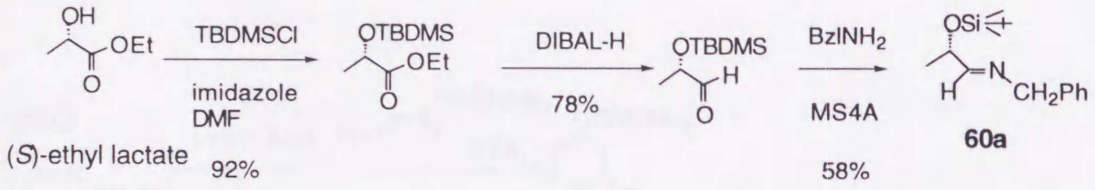
From these preliminary results, high *trans* selectivities could be anticipated in [4+2]type cycloaddition of chiral aldimines **60a–60c** which could easily be prepared from commercially available (*S*)-ethyl lactate and (*S*)-valine, and it is interesting to investigate the selectivities among four possible isomers (2 kinds of 2,6-*trans* isomers and 2 kinds of 2,6-*cis* isomers). In the next section, stereoselective synthesis of 2,6-disubstituted-4-piperidones by [4+2]type cycloaddition of chiral aldimines with 2-silyloxy-1,3-butadienes is described.

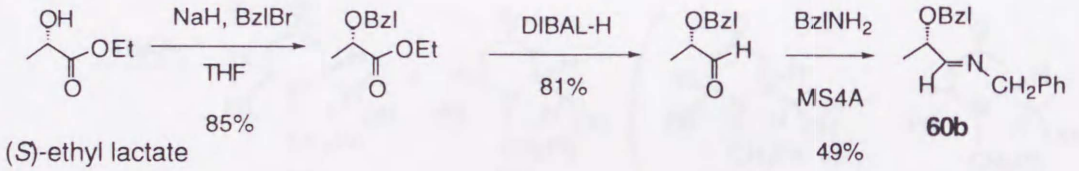


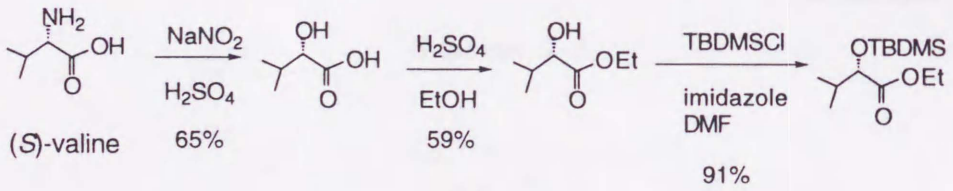
2-3. [4+2]Type Cycloaddition of α–Silyloxyaldimines

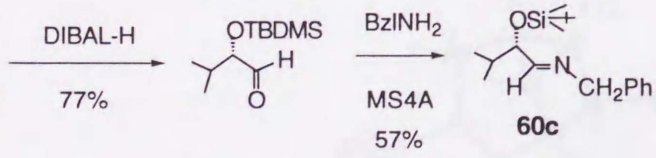
(A) Preliminary Observations

The α–silyloxyaldimines (**60a**, **60c**) and α–benzyloxyaldimine **60b** were easily prepared from commercially available (*S*)-ethyl lactate or (*S*)-valine as shown below.



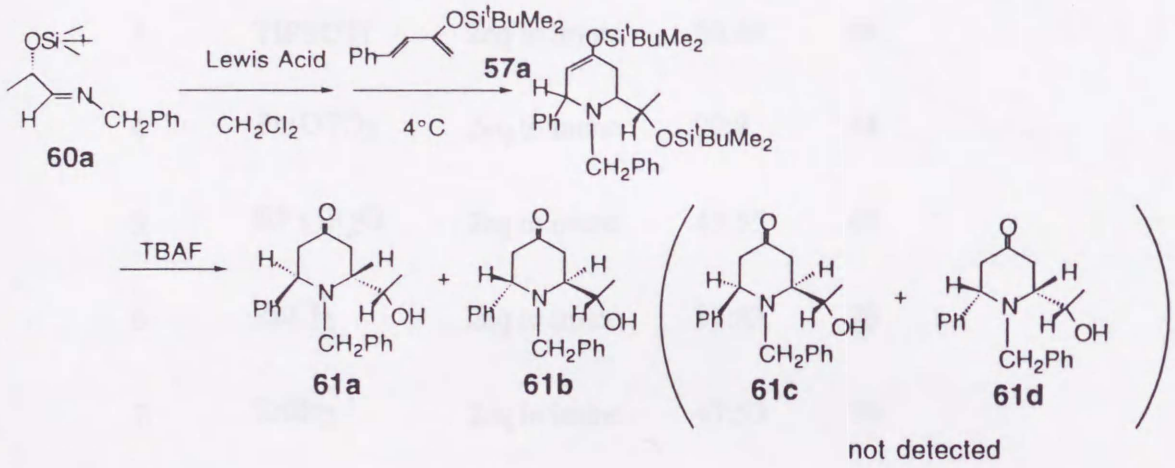






[4+2]Type cycloaddition of aldimine **60a** with 2 equiv of 2-silyloxy-1,3-butadiene **57a** was conducted by the use of trimethylsilyl triflate in dichloromethane at 4 °C (Scheme 2-3). As expected from the effect of bulkiness of the α–substituent in aldimines **56**, only the two 2,6-*trans* diastereomers (**61a** and **61b**) were obtained as a 77:23 mixture in high yield (entry 1, Table 2-2). 2,6-*Cis* isomers were not detected at all. The stereochemistry of the major diastereomer **61a** was determined by X-ray

analysis as an intramolecular hemiketal (Figure 2-1) and the relative stereochemistry of minor diastereomer **61b** was confirmed to be trans between the α–hydroxyethyl group and the phenyl group by DIFNOE experiments. Proton irradiation of the C-6 methine group (-NC<u>H</u>Ph-CH_2-: δ 3.80) of the ring resulted in intensity enhancement of signals of the methine proton (δ 4.48, 7.7 %) and the methyl protons (δ 1.20, 5.6 %) of the hydroxyethyl group, and no enhancement was observed of the signal of the C-2 methine group (δ 3.10).



Scheme 2-3

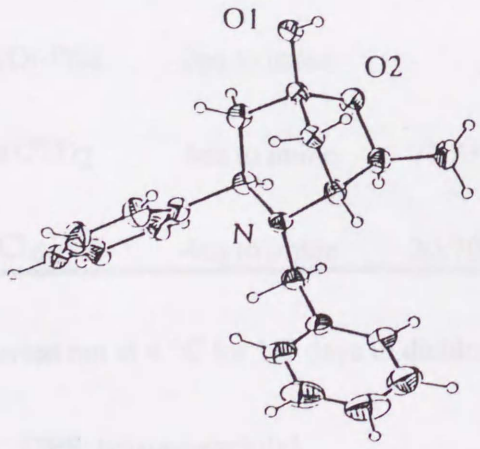


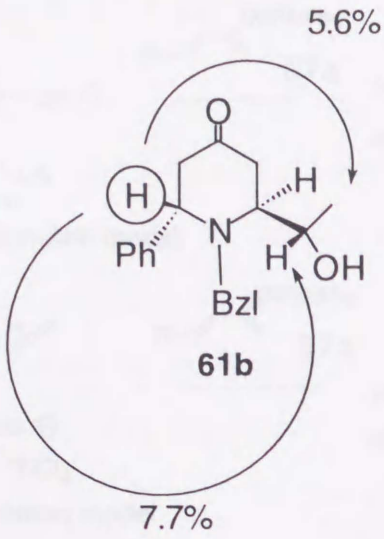
Figure 2-1. X-ray Crystallographic Structure of 61a.

Table 2-2. Effect of Lewis Acid on [4+2]Type Cycloaddition of an Aldimine (60a) with 2-Siloxy-1,3-butadiene (57a).

entry	Lewis acid	**57a**	**61a:61b**	yield(%)
1	TMSOTf	2eq to imine	77:23	90
2	H_3SiOTf	2eq to imine	55:45	91
3	TIPSOTf	2eq to imine	56:44	64
4	$Zn(OTf)_2$	2eq to imine	92:8	34
5	$BF_3{\cdot}Et_2O$	2eq to imine	45:55	45
6	$ZnCl_2$	2eq to imine	37:63	78
7	$ZnBr_2$	2eq to imine	47:53	76
8	$SnCl_4$	2eq to imine	37:63	24
9	$TiCl_4$	2eq to imine	19:81	50
10	$Ti(O\textit{i}\text{-}Pr)_4$	2eq to imine	-	0
11	$Zn(OTf)_2$	4eq to imine	77:23	98
12	$TiCl_4$	4eq to imine	30:70	86

*All reactions were carried out at 4 °C for 1-7 days in dichloromethane under nitrogen.

TMS: trimethylsilyl TIPS: triisopropylsilyl



DIF NOE experiment of **61b**

To achieve a higher degree of asymmetric induction from the α–chirality, we investigated the reaction with other Lewis acids under similar conditions (Table 2-2, entries 2-10). Parent silyl triflate (entry 2) and triisopropylsilyl triflate (entry 3) did not show good selectivities in comparison with TMSOTf. Among a series of Lewis acids, it was interesting that the major product in the case of $Zn(OTf)_2$ (entry 4) was **61a** while the major one by using $TiCl_4$ was **61b** (entry 9). Therefore, we tried to optimize reaction conditions with these Lewis acids and an increase in the amount of **57a** to 4 equiv was found to be effective (entries 11 and 12). In the reaction with $TiCl_4$, we found that the following procedure gave the best results: To a stirred solution of aldimine **60a** was added $TiCl_4$ and **57a** successively. Since longer reaction time (20 min) of aldimine **60a** with $TiCl_4$ before addition of **57a** did not give products at all, it was necessary to add **57a** immediately after $TiCl_4$ was added to aldimine **60a**.

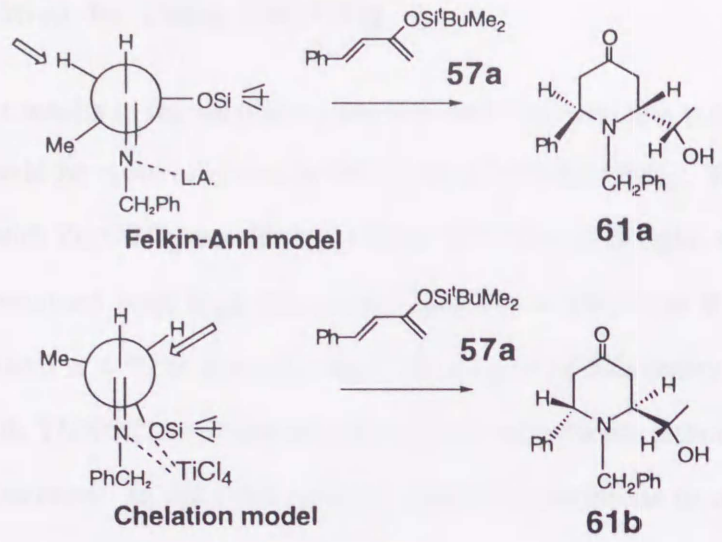


Figure 2-2

Formation of **61a** as in the case of $Zn(OTf)_2$ or TMSOTf can be explained by the non-chelation pathway and **61b** as with $TiCl_4$ by chelation model (Figure 2-2). The stereochemical outcome with $Zn(OTf)_2$ was a surprise for us but we reasoned that the formation of non-chelation product **61a** with $Zn(OTf)_2$ might be originated from the insolubility of $Zn(OTf)_2$ in dichloromethane. In the regular procedure, **57a** was added immediately after addition of aldimine **60a** within 5 sec to a solution of $Zn(OTf)_2$. Thus, the complexation of $Zn(OTf)_2$ with aldimine **60a** was slow in the solvent and the non-chelation reaction with **57a** took place before chelation of the catalyst toward the silyloxy group occurs. There might be a possibility concerning dissociation of polymeric $Zn(OTf)_2$. In fact, the yield of the chelation product (**61b**) was increased (**61a**:**61b** = 62:38) when the mixture of $Zn(OTf)_2$ and aldimine **60a** was stirred for 30 min before addition of **57a**.

(B) Cycloaddition by Using $Zn(OTf)_2$

Based on the results in the section A, we expected that even less polar solvents such as *n*-hexane would be more effective in the reaction with $Zn(OTf)_2$. The results of the solvent effect with $Zn(OTf)_2$ are shown in Table 2-3. To our delight, the diastereomer **61a** could be obtained with high selectivity (**61a**:**61b** = 89:11) in 93 % yield when $Zn(OTf)_2$ was used at 4 °C in dry *n*-hexane with 4 equiv of **57a** (entry 1). In contrast, the reaction with TMSOTf revealed no dependence on solvents although temperature effects were observed. In the final analysis, the best conditions to obtain **61a** were shown in entry 1.

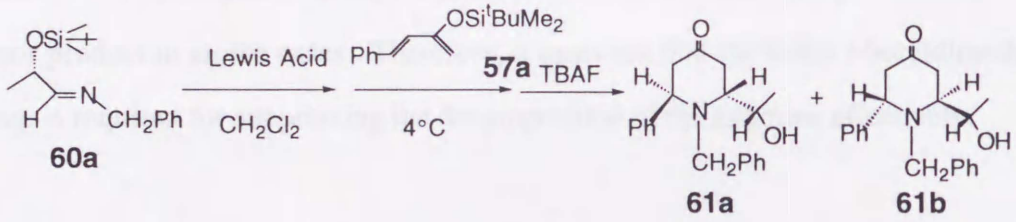
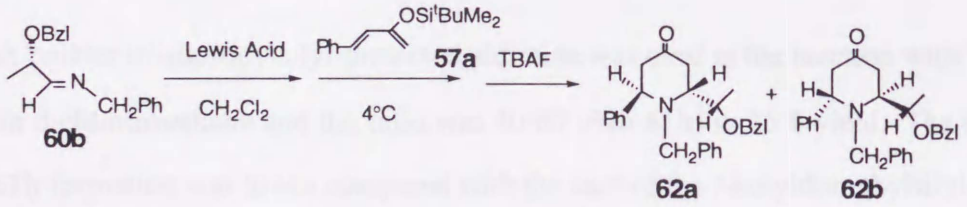


Table 2-3. Solvent Effect with TMSOTf or $Zn(OTf)_2$ as a Lewis Acid.

entry	solvent	Lewis acid	conditions	**61a**:**61b**	yield(%)
1	*n*-hexane	$Zn(OTf)_2$	4 °C, 2 days	89:11	93
2	*n*-hexane	$Zn(OTf)_2$	r.t., 1 day	94:6	53
3	toluene	TMSOTf	4 °C, 3 days	78:22	97
4	CH_2Cl_2	$Zn(OTf)_2$	4 °C, 4 days	77:23	98
5	CH_2Cl_2	TMSOTf	r.t., 3 days	66:34	76
6	CH_2Cl_2	TMSOTf	-78 °C, 7 days	51:49	39

(c) $TiCl_4$-Catalyzed Cycloaddition

Based on the chelation model, the use of a benzyl group instead of a TBDMS group for protection of a hydroxyl group was anticipated to yield **62b** with higher diastereoselectivity because chelation with $TiCl_4$ would become more facile (Scheme 2-4). The benzyl-protected aldimine **60b** was prepared and used in the reaction under similar conditions. The results are shown in Table 2-4. In spite of the use of 4 equiv of **57a**, yields were not good except for the case of TMSOTf (2 equiv of diene was used) and no product was obtained by using $TiCl_4$ (entries 1, 2, and 3, Table 2-4) because decomposition of **60b** had occurred. Benzyl group smaller than silyl group might not protect the α-hydrogen from deprotonation. In addition, chelation-product **62b** was the minor product in all the cases. Therefore, it turns out that the bulky *t*-butyldimethylsilyl group is required for suppressing the decomposition of the aldimine effectively.



Scheme 2-4

Table 2-4. [4+2]Type Cycloaddition of α–Benzyloxyaldimine 60b.

entry	Lewis Acid	solvent	temperature (°C)	**62a**:**62b**	yield(%)
1	$TiCl_4$	CH_2Cl_2	4	-	0
2	$TiCl_4$	CH_2Cl_2	-20	-	0
3	$TiCl_4$	CH_2Cl_2	-78	-	0
4	$ZnCl_2$	CH_2Cl_2	4	84:16	25
5	$Zn(OTf)_2$	CH_2Cl_2	4	70:30	51
6	TMSOTf	CH_2Cl_2	4	78:22	95

A bulkier triisopropylsilyl-protected aldimine was used in the reaction with $TiCl_4$ at 4 °C in dichloromethane and the ratio was 40:60 (**61a**:**61b**) in 75% yield. The selectivity of **61b** formation was lower compared with the case of the *t*-butyldimethylsilyl-protected aldimine (**61a**:**61b** = 30:70, Table 2-2, entry 12). The inferior selectivity of **61b** formation might be attributed to the difficulty of chelation by the bulky triisopropylsilyl group. These results might suggest the presence of equilibrium between the *N,O*-chelated $TiCl_4$ complex and the *N*-coordinated complex, and thus, the selectivity observed with the *t*-butyldimethylsilyl-protected aldimine **60a** might be related with the equilibrium ratio of these species. In order to confirm the assumption, we examined temperature and solvent effects in the reaction with $TiCl_4$ (Table 2-5), under the speculation that the *N,O*-cyclic chelated $TiCl_4$ complex should be preferable to the *N*-acyclic complexed compound at low temperatures and in polar solvents. No product was obtained in acetonitrile but the result might be due to nucleophilic attack of diene **57** at the acetonitrile cyano carbon. However, the use of bulkier isobutyronitrile and pivalonitrile

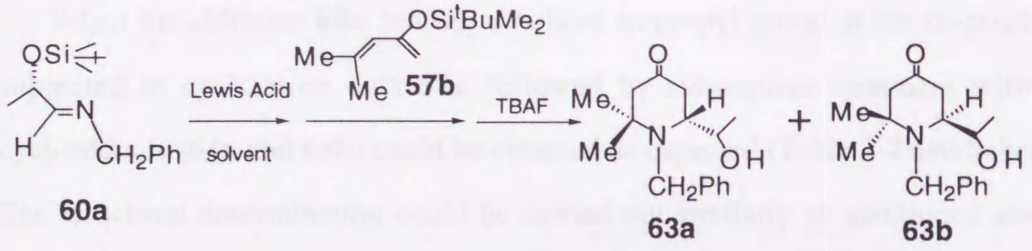
as polar solvents was effective in affording **61b** selectively (entries 2 and 3). The best result was obtained (**61b** was obtained exclusively in 87% yield, entry 10) by using low melting isobutyronitrile (mp -72 °C) at -30 °C. The reversed selectivity observed in *n*-hexane (entry 9) may be ascribed to heterogeneous reaction conditions as was described in the reactions with $Zn(OTf)_2$. Without the deprotection procedure, cycloadducts retaining enol silyl ether functionality and the *t*-butyldimethylsilyl group could be isolated. Thus, the *t*-butyldimethylsilyl group was not eliminated in the reaction with $TiCl_4$ under these conditions so the high selectivity is not a consequence of *t*-butyldimethylsilyl group elimination in **60a**.

Table 2-5. Solvent and Temperature Effect on the Stereoselectivity of 61b Formation by Use of $TiCl_4$.

entry	solvent	conditions	**61a:61b**	yield(%)
1	CH_3CN	4 °C, 1 day	—	0
2	*i*-PrCN	4 °C, 1 day	24:76	67
3	*t*-BuCN	4 °C, 1 day	18:82	60
4	CH_2Cl_2 +sulfolane	4 °C, 1 day	24:76	65
5	CH_2Cl_2	4 °C, 1 day	30:70	86
6	Et_2O	4 °C, 1 day	53:47	96
7	CCl_4	4 °C, 1 day	49:51	71
8	toluene	4 °C, 1 day	68:32	90
9	hexane	4 °C, 1 day	>98:<2	12
10	*i*-PrCN	-30 °C, 1 day	<2:>98	87

(D) The Scope for the [4+2]Type Cycloaddition

The reaction of **60a** with **57b** derived from mesityl oxide as shown in Scheme 2-5 was examined. The structural assignment for **63a** was carried out by X-ray crystal structure determination (Figure 2-3). The reactions using $Zn(OTf)_2$ and TMSOTf gave a mixture of **63a** and **63b** in the same ratio (43:57, Table 2-6, entries 2 and 3), and triisopropylsilyl-protected aldimine did not improve the ratio in the presence of TMSOTf at 4 °C in dichloromethane. However, **63b** could be obtained with high selectivity with $TiCl_4$ in *i*-PrCN (entry 1, Table 2-6).



Scheme 2-5

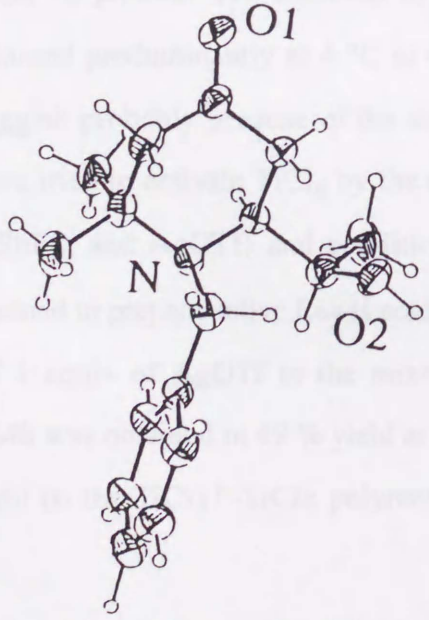
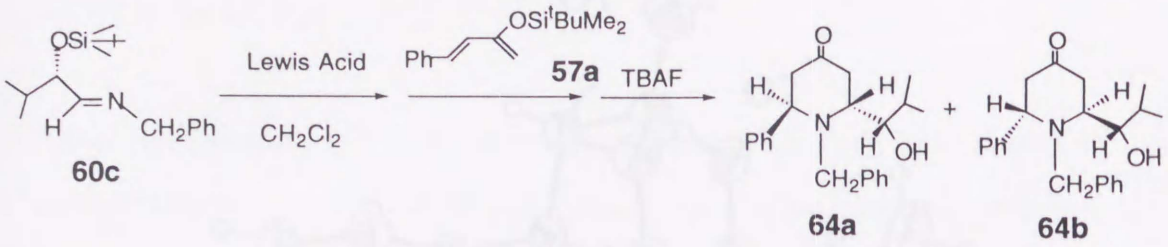


Figure 2-3. X-ray Crystallographic Structure of 63a.

Table 2-6. [4+2]Type Cycloaddition of Aldimine 60a with 57b.

entry	solvent	Lewis acid	conditions	**63a**:**63b**	yield(%)
1	*i*-PrCN	$TiCl_4$	-30 °C, 1 day	9:91	65
2	hexane	$Zn(OTf)_2$	4 °C, 2 days	43:57	75
3	CH_2Cl_2	TMSOTf	4 °C, 1 day	43:57	80

When the aldimine **60c** bearing a bulkier isopropyl group at the α–position was subjected to cyclization with **57a** followed by subsequent treatment with TBAF, cycloadducts (**64a** and **64b**) could be obtained as expected (Table 2-7 and Scheme 2-6). The structural determination could be carried out similarly as mentioned above, and Figure 2-4 shows the X-ray structure of **64a**. In this case, non-chelation product **64a** could not be obtained selectively (entries 1 and 2) similar to the case with 2-silyloxy-1,3-butadiene **57b**. In addition, no product was observed in isobutyronitrile at -30 °C although **64b** could be obtained predominantly at 4 °C in dichloromethane (entry 3). Thus, the reaction was sluggish probably because of the steric hinderance of the *i*-Pr group in **60c**. Therefore, we tried to activate $TiCl_4$ by the use of silver ions. Various silver ions ($AgClO_4$, $AgSbF_6$, and AgOTf) and conditions (the order of addition, temperature etc.) were examined to prepare active Lewis acids. After some experiments, we found that addition of 1 equiv of AgOTf to the mixture was quite effective in activating $TiCl_4$ and only **64b** was obtained in 49 % yield at -30 °C in *i*-PrCN (entry 5). The active Lewis acid might be the $TiCl_3^+$-$TiCl_4$ polymer catalyst judging from the experiments in Chapter 1.



Scheme 2-6

Table 2-7. [4+2]Type Cycloaddition of Aldimine 60c with 57a.

entry	solvent	Lewis acid	conditions	**64a**:**64b**	yield(%)
1	CH_2Cl_2	TMSOTf	4 °C, 7 days	43:57	91
2	CH_2Cl_2	$Zn(OTf)_2$	4 °C, 7 days	49:51	59
3	CH_2Cl_2	$TiCl_4$	4 °C, 11 days	30:70	91
4	*i*-PrCN	$TiCl_4$	-30 °C, 1 day	-	0
5	*i*-PrCN	$TiCl_4$-AgOTf	-30 °C, 1 day	<2:>98	49

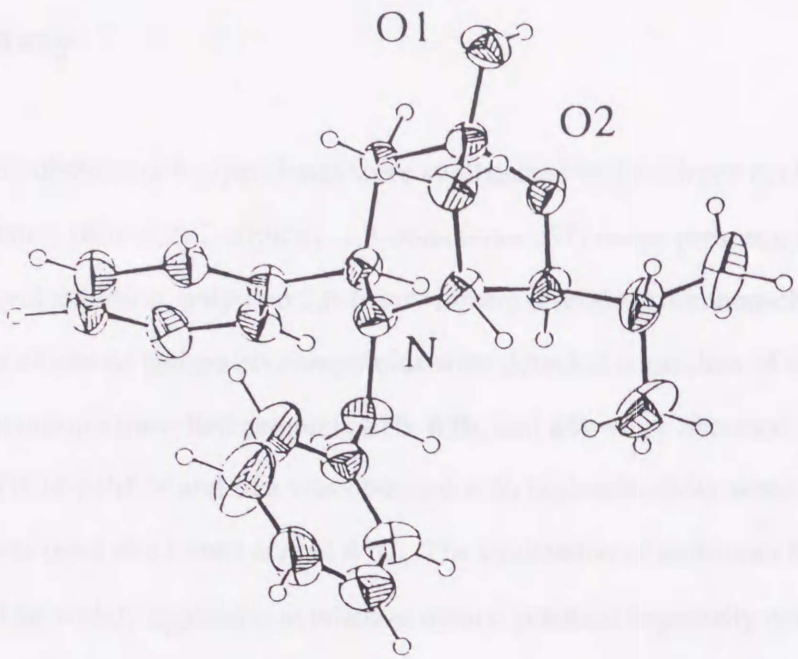
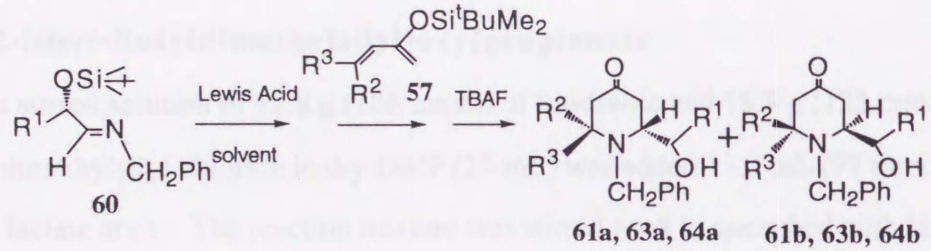


Figure 2-4. X-ray Crystallographic Structure of 64a.

The mechanism of [4+2]type cycloadditions involving aldimines is quite complex and a stepwise mechanism[20] and a concerted mechanism[16] have been suggested. Recently, Akiba et.al. reported on [4+2]type cycloaddition of diene **57** to chromone[21] and coumarin[22] activated by TBDMSOTf (*t*-butyldimethylsilyl triflate) and it was concluded that only the former proceeded through a silyloxyallyl cation intermediate based on a successful trapping experiment by the use of sterically hindered **57b**. Therefore, in order to gain insight on the mechanism of the reaction of **60a** with **57b** catalyzed by TMSOTf, the mixture was quenched after stirring for 15 min at 0 °C. However, only cyclic products **63** were obtained in 63% yield and no acyclic products were isolated. In addition, only cyclic products **61** were isolated in 20% yield when the reaction of **60a** with **57a** was carried out at 0 °C for 1 min in the presence of TMSOTf. These results suggest that the reaction proceeds through a concerted mechanism or a stepwise mechanism in which cyclization of cation intermediates is fast.

2-4. Summary

Trans-2,6-disubstituted-4-piperidones were synthesized by [4+2]type cycloaddition of chiral aldimines (**60**) with 2-silyloxy-1,3-butadienes (**57**) in the presence of Lewis acids. In the cycloaddition, only two 2,6-*trans* isomers (chelation and non-chelation products) were observed and no *cis* compounds were detected regardless of the Lewis acid used. Chelation-controlled products **61b**, **63b**, and **64b** were obtained selectively by the use of $TiCl_4$-*i*-PrCN and **61a** was obtained with high selectivity when TMSOTf or $Zn(OTf)_2$ was used as a Lewis acid at 4 °C. The cyclization of aldimines bearing α-hydrogens will be widely applied to synthesize natural products especially containing a piperidone fragment.



2-5 Experimental Section

^{1}H NMR spectra were recorded at 400MHz (JEOL EX400) in $CDCl_3$ in the presence of TMS as an internal standard. Melting points were taken on a micro melting point apparatus (Yanagimoto model) and are uncorrected. High-resolution mass spectra were recorded on a JEOL SX-102A spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400 CHN elemental analyzer. All reactions were conducted under an argon atmosphere.

Preparation of Ethyl (*S*)-*N*-2-[(*tert*-Butyldimethylsilyl)oxy]propylidene Benzylamine.

(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]propionate

To a stirred solution of 12.8 g (188 mmol) of imidazole and 18.8 g (125 mmol) of *t*-butyldimethylsilyl chloride in dry DMF (25 mL) was added 11.0 mL (97 mmol) of (*S*)-ethyl lactate at r.t.. The reaction mixture was stirred for 8 h, quenched with H_2O (30 mL), and extracted with ether (150 mL). The collected organic layers were washed with H_2O (100 mLx10), dried over $MgSO_4$, and the solvent was evaporated. The crude product was distilled (b.p. 95-105 °C / 2 mmHg, 20 g, 92% yield).

^{1}H NMR ($CDCl_3$) 0.06 (s, 3 H), 0.09 (s, 3 H), 0.90 (s, 9 H), 1.26 (t, 3 H, J = 7.0 Hz), 1.38 (d, 3 H, J = 6.8 Hz), 4.10-4.23 (m, 2 H), 4.29 (q, 1 H, J = 6.8 Hz).

(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]propanal

To a stirred solution of 8.53 mL (34 mmol) of ethyl (*S*)-2-[(*tert*-butyldimethylsilyl)oxy]propionate in dry CH_2Cl_2 (36 mL) was added slowly 36.3 mL (36.3 mmol) of diisopropylaluminum hydride (1.0 M in hexane solution) at -78 °C. The reaction mixture was stirred for 20 min, dry MeOH (3.6 mL) was added to the solution at -78 °C, then the mixture was stirred for 1.5 h at r.t.. After stirring, inorganic precipitate

was filtered through Celite and the filtrate was evaporated. The crude product was purified by distillation (b.p. 83-85 °C / 25 mmHg, 5.0 g, 78% yield).

^{1}H NMR ($CDCl_3$) 0.06 (s, 3 H), 0.09 (s, 3 H), 0.90 (s, 9 H), 1.27 (d, 3 H, J = 7.1 Hz), 4.10 (q, 1 H, J = 7.1 Hz), 9.62 (s, 1 H).

(*S*)-*N*-2-[(*tert*-Butyldimethylsilyl)oxy]propylidene Benzylamine

To a stirred mixture of 2.4 mL (22 mmol) of benzylamine and 20 g of molecular sieves 4A in dry ether (40 mL) was added 3.5 g (18 mmol) of (*S*)-2-[(*tert*-butyldimethylsilyl)oxy]propanal at r.t.. The reaction mixture was stirred at r.t. for 3 h and molecular sieves 4A was filtered off. The solvent of the filtrate was evaporated and the crude product was purified by vacuum distillation (b.p. 116-120 °C / 0.7 mmHg, 3.0 g, 58% yield).

^{1}H NMR ($CDCl_3$) 0.06 (s, 3 H), 0.09 (s, 3 H), 0.90 (s, 9 H), 1.22 (d, 3 H, J = 6.8 Hz), 4.29 (m, 1 H), 4.49 (s, 2 H), 7.15-7.26 (m, 4 H), 7.57 (d, 1 H, J = 5.4 Hz).

Preparation of (*S*)-*N*-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbutylidene Benzylamine.

(*S*)-2-Hydroxy-3-methylbutanoic Acid

To a stirred solution of 4.6 g (427 mmol) of (*S*)-valine in H_2O (330 mL) was added dropwise slowly 2 N H_2SO_4 (213 mL) by use of dropping funnel at 0 °C. After the valine dissolved into the solution, 2 N $NaNO_2$ (213 mL) was added dropwise to the solution. The rate of the additions of both reagents should be similar. After reaction mixture was stirred for 3 h at 0 °C and for 12 h at r.t., the mixture was extracted with CH_3COOEt (100 mLx3). The collected organic layers were dried over Na_2SO_4 and the solvent was evaporated. The crude product was purified by recrystallization (ether / hexane, mp 64-65 °C, 65% yield).

Ethyl (*S*)-2-Hydroxy-3-methylbutanoate

To a stirred solution of 19 g (161 mmol) of (*S*)-2-hydroxy-3-methylbutanoic acid and 99% EtOH (130 mL) was added slowly 4 mL of conc. H_2SO_4 at r.t.. The reaction mixture was refluxed for 12 h, and the solvent was evaporated. Then, the crude mixture was extracted with ether (150 mL), washed with sat.$NaHCO_3$ aq. (100 mLx2), and the collected organics were dried over Na_2SO_4. After the solvent was evaporated, crude product was purified by distillation (83-84 °C / 30 mmHg, 14 g, 59%).

^{1}H NMR ($CDCl_3$) 0.84 (d, 3 H, J = 6.9 Hz), 1.00 (d, 3 H, J = 6.9 Hz), 1.28 (t, 3 H, J = 6.8 Hz), 2.00-2.12 (m, 1 H), 2.77 (d, 1 H, J =6.0 Hz), 3.95(m, 1 H), 4.10-4.25 (m, 2 H).

Ethyl (*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-butanoate

To a stirred solution of 7.9 g (116 mmol) of imidazole and 10.7 g (71 mmol) of *t*-butyldimethylsilyl chloride in dry DMF (30 mL) was added 8.1 mL (58 mmol) of ethyl (*S*)-2-hydroxy-3-methylbutanoate at r.t.. The reaction mixture was stirred for 8 h, quenched with H_2O (30 mL), and extracted with ether (150 mL). The collected organic layers were washed with H_2O (100 mLx10), dried over $MgSO_4$, and the solvent was evaporated. The crude product was distilled (b.p. 127-129 °C / 24mmHg, 14 g, 91% yield).

^{1}H NMR ($CDCl_3$) 0.02 (s, 3 H), 0.04 (s, 3 H), 0.90 (s, 9 H), 0.85-0.95 (m, 6 H), 1.25 (t, 3 H, J = 7.3 Hz), 1.96-2.08 (m, 1 H), 3.92 (d, 1 H, J = 4.9 Hz), 4.10-4.21(m, 1 H).

(*S*)-2-[(*tert*-Butyldimethysilyl)oxy]-3-methylbutanal

To a stirred solution of 13.8 g (53 mmol) of ethyl (*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-butanoate in dry CH_2Cl_2 (50 mL) was added slowly 60 mL (60 mmol) of diisopropylaluminum hydride (1.0M in hexane solution) at -78 °C. The reaction mixture was stirred for 20 min, dry MeOH (5.6 mL) was added to the solution at -78 °C, then the

mixture was stirred for 1.5 h at r.t.. After stirring, inorganic precipitate was filtered through Celite and the filtrate was evaporated. The crude product was purified by distillation (b.p. 98-100 °C / 18 mmHg, 8.8 g, 77% yield).

^{1}H NMR ($CDCl_3$) 0.05 (s, 6 H), 0.93 (s, 9 H), 0.85-1.00 (m, 6 H), 1.90-2.08 (m, 1 H), 3.71 (dd, 1 H, J = 2.1, 4.9 Hz), 9.59 (d, 1 H, J = 2.1 Hz).

(*S*)-*N*-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methylbutylidene Benzylamine

To a stirred mixture of 4.9 mL (44 mmol) of benzylamine and 20 g of molecular sieves 4A in dry ether (40 mL) was added 8.8 g (41 mmol) of (*S*)-2-[(*tert*-butyldimethysilyl)oxy]-3-methylbutanal at r.t.. The reaction mixture was stirred at r.t. for 3 h and molecular sieves 4A was filtered off. The solvent of the filtrate was evaporated and the crude product was purified by vacuum distillation (b.p. 120-125 °C / 0.1 mmHg, 7.1 g, 57% yield).

^{1}H NMR ($CDCl_3$) 0.04 (s, 3 H), 0.10 (s, 3 H), 0.95 (s, 9 H), 0.95-1.01 (m, 6 H), 1.87-1.97(m, 1 H), 3.97 (t, 1H, J = 5.9Hz), 4.64 (s, 2 H), 7.25-7.40 (m, 5 H), 7.66 (d, 1 H, J = 6.4 Hz).

Preparation of (*S*)-N-2-Benzyloxypropylidene Benzylamine.

Ethyl (*S*)-2-Benzyloxypropionate

To a stirred solution of 11 g (285 mmol) of NaH in dry THF (30 mL) was added 27 mL (238 mmol) of (*S*)-ethyl lactate at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, benzyl bromide (34.8 mL, 292 mmol) and TBAI (1.01 g, 2.9 mmol) in dry THF (20 mL) was added to the solution slowly and stirred for 14 h at r.t.. The mixture was quenched with H_2O (40 mL), and extracted with ether (300 mL). Then, the collected organic layers were dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by distillation (b.p. 86-90 °C / 20 mmHg, 42 g, 85% yield).

^{1}H NMR ($CDCl_3$) 1.30 (t, 3 H, J = 6.8 Hz), 1.43 (d, 3 H, J = 6.8 Hz), 4.04 (q, 1 H, J = 6.8 Hz), 4.21 (dq, 2 H, J = 2.7, 6.8 Hz), 4.50 (d, 1 H, J = 12.3 Hz), 4.71 (d, 1 H, J = 12.3 Hz), 7.28-7.37 (m, 5 H).

(*S*)-2-Benzyloxypropanal

To a stirred solution of 30 mL (156 mmol) of ethyl (*S*)-2-benzyloxypropionate in dry CH_2Cl_2 (100 mL) was added slowly 162 mL (162 mmol) of diisopropylaluminum hydride (1.0 M in hexane solution) at -78 °C. The reaction mixture was stirred for 20 min, dry MeOH (16.5 mL) was added to the solution at -78 °C, then the mixture was stirred for 1.5 h at r.t.. After stirring, inorganic precipitate was filtered through Celite and the filtrate was evaporated. The crude product was used for next reaction without purification (21 g, 81% yield).

^{1}H NMR ($CDCl_3$) 1.31 (d, 3 H, J = 7.3 Hz), 3.85-3.90 (m, 1 H), 4.58 (d, 1 H, J = 11.7 Hz), 4.64 (d, 1 H, J = 11.7 Hz), 7.24-7.36 (m, 5 H), 9.65 (d, 1H, J = 1.5 Hz).

(*S*)-*N*-2-Benzyloxypropylidene Benzylamine

To a stirred mixture of 4.6 mL (42.4 mmol) of benzylamine and 20 g of molecular sieves 4A in dry ether (40 mL) was added 5.6 g (35 mmol) of (*S*)-2-benzyloxypropanal at r.t.. The reaction mixture was stirred at r.t. for 3 h and molecular sieves 4A was filtered off. The solvent of the filtrate was evaporated and the crude product was purified by vacuum distillation (4.1 g, 49% yield).

^{1}H NMR ($CDCl_3$) 1.38 (d, 3 H, J = 6.4 Hz), 3.85 (d, 1 H, J = 19.0 Hz), 4.10-4.18 (m, 1 H), 4.52-4.64 (m, 3 H), 7.26-7.37 (m, 10 H), 7.71 (d, 1 H, J = 5.3 Hz).

Typical Procedures for $TiCl_4$-catalyzed [4+2]Type Cycloadditions:

Titanium tetrachloride (0.38 mmol) and 1.36 mmol of **57a** were added to 0.34 mmol of **60a** in dry isobutyronitrile (2.8 mL) at -30 °C under nitrogen. After stirring at -30 °C for 1 day, the reaction mixture was poured into aq $NaHCO_3$ followed by extraction

with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The residue was dissolved in THF and 1.3 mmol of TBAF (in THF solution) was added to the solution. The reaction mixture was stirred for 10 h, quenched with water, extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$. After the solvent was removed in vacuo, the crude product was separated by recycle HPLC (JAI LC 908, JAIGEL-1H and 2H, 1,2-dichloroethane).

Typical Procedures for $Zn(OTf)_2$-catalyzed [4+2]Type Cycloadditions:

To a stirred solution of 0.38 mmol of $Zn(OTf)_2$ in dry hexane (4.1 mL) was added 0.34 mmol of **60a** at 0 °C under nitrogen. Following the addition of **57a** (1.36 mmol), the mixture was stirred at 4 °C for 3 days. The resulting mixture was poured into aq $NaHCO_3$ and extracted with CH_2Cl_2. After the combined organic layers were dried over $MgSO_4$, the solvent was evaporated. The residue was dissolved in THF and 1.3 mmol of TBAF (in THF solution) was added to the solution. The reaction mixture was stirred for 10 h, quenched with water, extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$. After the solvent was removed in vacuo, the crude product was separated by recycle HPLC (JAI LC 908, JAIGEL-1H and 2H, 1,2-dichloroethane).

Typical procedures for runs using TMSOTf were almost the same as for $TiCl_4$ except that dichloromethane or toluene was used as a solvent.

61a: colorless crystals (ether / *n*-hexane). mp 147-148 °C. ^1H NMR ($CDCl_3$): δ 1.20 (d, J = 6.4 Hz, 3 H), 1.56 (brs, 1 H), 1.81-2.08 (m, 4 H), 3.10 (d, J = 4.4 Hz, 1 H), 3.18 (d, J = 14.2 Hz, 1 H), 3.63 (d, J = 14.2 Hz, 1 H), 3.80 (dd, J = 5.4, 10.8 Hz, 1 H), 4.48 (q, J = 6.4 Hz, 1 H), 7.22-7.60 (m, 10 H). Anal. Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.89; H, 7.66; N, 4.58.

61b: colorless oil . ^{1}H NMR ($CDCl_3$): δ 1.04 (d, J = 5.8 Hz, 3 H), 1.55 (brs, 1 H), 2.30 (dd, J = 15.1, 3.9 Hz, 1 H), 2.58-2.95 (m, 4 H), 3.47 (d, J = 13.5 Hz, 1 H), 3.78-3.90 (m, 2 H), 4.52 (dd, J = 10.7, 3.9 Hz, 1 H), 7.13-7.39 (m, 10 H). HRMS: m/z Calcd for $C_{20}H_{23}NO_2$: 309.1729. Found: 309.1753.

62a: colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.31 (d, J = 6.4 Hz, 3 H), 2.41 (dd, J = 14.9, 3.4 Hz, 1 H), 2.66 (dd, J = 15.3, 6.3 Hz, 1 H), 2.74-2.77 (m, 2 H), 3.06-3.10 (m, 1 H), 3.50-3.59 (m, 1 H), 3.55 (d, J = 13.7 Hz, 1 H), 3.88 (d, J = 13.7 Hz, 1 H), 4.36 (d, J = 11.7 Hz, 1 H), 4.52 (d, J = 11.7 Hz, 1 H), 4.90 (dq, J = 4.9, 6.4 Hz, 1 H), 7.20-7.50 (m, 15 H). HRMS: m/z Calcd for $C_{27}H_{29}NO_2$: 399.2199. Found: 399.2202.

62b: colorless oil . ^{1}H NMR ($CDCl_3$): δ 1.17 (d, J = 6.4 Hz, 3 H), 2.50-2.55 (m, 4 H), 3.01-3.03 (m, 1 H), 3.48 (d, J = 13.6 Hz, 1 H), 3.63 (d, J = 13.6 Hz, 1 H), 3.96-4.03 (m, 1 H), 4.26-4.35 (m, 1 H), 4.42 (d, J = 11.5 Hz, 1 H), 4.63 (d, J = 11.5 Hz, 1 H), 7.05-7.45 (m, 15 H). HRMS: m/z Calcd for $C_{27}H_{29}NO_2$: 399.2178. Found: 399.2188.

63a: colorless crystals (ether / *n*-hexane). mp 106-107°C. ^{1}H NMR ($CDCl_3$): δ 0.94 (d, J = 6.8 Hz, 3 H), 1.06 (s, 3 H), 1.37 (s, 3 H), 1.60 (brs, 1 H), 2.20-2.31 (m, 2 H), 2.65-2.83 (m, 3 H), 3.35 (d, J = 17.1 Hz, 1 H), 3.88-3.91 (m, 1 H), 4.24 (d, J = 17.1 Hz, 1 H), 7.22-7.47 (m, 5 H). Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.38; H, 8.84; N, 5.76.

63b: colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.96 (d, J = 6.3 Hz, 3 H), 1.30 (s, 3 H), 1.32 (s, 3 H), 2.17-2.59 (m, 4 H), 3.13 (dt, J = 8.6, 4.3 Hz, 1 H), 3.52 (dq, J = 8.6, 6.3 Hz, 1 H), 3.80 (d, J = 15.8 Hz, 1 H), 4.00 (d, J = 15.8 Hz, 1 H), 7.24-7.42 (m, 5 H). HRMS: m/z Calcd for $C_{16}H_{23}NO_2$: 261.1729. Found: 261.1725.

64a: To an isobutyronitrile (2 mL) solution of **60a** (0.15 mL, 0.45 mmol) was added isobutyronitrile (4 mL) solution of titanium tetrachloride (0.08 ml, 0.68 mmol) and silver triflate (0.17 g, 0.69 mmol) at -30 °C under nitrogen. Following the addition of **57a** (0.45 mL, 1.8 mmol), the mixture was stirred at -30 °C for 1 day. The reaction mixture was poured into aq $NaHCO_3$ followed by extraction with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. The residue was dissolved in THF and 1.8 mmol of TBAF (in THF solution) was added to the solution. The reaction mixture was stirred for 10 h, quenched with water, extracted with CH_2Cl_2, and the combined organics were dried over $MgSO_4$. After the solvent was removed in vacuo, the crude product was separated by recycle HPLC (JAI LC 908, JAIGEL-1H and 2H, 1,2-dichloroethane). Subsequent recrystallization from ether / *n*-hexane gave **64a** (74 mg, yield 49 %) as colorless crystals.
^1H NMR ($CDCl_3$): δ 0.75 (d, J = 6.3 Hz, 3 H), 1.05 (d, J = 6.3 Hz, 3 H), 1.45-1.55 (m, 1 H), 1.86-2.10 (m, 4 H), 3.16 (d, J = 14.2 Hz, 1 H), 3.15-3.25 (m, 1 H), 3.60 (d, J = 14.2 Hz, 1 H), 3.70-3.85 (m, 1 H), 4.15-4.25 (m, 1 H), 7.15-7.60 (m, 10 H). Anal. Calcd for $C_{22}H_{27}NO_2$: C, 78.30; H, 8.06; N, 4.15. Found: C, 78.30; H, 8.27; N, 4.08.

64b: colorless oil . ^1H NMR ($CDCl_3$): δ 0.60 (d, J = 6.3 Hz, 3 H), 1.06 (d, J = 6.3 Hz, 3 H), 1.70-1.85 (m, 1 H), 2.36-2.45 (m, 1 H), 2.70-2.85 (m, 2 H), 2.98-3.10 (m, 1 H), 3.20-3.25 (m, 1 H), 3.62 (d, J = 14.0 Hz, 1 H), 3.58-3.63 (m, 1H), 3.90 (d, J = 14.0 Hz, 1 H), 4.63-4.70 (m, 1 H), 7.20-7.75 (m, 10 H).

Crystal Structure of 61a, 63a, and 64a.

Crystallographic data for **61a:** $C_{20}H_{23}NO_2$, FW = 309.0, *orthorhombic*, space group $P2_12_12_1$, a = 11.380(2) Å, b = 25.362(2) Å, c = 6.016(2) Å, V = 1736.4(7) $Å^3$, Z = 4, D cal = 1.18 g/cm^3, μ = 0.42 cm^{-1}. T = 297 K. Final R = 0.054 (Rw= 0.063) for

1389 observed reflections with F>3σ(*F*). Crystallographic data for **63a:** $C_{16}H_{23}NO_2$, FW = 261.4, *monoclinic*, space group $P2_1/n$, a = 15.878(4) Å, b = 7.721(2) Å, c = 13.083(4) Å, β = 111.53(2) °, V = 1492.1(7) Å^3, Z = 4, D cal = 1.16 g/cm^3, μ = 0.42 cm^{-1}. T = 297 K. Final R = 0.071 (Rw= 0.094) for 1645 observed reflections with F>3σ(*F*). Crystallographic data for **64a:** $C_{22}H_{27}NO_2$, FW = 337.0, *Trigonal*, space group $P322_1$, a = 10.478(2) Å, b = 10.478(2) Å, c = 31.20(1) Å, V = 2966(2) Å^3, Z = 6, D cal = 1.13 g/cm^3, μ = 0.39 cm^{-1}. T = 297 K. Final R = 0.076 (Rw= 0.066) for 1242 observed reflections with F>3σ(*F*).

Crystals suitable for X-ray structure determination were mounted on a Mac Science MXC3 diffractometer and irradiated with graphite-monochromated Mo *K*α radiation (λ = 0.71073 Å) for data collection. Lattice parameters were determined by least-squares fitting of 21-31 reflections with 27°<2θ<32°, 19°<2θ<30°, and 24°<2θ<35° for **61a**, **63a**, and **64a**, respectively. Data were collected with the 2θ/ω scan mode. The structure was solved by a direct method with a program, Monte Carlo-Multan.[25] Refinement on *F* was carried out by full-matrix least-squares. All non-hydrogen atoms were refined with anisotropic themal parameters. All hydrogen atoms in **61a** and **63a** could be found on a difference Fourier map; these coordinates were included in the refinement with isotropic thermal parameters. The hydrogen atoms in **64a** were included in the refinement on calculated positions (C-H = 1.0 Å) riding on their carrier atoms with isotropic thermal parameters. All the computations were carried out on a Titan-750 computer using the crystan-G program. Atomic coordinates, bond distances and angles, and crystallographic data show Table 2-8, 2-9, 2-10, 2-11 (**61a**), 2-12, 2-13, 2-14, 2-15 (**63a**), 2-16, 2-17, 2-18, and 2-19 (**64a**).

Table 2-8

Intramolecular Distances (A) with e.s.d. in parentheses

atom	atom	distance
O 1	--C 4	1.387 (6)
O 2	--C 20	1.435 (7)
O 2	--C 4	1.458 (6)
N 1	--C 7	1.472 (7)
N 1	--C 6	1.474 (6)
N 1	--C 2	1.488 (7)
C 2	--C 14	1.525 (7)
C 2	--C 3	1.543 (8)
C 3	--C 4	1.512 (8)
C 4	--C 5	1.517 (8)
C 5	--C 6	1.518 (8)
C 6	--C 20	1.534 (8)
C 7	--C 8	1.505 (8)
C 8	--C 9	1.36 (1)
C 8	--C 13	1.394 (9)
C 9	--C 10	1.41 (1)
C 10	--C 11	1.41 (2)
C 11	--C 12	1.32 (2)
C 12	--C 13	1.36 (1)
C 14	--C 15	1.373 (8)
C 14	--C 19	1.404 (8)
C 15	--C 16	1.390 (9)
C 16	--C 17	1.36 (1)
C 17	--C 18	1.38 (1)
C 18	--C 19	1.389 (9)
C 20	--C 21	1.523 (9)

Table 2-9

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom	atom	atom	angle
C 20	--O 2	--C 4	109.6 (4)
C 7	--N 1	--C 6	113.0 (4)
C 7	--N 1	--C 2	109.6 (4)
C 6	--N 1	--C 2	113.1 (4)
N 1	--C 2	--C 14	108.7 (4)
N 1	--C 2	--C 3	112.7 (4)
C 14	--C 2	--C 3	109.7 (4)
C 4	--C 3	--C 2	113.4 (4)
O 1	--C 4	--O 2	109.2 (4)
O 1	--C 4	--C 3	109.1 (4)
O 1	--C 4	--C 5	117.3 (4)
O 2	--C 4	--C 3	109.7 (4)
O 2	--C 4	--C 5	102.0 (4)
C 3	--C 4	--C 5	109.1 (4)
C 4	--C 5	--C 6	99.3 (4)
N 1	--C 6	--C 5	108.5 (4)
N 1	--C 6	--C 20	114.9 (5)
C 5	--C 6	--C 20	101.0 (4)
N 1	--C 7	--C 8	112.4 (5)
C 9	--C 8	--C 13	117.9 (6)
C 9	--C 8	--C 7	121.2 (5)
C 13	--C 8	--C 7	120.9 (6)
C 8	--C 9	--C 10	121.4 (7)
C 11	--C 10	--C 9	117.0 (9)
C 12	--C 11	--C 10	121.3 (9)
C 11	--C 12	--C 13	120.6 (9)
C 12	--C 13	--C 8	121.7 (8)
C 15	--C 14	--C 19	118.6 (5)
C 15	--C 14	--C 2	122.0 (5)
C 19	--C 14	--C 2	119.4 (5)
C 14	--C 15	--C 16	120.8 (6)
C 17	--C 16	--C 15	120.7 (7)
C 16	--C 17	--C 18	119.5 (6)
C 17	--C 18	--C 19	120.4 (7)
C 18	--C 19	--C 14	119.9 (6)
O 2	--C 20	--C 21	109.9 (5)
O 2	--C 20	--C 6	104.6 (4)
C 21	--C 20	--C 6	114.2 (5)

```
***** torsional angles *****

# ns1,atm1,ns2,atm2,ns3,atm3
no. 1   ( 1 H 20 )   ( 1 C 20 )   ( 1 C 6  )
# ns1,atm1,ns2,atm2,ns3,atm3
no. 2   ( 1 C 20 )   ( 1 C 6  )   ( 1 H 6  )

angle between plane no. a and no. b
  a  b   angle
  1  2   91.14

***** torsional angles *****

# ns1,atm1,ns2,atm2,ns3,atm3
no. 1   ( 1 H 6  )   ( 1 C 6  )   ( 1 C 5  )
# ns1,atm1,ns2,atm2,ns3,atm3
no. 2   ( 1 C 6  )   ( 1 C 5  )   ( 1 H 5 B)
# ns1,atm1,ns2,atm2,ns3,atm3
no. 3   ( 1 C 6  )   ( 1 C 5  )   ( 1 H 5 A)

angle between plane no. a and no. b
  a  b   angle   a  b   angle   a  b   angle
  1  2  129.77   1  3   77.80   2  3   51.97

***** torsional angles *****

# ns1,atm1,ns2,atm2,ns3,atm3
no. 1   ( 1 H 2  )   ( 1 C 2  )   ( 1 C 3  )
# ns1,atm1,ns2,atm2,ns3,atm3
no. 2   ( 1 C 2  )   ( 1 C 3  )   ( 1 H 3 A)
# ns1,atm1,ns2,atm2,ns3,atm3
no. 3   ( 1 C 2  )   ( 1 C 3  )   ( 1 H 3 B)

angle between plane no. a and no. b
  a  b   angle   a  b   angle   a  b   angle
  1  2  142.90   1  3   24.60   2  3  118.30
```

Table 2-10

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
O 1	-0.1562 (3)	-0.0264 (1)	-0.0226 (6)	3.8 (1)
O 2	-0.2192 (3)	0.0552 (2)	-0.1496 (6)	4.3 (1)
N 1	0.0081 (3)	0.1216 (2)	-0.0615 (6)	3.3 (1)
C 2	0.0236 (4)	0.0850 (2)	-0.2524 (9)	3.3 (2)
C 3	-0.0160 (5)	0.0283 (2)	-0.199 (1)	3.8 (2)
C 4	-0.1227 (4)	0.0258 (2)	-0.0492 (9)	3.3 (2)
C 5	-0.0988 (5)	0.0575 (2)	0.1600 (9)	3.3 (2)
C 6	-0.1020 (4)	0.1126 (2)	0.062 (1)	3.4 (2)
C 7	0.0214 (6)	0.1765 (2)	-0.138 (1)	4.4 (2)
C 8	0.0299 (5)	0.2149 (2)	0.052 (1)	4.2 (2)
C 9	0.1293 (6)	0.2187 (3)	0.177 (1)	5.7 (2)
C 10	0.137 (1)	0.2537 (4)	0.359 (2)	8.0 (3)
C 11	0.038 (1)	0.2861 (3)	0.400 (2)	8.6 (4)
C 12	-0.058 (1)	0.2829 (3)	0.275 (2)	8.6 (4)
C 13	-0.0639 (6)	0.2480 (3)	0.105 (2)	6.5 (2)
C 14	0.1528 (4)	0.0850 (2)	-0.3201 (9)	3.5 (2)
C 15	0.1886 (5)	0.1006 (2)	-0.528 (1)	4.2 (2)
C 16	0.3070 (6)	0.1001 (3)	-0.585 (1)	5.2 (2)
C 17	0.3900 (6)	0.0839 (3)	-0.437 (1)	5.2 (2)
C 18	0.3556 (6)	0.0668 (3)	-0.229 (1)	5.8 (2)
C 19	0.2376 (5)	0.0664 (3)	-0.170 (1)	4.8 (2)
C 20	-0.2129 (5)	0.1094 (2)	-0.083 (1)	4.0 (2)
C 21	-0.3255 (6)	0.1251 (3)	0.037 (1)	5.5 (2)
H 3 A	-0.030 (6)	0.013 (2)	-0.33 (1)	3.81 (0)
H 5 A	-0.023 (6)	0.045 (2)	0.23 (1)	3.34 (0)
H 2	-0.024 (5)	0.100 (2)	-0.39 (1)	3.33 (0)
H 21A	-0.327 (6)	0.112 (3)	0.20 (1)	5.54 (0)
H 6	-0.108 (5)	0.141 (2)	0.17 (1)	3.45 (0)
H 7	0.102 (6)	0.181 (2)	-0.23 (1)	4.44 (0)
H 3 B	0.050 (5)	0.004 (2)	-0.11 (1)	3.81 (0)
H 38	-0.040 (6)	0.181 (2)	-0.24 (1)	4.08 (0)
H 5 B	-0.162 (6)	0.051 (2)	0.27 (1)	3.34 (0)
H 9	0.191 (6)	0.193 (3)	0.13 (1)	5.70 (0)
H 12	-0.133 (8)	0.305 (3)	0.31 (2)	8.64 (0)
H 15	0.130 (6)	0.109 (2)	-0.63 (1)	4.21 (0)
H 19	0.209 (6)	0.053 (3)	-0.03 (1)	4.81 (0)
H 18	0.411 (6)	0.048 (3)	-0.12 (1)	5.76 (0)
H 17	0.474 (6)	0.085 (3)	-0.49 (1)	5.17 (0)
H 21B	-0.329 (6)	0.161 (3)	0.09 (1)	5.54 (0)
H 47	-0.202 (5)	-0.028 (2)	0.11 (1)	4.08 (0)
H 10	0.210 (7)	0.253 (4)	0.43 (2)	7.98 (0)
H 31	0.056 (6)	0.308 (2)	0.53 (1)	4.08 (0)
H 24	0.330 (6)	0.108 (2)	-0.74 (1)	4.08 (0)
H 13	-0.139 (7)	0.249 (3)	0.03 (1)	6.52 (0)
H 21C	-0.396 (6)	0.113 (3)	-0.05 (1)	5.54 (0)
H 20	-0.205 (6)	0.132 (3)	-0.21 (1)	3.99 (0)

Table 2-11

No	
formula	$C_{20}H_{23}NO_2$
mol wt	309.0
cryst syst	orthorhombic
space group	*P212121*
cryst dimens, mm	0.55 x 0.50 x 0.30
a, Å	11.380 (2)
b, Å	25.362 (4)
c, Å	6.016 (2)
α, deg	90
β, deg	90
γ, deg	90
V, Å^3	1736.4 (7)
Z	4
D_{calc}, g cm^{-3}	1.18
abs coeff, cm^{-1}	0.42
F(000)	664
radiation; λ, Å	Mo Kα, 0.71073
temp, °C	23 ± 1
2θ max, deg	50
scan rate, deg/min	2.0
linear decay,%	-
data collected	$-h,+k,+l$
total data collcd, unique,obsd	1847, 1794, 1389 (F>3σ(F)
R int	0.02
no of params refined	283
R, R_w, S^a	0.054, 0.063, 2.13
max shift in final cycle	0.50
final diff map, max, e/Å^3	0.19

[a] Function minimized was sum $[w(|Fo|^2-|Fc|^2)^2]$ which $w=1.0/[(\sigma|Fo|^2+0.0003|Fo|^2]$.
$R=\Sigma[(||Fo|-|Fc||)/\Sigma|Fo|$. $Rw=[\Sigma w(|Fo|-|Fc|)^2/\Sigma|Fo|^2]^{1/2}$.

Table 2-12

Intramolecular Distances (A) with e.s.d. in parentheses

atom	atom	distance
O 1	--C 4	1.227 (5)
O 2	--C 16	1.431 (6)
N 1	--C 6	1.456 (4)
N 1	--C 2	1.473 (5)
N 1	--C 7	1.475 (5)
C 2	--C 14	1.528 (6)
C 2	--C 15	1.534 (7)
C 2	--C 3	1.557 (7)
C 3	--C 4	1.481 (6)
C 4	--C 5	1.483 (6)
C 5	--C 6	1.541 (7)
C 6	--C 16	1.536 (5)
C 7	--C 8	1.514 (6)
C 8	--C 9	1.374 (7)
C 8	--C 13	1.402 (5)
C 9	--C 10	1.369 (7)
C 10	--C 11	1.358 (7)
C 11	--C 12	1.359 (9)
C 12	--C 13	1.402 (7)
C 16	--C 17	1.524 (6)

Table 2-13

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom	atom	atom	angle
C 6	--N 1	--C 2	112.3 (3)
C 6	--N 1	--C 7	114.6 (3)
C 2	--N 1	--C 7	115.4 (3)
N 1	--C 2	--C 14	110.4 (3)
N 1	--C 2	--C 15	109.7 (3)
N 1	--C 2	--C 3	110.3 (4)
C 14	--C 2	--C 15	107.7 (4)
C 14	--C 2	--C 3	110.6 (4)
C 15	--C 2	--C 3	108.1 (4)
C 4	--C 3	--C 2	111.0 (4)
O 1	--C 4	--C 3	122.9 (4)
O 1	--C 4	--C 5	121.6 (4)
C 3	--C 4	--C 5	115.4 (4)
C 4	--C 5	--C 6	110.1 (4)
N 1	--C 6	--C 16	113.4 (3)
N 1	--C 6	--C 5	112.9 (3)
C 16	--C 6	--C 5	111.6 (4)
N 1	--C 7	--C 8	114.0 (4)
C 9	--C 8	--C 13	117.3 (4)
C 9	--C 8	--C 7	123.3 (3)
C 13	--C 8	--C 7	119.2 (4)
C 10	--C 9	--C 8	122.0 (4)
C 11	--C 10	--C 9	121.2 (6)
C 10	--C 11	--C 12	118.6 (5)
C 11	--C 12	--C 13	121.7 (4)
C 12	--C 13	--C 8	119.2 (5)
O 2	--C 16	--C 17	111.7 (4)
O 2	--C 16	--C 6	109.1 (4)
C 17	--C 16	--C 6	111.1 (4)

Table 2-14

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
O 1	0.0909 (3)	0.6252 (4)	0.1267 (3)	7.9 (1)
O 2	0.1152 (2)	-0.0269 (4)	0.1805 (2)	6.4 (1)
N 1	0.1113 (2)	0.2626 (4)	0.3564 (2)	4.24 (9)
C 2	0.1200 (2)	0.4482 (5)	0.3844 (3)	5.0 (1)
C 3	0.1658 (3)	0.5459 (6)	0.3144 (4)	6.0 (1)
C 4	0.1184 (3)	0.5102 (5)	0.1958 (4)	5.6 (1)
C 5	0.1033 (4)	0.3245 (5)	0.1657 (4)	5.9 (1)
C 6	0.0611 (3)	0.2327 (5)	0.2399 (3)	4.4 (1)
C 7	0.1952 (3)	0.1602 (6)	0.4034 (4)	5.3 (1)
C 8	0.2023 (3)	0.0593 (5)	0.5055 (3)	4.8 (1)
C 9	0.1304 (3)	0.0334 (7)	0.5384 (4)	6.2 (1)
C 10	0.1378 (4)	-0.0651 (7)	0.6284 (4)	7.3 (2)
C 11	0.2172 (4)	-0.1426 (7)	0.6892 (4)	7.0 (2)
C 12	0.2902 (4)	-0.1181 (6)	0.6603 (4)	6.5 (2)
C 13	0.2846 (3)	-0.0204 (6)	0.5676 (4)	6.1 (1)
C 14	0.1741 (4)	0.4730 (8)	0.5070 (4)	7.4 (2)
C 15	0.0258 (3)	0.5269 (6)	0.3592 (4)	6.4 (2)
C 16	0.0432 (3)	0.0402 (5)	0.2102 (4)	5.4 (1)
C 17	-0.0488 (4)	0.0144 (8)	0.1188 (4)	7.4 (2)
H 6	-0.007 (3)	0.283 (6)	0.219 (3)	4.19 (0)
H 3 A	0.232 (4)	0.496 (7)	0.345 (4)	5.68 (0)
H 16	0.038 (3)	-0.026 (6)	0.277 (4)	5.06 (0)
H 12	0.341 (4)	-0.179 (8)	0.701 (5)	6.62 (0)
H 13	0.329 (4)	-0.003 (7)	0.543 (4)	5.96 (0)
H 7 A	0.248 (4)	0.217 (6)	0.423 (4)	5.01 (0)
H 5 A	0.159 (4)	0.262 (7)	0.179 (4)	5.47 (0)
H 7 B	0.198 (3)	0.070 (6)	0.344 (4)	5.01 (0)
H 3 B	0.162 (3)	0.672 (8)	0.328 (4)	5.68 (0)
H 10	0.077 (4)	-0.084 (7)	0.646 (4)	7.03 (0)
H 9	0.078 (4)	0.091 (7)	0.496 (4)	5.93 (0)
H 11	0.218 (4)	-0.225 (7)	0.756 (5)	6.89 (0)
H 14A	0.235 (4)	0.443 (8)	0.524 (5)	7.31 (0)
H 15A	0.032 (4)	0.636 (7)	0.394 (4)	6.05 (0)
H 17A	-0.064 (4)	-0.102 (8)	0.092 (5)	7.11 (0)
H 17B	-0.102 (4)	0.039 (8)	0.149 (5)	7.11 (0)
H 15B	-0.011 (4)	0.460 (7)	0.387 (4)	6.05 (0)
H 15C	0.000 (4)	0.547 (7)	0.285 (5)	6.05 (0)
H 2	0.104 (3)	-0.147 (7)	0.164 (4)	4.77 (0)
H 17C	-0.046 (4)	0.106 (8)	0.057 (5)	7.11 (0)
H 5 B	0.068 (3)	0.310 (6)	0.093 (5)	5.47 (0)
H 14B	0.178 (4)	0.584 (9)	0.520 (5)	7.31 (0)
H 14C	0.137 (4)	0.386 (8)	0.552 (5)	7.31 (0)

Table 2-15

No	
formula	$C_{16}H_{23}NO_2$
mol wt	261.4
cryst syst	monoclinic
space group	*P21/n*
cryst dimens, mm	0.75 x 0.60 x 0.25
a, Å	15.878 (4)
b, Å	7.721 (2)
c, Å	13.083 (4)
α, deg	90
β, deg	111.53 (2)
γ, deg	90
V, Å^3	1492.1 (7)
Z	4
D_{calc}, g cm^{-3}	1.16
abs coeff, cm^{-1}	0.42
F(000)	568
radiation; λ, Å	Mo Kα, 0.71073
temp, °C	23 ± 1
2θ max, deg	50
scan rate, deg/min	2.0
linear decay,%	-
data collected	$+h,-k,\pm l$
total data collcd, unique,obsd	2998, 2627, 1645 (F>3σ(F)
R int	0.05
no of params refined	242
R, R_w, S^a	0.071, 0.094, 1.99
max shift in final cycle	1.46
final diff map, max, e/Å^3	0.23

[a] Function minimized was sum $[w(|Fo|^2-|Fc|^2)^2]$ which $w=1.0/[(\sigma|Fo|^2+0.0003|Fo|^2]$.
$R=\Sigma[(||Fo|-|Fc||)/\Sigma|Fo|$. $Rw=[\Sigma w(|Fo|-|Fc|)^2/\Sigma|Fo|^2]^{1/2}$.

Table 2-16

Intramolecular Distances (A) with e.s.d. in parentheses

atom	atom	distance
O 1	--C 4	1.40 (1)
O 2	--C 4	1.427 (8)
O 2	--C 20	1.474 (8)
N 1	--C 7	1.46 (1)
N 1	--C 2	1.469 (9)
N 1	--C 6	1.47 (1)
C 2	--C 14	1.50 (1)
C 2	--C 3	1.54 (1)
C 3	--C 4	1.53 (1)
C 4	--C 5	1.53 (1)
C 5	--C 6	1.52 (1)
C 6	--C 20	1.550 (9)
C 7	--C 8	1.48 (1)
C 8	--C 9	1.36 (1)
C 8	--C 13	1.39 (1)
C 9	--C 10	1.37 (2)
C 10	--C 11	1.38 (1)
C 11	--C 12	1.36 (2)
C 12	--C 13	1.37 (1)
C 14	--C 15	1.37 (1)
C 14	--C 19	1.41 (1)
C 15	--C 16	1.38 (1)
C 16	--C 17	1.37 (2)
C 17	--C 18	1.40 (1)
C 18	--C 19	1.40 (1)
C 20	--C 21	1.55 (1)
C 21	--C 23	1.53 (1)
C 21	--C 22	1.54 (1)

Table 2-17

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom	atom	atom	angle
C 4	--O 2	--C 20	110.6 (4)
C 7	--N 1	--C 2	111.9 (7)
C 7	--N 1	--C 6	112.0 (5)
C 2	--N 1	--C 6	113.4 (5)
N 1	--C 2	--C 14	111.8 (5)
N 1	--C 2	--C 3	110.3 (7)
C 14	--C 2	--C 3	110.5 (5)
C 4	--C 3	--C 2	112.0 (5)
O 1	--C 4	--O 2	111.0 (5)
O 1	--C 4	--C 5	112.2 (8)
O 1	--C 4	--C 3	112.2 (6)
O 2	--C 4	--C 5	102.6 (5)
O 2	--C 4	--C 3	109.7 (7)
C 5	--C 4	--C 3	108.7 (5)
C 6	--C 5	--C 4	98.6 (7)
N 1	--C 6	--C 5	108.1 (5)
N 1	--C 6	--C 20	112.5 (7)
C 5	--C 6	--C 20	102.5 (6)
N 1	--C 7	--C 8	112.9 (8)
C 9	--C 8	--C 13	115.2 (8)
C 9	--C 8	--C 7	123.0 (7)
C 13	--C 8	--C 7	121.8 (8)
C 8	--C 9	--C 10	125.2 (8)
C 9	--C 10	--C 11	118 (1)
C 12	--C 11	--C 10	119 (1)
C 11	--C 12	--C 13	121.5 (9)
C 12	--C 13	--C 8	121.0 (9)
C 15	--C 14	--C 19	118.3 (7)
C 15	--C 14	--C 2	121.8 (9)
C 19	--C 14	--C 2	119.9 (6)
C 14	--C 15	--C 16	122 (1)
C 17	--C 16	--C 15	119.4 (8)
C 16	--C 17	--C 18	120.5 (8)
C 19	--C 18	--C 17	119 (1)
C 18	--C 19	--C 14	120.2 (7)
O 2	--C 20	--C 21	110.7 (6)
O 2	--C 20	--C 6	102.3 (5)
C 21	--C 20	--C 6	113.4 (7)
C 23	--C 21	--C 22	111.7 (7)
C 23	--C 21	--C 20	109.8 (8)
C 22	--C 21	--C 20	106.4 (7)

Table 2-18

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
O 1	0.1879 (5)	-0.7560 (5)	-0.1628 (2)	7.2 (2)
O 2	0.0262 (4)	-0.7586 (4)	-0.1113 (1)	5.7 (2)
N 1	0.2339 (6)	-0.4609 (6)	-0.0663 (2)	5.9 (2)
C 2	0.1727 (6)	-0.4434 (6)	-0.1068 (2)	5.0 (3)
C 3	0.2013 (7)	-0.5251 (7)	-0.1432 (2)	5.3 (3)
C 4	0.1706 (8)	-0.6780 (8)	-0.1292 (2)	5.6 (3)
C 5	0.2693 (8)	-0.6604 (8)	-0.0909 (2)	6.7 (3)
C 6	0.1946 (8)	-0.6144 (8)	-0.0575 (2)	5.9 (3)
C 7	0.1989 (9)	-0.3947 (8)	-0.0304 (2)	7.2 (3)
C 8	0.300 (1)	-0.3619 (9)	0.0066 (2)	6.8 (4)
C 9	0.449 (1)	-0.288 (1)	0.0026 (3)	11.6 (5)
C 10	0.546 (1)	-0.248 (1)	0.0359 (4)	13.5 (6)
C 11	0.491 (1)	-0.290 (1)	0.0766 (3)	9.8 (5)
C 12	0.342 (1)	-0.362 (1)	0.0824 (3)	9.6 (5)
C 13	0.247 (1)	-0.398 (1)	0.0483 (3)	8.7 (4)
C 14	0.2344 (8)	-0.2836 (8)	-0.1182 (2)	5.3 (3)
C 15	0.3831 (9)	-0.1893 (9)	-0.1226 (2)	6.6 (3)
C 16	0.4409 (9)	-0.0433 (9)	-0.1345 (2)	7.4 (4)
C 17	0.348 (1)	0.0101 (8)	-0.1424 (2)	7.7 (4)
C 18	0.194 (1)	-0.0821 (9)	-0.1387 (3)	7.6 (4)
C 19	0.1384 (8)	-0.2281 (8)	-0.1254 (2)	6.3 (3)
C 20	0.0290 (8)	-0.7249 (8)	-0.0653 (2)	6.2 (3)
C 21	-0.0310 (9)	-0.8670 (9)	-0.0381 (3)	7.7 (4)
C 22	-0.054 (1)	-0.826 (1)	0.0074 (3)	11.0 (5)
C 23	-0.175 (1)	-0.988 (1)	-0.0575 (3)	11.7 (5)
H 2	0.0627100 (	-0.5089000 (	-0.1038200 (	4.50 (0)
H 3 A	0.1291800 (	-0.5705600 (	-0.1737200 (	4.81 (0)
H 6	0.1696000 (	-0.6614000 (	-0.0247000 (	5.12 (0)
H 7 A	0.1889900 (	-0.2964200 (	-0.0364400 (	6.14 (0)
H 15	0.4615100 (	-0.2275000 (	-0.1149900 (	6.03 (0)
H 11	0.5487300 (	-0.2588900 (	0.1005500 (	9.34 (0)
H 19	0.0256500 (	-0.2714000 (	-0.1245800 (	5.54 (0)
H 7 B	0.0880700 (	-0.4665200 (	-0.0193600 (	6.14 (0)
H 3 B	0.3021100 (	-0.4722800 (	-0.1483600 (	4.81 (0)
H 5 A	0.3736900 (	-0.5798100 (	-0.0980700 (	5.72 (0)
H 5 B	0.2703300 (	-0.7533599 (	-0.0854100 (	5.72 (0)
H 20	-0.0328000 (	-0.6791700 (	-0.0565300 (	5.37 (0)
H 21	0.0292700 (	-0.9189700 (	-0.0384500 (	6.96 (0)
H 9	0.4996300 (	-0.2649000 (	-0.0269400 (	11.43 (0)
H 10	0.6572300 (	-0.1812600 (	0.0296200 (	13.48 (0)
H 12	0.3021000 (	-0.3886600 (	0.1119400 (	8.56 (0)
H 13	0.1366200 (	-0.4536100 (	0.0538000 (	7.59 (0)
H 16	0.5554700 (	0.0192200 (	-0.1371700 (	6.88 (0)
H 17	0.4018200 (	0.1204900 (	-0.1515800 (	7.19 (0)
H 18	0.1243400 (	-0.0459299 (	-0.1461300 (	6.86 (0)
H 22A	-0.0897800 (	-0.9103400 (	0.0283000 (	9.25 (0)
H 22B	0.0464800 (	-0.7438700 (	0.0194600 (	9.25 (0)
H 22C	-0.1220400 (	-0.7857499 (	0.0078600 (	9.25 (0)
H 23A	-0.2133400 (	-1.0782501 (	-0.0397600 (	11.24 (0)
H 23B	-0.2472700 (	-0.9498700 (	-0.0558600 (	11.24 (0)
H 23C	-0.1583000 (	-1.0039901 (	-0.0870600 (	11.24 (0)

H 1 0.0901600 (-0.8049299 (-0.1784099 (5.18 (0)

Table 2-19

No	
formula	$C_{22}H_{27}NO_2$
mol wt	337.0
cryst syst	trigonal
space group	*P3221*
cryst dimens, mm	0.70 x 0.50 x 0.20
a, Å	10.478 (2)
b, Å	10.478 (2)
c, Å	31.20 (1)
α, deg	90
β, deg	90
γ, deg	120
V, Å^3	2966 (2)
Z	6
D_{calc}, g cm^{-3}	1.13
abs coeff, cm^{-1}	0.39
F(000)	1092
radiation; λ, Å	Mo Kα, 0.71073
temp, °C	23 ± 1
2θ max, deg	50
scan rate, deg/min	4.0
linear decay,%	-
data collected	$+h,+k,+l$
total data collcd, unique,obsd	2172, 2047, 1242 (F>3σ(F)
R int	0.02
no of params refined	227
R, R_w, S^a	0.076, 0.066, 2.29
max shift in final cycle	3.34
final diff map, max, e/Å^3	0.27

[a] Function minimized was sum $[w(|Fo|^2-|Fc|^2)^2]$ which $w=1.0/[(\sigma|Fo|^2+0.0003|Fo|^2]$.
$R=\Sigma[(||Fo|-|Fc||)/\Sigma|Fo|$. $Rw=[\Sigma w(|Fo|-|Fc|)^2/\Sigma|Fo|^2]^{1/2}$.

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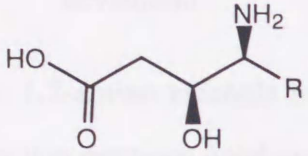
Chapter 3.

Stereoselective Synthesis of 1,2-Amino Alcohols by Nucleophilic Addition of Organometallic Reagents to α-Silyloxyimines

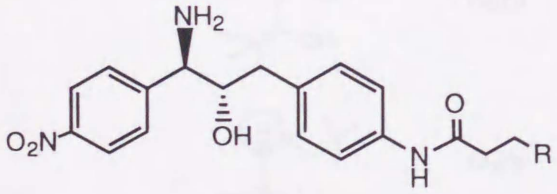
3-1. Introduction

There are a number of natural products containing a 1,2-amino alcohol unit which is found also in many important drugs.[1a-e] For example, Statin **65** and AHPPA **66** (3-amino-2-hydroxy-5-phenylpentanoic acid) are essential components of pepstatin and aphatinin, respectively, and both are natural peptidic inhibitors of acidic proteases such as renin and HIV-1-protease.[2] The biological activity of these analogues is found to depend strongly on the relative and absolute stereochemistry of γ-amino-β-hydroxy acid functionality.

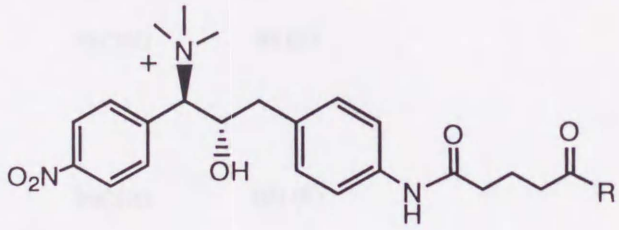


R=*i*-Bu : statin **65**
R=Bn : AHPPA **66**

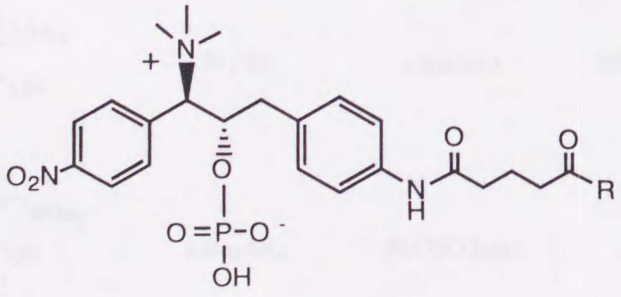
Recently, haptens (**67a**,**b**, **68a**,**b**, **69a**,**b**) containing a 1,2-amino alcohol functionality were synthesized with the goal of generating antibodies for the hydrolysis of ester and amide.[3]



67a: R=SH
67b: R=CH_2CO_2H

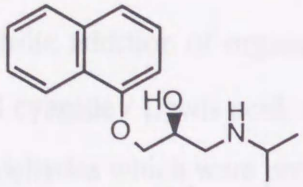


68a: R=N-hydroxysuccinimide
68b: R=OH

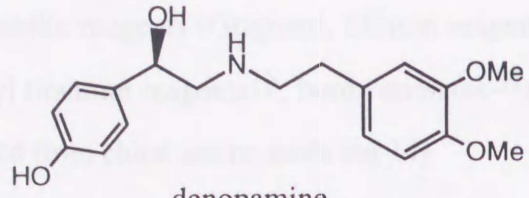


69a: R=N-hydroxysuccinimide
69b: R=OH

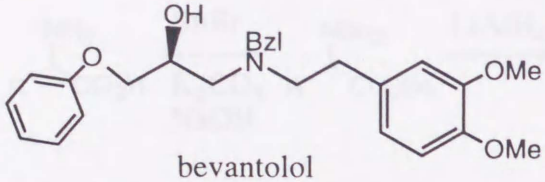
Other examples containing a 1,2-amino alcohol unit in natural products are shown below.



propranolol

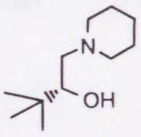
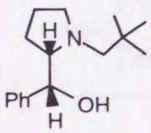
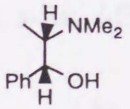
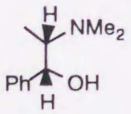
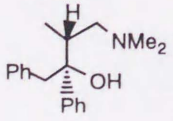
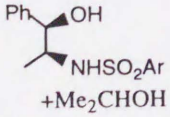


denopamine



bevantolol

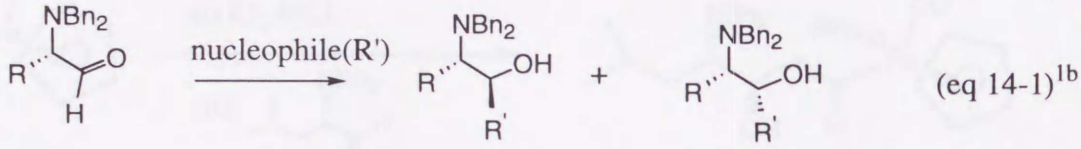
In addition, 1,2-amino alcohols have been used as chiral sources in many asymmetric induction reactions involving metal reagents as shown in Table.[4a,5]

Chiral Auxiliary	Reagent (equiv.)	Substrate (equiv.)	ee(%)
	Et_2Zn	PhCHO	98 (R)
	Et_2Zn	PhCHO	100 (R)
	Me_2CuLi	PhCHO	16.5 (R)
	Et_2Mg	t-BuCHO	20 (R)
	$n\text{-}Bu_4AlLi$	$PhCOCO_2Me$	43
 +Me_2CHOH	Me_4Ti	$o\text{-}NO_2C_6H_4CHO$	90 (R)

To synthesize these amino alcohols, some kinds of strategies have been reported.[1] Examples are shown as follows;

(i) nucleophilic addition of organometallic reagents (Grignard, lithium reagents, trialkylsilyl cyanide / Lewis acid, alkyl titanium reagents[1b], boron enolates[2d]) to α-amino aldehydes which were prepared from chiral amino acids (eq 14)

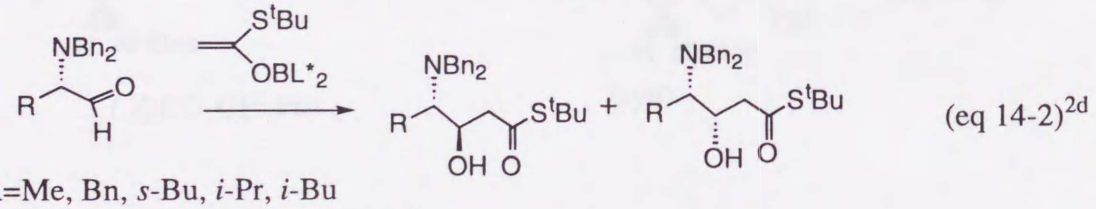
(preparation of starting materials)



(eq 14-1)[1b]

chelation product non-chelation product

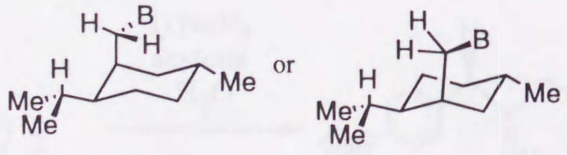
{ non-chelation product---R'MgX, R'_2CuLi, $R'CeCl_2$, R'_3SiCN / $ZnBr_2$, R'Li, $R'Ti(NEt_2)_3$
chelation product ---$TiCl_4$ / R'_2Zn, $SnCl_4$ / $R'SiMe_3$, $TiCl_4$ / R'_3SiCN

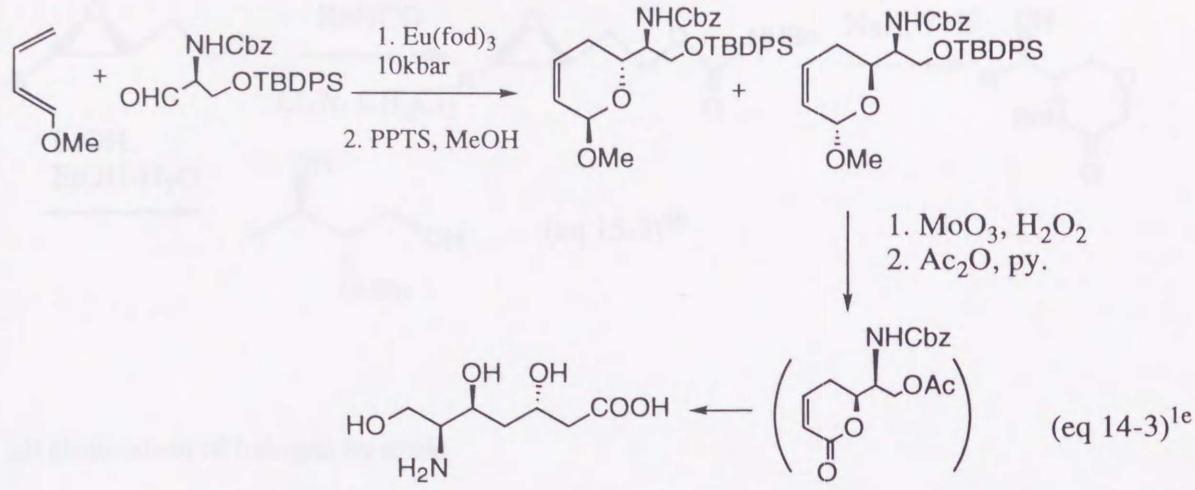


(eq 14-2)[2d]

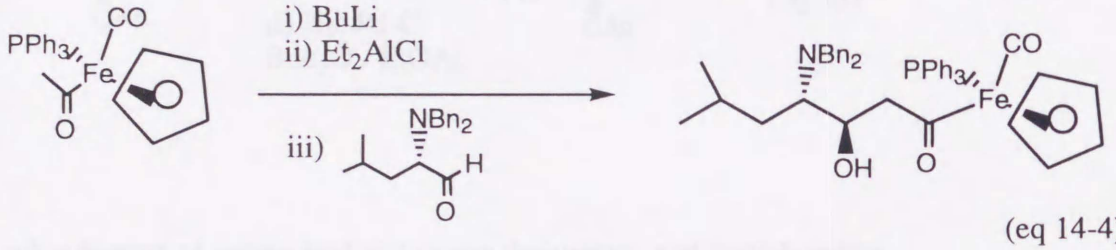
R=Me, Bn, *s*-Bu, *i*-Pr, *i*-Bu

L*=



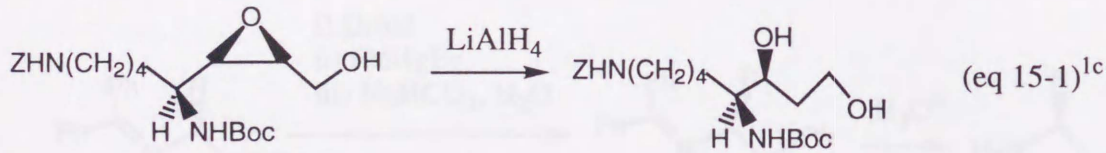


(eq 14-3)[1e]



(eq 14-4)[2a]

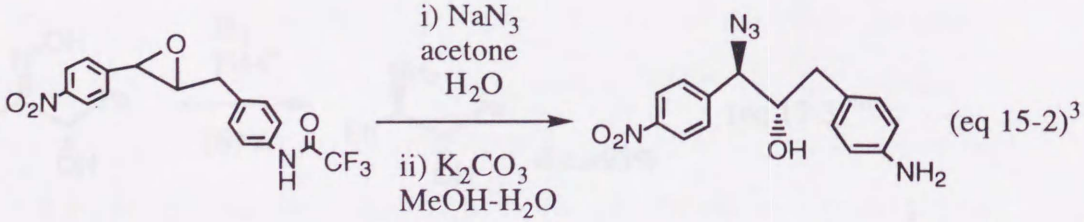
ii) epoxy-ring opening (eq 15)



(Z:CO_2CH_2Ph)

(syn)

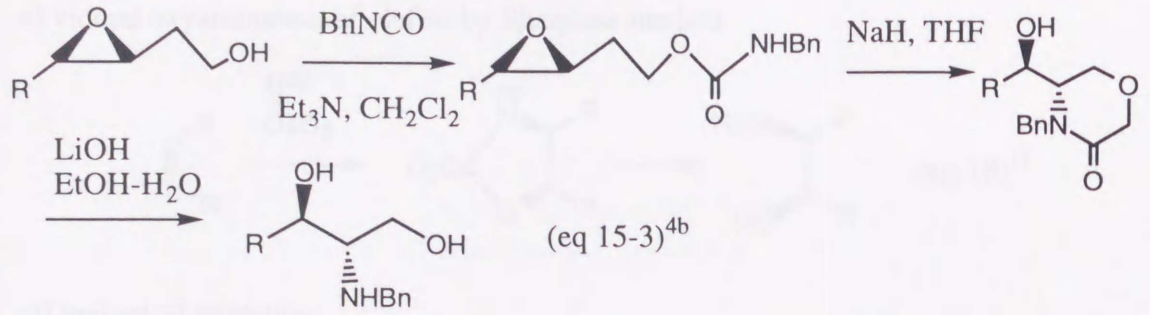
(eq 15-1)[1c]



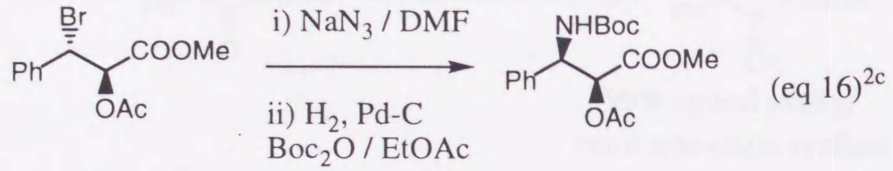
62%

(regioselectivity; 94:6)

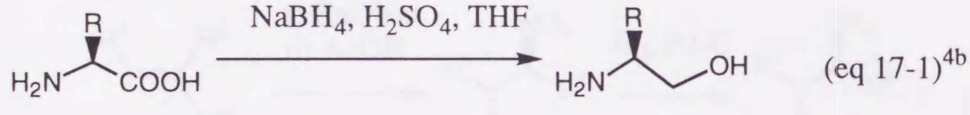
(eq 15-2)[3]

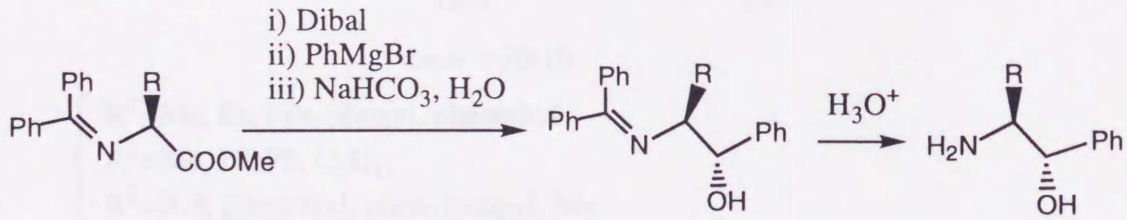


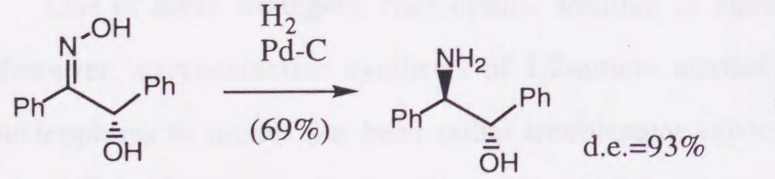
iii) elimination of halogen by azide

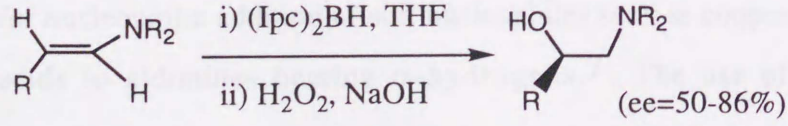


iv) reduction of amino acid and oxime derivatives, and hydroboration

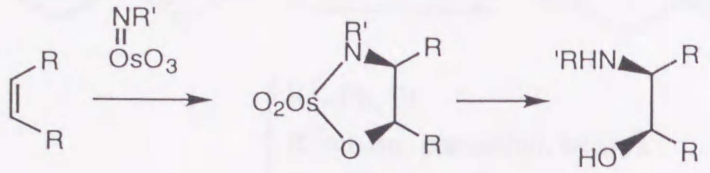






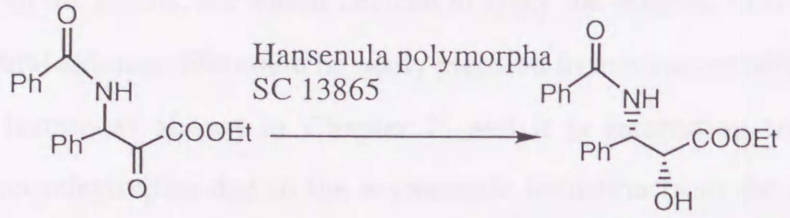


v) vicinal oxyamination of olefins by Sharpless method



(eq 18)[1f]

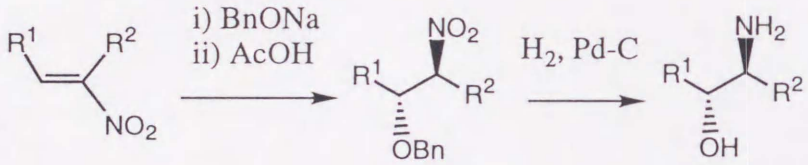
vi) biological reduction



(eq 19)[1h]

(99% optical purity)
taxol side-chain synthon

vii) Michael addition of an alkoxide

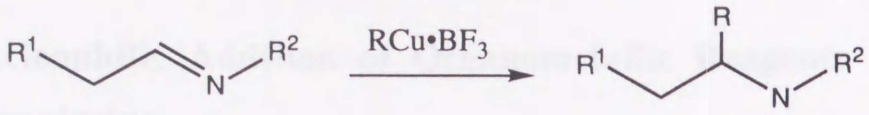


(eq 20)[1i]

d.e.= ≈90:10

R^1=Me, Et, *i*-Pr, phenyl, phenethyl
R^2=Me, Et, Ph, C_5H_{11}
R^3=Bzl, phenethyl, phenylpropyl, Me

One of these strategies, nucleophilic addition to imines will be presented. However, stereoselective synthesis of 1,2-amino alcohols by the addition of nucleophiles to imines has been rather troublesome especially with enolizable imines.[6] To circumvent the problem, Akiba et.al. had devised an efficient method for nucleophilic addition of soft nucleophiles such as copper reagents with Lewis acids to aldimines bearing α-hydrogens.[7] The use of organocopper•BF_3 complexes for the addition affords adducts in good yield whereas no product was obtained when Grignard reagents were used.

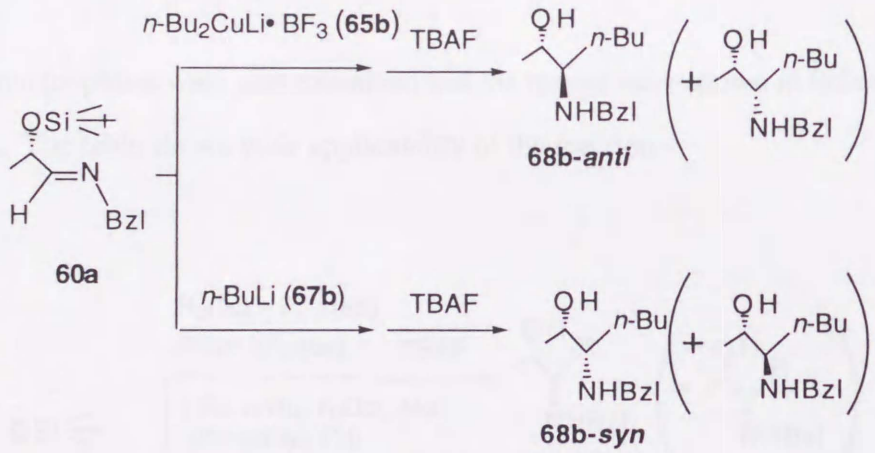


R^1=Ph, Et
R^2=n-Bu, phenethyl, benzyl
R=n-Bu, Me, phenethyl

From the results, the author decided to apply the reagents to chiral aldimines. The chiral aldimine **60a** could be easily prepared from commercially available (S)-ethyl lactate as shown in Chapter 2, and it is interesting to examine the diastereoselectivities due to the asymmetric induction from the chirality at α-position of the aldimine. In this Chapter, stereoselective synthesis of 1,2-amino alcohols by the nucleophilic addition of organocuprate•BF_3 complexes and organolithium reagents to an α-silyloxyimine is described. And anti or syn adducts could be obtained stereoselectively by the choice of organometallic reagents.

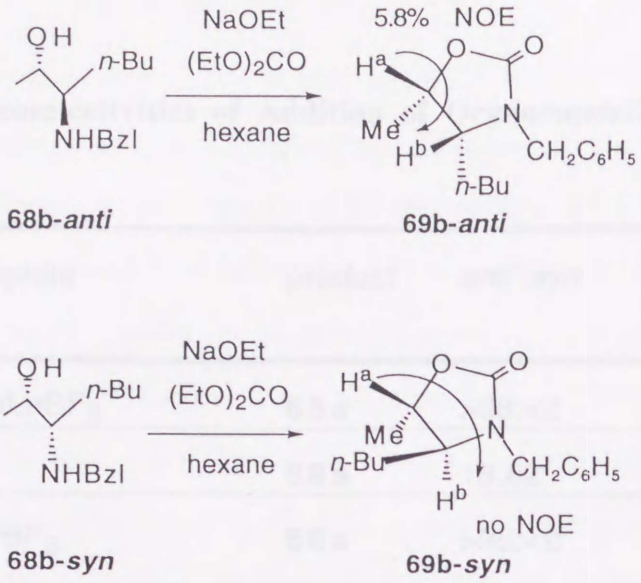
3-2. Nucleophilic Addition of Organometallic Reagents to an α-Silyloxyimine

At the beginning, reactions of di-*n*-butylcuprate•BF_3 complex to α-silyloxyaldimine **60a** was carried out to give *anti*-1,2-amino alcohol **68b-*anti*** diastereoselectively (*anti*:*syn* = >98:<2) in 80% yield after treatment with TBAF (Scheme 3-1). In addition, reaction with n-BuLi **67b** proceeded to give *syn* isomer **68b-*syn*** predominantly (*anti*:*syn* = 19:81, 49% yield). It is interesting that each diastereomer could be obtained with high selectivity.



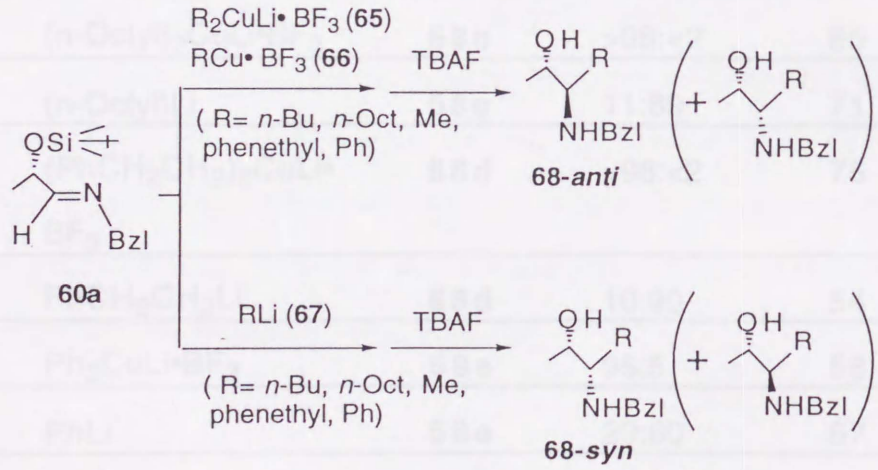
Scheme 3-1

These structures of 1,2-amino alcohols were determined by differential NOE spectrum of corresponding oxazolidin-2-ones **69b** prepared by the reaction of the amino alcohol with diethyl carbonate (Scheme 3-2).[13] In the case of the oxazolidin-2-one derivative of anti isomer **68b-*anti***, an NOE was observed between H^a and H^b (5.8%) whereas no NOE was observed for the *syn* derivative **68b-*syn***.



Scheme 3-2

Other nucleophiles were also examined and the results were shown in Scheme 3-3 and Table 3-1. The table shows wide applicability of the reaction.



Scheme 3-3

Table 3-1 . Stereoselectivities of Addition of Organometallic Reagents to 60a

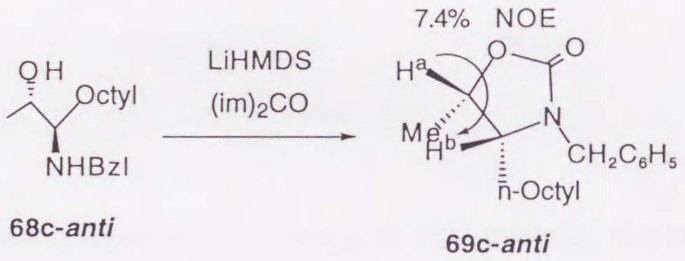
entry	nucleophile	product	*anti* :*syn*	yield (%)	$J_{Ha,Hb}$ (Hz) *anti/syn*	
1	$Me_2CuLi•BF_3$	**68a**	>98:<2	78	3.4	
2	MeLi	**68a**	18:82	41		6.4
3	$MeCu•BF_3$ (2.0 equiv.)	**68a**	>98:<2	93	3.4	
4	$n\text{-}Bu_2CuLi•BF_3$	**68b**	>98:<2	80	3.4	
5	n-BuLi	**68b**	19:81	43		7.8
6	$n\text{-}BuCu•BF_3$ (2.0 equiv.)	**68b**	>98:<2	52	3.4	
7	$n\text{-}Bu_2CuLi$	**68b**	-	0	-	
8	$(n\text{-}Octyl)_2CuLi•BF_3$	**68c**	>98:<2	85	3.4	
9	(n-Octyl)Li	**68c**	11:89	71		4.4
10	$(PhCH_2CH_2)_2CuLi•BF_3$	**68d**	>98:<2	75	3.6	
11	$PhCH_2CH_2Li$	**68d**	10:90	54		4.4
12	$Ph_2CuLi•BF_3$	**68e**	95:5	58	4.4	
13	PhLi	**68e**	20:80	67		8.3
14	Ph_2CuLi	**68e**	-	0	-	

Notable is the fact that fairly unreactive $Ph_2CuLi \cdot BF_3$[8] is also effective. The high levels of diastereoselectivities were not nucleophile dependent and only a small amount of the corresponding *syn* isomer was obtained in the case of $Ph_2CuLi \cdot BF_3$ (entry 12). Organocopper$\cdot BF_3$ complexes were also effective if two equivalents of these complexes were used (entries 3 and 6: with one equivalent of the complex, the yield was lower).[10] BF_3 played an essential role for the addition, and organocuprates themselves did not give any products in the absence of BF_3 (entries 7 and 14).[7] Recently, Lipshutz et.al. have discussed about the role of $BF_3 \cdot Et_2O$ in reaction of lower order organocuprates.[9] They found that the structure of an originally formed cuprate (R_2CuLi or RR'CuLi) is changed significantly upon exposure to $BF_3 \cdot Et_2O$ based on their low-temperature NMR experiments, and the peaks could be assigned to be R_3Cu_2Li, RLi and dimeric $(RCuLi)_2$ at -80°C in THF. In our experiment, the formation of organocuprate$\cdot BF_3$ complex prior to the reaction was also essential since the addition of organocuprate to the solution of **60a** and BF_3 was unproductive. The result shows that only activation by $BF_3 \cdot Et_2O$ of the aldimine does not maximize both reaction-rate and yield.

Reactions of **60a** with organolithium reagents **67** proceeded to give *syn* isomers predominantly (*anti* : *syn* = 10:90~20:80) (entries 2, 5, 9, 11 and 13).[11] From the table, there was no large difference about the selectivities even when aromatic or aliphatic lithium reagents were used. Thus each diastereomer could be prepared selectively only by changing the choice of organometallic reagents.

The relative stereochemistry of the 1,2-amino alcohols of **68** [a) R=Me, b) R=n-Bu, e) R=Ph] could be assigned according to an empirical rule, i.e., coupling constants of *anti* isomers (J=3.4-4.4Hz) are smaller than those of *syn* isomers (J=6.4-8.3Hz,Table 12).[12] However, in the case of **68** [c) R=n-octyl, d) R=phenethyl], the coupling constants were very similar, i.e., 3.4-3.6Hz (*anti*) and 4.4Hz (*syn*), and one cannot be confident on the assignment of relative stereochemistry.

In order to confirm the assignment, oxazolidin-2-one **69c** [14] was prepared from corresponding 1,2-amino alcohol (**68c**) as shown in Scheme 3-4. When H^a was irradiated, an NOE was observed for H^b of **69c-*anti*** (7.4%). Also, X-ray crystallographic structural analysis of **68e-*anti*** was carried out, supporting the assignment of relative stereochemistry by the coupling constant (Figure 3-1).



68c-*anti* **69c-*anti***

Scheme 3-4

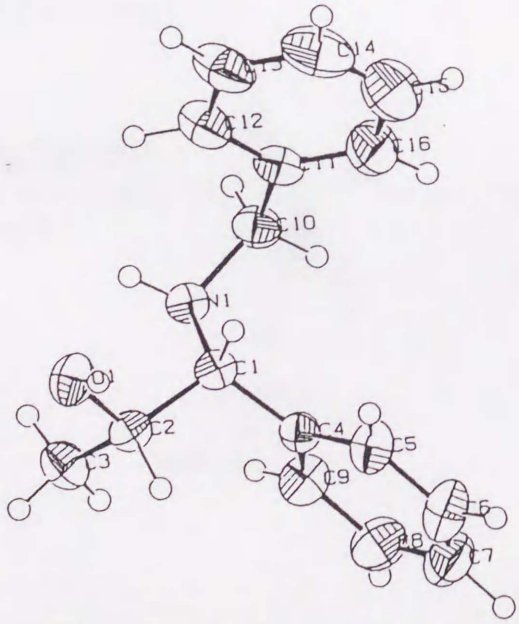
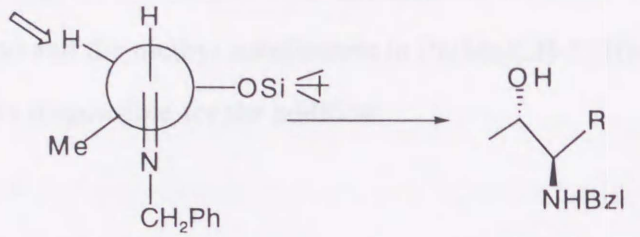
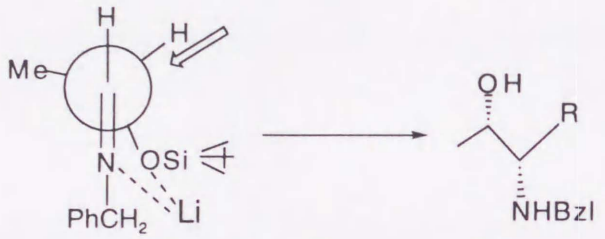


Figure 3-1. X-ray crystal structure of 68e-*anti*.

The *syn* addition of organolithium reagents can be explained by the chelation model and the *anti* selectivity with organocuprate•BF_3 complexes can be accounted for by the Felkin-Anh model (Scheme 3-5).



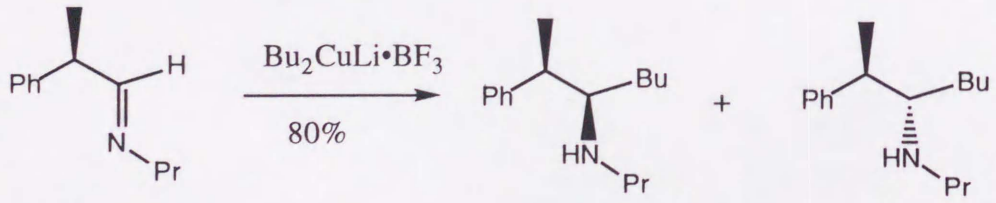
Felkin-Anh model **68-*anti***



Chelation model **68-*syn***

Scheme 3-5

The quite high *anti* selectivities are surprising in light of the fact that the addition of BuCu•BF_3 and Bu_2CuLi•BF_3 to Ph(Me)CH-C(H)=NPr gives a rather low diastereoselectivity (4:1, Scheme 3-6).[15]



80 : 20

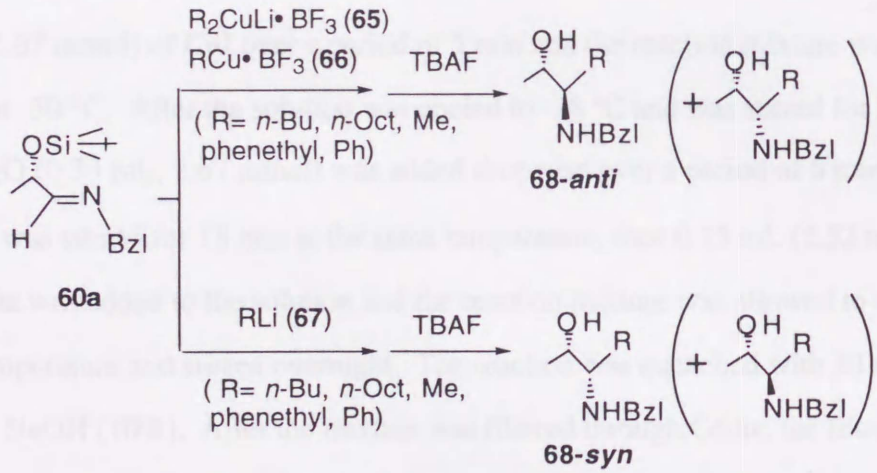
(Cram) (*anti*-Cram)

Scheme 3-6

The difference can be rationalized as follows. The Felkin-Anh conformer[16] shown in Scheme 3-5 should play a predominant role in the reaction of **60a** because of the electron-withdrawing effect of the oxygen atom and the bulkiness of the silyloxy group compared with the methyl group. In contrast, smaller difference of the steric and electronic effects between the phenyl and the methyl substituents in Ph(Me)CH-C(H)=NPr may lead to several conformers responsible for the addition.

3-3. Summary

1,2-Amino alcohols were synthesized by addition of organocuprate•BF_3 **65** (R=*n*-Bu, *n*-octyl, Me, phenethyl, Ph), organocopper•BF_3 **66** (R=Me, *n*-Bu), and organolithiums **67** (R=*n*-Bu, *n*-octyl, Me, phenethyl, Ph) to an α-silyloxyaldimine **60a** derived from commercially available (*S*)-ethyl lactate. The reactions with organocuprate•BF_3 **65** and organocopper•BF_3 **66** led to the *anti* isomers almost exclusively (*anti*:*syn*=>98:<2 for R=*n*-Bu, *n*-octyl, Me, phenethyl and *anti*:*syn*=95:5 for R=Ph, 52-93% isolated yields) and the *syn* isomers could be obtained with high stereoselectivities by using organolithiums (*anti*:*syn*=10:90~20:80, 41-71% isolated yields).



3-4. Experimental Section

^{1}H NMR spectra were recorded at 400MHz (JEOL EX400) in $CDCl_3$ in the presence of TMS as an internal standard. Melting points were taken on a micro melting point apparatus (Yanagimoto model) and are uncorrected. Thin-layer chromatography (TLC) was performed with Merck silica gel GF-245 plates. All reactions were conducted under an argon atmosphere. Aldimine **60a** was prepared as shown in Chapter 2.[17]

General Procedure for the Addition of Organocuprate•BF_3 with an α-Silyloxyimine (60a).

To a stirred solution of 5.04 mmol of RLi in dry THF (20 mL) at -30 °C was added 0.51 g (2.67 mmol) of CuI over a period of 5 min and the reaction mixture was stirred for 20 min at -30 °C. After the solution was cooled to -78 °C and was stirred for 20 min, BF_3•Et_2O (0.33 mL, 2.67 mmol) was added dropwise over a period of 5 min. The solution was stirred for 15 min at the same temperature, then 0.75 mL (2.52 mmol) of imine **60a** was added to the solution and the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with 30 mL of aqueous NaOH (10%). After the mixture was filtered through Celite, the filtrate was extracted with ether (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated to give the t-butyldimethylsilyl protected product which was purified by TLC (*i*-$PrNH_2$:hexane = 1:30).

To a stirred solution of t-butyldimethylsilyl protected amino alcohol containing a mixture of anti and syn isomers in THF (1.0 mL) was added TBAF in THF (1M, 0.46 mL, 0.46 mmol) at 0 °C and the reaction mixture was stirred for 2 h at 0 °C and at room temperature for 1 day. The mixture was treated with H_2O (30 mL) and was extracted with ether (50 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4.

After filtration, the solvent was evaporated and the residue was chromatographed (TLC, ether/*i*-$PrNH_2$ = 100:1) to give 1,2-amino alcohol.

General Procedure for the Addition of Organolithium Reagents to 60a.

To a stirred solution of the imine **60a** (0.75 mL, 2.52 mmol) in dry hexane (20 mL) at -78 °C was added 2.77 mmol of RLi solution in hexane over a period of 5 min and the reaction mixture was allowed to warm to room temperature and stirred for one day, followed by treatment with 30 mL of aqueous NaOH (10%). The mixture was extracted with ether (50 mL x 3), and the combined organic layer was dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated and the residue was chromatographed (TLC, *i*-$PrNH_2$:hexane = 1:40) to give *t*-butyldimethylsilyl protected product. Desilylation was carried out by similar procedures described above.

(2*S*,3*R*)-3-Benzylamino-2-heptanol (68b-*anti*).

The product could be purified by recrystallization (ether / hexane = 1/1). mp 92.2-92.7 °C, ^1H NMR ($CDCl_3$) 0.90-1.11 (m, 3H), 1.07 (d, 3H, *J* = 6.4 Hz), 1.24-1.65 (m, 7H), 2.35-2.45 (m, 1H), 2.50-2.55 (m, 1H), 3.80 (s, 2H), 3.88 (dq, 1H, *J* = 3.4, 6.4 Hz), 7.20-7.40 (m, 5H). Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 75.83; H, 10.67; N, 6.24.

(2*S*,3*S*)-3-Benzylamino-2-heptanol (68b-*syn*).

The product could be purified for NOE spectra by separation with recycle HPLC (1,2-dichloroethane). ^1H NMR ($CDCl_3$) 0.87-0.94 (m, 3H), 1.18 (d, 3H, *J* = 6.4 Hz), 1.30-1.65 (m, 7H), 2.32-2.45 (m, 2H), 3.47 (dq, 1H, *J* = 7.8, 6.4 Hz), 3.71, 3.87 (ABq,

2H, J = 12.7 Hz), 7.25-7.40 (m, 5H). This was converted to oxazolidinone (**69b-*syn***).

(1*R*,2*S*)-1-Benzylamino-1-phenyl-2-propanol (68e-*anti*).

The product could be purified by recrystallization (ether / hexane = 1/1). mp 84.0-85.0 °C, ^{1}H NMR ($CDCl_3$) 0.98 (d, 3H, J = 6.4 Hz), 3.29 (d, 1H, J = 9.3 Hz), 3.54, 3.69 (ABq, 2H, J = 13.2 Hz), 3.74 (dq, 1H, J = 9.3, 6.4 Hz), 7.22-7.39 (m, 10H). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.30; H, 7.94; N, 5.69.

(1*S*,2*S*)-1-Benzylamino-1-phenyl-2-propanol (68e-*syn*).

The product could be purified by recrystallization (ether / hexane = 1/1). mp 77.5-79.0 °C, ^{1}H NMR ($CDCl_3$) 1.01 (d, 3H, J = 6.4 Hz), 3.65, 3.77 (ABq, 2H, J = 13.2 Hz), 3.70 (d, 1H, J = 4.4 Hz), 4.01 (dq, 1H, J = 4.4, 6.4 Hz), 7.23-7.39 (m, 10H). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.26; H, 7.87; N, 5.64.

(2*S*,3*R*)-3-Benzylamino-2-butanol (68a-*anti*).

The product could be purified by recrystallization (ether / hexane = 1/1). mp 84.0-85.0 °C, ^{1}H NMR ($CDCl_3$) 1.01 (d, 3H, J = 6.4 Hz), 1.10 (d, 3H, J = 6.4 Hz), 2.72 (dq, 1H, J = 3.4, 6.4 Hz), 3.81 (s, 2H), 3.84 (dq, 1H, J = 3.4, 6.4 Hz), 7.24-7.36 (m, 5H). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.84; H, 9.61; N, 7.51.

(2*S*,3*S*)-3-Benzylamino-2-butanol (68a-*syn*).

^{1}H NMR ($CDCl_3$) 1.11 (d, 3H, J = 6.4 Hz), 1.18 (d, 3H, J = 6.4 Hz), 2.41 (dq, 1H, J = 8.3, 6.4 Hz), 3.34 (dq, 1H, J = 8.3, 6.4 Hz), 3.70, 3.94 (ABq, 2H, J = 13.2 Hz), 7.22-7.38 (m, 5H). HRMS(M+1) 180.1380 (calcd for $C_{11}H_{17}NO$ 180.1388).

(2*S*,3*R*)-3-Benzylamino-2-undecanol (68c-*anti*).

The product could be purified by recrystallization (ether / hexane = 1/1). mp 86.0-87.0 °C, ^{1}H NMR ($CDCl_3$) 0.88 (t, 3H, J = 6.8 Hz), 1.09 (d, 3H, J = 6.4 Hz), 1.10-1.50 (m,14H), 2.52-2.56 (m, 1H), 3.81 (s, 2H), 3.87 (dq, 1H, J = 6.4, 3.4 Hz), 7.20-7.40 (m, 5H). Anal. Calcd for $C_{18}H_{31}NO$: C, 77.92; H, 11.26; N, 5.05. Found: C, 78.18; H, 11.24; N, 5.08.

(2*S*,3*S*)-3-Benzylamino-2-undecanol (68c-*syn*).

^{1}H NMR ($CDCl_3$) 0.89 (t, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 6.8 Hz), 1.10-1.60 (m,14H), 2.36 (dt, 1H, J = 4.4, 6.8 Hz), 3.47 (dq, 1H, J = 4.4, 6.8 Hz), 3.72, 3.87 (ABq, 2H, J = 12.7 Hz), 7.21-7.38 (m, 5H). HRMS(M+1) 278.2466 (calcd for $C_{18}H_{31}NO$ 278.2484).

(2*S*,3*R*)-3-Benzylamino-5-phenyl-2-pentanol (68d-*anti*).

The product could be purified by recrystallization (ether / hexane = 1/1). mp 87.0-87.5 °C, ^{1}H NMR ($CDCl_3$) 1.11 (d, 3H, J = 6.4 Hz), 1.68-1.80 (m, 2H), 2.50-2.75 (m, 3H), 3.76, 3.80 (ABq, 2H, J = 13.2 Hz), 3.91 (dq, 1H, J = 3.6, 6.4 Hz), 7.10-7.35 (m, 10H). Anal. Calcd for $C_{18}H_{23}NO$: C, 80.25; H, 8.61; N, 5.20. Found: C, 80.48; H, 8.69; N, 5.25.

(2*S*,3*S*)-3-Benzylamino-5-phenyl-2-pentanol (68d-*syn*).

^{1}H NMR ($CDCl_3$) 1.21 (d, 3H, J = 6.4 Hz), 1.70-1.81 (m, 1H), 1.86-1.98 (m, 1H), 2.44 (dt, 1H, J = 4.4, 7.3 Hz), 2.62-2.75 (m, 2H), 3.57 (dq, 1H, J = 4.4, 6.4 Hz), 3.73, 3.86 (ABq, 2H, J = 12.7 Hz), 7.10-7.35 (m, 10H). HRMS(M) 269.1786 (calcd for $C_{18}H_{23}NO$ 269.1780).

(4*R*,5*S*)-cis-3-Benzyl-4-n-butyl-5-methyl-1,3-oxazolidin-2-one (69b-*anti*).

69b-*Anti* was prepared from **68b-*anti*** using diethyl carbonate and EtONa in hexane. The product was purified with recycle HPLC (1,2-dichloroethane). When H^a was irradiated, NOE was observed for H^b (5.8%) (Scheme 3-2). ^{1}H NMR ($CDCl_3$) 0.80 (t, 3H, J = 7.3 Hz), 1.26 (d, 3H, J = 6.3 Hz), 1.10-1.60 (m, 6H), 3.44 (dt, 1H, J = 3.4, 6.3 Hz), 3.98 (d, 1H, J = 15.6 Hz), 4.53 (quintet, 1H, J = 6.3 Hz), 4.73 (d, 1H, J = 15.6 Hz), 7.15-7.30 (m, 5H). HRMS(M) 247.1568 (calcd for $C_{15}H_{21}NO_2$ 247.1572).

(4*S*,5*S*)-trans-3-Benzyl-4-n-butyl-5-methyl-1,3-oxazolidin-2-one (69b-*syn*).

69b-*Syn* was prepared from **68b-*syn*** using diethyl carbonate and EtONa in hexane. The product was purified with recycle HPLC (1,2-dichloroethane). When H^a was irradiated, NOE was not observed for H^b (Scheme 3-2). ^{1}H NMR ($CDCl_3$) 0.79 (t, 3H, J = 7.9 Hz), 1.07-1.55 (m, 6H), 1.23 (d, 3H, J = 5.9 Hz), 2.98-3.04 (m, 1H), 3.95 (d, 1H, J = 15.1 Hz), 4.18 (quintet, 1H, J = 5.9 Hz), 4.73 (d, 1H, J = 15.1 Hz), 7.05-7.30 (m, 5H). HRMS(M) 247.1572 (calcd for $C_{15}H_{21}NO_2$ 247.1572).

(4*R*,5*S*)-cis-3-Benzyl-5-methyl-4-n-octyl-1,3-oxazolidin-2-one (69c-*anti*).

69c-*Anti* was prepared from **68c-*anti*** using lithium hexamethyldisilazide and carbonyl diimidazole. The product was purified with recycle HPLC (1,2-dichloroethane). When H^a was irradiated, NOE was observed for H^b (7.4%) (Scheme 3-4). ^1H NMR ($CDCl_3$) 0.88 (t, 3H, J = 6.8 Hz), 1.33 (d, 3H, J = 6.6 Hz), 1.23-1.56 (m, 14H), 3.51(dt, 1H, J = 3.4, 6.6 Hz), 4.05 (d, 1H, J = 15.6 Hz), 4.60 (quintet, 1H, J = 6.6 Hz), 4.80 (d, 1H, J = 15.6 Hz), 7.26-7.36 (m, 5H). HRMS(M) 303.2180 (calcd for $C_{19}H_{29}NO_2$ 303.2199).

Crystal Structure of 68e-*anti*.

Crystallographic data for **68e-*anti***: $C_{16}H_{19}NO$, FW =241.3, orthorhombic, space group $P2_12_12_1$, a = 13.662(2) Å, b = 18.822(3) Å, c = 5.261(1) Å, V = 1352.8(4) $Å^3$, Z = 4, Dcal = 1.18 g/cm^3, μ = 0.40 cm^{-1}. A Crystal suitable for X-ray structure determination was mounted on a Mac Science MXC3 diffractometer and irradiated with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) for data collection. Lattice parameters were determined by least-squares fitting of 31 reflections with $25°<2\theta<30°$. Data were collected with the $2\theta/\omega$ scan mode. The structure was solved by a direct method with a program, Monte Carlo-Multan.[18] Refinement on F was carried out by full-matrix least-squares. All non-hydrogen atoms were refined with anisotropic themal parameters. All hydrogen atoms could be found on a difference Fourier map; these coordinates were included in the refinement with isotropic thermal parameters. All the computations were carried out on a Titan-750 computer using the crystan-G program. The final cycle of full-matrix least-squares refinement was based on 1155 reflections [F >

3.00σ(F)] and 221 variable parameters with R(Rw) = 0.039 (0.044). Bond distances and angles, atomic coordinates, and crystallographic data are shown in Tables 3-2, 3-3, 3-4, and 3-5.

Table 3-2

Intramolecular Distances (A) with e.s.d. in parentheses

atom	atom	distance
O 1	--C 2	1.436 (3)
N 1	--C 1	1.471 (3)
N 1	--C 10	1.475 (4)
C 1	--C 4	1.523 (4)
C 1	--C 2	1.546 (4)
C 2	--C 3	1.512 (4)
C 4	--C 9	1.377 (4)
C 4	--C 5	1.377 (4)
C 5	--C 6	1.389 (4)
C 6	--C 7	1.366 (5)
C 7	--C 8	1.369 (5)
C 8	--C 9	1.393 (4)
C 10	--C 11	1.509 (4)
C 11	--C 16	1.378 (5)
C 11	--C 12	1.384 (4)
C 12	--C 13	1.382 (5)
C 13	--C 14	1.370 (6)
C 14	--C 15	1.360 (7)
C 15	--C 16	1.399 (6)

Table 3-3

Intramolecular Angles (degrees) with e.s.d. in parentheses

atom	atom	atom	angle
C 1	--N 1	--C 10	113.0 (2)
N 1	--C 1	--C 4	112.7 (2)
N 1	--C 1	--C 2	111.5 (2)
C 4	--C 1	--C 2	110.4 (2)
O 1	--C 2	--C 3	107.3 (2)
O 1	--C 2	--C 1	110.2 (2)
C 3	--C 2	--C 1	114.9 (2)
C 9	--C 4	--C 5	118.2 (2)
C 9	--C 4	--C 1	123.3 (2)
C 5	--C 4	--C 1	118.3 (2)
C 4	--C 5	--C 6	121.0 (3)
C 7	--C 6	--C 5	120.4 (3)
C 6	--C 7	--C 8	119.3 (3)
C 7	--C 8	--C 9	120.4 (3)
C 4	--C 9	--C 8	120.7 (3)
N 1	--C 10	--C 11	116.3 (2)
C 16	--C 11	--C 12	118.2 (3)
C 16	--C 11	--C 10	120.7 (3)
C 12	--C 11	--C 10	121.1 (3)
C 13	--C 12	--C 11	121.2 (3)
C 14	--C 13	--C 12	120.1 (4)
C 15	--C 14	--C 13	119.6 (4)
C 14	--C 15	--C 16	120.6 (4)
C 11	--C 16	--C 15	120.2 (4)

Table 3-4

Positional parameters and equivalent isotropic thermal parameters with e.s.d. in parentheses

atom	x	y	z	B(eq)
O 1	0.0909 (3)	0.6252 (4)	0.1267 (3)	7.9 (1)
O 2	0.1152 (2)	-0.0269 (4)	0.1805 (2)	6.4 (1)
N 1	0.1113 (2)	0.2626 (4)	0.3564 (2)	4.24 (9)
C 2	0.1200 (2)	0.4482 (5)	0.3844 (3)	5.0 (1)
C 3	0.1658 (3)	0.5459 (6)	0.3144 (4)	6.0 (1)
C 4	0.1184 (3)	0.5102 (5)	0.1958 (4)	5.6 (1)
C 5	0.1033 (4)	0.3245 (5)	0.1657 (4)	5.9 (1)
C 6	0.0611 (3)	0.2327 (5)	0.2399 (3)	4.4 (1)
C 7	0.1952 (3)	0.1602 (6)	0.4034 (4)	5.3 (1)
C 8	0.2023 (3)	0.0593 (5)	0.5055 (3)	4.8 (1)
C 9	0.1304 (3)	0.0334 (7)	0.5384 (4)	6.2 (1)
C 10	0.1378 (4)	-0.0651 (7)	0.6284 (4)	7.3 (2)
C 11	0.2172 (4)	-0.1426 (7)	0.6892 (4)	7.0 (2)
C 12	0.2902 (4)	-0.1181 (6)	0.6603 (4)	6.5 (2)
C 13	0.2846 (3)	-0.0204 (6)	0.5676 (4)	6.1 (1)
C 14	0.1741 (4)	0.4730 (8)	0.5070 (4)	7.4 (2)
C 15	0.0258 (3)	0.5269 (6)	0.3592 (4)	6.4 (2)
C 16	0.0432 (3)	0.0402 (5)	0.2102 (4)	5.4 (1)
C 17	-0.0488 (4)	0.0144 (8)	0.1188 (4)	7.4 (2)
H 6	-0.007 (3)	0.283 (6)	0.219 (3)	4.19 (0)
H 3 A	0.232 (4)	0.496 (7)	0.345 (4)	5.68 (0)
H 16	0.038 (3)	-0.026 (6)	0.277 (4)	5.06 (0)
H 12	0.341 (4)	-0.179 (8)	0.701 (5)	6.62 (0)
H 13	0.329 (4)	-0.003 (7)	0.543 (4)	5.96 (0)
H 7 A	0.248 (4)	0.217 (6)	0.423 (4)	5.01 (0)
H 5 A	0.159 (4)	0.262 (7)	0.179 (4)	5.47 (0)
H 7 B	0.198 (3)	0.070 (6)	0.344 (4)	5.01 (0)
H 3 B	0.162 (3)	0.672 (8)	0.328 (4)	5.68 (0)
H 10	0.077 (4)	-0.084 (7)	0.646 (4)	7.03 (0)
H 9	0.078 (4)	0.091 (7)	0.496 (4)	5.93 (0)
H 11	0.218 (4)	-0.225 (7)	0.756 (5)	6.89 (0)
H 14A	0.235 (4)	0.443 (8)	0.524 (5)	7.31 (0)
H 15A	0.032 (4)	0.636 (7)	0.394 (4)	6.05 (0)
H 17A	-0.064 (4)	-0.102 (8)	0.092 (5)	7.11 (0)
H 17B	-0.102 (4)	0.039 (8)	0.149 (5)	7.11 (0)
H 15B	-0.011 (4)	0.460 (7)	0.387 (4)	6.05 (0)
H 15C	0.000 (4)	0.547 (7)	0.285 (5)	6.05 (0)
H 2	0.104 (3)	-0.147 (7)	0.164 (4)	4.77 (0)
H 17C	-0.046 (4)	0.106 (8)	0.057 (5)	7.11 (0)
H 5 B	0.068 (3)	0.310 (6)	0.093 (5)	5.47 (0)
H 14B	0.178 (4)	0.584 (9)	0.520 (5)	7.31 (0)
H 14C	0.137 (4)	0.386 (8)	0.552 (5)	7.31 (0)

Table 3-5

No	
formula	$C_{16}H_{19}NO$
mol wt	241.3
cryst syst	orthorhombic
space group	*P212121*
cryst dimens, mm	0.90 x 0.35 x 0.20
a, Å	13.662 (2)
b, Å	18.822 (3)
c, Å	5.261 (1)
α, deg	90
β, deg	90
γ, deg	90
V, Å^3	1352.8 (4)
Z	4
D_{calc}, g cm^{-3}	1.18
abs coeff, cm^{-1}	0.40
F(000)	520
radiation; λ, Å	Mo Kα, 0.71073
temp, °C	23 ± 1
2θ max, deg	50
scan rate, deg/min	1.0
linear decay,%	-
data collected	$+h,-k,+l$
total data collcd, unique,obsd	1475, 1410, 1155 (F>3σ(F)
R int	0.00
no of params refined	221
R, R_w, S^a	0.039, 0.044, 1.49
max shift in final cycle	0.26
final diff map, max, e/Å^3	0.20

[a] Function minimized was sum $[w(|Fo|^2-|Fc|^2)^2]$ which $w=1.0/[(\sigma|Fo|^2+0.0003|Fo|^2]$.
$R=\Sigma[(||Fo|-|Fc||)/\Sigma|Fo|$. $Rw=[\Sigma w(|Fo|-|Fc|)^2/\Sigma|Fo|^2]^{1/2}$.

3-5. References

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公　表　論　文

List of Publications

1* Kin-ya Akiba, Toshihiro Motoshima, Kaori Ishimaru, Kazutaka Watanabe, Hiroshi Hirota and Yohsuke Yamamoto
[4+2]Type Cycloaddition of Aldimines Bearing α-Hydrogens with 2-Silyloxy-1,3-butadienes Catalyzed by Trimethylsilyl Triflate, *Synlett*, **1993**, 657-659.

2* Kaori Ishimaru, Kazutaka Watanabe, Yohsuke Yamamoto and Kin-ya Akiba
Stereocontrol in [4+2]Type Cycloaddition of an Aldimine Derived from (S)-Ethyl Lactate with 2-Silyloxy-1,3-butadienes, *Synlett*, **1994**, 495-498.

3* Kaori Ishimaru, Kazutaka Tsuru, Katsunori Yabuta, Makoto Wada, Yohsuke Yamamoto and Kin-ya Akiba
Stereoselective Synthesis of 1,2-Amino Alcohols by Addition of Organocuprate•BF_3 Complexes and Organolithium Reagents to an α-Silyloxyaldimine Derived from (*S*)-Ethyl Lactate, *Tetrahedron*, **1996**, *52*, 13137-13144.

*:これらは主論文の基礎となった原著論文である。