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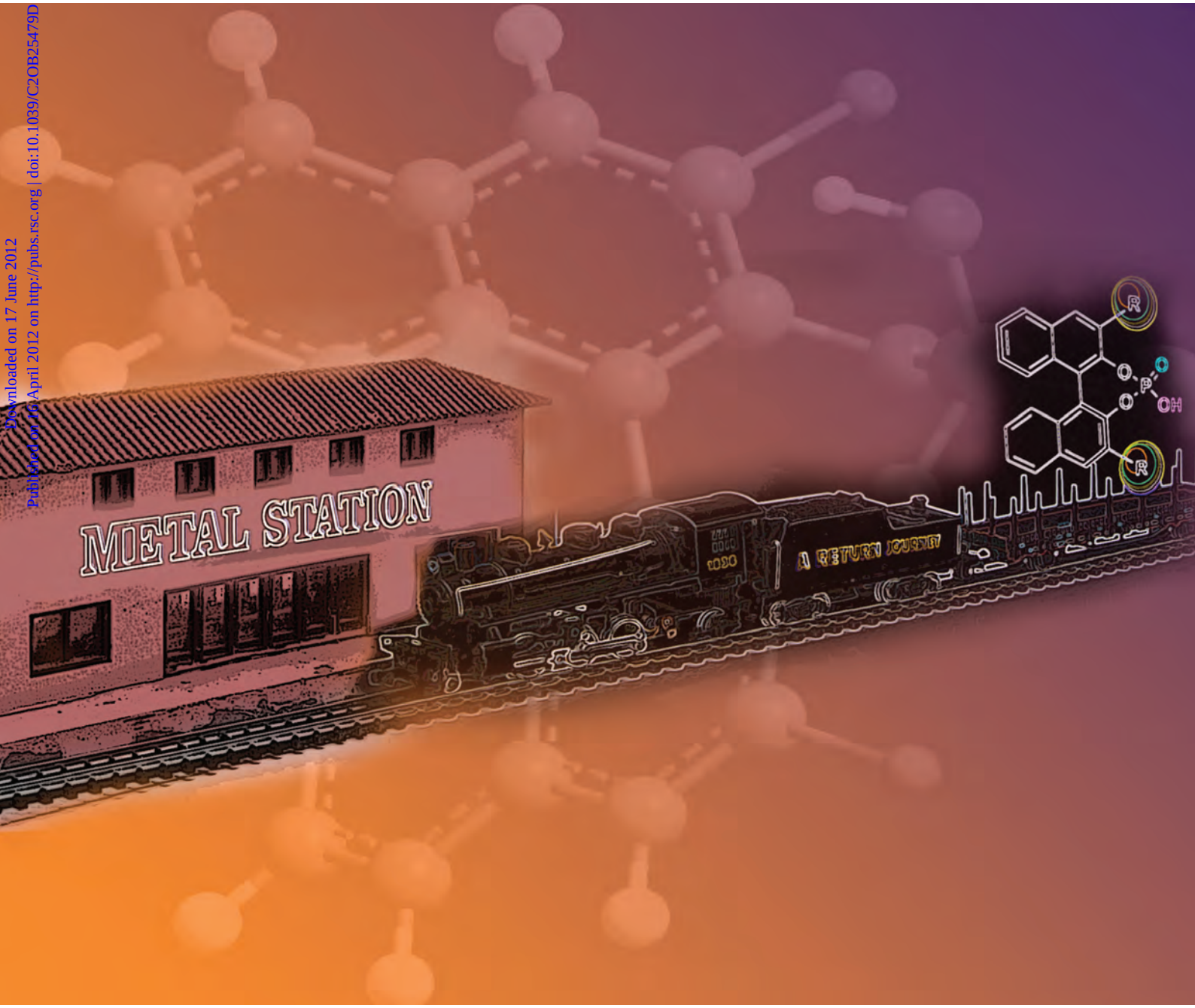

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PERSPECTIVE

Metallic organophosphates as catalysts in asymmetric synthesis: a return journey†

Alejandro Parra,*[a] Silvia Reboredo,[b] Ana M. Martín Castro[a] and José Alemán*[a]

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This perspective article provides a general overview of the most relevant topics in the applications of chiral metallic organophosphates. A brief introduction along with a historic comparative profile of the BINOL and phosphoric acid analogues are given. Next, a selection of the most outstanding uses of the catalysts according to the employed metal is presented.

1. Introduction

Since Pasteur first produced a pure sample of optically active tartaric acid in 1848,[1] much progress has been made in the field of the asymmetric synthesis. Mainly in the last three decades, numerous asymmetric syntheses based on metallic species have been accomplished using a large battery of novel and designed ligands.[2] Both the empirical experience and the chemists' intuition have disclosed that only a few scaffolds used as ligands have proved successful and, therefore, they have been called *privileged ligands*.[3] One of these privileged ligands (not based on the frequently used central chirality) is BINOL (1,1′-bi-2-naphthol) (based on axial chirality), which has received great attention from the scientific community.[4] Interestingly, this compound can be prepared directly by an asymmetric oxidative coupling [*e.g.* 2-naphthol with copper(II) chloride using (*S*)-(+)-amphetamine as a chiral ligand],[5] or alternatively by an intricate chiral resolution of *rac*-BINOL[6] *via* synthesis of the racemic hydrogen phosphate derivative (BNP acid).[7] This chiral phosphoric acid was isolated in two steps: (1) a classical chemical resolution with (+)-cinchonine and (2) [(+)-acid, (+)-base] salt acidification with HCl (Scheme 1).[7a,8] Then, the phosphoric acid was methylated and transformed into chiral (*S*)-BINOL by reduction with Red-Al (Scheme 1),[7b] providing a new entry to the synthesis of this useful compound.

After the extensively reported uses of metal BINOLates during the 80s and 90s, which were mainly prepared from (*S*/*R*)-

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†Dedicated to Prof. José Luis García Ruano on occasion of his 65th birthday.

Alejandro Parra

Alejandro Parra was born in 1980 in Toledo, Spain. He received his BS degree in chemistry at the Universidad Autónoma of Madrid (Spain) in 2004. In 2006, he spent four months in the laboratory of Prof. Andrew Myers at Harvard University, USA. He earned his PhD at the Universidad Autónoma de Madrid under the supervision of Prof. José Luis García Ruano in 2009. He is currently carrying out a postdoctoral stay at the Institute of Organic Chemistry, RWTH-Aachen University, Germany, with Prof. Magnus Rueping. His current research concerns asymmetric synthesis and organocatalysis.

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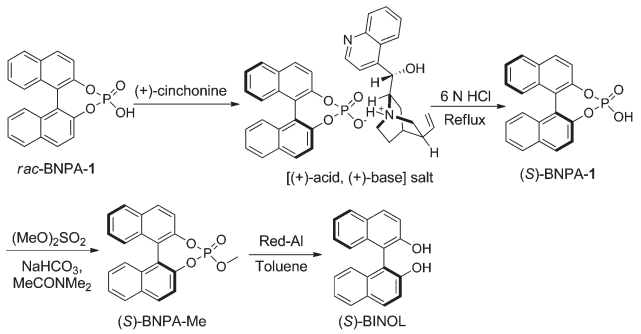
Silvia Reboredo was born in 1983 in Alonsotegi, Bizkaia. She studied chemistry at the Universidad del País Vasco, where she obtained her PhD for work on organocatalytic cycloadditions in 2011, under the supervision of Prof. Mª Dolores Badia and Prof. Jose Luis Vicario. During her PhD he performed a stay at RWTH Aachen University with Prof. Magnus Rueping. Currently she is a postdoctoral researcher with Prof. Nazario Martín at Universidad Complutense de Madrid. Her present research topics include materials science and asymmetric synthesis.



Scheme 1 Synthesis of (*S*)-BNPA-**1** and (*S*)-BINOL.

(−)-binaphthylphosphoric acids, these compounds fell into oblivion until the achievements on the organocatalysis field by Terada and Akiyama in 2004,[9] and only a few examples of the uses of this type of compounds can be found to date. Since the milestone reached by Jacobsen's work in 1998,[10] related to thiourea catalysis, and the subsequent development of the hydrogen-bond catalysis,[11] the chiral phosphoric acids were reintroduced as more active Brønsted acids in comparison with the analogous less acidic BINOLs. Thus, BNP acids can be considered as stronger Brønsted acids, in contrast to BINOL, thioureas and TADDOLs, which are considered neutral Brønsted acids. This fact has consolidated the evolution from chiral hydrogen-bond catalysis to chiral Brønsted-acid catalysis (Fig. 1).

Chiral binaphthyl phosphoric acid derivatives were reintroduced in 2004 by Terada and Akiyama[8] for different reasons:[12] (i) the appropriate acidity of these phosphoric acid derivatives makes possible a suitable hydrogen-bonding interaction between the substrate and the phosphate group, avoiding the generation of loose ion-pairs (common for acids with higher pK_a's). (ii) These acids are bonded to BINOL by two P–O bonds providing a cyclic structure without free rotation at the phosphorus atom. (iii) The substitution at 3 and 3′-positions allows the modulation of the steric and electronic properties providing a satisfactory chiral environment. (iv) This type of acids could form hydrogen bonds

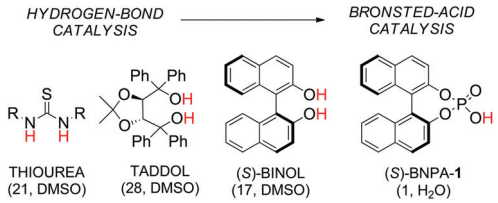


Fig. 1 Evolution from hydrogen bond catalysis to chiral Brønsted acid catalysis (pK_a values and solvents in parenthesis).

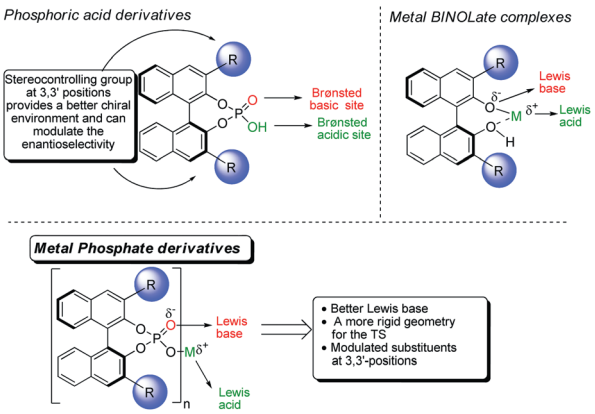


Fig. 2 Comparison of chiral BNP acids with BINOLates and metal phosphates.

with electrophiles (Brønsted acidic site), whereas the Brønsted basic site (oxygen lone electron pair at P═O) could participate in the reaction mediated by a dual function (for this reason this acid has also been called bifunctional catalyst by some researchers) (top-left, Fig. 2).

By contrast, metal BINOLate complexes have a Lewis acid position in place of the Brønsted acidic site at the phosphoric acid moiety, allowing these complexes to take part in a large variety of reactions (top-right, Fig. 2).[13] However, why should we move to phosphate complexes if researchers have been using

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Ana M. Martin Castro was born in Madrid, Spain, in 1964. She received her BS (1988) and PhD (1993) degrees under the supervision of Professors J. L. Garcia Ruano and J. H. Rodriguez Ramos at the Universidad Autonoma of Madrid (UAM). As a postdoctoral fellow she joined the groups of Professor P. R. Raithby at the University of Cambridge (U.K., 1997) and Professor V. K. Aggarwal at the University of Sheffield (U.K., 1998–2000). She then returned to UAM as an Associate Professor. Her present research interests include the development of novel asymmetric methodologies assisted by a chiral sulfinyl group.

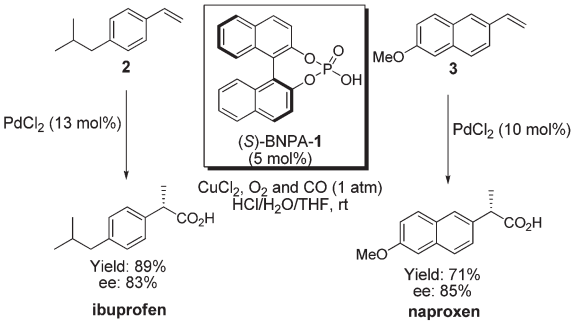
José Alemán

José Alemán obtained his MSc in 2002 under the supervision of Prof. José Luis García Ruano. In 2003, he spent six months in the laboratory of Prof. A. Padwa at Emory University, Atlanta, USA. He finished his PhD under the supervision of Prof. Jose Luis García Ruano in 2005. Then, he carried out his postdoctoral stay (2006–2008) at Center for Catalysis in Aarhus (Denmark) with Prof. K. A. Jørgensen. He came back to Spain in 2009 and is currently a "Ramón y Cajal" researcher at the Universidad Autónoma of Madrid (Spain). His research interests include asymmetric synthesis, and organocatalysis.

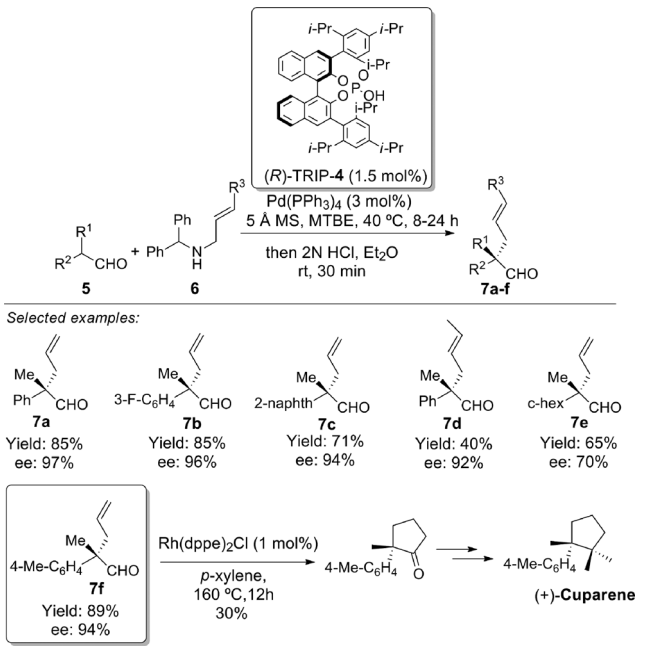
the BINOLates for decades? Three different reasons could answer this interesting question: (i) Ishihara and co-workers[14] pointed out that the main advantage of the use of these metal phosphates is related to the conjugate P═O moiety, which can act as a Lewis base activating nucleophiles (*e.g.* TMSCN)[13] much better than the corresponding oxygen of the metal BINOLate. The reason for that is the higher basicity of the P═O function in the phosphoric acid,[15] which can be increased as a result of the ionic conjugation of M–O–P═O in the corresponding metal salts. (ii) The distance of the Lewis base and Lewis acid site in the metallic phosphates (**O**═P–O–**M**) is longer than in the BINOLates (**O**–**M**), allowing a better accommodation of the electrophile and the nucleophile in the corresponding transition state. (iii) The achievements by Akiyama and Terada in the incorporation of substituents at the 3,3′-positions allowed, for the first time, a better modulation of the catalytic activity and also of the obtained enantioselectivity.

Interestingly, a controversy over the phosphoric acid/phosphate has developed in the last few years since they can be counterions or simply act as ligands. This fact depends on the behaviour of the acid; it could act as a counteranion (a phosphate) or as an anionic ligand. As this aspect has been surveyed in previous reviews,[16] herein we will focus our revision on the newly achieved goals, mainly during the last three years, by using chiral metal phosphates derived from BINOL, VAPOL, as well as TADDOL.

Notably, these phosphoric acids were initially used as ligands or counteranions with metals during the 90s. Then, in the 2000s decade their applications as organocatalysts were profusely developed. Finally, during the last few years, they have been used again, in combination with metals, in a *return journey*. In the following sections, these achievements will be chronologically presented according to the employed metal. Additionally, we will only cover those reactions where the metal and the phosphate are acting at the same time in a cooperative manner (as a counterion or as a ligand); tandem reactions where the metal acts first and then the phosphoric acid, or *vice versa*, will not be included.[17]



Scheme 2 Synthesis of ibuprofen and naproxen using a Pd-chiral phosphate.



Scheme 3 Asymmetric Tsuji–Trost allylation catalyzed by a Pd-chiral phosphate.

2. Organophosphate derivatives from BINOL and VAPOL

2.1 Palladium phosphates

We must go back to 1990 to find out the first reported example applying this concept. It was described by Alper *et al.* in the context of the synthesis of 2-arylpropionic acids using the chiral ligand (*S*)-1,1′-binaphtyl-2,2′-diyl phosphate (*S*)-BNPA-**1** and Pd as the metal.[18] This methodology was particularly useful in the synthesis of ibuprofen and naproxen, which are the most widely used non-steroidal anti-inflammatory drugs (Scheme 2).[19] When the optimal conditions (Scheme 2) were applied to two olefinic precursors **2** and **3**, the asymmetric palladium-catalyzed hydrocarboxylation was achieved in very good yields with good enantioselectivities. Thus, ibuprofen was obtained in 89% yield and 83% ee in its (*S*)-configuration (coincident with the pharmacologically active compound)[20] when 5 mol% of the (*S*)-BNPA-**1** was used. In the same way, similarly good results in yield and ee were obtained for naproxen (Scheme 2). Interestingly, the opposite enantiomer of the (*S*)-BNPA-**1** gave higher enantiomeric excesses (84% and 91% for ibuprofen and naproxen, respectively), providing the (*R*)-enantiomer. Other chiral ligands such as (−)-menthol, (+)-DET or (*S*)-BINAP were tested in a wide variety of conditions, but in all the cases practically racemic products (≤10% ee) were obtained. Although the authors did not propose a catalytic cycle, presumably a palladium organophosphate must be involved in the sequence.

In 2007, List *et al.* reported a method whereby a chiral phosphoric acid and palladium generated a chiral palladium phosphate.[21] In this case, a directed asymmetric counteranion Tsuji–Trost α-allylation of a series of aldehydes was reported for the construction of an α-quaternary stereogenic center in the aldehyde moiety (Scheme 3). These conditions were tested on substrates with a different aromatic substitution pattern, providing aldehydes **7a–f** with excellent ee's in good yields (Scheme 3). Only in the cases of di-aliphatic aldehydes the ee's values decreased (70% ee). The utility of one of the synthesized

aldehydes was shown in the formal synthesis of (+)-cuparene by way of a Rh-catalysed hydroacylation of **7f** (Scheme 3).

In a plausible catalytic cycle, depicted in Scheme 4, the phosphoric acid plays two important roles. First, it behaves as an acidic co-catalyst in the iminic condensation, and then the chiral phosphate is involved as a chiral counteranion and also as a chiral ligand in the Tsuji–Trost allylation. Thus, the condensation between the corresponding amine and an aldehyde afforded an enammonium phosphate which, in the presence of Pd(0), generates the asymmetric π-allyl complex. Next, an α-allylated iminium phosphate is generated, which, after hydrolysis, yields the α-branched aldehyde (Scheme 4).

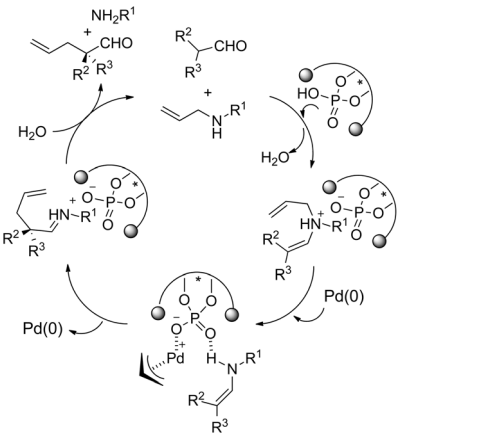
In 2011, List *et al.* published a modified α-allylation of aldehydes.[22] This transformation is also catalyzed by a palladium phosphate prepared from (*S*)-TRIP and $Pd(PPh_3)_4$. In this case the allylating agent is generated from different allylic alcohols (**8**), which are activated by a chiral phosphoric acid, forming the corresponding intermediate π-allyl-palladium complexes. These π-allyl-palladium complexes are trapped in an asymmetric manner by the enamine generated from aldehyde **5** and benzhydryl amine. As shown in Scheme 5, homoallylic aldehydes were obtained in excellent enantioselectivities and yields. In this methodology, three catalysts cooperate for achieving high enantioselectivities: (1) benzhydryl amine, which forms an intermediate enamine with the aldehyde; (2) Pd(II) complex and (3) the chiral counteranion derived from (*S*)-TRIP-**4**, which performs an ACDC process and also activates the allylic alcohol.

In 2011, List *et al.*[23] also reported the asymmetric Overman rearrangement catalyzed by a Pd-chiral phosphate in order to find a complementary approach to well-know protocols using cobalt and "iron sandwich complexes".[24] They proposed that the chiral soft Pd-π-Lewis acid complex, generated *in situ* from chiral phosphate and achiral Pd halide, played a similar role to the reported catalyst for this rearrangement. In this way, using the silver phosphate Ag[(*S*)-TRIP-**4**] and the palladium complex (*S*)-**11**, they expanded the ACDC concept to the asymmetric Overman rearrangement (Scheme 6). Notably, the methodology was successfully applied to wide range of substrates bearing different substitution in excellent yields and enantioselectivities.

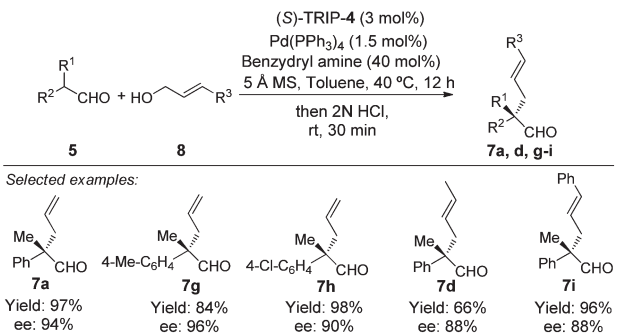
After a considerable effort, they isolated and characterized the active catalytic species involved in the process. Thus, when the dimeric palladium complex (*S*)-**11** was treated with 2 equiv. of Ag[(*S*)-TRIP-**4**] in $CHCl_3$, a new complex was quantitatively formed (Scheme 7). The so-generated complex actually catalyzed the Overman rearrangement with similar results to those obtained from the process where the catalyst was formed *in situ*.

2.2 Rhodium phosphates

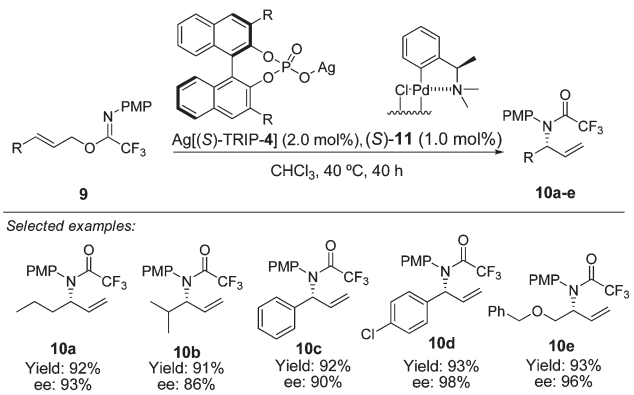
In 1992, Pirrung *et al.* reported the first asymmetric dipolar cycloaddition of a diazocompound catalyzed by a rhodium organophosphate.[25] The catalyst $Rh_2[(R)\text{-BNP-}\mathbf{1}]_4$ was prepared by exchange reaction with $Rh_2(OAc)_4$ and (*R*)-BNPA-**1** in 95% yield (Scheme 8). Once it was prepared, its reactivity was evaluated in the addition reaction of diazocyclohexane-1,3-dione to



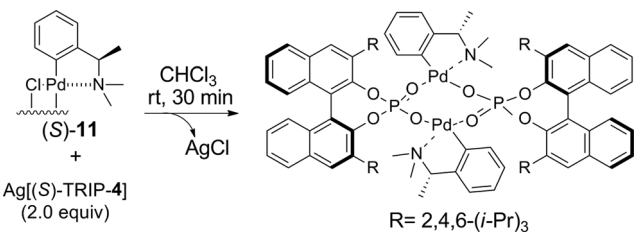
Scheme 4 A plausible catalytic cycle in the asymmetric Tsuji–Trost allylation.



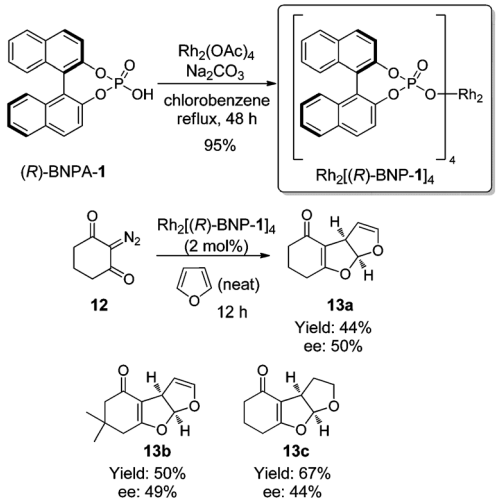
Scheme 5 Asymmetric α-allylation of aldehydes catalyzed by a Pd-chiral phosphate.



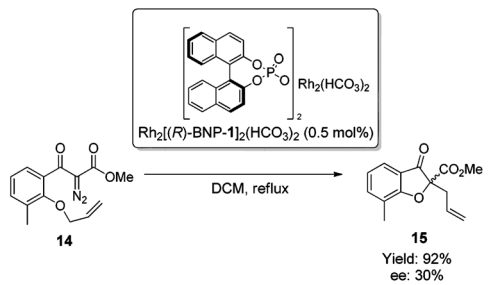
Scheme 6 Asymmetric Overman rearrangement catalyzed by a Pd-chiral phosphate.



Scheme 7 Asymmetric Overman rearrangement catalyzed by a Pd-chiral phosphate.



Scheme 8 Dipolar cycloaddition reaction of diazocompounds.



Scheme 9 Asymmetric α-diazocarbonyl decomposition catalyzed by $Rh_2[(R)\text{-BNP-}\mathbf{1}]_2(HCO_3)_2$.

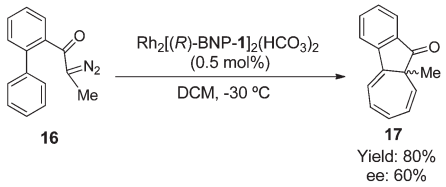
furan (used as reagent and solvent). The product **13a** was obtained in 44% yield with moderate 50% ee (Scheme 8). Accordingly, this methodology also proved successful when applied to another diazo-derivative, as well as to dihydrofuran, with similar results (**13b** and **13c**, Scheme 8).

Simultaneously, McKervey *et al.* carried out the synthesis and evaluation of $Rh_2[(R)\text{-BNP-}\mathbf{1}]_2(HCO_3)_2$ in a series of α-diazocarbonyl decompositions.[26] In this case, the catalyst was readily prepared by exchange of $Na_4[Rh_2(CO_3)_4]\cdot H_2O$ and (*R*)-BNPA-**1** in ethanol. As outlined in Scheme 6, just 0.5 mol% of complex was required to catalyze a 2,3-sigmatropic rearrangement, transforming the compound **14** into benzofuranone **15** in very good yield (92%) but with moderate enantioselectivity (30% ee) (Scheme 9).

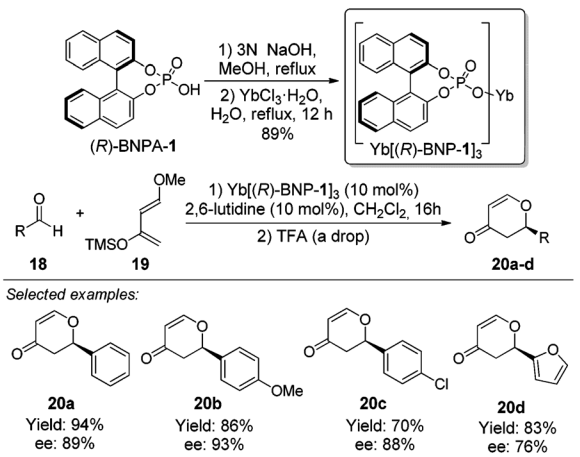
Using the same Rh(II)-organophosphate $Rh_2[(R)\text{-BNP-}\mathbf{1}]_2(HCO_3)_2$ as the catalyst, biphenyl diazoketone derivative **16** gave the aromatic cycloaddition product **17** in 80% yield with improved enantioselectivity (60% ee) (Scheme 10).

2.3 Ytterbium phosphates

In 1995, different chiral lanthanide(III) phosphates derived from BINOL were prepared by Inanaga *et al.*[27] Among the prepared salts, the ytterbium phosphate $Yb[(R)\text{-BNP-}\mathbf{1}]_3$ afforded the best stereochemical outcome (up to 73% ee) when it was applied to a cycloaddition reaction with benzaldehyde or

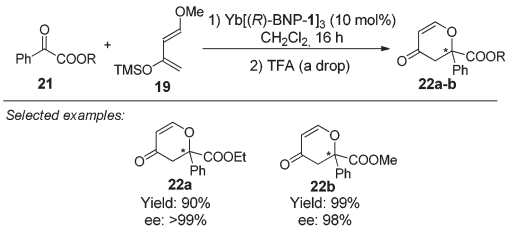


Scheme 10 Asymmetric aromatic cycloaddition catalyzed by $Rh_2[(R)\text{-BNP-}\mathbf{1}]_2(HCO_3)_2$.



Scheme 11 Hetero Diels–Alder reaction catalyzed by $Yb[(R)\text{-BNP-}\mathbf{1}]_3$.

2-formylnaphthalene and Danishefsky's diene. A few years later, in 1997, the same research group extended the scope of this asymmetric hetero Diels–Alder reaction.[28] They prepared the catalyst $Yb_3[(R)\text{-BNP-}\mathbf{1}]$ from (*R*)-BNPA-**1** and $YbCl_3\cdot H_2O$ in a very good yield (89%) by following the straightforward procedure shown in Scheme 11. With this rare-earth complex on hand, the hetero Diels–Alder reaction of a range of aldehydes and Danishefsky's diene was tested. It was evidenced that the presence of 10 mol% of 2,6-lutidine as an additive favoured the solubility of the complex and it was crucial to get high enantioselectivities. Under these conditions chiral 2,3-dihydro-4*H*-pyran-4-ones **20a–d** were obtained in excellent yields with high enantioselectivities (Scheme 11). As compared with other methods,[29] which require lower temperatures (usually −78 °C), this one is more practical since the products are obtained with complete conversion at room temperature. Although neither a clear structure for the catalyst nor the role played by 2,6-lutidine are disclosed, the authors propose that a satisfactory coordination of the carbonyl oxygen and the ytterbium atom takes place. Additionally, a plausible π,π-stacking interaction between the aldehyde and the catalyst is suggested to account for the obtained high enantioselectivities. Actually, when an aliphatic aldehyde was used in the reaction, only an 11% ee was obtained, which is in accordance with the above proposal. Finally a series of experiments revealed an asymmetric amplification,[30] which becomes the first reported example in ML_3 systems (metal : ligand). This fact was a consequence of the autogenetic formation of the enantiopure ytterbium complexes[31] that make lanthanide complexes even more interesting than they are as mere asymmetric catalysts.



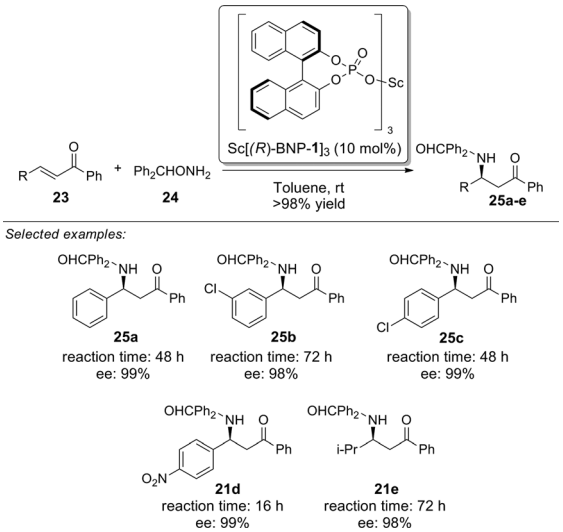
Scheme 12 Hetero Diels–Alder reaction involving glyoxylates **21**.

Further investigations carried out by Inanaga's research group[32] proved that the synthesis of these cycloadducts **20a–d** in the absence of 2,6-lutidine was also possible, thus demonstrating the high dependence of the enantioselectivity on the coordination of the substrate with the rigid structure. This interesting catalyst Yb[(*R*)-BNP-**1**]$_3$ allowed the effective reaction of glyoxylates with the consequent formation of quaternary asymmetric centers (Scheme 12) with excellent enantioselectivities due to the homogeneous catalysis resulting from the favourable coordination between the glyoxylate **21** and the bidentate ligand.[32a]

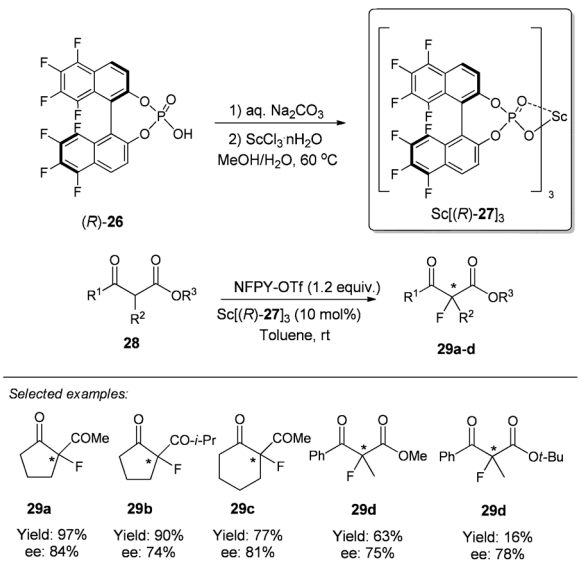
2.4 Scandium phosphates

Next Inanaga *et al.*, based on their studies of the selective epoxidation of conjugate enones,[31b] applied the same precatalyst system to the aziridination of chalcone with *O*-methylhydroxylamine.[33] Although the enantioselectivity of the process was remarkable, the isolated yield was low (38%). This reduced yield induced the authors to consider a stepwise process as a solution of the associated drawback. Therefore, initial works on an enantioselective Michael addition followed by aziridine ring formation were developed. For the Michael addition, the scandium complex Sc[(*R*)-BNP-**1**]$_3$ proved to be the most effective one, affording the corresponding adduct in good yield (81%) with moderate enantioselectivity (57% ee) (Scheme 13). The use of an *O*-alkylhydroxylamine different to the *O*-methylated derivative was found to be beneficial, producing enantioselectivities of up to 99% enantiomeric excesses when *O*-diphenylmethylhydroxylamine was used.[34] The scope of the reaction showed tolerance to a series of conjugate enones, with variable reaction times, yields above 98% and enantioselectivities ranging between 94 and 99%. This catalyst was also successfully recycled in the hetero-Diels–Alder reaction having been reutilized up to three times with similar levels of yield and enantioselectivity.[28]

The authors achieved an outstanding asymmetric amplification and it was also possible a kinetic resolution of a racemic β-methoxyaminoketone in the dehydromethoxylation step by way of an *in situ* prepared chiral lanthanum complex. Concerning the aziridine-ring formation, a catalytic amount of NaO*t*-Bu was found to give the target structures without loss of the substrate enantiopurities. More recently the same authors have reported the use of the perfluorinated complex Sc[(*R*)-**27**]$_3$, a variation of Sc[(*R*)-BNP-**1**]$_3$, as a catalyst of the fluorination reaction of β-ketoesters (Scheme 14),[35] a transformation widely studied in the last years.[36] The catalyst, exhibiting a stronger Lewis acidity than its analogous Sc[(*R*)-BNP-**1**]$_3$, was prepared according to a modified literature procedure.[37] The efficiency of the method



Scheme 13 Asymmetric Michael addition catalyzed by Sc[(*R*)-BNP-**1**]$_3$.

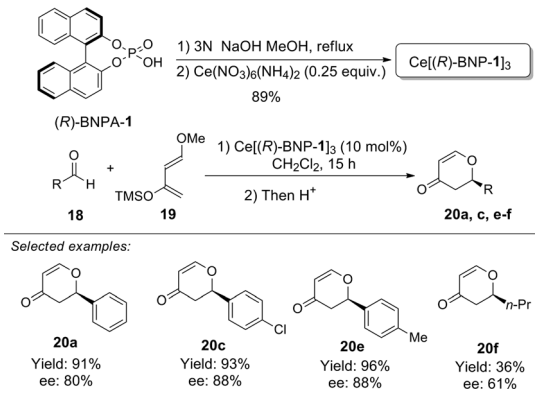


Scheme 14 Fluorination of α-ketoesters catalyzed by Sc[(*R*)-**27**]$_3$.

was confirmed for the fluorination of cyclic and acyclic substrates, both providing similarly high enantioselectivities. It also allowed the synthesis of the bulky *tert*-butyl ester with higher enantioselectivity and low yield.

2.5 Cerium phosphates

In 2003 Inanaga *et al.* published the hetero-Diels–Alder reaction catalyzed by a cerium phosphate.[38] In this report, the structure of the complex was not elucidated and only the provided indirect methods suggested the formation of Ce(III) species. Thus, from inductively coupled plasma (ICP) mass spectroscopy, ESCA analysis and magnetic susceptibility measurements, a trivalent cerium structure was envisaged. The hetero-Diels–Alder cycloaddition was tested as a model reaction in the presence of



Scheme 15 Hetero Diels–Alder reaction catalyzed Ce[(*R*)-BNP-**1**]$_3$.

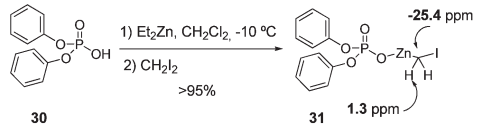
the Ce(III) species, finding, in general, similar or slightly lower ee's than for the other lanthanides (compare Schemes 11 and 15) The reaction was performed under homogeneous conditions and worked quite well with aromatic aldehydes. However, the use of aliphatic aldehydes provoked a dramatic drop in the obtained enantioselectivities, as well as in the reactivity of the system [36% yield and 61% ee (**20f**, Scheme 15)]. A positive non-linear effect was also evidenced. Thus, for example, when the optically impure catalyst prepared by mixing the Ce[(*R*)-BNP-**1**]$_3$ and the Ce[(*S*)-BNP-**1**]$_3$ complexes in 9 : 1 (80% ee) or 4 : 1 ratio (60% ee), the products were obtained with 90% or 81% ee, respectively.

Interestingly, when these two catalysts (both enantiomers) were mixed, heterogeneous conditions were developed. The precipitate was separated from the soluble complex, and both were independently used for the reaction. The soluble complex showed a high asymmetric amplification (positive non-linear effect) and the insoluble fraction complex exhibited a normal linear effect. However, this phenomenon is not clearly explained yet.

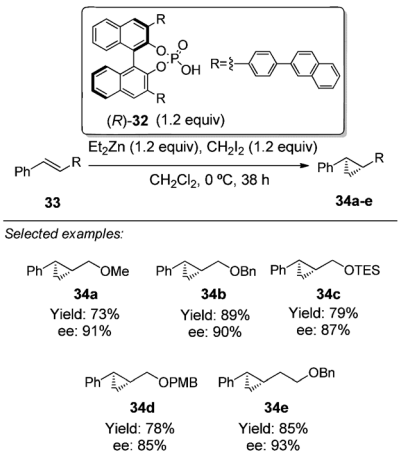
2.6 Zinc phosphates

Because of the characteristic, unusual reactivity of the cyclopropyl motif, its synthesis has always been an important challenge for the chemists.[39] Since the appearance of the Zn/Cu–CH_2I_2 couple introduced by Simmons and Smith in 1958,[40] further improvements and novel methods for the cyclopropanation have been developed.[41] Its asymmetric version has attracted special attention.[42] In this sense, in 2005, Charette *et al.* reported a new approach to the asymmetric synthesis of cyclopropyl derivatives, introducing an iodomethylzinc phosphate as a novel reagent for the enantioselective cyclopropanation.[43] Initial attempts in the achiral version used diphenylphosphate (DPP) (**30**) and diethylzinc (Scheme 16). Iodomethylzinc phosphate (**31**) was obtained in excellent yield as a white solid, and it was stable enough to be characterized by NMR (Scheme 16), or even by X-ray diffraction, which provides evidence that this zinc species crystallized as a dimeric structure with tetrahedral geometry with respect to the Zn atom.

Initially this iodomethylzinc phosphate was tested in the cyclopropanation reaction of usual alkenes. All the cases provided the cyclopropane ring in very good yields (62–95%),



Scheme 16 Synthesis of the phosphate derivative **31**.



Scheme 17 Cyclopropanation of alkenes.

using 1.2 equiv. of the cyclopropanating agent, even when an allylic alcohol was tested. Next, Charette *et al.* developed an enantioselective version using the chiral zinc phosphate derived from substituted (*R*)-3,3′-BINOL. As shown in Scheme 17, the cyclopropanes were obtained in very good yields with excellent enantioselectivities (85–93% ee). The main drawback of the process is the use of a stoichiometric amount of (*S*)-**32** (1.2 equiv.). The reaction was also assayed using only a 10 mol% of the phosphate derivative but unfortunately, maybe due to a background reaction, only 68% ee was obtained when TES allyl ether (**34c**) was treated under the standard conditions. Different additives were assayed and the use of 0.5 equiv. of 1,2-dimethoxyethane (DME) and 0.9 equiv. of $Zn(CH_2I)_2$ improved the enantioselectivity (up to 88% ee).

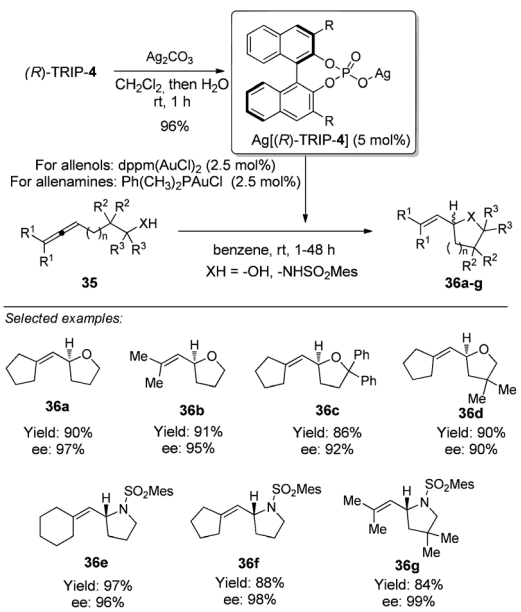
2.7 Gold phosphates

In the last decade, gold-catalyzed reactions have been documented as important tools in organic synthesis.[44] They have been employed in many different processes; however, only a few enantioselective transformations have been studied.[45] Some chiral phosphine–Au(I) complexes have been efficiently applied in some cases, but the scope of their usefulness was not general. In this regard, in 2007 Toste *et al.*[46] introduced the use of a chiral counterion in the field of gold catalysis by means of a combination of a chiral phosphate and a gold(I) catalyst, affording excellent results. The cyclization of allenols and allenamines was performed using chiral phosphines, but low enantioselectivities were obtained. In contrast, when silver phosphate Ag[(*R*)-TRIP-**4**], readily synthesized from Ag_2CO_3 and (*R*)-TRIP-**4**, and Au(I)–phosphine complexes were tested, different substrates containing a varied substitution afforded excellent isolated yields and ee's (Scheme 18). The authors also described an

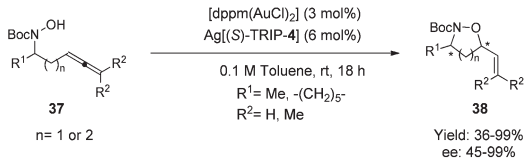
intramolecular hydrocarboxylation of allenes using the same methodology, where, in addition to the chiral phosphate Ag[(*R*)-TRIP-**4**], the chiral phosphine (*S*)-BINAP was required.

A few years later, in 2010, the same research group reported, following a similar design, the synthesis of isoxazolidines and oxazines catalyzed by a gold complex *in situ* prepared from Ag[(*S*)-TRIP-**4**] and [dppm(AuCl)$_2$] (Scheme 19).[47] Hydroxyamines cycled to afford the corresponding isoxazolidines in moderate to good yields and enantioselectivities. This procedure was applied to obtain six-membered oxazines and a similar result was obtained. The method was successfully applied to cyclic and linear allenes.

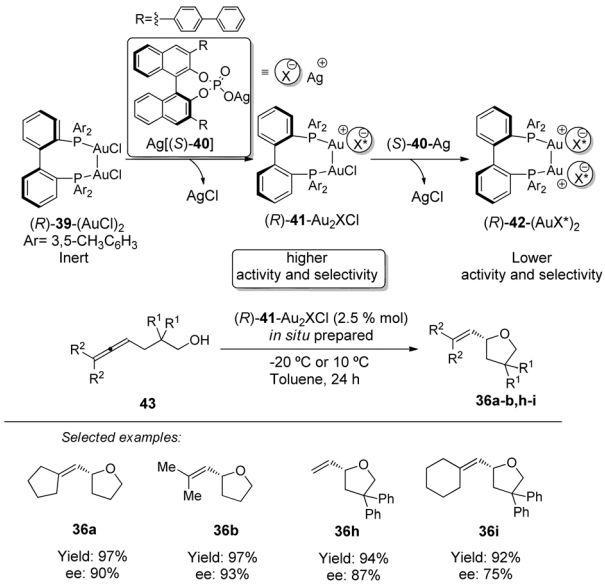
In 2009, Mikami *et al.*[48] prepared a series of chiral gold (biphep) catalysts by controlling the axial chirality using silver phosphate-BINOL derivatives. Starting from a racemic gold–biphep complex, gold–atropoisomeric catalysts were obtained with excellent enantioselectivities by formation of the corresponding chiral mono- and diphosphates. Then, these complexes were applied to the asymmetric hydroamination of allenes. In the same context, in 2010 it was found that the use of the chiral monophosphate gold complex (*R*)-**41**-Au$_2$XCl, containing only a chiral phosphate anion, provided also good results (Scheme 20).[49] This striking synergistic effect was applied to the synthesis of chiral tetrahydrofurans **36** in excellent yields and ee's. It is noteworthy that when other species such as (*R*)-**39**-(AuCl)$_2$ or (*R*)-**42**-(AuX*)$_2$ were involved, null or lower



Scheme 18 Hydroalkoxylation and hydroamination of allenyl derivatives.



Scheme 19 Synthesis of isoxazolidines.



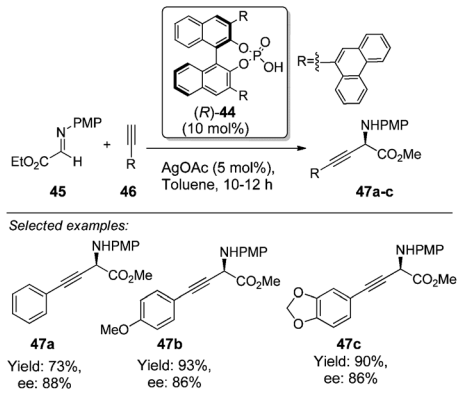
Scheme 20 Synthesis of chiral tetrahydrofurans.

effectiveness was observed in the process (Scheme 17). These examples illustrated that the chiral phosphate could be employed as a catalyst by itself, as well as a chiral template in the synthesis of other catalysts.

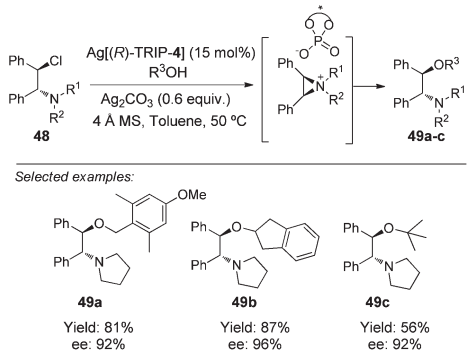
2.8 Silver phosphates

In 2007, Rueping *et al.*[50] published a combined enantioselective Brønsted acid and silver catalyzed alkynylation reaction. Thus, the asymmetric alkynylation of α-imino esters was performed *via* two parallel catalytic cycles; a chiral Brønsted acid activating the electrophile (the α-imino esters) and the metal salt activating the nucleophile, both proceeding simultaneously. Thus, they evaluated different parameters, such as different phosphoric acids, solvents and protecting groups at the imine, and a variety of metallic salts. The best results were obtained with the catalyst (*R*)-**44**, AgOAc, 30 °C, and PMP as the protecting group at the imine. The scope outlined in Scheme 21 is related to the use of aromatic substituted alkynes. Although two combined cycles were proposed, an exchange of the metal counterion, which reacted and formed a chiral silver complex, could not be disregarded.

Shortly afterwards, Toste *et al.* published a new activation mode where the chiral anion-mediated asymmetric ring-opening of *meso*-aziridiunium and episulfonium ions was described.[51] In the first part of this report, the authors described the synthesis of a substituted aziridinium ion using several insoluble basic silver compounds. A slight excess amount of Ag_2CO_3 and silver phosphate salt Ag[(*R*)-TRIP-**4**] (15 mol%) gave products **49** in good yields with excellent ee's. However, the use of more soluble silver sources, such as AgOTs, decreased the enantioselectivity due to a competition of the achiral anion (TsO^- in this case) with the chiral one (phosphate). They also demonstrated that both the chiral phosphoric acid and Ag_2CO_3 were necessary for the reaction to take place. The scope of this reaction was restricted to the use of diphenylaziridium salts and primary, secondary and tertiary alcohols, although an erosion in the reactivity was detected



Scheme 21 Alkynylation of imines catalyzed by (*R*)-**44** and AgOAc.



Scheme 22 Toste's desymmetrization of aziridinium salts.

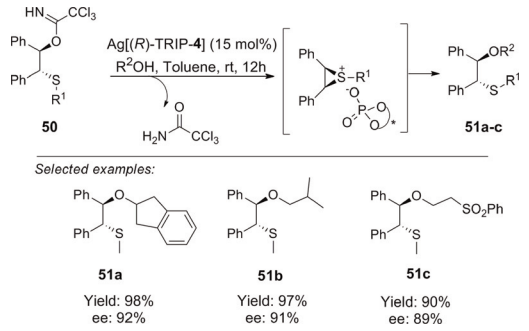
for sterically hindered alcohols (see Scheme 22). For example, the preparation of **49c** required the use of 30 equiv. of *t*-BuOH to get good results.

On the basis of these successful results, the authors considered that another cationic intermediate with a chiral counteranion as an ion pair could be employed. In the same report,[46] they extended this methodology to the desymmetrization of *meso*-episulfonium ions, which had not been explored previously. A trichloroacetimidate function acting as a leaving group was successfully activated by the chiral phosphate and the intermediate could be trapped by a nucleophile (see Scheme 23).

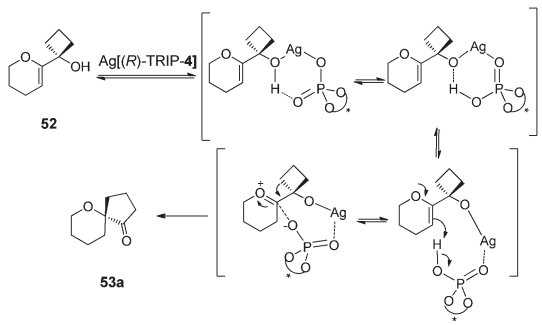
In 2009, Tu *et al.*[52] developed the enantioselective semipinacol rearrangement for the asymmetric synthesis of chiral spiroethers (Scheme 24). In this reaction, *in situ* generated Ag[(*R*)-TRIP-**4**] coordinated with the alcohol, forming a new six-membered intermediate species, which underwent rearrangement into the spiro-compound as outlined in Scheme 25. The scope of the rearrangement proved to be limited to the use of highly strained cyclobutanols bonded to five- or six-membered cyclic ethers. The obtained yields were good for most of the assayed substrates, and the ee's ranged from 74 to 98% (Scheme 25).

2.9 Lithium phosphates

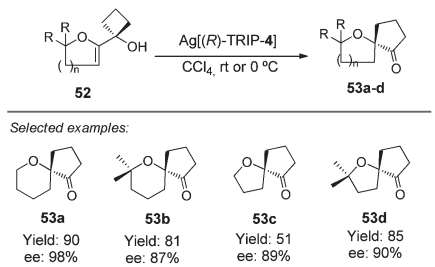
Although important contributions on enantioselective cyanation of aldehydes have been reported,[53] the use of ketones as electrophiles has been much less studied due to both the lower reactivity and the larger steric demand.[54] In this regard, in 2008



Scheme 23 Toste's desymmetrization of episulfonium salts.



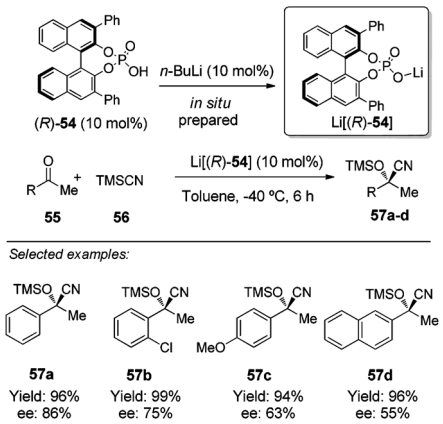
Scheme 24 Spiroethers obtained by semipinacol rearrangement catalyzed by silver phosphates.



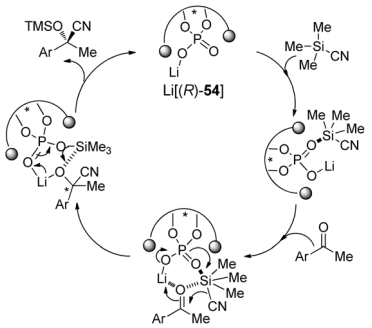
Scheme 25 Spiroethers obtained by semipinacol rearrangement catalyzed by silver phosphate Ag[(*R*)-TRIP-**4**].

Ishihara *et al.*[13] reported the enantioselective cyanosilylation of ketones mediated by the chiral lithium phosphate-BINOL Li-[(*R*)-**54**]. They focused on the use of this type of phosphate once this reaction had proved unsuccessful when using chiral lithium binaphtolates.[55] The intrinsic properties (higher reactivity and efficiency) of the lithium phosphate catalyst Li[(*R*)-**54**] allowed the cyanation to take place with better results (Scheme 26). Different alkali metals (sodium and potassium) were assayed as counterions, and it could be verified that the lithium derivative (*in situ* prepared by a ready acid–base reaction with *n*-BuLi) was the most active catalyst. Next, different 3,3′-disubstitution patterns at the chiral (*R*)-BINOL moiety of the phosphate derivative were evaluated, providing the catalyst (*R*)-**54** as the best candidate in terms of yields and ee's.

As indicated in Scheme 26, this methodology could be applied to aryl alkyl ketones, with opposite electronic features, in very good yields (59–99%) with enantiomeric excesses



Scheme 26 Asymmetric cyanosilylation of ketones catalyzed by Li[(*R*)-**54**].



Scheme 27 A plausible catalytic cycle in the enantioselective cyanosilylation of ketones.

ranging from moderate to good (32–86%). Unfortunately, when dialkyketones were used, very low ee's were obtained.

The proposed catalytic cycle is shown in Scheme 27. Given the bifunctional character of the phosphate group, the catalyst might activate both the TMSCN, through the silicon atom (Lewis basic site), and the carbonyl compound, by means of the lithium atom (Lewis acid site). In this manner, with both species activated, a cyclic transition state affording the (*R*)-*O*-silylcyanohydrins can be envisaged. Therefore, this double acid–base activation of the phosphate group is the key element with respect to other tested catalysts. The authors also proposed an interesting transition state to justify the stereochemical outcome of this process.

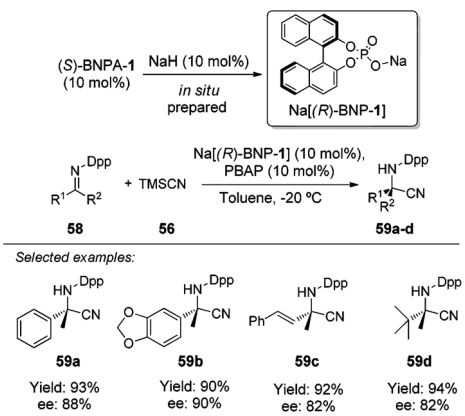
2.10 Sodium phosphates

The first example of the use of chiral sodium BINOL-phosphate was reported by Feng *et al.* in 2009.[56] The catalytic system was applied to an enantioselective Strecker reaction of ketimines. This work was based on the previous results of the same group by using chiral alkali-metal salts (sodium phenyl-glycinates). The optimization in the Strecker reaction with chiral sodium phosphates was quite complex and a large number of variables were studied: the type of catalyst with different substitution patterns at 3,3′-position of the naphthol-phosphate, the best procedure for generating the sodium phosphate (generated with NaH) from the BINOL derivative in enantioselective terms, and the most suitable additives (different phenol derivatives). Interestingly, in contrast to the Brønsted acid catalyst, the best conditions involved: non-substitution at 3-position of naphtol BINOLate catalyst Na[(*R*)-BNP-**1**], TMSCN as a cyanide source, and *para*-butyl-*ortho*-adamantyl phenol (PBAP) as the additive at −20 °C. The scope of this reaction was quite large and could be applied to different *N*-diphenylphosphinoyl aryl methyl ketimines, α,β-unsaturated ketimines, heteroaromatic, secondary, and tertiary ketimines with similarly good results (see representative examples in Scheme 28). The authors speculated about the role of PBAP, and once demonstrated that it was not involved in the generation of HCN, they proposed a reactive hexacoordinate silicon intermediate.

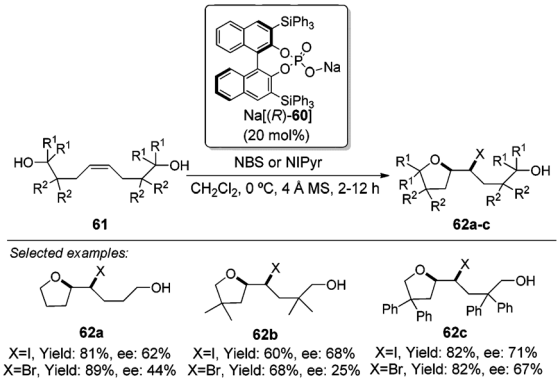
The second reported reaction with BINOL-sodium phosphates was developed by Hennecke *et al.*[57] The authors described an enantioselective haloetherification by asymmetric opening reaction of *meso*-halonium ions. Only a few reports about the halocyclizations with metal and non-metal methodologies have been reported,[58] this publication being the first one describing the desymmetrization of *in situ* generated *meso*-halonium ions. Thus, this strategy was assessed by using the 3-substituted $SiPh_3$ sodium binaphtolphosphate, Na[(*R*)-**60**] (*in situ* generated by reaction with Na_2CO_3), affording ee's up to 71% by using NBS or *N*-iodopyrrolidine (NIPy) as the electrophilic halogen source (Scheme 29).

2.11 Iridium phosphates

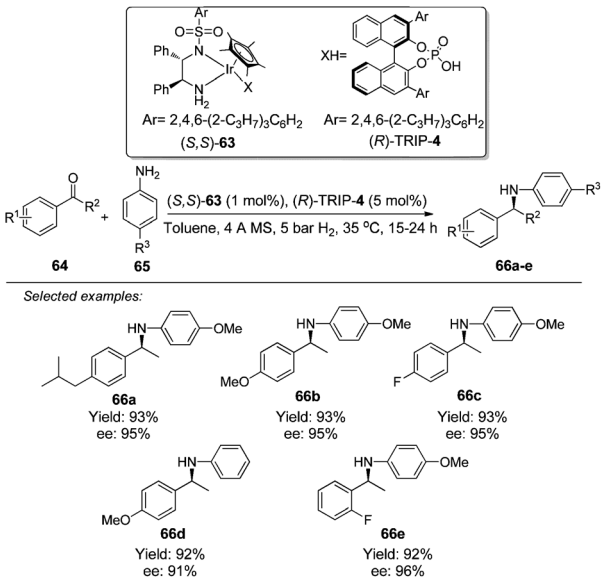
Over the last few years organic chemists have been searching for reliable and useful methods for the synthesis of non racemic chiral amines. Although the asymmetric hydrogenation of imines[59] is a good solution for giving access to these structures, only a few research groups have investigated the asymmetric reductive amination.[60] In this sense, Xiao *et al.*[61] have successfully applied an iridium-derived catalyst, previously employed in the enantioselective hydrogenation of cyclic and acyclic amines, to the reductive amination of *in situ* formed ketimines. The authors used a catalytic system constituted by a transition-metal complex and a phosphoric acid. The high stereoselectivities achieved in these reactions were attributed to the chiral



Scheme 28 Strecker reaction under sodium BINOL-phosphate Na[(*R*)-BNP-**1**] catalysis.



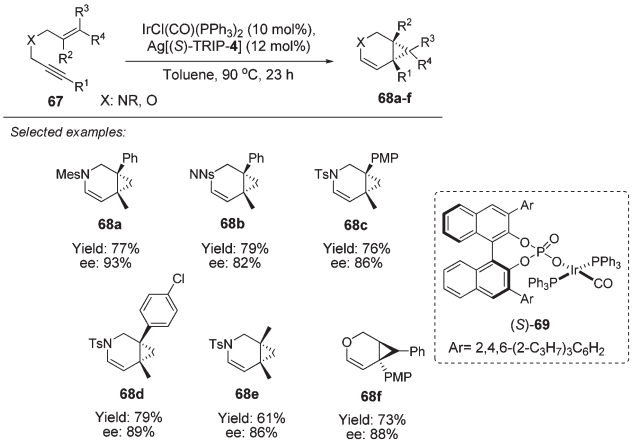
Scheme 29 Enantioselective haloetherification.



Scheme 30 Asymmetric reductive amination catalyzed by (*S*,*S*)-**63** and (*R*)-TRIP-**4**.

phosphate counteranion and the chiral ligand (1,2-diamine derivative) of the metal. Additionally, the phosphoric acid, acting as a Brønsted acid, is responsible for the *in situ* formation of the protonated imine, and the metal atom mediates in the activation of H_2. Under the optimized conditions, Xiao and coworkers reported high yields and stereoselectivities for the asymmetric hydrogenation of a wide range of substrates including aryl methyl ketones, as well as the sterically more demanding ketones, aryl ethyl and the dialkyl ketones (Scheme 30). It must be highlighted that the reducing conditions of dialkyl ketones were slightly different, a modified metal complex was used and the presence of the phosphoric acid was unnecessary. The aniline component was also evaluated and interesting results were obtained with a variety of amines (Scheme 30).

More recently, an interesting work where a different strategy was employed has been published.[62] The initial hypothesis, which was empirically corroborated, proposes that a loose ion pair is formed between the metallic center and the chiral phosphate in the reaction medium, establishing a hydrogen bond with the substrate. When the chiral silver salt Ag[(*S*)-TRIP-**4**] was assayed in the cycloisomerization of nitrogen-bridged enynes,



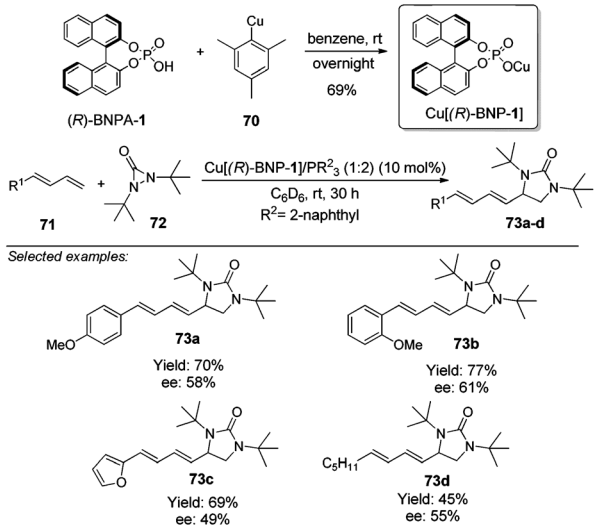
Scheme 31 Enantioselective Ir-catalysed carbocyclization of enynes.

only unsuccessful results were obtained. By contrast, a series of square planar species, more specifically a mixture of Vaska's complex and Ag[(*S*)-TRIP-**4**], proved very effective and yielded the corresponding products in high yields and ee's under the conditions shown in Scheme 31. A modified structure of the oxygen-bridged enyne allowed the formation of the final adduct in high yields and ee's but with the opposite absolute configuration with regard to its analogous nitrogen-bridged derivative (Scheme 31). Further investigations, including ^{31}P-NMR experiments, IR and DFT calculations, demonstrated that chiral phosphate (*S*)-**69**, which is formed from Vaska's complex, controls the enantioselectivity of the process.

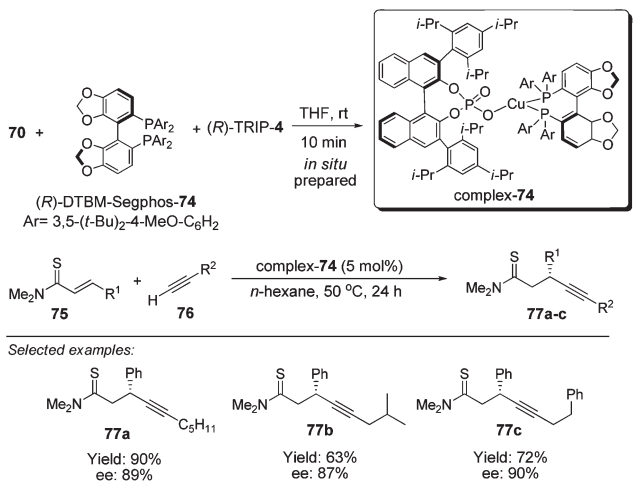
2.12 Copper phosphates

Shi *et al.*, on the basis of their previous work on Cu(I)-catalyzed diamination reported in 2008,[63] later on extended the scope of their studies and reported their achievements in asymmetric induction using chiral phosphate anions.[64] Among the evaluated Cu(I) salts, those with the most electronegative counteranions exhibited the best activities, the copper(I) diphenylphosphate being one of the best catalysts (Scheme 32). Additionally, Cu(I)-phosphate Cu[(*R*)-BNP-**1**] could be easily isolated as a solid (*i.e.*, this BINOL derivative was prepared in benzene at room temperature overnight in 69% yield). Although the catalyst was readily isolated, it gave similar results to those obtained from the *in situ* prepared salt. By adding tri(2-naphthyl)phosphine to the diamination process, the ee was improved when Cu[(*R*)-BNP-**1**] was used in C_6D_6 at room temperature. Conjugate dienes and trienes gave the corresponding products in good yields with moderate ee's, but only traces of the desired products were detected when aliphatic aldehydes were assayed.

In 2011 Shibasaki *et al.*[65] reported a direct catalytic asymmetric conjugate addition of alkynes to α,β-unsaturated thioamides by way of a cooperative-catalysis system. The initially expected soft–soft interaction between the basic α,β-unsaturated thioamides and a metal alkynilide should allow the process under proton transfer conditions. Their initial studies showed that the system formed by soft Lewis acid/hard Brønsted base prepared from $[Cu(CH_3CN)_4]PF_6$, (*R*)-3,5-i-Pr-4-Me$_2$N-MeOBIPHEP and Li(OC$_6$H$_4$-*p*-OMe) allowed the formation of a range



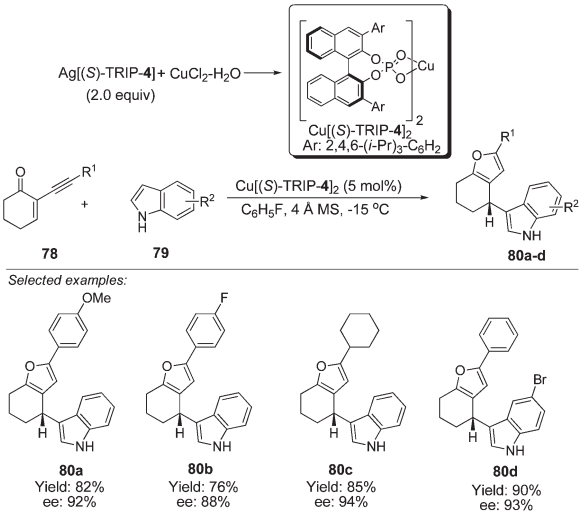
Scheme 32 Diamination of conjugate olefins.



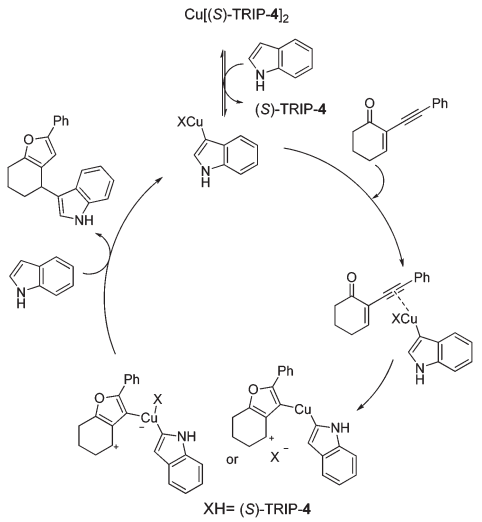
Scheme 33 Conjugate addition of aliphatic alkynes to α,β-unsaturated thioamides.

of β-alkynyl-β-aryl thioamides in high yields and enantioselectivities. However, saturated aliphatic terminal alkynes yielded only moderate enantioselectivities. Therefore, the authors carried out an additional screening, introducing a new stereocontrolling element in the catalytic system. Further investigations demonstrated that the use of a chiral phosphate counteranion derived from (*R*)-TRIP-**4** generated a new species, complex **74**, which, acting as a hard Lewis base, improved the enantioselectivities of the reactions of the series of aliphatic alkynes (Scheme 33). Further experiments, supported by the X-ray crystal structure for complex **74**, suggested that the phosphate anion could be involved in the transition state.

In the context of the applications of these metallic catalysts, Toste *et al.*[66] have published an enantioselective synthesis of substituted furans **80** from the cyclohexenone derivative **78** and indole **79**. After the evaluation of different catalysts, the complex Cu[(*S*)-TRIP-**4**]$_2$, derived from Cu(II) and a Ag[(*S*)-TRIP-**4**], proved to be the most effective catalyst, even better than its analogous Cu(I)-derivative, maybe due to its lower electrophilicity.



Scheme 34 Cycloisomerization-indole addition reaction.



Scheme 35 Proposed mechanism for the Cu(II)-catalyzed synthesis of substituted furans.

Once the optimal conditions were established, the scope of this reaction was evaluated (Scheme 34). Both aromatic and aliphatic alkynes afforded their respective adducts in high yields and enantioselectivities. As the indolinic component was concerned, both electron-withdrawing and electron-donating substituents may be present at the aryl skeleton. However, the reaction failed when 2-methyl indole was used as a substrate.

To explore the mechanism of the reaction, several experiments were performed, including monitoring the reaction by ^{1}H-NMR, UV-visible experiments and mass spectrometry. With their findings they postulated the mechanism depicted in Scheme 35.

2.13 Aluminium phosphates

In 2009, Wang, Zhu *et al.*,[67] who had previously developed an aluminium-complex catalyzed reaction of aldehydes and α-isocyanoacetamides,[68] reported the effect of the phosphoric acids in combination with an aluminium complex in the aforementioned

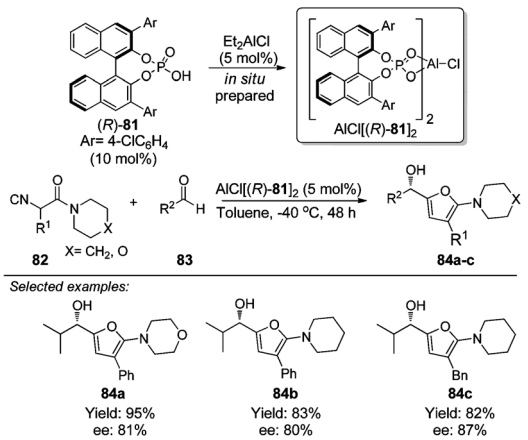
process. After several experiments, the authors realized that the chiral environment was closely dependent on the ratio of the phosphoric acid (*R*)-**81** to Et_2AlCl, *i.e.* the larger number of phosphate ligands associated with the metallic center, the better enantioselectivity the reaction afforded, the opposite enantiomer having been formed when the above ratio was 1 : 1. The reaction was tolerant with the presence of aliphatic aldehydes, giving higher ee's in the case of the α-branched aldehydes than when starting from the linear ones (Scheme 36). α-Phenyl, α-benzyl and α-methyl α-isocyanoacetamides reacted satisfactorily. It is worth mentioning that the results were very similar regardless of the employment of isolated or *in situ* generated catalyst (82% yield, 71% ee *vs*. 81% yield, 71% ee, respectively).

2.14 Manganese phosphates

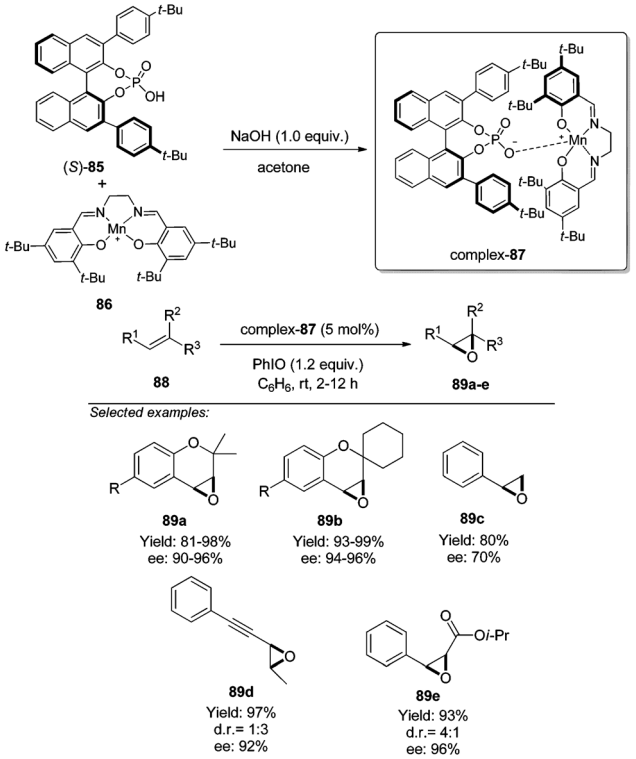
The interesting achievements reported by Kochi, Jacobsen and Katsuki,[69] inspired List *et al.* to develop an epoxidation of olefins catalyzed by a chiral ion pair formed by an achiral Mn–salen complex and a chiral phosphate counteranion, as shown in Scheme 37.[70] The high reactivity shown by this sterically overloaded manganese–phosphate Lewis pair (complex-**87**) was a consequence of the combination of two factors: the fixation in one of the two enantiomeric conformations executed by the salen–ligand backbone and the ability of the chiral anion stabilizing that conformation. As outlined in Scheme 37, under the optimized conditions, a wide range of olefins were epoxidized in short reaction times tolerating a variety of functional groups such as ether, nitro, ester, and cyano.

2.15 Iron phosphates

In 2010 Xia, Huang *et al.*[71] described a trifunctional catalytic system by combination of an iron salt and a chiral Brønsted acid. Its application to the asymmetric Friedel–Crafts alkylation of indoles with β-aryl α′-hydroxy enones was reported. The authors hypothesized that a cooperative catalytic system would be efficient for the aforementioned transformation. In this system a Lewis acid would be responsible for the activation of the electrophile, and the nucleophile could be activated by a hydrogen-bonding interaction. Additionally, this free proton source might



Scheme 36 α-Addition of isocyanides to aldehydes.

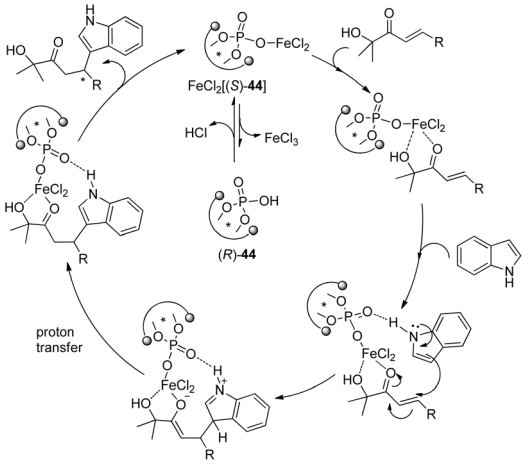


Scheme 37 Epoxidation of olefins catalyzed by the complex **87**.

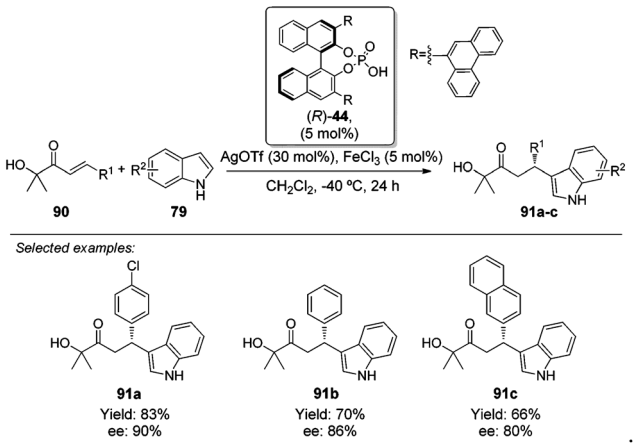
accelerate the process. A series of experiments including ESIMS studies, demonstrated that the Fe(III) phosphate salt ($FeCl_2$[(*R*)-**44**]) afforded the best results, this cooperative association being crucial for the process. The Brønsted acid provided the free proton source necessary for the acceleration of the proton-transfer step in the alkylation step, thus minimizing the non enantioselective $FeCl_3$-catalyzed background reaction (Scheme 38).

Under the optimized conditions, the *meta* and *para* electron-withdrawing substituents at β-aryl α-hydroxy enones proved to afford the desired products in high yields with good to excellent enantioselectivities (Scheme 39), though *ortho* substituents caused a considerable erosion in the enantioselectivity. It was also the case of β-enones derived from heteroaromatic or alkyl aldehyde compounds. The indole component was tolerant with the presence of electron-withdrawing groups. In contrast, electron-donating groups at the indole moiety proved detrimental to the reaction. It was also demonstrated that the role of the hydrogen atom bonded to the indolic nitrogen atom was vital for the reaction, since the enantioselectivity dropped dramatically when *N*-methylindole was tested.

Recently, Beller *et al.* have described an interesting enantioselective formation of chiral amines *via* an enantioselective hydrogenation by way of a cooperative catalysis.[72] Ru, Rh, Ir, and Pd catalysts were tested along with different chiral Brønsted acids but none of them induced the desired enantioselectivity. When the authors turned their attention to iron catalysts, good yields were obtained, and even excellent ee's were achieved in the case of the Knölker iron complex **92** (Scheme 40). NMR studies showed that the combination of (*S*)-TRIP-**4** and the iron complex **92**, allowed the formation of a coordinated species responsible for the hydrogenation of the imines. This reduction



Scheme 38 Proposed Friedel–Crafts reaction mechanism.

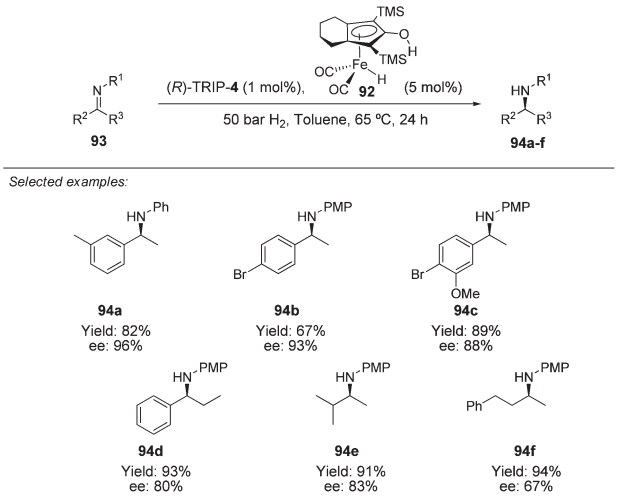


Scheme 39 Friedel–Crafts alkylation of enones catalyzed by an Fe–phosphate complex.

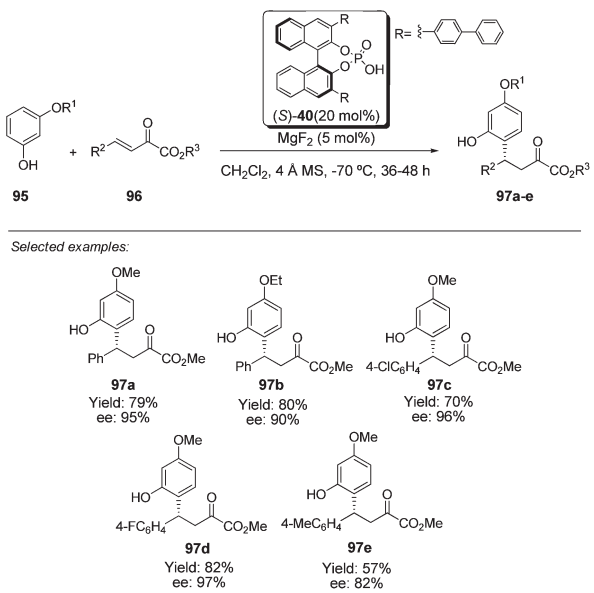
conditions were general enough to enable the use of differently substituted aromatic ketimines, heteroaromatic imines and even the less studied aliphatic imines.

2.16 Magnesium phosphates

In order to design a more active chiral acid, namely a stronger acid capable of promoting a wider range of reactions, in 2010 Luo *et al.*[73] reported that the combined use of a classic Lewis acid, such as MgF_2, along with chiral phosphoric acids derived from (*R*)-BINOL, allowed the enantioselective Friedel–Crafts reaction of β,γ-unsaturated α-ketoesters and phenols (Scheme 41). Once optimized the reaction conditions, which required checking a series of Lewis acids, solvents, and chiral Brønsted acid catalysts, the reaction was applied to different substrates in very good yields (57–82%) and enantioselectivities (Scheme 41). Curiously, the Friedel–Crafts reaction was not detected when 1,3-dimethoxybenzene was used as the substrate. It is worth mentioning that this catalytic system was also successful when indoles were used as nucleophiles, giving high ee's values (84–94% ee). Concerning the structure and the role



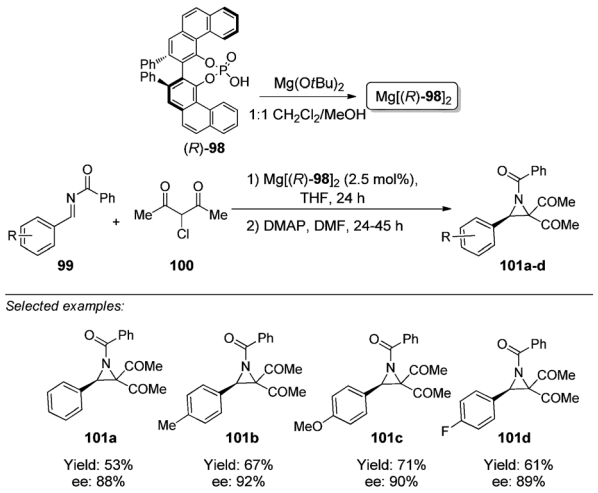
Scheme 40 Catalytic reductions in the presence of phosphoric acids and iron catalyst.



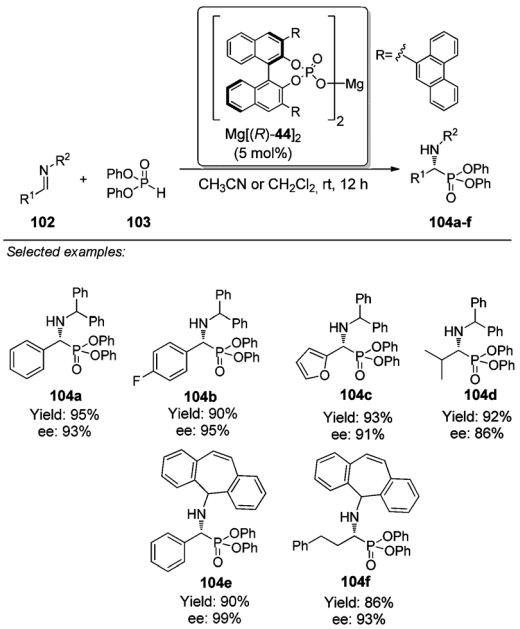
Scheme 41 Enantioselective Friedel–Crafts reaction of β,γ-unsaturated α-ketoesters.

played by the catalytic species, the authors proposed that the chiral phosphate/phosphoric acid could be involved as a ligand to generate a multiacidic center, which proved to have a synergistic effect between both acids. In fact, they found that MgF_2 itself did not promote this reaction and a ratio 4 : 1 (*S*)-**40**/MgF_2 was necessary to get high enantiomeric excesses.

More recently, Antilla *et al.*[74] reported the preparation and the use of the chiral magnesium phosphate Mg[(*R*)-**98**]$_2$. This catalyst, which was readily prepared from (*R*)-VAPOL [a phosphoric acid derived from (*R*)-2,20-diphenyl-3,30-(4-biphenanthrol)] and Mg(O*t*-Bu)$_2$, was then used in the asymmetric aza-Darzens reaction involving α-chloro-1,3-diketones and *N*-benzoyl imines (Scheme 42). Different chemical elements from groups 1 and 2 and different metal/chiral phosphate ratios were surveyed. The Na and Li phosphates gave low conversions and



Scheme 42 Asymmetric cyanosilylation of ketones catalyzed by Mg[(*R*)-**98**]$_2$.



Scheme 43 Asymmetric phosphination of aldimines catalyzed by Mg[(*R*)-**44**]$_2$.

enantioselectivities, whereas Mg salts, upon a ratio 1 : 2, provided excellent results. With the optimal conditions, the syntheses of the corresponding aziridines, bearing a series of substituents at the aromatic ring, were performed in very good yields (52–78%) with good ee's (57–92%) (Scheme 42). The authors accomplished a theoretical study in order to obtain information about the structure of the VAPOL-magnesium catalyst Mg[(*R*)-**98**]$_2$, and a transition state was proposed. In this sense, the catalyst could interact with both the electrophile and the nucleophile, generating a suitable chiral environment for the reaction.

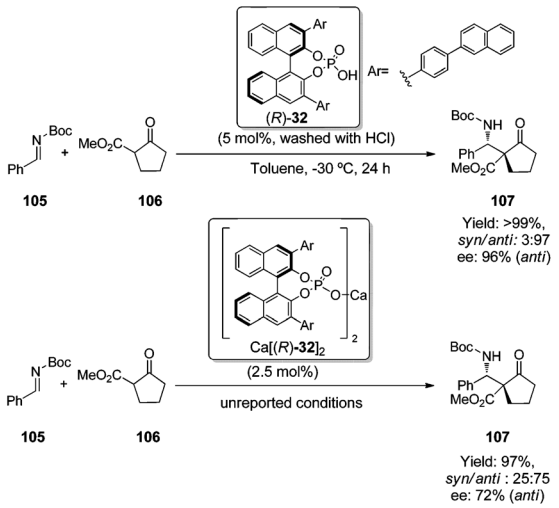
Simultaneously, Antilla *et al.*[75] also carried out the enantiomeric phosphination of aldimines, in this case using the chiral magnesium phosphate Mg[(*R*)-**44**]$_2$ (Scheme 43). An identical procedure to the previously described method was used to prepare the catalyst Mg[(*R*)-**44**]$_2$, albeit herein a skeleton derived from BINOL was used as the source of chirality. Once again, a series of chiral metallic phosphates were assayed, although the magnesium salt afforded the best results. This aza-Pudovik reaction was compatible with both aromatic and aliphatic *N*-benzhydrylaldimines and a wide structural scope was investigated. In all the tested cases, excellent yields (65–97%) and enantiomeric excesses (48–96%) were obtained (Scheme 43). The effect on the *N*-substitution was also investigated, having found that 5*H*-dibenzo[*a*,*d*]cyclohepten-5-amine improved the asymmetric induction (Scheme 43), probably due to π,π-stacking interactions between the imine and the catalyst. Deprotection of the resulting amines was performed and no erosion in the enantioselectivity was observed.

2.17 Calcium phosphates

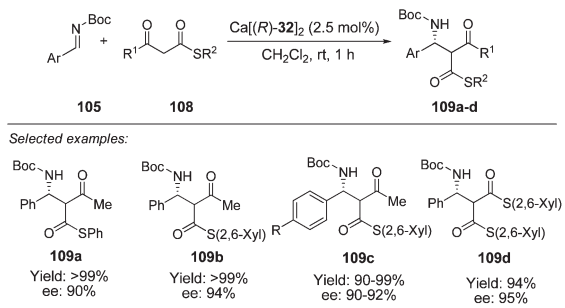
Interestingly, in 2008 Ding *et al.* reported that the catalytic activity of phosphoric acids in the Baeyer–Villiger reaction could be improved after washing the catalyst with HCl, and concisely they argued "the exact reason for the improvement of the activity is not yet clear, but it might be attributed to the removal of some trace amounts of impurities that poison the catalyst".[76] In the same year, Rueping *et al.* reported in a concise paragraph (in ref. 18 of this publication they mention their intention of working in this field in the future)[77] that calcium phosphates were disregarded for being the least reactive complexes.[78] These two previous works provoked some researchers to develop a procedure for eliminating these impurities since they were interested just in the Brønsted acid catalyst. It was in 2010 when Ishihara's group published the first work related to the use of calcium phosphates and their catalytic activity, this being a breakthrough in this field.[79] In that paper, they studied the addition of 1,3-dicarbonyl compounds to imines (Mannich-type reaction) catalyzed by metal phosphates; the reaction with the corresponding phosphoric acids was also investigated. Under the former conditions, 2-substituted 1,3-dicarbonyl compounds were subjected to study under a hydrogen phosphate, obtaining good enantio/diastereoselection and good yields for a large variety of substrates. However, when they compared these results with those derived from the use of a calcium derivative, the latter ones were poorer regarding diastereoselectivity and enantioselectivity (Scheme 44).

After that, they decided to try more challenging and suitable pronucleophiles such as β-ketoesters and thiomalonates (Scheme 45). Thus, the phenylthio derivative **108** led to the Mannich products **109a–d** in excellent yields (90–99%) with good ee's (90–95%). The results were improved when the phenyl group was substituted by a 2,6-xylyl group, thus obtaining up to 99% yield and 95% ee. The reaction was also carried out with different aromatic groups at the *N*-Boc-aldimine and thiomalonates with excellent yields and enantioselectivities (Scheme 45). The monothio and the thiomalonate derivatives were further transformed by decarboxylation and reduction into synthetically useful products.

Based on this preliminary work, in 2011 Antilla *et al.* published two consecutive papers on the functionalization of 3-substituted oxindoles using chiral VAPOL calcium phosphates. In



Scheme 44 Comparison of Mannich reaction under phosphoric acid (*R*)-**32** and calcium phosphate Ca[(*R*)-**32**]$_2$ catalysis.

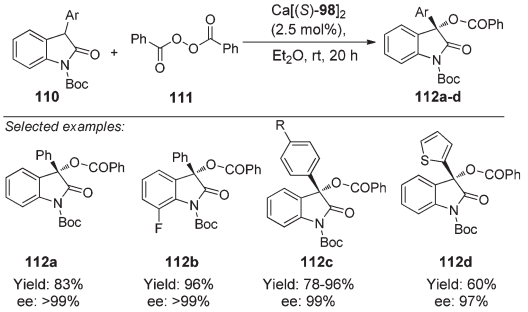


Scheme 45 Mannich-type reaction catalyzed by calcium phosphates.

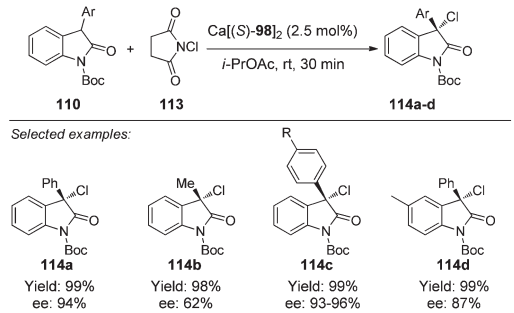
the first one,[80] the benzoyloxylation of 3-aryloxindoles was described, in the presence of a variety of metal phosphates; different results were reported, those obtained with calcium (2.5 mol%) and strontium phosphates (2.5 mol%) being remarkable. In both cases, good yields (83 and 82%, respectively) and excellent enantioselectivities (>99% ee for both cases) were obtained. However, in the case of the calcium phosphate Ca[(*S*)-**98**]$_2$, obtained from (*S*)-VAPOL and $Ca(MeO)_2$, the catalyst loading was lowered to 0.1 mol% without erosion either in the enantioselection or in the isolated yield. After optimizing the reaction conditions, the authors described fourteen examples, all of them with excellent enantioselectivities (91 to >99%), and good yields (Scheme 46).

Antilla's second work of this series is related to the chlorination and Michael-type addition of oxindoles.[81] In this paper, the authors described different metal phosphates, and once again the calcium catalyst Ca[(*S*)-**98**]$_2$ showed the best performance in terms of enantioselectivity. Some selected examples of asymmetric chlorination are outlined in Scheme 47. The reaction gave excellent yields in all the cases and excellent ee's for aryl-oxindoles; only a moderate ee was observed when an alkyl-oxindole was used.

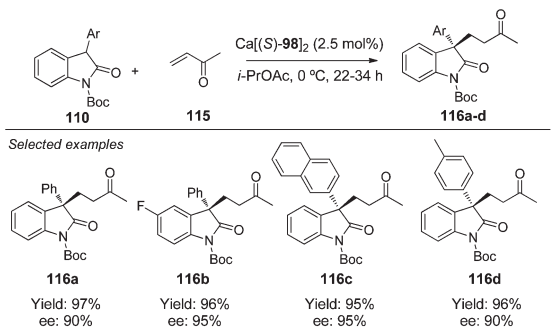
In this work, the authors also evaluated different Michael acceptors, obtaining only good results with methyl vinyl ketone and the same catalyst Ca[(*S*)-**98**]$_2$. Only four oxindoles were



Scheme 46 Benzoyloxylation reaction catalyzed by calcium phosphate Ca[(*S*)-**98**]$_2$.



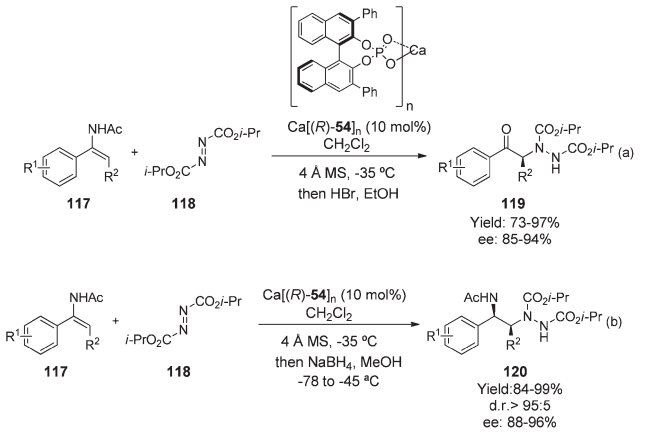
Scheme 47 Asymmetric chlorination catalyzed by calcium phosphate Ca[(*S*)-**98**]$_2$.



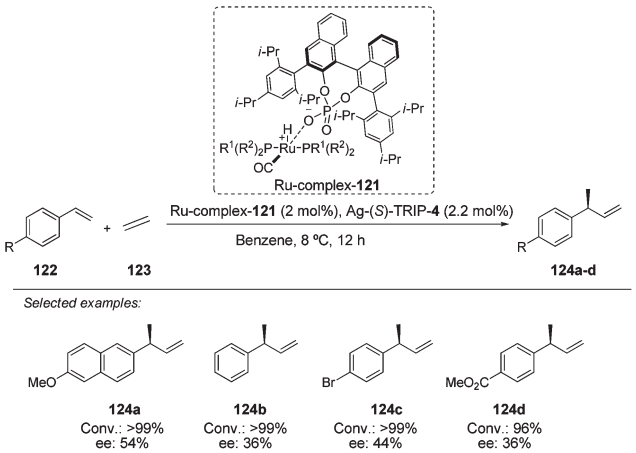
Scheme 48 Michael-type addition of oxindoles to methyl vinyl ketone.

tested and excellent yields and ee's were obtained with this calcium phosphate catalyst (Scheme 48).

In the same year, Zhu, Masson *et al.* reported that the chiral calcium phosphate Ca[(*R*)-**54**]$_n$ was an efficient catalyst for the enantioselective electrophilic amination of enamides.[82] In contrast to the widely studied enamines, the use of nucleophilic enantioselective addition of enamides to electrophilic species was scarce. On this basis, different hydrogen BINOL phosphates, with different substituents at the 3-position, were tested, observing that the less hindered substituents gave better yields and enantioselectivities. However, the authors realized, in agreement with Ding's observations,[71] that the yields and ee's were not reproducible, and worse results were obtained when the catalyst was washed with acid. For these reasons, a series of chiral calcium phosphates were synthesized and, to their delight, they



Scheme 49 Scope of the enantioselective Ca-phosphate catalyzed amination of enamides.



Scheme 50 Hydrovinylation reaction catalyzed by a ruthenium complex.

not only gave good yields (75%) and good ee's (95% ee), but also the results were reproducible. Next, they focused their attention on the scope of the reaction by surveying different enamine substitution, with homogenous results, (73–94% yield, 88–94% ee). Additionally, the obtained ketimines were hydrolyzed into the final ketones in a one-pot reaction (equation a, Scheme 49). The formed imines were also *in situ* reduced in an interesting one-pot reaction (instead of hydrolysis), obtaining the final diamine derivatives (useful building blocks and chiral ligands) in excellent yields and enantioselectivities (equation b, Scheme 49).

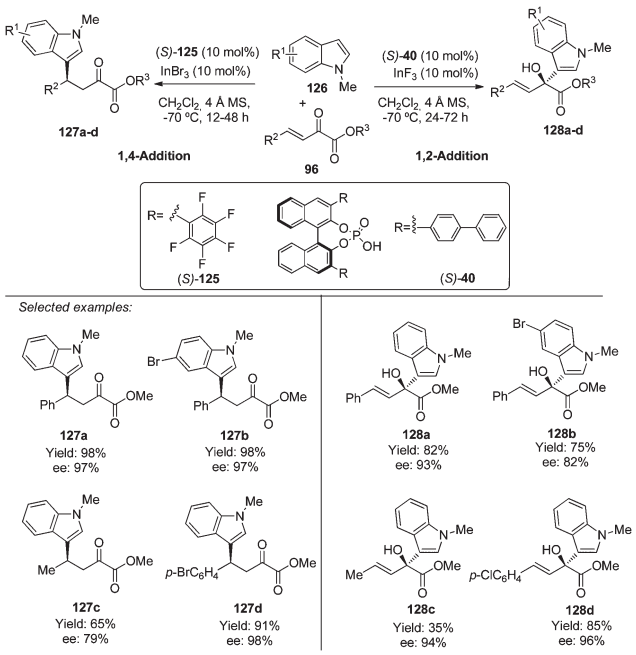
Only speculations and proposals in the above works have been done, and additional efforts in terms of understanding the structure of the catalyst and the mechanism action must be made since these calcium phosphate catalyzed reactions have interesting potential.[83]

2.18 Ruthenium phosphates

Based on the pioneering works of RajanBabu[84] and Connell[85] List and co-workers developed the combination of ruthenium complexes with silver salts.[86] Thus, a new catalytic system was synthesized by inserting a silver phosphate, instead of a chloride anion, in the ruthenium complex. A series of experiments revealed that the best ion pair catalyst for the hydrovinylation reaction in terms of conversion, selectivity and enantioselectivity was the combination of Ag-(*S*)-TRIP-**4** and the ruthenium complex **121**. Other possible combinations afforded less satisfactory results or the reaction was even unfeasible (Scheme 50). The authors performed the reaction with different styrene derivatives, obtaining quantitative conversion, high selectivity and moderate enantioselection (Scheme 50).

2.19 Indium phosphates

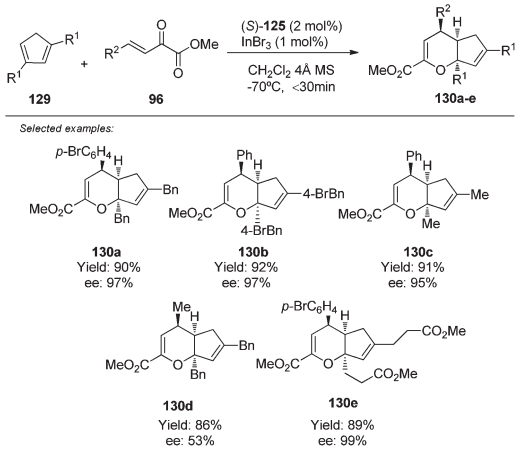
Recently, Luo *et al.*[87] reported the interesting role played by indium(III) salts in the regioselectivity and enantioselectivity in the addition of indols to α,β-unsaturated α-ketoesters (Scheme 51). The combination of chiral phosphoric acids, such as (*S*)-**40** and (*S*)-**125**, with two different indium halides yielded



Scheme 51 Enantioselective 1,2- and 1,4-addition catalyzed by (*S*)-**40**/InF_3 and (*S*)-**125**/$InBr_3$, respectively.

excellent results in convergent 1,2- and 1,4-addition processes. In this way, in the presence of $InBr_3$, exclusively 1,4-addition was observed, affording the products **127a–d** in very good yields and enantioselectivities (left, Scheme 51). On the other hand, when InF_3 was used along with catalyst (*S*)-**40**, only 1,2-addition took place with similar results (right, Scheme 51), without the formation of bisindole products.[88] Remarkably, under the two catalytic conditions, both aliphatic and aromatic ketoesters could be used. In order to understand this counteranion effect, the authors carried out ESI-MS experiments of a solution of the involved catalytic species, which suggested that this catalytic complex should derive from phosphoric acid and indium(III) in a 1 : 1 ratio.

Shortly afterwards, the same research group studied the synergistic effect of $InBr_3$ in connection with chiral phosphoric acids



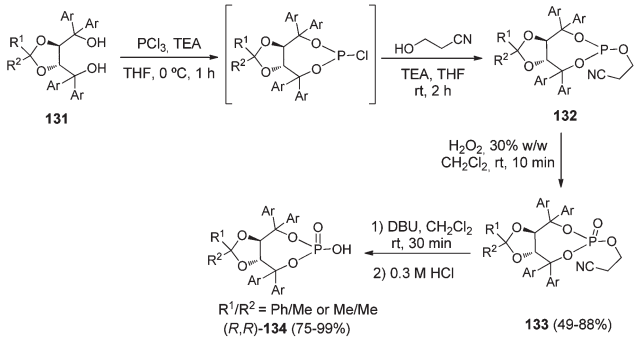
Scheme 52 Enantioselective HDA catalyzed by an indium phosphate.

derived from BINOL using α,β-unsaturated α-ketoesters (Scheme 52). The behaviour of different substituted cyclopentadienes in the Diels–Alder and hetero-Diels–Alder reaction was evaluated under (*S*)-**125** catalysis. When cyclopentadiene and mono-substituted cyclopentadienes were used, excellent yields and ee's were obtained, albeit constituting a mixture of Diels–Alder and hetero-Diels–Alder adducts. Herein, we just highlight those examples of reactions where bis-substituted cyclopentadienes were involved (Scheme 52). Thus, a combination of (*S*)-**125** and $InBr_3$ catalyzed the inverse-electron demanding cycloaddition with good yields in above 90% enantiomeric excesses (94–>99%). In the presence of an aliphatic α-ketoester, only 53% ee was obtained, though in 86% yield. The role attributed to the fluoride atom at the aromatic ring in the phosphoric acid by the authors is noteworthy, since it was responsible, by means of a remote fluoro-effect, for the stereocontrol of the process. The researches prompted a π,π-stacking interaction between this fluorinated-ring and cyclobutadiene to explain a favourable approach in the transition state.

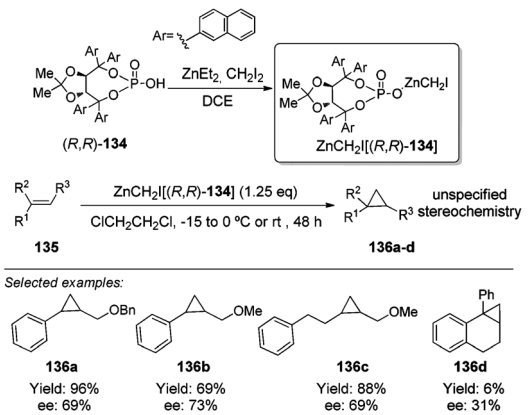
3. Organophosphates derived from TADDOL

Only one successful example of the use of metallic phosphates from TADDOL has appeared in the literature, reported by Charette *et al.* in 2006.[89] This research group compared the asymmetric induction and the reactivity of the enantioselective cyclopropanation exerted by these new structures and a chiral zinc phosphate obtained from (*R*)-**32**/Et_2Zn (see section 2.6). First, they focused on the synthesis of this chiral Brønsted acid and especially its zinc phosphate derivative. Although different procedures had been reported to prepare BINOL-derived phosphoric acids,[10] the authors were unsuccessful in the application of these new structures. Thus, an alternative protocol was employed to obtain the desired catalyst as shown in Scheme 53. Its X-ray structure was investigated by comparison with the BINOL-derived counterpart.[90]

These new chiral TADDOL-derived reagents were assayed as catalysts of the cyclopropanation of olefins. Among all of them, the catalyst (*R*,*R*)-**134**, prepared under classic conditions ($ZnEt_2$ and CH_2I_2 in DCE) (Scheme 54), provided the best results in terms of chemical yield and enantioselectivity. With the optimal



Scheme 53 Synthesis of the catalyst TADDOL-phosphoric acid (*R*,*R*)-**134**.



Scheme 54 Synthesis and application of $ZnCH_2I$[(*R*,*R*)-**124**].

conditions, the authors carried out the cyclopropanation of different aromatic, aliphatic, as well as tri-substituted olefins in moderate to good yields (6–96%) with moderate ee's (31–75%). The Simmons–Smith reaction catalyzed by BINOL-derived phosphate, reported by the same group (see section 2.6), provided comparatively better results in terms of asymmetric induction of the obtained cyclopropanes.

Conclusions

In this review, we have covered those reactions concerning the use of metallic organophosphates and their applications. The complexity involved in the combination of phosphoric acids and different transition and non-transition metals in a series of transformations with a wide range of reactivities in moderate to excellent enantioselectivities has been shown. The complexity of these catalytic systems makes more studies from a mechanistic point of view mandatory in order to get a better understanding of the interaction of the metal/phosphate and also the origin of the enantioselection. Moreover, the large number of plausible combinations between metals and phosphate derivatives would open new possibilities in the near future.

Addendum (April 2012)

During the reviewing process of this manuscript, different works related to the use of metal phophonates appeared in the literature.

Hong *et al*. reported a kinetic resolution of α-allenic alcohols by using chiral silver phosphates.[91] Nguyen and coworkers published different studies on the mechanism of homogeneous gold phosphonates.[92] Rueping *et al.* developed the enantioselective calcium-catalyzed addition reactions of styrene and indole derivatives with trifluoropyruvates.[93]

Acknowledgements

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