In the Arena of Enantioselective Synthesis, Titanium Complexes Wear the Laurel Wreath

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1. Introduction

Asymmetry is ubiquitous in every part of Nature[1] and has a great impact in many fields, not only in chemistry but also even in arts. In the pharmaceutical area, asymmetry plays an important role, since both enantiomers of a determinate drug do not necessarily have the same activity. The disastrous incident of thalidomide, in which each enantiomer has a totally different biological effect in humans,[2] has had an impact on society. The public demands for avoiding similar tragedies have been transferred first to the pharmaceutical and related companies,[3] mainly through the questions of regulatory agencies, and second to the scientific community, which in turn has to provide highly efficient and reliable methods of asymmetric synthesis. In fact, these demands have already had an important response, since the worldwide sales of single enantiomer drugs are continuously growing.

Enantioselective synthesis[4] is defined as the transformation of achiral reagents into only one of the two possible product enantiomers, mainly through the use of chiral catalyst, solvents, etc.,[5] and avoiding the annoying attachment and deattachment of chiral auxiliaries, typical of the related diastereoselective approaches. Although the first example was given in 1904,[6] it is only in the last three decades that the number and the quality of published reactions have undergone a true revolution, with the coronation being the awarding of the 2001 Nobel Prize in Chemistry to Professors Sharpless,[7] Knowles,[8] and Noyori[9] for their work on enantioselective synthesis.

Titanium is the seventh most abundant metal on Earth and has been extensively used in a multitude of asymmetric reactions (Figure 1), with the same position (fifth) being occupied for this metal in either asymmetric or enantioselective reactions in the ranking of metals.[10] However, the broad spectrum of reactions in which it is involved makes this metal unique,[11] compared with other metals with higher score, which are, in turn, more specific for some types of reactions. Thus, for instance, palladium is intimately connected with the nucleophilic allylic alkylation, rhodium and ruthenium with hydrogenation, Meerwein−Ponndorf−Verley, and Oppenauer processes, and copper with Michael addition.

Titanium is one of cheapest transition metals, and its products of hydrolysis, and even a lot of titanium compounds, are nontoxic and environmentally friendly, strongly contrasting with the high toxicity of many transition metals such as Hg, Pb, Cr, Ni, Mn, etc.[12] This low toxicity[13] has permitted the use of different titanium derivatives for medical purposes; among them, the most outstanding ones are their use in sunscreens,[14] removal of toxic metals,[15] and prostheses.[16]

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Diego J. Ramón (left) was born in Alicante (Spain) in 1965 and received his B.Sc. (1988), M.Sc. (1989), and Ph.D. (1993) degrees from the University of Alicante. After spending two years as a postdoctoral fellow at the Eidgenössische Technische Hochschule in Zürich (ETH-Zentrum), he returned to the University of Alicante and, after a short stay at Miguel Hernández University, became associate professor (2000) at the former university. Dr. Ramón has been visiting professor at Debye Institute (University of Utrecht, Netherlands, 2001). In 1994, he was awarded the Prize for Young Scientists of the Spanish Royal Society of Chemistry. His current research interest is focused on organometallic chemistry and asymmetric synthesis.

Miguel Yus (right) was born in Zaragoza (Spain) in 1947 and received his B.Sc. (1969), M.Sc. (1971), and Ph.D. (1973) degrees from the University of Zaragoza. After spending two years as a postdoctoral fellow at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr, he returned to Spain to the University of Oviedo, where he became associate professor in 1977, being promoted to full professor in 1987 at the same university. In 1988 he became chair of Organic Chemistry at the University of Alicante, where he is currently the head of the Organic Synthesis Institute. Professor Yus has been visiting professor at different institutions and universities such as ETH-Zentrum, Oxford, Harvard, Uppsala, Marseille, Tucson, Okayama, Paris, and Strasbourg. He is coauthor of more than 350 papers (among them five review articles in this journal) mainly in the field of the development of new methodologies involving organometallic intermediates. His current research interest is focused on the preparation of very reactive functionalized organometallic compounds and their use in synthetic organic chemistry, arene-catalyzed activation of different metals, and preparation of new metal-based catalysts for homogeneous and heterogeneous selective reactions. Among other awards, he has recently received the Spanish–French Prize (1999), the Japan Society for the Promotion of Science Prize (2000), and the Stiefvater Memorial Lectureship Award (2001). Professor Yus belongs to the advisory boards of the journals *Tetrahedron*, *Tetrahedron Letters*, *European Journal of Organic Chemistry*, *Chemistry Letters*, and *Trends in Organic Chemistry*. Last year, Professor Yus, Dr. Ramón, and other members of the ISO founded the new chemical company MEDALCHEMY S.L. to commercialize fine chemicals.

All the mentioned facts, together with its relative inertness toward redox processes and the possibility of adjusting its reactivity and selectivity by different ligands, make titanium the preferred candidate for any enantioselective reaction, even employing stoichiometric amounts of the titanium component.

The literature covered by this review begins mainly in 1999 because research for previous years has been comprehensively compiled,[17] although older works are commented upon if necessary. The review is arranged by the type of general process and subdivided by the type of reaction, clearly separating the preparation of compounds with tertiary stereocenters from those with quaternary stereocenters, owing to the higher difficulty of the preparation of this last class of products.[18]

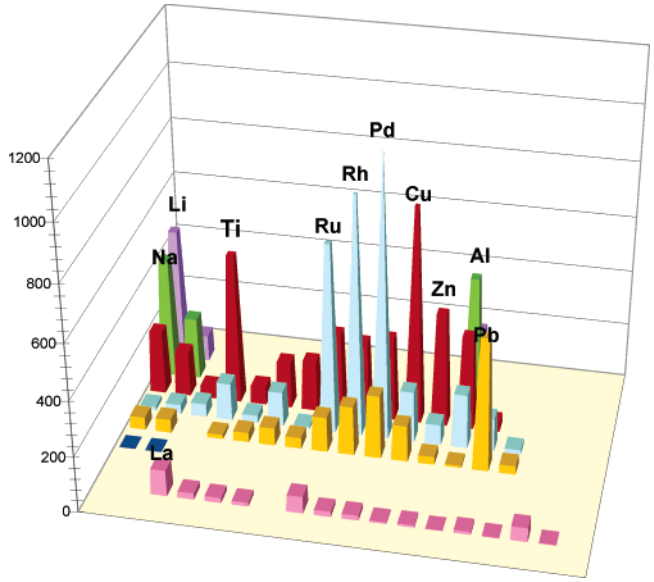


Figure 1. 3D bar graph showing the number of papers on asymmetric synthesis since 1999 classified by metal from the periodic table, excluding actinides.

2. Enantioselective Oxidation Processes

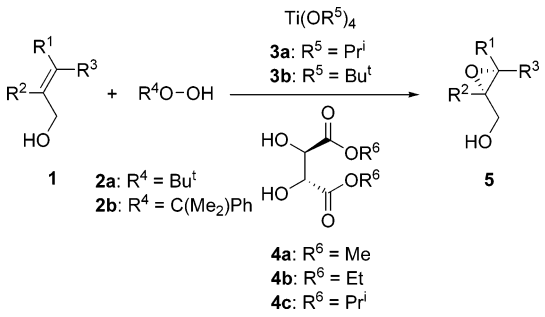
Any oxidation process has an intrinsic value owing to the preparation of new compounds but also serves as the starting point for further functionality manipulation in order to get a desired compound. In this section, we will present different enantioselective oxidation processes as well as direct transformations into final targets.

2.1. Sharpless Epoxidation

In 1980 a paradigmatic shift occurred with the introduction of the enantioselective epoxidation of allylic alchols.[19] There is no doubt that this reaction changed our vision of the enantioselective synthesis, and nowadays it is rare to find a total synthesis of a natural product in which it is not involved.[20]

The enantioselective epoxidation of allylic alcohols **1** was accomplished by reaction of an alkyl hydroperoxide **2**, in the presence of titanium alkoxide **3** and a chiral tartrate ester **4** (Scheme 1).[21] The enantioselectivity depends strongly on

Scheme 1. Sharpless Epoxidation

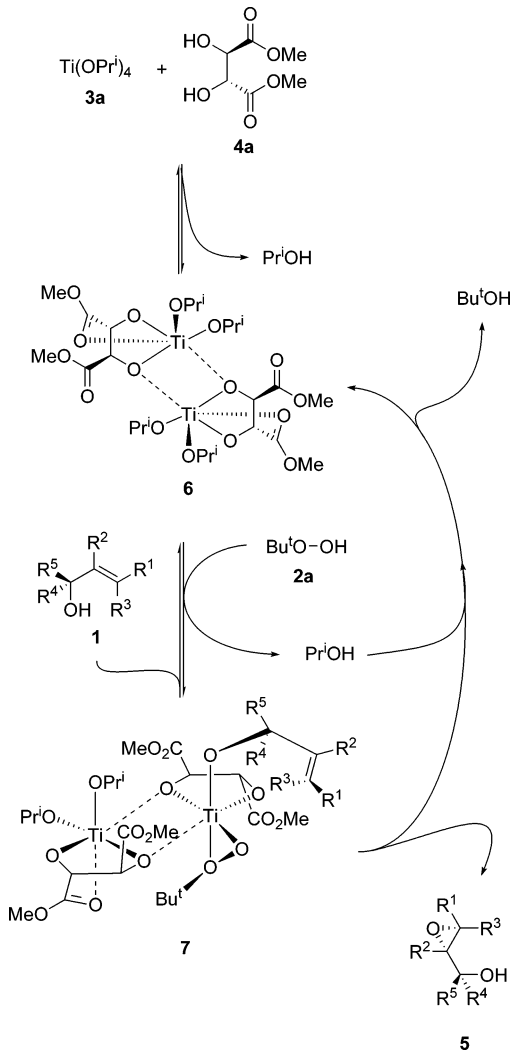


different variables. Thus, the titanium tetraisopropoxide (**3a**) is the titanium species of choice, although the use of the corresponding *tert*-butoxide has been recommended for reactions in which the final epoxy alcohol **5** is particularly sensitive to a ring opening process by the alkoxide.[22] Concerning chiral tartrates conventionally used, such as dimethyl, diethyl, and diisopropyl derivatives, they are

equally effective. *tert*-Butyl hydroperoxide is used as the oxidant although for some specific alcohols other oxidants can give better results.[23] Two aspects of the stoichiometry are very important in order to get excellent enantioselectivity: one is the ratio of titanium to tartrate used, which should have about 10% tartrate excess to guarantee the formation of chiral titanium complexes. The second stoichiometry consideration is the ratio of catalyst (titanium−tartrate complex) to allylic alcohol. Although, at the beginning, the ratio was usually 1:1 (stoichiometric amounts), the introduction of molecular sieves (zeolites) permitted the use of only 5−10 mol % of catalyst, with the enantioselectivity being kept.[24] It should be pointed out that, due to the low economical cost of both titanium compounds and tartrate derivatives, the use of stoichiometric amounts is still very common.

After some controversies,[25] the mechanism of the reaction including kinetics[26] and catalytic species[27] was finally accepted (Scheme 2). Comparison of the epoxidation rates

Scheme 2. Proposed Catalytic Cycle for the Sharpless Epoxidation

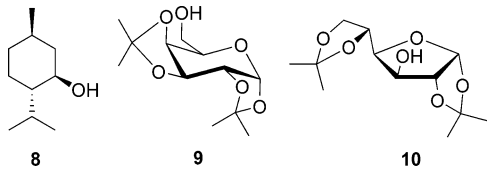


of several parasubstituted cinnamyl alcohols reveals that the olefin acts as a nucleophile toward the activated peroxide oxygen. The existence of different fast ligand exchanges is of fundamental importance, since it favors the incorporating of the dichelating tartrate **4a** into the metallic complex. In fact, and according to X-ray crystallography,[28] the real catalyst seems to be the bimetallic species **6**, which, after a double exchange between two isopropoxide ligands and both the hydroperoxide **2a** and the starting olefin **1**, gave the real catalytic species **7**. The hydroperoxide must occupy both the equatorial site and one of the two available axial coordination sites, with the allylic alcohol in the remaining axial site. To achieve the necessary proximity for transferring the oxygen atom to the olefin, the distal oxygen is placed in the equatorial position. The axial site on the lower face of the complex **7** is chosen for the more sterically demanding *tert*-butyl moiety, with the allylic alcohol binding to the remaining axial coordinating site. The enantioselective epoxidation takes place on this intermediate, in which the dihedral angle for the allyl moiety is very small (O−C−C=C, ca. 30°), delivering its olefinic group in an appropriate space. In fact, the bad enantioselectivity obtained for *Z*-substituted substrate (R^3) is attributed to steric hindrance with the ligand. Also, the depression of results with bulky C2-substituted systems is caused by the vicinity of tartrate ligand with the R^2-moiety, which deforms the ideal reaction conformation. The intermediate **7** suffers from steric hindrance when $R^4 \neq H$, and the epoxidation of such a substrate is strongly retarded. This model explains the kinetic resolution of racemic secondary allylic alcohols (see section 7) as well as the poor reactivity of tertiary allylic systems. It should be pointed out that this type of catalytic cycle, as well as the presence of bimetallic[29] titanium species, has become a general rule for other reactions in which titanium derivatives are involved, as will be presented later on in this review.

Previous to introducing the new results obtained from 1999, it should be clarified that they do not include epoxidations of chiral starting allylic alcohols,[30] as well as the use of chiral hydroperoxides,[31] since they must be noted, in a strict sense, as diastereoselective reactions and are out of the scope of this review.

2.1.1. Preparation of Molecules Containing Tertiary Stereocenters

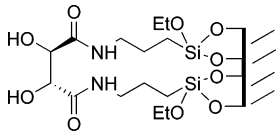
Somewhat surprisingly, relatively little effort has been exerted to introduce new chiral ligands or to improve the already known tartaric acid derivatives. The main reason for this is the relatively low cost and the high effectiveness of these derivatives, which tolerate their loss during the workup. Recently, the use of monodentate alcohols, such as menthol (**8**), 1,2:3,4-di-isopropylidene-α-D-galactopyranose (**9**), or 1,2:5,6-di-isopropylidene-α-D-glucofuranose (**10**), as chiral ligands has been introduced. However, they gave very poor results, with the enantioselectivity for the epoxidation of allylic alcohol derivatives never being higher than 22%.[32]



Another classical strategy for improving the properties of known chiral ligands is their attachment to a polymeric material, since, in this way, their final isolation is very easy.[33] Thus, different tartaric esters derived from a polystyrene cross-linked with divinyl benzene and tetraethyleneneglycol diacrylate have been prepared from the corresponding chloromethylated resins, with a large amount of the titanium source (25 mol %) and tartrate polymer (50 mol %) having

to be used[34] in order to obtain similar results to those of the substoichiometric homogeneous version (5 and 6 mol %, respectively). Under these new conditions, the resins were successfully used three times without changing any parameters of the reaction.

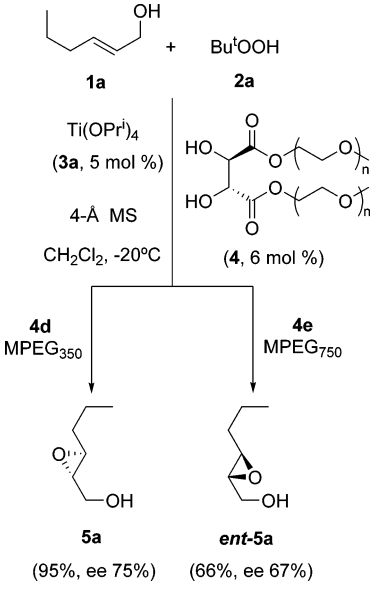
In comparison with the cases of the above organic polymers, the effectiveness of organic−inorganic hybrid materials obtained by grafting chiral tartaric acid derivatives onto the surface of silica (**11a**) and in the mesopores of MCM-41 (**11b**) material was higher. In fact, although the chemical yield was half that of the substoichiometric homogeneous version, the enantioselectivity was the same using similar amounts of chiral tartrate derivatives and titanium isopropoxide.[35] The lower yield was attributed to a slower diffusion of substrate and product in the polymeric material.



11a on SiO_2
11b in MCM-41

Tartaric derivatives have been attached not only to heterogeneous but also to homogeneous polymeric materials. These chiral systems have the advantage of their easy isolation by simple precipitation, thus avoiding the usual diffusion problems of heterogeneous materials. In this case, different tartrates **4d,e** derived from poly(ethylene glycol) monomethyl ether were prepared. The catalytic enantioselective epoxidation of the alcohol **1a** in the presence of these ligands gave the expected epoxide **5a** with similar enantioselectivity and yield to those using simply diethyl tartrate (**4b**).[36] A more careful study showed the presence of an unusual reversal enantioselectivity depending on the molecular weight of the ethylene glycol moiety (Scheme 3).[37] The

Scheme 3. Reversal of Enantioselectivity in the Sharpless Epoxidation Depending on the Length of the Achiral Polyethylene Glycol Moiety

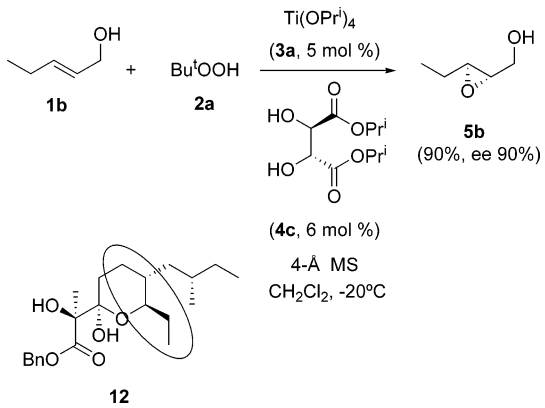


reactions were generally slower (6−8 h) than those using isopropyl tartrate (**4c**, 2−3 h), but the results were similar. The enantioselectivity can be improved using poly(ethylene glycol) derivatives of molecular weight either lower than 350 or higher than 750, yielding the epoxide **5a** or ***ent*-5a**, respectively. The change in the sense of the enantioselectivity of the reaction was attributed to the existence of different catalytic bimetallic species. Thus, the determination of molecular weight of the catalyst (the complex of titanium tetraisopropoxide and the tartrate derivative), by the isopiestic Signer method, confirmed the presence of different species: for the ligand **4d**, as well as for others with lower molecular weight, the main complex is a bimetallic system bearing two chiral ligands, as expected. However, for the ligand **4e**, as well as others with higher molecular weight, the main complex is a bimetallic system bearing only one chiral ligand. All these facts could explain the opposite enantioselectivity as well as the lower activity observed for the system **4e**.

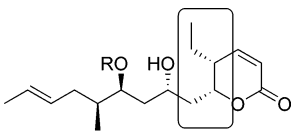
Most research done on the enantioselective Sharpless epoxidation during the period covered in this review has been focused on the use of this reaction as the main pillar for the creation of different chiral compounds. A comprehensive compilation of them follows.

The first example came from the synthesis of a C_5-unit of hydroxy acid moiety **12** of polyoxypeptins, which exhibited potent apoptosis against human pancreatic adenocarcinoma AsPC-1 cells and therefore attracted attention as potential anticancer agents. The enantioselective epoxidation of the alcohol **1b** using the standard substoichiometric version gave the expected epoxide **5b**.[38] Further crystallization of its *p*-nitrobenzoic ester derivative gave an enantiomeric excess of 99%. The epoxide opening by reaction with (*S*)-2-methylbutylmagnesium bromide followed by oxidation of the primary alcohol and other transformations gave, finally, compound **12**. In Scheme 4, the starting chiral C-5 unit incorporated into **12** is circled.

Scheme 4. Epoxidation of the Alcohol 1b



The chiral alcohol **5b** has been employed in the preparation of different pironetins **13**.[39] These lactones were isolated from the fermentation broths of *Streptomyces sp.* and have different remarkable biological activities.

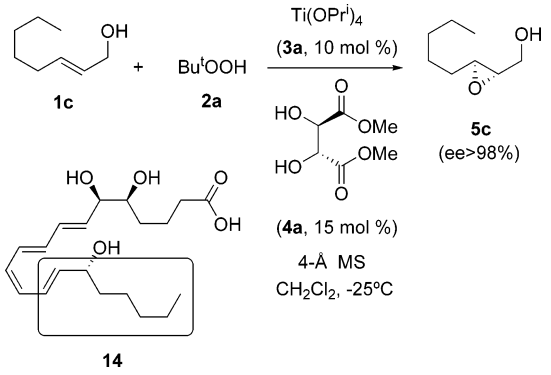


13

The 15-*epi*-lipoxin A_4 (**14**) is a new class of arachidonic acid metabolite, and it has been discovered that aspirin triggers a switch in the biosynthesis of lipoxins, initiating its formation. This compound is more active than lipoxin

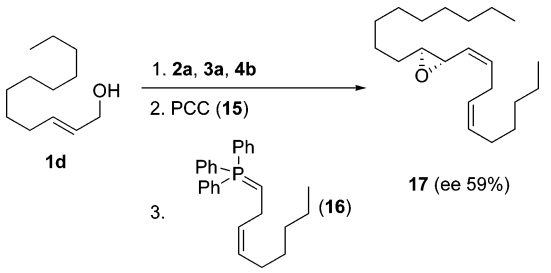
A_4 as an anti-inflammatory agent which in turn provokes the blocking of the broncoconstriction of leukotrienes in asthmatic subjects by inhalation. Its preparation has been initiated by epoxidation of the alcohol **1c** to give the epoxide **5c** with an excellent enantiomeric ratio after recrystallization (Scheme 5).[40]

Scheme 5. Epoxidation of the Alcohol 1c



Posticlure (**17**) is a sex pheromone component of the tussock moth (*Orgyia postica*) which has been easily prepared through the asymmetric epoxidation of the alcohol **1d** to yield the corresponding chiral epoxide alcohol with a moderated enantioselectivity (Scheme 6). The oxidation of

Scheme 6. Preparation of Posticlure

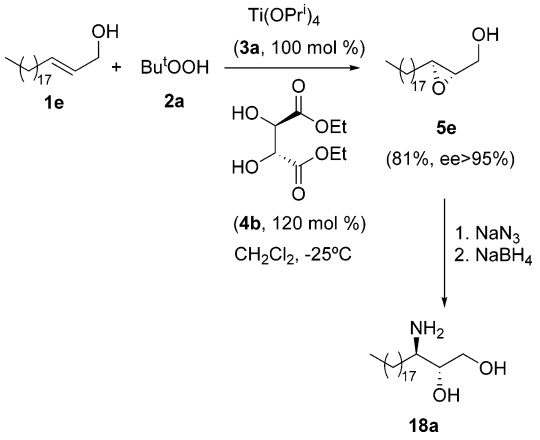


the primary alcohol to the corresponding aldehyde followed by a Wittig-type reaction with the ylide **16** yielded directly the epoxide **17**.[41]

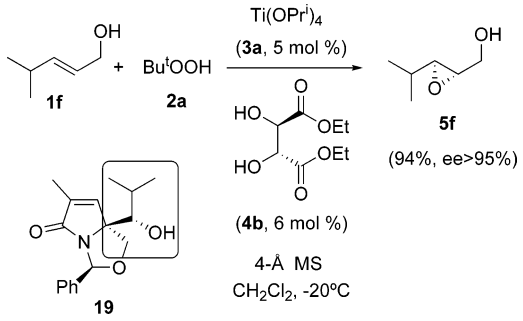
Although the previous low enantioselectivity could be attributed to the presence of a long chain in the allylic alcohol, the following examples show that this is not true. Thus, in the synthesis of four isomers of 3-hydroxy-4-methyltetradecanoic acid, which is a constituent of the cyclodepsipeptide W493, the enantioselective Sharpless epoxidation of (*Z*)-tridec-2-en-1-ol using diethyl tartrate (**4b**) and titanium tetraisopropoxide (**3a**) gave the corresponding epoxide with enantiomeric excess higher than 80%.[42] Moreover, the epoxidation of the allylic alcohol **1e** using the same reagents yielded the expected epoxide **5e** with excellent results.[43] Further nucleophilic ring opening by reaction with sodium azide, followed by reduction, led diastereoselectively to the corresponding amino diol **18a** (Scheme 7). This system can be considered as a sphingosine analogue. However, its in vitro cytotoxicity against six solid tumor cell lines, as well as its inhibition behavior of carrageenin-induced paw edema in rats, was not as high as expected.

Instead of a simple chain as a substituent of the double bond, a more crowded system can be used. For example, in the synthesis of an intermediate of (+)-lactacystin **19**, the enantioselective epoxidation of the alcohol **1f** gave the corresponding epoxide **5f** with an excellent result (Scheme 8).[44]

Scheme 7. Preparation of the Amino Diol 18a

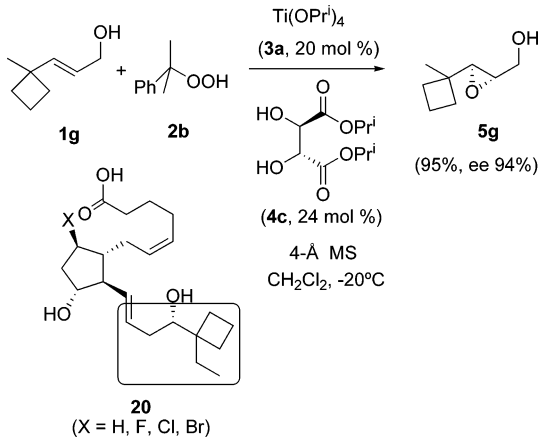


Scheme 8. Epoxidation of the Alcohol 1f



Increasing the hindrance from secondary to tertiary groups on the olefinic substituents did not give any appreciable decrease of the enantioselectivity. For example, in the synthesis of 9-halogenated prostaglandine F (PGF) analogues **20**, the asymmetric key step was the epoxidation of the alcohol **1g** to yield the corresponding compound **5g** with a very good result (Scheme 9).[45] These analogues have been biologically

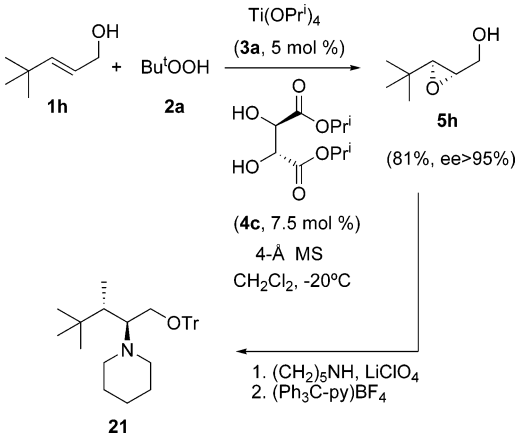
Scheme 9. Epoxidation of the Alcohol 1g



evaluated due to their affinity to the mouse G-protein coupled membrane receptors (EP1−4) receptors and their ability to increase the intracellular cyclic adenosine monophosphate (cAMP) concentration, showing a significant affinity.

The tolerance for bulky alkyl groups has been used to advantage for the modular synthesis of different amino alcohols of type **21**. The epoxidation of alcohol **1h** yielded the corresponding epoxide **5h** with an excellent enantioselectivity.[46] $LiClO_4$-catalyzed nucleophilic ring opening with piperidine, followed by protection of the primary alcohol as the trityl ether, led to the amino alcohol **21** (Scheme 10). It

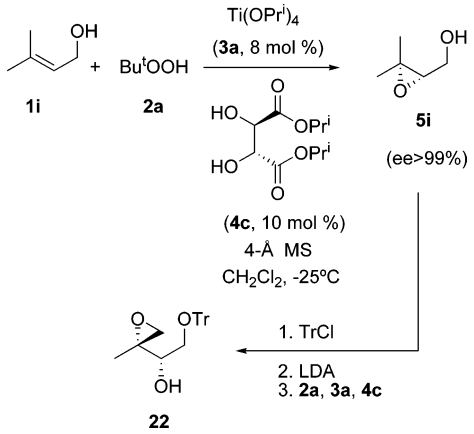
Scheme 10. Preparation of Chiral Ligand 21



should be pointed out that this amino alcohol was evaluated as promoter in the classical enantioselective addition of dialkylzinc reagents to aldehydes.[47] Other related systems with different amino substituents, protecting groups, and bulky alkyl substituents gave worse results as promoters of the aforementioned addition.

Following the study of increasing hindrance in the starting allylic alcohol, the next step is the epoxidation of the alcohol **1i** to yield the corresponding alcohol **5i** (Scheme 11), which

Scheme 11. Preparation of Compound 22

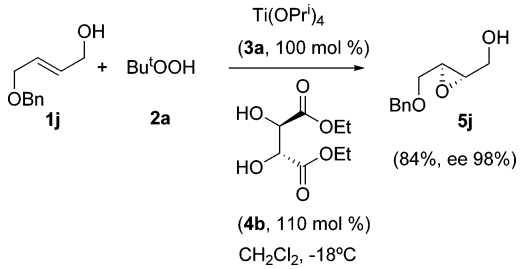


was accomplished with an excellent level of enantioselectivity. This epoxide was relatively unstable and was *in situ* derivatized as its trityl ether. On the other hand, the treatment of this compound with Lithium diisopropylamide (LDA) gave the corresponding chiral secondary alcohol, which in turn by a second diastereoselective Sharpless epoxidation gave (2*R*,3*S*)-3,4-epoxy-3-methyl-1-(triphenylmethyl)oxybutan-2-ol (**22**), which is a substructure found in some naturally occurring bioactive molecules such as toxin produced by fungus *Alternaria kikuchiana* (AK-toxins) and azinomycins.[48]

The oxidation of the epoxide **5i** to the corresponding aldehyde, followed by Wittig olefination using α-methoxycarbonyltriphenylphosphorane, has been used in the synthesis of methyl *trans*-chrysanthemate.[49]

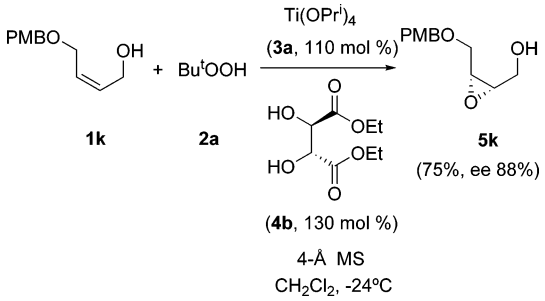
The scope of olefinic substrates for the Sharpless reaction is very broad, and it tolerates the presence of ether functionalities. Thus, the epoxidation of the alcohol **1j** yielded the expected epoxide with excellent enantioselectivity (Scheme 12). This epoxide has been used in turn as starting material in the preparation of asymmetric tris(hydroxymethyl)methane derivatives, which are interesting building blocks in synthetic organic chemistry.[50]

Scheme 12. Epoxidation of the Functionalized Alcohol 1j

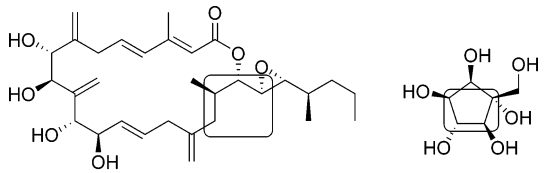


The use of the related *cis*-olefinic system **1k** seems to be more interesting,[51] since there is some important steric hindrance between both olefinic substituents (see structure **7** in Scheme 2). Its epoxidation under stoichiometric conditions gave the expected alcohol **5k** with 88% enantiomeric excess (Scheme 13).

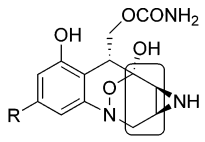
Scheme 13. Epoxidation of the Functionalized Alcohol 1k



The versatility of this chiral epoxide (as well as, in general, all the related systems) may be exemplified by its use in the synthesis of different natural products. Thus, alcohol **5k** has been successfully used in the syntheses of the macrocyclic amphidilone A (**23**)[52a] and of the aminocyclitol moiety (**24**)[52b] of (+)-trehazolin, which is a powerful trehalase inhibitor isolated from a culture broth of *Micromonospora*.



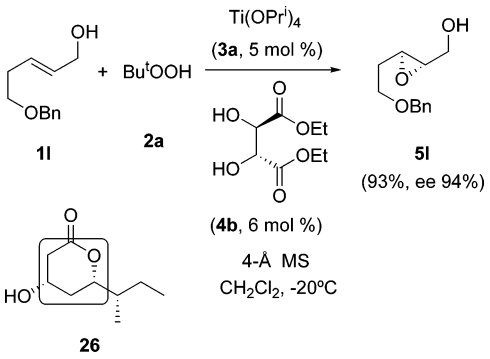
The alcohol **5k** was also used as starting chiral building block in the synthesis of (+)-FR66979 and (+)-FR900482 (**25**),[53] which are antitumor antibiotics obtained from the fermentation harvest of *Streptomyces sandaensis* and have been shown to form DNA interstrand cross-links at the $^{5'}$CpG$^{3'}$ steps in the minor groove.



25a: R = CH_2OH; FR66979
25b: R = CHO; FR900482

The epoxidation of the functionalized alcohol **1l** was the key step in the synthesis of the lactone moiety of quillajasaponins (Scheme 14).[54] Saponins from *Quillaja saponaria*, molina (rosaceae), have historically been used as commercial saponins, as well as foaming agents, in beverages, confec-

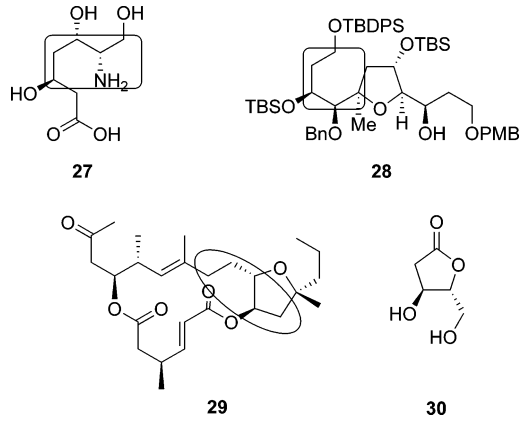
Scheme 14. Epoxidation of the Functionalized Alcohol 1l



tioneries, baked goods, dairy desserts, and cosmetics, and as potent immunological adjuvant agents. Despite the existence of 100 different saponin derivatives, one of the essential structural features in all of them is the lactone **26** isolated by alkaline hydrolysis.

The epoxidation of a related *p*-methoxybenzyl (PMB) ether alcohol using diisopropyl tartrate (**4c**) has been proposed as one of the asymmetry steps in the synthesis of (−)-galantinic acid **27**,[55] which is a component of the peptide antibiotic galantine I, isolated from a culture broth of *Bacillus pulvifaciens*.

A starting alcohol similar to **1l** but bearing a *tert*-butyldipropylsilyl (TBDPS) protecting group instead of a benzyl (Bn) has been epoxidized under the reaction conditions shown in Scheme 14, giving the corresponding alcohol with excellent results. This silylated ether has been used in the synthesis of the common C8−C18 fragment (**28**) of pectenotoxins,[56] which is responsible for the human intoxication caused by eating cultivated scallops. It has also been used in the synthesis of amphidinolide X (**29**),[57] which is a secondary metabolite of *Amphidinium sp.* with potent cytotoxicity against various cancer cell lines.



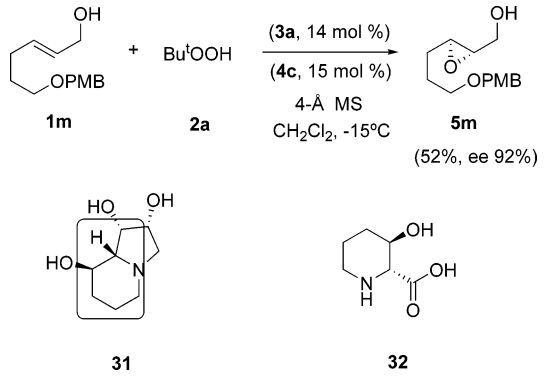
The aforementioned TBDPS ether (TBDPS instead of Bn in **5l**) was submitted to a regioselective opening reaction by treatment with benzyl alcohol and titanium tetraisopropoxide to give the expected 1,2-diol, which was protected as an acetonide. Deprotection of the silyl ether to yield the corresponding primary alcohol, followed by final oxidation, acid treatment, and catalytic hydrogenation, yielded the lactone **30**.[58] This lactone has an important biological activity since it increased the *c-fos* mRNA level, as does PGE_2, and antagonized TPA-induced terminal differentiation, demonstrating that **30** mimics the PGE_2 effects.

Finally, it should be pointed out that protection of alcohols of type **5l**, deprotection of the benzyl ether to yield a new chiral 3,4-epoxy alcohol, and then, mild oxidation led to the corresponding α,β-unsaturated aldehyde with good yield.[59] Presumably, the expected epoxy aldehyde intermediate was very unstable and underwent a β-elimination reaction to yield the corresponding unsaturated system.

The enantioselective epoxidation of the related *Z*-olefin of type **1l** was the key step in the preparation of different analogues of nucleosides homologated at the 3′ and 5′ positions.[60]

Oxido-functionalized longer chain allylic alcohols, such as compound **1m**, can be epoxidized under substoichiometric standard conditions, to give in this case the expected epoxide **5m** with a moderate yield but with an excellent enantioselectivity (Scheme 15). This epoxide has been used in the

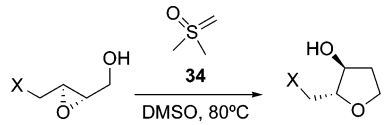
Scheme 15. Epoxidation of the Functionalized Alcohol 1m



synthesis of (−)-swainsonine (**31**)[61] and transformed into *trans*-3-hydroxypipecolic acid (**32**).[62] The former is a potent inhibitor of α-D-mannosidase and mannosidase II, as well as an anticancer agent.

Some of the previously described epoxides could be easy transformed into 2,3-disubstituted tetrahydrofurans **33** simply by reaction with the sulfoxonium ylide **34** (Scheme 16). The

Scheme 16. Transformation of Epoxides 5 into 3-Hydroxyfurans 33



5c: X = $(CH_2)_3Me$
5j: X = OBn
5k: X = OBn (*cis*)
5l: X = CH_2OBn
5m: X = $(CH_2)_2OPMB$

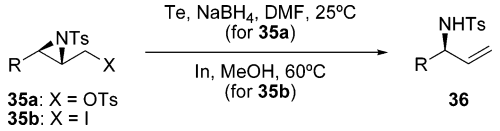
33c (17%)
33j (78%)
33k *cis* configuration (96%)
33l (85%)
33m (68%)

mechanism seems to begin as a Payne rearrangement; that is, under the basic reaction conditions the primary alcohol is deprotonated to the corresponding alkoxide, which in an intramolecular reaction with the 2,3-epoxide functionality leads to a 1,2-epoxide and a secondary alkoxide. The nucleophilic epoxide opening with the mentioned ylide at C1 leads to a new chiral sulfoxonium species, which can undergo a *5-exo-tet* ring closure to yield the 2,3-disubstituted tetrahydrofurans **33**, with the relative stereochemistry being the same as that in the original epoxide.[63]

Chiral epoxides **5** can be transformed into different aziridines either by aminolysis with diphenylmethylamine followed by hydrogenolysis and final exhaustive tosylation (to yield the chiral aziridine **35a**[64]) or by stereoselective ring opening by nucleophilic attack of sodium azide, followed by protection of the primary alcohol, reaction with PPh_3 (to

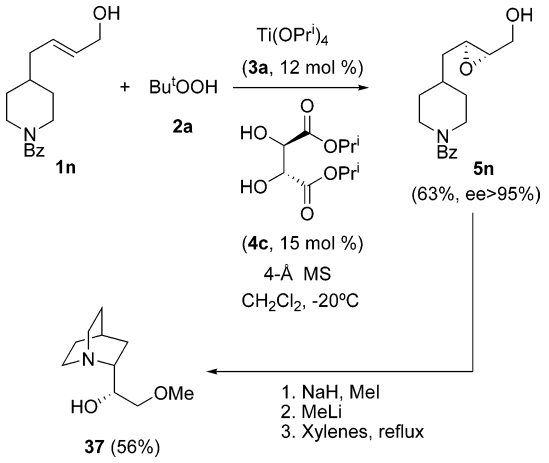
form the corresponding aziridine), and displacement of the primary alcohol by iodine (leading to the chiral aziridine **35b**[65]). These chiral aziridines can be stereoselectively transformed into the corresponding allylamines **36** either by reaction with reduced tellurium (for starting systems **35a**, yields around 80%) or by reaction with metallic indium (for systems **35b**, yields around 90%). In both cases, the presence of oxido functionalities did not have any influence on the final results (Scheme 17).

Scheme 17. Transformation of Aziridines 35 into Allylic Amines 36



The Sharpless epoxidation is also very efficient for allylic alcohols with amino functionalities. Thus, the epoxidation of the amino-functionalized alcohol **1n** yielded the expected compound **5n** with an excellent enantioselectivity.[66] Further methylation of the primary alcohol followed by liberation of the amino group by reaction with methyllithium and intramolecular nucleophilic opening of the epoxide led to the quinuclidine product **37** (Scheme 18).

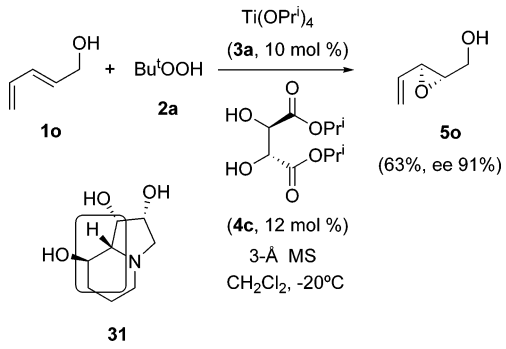
Scheme 18. Synthesis of the 2-Hydroxymethylquinuclidine Derivative 37



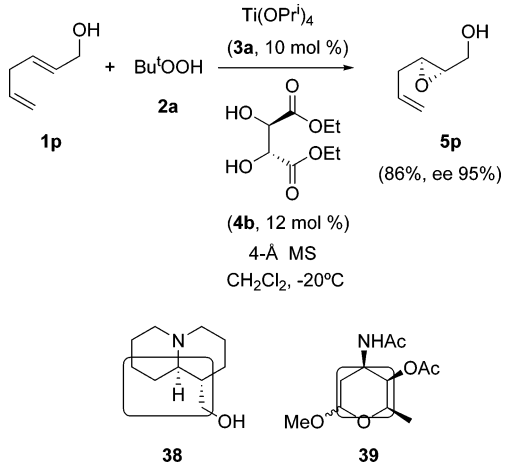
A very remarkable consequence of the presence of proposed catalytically active species **7** is the faster epoxidation of a double bound in the 2 position than another one, making it possible to monoepoxidize systems with several double bonds and permitting its further transformation by the presence of an extra double bound. Thus, the reaction of the alcohol **1o** gave the monoepoxide **5o** according to the procedure depicted in Scheme 19.[67] The epoxide **1o** has been used in the key step in the asymmetric synthesis of (−)-swainsonine (**31**). However, from an atom economy or efficiency[68] point of view, this synthesis is less efficient than that presented in Scheme 15, since the formation of the six-membered ring was done by a ring closing metathesis[69] which implies the loss of two carbon units.

The monoepoxidation of compound **1p** to yield the epoxide **5p** (Scheme 20) has been the key step in the asymmetric synthesis of the bicyclic alkaloid epilupinine (**38**),[70] in which the bicyclic structure was constructed by a double ring closing metathesis. The chiral epoxide **5p** is also the starting material for the synthesis of the 3-amino-2,3,6-

Scheme 19. Epoxidation of the Diene Alcohol 1o



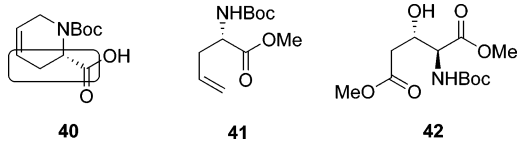
Scheme 20. Epoxidation of the Diene Alcohol 1p



trioxysugar derivative **39**,[71] with a degrading ozonolysis of the extra double bond being responsible for the aldehyde formation.

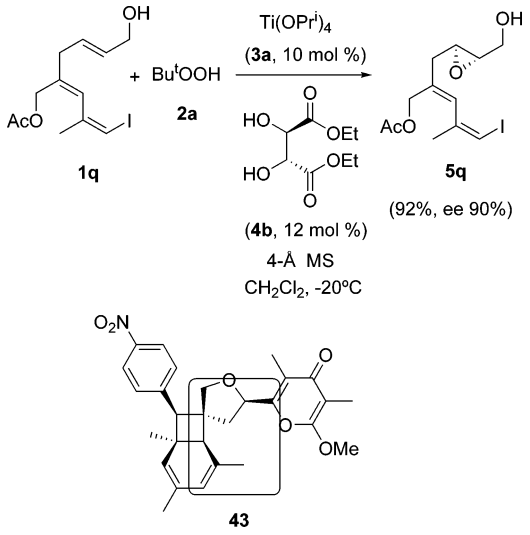
The *N*-protected baikiain **40** was prepared through the enantiomer ***ent*-5p**, which was obtained with similar results to those for the epoxide **5p** but using the corresponding ***ent*-4b** as chiral ligand.[72] In this case, the carboxylic acid functionality was obtained by a degrading periodate oxidation, and the ring was constructed by a ring closing metathesis, reducing in half the number of carbon atoms from the starting monoepoxide ***ent*-5p**. It should be pointed out that the catalytic hydrogenation of compound **40** yielded the corresponding pipecolic acid derivative.

The regioselective ring opening of the epoxide ***ent*-5p** with *p*-methoxybenzylamine to yield an 3-amino-1,2-diol system of type **18**, followed by degrading oxidation of this diol to an acid functionality, has been carried out for the synthesis of the unsaturated amino acid derivative **41**.[73] However, when the epoxide **5p** was treated with benzyl isocyanate under a strongly basic medium, the regioselective ring opening is the opposite one, and it has been used in the synthesis of *erythro*-*β*-hydroxyglutamic acid derivative **42**.[74]



SNF4435 C (**43**) is an immunosuppressant and multidrug resistance reversal agent isolated from the culture of *Streptomyces spectabillis*. In its biomimetic synthesis, the epoxidation of compound **1q** to yield the alcohol **5q** was the

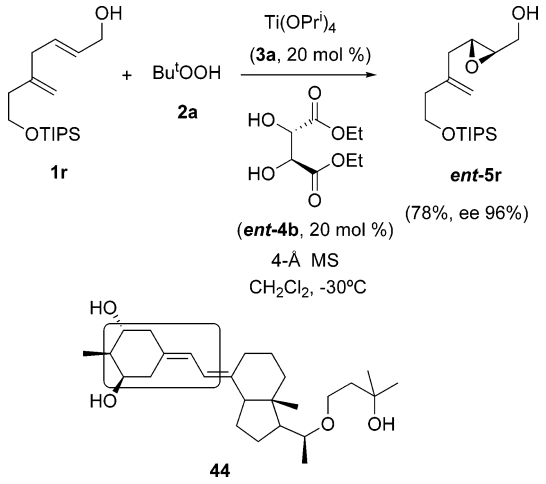
Scheme 21. Epoxidation of the Functionalized Triene Alcohol 1q



asymmetric key step (Scheme 21).[75] This is an illustrative example of the possibilities of the Sharpless epoxidation as well as of its tolerance to different functionalities including double bounds, even with oxymethyl moieties.

Another monoepoxidation of the multifunctionalized allylic alcohol **1r** is the starting asymmetric step in the synthesis of 2-methyl-19-nor-22 oxa vitamin D_3 analogue **44** (Scheme 22). The A-ring synthesis followed by a regioselective

Scheme 22. Epoxidation of the Diene Alcohol 1r

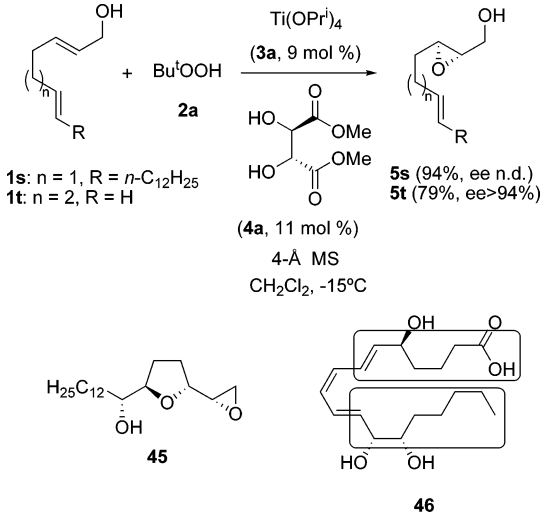


addition of methylmagnesium chloride, oxidation of the primary alcohol to an aldehyde, a diastereoselective ene reaction, and final Wittig olefination yielded compound **44**, which showed a significant activity in cell differentiation of HL-60 myelocytic leukemia.[76]

The acetogenin **45** has been obtained by monoepoxidation of alcohol **1s** (Scheme 23), followed by dihydroxylation of the isolated olefin and a final cyclization.[77] The oxidation of the alcohol **1t** seems to be more interesting since when only the chiral alcohol **5t** was used, different leukotrines were prepared.[78] As an illustrative example, lipoxin B_4 (**46**) was prepared using 2 equiv of epoxide **5t** as the only chiral component.

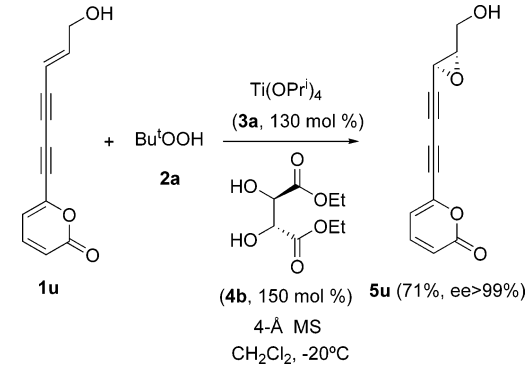
The presence of a triple bond in the substrate did not create any problem for the monoepoxidation reaction. Thus, (−)-nitidon (**5u**), which was isolated from the basidiomycete

Scheme 23. Epoxidation of Diene Alcohols 1s,t



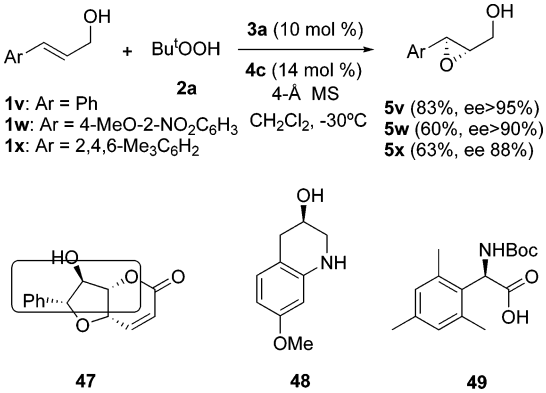
Junghuhnia nitida and exhibits cytotoxic activity against HL-60 and U-937 cells among other cell lines, has been obtained after monoepoxidation of the highly conjugated compound **1u** under stoichiometric conditions with excellent enantioselectivity, after recrystallization from a mixture of hexane and chloroform at low temperature (Scheme 24).[79]

Scheme 24. Epoxidation of the Diyne Alcohol 1u



The epoxidation of aryl substituted allyl alcohols **1v**−**x** has been performed with good to excellent results (Scheme 25). Thus, the enantioselective epoxidation of cinnamyl

Scheme 25. Epoxidation of Cinnamyl Alcohol Derivatives 1v−x



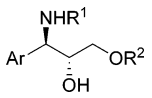
alcohol **1v** has been used as the key step in the synthesis of altholactone **47**,[80] which was isolated from various *Goniothalamous*.

The presence of different functional groups did not have any effect on the enantioselectivity, as in the case of compound **1w**, which has nitro and methoxy moieties. These functionalities in alcohol **5w** permitted the straightforward preparation of 1,2,3,4-tetrahydroquinoline **48**, just by a successive reduction of the benzylic epoxide, tosylation of the primary alcohol, and final reduction of the nitro group to an amine, which by a nucleophilic ring closing yielded the expected chiral compound **48**. It must be pointed out that many derivatives of this type of compound have been found to elicit potent biological responses leading to analgesic, antiarrhythmic, cardiovascular, immunosuppressant, antitumor, antiallergenic, anticonvulsant, and antifertility activities.[81]

The use of a much hindered aromatic compound such as the mesityl derivative **1x** also did not have any significant effect on the enantioselectivity (Scheme 25). The alcohol **5x** was easily transformed into the corresponding amino acid **49**, using the same methodology as that for the aforementioned compound **41**.[82]

The Lewis acid-catalyzed nucleophilic ring opening of alcohols **5v** and **5x** by different amines followed by protection of the primary alcohol as an ether led to the amino alcohols **18**,[83] which were used as chiral ligands in the enantioselective ruthenium-catalyzed[84] Meerwein−Ponndorf−Verly reduction[85] of ketones with modest results.

Primary amines of type **18** (R^1 = H) can be transformed into the corresponding bis(oxazoline) derivatives using the standard conditions: condensation with malonic acid derivatives to yield the expected diamide derivatives, mesylation of the secondary alcohol, and cyclization under basic conditions.[86] These bis(oxazoline) products were successfully used for the classical palladium-catalyzed allylic alkylation.[87]

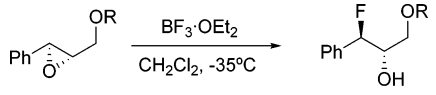


18

R^1 = H, Alkyl
R^2 = Me, Bn, Tr

The epoxide **5v** can suffer a hydrofluorination through a regioselective ring opening process by protection of the primary alcohol as ether **50** and reaction with boron trifluoride (Scheme 26). The reaction gave modest yields of

Scheme 26. Ring Opening Hydrofluorination Process from Epoxyether Derivatives 50

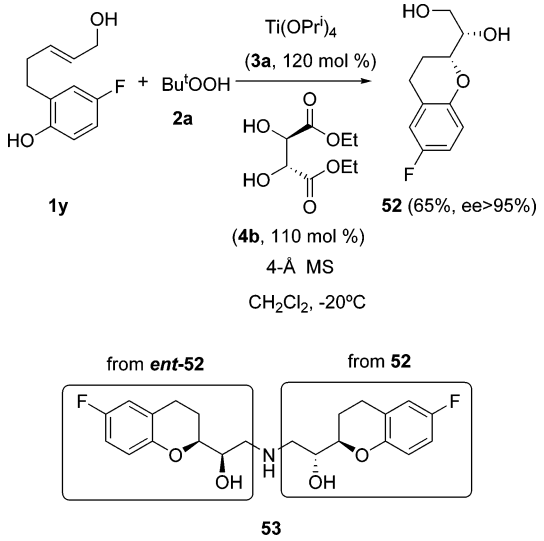


50 **51**

fluorohydrins **51** (around 60%), and it is limited to use of arylglycidyl ethers with non-electron-rich aromatic rings,[88] with the ether moiety having a limiting impact on the results.

The last example of this section is depicted in Scheme 27 and came from the asymmetric synthesis of nebivolol (**53**), which is a potent and selective β_1-adrenergic blocker with antihypertensive activity. The enantioselective epoxidation of the alcohol **1y** gave the expected chiral epoxide, which under the basic conditions of the workup suffered a cyclization process to yield the corresponding diol **52** with excellent enantioselectivity. The epimerization of the secondary alcohol through a Mitsunobu process, tosylation of the primary

Scheme 27. Epoxidation of the Alcohol 1y



1y **52** (65%, ee>95%)

53

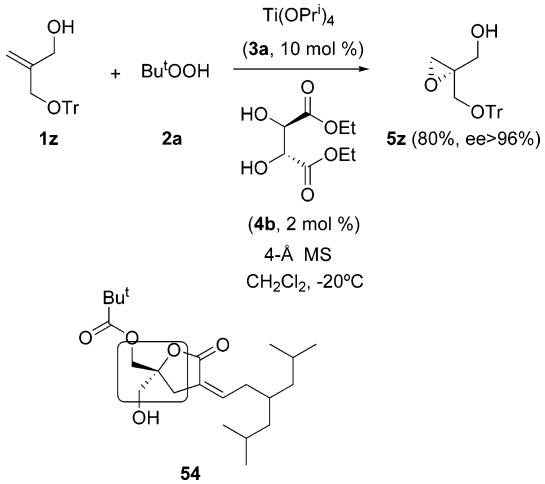
alcohol, and basic treatment gave the corresponding epoxide, which is half of the molecule. The other half was prepared using the same reaction but with the enantiomeric ligand ***ent*-4b**, yielding the expected enantiomer ***ent*-52**, which was tosylated as above, with the corresponding primary amine being prepared by nucleophilic substitution with sodium azide and final reduction. The final reaction of the amine part with the epoxide part yielded nebivolol **53**.[89]

2.1.2. Preparation of Molecules Containing Quaternary Stereocenters

As was noticed by the proposed catalytic species **7** in Scheme 2, there are some steric hindrances when the allylic system has substituents on the *cis*-double bond and when the olefinic carbon atoms are fully substituted. Despite these problems, and during the time covered by this review, there are some examples of epoxidation of alcohols leading to molecules with quaternary centers with a very high enantioselectivity.

The Sharpless epoxidation of methylenepropane-1,3-diol derivative **1z** was accomplished with excellent results to give the alcohol **5z**, which was used as the starting material in the synthesis of lactone **54** (Scheme 28).[90] This lactone is a

Scheme 28. Epoxidation of the Alcohol 1z



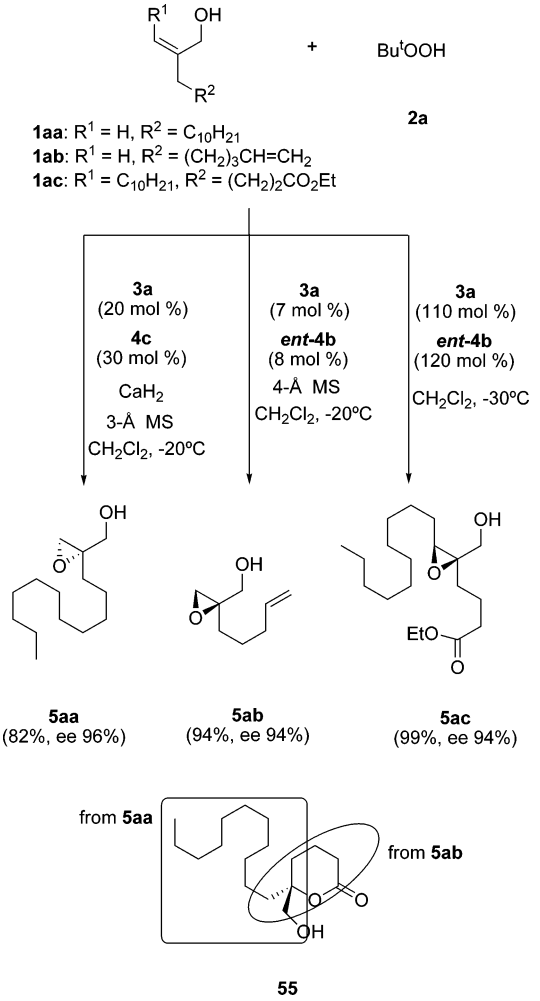
1z **2a** **5z** (80%, ee>96%)

54

potent competitive inhibitor of protein kinase C, displacing phorbol-12,13-dibutyrate, connected with signal transduction.

(+)-Tanikolide **55** is a biologically active δ-lactone isolated from the lipid extract of the marine cyanobacterium *Lyngbia majuscule*, which exhibits antifungal activity against *Candida albicans*, and has been synthesized through the epoxidation of different 2-substituted allylic alcohols (Scheme 29). Thus, the epoxidation of the nonfunctionalized olefin

Scheme 29. Epoxidation of Alcohols 1aa−ac



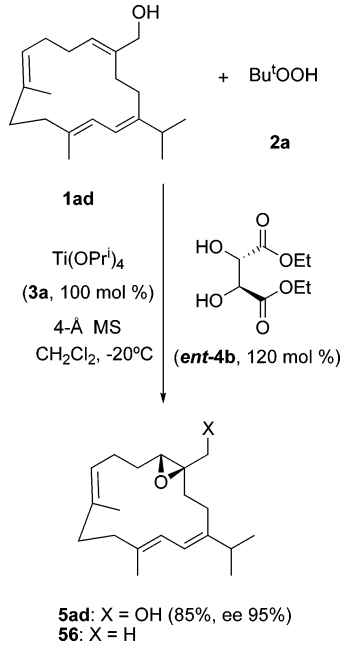
1aa under substoichiometric conditions gave the expected alcohol **5aa** with an excellent result.[91] Further ring opening by reaction with vinylmagnesium bromide, protection of the primary alcohol, acylation of the secondary alcohol with acryloyl chloride, and final ring closing metathesis yielded the corresponding lactone **55**.

Another possibility is the monoepoxidation of polyolefin **1ab**, under substoichiometric conditions using ***ent*-4b**, to yield the alcohol **5ab** with excellent enantioselectivity. Its ring opening, by reaction with decylmagnesium bromide and final degrading oxidation of the carbon−carbon double bond using oxone and osmium tetraoxide, yielded compound **55**.[92]

An alternative route is the epoxidation of the functionalized alcohol **1ac**. In this case the reaction was performed using stoichiometric conditions and ***ent*-4b**, giving similar results to those of the former as far as enantioselectivity is concerned. The protection of the alcohol as its silyl derivative, reduction of both the epoxide and the ester moiety with $LiHBEt_3$ (to the corresponding tertiary and primary alcohols, respectively), and final oxidation of the primary alcohol, lactonization, and deprotection yielded (+)-tanikolide (**55**).[93]

(+)-11,12-Epoxy-11,12-dihydrocembrene (**56**) is a novel cembrene epoxide, first isolated from the Australian soft coral *Sinularia grayi*, which has subsequently been found in various marine soft corals. Its synthesis was performed through the enantioselective epoxidation of the 14-membered ring alcohol **1ad** under stoichiometric conditions, leading to the alcohol **5ad** (Scheme 30). The standard iodination, using

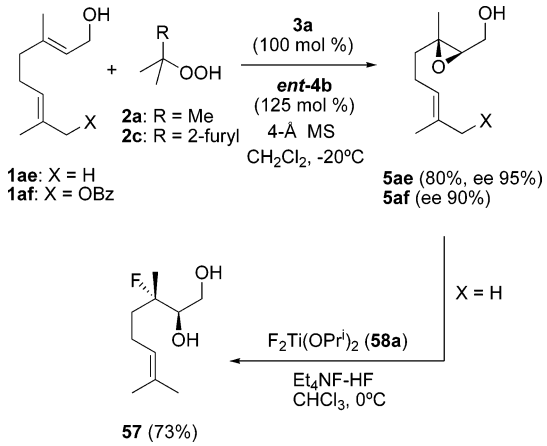
Scheme 30. Preparation of (+)-11,12-Epoxy-11,12-dihydrocembrene



iodine, PPh_3, and imidazole, and subsequent reductive dehalogenation with $NaBH_3CN$ furnished the mentioned compound **56**.[94]

2-Furyl-derived hydroperoxide **2c** has been proposed as an alternative oxygen donor in the enantioselective Sharpless epoxidation. The reaction using different allylic alcohols, such as geraniol **1ae**, under stoichiometric conditions gave the expected epoxide **5ae** (Scheme 31) with similar results[95]

Scheme 31. Epoxidation of Geranyl Derivatives 1ae,af and Ring Opening by a Fluorination Reaction

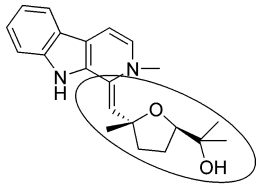


to those obtained using more classical oxygen donors, such as cumyl (**2b**) and *tert*-butyl hydroperoxide (**2a**). However, the authors pointed out the possibility of recovering α,α-dimethyl-2-furyl alcohol by flash chromatography and

recycling it as starting material through the synthesis of the corresponding hydroperoxide **2c**.

The former class of chiral epoxides can be regio- and stereoselectively transformed into 3-fluoro-1,2-diols of type **57**, just by a fluorinative ring opening using ammonium fluoride in the presence of difluorotitanium diisopropoxide (**58a**).[96]

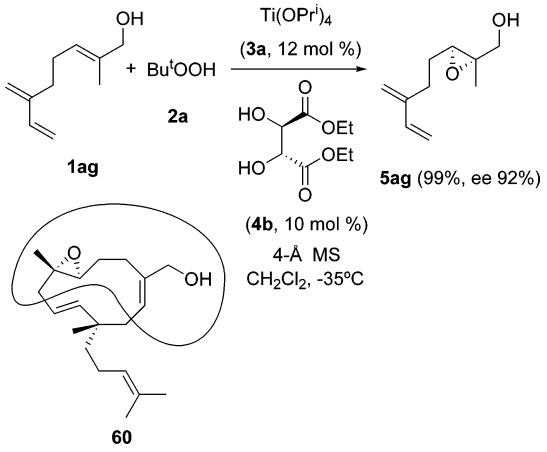
The epoxidation of the benzoyloxy geraniol derivative **1af** to lead to the corresponding epoxide **5af** (Scheme 31) has been proposed as the first step in the asymmetric synthesis of chrysotricine **59**, which was isolated from the Chinese herb medicine *Hedyotis chrysotricha* and exhibits an inhibitory activity against the growth of HL-60 cells in vitro.[97]



59

Vibsanin F (**60**), which was isolated from *Viburum awabuki*, is a diterpene with an unusual carbon skeleton (Scheme 32). Its synthesis was successfully carried out

Scheme 32. Epoxidation of the Triene Alcohol 1ag

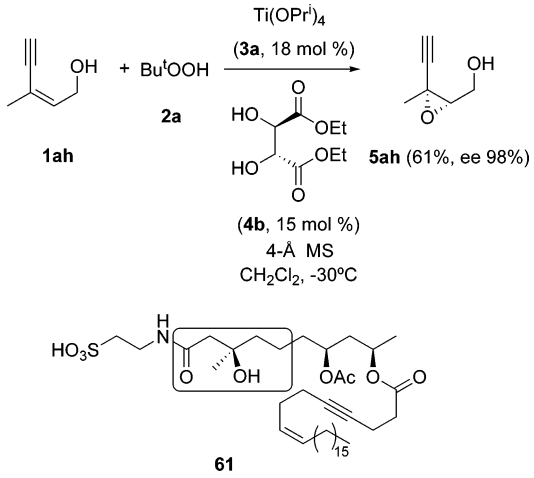


starting with a Sharpless monoepoxidation of the allyl alcohol **1ag** (readily available from myrcene) to lead to epoxide **5ag** with excellent enantioselectivity.[98]

The presence of a carbon−carbon triple bond in the structure of the substrate does not have any important influence on the enantioselectivity, as shown in Scheme 33. The epoxidation of the alcohol **1ah** under substoichiometric conditions gave the expected compound **5ah** with an excellent enantioselectivity. In this case, the presence of a large group in a *cis* position related to the alcohol moiety is very remarkable since, for this type of structure, the enantioselectivity usually dropped.[99] In turn, the alcohol **5ah** has been used in the synthesis of taurospongin A (**61**), isolated from the marine sponge *Hippospongia* sp., which inhibits DNA polymerase β and reverse transcriptase.

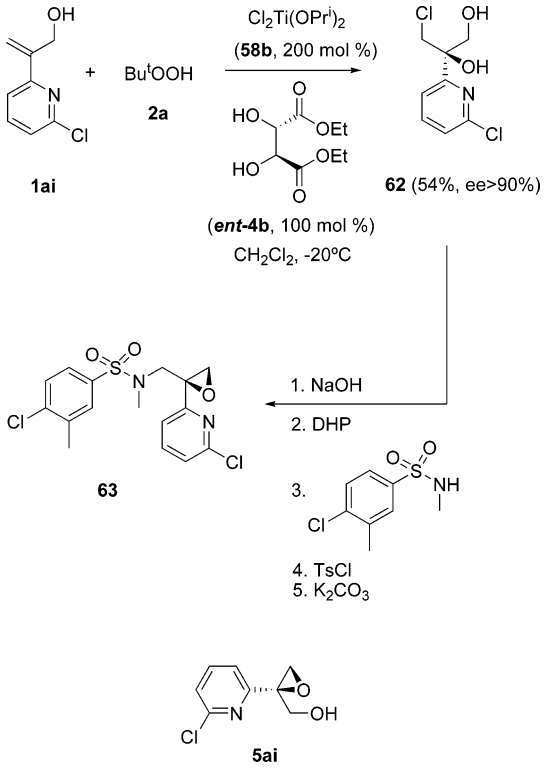
Different 2-aryl substituted oxiranylmethyl sulfonamide derivatives possess a great herbicidal activity against *Echinochloa oryzicola*, among other plant species, with the activity being different depending on the enantiomer used. Thus, the chiral herbicidal **63** was prepared through a tandem Sharpless epoxidation−ring opening variant since in the

Scheme 33. Epoxidation of the Enin Alcohol 1ah



classical protocol the expected epoxide **5ai** was unstable and suffered a ring opening process. This variant implied the use of an excess of dichlorotitanium diisopropoxide (**58b**) as the source of the epoxidation catalytic species, as well as the nucleophile for the subsequent ring opening process,[100] giving the chlorohydrine **62** with an excellent enantioselectivity (Scheme 34). It is worthy of note that the process was not

Scheme 34. Epoxidation of the Functionalized Alcohol 1ai and Preparation of Herbicidal 63



affected by the presence of the strongly basic nitrogen atom of the pyridine ring, with the presence of an extra basic-chelating atom in the starting material being responsible for a decrease in the enantioselectivity in almost every titanium-promoted process. The basic treatment yielded the expected chiral epoxide **5ai**, which after protection of the primary alcohol suffered a nucleophilic ring opening process by the amide. The regeneration of the epoxide was accomplished by a standard tosylation process and final basic treatment.[101]

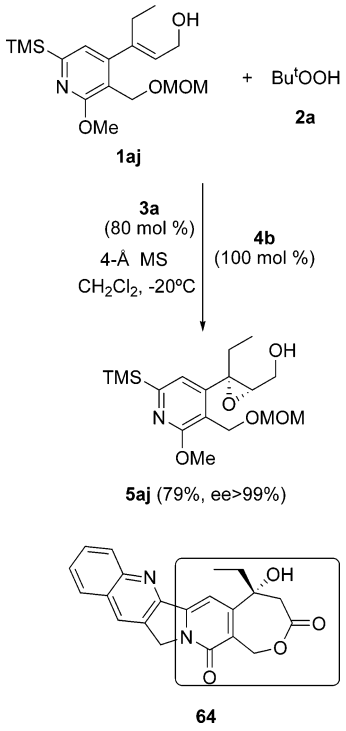
The herbicidal activity of the chiral system **63** was almost 10-fold higher than that of either the other enantiomer or the racemic mixture.

The enantioselective epoxidation of the related 2-benzylpropenol has been used as a starting point in the synthesis of different η^5,η^1-CpP-ruthenium complexes.[102]

The enantioselective epoxidation of (*E*)-3-phenyl-2-buten-1-ol was accomplished by standard substoichiometric protocols, yielding the corresponding (2*S*,3*S*)-2,3-epoxy-3-phenyl-1-butanol with 91% enantiomeric excess.[103] This epoxide was further transformed into α-methyl-α-phenylglycine[104] using the same strategy aforementioned for the amino acid **41**.

(20*R*)-Homocamptothecin (**64**) is a potent anticancer agent that acts on the so-called cleavable complex of DNA and enzyme topoisomerase I (Scheme 35), with the asymmetric

Scheme 35. Epoxidation of the Functionalized Alcohol 1aj

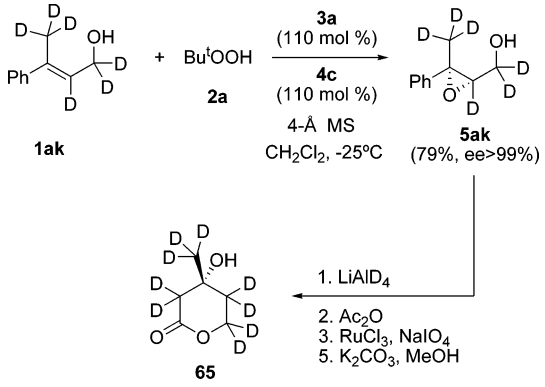


key step in its synthesis being the enantioselective epoxidation of the polyfunctionalized alcohol **1aj** to yield the expected epoxide **5aj**.[105]

In the multigram scaled synthesis of perdeuterated (*R*)-mevalonolactone (**65**), the Sharpless epoxidation of the alcohol **1ak** under stoichiometric conditions has been proposed as the asymmetric key step (Scheme 36). The further nucleophilic ring opening of the epoxide **5ak** with lithium aluminum deuteride, followed by protection of the corresponding chiral diol (as acetyl esters), the degradative oxidation of the phenyl moiety to carboxylic acid, and final hydrolysis, yielded the isotopic labeled compound **65**.[106]

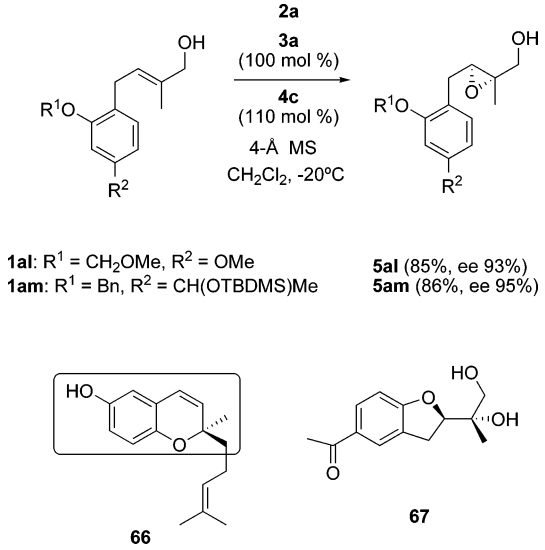
Other products with biological activity synthesized using the enantioselective epoxidation of an allylic alcohol are cordiachromene[107] (**66**, isolated from the acetone extract of *Cordia alliodora*) and (−)-(2*R*,10*S*)-megapodiol[108] (**67**, isolated from plant *Baccaris megapotamica*) with high activity in vivo against P_{388} leukemia in mice and high cytotoxicity in vitro against KB cells. The epoxidation of the starting material **1al** led to the corresponding alcohol **5al**, which in turn was transformed into compound **66**, while the

Scheme 36. Preparation of Perdeuterated (*R*)-Mevalonolactone (65)



epoxidation of the alcohol **1am** was the asymmetric step in the synthesis of product **67** (Scheme 37). In both cases, the

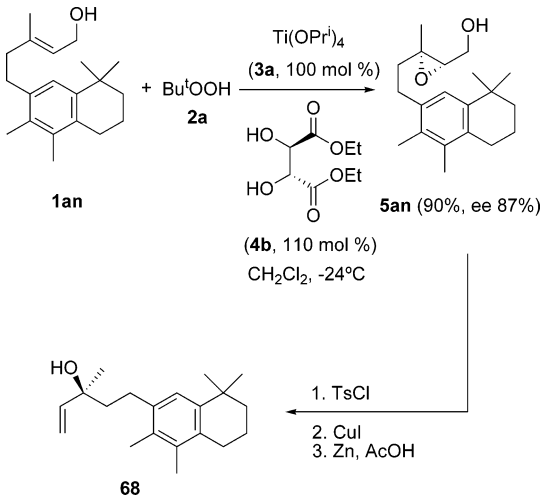
Scheme 37. Epoxidation of Alcohols 1am,al



results are quite similar, although the stoichiometric conditions have been optimized.

Isofregenedol (**68**) is a diterpene isolated from *Haplopappus parvifolius* (Scheme 38). Its synthesis starts from sclareol, which after different steps led to the allylic alcohol **1an**. Its enantioselective epoxidation using the standard

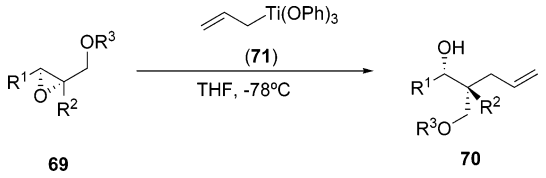
Scheme 38. Preparation of Isofregenedol (68)



stoichiometric conditions yielded the expected epoxide **5an** with a good enantioselectivity.[109] The tosylation of the primary alcohol, followed by iodine substitution and final reduction involving a β-elimination process, gave the tertiary alcohol **68**.

Finally, it should be pointed out that some of the aforementioned epoxides were transformed into the corresponding ethers of type **69**, which were stereoselectively converted into alcohols **70** by reaction with the allyltitanium alkoxide **71**.[110] Although the yields were never higher than 50%, Scheme 39 represents an interesting entry to molecules with a quaternary carbon stereocenter[18] difficult to access by other routes.

Scheme 39. Ring Opening Allylation Process from Epoxyether Derivatives 69



2.2. Thioether Oxidation

Chiral sulfoxides are important compounds, which are finding increasing uses as chiral auxiliaries in asymmetric synthesis and are also of interest in the pharmaceutical industry.[111] Among the various ways to prepare this type of compounds, the enantioselective oxidation of sulfides is one of the most attractive. For that purpose, different chiral ligands as well as metals have been introduced.[31,112] However, it was in 1984 when two groups introduced independently the use of titanium complexes in the enantioselective oxidation of unsymmetric sulfides.[113] The used protocols were slight modifications of the standard Sharpless conditions. The so-called Modena's protocol[113a] involves the use of titanium tetraisopropoxide and a large excess (usually around 4-fold) of a chiral tartrate ester **4**, whereas the so-called Kagan's protocol involves the use of titanium tetraisopropoxide and stoichiometric amounts of both the chiral ester **4** and water.[113b] Although both protocols gave excellent results for aryl alkyl thioethers **72**, for the related dialkyl derivatives the enantioselectivity usually dropped. To ensure a high enantioselectivity and reproducibility, a very important parameter is the premixing time of the titanium alkoxide and the chiral ligand,

Scheme 40. Proposed Mechanism Pathway for the Oxidation of Sulfides

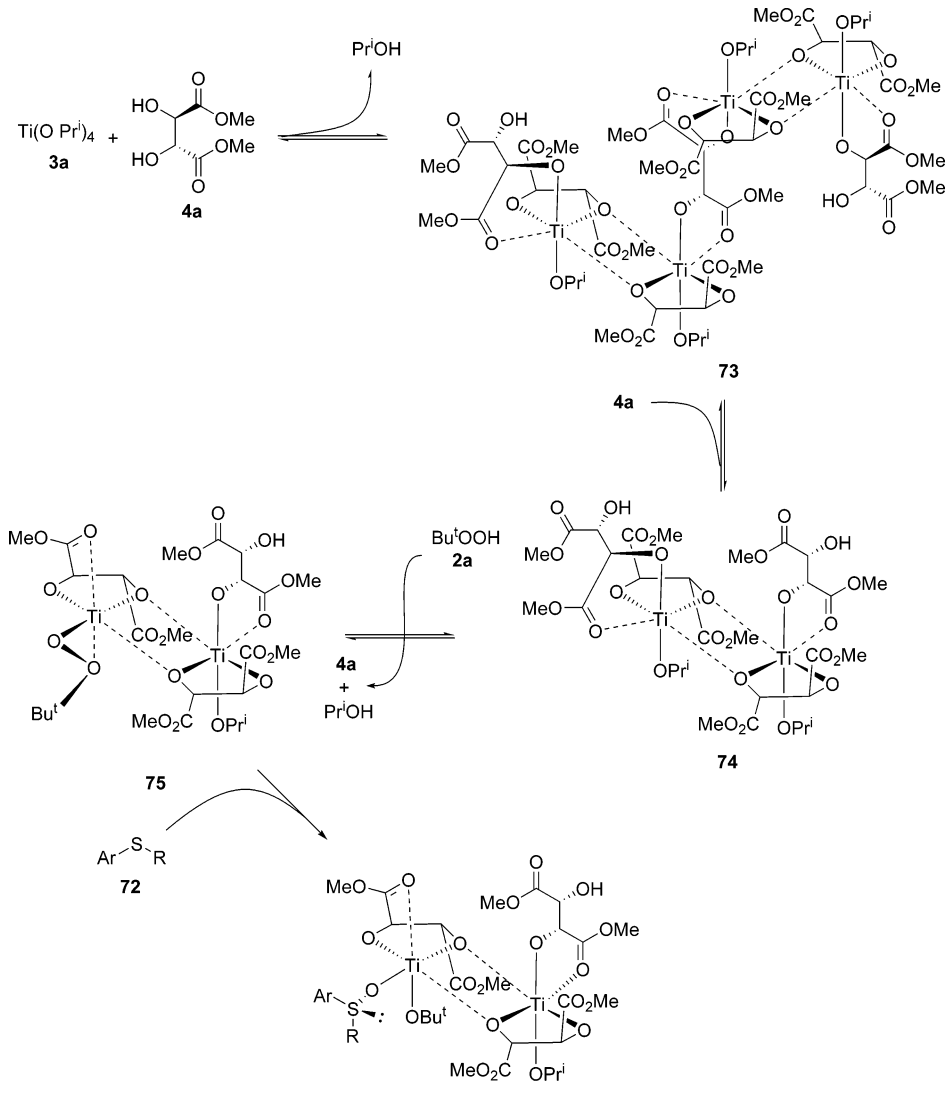
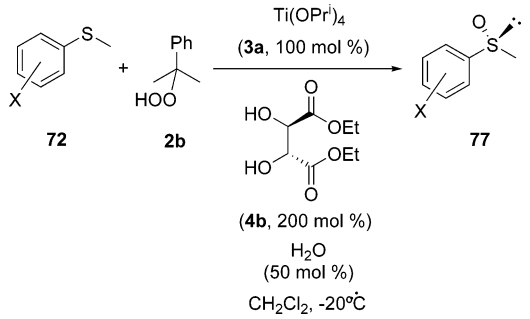


Table 1. Enantioselective Oxidation of Methylsulfanyl Arenes



entry	X	no.	yield (%)	ee (%)
1	2-Br	**77a**	77	83
2	3-Br	**77b**	67	97
3	4-Br	**77c**	88	95
4	2-Cl	**77d**	94	80
5	MeO	**77e**	86	88

as well as the temperature, which should be optimized for each substrate.

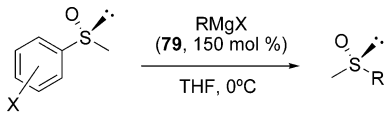
The addition of molecular sieves permitted the reduction of the amount of titanium tetraisopropoxide (**3a**) and the tartrate ester **4** up to 10 mol %; in this case it was necessary to use 10 mol % 2-propanol instead of water.[114] Although the role of molecular sieves is still unclear, it seems to be connected with the increasing of the rate of ligand exchange on the titanium complex.[115] Despite the obvious advantages of the aforementioned substoichiometric protocol, it has been scarcely ever used.

Concerning the possible mechanism pathway, it should be pointed out that the amount of the tartrate derivative is critical in order to obtained good results. Thus, for example, the standard Sharpless ratio of reagents (1:1 titanium alkoxide/tartrate derivative) gave racemic sulfoxides. In addition, an excess of tartrate, as well as the presence of water, inhibits the classical allylic alcohol oxidation. These differences in reagent stoichiometries and in behavior probably involve very different catalyst structures. On the contrary, the similar results obtained by both Modena and Kagan protocols seem to indicate that the reaction proceeds in these cases through the same intermediates. Molecular weight measurements indicated a dimeric species, and XANES and EXAFS data confirmed a TiO_6 core throughout the reaction. Although the direct NMR examination of both systems gave confusing information (owing to fast ligand exchange processes), the same experiments performed in the presence of 1,2-ethylenedisulfonamides permitted the direct observation of the tetrameric complex **73** (Scheme 40), which is in equilibrium with the related dimeric system **74**, with a constant value of about 1.[116] In fact, theses species, among others, were further observed in the mixture of Modena and Kagan catalysts. In the former protocol, the excess of the tartrate derivative forces the formation of dimeric species bearing more than four chiral ligands, whereas, in the last one, water is responsible for their formation. The final change of ligands by the hydroperoxide gave the catalytic species **75**, which is responsible for the enantioselective oxidation of the corresponding alkylsulfanyl arene **72**.

A general comment refers to the most convenient oxidant agent, which usually is cumyl hydroperoxide (**2b**). However, in some cases, other systems, such as *tert*-butyl derivative **2a**, can give similar and even better results.[117]

The drawback associated with the use of alkylsulfanyl alkanes **78** has been overcome by a new strategy, which implied the highly enantioselective oxidation of alkylsulfanyl arenes **72** to give the sulfoxide **77** (for some examples, see Table 1), followed by nucleophilic displacement of the aryl moiety by reaction with alkyl Grignard reagents **79** (Scheme 41).

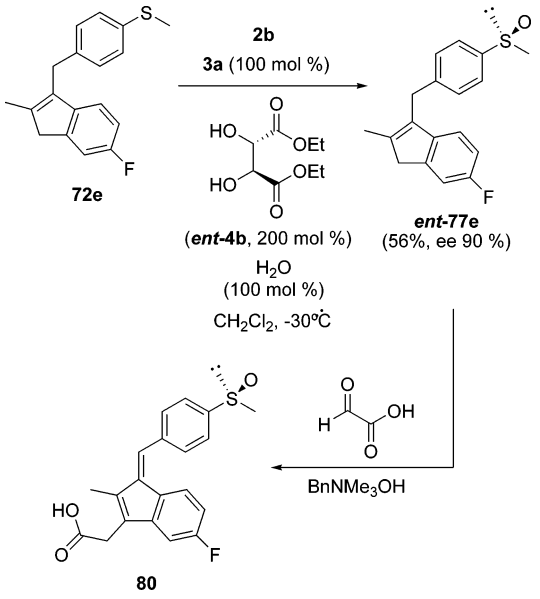
Scheme 41. Synthesis of Chiral Methyl Alkyl Sulfoxides



The substitution process occurred with full inversion of configuration at the sulfur stereogenic center and with practically no racemization on the final system.[118] It should be pointed out that, to ensure a high yield of product **78**, a slight excess of Grignard reagent must be added. These results seem to be independent of the nature of alkylmagnesium reagents; similar yields are obtained for primary as well as secondary organometallics.

Sulindac (**80**), which has been used therapeutically as a racemic mixture, is a nonsteroidal anti-inflammatory drug with some anticancer activity, chemopreventing chemically induced lung, mammary, and colon carcinogenesis and enhancing the cytotoxicity of other anticancer drugs. However, some other biological effects have been attributed to one of the two enantiomers. Its enantiomeric synthesis was accomplished by the enantioselective oxidation of methylsulfanyl arene **72e** using a slightly modified Kagan protocol to give the chiral sulfoxide ***ent*-77e** with a good enantioselectivity (Scheme 42). The reason for the modest yield was

Scheme 42. Synthesis of Chiral Sulindac (80)

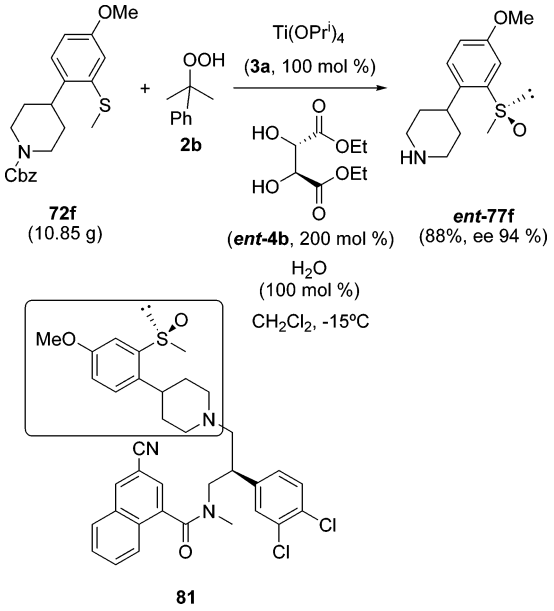


not explained; this issue is of capital importance in order to know if the process is a truly enantioselective reaction or a kinetic resolution one (vide infra, section 7), that is, oxidation of the sulfide to a sulfoxide and then a second asymmetric oxidation of the racemic sulfoxide, to give the corresponding achiral sulfone and the remaining chiral sulfoxide. The final reaction with glyoxylic acid catalyzed by Triton-B yielded the expected chiral drug. When the oxidation was performed

using the enantiomeric chiral tartrate **4b**, the opposite enantiomer **77e** was obtained with similar results.[119]

Another interesting example of the safety and robustness of the aforementioned process came from the large scale preparation (100 L) of the neurokinin antagonist candidate drug **81** (Scheme 43). In its synthesis, one of the asymmetric

Scheme 43. Oxidation of the Functionalized Methylsulfanyl Arene 72f

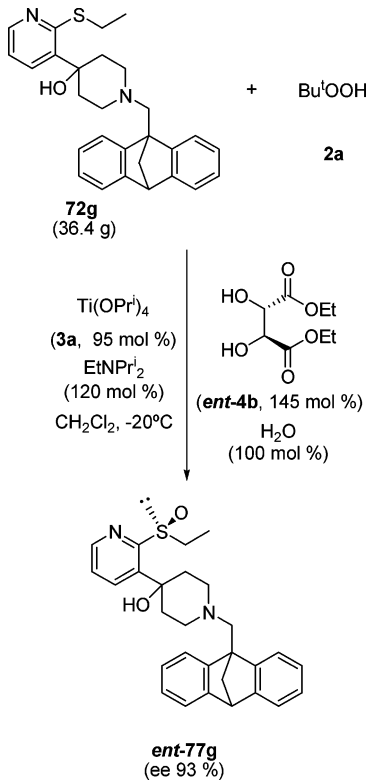


steps was the epoxidation of methylsulfanyl arene **72f** to yield the corresponding deprotected sulfoxide **77f** with an excellent result.[120] It is noticeable that the addition of the cumyl hydroperoxide (**2b**), used as the oxidant agent, was very exothermic and affected the final enantioselectivity. Therefore, the addition rate of the oxidant had to be adjusted to maintain the internal temperature of the reaction vessel. In this way, the reaction could be scaled up with a high reproducibility. The final basic hydrolysis gave chiral sulfoxide ***ent*-77f** after removal of the protective group of the amine with a high overall yield.

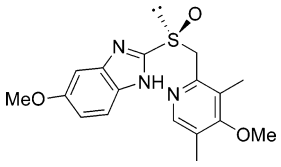
Not only methylsulfanyl arenes can be successfully enantioselectively oxidized but also compounds having larger substituents gave excellent results, even on a pilot plant scale. This is the case for the candidate drug ZD3638 (***ent*-77g**), which is an atypical antipsychotic agent for the treatment of schizophrenia. The reaction of the sulfanyl derivative **72g** using the standard conditions gave the expected sulfoxide with a moderate enantiomeric excess (60% ee), which could be improved by crystallization. However, the addition of 1 equiv of Hünig's base improved the results, avoiding the formation of the corresponding sulfone byproduct (Scheme 44). The role of this base is not very clear, but it has been speculated that it forms a supramolecular structure by hydrogen bonding with the substrate which favors the reaction.[121] Larger substituted alkyl chains did not raise the previous level of enantioselection.[122]

Esomeprazole (***ent*-77h**) is a potent gastric acid secretion inhibitor which was obtained by enantioselective oxidation of the corresponding benzylsulfanyl compound.[123] The reaction could be scaled up to 6.2 kg of the starting sulfide, giving the sulfoxide ***ent*-77h** with a 92% yield and 94% ee, which could be raised to 99.5% ee just by recrystallization from methyl isobutyl ketone. As in previous cases, the presence

Scheme 44. Oxidation of the Functionalized Ethylsulfanyl Arene 72g



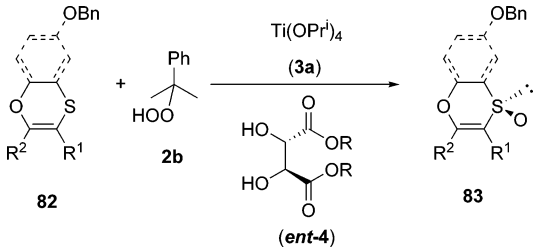
of *N*,*N*-diisopropylethylamine is of vital importance to obtain excellent results, while either other amines or more basic bases generally gave lower enantioselectivities.



(Methylthio)methylphosphonates have been enantioselectively oxidized to the corresponding chiral sulfoxides using Kagan's protocol. However, the enantioselectivity was never higher than 80%, and this approach was abandoned by a diastereoselective one.[124]

Not only can aryl sulfanyl derivatives be oxidized with a high level of enantioselectivity, but 1,4-oxathiine derivatives **82** have also been successfully used, as is shown in Table 2. The reaction for the 6-monosubstituted systems **82a,b** was performed using modified Modena conditions (200 mol % titanium tetraisopropoxide and 400 mol % diethyl tartrate), and the results were independent of the nature of substituent R^2. These chiral C-6 substituted 2,3-dihydro-4-oxo-1,4-oxathiines **82a,b** were practically quantitatively transformed into the corresponding chiral β-keto allyl sulfoxides just by treatment with lithium diisopropylamide.[125] On the contrary, the benzocondensated system **82c** was oxidized using a modified Kagan protocol (150 mol % titanium tetraisopropoxide, 300 mol % diethyl tartrate, and 150 mol % water), and as in other cases, the presence of stoichiometric amounts of *N*,*N*-diisopropylethylamine had a beneficial effect not only on the enantioselectivity and yield but also on the sulfoxide isolation process.[126] It should be pointed out that the

Table 2. Enantioselective Oxidation of 1,4-Oxathiine Derivatives

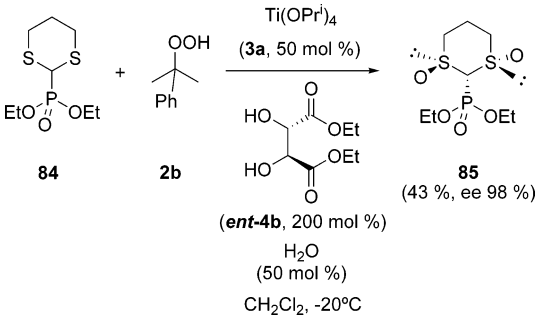


entry	R	no.	derivative	R^1	R^2	yield (%)	ee (%)
1	Et	**83a**	2,3-dihydro	H	Ph	90	98
2	Et	**83b**	2,3-dihydro	H	Bu^t	80	96
3	Pr^i	**83c**	benzo	3-BnOC$_6$H$_4$	4-IC$_6$H$_4$	86	99

benzocondensated system **83c** was used in the preparation of an estrogen receptor modulator.

Other sulfur-containing heterocycles have been successfully oxidized. Thus, the 1,3-dithian-2-ylphosphonate derivative **84** has been doubly oxidized to give the chiral bissulfoxide **85** (Scheme 45), which in turn has been used as

Scheme 45. Oxidation of the Dithiane Derivative 84

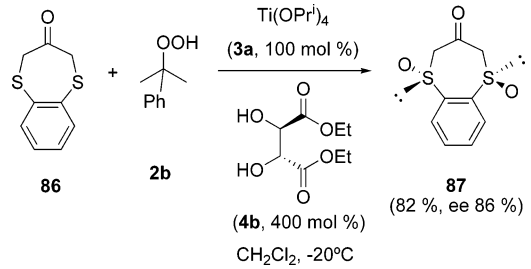


starting material in the synthesis of cispentacin, a compound isolated from *Baciluss cereus* with a potent activity against *Candida* species.[127] The whole process implied, first, an enantioselective monooxidation to a chiral sulfoxide and, then, a second oxidation, which is a diastereoselective process controlled by the chiral titanium complex (which preferred an *S* configuration for the sulfur center) and the monosulfoxide intermediate (which preferred a *trans* configuration). These two effects control the final high enantioselectivity as well as the sulfur configuration. This hypothesis was further confirmed by a careful study using the related ketene dithioacetal derivatives.[128]

Other heterocycles containing two sulfur atoms have also been doubly oxidized. Thus, the reaction of 1,5-benzodithiepan-3-one (**86**) with cumyl hydroperoxide in the presence of titanium tetraisopropoxide and a large excess of tartrate derivative **4b** (Modena's protocol) gave the expected disulfoxide derivative **87** (Scheme 46) with a lower enantioselectivity compared with that of the above disulfide **85**. The chiral ketone **87** has been used in the asymmetric desymmetrization of *meso*-diols through the formation of the corresponding ketal followed by ketal fission upon treatment with potassium hexamethyldisilazide and final acetylation of the resulting alcohol.[129]

Other systems with more sulfur atoms, such as 6,10-diethyl trithiolo[*h*]benzopentathiepin, have been monooxidized,[130] giving a mixture of all possible sulfoxides with good enantioselectivities.

Scheme 46. Oxidation of 1,5-Benzodithiepan-3-one

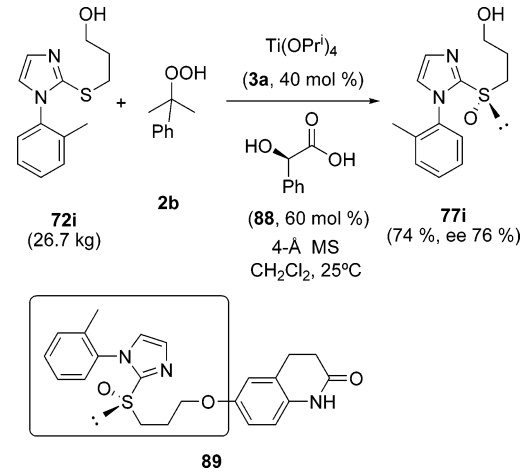


The general scheme of the aforementioned oxidation has suffered different modifications in order to improve its scope. Thus, the use of a mesoporous silica MCM-41 doped with titanium has been proposed instead of using soluble complexes of titanium.[131] In this case, the chosen silica possesses a regular structure of hexagonal arrays of uniform channels, whose diameters are controllable and large enough for both the preparation of the active titanium site inside them and for the diffusion of bulky molecules. However, the enantioselectivity found was very poor, even for simple methylsulfanyl arene derivatives (30% ee).

Another reported modification was the use of chiral C_2 symmetric 1,2-diols bearing tertiary alkyl groups instead of tartaric derivatives. However, this change in the ligand gave very bad results (ee lower than 14%).[132]

The results obtained using mandelic acid (**88**) as chiral ligand were more interesting. In fact, this ligand was used in the key step for the synthesis of the potent inhibitor of platelet adhesion OPC-29030 (**89** in Scheme 47), giving

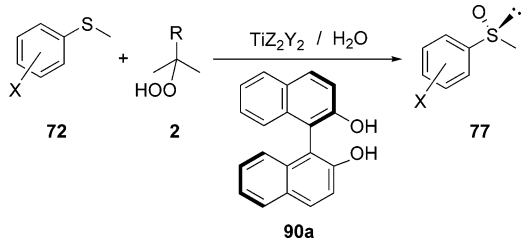
Scheme 47. Use of Mandelic Acid in the Oxidation of the Thioether 72i



better results than any other tartaric derivative or diol. It should be pointed out that the presence of water in the reaction medium did not have any significant influence on the enantioselectivity but the rate was slightly reduced. Another important point was the presence of a hydroxy group in the substrate **72i**, as well as the length of the carbon chain attached to it. These two facts could suggest that the substrate forms a rigid bichelated complex with the titanium catalytic species. The homogeneous results permitted scale-up of the reaction in a pilot plant with good enantiomeric excess, which could be further improved up to 99.7 % simply by recystallization.[133]

Since the introduction in 1992 of chiral binaphthol[134] **90a** and its derivatives[135] as ligands for the catalytic oxidation of alkylsulfanyl arenes, many modifications on the general

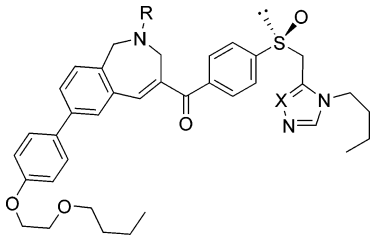
Table 3. Enantioselective Oxidation of Methylsulfanyl Arenes Using Binaphthol



entry	R	no.	TiY_2Z_2	no.	X	no.	yield (%)	ee (%)	ref
1	Me	**2a**	$Ti(OPr^i)_4$	**3a**	H	**77j**	86	63	134
2	Me	**2a**	$Ti(OPr^i)_4$	**3a**	4-Me	**77k**	88	73	134
3	Me	**2a**	$TiCp_2Cl_2$	**58c**	H	**77j**	65	39	136
4	Bu^t	**2a**	$TiCp_2Cl_2$	**58c**	4-Me	**77k**	95	45	136
5	2-furyl	**2c**	$Ti(OPr^i)_4$	**3a**	H	**77j**	69	85	137
6	2-furyl	**2c**	$Ti(OPr^i)_4$	**3a**	4-Me	**77k**	75	61	137

scheme have been performed (Table 3). Thus, dicyclopentadienyltitanium dichloride (**58c**) has been proposed as an alternative titanium source to the original titanium tetraisopropoxide, with the enantioselectivity being remarkably lower.[136] Concerning the oxidant, the hydroperoxide derived from furane **2c** can be used with similar results compared to those of the original protocol.[137] However, the reaction failed when it was performed using the related ethylsulfanyl arene and the reagent **2c**, indicating a strong dependence on the substrate nature. Finally, it is worthy to note the presence of a small positive nonlinear effect [(+)-NLE],[138] which could indicate the presence of a bimetallic titanium species bearing two chiral binaphthol moieties in the catalytic cycle.

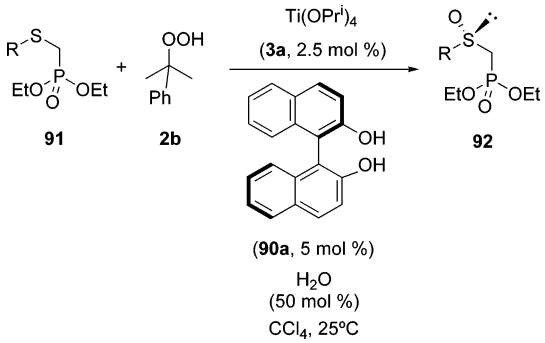
Despite the previously mentioned failure with ethylsulfanyl derivatives using the 2-furyl hydroperoxide derivative **2c**, the simple change of this hydroperoxide system by the most conventional cumene derivative **2b** permitted the successful oxidation of larger substituted thioethers. In this way, the chiral sulfoxides ***ent*-77l,m** were prepared using catalytic amounts of the corresponding binaphthol ***ent*-90a**. Although in both cases the enantioselectivity was excellent, in the second case the result could be due to a double process: first enantioselective oxidation to give the expected compound ***ent*-77m**, followed by a partial kinetic oxidative resolution giving the corresponding sulfone.[139] Compounds ***ent*-77l,m** are particularly interesting owing to their highly potent CC chemokine receptor 5 antagonistic activity. This receptor is the entry point for macrophage-tropic HIV-1 into cells, and therefore, **ent-77l,m** could be active against this virus.



***ent*-77l**: R = Pr^n, X = N (84 %, ee 96%)
***ent*-77m**: R = Bu^i, X = CH (45 %, ee 84%)

The use of chiral binaphthol **90a** permitted, in this case, the highly enantioselective oxidation of different substituted thiomethylphosphonate derivatives **91** (Table 4). The reaction is a genuine fully enantioselective process, since the formation of the corresponding sulfone can be avoided by controlling the amount of the oxidant **2b** and, therefore, avoiding any kinetic resolution process. The enantioselectivity is, in general, quite homogeneous, independent of the nature of the substitution on the starting phosphonate **91**.[140] The chiral sulfoxide **92** could be easily transformed into other sulfoxides by displacement of the methylphosphonate moiety just by reaction with organomagnesium reagents. This reaction occurred with inversion in the configuration at the sulfur center and with retention of the enantiomeric excess of the starting material **92**.

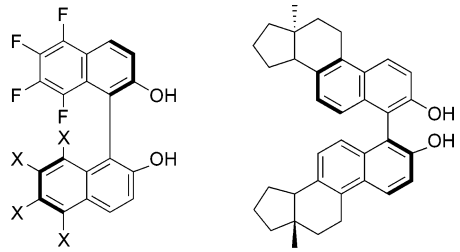
Table 4. Enantioselective Oxidation of Substituted Thiomethylphosphonates



entry	R	no.	yield (%)	ee (%)
1	Me	**92a**	85	>98
2	Et	**92b**	83	91
3	Ph	**92c**	52	94

Other binaphthol derivatives have been proposed as alternatives to the system **90a**. Thus, the fluorinated systems **90b,c** have showed a small increase in the enantioselectivity when the reaction was performed at low concentrations.[141] In fact, kinetic studies showed that the rate, using the system **90c**, was 5-fold faster than that when using compound **90a**. However, the opposite enantiomeric sulfoxide was obtained when fluorinated systems **90b,c** were used. The electron-deficient nature of aromatic rings increases the oxidative stability, as well as the acidity of compounds **90b,c** compared to that of **90a**, and as a consequence, it is conceivable that a different configurational stability forces a different aggregation state, which in turn is a likely cause for the observed change in the enantioselectivity.

The ligand ***ent*-90c** has been successfully used in the oxidation of different methylsulfanyl arenes,[142] with the level of enantioselectivity being similar to those obtained with simple binaphthol. The advantage of this ligand resides in the solvent used (THF), since other binaphthol systems required the use of chlorinated solvents, and, therefore, have evident environmental problems.



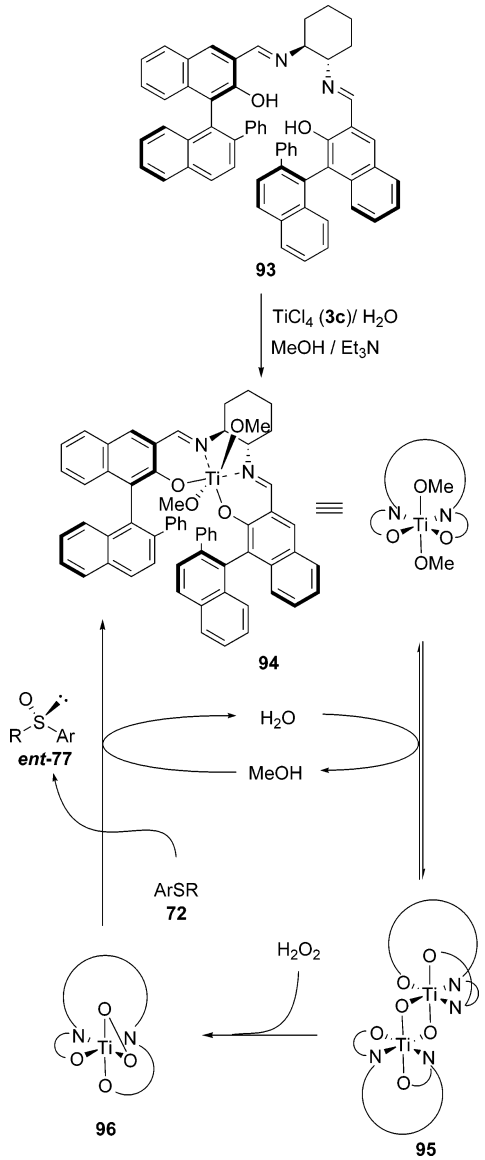
90b: X = H
90c: X = F

***ent*-90d**

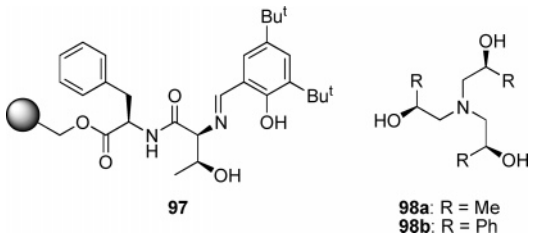
The ligand **93** is something different compared to the previously reported systems since it can use a new oxidant

source such as urea hydrogen peroxide.[143] The level of enantioselectivity was excellent for alkylsulfanyl arenes (ee up to 99%) without any appreciable overoxidation to the corresponding sulfone; the electronic nature and the position of substituents on the aromatic ring had a minimal effect on the final result. Concerning the mechanism pathway, the presence of the di-μ-oxo complex **95** (according to FAB mass spectrum) should be pointed out. This species is in equilibrium with the monomeric species **94**, and its presence is indicated by an important positive nonlinear effect. The ^{1}H NMR data also corroborated this hypothesis and showed equilibrium between a *cis*-β structure for the bimetallic species **95** and a square planar monomeric structure for complex **94**. The exchange of ligands with the bidentate peroxide gave a new monomeric species with a *cis*-β structure **96**, which could be detected by NMR studies. The final oxidation of the sulfide **72**, followed by ligand exchange, renews the starting species **94** (Scheme 48).

Scheme 48. Catalytic Cycle for the Enantioselective Oxidation of Thioethers Using the Ligand 93



The salen ligand derivative **97** can be used in the oxidation of alkylsulfanyl arenes with a very high chemical yield and good enantioselectivities (around 65%).[144] This system permitted a further improvement with the use of aqueous hydrogen hydroperoxide. The salen ligand derivative **97** formed an extremely robust titanium complex, and as the ligand was attached to a Wang resin, the system could be reused several times without erosion of either conversion or enantioselectivity. No leaching was detected in the reaction solvent.



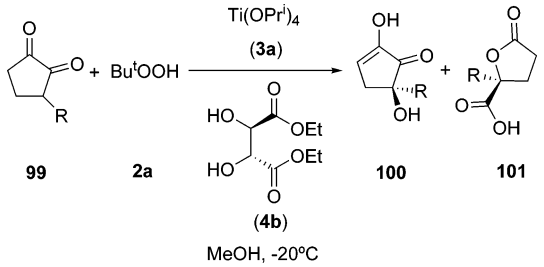
Despite the good results obtained using different chiral salen ligands, the use of simple chiral *N*-alkyl 1,2-diphenylethanol as chiral ligand did not give good results.[145] In all tested cases, a significant amount of sulfone was isolated and the enantioselectivity was never higher than 50%.

Finally, it should be mentioned that other diols can be used. This is the case of compounds with C_3 symmetry of type **98**, which could oxidize alkylsulfanyl arenes to the corresponding chiral sulfoxides with enantioselectivities up to 84% and good turnover numbers (from 50 to 100). As in the previous cases, although the presence of dimeric/oligomeric aggregates has been verified, the catalytic species seems to be a monomeric titanium complex.[146]

2.3. Miscellaneous Oxidations

Titanium complexes have been used in the oxidation of other compounds different from allylic alcohols and sulfides. Thus, the enantioselective oxidation of 3-substituted 1,2-cyclopentanediones **99** using titanium tetraisopropoxide (**3a**) and diethyl tartrate (**4b**), as well as the hydroperoxide **2a** as oxidant agent, gave a mixture of products (Scheme 49). It

Scheme 49. Enantioselective Oxidation of 1,2-Cyclopentanediones

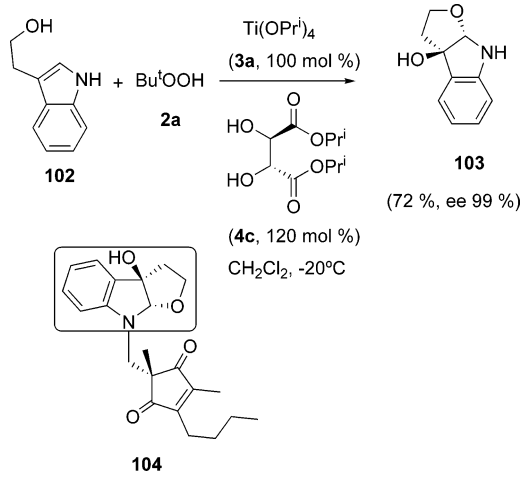


was possible to obtain preferentially one of them just by playing with the amounts of the different reagents.[147] Thus, using stoichiometric amounts or a slight excess of all reagents, the main product was the 2-hydroxy dione **100**, with yields never higher than 40% and excellent enantioselectivities. However, when the reaction was performed using a 2- or 3-fold excess of all reagents, the main product was the lactone **101**, as well as the related acid derivative. In this last case, the chemical yield reached up to 55% with retention of the previous enantioselectivity. The scope of this reaction seems to be very narrow since the reaction failed when it was performed using either 1,2-cyclohexanodiones or 1,3-cyclopentanodiones as starting materials. A similar reaction using 2-hydroxymethyl cycloalkanones gave the

corresponding oxidized 2-hydroxy-2-(hydroxymethyl)cycloalkanones in very low yield.[148]

The final example of enantioselective oxidation processes is depicted in Scheme 50. It comes from the synthesis of

Scheme 50. Enantioselective Oxidation of the Indole 102



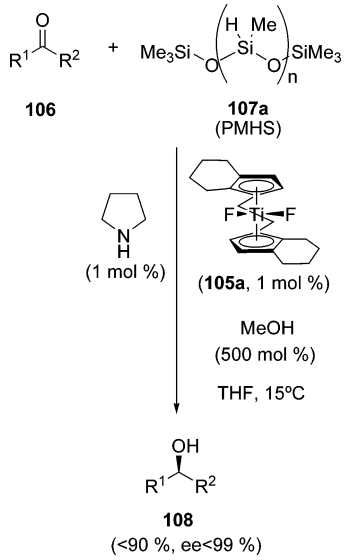
(+)-madindoline A (**104**), which is a potent inhibitor of the differentiation of osteoblast cells as well as interleukin 6, which is a multifunctional cytokine with a central regulatory role in host defense mechanisms. The oxidation of the indole **102** using stoichiometric amounts of titanium tetraisopropoxide and the tartrate **4c** furnished the hydroxyfuroindoline **103** with excellent enantioselectivity.[149] The absolute configuration was determined in this case by X-ray analysis.

3. Enantioselective Reduction Processes

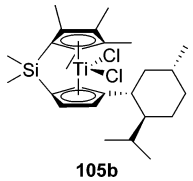
The enantioselective reduction is another fundamental process in organic synthesis,[150] in which the use of titanium complexes was very limited until the independent introduction of chiral titanocenes as chiral precatalyst for the reduction of ketones by the Halterman and Buchwald groups.[151] The use of chiral titanocenes **105** as precatalyst [the real catalyst seems to be the related hydride titanium(III)] gave different results depending not only on the nature of the titanocene but also on other factors, such as (a) the initial hydrogen source (H_2 or hydrosilane derivatives), (b) the activation procedure (addition of butyllithium, methyllithium, silanes), (c) the method of addition of the alkylating/reducting activator, (d) the maturation time, and, of course, (e) the presence of other additives such as water, alcohols, amines, etc. Despite these puzzling factors, there are several reduction protocols which have given excellent results. Thus, the hydrosilylation of ketones **106** using the chiral titanocene **105a** and polymethoxyhydrosiloxane (PMHS, **107a**) has been successfully performed (Scheme 51). The slow addition of methanol is compulsory, to obtain an excellent enantioselectivity. In fact, this additive also enhances the reaction rate, which is consistent with a catalytic pathway in which the enantioselective-determining step is different from the rate-determining step. The level of enantioselectivity is significantly lower for dialkyl ketones (ee around 50%) than for either aryl or alkenyl alkyl ketones (ee around 90%).[152]

In the hydrosilylation of ketones **106** using the chiral titanocene **105b**, the more reactive phenylsilane (**107b**) as initial hydrogen source, and butyllithium as activator, the

Scheme 51. Enantioselective Hydrosilylation of Ketones 106



enantioselectivity was a little bit lower than that in the former case.[153] An important trend in this case was the continuous



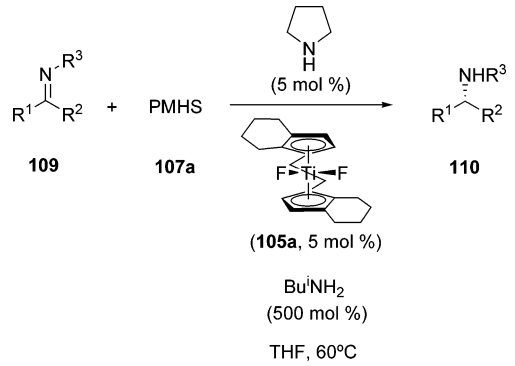
105b

decrease in the enantioselectivity as the reaction proceeded, which could indicate the presence of a secondary catalytic cycle modulated by the final product (autopoisoning). The addition of water (1 equiv referenced to titanium complex) has a beneficial effect on the enantioselectivity, destroying practically the autopoisoning effect. Finally, it should be pointed out that the presence of electron-donating groups in the aryl ring of the ketone has a beneficial effect both on the rate and on the enantioselectivity. This observation suggests that in the key intermediate there is a secondary interaction between the highly electropositive titanium atom and the electron-rich aromatic ring, which leads to a more rigid transition state.

The use of titanocenes as chiral precatalyst has been extended to the reduction of different imines (Table 5). Thus, the complex **105a** was able to reduce different imines **109** to give the expected amines **110**,[154] in general with excellent results. In this case, the reaction should be performed at higher temperatures, and for *N*-aryl imines, the additive of choice was isobutylamine. Under these conditions, the reaction gave excellent results for dialkyl imines and very disappointing enantioselectivity for aryl imine derivatives (Table 5, entry 4). However, a slight change in the standard protocol of reduction, for instance the use of methanol as additive instead of isobutylamine,[154a] improved the enantioselectivity, to as much as 97% ee (Table 5, entry 5). The hydrochloride salt of the amine **110e** activates the calcium receptor in the parathyroid gland, and therefore, it is in phase II clinical trials for the treatment of hyperparathyroidism. The (*R*)-isomer is 10- to 100-fold more potent than the corresponding (*S*)-enantiomer.

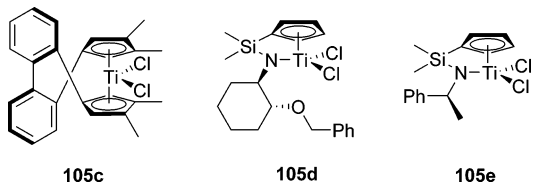
The related titanocenes **105c**−**e** have been used as precatalyst in the reduction of acetophenone *N*-benzylimine (**109f**; R^1 = Ph, R^2 = Me, R^3 = Bn) with different results.

Table 5. Enantioselective Hydrosilylation of Imines



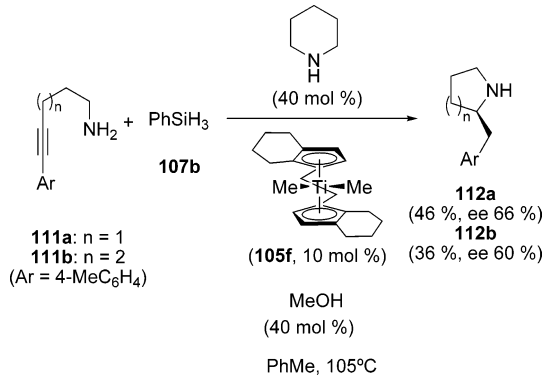
entry	R^1	R^2	R^3	no.	yield (%)	ee (%)
1	*c*-C_6H_{11}	Me	Ph	**110a**	63	99
2	*c*-C_6H_{11}	Me	4-$MeOC_6H_4$	**110b**	79	99
3	*n*-C_6H_{13}	Me	4-$MeOC_6H_4$	**110c**	70	88
4	Ph	Me	4-$MeOC_6H_4$	**110d**	100	13
5	3-$MeOC_6H_4$	Me	2-$ClC_6H_4(CH_2)_3$	**110e**	83	97

In all cases, hydrogen (150 bar, used as initial source of hydrogen) and toluene at 80 °C were chosen as the reduction conditions. The enantioselectivity was good (76% ee) for the titanocene **105c**.[155] However, for complexes **105d,e**[156] the ee of the final amine **110f** was never higher than 55%.



The titanocene **105f** has been used as the chiral catalyst in hydroamination/hydrosilylation sequences of alkylamines **111** to yield the cyclic amines **112** (Scheme 52). Although

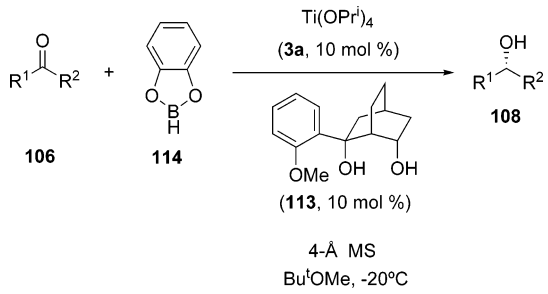
Scheme 52. Enantioselective Hydroamination/ Hydrosilylation of Alkynes 111



the results are not yet satisfactory, this sequential reaction opens up the field for using other ligands and substrates.[157]

Instead of titanocene derivatives, which drive the reduction reaction through a titanium(III) hydride derivative, it is possible to use a chiral titanium complex as Lewis acid to activate the ketone by coordination. In this way, the nucleophilic addition of the reducing agent gave enantioselectively the corresponding secondary alcohol derivative. Following this idea, the diol **113** (2,6-BODOL) has been introduced as an effective chiral ligand.[158] The reduction of

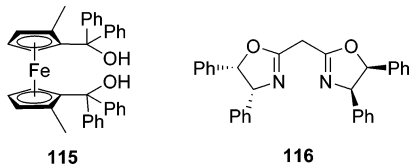
Table 6. Enantioselective Reduction of Ketones



entry	R^1	R^2	no.	yield (%)	ee (%)
1	Ph	Me	**108a**	>99	96
2	1,2-$C_6H_4(CH_2)_3$		**108b**	>99	96
3	4-$MeOC_6H_4$	Me	**108c**	>99	94
2	Bu^n	Me	**108d**	80	85
5	$Ph(CH_2)_2$	Me	**108e**	>99	56

different ketones **106** by catecholborane (**114**) gave the expected alcohols **108** with excellent results (Table 6). The enantioselectivity is very good for alkyl aryl ketones independent of size and substitution. The results are slightly lower for dialkyl ketones. Concerning the mechanism, the presence of a pronounced positive nonlinear effect[138] was attributed to the existence of bimetallic species bearing two chiral ligands. This fact was further corroborated by NMR experiments, in which the presence of a di-μ-oxo complex (Ti−O−Ti−O) was clearly identified. A computational study (at the BP86/LACVP* level) discriminated energetically between the three possible complexes bearing μ-oxo bridges, formed by two isopropoxide groups or by an isopropoxide ligand and either form of the BODOL-hydroxy moieties, with the dimer with μ-oxo bridges of one isopropoxide and the 6-BODOL-oxygen having the lowest energy level.

Ligands **115** and **116** have been used in the former approach, with the initial reducing agent being in both cases triethoxysilane (**107c**). However, whereas for ligand **115**[159]



the starting titanium complex was titanium tetraisopropoxide (**3a**) and the enantioselectivity found for the hydrosilylation of acetophenone (**106a**) was negligible, for ligand **116**[160] the starting titanium complex was titanium tetrafluoride (**3d**) and the enantioselectivities found for different alkyl aryl ketones were in the range 85−65%. In the later case, a broad study on the mechanism and reaction conditions was performed; the reaction that gave the best results used triethoxysilane compared to other silanes. The ligand **116** should be deprotonated at the α position by addition of butyllithium in order to obtain the chiral titanium complex; other bases assayed gave worse results. Titanium tetrafluoride (**3d**) emerged as the best component for the initial complex from a series of different compounds. The reason for this is not very clear, but it seems to be related to the hydrogen−fluorine exchange between the chiral titanium complex and the silane derivative. MP2 computations on the DFT-optimized structures showed that a titanium(IV) hydride complex was preferred to the related titanium(III) hydride, even when the solvent effect was taken into account. The

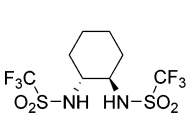
absence of paramagnetic species (NMR studies) might confirm the calculations.

4. Enantioselective Nucleophilic Addition Processes

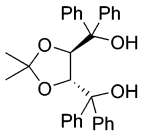
Among the enantioselective catalytic transformations, those involving carbon−carbon bond formation are, without any kind of doubt, of paramount importance in organic synthesis compared to group conversion on a given carbon skeleton.[161] The simplest approach for this process is the 1,2-nucleophilic addition of organometallic reagents[162] to a carbonyl compound derivative to give either a secondary or a tertiary alcohol (or an amine from imines), depending on the starting electrophile. The Michael-type addition is closely related to the aforementioned addition, and it is also a straightforward method for the formation of carbon−carbon bonds.[163] The following sections are classified first according to the nature of the transferred nucleophilic group and second according to the nature of the electrophilic carbonyl compound used. The reactivities of aldehyde and ketone derivatives are quite different from an electrophilic point of view (ketones are less electrophilic), as well as considering steric hindrance (the difference between the two substituents around the carbonyl moiety is always higher in aldehydes than in ketones). All these facts make more difficult the addition of any nucleophile to a ketone derivative than to an aldehyde one.[164]

4.1. Alkylation Reactions

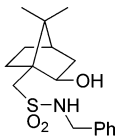
Since 1989, when the Yoshioka−Ohno group[165] introduced the use of chiral *trans*-1,2-bis(trifluromethanesulfonylamino)-cyclohexane (**117a**) as ligand for a new variant of the classical enantioselective addition of dialkylzinc reagents[166] to aldehydes[47] in the presence of titanium tetraisopropoxide, many other chiral dipodal systems have been introduced; some prototypes are TADDOL (**118a**),[167] BINOL (**90a**),[135] and *N*-substituted isoborneolsulfonamides (**119a**).[168]



117a



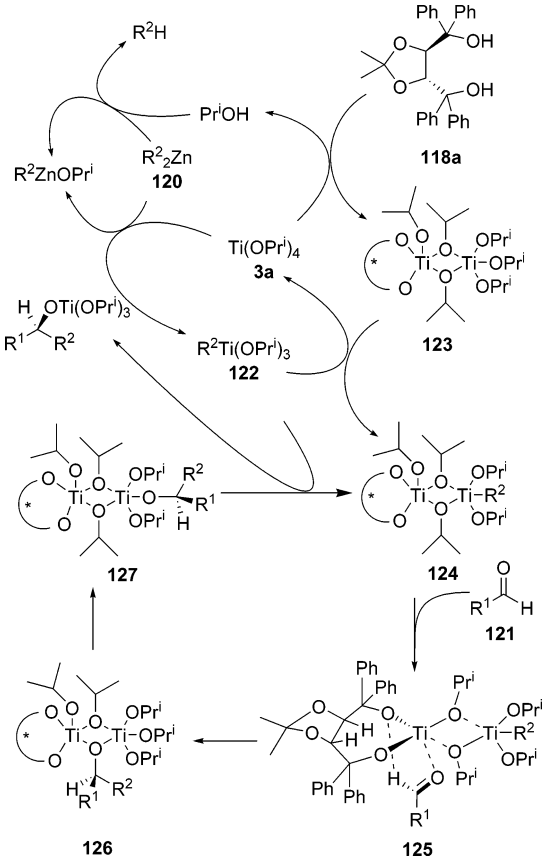
118a



119a

Albeit the exact mechanism of the enantioselective addition of dialkylzinc reagents (**120**) to aldehydes (**121**) in the presence of an excess of titanium tetraisopropoxide (**3a**) and substoichiometric amounts of chiral ligands is so far not well-known, a great effort has been done to elucidate it[169] using TADDOL derivatives (Scheme 53). The starting point is the alkyl exchange of the zinc reagent **120** with titanium isopropoxide (**3a**) to generate a new alkyl titanium complex **122**, which was detected by NMR studies. The role of titanium is not only for the preparation of the complex **122** but also for the formation of the bimetallic complex **123** bearing only one chiral ligand. This μ-oxo complex was assumed to be formed by two isopropoxide groups in the bridge, according to the symmetry of NMR spectra. The alkyl exchange between the complex **123** and either the alkyltitanium intermediate **122** or the starting dialkylzinc reagent gave the new complex **124**. In this complex the coordination of aldehyde takes place, and although there are two possible coordinating titanium atoms, the titanium atom coordinated to the chiral ligand is more active owing to a faster ligand

Scheme 53. Proposed Catalytic Cycle for the Enantioselective Alkylation of Aldehydes Using TADDOL (118a)



exchange, which is due to the bulkiness of the ligand compared to isopropoxide groups. The catalytically active species seems to be the bimetallic complex **125**. It should be pointed out that in this complex, and in general in all TADDOL compounds, the two phenyl substituents are placed in different conformational positions. The aryl groups placed in a pseudoaxial position are responsible for the enantioselectivity (range and sense) while the pseudoequatorial aryl groups are necessary for a fast exchange between the aldehyde and the isopropoxide group or between the final chiral bulky alkoxide (R^1R^2HCO) and isopropoxide. The fact that saturated, unsaturated, and aromatic aldehydes gave the same level of enantioselectivity, as well as topological reaction sense, seems to indicate that there is not π-stacking or charge transfer interactions between the aldehyde substrates and the aryl group on the TADDOL ligand, corroborating that only van der Waals interactions between pseudoaxial aryl groups and the aldehyde chain control the stereochemical outcome of the addition. Moreover, a hydrogen bond between the oxygen atom of the ligand and the hydrogen atom of the carbonyl moiety can favor this complexation process.[170] The final fast exchange of ligands liberates the chiral secondary alkoxide and regenerates the starting bimetallic complex **124**.

Although Scheme 53 shows the general picture for the enantioselective addition of dialkylzinc to aldehydes in the presence of titanium alkoxides and any other chiral ligand, depending on the ligand and the optimized reaction conditions, other factors and reaction pathways must be taken into account.[171] Thus, for example, in the case of using the disulfonamide **117a**, the dialkylzinc seems to deprotonate the chiral compound (prior to the formation of the chiral

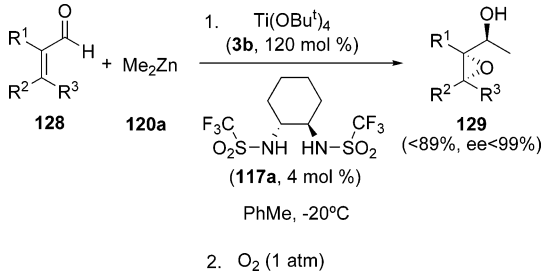
ligand−titanium complex) instead of the liberated 2-propanol (Scheme 53).

4.1.1. Aldehydes as Electrophiles

The sulfonamide **117a** has shown previously its great versatility in the enantioselective alkylation of aldehydes, using a broad range of different functionalized aldehydes and organozinc reagents, including the assembly of key intermediates in natural products.[172] Despite the glorious past of systems of type **117**, many other applications as well as mechanism clarifications have been reported during the period covered in this review.

One methodological example of using the ligand **117a** is outlined in Scheme 54. The enantioselective addition of

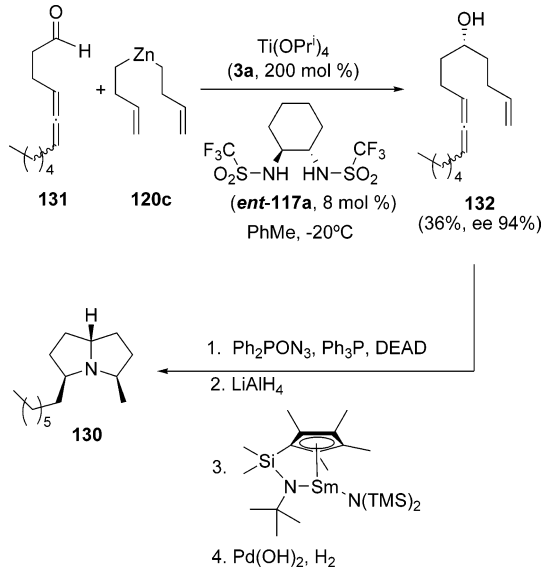
Scheme 54. One-Pot Asymmetric Methylation and Epoxidation of α,β-Unsaturated Aldehydes



dimethylzinc (**120a**) to α,β-unsaturated aldehydes **128** using titanium tetra-*tert*-butyloxide (**3b**), followed by a one-pot diastereoselective oxidation of the in situ generated allylic alcohoxide using an oxygen atmosphere, yielded the corresponding chiral epoxy alcohols **129**, after hydrolysis.[173] The chemical yield and enantioselectivity of the main isomer were good, and the diastereomeric ratio was excellent (never lower than 95%).

The enantioselective synthesis of (+)-xenovenine (**130**), a venom isolated from the ant *solenopsis xenoveneum*, is a typical example of the application of this reaction to natural product synthesis.[174] Thus, the enantioselective addition of the organozinc reagent **120c** to the allenic aldehyde **131** yielded the expected alcohol **132** (Scheme 55). Its further

Scheme 55. Synthesis of (+)-Xenovenine (130) through an Enantioselective Alkylation Process

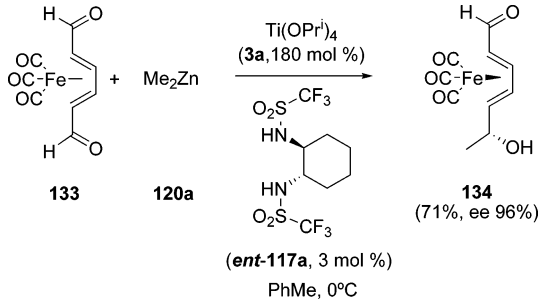


transformation into the corresponding amine followed by an organosamarium-catalyzed hydroamination−cyclization process and final hydrogenation yielded the alkaloid **130**.

The multigram scale enantioselective addition of dipentylzinc to 5-hexenal using the chiral sulfonamide **117a** under standard conditions has been reported as the starting point for the aglycon synthesis of different glycolipids with interesting activities against human breast cancer cell lines and severe immune disorders.[175] On the other hand, the use of chiral organozinc reagents in this addition has been demonstrated in the synthesis of antiviral glycolipid cycloviracin B_1.[176]

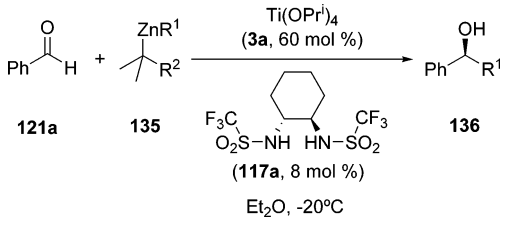
A special case appeared in the synthesis of different amino alcohol derivatives isolated from marine sponge.[177] The key step for their syntheses was the enantioselective addition of dimethylzinc (**120a**) to the dialdehyde−tricarbonyliron complex **133** to yield the alcohol **134** with excellent results. Besides the obvious stereogenic center due to the nucleophilic addition, a new axial stereogenic element was created in the process (Scheme 56).

Scheme 56. Enantioselective Methylation of Dialdehyde 133



One of the typical drawbacks of this reaction is that only one of the two dialkyl groups in the zinc reagents is transferable to the aldehyde. While the problem for simple dialkylzinc reagents is negligible, the problem for functionalized alkyl moieties can be very important. This drawback has been overcome elegantly by the introduction of neopentyl and neophyl groups as nontransferable alkyl moieties in mixed organozinc reagents **135** (Table 7).[178] The organozinc

Table 7. Enantioselective Addition of Mixed Zinc Reagents

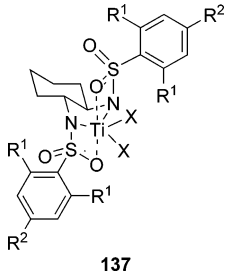


entry	R^2	no.	R^1	yield (%)	ee (%)
1	Me	**136a**	Me	92	93
2	Ph	**136a**	Me	69	94
3	Me	**136b**	Et	91	96
4	Me	**136c**	$(CH_2)_4OCOBu^t$	82	89
5	Ph	**136c**	$(CH_2)_4OCOBu^t$	71	89

reagents **135** were prepared by simple mixture of equimolecular amounts of either bis(neopentyl)zinc or bis(neophyl)zinc with the corresponding dialkylzinc intermediate. The results are quite homogeneous, independent of the nature of the nontransferable group (R^2 = Me or Ph in **135**) and of the nature of transferable moiety. Moreover, while the reaction with dimethylzinc and benzaldehyde using the chiral

ligand **117a** gave poor results due to the small size of the organozinc reagent (23% ee for **136a**), when the reaction was performed with the related mixed organozincs, the enantioselectivity reached over 90%, showing that the nontransferable groups play an important role in the reaction.

Concerning the mechanism using ligands of type **117**, it should be pointed out that several aspects give a more complete and complicated picture of the simple mechanism shown in Scheme 53. The X-ray crystal structures of different bis(sulfonamide)−titanium complexes **137** showed that the



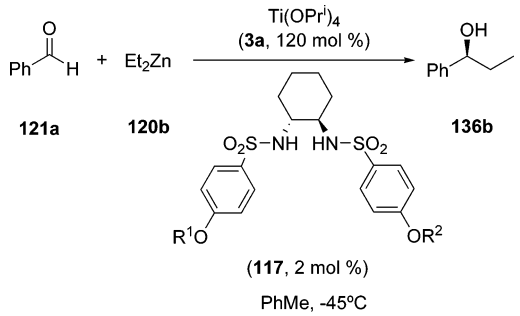
137

R^1 = H, Me, Pr^i
R^2 = Me, Pr^i
X = OPr^i, NMe_2

sulfonamide of type **117** is bonded to the titanium atom by a η^4 mode for no bulky aryl groups: two Ti−N and two Ti−O bonds are formed with the sulfonyl moiety. However, this general coordination mode can be changed drastically just by simple small modifications. Thus, the X group would affect the Lewis acidity of the titanium center and have an influence on the coordination of the sulfonyl oxygens. Moreover, the X-ray structure of complex **137a** ($R^1 = R^2 =$ Me, X = NMe_2) showed a different arrangement depending on the optical activity of the starting bis(sulfonamide): the hapticity is η^4 when the racemic bis(sulfonamide) is used whereas it is η^3 for the same resolved bis(sulfonamide). These unexpected differences were explained by considering the interactions in the solid state, with the lattice energies varying depending on the way the molecules must pack in the crystal.[179] Finally, the structure for the bulky system **137b** ($R^1 = R^2 =$ Pr^i, X = NMe_2) consisted of a five-coordinated titanium atom with the fifth position occupied by only one of the sulfonyl oxygen atoms.

The X-ray structures of complexes **137** revealed the possible origin of the topological outcome of the reaction. In the TADDOL ligand, the pseudoaxial aryl groups were responsible for the discrimination, and according to the X-ray structure of complex **137**, both aryl substituents of the sulfonamide were also placed in *anti* pseudoaxial positions, similar to the case for TADDOL. To confirm that this *anti* conformation was responsible for the outcome of the reaction, different sulfonamides **117b**−**d** were prepared in which, due to the length of the tether, the *anti* conformation was not allowed (Table 8). Thus, when the enantioselective reaction of diethylzinc (**120b**) with benzaldehyde (**121a**) to yield the expected alcohol **136** was conducted using the flexible ligand **117b**, the reaction was finished in only 1 h with an excellent result. When the reaction was performed with the cyclic ligand **117c**, in which the methylene chain is long enough to permit an *anti* conformation of the aryl moieties in the titanium complex, the enantioselectivity was slightly lower but the rate similar to the previous case. However, when the reaction was performed using ligand **117d**, in which the length of the methylenic chain is too short for permitting the *anti* conformation of the aryl moieties, the chemical yield

Table 8. Probing the *anti* Conformation for the Origin of the Enantioselectivity in Ligands 117



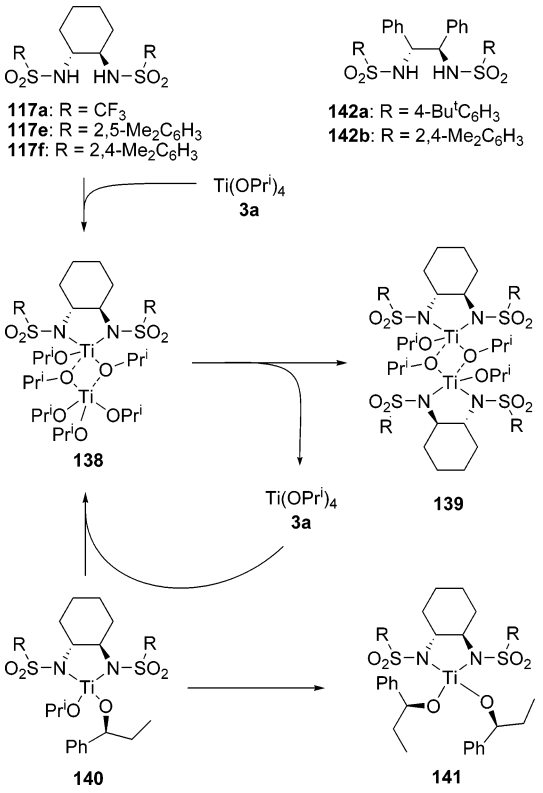
	ligand				product	
entry	no.	R^1	R^2	*t* (h)	yield (%)	ee (%)
1	**117b**	Me	Me	1	100	98
2	**117c**	-$(CH_2)_{22}$-		3	100	89
3	**117d**	-$(CH_2)_6$-		3	57	10 (*R*)

and the enantioselectivity were totally different. Even the specific rotation of the main product (*R*) was contrary to that obtained with the other related bis(sulfonamide) ligands, proving that the origin of the outcome of the reaction is the *anti* pseudoaxial position of the substituents of the sulfonamyl moiety in the titanium complex.[180]

More aspects of the aforementioned reaction should be addressed in order to get the possible mechanism picture. For example, depending on the order of the addition of reagents, the reaction presents a significative nonlinear effect.[138] Thus, when the enantioselective ethylation of benzaldehyde was performed using the ligand **117a** and the order of reagent addition was (1) titanium tetraisopropoxide, (2) ligand **117a**, and then (3) diethylzinc (**120b**) followed finally by (4) the addition of benzaldehyde (**121a**), a clear positive nonlinear effect was found, whereas when the addition was (1) diethylzinc (**120b**), (2) ligand **117a**, and then (3) titanium tetraisopropoxide, the nonlinear effect disappeared. This positive nonlinear effect was influenced by the temperature and the time of catalyst maturation previous to the organozinc addition; the higher temperature and the longer time provoked the highest positive nonlinear effect. This behavior was attributed to the existence of an equilibrium between the complexes **138** and **139**, which is not present when diethylzinc is added at first.[181] When the reaction is performed with ligands of different enantiomeric ratios, two types of dimeric complexes can be formed; the homochiral dimer **139** is usually more unstable than the related heterochiral complex, and this difference is responsible for the elimination of the minor enantiomer of the ligand from the reaction media (reservoir effect). The intermediate **138** is the complex working in the catalytic cycle (see Scheme 53; complex **138** is the equivalent to **123**), and therefore, this equilibrium has a great impact on the enantioselectivity.

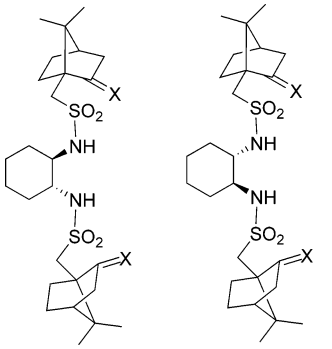
When the reaction was performed using ligand **117e** or **117f** and adding first the diethylzinc, a continuous increase of the enantioselectivity was observed (autoinduction effect). However, when the ligands used were of different enantiomeric ratios, the enantioselectivity decreased.[182] Moreover, a significant negative nonliner effect appeared under these conditions, with the deviation being small at low conversion but increasing as the reaction progressed. This behavior is due to the exchange of titanium alkoxide ligands between complexes of type **140** and the excess of titanium tetraisopropoxide to form intermediates of type **138**, renewing the

Scheme 57. Alternative Catalytic Species for Ligands of Bis(sulfonamide) Type



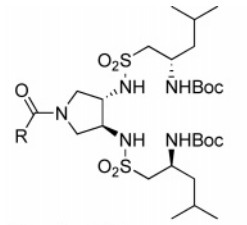
precatalyst system of the addition (Scheme 57). It is assumed that this exchange is usually much faster than the corresponding one to form the complex **141**. However, this is not true for ligands in which complexes of type **140** and **141** evolve very slowly to give the system **138**. The higher activity and enantiodiscrimination of complexes **140** and **141** are responsible for this nonlinear effect. The incorporation of the chiral alkoxide product into the catalyst of the enantioselective addition and its higher activity have also been observed for the ligand **142**.[183]

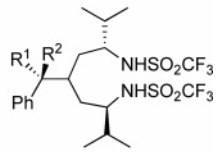
The aforementioned findings inspired the use of stoichiometric amounts of chiral Ti[(*S*)-OCH(Ph)Et]$_4$ (**3e**) and substoichiometric amounts of a anachiral bis(sulfonamide) ligand in the enantioselective addition of diethylzinc to 4-methylbenzaldehyde.[184] Although the enantioselectivity was not very high, it was modulated by the achiral ligand, and the results could drive the attention to the possible effect of achiral impurities on the enantioselective reaction. The further idea was the design of chiral ligands with extra functionalities able to modulate the enantioselective addition. So, chiral systems **143**−**144** were prepared to check this hypothesis. The enantioselective addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide (to yield the expected alcohol **136b**) gave similar enantioselectivity using both diastereomeric ligands **143a** and **144a**, while changing only the main enantiomer, which implies that the cyclohexylamine core is responsible for the stereooutcome of the reaction. However, the reaction rates for the two ligands were very different; after 15 min the yields were 75 and 16% for ligands **143a** and **144a**, respectively.[185] On the contrary, when the same reaction was performed using methylenic ligands **143b** and **144b**, the results were comparable not only in enantioselectivity but also in reaction rate. All these facts seem to point to the conclusion that the carbonyl oxygen atom of the camphor unit acts as a competitive inhibitor



binding reversibly to the active site of the catalyst and, thus, a mixture of diastereomeric ligands can be used without isolation of the pure ligand.

The great success found in the enantioselective addition of dialkylzinc to aldehydes using titanium tetraisopropoxide in the presence of substoichiometric amounts of bis(sulfonamide) ligands alerted many authors to the development of new systems of this type. Ligands **145** emerged from a small library of peptidosulfonamide tweezers;[186] the enantioselectivity for the ethylation of benzaldehyde using the homogeneous ligands was not good (56−58% ee for **136b**), but it was superior to that of the heterogeneous ligand **145c**. However, the same reaction using aliphatic aldehydes as electrophile gave a nearly racemic mixture.



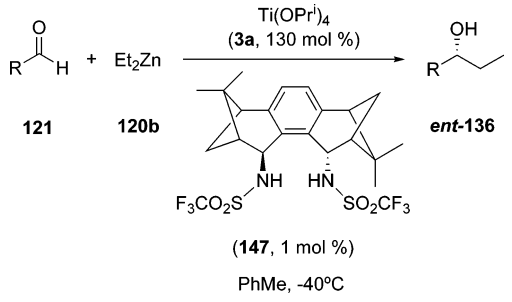


Chiral sulfonamides of type **146**, obtained easily from the corresponding chiral aziridines, seemed to be better catalysts, since the enantioselectivity for the ethylation of benzaldehyde was raised slightly.[187] From 23 different ligands tested, the best results were obtained using the benzylic systems **146**, and in three cases the results were practically the same (72−76% ee for **136b**), indicating that even when the benzyl moiety is far away from the reaction center, it has an important role due to the nitrogen chelation capacity. On the other hand, the addition of extra additives did not have any positive influence on the enantioselectivity.[188]

More successful results were obtained when the C_2 symmetric bis(sulfonamide) **147** derived from (+)-verbenone was used as the chiral ligand (Table 9).[189] The enantioselectivity was excellent for any kind of aldehydes, either for the classical aromatic or the less reactive aliphatic ones. However, the ee was moderate for the case of cinnamaldehyde (Table 9, entry 2), and this bad result was attributed to the coplanarity of the α- and β-trigonal carbon centers with the carbonyl π-bond, which must have diminished the energy differences between both planar conformations in the active catalytic complex.

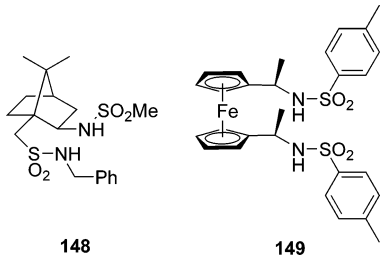
The bis(sulfonamide) derived from camphor **148** has been tested as chiral ligand in the ethylation and methylation of

Table 9. Enantioselective Ethylation of Aldehydes Using Ligand 147



entry	R	no.	yield (%)	ee (%)
1	Ph	***ent*-136b**	93	98
2	(*E*)-PhCH═CH	***ent*-136d**	81	72
3	$Ph(CH_2)_2$	***ent*-136e**	86	97
4	*n*-C_5H_{11}	***ent*-136f**	87	98
5	*c*-C_6H_{11}	***ent*-136g**	65	96

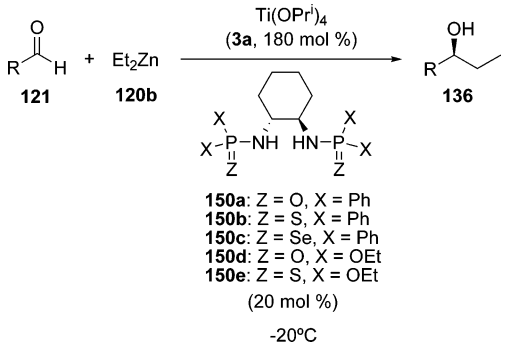
aldehydes, and although the results were modest for arenecarbaldehydes, the enantioselectivity was excellent (96% ee) for using aliphatic aldehydes as electrophilic partners of the reaction, with this behavior being quite unusual: The best results are generally obtained with aromatic systems, or the enantioselectivity is independent of the nature of the aldehyde. Another interesting observation is that the absolute configuration of the secondary alcohol ***ent*-116** was *R*.[190] However, when the reaction was performed with the related isobornylsulfonamide of type **119a**, the main enantiomer was *S*.[191] This change in the main enantiomeric product, keeping in both ligands the same stereogenic centers, reveals the great importance of the active complex conformation, which seems to be different for ligands **148** and **119a**.



The ligand **149** showed very disappointing behavior since only in the ethylation of benzaldehyde to yield alcohol **136b** was the enantioselectivity excellent;[192] for functionalized arenecarbaldehydes as well as α,β-unsaturated derivatives, the enantioselectivity was very low, even leading to racemic mixtures.

Not only sulfonamides but phosphoramides have been used as catalysts for the 1,2-addition (Table 10), with the results depending extremely on the ligand used. Thus, the reaction with diphenylphosphoramide **150a** gave homogeneously moderated results for the ethylation of aldehydes independent of the nature of the aldehyde. The same reaction using the related diphenylthiophosphoramide **150b** gave always lower enantioselectivities, and although the stereogenic centers were the same for both catalysts, the main enantiomer of the reaction was the opposite one.[193] The reaction using diphenylselenophosphoramide **150c** did not improve the results;[194] the topological outcome of the reaction was the same as that for the ligand **150a**. The reaction with the related diethoxyphosphoramide **150d** and diethoxythiophosphoramide **150e** systems gave the worst results of the series.[195] The change

Table 10. Enantioselective Ethylation of Aldehydes Using Phosphoramides 150

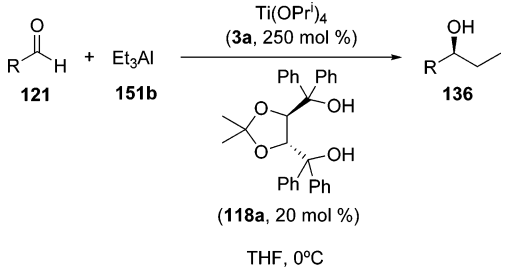


entry	ligand	R	no.	yield (%)	ee (%)
1	**150a**	Ph	***ent*-136b**	82	81
2	**150a**	(*E*)-PhCH═CH	***ent*-136d**	94	70
3	**150a**	*n*-C_4H_9	***ent*-136h**	92	62
4	**150b**	Ph	**136b**	80	40
5	**150b**	(*E*)-PhCH═CH	**136d**	91	41
6	**150b**	*n*-C_4H_9	**136h**	92	32
7	**150c**	Ph	***ent*-136b**	93	61
8	**150c**	(*E*)-PhCH═CH	***ent*-136d**	94	63
9	**150c**	*n*-C_4H_9	***ent*-136h**	92	53
10	**150d**	Ph	**136b**	80	32
11	**150e**	Ph	***ent*-136b**	82	18

of the amine partner from chiral cyclohexyldiamine to 1,1′-binaphthyl-2,2′-diamine in ligands **150** did not have any positive change on the enantioselectivity of the reaction.[196]

Now that the results using different diamide systems have been shown, another important class of ligands, such as diols, will be considered. Among them, probably the most popular is the TADDOL system **118**.[167] The first modification of the standard protocol for the enantioselective addition of dialkylzinc reagents to aldehydes in the presence of titanium tetraisopropoxide using TADDOL as chiral ligand was the replacement of dialkylzinc reagents by the related trialkylaluminum derivative (Table 11). Some aspects should be

Table 11. Enantioselective Addition of Triethylaluminum to Aldehydes Using TADDOL 118a

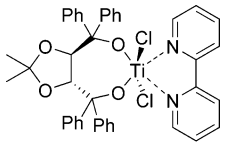


entry	R	no.	yield (%)	ee (%)
1	Ph	**136b**	94	84
2	(*E*)-PhCH═CH	**136d**	100	78
3	4-$MeOC_6H_4$	**136i**	91	79

pointed out, such as the role of solvent: The reaction gave the best results using THF as solvent; the reason for this fact is not very clear but seems to be connected with the coordinating activity of THF, which could coordinate the triethylaluminum reagent, lowering its Lewis acid character and therefore suppressing the uncatalyzed direct addition of the organoaluminum reagent to aldehydes. Another curiosity is the excessive amount of titanium complex used. And finally, the temperature is a little bit higher compared to the

standard protocols; this fact is probably the reason for the lower enantioselectivity found.[197]

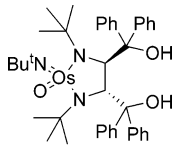
Another modification has been the preparation of new complexes with an extra achiral dicoordinating ligand, such as the complex **152a**[198] with C_2 symmetry according to the



152a

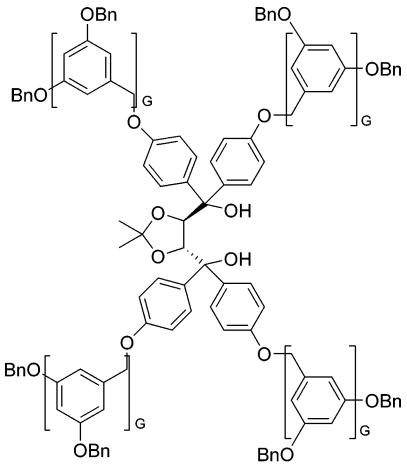
X-ray structure.[199] In the aforementioned addition of diethylzinc reagent to benzaldehyde using a substoichiometric amount of this complex, the alcohol **136b** was obtained with a poor enantioselectivity (31% ee). However, the enantioselectivity reached up to 85% when the same reaction was performed in the presence of titanium tetraisopropoxide. In the last case, titanium tetraisopropoxide reacts with the starting complex **152a** to form the bimetallic species **123** (see Scheme 53) and therefore conducts the reaction as in the classical protocols.

To improve some aspects of the classical protocols, and besides the aforementioned examples, the greatest efforts have been focused on the modification of the TADDOL structure itself. The first example was the use of compound **118b**, which catalyzed the enantioselective addition of dimethyl- and diethylzinc to different arenecarbaldehydes with enantiomeric excess never higher than 92%.[200]



118b

The TADDOL moiety has been used as the core for a dendritic structure[201] such as dendrimers **118c**−**f**. Their use



118c: G = 1
118d: G = 2
118e: G = 3
118f: G = 4

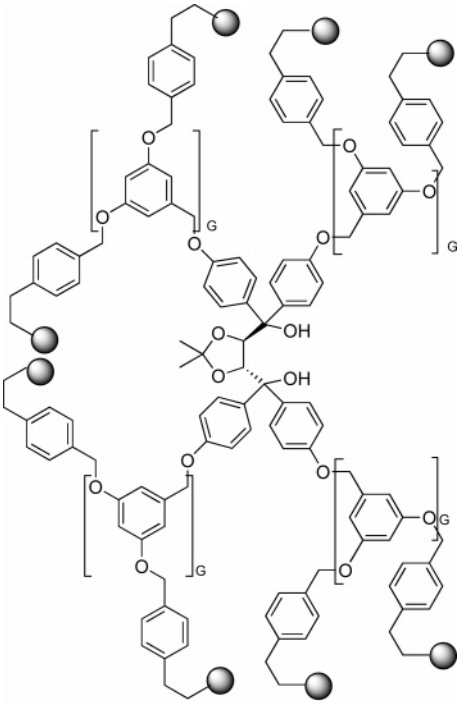
as chiral ligands for the ethylation of benzaldehyde gave the expected alcohol **136b** with different enantioselectivities depending on the achiral generation structure (G). Thus, for the first generations (ligands **118c** and **d**), the enantioselectivity was the same (96%) and a little bit lower than that for the original TADDOL **118a** (98% ee for **136b**). However, when the generation number was further increased, a continuous decrease in the enantioselectivity was detected (for **136b**: 91% ee with **118e** and 89% ee with **118f**). When the reaction rates were compared, a decrease in ee values was obtained when the generation increased, which could explain the loss in the enantioselectivity when the ratio of catalyzed pathway *versus* uncatalyzed reaction decreased.[202]

Another interesting modification of the TADDOL structure is its immobilization on different materials. There are two main ways to support a chiral ligand: (a) the copolymerization of a suitable functionalized ligand with polymerizable monomers and cross-linkers, and (b) the grafting of the desired ligand onto a preformed support containing reactive groups. While the former one offers many possibilities for generating and controlling a specific environment around the ligand within the polymer matrix (needing more synthetic efforts), the latter is often preferred since many suitable polymeric supports are commercially available. The main drawback of supported ligands is their reduced activity compared to those of their soluble analogues used under homogeneous conditions, owing either to diffusion problems or to the fact that the preferred conformation of the catalyst cannot be adopted in the polymer.[203]

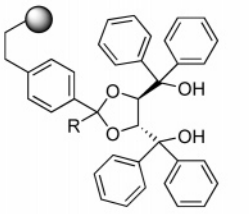
Different polymers have been created by radical copolymerization of stiryl-TADDOL derivatives with styrene to form the corresponding polystyrene−TADDOL beads **118g**−**j**.[204] In some cases, divinylbenzene was used as cross-linker while for dendritic derivatives the TADDOL compound itself acts as the cross-linker. All theses polymeric materials were tested as chiral ligands for the ethylation of benzaldehyde, giving practically the same results as far as enantioselectivity is concerned (96−86% ee). The lowest result obtained with ligand **118h** can be interpreted as resulting from the high degree of cross-linking achieved with the corresponding second-generation TADDOL cross-linker. It shout be pointed out that the enantioselectivity obtained with the polymeric material **118g** was kept over 20 cycles whereas other polymeric materials were losing activity over the cycles. In fact, the reaction kinetics declined during the reuse except for the case of ligand **118g**. These behaviors were attributed to the constant blocking of polymeric pores. Moreover, the swelling factor in toluene remained unchanged during 20 recycling steps for bead **118g**, which called attention to the constant accessibility for the substrates. The degree of loading has an important role on the kinetics: The higher loaded the polymer, the slower the reaction rate, due to a restricted diffusion. Thus, polymer **118g** with a diameter of ∼400 μm gave rise to a faster reaction rate than that of polymer with a diameter of ∼800 μm, with the unstirred suspension giving the same rate as the stirred one and, therefore, avoiding the abrasion phenomena.

TADDOL derivatives have also been grafted to different materials. Thus, the polymer fibers **118k** were obtained by preirradiated polyethylene fibers and radical copolymerization of the corresponding stiryl-TADDOL derivatives with styrene.[205] Although the enantioselectivity found for the ethylation of benzaldehyde using this ligand was excellent (94% ee for **136b**), the reaction rate was very slow.

TADDOL derivatives have been grafted not only on polyethylene fibers but also on silica gel of controlled-pore glass. The enantioselective ethylation of benzaldehyde using ligand **118l** gave excellent results (96% ee for **136b**). The

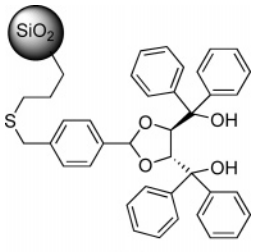


118g: G = 1
118h: G = 2



118i: R = H
118j: R = 4-$C_6H_4(CH_2)_2$—●
118k: R = Me

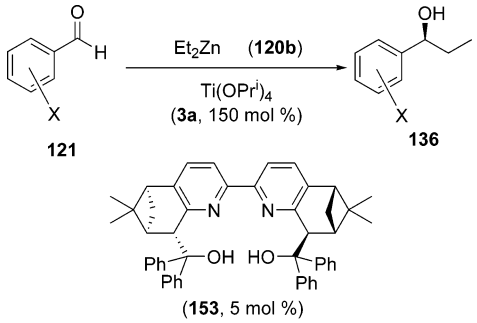
enantioselectivity of the reaction had somewhat decreased after 10 cycles, but the catalytic activity could be fully restored just by washing the silica gel successively with HCl, H_2O, and acetone and reloading it with titanium tetraisopropoxide (**3a**).[206]



118l

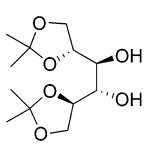
The ligand **153** is an interesting diarylmethanol system, which has been used as chiral promoter in the ethylation of different substituted benzaldehydes (Table 12). In this case, a systematic study on the influence of electronic effects on the enantioselectivity has been done. The correlation of Hammett substituent constants and enantiomeric excess for the ethylation of *meta*-substituted benzaldehydes was very good (the stronger the electron-withdrawing moieties, the higher the enantioselectivity found), whereas the related one for *para*- and *ortho*-substituted benzaldehydes was not very clear.[207]

Table 12. Electronic Effects on the Ethylation of Substituted Benzaldehydes Using Ligand 153

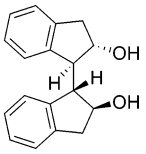


entry	X	no.	yield (%)	ee (%)
1	H	**136b**	67	91
2	3-MeO	**136j**	75	83
3	3-Cl	**136k**	96	98
4	3-NO_2	**136l**	21	>99
5	2-MeO	**136m**	79	6
6	2-Cl	**136n**	96	98
7	2-NO_2	**136o**	13	3
8	4-MeO	**136i**	70	91
9	4-Cl	**136p**	54	7
10	4-NO_2	**136q**	24	47

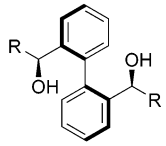
The diol **154** has been used as chiral ligand in the enantioselective addition of diethylzinc to arenecarbaldehydes with moderate success (ee never higher than 86%).[208] In this case, a NMR study, as well as FAB mass spectroscopy experiments, showed the presence of bimetallic species of type **123** (see Scheme 53) bearing only one chiral dialkoxide derived from compound **154** and the di-μ-oxo complex being formed by two isopropoxide groups, thus confirming the general character of the catalytic cycle presented in Scheme 53.



154



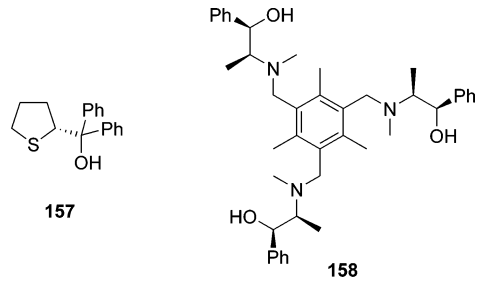
155



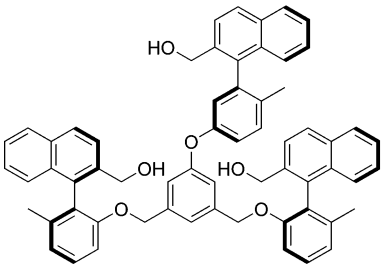
156a: R = CF_3
156b: R = *n*-C_7F_{15}

The enantioselectivity found for the aforementioned ethylation using ligand **155**[209] or **156**[210] was slightly superior (ee's up to 96%), but it was very influenced by the presence of functionalities on the aromatic ring and their relative position.

Other alcohols have also been tested as chiral ligands for the enantioselective addition of diethylzinc to aldehydes. The selectivity using simple alcohols with an extra donating group, as is the case of chiral thiolan-2-yldiphenylmethanol (**157**), was somehow low,[211] with the enantioselectivity for the product **136b** being 74%. The use of the triol **158** was clearly more disappointing since, under similar reaction conditions, it gave the alcohol **136b** with a very low 10% ee.[212] Besides these results, the C_3 symmetric tripodal ligand **159** was shown to be a good chiral ligand for the ethylation of different substituted benzaldehydes, with enantiomeric excess around 90%.[213] An interesting fact in this reaction is the temperature, which must be 40 °C in order to get the best enantioselectivity. This behavior is very strange since the normal protocols use low temperature (around −20 °C) in order to avoid the uncatalyzed reaction.



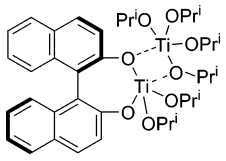
157 158



159

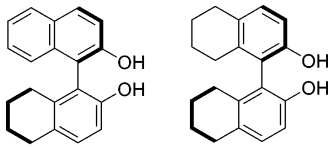
Another important class of ligands for the mentioned standard addition are phenol derivatives, with the most representative being BINOL[135] and salen derivatives.[214] Since 1997 when the groups of Nakai and Chan used BINOL (**90a**) as substoichiometric chiral ligand for the classical enantioselective addition of diethylzinc to aldehydes,[215] many studies on the modifications of the phenol structure have been performed, including mechanistic aspects.

Concerning the possible mechanism, a broad study has been done in which the catalytic cycle described in Scheme 53 has been confirmed for the BINOL ligand.[216] First, the enantioselective ethylation of benzaldehyde using stoichiometric amounts of both BINOL and titanium derivatives showed a small negative nonlinear effect, which is indicative of the presence of bimetallic species. When the reaction was performed using stoichiometric amounts of titanium and substoichiometric amounts of the chiral ligand, the negative nonlinear effect disappeared. Moreover, the reaction rates using stoichiometric and substoichiometric amounts of chiral ligand were quite different. The following question concerns the binding mode of BINOL−titanium, and it was analyzed by the preparation of different BINOL monoethers, which showed a totally different enantioselectivity as well as turnover frequencies. These facts can indicate that each BINOL unit is double bonded to only one titanium atom. The NMR study using a double amount of titanium tetraisopropoxide with respect to BINOL showed that the C_2 symmetry of BINOL was lost, as well as the presence of one isopropoxy group different from the other five. The X-ray structure of this compound **160** showed that the μ-oxo complex was formed by one isopropoxide and one phenol oxygen atom (compare with **123** in Scheme 53).[217]



160

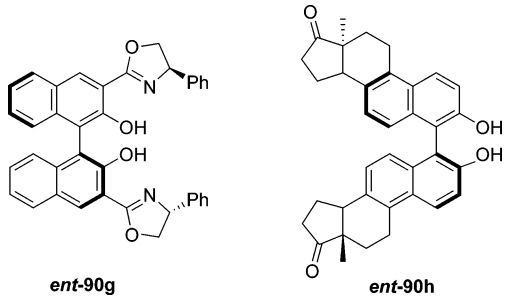
Although structural features of tetrahydro- and octahydrobinaphthol derivatives **90e,f** are similar to those of the aforementioned BINOL (**90a**), the dihedral angles between the aryl rings are larger for system **90e** and are the largest in the series for **90f**. These differences are responsible for the different enantioselectivities found. Thus, the ethylation of benzaldehyde to yield alcohol **136b** gave 85% ee for **90a**, 91% ee for **90e**[218] and 98% ee for **90f**, with the larger dihedral angle generating the higher enantioselectivity.



90e 90f

In the case of BINOL derivatives, and during the period covered by this review, a very small amount of effort has been expended in order to use other nucleophilic alkylating agents different from commercial dialkylzinc reagents. Only 1-ethoxy-1-trimethylsilylcyclopropane has been introduced as a new nucleophile, and the enantiomeric excess found for this alkylation is modest (ee < 72%).[219]

More work has focused on the modification of the initial BINOL structure. Thus, the introduction of an oxazolyl moiety in the general structure ***ent*-90g** did not introduce any additional advantage, and the enantioselectivity was very sensitive to the presence of different additives, as molecular sieves.[220] The use of the steroidal derivative ***ent*-90h** did not produce any important change in the enantioselectivity. In fact, the steroid structure did not have any influence on the enantioselectivity, since using a diastereomeric ligand containing the enantiomeric steroid and the same BINOL structure gave the same main enantiomer and similar enantiomeric excess.[221]

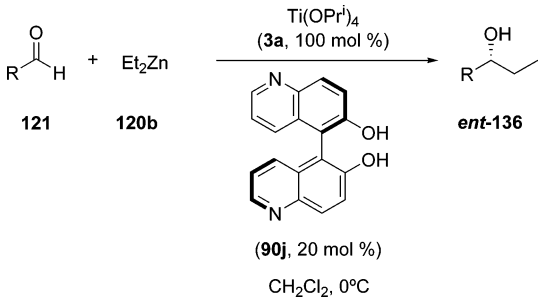


ent-90g *ent*-90h

The reaction using the quinoline derivative **90j** (BIQOL) showed some higher enantioselectivity (Table 13). The ligand obtained by oxidative coupling catalyzed by copper salts followed by HPLC preparative resolution behaved unusually.[222] It seems that the enantioselectivity is independent of the electronic character of substituents, and even independent of the nature of the aldehyde, which is in contrast to the phenomenon observed in the BINOL-catalyzed reaction, where arenecarbaldehydes usually gave better results than aliphatic derivatives, with naphthyl aldehydes giving even better results than benzaldehyde derivatives.

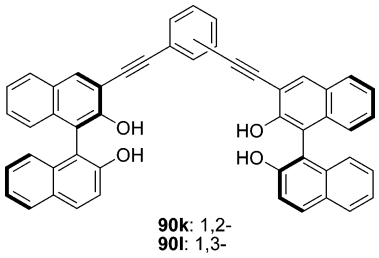
The presence of a bimetallic structure of type **160** in the catalytic cycle of the standard addition inspired the preparation of different BINOL compounds, which were able to chelate two titanium atoms at the same time. Thus, ligands **90k** and **l** were prepared through a double Sonogashira coupling reaction with the hope of improving the results. The ^{1}H NMR study of ligand **90k** in the presence of different amounts of titanium tetraisopropoxide did not show any

Table 13. Enantioselective Ethylation of Aldehydes Using BIQOL 90j



entry	R	no.	yield (%)	ee (%)
1	Ph	***ent*-136b**	100	90
2	4-MeOC$_6$H$_4$	***ent*-136i**	99	87
3	2-naphthyl	***ent*-136r**	100	84
4	*n*-C$_6$H$_{13}$	***ent*-136s**	62	83

change of the signals from ratio 1:2 to 1:10 ligand/titanium. When the aforementioned ratio was 1:1, two groups of

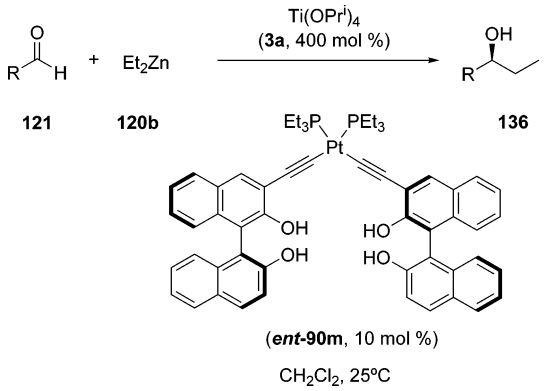


signals in the ^{1}H NMR spectra were detected, one from the free ligand **90k** and another from the bimetallic aggregate. These observations were interpreted as proof of the high stability of the bimetallic aggregate with the *ortho*-phenylenebis(ethynyl) tether. For ligand **90l**, a similar NMR titration experiment showed a change of the aggregate as a function of the amount of titanium tetraisopropoxide.[223] Besides these behavior differences, when they were tested as chiral promoters in the enantioselective ethylation of different aldehydes, both gave similar enantioselectivities, which were also similar to those found using simple BINOL **90a**.

Instead of the aforementioned phenyl tether, it is possible to use a platinum complex, as is the case of the ligand ***ent*-90m**. Its use as chiral ligand in the classical ethylation of different aromatic aldehydes gave satisfactory results (Table 14)[224] but not superior results to those achieved with simple BINOL. In this case, the same tendency was observed: the electron character of the substituent on the phenyl ring had a moderate impact on the enantioselectivity, while naphthyl aldehydes gave better results than benzaldehyde.

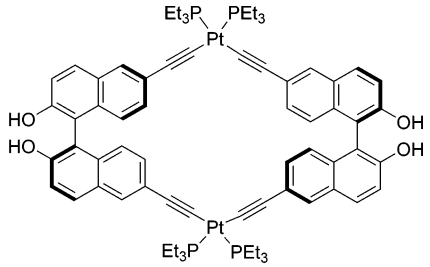
The use of organometallic structures permitted the preparation of the metallacyclophane ***ent*-90n**[225] and the organometallic triangle ***ent*-90o**.[226] When the enantioselective ethylation of different aldehydes was performed using the metallacyclophane ligand ***ent*-90n**, the results obtained were slightly poorer than those obtained with the open chain ligand ***ent*-90m**. However, for the case of 1-naphthaldehyde, the enantiomeric excess of product **136v** reached 94%. These differences were attributed to the rigid structure of the ligand, which maintains the dihedral angle of the naphthyl ring of BINOL moieties in the titanium complex, impeding its variation and, therefore, the good accommodation of aldehydes with a smaller ring than naphthyl. The system

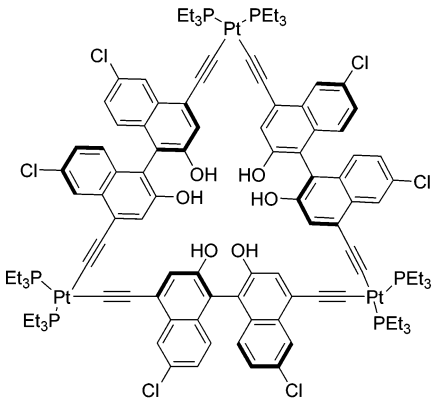
Table 14. Enantioselective Ethylation of Aldehydes Using Ligand 90m



entry	R	no.	yield (%)	ee (%)
1	Ph	**136b**	>95	80
2	4-MeC$_6$H$_4$	**136t**	99	91
3	4-CF$_3$C$_6$H$_4$	**136u**	100	79
4	1-naphthyl	**136v**	100	88

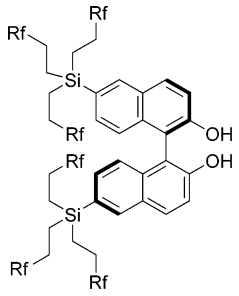
***ent*-90o**, which has more structural flexibility, recovered the initial broad substrate scope of system ***ent*-90m**.



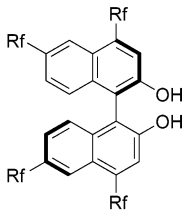


Different strategies have been followed in order to facilitate the recovery of the expensive chiral BINOL ligand. The first one is the introduction of fluorinated side chains on the BINOL structure, allowing the ligand to be isolated just by organic−fluorous extraction. It is well-known than perfluorinated side chains alter the electronic properties of an attached system by a strong electron withdrawing effect. For this reason, the ligand **90p** was designed with fluorinated chains bounded to a dimethylensilyl group, which is a blind for the naphthyl moiety. In this way the ligand **90p** was soluble in the fluorous phase, keeping the electronic properties of BINOL. In fact, the enantioselectivities found for the addition of dialkylzinc reagents to aldehydes in the presence

of titanium tetraisopropoxide were practically the same as those for BINOL (**90a**), with the ligand **90p** being recovered up to 100%, depending on the fluorinated phase used.[227]



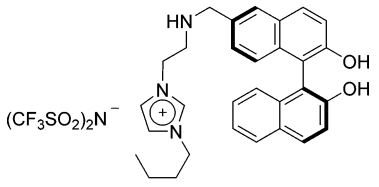
90p: Rf = *n*-C_6F_{13}



90q: Rf = *n*-C_8F_{17}

The enantioselectivities found for the addition of diethylzinc to aldehydes using ligand **90q** were significantly inferior (around 55%), probably due to the direct connection of the perfluorinated side chains to the BINOL core.[228] In this case, the change of source of the nucleophile from diethylzinc to triethylaluminum had a favorable impact, improving the enantiomeric excess (around 75%). In addition, the ligand could be reused up to nine times without any change in the selectivity or activity.

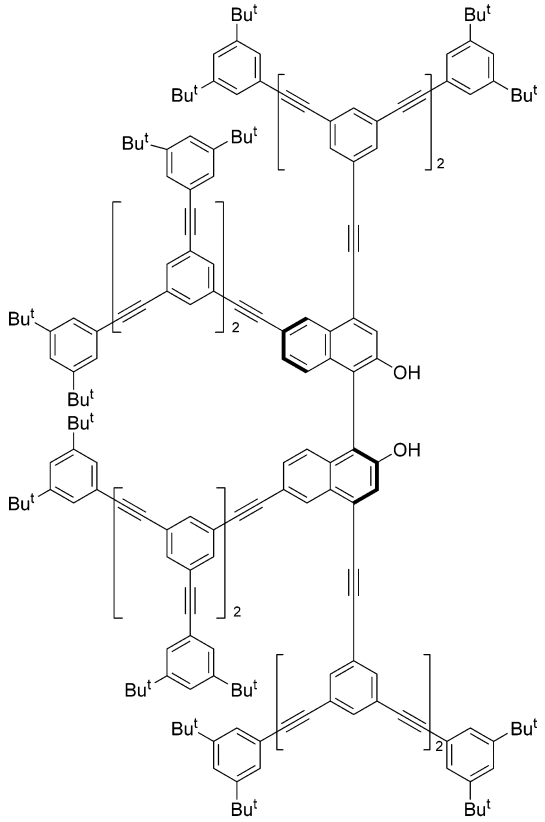
Another possibility to facilitate the recuperation of ligand is the attachment of an ionic tag. In this way the enantioselective ethylation of benzaldehyde using an excess of titanium tetraisopropoxide and the ligand ***ent*-90r** in dichloromethane yielded the expected alcohol **136b** with 82% ee and quantitative yield. The hydrolysis using hydrochloric acid (0.1 M), extraction with diethyl ether, and rapid filtration of the resulting heterogeneous aqueous phase afforded the pure ligand ***ent*-90r**, which could be reused five times without loss of activity and selectivity.[229]



***ent*-90r**

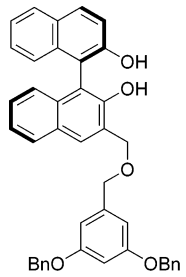
The BINOL structure has also been used as a core for the development of chiral dendrimers[201] able to catalyze the ethylation of benzaldehyde using titanium tetraisopropoxide. The reaction promoted by ligand ***ent*-90s** gave the expected alcohol **136b** with quantitative yield and enantioselectivity similar to those using BINOL. Here, the dendritic ligand ***ent*-90s** could be easily recovered from the reaction mixture by precipitation with methanol, owing to the large size differences between the ligand, reaction products, and reagents.[230]

The classical Féchet dendrons have been anchored to the BINOL unit to form a different generation of dendritic ligands **90t**−**x**. These ligands have been tested in the enantioselective ethylation of benzaldehyde to yield the compound **136b**, with the results being strongly dependent on the position of the Féchet dendron. Thus, the enantioselectivity was 82% for ligand **90t**; the increase of the generation, as well as the use of symmetrically 3,3′-disubstituted derivatives, did not have any impact on the enantiomeric excess of the final secondary alcohol. In the case of a 6-substituted system, ligand **90u** gave a similar enantiomeric excess (83%). Only for 6,6′-disubstituted

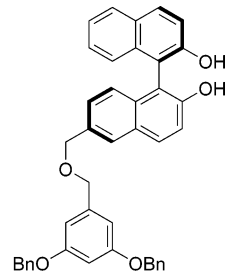


***ent*-90s**

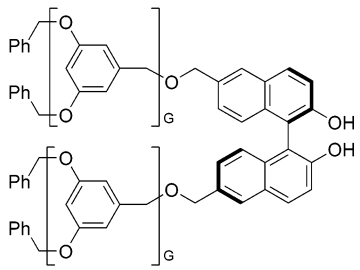
systems **90v**−**x** did the generation (that is the size) have a minimal positive influence on the enantioselectivity: 85, 87, and 86% for first (**90v**), second (**90w**), and third generation ligands (**90x**), respectively.[231] These results seem to indicate that the dihedral angle in the homogeneous titanium complex is very similar in the three generations.



90t



90u



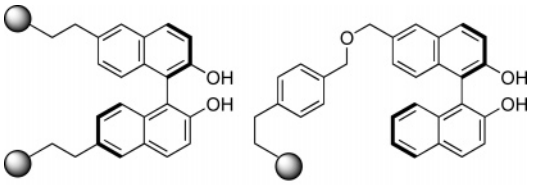
90v: G = 1
90w: G = 2
90x: G = 3

As in the case of TADDOL derivatives, the BINOL system has been attached to a large number of supports,[203] starting

from those in which both the chiral moiety is bonded to the polymer and the polymer is formed simultaneously.

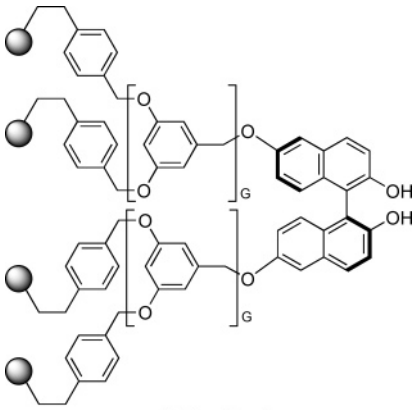
The first example is the polystyrene resins incorporating BINOL units **90y**, which was prepared by radical polymerization of styrene and the corresponding 6,6-divinylbinaphthol. Its use as chiral catalysts for the enantioselective addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide gave different enantioselectivities depending on the amount of cross-linker (6,6-divinylbinaphthol) used in the preparation, as well as on the loading,[232] with the best enantiomeric excess being 78%.

The previous modest result was attributed to diffusion problems of reagents from the solution to the surface of the polymer (15 h was necessary to form the titanium−BINOL complex). To avoid this problem, maintaining the recoverability of system, the soluble polystyrene derivative **90z** was prepared. However, the enantioselectivity found in the classical preparation of secondary alcohol **136b** was only 84%,[233] in the same range of the previous polymer or BINOL (**90a**).



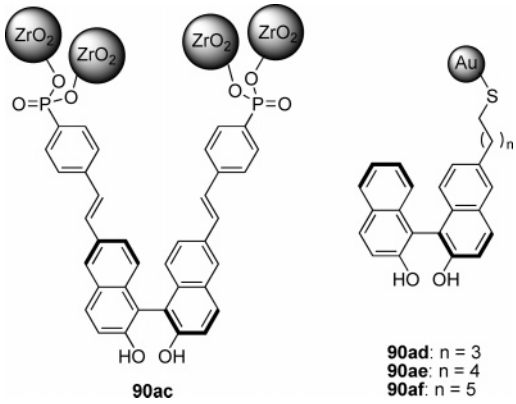
90y **90z**

Another possibility assayed was the use of different dendrimeric systems as cross-linkers, with the polymers **90aa,ab** being prepared by a usual radical styrene polymerization. In these cases, the enantioselectivities (86%) and the reaction rates were as good as those obtained with BINOL. As in the previous case, the loading of polymer had an important impact on the results; the decrease of loading increased slightly the enantioselectivity.[234] These polymers could be reused 20 times with a minimum loss of selectivity.



***ent*-90aa**: G = 1
***ent*-90ab**: G = 2

Not only can organic supports be used, but also BINOL units have been attached to some inorganic supports. Thus, the BINOL zirconium oxide material **90ac** was obtained by butanol reflux of zirconium tetrabutoxide and the corresponding diphosphoric-BINOL derivative. The precipitated material **90ac** was used as a chiral ligand in the standard ethylation of benzaldehyde, and the enantioselectivity was modest (59%).[235]

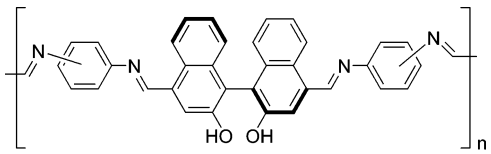


90ac

90ad: n = 3
90ae: n = 4
90af: n = 5

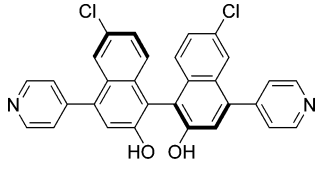
Another possibility is the monolayer BINOL-functionalized gold clusters **90ad**−**af**.[236] These clusters with a diameter less than 5 nm were prepared by reductive precipitation of gold salts in the presence of the corresponding sulfanyl derivative. The enantioselectivity found in the addition of diethylzinc to benzaldehyde in the presence of these gold clusters was dependent on the alkyl chain spacers, reaching 80, 86, and 72% for **90ad**, **90ae**, and **90af**, respectively. It should be pointed out that in a further reuse the selectivity dropped substantially.

The problems in the enantioselectivity and reproducibility of results using prepared chiral polymers were attributed to the badly defined microenvironment, which made it very difficult to systematically modify this microenvironment and, therefore, to improve the selectivity. For strictly controlling this environment,[237] different rigid and regular binaphthyl polymers **90ag,ah** were prepared by condensation of 1,2- or 1,4-diaminobenzene with the corresponding binaphthol aldehyde derivative.[238] The enantioselectivity found for the ethylation of benzaldehyde was 64 and 80% for **90ag** and **90ah**, respectively. The further preparation of the related polymer using a (*R*)-5,5′-diamino BINAP derivative[239] instead of diaminobenzene did not improve the previous results,[240] but it indicates that the synthetic route for this chiral polymer could be a good choice for the development of any other related system.



90ag: *ortho*
90ah: *para*

An interesting approach to the synthesis of materials bearing BINOL units uses the chiral naphthol derivative **90ai**.[241] The crystallization of $CdCl_2$ and **90ai** in MeOH/

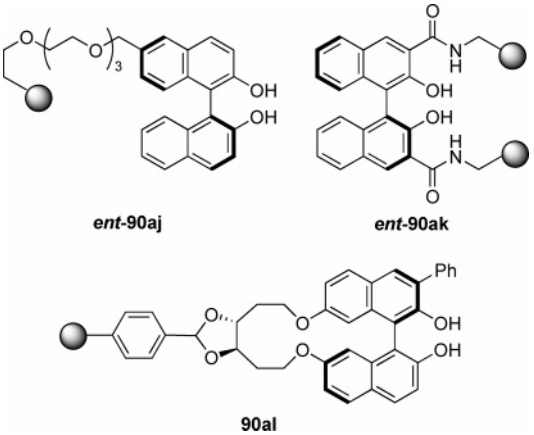


90ai

DMF by slow diethyl ether diffusion gave colorless crystals of $[Cd_3Cl_6$**90ai**$]\cdot 4DMF\cdot 6MeOH\cdot 3H_2O$. This crystal is a porous metal−organic framework analogous to zeolites, in which octahedrally coordinated Cd centers are doubly

bridged by the chlorine atoms to form zigzag chains. Each Cd center in these chains further coordinates to two pyridyl groups of two **90ai** ligands to form a noninterpenetrating tridimensional network with very large chiral channels (1.6 nm × 1.8 nm cross-section). The use of this crystal as chiral ligand in the enantioselective addition of diethylzinc to benzaldehyde gave the expected secondary alcohol **136b** with similar results compared to the homogeneous version of the reaction using BINOL **90a**.

The BINOL unit has also been grafted to different polymeric materials. Thus, the micelle-derived polymer ***ent*-90aj**



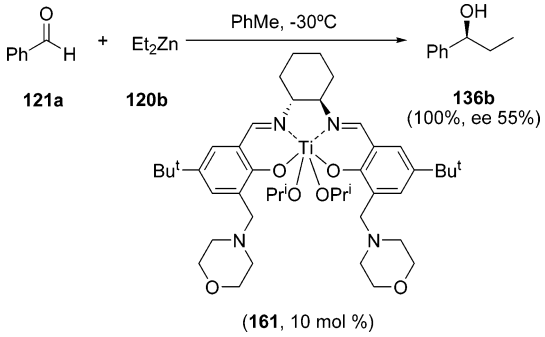
was prepared in a two steps synthesis.[242] The first step was the photo-copolymerization of styrene and the related triethyleneglycol styryl derivative in water to form spherical polymers possessing free hydroxy groups at the periphery ($M_w = 2.8 \times 10^4$; diameter = 3.2 nm). The second step was to graft the 6-chloromethyl binaphthol protected derivative by a simple S_N2 reaction and final acid deprotection. Its use as catalyst for the enantioselective addition of diethylzinc to benzaldehyde to yield the secondary alcohol **136b** was moderately successful (60% yield, 81% ee).

The BINOL unit has been grafted to aminomethylated polystyrene using the corresponding 3,3′-dicarboxilic BINOL derivative and classical peptide coupling protocols. Surprisingly, in most cases, the polymer-supported catalyst ***ent*-90ak** was found to be substantially more effective than the homogeneous version using BINOL **90a** in the addition of diethylzinc to different aldehydes (**136b**: 97% ee; **136d**: 93% ee; and **136r**: 94%).[243] On the other hand, the use of a related polymer, obtained from the corresponding mono 3-carboxilic BINOL derivative, gave worse results.

The last grafted example is the polystyrene-bound cyclo-BINOL **90al**, which was prepared from formylated polystyrene beads. This polymeric material gave excellent results when it was used as chiral ligand for the addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide (**136b**: 95% ee).[244]

Chiral salen ligands[214] have also been used as promoters in the enantioselective addition of diethylzinc to aldehydes. Thus, the complex **161**,[245] obtained by simple mixing of equimolecular amounts of the salen derivative and titanium tetraisopropoxide, is able to catalyze this addition (Scheme 58). It is difficult to get the structure of this catalyst since, in its crystallization, the complex evolves to μ-oxo-titanium dimeric species due to the presence of traces of water.[246] However, its role as a bifunctional catalyst[247] can be rationalized considering that the titanium center is a Lewis acid chelating the basic oxygen atom of the aldehyde, and

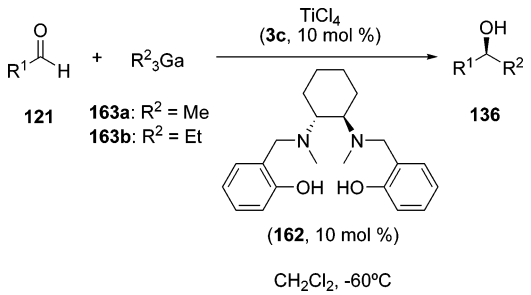
Scheme 58. Enantioselective Addition Promoted by the Bifunctional Catalyst 161



the nitrogen atom is a Lewis base chelating the zinc atom,[29] activating in this way both the nucleophile and the electrophile as well as approximating both reagents.

The phenol derivative **162** has been used as chiral ligand for the enantioselective addition of different organogallium reagents **163** to aldehydes in the presence of substoichiometric amounts of titanium tetrachloride (**3c**) (Table 15).[248]

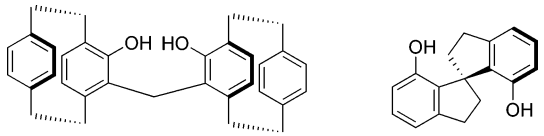
Table 15. Enantioselective Addition of Organogallium Reagents



entry	no.	R^1	R^2	yield (%)	ee (%)
1	**136a**	Ph	Me	50	70
2	**136b**	Ph	Et	55	54
3	**136p**	4-ClC_6H_4	Et	60	54
4	**136q**	4-$O_2NC_6H_4$	Et	75	81

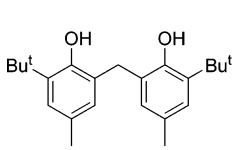
Although the reaction did not reach excellent levels of enantioselectivity, it shows the possibility to use other nucleophilic reagents different from the classical dialkylzincs.

The planar-stereogenic methylene bridge biphenol **164**,[249] which is based on the [2.2]paracyclophane skeleton,[250] has been used as chiral ligand for the enantioselective addition of diethylzinc to benzaldehyde in the presence of titanium tetraisopropoxide with very modest results. On the contrary, the spiro phenol **165** has proven to be more effective for this addition,[251] with the enantioselectivity found for a series of 4-substituted benzaldehydes being nearly constant at 85%.

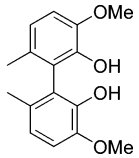


To finish the subject of phenol derivatives as promoters, it should be pointed out that some achiral ligands can improve the enantioselectivity of the reaction.[252] Thus, the very flexible achiral bisphenol **166** (20 mol %) could drive the enantioselective addition of diethylzinc to benzaldehyde in the presence of a slight excess of chiral Ti[(*S*)-OCH(4-

$MeC_6H_5)Et]_4$ (**3f**) from 9% ee (*R*) with no additive to 79% ee (*S*). The reason might be related to the existence of different complexes in which the achiral ligand takes a transitory chiral conformation although only one of these complexes has a very high activity, with the addition being catalyzed practically only by this complex.[253]



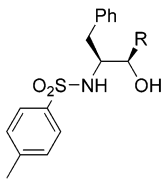
166



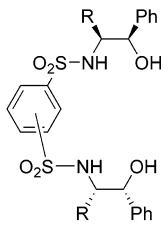
167

A little bit more elaborated is the use of the bisphenol **167**, which was combined with equimolecular amounts of titanium tetraisopropoxide and the TADDOL ligand **118** to yield a titanium complex. This new complex has two diastereomeric structures, according to the presence of a stereogenic ax in compound **167**, and the energetic difference between both complexes is 3.6 kcal/mol (molecular mechanics 2 calculations). In fact, the TADDOL unit forces the generation of only one chiral conformation of ligand **167**, giving a very active catalyst, which is able to catalyze the enantioselective addition of methyltitanium triisopropoxide (**122a**) to benzaldehydes with enantiomeric excess higher than 99%.[254]

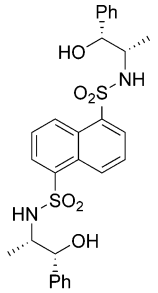
Since 1992, when the Katsuki group introduced chiral β-hydroxy sulfonamides as ligands for the nowadays classical enantioselective addition of dialkylzinc to aldehydes in the presence of an excess of titanium tetraisopropoxide, many examples have been reported.[255] These compounds are interesting ligands for titanium complexes because they contain two different functionalities, which can transform the titanium atom into a new stereogenic center, as well as for the great amount of different available building blocks, which permitted a very highly modular approach to their synthesis. The first example is the use of compound **168a** in the ethylation of benzaldehyde, which gave an excellent result (***ent*-136b**, 96% ee).[256] The use of other amino alcohols showed that the presence of two stereogenic centers was of capital importance and that the enantioselectivity relied mainly on the substituents of the carbon atom adjacent to the hydroxy group. In fact, the aforementioned ethylation using the ligand **168b** gave the final product **136b** with a very modest enantiomeric excess (4%), with the main enantiomer being (*R*).



168a: R = Ph
168b: R = *c*-C_6H_{11}



169a: *ortho*, R = Me
169b: *meta*, R = Me
169c: *meta*, R = Ph

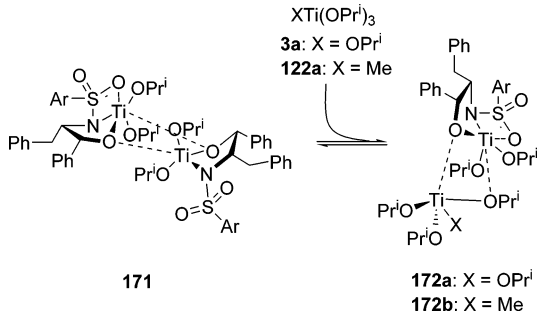


170

Bis-β-hydroxy sulfonamides **169** and **170** were designed supposing that the catalytic cycle described in Scheme 53 could be similar for β-hydroxy sulfonamides, and therefore, the key complex would be a bimetallic system of type **123**. In this way, these ligands could lodge two titanium atoms at the same time and, by playing with the length between them, the synergistic effect could be detected. The ethylation of benzaldehyde using ligands **169a,b** and **170** under the same conditions gave totally different results. Whereas ligands **169a** and **170** (with the smallest and largest distance between both sulfonamide moieties, respectively) yielded the alcohol **136b** with modest results (56%, 50% ee, and 30%, 50% ee, respectively) after 1 day of reaction, ligand **169b** gave alcohol **136b** in only 8 h with quantitative chemical yield and 84% ee. These facts were the first indirect evidence that the general picture of the catalytic cycle describe in Scheme 53 was also applicable to β-hydroxy sulfonamides. The use of the ligand **169c** with more crowded substituents improved the enantioselectivity up to 92%.[257]

A broad study using the ligand **168a** confirmed that the catalytic cycle described in Scheme 53 could also be applied for ligands of type β-hydroxy sulfonamide, as was previously presented for bis(sulfonamide) and binaphthol derivatives. The treatment of ligand **168a** with a titanium alkoxide derivative gave a crystalline complex with a bimetallic structure **171** (Scheme 59). The most interesting feature of

Scheme 59. Bimetallic Species Detected Using Ligand 168a



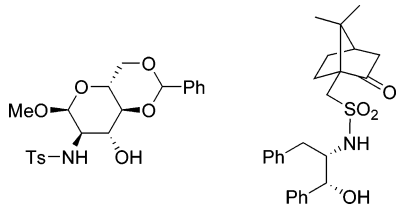
171

172a: X = OPr^i
172b: X = Me

this structure is the nonequivalence of the two titanium atoms owing to the different bonding modes of the sulfonamide in both chiral ligands. In solution and by ^{1}H NMR studies, at least four different species were detected, which implies the presence of different equilibriums. Moreover, the reaction of diethylzinc with benzaldehyde did not proceed when it was performed in the presence of the bimetallic complex **171**, which means that it is not included in the catalytic cycle. However, if the aforementioned reaction using **171** is performed with an equimolecular amount of titanium tetraisopropoxide, the results are excellent. When the ligand **168a** was crystallized in the presence of a double amount of titanium tetraisopropoxide, the complex **172a** was isolated (compare with structure **123** in Scheme 53). The X-ray analysis of this structure clearly revealed a pocket on the same side of the sulfonyl oxygen bond. Since the Ti−O bond (from the sulfonyl moiety) is very weak, the aldehyde was expected to access the six-coordinated metal center from this side, replacing the sulfonyl oxygen donor. However, a mixture of complexes was detected in solution, with the main one being **171**. The composition of this mixture is a function of the temperature and of the solvent, with the complex **172a** being the major one at high temperatures and in apolar solvents. In any case, the addition of diethylzinc to benzaldehyde using complex **172a** gave an excellent result. Finally, the reaction of complex **171** with 2 equiv of methyltitanium triisopropoxide (**122a**) gave the new complex **172b** (Scheme 59, compare with the intermediate **124** in Scheme 53), according to NMR studies. The reaction of complex **172b**

with benzaldehyde gave the same results as the reaction of dimethylzinc, titanium tetraisopropoxide, and the ligand **168a**.[258] All these facts confirm that the catalytic cycle described in Scheme 53 is a general picture for any ligand in this type of addition, with it only being necessary to modify some aspects due to the differences in the aggregation constants of the generated complexes.

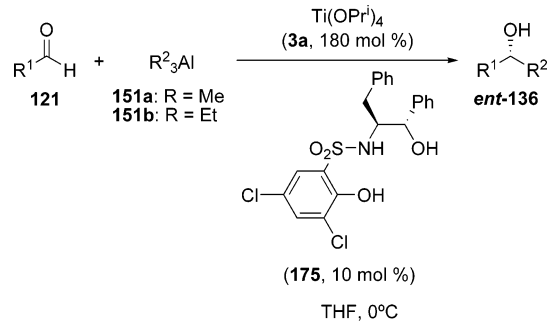
Other β-hydroxy sulfonamides, used substoichiometrically as chiral ligands for the enantioselective addition of diethylzinc to aldehydes, are compounds **173**[259] and **174**.[260] While the results using ligand **173** were good and practically constant independent of the nature of the aldehyde, the enantioselectivity using ligand **174** depended strongly on the nature of the substituents of the aldehyde, yielding good results for arenecarbaldehydes and very modest results for aliphatic derivatives.



173 **174**

The tridentate ligand **175** has been used in the enantioselective addition of trialkylaluminum reagents to aldehydes in the presence of titanium tetraisopropoxide (Table 16), with

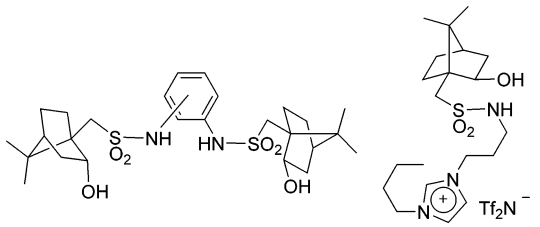
Table 16. Enantioselective Addition of Trialkylaluminum to Aldehydes Using the Ligand 175



entry	no.	R^1	R^2	yield (%)	ee (%)
1	***ent*-136a**	Ph	Me	100	98
2	***ent*-136b**	Ph	Et	98	96
3	***ent*-136d**	(*E*)-PhCH=CH	Et	100	88
4	***ent*-136g**	*c*-C_6H_{11}	Et	54	91
5	***ent*-136p**	4-ClC_6H_4	Et	100	94
6	***ent*-136v**	1-naphthyl	Et	94	92

the reaction being performed in THF as solvent in order to reduce the aluminum activity. The enantioselectivity seems to be nearly constant and independent of the nucleophile (trimethyl- or triethylaluminum reagent) and the electrophile used, with arenecarbaldehydes giving a slightly higher enantiomeric excess than aliphatic or α,β-unsaturated ones.[261] The presence of a phenol moiety on the ligand **175** is of vital importance to obtain good enantioselectivities, and the relative configuration of both stereogenic centers is also very important; any change in these two positions has a significant detrimental effect.

Not only β-hydroxy sulfonamides but also other hydroxy sulfonamides such as isoborneol sulfonamides have also been used as chiral promoters for the enantioselective addition of diethylzinc to aldehydes in the presence of titanium tetraisopropoxide. Thus, ligands **176**, which are able to lodge two titanium atoms, were easily prepared and tested in this reaction. As expected, the enantioselectivity depended strongly on the relative position of both metals; the best results were obtained with the *meta*-substituted compound (**136b**: 40% ee for **176a** and 66% ee for **176b**).[262] However, these results were slightly inferior to those obtained with the isoborneolsulfonamide **119a**, which can only lodge one titanium atom (72% ee for **136b**).[191]

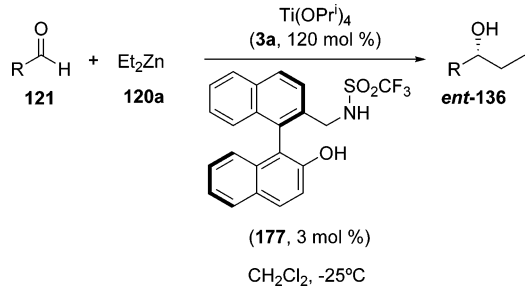


176a: *ortho* **119b**
176b: *meta*

The isolation of the mentioned isoborneolsulfonamide ligands can be facilitated by the incorporation of an ionic liquid tag, as in compound **119b**, which in the ethylation of benzaldehyde under standard conditions gave the secondary alcohol **136b** with 65% ee. The final hydrolysis of reaction media using 1 M HCl, followed by successive extraction with ether (to remove reagents and product) and with methylene chloride, recovered the pure compound **119b**, which could be reused four times without loss in the enantioselectivity.[263]

Chiral 2-triflamidomethyl-2′-hydroxy-1,1′-binaphthyl **177** has been successfully used as promoter for the classical ethylation of aldehydes (Table 17), with the enantioselectivity

Table 17. Enantioselective Ethylation of Aldehydes Using the Ligand 177

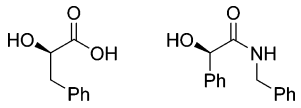


entry	no.	R	yield (%)	ee (%)
1	***ent*-136b**	Ph	99	99
2	***ent*-136d**	(*E*)-PhCH=CH	97	99
3	***ent*-136g**	*c*-C_6H_{11}	91	99
4	***ent*-136i**	4-$MeOC_6H_4$	96	91
5	***ent*-136p**	4-ClC_6H_4	95	98
6	***ent*-136v**	1-naphthyl	95	98

being excellent for any kind of aromatic, aliphatic, and α,β-unsaturated aldehydes.[264] The acidity of the triflamido group is crucial to get this level of enantioselectivity, so the reaction with the related methanesulfonyl or *p*-toluenesulfonyl amides instead of trifluoromethanesulfonyl gave a miserable enantioselectivity. The correlation of the enantiomeric excess of the ligand **177** with the enantiomeric excess of the product ***ent*-136b** showed a small negative nonlinear effect, similar to that found for bis(sulfonamides).

Other systems used as chiral ligands for the enantioselective addition of dialkylzinc reagents to aldehydes in the presence of titanium alkoxides were α-hydroxy carboxylic acids. In fact, mandelic acid (**88**) emerged as the best chiral ligand from a screening of nine different α-hydroxy carboxylic acids, with the enantioselectivity being always lower than 85%.[265] However, when the source of the nucleophile was changed from diethylzinc to triethylaluminum, the best hydroxy acid was compound **178**, with the enantioselectivity being similar to that using diethylzinc.[266]

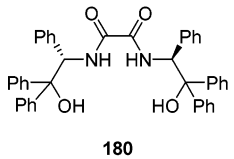
The related *N*-benzyl mandelamide **179** has also been used for the enantioselective addition of dimethylzinc to aldehydes in the presence of titanium tetraisopropoxide. The enantioselectivity was never higher than 90%, showing a strong dependence on the nature of the aldehydes, with the aliphatic ones giving lower results (around 60% ee).[267]



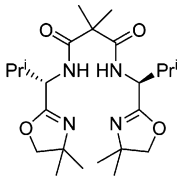
178 **179**

Other carboxamides with C_2 symmetry have also been tested for the enantioselective addition of diethylzinc to aldehydes. For instance, the aforementioned addition performed in the presence of substoichiometric amounts of the oxalamide **180** gave modest enantioselectivity independent of the aldehyde used.[268]

The chiral 2-(aminomethyl)oxazoline derivatives of type **181** did not produce any spectacular change in the enantioselectivity, compared with the cases of acid derivatives previously shown. It should be pointed out that ligand **181** gave the best results (<95% ee) from a selection of 12 other related compounds, bearing different substituents or stereogenic centers.[269]



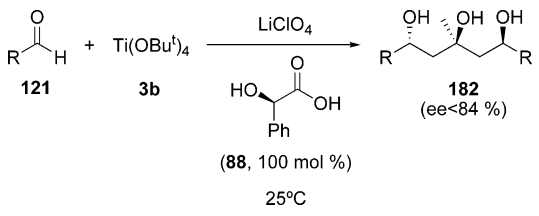
180



181

The last example of this section comes from an unusual alkylation of aldehydes where the source of the nucleophile is the titanium alkoxide (Scheme 60). The reaction of

Scheme 60. Unusual Alkylation of Aldehydes



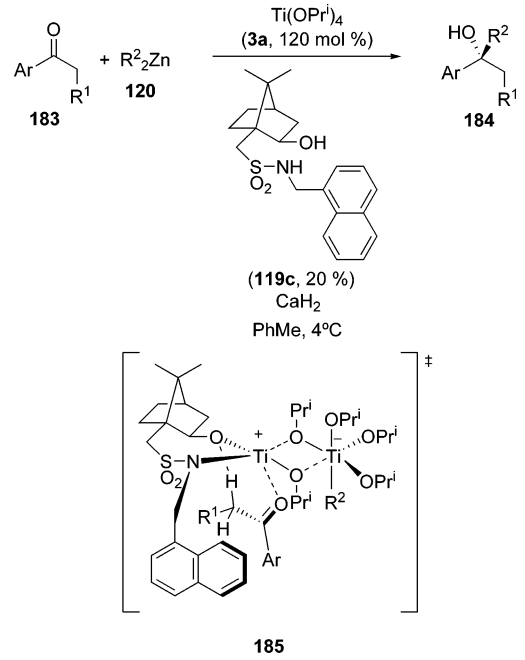
different aldehydes with equimolecular amounts of titanium *tert*-butoxide (**3b**) in the presence of lithium perchlorate and mandelic acid as chiral ligand gave the chiral *anti*-triol **182**. A careful study showed that in the beginning (under kinetic control) the first reaction product detected was the related *syn*-triol, which is a *meso*-form. However, this compound equilibrated after 2 days to give the chiral triol **182**. The hypothetical mechanism should involve the C−H activation of *tert*-butoxide to condense with a first molecule of aldehyde to give a 1,3-diol which after a similar second condensation process yielded the corresponding triol.[270] Although the enantioselectivity was strongly dependent on the aldehyde (the best result was found for benzaldehyde), this procedure opens up the field for other ligands as well as for conditions to improve the results.

4.1.2. Ketones as Electrophiles

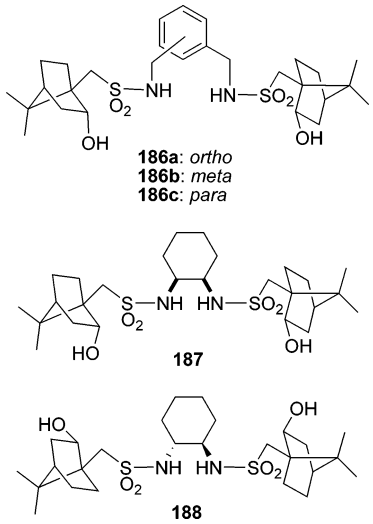
The enantioselective addition of organometallics to ketones is much more difficult than the related one to aldehydes for obvious reasons previously mentioned, and the difficulty is greatest when the reaction is performed using catalytic amounts of the promoters. On one hand, the use of poorly reactive organometallics, such as organozinc and tin reagents, is compulsory for promoting addition protocols, and on the other hand, the poor electrophilic ketone makes this reaction very difficult.[271] In fact, the addition of dialkylzinc reagents to normal simple ketones failed[272] until the introduction in 1998 of the use of isoborneolsulfonamide **119c** as the chiral promoter.[273] To learn more about this new enantioselective addition, a short mechanistic study was done, with the more remarkable facts being the presence of a small positive nonlinear effect when the reaction was performed using stoichiometric amounts of ligand **119c** and titanium tetraisopropoxide, which disappeared when the reaction was carried out using stoichiometric amounts of titanium tetraisopropoxide and substoichiometric amounts of ligand. This fact denotes the presence of a bimetallic complex in the catalytic cycle. Moreover, the enantioselectivity was irrespective of the chemical yield (no autoinduction) and of the electronic nature of the substituents on the aromatic ring of the ketone, but it was strongly dependent on the size of substituent around the carbonyl group. The use of methyltitanium triisopropoxide as the source of the nucleophile yielded the tertiary alcohol as a racemic mixture, showing the importance of the transmetalation equilibrium in this reaction. All theses facts fit perfectly with a catalytic cycle similar to that shown in Scheme 53, with the only changes being the chiral promoter and the carbonyl compound.[274] We introduced the zwitterionic complex **185** as the catalytic active species (compare with the complex **125**), in which the cationic titanium center[275] carried the chiral ligand and strongly activated the ketone, while the anionic titanium center carried the alkyl moiety, increasing its nucleophilic character. The preference for the ketone complexation is determined by a possible π-stacking between the naphthyl moiety of the ligand and the aromatic group of the ketone, as well as by a hydrogen bond between the oxygen of the ligand and the α-hydrogen of the ketone[276] (Scheme 61).

With the aim of favoring the hypothetical active species of type **185**, different bis(isoborneolsulfonamides) were prepared. In this way, by playing with the length and angles of the diamine tether, the flexible isopropoxy bridge might be eliminated and the synergetic effect due to the proximity of the two boarder titanium atoms might be increased. The first attempt was the xylylenediamine derivatives **186**, which gave different enantioselectivities depending on the relative position of the substitution. The enantiomeric excess of the tertiary alcohol **190a** obtained by the addition of diethylzinc to acetophenone catalyzed by titanium tetraisopropoxide was 78%, 86%, and 81% using ligands **186a**, **b**, and **c**, respectively. It is notable that the enantioselectivities of the ligands

Scheme 61. Enantioselective Alkylation of Ketones Using the Ligand 119c



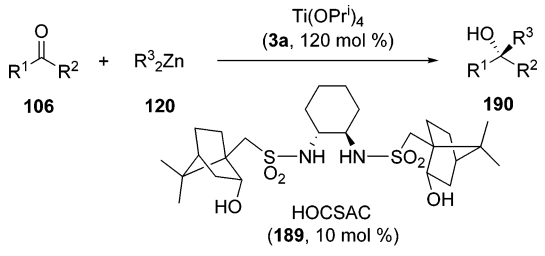
186c (large distance between both isobornyl moieties) and **186a** (small distance between the isobornyl moieties) gave similar results while ligand **186b** gave better results, not only in enantioselectivity but also in chemical yield and reaction rate.[277] This synergetic effect was also noticed in the classical addition of diethylzinc to benzaldehyde.



To improve the synergetic effect of these types of ligand, 1,2-diamines were tested, since they are conformationally more stable, so ligands **187** and **188** were prepared. However, the enantioselectivity shown was disappointing (**190a**: 24% and 36% using **187** and **188**, respectively). Finally, the chiral *exo*-diol derived from *trans*-camphorsulfonamido cyclohexane (HOCSAC, **189**) gave the best results (Table 18).[278] The reaction worked fairly well for dimethyl or diethylzinc. The presence of substituents of different electronic nature as well as the size of aromatic moiety seems not to have any significant impact on the results; the best ones are obtained for α,β-unsaturated ketones.

The enantioselective addition of diethylzinc using HOCSAC **189** as promoter worked equally well for dialkyl

Table 18. Enantioselective Alkylation of Ketones Using HOCSAC

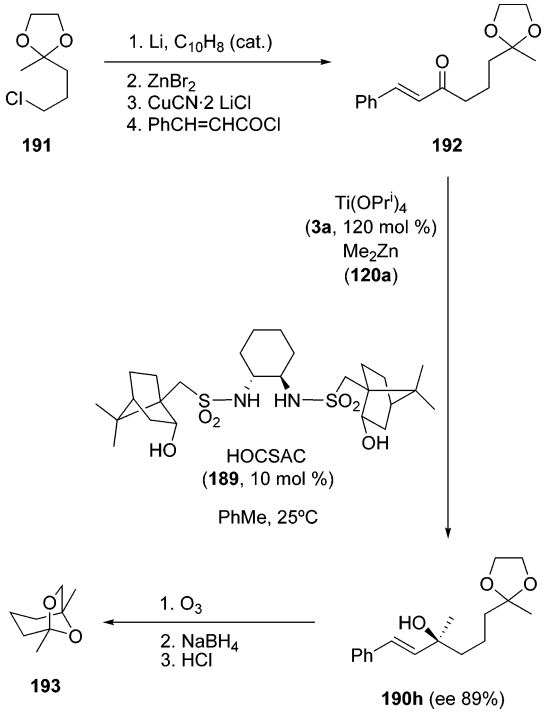


entry	no.	R^1	R^2	R^3	yield (%)	ee (%)
1	***ent*-190a**	Ph	Et	Me	>95	98
2	**190a**	Ph	Me	Et	80	98
3	**190b**	4-MeC$_6$H$_4$	Me	Et	90	95
4	**190c**	4-CF$_3$C$_6$H$_4$	Me	Et	90	93
5	**190d**	Ph	CH$_2$Br	Et	70	50
6	**190e**	2-naphthyl	Me	Et	>95	86
7	**190f**	(*E*)-PhCH=CH	Me	Et	90	>99
8	**190g**	PhC≡C	Me	Et	>95	>99

ketones[279] and for cyclic α,β-unsaturated ketones.[280] In the last case, the authors followed a previously reported strategy (Scheme 54): the diastereoselective epoxidation using oxygen of the in situ formed chiral allylic alcohol to form the corresponding chiral epoxides.

The enantioselective alkylation of simple ketones has permitted the synthesis of (−)-frontalin **193**,[281] which is an aggregation pheromone secreted from different pine beetles. Its synthesis started with the naphthalene-catalyzed lithiation[282] of the chlorinated dioxolane **191** to give the corresponding bishomoenolate, which was successively transmetalated with zinc and copper, and finally trapped by reaction with cinnamyl chloride, to yield the ketone **192**. The enantioselective addition of dimethylzinc to this ketone catalyzed by HOCSAC (**189**) gave the expected tertiary

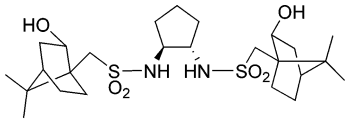
Scheme 62. Preparation of (−)-Frontalin through an Enantioselective Alkylation of the Ketone 192 Using HOCSAC



alcohol **190h** with 89% ee. The ozonolysis to cleave the double bond, followed by reduction and acid aqueous hydrolysis, gave the expected (−)-frontalin (**193**) without racemization (Scheme 62).

The substrate scope of the aforementioned reaction using HOCSAC **189** seems to be very broad, since different functionalized dialkylzinc reagents[166,172] can be used as the source of the nucleophile, giving excellent enantiomeric excess, as in the case of commercially available dimethyl- and diethylzinc.[283]

The related cyclopentane derivative **194** has also been prepared and tested in the new enantioselective addition of dialkylzinc to simple ketones using titanium tetraisopropoxide.[284] However, the enantioselectivity found was somewhat lower, being 91% for **190a** and 78% for **190f**.

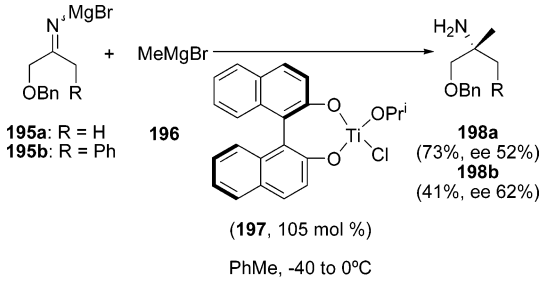


194

The complex **161** has been used as substoichiometric catalyst for the enantioselective addition of diethylzinc to α-ketoesters, yielding the expected substituted α-hydroxy esters with enantiomeric excess never higher than 78%, which could be improved by successive recrystallizations up to 98%.[285] The main handicap of this addition is the reagents' scope, since it only worked with very highly electrophilic ketones, such as α-ketoesters.

The last process of this section is a typical example of a modulated reaction.[164] In this case, the enantioselective addition of methylmagnesium bromide (**196**) to the metaloimines **195**, prepared by addition of the corresponding alkylmagnesium bromide to benzoxyacetonitrile, is modulated by the complex **197** (Scheme 63).[286] Although the

Scheme 63. Enantioselective Addition of Methyl Magnesium Bromide to Metaloimines



results are not excellent, the process should be taken into account since methods for the direct preparation of chiral amines are rather scarce and normally employ several complicated steps.

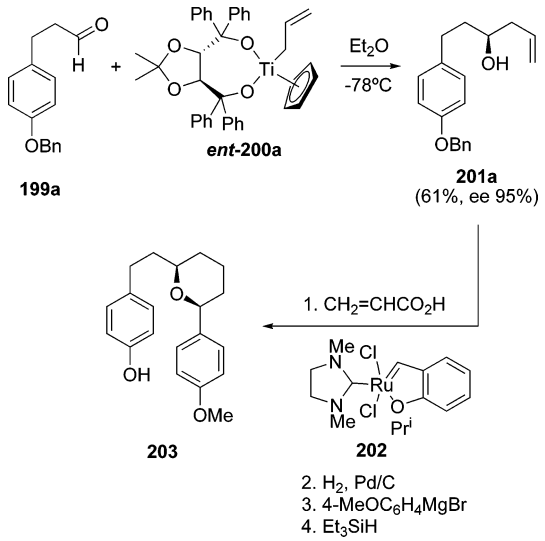
4.2. Allylation Reactions

Enantioselective allylation reactions are very interesting processes since, apart from the new stereogenic centers created, an extra double bond is added to the final product that could be further modified to give different functionalities, with this being the reason for the great effort already exerted in this area.[287]

4.2.1. Aldehydes as Electrophiles

The initial work of Duthaler's group in 1989 opened up the field for the stoichiometric use of chiral allyltitanium intermediates in synthesis.[288] Thus, during the period covered by this review a great number of applications have appeared.[289] The first example is depicted in Scheme 64, in

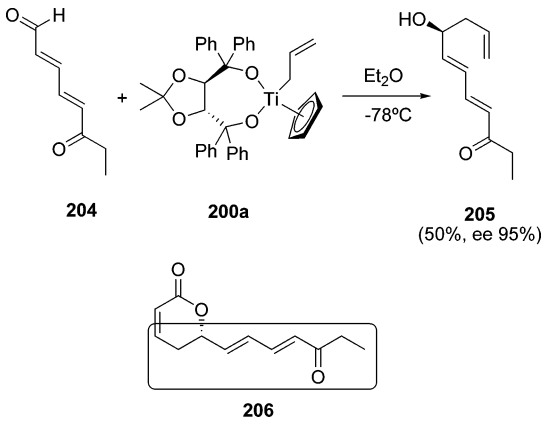
Scheme 64. Enantioselective Synthesis of (−)-Centrolobine (203)



which the synthesis of (−)-centrolobine started with the enantioselective addition of allyltitanium TADDOLate ***ent*-200a** to the aldehyde **199a**, yielding the homoallylic alcohol **201a** with good enantioselectivity.[290] The metathesis with acrylic acid using the catalyst **202**, followed by hydrogenolysis, addition of *p*-methoxyphenylmagnesium bromide (to the in situ formed lactone), and final reduction of the corresponding lactol, yielded the antiprotozoal compound **203** isolated from the heartwood of *Centrolobium robustum*.

The pyranone **206**, isolated from *Raimondia cf monoica*, possesses an interesting leishmanicide activity and was prepared by the enantioselective addition of the titanium complex **200a** to the aldehyde **204** to give the expected alcohol **205** with moderated yield (Scheme 65). The com-

Scheme 65. Preparation of Pyranone 206

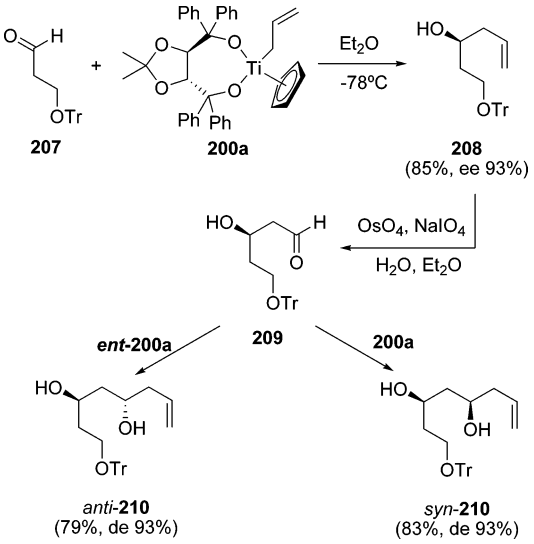


pound **206** was obtained from this alcohol following a strategy consisting of the formation of an acrylate ester and ring closing metathesis, with the absolute configuration being revised.[291]

The high enantioselectivity of the aforementioned allylation reaction was kept even using α-oxido functionalized aldehydes, and in this way different chiral 1,2-diols units were prepared with excellent results.[292] However, the strategy

based on an enantioselective allylation, followed by oxidative degradation to the corresponding aldehyde and final diastereoselective allylation, seems to be more interesting, since in this way different chiral 1,3-diols can be easily and predictably prepared. An iterative version of this process appears in Scheme 66,[293] in which the enantioselective

Scheme 66. Synthesis of 1,3-Diols by Iterative Asymmetric Allylation

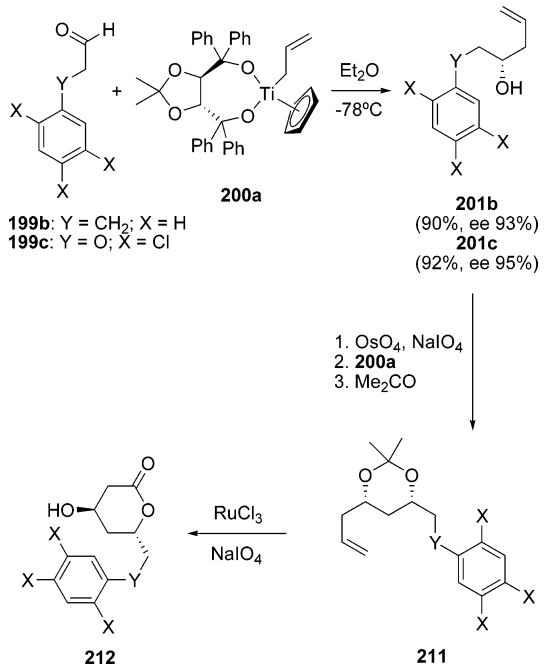


addition of the complex **200a** to the functionalized aldehyde **207** gave the homoallylic alcohol **208** with an excellent result, with its absolute configuration being predictable according to that of the complex used. The degradative oxidation of the terminal alkene gave a chiral β-hydroxy aldehyde **209**, which can be used as new starting material for the aforementioned allylation, giving both homoallylic alcohols **210**. In the strict sense, this is a diastereoselective reaction[294] (therefore, out of the subject of this review) and the outcome is governed by both reagents. In fact, in this type of addition, only the allyltitanium complex drives the reaction. The allylation of the aldehyde **209** using complex **200a** gave the *syn*-diol **210**, whereas the reaction with complex ***ent*-200a** gave the *anti*-diol **210** with excellent diastereoselectivity in both cases. The other two enantiomeric 1,3-diols can be easily prepared starting the iterative allylation process using the enantiomeric complex ***ent*-200a**.

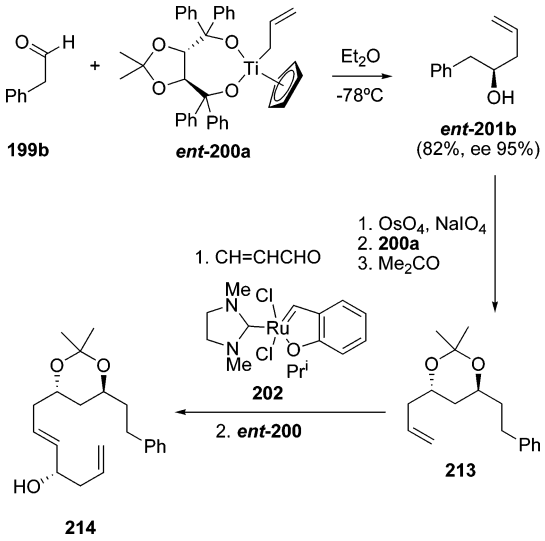
The possibility of preparing any one of the four 1,3-diol isomers through this iterative process has been extensively employed in the synthesis of different natural products. Thus, the lactones **212**, which are related to the natural products compactin and mevinolin, were prepared from the corresponding achiral aldehyde by an iterative allylation using complex **200a** to yield the corresponding homoallylic alcohols **201b** and **c** with good enantioselectivity, which were degradatively oxidized to the corresponding aldehydes and trapped by a second reaction with the complex **200a**, yielding the corresponding *syn*-diols, which were protected as the corresponding dioxane **211**. This last diastereoselective allylation gave the corresponding diols with a very high level of selectivity (>95% de).[295] The final oxidation of the double bond to the corresponding carboxylic acid gave directly the expected lactones **212** (Scheme 67).

Instead of the degradative oxidation of the double bond to obtain an aldehyde with a shorter carbon chain, it was possible to elongate the chain through a metathesis process

Scheme 67. Synthesis of Lactones 212 by Iterative Asymmetric Allylation



Scheme 68. Iterative Asymmetric Allylation Intercalating Degradative Oxidation and Cross-metathesis



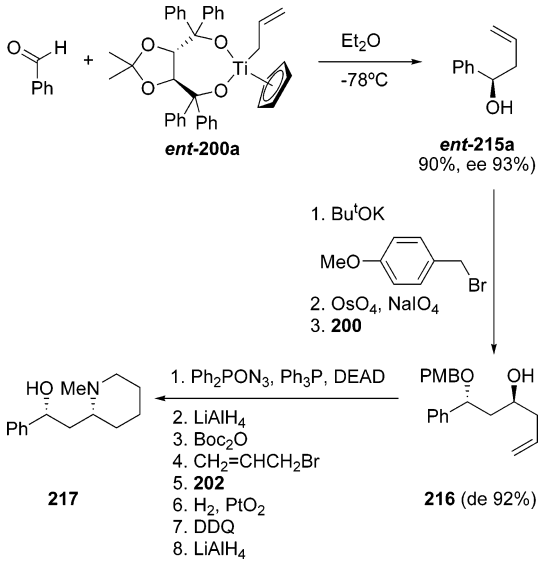
with acrolein (Scheme 68). Thus, when after the first allylation process to yield the homoallylic alcohol ***ent*-201b**, followed by degradative oxidation to the corresponding aldehyde, a new allylation process was carried out, the protection of the corresponding *anti*-diol gave compound **213**. The resulting homoallylic alcohol suffered a cross-metathesis process to yield the corresponding α,β-unsaturated aldehyde with an additional carbon unit in the chain. A final asymmetric allylation rendered the corresponding 1,5-diol **214**, which was easily transformed into (+)-strictifolione just by successive reaction with acryloyl chloride, ring closing metathesis (to yield the expected pyranone), and final hydrolysis of the ketal.[296]

The iterative allylation−oxidation process to yield 1,3-diol units has been successfully used in the synthesis of passifloricin A, which presents antifungal activity.[297] On the other hand, the iterative allylation−metathesis process to yield 1,5-diol units has been successfully employed in the

construction of the C1−C14 fragment of amphidinol 3, which also possesed antifungal activity.[298] The combination of both iterative processes permitted the synthesis of the C1−C13, C15−C25, and C27−C40 fragments of tetrafibricin.[299]

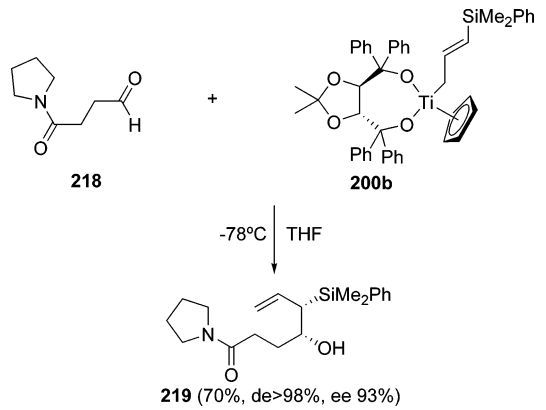
The iterative strategy rendering 1,3-diols can also be applied to produce 1,3-amino alcohols. Thus, after an enantioselective allylation of benzaldehyde to yield ***ent*-215a**, the protection of the hydroxy group as an ether, followed by degradative oxidation and a new diastereoselective allylation, yielded the *anti*-diol **216**, which can be transformed into the corresponding amine by standard protocols (Mitsunobu and reduction).[300] Finally, the alkaloid (+)-sedamine (**217**) was prepared following classical methodologies including a ring closing process (Scheme 69).

Scheme 69. Synthesis of (+)-Sedamine (217)



The above-mentioned stoichiometric allylation process can create in only one step two stereogenic centers with a high level of selection. As an illustrative example, the allylation of the aldehyde **218** with the complex **200b** at low temperature gave, after hydrolysis, the alcohol **219** with an excellent result (Scheme 70); this alcohol was further transformed into

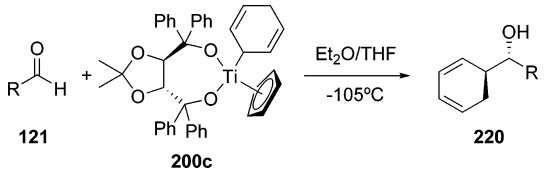
Scheme 70. Simultaneous Creation of Two Stereogenic Centers



bicyclo[3.2.0]hept-2-en-6-one through a [2+2]-cycloaddition process.[301]

More elaborate allylating agents such as the complex **200c** can also be successfully used (Table 19) with different aldehydes at low temperatures, yielding the expected alcohols

Table 19. Enantioselective Allylation of Aldehydes Using the Complex 200c



entry	no.	R	yield (%)	ee (%)
1	**220a**	Ph	83	96
2	**220b**	4-$MeOC_6H_5$	63	90
3	**220c**	4-BrC_6H_5	94	94
4	**220d**	1-naphthyl	96	98
5	**220e**	(*E*)-PhCH=CH	93	80
6	**220f**	PhC≡C	86	98
7	**220g**	*n*-C_5H_{11}	49	84

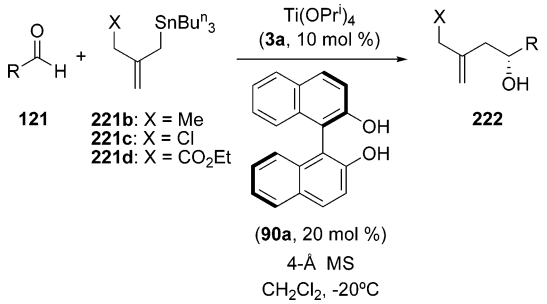
220 with very high diastereoselectivity (usually de > 99%). The enantioselectivity seems to be independent of the nature of the aldehyde, only decreasing for the case of using cinnamaldehyde and hexanal.[302] However, chemical yields appear to be connected with the electrophilic character of aldehyde; the better the electrophile, the higher the chemical yield obtained. This allylic desymmetrization process has been used as the key step in the synthesis of several natural occurring lactones.

Despite all the applications previously shown, the mentioned asymmetric allylation protocol has an important drawback, which is the use of the chiral complex in stoichiometric amounts. Although the TADDOL unit can be recovered after the final hydrolysis, it being possible even to recover a dimeric oxido complex of CpTi-TADDOL which can be transformed into the corresponding CpTi-TADDOL chloride by treatment with trimethylsilyl chloride, the whole process is very expensive, so the catalytic version of the reaction would be very much desired.

The catalytic enantioselective allylation of aldehydes using titanium complexes was independently published in 1993 by the groups of Tagliavini and Umani-Ronchi, and of Keck.[303] In both cases, the sources of the nucleophile and the chiral ligand were allyl tributylstannane (**221a**) and binaphthol **90a**, respectively. However, while Tagliavini and Umani-Ronchi's group used 20 mol % of dichlorotitanium diisopropoxide (**58b**) as well as BINOL **90a**, Keck's group proposed the use of a 10 mol % mixture of BINOL/titanium tetraisopropoxide (either 1:1 or 2:1), in both cases in the presence of 4-Å molecular sieves. Both protocols gave, in general, excellent enantioselectivities for the simple allylation.

The scope of the reaction has been amplified by the use of functionalized methallyl tin derivatives such as the corresponding methyl[304] (**221b**), chloromethyl[305] (**221c**), and ethoxycarbonylmethyl (**221d**) derivatives.[306] The enantioselectivity of the reaction is excellent for any kind of aldehydes such as aromatic, aliphatic, or even functionalized ones, as is shown from selected examples in Table 20. The functional group on the tin derivatives did not have any impact either on the enantiomeric excess or on the chemical yield. This reaction has been used in the asymmetric synthesis of the C16−C27 fragment of bryostatin 1 (using compound **221c**) and (+)-dactylolide (using compound **221d**), with the last compound being a cytotoxic metabolite isolated from sponge *Dactylospongia*,[307] as well as in the asymmetric synthesis of the C1−C13 fragment of dolabelide B (using compound **221b**).[308]

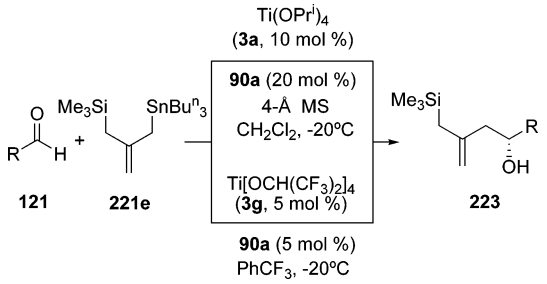
Table 20. Catalytic Enantioselective Allylation Using 2-Substituted Allylstannanes



entry	no.	R	X	yield (%)	ee (%)
1	**222a**	(*E*)-TBSOCH$_2$CH=CMe	Me	78	99
2	**222b**	Ph	Cl	96	98
3	**222c**	Ph	CO$_2$Et	96	98
4	**222d**	2-furyl	Cl	100	99
5	**222e**	2-furyl	CO$_2$Et	100	99
6	**222f**	Ph(CH$_2$)$_2$	Cl	84	99
7	**222g**	Ph(CH$_2$)$_2$	CO$_2$Et	98	99
8	**222h**	BnOCH$_2$	Cl	86	95
9	**222i**	BnOCH$_2$	CO$_2$Et	85	97

Another 2-substituted allylstannane used in catalytic enantioselective allylation of aldehydes is the silyl derivative **221e**. The results using titanium tetraisopropoxide were similar to those found for the previously shown compounds **221b**−**d** (compare Table 20 and entries 1 and 2 in Table 21).[309] However, a different protocol has also been checked

Table 21. Comparing Allylation Protocols



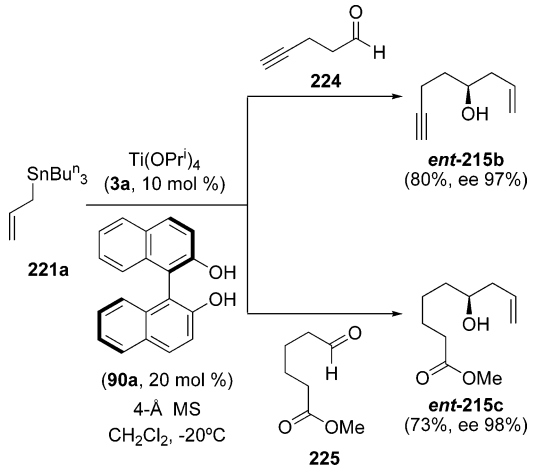
entry	Ti(OR′)$_4$	no.	R	yield (%)	ee (%)
1	**3a**	**223a**	2-furyl	96	92
2	**3a**	**223b**	Ph(CH$_2$)$_2$	92	96
3	**3g**	**223b**	Ph(CH$_2$)$_2$	74	91
4	**3g**	**223c**	Ph	89	96
5	**3g**	**223d**	(*E*)-PhCH=CH	54	93

for this nucleophile (Table 21, entries 3−5), so instead of using the commercially available titanium tetraisopropoxide and methylene chloride as solvent, the related fluorinated titanium complex **3g** and trifluromethylbenzene were employed.[310] The amount of the chiral promoter BINOL (**90a**), as well as that of the initial titanium compound, could be slightly reduced (5 mol %), with the enantioselectivity being similar in both protocols. Allylsilanes **223** were further used in the preparation of different chiral 2,6-disubstituted-4-methylene tetrahydropyrans, as well as in the synthesis of the tricyclic macrolactone core of bryostatins.[311]

The role of molecular sieves in the former process was unclear. The study of the reaction media using Fourier transform cyclotron resonance mass spectroscopy showed the formation of a large cluster which contained multiple titanium atoms (mass found: 189.0445). ^{1}H NMR spectral analysis revealed the presence of hydroxy groups and the dynamic coordination between a cluster of titanium and chiral BINOL. Finally, it should be noticed that the same spectra were obtained using a large amount of activated 4-Å molecular sieves or using a small amount of unactivated 4-Å molecular sieves. All these facts seem to indicate that the role of molecular sieves is as a water donor source, with trace amounts of water being responsible for the formation of the active titanium catalyst.[312]

The process of allylstannation of aldehydes has been used as the key step in the synthesis of several natural products (Scheme 71). Thus, the allylation of the aldehyde **224** under

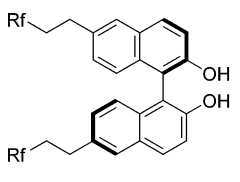
Scheme 71. Catalytic Enantioselective Allylstannation of Aldehydes



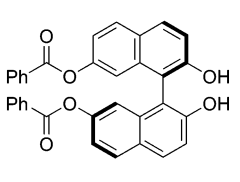
standard conditions yielded the corresponding homoallylic alcohol ***ent*-215b** with excellent results; this alcohol was the starting point in the synthesis of vitamin D ring A analogues.[313] The allylation of the aldehyde **225** under similar conditions gave the expected alcohol ***ent*-215c**, which in turn was used for the synthesis of lipoic acid.[314]

Notwithstanding the excellent results obtained using BINOL (**90a**) in the enantioselective allylation of aldehydes, some modifications have been made with the hope of improving some aspect of the reaction. One of the classical modifications is the incorporation of fluorinated side chains, as in compound **90am**. The enantioselective addition of the allyl tin derivative **221a** to aldehydes in the presence of 10 mol % of titanium tetraisopropoxide and 20 mol % of the ligand **90am** in a biphasic media gave the expected alcohols with good enantioselectivities (the best being for **215a** with 90% ee), but not superior to those for the classical protocol, with the ligand being recovered by continuous extraction.[315]

Another classical modification in binaphthol systems is their substitution in order to change the dihedral angle. The ligand **90an** emerged as the best one from a screening of five symmetrical 7,7-disubstituted binaphthol compounds.[316] The enantioselectivity found for the addition of the allyl tin derivative **221a** to benzaldehyde using 20 mol % of both ligand **90an** and dichlorotitanium diisopropoxide (**58b**) was as high as 92%, similar to that obtained using BINOL.

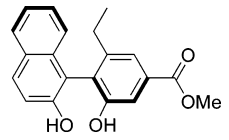


90am: Rf = *n*-C$_6$F$_{13}$



90an

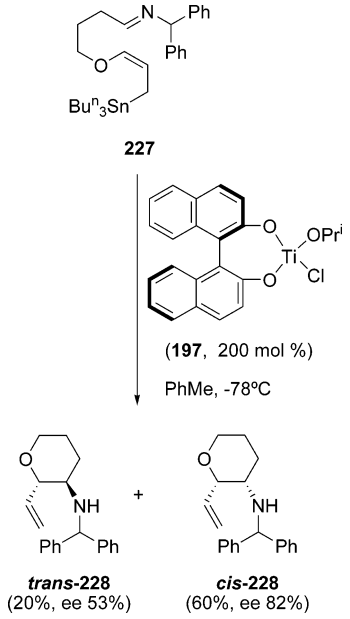
The phenol derivative **226** has also been tested in the enantioselective addition of allyl tin derivative **221a** to aldehydes in the presence of catalytic amounts of titanium tetraisopropoxide. Although the enantiomeric excess for compound **215a** was slightly superior to that for the standard procedures, the enantioselectivity in the case of other alcohols was clearly inferior. It should be pointed out that an important positive nonlinear effect was present, reinforcing the idea of aggregates as the true catalyst.[317]



226

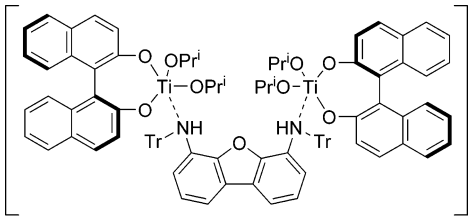
The asymmetric allylation process has been extended to the less electrophilic imines, as is depicted in Scheme 72.

Scheme 72. Enantioselective Intramolecular Allylstannation of Imines



In this case the intramolecular reaction is catalyzed by an excess of the complex **197**, giving a mixture of two possible diastereoisomers ***cis***- and ***trans*-228** with moderate enantioselectivity. However, this is one of the first examples of the use of imines in this reaction.[318]

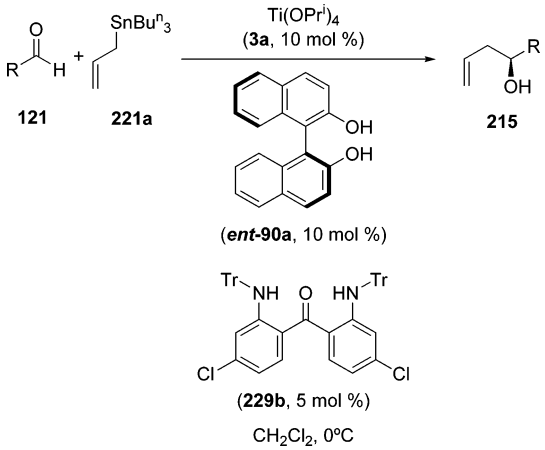
The continuous evidences of titanium−BINOL aggregates as the true catalyst for the aforementioned catalytic enantioselective allylation prompted the authors to force the preparation of aggregates of known structure. Thus, the presence of achiral bulky diamines, such as 4,6-bis(tritylamino)dibenzofuran (**229a**), has had a great favorable impact on the enantioselectivity.[319] The reason for this fact was speculated to be a function of the presence of a bimetallic aggregate of type ***ent*-230**, which can coordinate the carbonyl group in a double fashion, activating strongly the aldehyde. NOE experiments using *trans*-4-methoxy-3-buten-2-one as a carbonyl compound model showed that in the absence of the complex ***ent*-230**, a moderated NOE effect was detected for both α and β hydrogens of olefinic systems when the methyl group of the ketone was irradiated, which implies that both *s-cis* and *s-trans* conformers exist in a similar ratio. The addition of titanium tetraisopropoxide, BINOL, and monotritylaniline did not change the spectra. In marked contrast, however, in the presence of bistritylaniline (with formation of ***ent*-230** being assumed), the NOE changed drastically, appearing only on the β hydrogen. This fact implied the predominant existence of only the *s-trans* conformer, and that is due to a double carbonyl coordination.



***ent*-230**

Another achiral bulky diamine used as titanium linker for this allylation is the ketone **229b**. The enantioselective allylation of different aldehydes **121** in the presence of the BINOL ***ent*-90a** yielded the expected homoallylic alcohols **215** with excellent results (Table 22). Although the enantio-

Table 22. Catalytic Enantioselective Allylation Using in Situ Formed Bimetallic Complexes



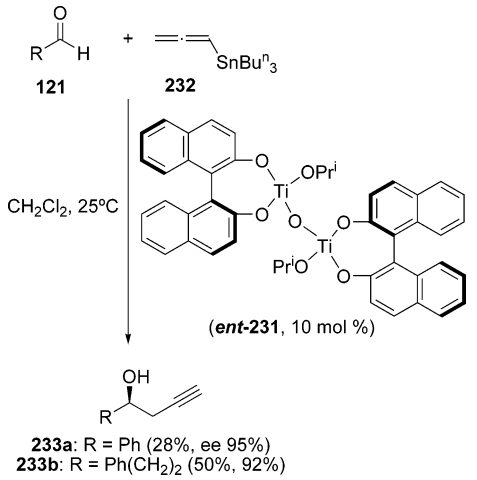
entry	no.	R	yield (%)	ee (%)
1	**215a**	Ph	95	99
2	**215d**	2-furyl	82	98
3	**215e**	(*E*)-PhCH=CH	79	97
4	**215f**	Ph(CH$_2$)$_2$	83	98
5	**215g**	Pr^i	54	98

selectivity was constant independent of the nature of the aldehyde, the chemical yields suffered an important decrease for simple aliphatic aldehydes.[320]

The success of the former new concept prompted the authors to change the flexible diamine of type **229** by the robust bonded catalyst ***ent*-231**,[321] which is easily prepared by treatment of the complex ***ent*-197** with 0.5 equiv of silver oxide. The highest impact on the reaction is on the reaction rate, reducing the reaction time to only a few hours and maintaining the enantioselectivity for the aforementioned allylation of aldehydes. This complex is also able to catalyze the reaction of the allenyl tin derivative **232** with aldehydes to yield nearly exclusively the propargyl alcohol **233** (Scheme 73) with excellent enantioselectivities but modest chemical yield.[322]

The nature of the catalyst ***ent*-231** has been studied and compared with the species formed by simple mixing of

Scheme 73. Catalytic Enantioselective Propargylation of Aldehydes



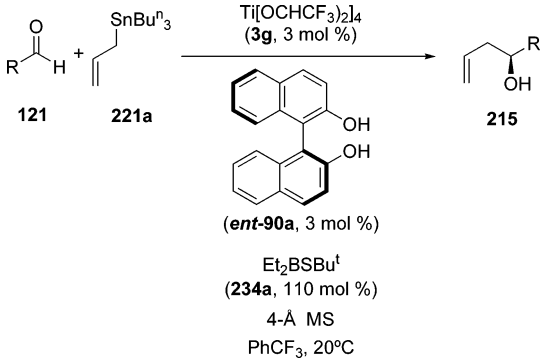
BINOL and titanium tetraisopropoxide. Both catalysts seem to be clearly different, since when using the complex ***ent*-231**, the reaction rate is faster, the amount of catalyst can be reduced, there is no influence of the temperature on the enantioselectivity, and this complex showed a high uniformity in enantioselectivities for the allylation process.[323] Although a positive nonlinear effect was found when the catalyst was prepared with partially resolved BINOL, this effect disappeared when the reaction was performed using different mixtures of both homochiral complexes ***ent*-231** and its enantiomer **231**. These facts imply that homochiral complexes of type **231** (each BINOL in this complex has the same absolute configuration) are more reactive than the corresponding heterochiral ones (each BINOL here has the opposite absolute configuration), and they are coordinatively stable (no exchange of titanium−BINOL units).

The catalytic allylation of the corresponding aldehyde catalyzed by complex ***ent*-231** has been used as the asymmetric key step in the synthesis of (*R*)-argentilactone and (*R*)-goniothalamin, which present an important biological activity.[324]

Another strategy to improve the initial results of the catalytic allylation of aldehydes[303] using tin derivatives has been the use of scavengers for the chiral tin alkoxide initially formed in the reaction media. Dialkylboron thiolates **234** are ideal scavengers for that purpose, due to the strong affinities between Sn−S and B−O bonds, as well as the relatively weaker S−B bond. In this way, the amount of chiral promoter and the reaction time could be reduced, and the reaction could be possible using functionalized aldehydes (Table 23), with any deactivation by the extra basic functionalities.[325] Thus, the allylation reaction using stoichiometric amounts of the boron derivative **234a** yielded the expected homoallylic alcohols with excellent enantioselectivities. The reaction conditions tolerated the presence of ketone and ester functionalities without a decrease of the enantiomeric ratio; these results were obtained even for aldehydes with very acidic hydrogens, such as benzoyl and Cbz-amino protected aldehydes.

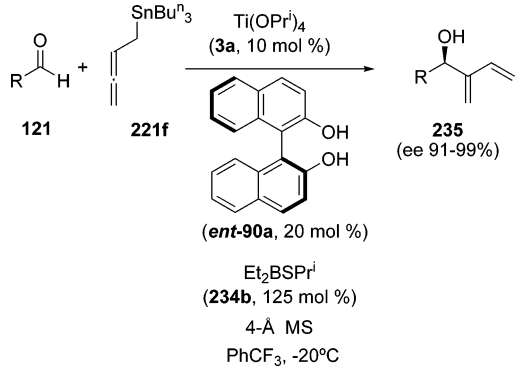
The reagents' scope of the former protocol with an extra Lewis acid as a synergetic reagent is very broad. Thus, for example, the buta-2,3-dienylstannane[326] **221f** was used as the source of the nucleophile, giving the corresponding dienyl alcohols **235** with excellent enantioselectivities (Scheme 74). Other successfully used systems were the corresponding

Table 23. Catalytic Enantioselective Allylation of Functionalized Aldehydes



entry	no.	R	yield (%)	ee (%)
1	**215h**	PhCO(CH$_2$)$_2$	86	97
2	**215i**	PhCO(CH$_2$)$_3$	83	95
3	**215j**	EtO$_2$C(CH$_2$)$_2$	81	98
4	**215k**	PhCONH(CH$_2$)$_2$	93	93
5	**215l**	BnO$_2$CNH(CH$_2$)$_2$	78	91

Scheme 74. Catalytic Enantioselective Dienylation of Aldehydes

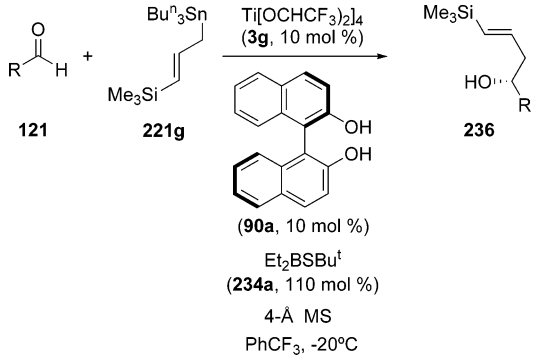


2-ethenyl- and 2-ethynyl-2-propenylstannane derivatives,[327] which permitted the enantioselective synthesis of (−)-ipsdienol and (−)-ipsenol.

A special case appeared when the allylation reaction was performed using the 3-trimethylsilyl-2-propenylstannane **221g**. Instead of obtaining the expected 3-silyl-4-hydroxy olefin, the 1-silyl-4-hydroxy derivative **236** was isolated with good enantioselectivities (Table 24), with the results being somewhat poorer for α,β-unsaturated aldehydes. The reason for this unusual reaction seems to be not very clear, but it must be related to the steric hindrance of the trimethylsilyl group.[328] In general, the allyl transfer from allyl tin derivatives to aldehydes catalyzed by Lewis acids might occur mainly via a S_E2' process. However, in this case, the sterically demanding trimethylsilyl substituent would not allow the appropriate orientation between the reagent, the substrate, and the catalyst. Therefore, the formation of compound **236** could be explained if in the reaction pathway, previous to the S_E2' carbonyl addition, a 1,3-shift equilibration of the tin moiety took place to render the corresponding mixture of enantiomers of the 1-trimethylsilyl-2-propenylstannane derivative, and only one enantiomer reacted with the carbonyl compound, with the other enantiomer shifting back again to the initial tin reagent to repeat the whole process.

The amount of achiral boron Lewis acid used in the aforementioned reaction is not necessarily stoichiometric. In fact, from a screening of 13 different Lewis acids, 4-(tri-

Table 24. Unexpected Catalytic Enantioselective Allyl Transfer Using the Silyl Derivative 221g

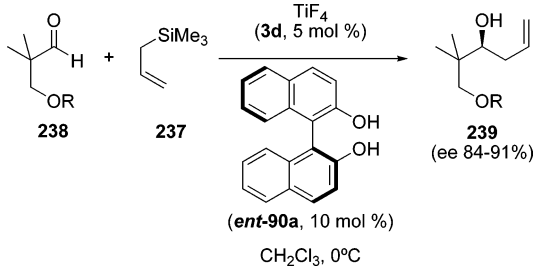


entry	R	no.	yield (%)	ee (%)
1	Ph	**236a**	83	91
2	PhC≡C	**236b**	71	88
3	(*E*)-PhCH═CH	**236c**	47	83
4	Ph(CH$_2$)$_2$	**236d**	74	93

fluoromethyl)phenylboroxin emerged as an excellent achiral synergetic acid. Thus, the simple allylation of aldehydes using the tin derivative **221a** could be performed using only 5 mol % of the aforementioned boronic ester, rendering the expected homoallylic alcohols with excellent enantioselectivities.[329]

The catalytic enantioselective allylation can also be performed with another source of the nucleophile that is less expensive and less toxic than tributyltin derivatives, such as allyl trimethylsilane **237**. In this case, the reaction should be performed using titanium tetrafluoride (**3d**), since this titanium complex served at the same time for the preparation of the chiral Lewis acid, and the fluorine atoms activated the silyl derivative.[330] The reaction with crowded α,α-disubstituted aldehydes **238** gave the expected homoallylic alcohols **239** with good enantioselectivities (Scheme 75);

Scheme 75. Catalytic Enantioselective Allylation of Aldehydes Using Allyl Trimethylsilane (237)

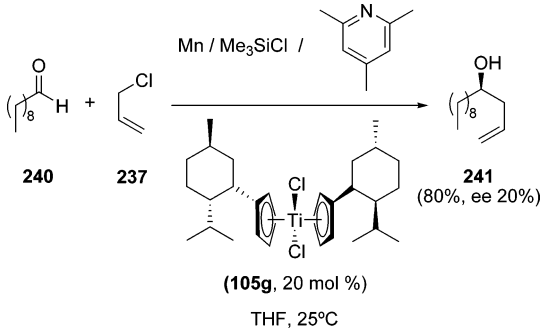


these alcohols were then starting materials for the synthesis of different polyketides.

Another organometallic compound used as source of the nucleophile was allyl diethyl aluminum (**151c**), which was able to add to different aldehydes, catalyzed by titanium tetraisopropoxide (**3a**) and the hydroxy sulfonamide **175**, under similar conditions to those shown in Table 16. In this reaction only the allyl group was transferred to the aldehyde (no ethylation products were detected), with the enantiomeric excess being excellent (for example: ***ent*-215a**, 90% ee).[261]

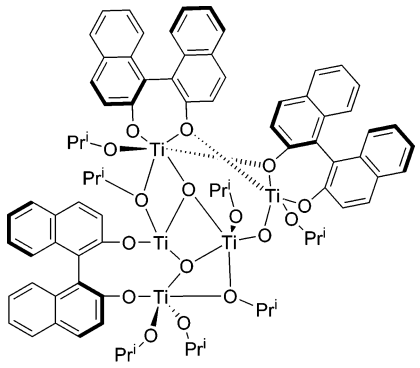
Very recently, the use of substoichiometric amounts of the titanocene **105g** has been introduced for the enantioselective allylation of decanal (**240**) to yield the corresponding homoallylic alcohol **241** with modest enantioselectivity (Scheme 76). The catalytic cycle started with the reduction

Scheme 76. Catalytic Enantioselective Allylation of Aldehydes Using the Titanocene 105g



of the titanium(IV) complex to the corresponding titanium(III) by manganese, followed by an asymmetric addition to form the titanium alkoxide, and completed with the liberation of this complex by formation of the corresponding silyl ether. Despite the poor enantiomeric excess, it is the first time that a chiral titanocene has been able to catalyze this reaction.[331]

Another totally different strategy for the enantioselective allylation is the use of a pericyclic ene reaction,[332] for which BINOL−titanium complexes are the most used chiral ligands.[333] An important effort has been put forth to determine the species involved in the catalytic cycle of the reaction (see structure **160**), as well as the role of some additives such as water.[312] The first fact discovered is that the reaction performed using hydrated 4-Å molecular sieves gave better results than the corresponding one performed under strict anhydrous conditions. To understand the role of water in the formation of different BINOL−titanium species, the reactivities of different mixtures of equimolecular amounts of titanium tetraisopropoxide (**3a**) and BINOL (**90a**) exposed to graded amounts of hydrated molecular sieves were tested: a maximum was detected by ^{1}H NMR when the ratio of components **3a**/**90a**/H$_2$O was 2:2:1. The ^{17}O NMR of the above ^{17}O enriched complex showed only one peak within the μ_3-oxo region, which suggested a tetranuclear nature of the active species. Indeed, the tetranuclearity of this complex [Ti$_4$(OPr^i)$_4$(BINOLate)$_4$O$_2$] was proven by vapor pressure osmometric molecular weight measurements in toluene. However, the crystallization of this tetranuclear complex only rendered the pentanuclear titanium complex **242**, which has a Ti$_4$(μ_2-OPr^i)$_2$(μ_3-O)$_2$ core attached to a Ti(μ_2-OAr)$_2$(μ_2-O) fragment.[334] The tetranuclear complex was modeled by computer on the basis of a Ti$_4$(μ_2-OAr)$_2$(μ_3-O)$_2$ core, and the resulting structure seems to match the observed ^{1}H NMR and NOE results.



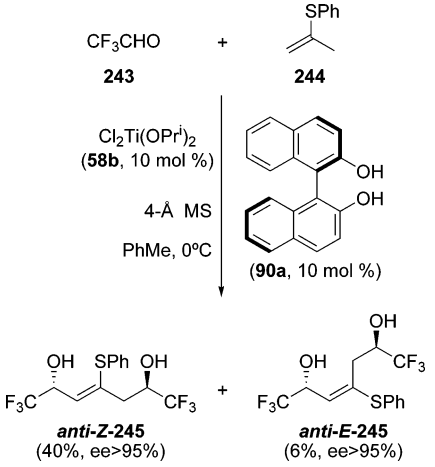
242

Despite the aforementioned effort to determine the species involved in the catalytic cycle (with the tetrameric titanium

complex being the initial complex which evolves to a trimeric BINOL-Ti complex), the exhaustive study of the data from the kinetic analysis of the positive nonlinear effect showed a dimeric rather than a trimeric nature for the true BINOL−titanium catalyst.[335]

Although the nature of the catalyst has yet to be determined, its utility is proven without a doubt. Thus, an intramolecular version of the ene reaction has been successfully used in the preparation of vitamin D ring A analogues.[336] More difficult seems to be the tandem and two-directional ene reaction depicted in Scheme 77, in which as

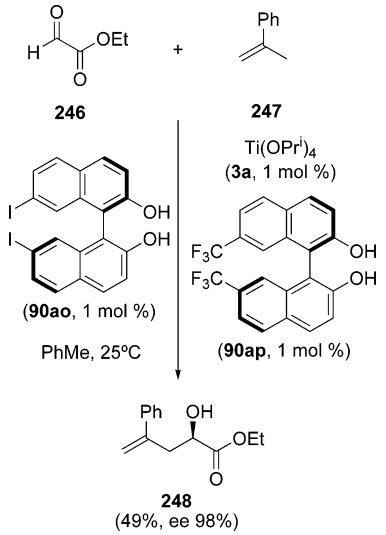
Scheme 77. Catalytic Enantioselective Two-Directional Ene Reaction



source of the titanium complex the more acidic dichlorotitanium diisopropoxide (**58b**) was used. The reaction of fluoral (**243**) with the sulfanyl derivative **244** gave a mixture of different products with excellent enantioselectivities, with some of them (**245**) resulting from a double ene process.[337]

The great complexity of intermediates formed between BINOL and titanium has permitted the use of either poisoning or activating agents of some complexes, to change the activity of the original system.[252] Thus, the mixture of two different BINOL derivatives of the same absolute configuration has been checked in order to prove that some combination gave better results than the use of only one BINOL derivative (Scheme 78). Although the results are

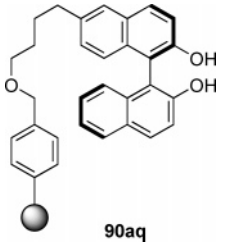
Scheme 78. Catalytic Enantioselective Ene Reaction Using an Equimolecular Mixture of Ligands 90ao and 90ap



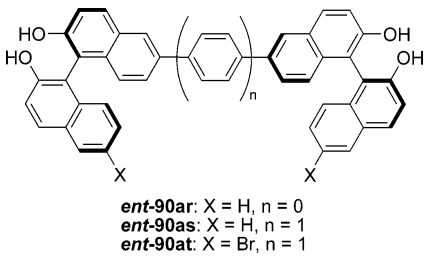
positive, the difference in enantioselectivities between using a mixture of BINOL or only one of the components is minimal (never higher than 3 units of ee).[338]

The aforementioned ene allylation using equimolecular amounts of ***ent*-90a** and fluorinated system **90c** is, on the contrary, a very impressive example. First, it should be noted that the reaction depicted in Scheme 78 using F_8-BINOL **90c** gave the homoallylic alcohol **248** (53%, ee 92%) with the opposite absolute configuration to that when the BINOL ***ent*-90a** is used. However, the reaction using the 1:1 mixture of BINOL enantiomers rendered the alcohol ***ent*-248** with a better result (95%, ee 99%) than that produced with either of the two BINOL derivatives alone.[339] Moreover, initial reaction rate studies indicated that the catalyst derived from F_8-BINOL **90c** was approximately 4 times slower than the catalyst derived from BINOL ***ent*-90a**, and therefore, the anticipated enantioselectivity should be low (around 60%), denoting the important synergistic behavior. The X-ray structure showed the homogeneous incorporation of both ligands, as well as the existence of a pseudocrystallographic inversion symmetry which was broken by a fluorine substitution, with the central core of the structure being composed of six titanium centers surrounding by BINOL ***ent*-90a** and F_8-BINOL **90c** halves.

The grafted soluble BINOL **90aq** has been used in the ene reaction shown in Scheme 77.[340] In this case, the amount of water added in the preparation of catalyst was the same as the amount of titanium tetraisopropoxide (**3a**) and all isopropoxy moieties were removed to force the self-assembled of two BINOLate units through a TiO_2Ti moiety. The elimination of all 2-propanol formed a very insoluble cross-linked material which catalyzed the reaction and gave good enantioselectivities (**248**, 88% ee), which were practically constant after five reuses.



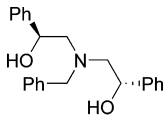
The use of titanium-bridged polymers (or oligomers)[203c] as insoluble enantioselective catalysts has been extensively studied with BINOL derivatives **90ar**−**at**. The material



obtained by mixing titanium tetraisopropoxide, water, and the corresponding bisBINOL in a 2:2:1 ratio was very insoluble, readily recycled, and reused for over one month. The powder X-ray diffraction patterns indicated that they were noncrystalline solids. For example, the enantioselective ene reaction using a titanium-bridged polymer derived from ***ent*-90ar** gave the alcohol ***ent*-248** with 88% ee (88%

chemical yield), and the same figures were obtained after five uses.[341] The presence of an electron withdrawing group in the backbone, such as in compound ***ent*-90at**, should improve the catalytic activity, owing to the Lewis acidity increase of the titanium complex. In fact, although the titanium−***ent*-90at** self-assembled framework gave a better result (***ent*-248**: 87%, 97% ee). The activity dropped substantially after five reuses.[342]

Not only have phenol derivatives been used as chiral ligands for the titanium-catalyzed ene reaction, but also simple alcohols such as the diol **249** have been proposed as chiral ligand alternatives. However, the obtained enantioselectivity was modest.[343]

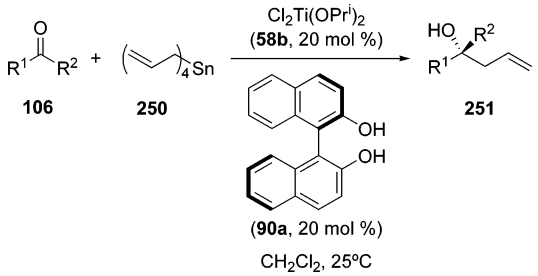


249

4.2.2. Ketones as Electrophiles

The enantioselective addition of allylmetal derivatives to ketones[164] using titanium complexes[288a] has been sensitively less developed than the related addition to aldehydes; the first catalytic enantioselective process was published in 1999. The reaction of the reactive tetraallyl tin (**250**) with different ketones in the presence of substoichiometric amounts of dichlorotitanium diisopropoxide (**58b**) and BINOL (**90a**) gave the corresponding homoallyl alcohols **251** (Table 25).[344]

Table 25. Catalytic Enantioselective Allylation of Ketones



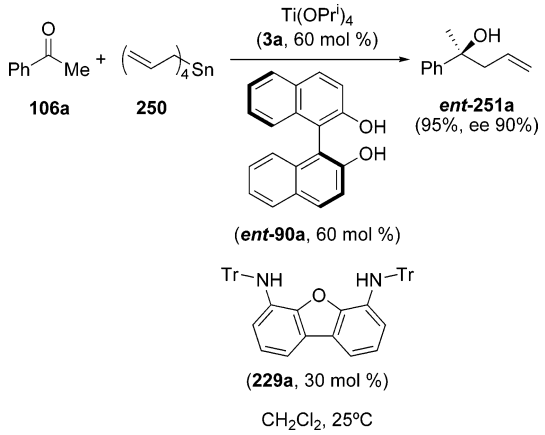
entry	no.	R^1	R^2	yield (%)	ee (%)
1	**251a**	Ph	Me	77	65
2	**251b**	4-$MeOC_6H_4$	Me	75	44
3	**251c**	4-$O_2NC_6H_4$	Me	80	47
4	**251d**	(*E*)-PhCH=CH	Me	83	51
5	**251e**	*n*-C_6H_{13}	Me	89	29

The enantioselectivity of the reaction seems to be independent of the electronic properties of the substituents on the aromatic ring but strongly dependent on the nature of the ketone, with aromatic ketones giving better results. A correlation between yield and enantioselectivity leaves aside the possibility of autoinduction.

A further evolution of the BINOL−titanium catalyst showed that the presence of a large excess of 2-propanol (2000 mol %) had a great and favorable impact on the enantioselectivity of the reaction, reaching up to 96% ee.[345] In this way, the initially used dichlorotitanium diisopropoxide (**58b**) could be replaced by the less acidic titanium tetraisopropoxide (**3a**), since the nucleophilic character of the initial tetraallyltin was enhanced by the presence of alcohols.[346]

The previously mentioned strategy of forming an in situ bimetallic complex has also been tested in the allylation of acetophenone (**106a**).[319] The enantioselective allylation using 4,6-bis(tritylamino)dibenzofuran (**229a**) as titanium linker gave an excellent result (Scheme 79), with the use of the

Scheme 79. Catalytic Enantioselective Allylation of Acetophenone 106a Using in Situ Formed Bimetallic Complexes

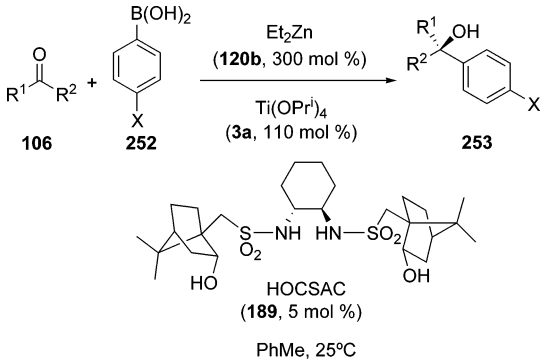


tritylamino derivative **229b** having an important impact on the enantioselectivities.[347]

4.3. Arylation/Alkenylation Reactions

The addition of sp^2-hybridized carbon nucleophiles to carbonyl compounds' mainly arylation processes will be considered in this section.[348] Surprisingly, only additions to poor electrophilic compounds such as ketones and imines have been published during the period covered by this review. The first example is the catalytic enantioselective addition of diphenylzinc (**120d**) to ketones using titanium tetraisopropoxide (**3a**) and substoichiometric amounts of chi ral HOCSAC (**189**), which has been accomplished successfully, with enantioselectivities up to 96%.[349,350] More interesting is the use of arylboronic acids (**252**) as the initial source of the nucleophile in the arylation of ketones (Table 26). The first step of this process is the transmetalation from

Table 26. Catalytic Enantioselective Arylation of Ketones Using HOCSAC 189



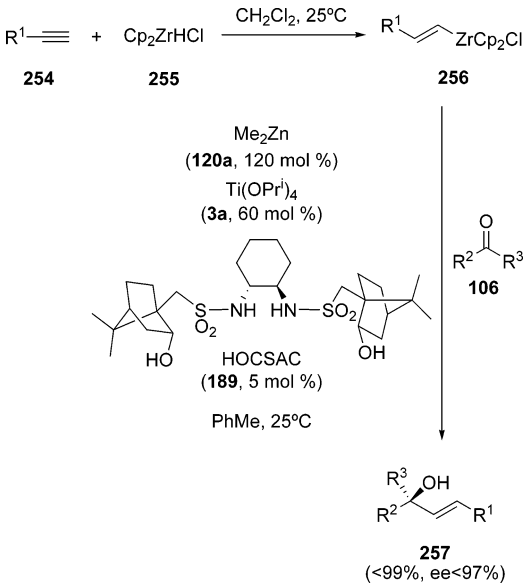
entry	no.	X	R^1	R^2	yield (%)	ee (%)
1	**253a**	H	4-BrC_6H_4	Me	79	81
2	***ent*-253a**	Br	Ph	Me	65	93
3	**253b**	Me	Ph	Me	58	84
4	**253c**	CF_3	Ph	Me	52	64
5	**253d**	H	4-BrC_6H_4	Et	91	68
6	**253e**	H	Bu^n	Me	65	30

the arylboronic derivative with diethylzinc to yield an arylzinc intermediate, which is further trapped by reaction

with ketones in the presence of an excess of titanium tetraisopropoxide and substoichiometric amounts of the chiral ligand HOCSAC (**189**), giving the expected alcohols **253**, in general, with excellent enantioselectivities.[349] The process was quite sensitive to the nature of the ketone (aromatic or aliphatic), to the presence of substituents in the aryl ring of the initial boronic derivative, and to the steric hindrance of ketone substituents.

A similar transmetalation strategy has also been used in the alkenylation of ketones (Scheme 80). The hydrozirconation of terminal alkynes **254** with the reagent **255** yielded the corresponding alkenylzirconium derivatives **256**, which in turn were transmetalated by treatment with dimethylzinc (**120a**) to give the corresponding alkenylzinc intermediates. These alkenylzinc intermediates were trapped by reaction with different ketones in the presence of titanium tetraisopropoxide and substoichiometric amounts of chiral HOCSAC (**189**), yielding after hydrolysis the expected allylic alcohols, in general, with excellent enantioselectivities.[351] The whole process was quite sensitive to the nature of the ketone (aromatic or aliphatic), as well as to the presence of extra functionalities on the starting alkyne. The use of the ligand **194** did not produce any improvement in the enantioselectivity.[284]

Scheme 80. Catalytic Enantioselective Alkenylation of Ketones Using HOCSAC 189

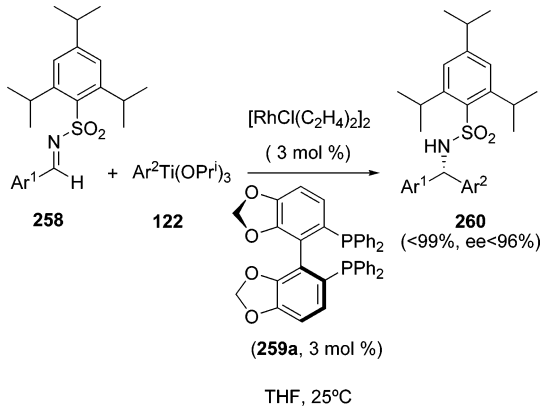


The last example of this section is the arylation of imine derivatives **258** using different aryltitanium triisopropoxide derivatives **122** catalyzed by the rhodium complex in the presence of the very narrow dihedral angle-containing diphosphine (*S*)-SEGPHOS (**259a**) to yield, after hydrolysis, the corresponding diarylamines **260** with excellent results (Scheme 81); the enantioselectivities are very constant independent of the nature of the substituents of both aryl groups.[352]

4.4. Alkynylation Reactions

Chiral propargylic alcohols have been extensively used as key intermediates in the synthesis of many complex organic molecules. Alkynyl−metal reagents are ideal functional carbon nucleophiles which can be prepared easily owing to the acidity of terminal alkynyl protons. Therefore,

Scheme 81. Catalytic Enantioselective Arylation of Imines

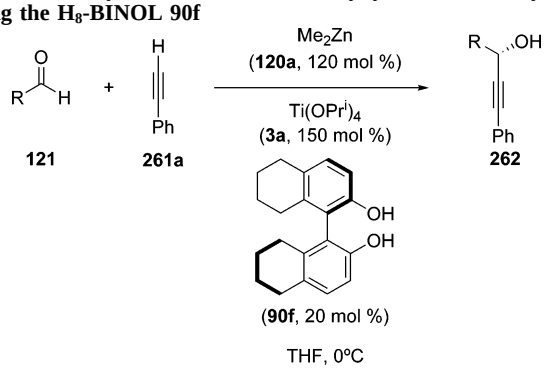


the enantioselective addition[353] of these intermediates to carbonyl compounds is an attractive alternative to the synthesis of the corresponding propargylic alcohols.[354]

4.4.1. Aldehydes as Electrophiles

The first example of an enantioselective catalytic alkynylation of aldehydes using titanium tetraisopropoxide (**3a**) was described in 2002. The reaction of a mixture containing phenylacetylene (**261a**), dimethylzinc (**120a**), titanium tetraisopropoxide (**3a**), and the corresponding aldehyde in the presence of the H_8-BINOL **90f** gave the expected propargylic alcohols **262** (Table 27). The enantioselectivity is modulated by the electronic character of the *para* substitutents on the aromatic ring of the aldehyde; the higher the electron withdrawing character, the higher the enantiomeric excess found. However, the steric hindrance and the nature of the aldehyde (aromatic or aliphatic) have a bigger effect on the results.[355] Under these reaction conditions, the use of BINOL **90a** as chiral promoter showed slightly poorer results.

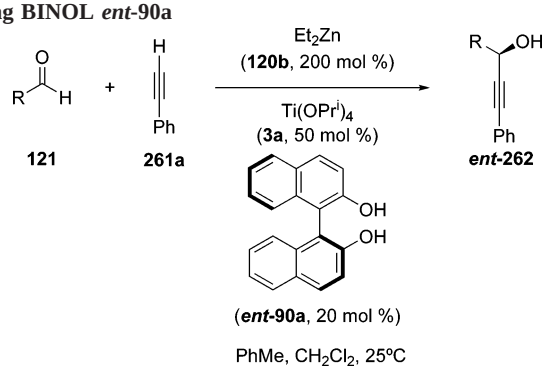
Table 27. Catalytic Enantioselective Alkynylation of Aldehydes Using the H_8-BINOL 90f



entry	no.	R	yield (%)	ee (%)
1	**262a**	Ph	85	92
2	**262b**	4-MeC_6H_4	84	86
3	**262c**	4-ClC_6H_4	91	94
4	**262d**	2-naphthyl	75	80
5	**262e**	*c*-C_6H_{11}	86	74

A small change in the alkynylation protocol[356] provoked an important improvement using BINOL ***ent*-90a** (Table 28). The main change was the previous preparation of the alkynylzinc derivative by refluxing diethylzinc (**120b**) and phenylacetylene (**261a**). Then, this mixture was added to the rest of the reagents in methylene chloride. In this way the expected propargylic alcohols ***ent*-262** could be obtained, in

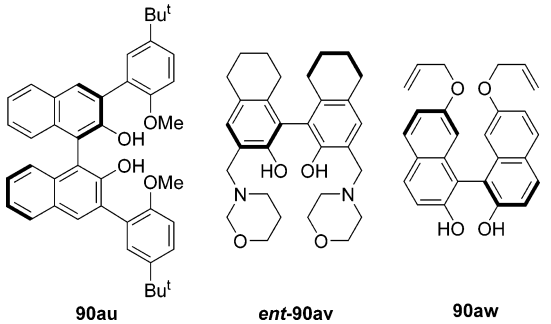
Table 28. Catalytic Enantioselective Alkynylation of Aldehydes Using BINOL *ent*-90a



entry	no.	R	yield (%)	ee (%)
1	***ent*-262a**	Ph	77	96
2	***ent*-262b**	4-MeC_6H_4	81	92
3	***ent*-262c**	4-ClC_6H_4	93	97
4	***ent*-262d**	2-naphthyl	77	98
5	***ent*-262e**	*c*-C_6H_{11}	58	95

general, with better enantioselectivities (compare Tables 27 and 28). The enantioselectivity still depends on the *para* substitutents on the aromatic ring of the aldehyde, but with this protocol the steric hindrance as well as the nature of the aldehyde has a marginal effect. The presence of a small negative nonlinear effect[138] in the process, as well as the possibility of use of other different terminal alkynes, should be noted.[357]

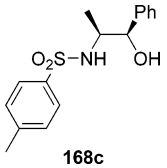
The compound **90au** emerged as the best promoter from a small library of 15 BINOL derivatives bearing different 3,3′-dianisyl groups.[358] From the results obtained in the alkynylation of aldehydes, a significant improvement of the enantioselectivity appeared, due to the presence of a *tert*-butyl group, with the presence of an unusual steric effect at the remote *para* position of the anisyl moieties being noted.



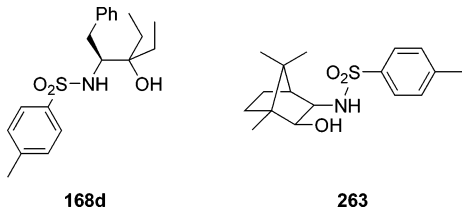
The ligand ***ent*-90av** has been introduced as an alternative to BINOL, but it did not overcome any of the previous parameters in the enantioselective alkynylation reaction.[359] The ligand **90aw** has also been tested in the enantioselective alkynylation of aldehydes with enantioselectivities ranging from 91 to 95% (similar to BINOL). However, in this case, the study of the influence of the dihedral angle by changing allyl substituents to other more crowded substituents showed no changes in the enantioselectivity.[360]

The introduction of coligands[252] into the standard BINOL-promoted enantioselective alkylation reaction has been more successful. Thus, the simple addition of 30 mol % of phenol increased the enantiomeric excess for alcohol **262a** from 91 to 96% (simple mixture of all reagents; for conditions, see Table 27). Other phenolic derivatives did not have any influence on the enantioselectivity, with some of them even having a detrimental effect.[361]

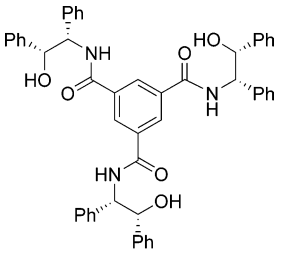
The use of the chiral coligand **168c** had a very positive impact on the enantioselective addition of phenylaceylene to aldehydes in the presence of dimethylzinc, titanium tetraisopropoxide, and a substoichiometric amount of BINOL (**90a**), permitting the reduction of the amount of chiral BINOL by up to 10 mol % (the same amount of β-hydroxy sulfonamide was added) and improving sensitively the enantiomeric excess (ranging from 92 to 99% for aromatic aldehydes).[362] It should be pointed out that the reaction using the β-hydroxy sulfonamide **168c** alone did not proceed.



Although the β-hydroxy sulfonamide **168c** was ineffective as promoter for the enantioselective alkynylation process, other β-hydroxy sulfonamides showed interesting activities. Thus, the ligand **168d** was an effective chiral promoter yielding the expected propargylic alcohols **262** with enantioselectivities close to 90%; this enantiomeric excess was practically independent of the temperature and slightly dependent on the amount of the chiral promoter.[363] The chiral isoborneolsulfonamide **263** gave similar results to those of the previously described β-hydroxy sulfonamides.[364]



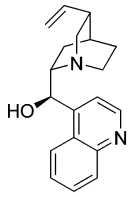
The C_3 symmetric hexapodal ligand **264** has been used as chiral promoter in the alkynylation of aldehydes using a similar protocol to that described in Table 28, that is, the preparation of an alkynylzinc intermediate before the addition of the electrophile. However, the enantioselectivities were somewhat lower than those for the original protocol. It should be noted that the deletion of either one or two β-hydroxy carboxiamides had an important and detrimental effect on the enantioselectivity of the reaction, demonstrating the higher activity of the C_3 symmetric ligand compared either to the C_2 symmetric or the C_1 symmetric one.[365]



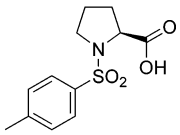
Other chiral promoters used in the catalytic enantioselective alkynylation of aldehydes were cinchonidine (**265**) and some *N*-protected amino acids such as compound **266**. In the first case, the amount of the chiral promoter had to be

40 mol %, while the amount of titanium tetraisopropoxide was 200 mol % and the enantiomeric excess found for the propargylic alcohol **262a** was only 79%, with the ee's being similar for other alcohols.[366]

Different amino acids have been tested for this reaction, with proline being the most promising. After it was found that this cyclic amino acid was the best choice, different typical protecting groups of the amino functionality were tested such as Boc, Cbz, Bz, and methyl, with the tosyl derivative **266** yielding the best results, with 71% enantiomeric excess for the propargylic alcohol ***ent*-262a** and similar ee's for other alcohols arising from aromatic aldehydes; the enantioselective alkynylation of aliphatic aldehydes was sensitively less satisfactory.[367]



265

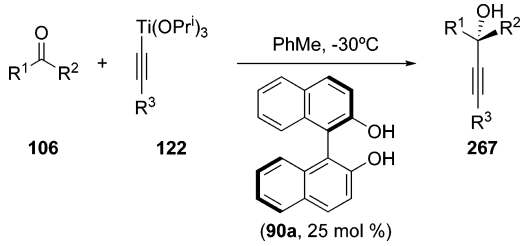


266

4.4.2. Ketones as Electrophiles

As expected, the related alkynylation of ketones is much less developed than that of aldehydes.[164] In fact, the first catalytic enantioselective alkynylation of ketones using titanium complexes was described by Cozzi's group in 2004. The reaction implied the direct addition of alkynyltitanium triisopropoxide (**122**) to ketones in the presence of catalytic amounts of simple BINOL (**90a**) to yield the expected tertiary propargylic alcohols **267**.[368] The first step of the process is the formation of the nucleophile, which was carefully prepared by deprotonation of the appropriate terminal alkyne moiety by butyllithium at −50 °C and further reaction with chlorotitanium triisopropoxide. Then, with an intelligent fine-tuning of the temperature, the reaction is promoted by the presence of BINOL with good enantioselectivities, avoiding the direct addition and the addition catalyzed by the LiCl salt present in the reaction medium (Table 29). The enantioselectivity seems to be independent of the electronic character of the *para*-substituted group in the aromatic ring of the ketone. However, the presence of other functional groups, either on the alkyl side chain of the ketone or on the acetylene derivative, had an important impact on the results. The use of other chiral ligands such as H_8-BINOL (**90f**) or TADDOL (**118a**) did not improve the enantioselectivity.

Table 29. Catalytic Enantioselective Alkynylation of Ketones



106 **122** **267**

entry	no.	R^1	R^2	R^3	yield (%)	ee (%)
1	**267a**	Ph	Me	Ph	89	70
2	**267b**	4-MeC_6H_4	Me	Ph	45	85
3	**267c**	4-ClC_6H_4	Me	Ph	53	88
4	**267d**	4-ClC_6H_4	CH_2Cl	Ph	63	51
5	**267e**	Ph	Me	Me_3Si	nd[a]	42

[a] Not determined.

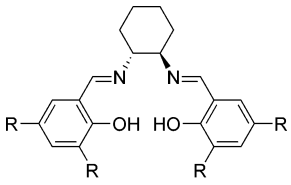
A similar alkynylation process has been performed starting from phenylacetylene (**261a**).[369] Its deprotonation by diethylzinc (**120b**) at room temperature followed by reaction with different ketones using 20 mol % of BINOL **90a** and titanium tetraisopropoxide (**3a**) as chiral catalyst gave the expected tertiary propargylic alcohols **267** with slightly higher enantioselectivities than those of the previous protocol (for **267a**: 67%, ee 85%; for **267b**: 64%, ee 87%; for **267c**: 73%, ee 89%).

4.5. Cyanation Processes

The asymmetric reactions of different cyanide sources with carbonyl compounds to yield the corresponding cyanohydrins,[370] as well as their related ones using imine derivatives to yield α-amino nitrile derivatives (Strecker reaction),[371] are very highly versatile synthetic transformations, with the final products occupying a fascinating niche at the interface between chemistry and biology.

4.5.1. Aldehydes as Electrophiles

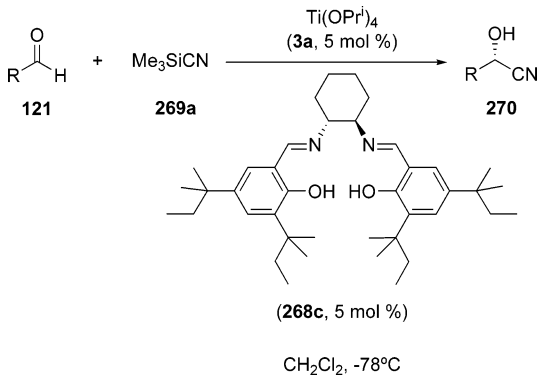
Since 1986, when the first example of enantioselective cyanation of aldehydes using titanium complexes and BINOL (**90a**) was published,[372] many other ligands have been reported as an alternative, with the most used being chiral imines derived from salicylaladehyde (salen)[214] of type **268**.



268a: R = H
268b: R = Bu^t
268c: R = CMe_2Et

The catalytic enantioselective addition of trimethylsilyl cyanide (**269a**) to different polyfunctionalized benzaldehydes in the presence of equimolecular substoichiometric amounts

Table 30. Catalytic Enantioselective Cyanation of Aldehydes Using the Ligand 268c

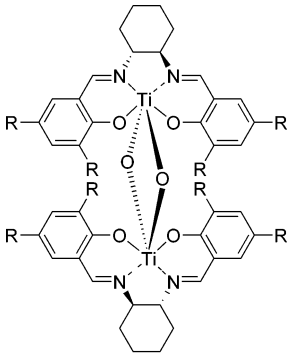


121 **269a** **270**

entry	no.	R	yield (%)	ee (%)
1	**270a**	Ph	92	97
2	**270b**	4-MeC_6H_4	96	94
3	**270c**	4-ClC_6H_4	89	97
4	**270d**	2-naphthyl	93	>97

of titanium tetraisopropoxide and a chiral salen **268** has been used as the key step in the syntheses of trifluromethylepinephrine[373] and fluoroepinephrines[374] (vasoconstrictors) with enantioselectivities near to 95%. The chiral derivative **268c** seems to be more effective than **268a,b** under similar conditions (Table 30), detecting only one enantiomer for 2-naphthylcarbaldehyde.[375]

However, an interesting breakthrough occurred in this field by serendipity when the standard cyanation of aldehydes was performed under strict anhydrous conditions. Under these conditions, the in situ prepared complexes between different sources of titanium and ligands **268** were ineffective in the cyanation process. Moreover, the same results were obtained when traces of water were present independent of the titanium source used, which indicated that in all cases the same catalytically active complex was present. In fact, the same crystalline solid **271** was obtained when ligands **268a,b**

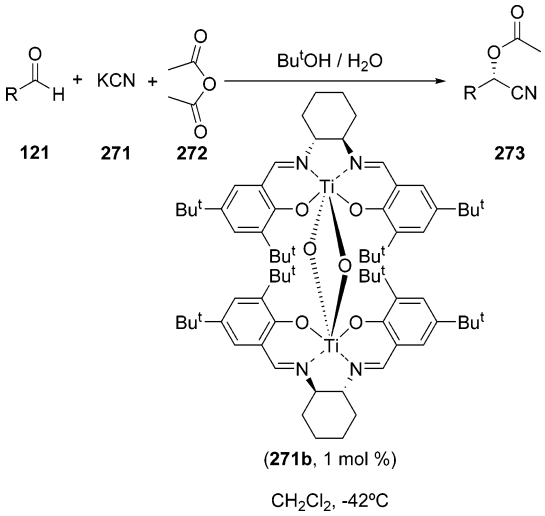


271a: R = H
271b: R = Bu^t

were treated either with titanium tetraisopropoxide (**3a**) in the presence of 1 equiv of water or with titanium tetrachloride (**3c**) with 1 equiv of water and 2 equiv of triethylamine. In the dimeric structures **271**, the requirement for the two bridging oxygen atoms to adopt relative *cis* positions means that the salen ligands cannot adopt a planar coordination around the titanium atoms. Rather, the salen ligands have to adopt a conformation in which one of the coordinating atoms is nonplanar with the other three coordinating groups. However, the complex retains overall C_2 symmetry since the ligands adopt a Δ-configuration around both titanium atoms. The molecular weight of complexes **271** was confirmed by ultracentrifugation measurements. Finally, it should be pointed out that the catalytic enantioselective cyanation of aldehydes using complex **271b** gave better results in shorter reaction times (for instance, using 0.1 mol % of complex at 0 °C: quantitative chemical yield, 92% ee for **270a**).[376]

The effectiveness of this type of complex has permitted the increase of the cyanide source scope by using KCN/$(MeCO)_2O$ as a very cheap and safe cyanating agent.[377] Among alkali metal cyanides, KCN gave the best enantioselectivity, while the carboxylic derivatives such as pivaloic, benzoic, or acetic anhydride had little impact on the preparation of the final ester **273**. More important for this asymmetric multicomponent reaction[378] seems to be the rotation speed of the reaction mixture stirring for the chemical yield, with a maximum yield being obtained at 280 rotations/min, as well as the presence of additives such as mixtures of water and *tert*-butyl alcohol (10 and 100 mol %) which greatly accelerated the reaction (Table 31). α-Acetoxy nitriles **273** could be easily transformed into the related α-acetoxy

Table 31. Catalytic Enantioselective Multicomponent Cyanation of Aldehydes



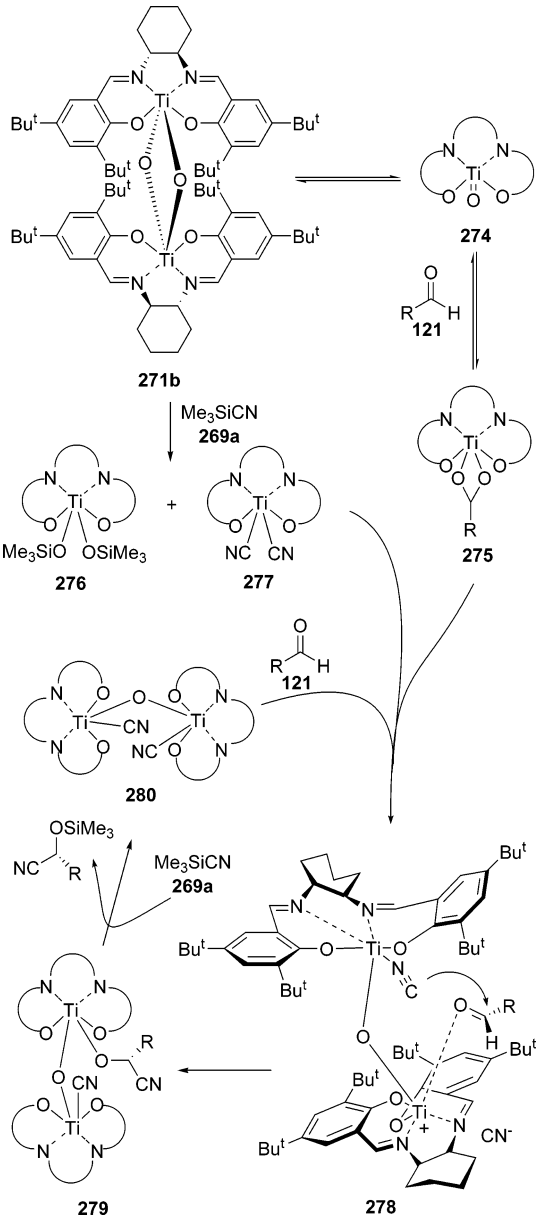
entry	no.	R	yield (%)	ee (%)
1	**273a**	Ph	93	90
2	**273b**	4-MeOC$_6$H$_4$	74	93
3	**273c**	4-FC$_6$H$_4$	98	92
4	**273d**	Bu^t	40	62

carboxamides by hydrolysis catalyzed by platinum(II) phosphinito complexes.[379] This protocol was also very effective with aldehydes grafted to 1% cross-linked Wang resin, keeping practically the enantioselectivity of the homogeneous version.[380]

Another cyanating agent, used in combination with complex **271b** and aldehydes, was ethyl cyanoformate,[381] which rendered the corresponding cyanohydrin derivatives with similar results to those presented in Table 31.

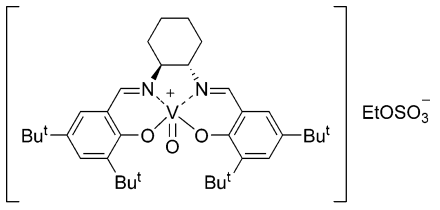
After the discovery of bimetallic complexes **271** as the common precatalysts for the aforementioned cyanation, a complete study was performed in order to shed light on the possible mechanism (Scheme 82). The first consideration was that the central four-membered ring was rectangular rather than square with two of the Ti−O bonds significantly shorter (1.80−1.82 Å) than the other two Ti−O bonds (1.86−1.88 Å). In fact, the ^{17}O NMR spectrum of complex **271b** showed a sharp peak characteristic of a Ti═O group, indicating the presence of an equilibrium between the dimeric species **271b** and the related monomer **274**. The presence of a metallacycle **275** was detected by NMR when hexafluoroacetone or formaldehyde was added to a solution of the dimer **271b**. In addition, new species of titanium were observed when the intermediate **271b** was mixed with trimethylsilyl cyanide (**269a**); the infrared spectra suggested that cyanide ligands were partially bonded to the titanium center. Moreover, the new absorption signals indicated the presence of Ti−OSi and O−Si bonds. The steric requirements of the trimethylsilyl groups ensured that the dinuclear complexes will have much longer distances between the two titanium atoms than their initial complex **271b**, which was consistent with the reduced shielding of hydrogens observed in the ^{1}H NMR spectra of the complex mixture of **276** and **277**. The addition of trimethylsilyl cyanide before the aldehyde had an impressive detrimental effect on the reaction rate, which might indicate that the initial step of the reaction is an interaction of complex **271b** with the aldehyde to form the corresponding metallacycle **275**. The same level of enantioselectivity was observed

Scheme 82. Catalytic Cycle for the Enantioselective Cyanation of Aldehydes



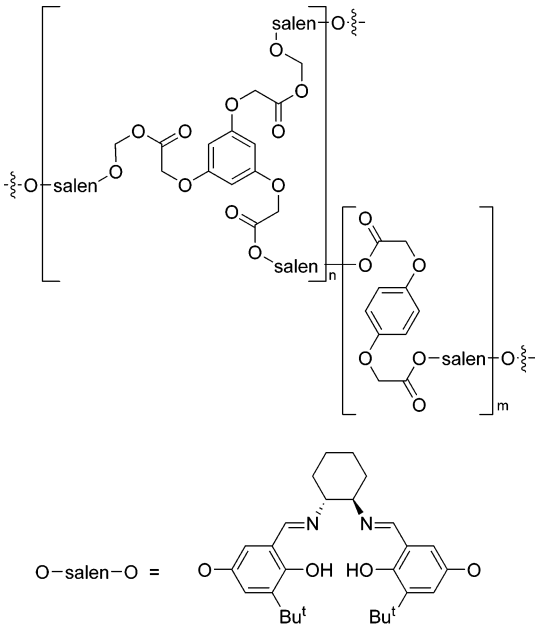
when the reaction was performed with HCN instead of trimethylsilyl cyanide (**269a**), which seemed to indicate that the catalyst did not contain large trimethylsilyloxy groups coordinated to the titanium in the transition state (**278**) of the reaction (Scheme 82). The kinetic studies showed that the reaction rate equation was zero order for the aldehyde and first order for trimethylsilyl cyanide, and they showed that for catalyst **271** values ranged from 1.3 to 1.8, depending on the catalyst tested, but were always higher than one, which could indicate that the catalytic species is dinuclear. Since the concentration of the aldehyde did not enter into the rate equation, the most likely rate-limiting step was that of silylation of the coordinated cyanohydrin, with formation of the product and complex **280**. This fact was supported by the negligible dependence of the reaction rate on the dielectric constant of the solvent, meaning that during this step no charges were lost or created.[382] The reaction using other sources of cyanide seems to follow the same catalytic cycle, changing only the corresponding trimethylsilyl moiety by the corresponding acyl moiety. Since the reaction with potassium cyanide in the presence of water and *tert*-butyl alcohol only modified the reaction rate, it seems that these additives only serve the hydrolysis of the related complex **279**, with the free cyanohydrin being further acylated by the corresponding anhydride.

In the aforementioned catalytic homobimetallic species **278**, a titanium atom is the Lewis acid center controlling the aldehyde chelation and its activation, while the other titanium center is the nucleophilic source. With this in mind, it is possible to think that a selective change of one of the two titanium atoms for another more active metal to give a heterobimetallic species could improve the previous results. To test this hypothesis, different mixtures of complexes **271b** and ***ent*-281** were used with the aim of improving the results previously obtained in the enantioselective cyanation of aldehydes using the homobimetallic titanium complex **271b** and trimethylsilyl cyanide (**269a**). First, it should be pointed out that the monomeric chiral ionic complex ***ent*-281** was shown to give higher enantioselectivity than complex **271b**, although the reaction rate was almost 2 orders of magnitude slower than that for the titanium complex. Moreover, the same stereochemical outcome of the reaction was obtained using **271b** or **281**, with two cationic vanadium complexes being involved in the rate-limiting step of the reaction.[383] Therefore, the enantioselective addition of cyanide **269a** to benzaldehyde using a 1:2 mixture of complexes **271b**/***ent*-281** should have given **270a** according to the relative reaction rate and supposing that both metallic complexes worked independently. Unexpectedly, the final cyanohydrin was ***ent*-270a** with 82% ee. To investigate the possible reasons for this result, different kinetic studies were performed, which set aside any type of autoinduction of reaction products, as well as any poisoning effect between the complexes, and led to the formation of a new heterobimetallic titanium−vanadium complex. Finally, the ratio of initial complexes **271b**/***ent*-281** was studied, and a maximum was obtained at the 1:1 value. Thus, it appears that, in the new in situ formed heterobimetallic titanium−vanadium complex, the resulting stereochemistry is determined by the vanadium center and its kinetic behavior is largely determined by the titanium-derived portions.[384]



***ent*-281**

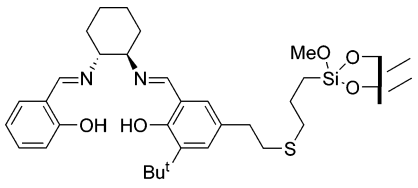
To control strictly the microenvironment and the recovery of the chiral ligand,[237] the salen structure has been immobilized in the polymer **282**. The enantioselective addition of potassium cyanide (**271**) to aldehydes in the presence of acetic anhydride (**272**) using titanium tetraisopropoxide, water, and the polymer **282** gave the expected chiral α-acetoxy nitrile **273** with excellent results (for example, 89% ee for **273a**).[385] The *m*/*n* ratio had a great impact on the enantioselectivity, so for ratios smaller than 2, the obtained highly cross-linked polymer was very rigid, which made it very difficult to form the catalytic bimetallic titanium species and, therefore, lowered the enantioselectivity. On the other hand, the linear polymer (*m*/*n* > 200) also gave



282

dissatisfactory results, which was attributed again to the difficulty of forming a bimetallic titanium species. The recycling ability was tested for the polymer **282** with $m/n = 200$, which gave the best results, and the recycling results were very discouraging. On the other hand, when the polymer **282** with $m/n = 4$ was reused five times, the same enantioselectivity and chemical yield were obtained (95%, 80% ee), showing that the cross-linked grade also had a great influence on the recycling ability.

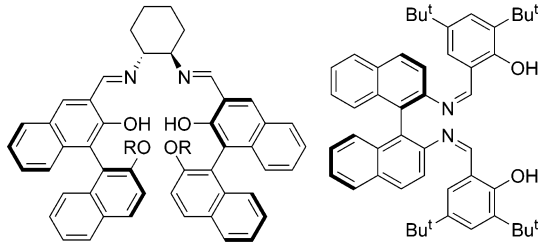
The salen structure has also been grafted in the mesoporous silica MCM-41 to yield the material **283**. The enantioselectivity in the classical cyanation of benzaldehyde to yield the cyanohydrin **270a** using titanium tetrachloride (**3c**) as titanium source was even higher than that obtained under homogeneous conditions (26%, 93% ee), with the chemical yield being clearly unsatisfactory.[386]



283

Other salen ligands derived from cyclohexylamine are compounds **284**.[387] The enantioselective cyanosilylation process using ligand **284a** worked modestly (never higher than 66% ee for **270a**). However, a simple modification of the initial structure, such as the ether formation, permitted the enantioselectivity to increase up to 89%. On the other hand, the binaphthyl salen derivative **285** has also been used in the aforementioned cyanation process, with enantiomeric excess up to 94%.[388]

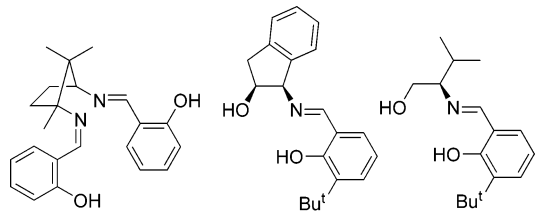
Other salen ligands used were the bis-Schiff base **286**[389] and the mono derivatives **287**.[390] In the last case, a complete study on the enantioselective effect of different substituents on the aromatic ring, as well as the substituents on the α-amino alcohol, has been performed. The presence of a



284a: R = H
284b: R = *n*-C_6H_{13}

285

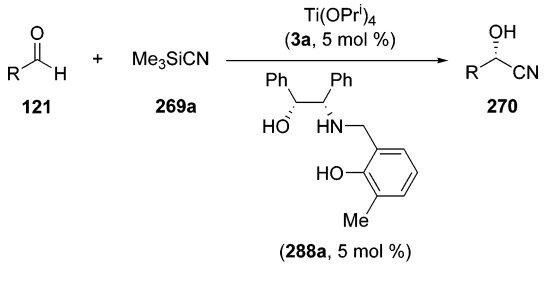
large group at the 3 position of the aromatic ring is fundamental in order to obtain good enantioselectivities. This fact has been related with the formation of a monometallic titanium complex bearing only one chiral ligand, with the *tert*-butyl group avoiding the formation of inactive dimeric complexes, or monomeric species with two chiral ligands. Although the cyanation process depends largely on steric interactions, increasing the number of stereogenic centers does not necessarily increase the enantioselectivity, so ligands **287a** and **287b** gave the same result. Finally, it should be noticed that the presence of a large group on the stereogenic carbon atom bearing the amino group was fundamental to reaching the maximum level of the enantioselectivity (85% ee for **270a**; see Table 30).



286 **287a** **287b**

Not only have ligands bearing salen structures been used for cyanation of aldehydes, but compound **288a** has also been successfully used as a chiral promoter (Table 32). Modifica-

Table 32. Catalytic Enantioselective Cyanation of Aldehydes Using the Ligand 288



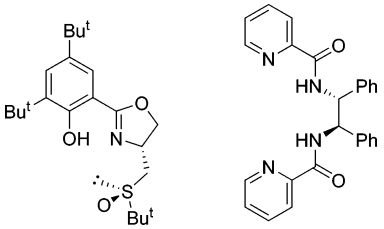
121 **269a** **270**

entry	no.	R	yield (%)	ee (%)
1	**270a**	Ph	99	94
2	**270b**	4-MeC_6H_4	90	93
3	**270c**	4-ClC_6H_4	98	87
4	**270d**	2-naphthyl	96	75
5	**270e**	(*E*)-PhCH=CH	96	82
6	**270f**	Pr^i	99	60

tions of the structure of the ligand, such as the presence of either electron-donating or electron-withdrawing groups on the position *para* to the phenolic OH group, did not increase further the enantioselectivity. Contrary to the results with

salen **287b**, the presence of two stereogenic centers was of vital importance for the high enantioselectivity. However, the concentration of reagents had an important effect on the enantioselectivities, with concentrations either higher or lower than 0.5 M for the aldehydes decreasing the results. The nature of the aldehyde also plays an important role, since the results using aliphatic or α,β-unsaturated, as well as very hindered, carbonyl compounds showed decreased enantioselectivity.[391]

Other masked iminic ligands used were the chiral sulfoxide **289** and the biscarboxyamide **290**. The former compound was designed with the idea in mind that an extra coordinated site, such as the sulfoxide moiety, could improve the results through a more rigid transition state. However, the obtained results were moderate (ee never higher than 61%).[392] Compound **290** is a tetradentated ligand with two acidic

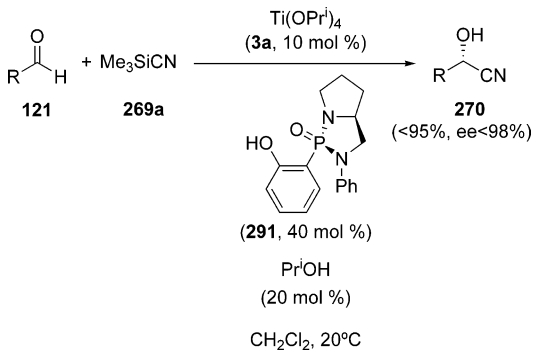


289 **290**

protons and two coordinating nitrogen atoms, such as in salen ligands **268**. In this case, a complete study of all parameters affecting the reaction was performed,[393] including solvent, relative amount of titanium tetraisopropoxide (**3a**), and reagent concentration. The relative amount of the catalyst and initial concentration of aldehyde had a clear effect on the results, with dilution decreasing the enantioselectivity. More interesting was the detection of an autoinduction process (the enantioselectivity increases with the chemical yield), which indicated the presence of catalytic titanium species bearing chiral cyanohydrin derivatives with a higher activity. However, the enantiomeric excess was never higher than 70%.

A new class of chiral ligands is represented by the chiral phosphonodiamide **291**, which has been used as chiral promoter in the cyanation of aromatic aldehydes in the presence of titanium tetraisopropoxide (Scheme 83). The

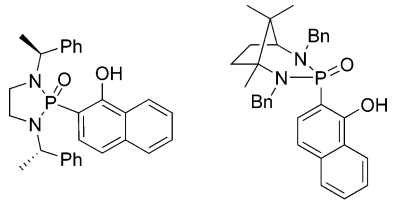
Scheme 83. Catalytic Enantioselective Cyanation of Aldehydes Catalyzed by Phosphonodiamide 291



121 **269a** **270** (<95%, ee<98%)

enantioselectivity was quite sensitive to the presence of additives such as 2-propanol (with the ee increasing from 31 to 95% just by addition of 20 mol % of the alcohol), to the presence of substituents on the aromatic ring of the aldehyde, and to the absolute configuration of the phosphorus center.[394]

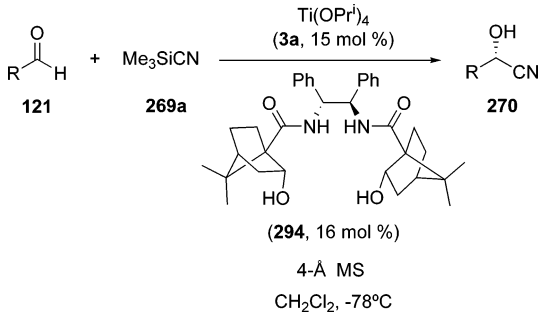
Other hydroxyarylphosphonodiamides, such as compounds **292**[395] and **293**,[396] have been proposed as alternatives, with the results being inferior to the previously introduced ones under similar reaction conditions. A ^{31}P NMR study of different mixtures of titanium tetraisopropoxide (**3a**) and the chiral ligand **293** showed the presence of several ligand−titanium complexes, in which the ratio changed as a function of the initial ratio of ligand/titanium source, with the main complex in all cases bearing two ligands per each titanium atom.



292 **293**

From the above presented results, it seems that only ligands bearing a chelating atom (such as a sp^2-hybrized nitrogen or oxygen) and an acidic hydrogen are able to catalyze effectively the enantioselective addition of trimethylsilyl cyanide to aldehydes. However, that is not true and, as an illustrative example, the tetradentate ligand **294** derived from (1*S*)-(+)-ketopinic acid and (1*R*,2*R*)-1,2-diphenylethylenediamine has reached an unbeatable level of enantioselectivity (Table 33). The results are very good for aromatic and α,β-

Table 33. Catalytic Enantioselective Cyanation of Aldehydes Using the Ligand 294

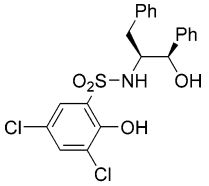


121 **269a** **270**

entry	no.	R	yield (%)	ee (%)
1	**270a**	Ph	87	93
2	**270d**	2-naphthyl	67	99
3	**270e**	(*E*)-PhCH=CH	49	97
4	**270g**	*c*-C_6H_{11}	90	>99

unsaturated aldehydes, and even in the cases of less electrophilic aldehydes such as cyclohexanecarbaldehyde, only one enantiomer was detected by HPLC.[397] The high level of enantioselectivity was due not only to the diamine system but also to the isoborneol structure, because other ligands bearing chiral hydroxy acids different from ketopenic acid decreased enormously the enantiomeric excess found for cyanohydrins **270**.

The β-sulfonylamino alcohol **295** has been used in substoichiometric amounts (10 mol %) as a chiral promoter for the classical cyanation of aldehydes with excellent results (ee up to 96%), with the relative configuration of the ligand being of great importance. When the ligand **175** with *anti* configuration was used, the enantiomeric excess for the cyanohydrin **270a** decreased from 96 to 8%.[398]

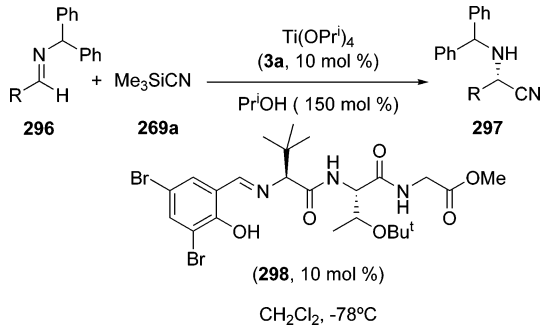


295

The polymeric BINOL system ***ent*-90aa** has also been tested as a ligand for the enantioselective cyanation process, giving enantioselectivities around 75%.[234] Surprisingly, the reuse of the polymer increased the enantioselectivity in the first five runs from 72 to 83%. However, a slight decrease from run 8 to 15 was detected, probably owing to leaching of the titanium complex from the polymer.

The enantioselective Strecker reaction of imine **296** with trimethylsilyl cyanide (**269a**) in the presence of substoichiometric amounts of titanium tetraisopropoxide and the tripeptide-salen ligand **298** has been successfully accomplished (Table 34). The peptide **298** gave the best result from a

Table 34. Catalytic Enantioselective Strecker Type Reaction



296 **269a** **297**

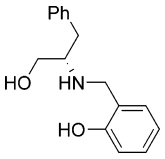
(**298**, 10 mol %)

CH_2Cl_2, -78°C

entry	no.	R	yield (%)	ee (%)
1	**297a**	Ph	99	97
2	**297b**	4-$MeOC_6H_4$	100	94
3	**297c**	(*E*)-PhCH=CH	98	84
4	**297d**	(*E*)-MeCH=CH	100	85
5	**297e**	Bu^t	100	88

screening of 60 different peptides, and the enantioselectivity was quite constant independent of the nature of the aldehyde used.[399] The slow addition of 2-propanol had a substantial effect only on the chemical yield, with the enantiomeric excess maintained. This result could be interpreted considering that the role of the alcohol is the formation of HCN from its reaction with trimethylsilyl cyanide. Moreover, the reaction using slow addition of HCN as the source of cyanide gave similar results to those presented in Table 34. Subsequent kinetic studies indicated that the reaction was first order in the catalyst system, with the absence of a nonlinear effect, and zero order in both the cyanide and aldehyde. The same reaction rate was obtained using Pr^iOD after a completed H/D exchange of acidic protons, which could be interpreted considering that the rate-limiting step in the catalytic cycle did not involve any cleavage or formation of CH, NH, or OH bonds. The Eyring plot gave a large and negative difference in the entropy of activation, which was consistent with a rapid and reversible hydrogen bond formation between HCN and a carbonyl group of the ligand. Semiempirical PM3 calculations supported a titanium atom bonded to the salen moiety and the carbonyl group of *tert*-leucine (from the ligand) and the imine derivative at the same time, with the hydrogen cyanide being bonded to the carbonyl group of threonine in the catalytically active species.[400] This enantioselective Strecker reaction with a polyfunctionalized benzaldehyde imine derivative has been used as the key asymmetric step in the synthesis of anti-HIV agent chloropeptin I.[401]

The previously introduced enantioselective Strecker reaction has also been performed with ligands simpler than tripeptides, such as the simple β-amino alcohol **288b**, which promoted the reaction using 10 mol % of both titanium tetraisopropoxide and the ligand **288b** with similar results to those presented in Table 34 (for comparison: 85%, 96% ee for **297a** and 85%, 91% ee for **297b**). The best solvent for this reaction was toluene, with the effect of temperature being quite interesting. Thus, the best enantioselectivities were obtained at 0 °C, with higher temperatures resulting in poorer selectivities, while at temperatures below 0 °C the reaction was very slow and the enantioselectivities dropped substantially.[402]

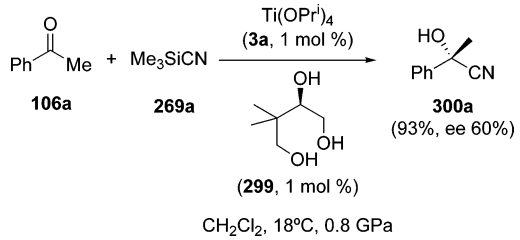


288b

4.5.2. Ketones as Electrophiles

The enantioselective cyanation of ketones is a challenging problem,[18c] which started to be solved in 1997.[403] The cyanation of acetophenone (**106a**) using substoichiometric amounts of the chiral triol ligand **299** and titanium tetraisopropoxide (**3a**) at high pressure (0.8 GPa) yielded the expected cyanohydrin **300a** (Scheme 84). The problem at

Scheme 84. First Catalytic Enantioselective Cyanation of Acetophenone under High Pressure



106a **269a** **300a** (93%, ee 60%)

(**299**, 1 mol %)

CH_2Cl_2, 18°C, 0.8 GPa

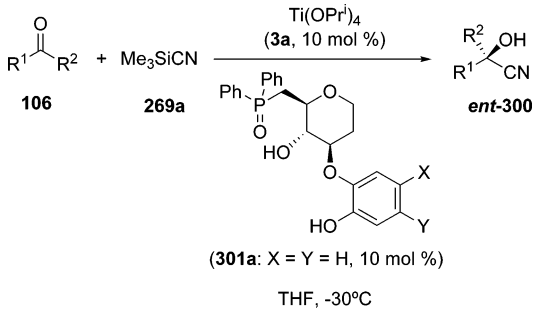
atmospheric pressure was the presence of an important racemization process due to the reversibility of the addition, competing with the very poorly enantioselective reaction. Despite the moderate selectivity, this work impelled the quest for other more active catalysts.

Very active catalysts are needed to avoid the background racemization process. This is the case of the homobimetallic titanium complex **271b** (see Table 31), which has been used in the cyanation of alkyl aryl ketones.[404] Although the enantioselectivity was only good (ee never higher than 72%), the concept of a very active catalyst as the only one able to promote the addition to ketones was proved. The kinetic studies[405] showed that the reaction was zero order in the ketone, first order in the silyl derivative **269a**, and 1.1 order in the catalyst **271b**. All these facts are similar to those found for aldehydes, and therefore, the previously catalytic cycle presented in Scheme 82 is applicable to ketones, only by changing the corresponding carbonyl compound. The related intermediate **278** with ketones explained the lack of reaction

of the catalyst with aryl alkyl ketones having larger alkyl chain lengths than ethyl, since this group was placed near to the cyclohexyl moiety of the catalyst, making the steric hindrance very important in this case.

The chiral ligand **301a** (X = Y = H), in combination with titanium tetraisopropoxide, has been able to promote the enantioselective addition of trimethylsilyl cyanide to ketones with excellent results. In this case, the enantioselectivity was practically independent of the nature of the substituents on the aromatic ring of the ketone (Table 35), with the cyanation

Table 35. Catalytic Enantioselective Cyanation of Ketones Using the Ligand 301a

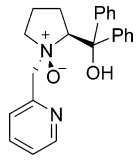


entry	no.	R^1	R^2	yield (%)	ee (%)
1	***ent*-300a**	Ph	Me	85	92
2	***ent*-300b**	4-MeC_6H_4	Me	80	90
3	***ent*-300c**	4-ClC_6H_4	Me	82	92
4	***ent*-300d**	(*E*)-PhCH=CH	Me	72	91
5	***ent*-300e**	*n*-C_5H_{11}	Me	88	76

of aliphatic ketones being accomplished for the first time.[406] Surprisingly, the reaction gave the best results using a coordinating solvent such as THF. Concerning the mechanism, it should be noticed that the titanium alkoxide reacted very fast with the ligand (liberating 2 equiv of 2-propanol) to form the corresponding chiral ligand complex, which by addition of trimethylsilyl cyanide was transformed into the corresponding chiral titanium cyanide. However, from labeling experiments using ^{13}Si and ^{14}N, the cyanide appeared to be transferred directly from the trimethylsilyl cyanide to the ketone but not from the titanium atom, with the titanium cyanide acting then as the more acidic center. The change of phosphine oxide to the related diphenylmethyl group gave much poorer results, indicating the presence of a typical dual activation mechanism,[247] with the titanium atom chelating the carbonyl group whereas the phosphine oxide coordinated the silyl moiety.

Some of the results presented in Table 35 could be improved by a fine-tuning of the structure of the chiral ligand. In fact, ligand **301b** (X = PhCO, Y = H) could reach 86% ee for the aliphatic cyanohydrin ***ent*-300e**.[407] The ligand **301c** (X = Y = Cl) emerged as the best one for the catalytic cyanation of 3-*tert*-butyldimethylsilyloxi-1-(3,4-dichlorophenyl)-1-propanone, which was the asymmetric key step in the synthesis of an intermediate of neurokinin receptor antagonists.[408]

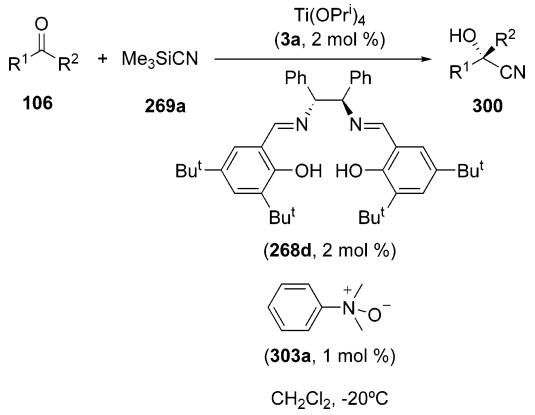
The chiral *N*-oxide **302**, in combination with titanium tetraisopropoxide, has been introduced as a new bifunctional catalyst for the enantioselective cyanation of ketones, with the enantiomeric excess never being over 69%.[409] The role of the 2-pyridylmethyl group was of capital importance to get the aforementioned results, since the use of benzyl or the related 3-pyridyl system dropped the enantioselectivity significantly.



302

The successful use of bifunctionalyzed catalyst for the catalytic enantioselective cyanation of ketones prompted the application of a method involving a separated double activation by two different catalysts (Table 36). In this way,

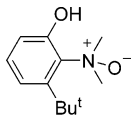
Table 36. Catalytic Enantioselective Cyanation of Ketones Using Separated Double Activation



entry	no.	R^1	R^2	yield (%)	ee (%)
1	***ent*-300a**	Ph	Me	75	85
2	***ent*-300b**	4-MeC_6H_4	Me	57	73
3	***ent*-300c**	4-ClC_6H_4	Me	58	84
4	***ent*-300d**	(*E*)-PhCH=CH	Me	79	64
5	***ent*-300e**	*n*-C_5H_{11}	Me	90	59

the reaction was performed on one hand by a titanium complex derived from the chiral salen **268d**, which served as the acid Lewis catalyst activating the carbonyl compound, and on the other hand by the achiral *N*-oxide **303a**, which acted as activator of the silyl cyanide by formation of a hypervalent silicon derivative.[410] Although the hypothesis proved to be satisfactory, the achieved results did not reach the previous high level (compare with Table 35).

A further evolution of the separated double activation by two different catalysts was the use an achiral *N*-oxide with an extra functionality able to chelate the chiral titanium complex and the silyl derivative at the same time, directly linking the electrophile with the nucleophile, such as compound **303b**.[411] However, the enantioselective cyanation of ketones using substoichiometric amounts of titanium tetraisopropoxide, the chiral salen ligand **268d**, and the achiral bifunctional compound **303b** did not produce any noticeable change with respect to the results presented in Table 36.

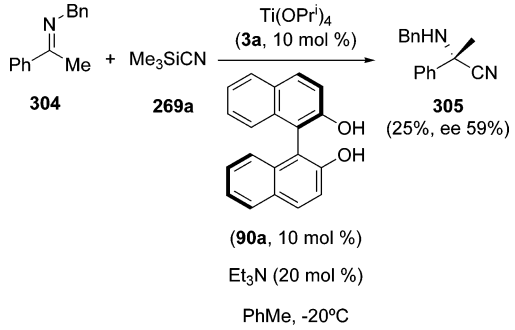


303b

As was presented in this section, the decrease in the electrophilic character of the carbonyl group has an important impact on the number of catalysts able to perform the

corresponding nucleophilic addition. For instance, although there are many catalysts able to perform the enantioselective cyanation of aldehydes, the number is lower for aryl alkyl ketones and only one for dialkyl ketones. The electrophilic character of the imine **304** derived from acetophenone is very low, which justifies the modest result obtained so far for its cyanation (Scheme 85). The result was highly modified by

Scheme 85. Enantioselective Strecker Reaction Using the Imine 304 Derived from Acetophenone



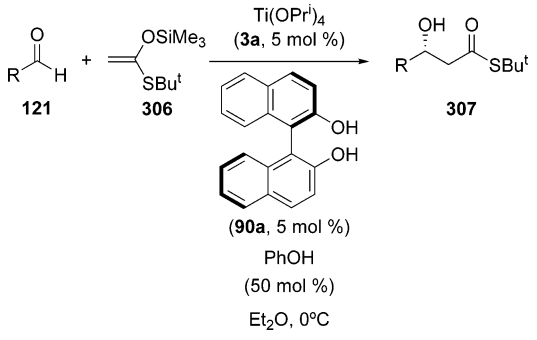
the presence of an achiral additive such as triethylamine (other bulky amines tested decrease the enantioselectivity),[412] which also has an influence on the chemical yield (owing to an autopoisoning effect[413]).

4.6. Aldol-Type Reactions

The condensation of an enolate derived from a carbonyl compound with another carbonyl compound derivative to yield the corresponding β-hydroxy (or amino) carbonyl product is a subject of constant and renewed interest in organic chemistry.[414]

Without any doubt, the BINOL-type ligand is historically the most used system in combination with titanium complexes. Thus, the simple silyl enol derivative **306** reacted with different aldehydes catalyzed by substoichiometric amounts of titanium tetraisopropoxide (**3a**) and BINOL (**90a**) in the presence of phenol as achiral additive to yield the expected β-hydroxy acid derivatives **307** (Table 37). The

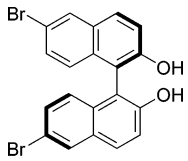
Table 37. Catalytic Enantioselective Aldol Reaction Using BINOL 90a



entry	no.	R	yield (%)	ee (%)
1	**307a**	Ph	71	96
2	**307b**	EtO_2C	65	63
3	**307c**	*n*-C_6H_{13}	76	93
5	**307d**	$TBDMSO(CH_2)_5$	22	95
6	**307e**	*n*-$PrO_2C(CH_2)_4$	70	>97

enantioselectivities were excellent in all cases independent of the nature of the aldehydes, even with those possessing different functional groups. The role of phenol was unclear since it did not change the enantioselectivity but permitted the reduction of catalyst loading and increased of the chemical yield. The alcohol **307** served as a chiral starting material in the preparation of (+)-lipoic acid.[415] The reaction can also be performed in supercritical fluids such as fluoroform without loss of the above high level of enantioselectivity.[416]

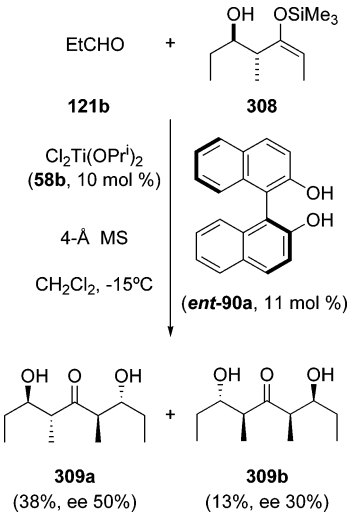
A screening of different BINOL derivatives showed that varying the electronic properties of substitutents at the 6 position had a remarkable influence on the enantioselectivity and the chemical yield, with the best BINOL being the ligand **90ax**, which could perform the aldol reaction in the absence of any additive with a wide scope of different functionalized aldehydes (for instance 57%, 92% for compound **307b**).[417] However, substituents at the 3 position of ligands had a detrimental effect.



90ax

The scope of nucleophiles for the former protocol is very ample. Thus, the reaction of the racemic silylenol ether **308** with propanal (**121b**) gave only two of all the possible diastereoisomers (Scheme 86). Each enantiomer **308** reacted

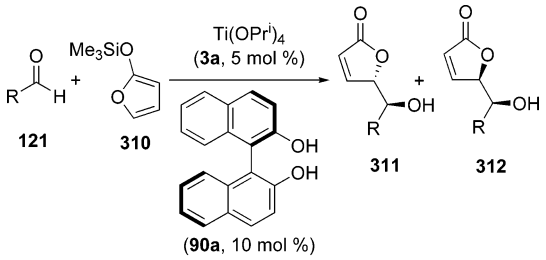
Scheme 86. Catalytic Enantioselective Resolution by an Aldol Reaction



with the chiral catalysts and the aldehyde in a different way and with different kinetics to yield mainly only one diasteroisomer **309**. Therefore, there is a kinetic resolution (see section 7), and although the enantioselectivities are not excellent, this example showed the wide scope of nucleophiles available.[418]

Not only silyl enol ethers can be used in this reaction but also conjugated silyl enol derivatives. Thus, the reaction of the silyl enol ether **310** with different aldehydes gave the corresponding diasteroisomeric γ-hydroxy lactones **311** and **312** (Table 38). The diastereoisomeric ratio and the enantioselectivity depended strongly on the nature of the aldehyde, with the best results being obtained for acyclic aliphatic aldehydes.[419] The reaction showed a positive nonlinear effect, which was rationalized involving the autoinductive effect of

Table 38. Catalytic Enantioselective Vinylogous Aldol Reaction Using the Nucleophile 310

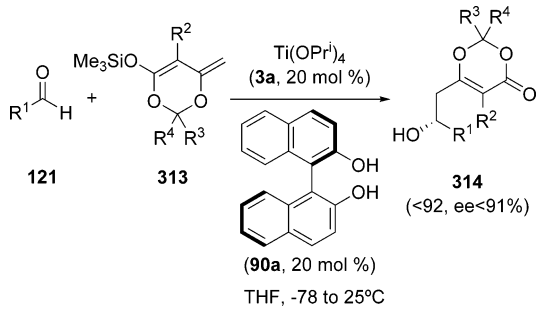


entry	R	no.	yield (%)	ee (%)	no.	yield (%)	ee (%)
1	Ph	**311a**	24	60	**312b**	75	90
2	*c*-C_6H_{11}	**311b**	45	71	**312b**	24	79
3	*n*-$C_{12}H_{25}$	**311c**	48	>96	**312c**	24	90

the final product. Thus, when the reaction was performed using the standard conditions, but adding a catalytic amount of chiral compound **311** derived from an acyclic aliphatic aldehyde, the final enantioselectivity of product **311** increased, while when the added compound was its enantiomer ***ent*-311**, the final enantioselectivity decreased. Moreover, if the reaction was carried out in the presence of either enantiomer of compound **312**, the results were the same as those in the absence of **312**. All these results suggested that the major chiral product of the reaction is incorporated into the catalyst to form a new catalyst which was more active than the initial one. This reaction has been applied to the synthesis of *iso*-cladospolide B.[420]

Other cyclic vinylogous nucleophiles **313** are depicted in Scheme 87. Their reaction with different electrophiles gave,

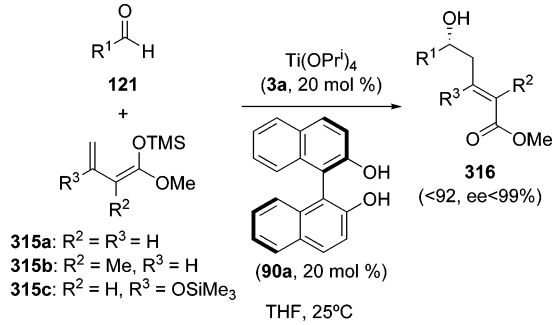
Scheme 87. Catalytic Enantioselective Vinylogous Aldol Reaction Using Cyclic Nucleophiles 313



after hydrolysis, the expected alcohols **314** with good enantioselectivities.[421] The substituents on the dioxane ring did not have any significant influence on the results, while the nature of the aldehyde was quite important, with the highest enantioselectivities being found using aromatic aldehydes. An important positive nonlinear effect was found, as in the vinilogous aldol reaction, which was attributed to the presence of an autocatalytic effect, with the grade of this effect being highly modified depending on the preparation procedure for the catalyst. When the same catalyst was prepared at high concentration, the nonlinear effect was smaller than when the partially resolved catalyst was prepared at low concentration and then diluted to the final concentration.[422] This catalytic enantioselective vinilogous aldol reaction has been used as the asymmetric key step in the synthesis of manoalide and cacospongionolide B, antiinflammatory sesterterpenes isolated from soft sponges.[423] The introduction of a extra methyl substituent at the vinyl group did not decrease the enantioselectivity, and as in the previous cases, the presence of a positive nonlinear effect was detected.[424]

The vinylogous aldol reaction has also been carried out with acyclic nucleophiles such as **315** (Scheme 88). The

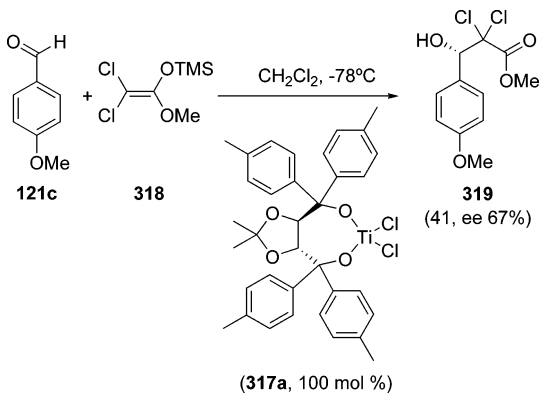
Scheme 88. Catalytic Enantioselective Vinylogous Aldol Reaction with Acyclic Nucleophile 315



reaction with nucleophiles **315a,b** gave enantioselectivities around 70% independent of the nature of the aldehyde, with the chemical yield being lower for aliphatic (around 20%) than for aromatic ones (around 40%).[425] The reaction with Chan's diene (**315c**) gave after hydrolysis the corresponding γ-hydroxy β-ketoester arising from the hydrolysis of the corresponding silyl enol ether **316** (R^3 = $OSiMe_3$) with excellent enantioselectivities.[426] A positive nonlinear effect was detected using nucleophiles **315**, which was dependent on the form of the catalyst preparation.[427]

Apart from BINOL derivatives, other ligands and titanium complexes have been used as catalysts for the enantioselective aldol reaction, such as complex **317a**,[428] which was used in the condensation between the chlorinated enol **318** and *p*-anisaldehyde (**121c**) to yield the expected β-hydroxy ester **319** with moderate results (Scheme 89). Compound **319** is

Scheme 89. Enantioselective Aldol Reaction Using the Complex 317a



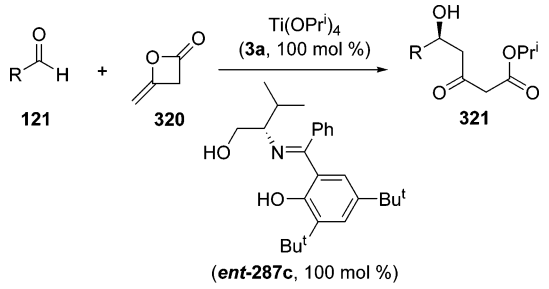
the key intermediate for the synthesis of diltiazem, one of the most potent calcium antagonists which has been used throughout the world as a remedy for angina and hypertension.

The complex **105h** has been employed in substoichiometric amounts as catalyst in the enantioselective aldol reaction of the enol trichloroacetate derived from cyclohexanone with different aromatic aldehydes.[429] The enantioselectivities were moderate (ee never higher than 58%), and only for anisaldehyde (**121c**) did the enantiomeric ratio of the major diastereoisomer reach 91%.

105h

Another nucleophilic alternative for the vinylogous aldol reaction is the diketene **320**, which reacted with different aldehydes in the presence of stoichiometric amounts of both titanium tetraisopropoxide (**3a**) and the salen ligand ***ent*-287c** to give the corresponding γ-hydroxy β-ketoester **321** (Table 39).[430] The chemical yields were in all cases moderated to

Table 39. Enantioselective Vinylogous Aldol Reaction Using Nucleophile Diketene 320

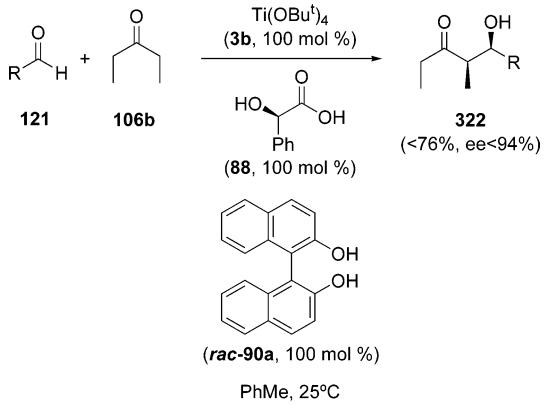


entry	no.	R	yield (%)	ee (%)
1	**321a**	Ph	65	91
2	**321b**	4-MeC_6H_4	74	88
3	**321c**	(*E*)-PhCH=CH	69	90
4	**321d**	PhC≡C	60	75
5	**321e**	Me_3SiC≡C	69	72

good whereas the enantioselectivity was strongly dependent on the nature of aldehyde, with aromatic systems giving the best results. Other salen derivatives, as well as BINOL (**90a**),[431] rendered worse results.

The direct aldol reaction is conceptually more interesting because it avoids the previous preparation of the corresponding enolate. Only very recently has the first example of this class of reaction using titanium complexes been reported (Scheme 90). The reaction was carried out using stoichio-

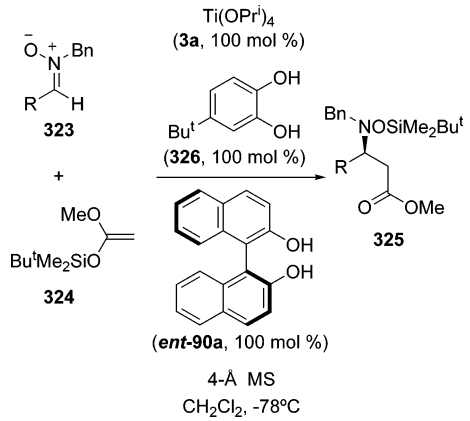
Scheme 90. Direct Enantioselective Aldol Reaction



metric amounts of titanium tetra-*tert*-butoxide (**3b**), racemic BINOL, and chiral mandelic acid (**88**).[432] The diastereomeric ratio of final products **322** was around 75%, and the enantioselectivities were dependent on the aldehyde used, with the best results being obtained for aromatic aldehydes. ^{13}C and ^{1}H NMR experiments on the catalyst mixture indicated the existence of at least seven different conformers between the titanium tetraisopropoxide and mandelic acid. The X-ray analysis showed a bimetallic titanium complex bearing only one chiral ligand, with the postulated precatalyst being similar to the previous one but exchanging the two nonbridged isopropoxide groups for one BINOLate moiety in one titanium atom.

The aldol reaction using imine derivatives, the so-called Mannich-type reaction,[433] could be performed using stoichiometric amounts of titanium complexes (Table 40). The

Table 40. Enantioselective Mannich Reaction



entry	no.	R	yield (%)	ee (%)
1	**325a**	Ph	99	92
2	**325b**	4-MeC_6H_4	66	88
3	**325c**	2-naphthyl	94	88
4	**32d**	3-pyridyl	90	80

presence of the catechol **326** was essential in order to obtain good enantioselectivities, with compound **325a** rendering 18% ee without the phenolic derivative.[434] The results were quite constant for aromatic aldehyde derivatives (R = aryl) independent of the presence of any extra functionality.

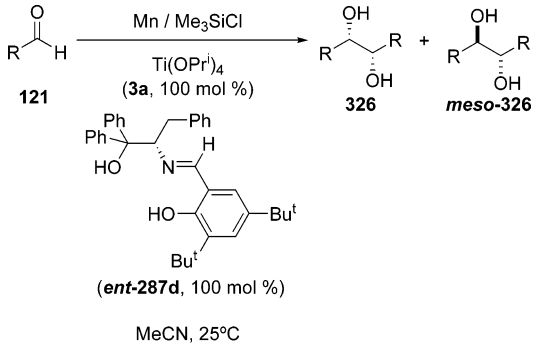
The vinylogous Mannich reaction using different *N*-aryl imines derived from arenecarbaldehydes and a nucleophilic furan **310** (see Table 38) has been performed using substoichiometric amounts of chiral BINOL (***ent*-90a**) and titanium tetraisopropoxide, giving the corresponding amines with good diastereoselectivity but with modest enantioselectivity (never higher than 54%).[435] However, this example proved the validity of this approach.

4.7. Pinacol Coupling Processes

The enantioselective titanium-catalyzed pinacol coupling[436] of aldehydes to give 1,2-diols, through the formation of the corresponding radical anion, was first reported by the group of Cozzi and Umani-Ronchi using substoichiometric amounts of the chiral salen ligand **268b** (see section 4.5.1). Although the enantioselectivity found was very modest,[437] it opened up the field to the use of other ligands and catalysts, as well as to its synthetic utility. Thus, the stoichiometric use of the ligand ***ent*-287d** in combination with titanium tetraisopropoxide (**3a**) and 325 mesh manganese metal as the initial reducing agent permitted the preparation of the corresponding chiral diols **326** with small amounts of achiral ***meso*-326**.[438] The examination of various substituted benzaldehydes showed a crucial electronic effect on the enantioselectivity, so while electron-donating groups gave a noticeable increase in the

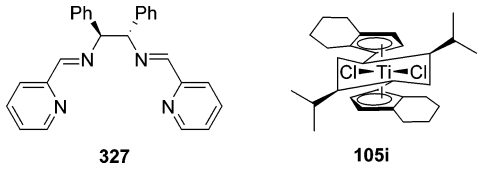
enantiomeric excess, the introduction of electron-withdrawing groups showed a strong negative effect on the selectivity (Table 41).

Table 41. Enantioselective Pinacol Coupling Reaction

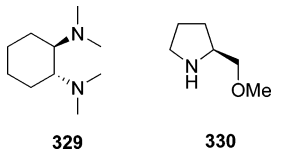


entry	no.	R	yield (%)	ee (%)
1	**326a**	Ph	>95	77
2	**326b**	4-MeC_6H_4	>95	91
3	**326c**	4-BrC_6H_4	>95	48

The ligand **327**, in combination with titanium tetrachloride (**3c**), has been proposed as an alternative to the reaction shown in Table 41. The found enantioselectivity and the effect of substituents were similar to the aforementioned ones, with the reaction being performed using substoichiometric amounts of both the ligand and the titanium source.[439] It should be pointed out that the reaction failed with aliphatic aldehydes. On the other hand, the chiral indenyl titanium dichloride **105i** did not produce any increase in the enantioselectivity.[440]



The pinacol coupling reaction has also been performed with a stoichiometric amount of titanium dichloride (**328**) and different amines. The reducing agent **328** was prepared by treatment of titanium tetrachloride (**3c**) with hexamethylsilane, followed by elimination of volatile materials. The reaction of benzaldehyde with stoichiometric amounts of titanium dichloride (**328**) and the amine **329** yielded the diol

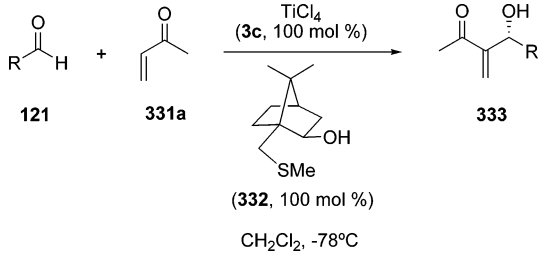


326a with a modest result (34%, ee 40%), which could be improved by the addition of larger amounts of the chiral amine. A careful study using small-angle X-ray scattering and atomic force microscopy revealed the presence of two main types of particles. The bigger ones had an average radius of 51 Å whereas the smaller ones had an average radius of 9 Å. The largest particles were considered to be a cluster, and the smallest might be a monomeric amine−titanium−THF complex, with the former being responsible for the low enantioselectivity.[441] Therefore, any change in the preparation protocol which deletes the presence of large clusters could improve the enantioselectivity. The use of the amine **330**, under similar conditions, did not produce any spectacular change in the enantioselectivity.[442]

4.8. Miscellaneous Additions

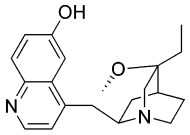
The Baylis−Hillman reaction[443] is another process which has been successfully performed using a titanium complex. Thus, the reaction of methyl vinyl ketone **331a** with different aldehydes in the presence of stoichiometric amounts of titanium tetrachloride (**3c**) and methylsulfanyl isoborneol **332** gave the expected β-hydroxy α-methylene ketones **333** with moderate enantioselectivity and chemical yields (Table 42).[444]

Table 42. Enantioselective Baylis−Hillman Reaction



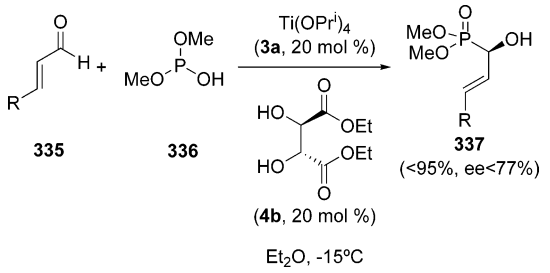
entry	no.	R	yield (%)	ee (%)
1	**333a**	4-ClC_6H_4	22	40
2	**333b**	4-$O_2NC_6H_4$	26	71
3	**333c**	$Ph(CH_2)_2$	43	74

The three component[378] version of the reaction shown in Table 42 seems to be more interesting. The reaction of aromatic aldehydes with tosylamide and methyl acrylate in the presence of substoichiometric amounts of titanium tetraisopropoxide (**3a**) and the chiral quinuclidine derivative **334** gave the corresponding β-tosylamido α-methylene ester with good results (enantiomeric excess around 65%).[445]



The enantioselective Pudovik reaction between α,β-unsaturated aldehydes **335** and dimethyl phosphite (**336**) catalyzed by diethyl tartrate (**4b**) in the presence of titanium tetraisopropoxide (**3a**) yielded the expected chiral α-hydroxy phosphonates **337** with moderate to good enantioselectivities (Scheme 91).[446] The enantioselectivities could be improved

Scheme 91. Catalytic Enantioselective Pudovik Reaction

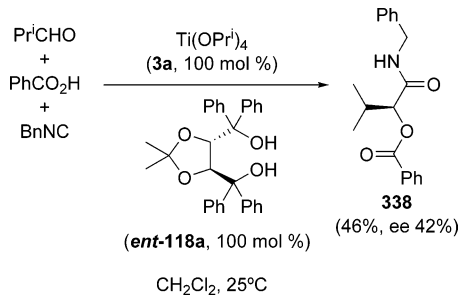


by a further crystallization or by a subsequent enzymatic kinetic resolution.[447] In turn, these chiral phosphonates **337**

have been used as starting materials for different transformations such as dimerizations through cross-metathesis.

The first enantioselective multicomponent[378] Passerini reaction has been published very recently (Scheme 92).[448]

Scheme 92. Enantioselective Passerini Reaction

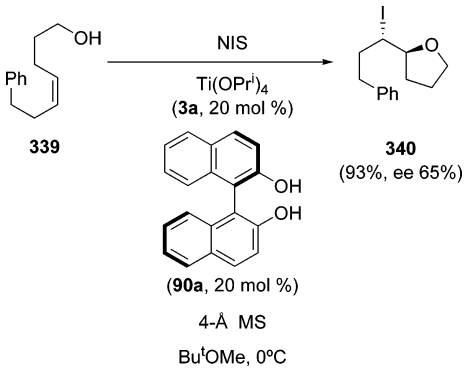


The catalyst emerged from a screening of 16 metallic Lewis acids, including aluminum, zirconium, zinc, copper, magnesium, and lanthanide salts, and 12 chiral ligands, and although the results are far from excellent, it demonstrates the versatility and efficacy of the titanium complex compared with those of other metals.

Another example in which the results are still very modest (ee lower than 15%) is the hydroamination of aminoallenes to yield the corresponding vinyl substituted heterocycle, which was accomplished by using mixtures of titanium tetrakisdimethylamide (**3h)** and different chiral α-amino alcohols.[449]

The intramolecular iodocyclization of γ-hydroxyalkenes is another addition to olefins, which was accomplished by using *N*-iodo succinimide (NIS) in the presence of a substoichiometric amount of titanium tetraisopropoxide (**3a**) and BINOL (**90a**) to give tetrahydrofuran **340** from the unsaturated alcohol **339** with relative success. It is worthy of note that any small change in the initial alkenes gave a very steep decrease in the enantioselectivity (Scheme 93).[450]

Scheme 93. Catalytic Enantioselective Iodocyclization Process



The cyclization of secone **341** to give the corresponding ketone **342** is recognized as a Torgov reaction (Scheme 94), which has been catalyzed by substoichiometric amounts of both titanium tetrachoride (**3c**) and salen ligand **287e.** The reaction is formally a classical ene addition followed by dehydration and double bond isomerization.[451]

The last examples of this section came from the field of the Michael-type addition.[163] The catalytic enantioselective 1,4-addition of different aryltitanium triisopropoxides **122** to α,β-unsaturated ketones **331** catalyzed by rhodium salts and BINAP (**259b**) yielded the expected ketones **343** with

Scheme 94. Catalytic Enantioselective Torgov Cyclization

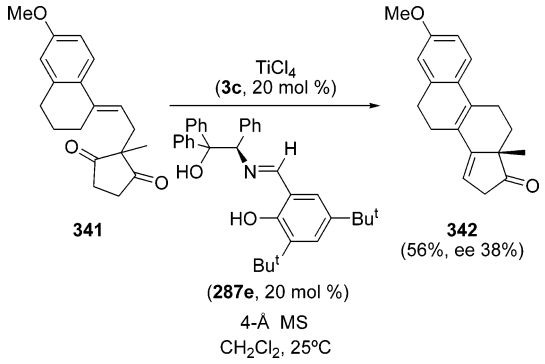
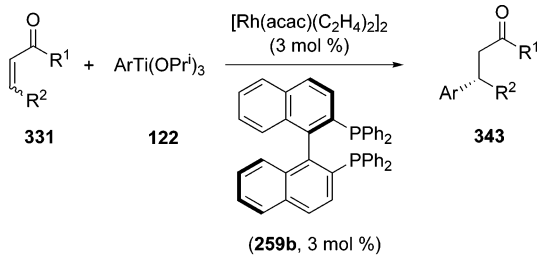


Table 43. Catalytic Enantioselective 1,4-Addition



entry	no.	Ar	R^1	R^2	yield (%)	ee (%)
1	**343a**	Ph	-$(CH_2)_3$-		84	99
2	**343b**	4-MeC_6H_4	-$(CH_2)_3$-		63	94
3	**343c**	4-FC_6H_4	-$(CH_2)_3$-		68	99
4	**343d**	Ph	Me	Pr^i	77	99
5	**343e**	Ph	N$(CO_2Bn)(CH_2)_2$		70	99

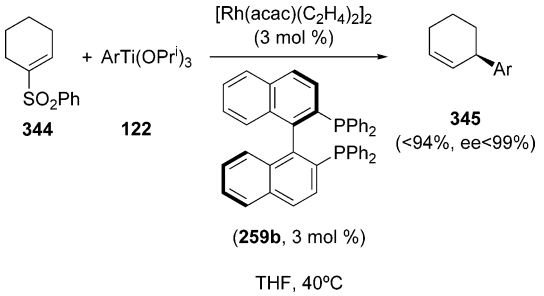
insuperable results (Table 43). The results were exceptionally good, were independent of the substituent on the aromatic ring of the titanium derivatives, and were independent of the nature of the ketone (cyclic or acyclic), and even of the presence of strongly coordinating functionalities such as amides.[452] The final ketone **343** could be *in situ* modified just by changing the normal quenching from using methanol (yielding protonated ketones **343**) to the addition of lithium isopropoxide (to generate the ate form of the corresponding titanium enolate), followed by addition of an electrophilic alkylating agent, thus yielding the corresponding 2-alkylated ketone. This procedure amplified its synthetic possibilities. The reaction has been extended to dienones and enynones simply by activating the nucleophile **122** by the addition of lithium isopropoxide, to yield the corresponding 1,6-addition product with excellent enantioselectivities.[453] Alternatively, the same titanium ate complex could be prepared by direct reaction of the corresponding aryllithium derivative with titanium tetraisopropoxide (**3a**).

When the same reaction was performed with the α,β-unsaturated sulfone **344**, instead of the Michael-type product, the alkene **345** was isolated with an excellent result. The product came from a Michael addition process, followed by a β-elimination of the sulfone moiety (Scheme 95).[454]

5. Enantioselective Friedel–Crafts Processes

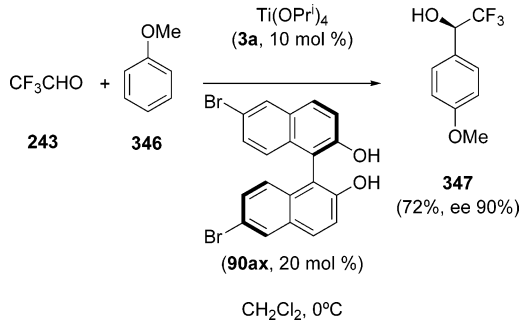
The reaction described in this section could be include in the previous section on enantioselective nucleophilic addition processes since in all examples a carbonyl compound is the partner in the reaction, but it has been separated mainly for

Scheme 95. Catalytic Enantioselective Arylation Process



historic reasons.[455] The first example was the reaction of highly electrophilic fluoral (**243**) with anisol (**346**) in the presence of equimolecular amounts of titanium tetraisopropoxide (**3a**) and the BINOL derivative **90ax** to give the alcohol **347**, with small amounts of the related *ortho*-derivative (Scheme 96).[456] The presence of electron-withdrawing

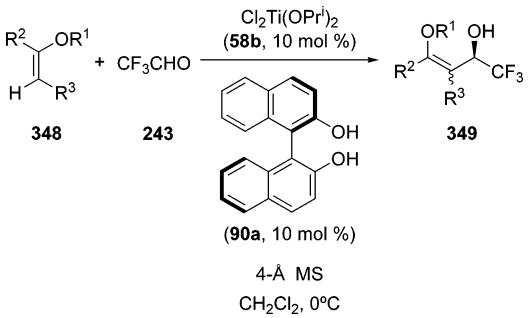
Scheme 96. Catalytic Enantioselective Friedel−Crafts Reaction



groups at the 6,6′ positions in the ligand was essential to reach a good level of enantioselectivity, and the further addition of an extra amount of BINOL **90ax** after the preparation of the catalyst improved the results (activation of catalyst). The scope of the reagents was increased by the use of other highly electrophilic aldehydes as ethyl glyoxylate (**246**) and *N*,*N*-dimethylaniline to give the corresponding aminomandelic acid derivatives with similar results.[457]

The Friedel−Crafts reaction of different vinyl ethers **348** with fluoral (**243**) has been performed using ligand **90a** (Table 44). The reaction gave a mixture of allylic alcohols

Table 44. Catalytic Enantioselective Friedel−Crafts Reactions of Vinyl Ethers



entry	no.	R^1	R^2	R^3	*E*:*Z*	yield (%)	ee (%)
1	**349a**	Me	Ph	H	1:2	54	72
2	**349b**	Me	4-MeC_6H_4	Me	5:1	64	85
3	**349c**	Bu^tMe_2Si	Ph	H	1:5	67	98
4	**349d**	Pr^i_3Si	Ph	H	1:5	90	96
5	**349e**	Bu^tMe_2Si	4-MeC_6H_4	Me	1:6	72	95

in which the main isomer was usually the *Z*-alkene. However, for methoxy derivatives the presence of other substituents around the double bound could change this tendency.[458] In the case of silyl enol ether derivatives, the size of the silyl group was determined in order to get the corresponding Friedel−Craft products **349**. When the reaction was carried out using less crowded trimethylsilyl enol ether, the only isolated product was the expected aldol.[459] It should be pointed out that the enantioselectivities found were much higher than those obtained for the corresponding aldol process. Therefore, the Friedel−Crafts reaction, followed by hydrolysis of the final silylenol ether **349** to give the corresponding carbonyl compound, could be shown as an attractive alternative to the direct aldol reaction.

6. Enantioselective Cycloaddition Processes

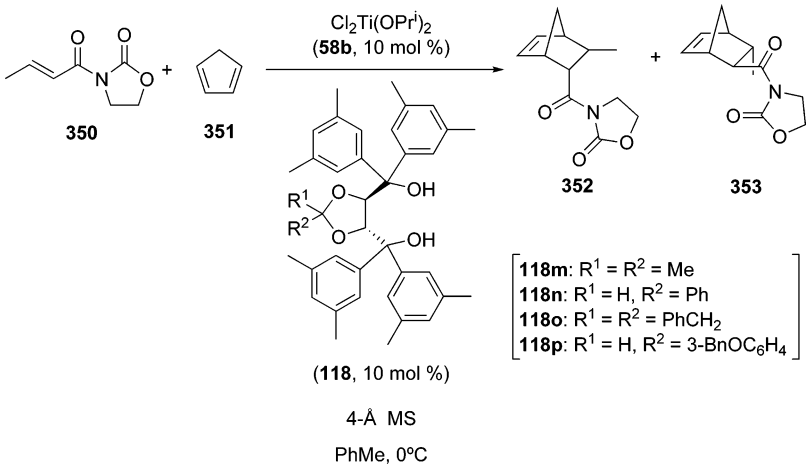
Cycloaddition reactions are among the most important tools for organic synthesis,[460] since they are crucial for the modern synthesis of natural products and biologically active molecules, allowing the selective creation of several stereocenters and their integration in the target molecule in only one synthetic operation.

6.1. Diels−Alder Reactions

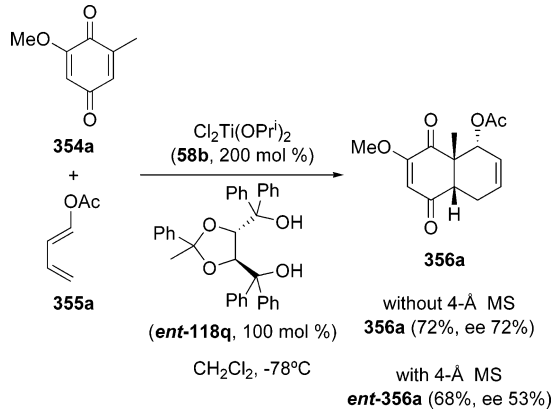
The Diels−Alder reaction[461] is the most useful synthetic reaction for the construction of the cyclohexane framework, with up to four continuous stereogenic centers being created in a single operation, with the relative stereochemistry being usually determined by the *endo*-favoring transition state. Although the amount of papers on this subject during the end of the pervious century was impressive, in the last few years the progression has decreased. For comparing different protocols, the standard reaction was the reaction of (*E*)-3-butenoyl-1,3-oxazolidin-2-one (**350**) with cyclopentadiene (**351**) to yield a mixture of the corresponding bicyclic compounds **352** and **353** (Scheme 97), with very interesting results being obtained in the case of using different TADDOLs containing 3,5-dimethylphenyl groups (**118m**−**p**). Thus, when the reaction was performed using the ligand **118m**, the enantiomeric excess for the main product **352** was 82%. However, when the reaction was repeated using the ligand **118n**, the main enantiomer changed to be ***ent*-352** (24% ee). This tendency was confirmed with the ligand **118o** (61% ee for ***ent*-352**); in both cases the ratio ***endo*-349**/***exo*-350** was nearly 75/25. This change in the topological outcome of the reaction was attributed to the existence of a strong π-stacking effect between the bulky aryl groups and the 2-substituent in the dioxolane ring.[462] Moreover, the main factor controlling the enantioselectivity was the dienophile/catalyst ratio for the case of the ligand **118p**. Indeed, for a very similar concentration of dienophile, the enantiomeric excess changed from 3 to 50% for ***ent*-352** as a function of this ratio. These changes in the enantioselectivity clearly indicated the presence of several reactive intermediates bearing compound **350** with different stoichiometries, which showed different selectivities and reactivities.[463] The incorporation of a fluorine atom in the dienophile had a detrimental effect on the enantioselectivity, decreasing the enantiomeric excess of the product to only 18%.[464]

The reversibility of the process was observed in the reaction of the dienophile **354a** and the diene **355a** to give the corresponding adduct **356a** (Scheme 98). When the reaction was performed using the ligand ***ent*-118q** in the

Scheme 97. Catalytic Enantioselective Diels−Alder Reaction Using the Dienophile 350

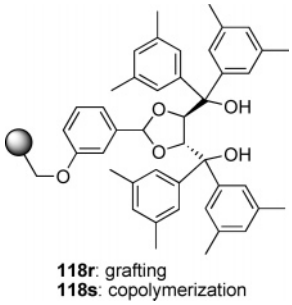


Scheme 98. Catalytic Enantioselective Diels−Alder Reaction Using the Dienophile 354a



absence of molecular sieves, the diketone **356a** was obtained with good results. However, when the reaction was repeated under similar conditions but in the presence of 4-Å molecular sieves, the results were somewhat poorer, with the final product being ***ent*-356a**. The reason for this reverse behavior was not clear, but the authors believed that the capture of HCl by the molecular sieves played a critical role in the formation of the catalytic species.[465]

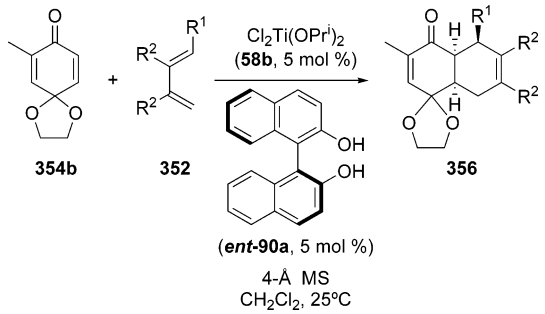
When the reaction presented in Scheme 97 was performed using the heterogeneous ligands **118r** and **118s**, different



results were obtained depending on the ligand heterogenation process. Thus, the reaction using the ligand prepared by grafting the corresponding TADDOL derivative to a polystyrene−divinylbenzene matrix surprisingly gave **352** as the main enantiomer (17% ee). However, the reaction using the ligand built by a copolymerization process gave ***ent*-352** (18% ee), indicating that in these cases the usually inert polymeric matrix was responsible for the reversal topicity.[466]

The BINOL ligand (***ent*-90a**) has also been used as chiral promoter for typical Diels−Alder reactions, as is outlined in Table 45. The catalytic enantioselective Diels−

Table 45. Catalytic Enantioselective Diels−Alder Reactions Using BINOL *ent*-90a



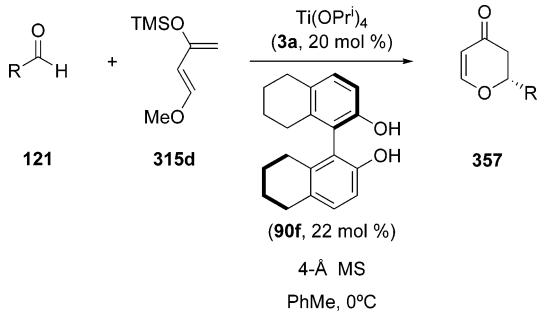
entry	no.	R^1	R^2	yield (%)	ee (%)
1	**356b**	Me	H	97	98
2	**356c**	H	H	91	81
3	**356d**	H	Me	88	84

Alder reaction of 1,4-quinone monoketal **354b** with different dienes gave the expected *endo*-products **356** with good results.[467] The monoketalic system has several advantages compared to simple 1,4-quinones of type **354a**, such as its higher Lewis basicity, the difficulty for the aromatization of the final products, the presence of two carbonyl groups clearly differentiated, and its facile preparation from different sources. As in previous examples, the presence of molecular sieves was critical in order to get good enantioselectivities.

One of the major improvements in the Diels−Alder reaction has been the introduction of different heteroatoms in the diene or dienophile starting materials. In this way, instead of obtaining cyclohexene frameworks, different heterocyclic systems could be prepared.[468] One of the most typical hetero-Diels−Alder reactions is the cycloaddition of aldehydes with Danishefsky's diene (**315d**) to give the corresponding pyranone **357**. There are two possible mechanisms to explain this reaction: one of them is a true hetero-Diels−Alder reaction through a six membered transition state, whereas another one involves a classical aldol reaction to give the corresponding β-hydroxy carbonyl compound followed by a cyclizing intramolecular addition−elimination process. The mechanistic pathway depends strongly on the

reaction conditions as well as on the catalysts used. The catalytic enantioselective hetero-Diels−Alder reaction catalyzed by H_8-BINOL **90f** was successfully accomplished in the presence of titanium tetraisopropoxide and after final treatment with trifluoroacetic acid (Table 46). The enantio-

Table 46. Catalytic Enantioselective Hetero-Diels−Alder Reactions Using H_8-BINOL 90f



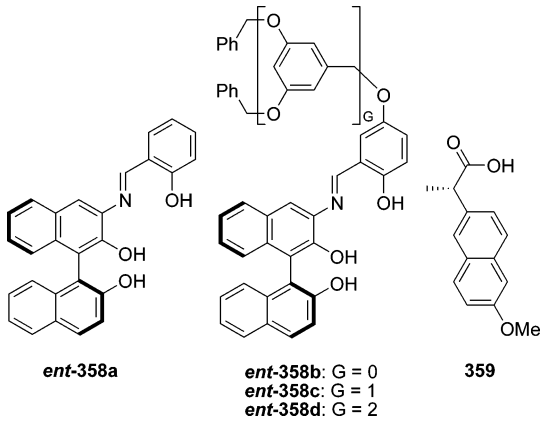
entry	no.	R	yield (%)	ee (%)
1	**357a**	Ph	92	97
2	**357b**	4-MeC_6H_4	60	99
3	**357c**	4-FC_6H_4	54	97
4	**357d**	2-furyl	78	96
5	**357e**	(*E*)-PhCH=CH	80	98
6	**357f**	*n*-C_8H_{17}	76	94

selectivity was excellent independent of the aromatic or aliphatic nature of the used aldehydes, even with functionalized ones. It should be pointed out that the use of other BINOL derivatives such as the dibromo derivative **90ax**, BINOL (**90a**), or H_4-BINOL (**90e**) did not produce any improvement. The enantioselectivity and the chemical yield were found to correlate directly with the dihedral angle of the BINOL ligand; the higher the angle, the better the results obtained. The presence of molecular sieves had a beneficial effect, while an increase of the amount of H_8-BINOL **90f** diminished the enantioselectivity.[469] However, the mixture of two different BINOL derivatives (**90e** and **90f**) had a great impact on the enantioselectivity, permitting a decrease of the amount of catalyst from an initial 20 mol % to 0.005 mol % while maintaining the results.[470] Concerning the possible mechanistic pathway, it should be pointed out that it seems to go through the aldol pathway, since the corresponding aldol intermediate was detected.

Other catalysts proposed, such as the combination of chiral BINOL (***ent*-90a**), the bulky diamine **229**, and titanium tetraisopropoxide (to form the bimetallic titanium species of type ***ent*-230**)[471] or the mixture of the chiral fluorinated diol **156a** and titanium tetraisopropoxide,[472] did not give any important improvement concerning results and reaction conditions.

It should be pointed out that when the reaction was performed using substoichiometric amounts of BINOL (**90a**), half the amount of titanium tetraisopropoxide (**3a**), and different polyfluorinated aliphatic aldehydes, chemical yields decreased when the methylene chain length decreased. However, the enantioselectivity was practically constant (around 95%).[473] This catalytic system was used in a hetero-Diels−Alder reaction using Danishefsky's diene (**315d**) and *β*-oxido functionalized propionaldehyde, which was the initial step in the synthesis of (+)-phorboxazole A.[474]

The aforementioned standard reaction was also conducted by the NOBIN derivative ***ent*-358a**, giving initially unusual but not reproducible results. A careful study showed that

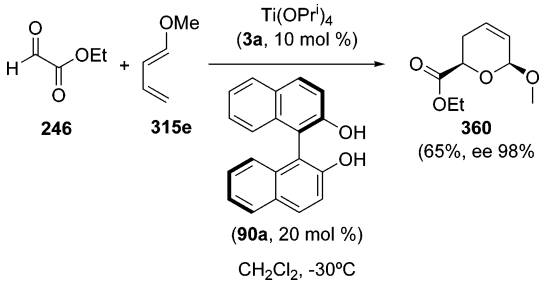


the reaction gave better results when aged benzaldehyde was used instead of using fresh distilled benzaldehyde. The reason was rationalized considering benzoic acid as a possible activator of the catalyst.[252] These results prompted authors to improved the initial results, so a library of 22 different NOBIN derivatives were tested. After finding ***ent*-358a** as the best ligand for titanium tetraisopropoxide, the reaction was repeated with 36 different acids, and from this last screening, naproxen (**359**) emerged as the best activator, reaching excellent enantioselectivities (for instance >99% for ***ent*-357a**).[475] The presence of nonlinear effects for NOBIN and naproxen derivatives implied the presence of both chiral compounds in the catalytic cycle. The X-ray structure of bis(NOBIN-***ent*-358a**)-titanium could be obtained for both the chiral ligand and the racemic one, and although the coordination patterns were similar for both systems, the spatial orientations of the Schiff base ligands around the titanium metal atom were quite different. For the chiral ligand ***ent*-358a**, the imino nitrogen atom and the two phenoxy oxygens were placed in a *cis* form. On the contrary, for the racemic ligand, the imino nitrogen atom of the ligand and the phenoxy oxygen atom of its enantiomer ligand bonded to a titanium atom in a *trans* form, with the whole complex possessing a C_1 symmetry and having two enantiomers of titanium complex molecules in its unit cell. In addition, in the case of chiral ligand, two phenoxy oxygen atoms of the ligand coordinated to a titanium atom in a *trans* form, with the whole complex possessing a C_2 symmetry. The ^{1}H NMR study showed that the addition of the acid **359** destroyed the initial bis(NOBIN-***ent*-358a**)-titanium complex for the case of chiral ligand giving a new titanium species bearing both compounds. This new species is as active and selective catalyst as the one obtained by simple mixture of both ligands. However, the bimetallic complex was very stable for the case of the racemic ligand, and no change was found when naproxen was added. This different behavior was responsible for the detected nonlinear effect.

To facilitate the recovery of the chiral ligand, different generations of Fréchet dendrons were attached to form ligands ***ent*-358b−d**. In fact, this premise was confirmed by the three-time reuse of ligand ***ent*-358c** in the hetero-Diels−Alder reaction of benzaldehyde and the diene **315d** in the presence of titanium tetraisopropoxide and naproxen (**359**). The active catalyst was recovered just by precipitation with hexane and filtration and reused without the necessity of further adding of naproxen and the titanium source. It should be pointed out that the enantioselectivity increased with the dendron generation, as well as the nonlinear effect, reaching the maximum with ligand ***ent*-358c**, and the enantiomeric excess was similar to that obtained with ligand ***ent*-358a**.[476]

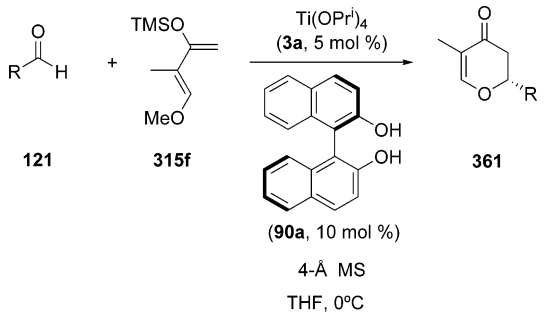
Another diene used in this hetero-Diels−Alder reaction is the compound **315e**, which after reaction with the aldehyde **246** gave the heterocycle **360** with an excellent enantioselectivity, with the diastereomeric excess being up to 80% (Scheme 99). The final product could be easily transformed into the polyketide (+)-goniothalamin.[477]

Scheme 99. Catalytic Enantioselective Hetero-Diels−Alder Reaction Using the Diene 315e



The diene **315f** reacted with different aldehydes in the presence of substoichiometric amounts of BINOL (**90a**) and titanium tetraisopropoxide to yield, after treatment with trifluoroacetic acid, the substituted pyranones **361**, which came from a formal hetero-Diels−Alder reaction (Table 47).

Table 47. Catalytic Enantioselective Hetero-Diels−Alder Reactions Using the Diene 315f



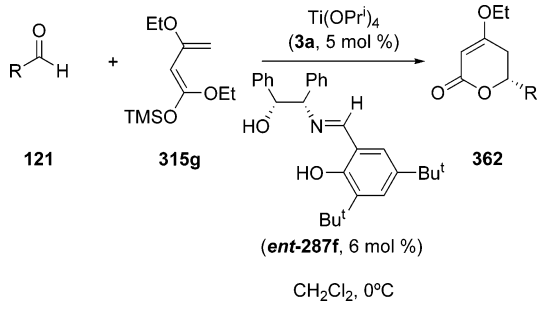
entry	no.	R	yield (%)	ee (%)
1	**361a**	Ph	86	99
2	**361b**	4-MeOC$_6$H$_4$	84	90
3	**361c**	4-FC$_6$H$_4$	73	94
4	**361d**	2-furyl	99	97
5	**361e**	(*E*)-PhCH=CH	47	85
6	**361f**	*n*-C$_6$H$_{13}$	41	87

In this case, the use of other BINOL derivatives such as H$_8$-BINOL (**90f**) or H$_4$-BINOL (**90e**) did not produce any improvement. The enantioselectivity and the chemical yield were found to be directly related to the dihedral angle of the BINOL ligand, with the smaller angle giving better results (compare with results from Table 46).[478]

Another diene used was the so-called Brassard's compound **315g** (Table 48). In this case, the formal hetero-Diels−Alder reaction was performed using the chiral salen derivative ***ent*-287f**, which rendered the corresponding heterocyclic compounds **362** with good and constant enantioselectivities. Other related systems such as **287a** gave worse results. However, the chemical yield seems to be dominated by the electrophilic character of the aldehyde, and the best results were obtained with benzaldehydes possessing strong electron-withdrawing groups.[479]

Not only aldehydes can be used as dienophiles, but also *N*-sulfinyl dienophiles **363** have been applied to hetero-

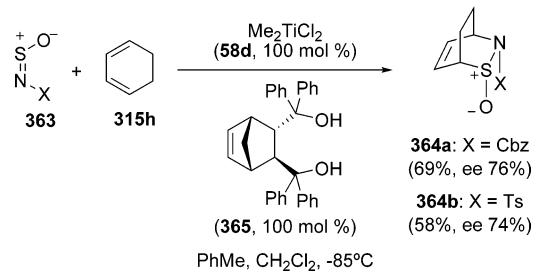
Table 48. Catalytic Enantioselective Hetero-Diels−Alder Reactions Using the Diene 315g



entry	no.	R	yield (%)	ee (%)
1	**362a**	Ph	71	93
2	**362b**	4-MeC$_6$H$_4$	36	90
3	**362c**	4-FC$_6$H$_4$	53	93
4	**362d**	2-naphthyl	99	97

Diels−Alder cycloadditions yielding the expected *endo*-sulfoxide derivative **364** with moderate results (Scheme 100). Different chiral ligands were tested, and from a set of

Scheme 100. Enantioselective Hetero-Diels−Alder Reaction Using *N*-Sulfinyl Dienophile 363

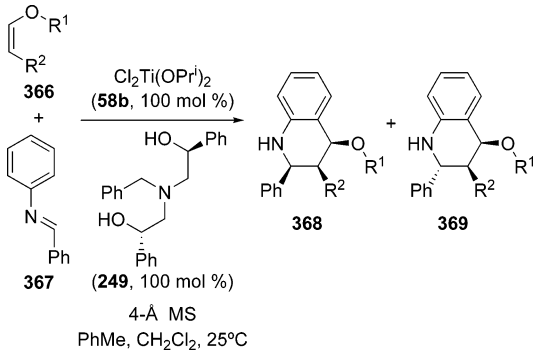


10 compounds, including TADDOL, BINOL, BODOL, and salen derivatives, the ligand **365** gave the best enantioselectivities. The initial source of titanium was intermediate **58d**, which gave the most reproducible results. Finally, it is worthy of note that a small positive nonlinear effect was detected and, therefore, a bimetallic complex was likely to act in the mechanism pathway.[480]

The inverse electron hetero-Diels−Alder reaction between different vinyl ethers **366** and *N*-benzilydeneaniline (**367**) has been accomplished using the chiral diol **249** and dichlorotitanium diisopropoxide (**58b**), giving a mixture of two possible diastereoisomers **368** and **369** (Table 49). In any case, the diastereomeric ratio and the enantioselectivity for all *cis* compounds **368** were good. The mixture of solvents used was critical to obtain the expected products since, for instance, the reaction in toluene alone failed.[481]

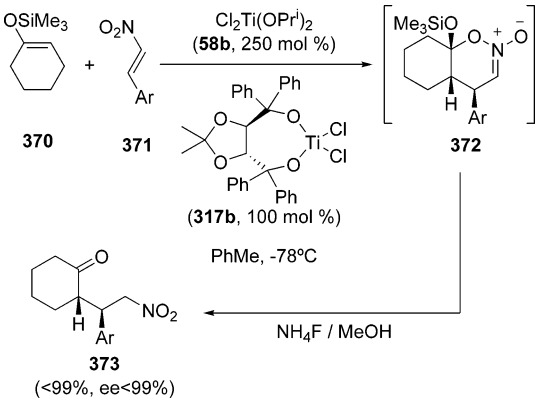
A really interesting enantioselective inverse electron demand hetero-Diels−Alder reaction is outlined in Scheme 101. The reaction of the silyl enol ether **370** with aryl nitroolefins **371**, in the presence of an excess of the titanium complex **58b** and the chiral complex **317b**, gave the expected bicyclic products **372.** After treatment with a fluoride source, ketones **373** were obtained, in general, with excellent results, as only one diastereoisomer. The whole process was a Michael-type-like addition.[482] The reaction was further expanded to other cyclic and acyclic silyl enol ethers with similar results, with the intermediate **372** also being trapped by reaction with alkynes.

Table 49. Enantioselective Inverse Electron Demand Hetero-Diels−Alder Reaction



entry	R^1	R^2	no.	yield (%)	ee (%)	no.	yield (%)	ee (%)
1	Et	H	**368a**	21	90	**369a**	44	50
2	-$(CH_2)_2$-		**368b**	35	82	**369b**	15	90
3	-$(CH_2)_3$-		**368c**	15	92	**369c**	45	10

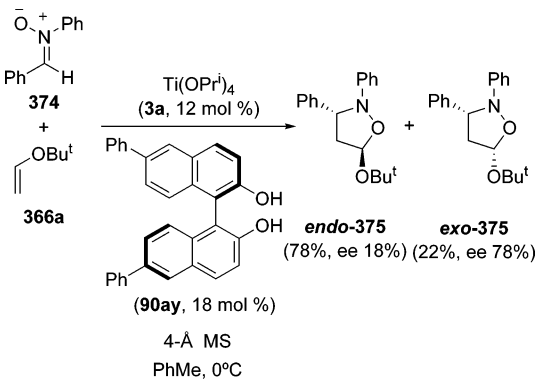
Scheme 101. Enantioselective Formal Michael Addition through an Inverse Electron Demand Hetero-Diels−Alder Reaction



6.2. [3+2]-Cycloaddition Reactions

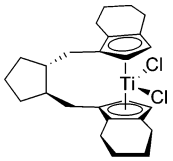
Enantioselective [3+2]-cycloaddition reactions are the most classical process to prepare compounds with different five-membered rings.[483] The reaction of the diphenyl nitrone **374** with *tert*-butyl vinyl ether (**366a**) in the presence of catalytic amounts of titanium tetraisopropoxide and the BINOL derivative **90ay** gave a mixture of heterocyclic compounds **375** with moderate or poor enantioselectivity (Scheme 102). After a great deal of effort, it was determined that he catalytic species was a tetranuclear titanium cluster

Scheme 102. Catalytic Enantioselective 1,3-Dipolar Cycloaddition



consisting of hexacoordinated titanium atoms where binaphthol units are directly bonded to different titanium atom centers and four hydroxyl groups (coming from the hydrolysis of the initial titanium isopropoxide complex with molecular sieves) are bridging three titanium centers (compare with structure **242**). This complex is extremely stable to aqueous acid or basic treatment.[484]

The use of other chiral ligands such as TADDOL or the bis(sulfonamide) **117a**,[485] as well as the titanocene **105j**,[486]

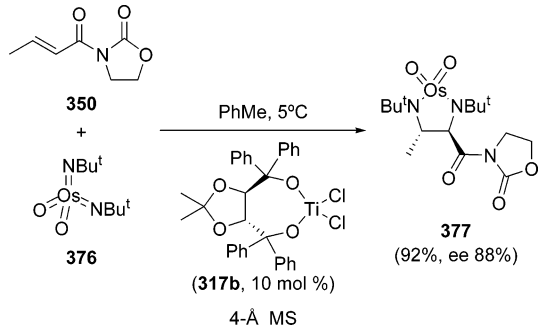


105j

did not improve the previous results using BINOL derivatives and electron-rich olefins. However, the reaction could be successfully performed using electron-poor olefins such as compound **350** and mixtures of ditosyltitanium diisopropoxide (**58e**) and polymeric TADDOL derivatives **118g**[204b] and **118l**[206] to yield the corresponding heterocyclic compound with diastereoselectivities and enantioselectivities around 90%, even after several reuses.

The final example of a [3+2]-cycloaddition is the diamination of the alkene **350** with bisimidoosmium oxidant **376** to yield the corresponding compound **377** (Scheme 103). The

Scheme 103. Catalytic Enantioselective Diamination Process



reaction gave the best results when the complex **317b** was prepared previously to its use; all attempts to reach the same level of enantioselectivity by *in situ* preparation of catalyst failed. Other chiral ligands tested, such as BINOL or diethyl tartrate, gave poor selection. Although the reaction was not limited only to compound **350** (other alkenoyl derivatives gave similar results), the use of the corresponding cynnamoyl derivative decreased the enantioselectivity.[487]

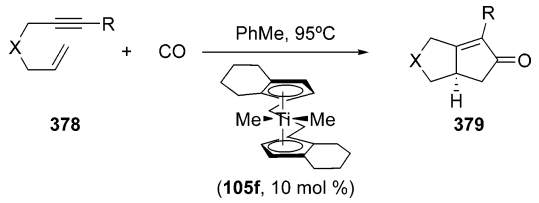
6.3. Pauson–Khand Reactions

The Pauson−Khand reaction[488] has also been catalyzed by some titanium complexes such as the titanocene **105f** (Table 50). The reaction of different enynes **378** with carbon monoxide at around atmospheric pressure (1.2 bar) in the presence of catalytic amounts of the titanocene **105f** gave the expected bicyclopentenones **379** with good results.[489] The reaction seems to be independent of the group X, whereas the substituent R has a slight influence on the enantioselectivity, with aromatic substituents giving the worst results.

6.4. Cyclopropanation Process

The enantioselective cyclopropanation reaction[490] can be performed using titanium complexes as shown in Scheme

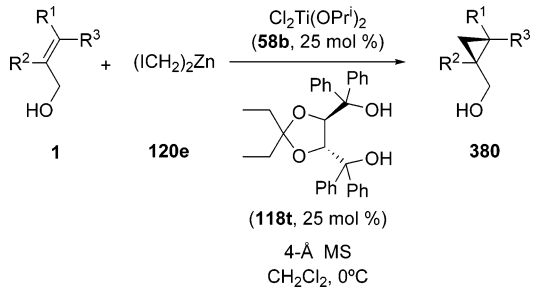
Table 50. Catalytic Enantioselective Pauson−Khan Reaction



entry	no.	X	R	yield (%)	ee (%)
1	**379a**	CH_2	Ph	87	70
2	**379b**	$C(CO_2Et)_2$	Me	87	90
3	**379c**	$C(CO_2Et)_2$	4-ClC_6H_4	90	82
4	**379d**	O	Ph	96	85
5	**379e**	$NCH_2CH{=}CH_2$	Me	94	91
6	**379f**	$NCH_2CH{=}CH_2$	Ph	92	81
7	**379g**	NBoc	Me	92	82

51. The reaction of bis(iodomethyl)zinc (**120e)** with different allylic alcohols **1** in the presence of dichlorotitanium diisopropoxide (**58b**) and the TADDOL derivative **118t** yielded the expected cyclopropyl methyl alcohols **380**. A complete and exhaustive study of all parameters of the reaction, such as the chiral ligand, the source of titanium, temperature, solvent, the presence of molecular sieves, and the zinc reagent, was performed, and the best conditions are outlined in Table 51. The substitution and the relative position on

Table 51. Catalytic Enantioselective Cyclopropanation Reaction



entry	no.	R^1	R^2	R^3	yield (%)	ee (%)
1	**380a**	Ph	H	H	85	94
2	**380b**	4-$MeOC_6H_4$	H	H	90	92
3	**380c**	4-ClC_6H_4	H	H	81	82
4	**380d**	2-furyl	H	H	73	92
5	**380e**	(*E*)-PhCH=CH	H	H	75	84
6	**380f**	H	H	Ph	62	72
7	**380g**	Ph	H	Me	80	88
8	**380h**	Ph	Me	H	80	50
9	**380i**	H	H	Pr	87	49
10	**380j**	Me	H	Me	89	72

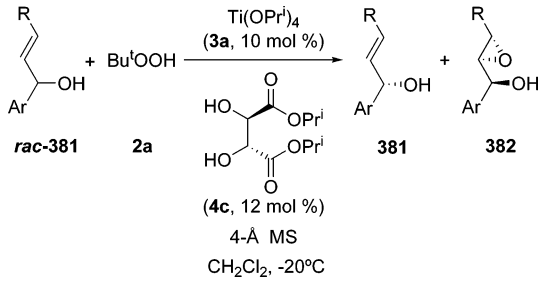
the allylic alcohol **1** are of vital importance in order to get excellent results.[491] Generally, higher enantioselectivities were obtained with *E*-alcohols rather than with their corresponding *Z*-isomers. In the same sense, the enantioselectivities for 3,3-disubstituted alcohols were higher than those for the related 2,3-ones. Quite interesting is the cyclopropanation of dienol derivatives, which produced only the monocyclopropanation with good enantioselectivity. Finally, it should be pointed out that the study of enantioselectivity *versus* chemical yield excluded the possibility of any autoinduction or autopoisoning effect, with the enantiomeric excess being practically constant over the reaction time.

7. Kinetic Resolution Processes

Despite the impressive progress in asymmetric synthesis, the dominant production method to obtain a single enantiomer on an industrial scale still consists of the resolution of racemates.[492] The resolution of a racemate could be divided into four main categories: (a) preferential crystallization, (b) crystallization of diastereomeric salts, (c) chromatography, and (d) kinetic resolution. The main inconvenience of the best procedure is the theoretical maximum yield of 50%, as well as the ecological−economical problem with the other 50% of product. The kinetic resolution is based on a high difference between the reaction rates of both enantiomers with a chiral reagent; in the ideal case, only one enantiomer reacts with the chiral regents to produce a new compound, while the opposite enantiomer remains unchanged. Although any reaction might be used in this section, only oxidation, reduction, and rearrangement processes have been utilized for that purpose. Following the general structure of this review, the epoxidation process will be introduced first.

The Sharpless epoxidation has been widely used for the kinetic resolution of different alcohols. The epoxidation of different substituted benzylic alcohols has been used to prepare either chiral alcohols **381** or epoxide derivatives **382** (Table 52). The different reaction rates between both

Table 52. Catalytic Enantioselective Kinetic Epoxidation of Benzylic Alcohols



entry	Ar	R	no.	yield (%)	ee (%)	no.	yield (%)	ee (%)
1	Ph	H	**381a**			**382a**	nd[a]	74
2	Ph	Ph	**381b**	42	>99	**382b**	52	90
3	4-$O_2NC_6H_4$	H	**381c**			**382c**	45	95
4	4-$MeSC_6H_4$	H	**381d**			**382d**	43	95

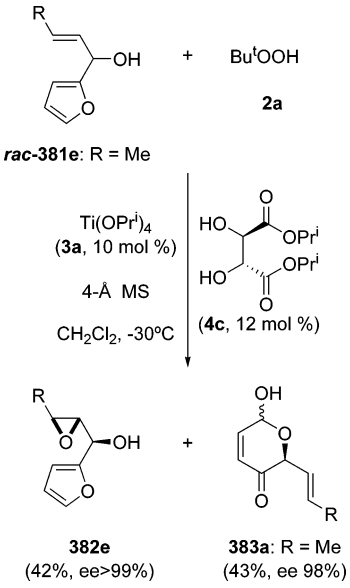
[a] Not determined.

enantiomers are so high that the reaction is usually stopped at 50% conversion, with the enantioselectivity being very high for both the remaining allylic alcohol and the newly formed epoxide.[493] The final epoxides of type **382** (or their enantiomers ***ent*-382**) have been used as chiral starting material in the synthesis of chromenes, diols, and pharmacologically active compounds such as (−)-chloroamphenicol and thiamphenicol.

A special case is the kinetic resolution of alcohols ***rac*-381e**, since the catalytic Sharpless epoxidation at 50% conversion gave a mixture of the expected epoxide **382e** and the pyranone **383a**, both with excellent enantioselectivity (Scheme 104). The chiral epoxide **382e** was further transformed into (+)-asperlin,[494a] which is a lactone with antitumor and antibacterial activities. The reaction with the related alcohol ***rac*-382f** (R = Ph) gave similar results, with the corresponding pyranone **383b** (R = Ph) having been used as the starting chiral material for the synthesis of isoaltholactone, isolated from plants of the *goniothalamus* family, which has different activities, including antitumor, antifungal, and antibacterial properties.[494b]

The aforementioned enantioselective kinetic resolution of allylic alcohols has been employed as the first step in the

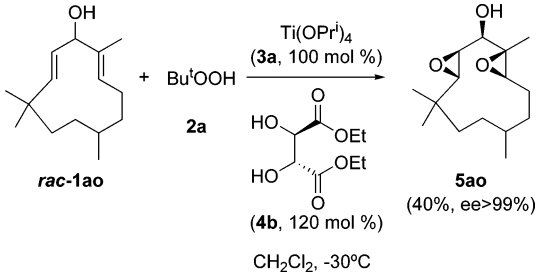
Scheme 104. Catalytic Enantioselective Kinetic Epoxidation of Alcohols *rac*-381e



homologation of functionalized allylic alcohols which, after resolution and reaction of the obtained chiral epoxide with trimethylsulfanyl ylide, yielded a new allylic diol.[495] A similar procedure has been performed for the preparation of different hydroxy lactones.[496]

The example outlined in Scheme 105 is probably more interesting, since the double epoxidation of the alcohol

Scheme 105. Enantioselective Kinetic Double Epoxidation of the Alcohol *rac*-1ao

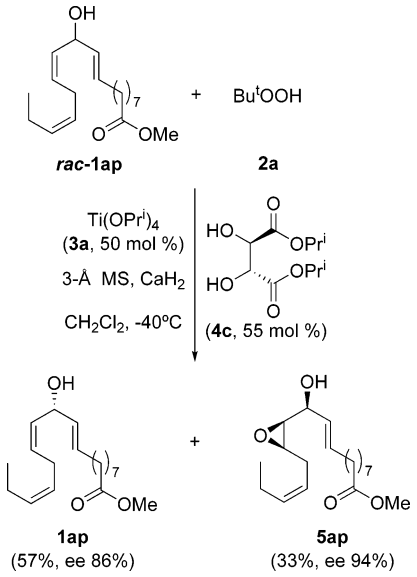


***rac*-1ao** gave the epoxide **5ao** with an excellent enantiomeric excess as the only product and the corresponding remaining alcohol **1ao** was unstable on the reaction medium and decomposed.[496] In this way a compound with five different stereogenic centers, one of them being quaternary,[18c] could be prepared in only one synthetic step.

The monoepoxidation in double allylic systems seems to be more complicated since, apart from the expected high difference of reaction rate between both enantiomers, the chiral reagent must discriminate between two similar double bonds. However, the monoepoxidation has been successfully accomplished by using standard protocols (Scheme 106). The epoxidation using only half the amount of *tert*-butyl hydroperoxide (**2a**) gave only one epoxide **5ap**, with the reaction proceeding with total regio- and diastereoselectivity.[498,499]

Electron-deficient alkenes are less susceptible to electrophilic epoxidation than their electron-rich analogues. However, α,β-unsaturated aldehydes can be epoxidated just by temporal conversion into the corresponding cyanohydrins. The enantioselective Sharpless epoxidation of *in situ* prepared allylic alcohols gave a mixture of the starting cyanohydrin

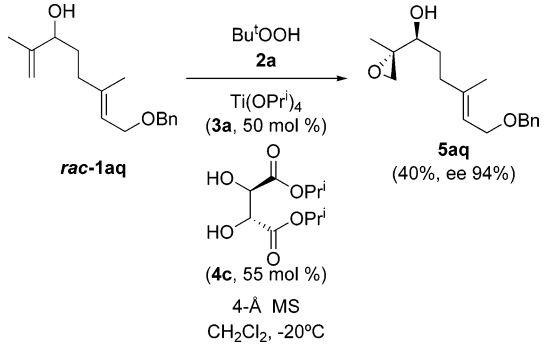
Scheme 106. Enantioselective Kinetic Monoepoxidation of the Alcohol *rac*-1ap



and epoxide derivatives with reasonable enantioselectivities (never higher than 87%).[500]

An example of kinetic resolution when forming quaternary carbon stereocenters has previously been presented (Scheme 105), but there are more examples of this type, such as that shown in Scheme 107. The kinetic resolution of the alcohol

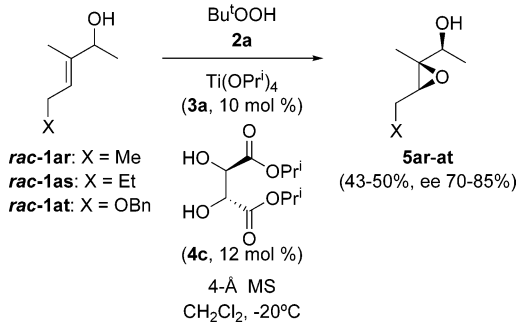
Scheme 107. Enantioselective Kinetic Resolution of the Alcohol *rac*-1aq



***rac*-1aq** provided the corresponding epoxy alcohol **5aq** with excellent enantioselectivity,[501] which was the starting material in the synthesis of a methyl isosartortuoate precursor.

Other racemic mixtures of allylic alcohols ***rac*-1ar-at**, which have been resolved kinetically by an enantioselective epoxidation, are presented in Scheme 108. The major isolated

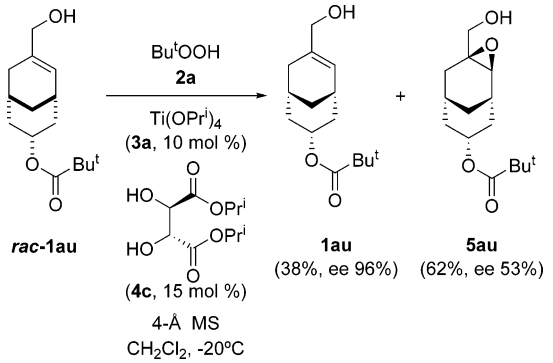
Scheme 108. Preparation of Chiral Epoxy Alcohols Containing a Quaternary Stereocenter by Enantioselective Kinetic Resolution of Allylic Alcohols



chiral epoxides were the corresponding *erythro* derivatives **5ar-at**, which were obtained with nearly the maximum possible chemical yield for this type of reaction.[502] Chiral compounds **5ar** and **5as** were used as the source for the corresponding silyl enol ethers which were trapped by reaction with different aldehydes with a normal Felkin−Ahn preference. The alcohol **5at** was used as starting material in the synthesis of different highly substituted tetrahydrofurans, as well as in the synthesis of the C1−C2 and C9−C17 fragments of amphidinolides O and P.

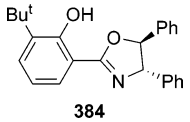
The last example of a kinetic resolution by epoxidation appeared in the synthesis of different modified adamantane derivatives (Scheme 109), in which the asymmetric key step

Scheme 109. Enantioselective Kinetic Resolution of the Allylic Alcohol *rac*-1au



was the resolution of the alcohol ***rac*-1au** using standard substoichiometric conditions. In this way, the corresponding epoxide **5au** (which was abandoned) and the chiral alcohol **1au** (which was the chiral starting point in the synthesis of chiral substituted adamantane derivatives) were obtained.[503]

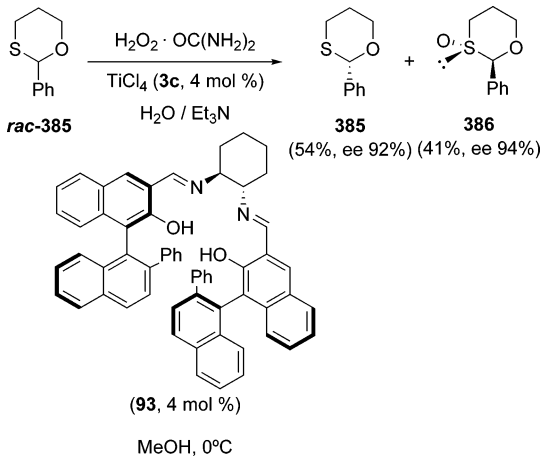
The kinetic resolution strategy has also been amply used in the preparation of chiral sulfoxides. In these cases, two processes are usually coupled: the first step is the already presented titanium-catalyzed enantioselective oxidation of thioethers followed by an *in situ* kinetic resolution of the sulfoxide by a second oxidation to a sulfone. In this way, and using BINOL (**90a**) as chiral ligand and *tert*-butyl hydroperoxide (**2a**) as oxidant under similar conditions to those presented in Table 3, the results could be clearly improved as far as the enantioselectivity is concerned, with the chemical yield being reduced by the formation of an achiral sulfone (62%, ee >99 for sulfoxide **77j** and 65%, ee>99 for sulfoxide **77k**).[504] The only change was the initial amount of the oxidant and the temperature, since the maximum enantioselectivity was not the same for the first process as that for the second one. The reaction started at 0 °C for the enantioselective sulfoxidation process, and after 10 h it was warmed to 20 °C for the kinetic resolution of the formed sulfoxide. This strategy has also been used with other chiral ligands such as the oxazoline **384**[505] and diethyl tatrate (**4b**)[506] but with rather less success.



384

Another example of kinetic resolution is the enantioselective oxidation of 2-substituted 1,3-oxathianes (Scheme 110), in which two different stereochemical problems have to be solved. The first one is the obvious different reaction

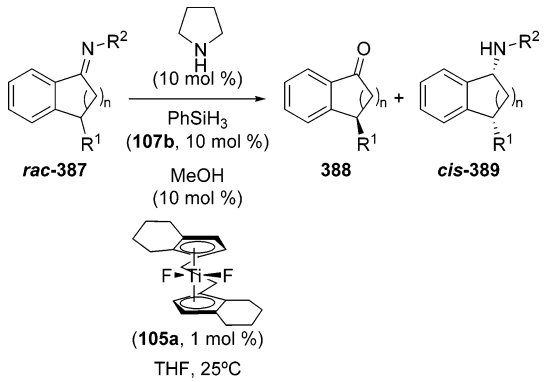
Scheme 110. Enantioselective Kinetic Resolution of 2-Phenyl-1,3-oxathiane (*rac*-385)



rate between both starting enantiomers, which is inherent to any kinetic resolution, but here there is a second problem which is the diastereoselection. In the case of 5-phenyl-1,3-oxathiane (***rac*-385**), the oxidation using a urea−hydrogen peroxide complex and substoichiometric amounts of bimetallic complex **95** (obtained by reaction of ligand **93** with titanium tetrachloride and partial hydrolysis, see Scheme 48) proceeded with excellent both diastereoselectively (only the *trans*-isomer detected) and enantioselectivity.[507] Other assayed 2-substituted 1,3-oxathianes showed the same tendency (only one diastereoisomer), but with worse enantioselectivity.

The kinetic resolution of 3-substituted indanone imines and 4-substituted tetralone imines (***rac*-387**) has been accomplished by catalytic enantioselective reduction using the titanocene complex **105a** (Table 53). The reaction was

Table 53. Catalytic Enantioselective Kinetic Resolution of Imines



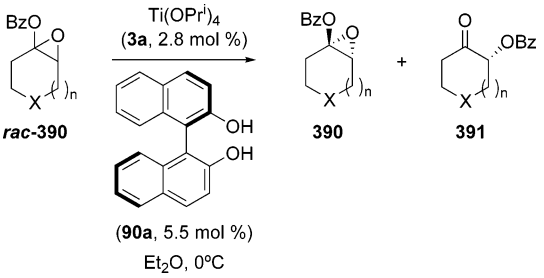
entry	*n*	R^1	R^2	no.	yield (%)	ee (%)	no.	yield (%)	ee (%)
1	1	Me	Me	**388a**	42	92	***cis*-389a**	52	94
2	1	Ph	Me	**388b**	48	83	***cis*-389b**	46	95
3	1	Me	Pr^n	**388c**	50	66	***cis*-389c**	44	90
4	1	Ph	Pr^n	**388d**	41	84	***cis*-389d**	52	86
5	2	Me	Me	**388e**	45	96	***cis*-389e**	50	95
6	2	Ph	Me	**388f**	38	98	***cis*-389f**	55	89

promoted by pyrrolidine and methanol, giving, after quenching, a mixture of the ketone **388** and the amine ***cis*-389**. As in all kinetic resolution processes, the enantioselectivity depends on the conversion, and in this case with around 50% conversion, the enantiomeric excesses for both products are good. The enantioselectivity clearly depended on the size of the *N*-substituent (the smaller this substituent, the higher

the enantioselectivity found) but not on the size of other substituents. It should be pointed out that, together with the amine ***cis*-389**, a small amount of the corresponding *trans*-derivative could be isolated with chemical yields less than 10%.[508] This protocol has been further extended to 2,5-disubstituted pyrrolines, obtaining similar results.[509]

The rearrangement of epoxides ***rac*-390** to give α-acyloxy ketones **391** has been used as the prototype reaction for the preparation of chiral compounds **390** (Table 54). A wide

Table 54. Catalytic Enantioselective Kinetic Resolution of Enol Ester Epoxides

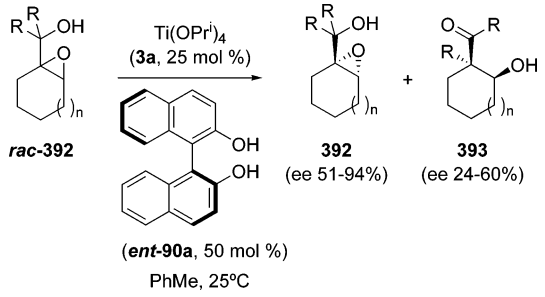


entry	*n*	X	no.	yield (%)	ee (%)	no.	yield (%)	ee (%)
1	0	CH_2	**390a**	49	91	**391a**	50	92
2	1	CH_2	**390b**	49	97	**391b**	50	90
3	2	CH_2	**390c**	45	99	**391c**	54	78
4	3	CH_2	**390d**	36	97	**391d**	63	71
5	1	O	**390e**	48	98	**391e**	51	93

variety of metals, as well as chiral diols and bis(sulfonamides), were tested, and it was found that BINOL (**90a**), in combination with titanium tetraisopropoxide (**3a**), was the best ligand.[510] The ratio of chiral ligand to metal was very important for both the reactivity and selectivity, with the best results being obtained when two or more equivalents of the chiral ligand were used per mole of titanium. The enantioselective rearrangement takes place in a few hours to give, after conversions around 50%, a mixture of the chiral epoxide **390** and α-acyloxy ketones **391** with, in general, excellent enantiomeric excess. The absolute configurations of the remaining epoxide **390** and the ketone **391** suggest that the reaction takes place through a complexation of the chiral Lewis acid with the epoxidic oxygen atom. Then, the carbonyl moiety acts as a nucleophile in an intermolecular S_N2 type reaction, rendering an inversion at the stereogenic carbon atom of the ketone. Another important aspect, which complicates the mechanistic understanding, is the presence of an important positive nonlinear effect.[138] The scope of the reaction seems to be limited to cyclic epoxides since the related acyclic epoxides gave very poor results. Finally, it should be pointed out that chiral epoxides **390** could be transformed into ketones **391** with retention of the configuration and good chemical yields by treatment with an achiral sulfonic acid. This last process represents a very elegant solution for the main problem of the kinetic resolution, which is the 50% maximum chemical yield.

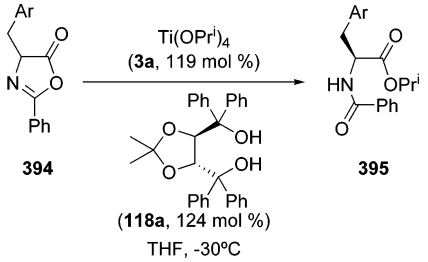
A related reaction was further reported for the kinetic resolution of epoxides ***rac*-392**, derived from allylic alcohols (Scheme 111). However, in this case with conversions around 65%, the results were accountably lower than those for the precedent rearrangement. In addition, the amount of catalyst needed was higher than that for compound ***rac*-390** and the presence of traces of impurities, such as 2-propanol (which arose from the preparation of catalyst), had an important detrimental effect on the enantioselectivity.[511]

Scheme 111. Enantioselective Kinetic Resolution via Semipinacol Rearrangement



The main problem of the simple kinetic resolution of a racemic mixture is the presence of important amounts of the starting material (around 50%). However, this low yield could be improved if the final chiral undesired compound or any intermediate can be racemized very fast or transformed into the initial racemic mixture. In this way the theoretical maximum chemical yield can change from 50 to 100% thanks to the *in situ* recycling of the substrate. This process, called dynamic kinetic resolution (or asymmetric transformation),[512] has been used in the resolution of azlactones **394** by treatment with titanium tetraisopropoxide and TADDOL (**118a**) to yield the corresponding α-amino esters **395** (Table 55), with the whole process involving a typical kinetic

Table 55. Catalytic Enantioselective Dynamic Kinetic Resolution of Azalactones

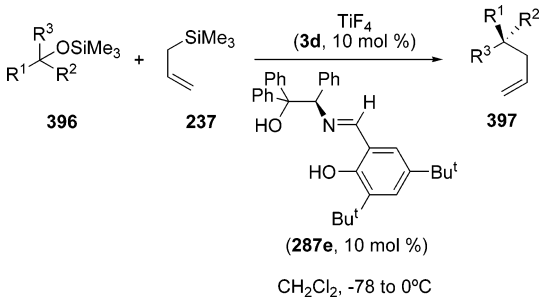


entry	no.	Ar	yield (%)	ee (%)
1	**395a**	4-MeC_6H_4	60	60
2	**395b**	4-$MeOC_6H_4$	65	54
3	**395c**	4-ClC_6H_4	48	64
4	**395d**	1-naphthyl	67	54
5	**395e**	2-thienyl	74	72

resolution (ring opening by a nucleophilic attack of the isopropoxide anion) and fast racemization of the starting azlactone due to an acid−base process. Although the enantioselectivity was not very good, it can be improved up to 99% just by simple recrystallization of compounds **395**. The method did not work with azlactones having nonaromatic substituents, and the amount of the chiral ligand could not be reduced.[513]

Another interesting example is the catalytic enantioselective dynamic kinetic transformation of silyl ethers **396** into allylic compounds **397** (Table 56). The reaction was catalyzed by substoichiometric amounts of titanium tetrafluoride (**3d**) in the presence of the chiral salen ligand **287e** with excellent results for benzylic derivatives, including acyclic and cyclic materials. However, for non-benzylic ethers, the enantiomeric excess dropped drastically. The essentially complete conversion of the racemic substrate into the allylation products **397** was rationalized by an enantioselective dynamic kinetic transformation. It was assumed that the

Table 56. Catalytic Enantioselective Dynamic Kinetic Transformation of Silyl Ethers



entry	no.	R^1	R^2	R^3	yield (%)	ee (%)
1	**397a**	Ph	Me	H	62	90
2	**397b**	1,2-$C_6H_4(CH_2)_2$		Me	96	99
3	**397c**	1,2-$C_6H_4(CH_2)_3$		Me	96	93
4	**397d**	$(CH_2)_4N(Cbz)$		H	82	56

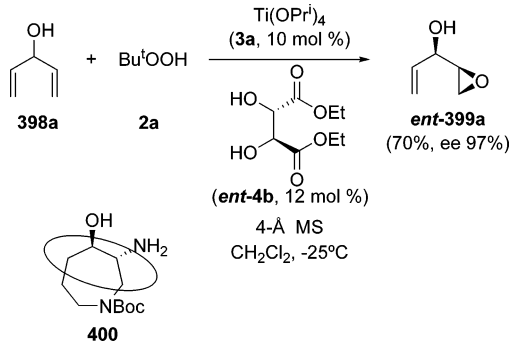
chiral titanium Lewis acid and both enantiomers of the silyl ether **396** form two diastereomeric contact ion pairs, which rapidly equilibrate via the planar classical achiral carbenium ion. In the subsequent reaction with allyl trimethylsilane (**237**), one of the diastereomeric ion pairs was postulated to react distinctly faster than its diastereomer, yielding the final product. Presumably the allyl residue attacks the cation from the face that is not occupied by the titanium.[514]

8. Enantioselective Desymmetrization Reactions

The efficient differentiation between two enantiotopic groups or centers related by any improper symmetry element, usually a plane, in an achiral molecule possessing a C_s, C_i, S_4, etc. symmetry is defined as desymmetrization.[515] Enantioselective desymmetrization is one of the most effective strategies for the synthesis of chiral compounds in which several different stereoelements are created simultaneously. Some processes covering this strategy have already been presented in the previous section due to their illustrative value. The rest of the examples are presented in this section, following the general structure of this review.

The Sharpless epoxidation has been used as an enantioselective reaction for the desymmetrization of different achiral bishomoallylic alcohols. Thus, the catalytic enantioselective monoepoxidation of the alcohol **398a** using the chiral tartrate ***ent*-4b** yielded the alcohol ***ent*-339a** with excellent enantioselectivity (Scheme 112), which was the key

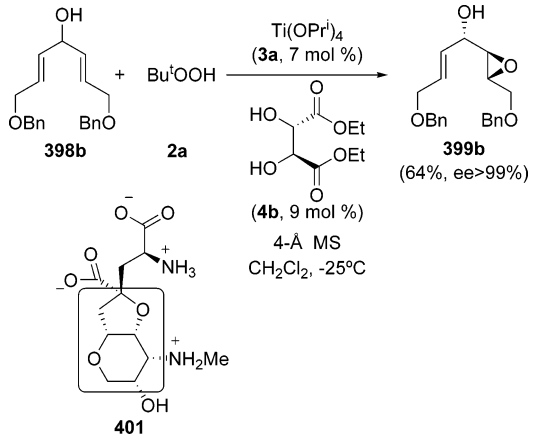
Scheme 112. Catalytic Enantioselective Desymmetrization of the Alcohol 398a



step in the synthesis of hexahydroazepine **400**.[516] The same desymmetrization reaction but using the ligand **4b** yielded the enantiomeric alcohol **399a**, which in turn was used as starting material in the synthesis of different *N*-hydroxypyrrolidine diols, through a Cope−House cyclization process.[517]

In the synthesis of (−)-dysiherbaine **401**, which is a potent neurotoxin isolated from the sponge *Dysidea herbacea*, the first step was the catalytic enantioselective desymmetrization of the alcohol **398b** to give the epoxide **399b** as only one enantiomer (Scheme 113). In this way with only one

Scheme 113. Catalytic Enantioselective Desymmetrization of the Alcohol 398b

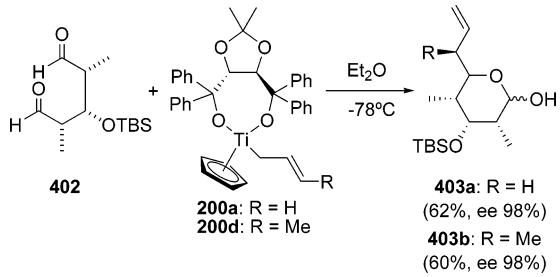


synthetic step, many different functional groups could be obtained.[518] This strategy has been used in the preparation of *syn*-1,3-diols, but using in this case the related alcohol with *Z*-geometry at the alkene moieties.[519]

An analogous desymmetrization of *meso*-decalin diallylic alcohols has been used as the key step in a novel approach to the synthesis of polyhydroxylated *celastraceae* sesquiterpene cores. Surprisingly, the reaction gave better results using zirconium alkoxide instead of the standard titanium tetraisopropoxide (**3a**).[520]

The allylation of the aldehyde **402** using titanium complexes **200a,d** has been used in a desymmetrization process to yield the lactol **403** with good results (Scheme 114),

Scheme 114. Enantioselective Desymmetrization of the Dialdehyde 402

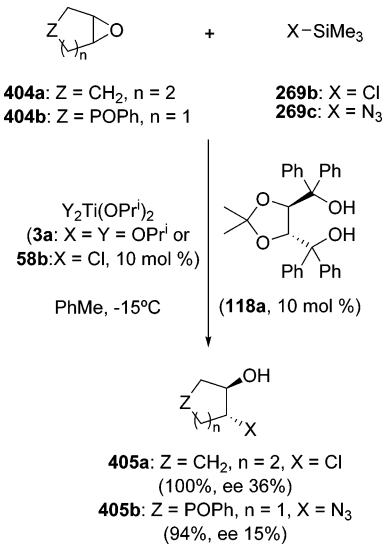


although the diastereoisomer arising from the reaction with the enantiotopic carbonyl compound could be detected in amounts ranging from 10 to 15%.[521] In this way, highly functionalized 1,3-diol derivatives could be obtained, as well as different subunits of scytophycin, rifamycin S, and discodermolide.

The catalytic enantioselective ring opening of different epoxides though an S_N2 process has been used to obtain, after hydrolysis, the corresponding alcohols. Thus, the reaction of the cyclohexene oxide (**404a**) with trimethylsilyl chloride (**269b**) in the presence of substoichiometric amounts of dichlorotitanium diisopropoxide (**58b**) and the TADDOL

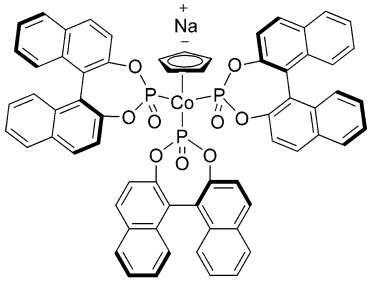
ligand **118a** at low temperature yielded the expected chlorohydrin **405a** with excellent chemical yield but with very modest enantioselectivity (Scheme 115).[522] The results were

Scheme 115. Catalytic Enantioselective Desymmetrization of Epoxides 404



similar when the reaction was performed using the phospholene epoxide **404b** as starting material, trimethylsilyl azide (**269c**) as the source of the nucleophile, and the less acidic Lewis acid titanium tetraisopropoxide (**3a**) and TADDOL **118a**, rendering after hydrolysis the corresponding alcohol **405b**.[523]

The mixture of the more complicated cyclopentadienyl-containing ligand ***ent*-406** (2 mol %) with the same amount

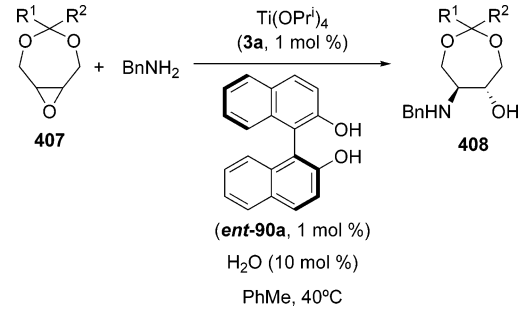


***ent*-406**

of dichlorotitanium diisopropoxide (**58b**) formed an active catalyst able to promoted the ring opening of cyclohexene oxide (**404a**) by trimethylsilyl azide (**269c**) to yield the expected alcohol **405c** (Z = CH_2, n = 2, X = N_3) in 74% yield and 23% enantiomeric excess.[524] All these modest results pointed out the inherent problems concerning the source of the high activity of the nucleophile and of the deactivation of the highly oxophilic catalyst by reaction with the final alcohol.

The reduction of the reactivity of the nucleophile improved the results of this type of desymmetrization. So, the reaction of benzylamine with different epoxides **407** catalyzed by substoichiometric amounts of titanium tetraisopropoxide (**3a**) and the chiral ligand ***ent*-90a** in the presence of water yielded the expected alcohols **408** (Table 57). Under these conditions, the catalyst did not interact with the final alcohols, probably due to the presence of water. The scope of substrate for this reaction is very limited since other epoxides did not react under similar conditions.[525] On the other hand, the replace-

Table 57. Catalytic Enantioselective Desymmetrization of Epoxides 407

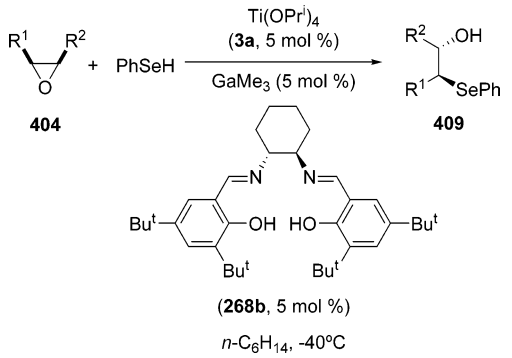


entry	R^1	R^2	no.	yield (%)	ee (%)
1	H	H	**408a**	56	20
2	Me	Me	**408b**	80	92
3	-$(CH_2)_5$-		**408c**	94	93

ment of the amine by 4-substituted thioanisol produced a strong decrease in the enantioselectivity (lower than 41%) in its reaction with cyclohexene oxide (**404a**).[526]

Despite all the former modest results, very recently a new protocol for the desymmetrization of epoxides giving good results has been discovered (Table 58). The goal of this

Table 58. Catalytic Enantioselective Desymmetrization of Epoxides 404 Using a Bimetallic Catalyst

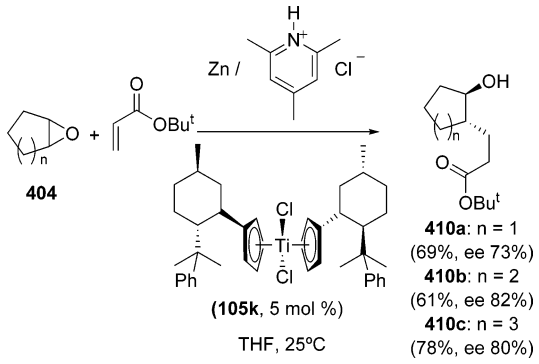


entry	R^1	R^2	no.	yield (%)	ee (%)
1	Me	Me	**409a**	87	87
2	Ph	Ph	**409b**	70	72
3	-$(CH_2)_3$-		**409c**	85	94
4	-$(CH_2)_4$-		**409d**	94	97
5	1,2-$CH_2C_6H_4CH_2$-		**409e**	92	90

procedure is the preparation of a chiral bimetallic catalyst derived from gallium and titanium. Thus, for example, the desymmetrization of cyclohexene oxide (**404a**) with selenophenol using substoichiometric amounts of the bimetallic complex obtained by reaction of the chiral salen ligand **268b** with titanium tetraisopropoxide (**3a**) and trimethyl gallium yielded the expected alcohol **409d** with excellent results. However, when the reaction was performed using the homometallic catalyst obtained by mixing only either trimethyl gallium or titanium tetraisopropoxide with the chiral salen **268b**, it gave the same alcohol **409d** but with lower enantioselectivities (35 and 39% ee, respectively).[527] This great increase in the enantioselectivity was explained assuming a synergistic work of both metallic centers, with the harder Lewis acidic titanium atom coordinating the oxygen atom of the epoxide and the softer Lewis acidic gallium atom chelating the selenium derivative, with both metals being chelated by the same chiral ligand.

The last example of this section is a very elegant and unique example of desymmetrization involving an electron transfer.[528] The titanocene **105k** was able to coordinate and asymmetrically transfer an electron to different epoxides **404** to give the corresponding radical, which could be trapped by reaction with *tert*-butyl acrylate to yield the corresponding compounds **410** practically as an only diastereoisomer, with good chemical yields and enantioselectivities (Scheme 116).

Scheme 116. Catalytic Enantioselective Desymmetrization by an Electron Transfer Reaction

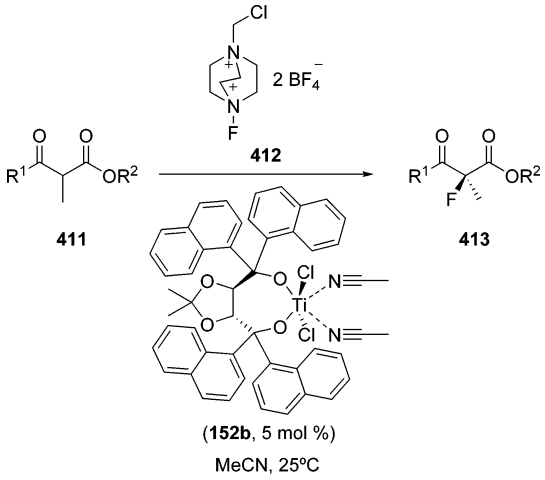


The reaction was also applicable to acyclic epoxides with excellent enantiomeric excesses (up to 92%), but in these cases, the chiral radical intermediate was tapped just by using water.

9. Miscellaneous Reactions

Although halogenated compounds serve as linchpins for further manipulations in organic synthesis, the number of protocols for the enantioselective preparation of these compounds has been remarkably scarce.[529] β-Ketoesters **411**, which are ideal candidates for halogenation reactions due to the relatively high acidity of their α-hydrogen atoms (pK_a ≈ 12), can form six-membered chelates with oxophilic Lewis acids at their carbonyl groups, thus promoting enolization of the β-ketone. Thus, the first catalytic enantioselective halogenation promoted by a titanium complex was performed using selectfluor (**412**) in the presence of the titanium complex **152b**,[530] giving the expected fluorinated compounds **413** with chemical yields ranging from 80 to 95% (Table 59). The enantioselectivity was strongly influenced by the size of the ester moiety (R^2) but not the size of the ketone substituent (R^1), with the best results being obtained for the most hindered esters. Mechanistically, the role of the Lewis acid consists of the activation of the nucleophile and not, as is more common, enhancement of the electrophilicity of the coordinated carbonyl group. The β-ketoester coordinates to the catalyst **152b** as an enolate substituting one of the two chlorines and one of the acetonitrile molecules. A density functional theory study showed the existence of eight possible chiral intermediates bearing the β-ketoester ligand. In particular, the most stable has the chlorine ligand in an axial position, with the equatorial plane being defined by the titanium center and the two coordinated TADDOL oxygen atoms. In this way the enolate fragment and one of the two face-on oriented naphthyl groups are almost perfectly parallel and, as a consequence, the *re*-face of the enolate is completely shielded and the fluorine atom is only delivered from the opposite side, predicting correctly the observed absolute configuration. The fluorine atom transfer was studied by QM/MM first-principles molecular dynamics, and

Table 59. Catalytic Enantioselective Fluorination of β-Ketoesters 411



entry	R^1	R^2	no.	ee (%)
1	Ph	Et	**413a**	62
2	Ph	Ph_2CH	**413b**	82
3	Et	Ph_2CH	**413c**	81
4	Et	2,4,6-$Bu^t_3C_6H_2$	**413d**	90

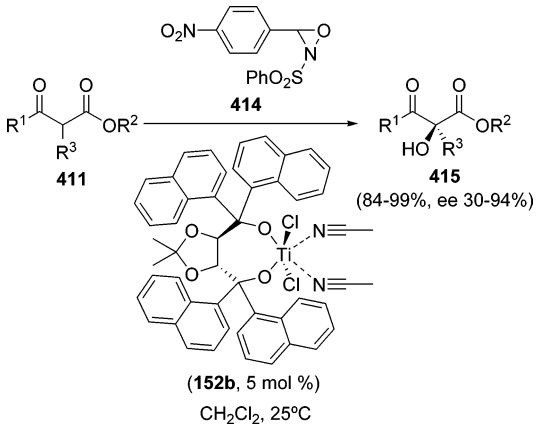
the results *in vacuo* indicated that the reaction proceeds by a single-electron transfer (SET) involving the formation of a [N−F]• radical. However, in acetonitrile solution, nonspontaneous SET was calculated. Despite these calculation studies, it should be pointed out that the relative stability of a cationic *versus* a radical form strongly depends on the temperature and the interaction with the solvent, with a SET process being possible before the transition state due to thermal fluctuations or dipole−charge interactions. In this case, a radical would be formed and could then react with the chloride present in solution, leading to the formation of the most stable chlorine radical, which is ultimately responsible for the observed chlorinated byproduct. The addition of a radical scavenger drastically diminished the amount of the chlorinated byproduct and, therefore, supported the SET mechanistic pathway for the halogen transfer.

The scope of reagents for the former reaction was increased by the use of *N*-chloro- and *N*-bromosuccinimide as halogenating compounds, yielding the corresponding α-chlorinated or α-brominated β-ketoesters. The enantioselectivity for the chlorination (ee never higher than 88%) was somewhat lower than that for the related fluorination. However, the bromo derivatives could not reach more than 23% ee.[531] As an alternative, dichloro(4-methylphenyl)iodine has been proposed as chlorinating agent, which did not introduce any significant improvement, neither in the results nor in the procedure.[532] Conceptually, the enantioselective double halogenation is more interesting,[533] since in a one-pot process it was possible to introduce two halogens (fluorine and chlorine) in the α position of a β-ketoester. The sequence of addition of the halogenating agents determines the absolute configuration of the final product, with the overall stereochemical outcome of the reaction being solely determined by the second enantioselective halogenation step.

Not only halogenation processes can be performed with the aforementioned protocol, but also other processes which involve the formation of a carbon−heteroatom bond, with the heteroatom being introduced as the electrophilic partner of the reaction. Thus, the oxidation of a different β-ketoester

411, or the related amides, has been performed following a similar protocol but using the oxaziridine **414** (Scheme 117).

Scheme 117. Catalytic Enantioselective Hydroxylation of *β*-Ketoesters 411

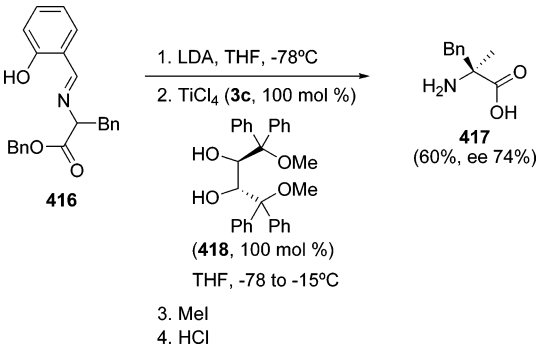


As in the halogenation process, the enantioselectivity was increased by increasing the steric hindrance of the ester residue, using in this case methylene chloride as the solvent. Another oxidant, such as dioxirane, can also be used, but the presence of traces of water in the reagents caused a progressive decomposition of the catalyst **152b** during the reaction and, therefore, decreased the product yield, although keeping the enantioselectivity. A possible mechanism for this transformation involves the epoxidation of the previously mentioned titanium-bound enolate form from the *β*-ketoester and subsequent ring opening to give the corresponding 2-hydroxylated 1,3-dicarbonyl derivative.[534]

Very recently, the use of phenylsulfenyl chloride as electrophilic sulfur agent has been introduced in the enantioselective sulfenylation of *β*-ketoesters **411** with good enantioselectivity for bulky ester derivatives.[535]

The electrophilic alkylation of enolates derived from α-amino acids has been used in the preparation of a α,α-disubstituted α-amino acid.[104] The deprotonation of the imine derivative **416** with lithium diisopropoyl amide at low temperature, followed by titanium metal exchange in the presence of the chiral diol **418**, yielded a chiral complex intermediate, which was trapped by reaction with iodomethane to give, after final hydrolysis, the α-amino acid **417** with moderate enantioselectivity (Scheme 118). Unfortu-

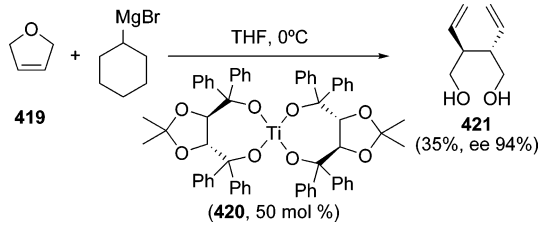
Scheme 118. Enantioselective Electrophilic Alkylation of Amino Acid Derivative 416



nately, the scope of the reaction is very narrow and only iodomethane can be used as electrophile. The use of other starting α-amino acid derivatives, as well as other chiral ligands such as TADDOL, BINOL, and tatrate esters, gave worse results.[536] All these facts have made that this approach for the synthesis of α-amino acids still practically unexplored.

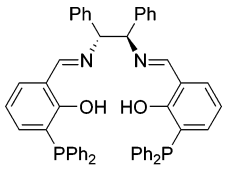
Another remarkable reaction is outlined in Scheme 119,

Scheme 119. Enantioselective Dihydrodimerization of 2,5-Dihydrofuran



in which the ring opening dimerization of 2,5-dihydrofuran (**419**) rendered diols **421** with an excellent enantioselectivity but with a very modest chemical yield.[537] The reaction of cyclohexylmagnesium bromide with the spiro titanate **420**, or another titanium alkoxide (Kulincovich reaction),[538] gave in this case a chiral titanium(II) intermediate bearing one TADDOLate and one cyclohexene moiety as ligands. The exchage of alkenes (cyclohexene by compound **419**) gave a new intermediate, which undergoes a ring opening process followed by a carbotitanation reaction with another equivalent of compound **419** to yield, after hydrolysis, the diol **421**.

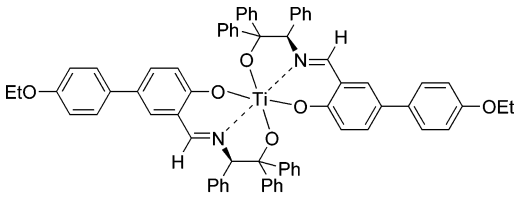
The chiral ligand **268e** has been used in combination with titanium tetraisopropoxide and rhodium salts in the enantioselective hydroformylation of vinyl acetate to give a mixture of linear and substituted aldehydes.[539] The supporting idea



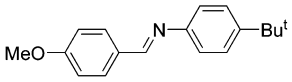
was that the *in situ* formed chiral bimetallic complex could combine the characteristic behaviors of both metals: the high enantioselectivity due to the rhodium salts as well as the favorable formation of branched aldehydes due to the titanium complexes. However, the results were very poor, with a total chemical yield of 21%, a 7:3 mixture of aldehydes, and an enantioselectivity of only 30%.

Chiral liquid crystalline compounds[540] are considered very interesting materials due to their technical applications, for example, in displays, polarizers, certain polymers, and paints or as coloring-effect materials. The chiral liquid materials have even been used as chiral promoters for enantioselective helical polyacetylene synthesis using achiral titanium alkoxides.[541] A particularly efficient and elegant route to chiral mesophases is based on the addition of small amounts of a chiral dopant to a nematic phase, so that the latter is converted into a cholesteric phase by helical arrangement in the previous nematic phase. The efficiency of a chiral dopant is quantified by its "helical twisting power", being dependent not only on the structure of the dopant but also on the nematic host compound. The bischelated titanium complex **422** displayed the highest helical twisting power value (740 μm^{-1}) reported so far, for the nematic phase obtained with imine **423**.[542] These values were measured in various nematic phases that differed significantly in their geometry and functional groups, and it seems that twisting is accomplished more easily when the size of the nematic molecule decreases,

as is the case for the imine **423**. Finally, it should be pointed out that the X-ray structure of complex **422** revealed that the ligands were arranged in a meridional position around the central titanium atom, which became a stereogenic center as a result of the complexation.

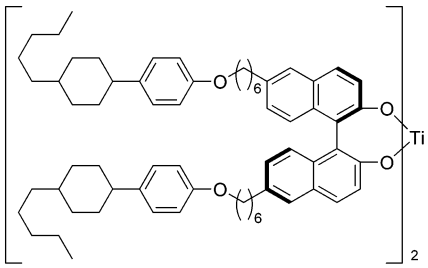


422

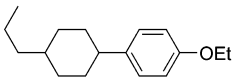


423

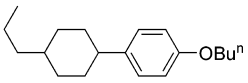
Titanium complex **424** has also been used as chiral dopant for the liquid crystal obtained from an equimolecular mixture of compounds **425**. In this case, the resulting chiral liquid crystal was used as catalyst for the asymmetric helical acetylene polymerization.[543] Other titanium complexes with different naphthyl tails used as chiral dopants gave lower values of helical twisting power.



424



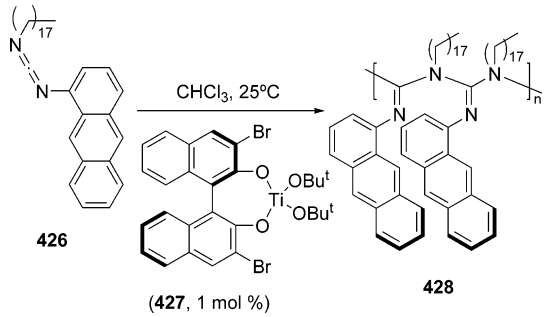
425a



425b

The last example comes from the asymmetric polymerization[544] of different carbodiimides catalyzed by chiral titanium complexes. Thus, the polymerization of the carbodiimide **426** in the presence of the chiral complex **427** yielded the well-defined regioregular and stereoregular chiral polymeric material **428** with a helix stereogenic element and a relatively narrow polymer dispersity index of 2.7 (Scheme 120). The surprisingly configurationally stable and chiral polymer results from the stereoselective orientation of both the aromatic substituents and the imine group, with the full racemization requiring more than 100 h in toluene at 80 °C.[545] Other assayed catalysts and monomers gave worse results.

Scheme 120. Enantioselective Polymerization of the Carbodiimide 426



10. Conclusions and Outlook

This report has shown the impressive amount of enantioselective synthetic uses that have been found for titanium catalysts and/or reagents in the last few years, from classical reactions such as 1,2- and 1,4-additions, Diels−Alder reactions, or oxidations and reductions to new procedures such as the enantioselective nucleophilic addition of "unreactive" organozinc reagents to poor electrophilic ketones, or the electrophilic α-halogenation of carbonyl compounds.

The types of reactions that can be catalyzed by titanium complexes are as ample as chemists' imaginations, and the improvements already achieved are impressive in some cases, although others are still in their early stages. Most importantly, completely new reactions have been exclusively promoted by titanium complexes. The economical, health, and environmental benefits compared to the use of other metal-based procedures are very significant.

Despite the impressive number of contributions and results obtained, however, many challenges remain. A better understanding of various processes, as well as the role of the aggregation of titanium complexes, is necessary, and there is room for improvement in both the scope and mildness of the reaction conditions for many of the described methods. Achieving higher turnover numbers of the catalytic cycles to favor a major impact on the industry can also be expected to be an area of major interest. Finally, one can reasonably anticipate that future studies will provide new applications, as well as a finer tuning of the reactions, with the opportunities of pursuing new protocols providing the driving force for future innovation in the fields of enantioselective reactions and chemistry as a whole.

11. Acknowledgments

The Spanish Ministerio de Educación y Deporte (Project CTQ2004-01261) and the Generalitat Valenciana (Projects GV05/157 and CTIDB/2002/318) are acknowledged for their continuous financial support. We thank Dr. Jaisiel Meléndez for the artistic preparation of Figure 1.

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