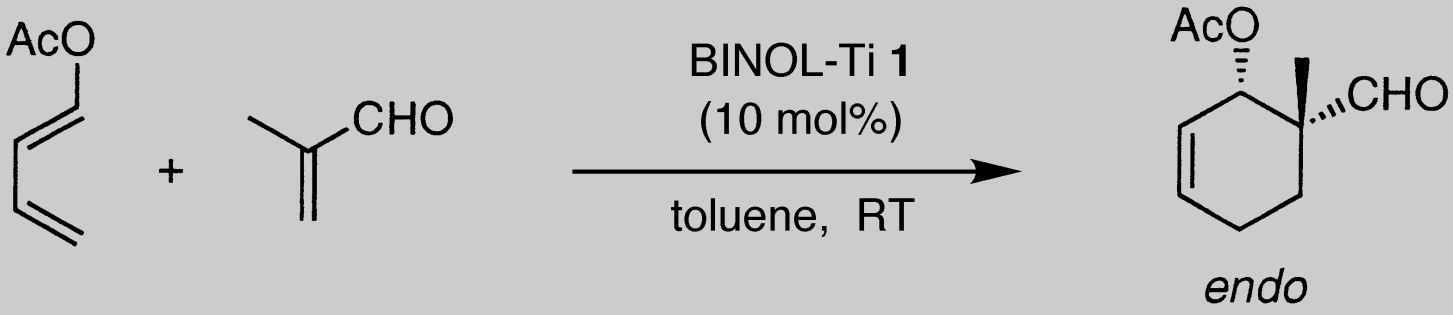
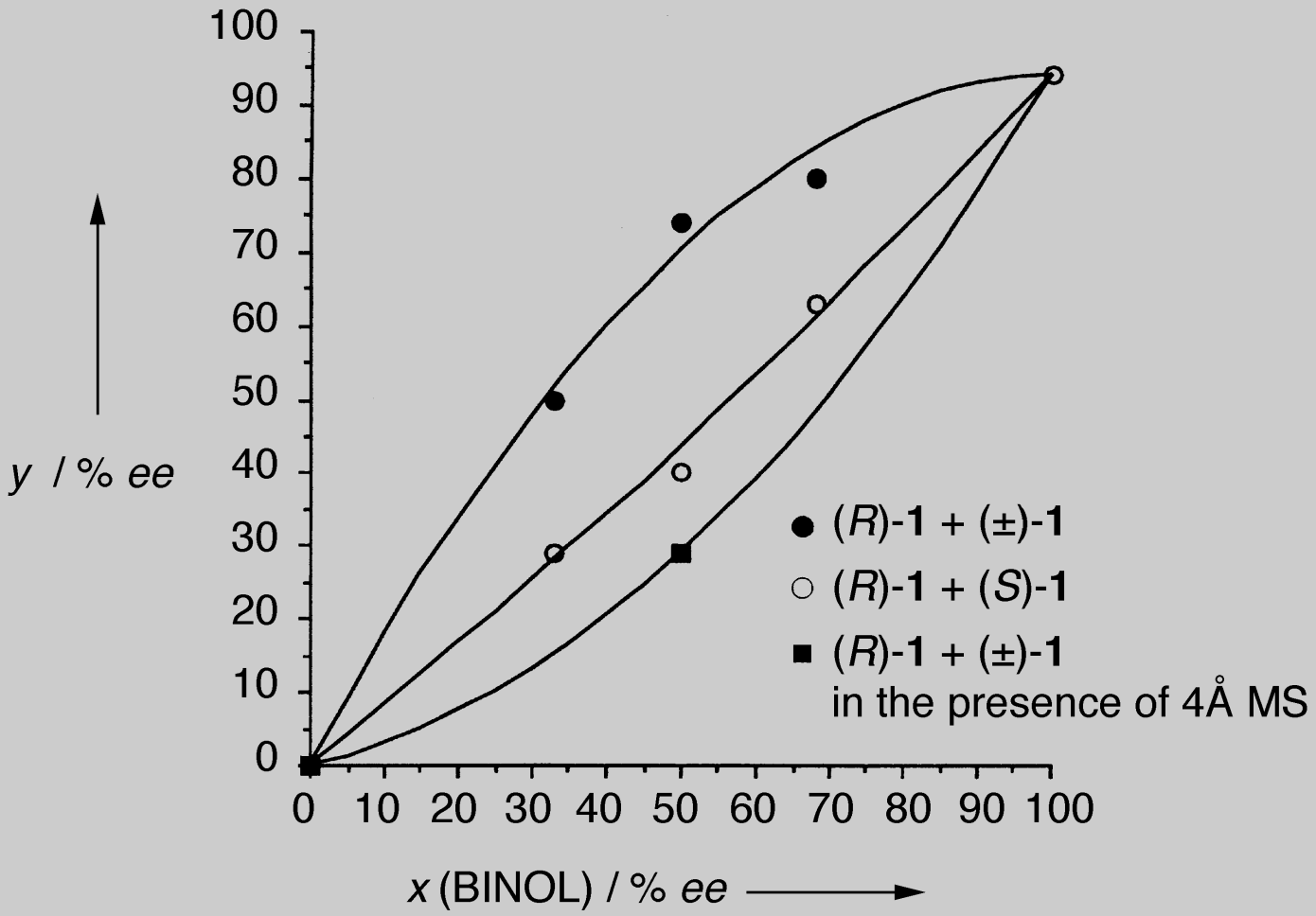
Positive and negative nonlinear effects, as well as linear relationships, between the *ee* values of catalyst components and products can be observed by varying the method of catalyst preparation.





Asymmetric Activation

Koichi Mikami,* Masahiro Terada, Toshinobu Korenaga, Yousuke Matsumoto, Makoto Ueki, and Rémy Angelaud

While nonracemic catalysts can generate nonracemic products with or without the nonlinear relationship in enantiomeric excesses between catalysts and products, racemic catalysts inherently give only a racemic mixture of chiral products. Asymmetric catalysts, either in nonracemic or racemic form, can be further evolved into highly activated catalysts with association of chiral activators. This asymmetric activation process is particularly useful in racemic catalysis through selective activation of one enantiomer of the racemic catalyst. Recently, a strategy whereby a racemic catalyst is selectively deactivated by a chiral additive has been reported to yield nonracemic products. However, reported herein is an alternative and conceptually opposite strategy in which a chiral activator selectively activates, rather than deactivates, one enantiomer of a racemic chiral catalyst. The advantage of this activation strategy over the deactivation counterpart is that the activated catalyst can produce a greater enantiomeric excess in the products—even with the use of a catalytic amount of activator relative to chiral catalyst—than that attained by the enantiomerically pure catalyst on its own. Therefore, asymmetric activation could provide a general and powerful strategy for not only the use of atropisomeric, racemic ligands but also chirally flexible and proatropisomeric ligands without enantiomeric resolution!

Keywords: asymmetric catalysis · chiral poisoning · high-throughput screening · nonlinear effects

1. Introduction

Asymmetric catalysis of organic reactions which provide enantiomerically enriched products is of central importance in modern synthetic and pharmaceutical chemistry.[1] Particularly, enantioselective catalysis is one of the most efficient processes in terms of chirality economy and environmental benignity. This technique affords a high proportion of the enantioenriched product and a small amount of waste material by taking advantage of a chiral catalyst. Therefore, the development of enantioselective catalysts is one of the most challenging and formidable endeavors in modern science and technology. Highly promising candidates for such enantioselective catalysts are metal complexes bearing chiral and nonracemic organic ligands, often in enantiopure form.

In the preparation of homogeneous asymmetric catalysts, Sharpless and co-workers emphasized the significance of "ligand-accelerated catalysis"[2] through the construction of an asymmetric catalyst from an achiral precatalyst by ligand exchange with a chiral ligand L* (Figure 1a). In heterogeneous asymmetric catalysis, the term "chiral modification"[3] is coined instead for the process of modifying an achiral heterogeneous catalyst, particularly on a surface, with a chiral modifier, called the chiral ligand in homogeneous systems (Figure 1a). However, in some cases the modifier is reported to interact preferentially with a substrate (Figure 1b)[4] rather than the achiral heterogeneous catalyst surface (Figure 1c).[5]

The chiral homo- or heterogeneous catalysts prepared through chiral-ligand acceleration or chiral modification can be further evolved into highly activated catalysts through addition of chiral activators (Figure 1a). The term "asymmetric activation" may be proposed for this process, in close analogy to the activation process of an achiral reagent or catalyst to provide an activated but achiral one, for example an activated zinc reagent.[6] This asymmetric activation process is particularly useful through selective activation of one enantiomer of a racemic catalyst (Scheme 1, Part 2).

While nonracemic catalysts thus developed can generate nonracemic products with or without the nonlinear relationship in enantiomeric excesses between catalysts and products,[7] racemic catalysts inherently give only a racemic mixture of chiral products. Recently, a strategy relying on one enantiomer of a racemic catalyst, whereby a chiral molecule selectively deactivates a racemic catalyst, has been

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reported to yield nonracemic products (Scheme 1, Part 1). However, the level of asymmetric induction does not exceed that attained by enantiopure catalysts, wherein selective complexation and deactivation with a chiral poison is indispensable (Scheme 1, Part 1a and 1b).[8,9] We have reported an alternative but conceptually opposite strategy to asymmetric catalysts in which a chiral activator selectively activates one enantiomer of a racemic catalyst (Scheme 1, Part 2).[10] The advantage of this activation strategy over the deactivation counterpart is that the activated catalyst can produce a greater enantiomeric excess (X_{act} % *ee*) in the products, even with catalytic use of the activator, than the enantiomerically pure catalyst on its own (X % *ee*). A chiral activator may selectively complex and activate one enantiomer of a racemic catalyst, to attain an enantioselectivity higher than that achieved with enantiopure catalysts (% $ee_{act} \gg$ % *ee*), in addition to a higher level of catalytic efficiency ($k_{act} \gg k$; Scheme 1, Part 2a). Asymmetric activation can also be established even by nonpreferential complexation, to give activated diastereomeric catalysts (Scheme 1, Part 2b), based on the turnover

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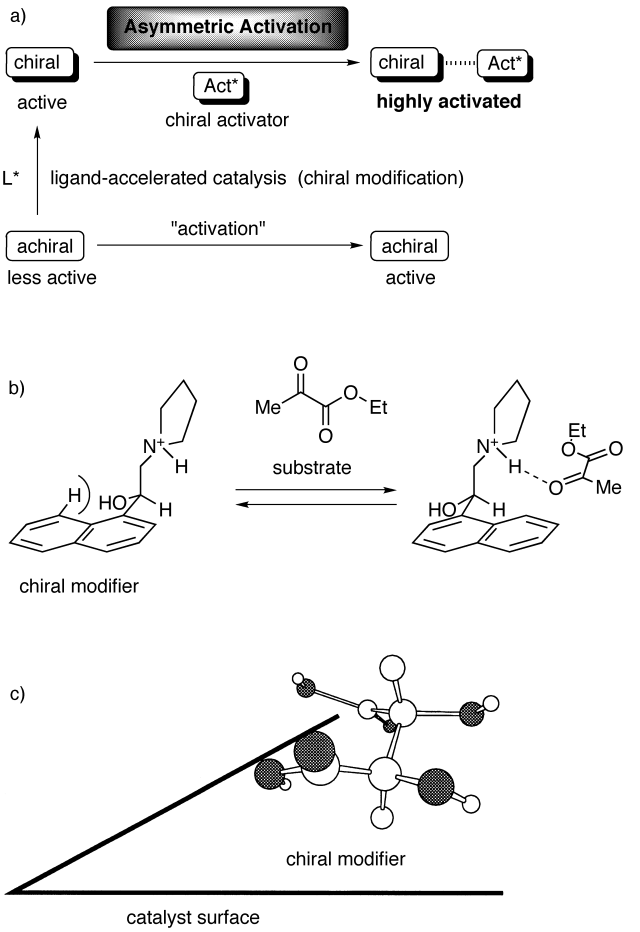
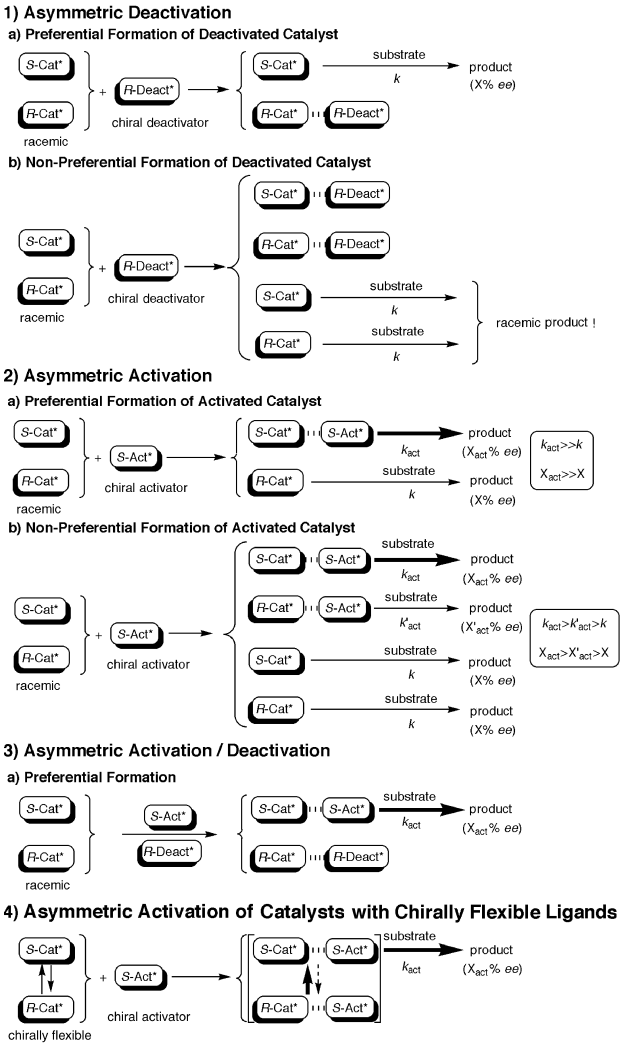


Figure 1. a) The principle of asymmetric activation. b), c) Interaction between a chiral modifier and a substrate or catalyst surface.

frequencies (catalytic activities) between the diastereomers ($k_{act} > k'_{act}$), which depend on substrates.[11] Furthermore, an asymmetric activation/deactivation protocol can achieve higher enantioselectivity regardless of the substrates (Scheme 1, Part 3), by maximizing the difference in catalytic activity between enantiomeric catalysts. The positive nonlinear effect ((+)-NLE) or asymmetric amplification (see below) is an important phenomenon in asymmetric catalytic process, in which very high enantioselectivity of the product can be achieved even if a low enantiopurity chiral ligand is employed in the catalyst. Therefore, an enantiomerically pure ligand is not necessarily utilized for getting a high level of enantioselectivity. Even so, one has to perform a partial resolution of the racemic catalysts. Asymmetric catalysis can be carried out with racemic catalysts through in-situ and partial activation (/deactivation) of the racemic catalysts by adding easily prepared enantiopure additives (Scheme 1, Part 4).

2. Positive Nonlinear Effect of Nonracemic Catalysts

A chiral catalyst is not necessarily prepared from an enantiopure ligand because deviation from the linear relationship between the enantiomeric purity of chiral catalysts and



Scheme 1. Asymmetric activation and deactivation..

the optical yields of the products, namely the nonlinear effect (NLE), is sometimes observed (Figure 2).[7, 12–14, 16, 17, 19–29] The convex deviation, which Kagan and co-workers[12] and Mikami and co-workers[13] independently referred to as positive nonlinear effect (abbreviated as (+)-NLE), has attracted attention and a higher level of asymmetric induction than the enantiopurity of the nonracemic (partially resolved) catalysts has now been achieved.[14]

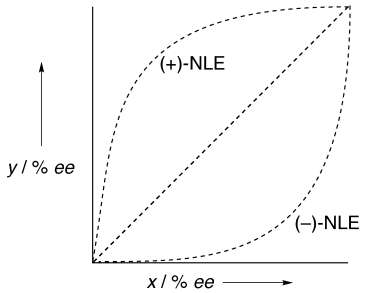
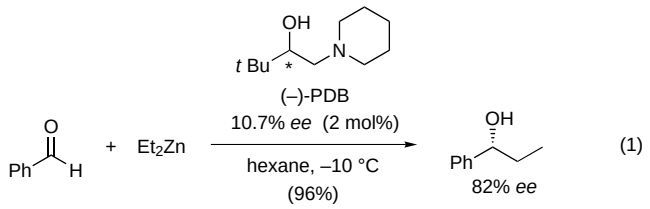


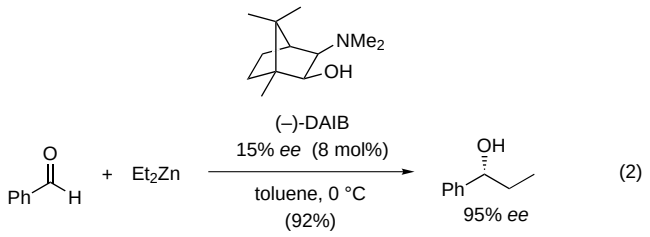
Figure 2. Possible relationships ((+)-NLE, linear, and (−)-NLE) between the enantiomeric purity of chiral ligands (x) and the optical yield of products (y).

Oguni et al. independently coined the term asymmetric amplification[15] for (+)-NLE in an asymmetric carbonyl addition reaction of dialkylzinc reagents catalyzed by chiral amino alcohols, such as 1-piperidino-3,3-dimethyl-2-butanol (PDB) [Eq. (1)].[16] In the same asymmetric carbonyl addition



(1)

reaction, Noyori and co-workers reported the use of a highly efficient amino alcohol catalyst, (2*S*)-3-*exo*-(dimethylamino)-isoborneol (DAIB) [Eq. (2)].[17] They reported a beautiful



(2)

mechanistic investigation on the asymmetric amplification in view of the stability of the heterochiral dimer of the zinc amino alcohol compared to the homochiral dimer (Figure 3). We also reported a positive nonlinear effect in a carbonyl-ene reaction[18] with glyoxylate catalyzed by a binaphthol (BINOL) derived chiral titanium complex [Eq. (3)].[13] Bolm reported (+)-NLE in the 1,4-addition reaction of diethylzinc with catalysis by a nickel complex and a pyridyl alcohol [Eq. (4)].[19]

Significant levels of (+)-NLE are also observed in the asymmetric catalysis by cationic complexes bearing *trans*-chelating tridentate ligands. Kanemasa et al. reported an aqua complex that exhibited a remarkable (+)-NLE; it was prepared from $Ni(ClO_4)_2 \cdot 6H_2O$ with 4,6-dibenzofurandiyl-2,2′-bis(4-phenyloxazoline) (DBFOX/Ph) as a tridentate ligand (Scheme 2 top).[20] Two mechanisms were involved in the (+)-NLE: the irreversible formation of heterochiral [(*R*,*R*),(*S*,*S*)] 2:1 ligand:metal complexes and the heterochiral oligomerization of 1:1 ligand:metal complexes with the help of water bridging (Scheme 2 below).

Evans studied the asymmetric catalysis of carbon–carbon bond forming reactions with C_2-symmetric bisoxazoline–Cu^{II} complexes.[21, 22] In an asymmetric aldol reaction catalyzed by a bis(oxazolinyl)pyridine (PYBOX)–Cu complex [Eq. (5)],[22] the (+)-NLE observed was explained as a result of the relative stabilities of the heterochiral [(*S*,*S*),(*R*,*R*)] and homochiral [(*S*,*S*),(*S*,*S*)] 2:1 ligand–metal complexes.

Negative nonlinear effect (abbreviated as (–)-NLE)[12, 13] stands, in turn, for the opposite phenomenon of concave deviation (Figure 2).[14l,m,n,z,ad,ag,ah, 23] The partially resolved catalyst provides the product in lower enantiomeric excess than calculated by linearity. In a conjugate addition reaction

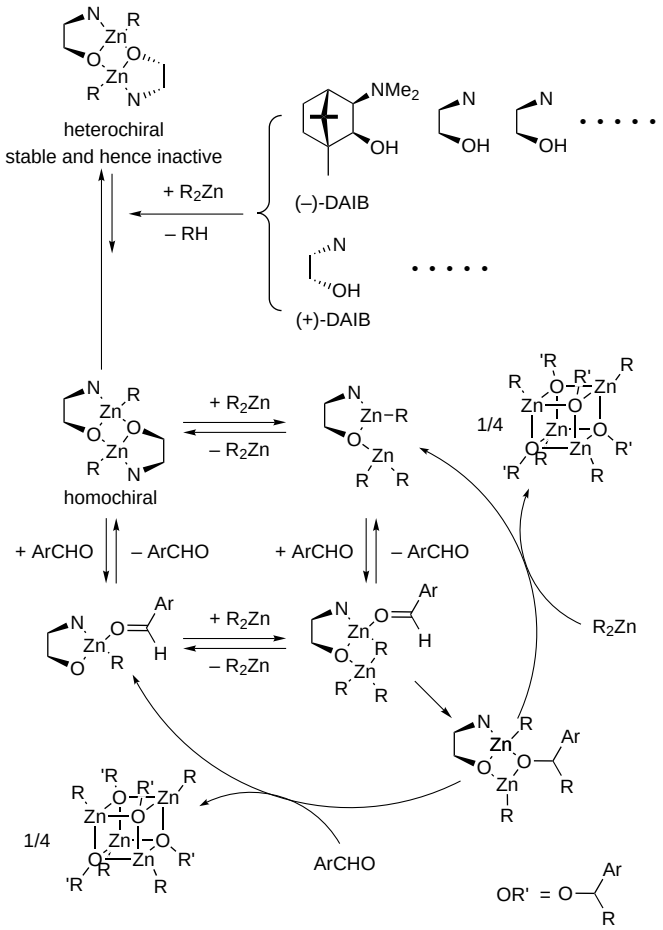
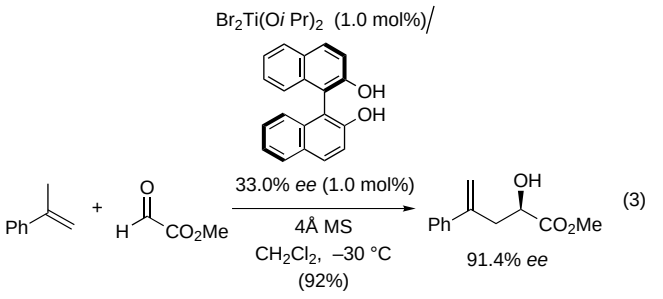


Figure 3. Mechanism of asymmetric amplification shown by Noyori et al.



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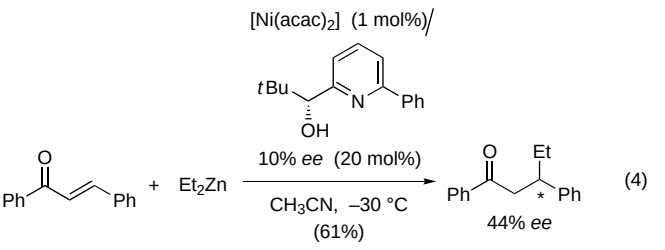
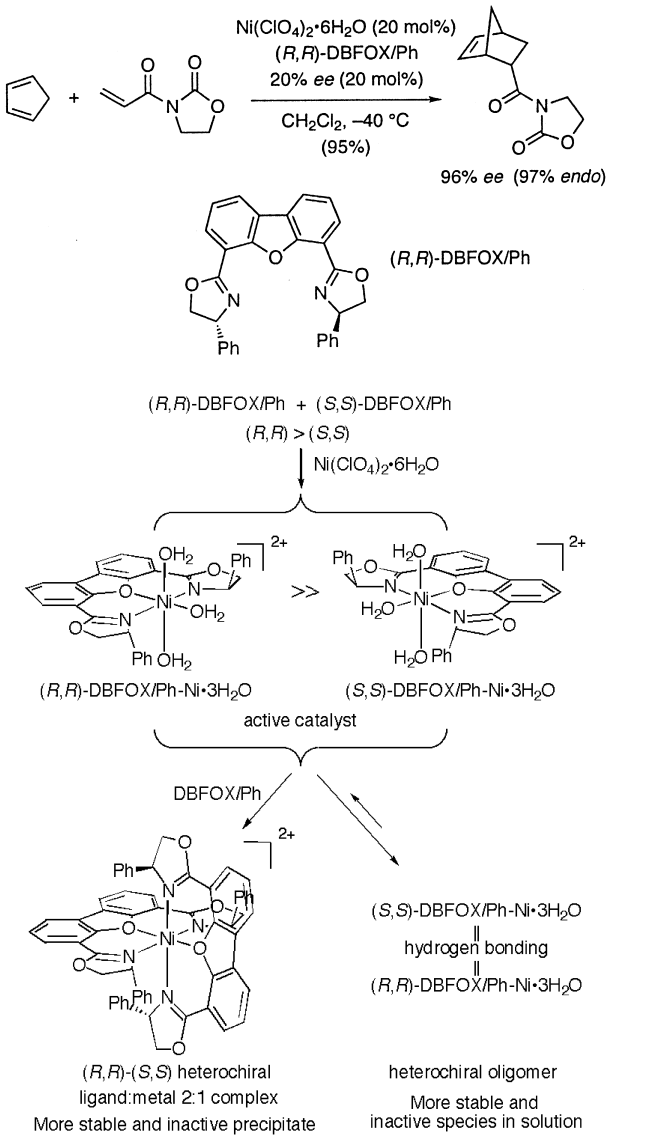
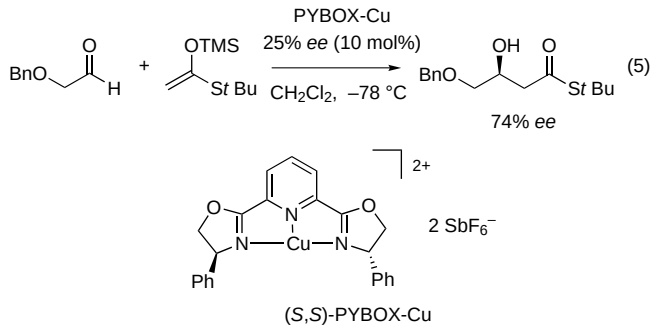


(4)

with an organocopper reagent, an interesting shape of NLE was found. The (+)-NLE was observed with a more enantiopure chiral ligand, whilst a less enantiopure ligand led to (–)-NLE (Scheme 3).[24] Kagan and co-workers suggested a tetrameric complex was the reactive species, by simulation of a mathematical model system of four chiral ligands.[12a] We

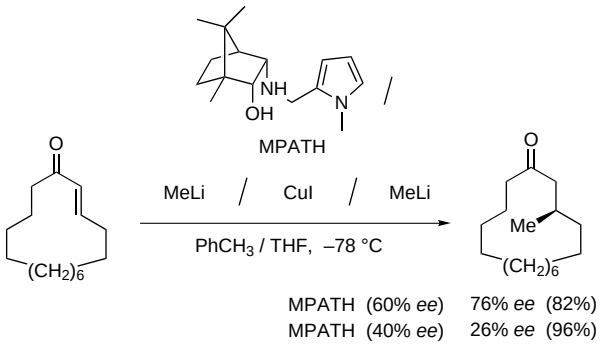


Scheme 2. Above: An asymmetric Diels–Alder reaction catalyzed by a DBFOX/Ph–Ni complex. Below: Mechanisms for the observed (+)-NLE.



could also reproduce the intriguing shape of the nonlinear curve on the basis of Kagan's equation for a tetrameric catalyst species (Figure 4).

Significantly, the mode of preparation of a catalyst sometimes determines not only the presence of a nonlinear effect (NLE) but also the direction (positive or negative) thereof.[14l, af, ag, 23, 25, 26] The BINOL–Ti catalyst **1** is prepared from partially resolved BINOL and $Cl_2Ti(OiPr)_2$ in the presence of



Scheme 3. Influence of ligand enantiopurity on the NLE during conjugated addition with organocopper compounds. The reagents were added in the following quantities: 367 mol% MPATH, 734 mol% MeLi, and 183 mol% CuI.

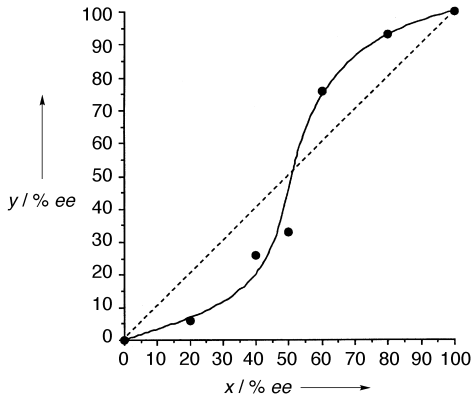


Figure 4. Relationship between the *ee* values of the ligand (x) and the product (y) for the reaction shown in Scheme 3. The complete line was calculated according to the method of Kagan and the experimental data are shown as points. The dotted line shows the expected result for a linear relationship.

4 Å molecular sieves, which are filtered off prior to the reaction;[25] when this catalyst is utilized in the asymmetric Diels–Alder reaction shown in Figure 5, a (+)-NLE is observed (Table 1, entry 1). The combined use of enantiopure (*R*)-**1** and racemic (±)-**1** catalysts in a ratio of 1:1 results in a

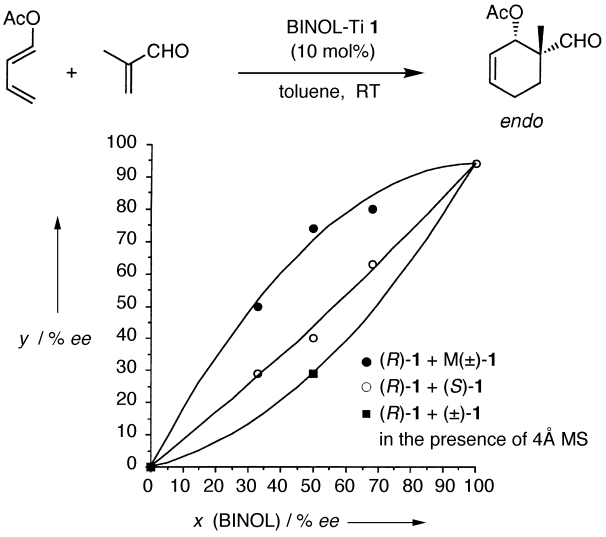


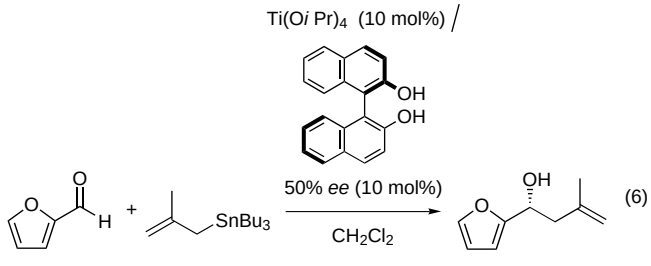
Figure 5. The graph shows the relationship of the NLE to the catalyst system for the asymmetric Diels–Alder reaction shown at the top. $y = ee$ value of the product.

Table 1. Dependence of the NLE on the catalyst system used for the asymmetric Diels–Alder reaction shown in Figure 5.

Entry	Preparation of the catalyst system	*ee* [%] of the catalyst system	Yield [%]	*endo* [%]	*ee* [%]
1	partially resolved BINOL (52% *ee*) and $Cl_2Ti(OiPr)_2$	52	41	98	76
2	(*R*)-**1**+(±)-**1** (1:1)	50	50	99	74
3	(*R*)-**1**+(*S*)-**1** (3:1)	50	62	99	40
4	(*R*)-**1**+(*S*)-**1** (3:1)+4 Å molecular sieves (removed prior to the reaction)	50	67	99	60
5	(*R*)-**1**+(±)-**1** (1:1)+4 Å molecular sieves	50	62	95	29
6	only 4 Å molecular sieves	–	20	–	–
7	(*R*)-**1**+(*S*)-**1** (3:1) in CH_2Cl_2	50	52	99	53

similar (+)-NLE (entry 2). By contrast, mixing enantiopure BINOL–Ti catalysts, (*R*)- and (*S*)-**1** in a ratio of 3:1 leads to a linearity (entry 3; no NLE!). However, when (*R*)- and (*S*)-**1** catalysts are mixed in the same ratio of 3:1, but in the presence of molecular sieves, which are then filtered off prior to the reaction, a (+)-NLE was observed (entry 4). Moreover, in dichloromethane, the combined use of (*R*)- and (*S*)-**1** catalysts (3:1), even without prior treatment with molecular sieves, exhibits a (+)-NLE (entry 7). These experimental results can be explained by the fact that the complex consists of oligomers, which do not interconvert in the absence of molecular sieves in toluene but do interconvert in dichloromethane (compare entries 3, 4, and 7). When the reaction is carried out in the presence of molecular sieves, however, a (−)-NLE is observed (entry 5), because the sieves act as an achiral catalyst for the Diels–Alder reaction (entry 6).

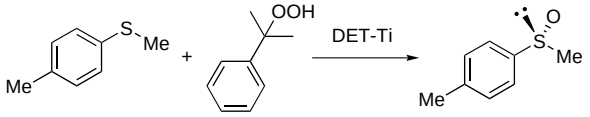
Keck et al. reported that BINOL-derived titanium catalysts prepared in the presence or absence of 4 Å molecular sieves showed a (+)-NLE or a linearity, respectively [Eq. (6)].[26] In the presence of 4 Å sieves, the enantiopurity of the allylated product exceeded that of the BINOL used.



BINOL : $Ti(OiPr)_4$ = 1 : 1 / 4Å MS ; reflux for 1 h 88% *ee* (99%)
BINOL : $Ti(OiPr)_4$ = 1 : 1 ; 23 °C, 1 h 50% *ee* (56%)

Kagan et al. pointed out the NLE as an indicator for distinction of closely related chiral catalysts (Scheme 4).[23] In the asymmetric oxidation of sulfides with hydroperoxides promoted by chiral diethyl tartrate (DET)–Ti complexes, a wide diversity of titanium species was observed by minor modifications in the catalyst preparation step. Stoichiometric use of a 1:4 mixture of $Ti(OiPr)_4$ and DET exhibited a (−)-NLE. Addition of *i*PrOH to this mixture (1:4:4 mixture of $Ti(OiPr)_4$, DET, and *i*PrOH) provided a (+)-NLE, while catalytic use of this ternary system led to the disappearance of the NLE.

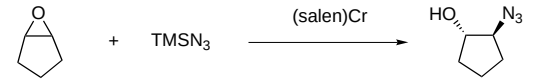
The study of the NLE in asymmetric catalysis can be useful for getting mechanistic insight and information about the



	DET % *ee*		
$Ti(OiPr)_4$: (*R*,*R*)-DET = 1:4 (100 mol%)	50% *ee*	26% *ee*	(–)-NLE
	100% *ee*	82% *ee*	
$Ti(OiPr)_4$: (*R*,*R*)-DET : *i*PrOH = 1:4:4 (100 mol%)	50% *ee*	74% *ee*	(+)-NLE
	100% *ee*	90% *ee*	
$Ti(OiPr)_4$: (*R*,*R*)-DET : *i*PrOH = 1:4:4 (10 mol%)	50% *ee*	39% *ee*	linear dependence
	100% *ee*	89% *ee*	

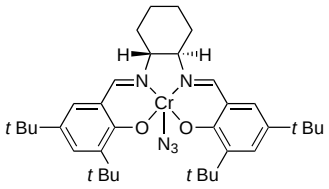
Scheme 4. (+)-NLE, (−)-NLE, and linear relationships can be obtained by variation of the catalyst preparation.

active species involved in the catalytic cycle, and their behavior in solution.[27] Jacobsen and co-workers used the NLE as a mechanistic probe for the asymmetric ring opening of epoxides with trimethylsilyl azide catalyzed by a chiral Cr(salen)-type complex (Scheme 5).[28] The observation of

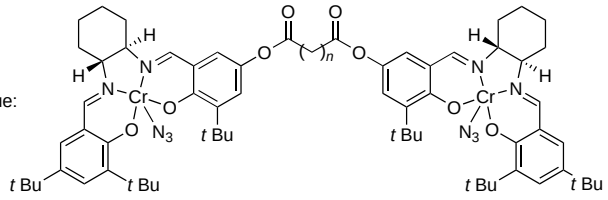


monomeric complex (1 mol%, 24 h, 100%) 93% *ee*
dimeric analogue (*n* = 5) (0.05 mol%, 24 h, 100%) 93% *ee*

monomeric complex:



dimeric analogue:

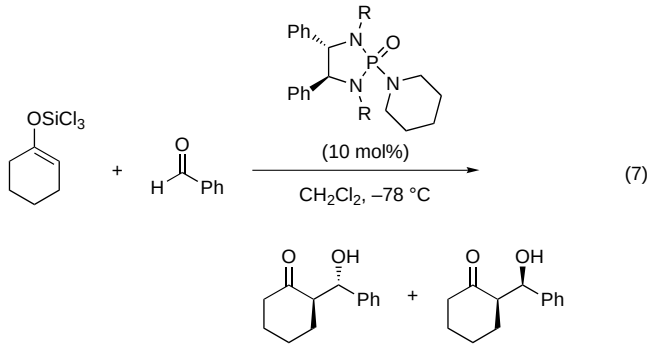


Scheme 5. The NLE as a mechanistic technique.

significant (+)-NLE coupled with a second-order kinetic dependence on the Cr(salen) catalyst led to a mechanistic proposal for simultaneous activation of both the epoxide and the azide by two different Cr(salen) complexes. On the basis of this cooperative mechanism they designed dimeric analogues of the Cr(salen) complex. Covalent linkage of the Cr(salen) complex unit with a suitable tether length and

position resulted in catalysts between one and two orders of magnitude more reactive than the monomeric analogues without any loss of enantioselectivity (Scheme 5).

On the basis of NLE studies coupled with kinetic analyses, Denmark et al. disclosed that the mechanism of rate acceleration by chiral phosphoramides in asymmetric aldol reactions of trichlorosilyl enolates with aldehydes stemmed from the ionization of the enolate by the phosphoramides [Eq. 7].[29] Sterically demanding phosphoramides (R = Ph),



(7)

which exhibit a linear relationship, bind to the enolate in a 1:1 fashion. The resulting pentacoordinated cationic siliconate favors a boatlike transition state. In contrast, sterically less demanding phosphoramides (R = Me) with a (+)-NLE can bind in a 2:1 fashion. The resulting hexacoordinated cationic siliconate favors a chairlike arrangement.

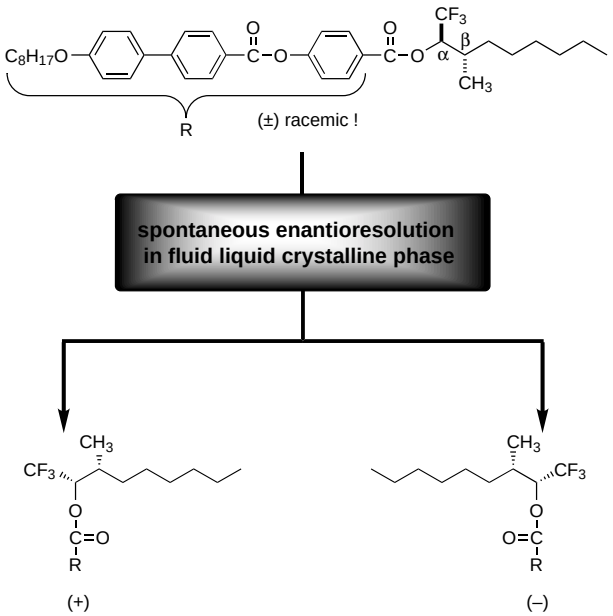
Recently Blackmond demonstrated[30] a detailed analysis of the experimental reaction rate in these nonlinear catalytic systems; this analysis can give an independent confirmation of the mathematical models developed by Kagan and co-workers.[12a] Consideration of the kinetic behavior of nonlinear catalytic reactions can provide valuable mechanistic insights into the NLE by comparison of the predictions of the models.

3. Autocatalysis

Another aspect of NLE is asymmetric autocatalysis as an event following symmetry breaking in nature. On the origin of chirality in nature, two major mechanisms have been proposed:[31] 1) A chance mechanism to generate an optically active molecule followed by self-replication; 2) a determining mechanism to favor one enantiomer. Some physicochemical elements are determining factors which provide a nonequivalence of enantiomers. Nonconservation of the parity of weak interactions may lead to small differences in energy between two enantiomeric forms.[32] A solid chiral adsorbent, such as quartz, can be another factor.[33, 34] Circular polarized light[35] and geophysical fields, such as the rotation of the earth and magnetic fields,[36] have long been proposed as determining factors.

Pasteur showed an autocatalytic crystallization process ("spontaneous enantioresolution") from a racemic mixture of the double salt sodium ammonium tartrate to give a conglomerate of one enantiomer.[37] Later, Havinga reported dynamic crystallization of one enantiomer from an interconverting mixture of antipodes[38] under two "bistable" states.[39] A racemic chiral compound can crystallize in three different forms: As a racemic compound, a pseudoracemate (solid solution), or, preferably, as a conglomerate.[40] In the crystallization of a pseudoracemate, preferential enrichment[41] of one enantiomer may occur in the mother liquid. However, spontaneous enantioresolution to give a conglomerate is rather difficult in fluid systems, such as liquid crystals, due to thermal fluctuations and/or molecular diffusion. Indeed, no one has succeeded in observing the same phenomenon in a fluid phase rather than in a static crystalline phase or on a surface; a monolayer film on a mica plate has shown two-dimensional conglomeration.[42] A similar two-dimensional conglomerate has been observed from a racemic liquid-crystalline molecule, however, on a crystalline graphite surface, rather than in a fluid smectic phase.[43] We have reported spontaneous enantioresolution (Scheme 6) of racemic CF_3-containing liquid crystalline molecules with large spontaneous polarization (P_s) into a three-dimensional conglomerate, which exhibits an electrooptic response.[44] This success is the result of accurate discrimination between the enantiomers of the racemate through the double stereogenic part of the molecule, even in the fluid condensed matter!

The nonequivalence of enantiomers through the spontaneous breaking of mirror symmetry in nature is amplified with asymmetric autocatalytic reactions[45] (Frank's spontaneous asymmetric synthesis;[46, 47] see Figure 6). Alberts and Wynberg reported an enantioselective autoinduction in which a chiral lithium alkoxide product might be involved with the reactant to increase the enantioselectivity [Eq. (8)].[48] The enantiomeric excess of the product, however, did not exceed the *ee* value of the catalyst. In the asymmetric hydrocyanation catalyzed by cyclic dipeptides, the *S*-cyanohydrin product made a complex with the cyclic peptide which increased the enantioselectivity in the *S*-cyanohydrin product in the course of the reaction up to 95.8 % *ee* (Scheme 7).[49] In the presence of an achiral amine, (*R*)-1-phenylpropan-1-ol catalyzed the carbonyl-addition reaction of diethylzinc to benzaldehyde, with the product showing a lower *ee* value than that of the catalyst employed.[50]



Scheme 6. Spontaneous enantioresolution in the fluid liquid crystalline phase.

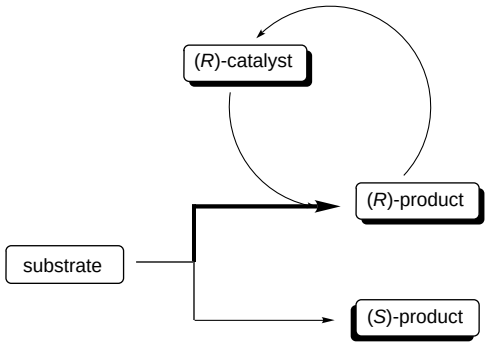
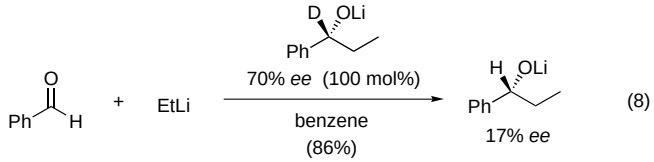
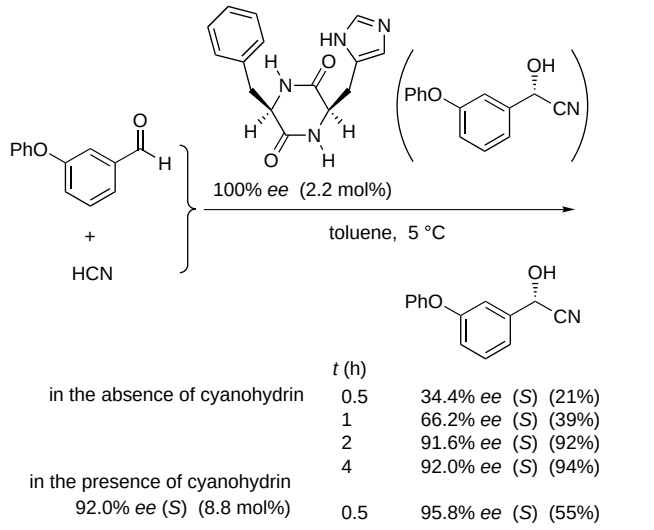


Figure 6. Spontaneous asymmetric synthesis.



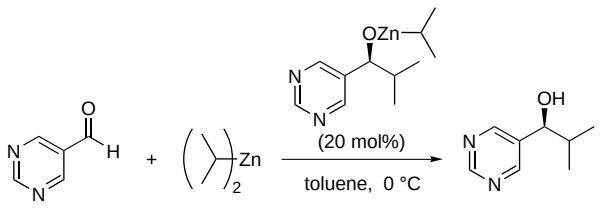
(8)



	t (h)	
in the absence of cyanohydrin	0.5	34.4% *ee* (*S*) (21%)
	1	66.2% *ee* (*S*) (39%)
	2	91.6% *ee* (*S*) (92%)
	4	92.0% *ee* (*S*) (94%)
in the presence of cyanohydrin 92.0% *ee* (*S*) (8.8 mol%)	0.5	95.8% *ee* (*S*) (55%)

Scheme 7. Autocatalysis in the asymmetric hydrocyanation catalysed by cyclic dipeptides.

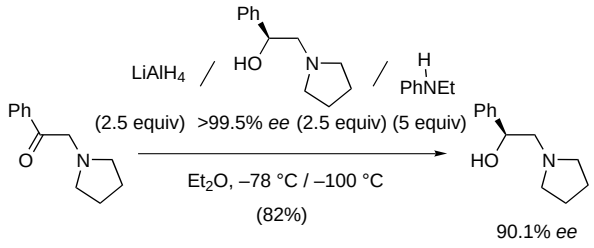
Soai et al. have reported the remarkable example of asymmetric autocatalysis in carbonyl-addition reactions of diisopropylzinc.[51–56] Usually, zinc alkoxide forms an inactive tetramer. However, the use of pyridyl aldehyde as a substrate, to give a pyridyl alcohol product, can loop the catalytic cycle without formation of the inactive tetramer.[51] In this autocatalytic system the *ee* value of the product does not exceed the level of the catalyst *ee* value,[52] while the use of a chiral quinolyl alcohol as the catalyst, instead of the pyridyl counterpart, gives the product without any loss of enantiopurity.[53a] A (+)-NLE is also observed when the quinolyl alcohol is used as the catalyst.[53b] A significant improvement of (+)-NLE is achieved, however, by Soai in a similar carbonyl-addition reaction to pyrimidylcarbaldehyde.[54] Starting from the *S* alcohol in 2% *ee* (20 mol%), the first reaction provides the *S* alcohol in 10% *ee* and after the fourth reaction the value is 88% *ee* (by way of 57 and 81% *ee*, Scheme 8).[54a] Soai and co-workers have also investigated an enantioselective autoinduction in the reduction of α-amino



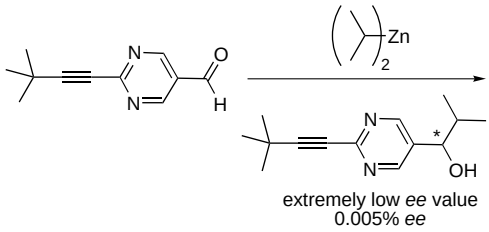
	catalyst	mixture of catalyst and product	product
1st	2% *ee*	10% *ee* (46%)	16% *ee* (26%)
2nd	10% *ee*	57% *ee* (75%)	74% *ee* (55%)
3rd	57% *ee*	81% *ee* (80%)	89% *ee* (60%)
4th	81% *ee*	88% *ee* (75%)	90% *ee* (55%)
5th	88% *ee*	88% *ee* (79%)	88% *ee* (59%)

Scheme 8. Autocatalysis in the addition of diisopropylzinc to pyrimidinylcarbaldehyde.

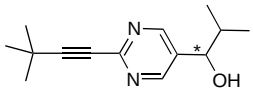
ketones with lithium aluminum hydride modified with a chiral 1,2-amino alcohol and an achiral amine [Eq. (9)].[55] Recently, they demonstrated amplification of a quite small nonequivalence of enantiomers on the basis of asymmetric autocatalysis [Eq. (10)].[56] Thus, a small nonequivalence of enantiomers



(9)



(10)



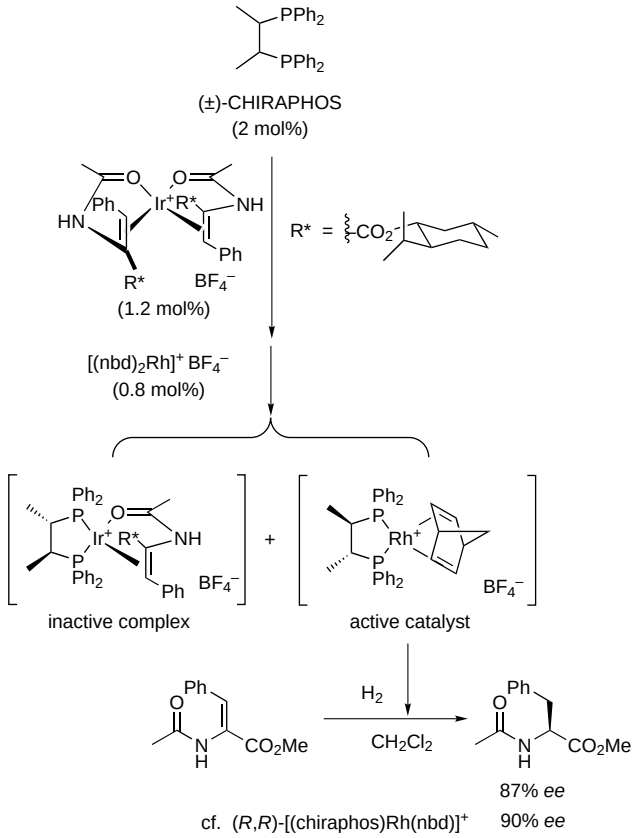
extremely high *ee* value
>99.5% *ee*

caused by symmetry breaking can be amplified through asymmetric autocatalysis to a large enantiomeric nonequivalence in molecules, as found in nature.

4. Asymmetric Deactivation of Racemic Catalysts

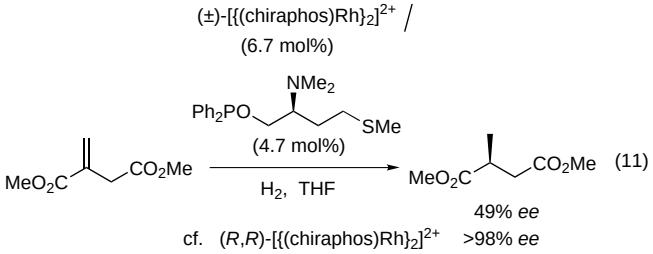
Whilst nonracemic catalysts can generate nonracemic products, with or without the NLE or asymmetric autocatalysis, racemic catalysts (0% *ee*) inherently produce only racemic (0% *ee*) products. A strategy whereby a racemic catalyst is enantioselectively deactivated by a chiral molecule

acting as a catalyst poison has recently been shown to yield nonracemic products (Scheme 1, Part 1 a).[8] A unique resolution of racemic CHIRAPHOS has been attained with a chiral iridium complex to give a deactivated form, which leads to a chiral rhodium complex in association with the remaining enantiomer of CHIRAPHOS.[8a] This process eventually results in a nonracemic hydrogenation product (Scheme 9).

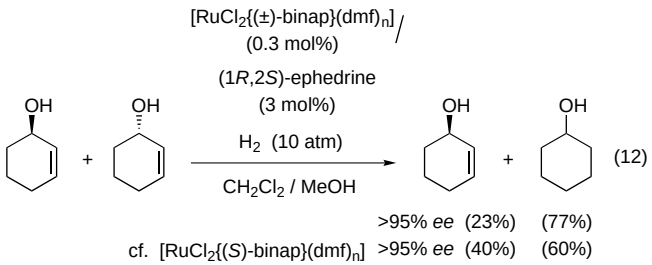


Scheme 9. Asymmetric deactivation by a chiral iridium complex.

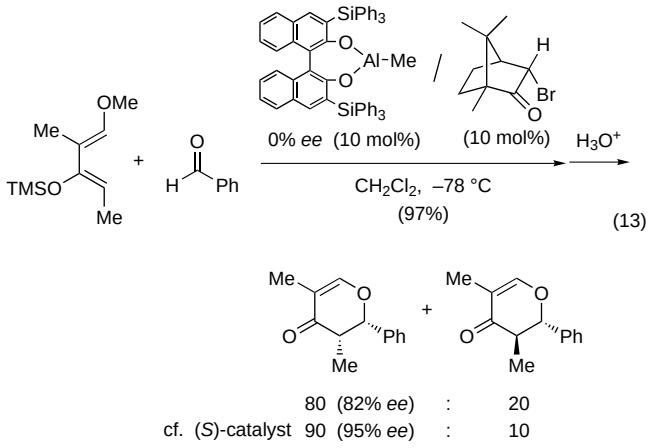
More recently, chiral poisoning,[9, 57] in such a deactivating strategy, has been named as a factor in the context of hydrogenation by asymmetric catalysis with a similar CHIRAPHOS – Rh complex [Eq. (11)].[9a,b] A chiral amino alcohol,



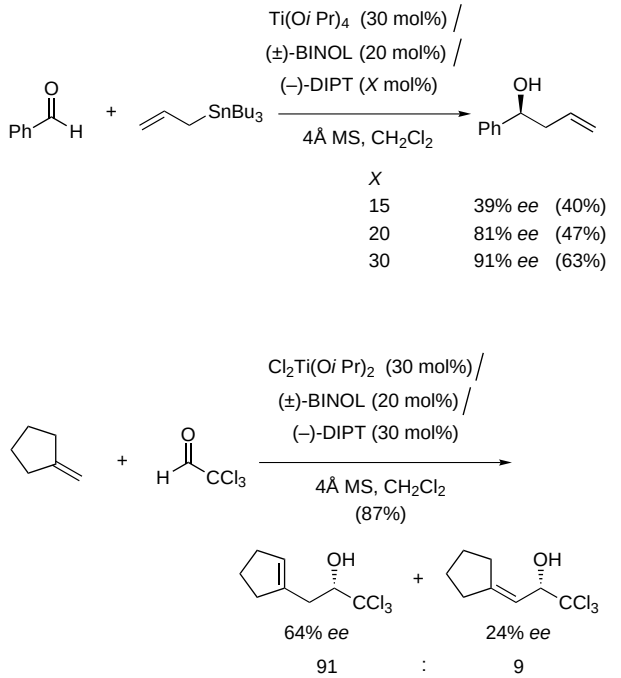
(1*R*,2*S*)-ephedrine, is also employable as a poison in the kinetic resolution of cyclic allylic alcohols using racemic BINAP [Eq. (12)].[9b,c] However, the level of asymmetric induction does not exceed the level attained by the enantiopure catalyst (see Scheme 1, Part 1 a). A racemic aluminum reagent has been discriminated using chiral unreactive



ketones to yield hetero Diels – Alder products in a reaction catalyzed by the remaining enantiomer of the aluminum reagent [Eq. (13)].[8c]



Enantiomerically pure diisopropoxytitanium tartrate (DIPT) can also be used as a poison for racemic binaphthol – titanium complexes (Scheme 10).[9d,e] The *ee* value of the product increases with an increase in the amount of DIPT employed.



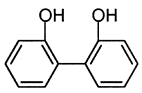
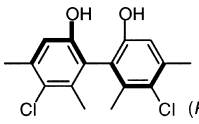
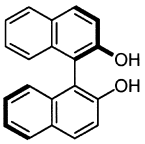
Scheme 10. DIPT as a poison for racemic binaphthol – titanium complexes.

5. Asymmetric Activation of Racemic Catalysts

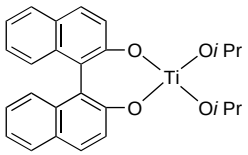
We have reported an alternative but conceptually opposite strategy to asymmetric catalysis by racemic catalysts: a chiral activator selectively activates one enantiomer of a racemic catalyst. A higher level of catalytic efficiency by more than two order of magnitude ($k_{act} > k \times 10^2$), in addition to a higher enantioselectivity, than that achieved by an enantiopure catalyst might be attained (X_{act} % *ee* > *X* % *ee*; Scheme 1, Part 2).

The ene reaction is one of the simplest methods for C–C bond formation; it converts readily available olefins, with C–H bond activation at an allylic site and allylic transposition of the C=C bond, into more functionalized products. The ene reaction encompasses a vast number of variants in terms of the enophile used.[18b, 58] Amongst these, the ene reactions of carbonyl enophiles, aldehydes in particular, which we refer to as carbonyl-ene reactions,[18] should in principle constitute a more efficient alternative to the carbonyl-addition reaction of allylmetals for stereocontrol.[59] Catalysis of carbonyl-ene reactions with racemic BINOLato–Ti(O*i*Pr)$_2$ (**2**) achieves extremely high enantioselectivity by adding another enantiopure diol for the enantioselective activation [Eq. (14)] (Table 2).[10b] Significantly, a remarkably high enantioselectivity (89.8 % *ee*, *R* isomer) was achieved adding (*R*)-BINOL activator to the racemic (±)-BINOLato–Ti(O*i*Pr)$_2$ complex (**2**).

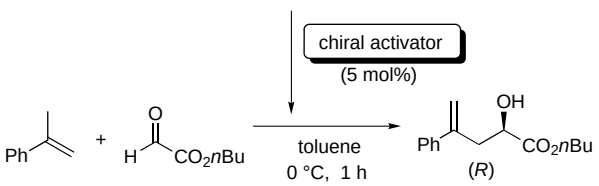
Table 2. Enantioselective activation of racemic (±)-**2** [Eq. (14)].

Entry	Chiral activator	Yield [%]	*ee* [%]
1	–	5.9	0
2		20	0
3		38	80.8
4		52	89.8
5[a]	(*R*)	35	80.0

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



(±)-BINOLato-Ti(O*i* Pr)$_2$ **2**
(10 mol%)



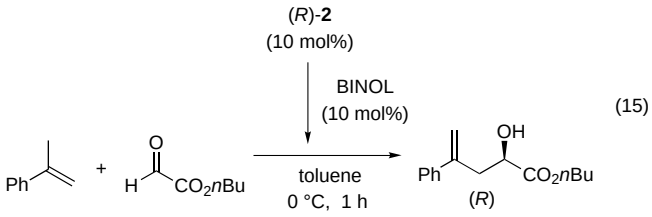
(14)

The activation of the enantiopure (*R*)-**2** catalyst can also be synthetically useful, by further addition of (*R*)-BINOL [Eq. (15)] (Table 3). The reaction proceeded quite smoothly to provide the carbonyl-ene product in higher chemical yield (82.1 %) and enantioselectivity than without additional BINOL (entries 2 and 1, respectively). Comparing the results of enantioselective activation of the racemic catalyst (Table 2, entry 4) with those of the enantiopure catalyst with or without activator (entries 2 and 1), the reaction catalyzed by the (*R*)-BINOLato–Ti(O*i*Pr)$_2$/(*R*)-BINOL complex (R/R_{Act})-**2′** was calculated to be 26.3 times faster than that catalyzed by the (*S*)-**2** in the racemic case (Scheme 11 a). Indeed, kinetic studies showed that the reaction catalyzed by the (*R*)-**2**/(*R*)-BINOL complex (R/R_{Act})-**2′** was 25.6 times ($= k_{act}/k$) faster than that catalyzed by (*R*)-**2**. These results imply that the racemic (±)-(**2**) and half-molar amount of (*R*)-BINOL assemble preferentially into the (R/R_{Act})-**2′** and the (*S*)-**2** remains unchanged. In contrast, the enantiomeric form of the additional chiral ligand ((*S*)-BINOL) activates the (*R*)-**2** to a smaller degree, which provides the carbonyl-ene product in lower optical and chemical yields than (*R*)-BINOL does (Table 3, entry 3).

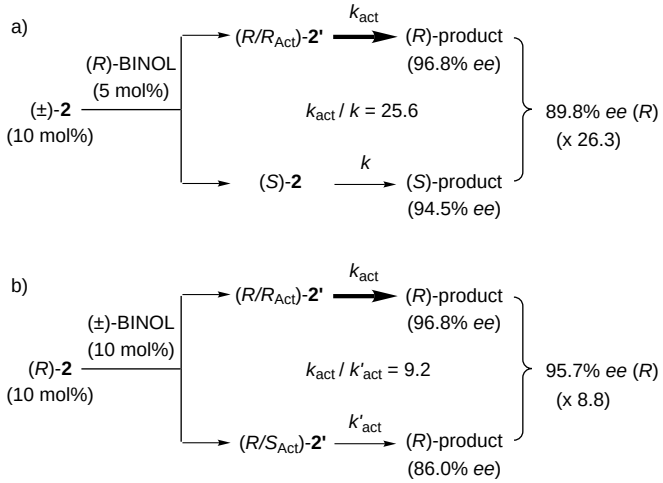
Another possibility was explored using racemic BINOL as an activator. Racemic BINOL was added to (*R*)-**2**, giving higher yield and enantioselectivity than that obtained without

Table 3. Asymmetric activation of enantiopure (*R*)-**2** [Eq. (15)].

Entry	BINOL	Yield [%]	*ee* [%]
1	–	19.8	94.5
2	*R*	82.1	96.8
3	*S*	48.0	86.0
4	±	69.2	95.7



(15)



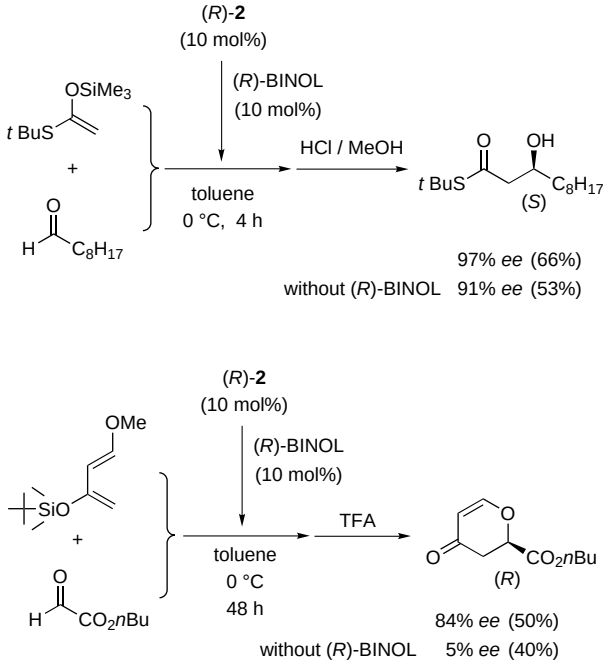
Scheme 11. Kinetic features of the asymmetric activation of BINOLato-Ti(O*i*Pr)$_2$.

additional BINOL (compare entries 4 and 1 in Table 3). Comparison of the results from the racemic activator with those of enantiopure catalysts (R/R_{Act})-**2′** or (R/S_{Act})-**2′** (entry 4 compared with entries 2 and 3) shows that the reaction catalyzed by the (R/R_{Act})-**2′** complex is 8.8 times faster than that catalyzed by (R/S_{Act})-**2′** (Scheme 11 b). Kinetic studies also showed the reaction catalyzed by (R/R_{Act})-**2′** to be 9.2 ($=k_{act}/k'_{act}$) times faster than that catalyzed by (R/S_{Act})-**2′**.

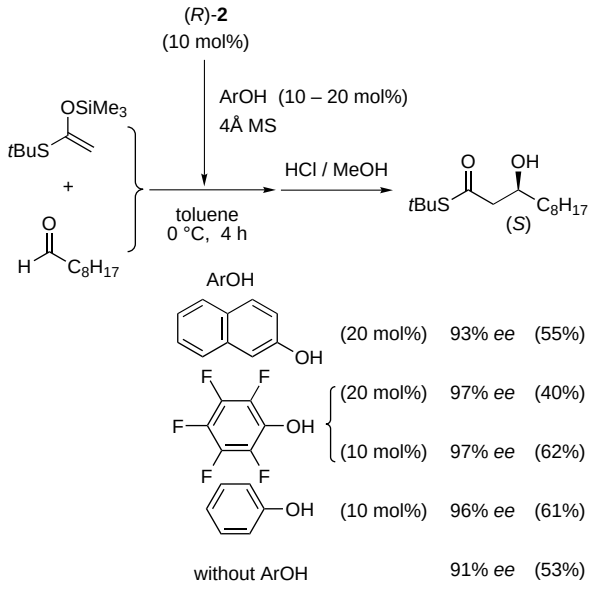
The great advantage of asymmetric activation with the racemic complex **2** is highlighted in a catalytic version (Table 2, entry 5). High enantioselectivity (80.0% *ee*) is obtained by adding less than the stoichiometric amount (0.25 mol% based on (±)-**2**) of additional (*R*)-BINOL. A similar phenomenon of enantioselective activation has been observed in aldol[10a] and hetero Diels–Alder reactions,[10c] catalyzed not only by a racemic but also by an enantiomerically pure BINOLato–Ti(O*i*Pr)$_2$ catalyst **2** (Scheme 12). Asymmetric activation of (R)-**2** by (*R*)-BINOL is essential to provide higher levels of enantioselectivity than those attained by the enantiopure catalyst **2** (84 instead of 5% *ee*) in the hetero Diels–Alder reaction of glyoxylates with the Danishefsky diene (Scheme 12 bottom).

Activation of **2** by phenolic alcohols as achiral rather than chiral activators[10a, b] is also effective for providing higher levels of enantioselectivity than those attained by the parent enantiopure catalyst **2** in the Mukaiyama aldol reaction of silyl enol ethers (Scheme 13).[60]

Catalytic asymmetric hydrogenation has been shown to be one of the most efficient processes for the asymmetric functional group transformation of organic molecules. Noyori and co-workers have reported a remarkable example of enantioselective catalysis by the enantiopure [$RuCl_2$(binap)(dmf)$_n$] complex **3c** together with an enantiopure diamine and KOH to provide hydrogenation products of

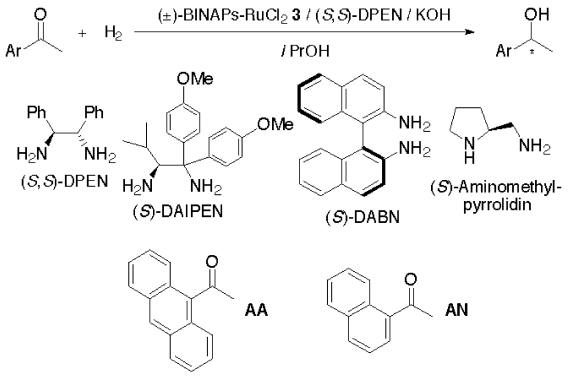


Scheme 12. Enantioselective activation of aldol and hetero Diels–Alder reactions.



Scheme 13. Enantioselectivity in the Mukaiyama aldol reaction of silylenolethers is improved by achiral activation.

carbonyl compounds with high enantioselectivity.[11] We examined a variety of amines for asymmetric activation of a racemic BINAPs-$RuCl_2$ catalyst (**3**) for the enantioselective catalysis of the carbonyl hydrogenation (Scheme 14).[61] The hydrogenation was performed in a mixture of racemic **3a**[63] or **3b**,[64] an enantiopure diamine, such as (*S*,*S*)- or (*R*,*R*)-1,2-diphenylethylenediamine (DPEN),[65] and KOH in a ratio of 1:1:2, in a modification of the reported procedure with the enantiopure **3c** (Table 4[62] and Scheme 14[61]).



Scheme 14. Asymmetric activation of the racemic BINAPs-$RuCl_2$ catalyst **3** in the hydrogenation of carbonyl compounds. **a**: Ar = 4-methylphenyl (ligand = TolBINAP),[63] **b**: Ar = 3,5-dimethylphenyl (ligand = Xylyl- or DM-BINAP),[64] **c**: Ar = phenyl (ligand = BINAP). **AA** and **AN** are the ketones used in the asymmetric hydrogenation (see Tables 4 and 6).

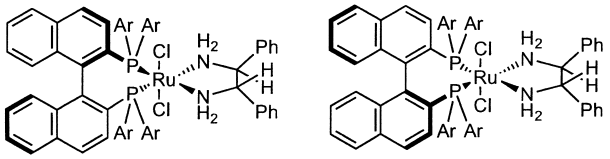
A chiral diamine leads to a nonracemic hydrogenation product, supporting the importance of chirality in the diamine activator for selective activation of one enantiomer of (±)-**3a** (compare entries 2 and 3). Thus, even the asymmetric activation of the racemic catalysts (±)-**3a** by the chiral diamine affords higher levels of asymmetric induction and catalytic activity than those attained by the enantiopure catalyst (+)-**3a** alone (compare entries 1 and 3). The enan-

Table 4. Asymmetric activation of racemic BINAPs-$RuCl_2$ catalyst **3** by enantiopure DPEN (Scheme 14).[a]

Entry	**3**	T [°C]	t [h]	Yield [%]	*ee* [%]
1[b]	(*R*)-**3a**	28	18	2	29 (*S*)
2[b]	(±)-**3a**	28	18	< 1	0
3	(±)-**3a**	28	18	28	80 (*R*)
4	(±)-**3a**	80	10	99	80 (*R*)
5	(*R*)-**3a**	80	10	99	81 (*R*)
6	(*S*)-**3a**	80	10	91	40 (*R*)
7	(±)-**3b**	28	4	99	80 (*R*)
8	(±)-**3b**	−35	7	95	90 (*R*)
9[c]	(±)-**3b**	−35	7	90	90 (*R*)
10	(*S*)-**3b**	28	4	99	> 99 (*R*)
11	(*R*)-**3b**	28	4	99	56 (*S*)

[a] Under an H_2 atmosphere (8 atm). Catalyst **3a** was used in reactions with ketone **AA**, catalyst **3b** was used in reactions with ketone **AN** (see Scheme 14). Ketone:**3**:(*S*,*S*)-DPEN:KOH = 250:1:1:2. [b] In the absence of (*S*,*S*)-DPEN. [c] 0.5 mol% of (*S*,*S*)-DPEN was used based on the quantity of (±)-**3b**. **AN**:**3b**:DPEN:KOH = 250:1:0.5:2.

tioselectivity obtained by the (±)-**3a** and (*S*,*S*)-DPEN is very close to that obtained by the matched pair[66] of (*R*)-**3**/(*S*,*S*)-DPEN complex (**A**; compare entry 4 with 5 and 6). However,



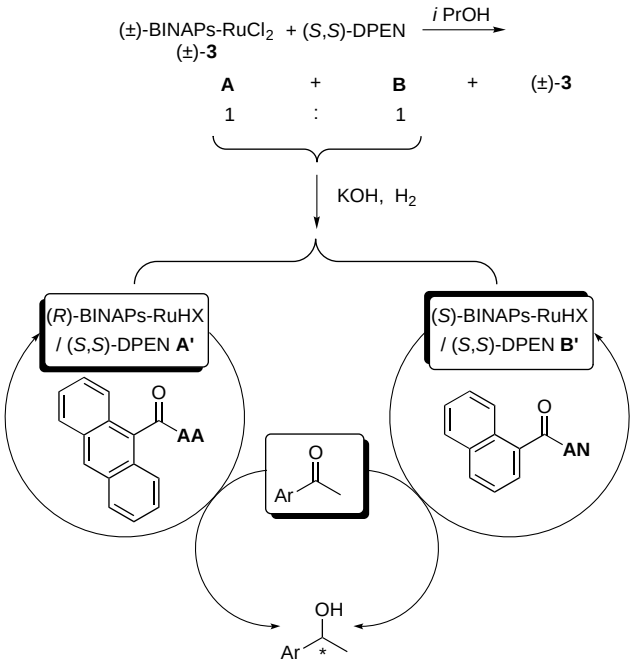
(*R*)-BINAPs-$RuCl_2$/(*S*,*S*)-DPEN **A** (*S*)-BINAPs-$RuCl_2$/(*S*,*S*)-DPEN **B**

the matched pair is dramatically changed over on going from 9-acetylanthracene (**AA**) to 1′-acetonaphthone (**AN**; entries 7–11); in the latter case, the (*S*)-**3**/(*S*,*S*)-DPEN complex **B** is the more enantioselective combination (entries 10 and 11).

The dichotomous sense in enantioselectivity is determined by the ratio (which is 1:1 in this case though) and catalytic activity (turnover frequency) of mono- or dihydrido complexes[67] **A′** and **B′**, which are derived from diastereomeric complexes **A** and **B**, respectively, under hydrogenation conditions (Scheme 15). It should be noted here that the catalytic activity critically depends on the nature of the carbonyl substrates. Interestingly, the use of a catalytic amount of diamine affords an equally high level of enantioselectivity to that obtained by an equimolar amount of diamine (Table 4, compare entries 9 and 8). Indeed, the ^{31}P NMR spectrum of a mixture of (±)-**3a** and a catalytic amount of (*S*,*S*)-DPEN (0.5 mol% based on Ru) is identical to that of the 1:1 mixture, except for the remaining (±)-**3a** (entry 2).

6. The Continuum from Preferential Activation to Substrate Dependence

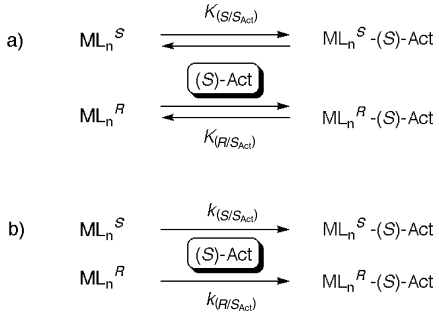
The asymmetric activation can be interpreted through a continuum from the preferential complexation with one enantiomer of the catalyst selectively giving the single, activated diastereomer, to the 1:1 complexation giving the



Scheme 15. Dichotomy in enantioselectivity shown by the diastereomeric BINAPs-RuHX/(*S*,*S*)-DPEN complexes **A′** and **B′** (X = H, Cl) for the conversions shown in Table 4.

activated diastereomeric mixture (1:1) of which the catalyst efficiency (turnover frequency) depends critically on the substrates employed.

For the sake of simplicity, the formation of the activated complexes can be discussed starting from the complexation of the chiral activator with racemic parent catalyst in monomeric form; this follows the thermodynamic and/or kinetic features (Scheme 16). 1) Under equilibrium conditions between the



Scheme 16. Formation of activated diastereomeric catalysts under thermodynamically (a) or kinetically (b) controlled conditions.

activated catalyst and the parent catalyst (Scheme 16a), the ratio of the activated diastereomeric catalysts depends on the thermodynamic stability. 2) Under nonequilibrium conditions, the ratio reflects the relative rate of the reaction of the enantiomeric catalyst with the chiral activator (Scheme 16b). Of course, the use of 1.0 equivalent of the activator per parent catalyst leads to a 1:1 mixture of the diastereomeric complexes. The kinetic or thermodynamic features described above are more apparent after treatment with less than 1.0 equivalent of the activator. Even with

0.5 equivalents of the activator, once a 1:1 mixture is formed, the relative activity of these activated diastereomeric catalysts to the substrate is the factor which determines the outcome, in terms of enantioselectivity, of the asymmetric reaction. In other words, the turnover efficiency of these activated diastereomers should be dependent on the complex with the substrate used.

Figure 7, for example, shows the variation of the relative rate $K_{rel\text{-}act}$ (logarithms from 0.01 to 100). In the case where

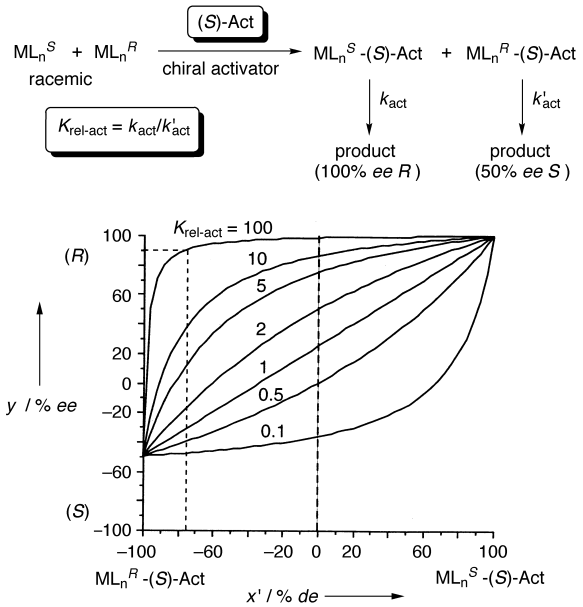


Figure 7. Influence of the *de* value of an activated diastereomeric catalyst (x') on the *ee* value y of the products in an asymmetric reaction with dependence upon $K_{rel\text{-}act}$.

one activated diastereomeric complex provides the product in 100% *ee* (*R*) and the other diastereomer provides the opposite enantiomeric product in 50% *ee* (*S*), if the relative rate of the two activated diastereomers is 100 ($\log K_{rel\text{-}act} = 2$), the product with more than 98% *ee* can be attained even when two activated diastereomer complexes are formed in 1:1 ratio (dotted line at 0% *de*). In a similar case, $K_{rel\text{-}act} = 100$, the product in more than 90% *ee* can be attained even in the presence of only 12.5% of the favorable diastereomer (dotted line at −75% *de*). Thermodynamically unstable and, hence, catalytically more active complexes may often be found.[68] An alternative representation of a similar phenomenon can be drawn for the 1:1 formation of diastereomers. A relative rate of 14 ($\log K_{rel\text{-}act} = 1.15$) is sufficiently high to provide the desired product in more than 90% *ee* (Figure 8).

7. Asymmetric Activation/Deactivation of Racemic Catalysts

In an asymmetric deactivation strategy for racemic catalysis (Scheme 1, Part 1), enantioselective complexation and deactivation of a racemic catalyst with a chiral poison is indispensable (Scheme 1, Part 1a). Asymmetric activation is an alternative but conceptually opposite strategy to racemic catalysis, in which a chiral activator selectively activates one

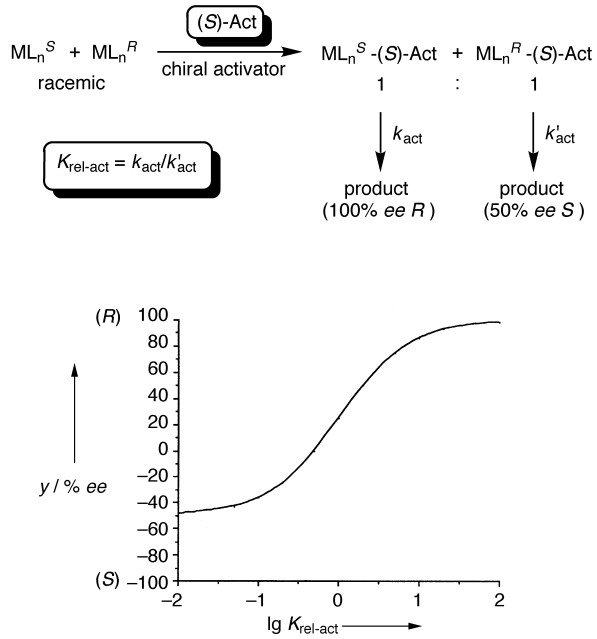


Figure 8. Influence of the relative rate $K_{rel\text{-}act}$ on the *ee* values of the products for an asymmetric reaction (shown above) catalyzed by an activated 1:1 diastereomeric mixture.

enantiomer of a racemic chiral catalyst (Scheme 1, Part 2). Significantly, asymmetric activation can also be established by nonpreferential complexation, to give activated diastereomeric catalysts (Scheme 1, Part 2b), when the turnover frequencies (catalytic activities) between the diastereomers ($k_{act} > k'_{act}$) are critically dependent on the substrates. In combination, an asymmetric activation/deactivation protocol can achieve higher enantioselectivity, regardless of the substrates (Scheme 1, Part 3), by maximizing the difference in catalytic activity between enantiomeric catalysts.[69]

In Ru-catalyzed hydrogenation, the preferential complexation of (*S*)-BINAP-RuCl$_2$ with (*S*)-3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl (DM-DABN) was highly predictable by a modeling study (Figure 9a); the structure was confirmed by

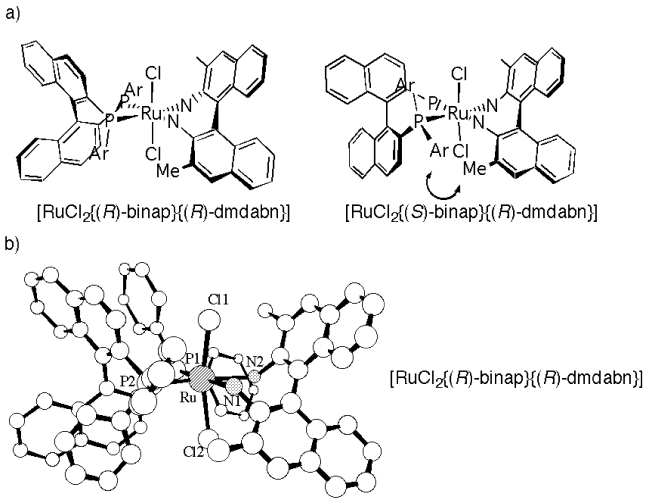
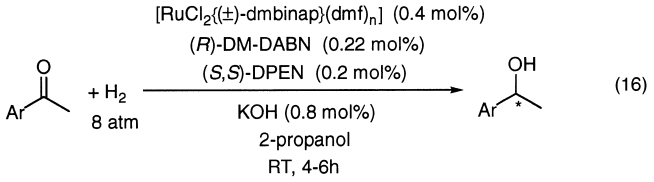


Figure 9. a) Model studies of the relative stability of diastereomeric [RuCl$_2$(binap){(*S*)-dmdabn}] complexes. The (*R*)-BINAP isomer is favored over the (*S*)-BINAP isomer. b) X-ray crystal structure analysis of [RuCl$_2$(binap){(*R*)-dmdabn}].

single-crystal X-ray analysis (Figure 9b). The addition of a racemic DM-BINAP-$RuCl_2$ species to one equivalent of (*R*)-DM-DABN resulted in preferential complexation into the single diastereomeric (*R*)-DM-BINAP-$RuCl_2$/(*R*)-DM-DABN complex. The remaining (*S*)-DM-BINAP-$RuCl_2$ enantiomer gave a different complex with the sequential addition of enantiopure (*S*,*S*)-DPEN. The two dichloro complexes with DM-DABN and DPEN may be further converted into mono- or dihydrido Ru species under hydrogenation conditions, while the DM-DABN complex is far less catalytically active under such conditions.

A racemic BINAP–Ru catalyst achieves higher enantioselectivity in carbonyl hydrogenation [Eq. (16)] using an activation/deactivation protocol (sequential addition of two different types of chiral diamines) than is attained by simple activation. The resultant (*R*)-DM-BINAP-$RuCl_2$/(*R*)-DM-DABN and (*S*)-DM-BINAP-$RuCl_2$/(*S*,*S*)-DPEN complexes give higher chiral efficiency than the racemic (±)-BINAP-



(16)

$RuCl_2$/(*S*,*S*)-DPEN (diastereomeric (*S*)-DM-BINAP-$RuCl_2$/(*S*,*S*)-DPEN and (*R*)-DM-BINAP-$RuCl_2$/(*S*,*S*)-DPEN) mixture. This asymmetric activation/deactivation strategy is also better than the simple asymmetric activation of the racemic BINAP–Ru catalyst, in terms of the wide scope of the ketonic substrates which can be accomodated by tuning the chirality of the activator employed. The enantioselectivity is higher than that obtained using the (±)-DM-BINAP-$RuCl_2$/(*S*,*S*)-DPEN complex at the same temperature and pressure (Table 5). Thus, the present asymmetric activation/deactivation protocol can be regarded as a paradigm shift in racemic catalysis by maximizing the difference in catalytic activity between enantiomeric catalysts.

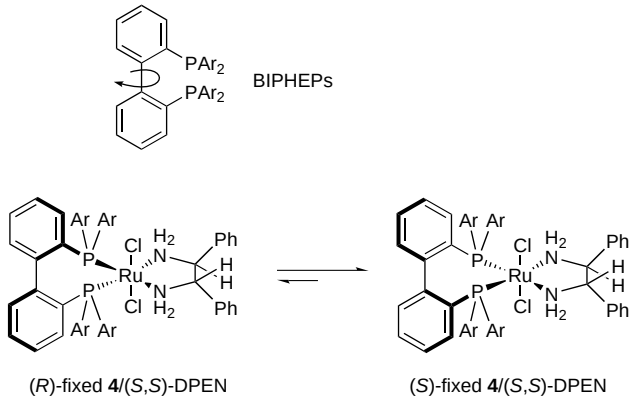
8. Asymmetric Activation of Catalyst with Chirally Flexible Ligands[70]

An advanced strategy for asymmetric activation can be seen in using chirally flexible ligands that achieve higher enantioselectivity than that attained by chirally rigid and, hence, racemic ligands. As described in Section 5, combination of a racemic BINAPs–$RuCl_2$ **3** species with even half an equimolar amount of an enantiomerically pure diamine gives a 1:1 mixture of two diastereomeric **3**/DPEN complexes. When the chirally rigid BINAPs is replaced by a flexible[71] and proatropisomeric BIPHEPs ligand (to form complex **4**),[72] the diastereomeric complexes are formed, in principle, in unequal amounts (Scheme 17).[73] When the major diastereomer shows higher chiral efficiency than the minor isomer, this strategy becomes more effective than the use of similar, but chirally rigid, analogues. The initially formed mixture of (*S*)- and (*R*)-**4b**/(*S*,*S*)-DPEN in [D_8]2-propanol ($CDCl_3$:

Table 5. Asymmetric activation/deactivation of DM-BINAP-$RuCl_2$ complex in Equation (16).

Entry	Ar	*ee* [%][a]
1	1-naphthyl	**96 (*R*)**, 80 (*R*)
2	2-naphthyl	**91 (*R*)**, 45 (*R*)
3	phenyl	**95 (*R*)**, 70 (*R*)
4	2-tolyl	**95 (*R*)**, 82 (*R*)
5	3-tolyl	**95 (*R*)**, 60 (*R*)
6	4-tolyl	**93 (*R*)**, 60 (*R*)

[a]The ee values printed in bold were obtained with (*R*)-DM-DABN and those in normal type were obtained without. The yields for all the reactions were over 99%.



Scheme 17. Stereomutation of BIPHEPs-$RuCl_2$/DPEN complexes **4**. **a**: Ar = phenyl (ligand = BIPHEP), **b**:Ar = 3,5-dimethylphenyl (ligand = Xylyl- or DM-BIPHEP).

$(CD_3)_2CDOD$ = 1:2), when allowed to stand at room temperature (or at 80 °C), was found to give a 1:3 mixture of diastereomers, with (*S*)-**4b**/(*S*,*S*)-DPEN as the major component (Scheme 17). The equilibration occurred readily due to the conformational flexibility of the **4**/diamine complexes. The dichloro complexes may further be converted into active mono- or dihydrido Ru species under hydrogenation conditions.[67]

The significant effect of the chirally flexible **4**/diamine complexes, in comparison with the enantioselectivity obtained using the **3b** catalyst, can be seen in the hydrogenation of 1′-acetonaphthone (**AN**; see Scheme 14). The enantioselectivity obtained with **4b** is higher than with the analogous **3b** (Table 6, compare entries 1 and 2). Further increase in enantioselectivity was attained at a lower reaction temperature (entry 3). The enantioselectivity attained with **4b**/(*S*,*S*)-DPEN was higher than with **3b**/(*S*,*S*)-DPEN complex at the same low temperature and high pressure (entry 4). Thus, (*R*)-1-(1-naphthyl)ethanol was obtained in quantitative yield with

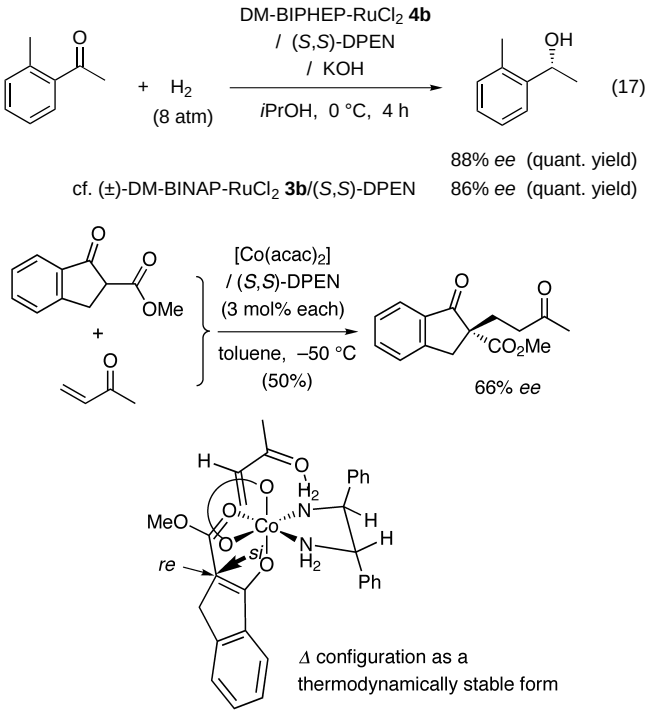
Table 6. BIPHEP ligand for enantioselective hydrogenation of **AN**.[a]

Entry	Ligand	H_2 [atm]	*T* [°C]	*t* [h]	*ee* [%]
1	**4b**	8	28	4	84
2[b]	(±)-**3b**	8	28	4	80
3	**4b**	40	−35	12	92
4[b]	(±)-**3b**	40	−35	7	

[a] **4**/(*S*,*S*)-DPEN in 2-propanol was preheated at 80 °C for 30 min; **3** was used without preheating. Ketone:ligand:(*S*,*S*)-DPEN:KOH = 250:1:1:2. Yields were greater than 99% in all cases.

a 92% *ee* value. **4b**/(*S*,*S*)-DPEN was also useful in the reduction of *ortho*-methylacetophenone [Eq. (17)].

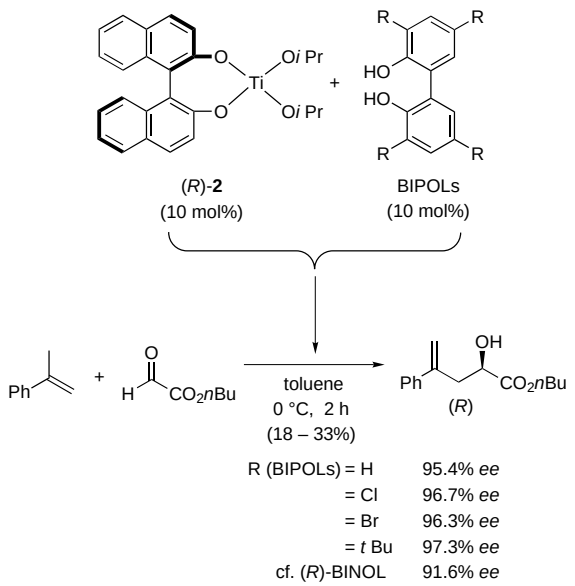
Brunner and Hammer have already reported the use of (*S*,*S*)-DPEN to control the chirality of the octahedral [$Co^{II}(acac)_2$]/diamine complex.[70] This chiral complex [Co-(acac)$_2$\{(*S*,*S*)-dpen\}] catalyzes the Michael addition reaction at $-50\,^{\circ}C$ to give the product in up to 66% *ee* (Scheme 18).[74] The *S*,*S* configuration of the DPEN ligand means the Δ conformation of the cobalt complex is thermodynamically more stable than the Λ conformation.[70,75] Thus, the formation of *R* product is rationalized on the assumptions that the ketone group occupies an axial position and the ester group an equatorial one, and that methyl vinyl ketone is directed to the *Si* face of the ketoester complex by hydrogen bonding of the vinyl ketone oxygen to one of the NH groups (Scheme 18).



Scheme 18. Function of (*S*,*S*)-DPEN in the asymmetric Michael addition catalysed by [$Co^{II}(acac)_2$].

Self-organization of ligands in multicomponent titanium catalysts[76] with conformationally flexible biphenols (BIPOLs) is also found in the enantioselective glyoxylate-ene reaction[10b] to give significantly higher enantioselectivity (Scheme 19).[77] Some molecular modeling studies reported that the hexacoordination of the titanium atom would make the central titanium atom a center of chirality and that the Λ isomer was more favorable than the Δ isomer (Figure 10).

Katsuki and co-workers extensively studied the asymmetric epoxidation of nonfunctionalized olefins catalyzed by chiral Mn(salen) complexes. Recently they proposed that the ligands of Mn(salen) complexes take a nonplanar, stepped conformation and the direction of the folding ligands is strongly related to the sense of chirality in the asymmetric epoxidation.[78] On the basis of this proposal for conformational control by the achiral Mn(salen) complex, two enantio-



Scheme 19. Influence of the conformationally flexible biphenol BIPOLs on the enantioselectivity of the glyoxylate-ene reaction.

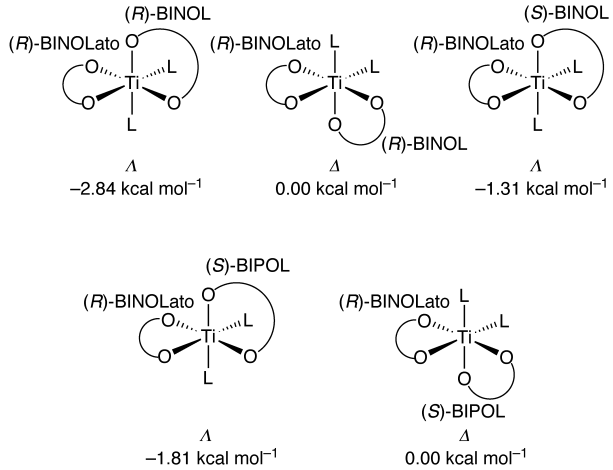
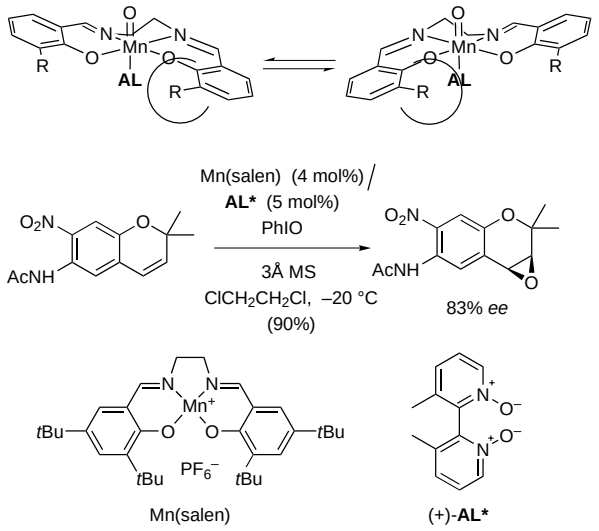


Figure 10. Relative energies of the Λ and Δ isomers of the complexes of (R)-BINOLato-Ti(O*i*Pr)$_2$ with BINOL or BIPOL (R = *t*Bu), L = O*i*Pr.

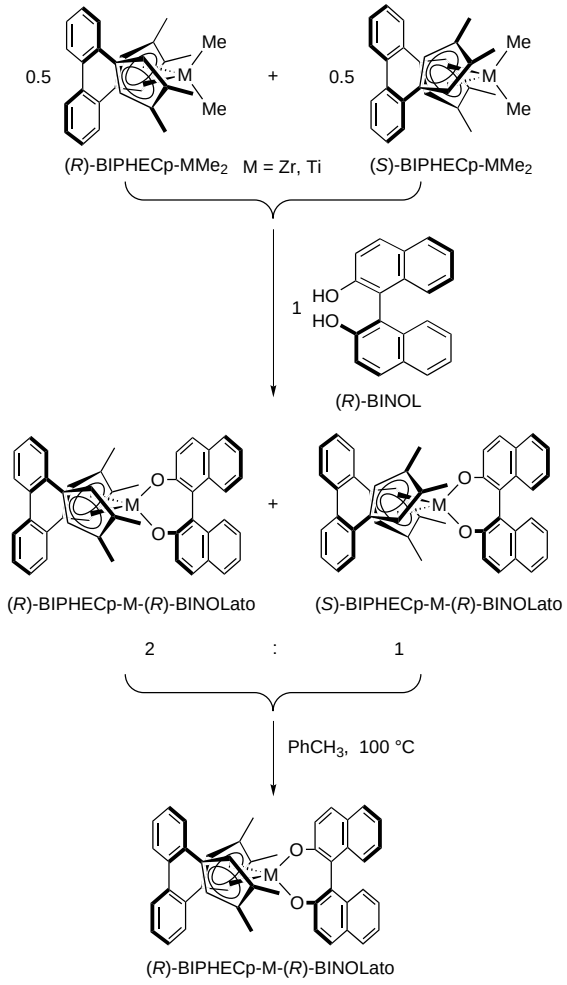
mericforms can be obtained by the use of chiral axial ligands AL*.[79] In actual fact, the achiral Mn(salen) complex gave the epoxides in high enantiopurity in the presence of chiral bipyridine *N*,*N*′-dioxide which acts as an axial ligand (Scheme 20).

Chiral *ansa*-metallocene complexes have become useful catalysts in asymmetric polymerization reactions.[80] While enantioresolution of *ansa*-metallocene racemates cannot yield more than 50% of a particular enantiomer, the readily accessible racemate of a biphenyl-bridged metallocene BIPHECp-M (M = Ti, Zr) has quite recently been reported to give enantiopure *ansa*-titanocene and -zirconocene complexes through BINOL-induced asymmetric transformation (Scheme 21).[81] In the presence of *n*BuLi, the (*R*)-BIPHECp-$TiCl_2$ complex obtained was an efficient asymmetric catalyst of imine hydrogenation (Scheme 22).

Thus, the chirally rigid ligands can be replaced by flexible and, hence, proatropisomeric ligands to give preferentially the

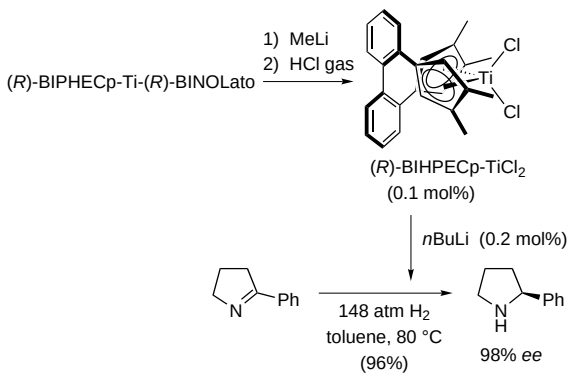


Scheme 20. Asymmetric activation of achiral Mn(salen) complexes.



Scheme 21. BINOL-induced asymmetric transformations of biphenyl-bridged metallocene complexes.

favorable diastereomer with higher chiral efficiency than the minor isomer. This strategy with flexible and proatropisomeric ligands becomes more beneficial than the use of structurally similar, but chirally rigid, ligands.



Scheme 22. Hydrogenation of imines with the titanium complex formed in Scheme 21 as a catalyst precurser.

9. High-Throughput Screening of Chiral Ligands and Activators

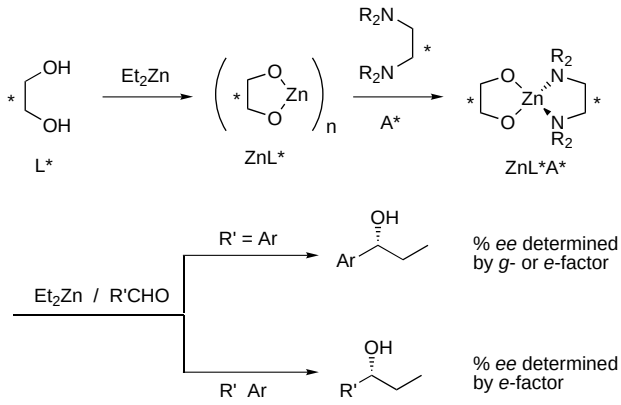
Combinatorial chemistry has been well recognized as a useful strategy for the discovery and optimization of bioactive drugs, coordination complexes, and solid-state materials.[82] Between the split-and-mix and parallel-matrix methodologies for combinatorial chemistry, the latter is more employable for lead optimization, wherein the high-throughput screening (HTS) is an essential technique for tuning a variety of modulation.[83] However, only a limited number of investigations has so far been reported, even on chiral ligand optimization for coordination complexes,[84] due to the lack of HTS methods. In particular reactions, UV/Vis spectroscopy can be used; however, this gives only a rough estimation of hits.[85] IR thermography can also be used for qualitative analysis.[86] Quite recently, mass spectroscopy has been used to determine the enantiomeric excesses of limited types of samples.[87] In the quantitative determination of *ee* values, high-performance liquid chromatography (HPLC) has long been used in combination with chirally modified columns to separate enantiomers. If the *ee* value can be determined using achiral columns, the separation of enantiomers using chiral columns would no longer be necessary. A circular dichroism method can be applied in the combinatorial search for enantioselective catalysts through asymmetric activation, using a JASCO-CD-995 (1595) instrument with achiral columns.[88] This method involves the simultaneous monitoring of the CD signal ($\Delta\varepsilon$), the absorption (ε), and their ratio to each other, called the dissymmetric or anisotropy factor g ($=\Delta\varepsilon/\varepsilon$), at a fixed wavelength in a flow system. The g-factor was introduced by Kuhn[89] in 1930, refined by Mason and coworkers[90] in 1980, and further developed by Salvadori et al.[91] and Mannschreck.[92] The g-factor is independent of concentration and is linearly related to the enantiomeric excess.[93] With this technique, the *ee* value of the product could be determined within a minute on achiral stationary phases without separation of the enantiomeric products. Therefore, application of HPLC-CD provides a "super high throughput screening" (SHTS) system for finding the most effective catalyst through asymmetric activation.[88] Chiral catalysts obtained by ligand exchange with chiral ligands (L^1*, L^2*, etc.) may be further developed, in parallel combination

with chiral activators (A^{1*}, A^{2*}, etc.), to form the most catalytically active and enantioselectively activated catalyst (Scheme 23).

Scheme 23. General principle for the creation of a catalyst library of asymmetric activation catalysts.

The super high throughput screening (SHTS) of parallel solution libraries of activated catalysts by HPLC-CD is demonstrated for diol–Zn catalysts in the addition of diethylzinc to aldehydes. Amongst asymmetric catalysis of C–C bond forming reactions, enantioselective addition of diorganozinc reagents to aldehydes constitutes one of the most important and fundamental asymmetric reactions.[1c, 7e, 94] Since the initial report by Oguni,[95] various chiral ligands, including β-amino alcohols, have been used for this type of reaction. However, less attention has been paid to C_2-symmetric binaphthol (BINOL) derivatives,[96] despite their wide application as chiral ligands for B,[97] Al,[98] Ti,[99] Zr,[100] and Ln[101] catalysts in, for example, enantioselective aldol and ene reactions. This is due to their lower catalytic activity and enantioselectivity for the organozinc addition reaction.[102] Only very recently, some modified BINOLs[103] were reported to be effective but the simple BINOL itself is less effective in the reaction.[102]

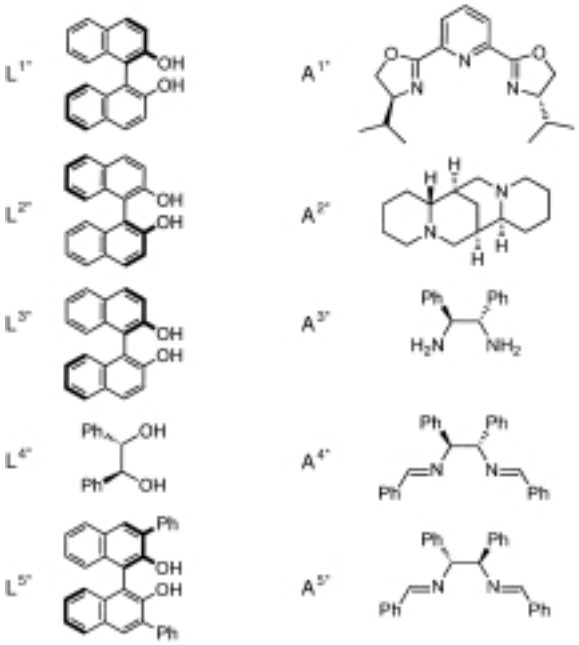
It is reasonable to assume that the active catalyst species is a monomeric zinc alkoxide in the addition of diethylzinc to aldehydes; the cleavage of the higher aggregates could result in activation of the overall catalyst system (Scheme 24).[14p, 104]



Scheme 24. Asymmetric activation of chiral diol–zinc catalysts by chiral nitrogen ligands.

The addition of chiral nitrogen activators should be one of the most efficient ways for activation of the BINOL–zinc catalyst system because of the strong coordinating ability of the nitrogen towards the zinc cation; this would facilitate the alkyl transfer. As a result, a monomeric zinc complex is expected to be formed in a similar manner to that of chiral salen–zinc complexes.[105] Furthermore, bimolecular combination of chiral activators with the diol–zinc complexes should be more convenient than the unimolecular combination. Thus, the primary combinatory library of chiral ligands L^{1*}–L^{5*} and chiral activators A^{1*}–A^{5*} was initially examined, from which the leads can be further optimized for the next generation of the chiral ligands and activators.

An activation effect was actually observed in the random screening of chiral ligand/activator combinations. Enantioselectivity of the reaction is also increased by matched combinations of diol ligands and nitrogen activators. Substitution at the 3 and 3′ positions with bulky phenyl groups, such as 3,3′-diphenyl-1,1′-bi-2-naphthol (L^{5*}), may further



prevent the aggregation of BINOLato–Zn because of their steric demands and may increase the enantioselectivity; (*S*)-1-phenylpropanol was obtained in quantitative yields with up to 65 % *ee*.

On the basis of the results collected from the primary combinatorial library, we then created the next generation library of diimine activators with twelve members A^{4*}–A^{15*}. All library members significantly activate the L^{5*}–Zn

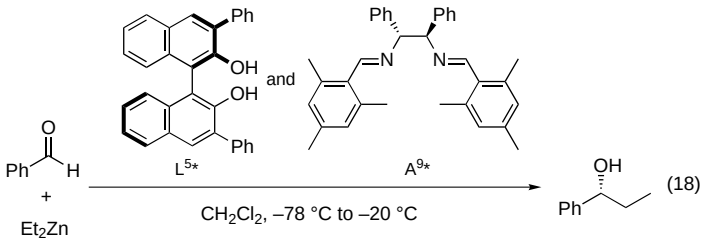
A^{4*} :	*S*,*S*	Ph
A^{5*} :	*R*,*R*	Ph
A^{6*} :	*S*,*S*	2,6-$Cl_2C_6H_3$
A^{7*} :	*R*,*R*	2,6-$Cl_2C_6H_3$
A^{8*} :	*S*,*S*	2,4,6-$Me_3C_6H_2$
A^{9*} :	*R*,*R*	2,4,6-$Me_3C_6H_2$

A^{10*} :	*S*,*S*	Ph
A^{11*} :	*R*,*R*	Ph
A^{12*} :	*S*,*S*	2,6-$Cl_2C_6H_3$
A^{13*} :	*R*,*R*	2,6-$Cl_2C_6H_3$
A^{14*} :	*S*,*S*	2,4,6-$Me_3C_6H_2$
A^{15*} :	*R*,*R*	2,4,6-$Me_3C_6H_2$

complex and produce 1-phenylpropanol in higher yields and with higher enantioselectivities than those obtained by only using the ligand. The steric hindrance of the chiral activators is

crucial, and hence the activator A^{9}* provides the best results. The reaction catalyzed by the best combination L^{5}*/A^{9}* is further optimized by lowering the reaction temperature. (*S*)-1-Phenylpropanol is obtained in quantitative yield and with 99% *ee* [Eq. (18)]. Even if only 2 mol% of L^{5}*/A^{9}* is used in the reaction, (*S*)-phenylpropanol can be obtained in quantitative yield and with 97% *ee*.

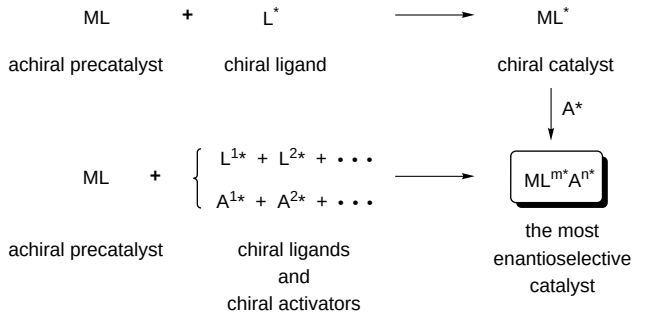
The best combination of chiral ligands and activators can easily be found in an efficient way by super high throughput screening (SHTS). The dissymmetry or anisotropy factor (*g*-factor) can be employed for UV-active aromatic compounds,[88] and the optical rotation per refractive index unit or the enantiomeric factor (*e*-factor)[106] can be used not only for UV-inactive aliphatic compounds or carbohydrates but also for UV-active aromatic compounds.



(18)

10. Smart Self-Assembly into the Most Enantioselective Catalyst

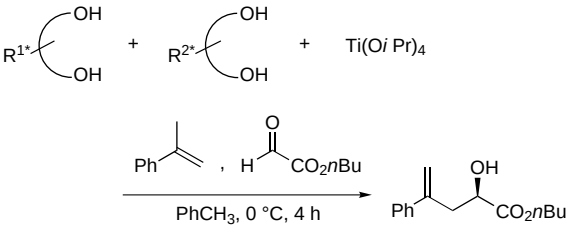
Sharpless and co-workers demonstrated the significance of ligand accelerated catalysis[2] through the construction of an asymmetric catalyst from an achiral precatalyst by ligand exchange with a chiral ligand. By contrast, an achiral precatalyst combined with several chiral ligand components (L^{1}*, L^{2}*, etc.) may selectively assemble into the most catalytically active and enantioselectively activated catalyst ($ML^{m}*A^{n}*$) possible from the combinatorial library by association with chiral activators (A^{1}*, A^{2}*, etc.; Scheme 25).[75]



Scheme 25. General principle of ligand exchange based on smart self-assembly.

Two patterns of self-assembly are conceivable for an achiral precatalyst Ti(O*i*Pr)$_4$ and couples of chiral diol components to form a single chiral titanium complex. In one case (Scheme 26a), a combination of acidic (*R*)-BINOL and a relatively basic diol, such as TADDOL,[107] in a molar ratio of 1:1:1 suggests a push-pull assembly into a single (*R*)-BINOLato-Ti-(*R*)-TADDOLato complex **6a**; no isopropanol was observed after azeotropic removal with toluene. This complex **6a**, in the case of matched chirality, is obtained from (*R*)-TADDOLato-Ti(O*i*Pr)$_2$ **5a** with (*R*)-BINOL or from (*R*)-BINOLato-Ti(O*i*Pr)$_2$ **2** with (*R*)-TADDOL. In the other pattern (Scheme 26b), upon addition of (*R*)-BINOL and a more acidic diol (*R*)-5-Cl-BIPOL to Ti(O*i*Pr)$_4$, the (*R*)-**2**/(*R*)-BIPOL complex **6b** is obtained. This complex is derived not only from **2**[108] with 5-Cl-BIPOL[10b] but also from 5-Cl-BIPOLato-Ti(O*i*Pr)$_2$ **5b** with BINOL.

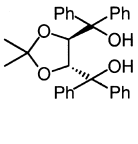
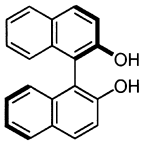
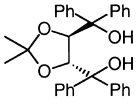
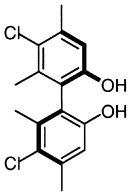
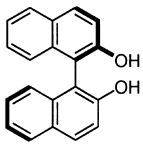
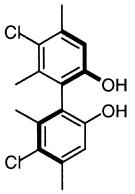
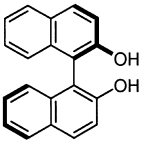
The role of multicomponent ligand assembly to form a highly enantioselective catalyst was exemplified in the investigation of enantioselective catalysis of the carbonyl-ene reaction [Eq. (19)]. The catalyst was prepared by mixing an

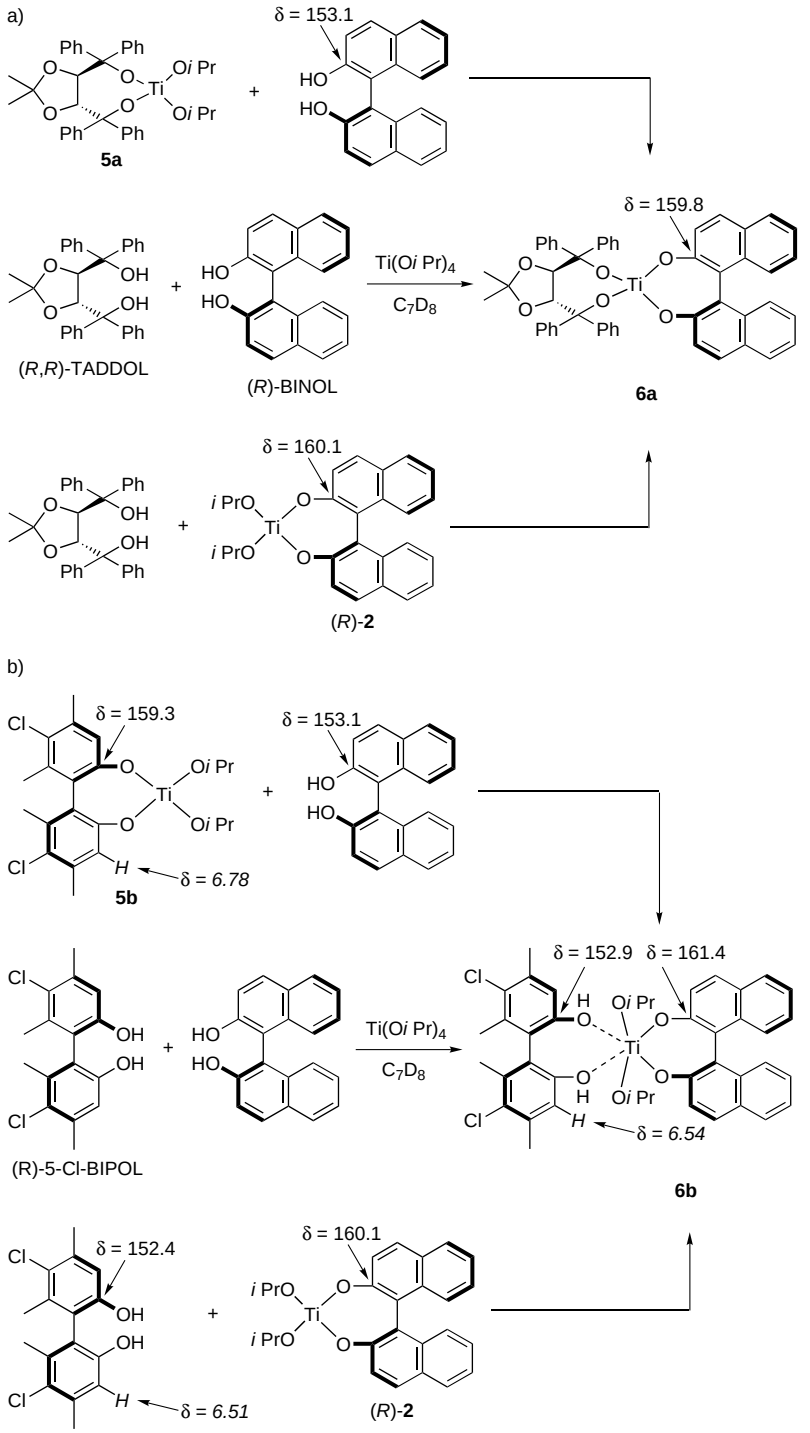


(19)

achiral precatalyst Ti(O*i*Pr)$_4$ with a combination of BINOL and various chiral diols, such as TADDOL and 5-Cl-BIPOL, in a molar ratio of 1:1:1 (10 mol% with respect to the olefin and glyoxylate) in toluene (Table 7). A quantum jump in

Table 7. Asymmetric catalysis by multicomponent ligand-cooperation in the reaction shown in Equation (19).

Entry	R^{1}*$(OH)_2$	R^{2}*$(OH)_2$	Yield [%]	*ee* [%]
1			50	91
2		–	0	–
3			66	97
4		–	13	75
5		–	20	95



Scheme 26. Smart self-assembly of the highly activated Ti catalysts **6a** (a) and **6b** (b). The δ values refer to the ^{13}C (normal text) and ^{1}H (italicized text) NMR spectra. It is important in the characterization of **6a** that the *i*PrO signals are absent from the NMR spectra.

chemical yield from 0% to 50% was attained, in addition to a high enantioselectivity (91.0% *ee*, *R*), when a combination of (*R*)-TADDOL and (*R*)-BINOL was employed (compare entries 1 and 2). With a combination of (*R*)-BIPOL and (*R*)-BINOL, the reaction proceeded quite smoothly to produce the carbonyl-ene product in the highest chemical yield and with the highest enantioselectivity (entry 3). This finding is in direct contrast to the lower enantiomeric excesses and chemical yields obtained with (*R*)-**5b** or (*R*)-**2** (entries 4 and 5, respectively).

Hill and Zhang reported the results of an elegant study in which smart self-assembly resulted in the creation of an achiral, "immortal" catalyst.[109] We have reported an example of asymmetric catalysis through smart self-assembly into the most enantioselective chiral catalyst by virtue of multicomponent ligand cooperation. Thus, the present work represents chiral evolution from the studies of Hill and Zhang on an achiral catalyst.

11. Future Perspectives

Molecular chirality (handedness) is a principal element in nature that plays a key role in science and technology. Among various approaches to generate optically active molecules, asymmetric catalysis of organic reactions is the most efficient process. The candidates for such enantioselective catalysts are metal complexes bearing chiral and nonracemic organic ligands, often in enantiopure form. Therefore, tuning the catalysts to achieve the perfect match among chiral ligand, metallic ion, substrate, and chiral activator is the key for achieving the maximum chiral discrimination.

Catalytic systems that permit precise recognition among enantiotopic atoms, groups, or faces in prochiral substrates must be created efficiently by employment of chiral activators. Kagan stated that one must no more ignore the modern methods of combinatorial chemistry and high-throughput screening for finding the new catalyst or best catalyst tuned for asymmetric reactions.[110]

Asymmetric activation (Scheme 1) will provide a general effective strategy for asymmetric catalysis involving even racemic or chirally flexible ligands without optical resolution. Not only chiral organic molecules but also chiral metal complexes can be used as chiral activators through heteromultimetallic activation. Asymmetric activation will be further employed as a new chiral doping technique in liquid crystalline material science. Furthermore, a chiral command surface might be built up as an alignment layer in the interface between liquid crystalline and solid phases. Asymmetric activation may also be extended to solid-state processes or cluster chemistry. For example, the spontaneous crystallization (spontaneous resolution) of racemic mixtures could be facilitated by seeding with the crystals of one enantiomer. This could be done by a different but enantiopure molecule in the same, or a similar, crystalline structure as the seed. Asymmetric activation will be effective in molecular biology

processes. External chiral molecules may accelerate signal-transduction processes[111] through association with a ligand/receptor complex. In the model system with the mutants of human growth hormone (hGH) and the hGH receptor, achiral indole analogues were employed as exogenous small molecules to activate growth hormone signaling.[112]

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