Symmetry Breaking in Asymmetric Catalysis: Racemic Catalysis to Autocatalysis

Koichi Mikami* and Masahiro Yamanaka

Department of Applied Chemistry, Tokyo Institute of Technology, Meguro-ku, Tokyo 152-8552, Japan

Received February 24, 2003

Contents

> Any man who, upon looking down at his bare feet, doesn't laugh, has either no sense of symmetry or no sense of humor.
>
> Descartes

1. Introduction: Symmetry Breaking Concept

Living molecules and their components in Nature are homo-chiral rather than hetero-chiral despite the structural possibility of two enantiomeric "right-handed" and "left-handed" forms. [A homo-chiral relationship occurs in a series of homologous molecules of identical absolute configurations (cf. Damewood, J. R., Jr. *Chem. Eng. News* **1985**, Nov 4, 5. Eliel, E. L.; Wilen, S. H. *Chem. Eng. News* **1990**, Sept 10, 2).] Homogeneiety in chirality, either right- or left-handed biomolecules, has been recognized as a fundamental principle in Nature.[1] For instance, DNA and RNA, composed of D-(2-deoxy)ribose, store and transfer genetic information, and highly ordered structures of proteins derived from L-amino acids are essential for the structural backbones and chemical transformations in the biosphere. The scenario of successive evolution, proposed by Pearson, suggests that molecular formations at the early stages of evolution might involve a nonracemic composition, and subsequent evolutionary processes account for the appearance of an excess of molecules with homo-chirality.[2] A homogeneous chirality sense in Nature, obtained by catastrophic self-replication after symmetry breaking in the racemic world or the delivery of exochirality, external chiral substances on the primitive (prebiotic) Earth, is the key for the quest of molecular evolution and the continuity of life. Therefore, the fundamental question about the generation stage of homo-chirality in Nature has long received widespread attention, and theoretical models of the origin of chirality on Earth have been proposed.[3]

The origins of homo-chirality in Nature can be divided into two categories, namely abiotic and biotic, as tabulated in Figure 1. Biotic theories presumed that life on Earth originated at some advanced stage of molecular evolution with the particular choice of one enantiomer, e.g., L-amino acids and D-sugars, as the most efficient for continuous progress into higher organized forms.[4] In abiotic theories, by contrast, generation of homo-chirality could not be originated without some initial asymmetric abiotic bias. Abiotic theories are further classified into chance and determinant ones:[3a,b] (1) a "chance mechanism" to generate an optically active molecule randomly and (2) a "determining mechanism" to favor one enantiomer by internal or external chiral bias. Spontaneous multiplication after an initial enantiomeric imbalance induced either by a chance or determinant mechanism would be amplified to link with the homo-chiral world on the current Earth. To explain amplification of chirality, the concept of autocatalysis in a life model was first reported by Frank in 1953.[5] Later, Calvin also drew the process of "stereospecific autocatalysis" to give enantiopure materials.[6] As shown in Figure 2, in two rapidly equilibrating enantiomeric reactants (*d*)-S and (*l*)-S, the product enantiomer (*d*)-P acts stereospecifically as an autocatalyst to produce more (*d*)-P than (*l*)-P at a faster rate than the original noncatalytic reaction. In statistical fluctuations, the enantiomeric substrates (*d*)-S and (*l*)-S are not in equal amounts. In the case of a slight excess of (*d*)-S, (*d*)-P formed in slight excess can rapidly catalyze the synthesis of (*d*)-P, leading to homo-chirality.

Although various theoretical models for spontaneous amplification of chirality have been proposed,[7] experimental evidence has been limited for a random generation of chiral molecules. Spontaneous resolution during the crystallization of racemic or prochiral compounds is a typical example for spontaneous generation of optical activity without any chiral bias,

* To whom correspondence should be addressed. Tel.: 81-3-5734-2142. Fax: 81-3-5734-2776. E-mail: kmikami@o.cc.titech.ac.jp.

10.1021/cr000260z CCC: $44.00
Published on Web 08/13/2003

Koichi Mikami was born in 1953 in Bousou, Chiba, Japan. He received his Ph.D. in 1982 under the supervision of Professors Takeshi Nakai and Nobuo Ishikawa at the Tokyo Institute of Technology. He was a postdoctoral fellow at Yale University with Professor Frederick E. Ziegler (1982–1983), and then returned to the Tokyo Institute of Technology as an Assistant Professor. He became an Associate Professor in 1987. He has received the Tejima award for stereocontrol based on [2,3]-sigmatropic rearrangements, the Chemical Society of Japan Award (Shinpo-Sho) for asymmetric transmission and asymmetric synthesis based on [2,3]-Wittig rearrangements, the Society of Synthetic Organic Chemistry Japan Award (Asahi-Kasei Award) for asymmetric synthesis based on carbonyl–ene reactions, the IBM award for highly efficient asymmetric catalysis, and Ichimura Science Award for industrial application of asymmetric catalytic Friedel-Crafts reactions. He was the Bristol-Myers-Squibb Lecturer (Colorado State University), the Lilly Research Laboratories Lecturer (Ohio State University), and the Boehringer Ingelheim Award Lecturer (Université de Montréal), and has held Visiting Professorships at the Université Paris-Sud and in Taiwan.

Masahiro Yamanaka was born in 1973 in Chiba, Japan. He received his M.S. degree under the direction of Professor Takahiko Akiyama from Gakushuin University in 1998, and then began his Ph.D. work on the theoretical studies on transition-metal-assisted reactions, based particularly on Cu, Co, and Rh. He received his Ph.D. degree under the supervision of Professor Eiichi Nakamura from The University of Tokyo in 2001. He joined the group of Prof. Keiji Morokuma in Emory University for a couple of months. He took a position as an Assistant Professor in the group of Professor Koichi Mikami in the Department of Applied Chemistry, Tokyo Institute of Technology in 2001. His current research interests lie between theoretical chemistry and organometallic chemistry, particularly in the design and development of dynamically controlled asymmetric catalysis systems and the nature of metal–ligand–substrate interactions, further with the third component (chiral controller, activator, and deactivator).

and is closely associated with the discovery of chirality in molecules. In a pioneering work by Pasteur in 1848, it was found that the conglomerate of a 1:1 mechanical mixture of two enantiomers of sodium ammonium tartrate (*racemes*: *acide racémique*) was made up by an autocatalytic crystallization process

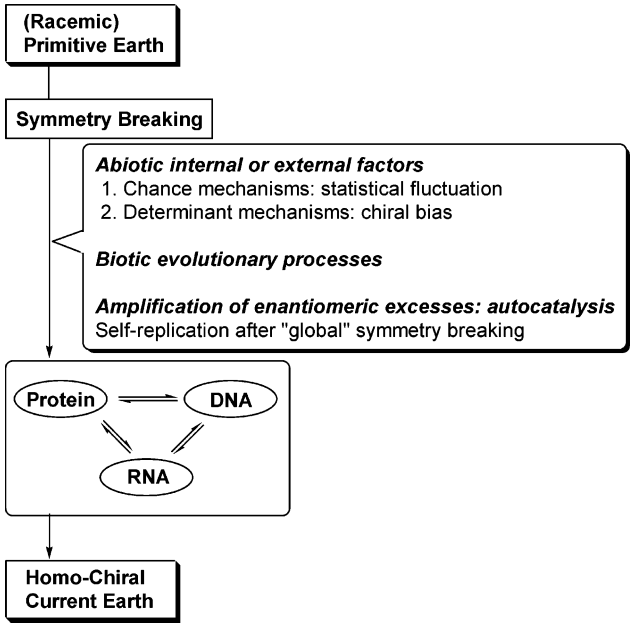


Figure 1. The origins of homo-chirality in Nature.

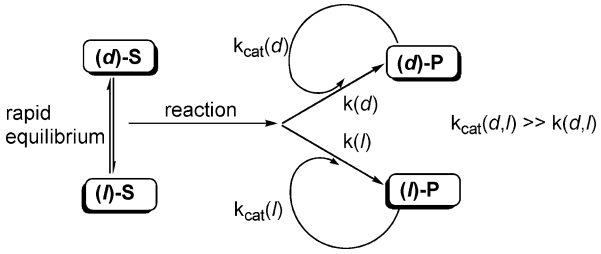


Figure 2. Calvin's autocatalysis model.

from a racemic mixture (spontaneous enantiomer resolution).[8] Later, in 1941, preferential enantiomorphic crystallization of ammonium salts through a dynamic equilibrium between two enantiomeric forms was reported by Havinga.[9] In 1971, Pincock studied the spontaneous generation of optical activity in the crystallization of 1,1′-binaphthyl.[10] The enantiopure crystals differ in energy and kinetics of formation from the diastereomeric racemate crystals. If the enantiopure form is lower in energy and nucleation of the crystal occurs from a single site, then spontaneous generation of optically active crystals would be achieved. In general, spontaneous enantiomer resolution is thus rather difficult in a fluid phase due to thermal fluctuations and/or molecular diffusion. Therefore, only a two-dimensional conglomerate has been reported in a monolayer film but on a crystalline surface.[11] Very recently, the first example of spontaneous enantiomer resolution of a racemic molecule into a three-dimensional conglomerate in a fluid liquid-crystalline phase has been reported by us.[12] Some intrinsic internal or external physical and chemical forces are the determining factors to provide a non-equivalence of enantiomers.[3,6] Stereoselective adsorption on crystalline quartz of one of the enantiomers of racemic compounds has been argued as another mechanism to generate a chiral bias in Nature.[13] Experimental evidence has also been reported for asymmetric adsorption of racemic amino acids on quartz.[14] Nonconservation of equivalent weak interactions may lead to small differences in

energy [$(2-6) \times 10^{-14}$ J/mol] between two enantiomeric forms.[15] The weak interaction establishes an intrinsic left chirality for the electron and right chirality for the positron and leads to the chemical expectation that β-decay of nucleides should induce an enantiodifferentiating radiolysis of racemic mixtures. However, no clear-cut enantioselective radiolysis of racemic mixtures has been reported to result from such a very weak energy ($\sim 10^{-18}$ eV). Circular polarized light (CPL)[16] and geophysical fields such as rotation of the earth and magnetic fields[17] have long been examined as determining factors. However, these physical forces should account for homo-chirality in Nature.

Irrespective of the mechanism providing enantiomeric excesses, the "symmetry breaking" concepts are fundamental aspects of how natural fluctuation from a completely racemic state followed by asymmetric multiplication leads to a homo-chiral state. Therefore, the efforts toward finding the origin of the generation of chirality at the molecular level as well as at the macromolecular level are closely associated with current progress in asymmetric synthesis. Synthetic chemists have long studied asymmetric synthesis, since the discovery of molecular chirality in the times of Pasteur. The term "asymmetric synthesis" was first coined by Fisher:[18] "*Diese Vorstellung giebt, wie mir scheint, eine einfache Losung fur das Rathsel der naturlichen asymmetrichen Synthese.*" Thus, he showed that the D-series of sugars were synthesized from (+)-glyceraldehyde and that the L-series was from the (−)-enantiomer. Marckwald defined asymmetric synthesis: "*Asymmetrische Synthesen sind solche, welche aus symmetrisch constituirten Verbindungen unter intermediarer Benutzung optisch-activer Stoffe, aber Vermeidung jades analytischen Vorganges, optitsch-activen Substanzen erzeugen*" [translation: Asymmetric syntheses are those reactions which produce optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical (resolution) processes.].[19] Later, Morrison and Mosher reported a wider definition: "Asymmetric synthesis is a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts".[20] Reactants include not only the usual chemical reagents but also catalysts. The development of enantioselective catalysts, which provide enantiomerically enriched products, is of central importance in modern asymmetric synthesis[21] in terms of 'chirality economy', namely the ratio of product % ee × product % yield/catalyst % ee × catalyst mol % (the racemic catalysis should be *infinitely* efficient and economical), and hence is an environmentally "green" process.[22] Standard methods for such enantioselective catalysis are the employment of metal complexes bearing chiral and nonracemic organic ligands, normally in enantiopure form (Figure 3a). The key for efficient asymmetric catalytic reactions is to develop chiral catalysts with a suitable chiral environment. The studies on the origin of chirality in Nature might provide the basis

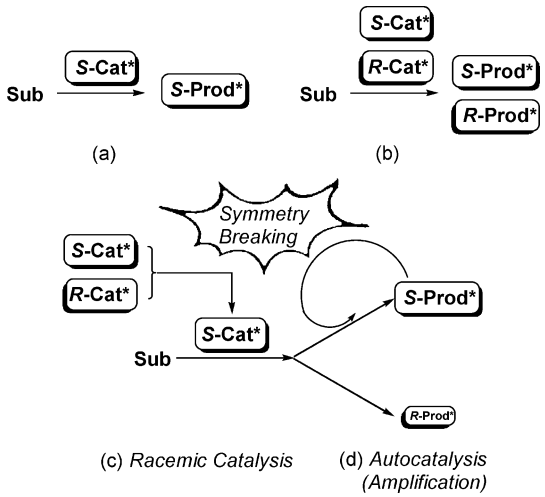


Figure 3. Asymmetric catalysis based on the symmetry breaking concept.

for the new paradigm for the current stage of asymmetric catalysis starting from racemic catalysts. While nonracemic catalysts can generate nonracemic products, racemic catalysts inherently produce only racemic products (Figure 3b). On the basis of the symmetry breaking concept, asymmetric catalysis consisting of enantiomeric fluctuation (or discrimination) by the external chiral bias and subsequent amplification of chirality through autocatalysis can be developed. Recently, novel approaches for symmetry breaking in asymmetric catalysis have been reported. The racemic catalysts can be enantiomer-selectively transformed into a highly activated (or deactivated) enantiomeric catalyst by additional chiral sources (Figure 3c). The nonequivalence of enantiomeric catalysts resulting from the spontaneous breaking of racemic catalysts is amplified by an asymmetric autocatalytic process (Figure 3d).[23] In this review, recent progress in chirally economical racemic catalysis (section 2) will be discussed and followed by asymmetric amplification (section 3) and autocatalysis (section 4).

2. Racemic Catalysis

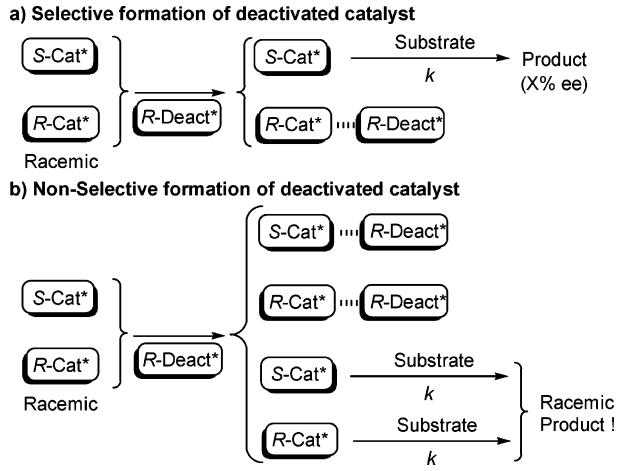
While nonracemic catalysts can generate enantioenriched products, racemic catalysts generally give only a racemic mixture of chiral products. In view of the fluctuation of the racemic environment in Nature, we might be able to develop asymmetric reactions through preferential discrimination of racemic catalysts by a certain chemical or physical source. Indeed, as a new stage of asymmetric catalysis emphasizing chiral economy, chiral symmetry breaking, i.e., in situ resolution of racemic catalysts, has been reported recently. A strategy for racemic catalysis by addition of chiral sources can be classified into two extremes:[24] (1) 'asymmetric deactivation'[33a] and (2) 'asymmetric activation'.[33a] In the asymmetric deactivation strategy, enantiomer-selective deactivation of a racemic catalyst by chiral sources (e.g., chiral poison) achieves chiral symmetry breaking of a racemic state to yield nonracemic products. As a strategy conceptually opposite, the asymmetric activation has been developed. A chiral activator selec-

tively activates one enantiomer of a racemic catalyst. Therefore, racemic catalysts can be evolved into chirally active catalysts, leading to enantioenriched products after symmetry breaking by association with chiral deactivators or activators.

2.1. Asymmetric Deactivation[33a]

A racemic catalysis via enantiomer-selective deactivation by a chiral source as a "catalyst poison" leads to the enantiomer-selective formation of a catalyst−deactivator complex with low reactivity (Scheme 1). The chiral poisoning strategy is effective only in the case that a chiral deactivator exclusively complexes with one enantiomer of a racemic catalyst (Scheme 1a). In this case, the chiral deactivator leaves the other enantiomer of the racemic catalyst unchanged, thus affording the enantioenriched product. Therefore, in principle, the level of enantiomeric excess could not exceed that attained by the enantiopure catalyst. On the other hand, nonselective complexation of a chiral deactivator to equally kill racemic catalysts leads to a racemic product (Scheme 1b). Though there would be a significant advantage in reducing cost or synthetic effort by use of the readily available racemic catalyst and inexpensive chiral deactivator, the chiral deactivator tends to be used in an excess amount relative to the catalyst enantiomers.

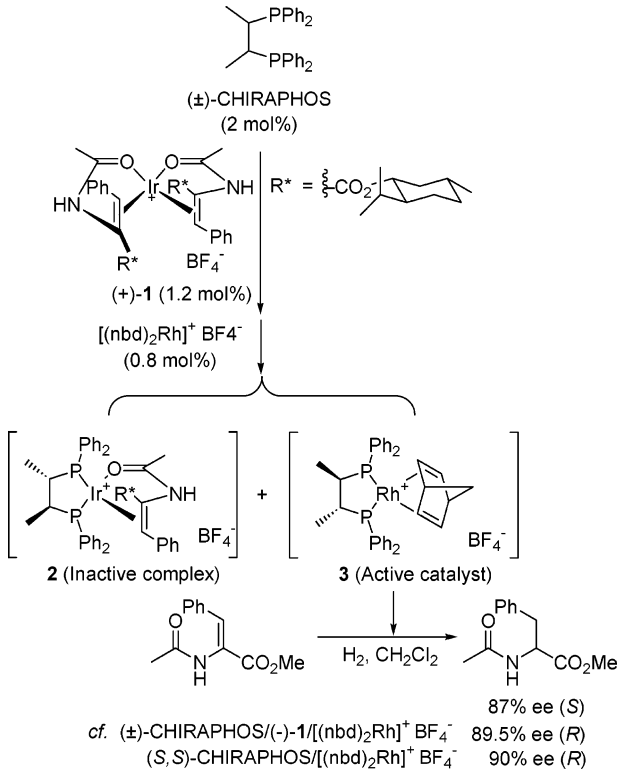
Scheme 1



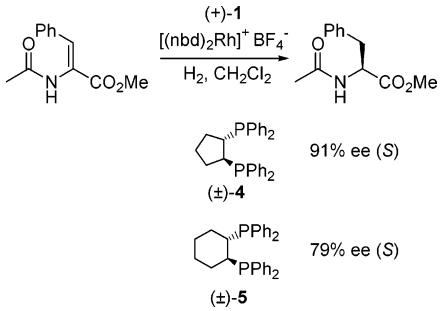
Asymmetric hydrogenation of a dehydroamino ester has been achieved after kinetic resolution of racemic CHIRAPHOS by association with a chiral iridium amide complex (Scheme 2).[25] The chiral iridium enamide complex (+)-**1** reacts with (*S*,*S*)-CHIRAPHOS selectively to form the deactivated iridium complex **2** and remaining (*R*,*R*)-CHIRAPHOS affords a chiral rhodium complex **3**, which catalyzes asymmetric hydrogenation to give the (*S*)-hydrogenation product with 87% ee. The opposite enantiomer (−)-**1** gave the (*R*)-product with 89.5% ee, which is the same value of enantiomeric excess given by using optically pure (*S*,*S*)-CHIRAPHOS. The readily available racemic diphosphine ligands **4** and **5** were employed to afford the (*R*)-hydrogenation product in 91% and 79% ee, respectively (Scheme 3).

More recently, the term "chiral poisoning", coined by Faller, has been used for such a deactivating

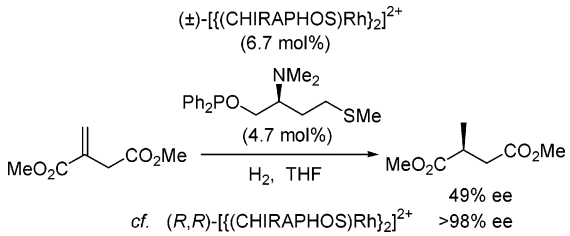
Scheme 2



Scheme 3

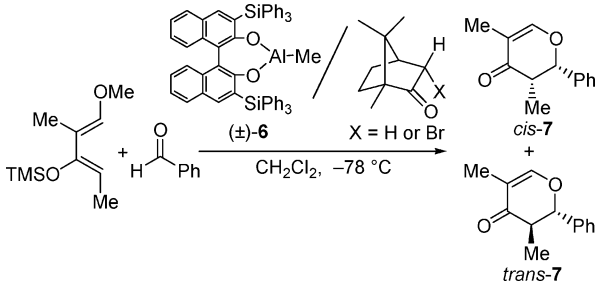


Scheme 4



strategy in the context of an asymmetric hydrogenation reaction of dimethyl itaconate catalyzed by the same CHIRAPHOS−Rh complex (Scheme 4).[26] (*S*)-METHOPHOS ((*S*)-[$Ph_2POCH_2CH(NMe_2)CH_2CH_2$-SMe]), readily prepared from methionine, was employed as a chiral deactivator. Although the (*S*)-METHOPHOS−Rh complex gave the hydrogenation product in <2% ee, the combination of racemic CHIRAPHOS and (*S*)-METHOPHOS yielded the (*S*)-product in 49% ee (Scheme 4). Since hydrogenation using the pure (*R*,*R*)-CHIRAPHOS−Rh complex affords the (*S*)-product in 98% ee, it is concluded that (*S*)-METHOPHOS binds (*S*,*S*)-CHIRAPHOS−Rh complex preferentially.

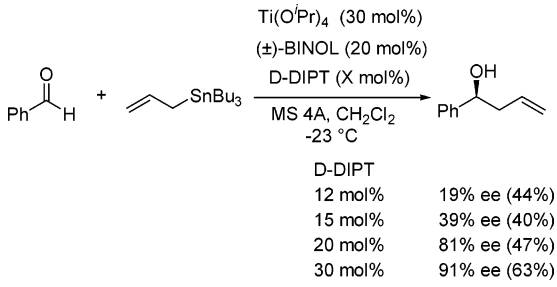
Table 1. Asymmetric Hetero Diels−Alder Reaction



chiral ketone (equiv)	**6** (equiv)	% yield *cis*-**7**/*trans*-**7**	% ee *cis*-**7**
X = H (0.15)	(±)-**6** (0.3)	80/17	22
X = Br (0.15)	(±)-**6** (0.3)	66/32	70
X = Br (0.3)	(±)-**6** (0.3)	84/12	68
X = Br (0.1)	(±)-**6** (0.1)	78/19	82
−	(*S*)-**6** (0.1)[a]	86/9	95

[a] The reaction was carried out in toluene at −20 °C.

Scheme 5

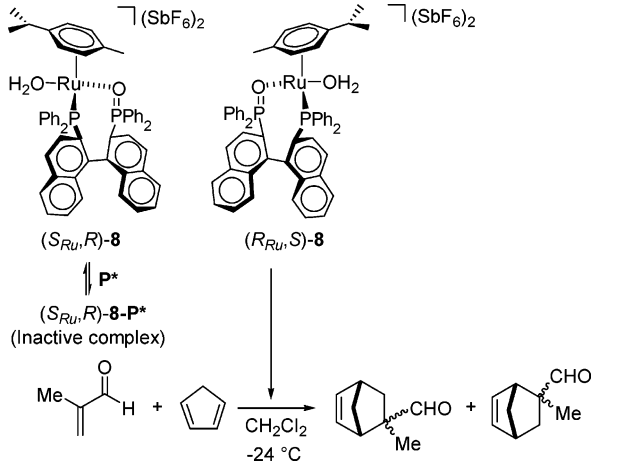


D-DIPT	
12 mol%	19% ee (44%)
15 mol%	39% ee (40%)
20 mol%	81% ee (47%)
30 mol%	91% ee (63%)

The racemic aluminum reagent **6** has been discriminated using a chiral ketone by diastereoselective complexation, and the remaining chiral aluminum reagent (*R*)-**6** or (*S*)-**6** catalyzed an asymmetric hetero-Diels−Alder reaction (Scheme 5).[27a] Here, a chiral ketone acts as a chiral deactivator for one enantiomer of racemic organoaluminums. Maruoka and Yamamoto explored several terpene-derived chiral ketones as chiral deactivators, and finally commercially available (1*R*)-*endo*-(+)-3-bromocamphor was found to be the most effective chiral deactivator for (*R*)-**6**. In the presence of (1*R*)-*endo*-(+)-3-bromocamphor and racemic **6** in a 1:1 ratio, an enantioselective hetero-Diels−Alder reaction was achieved to yield the cis adduct **7** preferentially with 82% ee, which is comparable to the ee obtained from enantiopure (*S*)-**6** (95% ee).[27b] Combination of racemic **6** and chiral ketone in a 1:1 ratio gave a better enantiomeric excess than that in a 2:1 ratio. This indicates that one diastereomer of a **6**/chiral ketone complex readily decomposed to optically pure **6** and chiral ketone rather than the other diastereomeric complex upon the addition of aldehydes for an asymmetric hetero-Diels−Alder reaction (Table 1).

Asymmetric deactivation has been applied to the racemic [*p*-cymeneRu(H_2O)(BINAPO)](SbF_6)$_2$ complex **8**-catalyzed asymmetric Diels−Alder reaction of methacrolein with cyclopentadiene (Table 2).[28] Treatment of the racemic [*p*-cymeneRuCl(BINAPO)]SbF_6 with 1 equiv of $AgSbF_6$ resulted in the racemic **8**, and subsequent addition of L-proline or L-prolinamide as a chiral deactivator (**P***) established an equilibrium between the active aqua-Ru complex **8** and the

Table 2. Asymmetric Diels−Alder Reaction



P* (equiv)	(±)-**8** (equiv)	% conv	% de (exo:endo)	% ee (config)
L-proline (0.1)	0.2	76	98	8 (*S*)
L-proline (0.1)	0.1	28	95	54 (*S*)
L-proline (1.0)	0.2	35	95	59 (*S*)
L-prolinamide (0.1)[a]	0.2	48	95	30 (*S*)
L-prolinamide (0.1)[a]	1.25	92	96	60 (*S*)

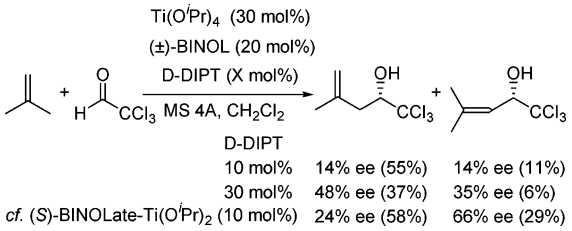
[a] The reaction was carried out in toluene at −78 °C.

deactivated Ru complex **8-P***. The enantioselectivity of the Diels−Alder product became ca. 60% ee when the chiral deactivator was used in stoichiometric amounts or greater with respect to (±)-**8**. The most successful chiral deactivators, L-proline and L-prolinamide, preferentially deactivate the (S_{Ru},*R*)-**8** via different deactivation modes − selective displacement of the aqua ligand by L-proline and of the BINAPO ligand by L-prolinamide − and the remaining (R_{Ru},*S*)-**8** is free to catalyze the asymmetric Diels−Alder reaction.

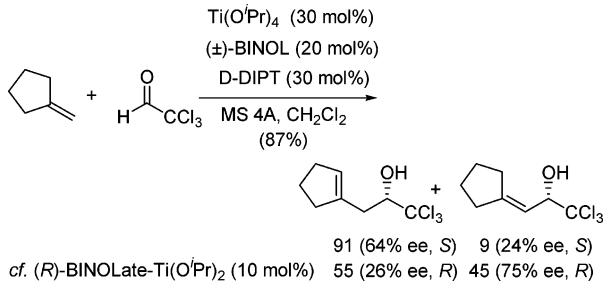
The enantiomerically pure diisopropoxytitanium tartrate complex, prepared in situ from Ti(O^{i}Pr)$_4$ and diisopropyl D-tartrate (D-DIPT), can be effectively used as a chiral deactivator for racemic BINOLate−Ti(O^{i}Pr)$_2$ **9**-catalyzed synthesis of homoallylic alcohols (Scheme 5).[29] The enantiomeric excess of the product increases depending on the amount of D-DIPT employed. When Ti(O^{i}Pr)$_4$ and D-DIPT as a chiral deactivator for (±)-**9** were employed in a ratio of 1:3, the enantioselectivity of the (*S*)-homoallylic alcohol product was increased up to 91% ee and 63% yield from 19% ee and 44% yield obtained by using a ratio of 1:1. While using pure (*S*)-**9** catalyst with the Ti(O^{i}Pr)$_4$/D-DIPT deactivator led to the (*S*)-product in >95% ee and 20% yield, no homoallylic alcohol was obtained by using enantiopure (*R*)-**9** with the Ti(O^{i}Pr)$_4$/D-DIPT, which showed no catalytic activity on its own. These results indicate that the Ti(O^{i}Pr)$_4$/D-DIPT complex therefore selectively deactivates (*R*)-**9** and the remaining (*S*)-**9** effectively catalyzes the reaction in association with an excess of D-DIPT.

The Ti(OPr^i)$_4$/D-DIPT deactivator has been also used for the BINOLate−Ti(OPr^i)$_2$-catalyzed asymmetric carbonyl−ene reaction of some olefins with chloral.[30] Comparable or enhanced enantioselectivity has been achieved relative to that obtained with the use of enantiopure (*S*)- or (*R*)-**9** (Schemes 6 and 7).

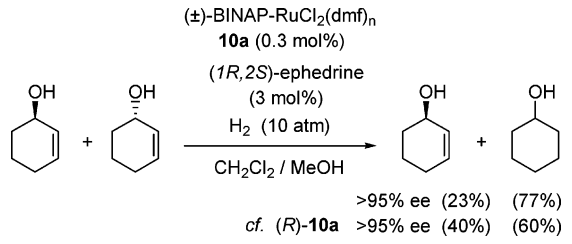
Scheme 6



Scheme 7



Scheme 8



By using the Ti(OPr^i)$_4$/D-DIPT deactivator in a 1:3 ratio, not only the regioselectivity but also the enantioselectivity of the ene product were improved.

A chiral amino alcohol, (1*R*,2*S*)-ephedrine, is also employed as a chiral deactivator in the kinetic resolution of cyclic allylic alcohols using racemic BINAP−$RuCl_2$ **10a** (Scheme 8).[31] Using (±)-**10a** with (1*R*,2*S*)-ephedrine, (*R*)-2-cyclohexenol was obtained in >95% ee at 77% conversion (the relative rate $k_f/k_s > 6.4$). Since the enantiopure (*R*)-**10a** is effective for the kinetic resolution of 2-cyclohexenol, where (*S*)-2-cyclohexenol was obtained in >95% ee at 60% conversion ($k_f/k_s > 15$), (*R*)-**10a** hydrogenated (*R*)-2-cyclohexenol much faster than (*S*)-2-cyclohexenol. Addition of (1*R*,2*S*)-ephedrine noticeably slows the reaction. These results indicate that (1*R*,2*S*)-ephedrine can selectively deactivate the (*R*)-BINAP−Ru component of the racemic catalyst.

As an ultimate chiral deactivator for racemic BINAP−Ru complexes **10**, 3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl (DM-DABN) was designed by us, in which the methyl groups in (*R*)-DM-DABN would interact with PAr_2 groups in (*R*)-BINAP but not in (*S*)-BINAP (Figure 4).

Complete resolution and asymmetric deactivation of the racemic XylBINAP−$RuCl_2$ (±)-**10b** by DM-DABN are shown to be very effective in the kinetic resolution of 2-cyclohexenol.[32] The addition of just a 0.5 molar amount of (*S*)-DM-DABN deactivator to racemic **10b** gave enantiopure (*S*)-2-cyclohexenol. Racemic cyclohexenol was kinetically resolved in the same (53%) conversion as enantiopure **10b** (Scheme 9). Indeed, the relative rate of hydrogenation of (*R*)-vs (*S*)-2-cyclohexenol in the presence of just a 0.5 molar amount of (*S*)-DM-DABN added to (±)-**10b** is large enough ($k_f/k_s = 102$). Asymmetric hydrogenation of β-keto esters was also catalyzed by combination of (±)-**10b** with (*S*)-DM-DABN as a chiral deactivator to give 99% ee of (*R*)-methyl 3-hydroxybutanoate quantitatively. The enantioselectivity (99.3% ee) was very close to that (99.9% ee) obtained by using enantiopure (*R*)-catalyst in our work (Scheme 10).

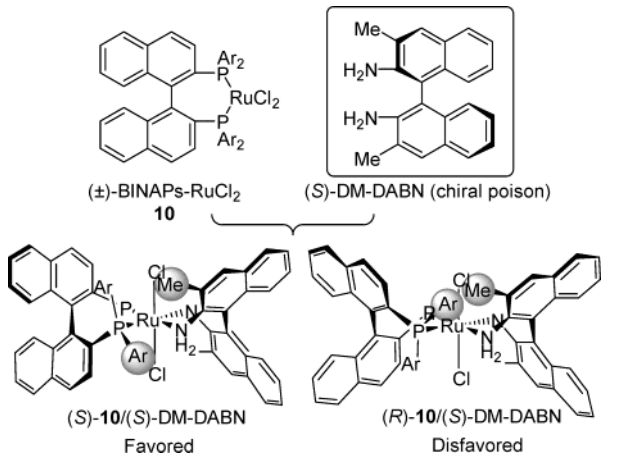
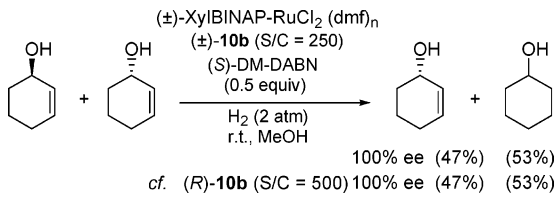
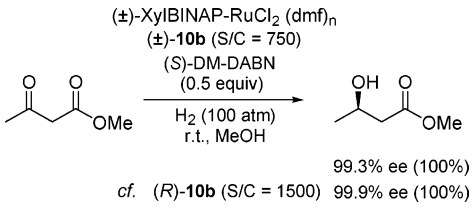


Figure 4. Design of the chiral deactivator for racemic BINAP−$RuCl_2$ complexes.

Scheme 9



Scheme 10

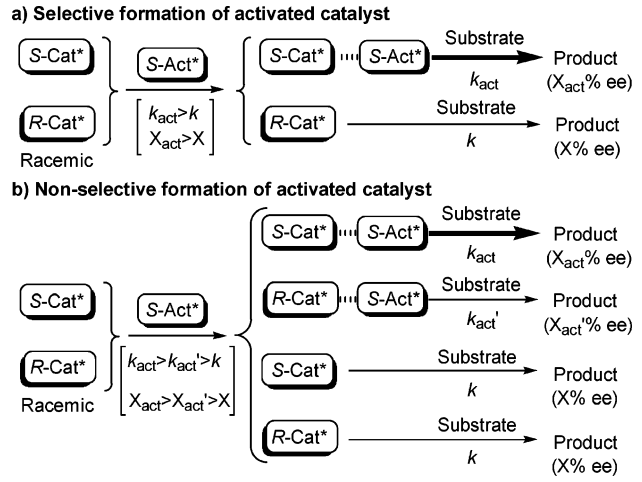


2.2. Asymmetric Activation[33a] of *Atropos* Catalysts

The racemic chiral catalysts can be evolved to highly activated chiral catalysts by addition of chiral sources as chiral activators (Scheme 11). The advantage of the activation strategy over the deactivation counterpart is that the activated catalyst can lead to products with a greater enantiomeric excess (x_{act}% ee) than the enantiomerically pure catalyst on its own (x% ee), even in the ideal case of catalytic use of the activator per chiral catalyst. Therefore, the most crucial step determining the overall enantioselectivity is the complexation of the catalytically active species with the substrate.

Asymmetric activation can also be established in the case of a nonselective complexation giving activated diastereomeric catalysts (Scheme 11b), as the

Scheme 11



result of a difference in turnover frequencies (catalytic activities) between the diastereomers ($k_{act} > k'_{act}$), which depend on the substrates. The use of 1.0 equiv of the activator per parent catalyst often affords a 1:1 mixture of the diastereomeric complexes. In this case, a higher level of enantioselectivity than that achieved by using an enantiomerically pure catalyst (x_{act}% ee > x% ee) can be obtained hopefully, by a difference of more than 2 orders of magnitude in the catalytic efficiency ($k_{act}/k > 10^2$). Figure 5, for example, shows the effect of the variation of the relative rate ($k_{rel} = k_{act}/k_{act}'$ ranges from 0.01 to 100) in the case where one activated diastereomeric complex ((*R*)-ML$_n$/(*R*)-Act*) provides the product in 100% ee (*R*) and the other diastereomer ((*S*)-ML$_n$/(*R*)-Act*) leads to the opposite enantiomeric product in 50% ee (*S*). Even when the two diastereomeric activated complexes are formed in a 1:1 ratio, a product with

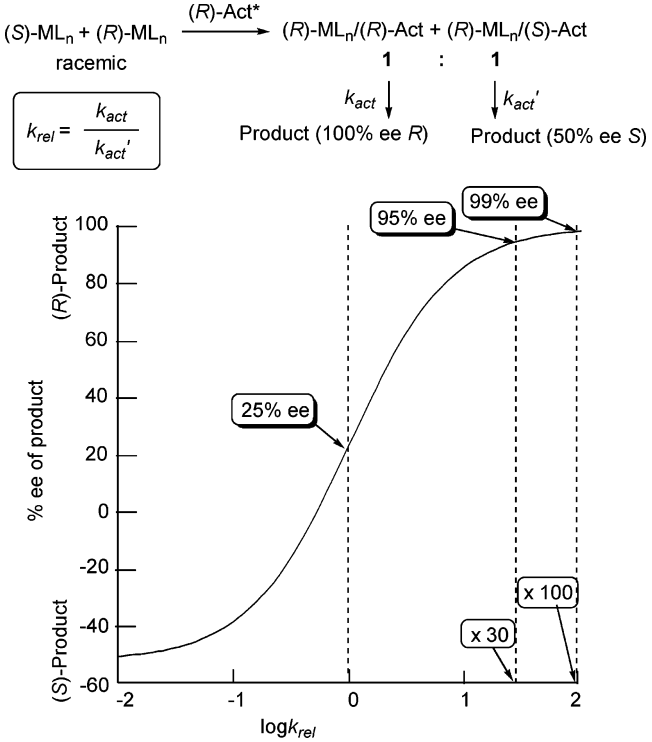
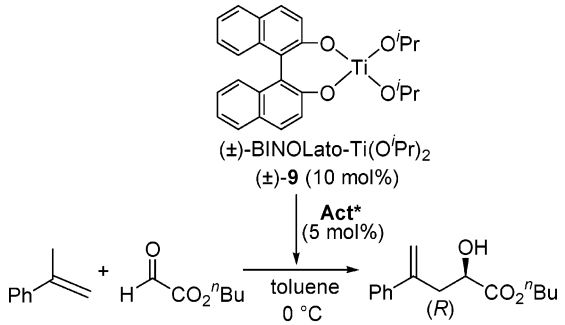
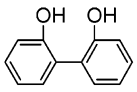
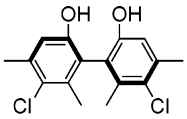
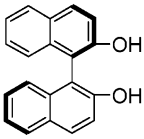


Figure 5. Influence of the relative rate k_{rel} on the ee value of the product.

Table 3. Asymmetric Activation of (±)-9 in the Carbonyl−Ene Reaction



Act*	% yield	% ee
—	5.9	0
	20	0
	38	80.8
	52	89.8
	35	80.0[a]

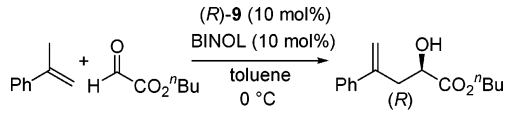
[a] Only 2.5 mol% of (*R*)-BINOL was used as a chiral activator.

more than 99% ee can be obtained if the relative rate of the two activated diastereomers is 100 (log k_{rel} = 2) (Figure 5). Asymmetric catalysts are generally metal complexes bearing chiral and atropisomeric ligands such as BINOL or BINAP, which can usually provide the C_2-symmetric reaction center to achieve asymmetric catalysis. The term "atropisomerism" was coined to cover isomerism caused by blocking the internal turn around a single bond.[62] Since the word *atropos* consists of "*a*" meaning "not" and "*tropos*" meaning "turn" in Greek, with respect to the dynamic behavior of a ligand with a chiral axis, the chirally rigid or flexible nature of a ligand was called *atropos* or *tropos*, respectively.[24b]

The asymmetric activation concept has been applied for the first time in the ene, aldol, and Diels−Alder reactions catalyzed by the *atropos* BINOLate−Ti(O^{i}Pr)$_2$ complex **9**. The racemic BINOLato−Ti(O^{i}Pr)$_2$ (±)-**9**-catalyzed carbonyl−ene reactions of carbonyl enophiles achieved extremely high enantioselectivity by addition of another diol, leading to enantiomer-selective activation (Table 3).[33] High enantioselectivity (89.8% ee, *R*) can be achieved by adding just 5 mol % of (*R*)-BINOL as an activator to 10 mol % of (±)-**9**. The advantage of asymmetric activation of (±)-**9** is highlighted in a catalytic version. High enantioselectivity (80.0% ee) is obtained by adding even less than the stoichiometric amount (0.25 equiv per (±)-**9**) of additional (*R*)-BINOL.

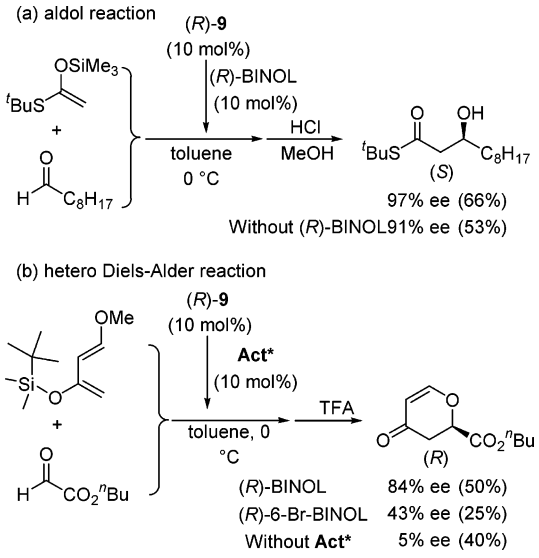
Activation of enantiopure (*R*)-**9** can also be done by further addition of (*R*)-BINOL as an activator (Table 4). The reaction proceeds quite smoothly to provide the carbonyl−ene product in higher chemical

Table 4. Asymmetric Activation of Enantiopure (*R*)-9 in the Carbonyl−Ene Reaction



BINOL	% yield	% ee
−	19.8	94.5
(*R*)-BINOL	82.1	96.8
(*S*)-BINOL	48.0	86.0
(±)-BINOL	69.2	95.7

Scheme 12

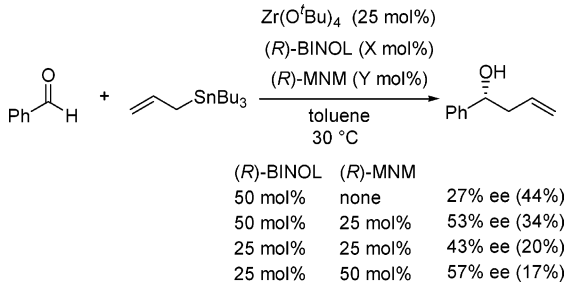


yield (82.1%) and enantioselectivity (96.8% ee) than those attained without additional BINOL activator (19.8%, 94.5% ee). Kinetic studies showed that the reaction catalyzed by (*R*)-BINOLato−Ti(O^iPr)$_2$/(*R*)-BINOL complex (R,R_{act})-**9** is 25.6 times as fast as that catalyzed by (*R*)-**9**. These results imply that (±)-**9** and a half-molar amount of (*R*)-BINOL self-assemble into (R,R_{act})-**9** and leave (*S*)-**9** unchanged. In contrast, additional (*S*)-BINOL activates (*R*)-**9** to a smaller degree, providing the carbonyl−ene product in lower optical (86.0% ee, *R*) and chemical (48.0%) yields than (*R*)-BINOL.

A similar phenomenon of enantiomer-selective activation has been observed in aldol[34] and hetero-Diels−Alder reactions.[35] Asymmetric activation of (*R*)-**9** by addition of (*R*)-BINOL is also effective to provide higher levels of enantioselectivity (97% ee) than those attained by the parent (*R*)-**9** (91% ee) in the Mukaiyama aldol reaction of silyl enol ethers (Scheme 12a). Asymmetric activation of (*R*)-**9** by (*R*)-BINOL is essential to provide higher levels of enantioselectivity (84% ee) than those obtained by using (*R*)-**9** (5% ee) in the hetero-Diels−Alder reaction of glyoxylates with the Danishefsky diene. Since activation of (*R*)-6-Br-BINOL gave lower yield (25%) and enantioselectivity (43% *ee*) than those obtained by using (*R*)-BINOL (50%, 84% ee), not only steric factors but also electronic factors are important for a chiral activator. (Scheme 12b).

Asymmetric activation was also observed in the combination of (*R*)-BINOL and Zr(O^tBu)$_4$-promoted enantioselective synthesis of homoallylic alcohols

Scheme 13

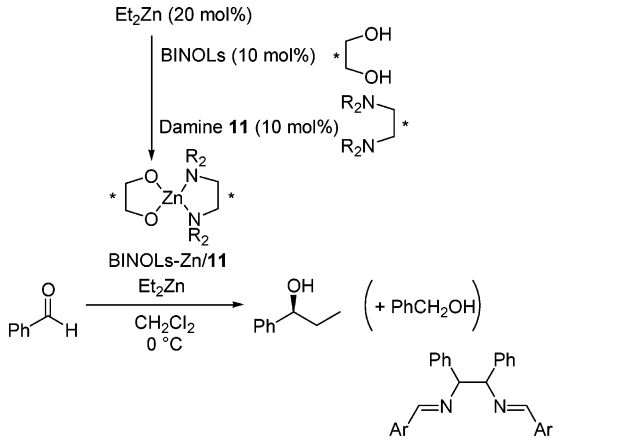


(Scheme 13).[36] The use of (*R*)-BINOL and Zr(O^tBu)$_4$ in a 2:1 ratio without any other chiral source afforded the homoallylic alcohol product in 27% ee and 44% yield. Since addition of (*R*)-(+)-α-methyl-2-naphthalenemethanol ((*R*)-MNM) led to higher ee (53% ee) than those obtained by using only (*R*)-BINOL (27% ee), (*R*)-MNM can act as a chiral activator for the reaction. With use of (*R*)-BINOL and Zr(O^tBu)$_4$ in a 1:1 ratio, 2 equiv of (*R*)-MNM led to higher ee (57% ee) than that obtained by addition of 1 equiv of (*R*)-MNM (43% ee). A higher ee and activation effect for the allylation of benzaldehyde were thus attained by addition of (*R*)-MNM as a product-like activator.

Chiral organozinc reagents constitute one of the most fundamental asymmetric catalysts for carbon−carbon bond-forming reactions. In an enantioselective addition of diorganozinc reagents to aldehydes, various chiral ligands including β-amino alcohols have been explored since its initial report by Oguni.[37,38] However, less attention has been paid to C_2-symmetric and *atropos* BINOLs[39] for Zn catalysts, despite their wide application as chiral ligands for B,[40] Al,[41] Ti,[42] Zr,[43] and Ln[44] catalysts in enantioselective aldol, ene reactions and so forth, due to their lower catalytic activity and enantioselectivity for the organozinc addition reaction.[45] More recently, some modified BINOLs[46−48] have been reported to be effective, but the simple BINOL itself is less effective in the reaction. The addition of chiral amine activators for activation of BINOL−zinc catalysts should facilitate the alkyl transfer efficiently because of its strong ability to coordinate to the zinc center. As a result, a monomeric zinc complex might be expected to form in a manner similar to that of the chiral salen−zinc catalyst system.[49]

The bimolecular combination of the BINOLs, diethylzinc reagent, and various chiral amines **11**, which can act as chiral activators, greatly enhanced the reactivity and enantioselectivity in the asymmetric alkylation of benzaldehyde (Table 5).[50] When either (*R*)-BINOL or the chiral amine **11a** was employed, (*S*)-1-phenylpropanol was obtained with only 8.2% ee (54% yield) or 1.1% ee (64% yield). In this case, the reduction product (in parentheses) was also formed as a side product. However, the combined use of (*R*)-BINOL and **11a** afforded quantitatively the product with 37.4% ee. The enantioselectivity of the reaction is further increased by using a matched combination of a modified BINOL and certain chiral diamine activators. The replacement at the 3- and 3′-positions with sterically demanding phenyl groups, (*R*)-3,3′-diphenyl-1,1′-bi-2-naphthol ((*R*)-Ph_2-BINOL) led to (*S*)-1-phenylpropanol in up to 65% ee and

Table 5. Screening of Chiral Ligand/Activator Combinations in the Addition of Diethylzinc



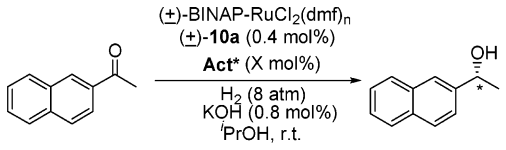
BINOLs	11	% yield	% ee
(*R*)-BINOL	—	54	8.2
—	**11a**	64	1.1
(*R*)-BINOL	**11a**	100	37
(*R*)-Ph_2-BINOL	**11a**	100	65
(*R*)-Ph_2-BINOL	**11b**	100	65
(*R*)-Ph_2-BINOL	**11c**	100	90
(*R*)-Ph_2-BINOL	**11c**	100	99[a]

[a] The reaction was carried out at -78 °C

quantitative yields in association with either the chiral amine **11a** or **11b**. The absolute configuration of the product can be determined primarily by that of BINOLs, since use of the chiral amine **11b**, having opposite chirality to that of **11a**, led to the same enantiomers as with **11a**. The chirality of the diamine activators thus has little effect on the absolute configuration of the product, but it greatly affects the level of enantioselectivity. The steric hindrance of the chiral activators is also crucial. The chiral activator **11c** was finally found to lead to the best results. The reaction catalyzed by the best combination of (*R*)-Ph_2-BINOL/**11c** was further optimized by tuning the lower reaction temperature to −78 °C, and hence (*S*)-1-phenylpropanol was obtained in quantitative yield with 99% ee. All amine activators significantly activate the BINOL−Zn catalyst complexes to enhance the yields and enantioselectivities of 1-phenylpropanol above those obtained by using only the ligands themselves. The best combination of chiral ligands and activators can easily be determined in an efficient way by super-high-throughput screening[52] to afford the most enantioselective and activated catalyst.

Noyori has reported the Nobel-award-winning catalysis of enantioselective hydrogenation of simple ketones. The enantiomerically pure $RuCl_2$(BINAP)-$(dmf)_n$ complex (**10a**:BINAP, **10b**:XylBINAP,[51] **10c**: TolBINAP[52]), an enantiopure diamine such as (*S*,*S*)-1,2-diphenylethylenediamine (DPEN),[53] and KOH to provide hydrogenation products of carbonyl compounds with high enantioselectivity.[54,55] The asymmetric activation concept could be applied to the racemic BINAP−$RuCl_2$ catalysts **10** for the enantioselective catalysis of carbonyl reduction (Table 6).[56b] A chiral diamine leads to a nonracemic hydrogenation product. Exploring various chiral diamines, we

Table 6. Asymmetric Activation of Racemic BINAP−$RuCl_2$ Complex in the Hydrogenation



Act* (mol%)	% yield	% ee
(*S*,*S*)-**12** (0.2)	91	20
(*S*,*S*)-**12** (0.4)	99	79[a]
(*S*)-**13** (0.2)	99	23
(*S*)-**13** (0.4)	99	76[a]
(*S*)-**14** (0.2)	53	4
(*S*)-**14** (0.4)	47	30[a]
(*S*)-**15** (0.2)	96	4

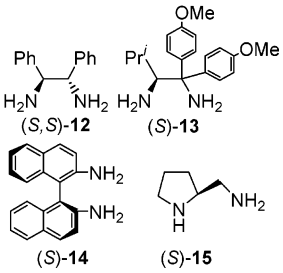
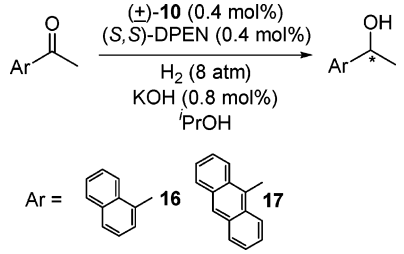


Table 7. Asymmetric Activation of Racemic BINAP−$RuCl_2$ Complexes in the Hydrogenation with (*S*,*S*)-DPEN



catalyst	ketone	temp (°C)	% yield	% ee
(±)-**10b**	**16**	−35	95	90 (*R*)
(±)-**10b**	**16**	−35	90	90 (*R*)[a]
(*R*)-**10b**	**16**	28	99	56 (*S*)
(*S*)-**10b**	**16**	28	99	>99 (*R*)
(±)-**10c**	**17**	80	99	80 (*R*)
(*R*)-**10c**	**17**	80	82	81 (*R*)
(*S*)-**10c**	**17**	80	48	40 (*R*)

[a] 0.2 mol % of (*S*,*S*)-DPEN was used.

found (*S*,*S*)-DPEN to be the most effective chiral activator to give the highest enantioselectivity in contrast to 2,2′-diamino-1,1′-binaphthyl (DABN) as a chiral deactivator.

Hydrogenation of ketones with (±)-**10b** or (±)-**10c**, an enantiomerically pure diamine, (*S*,*S*)-DPEN, or the (*R*,*R*)-DPEN, and KOH in a 1:1:2 ratio was carried out (Table 7).[56b] The use of (*S*,*S*)-DPEN led to the nonracemic hydrogenation product, even when starting from (±)-**10c**. The asymmetric activation of (±)-**10c** by (*S*,*S*)-DPEN affords almost the same level of asymmetric induction (80% ee) and catalytic activity as those attained by using the matched pair (*R*)-**10c**/(*S*,*S*)-DPEN complex (81% ee). In contrast, the mismatched pair (*S*)-**10c**/(*S*,*S*)-DPEN complex leads to a much lower level of enantioselectivity (40% ee), supporting the importance of chirality in the diamine activator for selective activation of one enantiomer of (±)-**10c**. It is noted that the matched pair is dramatically changed on going from 9-acetylanthracene **17** to 1′-acetonaphthone **16**; in the latter case, the (*S*)-**10b**/(*S*,*S*)-DPEN complex is a more enantioselective combination (>99% ee) than the (*R*)-**10b**/(*S*,*S*)-DPEN one (56% ee). This directly indicates that the catalytic activity critically depends on the

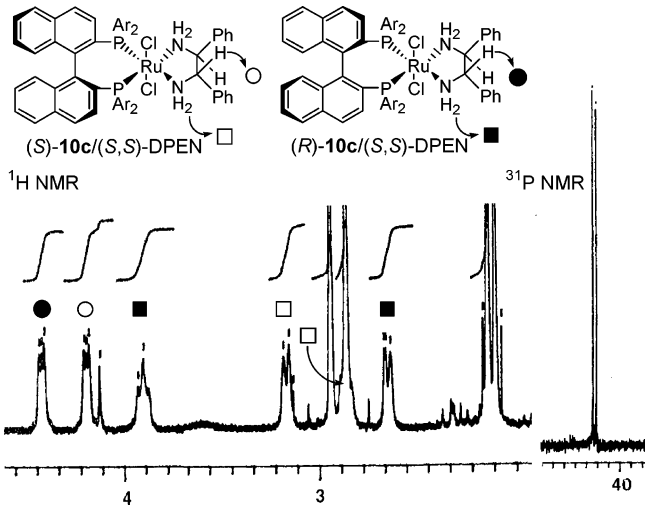


Figure 6. ^{1}H and ^{31}P NMR measurement of (±)-TolBINAP−$RuCl_2$ **10c** and 1.0 molar amount of (*S*,*S*)-DPEN per (±)-**10c**.

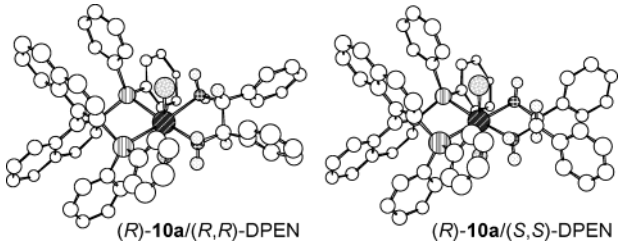


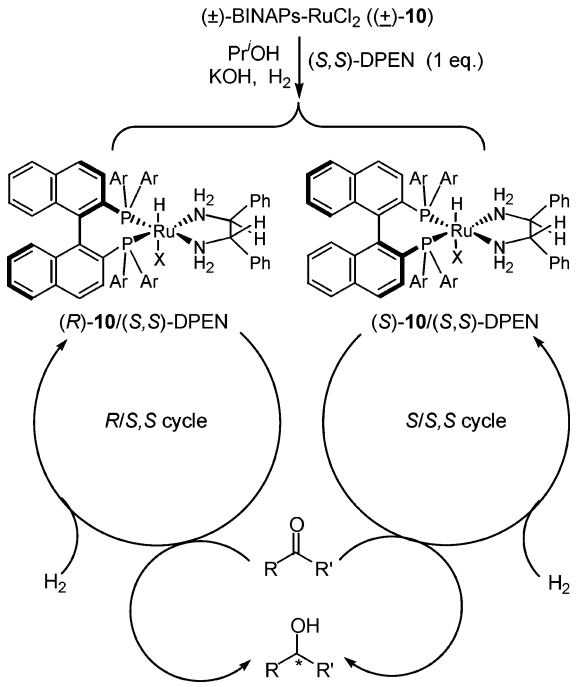
Figure 7. Computational modeling studies of (*R*)-BINAP−$RuCl_2$/(*R*,*R*)-DPEN and (*R*)-BINAP−$RuCl_2$/(*S*,*S*)-DPEN.

nature of the carbonyl substrates. Interestingly, the use of a catalytic amount of DPEN affords an equally high level of enantioselectivity as the one obtained by using an equimolar amount.

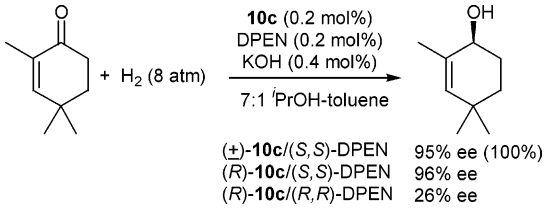
The ^{1}H and ^{31}P NMR spectra of a mixture of (±)-**10c** and a 0.5 molar or 1.0 molar amount of (*S*,*S*)-DPEN per (±)-**10c** are identical to those of the 1:1 mixture (Figure 6). The combination of a racemic BINAP−$RuCl_2$ species with even a 0.5 equimolar amount of an enantiopure diamine, DPEN in particular, gives a 1:1 mixture of two diastereomeric $RuCl_2$(BINAP)/DPEN complexes. Computational modeling studies showed that the two diastereomeric complexes have almost the same steric energies, and that the structures are in close analogy to those obtained by X-ray diffraction analysis (Figure 7). Therefore, the dichotomous sense of the matched pair leading to the higher enantioselectivity (*S*/*S*,*S* cycle for **16** and *R*/*S*,*S* cycle for **17** case, respectively) might be determined by the ratio and catalytic activity (turnover frequency) of mono- or dihydrido RuHX(BINAP)/DPEN complexes (X = H or Cl)[57] derived under the hydrogenation conditions from the diastereomeric complexes of BINAP−$RuCl_2$/DPEN (Scheme 14).

A similar asymmetric activation of a racemic BINAP−$RuCl_2$/DPEN catalyst system for hydrogenation has also been reported by Noyori. The (*S*)-allyl alcohol was quantitatively obtained in 95% ee by enantioselective hydrogenation of 2,4,4-trimethyl-2-cyclohexenone in the presence of (±)-**10c**, (*S*,*S*)-DPEN, and KOH under 8 atm of H_2 (Scheme 15).[56a]

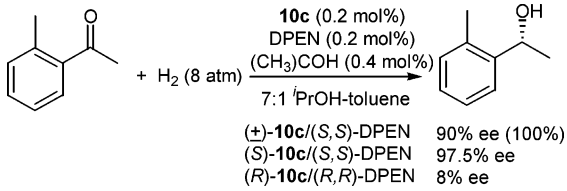
Scheme 14



Scheme 15



Scheme 16



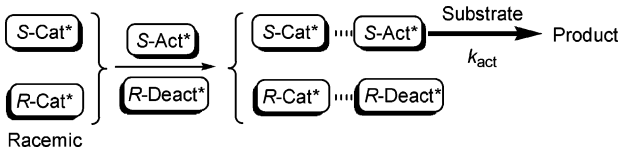
The enantiomeric purity was very close to 96% ee attained with the combination of enantiopure (*R*)-**10c** and (*S*,*S*)-DPEN. Employing the diastereomeric (*R*)-**10c**/(*R*,*R*)-DPEN combination caused the reaction rate to slow to afford the (*S*)-allyl alcohol in only 26% ee. During hydrogenation of 2,4,4-trimethyl-2-cyclohexenone, the *R*/*S*,*S* cycle with 96% ee of *S*-enantioselectivity occurs 121 times faster than the *S*/*S*,*S* cycle with 26% ee of *R*-enantioselectivity (cf. Scheme 14). The rate of hydrogenation catalyzed by (±)-**10c** was enhanced by increasing the amount of (*S*,*S*)-DPEN, and the maximum rate was observed with a molar ratio of Ru to diamine of 1:1. On the other hand, the ee value of the product was consistently high, and ca. 90% ee of the (*S*)-product was obtained even when employing a molar ratio of Ru to diamine of 1:0.25. When *o*-methylacetophenone was used as a substrate, (*S*)-**10c** was more activated by addition of (*S*,*S*)-DPEN than (*R*,*R*)-DPEN, in contrast to the case using 2,4,4-trimethyl-2-cyclohexenone as a substrate. The hydrogenation of *o*-methylacetophenone was carried out by using (±)-**10c**, (*S*,*S*)-DPEN, and

KOH under 4 atm of H_2 to quantitatively afford the (*R*)-alcohol product in 90% ee (Scheme 16). Separate experiments revealed that the enantiopure (*S*)-**10c** combined with (*S*,*S*)-DPEN catalyzes the reaction, giving the (*R*)-product in 97.5% ee, and that the reaction with (*R*,*R*)-DPEN affords the (*R*)-product in only 8% ee. During hydrogenation of *o*-methylacetophenone, the *S*/(*S*,*S*) cycle with 97.4% ee of *R*-enantioselectivity occurs 13 times faster than the *R*/(*S*,*S*) cycle with 8% ee of *S*-enantioselectivity (cf. Scheme 14).

2.3. Asymmetric Activation/Deactivation

Asymmetric activation and deactivation of racemic catalysts are two extremes in racemic catalysis. The asymmetric activation protocol coupled with the asymmetric deactivation protocol, namely "asymmetric activation/deactivation", maximizes the difference in catalytic activity between the two enantiomers of racemic catalysts through selective activation and deactivation of one enantiomeric catalyst (Scheme 17).

Scheme 17



The catalyst system of DM-DABN, DPEN, and racemic BINAP−$RuCl_2$ led to highly enantioselective hydrogenation, regardless of ketonic substrates.[58] Complexation of BINAP−$RuCl_2$(dmf)$_n$ (**10a**:BINAP−$RuCl_2$, **10b**:XylBINAP−$RuCl_2$) with chiral diamines gives stable *trans*-**10**/diamine complexes which catalyze hydrogenation of simple ketones. However, DPEN as a chiral activator forms both diastereomeric complexes with (±)-**10** in equal amounts. It is inevitable that the degree of asymmetric induction highly depends on the substrates obtained by the nonselective complexation of DPEN with (±)-**10**. On the other hand, (*S*)-DM-DABN as a chiral deactivator complexes selectively with (*S*)-**10**. On the basis of DFT model studies, the less catalytically active BINAP−Ru(II)/DM-DABN complex **19-I** stems from the electron delocalization from the Ru center to the diamine moiety, in contrast to the BINAP−Ru(II)/DPEN complex **18-I**, where the highest electrons are localized on the Ru−N region (Figure 8b). Indeed, the activation energy of the hydrogen cleavage in a heterolytic manner (**I** → **II** → **III**), which would be the turnover-limiting step because of the rate dependency of the H_2 pressure, is 4.0 kcal/mol smaller in the case using DPEN model of **18** (+11.2 kcal/mol) than that using DM-DABN model of **19** (+15.2 kcal/mol) (Figure 8a).[58b]

Since **10**/DM-DABN complexes are far less catalytically active than **10**/DPEN complexes for hydrogenation, (±)-**10b** coupled with these two chiral diamines as a chiral deactivator and activator can achieve higher enantioselectivities than those attained by simple activation. By sequential addition of first DM-DABN and then DPEN, (±)-**10b** can be completely discriminated with DM-DABN and used as a catalyst that is equally effective as the enantiopure **10b**, which is eventually activated by DPEN (Table 8).[58a] All the ketones employed were readily hydrogenated at room temperature with high enantiomeric excesses (>90% ee) in quantitative yield. Thus, the asymmetric activation/deactivation strategy can achieve higher levels of enantioselectivity than those obtained using the (±)-**10b**/(*S*,*S*)-DPEN complexes, even at the same temperature and pres-

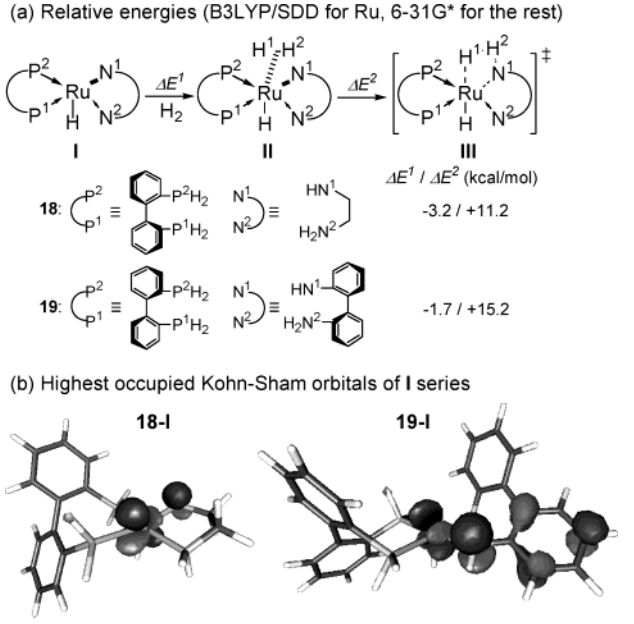
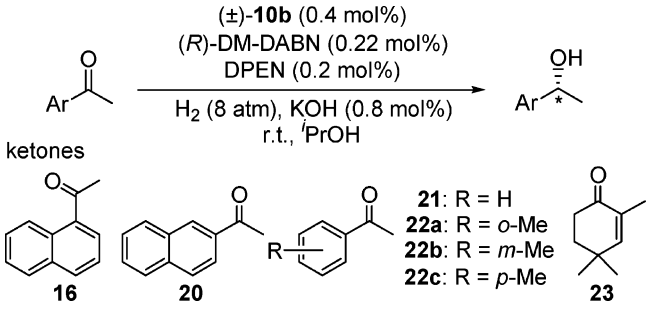


Figure 8. (a) The stabilization energies (ΔE^1) resulting from coordination of a hydrogen molecule and the activation energies (ΔE^2) of hydrogen cleavage. (b) The highest occupied Kohn−Sham orbitals of **18-I** and **19-I**.

Table 8. Hydrogenation of Ketones with (±)-10b through Asymmetric Activation/Deactivation



ketone	DABN[a]	DPEN	% yield	% ee
16	+	(*S*,*S*)	>99	96
16	−	(*S*,*S*)	>99	80
20	+	(*S*,*S*)	>99	91
20	−	(*S*,*S*)	>99	45
21	+	(*S*,*S*)	>99	95
21	−	(*S*,*S*)	>99	70
22a	+	(*S*,*S*)	>99	95
22a	−	(*S*,*S*)	>99	82
22b	+	(*S*,*S*)	>99	95
22b	−	(*S*,*S*)	>99	60
22c	+	(*S*,*S*)	>99	93
22c	−	(*S*,*S*)	>99	60
23	+	(*R*,*R*)	>99[b]	92
23	−	(*R*,*R*)	>99[b]	84

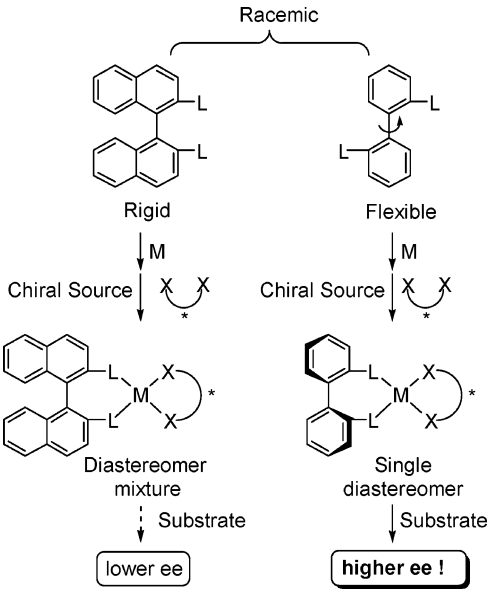
[a] "+" denotes the presence of (*R*)-DM-DABN. [b] (±)-**10c** was used.

sure. The superiority of the asymmetric activation/deactivation concept is shown in the case of 2-naphthylmethyl ketone **20**, where the enantioselectivity of (*R*)-1-(2-naphthyl)ethanol using (*R*)-DM-DABN is increased to 91% ee in contrast to only 45% ee obtained by simple asymmetric activation without deactivation. (*R*)-2,4,4-Trimethyl-2-cyclohexenone **23** was also hydrogenated in high enantioselectivity (92% ee) by changing the chirality of DPEN from *S* to *R*.

2.4. Asymmetric Activation of *Tropos* Catalysts

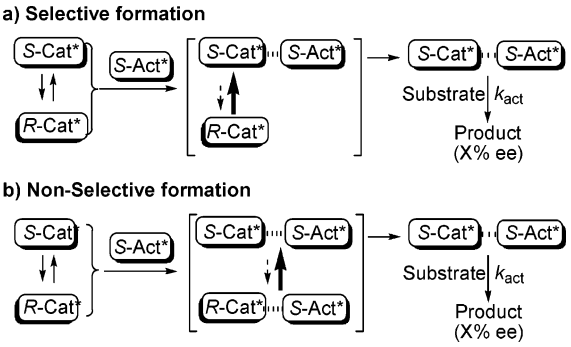
To prepare enantiopure compounds, asymmetric synthesis or resolution is indispensable. By contrast, *tropos* ligands can be used without their asymmetric synthesis or resolution. Thus, a further advanced strategy for 'asymmetric activation' can be highlighted in the combination of *tropos* and racemic ligands.[24b] This promising approach is roughly classified into two categories: (1) the *tropos* catalyst enantiomers can be discriminated by a chiral activator but evolved into a single enantiomeric catalyst and (2) the chirality of the *tropos* catalyst can be controlled by a chiral activator through complexation. As shown in section 2.2, an *atropos* catalyst with a chiral activator usually produces a diastereomeric mixture of the resulting complex. The ee of the product strongly depends on the difference in reactivity between the diastereomers. However, combination of a *tropos* ligand, such as a biphenyl ligand, a chiral activator, and a metal atom can, in principle, form a single diastereomeric complex. Upon controlling the chirality through diastereomer interconversion (e.g., *tropo*-inversion of the chiral axis), the catalytic activity is increased and the chiral environment of the resulting catalyst is amplified in asymmetric catalysis (Scheme 18).

Scheme 18



For example, the dynamic asymmetric activation can be attained by incorporating a chiral activator with a *tropos* catalyst through in situ diastereomer interconversion (Scheme 19). In one case, selective

Scheme 19



complexation of a chiral activator with one enantiomer of a *tropos* and thus racemic catalyst along with the remaining enantiomeric catalyst, which may racemize, followed by complexation with the chiral activator to afford the single diastereomer (Scheme 19a). The other case involves non-selective complexation of a *tropos* catalyst with a chiral activator initially provides a 1:1 ratio of activated diastereomers, which would epimerize to the single diastereomer (Scheme 19b).

The dynamic asymmetric activation phenomena can be interpreted through a continuum from nonselective to selective complexation with a chiral activator. Figure 9, for example, shows the difference of the influence on the relative rate (k_{act}/k_{act}' ranges from 0.01 to 100) in the range from a 1:1 to 99:1 ratio of the diastereomeric catalysts when one activated diastereomer ((*R*)-ML$_n$/(*R*)-Act*) provides the product in 100% ee (*R*) and the other diastereomer ((*S*)-ML$_n$/(*R*)-Act*) leads to the opposite enantiomeric product in 50% ee (*S*). A relative rate of 100 (log k_{rel} = 2)

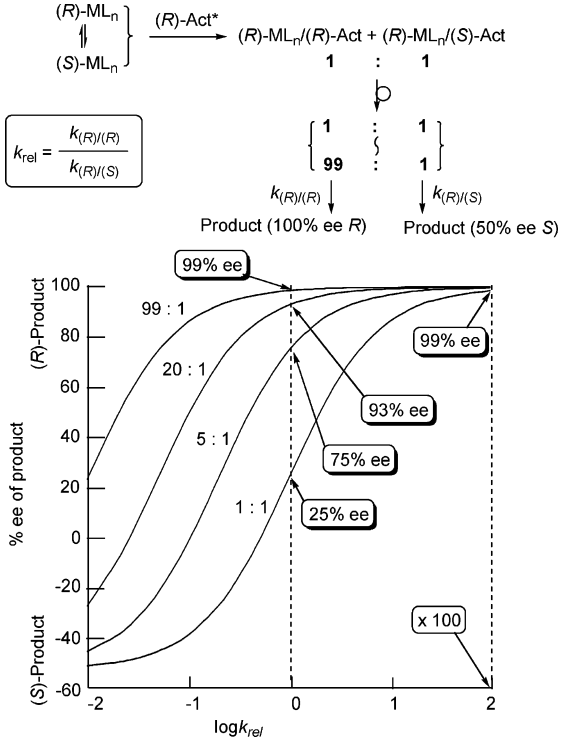
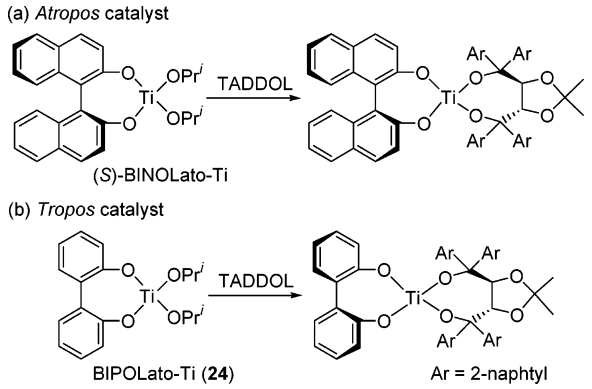


Figure 9. Continuum from nonselective to selective complexation with a chiral activator in the ee value of the product.

Scheme 20



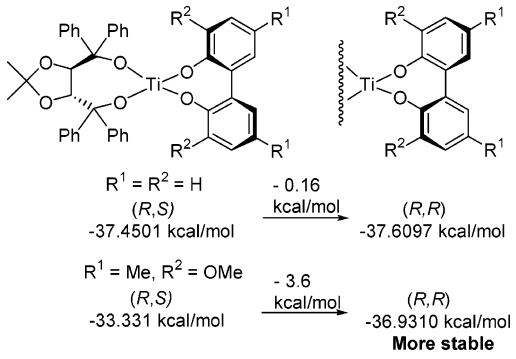
achieves a high enantioselectivity (e.g., 99% ee), even when the diastereomeric catalysts are formed in a 1:1 ratio. In the case of a 20:1 ratio between the diastereomeric catalysts, and if the former activated catalyst is more active (log $k_{rel} = 1$), a product with more than 99% ee can be obtained. Even when the relative rate of the diastereomeric catalysts is the same (log $k_{rel} = 0$), a high level of enantioselectivity (e.g., up to 99% ee) can be achieved if the diastereomeric catalysts are formed in a 99:1 ratio.

Recently, Davies, Sibi, and Renaud reported the "chiral relay" concept:[59] chirality originates from an internal or an external chiral source but is then enhanced via an achiral template. In this case, the steric interaction of the flexible achiral group in the *substrate* with the chiral auxiliary (internal) or the chiral Lewis acid (external) defines the conformation, in which one face of the reactive center can be shielded effectively, to achieve asymmetric induction. However, the asymmetric activation of a *tropos* catalyst clearly differs from the chiral relay concept based on the substrate conformational control. The chiral environment of the catalyst bearing the *tropos* ligand can be controlled by the external chiral additional source (shown in section 2.4.1) or in a chiral catalyst can be amplified by the external flexible achiral source (shown in section 2.4.2).

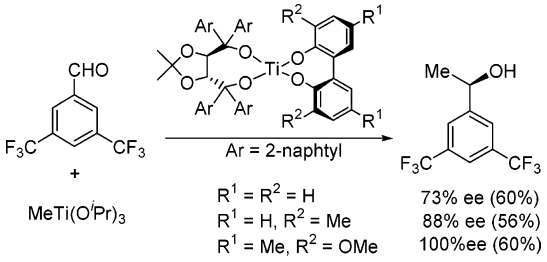
2.4.1. Asymmetric Activation by Chiral Activators

Flexible achiral ligands possess various chiral conformations. The conformational chirality of simple acyclic molecules has long been studied, mostly spectroscopically and theoretically.[60] For example, capture of enantiomeric conformation of ethane analogues, e.g., 1,2-dihaloethanes, XCH_2CH_2X (X = Cl or Br), has been reported in host−guest chemistry but not from the point of view of asymmetric catalysis.[61] In view of the prime importance of atropisomeric ligands such as BINOL or BINAP, the *tropos* biphenol (BIPOL) or biphenylphosphine (BIPHEP) has replaced the enantiopure form of *atropos* BINOL or BINAP. The chiral Ti catalysts obtained by self-assembly of a TADDOL−BINOL combination exhibit higher catalytic activity and enantioselectivity through asymmetric activation. It is expected that the enantiopure TADDOL combined with the BIPOLate−Ti catalyst **24** would control the chirality of the *tropos* BIPOL moiety and increase the catalytic activity of **24** (Scheme 20b). Molecular mechanics (MM2) calculations of the two diastereomeric complexes (3,3′-$(MeO)_2$-BIPOLato)(TADDOLato)−Ti show that the (*R*)/(*R*)-diastereomer is more stable than the (*R*)/(*S*)-diastereomer by 3.6 kcal/mol (Scheme 21). The steric effect of the 3-methoxy group is significant in maximizing the difference in relative thermodynamic stability between the diastereomeric complexes from the parent BIPOLate diastereomers.

Scheme 21



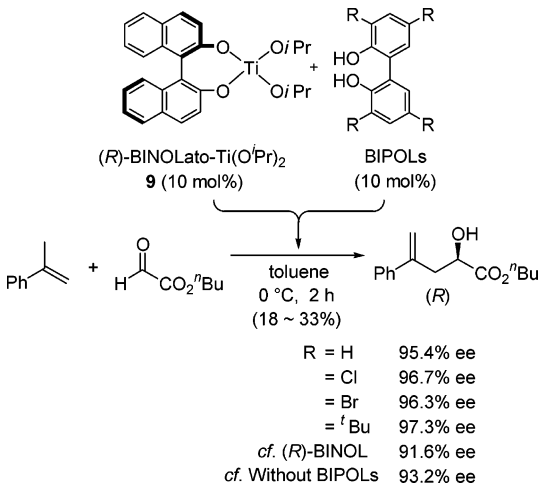
Scheme 22



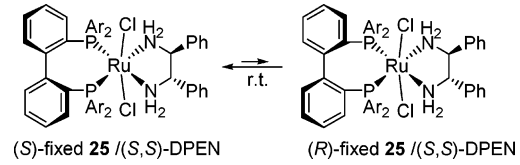
The BIPOLate/TADDOLate−Ti catalysts prepared by sequential addition of BIPOL and TADDOL to $Ti(O^iPr)_4$ catalyzed methylation with an achiral methyltitanium reagent to afford highly enantiomerically pure methylcarbinol. Since the introduction of sterically bulky 3,3′-substituents leads to an increase in enantioselectivity, the chirality of **24** can be dynamically controlled by the chiral TADDOL moiety (Scheme 22).[63] Particularly, the 3,3′-dimethoxy derivative gave virtually complete enantioselectivity (100% ee), in sharp contrast to the moderate enantioselectivity obtained with the parent BIPOL (73% ee). This indicates the possibility of the chelation of 3-methoxy group in the three-dimensional arrangement.

Such a self-assembly of a chiral titanium catalyst bearing two different chiral diol components was also found in the enantioselective carbonyl−ene reaction (Scheme 23).[64] Addition of *tropos* BIPOL to (*R*)-BINOL−$Ti(O^iPr)_2$ **9**, which formed a new catalytic species, led to higher enantioselectivity (95.4% ee) in the carbonyl−ene reaction of glyoxylate with α-methylstyrene than in the absence of BIPOLs (93.2% ee). Substitution in the 3,3′-positions greatly increased the enantioselectivity of the ene product (R = Cl, 96.7% ee; Br, 96.3% ee; ^{t}Bu, 97.3% ee). Due to polymerization of glyoxylate, the reaction afforded the ene product in poor yields (18−33%). Use of ethyl glyoxylate improved the yields with only slightly lower ee values (R = H, 42%, 85.2% ee; Cl, 62%, 92.1% ee). The enantiomerically pure **9**, with the

Scheme 23



Scheme 24



tropos BIPOL ligands, preferentially forms the most favorable conformation in the activated catalyst upon reaction. Molecular modeling studies on the catalytic species generated in situ indicate that the hexacoordinated titanium complex, bearing two different diol ligands and 2-propanol (L), would have a center of chirality at the titanium atom (i.e., ^{i}PrOH groups are located cis). The authors reported that the Λ isomer is clearly more favorable than the Δ isomer (Figure 10).

In a manner similar to BIPOL, the *atropos* BINAP can be also replaced by the *tropos* BIPHEP.[65,66] The *tropos* metal catalysts with BIPHEP ligands can be used as activated diastereomeric complexes with chiral diamines. Upon addition of DPEN to BIPHEP−$RuCl_2$ catalysts (**25a**:BIPHEP, **25b**:XylBIPHEP, **25c**:TolBIPHEP), diastereomeric complexes were formed, initially in equal amounts. However, this mixture of (*S*)- and (*R*)-**25b**/(*S*,*S*)-DPEN in 2-propanol-d_8, when allowed to stand at room temperature, was found to give a 3:1 mixture in favor of the (*S*)-**25b**/(*S*,*S*)-DPEN diastereomer (Scheme 24). The equilibration took place due to the *tropos* nature of **25**/DPEN complexes.

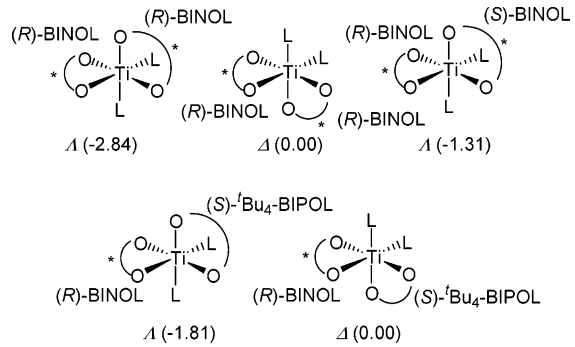
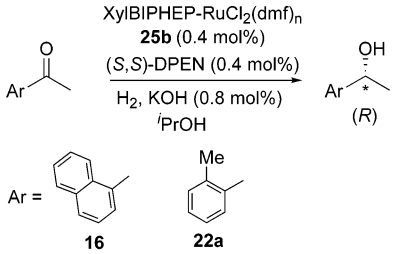


Figure 10. Relative energies (in kcal/mol) of the Λ and Δ isomers of **9** with BINOL or ^{t}Bu$_4$−BIPOL.

Table 9. Asymmetric Hydrogenation by XylBIPHEP−$RuCl_2$ with (*S*,*S*)-DPEN



ketone	catalyst	H_2 (atm)	temp (°C)	% yield	% ee
16	**25b**	8	28	>99	84
16	**10b**[a]	8	28	>99	80
16	**25b**	40	−35	>99	92
16	**10b**[a]	40	−35	>99	89
22a	**25b**	8	0	>99	88
22a	**10b**[a]	8	0	>99	86

[a] (±)-XylBINAP−$RuCl_2$(dmf)$_n$ (**10c**) was used.

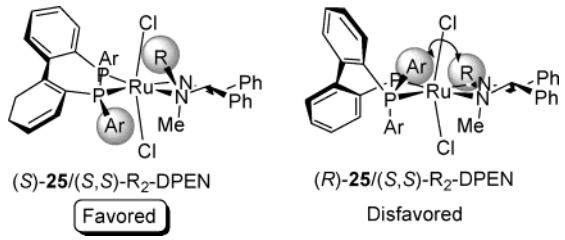


Figure 11. Design of DM-DPEN for controlling of chirality in the BIPHEP−$RuCl_2$ counterpart.

The significant effect of the *tropos* complex of **25b** with (*S*,*S*)-DPEN can be seen in hydrogenation (Table 9)[66] of 1′-acetonaphthone **16** in comparison with the enantioselectivity obtained using the *atropos* (±)-$RuCl_2$(XylBINAP) complex (±)-**10b**/(*S*,*S*)-DPEN. A further increase in enantioselectivity was attained at a lower reaction temperature. The enantioselectivity given by *tropos* **25b**/(*S*,*S*)-DPEN was higher than that attained by *atropos* **10b**/(*S*,*S*)-DPEN at the same low temperature and high pressure. The *tropos* **25b**/(*S*,*S*)-DPEN catalyst gave (*R*)-1-(1-naphthyl)-ethanol with 92% ee in quantitative yield. In addition, **25b**/(*S*,*S*)-DPEN was useful for the reduction of *o*-methylacetophenone **22a** to afford (*R*)-1-(1-*o*-methylphenyl)ethanol quantitatively with 88% ee, which is slightly higher than 86% ee obtained by use of the (±)-$RuCl_2$(XylBINAP) complex (±)-**10b**/(*S*,*S*)-DPEN. To obtain a single diastereomeric **25**/DPEN complex, *N*,*N*-dimethyl-1,2-diphenylethylenediamine (DM-DPEN) was designed as a chiral activator with primary amine function to discriminate between the enantiomeric BIPHEP−$RuCl_2$ catalysts; the enantiomer-selective complexation of (*S*)-**25b** with (*S*,*S*)-DM-DPEN was highly predictable by a computational modeling study. This model showed a severe steric repulsion between *N*-methyl and *P*-phenyl groups for the other diastereomer (Figure 11). Through nonselective complexation of **25b** with (*S*,*S*)-DM-DPEN, (*R*)-**25b**/(*S*,*S*)-DM-DPEN completely isomerized to (*S*)-**25b**/(*S*,*S*)-DM-DPEN in 2-propanol at 50 °C after 1 h, as observed by ^{1}H NMR. The single diastereomer (*S*)-**25b**/(*S*,*S*)-DM-DPEN showed a spectrum quite similar to that of (*S*)-**10**/(*S*,*S*)-DPEN. Indeed, the (*S*)-configuration of BIPHEP was con-

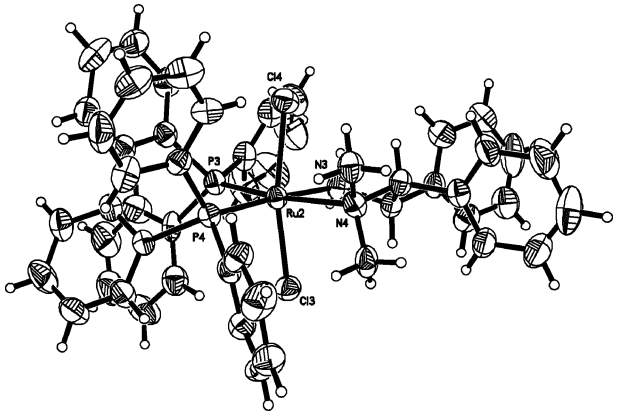
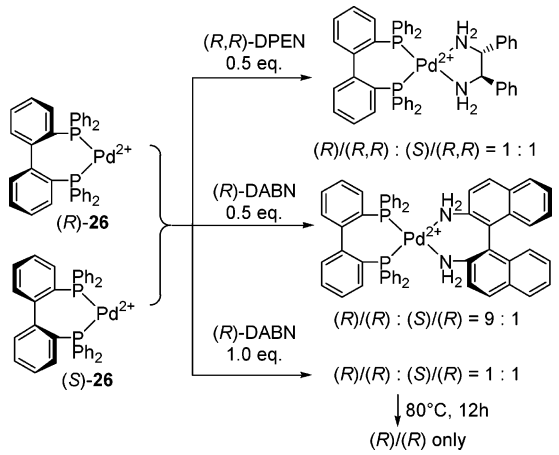


Figure 12. X-ray single-crystal structure of the (*S*)-BIPHEP−$RuCl_2$/(*S*,*S*)-DM-DPEN complex.

Scheme 25



firmed by single-crystal X-ray analysis of XylBIPHEP− and BIPHEP−$RuCl_2$ with (*S*,*S*)-DM-DABN (Figure 12).[67] Unfortunately, however, the enantioselectivity was found not to be high. In hydrogenation of **16**, the enantioselectivity (81% ee at room temperature) obtained with the diastereomerically pure (*S*)-**25b**/(*S*,*S*)-DM-DPEN is comparable to that (84% ee) obtained with the 3:1 diastereomeric mixture of **25b**/(*S*,*S*)-DPEN.

While complexation of BIPHEP−Pd(II) **26** was observed with DPEN in a nonselective manner even with a half-molar amount of enantiopure DPEN, a highly selective (9:1) complexation of one enantiomer of **26** was observed upon addition of 0.5 equiv of (*R*)-DABN, the (*R*)-**26**/(*R*)-DABN complex being formed as the major diastereomer. With 1.0 equiv of (*R*)-DABN, however, complexation of both enantiomers took place to afford a 1:1 ratio of a diastereomeric mixture of (*R*)-**26**/(*R*)-DABN and (*S*)-**26**/(*R*)-DABN. The diastereomeric mixture of **26**/(*R*)-DABN did not epimerize at room temparature over 3 days, but exhibited *tropo*-inversion of the BIPHEP moiety at 80 °C after 12 h to afford the favorable (*R*)-**26**/(*R*)-DABN exclusively (Scheme 25).[68] This indicates that the BIPHEP moiety in the complex of **26** with DABN shows a *tropo*-inversion at 80 °C but not at room temparture. The (*R*)/(*R*)-configuration of the diastereomer was determined by X-ray analysis of a single crystal obtained from a hexane−chloroform solution at room temparture (Figure 13).

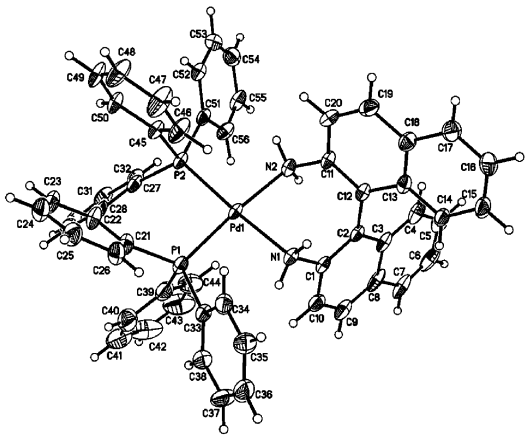
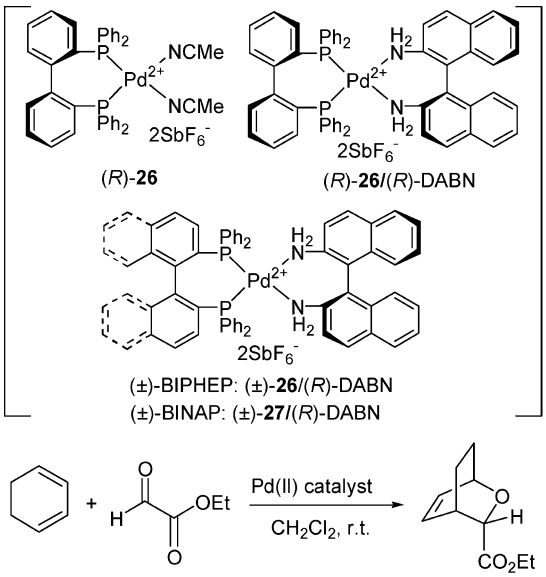


Figure 13. X-ray single-crystal structure of the (*R*)-BIPHEP−Pd/(*R*)-DABN complex.

In contrast, a highly effective resolving agent such as DM-DABN, which would not lead to a mixture of diastereomers, was also employed to determine whether the remaining enantiomer of **26** shows a *tropo*-inversion or not.[69] Combination of **26** even with 1.0 equiv of (*R*)-DM-DABN formed the single (*R*)-**26**/(*R*)-DM-DABN diastereomer, along with the remaining (*S*)-**26** and (*R*)-DM-DABN. There was no *tropo*-inversion of the remaining (*S*)-**26** at room temperature, even after 3 days. On the other hand, after 12 h at 80 °C, the complete *tropo*-inversion of (*S*)-**26** was achieved to give the single diastereomer (*R*)-**26**/(*R*)-DM-DABN without any remaining (*S*)-**26** or (*R*)-DM-DABN. It was thus clarified that **26** could be resolved as an *atropos* metal complex at or below room temperature. Thus, the metal complexes derived from *tropos* ligands can be used as asymmetric catalysts for carbon−carbon bond-forming reactions in the same manner as *atropos* catalysts. The BIPHEP−Pd(II) catalysts, in particular, can lead to products with high enantioselectivity. The single diastereomer (*R*)-**26**/(*R*)-DABN can be used as an activated asymmetric catalyst for the hetero-Diels−Alder reaction at room temperature (Table 10).[68,69] This is exemplified by high chemical yields and enantioselectivity (62%, 94% ee) in the hetero-Diels−Alder reaction of ethyl glyoxylate with 1,3-cyclohexadiene attained by using 0.5 mol % of the (*R*)-**26**/(*R*)-DABN catalyst.[68] The efficiency of (*R*)-DABN as a chiral activator is highlighted by the higher levels of enantioselectivity and catalytic activity than those (11%, 75% ee) attained by using the enantiopure (*R*)-**26** without (*R*)-DABN. A higher chemical yield and enantioselectivity (75%, 92% ee) were obtained by using 2 mol % of (*R*)-**26**/(*R*)-DABN catalyst than those attained by using the *atropos* and racemic BINAP counterpart with DABN activator (61%, 7% ee), and by using the racemic BIPHEP−Pd(II) with DABN (64%, 9% ee).

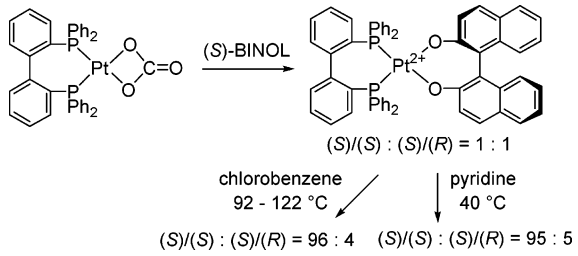
In a very similar approach, enantiopure BIPHEP−Pt(II) **28**-catalyzed enantioselective Diels−Alder and carbonyl−ene reactions were also reported by Gagné.[70] Reaction of BIPHEP−Pt(CO_3) with (*S*)-BINOL yielded **28**/(*S*)-BINOL complexes as a 1:1 mixture of diastereomers. The thermodynamically favored (*S*)/(*S*)-isomer can be obtained in a 96:4 ratio at 92−122 °C via *tropo*-inversion of the BIPHEP unit (Scheme 26). Eyring analysis for the thermal conversion of the (*R*)/

Table 10. Asymmetric Hetero-Diels–Alder Reaction of Glyoxylate with 1,3-Cyclohexadiene by (*R*)-BIPHEP–Pd/(*R*)-DABN



catalyst	mol %	% yield	% ee
(*R*)-**26**	0.5	11	75 (1*R*,3*S*,4*S*)
(*R*)-**26**/(*R*)-DABN	0.5	62	94 (1*R*,3*S*,4*S*)
(*R*)-**26**/(*R*)-DABN	2	75	92 (1*R*,3*S*,4*S*)
(±)-**27**/(*R*)-DABN	2	61	7 (1*S*,3*R*,4*R*)
(±)-**26**/(*R*)-DABN	2	64	9 (1*S*,3*R*,4*R*)

Scheme 26



(*S*)- to the (*S*)/(*S*)-isomer established $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ of 27 kcal mol^{-1} and −5 eu, respectively. In addition, the (*R*)/(*S*)-isomer can be converted to a 95:5 ratio of (*S*)/(*S*)-major isomer in pyridine at 40 °C. The thermodynamically less preferred (*R*)/(*S*)-isomer can be provided by recrystallization from CH_2Cl_2. The X-ray structure of the mismatched (*R*)/(*S*)-isomer illustrates the origin of the diastereoselectivity of the **28**/BINOL complexes from the point of view of the relative stereochemistry of BIPHEP and BINOL fragments. The structure of the BIPHEP moiety of the (*R*)/(*S*)-isomer is greatly distorted and does not have the C_2-symmetry to minimize the interaction between pseudoequatorial P–Ph groups of (*R*)-BIPHEP and the 3,3′-CH groups of BINOL (Figure 14).[70a] Indeed, one side of BIPHEP has two P–Ph groups eventually disposed around the square plane (neutral axial and equatorial positions), while the other side has overemphasized the axial and equatorial positions. On the other hand, the 3,3′-CH groups in the thermodynamically favored (*S*)/(*S*)-isomer are expected toward the less hindered pseudoaxial P–Ph groups of (*S*)-BIPHEP.

The reaction of the diastereopure **28**/BINOL complexes with HCl followed by traditional AgOTf treatments provides the enantiopure **28** with retention of configuration. The enantiopure **28** can act as a chiral Lewis acid to be employed for the enantioselective Diels–Alder and carbonyl–ene reactions. The Diels–Alder products were obtained in 92–94% ee (93:7 endo:exo) and 92–94% ee (94:6 endo:exo) from (*R*)- and (*S*)-**28**, respectively (Scheme 27a).[70b] On the basis of the stereochemical model for the (*R*)-BINAP–Pt(II)$(OTf)_2$ complex, the (*S*)- and (*R*)-products can be expected for the absolute stereochemistry of the products. In the carbonyl–ene reaction, where the dication species were generated from BIPHEP–Pt(II)Cl_2 and $AgSbF_6$, the (*S*)- and (*R*)-ene products were obtained with 71% ee (99% conversion at room temperature) and 70% ee (90% conversion at room temperature) from (*R*)- and (*S*)-**28**, respectively (Scheme 27b).[70b]

The mechanism of the *tropo*-inversion of the BIPHEP moiety is the fundamental issue in activa-

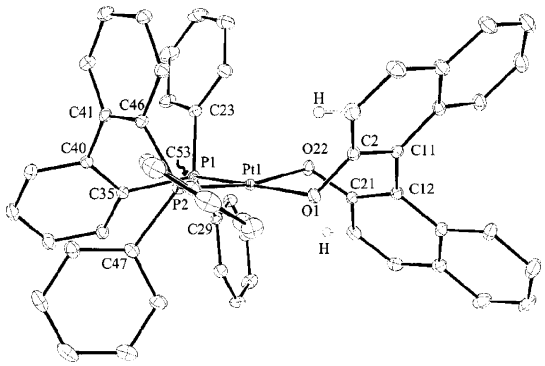
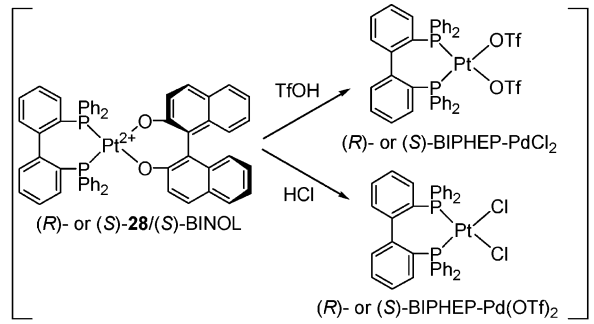
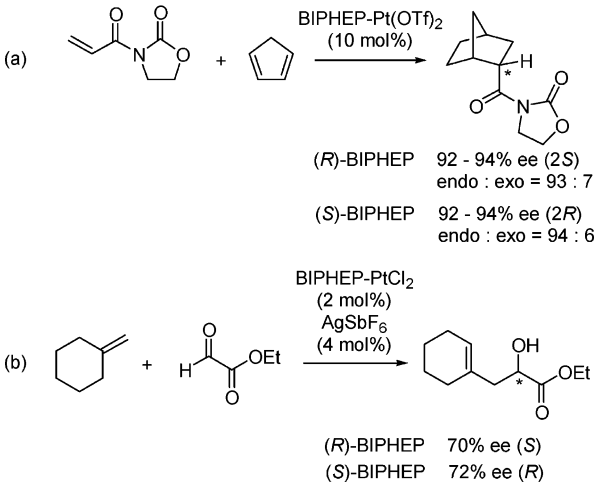


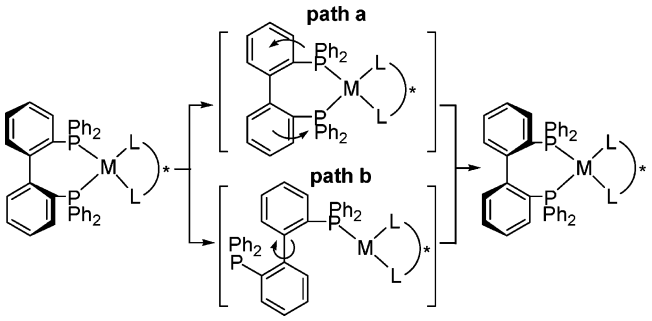
Figure 14. X-ray single-crystal structure of the (*R*)-BIPHEP–Pt/(*S*)-BINOL complex.

Scheme 27





Scheme 28



tion of a chirally flexible catalyst with a chiral activator. Two possible mechanisms can be proposed for the *tropo*-inversion of the BIPHEP−metal complex: (a) internal rotation between the biphenyl rings and (b) dissociation of one phosphine−metal (P−M) coordination and rotation back to the enantiomeric BIPHEP−metal complex (Scheme 28). On the basis of experimental evidence, in which interconversion of the BIPHEP−Ru moiety can readily occur at room temperature in contrast to the BIPHEP−Pd (80 °C) and −Pt (92−122 °C) moieties, the energetic cost of the *tropo*-inversion of BIPHEP would depend on the strength of the phosphine−metal interaction (P−Ru ≪ P−Pd, P−Pt). In the case of the BIPHEP−Pt complex, the *tropo*-inversion of BIPHEP was also affected by solvent, and in particular, the activation energy barrier for interconversion of the BIPHEP moiety was greatly decreased by the use of pyridine (40 °C) as a solvent, which can coordinate on the coordinatively unsaturated metal center in path b. These results indicate that a mismatched BIPHEP−metal diastereomeric complex can be converted to the thermodynamically preferred diastereomer via path b.[67,71]

Furthermore, the *tropo*-inversion mechanism was theoretically studied with respect to the (*S*)/(*S*,*S*)-**29** model complex (B3LYP/SDD for Ru and 6-31G* for the rest) (Figure 15).[71] In the transition state of the internal rotation of biphenyl rings (path a, **TS1**), the biphenyl rings were fixed on the same plane to optimize the other variables of the structure under C_2 symmetry. The activation energy of the internal rotation (path a, **TS1**) is 36 kcal/mol. The 55 kcal/mol-activation energy of one P−Ru dissociation (path b, **TS2**) is 19 kcal/mol larger than that of **TS1**. However, the trigonal bipyramidal structure of **TS2** indicates that **TS2** can be stabilized by solvent coordination on the vacant site of the Ru center. In contrast, since the Ru center is saturated in **TS2**, solvents cannot coordinate on the Ru center. Therefore, the activation energy for the solvated transition state of **TS2s** is eventually decreased to 22 kcal/mol by coordination of MeOH as a solvent model, which is lower than the energy of internal rotation by 14 kcal/mol. Since the rotational barrier around the biphenyl single bond of BIPHEP is ca. 22 kcal/mol,[72] the rotation of the biphenyl rings after the first dissociation step can readily proceed at room temperature. Therefore, the internal rotation pathway via **TS1** is very unlikely to occur. Solvent-assisted mutation[73] around the biphenyl single bond through the so-called cog-wheeling effect,[74] and subsequent recoordination of phosphine to the Ru center would then result in isomerization to afford the favorable diastereomer. The mechanism of the *tropo*-inversion described herein might be widely applied for the transition metal complex with the BIPHEP ligands.

As a closely related system, a *tropos* quaternary ammonium bromide bearing a biaryl subunit with a three-atom tether has been reported by Maruoka as a phase-transfer catalyst. The chiral C_2-symmetric quaternary ammonium bromide **30** bearing a chiral and *atropos* binaphthyl subunit catalyzed phase-transfer alkylation of the glycine Schiff base to afford α-amino acids enantioselectively (Table 11).[75] The dramatic effect of 3,3′-bisaryl substituents of the catalysts **30** on the reactivity as well as on the enantioselectivity was observed in the asymmetric phase-transfer alkylation. The ee of the (*R*)-alkylation product is eventually increased by use of the catalyst **30c** with the sterically demanding β-naphthyl group

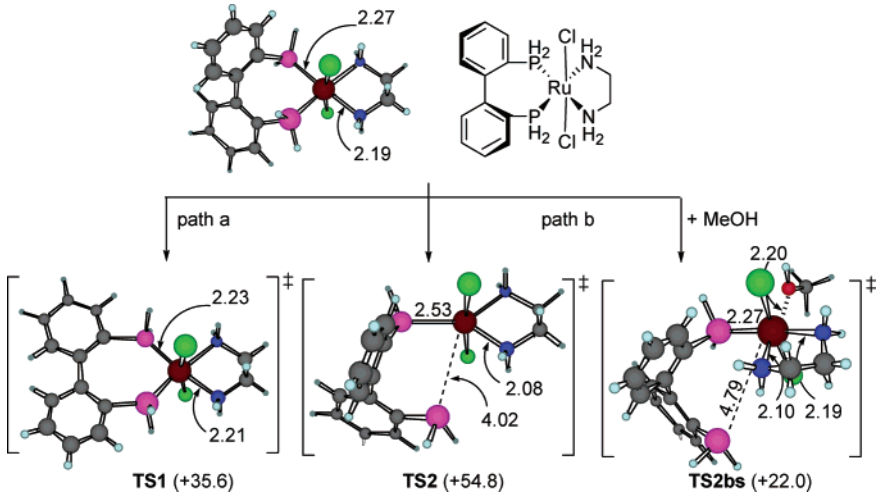
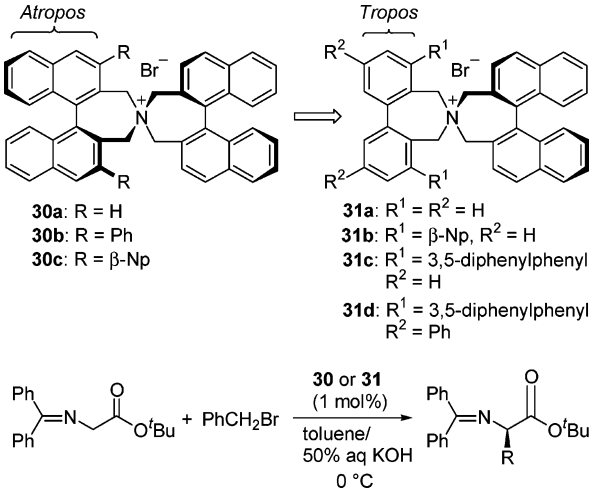


Figure 15. Energetics and geometries of two *tropo* inversion pathways of the (*S*)/(*S*,*S*)-**29** model complex: internal rotation (path a, **TS1**) and dissociation−rotation with and without solvent coordination (path b, **TS2s** and **TS2**). The activation energies (in kcal/mol) are shown in parentheses. Bond lengths are shown in angstroms. Color code: Ru, brown; P, purple; N, blue; O, red; Cl, green; C, gray; H, small blue spheres.

Table 11. Catalytic Enantioselective Phase-Transfer Alkylation



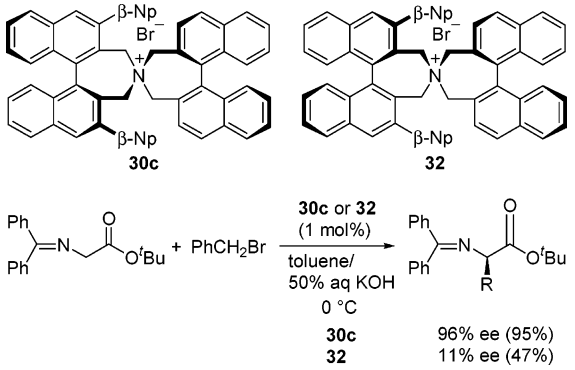
catalyst	time (h)	% yield	% ee
30a	6	73	79
30b	0.5	81	89
30c	0.5	95	96
31a	36	62	64
31b	18	85	87
31c	27	95	92
31d	48	81	95

(**30a**, 73% yield, 79% ee; **30c**, 95% yield, 96% ee). A C_2-symmetric *tropos* quaternary ammonium bromide replaced one of the two *atropos* binaphthyl units. The *tropos* phase-transfer catalysts **31** also attained sufficient reactivity and enantioselectivity in the enantioselective synthesis of α-amino acids.[76] In a manner similar to the *atropos* catalysts **30**, the presence of a *β*-naphthyl group at the 3,3′-position of the flexible biphenyl moiety in **31** greatly enhanced both the chemical yield and the enantioselectivity (**31a**, 62% yield, 64% ee; **31b**, 85% yield, 87% ee). Furthermore, the ee obtained by employing the more hindered 3,5-diphenylphenyl substituent of the *tropos* catalysts (**31c**, 92% ee; **31d**, 95% ee) is almost the same as that obtained by using the *atropos* catalysts (96% ee).

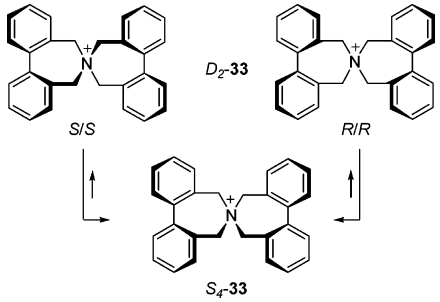
The origin of the chiral efficiency of the *tropos* catalyst **31** is the considerable difference in catalytic activity between diastereomeric homo- and heterochiral isomers resulting from conformational interconversion. Indeed, in contrast to the case with the matched homochiral catalyst **30c**, the benzylation by the mismatched heterochiral catalyst **32** proceeds slowly to afford the (*R*)-product in 47% yield with low enantiomeric excess (11% ee). Therefore, the homochiral **30c** is primarily responsible for the efficient asymmetric phase-transfer catalysis with a high level of enantioselectivity. Indeed, analysis of variable-temperature (VT) ^{1}H NMR clearly showed that the existence ratio of the homochiral isomer increased as the temperature lowered. This VT ^{1}H NMR experiment resulted in positive enthalpy ($\Delta H° = 5.74$ kcal mol^{-1}) and large entropy ($\Delta S° = 23.1$ cal mol^{-1} K^{-1}) for the interconversion from a homochiral to a heterochiral diastereomer.

Such a conformational preference and configurational control of spiro-bi[dibenzazepinium] **33**, which contains two *tropos* biphenyl subunits, was also

Scheme 29



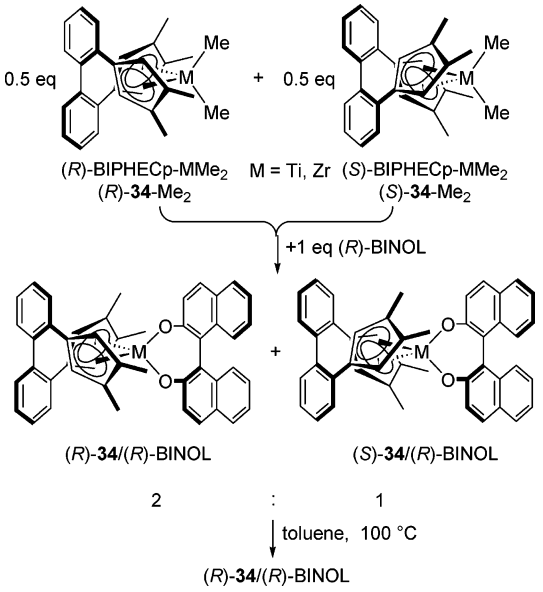
Scheme 30



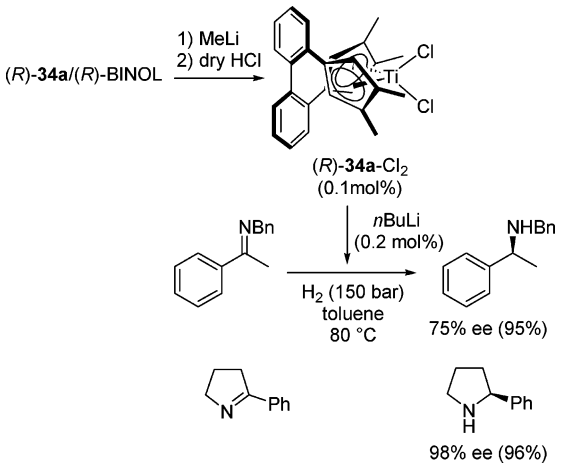
detected by VT NMR analysis (Scheme 30).[77] Interconversion between the D_2-symmetric homochiral (*S*/*S* and *R*/*R*) and S_4-symmetric heterochiral (meso) isomers of **33** can rapidly occur in solution, and the equilibrium between them shifts toward the thermodynamically favored homochiral isomer (diastereomeric ratio is >24:1 at −40 °C).

Chiral *ansa*-metallocene complexes have become useful catalysts in asymmetric polymerization reactions.[78] While enantiomer resolution of *ansa*-metallocene racemates cannot yield more than 50% of a particular enantiomer, the readily accessible racemate of a biphenyl-bridged metallocene complex (abbreviated to BIPHECp−M; M = Ti, Zr) has been reported to give enantiopure *ansa*-titanocene and -zirconocene complexes through BINOL-induced asymmetric transformation (Scheme 31).[79] Enantiopure BIPHECp−M complexes **34** (**34a**, M = Ti; **34b**, M = Zr) have been obtained by association with BINOL and subsequent transformation of the mixture of diastereomers, leading to the thermodynamically favored diastereomer. The reaction of (±)-**34a**-Me_2 with 1 equiv of enantiopure (*R*)-BINOL at room temperature yielded the diastereomers (*R*)-**34a**/(*R*)-BINOL and (*S*)-**34a**/(*R*)-BINOL in a ratio of about 2:1, rather than 1:1. The diastereomeric mixture of **34a**/(R)-BINOL can epimerize at 100 °C for 4 days to afford the thermodynamically preferred (*R*)-**34a**/(*R*)-BINOL ((*R*)-**34b**/(*R*)-BINOL at 100 °C for 2 days), which reacts with MeLi as a methyl-transfer agent at −20 °C to regenerate enantiopure (*R*)-**34a**-Me_2 with no racemization ($AlMe_3$ for (*R*)-**34b**-Me_2). Then, (*R*)-**34a**-Me_2 is finally converted to the dichloride derivative (*R*)-**34a**-Cl_2 with dry HCl at room temperature (dry Me_2SiCl_2 for (*R*)-**34b**-Cl_2). The biphenyl-bridged complex (*R*)-**34a**-Cl_2 in the presence of *n*-BuLi served as an efficient asymmetric catalyst for imine hydrogenation (Scheme 32).

Scheme 31

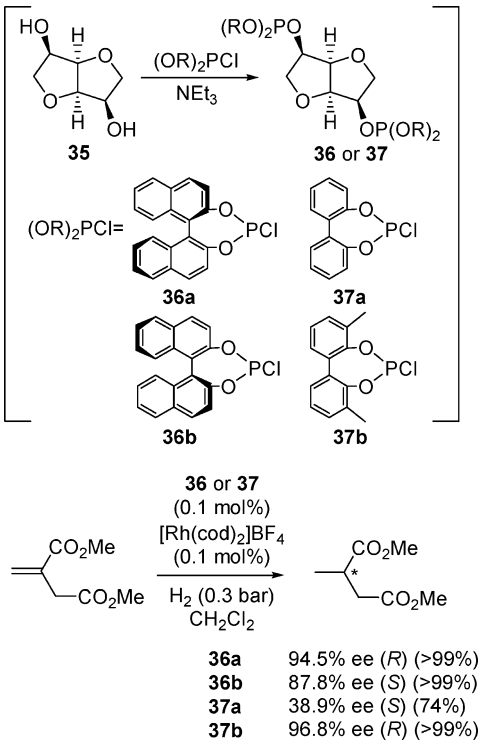


Scheme 32



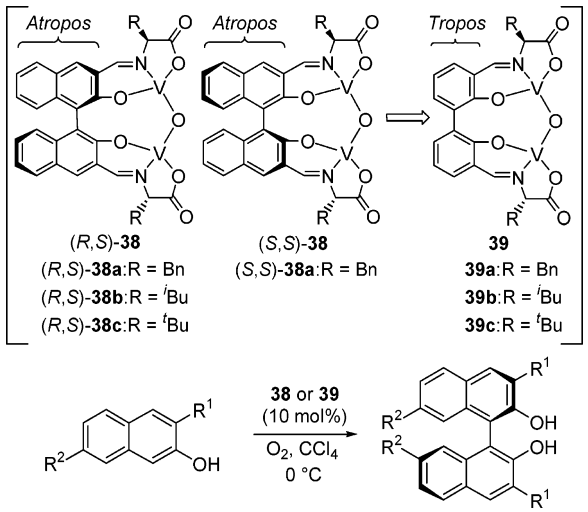
A different but closely related approach to asymmetric activation of *tropos* catalysts is the diastereomeric control of *tropos* ligands combined with a chiral subunit, which adopts a preferential conformation of a diastereomeric complex.[80] Recently, the *atropos* unit in the chiral catalysts has been replaced with a *tropos* unit. Reetz has reported the advantageous application of incorporating the *tropos* BIPOL unit into chiral diphosphite ligands prepared by the reaction of 1,4:3,6-dianhydro-D-mannite **35** as a chiral diol backbone and *tropos* biphenyl phosphorochlorides. When employing chiral diphosphites **36a** and **36b** bearing (*R*)- and (*S*)-BINOL for the Rh(I)-catalyzed hydrogenation of dimethyl itaconate, the (*R*)- and (*S*)-products were formed in 94.5% and 87.8% ee, respectively (Scheme 33).[81] Therefore, the absolute configuration is determined by the chiral axis of the binaphthyl and not by the bicyclic chiral diol backbone, and the use of (*R*)-BINOL leads to the more effective combination. By replacement of *atropos* BINOL groups *with tropos* BIPOLs (e.g., **37a**), an ee value of only 38.9% was reached for the (*S*)-product. However, diphosphite ligand **37b** with ortho-methyl groups is superior to **37a** and achieves 96.8% ee of the (*R*)-product (Scheme 33). In the case of the

Scheme 33



36a	94.5% ee (*R*) (>99%)
36b	87.8% ee (*S*) (>99%)
37a	38.9% ee (*S*) (74%)
37b	96.8% ee (*R*) (>99%)

Table 12. Enantioselective Oxidative Coupling of 2-Naphthols

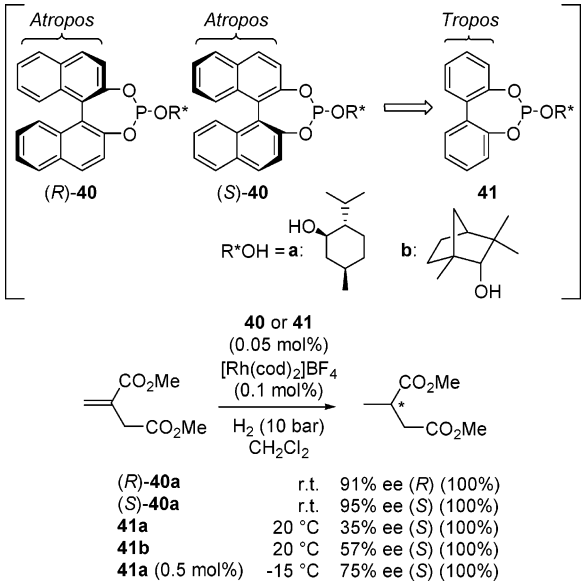


catalyst	R^1	R^2	% yield	% ee
(*S*,*S*)-**38a**	H	H	70[a]	6[a]
(*R*,*S*)-**38a**	H	H	75[a]	39[a]
(*R*,*S*)-**38b**	H	H	93	83
(*R*,*S*)-**38c**	H	H	63	71
(*R*,*S*)-**38b**	OMe	H	trace	–
(*R*,*S*)-**38b**	H	OMe	88	98
39a	H	H	77	80
39b	H	H	89	89
39c	H	H	56	79
39b	OMe	H	trace[b]	–
39b	H	OMe	95[b]	95[b]

[a] Reaction was carried out at 20 °C. [b] 5 mol % of **39b** was carried.

ligand with a *tropos* BIPOL unit such as **37**, three interconverting diastereomeric Rh(I) complexes are expected (e.g., *R*/*R*, *S*/*S*, and *R*/*S* combinations in the BIPOL moieties). According to the higher enantio-

Scheme 34

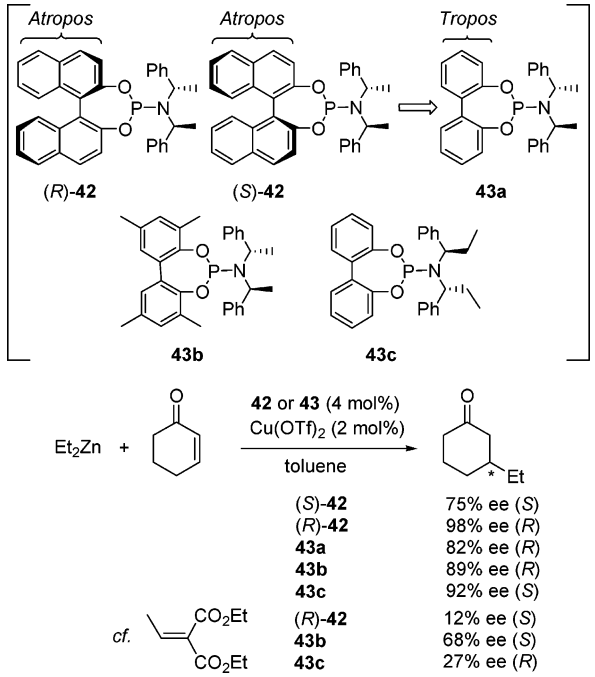


meric excess in the matched (*R*)-BINOL combination leading to (*R*)-configuration of the product, the most active catalyst displays the (*R*)/(*R*)-configuration. Indeed, the catalysts **36a** and **36b** exhibit extremely different kinetic profiles, in which the reaction rate using **36a** increased continuously through the reaction, but that using **36b** decreased.[81b]

Chiral oxovanadium(IV) complexes **38**, prepared by the condensation of chiral 3,3′-diformyl-2,2′-dihydroxy-1,1′-bi-2-naphthol with enantiopure amino acids, have been designed for asymmetric catalytic oxidative coupling of 2-naphthols (Table 12).[82] Since the combination of two chiral centers on the axially chiral binaphthyl and the amino acid units eventually affects the enantioselectivity of the coupling product, both (*R*,*S*)-**38** and (*S*,*S*)-**38** show almost the same reactivity, but the (*R*,*S*)-**38** achieves much higher enantioselectivity than the (*S*,*S*)-**38**. According to the results, it was anticipated that the diastereomers will be generated by employing *tropos* oxovanadium complexes **39** with BIPOL unit instead of an *atropos* BINOL unit. One diastereomer with matching chirality between two chiral centers, which might be more stable than the other with mismatching chirality, should achieve high enantioselectivity for oxidative coupling.[82b] Indeed, the *tropos* **39** gave higher or comparable enantioselectivities in comparison with those obtained by their 1,1-binaphthyl analogue (*R*,*S*)-**38**, even though **39** is employed as a mixture of diastereomers. According to the high level of enantioselectivity obtained by matching (*R*,*S*)-**38**, the major diastereomer was expected to have an axial chirality similar to that of (*R*,*S*)-**39**. In both catalyst systems **38** and **39**, the methoxy groups at C7 and C3 of 2-naphthol increased the ee value (**38b**, 98% ee; **39b**, 95% ee) and suppressed the coupling reactivity, respectively.

Tropos monodentate phosphite ligands have also been reported for the Rh(I)-catalyzed hydrogenation of dimethyl itaconate (Scheme 34).[83] The monodentate phosphite ligands **40a**, bearing (*R*)- and (*S*)-BINOL units, in reaction with L-menthol showed

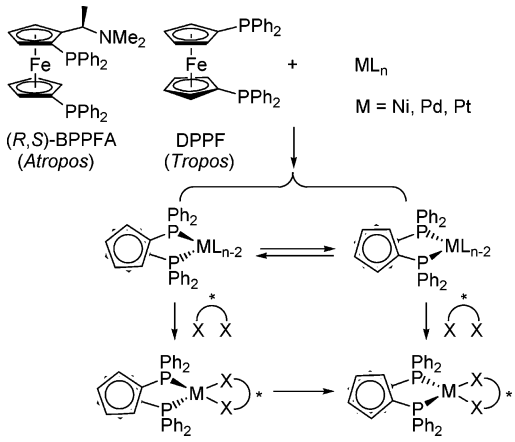
Scheme 35



almost the same reactivity but slightly different enantioselectivities in the (*R*)- (91% ee) and (*S*)-products (95% ee). Thus (*S*)-**40a** would be a matched combination. In the case of chirally flexible monodentate phosphite ligands **41a**,**b**, the steric bias of the chiral alcohol is not enough to discriminate two diastereomers on the basis of the chirality of the BIPOL unit. Two signals with the same intensities were observed in ^{31}P NMR. However, the equal intensities between the two diastereomers of **41b** did break down upon addition of half equivalent of [Rh(COD)$_2$][BF$_4$] to produce a ratio of 1:5 in ^{31}P NMR. When the diastereomeric Rh(I)/**41b** complexes, which exist as a nonequimolar mixture in solution, were employed, enantioselective hydrogenation of dimethyl itaconate was achieved to afford the enantioenriched product with 57% ee. The ee value for **41b** was increased to 75% ee when the temperature was lowered (68% ee at 0 °C, 75% ee at −15 °C).[83b]

According to such a concept, the phosphoramidite ligands based on a chiral amine unit and a *tropos* BIPOL unit have been employed in the copper-catalyzed conjugate addition of dialkylzinc reagents to induce high enantioselectivities (Scheme 35).[84,85] The chiral phosphoramidite ligand **42**, bearing two chiral moieties in the *atropos* BINOL and the exocyclic amino units, has been employed in the asymmetric conjugate addition. While the configurationally matched ligand (*R*)-**42** affords 98% ee,[84a] the mismatched (*S*)-**42** gave only 75% ee. Since the mismatched ligand (*S*)-**42** leads to the opposite enantiomer to that obtained by using the matched ligand, the absolute stereochemistry of the conjugate adduct can be caused by the chiral axis of the BINOL unit. The *tropos* phosphioramidite ligand **43a** gave very good enantioselectivity with cyclohexanone (82% ee), but did not attain the high level of ee obtained by the use of the parent matched ligand (*R*)-**42** (98% ee). Adding a substituent in the ortho position of the BIPOL moiety in the ligand **43b**, and a sterically

Scheme 36



demanding ligand at the exocyclic amino moiety in the ligand **43c**, greatly improved the enantioselectivity up to 89% and 92% ee, respectively.[85b] Depending on the substrates, the enantioselectivity of the conjugate adduct was eventually increased with **43b** or **43c** instead of (*R*)-**42**. In particular, **43b** afforded significantly higher enantioselectivities with ethylidene malonate (68% ee instead of only 12% ee for (*R*)-**42**).

In sharp contrast to the BIPHEP−Pd complex, the diphenylphosphinoferrocene (DPPF) counterpart has the *tropos* nature even at room temparature. The DPPF−metal complexes are thus chirally dynamic and subject to more facile chirality control by chiral diamines than the BIPHEP−metal complexes. Ferrocenyl-bis(phosphine) ligands with appendages of chiral centers, such as (*R*)-*N*,*N*-dimethyl-(*S*)-1′,2-bis-(diphenylphosphino)ferrocenylethylamine ((*R*,*S*)-BPPFA),[86] are often used as chiral ligands for asymmetric catalysis. By contrast, asymmetric catalysis with *tropos* DPPF ligands, which have never been used as chiral ligands because they have no central and planar chirality, can be established only through control of dynamic axial chirality by use of a chiral controller (Scheme 36).[87] Chiral diamines such as DPEN, DABN, and DM-DABN readily coordinated and controlled the axial chirality of DPPF−Pd **44a** and −Pt **44b** complexes to afford the single diastereomers within seconds.[88] The (*P*)/(*R*)-configuration of the **44a**/DABN diastereomer obtained from dichloromethane−hexane was determined by X-ray analysis (Figure 16).

Asymmetric catalysis with the DPPF ligand can be established through prompt control, by use of a chiral diamine, of dynamic axial chirality not only in the Pd and Pt catalysts but also in the Ni catalyst, which is rarely used as an asymmetric Lewis acid catalysts. Significantly, the DPPF−Ni **44c**/(*R*)-DABN catalyst was found to exhibit higher levels of enantioselectivity in the ene reaction (Scheme 37).[87] The **44c**/(*R*)-DABN complex gave good yields and higher levels of enantioselectivity (90% ee) at room temperature than without DPPF ligand (75% ee). It is noted that the choice of the counteranion is critical to obtain high enantioselectivity and chemical yield; the perchlorate counterpart gave lower chemical yield and enantioselectivity (76% ee) than those obtained with the hexafluoroantimonate complex.

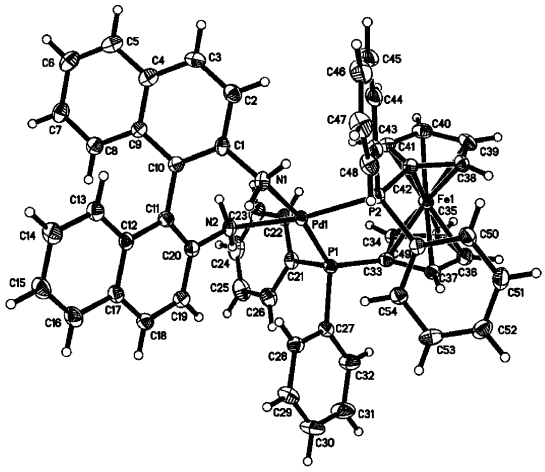
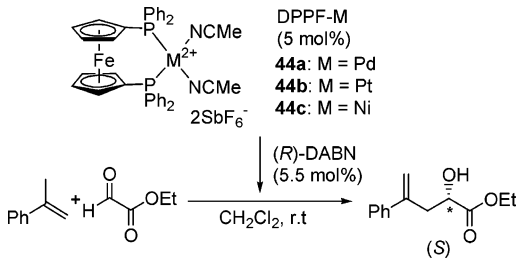


Figure 16. X-ray single-crystal structure of the (*P*)-DPPF−Pd/(*R*)-DABN complex.

Scheme 37



	44a	27% ee (92%)
	44b	7% ee (96%)
	44c	90% ee (84%)
cf.	$Ni(SbF_6)_2$	75% ee (87%)
	$Ni(dppf)(ClO_4)_2$	76% ee (52%)

In relation to the asymmetric activation of the *tropos* catalyst, Katsuki has reported enantioselective epoxidation using the flexible achiral Mn(III)−salen complex with a chiral additive (Scheme 38).[89] Such an achiral Mn(III)−salen complex **45** should exist as an equilibrium mixture of "stepped" enantiomers (**A** and **B**), both of which can catalyze epoxidation equally to afford a racemic epoxide. On the basis of the asymmetric activation concept, conformational control of the enantiomeric confomation of **45** would be achieved by association of a certain chiral axial ligand because of the interaction between the axial substituent (R′) and the chiral axial ligand (**AL***). The achiral Mn(III)−salen complexes catalyzed asymmetric epoxidation to afford high enantioselectivities up to 83% ee with the chiral bipyridine *N*,*N*′-dioxide (+)-**47** as an asymmetric activator.[89a]

2.4.2. Asymmetric Activation by Achiral/Meso Activators

In a similar manner of asymmetric activation of a chirally flexible achiral catalyst by a chiral activator, a chiral environment in an enantiopure catalyst would be further amplified by association with sterically demanding achiral[90] or meso source. The conformational preferences of the achiral ligand are influenced by the interaction with the chiral ligand and are largely responsible for defining the chiral environment. The strategy of chiral environment amplification has been applied by Walsh to the

Scheme 38

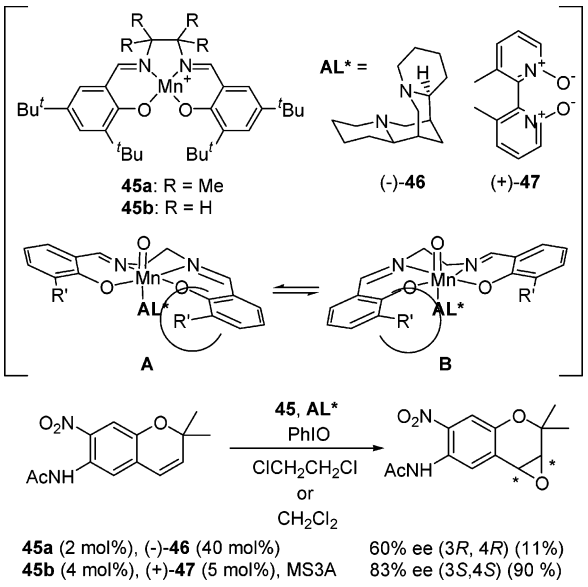
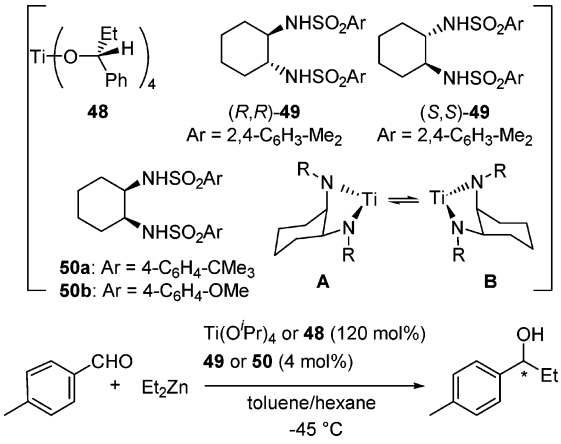


Table 13. Enantioselective Addition of Diethylzinc to Aldehydes



catalyst	ligand	% conv (time)	% ee
$Ti(^iPr)_4$	(*R*,*R*)-**48**	20 (15 min) 63 (60 min)	79 (*S*)
48	(*R*,*R*)-**48**	11 (15 min)	84 (*S*)
48	(*S*,*S*)-**48**	22 (15 min)	81 (*R*)
48	50a	62 (15 min)	84 (*R*)
48	50b	53 (15 min)	78 (*R*)

asymmetric addition of diethylzinc to aldehydes in the presence of $Ti(OR)_4$ and bis(sulfonamide) (Table 13).[91] The achiral $Ti(O^iPr)_4$ promoted the alkylation in the absence of bis(sulfonamide) ligands to afford the racemic alcohol product. By employing the chiral titanium alkoxide **48**, the (*S*)-alcohol was obtained with 42% ee. When the chiral bis(sulfonamide) ligand (*R*,*R*)-**49** was used with $Ti(O^iPr)_4$ and **48**, the (*S*)-alcohol product was formed in 79% and 84% ee, respectively. On the other hand, the reaction performed using the enantiomer of the ligand (*S*,*S*)-**49** and -**48** led to the (*R*)-enantiomer of the product in 81% ee. While the chiral bis(sulfonamide) ligand clearly controls the absolute configuration of the alcohol product, the chirality on **48** has little influence. However, higher enantioselectivity of the alcohol can be also achieved by combination of **48** with the achiral and meso bis(sulfonamide) ligands **50**

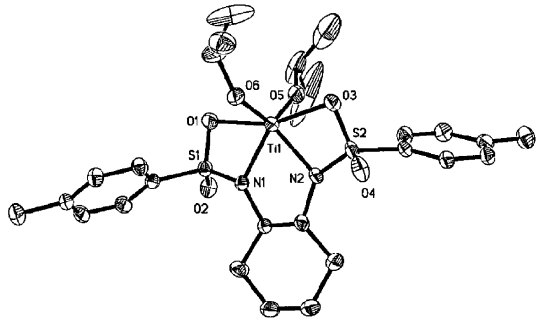
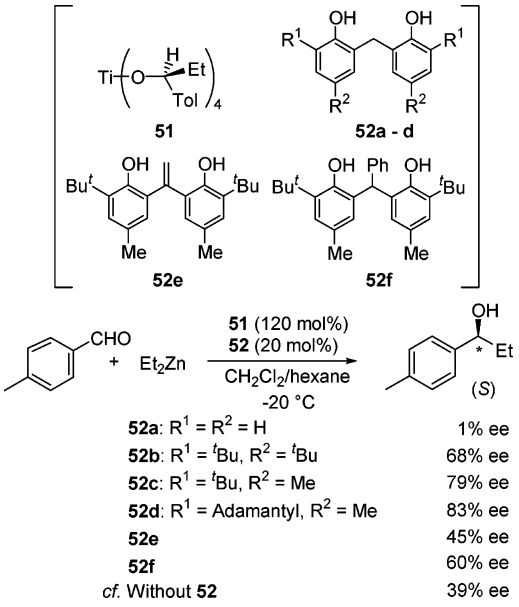


Figure 17. X-ray single-crystal structure of the $Ti(O^iPr)_2$/(*S*,*S*)-**49** (Ar = 4-C_6H_4-Me) complex.

Scheme 39



(**50a**, 84% ee, Ar = 4-*tert*-butylbenzene; **50b**, 78% ee, Ar = 4-methoxybenzene). Thus, incorporating **50** with **48** can lead to desymmetrization and amplification of the asymmetric environment of the reaction center. In this case, the meso ligand **50** has two static chair conformations, which interconvert by cyclohexane ring-flip in solution (**A** and **B**), and hence this enantiomeric interconversion of the meso ligand moiety can induce diastereomeric conformations of the catalyst system consisting of **48** and **50**. If one diasteromer is formed preferentially, the meso ligand can amplify the asymmetric environment of the catalyst. Furthermore, coordination of the sulfonyl oxygens to the titanium center, which was observed in the X-ray structures of the bis(sulfonamido)Ti-$(O^iPr)_2$ complexes derived from *trans*-1,2-diaminocyclohexane, may be important in the transition state of the enantioselective alkylation (Figure 17).[92] Such a coordination structure can generate the stereogenic centers on the sulfur atoms to extend the chiral environment.

In the same reaction of diethylzinc with aldehydes in the presence of $Ti(OR)_4$, members of the achiral methylene-bis(phenol) (MBP) ligand series have been employed as achiral ligands rather than the meso bis(sulfonamido) ligands (Scheme 39).[93] When the chiral titanium complex **51** was used without any other ligands, the asymmetric alkylation resulted in the

formation of the (*S*)-alcohol with only 39% ee. The addition of substituted 2,2′-MBP ligands **52** with **51** eventually had an effect on the ee of the product. While **52a**, with small substituents $R^1 = R^2 = H$, led to lower enantioselectivities than those obtained in the background reaction without **52**, larger R group such as a *tert*-butyl group increased remarkably the enantioselectivity of the (*S*)-alcohol product (68−79% ee). In addition, **52d**, bearing an adamantyl group, increased the ee value of the product to 83% ee. On the other hand, substitution in the methylene position of **52** (e.g., **52e**,**f**) decreased the ee values. On the basis of the concept that symmetric ligand coordination on the metal can become asymmetric upon binding the substrate, six trigonal bipyramidal isomers can be formed in solution, where the MBP ligand is bound in apical and equatorial positions. As shown in Figure 18, the X-ray structure of **52c**/$Ti(OR^*)_2(NMe_2H)$ [OR* = (*S*)-OCHEt(4-C_6H_4-Cl)] showed that the $HNMe_2$ as a substrate analogue is trans to the axial **52c** phenoxide oxygen in the distorted trigonal bipyramidal geometry.

The chiral environment amplification involving modification of the achiral ligand combined with a chiral catalyst has been also applied in the BINOL−Zn-catalyzed enantioselective addition of an alkyl group to aldehydes. As shown in section 2.2, the same reaction led to very high enantioselectivity with the matched combination of the chiral Ph_2-BINOL−Zn catalyst with the chiral diimine activator. Later, various achiral diimine and diamine ligands with ethylenediamine, meso diamine, and 2,2′-diaminobiphenyl backbones were examined by Walsh as activators of the chiral Ph_2-BINOL−Zn-catalyzed asymmetric alkylation.[94] The (*S*)-Ph_2-BINOL−Zn catalyst was used without any achiral ligands for the reaction to yield the (*S*)-alcohol in 44% ee. As a simple analogue of the catalyst system consisting of the chiral BINOL−Zn and the chiral diimine activator, the most simple achiral diimine ligands **53** were examined. Though addition of the achiral diimine ligand **53a** derived from smaller aldehydes increased the catalytic efficiency, the enantioselectivities of the product were moderate with use of the (*S*)-enantiomer (Scheme 40). It is noted that the opposite enantiomer of the product was obtained with moderate to good enantioselectivities (30−87% ee) by addition of the diimine ligands **53b**−**d** derived from sterically demanding aldehydes.

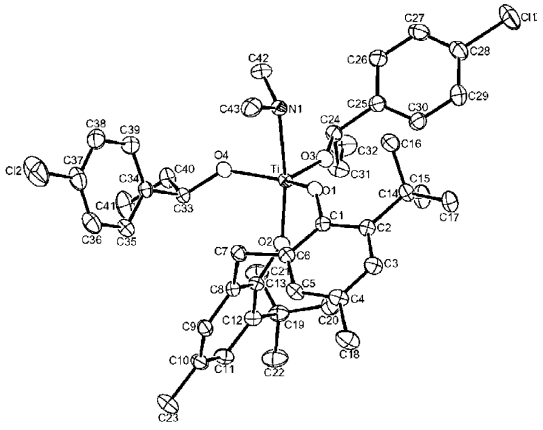
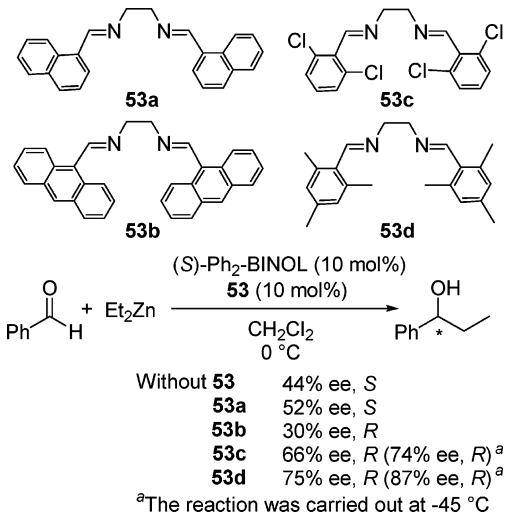
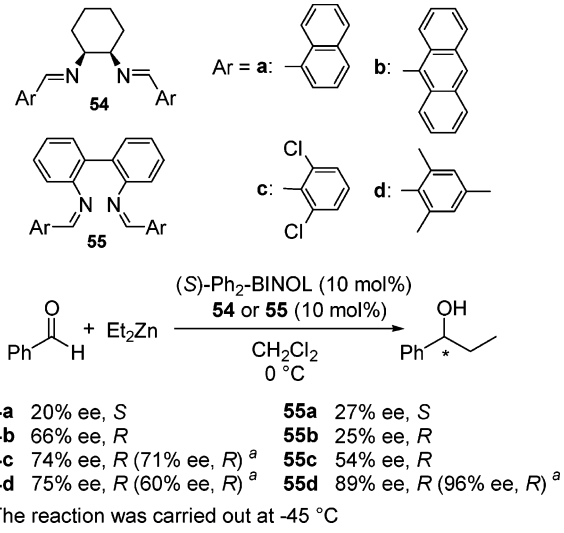


Figure 18. X-ray single-crystal structure of the **52c**/$Ti(OR^*)_2(NMe_2H)$ complex [OR* = (*S*)-OCHEt(4-C_6H_4-Cl)].

Scheme 40



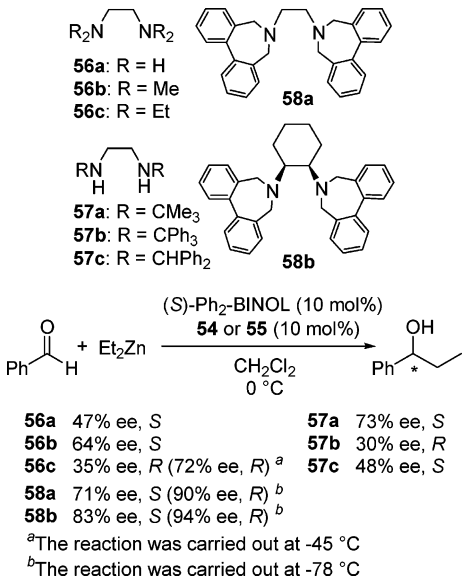
Scheme 41



The (*S*)-Ph_2-BINOL−Zn catalyst, incorporating the achiral diimine ligand **54** and the **55** series, showed results quite comparable to those obtained with the **53** series. In both cases, the diimine ligands bearing larger aryl groups yielded the higher enantioselectivities (Scheme 41). When the ligands **54a** and **55a** derived from smaller aldehydes were employed, the (*S*)-enantiomer tended to be obtained with low to moderate enantioselectivities. Thus, no additional effect on the enantioselectivity of the product was found originating from the meso or biphenyl backbone. Irrespective of the backbone structures of achiral diimines, the ligands **54d** and **55d** derived from 2,4,6-trimethylbenzaldehyde formed the most enantioselective catalyst (up to 75% and 96% ee, respectively), where (*S*)-Ph_2-BINOL−Zn moiety would control the position of the mesityl groups. Therefore, the sterically demanding aryl groups on the achiral diimine ligands are fundamental in amplification of the chiral environment of the catalysts.

A series of achiral diamine ligands **56** and **57** showed a different tendency in enantioselectivity from achiral diimines (Scheme 42). While the most

Scheme 42

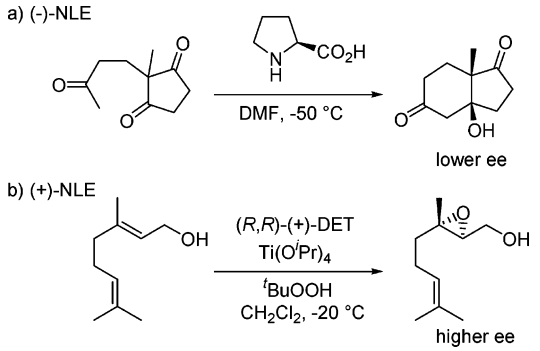


simple ethylenediamine **56a**-combined catalyst showed almost the same enantioselectivity as (*S*)-Ph$_2$-BINOL−Zn alone (47% vs 44% ee), TMEDA **56b** further increased the ee of the (*S*)-product to 64% ee. Surprisingly, the bulkier *N*,*N*,*N*′,*N*′-tetraethylethylenediamine **56c** afforded the opposite enantiomer of the (*R*)-product with 36% ee at 0 °C and 72% ee at −45 °C. When the achiral diamines **57** that can form stereocenters upon coordination to zinc are employed, the C_2-symmetric Ph$_2$-BINOL−Zn moiety is expected to cause the diamine structure to bind in one of the C_2-symmetric modes. With bulkier chiral diamine **57a**, the highest enantioselectivity of the (*S*)-product (73% ee) was attained. On the other hand, the further bulkier N-alkyl groups derived from tritylamine resulted in a reversal of the absolute configuration of the product with lower enantioselectivity (**57b**, 30% ee). In the achiral diamines **58** with *tropos* pendant biphenyl groups, the configuration of the biphenyl subunit in **58** would be controlled via *tropo* inversion by association with the (*S*)-Ph$_2$-BINOL−Zn moiety and would extend the chiral environment of the resulting (*S*)-Ph$_2$-BINOL−Zn/**58** complex. Regardless of the tether length and the conformation of **58**, the (*R*)-enantiomer of the product was predominantly formed with moderate to high enantioselectivities, and hence the *tropos* biphenyl moiety exclusively determines the absolute configuration of the product. In particular, **58b** with a *cis*-1,2-diaminocyclohexane backbone achieved the highest enantioselectivities (up to 94% ee at −78 °C) in the achiral diamine series. Thus, the simple achiral diamine ligands showed that the ee of the product is very sensitive to the size of the N-alkyl groups in the diamine backbone.

3. Asymmetric Amplification (Positive Nonlinear Effect)

While racemic catalysts inherently give only a racemic mixture of chiral products, the nonlinear relationship in enantiomeric excesses between catalysts and products is caused by self-assembly of

Scheme 43



nonracemic catalysts, leading to diastereomeric perturbations. The relationship of the ee values between the chiral ligand and the product deviates from linearity to achieve higher enantiomeric enrichment of the product than that of the catalyst (Figure 19). Kagan has opened the door to such a deviation from the linear relationship, namely the nonlinear effect (NLE), which is often observed between the enantiomeric purity of chiral catalysts and the optical yields of the products (Figure 19a).[95] In particular, a positive nonlinear effect (abbreviated as (+)-NLE), that is, asymmetric amplification, has attracted current attention because an enantiopure chiral catalyst is not needed to prepare a chiral product with high enantiomeric excess.[96,97] Recently, Blackmond demonstrated[98] that, in these nonlinear catalytic systems, a detailed analysis of the reaction rate can give an independent confirmation (Figure 19b) of the mathematical models developed by Kagan.[96a] Consideration of the kinetic behavior of these nonlinear catalytic reactions can provide valuable mechanistic insights into the NLE by comparison of the prediction of the models. A strong (+)-NLE in the product enantioselectivity severely suppresses the rate of product formation.

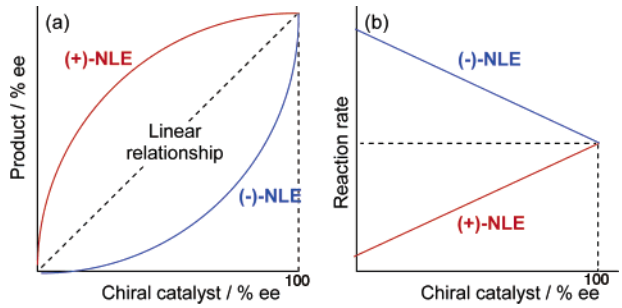
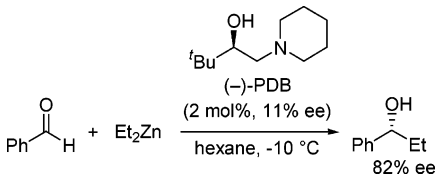


Figure 19. Possible relationship between the enantiomeric purity of chiral catalysts and (a) the optical yield of products and (b) the reaction rate.

The first report to show a slight NLE, but unfortunately a negative one ((−)-NLE), in the asymmetric aldol reaction of a triketone in the presence of (*S*)-prolin is that of Agami and Kagan (Scheme 43a).[96b] This earliest example of (−)-NLE was recently challenged by List.[99] On the basis of kinetic, stereochemical, and dilution experiments, he suggested that only one proline could catalyze the aldol reaction, but the conventional two-proline mechanism cannot be completely ruled out. A (+)-NLE has been obviously observed in asymmetric epoxidation of geraniol in the

Scheme 44



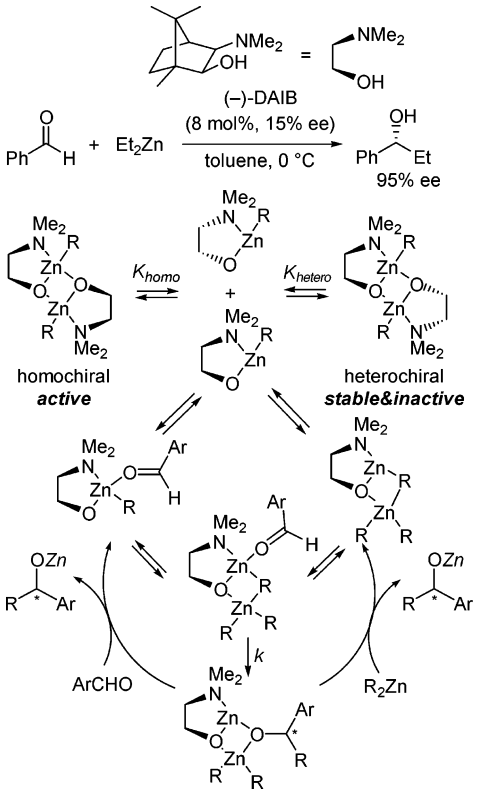
presence of $Ti(O^iPr)_4$ and (*R*,*R*)-diethyl tartrate (DET). This (+)-NLE can be explained by the intervention of a dimeric complex that generates two tartrate units in the active species, as proposed by Sharpless.[100] The heterochiral dimer is more stable and thus less reactive than its homochiral dimer (Scheme 43b).

Oguni independently coined the term "asymmetric amplification"[101] for (+)-NLE in an asymmetric carbonyl addition reaction of dialkylzinc reagents in the presence of chiral amino alcohols.[102] Benzaldehyde is alkylated enantioselectively to afford (*R*)-1-phenylpropanol with 82% ee, even by treatment of an 11% ee of (−)-1-piperidino-3,3-dimethyl-2-butanol ((−)-PDB) with diethylzinc. This amplification in the enantioselectivity of the product can be also explained by the intervention of dimeric zinc species in solution. Furthermore, kinetic study showed that the reaction with zinc catalyst derived from a 60% ee of (−)-PDB was 5.5 times faster than that from racemic PDB (Scheme 44).

In the same asymmetric alkylation reaction, Noyori and Kitamura reported a strong (+)-NLE by using partially resolved (2*S*)-3-*exo*-(dimethylamino)isoborneol ((−)-DAIB).[103] The zinc catalyst prepared from lower resolved (−)-DAIB (15% ee) can achieve the high level of enantioselectivity of (*S*)-1-phenylpropanol (95% ee), which is close to the 98% ee obtained with enantiopure (−)-DAIB (Scheme 45). They reported a beautiful mechanistic work on the asymmetric amplification in view of the stability of the heterochiral zinc amino alcohol dimer compared to the homochiral dimer. They clarified a delicate balance between monomeric and dimeric forms in equilibrium during the course of the reaction. The remaining monomer is the more active catalyst and thus should be preferentially implicated in the catalytic cycle (Scheme 45).[103a]

Indeed, the dynamic behavior of the dimeric species in solution was revealed by ^{1}H NMR measurement, where the heterochiral dimer exists predominantly and dissociates to the monomer very slowly during the time that the homochiral dimer is in equiliblium with the monomer in toluene solution ($K_{homo} > K_{hetero}$).[103d] The quantitative analysis of NLE using experimentally available parameters — the equilibrium constant *K*, the rate constant *k*, the ee of DAIB, and the concentrations of DAIB, R_2Zn, and aldehyde — has been carried out. It has been clarified mathematically that the NLE observed can originate from the competition of two enantiomorphic cycles with the monomeric zinc catalysts, as shown in Scheme 2, and not from diastereomorphic cycles with the dimeric zinc catalysts.[103e] X-ray analysis indicated that the labile Zn−O and Zn−N bonds in the homochiral dimer are longer than those in the heterochiral

Scheme 45



dimer. An ab initio molecular orbital study of a simplified model supported these experimental results. The heterochiral dimer is more stable than the homochiral one by 3.1 kcal/mol due to the repulsive interaction of the 1,3-syn-oriented Zn−Me bonds (Figure 20).[103c,d] Upon employing diphenylzinc in the presence of (−)-DAIB, a slight asymmetric amplification was observed in the enantioselective alkylation of ketones. The remarkable (+)-NLE was also observed in the same reaction using diethylzinc promoted by various ee's of the 2-pyridylalkanol (*R*)-**59**.[104] In a similar manner, asymmetric amplification can be explained by preferential intervention of the heterochiral dimer (Scheme 46).

Recently, Bolm reported the (+)-NLE in the same asymmetric carbonyl addition reaction of dialkylzinc

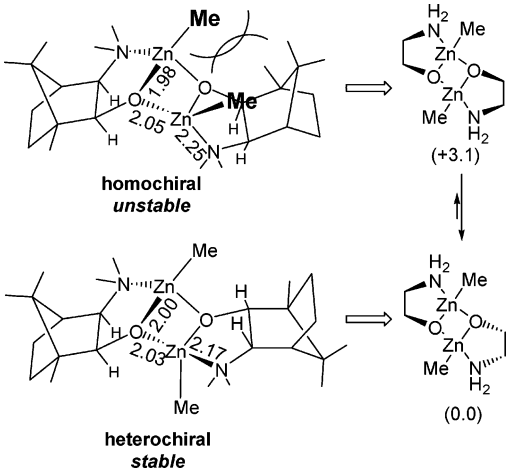
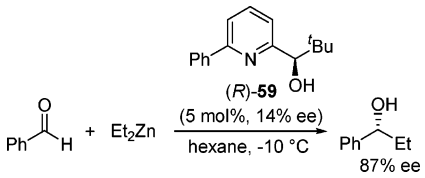
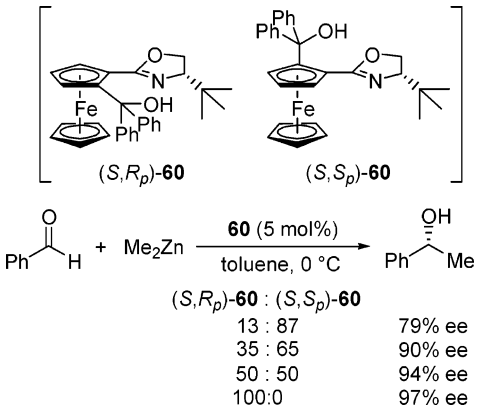


Figure 20. Molecular structures of homochiral and heterochiral dimers. Bond lengths are shown in Å, and relative energies of model dimers (in parentheses) are in kcal/mol (MP2//HF).

Scheme 46



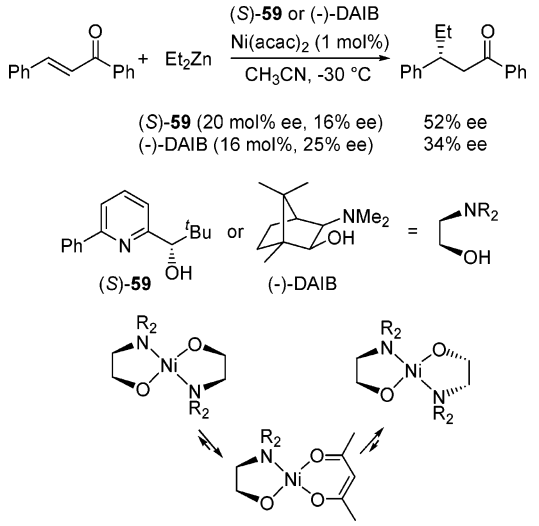
Scheme 47



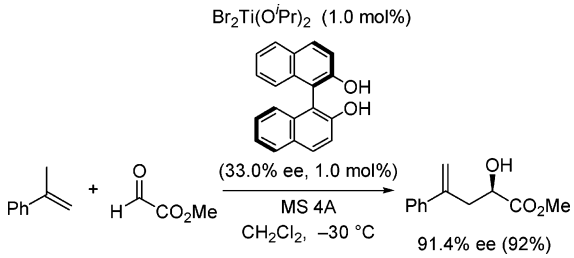
reagents but with diastereomeric mixtures of chiral ferrocenes **60**.[105] No deviation from linearity was observed resulting from the use of enantiomeric mixtures of the ferrocene bearing a planar chility (Scheme 47). In Bolm's case, however, even with 1:1 diastereomeric mixtures of the ferrocenes (S,R_p)-**60** and (S,S_p)-**60**, the enantiomeric excess of the (*R*)-product was still 94% ee, which is close to the 97% ee obtained with diastereomerically pure (S,R_p)-**60**. This strong asymmetric amplification may be attributed to the significantly different activities of the two diastereomeric catalysts derived from (S,R_p)-**60** and (S,S_p)-**60** rather than participation of higher aggregates.

The use of dialkylzinc reagents, far from being limited to the 1,2-addition, can also be expanded to conjugate addition. Bolm[106] and Feringa[107] independently reported the (+)-NLE in the conjugate addition of dialkylzinc catalyzed by a Ni complex with chiral amino alcohol ligands such as substituted 2-pyrimidylalkanol (*S*)-**59** and (−)-DAIB, respectively (Scheme 48). It is noted that the enantioselectivity and the amplitude of the (+)-NLE were very sensitive to the ligand concentration, Ni content, and conversion. A type of diastereomeric perturbation similar to that in the 1,2-addition was speculated between homochiral and heterochiral species prepared from chiral ligand and Ni(acac)$_2$ in a ratio of 2:1 (Scheme 48). The (+)-NLE might be due to the slow dissociation of an inactive heterochiral structure or the formation of other Ni species during the reaction. A dependence of enantioselectivity on conversion indicates that active monomeric catalysts might be formed from homochiral and heterochiral Ni dimers by the association with a substrate.[106] Furthermore, in Feringa's study, even in the absence of Ni, the reaction took place to give the opposite enantiomeric product, presumably obtained by the zinc complexes with the chiral ligand.[107] At low substrate concentrations, the Ni catalysts might be stable, as inactive

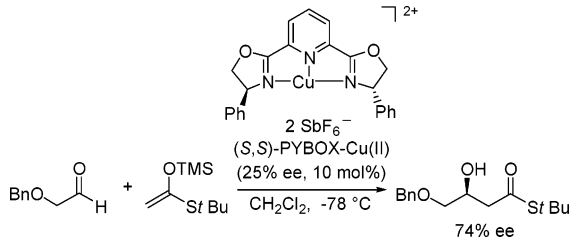
Scheme 48



Scheme 49



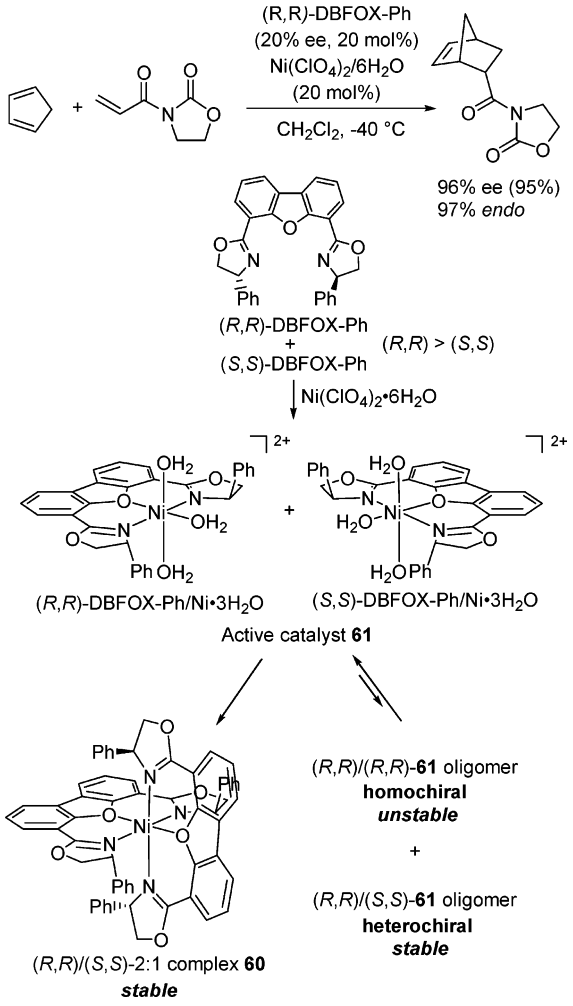
Scheme 50



dimers and hence Zn catalysts might compete with Ni catalysts.

The (+)-NLE in the carbonyl−ene reaction with glyoxylate catalyzed by a BINOL−Ti complex has been reported by us.[33b,97] The partially resolved titanium complex (33.0% ee) derived from BINOL and Br$_2$Ti(O^{i}Pr)$_2$ was employed for the glyoxylate−ene reaction with α-methylstyrene to afford the chiral homoallyl alcohol with 91.4% ee (Scheme 49). Kagan and Blackmond independently applied the modified Kagan's two-ligand model (e.g., ML$_2$)[95,98] with different parameters to prove a good fit to support our results. However, Blackmond also reported a smaller suppression of activity for racemic catalyst than that observed experimentally, because the reversible dissociation might not reach equilibrium, giving a steady-state concentration of monomeric species smaller than predicted. Evans studied the asymmetric amplification in the enantioselective aldol reaction with C_2-symmetric bis(oxazolinyl)pyridine (PYBOX)−Cu(II) complexes (Scheme 50).[108] The (+)-NLE was explained as a result of the relative stabilities of the heterochiral and homochiral ligand complexes with metal in a ratio of 2:1.[109]

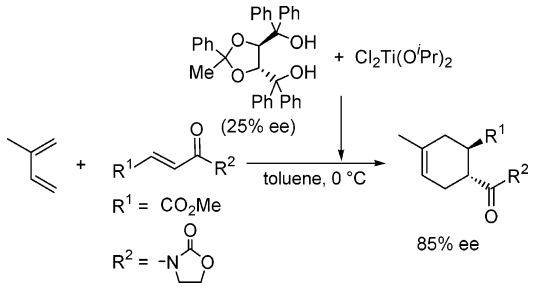
Scheme 51



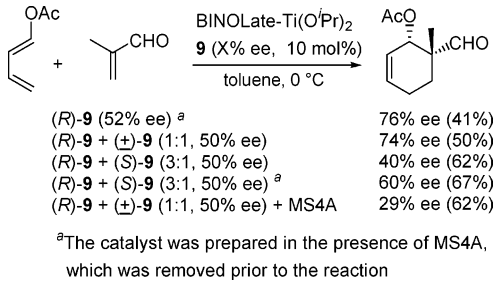
Significant levels of (+)-NLE are also observed in the asymmetric catalysis by cationic complexes bearing trans-chelating tridentate ligands. Kanemasa reported an aqua complex prepared from $Ni(ClO_4)_2 \cdot 6H_2O$ and 4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (DBFOX-Ph) as a tridentate ligand to exhibit a remarkable (+)-NLE (Scheme 51).[110] Two mechanisms were involved in this (+)-NLE: the irreversible formation of heterochiral ligand complexes with Ni in a ratio of 2:1 (2:1 complex **60**) and the water-bridged oligomerization of homo- or heterochiral ligand complexes with Ni in a ratio of 1:1 (1:1 complex **61**). In the chirality enhancement process, the aqua ligands play an essential role to form the associated homo- or hetero-chiral oligomers via a hydrogen-bonding network. On the basis of the packing structure of **61**, it is suggested that the heterochiral aggregation is much stronger than the homochiral one. In solution, the less stable homochiral oligomer should be predominantly dissociated to generate the reactive monomeric form.

A (+)-NLE has been observed in the enantioselective Diels−Alder reaction catalyzed by TADDOLate−Ti catalyst. When the partially resolved TADDOL (25% ee) was employed, the cycloadduct was obtained with 83% ee (Scheme 52).[111] The white Ti species that precipitated was generated as a heterochiral dimer (or oligomer) in a 1:1 ratio upon completion of the

Scheme 52



Scheme 53

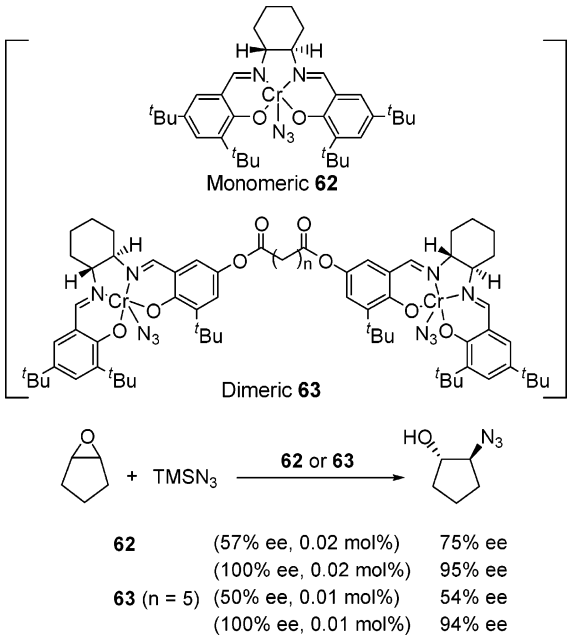


[a]The catalyst was prepared in the presence of MS4A, which was removed prior to the reaction

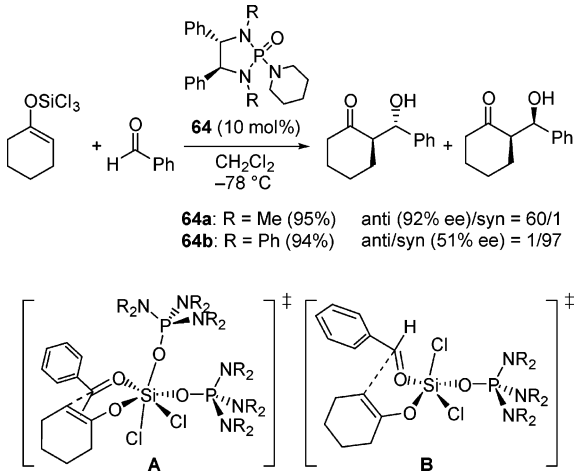
reaction. Also in the case of the BINOLate−Ti catalyst **9**, a (+)-NLE has been observed in the enantioselective Diels−Alder reaction (Scheme 53).[112] It is noted that the asymmetric amplification strongly depends on the way that partially resolved **9** is prepared. When the MS-free (*R*)-**9** was prepared from partially resolved BINOL (52% ee) and $Cl_2Ti(O^iPr)_2$ in the presence of 4-Å molecular sieves (MS), which were filtered off prior to the reaction, the cycloadduct was obtained with 76% ee. The combined use of an enantiopure (*R*)-**9** and racemic **9** in a ratio of 1:1 resulted in a similar (+)-NLE (74% ee). By contrast, mixing enantiopure (*R*)- and (*S*)-**9** in a ratio of 3:1 led to a linearity (40% ee). However, the same catalyst system obtained by mixing (*R*)- and (*S*)-**9** in the presence of MS, which are filtered off prior to the reaction, showed a slight (+)-NLE (60% ee). On the other hand, a (−)-NLE was observed in the reaction carried out in the presence of MS (29% ee), because MS acts as an achiral catalyst for the Diels−Alder reaction. Keck also reported BINOL−titanium catalysis in the presence or absence of 4-Å MS.[113]

The study of NLE in asymmetric catalysis can be useful in getting mechanistic insight into the active species involved in the catalytic cycle and their behavior in solution.[114] Jacobsen has provided the participation of the bimetallic pathway in the asymmetric ring opening of epoxides with trimethylsilyl azide catalyzed by the chiral Cr(salen) complex **62** (Scheme 54).[115] The observation of a significant (+)-NLE, coupled with a second-order kinetic dependence on **62,** led to a mechanistic proposal for simultaneous activation of both the epoxide and the azide independently by two Cr(salen) complexes **62**. On the basis of this cooperative mechanism, the dimeric analogues of the Cr(salen) complex **63** were designed. While monomeric **62** exhibited a (+)-NLE, dimeric **63** displayed a strict linear relationship between the ee of the product and the catalyst. This indicated participation of an intramolecular bimetallic pathway in the use of **63**. Covalent linkage of the Cr(salen)

Scheme 54



Scheme 55



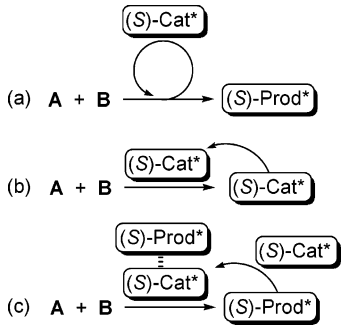
complex unit with a suitable tether length and position resulted in an increase in catalytic activity by up to 2 orders of magnitude as compared to the monomeric analogues without any loss of enantioselectivity.

On the basis of NLE studies coupled with kinetic analyses, Denmark reported mechanistic insight into the rate acceleration by chiral phosphoramides **64** in asymmetric aldol reactions of trichlorosilyl enolates with aldehydes (Scheme 55).[116] Sterically less hindered **64a** (R = Me), which afforded the anti product predominantly, resulted in a slight (+)-NLE, and thus the transition structure with more than one phosphoramide molecule was expected. On the basis of Kagan's ML_2 model,[95] **64a** would bind to the enolate in a 2:1 fashion, and the resulting hexacoordinated silicate **A** favors a chairlike arrangement to give the anti product. In contrast, sterically demanding **64b** (R = Ph) exhibited a linear relationship and thus can bind to the enolate in a 1:1 fashion. The resulting pentacoordinated silicate **B** favors a boatlike transition state to give the syn product.

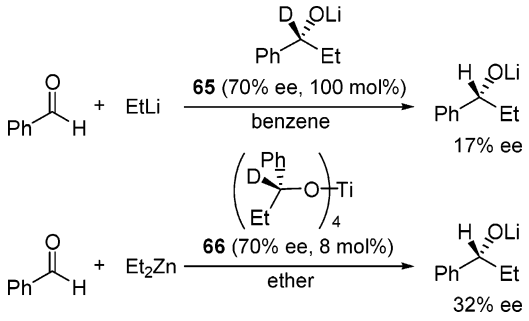
4. Autocatalysis

Another aspect of NLE is asymmetric autocatalysis following the statistical fluctuations of racemic states in catalysts. In view of the spontaneous generation of molecular chirality on the Earth, asymmetric autocatalysis attracts special interest, where the chiral product can act as the asymmetric catalyst for its own production. In an usual asymmetric catalysis, an increased amount of enantioenriched products can be obtained by use of a catalytic amount of asymmetric catalysts, which have structures different from those of the products (Scheme 56a). On the other hand, asymmetric autocatalysis is defined as the asymmetric catalysis where the chiral product can act as a chiral catalyst to cause its own multiplication (Scheme 56b). This asymmetric autocatalytic process is an efficient method for spontaneous multiplication of chiral molecules without any chiral ligands.

Scheme 56

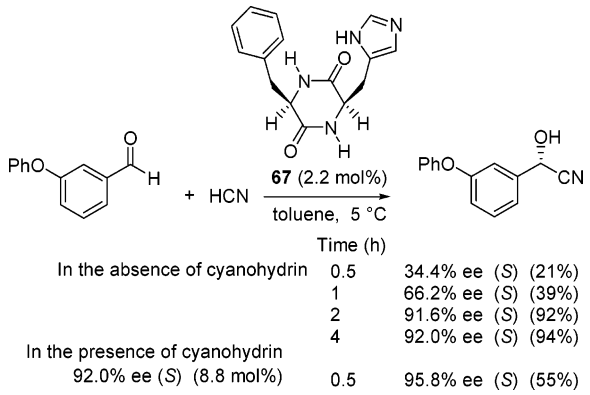


Scheme 57

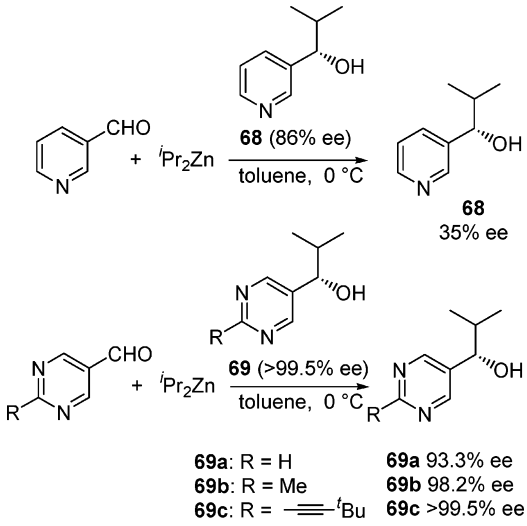


In view of enantiomeric recognition and interaction of chiral molecules, Alberts and Wynberg reported the first experimental result in the enantioselective autoinduction in the asymmetric addition of ethyllithium or diethylzinc to benzaldehyde (Scheme 57).[117] The mixed aggregates derived from the chiral lithium alkoxide **65** or titanium alkoxide **66** and the alkoxide product would affect the chiral environment of the reaction center to increase the enantioselectivity of the product. The ee of the product, however, did not exceed the ee of the catalyst. In the asymmetric hydrocyanation catalyzed by cyclic dipeptides **67**, the (*S*)-cyanohydrine product formed an active complex with the cyclic peptide to increase the enantioselectivity of the (*S*)-cyanohydrine product upon reaction to 95.8% ee (Scheme 58).[118] The asymmetric autoinduction is closely related to but significantly different from the approach to asymmetric autocatalysis because, in asymmetric autoinduction,

Scheme 58



Scheme 59

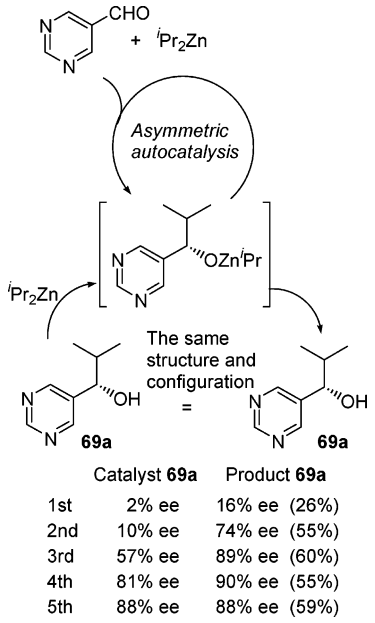


a chiral product itself cannot promote the reaction without formation of reactive catalyst by association with any other chiral catalysts (Scheme 56c).

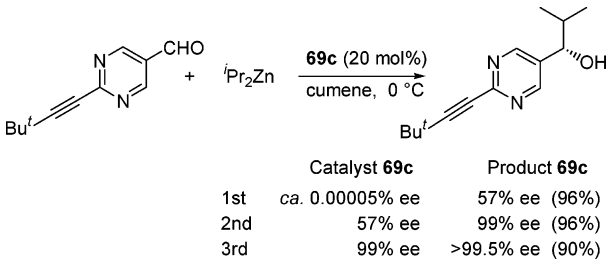
Recently, Soai has reported a remarkable experimental proof for asymmetric autocatalysis in carbonyl addition reactions of diisopropylzinc.[119,120] Usually, zinc alkoxide forms an inactive cubic tetramer. However, the use of pyridyl aldehyde as a substrate gives an enantioenriched pyridyl alcohol product **68**, which can loop the catalytic cycle without formation of the inactive tetramer. In this autocatalytic system, the product % ee (35% ee) did not exceed the level of catalyst % ee (86% ee),[120a] while use of chiral 5-pyrimidylalkanols **69** as asymmetric autocatalysts instead of their pyridyl counterparts gave the product without any loss of enantiopurity (Scheme 59).[120b] In particular, **69c** possessing an alkynyl group at the 2-position of the pyrimidine ring can act as a very efficient asymmetric autocatalyst to achieve practically perfect asymmetric autocatalysis (the product with >99.5% ee).[120c] A significant asymmetric amplification is achieved in the same carbonyl addition reaction with the pyrimidyl alkanol. Starting from the (*S*)-alcohol in 2% ee (20 mol %), the first reaction provides the (*S*)-alcohol in 16% ee. The fourth reaction provides 90% ee via **74** and then 89% ee's (Scheme 60).[120d]

Kinetic studies of such an autocatalytic reaction using the modified ML_2 model proposed by Blackmond have clarified a statistical distribution of dimers.[121] Very recently, Soai reported amplification of chirality from an extremely small enantiomeric imbalance (ca. 0.00005% ee) to give practically enantiomerically pure product **69c** (>99.5% ee) in only three consecutive cycles. This indicates that the ee of catalyst **69c** can be enhanced by inducing enantiomeric imbalance of chirality, even if it is very small, and subsequent asymmetric autocatalysis (Scheme 61).[120e]

Scheme 60

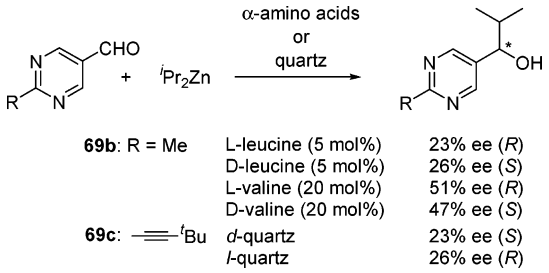


Scheme 61



Circularly polarized light (CPL) or quartz has long been proposed as an origin of chirality of organic compounds (shown in section 1). As an initiator of a slight enantiomeric imbalance, an α-amino acid such as L- or D-leucine was examined because enantioenriched leucine (ca. 2% ee) can be obtained by asymmetric photolysis of a racemic amino acid with CPL.[122] In the presence of L- and D-leucine with ca. 2% ee, (*R*)- and (*S*)-**69b** with amplified ee's of 23% and 26% were obtained, respectively. Another α-amino acid, valine, with only ca. 1% ee, can act as a chiral initiator, and hence (*R*)- and (*S*)-**69b** (51% and 47% ee) were also obtained from L- and D-valine, respectively (Scheme 62).[123a] A chiral inorganic crystal such as quartz, which interacts with organic compounds weakly, can also attain a slight asymmetric induction. In asymmetric autocatalysis using dextrorotatory *d*- and levorotatory *l*-quartz as a chiral initiator, (*S*)- and (*R*)-**69c** were respectively obtained with high enantioselectivities (both 97% ee) (Scheme 62).[123b] These results are the first correlation between the

Scheme 62



imbalance induced by CPL or the chirality of the quartz and an organic compound with high ee. Thus, a little nonequivalence of enantiomers caused by statistical fluctuation or chiral physical force can be amplified through asymmetric autocatalysis to the large enantiomeric nonequivalence in molecules found in Nature.

5. References

(1) Pasteur, L. Recherches sur la **Dissymmetrie** Moleculaire des Produits Organiques Naturels. *Proc. R. Soc. London* **1857**, *8*, 254. (However, this title was mistranslated in English to Researches on the Molecular **Asymmetry** of Natural Organic Products.)

(2) Pearson, K. *Nature* **1898**, *58*, 495. Also see: Japp, F. R. *Nature* **1898**, *58*, 452.

(3) (a) Mason, S. F. *Nature* **1984**, *311*, 19. (b) Bonner, W. A. *Top. Stereochem.* **1988**, *18*, 1. (c) Orgel, L. E. *Nature* **1992**, *358*, 203. (d) Avetisov, V.; Goldanskii, V. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 11435. (e) Feringa, B. L.; van Delden, R. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3418. (f) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Chem. Commun.* **2000**, 887. (g) Paul, N.; Joyce, G. P. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 12733.

(4) Brack, A. In *The Chemistry of Life's Origin*: *Chirality and the Origins of Life, Early Proteins*; Greenberg, J. M., Mendoza-Gomez, C. X., Pirronello, V., Eds.; NATO ASI Series 416; Kluwer Academic Publ.: Dordrecht, 1993; pp 345−355, 357−388. Also see: Saghatelian, A.; Yokobayashi, Y.; Ghadiri, M. R. *Nature* **2001**, *409*, 797.

(5) Frank, F. C. *Biochim. Biophys. Acta* **1953**, *11*, 459.

(6) Calvin, M. *Chemical Evolution*; Oxford University Press: Oxford, 1969; pp 149−152.

(7) For examples, see: (a) Seelig, F. F. J. *Theor. Biol.* **1971**, *31*, 355. (b) Seelig, F. F. J. *Theor. Biol.* **1971**, *32*, 93. (c) Decker, P. *J. Mol. Evol.* **1973**, *2*, 137. (d) Decker, P. *J. Mol. Evol.* **1974**, *4*, 49. (e) Decker, P. In *Origins of Optical Activity in Nature*; Walker, D. C., Ed.; Elsevier: Amsterdam, 1979; pp 109−124. (f) Iwamoto, K.; Seno, M. *J. Chem. Phys.* **1979**, *70*, 5851. (g) Iwamoto, K.; Seno, M. *J. Chem. Phys.* **1979**, *70*, 5858. (h) Iwamoto, K.; Seno, M. *J. Chem. Phys.* **1982**, *76*, 2347. (i) Kondepudi, D. K.; Nelson, G. W. *Phys. Rev. Lett.* **1983**, *50*, 1023; *Nature* **1985**, *314*, 438. (j) Goldanskii, V. I.; Kuz'min, V. V. Z. *Phys. Chem. Leipzig* **1988**, *269*, 216. (k) Czege, J.; Fajszi, C. *Origins Life* **1977**, *8*, 271. (l) Fajszi, C.; Czege, J. *Origins Life* **1981**, *11*, 143.

(8) Pasteur, L. *C. R. Acad. Sci.* **1848**, *26*, 535.

(9) (a) Havinga, E. *Chem. Weekbl.* **1941**, *38*, 642. (b) Havinga, E. *Biochim. Biophys. Acta* **1954**, *13*, 171.

(10) (a) Pincock, R. E.; Wilson, K. R. *J. Am. Chem. Soc.* **1971**, *93*, 1291. (b) Pincock, R. E.; Perkins, R. R.; Ma, A. S.; Wilson, K. R. *Science* **1971**, *174*, 1018.

(11) (a) Echardt, C. J.; Peachy, N. M.; Swanson, D. R.; Takacs, J. M.; Khan, M. A.; Gong, X.; Kim, J.-H.; Wang, J.; Uphaus, R. A. *Nature* **1993**, *362*, 614. (b) Viswanathan, R.; Zasadzinski, J. A.; Schwartz, D. K. *Nature* **1994**, *368*, 440. (c) de Feyter, S.; Grim, P. C. M.; Rucker, M.; Vanoppen, P.; Meiners, C.; Sieffert, M.; Valiyaveettil, S.; Mullen, K.; de Schryver, F. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1223. (d) Bohringer, M.; Morgenstern, K.; Schneider, W. D.; Berndt, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 821. (e) Addazi, L.; Berkovitch-Yellin, Z.; Weissbuch, I.; van Mil, J.; Shimon, L. J. W.; Lahav, M.; Leiserowitz, L. *Angew. Chem., Int. Ed.* **1985**, *24*, 466. (f) Ohtani, B.; Shintani, A.; Uosaki, K. *J. Am. Chem. Soc.* **1999**, *121*, 6515. (g) Stevens, F.; Dyer, D. J.; Walba, D. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 900.

(12) (a) Mikami, K.; Yajima, T.; Terada, M.; Suzuki, Y.; Kobayashi, I. *Chem. Commun.* **1997**, 57. (b) Takanishi, Y.; Takezoe, H.; Suzuki, Y.; Kobayashi, I.; Yajima, T.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 8, 2354.

(13) Mason, S. F. *Int. Rev. Phys. Chem.* **1983**, 217.

(14) Kavasmaneck, P. R.; Bonner, W. A. *J. Am. Chem. Soc.* **1977**, *99*, 44.

(15) (a) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C.; Barron, L. D. *Chem. Rev.* **1998**, *98*, 2391. (b) Mason, S. F.; Tranter, G. E. *Chem. Phys. Lett.* **1983**, *94*, 34. (c) Mason, S. F.; Tranter, G. E. *J. Chem. Soc., Chem. Commun.* **1983**, 117.

(16) (a) Buchardt, O. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 179. Rau, H. *Chem. Rev.* **1983**, *83*, 535. (b) Huck, N. P. M.; Jager, W. F.; de Lange, B.; Feringa, B. L. *Science* **1996**, *273*, 1686. (c) Bailey, J. *Origin Life Evol. Biosphere* **2001**, *31*, 167.

(17) (a) Zadel, G.; Eisenbaun, C.; Wolff, G. J.; Breitmaier, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 454. (b) Feringa, B. L.; Kellogg, R. M.; Hulst, R.; Zondervan, C.; Kruizinga, W. H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1458. (c) Kaupp, G.; Marquardt, T. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1459.

(18) Fischer, E. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 3231.

(19) Marckwald, V. *Chem. Ber.* **1904**, *37*, 1368.

(20) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reaction*; Prentice Hall: Englewood Cliffs, NJ, 1971.

(21) (a) Gawley, R. E.; Aube, J. *Principles of Asymmetric Synthesis*; Pergamon: London, 1996. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (c) Brunner, H.; Zettlmeier, W. *Handbook of Enantioselective Catalysis*; VCH: Weiheim, 1993. (d) *Catalytic Asymmetric Synthesis*, 2nd ed; Ojima, I., Ed.; VCH: New York, 2000.

(22) (a) Anastas, P. T.; Heine, L. G.; Williamson, T. C. Green Chemical Syntheses and Processes: Introduction. In *Green Chemical Syntheses and Processes*; Anastas, P. T., Heine, L. G., Williamson, T. C., Eds.; American Chemical Society: Washington, DC, 2000; Chapter 1. (b) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998. (c) Anastas, P. T.; Kirchhoff, M. M. *Acc. Chem. Res.* **2002**, *35*, 686. (d) Anastas, P. T. *Green Chem.* **2003**, *5*, G29.

(23) (a) Wynberg, H. *Chimia* **1989**, *43*, 150. (b) Wynberg, H. *J. Macromol. Sci. Chem.* **1989**, *A26*, 1033. (c) Bolm, C.; Bienewald, F.; Seger, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1657.

(24) (a) Mikami, K.; Terada, M.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Angelaud, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3532. (b) Mikami, K.; Aikawa, K.; Yusa, Y.; Jodry, J. J.; Yamanaka, M. *Synlett* **2002**, 1561. (c) Mikami, K.; Terada, M.; Korenaga, T.; Matsukawa, S. *Acc. Chem. Res.* **2000**, *33*, 391.

(25) (a) Alcock, N. W.; Brown, J. M.; Maddox, P. J. *J. Chem. Soc., Chem. Commun.* **1986**, 1532. (b) Brown, J. M.; Maddox, P. J. *Chirality* **1991**, *3*, 345.

(26) (a) Faller, J. W.; Parr, J. *J. Am. Chem. Soc.* **1993**, *115*, 804. (b) Faller, J. W.; Mazzieri, M. R.; Nguyen, J. T.; Parr, J.; Tokunaga, M. *Pure Appl. Chem.* **1994**, *66*, 1463.

(27) (a) Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 789. (b) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310.

(28) Faller, J. W.; Lavoie, A. R.; Grimmond, B. J. *Organometallics* **2002**, *21*, 1662.

(29) Faller, J. W.; Sams, D. W. I.; Liu, X. *J. Am. Chem. Soc.* **1996**, *118*, 1217.

(30) Faller, J. W.; Liu, X. *Tetrahedron Lett.* **1996**, *37*, 3449.

(31) Faller, J. W.; Tokunaga, M. *Tetrahedron Lett.* **1993**, *34*, 7359.

(32) Mikami, K.; Yusa, Y.; Korenaga, T. *Org. Lett.* **2002**, *4*, 1643.

(33) (a) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613. (b) Mikami, K.; Terada, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; p 1143. (c) Mikami, K. In *Modern Carbonyl Chemistry* Otera, J., Ed.; Wiley VCH: Weinheim, 2000; p 185.

(34) Matsukawa, S.; Mikami, K. *Enantiomer* **1996**, *1*, 69.

(35) Matsukawa, S.; Mikami, K. *Tetrahedron Asymmetry* **1997**, *8*, 815.

(36) Volk, T.; Korenaga, T.; Matsukawa, S.; Terada, M.; Mikami, K. *Chirality* **1998**, *10*, 717.

(37) Reviews: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833. (c) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.

(38) Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823.

(39) Reviews: (a) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (b) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (c) Pu, L. *Chem. Rev.* **1998**, *98*, 2405.

(40) (a) Kaufmann, R. B. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 545. (b) Hattori, K.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 3264. (c) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamamoto, H, *J. Am. Chem. Soc.* **1998**, *120*, 6920.

(41) (a) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310. (b) Bao, J.; Wulff, W. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 3814. (c) Heller, D. P.; Goldberg, D. R.; Wulff, W. D. *J. Am. Chem. Soc.* **1997**, *119*, 10551. (d) Graven, A.; Johannsen, M.; Jorgensen, K. A. *Chem. Commun.* **1996**, 2373.

(42) (a) Reetz, M. T.; Kyung, S. H.; Bolm, C.; Zierke, T. *Chem. Ind. (London)* **1986**, 824. (b) Seebach, D.; Beck, A. K.; Imwinkelried, R.; Roggo, S.; Wonnacott, A. *Helv. Chim. Acta* **1987**, *70*, 954. (c) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940. (d) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.*

1990, *112*, 3949. (e) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255. (f) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Org. Synth.* **1992**, *71*, 14. (g) Ketter, A.; Glahsl, G.; Herrmann, R. *J. Chem. Res. (M)* **1990**, 2118. (h) Mukaiyama, T.; Inubushi, A.; Suda, S.; Hara, R.; Kobayashi, S. *Chem. Lett.* **1990**, 1015. (i) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. (j) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (k) Maruoka, K.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938. (l) Gauthier, D. R., Jr.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363. (m) Weigand, S.; Brückner, R. *Chem. Eur. J.* **1996**, *2*, 1077. (n) Harada, T.; Takeuchi, M.; Hatsuda, M.; Ueda, S.; Oku, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2479. (o) Yu, C.-M.; Choi, H.-S.; Jung, W.-H.; Lee, S.-S. *Tetrahedron Lett.* **1996**, *37*, 7095. (p) Yamago, S.; Furukawa, M.; Azuma, A.; Yoshida, J. *Tetrahedron Lett.* **1998**, *39*, 3783.

(43) (a) Casolari, S.; Cozzi, P. G.; Orioli, P.; Tagliavini, E.; Umani-Ronchi, A. *Chem. Commun.* **1997**, 2123. (b) Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431. (c) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979.

(44) (a) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083. (b) Kobayashi, S. *Synlett* **1994**, 689. (c) Kitajima, H.; Katsuki, T. *Synlett* **1997**, 568. (d) Marko, I. E.; Evans, G. R.; Seres, P.; Chelle, I.; Janousek, Z. *Pure Appl. Chem.* **1996**, *68*, 113. (e) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236 and references therein.

(45) Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **1996**, *7*, 1957.

(46) (a) Kitajima, H.; Ito, K.; Katsuki, T. *Chem. Lett.* **1996**, 343. (b) Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 207. (c) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10. (d) H.; Long, J.; Hu, J.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 4349.

(47) (a) Hu, Q. S.; Huang, W. S.; Vitharana, D.; Zhang, X. F.; Pu, L. *J. Am. Chem. Soc.* **1997**, *119*, 12454. (b) Huang, W. S.; Hu, Q. S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 1364. (c) Hu, Q. S.; Huang, W. S.; Pu, L. *J. Org. Chem.* **1998**, *63*, 2798. (d) Moore, D.; Huang, W.-S.; Xu, M.-H.; Pu, L. *Tetrahedron Lett.* **2002**, *43*, 8831. (e) Xu, M.-H.; Pu, L. *Org. Lett.* **2002**, *4*, 4555. (f) Huang, W. S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222.

(48) (a) Yoshikawa, N.; Kumagai, N.; Masunaga, S.; Moll, G.; Ohshima, T.; Suzuki, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2466. (b) Kumagai, N.; Matsunaga, S.; Yoshikawa, N.; Ohshima, T.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 1539. (c) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2001**, *3*, 4251. (d) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169.

(49) Cozzi, P. G.; Papa, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 4613.

(50) (a) Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 497. (b) Mikami, K.; Ding, K.; Ishii, A.; Tanaka, A.; Sawada, N.; Kudo, K. *Chromatography* **1999**, *20*, 65. (c) Angelaud, L.; Matsumoto, Y.; Korenaga, T.; Kudo, K.; Senda, M.; Mikami, K. *Chirality* **2000**, *12*, 544. (d) Mikami, K.; Angelaud, L.; Ding, K.; Ishii, A.; Tanaka, A.; Sawada, N.; Kudo, K.; Senda, M. *Chem. Eur. J.* **2001**, *7*, 730−737. Also see an excellent introductory review on high-throughput screening (HTS): Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284.

(51) XylBINAP = 2,2′-bis(di-3,5-xylylphosphanyl)-1,1′-binaphthyl: (a) Mashima, K.; Matsumura, Y.; Kusano, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Chem. Soc., Chem. Commun.* **1991**, 609. (b) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K. Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529.

(52) TolBINAP = 2,2′-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl: (a) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629. (b) Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1992**, *71*, 1.

(53) (a) Mangeney, P.; Tejero, T.; Alexakis, A.; Grosjean, F.; Normant, J. *Synthesis* **1988**, 255. (b) Pikul, S.; Corey, E. J. *Org. Synth.* **1992**, *71*, 22.

(54) Reviews: (a) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (b) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

(55) (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2675. (b) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417. (c) Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1996**, *61*, 4872. (d) Ohkuma, T.; Ikehira, H.; Ikariya, T.; Noyori, R. *Synlett* **1997**, 467. (e) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703.

(56) (a) Ohkuma, T.; Doucet, H.; Pham, T.; Mikami, K.; Korenaga, T.; Terada, M.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 1086. (b) Mikami, K.; Korenaga, T.; Matsumoto, Y.; Ueki, M.; Terada, M.; Matsukawa, S. *Pure Appl. Chem.* **2001**, *73*, 255.

(57) The real catalyst has been suggested to be a mono- or dihydride species (X = H or Cl): (a) Abdur-Rashid, K.; Lough, A. J.; Morris, R. H. *Organometallics* **2000**, *19*, 2655. (b) Abdur-Rashid, K.; Lough, A. J.; Morris, R. H. *Organometallics* **2001**, *20*, 1047. (c) Abdur-Rashid, K.; Faatz, M.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7473. (d) Hartmann, R.; Chen, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 3581.

(58) (a) Mikami, K.; Korenaga, T.; Ohkuma, T.; Noyori, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3707. (b) Mikami, K.; Korenaga, T.; Yusa, Y.; Yamanaka, M. *Adv. Synth. Catal.* **2003**, *345*, 246.

(59) (a) Bull, S. D.; Davies, S. G.; Epstein, S. W.; Ouzman, J. V. A. *Chem. Commun.* **1998**, 659. (b) Corminboeuf, O.; Quaranta, L.; Renaud, P.; Liu, M.; Jasperse, C. P.; Sibi, M. P. *Chem. Eur. J.* **2003**, *9*, 28.

(60) (a) Morino, Y. *J. Mol. Struct.* **1985**, *126*, 1. (b) Mizushima, S.-I. *Structure of Molecules and Internal Rotation*; Academic Press: New York, 1954.

(61) Toda, F.; Tanaka, K.; Kuroda, R. *Chem. Commun.* **1997**, 1227.

(62) Kuhn, R. In *Molecular Asymmetrie In Stereochemie*; Freuberg, H., Ed.; Franz, Deutike: Leipzig-Wien, 1933; p 803.

(63) Ueki, M.; Matsumoto, Y.; Jodry, J. J.; Mikami, K. *Synlett* **2001**, 1889.

(64) (a) Mikami, K.; Matsukawa, S.; Volk, T.; Terada, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2768. (b) Chavarot, M.; Byrne, J. J.; Chavant, P. Y.; Pardillos-Guindet, J.; Vallee, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 3889. (c) Bolm, C.; Beckman, O. *Chirality* **2000**, *12*, 523.

(65) BIPHEP = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl; this ligand was also named BPBP, but in contrast to what was claimed in the publication, it was unsuccessfully synthesized to give instead the monophosphine derivative: (a) Uehara, A.; Bailar, J. C., Jr. *J. Organomet. Chem.* **1982**, *239*, 1. (b) Bennett, M. A.; Bhargava, S. K.; Griffiths, K. D.; Robertson, G. B. *Angew. Chem., Int. Ed.* **1987**, *26*, 260. (c) Desponds, O.; Schlosser, M. *J. Organomet. Chem.* **1996**, *507*, 257. (d) Desponds, O.; Schlosser, M. *Tetrahedron Lett.* **1996**, *37*, 47. (e) Mikami, K.; Aikawa, K.; Korenaga, T. *Org. Lett.* **2001**, *3*, 243.

(66) Mikami, K.; Korenaga, T.; Terada, M.; Ohkuma, T.; Pham, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1999**, *38*, 495.

(67) Korenaga, T.; Aikawa, K.; Terada, M.; Kawauchi, S.; Mikami, K. *Adv. Synth. Catal.* **2001**, *343*, 284.

(68) Mikami, K.; Aikawa, K.; Yusa, Y. *Org. Lett.* **2002**, *4*, 95.

(69) Mikami, K.; Aikawa, K.; Yusa, Y.; Hatano, M. *Org. Lett.* **2002**, *4*, 91.

(70) (a) Tudor, M. D.; Becker, J. J.; White, P. S.; Gagné, M. R. *Organometallics* **2000**, *19*, 4367. (b) Becker, J. J.; White, P. S.; Gagné, M. R. *J. Am. Chem. Soc.* **2001**, *123*, 9478.

(71) Yamanaka, M.; Mikami, K. *Organometallics* **2002**, *21*, 5847.

(72) Desponds, O.; Schlosser, M. *Tetrahedron Lett.* **1996**, *37*, 47.

(73) Epimerization of (*R*)-$RuCl_2$(XylBIPHEP)/(*S*,*S*)-DPEN to (*S*)-$RuCl_2$(XylBIPHEP)/(*S*,*S*)-DPEN was very slow at room temperature in CD_2Cl_2, but accelerated in 2-propanol to give 3:1 ratio of diastereomeric complexes within 2−3 h.

(74) (a) Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618. (b) Rousel, C.; Liden, A.; Chanon, M.; Metzger, J.; Sandstrom, J. *J. Am. Chem. Soc.* **1976**, *98*, 2847. (c) Nilsson, B.; Martinson, P.; Olsson, K.; Carter, R. E. *J. Am. Chem. Soc.* **1974**, *96*, 3190.

(75) (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (c) Ooi, T.; Takeuchi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7640.

(76) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551.

(77) Vial, L.; Lacour, J. *Org. Lett.* **2002**, *4*, 3939.

(78) Reviews: (a) Okamoto, Y.; Nakano, T. *Chem. Rev.* **1994**, *94*, 349. (b) Brintzinger, H. H.; Fischer, D.; Mulhaupt, R.; Rieger, B.; Waymouth, R. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1143. (c) Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262. (d) Mikami, K.; Terada, M.; Osawa, A. *Kobunshi/High Polymers Jpn.* **1997**, *46*, 72.

(79) Ringwald, M.; Stürmer, R.; Brintzinger, H. H. *J. Am. Chem. Soc.* **1999**, *121*, 1524.

(80) Muñiz, K.; Bolm, C. *Chem. Eur. J.* **2000**, *6*, 2309.

(81) (a) Reetz, M. T.; Neugebeauer, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 179. (b) Blackmond, D. G.; Rosner, T.; Neugebauer, T.; Reetz, M. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2196.

(82) (a) Luo, Z.; Liu, Q.; Gong, L.; Cui, X.; Mi, A.; Jiang, Y. *Chem. Commun.* **2002**, 914. (b) Luo, Z.; Liu, Q.; Gong, L.; Cui, X.; Mi, A.; Jiang, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4532.

(83) (a) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 2897. (b) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2001**, *42*, 8737.

(84) (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vires, A. H. M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2620. (b) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.

(85) (a) Alexakis, A.; Frutos, J.; Mangeney, F. *Tetrahedron: Asymmetry* **1993**, *12*, 2427. (b) Alexakis, A.; Rosset, S.; Allamand, J.; March, S.; Guillen, F.; Benhaim, C. *Synlett* **2001**, 1375.
(86) (a) Togni, A., Hayashi, T., Eds. *Ferrocenes*; VCH: Weinheim, 1995. (b) Hayashi, T.; Ohno, A.; Lu, S.; Matsumoto, Y.; Fukuyo, E.; Yanagi, K. *J. Am. Chem. Soc.* **1994**, *116*, 4421. (c) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377.
(87) Mikami, K.; Aikawa, K. *Org. Lett.* **2002**, *4*, 99.
(88) Configuration of the dppf chirality is denoted by using the descriptors of chirality chirality: (*P*), plus, clockwise, and (*M*), minus, counterclockwise.
(89) (a) Hashihayata, T.; Ito, Y.; Katsuki, T. *Synlett* **1996**, 1079. (b) Hashihayata, T.; Ito, Y.; Katsuki, T. *Tetrahedron* **1997**, *53*, 9541.
(90) An excellent review has just been reported on achiral additives as a poison to kill an undesired catalyst species and/or to deoligomerize less active catalysts: Vogl, E. M.; Groger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 1570.
(91) (a) Balsells, J.; Walsh, P. J. *J. Am. Chem. Soc.* **2000**, *122*, 1802.
(92) Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423.
(93) Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 2161.
(94) Costa, A. M.; Jimeno, C.; Gavenonis, J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336.
(95) Reviews: (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2923. (b) Avalos, M.; Babiano, R.; Cintas, P.; Jimenez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1997**, *8*, 2997. (c) Kagan, H. B.; Girard, C.; Guillaneux, D.; Rainford, D.; Samuel, O.; Zhang, S. Y.; Zhao, S. H. *Acta Chem. Scand.* **1996**, *50*, 345. (d) Bolm C. In *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Blackie Academic and Professional: New York, 1996; pp 9−26. (e) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49.
(96) (a) Guillaneux, D.; Zhao, S. H.; Samuel, O.; Rainford, D.; Kagan, H. B. *J. Am. Chem. Soc.* **1994**, *116*, 9430. (b) Puchot, C.; Samuel, O.; Duñach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353.
(97) (a) Terada, M.; Mikami, K.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1623. (b) Mikami, K.; Terada, M. *Tetrahedron* **1992**, *48*, 5671. (c) Terada, M.; Mikami, K. *J. Chem. Soc., Chem. Commun.* **1994**, 833. (d) Mikami, K.; Motoyama, Y.; Terada, M. *Inorg. Chim. Acta* **1994**, *222*, 71.
(98) (a) Blackmond, D. G. *J. Am. Chem. Soc.* **1997**, *119*, 12934. (b) Blackmond, D. G. *J. Am. Chem. Soc.* **1998**, *120*, 13349. (c) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402.
(99) Hoang, L.; Bahmanyar, S.; Houk, K. N.; List, B. *J. Am. Chem. Soc.* **2003**, *125*, 16.
(100) Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113. Also see: Katsuki, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
(101) However, "chirality amplification" has been already used in describing chiroptical methods: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 1057−1059.
(102) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877.
(103) (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (b) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832. (c) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327. (d) Kitamura, M.; Yamakawa, M.; Oka, H.; Suga, S.; Noyori, R. *Chem. Eur. J.* **1996**, *2*, 1173. (e) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800. (f) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605.
(104) Bolm, C.; Schlingloff, G.; Harms, K. *Chem. Ber.* **1992**, *125*, 1191.
(105) Bolm, C.; Muńiz, K.; Hildebrand, J. P. *Org. Lett.* **1999**, *1*, 491.
(106) (a) Bolm, C. *Tetrahedron: Asymmetry* **1991**, *2*, 701. (b) Bolm, C.; Felder, M.; Muller, J. *Synlett* **1992**, 439. (c) Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205.
(107) de Vries, A. H. M.; Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron* **1994**, *50*, 4479.
(108) Diels−Alder reaction: (a) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (b) Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798. Aldol reaction: (c) Evans, D. A.; Murry, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 5814. (d) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893. (e) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686. Hetero-Diels−Alder reaction: (f) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3372. (g) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895. Ene reaction: (h) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824. Michael reaction: (i) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994.
(109) (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669. (b) Evans, D. A.; Lectka, T.; Miller, S. J. *Tetrahedron Lett.* **1993**, *34*, 7027.
(110) Kanemasa, S.; Oderaotoshi, Y.; Sakaguchi, S.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Am. Chem. Soc.* **1998**, *120*, 3074.
(111) Iwasawa, N.; Hayashi, Y.; Sakurai, H.; Narasaka, K. *Chem. Lett.* **1989**, 1581.
(112) Mikami, K.; Motoyama, Y.; Terada, M. *J. Am. Chem. Soc.* **1994**, *116*, 2812.
(113) (a) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543. (b) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363.
(114) Linear relationship as a probe for stereodeterming step: (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321. (b) Schwenkreis, T.; Berkessel, A.; *Tetrahedron Lett.* **1993**, *34*, 4785. (c) Giardello, M. A.; Conticello, V. P.; Bard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241. (d) Bolm, C.; Bienewald, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2640. (e) Ramon, D. J.; Guillena, G.; Seebach, D. *Helv. Chim. Acta* **1996**, *79*, 875. (f) Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520. (g) Denmark, S. E.; Christenson, B. L.; O'Connor, S. P. *Tetrahedron Lett.* **1995**, *36*, 2219. (h) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444. (i) Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233. (j) Guo, C.; Qiu, J.; Zhang, X.; Verdugo, D.; Larter, M. L.; Christie, R.; Kenney, P.; Walsh, P. J. *Tetrahedron* **1997**, *53*, 4145. (k) Ramon, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651. (l) Pritchett, S.; Woodmansee, D. H.; Gantzel, P.; Walsh, P. J. *J. Am. Chem. Soc.* **1998**, *120*, 6423. (m) Ford, A.; Woodward, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 335. (n) Simonsen, K. B.; Bayon, P.; Hazell, R. G.; Gothelf, K. V.; Jorgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845. (o) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879.
(115) (a) Hansen, K. B.; Leighton, J. L.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 10924. (b) Konsler, R. G.; Karl, J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 10780.
(116) Denmark, S. E.; Su, X.; Nishigaichi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 12990.
(117) (a) Alberts, A. H.; Wynberg, H. *J. Am. Chem. Soc.* **1989**, *111*, 7265. (b) Alberts, A. H.; Wynberg, H. *J. Chem. Soc. Chem. Commun.* **1990**, 453.
(118) (a) Danda, H.; Nishikawa, H.; Otaka, K. *J. Org. Chem.* **1991**, *56*, 6740. (b) Shvo, Y.; Gal, M.; Becker, Y.; Elgavi, A. *Tetrahedron: Asymmetry* **1996**, *7*, 911.
(119) Reviews: (a) Soai, K.; Shibata, T. In *Catalytic Asymmetric Synthesis*, 2nd ed; Ojima, I., Ed.; VCH: New York, 2000; p 699. (b) Soai, K.; Shibata, T.; Sato, I. *Acc. Chem. Res.* **2000**, *33*, 387. (c) Soai, K.; Sato, I. *Chirality* **2002**, *14*, 548.
(120) (a) Soai, K.; Niwa, S.; Hori, H. *J. Chem. Soc., Chem. Commun.* **1990**, 982. (b) Shibata, T.; Morioka, H.; Hayase, T.; Choji, K.; Soai, K. *J. Am. Chem. Soc.* **1996**, *118*, 471. (c) Shibata, T.; Yonekubo, S.; Soai, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 659. (d) Soai, K.; Shibata, T.; Morioka, H.; Choji, K. *Nature* **1995**, *378*, 767. (e) Sato, I.; Urabe, H.; Ishiguro, S.; Shibata, T.; Soai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 315.
(121) (a) Blackmond, D. G.; McMillan, C. R.; Ramdeehul, S.; Schorm, A. Brown, J. M. *J. Am. Chem. Soc.* **2001**, *123*, 10103. (b) Blackmond, D. G. *Adv. Synth. Catal.* **2002**, *344*, 156. More recently, Blackmond proposed a tetrameric transition state consisting of two molecules of the zinc alkoxide and two molecules of R_2Zn coordinated with pyrimidyl aldehyde. In sharp contrast to usual cases of asymmetric amplification involving a dissociated or remaining monomer, this autocatalytic case showed no stability difference between homo- and hetero-chiral dimers but the relative inactivity of hetero-chiral dimer: Buono, F.; Blackmond, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 8978.
(122) Flores, J. J.; Bonner, W. A.; Massey, G. A. *J. Am. Chem. Soc.* **1977**, *99*, 3622.
(123) (a) Shibata, T.; Yamamoto, J.; Matsumoto, N.; Yonekubo, S.; Osanai, S.; Soai, K. *J. Am. Chem. Soc.* **1998**, *120*, 12157. (b) Soai, K.; Osanai, S.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Sato, I. *J. Am. Chem. Soc.* **1999**, *121*, 11235.

CR000260Z