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Application of Chiral Cyclic Diols to Asymmetric Synthesis

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CONTENTS

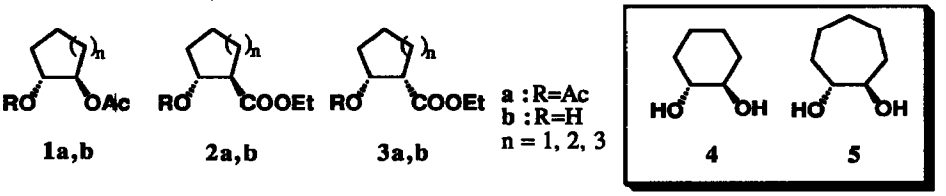
1. Introduction

A chiral source is a prerequisite for asymmetric reactions. For the preparation of optically active compounds, the optical resolution method and the chiral pool method (the use of optically active natural products) have been commonly used.[1] Among various types of chiral auxiliaries and chiral ligands, optically active diols of C_2-symmetry have been applied as the chiral source for asymmetric reactions.[2] In most cases, however, the chiral source has been acyclic diols such as chiral butane-2,3-diol and pentane-2,4-diol, etc. The use of chiral cyclic diols is rare except for the cases when the diols derived from tartaric acid[3] and binaphthol (BINOL)[4] are used. In developing a new type of asymmetric reaction, it is desirable to set up a series of optically active diols including skeletal isomers because the diversified information obtained from the results of using these compounds as a chiral source is important to study the attempted asymmetric reaction itself.

Taking the above points into consideration, we have developed an enzymatic preparation of enantiomerically pure cyclic alcohols.[5] Various cyclic alcohols could be kinetically resolved by *Pseudomonas fluorescens* lipase (PFL)-catalysed hydrolysis of the corresponding racemic acetates **1-3a**. All of the hydrolyzed alcohols **1-3b** were enantiomerically pure (>99% e.e.) and the absolute configuration of the stereogenic center attached to the hydroxy group was invariably *R*. By this method, both enantiomers of the C_2-symmetric

cyclohexane-1,2-diol **4** and cycloheptane-1,2-diol **5** were obtained in an enantiomerically pure form in 38-45% yields (theoretical maximum 50%) from the racemic diacetates.

Fig. 1



In the present review, our studies on asymmetric reactions using optically active **4** and **5** are summarized.

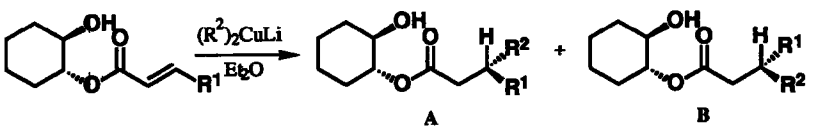
2. Use as a chiral ester

2.1. Asymmetric conjugate addition[6]

Conjugate addition of organocopper reagents to α,β-unsaturated ketones or esters is a convenient procedure for carbon-carbon bond formation. Asymmetric conjugate addition has been widely studied for the synthesis of optically active β-substituted or α,β-disubstituted carbonyl compounds.[7]

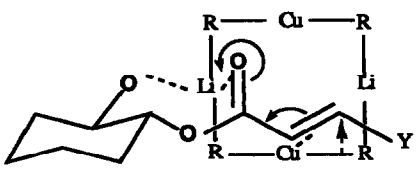
From the results of preliminary studies on diastereoselective conjugate additions to chiral α,β-unsaturated esters derived from the alcohols in Fig. 1, optically active cyclohexane-1,2-diol **4** was found to be an effective auxiliary for the attempted reaction. The generality of the asymmetric induction was also confirmed from the results in Table 1. The stereochemical course may be rationalized by assuming the transition state shown in Fig. 2. A free hydroxy group and an ester carbonyl group of the substrate play an important role for the formation of a chelation complex with dialkylcuprate. After formation of the copper(I)-alkene π-complex, a shift of the R-substituent may occur from the *re*-face in a stereocontrolled manner.

Table 1. Asymmetric Conjugate Addition of R_2CuLi



Entry	R^1	R^2	Product Yield(%)	Diast. Ratio (A : B)	Abs. Config.
1	Me	Ph	66	94 : 6	*R*
2	Me	Bu	91	86 : 14	*S*
3	Ph	Bu	79	91 : 9	*S*
4	Ph	Me	71	92 : 8	*S*
5	Et	Ph	63	86 : 14	*R*

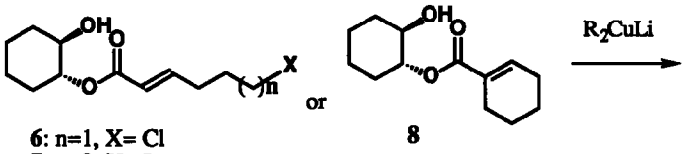
Fig. 2



2.2. Enantio- and diastereoselective synthesis of β-substituted cycloalkanecarboxylates[8]

For enantio- and diastereoselective syntheses of β-substituted five- or six-membered cycloalkanecarboxylates using (*R*,*R*)-**4** as a chiral auxiliary, two types of reactions were performed. One was based on the diastereoselective conjugate addition and subsequent cyclization[9] of the resulting enolate using substrates **6** and **7** (Table 2, entries 1-4). The other was based on the diastereoselective conjugate addition to cycloalkenyl substrate **8** and subsequent protonation (entries 5 and 6). Reaction of **6** and **7** with R_2CuLi gave the *trans*-cyclized products (**A**:**B**=7-9:1), and that of six-membered **8** afforded *cis*-oriented products (**C**:**D**=2-3.5:1), which could be easily separated in optically pure form by usual silica-gel column chromatography. From the above results, it is concluded that (1*R*,2*R*)-products **A** were predominantly obtained from substrates **6** and **7**, and (1*S*,2*R*)-products **C** from **8**. Diastereoselective intramolecular alkylation (entries 1-4) of the resulting *E*-enolate might be caused by a favorable allylic strain (Fig. 3, **I**), which adopts a syncoplanar disposition between H-3 and the C-C double bond to afford 1,2-*trans* product **A**. Diastereoselective protonation of the enolate **II** might be rationalized by attack of a proton from the less hindered side to give the 1,2-*cis* product **C**.

Table 2. Diastereo- and Enantio-selective Preparation of 2-Substituted Cycloalkanecarboxylates

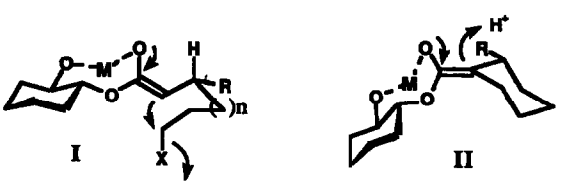


6: n=1, X= Cl
7: n=2, X= I

8

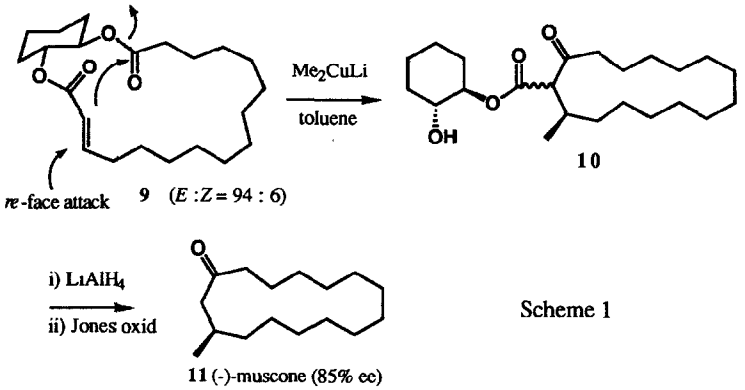
Entry	Substrate	A	B	C	D
1	**6** n=1, R= Ph	44%	6%	---	---
2	**6** n=1, R= Bu	46%	5%	---	---
3	**6** n=1, R= Me	50%	7%	---	---
4	**7** n=2, R= Ph	54%	7%	---	---
5	**8** n=2, R= Ph	----	---	49%	14%
6	**8** n=2, R= Bu	----	---	59%	29%

Fig. 3



2.3. Asymmetric synthesis of muscone[10]

Diastereoselective conjugate addition and subsequent intramolecular trapping of the resulting enolate provided a new synthetic route to (-)-muscone. The designed 20-membered ring diester **9** should have several synthetic advantages: 1) the α,β-unsaturated ester in the 20-membered ring conformationally favours the *s-trans* form; 2) reagents attack, in a diastereoselective manner, the α,β-unsaturated ester from outside the 20-membered ring and the two closely located esters subsequently undergo Dieckmann cyclization; 3) the 3-methylated 15-membered cyclic β-keto ester is converted to (-)-muscone *via* decarboxylation with recovery of the chiral auxiliary. Compound **9** synthesized as a mixture of *E*- and *Z*-isomers (94:6) reacted with Me_2CuLi to afford cyclized **10**, which could be easily converted to **11** (*R*)-(-)-muscone of 85% e.e (Scheme 1).



Scheme 1

2.4. Asymmetric induction to meso-cyclohexane-1,2-diol based on diastereoselective elimination[11]

In our study of diastereoselective alkylation (section 3.1.), the C-O bond of β-keto ester acetal was found to be easily cleaved by treatment with a base to afford an enol ether. This finding allowed us to design the novel asymmetric induction to *meso*-cyclohexane-1,2-diol based on diastereoselective elimination. The designed substrates *syn*- and *anti*-**12** were prepared as a diastereomeric mixture at C1. By treatment with $(TMS)_2NK$, HMPA in THF at -78°C, both substrates afforded the same (1*S*,2*R*)-**14** of 72% e.e. after methoxyethoxymethylation of resulting **13a,b** and subsequent hydrolysis of enol ether function (Scheme 2 and Table 3).

Scheme 2

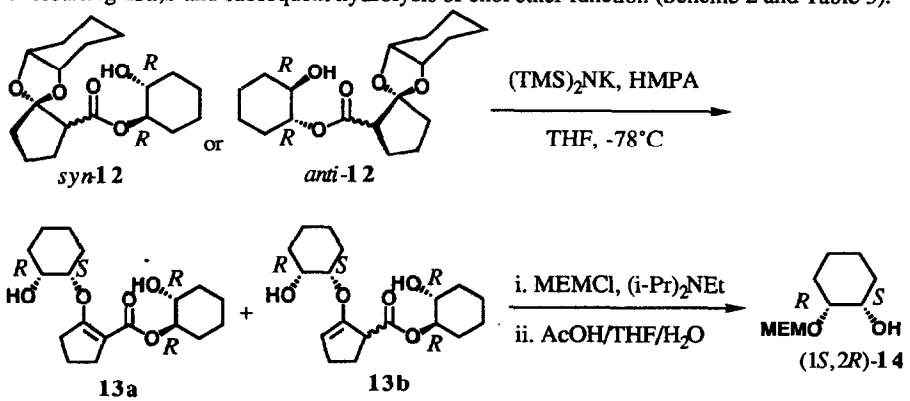
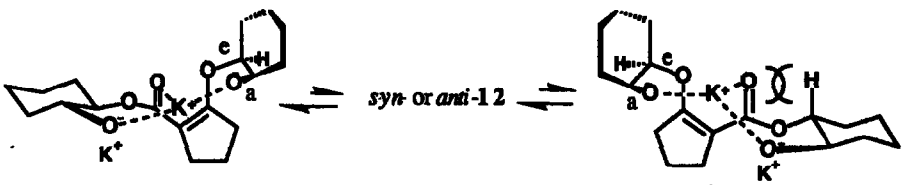


Table 3. Reaction of *syn*- and *anti*-12 with Base.

Entry	Substrate	Combined yield of 13a,b (%) (Conversion yield)	Optical purity of 14 Product	% e.e.
1	*syn*-12	67 (88)	(1*S*,2*R*)-14	72
2	*anti*-12	65 (90)	(1*S*,2*R*)-14	72



Scheme 3

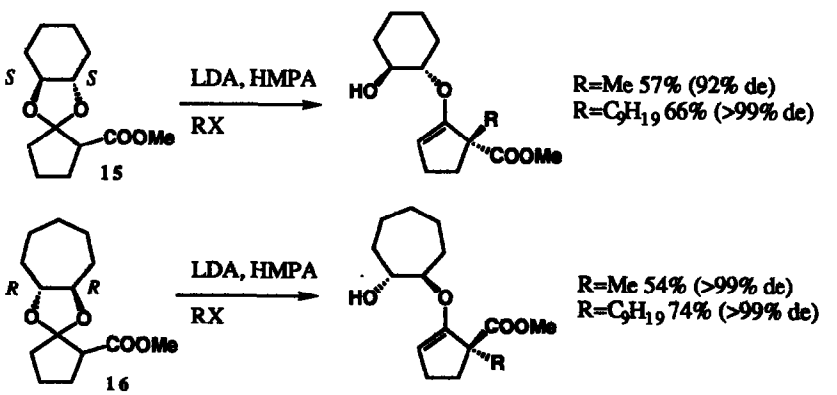
The possible reaction pathway was considered to be as follows. In an equilibrium between chelated enol ethers (A and B in Scheme 3) *via* acetal substrates, the chelation intermediate B might be unfavorable because of steric hindrance between the carbonyl function and C1'-axial-H. That is to say, the reaction might proceed *via* the favorable intermediate A in thermodynamically controlled fashion to afford finally (1*S*,2*R*)-14 predominantly.

3. Use as a chiral acetal

3.1. Asymmetric alkylation to prepare a quaternary carbon[12]

For construction of a chiral quaternary carbon based on asymmetric alkylation, compounds 4 and 5 have been found to be an effective chiral auxiliary. Alkylation of chiral acetals (15-17) derived from corresponding β-keto esters and optically active cycloalkane-1,2-diols (4,5) afforded the alkylated enol ether in highly diastereoselective manner. In particular, (*R*,*R*)-cycloheptane-1,2-diol 5 is superior as a chiral auxiliary to acyclic chiral diols such as (*R*,*R*)-2,3-butanediol and (*R*,*R*)-2,4-pentanediol, which afforded methylated products of 37% and 73% d.e., respectively, on alkylation of 5-membered substrates. Furthermore, (*R*,*R*)-4 was also applicable to alkylation of acyclic β-keto ester for complete distinction of diastereofaces (Scheme 4).

Scheme 4



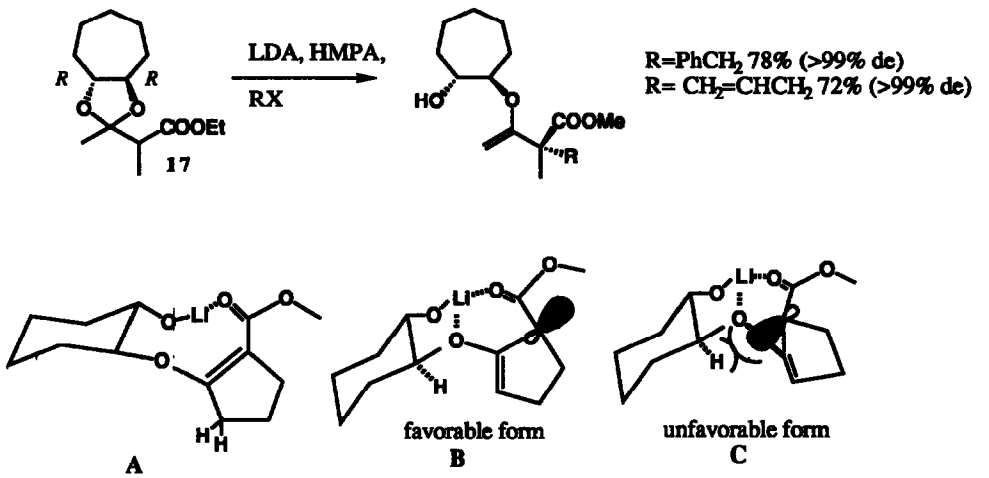
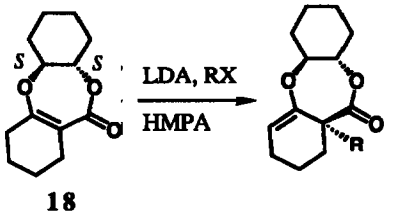


Fig. 4

The stereochemical course of this reaction was considered as follows. The enol ether A (Fig. 4) might be first formed by opening of the acetal ring under strong basic conditions. In the next step, it is reasonable that the excess of base abstracts the allylic proton to afford the dianion (B or C). High diastereoselectivity in the above alkylation may be rationalized by considering the favorable intermediate B to be preferable.

For construction of a stereogenic quaternary carbon, optically active cyclohexane-1,2-diol 4 could be applicable in another way. Alkylation of tricyclic lactone **18** afforded alkylated products in highly regio- and diastereoselective manner (Scheme 5).[13] The absolute configuration of the newly generated stereogenic center is contrary to that in the cases of alkylation of acetal derivatives **15-17**, which suggests a difference in the steric course of the reaction.



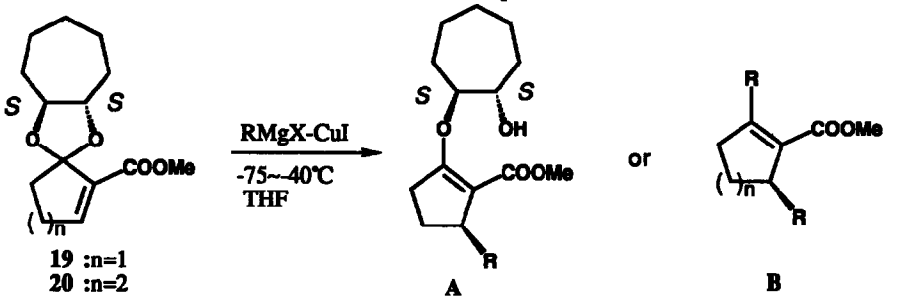
RX	Yield (%)	D.e. (%)
MeI	86	94
CH_2=$CHCH_2$I	51	94
BnBr	52	>99

Scheme 5

3.2. Asymmetric double Michael reaction[14]

A new type of double Michael reaction was developed by the reaction of **19** with a mixed cuprate. Reaction of **19** with RMgBr/CuI afforded enol ether **21A** (89% d.e.) and **22A** (81% d.e.) in the cases of R=Me and Bu^t (Table 4, entries 1 and 2). In the latter case, the two diastereomeric products could be easily separated by silica-gel column chromatography in an enantiomerically pure form. On the other hand, reaction of **19** with PhMgBr and Bu^nMgCl/CuI (entries 3 and 4) afforded β,β'-disubstituted cycloalkenecarboxylates **23B** (93% e.e.) and **24B** (81% e.e.), respectively.

Table 4. Reaction of homochiral acetals with mixed cuprates



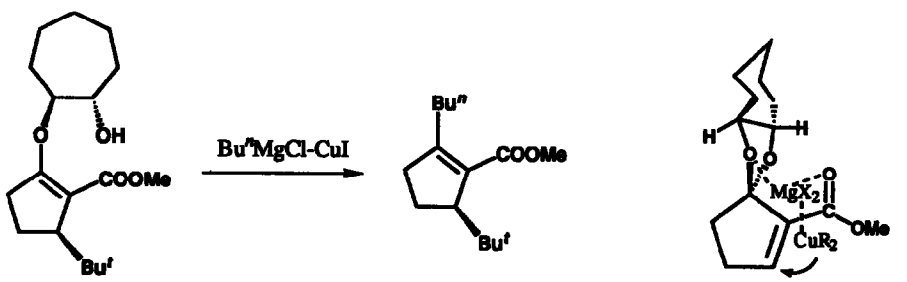
19 :n=1
20 :n=2

A B

Entry	Substrate	RMgX		Yield(%)	% D.e. (confign)		Yield(%)	% E.e. (confign)
1	19	MeMgBr	21A	85	89 (*S*)	---	---	---
2	19	Bu^{t}MgCl	22A	83	81 (*R*)	---	---	---
3	19	PhMgBr	---	---	---	23B	69	93 (*R*)
4	19	Bu^{n}MgCl	---	---	---	24B	81	81 (*S*)
5	20	Bu^{n}MgCl	---	---	---	25B	79	63 (*S*)

* Reaction time: 24-48 h for entries 1-2, and 2-4 h for entries 3-5.

Diastereomerically pure (3*R*)-22A did not react with Bu^{t}MgCl/CuI, but the reaction with Bu^{n}MgCl/CuI afforded 26 of >99% e.e. (Scheme 6). These results suggest that the formation of B proceeds *via* A by an addition-elimination process[15] without epimerization at the stereogenic center of A. That is to say, the e.e. of B should be reflected in the d.e. of intermediary A. Furthermore, the selection of products (A or B) might be attributable to the nucleophilicity of mixed cuprates. Distinction of diastereofaces might be rationalized by assuming the favorable chelation intermediate (I), which resulted in the *si*-face attack of the reagent at β-position of carboxylate. The formation of a chelation intermediate at the opposite diastereoface might be unfavorable because of steric hindrance.



(3*R*)-22A
(>99% d.e.)

26 (89% yield, >99 % e.e.)

favorable chelation intermediate (I)

Scheme 6

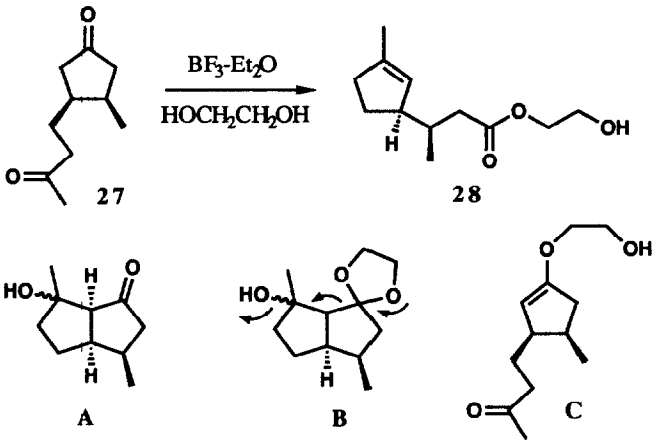
4. Non-bonded utilization

4.1. Asymmetric ring transformation[16]

In our previous study of a new ring transformation reaction,[17] which is typically presented in Scheme 6, a new concept for the activation of the carbonyl function with BF_3-1,2-diol system was suggested.

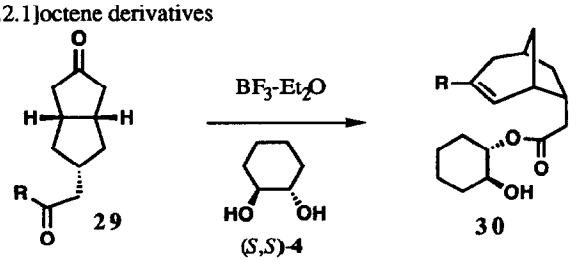
The reaction of **27** with BF_3-Et_2O and ethylene glycol afforded ring transformed product **28** in 69% yield (Scheme 7). We had proposed the reaction mechanisms *via* aldol **A** and subsequent acetal intermediate **B**. The reaction without ethylene glycol afforded neither **28** nor intermediary **A**, but starting **27** was recovered; this result suggested a new intermediate **C** for aldol condensation at the first stage. That is to say, ethylene

Scheme 7



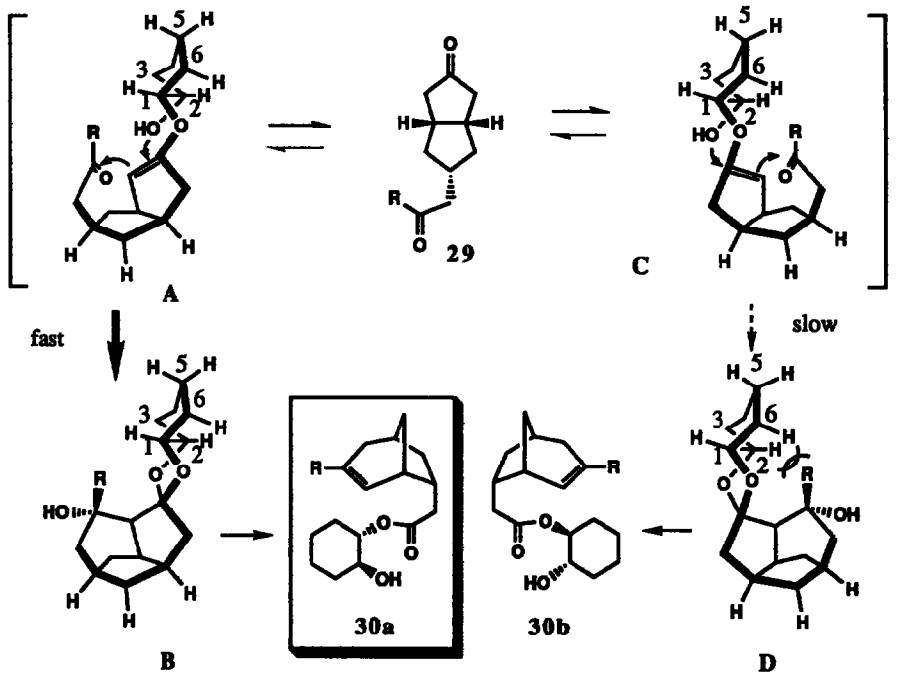
glycol might act for both activation of the carbonyl function and subsequent Grob's fragmentation[18] in this ring transformation. Based on the above concept, asymmetric ring transformation was studied using *meso*-substrate **29** and optically active **4** (or **5**) instead of ethylene glycol.

Table 5. Asymmetric ring transformation of *meso*-7-substituted bicyclo[3.3.0]octanones into bicyclo[3.2.1]octene derivatives



Entry	R	Yield (%)	D.e. (%)
1	Me	66	26
2	Bu^n	52	44
3	Cyclohexyl	71	81
4	Phenyl	61	93

The best result (93% d.e.) in regard to the d.e. of **30** was obtained in entry 4 (R=Ph)(Table 5). This reaction seems to be remarkably affected by the bulkiness of the terminal substituent (R). The possible stereochemical course was considered as depicted in Scheme 8. Polycyclic acetal intermediates **B, D** might be required for subsequent ring cleavage. Intermediate **D** is considered to be unfavorable relative to **B** because of steric hindrance between the alkyl group (R) and C2'-, C6'-axial H on the cyclohexane ring. Each intermediate **B, D** might be derived from enol ether **A** and **C**, respectively, which are in equilibrium *via* substrate **29**. In conclusion, the ring cleaved **30a** might be obtained *via* **A** and **B** prior to **30b**.



Scheme 8

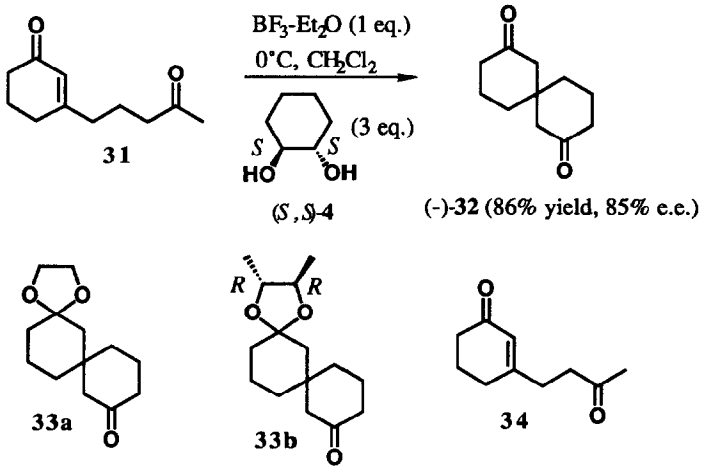
4.2. Asymmetric spirocyclization[19]

The combination of Lewis acid and chiral diol also provided a new type of asymmetric spirocyclization. Reaction of **31** with BF_3-Et_2O in CH_2Cl_2 at room temperature was so slow that no change was observed after 24 h. After being stirred for 3 days, a small amount of the desired spirocyclic diketone **32** (30%) was obtained accompanied with recovery of **31** (60%). On the other hand, the reaction in the presence of ethylene glycol was obviously accelerated to afford **32** (52%) and mono ethylene acetal **33a** (19%) after being stirred for 1.5 h at room temperature. Reaction of **34** under the same conditions resulted in recovery of the substrate. These results were rationalized based on Baldwin's rule.[20] That is to say, cyclization of **31** could be considered as favorable 6-(Enolendo)-Exo-Trig and that of **34** as unfavorable 5-(Enolendo)-Exo-Trig.

The development of this reaction into an asymmetric version by using optically active 1,2-diols such as (*R,R*)-butane-2,3-diol and (*S,S*)-**4** was studied. The reaction of **31** with BF_3-Et_2O (7 eq.) and (*R,R*)-butane-2,3-diol (3 eq.) at room temperature afforded (+)-**32** (12%) of 25% e.e. and corresponding monoacetal **33b**

(39%) of 24% d.e. On the other hand, the reaction at 0°C for 6 h with BF_3-Et_2O (1 eq.) and (*S*,*S*)-**4** (3 eq.) in CH_2Cl_2 afforded (-)-**32** (86%) of 85% e.e. (Scheme 9).

Scheme 9



These results support the new concept that activation of the carbonyl function as an enol ether provides a new type of nucleophile.

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