Update 1 of: BINOL: A Versatile Chiral Reagent

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Jean Michel Brunel was born in 1968 in Marseille, France. He graduated from the School of Chemistry (Ecole Supérieure de Chimie de Marseille, ESCM) in 1991. He obtained his Ph.D. degree in 1994 from Université Aix Marseille III in the field of enantioselective synthesis and organophosphorus chemistry. In 1994, he joined the group of Prof. H. B. Kagan (Université Paris Sud) as a postdoctoral fellow working on the enantioselective catalytic oxidation of sulfides (1994–1996). In 1997, he joined the CNRS as Chargé de Recherche, and he is now working in the Institut Méditerranéen de Recherche en Nutrition (IMRN INRA 1111). His research program is focused on the development of novel synthetic methods in asymmetric catalysis as well as the synthesis of a new class of antifungal agents.

1. Introduction

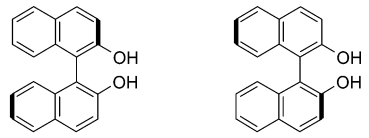
Over the last 20 years an explosive growth of the research in the field of asymmetric synthesis has occurred.[1−9] The aim of enantioselective synthesis, or catalysis, is to produce chiral products (a single enantiomer as the ultimate goal) starting from achiral substrates, by exploiting the presence of chiral reagents. The role of these latter is to generate diastereomeric transition states leading to the two enantiomers, so that one of them is preferentially formed. In such a schematic representation, only two competitive pathways are present: one leading to the *R* enantiomer and the other giving rise to the *S* one. Actually, the situation can be more complex: for instance, both the substrate and the reagent can exist as a mixture of conformational isomers, several conformations can be significantly populated, and they can also exist in different states of aggregation or solvation, with each of these species showing its own reactivity. The final result is a weighted average depending on the distribution and reactivity of the species involved, and a low stereoselectivity is generally obtained. A rational approach to the control of stereoselectivity is based on the use of molecules possessing only symmetry elements of pure rotation and belonging to the C_n or D_n symmetry groups, allowing the prediction of the enantioselectivity due to the presence in solution of only a single defined reactive species. Under these assumptions, interest in the applications of chiral atropoisomers, especially binaphthalene systems, has blossomed.[10,11] This review deals exclusively with the synthesis and resolution of BINOL as well as its use as a chiral reagent or ligand and does not cover its substituted derivatives.[12,13] Thus, since 1990 the enantiomeric atropoisomers of 1,1′-binaphthyl-2,2′-diol (BINOL) have become among the most widely used ligands for both stoichiometric and catalytic asymmetric reactions. In the first part of this review, we will describe the different methods of preparation of racemic and enantiopure BINOL **1** and its application as ligands or chiral auxiliary in enantioselective reduction or oxidation reactions. In the second part, C−C bond forming reactions, catalyzed or not, involving BINOL **1** as a reagent or ligand will be discussed.

2. BINOL Synthesis and BINOL-Mediated Asymmetric Oxidation and Reduction Reactions

2.1. Properties and Synthesis of Racemic BINOL

2,2′-Disubstituted derivatives of 1,1′-binaphthyl have been widely used in organic synthesis. The stability of the enantiomers, with barriers of rotation ranging from 23.8 kcal/mol for 1,1′-binaphthyl to more than 46 kcal/mol for 2,2′-diiodo-1,1′-binaphthyl, enables their use as chirality inducers in asymmetric reactions. The most important compound of this type is 1,1′-binaphthyl-2,2′-diol (BINOL) ($C_{20}H_{14}O_2$, mp: 215−217 °C), whose chiral atropoisomers, (*R*)-**1** ($[\alpha]_D^{20}$ = +35.5 (THF, *c* = 1), mp: 205−211 °C) and (*S*)-**1** ($[\alpha]_D^{20}$ = − 34.5 (THF, *c* = 1), mp: 205−211 °C), are stable at high temperature[15] and allow numerous asymmetric reactions under various experimental conditions (Scheme 1).

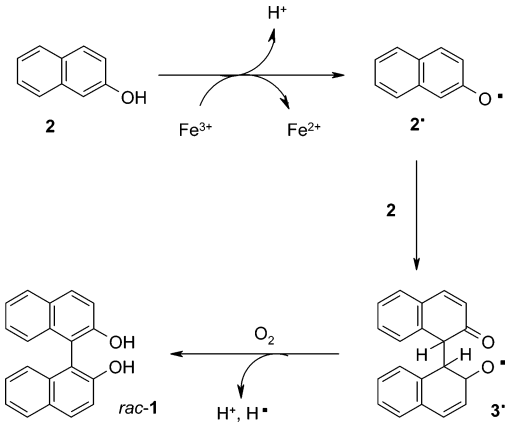
Scheme 1



(*R*)-(+)-BINOL **1** (*S*)-(-)-BINOL **1**

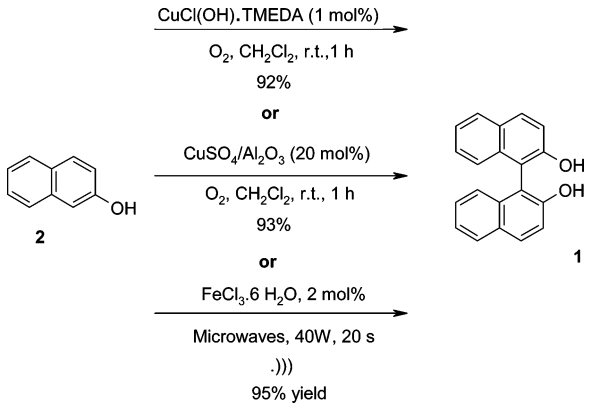
BINOL **1** is the best known representative of axially chiral molecules[16] and was first prepared as a racemate in 1873 by von Richter.[17] Since this date, the preparation of racemic BINOL **1** has been widely studied, and a well-established method is the oxidative coupling of 2-naphthol using $FeCl_3$,[18−21] $K_3Fe(CN)_6$,[22] $Mn(acac)_3$ (acac - acetylacetone),[23,24] Cu−amine complexes,[25−27] $TiCl_4$,[28] or $Ru(OH)_x/Al_2O_3$ [29] as coupling agents, with chemical yields up to 90% being commonly reached. A mechanistic rationale implying that the formation of one molecule of **1** requires 1 equiv of Fe^{3+} has been proposed. This suggests that the radical species **2**•, resulting from a one electron oxidation of **2** with Fe^{3+}, adds to another neutral **2** to form a new C−C bond and generates carbinyl radical **3**•, which eliminates H• and is further oxidized by O_2 to release H^+ and regain aromaticity (Scheme 2).[18,30,31]

Scheme 2



These coupling reactions are not catalytic processes and require more than stoichiometric amounts of the metal salts. A few exceptions are the coupling that proceeds catalytically under ultrasonic irradiation of aerated powder mixtures of 2-naphthol and $FeCl_3 \cdot 6H_2O$ (2 mol %) at 50 °C,[20,32,33] $FeCl_3/Al_2O_3$,[34,35] the use of Cu(II)−amine complex (1 mol %),[27,36−38] $VO(acac)_2$,[39] methyltrioxo rhenium,[40] an alumina-supported copper(II) sulfate catalyst (20 mol %) under aerated conditions,[41−43] a vanadyl phosphate (VOPC),[44] and mesoporous molecular sieves[45] (Scheme 3).

Scheme 3



2.2. Preparation of (*R*) and (*S*)-BINOL

The synthesis of enantiomerically pure (*R*)- or (*S*)-BINOL **1** has been extensively studied, and two major different approaches have been developed: enzymatic or chemical resolution of racemic BINOL **1** and direct stoichiometric or catalytic oxidative coupling synthesis.[46]

2.2.1. Resolution of Racemic BINOL

2.2.1.1. Enzymatic Resolution of Racemic BINOL. The recent development of enzyme catalysis in organic synthesis for kinetic resolution of racemates has attracted the attention of organic chemists because of its synthetic utility. One of the first efficient methods for enzymatic resolution of *rac*-BINOL **1** was described in 1989 by Kazlaukas. It is based on the cholesterol esterase-catalyzed enantiospecific hydrolysis of binaphthol esters.[47−51] A simple synthetic scale (200 g) procedure has been detailed for hydrolysis of the dipentanoate ester catalyzed by crude, inexpensive enzyme (bovine pancreatic acetone powder (PAP)). Each enantiomer was obtained in more than 60% theoretical yield and 99% enantiomeric purity (Scheme 4).

Scheme 4

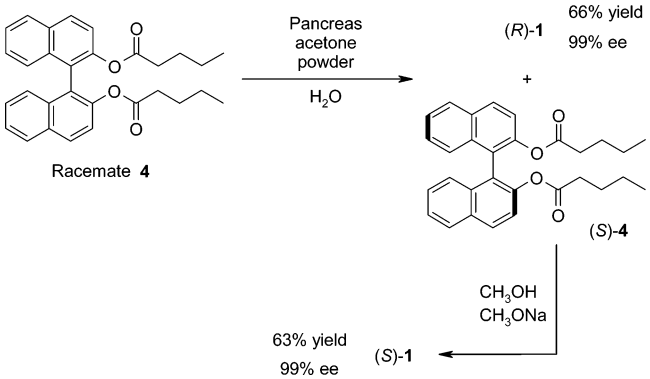
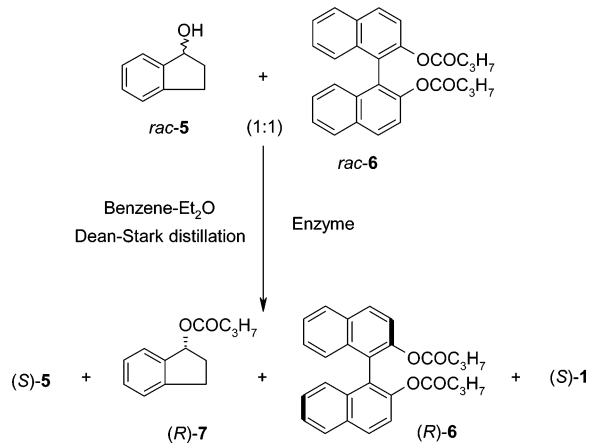


Table 1. Enzyme-Catalyzed Enantioselective Transacylation

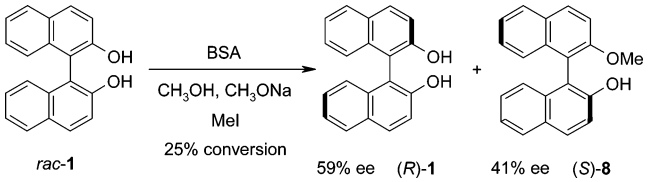


enzymes	relative rate	yield ratio (%) of (*S*)-**5**/(*R*)-**7**/(*R*)-**6**/(*S*)-**1**	ee of (*S*)-**5**	ee of (*R*)-**7**	ee of (*R*)-**6**	ee of (*S*)-**1**
PPL	1	24:23:23:23	>99	>99	98	98
PN	0.3	21:23:21:23	99	>99	97	98
PAP	0.5	23:22:21:22	98	97	95	95

Furthermore, an enantioselective enzyme-catalyzed transacylation reaction has been reported by Lin et al.[52,53] In this case, the enantioselective transacylation of *rac*-1-indanol **5** with *rac*-1,1′-binaphthyl-2,2′-dibutyrate **6** afforded (*S*)-1-indanol **5**, (*R*)-1-indanylbutyrate **7**, (*S*)-1,1′-binaphthyl-2,2′-diol **1**, and (*R*)-1,1′-binaphthyl-2,2′-dibutyrate **6**. Among many enzymes tested, porcine pancreatic lipase (PPL) showed the best results in both chemical yield and enantioselectivity. Porcine pancreatin (PN) and crude cholesterol esterase from PAP had moderate reaction rates and high enantioselectivities (Table 1).

Cavazza et al. reported an enzymatic resolution of *rac*-BINOL **1** based on a monomethyl etherification reaction promoted by a transport protein, bovine serum albumin (BSA).[54−56] In this case, enantiomeric excesses only up to 59% and 41% have been encountered respectively for (*R*)-BINOL **1** and the methylated (*S*)-product **8** (Scheme 5).

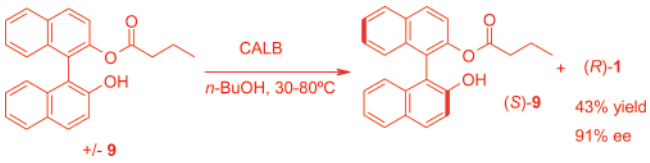
Scheme 5



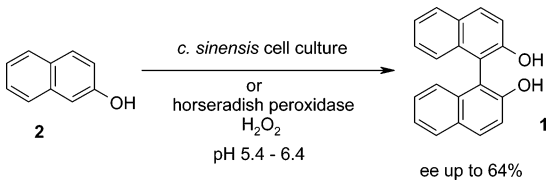
On the other hand, better results have been obtained using lipoprotein lipase enzymes from *Pseudomonas sp.* and *Pseudomonas fluorescens* for the enantioselective resolution and desymmetrization of racemic BINOL **1**, leading to enantioselectivities up to 80% ee.[57] Moreover, candida antartica lipase B (CALB) was found to efficiently catalyze hydrolysis of *O*-butyryl-BINOL, yielding optically active (*R*)-BINOL **1** with 91% ee at 80 °C in 45% yield. It is noteworthy that the reaction temperature and the nature of the acyl group of the substrate had a good influence on the reactivity and enantioselectivity (Scheme 6).[58]

More recently, optically active 1,1′-binaphthyl-2,2′-diol **1** was synthesized by oxidative coupling of 2-naphthol using *camellia sinensis* cell culture[59] or horseradish peroxidase[60,61]

Scheme 6



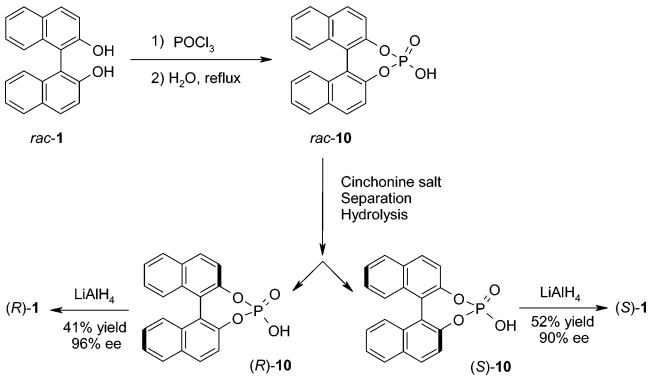
Scheme 7



as a catalytic system. In these cases, enantiomeric excesses of up to 64% have been encountered (Scheme 7).

2.2.1.2. Chemical Resolution of Racemic BINOL. The chemical resolution of *rac*-BINOL **1** has been extensively reported in the literature, and in all cases the methods are based on the easy separation of the pair of diastereomers derived from the reaction of *rac*-BINOL **1** with a chiral auxiliary. Thus, Jacques et al. were the first to describe the synthesis of cyclic binaphthyl phosphoric acids **10** from *rac*-BINOL **1** and their successful resolution via their cinchonine salts.[62−64] The (*R*)- and (*S*)-enantiomers of BINOL **1** were obtained in respectively 24% (96% ee) and 26% isolated yield (90% ee) (Scheme 8).

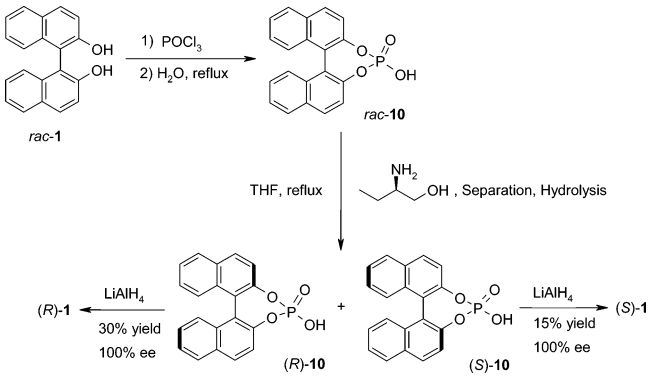
Scheme 8



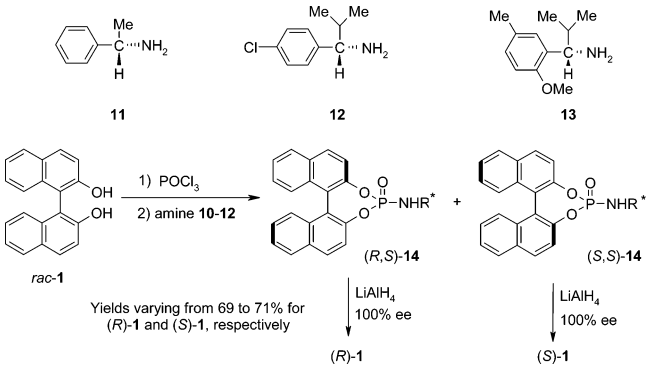
Nevertheless, the overall resolved yield is only moderate and the enantiomeric purity is not satisfactory (respectively 96% and 90% ee for (*R*)-**1** and (*S*)-**1**). Moreover, cinchonine is expensive and often recovered in contaminated form. In 1990, a similar method was reported by Miyano et al. by replacement of the cinchonine salt by the less expensive (*R*)-2-aminobutanol.[65] In this case, although both enantiomers are pure, they are obtained in even lower yield (respectively 30 and 15% for (*R*)-**1** and (*S*)-**1**) (Scheme 9).

On the other hand, Hu et al.[66,67] and De Lucchi et al.[68,69] have reported independently the resolution of *rac*-BINOL **1** via the formation of phosphoramidates derived from optically active phenethylamines **11**−**13**, which are readily accessible and widely used basic resolving agents. Compared to the above-mentioned methods, a significant enhancement of overall yield (up to 69% for (*R*)-**1** and 71% for (*S*)-**1**) and enantiomeric purity (100% for both enantiomers) has been achieved with all three amines **11**−**13**. Moreover, the resolving agents can be recovered in 80% yield with their original enantiomeric purity (Scheme 10).

Scheme 9

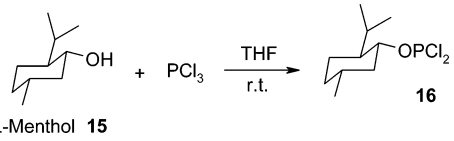


Scheme 10



Another efficient, practical, and inexpensive method described in 1993 by Brunel et al.[70] involves the tricoordinated compound **16**, easily prepared from phosphorus trichloride and L-menthol (Scheme 11). This methodology has been recently reproduced and improved by Tang et al.[71,72]

Scheme 11



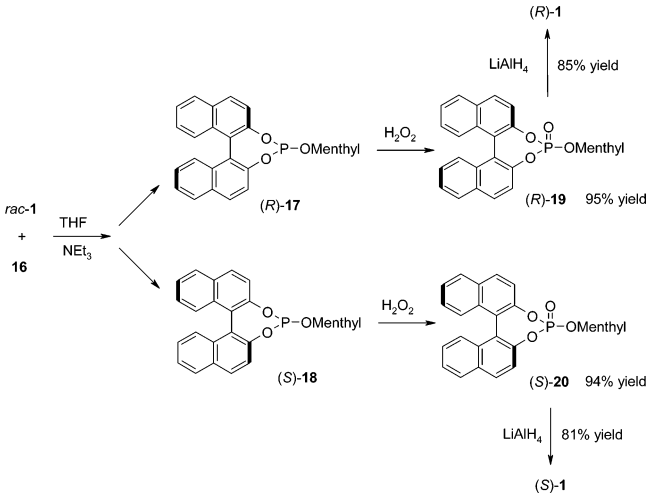
Compound **15** reacts with *rac*-BINOL **1**, leading to a 1:1 mixture of diastereomers **17** and **18** in quantitative yield. Complete separation of the two diastereomers was achieved in a single recrystallization from diethyl ether. Oxidation with 30% hydrogen peroxide led to the expected compounds **19** and **20**, which were reduced with $LiAlH_4$ to afford enantiomerically pure (*R*)-**1** and (*S*)-**1** in 81 and 85% overall yield, respectively (Scheme 12).

The preparation of enantiomerically pure BINOL **1** has also been achieved from *rac*-BINOL **1** via cyclic borate ester **23**, formed from the reaction of racemic 1,1′-binaphtholborane **21** with cinchonine **22** in THF.[73−75] Thus, under the chosen experimental conditions, one diastereomer is soluble while the other precipitates (Scheme 13).

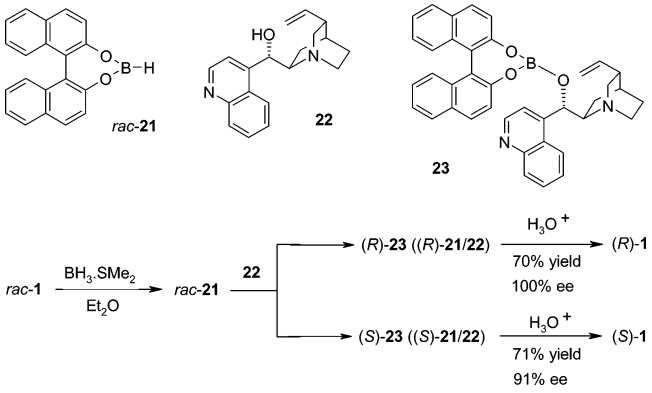
The same methodology has been applied using (*S*)-proline instead of cinchonine, but a decrease of enantioselectivity (down to 86% ee) was noticed.[76−78]

Recently, methods of resolution using chiral acyl chlorides for a simple two-step separation of pure enantiomers of BINOL **1** in 80−95% yield have appeared in the literature (Scheme 14).[69,79−81]

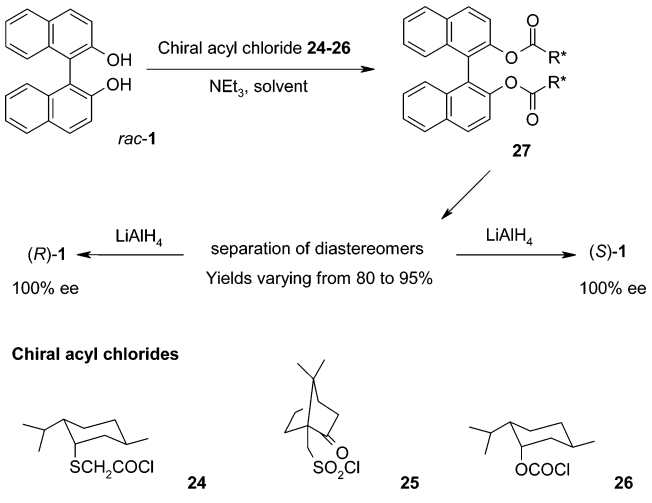
Scheme 12



Scheme 13



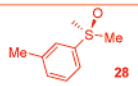
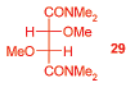
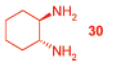
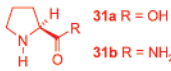
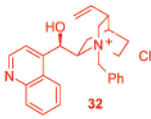
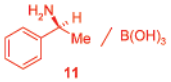
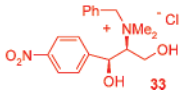
Scheme 14



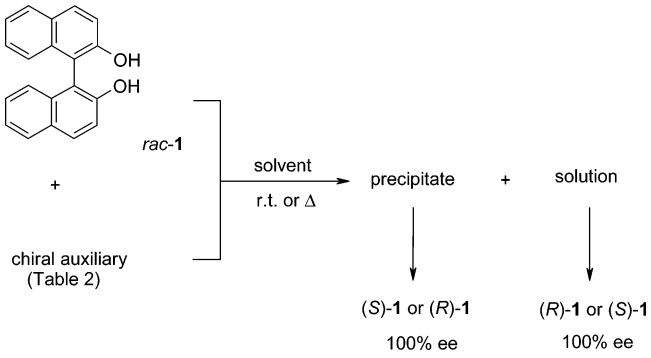
Chiral acyl chlorides

Simple and convenient methods of resolution of *rac*-BINOL **1** have been widely developed through selective crystallization of diastereomeric complexes obtained using various chiral auxiliaries. Thus, chiral *m*-tolyl methyl sulfoxide **28**,[82,83] chiral tartaric acid derivative **29**,[84,85] (1*R*,2*R*)-diaminocyclohexane **30**,[86−88] (*S*)-proline derivatives **31a**−**31b**,[89−92] and, more recently, chiral *N*-benzylcinchonidinium chloride **32**,[93−99] (*R*)-α-methylbenzylamine **11**,[73,100] and *threo*-(1*S*,2*S*)-*N*-benzyl-*N*,*N*-dimethyl-[1,3-difydrocyl-1-(4′-nitrophenyl)]-2-propyammonium chloride **33**[101] proved to be efficient (Scheme 15).

Table 2. Resolution of BINOL 1 Using Various Resolving Agents

Entry	Chiral auxiliary	(*R*)-**1** Yield (%)	(*R*)-**1** ee (%)	(*S*)-**1** Yield (%)	(*S*)-**1** ee (%)
1	 **28**	86	85	83	100
2	 **29**	59	100	72	100
3	 **30**	85	>99.8	81	>99.8
4	 **31a** R = OH **31b** R = NH_2	38 74	63 70	52 75	66 39
5	 **32**	95	>99.8	99	99
6	 **11**	53	56	58	99
7	 **33**	70	100	85	100

Scheme 15



In all cases, the resolution was achieved in moderate to very good chemical yields (38−99%) and in enantiomeric excesses varying from 66 to 99% ee depending on the nature of the chiral auxiliary used (Table 2).

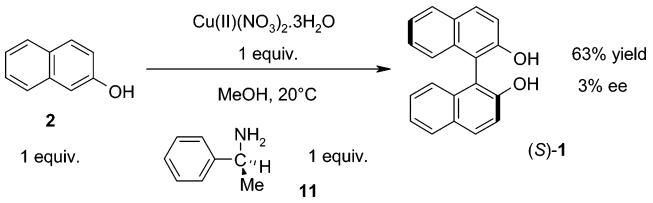
*2.2.2. Enantioselective Synthesis of BINOL **1** by Oxidative Coupling of 2-Naphthol*

Although enantioselective oxidative coupling of 2-naphthol with chiral catalysts provides one of the simplest routes to optically active BINOL **1**, only a few attempts to develop such an approach have been reported. Wynberg et al. were the first to describe an oxidative coupling of 2-naphthol by stirring a mixture of cupric-(*S*)-phenylethylamine **32** complex and 2-naphthol **2** in equimolar quantities at room temperature under a nitrogen atmosphere (Scheme 16).[26]

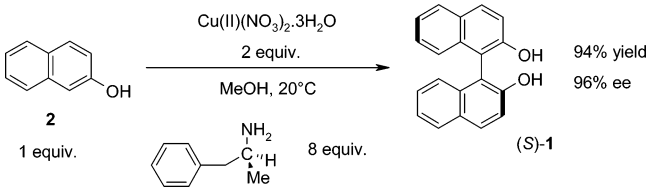
Although BINOL **1** was obtained in 63% yield, only 3% ee was obtained. On the basis of these results, Brussee et al. found that the replacement of (*S*)-phenylethylamine **32** by (*S*)-α-methylphenylethylamine (amphetamine) led to a beneficial increase of enantioselectivity.[102,103] Under these conditions, (*S*)-BINOL **1** was obtained in 94% yield and an enantiomeric excess up to 96% ee (Scheme 17).

Nevertheless, this system requires a large amount of chiral amine, up to 8 equiv with respect to 2-naphthol **2**. Recently,

Scheme 16



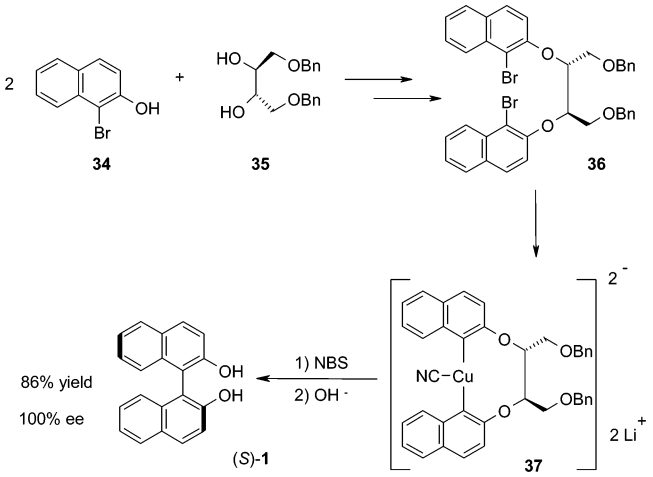
Scheme 17



Kocovsky et al. improved this reaction using a $CuCl_2$-sparteine complex (1/1 ratio) in a stoichiometric amount, leading to the formation of the expected chiral BINOL **1** in very high enantiomeric excesses but in only 36% chemical yield.[104−109]

Lipshutz et al. reported in 1994 an asymmetric synthesis of BINOL **1** involving an intramolecular oxidative coupling of cyanocuprate intermediates.[110] In this approach, inexpensive 1-bromo-2-naphthol **34** was converted to dibromide **36** with chiral diol **35**. Subsequent treatment with *tert*-BuLi followed by addition of solubilized CuCN presumably led to the in situ formation of a cyanocuprate **37** which produced enantiomerically pure (*S*)-BINOL **1** in 86% yield upon exposure to NBS (Scheme 18).

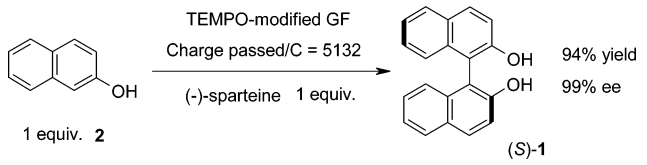
Scheme 18



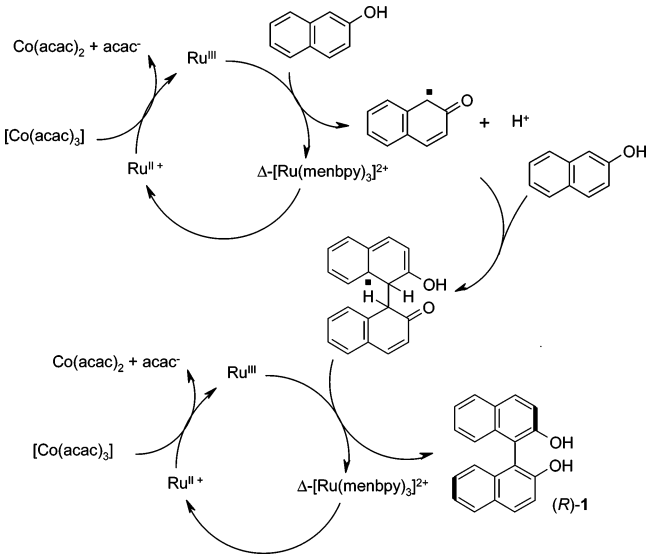
A remarkable result was obtained using an enantioselective electrocatalytic oxidative coupling of 2-naphthol **2** on a 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO)-modified graphite felt electrode in the presence of (−)-sparteine. It allowed the synthesis of (*S*)-BINOL **1** in 94% yield and 99% ee (Scheme 19).[111]

On the other hand, Ohkubo et al. reported a novel photoaccelerated asymmetric synthesis of an (*R*)-BINOL catalyzed by Δ-$[Ru(menbpy)_3]^{2+}$ with $Co(acac)_3$ as oxidant. Because the one-electron oxidation potential of 2-naphthol is +1.34 V vs SCE in MeCN, Δ-$[Ru(menbpy)_3]^{3+}$, formed by an oxidative quenching of Δ-$[Ru(menbpy)_3]^{2+}$ with $Co(acac)_3$, can oxidize 2-naphthol **2** efficiently so as to generate

Scheme 19



Scheme 20

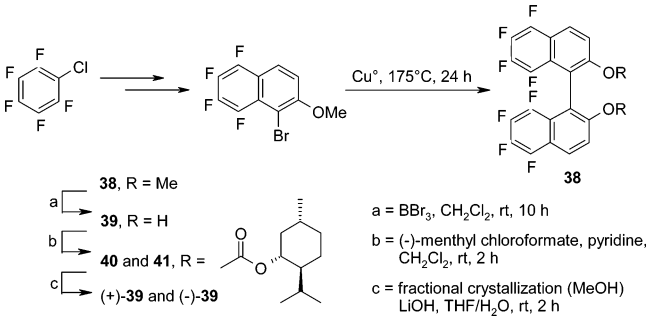


the corresponding radical, which produces a precursor of (*R*)-BINOL **1** (Scheme 20).[112,113]

In the same area, Katsuki et al. reported the enantioselective synthesis of (*R*)-BINOL **1** with moderate to good enantioselectivity (65% ee) via aerobic oxidative coupling of 2-naphthol using chiral (NO)Ru(II)−salen complex as a catalyst under irradiation of visible light.[114]

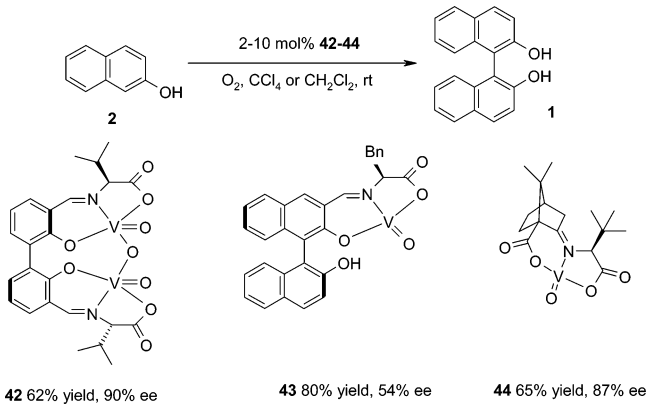
Among the numerous syntheses of BINOL derivatives described in the literature, we have decided to focus our interest on slightly modified BINOL's. In this context, we only report the synthesis of F_8BINOL derivative, an electronically perturbed version of BINOL with remarkable configurational stability. Thus, the electron deficient nature of the aromatic rings raises the oxidative stability of **39** compared to **1** as well as increases the acidity of the hydroxyl groups. Racemic **39** was prepared from commercially available starting materials and resolved by fractional crystallization of diastereomeric bis[(−)menthoxycarbonyl] derivatives **40** and **41** (Scheme 21).[115]

Scheme 21



More recently, several novel chiral oxovanadium(IV) complexes **42**−**44** have been designed and prepared for the asymmetric catalytic oxidative coupling of 2-naphthols with

Scheme 22



high enantioselectivities of up to 80% ee depending on the nature of the catalyst considered (Scheme 22).[116−121]

3. BINOL-Mediated Asymmetric Oxidation and Reduction Reactions

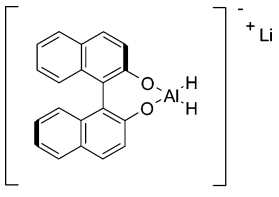
3.1. Enantioselective Reduction Reactions

3.1.1. Reduction of Ketones

Among a wide variety of asymmetric reactions, enantioselective reduction of prochiral carbonyl compounds is one of the most extensively studied transformations.[122] A standard method to this end stems from the use of complex metal hydride reagents bearing chiral alkoxyl or amino ligands. In this area, a number of reagents have been elaborated by modification of lithium aluminum hydride ($LiAlH_4$) with alkaloids, sugars, etc. Nevertheless, the general difficulty in obtaining a high level of stereoselectivity was attributed to the presence of multiple reactive species which are placed in different chemical and chiral environments. In this context, only Al reagents bearing a ligand with a C_2 axis (such as BINOL **1**) led to high enantiomeric excesses in the enantioselective reduction of aromatic ketones.

A reducing agent called (*R*)-BINAL-H **45** was prepared by mixing $LiAlH_4$ and an equimolar amount of enantiomerically pure BINOL **1** in THF (Scheme 23).[123−127] However,

Scheme 23



this initial attempt failed to reduce prochiral acetophenone in significant enantiomeric excess (2% ee). This result prompted Noyori et al. to examine a further modification of the reagent by adding a second simple alcohol (EtOH): replacement of either hydrogen by an EtO moiety produces an identical, single aluminum hydride reagent (Scheme 24).[128]

A series of prochiral alkyl phenyl ketones were reduced with 3 equiv of (*R*)-**46** or (*S*)-**46** at low temperature (−100 to −78 °C) and gave the corresponding carbinols in high enantiomeric excess with generally good enantioface differentiation, as shown in Table 3, entries 10−11. This methodology was recently applied to the synthesis of chiral lactones through enantioselective reduction of a carbonyl group in *meso*-1,2-dicarboxylic anhydrides.[129,130]

Scheme 24

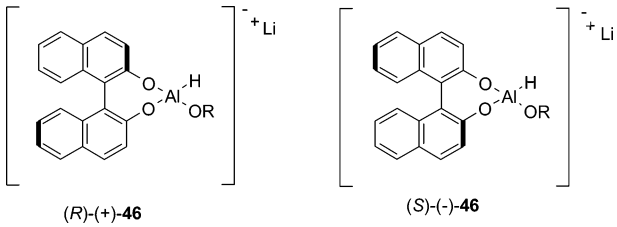
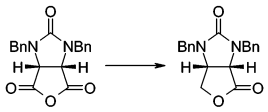
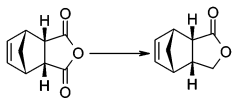


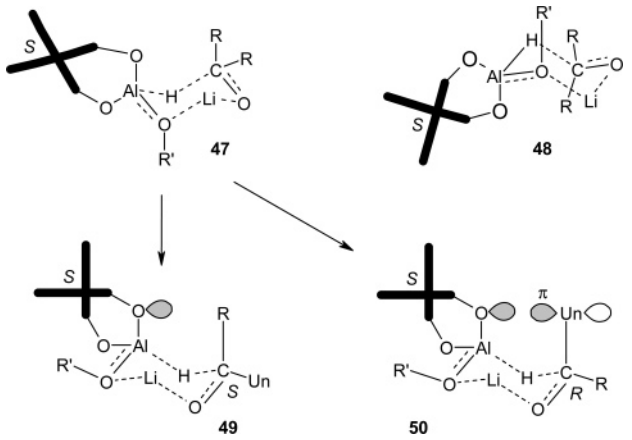
Table 3. Enantioselective Reduction of Carbonyl Group with BINAL-H 46

Entry	Ketone	BINOL **1** confign in **46**	Yield (%)	ee (%)
1	$C_6H_5COCH_3$	*R*	61	95 (*R*)
2	$C_6H_5COC_2H_5$	*S*	62	98 (*S*)
3	C_6H_5CO-*n*-C_3H_7	*S*	92	>99 (*S*)
4	C_6H_5CO-*n*-C_4H_9	*S*	64	>99 (*S*)
5	$C_6H_5COCH(CH_3)_2$	*S*	68	71 (*S*)
6	$C_6H_5COC(CH_3)_3$	*R*	80	44 (*R*)
7	α-tetralone	*R*	91	74 (*R*)
8	$C_6H_5COCH_2Br$	*R*	97	95 (*S*)
9	(*E*)-*n*-C_4H_9CH=CHCOCH$_3$	*R*	47	79 (*R*)
10	(*E*)-*n*-C_4H_9CH=CHCO-*n*-C_5H_{11}	*R*	91	91 (*R*)
11	(*E*)-*cyclo*-C_5H_9CH=CHCO-*n*-C_5H_{11}	*R*	91	92 (*R*)
12		*R*	76	90
13		*R*	69	84

The reactivity of the carbonyl substrates toward BINAL-H reduction seems to be greatly influenced by steric effects, various electronic factors including LUMO level and electron density at the carbonyl carbon, flexibility of the molecule, etc. Thus, the early or late nature of the transition state (energy, shape, tightness, atomic distances, etc.) varies subtly from reaction to reaction. Although it is not easy to present a unifying view, the stereochemistry of carbonyl group reduction may be rationalized as proceeding through the pathway depicted in Scheme 25.

The reaction is initiated by the complexation of the Li^+ cation to the oxygen atom of the C═O group, which is thus activated. The product-determining hydride transfer then occurs from Al to the carbonyl carbon by way of a six-membered ring transition state (Zimmerman−Traxler). In this case, the two binaphthoxy oxygens of (*S*)-BINAL-H **46** are diastereotopic, and therefore, two types of chairlike transition states **47** and **48** are possible. When a prochiral unsaturated ketone, UnCOR, is for example put into **47**, there emerges two diastereomeric transition states **49** and **50**. A series of (*S*)-BINAL-H reductions, giving *S* products selectively, indicates that transition state **49** is generally favored over the *R*-generating transition state **50**. This **49** vs **50**

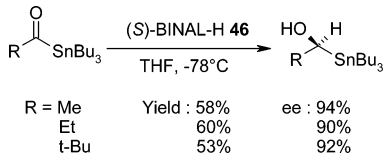
Scheme 25



relative stability would be controlled primarily by interactions between the axially located groups. Thus, transition state **50** possessing axial-Un and equatorial R groups is destabilized by the substantial n/π type electronic repulsion between the axially oriented binaphthoxyl oxygen and the unsaturated moiety.

It is noteworthy that, in 1988, Chong et al. had already mentioned this methodology for the asymmetric reduction of acylstannanes in order to prepare enantiomerically enriched α-alkoxystannanes[131] in enantiomeric excesses up to 94% ee (Scheme 26).

Scheme 26



R = Me	Yield : 58%	ee : 94%
Et	60%	90%
t-Bu	53%	92%

Among all the enantioselective methods described in the literature, borane reduction of C═O or C═N groups has appeared to be one of the most convenient. Thus, examples have recently been described using **51**, a chiral catalyst obtained from lanthanum triisopropoxide and (*R*)-BINOL **1** (Scheme 27).[132] Some typical results are summarized in Table 4.

Scheme 27

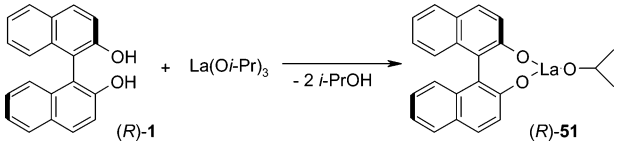
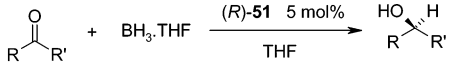
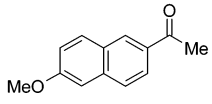


Table 4. Ketone Reduction with Borane and (*R*)-51 Catalyst

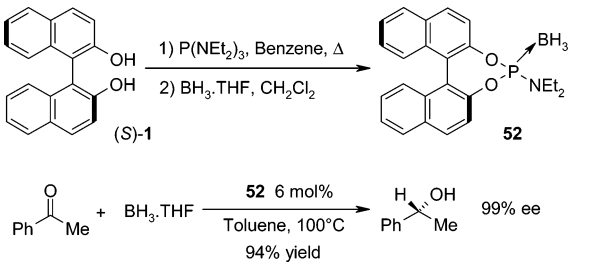


Entry	Ketone	Yield (%)	ee (%)
1	$PhCOCH_3$	95	39 (*S*)
2	$PhCOC_3H_7$	95	24 (*S*)
3	*tert*-$BuCOCH_3$	70	24 (*S*)
4	2-Octanone	73	23 (*S*)
5		95	62 (*S*)

As an extension of this catalytic system, Uang et al. have used a chiral aluminum complex generated in situ from aluminum isopropoxide and (*R*)-BINOL **1**. Under these conditions, alcohols were obtained in high yields and ee's of up to 83%.[133,134]

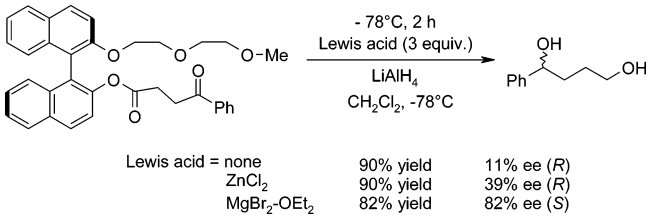
Recently, Tang et al. reported the synthesis of a new 2,2′-*O*,*O*-(1,1′-binaphthyl)-dioxo-*N*,*N*-diethylphospholidine borane complex **52** and its use as a catalyst in the enantioselective borane reduction of acetophenone leading to the expected alcohol in 99% ee at 100 °C (Scheme 28).[135]

Scheme 28



The diastereoselective reduction of chirally modified keto acids is a practical asymmetric method for the synthesis of hydroxy acid derivatives. Thus, using (*R*)-BINOL **1** as chiral auxiliary in the diastereoselective reduction of γ-keto acid esters led to enantiomeric excesses up to 82% ee (Scheme 29).[136]

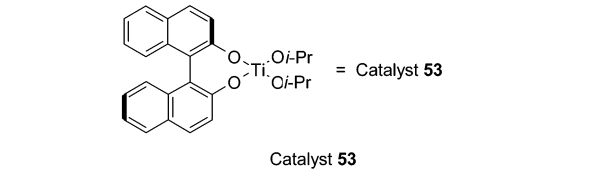
Scheme 29



Lewis acid = none	90% yield	11% ee (*R*)
$ZnCl_2$	90% yield	39% ee (*R*)
$MgBr_2$-OEt_2	82% yield	82% ee (*S*)

An enantioselective synthesis of chiral alcohols has been developed by Nakai et al. It involves an asymmetric catalytic hydrosilylation of prochiral ketones with $HSi(OEt)_3$ using (*R*)-BINOL−$Ti(Oi\text{-}Pr)_2$ **53** complex. Moderate enantioselectivities ranged from 10 to 55% ee depending on the nature of the ketones (Scheme 30).[137]

Scheme 30

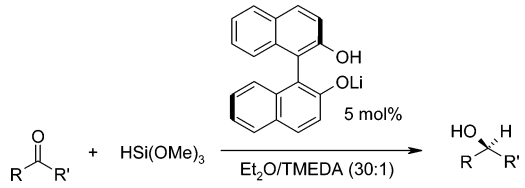


R = *n*-C_4H_{10}	50% yield	10% ee (N.D.)
m-NO_2Ph	98% yield	39% ee (*R*)
Ph	98% yield	55% ee (*R*)

The catalytic asymmetric reduction of different ketones with transient hypervalent silicon hydrides has been also described (Table 5).[138]

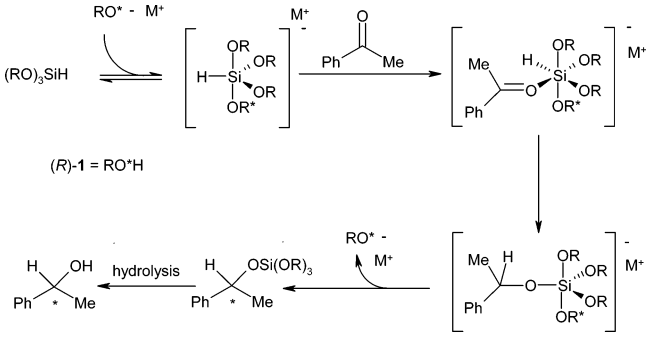
Trialkoxysilanes, upon activation by a small amount of a chiral nucleophile such as BINOL **1**, underwent addition to the carbonyl group, forming the corresponding silyl protected

Table 5. Enantioselective Reduction of Ketones with BINOL-Modified Silicon Hydrides



entry	ketone	conditions	yield (%)	ee (%)
1	acetophenone	6 h, 0 °C	80	61 (*S*)
2	isobutyrophenone	24 h, 0 °C	60	90 (*R*)
3	α-tetralone	24 h, 0 °C	39	93 (*R*)
4	methyl benzoylpropionate	24 h, 0 °C	63	65 (*S*)
5	4′-methylbenzophenone	24 h, 0 °C	74	0
6	2′-bromoacetophenone	24 h, 0 °C	91	66 (*S*)

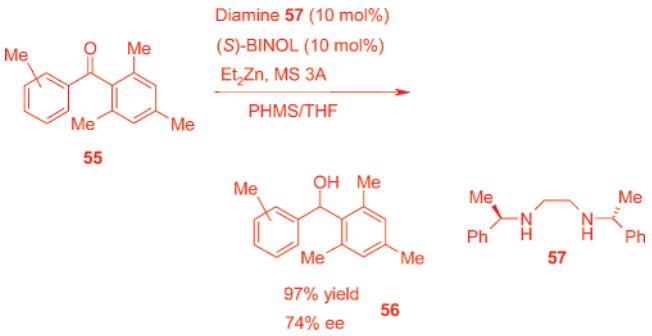
Scheme 31



alcohols, which were cleaved during the workup to give the enantiomerically enriched product alcohols (Scheme 31).

Recently, the asymmetric reduction of benzophenones multisubstituted at the *ortho*-positions was achieved in good enantiomeric excesses via hydrosilylation catalyzed by in situ generated chiral diamine **57**−Zn−BINOL complex under mild conditions wherein PHMS served as a safe and inexpensive source of hydride (Scheme 32).[139]

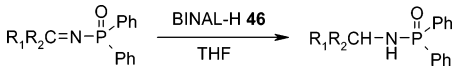
Scheme 32



3.1.2. Reduction of Imines

In contrast to the various studies dealing with the asymmetric reduction of the carbonyl group using chiral BINOL reagents, few examples dealing with the asymmetric reduction of the C=N group are known.[140] To our knowledge, the first example using a BINAL-H **46** reagent was described in 1987 by Hutchins et al., where prochiral diphenylphosphinylimines had been asymmetrically reduced to chiral diphenylphosphinylamines in quite good yields and moderate enantioselectivities (Table 6).[141]

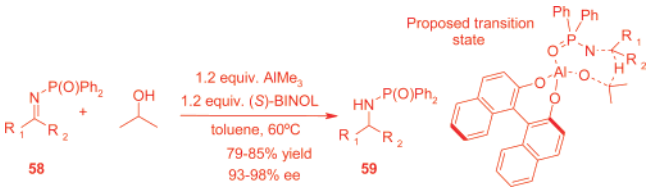
Table 6. Asymmetric Reduction of Diphenylphosphimylimines Using Reagent BINAL-H 46



entry	R_1	R_2	reagent	*T* (°C)	yield (%)	ee (%)
1	Me	Ph	(*S*)-**46**	−78	84	13
2	Me	Ph	(*S*)-**46**	25	35	77
3	Me	*β*-naphthyl	(*S*)-**46**	25	16	98
4	Me	α-naphthyl	(*R*)-**46**	−78	66	52
5	Me	Et	(*S*)-**46**	−40	63	40
6	Me	*c*-C_6H_{11}	(*R*)-**46**	−78	56	52

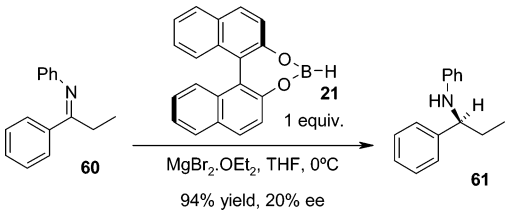
In 2006, a highly enantioselective Meerwein−Schmidt−Ponndorf−Werley reduction of *N*-phosphinoyl ketimines by (BINOL)Al(III)/2-propanol was reported. Yields ranging between 79 and 85% with high enantiomeric excesses (93−98%) are observed for a wide range of stucturally diverse ketimines. A bicyclic chelation model has been proposed to account for this high selectivity (Scheme 33).[142]

Scheme 33



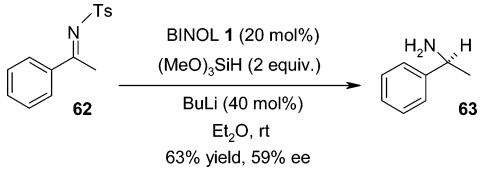
In 1992, Hino et al. reported a preliminary communication on the asymmetric reduction of imine **60** promoted by stoichiometric chiral dialkoxyborane reagent **21** (Scheme 34).[143] However, although the reduction was achieved in a good chemical yield, amine **61** was obtained in low enantiomeric excess (20% ee).

Scheme 34



Recently, an optically active lithium-alkoxide-catalyzed asymmetric reduction of imines with trimethoxyhydrosilane was reported by Hosomi et al., affording the expected amines in moderate ee (up to 72% ee) (Scheme 35).[144]

Scheme 35



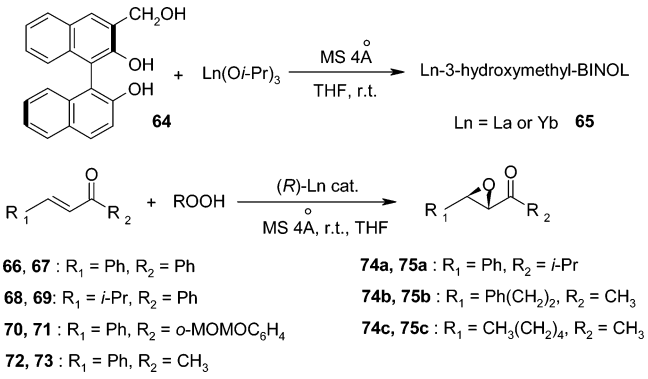
3.2. Enantioselective Oxidation Reactions

3.2.1. Epoxidation of Olefins

The asymmetric epoxidation of olefins is one of the most useful and challenging reactions in modern organic chem-

istry. In this area, chiral BINOL **1** has been extensively used in order to develop catalytic or stoichiometric methods of enantioselective epoxidation. Recently, Shibasaki et al. used lanthanum- or ytterbium-modified BINOL derivatives as catalysts in the asymmetric epoxidation of enones using hydroperoxides such as *tert*-butyl hydroperoxide (TBHP) (Table 7).[145−148]

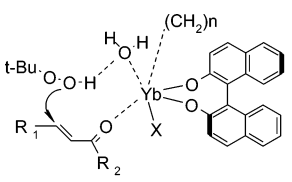
Table 7. Enantioselective Epoxidation of Enones Using (*R*)-Ln Catalysts



entry	enone	epoxide	Ln cat (mol %)	time (h)	yield (%)	ee (%)
1	66	67	La (5)	7	93	91
2	66	67	La (1)	44	95	89
3	68	69	La (5)	7	95	94
4	70	71	La (5)	96	78	83
5	72	73	Yb (5)	96	83	94
6	74a	75a	Yb (5)	159	55	88
7	74b	75b	Yb (8)	118	91	88
8	74c	75c	Yb (8)	67	71	91
9	66	67	La (8) + 15 mol % Ph_3PO	0.5	99	96
10	72	73	Yb (5) + H_2O (5 equiv./Yb)	48	92	94

It appears that the enones were best converted to the corresponding epoxides by using the ytterbium complex generated from Yb(O*i*-Pr)$_3$, BINOL derivative **64**, and molecular sieves (MS) 4 Å in THF. It seems likely that the difference in ionic radius between lanthanum and ytterbium as well as the difference in Lewis acidities accounts for the observed metal effects. It is noteworthy that the enantioselective epoxidation of α,*β*-unsaturated ketones catalyzed by (*R*)-Ln BINOL complexes was greatly improved (up to 98% ee) by adding of a small amount of triphenylphosphine oxide[149,150] or water (ca. 5 equiv to Ln).[151] In the latter case, the role of water can be explained in the following way. Water molecules coordinate to the Yb (atoms) and thereby control the orientation of the hydroperoxide to form an appropriate asymmetric environment for epoxidation (Scheme 36).

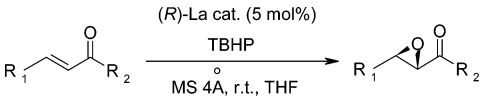
Scheme 36



X = (*R*)-BINOL **1** or other ligand

Despite excellent yields and enantiomeric excesses, this catalytic process is still unsatisfactory in terms of its rather low reactivity. This catalytic process has been improved using a novel multifunctional asymmetric catalyst, the La−BINOL−triphenyl arsine oxide ($Ph_3As{=}O$) complex exhibiting higher activity and selectivity compared to those of Ln-BINOL complexes and affording optically active epoxy ketones with broad generality in up to 99% yield and more than 99% ee (Table 8).[152]

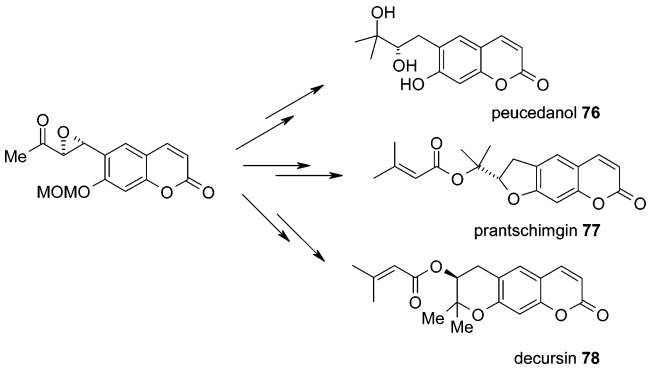
Table 8. Enantioselective Epoxidation of Enones Using (*R*)-La Catalysts



entry	R_1	R_2	time (h)	yield (%)	ee (%)
1	Ph	Ph	0.25	99	96
2	*i*-Pr	Ph	1.5	95	94
3	Ph	*tert*-Bu	7	94	98
4	Ph	Me	6	92	99
5	Me	C_5H_{11}	1.5	89	95

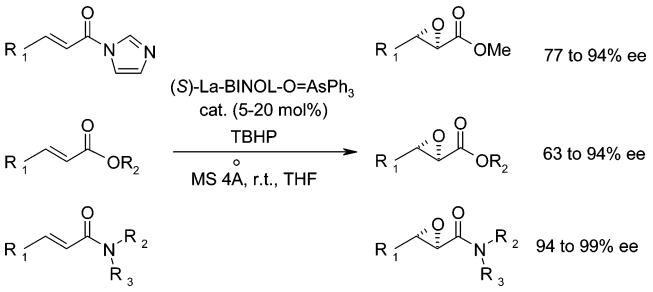
This catalytic system has been successfully applied in the enantioselective total syntheses of protein kinase C activator (+)-decursin **78** and its derivatives, peucedanol **76** and prantschimgin **77** (Scheme 37).[153,154]

Scheme 37



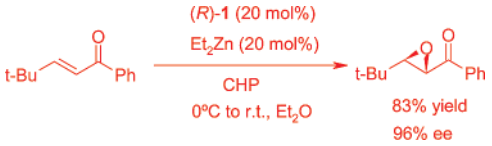
As an extension of this study, the catalytic asymmetric synthesis of α,*β*-epoxy esters, aldehydes, amides, and *γ*,*δ*-epoxy-*β*-ketoesters has been investigated with high enantioselectivities. This methodology is illustrated in Scheme 38, with the reaction proceeding smoothly with high substrate generality (Scheme 38).[155−158]

Scheme 38



Combination of (*R*)-BINOL **1** and Et_2Zn affords, in situ, a catalyst for homogeneous epoxidation of (*E*)-α,*β*-enones

Scheme 39

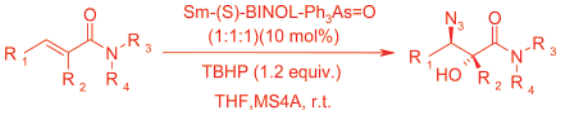


to the corresponding *trans*-epoxy ketones using cumylhydroperoxide (CHP) as oxidant. Values of ee of up to 96% can be achieved conveniently at room temperature (Scheme 39).[159]

A mechanistic rationale has been postulated suggesting an electrophilic activation of the substrate by the chiral BINOL−Zn catalyst and a subsequent nucleophilic attack of the oxidant.

In 2005, Shibasaki et al. reported works describing a one pot sequential catalytic asymmetric epoxidation−regioselective epoxide-opening process. The Sm−BINOL−Ph_3As=O complex, the catalyst for highly enantioselective epoxidation of α,*β*-unsaturated amides, undergoes dynamic ligand exchange by the subsequent addition of Me_3SiN_3. The newly generated samarium azide complex works as a highly reactive reagent for the regioselective ring opening of α,*β*-epoxyamides, affording *anti*-*β*-azido-α-hydroxyamides in up to 99% yield and up to greater than 99% ee (Table 9).[160]

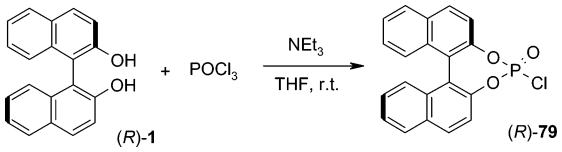
Table 9. One Pot Sequential Catalytic Asymmetric Epoxidation Regioselective Epoxide-Opening Process with Various α,*β*-Unsaturated Amides



entry	R_1	R_2	NR_3R_4	yield (%)	ee (%)
1	Ph	H	NMe_2	99	99
2	1-naphthyl	H	NMe_2	98	98
3	2-furyl	H	NMe_2	45	99
4	3-furyl	H	NMe_2	94	99
5	*n*-propyl	H	NMe_2	85	98
6	cyclohexyl	H	NMe_2	75	99

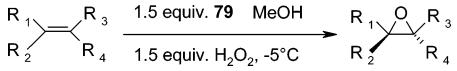
Another example of epoxidation of olefins, using a stoichiometric amount of a chiral reagent (*R*)-**79** generated from phosphoryl chloride and (*R*)-BINOL **1**, has been described by Berkessel et al. (Scheme 40).[161]

Scheme 40



Only low enantiomeric excesses were obtained (maximum 22% ee) (Table 10). A possible mechanistic interpretation involving a chiral $(RO)_2P(O)$−OOH intermediate has been suggested.

Table 10. Enantioselective Epoxidation of Olefins Using Hydroperoxide Generated from 79

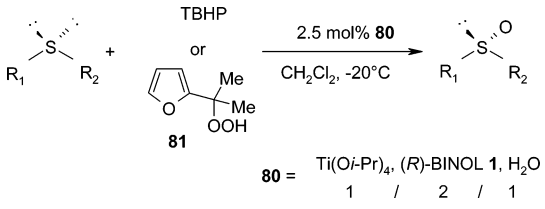


entry	olefin	reaction time (h)	yield (%)	ee (%)
1	1,2-dihydronaphthalene	4	55	20
2	1-methylcyclohexene	2	60	0
3	(*E*)-*β*-methylstyrene	4	40	16
4	styrene	6	16	22
5	(*E*)-stilbene	12	5	0
6	1-octene	24	20	10

3.2.2. Oxidation of Sulfides

The catalytic asymmetric oxidation of sulfides to chiral sulfoxides in moderate yield with *tert*-butyl hydroperoxide and renewable furylhydroperoxide **81** was achieved using titanium complex **80** produced in situ from a titanium alkoxide and (*R*)-BINOL **1** (Table 11).[162−168] The highest enantioselectivities (up to 93% ee) were obtained with 2.5 mol % of catalyst **80**. The presence of more than 1 equiv of water with respect to sulfide was essential for the oxidation, and it was found that the water was necessary, not only to produce an effective catalyst for a highly enantioselective oxidation, but also to maintain the catalytic activity of complex **80** for a longer period of time. A moderate level of asymmetric amplification was observed with this catalytic system. From a mechanistic standpoint, it was revealed that the initial asymmetric oxidation to the chiral sulfoxide is followed by the kinetic resolution of the sulfoxide. The nature of the active species involved in this process has not yet been clearly established.[169]

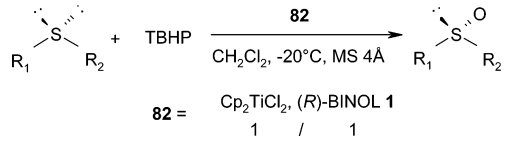
Table 11. Enantioselective Oxidation of Sulfides Using Catalyst 80



entry	R_1	R_2	oxidant	yield (%)	ee (%)
1	*p*-tolyl	Me	TBHP	67	93
2	*p*-tolyl	Me	**81**	71	49
3	Ph	Me	TBHP	80	65
4	Ph	Me	**81**	69	85
5	*p*-bromophenyl	Me	TBHP	57	93
6	*p*-bromophenyl	Me	**81**	79	51
7	2-naphthyl	Me	TBHP	73	51
8	*n*-octyl	Me	TBHP	64	69

Investigations were also carried out on the oxidation of sulfides to sulfoxides by Scettri et al. using Cp_2TiCl_2 as transition metal catalyst in the presence of (*R*)-BINOL **1** as chiral ligand and activated 4 Å molecular sieves. In this case, methyl aryl sulfoxides are isolated in good yields and moderate ee's (Table 12).[170]

Table 12. Enantioselective Oxidation of Sulfides Using Cp_2TiCl_2/BINOL Sytem 82



entry	R_1	R_2	yield (%)	ee (%)
1	*p*-tolyl	Me	95	45
2	Ph	Me	65	39
3	*p*-bromophenyl	Me	83	37
4	*p*-chlorophenyl	Me	81	38
5	*p*-methoxyphenyl	Me	80	40

4. BINOL-Mediated Asymmetric C–C Bond Forming Reactions

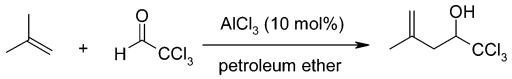
4.1. Ene Reaction

4.1.1. Introduction

The ene reaction, initially known as the "Alder-ene reaction", goes back to 1943, when Alder found that propene reacts with maleic anhydride in benzene at high temperature and pressure to give allylic succinic anhydride.[171] The first example of an intramolecular ene reaction (actually a carbonyl ene reaction) was even described earlier by Schmidt in 1927 with the thermal cyclization of citronellal into isopulegol.[172] However, because of the high activation energy (higher than that of the corresponding Diels−Alder reaction),[173] ene reactions generally require high temperature and pressure, a fact that has limited the widespread use of this reaction in its uncatalyzed version.

The first Lewis acid-catalyzed ene reaction was due to Colonge[174] and Normant[175] in the mid-1950s. It involved chloral, isobutene, and $AlCl_3$ (Scheme 41).

Scheme 41

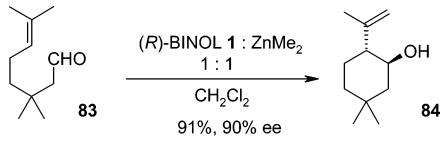


Blomquist[176] (limonene; formaldehyde; BF_3-dihydrate) and Snider[177] (*β*-pinene; acrolein, methyl acrylate, or methyl vinyl ketone; $AlCl_3$) then provided examples that proved the usefulness and efficiency of Lewis acid catalysis for the ene reaction. Over the years, examples of Lewis acid promoted ene reactions became more and more frequent, and several reviews can be found in the literature.[178−182] One of the big advantages of this reaction over the addition of allylmetals to carbonyl compounds is atom economy.

With respect to the use of BINOL, nearly all reported examples involve Ti-centered Lewis acids. However, the first successful example of asymmetric induction, which deals with a cyclization, was reported by Yamamoto with a BINOL−Al catalyst.[183,184] Indeed, a catalyst prepared in situ from dimethyl zinc and optically pure (*R*)-(−)-BINOL **1** promoted the cyclization of 3-methylcitronellal **83** into methylisopulegol **84** as a single isomer of 90% ee, but it needed to be used in excess (Scheme 42).

The same catalyst cyclized (*Z*)-methylfarnesal in 91% ee, but (*E*)-methylfarnesal only gave 32% ee and 3-dimethylcitronellal gave 0% ee.[185,186] Finally, Yamamoto reported the first example of an asymmetric intermolecular ene reaction promoted by chiral catalysts which were prepared from both enantiomers of 3,3′-bis(triphenylsilyl)-BINOL and Me_3Al.[187]

Scheme 42

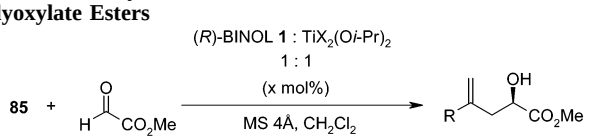


Ti-centered Lewis acids have had a major impact on the development of the asymmetric carbonyl-ene reaction.

4.1.2. Addition of Enes to Glyoxylate Esters and Fluoral

The greatest contribution in the field is due to Nakai and Mikami,[188] who, since 1989, studied the glyoxylate-ene reaction in great detail. Extensive screening of various chiral catalysts derived from optically active diols indicated that BINOL−Ti catalysts provided the best levels of enantiocontrol (Table 13).[189−192]

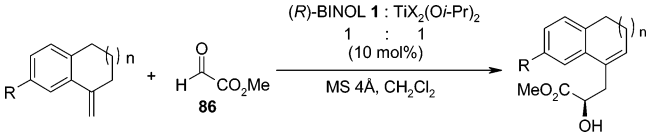
Table 13. Catalytic Enantioselective Addition of Enes to Glyoxylate Esters



Entry	Ene **85**	X	Catalyst amount (mol%)	Yield (%)	Ee (%)
1		Cl	1	97	97
2		Br	1	98	94
3		Cl	10	72	95
4		Br	10	87	94
5		Cl	10	82	97
6		Br	5	89	98

Feringa showed that optically active α-hydroxy propionic ester-substituted indenes and naphthalenes can be produced under similar conditions (Table 14).[193]

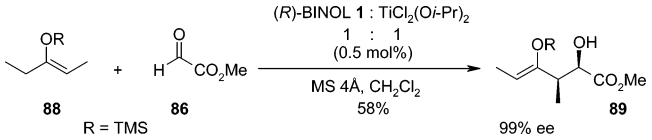
Table 14. Enantioselective Synthesis of α-Hydroxy Propionic Ester Substituted Indenes and Naphthalenes



entry	R	*n*	X	yield (%)	ee (%)
1	H	1	Cl	66	94
2	H	1	Br	69	94
3	H	0	Cl	62	18
4	H	0	Br	60	63
5	OMe	1	Br	52	>99

Mikami also showed that, under BINOL−$TiCl_2$ catalysis, ketene silyl enol ethers and glyoxylate esters do not lead to a Mukaiyama aldol adduct but rather to the ene adduct, which

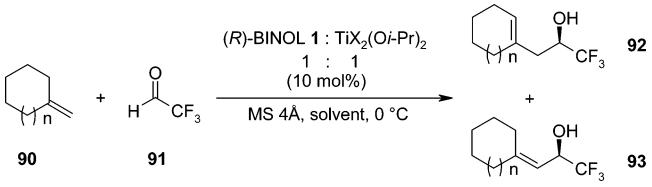
Scheme 43



is formed with complete control of absolute and relative stereochemistry (Scheme 43).[194]

To expand the scope of the reaction and its applicability in synthesis, Mikami developed a fluoral-ene reaction which led to the expected homoallylic alcohols, with enantioselectivity above 95% ee, and the Friedel−Crafts adducts, also with excellent enantioselectivity.[195] The sense of induction was the same as the one observed with glyoxylate esters: (*R*)-BINOL−Ti leads to (*R*)-α-CF_3-alcohols. Results with chloral were not as good with respect to both regioselectivity and enantiocontrol (Table 15).

Table 15. Asymmetric Synthesis of Homoallylic Alcohols

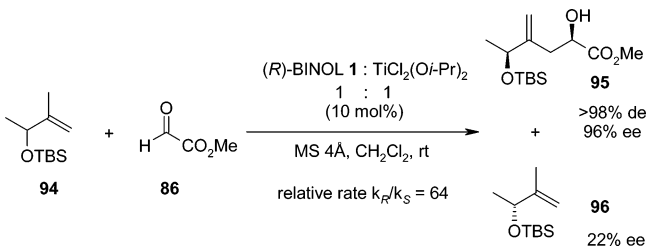


entry	n	X	solvent	yield (%)	**92** (ee %)/**93** (ee %)
1	0	Cl	CH_2Cl_2	78	62 (>95):38 (>95)
2	0	Cl	toluene	82	77 (>95):23 (>95)
3	1	Cl	CH_2Cl_2	93	76 (>95):24 (>95)
4	1	Br	CH_2Cl_2	95	79 (>95):21 (>95)

4.1.3. Kinetic Optical Resolution, Double Asymmetric Induction, and Asymmetric Desymmetrization

The kinetic optical resolution of a racemic compound can be regarded as an intermolecular desymmetrization process (vide infra) exemplified by the ene-reaction depicted in Scheme 40. Thus, the syn ene-adduct was obtained almost exclusively with an excellent level of optical purity by Mikami (Scheme 44).[196]

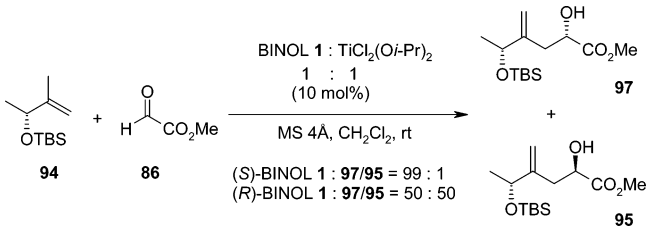
Scheme 44



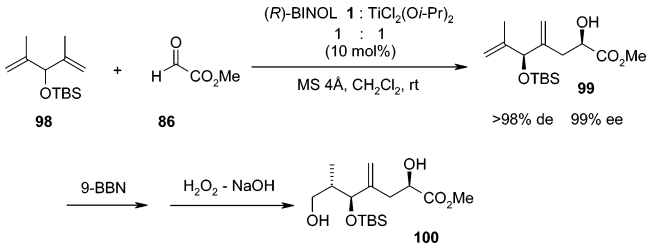
Moreover, the double asymmetric induction involving the "matched" pair [(*S*)-BINOL/(*R*)-ene] led to a single diastereoisomer in high yield whereas the "mismatched" pair [(*R*)-BINOL/(*R*)-ene] resulted in the formation of a 1:1 mixture of diastereomers in low yield (Scheme 45).

The same group also performed the asymmetric desymmetrization of the following symmetrical bis-allylic ether under the same experimental conditions. A single ene-adduct was obtained with very high diastereoselection and optical purity (Scheme 46).

Scheme 45



Scheme 46



Finally, double asymmetric induction is also described with chiral ene-like (−)-*β*-pinene or (+)-α-fenchene under (+)- or (−)-BINOL−Ti complex catalysis,[197] and other examples of desymmetrization were described by Mikami using formaldehyde and vinyl or alkynyl analogues of glyoxylates.[196]

4.1.4. Nonlinear Effect (NLE) and Structure of the Active Species

The fact that the optical purity of the products of a given reaction can exceed the optical purity of the catalysts (or chiral auxiliaries) involved has been known since Kagan's pioneering work in the field.[198,199] It is commonly referred to as a "positive nonlinear effect"[167,200−204] or "asymmetric amplification".[205,206]

Mikami and Nakai reported a remarkable level of positive NLE for the ene reaction between methylstyrene and methylglyoxylate.[200,207] Thus, the following graph shows the variation of ee of the ene adduct **102** as a function of the ee of the BINOL ligand. It clearly indicates that the use of BINOL of only 35−40% ee is good enough to provide the same level of enantiomeric excess for the ene adduct than when prepared from enantiomerically pure BINOL (Scheme 47, Figure 1).

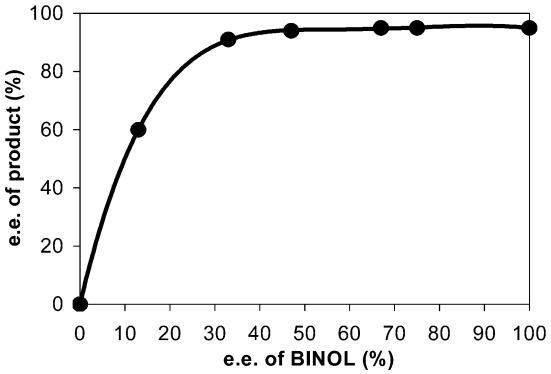
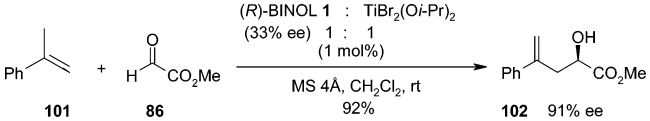


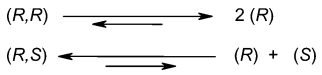
Figure 1.

Scheme 47



Considering the fact that the chiral Ti complex derived from a 100% ee BINOL reacted 35 times faster than the counterpart derived from *rac*-BINOL, the authors proposed that this remarkable effect resulted from a marked difference in the stabilities of the diastereomeric dimer forms of the catalyst.[208] The meso dimer (*R,S*) is the most stable and hence the less reactive, and therefore, it acts as a trap toward the minor (*S*)-enantiomer of the ligand (Scheme 48).

Scheme 48



These results on NLE and their interpretation in terms of dimeric forms of the catalyst initiated further studies on the structure of the active species. Thus, Mikami[209,210] and Nakai[211] independently reported the activity of a complex obtained in the absence of 4 Å molecular sieves. A dimeric Ti-μ_3-oxo structure was proposed for this complex, which displayed a high level of positive nonlinear effect.

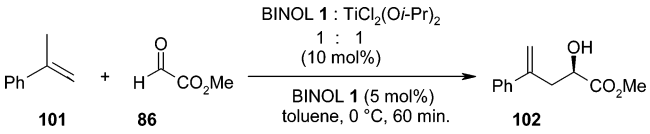
4.1.5. Asymmetric Activation

The asymmetric activation of catalysts can occur according to several different strategies: (a) starting from a racemic catalyst, it is possible to introduce a chiral deactivating catalyst, (b) or a chiral activating ligand, or (c) starting from a chiral catalyst, it is possible to add a racemic or chiral activating ligand.

The first approach, known as the chiral poisoning strategy, was used successfully by Faller. Starting from chloral, he established that a *rac*-BINOL/$TiCl_2$(O*i*-Pr)$_2$ catalyst can be poisoned by an inactive enantiopure catalyst [$TiCl_2$(O*i*-Pr)$_2$/(D)-DIPT] to yield a catalyst capable of a better asymmetric induction than the one obtained from catalysts directly prepared from enantiopure BINOL.[212,213]

Mikami applied the second and third strategies to the ene reaction. Indeed, he established that the reaction of methylstyrene with methylglyoxylate under a *rac*-BINOL/$TiCl_2$-(O*i*-Pr)$_2$ catalyst could be improved by adding (*R*)-BINOL as a chiral ligand. The same group also showed through kinetic studies that the catalyst prepared from (*R*)-BINOL and $TiCl_2$(O*i*-Pr)$_2$ could be activated by adding (*R*)-BINOL, *rac*-BINOL, or other chiral diols (Table 16).[214,215]

Table 16. Asymmetric Activation of Catalysts in the Ene Reaction



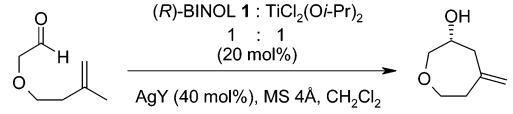
entry	BINOL (cat.)	BINOL (ligand)	yield (%)	ee (%)
1	rac	(*R*)	52	90
2	(*R*)	none	20	95
3	(*R*)	(*R*)	82	97
4	(*R*)	rac	69	96

Finally, Vallée recently obtained similar results with conformationally flexible biphenols and (*R*)-BINOL/Ti(O*i*-Pr)$_2$. He proposed that a new catalytic species is responsible for the high enantiomeric excesses found.[216]

4.1.6. Ene Cyclization

Although examples of ene cyclization are numerous in the literature, examples of intramolecular ene reactions promoted by chiral Lewis acids are scarce, and this is even more true for BINOL−Lewis acids. Mikami reported the efficient synthesis of six- and seven-membered ring carbocycles and heterocycles by using a BINOL-derived titanium perchlorate catalyst.[217,218] The triflate catalyst also gave a high level of enantioselectivity, but the tetrafluoroborate counterpart provided only moderate optical purity and very low yield (Table 17).

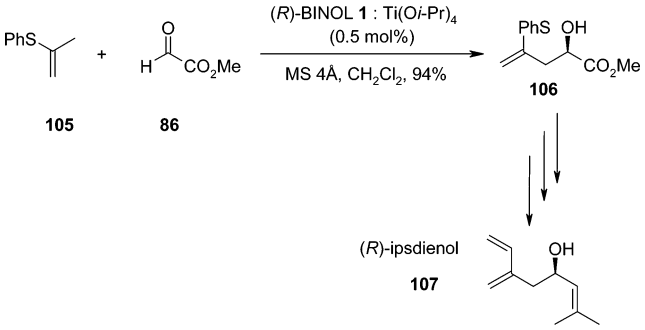
Table 17. Asymmetric Ene Cyclization by Various Chiral Lewis Acids



entry	AgY	*T* (°C)	yield (%)	ee (%)
1	none	0	64	88
2	$AgClO_4$	rt	43	91
3	AgOTf	rt	40	92
4	$AgBF_4$	rt	16	55

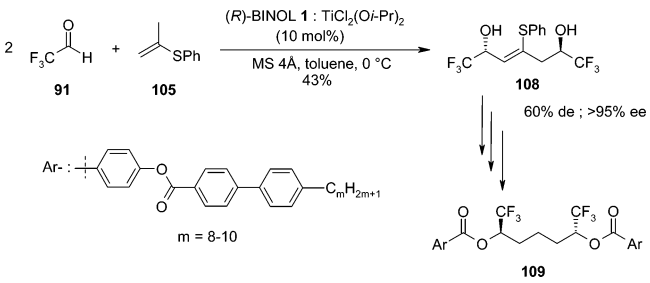
Finally, ene cyclization has been applied to the preparation of natural product precursors (*vide infra)*. Two syntheses of (−)-ipsdienol **107**, an aggregation pheromone of bark beetles, involving a glyoxylate ene reaction were reported by Mikami.[219,220] The following one takes advantage of the reactivity of vinylsulfides and allows the obtention of the target molecule (Scheme 49).

Scheme 49



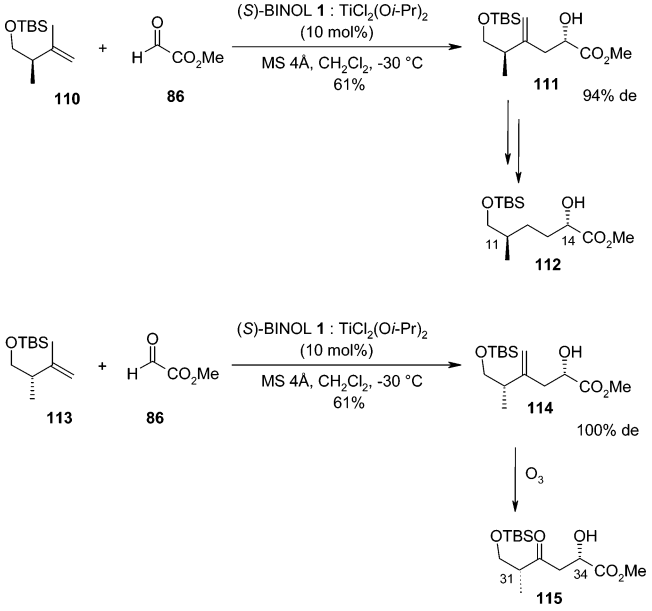
Vinylsulfides were also involved in a very nice application of a tandem and two directional asymmetric fluoral ene reaction to the synthesis of a new antiferroelectric liquid crystalline molecule **109** (Scheme 50).[221,222]

Scheme 50



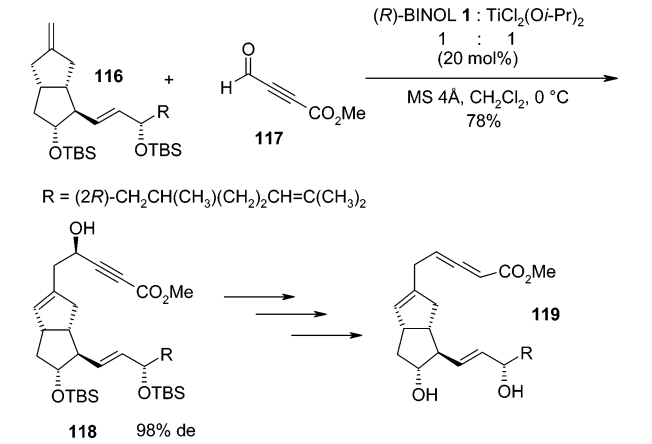
The carbonyl−ene reaction was also useful for the construction of more complex natural products such as the C_{10}−C_{15} and C_{30}−C_{35} fragments of rapamycin, in which the 1,4 remote stereocontrol was ensured by a double asymmetric induction (Scheme 51).[223]

Scheme 51



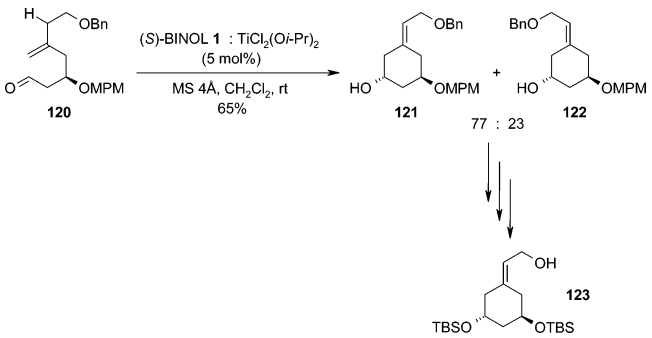
The same group also applied the reaction to alkynylogous and vinylogous glyoxylates and proposed, starting from a chiral ene, a double asymmetric synthesis of isocarbacyclin analogues **119** bearing a 2-allenyl side chain (Scheme 52).[224]

Scheme 52



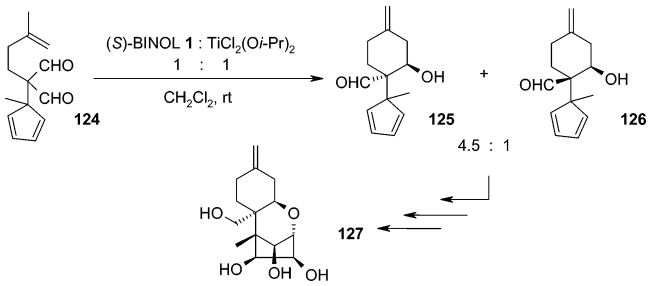
The synthesis of the A ring of vitamin D was also proposed by Mikami based on a regioselective propiolate ene reaction/enantioselective epoxidation/BINOL−Ti-catalyzed carbonyl ene cyclization sequence.[225,226] A more recent paper established the superiority of 6,6′-Br_2-BINOL over BINOL in that specific case (Scheme 53).[227]

Scheme 53



Although less efficient, the cyclization of malondialdehyde is also noteworthy. Indeed, the major isomer is an intermediate in the synthesis of the highly functionalized carbon ring skeleton of the trichlothecene anguidine **127** (Scheme 54).[228]

Scheme 54

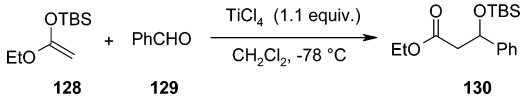


4.2. Aldol and Related Reactions

4.2.1. Introduction

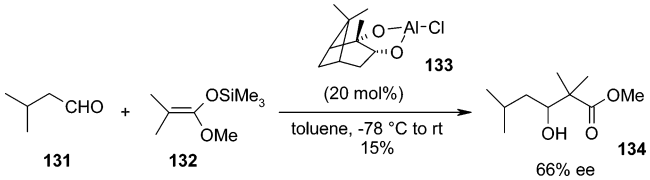
Although the Lewis acid-promoted aldol-type reaction of nucleophilic alkenes with carbonyl compounds has been known since the late 1930s, the introduction of silyloxyalkenes by Mukaiyama in 1973 marked a major breakthrough. Indeed, under $TiCl_4$ catalysis, silyl ketene acetal **128** reacts with benzaldehyde **129** to give the corresponding aldol adduct **130**.[229−232] The versatility of the Mukaiyama reaction, as it is commonly referred to, has since then been widely recognized and discussed in a number of reviews (Scheme 55).[233−235]

Scheme 55



The first successful enantioselective Mukaiyama reaction with substoichiometric amounts of a chiral Lewis acid was reported in 1986 by Reetz.[236] The best enantiomeric excess (66% ee) was obtained with a pinanediol−Al(III) **133** catalyst, but the yield remained low (15%) (Scheme 56).

Scheme 56

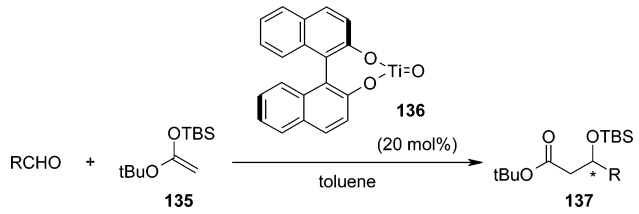


A BINOL−Ti(IV) catalyst, prepared from (*S*)-BINOL bislithium alkoxide and $TiCl_4$, had also been tried by the same authors, but the results were disappointing (enol ether **132** and isobutyraldehyde **131**: 8% ee).

However, a few years later Mukaiyama reported more encouraging results with a closely related BINOL−Ti complex.[237] Up to 85% ee's were reported with a complex formed from (*R*)-BINOL and (*i*-PrO)$_2$Ti(O) and for which structure **136** was proposed (Table 18).

These two results underline an important observation pointed out by Nelson in his excellent review[233] on catalyzed enantioselective aldol additions of latent enolate equivalents and that we have already mentioned: *enantiomeric excesses are highly sensitive to minor variations in Ti-based catalyst preparation.*

Table 18. Enantioselective Mukaiyama Reaction Catalyzed by 136



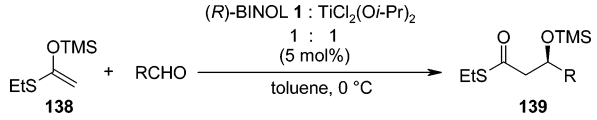
entry	R	*T* (°C)	yield (%)	ee (%)
1	Ph	−43	91	60
2	*p*-ClPh	−78	91	44
3	*β*-naphthyl	−78	98	80
4	(*E*)-PhCH═CH	−78	98	85

The Mukaiyama group[238−241] also studied other types of catalysts principally based on Sn(II) but which do not use BINOL as ligand and are therefore beyond the scope of the present review.

4.2.2. Titanium-Catalyzed Aldol Reaction

Mikami studied the addition of ketene silyl acetals of esters or thioesters to various aldehydes catalyzed by 5 mol % of a complex prepared from (*R*)-BINOL and $TiCl_2(Oi\text{-}Pr)_2$. The reaction led to the silyl ether of the expected aldol product in good yield and enantiomeric excesses. A series of crossover experiments involving "labeled" ketene acetals allowed the authors to propose a silatropic ene mechanism in which the silyl group undergoes a [1,3] O−O migration (Table 19).[243]

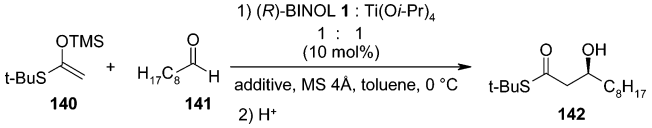
Table 19. Enantioselective Aldol Reaction Catalyzed by the $TiCl_2(Oi\text{-}Pr)_2$/1 System



entry	R	yield (%)	ee (%)
1	$BnOCH_2$	81	94
2	$n\text{-}C_8H_{17}$	60	91
3	*i*-Pr	61	85
4	(*E*)-CH_3CH═CH	60	81
5	$n\text{-}BuO_2C$	84	95

Further studies showed that the introduction of alcohols as additives often resulted in an increase in the optical yields of the reaction. Best results were obtained with phenols (Table 20).[244,245]

Table 20. Effects of Additives in the Enantioselective Aldolization Reaction Catalyzed by the Ti(*Oi*-Pr)$_4$/1 System

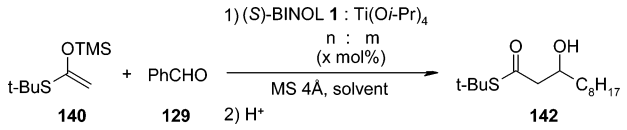


entry	additive	equiv/Ti	yield (%)	ee (%)
1	none		53	91
2	$(CF_3)_2CHOH$	2	56	92
3	C_6F_5OH	1	62	97
4	C_6H_5OH	1	61	96

In the same paper, Mikami also showed that enoxysilacyclobutane is more effective as a silyl nucleophile than the usual trimethylsilyl enol ether in the enantioselective catalysis of the reaction. Furthermore, the same group then established that the observed anomalous nonchelation complexation with benzyloxyaldehydes resulted from the steric hindrance of this particular silyl group.[246]

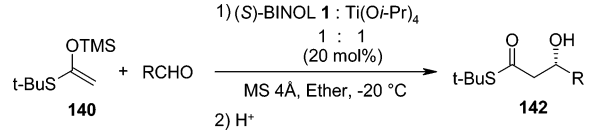
Almost contemporaneously with Mikami's initial study on the silatropic ene mechanism, Keck reported results that highlight the sensitivity of enantiomeric excesses to reaction variables on a very similar system: the addition of 1-(*tert*-butylthio)-1-((trimethylsilyl)oxy)ethene (**140**) to aldehydes under different BINOL−Ti complexes catalysis.[247] Both the stoichiometry of the catalyst components and the solvent had a significant effect on the results of the reaction (Table 21).

Table 21. Enantioselective Catalyzed Aldolization of Benzaldehyde under Keck's Conditions



	catalyst					
entry	*n*/*m*	mol %	solvent	*T* (°C)	yield (%)	ee (%)
1	1:1	10	CH_2Cl_2	0	27	36
2	2:1	10	CH_2Cl_2	0	45	62
3	2:1	20	toluene	0	54	95
4	1:1	20	diethyl ether	−20	90	97
5	2:1	20	diethyl ether	−20	86	91

Table 22. Enantioselective Catalyzed Aldolization of Various Aldehydes under Keck's Conditions



entry	R	yield (%)	ee (%)
1	Ph	90	97
2	$n\text{-}C_8H_{17}$	74	98
3	furyl	88	>98
4	cyclohexyl	70	89
5	PhCH═CH	76	89

The conditions reported in entry 4 were then successfully applied to various aldehydes (Table 22).

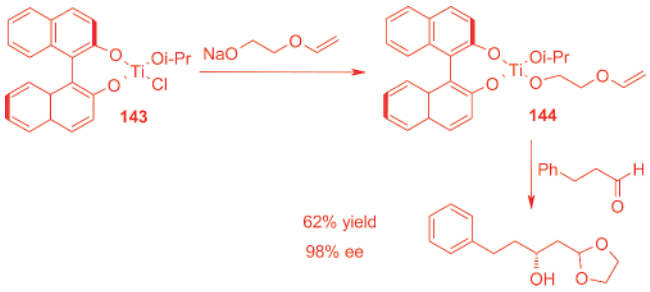
The same group then studied the condensation of the Danishefsky diene with a selection of different aldehydes under the catalysis of the 2:1 BINOL/Ti(O*i*-Pr)$_4$ complex and in the presence of catalytic amounts of CF_3CO_2H. The *β*-hydroxy vinylogous esters could then be transformed into the corresponding dihydropyrone derivatives in the presence of trifluoro acetic acid (see hetero-Diels−Alder section).[248]

The basic reagent vinyloxyethoxy titanium triisopropyloxide easily modified by replacing two of the ispropyloxides with (*R*)-BINOL reacts with simple, prochiral aldehydes to give chiral *β*-hydroxy-1,3-dioxolanes in good chemical yields and with enantiomeric ratios up to 99:1 (Scheme 57).[249]

4.2.3. Titanium-Catalyzed Vinylogous and Homoaldol Reactions

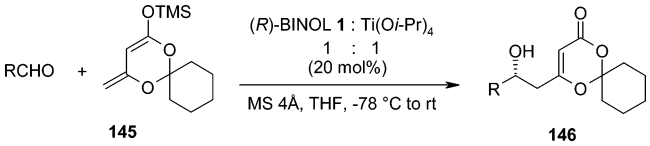
BINOL complexes have also been used in various vinylogous aldol reactions involving acyclic[250] or cyclic enol

Scheme 57



ethers. Thus, in the presence of BINOL−Ti catalyst, silyoxydioxine **145** and benzaldehyde led to the corresponding alcohol **146** with very good yield and enantiomeric excess.[251] Yields obtained with cinnamaldehyde and pentanal were lower although the enantiomeric excess remained good (Table 23).[252−260]

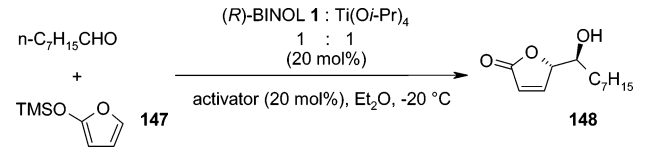
Table 23. Vinylogous Catalyzed Aldol Reaction Using Acyclic and Cyclic Enol Ethers



entry	R	yield (%)	ee (%)
1	Ph	93	92
2	(*E*)-PhCH=CH	58	79
3	*n*-Bu	37	76

Figadère studied the condensation of 2-trimethylsilyloxyfuran **147** on various aldehydes in the presence of a BINOL−Ti catalyst and different activators,[261−263] including the product of the reaction. As the result of a careful study, he was able to report the first example of a catalytic asymmetric autoinductive aldol reaction (Table 24).

Table 24. Catalytic Asymmetric Autoinductive Aldol Reaction

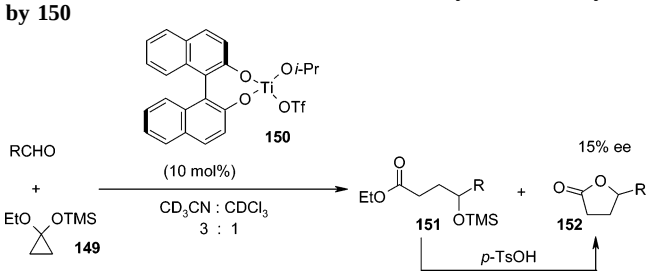


entry	activator	yield (%)	*syn*/*anti*	*syn* ee (%)
1	none	99	70/30	70 (*S*,*S*)
2	(*S*,*S*)-**148**	99	70/30	>96 (*S*,*S*)
3	(*R*,*R*)-**148**	99	70/30	40 (*S*,*S*)
4	(+)-TADDOL	99	70/30	82 (*S*,*S*)

2-Trialkylsilyloxyfurans were also added to aldimines in the presence of a BINOL−Ti(O*i*-Pr)$_4$ catalyst by Martin: yields were good with diastereomeric excesses (*erythro*/*threo*) between 42% and 92% and enantiomeric excesses up to 54%.[264]

Finally, 1-ethoxy-1-trimethylsilyloxy cyclopropane **149** was recently added to different aldehydes in the presence of two BINOL−Ti(X)(OTf) catalysts (X = O*i*-Pr or OTf).[265] Yields of the homoaldol adducts and corresponding lactones were good to excellent, but enantiomeric excesses, measured on the experiments on benzaldehyde, were low with both

Table 25. Homoaldol Adducts and Lactones Synthesis Catalyzed by 150



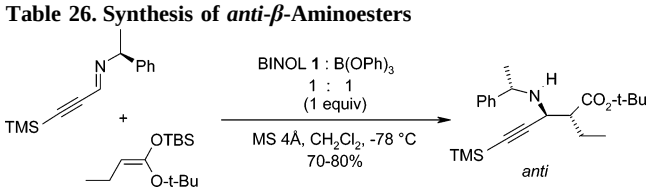
entry	R	*T* (°C)	lactone yield (%)
1	Ph	0	99
2	*p*-ClPh	0	84
3	TMS−C≡C	0	82
4	*t*-Bu	45−50	52

catalysts (X = OTf, 17% ee; X = O*i*-Pr, 15% ee) (Table 25).[266]

4.2.4. Other Metals

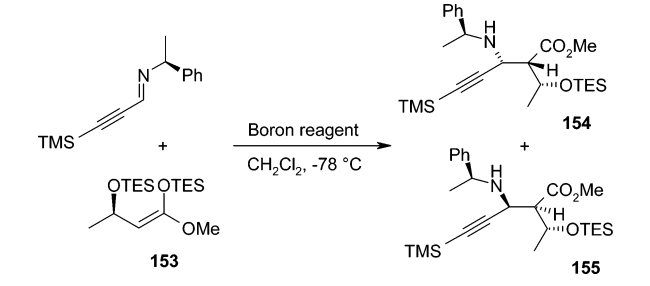
4.2.4.1. Boron Lewis Acids. In 1993, Yamamoto proposed the diastereoselective synthesis of anti β-amino esters from optically active aldimines, under the catalysis of complexes formed from (*R*)- or (*S*)-BINOL and triphenyl borate at room temperature in CH_2Cl_2.[267,268] The products were then converted into β-lactams (Table 26).

Table 26. Synthesis of *anti*-β-Aminoesters



entry	catalyst	*anti*/*syn*	*anti* de (%)
1	(*R*)-BINOL−B(OPh)$_3$	40/1	98
2	(*S*)-BINOL−B(OPh)$_3$	2/1	88

Table 27. Stereoselective Synthesis of Syn β-Aminoesters Using Chiral Silylketene Acetal 153



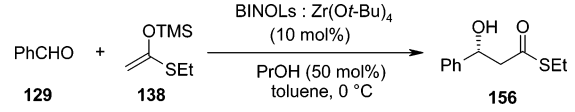
entry	catalyst	yield (%)	syn/anti	**154**/**155**
1	B(OPh)$_3$	75	92/8	98/2
2	(*R*)-BINOL−B(OPh)$_3$	53	100/0	33/67
3	(*S*)-BINOL−B(OPh)$_3$	83	100/0	2/98

It is interesting to note that, when using a chiral silylketene acetal **153**, the stereoselectivity could be reversed and syn adducts were obtained predominantly (Table 27).

4.2.4.2. Zr Lewis Acids. Recently, Kobayashi reported the use of chiral zirconium catalysts prepared from (*R*)-

BINOLs and Zr(O*t*-Bu)$_4$. The reactions were carried out with 10 mol % catalyst and in the presence of an additive (propanol in most examples).[269] Enantiomeric excesses with (*R*)-BINOL were modest but increased when using (*R*)-3,3′-diiodo-BINOL. The catalyst prepared from this ligand also allowed the preparation of anti aldol adduct (up to 90% de) while aldol reactions are generally syn stereoselective (Table 28).

Table 28. Zirconium-BINOL-Catalyzed Synthesis of Aldol Adduct 156

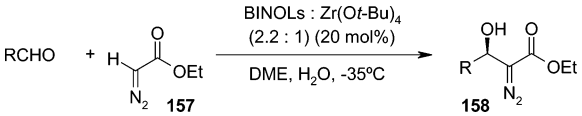


129 138 156

entry	ligand	yield (%)	ee (%)
1	(*R*)-BINOL	72	57
2	(*R*)−3,3′-I$_2$−BINOL	81	92
3	(*R*)−3,3′-Br$_2$−BINOL	54	61
4	(*R*)−3,3′-Cl$_2$−BINOL	48	35

In the same area, Wang et al. have recently demonstrated that the direct aldol-type condensation of aldehydes with ethyl diazoacetate catalyzed by the chiral complex of BINOL derivatives−Zr(O*t*-Bu)$_4$ gave *β*-hydroxy α-diazo compounds with moderate enantioselectivities (53−87% ee) (Table 29).[270]

Table 29. Zirconium−BINOL-Catalyzed Aldol-Type Condensation of Aldehydes with Ethyl Diazoacetate

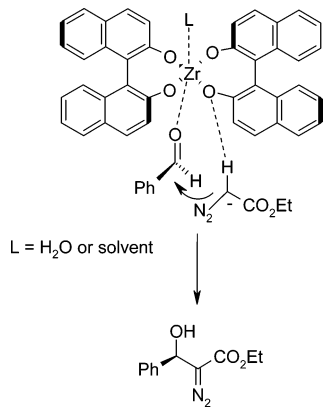


157 158

entry	aldehyde	yield (%)	ee (%)
1	PhCHO	40	65
2	3-F$_3$CC$_6$H$_4$CHO	61	65
3	4-ClC$_6$H$_4$CHO	59	72
4	3-BrC$_6$H$_4$CHO	47	78
5	*n*-C$_3$H$_7$CHO	82	57
6	furyl-CHO	82	57

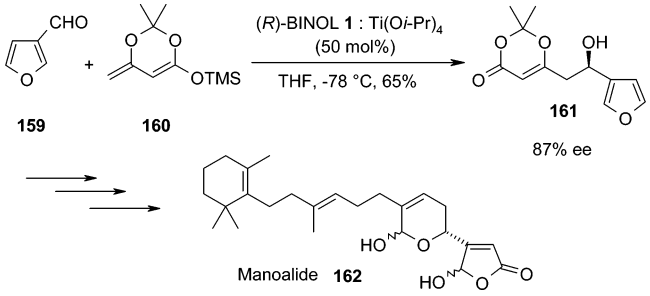
A mechanism of this enantioselective condensation is outlined in Scheme 58. In this case, it has been postulated that the Zr(IV) catalyst acts as a Lewis acid activating the aldehyde (Scheme 58).

Scheme 58



Two syntheses of natural products benefit from an application of a vinylogous aldol reaction. Figadère proposed a synthesis of (+)-muricatacin[262] and (+)-amino muricatacin[271] as direct applications of his study on the reactivity of 2-trimethylsilyloxyfuran under BINOL−Ti catalysis. Scettri reported a study on the synthesis of a nonracemic 6-(furan-3-yl)-5,6-dihydropyran-2-ones[255] and its implementation to the synthesis of manoalide **162**, a sesquiterpene of marine origin (Scheme 59).[258,272]

Scheme 59

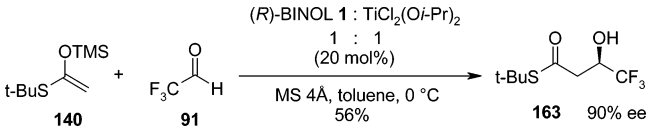


159 160 161 87% ee

Manoalide 162

Mikami also showed that the reaction involving the ketene silyl acetal of thioesters could be applied to fluoral **91**, allowing an enantioselective synthesis of CF_3 substituted aldol **163** of biological importance (Scheme 60).[195,273]

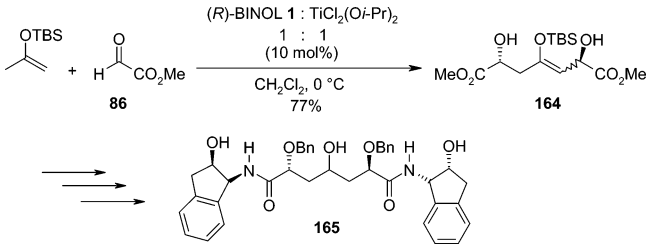
Scheme 60



140 91 163 90% ee

Finally, a particularly attractive version of the reaction was proposed by the same group: a tandem and two directional enantioselective aldolization. The pseudo-C_2 symmetric product of the condensation between the silyl enol ether and two molecules of the methyl glyoxylate led, through five steps, to a potentially powerful analogue of HIVP inhibitor **165** (Scheme 61).[274]

Scheme 61

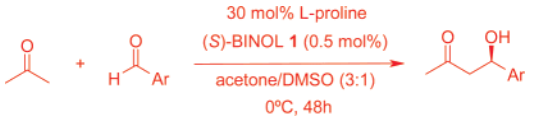


86 164 165

In 2006, the chiral Bronsted acid (*R*)-BINOL **1** was explored as an additive in the l-proline-catalyzed aldol reaction, and the enantioselectivity was improved from 72% ee without additive to 98% ee. This improvement could be attributed to a hydrogen bonding interaction among the chiral diol, the aldehyde, and l-proline which activated the substrate and stabilized the transition state (Table 30).[275]

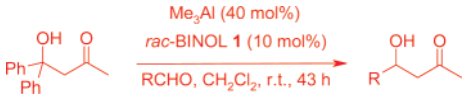
Solid crystalline and stable 1,1-diphenyl-1-hydroxy-3-butanone was shown to serve as an excellent precursor of the Al−enolate of acetone generated in situ for Al−BINOL-catalyzed aldol-transfer reactions of aldehydes. The best yields were obtained with electron rich aromatic aldehydes

Table 30. Direct Aldol Reaction in the Presence of l-Proline and a Catalytic Amount of (*S*)-Binol 1



entry	R	yield (%)	ee (%)
1	Ph	56	98
2	1-naphthyl	64	79
3	9-anthryl	23	87
4	4-BrC_6H_4	76	97

Table 31. Aldol-Transfer Reactions of Aldehydes with 1,1-Diphenyl-1-hydroxy-3-butanone



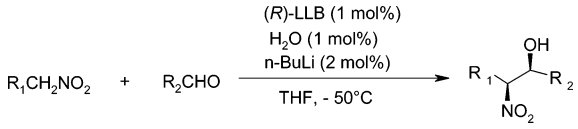
entry	R	yield (%)
1	Ph	26
2	1-naphthyl	48
3	9-anthryl	23
4	4-ClC_6H_4	15
5	pyridine-2	79
6	furan-2	24
7	4-MeOC_6H_4	70
8	thiophene-2	30

and 2-pyridine carbaldehyde, and the latter gave 1-hydroxy-1-(2-pyridyl)-3-butanone in 79% yield (Table 31).[276]

4.2.5. Catalytic Asymmetric Nitroaldol Reaction

The concept of heterobimetallic chiral catalysts has been applied in asymmetric nitroaldol reactions. In this case, the most efficient catalyst was found to be the lanthanum−lithium−BINOL complex (LaLi−BINOL (**LLB**)) leading to enantiomeric excesses varying from 40 to 96% ee (Table 32).[277−279]

Table 32. Catalytic Asymmetric Nitroaldol Reaction

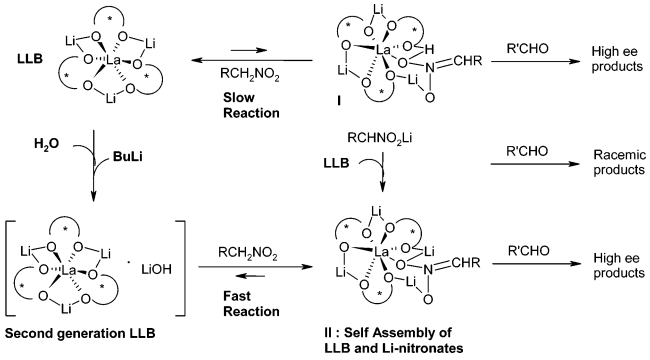


entry	R_1	R_2	yield (%) (syn/anti)	ee (%) of syn
1	H	C_6H_{11}	94	40
2	Me	CH_2Bz	83 (89/11)	94
3	Et	CH_2Bz	84 (95/5)	95
4	CH_2OH	CH_2Bz	76 (94/6)	96

A proposed reaction course for an improved catalytic asymmetric nitroaldol reaction is shown in Scheme 62.

First, the tight complex of LaLi−BINOL and LiOH or the high rate of aggregation between LaLi−BINOL and lithium nitronates results in the formation of products with high enantiomeric excesses. Second, much higher reaction rates were observed in all cases; this suggests that heteropolymetallic intermediates such as **II** react with carbonyl compounds much more quickly than heterobimetallic intermediates such as **I** or that the rate of reverse reactions of

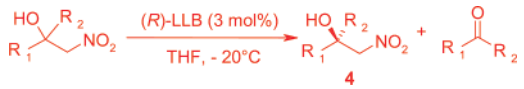
Scheme 62



the type **II** to LaLi−BINOL is much lower than the rate of reactions of the type **I** to LaLi−BINOL.

As an extension of this work, Shibasaki et al. achieved a kinetic resolution of tertiary nitroaldols derived from simple ketones. In this context, the LaLi−BINOL heterobimetallic complex possesses an excellent selectivity (80−97% ee with 30−47% recovery yield) (Table 33).[280]

Table 33. Kinetic Resolution of *tert*-Nitroaldols



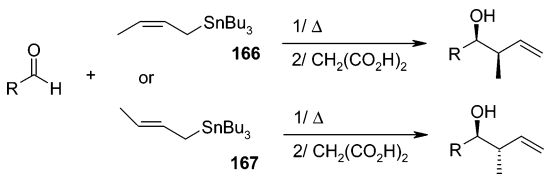
entry	R_1	R_2	yield **4** (%)	ee (%)
1	cyclohexyl	Me	47	90
2	*i*-Bu	Me	40	97
3	Ph	Me	30	88
4	Ph$(CH_2)_2$	Me	40	80

4.3. Allylation

4.3.1. Introduction

The allylation of carbonyl compounds with allyltin or allylsilane derivatives is a fairly recent reaction. Indeed, the first example of a thermal reaction between allyltin and aldehydes to produce homoallylic alcohols was reported by König and Neumann in 1967.[281] In the same paper, they also established that the reaction rate could be enhanced by adding $ZnCl_2$ to the reactants. Pereyre then showed that the thermal reaction occurs with allylic rearrangement and remarkable stereospecificity in the case of both isomers of crotyl tri-*n*-butyltin **166** and **167** (Scheme 63).[282,283]

Scheme 63



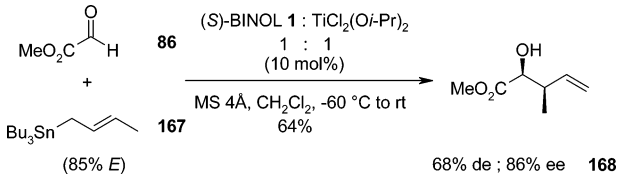
Calas[284,285] showed that the same kind of reaction could be performed with allylsilane derivatives if Lewis acids such as $AlCl_3$ or $TiCl_4$, respectively, were used. With respect to enantioselective catalysis, the first breakthrough is due to Seebach, who prepared optically active dichlorodialkoxytitanium derivatives from (*S*)-(−)-1-phenylethanol.[286]

Once again, BINOL−Ti Lewis acids dominate the literature in the field.

4.3.2. Titanium-Catalyzed Allylation Using Allyltin Reagent

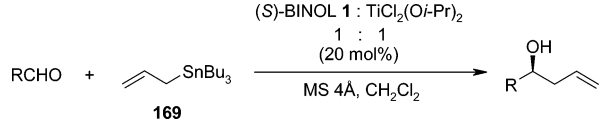
In 1993, after Yamamoto had obtained respectable enantiomeric excesses by using chiral acyloxyborane complexes,[287] three groups discovered simultaneously that tri-*n*-butylallyltin undergoes enantioselective reactions with a wide variety of aldehydes provided optically active BINOL−Ti(O*i*-Pr)$_2$ or BINOL−TiCl$_2$ was used. Thus, Mikami and Nakai used a complex prepared in situ from (*S*)-BINOL and TiCl$_2$(O*i*-Pr)$_2$ in the presence of 4 Å molecular sieves. Such a complex used in 10 mol % catalyzes the condensation of various tri-*n*-butylallyltins on glyoxylates with both good diastereoselectivity and enantioselectivity.[288,289] Condensations also occur with different substituted allylsilanes, but yields were lower (vide infra) (Scheme 64).

Scheme 64



The same catalyst, used by Tagliavini and Umani-Ronchi in 20 mol %, also in the presence of activated 4 Å MS, promotes the allylation of simple achiral aldehydes with good chemical yields and excellent enantiomeric excesses (Table 34).[290]

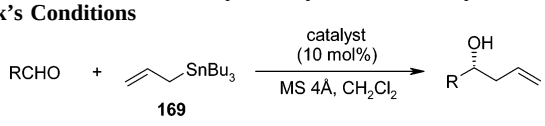
Table 34. Ti−BINOL-Catalyzed Allylation of Achiral Simple Aldehydes



entry	R	*T* (°C)	yield (%)	ee (%)
1	C_7H_{15}	−20	83	97
2	C_5H_{11}	−20	75	98
3	PhCH=CH	−20	38	94
4	Ph	rt	96	82

Keck prepared a similar chiral catalyst by two different methods: first (method A), by heating a mixture of (*R*)-BINOL and Ti(O*i*-Pr)$_4$ (1:1) with powdered 4 Å MS; second (method B), by heating a 2:1 mixture of (*R*)-BINOL/Ti(O*i*-Pr)$_4$ in the presence of catalytic amounts of CF_3CO_2H (3 mol % relative to Ti). Both catalysts were then employed successfully at 10 mol % (Table 35).[291,292]

Table 35. Ti−BINOL-Catalyzed Allylation of Aldehydes under Keck's Conditions

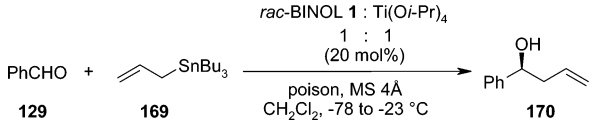


entry	R	catal (method)[a]	yield (%)	ee (%)
1	Ph	A	88	95
2	Ph	B	98	92
3	cyclohexyl	A	66	94
4	cyclohexyl	B	95	92
5	(*E*)-Ph-CH=CH	B	78	77

[a] A = (*R*)-BINOL/Ti(O*i*-Pr)$_4$ (1:1), MS 4 Å; B = (*R*)-BINOL/Ti(O*i*-Pr)$_4$ (2:1), CF_3CO_2H, 3 mol % relative to Ti.

Keck also noticed a case of chiral amplification (positive NLE): in one case, the use of a (*R*)-BINOL, of only 50% ee, gave the homoallylic alcohol with 88% ee.[293] This observation was confirmed later by Faller, who proposed an explanation similar to the one put forward by Mikami for the glyoxylate−ene reaction (vide supra). The fact that the positive NLE could result from the formation of a rather inactive *meso* dimeric catalyst led Faller to propose a chiral poisoning strategy.[212] Thus, a racemic BINOL−Ti(O*i*-Pr)$_2$ catalyst was poisoned by an enantiopure D-DIPT−Ti(O*i*-Pr)$_2$ catalyst (which is inactive). Results reported clearly show the effectiveness of this approach (Table 36).

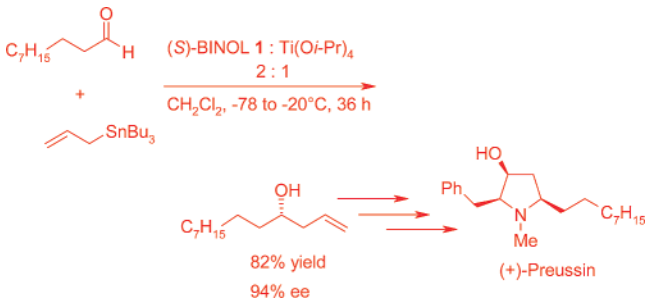
Table 36. Influence of Poison Amount on the Enantioselectivity in the Ti−BINOL-Catalyzed Allylation of Benzaldehyde



	poison		yield	ee
entry	D-DIPT	Ti(O*i*-Pr)$_4$	(%)	(%)
1	none	none	65	0
2	15 mol %	10 mol %	40	39
3	20 mol %	10 mol %	47	81
4	30 mol %	10 mol %	63	91

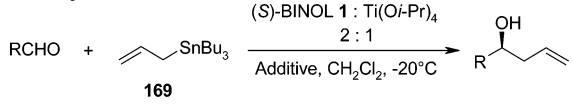
Recently, such a methodology was successsfully applied by Barua et al. in the first step of a concise total synthesis of the antifungal antibiotic (+)-Preussin LLL (Scheme 65).[294]

Scheme 65



Always with the goal of reaction rate enhancing and greater selectivity, Yu proposed various accelerators of general structure R$_n$MSR′ (M = Si, B, Al).[295−300] The key to this approach, which proved to be efficient, is the strong Sn−S and M−O bonds relative to the weaker M−S bond (Table 37).

Table 37. Influence of "Accelerator" Amount on the Enantioselectivity in the Ti−BINOL-Catalyzed Allylation of Benzaldehyde

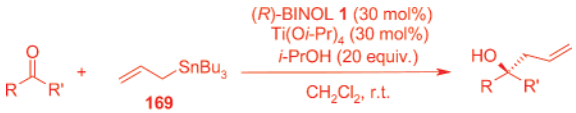


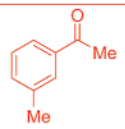
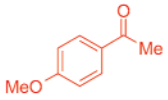
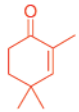
entry	R	catal (%)	additive	yield (%)	ee (%)
1	$PhCH_2CH_2$	10	*i*-PrSSiMe$_3$	87	94
2	$PhCH_2CH_2$	10	Et$_2$BS-*i*-Pr	93	97
3	*n*-C_6H_{13}	10	*i*-PrSSiMe$_3$	83	92
4	*n*-C_6H_{13}	10	Et$_2$BS-*i*-Pr	87	97
5	Ph	10	*i*-PrSSiMe$_3$	91	97
6	Ph	10	Et$_2$B-*i*-Pr	89	96

The same authors also proposed an approach involving the use of a Lewis acid, $B(OMe)_3$.[297]

In 2007, Walsh et al. developed a new catalyst for the asymmetric allylation of ketones readily prepared from titanium isopropoxide and BINOL (1:2 ratio) in the presence of 2-propanol. This catalyst functions under concentrated reaction conditions providing tertiary homoallylic alcohols with a high level of enantioselectivity (Table 38).[301]

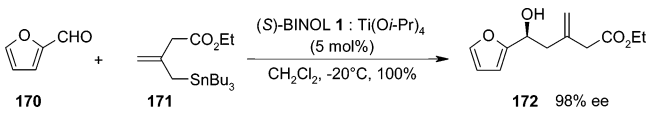
Table 38. Enantioselective Allylation of Ketones under Highly Concentrated Concentrations with a 1:2 Ti/(*R*)-BINOL Ratio



Entry	Ketone	Yield (%)	Ee (%)
1		93	95
2		99	88
3		80	91
4		99	87

Allylation with functionalized allyltin under BINOL−Ti catalysis is rare. Thomas reported the reactivity of a chiral silyloxy reactant,[302] and Keck, the use of allyltin derivatives with various aldehydes including furaldehyde, benzaldehyde, and benzyloxyethanal. All enantiomeric excesses were excellent (93−99%); the most spectacular was obtained with furaldehyde **170** with only 5 mol % catalyst (Scheme 66).[303]

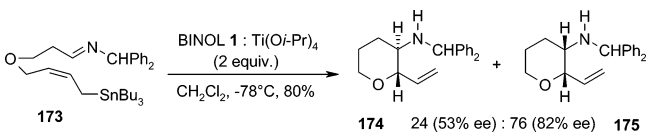
Scheme 66



Since these works, numerous studies have appeared in the literature increasing the performance of the catalyst by using numerous additives.[304−315]

Finally, the only example of cyclization promoted by a BINOL−Ti catalyst we are aware of was performed by Yamamoto on the following iminoallyltin reactant **173**. Unfortunately, the Ti complex had to be used in excess to achieve good enantioselectivity (Scheme 67).[316]

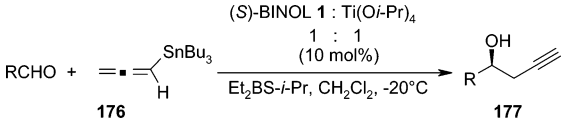
Scheme 67



4.3.3. Titanium-Catalyzed Allylation Using Propargyl and Allenyltin Reagents

The substitution of allyltin reagents by allenyl tri-*n*-butyltin **176** in an enantioselective transformation involving BINOL was proposed by Keck in 1994.[317] Good to excellent ee's (82−99%) were obtained on various aldehydes, but 50−100 mol % catalyst was necessary and reaction times were all >72 h. These drawbacks were overcomed by Yu, who applied his accelerator strategy to this problem. Indeed, by using R_nMSR' accelerators, the BINOL−Ti could be reduced to 10 mol % and reaction times to 10−20 h (Table 39).[295]

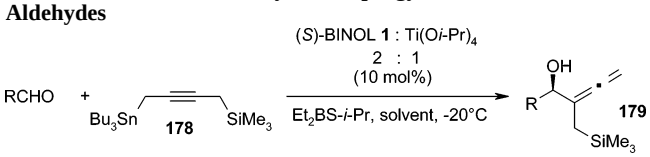
Table 39. "Accelerator" Influence on the Enantioselectivity in the Ti−BINOL-Catalyzed Allenyltin Addition to Aldehydes



entry	R	*t* (h)	yield (%)	ee (%)
1	$PhCH_2CH_2$	9	86	94
2	n-C_6H_{13}	9	75	92
3	Ph	15	52	92

The same approach proved also to be efficient when applied to propargyltin. Indeed, optically active allenyl alcohols were obtained in that way.[318,319] Finally, when 1,4-bis(tri-*n*-butyltin)but-2-yne or 1-trimethylsilyl-4-tri-*n*-butyltin-but-2-yne **178** was used, alcohols **179** were prepared in good yields and excellent enantiomeric excesses (Table 40).[312,320−323]

Table 40. Ti−BINOL-Catalyzed Propargyltin Addition to Aldehydes



entry	R	*t* (h)	solvent	yield (%)	ee (%)
1	n-C_6H_{13}	18	CH_2Cl_2	60	90
2	n-C_6H_{13}	18	$PhCF_3$	83	97
3	$PhCH_2CH_2$	18	CH_2Cl_2	62	92
4	$PhCH_2CH_2$	18	$PhCF_3$	78	97

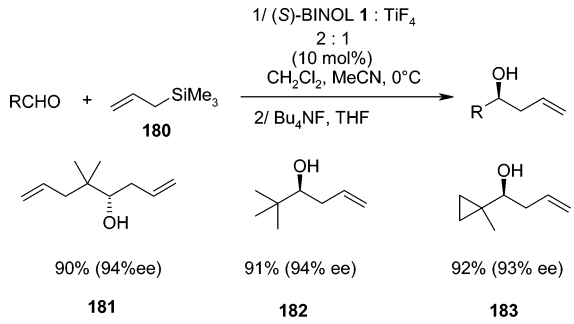
4.3.4. Other Allylmetal Reagents

Examples of enantioselective allylation using allyltrimethylsilane are scarce, since the addition of this reagent is 10^3−10^4 time slower than that of allyl tri-*n*-butyltin.[324] Therefore, the above-mentioned catalysts are not sufficiently Lewis acidic to promote the reaction with good results. For example, the use of (*S*)-BINOL−$TiBr_2$ only enabled the preparation of homoallylic alcohols with 40% yield and 30% ee. Carreira overcame the problem by using a catalyst prepared from enantiopure BINOL and TiF_4. Yields and ee increased to 90−94% on various aldehydes,[311,325] owing to the greater electronegativity of fluorine compared to chlorine or bromine and the strong Ti−F bond (E_{diss} = 140 kcal/mol), which prevents desilylation of the formed trimethylsilyl ethers to give trimethylsilylfluoride (Si−F bond: E_{diss} = 135 kcal/mol) (Scheme 68).

Majumdar explored the reactivity of various aldehydes in a Sn(II)-mediated Barbier-like reaction under BINOL−Ti-(O*i*-Pr)$_2$ catalysis. The ee's of the resulting homoallylic alcohols ranged from 18 to 63%.[326]

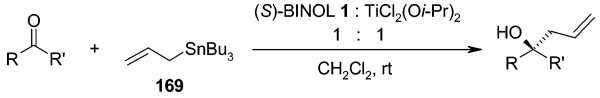
Finally, Tagliavini expanded the scope of the reaction to ketones by using tetraallyltin as allylating reactant in the

Scheme 68



presence of a BINOL−Ti(O*i*-Pr)$_2$ catalyst. Enantiomeric excesses are moderate to good with aromatic and α,*β*-unsaturated ketones but remain low with aliphatic ones (Table 41).[327]

Table 41. Catalyzed Allylation of Ketones Using the TiCl$_2$(O*i*-Pr)$_2$/BINOL System

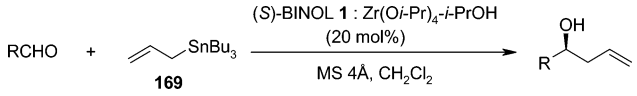


entry	R	R′	catal (%)	*t* (h)	yield (%)	ee (%)
1	Ph	Me	20	20	75	52
2	2-naphthyl	Me	40	4	94	80
3	(*E*)-PhCH=CH	Me	20	1	83	51
4	*n*-C$_6$H$_{13}$	Me	20	3	89	29

4.3.5. Zr Lewis Acids

Although the synthesis of homoallylic alcohols is very efficient with BINOL−Ti catalysts, reaction times are often very long when no activator is used. This observation led Bedeschi et al. to study a Lewis acid catalyst obtained from Zr(O*i*-Pr)$_4$−*i*-PrOH and BINOL. Results were very satisfying for aromatic aldehydes (good yields and ee, along with a dramatic reduction in reaction times) but not as good for aliphatic aldehydes (lower yields) (Table 42).[307,328]

Table 42. Catalyzed Allylation of Aldehydes Using the Zr(O*i*-Pr)$_4$/*i*-PrOH/BINOL System

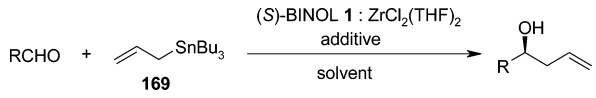


entry	R	*T* (°C)	*t* (h)	yield (%)	ee (%)
1	*n*-C$_7$H$_{15}$	0	6	58	87
2	*n*-C$_5$H$_{11}$	0	10	84	89
3	(*E*)-PhCH=CH	−20	3	81	91
4	Ph	−40	6	79	93

Although 4 Å MS are not necessary for the catalyst preparation, their inclusion is essential to achieve good enantioselectivity and in a reasonable time.[306] Later, the same authors showed that the reaction could also be performed with ee's up to 85−87% with a catalyst obtained from ZrCl$_4$ and BINOL. The introduction of 4-*tert*-butylcalix[4]arene allowed a diminution of the catalyst and an enhancement of the ee (Table 43).[329]

Finally, Mikami proposed to use a catalyst, prepared from BINOL and Zr(O*t*-Bu)$_4$, associated with a product-like activator, (*R*)-(+)-α-methyl-2-naphthalene-methanol. Although, the ee remained moderate (40−57%), the influence of the activator is clear.[330]

Table 43. Catalyzed Allylation of Aldehydes Using ZrCl$_2$(THF)$_2$/BINOL System

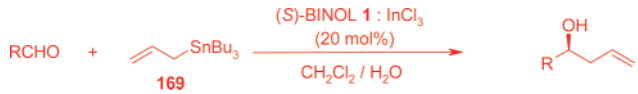


entry	R	BINOL:Zr	additive (%)	yield (%)	ee (%)
1[a]	*n*-C$_7$H$_{15}$	2:1	none	65	85
2[a]	Ph	2:1	none	40	87
3[b]	*n*-C$_7$H$_{15}$	1:1	calix[4]arene (5)	65	96
4[b]	Ph	1:1	calix[4]arene (5)	85	85

[a] Reaction performed using 10 mol % of catalyst in Et$_2$O. [b] Reaction performed using 5 mol % of catalyst in CH$_2$Cl$_2$.

In 2005, Loh et al. reported an efficient catalytic enantioselective allylation of aldehydes involving a moisture-tolerant chiral BINOL−indium complex. Thus, the allylation of a variety of aromatic α,*β*-unsaturated and aliphatic aldehydes resulted in both moderate to good yields and high enantioselectivities of up to 86% ee (Table 44).[331,332]

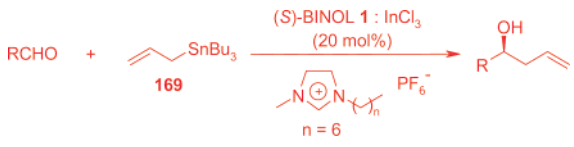
Table 44. Enantioselective Allylation of Various Aldehydes Catalyzed by the Chiral (*S*)-BINOL−In(III) Complex



entry	R	yield (%)	ee (%)
1	*n*-C$_8$H$_{17}$	75	78
2	Ph	53	83
3	2-naphthyl	47	78
4	BnO(CH$_2$)$_2$	46	86

Finally, this reaction has been performed in ionic liquid [hmim],[333] which has been demonstrated to be an efficient and enantiomerically friendly reaction medium for the enantioselective allylation of aldehydes via a chiral indium(III) complex. Thus, allylation of a variety of aromatic, α,*β*-unsaturated, and aliphatic aldehydes resulted in moderate to good yields and enantioselectivities of up to 92% ee (Table 45).[334]

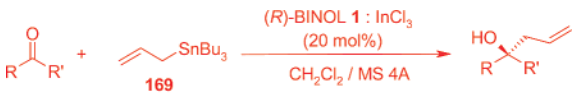
Table 45. Enantioselective Allylation of Various Aldehydes Catalyzed by the Chiral (*S*)-BINOL−In(III) Complex in [hmim][PF$_6^-$]



entry	R	yield (%)	ee (%)
1	*n*-C$_8$H$_{17}$	72	26
2	Ph	62	70
3	2-naphthyl	46	78
4	PhCH$_2$CH$_2$	40	74

Having optimized the reaction parameters for the allylation process, Loh et al. have extended the catalytic enantioselective addition of allyltrimethylstannane to a selection of ketones. In all cases, the homoallylic alcohols were obtained

Table 46. Enantioselective Allylation of Various Ketones Catalyzed by the Chiral (*R*)-BINOL−In(III) Complex

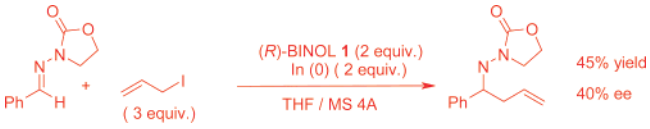


Entry	Ketone	Yield (%)	Ee (%)
1	Acetophenone	74	82
2	Benzalacetone	82	90
3	Naphthylmethylketone	80	84
4		61	90

in good enantioselectivities not only with aromatic but also with aliphatic and cyclic aromatic ketones (Table 46).[335]

Recently, an extension of such a reaction has been realized and applied to the enantioselective indium-mediated allylation of hydrazones, leading to moderate results using (*R*)-BINOL as ligand (Scheme 69).[336]

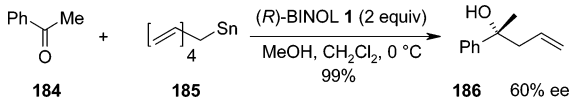
Scheme 69



4.3.6. Other Complexes

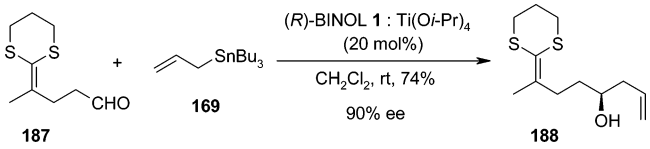
Baba showed that a tetraallyltin/(*R*)-BINOL system associated with methanol as an additive could lead, from acetophenone **184**, to the obtention of the corresponding homoallylic alcohol **186** with up to 60% ee (Scheme 70).[337]

Scheme 70

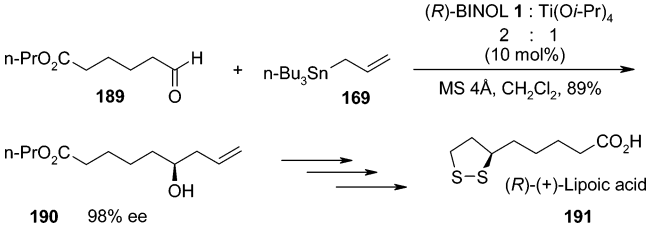


In 1996, Kocienski reported a synthesis of the C_1-C_{21} fragment of the immunosuppressant rapamycin, which involved an asymmetric allylation to introduce the first stereogenic center of the target molecule. The reaction was run on a 350 mmol scale and (*R*)-BINOL was recycled (Scheme 71).[338]

Scheme 71



Scheme 72

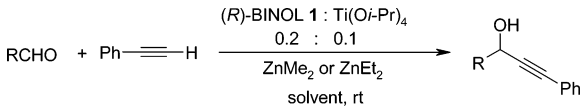


More recently, Zimmer achieved a formal synthesis of (*R*)-α-lipoic acid **191** and its (*S*)-antipode based on the asymmetric synthesis (98% ee) of both enantiomers of 6-hydroxy-8-nonene carboxylates under (*R*)- or (*S*)-BINOL−Ti(O*i*-Pr)$_2$ catalysis (Scheme 72).[339]

4.4. Alkynylation

Optically active propargylic alcohols are versatile precursors for the synthesis of many chiral organic compounds. Thus, the asymmetric addition of alkynylzinc to aldehydes is an iñportant method of synthesizing such compounds.[340−344] Nevertheless, a single and pratical method to make chiral propargylic alcohols from aromatic aldehydes has been developed in the presence of a titanium alkoxide catalyst prepared in situ from Ti(O*i*-Pr)$_4$ and (*R*)-BINOL **1**, leading to excellent enantioselectivity of up to 96% ee (Table 47).[321,345−348]

Table 47. Enantioselective Addition of Phenylacetylene to Aromatic Aldehydes Promoted by the BINOL−Ti Complex

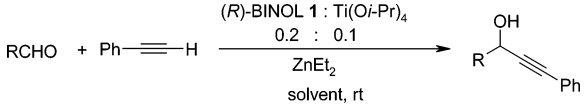


entry	R	yield (%)	ee (%)
1	Ph	77	96
2	*p*-F-Ph	74	96
3	*p*-NO_2-Ph	79	97
4	*p*-Cl-Ph	81	92
5	*p*-Me-Ph	93	97
6	*o*-Me-Ph	81	96
7	*m*-Me-Ph	77	94
8	*p*-MeO-Ph	97	94

It is noteworthy that activation of chiral titanium(IV) complexes with chiral or achiral activators has been found to provide higher levels of enantioselectivities than those attained with an enantiopure catalyst.

Since these pioneering studies, Pu et al. have extended the scope of this reaction, demonstrating that the BINOL−Ti(O*i*-Pr)$_4$ catalyst system is also highly enantioselective for the phenylacetylene addition to aliphatic aldehydes as well as α,*β*-unsaturated aldehydes (Table 48).[349,350]

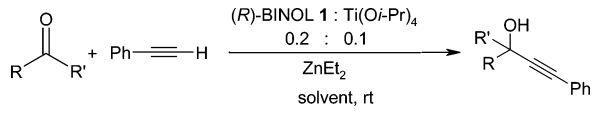
Table 48. Enantioselective Addition of Phenylacetylene to Aliphatic and α,*β*-Unsaturated Aldehydes Promoted by the BINOL−Ti Complex



entry	aldehyde	yield (%)	ee (%)
1	Me-$(CH_2)_7$-CHO	96	91
2	Me-$(CH_2)_6$-CHO	70	93
3	Me-$(CH_2)_3$-CHO	91	93
4	Me-CH_2-CHO	60	94
5	Ph-CH_2-CHO	93	91
6	allyl-CHO	92	96
7	cinnamaldehyde	89	97

Recently, this reaction was successfully applied to the phenylacetylene additions to ketones. In this case, most of the chiral tertiary propargyl alcohols that were generated from aromatic ketones were obtained with 85−92% ee at room temperature (Table 49).[351]

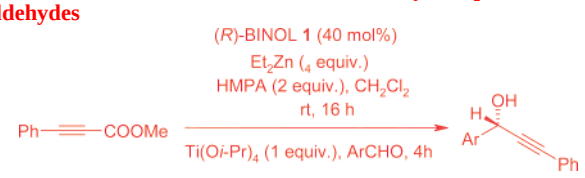
Table 49. Enantioselective Addition of Phenylacetylene to Ketones Promoted by the BINOL−Ti Complex



entry	ketone	yield (%)	ee (%)
1	acetophenone	67	85
2	3′-methoxyacetophenone	81	92
3	3′-methylacetophenone	66	90
4	3′-bromoacetophenone	68	86
5	1′-naphthacetophenone	71	91
6	4-methyl-2-pentanone	91	63
7	benzalacetone	88	73

As an extension of these studies, Pu et al. discovered the first highly enantioselective reaction of an alkynoate with aromatic and α,β-unsaturated aldehydes for the synthesis of optically active γ-hydroxy-α,β-acetylenic esters in enantiomeric excesses of up to 95% ee in numerous cases (Table 50).[352,353]

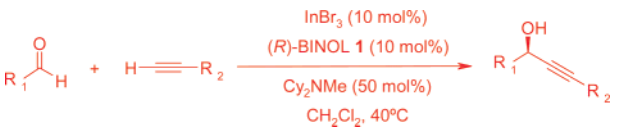
Table 50. Enantioselective Addition of Methyl Propiolate to Aldehydes



entry	ArCHO	yield (%)	ee (%)
1	benzaldehyde	69	91
2	2-methylbenzaldehyde	96	91
3	2-methoxybenzaldehyde	91	90
4	4-bromobenzaldehyde	82	93
5	1-naphthylbenzaldehyde	87	95

In 2005, Shibasaki et al. developed a new catalytic asymmetric alkynylation of aldehydes promoted by In(III)/BINOL complex and Cy_2NMe. Dual activation of both substrates due to the bifunctional character of In(III) would make possible a broad range of substrate generality with high enantioselectivity (Table 51).[354]

Table 51. In(III)−BINOL Complex-Catalyzed Asymmetric Alkynylation of Various Aldehydes



entry	R_1	R_2	yield (%)	ee (%)
1	Ph	Ph	84	95
2	cyclohexyl	Ph	95	98
3	cyclohexyl	$PhCH_2CH_2$	77	99
4	3-furyl	Ph	84	98

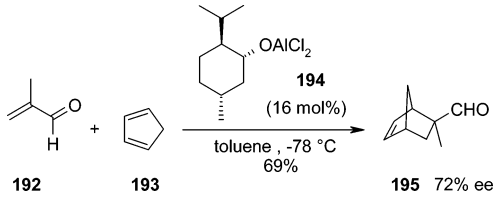
4.5. Diels–Alder Reaction

4.5.1. Titanium-Catalyzed Diels–Alder Reaction

Since the landmark publication of Yates and Eaton,[355] on the Lewis acid-catalyzed Diels−Alder reaction,[356] the use of these catalysts has became very popular. Indeed, they both accelerate the reaction and enhance its selectivity. As one of the consequences of this success, a number of reviews are devoted to this area of research.[357−361]

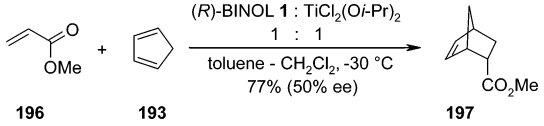
The use of chiral Lewis acids to induce enantioselectivity is only 25 years old. The first report by Guseinov[362] in 1976 cited a poor enantiomeric excess, but three years later, Koga obtained bicyclic derivatives with up to 72% ee when using chiral alkoxyaluminum dichlorides **194** as Lewis acids (Scheme 73).[363]

Scheme 73



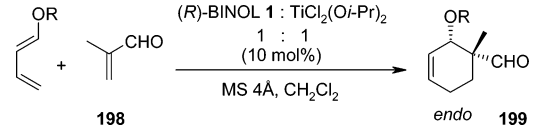
As for the use of BINOL as chiral ligand, early studies are due to Seebach[364] and Reetz,[236] who both used BINOL−Ti complexes, BINOL−Ti(O*i*-Pr)$_2$ and BINOL−$TiCl_2$, respectively. The most encouraging results were obtained with the latter (Scheme 74).

Scheme 74



Mikami and Nakai extended their studies on catalysts such as BINOL−TiX_2 (X = Cl, Br), which were prepared in situ from Ti(O*i*-Pr)$_2$X$_2$, (*R*)-BINOL, and 4 Å molecular sieves, to the Diels−Alder cycloaddition of 1,3-dienol derivatives added to methacrolein.[219,365] The *endo*/*exo* ratios were very high, and enantiomeric excesses were in the 71−86% range. A few years later, Mikami reported that endo- and enantioselectivity could be enhanced by using a MS-free BINOL−Ti catalyst (i.e. the catalyst is prepared in the presence of molecular sieves which are then removed by centrifugation).[366] The same catalyst also exhibits a significant positive nonlinear effect (NLE) (Table 52).

Table 52. Influence of the Catalyst Preparation on the Diels−Alder Cycloaddition of 1,3-Dienol Derivatives with Methacrolein



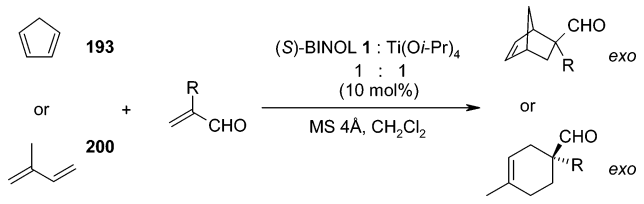
entry	R	MS 4 Å	*T* (°C)	yield (%)	*endo* (%)	ee (%)
1	Me	yes	−30	43	87	71
2	Me	removed	−30	40	93	85
3	COMe	yes	rt	69	97	78
4	COMe	removed	rt	63	99	94

Mikami also showed that the use of 6,6′-Br_2-BINOL−$TiCl_2$ leads to improvement of endo- and enantioselectivity with respect to the parent BINOL complex when methacrolein was involved but not when 2-bromoacrolein was used.[367]

Finally, Keck studied the selectivity of the reaction between cyclopentadiene **193** or isoprene **200** and methac-

rolein or 2-bromoacrolein in the presence of (*S*)-BINOL−Ti(O*i*-Pr)$_2$ [prepared from (*S*)-BINOL, Ti(O*i*-Pr)$_4$, and 4 Å MS]. Exo selectivity ranged from 10:1 to 17:1, and enantiomeric excesses were up to 94% in the case of cyclopentadiene **193** and 2-bromoacrolein (Table 53).[368]

Table 53. Selectivity of the Diels−Alder Reaction Catalyzed by the Ti(O*i*-Pr)$_4$/BINOL/MS 4 Å System

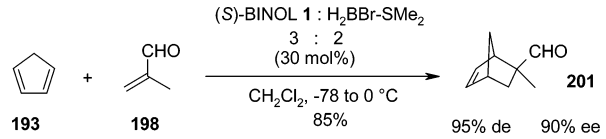


entry	diene	R	*T* (°C)	yield (%)	*exo*/*endo*	ee (%)
1	**193**	Br	−78	94	17/1	94
2	**200**	Br	−20	75	10/1	80
3	**193**	Me	−20	75	10/1	58

4.5.2. B– and Al–BINOL Complexes

In 1990, Kaufmann reported the synthesis and X-ray structure of a C_3-symmetric tetradecacyclic diborate complex (propeller complex) which efficiently catalyzed the reaction between cyclopentadiene **193** and methacrolein **198**. The catalyst is obtained from (*S*)-BINOL (3 equiv) and bromoborane−dimethyl sulfide complex (2 equiv) (Scheme 75).[369,370]

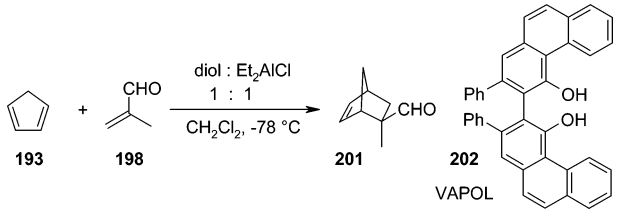
Scheme 75



The same reaction was studied by Wulff with similar catalysts obtained from vaulted biaryls[371] and by Oh with catalysts prepared from 1,8-naphthalenediyl bis(dichloroborane), a bidentate Lewis acid,[372] and various chiral ligands including BINOL.

Wulff also worked on the influence of catalysts obtained from diethylaluminum chloride and BINOL (or various vaulted biaryls).[373] Although good to excellent *exo* selectivities were obtained in all cases, enantiomeric excesses were only modest with BINOL (13−41%) compared to the ones reached with a vaulted biphenanthrol (VAPOL) **112**, 88−98% (Table 54).

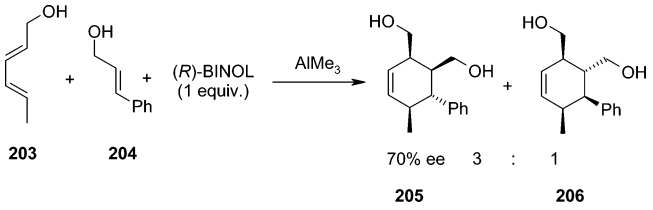
Table 54. Selectivity of the Diels−Alder Reaction Catalyzed by the Et$_2$AlCl/Diol System



entry	diol	catal (mol %)	yield (%)	*exo*/*endo*	ee (%)
1	(*S*)-BINOL	10	99	97/3	23
2	(*S*)-VAPOL	10	100	98/2	98
3	(*S*)-VAPOL	0.5	98	97/3	88

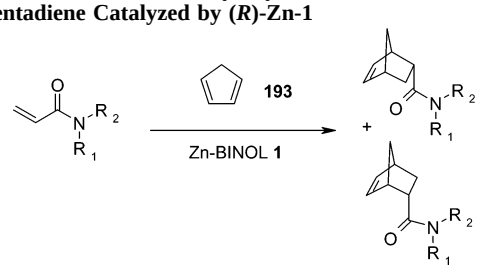
Recently, as part of a study directed toward the Diels−Alder reaction between "noncompatible" dienes and dienophiles by means of a temporary Al or Zr tethering, Olsson reported an interesting result.[374] Noteworthy is the fact that (−)-menthol and (−)-8-phenylmenthol did not lead to any enantiomeric excess (Scheme 76).

Scheme 76



Dialkylzinc represents an attractive alternative to trialkylaluminum for preparation of mild Lewis acids.[375] The Lewis acid obtained from dimethylzinc and BINOL **1** was investigated for the Diels−Alder reaction of *N*-alkylacrylamides providing good results in terms of enantioselectivity (Table 55).

Table 55. Reaction of *N*-Alkoxyacrylamides with Cyclopentadiene Catalyzed by (*R*)-Zn-1



entry	R_1	R_2	*endo*:*exo*	*endo* ee (%)
1	Me	OMe	7:1	89
2	*tert*-Bu	OMe	nd	60
3	Ph	OMe	54:1	96
4	Ph	OMe	41:1	90
5	Ph	OEt	29:1	86
6	Ph	O*i*-Pr	14:1	76

Thus, the superiority of the Zn−BINOL experimental procedure makes it very attractive from a synthetic point of view.[376,377]

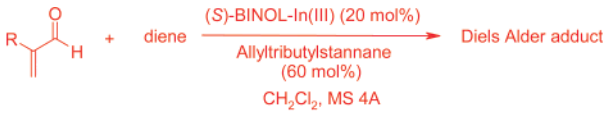
Loh et al. developed in 2005 the first chiral indium complex for catalytic asymmetric Diels−Alder reaction by designing a novel catalyst containing $InCl_3$, (*S*)-BINOL, and allyltributylstannane. The cycloaddition of a variety of cyclic and open-chained dienes to 2-methacrolein and 2-bromoacrolein resulted in good yields and excellent enantioselectivities (up to 98% ee) (Table 56).[378]

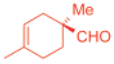
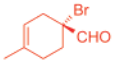
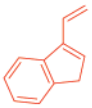
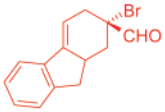
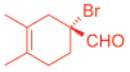
On the other hand, Ward et al. demonstrated the first examples of Diels−Alder reactions where the regio-, diastereo-, and enantioselectivity are controlled by simultaneous coordination of the components to a novel binuclear Lewis acid template (Scheme 77).[379,380]

4.5.3. BINOL–Lanthanide Complexes

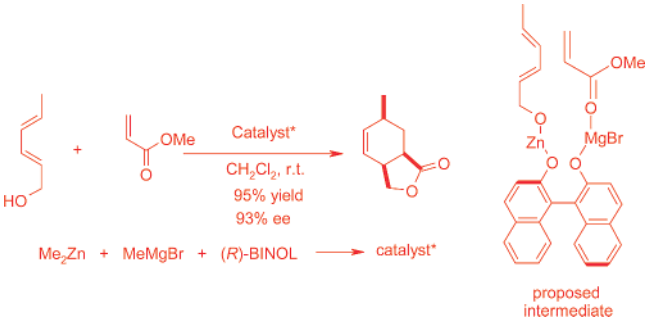
As part of his systematic study of lanthanide triflates as Lewis acids, Kobayashi published in 1993−94 a series of papers describing the enantioselectivity induced by BINOL−ytterbium[381] (or −scandium[382]) triflates in the reaction between cyclopentadiene and various acyl-1,3-oxazolidin-2-ones. Both catalysts were prepared by mixing the metal

Table 56. Diels−Alder Reaction of Open-Chained 1,3-Dienes



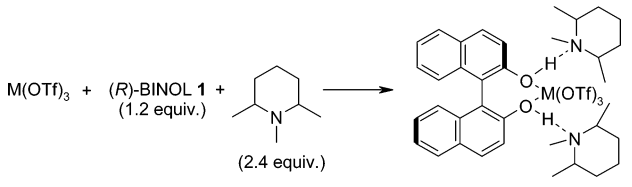
Entry	Diene	Product	Yield (%)	Ee (%)
1			47	90
2			70	96
3			72	98
4			74	98

Scheme 77



triflate with BINOL in the presence of 4 Å molecular sieves and then adding 2.4 equiv of a tertiary amine. The proposed structure, based on ^{13}C NMR and IR data, involves a Lewis acid−Lewis base interaction between the metal and the oxygen and hydrogen bonds between the nitrogen of the tertiary amine and the proton of the hydroxy functions (Scheme 78).[383]

Scheme 78

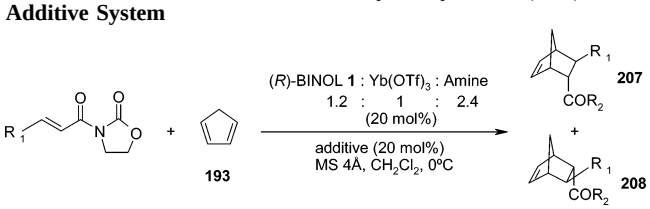


Different groups also showed that both enantiomers of the cycloadduct could be obtained by using the same enantiomer of BINOL and only changing an achiral ligand (3-phenylacetylacetone, PAA) (Table 57).[384−386]

This result was accounted for in the following way by the authors: in the absence of PAA, the dienophile approaches on site A, while when PAA is present, it preferentially binds to site A, forcing the dienophile to approach on site B (Scheme 79).

Marko then used the same catalysts in an inverse electron demand Diels−Alder reaction between vinyl ethers or vinyl sulfides and 3-carbomethoxy-2-pyrone. The enantiomeric excess reached 85% with vinyl ethers and 95% with vinyl sulfides (Table 58).[387,388]

Table 57. Diels−Alder Reaction Catalyzed by the Yb(OTf)$_3$/1/ Additive System



entry	additive	R_2	yield (%)	*endo*/*exo*	**207**/**208**	ee (%)
1	none	Me	77	89/11	97.5/2.5	95
2	PAA	Me	83	93/7	9.5/90.5	81
3	none	*n*-Pr	81	80/20	91.5/8.5	83
4	PAA	*n*-Pr	81	91/9	10/90	80

Scheme 79

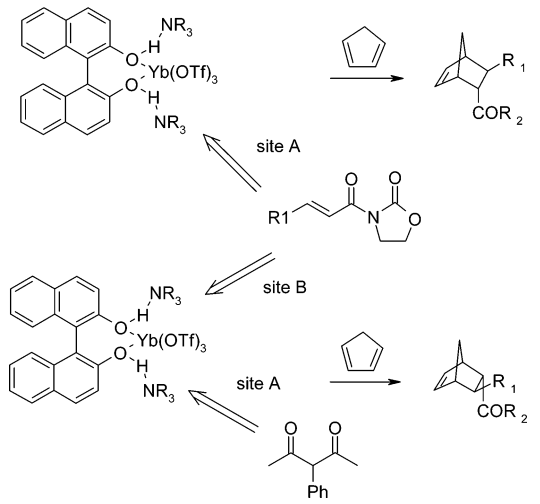
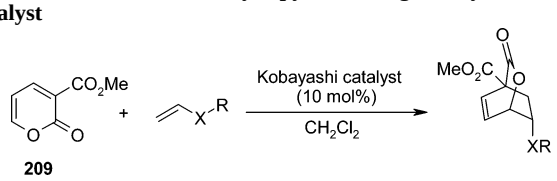


Table 58. Diels−Alder Reaction between Vinyl Ethers or Vinyl Sulfides and 3-Carbomethoxy-2-pyrone Using Kobayashi Catalyst



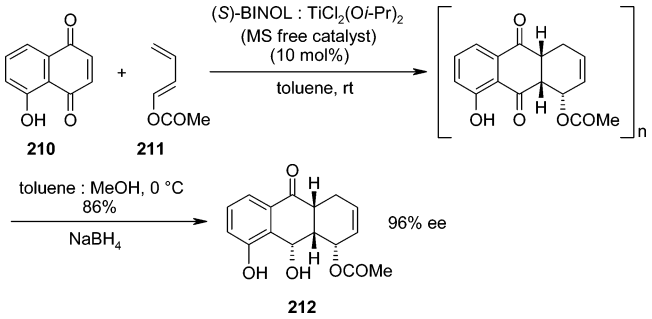
entry	X	R	yield (%)	ee (%)
1	O	Et	90	27
2	O	cyclohexyl	91	82
3	O	adamantyl	97	85
4	S	Et	96	30
5	S	cyclohexyl	88	86
6	S	Ph	91	>95

Mikami reported the reaction of juglone with butadienyl acetate using a MS-free BINOL−Ti catalyst. The use of the MS-free catalyst was crucial since, with the classical one, the enantiomeric excess dropped to 9%. The obtention of the cycloadduct provided an efficient entry to the asymmetric synthesis of anthracycline and tetracycline antibiotics (Scheme 80).[389]

Posner applied the inverse electron demand approach to the synthesis of the A-ring of vitamin D derivatives (Scheme 81).[390,391]

As an extension of this methodology, Corey et al. have found that achiral 1,4-quinone monoketals function well as dienophiles in enantioselective Diels−Alder reactions cata-

Scheme 80



Scheme 81

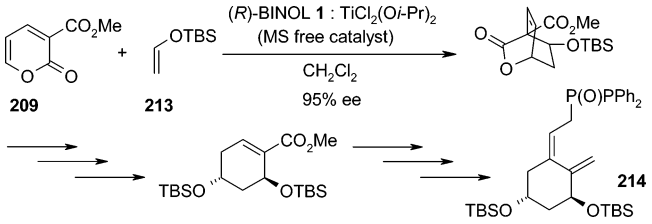
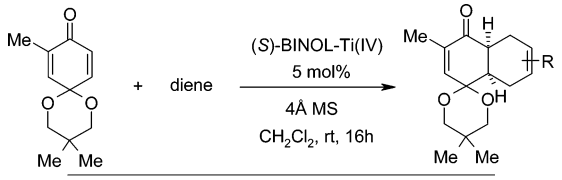
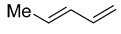
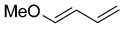


Table 59. Enantioselective Diels−Alder Reactions of Quinone Monoketal 215 with Various Dienes Catalyzed by (*S*)-BINOL−Ti(IV)−MS 4 Å



Entry	Diene	Yield (%)	Ee (%)
1		90	99
2		90	99
3		95	95
4		95	90
5		91	96

lyzed by a chiral Ti(IV) Lewis acid. The results are excellent, as shown in Table 59.

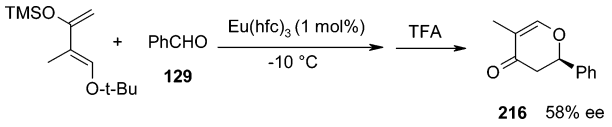
Nevertheless, although the Mikami catalyst system is very useful in this connection, there is a need for the development of more clearly defined, more structurally homogeneous, and more efficacious catalysts.[392]

4.6. Hetero-Diels–Alder Reaction

4.6.1. Introduction

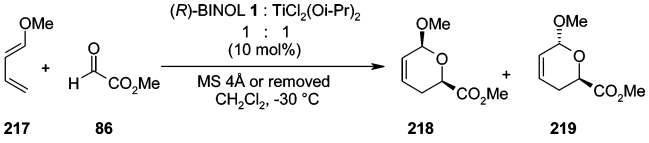
Although less studied than the all-carbon version of the reaction, the hetero-Diels−Alder reaction has attracted over the past decades more attention. It provides a versatile regio- and stereoselective approach toward heterocyclic compounds from heterodienes[393] or heterodienophiles.[394] The use of Lewis acid catalysis in these reactions is overwhelmingly associated with heterodienophiles, with the most known example being the cyclocondensation developed by Danishefsky between activated dienes and aldehydes.[395,396] The first successful use of a chiral Lewis acid is precisely due to Danishefsky, who obtained a very promising result with catalytic amounts of chiral shift reagent (Scheme 82).[397]

Scheme 82



As for BINOL, the first example of its use in such a reaction was reported by Nakai and Mikami in 1991. They prepared dihydropyran dicarboxylates with high enantiomeric excess from methoxy butadiene and methyl glyoxylate in the presence of a (*R*)-BINOL−$TiCl_2$ catalyst.[219] A few years later, Mikami showed that, as in the case of the all-carbon version of the reaction, the use of molecular sieve-free catalyst improves the endo- and enantioselectivity of the reaction between glyoxylates and methoxydienes (Table 60).[366]

Table 60. Hetero-Diels−Alder Reaction Catalyzed by the $TiCl_2$(O*i*-Pr)$_2$/BINOL System

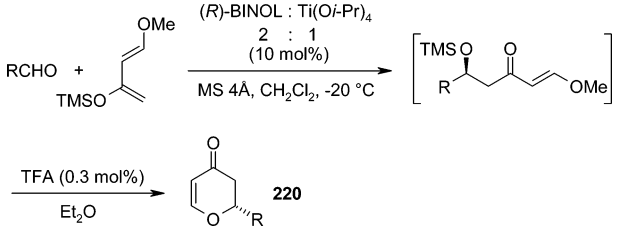


entry	MS 4 Å	yield (%)	**218** (ee)	**219** (ee)
1	yes	77	78 (94)	22 (>90)
2	removed	78	88 (96)	12 (>90)

Similarly, the use of 6,6′-Br_2-BINOL−Ti catalyst also enhanced the selectivities of the reaction.[367]

Attempts were also made with Danishefsky's diene and various aldehydes with catalysts prepared from BINOL and Ti(O*i*-Pr)$_4$. Thus, Keck showed that enantiomeric excesses up to 97% could be obtained provided the catalyst was prepared using a 2:1 BINOL/Ti(O*i*-Pr)$_4$ stoichiometry in the presence of 4 Å molecular sieves and 0.003 equiv of trifluoroacetic acid (TFA). TFA is necessary to induce the cyclization step, since the chiral Lewis acid only induces the formation of the Mukaiyama aldol product **220** (Table 61).[248,398,399]

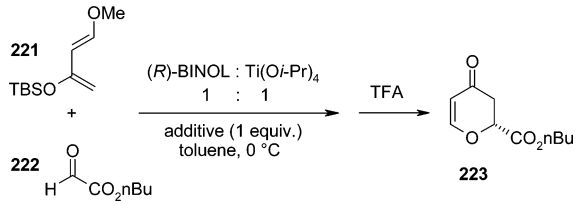
Table 61. Hetero-Diels−Alder Reaction Catalyzed by the Ti(O*i*-Pr)$_4$/1/MS 4 Å System



entry	R	yield (%)	ee (%)
1	Ph	40	55
2	$BnOCH_2$	60	97
3	furyl	61	97
4	*n*-C_8H_{17}	88	97

Mikami then showed that the addition of chiral activators, including BINOL itself, could enhance the level of enantioselectivity promoted by a 1:1 BINOL/Ti(O*i*-Pr)$_4$ catalyst between Danishefsky's dienes and butylglyoxylate (Table 62).[400]

Table 62. Influence of the Additive in the Hetero-Diels−Alder Reaction Catalyzed by the Ti(O*i*-Pr)$_4$/1 System

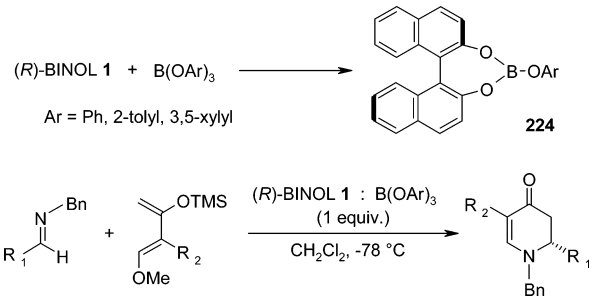


entry	additive	yield (%)	ee (%)
1	none	40	5
2	(*R*)-BINOL	50	84
3	(*R*)-5-Cl-BIPOL	53	26
4	(*R*)-6-Br-BINOL	25	43

4.6.2. BINOL−B and −Al Complexes

To the best of our knowledge, boron Lewis acids have been widely dedicated to the aza-Diels−Alder reaction. Yamamoto reported in 1992 the preparation of chiral Lewis acids from (*R*)-BINOL and triarylborates, B(OAr)$_3$.[401] Enantiomeric excesses, up to 90%, were obtained for the aza-Diels−Alder cycloaddition between Danishefsky's dienes and aldimines (Table 63).[402]

Table 63. Aza-Diels−Alder Reaction Catalyzed by the B(OAr)$_3$/1 System



entry	R_1	R_2	Ar	yield (%)	ee (%)
1	Ph	H	Ph	75	82
2	Ph	H	2-tolyl	76	84
3	Ph	H	3,5-xylyl	75	86
4	Ph	Me	Ph	72	81
5	3-Pyr	H	Ph	71	90

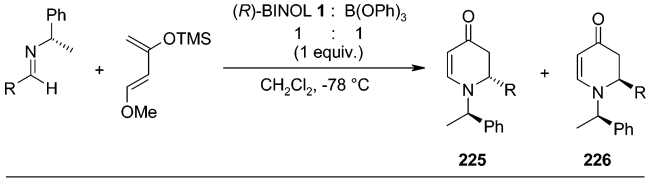
In further publications, the same authors also studied the double asymmetric induction (chiral Lewis acid and chiral aldimines) of the reaction. The approach was successful for both aliphatic and aromatic aldimines, and diastereomeric excesses up to 98% were reached (Table 64).[403,404]

Finally, Yamamoto also showed that, provided a 2:1 mixture of BINOL and trialkylborate was used, a Bronsted acid-assisted chiral Lewis acid (BLA) **227** could be obtained (Scheme 83).[405−408]

This BLA was likewise efficient for the double asymmetric induction of the aza-Diels−Alder reaction of a chiral aldimine and Danishefsky's diene (up to 99% de). It is worth noting that, in all these aza-Diels−Alder reactions, the boron Lewis acid was used in stoichiometric quantities.

A BINOL−AlMe catalyst, obtained from (*S*)-BINOL and AlMe$_3$, has been used by Jorgensen to promote preferentially the hetero-Diels−Alder cycloadduct (vs the ene adduct) in the reaction between conjugated dienes having allylic C−H bonds, such as isoprene, and glyoxylate esters (Table 65).[409]

Table 64. Aza-Diels−Alder Reaction Catalyzed by the B(OPh)$_3$/1 System



entry	R	yield (%)	**225**/**226**
1	Ph	61	99/1
2	3-pyridyl	63	99/1
3	cyclohexyl	31	99/1
4	*n*-propyl	49	95/5

Scheme 83

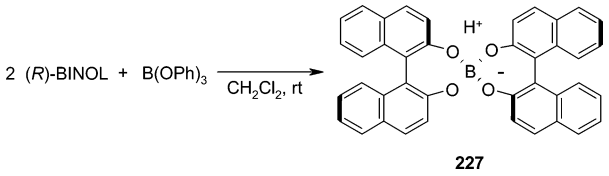
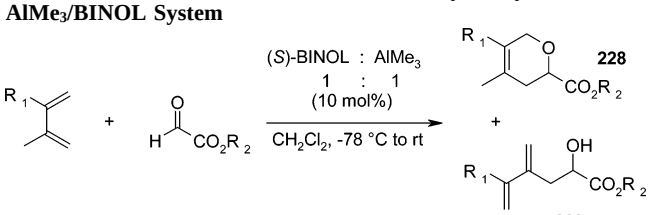


Table 65. Hetero-Diels−Alder Reaction Catalyzed by the AlMe$_3$/BINOL System



			228		**229**	
entry	R_1	R_2	yield (%)	ee (%)	yield (%)	ee (%)
1	Me	Me	37	94	12	56
2	H	Me	13	70	3	27
3	Me	Et	73	97	9	88
4	H	Et	29	97	14	88

4.6.3. BINOL−Ln Complexes

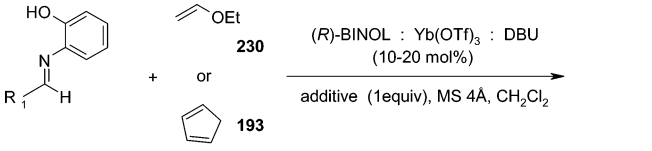
A significant improvement in the asymmetric aza-Diels−Alder reaction was made with the introduction of chiral lanthanide Lewis acids. Kobayashi reported the first examples of such reactions promoted with substoichiometric quantities of Lewis acid.[410] It must also be noted that the reaction involves an azadiene and not, as in all other cases reported so far, an azadienophile. The chiral catalyst is prepared from Yb(OTf)$_3$, (*R*)-BINOL, and DBU and is used in 10−20 mol % in the presence of 1 equiv of an additive (Table 66).

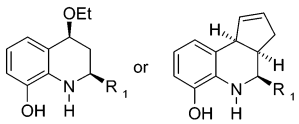
Yb(OTf)$_3$, associated with (*R*)-BINOL and 2,6-lutidine, was also used in 10 mol % to promote the cycloaddition between Danishefsky's diene and aldimines. However, the best enantiomeric excess with this combination (41%) exceeded the ones obtained with Cu- and Mg-centered Lewis acids associated with chiral diamines.[411]

Mikami and Nakai applied their methodology to the synthesis of the lactone portion of mevinolin **233** (Scheme 84).[219,412]

Piperidine alkaloids (−)-anabasine **234** and (+)-coniine were synthesized by Yamamoto as an application of the aza-

Table 66. Aza-Diels−Alder Reaction Catalyzed by the Yb(OTf)$_3$/1/DBU System



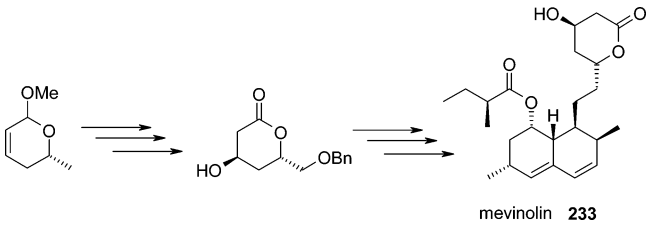


DPP : 2,6-diphenylpyridine
DTBP : 2,6-di-*tert*-butylpyridine
DTBMP : 2,6-di-*tert*-butyl-4-methylpyridine

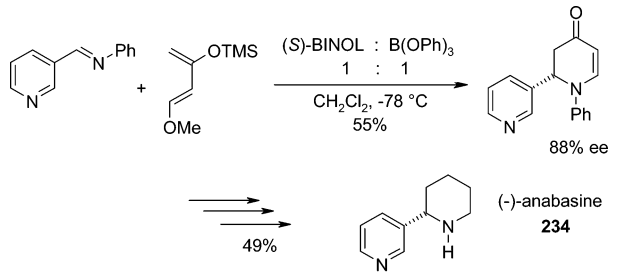
231 232

entry	R_1	alkene	additive	yield (%)	cis/trans	ee (%)
1	Ph	230	DTBP	52	94/6	77
2	α-naphthyl	230	DPP	65	99/1	91
3	α-naphthyl	230	DTBMP	74	>99/1	91
4	α-naphthyl	193	DTBMP	69	>99/1	68
5	cyclohexyl	193	DTBMP	58	>99/1	73

Scheme 84



Scheme 85



Scheme 85

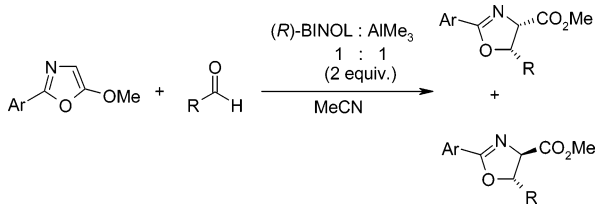
Diels−Alder reaction promoted by the BINOL−B(OPh) catalyst (Scheme 85).[267]

4.7. Miscellaneous

4.7.1. [3+2] Cycloadditions and 1,3-Dipolar Cycloadditions

4.7.1.1. [3+2] Cycloadditions. Racemic BINOL, associated with aluminum, was first used in 1991 by Suga to catalyze the [3+2] cycloaddition between 2-aryl-5-methoxyoxazoles and aldehydes.[414,415] 2-Oxazoline-4-carboxylates, which are useful building blocks, were obtained with high *cis*-selectivity. Only recently did the same authors report results obtained with a chiral catalyst which was prepared in situ from (*R*)- or (*S*)-BINOL and Me_3Al in hexane: four different oxazoles were involved with various substituted benzaldehydes. The resulting *cis*-2-oxazoline-4-carboxylates were obtained with up to 90% ee.[416,417] It is, however, worth noting that the catalyst is used in excess (2 equiv) in most examples (Table 67).

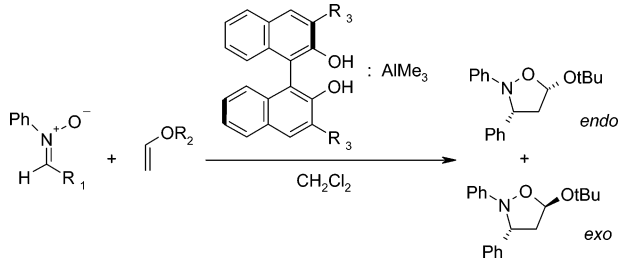
Table 67. [3+2] Cycloaddition between 2-Aryl-5-methoxyoxazoles and Aldehydes Catalyzed by the AlMe$_3$/1 System



entry	Ar	R	*T* (°C)	yield (%)	cis/trans	*cis* ee (%)
1	*p*-MeOPh	Ph (1 equiv)	20	40	60/40	90
2	*p*-MeOPh	Ph (3 equiv)	−10	81	92/8	88
3	*p*-MeOPh	*p*-NO_2Ph (3 equiv)	−10	81	82/18	73
4	*p*-MeOPh	*p*-ClPh (3 equiv)	−10	93	87/13	51
5	*o*-MeOPh	*p*-ClPh (3 equiv)	5	89	87/13	87
6	*o*-MeOPh	*m*-MePh	5	51	88/12	88
7	*o*-MeOPh	*m*-MeOPh	5	70	87/13	90

4.7.1.2. 1,3-Dipolar Cycloadditions. Among this class of reactions, the 1,3-dipolar cycloaddition between nitrones and alkenes leading to isoxazolidine derivatives is of particular interest. Indeed, these molecules can be converted to 1,3-amino alcohol equivalents under mild conditions. The first attempt to prepare optically active isoxazolidines by means of a chiral catalyst is due to Jorgensen in 1994, who studied the reaction between nitrones and 3-crotyloxazolidinone in the presence of catalytic amounts of various chiral titanium catalysts generated in situ from $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ and chiral diols.[418,419] Up to 62% ee was obtained with TADDOL, but results with BINOL were disappointing (8% ee). More recently, the same authors studied the formation of isoxazolidines through an inverse electron demand 1,3-dipolar cycloaddition between aromatic nitrones and vinyl ethers under catalysis of different BINOLs−AlMe complexes. Although the ee remained very low (<5%) with parent BINOL, up to 97% was obtained with 3,3′-bisphenyl-BINOL (Table 68).[420]

Table 68. 1,3-Dipolar Cycloaddition between Nitrones and Alkenes Catalyzed by the AlMe$_3$/1 System



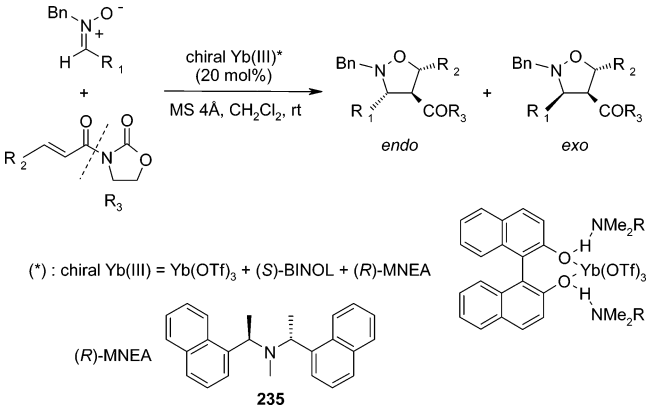
entry	R_1	R_2	R_3	catal (mol %)	yield (%)	*endo*/*exo*	*endo* ee (%)
1	Ph	*tert*-Bu	H	20	90[a]	27/73	<5
2	Ph	*tert*-Bu	Ph	20	95[a]	95/5	89
3	*p*-ClPh	*tert*-Bu	Ph	10	74	83/17	78
4	*p*-ClPh	Et	Ph	10	66	95/5	97

[a] Conversion.

Isoxazolidines can also be prepared diastereo- and enantioselectively in the presence of chiral lanthanide catalysts. Indeed, Kobayashi, as part of his exploration of the potentialities of lanthanide triflates as Lewis acids, discovered a

heterochiral catalyst that combines the chirality of BINOL and of an amine, (*R*)-methyl-bis[1-(1-naphthyl)ethyl]amine ((*R*)-MNEA) **235**, and leads to an excellent *endo*/*exo* ratio and up to 96% ee (Table 69).[422,423]

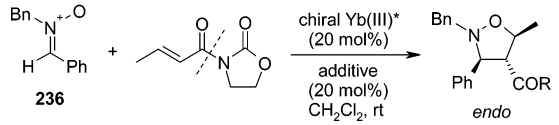
Table 69. Preparation of Isoxazolidines Using Yb(OTf)$_3$/1/MNEA Catalyst



entry	R_1	R_2	yield (%)	*endo*/*exo*	*endo* ee (%)
1	Ph	Me	92	99/1	96
2	*p*-ClPh	Me	93	99/1	92
3	2-furyl	Me	89	95/5	89
4	Ph	H	91	>99/1	79
5	Et	Me	88	53/47	96

Later, the same authors reported that molecular sieves 4 Å (MS 4 Å) were essential to secure high enantioselectivity.[424] Suprisingly, the absence of MS led to an inversion of enantioselectivity, which was not the case for the Diels−Alder reaction. In the absence of MS, additives such as NMO, pyridine oxide, or even the starting nitrone **236** helped to reach ee's of around 65−83% (Table 70).

Table 70. Influence of the Additives in the Preparation of Isoxazolidines Using Yb(OTf)$_3$/1/MNEA Catalyst

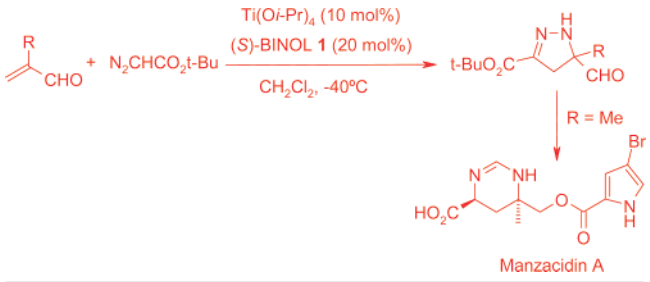


entry	additive	yield (%)	*endo*/*exo*	*endo* ee (%)
1	none	83	98/2	50
2	NMO	68	98/2	81
3	pyridine oxide	78	99/1	65
4	nitrone **236**	90	99/1	83

In 2006, Maruoka et al. developed an enantioselective 1,3-dipolar cycloaddition reaction between diazoacetates and α-substituted acroleins which gives 2-pyrazolines with an asymmetric tetrasubstituted carbon center. This methodology was successfully applied to the short synthesis of manzacidin A (Table 71).[425]

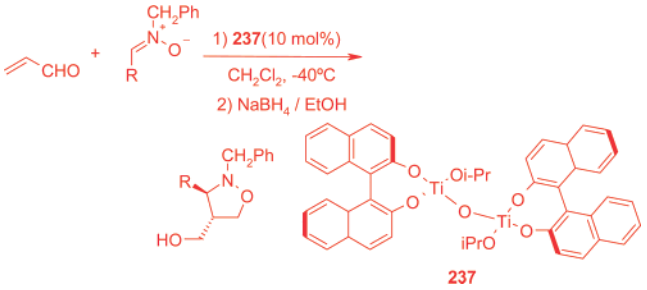
As an extension of this reaction, the same authors have investigated an asymmetric 1,3-dipolar cycloaddition reaction between various nitrones and acrolein catalyzed by the μ-oxo-type chiral bis-Ti(IV) oxide (*S*,*S*)-**1** which gave rise to the corresponding isoxazolidines with high to excellent enantioselectivities (Table 72).[426]

Table 71. Enantioselective 1,3-Dipolar Cycloaddition between *tert*-Butyl Diazoacetate and α-Substituted Acroleins



entry	R	yield (%)	ee (%)
1	Me	84	95
2	Et	95	98
3	cyclohexyl	77	99
4	*i*-Pr	84	98

Table 72. Asymmetric 1,3-Dipolar Cycloaddition between Nitrones and Acrolein

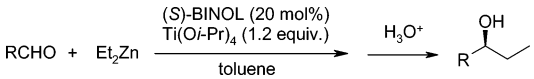


entry	R	yield (%)	ee (%)
1	Ph	94	93
2	4-ClPh	85	88
3	cyclohexyl	62	70
4	2-naphthyl	92	93

4.7.2. Addition of Dialkylzinc and Trialkylaluminum to Aldehydes and Ketones

Nakai[427] and Chan[428] independently reported in 1997 the asymmetric alkylation of aldehydes with diethylzinc catalyzed by BINOL−Ti complexes (obtained from (*S*)-BINOL and Ti(O*i*-Pr)$_4$). Nakai used a large excess of Ti(O*i*-Pr)$_4$ (vs BINOL) and 3 equiv of Et_2Zn; thus, the typical proportions were RCHO/Et_2Zn/BINOL/Ti(O*i*-Pr)$_4$ = 1:3:0.2:1.2 (Table 5) (Table 73). It is noteworthy that structures of binolate titanium complexes as well as mechanistic studies of the asymmetric addition of alkyl groups to aldehydes have been reported by Walsh et al.[429−431]

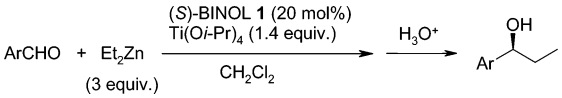
Table 73. Addition of Diethylzinc to Aldehydes Catalyzed by the Ti(O*i*-Pr)$_4$/1 System



entry	R	*T* (°C)	yield (%)	ee (%)
1	*n*-C_8H_{17}	−30	94	86
2	cyclohexyl	−30	75	85
3	(*E*)-Ph-CH=CH	0	97	82
4	TBS−C≡C-	0	98	79

Chan studied the influence of the BINOL/Ti(O*i*-Pr)$_4$ ratio and of the temperature on the enantioselectivity of the addition of Et_2Zn on aromatic aldehydes. The conclusions were in agreement with those reported by Nakai (Table 74).

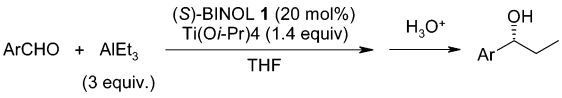
Table 74. Addition of Diethylzinc to Various Aldehydes Catalyzed by the Ti(O*i*-Pr)$_4$/1 System



entry	Ar	*T* (°C)	conv (%)	ee (%)
1	Ph	−78	64	96
2	Ph	−20	87	93
3	Ph	0	100	92
4	*m*-MeOPh	0	100	94
5	*p*-FPh	0	100	86
6	*p*-MePh	0	99	88

These authors then established that all ee's were increased if the BINOL−Ti complex was substituted by a H_8-BINOL−Ti catalyst.[432] The same observation was also made during the study of the asymmetric alkylation of aromatic aldehydes with triethylaluminum under titanium catalysis (Table 75).[433]

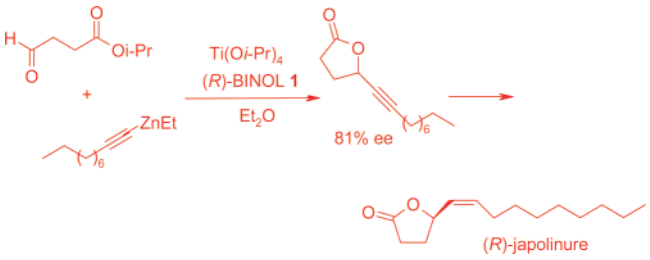
Table 75. Addition of $AlEt_3$ to Various Aldehydes Catalyzed by the Ti(O*i*-Pr)$_4$/1 System



entry	Ar	yield (%)	ee (%) (*R*) with (*S*)-BINOL	ee (%) (*S*) with (*S*)-H_8-BINOL
1	Ph	100	81	96
2	*o*-FPh	82	52	91
3	*o*-ClPh	83	62	91
4	*p*-FPh	90	78	94
5	*p*-ClPh	93	81	90

Such a methodology has been recently applied as the key step in the enantioselective synthesis of japonilure, a sex pheromone of females of the japanese beetle, *popillia japonica* (Scheme 86).[434]

Scheme 86

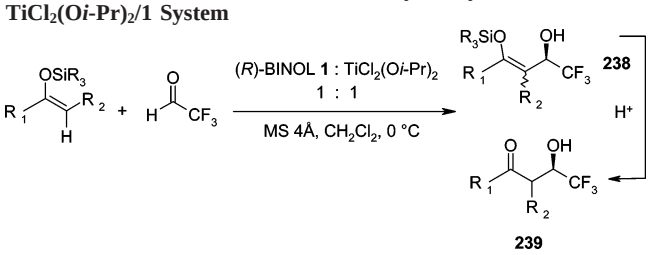


Finally, the enantioselective addition, under Ti catalysis, of dimethylzinc and diethylzinc to prostereogenic ketones has been studied by Yus.[435] The best results were obtained with camphorsulfonamide titanium alkoxide derivatives (up to 89% ee). On the contrary, BINOL complexes led to poor yields and modest ee (35%).

4.7.3. Friedel–Crafts Reaction

Although the Friedel−Crafts reaction is both one of the oldest Lewis acid-catalyzed reactions and one of the most important carbon−carbon bond-forming reactions in organic synthesis, its application to catalytic asymmetric synthesis has been quite limited. With respect to BINOL, reports are even more recent. Thus, Mikami showed in 1999 that such a reaction was occurring, under Mukaiyama reaction conditions, between fluoral and silyl enol ethers under BINOL−Ti complex catalysis.[436] The Friedel−Crafts product, which was obtained in good yield and high ee (up to 98%) along with the classical aldol adduct, could be further transformed into the latter. This observation led Mikami to propose a Friedel−Crafts mechanism for the Mukaiyama aldol reaction with fluoral (Table 76).

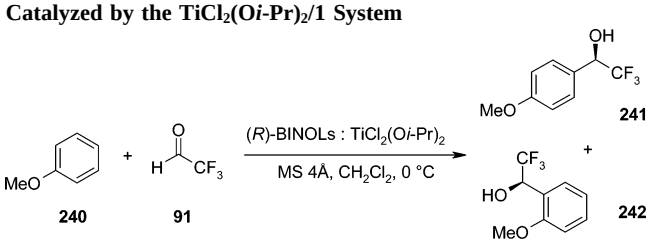
Table 76. Friedel−Crafts Reaction Catalyzed by the $TiCl_2$(O*i*-Pr)$_2$/1 System



entry	SiR_3	R_1	R_2	cat. (%)	yield (%) **238** (*E*/*Z*)	(*Z*) ee (%)	yield (%) **239**
1	$SiMe_2t$-Bu	Ph	H	5	67 (1/5)	98	14
2	Si(*i*-Pr)$_3$	Ph	H	1	90 (1/5)	96	4
3	$SiMe_2t$-Bu	*p*-MePh	Me	20	77 (1/6)	94	10
4	$SiMe_2t$-Bu	*p*-MeOPh	Me	20	68 (1/5)	95	22

A few years later, the same group extended the reaction of fluoral to aromatic substrates.[437] The sense of asymmetric induction was identical to the one observed in BINOL−Ti-catalyzed carbonyl−ene or Mukaiyama reactions. Although the ee's were not improved by using a H_8-BINOL−Ti complex, they could be enhanced with a 6,6′-Br_2-BINOL−Ti complex (Table 77).

Table 77. Reaction of Fluoral with Aromatic Substrates Catalyzed by the $TiCl_2$(O*i*-Pr)$_2$/1 System



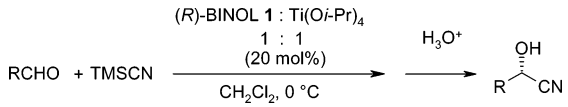
entry	ligand	cat. (%)	yield (%)	**241**/**242**	**241** ee (%)
1	(*R*)-BINOL	30	82	4/1	73
2	(*R*)-H_8-BINOL	5	11	4/1	22
3	(*R*)-6,6′-Br_2-BINOL	5	94	4/1	84

4.7.4. Addition of Trimethylsilyl Cyanide to Carbonyl Compounds and Imines (Strecker Reaction)

Nakai studied the addition of trimethylsilyl cyanide to aldehydes and imines under BINOL−Ti(O*i*-Pr)$_2$ catalysis.[438,439] Good results were obtained with aliphatic aldehydes (up to 75% ee) when the reaction was carried in CH_2Cl_2 at 0 °C while ee's were disappointingly low with aromatic aldehydes (<10%) and an aromatic imine (30%) (Table 78).

^{1}H NMR experiments led the authors to propose that the active catalyst in this reaction is a BINOL−Ti(CN)$_2$ complex.

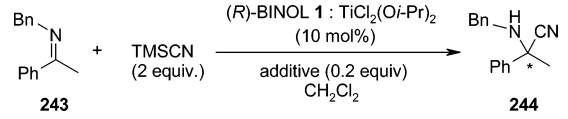
Table 78. Enantioselective Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by the Ti(O*i*-Pr)$_4$/1 System



entry	R	yield (%)	ee (%)
1	*n*-C_8H_{17}	92	72
2	*tert*-Bu	>90	75
3	Et	>90	<10
4	Ph	>90	<10
5	*p*-MeOPh	>90	<10

In 2000, Vallée reported the condensation of TMSCN on ketimines under TADDOL− and BINOL−Ti complexes catalysis in the presence of various activators (diols, ethers, amines).[14] The best result was obtained with BINOL−Ti-(O*i*-Pr)$_2$ as catalyst (10 mol %) and TMEDA as activator (20 mol %) (Table 79).

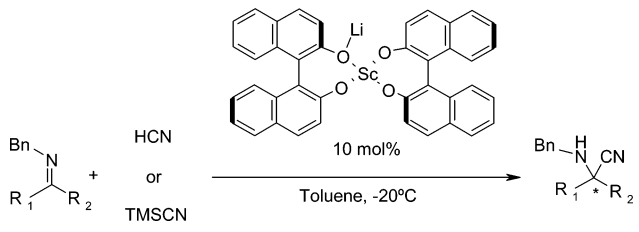
Table 79. Enantioselective Addition of Trimethylsilyl Cyanide to Imines Catalyzed by the TiCl$_2$(O*i*-Pr)$_2$/1 System



entry	additive	conv (%)	ee (%)
1	(*R*)-BINOL	80	33
2	Et_2O	85	37
3	TMEDA	80	56
4	Et_3N	66	50

The same group improved this system by preparing a new chiral heterobimetallic complex, Sc(BINOL)$_2$Li, affording the expected cyanohydrins in good yields and high ee's (Table 80).[440]

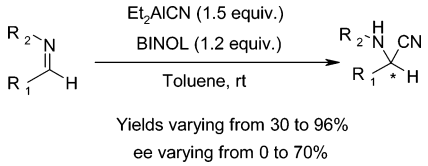
Table 80. Enantioselective Addition of TMSCN or HCN to Imines Using Sc(BINOL)$_2$Li Catalyst



entry	XCN	R_1	R_2	conv (%)	ee (%)
1	TMSCN	Ph	Me	95	88
2	HCN	Ph	Me	95	81
3	TMSCN	β-naphthyl	H	45	65
4	HCN	β-naphthyl	H	80	86

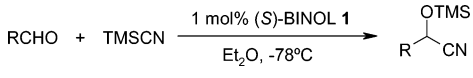
Very recently, an enantioselective Strecker-type reaction of imines with Et_2AlCN in the presence of chiral additives such as BINOL has been examined by Toru et al. The enantioselectivity varied depending on the substituents of the imino group as well as the chiral additives used. Thus, α-aminonitriles were obtained in good yields with good enantioselectivities of up to 70% ee in the reaction of *N*-benzylidenebenzhydrylamine with Et_2AlCN and BINOL (Scheme 87).[441]

Scheme 87



Kagan and Holmes have investigated the addition of TMSCN to aldehydes catalyzed by lithium salts of chiral phenols. Taking advantage of the propensity of silicon to form strongly Lewis acidic complexes with valences of 5 and 6, templated asymmetric additions have been performed. This process is of note, as it removes the need for a transition metal, by using the metalloid silicon, inherent in the reaction, instead. (*S*)-(−)-BINOL **1** has been identified as a precursor to active enantioselective catalysts which, after optimization of the reaction conditions, were used to convert a range of aldehydes to their corresponding cyanohydrins with ee's of up to 56% (Table 81).[442]

Table 81. Enantioselective Addition of TMSCN to Aldehydes Using Hypervalent Silicon Species



entry	aldehyde	yield (%)	ee (%)
1	benzaldehyde	96	56 (*S*)
2	*p*-anisaldehyde	95	54 (*S*)
3	cyclohexanecarbaldehyde	94	30 (*S*)
4	pivaldehyde	62	26 (*S*)

While this procedure is interesting from a mechanistic point of view, the highly exothermic nature of the reaction and the poor substrate tolerance render it currently only of academic interest. Also, it is unclear whether hypervalent silicon intermediates are responsible for the observed reactions or whether lithium is acting as a Lewis acid.

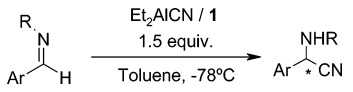
As an extension of this work, Ishihara et al. developed a highly enantioselective cyanation of aromatic aldehydes using a simple and inexpensive chiral lithium binaphtholate alcohol complex. The chemical yields and the enantiomeric excesses are excellent, whatever the considered aldehydes (Table 82).[443]

Table 82. Cyanation of Aldehydes Catalyzed by (*R*)-BINOL 1/*i*-PrOH

entry	R	yield (%)	ee (%)
1	Ph	99	97
2	1-naphthyl	95	81
3	3-furyl	96	98
4	4-BrC_6H_4	98	93
5	4-ClC_6H_4	98	92

Recently, a new approach to enantioselective cyanation of imines with Et_2AlCN in the presence of various chiral additives has been examined. The enantioselectivity varied depending on the substituents of the imino group as well as the chiral additives used. Thus, α-aminotriles were obtained in good yields with good enantioselectivities of up to 70%

Table 83. Enantioselective Cyanation of Imines with Et_2AlCN in the Presence of BINOL 1 as Chiral Additive

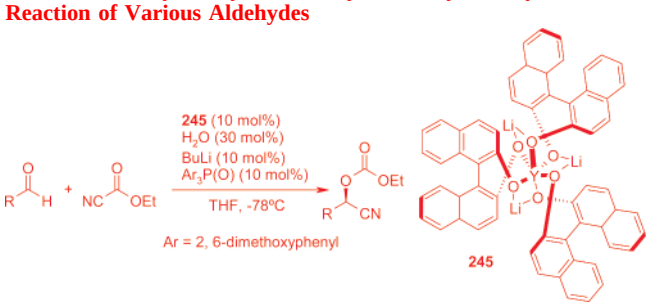


entry	Ar	R	yield (%)	ee (%)
1	Ph	Ph	96	61
2	Ph	Flu	93	22
3	Ph	Ph_2CH	98	70
4	1-Naph	Ph_2CH	99	70
5	*p*-ClC_6H_4	Ph_2CH	99	64

ee in the reaction of *N*-benzylidenebenzhydrylamine with Et_2-AlCN and BINOL **1** (Table 83).[441]

In 2005, Shibaski et al. developed a catalytic enantioselective cyanoethoxycarbonylation reaction of aldehydes with ethyl cyanoformate using a heterobimetallic Y−Li_3−tris(binaphthoxide) **245**. Under optimized conditions, achiral additives, H_2O, tris(2,6-dimethoxyphenyl)phosphine oxide, and BuLi had key roles in achieving high reactivity and enantioselectivity (up to 99% yield and up to 98% ee) (Table 84).[444]

Table 84. Catalytic Asymmetric Cyanoethoxycarbonylation Reaction of Various Aldehydes



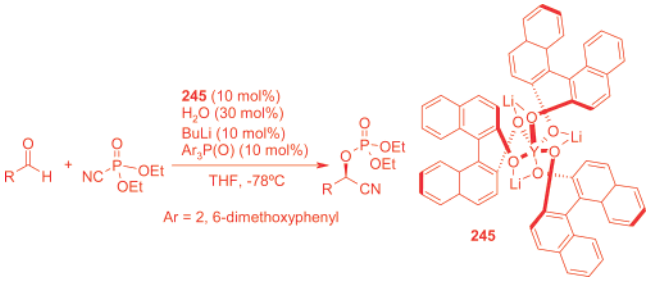
entry	R	yield (%)	ee (%)
1	Ph	96	94
2	1-naphthyl	97	90
3	Et	79	92
4	*i*-Pr	88	98
5	*tert*-Bu	93	87
6	PhCH=CH	99	91

The same authors have extended this reaction to the catalytic asymmetric cyanophosphorylation of aldehydes in good yields (up to 98%) and enantiomeric excesses (up to 97% ee) (Table 85).[445]

4.7.5. Baylis–Hillman Reaction

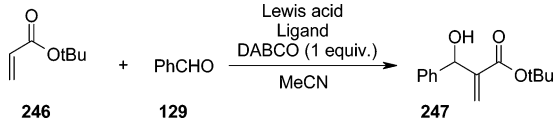
The Baylis−Hillman reaction (reaction between an unsaturated ester and an aldehyde catalyzed by DABCO, for example) is useful in organic synthesis but suffers from low reaction rates. Aggarwal investigated the Lewis acid catalysis of the reaction and found that the use of lanthanide triflates (5 mol %) induced a significant rate acceleration (4.5−5-fold).[208,446,447] Noteworthy is the fact that more classical Lewis acids, such as BF_3−OEt_2 or $TiCl_4$, induced a deceleration of the reaction, presumably because of the formation of a too stable amine−Lewis acid complex. Although this problem is less serious with lanthanide Lewis acids, the authors also established that the addition of ligands would increase the rate of the reaction. Among these ligands, (+)-

Table 85. Catalytic Asymmetric Cyanophosphorylation of Various Aldehydes



entry	R	yield (%)	ee (%)
1	Ph	97	92
2	*i*-Pr	82	96
3	cyclohexyl	90	92
4	2-naphthyl	98	81

Table 86. Baylis−Hillman Reaction Catalyzed by Different Lewis Acid/1 Systems

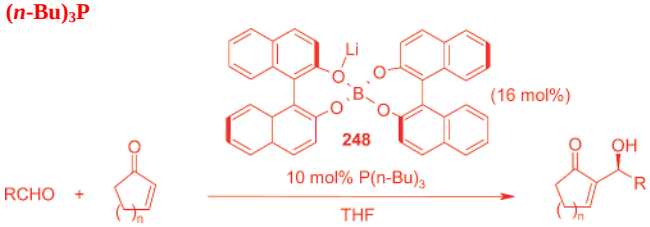


entry	Lewis acid (5 mol %)	ligand (5 mol %)	relative rate
1	none	none	1
2	BF_3−OEt_2	none	<0.1
3	$TiCl_4$	none	<0.1
4	$Yb(OTf)_3$	none	3.6
5	$La(OTf)_3$	none	4.7
6	$Yb(OTf)_3$	(*R*)-BINOL	14.4
7	$La(OTf)_3$	(*R*)-BINOL	14.6

BINOL (5 mol %) gave one of the largest rate accelerations observed but no significant asymmetric induction (however, the authors observed that racemic BINOL had no influence on the rate of the reaction) (Table 86).

Finally, Sasai et al. have reported a new double-activation catalysis for the Morita−Baylis−Hillman reaction (MBH) of an α,*β* unsaturated ketone and an aldehyde by the combined use of a heterobimetallic asymmetric complex and tributylphosphine to afford the α-methylene-*β*-hydroxy ketone with up to 99% ee (Table 87).[448]

Table 87. Enantioselective MBH Reaction Promoted by Boron−Lithium-Mono(binaphthoxide) in the Presence of $(n\text{-Bu})_3P$

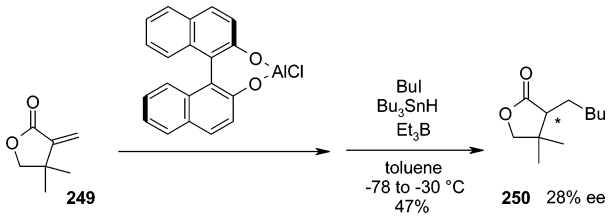


entry	R	*n*	yield (%)	ee (%)
1	$PhCH_2CH_2$	1	70	64
2	$PhCH_2CH_2$	2	49	58
3	Et	2	23	85
4	*i*-Pr	2	94	99
5	Ph	1	93	19
6	Ph	2	32	15
7	C_6H_{11}	1	88	93
8	C_6H_{11}	2	71	63

4.7.6. Radical Addition and Cyclization

Over the past decade, remarkable progress has been made on the stereoselectivities of radical carbon−carbon bond formation, and Lewis acids have played an important role via the formation of chelates that induce facial differentiation.[449−452] Examples in which the Lewis acid also has a radical acceptor activation role are more rare. The first paper on the topic is due to Sato, who studied the Lewis acid-enhanced reactivity of α,β-unsaturated esters and amides toward radical addition.[453] In the same paper, the authors also reported the first example of asymmetric radical addition controlled by a chiral BINOL−Al Lewis acid (Scheme 88).

Scheme 88

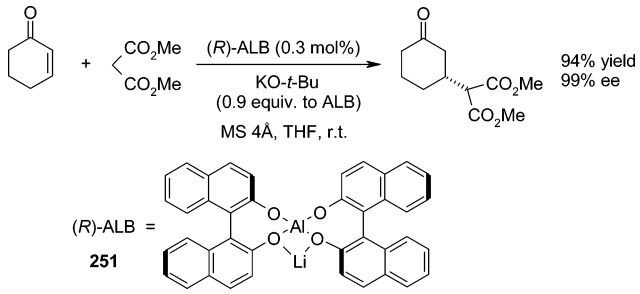


Nishida then studied the influence of chiral Lewis acids, prepared from various BINOLs and trimethylaluminum, on a 5-*exo*-*trig* radical cyclization. Enantiomeric excesses were poor with (*R*)-BINOL−AlMe (2%) and modest with 3,3′-bis(triphenylsilyl)−BINOL−AlMe (36−18%) but provided the latter was used in excess (4 equiv).[454]

4.7.7. Catalytic Asymmetric Michael Addition

In 1998, Shibasaki et al. described the use of a heterobimetallic asymmetric complex as catalyst in a Michael addition reaction. Thus, Al−bis(binaphthoxide) complex (ALB) was the most effective catalyst in the presence of 1 equiv of base, such as BuLi or KO-*t*-Bu, which accelerates the reaction rate (Scheme 89).[455−457]

Scheme 89

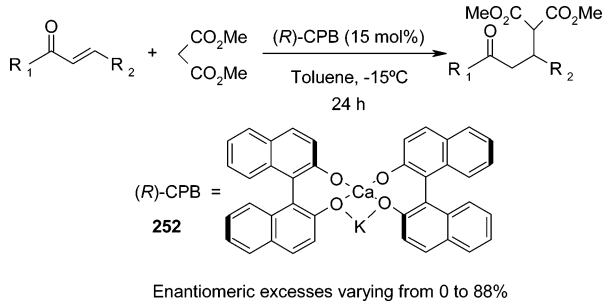


Immobilization of this multifunctional catalyst on an insoluble polymer led to similar results in terms of enantioselectivity (88% ee instead of 99% ee in the homogeneous case). Nevertheless, in this case, easy separation, reusability, stability, and less toxicity of immobilized species may be noticed.[458] It is noteworthy that this reaction has also been performed using microwaves, with comparable enantioselectivities in a remarkably shorter reaction time.[459]

Recently, a new calcium−BINOL catalyst has been developed for asymmetric Michael addition reactions of enones and enals in good yields but with moderate enantioselectivities of up to 87% ee (Scheme 90).[460]

In the same area, enantioselective Michael additions of α-nitroesters with α,β-unsaturated ketones were carried out

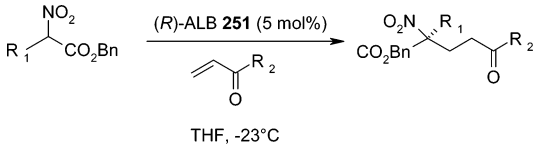
Scheme 90



Enantiomeric excesses varying from 0 to 88%

in the presence of a catalytic amount of (*R*)-ALB **251**. The enantioselectivity proved to be extremely temperature dependent with a maximum of enantiomeric excess obtained at −23 °C. Numerous examples have been investigated with enantiomeric excesses varying from 5 to 80% ee depending on the nature of the considered substrates (Table 88).[461,462]

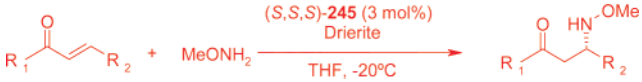
Table 88. Enantioselective Michael Additions of α-Nitroesters with α,β-Unsaturated Ketones



entry	R_1	R_2	yield (%)	ee (%)
1	Me	Me	81	80
2	Me	Et	86	55
3	Et	Et	84	33
4	Me	Ph	86	5
5	Me	OEt	<5	<5

In 2005, Shibasaki et al. demonstrated that the rare earth−alkali metal heterobimetallic complex **245** functions as a Lewis acid−Lewis acid cooperative catalyst promoting catalytic asymmetric 1,4-addition of methoxylamine to enones in excellent yields and enantiomeric excesses of up to 96% ee (Table 89).[463]

Table 89. Catalytic Asymmetric Aza-Michael Reaction of Various Enones



entry	R_1	R_2	yield (%)	ee (%)
1	Ph	Ph	97	95
2	Ph	2-thienyl	96	95
3	Ph	2-furyl	80	92
4	Ph	*i*-Pr	97	86
5	Ph	cyclohexyl	98	82
6	Ph	4-pyridyl	91	85

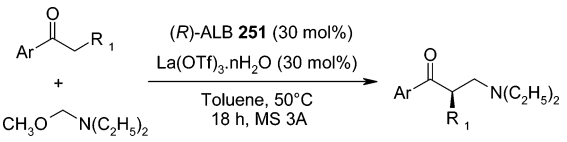
4.7.8. Catalytic Asymmetric Mannich-Type Reaction

Using the same heterobimetallic chiral complex (ALB), the first direct catalytic asymmetric Mannich-type reaction has been achieved by Shibasaki et al., leading to moderate enantiomeric excesses up to 44% ee (Table 90).[464,465]

4.7.9. Asymmetric Addition of Alkyl Groups to Aldehydes

In 1993, Greeves et al. reported the use of homochiral organolanthanide (Ln = Ce, Yb) reagents in enantioselective

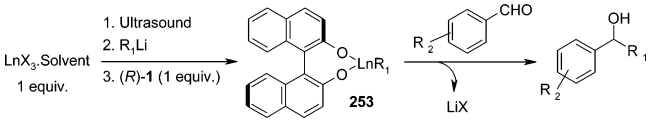
Table 90. Direct Catalytic Asymmetric Mannich-Type Reaction



entry	Ar	R_1	yield (%)	ee (%)
1	Ph	Me	65	40
2	Ph	Et	69	34
3	4-anisyl	Me	76	31
4	2-naphthyl	Me	61	44
5	6-MeO-2-naphthyl	Me	69	44

additions of alkyl groups to aldehydes to produce secondary alcohols in moderate to high enantiomeric excesses. The reagents were prepared by reaction of (*R*)-**1** with the desired trialkyllanthanide species that was generated from 2.8 equiv of alkyllithium and 1 equiv of anhydrous lanthanide(III) chloride or triflate. This stoichiometry was essential to ensure that no unreacted organolithium precursor, which would be detrimental to the enantiomeric excess, was present (Table 91).[466−470]

Table 91. Generation of Reagents and Their Reaction with Aromatic Aldehydes



entry	LnX_3	R_1	R_2	yield (%)	ee (%)
1	$Yb(OTf)_3$	*n*-Bu	H	87	33
2	$CeCl_3$	*n*-Bu	4-OMe	87	52
3	$CeCl_3$	Me	4-OMe	75	68
4	$CeCl_3$	Me	4-Cl	53	75
5	$CeCl_3$	*n*-Bu	4-Me	71	85
6	$Ce(OTf)_3$	Me	4-Me	62	57
7	$Yb(OTf)_3$	Me	4-Me	56	65

4.7.10. Synthesis of α-Hydroxy- and Aminophosphonates

$LaLi_3$tris(binaphthoxide) catalyst (LLB), which is prepared from $LaCl_3 \cdot 7H_2O$, (*R*)-BINOL **1** dilithium salt, and NaO-*t*-Bu, is effective for the hydrophosphonylation of various aldehydes.[471−473] Thus, despite all the different catalysts tested, the desired α-hydroxyphosphonates are obtained in up to 95% ee and 88% yield using the Al−Li−BINOL complex (Table 92).[474−476]

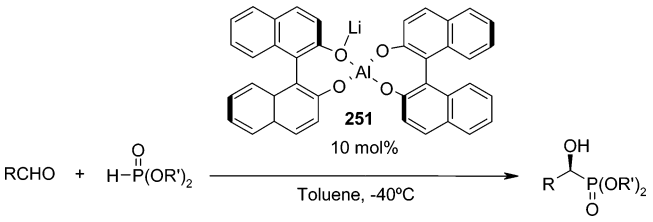
On the basis of numerous experiments, a mechanism involving the activation of both the nucleophile and the electrophile by the heterobimetallic catalyst was proposed (Scheme 91).[477−479]

As an extension of this work, Shibasaki et al. have described the catalytic and enantioselective hydrophosphonylation of imines using YbPB catalyst. In this area, excellent results have been obtained on cyclic imines with up to 96% ee and up to 90% yield (Scheme 92).[480]

4.7.11. Enantioselective Cyclization of Polyprenoids

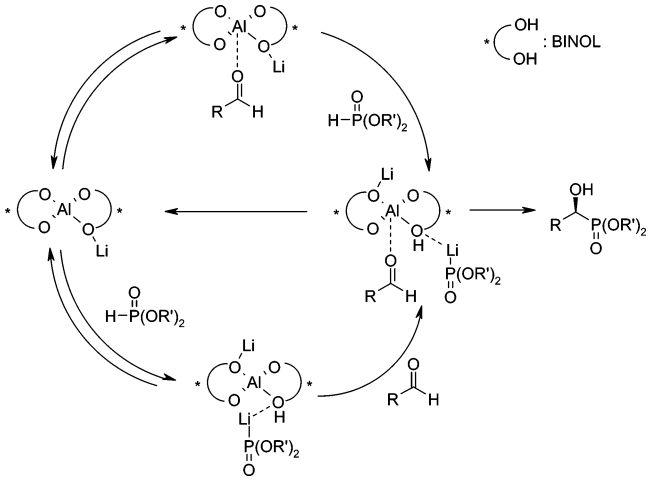
A selective formation of polycyclic terpenoids has been described using $SnCl_4$−BINOL. Thus, the cyclization oc-

Table 92. Asymmetric Synthesis of α-Hydroxy- and Aminophosphonates

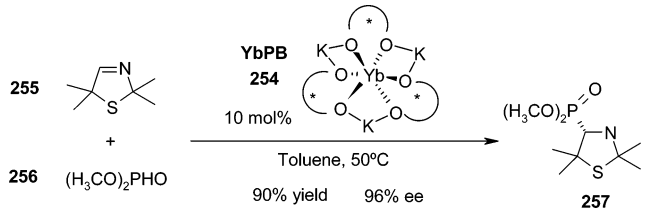


entry	R	R′	yield (%)	ee (%)
1	Ph	Et	39	73
2	Ph	Me	90	85
3	*p*-Cl−Ph	Me	80	83
4	*p*-Me-Ph	Me	82	86
5	*p*-MeO-Ph	Me	88	78
6	(*E*)-PhCH═CH	Me	85	82
7	$(CH_3)_2C$═CH	Me	72	68
8	(*E*)-$CH_3(CH_2)_2CH$═CH	Me	53	55

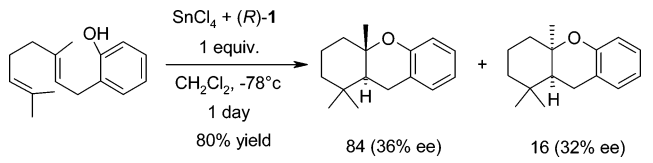
Scheme 91



Scheme 92



Scheme 93



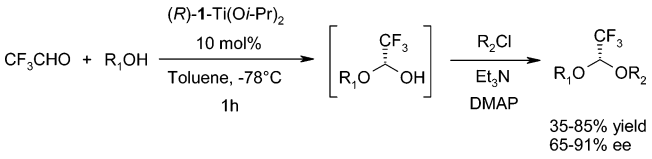
curred in CH_2Cl_2 at −78 °C and afforded the *trans*-fused tricyclic compound in 67% yield and 36% ee (Scheme 93).[481,482]

4.7.12. Asymmetric Synthesis of 1-Alkoxy-2,2,2-trifluoroethanol Derivatives

Reaction of trifluoroacetaldehyde with an alcohol in the presence of a catalytic amount of (*R*)-BINOL−$Ti(Oi\text{-}Pr)_2$ gives 1-alkoxy-2,2,2-trifluoroethanol with enantiomeric ex-

cesses varying from 65 to 91% ee depending on the nature of the substrate (Scheme 94).[483]

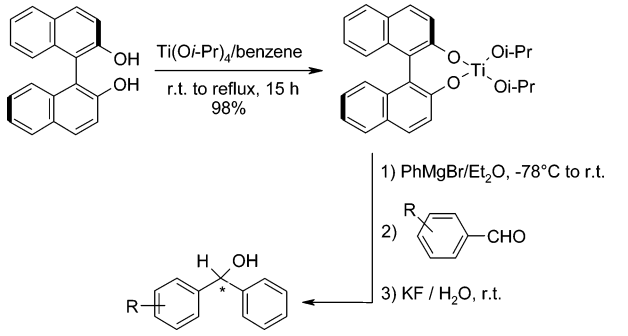
Scheme 94



4.7.13. Asymmetric Synthesis of Substituted Chiral Benzhydrols

On the other hand, a series of substituted chiral benzhydrols were synthesized by reaction of aromatic aldehydes with the chiral intermediates formed from arylmagnesium halides and chiral titanates generated from (*R*)-BINOL **1**. The effect of substituents on the enantioselectivity of the reaction has been studied, and enantiomeric excesses varying from 24 to 100% ee have been encountered (Table 93).[484]

Table 93. Asymmetric Synthesis of Substituted Chiral Benzhydrols



entry	R	yield (%)	ee (%)
1	4-NO_2	73	90
2	3-Br	81	95
3	2,4-di-OMe	83	24
4	4-Cl	57	100

4.7.14. Hydrodimerization of β-Monosubstituted Acrylic Acid Amides

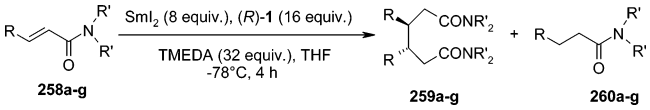
The chiral samarium(II) complex prepared from SmI_2, (*R*)-BINOL **1**, and an achiral tertiary amine promoted the reductive homocoupling reaction of β-monosubstituted acrylic acid amides **258a**−**g** to give the corresponding 3,4-*trans*-disubstituted adipamides **259a**−**g** with high enantioselectivities (up to 85% ee) (Table 94).[485,486]

4.7.15. Catalytic Enantioselective meso-Epoxide Ring Opening Reaction

In 1998, Hou et al. reported a simple route to chiral β-amino alcohols by ring opening of *meso*-epoxides catalyzed by $Yb(OTf)_3$ and (*R*)-BINOL **1**. The reaction proceeds smoothly at −78 °C, affording the desired amino alcohols in good to high chemical yields and ee up to 80% (Scheme 95).[487,488]

In 2006, Kureshy et al. reported that the catalytic enantioselective ring opening reaction of *meso*-stilbene oxide with anilines was catalyzed by BINOL−Ti complexes at ambient temperature to obtain β-amino alcohols in good yields (of up to 95%) and enantioselectivity (78% ee) (Table 95).[489]

Table 94. Hydrodimerization of β-Monosubstituted Acrylic Acid Amides



	substrate		product/yield (%)		259a−g	
entry	R	R′	259a−g	260a−g	*dl*/*meso*	ee (%)
1	Me	Bn	70	20	*dl* only	71 (+)
2	Et	Bn	45	42	*dl* only	82 (+)
3	*n*-Pr	Bn	35	46	*dl* only	82 (+)
4	$BnCH_2$	Bn	20	52	*dl* only	85 (+)
5	*i*-Pr	Bn	−	95		
6	*t*-Bu	Bn	−	99		
7	Me	Ph	55	44	63:37	44 (−)

Scheme 95

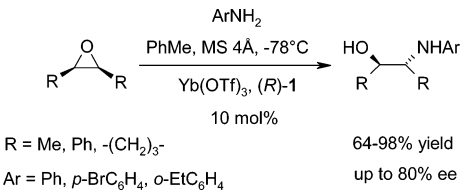
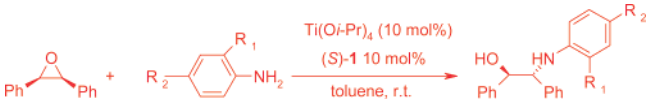


Table 95. Asymmetric Catalytic Ring Opening of *meso*-Stilbene Oxide with Anilines Using $Ti(Oi\text{-}Pr)_4$/(*S*)-1 Catalyst

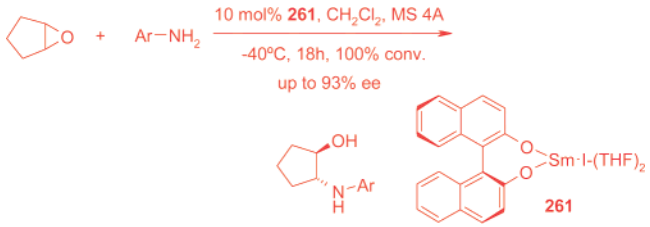


entry	R_1	R_2	yield (%)	ee (%)
1	H	H	90	67
2	H	OMe	72	78
3	H	Cl	95	64
4	H	Me	80	71

As an extension of such a methodology, this reaction has been successfully performed under microwave irradiation in high yields (up to 95%) and good enantioselectivities (ee up to 55%).[490]

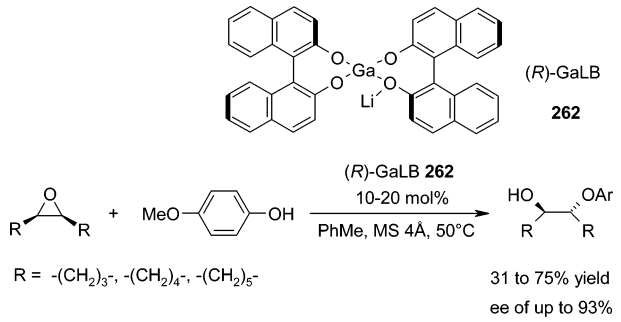
Moreover, Collin et al. found recently that samarium iodobinaphthoxide catalyzes enantioselective aminolysis of cyclic *meso*-epoxides, producing β-amino alcohols with high enantiomeric excesses of up to 93% ee (Scheme 96).[491]

Scheme 96



On the other hand, Shibasaki et al. recently described the first catalytic enantioselective *meso*-epoxide ring opening reaction with phenolic oxygen nucleophile promoted by praesidium[492] or gallium heterobimetallic multifunctional complexes such as (*R*)-GaLB **262** (Ga = gallium, L = lithium, B = (*R*)-BINOL).[458,493] Thus, using 10−20 mol % of (*R*)-GaLB catalyst, a variety of epoxides were smoothly cleaved with phenolic oxygen nucleophiles and the expected

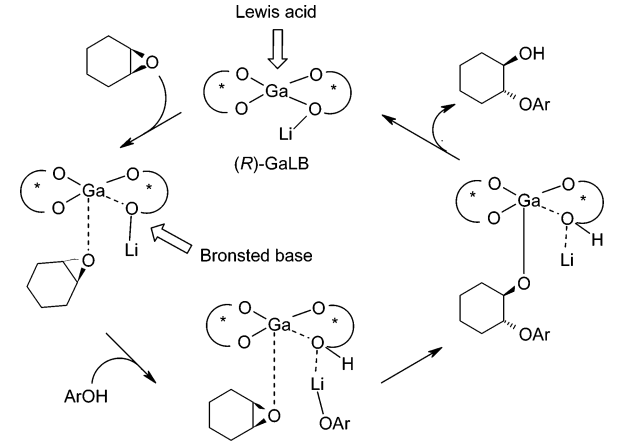
Scheme 97



products were obtained in enantiomeric excesses varying from 67 to 93% ee and with modest to good yields (31−75%) (Scheme 97).

On the basis of mechanistic studies of other asymmetric reactions catalyzed by various heterobimetallic complexes, the authors have envisioned that group 13 element Ga could act as a Lewis acid in a similar manner as Al to activate epoxides and lithium binaphthoxide could function as a Bronsted base to activate 4-methoxyphenol (Scheme 98).

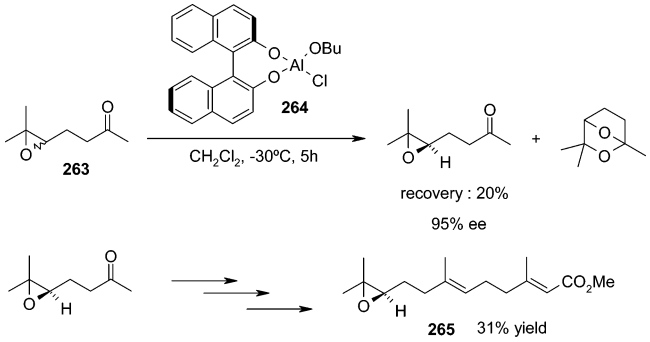
Scheme 98



4.7.16. Kinetic Resolution

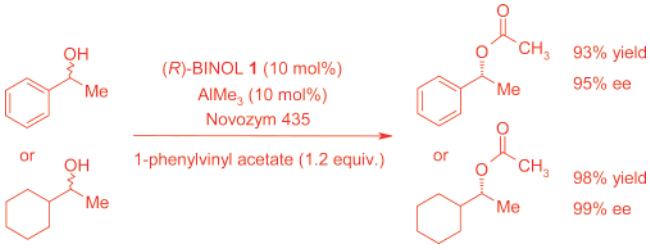
In 1988, Yamamoto et al. reported for the first time the use of chiral organoaluminum reagent **264** as a catalyst to resolve simple ketoepoxides. Thus, the optically pure ketoepoxide **263** was recovered after 80% conversion and was found to be a useful chiral building block for a short asymmetric synthesis of the juvenile hormone **265** in 31% overall yield (Scheme 99).[494,495]

Scheme 99



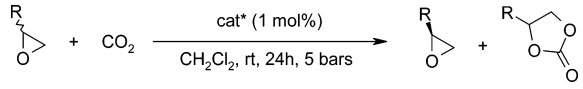
In 2006, Berkessel et al. demonstrated that chemoenzymatic dynamic kinetic resolution of secondary alcohols is possible in high yield and high enantioselectivity through the use of inexpensive and readily available aluminum catalysts generated in situ in combination with a lipase (Scheme 100).[496]

Scheme 100



Recently, the kinetic resolution of oxiranes by use of chiral Lewis acids has been described proceeding with moderate enantioselectivities up to 39% in the insertion of CO_2 (Table 96).[497,498]

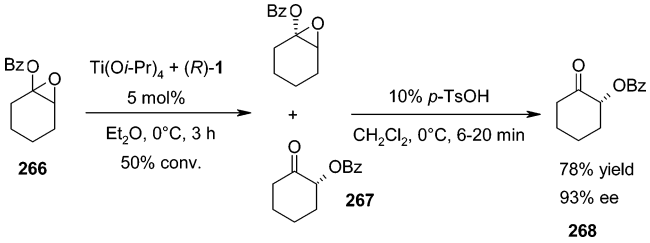
Table 96. Kinetic Resolution of Oxiranes Using Various Lewis Acid/1 Catalysts



entry	R	catalyst	sel (%)	conv (%)	ee (%)	s
1	CH_2Cl	Ti(O*i*-Pr)$_4$/BINOL	98	48	17	1.7
2	CH_2Cl	CpTiCl$_3$/Li$_2$Binolate	100	22	9	2.3
3	CH_2Cl	Zr(O*t*-Bu)$_4$/BINOL	100	20	10	2.5
4	Ph	Ti(O*i*-Pr)$_4$/BINOL	83	41	24	2.6
5	Ph	CpZrCl$_3$/Li$_2$Binolate	97	66	27	1.5

Kinetic resolution of racemic enol ester epoxides catalyzed by (*R*)-**1**/Ti(O*i*-Pr)$_4$ has been achieved by Shi et al.[499−501] High resolution efficiency was obtained for a number of cyclic systems. Both enantiomerically enriched enol ester epoxides and α-acyloxy ketones were obtained through this resolution. Thus, a racemic enol ester epoxide can be completely converted into an enantiomerically enriched α-acyloxy ketone by sequential treatment with a catalytic amount of a chiral Lewis acid and a catalytic amount of an achiral acid (Scheme 101).

Scheme 101

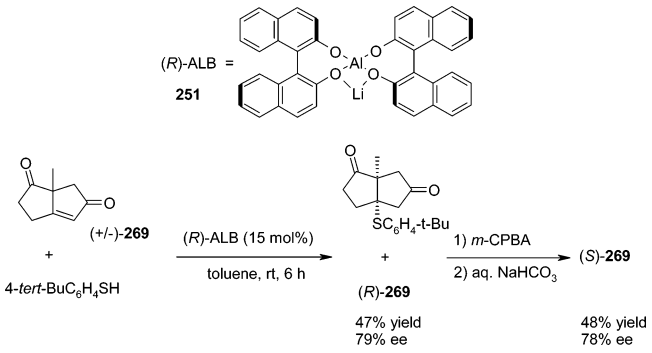


Numerous examples have been reported with enantioselectivities varying from 38 to 93% ee and excellent chemical yields. As an extension of such a study, Tu et al. have investigated a new method for the enantioselective preparation of β-hydroxy ketones containg a stereogenic quaternary carbon center and tertiary α-hydroxy epoxides. Although the maximum possible yield is 30−40%, the method uses easily accessible racemic starting materials, and conversion levels can be manipulated so that completely enantiopure samples

of substrate enantiomers are obtained with enantiomeric excesses of up to 60%.[502]

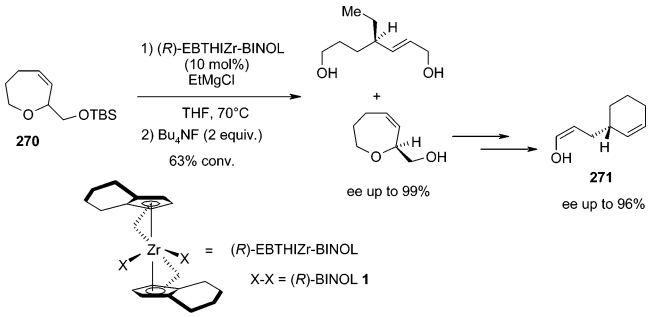
The kinetic resolution of racemic 5-methylbicyclo[3.3.0]-oct-1-ene-3,3-dione catalyzed by Al−Li−bis(*R*)-BINOL with Michael addition of 4-*tert*-butyl(thiophenol) has been developed, leading to the two enantiomers (*R*)-**269** and (*S*)-**269** in enantiomeric excesses up to 79% ee (Scheme 102).[503,504]

Scheme 102



Recently, Hoveyda et al. reported that various medium-ring heterocycles, bearing a C2-substituent that contains an accessible Lewis basic heteroatom, may react with Grignard reagents with high levels of regio- and stereochemical control. The key substrates were prepared enantiomerically pure through the Zr-catalyzed kinetic resolution (Scheme 103).[505]

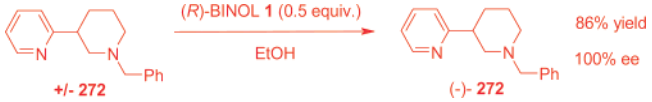
Scheme 103



4.7.17. BINOL as a Chiral Resolving Agent

An efficient and practical resolution of racemic alkaloid 1-benzylisoanabasine has been achieved through molecular complexation with (*R*)-BINOL **1** or (*S*)-BINOL **1** to afford pure enantiomers of the natural alkaloid isoanabasine (Scheme 104).[506]

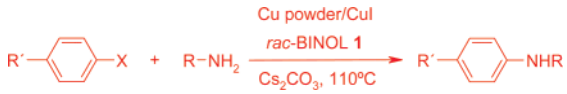
Scheme 104



4.7.18. Copper-Catalyzed Amination of Aryl Halides with Amines

Recently, Wan et al. reported a highly effective copper-catalyzed system using *rac*-BINOL as the ligand for amination of aryl halides with alkylamines and N−H heterocycles in high chemical yields varying from 62 to 98% depending on the nature of the starting materials (Table 97).[507]

Table 97. Coupling of Aryl Halides with Various Amines

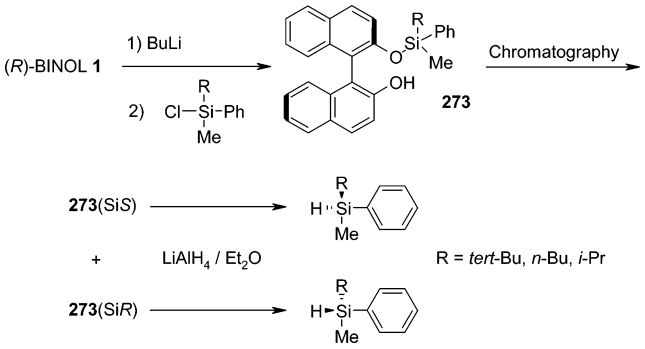


entry	R	R′	yield (%)
1	Bn	H	95
2	*n*-Hex	H	69
3	Bn	*tert*-Bu	88
4	pyrazole	CN	89

4.7.19. Synthesis of Silane Derivatives and Use of Chiral Proton Donor Reagents

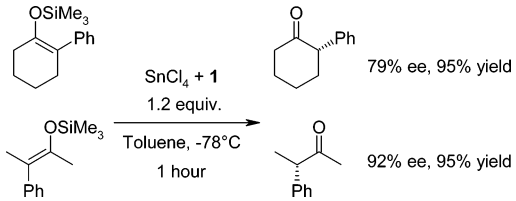
Recently, Asztemborska et al. have performed the resolution of chiral silanes from the corresponding racemic silyl chlorides via diastereomeric derivatives **273** (Scheme 105).[508]

Scheme 105



Enantioselective protonation of prochiral enol derivatives is a very simple and attractive route for the preparation of optically active carbonyl compounds.[509] In 1994, Yamamoto et al. reported a new Lewis acid assisted chiral Bronsted acid for enantioselective protonation of prochiral silyl enol ethers and ketene bis(trialkylsilyl)acetals with high enantioselectivities and in quantitative yield (Scheme 106).[510,511]

Scheme 106



In the same area, an asymmetric protonation of a *meso*-1,2-enediol bis(trimethylsilyl)ether using a (*S*)-BINOL monomethyl ether **274**−$SnCl_4$ complex has been described by Ogasawara et al. in order to realize an alternative route to chiral (−)-ketodicyclopentadiene and (−)-ketotricyclononene (Scheme 107).[512]

4.7.20. Titanium-Catalyzed Intermolecular Hydroamination of Terminal Alkynes

In 2005, Beller et al. investigated the control of regioselectivity by using $Ti(NEt_2)_4$ catalyst with different ligands in the hydroamination of unsymmetrical alkynes. Thus, the use of *rac*-BINOL as ligand led preferentially to the

Scheme 107

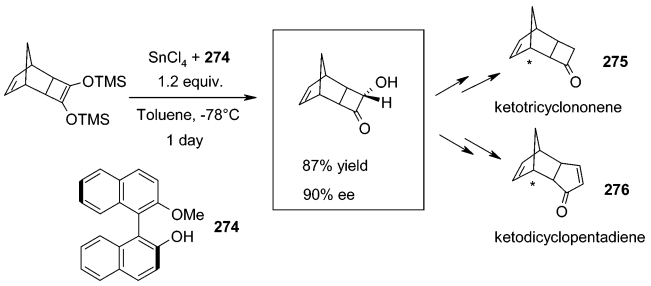
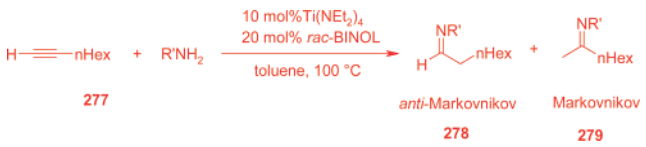


Table 98. Hydroamination of 1-Octyne with Different Amines Using $Ti(NEt_2)_4$−1 Catalyst



entry	amine	yield (%)	*anti*-**278**/**279** ratio
1	benzylamine	52	33:67
2	*sec*-butylamine	88	62:38
3	*tert*-butylamine	36	86:14

formation of the anti-Markovnikov product depending on the nature of the considered amines (Table 98).[513]

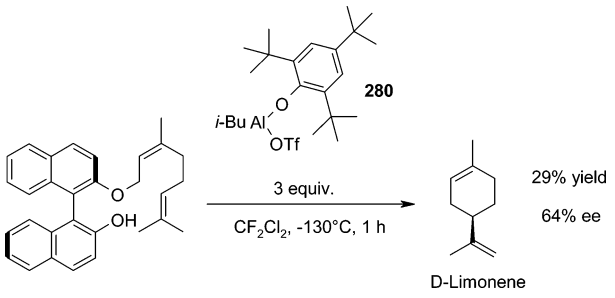
4.7.21. Use of BINOL as Chiral Auxiliary

(*R*)-BINOL **1** has been used as chiral leaving group for the asymmetric synthesis of monocyclic terpenes such as limonene. Whatever the experimental conditions, low yields (29% yield) and moderate enantiomeric excesses up to 64% ee were reached (Scheme 108).[183−186]

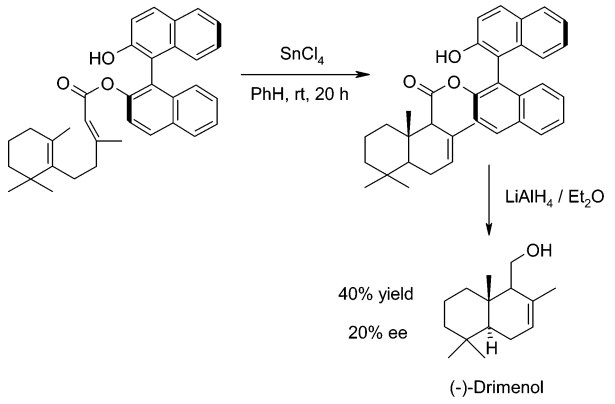
A similar approach has been developed by Lee et al. for the asymmetric synthesis of (−)-drimenol (Scheme 109). In this case, use of (*R*)-BINOL **1** in the acid-catalyzed cyclization of monocyclofarnesate resulted in low chiral induction (20% ee).[514]

In another context, the preparation of a variety of enantiomerically pure uncommon α-amino acids by alkylation of chiral glycine derivatives possessing axially chiral BINOL as an auxiliary has been depicted by Fuji et al. Thus, depending on the nature of the electrophile, enantiomeric excesses varying from 69 to 86% ee were obtained (Scheme 110).[515]

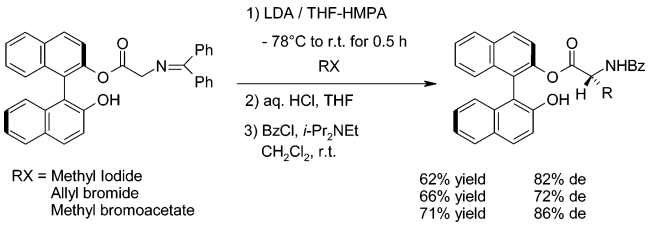
Scheme 108



Scheme 109

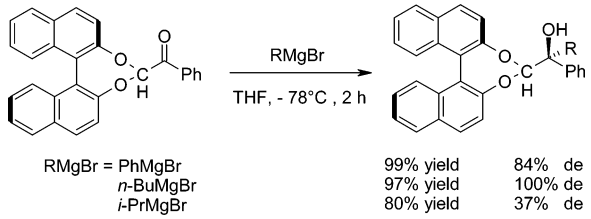


Scheme 110



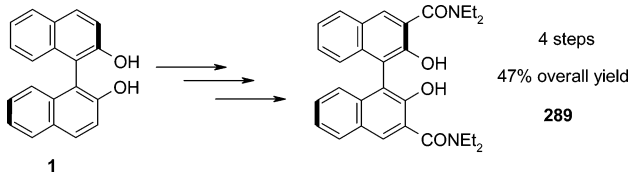
Arylglyoxals, protected at the aldehyde function with (*R*)-BINOL **1**, and readily prepared by direct nucleophilic substitution of BINOL-salt on dibromoacetophenone, react diastereoselectively with Grignard reagents to afford protected atrolactaldehyde and related compounds in high yields (Scheme 111).[516]

Scheme 111



On the other hand, Tamai et al. have widely studied 1,8- to 1,12-asymmetric induction in Grignard reactions of ω-keto esters. Thus, efficient diastereoselective alkylation of δ- and ϵ-keto acids with Grignard reagents was achieved in up to 97% enantiomeric excess by conversion into the 2′-[3-(2-methoxyethoxy)propoxyl]-(1,1′-binaphthyl)-2-ol esters, while the corresponding alkylation of ξ- to θ-keto acids could effectively be carried out in up to 88% ee (Table 99).[517,518]

Scheme 112

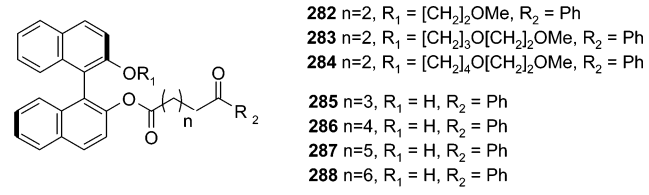


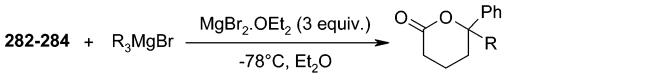
Optically active *N*,*N*,*N*′,*N*′-tetraalkyl-2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxamides easily prepared from (*R*)-BINOL **1** (Scheme 112) were found to be efficient auxiliaries for the asymmetric Simmons−Smith cyclopropanation of allylic alcohols with enantioselectivities up to 94% ee (Table 100).[519,520]

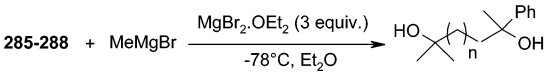
4.7.22. Synthesis of Chiral Organophosphorus Ligands from BINOL

A wide variety of chiral organophosphorus ligands such as BINAP has been developed from BINOL **1** and sucessfully used in numerous asymmetric reactions. Nevertheless,

Table 99. Diastereoselective Alkylation of δ- and ϵ-Keto Acids with Grignard Reagents

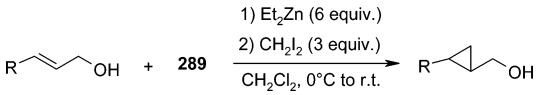






entry	substrate	R_3MgBr	yield (%)	ee (%)
1	282	MeMgBr	73	59
2	283	MeMgBr	80	93
3	283	$C_9H_{19}MgBr$	82	97
4	284	MeMgBr	79	74
5	285	MeMgBr	91	61
6	286	MeMgBr	92	88
7	287	MeMgBr	86	85
8	288	MeMgBr	88	81

Table 100. Asymmetric Simmons−Smith Cyclopropanation of Allylic Alcohols



entry	R	yield (%)	ee (%)
1	Ph	44	92
2	*p*-MeOPh	78	94
3	*p*-ClPh	59	90
4	$PhCH_2$-	65	89
5	$TBDPSOCH_2$-	88	88

this point will not be discussed here since it is beyond the scope of the present review and would deserve a coverage of its own.[521]

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