Chiral Poisoning and Asymmetric Activation

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I. Introduction

Catalytic asymmetric synthesis has seen great advances, and the awarding of the 2001 Nobel prize in chemistry to Ryoji Noyori, William Knowles, and Barry Sharpless for asymmetric catalytic hydrogenations and oxidations emphasizes the importance of the area. Homogeneous catalysts for hydrogenations, in particular, are often comprised of precious metals and enantiopure ligands. The term *precious metal* may actually be misleading in this context because the ligands are often more expensive than the metal. The chiral multiplication wherein a single chiral catalyst molecule can transmit chirality to a large number of product molecules can make the use of these *precious ligands* economically viable for practical applications. Enantiopure ligands can be synthesized from the chiral pool, but often their preparation involves a resolution step that adds to the cost of the ligand. As a consequence, the racemic ligand is usually substantially less expensive than the enantiomerically pure ligand. An attractive concept is the use of the racemic, but still relatively expensive, ligand in the preparation of the catalyst and adding an inexpensive chiral modifier to yield a new catalyst system that will produce an enantiomerically enriched product. This review will focus on the effects of nonracemic chiral additives to racemic homogeneous catalyst systems.

Ideally, the chiral modifier would react completely with one enantiomer of a racemic catalyst and either deactivate that enantiomer or increase its catalytic activity relative to the unactivated enantiomer. An ideal deactivation scenario would be one in which an inhibitor selectively binds to only one of the enantiomers of the catalyst, leaving the other enantiomer free to catalyze the reaction (Figure 1).

In reality, it is unlikely that a poison will be so selective that it will only bind to one enantiomer of the catalyst. There would generally be a preference for one of the two enantiomers of the catalyst, so that both would be poisoned to some degree, but one would be inhibited to a much greater extent than the other.

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Jack Faller was born and raised in Louisville, Kentucky. He received his B.S. and M.S. degrees from the University of Louisville in 1963 and 1964. He received his Ph.D. degree from the Massachusetts Institute of Technology in 1967, where he worked with Alan Davison and Al Cotton on their pioneering efforts with stereochemically nonrigid molecules. Accepting a position at Yale University in 1966, he continued with studies of organometallic conformational equilibria, fluxional molecules, and applications of NMR spectroscopy to stereochemical and mechanistic problems. He developed reagents for asymmetric synthesis using electronically asymmetric organometallics. During one of his many sabbatical visits to collaborate with John Osborn at the Université Louis Pasteur in Strasbourg he became acquainted with Jon Parr, who eventually did postdoctoral research at Yale and became a frequent collaborator. Professor Faller's recent work has emphasized development of new approaches to asymmetric catalysis using transition-metal catalysts.

Adrien R. Lavoie was born in Manchester, NH, and was raised in Eagle, ID. He was awarded his B.S. degree in Chemistry from Albertson College in 1998, completing undergraduate research at the University of Kansas, U.C. Berkeley, and Cornell University. He received his Ph.D. degree from Yale University in 2002 under the supervision of J. W. Faller, where his dissertation research involved catalytic asymmetric synthesis and chiral poisoning for which he received the Richard Wolfgang Prize for the best dissertation in the Department of Chemistry, Yale University (2002–2003). Currently, he is a NIH postdoctoral research fellow in the laboratory of Robert M. Waymouth at Stanford University.

A general feature of this poisoning mechanism is that as the enantioselectivity of the process is increased, the turnover frequency for the system as a whole will decrease. This decrease is the result of there being fewer molecules of the catalyst available to promote the reaction. In the limit with no complicating factors, the rate of formation of product would be one-half of that for the case where an equivalent amount of the enantiopure catalyst were used, and furthermore, the enantiomeric purity would be the same as that achieved by the enantiopure catalyst.

Jonathan Parr grew up in West Knighton, a small village in rural Dorset, not far from Dorchester. After Hardye's School and three years at BDH Chemicals Ltd., he took the GRSC by examination at Kingston Polytechnic (1986) before going on to doing Ph.D. research with Professor Dennis Evans at Imperial College (1989). Postdoctoral visits in the laboratories of Professor Raymond Weiss (Poste Rouge, Université Louis Pasteur, Strasbourg), Professor J. W. Faller (Yale University), and Professor Sir Geoffrey Wilkinson (Imperial College) preceded his appointment as Lecturer in Inorganic Chemistry at Loughborough University (1992–2001). He is currently at Yale, working for Professor H. H. Wasserman, conducting research in polycarbonyl reaction methodology. He has authored or co-authored more than 40 publications in the fields of main-group element coordination chemistry, chiral organometallic catalysts and reagents, and the use of polyketones in the synthesis of non-proteinogenic amino acids.

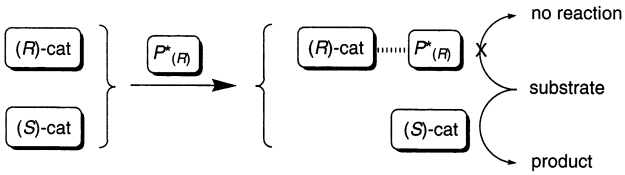
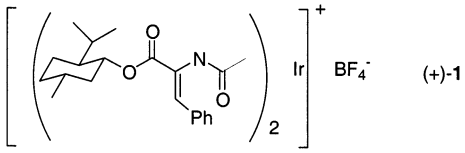


Figure 1. A 100% selective poison or inhibitor for the (*R*)-catalyst, $P^*_{(R)}$, allows the (*S*)-catalyst to produce chiral nonracemic product.

A "proof of principle" of this approach for an analogous situation was suggested by Alcock, Brown, and Maddox[1,2] in an approach called *in situ resolution*. In this experiment an iridium complex prepared from enantiopure (*R*)-menthyl-(*Z*)-α-benzamidocinnamate, $[(L^*)_2Ir]^+$, (+)-**1**, reacted with 2 equiv of racemic CHIRAPHOS to selectively bind only the (*S*,*S*)-enantiomer of the bisphosphine. Subsequent



addition of Rh(I) then allowed the remaining free (*R*,*R*)-CHIRAPHOS to form a Rh complex that was used to selectively hydrogenate methyl (*Z*)-α-benzamidocinnamate (Figure 2).

The in situ resolution procedure does not represent a *chiral poisoning* as defined in Figure 1, since it uses an expensive additive and it is not inhibiting the catalyst per se. The first homogeneous catalyst example that appears to be completely consistent with chiral poisoning was the catalysis of a hetero-Diels–Alder reaction using a racemic aluminum Lewis acid catalyst poisoned by a chiral ketone. This

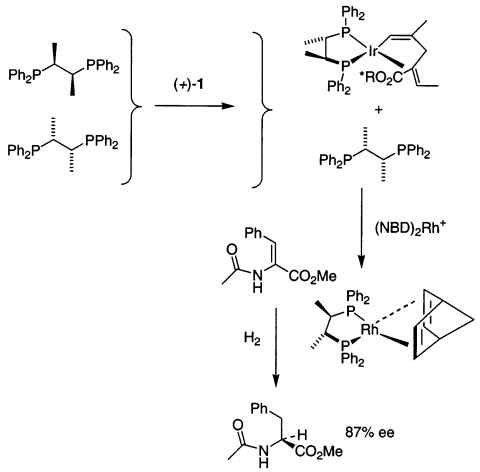


Figure 2. In situ resolution of (*R*,*R*)-CHIRAPHOS via the generation of an Ir complex allows for the generation of an (*R*,*R*)-CHIRAPHOS−Rh complex which enantioselectively hydrogenates methyl (*Z*)-α-benzamidocinnamate.

was termed "discrimination of racemates" by Maruoka and Yamamoto[3] and has subsequently also been referred to as *racemate discrimination*. The most effective chiral ketone poison for this reaction was found to be (+)-3-bromocamphor, which sequesters the (*R*)-BINOL complex, (*R*)-**2** (Figure 3). The poisoned mixture of Lewis acids yields a product in 82% ee, whereas the pure (*S*)-BINOL complex, (*S*)-**2**, yields the adduct in 95% ee (Figure 4).

Preformed catalysts containing racemic CHIRAPHOS that follow the chiral poisoning strategy of Figure 1 were first studied by Faller and Parr.[4] In this case, the poison was (*S*)-METHOPHOS, (*S*)-[$Ph_2POCH_2CH(NMe_2)CH_2CH_2SMe$], that is readily prepared from methionine. The precatalyst is a dimer of (CHIRAPHOS)Rh^+ that was treated with the poison, *P**, in a ratio of *P**:Rh = 0.7:1. Hydrogenation of dimethyl itaconate with this modified catalyst provided (*S*)-dimethyl methylsuccinate in 49% ee. The pure [(*R*,*R*)-CHIRAPHOS]Rh^+ catalyst yields (*S*)-dimethyl methylsuccinate in >98% ee. In this case, the poisoning is reasonably effective but its selectivity is not comparable to the pure catalyst (Figure 5).

A significant feature of this reaction is that the (*S*)-METHOPHOS itself forms a poorly enantioselective catalyst with rhodium, (ee < 2% for the same hydrogenation), and hence, any [(METHOPHOS)Rh]$^+$ formed is not contributing significantly to enantioselectivity. In fact, any of this complex that formed would serve to reduce the enantioselectivity of the modified catalyst since it would dilute the enantiopurity of the product generated by the [(*R*,*R*)-CHIRAPHOS]Rh^+ component. Another mechanistic factor that might influence the enantioselectivity of this mixture of components in the modified catalyst is *chiral amplification*.[5] This phenomenon can modify the enantioselectivity since the homochiral dimers and meso dimers have different equilibrium constants for dissociation to active monomeric catalysts (this will be discussed in more detail in section III.B). Regardless of the origins of the effect, the significant practical aspect is that addition of a chiral nonracemic modifier to a racemic catalyst produces a modified catalyst system that has useful enantioselectivity.

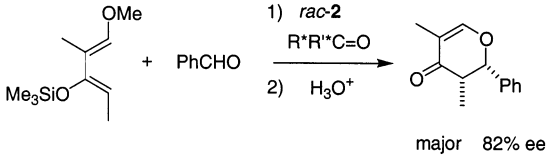


Figure 4. Hetero-Diels−Alder reaction.

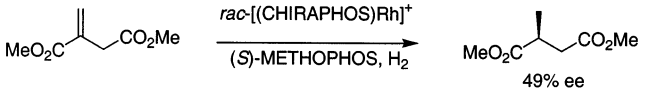


Figure 5. Hydrogenation of dimethyl itaconate to yield (*S*)-methylsuccinate.

II. Background of Chiral Nonracemic Additives in Heterogeneous Systems

This review will focus on homogeneous systems; however, the exploration of the addition of modifiers to nonselective catalysts to yield new catalysts that give rise to nonracemic products began with heterogeneous catalytic systems. Historically, the first system that provided a reasonably useful and reliable asymmetric hydrogenation consisted of palladium on silk. This catalyst was shown to be effective with ketones and oximes as substrates and was reported

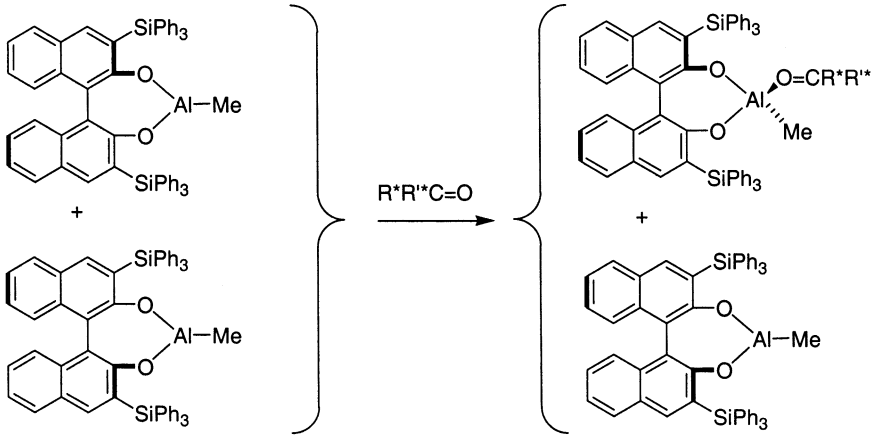


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Figure 3. Racemate discrimination with a chiral ketone leads to a "chiral-poisoned" mixture.

in 1956.[6] The potential of chiral adsorbents to modify Raney nickel and thereby influence the outcome of hydrogenations was noted as early as the 1930s.[7,8] Since that time there have been advances that have provided heterogeneous catalysts modified with chiral nonracemic additives that are very effective for asymmetric catalysis. There are a number of recent reviews of this area,[8−11] and as such, it will not be discussed in detail. High and reproducible enantioselectivities were first produced with the hydrogenation of β-ketoesters by tartrate-modified Raney nickel.[12] This system has been refined and continues to be developed.[13] Under optimized conditions, hydrogenation of methyl acetoacetate yields the product in 86% ee; however, ee's in the range of 90−98% are obtained from β-ketoesters having substitution at the γ-position. Systems that have been successful for the hydrogenation of α-keto esters include platinum catalysts modified with cinchona alkaloids and their mimics.[14] The feature of interest here is the mechanism by which the modifiers affect the enantioselectivity. In most cases it would appear that an active site is modified in much the same manner as one assumes a chiral ligand affects a homogeneous catalyst. One could propose, however, that enantiomeric chiral sites are poisoned to different extents. This follows from the notion that multiple types of sites may be available on a catalyst and these different types of sites can be responsible for particular reactions or have different selectivities. Thus, the overall selectivity of a catalyst reflects the average of the reactions occurring at all of the different sites. Poisoning in heterogeneous catalysts is often viewed as blocking or deactivating one type of site which allows the remaining sites to carry out transformations on a greater percentage of the substrate. Hence, the selectivity of the modified or poisoned catalyst is improved. The potential importance of chiral sites in a heterogeneous catalyst and their potential modification was recognized by Pino in olefin polymerization.[15]

As early as 1955 prochiral olefins were stereospecifically polymerized to yield isotactic polymers.[16] Pino suggested that although this synthesis does not yield optically active compounds, it "can be considered an asymmetric synthesis catalyzed by racemic transition metal complexes".[15] Modification of a $TiCl_4$/$MgCl_2$ Lewis-acid-catalyzed polymerization of racemic 4-methyl-1-hexene with (−)-menthyl-*p*-methoxybenzoate led to alterations in the percentage of isotactic and atactic polymers that were produced while generating an ee in the remaining monomer. It was suggested that these data support the existence of multiple catalytic sites with different selectivities in catalysis. Regarding the stereoselective centers, the observation of an enantiomeric excess in the monomer remaining after the polymerization reflects the "different tendencies of the chiral catalytic centers to form complexes (and then lose or decrease their catalytic activities) with the chiral base".[17]

A more recent application of a poisoning approach has been in molecularly imprinted polymers or other matrices wherein surface sites are often more reactive but less selective than internal sites. Poisoning of the surface sites thus allows for greater selectivity as an increased proportion of the reaction takes place in the cavities within the polymer.[18,19] Chiral molecularly imprinted cavities within the polymer formed from racemic BINOL and site poisoning by (*R*)- and (*S*)-binaphthyldiamine, BINAM, have been investigated by Koh and Gagné[20] (Figure 6). Site selectivity

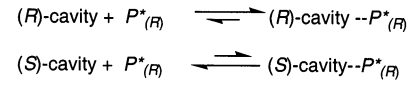


Figure 6. Chiral site poisoning in molecularly imprinted cavities.

for a specific BINAM enantiomer was noted, but in this case, product enantioselectivities were not significantly affected by the poisons. However, relative selectivities are also important parameters in homogeneous systems and are relevant to the primary focus of this review as discussed in the following section.

Although not strictly heterogeneous catalyst systems, there are situations where addition of a small quantity of heterogeneous chiral material can drastically affect the enantioselectivity of a homogeneous catalytic reaction (see section III.B).

III. Some Parameters for Successful Poisoning in Homogeneous Systems

A. Poisoning Equilibria

For catalytic transformations of a prochiral substrate, one would anticipate the ee of the product to be related to the relative populations of the substrate-bound catalyst complex (Figure 7).

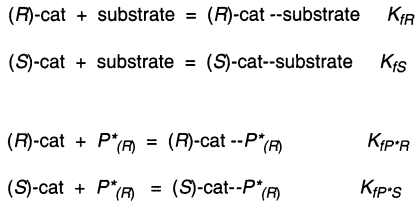
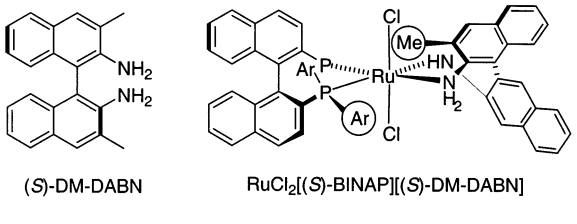


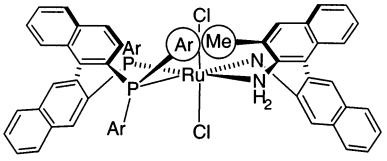
Figure 7. Important equilibria for chiral poisoning.

For the simplest view of chiral poisoning there are four relevant equilibria. Given that the substrate is achiral, then $K_{fR}/K_{fS} = 1$ for substrate binding. Then, if there is preferential binding of the poison to the (*R*)-catalyst, $K_{fP*R}/K_{fP*S} > 1$. If these are the only equilibria involved (particularly if no catalyst dimerization is involved), then $K_{fP*R}/K_{fP*S} > 10$ would be required to achieve significant enantioselectivity in the (*S*)-product. This would give a ratio of [(*R*)-cat]:[(*S*)-cat] = 10:1 if sufficient poison were available and $K_{fP*S} \gg 1$. In the case where the enantiopure catalyst yields 100% ee, then this 10:1 ratio would be expected to produce an 82% ee. It is important to recognize that a large binding constant for the poison is required for typical catalyst reaction conditions; otherwise, the cat−*P** complex will largely remain dissociated. If the condition that $K_{fP*} \gg 1$ is not met, a molar ratio of [*rac*-cat]:[*P**] may well have to be much greater than 1 in order to give a useful process.

An appealing aspect of poisoning is that thermodynamics control the important equilibria. The usual difficulty in the design of enantioselective catalysts is not involved since the enantiopure version has usually already been optimized to yield high selectivity. Thus, it is possible to use molecular modeling to aid the prediction of potential poisons since one generally is interested in comparing the relative stabilities of two complexes. As the binding of a poison involves a comparison of two species with equivalent compositions, a molecular mechanics approach is fairly reliable. For example, effective determination of the binding preference of (*S*)-DM-BINAM, [3,3′-dimethyl-1,1′-binaphthyl-2,2′-diamine], for (*S*)-BINAP$RuCl_2$ relative to (*R*)-BINAP$RuCl_2$ was successfully evaluated by molecular mechanics calculations for stabilities of diastereomers of (BINAP)-(DM-BINAM)$RuCl_2$.[21] Often a single strong steric repulsion is responsible for the selective complexation (a phenyl−methyl interaction in the BINAP-DM-BINAM case above) and relatively simple calculations can provide a rationale for their relative stabilities. Several studies at various levels of sophistication have also been used to evaluate stabilities in similar systems.[22,23] Alternatively, one can sometimes carry out competitive binding experiments and/or evaluate the relative stabilities of the two diastereomers by analysis of populations by NMR.[21,24−26] This is particularly suitable for Lewis acid catalysts poisoned by bases. In other cases, e.g., hydrogenation catalysts, one can usually only evaluate stability constants for precursors and not for the active catalysts.



(*S*)-DM-DABN $RuCl_2$[(*S*)-BINAP][(*S*)-DM-DABN]



$RuCl_2$[(*R*)-BINAP][(*S*)-DM-DABN]

One must also ascertain whether the ligands redistribute to a significant extent, as this can further complicate the interpretation of the observed enantioselectivity owing to the presence of more paths for the reaction. Thus, in the example above, the (BINAP)(DMBINAM)$RuCl_2$ complex does not disproportionate to $(BINAP)_2RuCl_2$ and $(DMBINAM)_2RuCl_2$,[27] either of which might be an excellent catalyst for the reaction but with varying selectivity. A final constraint is that the poison must bind better to the catalyst than the substrate does, i.e., $K_{fP^*R} \gg K_{fR}$. If this condition is not met, the substrate, which is in greater concentration than the poison under normal reaction conditions, will displace the poison. In this context, it is surprising that the racemate discrimination of the racemic Lewis acid[3] illustrated in Figure 3 was successful, as one might have expected that the bromocamphor would be displaced by the aldehyde that was present in excess.

An alternative for selecting potential poisons is the use of combinatorial methods[28,29] that have been successful in optimization of enantioselective catalysts. Although this approach has not been used extensively at this time for chiral poisoning, these preliminary investigations indicate that it should be successful.[30−32] This subset will be discussed further in section IV.B.4.

B. Chiral Amplification and Nonlinear Effects

Nonlinear effects (NLE's) in asymmetric catalysis were first reported and analyzed by Kagan in 1986.[5] A positive NLE gives rise to *chiral amplification* or *asymmetric amplification* since product enantioselectivities are observed that are larger than those expected on the basis of the enantiomeric purity of the ligands or their complexes used for the catalyst. The effects are particularly large in the addition of diethylzinc to aldehydes in the presence of nonracemic amino alcohols.[33−35] This effect can potentially be important for additions of chiral additives to racemic systems that will be discussed later. Some important concepts will be presented here, but there are a number of comprehensive reviews that can be consulted for more detail.[36−39] The studies concerning competition of dimer formation in pseudoenantiomeric complexes investigated by Kagan et al.[40] and those of Blackmond on the kinetics of nondiastereomerically pure catalysts are particularly relevant.[41] Detailed mechanistic studies of particular significance in this regard are those of Noyori,[42] Blackmond,[43,44] and Singleton.[45]

The initial explanations of chiral amplification were based on a central theme of a single metal binding to two ligands, $ML_nL'_{2-n}$.[5] This model was ultimately superseded by a model involving dissociation of catalytically inactive dimers, $[(ML)_n(ML')_{2-n}]$, to form active monomers, which was found to be more appropriate in many cases.[42,46] The addition of a chiral poison can change the relative populations of enantiomeric monomers of a catalyst that was initially racemic (as shown in Figure 7). A catalyst will often be a coordinatively unsaturated species that would tend to bind to a base, such as an amine, olefin, or carbonyl moiety. This Lewis acidic character may allow the catalyst to dimerize if there are additional peripheral donor sites on the bound ligands. For the earlier example (Figure 5) of poisoning using [CHIRAPHOS]Rh^+, the cation of [(*S*,*S*)-CHIRAPHOS]Rh^+ has been shown to dimerize and form the homodimer $\{[(S,S)\text{-CHIRAPHOS}]Rh\}_2^{2+}$ (Figure 8). Thus, in a solution of the racemic or nonracemic mixture there are three equilibria to be considered in addition to

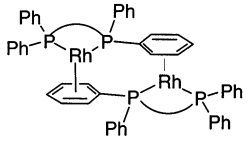


Figure 8. Dimer formed by [(CHIRAPHOS)Rh]$^+$.

Figure 9. Dimer−monomer equilibria.

those relating to binding of substrates or solvents (Figure 9). The homodimers have equal formation constants, K_{SS} and K_{RR}. If the formation constant for the meso dimer K_{SR} is greater than K_{SS}, an original enantiomeric excess in the ligand or monomer would be amplified to a larger value. If $K_{SR} \gg K_{SS}$ and there were an excess of the (*S*)-enantiomer, virtually all of the (*R*)-enantiomer would be sequestered in forming the meso dimer, leaving nearly enantiopure (*S*)-monomer to carry out the catalysis. Hence, if these conditions apply, a small enantiomeric excess in the ligand can yield a product in high enantiomeric purity. One should note, however, that since much of the catalyst is tied up in an unreactive dimer, the reaction rate will be much slower. These conditions appear to occur in the [CHIRAPHOS]Rh system.[4,47] These chiral amplification effects also are prevalent in the use of additives to amino alcohol/$ZnEt_2$ alkylation of aldehydes, and this has been studied extensively (see section IV.B.4).

There are situations where addition of a small quantity of heterogeneous chiral material can drastically affect the enantioselectivity of a reaction. These processes are examples of *asymmetric autocatalysis* or *asymmetric automultiplication*.[48−51] Thus, enantiomorphic crystals, such as $NaClO_3$ and quartz, can produce an imbalance in the solution population of enantiomers by selective absorption.[52,53] For example, pyrimidylalkanols were produced with high ee values (96−98%) in the addition of diisopropylzinc to 2-(*tert*-butylethynyl)pyrimidine-5-carboxaldehyde in the presence of D- or L-$NaClO_3$[52] (see Figure 10). The function of the enantiomorphic crystals were to selectively absorb one enantiomer of the initially produced racemic pyrimidylalkanol, giving a nonracemic solution of this ligand. Chiral amplification with ligand acceleration from the product then can give high enantiomeric purities of products in catalysis. More cases can be anticipated where a completely racemic system could result in high enantiomeric purity products if spontaneous resolution were combined with chiral amplification and asymmetric autocatalysis.[54] One should note that it is difficult to avoid nonracemic impurities and these impurities can potentially give results that could easily be misinterpreted.[55]

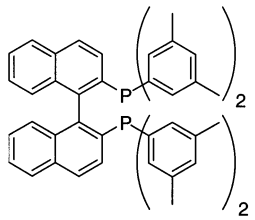
IV. Survey of Examples Attributed to Chiral Poisoning in Homogeneous Samples

There have been several papers which have partially summarized results on chiral poisoning.[21,27,47,56] These will be discussed by reaction class.

A. Hydrogenations.

1. Ketone Hydrogenation

Prochiral ketone hydrogenations, particularly β-keto esters, have represented some of the most effective of the asymmetric hydrogenation catalyses.[27,57] Elaboration of BINAP has shown that 2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl, XylBINAP, complexes of ruthenium are very effective for these hydrogenations.[58,59] One of the most efficient chiral poisoning systems discovered to date has recently been reported by Mikami, wherein a *rac*-$RuCl_2$(XylBINAP)(dmf)$_n$ precursor was selectively deactivated by 3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl (DM-DABN).[60]



XylBINAP

In this case it appears that the selectivity is so high that only 0.5 mol equiv of (*S*)-DM-DABN is needed to effectively sequester the [(*S*)-XylBINAP]$RuCl_2$ moiety and leave the [(*R*)-XylBINAP]$RuCl_2$ virtually uncoordinated by DM-DABN when added to the [*rac*-XylBINAP]$RuCl_2$ complex. This is close to the idealized case indicated in Figure 1. As shown in section III.A, molecular modeling suggested that interaction of the methyl groups of the DMDABN with the aryl substituents of the phosphines accounts for the selectivity. These are precursors to the active catalyst rather than the active catalyst itself; nevertheless, the results suggest that similar selectivity still persists under hydrogenation conditions (Figure 11).

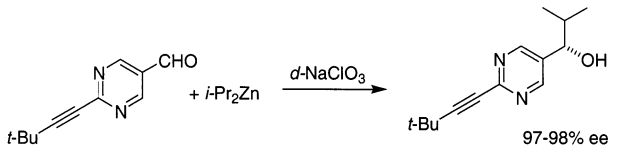


Figure 10. Chiral amplification occurs after preferential absorption of initially racemic product by the solid.

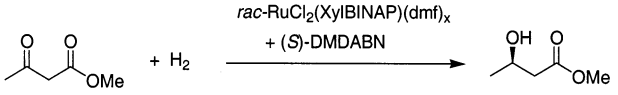


Figure 11. Hydrogenation of methyl 3-oxobutanoate by a racemic ruthenium catalyst poisoned by (*S*)-DMDABN in a ratio of Ru:DMDABN = 2:1.

With a ratio of Ru:DMDABN of 2:1, the catalyst yielded the (*R*)-product in 99.3% ee, a result that compares favorably with 99.9% ee for the pure [(*R*)-XylBINAP]$RuCl_2$ catalyst precursor. These results reflect a near complete sequestering of the [(*S*)-XylBINAP]Ru complex with 0.5 mol equiv of DM-DABN.

2. Olefin Hydrogenation and Kinetic Resolution

Kinetic resolution offers an effective method for the preparation of cyclic allylic alcohols in high enantiomeric purity, although separation of products can be a problem.[61] In this approach the relative rate constants (or turnover frequencies) for reaction with

the (*R*)- and (*S*)-enantiomer of the substrate are an important factor in controlling the extent to which the conversion must be carried out in order to achieve an acceptable ee.[38,62,63] In general, a rate constant ratio of $s = k_f/k_s > 5$ can yield a useful system and $s > 10$ a very good system. In 1993, Faller and Tokunaga showed that [*rac*-BINAP]$RuCl_2(dmf)_x$ could be poisoned with (−)-(1*R*,2*S*)-ephedrine to yield >95% ee of the (*R*)-cycloalkenol after 77% conversion[64] (Figure 12). This was improved in 2002 by Mikami

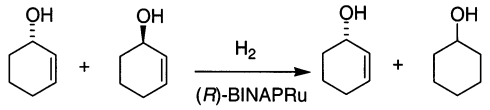


Figure 12. Kinetic resolution of 2-cyclohexenol.

using the [*rac*-XylBINAP]$RuCl_2$/(*S*)-DMDABN system, which gave 100% ee of the (*S*)-alcohol after 53% conversion,[60] indicating a $k_f/k_s \approx 100$. This is one of the best poisoning systems among those that have been found to date.

3. Imine Hydrogenation

Hydrogenation of imines in high enantioselectivity is generally a more difficult task than the hydrogenation of comparable ketones. In comparing relatively inexpensive ligands, the (*S*,*S*)-DIOP ligand, 2*S*,3*S*-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, proved to be the most effective in a complex with iridium for a specific substrate of interest[65] (Figure 13).

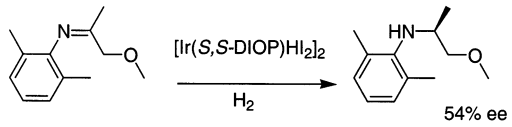
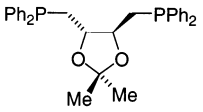
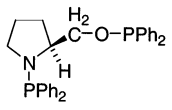


Figure 13. Asymmetric imine hydrogenation.



(*S*,*S*)-DIOP

Preparation of the $[Ir(DIOP)HI_2]_2$ catalyst using *rac*-DIOP yields a mixture of homo and meso dimers. When these dimers were treated with the aminophosphinephosphonite, (*S*)-PRONOP, derived from PPh_2Cl and (*S*)-2-pyrrolidinemethanol, a complex mixture of diastereomers was formed. The catalyst containing enantiomerically pure DIOP only yields an ee of 54%; hence, the best ee that could be expected based on these diastereomeric ratios would be 54%, so that expectations of success were limited. This mixture with *rac*-DIOP and (*S*)-PRONOP ligands yields up to 19% ee of the (*R*)-amine when the imine was hydrogenated.[66]



(*S*)-PRONOP

B. Aldehyde and Enal Activation

1. Diels–Alder

In a recent report Faller et al. reported on the utility of enantiomerically pure [(R_{Ru},*S*)-*p*-cymeneRuCl(BINPO)]SbF_6, where BINPO is the monoxide of BINAP, also known as BINAP(O), as a precatalyst for a highly enantioselective Lewis-acid-catalyzed asymmetric Diels−Alder reaction between methacrolein and cyclopentadiene[67] (Figure 14). When this

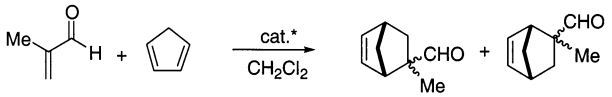


Figure 14. Diels−Alder condensation of methacrolein with cyclopentadiene.

reaction was carried out at −78 °C, (*S*)-(+)-exo-2-methylbicyclo[2.2.1]hept-5-ene-2-carboxaldehyde was obtained in high conversion with a de of 93% and an ee of 99%.

These investigations were subsequently extended to the first reported example of a conventional asymmetric Diels−Alder reaction using a racemic catalyst.[24] In this investigation, [*rac*-*p*-cymeneRuCl(BINPO)]SbF_6 was converted into the corresponding dication [*rac*-*p*-cymeneRu(BINPO)]$(SbF_6)_2$ upon reaction with $AgSbF_6$. The additions of chiral poisons were found to decrease the catalytic efficiency of one catalyst enantiomer, thus leading to increased yield of product via catalysis by the antipodal catalyst.

During the course of these investigations it was recognized that different chiral poisons may lead to different modes of deactivation of the catalyst. For example, the use of L-proline with the racemic catalyst led to selective sequestering of the [(S_{Ru},*R*)-*p*-cymeneRu(BINPO)]$(SbF_6)_2$ enantiomer, thus leading to enantioselective catalysis predominantly by [(R_{Ru},*S*)-*p*-cymeneRu(BINPO)]$(SbF_6)_2$ (Figure 15). This transformation was found to proceed via a chiral poisoning or asymmetric deactivation mechanism (Figure 1), noting that the selectivity of a poison for a given catalyst enantiomer may not be 100%. In contrast, the reaction of L-prolinamide with the racemic catalyst led to selective displacement of (*R*)-BINPO from the (S_{Ru},*R*)-catalyst enantiomer to generate a catalytically incompetent complex (referred to as Ru−prolinamide) and free (*R*)-BINPO (Figure 16). As a result, excess of the (R_{Ru},*S*)-catalyst enantiomer was available to activate the substrate for the enantioselective reaction, thus producing an ee of 59%.

Upon addition of L-prolinamide to a solution of *rac*-[*p*-cymeneRu(BINPO)]$(SbF_6)_2$, the BINPO ligand in the (S_{Ru},*R*)-enantiomer was preferentially displaced. As a result, an increased population of the (R_{Ru},*S*)-catalyst enantiomer was responsible for the observed product ee's (up to 60%).

2. Chloral-Ene

The Ti(O-*i*-Pr)$_2Cl_2$/(*S*)-BINOL complex is effective in the asymmetric catalysis of some ene reactions of activated aldehydes.[68,69] The analogue prepared from D-diisopropyl tartrate, D-DIPT, however, is inactive

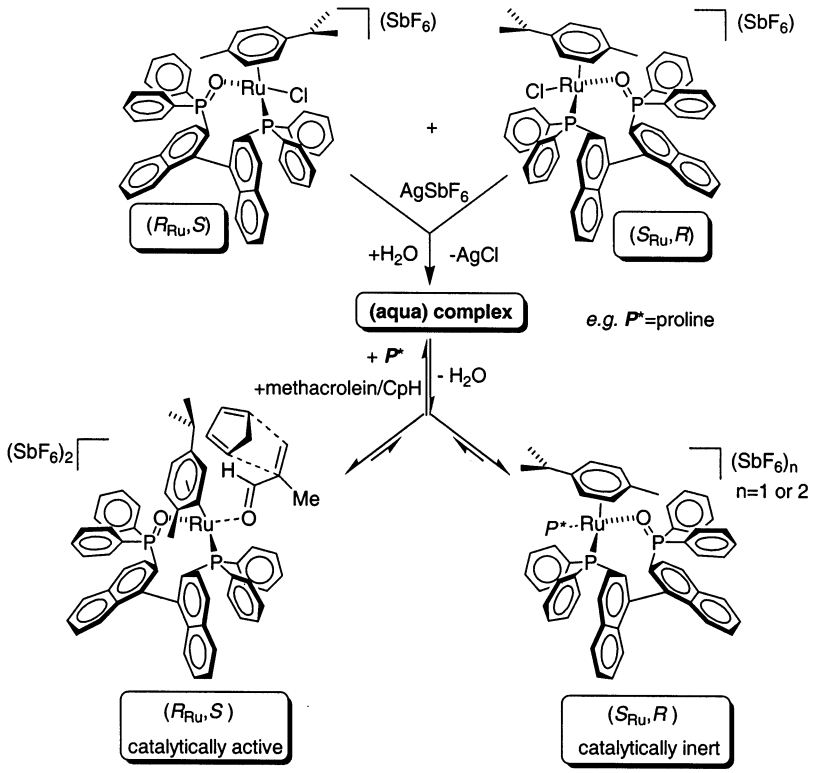


Figure 15. Generation of a Lewis-acidic catalyst and competitive equilibria. Note: The subscript ($n = 1$ or 2) depends on whether the poison is bound as a neutral or anionic ligand. (Reprinted with permission from ref 24. Copyright 2002 American Chemical Society.)

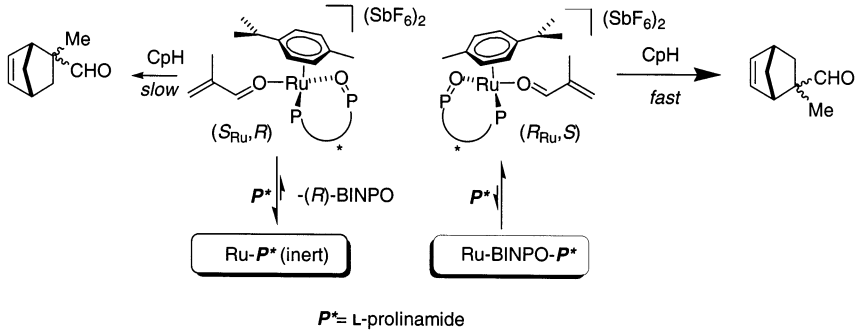


Figure 16. Upon addition of L-prolinamide to a solution of the *rac*-dication, the BINPO ligand in the (S_{Ru},*R*)-enantiomer was preferentially displaced. As a result, an increased population of the (R_{Ru},*S*)-catalyst enantiomer was responsible for the observed enantiomeric excess in the product.

in these transformations. The racemic catalyst Ti(O-*i*-Pr)$_2$Cl$_2$/*rac*-BINOL appears to consist of dimeric structures. The observation of nonlinear effects in nonracemic mixtures suggests that the meso dimer, Ti$_2$Cl$_2$[(*R*)-BINOL][(*S*)-BINOL], is less active than the homochiral dimers.[70,71] Mixing of the racemic catalyst, Ti(O-*i*-Pr)$_2$Cl$_2$/(*rac*-BINOL) with the inactive catalyst Ti(O-*i*-Pr)$_2$Cl$_2$/D-DIPT generates a catalyst that yields products in moderate ee[72] (Figure 17). Addition of excess D-DIPT further enhanced the enantioselectivity. The analysis of enantioselectivity was complicated by the subsequent interconversion of the initial products with time and nonlinear effects. In this case the mechanism is likely to be more complicated than a simple deactivation of a single species and probably involves reactive dimers (see sections III.B and V.C). One should note that molecular sieves are often used in these reactions and the state of hydrolysis of the catalysts may be in question.

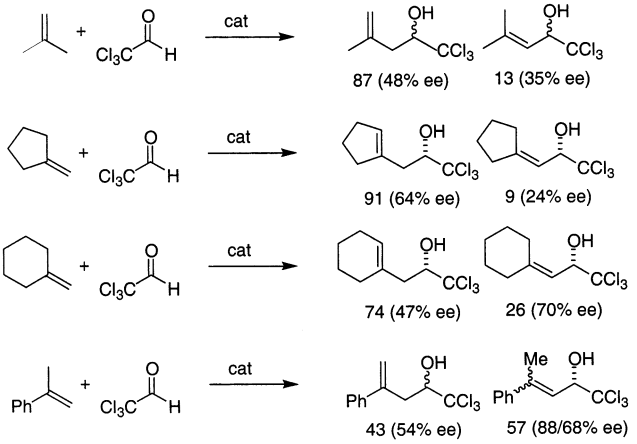


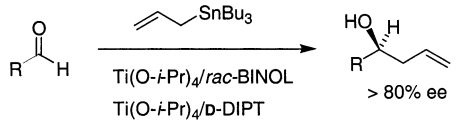
Figure 17. Product ratio and ee for a chloral−ene reaction catalyzed by Ti(O-*i*-Pr)$_2$Cl$_2$ (0.3 mmol)/*rac*-BINOL (0.2 mmol)/diisopropyl D-tartrate (0.3 mmol).

Bridging oxo dimers or oligomers could also be involved;[71,73] hence, some skepticism is warranted when considering published discussions of the catalytic species present.

3. Homoallylic Alcohols from Allylation of Aldehydes

A similar Ti(O-*i*-Pr)$_4$/*rac*-BINOL/D-DIPT catalyst was also found to be moderately effective for the promotion of the addition of allyltributyltin to aldehydes. The yields were modest, but high enantioselectivities were obtained[74] (Table 1).

Table 1. Chiral Poisoning of *rac*-BINOL/titanium Isopropoxide



R in RCHO	yield(%)[a]	ee	configuration
Ph	63	91	(S)
cy	33	82	(S)
trans-PhCH=CH	25	86	(S)
2-furyl	37	92	nd[b]

[a] Catalyst 0.4 mmol of *rac*-BINOL, 0.6 mmol of Ti(O-*i*-Pr)$_4$, 0.6 mmol of d-DIPT. [b] Not determined.

The Ti(O-*i*-Pr)$_4$/D-DIPT mixture did not catalyze the reaction; whereas the Ti(O-*i*-Pr)$_4$/*rac*-BINOL was a catalyst of low activity. An interesting feature of this system is that mixing two mediocre catalysts produces a new catalyst of moderate activity that yields products of high enantiomeric purity.

The logic of the chiral poisoning strategy followed from the consideration of catalyst dimers that had little or no catalytic activity that would dissociate into monomer species that are catalytically active. If one of the enantiomers of the monomer were intercepted by a chiral poison, then the idealized mode of poisoning as shown in Figure 1 would be active. In this case the strong preference for the formation of dimers suggested that a second chiral titanium monomer unit might provide the best poison; hence, the use of Ti(O-*i*-Pr)$_2$[D-DIPT] as a poison. However, it seems likely that the actual mode of poisoning is a more complex than this and has components of nonlinear effects (section III.B). This particular system may well involve reactive dimers in addition to catalytic monomers.

4. Enantioselective Addition of Diethylzinc to Aldehydes with Racemic Amino Alcohols

Nonlinear effects (section III.B) have been most dramatically shown in the addition of diethylzinc to aldehydes[33−35] where ligands of low enantiomeric purity generated catalysts that produce product alcohols in high ee. These results were again interpreted in terms of homo and meso dimers that dissociated to different degrees and thereby increased the relative concentration of one enantiomer of an active monomer. If a racemic amino alcohol were used, a racemic product would be expected. These monomer−dimer equilibria could be perturbed by the addition of another chiral additive, such as an amino acid, tartaric acid, diol, diamine, or another amino alcohol. The additive would allow formation of a new complex comprised of Zn, L, and L* owing to preferential non-self-recognition of one enantiomer of the *rac*-amino alcohol complex and forming a stable unreactive hetero dimer (Figure 18). Using a library of racemic amino alcohols, ***DB***, and enantiomerically pure amino alcohols, ***AA***, Long and Ding[30] found that combinations of *rac*-***DB1*** and ***AA1*** or ***AA2*** gave high ee's. A selected set of results from their experiments is shown in Table 2.

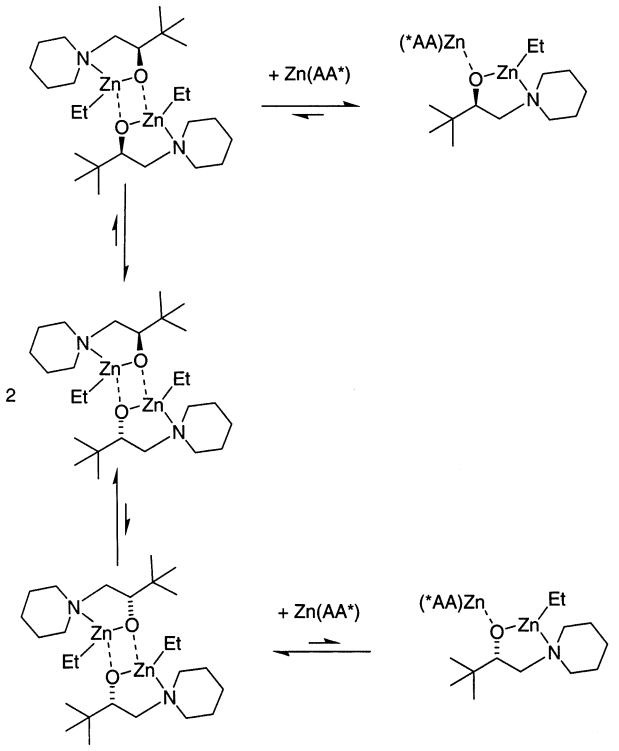
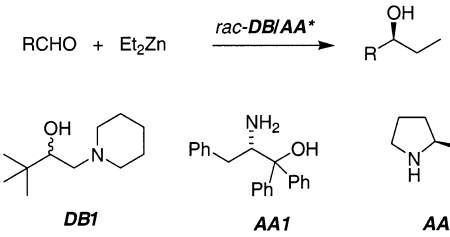


Figure 18. Non-self-recognition in zinc dimers. Selective sequestration of the (*R*)-isomer as a [(*R*)-EtZn(DB)-Zn-(AA*)] heterodimer increases the relative concentration of the [(*S*)-EtZn(DB)]$_2$, allowing it to dissociate to provide the dominant reactive species, the (*S*)-EtZn(DB) monomer.

Table 2. Ethylation of Aldehydes by Et_2Zn in the Presence of Racemic *DB* and Enantiomerically Pure *AA*[a,b]



	ee(%)	
R	*AA1*/***DB***	*AA2*/***DB***
phenyl	86.0	92.7
p-chlorophenyl	69.9	84.6
p-anisyl	87.5	90.0

[a] Data from Long and Ding.[30] [b] Reaction at −40 °C for 48 h with catalysis by *rac*-***DB1*** (10 mol %) and ***AA*** (5 mol %).

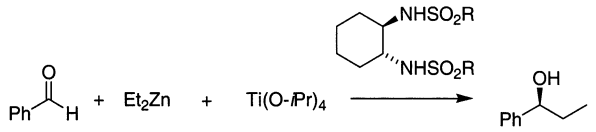
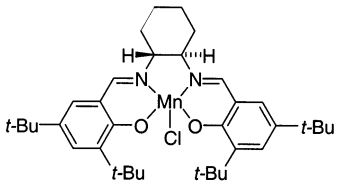


Figure 19. Enantioselective ethylation of benzaldehyde.

Clearly, a complex of ***AA2***, for example, would also have the potential of yielding a nonracemic product. In a control experiment with ***AA2*** as the only chiral inducer, (*R*)-2-phenyl-1-propanol was produced in 16% ee. A significant synergistic effect was observed when racemic **DB1** was added to resolved **AA2**, and the enantioselectivity was improved giving (*S*)-2-phenyl-1-propanol in 66% ee.

Diastereomeric interactions with an intramolecularly bound poison have been explored by Balsells and Walsh.[75] Bis(sulfonamido)titanium(O-*i*-Pr)$_2$ complexes have been implicated in the catalysis of the ethylation of aldehydes with Et_2Zn.[76−78] The (*R,R*)-cyclohexyldiamine derivatives yield the (*S*)-alcohol product in >84% ee for a range of sulfonamides (Figure 19). If diastereomeric sulfonamides prepared from (*R,R*)- and (*S,S*)-cyclohexyldiamine and (1*S*)-10-camphorsulfonyl chloride were used, the (*R,R,S,S*)- and (*S,S,S,S*)-complexes with titanium provided 2-phenyl-1-propanol in 93% (*R*) and 84% (*S*) ee, respectively. Even though the individual complexes had comparable enantioselectivity when isolated, a 1:1 mixture of the (*R,R,S,S*)- and (*S,S,S,S*)-complexes yielded a product of 75% (*S*) ee with fast addition of benzaldehyde. Slow addition of benzaldehyde yielded a product of 84% (*S*) ee. These results arise from a significant difference in turnover frequencies of the two diastereomers. It has been suggested that the carbonyl oxygen atoms of the sulfonamides are competitive inhibitors of substrate binding, but the inhibition in the (*S,S*)-diamine is more effective.[75]



(*R,R*)-(salen)Mn

C. Epoxidations

Katsuki published several accounts of the effects of chiral amines, such as (−)-sparteine on epoxidations with "achiral" (salen)Mn(III) complexes[79−81] (Figure 20). Chirally modified (salen)Mn complexes, such as those prepared from 1,2-diaminocyclohexane, have been shown to be effective catalysts for asymmetric epoxidation of conjugated olefins[82,83] (Table 3). Manganese complexes of salen-type ligands with symmetrically substituted backbones actually exist as a racemic mixture of conformers in solution (Figure 21). One interpretation of the observed enantioselectivity of an "achiral" (salen)Mn system is that the enantiopure chiral ligand, such as sparteine, selects one conformer preferentially or induces chirality at the metal. (This type of induction has been termed "chiral environment amplification" [84] or "dynamic chirality control" and is covered in detail in the review by Walsh.[85]) As the authors suggest, "another possibility is that the optically active donor ligand activates or deactivates one of the two isomers".[79]

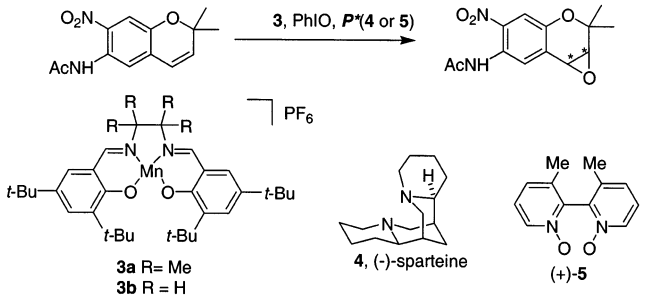


Figure 20. Asymmetric epoxidation of 2,2-dimethylchromenes.

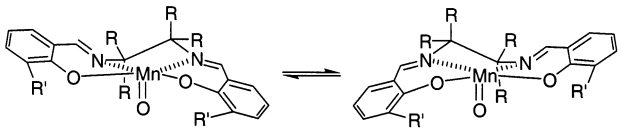


Figure 21. Enantiomeric conformations of **3**.

Table 3. Asymmetric Epoxidation of a 2,2-Dimethylchromene by 3 and a Chiral Additive[a]

entry	(salen) Mn	additive	mol %	temp (°C)	yield	% ee	config
1	3a	4	10	0	65	30	3*R*,4*R*
2	3a	4	20	0	58	31	3*R*,4*R*
3	3a	4	40	0	28	52	3*R*,4*R*
4	3a	4	40	−20	05	37	3*R*,4*R*
5	3b	5	5	−20	90	83	3*S*,4*S*
6	3b	5	20	−20	58	31	3*S*,4*S*

[a] Data from refs 79 and 81.

Initially the phenomenon was observed with sparteine and yields were low for the reactions with the highest enantioselectivity.[79] Subsequently it was found that chiral pyridine *N*-oxides were superior additives. The authors favor the interpretation that one of the two ligand conformations (Figure 21) is selected upon binding of the additive. Even though conformers may be an enantiomer pair, and at any instance, the mixture of conformers always exists as a racemate, as there is no preference in the formation of either conformer. However, when averaged over time, the complex is achiral. Addition of a chiral nonracemic additive has the effect of shifting the equilibrium between the conformers through the formation of diastereomers. As the diastereomers have energies that are different, the conformer ratio is shifted. This is different from the effect of adding a chiral additive to a static or noninterconverting racemate. In this case, the addition to equilibrating conformers actually changes the equilibrium population rather than simply binding to a greater or lesser extent to the individual enantiomers. Any remaining uncoordinated **3** would still exist as a racemic mixture of conformers. If one assumes that the activity of **3** coordinated to **5** were low, the addition of 5 mol % of (+)-**5** would be expected to give a product with

~5% ee if the conformers did not interconvert or ~0% ee if they did interconvert. Since this was not the case, the formation of the product in high ee indicates that a conventional poisoning mechanism (Figure 1) is not taking place. The observations are more consistent with the formation of new catalyst upon addition of a chiral ligand and a marked acceleration in the rate of product formation (i.e., asymmetric activation). This system is an excellent example of a case where addition of a chiral nonracemic additive to a racemic catalyst gives a system which can produce an enantiomerically enriched product but for which the mechanism of how it works may not be obvious.

V. Mechanism of Enantioselectivity Enhancement by Chiral Modification of Racemic Catalysts

Although the simple or idealized view of chiral poisoning shown in Figure 1 provides a starting point for consideration of chiral modification of racemic catalysts, it is clear that an evaluation of more complicated models must be considered (see section III). Thus, as previously discussed, the selectivity of the poison for a particular enantiomer of the catalyst in most cases will not be perfect. This is illustrated in Figure 22, which shows the differences in the dissociation constants of diastereomeric complexes.

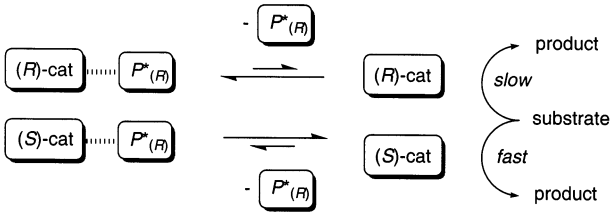


Figure 22. The magnitude of K_{eq} in chiral poisoning will depend on the "stability" of the diastereomeric cat−*P** complexes. In turn, the catalyst−poison complex with the higher dissociation constant will yield the active species that will predominantly catalyze the reaction in an enantioselective manner. (Note that only one set of relative magnitudes for the *K*'s is illustrated.)

A. Multiple Pathways and Secondary Racemic Paths

Even if the equilibrium constants are determined, the expected results may be diminished owing to multiple paths being available for forming the product with varying selectivities. For example, with Lewis acid catalysts, the presence of a protonic acid, or protons lost from an aqua complex of the Lewis acid, or excess silver ion used in the preparation of the Lewis acid by halide abstraction may provide a racemic path to the product in addition to that from the chiral catalyst. The slower rates from a poisoned catalyst may lead to these alternate routes to product assuming a greater role, and thus, the overall enantiomeric purity of the product could be reduced. Alternatively, a poison could deactivate these secondary paths and improve the ee above what was expected.

In general, one assumes that the equilibria are established much more rapidly than the reaction occurs. In principle, this does not have to be the case. Even the chiral amplification aspect can show anomalies. Recent cases have shown that the diethylzinc addition to certain aldehydes can be affected by slow attainment of dimer equilibria.[86] Additionally, the models generally assume that a poisoned species has no activity whatsoever or at least a much reduced activity, which may not be the case.

Within the parameters discussed to this point one would assume that the best outcome of a chiral poisoning experiment would be one in which the ee obtained was equal to that obtained with the enantiomerically pure ligand. Perhaps the best example at this point in time was that of Mikami, Noyori, et al.,[57,87] who reported a poisoning that gave 99.3% ee compared to 99.9% for the enantiopure case. As suggested earlier, it might be possible to get a higher ee if the poison were very effective and also deactivated some racemic pathways existing in the unpoisoned system. A more common phenomenon is that a new catalyst can be created that gives higher enantioselectivity. This was observed in the "chiral poisoning" of chloral−ene reactions by Luo and Faller in 1996[72] where analysis of products indicated an ee higher than would be expected for the enantiopure catalyst.

A chiral modifier added to a racemic catalyst may not give rise to a poisoning effect as illustrated in Figure 1 but lead to the formation of a completely new enantioselective catalytically active species. Being a different compound, it may catalyze the reaction to give either an increased or decreased ee and thereby affect the overall efficiency of the system in a way that may be difficult to rationalize. For example, if the additive completely displaced one enantiomer of the original chiral ligand, then the solution would contain a mixture of the newly generated catalyst as well as one enantiomer of the initial catalyst. Several results could be observed depending on the efficiency of the new catalyst relative to the original one. If the new catalyst had a much higher turnover frequency and had good enantioselectivity, a high ee would result. If both were efficient catalysts with similar turnover frequencies, a high ee would result if they both preferentially formed the same enantiomer of the product. A low ee would result if they produced opposite enantiomers. A high ee would also result if the newly generated compound were a poor catalyst relative to the remaining enantiomer of the original catalyst.

This type of poisoning was observed in the treatment of *rac*-[(R^*_{Ru},S^*)-*p*-cymeneRu(BINPO)]$(SbF_6)_2$ with L-prolinamide that led to selective displacement of (*R*)-BINPO from the (S_{Ru},*R*)-catalyst enantiomer to generate a catalytically incompetent complex and free (*R*)-BINPO (Figure 15). As a result, the remaining (R_{Ru},*S*)-catalyst enantiomer activated the substrate for reaction leading to a product enriched in one enantiomer.[24]

B. Asymmetric Activation

Alternatively, reaction of a racemic catalyst with a chiral modifier could yield new diastereomeric catalysts that could have very different activities. For the case where one of the new diastereomeric cata-

lysts is much more active than the original catalyst, this strategy was initially designated as "chiral drugging"[88] but has subsequently been referred to as *asymmetric activation* by Noyori and Mikami.[87,89] The possibilities of diastereomeric catalysts or pseudoenantiomeric catalysts, as well as the diastereomeric interactions of a chiral catalyst with enantiomeric substrates, were considered early on by Kagan.[5,40,46,90] Given that activation of racemic catalysts may result in the generation of several different complexes (including at least two diastereomers), it should be noted that each of these species may contribute to catalysis. For a diastereomeric pair of catalysts, however, the respective products will be produced at different rates and with different enantioselectivities (see, for instance, examples of *dual enantioselective control* of Kim[91]or *chiral cooperativity* of Togni and Pastor[92,93] or studies of the *effect of multiple stereogenic elements* by Bolm[94]). Furthermore, the principal enantiomeric products for diastereomeric catalysts may even have opposite chiralities. In any event, if the diastereomers have comparable activity, their simultaneous conversion of substrate will yield a product with overall reduced enantioselectivity (unless both give the same enantiomer in high ee). Discussions concerning the use of competing (often diastereomeric) catalysts have previously been reported.[5,40,46,75,90,95−97] *The crucial message that these reports emphasize is that the resultant product ee is a function of the relative catalyst concentrations and their respective activities (i.e., turnover frequencies) as well as their enantioselectivities*. One should also note that the effectiveness of a given activated system can be substrate dependent.[98]

Many of the strategies for consideration of these diastereomeric interactions follow from the concept of *matched* and *mismatched* pairing developed by Masamune et al.[99] in their approach to "double asymmetric synthesis" or *double diastereoselection*. If one shows that the effect of the chiral additive is to produce a new catalyst that is more active, then it acts as a *chiral activator* rather than a *chiral poison* or *chiral deactivator*. This lends itself to a model shown in Figure 23 for asymmetric activation.

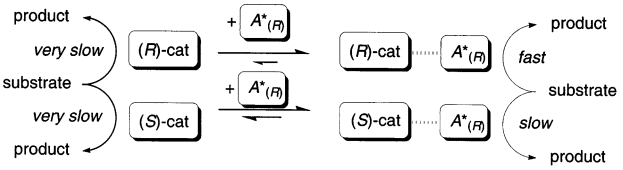


Figure 23. The asymmetric activation strategy enantioselectively activates the *rac*-catalyst (generating cat−*A**), thus leading to the enhanced turnover frequency for the production of one enantiomer.

The newly formed diastereomer must be competent in terms of being highly enantioselective and also have a high enough turnover frequency for a significant amount of product to be formed via that catalyst.

It is possible that the interaction of the racemic catalyst and the chiral additive is ∼100% diastereoselective in its binding, and this is one model analogous to Figure 1 for ideal poisoning. The general situation, however, would be that both diastereomers would be formed to some degree if not to a great extent. Since the diastereomers are different catalysts, they would have different turnover frequencies and product enantioselectivities associated with each of them. Ideally the rate associated with the matched pair would be much faster than either the mismatched pair or the initial unactivated catalyst for a specific substrate. The phenomenon of an activator binding and the rate of catalysis increasing as a result is known as *ligand-accelerated catalysis*.[100] Mikami[56] developed a number of very effective systems where these criteria are met and successful asymmetric activation has been achieved, and they will be reviewed in the next section.

The results of chiral modifier experiments tend to focus on enantioselectivity. The mechanism or the model by which the enantioselectivity is enhanced will require investigations of kinetics or at least an observation of relative rates. A simple chiral poisoning model (Figure 1) should have a rate or turnover frequency slower than that of the enantiomerically pure catalyst at the same concentration. The ligand acceleration associated with asymmetric activation (Figure 23) should result in an enhanced rate or turnover frequency. Complications, such as the dimerization responsible for chiral amplification, can potentially modify this simple assessment of the mechanism if comparisons are made to the rate for the racemic catalyst. In many cases a more detailed assessment of kinetics is required to ascertain the mechanism or develop an appropriate model.

In attempting to evaluate a chiral poisoning experiment, it is important to demonstrate that a new catalyst has not been produced that is giving rise to the enantioselectivity in the product. One approach to determining if the mechanism involves chiral poisoning has recently been reported.[24] The method allows one to determine whether an observed ee is due to chiral poisoning or to a newly generated species by comparison of the enantioselectivity of matched and mismatched pairs of enantiomerically pure catalysts and poisons. The method was applied in the chiral poisoning of *rac*-[*p*-cymeneRu(BINPO)]$^{2+}$ with L-prolinamide in the catalysis of a Diels−Alder reaction, which has been previously discussed in section IV.B.1. It was determined that the poison led to preferential displacement of the (*R*)-BINPO ligand from the (S_{Ru},*R*)-catalyst diastereomer. As such, it was possible that a Ru−prolinamide complex, not a (*R*)-BINPO complex, could be the most active catalyst and could be responsible for some of the observed enantioselectivity. This possibility was subsequently ruled out following the double diastereoselection experiments shown in Table 4.

The authors rationalized that if a given Ru−***P**** catalyst were capable of acting as a successful catalyst, then the ee arising from a reaction catalyzed by such species would vary depending upon whether the complexes with ***P**** were "matched" or "mismatched"pairs. If the catalyst used in entry 3 of Table 4, for example, combined with D-proline to form a complex, Ru−***P****, that was catalytically active, then the ee observed from it should be different from that formed from L-proline. Comparison of entries 3 and

Table 4. Catalytic Results for the Diels−Alder Reactions of Methacrolein and Cyclopentadiene with Enantiopure Catalysts in the Presence of Chiral Poisons

entry[a]	enantiopure cat.	P*	conv (%)	de (*exo*:*endo*)	%ee (config)
1	(*R*Ru,*S*)	none	100	95	89 (*S*)
2	(*S*Ru,*R*)	none	95	96	89 (*R*)
3	(*R*Ru,*S*)	D-proline	93	95	89 (*S*)
4	(*R*Ru,*S*)	L-proline	95	96	89 (*S*)
5	(*S*Ru,*R*)	L-prolinamide	81	95	90 (*R*)
6	(*R*Ru,*S*)	L-prolinamide	93	97	88 (*S*)

[a] From ref 24.

4 of Table 4 shows that this is not the case, and therefore, it is unlikely that Ru−***P**** complexes are contributing greatly to the formation of product. If the Ru−***P**** complexes showed significant catalytic activity, the selectivity of the catalysts should be greatly altered, and this would lead to a change in observed ee.

If there was a significant difference, however, the interpretation is less clear. For example, Ru−***P**** could generate the same enantiomer of the product as the Ru−BINPO catalyst but with a higher or lower enantioselectivity and yield a modest improvement or decrease in observed ee. If the Ru−*P** generated the antipodal product in comparable amounts, a large decrease in ee or even a reversal of enantioselectivity might be observed. Decreased conversion for a given time would be expected owing to lowered catalyst concentration by *P** deactivation, particularly for the matched pair. If a parallel path catalyzed by an impurity existed that yielded racemate, then the slower rate of the catalyst/poison pair could result in a decrease of the ee, even if the Ru−*P** complex were inactive.

C. Formation of a Deactivated Catalyst or a New Active Catalyst

The formation of a new complex that is a kinetically incompetent catalyst is an essential feature of an effective chiral poisoning system. Alternatively, if the additive produces a new complex that is a more active catalyst than the original one, i.e., ligand-accelerated catalysis is involved, then there is effectively an *asymmetric activation*. In an asymmetric activation, the desired result of adding a nonracemic chiral additive to a racemic catalyst to obtain an enantioselective catalyst is achieved, but the mechanism by which this happens is not the same as that represented in Figure 1. In this case, a selective activation improves the rate of production of one of the possible enantiomers with respect to the rate of reaction performed with no additive. Rather than a selective deactivation, one enantiomer of the initial catalyst reacts with the additive to form a new, possibly quite different, active catalyst that allows the production of one enantiomer of the product at a higher rate.

Another way in which the catalytically active species may be functionally different from expectations is through dimer formation. Catalysts are often designed to be coordinatively unsaturated in order to facilitate the binding of substrate molecules in the course of the reaction. This can lead to a dimerization of the catalytic species via binding of some peripheral donor on a ligand in one monomer to the metal in another. A good example of a characterized dimer of this kind is $\{[(S,S)\text{-CHIRAPHOS}]Rh\}_2^{2+}$. Chiral amplification can be attributed to such dimer processes; but it is also possible that the dimers themselves are active catalysts, giving a further mode of stereocontrol for product formation.

The most common rationale for chiral amplification is the dissociation of unreactive dimers to yield reactive monomers as discussed in section III.B. There are cases, for example, where dimers have been implicated as the principal reactive species in some diol−titanium reactions.[71,101−103]

Some "poisoning" experiments involving titanium-containing catalysts give results that indicate that new catalyst species were formed under conditions of "poisoning" experiments and that these new species, probably hetero-dimers, are also sufficiently reactive to enhance the enantioselectivity of the system. Hence, there is the possibility of parallel pathways involving asymmetric activation existing together with a poisoning mode of providing enantioselectivity[72,74] (see sections IV.B.2 and IV.B.3).

VI. Asymmetric Activation

A. Hydrogenation

The asymmetric activation of racemic metal complexes with regard to asymmetric catalytic hydrogenation has previously been reviewed.[21,27,32,96,104] The first account of asymmetric activation applied to hydrogenation was reported for reactions catalyzed by $RuCl_2$[*rac*-TOLBINAP](dmf)$_n$/(*S*,*S*)-DPEN, where TOLBINAP = 2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl and DPEN = 1,2-diphenylethylenediamine.[98] Catalyst preparations were carried out by reacting 1 mol equiv of this racemic $RuCl_2$[*rac*-TOLBINAP](dmf)$_n$ complex with 1 mol equiv of (*S*,*S*)-DPEN. This protocol also resulted in the formation of the two possible diastereomeric complexes with ligand combinations of (*R*)-BINAP/(*S*,*S*)-DPEN and (*S*)-BINAP/(*S*,*S*)-DPEN.[105] The authors then used this mixture to catalyze the hydrogenation of aryl ketones and 2,4,4-trimethyl-2-cyclohexenone (Figure 24). The catalytic efficiency (in terms of both ee and kinetic competence) was found to be far superior using the Ru/(*R*)-BINAP/(*S*,*S*)-DPEN catalyst for 2,4,4-trimethyl-2-cyclohexenone [ee = 94% (*S*)]. Notably, the hydrogenation of 2,4,4-trimethyl-2-cyclohexenone with the (*R*)-BINAP/(*R*,*R*)-DPEN system was found to be slower and inferior in terms of enantioselectivity [ee = 26% (*S*)].[98]

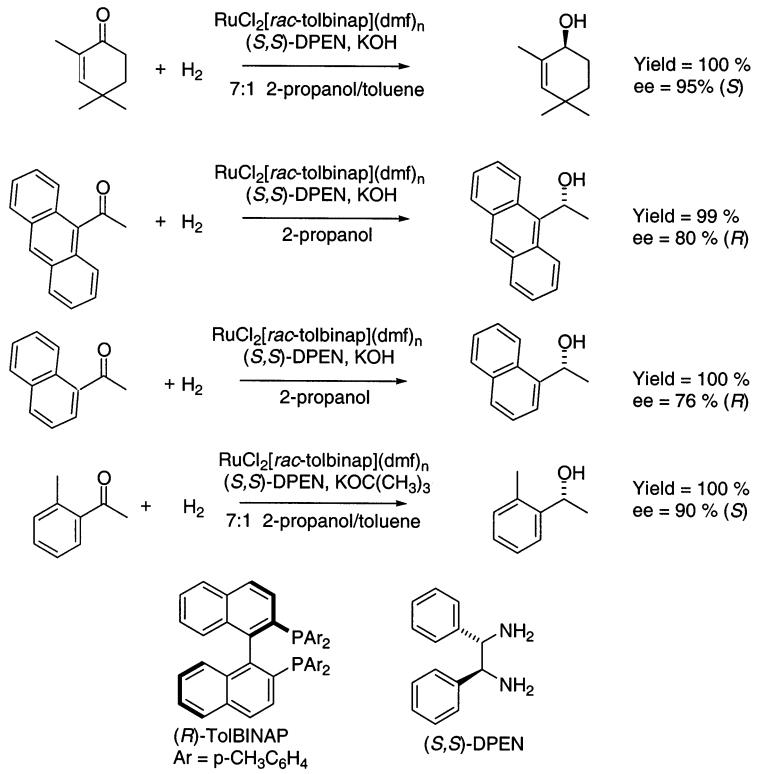


Figure 24. A series of asymmetric ketone hydrogenations via asymmetric activation of a racemic Ru complex with (*S*,*S*)-DPEN.

These authors suggested that formation of the analogous {Ru[(*R*)-TOLBINAP][(*S*,*S*)-DPEN]} fragment was virtually irreversible under the reaction conditions. This was determined by reacting the *rac*-$RuCl_2$(TOLBINAP)$(DMF)_n$ precursor with an equimolar amount of (*S*,*S*)-DPEN, presumably forming $RuCl_2$[(*R*)-TOLBINAP][(*S*,*S*)-DPEN]} with one enantiomer of the precursor and $RuCl_2$[(*S*)-TOLBINAP]-[(*S*,*S*)-DPEN]} with the other. This was followed by the addition of (*R*,*R*)-DPEN to yield a solution ultimately equimolar in both enantiomers of DPEN. The mixture was then used to catalyze the hydrogenation of 2,4,4-trimethyl-2-cyclohexenone and yielded the (*S*)-enol in 91% ee at 100% conversion. These results suggest that the preformed bisphosphine/diamine complexes were kinetically stable to amine exchange under the reaction conditions and during a reaction time of ca. 6 h.

The enantioselectivity arising from the asymmetric activation in these complexes is a function of the relative concentration and reactivities of the diastereomeric ruthenium centers.[5,46] The $RuCl_2$(bisphosphine)$(DMF)_n$ compounds are believed to exist as aggregates[106] that have been shown to be poor catalysts for the hydrogenation of simple ketones.[98] They could potentially be involved in chiral amplification, but they are completely consumed in reaction with the diamines to form monomeric complexes of the general composition [$RuCl_2$(bisphosphine)(diamine)]. The formation constants for these mixed-ligand species are believed to be very large, and thus, reversion to $RuCl_2$(bisphosphine)$(solvent)_n$ compounds in the presence of diamine is considered to be negligible. As such, once formed, the mixed-ligand complexes are precursors to mono- or dihydrides upon reaction with alkaline base/2-propanol/H_2.[107−109]

It should be noted that another Ru/bisphosphine/diamine system involving two different diamines and using a combination of both asymmetric activation and chiral poisoning also produces high enantioselectivities (see section VII).[87]

1. Atropisomers and Chiral Induction in Conformationally Flexible Ligands

While the enantiopure asymmetric ligands used to prepare catalysts for catalytic syntheses typically included stereogenic chiral centers, the use of enantiopure *atropisomeric* ligands (stereoisomers resulting from restricted rotation about single bonds where the rotational barrier is high enough to permit isolation of the isomeric species)[110] has yielded some of the most useful ligands, such as BINAP. In the case of bis(phosphinyl)biphenyl (BIPHEP) ligands, the respective atropisomers may often be resolved in cases where steric interactions from bulky substituents preclude racemization (Figure 25). Notably, the activation barrier to axial torsion in selectively deuterated BIPHEP was found to be only 22 ± 1 kcal mol^{-1}, which suggests that axial rotation takes place slowly at room temperature.[111] For 6,6′-substituted analogues, the barriers are significantly higher,[112]

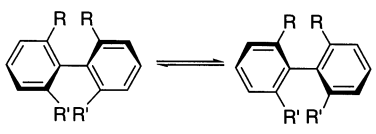


Figure 25. Atropisomers of substituted biphenyls have high barriers to rotation about the C−C bond, and the enantiomers can be resolved. With insufficient steric interactions between ortho substituents, they are conformationally flexible and the configurations interconvert rapidly preventing resolution.

such that those ligands with high barriers to racemization can be resolved by conventional resolution procedures. Mikami[21] adopted the terms *atropos* isomers[113] for those with high barriers and *tropos* isomers[113] for those with low barriers to interconversion. A half-life for racemization of 1000 s has been suggested as a minimal requirement for an *atropos* biphenyl.[114,115] This acceptable rate of racemization provides an *arbitrary* dividing line and reflects a temperature (usually room temperature) at which one can effectively utilize the ligand. Since most reactions are carried out above or below room temperature, the distinction is not especially useful, particularly in cases near the dividing line.

A molecule with a lower barrier can actually be an effective ligand, however, if coordination to a rigid asymmetric environment on a metal induces the ligand to adopt a preferred enantiomeric configuration. This chiral induction upon coordination can potentially be used in a number of conformationally flexible ligands that have enantiomeric configurations other than the case of those involving hindered biphenyls. This effect was originally termed *chiral environment amplification*,[84] but terms such as *conformational dependence on chirality*,[85] *dynamic chirality control*,[22] *asymmetric activation of catalysts with chirally flexible ligands*,[96] and *asymmetric activation of tropos catalysts*[21] appear to be gaining greater acceptance. This is an extension of the general phenomenon where fixed chirality in one portion of a molecule influences the preferred conformation in another (e.g., the orientation of phenyls in CHIRAPHOS[116] or Ph_3P[117]) or the selection of a preferred configuration at a metal.[118] It would appear that the term *dynamic chirality control* is probably the simplest term for this "chiral induction in conformationally flexible ligands", and this topic is covered in detail in Walsh's review in this issue of *Chemical Reviews*.[85]

Mikami and Noyori et al. investigated the use of $RuCl_2$(BIPHEP) complexes with chiral diamines, such as (*S*,*S*)-DPEN.[22,104,119] These authors suggested that the interaction of the conformationally flexible BIPHEP ligand with a $RuCl_2$/DPEN scaffold allows for the adoption of a preferred enantiomeric BIPHEP conformation. As a result, diastereomeric mixed-ligand complexes are generated. Experimentally, this was determined by allowing the initially formed ~1:1 mixture of diastereomers from mixing $RuCl_2$(BIPHEP)$(DMF)_n$ and (*S*,*S*)-DPEN to equilibrate in 2-propanol-d_8.[119] After 3 h at room temperature (or at 80 °C for 30 min), equilibrium was reached between the two diastereomers yielding a 3:1 mixture of the (*S*)/(*S*,*S*)- and (*R*)/(*S*,*S*)-diastereomers of $RuCl_2$(BIPHEP)(DPEN), **6**. Catalytic hydrogenations with solutions of this diastereomeric mixture allowed the conversion of 1-acetonaphthone to (*R*)-1-(1′-naphthylethanol) with 92% ee and >99% yield (12 h at −35 °C) (Figure 26).

It is interesting to note that using this chiral induction or dynamic chirality control with BIPHEP may have significant advantages relative to the use of the atropisomers of *rac*-BINAP as the bisphosphine component of complexes such as **6**. With BINAP the possibility exists, owing to the large formation constants and the presence of sufficient ligand, that both diastereomers of a mixed-ligand complex could be produced in equal amounts. Thus, the matched pair might give rise to the product in excellent ee, but the unmatched pair could be less selective (or even produce the other enantiomer preferentially) and thereby serve to lower the overall selectivity. Since the stereochemically flexible ligand can adopt a configuration complementary to the additive, there is the potential of having a large concentration of a single diastereomer. The major diastereomer would probably be responsible for most of the turnovers in catalysis, but it is possible that the minor diastereomer could have a higher turnover frequency.

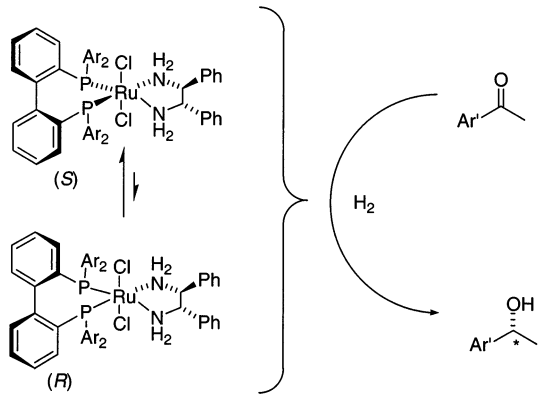


Figure 26. Enantioselective hydrogenation of aryl ketones via a diastereomerically enriched, dynamic equilibrium-dependent mixture of $[RuCl_2(BIPHEP)(DMF)_n]$/(*S*,*S*)-DPEN. The conformationally flexible BIPHEP ligand shows a 3:1 preference for the (*S*)-configuration as induced by the fixed chirality of the (*S*,*S*)-DPEN ligand in the precatalyst.

Gagné et al. also reported on mechanistic implications of interconversion of atropisomers in BIPHEP−Pd complexes.[20,120] While these investigations involved the use of a BIPHEP ligand, it should be noted that analogous results might occur with the use of other more conventional bisphosphines, such as DPPE and DPPF, which are conformationally flexible ligands that would adopt asymmetric configurations upon coordination to an asymmetric metal scaffold. Once coordinated, the configuration of BIPHEP is stable; however those of DPPE and DPPF interconvert rapidly (vide infra, section IV.B.2). Chen and Xiao recently reported on similar examples of asymmetric activation in enantioselective hydrogenation using catalysts comprised of ligands with conformationally flexible monodentate phosphinites.[121] The chiral bisphenylphosphinites were generated from the reaction of chiral alcohols, biphenyl phosphorochlorite, and Et_3N. The goal of this strategy was to force the flexible biphenyl moiety to adopt an asymmetric conformation (Figure 27). However, these modified chiral ligands were synthesized as an approximately 1:1 diastereomeric mixture. These ligands were then treated with $[Rh(COD)_2]BF_4$ to form a 5:1 diastereomeric mixture of hydrogenation catalysts. Hydrogenation of dimethyl itaconate with these diastereomeric catalyst mixtures to yield methylsuccinate proceeded with modest enantioselectivity (ranging from 2%−75% ee). It should be noted, however, that this mixture probably contained a series of

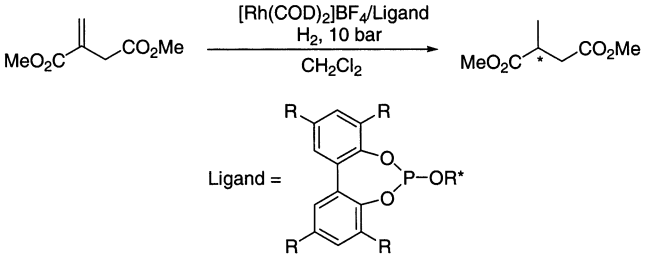
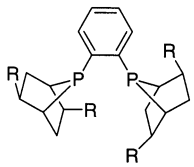


Figure 27. Asymmetric hydrogenation of dimethyl itaconate with a mixture of in-situ-generated catalysts. The conformationally flexible ligand adopts an asymmetric conformation as dictated by the enantiopure alcohol.

competing catalysts leading to the generation of products of the opposite configuration and thus an overall reduction in product ee.

The effect of the addition of achiral modifiers on asymmetric reactions, including hydrogenations and hydrosilylations, has been reviewed.[122] While reference to the review by Vogl, Groger, and Shibasaki[122] is recommended for complete coverage, we believe that several examples deserve comment within the context of this discussion due to their potential relevance to asymmetric activation. For example, Heil et al.[123] reported in 1979 that triethylamine had a significant effect on the enantioselectivity of ketone hydrogenations using chiral phosphine rhodium catalysts. More recently, Jiang, Zhang, et al.[124] reported large additive effects on ketone hydrogenation with Rh−bisphosphine complexes. For the hydrogenation of acetophenone using a rigid bisphosphine based on *endo*-2,5-dimethyl-7-phosphabicyclo[2.2.1]heptane, PENNPHOS, a yield of 45% (with 57% ee) was increased to 97% with 95% ee upon addition of 0.3 equiv of 2,6-lutidine. Buchwald et al.[125] reported that



ee's and yields were enhanced upon addition of isobutylamine to titanocene catalysts for the hydrosilylation of imines as shown in Figure 28. In particular, for the reaction of *N*-benzyl-1-indanimine, the

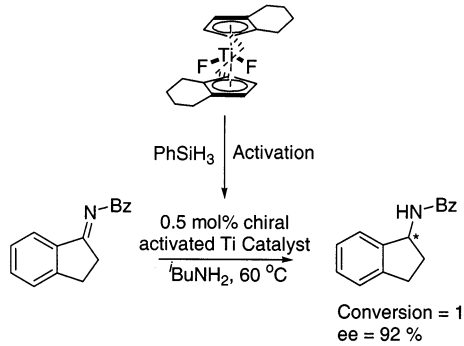


Figure 28. Asymmetric hydrosilylation of an *N*-benzyl-1-indanimine with a chiral titanocene reagent. Notably, the ee and yield were increased on addition of an achiral reagent.

conversions improved from 5% (no reported ee) to 100% (with 92% ee) upon addition of base. While the mechanisms for many of these "additive effects" have not been elucidated, one might expect that some additives may serve to limit side reactions (e.g., bases acting as proton scavengers). Also, the activity of catalysts often varies dramatically with the degree of protonation and/or the charge of the active species, both of which can be altered by the addition of base.

B. Activation of Aldehydes

1. Mukaiyama Aldol

The first example claiming to illustrate *asymmetric activation* was reported for the Mukaiyama aldol reaction of a trimethylsilyl enol ether with an aldehyde.[88] The catalyst for this system was generated in situ by combining [*rac*-BINOL]Ti(O-*i*-Pr)$_2$ with an additional equivalent of enantiopure BINOL (Figure 29). As a proposed "proof of concept", these authors

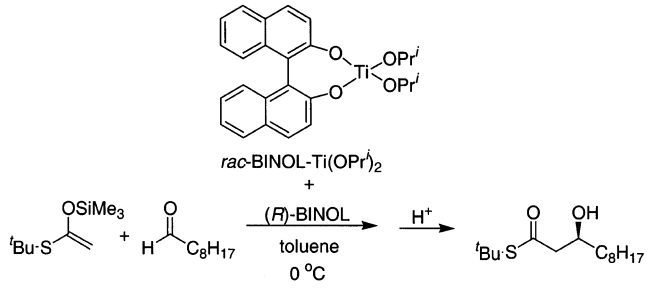


Figure 29. Mukaiyama aldol reaction with the *rac*-BINOL-Ti(OPr^i)$_2$/(*R*)-BINOL catalyst system via the asymmetric activation strategy.

conducted a catalytic reaction with the enantiopure [(*R*)-BINOL]Ti(O-*i*-Pr)$_2$ catalyst (yield = 53%, ee = 91%) and compared the outcome of this with a reaction that was performed in the presence of [(*R*)-BINOL]Ti(O-*i*-Pr)$_2$/(*R*)-BINOL mixture (yield = 66%, ee = 97%). On the basis of this increased ee, these authors suggested that activation had occurred. Since the titanium system is prone to chiral amplification through the formation of meso and homo dimers (section III.B), the mechanism of enantioselectivity enhancement is not clear. Nevertheless, it is interesting to note that an enhanced level of enantioselectivity (95% ee) was also observed when the authors treated the [(*R*)-BINOL]Ti(O-*i*-Pr)$_2$ precatalyst with *rac*-BINOL.

2. Carbonyl–Ene Reaction

The utility of the [*rac*-BINOL]Ti(O-*i*-Pr)$_2$/(*R*)-BINOL catalyst system has been extended to include the catalyzed carbonyl−ene reaction.[104,126−129] The existence of an "activation" mechanism in these reactions was examined by the addition of either enantiopure chiral or achiral activators. The authors found that the activated reactions were up to 26 times faster than the corresponding nonactivated ones. In one case, the addition of conformationally flexible 2,2′-biphenol in combination with a *rac*-

BINOL−Ti complex resulted in the generation of racemic carbonyl−ene product. However, addition of either enantiopure 5,5′-dichloro-4,4′,6,6′-tetramethylbiphenol or (*R*)-BINOL to this reaction resulted in the formation of carbonyl−ene products with ee's of 80.8% (38% yield) and 89.8% (52% yield), respectively (Figure 30). Other similar investigations concerning

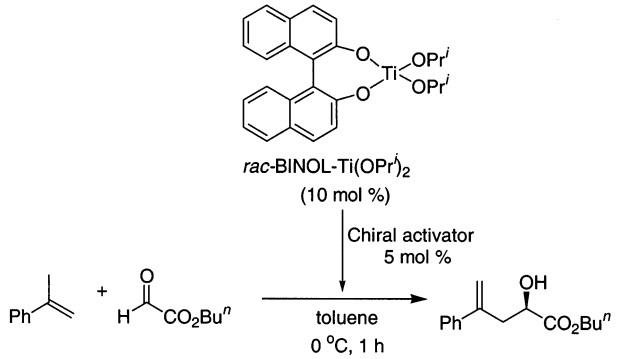


Figure 30. Carbonyl−ene reaction with the *rac*-BINOL-Ti(OPr^i)$_2$/(*R*)-BINOL catalyst system via the asymmetric activation strategy.

the use of multicomponent ligand cooperation with conformationally flexible biphenols and BINOL have also been reported.[130−132]

In related investigations, Mikami et al.[133] synthesized Pd, Pt, and Ni compounds of the type M(DPPF)(diamine)$(X)_2$ (where X = SbF_6^- or ClO_4^- and DPPF = 1,1′-(bisdiphenylphosphino)ferrocene). These exist as single diastereomers in the solid state. The authors assert that single diastereomers exist in solution as well. Although there is apparently only one isomer by NMR at room temperature, the possibility exists that there is a rapidly inconverting mixture of diastereomers that yields an averaged NMR spectrum and the diastereomer observed in the solid is a result of a crystallization-induced asymmetric transformation. In these cases the diamine appears to control the chirality of the conformationally flexible DPPF ligand, at least in the solid. It is possible that a single diastereomer exists in solution, but it is more likely that diastereomeric conformers with different populations are involved in the catalysis. These compounds were used as catalysts for the glyoxylate−ene reaction between ethyl glyoxylate and methylene cyclohexane. In catalytic trials with (DPPF)Ni[(*R*)-DABN]$(SbF_6)_2$, enantiomeric purities of up to 92% were reported.[133]

3. Hetero-Diels–Alder Reaction

Mikami et al. also applied the *rac*-BINOL-Ti(O-*i*-Pr)$_2$/(*R*)-BINOL catalytic system to the hetero-Diels−Alder reaction of Danishefsky's diene with glyoxylates.[88,126] In this report, the authors observed that an ee of 5% was obtained using the enantiopure BINOL-Ti(O-*i*-Pr)$_2$ complex. However, reaction of (±)-BINOL-Ti(O-*i*-Pr)$_2$ with (*R*)-BINOL (as an "activator") increased the product ee to 50% (Figure 31). The authors suggested that the increased ee may be due to a "kind of positive nonlinear effect".

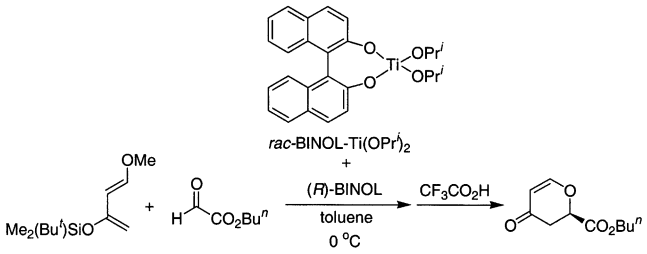
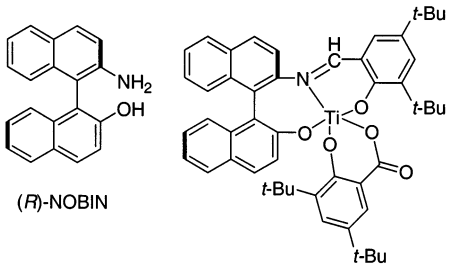
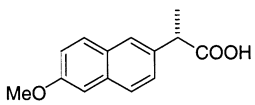


Figure 31. Hetero-Diels−Alder reaction with the *rac*-BINOL-Ti(OPr^i)$_2$/(*R*)-BINOL catalyst system via the asymmetric activation strategy.

Ding et al.[134,135] also studied similar hetero-Diels−Alder reactions using Schiff-base−titanium catalysts derived from NOBIN. These show an exceptional



dependence on the nature of a second ligand containing a carboxylic acid, in particular 3,5-di-*tert*-butylsalicylic acid. A library involving variously substituted salicylaldehydes and a library of 36 carboxylic acids were utilized to combinatorially optimize the catalyst system. Naproxen was found to be an especially effective carboxylic acid additive for increasing the yield and the enantioselectivity of the reaction (e.g., 99% yield and 97% ee for benzaldehyde with 1-methoxy-3-(trimethylsilyloxy)buta-1,3-diene). Although the predominant study of this system involved nonracemic chiral additives and a nonracemic catalyst, it emphasizes the importance of diastereomeric interactions. The use of partially resolved NOBIN gave a system that showed significant variations in nonlinear effects as a result of the differing reactivity of the two diastereomeric catalysts; hence, one would expect asymmetric activation to be possible. Using a mixture of the *rac*-NOBIN-based titanium catalyst and (*S*)-naproxen, the hetero-Diels−Alder product was obtained in 55% ee in 70% yield.[134]



Naproxen

Palladium catalysts derived from BIPHEP and enantiopure (*R*)-DABN have been reported[136,137] and were synthesized via the reaction of *rac*-[Pd(BIPHEP)$(CH_3CN)_2$]$(SbF_6)_2$ with 1 mol equiv of (*R*)-DABN. Subsequent epimerization of the chirality at the BIPHEP−Pd moiety led to a conversion of the [BIPHEP−Pd−DABN]$(SbF_6)_2$ diastereomers into a single[(*R*)-BIPHEP−Pd−(*R*)-DABN]$(SbF_6)_2$ diastereomer after 12 h at 80 °C. This compound was then applied in the catalytic reaction of 1,3-cyclohexene

and ethyl glyoxylate. In the best examples, ee's of up to 94% (62% yield) were observed. This same compound was then treated with trifluoromethanesulfonic acid in acetonitrile at 0 °C to yield enantiopure [(*R*)-BIPHEP−Pd−$(CH_3CN)_2]^{2+}$. Subsequent use of this catalyst led to products with ee's of up to 82% (60% yield).[137]

4. Enantioselective Addition of Diethylzinc to Aldehydes with Racemic Amino Alcohols

As discussed in section III.B on the potential of chiral amplification in chiral poisoning, numerous catalytic examples of the addition of diethylzinc to aldehydes have been reported. Ding, Ishii, and Mikami[138] reported an "*asymmetric activation*" of this reaction. It is not clear that this fits within the context that has been used in this review, given that neither racemic catalysts, ligands, nor activators were applied. Rather, these investigations involved the reaction of a series of metal complexes with two enantiopure ligands selected in a combinatorial manner. Mikami,[56] however, expanded the original definition of the term "*asymmetric activation*" to include enantiopure catalysts that are activated into more reactive and enantioselective ones. In this case, addition of a different enantiopure ligand (a diamine) to a zinc reagent activated it relative to that observed when using one chiral enantiopure ligand (a diol) alone. Although conceptually different from other examples of *asymmetric activation* in this review, this investigation further suggests that the complementary use of two different enantiopure ligands may lead to favorable results. This is analogous to the double-asymmetric induction case for a matched pair in asymmetric syntheses.[30,32,139]

Subsequently, Long and Ding[30] used the term "*asymmetric deactivation*" for the effect of chiral additives on zinc complexes of racemic amino alcohols that deactivated some enantiomeric complexes and which, in turn, promoted chiral amplification in the remaining mixture (this was also discussed in section IV.B.4, Figure 18). This method combines nonlinear effects and chiral poisoning in order to generate high product ee's with addition of a minimal amount of chiral poison.[30] It should be noted that for the pure racemic catalyst the meso dimers of the zinc complexes are very stable and the catalyst has limited activity; hence, this is a case where poisoning could increase the rate of a reaction rather than the usual situation for a poisoned reaction where the rate is slower. Hence, it is possible for the mechanism to involve poisoning yet yield a product at a faster rate. Thus, there is the potential for confusion in which reactions proceed by an "activation" or "deactivation" mechanism.

Walsh et al. investigated the addition of diethylzinc to aldehydes using meso ligands and by modification of achiral methylene bis(phenol) ligands.[75,84,140] This concept was referred to as *metal geometry-induced ligand asymmetry*.[140] Though conceptually analogous to Katsuki's concept of "dynamic control over ligand conformation", the difference between these two concepts is that Katsuki's catalysts were conformationally dynamic and thus interconverting between

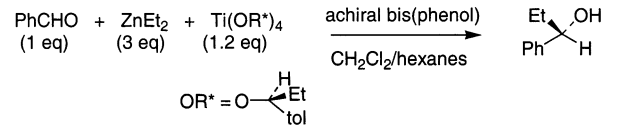
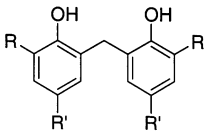


Figure 32. Diethylzinc addition to benzaldehyde as mediated by titanium complexes via a "metal geometry-induced ligand asymmetry" mechanism.

enantiomers.[79−81] In this case there are multiple coordination geometries of which some were symmetric but could become asymmetric on binding an additional ligand. This can be viewed as a chiral induction or dynamic control of configuration, which is discussed in more detail in the review by Walsh.[85] Under optimized conditions, ee's of up to 83% were obtained for the diethylzinc alkylation of benzaldehyde as mediated by these Ti−[methylene bis(phenol)] compounds (Figure 32).



a methylene bis(phenol)

5. Aryl Alcohol Synthesis via Aldehyde Methylation

Another example of chiral induction by a racemic catalyst involves the synthesis of aryl alcohols via aldehyde methylation.[141] Catalysts for this transformation were synthesized by the reaction of (*R*)-TADDOL with *rac*-Ti−BIPOL(O-*i*-Pr)$_2$ (BIPOL = biphenol). Upon substitution of the isopropoxide ligands by the TADDOL chelate, an asymmetric induction yielded a preferred diastereomer in the resulting complex. MM2 calculations by the authors suggested that the Ti[(*R*,*R*)-TADDOL][(*R*)-BIPOL] structure was favored over the other diastereomer by 3.6 kcal/mol, but there was no confirmation of this by spectroscopic methods. As a result, this (*R*,*R*)-Ti complex was suggested as an enantioselective methyl transfer catalyst in combination with stoichiometric TiMe(O-*i*-Pr)$_3$ for the methylation of 3,5-bis(trifluoromethyl)benzaldehyde. In this case, the corresponding aryl alcohol was obtained with a reported 100% ee (Figure 33).

6. Friedel–Crafts Reaction

Derivatives of 1-aryl-2,2,2-trifluoroethanol have been prepared through the reaction of fluoral with aryl ethers using various BINOL−Ti catalysts.[132] Initially, the regioselectivities for this reaction were poor (typically 4:1 *para*:*ortho*) and the enantioselectivities were modest (ee's between 22 and 84%). However, the efficiency of the reaction and the product enantioselectivity were subsequently increased through "asymmetric activation" and chiral induction, implementation of polar solvents, and by increasing the steric bulk of the aryl ether moiety. In one case, the catalyst derived from (*R*)-6,6′-Br$_2$-BINOL−Ti(O-*i*-Pr)$_2$ was activated by the addition of either (*R*)-5-Cl-BIPOL (5-Cl-BIPOL = 5,5′dichloro-4,4′,6,6′-tetramethylbiphenol) or (*R*)-6,6′-Br$_2$-BINOL.

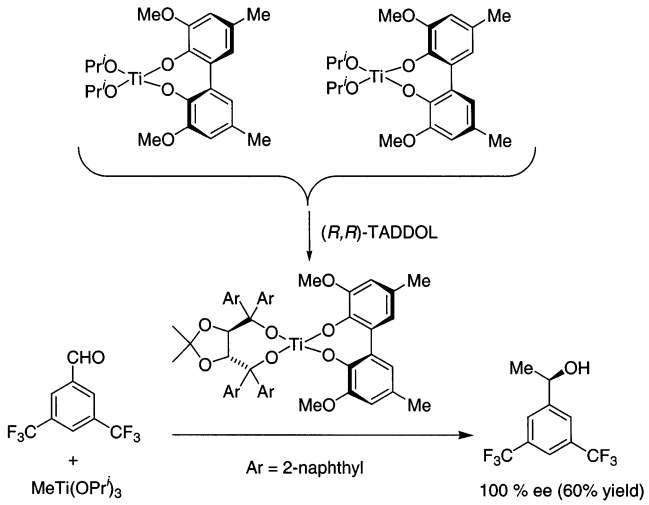


Figure 33. Reaction of a (±)-Ti−BIPOL with enantiopure (*R*,*R*)-TADDOL leads to a conformational interconversion and has been claimed to generate enantiopure Ti[(*R*,*R*)-TADDOL][(*R*)-BIPOL]. This complex was then used for the catalytic methylation of 3,5-bis(trifluoromethyl)benzaldehyde.

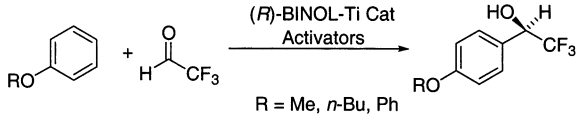
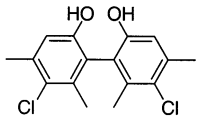


Figure 34. Friedel−Crafts reaction of aryl ethers with fluoral mediated by various asymmetric BINOL−Ti catalysts.

The addition of these activators served to increase yields and ee's up to 90% (Figure 34).



C. Epoxidation

Katsuki et al. investigated the use of conformationally dynamic (salen)Mn complexes for asymmetric epoxidation.[79−81] This was discussed previously in section IV.C but will be reviewed here in the context of dynamic chirality control and asymmetric activation. Shifting the conformational equilibrium with an asymmetric additive favors one of the diastereomeric catalysts and is another example of chiral induction as shown in Figure 35. This strategy might also be considered to be an example of asymmetric activation since a new active catalyst is formed, though it was (at the time of publication) referred to as "dynamic control over ligand conformation". In the best case for enantioselectivity, an ee of 86% was obtained with 29% yield for the epoxidation of 6-acetamido-7-nitro-2,2-dimethylchromene using a catalyst system derived from resolved 3,3′-dimethyl-2,2′-bipyridine-*N*,*N*′-dioxide (as an additive) and a dynamic chiral racemic (salen)Mn compound.[81] The use of dichloroethane as the solvent and a 48 h reaction time improved the yield to 90% and gave an ee of 83%. These types of compounds were also applied to the asymmetric oxidation of methyl phenyl sulfide, though low ee's (25%) were observed.[80]

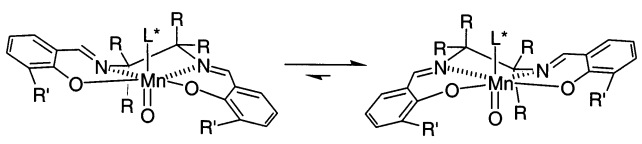


Figure 35. Shifting the conformational equilibrium with an asymmetric additive favors one of the diastereomeric catalysts and is another example of chiral induction in a flexible system.

Although it is reasonable to consider these systems as examples of asymmetric activation, it illustrates the potential difficulty of assessing activation versus deactivation. Oxo transfer reactions in Mn=O systems can often be promoted by binding a ligand trans to the oxo group, particularly a pyridine; hence, activation by an additive or modifier is a logical assumption. If the additive strongly binds to both enantiomers of the original catalyst *and is added in excess*, two new diastereomeric catalysts will be formed. It is possible, however, that neither is as active as the original catalyst; nevertheless, one would still be more active than the other. Hence, for conformationally flexible ligands, activation or deactivation could yield an effective enantioselective catalyst.

VII. Simultaneous Asymmetric Activation and Deactivation

Mikami, Noyori, et al. outlined an asymmetric activation/deactivation strategy for use in hydrogenations with racemic [$RuCl_2$(XylBINAP)$(DMF)_n$].[87] This methodology relies upon the selective deactivation of one enantiomer of the complex with a chiral poison or asymmetric deactivator. Preferential deactivation of one enantiomer, leads to a higher population of the antipode which, when complexed by a "chiral activator", was applied to the enantioselective hydrogenation of aryl ketones. These authors suggest that this method allows for higher enantioselectivity than may otherwise be achieved with the enantiopure [$RuCl_2$(XylBINAP)$(DMF)_n$] precatalysts. One should note, however, that this strategy does not formally employ the "original catalyst" during catalysis. Rather, the racemic complex is a synthetic starting material for the generation of a new diastereomeric catalyst (Figure 36). It is further notable that ee's > 99% were observed for a hydrogenation yielding 1-(1′-naphthyl)-ethanol for the reaction that followed this asymmetric activation/deactivation strategy. This is comparable to that observed using the single enantiopure diastereomer.

VIII. Racemic Catalysts, Pseudoenantiomers, and Kinetic Resolutions

Kinetic resolutions provide an important method of isolating enantiomeric materials in high optical purity from racemic starting materials. Recent advances in high-throughput analysis[28,32,138] of enantioselective catalysts suggest other applications of combinations of racemic and enantiomeric substrates for catalytic applications.

Pseudoenantiomers are similar compounds which differ in the sense of absolute configuration and that

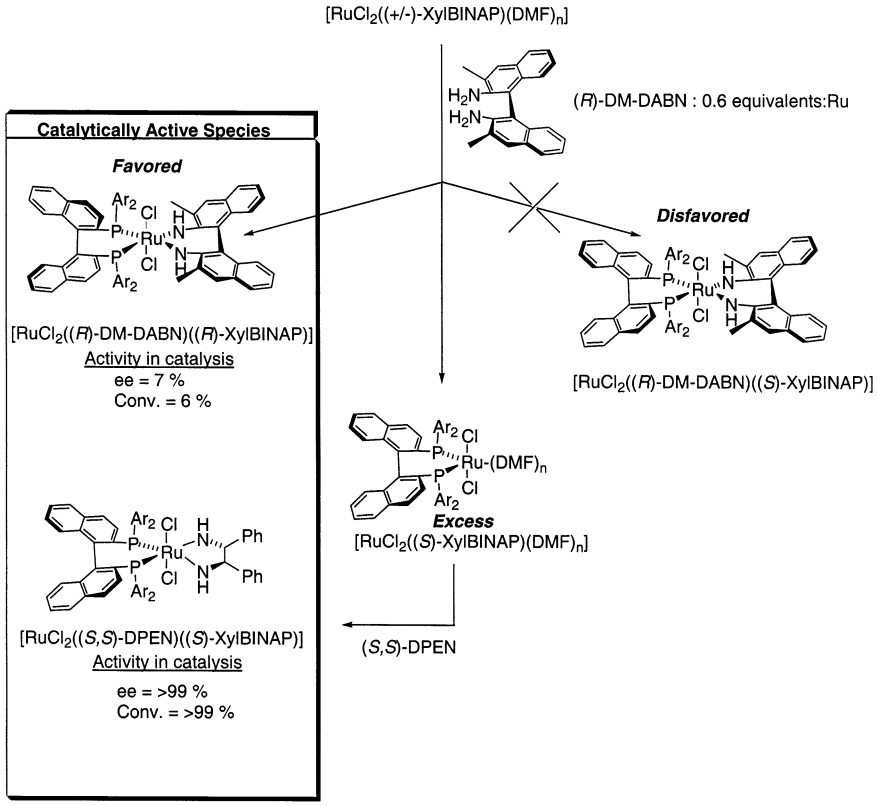


Figure 36. Generation of an "activated" Ru complex from a racemic precatalyst and the relevant competitive equilibria.

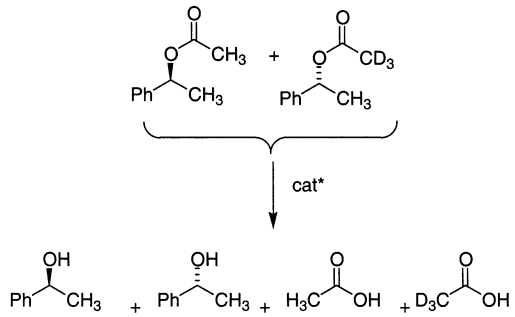


Figure 37. An example of ester hydrolysis using pseudoenantiomers.

would be enantiomers except for having a substituent that differs in a minor manner (e.g., an isotopic substitution, a Cl instead of a Br, etc.). A 1:1 mixture of pseudoenantiomers has the potential of being separated by selective reaction with a nonracemic chiral catalyst. This provides one of the convenient analytical methods for high-throughput screening of enantioselective catalysts. This was demonstrated by Reetz et al.[142] for the hydrolysis of acetate esters that were pseudoenantiomeric owing to deuteration of the acetate methyl, which allowed analysis of enantioselectivity by mass spectroscopy (Figure 37). Other methods have been developed where the substituents carry dyes or groups that are fluorescent but are presumably far enough removed so that the reactive site is not affected significantly.[143,144]

Another variation that could be considered is the interaction of a racemic catalyst with a chiral nonracemic substrate. Initially it might appear that no selectivity information might be forthcoming from such an experiment; nevertheless, in some cases this can be used to evaluate the selectivity of a pure enantiomer of a catalyst using the racemic catalyst.[145] This strategy requires that saturation kinetics are in effect, which implies that both substrate enantiomers are consumed at the same rate.[5] The simplest example to consider is when the enantiomers of the catalyst are 100% enantioselective ($s = \infty$) with respect to the substrate with which they react. This results in an enhancement of the ee of the starting nonracemic substrate with time, i.e., *a kinetic resolution with a racemic catalyst.* For example, if there were a 80:20 starting ratio of enantiomers and 20% were consumed, the final ratio would be 70:10, i.e., an increase in ee from 60% to 75%. If the enantiomers of the catalyst are unselective ($s = 1$), both enantiomers would be removed with a rate proportional to their concentration and the ee of the substrate would remain the same. Intermediate cases and analysis of the substrate ee with time allow the evaluation of the selectivity factor.[145]

IX. Concluding Remarks

The practical utility of the addition of a chiral modifier depends on the resulting system generating a product in high ee. The origin of the enantioselectivity can be attributed to chiral poisoning or asymmetric activation with some possible further influence of chiral amplification. The elucidation of the mechanism, however, can often be complicated by the availability of parallel pathways that may have different mechanisms that are immediately apparent. Several situations illustrate this potential complication, for example, ligands such as Ph_3P,[146,147] BINAP,[148−150] and BIPHEP[150,151] analogues may bind

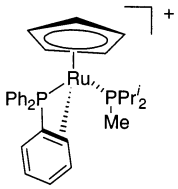


Figure 38. The $\eta^2,\kappa P$-bonding found in a triphenylphosphine complex.

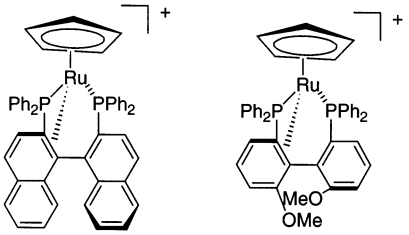


Figure 39. The $\eta^2,\kappa P$-bonding found in BINAP and BIPHEP derivatives.

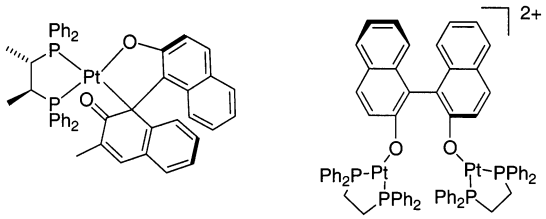


Figure 40. Unusual types of bonding found in BINOL derivatives.

not only via the phosphorus atoms but under some circumstances via one of the aryl double bonds (Figures 38 and 39). Gagné observed that BINOL can bind in a keto form (Figure 40) as well as a bridging form than spans two metals (Figure 40).[152] These situations provide new elements of chirality that can offer competitive equilibria and new catalysts that can contribute to the overall enantioselectivity observed with a catalyst system. Finally, the fact that achiral additives can sometimes drastically improve the enantioselectivity in asymmetric catalysis[122−125] suggests that rationalizing the effect of chiral additive solely on the basis of diastereomeric interactions may not always be warranted. This suggests that modifier studies will provide fertile ground for mechanistic studies as well as offering practical alternatives for the use of enantiopure ligands in asymmetric catalysis.

The difference in reactivity of diastereomers is a key feature of chiral poisoning and asymmetric activation. The discovery that two different chiral ligands within the same catalyst may provide outstanding enantioselectivity for one of the enantiopure diastereomeric catalysts[29−32,105,134] as well adds an additional dimension that should lead to improved enantioselective catalysts in the future.

X. Acknowledgment

We thank the National Science Foundation (Grant CHE0092222) for support of our research on chiral poisoning. We also thank H.-U. Blaser, J. P. Collman, and R. M. Waymouth for helpful suggestions. The mineral specimen containing realgar and orpiment used for the cover art was made available by the Yale Peabody Museum from the Brush mineral collection. These minerals are sources of arsenic, compounds of which are classically used as poisons. A chiral alchemical symbol for arsenic is shown on the cover.

XI. Glossary of Ligand Abbreviations

Often phenols and alcohols and sometimes amines may bind to metals with loss of protons. Sometimes it is not clear whether the protons are lost or not under the experimental conditions. A nomenclature purist would likely suggest that a distinction be made between BINOL (2,2′-binaphthol) and the dianion resulting from the loss of the phenolic protons, for example, BINOLate. For the sake of simplicity, many authors do not make this distinction and will frequently refer to a ligand such as BINOL and its metal complex of the dianion as M(BINOL), even though there a difference of two protons in the formulation. Although lacking precision in describing the composition of the ligand, such a *laissez faire* approach has the advantage of the meaning being obvious in most cases and also being conveniently vague when discussing complexes of amino alcohols, where the state of protonation of the amino moiety may be uncertain.

BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL = 2,2′-binaphthol and its dianion
BINPO = BINAP(O) = BINAP monoxide
BINAM = "binaphthyldiamine" = "diaminobinaphthyl" = 2,2′-diamino-1,1′-binaphthyl
BIPOL = 2,2′-biphenol and its dianion
BIPHEP = a flexible biphenylphosphine ligand, also known as BPBP = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl. BIPHEP, was named after 6,6′-substituted MeO-BIPHEP.[22,112] Strem chemical, however, sells 2,2′-bis(diphenylphosphino)-1,1′-biphenyl as BIPHEP
CHIRAPHOS = 2,3-bis(diphenylphosphino)butane
DABN = 2,2′-diamino-1,1′-binaphthyl
DIPT = diisopropyl tartrate
DM-BINAM = [3,3′dimethyl-1,1′-binaphthyl-2,2′-diamine]
DMDABN = 3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl
DM-DPEN = *N*,*N*-dimethyl-1,2-diphenylethylenediamine
DPEN = 1,2-diphenylethylenediamine
DPPE = bisdiphenylphosphinoethane
DPPF = 1,1′-bis(diphenylphosphino)ferrocene
METHOPHOS = $Ph_2POCH_2CH(NMe_2)CH_2CH_2SMe$]
TADDOL = *trans*-α,α′-(dimethyl-1,3-dioxolane-4,5-diyl)bis-(diphenylmethanol) and its dianion
TOLBINAP = 2,2′-bis(di-*p*-tolylphosphino-1,1′-binaphthyl
XylBINAP = (2,2′-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl

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