# Modified BINOL Ligands in Asymmetric Catalysis†

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## Contents



† This review is dedicated to Professor George A. Olah on the occasion of his 75th birthday.

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## I. Introduction

Enantioselective catalysis using chiral metal complexes provides one of the most general and flexible methods for asymmetric synthesis.[1] Metals are known to possess a range of activities that can be influenced by ligand properties. The ligand, optimized for a given transformation, must have suitable functionalities, appropriate elements of symmetry, and substituents capable of differentiating the available space in the vicinity of the metal center. Such ligands act as templates that regulate reactions occurring in the coordination sphere of a metal ion.[2] Electron deficiency or Lewis acidity of the metal center is one of the fundamental properties explored in many asymmetric transformations. A delicate balance between steric and electronic factors determines the efficiency of a given process. In terms of ligand symmetry, $C_2$-symmetrical ligands possessing axial chirality have found particularly wide utility in asymmetric catalysis.[3]

Oxophilic metals, such as early transition metals, have been widely used as Lewis acids in combination with oxygen-containing ligands. 2,2′-Binaphthol (BINOL) and its derivatives have generated particular interest because their versatile backbone can be modified, thereby affecting the reaction environment by influencing the properties of the metal center. Substitution of BINOL may affect not only the steric environment around the metal center but also the electronic properties of the oxygen atoms, which are common constituents of the Lewis acidic metal complexes.

Although BINOL was first synthesized in 1926,[4] its potential as a ligand for metal-mediated catalysis was first recognized in 1979 by Noyori in the reduction of aromatic ketones and aldehydes.[5] BINOL itself, however, does not always give satisfactory results in asymmetric catalysis, and since Noyori's discovery there has been an ongoing interest in modified BINOL ligands. The outcome of a given asymmetric transformation depends on both steric and electronic properties of the chiral ligand. There-

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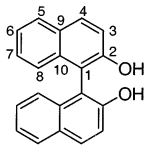
Shahla Yekta was born in Tehran, Iran, in 1977. She received her B.Sc. degree in chemistry at the University of Toronto in 1999, where she worked under the supervision of Professor Mark Lautens for two summers. She joined the group of Professor Andrei K. Yudin for her final year research project and is currently pursuing her Ph.D. degree in the Yudin group in the area of catalytic applications of fluorine-containing binaphthyls.

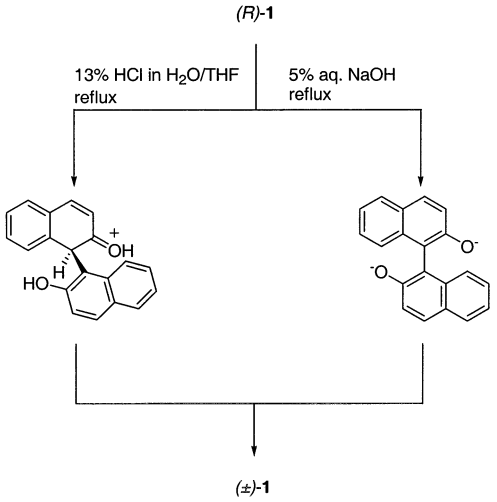



**1**

**Figure 1.**

Andrei K. Yudin received his bachelor's degree (Honors) in 1992 from Moscow State University. He then entered the graduate program in chemistry at the University of Southern California, Los Angeles, where he worked in the laboratories of Professors G. K. S. Prakash and George A. Olah. In 1996, he received his Ph.D. degree, working on applications of selective introduction of fluorine into organic molecules. Shortly thereafter, he joined the research group of Professor K. Barry Sharpless at the Scripps Research Institute, La Jolla, CA, where he carried out research in transition metal catalysis. In 1998, he accepted an Assistant Professor position at the Department of Chemistry, University of Toronto, and became Associate Professor in 2002. Dr. Yudin is the recipient of a Research Innovation Award (Research Corporation), Premier's Research Excellence Award, and Cottrell Scholar Award. His research interests are in design and development of new chemo- and stereoselective transformations, with particular emphasis on nitrogen-transfer methodologies, selective fluorine transfer, asymmetric synthesis, and electrosynthesis.

**Scheme 1**




fore, strategic placement of substituents within the framework of a given BINOL derivative may lead to improved catalysts.

The purpose of this review is to discuss the synthesis of modified BINOL ligands as well as their applications in asymmetric homogeneous catalysis through the end of 2002. Examples that demonstrate the power of BINOL-derived ligands in asymmetric catalysis will be discussed.

## *II. Synthesis of Modified BINOL Ligands*

BINOL **1** (Figure 1) is a white solid with a melting point of 208−210 °C and a p$K_a$($H_2O$) value of 10.28.[6b]

BINOL is soluble in most organic solvents (such as THF, MeCN, DMSO, methanol, dichloromethane, etc). Although resistant toward racemization under neutral conditions, BINOL is known to racemize under basic or acidic conditions (Scheme 1).[6] Under acidic conditions, the $C_1$ atom is protonated, resulting in a cationic species in which the naphthyl rings can rotate about the C($sp^2$)−C($sp^3$) bond. In basic media, the hydroxyl groups are easily deprotonated. The resulting dianionic intermediate undergoes rotation about the C1−C1′ bond due to diminished steric hindrance, leading to partial racemization.[6a]

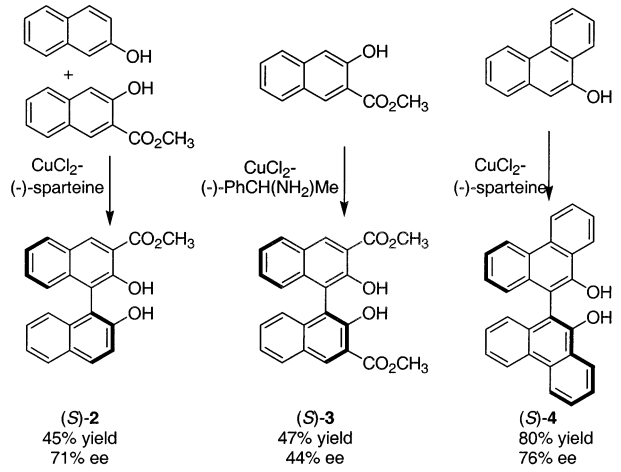
The original synthesis of BINOL, reported by Pummerer et al. in 1926, involves facile oxidative coupling of the two naphthol units induced by $FeCl_3$.[4] Since then, a wide range of other coupling methods for the preparation of both enantiomerically pure and racemic BINOL ligands have been developed. Gener-

ally, there are two methods for the preparation of chiral binaphthol ligands: (a) through coupling reactions of substituted naphthol units and (b) through regioselective modification of the binaphthol scaffold. Both methods have received considerable attention.

## A. Coupling Methods

Smrčina and Kočovský reported an enantioselective oxidative coupling of naphthols induced by a $CuCl_2$/chiral amine combination.[7] In the presence of a stoichiometric amount of the coupling reagent ($CuCl_2$−chiral amine), both the cross-coupling product **2** and the self-coupling products **3** and **4** were obtained in fair to good chemical yields and enantioselectivities (Scheme 2).[8]

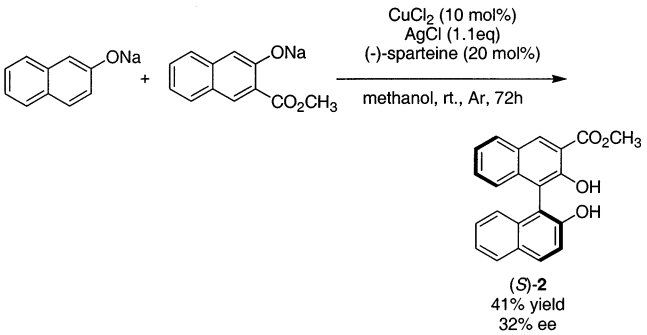
**Scheme 2**



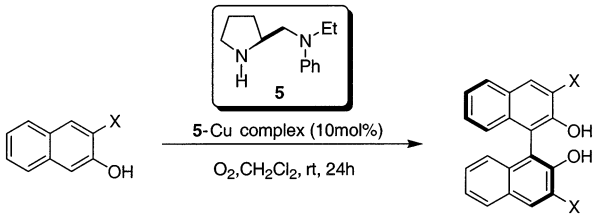

A catalytic version of the cross-coupling between the sodium salts of 2-naphthol and 3-(methoxycarbonyl)-2-naphthol was also described in detail. Using 10 mol % of $CuCl_2$ (with 1.1 equiv of AgCl) and 20 mol % of (−)-sparteine, the cross-coupling product **2** was obtained with 32% enantiomeric excess (ee) and 41% yield (Scheme 3). Although the yield and enantioselectivity were moderate, this is the first example of a catalytic, oxidative asymmetric coupling reaction to afford a binaphthol system.

Nakajima and co-workers later reported a more efficient process for the aerobic oxidative coupling of 2-naphthol derivatives.[9] These oxidative couplings proceed smoothly in the presence of a catalytic amount of Cu(OH)Cl·TMEDA (>90% yield). By introducing chiral diamines derived from L-proline as chiral ligands, the enantioselective oxidative coupling

**Scheme 3**




**Scheme 4**




| X | Yield (%) | ee (%) |
|---|---|---|
| $CO_2Me$ | 85 | 78 |
| COMe | 71 | 37 |
| H | 89 | 17 |
| $^i$Pr | 58 | 5 |

of 2-naphthols was achieved in good yields (Scheme 4). The diamine **5**, containing secondary nitrogen in the pyrrolidine ring and an ethylaniline moiety as the side-chain nitrogen center, was found to be a superior choice for asymmetric induction. The ester group at the 3-position of the naphthol ring was also found to be a crucial determinant for the enantioselectivity of this oxidative coupling. The best result was obtained in the coupling of 3-(methoxycarbonyl)-2-naphthol (85% yield, 78% ee). A variety of 2-naphthols having ketone, amide, alkyl, or alkoxy substituents at the 3-position were examined under similar reaction conditions. In all cases, the corresponding modified binaphthols were obtained with low enantioselectivities (<37% ee).

Kozlowski described another enantioselective oxidative coupling of 2-naphthol derivatives, catalyzed by a CuI−1,5-diaza-*cis*-decalin (Figure 2) complex.[10] Similar to Nakajima's example, the best result was observed in the homocoupling of 3-(methoxycarbonyl)-2-naphthol (93% ee, 85% yield). The enantioselectivity was dramatically reduced in the absence of the 3-carboxylate functionality.

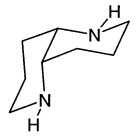
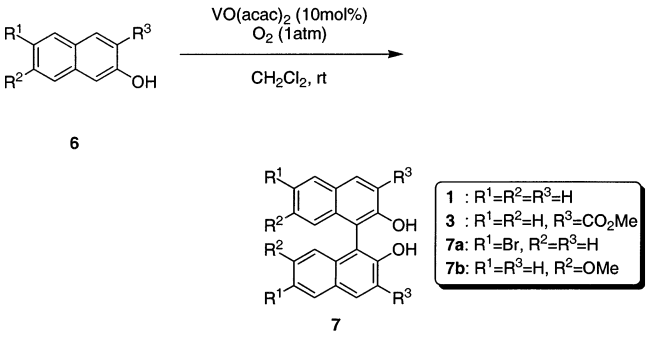



**Figure 2.**

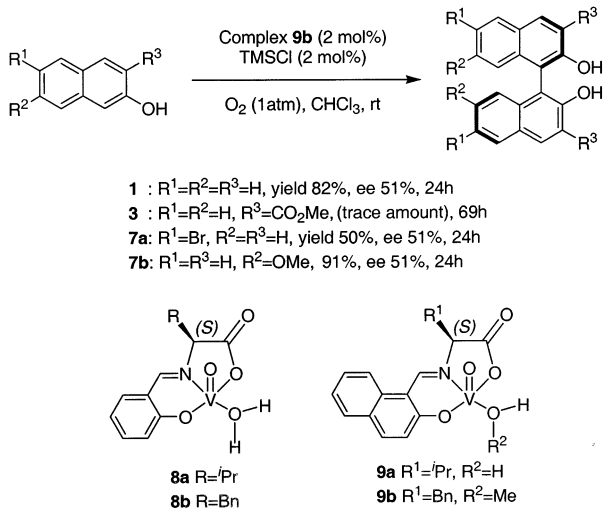
Uang and co-workers reported a catalytic oxidative coupling of 2-naphthols induced by $VO(acac)_2$.[11] Molecular oxygen and dichloromethane were found to be the best oxidant and solvent, respectively, for this coupling reaction. Under optimized conditions, the parent BINOL **1** and 6,6′-dibromo-BINOL **7a** were obtained in greater than 90% yields in 24 h, whereas 7,7′-dimethoxy-BINOL **7b** was obtained in lower yield (76%) after 9 h. The reaction of 3-(methoxycarbonyl)-2-naphthol **3** was very sluggish. The corresponding product was obtained in 35% yield after 120 h, and 62% of the starting material was recovered (Scheme 5).

Replacement of the acac ligand in this catalyst by chiral bidentate ligands, such as 3-formylcamphor and 3-heptafluorobutyrylcamphor, did not lead to any

**Scheme 5**



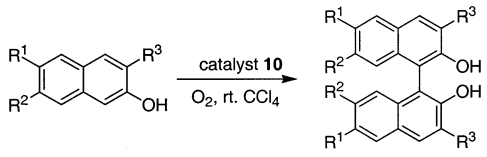

**Scheme 6**



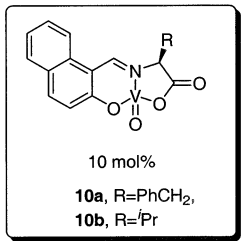

enantioselectivity in coupling products. The authors further employed chiral tridentate oxovanadium complexes **8** and **9**[12] in the coupling reaction.[13] It was found that, by adding 2 mol % of TMSCl, complex **9b** (2 mol %) exhibited the highest enantioselectivity and reactivity in chloroform. A yield of 82% with 51% ee was observed in the coupling reaction of 2-naphthol. The same enantioselectivity was observed in the coupling reaction of other 2-naphthol derivatives, but the reaction rate increased with the electron-donating capacity of the substituents on the 2-naphthol. The reaction was completely suppressed in the presence of the 3-(methoxycarbonyl) substituent (Scheme 6).

Chen and co-workers reported an asymmetric coupling of 2-naphthol derivatives catalyzed by chiral tridentate oxovanadium(IV) complexes derived from salicylaldehyde/hydroxy-substituted naphthaldehydes and α-amino acids.[14] Among the 17 vanadyl catalysts tested in the coupling reaction of 2-naphthols, catalysts **10a** and **10b** provided the best results (Scheme 7). Various 3,3′-, 6,6′-, and 7,7′-substituted bi-2-naphthols can be synthesized using this method in high yields (75−100%) with marginal to modest enantioselectivities (35−68%). A reversal in asymmetric induction is observed only when an alkoxy substituent is at the C3 of 2-naphthol ($R^1$ = OMe, OBn). Increasing the steric bulk at this position ($R^1$ = $CPh_2(OH)$) reduced the enantioselectivity of the coupling process (35% ee). Substitutions with methoxycarbonyl and hydroxymethyl groups at the C3 of 2-naphthol suppressed the coupling entirely.

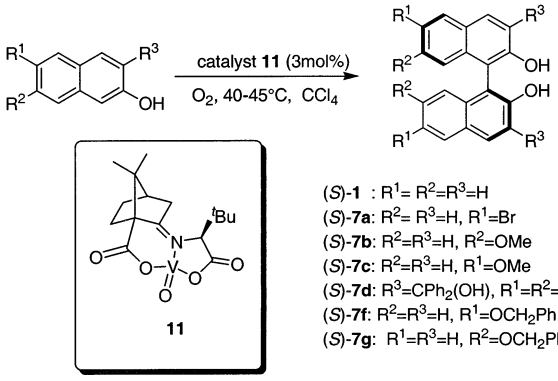
**Scheme 7**




(*R*)-**1** ($R^1$=$R^2$=$R^3$=H): yield = 94%, ee = 62%
(*R*)-**7a** ($R^1$=Br, $R^2$=$R^3$=H): yield = 97%, ee = 52%
(*R*)-**7b** ($R^1$=OMe, $R^2$=$R^3$=H): yield = 100%, ee = 39%
(*R*)-**7c** ($R^1$=$R^3$=H, $R^2$=OMe): yield = 86%, ee = 58%
(*R*)-**7d** ($R^3$=$CPh_2(OH)$, $R^1$=$R^2$=H): yield = 98%, ee = 35%
(*S*)-**7e** ($R^3$=OMe, $R^1$=$R^2$=H): yield = 75%, ee = 56%



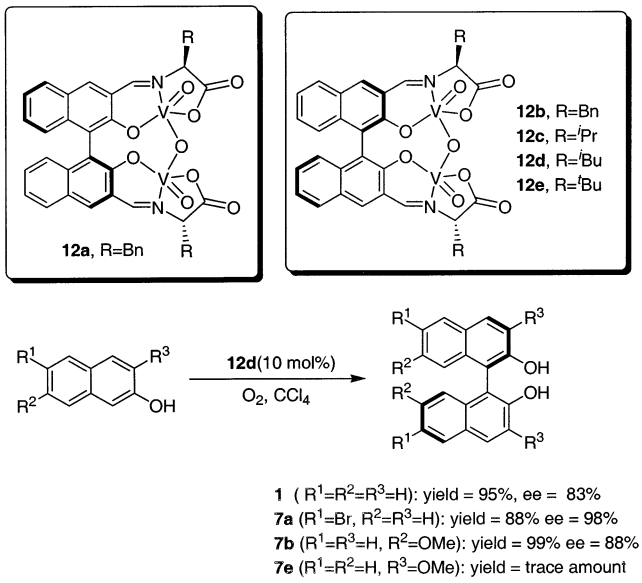

**Scheme 8**



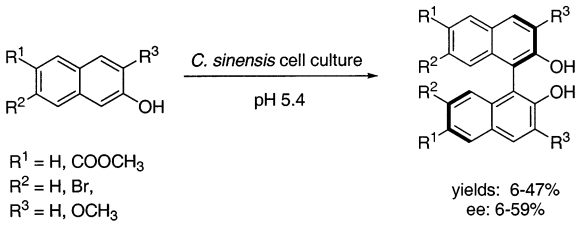

The tridentate *N*-ketopinidene-based oxovanadium-(IV) complex **11** was developed for the oxidative coupling of 2-naphthols (Scheme 8).[15] It was found that the coupling rates and enantioselectivities were highly dependent on the sterically demanding $^t$Bu group of the catalyst. Under optimal reaction conditions (40−45 °C, with a stream of oxygen gas, 3 mol % of catalyst **11**), moderate to good enantioselectivities (42−87% ee) were achieved in the asymmetric coupling reactions of 2-naphthols with various C3, C6, and C7 substituents. Lower asymmetric inductions were observed in the couplings of 6-substituted 2-naphthols (42−64% ee). The coupling reactions of 3-substituted 2-naphthols either were far less enantioselective or did not proceed at all. The only satisfactory example reported was 3-(1-hydroxy-1,1-diphenylmethyl)-2-naphthol, whose coupling product (*S*)-**7d** was obtained in 76% ee and 61% yield (Scheme 8).

Gong and co-workers described another class of chiral oxovanadium(IV) complexes **12** for enantioselective oxidative coupling of 2-naphthols (Scheme 9).[16] Catalyst **12d** gives rise to the highest enantioselectivities. 7,7′-Dimethoxy-BINOL **7b** was produced in 88% yield and 98% ee. This is the best result for this type of catalytic asymmetric coupling reactions reported thus far. Substitution with a methoxy group at the C3-position of 2-naphthol suppressed the

**Scheme 9**




**Scheme 10**



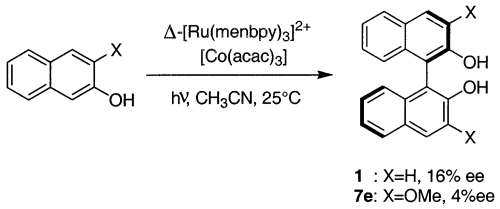

coupling reactivity. 3,3′-Dimethoxy-BINOL **7e** was not produced using this catalyst system. In both Chen's and Gong's examples, the reactions were sluggish. It generally took more than 7 days for the reactions to complete.

Enantioselective oxidative coupling of 2-naphthol derivatives has also been accomplished using *Camellia sinensis* cell cultures as catalysts.[17] *Camellia sinensis* cell culture is an efficient source of peroxidase enzymes, and it was originally applied to the oxidative coupling of dibenzylbutanolides with quantitative yield.[18] Maximum yield and enantioselectivity were obtained in the case of (*R*)-BINOL (47% and 59% respectively) when the reaction was performed at room temperature with freely suspended cell culture in B5 medium at pH 5.4 with 0.5 mL of 30% $H_2O_2$. In the absence of foreign hydrogen peroxide, both yields and enantioselectivities were lower. When the naphthol was substituted, both lower yields and enantioselectivities were obtained (Scheme 10).

Ohkubo et al. reported a photocatalytic asymmetric synthesis of (*R*)-(+)-1,1′-bi-2-naphthol derivatives by oxidative coupling of 2-naphthols using the chiral ruthenium complex M($C_3$)-Δ-[Ru(menbpy)$_3$]$^{2+}$ (menbpy = 4,4′-di-(1*R*,2*S*,5*R*)-(−)-menthoxycarbonyl-2,2′-bipyridine) with [Co(acac)$_3$] as the oxidant (Scheme 11).[19] Only 16% ee was obtained in the coupling reaction of 2-naphthol, and 4% ee was observed in the reaction of 3-methoxy-2-naphthol.

Photoactivated asymmetric aerobic oxidative coupling of 2-naphthol derivatives can also be achieved using the chiral (NO)Ru(II)−Salen complex **13** shown in Figure 3.[20] The reaction occurs under irradiation

**Scheme 11**




with visible light generated by a halogen lamp at room temperature in toluene to give BINOL as the sole product in 65% yield and 57% ee.[21] Although the mechanism is not clear, it has been suggested that a single electron-transfer process is involved in the oxidative coupling.

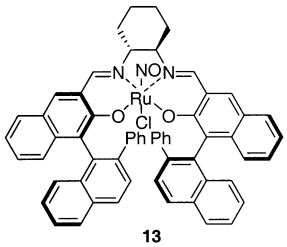
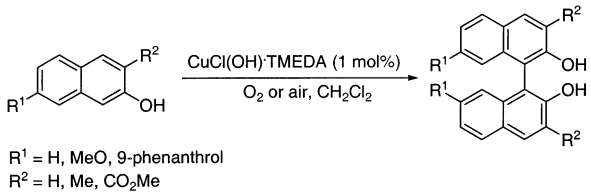



**Figure 3.**

Aerobic oxidative couplings with CuCl−amine complexes have also been successful with substituents at the 7-position of the naphthol moiety. Noji and coworkers reported an efficient oxidative coupling of naphthol derivatives using a catalytic amount of Cu(OH)Cl·TMEDA (1 mol %).[22] A variety of substituted 2-naphthols were coupled to give 7,7′-substituted binaphthols in high yields (Scheme 12).

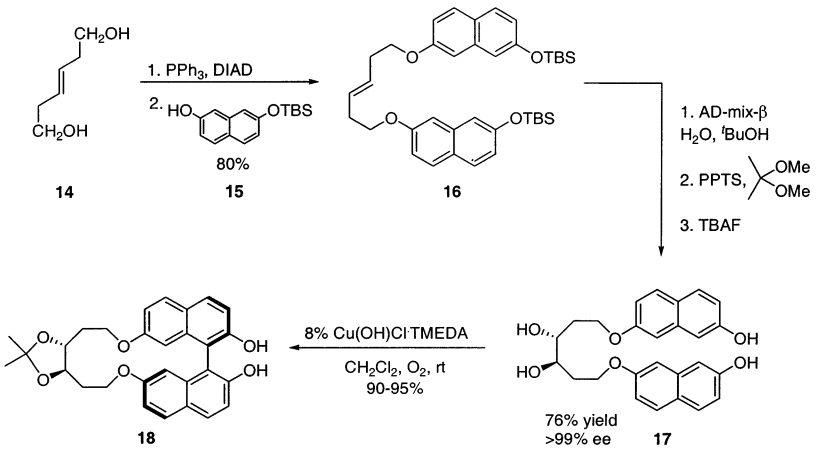
**Scheme 12**



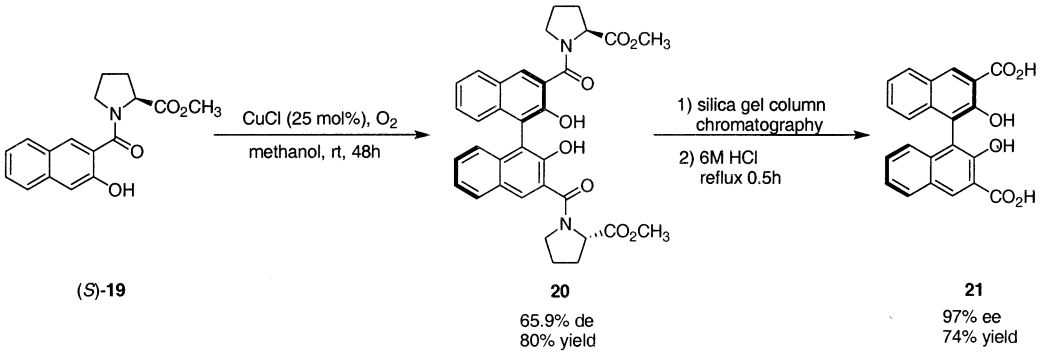

Reaction temperatures were varied, depending on the substrate. In the case when $R^1$ and $R^2$ are hydrogens, the reaction was run at 0 °C with 96% yield. When $R^2$ was an ester, the corresponding product was obtained in 99% yield at reflux. When $R^1$ was MeO, the product was obtained at room temperature in 95% yield. Yields were similar whether the oxidant was air or $O_2$; however, reaction times were considerably shorter when $O_2$ was used as the oxidant.

Lipshutz and co-workers have reported an intramolecular asymmetric coupling approach to the synthesis of binaphthol analogues.[23] This approach involves linking two naphthol moieties with a chiral tether, followed by an intramolecular copper-catalyzed oxidative coupling to generate nonracemic binaphthol products (Scheme 13). Diol **14** was prepared by reduction with LAH of commercially available (*E*)-β-hydromucconic acid. A double Mitsunobu reaction using monosilylated naphthalenediol **15** afforded **16** in 80% yield. Sharpless asymmetric

**Scheme 13**




**Scheme 14**



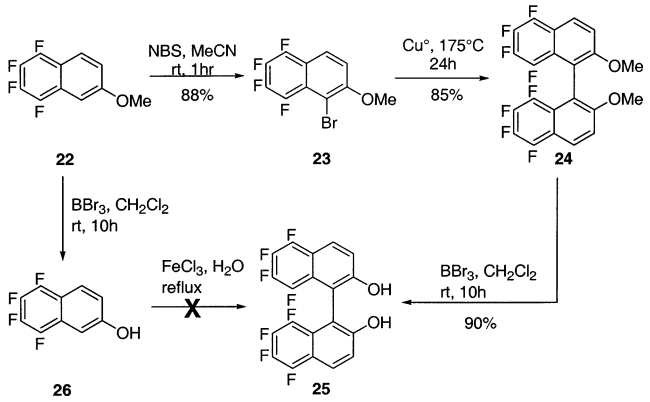

dihydroxylation using AD-mix-$\beta$, followed by protection and deprotection steps, resulted in compound **17** in high enantioselectivity. Oxidative coupling using CuCl(OH)·TMEDA in $CH_2Cl_2$ in the presence of oxygen gave the desired binaphthol **18** in 90−95% isolated yield as a 12:1 mixture of separable diastereomers.

Wang's group described a synthesis of 2,2′-dihydroxy-1,1′-binaphthyl-3,3′-dicarboxylic acid **21** by the CuCl-catalyzed diastereoselective oxidative coupling reaction of (*S*)-**19** (Scheme 14).[24] The diastereomeric excess (de) of 66% and chemical yield of 80% for the amide product **20** were obtained in methanol using 25 mol % of CuCl as catalyst after 48 h. Silica gel column chromatography and hydrolysis in 6 M aqueous HCl afforded **21** in 74% yield with 97% ee.

Microwave-assisted oxidative coupling of 2-naphthols has also been reported recently.[25] The advantage of such processes is much shorter reaction times (1−180 min). Yields are generally between 80 and 90%, depending on the substrate.

Partially fluorinated binaphthols have been recently synthesized through reductive coupling of the tetrafluoronaphthol derivatives (Scheme 15). 2-Methoxy-5,6,7,8-tetrafluoro-2-naphthol (**22**) was prepared through a Diels−Alder reaction between tetrafluorobenzyne and 3-methoxythiophene. An in situ extrusion of sulfur gave **22** in 52% yield.[6b] Demethylation with $BBr_3$ gave 5,6,7,8-tetrafluoronaphthol **26**, which did not undergo the $FeCl_3$-catalyzed oxidative coupling commonly used for the preparation of BINOL.[4] This lack of reactivity is believed to be a result of the relatively high oxidation potential of **26**

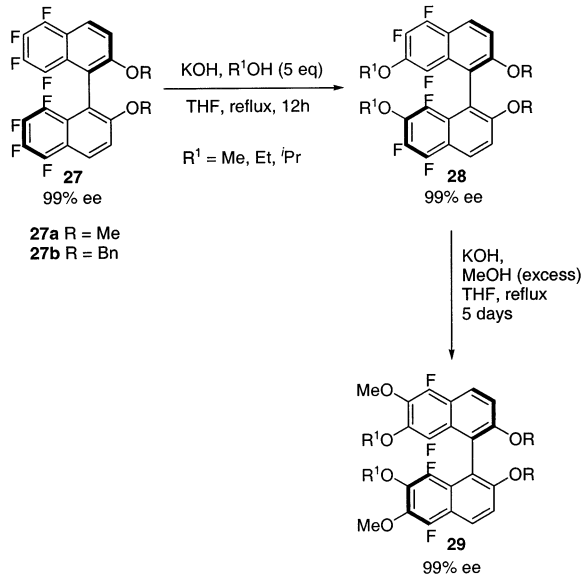
**Scheme 15**



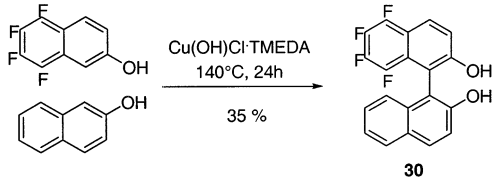

(1.84 V vs Ag/AgCl). The reductive Ullmann coupling was therefore chosen through the brominated derivative **23** to give the desired bis(methoxy) product **24** in 85% yield. Demethylation gave racemic product **25**, which was resolved through fractional crystallization of the bis[(−)-menthoxycarbonyl] derivatives to afford enantiomerically pure $F_8$-BINOL **25**.

These fluorinated ligands can be readily modified through nucleophilic aromatic substitution of fluorines at the 7,7′- and 6,6′-positions.[26] This chemistry provides a mild route to develop functionalized ligands with axial chirality. The enantiomeric purity of the ligand does not change during these substitutions. Various alcohols have been used as nucleophiles (Scheme 16), and the corresponding products can be obtained in moderate to good yields (69−80%). It should be noted that the 2,2′-hydroxyl groups on

**Scheme 16**




**Scheme 17**[a]




[a] TMEDA = tetramethylethylenediamine.

$F_8$-BINOL require protection (compound **27**), because when the unprotected ligand was subjected to sodium alkoxide, a complicated mixture of poly(alkoxylated) products was obtained. Compound **29** was obtained in 32% yield by refluxing the 7,7′-substituted **28** with excess sodium methoxide for 5 days.

Tetrafluorobinaphthol ($F_4$-BINOL, **30**) has also been successfully synthesized.[27] Oxidative cross-coupling with Cu(OH)Cl·TMEDA was successful only in moderate yields (Scheme 17). A reductive pathway similar to that of $F_8$-BINOL was therefore attempted in order to improve the overall yield of the reaction. However, Ullmann coupling between **23** and 1-bromo-2-methoxynaphthol resulted in only 5% yield of the desired product, and the major product observed was $F_8$-BINOL in 85% yield. This result was not surprising since the reductive coupling reaction is in favor of electron-poor substrates. To increase the yield of the cross-coupling reaction, aldehyde **31** was used instead of 1-bromo-2-methoxynaphthol in the Ullman coupling reaction (Scheme 18).

Aldehyde **32** was then oxidized through a Baeyer−Villiger reaction with *m*-CPBA, followed by hydrolysis to give alcohol **33** in 64% yield (two steps). Demethylation with $BBr_3$ afforded racemic $F_4$-BINOL in 92% yield (28% overall yield). Resolution was accomplished using a procedure similar to that used with $F_8$-BINOL. Well known for its sensitivity to steric bulk around the incipient C−C bond, Suzuki coupling has never been successful in attempts to make $F_4$-BINOL.

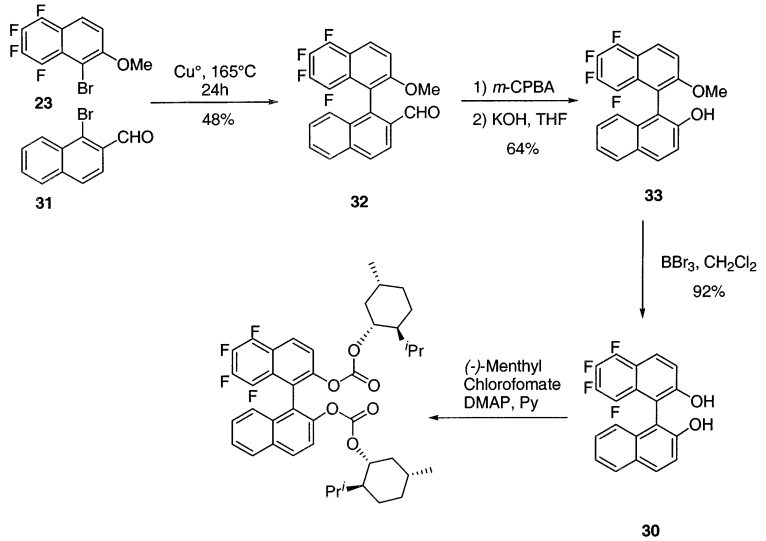
## B. Substitution on BINOL

### *1. 3,3′-Substituted BINOL Ligands*

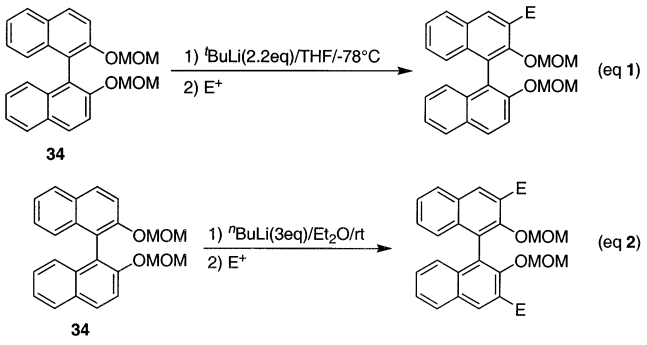
Substituents at the 3-position of BINOL are normally introduced via a two-step protocol that involves treatment of a suitably protected BINOL with an organolithium reagent, followed by reaction with an electrophile. For instance, Cram and co-workers prepared a series of 3,3′-disubstituted BINOLs via Mannich intermediates[28] and, in two diaryl cases, by Grignard cross-coupling reaction of 3,3′-dibromo-BINOL dimethyl ether and arylmagnesium bromides employing dichlorobis(triphenylphosphine)nickel(II) as the catalyst.[29]

Snieckus and co-workers reported an expedient synthetic route to 3- or 3,3′-substituted 1,1′-bi-2-naphthols by directed ortho-metalation and Suzuki cross-coupling methods.[30] 3-Substituted or 3,3′-disubstituted products can be obtained by controlling the amount of the organolithium reagent ($^t$BuLi). Using 2.2 equiv of $^t$BuLi (THF/−78 °C/1 h) was found to be the optimal condition for the preparation of 3-substituted BINOLs (Scheme 19, eq 1). The generation of the dianion of methoxymethyl (MOM)-

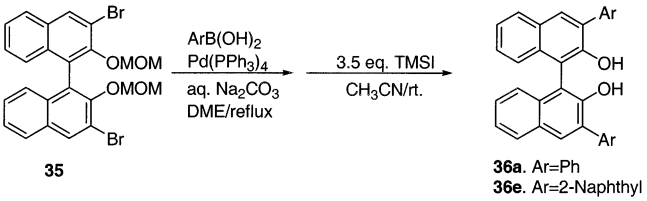
**Scheme 18**



**Scheme 19**




**Scheme 20**




BINOL **34** was optimally achieved by using 3 equiv of $^n$BuLi in $Et_2O$ at room temperature (Scheme 19, eq 2). These mono- or dianions can be further treated with diverse electrophiles in situ to afford the desired 3-substituted or 3,3′-disubstituted BINOL derivatives in good to excellent yields with no loss of enantiomeric purity. 3-Substituted MOM-BINOL can be used to introduce different substituents at the 3′-position, resulting in the 3,3′-disubstituted derivatives. Metalation/chlorination or bromination of 3-substituted MOM-BINOL (E = SPh) has led to 3-chloro or 3-bromo-3′-thiophenyl products in 84% and 72% yield, respectively.

Treatment of **35** with phenyl- or 2-naphthylboronic acids under modified Suzuki cross-coupling conditions, followed by MOM deprotection, gave **36a** and **36e** in 87% and 85% yields, respectively (Scheme 20).

Jørgensen et al. reported another synthetic route toward 3,3′-diaryl-BINOLs **36** by the reaction of the 3,3′-diboronic acid of bis(methoxy)-BINOL with commercially available aromatic bromides by a Suzuki cross-coupling reaction (Scheme 21).[31] In most cases, the overall yield of the final product **36** was good (65−73%). However, the 3,3′-bis(2,6-dimethylphenyl)-BINOL was formed only in 22% yield, likely due to steric factors. The main byproduct was found to be the mono-arylated BINOL. Heteroaromatic bromides, such as 2-bromopyridine and 2-bromothiophene, were also tried for the preparation of 3,3′-bis(heteroaryl)-BINOLs; however, only low yields were obtained.

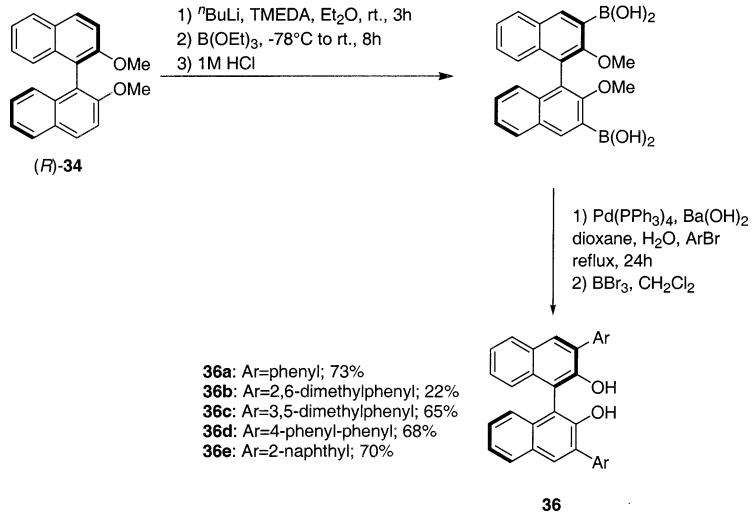
The synthesis of sterically hindered chiral 3,3′-bis-(trialkylsilyl)-1,1′-bi-2-naphthol (*R*)-**38** or (*S*)-**38** was reported by Yamamoto and co-workers, based on a facile 1,3-rearrangement of bis(trialkylsilyl ether) **37** with $^t$BuLi, as illustrated in Scheme 22.[32]

Pu and co-workers synthesized (*S*)-**41**, where multiple electron-withdrawing fluorine atoms were introduced to the 3,3′-aryl groups, by the Suzuki coupling of **39** with aryl bromides **40a**−**e**, followed by acidic hydrolysis (Scheme 23). Treatment of (*S*)-**41b** with bromine selectively introduced bromine atoms to the 6,6′-positions of the binaphthyl unit to generate ligand (*S*)-**41f**.[147]

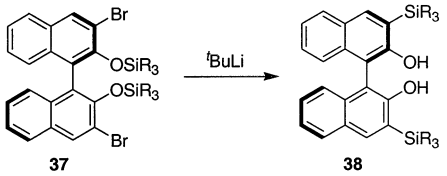
Ohta and co-workers described the synthesis of 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthol (BINOL-Box) ligands **43** starting from (*S*)-BINOL (Scheme 24).[33] The MOM-protected BINOL was subjected to ortho-lithiation, followed by carboxylation, to give the corresponding 3,3′-dicarboxylic acid. The acid was then transformed into acid chloride by exposing it to thionyl chloride, followed by treatment with chiral amino alcohols, to afford amides **42**. The amides **42** were halogenated with thionyl chloride, and the resulting compounds were cyclized in the presence of potassium carbonate to afford the BINOL-Box in good yields.

Katsuki and co-workers reported the synthesis of a new type of BINOL derivatives, 1,1′-bi-2-naphthol-3,3′-dicarboxamides **44**, and their application as chiral ligands in the asymmetric Simmons−Smith cyclopropanation of (*E*)-allylic alcohols.[34] Ligands **44** were prepared from (*R*)-BINOL in six steps, as outlined in Scheme 25. Reduction of **44** by $LiAlH_4$ gave **45** bearing tertiary aminomethyl groups at the 3,3′-carbons.

**Scheme 21**



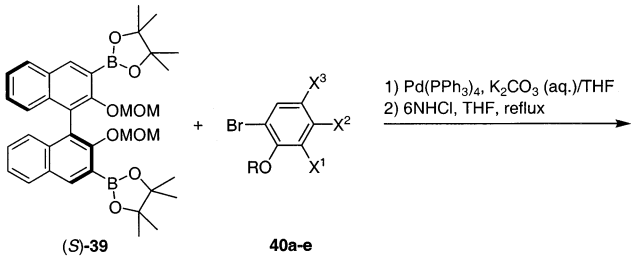
**Scheme 22**



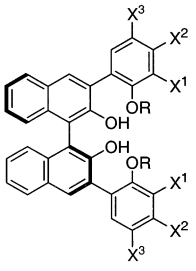

37 38

**38a**: R=Me
**38b**: $R_3$=$^t$BuMe$_2$
**38c**: R=Ph
**38d**: R=4-$^t$Bu-C$_6$H$_4$
**38e**: $R_3$=$^t$BuPh$_2$
**38f**: R=3,5-Xylyl

**Scheme 23**

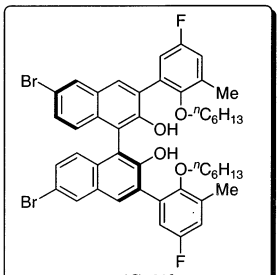



(*S*)-**39** **40a-e**




(*S*)-**41a-e**

**40-41a**: R=$^n$C$_6$H$_{13}$, X$^1$=X$^2$=H, X$^3$=F
**40-41b**: R=$^n$C$_6$H$_{13}$, X$^1$=Me, X$^2$=H, X$^3$=F
**40-41c**: R=$^n$C$_6$H$_{13}$, X$^1$=X$^2$=X$^3$=F
**40-41d**: R=$^n$C$_6$H$_{13}$, X$^1$=H, X$^2$=X$^3$=F
**40-41e**: R=Me, X$^1$=H, X$^2$=X$^3$=F




(*S*)-**41f**

Qian's group synthesized (*S*)-3,3′-bis(methoxyethyl)-BINOL **46** in an overall yield of 37% from (*S*)-BINOL in four steps (Scheme 26).[35]

Shibasaki and co-workers reported a novel class of linked BINOL ligands **47** (Figure 4), which introduced new possibilities for multifunctional asymmetric catalysis. The syntheses of both carbon-linked BINOLs **47a**−**c**[36] and oxygen-linked BINOL **47d**[37] have been described.

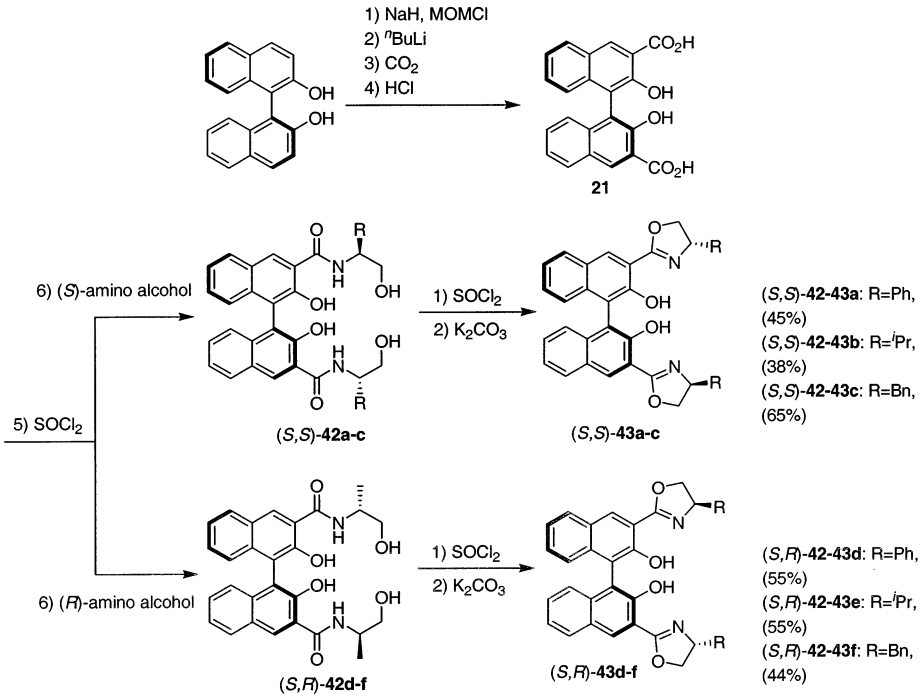
To synthesize (*R*,*R*)-**47a** (methylene-bridged bis-BINOL), the 3-lithiated MOM-protected BINOL was reacted with aldehyde **48** at −78 °C. After warming of the reaction to room temperature and workup, alcohol (*R*,*R*)-**49** was obtained in 62% yield. Treatment with sodium borohydride in trifluoroacetic acid afforded (*R*,*R*)-**47a** in 50% yield as pale yellow crystals (Scheme 27).

A synthetic approach to (*R*,*R*)-**47b** is outlined in Scheme 28. Reduction of aldehyde (*R*)-**50** with $NaBH_4$ in MeOH/THF at 0 °C yielded 3-(hydroxymethyl)-BINOL, which after mesylation, filtration of $Et_3N$·HCl, and treatment with LiBr in DMF gave the brominated compound in 83% overall yield. Reductive coupling of the latter in THF at 50 °C, followed by deprotection of the MOM group, afforded (*R*,*R*)-**47b** in 87% yield.

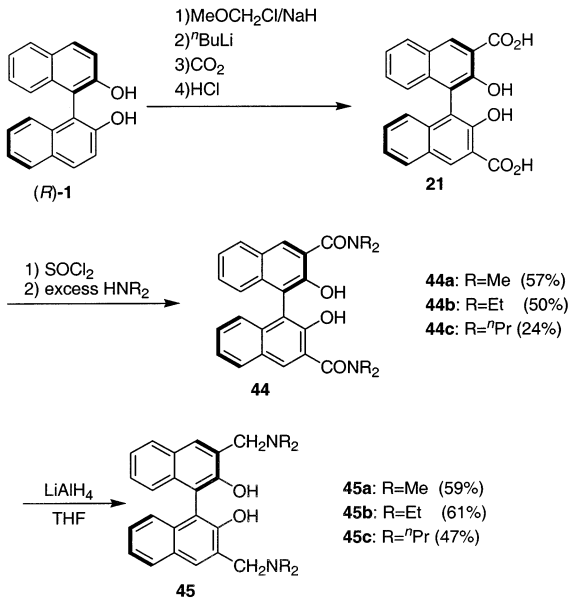
It is presumed that the oxygen atom in the linker coordinates to the metal center, creating complexes with suitable asymmetric environments. The Shibasaki group further prepared the oxygen-linked chiral ligand **47d** on the basis of the reports by Cram (Scheme 29).[37]

With the goal of developing novel Lewis acid−Brønsted base bifunctional catalysts, Shibasaki and Yoshikawa designed another class of oxygen-linked BINOL, **53a**.[38] Compared to ligand **47**, ligand **53a** consists of two hydroxyethyl groups at the 3′-positions of each binaphthol moiety. This newly devel-

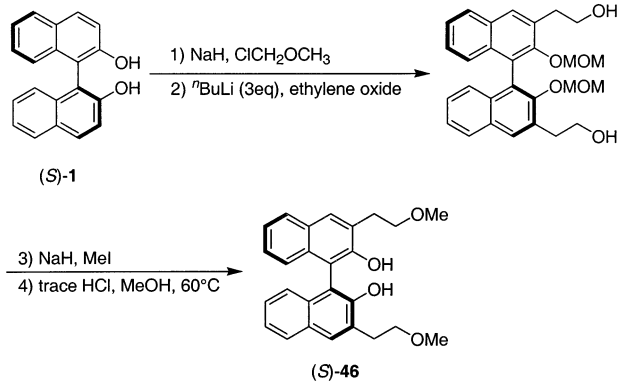
**Scheme 24**



**Scheme 25**




**Scheme 26**




oped Lewis acid−Brønsted base is different from the conventional heterobimetallic[39] and heteropolymetallic catalysts.[40] Scheme 30 summarizes the sequence for the synthesis of ligand **53a** starting from MOM-protected (*R*)-BINOL. The two hydroxyethyl groups were introduced at the 3,3′-positions of the naphthyl ring by treatment of the lithiated MOM-BINOL with an excess amount of ethylene oxide in the presence of $BF_3$·$OEt_2$. After one of the two hydroxyl functionalities was protected as an allyl ether, the MOM groups were replaced by benzyl groups. The remaining hydroxyl group was oxidized to aldehyde **52** by using Dess−Martin periodinane. The symmetrical ether was formed by reductive coupling of the aldehyde using triethylsilane in the presence of trimethylsilyl triflate. After deprotection of the allyl and benzyl groups, compound **53a** was obtained in 6% overall yield.

The phosphine oxide ligand **54** was synthesized in the Shibasaki laboratory from the MOM-protected

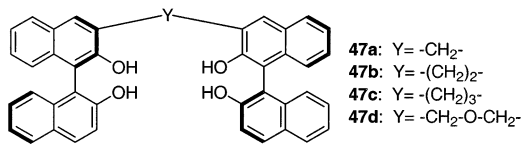
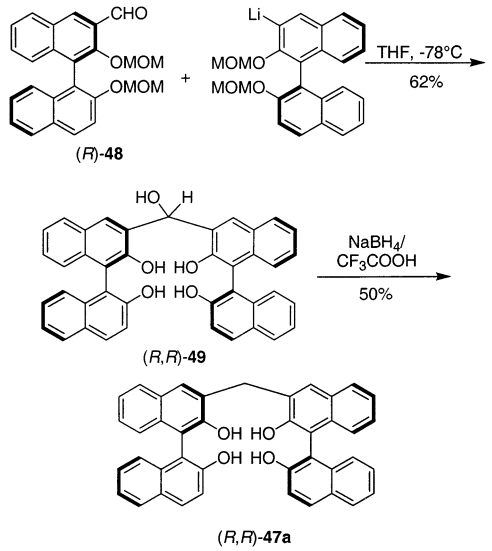
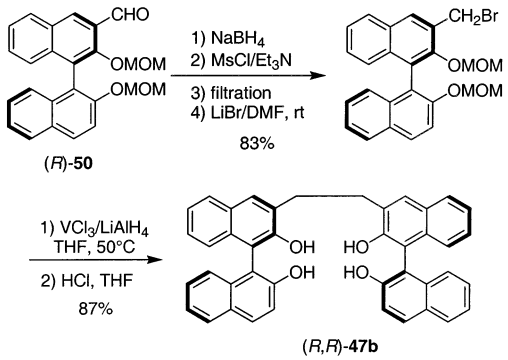



**Figure 4.**

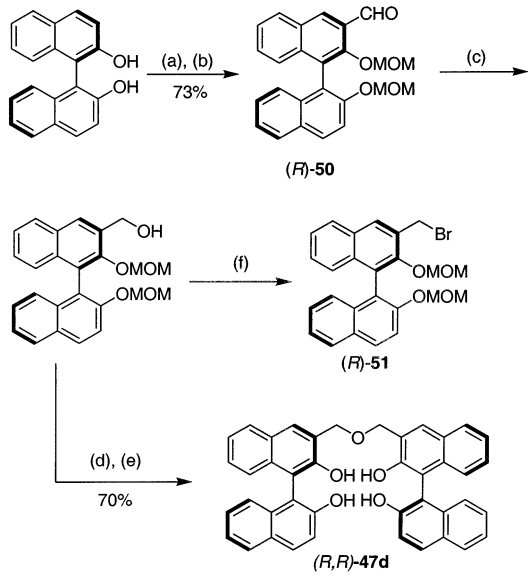
**Scheme 27**




**Scheme 28**



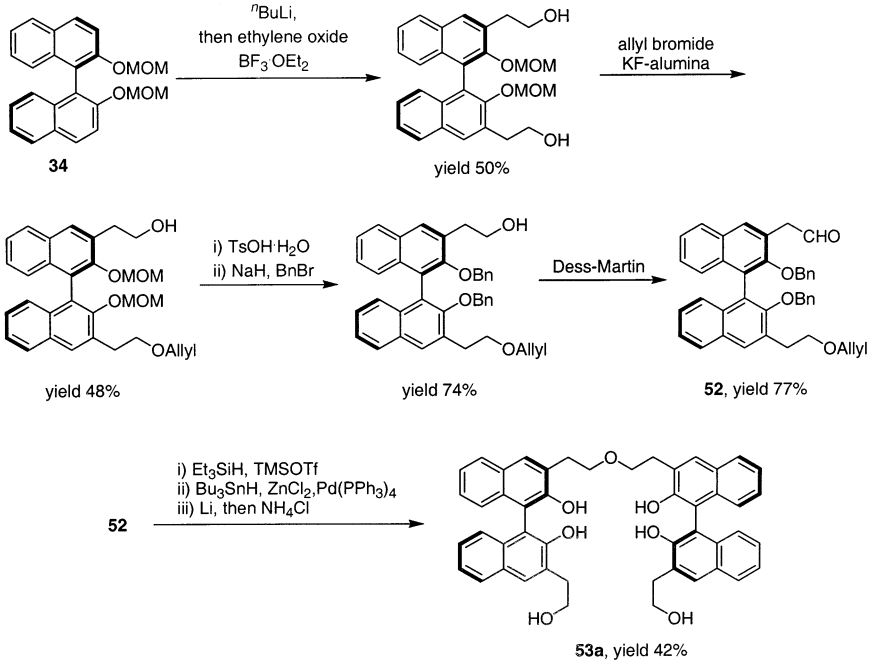

**Scheme 29**[a]



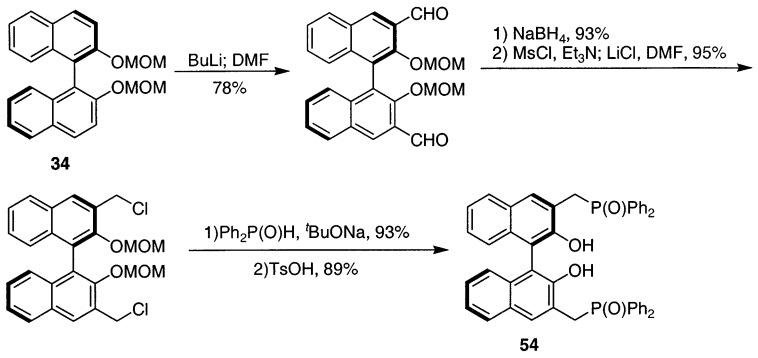

[a] Reagents and conditions: (a) NaH, MOMCl, DMF 0 °C, 5 h; (b) (i) BuLi, TMEDA, THF, −78 °C, (ii) DMF, −78 to 0 °C; (c) $NaBH_4$, THF, MeOH, 0 °C, 15 min; (d) (i) NaH, THF, DMF, 0 °C, 60 min, (ii) (*R*)-**51**, room temperature, 64 h; (e) TsOH−$H_2O$, $CH_2Cl_2$, MeOH, 40 °C, 36 h; (f) (i) MsCl, toluene, AcOEt, 0 °C, (ii) LiBr, DMF, room temperature.

BINOL derivative in high overall yield, as outlined in Scheme 31.

**Scheme 30**




**Scheme 31**




### *2. 6,6′-, 7,7′-, and/or 4,4′-Substituted BINOL Ligands*

The most common precursor to the 6,6′-disubstituted BINOL ligands described in the literature is the 6,6′-dibromo-1,1′-bi-2-naphthol (R = Br in Figure 5).

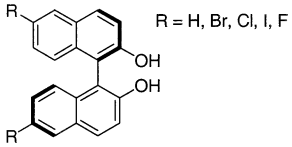
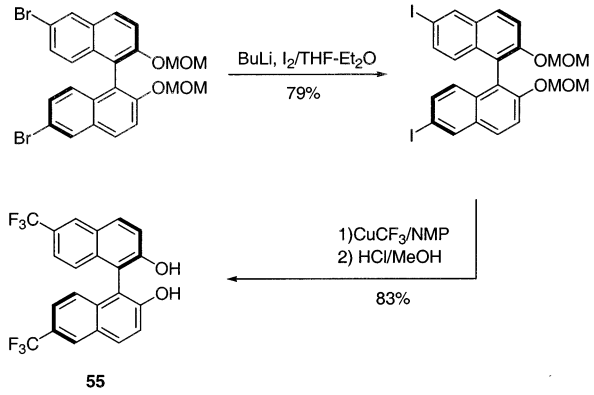



**Figure 5.**

This BINOL derivative is prepared via electrophilic aromatic bromination of BINOL.[41] Remarkably, if enantiomerically pure precursors are used, the enantiomeric purity of the BINOL starting material is maintained. The $Br_2$-BINOL is inexpensive and commercially available.[42] This readily available material has been used as an entry into a wide range of other derivatives. The protection of the hydroxyl groups (via formation of the MOM ether) allows for lithiation of the aryl bromide with $^n$BuLi, followed by reaction with various electrophiles, resulting in a variety of different 6,6′-disubstituted BINOL ligands (Figure 5).[43]

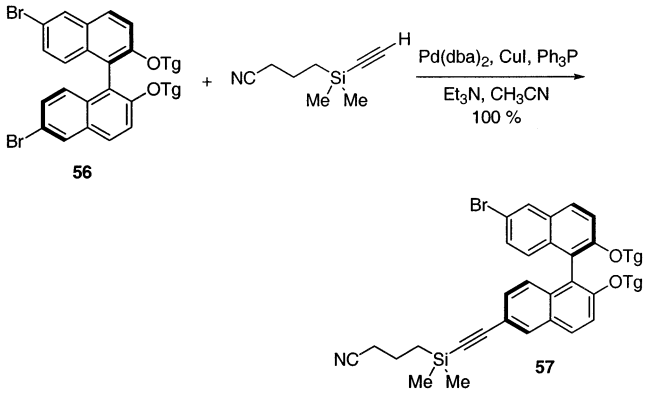
**Scheme 32**




Kobayashi and co-workers synthesized (*R*)-6,6′-bis-(trifluoromethyl)-1,1′-bi-2-naphthol (6,6′-$(CF_3)_2$-BINOL) by converting the bromo substituents at the 6,6′-positions into the iodo groups using $I_2$, and then to trifluoromethyl groups using $CuCF_3$ in *N*-methylpyrrolidin-2-one (NMP).[43] After deprotection of the MOM groups, 6,6′-$(CF_3)_2$-BINOL **55** was isolated (Scheme 32).

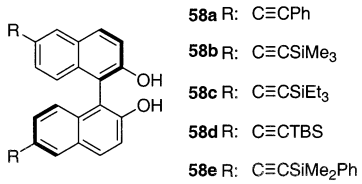
Other 6,6′-disubstituted ligands **57** and **58a**−**e** have been prepared through the Sonogashira cou-

**Scheme 33**[a]




[a] OTg = $O(CH_2CH_2O)_3CH_3$.

pling of $Br_2$-BINOL derivatives such as **56** with different alkynes (Scheme 33 and Figure 6). These substituents are especially useful in hetero-bimetallic catalysts. It is believed that these substituents modulate asymmetric space around the metal center of the catalyst.[45]




**58a** R: C≡CPh
**58b** R: C≡CSiMe$_3$
**58c** R: C≡CSiEt$_3$
**58d** R: C≡CTBS
**58e** R: C≡CSiMe$_2$Ph

**Figure 6.**

Other modifications on the binaphthol scaffold can be achieved in a similar way. The syntheses of selected examples of 3,3′,6,6′-substituted binaphthol derivatives are shown in Schemes 34 and 35. Compounds **59** and **61** are generated through the nucleophilic aromatic substitution of the $SiMe_3$ groups on binaphthol **60**. In turn, compounds **60** and **63** are

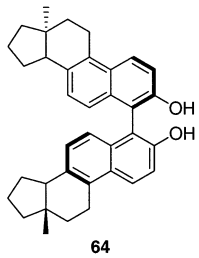



**Figure 7.**

synthesized using the typical 3,3′-substitution method with $^s$BuLi and $I_2$. Compound **62** is obtained by a coupling reaction with the corresponding 6,6′-diiodobinaphthol derivative.

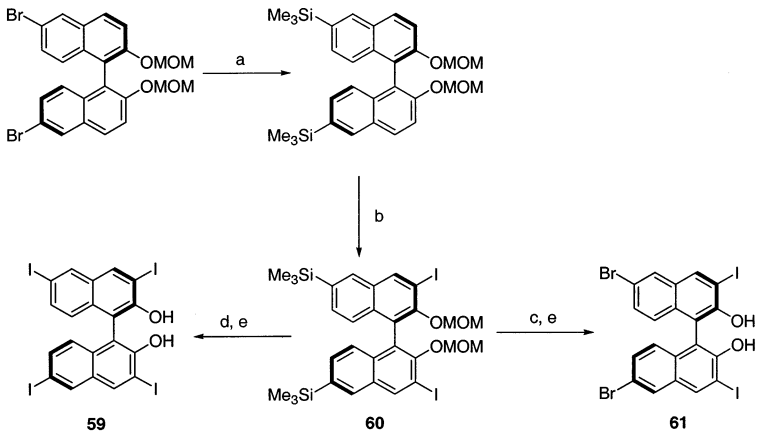
Other BINOL derivatives that have found application in asymmetric catalysis include steroid-derived systems (Figure 7). These ligands have been suitable for the Lewis acid-mediated asymmetric Torgov cyclizations[46] as well as the asymmetric sulfoxidation reactions (vide infra).[47] Ligand **64** was synthesized from the corresponding steroidal precursor equilenine **65**, as shown in Scheme 36.[48]

Equilenine was deoxygenated prior to the oxidative coupling, which afforded the diastereomers in a 1:1.5 ratio. The diastereomers were easily separated by column chromatography.

Fluorous BINOLs have proven to be efficient ligands in catalysis since they can be easily recovered and reused.[49−54] Fluorous BINOLs can be prepared through perfluoroalkylation of the corresponding bromo-BINOL **66** with Cu/$R_f$I in DMSO at elevated temperatures of 90−160 °C (Scheme 36).[53]

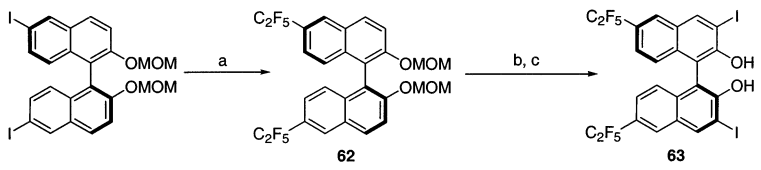
The corresponding perfluoroalkylated products such as **67** can be resolved by conventional methods through the formation of diastereomers by reaction with camphorsulfonyl chloride, followed by chromatographic separation.

**Scheme 34**[a]



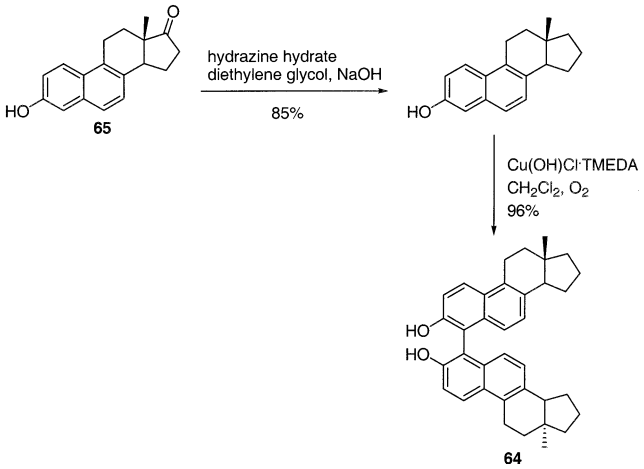

[a] Reagents: (a) $^n$BuLi, $Me_3SiCl$/THF; (b) $^s$BuLi, $I_2$/THF; (c) $Br_2/CCl_4$; (d) ICI/$CCl_4$; (e) HCl/MeOH.

**Scheme 35**[a]




[a] Reagents: (a) $Me_3SiC_2F_5$; KF, CuI/DMF; (b) $^s$BuLi, $I_2$/THF; (c) HCl/MeOH.

**Scheme 36**




Substituents at the 7,7′-positions of the binaphthol system have also proven useful in increasing the enantioselectivity of reactions by increasing steric bulk around the metal center. One such example is ligand **70**, prepared by Mikami and co-workers for the titanium Lewis acid-catalyzed [2 + 3] cycloaddition reaction between olefins and nitrones (Scheme 38).[55] Commercially available **68** was transformed to 7-bromo-2-naphthol **69** in 30% yield with $PPh_3$ and $Br_2$ at 300 °C. Oxidative coupling with Cu(OH)Cl·TMEDA (3 mol %) gave the 7,7′-substituted BINOL **70**, which was resolved by forming diastereomers with camphorsulfonyl chloride. The diastereomers were separated by column chromatography, and enantiopure **70** was obtained by hydrolysis with sodium hydroxide. Suzuki coupling of (*R*)-**70** with phenylboronic acid afforded the product **71** in 70% yield.

Binaphthyl-containing metalloporphyrins were synthesized from 6,6′-substituted binaphthol **7a** and were used in asymmetric hydroxylation, epoxidation, and sulfoxidation reactions.[56] Scheme 39 highlights the synthesis of these ligands. Methylation of **7a** with dimethyl sulfate in the presence of sodium methylate afforded the protected 2,2′-dimethoxy product, which was converted in situ to the corresponding 6,6′-dilithium derivative, which then reacted directly with dry carbon dioxide and finally was converted to the corresponding diacid dichloride **72**. This diacid dichloride was reacted with α,*β*,α,*β*-TAPP to afford the final product **73** in 79% yield.

Diederich and co-workers took advantage of the 7,7′-substitution on the binaphthyl scaffold to obtain optically pure ligands using chiral recognition of cinchona alkaloids.[57,58] The binaphthol derivative was synthesized through coupling of 2-benzyloxy-7-hydroxynaphthalene **74** with $CuCl_2$ and $^tBuNH_2$ (Scheme 40). Optical resolution of **7g** using cyclic phosphate intermediates **75** was performed by fractional crystallization of the diasteriomeric salts formed with cinchonine or chinconidine. Dephosphorylation resulted in optically pure **7g**.

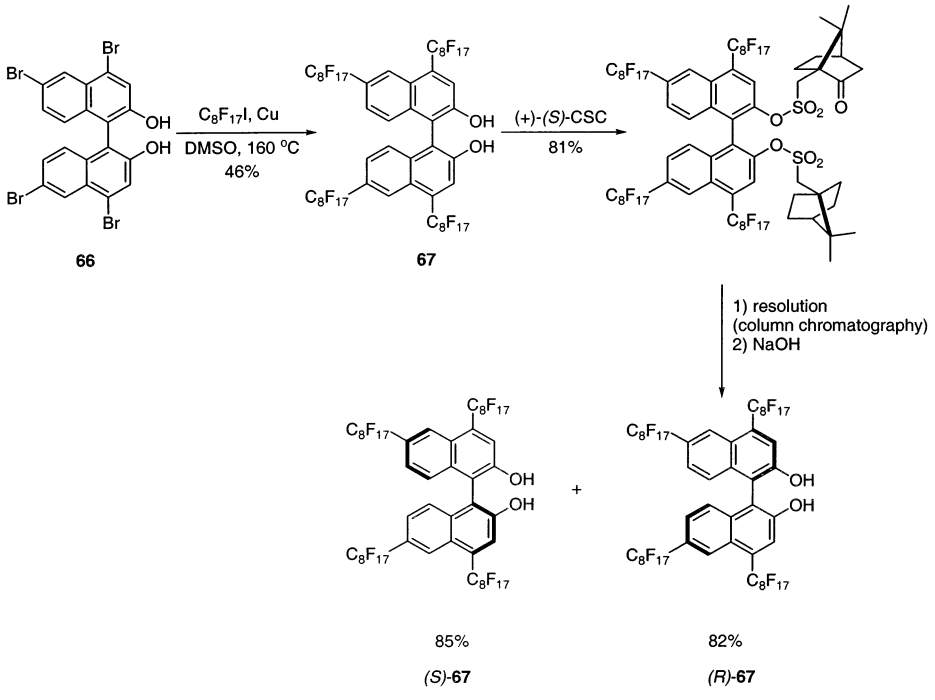
Partially hydrogenated BINOL ligands have also been synthesized from BINOL (Scheme 41).[28] If the reaction is conducted at 25 °C, the optical purity of the starting material is maintained. (*R*)-BINOL can thereby be reduced with hydrogen over platinum in glacial acetic acid to give (*R*)-**76** ($H_8$-BINOL) in 92% yield.

## *III. Carbon–Carbon Bond-Forming Reactions*

### A. Mannich-Type Reaction

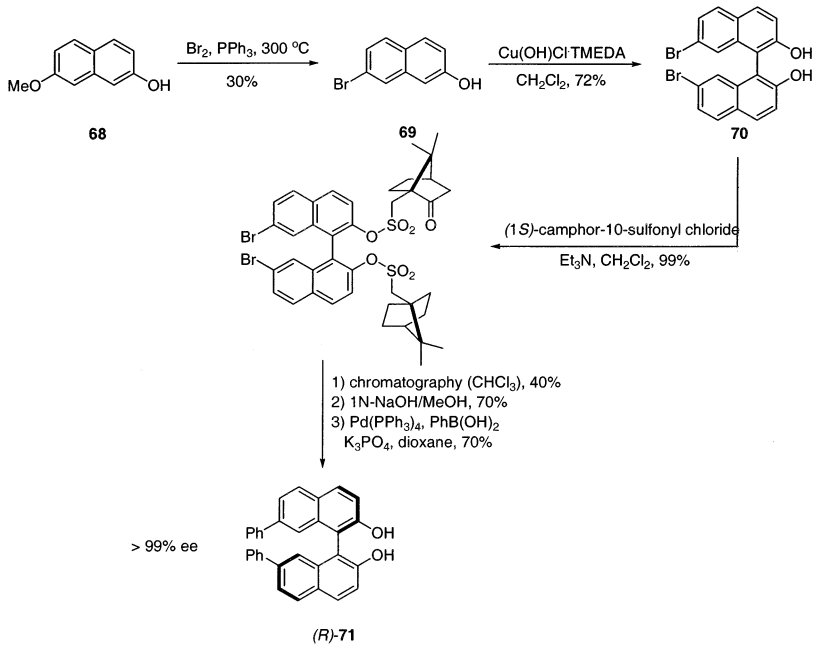
Asymmetric Mannich-type reactions provide useful routes to chiral *β*-amino ketones or esters, which are versatile chiral building blocks for the synthesis of

**Scheme 37**[a]

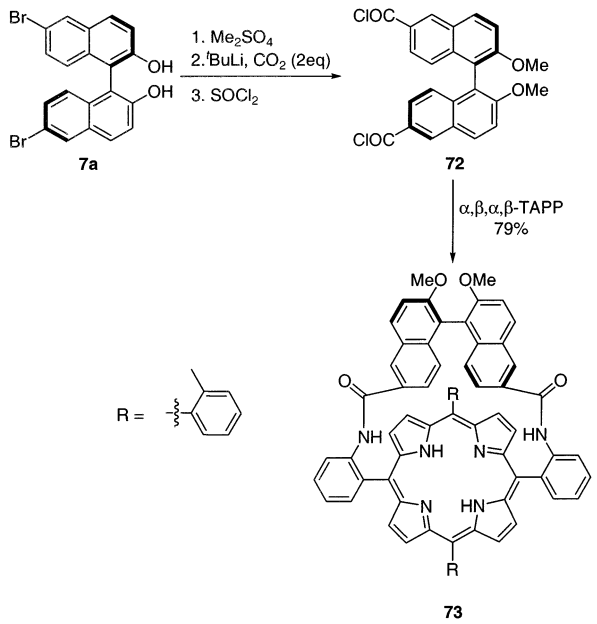



[a] CSC = camphorsulfonyl chloride.

**Scheme 38**

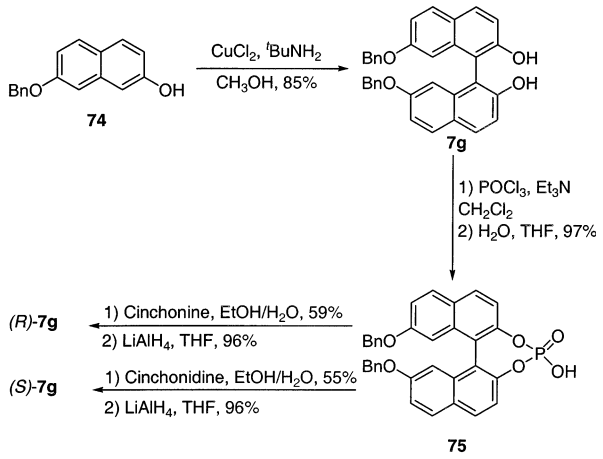



**Scheme 39**[a]

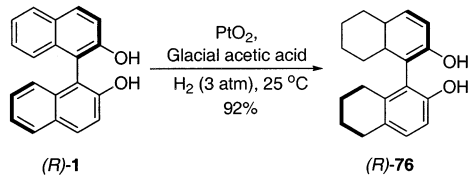



[a] α,β,α,β-TAPP = 5α,10β,15α,20β-tetra(*o*-aminophenyl)porphyrin.

**Scheme 40**




**Scheme 41**

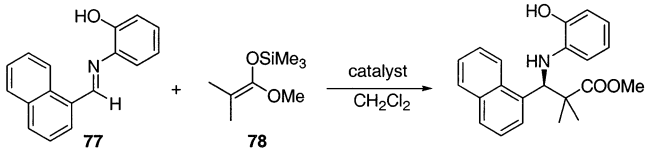



many biologically important nitrogen-containing compounds including β-amino acids and β-lactams.[59]

In 1997, Kobayashi and co-workers reported the first example of a catalytic enantioselective Mannich-type reaction of aldimines with silyl enolates.[60] Zirconium(IV) emerged as the metal of choice as a result of these studies.

One of the drawbacks of the Mannich reaction is the flexibility of the aldimine−metal complex, which often has several stable conformations. To address this problem, Kobayashi and co-workers chose the bidentate aldimine **77** as the imine substrate, in which both the nitrogen atom of the imine and the oxygen atom of the hydroxyl group can coordinate to Zr to form a rigid intermediate complex.[60] The effect of several parameters was investigated in the model reaction between **77** and silyl enolate **78** (Scheme 42). Moderate selectivity was observed when the catalyst was prepared from Zr(O$^t$Bu)$_4$ (10 mol %) and 2 equiv of (*R*)-BINOL (20 mol %). While homogeneous solutions were obtained after mixing Zr(O$^t$Bu)$_4$ and (*R*)-BINOL in dichloromethane, precipitates appeared after 20 min. The precipitate is thought to result from oligomeric or polymeric catalyst aggregates, which lead to low selectivities in the Mannich reaction. The effect of several additives was studied in order to avoid the formation of these precipitates, and *N*-methylimidazole (NMI) was found to be the best additive, resulting in 80% yield and 70% ee.

**Scheme 42**




| [Zr] (mol%) | ligand | additive | yield (%) | ee(%) |
|---|---|---|---|---|
| 10 | *(R)*-**1** | - | Quant. | 38 |
| 10 | *(R)*-**1** | NMI | 80 | 70 |
| 10 | *(R)*-**7a** | NMI | Quant. | 92 |
| 5 | *(R)*-**7a** | NMI | 69 | 95 |
| 5 | *(R)*-**7a** | DMI | Quant. | 91 |

To further optimize the yield and enantioselectivity of the reaction, the Kobayashi group increased the Lewis acidity of the zirconium center by introducing electron-withdrawing groups at the 6,6′-positions of BINOLs. Indeed, the enantiomeric excess was dramatically increased to 90% when (*R*)-6,6′-dibromo-BINOL (6,6′-$Br_2$-BINOL) was used. Similar yields and selectivities were obtained when either (*R*)-6,6′-dichloro-BINOL or (*R*)-6,6′-difluoro-BINOL was used. It was also noted that high yields and enantioselectivities were retained when the catalyst loading was reduced to 2−10 mol %. The trifluoromethyl group

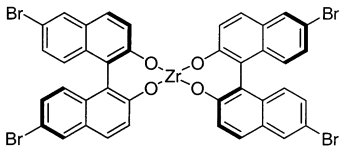


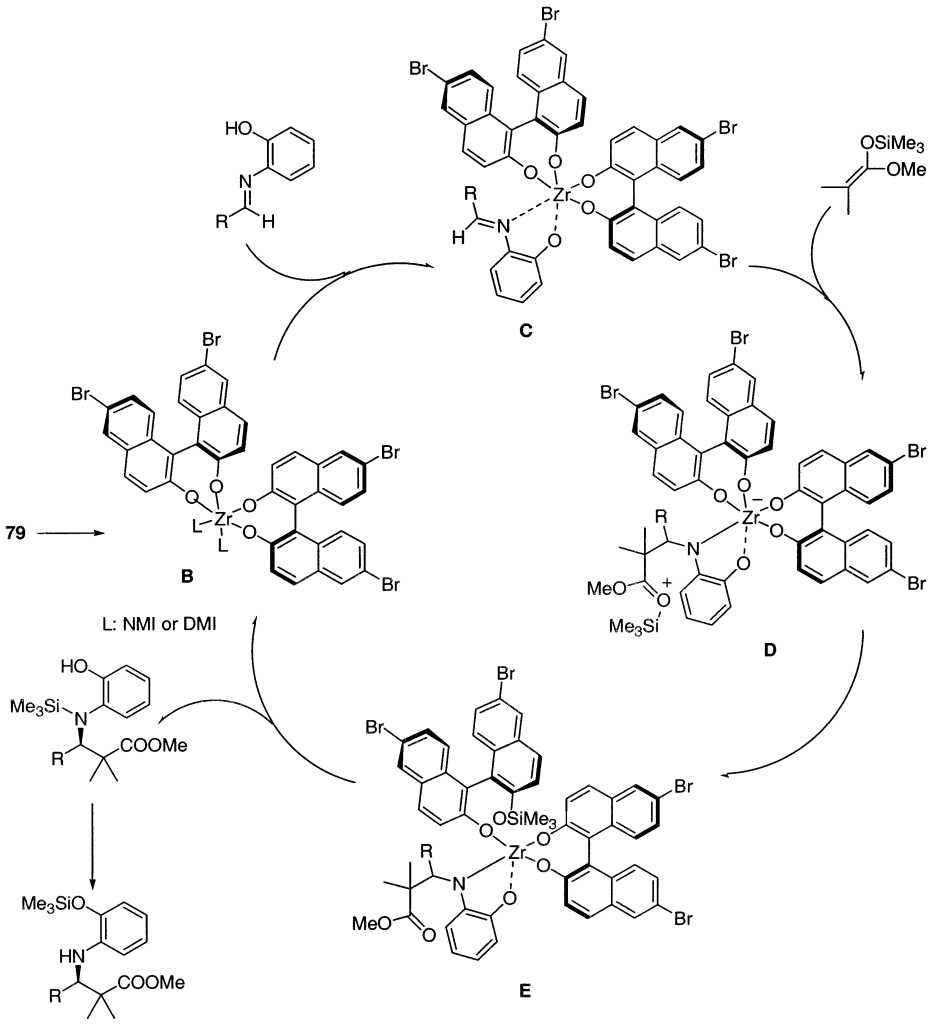

**Figure 8.**

was chosen as one of the strongest electron-withdrawing groups. The corresponding (*R*)-6,6′-bis(trifluoromethyl)-BINOL **55** (see Scheme 32) gave an enantiomeric excess of 96% with only 0.5 mol % of catalyst.

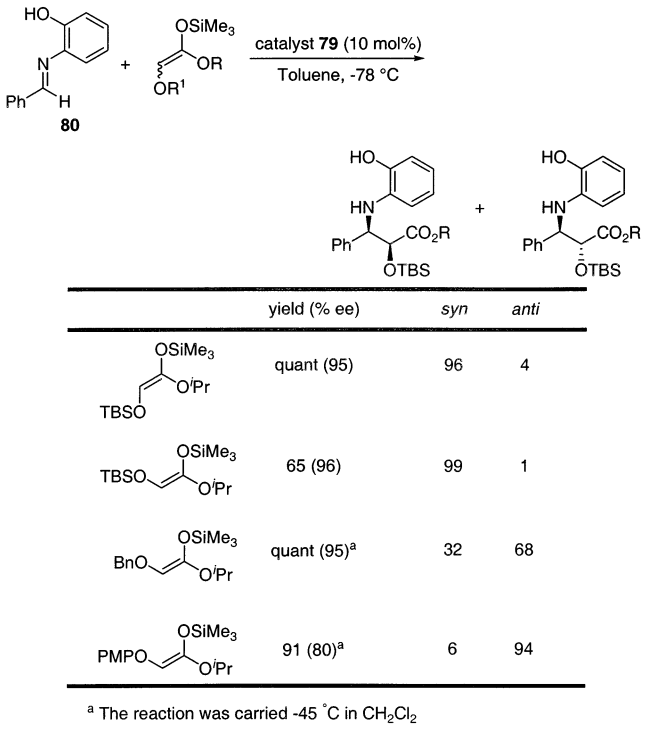
At the same time, it was noted that the hydroxyphenyl group of the aldimine is essential to reaction selectivity. When the aldimines prepared from 1-naphthylaldehyde and aniline or 1-naphthylaldehyde and 2-methoxyaniline were used, almost no chiral induction was obtained.

Kobayashi and co-workers proposed a catalytic cycle for this Mannich-type reaction using 6,6′-$Br_2$-BINOL (Scheme 43). They assumed the isomerization of the highly symmetrical structure of complex **79** (Figure 8) to **B** to be the key step. This step is essential to allow the bidentate aldimine to coordinate to zirconium in order to form complex **C**. The silyl enolate then attacks the aldimine to produce

**Scheme 43**



**Scheme 44**




**D** and then **E**, whose trimethylsilylated oxygen atom attacks the zirconium center to release the product and regenerate catalyst **B**.[43]

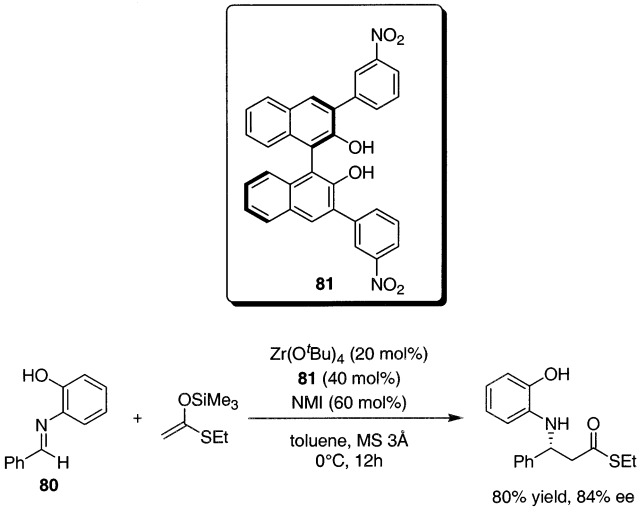
Mannich-type reactions can also be used in the synthesis of $\beta$-amino alcohol units. It is well known that the Sharpless aminohydroxylation (AA) affords *syn*-$\beta$-amino alcohols directly from olefins in high enantioselectivities.[61] Using the Mannich-type reactions, an alternative method has been presented which allows for the preparation of both *syn*- and *anti*-$\beta$-amino alcohols, depending on the enolates (selected results are shown in Scheme 44).[62,63]

After various reaction conditions were screened, the best results for the *syn*-$\beta$-amino alcohol formation were obtained with α-TBSO-ketene silyl acetal using 10 mol % of zirconium catalyst **79** (Figure 8) in toluene at −78 °C (Scheme 44). On the other hand, *anti*-$\beta$-amino alcohols were obtained by the reaction of aldimine **80** with α-benzyloxy-ketene silyl acetal under similar reaction conditions.

Upon switching the ligand (*R*)-6,6′-dibromo-binaphthol to (*R*)-3,3′-di-(3-nitrophenyl)-binaphthol **81**, the Mannich product in the reaction of imine **80** with *S*-ethylthio-1-(trimethylsiloxy)ethene was obtained in 84% ee and 80% yield with reversed configuration of the newly constructed stereogenic center (Scheme 45).[64]

Kobayashi and co-workers recently applied their chiral zirconium-catalyzed asymmetric Mannich-type reaction in the synthesis of HPA-12 compounds (Figure 9).[65] Compound **82**, an intermediate toward the synthesis of HPA-12, was obtained through a three-component Mannich reaction (Scheme 46).[66] The alkoxy part of the aldehyde significantly influenced the enantioselectivity of the product. A high level of selectivity was observed when the *tert*-butyldimethylsiloxy group was used. The benzyloxy

**Scheme 45**




group and the bulkier *tert*-butyldiphenylsiloxy group gave much lower enantioselectivities.

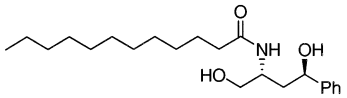
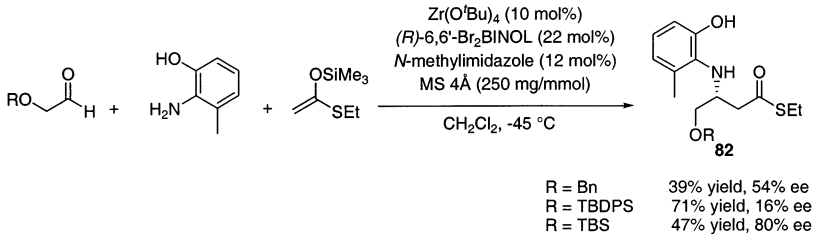



**Figure 9.**

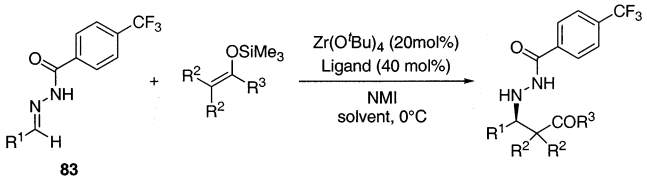
The Kobayashi group further investigated this catalyst system and expanded the substrate scope of the asymmetric Mannich-type reaction.[67] When the acylhydrazone **83** served as the imine substrate (Scheme 47), the reaction did not occur under conditions which were effective for aldimine **80**. Interestingly, the desired Mannich-type product was formed in 38% yield without 1-methylimidazole additive; however, no chiral induction was obtained. The product, nonetheless, was obtained in 66% yield and 66% ee when 3,3′-dibromo-1,1′-bi-2-naphthol [(*R*)-3,3′-$Br_2$-BINOL] was used as the ligand instead of (*R*)-6,6′-$Br_2$-BINOL. The ee value was further improved to 86% when the reaction was run in toluene instead of dichloromethane. A variety of hydrazones derived from aliphatic, aromatic, and α-halogenated aldehydes were successfully employed under similar conditions.

Since these Lewis acids are air- and moisture-sensitive, they are prepared in situ and cannot be preserved for extended periods of time. Kobayashi and co-workers recently developed a new air-stable zirconium-based chiral Lewis acid that can be stored in air for up to 3 months and is highly selective in asymmetric Mannich-type reactions.[68] The catalyst was prepared from $Zr(O^tBu)_4$ (1 mmol), (*R*)-6,6′-bis-(pentafluoroethyl)-1,1′-bi-2-naphthol (2 mmol), NMI (4 mmol), and powdered 5-Å molecular sieves (MS) (6 g/mmol) in benzene at 80 °C for 2 h. This chiral zirconium catalyst was tested in a series of Mannich-type reactions, and results similar to previous reports were obtained. The enantioselectivities ranged from 85 to 96%, and the yields ranged from 60% to quantitative, depending on substrates used. The catalyst is reusable up to three times, giving similar yields and enantioselectivities. Finally, a similar

**Scheme 46**



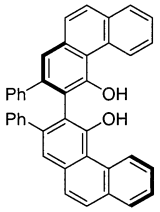

**Scheme 47**




| ligand | solvent | yield (%) | ee (%) |
|---|---|---|---|
| *(R)*-6,6′-$Br_2$BINOL | $CH_2Cl_2$ | 38 | 0 |
| *(R)*-3,3′-$Br_2$BINOL | $CH_2Cl_2$ | 66 | 66 |
| *(R)*-3,3′-$Br_2$BINOL | toluene | 66 | 86 |

catalyst prepared from (*R*)-3,3′-$Br_2$-BINOL and powdered 3-Å MS (without NMI) was used in the reaction of **77** and silyl enol ethers, giving the corresponding product in 80% yield and 97% ee (Scheme 42). This catalyst was stable for up to 12 days.

Wulff et al. have used VAPOL-derived catalysts **84** (Figure 10) in the asymmetric Mannich-type reaction.[69] The VAPOL/Zr catalysts are temperature-independent, giving the product (Scheme 42) in good enantioselectivities (85−91%) at both room temperature and higher temperatures (up to 40 °C), with excellent yields (>90%). The reaction is conducted under the same conditions as mentioned above with Kobayashi's catalyst **79** (Figure 8).[60] Although the best enantioselectivity was obtained at −45 °C, only a small drop in ee (89%) occurs at room temperature.



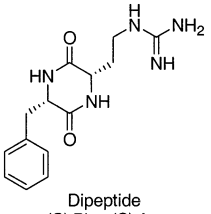
*(S)*-VAPOL **84**

**Figure 10.**

The mechanism is believed to be similar to that of complex **79**, and a clean NMR spectrum is observed with 2 equiv of VAPOL relative to zirconium. The spectrum is consistent with a single $C_2$-symmetrical species bearing NMI ligands bound to zirconium in trans configuration.

## B. Strecker-Type Reactions

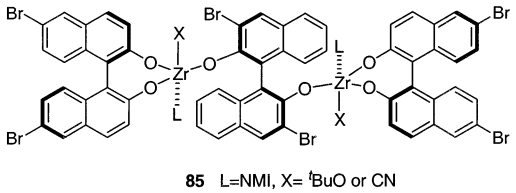
The Strecker-type reaction of aldimines with cyanide nucleophiles provides one of the most efficient ways to synthesize α-aminonitriles. The latter are useful intermediates for the synthesis of amino acids.[70] Lipton reported the first enantioselective Strecker-type reaction in 1996, using dipeptide ligand as a catalyst (Figure 11).[71] Although high yields and enantioselectivities were obtained, the scope of the reaction was limited to α-aminonitriles derived from benzaldehyde derivatives. Reaction of aldimines derived from aliphatic or heterocyclic aldehydes gave poor results.



Dipeptide
*(S)*-Phe,*(S)*-Arg

**Figure 11.**

Kobayashi and co-workers applied the zirconium catalyst **85** in asymmetric Strecker-type reactions (Figure 12).[72] The zirconium catalyst was prepared from $Zr(O^tBu)_4$ (1 equiv), (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol (2 equiv), (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol (1 equiv), and *N*-methylimidazole (NMI, 3 equiv). The first reaction attempted was between the bidentate substrate **77** (R = naphthyl) and $Bu_3SnCN$. A mixture of benzene/toluene (1/1) proved to be the best solvent system for the reaction (Scheme 48).

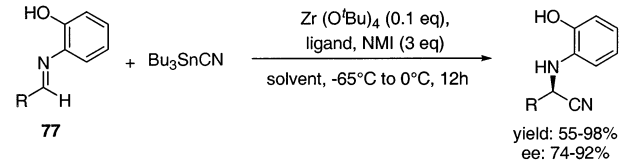


**85** L=NMI, X= $^t$BuO or CN

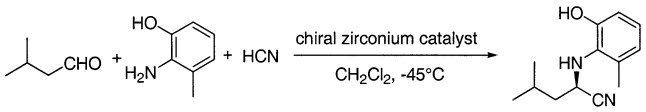
**Figure 12.**

As in Kobayashi's Mannich reactions, the product was obtained in much lower yields and with lower enantioselectivities when the aldimines prepared from aniline or 2-methoxyaniline were used (aniline, 29% yield, 1% ee; 2-methoxyaniline, 45% yield, 5% ee). The structure of the zirconium catalyst **85** (Figure 10) was carefully examined by NMR. Spectroscopic evidence suggests that a binuclear complex was formed under the reaction conditions. This

**Scheme 48**



**Scheme 49**




complex consists of two zirconium centers, two (*R*)-6,6′-$Br_2$-BINOLs, two NMI units, and one (*R*)-3,3′-$Br_2$-BINOL unit. This structure is very stable and is formed even with different molar ratios of $Zr(O^tBu)_4$, (*R*)-6,6′-$Br_2$-BINOL, (*R*)-3,3′-$Br_2$-BINOL, and NMI.

Several Strecker-type reactions were examined, and aldimines derived from aromatic as well as aliphatic and heterocyclic aldehydes reacted with $Bu_3SnCN$ to afford the corresponding α-aminonitrile derivatives in high yields with high enantiomeric excesses (Scheme 48).

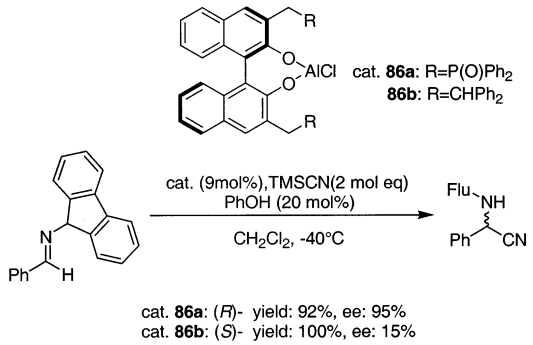
In the course of their investigations, Kobayashi and co-workers developed a method for the catalytic enantioselective Strecker-type reaction using an amine, an aldehyde, and hydrogen cyanide with their zirconium catalyst described above (Figure 10).[73] The Strecker-type three-component reaction was performed with isobutylaldehyde, 2-amino-3-methylphenol, and hydrogen cyanide in the presence of **85**. The reaction proceeded in dichloromethane at −45 °C to afford the corresponding α-aminonitrile derivative in 99% yield and 94% ee (Scheme 49). To clarify the role of the two different BINOL ligands in the catalytic system, several BINOLs and biphenols were examined. It was suggested that a combination of the two different BINOLs was crucial for optimal catalyst formation. When (*R*)-6,6′-$Br_2$-BINOL and (*S*)-3,3′-$Br_2$-BINOL were combined, much lower selectivity was obtained (Scheme 49). NMR studies showed that clear formation of binuclear zirconium catalysts such as **85** was not observed in this case. Moderate selectivity was obtained when (*R*)-6,6′-$Br_2$-BINOL and racemic 3,3′-$Br_2$-BINOL or 6,6′-$Br_2$-BINOL and (*R*)-3,3′-$Br_2$-BINOL were combined.

Both the two-component reactions (reactions of imines with HCN) and the three-component reactions of aldehydes, amines, and HCN proceeded smoothly using catalyst **85**. When an aliphatic imine was used in the two-component reaction, a lower yield was obtained, although with high enantioselectivity. This was attributed to the instability of the aliphatic imine moiety.

$^1H$ NMR studies revealed the formation of a zirconium cyanide complex **85** under the reaction conditions (2 equiv of $^t$BuO groups removed from the catalyst). However, control experiments showed that cyano groups attached to the zirconium center did not work as cyanide nucleophiles in this Strecker-type reaction.

Shibasaki and co-workers also reported a Strecker-type reaction controlled by their bifunctional Lewis acid−Lewis base catalyst **86** (Scheme 50).[74] The nature of substituent on the nitrogen atom of imines has a dramatic effect on the enantioselectivity of the reaction. While using *N*-allylbenzaldehydeimine as a substrate gave only 4% ee and 67% yield after 62 h, the reaction of *N*-benzhydrylimine gave the product in 78% ee with 84% yield after 85 h. The enantioselectivity was further increased to 95% (97% yield) in the reaction with *N*-fluorenylimine (111 h). Protic additives such as alcohols and phenols had a beneficial effect on the reaction rate without changing the nature of the catalytic species. The best protic additive, phenol, was used in a catalytic amount (20 mol %) under optimized reaction conditions. Aromatic aldimines including heterocyclic aldimines, α,β-unsaturated aldimines, and aliphatic aldimines were transformed to the corresponding Strecker-type products in moderate to excellent yields (66−97%) and enantioselectivities (70−96% ee, Scheme 50).

**Scheme 50**




It is noteworthy that simultaneous activation of imines and TMSCN by the Lewis acid (Al) and the Lewis base (oxygen atom of the phosphine oxide substituent) is crucial for highly enantioselective catalysis (for reaction mechanism, see Scheme 51). This dual-activation mechanism is supported by a control experiment where catalyst **86b** was used. Since this catalyst contains a diphenylmethyl group instead of the diphenylphosphane oxide moiety in **86a**, it has no Lewis base functionality, and the substituent only creates steric hindrance. As outlined in Scheme 50, catalyst **86a** produced the (*R*)-enantiomer of the product with 92% yield and 95% ee, while catalyst **86b** afforded the (*S*)-enantiomer with 100% yield but only 15% ee. TMSCN was found to be more reactive than HCN, thus making it possible to use this unique system with a catalytic amount of TMSCN and a stoichiometric amount of HCN.

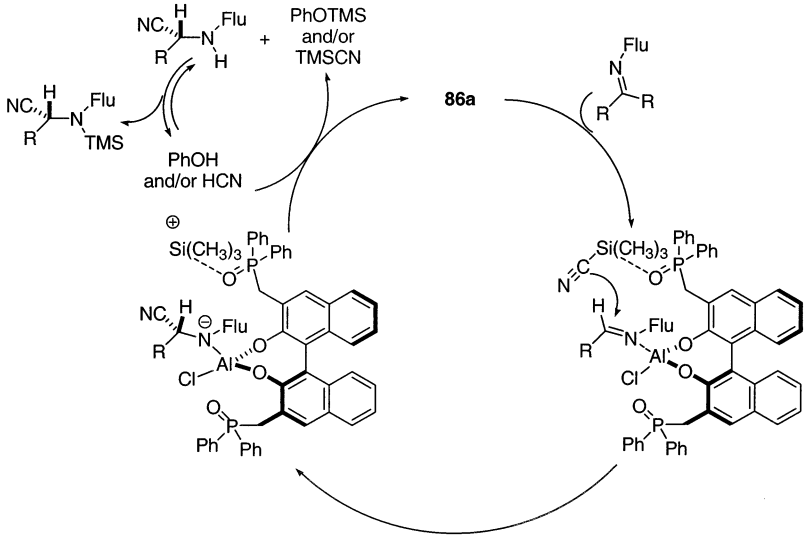
## C. Diels–Alder Reaction

3,3′-Diphenyl-BINOL **36a** was used by Kelly et al. in an attempt to modify chiral boron Lewis acids to promote asymmetric Diels−Alder reactions.[75] More than 98% ee of product **88** was obtained when the sterically bulkier (*S*)-**36a** was used, but the enantioselectivity was reduced to 70% ee when the sterically less hindered (*S*)-**87** was employed. Two equivalents of the chiral boron-BINOL reagent were required (Scheme 52).

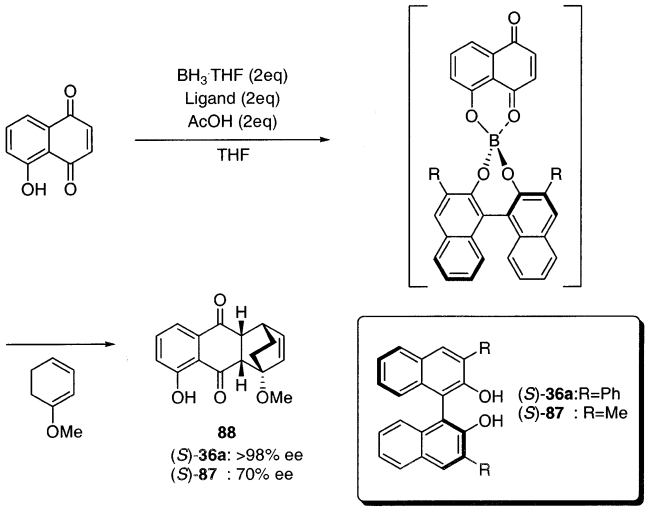
Larsen's group later extended the Kelly catalyst to reactions of 5-hydroxy-1,4-naphthoquinone with chiral "semi-cyclic" diene systems to produce the asymmetric syntheses of angucyclinone antibiotics.[76]

This methodology was also introduced to the total synthesis of (+)-diepoxin $\sigma$ by Wipf and Jung.[77] In Kelly's case, the substituent on the diene plays an important role in asymmetric induction by interacting with the substituents on the BINOL ligand.

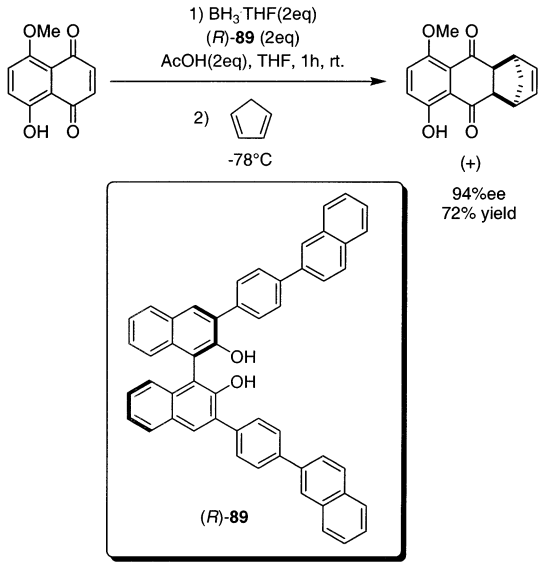
**Scheme 51**




**Scheme 52**

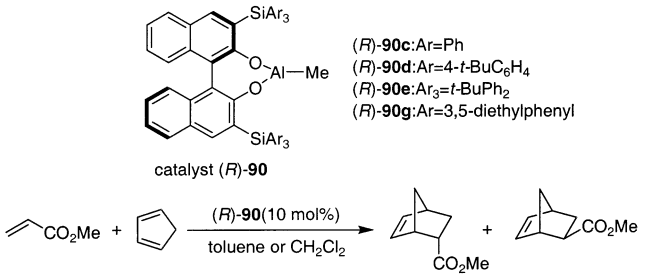



**Scheme 53**




However, in Wipf's case, smaller symmetrical dienes (cyclopentadiene) were used (Scheme 53). To compensate for this lack of a differentiating end group, Wipf and Jung hypothesized that chiral binaphthol auxiliaries with very bulky substituents at the 3,3′-positions would be required, and several analogues were prepared using Cram's method[78] or Jørgensen's Suzuki coupling method.[31] When *p*-(2-naphthyl)-phenyl-substituted chiral ligand **89** was used, the key intermediate of (+)-diepoxin $\sigma$ was obtained in 94% ee with 72% yield.

**Scheme 54**



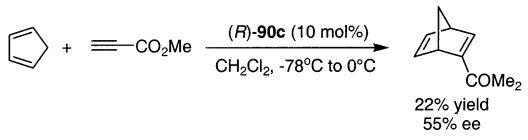

(*R*)-**90c**: yield 81%; *endo/exo* 95:5; ee 64%
(*R*)-**90d**: yield 35%; *endo/exo* 95:5; ee 65%
(*R*)-**90e**: yield 62%; *endo/exo* 97:3; ee 69%
(*R*)-**90g**: yield 65%; *endo/exo* 96:4; ee 36%

Yamamoto and co-workers reported an asymmetric Diels−Alder reaction of cyclopentadiene and methyl acrylate, which is usually considered to be a relatively unreactive dienophile.[79] This process was catalyzed by 10 mol % of chiral organoaluminum reagents (*R*)-**90c**−**g** (Scheme 54). The aryl groups on the silyl substituents were modified in order to test the steric effect on product selectivity. The reaction appeared to be generally insensitive to the silyl groups, except for catalyst **90g**, giving the product in 36% ee, lower than the others.

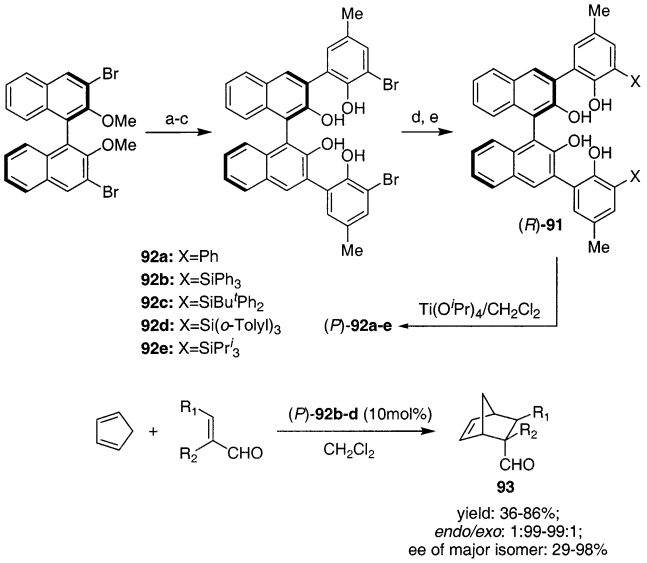
This methodology was further found to be applicable to the asymmetric Diels−Alder reaction of methyl propiolate and cyclopentadiene. The corresponding cycloadduct was obtained in 55% ee and 22% yield by using catalyst (*R*)-**90c** (Scheme 55). This was the first example of an asymmetric Diels−Alder reaction between an acetylenecarboxylate and a cyclopentadiene promoted by a chiral Lewis acid.

The same group later introduced chiral helical Lewis acids (*P*)-**92** as templates for conformational fixation of $\alpha,\beta$-unsaturated aldehydes in Diels−Alder

**Scheme 55**




**Scheme 56**[a]




[a] Reagents: (a) 2-methoxy-5-methylphenylboronic acid, Pd(PPh$_3$)$_4$, Ba(OH)$_2$, DME, H$_2$O; (b) BBr$_3$, CH$_2$Cl$_2$; (c) Br$_2$, CH$_2$Cl$_2$; (d) Ar$_3$SiX, imidazole, DMF; (e) $^t$BuLi, THF.

reaction.[80] (*P*)-**92** was made by treatment of titanium tetraisopropoxide with (*R*)-**83** with azeotropic removal of 2-propanol (Scheme 56). The chiral ligands **91** were prepared from (*R*)-(+)-3,3′-dibromobinaphthol dimethyl ether via a Pd$^0$-catalyzed coupling reaction, followed by demethylation of the resulting coupling product with BBr$_3$. Complex (*P*)-**92a** (10 mol %) was first tested in the reaction of cyclopentadiene with acrolein in CH$_2$Cl$_2$ at −40 °C and gave rise to Diels−Alder adducts in 99% yield, with the major endo isomer **93** in 46% ee. Introduction of triarylsilyl moieties into the 3-position of the 3,3′-phenyl groups in ligands **91** greatly increased the enantioselectivity. Under the influence of (*P*)-**92b** (10 mol %), the major endo adduct **93** (R$^1$ = R$^2$ = H) was obtained in 88% ee with 55% yield. The enantiomeric excess of **93** was further improved to 92% and 96% when (*P*)-**92c** and (*P*)-**92d** were used, respectively. In contrast, (*P*)-**92e** led to 55% ee of *endo*-**93**. Using 10 mol % of the most effective titanium complex, (*P*)-**92d**, the Diels−Alder adducts of several other α,β-unsaturated aldehydes with dienes were produced in a uniformly high level of enantioselectivity (81−98% ee).

Subsequently, the same group introduced a Brønsted acid-assisted chiral Lewis acid catalyst (BLA) (Figure 13) for the asymmetric Diels−Alder reaction.[81] Reaction of **94** with B(OMe)$_3$ in CH$_2$Cl$_2$ at reflux gave the BLA (*R*)-**95** as a white solid (Scheme 57). In the presence of 10 mol % of (*R*)-**95**, a variety of α-substituted α,β-enals reacted with reactive dienes, such as cyclopentadiene, to afford the Diels−Alder adducts in high enantioselectivities (range from 92 to 99%) as well as high exo selectivity (exo/endo ratios from >97:3 to >99:1) with almost quantitative yields.

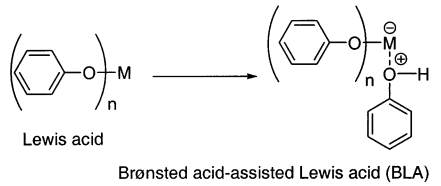
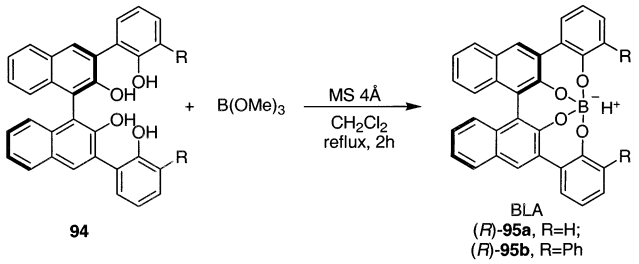
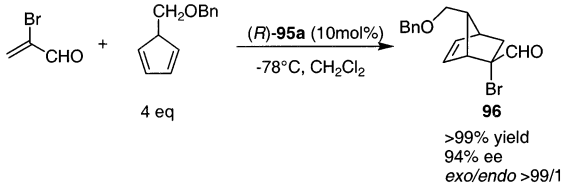



**Figure 13.**

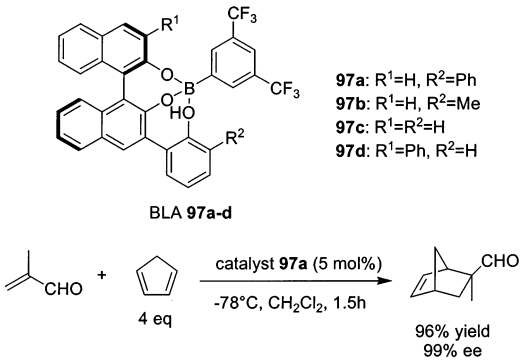
**Scheme 57**




**Scheme 58**



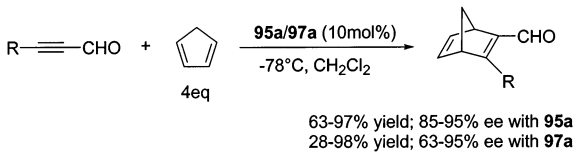

**Scheme 59**



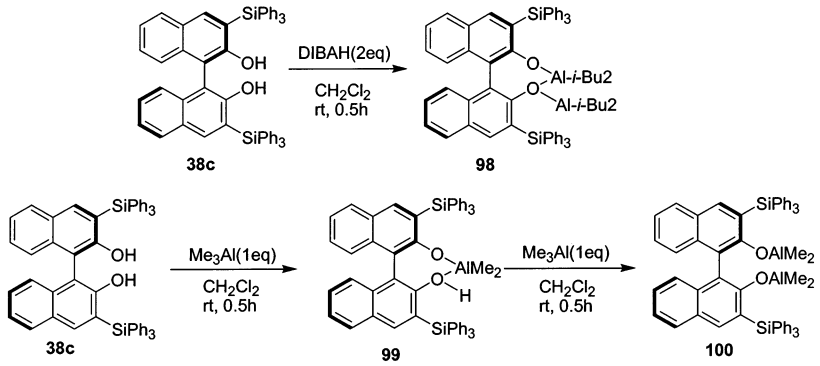

It is worthy of note that product **96**, an important intermediate for prostaglandin synthesis,[82] was synthesized with remarkable ease using this method (Scheme 58).

Like most chiral Lewis acids, (*R*)-**95** exhibited low enantioselectivity and/or reactivity in the corresponding reactions of α-unsubstituted α,β-enals such as acrolein and crotonaldehyde. In the reaction of acrolein and cyclopentadiene catalyzed by (*R*)-**95a**, only 40% ee of the major endo product was obtained with 91% yield. The enantioselectivity was raised to 92% using (*R*)-**95b**.[83] To further improve the catalytic activity of this BLA system, BLA **97** (Scheme 59) was prepared from the corresponding chiral triol with 3,5-bis(trifluoromethyl)benzeneboronic acid. In the test

**Scheme 60**



**Scheme 61**




reaction of methacrolein and cyclopentadiene, 99% ee with 96% yield was obtained using **97a**, while a dramatic decrease of reaction rate and selectivity was observed with **97b**−**d** as well as the parent (*R*)-BINOL. Further studies proved **97a** to be highly effective in enantioselective cycloaddition of α-substituted, α-unsubstituted, and the less reactive *β*-substituted α,*β*-enals with various dienes (65 → 99% yield and 91 → 99% ee with α-substituted α,*β*-enals; 84 → 99% yield and 95 → 99% ee with α-unsubstituted α,*β*-enals; 73−94% yield and 80−98% ee with *β*-substituted α,*β*-enals).[84]

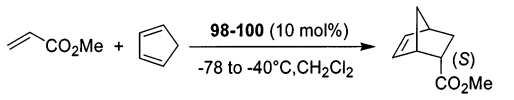
Both BLA **95a** and BLA **97a** were employed in the enantioselective catalytic Diels−Alder reaction of dienes and acetylenic dienophiles.[85] Overall, the reaction catalyzed by BLA **95a** proceeded with good enantioselectivity and chemical yields (63−97% yield, 85−95% ee). In some cases, BLA **97a** gave an even higher enantioselectivity than **95a** (Scheme 60). Interestingly, the absolute configuration of the products obtained using **95a** are opposite to those obtained using **97a**.

Chiral dialuminum and trialuminum Lewis acids prepared from organoaluminum reagents and enantiomerically pure BINOL derivatives were designed by Yamamoto and co-workers and successfully employed in asymmetric Diels−Alder reactions.[86] Chiral dialuminum compounds **98** and **100** were quantitatively prepared from (*R*)-3,3′-bis(triphenylsilyl)binaphthol with organoaluminum reagents, as outlined in Scheme 61.

In the reaction of methyl acrylate with cyclopentadiene, catalyst **98** promoted 86% ee with 46% yield of the product at −78 °C, and the chemical yield was further increased to >99% by raising the reaction temperature to −40 °C, with a slight loss of enantioselectivity (80% ee). In both cases, the ratio of endo/exo was 97:3. However, with catalysts **99** and **100**, much lower enantioselectivities (55% yield and 64% ee with **99**; 58% ee and 54% yield with **100**) were obtained, with similar endo/exo ratios. The catalyst **98** was less effective for the enantioselective Diels−Alder reaction of α,*β*-enals (Scheme 62).

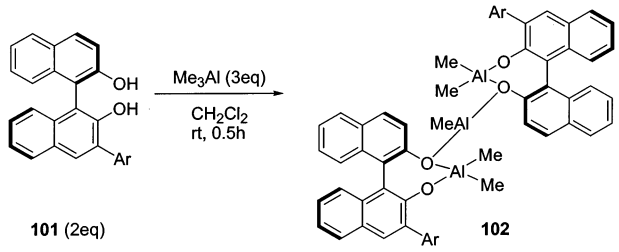
Trialuminum complex **102** was quantitatively prepared from enantiomerically pure **101** and trimethylaluminum in $CH_2Cl_2$ at room temperature (Scheme 63). Although **102** proved ineffective in the asymmetric Diels−Alder reaction of methyl acrylate with cyclopentadiene, it promoted 72% ee in the reaction of methacrolein with cyclopentadiene in 99% yield of

**Scheme 62**

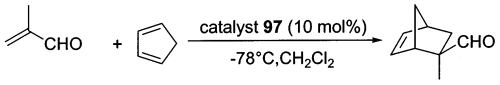



>99% yield, 80%ee, *endo:exo*= 97:3 with **98**
55% yield, 64%ee, *endo:exo*=96:4 with **99**
54% yield, 58%ee, *endo:exo*=98:2 with **100**

**Scheme 63**




**102a**, Ar = 9-Anthracenyl,
**102b**, Ar=2,4,6-*i*-$Pr_3C_6H_2$
**102c**, Ar=Ph,
**102d**, Ar=$SiPh_3$,
**102e**, Ar=2,6-$Ph_2C_6H_3$,
**102f**, Ar=2,4,6-$Me_3C_6H_2$



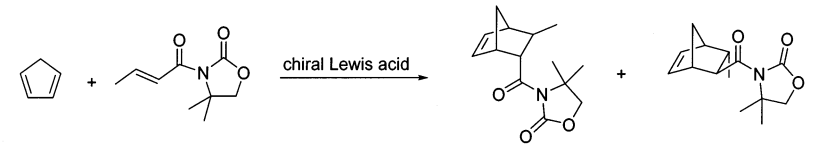

86% yield, 73%ee, *exo:endo*=97:3 with **102a**
99% yield, 72%ee, *exo:endo*=93:7 with **102b**
70% yield, 36%ee, *exo:endo*=95:5 with **102c**
37% yield, 9%ee, with **102d**
78% yield, 55%ee, *exo:endo*=94:6 with **102e**
86% yield, 69%ee, *exo:endo*=94:6 with **102f**

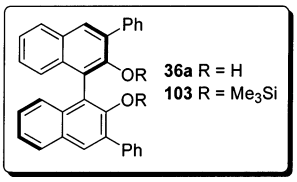
the exo product. Ligand **101** was found to be more effective for asymmetric induction with bulky aryl substituents at the 3-position, such as 9-anthracenyl and 2,4,6-triisopropylphenyl groups, but much lower and opposite enantioselectivity was observed when the 3-position substituents became too bulky, such as triphenylsilyl and 2,6-diphenylphenyl groups.

Chapuis and co-workers applied 3,3′-substituted binaphthols in the asymmetric Diels−Alder reaction of cyclopentadiene and a bidentate dienophile (Scheme 64).[87] Lewis acid screening revealed that titanium catalysts exhibited higher endo/exo selectivity as well as *π*-face selectivity than their aluminum analogues. In general, the products were obtained in excellent yields and high diastereoselectivities.

Renaud and co-workers reported an asymmetric Diels−Alder reaction of *N*-hydroxy-*N*-phenylacryla-

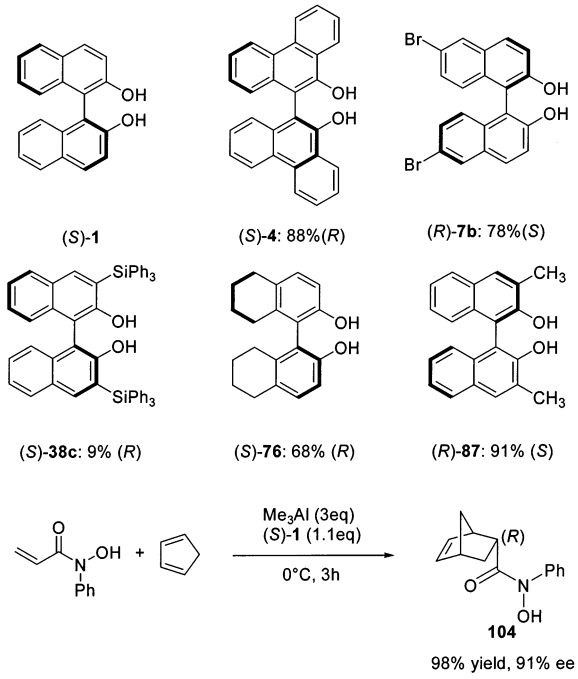
**Scheme 64**




| ligand | Lewis acid | yield (%) | *endo/exo* | d.e. (%) |
|---|---|---|---|---|
| **36a** | $Et_2AlCl$ | 92 | 68:32 | 88 |
| **36a** | $EtAlCl_2$ | 92 | 76:24 | 95 |
| **103** | $TiCl_4$ | 99 | 94:6 | 98 |

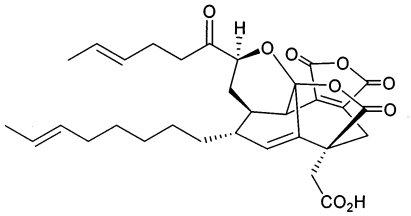
**Scheme 65**




mides with cyclopentadiene, catalyzed by a chiral Lewis acid prepared from 3 equiv of trimethylaluminum and 1.1 equiv of BINOL derivatives (Scheme 65).[88] Among the BINOL derivatives screened in the model reaction between *N*-hydroxy-*N*-phenylacrylamide and cyclopentadiene, (*S*)-BINOL proved to be the best, producing product **104** in 91% ee and 98% yield. The 3,3′-substituted BINOLs **87** and **4** gave enantioselectivities close to those observed with (*S*)-BINOL. The enantioselectivity dramatically dropped to 9% ee when a sterically bulky substituent ($SiPh_3$, **38c**) was introduced to the 3,3′-positions of the BINOL ligand.

The total synthesis of CP compounds (**105**, CP-263,114 (phomoidride B), and **106**, CP-225,917 (phomoidride A)) has drawn a great deal of attention since their discovery in the mid-1990s by a group at Pfizer (Figure 14).[89] In 1999, Nicolaou and co-workers reported the first total syntheses of **105** and **106** in their racemic forms.[90] In 2000, they determined the absolute configurations of those compounds by way of asymmetric synthesis.[91] The key step in Nicolaou's total synthesis of the CP molecules is a type II intramolecular Diels−Alder reaction, which generates the core skeleton of the compounds (Scheme 66). A study of this intramolecular process with a number of asymmetric catalysts has led to Lewis acid **107** as the optimal inducer of asymmetry. However, the enantioselectivity in the corresponding Diels−Alder reaction was only 20% ee.

Further studies on a substrate-based control of the diastereoselectivity of the intramolecular cycloaddition led to the optimum condition when ketone **108** was employed. The use of catalyst **109** in toluene at −80 °C gave a ratio of 5.7:1 of the diastereomeric Diels−Alder products **110a** and **110b** (Scheme 67).[92] The structure of the Lewis acid catalyst had only a moderate effect on the diastereoselectivity of the intramolecular Diels−Alder reaction. None of the



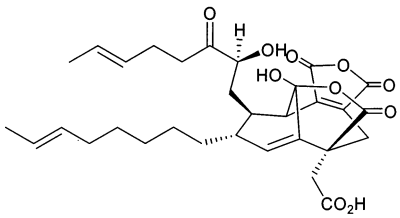
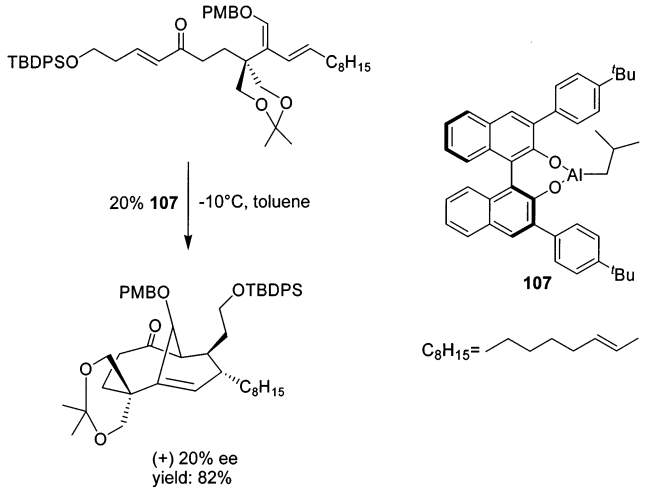
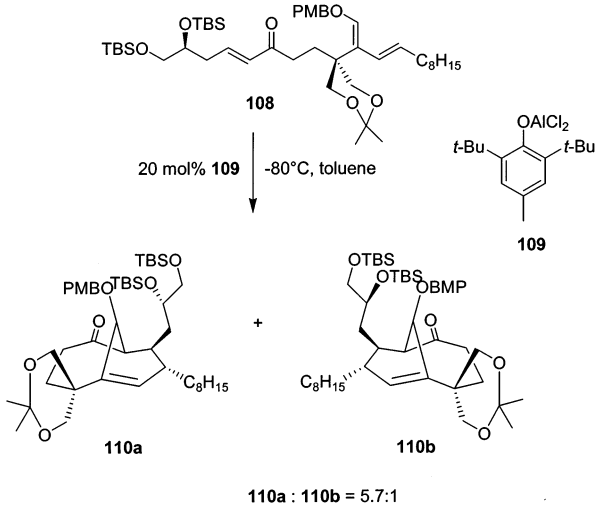




**Figure 14.**

**Scheme 66**



**Scheme 67**




chiral aluminum Lewis acids prepared from BINOL derivatives gave better results than **109**.

Heterobimetallic complexes **111** (Figure 15) have also been used as chiral Lewis acids to catalyze Diels−Alder reactions.[39,93] These catalysts function as both Lewis acids and Brønsted bases. The central metal acts as the Lewis acid, and the alkali metal binaphthoxide moieties act as Brønsted bases. The balance and cooperation between these functionalities are important to asymmetric induction. After testing a series of lanthanides (La, Ga, Gd, Sm, Pr, Dy, Yb), lanthanum-derived catalysts **111**/La have been found to give the best results. The 6,6′-substituted catalysts showed high enantioselectivities in the Diels−Alder reaction, with **111a**/La giving the best result (86% ee, 100% yield, and a high endo/exo ratio of 36:1), as shown in Scheme 68. Catalysts **111b**/La and **111c**/La gave lower yields and enantioselectivities under similar reaction conditions (89% yield, 74% ee, endo/exo = 16:1 for **111b**/La and 93% yield, 78% ee, endo/exo = 19:1 for **111c**/La).

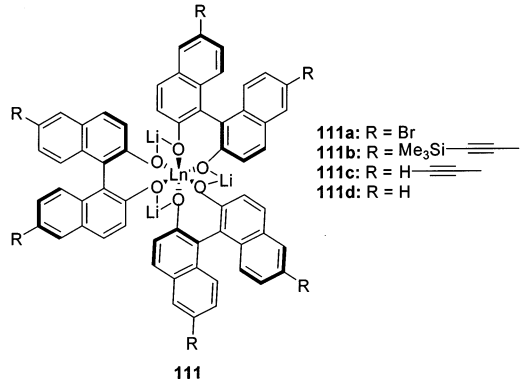
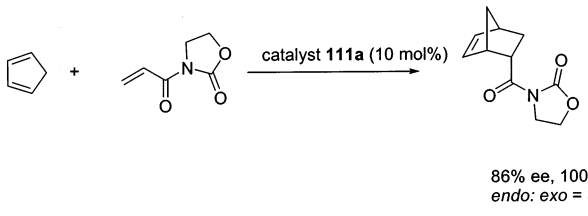
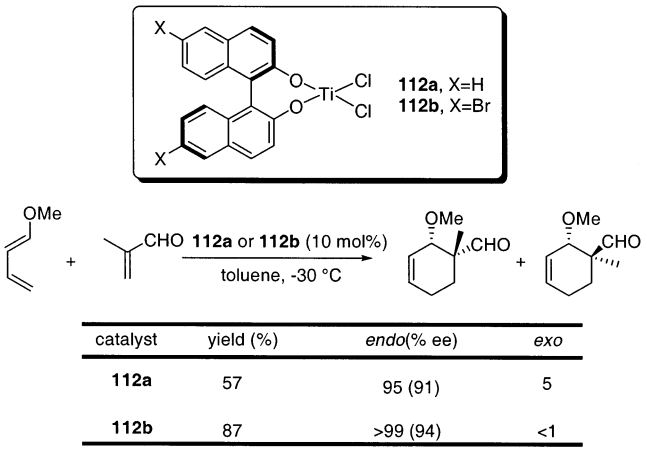



**Figure 15.**

**Scheme 68**

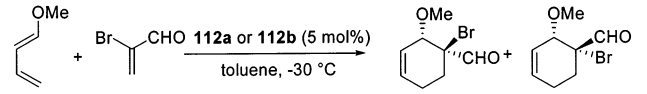



**Scheme 69**



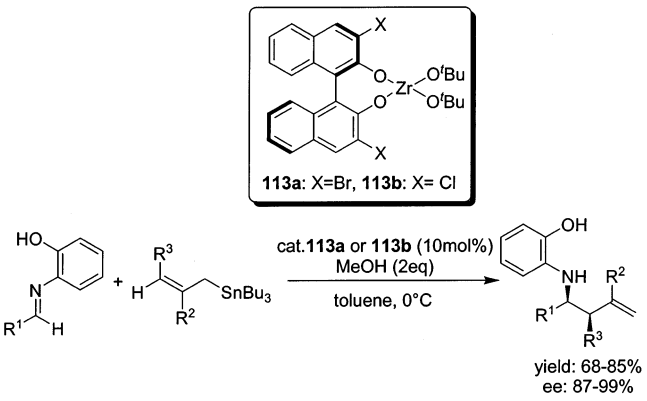

| catalyst | yield (%) | *endo*(% ee) | *exo* |
|---|---|---|---|
| **112a** | 57 | 95 (91) | 5 |
| **112b** | 87 | >99 (94) | <1 |

**Scheme 70**




| catalyst | yield (%) | *endo*(% ee) | *exo* |
|---|---|---|---|
| **112a** | 70 | 97 (81) | 3 |
| **112b** | 71 | 95 (60) | 5 |

**Scheme 71**

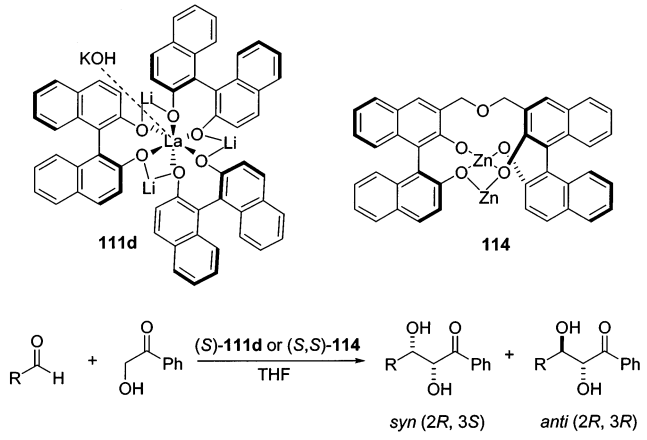



Mikami and co-workers found that the 6,6′-$Br_2$-BINOL/Ti complex **112b** is more effective than the parent BINOL/Ti complex (**112a**) in the asymmetric catalysis of the Diels−Alder reaction between 1-methoxydienes and methacrolein (Scheme 69).[94] When bromoacrolein is used, these results are reversed (Scheme 70).

## D. Allylation of Imines

Kobayashi and co-workers reported an enantioselective allylation of imines catalyzed by chiral zirconium complexes **113a** and **113b** (Scheme 71).[95] As mentioned in the Mannich reaction section, the imine substrates must contain a hydroxy functionality at the ortho posituon of the imine nitrogen atom. The presence of a free hydroxy functionality in the allylstannanes (the allylating agent) is preferred for both satisfactory reaction rate and high enantioselectivity. After screening several different BINOL derivatives, the authors found that the catalyst prepared from $Zr(O^tBu)_4$ and an equimolar amount of (*R*)-3,3′-$Br_2$-

**Scheme 72**




BINOL (catalyst **113a**) or (*R*)-3,3′-$Cl_2$-BINOL (catalyst **113b**) in toluene gave satisfactory results. Changing the nature of the allylstannane allowed the authors to obtain the highest ee value of 95% with 81% yield. These results can be further improved by preparing the catalyst in THF instead of toluene with 2 equiv of methanol as an additive. The use of water instead of methanol as an additive was also found to be effective: even 1 equiv of water was sufficient for the reaction, and comparable results were obtained. Nearly identical yields and asymmetric inductions were observed with both catalysts **113a** and **113b**. The additives in this case are assumed to de-oligomerize the less selective oligomeric catalyst structures, which should result in the formation of the desired active monomeric catalyst species.

## E. Aldol Reaction

The catalytic asymmetric aldol reaction has been a valuable contribution to asymmetric synthesis.[96] Shibasaki and co-workers reported a direct catalytic asymmetric aldol reaction catalyzed by their (*S*)-heterobimetallic catalyst **111d**·KOH and (*S*,*S*)-Zn−Zn-linked BINOL complex **114**.[97]

The heterobimetallic catalyst **111d** was effective in producing 1,2-*anti*-diols with a variety of primary aldehydes and 2-hydroxyacetophenone (Scheme 72). In the presence of 5−10 mol % of **111d**, the aldol products were formed in high yields (78−90%) and enantiomeric excess (90−95% for 1,2-*anti*-diol, 74−84% for 1,2-*syn*-diols) with a 5:1 ratio of the anti/syn diols. Since the *anti*-1,2-diols are the major diastereomers, this method can be viewed as a supplement to the Sharpless AD process. Catalyst **111d** was ineffective in the reaction with secondary and tertiary aldehydes. The problem was partially solved by introducing the (*S*,*S*)-Zn−Zn-linked BINOL complex **114**, which can promote the reaction with secondary aldehydes in modest to good ee values (anti, 67−81% ee; syn, 77−86% ee) with good chemical yields (79−92%). In contrast, **114** produced the *syn*-1,2-diols as the major products (anti/syn between 1:2 and1:7).

The same group developed another type of heterobimetallic catalysts possessing both Lewis acid and Brønsted base functionalities. These catalysts were applied in the direct asymmetric aldol reaction of aromatic ketones as well as the less acidic dialkyl

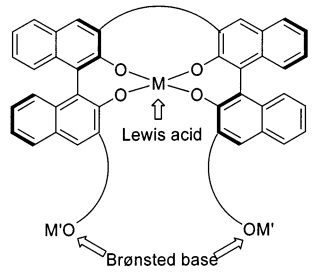
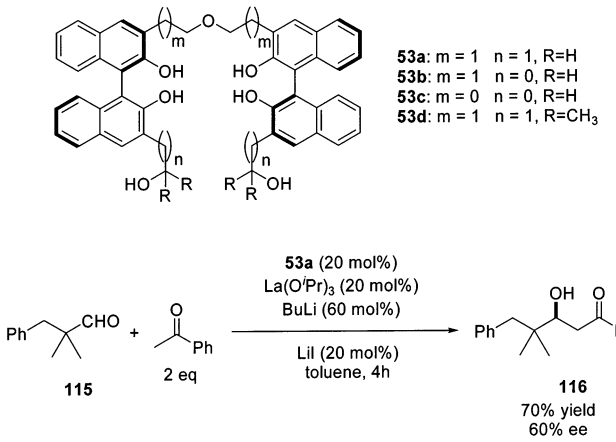



**Figure 16.**

**Scheme 73**



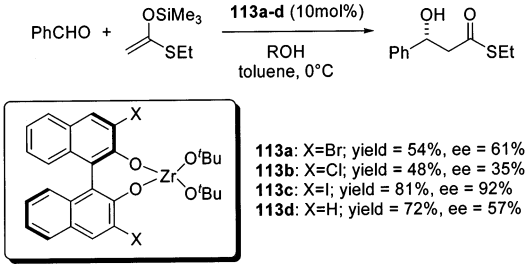

ketones, affording aldol products in moderate yields and enantioselectivities.[98] The new catalyst consists of a central metal M acting as a Lewis acid and a metal−alkoxide moiety OM′ acting as a strong Brønsted base (Figure 16). The novel strategy here is to attach the Brønsted base moiety covalently to the naphthyl ring through a carbon tether, which is different from the cases of conventional heterobimetallic and heteropolymetallic catalysts.[39]

The catalyst prepared from **53a**, La(O-$^i$Pr)$_3$, and BuLi was tested in the model reaction between aldehyde **115** and acetophenone. Product **116** was obtained in 70% yield and 67% ee (Scheme 73). The length of both the tether and the linker significantly affected the reactivity and selectivity. The use of a shorter tether (ligand **53b**) was found to decrease the selectivity (55% yield, 35% ee, 19 h). A catalyst with a shorter linker and tether (ligand **53c**) promoted much lower selectivity (3% ee) and reactivity (48% yield, 22 h).

Catalyst **53a**/La proved to be effective in the aldol reaction of the less acidic aliphatic ketones such as isopropyl methyl ketone and α,β-unsaturated ketones, which are normally poor substrates in the direct aldol reaction. In the reaction of aldehyde **115** with 3-pentenone, the catalyst derived from ligand **53a** promoted only 15% yield and less than 10% ee. The authors then designed a catalyst which possesses a tertiary alkoxide (ligand **53d**). The yield and enantioselectivity of the aldol products were marginally improved in this case.

Kobayashi and co-workers reported an *anti*-selective asymmetric aldol reaction catalyzed by the chiral zirconium complex **113** (Scheme 74).[99] The 3,3′-$I_2$-BINOL **113b** was found to be a better choice than **113a**, **113c**, or **113d**. Propanol (50 mol %) was found

**Scheme 74**




to be the most suitable proton source in this reaction, which is necessary in order to react with the intermediate to regenerate the catalyst and accelerate the reaction. Aromatic, α,β-unsaturated, and aliphatic aldehydes all reacted with silyl enolates to afford the corresponding aldol adducts in high enantioselectivities and, in most cases, also in good yields and diastereoselectivities. Moreover, high anti selectivities were obtained when both (*E*)- and (*Z*)-silyl enolates were applied.

Kobayashi and co-workers reported another type of catalysts, prepared from zirconium(IV) *tert*-butoxide ($Zr(O^tBu)_4$), (*R*)-3,3′-$I_2$-BINOL, a primary alcohol ($^n$PrOH, 80 mol %), and a small amount of water (20 mol %).[100] The primary alcohol played an important role in completing the catalytic cycle, and the small amount of water was essential for obtaining high selectivities. The activity of the chiral zirconium catalysts was enhanced by introducing electron-withdrawing groups at the 6,6′-positions of the binaphthol scaffold (Figure 17, X = Br, I, $C_2F_5$). Even less reactive substrates reacted smoothly when this novel zirconium catalyst was used.

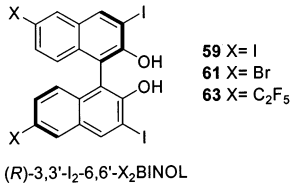


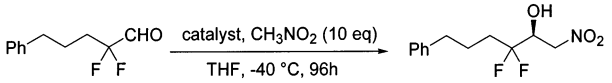

**Figure 17.**

NMR studies of these catalysts suggested that the catalyst forms a dimeric structure and water affects the catalyst formation. It was also found that, with (*R*)-3,3′-$I_2$-6,6′-$X_2$-BINOL (X = Br, I, $C_2F_5$) as ligands, the enantioselectivities can be increased up to 99%. In the case of normal linear aliphatic aldehydes such as hexanal and butanal, the reactions proceeded with high selectivities. γ-Branched aldehydes also reacted smoothly to afford the desired anti-adducts in good yields with high diastereo- and enantioselectivities. Unfortunately, the catalyst did not work well in the reactions of α- and β-branched aliphatic aldehydes. These effects seemed to be caused by steric interactions between the BINOL parts (especially large diiodo atoms at the 3,3′-positions) and the alkyl moieties of the aldehydes. Catalysts prepared from the electron-withdrawing functionalized 6,6′-substituted 3,3′-$I_2$-BINOL showed higher activities and reaction rates than the original catalyst prepared from 3,3′-$I_2$-BINOL. To understand the catalyst activity, the charges on the oxygen atoms of the

**Table 1. Calculated Charges at Oxygen Atoms of Substituted BINOLs**

| BINOL derivatives | charge |
|---|---|
| BINOL | −0.227 |
| 3,3′-$I_2$BINOL | −0.204 |
| 3,3′-$U_2$-6,6′-$Br_2$BINOL | −0.201 |
| 3,3′-6,6′-$I_4$BINOL | −0.202 |
| 3,3′-$I_2$-6,6′-$(C_2F_5)_2$BINOL | −0.197 |

**Scheme 75**




| catalyst (20 mol%) | yield (%) | ee (%) |
|---|---|---|
| Sm-**111d** | 67 | 74 |
| Sm-**111a** | 69 | 89 |
| Sm-**111b** | 58 | 94 |

BINOL derivatives were calculated (Table 1).[101] The order of the catalyst activities showed a good correlation with the order of electron density of the BINOL derivatives. It was found that the lower the electron density, the higher the catalyst activity.

Shibasaki and co-workers applied their heterobimetallic BINOL-derived asymmetric catalysts **111** in asymmetric nitroaldol reactions.[102] One example is the catalytic asymmetric nitroaldol reaction of α,α-difluoro aldehydes (Scheme 75).[95a] $Sm(O^iPr)_3$ proved to be the best lanthanide source for this reaction. Catalyst **111b**/Sm gave the best enantioselectivity of the product (94%) in 58% yield. Other difluoro aldehydes also gave good results using this catalyst, with yields in the 52−73% range and enantioselectivities varying from 70% to 95%.

Since asymmetric nitroaldol reaction proved promising with catalysts **111**, Shibasaki et al. used the reaction in the synthesis of a key intermediate to (*R*)-Arbutamine (Figure 18),[103] which is a catecholamine

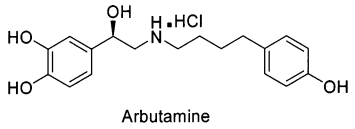


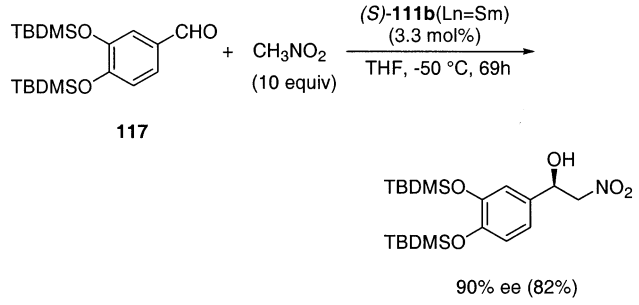

**Figure 18.**

with potential applications in coronary artery disease.[104] After several optimization reactions, the best results were obtained with complex **111b**/Sm (3.3 mol %), using protected diol **117** in THF at −50 °C. The product was obtained in 82% yield with 90% ee (Scheme 76).

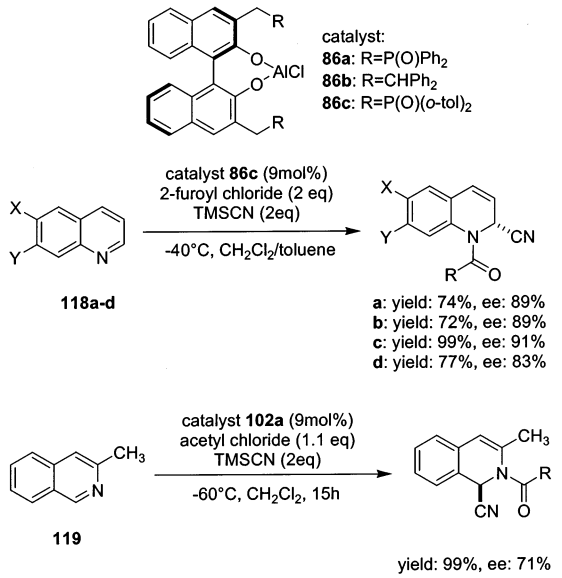
## F. Reissert-Type Reaction

Shibasaki and co-workers reported an asymmetric Reissert-type reaction, promoted by the Lewis acid−Lewis base bifunctional catalyst **86** (Scheme 77).[105] The Lewis acid (Al) activates acyl quinolinium ion, and the Lewis base (oxygen atom of the phosphine oxide) activates the TMSCN, simultaneously. Acid chlorides were found to affect the enantioselectivity of the process. The more electron-rich and therefore less reactive 2-furoyl chloride was found to afford the

**Scheme 76**

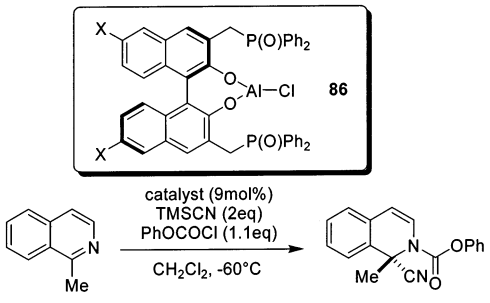



**Scheme 77**




best enantioselectivity. Furthermore, when the steric bulk of the phosphine oxide's aryl groups is increased (from Ph in catalyst **86a** to *o*-tol in catalyst **86c**), both the chemical yield and enantioselectivity is improved. In the case of catalyst **86b**, the desired product was obtained with opposite configuration in much lower enantiomeric excess. Since the diphenylmethyl groups contained in **86b** provide only steric hindrance without Lewis basicity, this result implied the dual

**Scheme 78**




| | X | yield (%) | ee (%) |
|---|---|---|---|
| **86a** | H | 72 | 56 |
| **86d** | Br | 91 | 84 |
| **86e** | F | 74 | 71 |
| **86f** | Cl | 88 | 81 |
| **86g** | I | 85 | 81 |
| **86h** | $CF_3$ | 68 | 48 |

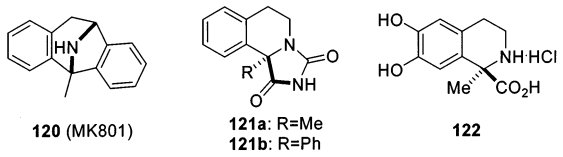



**Figure 19.**

activation mechanism by catalysts **86a** and **86c**. Under optimal conditions, Reissert-type products were obtained in up to 91% ee and 99% yield using the reactive, electron-rich quinolines **118** and isoquinoline derivative **119**. This reaction was later successfully applied in an efficient catalytic asymmetric synthesis of a potent NMDA receptor antagonist (−)-L-689,560.[106]

Catalyst **86a** proved to be unsatisfactory in the enantioselective Reissert-type reaction aimed at construction of quaternary stereocenters. To further improve its efficiency, the bifunctional catalyst was electronically tuned.[107] The strategy to increase the Lewis acidity by introducing an electron-withdrawing groups at the 6,6′-positions of the binaphthol ring proved to be successful. As shown in Scheme 78, catalysts derived from the 6,6′-dihalogen-substituted BINOLs improved both the activity and enantioselectivity. Among them, 6,6′-dibromo-substituted catalyst **86d** gave the best results (91% yieldm with 84% ee). The use of vinyl chloroformate instead of phenyl chloroformate as the acylating reagent further improved the yield to 93% with 88% ee. After optimizing the reaction conditions, the authors found that Reissert-type reactions proceeded smoothly with a broad range of 1-substituted isoquinolines to give products in both excellent yields (up to 95%) and enantioselectivities (up to 95% ee). As an application of this reaction, several biologically relevant compounds, **120**−**122**, were efficiently synthesized (Figure 19).

## G. Olefin Metathesis

Schrock and Hoveyda recently reported the synthesis of Mo-based chiral catalysts and their application in asymmetric olefin metathesis.[108,109] These catalysts efficiently and selectively induce the formation of optically pure or enriched carbo- and heterocycles through asymmetric ring-closing and ring-opening metathesis (ARCM and AROM), respectively. Biphen-based chiral Mo catalysts **123a**,**b** (Figure 20) showed high enantioselectivity in the ARCM of 1,6-dienes, to afford five-membered carbo- and heterocycles. They are, however, significantly less effective

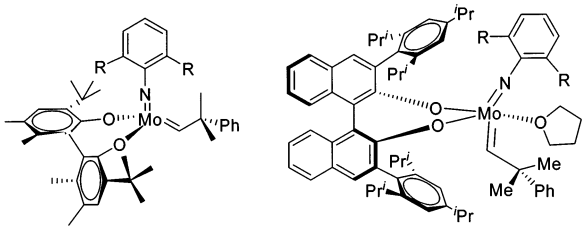



**Figure 20.**

**Scheme 79**

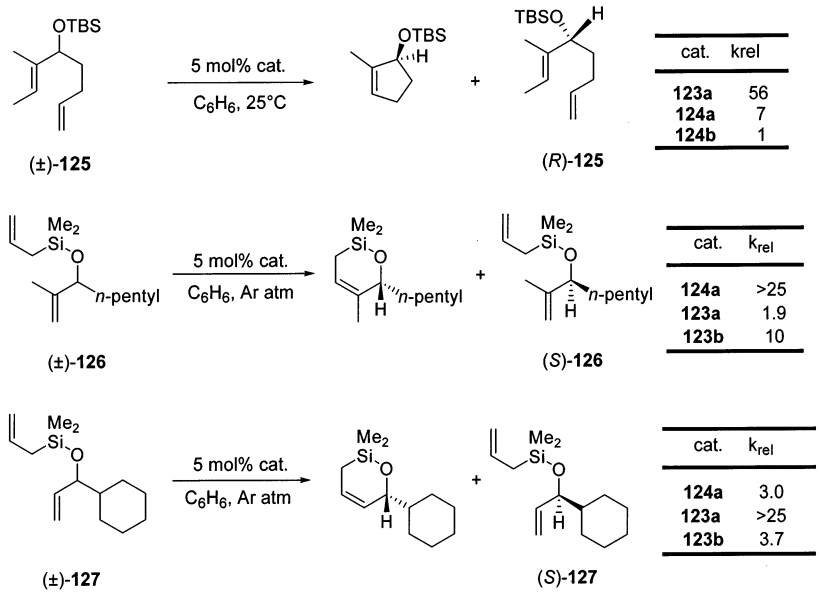
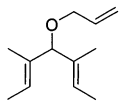
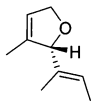
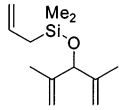
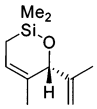
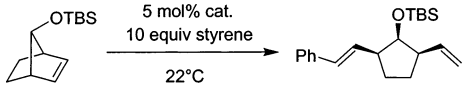



**Table 2. Enantioselective Synthesis of Heterocycle by Mo-Catalyzed Desymmetrization**

| substrate | product | catalyst | yield (%) | ee (%) |
|---|---|---|---|---|
|  |  | **124a** | - | - |
| | | **124b** | 77 | 89 |
| | | **123b** | 83 | 99 |
| **128** | **129** | | | |
|  |  | **124a** | 98 | >99 |
| | | **123a** | 17 | 65 |
| | | **123b** | 20 | 85 |
| **130** | **131** | | | |

**Scheme 80**




**131**

| catalyst | conversion (%) | ee (%) |
|---|---|---|
| **124a** | 18 | 86 |
| **123a** | 39 | 98 |
| **123b** | 51 | 79 |

in promoting the formation of analogous unsaturated pyrans and cyclohexenes, affording low yields and/or selectivities. In contrast, as shown in Scheme 79, the BINOL-based complex **124a** showed excellent enantioselectivity in the ARCM of 1,7-dienes ($k_{rel}$ > 25 with **124a** vs $k_{rel}$ = 1.9 with **123a** for **126**) but significantly reduced selectivity in the formation of five-membered rings by the ARCM of 1,6-dienes ($k_{rel}$ = 7 with **124a** vs $k_{rel}$ = 56 with **123a** for **125**).[110−112] In the case of two terminal alkenes as reaction partners, **123a** is superior to **124a** ($k_{rel}$ = 3.0 with **124a** vs $k_{rel}$ > 25 with **123a** for **127**).

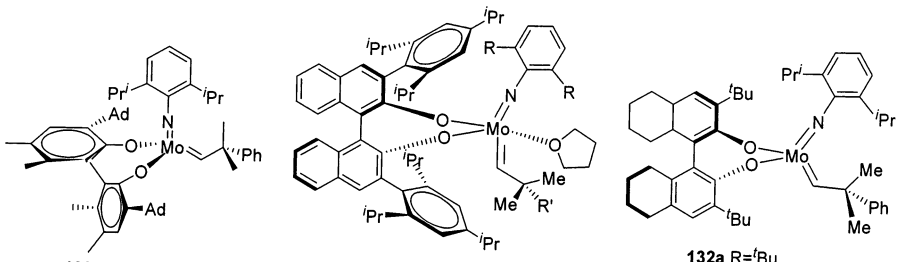
In the process of catalytic desymmetrization of 1,6-dienes, **124a** is unable to initiate the RCM. It is the sterically less demanding complex **124b** that effectively initiates the ARCM of **128**. The biphen complex **123b** proved to be the best choice for the asymmetric formation of the five-membered ring (*R*)-**129**. In contrast, **124a** showed excellent enantioselectivity and reactivity in the asymmetric formation of the six-membered ring (*R*)-**131**. (*R*)-**131** was obtained in >99% ee and 98% isolated yield. The biphen-based catalysts **123a** and **123b** are significantly less effective for substrate **130** (Table 2).

The catalytic AROM/CM with silyl ether **132** and styrene in the presence of **123a**, **123b**, and **124a** was also studied (Scheme 80).[113,114] The BINOL-based catalyst **125a** proved to be less effective than the biphen-based complex **123a** (98% ee and 39% conversion with **123a** vs 86% ee and 18% conversion with **124a**). One notable drawback in this example is that, if the disubstituted olefin is not sterically protected (e.g., norbornene), competitive polymerization of this strained olefin occurs.

Due to the notable difference between the biphen-based catalyst **123** and BINOL-based catalyst **124** and the practical difficulty of preparation of **123**, the authors designed a "biphenol-type" ligand **132** (Scheme 81).[115] **132** was synthesized from the enantiomerically pure binaphthol in three steps and in 46% overall yield. The more easily and efficiently prepared catalyst **132** showed similar or higher levels of selectivity than **123** in both the catalytic kinetic resolution of dienes as well as the catalytic asymmetric desymmetrization of trienes. Moreover, the results showed that **132** can also be employed to promote asymmetric olefin metatheses that are typically best performed by catalyst **124**.

The enantioselective synthesis of unsaturated cyclic tertiary ethers by a tandem asymmetric ring-closing/ring-opening metathesis (ARCM/ROM) was later described.[116,117] In the initial study of cyclopentene **133**, the BINOL-based catalysts **124c** and **124d** exhibited the highest levels of asymmetric induction (Scheme 81). Although high conversion was observed in the case of biphen-based catalyst **132a**, the enantioselectivity was much lower. A variety of cyclopentenyl substrates underwent enantioselective Mo-

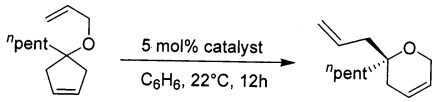
**Scheme 81**



**123d**, Ad=adamantyl

**124c**, R= $^{i}$Pr, R'=Ph
**124d**, R=Cl, R'=Me

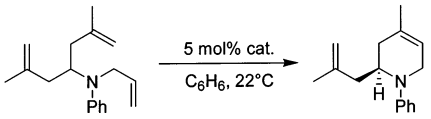
**132a** R=$^{t}$Bu
**132b** R=2,4,6-$Me_3C_6H_2$
**132c** R=$CHPh_2$



**133**

| catalyst | conversion (%) | ee (%) |
|---|---|---|
| **123d** | 18 | 86 |
| **124c** | 39 | 98 |
| **124d** | 51 | 79 |
| **132a** | 90 | 14 |

**Scheme 82**



**134** **135**

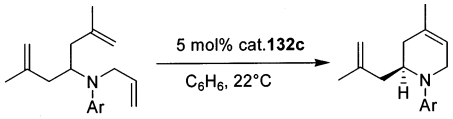
| catalyst | conversion (%) | ee (%) |
|---|---|---|
| **123a** | 95 | 98 |
| **123d** | 95 | 91 |
| **124c** | 84 | 51 |
| **132a** | 95 | 94 |
| **132b** | 95 | 80 |
| **132c** | 95 | 61 |

catalyzed rearrangement to afford the desired pyrans in >90% ee and >70% yield in the presence of **124c**. The catalytic asymmetric desymmetrization of trienes was also studied using **124c**. High yields and good enantioselectivities were obtained only at elevated temperatures.

Catalytic asymmetric ring-closing metathesis was introduced to the synthesis of *N*-containing heterocycles by the same group.[118] In the Mo-catalyzed kinetic resolution of acyclic amines, the available catalysts **123**, **124**, and **132** did not provide satisfactory results. The authors' attention was then turned to the Mo-catalyzed desymmetrization processes. The ability of chiral complexes **123a**, **123d**, and **124a**−**c** to generate the six-membered heterocycle **135** through the ARCM of triene **134** was examined. Complexes **123a** and **132a** proved to be the most effective catalysts (Scheme 82).

When arylamines that bear an ortho substituent were studied, less than 5 mol % conversion was observed using **123a** (5 mol %). The chiral binaphtholate complex **132c** promoted the ARCM of **136a**,**b** in >98% conversion within 20 min to afford the six-membered ring amines **137a**,**b** in 84% and 82% ee, respectively (Scheme 83).

**Scheme 83**



**136a**, Ar=*o*-MeOPh
**136b**, Ar=*o*-BrPh

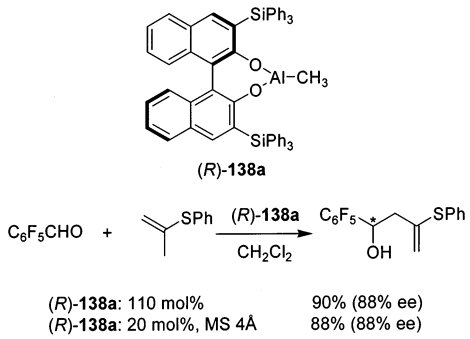
**137a**, Ar=*o*-MeOPh, 77% yield, 84% ee
**137b**, Ar=*o*-BrPh, 90% yield, 82% ee

## H. Ene Reaction

Yamamoto and co-workers reported an asymmetric ene reaction of aldehydes and alkenes catalyzed by a chiral organoaluminum complex.[119] The use of a stoichiometric amount of the chiral Lewis acid was indispensable in the reaction in order to get reproducible results. The presence of 4-Å MS (activated powder) allowed the Lewis acid complex to be used in a catalytic amount (20 mol %) and afforded the products with chemical yields and enantioselectivities similar to and with reaction times comparable to those of the stoichiometric system in some substrates. However, the catalytic amount of chiral Lewis acid did not work well with the less reactive methylene compounds. The steric hindrance of the substituents at the 3,3′-position of the BINOL ligand was crucial to high enantioselectivity. The sterically bulky ligand (*R*)-3,3′-bis(triphenylsilyl)binaphthol promoted the reaction with 90% yield and 88% ee, whereas the less hindered 3,3′-diphenylbinaphthol ligand only gave racemic product in low yield under comparable reaction conditions (Scheme 84).

BINOL-based titanium complexes have also been shown to catalyze the glyoxylate−ene reaction.[120,121] Although these catalysts give products in high enantioselectivities with mono- and disubstituted olefins, low to moderate levels are obtained for trisubstituted olefins. Mikami later reported binaphthyl-derived

**Scheme 84**




chiral titanium complexes (Scheme 85) that enhance the enantioselectivities and give products in high syn/anti ratios.[122,123] The enantioselectivity is highly dependent on the nature of the titanium complex. Much higher levels of enantioselectivity were observed when chiral titanium complex **140c** was used with 6,6′-$Br_2$-BINOL. The syn product **139** was significantly dominant when this catalyst was used. The authors attribute the increased enantioselectivity to shielding over the enantioface of glyoxylate by the halide ligands through the compression of the internal X−Ti−X bond angle.

It was expected that the bulky trifylamine groups of **140b** will direct the enantiofacially selective attack of the ene components to the glyoxylate. However, complex **140b** provided low levels of asymmetric induction.

Mikami and co-workers reported the synthesis of a series of 19-nor-1α,25$(OH)_2D_3$ A-ring analogues based on the carbonyl−ene cyclization catalyzed by **140c**.[124,125] This stereospecific ene cyclization is a key feature in the synthesis of the A-ring analogues. The carbonyl−ene cyclization catalyzed by the (*R*)-6,6′-$Br_2$-BINOL/Ti complex gave the (*Z*)-product as the major product in high enantioselectivity (Scheme 86). The *E*/*Z* stereoselectivity of the product depends on the allylic strain and steric repulsion with the carbonyl/Lewis acid complex. The carbonyl−ene cyclization proceeds via a chair-like transition state (Figure 21). The (*R*)-6,6′-$Br_2$-BINOL/Ti catalyst leads to the 3-(*R*)-hydroxy products through *Re* face control. The (*S*)-6,6′-$Br_2$-BINOL/Ti catalyst provides the opposite endo enantiomer via the transition state with the aldehyde in the equatorial position through *Si* face control.

Complex **140c** can also selectively catalyze the carbonyl−ene reaction between isoprene and fluoroalkyl glyoxylate instead of the corresponding hetero-Diels−Alder (HDA) reaction, to give the final ene product in 84% yield and >99% ee (Scheme 87).[126] The electron-withdrawing $CF_3$ group in glyoxylate is important since, in its absence, greater amounts of the HDA product were seen.

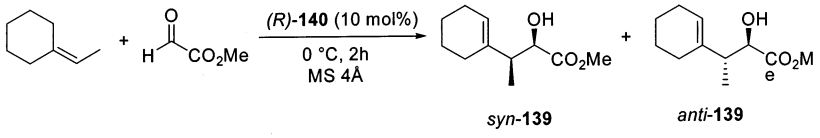
Mikami and co-workers found that the chiral binaphthol−titanium-catalyzed carbonyl−ene reactions display a remarkable positive nonlinear effect.[127] This was attributed to the increased activity of the homochiral BINOL/Ti complexes **A** and **B** compared to that of the more stable meso adduct **C** (eq 3). Yudin and co-workers assembled highly enantioselective "pseudo-meso" aggregates by combining one of the enantiomers of BINOL with its fluorinated counterpart, $F_8$-BINOL.[128]

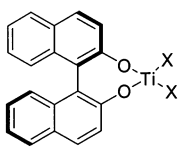
$$\underset{}{M + \textit{rac}\text{-}L \rightarrow} \underset{\textbf{A}}{ML_RL_R} + \underset{\textbf{B}}{ML_SL_S} + \underset{\textbf{C}}{ML_RL_S} \quad (3)$$

$$M = \text{Ti(IV)};\ L = \text{BINOL}$$

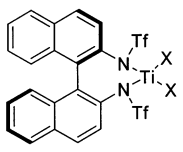
The reaction between ethyl glyoxylate and α-methylstyrene in the presence of 10 mol % of (*S*)-$F_8$-BINOL/Ti$(O^iPr)_4$ (2:1 ratio) afforded the corresponding ene product in 53% yield and 92% ee (Scheme 88). Initial rate studies indicated that the reaction

**Scheme 85**

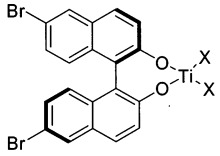



(*R*)-**140a**



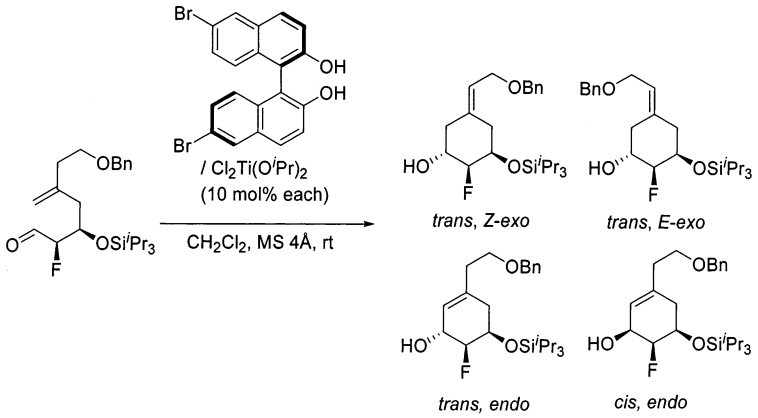

(*R*)-**140b**




(*R*)-**140c**

| **140** (X) | yield | *syn* (ee%) | *anti* |
|---|---|---|---|
| **140a** (Cl) | 61 | 93 (69) | 7 |
| **140a** (Br) | 71 | 94 (50) | 6 |
| **140b** (Cl) | 52 | 78 (3) | 22 |
| **140c** (Cl) | 60 | 93 (88) | 7 |
| **140c** (Br) | 84 | 94 (89) | 6 |

**Scheme 86**




| catalyst | yield (%) | *trans,Z-exo* | *trans,E-exo* | *trans-endo* | *cis-endo* |
|---|---|---|---|---|---|
| *(R)*-6,6'-$Br_2$BINOL-Ti | 94 | 71 | 8 | 11 | 6 |
| *(S)*-6,6'-$Br_2$BINOL-Ti | 63 | 40 | 12 | 25 | 22 |

catalyzed by $F_8$-BINOL/Ti($O^iPr$)$_4$ was 4 times slower than the reaction catalyzed by BINOL/Ti($O^iPr$)$_4$. These results suggest that moderate enantioselectivity is to be expected when (*R*)-$F_8$-BINOL/(*S*)-BINOL/Ti($O^iPr$)$_4$ catalyst is used. As shown in Scheme 88, however, the reaction proceeded with excellent enantioselectivity and significant yield improvement compared to the cases when either BINOL or $F_8$-BINOL was used alone.

## I. Friedel–Crafts Reaction

The Friedel–Crafts reaction is well known and one of the most fundamental C–C bond-forming reactions. Although it is a synthetically valuable process, only limited attention has been paid to its catalytic asymmetric variants.[129]

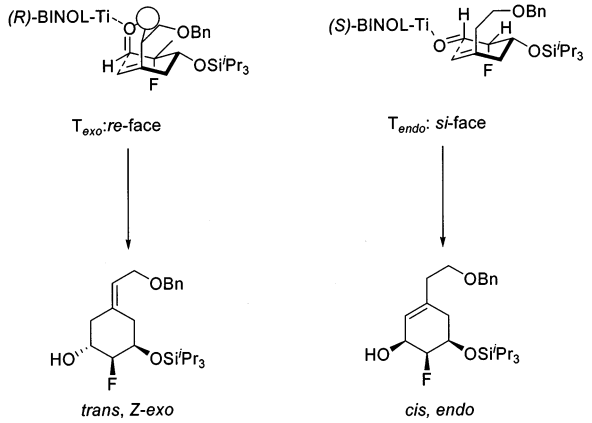
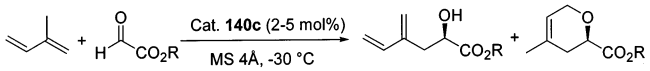


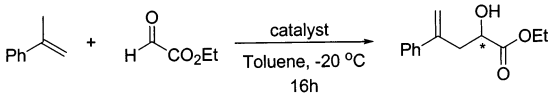

**Figure 21.**

**Scheme 87**




| | ene | | HDA |
|---|---|---|---|
| R | yield (%) | ee (%) | yield (%) |
| Me | 83 | 99 | 17 |
| $(CH_2)_3Me$ | 85 | >99 | 15 |
| $CH(Me)_2$ | 90 | 92 | 10 |
| $CH_2CF_3$ | 92 | >99 | 8 |

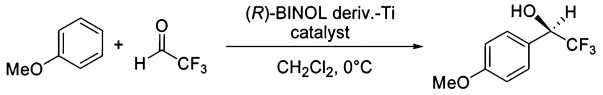
**Scheme 88**




| catalyst | yield (%) | ee (%) |
|---|---|---|
| *(S)*-**27** (10 mol%), Ti($O^iPr$)$_4$ (5 mol%) | 53 | 92 *(S)* |
| *(R)*-**27** (5 mol%), *(S)*-**1** (5 mol%) Ti($O^iPr$)$_4$ (5 mol%) | 95 | 99 *(S)* |
| *(R)*-**27** (5 mol%), *rac*-**1** (5 mol%) Ti($O^iPr$)$_4$ (5 mol%) | 65 | 78 *(R)* |

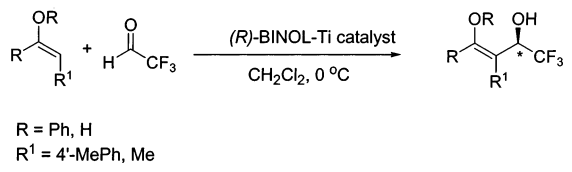
Mikami and co-workers reported a Friedel–Crafts reaction with fluoral catalyzed by BINOL-derived titanium catalysts (Scheme 89).[130] The catalytic activity of the BINOL/Ti catalysts was influenced by the substituents on the binaphthol ring scaffold. The catalyst prepared from (*R*)-6,6′-$Br_2$-BINOL was more effective than the one made of (*R*)-BINOL or (*R*)-$H_8$-BINOL, which meant that this reaction required a stronger Lewis acid. While (*R*)-6,6′-$Br_2$-BINOL gave the para product in 75% yield and 84% ee, the para product was obtained in only 66% yield and 73% ee with (*R*)-BINOL and 9% yield with 22% ee with (*R*)-$H_8$-BINOL.

**Scheme 89**

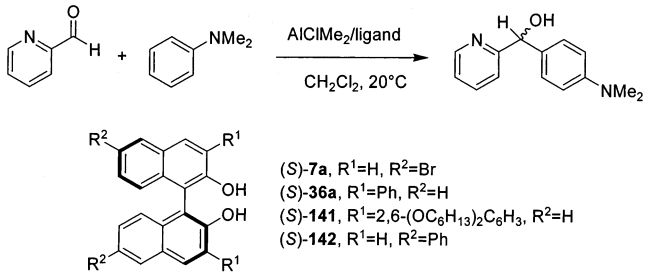



Asymmetric Friedel–Crafts reaction of vinyl ethers with fluoral can be similarly catalyzed by modified BINOL/Ti complexes.[131] The catalyst prepared from (*R*)-6,6′-$Br_2$-BINOL/Ti($O^iPr$)$_4$ (2:1),[130] which was the most effective catalyst for the Friedel–Crafts reaction

**Scheme 90**




**Scheme 91**




| ligand | yield (%) | ee (%) |
|---|---|---|
| **1** | 63 | 43 |
| **7a** | 52 | 16 |
| **36a** | 14 | 13 |
| **141** | 50 | 29 |
| **142** | 26 | 36 |

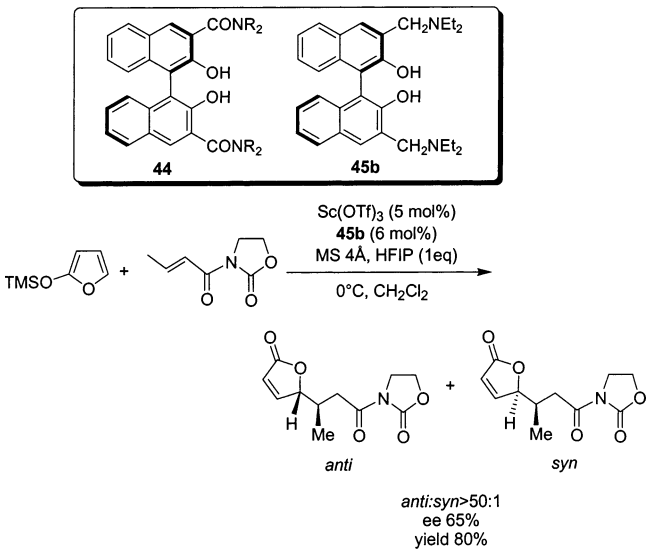
of aromatic compounds, gave only the aldol product. It was proposed that the acidic protons of the [(*R*)-6,6′-$Br_2$-BINOL]$_2$/Ti(O$^i$Pr)$_2$ hydrolyze the corresponding Friedel−Crafts product. Indeed, the catalyst prepared in isolated form from (*R*)-6,6′-$Br_2$-BINOL and $Cl_2$Ti(O$^i$Pr)$_2$ in the presence of 4-Å MS[132] gave the Friedel−Crafts product (72−85% ee), together with a small amount of the aldol product (Scheme 90).

Jørgensen and co-workers reported an asymmetric Friedel−Crafts reaction between pyridine-2-carboxaldehyde and *N*,*N*-dimethylaniline mediated by aluminum complexes containing chiral BINOL or modified BINOL ligands. The results were still unsatisfactory: first, due to the strong Al−O bond between the product alcohol and the chiral Lewis acid, a stoichiometric amount of Lewis acid was required; and second, even with the stoichiometric amount of Lewis acid, the yields and enantioselectivities of this reaction were still quite low. The highest ee of 50% was obtained with only 25% yield in benzene when (*R*)-BINOL was used as the ligand (Scheme 91). In nitromethane, the highest yield (93%) was observed with only 5% ee.[133] The 3,3′-substituted or 6,6′-substituted BINOL derivatives were also examined in the reaction. Under the same reaction conditions, none of these substituted BINOL derivatives showed better results than (*R*)-BINOL.

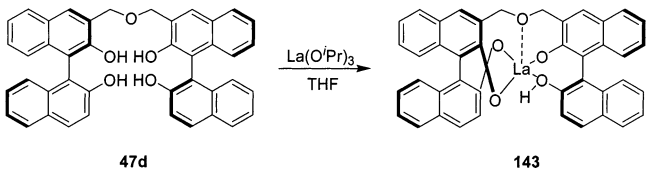
## J. Michael Addition Reaction

Katsuki and co-workers described an asymmetric Michael addition reaction of 2-(trimethylsilyloxy)-furans to oxazolidinone enoates, catalyzed by Sc(OTf)$_3$ and 3,3′-bis(diethylaminomethyl)-1,1′-bi-2-naphthol **45b** (Scheme 92).[134] Excellent anti selectivity (anti/syn > 50:1) and moderate enantioselectivity

**Scheme 92**




**Scheme 93**



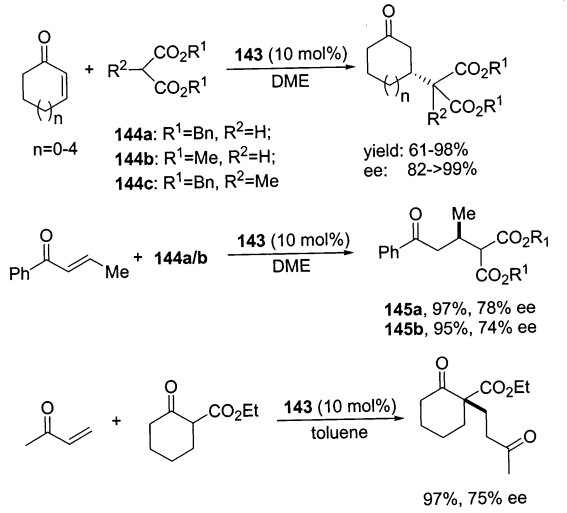

(73% ee) were observed with a modest chemical yield (44%); however, in the case of a combination of either Sc(OTf)$_3$ and (*R*)-BINOL or Sc(OTf)$_3$ and *N*,*N*,*N*′,*N*′-tetraalkyl-BINOL-3,3′-dicarboxamides **44**, both the chemical yield and enantioselectivity of the desired product were found to be modest. Addition of 1 equiv of hexafluoroisopropyl alcohol (HFIP) to the reaction system increased the yield to 80%, with a slight loss in enantioselectivity (65% ee). It was also found that the enantioselectivity decreased dramatically when the ethyl groups on the amino nitrogen atoms in compound **45b** were replaced by other alkyl groups.

High reactivity and enantioselectivity were reported in an asymmetric Michael reaction by Shibasaki and co-workers, using their La-linked BINOL complex (*R*,*R*)-**143** as the catalyst.[135] Complex **143** was easily prepared from La(O$^i$Pr)$_3$ and 1.0 equiv of linked BINOL **47d** in THF and functioned as both a Lewis acid (La) and a Brønsted base (lanthanum naphthoxide moiety, Scheme 93).

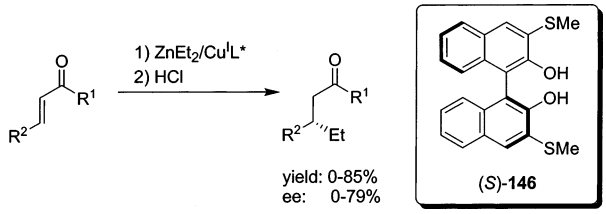
As shown in Scheme 94, (*R*,*R*)-**143** not only showed good reactivity and enantioselectivity, but also had a broad generality. A variety of cyclic (from five- to nine-membered rings) and acyclic enones reacted with malonates or β-keto esters to afford Michael adducts under the promotion of complex **143**. Furthermore, **143** was highly stable and could be easily recovered from the reaction mixture. The recovered complex **143** was reused several times with almost the same enantioselectivity and only a slight loss of reactivity.

A copper-catalyzed asymmetric 1,4-addition of $ZnEt_2$ to linear aliphatic enones was described by Woodward and co-workers.[136] 3,3′-Dimethylsulfanyl-BINOL (*S*)-**146** was used as the chiral ligand in their system. The best yield reported was 85%, with 72% ee. On

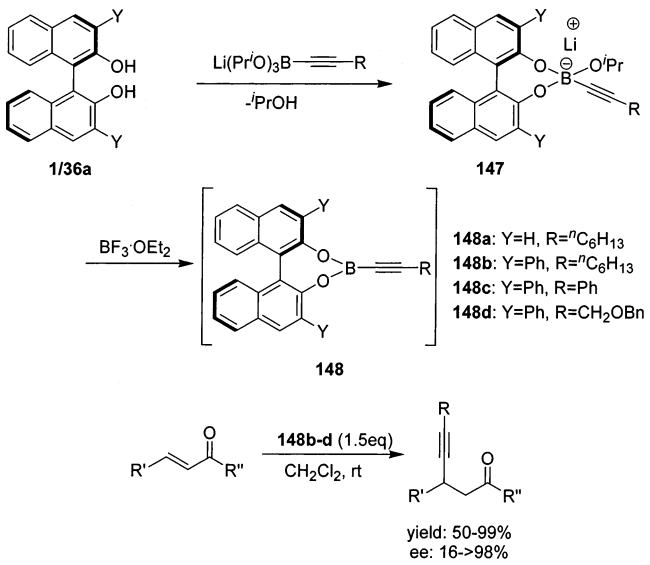
**Scheme 94**




**Scheme 95**



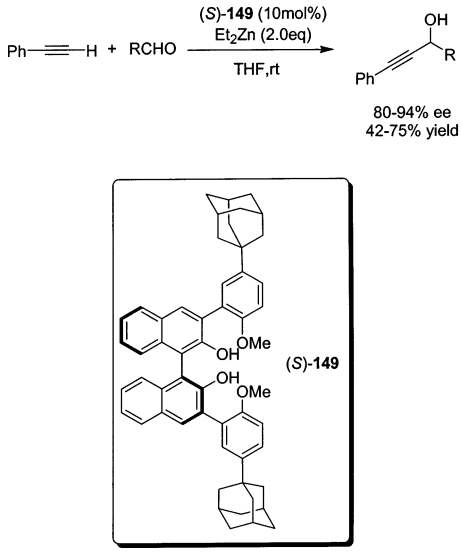

**Scheme 96**




the other hand, the highest ee was 79%, with 43% yield. In the case of most enones tested, the catalyst system $ZnEt_2$/(*S*)-**146**/$[Cu(MeCN)_4]BF_4$ affords only marginal results (Scheme 95).

Chong and co-workers reported the first example of enantioselective conjugate addition of alkynyl groups to enones,[137] which was an important limitation to the Michael addition of organocopper reagents, since usually the organocopper reagents do not efficiently transfer alkynyl groups to organic substrates. Borate **147** was prepared from binaphthols **1** or **36a** with lithium *B*-1-octynyltriisopropylborate, followed by removal of $^i$PrOH (Scheme 96). Treatment with $BF_3$·$OEt_2$ converted **147** to the reactive trivalent boronate **148** in situ. The observed enantioselectivity was only 31% in the reaction of **148a** and chalcone, though the yield was as high as 90%. Higher enantioselectivities could be obtained in the conjugate addition to chalcone when 3,3′-diphenylbinaphthol **148b** (85% ee and 88% yield) was used in place of the parent BINOL **148a**. In all cases, reactions using the 3,3′-diphenylbinaphthol reagents (**148b**−**d**) were much more selective than those with **148a**. Good to excellent yields and enantioselectivities were obtained for a variety of enone substrates using **148b**−**d** as the alkynylating reagents (yield up to 99%, ee up to 98%). The reaction is also substrate dependent. An aryl group directly attached to the carbonyl carbon of the enone is preferred for high reactivity, while both the size and electronic character of the $\beta$-substituent are also important for enantioselectivity. The best selectivities were observed when the $\beta$-substituents contained electron-rich $\pi$-systems.

**Scheme 97**



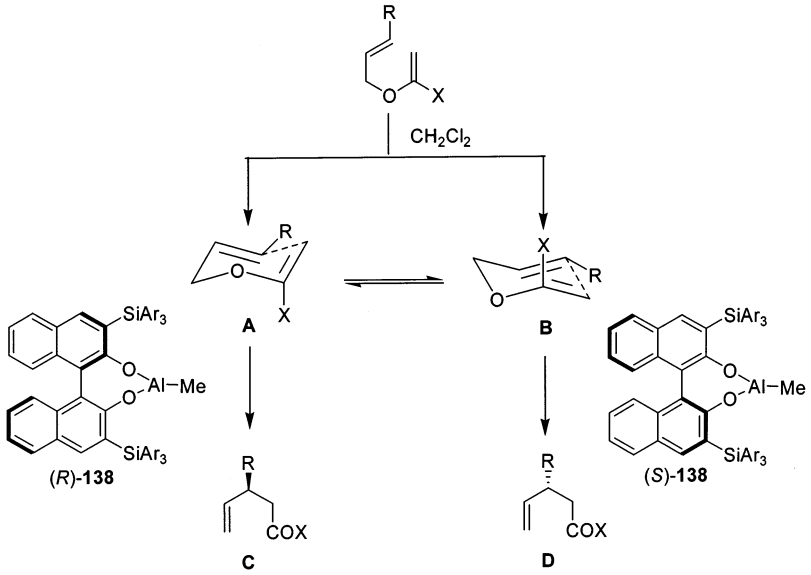

## K. Phenylacetylene Addition to Aromatic Aldehydes

Pu and co-workers reported an asymmetric phenylacetylene addition to aromatic aldehydes.[138] The catalyst contains a 1,1′-binaphthyl portion with bulky 3,3′-aryl substitutents ((*S*)-**149**). The enantioselectivities range from 80% to 94% ee for the reaction of phenylacetylene with different aromatic aldehydes containing electron-donating or electron-withdrawing substituents. Unlike the parent BINOL catalyst,[139] this new catalytic system does not require the use of $Ti(O^iPr)_4$ and a separate step to prepare the alkynylzinc reagent (Scheme 97).

## L. Claisen Rearrangement

In 1990, Yamamoto and co-workers reported the first successful example of the asymmetric Claisen rearrangement of *trans*-allylic vinyl ethers catalyzed by a chiral organoaluminum reagent, (*R*)-**138** or (*S*)-**138** ($Ar_3$ = $^t$Bu$Ph_2$) (Scheme 98).[140] The reactions involve a [3,3]-sigmatropic rearrangement and take place by a concerted mechanism through a cyclic six-

**Scheme 98**



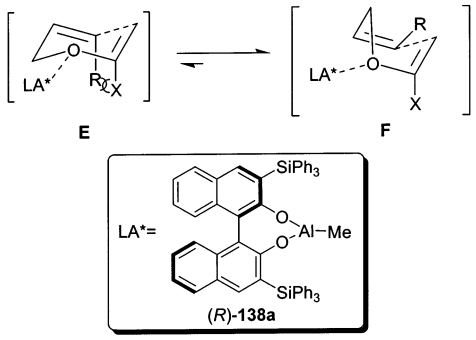

membered chair-like transition state.[141] For the asymmetric rearrangement, two possible chair-like transition-state structures, **A** and **B**, need to be considered, each of which is readily converted to enantiomers **C** and **D** (Scheme 98). No rearrangement occurred when 3,3′-diphenylbinaphthol was used as ligand. Among the various trialkylsilyl substituents introduced at the 3,3′-positions of the binaphthol system, the bulky *tert*-butyldiphenylsilyl group exhibited the highest enantioseclectivities (71−93% ee, depending on the substrate). The reaction was also found to be highly dependent on the substrate as well as the solvent. Good yields and enantioselectivities were obtained only when substituent X in the substrate was $SiMe_3$ or $GeMe_3$.

Further studies indicated that the asymmetric Claisen rearrangement of *cis*-allylic vinyl ethers with chiral organoaluminum reagent **138** produced optically active products with the same absolute configuration as those from *trans*-allylic vinyl ethers.[142] The rearrangement of *cis*-allylic vinyl ethers was believed to proceed via a boat-like transition state rather than the normal chair-like transition state described in the rearrangement of *trans*-allylic vinyl ethers, due to the severe 1,3-diaxial interaction between R and the bulky group X in **E**. The more hindered aluminum reagent (*R*)-**138** seemed to destabilize the boat-like transition state **F** and resulted in lower enantioselectivity than the less hindered (*R*)-**138a** (Scheme 99).

## M. Organozinc and Organoaluminum Addition to Aldehydes

Enantioselective addition of dialkylzinc to aldehydes is one of the most reliable methods to prepare chiral *sec*-alcohols[143] and also a standard reaction to test the reactivity and enantioselectivity of newly designed chiral ligands. Katsuki and co-workers described the application of 1,1′-bi-2-naphthol-3,3′-dicarboxamide as a chiral ligand in the enantioselective addition of diethylzinc to a variety of aldehydes (Figure 22).[144] Among the ligands they used, **44d** exhibited high yields and excellent enantioselectivities in the reaction of aromatic aldehydes. On the other hand, **44e** induced excellent enantioselectivities with moderate yields in the reaction of α,β-unsaturated and α-branched aliphatic aldehydes.

**Scheme 99**



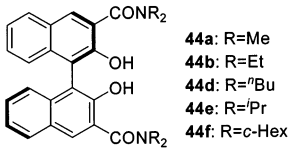
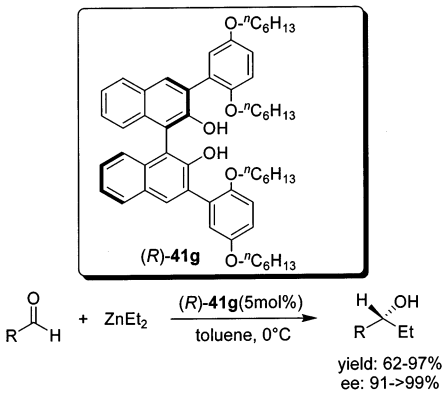




**Figure 22.**

(*R*)-3,3′-Diaryl-BINOL **41g** was synthesized by the Pu laboratory and showed excellent enantioselectivity (91−99% ee) in the diethylzinc addition to various aldehydes, including ortho-, meta-, and para-substituted benzaldehyde, linear or branched aliphatic aldehydes, and alkyl- or aryl-substituted α,β-unsaturated aldehydes (Scheme 100).[145]

Due to its excellent catalytic activity, (*R*)-**41g** was further applied to the asymmetric diarylzinc addition to aldehydes.[146] Through variation of solvent, reaction temperature, concentration of the aldehydes, and amount of catalyst (*R*)-**41g** used, and with the use of additives such as diethylzinc or methanol, good to excellent enantioselectivities (83−94% ee) for the addition of diphenylzinc to various aromatic aldehydes and an α,β-unsaturated aldehyde have been achieved.

**Scheme 100**

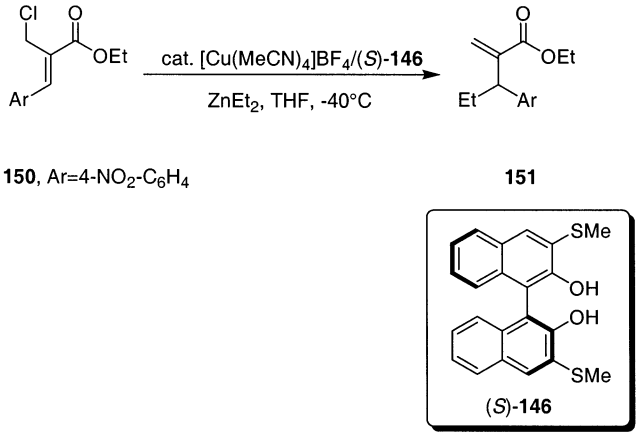



The main challenge in this reaction is to overcome uncatalyzed reaction of diphenylzinc with aldehydes. This requires the chiral catalyst-mediated reaction to be much faster than the background reaction. The strategy to increase the catalytic activity of the ligand (*R*)-**41g** was therefore undertaken by introduction of electron-withdrawing substituents in order to increase the Lewis acidity of the zinc center which was generated in situ from the reaction of (*R*)-**41g** with diethylzinc. Thereby, a series of chiral ligands, (*S*)-**41a**−**e** (see Scheme 23), where multiple fluorine atoms are introduced to the 3,3′-aryl groups, were synthesized by Suzuki coupling. In the diphenylzinc addition to cinnamaldehyde, the latter ligands exhibited much better enantioselectivities than (*R*)-**41g** without addition of methanol. Ligand (*S*)-**41d**, with two fluorine atoms on each of the 3,3′-aryl substituents, showed the highest enantioselectivity (87% ee). In contrast, ligand (*S*)-**41c**, containing three fluorine atoms on each of the 3,3′-aryl substituents, did not enhance the enantioselectivity over (*S*)-**41d** any further and gave 81% ee in the reaction. When electron-withdrawing bromine substituents are introduced to the 6,6′-positions of the binaphthyl ring, the coordination between diphenylzinc and the binaphthol oxygen atom is reduced, disfavoring the chiral ligand-controlled addition. Therefore, lower enantioselectivity was induced by ligand (*S*)-**41f** (70% ee) compared to (*S*)-**41b** (81% ee). Swapping the hexyloxy groups of (*S*)-**41d** to smaller methoxy groups in (*S*)-**41e** also led to reduced enantioselectivity. Ligand **41d** was further examined in the reaction of various aryl aldehydes, and good to excellent enantioselectivities were obtained (80−95% ee).[147]

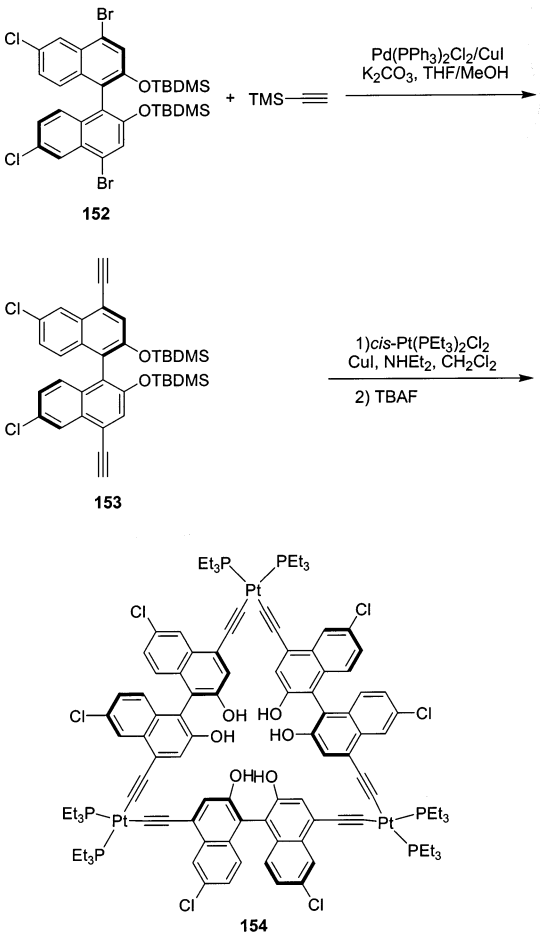
3,3′-Dimethylsulfanyl-BINOL (*S*)-**146** was used as a chiral ligand in the asymmetric $S_N2'$ addition of organozinc reagents to allylic compounds **150**.[148] Compound **150** was found to be the best substrate, with chloride as the leaving group. In the presence of the $[Cu(MeCN)_4]BF_4$/(*S*)-**146** complex, product **151** was obtained in 64% ee at −40 °C (Scheme 101).

Lin and co-workers described a chiral organometallic triangle **154**, which was synthesized from enantiomerically pure **152**[149] in two steps (Scheme 102).[150] Compound **154** showed high enantioselectivity in the diethylzinc addition to various aromatic aldehydes. The enantiomeric excess of the resulting secondary alcohols ranged from 89% to 92%.

**Scheme 101**



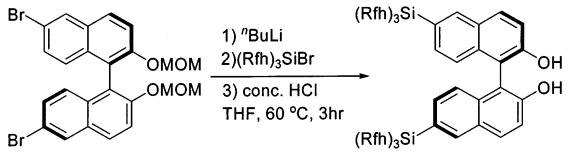

**Scheme 102**




Fluorous BINOLs (F-BINOLs) have been synthesized[49] as ligands and have been used to catalyze the asymmetric addition of diethylzinc to aromatic aldehydes in an organic and FC-72 ($CF_3(CF_2)_4CF_3$) biphasic system.[50,51] The synthesis of these ligands is shown in Scheme 103.

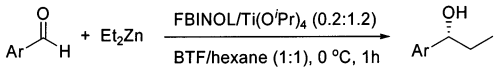
The asymmetric addition of diethylzinc to aromatic aldehydes was carried out under reaction conditions similar to those reported by Nakai[52] in order to compare chemical yields and enantioselectivities (Scheme 104). The results obtained were similar to those reported by Nakai (97% yield and 85% ee for benzaldehyde). (*R*)-$F_{13}$-BINOL/Ti($O^iPr$)$_4$ gave 92% yield and 84% ee, and (*R*)-$F_{17}$-BINOL/Ti($O^iPr$)$_4$ gave

**Scheme 103**




Rfh = $C_6F_{13}CH_2CH_2$- ; *(R)*-$F_{13}$BINOL yield: 89% (2 steps)
Rfh = $C_8F_{17}CH_2CH_2$- ; *(R)*-$F_{17}$BINOL yield: 76% (2 steps)

**Scheme 104**[a]




*(R)*-$F_{13}$BINOL/Ti(O$^i$Pr)$_4$ : yield = 92%, ee = 84%
*(R)*-$F_{17}$BINOL/Ti(O$^i$Pr)$_4$ : yield = 86%, ee = 83%

[a] BTF = benzotrifluoride.

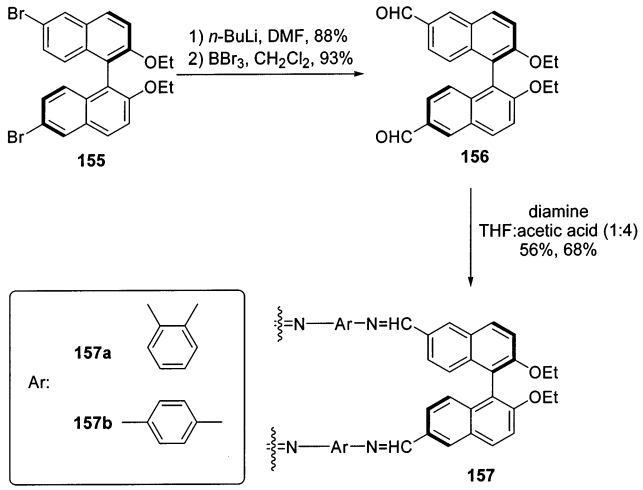
86% yield and 83% ee. In both cases, the ligands were quantitatively recovered. The highest enantioselectivity was obtained using $F_{13}$-BINOL and 1-naphthaldehyde, giving the corresponding product in 98% yield with 91% ee. The ligand was reused five times, and the yield and enantioselectivity remained the same throughout the runs.

Perfluorobutyl- and perfluorooctyl-BINOL derivatives substituted at the 4,4′-, 6,6′-, or 4,4′,6,6′-positions have also been prepared by Chan and co-workers.[53] These fluorous BINOL ligands were used in similar asymmetric addition of diethylzinc to aromatic aldehydes in fluorous biphase systems (perfluoro(methyldecalin)/hexane), as mentioned above.[54] Lower enantioselectivities than in the previous example were obtained. For the reaction of benzaldehyde with diethylzinc, ligand **67** (Scheme 37) gave enantioselectivities in the range of 25−60% and chemical yields between 70% and 80%.

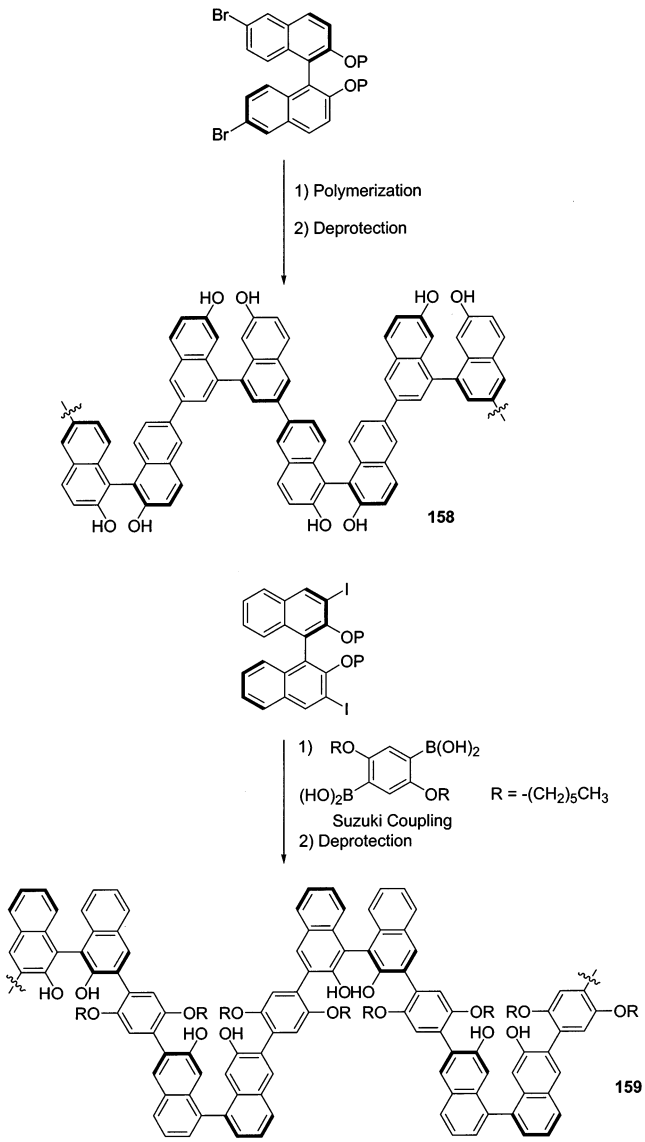
Chiral polymeric BINOL/Ti-derived catalysts were also used in the asymmetric addition of diethylzinc to aromatic aldehydes.[151] These catalysts are attractive because they can be separated from the products by simple filtration. Most chiral polymer catalysts were prepared by attaching the chiral ligand to a polymer backbone.[152] This system makes it difficult to fine-tune the catalytic center. Chan and co-workers described a new synthetic route to chiral polymers starting from **155** (Scheme 105). The active catalyst was formed by mixing the polymer with Ti(O$^i$Pr)$_4$ in a 1:1 molar ratio. The polymer **157b**/Ti complex proved to be more enantioselective than the polymer **157a**/Ti catalyst, giving 1-phenyl-2-propanol from the reaction of benzaldehyde with diethylzinc in 92.5% conversion and 80% ee. On the other hand, polymer **157a**/Ti gave the product in 91% conversion, with 63.9% ee.

Pu and co-workers also introduced functionalized chiral polybinaphthols in the asymmetric addition of diethylzinc to aldehydes.[153−155] Depending on whether polymerization occurs at the 6,6′-positions of the binaphthyl moiety or its 3,3′-positions, it is possible to systematically adjust the steric and electronic properties of the metal centers in the polymer and optimize their catalytic activity (Scheme 106). The authors defined these polymers as "major-groove" and

**Scheme 105**

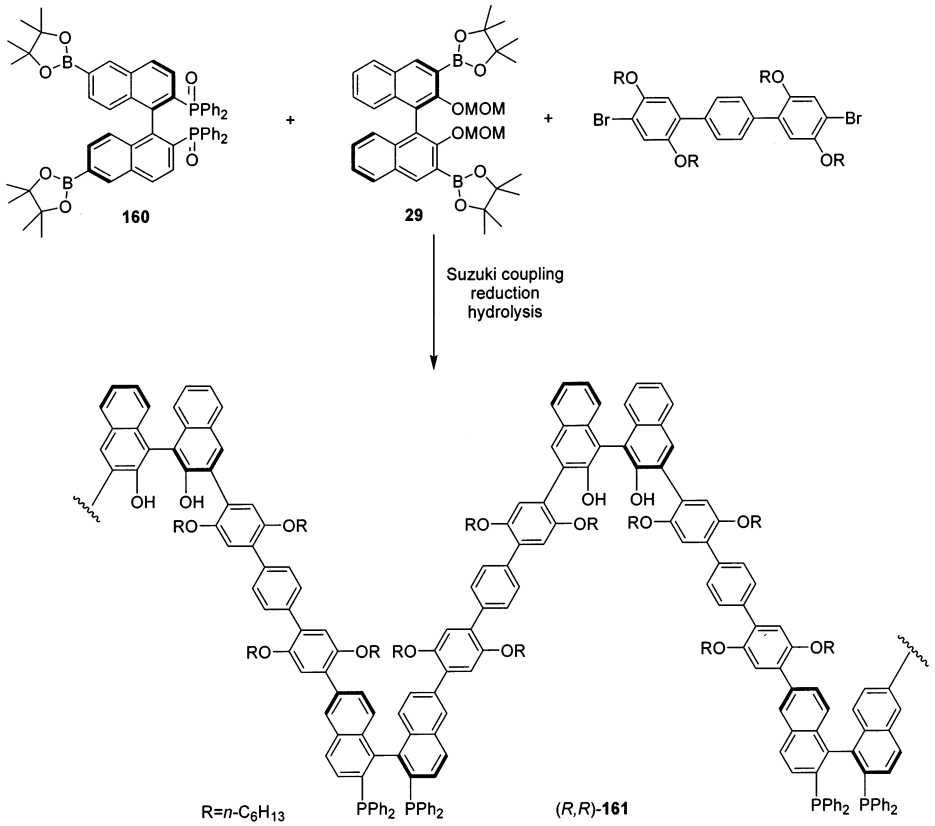



**Scheme 106**




"minor-groove" polybinaphthyls. All of the reactions were carried out in the presence of approximately 5 mol % of the polymer and 1−2 equiv of diethylzinc. The "major-groove" polymer gave the product in 100% conversion, with 13% ee. The "minor-groove" polymer,

**Scheme 107**




on the other hand, gave the desired product in 100% conversion, with 92% ee, and no byproduct was observed. In all the reactions conducted, the 3,3′-substituted polymer (minor groove) could be easily recovered by precipitation in methanol. The recycled polymer showed similar enantioselectivity.

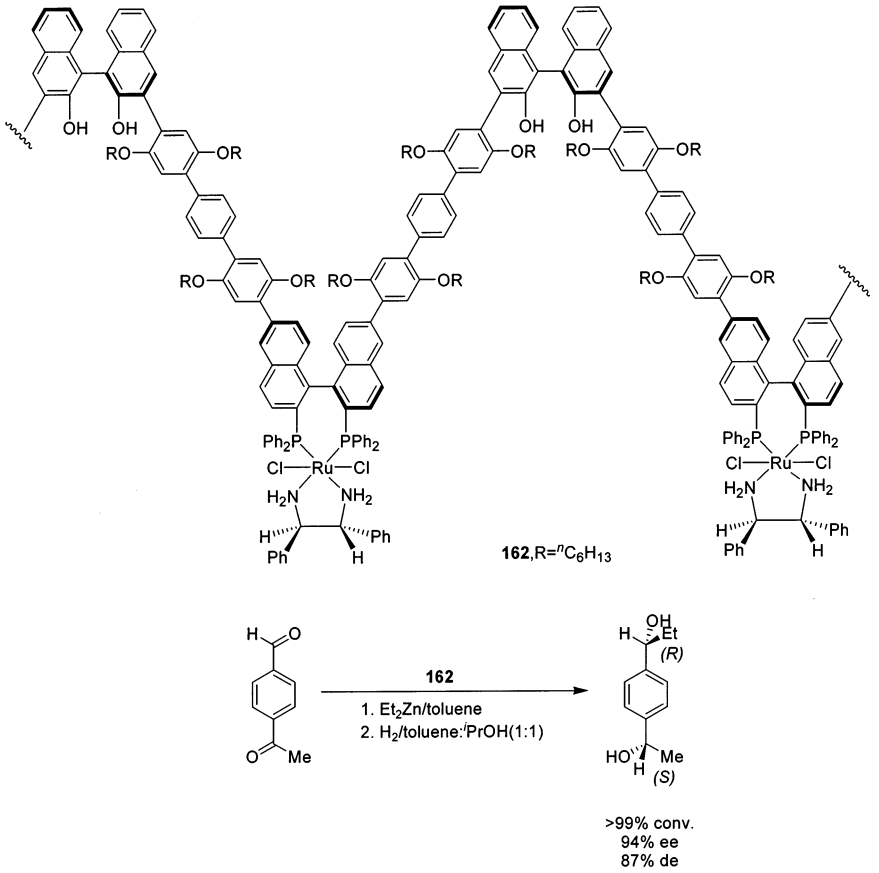
By using a triphenylene dibromide linker molecule, Pu and co-workers synthesized the copolymer (*R*,*R*)-**161** from (*R*)-**39** and (*R*)-**160** in a 1:1 ratio (Scheme 107).[156] In this polymer, the BINOL and BINAP units are expected to be distributed randomly along the polymer chain. The polymer (*R*,*R*)-**161** can be dissolved in common organic solvents such as $CH_2Cl_2$, THF, toluene, and DMF. By reaction with $[RuCl_2(C_6H_6)]_2$ and (*R*,*R*)-DPEN, (*R*,*R*)-**161** was then converted to the polymeric ruthenium(II) complex **162** (Scheme 108). The catalytic reactivity of **162** was examined in a tandem catalytic asymmetric diethylzinc addition and asymmetric hydrogenation of *p*-acetylbenzaldehyde. The ee for the diethylzinc addition was 92%, and the de for the hydrogenation step was 86%. This result showed that the stereoselectivities of the copolymer catalyst are similar to those of the corresponding monomer catalysts.[157−159] Good stereoselectivities were also observed in the tandem asymmetric diethylzinc addition/hydrogenation of *m*-acetylbenzaldehyde using **162** (94% ee in the diethylzinc addition and 75% de in the hydrogenation step). It is noteworthy that this bifunctional polymer catalyst can also be used as either a BINOL or BINAP catalyst for individual asymmetric reactions in addition to the uses in the tandem asymmetric reactions. For example, **162** can catalyze the asymmetric hydrogenation of acetophenone to (*S*)-1-phenylethanol in 84% ee and >99% conversion. **162** can also catalyze the diethylzinc addition to aldehydes to generate (*R*)-1-(*p*-acetylphenyl)propanol in 95% ee with complete conversion. The copolymer catalyst **162** can be easily recovered. Similar reactivity and enantioselectivity were obtained by using the recovered catalyst (93% ee in diethylzinc addition and 78% de in the hydrogenation step, with >99% conversion in the reaction of *p*-acetylbenzaldehyde).

Fan and Chan described two soluble bifunctional polymeric ligands, (*R*,*R*)-**165a** and (*R*,*R*)-**165b**.[160] Copolymers (*R*,*R*)-**165** were prepared via the direct condensation reaction of **163** with (*R*)-**164** using glacial acetic acid as solvent (Scheme 109).

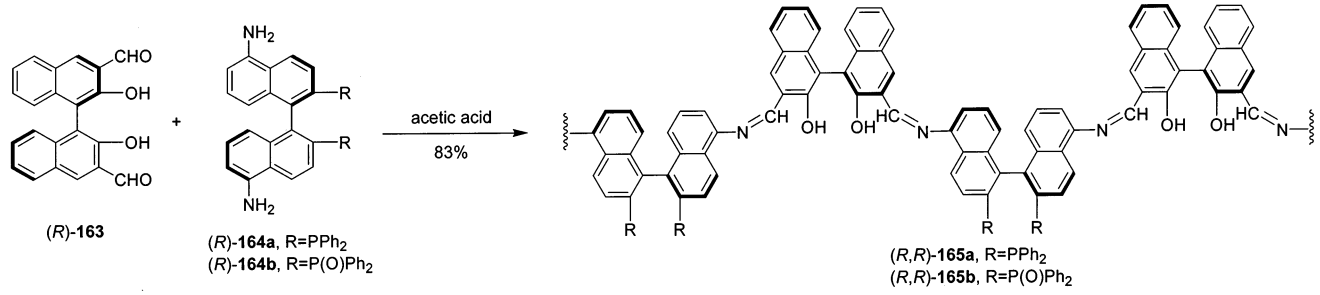
Both polymers (*R*,*R*)-**165a** and (*R*,*R*)-**165b** can be dissolved in common organic solvents such as $CH_2Cl_2$, THF, and toluene. They were active in the addition of diethylzinc to benzaldehyde (Scheme 110). The (*R*,*R*)-**165a**/Ti(IV) catalyst has efficiency similar to that of the parent catalyst (*R*)-BINOL/Ti(IV), giving product 1-phenyl-2-propanol in 84% ee, while (*R*,*R*)-**165b**/Ti(IV) gave the corresponding alcohol in only 48% ee. Moreover, in the absence of $Ti(O^iPr)_4$, polymers (*R*,*R*)-**165a** and (*R*,*R*)-**165b** still promoted the reaction in 100% conversion with 38% ee and 98% conversion with 16% ee, respectively. In contrast, the reactivity of the parent ligand (*R*)-BINOL was dramatically reduced in the absence of $Ti(O^iPr)_4$.

Dimitrov and co-workers reported the use of steroidal axially chiral binaphthols in the asymmetric addition of diethylzinc to aromatic aldehydes.[161] Diol **166** was obtained from estrone in two steps.[162] The catalysts were prepared in situ by adding equimolar amounts of $Ti(O^iPr)_4$ to binaphthols **166** and **64** (Scheme 111). The additions were relatively fast

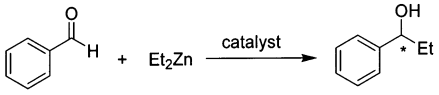
**Scheme 108**




**Scheme 109**



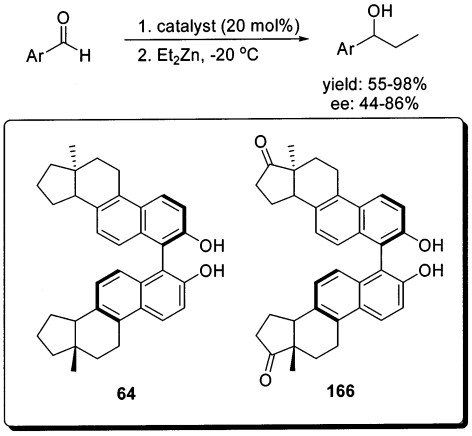

**Scheme 110**




| catalyst | ee (%) | conv. (%) |
|---|---|---|
| (*R*)-BINOL+Ti(O$^i$Pr)$_4$ | 85 | 98 |
| (*R,R*)-**165a**+Ti(O$^i$Pr)$_4$ | 84 | 95 |
| (*R,R*)-**165a**+Ti(O$^i$Pr)$_4$ | 84 | 99 |
| (*R,R*)-**165b**+Ti(O$^i$Pr)$_4$ | 48 | 100 |
| (*R*)-BINOL | 5 | 19 |
| (*R,R*)-**165a** | 38 | 100 |
| (*R,R*)-**165b** | 16 | 98 |

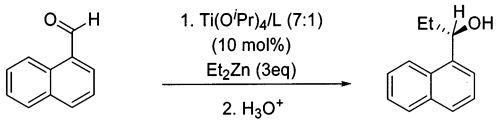
using (*R*)-**166**, whereas they were much slower with the (*S*)-**166** diastereomer. Complex **64**/Ti catalyzed the reaction with excellent yield in relatively short reaction times; however, the enantioselectivities were much lower than those obtained with ligand **166**.

**Scheme 111**




Yudin and co-workers have also tested the efficiency of their fluorinated binaphthol ligands in the asymmetric addition of diethylzinc to naphthaldehyde.[26] The catalysts were formed by mixing Ti-

**Scheme 112**




| L | % ee |
|---|---|
| *(R)*-**1** | 89 *(R)* |
| *(R)*-**25** | 89 *(R)* |
| *(R)*-7,7′-(CH$_3$O)$_2$-5,5′,6,6′,8,8′-F$_6$-BINOL | 88 *(R)* |

(O$^i$Pr)$_4$ with BINOL, F$_8$-BINOL, or 7,7′-substituted F$_8$-BINOL under the conditions where formation of the monomeric catalyst precursors of 1:1 composition is favored (7:1 Ti/L ratio). All three catalysts gave similar enantioselectivities (Scheme 112). This indicates that steric (substitution at the 7,7′-positions) and electronic effects are relatively insignificant in this case.

Mikami and co-workers reported the asymmetric activation of chiral BINOL−zinc catalysts by chiral nitrogen activators for the enantioselective addition of diethylzinc to aldehydes (Figure 23).[163,164] Using high-throughput screening of parallel solution libraries of chiral ligands and activators, they were able to fine-tune the catalytic system and obtain quantitative yields and enantioselectivities of up to 99%.

The initial library studied consisted of a variety of binaphthol derivatives (Figure 24) and diamines (A1−A3). The enantioselectivity of the reaction was increased by matched combination of the diol ligands and nitrogen activators. For example, **1** and A3 independently give (*S*)-1-phenylpropanol with 8.2% ee (54% yield) and 1.1% ee (64% yield), respectively. The best combination was found to be **36a**/A3 (Ar = 2,4,6-Me$_3$C$_6$H$_2$), where the product was obtained quantitatively with 99% ee.

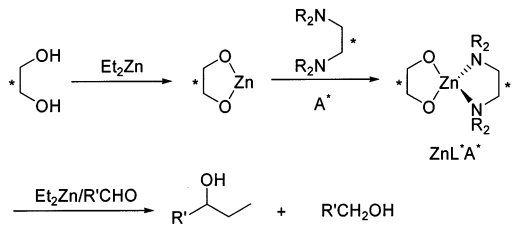



**Figure 23.**

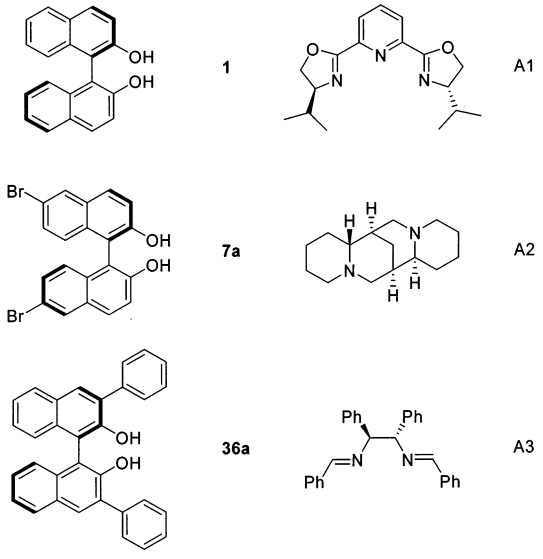
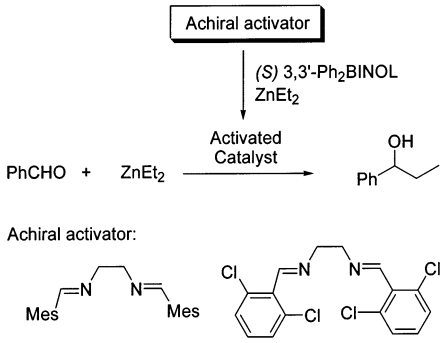
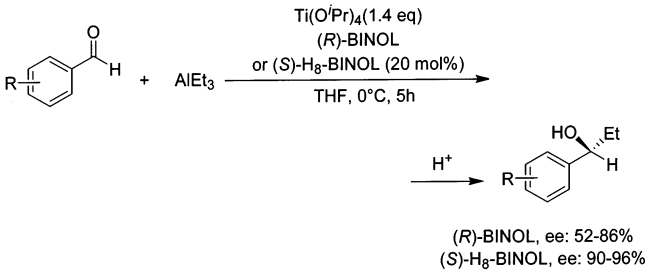



**Figure 24.**

**Scheme 113**



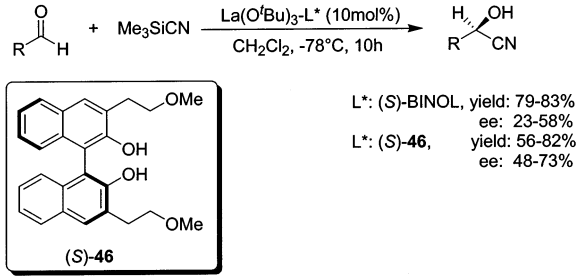

**Scheme 114**




Walsh and co-workers have applied achiral activation to the asymmetric addition of diethylzinc to aldehydes using enantiopure 3,3′-Ph$_2$-BINOL (**36a**, Figure 24) and an achiral ligand.[232] After careful selection, several achiral diimine ligands were chosen. Under their conditions, (*S*)-3,3′-Ph$_2$-BINOL (10 mol %) with no added achiral ligand gave the product (*S*)-1-phenyl-1-propanol with low enantioselectivity and poor efficiency. With the addition of the achiral ligand (10 mol %), the enantioselectivity of the product increased to 87% at −45 °C (Scheme 113).

Chan and co-workers reported an asymmetric alkylation of aromatic aldehydes catalyzed by (*R*)-BINOL/Ti or (*S*)-H$_8$-BINOL/Ti complexes (Scheme 114).[165] Triethylaluminum was used as the alkylating agent. (*R*)-BINOL and (*S*)-H$_8$-BINOL were examined as the chiral auxiliaries. Under the selected reaction conditions, side reactions such as the reduction of aldehydes to primary alcohols were reduced to a minimum, and in most cases the desired *sec*-alcohols were obtained in almost quantitative yields. Although both (*R*)-BINOL/Ti and (*S*)-H$_8$-BINOL/Ti complexes promoted high chemical yields, (*S*)-H$_8$-BINOL/Ti induced better enantioselectivities than (*R*)-BINOL/Ti (>90% ee with (*S*)-H$_8$-BINOL/Ti vs 52−86% ee with (*R*)-BINOL/Ti). In the (*R*)-BINOL/Ti system, the substituent R on the aldehyde substrates influenced the enantioselectivity of the reaction, whereas in the (*S*)-H$_8$-BINOL/Ti system, this substituent effect was less significant. When trimethylaluminum was used as the alkylating agent, the ee values of the products were found to be much lower (<53% ee). Only reduction products of the aldehydes were obtained when triisobutylaluminum was used under the same condition.

**Scheme 115**




## N. Cyanation of Aldehydes

Qian and co-workers reported an example of enantioselective trimethylsilylcyanation of aldehydes catalyzed by chiral lanthanoid alkoxides.[35] A significant substituent effect of BINOL ligands on the enantioselectivity of the reaction was observed. Sterically hindered ligands such as 3,3′-bis(trimethylsilyl)-BINOL and 3,3′-diphenyl-BINOL produced α-hydroxynitriles with lower enantioselectivity than simple BINOL. An increase in the enantioselectivity was achieved when the tetradentate ligand **46** was applied (Scheme 115).

Shibasaki and co-workers reported a bifunctional asymmetric catalyst consisting of both Lewis acid and Lewis base moieties, which activate both electrophiles and nucleophiles simultaneously at defined positions (Figure 25).[166] It was found that the phosphine oxide-containing ligand **86a** showed both superior reactivity and enantioselectivity to the phosphorus-containing ligand **86f** and the sulfur-containing ligand **167** in the model reaction of TMSCN with benzaldehyde. A key issue for designing a Lewis acid−Lewis base catalyst is how to prevent the internal complexation of the two fragments. This can be solved by changing the linker length between the phosphine oxide and the BINOL scaffold. Molecular modeling studies suggested that **86a** would avoid such a problem because the coordination of the Lewis base to the internal aluminum seemed to be torsionally disfavored.

When considering **86d**, which contains an ethylene linker, the internal coordination seemed to be quite stable and strain-free. In accordance with this expectation, the reaction of TMSCN with benzaldehyde, catalyzed by **86d**, proceeded slowly at −40 °C (37 h) and gave the cyanohydrin in only 4% yield because the strong intramolecular binding of the phosphine oxide reduced the Lewis acidity of the aluminum center and therefore diminished the catalytic efficiency of **86d**. In contrast, under the same conditions, **86a** afforded the product in 91% yield with 87% ee, which means that the intramolecular binding of the phosphine oxide to aluminum is labile enough to allow coordination of the aldehyde to the metal center. Aliphatic aldehydes afforded very low enantioselectivities under the same conditions since there was competition between the two reaction pathways. The desired pathway involves dual interaction between the Lewis acid and the aldehyde as well as between the Lewis base and TMSCN, whereas the undesired pathway involves mono-activation by the Lewis acid. The authors further investigated the effect of additives which coordinate to the aluminum and reduce its Lewis acidity, thereby more efficiently differentiating the competitive pathways. It was found that $Bu_3P(O)$ was a good additive for aliphatic and α,β-unsaturated aldehydes, whereas $CH_3P(O)Ph_2$ was a good additive for aromatic aldehydes. Both high yields (86−100%) and excellent enantioselectivities (83−98% ee) were observed with various aliphatic, α,β-unsaturated, and aromatic aldehydes (Scheme 116).

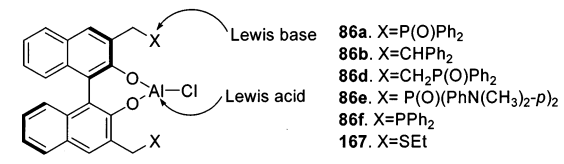
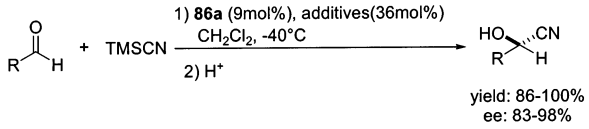


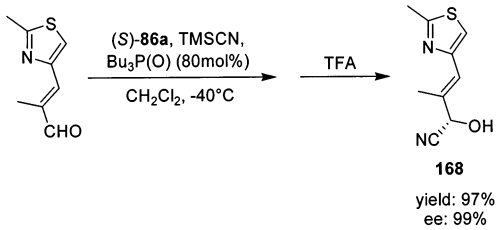

**Figure 25.**

**Scheme 116**[a]




[a] Additives = $Bu_3P(O)$ or $CH_3P(O)Ph_2$.

**Scheme 117**

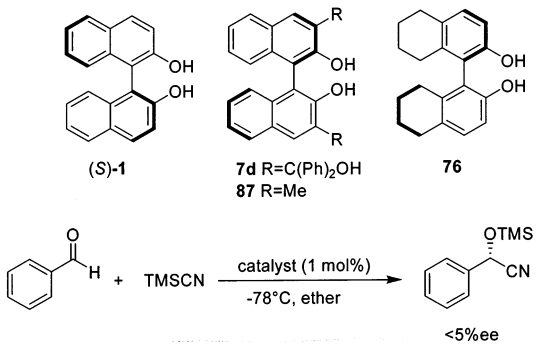



Later, catalyst (*S*)-**86a** was successfully employed in the total synthesis of epothilone.[167] With 10 mol % of (*S*)-**86a**, the intermediate cyanohydrin **168** was obtained in excellent yield and enantiomeric excess through an asymmetric cyanosilylation (97% yield, 99% ee) (Scheme 117).

Asymmetric addition of trimethylsilylcyanide to aldehydes catalyzed by the mono-lithium salt of (*R*)-BINOL was described by researchers from the Kagan laboratory.[168] Although the chemical yields were high with most aldehydes, the enantioselectivities were generally low. The best ee obtained was only 59% with *p*-tolualdehyde. To improve the enantioselectivity for the cyanide group transfer, several analogues of BINOL **1** (**87**, **7d**, and **76**) were further screened by using benzaldehyde as a model substrate under the optimal conditions obtained for (*S*)-**1**.[169] None of these BINOL derivatives induced more than 5% ee, although all compounds gave high yields of the desired product (Scheme 118).

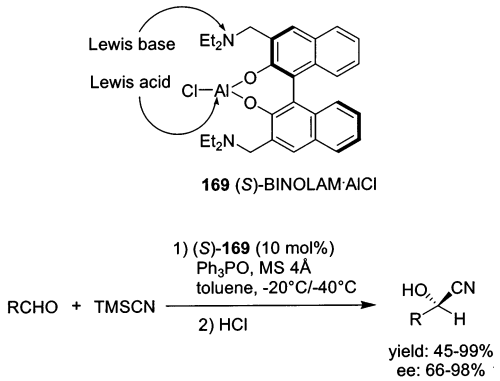
The bifunctional catalyst **169** was applied in the asymmetric synthesis of cyanohydrins by Nájera and Saá.[170] In **169**, the aluminum atom acts as a Lewis acid center to ligate the aldehyde, while the amino group works as a Lewis base to activate the nucleophile (TMSCN, Scheme 119). The presence of both 4-Å MS (1 equiv) and triphenylphosphane oxide was crucial in achieving high enantioselectivities. Under optimized reaction conditions, aromatic aldehydes and an α,β-unsaturated aldehyde (cinnamaldehyde)

**Scheme 118**[a]

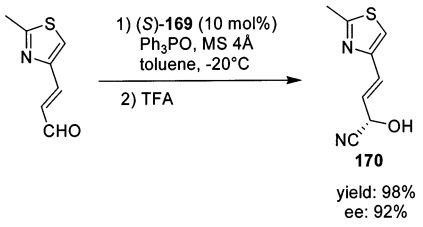



[a] Catalyst = $^n$BuLi + BINOL-derived ligands.

**Scheme 119**




**Scheme 120**



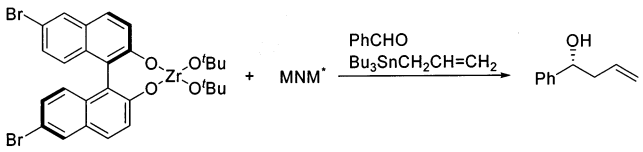

reacted smoothly to afford the desired cyanohydrin products in excellent yields and enantioselectivities (99% yield in all cases, 92−98% ee), with the only exception of *p*-phenoxybenzaldehyde (45% yield, 78% ee at −40 °C). On the other hand, lower enantioselectivity was obtained with aliphatic aldehydes (66% ee was observed with heptaldehyde).

Furthermore, compound **170** was prepared in 98% yield and 92% ee through this methodology, which constitutes one of the key steps in the synthesis of epothilone (Scheme 120).[171]

## O. Allylation of Aldehydes

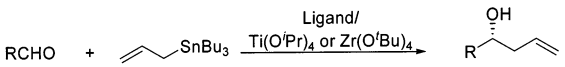
Mikami and co-workers described an asymmetric allylation in which a product-like activator is used to activate chiral BINOL−zirconium catalysts in the reaction of benzaldehyde with allyltin reagents (Scheme 121).[172] Without any activator, in the presence of an extra 1 equiv of (*R*)-BINOL as an additive, the product is obtained in 44% yield and 27% ee. Addition of the chiral activator (MNM*, Scheme 121) enhances the enantioselectivity of the reaction to 53%, with 35% yield. Using (*R*)-6,6′-$Br_2$-BINOL as the ligand with 2 equiv of the activator results in a lower yield (25%) with similar enantioselectivity (52%).

**Scheme 121**[a]



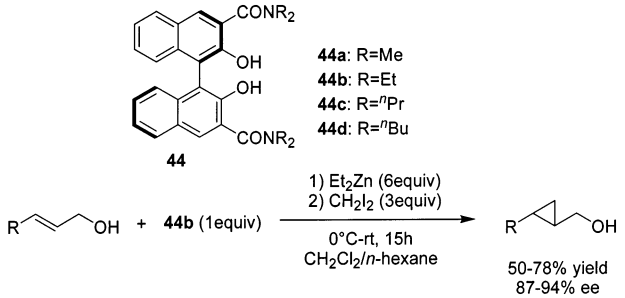

[a] MNM* = (*R*)-(+)-α-methyl-2-naphthalenemethanol.

**Scheme 122**




| R | ligand | $ML_n$ | yield (%) | ee (%) |
|---|---|---|---|---|
| $C_7H_{15}$ | 3,3'-$Br_2$BINOL | $Ti(O^iPr)_2Cl_2$ | 70 | 72 |
| $C_7H_{15}$ | 7,7'-$Br_2$BINOL | $Zr(O^tBu)_4$ | 60 | 54 |
| Ph | 7,7'-$Tol_2$BINOL | $ZrCl_4$ | 43 | 60 |

**Scheme 123**




Umani-Ronchi and Spada applied 7,7′-substituted binaphthols in the asymmetric allylation of aldehydes.[173] The results are summarized in Scheme 122. The dibromo- and ditolyl-substituted BINOL ligands afford moderate enantioselectivity, regardless of the position of substituents. It is not clear whether this effect is due to a change in the electronic properties of the ligand or the different structure of the Lewis acid formed.

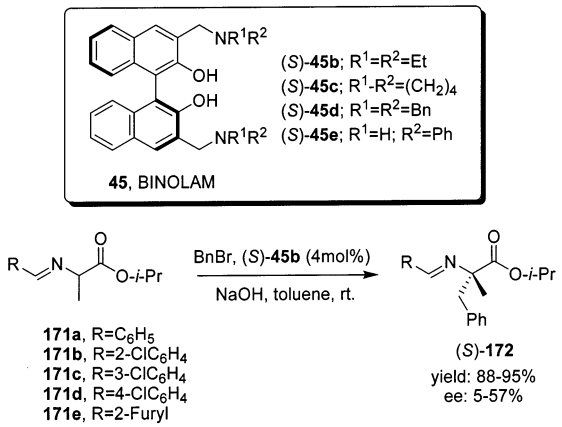
## P. Simmons–Smith Cyclopropanation

1,1′-Bi-2-naphthol-3,3′-dicarboxamides **44** were first examined in the Simmons−Smith reaction of cinnamyl alcohol by Katsuki and co-workers (Scheme 123).[34,174] Ligand **44b**, with the diethylamide group, exhibited the highest enantioselectivity of 94% ee. The reaction of both conjugated and nonconjugated (*E*)-allylic alcohols, catalyzed by **44b**, showed good enantioselectivity (87−94% ee) in moderate yields (50−78%). However, in the case of (*Z*)-allylic alcohol, a lower chemical yield and enantioselectivity were observed (34% yield, 65% ee).

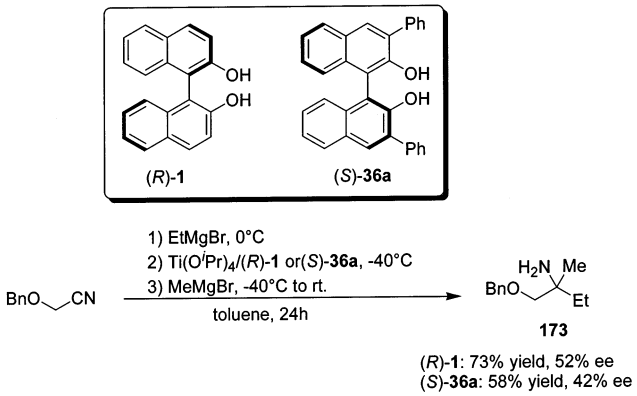
## Q. *C*-Alkylation of Alanine-Derived Iminoesters

The enantioselective synthesis of (*S*)-α-methylphenylalanine using (*S*)-BINOLAMs as phase-transfer catalysts was reported by Nájera and Saá.[175] (*S*)-BINOLAMs **45** were prepared from diacid **21**[176] and used as solid−liquid phase-transfer catalysts in the *C*-alkylation reaction of alanine-derived isopropyl iminoesters **171** with benzyl bromide as electrophile, affording (*S*)-**172** in high yields (>95%) (Scheme 124).

**Scheme 124**




**Scheme 125**




Among the ligands **45b**−**e**, (*S*)-BINOLAM **45b** was found to be the most efficient catalyst for this process, inducing 57% ee and 95% yield when **171a** was used as the substrate.

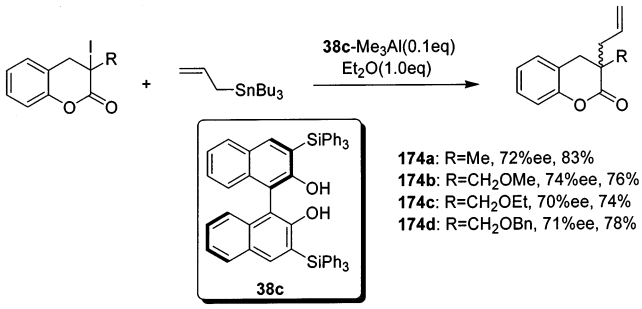
## R. Nucleophilic Addition to *O*-Protected Cyanohydrins

Charette and Gagnon reported an enantioselective double-nucleophilic addition reaction of Grignard reagents to *O*-protected cyanohydrins.[177] Both (*R*)-BINOL **1** and (*S*)-3,3′-diphenylbinaphthol **36a** were tested as chiral diol ligands in the reaction system (Scheme 125). (*R*)-**1** gave 52% ee and 73% yield. (*S*)-**36a** induced 42% ee with 58% yield. Interestingly, both of them gave the (*R*)-enantiomer of amine as the major enantiomer.

## S. Radical-Mediated Allylation of α-Iodolactones

Hoshino and co-workers described the first example of the construction of chiral quaternary carbon centers by enantioselective radical reactions.[178] An efficient enantioselective radical-mediated allylation of α-alkyl-α-iodolactones was realized by use of a chiral Lewis acid prepared from **38c** (3,3′-bis(triphenylsilyl)-BINOL) and $Al_3Me$ in the presence of 1 equiv of diethyl ether as an additive (Scheme 126). High enantioselectivity (81−91% ee) and chemical yield (76−85%) were observed in the presence of a stoichiometric amount of the chiral aluminum catalyst. However, it was found that there was no significant loss in either chemical yield or enantioselectivity, even when the amount of the catalyst was reduced to 0.1 equiv (70−74% ee and 74−83% yield). It is noteworthy that the use of diethyl ether as an additive (1 equiv) is crucial for obtaining high enantioselectivity in this system.

**Scheme 126**




## T. Torgov Cyclization

Catalytic asymmetric cyclization of methyl secone **176** is the key process in the Torgov synthesis of estrone (Scheme 127).[179] Enev and co-workers have developed an asymmetric route to the cyclization of secone **176**, catalyzed by a chiral BINOL-derived titanium Lewis acid.[180] Compound **177** is a side product in the reaction. Catalyst **175** gave the desired product **178** in 72% yield (98% conversion) with 70% ee. The parent BINOL/Ti catalyst gave the product in 63% yield (90% conversion) with 47% ee. Compound **177** was obtained in 20% yield and 36% ee using catalyst **175**. The BINOL/Ti complex gave this byproduct in similar yield and enantioselectivity of 23% and 28%, respectively.

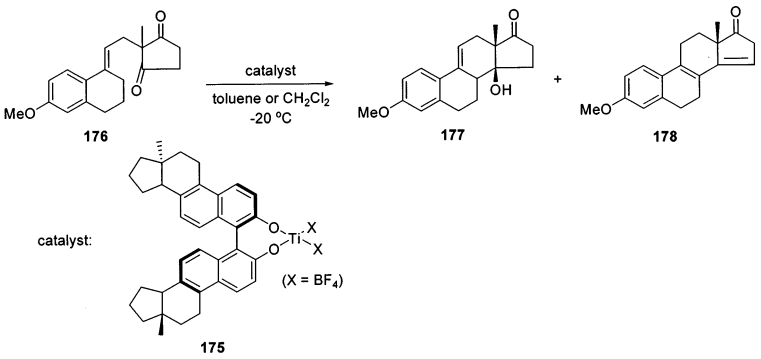
The mechanism for this reaction is explained in terms of a multistep cationic cyclization (Scheme 128). The initial step requires isomerization of **176** to **176a**. The chiral Lewis acid induces a Prins-type cyclization to the chiral cation **176b**. Subsequently, the regioselective elimination of **176b** results in the two isomers, **177** and **178**.

# *IV. Applications in Catalytic Asymmetric Heteroatom-Transfer Reactions*

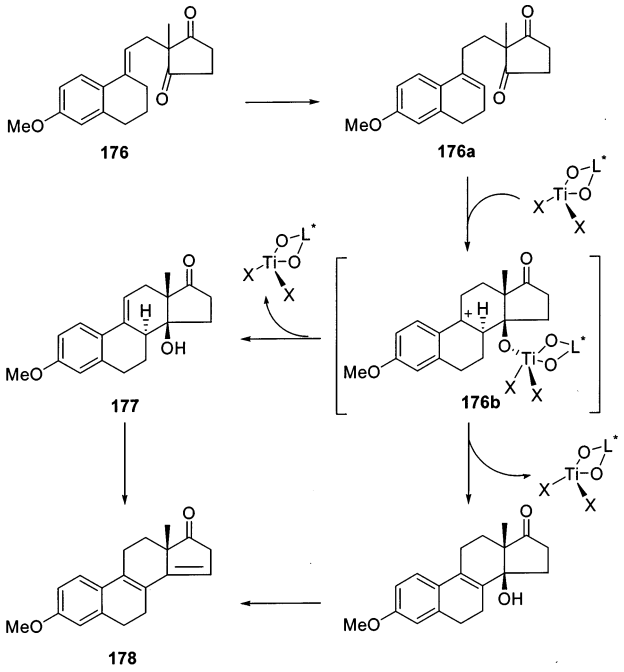
## A. Ring Opening of Epoxides

Enantioselective ring opening of achiral epoxides is an invaluable development in organic synthesis since it simultaneously assembles two contiguous stereogenic centers. Jacobsen and co-workers reported the enantioselective ring opening of symmetrical epoxides with carboxylic acids and an efficient kinetic resolution of racemic terminal epoxides with water by using a (salen)$Co^{II}$ catalyst (salen = *N*,*N*′-bis(salicylidene)ethylenediamine dianion).[181] However, this type of reaction has not been realized so far with alcohols or phenols. On the basis of their previously developed catalysts (Figure 13),[182] Shibasaki and co-workers reported the asymmetric opening of cyclohexene oxide with nucleophiles such as $PhCH_2SH$. The use of catalyst **111**/La resulted in poor yields (1−10%), although modest to high enantiomeric excess values (27−86% ee) were obtained. To develop more reactive catalysts, heterobimetallic complexes

**Scheme 127**




**Scheme 128**




were prepared using group 13 elements (B, Ga, In) other than Al.[183] Of these, the gallium−lithium−bis-[(*R*)-binaphthoxide] complex (**179a**, (*R*)-GaLB) (Figure 26) showed promising catalytic activity for the aforementioned reaction (40% ee in toluene with 87% yield). These complexes were easily prepared from $GaCl_3$, binaphthol, and BuLi (4 mol equiv to $GaCl_3$) in THF.

The reaction of cyclohexene oxide did not occur at all in the presence of catalytic or stoichiometric amounts of bases such as $^n$BuLi, NaO$^t$Bu, KO$^t$Bu, $K_2CO_3$, and $Cs_2CO_3$. The addition of Lewis acids such as $BF_3$·$Et_2O$ and $ZnCl_2$ was also ineffective for the reaction. The Ga−Li−bis(binaphthoxide) (GaLB) complex catalyzed reactions of a wide range of unfunctionalized and functionalized symmetrical epoxides with 4-methoxyphenol and other hydroxyarenes (Scheme 129).[184]

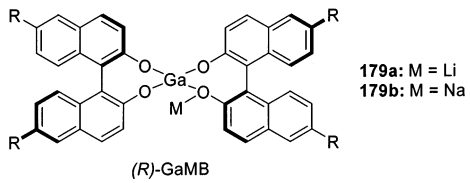
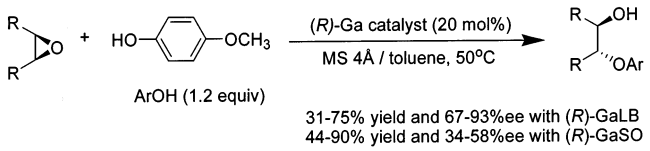
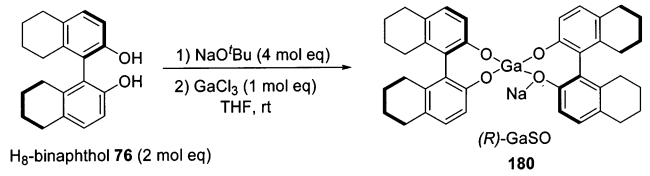



**Figure 26.**

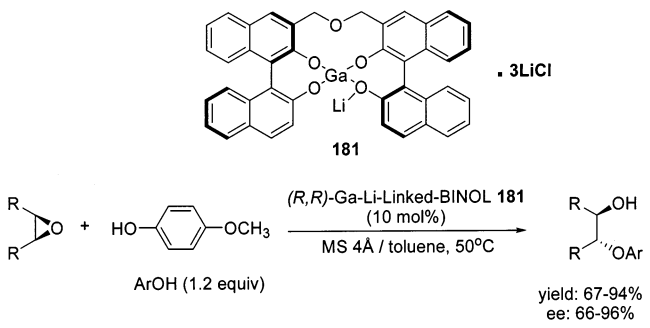
**Scheme 129**




**Scheme 130**




**Scheme 131**

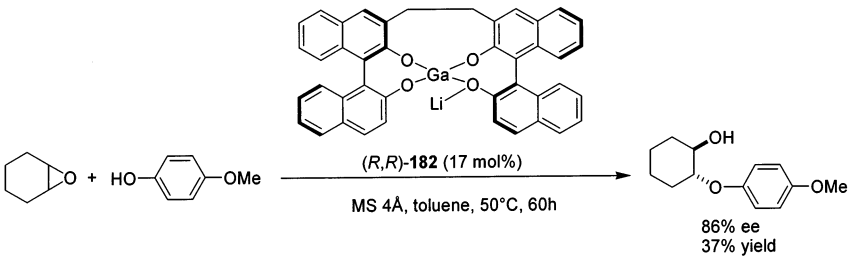



These nucleophiles are useful because the corresponding aryl ether products can be easily converted into 1,2-diols. The reduced yields are attributed to the undesired ligand exchange of hydroxyarene for BINOLs, resulting in formation of side products. After several attempts, it was noted that the use of GaLB*, prepared from (*R*)-6,6′-bis((triethylsilyl)ethynyl)binaphthol, improved the yields of the ring-opening reactions. This could be a result of higher stability of GaLB* than GaLB with respect to ligand exchange.[185]

Attempts to make more effective catalysts resulted in complex **180**, shown in Scheme 130. This complex exhibited higher catalytic activity for the epoxide ring-opening reaction. The reaction of cyclopentene oxide with 4-methoxyphenol in the presence of 20 mol % of GaSO proceeded smoothly in toluene at 50 °C in only 4 h to give the product in 73% yield, even though enantioselectivity was modest (56% ee).

In contrast to GaLB, sodium was the most suitable alkali metal to make the heterobimetallic gallium $H_8$-binaphthoxide complex effective. It is likely that this

**Scheme 132**




is due to the difference in Na−O versus Ga−O bond lengths.

Shibasaki and co-workers developed a novel linked BINOL concept.[37] It was assumed that, if the two BINOL units in the catalyst are linked, the complex would become more stable toward ligand exchange without having any adverse effects on the asymmetric environment. The designed catalyst **181** is shown in Scheme 131. When designing the ligand, the length of the linker was a key issue, since it had to be relatively short to limit the flexibility of the BINOL units. The crown ether linker design was based on the work of Cram et al.[186] Complex **181** was prepared from $GaCl_3$ (1 mol equiv), (*R*,*R*)-linked BINOL (1 mol equiv), and BuLi (4 mol equiv). It was found to be far more stable than GaLB and very effective for the epoxide ring-opening reaction. In addition, lower catalyst loadings (10 mol %) were required (Scheme 131).

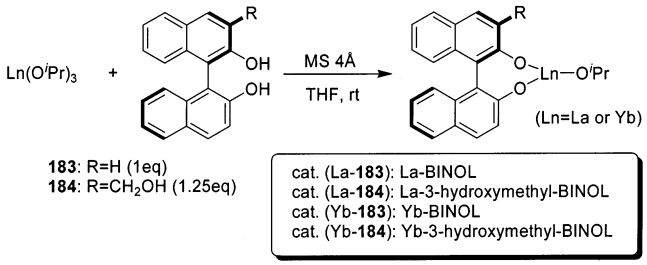
The presence of excess LiCl salt was crucial to increasing the enantioselectivity of the reaction.[187] When LiCl-free complex was used, the reaction of 4-methoxyphenol and cyclohexene oxide proceeded in good yield (85%) but somewhat lower ee (74%). Treating the LiCl-free catalyst with 3 mol equiv of LiCl in THF prior to use resulted in an increase in the enantiomeric excess to 90%, suggesting the formation of the same catalyst system **181**. It is well known that lithium halides function effectively as achiral additives to increase enantioselectivity.[188]

The reactivity of the ethylene-bridged bis-BINOL (*R*,*R*)-**182** was tested in the ring-opening reaction of cyclohexene oxide with 4-methoxyphenol (Scheme 132).[189] Catalyst (*R*,*R*)-**182** was prepared in a manner similar to that used for GaLB.[166] The ring-opening product was obtained in 86% ee with 37% yield by the catalysis of 17 mol % of **182**. The result is close to what was obtained using (*R*)-BINOL as ligand (20 mol % of catalyst, 72 h, 48% yield, 93% ee).

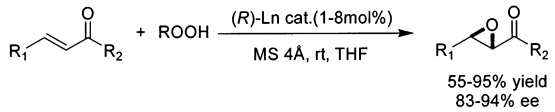
## B. Epoxidation

Shibasaki and co-workers reported a catalytic asymmetric epoxidation of α,β-unsaturated ketones promoted by lanthanide−BINOL complexes.[190] In their previous study, several kinds of heterobimetallic chiral catalysts,[34] such as La−$Na_3$−tris(binaphthoxide) complexes (LSB), Al−Li−bis(binaphthoxide) complexes (ALB), and Ga−Na−bis(binaphthoxide) complexes (GaSB) were examined. Although good enantioselectivity and reactivity were observed in some cases, these heterobimetallic complexes were not efficient for many enone substrates. In contrast, the lanthanum−BINOL complex (La-**183**) was found to

**Scheme 133**




**Scheme 134**[a]




[a] ROOH = CMHP/TBHP.

be applicable to a range of aromatic-substituted enone substrates (Scheme 133). Furthermore, catalytic activity was improved by introducing (*R*)-3-(hydroxymethyl)-BINOL (La-**184**). The ytterbium−BINOL complex (Yb-**184**) proved to be complementary in the aliphatic-substituted enone substrates, where the use of either La-**184** or Yb-**183** afforded less satisfactory results. High enantioselectivities and yields were obtained in a variety of aromatic and aliphatic enones using these lanthanide catalysts (83−94% ee, 55−95% yield) (Scheme 134).

Addition of a small amount of water (ca. 5 equiv to Yb) to the Yb-**183** system was later reported[191] to dramatically increase the enantioselectivity from 25% ee under strictly anhydrous conditions to 94% ee. In contrast to the Yb-**183** system, the La-**183** system was not affected by the addition of water. In the case of the Ln-**184** system, addition of water caused a decrease of the catalyst turnover, although the optical purity of the products was retained. The authors proposed that in the Yb-**183** system, the water molecules coordinate to the Yb atom and thereby controls the orientation of the hydroperoxides to form an appropriate asymmetric environment for the epoxidation. In the Ln-**184** catalyst system, the 3-hydroxymethyl substituent plays a role in delivering the hydroperoxide moiety, just as water molecules do in the Ln-**183** catalyst system (Figure 27).

Qian and Vries reported an enantioselective epoxidation of α,β-enones catalyzed by lanthanum and gadolinium complexes.[192] A series of BINOL derivatives were screened as ligands in the epoxidation of chalcone. The results showed that the steric bulk of the 3,3′-substituents on binaphthol rings is detrimental to the enantioselectivity of the reaction. While (*S*)-BINOL **1** induced 82% ee in the product, the 3,3′-

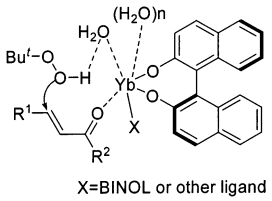
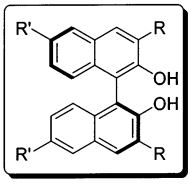
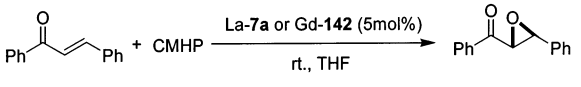



**Figure 27.**

**Scheme 135**

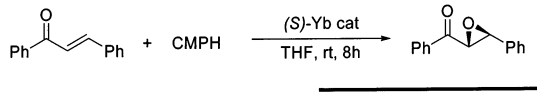


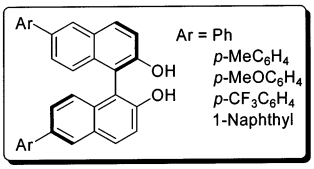
(*S*)-**1**, R=R'=H;
(*S*)-**7a**, R=H, R'=Br;
(*S*)-**38a**, R=SiMe$_3$, R'=H;
(*S*)-**87**, R=Me, R'=H;
(*S*)-**142**, R=H, R'=Ph;
(*S*)-**185a**, R=Br, R'=H;
(*S*)-**185b**, R=$CH_2CH_2OCH_3$, R'=H;
(*S*)-**185c**, R=*o*-$MeOC_6H_4$, R'=H;
(*S*)-**185e**, R=H, R'=Me




86-93% yield, 81-94% ee with La-**7a**
81-95% yield, 73-95% ee with Ga-**142**

**Scheme 136**[a]




| ligand | yield (%) | ee (%) |
|---|---|---|
| (*S*)-**1** | 95 | 44 |
| Ar=1-Naphthyl | 84 | 63 |
| Ar=ph | 91 | 97 |
| Ar=*p*-$CF_3C_6H_4$ | 88 | 89 |

[a] CMPH = cumene hydroperoxide.

substituted BINOLs gave only low to moderate ee's (8−65% ee). In contrast, 6,6′-dibromo- and 6,6′-diphenyl-BINOLs exhibited better enantioselectivities ((*S*)-**7a**, 92% ee; (*S*)-**142**, 86% ee). With electron-donating substituents at the 6,6′-positions such as (*S*)-**185e**, only 75% ee was obtained under similar conditions. This result implied that, with the inductive electronic effect of the electron-withdrawing groups at the 6,6′-positions, a more favorable coordination environment between the ligand and the lanthanide is produced, leading to improvement in the asymmetric induction. A variety of enones were transformed to the corresponding epoxides in both good to excellent yields and enantioselectivities by using La-**7a** or Gd-**142** as catalyst (Scheme 135).

Qian and co-workers also developed the catalytic epoxidation of α,*β*-unsaturated ketones using 6,6′-substituted binaphthols to generate ytterbium complexes.[193] Substituents at these positions can affect both electronic and steric properities of the catalyst and can thus have a significant effect on the activity and enantioselectiviy of the reaction. Indeed, it was found that (*S*)-6,6′-diphenyl-BINOL catalyzes the epoxidation of chalcone in 91% yield and 97% ee, compared with (*S*)-BINOL, which gives the product in 95% yield and 44% ee (Scheme 136).

Another interesting binaphthol-derived catalyst for asymmetric epoxidation has been recently developed by Takata and co-workers, based on a poly(binaphthyl salen manganese) complex.[194] This polymer adopts a helical conformation due to twisted connecting chiral units (Figure 28).[195] The catalyst was originally made as the Zn(II) complex (instead of the salen manganese complex) and used in the asymmetric addition of diethyl zinc to aldehydes with enantioselectivities of up to 95%.[138] With these results in hand, the authors synthesized complex **186**, as shown in Scheme 137. The polymeric complex **186** was used in the epoxidation of alkenes. Very low or almost no enantioselectivity was observed in all cases except for catalyst **186b**, where 17% ee was observed. The steric hindrance of the 2,2-dimethyl-1,3-propanediyl unit is significant, although the exact mechanism for the asymmetric induction is not known. The corresponding monomeric unit gave no enantioselectivity, which led the authors to believe that the helical shape of the catalyst is important in enantioselectivity determination. Longer polymer chains gave similar results.

Katsuki and co-workers have also used similar (salen)manganese(V)−binaphthol complexes in epoxidation of olefins.[196] The catalyst (Scheme 138) was designed to bear chiral elements at both the ethylenediamine part and the C3 and C3′ substituents, since it was rationalized that the olefin approaches parallel to the salen ligand, orienting any sterically bulky and/or *π*-electron-rich substituent away from the C3′ substituents of the ligand in order to minimize steric and electronic repulsions.

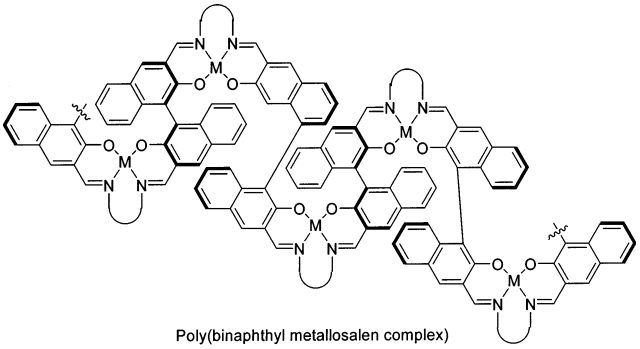
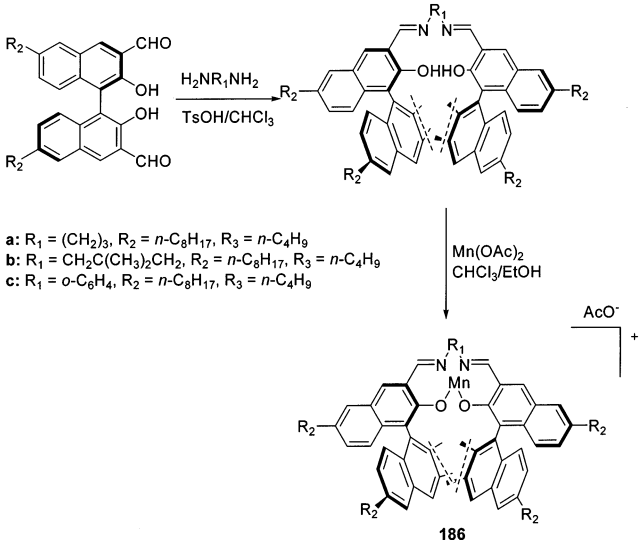
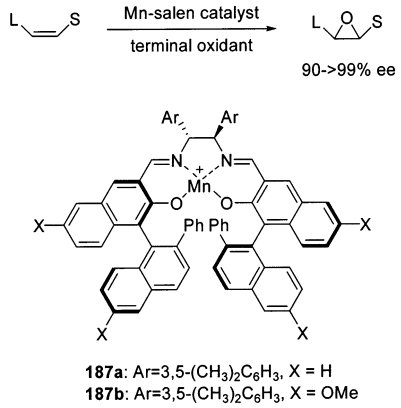



**Figure 28.**

**Scheme 137**



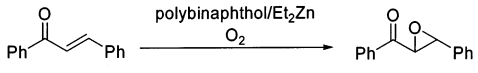
**Scheme 138**[a]




**187a**: Ar=3,5-$(CH_3)_2C_6H_3$, X = H
**187b**: Ar=3,5-$(CH_3)_2C_6H_3$, X = OMe

[a] L = alkenyl, alkynyl, or aryl.

**Scheme 139**




| *(R)*-**159**/$Et_2Zn$/ketone | yield (%) | ee (%) |
|---|---|---|
| 1:0.95:0.90 | 41 | 71 |
| 1:1.9:0.90 | 99 | 50 |
| 1:1.9:0.90[a] | 11 | 58 |

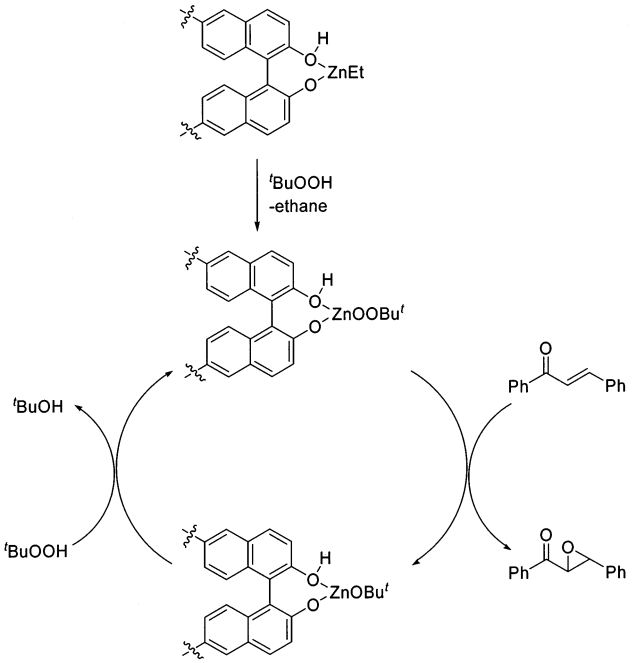
[a] reaction run at r.t.

Catalyst **187a** gave remarkably high enantioselectivities in the epoxidation of conjugated *cis*-di- and trisubstituted olefins. The epoxidation of 1,3-cycloalkadienes and dialkyl-substituted olefins, however, occurred with low enantioselectivities, probably due to reduced or no $\pi$-electronic repulsion between the salen ligand and the substrates.[197] A maximum enantioselectivity of 72% in this case was obtained for the reaction of 1,3-cyclooctadiene at 0 °C in acetonitrile.

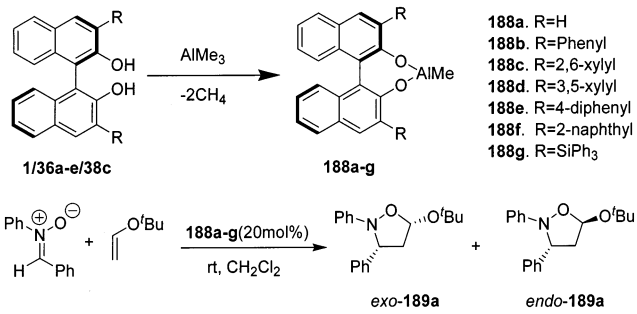
Pu and co-workers have enhanced the enantioselectivity of the asymmetric epoxidation of $\alpha,\beta$-unsaturated ketones by using chiral polybinaphthyl zinc complexes.[198] Catalysts based on these polymers had previously shown very high enantioselectivity for the organozinc addition to aldehydes (see section III.M).[153,155] Using previously developed conditions in the presence of a stoichiometric amount of a zinc complex,[199] epoxidation of *trans*-chalcone in the presence of a stoichiometric amount of polymer **159** or **161** with oxygen and diethylzinc was carried out (Scheme 139). Since the results were unsatisfactory, the authors decided to use $^t$BuOOH in place of oxygen as the oxidant. In the presence of 5 mol % of **159** and 10 mol % of diethylzinc, chalcone was oxidized by $^t$BuOOH in 95% yield with >99% de and 28% ee. The proposed mechanism for this reaction is demonstrated in Scheme 140.

Binaphthylmetalloporphyrin **73** (Scheme 39) was also used in the asymmetric epoxidation with $Fe^{III}$-Cl and $Mn^{III}Cl$.[56] Both the yield and the enantiomeric excess were low in the reaction. The highest enantioselectivity was obtained for the epoxidation of *trans*-2-pentene (72%); however, the yield was only

**Scheme 140**




**Scheme 141**

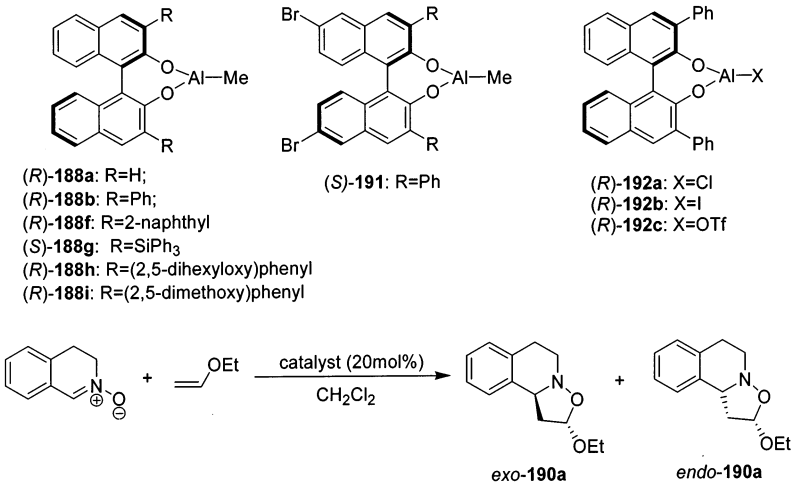



9%. Indene gave the highest yield of the corresponding epoxide (73%), with 20% ee.

## C. 1,3-Dipolar Cycloaddition Reactions

The 1,3-dipolar cycloaddition reaction is a very important reaction for the construction of five-membered heterocycles and has been used in numerous syntheses with 1,3-dipoles such as nitrones, nitrile oxides, azomethine ylides, and nitronates. The inverse-electron-demand 1,3-dipolar cycloaddition reaction of nitrones with alkenes requires a dominant interaction of the $LUMO_{nitrone}$ with the $HOMO_{alkene}$. Such a reaction requires activation of the nitrone. Jørgensen et al. reported a catalytic asymmetric inverse-electron-demand 1,3-dipolar cycloaddition reaction of aromatic nitrones with vinyl ethers, catalyzed by chiral aluminum complexes **188** (Scheme 141).[200] The catalytic activity of **188a**−**g** was examined in the reaction of nitrone with *tert*-butyl vinyl ether. The sterically hindered 3,3′-disubstituted BINOL ligands **36a**−**e** and **38c** were found to give much better enantioselectivities than the parent BINOL **1** (65−89% ee with **36a**−**e** or **38c** vs <5% ee with **1**). Among them, catalyst **188b** gave the best results. However, any further increase of steric bulk at the 3,3′-substituents induced a decrease in enantioselectivity. When the sterically demanding triph-

**Scheme 142**



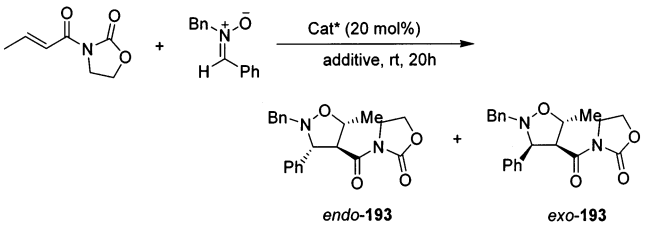

| catalyst | conv. (%) | *exo*-**190a**:*endo*-**190a** | ee *exo*-**190a** (%) |
|---|---|---|---|
| (*S*)-**188a** | 30 | 78:22 | 50 |
| (*R*)-**188b** | 95 | 95:5 | 78 |
| (*R*)-**188f** | 78 | 87:13 | 67 |
| (*R*)-**188h** | 96 | 89:11 | 58 |
| (*R*)-**188i** | 74 | 98:2 | 82 |
| (*R*)-**188j** | 11 | 85:15 | 24 |
| (*S*)-**191** | 98 | 98:2 | 68 |
| (*R*)-**192a** | 98 | 87:13 | 48 |
| (*R*)-**192b** | 100 | 27:73 | 66 |
| (*R*)-**192c** | 100 | 42:58 | 13 |

enylsilyl group was introduced into the 3,3′-positions of BINOL, the other enantiomer of *exo*-**189a** was obtained in 65% ee. The product isoxazolidine *exo*-**189a** was obtained in 89% ee with a ratio of *endo*-**189a**/*exo*-**189a** of 5:95 in the presence of 20 mol % of **188b**. Further study showed that the catalyst loading could be reduced to 10 mol %. The reactions of various aromatic nitrones with vinyl ethers occurred smoothly in the presence of 10 mol % of **188b** (50−84% yield; *endo*/*exo* ratio from 17:83 to <5:>95; ee of *exo*, 77−97%).

Different chiral Lewis acids prepared from BINOL derivatives and aluminum salts were tested for their ability to induce regio-, diastereo-, and enantioselectivity in the reaction of 3,4-dihydroisoquinoline *N*-oxide with ethyl vinyl ether (Scheme 142).[201] Both low yield and ee of the major diastereomer *exo*-**190a** were obtained when catalyst (*R*)-**188a** was used (11% conversion after 42 h; *exo*/*endo* = 85:15; 24% ee with *exo*-**190a**). The 3,3′-diaryl-substituted BINOL−AlMe catalysts (*R*)-**188b**−**f** have led to significant increases in both conversion and stereoselectivity (see Scheme 142). The best results were obtained with catalysts **188b** and **188i**. Introduction of bromine substituents at the 6,6′-position of the catalyst gives no significant change in conversion and diastereoselectivity; however, a small decrease in enantioselectivity was observed compared to that with catalyst (*R*)-**188b**. The third substituent on the aluminum Lewis acid was found to have a significant influence on the stereoselectivity. The use of (*R*)-**192a**−**c** instead of (*R*)-**188b** dramatically reduced both the enantioselectivity and diastereoselectivity. Several isoquinoline derivatives were prepared by using 20 mol % of (*R*)-**188b** or (*R*)-**188i** as catalyst (24−92% yield; *exo*/*endo* ratio from 95:5 to 100:0; ee of *exo*, 10−85%).

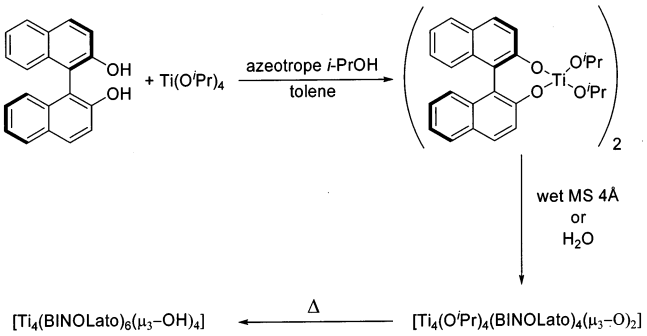
The chirality of the oxazoline ring of the BINOL-derived ligands, 3,3′-bis(2-oxazolyl)-1,1′-bi-2-naphthols (BINOL-Box) **43a**−**f** (Scheme 24), was found to affect both the enantioselectivity and absolute configuration of products in the 1,3-dipolar cycloaddition of nitrones to alkenes.[33] In the model reaction of 3-((*E*)-2-butenoyl)-1,3-oxazolidin-2-one and *N*-benzylidenebenzylamine *N*-oxide with $Sc(OTf)_3$ as metal triflate, parent (*S*)-BINOL **1** showed 30% ee of the *endo* isomer (*endo*/*exo* = 98:2) in 81% yield (Scheme 143). The application of (*S*,*S*)-**43a** led to similar yield (80%), diastereoselectivity (endo/exo = 97:3), and enantioselectivity (31% ee), but with opposite configuration of the product. The use of (*S*,*R*)-**43d**, the diastereomeric isomer of (*S*,*S*)-**43a**, resulted in much higher enantioselectivity (83% ee) with similar yield (86%) and lower diastereoselectivity (*endo*/*exo* = 92:8) of the product. In this case, the product has the same configuration as the one obtained using (*S*,*S*)-**43a**. Both (*S*,*R*)-**43e** and (*S*,*R*)-**43f** exhibited lower enantioselectivity (7% ee with (*S*,*R*)-**43e**, 72% ee with (*S*,*R*)-**43f**) and reversed asymmetric induction as

**Scheme 143**[a]

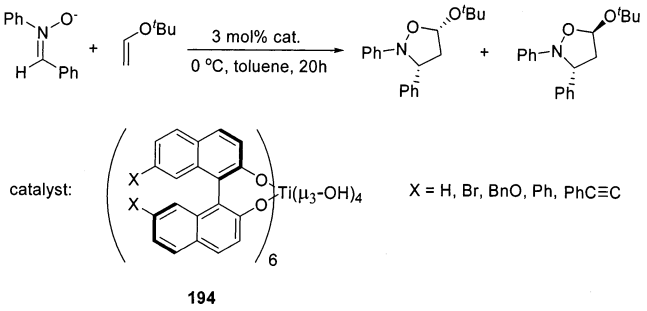



[a] Cat* = $Sc(OTf)_3$ + **1**/**43**.

**Scheme 144**




**Scheme 145**

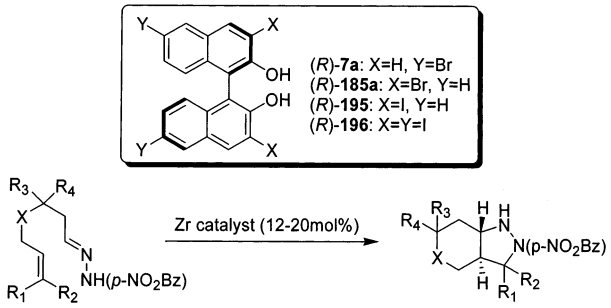



compared to (*S*,*R*)-**43d**. Under the optimized conditions (6 mol % of (*S*,*R*)-**43d** and 5 mol % of $Sc(OTf)_3$ in the presence of 4-Å MS), the reaction of 3-((*E*)-2-butenoyl)-1,3-oxazolidin-2-one and *N*-benzylideneben-zylamine *N*-oxide proceeded to give the product **193** in 94% yield, with an endo/exo ratio of 97:3 and 87% ee of the endo product.

Mikami and co-workers reported a titanium−binaphtholate cluster modified at the 7,7′-positions, stable to water, acid, and base, used in the [2 + 3] cycloaddition reaction with nitrones.[55] The complex is a tetranuclear titanium cluster consisting of hexacoordinated titanium atoms and is prepared as shown in Scheme 144. After a 1:1 mixture of $Ti(O^iPr)_4$ and (*R*)-BINOL in dry toluene was stirred for 1 h, a solution of 0.5 M $H_2O$/THF was added over 1 h, and the reaction mixture was heated for 2 h. After removal of solvents, cluster **194** was obtained and its structure confirmed by X-ray crystallography (Scheme 145).[186]

Introduction of sterically bulky substituents at the 7,7′-positions leads to an increase in the enantioselectivity, especially for the exo product. The highest yields and enantioselectivities (99% yield; *endo*/*exo* = 78:22; *endo*, 18% ee; *exo*, 78% ee) were obtained when X = Ph. When BINOL was used, the products were obtained in 73% yield, and the *endo*/*exo* ratio

**Scheme 146**




| $Zr(OR)_4$ | BINOL (mol%) | additive | yield (%) | ee (%) |
|---|---|---|---|---|
| $Zr(O^tBu)_4$ | **7a**(20) | - | 35 | 9 |
| $Zr(O^tBu)_4$ | **185a**(20) | - | 86 | 75 |
| $Zr(O^tBu)_4$ | **185a**(12) | PrOH | 92 | 93 |
| $Zr(OPr)_4$ | **195**(12) | - | 86 | 92 |
| $Zr(OPr)_4$ | **196**(12) | PrOH | 99 | 96 |

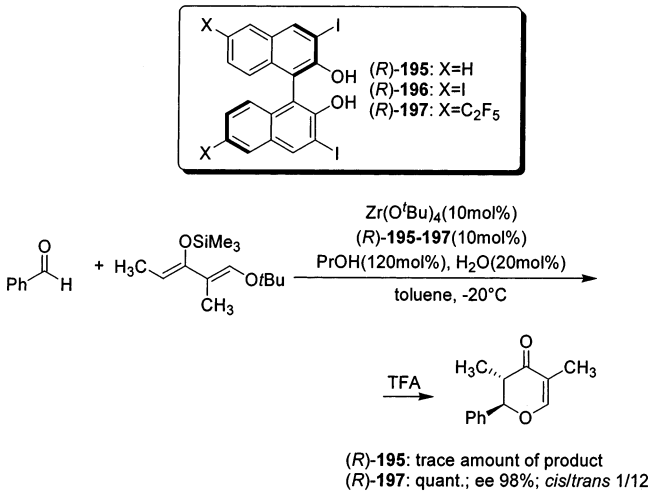
was 7:3, with 18% and 62% ee of each product, respectively.

An asymmetric intramolecular [3 + 2] cycloaddition reaction of hydrazones with olefins using a chiral zirconium catalyst was reported by Kobayashi and co-workers (Scheme 146).[202] The intramolecular [3 + 2] cycloaddition reaction of 4-nitrobenzoylhydrazone was selected as a model reaction in their study. It was found that a chiral zirconium catalyst prepared from $Zr(O^tBu)_4$ and (*R*)-3,3′-$Br_2$-BINOL **185a** gave promising results, affording the desired pyrazolidine derivative solely as a trans isomer in 86% yield with 75% ee. When (*R*)-6,6′-$Br_2$-BINOL **7a** was used as a ligand, a much lower yield and enantioselectivity were observed (35% yield, 9% ee). The catalyst prepared from $Zr(OPr)_4$ and (*R*)-3,3′-$I_2$-BINOL **195** showed even better selectivity than **185a** (92% ee). Addition of propanol to the catalyst system was found to lead to dramatic improvements in both the yield and enantioselectivity (92% yield, 93% ee with **185a** with propanol as additive). The complex prepared from $Zr(OPr)_4$, PrOH, and (*R*)-3,3′,6,6′-$I_4$-BINOL **196** gave the best results (99% yield, 96% ee). Other substrates were examined by the catalysis of (*R*)-**196**. In most cases, good to excellent results were observed (38−99% yield, 72−97% ee).

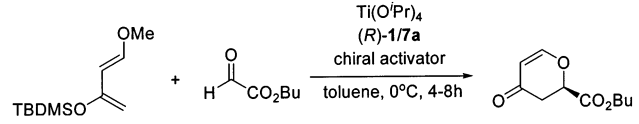
## D. Hetero-Diels–Alder Reactions

Kobayashi and co-workers reported the use of chiral zirconium complexes as catalysts in the HDA reaction between aldehydes and Danishefsky's dienes to selectively produce the trans-disubstituted pyranone derivatives.[203] By using Zr-(*R*)-**195** as catalyst, both aromatic and aliphatic aldehydes reacted smoothly with dienes to give the pyranone derivatives in moderate to good yields with high enantioselectivities (58% to quantitative yield, 84−98% ee). The reaction did not proceed when the less reactive diene substrate 1-*tert*-butoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene was employed. The authors further introduced electron-withdrawing groups ($C_2F_5$, I) at

**Scheme 147**




**Scheme 148**



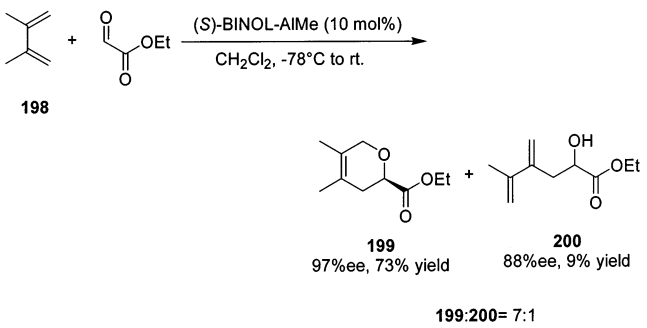

the 6,6′-positions of the BINOL derivative in order to increase the Lewis acidity of the zirconium catalyst. In the presence of the newly generated catalyst (Scheme 147), the reaction between benzaldehyde and 1-*tert*-butoxy-2-methyl-3-(trimethylsiloxy)-1,3-pentadiene proceeded smoothly to afford the desired product in 98% ee and quantitative yield, with a *cis*/*trans* ratio of 1:12.

Mikami and co-workers have used 6,6′-$Br_2$-BINOL/Ti complexes in the asymmetric catalysis of hetero-Diels−Alder reactions with chiral activators.[204] The catalyst was prepared by mixing binaphthol ligands with $Ti(O^iPr)_4$ in a 1:1 ratio, followed by addition of 1 equiv of a chiral activator such as BINOL **1** or 5,5′-dichloro-4,4′,6,6′-tetramethylbiphenol. The Diels−Alder reaction was carried out using the Danishefsky diene and *n*-butyl glyoxylate (Scheme 148). The highest enantioselectivity (84%) was obtained when the (*R*)-BINOL/Ti complex was used along with (*R*)-BINOL as an activator. When (*R*)-6,6′-$Br_2$-BINOL ((*R*)-**7a**)) was used as the chiral activator, the product was obtained in 25% yield and 43% ee.

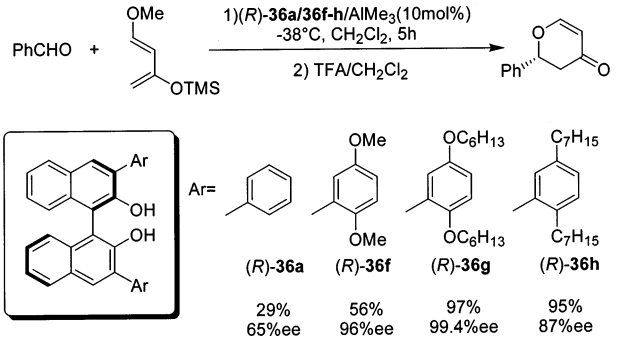
An HDA reaction of conjugated dienes containing allylic C−H bonds with glyoxylate esters, catalyzed by chiral BINOL−AlMe complexes, was described by Jørgensen and co-workers.[205] Compared to the substituted BINOL derivatives ((*R*)-3,3′-biphenyl-BINOL and (*S*)-3,3′-bis(triarylsilyl)-BINOL), the parent BINOL showed both higher chemo- and enantioselectivity as well as better reactivity. In the reaction of diene **198** and ethyl glyoxylate, the HDA product was obtained in 73% yield and 97% ee using the (*S*)-(−)-BINOL−AlMe complex. It was noted that the 3,3′-substituted BINOL ligands gave opposite asymmetric induction to the parent BINOL ligand (Scheme 149).

Jørgensen and co-workers reported a highly enantioselective hetero-Diels−Alder reaction of benzaldehyde with activated dienes, catalyzed by hypercoordinating chiral aluminum complexes.[206] To investigate the stereoelectronic factors influencing the reaction, the authors prepared a series of BINOL derivatives (*R*)-**36a**/**36f**−**h**,[145] with varying substituents on the phenyl groups situated at the 3,3′-positions of the BINOL ring (Scheme 150). Ligand (*R*)-**36a** was used to probe the steric effect of a single phenyl substituent on the catalytic activity, whereas (*R*)-**36f** and (*R*)-**36g** were prepared to study the ligands with similar coordinating properties but different steric characteristics. (*R*)-**36h** was selected as a ligand with steric requirements similar to those of (*R*)-**36g**, but with no possibility of coordination of the ether oxygen atoms to the aluminum reactive center. The results outlined in Scheme 150 showed that ligand (*R*)-3,3′-bis(2,5-dihexyloxyphenyl)-BINOL **36g** gave the best results. Pyranone was obtained in 99.4% ee with 97% yield. Ligand (*R*)-**36a**, which has neither the steric bulk nor the coordinating ether oxygen atoms, promoted the reaction in only modest chemical yield and enantioselectivity (29% yield, 65% ee). Ligand (*R*)-**36f**, substituted with methoxy groups, is nearly as efficient as (*R*)-**36g** in enantioselectivity but with a much lower yield (56% yield, 96% ee). Ligand (*R*)-**36h**, with steric properties similar to those of (*R*)-**36g**, promoted the reaction in 87% ee and 95% yield. The lack of ether oxygen atoms capable of coordinating to the aluminum center in (*R*)-**36h** markedly reduced the enantioselelctivity. These results indicate that hypercoordination to the aluminum center should be considered as a contributing factor.

**Scheme 149**

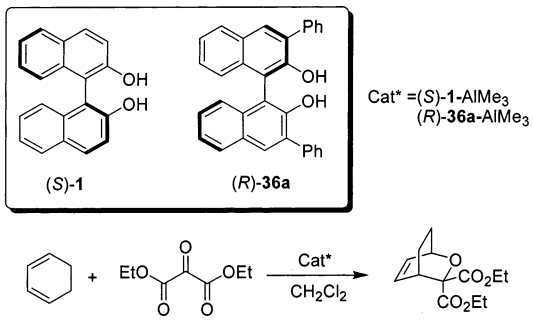



**Scheme 150**

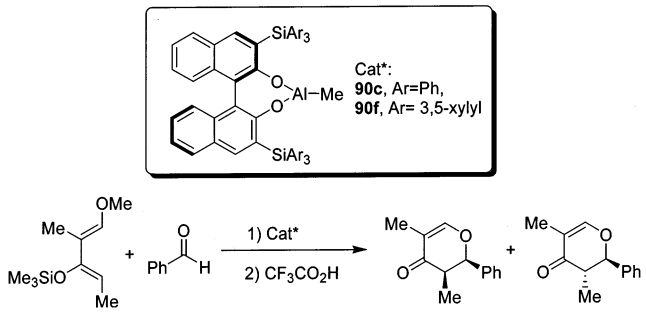



The combination of BINOL ligands (*S*)-**1** or (*R*)-**36a** with $AlMe_3$ was also tested in the hetero-Diels−Alder reaction between 1,3-cyclohexadiene and ketomalonate. However, neither of them proved to be efficient in this case.[207] No product was isolated after 18 h with use of (*S*)-**1**−$AlMe_3$ as the catalyst, whereas

**Scheme 151**




**Scheme 152**




the phenyl-substituted (*R*)-**36a**-$AlMe_3$ catalyzed the reaction between the diene and ketomalonate to afford the product in only 13% yield and 33% ee (Scheme 151).

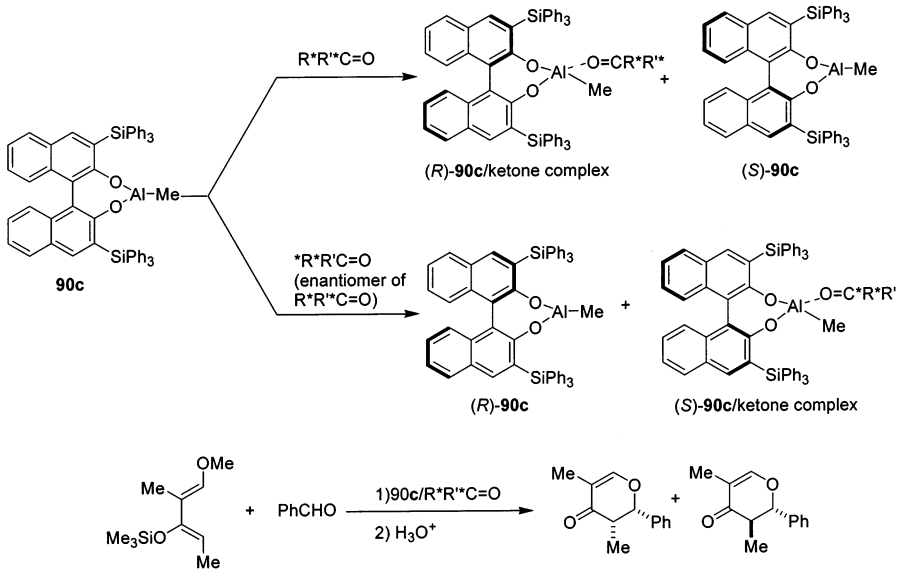
Yamamoto and co-workers reported an HDA reaction promoted by a chiral organoaluminum complex. With 3,3′-bis(triarylsilyl)binaphthol ligand, the aluminum complex gave high enantioselectivity (97%) and yield (93%). The cis adduct was the predominant product in this case (cis/trans = 30:1, Scheme 152).[208]

The choice of the bulky triarylsilyl moiety in the ligand is crucial for obtaining high enantiofacial differentiation of prochiral aldehydes. Switching the triarylsilyl substituent to a *tert*-butyldimethylsilyl or trimethylsilyl group led to eminent loss of enantioselectivity as well as cis selectivity. The chiral organoaluminum complex derived from $Me_3Al$ and (*R*)-(+)-3,3′-dialkylbinaphthol (alkyl = H, Me, Ph) was employed as a stoichiometric reagent and gave less satisfactory results in both reactivity and enantioselectivity.

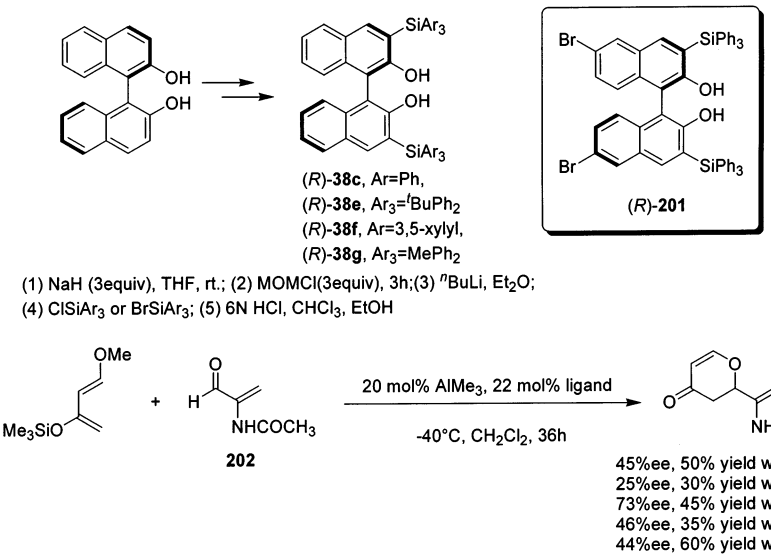
This group discovered that the bulky organoaluminum reagent methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide (MAD) was capable of forming a 1:1 complex with certain carbonyl substrates.[209] Therefore, it was expected that certain chiral ketones might discriminate between racemic organoaluminum reagents by diastereoselective complexation and the remaining chiral organoaluminum reagent (*R*)-**90c** or (*S*)-**90c** would be utilized in situ as a chiral Lewis acid for the asymmetric synthesis, as illustrated in Scheme 153. The expectation was realized by applying the in situ generated catalyst in the asymmetric HDA reaction. D-3-Bromo-camphor was found to be the best chiral ketone. Combination of the racemic compound **90c** and chiral ketone in a 1:1 ratio gave a better result than that in a 2:1 ratio. As well, the catalytic use of the reagent exhibited higher enantioselection than the stoichiometric use. In this reaction, the chiral ketone plays the role of chemical antagonist toward one enantiomer of racemic organoaluminums.

Pu reported a concise three-step synthesis of (*R*)-**38c**,**e**−**g** which contain various bulky 3,3′-substituents by using Snieckus ortho-aromatic metalation strategy (Scheme 154).[210] (*R*)-**38c** was converted to (*R*)-**201** in 70% yield by treatment with bromine in acetic acid and dichloromethane at −20 °C. The chiral Lewis acid complexes made from (*R*)-**38** or **201** with $AlMe_3$ were applied as catalysts in the asymmetric hetero-Diels−Alder reaction of Danishefsky's diene with dienophile **202**. The sterically bulkier ligand (*R*)-**38f** showed much higher enantioselectivity (73% ee) than (*R*)-**38c** (45% ee). Introduction of the electron-withdrawing 6,6′-bromine atoms in (*R*)-**201** increased the acidity of the hydroxyl groups, but showed no improvement in enantioselectivity (44% ee). In all cases, the chemical yield was only low to moderate (30−60%).

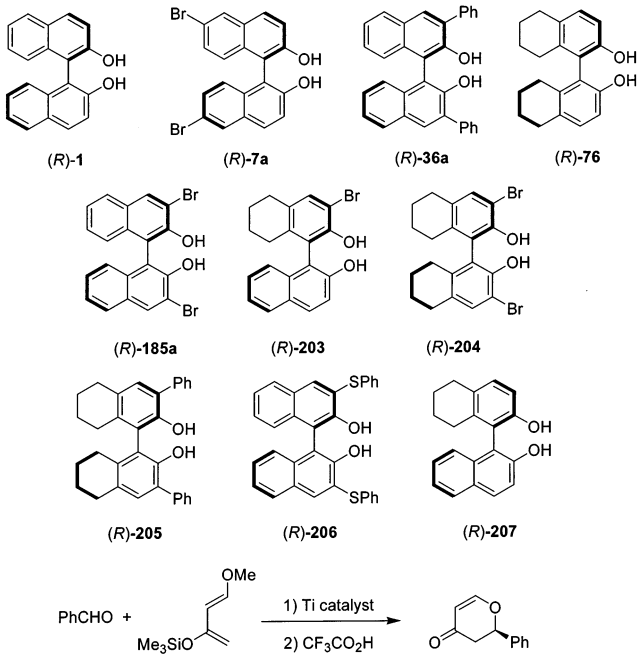
**Scheme 153**



**Scheme 154**

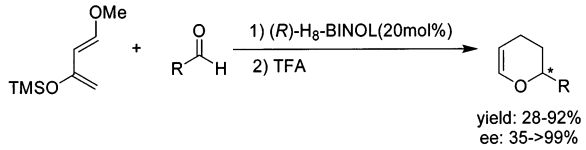



**Scheme 155**




Ding and co-workers recently reported a hetero-Diels−Alder reaction with a catalyst found using high-throughput screening of a combinatorial library of chiral titanium complexes.[211,212] The combinatorial library was generated by combining one diol ligand with Ti(O$^i$Pr)$_4$ and an alternative diol ligand (Scheme 155). In the model reaction of Danishesky's diene with benzaldehyde, the diol ligand (*R*)-**1**-, (*R*)-**7a**-, (*R*)-**76**-, and (*R*)-**207**-modified catalysts were found to be outstanding in terms of both enantioselectivities and yields. The steric hindrance at the 3,3′-positions proved to be detrimental for the reaction. After further screening of the reaction conditions, (*R*)-**207**/Ti/(*R*)-**207** and (*R*)-**76**/Ti/(*R*)-**207** were found to be the best catalysts combinations, inducing high yields (up to 99%) and excellent enantioselectivities (up to 99.8% ee) in the reaction of a variety of aldehydes with Danishesky's diene under a low catalyst loading (0.1−0.005 mol %) and solvent-free conditions.

**Scheme 156**




Jiang and co-workers found a similar result, applying their 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol/Ti complex (**76**/Ti). Using 20 mol % of the catalyst gave the product of the hetero-Diels−Alder reaction between benzaldehyde and Danishefsky's diene in 92% yield and 97% ee (Scheme 156).[213] Other aldehydes gave excellent results, with yields of up to 92% and enantioselectivities of >99%. The authors were also able to expand the scope of the reaction and use a variety of different aldehydes, including aliphatic aldehydes. In each case, the product was obtained in moderate to high yields with good enantioselectivities.[214]

Asymmetric aza-Diels−Alder reactions are useful routes to optically active heterocycles, such as piperidines and tetrahydroquinolines. Few accounts of enantioselective reactions have been reported so far.[215] Yamamoto et al. reported an enantioselective aza-Diels−Alder reaction using their Brønsted acid-assisted chiral Lewis acid system (BLA, Figure 29).[216,217]

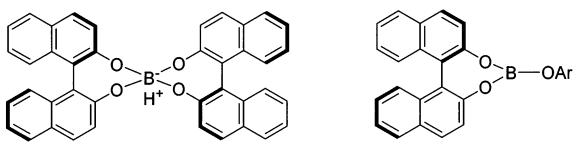
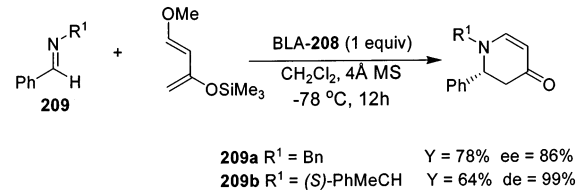


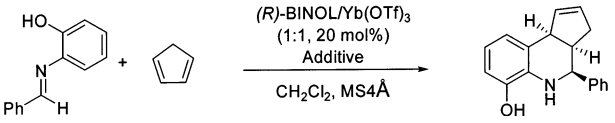

**Figure 29.**

Complex BLA-**208** was prepared in situ by mixing a 1:2 molar ratio of triphenyl borate and optically active BINOL in dichloromethane. A phenol-free solution can also be prepared by the reaction of B(OMe)$_3$ and enantiomerically pure BINOL in dichloromethane at reflux. Complex BLA-**208a** can be

**Scheme 157**

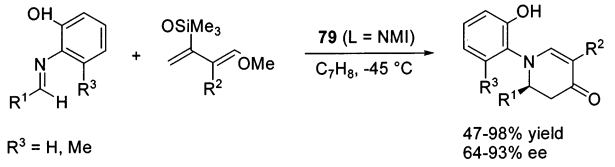



**Scheme 158**[a]




[a] Additive = NMI, 2,6-di-*tert*-butylpyridine, 2,6-dimethylpyridine, 2,6-di-*tert*-butyl-4-methylpyridine.

**Scheme 159**




prepared similarly from a 1:1 molar ratio of triaryl borate and binaphthol.

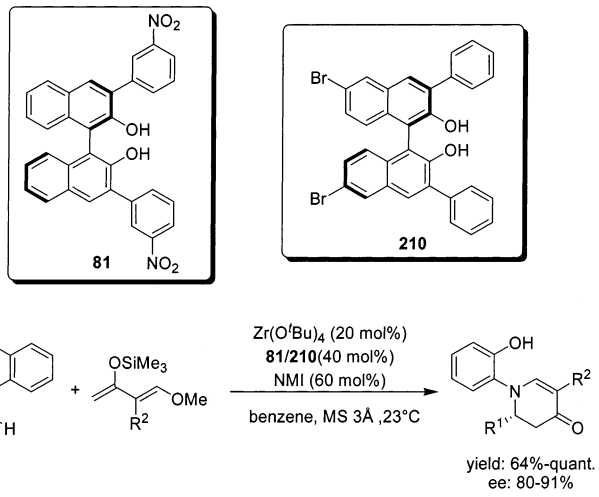
It was discovered that the method of catalyst preparation greatly affects the enantioselectivity of the reaction. If chiral imine **209b** (Scheme 157) is premixed with BLA-**208a** and $B(OPh)_3$, yellow crystals of (*R*)-**208a**−(*S*)-**209b**−PhOH are obtained after 1 h. The reaction between this complex and Danishefsky's diene results in the corresponding product in 64% yield and >99% ee.

Kobayashi and co-workers reported a stereoselective aza-Diels−Alder reaction of azadienes with dienophiles using chiral lanthanide catalysts (Scheme 158).[218] The enantioselectivities for this reaction ranged from 56 to 91%, depending on the additive. The products were limited to 8-hydroxytetrahydroquinoline derivatives. To overcome the narrow substrate scope, catalyst **79** (see Figure 8), previously prepared for the asymmetric Mannich-type reactions, was introduced.[28] After optimization, the best conditions proved to be 10−20 mol % of catalyst in toluene at −45 °C (Scheme 159).[219] A range of aldimines were employed as substrates in this reaction, with enantioselectivities up to 93%.

By switching the ligand (*R*)-6,6′-$Br_2$-BINOL **7a** to (*R*)-6,6′-dibromo-3,3′-diphenyl-1,1′-binaphthol (*R*)-**210** or (*R*)-3,3′-di-(5-nitrophenyl)-1,1′-binaphthol ((*R*)-**81**), the HDA products were obtained with reverse configurations under the same reaction conditions as mentioned above (Scheme 160).[220]

While high yields and selectivities were obtained in these reactions in several cases, further optimization of the catalyst structure was still desired.[221] The authors divided the catalyst into three parts (**X**, **Y**, and **Z** in Figure 30). First, part **Y** was optimized using the solid-phase approach. Polymer-supported BINOL derivatives **212** were prepared starting from (*R*)-BINOL and then treated with $Zr(O^tBu)_4$ to form the polymer-supported zirconium complex **213** (Scheme 161). In the presence of 20 mol % of **213**,

**Scheme 160**




the model aza-Diels−Alder reaction of aldimine **214** with Danishefsky's diene **215** was performed. Among the various zirconium complexes **213** tested, the one with 4-fluorophenyl groups at the 3,3′-positions of the BINOL ring was the most promising in terms of both yields and selectivities (80% yield, 83% ee).

Next, the **X** and **Z** parts of the zirconium catalyst were optimized using liquid-phase methods. It was found that higher enantioselectivities were observed in the model reaction of **214** with **215** in cases when electron-withdrawing cyano groups were introduced at the $R^4$ positions (Figure 30) or electron-withdraw-

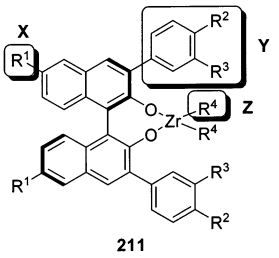
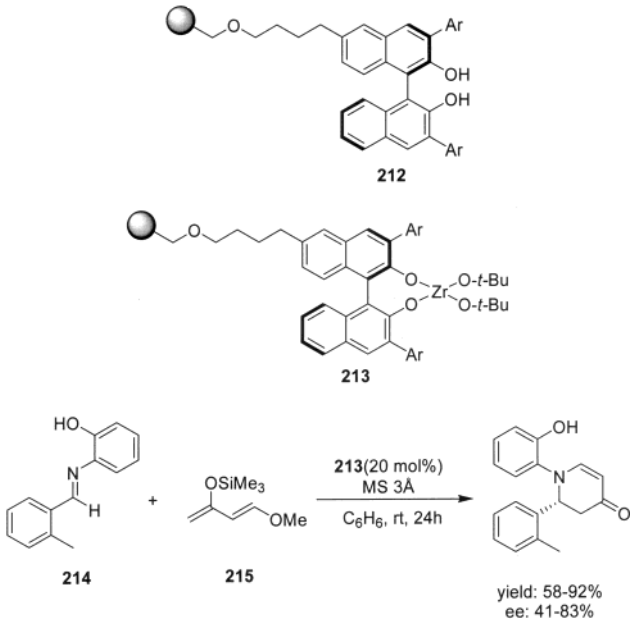
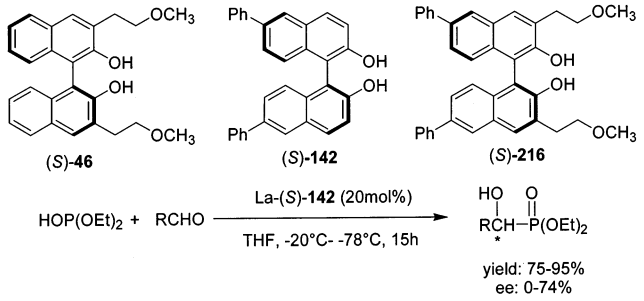



**Figure 30.**

**Scheme 161**



**Scheme 162**




ing groups (e.g., fluoro and trifluoromethyl groups) were employed at the $R^2$ and $R^3$ positions. Finally, complex **211**, with $R^1 = R^2 = H$, $R^3 = CF_3$, and $R^4 =$ CN, was found to be the best catalyst (61−93% yields, 83−94% ee).

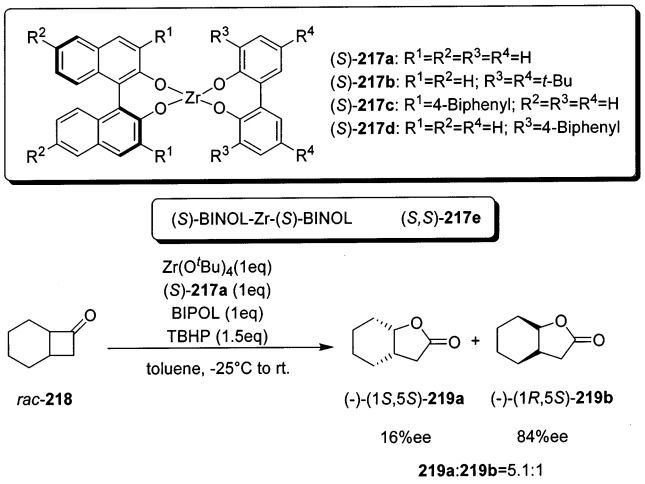
## E. Pudovik Reaction

Qian and co-workers reported the synthesis of 3,3′-, 6,6′-, and 3,3′,6,6′-substituted binaphthols (*S*)-**46**, (*S*)-**142**, and (*S*)-**216** from (*S*)-BINOL and their application in the asymmetric Pudovik reaction (Scheme 162).[222] A profound effect of the substituents of BINOL on enantioselectivity was observed. In the Pudovik reaction, the steric effects become of overriding importance in determining the reactivity and structure of the lanthanide complexes. Because of the large radius of the lanthanide ion, the enhanced steric hindrance of the ligand tends to lengthen the M−O bonds of the lanthanide oxide, increasing the space around the chiral ligand, thereby leading to reduced asymmetric induction. The results showed that, compared to the parent (*S*)-BINOL, the steric bulk of the 3,3′-substituents on both (*S*)-**46** and (*S*)-3,3′-bis(trimethylsilyl)-1,1′-bi-2-naphthol lowers the enantioselectivity of the reaction. With phenyl groups at the 6,6′-positions at the BINOL ring, both (*S*)-**142** and (*S*)-**216** gave better results than (*S*)-**46**. This could be due to the fact that phenyl groups at the 6,6′-positions increase the Lewis acidity of the catalyst. (*S*)-**142** promoted better results than (*S*)-**216** due to the harmful steric hindrance on the ligand (*S*)-**216** to the asymmetric induction. Using (*S*)-**142** as a chiral ligand, a variety of aldehydes react with diethyl phosphite to afford the desired products in moderate enantioselectivities with good yields.

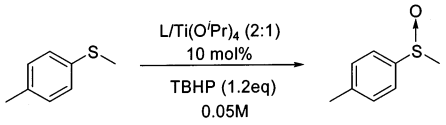
## F. Baeyer–Villiger Reaction

A zirconium-mediated asymmetric Baeyer−Villiger reaction of bicyclic and monosubstituted cyclobutanones was reported by Bolm et al., who used enantiomerically pure BINOL and its derivatives as ligands in zirconium complexes.[223] It was found that 1 equiv of (*S*)-BINOL in complex (*S*,*S*)-**217e** could be replaced by the pro-atropisomeric 2,2′-biphenol (BIPOL) without significant loss in the enantioselectivity of the lactones formed. The (*S*)-BINOL was found to be superior to both (*S*)-6,6′-$Br_2$-BINOL and (*S*)-3,3′-*N*,*N*-diethylcarbamoyl-BINOL in both reactivity and enantioselectivity. Under optimized conditions, the product lactone of bicyclooctanone *rac*-**218** was formed in 16% ee of (−)-(1*S*,5*S*)-**219a** and 84% ee of (−)-(1*R*,5*S*)-**219b**, with a **219a**/**219b** ratio of 5.1:1 (Scheme 163).

**Scheme 163**




**Scheme 164**



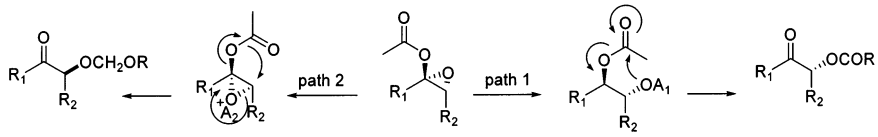

## G. Oxidation of Sulfides to Sulfoxides

Optically active sulfoxides are useful intermediates in the synthesis of various complex chiral molecules.[224] Yudin and co-workers compared the activities of (*R*)-BINOL with (*R*)-$F_8$-BINOL in the asymmetric oxidation of sulfides to sulfoxides in the presence of *tert*-butyl hydrogen peroxide (TBHP) (Scheme 164).[225] It was found that the (*R*)-$F_8$-BINOL/Ti system catalyzed the reaction with higher enantioselectivity (60% in $CH_2Cl_2$) than the *(R)*-BINOL/Ti system (7% in $CH_2Cl_2$ and 22% in $CCl_4$) at 0.05 M concentration. A similar protocol by Uemura led to high enantioselectivities at high concentrations; however, a significant amount of the sulfone byproduct is produced.[226] Due to the electrophilic character of $F_8$-BINOL, (*R*)-$F_8$-BINOL/Ti-catalyzed reactions tend to produce more sulfone than the BINOL-mediated reactions. The low enantioselectivities of (*R*)-BINOL/Ti-catalyzed reactions suggested that the species responsible for enantioselective oxygen transfer was not produced in the 1:1 system.

Reaction optimization showed that cumyl hydrogen peroxide in chloroform increased the enantioselectivity of the reaction up to 86%. Water was also found to be crucial for the system. Two equivalents of water are required for the turnover to take place. With these results in hand, ligand **28** (Scheme 16) was used under similar reaction conditions.[26] The enantioselectivity with the **28**/Ti catalyst was 51%, which indicates that the bis-substitution may lead to different catalytic activity.

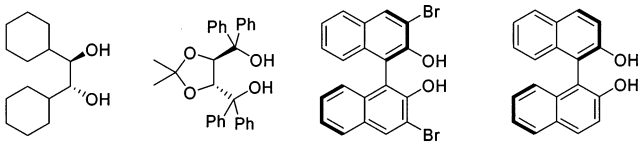
Bolm and co-workers used bis-steroidal binaphthols such as **64** in asymmetric sulfoxidation using Uemura's system (BINOL/Ti($O^iPr$)$_4$)[226] as the reference point.[47] Methyl phenyl sulfide was used as the substrate, with an aqueous solution of TBHP as

**Scheme 165**




**Scheme 166**

Ligands:



oxidant in THF, giving the product in 80% yield and 90% ee. In contrast to the previous reports, chlorinated solvents such as $CH_2Cl_2$ gave low enantioselectivities. The byproduct sulfone was rarely seen in THF, which most likely explains the higher yields.

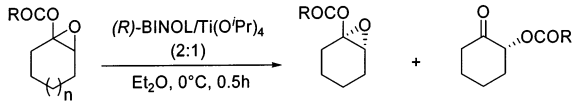
Ligand **73** (Scheme 39) was also used in asymmetric sulfoxidation with $Fe^{III}Cl$-containing complexes, where the porphyrin active site transfers oxygen from the metal center to the substrate.[56] Methyl phenyl sulfide was thus oxidized to the corresponding sulfoxide in 84% yield with 24% ee. Small amounts of sulfone were detected. Although the yields were generally high (67−88%), low enantioselectivities (less than 50%) were observed.

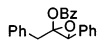
## H. Kinetic Resolution of Racemic Enol Ester Epoxides

Enol ester epoxides can be rearranged to α-acyloxy ketones or aldehydes under protic or Lewis acidic conditions. Shi and co-workers found that this rearrangement can occur along two distinct pathways, one with retention of configuration and the other with inversion (Scheme 165).[227] The strength of the acid catalyst is important in determining the path which the reaction follows. Strong acids favor retention of configuration (path 1), while weak acids favor inversion (path 2). Initial studies revealed the BINOL/Ti-($O^iPr$)$_4$ system to be a promising Lewis acid catalyst for the resolution (see Scheme 166 for selected examples).[228] The best results were obtained with 2 equiv or more of BINOL per titanium. The reaction was best conducted in $Et_2O$ and $CH_2Cl_2$. The catalyst was suitable for a number of different ester groups with a variety of steric and electronic properties (Scheme 167). Five-, seven-, and eight-membered ring systems can also be successfully rearranged using the BINOL/Ti Lewis acid catalyst. The system, however, is not suitable for acyclic epoxides (last entry in Scheme 167). In these cases, the recovered starting material was obtained in high enantioselectivity and reasonable yield. The reactions were generally fast (0.5−2.2 h); however, the larger ring sizes as well as the acyclic epoxides took much longer (68.5 h for the eight-membered ring system) (163 h).

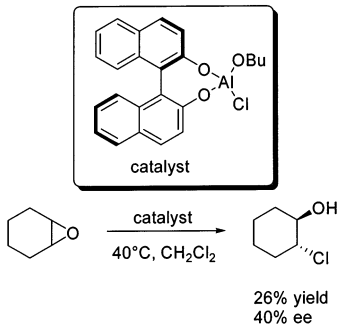
Yamamoto and co-workers have also used chiral Lewis acids based on binaphthol systems in the kinetic resolution of epoxides.[229] The initial studies involved ring opening of oxiranes into α-chlorohydrins. The catalyst for this system was prepared from

**Scheme 167**




| R | conv. (%) | recov'd S.M. ee (%) | epoxide yield (%) | product ee (%) |
|---|---|---|---|---|
| Ph (n=1) | 50 | 97 | 34 | 90 |
| *p*-$NO_2$Ph (n=1) | 49 | 96 | 39 | 96 |
| $^t$Bu (n=1) | 54 | 97 | 22 | 88 |
| Ph (n = 2) | 63 | 97 | 32 | 71 |
|  | 58 | 54 | -- | 38 |

**Scheme 168**



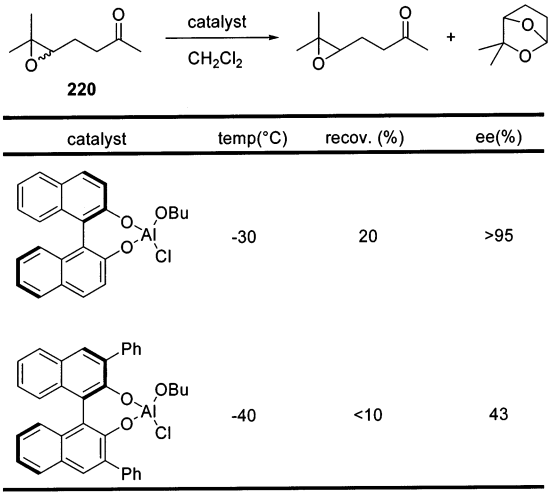

(*R*)-BINOL, diethylaluminum chloride, and lithium butoxide. The epoxide was treated with the catalyst at −78 °C, gradually warmed to ambient temperature, and then refluxed for 1.5 days to generate the corresponding chlorohydrin in 40% ee (Scheme 168).

The scope of the reaction was then expanded to other epoxides, including ketoepoxide **220**, shown in Scheme 169. The catalyst prepared using (*R*)-BINOL proved to be the most efficient, giving the cyclized product in >95% ee, while (*R*)-3,3′-$Ph_2$-BINOL **36a** gave the product in only 43% ee.

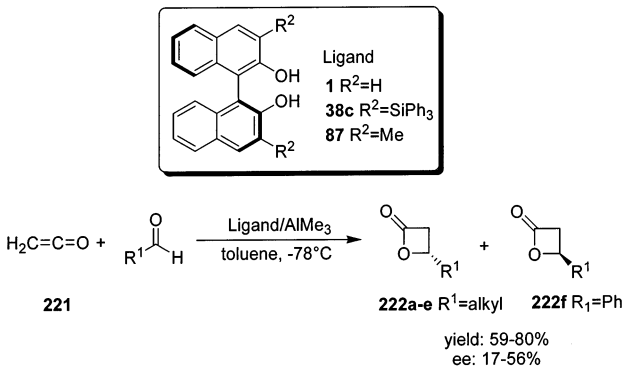
## I. [2 + 2] Cycloaddition of Ketenes with Aldehydes

Asymmetric synthesis of 4-substituted oxetan-2-ones by [2 + 2] cycloaddition of ketene **221** with aldehydes was described by Miyano's group.[230] The reaction was catalyzed by a stoichiometric amount of chiral binaphthol/$AlMe_3$ complexes (Scheme 170), prepared from BINOL derivatives and trimethylaluminum. The sterically more hindered ligand **38c** induced higher ee compared to the ligands **1** and **87**. In the presence of a stoichiometric amount of complex **38c**/$AlMe_3$, optically active 4-substituted oxetan-2-ones **222** were synthesized in moderate to good yields with up to 56% ee (Scheme 170).

**Scheme 169**



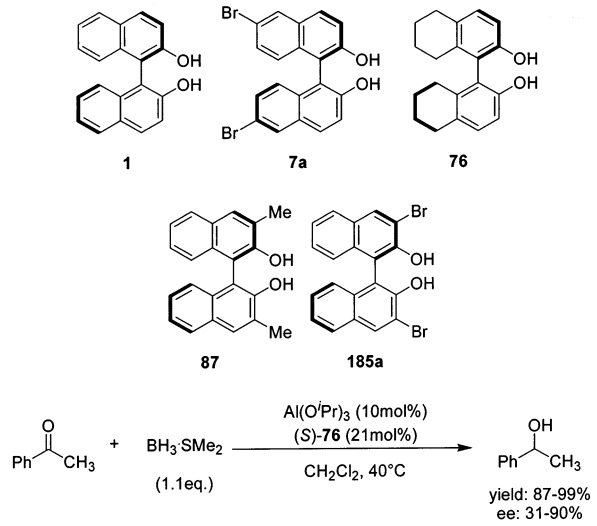

**Scheme 170**




## V. Application in Catalytic Asymmetric Borane Reduction of Aromatic Ketones

Uang and co-workers reported an asymmetric borane reduction of aromatic ketones by using the BINOL derivatives shown in Scheme 171 as chiral ligands in an aluminum catalyst.[231] Compared to Lewis acid $Al(O^iPr)_3$, the catalysts prepared from these BINOL-derived ligands and $Al(O^iPr)_3$ dramatically increased the reaction rate from 1 day to less than an hour, with a slight increase in yields.

**Scheme 171**




Comparing with (*R*)-BINOL **1**, which induced 97% yield and 60% ee with an absolute configuration of the resultant carbinols as (*S*), both 3,3′-substituted BINOLs **185a** and **87** gave lower enantioselectivities with an opposite absolute configuration of the products (94% yield and 46% ee with **185a**; 97% yield and 10% ee with **87**). The 6,6′-substituted BINOL **7a** induced no enantioselectivity in this reaction. (*R*)-$H_8$-BINOL **76** induced the highest ee of 71% with 95% yield. A variety of aromatic ketones were reduced by using 10 mol % of $Al(O^iPr)_3$ and 21 mol % of (*S*)-**76**. The enantioselectivities range from 31% to 90%, with yields varying from 87% to 99%.

## VI. Concluding Remarks

This review discussed the synthesis and applications of modified binaphthols as chiral ligands in asymmetric catalysis. Since Noyori first reported the application of BINOL in asymmetric catalysis in 1979, BINOL derivatives have played a significant role in asymmetric catalysis, and have attracted a great deal of interest. Many new examples have emerged in this field, especially during the past 5−6 years. Various modified BINOL ligands were successfully applied to a wide range of reactions.

The enantiomers of BINOL are inexpensive and commercially available compounds. By modifying the BINOL scaffold, chemists can easily and effectively tune both the steric and electronic character of the chiral metal−BINOL complexes. Using the techniques of parallel synthesis, diverse BINOL derivatives can be synthesized and screened in a particular reaction with the ultimate goal of finding the best catalyst/substrate combination. There are two general methods to synthesize modified BINOL ligands: (a) by replacing the hydrogen atoms of the BINOL ring with different functional groups through aromatic substitution reactions or (b) by coupling reaction of the substituted 2-naphthols. Thus far, it appears that the aromatic substitution of the BINOL ring is the method of choice.

The majority of modified BINOL ligands introduced in asymmetric catalysis are 3,3′- and/or 6,6′-substituted BINOLs, although a few examples highlight applications of other substituted BINOLs. By introducing different functional groups into the 6,6′-positions, one can effectively tune the electronic characteristics of the binaphthol system, thereby changing the character of the chiral metal center. On the other hand, the 3,3′-substituted BINOLs are more often applied in the sterically demanding cases and usually provide a sterically modulated environment for the asymmetric processes, although in a few cases they were also involved in tuning the electronic character of the metal−BINOL complexes.

## VII. Acknowledgments

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