Chiral Catalysts

DOI: 10.1002/anie.200705241

Nonlinear Effects in Asymmetric Catalysis

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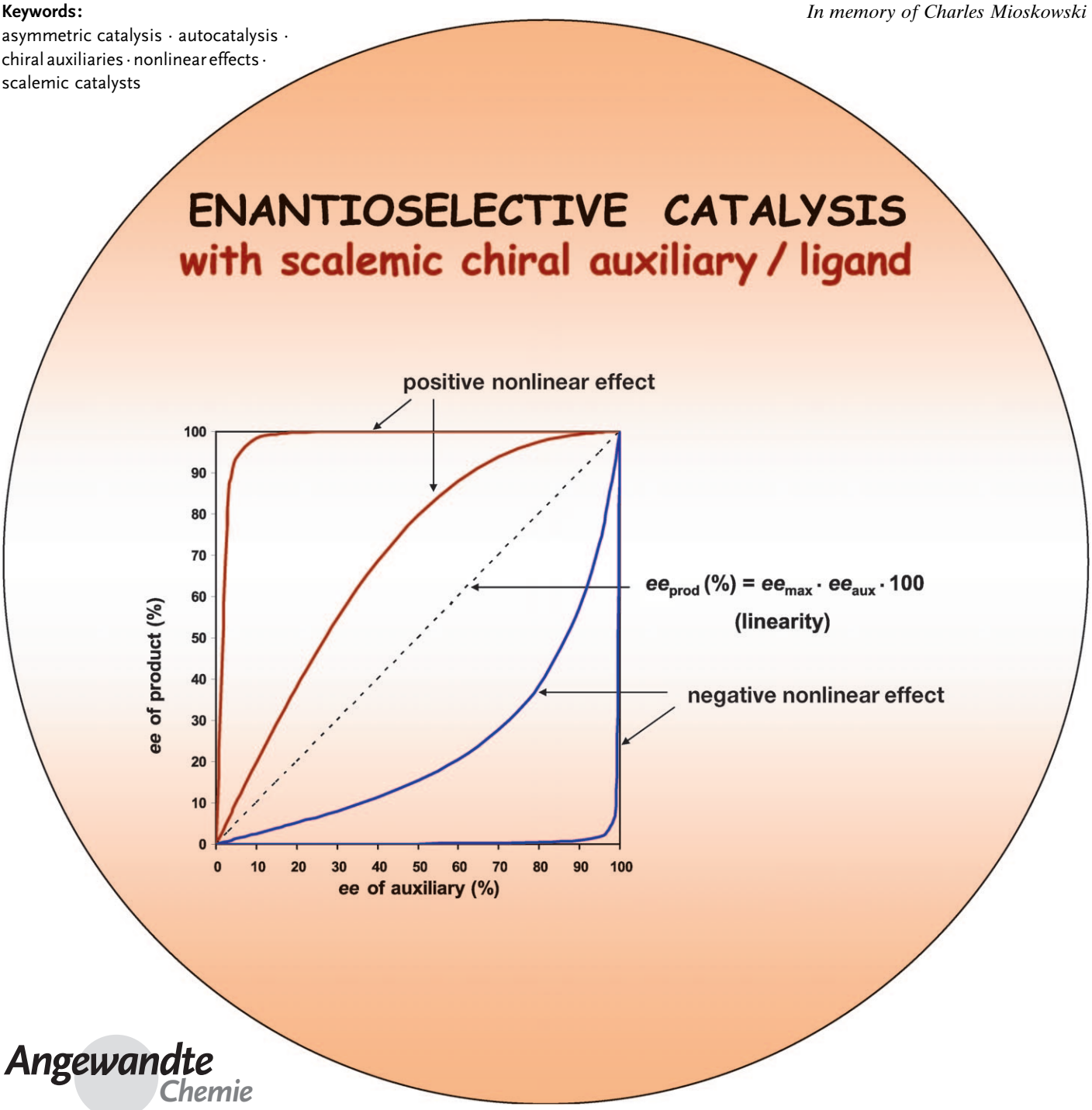
Keywords:
asymmetric catalysis · autocatalysis · chiral auxiliaries · nonlinear effects · scalemic catalysts

In memory of Charles Mioskowski



There is a need for the preparation of enantiomerically pure compounds for various applications. An efficient approach to achieve this goal is asymmetric catalysis. The chiral catalyst is usually prepared from a chiral auxiliary, which itself is derived from a natural product or by resolution of a racemic precursor. The use of non-enantiopure chiral auxiliaries in asymmetric catalysis seems unattractive to preparative chemists, since the anticipated enantiomeric excess (ee) of the reaction product should be proportional to the ee value of the chiral auxiliary (linearity). In fact, some deviation from linearity may arise. Such nonlinear effects can be rich in mechanistic information and can be synthetically useful (asymmetric amplification). This Review documents the advances made during the last decade in the use of nonlinear effects in the area of organometallic and organic catalysis.

From the Contents

1. Introduction

Asymmetric synthesis is now an established field which is widely used in research laboratories and in industry.[1,2] It is especially important in the pharmaceutical industry to quickly prepare small amounts of many drug candidates of defined configurations for biological tests. An appropriate process has to be devised later to produce enantiomerically pure drugs. In stoichiometric or catalytic asymmetric synthesis, a chiral auxiliary is needed, which can be prepared from a natural product or a compound obtained from the resolution of a racemic mixture. In many cases it is difficult to obtain the chiral auxiliary in an enantiomerically pure form. For example, commercial α-pinene, a useful starting material to prepare many chiral borane reagents, usually has a purity of 70–90% *ee*, and its upgrading to 99% *ee* is a costly operation.[3] If a reagent or catalyst system contains a non-enantiopure chiral auxiliary with an enantiomeric excess ee_{aux}, an enantiomerically enriched product with an enantiomeric excess of ee_{prod} can be obtained. The calculation of the enantiomeric excess of the product (ee_{max}) for an enantiopure auxiliary can easily be done if one assumes that the enantiomers of the auxiliary (in the reagent or the catalyst) act independently.[4,5] The proportionality between ee_{aux} and ee_{prod} in Equation (1) allows the ee_{max} value to be calculated (*ee* values between 0 and 1).

$$ee_{prod}(\%) = ee_{max}\, ee_{aux}\, 100 \quad (1)$$

When autoassociation or formation of multiligand catalysts occur, Equation (1) generally is no longer obeyed, because diastereomeric species may be produced which are impossible to generate from the enantiopure auxiliaries.

1.1. First Examples of Nonlinearity in Asymmetric Catalysis

In 1986 Kagan et al.[6] studied three catalytic asymmetric reactions using non-enantiopure auxiliaries. This study considered the Sharpless epoxidation of geraniol with scalemic (nonracemic) (*R*,*R*)-(+)-diethyl tartrate (DET). The *ee* values of the epoxide were greater than those calculated for a linear correlation based on the *ee* values of the scalemic (*R*,*R*)-(+)-DET; ee_{DET}). Such a deviation from the linear correlation was termed a positive nonlinear effect [(+)-NLE].[7] The effect was interpreted by the involvement of diastereomeric dimeric complexes of the type proposed by Finn and Sharpless.[8] It was suggested that the heterochiral dimer was more stable and less active than the homochiral species. Thus, the heterochiral dimer removes some racemic DET from the catalytic cycle, thereby allowing enantioenriched (*R*,*R*)-(+)-DET to take part in the catalytic cycle, hence leading to a (+)-NLE.

In the same report,[6] sulfide oxidation by a "water-modified Sharpless reagent in the presence of scalemic (*R*,*R*)-(+)-DET was also investigated.[9] Here, the *ee* values of the products were found to be lower than calculated for a linear correlation with ee_{DET}. This phenomenon was termed a negative nonlinear effect [(−)-NLE].[7] A (−)-NLE was obtained up to a value of 70% ee_{DET}, and then a linear relationship occurred. A complex structure, including at least two tartrate ligands, was suggested for the active species. The heterochiral dimer was proposed to be more reactive than the homochiral species to explain the (−)-NLE.

The asymmetric Robinson annulation of a triketone using enantioimpure (*S*)-proline as a catalyst was also investigated.[6] A slight (−)-NLE was observed when the *ee* value of the ketol was plotted against $ee_{proline}$. The involvement of two

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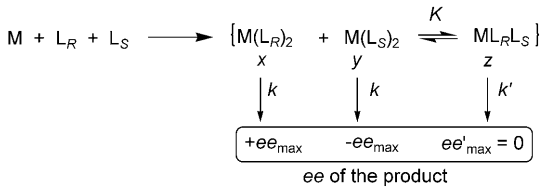
proline molecules in the catalytic cycle was suggested. However, later studies of this reaction suggested the absence of an NLE and the involvement of only one molecule of proline (see Sections 3.1 and 4.3). The mechanistic aspects of NLEs have been described by using simplified mathematical models of various catalytic systems.[10] The early results on NLEs were reported in a review in 1998.[11] The majority of known examples of NLEs include complexes bearing two chiral ligands, and in Section 1.2 we present only a short overview of these models. Many examples of nonlinear effects are now known and have been reviewed.[11–21] The present article will focus on the results published in the last decade.[11]

1.2. Models involving Two Chiral Ligands

For systems with two ligands, one can envisage mainly ML_2 or $(ML)_2$ complexes, where M and L stand for metal and ligand, respectively. When the ligand is not enantiopure, such systems result in the formation of at least two kinds of diastereomeric species, which are either homochiral or heterochiral. For example, Scheme 1 presents the situation



Scheme 1.

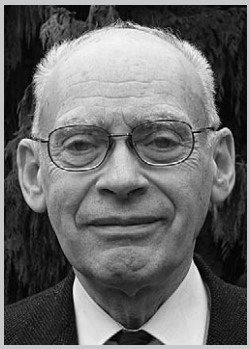
for the ML_2 system, assuming a dynamic equilibrium between the three complexes, ML_RL_R, ML_SL_S (homochiral), and ML_RL_S (*meso* structure for simplicity), and fast exchange of the enantiomeric ligands (L_R and L_S) at the metal center. According to this model, the homochiral and *meso* species generate, respectively, the enantiomeric and the racemic products. The homochiral and *meso* complexes are characterized by their relative reactivity ($g = k'/k$) and their relative concentrations [$\beta = z/(x+y)$] (Scheme 1).[10] A simple kinetic treatment gives Equation (2), in which ee_{prod} is expressed as a

$$ee_{prod} = (ee_{max}\, ee_{aux})\frac{1+\beta}{1+g\beta} \quad (2)$$

function of ee_{aux}.[10] The entities g, β, and ee_{max} take fixed values for a given system. β can be derived from the equilibrium constant K between the homochiral and heterochiral complexes.[10] The calculation leading to Equation (2) assumes that the initial ligand (with ee_{aux}) is fully transferred into the set of ML_2 complexes, or that the external ligand retained the initial value of ee_{aux}. A plot of ee_{prod} as a function of ee_{aux} affords three types of correlations: 1) a (+)-NLE for $g < 1$ (more reactive homochiral complex), 2) a (−)-NLE for $g > 1$ (more reactive *meso* complex), and 3) Equation (2) reduces to $ee_{prod} = ee_{max}\, ee_{aux}$ (linear correlation), if $\beta = 0$ or $g = 1$.

Equation (2) applies even when the proportions of x, y, and z are fixed through an irreversible formation of diastereomeric complexes. The strength of the NLE will be higher when diastereomers are irreversibly formed than when they are reversibly formed.[17] The discussion can be extended to the similar model $(ML)_2$.[11]

The reservoir model[10] describes the case when several metal complexes are generated during the catalyst preparation, one being the catalytically active species. One can envision several models, such as the couples monomer/dimer, dimer/trimer, dimer/tetramer etc., for the reservoir effect. A non-enantiopure ligand simultaneously generates the catalytically active monoligated complex ML and, for example the inactive stable *meso* dimer $(ML_R)(ML_S)$ or *meso* complex ML_RL_S. Here, the *meso* species serves as the trap for the racemic part of the non-enantiopure ligand, thus enabling the enantio-enriched ligand to take part in the catalytic cycle as the monoligated complex (ML). A mechanism related to a reservoir effect is found in the enantioselective addition of Et_2Zn to benzaldehyde.[12e] It may sometimes be difficult to differentiate a reservoir effect from other catalytic models such as the ML_2 system. However, this problem can be solved by additional studies, such as analysis of the reaction kinetics or NMR studies on the diastereomeric complexes.



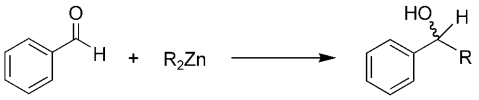
Henri B. Kagan was born in Boulogne-Billancourt (France) in 1930. He graduated from the Sorbonne and Ecole Nationale Supérieure de Chimie de Paris in 1954, and completed his PhD with Dr. J. Jacques. After research at the Collège of France (Prof. A. Horeau) and the University of Texas (Prof. T. Mabry), in 1968 he joined the Université Paris-Sud, Orsay, where in 1999 he became emeritus professor. He is a member of the French Academy of Sciences. His awards include the Prelog Medal, the August-Wilhelm-von-Hofmann Medal, the Chirality Medal, the Wolf Prize for Chemistry, the Ryoji Noyori Prize, and the Bower award.

Tummanapalli Satyanarayana was born in Jagitial, Andhrapradhesh (India) in 1976. He studied chemistry at the University of Hyderabad (MSc 1998), and completed his PhD (2004) with Prof. D. Basavaiah on applications of Baylis–Hillman adducts. After postdoctoral research with Prof. H. B. Kagan at Université Paris-Sud, Orsay, on nonlinear effects in asymmetric catalysis and on kinetic resolution, in 2006 he joined Syngene International ltd, Bangalore. In 2007, he moved to Singapore where he is a Senior Research Scientist at the Albany Molecular Research Singapore Research Center.

2. Nonlinear Effects in Homogeneous Organometallic Catalysis

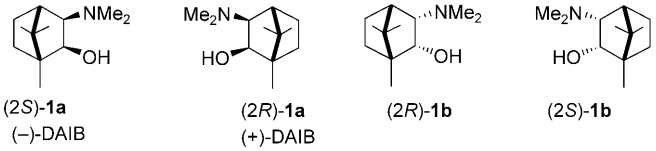
2.1. Addition of Dialkylzinc Reagents to Aldehydes

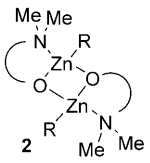
The asymmetric addition of organozinc compounds to aldehydes is a synthetically very useful reaction [Eq. (3)]. Nonlinear effects have frequently been used as a method to study the catalytic species in this reaction.



(3)

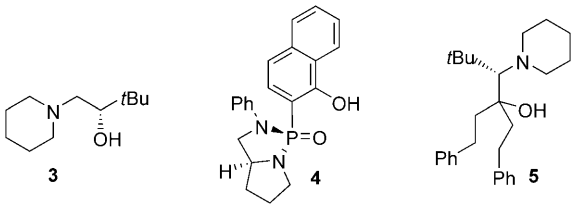
A (+)-NLE was first noticed in this reaction by Oguni et al.[23] in 1988 by using non-enantiopure chiral β-amino alcohols as catalysts. Subsequently, Noyori and co-workers[22,24] Bolm et al.,[25] and Kellogg and co-workers[26] reported the presence of an NLE in this class of reactions. The formation of stable and catalytically inactive heterochiral dimers **2** was suggested as a possible explanation for the



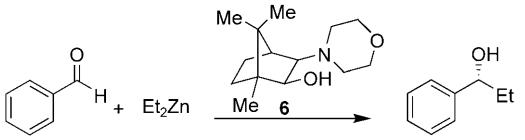


occurrence of the NLE. Noyori and co-workers[24,27] made an extensive study to understand the mechanism of the asymmetric amplification, and demonstrated that **1a** (DAIB) and **1b** are excellent catalysts for the addition of dialkylzinc to benzaldehyde. A very strong asymmetric amplification was found with ligands of type **1**. It was noticed that the rate of the reaction decreased significantly as the *ee* value of the DAIB was lowered. The (+)-NLE was attributed to the reversible formation of homochiral and heterochiral dimeric zinc amino alkoxide species from dialkylzinc and enantiomers of **1**. The pronounced nonlinear deviation was simulated using experimentally available data. Based on these results, the authors suggested that the nonlinear effects resulted from the competition of two enantiomorphic catalytic cycles involving the monomeric chiral zinc catalysts. It was pointed out that apart from the *ee* value of the catalyst, the concentrations of the catalyst, reagent, and substrate as well as the extent of conversion also contribute quantitatively to the nonlinear effects. Noyori and co-workers[27b] examined the relative reactivities of various substituted benzaldehyde and organozinc compounds in the presence of enantiopure and racemic catalysts. The results of these experiments supported the monomeric rather than dimeric alkoxy alkylzinc species as being the active catalyst

In later studies, several research groups used nonlinear correlations between the *ee* values of the product and the ligand (**3**–**5**) to support the formation of dimeric species in related reactions.[28–31]



Walsh and co-workers[32a] discovered a substrate dependency of the NLE in the addition of diethylzinc to aromatic aldehydes in the presence of ligand **6** [Eq. (4)]. Reactions of



(4)

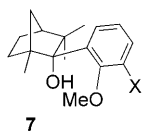
aromatic aldehydes with electron-donating substituents on the aromatic ring exhibited a greater NLE than those of substrates with electron-withdrawing substituents. These results contradict Noyori's model,[27b] which predicts a decrease in the ee_{prod} value for aldehydes that bind more tightly to the catalyst, thus giving lower NLEs than aldehydes that bind weakly. In the extreme case of a very high association constant for the formation of the aldehyde–catalyst adduct (K_{assoc}), the equilibrium should shift completely in favor of monomers, thus leading to the disappearance of the NLE; this scenario is contrary to the observations of Walsh and co-workers.[32a] These contradictory results were subsequently rationalized by Buono, Walsh, and Blackmond, who suggested a minor modification to the original Noyori model.[32b]

Susan Abraham was born in Ernakulam, Kerala (India). After obtaining her MSc at Kerala University, she joined the Indian Institute of Technology, Chennai, where she received her PhD in Chemistry in 2007 for her work on asymmetric Michael addition reactions with chiral promoters under the guidance of Prof. G. Sundararajan. Since 2007 she has been a postdoctoral fellow with Prof. H. B. Kagan at the Université Paris-Sud, Orsay. Her research interests include homogeneous and heterogeneous asymmetric catalysis.

It was previously pointed out by Blackmond[17] that kinetic studies, in addition to quantification of the NLE, can be helpful for understanding the mechanistic details of a reaction. She emphasized the need when performing an NLE study to consider factors such as conversion-dependent stereoselectivity, conversion-dependent kinetic behavior, and catalyst modification during the reaction (autoinduction). It was shown that, with an initial distribution of homochiral and heterochiral dimers, a nearly linear relationship between ee_{prod} (or reaction rate) and $ee_{catalyst}$ would be obtained if a reversible monomer–dimer association is involved. A NLE would be apparent only if the heterochiral dimerization was irreversible. A transformation with a strongly binding substrate was considered as a limiting case. Here, none of the heterochiral dimer dissociates, while all of the homochiral dimer enters into the catalytic cycle through dissociation to the monomer. This limiting case leads to a greater asymmetric amplification for the strongly binding substrate.[32b] The results of Walsh and co-workers[32a] were thus attributed to a non-thermodynamically controlled monomer/dimer partitioning, which may be considered as an extension of the original Noyori model.

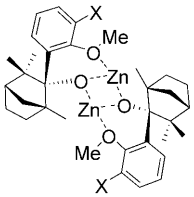
Asakura et al.[33] found that the (+)-NLE differed in the addition of Et_2Zn to benzaldehyde in the presence of catalyst **3** when the order in which the reagents were introduced was changed. It was also observed that the ee_{prod} value changed during the course of a reaction involving asymmetric amplification. A kinetic model was formulated to explain these findings.

While studying the addition of dialkylzinc to benzaldehyde, Steigelmann et al.[34] encountered a remarkable (−)-NLE in the presence of ligands **7a** and **7b** while a linear

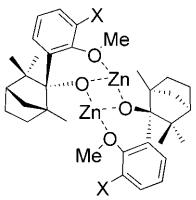


7

a : X = H
b : X = Me
c : X = $SiMe_3$
d : X = *t*Bu



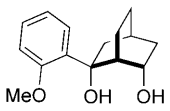
(*R*,*R*)-**8**
homochiral dimer



(*R*,*S*)-**9**
heterochiral dimer

correlation was found in the case of ligands **7c** and **7d** with sterically bulky substituents. The asymmetric depletion with **7a** and **7b** was attributed to the formation of inactive homochiral dimeric alkylzinc fencholates **8**, as the corresponding monomer functions as the active catalyst. This hypothesis was in agreement with computations which established the higher stability of *syn*-homochiral dimers over the *syn*-heterochiral dimers. The linear correlation in the case of ligands **7c** and **7d** was explained by the similar stabilities of the heterochiral and homochiral dimers.

Frejd and co-workers[35a] identified a strong (+)-NLE in the case of diol **10**. The authors suggested the participation of dimeric or oligomeric **10**/Zn complexes in the catalytic cycle, in analogy with the previously detected dimeric complexes of $Ti(OiPr)_4$ with **13** (see Section 3.5).[35b] Bulman Page et al.[36]



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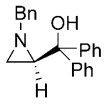

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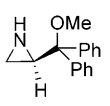

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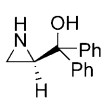
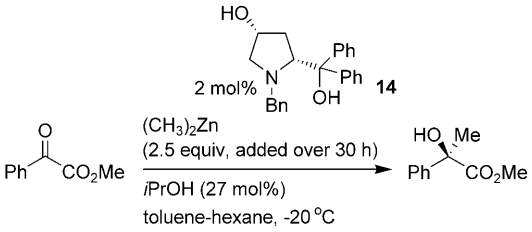


13

developed several aziridine-based ligands for the asymmetric addition of diethylzinc to aromatic aldehydes. A moderate (+)-NLE was detected with **11** and **12**, where the involvement of dimeric zinc species was assumed. A substrate-dependent (−)-NLE was found with **13**, similar to the effect reported by Walsh and co-workers.[32] A modification of the catalyst or inhibition of the product was suggested as a cause for these effects.

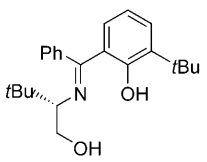
A strong (+)-NLE was observed by Shibasaki and co-workers[37] in the catalytic enantioselective addition of Me_2Zn to α-ketoesters in the presence of **14** [Eq. (5)]. The effect was attributed to the formation of a stable heterochiral dimer similar to the Noyori system.[27] The selectivities and reactivities were higher when *i*PrOH was added as an additive, but the absence of an NLE suggested the breakdown of the in situ formed dimer (ZnL-ZnL) with generation of the mixed aggregate [ZnL-Zn(O*i*Pr)], which affords a higher *ee* value and yield.



2 mol% **14**
$(CH_3)_2Zn$
(2.5 equiv, added over 30 h)
*i*PrOH (27 mol%)
toluene-hexane, −20 °C

(5)

Hayashi and co-workers[38] reported a highly enantioselective addition of diethylzinc to aldehydes (up to 96% *ee*) by using the tridentate chiral Schiff base ligand **15**. The previously discussed examples all involved bidentate ligands. A moderate (+)-NLE was noticed with the non-enantiopure **15**. The authors suggested an involvement of zinc aggregates instead of dimers (as in the Noyori-type model) in the catalytic cycle.



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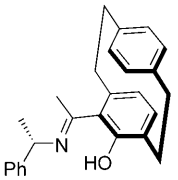
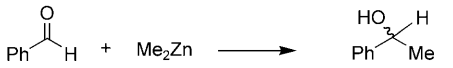


(S_P,*S*)-**16**

Nonlinear effects were observed with bulky [2.2]paracyclophane-based bidentate ligands, which are usually expected to disfavor the dimerization of the corresponding organozinc species. Bräse and co-workers[39] found that **16**

afforded a (+)-NLE in the addition of Et_2Zn to cyclohexanecarbaldehyde. The effect was pronounced at a high ligand concentration, while a linear correlation was noticed under dilute conditions. The formation of an insoluble heterochiral dimer at high concentration causes the (+)-NLE. Under dilute reaction conditions, the heterochiral dimer is soluble and enters into the catalytic cycle upon its break down into monomers, thereby resulting in the absence of an NLE.

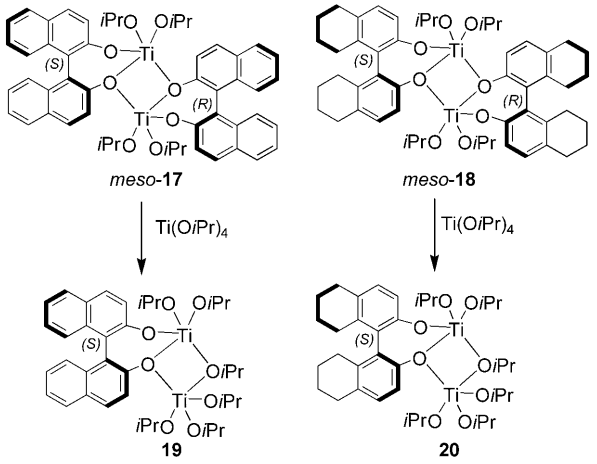
Walsh and co-workers[40] detected a weak (−)-NLE in the case of the asymmetric addition of dimethylzinc to aldehydes mediated by binolate–titanium complexes (10 mol% binol) [Eq. (6)]. The (−)-NLE was also previously noticed by Mori



(6)

and Nakai with diethylzinc.[41] Walsh and co-workers found that the NLEs disappeared under catalytic conditions.[40] The authors ruled out the involvement of oligomeric species and the possibility of binol acting as a monodentate ligand. It was assumed that in catalytic reactions, [(binolate)Ti(O*i*Pr)$_2$] preferentially associates with Ti(O*i*Pr)$_4$ to form the catalyst [(binolate)Ti(O*i*Pr)$_2$]·Ti(O*i*Pr)$_4$, which provided the linear correlation between ee_{prod} and ee_{binol}.

Under stoichiometric conditions (100 mol% binol), [(binolate)Ti(O*i*Pr)$_2$ dimerizes to *meso*-[{(binolate)Ti(O*i*Pr)$_2$}$_2$] (**17**; M_2L_2 system)]. It was demonstrated that the



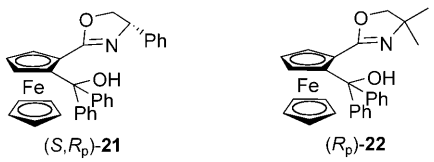
dimeric species do not catalyze the reaction; an in situ formed [(binolate)Ti(O*i*Pr)$_2$-(aldehyde)MeTi(O*i*Pr)$_3$] complex was presumed to be the active species. Subsequent studies using H_8-binol revealed similar NLEs.[42] *rac*-H_8-Binol and one equivalent of Ti(O*i*Pr)$_4$ resulted in the formation of *meso*-**18**, as characterized by single-crystal analysis. The *meso* dimers were found to be in equilibria with the corresponding homochiral dimers in solution. Under catalytic conditions, the dimers **17** and **18** break down into dinuclear complexes **19** and **20**, respectively, through the coordination of excess Ti(O*i*Pr)$_4$, thereby leading to the linear correlation. The structures of **19** and **20** were established by X-ray crystallography.

Burguete et al. noticed an efficient chirality switching in the addition of dialkylzinc to benzaldehyde in the presence of nickel catalysts prepared from α-amino amides and Ni(OAc)$_2$.[43] Studies on the catalysts suggested the presence of monomeric and oligomeric species in equilibrium. The 1:2 complexes were more stable than the 1:1 complexes. The chirality switching is achieved by changing the metal to ligand ratio. The 1:1 complex resulted in a strong negative NLE, which is suggestive of the formation of an aggregate. No NLE was observed with the 1:2 complex.

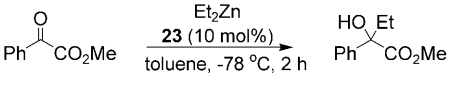
2.1.1. *Absence of NLEs in Organozinc Additions*

The absence of an NLE in a reaction may, as already discussed, provide some mechanistic information. For example, when an NLE is absent in a catalytic enantioselective reaction with a chiral ligand L and metal M, then one can likely assume that 1) phenomena such as dimerization $(ML)_2$ or oligomerization $(ML)_n$ are absent and 2) the metal species bear only one chiral ligand. However, these conclusions are merely preliminary assumptions, they become invalid for some special cases such as ML_2 where hetero- and homochiral catalysts can have identical reactivities ($g = 1$) or there is no formation of the heterochiral catalyst ($\beta = 0$) [Eq. (2)]. We will discuss here some recent important examples.

Bolm et al.[44a,b] found a strict linear correlation between ee_{prod} and the *ee* value of bulky ligands (S,R_p)-**21** and R_p-**22** in the addition of diethylzinc to aldehydes. This finding was



considered as an indication of the absence of dimerization.[44a] DiMauro and Kozlowski[45] proposed a monomeric form for the catalyst, based on the linear correlation between ee_{prod} and the *ee* value of **23** in the enantioselective addition of organozinc reagents to α-ketoesters [Eq. (7)]. Braga et al.[46] employed the chiral disulfide **24** as the catalyst for the addition of diethylzinc to benzaldehyde. The absence of an NLE led to the suggestion that the *R*/*S*-heterodimeric Zn



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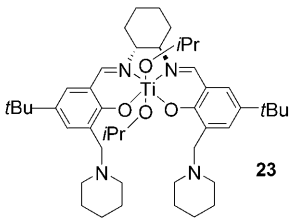
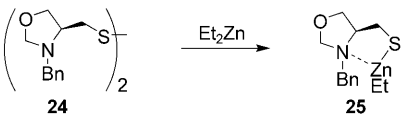
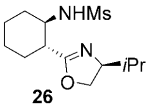


complexes of the sulfide ligand **25** [Eq. (8)] are either not formed or dissociate quickly into their monomeric intermediates because of steric effects.



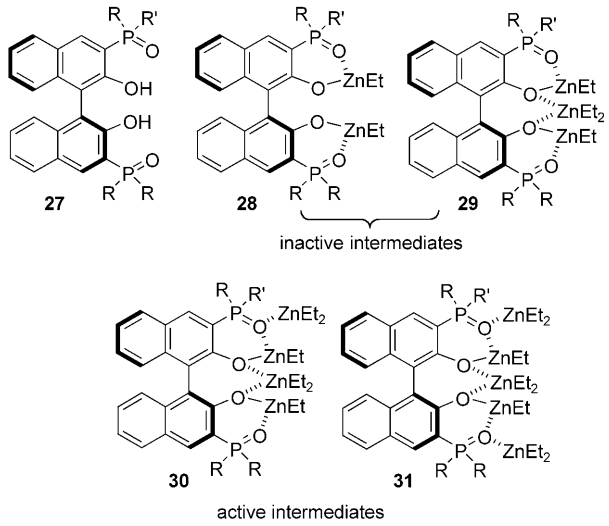
24 **25** (8)



26

Wipf et al.[47] used the absence of an NLE to interpret the high turnover numbers of catalyst **26** in the asymmetric addition of diethylzinc to benzaldehyde. Ligand **26** provided consistent enantioselectivity (85–88% *ee*) over a broad concentration range (from 5 to 0.1 mol%). The turnover number was found to be as high as 1000–2000.

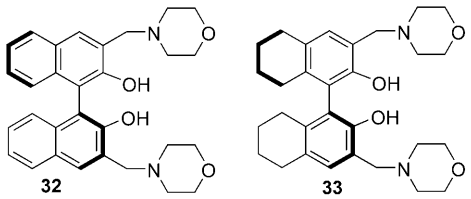
Bifunctional binol ligands **27**, bearing both Lewis acidic and Lewis basic groups have been employed, in an enantioselective addition of dialkylzinc to a variety of aldehydes.[48]



27 **28** **29** **30** **31**

The presence of two P=O moieties at the 3,3′-positions in the binol skeleton was found to be necessary to achieve high catalytic activity. The authors noticed a linear correlation between ee_{prod} and the *ee* value of **27**,and concluded that the active catalyst had a monomeric form. Further studies, including ^{31}P NMR experiments of their Zn^{II} complexes, led to the conclusions that **28** and **29** are inactive, while **30** and **31** are catalytically active and would be predominant under the catalytic conditions.

The bifunctional ligands (*S*)-**32** and (*S*)-**33** were found to offer high *ee* values in the enantioselective addition of diphenylzinc to aliphatic and aromatic aldehydes.[49] The absence of an NLE and some experimental data led the authors to propose a mechanism similar to one of previous studies.[48]

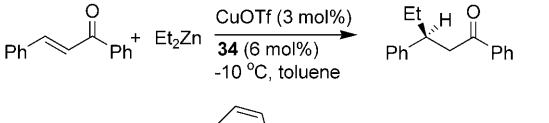


32 **33**

2.2. Conjugate Additions to Enones

Bolm et al.[50] and Feringa and co-workers[51] reported (+)-NLEs for nickel-catalyzed 1,4-additions to enones. The authors proposed the intervention of $[NiL_2]$ species in the catalytic cycle. The (+)-NLE was attributed to a greater stability and a lower activity of the heterochiral complex ($[NiL_RL_S]$). Zhou and Pfaltz[52] as well as van Koten[53] observed a different type of NLE in the copper-catalyzed 1,4-addition of diethylzinc to enones. In one case a (−)-NLE with a multishaped curve was found,[52] while in another case a multishaped NLE consisting of both (+)- and (−)-NLEs was identified.[53] Kagan and co-workers previously suggested, on the basis of simulations of NLE curves, that the formation of a tetrameric complex, which is common for copper complexes, may be responsible for multishaped NLEs.[10] Mikami et al. later revisited this approach.[54]

Feringa and co-workers[55] employed a variety of new chiral phosphoramidites as chiral ligands in the copper-catalyzed enantioselective conjugate addition of diethylzinc to cyclohexenone and chalcone to provide products with high levels of enantioselectivity. A (−)-NLE was detected using non-enantiopure ligands **34a** and **34b** [Eq. (9)] as ligands. The coordination of two ligands to the copper atom in the catalytic cycle has been suggested. The (−)-NLE arises from the greater reactivity of the heterochiral catalyst.



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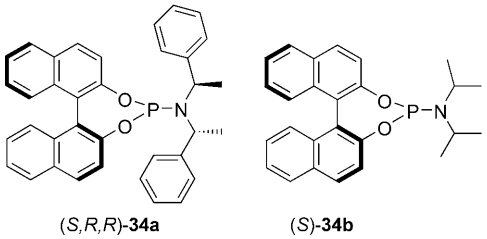
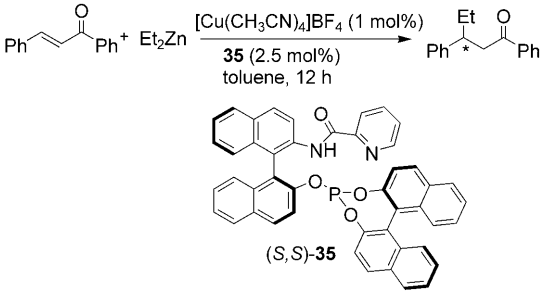


(*S,R,R*)-**34a** (*S*)-**34b**

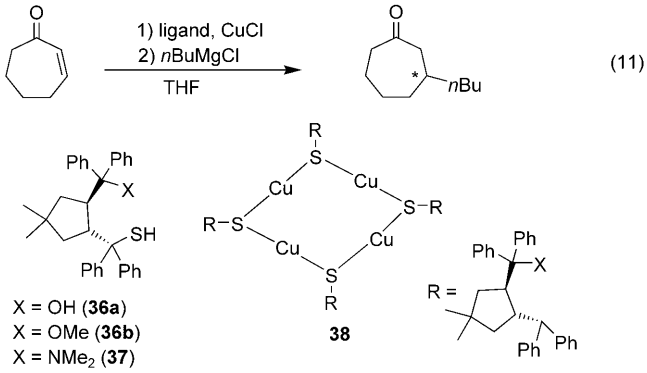
Hu et al.[56] found a (+)-NLE in the copper-catalyzed addition of Et_2Zn to chalcone in the presence of the bidentate P,N ligand **35** [Eq. (10)]. This effect occurred when 2.5 mol% of a scalemic mixture of (*S,S*)-**35** and its enantiomer (*R,R*)-**35** was used. The experimental curve perfectly fitted with the simulated curve for the ML_2 system with $g = 0.2$ and $K = 4$.

The authors thus proposed that the active catalyst is [Cu(**35**)$_2$].



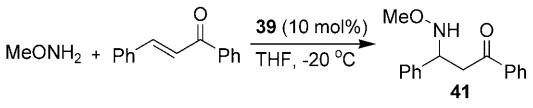
(10)

A (+)-NLE in the enantioselective 1,4-addition of BuMgCl to cycloheptenone in the presence of CuCl and the thiols **37** [Eq. (11)] suggested the involvement of several ligands and metals in the reaction mechanism.[57] The structures of the actual catalysts or catalyst precursor were subsequently established as tetranuclear copper–thiolate complexes **38** [Eq. (11)] by X-ray analysis of a single crystal obtained by treatment of **37** with *n*BuLi followed by the addition of CuCl.



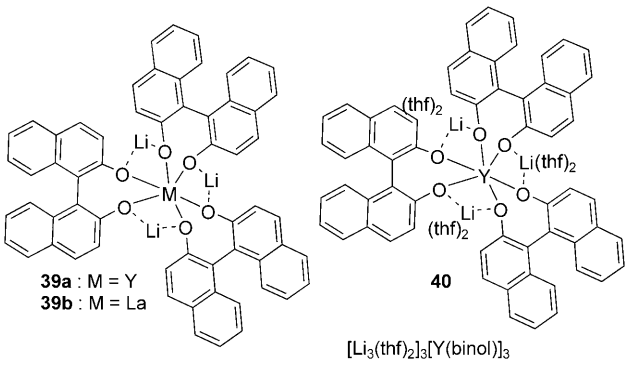
(11)

Shibasaki and co-workers[58a] proposed the involvement of inactive heterochiral complexes [(*S*,*R*,*R*)-**39** and (*R*,*S*,*S*)-**39**] and reactive homochiral complexes [(*R*,*R*,*R*)-**39** and (*S*,*S*,*S*)-**39**] in the aza-Michael reaction of methoxylamine with chalcone on the basis of the (+)-NLE found with non-enantiopure binaphtholate complexes **39** [Eq. (12)]. A (+)-NLE was also previously detected in a nitroaldol reaction



(12)

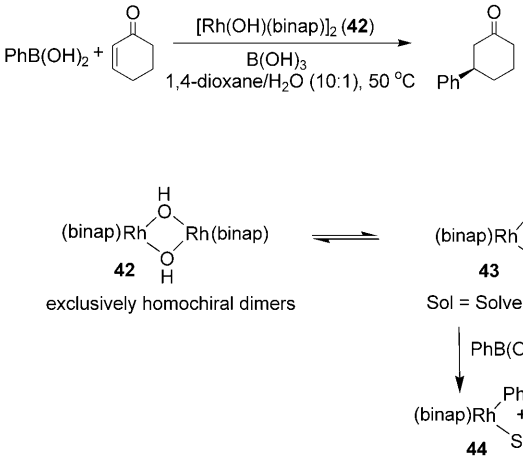
catalyzed by a similar catalyst **40**.[58b] Racemic binol resulted in the exclusive formation of heterochiral complexes, in agreement with earlier observations by Aspinall et al.[59] (**40**) and Shibasaki and co-workers (**39a**).[58a] A 1:1 mixture of (*S*,*R*,*R*)-**39a** and (*R*,*S*,*S*)-**39a** (heterochiral) was formed from



a 1:1 mixture of pure homochiral complexes (*R*,*R*,*R*)-**39a** and (*S*,*S*,*S*)-**39a**.

An aza-Michael addition of aromatic amines to α,β-unsaturated *N*-imides was catalyzed by the cationic palladium complex [{(*R*,*R*)-binap}Pd(OH$_2$)$_2$]$^{2+}$[TfO]$^-$. A combination of experiments, including NLE studies, was helpful for the elucidation of the mechanism. A linear relationship was found between ee_{binap} and ee_{prod} (reactions performed in THF), but a (+)-NLE was observed in toluene because of the insolubility of some of the diastereomeric complexes (see Section 5).[60]

Hayashi and co-workers found a (−)-NLE in the Rh/binap-catalyzed asymmetric 1,4-addition of PhB(OH)$_2$ to 2-cyclohexenone [Eq. (13), Scheme 2].[61] The reaction order was found to be 0.5 with respective to the rhodium concen-



(13)

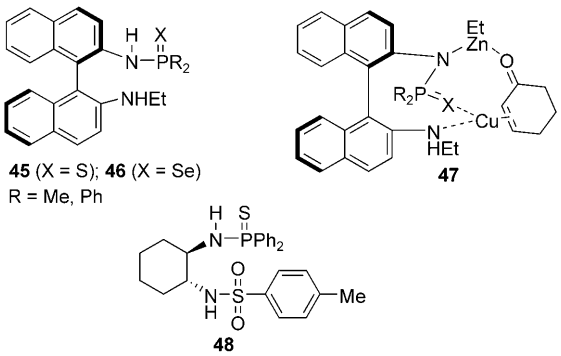
Scheme 2.

tration, which supports the involvement of dimers. Identical ^{31}P NMR spectra in the cases of the racemic and enantiopure binap-hydroxorhodium complexes indicated the preferential formation of the homochiral dimer **42**. Previous studies[62] revealed that transmetalation of the phenyl group from boron to hydroxorhodium generates the key intermediate **44**, from which the phenyl group transfers to the enone. The formation of an inactive homochiral dimeric hydroxorhodium complex **42** was suggested on the basis of the (−)-NLE combined with the kinetic and NMR data. An equilibrium between **42** and

43, with **43** reacting with $PhB(OH)_2$ to generate **44**, was proposed (Scheme 2).

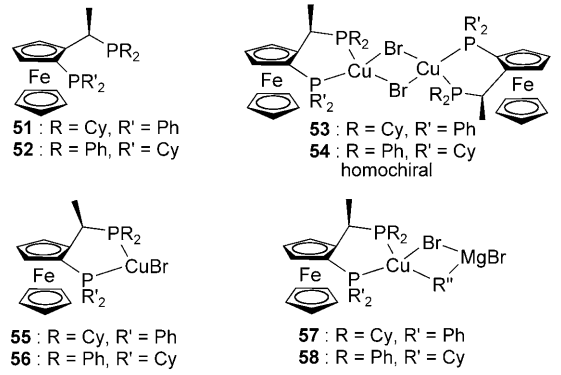
2.2.1. Absence of NLEs in Conjugate Additions

Shi et al.[63,64] reported an efficient asymmetric conjugate addition of organozinc compounds to enones catalyzed by Cu complexes generated in situ from **45** or **46**. ^{31}P NMR and

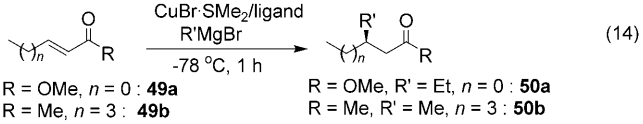


^{13}C NMR spectroscopic experiments revealed that **45** and **46** act as N,X ligands. A linear correlation suggests that the Cu complex bears a single chiral ligand, and a bimetallic species **47** was proposed as the possible intermediate in the reaction. A mechanism involving a bimetallic species similar to **47** was also envisaged with the bidentate ligand **48**.

Copper complexes derived from chiral diphosphine **51** (Cy = cyclohexyl) or **52** and $CuBr{\cdot}SMe_2$ are effective catalysts for the enantioselective conjugate addition of Grignard



reagents to acyclic α,β-unsaturated methyl esters **49a** and ketones **49b** (up to 99% *ee*)[65,66] [Eq. (14)].



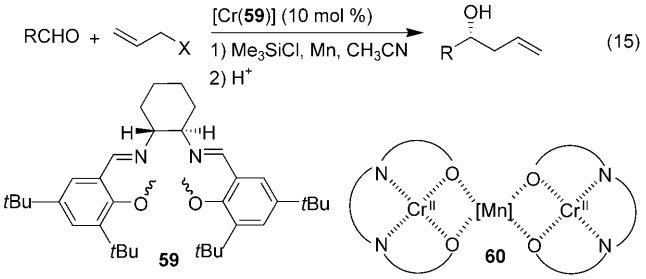
(14)

Subsequent ESI-MS and IR spectroscopic studies showed a solvent-dependent equilibrium between a dinuclear (**53** or **54**) and a mononuclear (**55** or **56**) species; in some cases this was confirmed in some cases by single-crystal X-ray analyses.[67] A dinuclear complex (**53** or **54**) was predominant in ether and halogenated solvents, while a mononuclear complex (**55** or **56**) was dominant in CH_3CN and MeOH. On the basis of a linear correlation between ee_{prod} and the *ee* value of the ligand (**51** or **52**), the catalytically active species was assumed to contain only one ligand molecule. This hypothesis was in agreement with the first order dependency of the reaction kinetics on the precatalyst. The dinuclear complexes (**53** or **54**) were presumed to be the precatalyst (homo- and heterochiral) which, upon the addition of Grignard reagents R″MgBr, breaks down into the actual catalytically active monomeric species (**57** or **58**).

2.3. Allylation of aldehydes

Several research groups have employed NLE studies to determine the active species in the addition of allylzinc compounds to aldehydes catalyzed by binol complexes.[67–70] Keck et al.[67] and Faller et al.[69] noticed a (+)-NLE when a binol-$Ti(OiPr)_4$ catalyst prepared in the presence of molecular sieves was used. A linear correlation was obtained in the absence of molecular sieves. Tagliavini and co-workers[68] found a strong (+)-NLE when using the catalyst prepared from binol and $[Ti(OiPr)_2Cl_2]$ in the presence of molecular sieves. Gauthier and Carreira[70] observed a similar deviation from linearity in the allylation of pivalaldehyde with allyltrimethylsilane by using a binol–titanium catalyst prepared from binol and TiF_4. In all the cases[67–70] the NLEs were attributed to the formation of a stable and less-active heterochiral complex during the preparation of the catalyst.

Bandini et al. developed a highly diastereo- and enantioselective [Cr(salen)]-catalyzed reaction of allyl halides to aldehydes in the presence of weak Lewis acids such as manganese salts [Eq. (15)].[71] The presence of a (−)-NLE

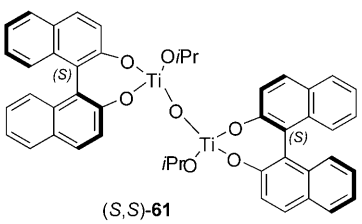


(15)

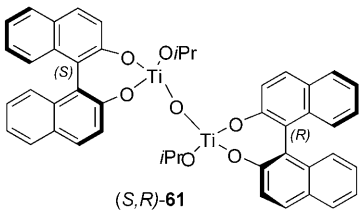
with triple-shaped curves led the authors to suggest the involvement of tetrameric species on the basis of previous predictions of multishaped NLEs curves in ML_4 models by mathematical simulations.[10] Bandini et al.[71] hypothesized the involvement of a catalytically active dimeric aggregate $[(\mathbf{59})_2Cr_2X_2]$ (structure **60** shows a simplified description) and a catalytically inactive tetrameric aggregate $[(\mathbf{59})_4Cr_4X_4]$. A reaction order of 0.5 in the chromium concentration suggested that two molecules of the catalyst are involved in the

rate-determining step of the reaction. This suggestion is in agreement with the hypothesis of dimeric and tetrameric aggregates.

Maruoka and co-workers[72,73] prepared a binolate–Ti^{IV} catalyst **61** for asymmetric allylation with allyltributyltin [Eq. (16)]. The structure of **61** was established by mass

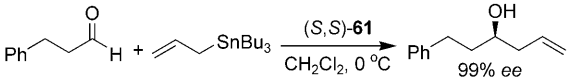


(*S*,*S*)-**61**
homochiral: active species



(*S*,*R*)-**61**
heterochiral: inactive species

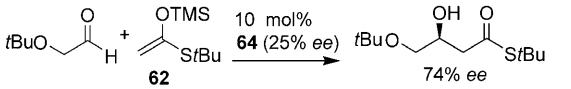
spectrometry. Since it was not certain that this structure would remain intact after the addition of substrates, the authors took advantage of the presence of a nonlinear effect to study the structure of the catalyst in the catalytic cycle.[72] A strong (+)-NLE was observed with **61** prepared from partially resolved (*S*)-binol. However, a linear correlation was obtained when enantiomerically impure **61** was prepared by mixing enantiopure (*S*,*S*)-**61** and (*R*,*R*)-**61** in different ratios. These studies suggested that bis-Ti^{IV} oxide **61** exists as a monomeric species and is coordinatively stable, and does not undergo any scrambling during the reaction.



(16)

2.4. Aldol and Mannich Reactions

Keck and Krishnamurthy [74] noticed a (+)-NLE in the catalyzed Mukaiyama aldol condensation of benzaldehyde with a ketene acetal [**62**; see Equation (17)]. The catalyst was prepared from binol and $Ti(OiPr)_4$ in the presence of molecular sieves. A ML_2 model was suggested to explain the occurrence of the NLE. Evans et al. found that [Cu(Ph-pybox)]$(SbF_6)_2$ (**64**, Scheme 3) is an efficient catalyst for the Mukaiyama aldol reaction described in Equation (17)



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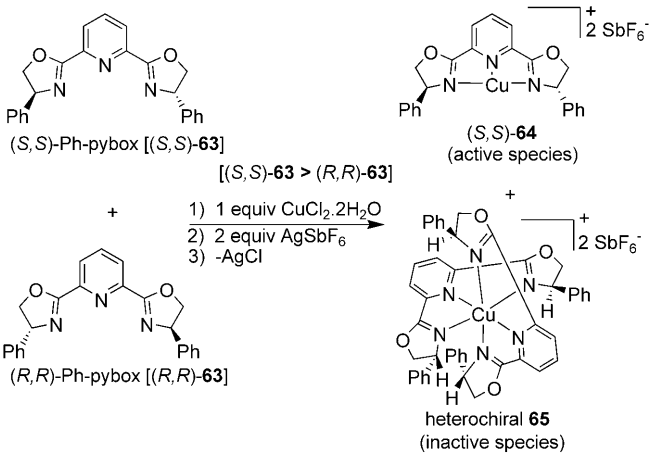
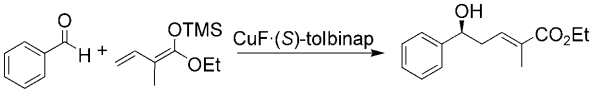


Scheme 3.

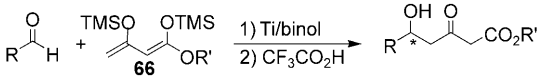
(TMS = trimethylsilyl).[75] A strong (+)-NLE was observed when an enantioimpure Cu catalyst was prepared from non-enantiopure **63** and the Cu reagent. Thus, authors proposed the formation of a stable heterochiral ML_2 complex **65**. Semiempirical calculations (PM3) and single-crystal X-ray analyses also indicated the higher stability of heterochiral **65**. Subsequent examination of the hetero-Diels–Alder reaction[76] and glyoxylate–ene reaction[77] using the same catalyst **64** did not show any such nonlinear effects. It was suggested that, under the hetero-Diels–Alder and glyoxylate–ene reaction conditions, the ML_2 complexes **65** might be unstable.

Bluet and Campagne[78] described catalytic asymmetric vinylogous Mukaiyama reactions using different enolate activators, such as CuF·(*S*)-tolbinap, and various chiral non-racemic ammonium fluorides derived from cinchona alkaloids [Eq. (18)]. A multishaped curve, involving a small (−)-NLE for lower *ee* values of the ligand and a very slight (+)-NLE for higher (> 40 %) *ee* values, was noticed. The involvement of ML_4 complexes which can produce multishaped NLE curves may be envisaged in this case.[10]



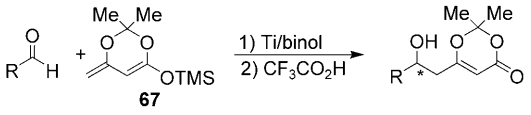
(18)

The aldol condensation of masked alkylated acetoacetates [Chan's diene, **66**, Eq. (19)][79] and *O*-silyldienolates **67** [Eq. (20)][80] was promoted by complexes formed between $Ti(OiPr)_4$ and scalemic binol.



(19)

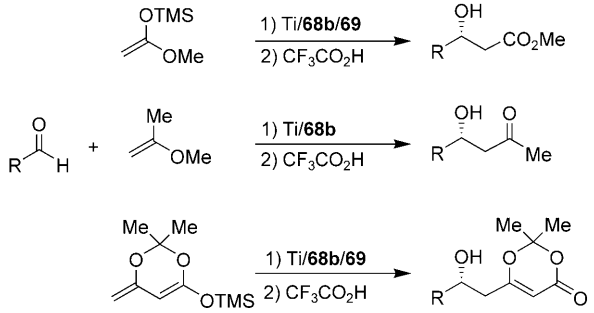
In both cases a (+)-NLE was detected,[79,80] which was attributed to the in situ formation of active homochiral and ineffective heterochiral oligomers. A linear relationship



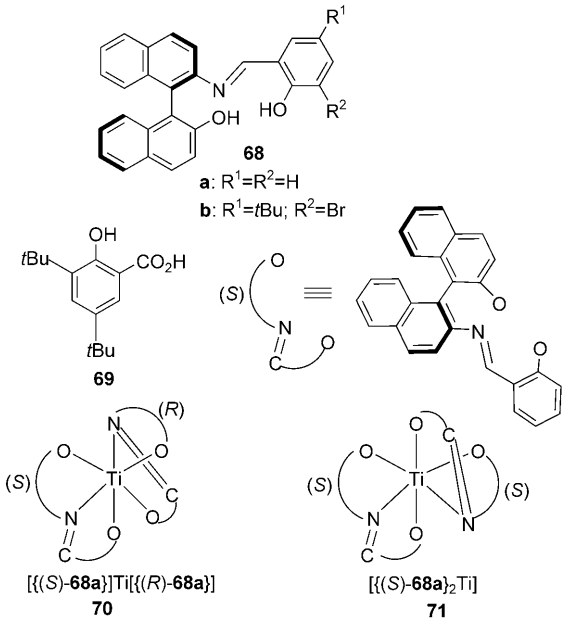
(20)

between ee_{prod} and ee_{cat} was noticed when the catalyst was prepared by mixing enantiopure (*S*)- and (*R*)-binol–titanium complexes, both prepared at the same concentrations.[79,80] In contrast, NLEs were observed when the enantiopure (*S*)- and (*R*)-binol–titanium complexes were prepared at different concentrations; the catalyst at higher concentration in solution always dominated the reaction.[79a,80] It was pointed out that an autoinductive Walsh-type process would also be operative.[81]

Ding and co-workers[82,83] later extended the study to the Carreira aldol condensation of aldehydes[84] with various enol ethers in the presence of **68b** (Scheme 4). Similar (+)-NLEs

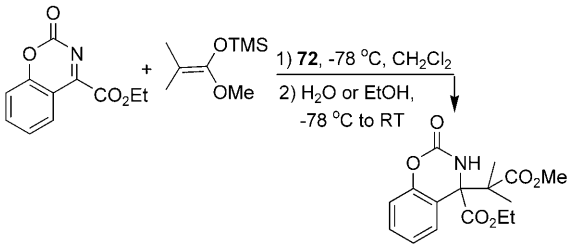


Scheme 4.



were again encountered. The titanium complexes prepared from (±)-**68a** and enantiopure (*S*)-**68a** with $Ti(OiPr)_4$ (2:1 molar ratio) had the structures **70** and **71**, respectively, as established by single-crystal X-ray analysis. Complex **70** was found to be inert, while **71** was catalytically very active (see also Section 2.5). The NLE observed in the presence of **68b** was attributed to the formation of a stable hexacoordinated heterochiral complex.

The Lewis acid catalyzed enantioselective alkylation of imines using chiral zinc complex **72** was reported by Jørgensen et al. [Eq. (21)].[85] A (+)-NLE was observed,



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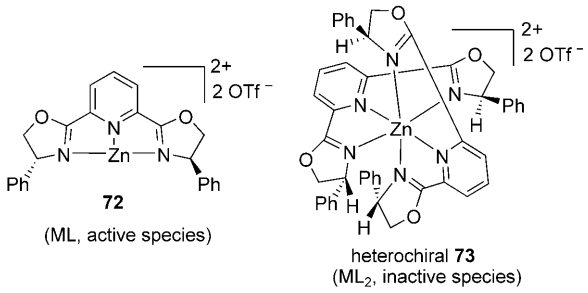
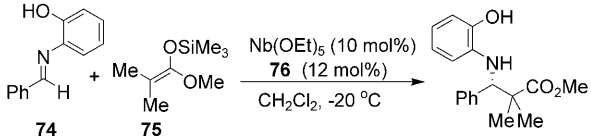


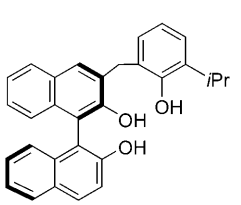
with a catalyst of 30% *ee* affording the product with 90% *ee*. The reaction of $Zn(OTf)_2$ with (*R*,*R*)-Ph-pybox and (*S*,*S*)-Ph-pybox resulted in the formation of 1:2 metal–ligand complexes, and a single-crystal X-ray analysis confirmed the structure **73**. The insolubility of heterochiral complex **73** in most organic solvents led to the assumption that it served as a catalytically inactive reservoir for racemic **72**.

Kobayashi et al.[86] employed NLE studies to confirm the formation of dimeric species in the catalytic cycle of the asymmetric Mannich type reaction of imines **74** with enolates **75** using an in situ generated catalyst from polyphenol **76** and niobium alkoxides [Eq. (22)]. A significant (+)-NLE was



(22)

found with scalemic **76**, while a slight (−)-NLE was obtained in the presence of the non-enantiopure catalyst obtained by mixing samples of enantiopure catalysts separately prepared from (*R*)- and (*S*)-**76**. The authors concluded the involvement of a stable dimeric species, that is, the absence of ligand exchange, during the course of the reaction, with the homochiral dimers being the more reactive dimers. NMR spectroscopic analysis indicated structure **77** in solution, while



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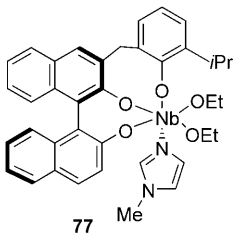

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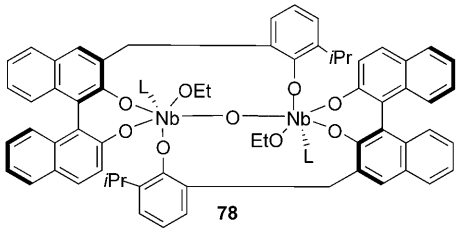

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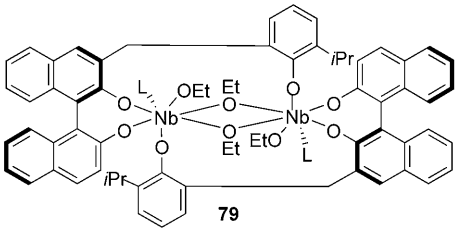
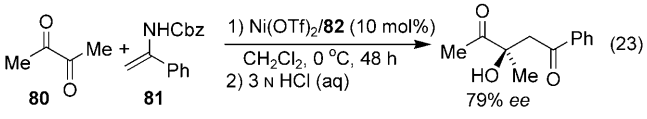


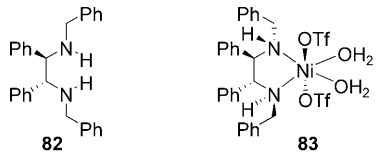
79

X-ray analysis of an isolated complex provided structure **78**. Complex **79** was proposed as the probable structure of the catalyst precursor. The presence of minor water impurities, was given as an explanation for the formation of **78**.

A strong (+)-NLE was detected in the nucleophilic addition of enecarbamate **81** on diketone **80** catalyzed by a complex generated in situ from nickel(II) triflate and scalemic (*R*,*R*)-**82** [Eq. (23); Cbz = carbobenzyloxy].[87] The monomeric aquanickel(II) complex **83**, whose structure was established by X-ray crystallography, could be the catalyst precursor.[88] The strong (+)-NLE was tentatively attributed to the formation of ineffective heterochiral [NiL_2] complex.



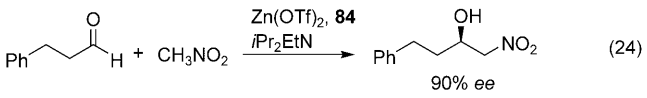
80 81 (23)



82

83

Palomo et al.[89] found a (+)-NLE in an enantioselective Henry reaction of nitromethane [Eq. (24)]. The experimental NLE data were interpreted by using a ML_2 model. The



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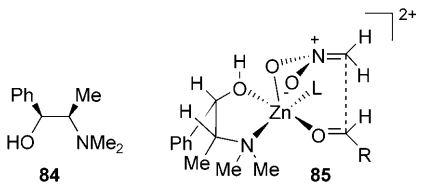
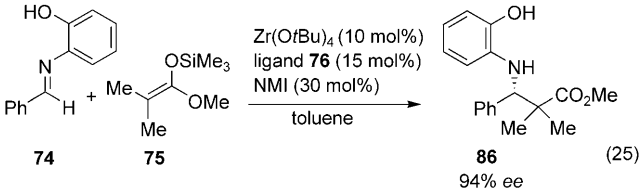


84 85

magnitude of the NLE was found to be independent of the catalyst loading and conversion. Therefore, the involvement of mechanisms such as the reservoir effect or the self-induction by nitroaldol product were ruled out. The observed (+)-NLE could be due to the formation of an unreactive heterochiral complex. The asymmetric induction was explained by using the transition-state model **85**.

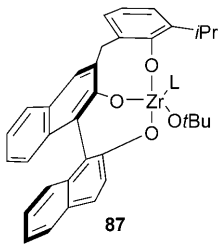
2.4.1. *Absence of NLEs in some Mannich Reactions*

The [Zr(**76**)]-catalyzed Mannich reaction of imine **74** with ketene silyl acetal **75** provides the secondary amine **86** in good yields and enantioselectivity [Eq. (25); NMI = *N*-methylimidazole].[90] A strict linear correlation led to the assumption of



74 75 86 (25)

a single ligand being involved in the actual catalytically active species. Together with extensive NMR data and DFT calculations, the authors proposed **87** as the active catalyst, and **88** as the possible reaction intermediate.



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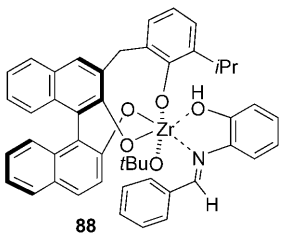
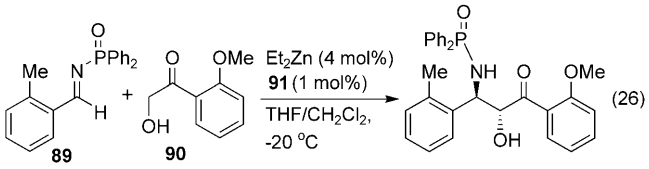
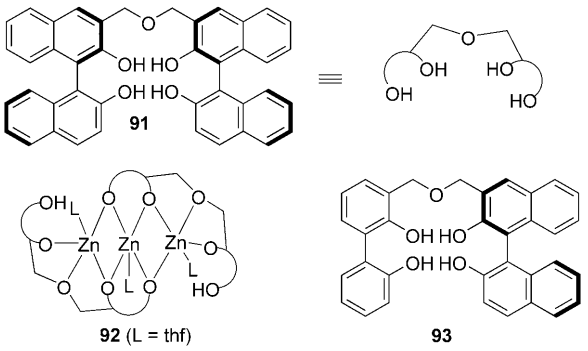


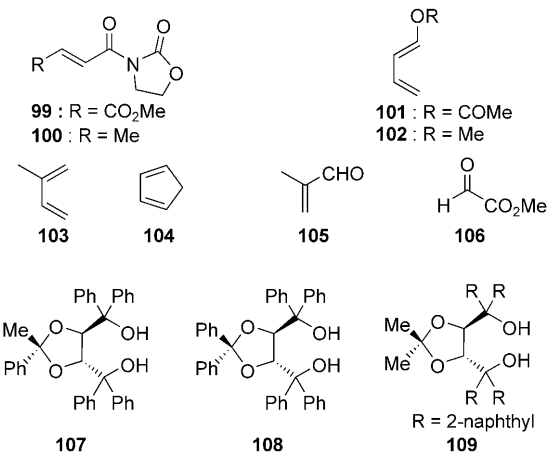
88

Subsequently, Kobayashi and co-workers[91] observed no NLE in the Mannich reaction of **89** with **90** catalyzed by the in situ formed Zn complex from linked-binol **91** and Et_2Zn [Eq. (26)]. The 3:2 Zn/**91** complex **92**, with free OH groups,

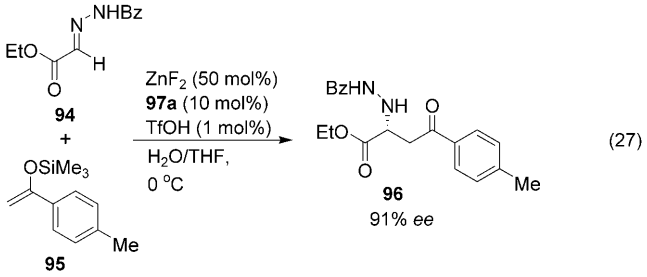


89 90 (26)





was identified as the precatalyst. The absence of an NLE was explained by the preferential formation of a homochiral complex over a heterochiral complex. The participation of the monomeric ZnF_2 complex **98** (X = F) in the catalytic cycle of the enantioselective Mannich reactions of α-hydrazono ester **94** with silicon enolates **95** was suggested on the basis of the linear correlation between the *ee* value of **97a** and that of product **96** [Eq. (27)].[92] The structure of **98a** was proposed in



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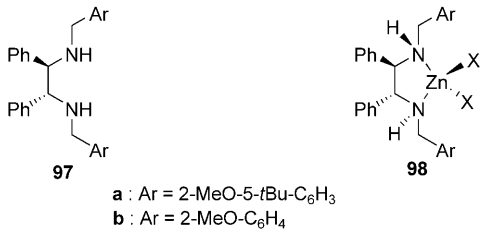
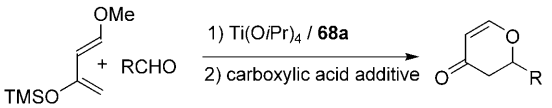


analogy to the structure of the isolated $ZnCl_2$ complex **98b**, which was determined by X-ray crystallography.

2.5. Diels–Alder Reactions

In 1989, Narasaka and co-workers[93] described a (+)-NLE in the titanium-catalyzed Diels–Alder reaction between **99** and **100** in the presence of taddol **107** as chiral ligands. The catalyst was prepared in situ from $Ti(OiPr)_4$ and **107**. Later, Irrure et al.[94] similarly examined the NLE in the titanium-catalyzed reaction of **100** and **104** by using diol **108** as the chiral auxiliary, and again a (+)-NLE was observed. In both cases, nonlinear effects were due to the involvement of stable, partially insoluble and inactive heterochiral complexes. Mikami et al.[95] examined the titanium-binol-catalyzed cycloaddition of **101** and **105**. A (+)-NLE was obtained when the non-enantiopure titanium-binol catalyst was prepared by mixing the titanium-binol complexes obtained separately from enantiopure and racemic binols. In contrast, a linear correlation was noticed if the scalemic catalyst was prepared by mixing the enantiopure (*R*)- and (*S*)-binol-titanium complexes. Ligand exchange was slow in the absence of molecular sieves, which are essential for the observation of an NLE. Kobayashi et al.[96] noticed that the sign of the NLE depended on the type of metal employed to catalyze the hetero-Diels–Alder reaction between **102** and **106**: a (+)-NLE was seen with a scandium-binol catalyst, while a (−)-NLE was obtained with an ytterbium-binol catalyst. Variations in the aggregation pattern between the scandium and ytterbium complexes explain the shift in the sign of the NLE. Seebach et al.[97] encountered a (+)-NLE in the Diels–Alder reaction between **102** and **106**, with a catalyst derived from **109** and [Ti-$(OiPr)_2Cl_2$]. The reaction mixture was found to be a homogeneous solution, and the NLE was attributed to the formation of an inactive heterochiral complex.

Ding and co-workers[82] developed an asymmetric hetero-Diels–Alder reaction of Danishefsky's diene and benzaldehyde catalyzed by $Ti(OiPr)_4$ in the presence of tridentate Schiff base ligand **68a** and a carboxylic acid [Eq. (28)].



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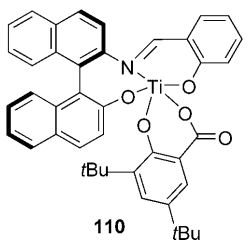
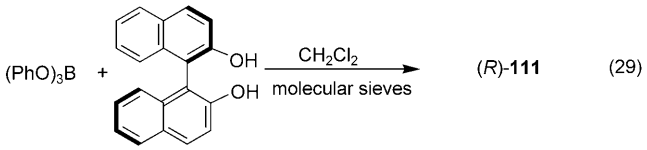


Almost racemic products were obtained in the absence of carboxylic acid additives, while the enantioselectivity of the reaction was increased to 86% *ee* in the presence of 5 mol% of some salicylic acid derivatives and 4 Å molecular sieves. A (+)-NLE suggested the formation of stable and less-reactive heterochiral complexes [Ti{(*S*)-**68a**}{(*R*)-**68a**}], which remove some racemic **68a** from the catalytic cycle. The remaining homochiral complex [Ti{(*S*)-**68a**}{(*S*)-**68a**}] reacts with the salicylic acid additive to form the active species **110**, which operates in the catalytic process. The air-stable titanium complex derived from racemic **68a** could be isolated and fully identified as heterochiral structure **70** (see Section 2.4).

A chiral boron catalyst **111** [Eq. (29)] prepared in situ by mixing enantiopure binol and $(PhO)_3B$ (1:1) was used for asymmetric aza-Diels–Alder and other asymmetric reactions [Eq. (30); Bn = benzyl].[98,99]



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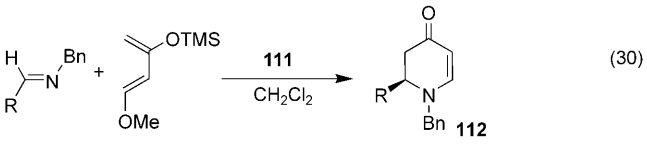
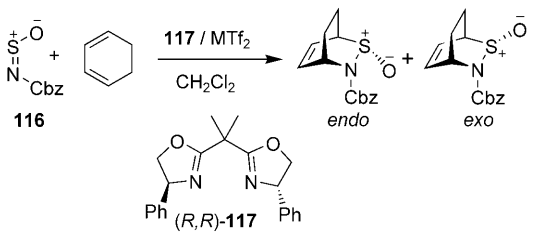


(30)

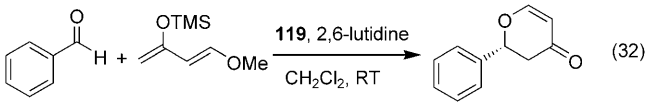
Hattori and Yamamoto[98a] proposed the monomeric binol-boron complex (*R*)-**113** as the most likely catalytic species. Attempts to develop an alternate synthesis of boron complex **113**, by refluxing two equivalents of (*R*)-binol with one equivalent of $(MeO)_3B$ in CH_2Cl_2 in the presence 4 Å molecular sieves, gave a crystalline borate species (*R*,*R*)-**114**.[98c] This complex catalyzed the formation of (*R*)-**112** with the same level of enantioselectivity (86% *ee*) as (*R*)-**111** [82% *ee*, Eq. (30)]. Cros et al.[99] employed nonlinear effects to probe whether the catalytic species **111** actually contains one or more equivalent of binol. They used scalemic binol (*ee* ranging from 0 to 80%) to catalyze aza-Diels–Alder reactions following the earlier procedure of Yamamoto et al. (binol/$(PhO)_3B$ 1:1, −78 °C), and found a significant (+)-NLE. The (+)-NLE was enhanced with a binol/$(PhO)_3B$ ratio of 2:1, but under otherwise identical conditions. Several other experiments confirmed the requirement of two equivalents of binol for better enantioselectivity. The authors[99] suggested that either (*R*,*R*)-**114** (as proposed by Yamamoto et al.) or (*R*,*R*,*R*)-**115**[100] was the most probable catalytically active species.

A (+)-NLE was also encountered in asymmetric hetero-Diels–Alder reactions of *N*-sulfinyl dienophiles **116** with cyclic and acyclic dienes in the presence of stoichiometric amounts of bis(oxazoline)-copper(II) or bis(oxazoline)-zinc(II) triflates [Eq. (31)].[101,102] The NLE was greater in the case of the zinc catalyst. A precipitate was detected when partially resolved ligand **117** was employed; thus the involvement of dimeric or higher aggregated complexes was suggested.



(31)

Inanaga and co-workers[103–105] observed a remarkably high (+)-NLE in the lanthanide-catalyzed (**119**) hetero-Diels–Alder reaction shown in Equation (32). It was the



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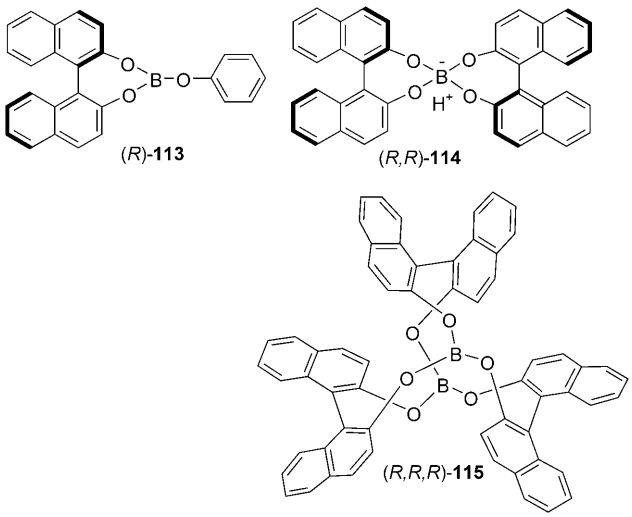
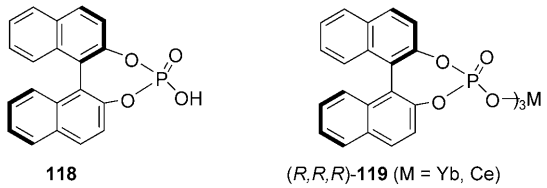
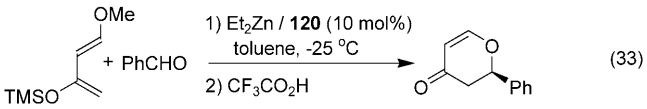




first example of an ML_3 system. Asymmetric amplification was seen in two cases: 1) when the catalyst was prepared by mixing enantiopure (*R*,*R*,*R*)-**119** and (*S*,*S*,*S*)-**119** in different ratios and 2) when non-enantiopure catalyst **119** was prepared from the non-enantiopure ligand **118**. Stronger asymmetric amplification was observed in the second case (products with 90% *ee* were obtained from **118** with only 20% *ee*). An

insoluble complex precipitated when the catalyst was prepared from **118** with 50% *ee*. The binol recovered from the insoluble precipitate had a very low *ee* value (7% *ee*) while binol with 98% *ee* was obtained from the catalyst present in solution. Based on these results, the authors presumed the formation of very stable heterochiral complexes (*R*,*R*,*S*)-**119** and (*S*,*S*,*R*)-**119** with almost no catalytic activity.

Ding and co-workers[106] found that the binolate-zinc complexes prepared in situ by the reaction of various binol derivatives with Et_2Zn are efficient chiral Lewis acid catalysts for the hetero-Diels–Alder reaction. The complex obtained from 3,3′-dibromo-binol (**120**) was an excellent catalyst and afforded the cycloadduct quantitatively with up to 98% *ee* [Eq. (33)]. The catalytic system exhibited a strong (−)-NLE



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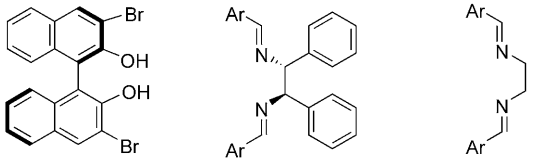
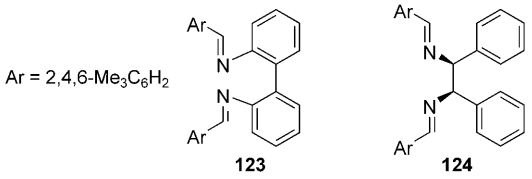
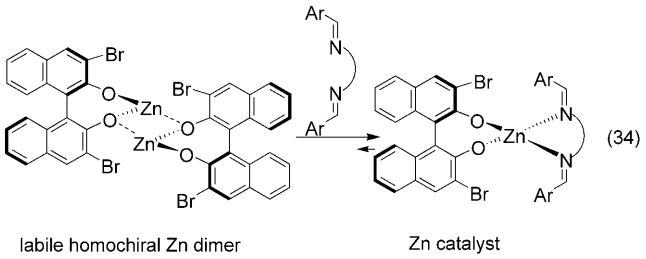




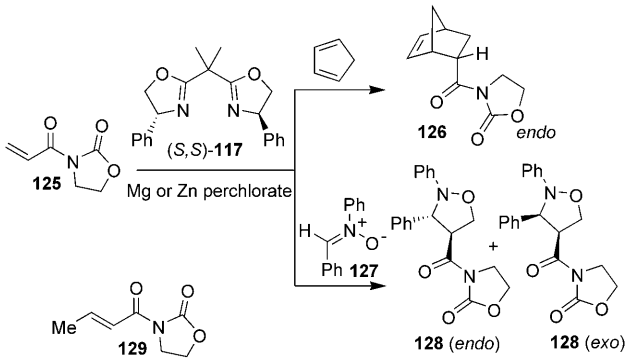
with **120** of low *ee* value, and switched to a weak (+)-NLE with **120** of higher *ee* values. The absolute configuration of the product changed from *R* to *S* when the *ee* value of (*R*)-**120** fell below 40%. In subsequent studies, Ding and co-workers[107] found that the addition of diimine activators afforded better enantioselectivity, with **121** emerging as the best chiral additive. The effect of achiral (**123**) and *meso* (**124**) additives on the NLEs were investigated. A multishaped curve consisting of a (+)-NLE for $ee > 20\%$ and a very weak (−)-NLE for $ee < 20\%$ was obtained with scalemic **120** in the presence of diimine activators, while an unusual NLE with a switching of the absolute configuration of the product[107] was found in the absence of the diimine activators. This observation indicated the involvement of diimine additives in the catalytic cycle. A precipitate was noticed during the preparation of the catalyst (from **120** with 40% *ee*) in the presence of **123**. The recovered **120** from the isolated solid and the supernatant was found to have 19.2% *ee* and >99% *ee* respectively. The occurrence of an NLE was explained by formation of stable heterochiral and labile homochiral dimeric Zn complexes and formation of the active Zn catalyst according to Equation (34). The **120**/Et_2Zn/diimine system was further employed successfully in the enantioselective



(34)

catalytic addition of diethylzinc to aldehydes;[107] **124** was the best activator in this reaction.

Acrylamide **125** undergoes both an enantioselective Diels–Alder reaction with cyclopentadiene and an enantioselective 1,3-dipolar cycloaddition with diphenylnitrone **127** catalyzed by Zn^{II}- or Mg^{II}-bis(oxazoline) chiral complexes (Scheme 5).[108,109] The magnesium(II)-based catalysts exhib-



Scheme 5.

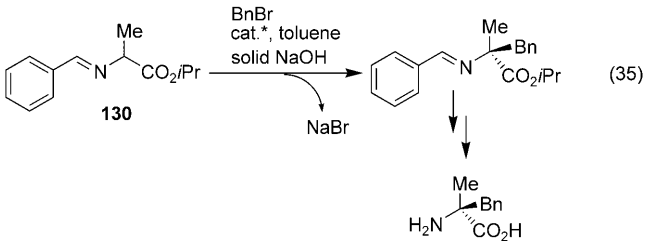
ited a linear relationship between the *ee* value of ligand **117** and that of the reaction products (**126** or **128**). A significant (+)-NLE was observed in both cycloadditions catalyzed by the Zn^{II} complex.[110] The absence of an NLE with the Mg^{II} catalyst was attributed to the lower affinity of the magnesium cation for the bis(oxazoline) **117**. NMR spectra recorded in CD_3CN indicated the formation of a 1:1:1 complex between **117**, Mg^{II}, and **129**. This means that the heterochiral dimeric magnesium(II) complex is not very stable and breaks down readily into monomeric species. The addition of **129** to the heterochiral Zn^{II} complex does not affect the reaction, thus indicating the higher stability of the heterochiral Zn^{II} complex. The heterochiral Zn^{II} complex (*meso* structure) is almost insoluble in dichloromethane and precipitates out during preparation of the catalyst, as confirmed by NMR spectroscopic and X-ray analysis. Therefore, the origin of the (+)-NLE in the Zn^{II}-catalyzed reactions was assigned to the formation of the insoluble inactive heterochiral Zn complex.

2.6. C-Alkylations

2.6.1. Chiral Phase-Transfer Catalysis

C-Alkylation by enantioselective phase-transfer catalysis (PTC) has been used successfully for the asymmetric syn-

thesis of amino acids. NLE studies were recently employed as a simple way to derive some mechanistic details about this reaction. For example, Belokon et al.[111] used chiral salen-copper complex **131** [Eq. (35)] as an efficient phase-transfer



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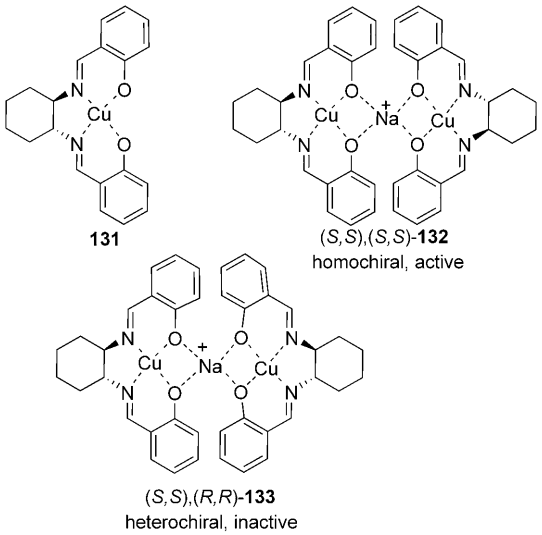
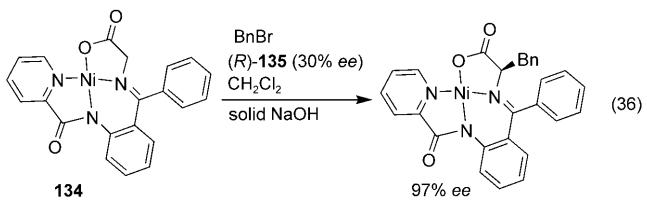


catalyst for the synthesis of chiral α-amino acids by C-alkylation of Schiff base **130** with alkyl bromides. The authors detected a strong positive nonlinear effect, in agreement with the involvement of dimeric copper complexes in the catalytic cycle. Here, the reactive dimer (*S*,*S*),(*S*,*S*)-**132** arises from the homochiral association of monomeric copper-salen complex **131** while the inactive (*S*,*S*),(*R*,*R*)-**133** results from a heterochiral association. It was suggested that the stereoselective alkylation of **130** occurs on **132**.

In subsequent studies, Belokon et al.[112,113] observed a strong (+)-NLE in the enantioselective C-alkylation of glycine-nickel chelate **134** in the presence of 10% mol (*S*)- or (*R*)-**135** (nobin) under PTC conditions [Eq. (36)]. Glycine complex **134** was sparingly soluble in dichloromethane or tetrachloroethane, and the solubility increased greatly in the



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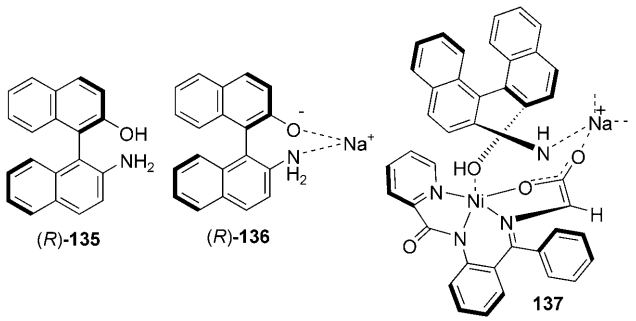
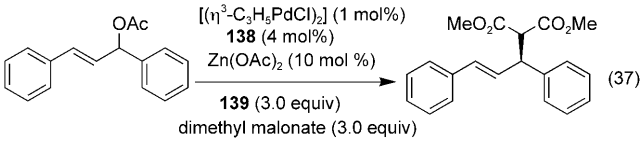


presence of the enantiopure sodium salt **136**, but not on addition of the racemic sodium salt. The authors suggested that enantiopure **136** exists as an active monomer which forms, with **134**, a highly soluble intermediate complex **137**, which undergoes an asymmetric C-alkylation.

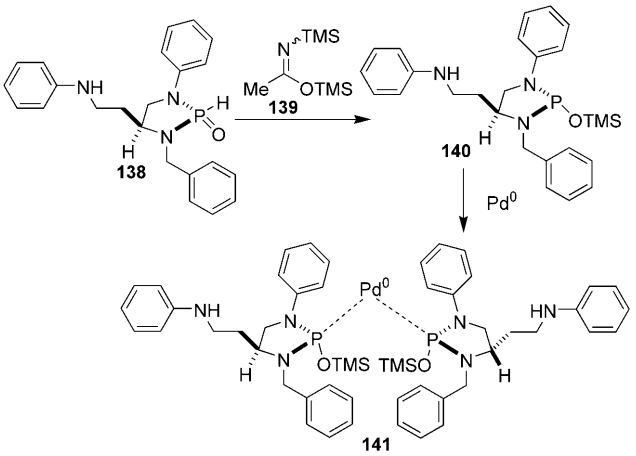
2.6.2. *Allylic Substitution*

Allylic substitution is another way to achieve C-alkylation. Nemoto et al.[114] employed NLE studies to understand the mechanistic details of the palladium-catalyzed asymmetric construction of tertiary and quaternary carbon atoms in the presence of a new class of chiral phosphorus ligands [Eq. (37)]. The trivalent phosphorus species **140** was gener-



(37)

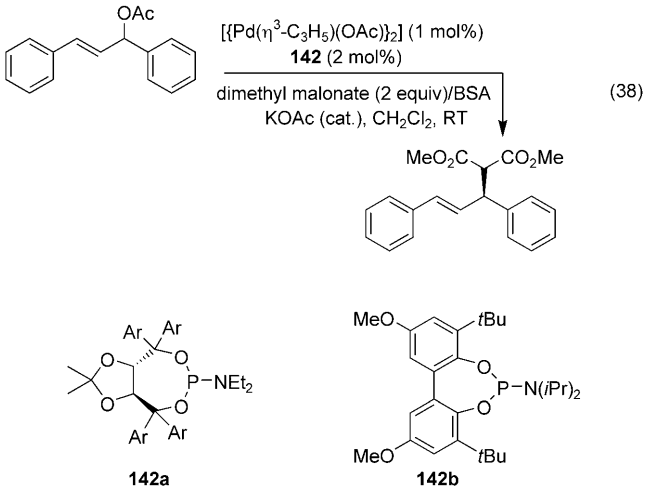
ated in situ by a **139**-induced P^V to P^{III} transformation of **138** (Scheme 6). The observation of a (+)-NLE when the C-alkylation was performed using non-enantiopure **138** led to the proposition that two ligands **140** coordinated to the Pd catalyst (ML_2 type). Furthermore, the catalytic inactivity of the Pd complex prepared by treating $[(\eta^3\text{-}C_3H_5PdCl)_2]$ and



Scheme 6.

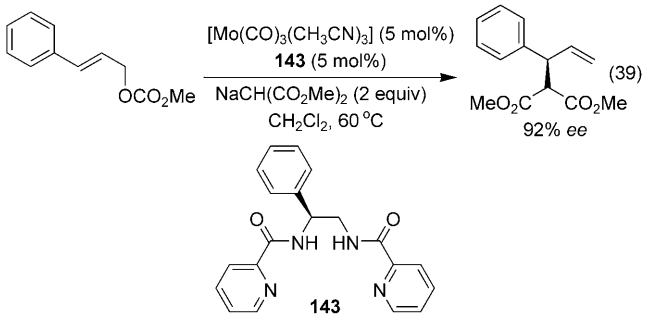
140 in a ratio of 1:1 also emphasizes that the active species is a 1:2 complex of Pd/**140**. The structure of **141** was tentatively assigned for the active species.

A linear correlation was encountered in the palladium-catalyzed allylic alkylation using the bulky monodentate phosphoramidite **142a** [Eq. (38); BSA = *N*,*O*-bis(trimethylsilyl)acetamide].[115] The involvement of only one **142a** ligand in the catalytically active Pd species [Pd(C_3H_5)(**142a**)(OAc)] was suggested. ^{1}H and ^{31}P NMR spectroscopy and X-ray diffraction studies on an isolated analogous complex [Pd(C_3H_5)(**142b**)(Cl)] also revealed a monocoordination of the phosphoramidite ligand.



(38)

The molybdenum-catalyzed allylation of $NaCH(CO_2Me)_2$ in the presence of chiral ligand **143** provided a high enantioselectivity [Eq. (39)].[116] A weak (+)-NLE was detected when scalemic **143** was employed. Since previous crystallographic studies indicated that the active intermediate in such reactions was a monocoordinated allylic complex [Mo(CO)$_2$L(allyl)],[117] the authors suggested an equilibrium between the active Mo(L) and inactive (Mo)$_n$(L)$_2$ complex ($n = 1$ or 2), which serves as a racemic trap.

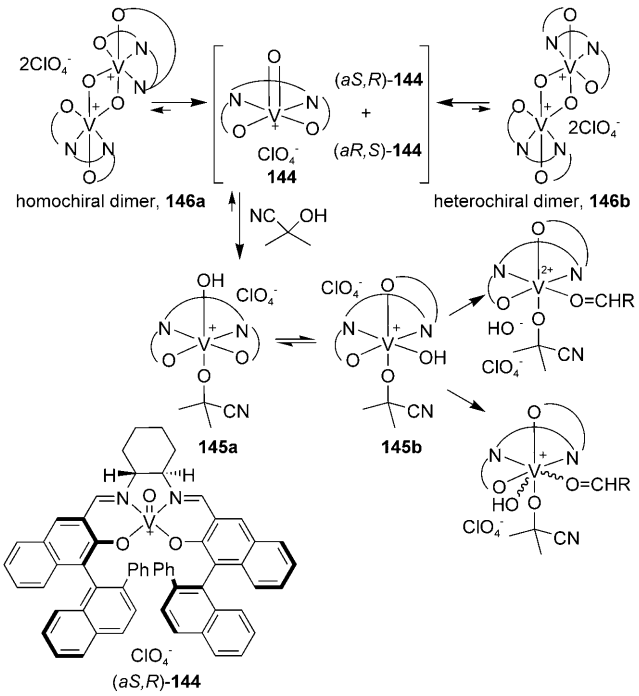


(39)

2.7. Cyanide Addition to Carbonyl Groups

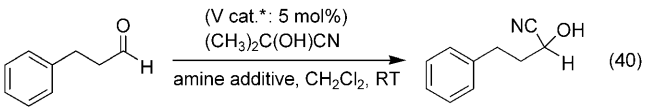
The first example of an NLE in this class of reaction was noticed by Oguni and co-workers in the asymmetric cyanation of carbonyl compounds with trimethylsilylcyanide (TMSCN). The catalyst was prepared by freeze-drying a solution of an equimolar mixture of scalemic diisopropyl tartrate (DIPT) and Ti(O*i*Pr)$_4$ in isopropanol.[118] Spectroscopic analysis of the catalyst suggested it had an oligomeric nature—[{Ti(O*i*Pr)$_2$-(DIPT)}$_n$]—that breaks down to a simpler structure upon addition of isopropanol to the mixture.[118b]

Katsuki and co-workers[119] used NLE studies as an indirect method to support the transformation of oxovanadium complex **144** (with a square-planar tetradentate chiral ligand) into the *cis*-β isomer **145b** (Scheme 7). The authors



Scheme 7.

found a (+)-NLE in the cyanation of 3-phenylpropanal with **144** as the catalyst [Eq. (40)]. A fern-green precipitate was noticed when a solution of enantiopure (a*S*,*R*)-**144** in

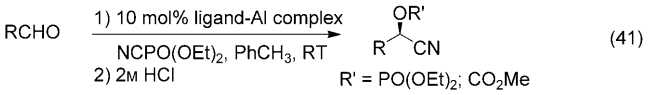


(40)

dichloromethane was added to a solution of the corresponding enantiopure (a*R*,*S*)-**144**. CD measurements on a solution of the recovered precipitate in dichloromethane indicated a 1:1 mixture of (a*S*,*R*)-**144** and (a*R*,*S*)-**144**. The authors thus suggested the formation of stable heterochiral (**146b**) and unstable homochiral dimeric (**146a**) complexes. Since such a dimerization of **144** is possible only with a *cis*-β geometry, it was also logically assumed that the reaction proceeds through the *cis*-β vanadium(V)-salen species **145b**. Similarly, the presence of a (+)-NLE in the asymmetric sulfoxidation with

a chiral Ti-salen complex led to the hypothesis that the square-planar monomeric monomeric [Ti(salen)] complex isomerizes into the corresponding *cis*-β-Ti(salen) (see Section 2.8).[120] However, the involvement of a μ-oxovanadium species was not ruled out.

In another study, the enantioselective cyanophosphorylation of aldehydes by aluminum complexes **148** with diethyl cyanophosphonate as the cyanide source were reported [Eq. (41)].[121a] Presumably, **148** works as a bifunctional



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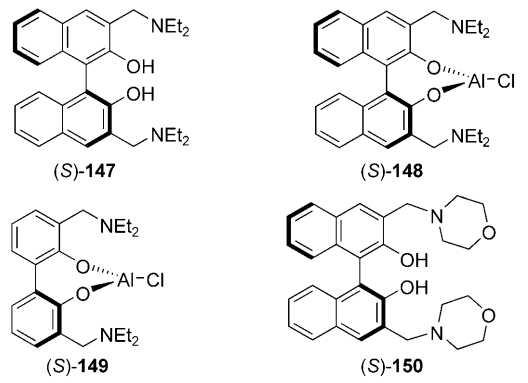
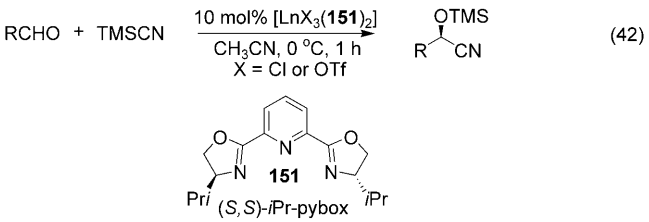


Lewis acid/Brönsted base catalyst. The presence of a strong (+)-NLE and the fact that the reaction rate is faster with enantiopure (*S*)-**147** than with scalemic or *rac*-**147** suggested the involvement of dimeric (or higher oligomer) species in the catalytic cycle. This was supported by computations on simplified molecule **149** which indicated that the heterochiral tetramers were more stable than the homochiral tetramers. The participation of similar intermediates in the cyanoalkoxycarbonylation of aldehydes with alkyl cyanoformates (the cyanide source) were subsequently proposed on the basis of a (+)-NLE.[121b] Analogous (+)-NLEs were also detected by Qin et al. in the enantioselective cyanophosphorylation of aldehydes catalyzed by the [Al(**150**)] complex.[122] Aggregated Al complexes are presumably involved.

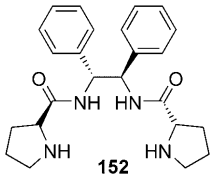
Aspinall et al.[123] made use of NLEs to understand the mechanistic details of the enantioselective silylcyanation of aromatic and aliphatic aldehydes by catalysts derived from lanthanide salts and **151** [Eq. (42)]. The NLEs were found to be dependent on the ionic radius of the lanthanides. A linear correlation between the *ee* value of **151** and ee_{prod}, with



(42)

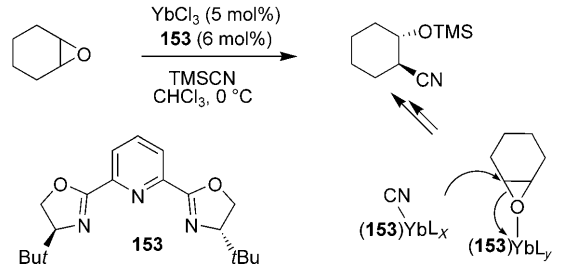
quantitative conversion, was observed in the case of Yb and Gd catalysts. The Eu catalyst gave a clear (+)-NLE. The heterochiral complex $[Eu(OTf)_3\{(R)\text{-}\mathbf{151}\}\{(S)\text{-}\mathbf{151}\}]^+$ was formed exclusively when $Eu(OTf)_3$ was treated with two equivalents of *rac*-**151**. In contrast, the reaction of $Yb(OTf)_3$ with two equivalents of *rac*-**151** provided exclusively a 1:1 mixture of homochiral complexes $[Yb(OTf)_2\{(R)\text{-}\mathbf{151}\}_2]^+$ and $[Yb(OTf)_2\{(S)\text{-}\mathbf{151}\}_2]^+$. It was suggested that, in all cases the active catalyst was a homochiral, monometallic complex of type $[LnCl_3(\mathbf{151})_2]$. The linearity in the case of the Yb and Gd catalysts arises from the selective formation of the homochiral species $[Yb(OTf)_2\{(R)\text{-}\mathbf{151}\}_2]^+$ and $[Yb(OTf)_2\{(S)\text{-}\mathbf{151}\}_2]^+$, while the (+)-NLE in the case of the Eu catalyst originates from the preferential formation of inactive heterochiral species which serves as a racemic trap.

Feng and co-workers[124a] noticed a (−)-NLE in the asymmetric addition of TMSCN to benzaldehyde catalyzed by the C_2-symmetric chiral tetraaza-Ti^{IV} complex prepared from non-enantiopure **152** and Ti(O*i*Pr)$_4$. The involvement of polymeric [(**152**)Ti(O*i*Pr)$_4$] complexes in the stereodiscriminating step of the reaction was considered. These authors extended their study to a mononuclear salen-Ti(O*i*Pr)$_4$ complex, which showed a weak NLE.[124b]



2.8. Epoxide Opening and Epoxide Rearrangement

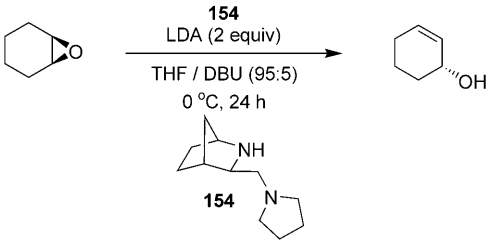
The finding of a (+)-NLE and second-order kinetics in the asymmetric nucleophilic ring-opening of *meso*-epoxides catalyzed by a chiral salen-Cr^{III} complex led Jacobsen and coworkers[125a] to propose the formation of a bimetallic intermediate. One chiral salen-chromium unit activates the epoxide, while the other unit (an azido salen-chromium species) assists the nucleophilic attack. A similar catalyst aggregation around the substrate during the course of the reaction course was discussed in the asymmetric ring opening of *meso*-epoxides with TMSCN catalyzed by [(**153**)YbCl$_3$] complexes. In this case, a (+)-NLE and second-order dependence in the catalyst was also encountered (Scheme 8).[125b] Mai and Schneider have employed some scandium-bipyridine complexes for the aminolysis of *meso*-epoxides to yield products in excellent yields and enantioselectivity (up to 97% *ee*). A strong (+)-NLE in the aminolysis of *cis*-stilbene



Scheme 8.

oxide supports the hypothesis of the aggregation of two or more monomeric catalyst species into catalytically inactive complexes.[126]

In the enantioselective epoxide rearrangement to allylic alcohols in the presence of chiral bases, Sodergren and Andersson observed beneficial effects of adding hexamethyl phosphoramide (HMPA) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to the catalytic enantioselective epoxide deprotonation using lithium amides derived from **154** [Eq. (43),



(43)

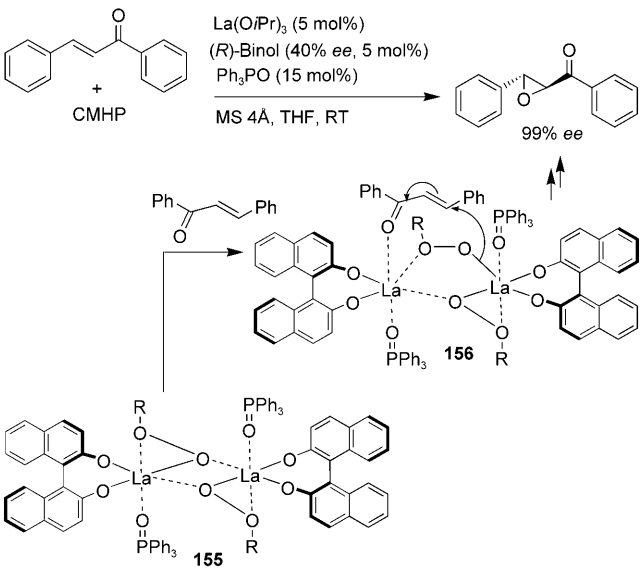
LDA = lithium diisopropylamide].[127] Chelating cosolvents prevent the formation of highly reactive but unselective aggregates of the chiral lithium amide salts of **154**.[128] NLE studies supported this hypothesis, since a strong (−)-NLE was observed at low DBU loadings (0–3 equiv with respect to chiral amines **154**), while a strict linear correlation between the *ee* value of **154** and the ee_{prod} value was obtained at high concentrations of DBU. This finding confirms that DBU inhibits the formation of highly reactive, but less enantioselective, heterochiral aggregates $[Li^+\{(R)\text{-}\mathbf{154}\}^-\cdot Li^+\{(S)\text{-}\mathbf{154}\}^-]_n$ by forming an active complex such as $[Li^+(\mathbf{154})^-\cdot DBU]$.

2.9. Enantioselective Oxidation

2.9.1. Epoxidation

In their early reports on NLEs, Kagan and co-workers examined the Sharpless epoxidation of allylic alcohols.[6,10] A moderate (+)-NLE was detected in this reaction, which was interpreted by the involvement of diastereomeric dimeric complexes, with the heterochiral dimer being more stable and less active than the homochiral species. Later, Inanaga and co-workers observed a strong (+)-NLE in the epoxidation of enones using a chiral lanthanum complex generated in situ from lanthanum triisopropoxide, (*R*)-binol, triarylphosphine oxide, and cumyl hydroperoxide (CMHP; 1:1:1:1).[129] The (+)-NLE was explained by the formation of thermodynamically stable heterochiral aggregates, with the homochiral binuclear μ-complex **155** being the probable catalytically active species (Scheme 9). The stereocontrol was explained by a catalytic cycle involving intermediate **156**, in which one of the lanthanum centers acts as a Lewis acid to activate the substrate while the peroxide attached to the other lanthanum center delivers an oxygen atom to the olefin (Scheme 9).

Minatti and Dötz[130] noticed a moderate (+)-NLE in the enantioselective epoxidation of chalcone by a catalyst system composed of binol and dialkylzinc; the oxidant was CMHP or TBHP. The authors suggested the formation of heterochiral

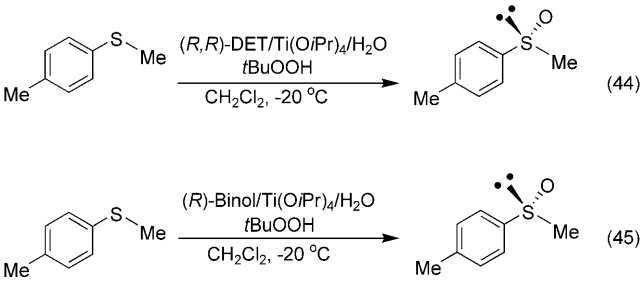


Scheme 9.

dimers or oligomeric species of lower reactivity. ^{1}H NMR spectroscopic data indicated the formation of zinc-binolate aggregates, and a monomeric zinc-binolate complex was believed to be the reactive catalytic precursor.

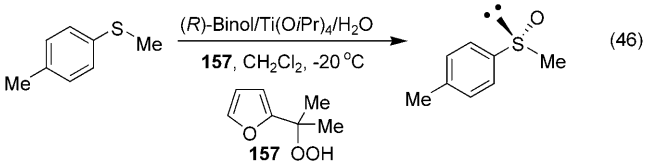
2.9.2. Sulfoxidation

Kagan and co-workers, in their initial report on NLEs,[6] studied sulfoxidation by a water-modified Sharpless reagent[10] [Eq. (44)]. A (−)-NLE was observed with the DET ligand up to 70% *ee* and then a linear relationship was observed with DET up to 100% *ee*. A complex structure of the active species with at least two tartrate ligands was suggested.[10] Uemura and co-workers[131] found a (+)-NLE in the asymmetric oxidation of sulfides by a similar chiral binol-titanium-H_2O catalyst [Eq. (45)]. This reaction was later found to be accompanied by a simultaneous kinetic resolution (by over oxidation to sulfone).[132] The complexity of the whole reaction meant that the causes of the NLE could not be analyzed.



Scettri and co-workers[133] noticed a (+)-NLE in the enantioselective oxidation of methyl *p*-tolyl sulfide using the $Ti(OiPr)_4$/(*R*)-binol/H_2O catalytic system and **157** as the

oxidant [Eq. (46)]. Capozzi et al.[134] found a (+)-NLE in the catalytic oxidation of benzyl *p*-bromophenyl sulfide using *tert*-butylhydroperoxide (TBHP) in the presence of chiral titanium complexes generated in situ from scalemic **158** [Eq. (47)]. In neither report was there an explanation for the observed (+)-NLE. Presumably the effect is an indication of the formation of dimeric or oligomeric oxo-bridged Ti-binolate species. Salvadori and co-workers[135] used NMR, CD, and MS sudies to show that the $[(binolate)_6Ti_4(\mu_3\text{-}OH)_4]$ complex was the catalytic species in the sulfoxidation. Studies with racemic binol led these authors to observe several heterochiral species $[(binolate)_6Ti_4(\mu_3\text{-}OH)_4]$, in agreement with the reported NLE in this reaction.[135] Mikami et al. had previously isolated this complex, which catalyzed [2+3] nitrone cycloadditions,[136] and its tetranuclear structure was confirmed by X-ray analysis. Subsequently, Yudin and co-workers[137] employed the analogous complex $[(F_8binolate)_6Ti_4O_4]$ as a sulfoxidation catalyst, whose structure was established by X-ray crystallography. On this basis, the tetranuclear complex, $[(binolate)_6Ti_4(\mu_3\text{-}OH)_4]$ may be considered as the actual catalytic species, with the heterochiral species being of lower activity than the homochiral tetrameric species.



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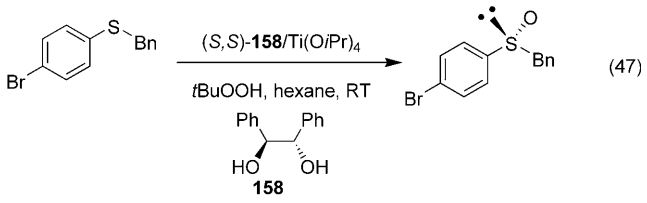
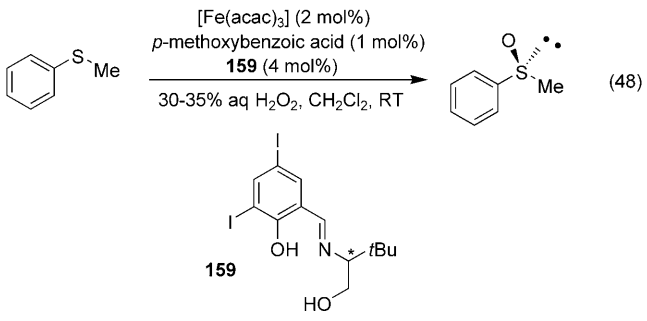


(47)

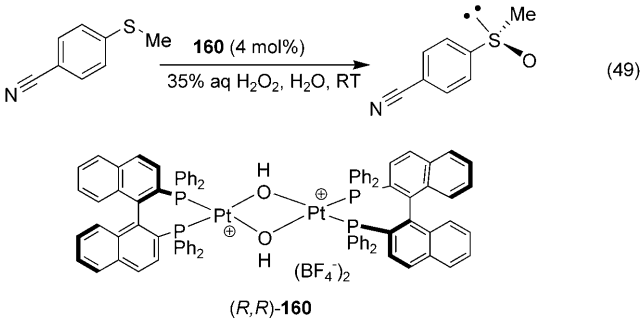
Legros and Bolm[138] reported enantioselective sulfoxidations by using a chiral iron catalyst generated in situ from $[Fe(acac)_3]$, Schiff base **159**, and an additive (*p*-methoxybenzoic acid). Aqueous hydrogen peroxide was employed as the oxidant, and the reaction occurred in high enantioselectivity (up to 90% *ee*) [Eq. (48)].



(48)

Nonlinear effects were observed in the reaction and were employed to discuss the nature of the catalytic species and the role of the carboxylic acid additives.[138c] A pronounced (+)-NLE in the presence of *p*-methoxybenzoic acid may indicate the presence of the additive in the active catalytic precursor. A bridged diiron(III) complex composed of anions of Schiff base **159** and $ArCO_2H$ (similar to the reported (μ-oxo)(μ-carboxylato)diiron core structure),[139] was proposed as the key intermediate in the catalytic cycle.

Scarso and Strukul[140] reported that the enantioselective oxidation of prochiral aryl alkyl sulfides can be carried out in a water–surfactant medium by the chiral dimeric Pt–binap complex **160** with H_2O_2 as the oxidant [Eq. (49)]. Sodium dodecyl sulfate (SDS) was the best surfactant, and provided high yields and poor to moderate *ee* values, with negligible formation of sulfone. The significant (+)-NLE detected in this reaction was related to the lower activity of the heterochiral complex with respect to the homochiral complex.

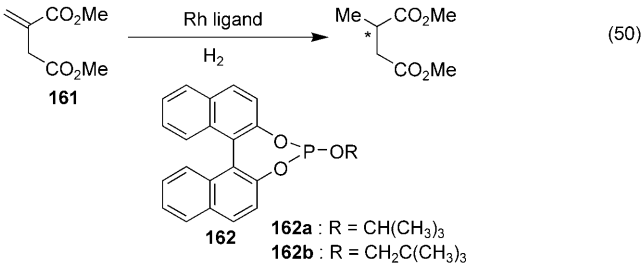


(49)

2.10. Reductions

2.10.1. Asymmetric Hydrogenation

A (+)-NLE was observed in the [Rh(norbornadiene)(chiraphos)]BF_4-catalyzed hydrogenation of dimethyl itaconate (**161**) in THF [Eq. (50)].[141] The formation of dimeric

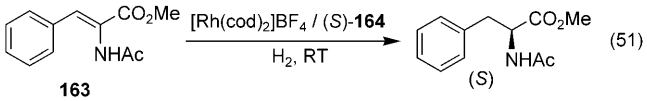


(50)

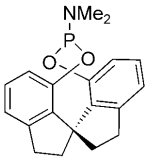
[{Rh(chiraphos)$_2$}$_2$] species was proposed,[142,143] which partially dissociate to provide the catalytically active monomeric species. It was established by ^{31}P NMR spectroscopy that the heterochiral dimer was more stable than the homochiral one in THF, thus leading to the (+)-NLE. Reetz noticed a (+)-NLE in the rhodium-catalyzed hydrogenation of olefin **161** in the presence of binol-derived monodentate phosphite **162a**

[Eq. (50)].[144] The theoretical curve, based on an ML_2 model with $K=4$ and $g=0$, was found to fit well with the experimental curve, and the stochastic formation of catalytically active homochiral and catalytically inactive heterochiral complexes was proposed. The ML_2 model was supported by mechanistic studies on the (+)-NLE obtained with the Rh/**162b** catalyst.[145] Blackmond[146] had previously demonstrated that relative reaction rates are a function of ee_{cat} in relation to the distribution of diastereomeric species in the ML_2 model. The possibility of a Rh catalyst having only one monodentate phosphite ligand (ML model) with an inactive ML_2 acting as a reservoir was ruled out. The coordination of two monodentate ligands of **162** on the metal center was further ascertained by kinetic and NMR experiments.

Zhou and co-workers[147] reported a highly enantioselective hydrogenation using Rh complexes of the siphos ligand (**164**) [Eq. (51); cod = cyclooctadiene]. A (+)-NLE was obtained in the hydrogenation of **163** by using the Rh/**164**



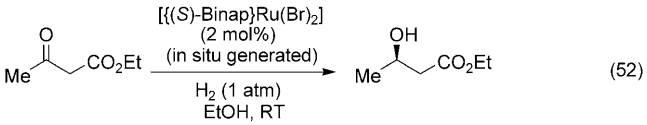
163 (51)



(*S*)-**164**

catalytic system. A lowering of the reaction rate as the ligand loading increased—an effect previously observed in other studies.[148,149] X-ray analysis of a single crystal indicated the structure $[Rh(cod)\{(S)\text{-}\mathbf{164}\}_2]^+$.[147] Only one ligand was suggested to be bonded to the rhodium center in the active catalyst (ML model).[147] However, this is unlikely in view of the mechanistic studies of Reetz, Blackmond, et al.[145]

A strong (+)-NLE was observed in the asymmetric hydrogenation of ethyl acetoacetate promoted by [(binap)-$Ru(Br)_2$] prepared in situ from scalemic (*S*)-binap [**165**; Eq. (52)].[150] The extent of the NLE was found to be dependent on the conversion, with a lower asymmetric induction noticed for extended reaction times. Also, non-enantiopure binap gave lower conversions than enantiopure binap. The existence of an NLE together with the observation of precipitation when the catalyst was non-enantiopure suggested the formation of dimeric or trimeric species of the catalyst precurser. ^{31}P NMR studies supported the presence of trinuclear (**166**) and dinuclear (**167**) complexes. Based on the NMR analysis, it was assumed that the supernatant solution contained the trinuclear species **166**, while the isolated precipitate was the dinuclear complex **167**. ^{31}P NMR analysis showed that the solid precatalyst could be either dimeric **167** or dimeric **168**. The dimeric precatalyst species were proposed to consist of both heterochiral and homochiral dimers, with the heterochiral dimer being the more stable. Therefore, during the hydrogenation of the dimeric precatalyst species, the homochiral dimers generates catalytically active monomers **169**.



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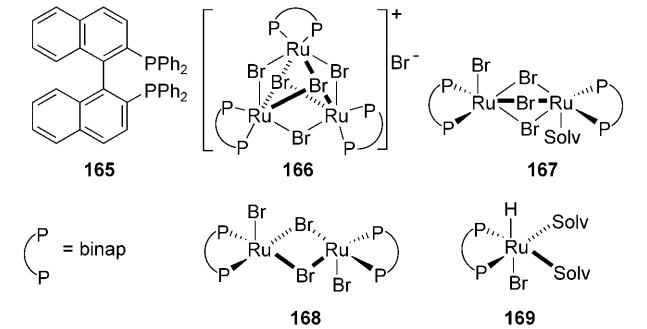
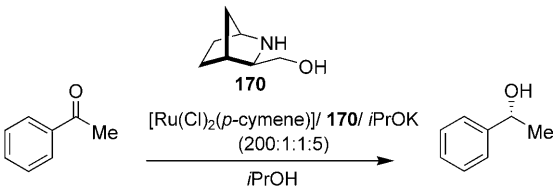


165 **166** **167**

P = binap **168** **169**

2.10.2. Asymmetric Transfer Hydrogenation

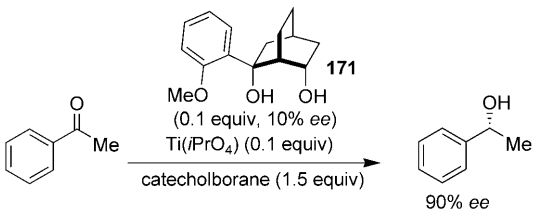
Andersson and co-workers[151] employed 2-azanorbornyl-derived amino alcohols as ligands in the Ru^{II}-catalyzed asymmetric transfer hydrogenation of aromatic ketones to provide the alcohols in high enantioselectivity. A moderate (−)-NLE was encountered in the transfer hydrogenation of acetophenone [Eq. (53)]. It was hypothesized that the heterochiral dimeric species possess higher catalytic activity than the respective homochiral dimer.



(53)

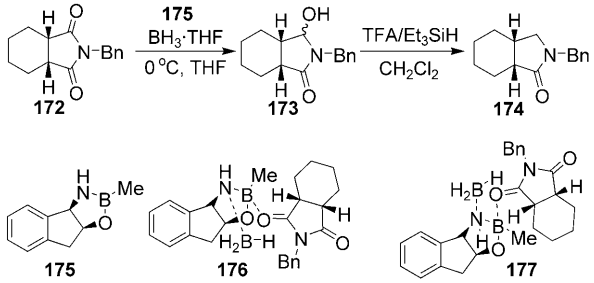
2.10.3. Asymmetric Reduction by Boron Reagents

The 1,3-diol **171** was employed as the ligand in the titanium-catalyzed asymmetric reduction of ketones with catecholborane.[152] A moderate (+)-NLE was observed during the reduction of acetophenone with scalemic **171** [Eq. (54)]. The exact cause for the (+)-NLE was not given, but the formation of dimeric species $[(Ti\text{-}\mathbf{171})_2]$ from **171** and $Ti(OiPr)_4$ were detected by NMR spectroscopy in deuteriated solvents.



(54)

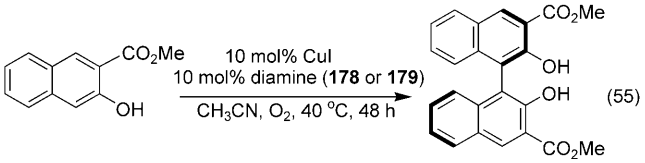
A linear correlation between the *ee* value of **175** and $ee_{product}$ in the reaction shown in Scheme 10 led to the suggestion of the involvement of only one molecule of **175** in the configuration-determining step.[153] By considering some additional experimental results, the authors proposed **176** and **177** as the plausible intermediates leading to the major and minor enantiomeric products.

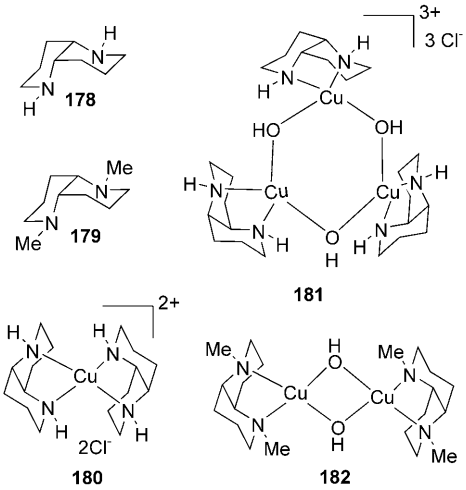


Scheme 10.

2.11. Miscellaneous Reactions

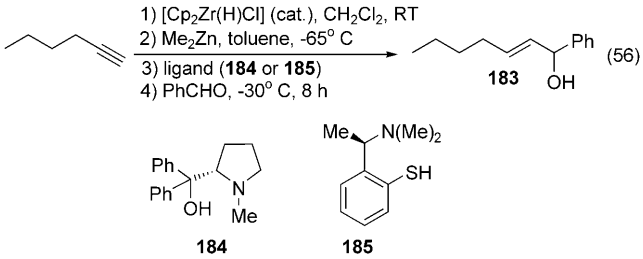
Kozlowski et al.[154] found that copper(II) complexes generated from the chiral diamine ligands **178** and **179** are efficient for catalyzing the synthesis of chiral 3,3′-disubstituted binol derivatives through an oxidative coupling [Eq. (55)]. A clear (+)-NLE was noticed, irrespective of the





mode of preparation of the non-enantiopure catalyst (either from non-enantiopure ligand and a Cu reagent or by mixing enantiopure *R* and *S* copper catalysts. Diamine **178** (100% *ee*) resulted in the formation of complex **180** (inactive) and trimer **181** with μ-hydroxo bridging (active catalyst), while *N*,*N*′-dimethyldiamine **179** generated only complex **182**. Both homo- and heterochiral **180** were formed with racemic **178** as ligand, but only homochiral trimer **181** was obtained. Vapor phase osmometry measurements suggested a rapid equilibrium between ML_2 and $(ML)_3$ complexes (**180** and **181**). The (+)-NLE obtained with diamine **179** was tentatively attributed to the different reactivities of the homo- and heterochiral dimers **182**.

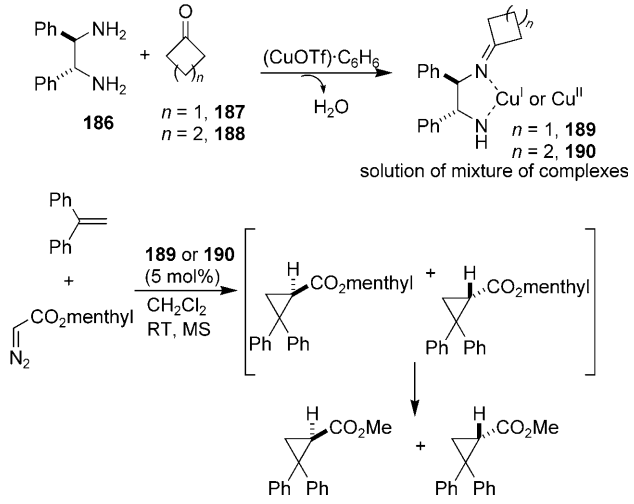
Wipf et al.[155] noticed some interesting NLEs in the addition of 1-hexyne to benzaldehyde, the reaction was performed in the presence of zirconocene hydrochloride, dimethylzinc, and chiral ligand [**184** or **185**; Eq. (56)]. The



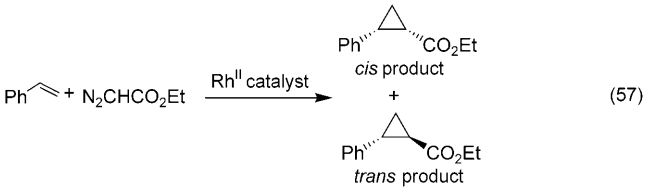
detection of a (+)-NLE in the case of non-enantiopure **185** was interpreted by the involvement of homo- and heterochiral dimers. A multishaped NLE curve, consisting of linearity and a (−)-NLE, was obtained with amino alcohol **184**. The *ee* value of product (*S*)-**183** decreased almost linearly from 81% *ee* with enantiopure **184** to 24% *ee* with 50% *ee* **184**. A further reduction in the enantiomeric excess of **184** led to a (−)-NLE. A reversal in the enantioselectivity, favoring the formation of (*R*)-**183**, was observed at 35% *ee* and at 20% *ee* of ligand **184**. This unusual NLE profile has been hypothesized to arise from the participation of several monomeric and aggregated metal–ligand species in the catalysis. The presence of hard Lewis acidic zirconocene species in the reaction mixture must facilitate the generation of tricoordinate zinc species by coordination of **184** to the Zn center. The absence of such unusual effects in the case of aminothiols was attributed to stronger complexation with the zinc center, which is less likely to be perturbed by the zirconocene group.

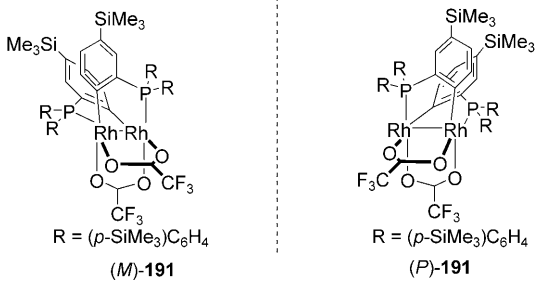
The asymmetric intermolecular cyclopropanation reaction between (−)-menthyl diazoacetate and 1,1-diphenylethylene was efficiently realized by using complexes **189** and **190**. Cyclopropane carboxylates with up to 78% *de* were isolated (Scheme 11).[156] A (−)-NLE was noticed when an enantioimpure catalyst **189** was prepared by mixing the enantiopure complexes **189** derived separately from enantiopure (1*R*,2*R*)-**186** and (1*S*,2*S*)-**186**. The formation of aggregates or the involvement of two or more ligands have been given as an explanation for this result.

The cyclopropanation of styrene with ethyl diazoacetate has been catalyzed by **191** to give enantioselectivities up to 91% *ee* and diastereoselectivities up to 90% *de* [Eq. (57)]].[157] A (+)-NLE between the *ee* value of the *cis* product and that of the scalemic complex **191**, prepared by



Scheme 11.

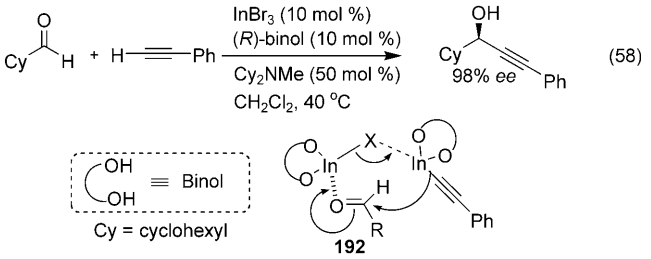




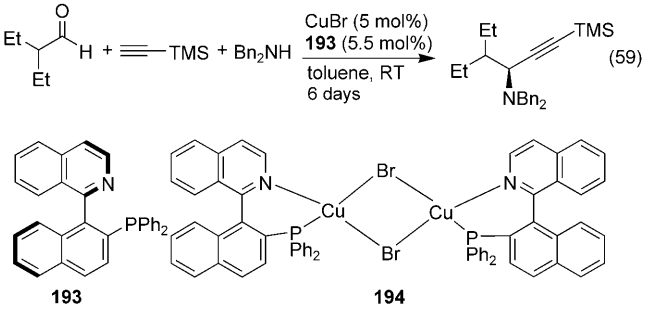
mixing enantiomeric (*M*)-**191** and (*P*)-**191**, was noticed (pentane as the solvent). A precipitate formed upon mixing (*M*)-**191** and (*P*)-**191** (70:30) in pentane. The catalyst isolated from the filtered solution provided the *cis* product with 85% *ee*. The precipitate consisted of inactive *rac*-**191**, consequently enriching the *ee* value of the catalyst remaining in solution.

Shibasaki et al. developed the concept of bifunctional catalysis, for example, heterobimetallic catalysis and Lewis acid/Lewis base catalysis.[158] Such a strategy was applied to the asymmetric alkynylation of aldehydes using a chiral In^{III}/binol catalyst which acts as an activator of both the soft nucleophilic alkyne and the hard electrophilic carbonyl compounds [Eq. (58)].[159] Based on the very strong (+)-NLE observed, the authors tentatively suggested an involvement of a bimetallic species **192** in the catalytic cycle.[159,160]

A strong (+)-NLE was observed in the one-pot three-component reaction of a terminal alkyne, an aldehyde, and a secondary amine in the presence of [CuBr(**193**)], which

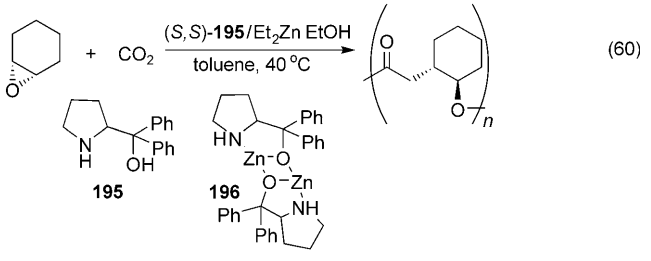


provided propargylamines [Eq. (59)].[161] The structure of the dimeric homochiral complex **194** was established by single-crystal X-ray crystallography.[162] A lower reactivity of the heterochiral complex **194** as compared to the homochiral complex **194** explains the (+)-NLE.



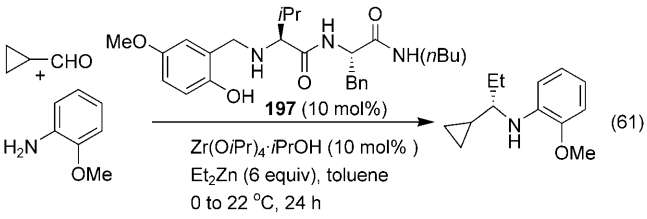
A (+)-NLE was detected in the copolymerization of cyclohexene oxide and carbon dioxide catalyzed by the chiral zinc complex **196**, prepared from diethylzinc (5.0 mol%), **195**, (5.0 mol%), and ethanol (2.0 mol%) [Eq. (60)].[163] A significant decrease in the catalytic activity was observed when **196**, was derived from racemic **195**, instead of enantiopure **195**. An X-ray diffraction study on the zinc complex obtained from an equimolar mixture of Et_2Zn and *rac*-**195**, revealed a heterochiral dimeric structure **196**. An equimolar mixture of isolated (*S*,*S*)-**196** and (*R*,*R*)-**196** also provided lower yields in the polymerization compared to enantiopure (*S*,*S*)-**196**. Presumably the two homochiral zinc dimers dissociate into monomers under the reaction conditions and recombine into a more stable and less active heterochiral zinc dimer.

A zirconium-catalyzed three-component reaction of diethylzinc with the in situ formed imine and ligand **197** [Eq. (61)] gave a (+)-NLE, thus suggesting the involvement of dimeric or oligomeric complexes.[164] Earlier studies



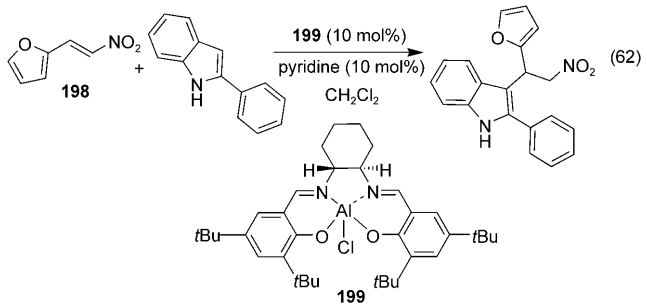
showed that **197** linked to a polystyrene solid support exhibited a similar efficiency and selectivity as the homogeneous system. This finding was taken as an indication of the monomeric nature of the catalytic species. Therefore, it was tentatively proposed that the catalytic cycle involves monomeric species, while the formation of less-reactive heterochiral Zr dimers in the case of a scalemic ligand serves as a trap for the racemic ligand.

A linear correlation was detected in the Friedel–Crafts alkylation of 2-phenylindole with **198** in the presence of



(61)

catalytic amounts of complex **199** and pyridine. This result was interpreted by the absence of aggregation [Eq. (62)], with the enantiodiscriminating step involving only one molecule of **199**.[165]

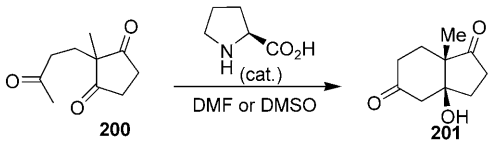


(62)

3. Homogeneous Organocatalytic Reactions

3.1. Catalysis by Proline

Enantioselective reactions catalyzed by organic molecules without the involvement of a metal ion have recently been developed.[166] The proline-catalyzed intramolecular aldol reaction, discovered in the 1970s,[167] is one of the landmarks in asymmetric synthesis that led recently to the rapid growth of asymmetric organocatalytic reactions. Much work has been carried out to understand the mechanism of this useful reaction. In their early report on NLE studies,[6] Agami, Kagan, and co-workers observed a weak (−)-NLE in the asymmetric Robinson annulation of triketone **200** [Eq. (63)]. The *ee* value of the reaction product **201** was measured by polarimetry. The involvement of two proline molecules in the catalytic cycle was suggested, as depicted in structure **202**. Later, List, Houk, and co-workers reexamined this reaction, and observed a linear correlation between the *ee* value of



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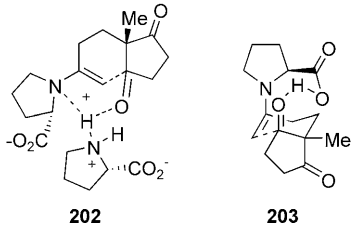
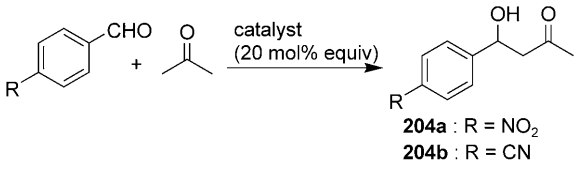


proline and that of the product; the *ee* values in this case were determined by HPLC on a chiral stationary phase.[168a] This finding is in agreement with the involvement of one proline molecule in the catalytic cycle (see structure **203**), and was supported by kinetic studies and theoretical calculations.[168b]

Barbas III and co-workers reported that (*S*)-proline and thioazolidine **205** catalyzed the intermolecular aldol reaction of acyclic and cyclic ketones with aromatic and aliphatic aldehydes (up to > 99 % *ee*).[169] A linear correlation between the *ee* value of (*S*)-proline and that of aldol **204** was found [Eq. (64)]; this finding is in agreement with the involvement of only one molecule of proline in the catalytic cycle. It was assumed that the reaction proceeds via a metal-free Zimmer-



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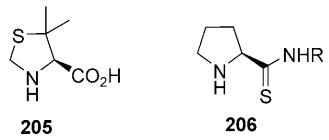
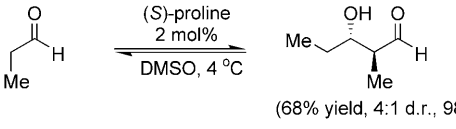


man–Traxler transition state. Gryko and Lipinski[170] reported that (*S*)-prolinethioamides **206** are excellent enantioselective catalysts for direct aldol reactions of acetone with aromatic aldehydes [Eq. (64)]. See also Ref. [171] for related catalyst systems. A linear correlation between the ee_{cat} and the ee_{prod} values was noticed,[170] which supports the enamine mechanism involving only one molecule of the amine in the catalytic cycle.

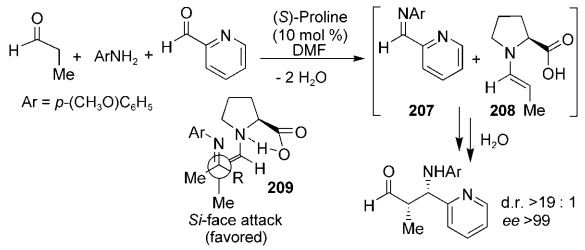
(*S*)-Proline catalyzed the aldol condensation of propionaldehyde in 98 % *ee* [Eq. (65)]. This reaction led to a (+)-NLE, which was interpreted as resulting from an in situ kinetic resolution of the catalyst by the resulting aldol.[172] An asymmetric amplification in an (*S*)-proline-catalyzed Mannich reaction between propionaldehyde and an N-protected

α-imino glyoxylate was also observed.[172b] The resulting α-iminoester acts as a resolving agent of the catalyst through formation of an oxazolidinone intermediate. The importance of oxazolidinones in proline catalysis has been discussed by Seebach and Eschenmoser.[172c]



(65)

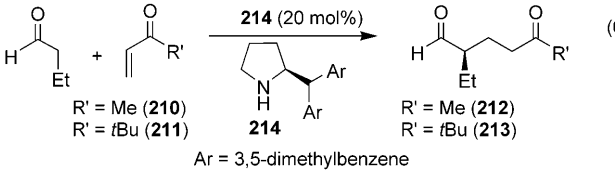
No NLE was observed in the highly *syn*-selective, enantioselective proline-catalyzed three-component asymmetric cross-Mannich reaction of propionaldehyde (aldehyde donor) with *p*-anisidine and 2-pyridylcarbaldehyde (acceptor aldehyde; Scheme 12).[189] The involvement of a reactive enamine derived from the aliphatic donor aldehyde was assumed. The NMR analysis indicated the complete formation of the imine within five minutes at room temperature. Imine **207** and enamine **208** react via a six-membered transition state.



Scheme 12.

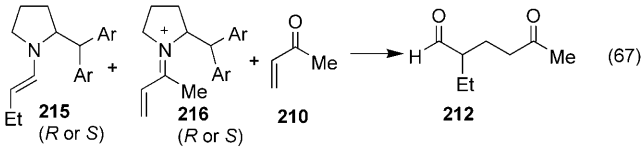
3.2. Catalysis by Amines

Chiral amines such as **214** catalyze the enantioselective Michael addition of simple aldehydes to vinyl ketones, such as **210** or **211** [Eq. (66)], in good yields and enantioselectivity.[174a]

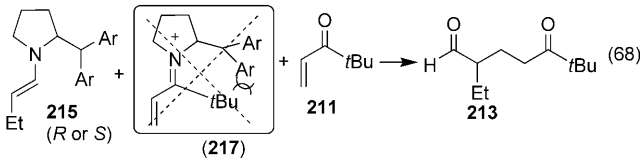


(66)

A smaller (−)-NLE was detected in the case of the addition of butanal to **210** catalyzed by non-enantiopure **214**. The authors proposed that the reactions of ketones **210** or **211** proceed via the enamine intermediate **215** formed by reaction of the aldehyde with the amine catalyst [Eq. (67)]. They suggested that the more reactive iminium ion **216** will also be formed in the case of **210**. They further proposed that product **212** is obtained competitively by the reaction of enamine **215** with both ketone **210** and the minor, but more reactive, iminium ion **216** [Eq. (67)]. The absence of an NLE in the case of bulky ketone **211** was explained by the difficulty in forming iminium ion **217** [Eq. (68)].

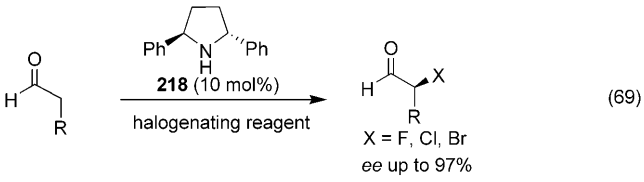


(67)

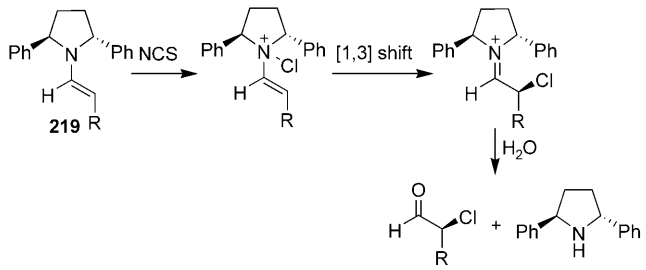


(68)

Jørgensen and co-workers extended organocatalysis to the asymmetric α-halogenation of aldehydes [Eq. (69)].[174b] The linear relationship observed between the *ee* value of **218** and that of the chlorination product led to the proposal of a mechanism involving the participation of a single molecule of the catalyst **218** (intermediate **219**; Scheme 13).



(69)

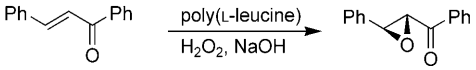


Scheme 13.

3.3. Miscellaneous Reactions

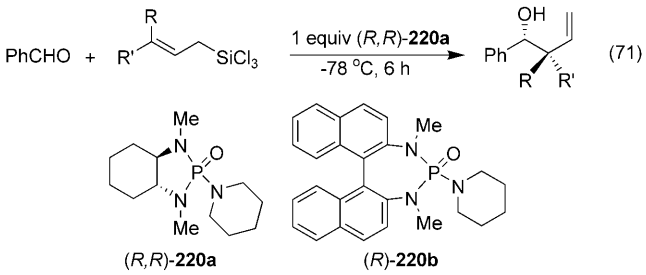
There is a significant asymmetric amplification in the poly(L-leucine)-mediated Julia–Colonna epoxidation of chalcone [Eq. (70)].[175a] Polyleucine synthesized from non-enantiopure leucine-*N*-carboxyanhydride of low enaniomeric excess provided the chalcone epoxide in high *ee* value (2.1 to 5.6 times higher than the *ee* value of the initial leucine-*N*-carboxyanhydride). The experimental results suggested the

catalytic center featured five consecutive leucine residues at the N-terminal position, thus corresponding to an L_5 catalyst. A kinetic analysis of this system allowed some mechanistic details to be established.[175b]



(70)

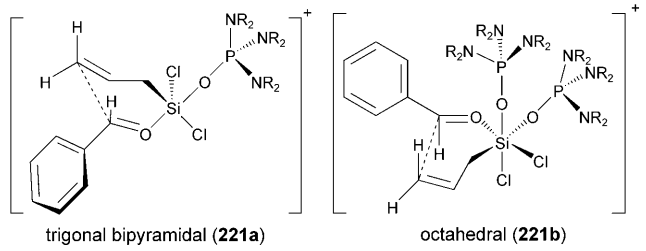
Denmark et al.[175c,d] noticed a moderate (+)-NLE in the enantioselective allylation of benzaldehyde in the presence of catalyst **220a** [Eq. (71)]. They suggested two competitive



(71)

(*R*,*R*)-**220a** (*R*)-**220b**

pathways involving intermediates **221a** and **221b**, with the one involving two phosphoramides bound to the chlorosilane (**221b**) being more selective than the other one with only one



trigonal bipyramidal (**221a**) octahedral (**221b**)

catalyst molecule (**221a**). This hypothesis was in accordance with a reaction that was second-order in **220a**. Denmark et al. also studied the ring opening of *cis*-styrene epoxide by $SiCl_4$ in the presence of a **220b** catalyst.[175e] The weak NLE observed was in agreement with more than one catalyst molecule being bound to $SiCl_4$ in the configuration-determining transition structure.

4. Nonlinear Effects through Partial Solubility

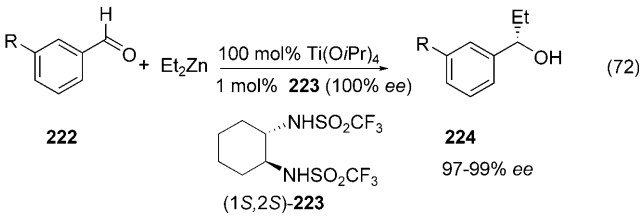
4.1. Partial Solubility

The diastereomeric complexes formed in situ in an organometallic reaction when the chiral auxiliary is non-enantiopure are usually assumed to be soluble (homogeneous mixture). However, this may not be true in every case; for example, if one of the diastereomeric complexes formed in situ from non-enantiopure chiral auxiliary is less soluble in the given reactions conditions, the reaction may even become heterogeneous. Such a situation may lead to a reservoir effect. A (+)-NLE will be seen if insoluble heterochiral diastereomers consitute the reservoir. This has to be considered in the mechanistic discussions when an NLE is observed. A similar situation may also arise in organocatalytic reactions.

One should be able to differentiate the NLEs arising from the insolubility of the chiral auxiliary itself, or derivatives formed in situ, from aggregation effects in solution. It is well known that racemate crystals and conglomerate crystals possess different properties.[176] Therefore, a partially soluble reaction mixture of the non-enantiopure auxiliary or complex will provide a soluble part with an enriched or depleted *ee* value, depending on the eutectic composition of the the solid and solution.[177] For example, when racemate crystals are less soluble than conglomerate crystals then: 1) a partially resolved chiral auxiliary with an *ee* value lower than the eutectic composition will lead to enrichment in the *ee* value in soluble part, thus providing a (+)-NLE. 2) A partially resolved chiral auxiliary with an *ee* value greater than the eutectic composition will lead to depletion in the *ee* value of the soluble part, thus generating a (−)-NLE. Consequently, mechanistic details may be wrongly interpreted if these NLEs are confused with NLEs arising from aggregation effects in solution.[178] In the subsequent section, we discuss examples that exhibit NLEs because of the partial solubility of one component of the catalyst system.

4.2. Organometallic Catalysis

The partial precipitation of heterochiral complexes was noticed in some NLE studies, as mentioned in the previous sections. This may account in part for the (+)-NLE observed. We recently discovered an example where the NLE in an organometallic reaction comes from the insolubility of the organic chiral auxiliary.[179] In 2002, a strong asymmetric amplification was found in the addition of Et_2Zn to aldehydes following the Ohno–Kobayashi procedure [Eq. (72)].[180,181] In

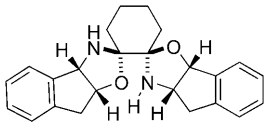


(72)

this procedure 1 mol% of the bis(sulphonamide) **223** and 100 mol% of $Ti(OiPr)_4$ were kept in toluene at 40 °C before cooling to −78 °C and adding Et_2Zn and the aldehyde **222**. An alternate procedure, developed by Walsh et al., involving first mixing **223** and Et_2Zn at 23 °C before adding $Ti(OiPr)_4$ and aldehyde **222**, showed no NLE.[182] The origin of the (+)-NLE in the Ohno-Kobayashi procedure was investigated by us.[179] Analysis of the composition of the solution of **223** at −78 °C,

before addition of the reactants, revealed that the *ee* value of the soluble part of **223** was enriched to 96–98% starting from an *ee* value as low as 10%. The eutectic composition of **223** was found to be 96% *ee*. The addition of Et_2Zn to **222** (R = OMe) at −78 °C in toluene in the presence of **223** with 15% *ee* gave the corresponding alcohol with 97% *ee*. The asymmetric amplification in the Ohno–Kobayashi protocol was a consequence of a strong enhancement of the *ee* value of the soluble precatalyst **223** because of racemate crystallization, while the Walsh protocol gave a homogeneous system.

A similar effect was discovered by Liu and Wolf in the addition of diethylzinc to benzaldehyde catalyzed by a zinc complex prepared from bisoxazolidine **225**.[183] Scalemic **225** provided a strong (+)-NLE because of the insolubility of racemic **225** in a mixed solvent of toluene and hexane.

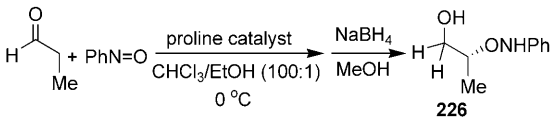


225

4.3. Organocatalysis

In 2006 Hayashi and Blackmond independently found that enantioenriched proline may not be fully soluble in some solvent systems.[177,178,184] The results obtained by these two research groups were discussed by Kellogg in a recent highlight.[185]

Hayashi et al.[184] observed that a solution of proline with a high *ee* value can be obtained by dissolving solid proline with a low *ee* value. As proline is only sparingly soluble in pure $CHCl_3$, 1% EtOH was added as cosolvent. A solution of proline with very high *ee* value (97–99% *ee*) could thus be prepared from proline with a very low *ee* value (1.0 and 10% *ee*). The enantiomeric enrichment in solution is linked to the different crystal packing in the racemic compound and in the conglomerate crystals, as revealed by powder X-ray diffraction studies. In crystals of the racemic compound, the crystal packing is more compact due to NH···O hydrogen bonds and weak CH···O interactions, while the crystal packing in the conglomerate is extended only by NH···O hydrogen-bonding interactions. The authors examined the α-aminoxylation of propanal by using non-enantiopure proline as the catalyst [Eq. (73)].[184] The product **226** was obtained with

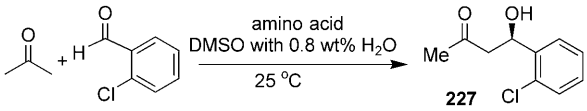


(73)

226

19% *ee* when a solution of proline prepared from solid proline of 10% *ee* was used without filtering off the precipitate. However, the reaction using the solution of proline obtained after separating the precipitate by filtration gave **226** with 96% *ee*. Blackmond and co-workers[177] showed that crystals of the racemic compound obtained by crystallization from $CHCl_3$ exists as cocrystals of a 1:1 mixture of D- and L-proline with one molecule of $CHCl_3$. The powder X-ray diffraction pattern indicated a more-compact packing in these cocrystals, with extensive hydrogen bonding including a hydrogen bond from the CH group of chloroform. The cocrystals are more stable than the usual racemate crystals and thus have lower solubility.

Blackmond and co-workers investigated the asymmetric amplifications in amino acid catalyzed aldol reactions.[178] They discovered that the partial solubility of a non-enantiopure catalyst such as proline leads to a substantial enrichment in the *ee* value for the soluble part [Eq. (74)].



(74)

227

This effect was found to be common to many amino acids. No NLE was found when the reaction of Equation (74) was performed at a lower concentration of proline (below 0.025 M; namely under homogeneous conditions). This finding was in agreement with the linear correlation observed by the research groups of List[168] and Barbas.[169] However, NLEs were present in this reaction when proline was employed at higher concentrations (above 0.1 M; namely under heterogeneous conditions). A (+)-NLE was obtained with proline of $ee < 20\%$, while proline with $ee > 80\%$ provided a (−)-NLE. Interestingly, the *ee* value of the aldol product **227** remained constant in all the reactions catalyzed by proline with an *ee* value between 20 and 80%. The NLEs were attributed to the solid/liquid equilibrium that leads to crystallization of racemic proline when $ee < 20\%$, thereby leaving the excess enantiomer in solution, or vice versa when $ee > 80\%$. The *ee* value of the eutectic composition of proline was found to be 50% *ee*, and the flat profile for the *ee* value of **227** if $20\% < ee_{proline} < 80\%$ was attributed to the existence of consistently only the eutectic composition (proline of 50% *ee*) in solution in this range of $ee_{proline}$ values. Serine has been found to possess >99% *ee* at its eutectic composition. Thus, serine with as low as 1% *ee* catalyzes the formation of aldol product **227** with 43.9% *ee*—which is virtually same as that obtained with enantiopure serine (43.4% *ee*). The NLE is due to selective crystallization of the racemic part of the non-enantiopure chiral auxiliary. Subsequently, Blackmond and co-workers also proposed a method for the determination of the eutectic composition of various other amino acids,[177] and gave an interpretation for the NLE observed by Agami and Kagan in the proline-catalyzed intramolecular aldol reaction.[6] The explanation is based on the concept of "kinetic conglomerates", where a scalemic mixture of D and L solids start to dissolve with initial generation of equimolar amounts of the two enantiomers.

The involvement of a solid/liquid equilibrium for amino acid catalysts in intramolecular asymmetric adol reactions was later studied by Córdova et al.[186] This can lead to very strong asymmetric amplification.

It is worth mentioning a previous report in 2000 of a (*S*)-proline-catalyzed asymmetric conjugate addition of nitroalkanes to enones in chloroform.[187,188] A linear correlation was obtained when piperidine was used as an additive (3–7 mol%), but a significant NLE was evident when the additive was *trans*-2,5-dimethylpiperazine or quinine. The NLE curve consisted of a (+)-NLE (for proline < 20% *ee*), a (−)-NLE (for proline > 80% *ee*), and a flat profile for proline between 20–80% *ee*. This NLE curve is identical to the NLE curve later obtained by Blackmond and co-workers using the proline catalyst in $CHCl_3$ solvent.[177] Since the solubility of proline is usually very poor in $CHCl_3$, the observed NLE in this reaction may arise from crystallization of the racemic compound.

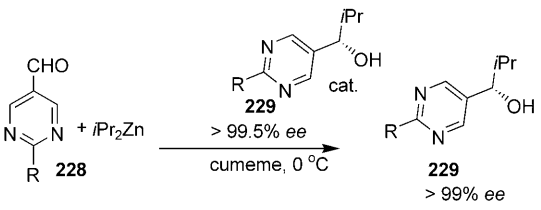
5. Asymmetric Autocatalysis and Self-Replication

5.1. Asymmetric Autocatalysis

The origin of molecular homochirality, which is directly related to the origin of life on Earth, has fascinated the scientific community. Several theories have been put forward to explain how the homochirality could have originated in the prebiotic era.[189] An organo-autocatalytic process is more relevant to the origin of homochirality because of the environmental conditions in the prebiotic era. Frank[189a] envisaged an asymmetric autocatalytic model, where one enantiomer catalyzes its own production and at the same time inhibits the formation of its opposite enantiomer. Thus, in this model, even an asymmetric reaction that is not 100% enantioselective can provide a very high asymmetric amplification in an autocatalytic process. It is closely related to the reservoir mechanism in NLEs (see Section 2).[10] A spontaneous asymmetric synthesis arising from a minor imbalance in the enantiomeric ratio because of classical statistical fluctuation can be envisioned with this model. An autocatalytic process without the involvement of an NLE cannot propagate asymmetric amplification during the course of a reaction process, unless the autocatalytic reaction is 100% enantioselective. Otherwise the *ee* value will erode continuously over the course of the reaction. It was pointed out that the (+)-NLE must be working in parallel with autocatalysis to provide the asymmetric amplification.[11] Blackmond[190] clearly showed the erosion of the *ee* value with conversion by simulation with a mathematic model.

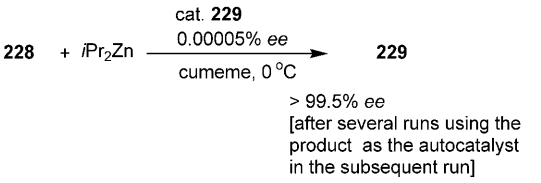
Soai et al.[191] described a spectacular example of an asymmetric autocatalytic process. Very high *ee* values (> 99%) were achieved in the reaction shown in Equation (75) starting from an autocatalyst **229** of less than 99.5% *ee*.[192]

A strong asymmetric amplification was observed in the reaction when non-enantiopure **229** was used.[193] The addition of diisopropylzinc to **228** in the presence of the catalyst **229** of extremely low initial *ee* value provided a product with a very high *ee* value (> 99.5%) after recycling the product (of



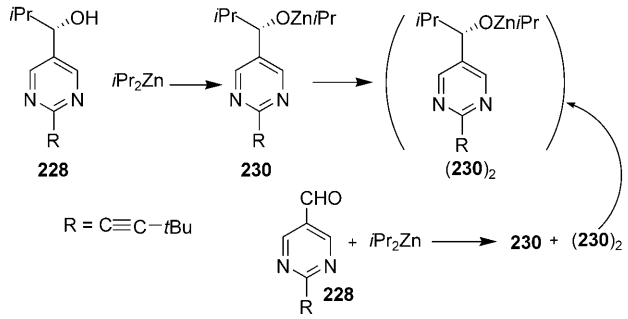
(75)

enriched *ee*) several times and using it as the autocatalyst in consecutive runs [Eq. (76)].[193d] Soai et al. subsequently detected the spontaneous and random production of an enantiomeric excess, without any added chiral source.[193e]



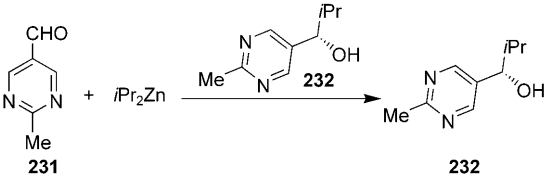
(76)

These intriguing reports stimulated many mechanistic studies. Soai and co-workers[194] found that the autocatalytic process is first order with respect to **228** and diisopropylzinc and second order with respect to the alkylzinc alkoxide **230**. It was suggested (Scheme 14) that the catalytic species was a dimer $(\mathbf{230})_2$. The overall reaction profile (conversion versus time) was S-shaped, which is an indication of an autocatalytic reaction.

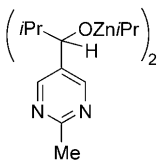


Scheme 14.

Blackmond, Brown, et al[195] proposed the involvement of homo- and heterochiral dimers of **233**, on the basis of the results obtained in kinetic studies (microcalorimetery) on **231** [Eq. (77)]. The effective concentration of the active catalyst was measured as a function of the *ee* value of the catalyst. The

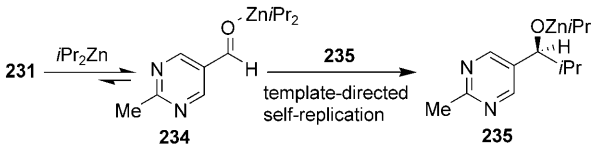


(77)



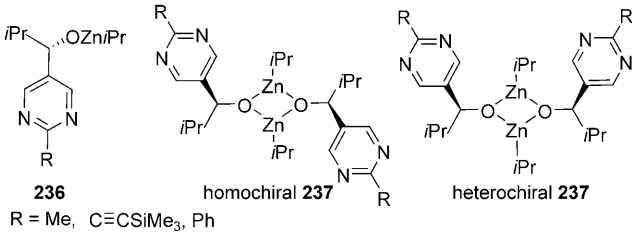
233

hetero- and homodimers **233** were found to have similar stabilities. The heterochiral dimer was suggested to be less reactive, thus explaining the amplification of the *ee* value during the course of the reaction. ^{1}H NMR experiments also supported such a dimeric nature of the catalyst.[195] In subsequent studies, it was established that the concentration of iPr$_2$Zn does not participate in the rate expression.[196] This was rationalized by the formation of **234** prior to the alkyl transfer step (Scheme 15). A modified rate expression was derived, which included the square of the concentration of **234**.



Scheme 15.

Soai and co-workers[197] also found that the experimentally determined *ee* values and yields are higher than the theoretical values obtained from a kinetic model with a dimeric catalytic species. Later, Gridnev et al.[198a] carried out extensive studies on the dimer of **236** and favored the



involvement of the square-planar $[ZnO]_2$ dimer **237**. NMR analysis indicated a statistical distribution between (*R*,*R*)-**237** and (*R*,*S*)-**237**. The dimer **237** was found to have a significant affinity for the complexation of iPr$_2$Zn, and under typical autocatalytic turnover conditions the (**236**)$_2$-iPr$_2$Zn complex was detected. Gridnev summarized the ^{1}H NMR and computational studies done on the Soai system.[198b] The dimers of **236** can give rise to oligomers or dissociate to monomers, thus making the disussion very difficult, because of an interplay between kinetic and thermodynamic parameters.

Singleton and Vo[199] carried out detailed investigations on the spontaneous autocatalytic reactions of pyrimidine aldehyde **231** [Eq. (77)]. In the absence of **232**, the final product **232** was isolated with random *ee* values after several runs. It was suggested that the few initial product molecules, generated in situ by the uncatalyzed reaction, would contain a minor imbalance in the enantiomeric ratio, which in subsequent autocatalytic reactions could amplify to higher *ee* values. Brown and co-workers proposed that the statistical fluctuation in the enantiomer distribution arising from the classical binomial distribution serves as a natural seeding mechanism for the subsequent amplification of chirality, without any external chiral perturbations.[200]

A racemic compound generated from achiral precursors, without asymmetric influences, should give a product distribution with an excess of one enantiomer on a purely statistical basis—analogous to the excess of heads or tails in a coin-tossing game. The standard deviation $\sigma = \sqrt{P/2}$ provides a measure of the possible statistical fluctuations in the enantiomeric ratio (P is number of events giving either R or S product). The Goldanskii and Kuzmin parameter is defined as $\eta = [n(R) - n(S)]/[n(R) + n(S)]$, where $n(R)$ and $n(S)$ are the number of R- and S-enantiomeric molecules, respectively, and $[n(R) + n(S)] = 2P$}.[200,201] The parameter η is equivalent to the *ee* value in a large sample, and it is relevant only in the case of a small number of product molecules. The statistical enantiomeric excess was estimated to be sufficient for the spontaneous generation of chirality, because of the significant half-life of around 30 seconds of the individual dimers in the normal temperature range of autocatalysis (273 K). Buhse hypothesized a self-replication mechanism for asymmetric amplification in Soai's autocatalysis.[202] Later, a kinetic model in which monomeric zinc alkoholate **236** catalyzed the reaction and involving the formation of dimer **237** was proposed to rationalize the spontaneous asymmetric synthesis in Soai's reaction.[203] Blackmond and co-workers[204] envisaged that the amplification of ee_{prod} in Soai's system comes from the synergistic combination of chemical and physical processes. A precipitate was observed during the course of the autocatalytic reaction of aldehyde **231** [Eq. (77)] in various solvents.[204a] Analysis of the precipitate and solution revealed that the **232** obtained from the toluene solution had a greater *ee* value than that in the precipitate. In diethyl ether, the **232** had a greater *ee* value in the precipitate than in solution. The heterochiral *R*,*S* dimer is less soluble in toluene solution than the homochiral dimer, while the reverse is true in diethyl ether. Only the homochiral dimers are catalytically active, while the heterochiral dimer is completely inactive.[205] A minute enantiomeric imbalance in the racemic sample that gives rise to very high final *ee* values in Soai's reaction was attributed to a combination of amplification processes involving both asymmetric autocatalysis and selective precipitation.

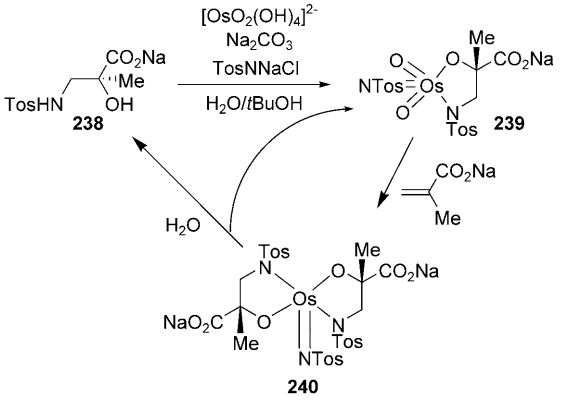
The Soai autocatalytic system attracts a lot of interest because it can generate enantiomeric excess spontaneously.[206a,b] Even though all the mechanistic details are not clarified, it is clear that highly associated and inert heterochiral organozinc species are formed and are key for the observed (+)-NLE.

A purely organic autocatalytic reaction has recently been described by Mauksch, Tsogoeva, et al.[206a] The reaction between acetone and an α-iminoester was catalyzed by the product, and gave an *ee* value of up to 96%. Product with random small *ee* values was formed under achiral conditions.[206b] Similarly, an aldol reaction gave a spontaneous chiral symmetry breaking.

Enantioselective autoinduction in catalysis occurs when the product of a reaction modifies the catalyst, thereby affording new reactivity and stereoselectivity.[191d,207] There are few examples of autoinduction occuring in asymmetric organometallic catalysis[207a–e] or in asymmetric organocatalysis.[207g] Enantioselective autoinduction is, strictly speaking, not related to enantioselective autocatalysis, since the initial catalyst is not produced in the reaction. However, an autoinduction can influence the shape of NLE curves if the values of ee_{prod} are conversion-dependent. This aspect has been discussed by Walsh et al. in the addition of diethylzinc to benzaldehyde with a catalyst system of chiral bis(sulfonamide) ligands and one equivalent of $Ti(OiPr)_4$.[207b] Some ligands generated a (−) NLE. Ligand exchange (alkoxide exchange of O*i*Pr/OCH(Et)Ph at Ti) plays a role in the value of ee_{prod}, which may change with conversion. A detailed study has given good insight into the in situ alkoxide exchange. Similar studies have been realized with binol/Ti catalysts.[207c]

5.2. Self-Replication

Self-replication is similar to autocatalysis and involves a template synthesis. In organometallic reactions, if the chiral auxiliary bound to the metal center catalyzes its own production, then it is known as template-directed self-replication.[208,209] Muñiz[209b] reported one such asymmetric self-replication in the Sharpless asymmetric aminohydroxylation of sodium methacrylate (Scheme 16; Tos = toluene-4-sulfonyl) in the presence of a non-enantiopure osmium complex **239**. Both homochiral and heterochiral **240** undergo hydrolysis in situ to provide **238**, with regeneration of catalyst **239**. The *ee* value of **238** continuously decreased over the course of the reaction because of the absence of an inhibitory process, thus resulting in the continuous lowering of the *ee* value of catalyst **239**.



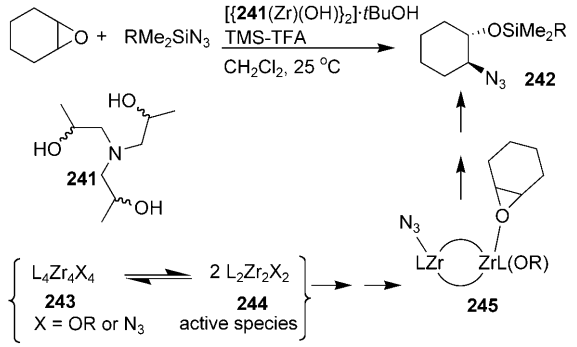
Scheme 16.

6. Other Nonlinear Processes

6.1. Mixtures of Non-diastereopure Ligands

It is possible to gain some information on reaction mechanisms by examining the behavior of a mixture of two chiral auxiliaries. A prediction of the ee_{prod} value can be made if one assumes that the two chiral auxiliaries act independently in the reaction. In this case, a straight line is predicted in the plot of ee_{prod} versus various combinations of two chiral auxiliaries, taking into account their known reaction rates. If the experimental curve deviates from linearity, the presence of the NLE may be an indication of an aggregation of the catalyst or ligand in the course of the reaction. This topic was already mentioned in our 1999 review on NLEs.[11] Although few cases were known at that time,[24,210] some additional examples are discussed below.

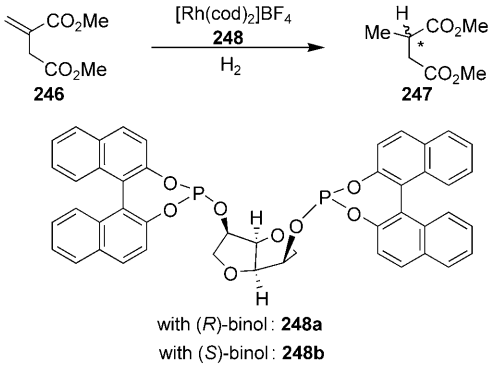
Finn and co-workers[211] have employed NLE studies with the diastereomeric C_3-symmetric ligands **241** to analyze the mechanism of the [Zr(**241**)]-catalyzed enantioselective ring-opening of cyclohexene oxide by Me_3SiN_3 (Scheme 17; TFA = trifluoroacetic acid). A catalyst obtained from readily available (*R*,*S*,*S*)-**241** generated the product **242** with nearly racemic composition, while the catalyst obtained from diastereomeric (*S*,*S*,*S*)-**241** provided **242** in 93% *ee*. A (+)-NLE was encountered when a mixture of (*R*,*S*,*S*)-**241** and (*S*,*S*,*S*)-**241** with various *de* values was employed. This led the authors to consider the involvement of dimeric species in the reaction. Vapor pressure experiments indicated that the molecular weights of the precatalyst species coincided with an average trimeric aggregation. A half-order dependence on the total zirconium concentration was found in kinetic studies. All these observations suggested that a preequilibrium interconversion between dimeric **244** and tetrameric **243** occurs rapidly, with **245** being the active catalyst and kinetically dominant (Scheme 17). It was also proposed that the catalytic activity requires the cooperative action of two zirconium centers for the binding and delivery of an azide group to the epoxide, as depicted in structure **245**. A similar mechanism has previously been described with a salen-chromium catalyst.[125]



Scheme 17.

Blackmond, Reetz, et al.[145] have proposed that if two pure diastereomeric catalysts follow different reaction rate

laws, then a mixture of catalysts can lead to NLEs. They Rh catalysts examined in the enantioselective hydrogenation of **246** were prepared from diastereomeric ligands **248a** and **248b** and $[Rh(cod)_2]BF_4$ [Eq. (78)].[212] The two catalysts provided the product **247** with opposite configuration and almost identical *ee* values. The *ee* value of the product remained constant over the course of the reaction. The curves plotted for reaction rate versus conversion revealed two different kinetic profiles for the reactions with **248a** and **248b**. The observed NLE was attributed to differences in the kinetic profiles of the Rh catalyst generated from **248a** and **248b** acting independently throughout the reaction. An alternate explanation could be the presence of resting dimeric cationic rhodium complexes, as evidenced in reference [141].



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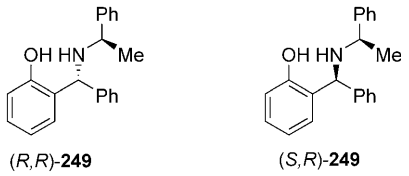
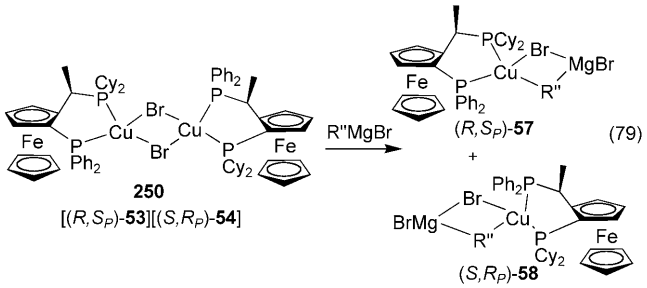
Palmieri[213] employed various *o*-hydroxybenzylamines such as **249** as chiral ligands in the addition of diethylzinc to aromatic aldehydes. (*R*,*R*)-**249** generated the product with



S configuration and 89% *ee*, while the corresponding diastereomeric ligand (*S*,*R*)-**249** led to the *R* product with 60% *ee*. The use of non-diastereopure **249** resulted in a strong positive nonlinear relationship between the *de* value of the chiral ligand and the *ee* value of the product. Palmieri, therefore, suggested a mechanism similar to the one proposed by Noyori and co-workers,[27] with the active catalyst being a monomeric Zn complex, and the NLEs were attributed to the formation of a stable and inactive heterochiral binuclear complex.

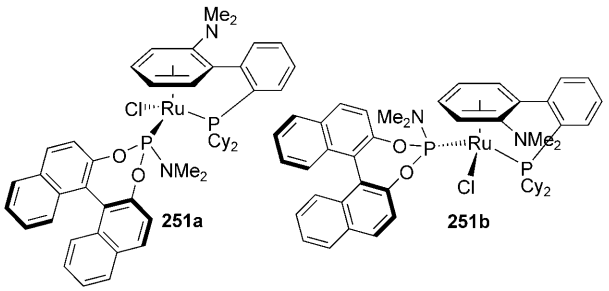
Bolm et al.[44] employed a mixture of diastereomeric ferrocenyl hydroxyloxazolines (S,R_p)-**21** and (S,S_p)-**21** (see Section 2.1.1) as chiral ligands in the addition of diethylzinc to benzaldehyde. A strong (+)-NLE was noticed, which was attributed to the superior reactivity of (S,R_p)-**21** dominating the reaction, even in the presence of an excess of (S,S_p)-**21**.

Feringa and co-workers[65,66] noticed the absence of an NLE in the copper-catalyzed enantioselective conjugate addition of a Grignard reagent to acyclic α,β-unsaturated methyl esters using scalemic diphosphine ligands **57** or **58** [see Section 2.3 and Equation (14)]. The involvement of a single ligand molecule in the enantioselective step was suggested. They also examined pseudo-enantiomeric ligands (*R*,*S*)-**51** and (*S*,*R*)-**52**. Complex **53** is a poor catalyst, while **54** afforded the *R* product with 98% *ee* (Section 2.3). The heterocomplex **250** [Eq. (79)] provided almost identical results as obtained with the most efficient catalyst **54**. This result is an indication for **250** breaking down to monomeric complexes **57** and **58**, which act independently during the course of the reaction and thus lead to a linear correlation.

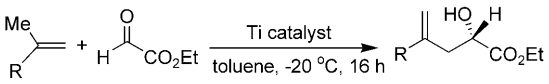


(79)

Diastereomeric ruthenium complexes **251a** and **251b** have been employed in the Diels–Alder reaction of methacrolein with cyclopentadiene.[214] A 1:1 mixture of **251a** and

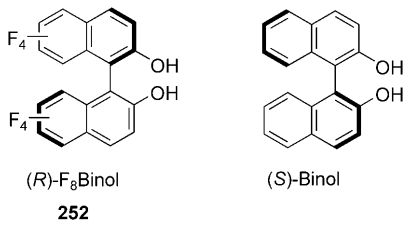


251b gave an *ee* value lower than that calculated by a linear correlation value. Complex **251a** was estimated to be approximately three times more reactive than **251b** to explain the observed (−)-NLE. The glyoxylate-ene reaction catalyzed by a binol-titanium complex [Eq. (80)] gave some early examples of a very strong (+)-NLE. This reaction was discussed in our previous review.[11] This system was analyzed by Mikami and Matsumoto by kinetic and NLE experiments,[215] where a dimeric structure of the catalyst was found.[216]



(80)

Yudin and co-workers[217] examined the use of the Ti catalyst prepared from a mixture of pseudo-enantiomeric binol and F_8binol (**252**) in the same reaction [Eq. (80)]. In the



(*R*)-F_8Binol (*S*)-Binol

252

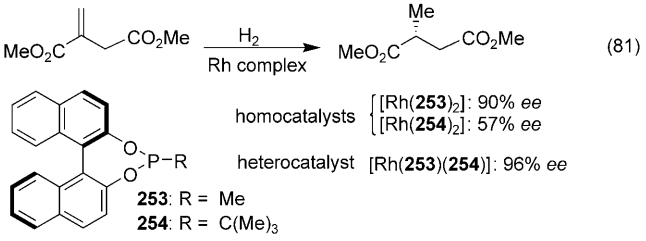
case of aryl-substituted olefins, the individual Ti/(*R*)-F_8binol and Ti/(*S*)-binol catalysts afforded the corresponding *S* product with the same level of asymmetric induction, while the Ti catalyst obtained from the mixture of pseudo-enantiomeric (*S*)-binol and (*R*)-F_8binol had better selectivity and activity. The binol-derived catalyst is approximately four times faster than the catalyst derived from F_8binol. No conversion of aliphatic olefins was found when Ti/F_8binol or Ti/binol complexes were employed alone, but the Ti catalyst derived from a mixture of pseudo-enantiomeric (*S*)-binol and (*R*)-F_8binol offered the highest enantioselectivity (> 99 % *ee*) and moderate conversion. The synergetic effect is related to the better activity and selectivity of a preferentially formed novel catalytic species (pseudo-*meso* aggregate). X-ray analysis of an isolated single crystal from a mixture of (*S*)-binol, (*R*)-F_8binol, and Ti(O*i*Pr)$_4$ confirmed the structure of the pseudo-heterochiral complex with oxo bridges between the Ti centers.

An intriguing possibility has been raised by Walsh and co-workers. Their strategy relies on the use of diastereomeric ligands in which one ligand has a specific interaction with the metal center that decreases the catalytic activity with respect to the diastereomeric ligand.[207c,218] This concept of self-inhibiting catalysts may have useful applications in the preparation of modular chiral ligands

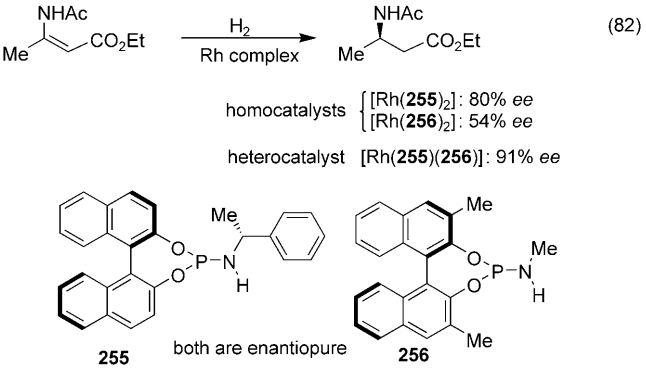
6.2. Mixtures of Nondiastereomeric Chiral Complexes

This strategy was recently developed independently by Reetz et al.[219] and Feringa and co-workers.[220] In the case of a simple ML_2 model with a mixture of two different enantiopure monodentate ligands, L^x and L^y, three types of catalysts, $M(L^x)_2$, $M(L^y)_2$, and ML^xL^y, will be generated in situ, analogously to homochiral and heterochiral complexes in the ML_2 model (Section 2.1). The heterocatalyst ML^xL^y may sometimes possess better activity and enantioselectivity than the homocatalysts $M(L^x)_2$ and $M(L^y)_2$. In this case, a mixture of ligands is advantageous over the use of a single ligand (L^x or L^y).

Reetz et al.[219] used the mixture of two different monodentate ligands for enantioselective rhodium-catalyzed hydrogenation. In some cases the heterocatalyst offered the highest enantioselectivities. For example, [Rh(**253**)(**254**)] was found to be superior to [Rh(**253**)$_2$] or [Rh(**254**)$_2$] [Eq. (81)].[220a] In some cases the heterocatalyst even exhibited opposite enantioselectivity.[220c] This approach was also employed in rhodium-catalyzed hydroformylation.[220f] Reetz et al. extended their studies with non-enantiopure ligand (L^x_R, L^x_S) while the partner ligand was kept enantiopure (L^y_R).[219g] A complex situation arises, comprising a mixture of six complexes, from the homo- and heterocombinations together with the homo- and heterochiral diastereomers. In the case of **253** (non-enantiopure) and **254** (enantiopure), a (+)-NLE was detected. These studies provided useful information about the structural requirements of the ligands as well as certain mechanistic details.



Feringa and co-workers[220b] reported the use of a mixture of two monophosphoramidites (**255**, **256**) in the rhodium-catalyzed asymmetric hydrogenation of dehydro precursors of β-amino acids. The heterocatalysts [Rh(**255**)(**256**)] provided better yields and enantioselectivities than the corresponding homocatalysts [Rh(**255**)$_2$] or [Rh(**256**)$_2$] [Eq. (82)]. Beneficial effects of a mixture of ligands were also noticed in the asymmetric rhodium-catalyzed Michael addition of arylboronic acids to activated alkenes.[220b]

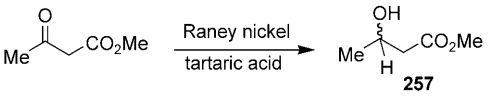


Classical nonlinear effects can be considered to result from a library of complexes built from two enantiomeric ligands (ML_2, ML_3, ML_4 etc). The use of a mixture of different ligands creates a more complicated library of complexes, which can give rise to interesting nonlinear effects. The in situ formation of catalytic hetero-bimetallic species can also be detected by a methodology related to nonlinear effects. This has been exemplified in the enantioselective trimethylsilylcyanation of benzaldehyde catalyzed by a salen-vanadium(V) or a salen-titanium(IV) complex.[221] The chiral salen ligand is derived from **59**. It was found that a mixture of the two

complexes in various proportions gave ee_{prod} values which were different from the values predicted from the knowledge of the two independent catalysts. It could be established that this occurred because of the in situ formation of a heterobimetallic catalyst [(salen-V^V)(salen-Ti^{IV})] with a 1:1 stoichiometry.

6.3. Heterogeneous Metal-Based Catalysis

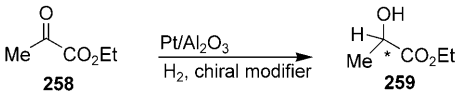
The first example of heterogeneous asymmetric metal-based catalysis was the silk-palladium catalyst prepared by Akabori et al. in 1956.[222] Subsequently, Isoda et al. reported asymmetric hydrogenation using an amino acid/palladium catalyst.[223] Since the efficiency of a chiral modifier mainly depends on its adsorption on the metal surface, a quick and simple tool is needed to find out the adsorption strength. Experiments on nonlinear effects has evolved as a simple probe to estimate the relative adsorption of various chiral modifiers on a particular metal in situ. As early as 1968, Tatsumi, during his investigation on asymmetric hydrogenation with various modified Raney nickel catalysts, examined the effect of the enantiomeric excess of the chiral modifier (tartaric acid) on the *ee* value of product **257** [Eq. (83)].[224] He obtained a linear correlation between the *ee* value of **257** and that of the tartaric acid. On this basis, and together with results from several other experiments, he suggested that a chiral modifier has little or no effect when it loses its ability to get adsorbed on Raney nickel.



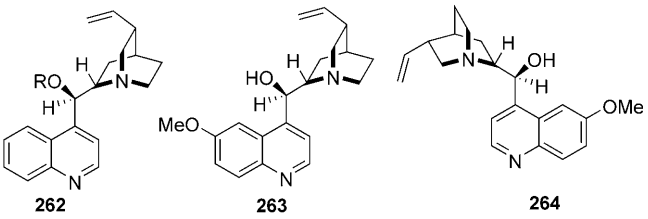
(83)

Baiker and co-workers applied NLE studies to evaluate the relative adsorption strengths of chiral modifiers by enantioselective heterogeneous hydrogenation.[225] They examined the *ee* values of the product by using a mixture of two different chiral modifiers (the related case of mixtures of ligands in homogenous catalysis is described above). The authors assumed that, under ideal conditions, the relative concentration of the chiral modifiers in solution and on the metal surface remain constant throughout the course of the reaction and that the reaction rates and *ee* values are linear combinations of those measured for the two modifiers alone.[225a,b] A linear correlation will be obtained between the *ee* value of the product and the amount of major chiral modifier (mol%) if the two chiral modifiers behave identically (that is, have the same catalytic activity and adsorption). If the experimental curves deviate from the calculated linear behavior, then it is considered an NLE.

Under ambient conditions, cinchonidine (**262a**) affords (*R*)-**259** with 90% *ee* while quinidine **264** gives (*S*)-**259** (94% *ee*, and a slightly faster reaction rate in acetic acid) [Eq. (84)].[225a] A significant (+)-NLE was observed when a mixture of **262a** and **264** was used in the hydrogenation of ethyl pyruvate **258** over Pt/Al_2O_3. Several studies of NLEs,



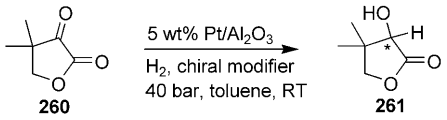
(84)



a : R = H
b : R = Me
c : R = Et
d : R = Ph
e: R = $SiMe_3$

such as varying the addition sequences of **262a** and **264**, clearly revealed that **262a** (cinchonidine) has a stronger adsorption than **264** (quinidine). The latter has a better adsorption capacity than **262d**, as shown by using NLE studies with a 1:1 mixture of **264** and **262d** that gave opposite enantiomers of product **259**.[225a,b]

A similar (+)-NLE was found in the asymmetric hydrogenation of ketopantolactone **260** [Eq. (85)]. Cinchonidine (**262a**) controlled the enantioselection, even in a modifier

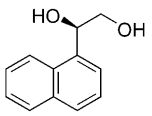


(85)

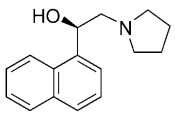
mixture at only 0.7 mol%.[225c] On the basis of the above experiments the following order of adsorption strength on Pt in the hydrogenation of **258** and **260** was proposed: **262a** > **262b** > **262c** > **262d** ≈ **262e**.[225] The authors emphasized that no known physicochemical methods can offer such a simple way to find out the relative adsorption strengths. The greater adsorption of **262a** over **262d** on Pt was also confirmed by in situ attenuated total reflection infrared (ATR-IR) spectroscopy and DFT calculations.[226]

A (+)-NLE was obtained by using a mixture of diastereomeric **263** and **264** in the hydrogenation of **258** [Eq. (84)].[225a,b] Since the anchoring moieties of both **263** and **264** are the same, a difference in the adsorption strength on Pt was ruled out as the cause of the NLE. Instead, a strong attractive mutual interaction between **263** and **264** was suggested (formation of **263**-**264** pairs, similar to the heterochiral diastereomers leading to NLEs in homogeneous organometallic catalysis). This interaction affects the adsorption strength of the **263**-**264** pair and also their interaction with other surface species.

The better adsorption of **266** than **265** on Pt was later revealed by studying the NLE in the hydrogenation of



265

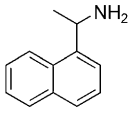


266

ketopantolactone **260** [see Eq. (85)][227] Despite both chiral modifiers possessing identical anchoring moieties (naphthalene ring), **266** controlled the configuration of the product. Even a 1:9 mixture of **266** and **265** gave the same *ee* value as that obtained with pure **266**. This result was explained by a stronger adsorption of **266** on Pt because of the presence of a basic nitrogen atom.

A NLE was observed in the hydrogenation of **260** on a Rh/Al_2O_3 catalyst with mixtures of **262a** and **262d**.[228] Compound **262a** controlled the enantioselection, thus revealing the stronger adsorption strength of **262a** over **262d** on rhodium.

Baiker and co-workers[229,230] also employed **267** and some derivatives such as **268** in the enantioselective hydrogenation of **260** in the presence of a Pt catalyst [Eq. (85)]. There was a



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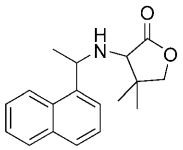

268

linear correlation between the *ee* values of product **261** and those of chiral modifier **268**. However, a strong nonlinear phenomenon was noticed when the anchoring moieties of the two modifiers were different. For example, a mixture of cinchonidine (**262a**) with (*S*)-**267** or (*S*,*S*)-**268** resulted in a clear nonlinear correlation, with the ee_{prod} value mostly controlled by **262a**, even when present in trace amounts. These observations indicate that the quinoline moiety (present in all cinchona alkaloids) is a stronger anchoring moiety than the naphthalene group.

Murzin and Toukoniitty[231] discussed the kinetic aspects of an NLE in heterogeneous enantioselective catalysis by a binary modifier mixture. A kinetic model was developed based on a molecular mechanism, which considered a 1:1 interaction between the modifier and the substrate on the catalyst surface. The catalyst surface was assumed to possess three kinds of active sites: two modified sites and the one from unmodified metal, which gives racemic product. The final selectivity was expressed by a simple equation, which allowed the nonlinear phenomena to be analyzed in terms of rate constants and adsorption enthalpies.

7. Summary and Outlook

The plot of ee_{prod} as a function of ee_{aux} is a simple tool for obtaining information on an enantioselective catalytic reaction. Linearity is expected if only one molecule of the chiral auxiliary is involved in the molecular species (whether catalytically active or not). Since our initial report in 1986, many examples of departure from linearity have been reported in the literature, especially in organometallic catalysis. Nonlinear effects may be an indication of aggregation or the formation of multiligand species. Some special points may be helpful for determining the origins of NLEs and for appropriate mechanistic interpretations:

a) The absence of an NLE is a good indication of the involvement of one ligand or chiral auxiliary in the catalytic cycle. However, this is not a proof, since linearity, for example, is possible with a ML_2 system when $g = 1$ (Section 2).
b) A (+)-NLE will be accompanied by reduced reaction rates with respect to the enantiopure system.[17]
c) A (−)-NLE is indicative of a catalyst with more than one ligand and is characterized by enhanced reaction rates.
d) A competition between the enantioselective catalytic reaction (with linearity) and a background reaction may create an apparent (−)-NLE.
e) Multishape NLE curves may originate from the oligomerization of catalysts species ($ML_{n>2}$, see Section 2). The competition between catalysts providing a (+)-NLE and the background reaction can also generate a multishape NLE curve.
f) A scalemic organometallic catalyst can be prepared either directly from the scalemic ligand or by mixing two enantiopure catalysts. If there is an NLE in the first case and not in the second one, it is good evidence that the catalyst retains its integrity during the reaction.
g) The activity of the organometallic catalysts may be sensitive to remote modification of the substrate structure. The change in the NLE can give some mechanistic information.[32] Coordination chemistry is also a useful tool for analyzing the origin of some nonlinear effects.[232]
h) The NLE curves are influenced by experimental conditions, such as temperature, concentration, and solvent. They are also sensitive to the extent of conversion and to the experimental protocol.[17,27b,33]
i) Autoinduction, for example, through a change of the catalyst by the reaction products, may give some complexity to the curve $ee_{prod} = f(ee_{aux})$. It can, in some cases, lead to the in situ kinetic resolution of the catalyst and hence to a (+)-NLE (asymmetric amplification).
j) The partial solubility of non-enantiopure auxiliaries or complexes in the experimental conditions of the reaction may generate NLEs (see Section 4). The insoluble racemate compound usually acts as a reservoir of the racemic auxiliary, hence enhancing the *ee* value of the actual catalyst.
k) The principles behind the origin of NLEs can be extended in part to chiral reagents and to kinetic resolution, and also apply to mixtures of chiral ligands or complexes (Section 6).

In conclusion, studies on NLEs provide an easy way to obtain details about a chiral catalytic system. The special case of a strong (+)-NLE (asymmetric amplification) attracts much interest because of the possibility of using non-

enantiopure auxiliaries in preparative enantioselective catalysis, and because of its usefulness in autocatalysis and in discussions related to the origin of homochirality (Section 5).

We thank the Université Paris-Sud and the CNRS for financial support. T.S. acknowledges The Université Paris-Sud and Pierre Fabre Co for postdoctoral fellowships. S.A. acknowledges the Institut de Chimie des Substances Naturelles (CNRS, Gif-sur-Yvette) for financial support.

Received: November 14, 2007
Revised: April 11, 2008

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