Chapter 8. Chiral Catalysts

José M. Fraile, José I. García, José A. Mayoral

1. The Origin of Enantioselectivity in Catalytic Processes: the Nanoscale of Enantioselective Catalysis.

Enantiomerically pure compounds are extremely important in fields such as medicine and pharmacy, nutrition, or materials with optical properties. Among the different methods to obtain enantiomerically pure compounds, asymmetric catalysis[1] is probably the most interesting and challenging, in fact one single molecule of chiral catalyst can transfer its chiral information to thousands or even millions of new chiral molecules.

Enantioselective reactions are the result of the competition between different possible diastereomeric reaction pathways, through diastereomeric transition states, when the prochiral substrate complexed to the chiral catalyst reacts with the corresponding reagent. The efficiency of the chirality transfer, measured as enantiomeric excess [% ee = $(R-S)/(R+S) \times 100$], depends on electronic and steric factors in a very subtle form. A simple calculation shows that differences in energy of only 2 kcal/mol between these transition states are enough to obtain more than 90% ee, and small changes in any of the participants in the catalytic process can modify significantly this difference in energy. Those modifications may occur in the near environment of the catalytic centre, at less than 1 nm scale, but also at longer distances in the catalyst, substrate, reagent, solvent, or support in the case of immobilized catalysts. This is the reason because asymmetric catalysis can be considered a nanometric phenomenon that requires a careful control of different variables.

2. Parameters Affecting the Geometry of the Metal Environment.

2.1. The Modification of the Chiral Pocket

Chiral catalysis can be represented in a general picture as a process that takes place in a so-called chiral pocket (Figure 1) formed by the catalytic centre (in many cases a metal) and the bulky groups in the near environment that restrict the mobility of molecules around the coordinated substrate, provoking

the enantioselection. The most obvious method to modify enantioselectivity is the modification of this chiral pocket, either by changing the shape and size of the bulky groups or by changing the coordination of metal, using a different metal or the same one with different oxidation state. When searching the optimal chiral pocket for a given reaction, bulky groups and metal must be considered as a whole, given that the accommodation of the substrate in the chiral pocket and the efficient shielding of one of its prochiral faces are conditioned by the global geometry of this environment.

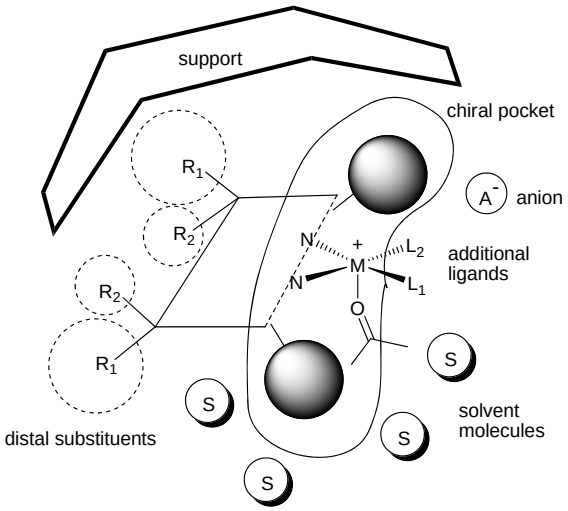


Figure 1. Parameters in the nanoenvironment of the catalytic center that can affect enantioselectivity.

2.2. Distal Modifications and Conformational Consequences

Chiral ligands are usually complicated molecules with ample possibilities of variability, not only in the bulky groups forming the chiral pocket, but also in positions relatively far from the catalytic centre, represented as R_1 and R_2 in Figure 2.1. However, the variations in such distal positions may produce important differences in the conformational preferences of the chiral ligand and hence of the chiral complex, the corresponding reaction intermediate and the diastereomeric transition states. Those conformational variations have also consequences in the relative energy of the transition states and hence in the enantioselectivity. This is one of the reasons because sometimes simplified models are not able to explain the enantioselective process, as those conformational effects of *a priori* non-relevant groups are not considered.

2.3. Additional Ligands: Anions, Solvents and Additives

Other possibility of variation in a chiral catalytic system is the presence of additional ligands on the metal centre. The origin of those ligands can be multiple. If the metal is not in zero oxidation state, it will require the presence of an anion that would act as a ligand in the case of coordinating anions (chloride for example) or not in the case of non-coordinating anions (perchlorate for example). If chiral ligand and substrate are not able to saturate the coordination sphere of the metal, solvent molecules can enter to play this role. Donor ability and bulkiness of solvent molecules will condition the geometry of the chiral pocket, but other parameters such as dielectric constant may also modify the conformational preferences of the whole complex, with the same effects commented above. Finally, the saturation of the coordination sphere of metal can be produced by additives, whose properties can be tailored to optimize the chirality transfer.

2.4. Parameters beyond the Molecular Scale: Aggregates and Supported Catalysts

All the above considerations assume the existence of ideal catalytic monomeric species in solution that are attacked by a perfectly dissolved reagent. However, this is not the case in many catalytic processes. Depending on the reaction solvent, catalyst molecules may aggregate provoking steric and electronic interactions between catalyst molecules with consequences on enantioselectivity difficult to predict. Finally, in order to facilitate the recovery and reuse of the catalyst, the complex can be supported in a phase different from that of the substrate and reagent, either another liquid phase or a solid phase. In the case of immiscible liquid phases, the reaction may take place either in one liquid phase, due to partial solubility of the components, or in the interface, with possible consequences on enantioselectivity. In the case of catalysts immobilized on solid supports, the existence of possible catalyst-support interactions of different nature (coordinating, steric, diffusion limitations) cannot be discarded and effects on enantioselectivity are expected.

Along the rest of the chapter different effects of all those parameters will be presented, using as cases of study some well-known reactions from a mechanistic point of view.

3. Case of study (1): Bis(oxazoline)-Cu Catalysts for Cyclopropanation.

Cyclopropanation reactions promoted by bis(oxazoline)-copper (Box-Cu)* complexes constitute a good case of study. The mechanistic aspects of the catalysis have been thoroughly studied both from the experimental and theoretical viewpoints and a good model for the stereoselection has been developed in the case of enantioselective homogeneous catalysis. This catalytic system has been shown to be very sensitive to multiple "surrounding" effects, such as solvent, counter-anion, remote substituents, and support, in the case of immobilized catalysts (Figure 2). In the next sub-sections these effects will be analyzed, and put in the context of the nanoenvironment effects.

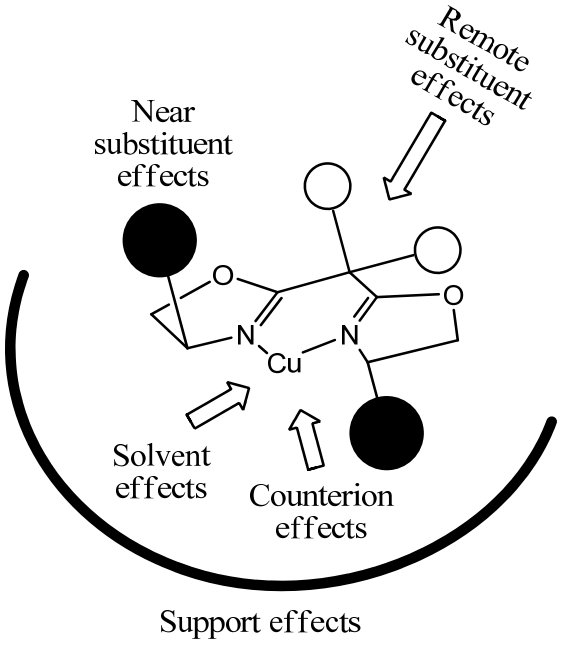


Figure 2. Survey of nanoenvironment effects in Box-copper catalytic systems.

* C_2-symmetric Box ligands will be represented as RBox, with R being the same substituent in 4-position of both oxazoline rings. In case of Box ligands with different substitution in each oxazoline ring, both substituents will be presented as RR'Box.

3.1. The Mechanism of Chiral Induction

The mechanism of cyclopropanation reactions by copper complexes has been experimentally investigated by several groups,[2] demonstrating by kinetic experiments that the rate-determining step of the cyclopropanation mechanism is the dinitrogen extrusion from the diazocompound, to form (supposedly) a copper-carbene intermediate, a very reactive species, and therefore very elusive to experimental detection.[3] Subsequent addition of the carbenoid moiety of this intermediate to the olefin double bond results in the cyclopropane products.

As the rate-determining step of the mechanism turns to be the formation of the copper carbene complex, the mechanistic issues posterior to this step, including the addition of the carbene to the olefin C=C double bond, which is the stereochemistry-determining step, are not accessible for experimental kinetic studies.

Happily, computational mechanistic studies do not suffer from this drawback (they have their own, however!), and hence, the mechanism of the chiral induction in these catalytic systems has been investigated using these techniques. In pioneering works, both Mayoral and co-workers[4] and Norrby and co-workers[5] studied the mechanism of model enantioselective cyclopropanation reactions, catalyzed by Box-Cu(I) complexes. Both studies agreed in the final stereoinduction mechanism proposed. Thus, the *trans*/*cis* selectivity in the cyclopropane products is governed by the steric interacion between the olefin substituent and the ester group linked to the carbene carbon in the addition transition states (TS) (Figure 3). On the other hand, the enantioselectivity is governed by the steric interactions between the ester group linked to the carbene carbon and the substituents on the 4-position of the ligand oxazoline ring, induced by the olefin approach in the different addition TS (Figure 3).

In subsequent works of Mayoral and co-workers, the model system used in mechanistic computational studies using the hybrid QM/MM approach is almost identical to the experimental one.[6] The results obtained with this sophisticated model support the mechanism of the stereoselection schematized in Figure 3. In particular, the enantioselectivity is determined by the presence or absence of an intramolecular ester-oxazoline substituent in the addition TS, induced by the approach of the olefin through the different reaction channels.

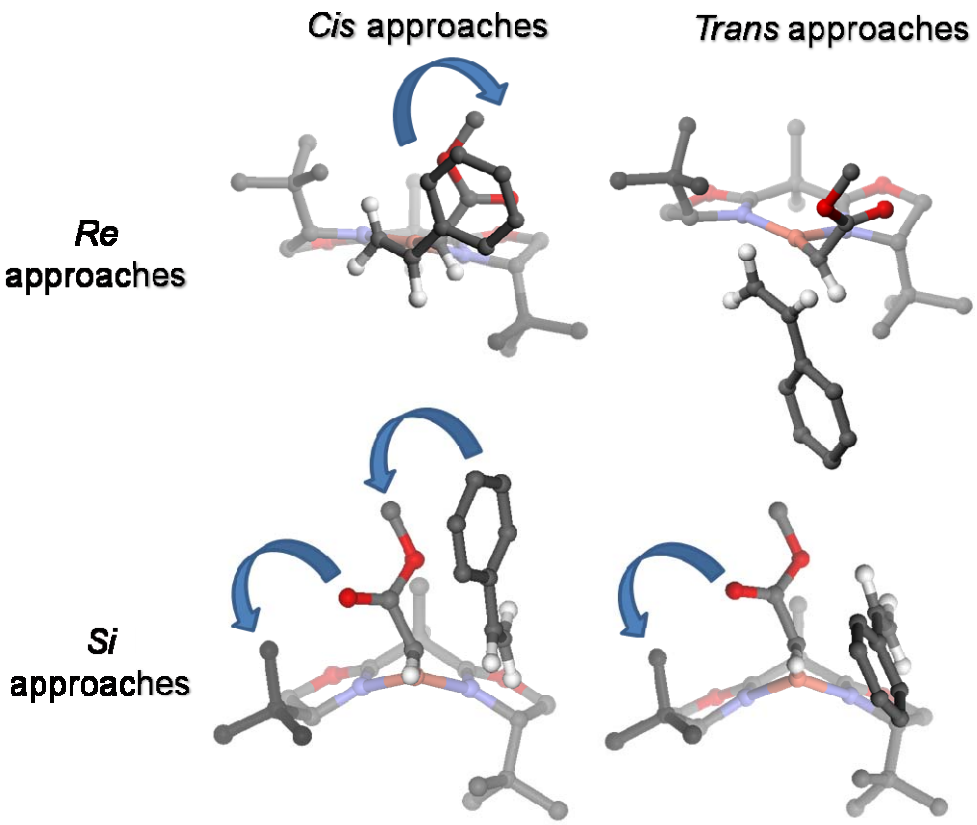


Figure 3. Main steric interactions in the different cyclopropanation TS, responsible for the reaction stereoselectivities.

3.2. The Importance of Symmetry: C_1 vs C_2

C_2-symmetric ligands are usually preferred over C_1-symmetric (asymmetric, in the sense of lack of any symmetry element) ligands for catalytic enantioselective transformations. Those C_1-symmetric ligands that are successful for catalytic applications are generally both electronically and sterically asymmetric, as for instance salicylaldimines[7] and phosphino-oxazolines (Figure 4).[8] There are evident advantages in using C_2-symmetric ligands: Arguably most important, less reaction channels are possible for the reaction, simplifying the prediction of chiral induction.

Box family ligands display C_2 symmetry in the vast majority of cases. Given that all these ligands have two electronically and sterically equivalent coordinating centers, the possibility exists of modifying the steric surroundings in proximity of one of these centers, thus leading to electronically equivalent, but sterically different coordinating points. These ligands would be "halfway" between the above mentioned C_1-symmetric ligands and the usual C_2-symmetric

ligands. Some illustrative examples based on the oxazoline motif are shown in Figure 4.

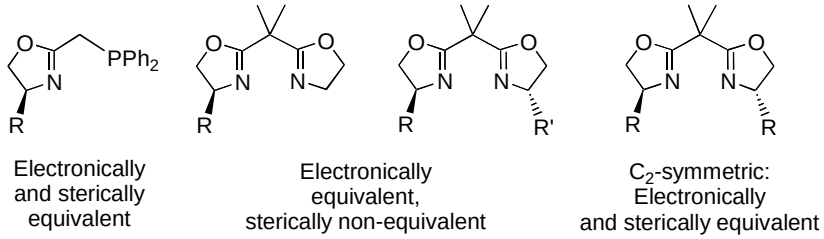


Figure 4. Some examples of chiral ligands, based on the oxazoline motif, with different degree of electronic and steric equivalency.

In general, in those cases in which C_2-symmetric ligands lead to good enantioselectivities, the use of electronically equivalent (e.g. in the sense of a close similarity of the coordinating groups) but sterically non-equivalent analogs results in a dramatic worsening of the results. Analogously, the use of an asymmetric pyridineoxazoline (pybox) in the copper-catalyzed cyclopropanation reaction of styrene with ethyl diazoacetate leads to virtually racemic products.[9] Similar observations have also been described for chiral unsymmetrical 2,2'-bipyridyl ligands in the same reaction.[10] However, there is at least one case in which the use of sterically non-equivalent ligands results in enantioselectivities comparable to those obtained with the corresponding C_2-symmetric analogs, namely the so-called "single-chiral" pybox ligands, described by Nishiyama and co-workers (Figure 5).[11]

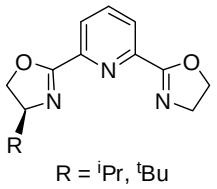


Figure 5. Structure of the Nishiyama asymmetric pybox ligands.

When these ligands are used in the ruthenium-catalyzed cyclopropanation reaction of styrene with alkyl diazoacetates (Figure 6) very good enantioselectivities are obtained for the *trans*-cyclopropanes (up to 94% *ee*).[12] A mechanistic explanation for this unusual result has been offered, based on computational studies.[12]

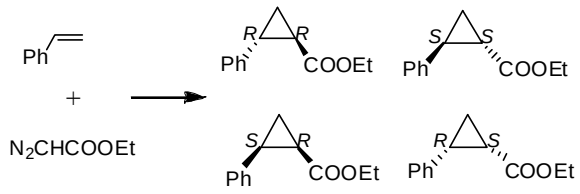


Figure 6. Cyclopropanation reaction between styrene and ethyl diazoacetate.

Only very recently C_1-symmetric Box and azabis(oxazolines) (azaBox) have been described (Figure 7)[13] and tested in the homogeneous catalysis of the benchmark cyclopropanation reaction.[14]

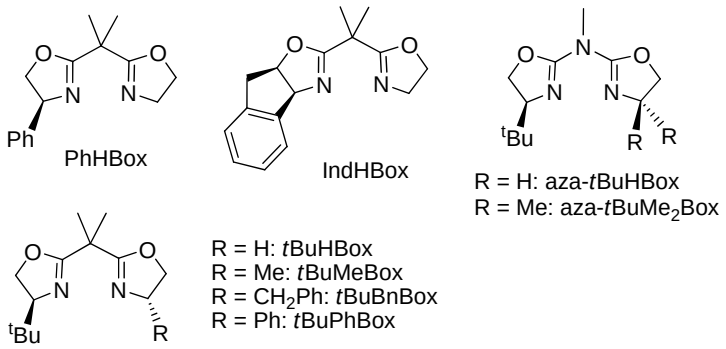


Figure 7. Structures of the asymmetric Box and azaBox ligands used in the catalytic experiments.

Table 1 gathers the results obtained with these ligands, and compare them with those obtained with the related C_2-symmetric ligands, when applicable. These results allow concluding that C_2-symmetry is not mandatory to obtain reasonable levels of enantioselection. Ligands bearing one "big" and one "small" group on the oxazoline rings, like *t*BuMeBox, allow to obtain good levels of enantioselectivity. Even ligands bearing only one stereogenic center, like aza-*t*BuMe$_2$Box, are able to induce stereoselectivity levels close to the best obtained with the classical C_2-symmetric ligands.

Table 1. Results of the cyclopropanation reaction of styrene with ethyl diazoacetate, catalyzed by chiral Box-CuOTf complexes.

Ligand	*Trans/cis*	%ee *trans*[b]	%ee *cis*[b]
PhBox	68/32	60	51
PhHBox	71/29	20	8
IndBox	60/40	85	81
IndHBox	69/31	33	25
*t*BuBox	71/29	94	91
*t*BuHBox	68/32	29	8
*t*BuMeBox	67/33	84	79
*t*BuBnBox	64/36	83	75
*t*BuPhBox	72/28	82	69
aza-*t*BuBox	73/27	92	84
aza-*t*BuHBox	73/27	23	9
aza-*t*BuMe$_2$Box	71/29	85	68

The origin this behavior has been studied through computational mechanistic studies, which show a very good agreement with experimental observations. In particular, the enantioselection mechanism comes from the differently favored reaction channels, leading to one of another cyclopropane enantiomer, as a function of the different steric interactions between the ester group and the bisoxazoline substituents (Figure 8). The calculated ee for ligands *t*BuMeBox and aza-*t*BuMe$_2$Box are 88% and 90% ee, respectively, which compare very well with the experimental values. This experimental-theoretical agreement should allow to theoretically investigating the behavior of new ligands before their synthesis and testing, facilitating the design of tailored catalytic systems for this reaction. It is clear from these studies that once the stereoselection mechanism is well understood, and the definition of the chiral pocket is clearly established, C_2-symmetry is no longer required, adding more versatility to the ligand design with specific purposes (for instance, supporting).

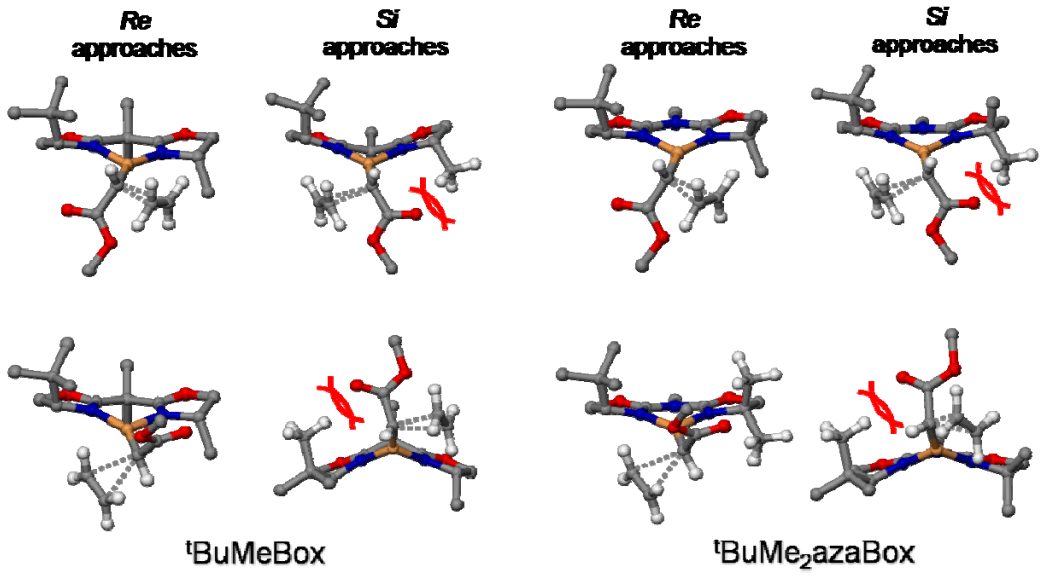


Figure 8. Some selected calculated (at the B3LYP/6-31G(d) theoretical level) geometries of transition structures of the reaction of ethylene with methyl diazoacetate, catalyzed by the *t*BuMeBox-Cu(I) (**5d**-Cu) and the aza-*t*BuMe$_2$Box-Cu(I) (**5h**-Cu) complexes.

3.3. Distal Modifications: Substitution in the Methylene Bridge

It is generally assumed that, for a good catalyst enantiodiscrimination, bulky groups defining the chiral pocket must be near the catalytic center. However, distal substituents may also have a significant role in determining the stereoselectivity of the catalytic reaction.

In the case of Box-copper complexes, such distal effects have been reported for the cyclopropanation reaction, in connection with the support of these kinds of complexes.[15] Thus, when a homopolymer obtained from a modified Box precursor (Figure 9) bearing 4-vinylbenzyl groups in the central methylene bridge is charged with copper and used as catalyst of the benchmark cyclopropanation reaction (Figure 9), an unexpected *cis*-selectivity is obtained (37:63 *trans*/*cis* ratio, when the usual value with this family of ligands is ca. 70:30). Furthermore, the enantioselectivities in *trans*- and *cis*-cyclopropanes are also lower, when compared with the traditional ligand used in homogeneous phase, bearing an isopropylidene bridge (78% vs 94% ee in *trans*-cyclopropanes and 72% vs. 90% ee in *cis*-cyclopropanes).

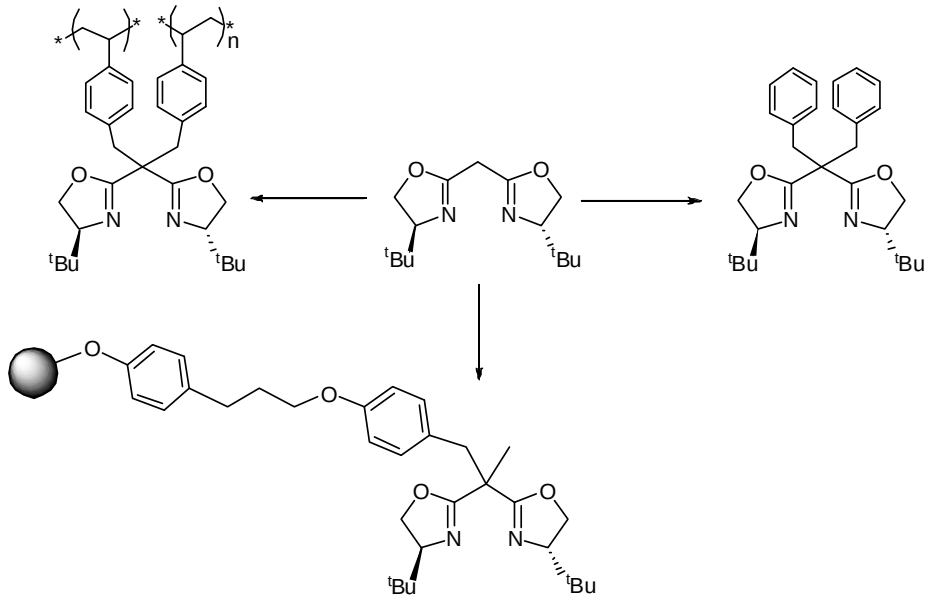


Figure 9. Some Box ligands benzylated in the central bridge.

These effects are not due to the presence of the polymeric backbone, because when the corresponding Box ligand, dibenzylated in the central methylene bridge, is used in homogeneous catalysis experiments, virtually identical results are obtained, which indicates that the effect is due to the substitution pattern of the methylene bridge of the Box ligand, constituting a genuine case of distal effect on the stereodiscrimination of the catalyst.

It is worth noting that this effect is only clearly observed when the Box ligand bears *tert*-butyl groups in 4-position. When these positions are occupied by phenyl groups, the cyclopropanation is less *cis*-selective (52:48 *trans*/*cis* ratio), and enantioselectivities obtained are nearly identical to those obtained in the homogeneous catalysis with the analogous ligand with isopropylidene bridge. It seems that there is an interplay between the substituents in the methylene bridge and in 4-position of the oxazoline ring to configure the shape of the chiral pocket leading to this unexpected stereoselectivity change. No analogous homogeneous experiments have been carried out with a monobenzylated Box ligand, but a similar system has been described by Annunziata et al., in which the ligand is linked to a poly-ethylene glycol chain through a spacer containing a single benzyl group bonded to the Box methylene bridge (Figure 9).

When the corresponding copper complex is used in the homogeneous catalysis of the benchmark cyclopropanation reaction, up to 77:33 *trans*/*cis* selectivity and 91% ee in *trans*-cyclopropanes is obtained, which seems to indicate that the presence of two benzyl groups is necessary to observe their remote effect in the stereoselectivity, probably due to a decrease in the mobility of the catalytic intermediates, and in the number of possible reaction channels (due to the C_2 symmetry). The ultimate reason for this particular behavior remains, however, unveiled.

3.4. Effect of Anion

Cationic Box-copper complexes require the presence of anions to keep electroneutrality. These anions usually come from the copper salt, and their nature has an enormous influence on the activity and enantioselectivity of the Box-copper catalysts in homogeneous phase.[16] For instance, when the counteranion is changed from triflate to chloride, the enantioselectivity of the cyclopropanation reaction of styrene with ethyl diazoacetate, catalyzed by the *t*BuBox-Cu(I) complex in dichloromethane, drops from 94 to 3% ee for the *trans*-cyclopropanes, and from 92 to 8% ee for *cis*-cyclopropanes.

When these cationic complexes are immobilized by electrostatic interactions onto anionic supports (through a cation-exchange procedure), the enantioselectivity pattern also follow a similar scheme. Thus, when the anionic moiety has a fluorosulfonate structure (Nafion, Nafion-silica nanocomposites), copper complexes of PhBox lead to results (59% ee in the *trans*-cyclopropanes) almost identical to those obtained in homogeneous phase with copper triflate salts. On the other hand, when other anionic supports, such clays or sulphonic acid resins, are used, a marked decrease in enantioselectivity is observed, up to only 17% ee in the *trans*-cyclopropanes.[17]

This dramatic influence of the counteranion on the enantioselectivity has been ascribed in homogeneous phase (and, in part, also in heterogeneous phase) to its higher or lower coordinating character. The correctness of this hypothesis has been verified through computational studies.[18] Thus, a computational study at the DFT theoretical level) of a model cyclopropanation reaction, catalyzed by Box-Cu(I) complexes bearing or not a chloride anion coordinated to the metal,

have shown that the geometrical changes induced in the key transition states by the presence of the anion are the responsible for the decrease in enantiodiscrimination of the catalyst. Figure 10 illustrates these differences and the steric interactions responsible for the enantioselectivity.

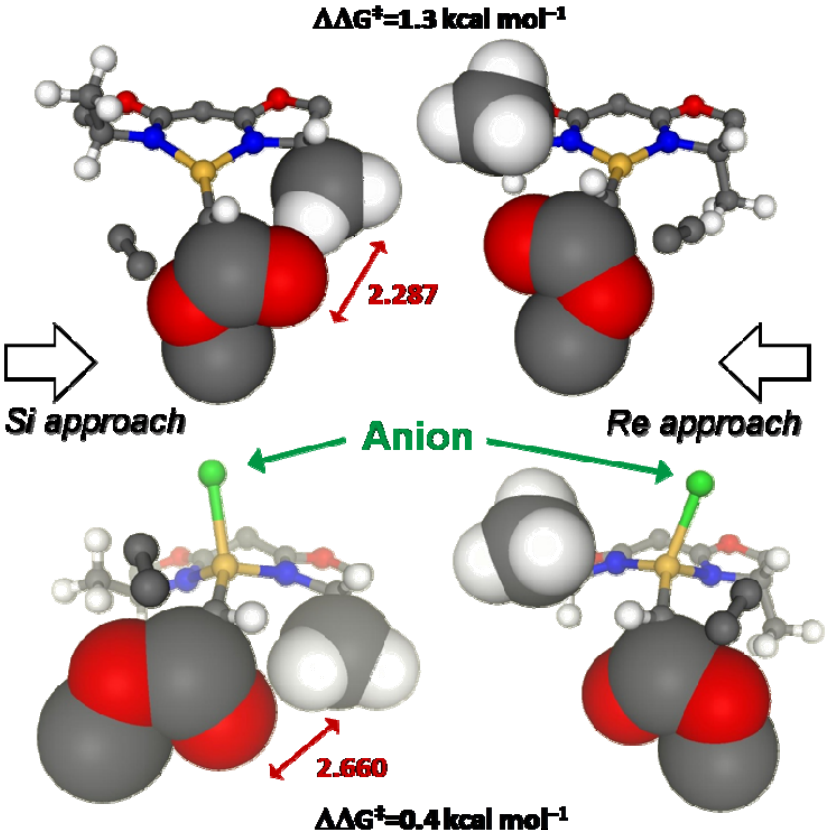


Figure 10. Differences in steric enantiodiscriminating interactions induced by the presence of the counteranion.

As stated in section 3.1, the main steric interaction responsible for the enantiodiscrimination lies in the steric repulsion between the ester group and one of the substituents in 4-position of the oxazoline ring, which appears only when the alkene approaches the carbene carbon by its *Si* face. In the case of the cationic complexes with weakly coordinating counteranions, the ester group and the oxazoline substituent become closer in the less-favored *Si* transition state (Figure 10), increasing the energy difference with regard to the corresponding *Re* transition state (1.3 kcal mol^{-1} in the model shown in Figure 10). However, when a chloride anion is coordinated to the copper center, the deformation induced in the neighborhood of the metal results in a longer distance between the ester group and the oxazoline substituent, and hence in la lower steric repulsion,

giving rise to closer transition state energies (0.4 kcal mol^{-1} in the model shown in Figure 10), and hence to lower enantioselectivities. Of course, greater or lesser coordinating abilities of the counteranion may lead to different degrees of geometry changes in the nanoenvironment of the metal, giving rise to stereoselectivity changes that may vary from modest to dramatic ones.

3.5. Beyond the Coordination Sphere: Supports that Change the Dimensionality

In general it is considered that immobilized catalysts should be designed to minimize the possible interactions between the catalytic sites and the support, to avoid unpredictable effects of the latter on the stereochemistry of the reaction. However this interaction can be used to improve and even to change the stereochemical results, in this way the solid catalyst leads to products difficult to obtain in solution and its use is clearly justified. It must be recall that the support may block very efficiently some of the reaction channels. Usually, this blocking is at random, due to the amorphous character of the support and/or the lack of a rigid disposition of the catalyst with respect to the support, resulting in the absence of any support-induced stereoselectivity. However, in the case of the electrostatic support of cationic Box-copper complexes on lamellar anionic solids (clays), through an ion-exchange process, a marked support effect has been reported.

Mayoral and co-workers reported a complete change in the stereoselectivity when cyclopropanation between styrene and ethyl diazoacetate was carried out in styrene as the reaction media using laponite immobilized PhBox–Cu complex as catalyst.[19] Complete reversal of the *trans*/*cis* diastereoselectivity (31:69) was observed and, even more interestingly, the major *cis*-cyclopropane obtained has the opposite absolute configuration, with regard to homogeneous phase results. Furthermore the effect is not permanent, when the solid used in styrene is recovered and reused in dichloromethane, the ‘‘normal’’ stereochemical results are obtained again. This effect is not due to a particular behavior as it is also observed with other solvents with a low dielectric constant. Depending on the reaction conditions, with the same complex one can pass from 70:30 *trans*/*cis* selectivity and 60% ee in *trans*-1*R* cyclopropane in homogeneous conditions, to 20:80 *trans*/*cis* selectivity and 72% ee in *cis*-1*S*

cyclopropane in heterogeneous catalysis.[20] Note that enantioselectivity is even better in heterogeneous phase, which clearly illustrates the great effect of the nanoenvironment of the catalyst in the case of supported complexes.

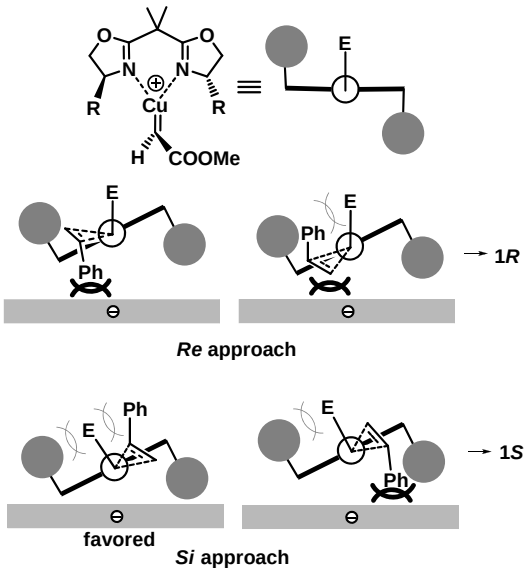


Figure 11. Styrene approaches in cyclopropanation reactions catalyzed by Box-Cu complexes immobilized onto laponite.

An explanation to the reversal of selectivity has been offered, based on the key insertion step of carbene to styrene, responsible for the stereoselectivity. As shown in Figure 11, the presence of the support surface disfavors most of transition states (TS), and particularly those leading to the major products in homogeneous phase, due to the new steric interactions between styrene and the surface. The only TS lacking these interactions is precisely that leading to the major product obtained in heterogeneous phase. A reaction medium with low dielectric permittivity favors the close proximity of the cationic complex to the anionic support, enhancing the confinement effect. In this case, the planarity of the surface of the support is a key point, because it effectively blocks half of reactive trajectories, resulting in a genuine confinement effect.

It is clear that a closer proximity of the complex to the support is desirable to maximize the effect. Following the model depicted in Figure 11, this should be feasible if C_1-symmetric ligands were used instead of the traditional C_2-symmetric ones (Figure 12).

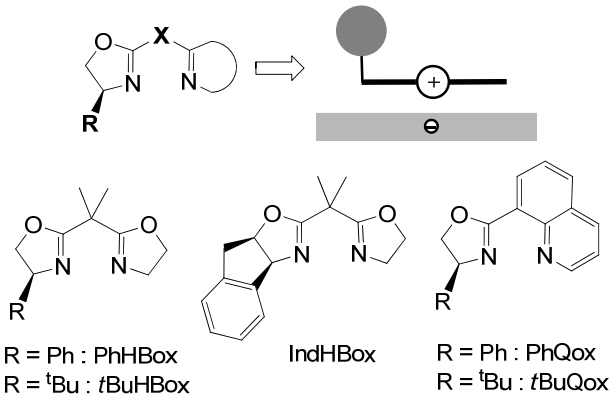


Figure 12. Structure of C_1-symmetric ligands and its consequences on the catalyst supporting.

Two families of this kind of ligand have been tested in the clay-supported catalysis of the benchmark reaction,[20,21] and some of the most relevant results described are shown in Table 2.

Table 2. Results of the cyclopropanation reaction of styrene with ethyl diazoacetate catalyzed by chiral Box- and Qox-Cu complexes.

	Homogeneous (CH_2Cl_2 as solvent)			Heterogeneous (styrene as solvent)		
Ligand	*trans*/*cis*	%ee *trans*	%ee *cis*	*trans*/*cis*	%ee *trans*	%ee *cis*
*t*BuHBox	71/29	20	8	9/91	15	–41
PhHBox	68/32	29	8	15/85	13	–48
IndHBox	69/31	33	25	16/84	30	–32
PhQox	71/29	24	25	14/86	39	30
*t*BuQox	68/32	48	28	23/77	24	33

[a] Negative sign indicates that 1*S*-cyclopropanes are the major enantiomers.

Concerning the *trans*/*cis* selectivity, it is clear that the use of C_1-symmetric ligands suppose a clear improvement, given that up to 91% *cis*-cyclopropane can be obtained with *t*BuHBox ligand, i.e. that in which the steric asymmetry is the highest (see Figure 4 in section 3.2). It must be noted that *cis*-cyclopropanes are usually more difficult to obtain, and relatively few catalytic methods have been described that show this preference, most of them based on the use of rather special ligands (see section 5.3 for some examples). Support confinement effects are therefore very useful in this context, since the same

ligand can lead preferentially to *trans*- or *cis*-cyclopropanes depending on it is used in homogeneous or heterogeneous catalysis.

Concerning enantioselectivity, results are much less clear. Homogeneous phase enantioselectivities are consistently low (except maybe the 48% ee obtained in *trans*-cyclopropanes with ligand *t*BuQox). With Box ligands, a reversal in the absolute configuration of the major *cis*-cyclopropanes is obtained, but with low enantioselectivities. Surprisingly, when the quinolinoxazolines are used in heterogeneous catalysis, no such reversal is observed, and the enantioselectivities are similar to those obtained in homogeneous catalysis. These results point to a surface confinement model more complicated than that previously proposed, with more geometrical possibilities of the key carbene intermediate with regard to the support surface. On the one hand, multiple dispositions of the ester group of the carbene intermediate with regard to the oxazoline substituent and to the support surface are possible. On the other hand, intermediates and transition structures have some degree of flexibility, so they can adopt conformations in which the steric repulsion with the support is minimized (for instance, the substituent on the oxazoline ring can adopt a pseudo-equatorial disposition, more parallel to the support surface, as can do it the ester group of the carbene moiety). These circumstances lead to an increase in the number of possible reaction channels, and hence to a decrease in the final enantioselectivity.

4. Case of study (2): Catalysts for Diels–Alder Reactions.

4.1. Enantioselectivity in Diels–Alder Reactions

Enantioselective Diels–Alder reactions promoted by chiral Lewis acids constitute a powerful tool for the preparation of enantiomerically pure cyclic compounds. Therefore this kind of reactions has been extensively investigated[22] allowing the identification of factors influencing the extension and the sense of the asymmetric induction.

One of the key points for enantiodiscrimination is the control of the conformation of the dienophile. It can adopt an s-*cis* or s-*trans* conformation and each conformer shows reversal topicity of the upper and lower faces, thus

leading to different enantiomers (Figure 13). In this regard both theoretical and experimental studies have shown a preference for s-*cis* conformation.

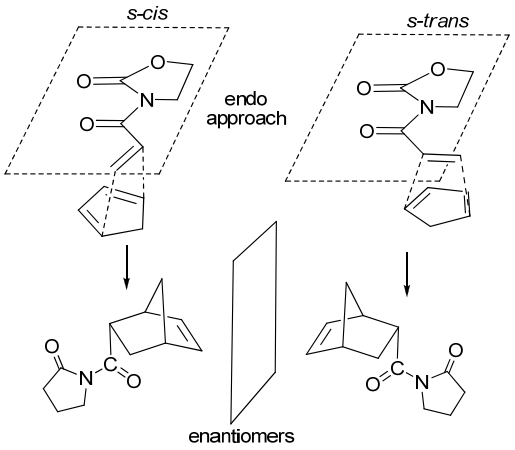


Figure 13. Reversal of enantioselectivity with dienophile conformation.

4.2. Chiral Pocket in Box-Metal Complexes: Ligand, Metal, and Additives

Several groups have made important contributions related to the use of metal complexes of C_2-symmetric Box as catalysts in Diels–Alder reactions, mainly with oxazolidinone derivatives. In the short range, dienophile is included in the chiral pocket of the complex, which is primarily defined by the bulky groups of the chiral ligand shielding some spatial zones, and the coordinating sphere of the metal, that controls the geometry of the dienophile-catalyst complex. In fact bis(oxazolines) are able to form catalytic complexes with a large variety of metals, for example Fe^{3+}, Mg^{2+}, and Cu^{2+}, all of them efficient catalysts for Diels–Alder reaction. Corey,[23] Evans,[24] and Gosh[25] showed that both the extension and the sense of the enantioselection (Table 3) depend on the geometry of this intermediate, octahedral, tetrahedral, or square-planar (Figure 14), imposed by the metal. This coordination geometry modifies the dihedral angle between the Box ligand and the dienophile planes, from perpendicular in the case of Mg to coplanar in the case of Cu.

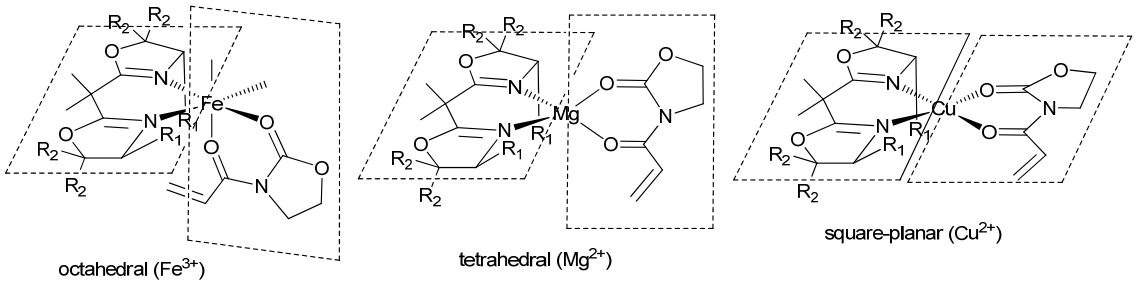
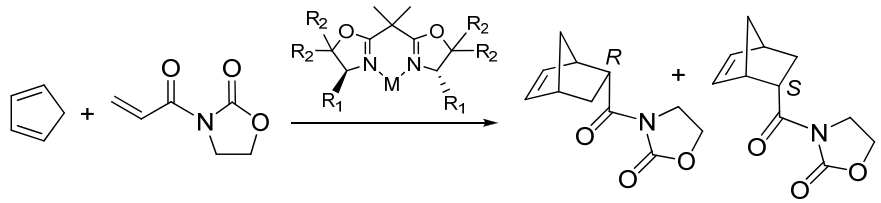
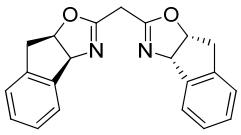


Figure 14. Modification of the geometry of the chiral pocket with different Box-metal complexes.

Table 3. Variation of enantioselectivity in Diels–Alder reactions with the shape of the chiral pocket in Box-metal complexes.



Metal	R_1	R_2	% ee (major isomer)
Fe	Ph	H	82 (*R*)
	Ph	Me	86 (*R*)
	^{t}Bu	H	24 (*R*)
Mg	Ph	H	76 (*R*)
	Ph	Me	91 (*R*)
	^{t}Bu	H	0
Cu	Ph	H	30 (*S*)
	Ph	Me	10 (*S*)
	^{t}Bu	H	98 (*S*)
Mg			61 (*S*)
Cu			99 (*R*)

In this way the position of the C=C double bond with respect to the bulky groups changes and the unshielded face that suffers the diene attack is different, *Si* face for octahedral and tetrahedral complexes, *Re* face for square planar complex (Figure 15), leading to the observed change in the sense of the asymmetric induction. Another consequence of this change in the orientation of the dienophile in the chiral pocket is the different optimum substituents of the Box ligand depending on the metal, phenyl for Fe and Mg, *tert*-butyl for Cu.

Even more subtle effects, such as the increase of bulkiness of R_2 from H to methyl, have different consequences depending on the geometry of the metal-dienophile complex.

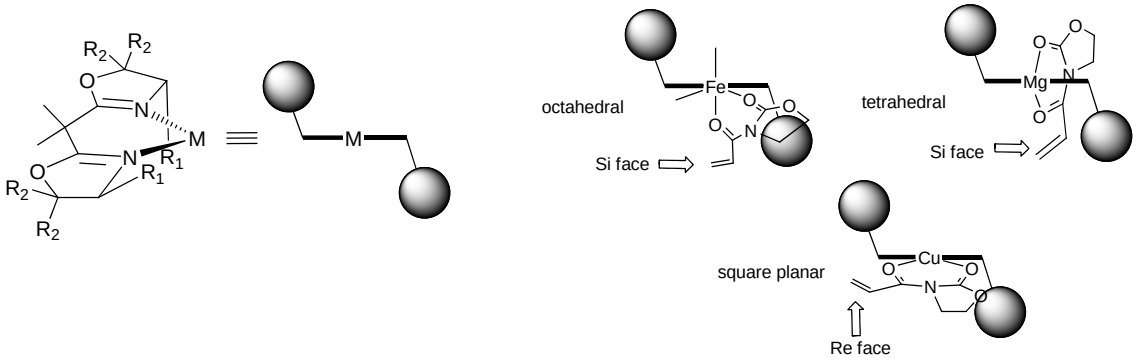


Figure 15. Proposed variations of face discrimination with different Box-metal complexes.

Another method to modify the geometry of the chiral pocket is the use of different counter-ion and/or Lewis bases.[26] In the case of Mg complex of the same Box, the use of $Mg(ClO_4)_2$ leads to a tetrahedral intermediate, that favors the attack of the diene on the *Re* face of the dienophile (Figure 16). The addition of two equivalents of a monodentate additional ligand, such as water or tetramethylurea (TMU), or one equivalent of a bidentate ligand, such as ethylene glycol, modifies the geometry of the intermediate, leading to a preference for octahedral coordination, with the additional ligands in *cis* relative position (Figure 16), that favors the attack of the diene on the *Si* face of the alkene, and consequently the sense of the asymmetric induction changes (Table 4). In the case of the more coordinating triflate anion, the intermediate is always octahedral, but both triflates are placed in *trans* relative position (Figure 16), favoring an attack on the *Si* face of the dienophile, in a similar way to that observed in the case of the square planar Cu complex (Figure 15). The geometry of this intermediate does not change by the addition of external ligands, as shown by the same results in the presence of water or TMU.

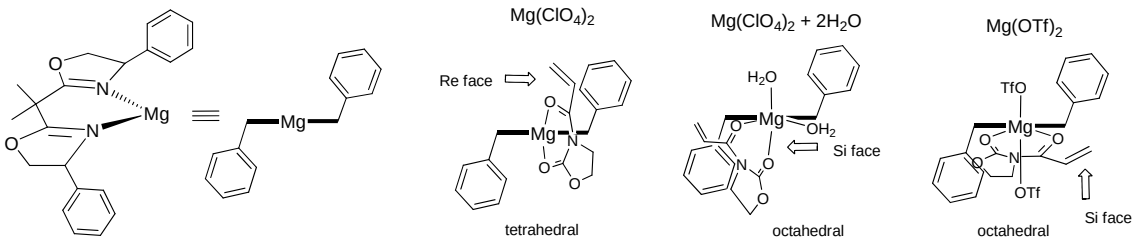
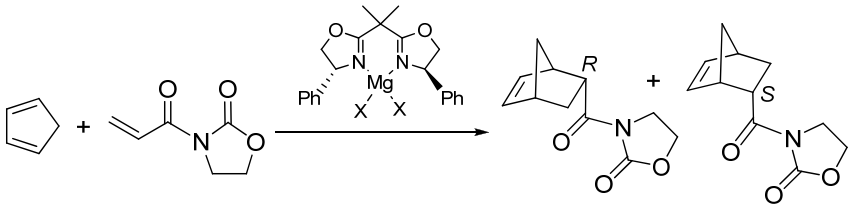


Figure 16. Proposed effect of anion and coordinating water molecules on enantioselectivity of Box-Mg complexes.

Table 4. Variation of enantioselectivity in Diels–Alder reactions with the counter-ion and/or additives in Box-Mg complexes.



Counter-ion	Additive	% ee (major isomer)
ClO_4^-	-	73 (*S*)
	2 H_2O	73 (*R*)
	2 MeOH	42 (*R*)
	$HOCH_2CH_2OH$	58 (*R*)
	2 TMU	51 (*R*)
TfO^-	-	88 (*R*)
	2 H_2O	86 (*R*)
	2 TMU	88 (*R*)

As can be seen, these results have been explained according to proposed models, in many cases without additional experimental or theoretical evidences apart from the sense of the chiral induction.

4.3. The Poorly Understood Effect of Surface

Amorphous silica has been used as a support for complexes bearing triflate anions due to the capacity to form hydrogen bonds between the surface silanol groups and the fluorine atoms of triflate (Figure 4.4). This type of immobilization has shown to affect the enantioselectivity in the case of complexes using a Box with phenyl groups.[27]

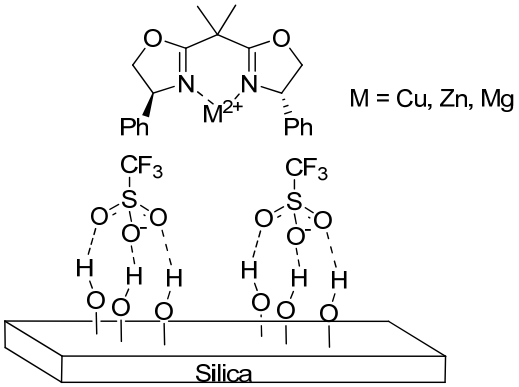


Figure 17. PhBox-metal complexes immobilized on silica by hydrogen bond interactions.

With the three metals tested (Cu, Zn, Mg) a reversal in enantioselectivity was observed in the immobilized catalysts with respect to the homogeneous ones, for example from 60% ee (*S*) in solution to 30% ee (*R*) with the heterogeneous catalyst in the case of the Mg catalyst. This reversal was ascribed to a change in the coordinating ability of the anion, as described above for $Mg(ClO_4)_2$ and $Mg(OTf)_2$ complexes in solution, but in this case the reduction in the coordinating ability of the anion must be produced by the hydrogen bonds between silanols and triflates.

However, this explanation cannot be applied to the copper catalyst, as the reversal is not observed in solution. In this case new interactions of unknown origin must affect the geometry of the complex and the corresponding transition states, modifying the relative energies.

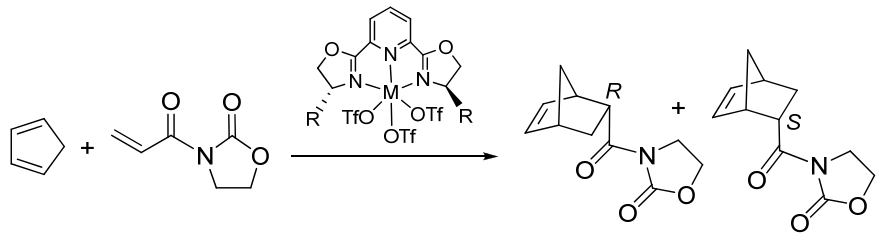
4.4. Similar but not the Same: Control of Induction Sense with Different Lanthanides

We have seen how the change from a square planar geometry to a tetrahedral or octahedral disposition may change completely the sense of the asymmetric induction. This situation is even more complicated when metals with higher coordination numbers are involved. Pyridinebis(oxazoline) complexes with lanthanide metals are also chiral Lewis acids able to catalyze Diels–Alder reactions. The sense of the enantioselection does not depend only on the metal, but also ligands of the same absolute configuration with different bulky

substituents lead to opposite enantiomers with the same lanthanide metal (Table 5).[28]

From those results it is clear that both ligands, with the same absolute configuration and the same metal, lead to major products of opposite configuration. Furthermore the induction sense changes from scandium to the rest of lanthanides. Based on X-ray structures a model was proposed for the ligand with R = Ph (Figure 4.5). Scandium, with a coordination number of 7, is complexed to pybox ligand in equatorial, whereas dienophile docks with the exocyclic carbonyl group in the apical position, in such a way that phenyl group efficiently shields the *Si* face. However lanthanum, with a coordination number of 9, keeps two triflates in apical positions and the dienophile coordinates in the equatorial plane, living *Si* face more accessible to the attack of diene. However, the explanation for the reversal in enantioselectivity when using the ligand with isopropyl groups requires the coordination of dienophile in a completely different orientation, probably due to the role of water, that it is excluded in that case by the use of 4Å MS.

Table 5. Variation of enantioselectivity in Diels–Alder reactions with the shape of the chiral pocket in pyridinebis(oxazoline)-metal complexes.



		% ee (major isomer)	
Metal	Ionic radius (Å)	R = iPr[a]	R = Ph[b]
Sc	0.870	84 (*R*)	20 (*S*)
Yb	0.985	0	66 (*R*)
Eu	1.068	58 (*S*)	38 (*R*)
La	1.160	17 (*S*)	78 (*R*)

[a] With 4Å MS. [b] Without 4Å MS.

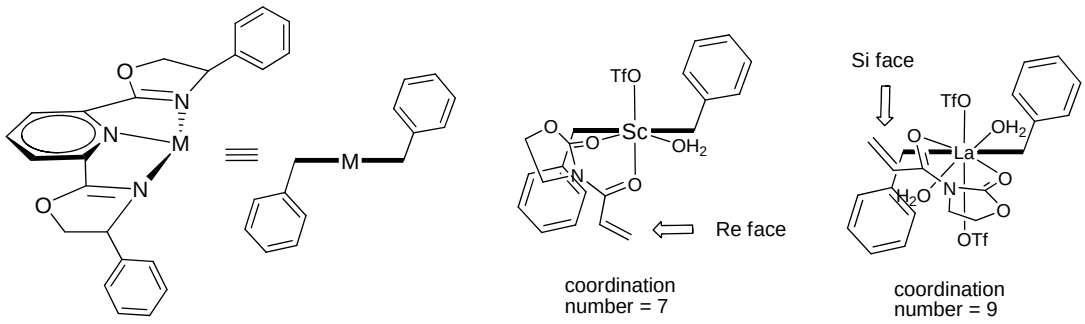
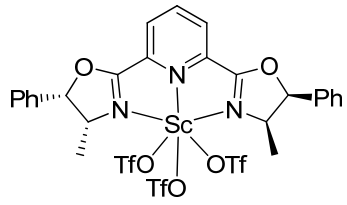
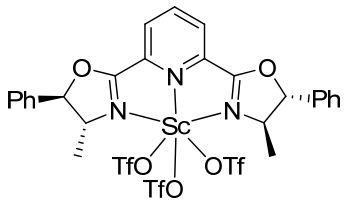


Figure 18. Proposed models to explain the change of the sense of chiral induction with different lanthanide metals.

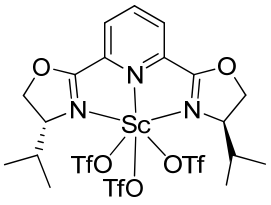
In this kind of system distal electronic and steric effects have been demonstrated. In the case of electronic effects, substitution in position 4 of the pyridine ring with electron-donating groups is detrimental, whereas substitution with electron-withdrawing groups is positive, probably due to a more electrophilic character of Sc(III) that would bind more tightly the dienophile, improving the discriminating capacity of the ligand.[29] The other distal effect is that of substitution in position 5 of the oxazoline ring (Figure 19). In principle this position is quite far from the reaction centre, but it has a decisive influence in the stereochemical course of the reaction.[30] The presence of a phenyl group in that position is able to efficiently shield the attack to the Sc-coordinated dienophile, in conjunction with a small methyl group in position 4. In fact the phenyl group in *cis* of the methyl group leads to almost the same enantioselectivity as the isopropyl group, and in *trans* reverts completely the induction sense up to almost complete enantioselection. The case with a phenyl group in position 4 is even more complex, as it depends on the metal and it also provokes important variations in the *endo/exo* selectivity. Again the presence of the second *cis* phenyl in position 5 improves the results obtained with one single phenyl, either in one induction sense (Sc) or in the opposite (Eu, La). The presence of the *trans* phenyl controls the induction sense, which is thus independent on the metal, with very high values for La and Eu. The explanation for this complicated pattern of results is not straightforward.



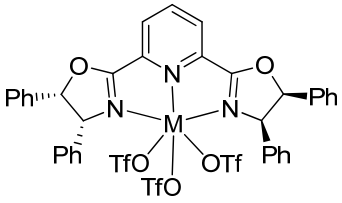
77% ee (*R*)

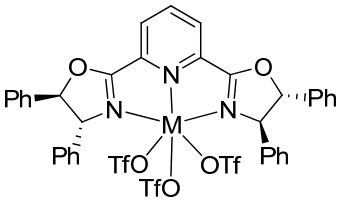


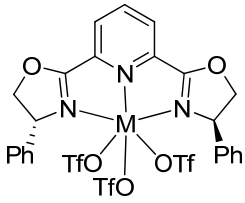
97% ee (*S*)



84% ee (*R*)







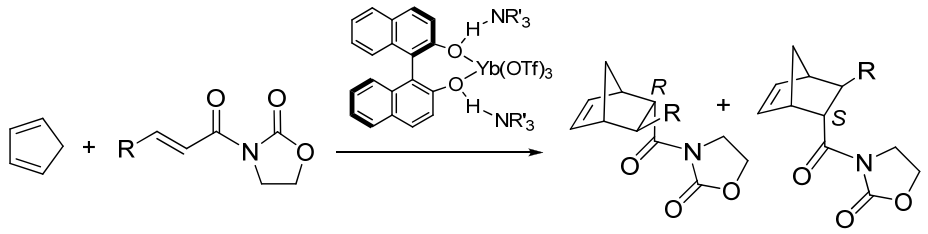
		% ee			% ee			% ee	
M	endo/exo	endo	exo	endo/exo	endo	exo	endo/exo	endo	exo
Sc	91:9	55 (*S*)	74 (*S*)	98:2	76 (*R*)	26 (*R*)	90:10	19 (*S*)	45 (*S*)
Eu	72:28	52 (*R*)	95 (*R*)	48:52	90 (*R*)	>99 (*R*)	77:23	0	50 (*R*)
La	65:35	88 (*R*)	98 (*R*)	71:29	96 (*R*)	>99 (*R*)	74:26	71 (*R*)	93 (*R*)

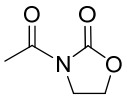
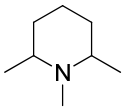
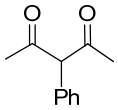
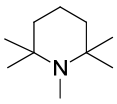
Figure 19. Variations in enantioselectivity and sense of chiral induction with different lanthanide metals and pybox ligands substituted in position 5.

In the case of lanthanides the presence of water or coordinating anions, acting as ligands, may dramatically change the stereochemical course of the reaction. The addition of other non-chiral ligands can be used to get both enantiomers using the same chiral ligand, in this case BINOL.[31] When 3-acetyl-1,3-oxazolidin-2-one is added, the 2*S endo* cycloadduct is preferentially obtained (Table 6), whereas the 2*R endo* cycloadduct is the major one when 3-phenylacetylacetone is used as additional ligand.

The existence of two binding sites due to the coordination number of Yb has been proposed as the origin of this change in enantioselection. 3-Acetyl-1,3-oxazolidin-2-one would compete with the dienophile for the site A, favoring the formation of 2*S* enantiomer, whereas 3-phenylacetylacetone would block this site, imposing the coordination of dienophile to site B, leading to the 2*R* enantiomer. However this effect is less simple than exposed here, as the amine plays an important role, probably due to the transmission of the axial chirality of BINOL to the amines, which efficiently shield one or another face of the dienophile as an effective part of the chiral pocket. In addition to this effect, the presence of 3-phenylacetylacetone introduces a non-linear effect on enantioselectivity, indicating the possible role of aggregates.

Table 6. Variation of enantioselectivity in Diels–Alder reactions with additional achiral ligands in BINOL-Yb complexes.



Added ligand	NR'_3	R	% ee
		Me	93 (2*S*)
		Ph	83 (2*S*)
		nPr	86 (2*S*)
		Me	81 (2*R*)
		Ph	83 (2*R*)
		nPr	80 (2*R*)

4.5. Chiral Relay Effects

The concept of "chiral relay" was introduced by Davies in chiral auxiliary controlled reactions.[32] This strategy is based on the use of conformationally flexible protecting groups that are inserted between the stereogenic centre and the prochiral reactive centre. Due to steric interactions with the stereogenic centre, the conformationally flexible group adopts a defined conformation that efficiently shields one face of the reactive centre. By this process the chiral information is relayed and even amplified, thus enabling an efficient control of the diastereoselectivity.

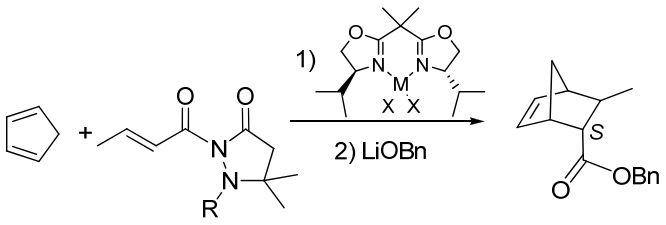
Later on several authors have used this concept in reactions catalyzed by chiral Lewis acids, in which the chiral information comes from a chiral catalyst and not from a chiral auxiliary directly bonded to one of the reagents.[33] In this strategy the chiral Lewis acid would convert an achiral template into a chiral auxiliary, so that in most cases both the chiral catalyst and the template will influence the stereochemical course of the reaction. If the template is "structured" in such a way that it matches the chiral catalyst, the result will be the amplification of the enantioselectivity. However, in a mismatched scenario,

the selectivity will be reversed in comparison to that obtained by the use of the chiral Lewis acid alone.

Two methodologies can be followed to transfer the chirality to the template. In the first one a conformationally flexible template is used, and complexation with the chiral catalyst locks the template into a chiral conformation. In the second one, complexation of an enantiotopic group generates a new stereogenic unit.

Following the first approach pyrazolidinones (Table 7) have been used to substitute the commonly employed oxazolidinones.[34] The tetrahedral N(1) atom of the template inverts rapidly, but in the presence of the chiral catalyst it preferentially exists in one of the forms, acting as a new stereogenic centre. As it is close to the reactive centre, it strongly influences the stereoselectivity of the reaction. The results show a correlation between the enantioselection and the size of the relay group (Table 7). The same effect is also shown by other Lewis acids able to adopt square planar geometry,[35] which points to a model with the Box occupying two coordination sites and with bidentate coordination of the dienophile in s-*cis* conformation.

Table 7. Chiral relay effect in enantioselective in Diels–Alder reactions with pyrazolidinone derivatives.



MX_2	R	% ee
$Cu(OTf)_2$	H	8
	Et	56
	Bn	71
	CH_2-1-Napht	92
$Cu(ClO_4)_2$	Bn	86
$Pd(ClO_4)_2$	Bn	96
$Mg(ClO_4)_2$	Bn	23
$Zn(OTf)_2$	Bn	45
$Yb(OTf)_3$	Bn	3

The proposed model (Figure 20) places the relay group shielding one face of the crotonate, reinforcing the role of one isopropyl group of the Box. The authors have not a clear explanation of the preferred positions of the fluxional substituents and they propose that when the substituent is placed on the opposite side of the dienophile, both sides are efficiently shielded and the conformation is not reactive. Thus the conformation with isopropyl and fluxional group at the same side of dienophile is more reactive and, in Curtin–Hammett conditions, directs the reaction. Moreover, the substituents in position 5 of pyrazolidinone force the conformational equilibrium of the fluxional substituent.

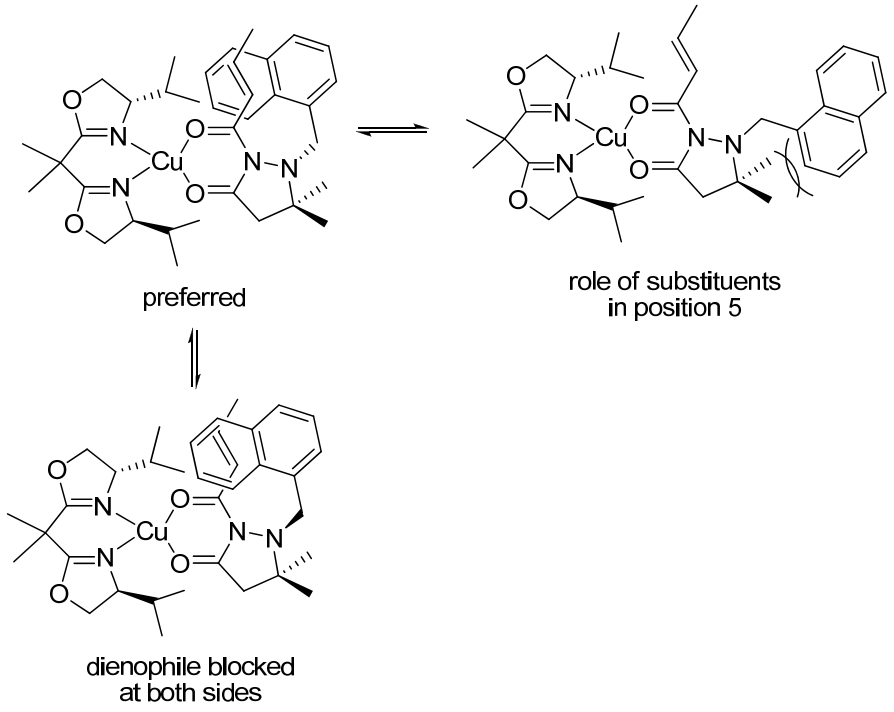
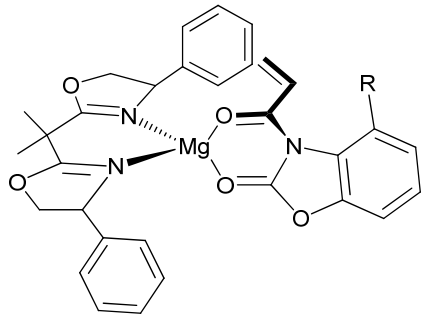


Figure 20. Proposed model for chiral relay in Diels–Alder reaction of pyrazolidinone derivatives catalyzed by Box-Cu complexes.

Another example uses 4-substituted 1,3-benzoxazol-2(3*H*)-ones as templates.[36] Under chelate control with a chiral Lewis acid, the acryloyl group cannot be coplanar with the aromatic ring but strongly twisted, generating two possible diastereomeric conformers that differ in the absolute configuration of the chirality axis in the template (Figure 21). The bulkiness of R modifies the twisting angle, which seems to be optimal around 45º. As observed in other cases, the anion and the hydration degree of the Mg salt affect the results by changing the coordination from tetrahedral to octahedral, obtaining even a

reversal in the enantioselectivity from 70% ee (*R*) for R=H to 88% ee (*S*) for R=Bn, making even more difficult the rationalization of the results.



Calculated (AM1) angles

R	ϕ	% ee
H	14º	14
Me	43º	74
Et	47º	76
Bn	46º	86
$CHPh_2$	59º	72
$SiMe_3$	59º	40

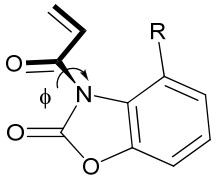
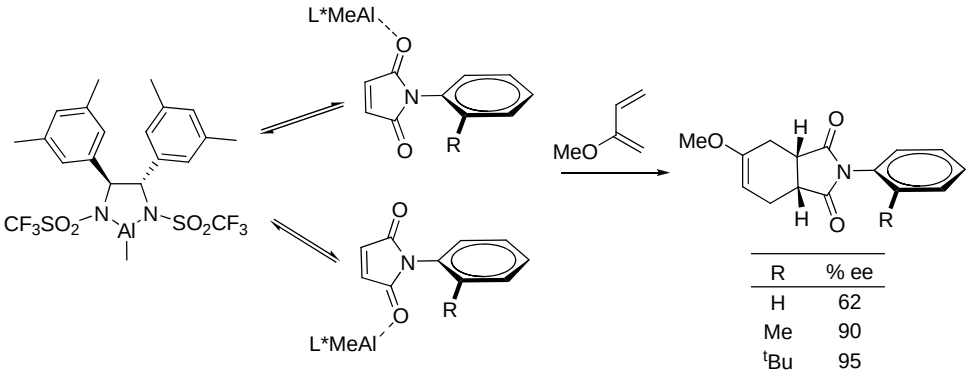


Figure 21. Proposed model for chiral relay effect with 4-substituted 1,3-benzoxazol-2(3*H*)-ones.

In the second strategy, a new stereogenic centre is generated by complexation of an enantiotopic group. A first example is the Diels–Alder reaction of *ortho*-substituted N-arylmaleimides (Figure 22).[37] Both carbonyl groups of maleimide are enantiotopic, and complexation with a chiral Lewis acid produces two diastereomeric complexes. Increasing the size in the *ortho* position has a very positive effect on enantioselectivity, that can be envisaged as a cumulative effect of ligand control and chiral relay.



R	% ee
H	62
Me	90
^tBu	95

Figure 22. Generation of a new stereogenic center by complexation of an enantiotopic group.

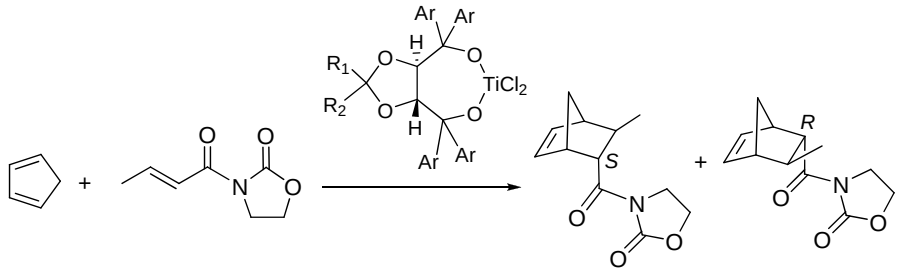
4.6. Subtle Changes in TADDOLate Geometry: Substitution and Immobilization

TADDOLs (α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols) and their derivatives constitute one of the most successful families of chiral ligands that, coordinated to a large variety of metals, has produced excellent results in many different enantioselective reactions in which they have been used as chiral catalysts.[38] In particular Ti-TADDOLates have acted as efficient chiral Lewis

acids in Diels–Alder reactions. As in many of the other examples, 3-enoyl-1,3-oxazolidin-2-ones were identified as suitable dienophiles, able to form intermediate chelate complexes.

The comparison of several TADDOLs in the Diels–Alder reaction between cyclopentadiene and (E)-3-butenoyl-1,3-oxazolidin-2-one (Table 8, entries 1-6) showed that enantioselectivity depends not only on the nature of the aromatic substituents, whose influence was expected due to the role in the construction of the chiral pocket, but also on the nature of the distal substituents R_1 and R_2.[39] The effect is significant in case of comparing phenyl and 2-naphthyl aromatic groups, but it is really dramatic in the case of 1-naphthyl group, given that 2*R endo* cycloadduct is obtained as major product in contrast with 2*S* obtained with the other ligands.

Table 8. Effect of TADDOL substituents on the enantiomeric ratio of Diels–Alder reaction.



Entry	R_1	R_2	Ar	2*S*/2*R*
1	Me	Me	Ph	72:28
2	Me	Me	2-Napht	94:6
3	Ph	Me	Ph	94:6
4	Ph	Me	2-Napht	71:29
5	Ph	H	Ph	69:31
6	Ph	Ph	Ph	90:10
7	3-(P1)O-C_6H_4-[a]	H	3,5-diMePh	38:62
8	3-(P2)O-C_6H_4-[b]	H	3,5-diMePh	59:41
9	3-BnO-C_6H_4-	H	3,5-diMePh	31:69
10	3-BnO-C_6H_4-	H	Ph	67:33
11	Ph	H	3,5-diMePh	31:69
12	Ph	Me	3,5-diMePh	38:62
13	Ph	Ph	3,5-diMePh	50:50
14	Me	Me	3,5-diMePh	91:9
15	Ph	Ph	Ph	90:10

16	Me	Me	Ph	72:28

[a] P1 = Merrifield resin (1% cross-linking). [b] P2 = Monolithic polymer obtained by copolymerization of TADDOL monomer (R_1 = 3-(4-vinylbenzyloxy)phenyl) and divinylbenzene (monomer/DVB ratio = 40:60).

An even deeper influence of the dioxolane substitution was found in studies devoted to the immobilization of TADDOLs by covalent bonding to polymers.[40] TADDOLs bearing 3,5-dimethylphenyl aromatic groups (Table 8, entries 7-9, 11-14) lead cycloadduct *endo* 2*R* as the major enantiomer when only one of the substituents of the dioxolane ring is an aromatic group, including the case of TADDOL grafted to a Merrifield resin (P1 support). The reaction is not enantioselective when both substituents in the dioxolane ring are aromatic and the presence of two methyl groups produces a reversal in the enantioselection, leading to *endo* 2*S* cycloadduct. This influence is particular for 3,5-dimethylphenyl groups and it has not been detected for other aromatic groups. The existence of some kind of interaction between 3,5-dimethylphenyl groups and the aromatic substituent of the dioxolane ring was made evident by the comparison between the effect of a flexible (P1) and a rigid monolithic (P2) polymeric support. Other flexible TADDOL-containing polymers do not show any similar reversal effect on the enantioselection. In those cases the polymerization position plays a crucial role on enantioselectivity, and very low values were obtained when the polymer was linked to two aromatic groups of the α,α' positions.[41]

The explanation for these results is not straightforward. From X-ray structures of several TADDOL ligands, the existence of an intramolecular H-bond in the most stable conformers has been considered as a good model for the Ti-chelate complexes as the H-bond falls nearly along the C_2 axis, in the same position occupied by Ti in the complex (Figure 23). The substitution at the ketal carbon must influence the conformation around the C-aryl bond, modifying in a subtle way the chiral pocket around the metal position. The dramatic change in enantioselectivity from phenyl or 2-naphthyl aromatic groups to 1-naphthyl groups can be also explained by the difference in disposition of the fused aromatic ring following the same model (Figure 23). Whereas in 2-naphthyl the second fused aromatic ring is placed far from the catalytic center, in 1-naphthyl

the fused ring extends forward in the quasi-equatorial position but back in the quasi-axial position, producing a strong difference in shielding properties of both aromatic groups.

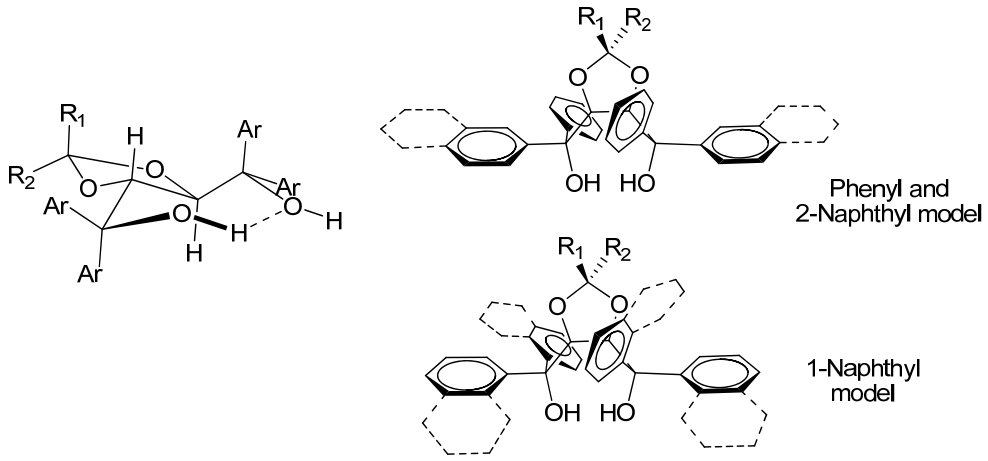


Figure 23. Models based on TADDOL conformations to explain the effect of α-aryl substituents.

The dramatic variations in enantioselectivity, produced by slight changes in the ligand structure, show that the mechanism determining the stereochemical outcome of the reaction is not simple. In fact, under Curtin–Hammett conditions, selectivity depends on the energy differences between the transition states leading to the different products. Better explanations should be obtained by considering the catalyst-dienophile intermediate complexes and several studies have been devoted to this point, with some controversial degree.

The coordination of the commonly used dienophiles can lead to five diastereomeric complexes and X-ray and NMR studies of different TADDOLate-$TiCl_2$-dienophile complexes[42,43] have shown that the complex bearing the two chlorine atoms in relative *trans* position (species A in Figure 24) is the most abundant, and hence the most stable. The main controversy comes from the relative reactivity of these intermediates. In fact in a Curtin–Hammett scenario it is the most reactive intermediate and not the most stable which determines the stereochemical result of the reaction. Whereas some authors proposed also a higher reactivity of species A, theoretical calculations seemed to indicate a higher degree of Lewis acid activation in the case of intermediates B.[44]

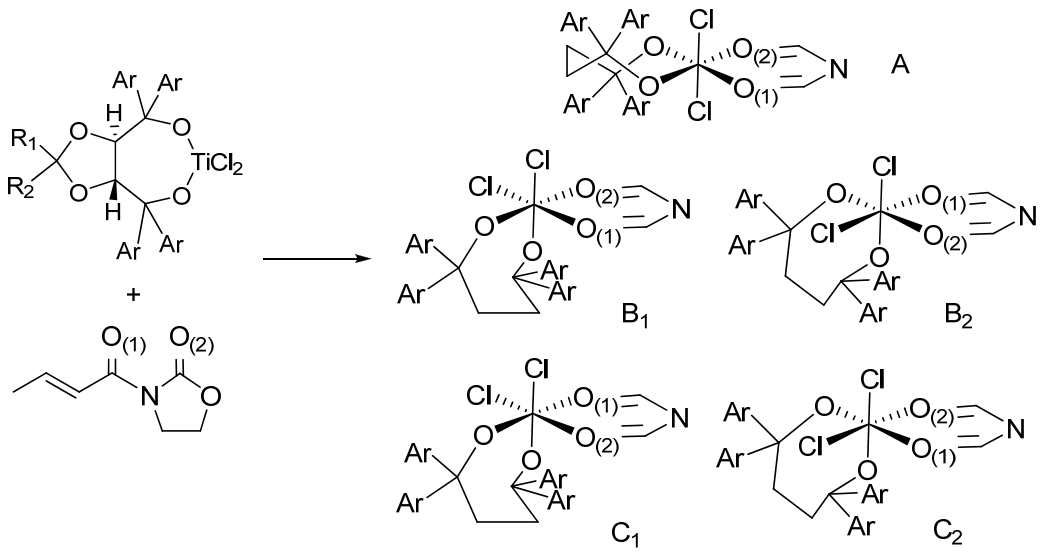


Figure 24. Possible TADDOL-Ti-dienophile intermediate complexes.

With regard to enantioselectivity, the hypothesis favoring intermediate A was not able to explain the experimental results, both the high enantioselectivity obtained in some cases and the variations in the sense of asymmetric induction with TADDOLs bearing 3,5-dimethylphenyl substituents. Molecular mechanics and molecular dynamic calculations, using the MM2 force field,[42b] showed that relative energies of B_1 and B_2 intermediates (Figure 24) are determined by the substitution pattern of dioxolane ring for those TADDOLs bearing 3,5-dimethylphenyl substituents. As both intermediates show shielding of a different face of the C=C double bond, they lead to different cycloadducts, and the energy changes may be the origin of the enantioselectivity changes experimentally observed. Differences in the substitution of the dioxolane ring provoke energy differences in good qualitative agreement with the experimental results (Table 8), and the existence of π-stacking interaction between one of the 3,5-dimethylphenyl groups and a phenyl group in the dioxolane ring has been proposed as the responsible for the energy approach between B_1 and B_2 given that this interaction would be present in both intermediates (Figure 25).

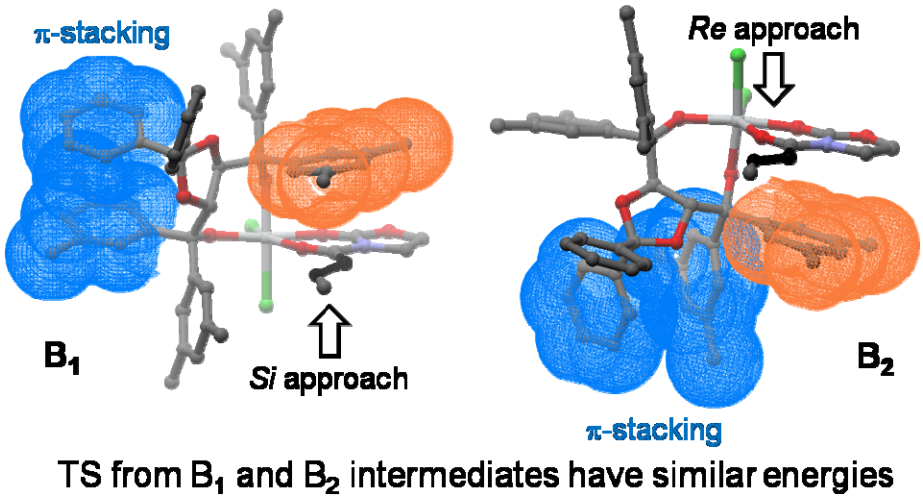


Figure 25. Effect of a possible π-staking in the TADDOL-Ti catalyzed Diels-Alder.

It is clear that the exact mechanism of this reaction is still controversial and more complicated than expected. It is possible that the relative reactivity of the different intermediates changes from one to another TADDOL ligand. In fact the subtle conformational changes and the existence of interactions between the different groups may modify the relative energy of the different diastereomeric transition states.

5. Case of study (3): Salen-Based Catalysts.

5.1. The Structural Variations of Salen Ligands and Complexes

Salen stands for bis(salicylidene)ethylenediamine, whose chiral derivatives have been used as ligands for a large variety of metal complexes able to catalyze different enantioselective reactions. These ligands and their complexes present an ample array of possible structural variations (Figure 26). Salicylidene moiety can be substituted in different positions, although the most usually are C3 and C5 ones (R_3 and R_5 respectively in Figure 26). In most cases those substituents are bulky ones, and even R_3 may contain a stereogenic element, either a carbon atom or an axis. The main (and mostly the only) chirality source of the ligand is the diamine moiety, that generally presents a C_2 symmetry axis (R=R'), and this symmetry is extended to the whole chiral ligand when R_3=R_3' and R_5=R_5'. Once the complex is formed, other elements such as

the anion and its coordinating ability, or the presence of additional chiral or achiral ligands (L in Figure 26) are factors that may influence significantly the diastereo- and enantioselectivity obtained in the catalytic reaction. Salen complexes of Mn, Ru, V, Ti, Al, Co, Cr, Cu, Zn or Zr have been described as catalysts for reactions such as epoxidation, aziridination, epoxide ring opening, cyclopropanation, sulfoxidation, hetero-Diels-Alder, sulfimidation, conjugate addition, Baeyer-Villiger, etc.[45] In this section we will analyze only two significant cases: epoxidation and cyclopropanation.

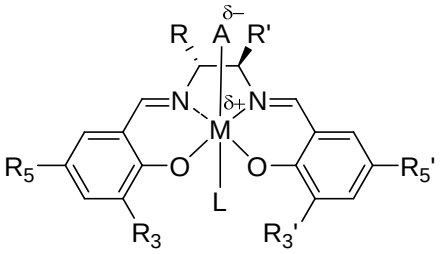


Figure 26. General structure of salen-metal complexes.

5.2. Effects of the Structural Variations in Epoxidation Reactions Catalyzed by Salen-Mn Complexes

Chiral salen-Mn complexes were described as catalysts for enantioselective epoxidation reactions in the early 90s,[46] but the mechanism for this reaction is still under debate and the contribution of each structural parameter is not fully understood.

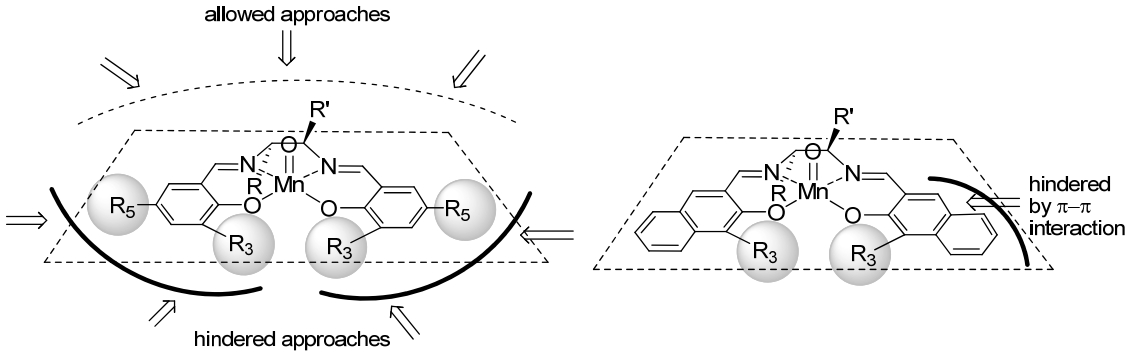


Figure 27. Proposed role of the different substituents in the approach restrictions to salen-Mn catalysts.

Which seems clear is that the intermediate is a Mn^{V}=O species, and alkene must approach to the oxo group. The main role of the R_3 and R_5 groups is

to hinder the approach of the alkene through a number of possible trajectories, allowing only the approach by the zone under the influence of the stereogenic centers of the chiral diamine (Figure 27). The approach of the alkene parallel to the main plain of the complex also explains the strong preference of this catalytic system for *cis*-alkenes, able to place both substituents far away from the complex, minimizing in this way the steric interaction. Moreover, the best results are obtained in the epoxidation of alkenes conjugated with aryl groups. This fact has been explained by a possible π–π repulsion of the approaching alkene and the aromatic rings of the salicylidene moieties. In fact, this repulsion can be increased by extending the aromatic system with naphthyl groups (Figure 27), which led to better results.[47]

However, this scheme showed to be too simplistic, as some features of the reactions remained unexplained. In fact, the complex can adopt different conformations depending on that of the ethylenediamine-metal five-member chelate, either half-chair or envelope, leading to the so-called stepped and umbrella conformations (Figure 28).[48] The two stepped conformations become diastereomeric by the presence of stereogenic centres in the ethylenediamine moiety and several experimental results seem to indicate the preference for the stepped conformation that places the two substituents in pseudo-equatorial positions.

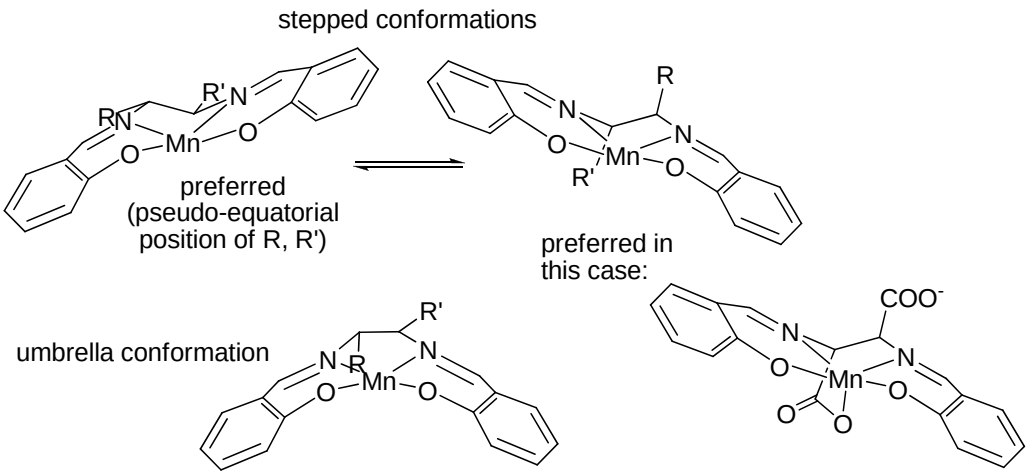


Figure 28. Stepped and umbrella conformations of salen-Mn complexes.

It is also remarkable the reversal of enantioselectivity obtained when the R substituent of the diamine moiety is a carboxylate group, able to coordinate to

Mn, forcing in this way the stepped conformation with the R groups in the pseudo-axial position (Figure 28). Moreover the preference for one of the two stepped conformations may not be due to salen substituents. The use of a chiral axial ligand would produce the same type of diastereodifferentiation, with a preference for one of the two conformers. Such effect was confirmed by the moderate enantioselectivity (73% ee) obtained in epoxidation using achiral salen ligand with bulky R_3 and R_5 substituents (*tert*-butyl) and enantiopure sparteine as axial ligand. In fact, the donor character of the axial ligands and/or anion seems to be responsible for the distortion degree in the preferred conformations, as shown by the recent studies in model compounds,[49] and hence for the observed differences in enantioselectivity.

The general picture of the selectivity control is even more complicated than exposed until now due to several additional factors. In some cases a dependence of enantioselectivity on the nature of the hypervalent iodine oxidant (PhIO, C_6F_5IO, MesIO) has been observed.[50] The only possible explanation for this fact is the participation of a new oxidizing species based on coordination of the oxidant to salen-Mn, acting in this case as a Lewis acid without oxygen transfer (Figure 29).

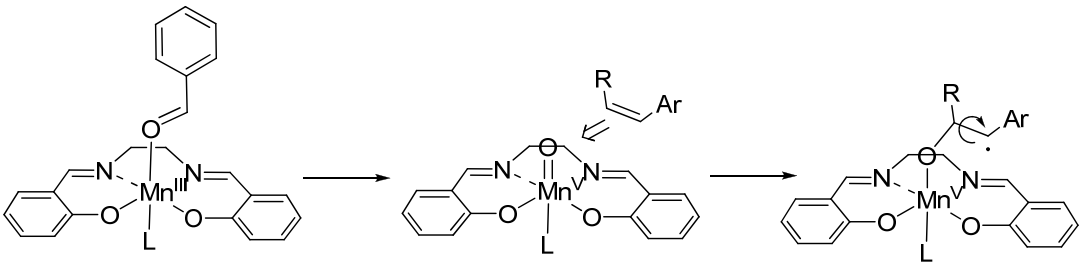


Figure 29. Possible intermediates in the epoxidation reaction catalyzed by salen-Mn complexes.

The existence of this new oxidation pathway is highly dependent on the nature of the donor ligand (L) and the oxidant. Moreover, the classical reaction pathway involves the formation of a radical upon addition of Mn=O to the alkene (Figure 29), with free rotation around the single C-C bond. This explains the observed yield of *trans*-epoxide from *cis*-alkene, but the variable amounts of *trans*-epoxide with metal (Cr > Mn), anion, oxidant, temperature, and donor ligand are more difficult to explain. In fact, the proper choice of all those

parameters allowed obtaining high yields and enantioselectivities of *trans*-epoxides from *cis*-alkenes with salen-Cr complexes and triphenylphosphine oxide as donor ligand.[51]

5.3. Control of the Sense of Asymmetric Induction in Salen-Ru Complexes

Probably the most dramatic effect on enantioselectivity observed with salen-metal complexes is the reversal of induction sense in the case of Ru-catalyzed cyclopropanation. Salen-Co(III) complexes had shown high efficiency in enantioselective cyclopropanation when R_3 substituents were absent. However, the use of Ru instead of Co allowed the presence of bulky R_3 substituents with dramatic influence in the final results. A salen ligand derived from binaphthyl units (Figure 30) led to the best results of enantioselectivity, with an important match-mismatch effect in the two sources of chirality, the cyclohexanediamine and the binaphthyl units. The use of (*R*)-binaphthyl and (*S*)-diamine led to low *trans*-preference in the cyclopropanation of styrene with *tert*-butyl diazoacetate and 51% ee in the *trans* isomers. On the contrary, the combination of (*R*)-binaphthyl and (*R*)-diamine led to a high *cis*-preference, not usual with most of homogeneous catalysts, and up to 89% ee in the *cis* isomers.[52] These results in the absence of solvent were even improved by the use of THF, with 96:4 *cis*/*trans* selectivity and 99% ee in the *cis* isomers. Regarding the mechanism for the high *cis* preference and the high enantioselectivity, a mechanism has been proposed using an analogous PNNP ligand (Figure 30b).[53] The key point for the high *cis* preference is the conformation of the Ru-carbene intermediate, that places the H in the hindered zone of the chiral ligand, and styrene approaches with its phenyl group also far from that zone (Figure 30c). The presence of the cyclohexanediamine moiety is the main responsible for the energy difference between the two *cis* transition states (>7 kcal/mol), in agreement with the very high enantioselectivity.

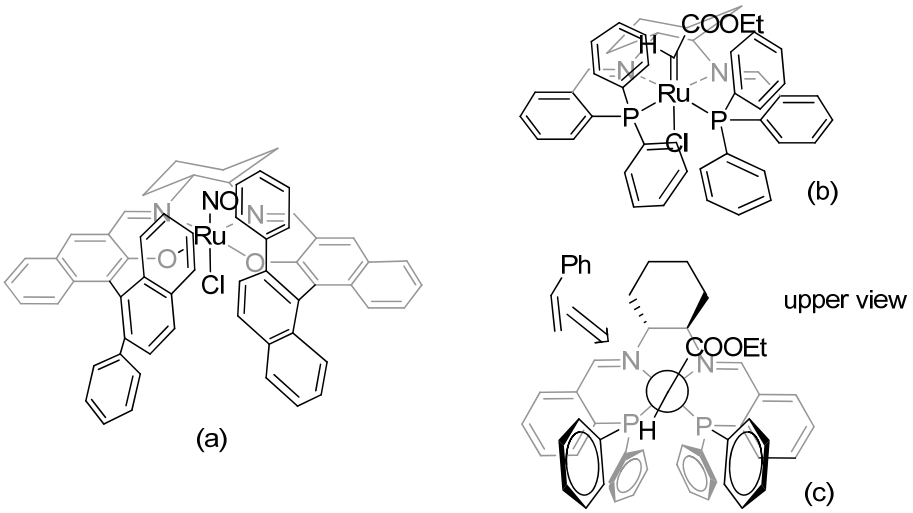


Figure 30. Proposed models for *cis* selectivity in salen-Ru catalyzed cyclopropanation.

With the salen-Ru complex a complete reversal of enantioselectivity was observed when solvents such as THF or ethyl acetate were changed by diisopropyl ether or hexane, obtaining up to 83% ee of the *cis* isomer with opposite absolute configuration. The proposed explanation for this dramatic solvent effect was the poor solubility of the complex in the latter type of solvents. The true catalyst was in such case aggregates, whereas in THF the complete solution of the complex led to monomeric species. A similar effect was observed in the case of using less hindered salen and some donor ligands (Figure 31). The use of triphenylphosphine as donor ligand leads, in the case of a salen ligand with withdrawing nitro groups, to a reversal in the enantioselectivity. The proposed mechanism is the formation of the Ru-carbene intermediate by breakage of a N–Ru bond, instead of the usual Ru–L proposed for the rest of salen and donor ligands.

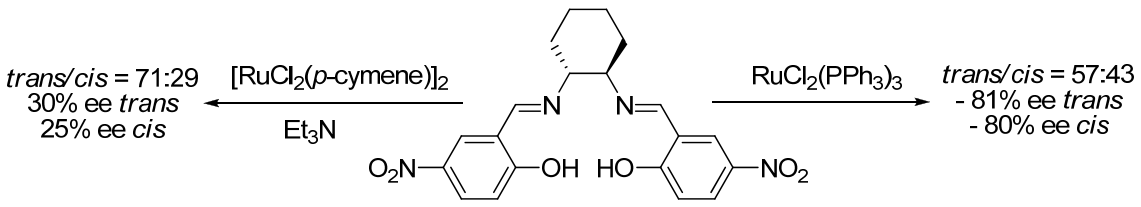


Figure 31. Reversal of enantioselectivity with the Ru precursor.

6. Case of study (4): Multifunctional Catalysis.

6.1. Cooperative Effects

Some enantioselective catalytic reactions require the simultaneous activation of the two partners involved, generally speaking a nucleophile and an electrophile, in a phenomenon known as cooperative effect. The activation of only one reagent is not enough to produce the reaction in high yield, and usually enantioselectivity is also very low. Enzymes play the same role with the presence of several catalytic centers (Brønsted and Lewis acids and bases) that simultaneously participate in the catalytic process. Apart from catalysts using some organic functionality, either acid or base, as one of the cooperative centers, in the case of processes requiring two metal centers, four types of catalytic systems can be considered (Figure 32): homo- or heterobimetallic catalysis in an inter- or intramolecular way. A chiral environment around both metals seems to be crucial to obtain high enantioselectivities, probably by the need of a strict control on the geometry of the transition state, in theory better controlled in case of intramolecular systems by the link between both metals or complexes. Homobimetallic systems present the limitation of the same metal having to activate both reagents, although this limitation is less important in case of intramolecular systems, as the electronic and steric environment of both metals can be different enough to selectively activate one or another reagent.

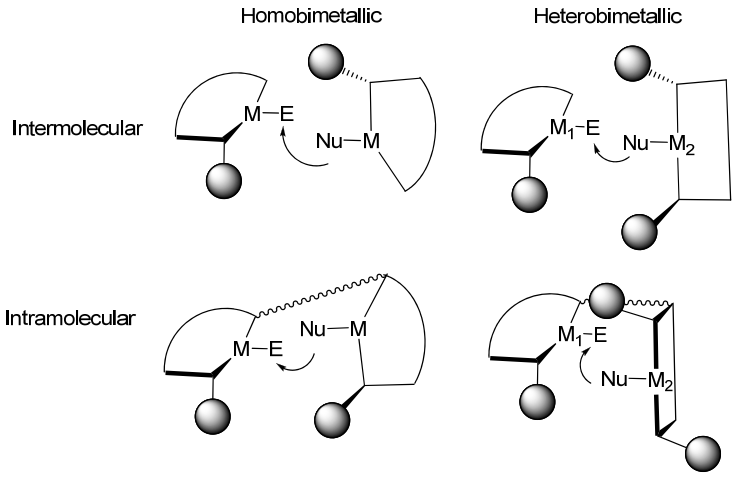


Figure 32. Types of catalytic systems with cooperative effects.

6.2. Intermolecular homobimetallic catalysis

Different salen-metal complexes have shown cooperative effects in several enantioselective reactions. One example is salen-Cr as catalyst for the enantioselective opening (desymmetrization) of *meso*-epoxides with azide (Figure 33).[54] The same complex is able to coordinate both azide and epoxide, but kinetic evidences point to an intermolecular transfer of azide to coordinated epoxide (Figure 33).

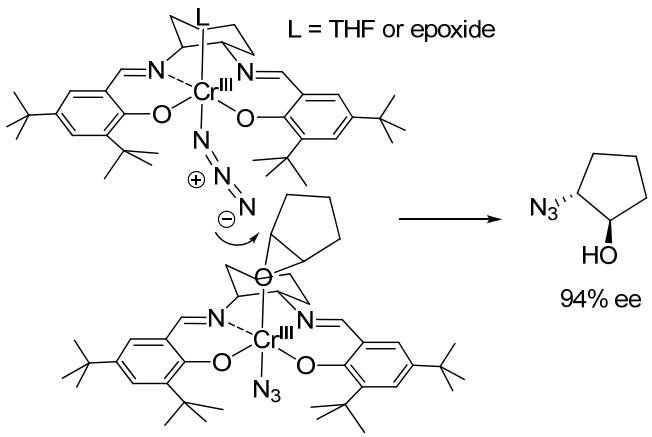


Figure 33. Proposed mechanism of intermolecular desymmetrization of meso-epoxides.

A similar case has been described for the conjugate addition of cyanide to α,β-unsaturated imides catalyzed by salen-Al complexes.[55] In this case spectroscopic evidences show the formation of two different species in solution, probably salen-Al-CN and salen-Al-imidate (Figure 34). The second order dependence of reaction rate on catalyst concentration indicates the existence of a cooperative homobimetallic intermolecular mechanism, although this double coordination requires a large amount of catalyst.

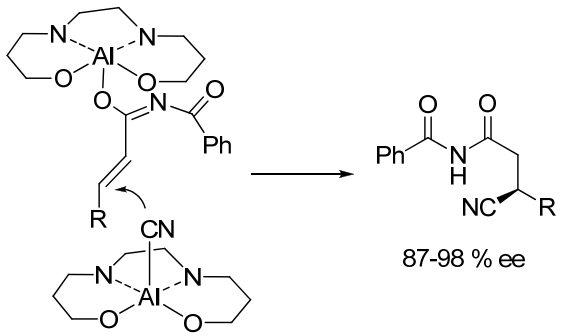


Figure 34. Homobimetallic intermolecular mechanism of conjugate addition of cyanide.

6.3. Intermolecular heterobimetallic catalysis

The same metal may not be the best to activate both nucleophile and electrophile. This is the case of the above-mentioned conjugate addition of cyanide to α,β-unsaturated imides, given that aluminum catalysts are not the optimum for cyanide activation. The same authors demonstrated that the combination of salen-Al complex with a pybox-$ErCl_3$ complex was able to efficiently catalyze the same reaction (Figure 35) with much lower amount of catalysts (2% salen-Al and 3% pybox-Er instead of 10% or even 15% salen-Al),[56] due to the specialization of each type of complex, in this case the ability of lanthanide complexes to activate cyanide. Activation of imide was proven to be also necessary by the almost no conversion obtained with pybox-Er alone. Both catalysts are involved in the transition state, and match in the chirality of both catalysts is necessary in order to obtain high enantioselectivity. In fact, with both (*S*) catalysts 96% ee was obtained (R = nPr), whereas enantioselectivity was reduced if (*R*)-pybox (72% ee) or a non-chiral analogous (84% ee) were used. The same effect was observed if a non-chiral salen ligand was used in combination with the enantiopure pybox (78% ee).

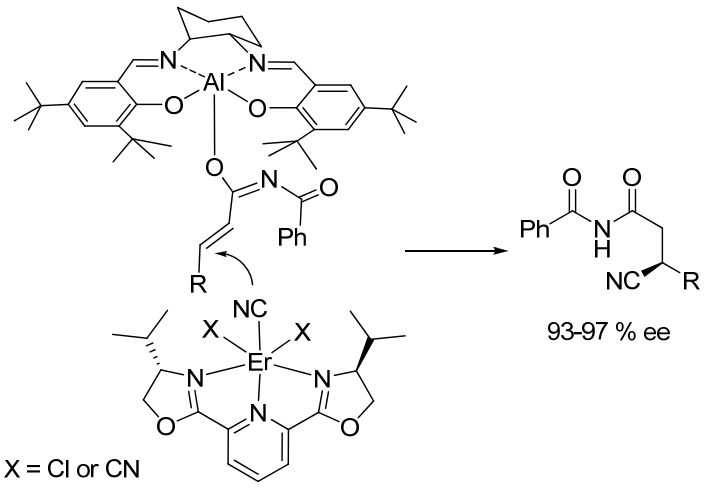


Figure 35. Heterobimetallic intermolecular mechanism of conjugate addition of cyanide.

6.4. Intramolecular homobimetallic catalysis

Shibasaki and his group are probably the authors that have explored most widely the intramolecular bimetallic catalytic systems.[57] In the case of homobimetallic systems, the same metal has to play two different roles in the

activation of both reaction partners. Several examples of this type of systems have been described with linked-BINOL ligands (Figure 36). In this way the ligand has up to 5 coordination centers able to form bimetallic complexes. When one mol of this ligand was made react with 2 mol of Et_2Zn, an oligomeric species was formed in which one phenol group of each ligand remained free and the oxygen of the linker played an important role in the coordination of Zn (Figure 36).[58]

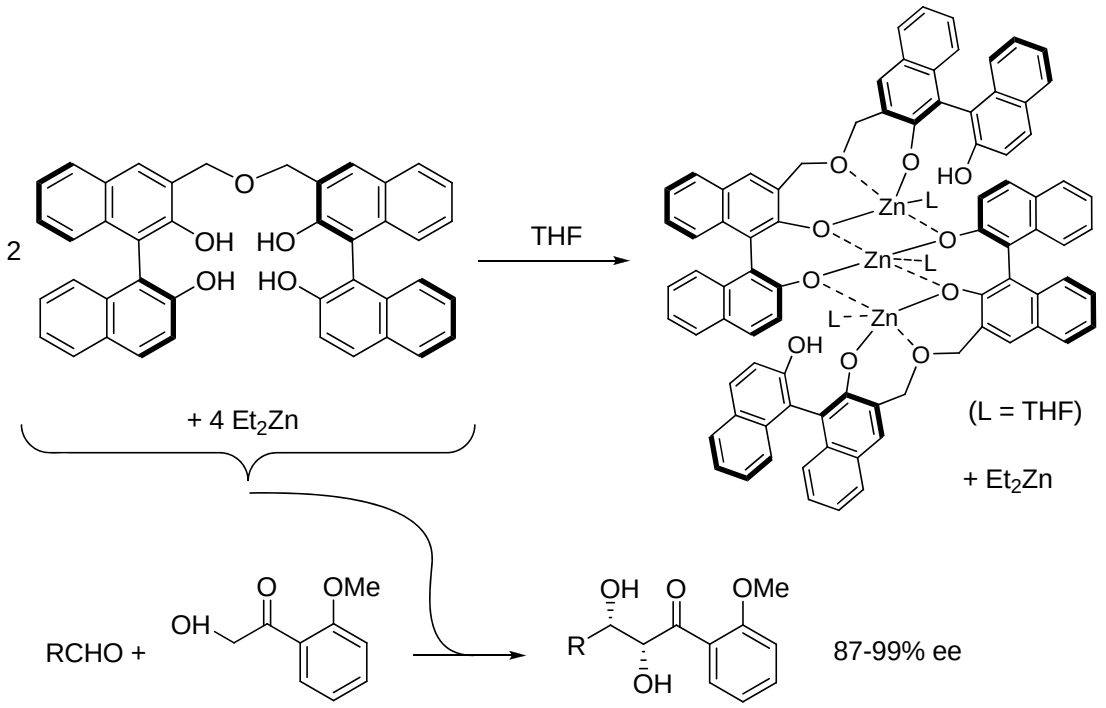


Figure 36. Structure of the major (linked-BINOL)$_2$Zn$_3$(THF)$_3$ species in solution and catalytic enantioselective aldol reaction.

However, when this system was used as catalyst in the aldol reaction between an aldehyde and the α-hydroxyketone shown in Figure 36, the true intermediate of the reaction was more complicated, as shown by CSI-MS (cold spray ionization mass spectrometry), formed by Zn, linked-BINOL and hydroxyketone in 7:3:4 ratio. The key parameters seem to be the control of the relative position of the Zn atoms to carry out the cooperative effect, demonstrated by the poor results obtained with BINOL, the participation of the linker oxygen in the coordination of Zn, as the linker without heteroatom also gave poor results, the hydroxyl in α position of the substrate that stabilizes the

enolate, and finally the presence of the *ortho*-methoxy group that helps to fix the relative position of the enolate to the intermediate complex (Figure 37).

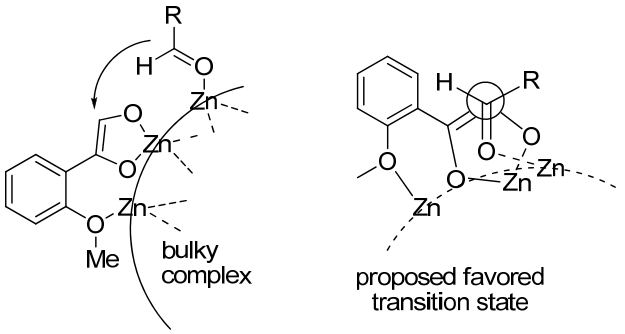


Figure 37. Proposed role of the multicenter Zn homometallic catalyst.

Homomultimetallic complexes of Zn, Y, In, and La have been used in reactions with other nucleophiles, such as α,β-unsaturated carbonyl compounds (Michael reactions), N-diphenylphosphinoyl-imines or N-tosyl-imines (Mannich reactions), and other electrophiles, such as N-(2-hydroxyacetyl)pyrrole or dialkyl malonate.

One general conclusion from these results was the possibility of getting good results with simpler modified BINOL ligands without C_2-symmetry. In fact the systematic study of several modified BINOLs showed that the only requirements were the presence of a second aromatic groups linked to BINOL by a linker with a heteroatom, the functionalization of this second aromatic group with an additional phenol in position 2', and the presence of a substituent in position 3' (Figure 38). The axial chirality in this second group and the presence of a fourth phenol are not necessary.

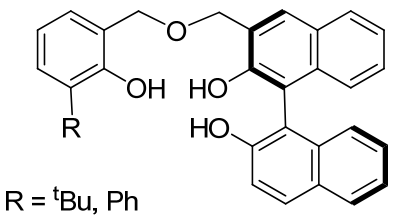


Figure 38. Minimum structure required to obtain high enantioselectivity with linked-BINOL ligands.

6.5. Intramolecular heterobimetallic catalysis

In the case of heterobimetallic systems, the relative position of both metals has to be controlled by the correct design of the chiral ligand with the

suitable coordination centers. As an example, nitro-Mannich reactions have been catalyzed by Cu-Sm bimetallic complexes (Figure 39).[57] The control of the relative positions of both metals was carried out with a hexadentate ligand, able to form trimeric complexes in the presence of $Cu(OAc)_2$ and $Sm(O^iPr)_3$, using one μ-isopropoxy and one μ-oxo ligands (Figure 39). However the active species is a monomeric complex formed by reaction with 4-*tert*-butylphenol (Figure 39). Formation a Sm-nitronate by deprotonation of the nitro compound and coordination of Boc group to Cu bring both partners together in a suitable position to react with 83-98% ee depending on R'. The same ligand is able to form bimetallic complexes with other metals, expanding in this way the applicability of this kind of system. As an example, recently the Pd-La complex was described to be optimum to catalyze nitro-aldol reactions between aldehydes and nitro compounds.[59]

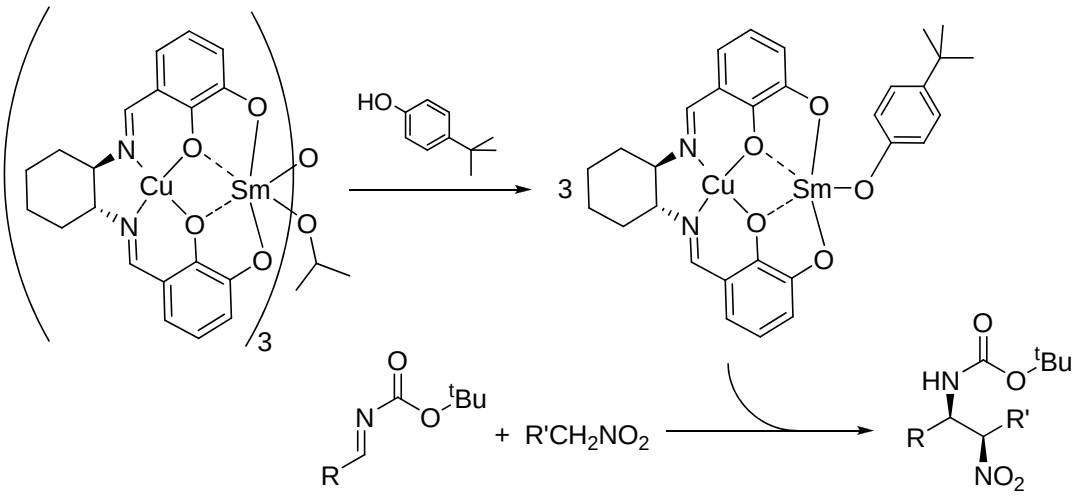


Figure 39. Trimeric structure of Cu-Sm bimetallic system, formation of the monomeric catalytic species and enantioselective nitro-Mannich reaction.

In the previous examples one of the roles played by the catalysts is that of base, able to deprotonate one partner, whereas one of the metals coordinates efficiently the formed enolate and the other one acts as a Lewis acid. However, in other cases both metals can play the role of Lewis acid and in such case the choice of metals is really important. An example is the *aza*-Michael addition of methoxyamine to enones (Figure 40). A rare-earth metal, Y in this case, is used to coordinate the enone, whereas methoxyamine is coordinated through an alkaline metal, Li in this case, with BINOL as a chiral ligand. Complexes

include Y, Li and ligand in a 1:3:3 ratio (Figure 40), the cooperative effect is demonstrated by the lack of efficiency of Y-BINOL and Li-BINOL systems, and the poor performance of the Y-K-BINOL system shows the specificity of the Y-Li pair for this reaction. The simultaneous coordination of methoxyamine to Li and enone to Y brings both reagents together in a suitable fashion to react with high efficiency and enantioselectivity.

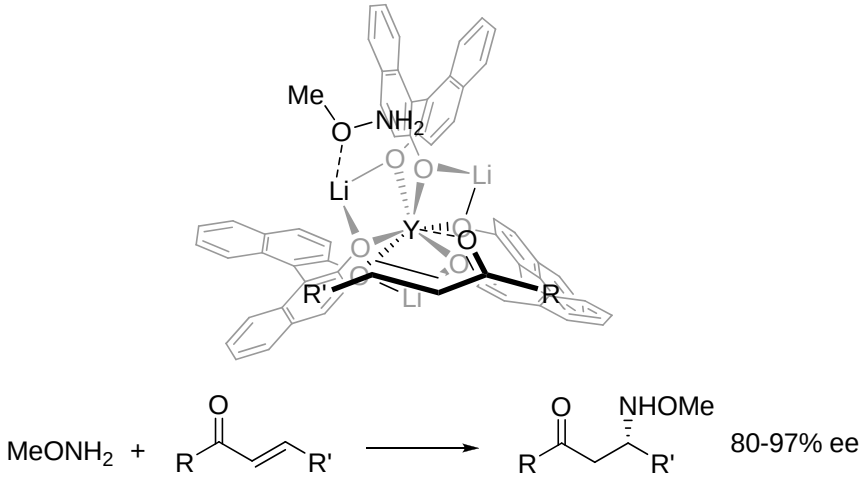


Figure 40. Y-Li-BINOL system and enantioselective *aza*-Michael addition.

7. Conclusions

Chiral catalysis is the tool selected by nature to transfer chirality and the process is as complex as nature itself. Given the small energy differences involved in enantioselectivity, a couple kcal mol^{-1} often makes all the difference between success and failure, subtle factors have a decisive influence. In the nanoenvironment of a chiral catalyst there are many elements that can influence decisively the stereochemical course of a reaction. Some of them, such as close substituents, counterions, auxiliary ligands or solvent molecules, can be in the immediate neighborhood of the catalytic center (usually a metal), and its influence is easier to ascertain, at least in principle. Other elements, such as remote substituents, support, or even other co-catalytic species are usually located farther apart from the catalytic center, but they can still exert a strong influence by inducing conformational changes and, in general by determining preferential reaction channels. In that regard asymmetric catalysis should be considered as a nanometric phenomenon in which all the actors taking part in the reaction are important.

Deep knowledge on the mechanism of the stereodifferentiation in a catalytic process is rather unusual, but in those cases where a good knowledge of the steric requirements of the chiral pocket is achieved, either through mechanistic studies or by trial-error experiments, this knowledge can be effectively used to design new ligands taking advantage of the different nanoenvironmental factors, to improve the catalytic results.

References

[1] a) Catalytic Asymmetric Synthesis, I. Ojima Ed., Wiley-VCH, New York, 2000. b) R. Noyori, Asymmetric Catalysis in Organic Synthesis, Wiley-Interscience, New York, 1994. c) Comprehensive Asymmetric Catalysis, E. N. Jacobsen, A. Pfaltz, H. Yamamoto Eds., Springer, Berlin, 1999.

[2] a) R. G. Salomon, J. K. Kochi, J. Am. Chem. Soc. 1973, 95, 3300. b) M. Díaz-Requejo, T. R. Belderrain, M. C. Nicasio, F. Prieto, P. J. Pérez, Organometallics 1999, 18, 2601.

[3] Only one Cu-carbene complex has been isolated and characterized by X-ray diffraction analysis: X. Dai, T. H. Warren, J. Am. Chem. Soc. 2004, 126, 10085.

[4] J. M. Fraile, J. I. García, V. Martínez-Merino, J. A. Mayoral, L. Salvatella, J. Am. Chem. Soc. 2001, 123, 7616.

[5] T. Rasmussen, J. F. Jensen, N. Èstergaard, D. Tanner, T. Ziegler, P.-O. Norrby, Chem. Eur. J. 2002, 8, 177.

[6] J. I. García, G. Jiménez-Osés, V. Martínez-Merino, J. A. Mayoral, E. Pires, I. Villalba, Chem. Eur. J. 2007, 13, 4064.

[7] Aratani's catalysts, industrially used in the production of chrisantemic acid derivatives: T. Aratani, Pure Appl. Chem. 1985, 57, 1839.

[8] O. Reiser, Angew. Chem. Int. Ed. 1993, *32*, 547.

[9] A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, C. I. Herrerías, G. Legarreta, V. Martínez-Merino, J. A. Mayoral, J. Mol. Catal. A 2003, 196, 101.

[10] M. P. A. Lyle, N. D. Draper, P. D. Wilson, Org. Biol. Chem. 2006, 4, 877.

[11] H. Nishiyama, N. Soeda, T. Naito, Y. Motoyama, Tetrahedron:Asymmetry 1998, 9, 2865.

[12] A. Cornejo, J. M. Fraile, J. I. García, M. J. Gil, V. Martínez-Merino, J. A. Mayoral, Angew. Chem., Int. Ed. 2005, 44, 458.

[13] a) J. I. García, J. A. Mayoral, E. Pires, I. Villalba, Tetrahedron: Asymmetry, 2006, 17, 2270. b) H. Werner, R. Vicha, A. Gissibl, O. Reiser, J. Org. Chem. 2003, 68, 10166.

[14] J. M. Fraile, J. I. García, A. Gissbl, J. A. Mayoral, E. Pires, O. Reiser, M. Roldán, I. Villalba, Chem. Eur. J. 2007, 13, 8830.

[15] M. I. Burguete, J. M. Fraile, J. I. Garcia, E. Garcia-Verdugo, C. I. Herrerias, S. V. Luis, J. A. Mayoral, J. Org. Chem. 2001**,** 66, 8893.

[16] a) D. A. Evans, K. A. Woerpel, M. M. Hinman, M. M. Faul, J. Am. Chem. Soc. 1991, 113, 726. b) J. M. Fraile, J. I. García, J. A. Mayoral, T. Tarnai, J. Mol. Catal. A 1999, 144, 85.

[17] a) J. M. Fraile, J. I. García, J. A. Mayoral, T. Tarnai, M. A. Harmer, J. Catal., 1999, 186, 214. b) M. J. Fernández, J. M. Fraile, J. I. García, J. A. Mayoral, M. I. Burguete, E. García-Verdugo, S. V. Luis, M. A. Harmer, Topics in Catalysis, 2000, 13, 303. c) J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, M. Harmer, J. Catal., 2004, 221, 532.

[18] J. M. Fraile, J. I. García, M. J. Gil, V. Martínez-Merino, J. A. Mayoral, L. Salvatella, Chem. Eur. J., 2004, 10, 758.

[19] A. I. Fernández, J. M. Fraile, J. I. García, C. I. Herrerías, J. A. Mayoral, L. Salvatella, Catal. Commun., 2001, 2, 165.
[20] J. I. García, B. López-Sánchez, J. A. Mayoral, E. Pires, I. Villalba, J. Catal., 2008, 258, 378.
[21] J. M. Fraile, J. I. García, G. Jiménez-Osés, J. A. Mayoral, M. Roldán, Organometallics, 2008, 27, 2246.
[22] a) M. P. Sibi, M. Liu, Current. Org. Chem. 2001, 5, 719-755. b) G. Desimoni, G. Faita, K. A. Jørgensen, Chem. Rev. 2006, 106, 3561.
[23] a) E. J. Corey, N. Imai, H. Y. Zhang, J. Am. Chem. Soc. 1991, 113, 728. b) E. J. Corey, K. Isihara, Tetrahedron Lett. 1992, 33, 6807.
[24] a) D. A. Evans, J. A. Murry, P. von Matt, R. D. Norcross, S. J. Miller, Angew. Chem. Int. Ed. 1995, 34, 798. b) D. A. Evans, S. J. Miller, T. Lectka, P. von Matt, J. Am. Chem. Soc. 1999, 121, 7559. c) D. A. Evans, M. C. Kozlowski, J. S. Fedrow, Tetrahedron Lett. 1996, 37, 7481.
[25] A. K. Ghosh, P. Mathivanan, J. Cappiello, Tetrahedron Lett. 1996, 37, 3815.
[26] a) G. Desimoni, G. Faita, P. P. Righetti, Tetrahedron Lett. 1996, 37, 3027. b) G. Desimoni, G. Faita, A. G. Invernizzi, P. Righetti, Tetrahedron 1997, 53, 7671. c) P. Carbone, G. Desimoni, G. Faita, S. Filippone, P. Righetti, Tetrahedron 1998, 54, 6099.
[27] H. Wang, X. Liu, H. Xia, P. Liu, J. Gao, P. Ying, J. Xiao, C. Li, Tetrahedron 2006, 62, 1025.
[28] G. Desimoni, G. Faita, M. Guala, C. Pratelli, J. Org. Chem. 2003, 68, 7882.
[29] H. Wang, H. Wang, P. Liu, H. Yang, J. Xiao, C. Li, J. Mol. Catal. A 2008, 285, 128.
[30] a) G. Desimoni, G. Faita, M. Guala, A. Laurenti, Eur. J. Org. Chem. 2004, 3057. b) G. Desimoni, G. Faita, M. Guala, A. Laurenti, M. Mella, Chem. Eur. J. 2005, 11, 3816.
[31] a) S. Kobayashi, H. Ishitani, J. Am. Chem. Soc. 1994, 16, 4083. b) S. Kobayashi, H. Ishitani, I. Hachiya, M. Araki, Tetrahedron 1994, 50, 11623.
[32] a) S. D. Bull, S. G. Davies, S. W. Epstein, M. A. Leech, J. V. A. Ouzman, J. Chem. Soc. Perkin Trans. 1 1998, 2321. b) S. D. Bull, S. G. Davies, D. J. Fox, T. G. R. Sellers, Tetrahedron: Asymmetry 1998, 9, 1483. c) S. D. Bull, S. G. Davies, J. V. A. Ouzman, Chem. Commun. 1998, 659.
[33] O. Corminboeuf, L. Quaranta, P. Renaud, M. Liu, C. P. Jasperse, M. P. Sibi, Chem. Eur. J. 2003, 9, 29.
[34] M. P. Sibi, L. Venkatraman, M. Liu, C. P. Jasperse, J. Am. Chem. Soc. 2001, 123, 8444.
[35] M. P. Sibi, L. M. Stanley, X. Nie, L. Venkatraman, M. Liu, C. P. Jasperse, J. Am. Chem. Soc. 2007, 129, 395.
[36] L. Quaranta, O. Corminboeuf, P. Renaud, Org. Lett. 2002, 4, 39.
[37] a) E. J. Corey, D.-H. Lee, J. Am. Chem. Soc. 1994, 116, 12089. b) E. J. Corey, M. A. Letavic, J. Am. Chem. Soc. 1995, 117, 9626.
[38] D. Seebach, A. K. Beck, A. Heckel, Angew. Chem. Int. Ed. 2001, 40, 92.
[39] D. Seebach, R. Dahinden, R. E. Marti, A. K. Beck, D. A. Plattner, F. N. M. Kühnle, J. Org. Chem. 1995, 60, 1788.
[40] a) B. Altava, M. I. Burguete, B. Escuder, S. V. Luis, R. V. Salvador, J. M. Fraile, J. A. Mayoral, A. J. Royo, J. Org. Chem. 1997, 62, 3126. b) B. Altava, M. I. Burguete, J. M. Fraile, J. I. García, S. V. Luis, J. A. Mayoral, A. J. Royo, M. J. Vicent, Tetrahedron: Asymmetry 1997, 8, 2561. c) B. Altava, M. I. Burguete, J. M. Fraile, J. I. García, S. V. Luis, J. A. Mayoral, M. J. Vicent, Angew. Chem. Int. Ed. 2000, 39, 1503.
[41] D. Seebach, R. E. Marti, T. Hintermann, Helv. Chim. Acta 1996, 79, 1710.
[42] a) K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, J. Am. Chem. Soc. 1995, 117, 4435. b) K. V. Gothelf, K. A. Jørgensen, J. Org. Chem. 1995, 60. 6847.
[43] C. Haase, C. R. Sarko, M. DiMare, J. Org. Chem. 1995, 60, 1777.
[44] J. I. García, V. Martínez-Merino, J. A. Mayoral, J. Org. Chem. 1998, 63, 2321.
[45] P. G. Cozzi, Chem. Soc. Rev. 2004, 33, 410.

[46] a) E. N. Jacobsen, W. Zhang, A. R. Muci, J. R. Ecker, L. Deng, J. Am. Chem. Soc. 1991, 113, 7063. b) R. Irie, K. Noda, Y. Ito, N. Matsumoto, T. Katsuki, Tetrahedron: Asymmetry 1991, 32, 1055.

[47] H. Sasaki, R. Irie, T. Hamada, K. Suzuki, T. Katsuki, Tetrahedron 1994, 50, 11827.

[48] T. Katsuki, Chem. Soc. Rev. 2004, 33, 437.

[49] T. Kurahashi, H. Fujii, Inorg. Chem. 2008, 47, 7556.

[50] J. P. Collman, L. Zeng, J. I. Brauman, Inorg. Chem. 2004, 43, 2672.

[51] A. M. Daly, M. F. Renehan, D. G. Gilheany, Org. Lett. 2001, 3, 663.

[52] a) T. Uchida, R. Irie, T. Katsuki, Synlett 1999, 1163. b) T. Uchida, R. Irie, T. Katsuki, Synlett 1999, 1793.

[53] S. Bachmann, M. Furler, A. Mezzetti, Organometallics 2001, 20, 2102.

[54] K. B. Hansen, J. Leighton, E. N. Jacobsen, J. Am. Chem. Soc. 1996, 118, 10924.

[55] G. M. Sammis, E. N. Jacobsen, J. Am. Chem. Soc. 2003, 125, 4442.

[56] G. M. Sammis, H. Danjo, E. N. Jacobsen, J. Am. Chem. Soc. 2004, 126, 9928.

[57] S. Matsunaga, M. Shibasaki, Bull. Chem. Soc. Jpn. 2008, 81, 60.

[58] N. Kumagai, S. Matsunaga, T. Kinoshita, S. Harada, S. Okada, S. Sakamoto, K. Yamaguchi, M. Shibasaki, J. Am. Chem. Soc. 2003, 125, 2169.

[59] S. Handa, K. Nagawa, Y. Sohtome, S. Matsunaga, M. Shibasaki, Angew. Chem. Int. Ed. 2008, 47, 3230.