Chiral phosphine oxides in present-day organocatalysis†

Maurizio Benaglia* and Sergio Rossi

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The design and synthesis of new chiral Lewis bases is a field of extraordinary activity; in this context, while *N*-oxides derived from both *N*-heterocyclic systems and aliphatic amines have found widespread applications in organocatalysis, quite surprisingly phosphine oxides have been used less frequently. This contribution will highlight the relatively few examples of stereoselective transformations organocatalyzed by chiral phosphine oxides, discussing the different proposed reaction mechanisms and identifying topics for future investigation in what can be most certainly defined as an "Emerging Area".

Introduction

The design and synthesis of new chiral Lewis bases is a field of extraordinary activity, expression of the never ending research towards new catalytic systems of major efficiency and novel synthetic methodologies. Small organic Lewis bases, able to promote a wide variety of synthetic transformations, are protagonists of an incredibly rich chemistry that has been the subject of a recent, very comprehensive review.[1] They include different classes of compounds, such as naturally-occurring alkaloids and amino acids, but also synthetic amine-based catalysts and *N*-oxides. Also, phosphines have witnessed a renewed importance as Lewis basic organic catalysts; they are less basic but more nucleophilic than structurally related amines and endowed with easily adjustable electronic properties by a judicious choice of substituents; triarylphosphines are much less nucleophilic than trialkylphosphines, which are about 100 times stronger nucleophiles than trialkylamines, even if they are 100 times less basic.[2] It has been demonstrated that these unique properties of phosphines and amines may lead to different mechanistic pathways, so that the nature of the Lewis base may allow orientation of the course of reaction.[3]

While *N*-oxides derived from both heteroaromatic systems[4] and aliphatic amines[5] have found widespread application in organocatalysis, quite surprisingly phosphine oxides have been scarcely used. This is even more surprising if one thinks that very often chiral phosphine oxide derivatives are well known compounds, prepared in enantiomerically pure form basically through resolution processes, as precursors of the corresponding phosphines, widely employed as chiral ligands in organometallic catalysis.[6] It is true that the synthesis of enantiomerically pure phosphine oxide may be not straightforward, and the resolution process of the racemic mixture is not always easily accomplished. However if one considers the immense plethora of current commercial chiral phosphines it becomes immediately clear how many readily available phosphine oxides are ready to be investigated in Lewis base-organocatalyzed reactions.

Dipartimento di Chimica Organica e Industriale, Universita' degli Studi di Milano, Via Golgi 19, I-20133 Milano, Italy. E-mail: Maurizio.Benaglia@unimi.it

† Dedicated to Prof. Saverio Florio for his 70th birthday.

Maurizio Benaglia

Maurizio Benaglia was born in Bergamo in 1966. He received his laurea in Chemistry at the University of Milano in 1991 and his PhD in 1994 working with Prof. Mauro Cinquini. He spent two years as a postdoctoral fellow with Prof. Jay Siegel at the University of California at San Diego working on the stereoselective synthesis of supramolecular structures. He then returned to Milano, where he is now Associate professor. His research projects concern polymer supported catalysis; development of new synthetic methods; stereoselective organocatalysis; synthesis of chiral supramolecular systems and molecular devices.

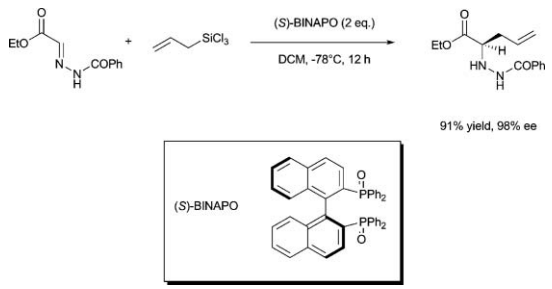
Sergio Rossi

Sergio Rossi was born in Bergamo in 1983. He received his laurea in Chemistry in 2007 and is currently completing his PhD program under the supervision of professor Maurizio Benaglia at the University of Milano. He is working on the synthesis of novel chiral heteroaromatic phosphine oxides and the development of new stereoselective reactions promoted by chiral Lewis bases.

This contribution will highlight the relatively few examples of phosphine oxide-organocatalyzed stereoselective transformations in what can be most certainly defined as an "emerging area".

Discussion

The first example of a reaction promoted by a chiral phosphine oxide[7] as chiral Lewis base may be considered the allyltrichlorosilane addition to *N*-benzoyl hydrazones reported by Kobayashi.[8] In that case, bis-(diphenylphosphanyl)-binaphthyl dioxide (BINAPO) was employed in the reaction of α-hydrazono esters (obtained from ethyl glyoxylate and benzhydrazide) with allyltrichlorosilane, affording the product in high yields and enantioselectivities at −78 °C in dichloromethane (Scheme 1). The reaction is stereospecific, in that (*E*)-crotyltrichlorosilanes afford the *syn* isomers, and (*Z*)-crotyltrichlorosilanes their *anti* counterparts.

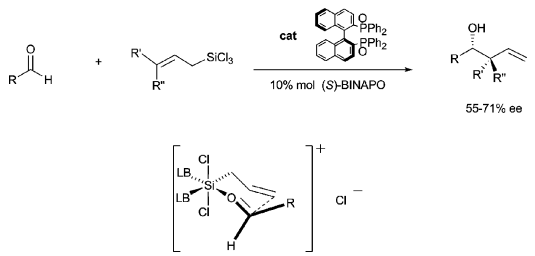


Scheme 1 Stereoselective addition of allyltrichlorosilane to hydrazones.

It must be noted that a more than stoichiometric amount of what was called *NCO* (Neutral Coordinate-Organocatalyst) was necessary in order to achieve high stereoselectivities, while 0.2 equivalents of BINAPO catalyzed the reaction in only 11% yield and 56% ee. Another drawback of the methodology is represented by the reductive cleavage of the N–N bond, accomplished by using SmI_2, required in order to obtain synthetically useful compounds. Even if the chiral source could be recovered without loss of stereochemical integrity, it is obvious that the reaction cannot be considered "organocatalyzed"; however, it has some merit since it represents the first example, and still one of the few cases, of enantioselective allylation of a carbon–nitrogen double bond involving a metal-free "promoter".[9]

One year later a true organocatalytic reaction promoted by chiral phosphine oxides was reported by Nakajima.[10] For the first time it was demonstrated that BINAPO can act as organocatalyst in the enantioselective addition of allyltrichlorosilane to aldehydes. Recently, different chiral Lewis bases have been developed for this kind of reaction involving polyhalosilanes.[1,11] Following preliminary studies by Hosomi[12] and Kobayashi,[13] in 1994 Denmark reported the first enantioselective, non-catalytic, addition of allyltrichlorosilane to aldehydes promoted by chiral phosphoroamides.[14] The reaction was shown to proceed *via* a chair-like transition state that involves hexacoordinated hypervalent silicates, in which the addition of (*E*)- and (*Z*)-silane affords stereospecifically the *anti*- and *syn*-product, respectively.[1] (Scheme 2)

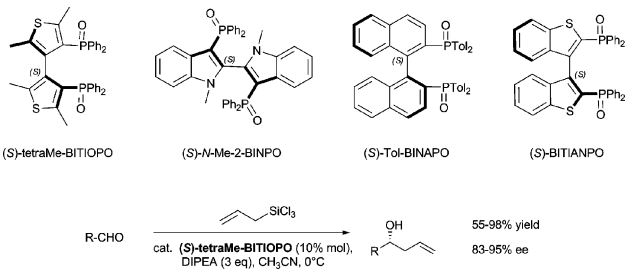
Nakajima showed that not only chiral phosphoroamides, pyridine *N*-oxides and formamidines,[1,11] but also chiral phosphine



Scheme 2 BINAPO-catalyzed stereoselective addition of allyltrichlorosilane to aldehydes.[10]

oxides may be used as organocatalysts for the allylation of aldehydes. In the presence of 10% mol amount of (*S*)-BINAPO the homoallylic alcohol was obtained in DCM in only 32% yield and 36% ee (Scheme 2). By employing a proper additive such as $Bu_4N^+I^-$ and 5 equiv. of DIPEA (*N*,*N*-diisopropyl ethyl amine) the yield was improved to 92% after only 4 h at room temperature, even if with still modest enantioselectivity (43% ee), definitely lower than that obtained with the best phosphoroamide-derived catalysts. The reduced chemical activity might be ascribed to the different electronic properties of the ligands. However, for this kind of reaction it had been already suggested that the effectiveness of a catalyst is determined not only by the donor properties of the Lewis base, but also by the steric hindrance at the oxygen atom.[15] For example, dimethylphosphinic *N*,*N*-dimethylamide is a better promoter for the allylation of benzaldehyde than methylphosphonic di-(*N*,*N*-dimethylamide) that, in turn, is better than HMPA (hexamethylphosphoric triamide). However, if in dimethylphosphinic *N*,*N*-dimethylamide a methyl group is replaced by an isopropyl group, the chemical efficiency of the catalyst dramatically decreases, clearly pointing at the importance of the steric accessibility of the oxygen atom.

A marked improvement of the catalytic efficiency of chiral phosphine oxides was obtained by our group exploring the characteristics of heteroaromatic systems (Scheme 3).[16] The advantages offered by the biheteroaryldiphosphine oxides, with respect to carbocyclic aromatic derivatives, reside in their greater synthetic accessibility and in the possibility of testing a series of catalysts displaying different electronic properties, where the influence of both the electronic availability of the heterocyclic system and of the position of the phosphorus atoms on the latter may be investigated.

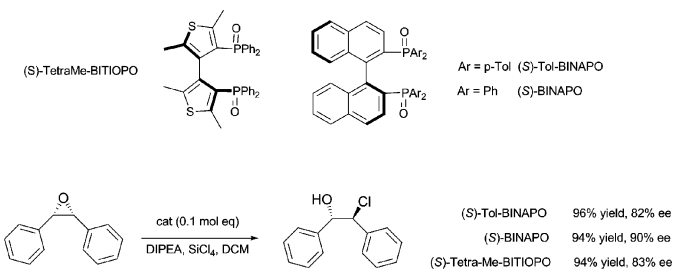


Scheme 3 (*S*)-TetraMe-BITIOPO-catalyzed addition of allyltrichlorosilane to aldehydes.

The most electron deficient diphosphine oxide BITIANPO did not promote the reaction in appreciable yields, while more electron-rich compounds showed a significant catalytic activity, promoting the addition of allyltrichlorosilane to benzaldehyde at 0 °C in higher yield (85%) than medium electron rich diphosphine

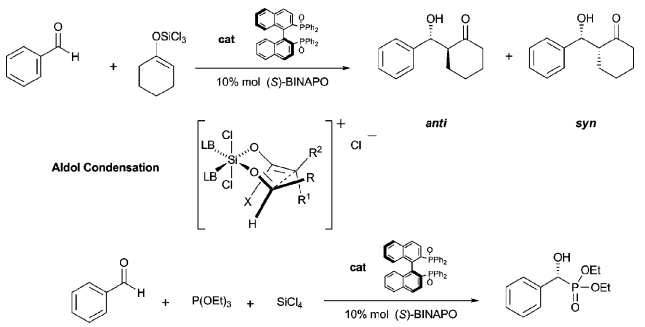
oxide Tol-BINAPO. Biheteroaromatic diphosphine oxides showed also an extraordinary ability in determining the stereochemical outcome of the reaction, being (*S*)-*N*-Me-2-BINPO able to catalyze the reaction in 81% ee, a result clearly higher than that obtained with (*S*)-Tol-BINAPO (51%). The catalyst of choice was found to be (*S*)-tetramethyl-bithiophene phosphine oxide, (*S*)-tetraMe-BITIOPO, which promoted the allylation of benzaldehyde in 93% ee, a very high level of enantioselectivity, comparable to those obtained with the best known organocatalysts. The same catalyst efficiently promoted the addition of allyltrichlorosilane to aromatic aldehydes bearing electron-withdrawing groups as well as electron-donating groups with enantioselectivities constantly higher than 90%.

An enantioselective ring opening of *meso*-epoxides catalyzed by BINAPO to give optically active chlorohydrins was also reported.[17] The ring opening of *meso*-stilbene oxide with a solution of tetrachlorosilane in dichloromethane using 10% mol (*S*)-BINAPO at −78 °C afforded smoothly the corresponding chlorohydrin in high yield and 59% ee. Only an extensive screening of the reaction conditions allowed individuation of diisopropylethylamine as the best additive necessary to increase enantioselectivity up to 90% ee. (*S*)-Tol-BINAPO catalyzed the reaction in 82% ee, a level of stereoselection comparable to that obtained with (*S*)-tetraMe-BITIOPO, that promoted the opening of *cis*-stilbene oxide in DCM at −78 °C in the presence of DIPEA, in quantitative yield and 81% ee (Scheme 4).[16]



Scheme 4 Lewis base-catalyzed stereoselective ring opening of epoxides.

BINAPO was also employed as organocatalyst in the stereoselective aldol reaction of trichlorosilyl enolethers; after seminal work by Denmark[18] with phosphoroamide-based catalysts, it was demonstrated that the reaction proceeds *via* a chair-like transition state involving a hypervalent silicate. Nakajima showed that also phosphine oxides may promote the condensation as well.[19] The aldol adduct was obtained in moderate yield and diastereoselectivity, with 82% enantioselectivity for the *anti* isomer (Scheme 5). By the addition of DIPEA both chemical and stereochemical efficiency was increased, the product being isolated at −78 °C in DCM in 94% yield, 86% of *anti* diastereoselectivity and 87% ee for the *anti* isomer. It was proposed that the tertiary amine additive not only may work as acid scavenger to neutralize the hydrogen chloride produced by adventitious hydrolysis of trichlorosilyl enolethers, but also it accelerates the reaction rate by promoting the dissociation of phosphine oxide from the silicon atom. The Lewis-base promoted condensation afforded *anti* adducts starting from (*E*)-silanes and *syn*-adducts from (*Z*)-silanes, confirming the hypothesis that a cyclic, six -membered transition state is involved, similarly to the allylation reaction (Scheme 5).

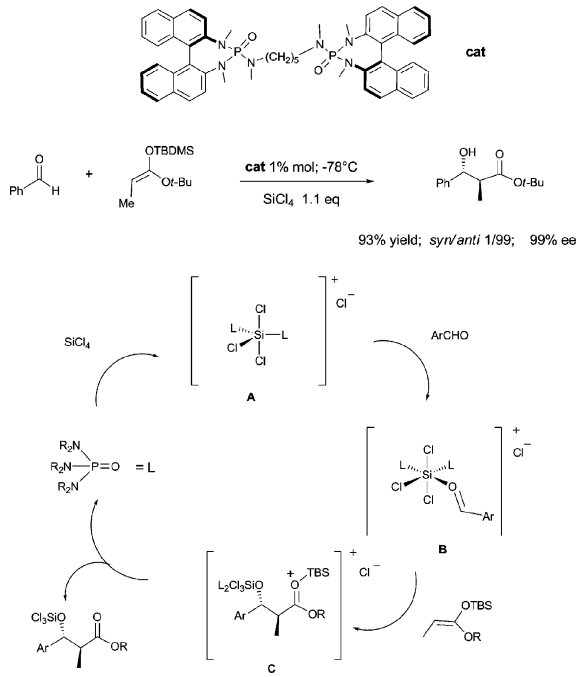


Scheme 5 BINAPO-promoted stereoselective nucleophilic additions to benzaldehyde.

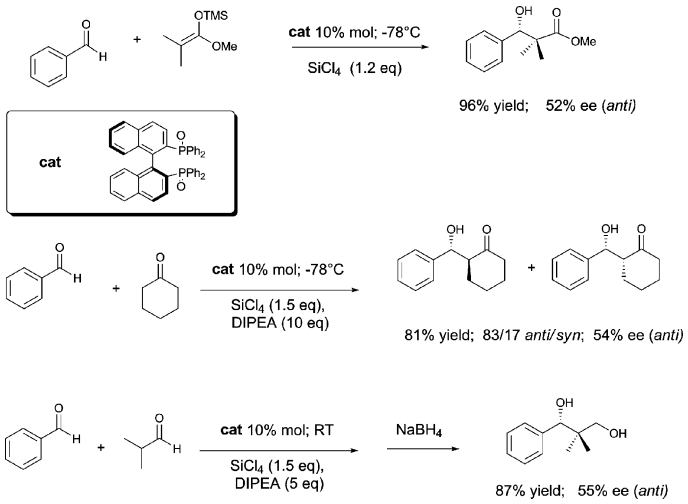
In the attempt to further explore new synthetic methodologies based on the use of trichlorosilyl derivatives activated by chiral Lewis bases, the enantioselective addition of trialkylphosphites to achiral aldehydes was investigated.[20] However, the catalytic Abramov-type phosphonylation of carbonyl compounds promoted by tetrachlorosilane in the presence of catalytic amounts of (*S*)-BINAPO was met with limited success, affording the corresponding α-hydroxyphosphonate in 86% yield but only 41% enantioselectivity (Scheme 5). Once again the role of diisopropylethylamine as additive was decisive to achieve high chemical yields, but did not improve the stereocontrol. Even if the level of stereoselectivity is unsatisfactory the work is worth mentioning because it represents the first organocatalytic enantioselective Abramov-type phosphonylation of aldehydes and the first report where different classes of chiral phosphine oxides other than the bis(diarylphosphanyl)-binaphthyl dioxides were taken in consideration, although without success in this kind of reaction.

A significant breakthrough in the field was accomplished by Denmark who explored the possibility to develop chiral hypervalent silicates to be used as Lewis acids, according to the mode of activation described in Scheme 6.[21] A highly efficient enantioselective aldol reaction of silyl keteneacetals catalyzed by a Lewis base activated with tetrachlorosilane was reported. Catalytic amounts of a binaphthyldiamino-based phosphoramide (1% mol) in the presence of a stoichiometric amount of tetrachlorosilane promoted the addition of silyl keteneacetals to aromatic aldehydes in high enantioselectivities.

In the proposed mechanism a basic ligand is employed to enhance the activity of a Lewis acid. The coordination of a Lewis base to a Lewis acid makes it more electrophilic; since a cationic species is generated, the result is a significantly increased Lewis acidity of the new adduct. In this aspect the combination of a chiral Lewis base and silicon tetrachloride to generate a strong Lewis acid is different from most of the other chiral Lewis acid-promoted reactions. Lewis base coordination to $SiCl_4$ activates the Lewis acid, while complexation of a basic chiral ligand to a Lewis acid precursor normally decreases the reactivity of the chiral complex. It is correct to say that these are not Lewis acid-catalysed reactions; the fact that the aldol products are trichlorosilyl ethers, as demonstrated by NMR, is clear evidence that each molecule of tetrachlorosilane participating in the catalytic cycle is incorporated into the product. In the course of the last years it was shown that an *in situ* generated chiral phosphoroamide-bound trichlorosilyl cation is an active catalyst for different transformations,[22] which



Scheme 6 Lewis base-catalyzed Lewis acid-mediated reactions.



Scheme 7 BINAPO-catalyzed Lewis acid-mediated reactions

may be properly defined as phosphoroamide-catalyzed and $SiCl_4$-mediated reactions, as proposed by Denmark.[1]

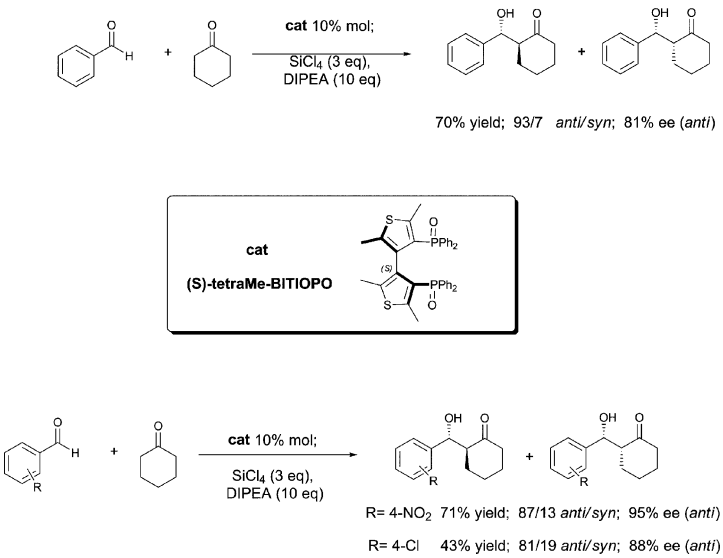
In the case of the reaction of silyl ketene acetal, the hypothesized catalytic cycle involves the chiral trichlorosilyl cation **A** that binds the aldehyde to give adduct **B**, that is attacked by the silyl ketene acetal to afford the intermediate **C** that after dissociation from the catalyst leads to the product as a trichlorosilyl ether (Scheme 6). Not only is the reaction *anti* selective, but it is also diastereoconvergent, affording the same stereoisomer independently from the geometry of the starting enolate. The behavior was tentatively rationalized by proposing that the decisive factor responsible for the observed trend in diastereoselectivity is the interaction between the α-substituent and the bound silyl cation complex in an open, acyclic transition structure.

Very recently it was demonstrated that chiral phosphine oxides are also able to promote the silyl ketene acetals addition to aromatic aldehydes in the presence of a stoichiometric amount of silicon tetrachloride (Scheme 7).[23] The reaction of benzaldehyde with the trimethylsilyl ketene acetal derived from methyl isobutyrate in the presence of 1.2 equiv. of tetrachlorosilane and 0.1 equiv. of chiral phosphine oxide BINAP dioxide (BINAPO) smoothly afforded the aldol adduct in high yield but moderate enantioselectivity (52% ee).

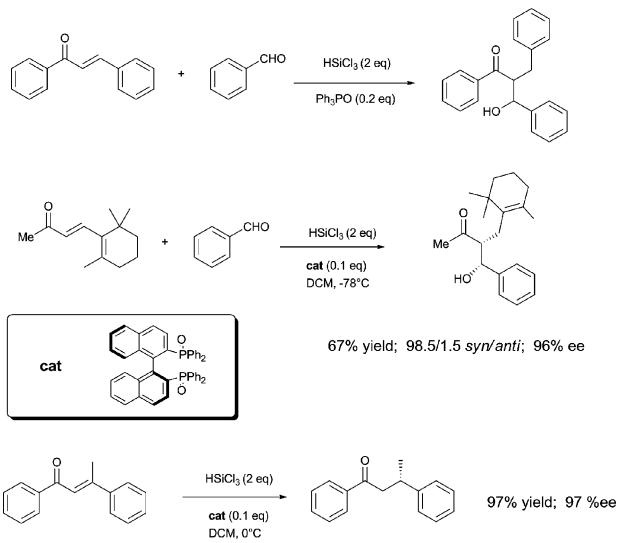
A more interesting work has been recently reported by the group of Nakajima where the *in situ* preparation of trichlorosilyl enol ether was investigated.[24] The aldol reaction of trichlorosilyl enol ethers developed by Denmark suffers from the major drawback of requiring the preparation of the trichlorosilyl derivatives according to an environment-unfriendly procedure that involves the use of mercuric salts. To improve the efficiency of the methodology, the direct synthesis of the enol ethers directly from the carbonyl compounds with tetrachlorosilane in the presence of phosphine oxides was realized; the resulting trichlorosilyl enol ether was simultaneously activated by phosphine oxide to react with aldehydes, to afford a β-hydroxy ketone in a direct aldol-type reaction of two carbonyl compounds. After the usual screening of several experimental conditions, propionitrile was found to be the solvent of choice; under the best conditions the adduct was isolated in high yield with a good diasteroselectivity but moderate enantioselectivity (0 °C, 2 h, 81% yield, *syn*/*anti* = 17/83, 54% ee for the *anti* isomer).

It is worth mentioning that, taking advantage of the poor reactivity of aliphatic aldehydes as electrophiles, a direct aldol-type reaction between two different aldehydes was also positively accomplished. The reaction between benzaldehyde and isobutyraldehyde in the presence of (*S*)-BINAPO leads to the expected β-hydroxy aldehyde that was reduced to the corresponding diol in order to facilitate the isolation of the product. Also in this case the enantioselectivity was not really satisfactory (55% ee).

Also, our group has been deeply involved in the development of new reactions promoted by catalytic amounts of chiral phosphine oxides derived from biheteroaromatic systems, already employed with success in the allyltrichlorosilane addition. The possibility to investigate the reaction promoted by a chiral Lewis acid generated through coordination to $SiCl_4$ by an enantiomerically pure phosphine oxide was obviously very attractive. Since electron-rich (*S*)-tetraMe-BITIOPO had already shown higher performances than (*S*)-BINAPO in the allylation, we thought that such a Lewis base could successfully produce by reaction with $SiCl_4$ the chiral cationic hypervalent silicon species, an active catalyst for the addition of several nucleophiles to carbonyl compounds. The direct aldol condensation of a ketone to aromatic aldehydes was selected for a preliminary study in view of its importance in synthetic organic chemistry, and of its simple procedure that does not involve the preparation of enol ethers or ketene acetals; the trichlorosilyl enol ether generated *in situ* from the ketone in the presence of tetrachlorosilane is simultaneously activated by phosphine oxide to react with aldehydes, coordinated as well as activated by the chiral cationic hypervalent silicon species. Once again (*S*)-tetraMe-BITIOPO demonstrated performance better than (*S*)-BINAPO and higher levels of stereocontrol were reached (Scheme 8).[25] For example, the direct condensation of cyclohexanone with benzaldehyde at 0 °C in DCM, in the presence of 3 equiv. of $SiCl_4$, 10 equiv. of DIPEA and 0.1 equiv.



Scheme 8 (*S*)-TetraMe-BITIOPO-catalyzed $SiCl_4$-mediated direct aldol condensation.



Scheme 9 (*S*)-BINAPO-catalyzed reductive aldol condensation.

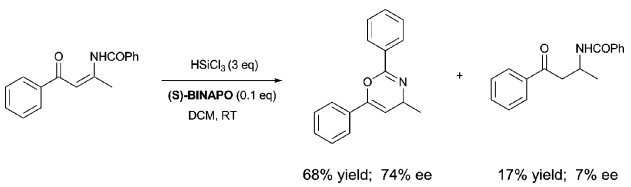
of (*S*)-tetraMe-BITIOPO afforded the aldol product in 12/88 *syn*/*anti* stereoselectivity and 75% ee for the *anti* isomer. At lower temperature (–25 °C) both the diastereoselectivity and the enantioselectivity were improved up to 81% ee for the *anti* isomer.

Even better results were obtained in the addition of ketones to aromatic aldehydes bearing electron-withdrawing groups. For example, the reaction of cyclohexanone with 4-nitrobenzaldehyde at –25 °C afforded the β-hydroxyketone in 87/13 *anti*/*syn* ratio and 95% ee for the *anti* diastereoisomer; with 4-chlorobenzaldehyde 88% enantioselectivity for the *anti* isomer was obtained.

The very promising results of these studies pave the way towards the application of this methodology to other nucleophilic attacks to activated C=O, C=N and even C=C promoted by chiral hypervalent silicon Lewis acids. A very nice example came last year from the Nakajima group, that reported on an alternative methodology for organocatalytic conjugate reduction of enones and subsequent reaction with aldehydes, to realize a reductive aldol reaction. The method employs phosphine oxides as Lewis base-catalysts and trichlorosilane as a reductant.[26] The idea was to activate the silane with a suitable Lewis base to perform the 1,4-reduction *via* a six-membered transition state; then, with the assistance of the same Lewis base, the generated trichlorosilyl enolate should react with the electrophilic aldehyde (Scheme 9). Triphenylphosphine oxide was shown to be able to catalyze the three-component reaction of chalcone, benzaldehyde and trichlorosilane (reductive aldol reactions) to afford the corresponding aldol product in 78% yield.

Preliminary experiments with (*S*)-BINAPO as chiral Lewis base were very promising in terms of stereocontrol. The reduction of 1,3-diphenylbutenone promoted by catalytic amounts of BINAPO at 0 °C in the presence of two equivalents of trichlorosilane was successfully accomplished leading to the corresponding saturated compound in 97% yield and a somewhat surprising, but very good, 97% ee. 2,2′-Bis(diphenylphosphanyl)-1,1′-binaphthyl dioxides gave even more appealing results in the reductive aldol reduction of β-ionone with benzaldehyde, where a very high *syn* stereoselectivity was observed along with 96% enantioselectivity for the *syn* isomer.

A great variety of Lewis base-catalyzed stereoselective transformations are currently under investigation, and novel synthetic methodologies have been developing as well. An example comes from a very recent report where, by studying the stereoselective synthesis of *N*-acylated β-amino ketones, it was unexpectedly found that optically active 4*H*-1,3-oxazines could be directly obtained *via* reductive cyclization of *N*-acylated β-amino enones using trichlorosilane and chiral Lewis base catalysts (Scheme 10).[27] The reaction of trichlorosilane in the presence of catalytic amounts of BINAPO with (*Z*)-*N*-benzoyl enone, derived from 3-amino-1-phenylbutane-1,3-dione, surprisingly afforded the 4*H*-1,3-oxazine as major product in 56% yield and 71% enantioselectivity. Similar yields and stereoselectivity (up to 81% ee) were obtained by extending the reaction to other five substrates; among different chiral phosphine oxides investigated, BINAPO was found to secure the best performances. From some preliminary experiments it was observed that trichlorosilane does not act only as a reductant, but also as a dehydrating agent. In the reaction different ratios of oxazine and the expected β-keto amide were formed, depending on the variation of experimental conditions. Interestingly, it was observed that the two products were obtained with different levels of stereoselection, and sometimes even with a different absolute configuration.

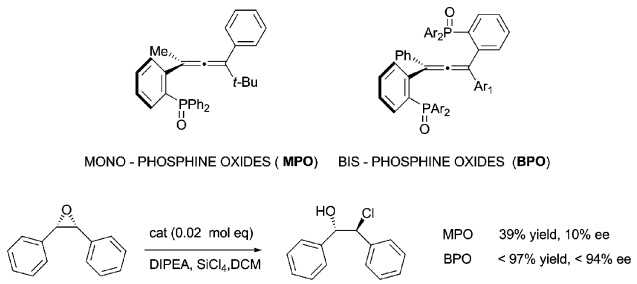


Scheme 10 BINAPO-catalyzed synthesis of oxazines.

The result was tentatively explained by assuming that the oxazine was not derived from the ketoamide by simple dehydration. It was proposed that 4*H*-1,3-oxazine was generated *via* the conjugate reduction of *N*-acylated β-amino enone, followed by cyclization of the resulting enolate and elimination of $HOSiCl_3$, whereas the ketoamide originates from the 1,2-reduction of the *N*-acyl imine generated *via* equilibration of the enamide. Further studies will be

necessary to fully understand the reaction mechanism, in order to design more efficient catalysts.

The great variety of structurally different chiral phosphine oxides, directly derived from the corresponding enantiomerically pure phosphines, was further enriched by a late report where optically active mono- and bis-phosphine oxides containing an allene backbone were prepared in enantiomerically pure form and used as organocatalysts (Scheme 11). [28]



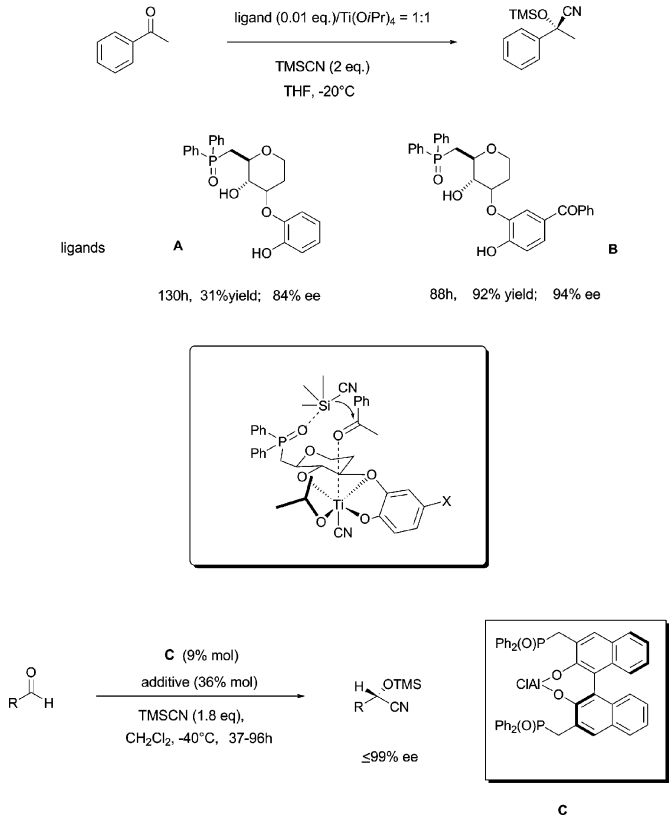
Scheme 11 Ring opening of epoxides catalyzed by chiral allenes-containing phosphine oxides.

The novel chiral allenes were tested in the opening of *meso* epoxides by addition of silicon tetrachloride. It was observed that bisphosphine oxides performed much better than monophosphine oxide. It must be said that in the solid state, bisphosphine oxide adopts a conformation characterized by π-stacking interactions involving two phenyl rings of the phosphine oxides and one of the backbone phenyl rings. As a consequence of this arrangement the two oxygen atoms project in roughly the same direction. The catalyst of choice (Scheme 11, $Ar_1 = Ar_2 = Ph$) was found to be a really effective catalyst that could be employed at 0.1% mol cat. loading, clearly indicating that a completely unexplored novel class of chiral phosphine oxide, based on the allene backbone, is now available as suitable catalysts.

Finally, it is worth mentioning that the phosphine oxide group could be part of a multifunctional chiral catalyst. The design of small organic molecules where basic and acidic sites are combined in order to properly orient substrates and reagents might be seen as the chemist's attempt towards the development of catalysts with enzyme-like reactivity and selectivity. The search for a system that exhibits simultaneous activation of two separate reactants is therefore extremely active. However, it should be noted that so far only bifunctional catalysts bearing a phosphine oxide group and Lewis acid metal sites were reported, and no example of a "metal-free" bifunctional catalyst containing phosphine oxide as Lewis base has been reported.

In this context, of particular interest is the work by the Shibasaki group, who reported the activity of a new bifunctional catalyst based on a titanium complex generated *in situ* from the phosphine oxide **A** and titanium tetraisopropoxide (Scheme 12).

The products of cyanosilylation of ketones are obtained with high enantioselectivity.[29] In 2001 a novel catalyst **B** was developed, different from **A**, due to the presence of a benzoyl group at the catechol moiety.[30] The benzoyl substituent has a positive effect in terms of enantioselectivity and yield, probably due to steric and electronic factors. Since the benzoyl group can enhance the acidity of the phenol hydroxy group, these results seem to point to an involvement of this group in the catalytic cycle.



Scheme 12 Reactions promoted by bifunctional catalysts containing phosphine oxides.

With aryl ketones ligand **B** has been used with a loading of 1% mol, while in the case of aliphatic ketones a loading of 2.5% mol is required. In both conditions the cyanohydrins have been obtained in high yield and with excellent enantioselectivity. The authors have proposed the transition state shown in Scheme 12: the titanium atom acts as a Lewis acid on the ketone, while the phosphine oxide oxygen coordinates the silicon atom of TMSCN generating a pentacoordinated silicon species and thus increasing the nucleophilicity of the cyanide group.

In 2001 the new bifunctional catalyst **C** was published, characterised by the simultaneous presence of one Lewis-acidic site (the metal) and two Lewis-basic sites (the phosphine oxide oxygen atoms).[31] In this case, the stereoselective cyanosilylation of aldehydes is promoted *via* a dual activation: the aldehyde is activated by coordination with the metal, while the silicon reagent (trimethylsilyl cyanide), that in this process acts just as a nucleophilic species, is activated by the Lewis basic centers, the phosphine oxides. Quite inexplicably the best results have been obtained using an additive: $Bu_3P(O)$ for aliphatic and α-β-unsaturated aldehydes and $MeP(O)Ph_2$ for aromatic aldehydes (Scheme 12).

Outlook and perspectives

The development of Lewis-base-catalyzed reactions for regio- and stereochemical bond formation is a topic of primary importance in modern organic chemistry. Chiral small-molecules able to donate electron-pairs have been demonstrated to promote a wide variety of synthetic transformations. Quite unexpectedly

among the different classes of Lewis bases currently employed in organocatalysis, phosphine oxides have received little attention so far. Their use as chiral Lewis basic metal-free catalysts has been limited to relatively few reactions. Chiral phosphine oxides have been studied in polyhalosilane chemistry, as clearly shown above, but a variety of different reactions with different mechanisms are suitable to be explored.

The development of new Lewis base-catalyzed methodologies for increasing molecular diversity and complexity is another field where enantiomerically pure phosphine oxides may find extensive application, as demonstrated for example by the reported reductive aldol reaction promoted by BINAPO.[26]

Another point worth considering is that relatively few classes of phosphine oxides have been investigated; basically only bis(diphenylphosphanyl)binaphthyl dioxides (BINAPO) have been used; only in two works[20,27] other phosphine oxides have been screened as promoters in stereoselective reactions, although with no success. However it should be noted that not only carbocyclic aromatic but also heteroaromatic-based phosphine oxides my be considered.[16,25] These compounds offer new possibilities of development, since the electronic and steric properties of the ligands could be modulated by a proper choice of substituents.

It is remarkable that alkyl phosphine oxides have been basically unexplored and, to the best of our knowledge, no studies on their use in organocatalysis have been reported so far. In view of further enlarging the structural variety of suitable Lewis bases, it would be interesting to also investigate C_1 monophosphine oxides or P-stereogenic phosphine oxides, but at present basically only C_2 symmetric diphosphine oxides have been used.[28]

Finally, the design and development of multifunctional organocatalytic systems where the phosphine oxide group is present together with another metal-free catalytically active residue, typically an acidic group, is totally unexplored.[32] Only examples of bifunctional catalysts where a metal Lewis acid is combined with a Lewis basic phosphine oxide have been investigated. However, simply considering the number of reactions promoted by chiral thiourea/amine bifunctional organocatalysts,[33] it is clear how many more options and possibilities could be offered by the availability of properly designed multifunctional phosphine oxide-based catalysts.

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