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REVIEW

Stereoselective reactions promoted by alkali metal salts of phosphoric acid organocatalysts

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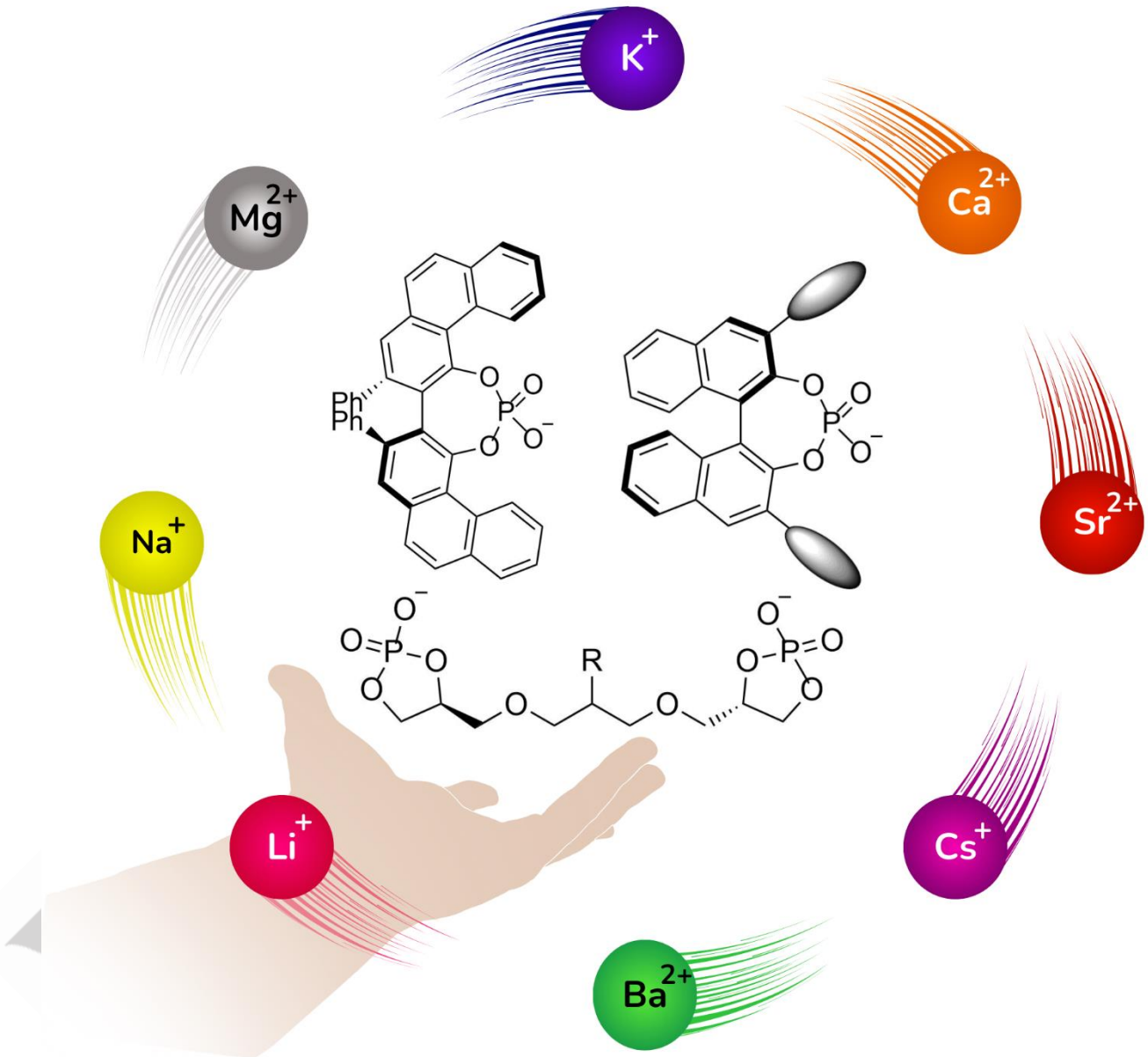

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REVIEW

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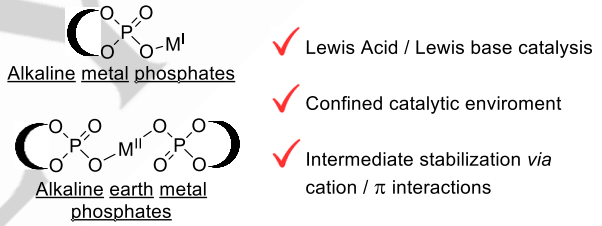
Abstract: The catalytic application of chiral phosphoric acids (CPAs) from 2004 to date represents a true milestone for asymmetric organocatalysis. However, not only the free acids can be conveniently employed in numerous different asymmetric synthetic methodologies, thus being strictly compliant to the concept of "organocatalysis", but also their metal salts. This review focuses on asymmetric reactions in which the catalyst is a chiral alkali or alkaline-earth metal phosphate.

1. Introduction

The development of chiral catalysts has been widely recognized as a key strategy in the preparation of enantiopure molecules, known as "fourth generation asymmetric synthesis".[1] The importance of optically active compounds in multiple relevant industrial sectors, including those belonging to pharmaceutical, agrochemical and material chemistry, has been pushing the development of novel, simple and generally applicable chiral catalysts over the decades. Within this scenario, notable advantages are offered, both from an economical and environmental perspective, by catalysis from small chiral organic molecules not bearing any metal center in the catalytically active site, namely asymmetric organocatalysis.[2] A wide range of catalytically active chiral compounds fulfilling the aforementioned definition are available in the literature,[3] including inexpensive and naturally available compounds such as amino acids[4] and alkaloids,[5] as well as more structurally complex and highly potent molecules like phosphoric acids,[6] their derivatives[7, 8] and disulfonimides,[9] ureas and thioureas.[10] However, nowadays a considerable part of the research on this area deals with the development of synthetic methodologies in green fashion[11] or unconventional reaction conditions.[12] While organocatalysts display different activation modes, they are even able to self-aggregate[13] or act synergistically with other organic or metal-based catalytic species,[14] thus going beyond the borders strictly individuated by the definition of organocatalysis.
Within this scenario, alkali and alkaline-earth metal salts of chiral organic phosphoric acids expand the common Brønsted acid activity of these organic compounds to Lewis acid catalysis establishing some peculiar key-features to this relatively unexplored research field (Scheme 1). Indeed, if on one hand the stoichiometry of alkaline metal phosphates is one to one on the other it might be possible to access a confined catalytic environment by simply moving to alkaline earth metal salts. Moreover, the presence of a soft cation is in some cases crucial in order to achieve outstanding catalytic activity by stabilizing the reaction intermediates via secondary interaction (i. e. cation / π interactions). Finally, similarly to phosphoric acid catalysis, their domain might be ascribed in a more general way within Asymmetric Counteranion Directed Catalysis (ACDC),[15] in which the metal cation activates the substrates, while the stereoselectivity is ensured by the chiral enantiopure anion.

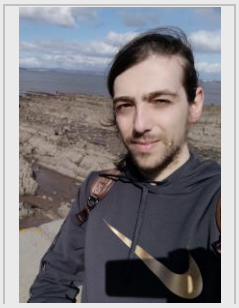


Scheme 1. Representative chiral alkaline and alkaline earth metal phosphates.

Due to the central importance of chiral phosphoric acids in asymmetric organocatalysis, with respect to other organic acids, the present review will be focused on historical background, catalytic applications and mechanistic insights involving chiral enantiopure alkaline and alkaline-earth metal phosphates. The metal phosphates will be presented, by group, according the Lewis acid character of the metal cation even though this is not strictly related to the stereoinduction of the reaction.

2. Structural features and historical background

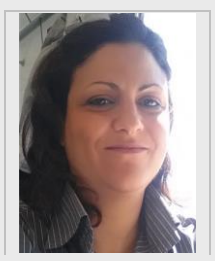
Within the framework of asymmetric organocatalysis, phosphoric acid is a term commonly referred to phosphoric acid diesters having the general molecular formula R_2HPO_4, the two R groups belonging to the same scaffold, which is usually a C_2-symmetric structure. The design of the very first chiral phosphoric acids from BINOL (acronym BPA, BINOL-based Phosphoric Acid), was accomplished in order to access a resolution agent for chiral amines.[16]



Emanuele was born in Rome in 1994, and graduated from "Sapienza" University of Rome (B. Sc. 2017 and M. Sc. 2019), under the supervision of Prof. Antonella Dalla Cort. Following his passion, he moved to Tohoku University to work as a research fellow under the supervision of Prof. Yujiro Hayashi; there he studied the reactivity of α-dicyano compound from October 2020 to September 2021. In November 2021 he started his Ph.D. at the University of L'Aquila under the supervision of Prof. Armando Carlone, working in organocatalysis and synthesis of small molecules of pharmaceutical interest.

Dr. Achille Antenucci was born in Campobasso in 1991 and earned his PhD in Chemical Sciences from "Sapienza" University of Rome in 2019. His research interests mainly reside in the field of organic chemistry, with particular interest devoted to the areas of asymmetric organocatalysis, green chemistry and relative metrics, deep eutectic solvents and exploitation of renewable feedstocks. His experience has been developed both in the context of the academia and of the chemical industry.

Armando Carlone graduated in industrial chemistry at the Università di Bologna (Italy), where he also obtained a PhD in chemistry in asymmetric organocatalysis, under the supervision of Prof. Melchiorre and the direction of Prof. Bartoli, with a 9-month stay in Prof. Jørgensen's group. He moved to Edinburgh (UK) as MCIEF with Prof. Leigh working at the interface of organocatalysis, supramolecular chemistry, and molecular motors. After 7 years in pharma industry with Dr. Reddy's (Cambridge, UK), Armando eventually returned to academia and to Italy when he was appointed associate professor in organic chemistry at the Università degli Studi dell'Aquila.



Prof. Paola Manini graduated in chemistry from the university of Napoli "Federico II" in 1997 and earned the PhD title from the same university in 2002. Since 2018 she is associate professor at the Department of Chemical Sciences of the University of Napoli "Federico II". The main research activity deals with the synthesis and application of Nature-inspired luminescent materials and with the design of melanin-based materials for applications in different fields, from organic electronics to functional materials.

Fabio Pesciaioli was born in 1982 in Narni, Italy. In 2011, he earned his PhD in Chemical Sciences under the supervision of Prof. Giuseppe Bartoli and Prof. Paolo Melchiorre. In 2011, he started the post-doc in Prof. Dr Benjamin List group at Max Planck Institut für Kohlenforschung, where he worked on Brønsted and Lewis acid based organocatalysis. After a research stay as a Cariplo Fellow at Pavia University in the group of Prof. Zanoni, he joined the group of Prof. Lutz Ackermann at Göttingen University focusing mainly on asymmetric C-H activation using catalytic amounts of 3d transition metal based catalysts. Between July 2020 and August 2023 he was appointed as fixed-term researcher (RTDa), and now he is a post-doc in the group of Prof. Armando Carlone at the same University.

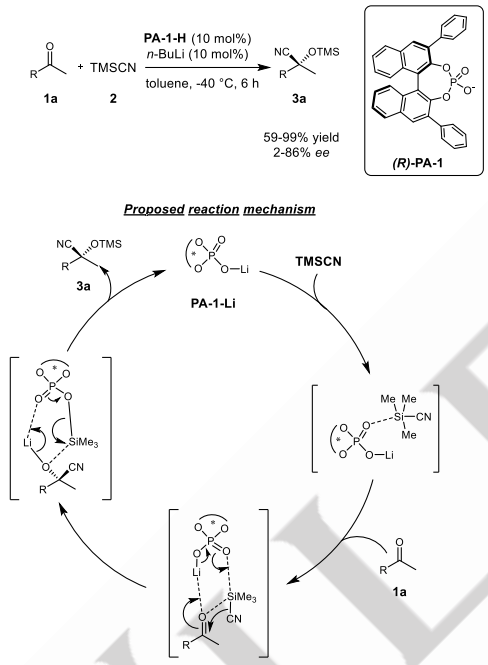
Stefano Dughera is an Associate Professor at the Department of Chemistry University of Turin (Italy). His research lines, always linked to organic synthesis, are focused on sustainable synthesis and catalysis. In particular, he studied several strong organic Brønsted acids as safe and green homogeneous catalysts. Moreover, homogeneous and heterogeneous chiral Brønsted acid catalysts which C_2-symmetry were designed. These adducts turned out to be excellent chiral catalysts in multicomponent reactions, usually in green conditions.

The possibility of functionalization of BINOL in the 3,3' positions in a robust fashion paved the way to the successful synthesis and application BPAs libraries in asymmetric catalysis.[6c-d]Later on, the phosphorylation of other C_2-symmetric diols, such as vaulted biaryls, namely VANOL and VAPOL,[17] and derivatives of TADDOL[18] and SPINOL[19] also afforded efficient chiral organocatalysts (VPAs, TPAs and SPAs, respectively) for different asymmetric synthetic methodologies. More recently, from a chronological point of view, Antenucci and Dughera presented cycloglycerophosphates (cGPAs),[20] which were directly isolated in the form of alkali phosphates due to the instability of the free acid in aqueous environment.[20a], [21] Excluding the latter example, the most common 8- and 7-term cyclic phosphoric acid organocatalysts are stable either in acid or basic environment, and their isolation in the form of free acids after the synthesis and purification is the preferred protocol, as any possible basic treatment with amines or other bases can be further accomplished. In 2008, Ding[22] and Rueping[23] groups, among others,[24], [25] envisioned the possibility of employing chiral alkali and alkaline-earth metal phosphates, respectively, as Lewis acid in catalytic reactions. Hereafter, a review on this research field (divided on the basis of the metal cation involved) with the aim of giving an inspiring and critical overview.

3. Asymmetric reactions promoted by alkali and alkaline-earth metal phosphates

3.1. Lithium phosphates (Li)

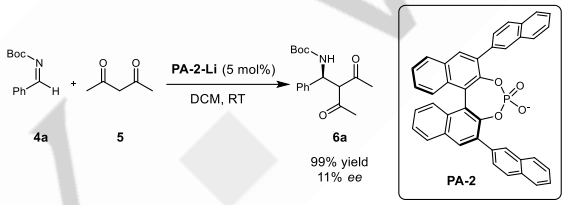
Since lithium is the smallest among the cations of alkali and alkaline-earth metal, and thus the strongest coordinating Lewis acid, one might expect that it was the most exploited counterion for chiral phosphates. On the contrary, only few examples of efficient asymmetric protocols based on lithium phosphates can be found in the literature, together with other examples of different chiral lithium salts, such as those from binaphthyl diols, binaphthyl diamines and derivatives thereof,[27] amide bases[28] and metallocomplex anions.[29] The very first lithium phosphate-catalyzed can be found in the previously mentioned pioneering work by the Ishihara group, displaying also interesting results.



Scheme 2. Lithium phosphate-promoted catalytic asymmetric cyanosilylation of methyl ketones.

A 3,3'-diphenyl substituted lithium BINOL phosphate (**PA-1-Li**) was the catalyst for this protocol, the alkali cation introduced by deprotonation *in situ* with *n*-BuLi. Interestingly, an initial screening with BPA and different bases revealed that not only solvent, temperature and reaction time were determinant parameters for obtaining satisfying results, but also the base strength, fixed the metal cation. Thus, in the case of Li, *n*-BuLi was preferred over LiO*t*-Bu in toluene at -40 °C for 12 hours, since significant differences were observed both in terms of yield (82% vs 49%) and *ee* (36% vs 13%) for the silylated cyanohydrin product. A single reaction, performed on acetophenone in similar conditions with a chiral BINAM lithium phosphate as the catalyst, was also presented by the authors. The mechanistic rationale was postulated on the basis of the general activation mode of phosphoric acids and phosphates, the metal cation acting as a Lewis acid and the oxygen atom of the P=O double bond being a Lewis basic site.[30] In this mechanistic hypothesis, the Si atom can be coordinated by the oxygen atom of the phoshphoryl group, while the carbonyl is subsequently oriented for the cyanide attack on the carbonyl carbon through coordination by both the Si atom of TMSCN and the Li atom of the catalyst. A final rearrangement regenerates the lithium phosphate for the following cycle and returns the silylated cyanohydrin (Scheme 2). Moreover, an analysis of four possible transition states could justify the Si-attack of CN^- on the carbonyl prochiral face and the related enantioselectivity.[8, 24]

Another attempt to use a chiral lithium phosphate can be found in the initial screening of the subsequent work from the same group, in which this species, **PA-2-Li**, generated *in situ* by the use of equal amounts of PA-2 and Li(O*i*-Pr), proved to be an excellent catalyst for the Mannich reaction of acetylacetone and N-Boc benzaldimine, albeit achieving low enantioselectivity (Scheme 3).[25]



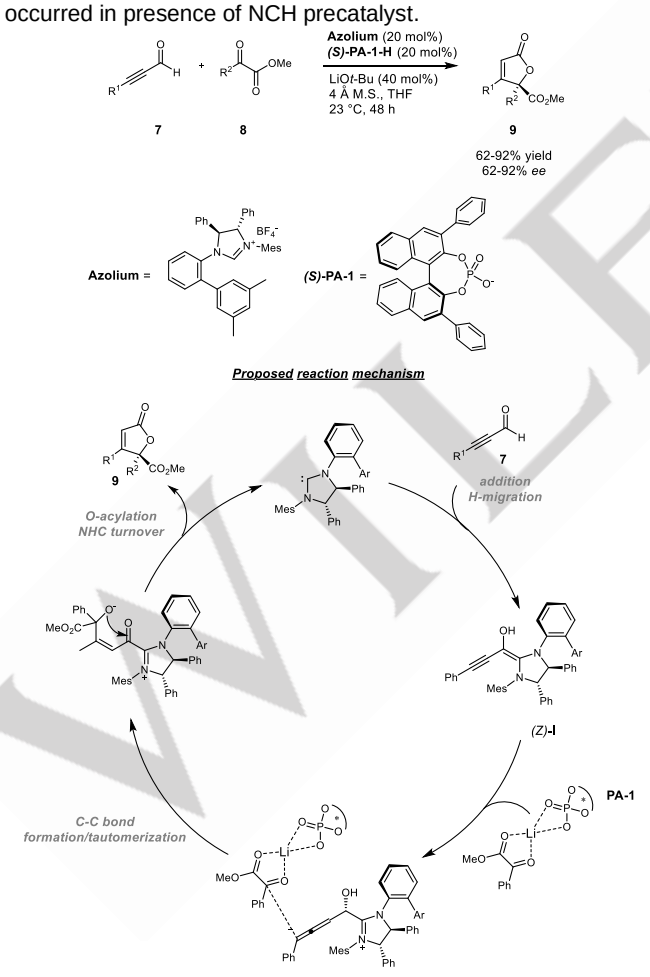
Scheme 3. Mannich reaction promoted by chiral lithium phosphate.

Other sporadic use of chiral lithium phosphates can be found in catalyst screenings of two experimental works, the first one concerning the catalytic aza-Darzens reaction of N-benzoyl-3-methoxybenzaldimine with 2-chlorobutan-1,3-dione, where the lithium salt of VAPOL phosphate afforded the desired substituted aziridine product in 83% yield and only 4% *ee*.[31] Regarding the second work, it deals with a Michael-type hydrocyanation, in which 20 mol% of a chiral 6,6'-diadamantyl BINOL lithium phosphate, generated in situ with equimolar amounts of the corresponding acid and t-BuLi, allows to afford the 1,4-adduct from the model substrate in 89% yield and 32% *ee*. These protocols will be, however, discussed in detail in the following sections, i.e.: chiral sodium and magnesium phosphates, respectively.[32]

A more efficient outcome in terms of the development of truly stereoselective protocols was instead achieved only in 2014 by Lee and Scheidt, who presented an asymmetric [3+2] annulation reaction of alkynyl aldehydes with α-ketoesters.[33] In this work, the catalytic system is constituted by two distinct elements, namely a chiral *N*-heterocyclic carbene (NHC) and a chiral lithium phosphate (obtained *in situ* upon treatment of ***(S)*-PA-1-H** with LiO*t*-Bu), actively cooperating in promoting the reaction in a complex fashion, whose rationale could not be clearly explained by the authors. Indeed, while the role of the lithium cation, of the NHC and of the phosphate in the optimal reaction conditions has been assessed, additional investigation appears to be needed to delineate the separate contributions of such elements. For instance, it seems that the chirality of the NHC, which is generated *in situ* from the corresponding chiral azolium salt precursor, is crucial to the enantioselectivity of the product, since the

cooperativity with achiral lithium phosphates also affords the product in slightly lower yield and *ee* than in the case of the use of an enantiopure phosphate. Moreover, no mismatch effect in the enantioselectivity of the product was observed upon employment of one or the other enantiomer of the chiral lithium phosphate.

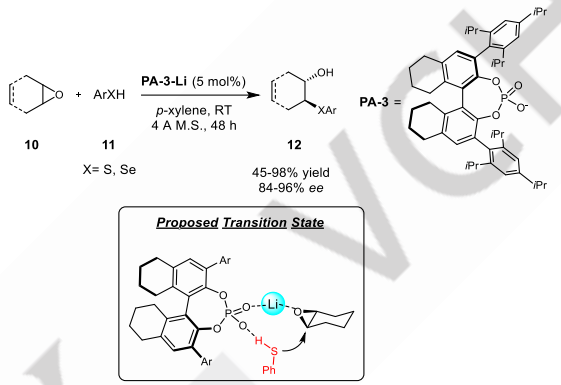
In summary, the best results were achieved in the presence of catalytic and equimolar amounts of a chiral azolium salt and a chiral phosphoric acid with double this amount of Li(O*i*-Pr), serving as a base to generate both the lithium phosphate and the NHC. Interestingly, a ^{31}P NMR study of the species involved in all the stages of the reaction has been also performed by the authors. The proposed reaction mechanism involves the generation of a Breslow intermediate (Z)-**I** from the NHC and the alkynylaldehyde, which then turns into an NHC-bound allenolate that acts as a nucleophile towards the ketone carbonyl of the α-ketoester, activated by the lithium phosphate. Finally, the intramolecular O-acylation affords the final cyclic product regenerating the NHC (Scheme 4). ^{31}P NMR analyses were also carried out in order to probe the state of the phosphoric acid/phosphate under the reaction conditions. In presence of the lithium *tert*-butoxide a noticeable change in the chemical shift of the phosphorus was observed (from 2.71 to 2.82 ppm) while, in presence of the α-ketoester, a slight downfield shift of the ^{31}P signal was observed, meaning a coordination of the lithium ion with both the α-ketoester and phosphate occurred. A similar downfield chemical shift occurred in presence of NCH precatalyst.



Scheme 4. Asymmetric [3+2] annulation of alkynyl aldehydes with α-ketoesters promoted by chiral NHC/chiral lithium phosphate cooperative catalysis.

Moreover, the azolium phosphate alone posses more pronounced downfield chemical shift. All these experimental observations suggest a possible competition between the azolium and the lithium cation for coordination with the phosphate anion, with the lithium-phosphate pair being more likely to form.

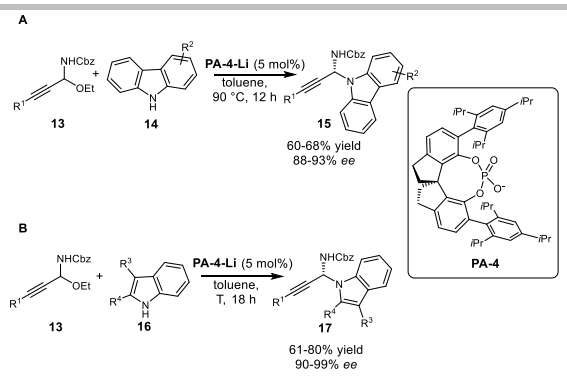
The only work specifically focused on a chiral lithium phosphate-catalyzed reaction and displaying high degree of stereoselectivity is the desymmetrization of meso-epoxides by arylthiols published by Antilla in 2014 (Scheme 5), in which the phosphate **PA-3-Li** has been used.[34]



Scheme 5. Lithium phosphate-catalyzed desymmetrization of meso-epoxides by arylthiols and phenylselenol.

In this work, besides the importance of the size and geometry of the catalyst's scaffold for the enantioselectivity, the role of the metal cation as a Lewis acid is pretty clear. Indeed, Ca and Mg phosphates exhibited no conversion of the substrate, while Sr showed lower reactivity (*i.e.*, lower yield). Only Li and Zn phosphate afforded good yields, the first being preferable also in terms of asymmetric induction of the catalytic species. It is also remarkable the inefficiency of the corresponding Brønsted acidic phosphoric acid. The reaction showed to suffer polar solvents (*i.e.*, the solvent is *p*-xylene and molecular sieves are employed), but proved to efficiently perform, in the presence of thiophenol, on 5- to 7-membered cyclic epoxides; bifunctional cyclic epoxides, on one or both the epoxide moieties (depending on the catalyst loading); hindered epoxides.

Moreover, Shao and coworkers proposed an asymmetric propargylation of carbazoles and indoles using a spinol derived Li-phosphate **PA-4** (Scheme 6):[35] in this approach, the phosphate promote the EtOH elimination from compound 1B allowing the *in situ* formation of a difficult accessible C-alkynyl *N*-Cbz/*N*-Boc imine that subsequently undergoes an asymmetric *N*-propargylic alkylation, with up to 80% yields and 99% *ee*. Furthermore, an interesting diastereoselectivity (d.r.>95:5) and enantioselectivity (96% *ee*), with a 74% isolated yield of the anti-*(1S,2R)* stereoisomer of the ene-carbamate product, was observed upon employment of TRIP lithium phosphate in the catalytic α-bromination of *N*-Cbz *(E)*-propenamine scaffold with NBS. The authors then selected the corresponding calcium salt, which protocol will be discussed later in the respective chapter 3.6, as the best catalyst for the reaction scope.[36]



Scheme 6. Asymmetric carbazoles and indoles propargylation reported by Shao's group.

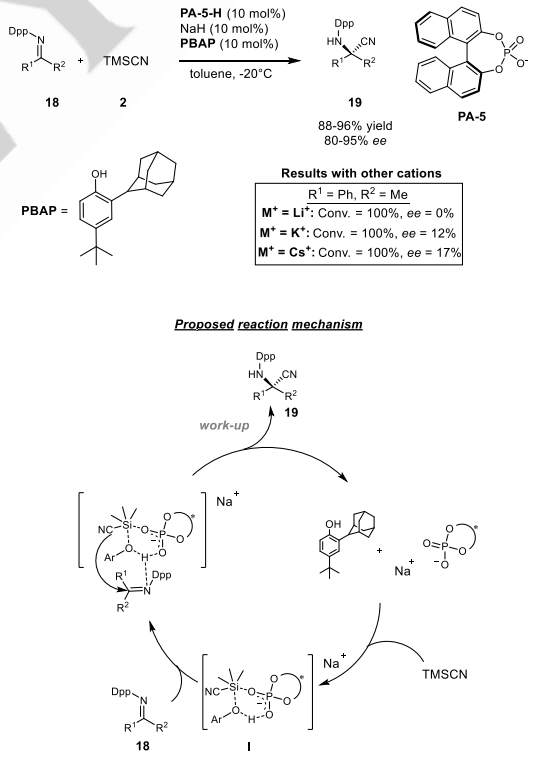
3.2. Sodium phosphates (Na)

Most of the procedures relying on the use of a sodium phosphate as the privileged catalyst deal with the use of a cyanide source as the nucleophile. Notably, the Strecker reaction of TMSCN on *N*-Dpp protected ketimines by the Feng group is one of the first procedures regarding the use of alkali metal phosphates in asymmetric catalysis. In this work, equimolar amount of *in-situ* generated sodium BINOL phosphate (**PA-5-H** and sodium hydride), and a hindered proton source (2-adamantyl-4-*t*-butylphenol (PBAP)) mediate the cyanide addition to the electrophilic carbon of the imine C=N double bond. The proposed mechanism, shown in Scheme 7, was proposed by the authors on the basis of the collected experimental evidences and literature background on the topic.[37] **PA-5** and **PBAP** activate cooperatively the TMSCN *via O*-nucleophilic coordination on the silicon center (intermediate **I**).

Control experiments reveal TMSCN's superiority over HCN as a cyanide source, with HCN negatively impacting enantioselectivity. Noteworthy, the protic additive is necessary to increase both the yield and the *ee*, albeit this compound does not concur in the generation of HCN, and the nature of the base affects *in-situ* the catalytic species efficiency, with stronger bases yielding higher enantioselectivity. When using bases with sodium as a counterion (*i.e.*, NaH, NaOMe, Na_2CO_3), it was shown that the stronger the base, the higher the yield and the enantioselectivity. High yields are linked with the deprotonation with a lithium base (*t*-BuLi or hydrated lithium hydroxide), but the product was racemic in all cases. Toluene was selected as the solvent affording the best yield, and a temperature of -20 °C was found to be the best compromise between reaction time, yield and ee.

Employing α,β-unsaturated carbonyl compounds (*e.g.* enones) as the substrates, Chen et al. showed that BPA sodium salts (generated *in situ* by deprotonation of the corresponding phosphoric acids with NaOH) can selectively activate TMSCN as a soft nucleophile towards the 1,4-addition rather than the 1,2-addition, that would occur in the presence of hard nucleophiles (Scheme 8). The enantioselectivity does not seem to rely just on C_2-symmetry nor on confinement, since none of the screened 3,3'-disubstituted BPA sodium salts did afford appreciable *ee* values. The best catalyst was indeed found to derive from the 6,6'-diadamantyl substituted BINOL scaffold (**PA-6**). As well as for the Strecker protocol by Feng, the reaction is performed in toluene and in the presence of a protic additive, namely 2-*t*-butylphenol, in equimolar amount with respect to the catalyst (20 mol%).[38]

In their following paper on the topic, Chen and co-workers showed that even better results could be achieved by replacing TMSCN with the cyanohydrin of benzophenone as the cyanide source (Scheme 9). Reaction conditions remained still set to 80 °C in toluene, in the presence of catalytic amount of 2-*t*-butylphenol equimolar to the catalyst. Noteworthy, the addition of the cyanide donor at high temperature was crucial for the outcome of the catalytic reaction. Catalyst loading could be as low as 5%, depending on the substrate. Regarding the formal 1,4-nucleophilic attack of CN^- it has to be specified that a stepwise generation of HCN from the cyanohydrin of benzophenone is likely involved. Indeed, in a control experiment, the authors employed the enantiopure cyanohydrin of the substrate as the cyanide source, affording the Michael adduct in 17% yield and in 0% *ee*.[32] A Meerwin-Ponndorf-Verley-type cyanide transfer must be excluded then, since the enantiopurity of the reactant would have been preserved in the product on the contrary.[1] To summarize, while HCN is gradually generated from the cyanohydrin, it can protonate the phosphate catalyst, which facially shields the cyanide anion during its 1,4-attack on the chalcone. The sodium enolate of the conjugate addition product can subsequently be protonated by the phenol, whose conjugate base regenerates the active phosphate catalyst through deprotonation, allowing the cycle to restart.



Scheme 7. Sodium phosphate-catalyzed Strecker reaction of *N*-Dpp protected ketimines with TMSCN.

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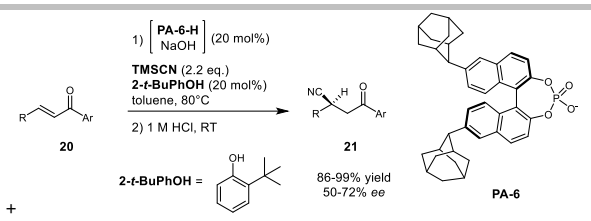
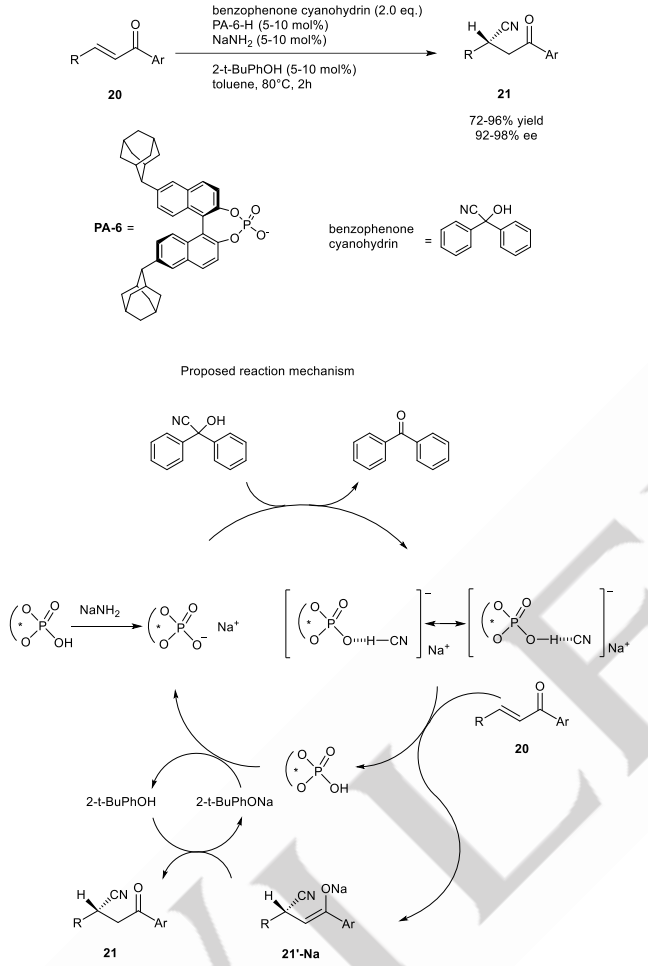
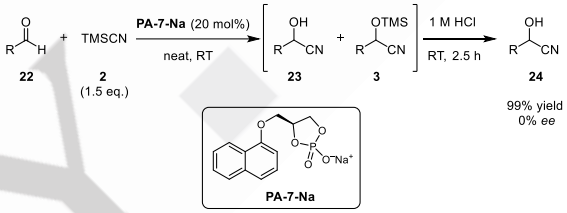


Scheme 8. Sodium phosphate-catalyzed conjugate addition of TMSCN to aromatic enones.



Scheme 9. Sodium phosphate-catalyzed conjugate hydrocyanation of aromatic enones.

Still remaining in the field of enantioselective cyanations, Antenucci and Dughera recently proposed a completely different class of sodium phosphate catalysts, namely cycloglycerophosphates (cGPAs). In this, no sodium base screening was needed for the in-situ generation of the catalyst. Indeed, these phosphates must be isolated and handled as salts due to their inherent instability in acidic aqueous environments, where they undergo non-regioselective hydrolysis of the cyclic phosphodiester bond.[20a], [21]A representative sodium cGPA (**PA-7-Na**) was straightforwardly prepared from enantiopure solketal (*i.e.*, the acetonide of glycerol), the last step of this route being the work-up, composed by: quenching of the phosphorylation reaction with a saturated sodium bicarbonate aqueous solution; evaporating water from the reaction crude and trituration with methanol and ethanol. In a similar fashion, the corresponding potassium phosphate could be prepared by replacing sodium bicarbonate with potassium bicarbonate. However, the sodium and the potassium cGPA salts were employed in a solventless addition of TMSCN to aldehydes at room temperature, to afford *gem*-cyanohydrins. Using 3-nitrobenzaldehyde as the model compound, while the reaction could not reach full conversion in the absence of catalyst, it was complete over 24 hours in the presence of 20 mol% potassium cGPA. Noteworthy, only 5 minutes were necessary in the presence of 20 mol% sodium cGPA; on the other hand, no enantioselectivity was observed in any case (Scheme 10). This behaviour can be explained with an intrinsically low asymmetric induction exerted by the 5 membered phosphatidic acid scaffold, having the stereogenic center far from the catalyst active site and not supported by steric hindrance effects, because of the free rotation around the exocyclic bond bearing the bulky α-naphthyloxy group.[20a], [40]



Scheme 10. Sodium cGPA-catalyzed addition of TMSCN to aldehydes.

Introducing C_2-symmetry, preparing two novel cycloglycerodiphosphates (**PA-8-Na$_2$**) from symmetric bifunctional scaffolds obtained by reaction of solketal with epichlorohydrin or 3-chloro-2-(chloromethyl)prop-1-ene, resulted into an outstanding enantiocontrol of the reaction. A DFT study on a simplified model of the structure of the catalyst (lacking the central substituent) revealed that, in the most stable conformation, the two symmetric 5-membered phosphodiester moieties are *syn* to each other and form a "catalytic pocket" through electrostatic interactions with two sodium cations. Therefore, the successful stereochemical outcome (namely, up to 99% yield and up to 99.5% ee, Scheme 11) of the reaction could be ascribed to both the symmetry and the confined geometry[41] of the transition state[20a] In both cases the phosphate catalyst could be easily recovered and reused. The reaction mechanism, investigated on a minimal model of the catalyst (namely, the sodium salt of the phosphatidic acid of ethylene glycol) with a DFT method, involves several transition states. In all cases, the Si-CN bond breaking event is the first and also the rate-determining step. Then, the oxygen of the phosphate moiety binds to the Si atom, while the sodium cation is coordinated to the other oxygen and the cyanide anion, and also to the carbonyl oxygen of the substrate in a subsequent step. Thus, the attack of the cyanide anion on the carbonyl is somehow directed by the sodium cation through coordination, and in the last steps the silylated/unsilylated cyanohydrin is released, together with the free/SiMe$_3$ protected catalyst. A calculation of the most stable conformation of the

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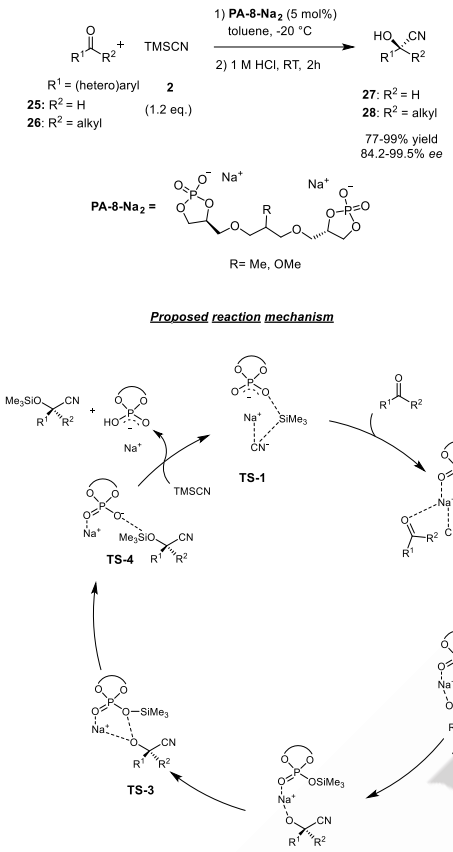
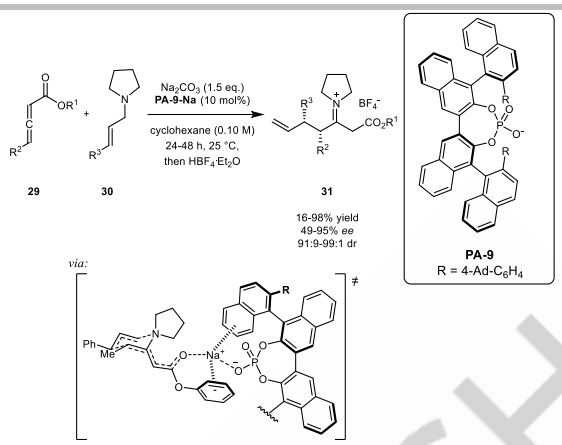
model catalyst for both C_2-symmetric cycloglycero-diphosphates (lacking any central substituent), instead, accounts for the enantioselectivity, since the two cyclic phosphatidic moieties are *syn*, creating a confined pocket for the reactants through electrostatic interactions involving the sodium cations.



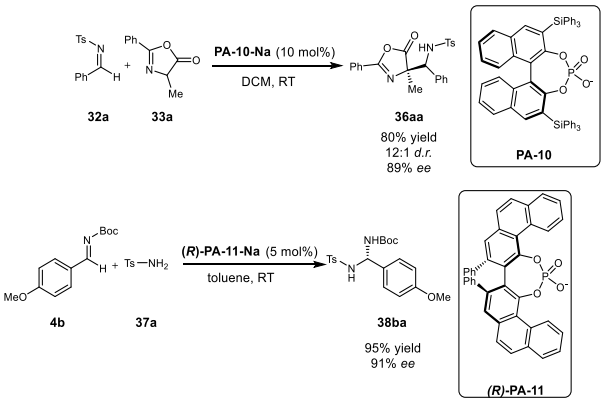
Scheme 11. Bifunctional sodium cGPA-catalyzed enantioselective addition of TMSCN to carbonyl compounds.

The last protocol shown here based on a sodium BPA phosphate catalyst has been presented by Toste *et al.* but it does not deal with cyanide addition to carbonyl compounds. Indeed, Toste and coworkers found doubly-axial chiral phosphoric acids (DAP) sodium salts can be used as catalysts in the allenoate-Claisen rearrangement, in which an allenoate ester reacts with a tertiary allylamine to form a zwitterionic allyl-vinylammonium intermediate, containing charge separation to facilitate a [3,3]-sigmatropic rearrangement (Scheme 12).[42] The DAP structure of **PA-9** was fundamental to achieve an extensive chiral pocket, while a weak coordination of phosphates to cations would create an adaptable environment and potentially allow additional stabilizing interactions between the phosphate and the ammonium moiety of the intermediate. The sodium cation proved to be the best counterion for this reaction stabilizing the transition state *via* cation-π interaction with one of the outer naphthyl moieties of the DAP and the phenolate of the allenoate, while activating the ester moiety through a Lewis acid/base coordination.



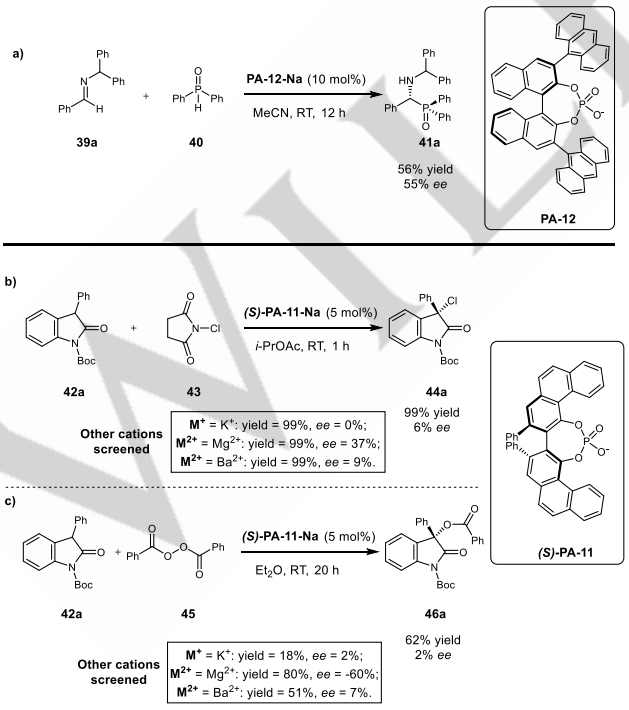
Scheme 12. Allenoate Claisen rearrangement catalyzed by sodium DAP developed by the group of Toste.

The protocols described above represent the only well-established catalytic methodologies based on the use of a chiral sodium phosphate. Nevertheless, as well as for lithium, seven isolated examples are reported in the literature, where a catalyst screening is used to test the catalytic efficiency of some sodium phosphates. Among these, the outcome of the two reactions depicted in Scheme 13 is interesting, albeit the sodium species have not been selected as the privileged catalysts in the corresponding procedures, due to the possibility of affording the desired products in higher yield, with better stereoselectivity and sometimes with a lower catalyst loading with another metal cation. The first one is the addition of a substituted phenyloxazolone to *N*-Ts benzaldimine, to access protected α,β-aminoacids, by the Hui group. A 3,3'-disubstituted BPA bearing bulky triphenylsilyl groups (**PA-10-Na**) is the privileged phosphate, the highest efficiency belonging to the silver salt. Nevertheless, in the presence of 10 mol% of the corresponding sodium phosphate, the product could be diastereoselectively (d.r.= 12:1) isolated in 80% yield, the major diastereomer having 89% *ee*.[43]



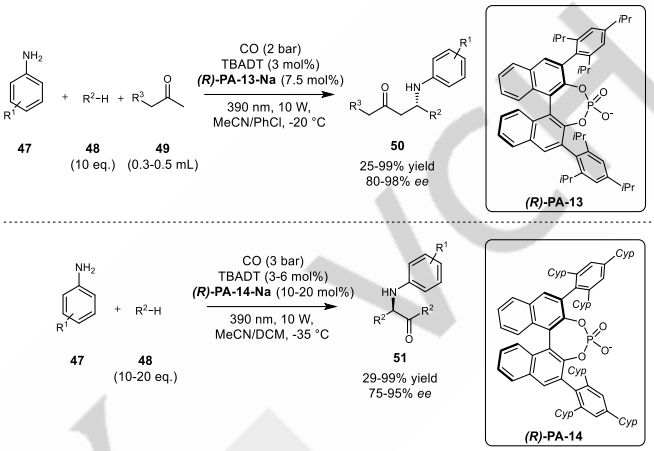
Scheme 13. Isolated examples of efficient stereoselective reactions catalyzed by chiral sodium phosphates.

On the other hand, the Antilla group reported a catalytic asymmetric synthesis of chiral unsymmetrical protected aminals by addition of *p*-toluenesulfonamide to *N*-Boc protected aromatic aldimines. During the catalyst screening on *p*-methoxybenzaldehyde, 5 mol% *(S)*-VAPOL sodium phosphate (***(R)*-PA-11-Na**) (toluene, room temperature, 15 hours) affording the product in 95% yield and 91% *ee*, even if in the end the corresponding calcium phosphate was more efficient, and thus brought further for the reaction scope.[44]Other five examples, summarized in Scheme 14, show modest stereoselectivity using a chiral sodium phosphate salt catalyst. Moderate *ee* (55%) was obtained by Antilla in the addition of diphenylphosphine oxide to *N*-benzhydryl protected benzaldimine catalyzed by 3,3'-(9-anthranyl) disubstituted sodium BPA (**PA-12-Na**) at room temperature in acetonitrile, the product being moreover isolated in 56% yield.[45] Similarly moderate *ee* (40%) for the anti-*(1S,2S)* product, but higher yield (95%) was reported by Della Sala in the desymmetrization with of a meso-aziridine with trimethyl(phenylthio)silane in the presence of sodium (S)-VAPOL phosphate (10 mol% loading, 1,2,3 trichloroethane, room temperature, 12 hours).[46] Almost no enantioselectivity was instead observed in the Mannich reaction of acetylacetone and *N*-Boc benzaldimine (DCM, room temperature, 1 hour) performed by Ishihara and co-workers with 3,3'-(2-naphthyl) disubstituted BPA, in which the final product was afforded in 88% yield and 9% *ee*.[25],[27c] Similar results were produced by the use of ***(S)*-PA-11-Na** for the functionalization of *N*-Boc 3-phenyloxyndole: both chlorination (2.5 mol% catalyst loading, 1 hour at room temperature in *i*-PrOAc)[44] and benzoyloxylation (2.5 mol% catalyst loading, 20 h at room temperature in diethyl ether)[48] were pretty unsuccessful (99% yield, 6% *ee* and 62% yield, 2% *ee*, respectively).



Scheme 14. Isolated examples of poorly stereoselective reactions catalyzed by chiral sodium phosphates.

An elegant and recent application of a chiral sodium phosphate has been reported by Gong and coworkers towards the enantioselective synthesis of α- and β-amino ketones through reversible alkane carbonylation (Scheme 15).[49] Merging the use of a chiral sodium phosphate (whether *(R)*-PA-13 or *(R)*-PA-14) with the decatungstate TBADT, they performed a cascade carbonylation/asymmetric Mannich reaction, with excellent yields and enantioselectivity (with both up to 99%).



Scheme 15. Cascade carbonylation/asymmetric Mannich reaction developed by Gong's group.

The proposed mechanism (reported in Scheme 16) starts with the photoexcitation of the decatungstate catalyst forming the triplet excited state **A*** able to perform a hydrogen atom transfer (HAT) on **48** to form the alkyl radical **I** and reducing itself to form the reduced decatungstate **B**. Then **B** can undergo a disproportion to **A** and the doubly reduced **C**; meanwhile the alkyl radical **I** can give a reversible alkylation on carbon monoxide to form the acetyl radical **II**. A reversible HAT process between **II** and **B** can give the aldehyde **III**, readily subjected to an imination process with **47** forming the imine **IV**. Then three possible pathways are possible: in presence of the ketone **49**, an enantioselective Mannich reaction promoted by the chiral sodium phosphate through **TS-1** occurs to give the β-amino ketone **50** while, in absence of **49**, the imine **IV** can react with the acyl radical **II** in two different ways. The first one, passing by **TS-2**, is a radical recombination process that sees a coordination of both **IV** and **II** to the chiral sodium catalyst followed by radical addition of **II** to **IV**, giving a radical nitrogen specie that undergoes a single-electron transfer by **C** and is subsequently protonated to give the α-amino ketone **51**. In the second pathway, **IV** is reduced to the amino radical **V** by **C**, then the chiral sodium phosphate coordinates both **V** and **II** to give a radical recombination through **TS-3** that leads to **51**.

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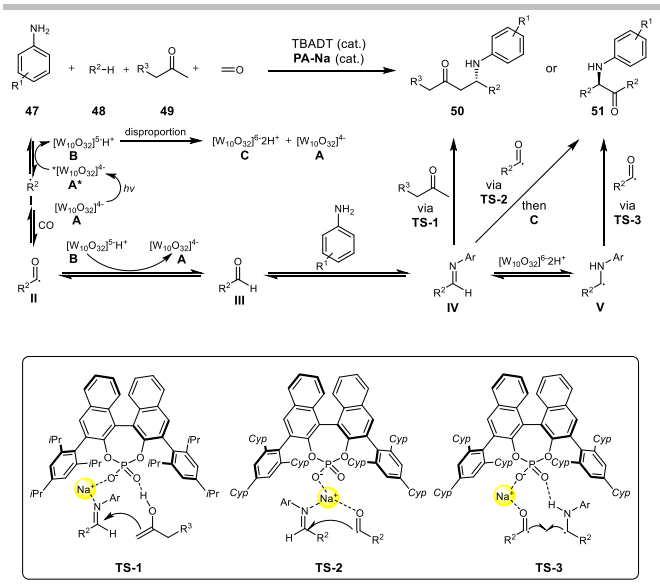


Scheme 16. Proposed reaction mechanism for the reversible alkane carbonylation and the following Mannich reaction.

Moreover, two additional cases are present in the literature, in which chiral sodium phosphates have been tested as catalyst, albeit they did not even promote any substrate conversion.[31],[50]

3.3. Potassium phosphates (K)

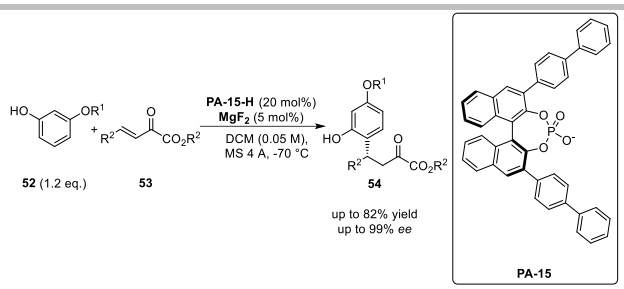
The use of potassium as the counterion of metal phosphates has been taken into account since the beginning of the history of alkali metal phosphate catalysts. Nevertheless, the few cases in which a chiral potassium phosphate has been tested led to moderate results. In 2008, Ishihara isolated the acetophenone cyanohydrin by addition of TMSCN to acetophenone (Scheme 2) in 28% yield and 7% *ee* over 24 hours in toluene at room temperature, the catalyst being generated *in situ* from 10 mol% of **(S)-PA-1-H** and KO*t*-Bu. Interestingly, potassium and sodium salts afforded a poorly enantioenriched mixture with respect to the opposite enantiomer of the product than with Li as the phosphate cation.[24] The same nucleophilic addition, performed in 2009 by Feng on the *N*-Dpp protected acetophenone imine in the presence of 20 mol% the same *in situ* generated catalyst (reaction conditions in Scheme 7), led to full conversion but poor enantioselectivity (*i.e.*, 12% *ee*).[37] The outcome of two protocols by Antilla on *N*-Boc 3-phenylbenzoxyndole employing 5 mol% of VAPOL potassium phosphate as catalyst strictly depended on the electrophile used. Indeed, in the case of 3-benzoyloxylation (Scheme 14c), the product was afforded in 18% yield and 2% *ee*;[46] the 3-chlorination (Scheme 14b) was instead quantitative, but the product was racemic.[47] The latter result was pretty similar to another protocol by Antilla, in which 10 mol% of potassium VAPOL phosphate mediated the addition of *p*-toluenesulfonamide to *p*-methoxybenzaldehyde *N*-Boc imine, the output being 97% yield and 3% *ee* (reaction conditions reported in Scheme 13).[43] So far, the best outcome, in terms of enenantioselectivity, through the use of a chiral potassium phosphate, was the conjugate addition of TMSCN to *(E)*-chalchone, the catalytic active species being generated *in situ* with KOH as the base (*i.e.*, 51% yield and 72% *ee*, reaction conditions reported in Scheme 8).[32] Moreover, our group tested a simple potassium cGPA in the neat addition of TMSCN to 3-nitrobenzaldehyde (reaction conditions in Scheme 8),[20a] for which the conversion was complete over 24 hours, albeit the reaction completely lacked any enantioselectivity.[40]

3.4. Cesium phosphates (Cs)

Even though not widely tested (with three isolated examples available only), cesium deserves the same discussion as potassium. The asymmetric Strecker reaction by Feng on the *N*-Dpp protected acetophenone imine (Scheme 7) afforded nearly the same result as in the case of Potassium, namely quantitative yield and 17% *ee*. In this case, the catalyst was generated *in situ* by deprotonation of *(S)*-BPA with monohydrated cesium hydroxide.[37] In the case of the conjugate addition of TMSCN to *(E)*-chalchone, the deprotonation *in situ* of the privileged binaphthyl phosphoric acid with Cs_2CO_3 rather than KOH led to slightly higher yield (68%), but remarkably lower *ee* (27%).[32] Last but not least, the addition of 3-phenylbenzoxyndole to diethylazodicarboxylate in the presence of pre-generated 3,3'-disubstituted pentafluorophenyl BPA caesium salt (reaction conditions later on reported in Scheme 45c) allowed to obtain the final adduct in 89% yield and 32% *ee*.[51]

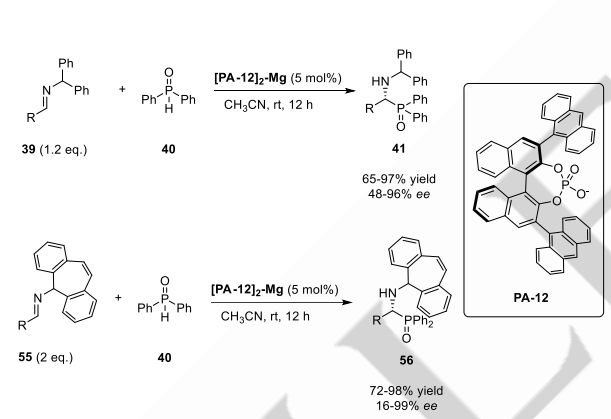
3.5. Magnesium phosphates (Mg)

Besides beryllium, for which no examples of chiral phosphate catalysts are available in literature, magnesium is the smallest between the alkaline earth metals, and its application as the counterion for phosphate catalysts has been investigated since the preliminary findings of Ishihara[25] and List.[26] In these seminal contribution is shown that phosphoric acids used directly after column chromatography are not pure, and their metal salts even being active catalysts for other transformations than those promoted by the corresponding free acids. Two of the first applications of a magnesium phosphate catalyst have been reported by Luo's group[52] and, one year later, by Antilla's group.[31], [45] Even though it cannot be defined an use of a magnesium-phosphate salt in the strict term, Luo proposed a combined approach of chiral phosphoric acids (the best of which was **PA-15-H**) with Lewis acids in the asymmetric Friedel-Craft alkylation addition of phenols or indoles with β,γ-unsaturated α-keto esters (Scheme 17). Between all the bivalent cationic Lewis acids screened in order to increase the efficiency of the chiral phosphoric acid, magnesium salts exhibited superior performances both in terms of activity and stereoselectivity as Lewis acids and, among them, MgF_2 was identified as the best one, showing catalytic activity in the presence of the chiral phosphoric acid.



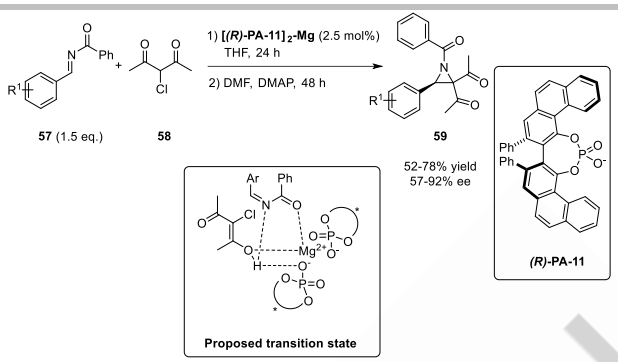
Scheme 17. Asymmetric Friedel-Craft alkylation of phenols developed by Luo's group.

On the other hand, the first approaches proposed by Antilla's group regard the use of a proper magnesium phosphate salt.[31, 45] A BINOL-derived magnesium phosphate (**[PA-12]$_2$-Mg**) was successfully used in the enantioselective phosphination of imines with diphenylphosphine oxide (Scheme 18): several alkali and alkaline earth metal phosphate salts were tested, but the best enantioselectivity (up to 93% *ee*) was obtained in the presence of magnesium as counterion of the 3,3'-(9-anthryl)-binaphtyl phosphate. Furthermore, the *ee* dropped to 80% if the chiral phosphate was washed with hydrochloric acid, thus affording the free phosphoric acid.[45]



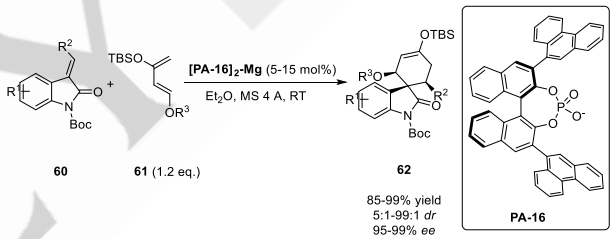
Scheme 18. Antilla's enantioselective phosphination reaction of imines.

Similarly, VAPOL-derived magnesium salt **[*(R)*-PA-11]$_2$-Mg** was used in the asymmetric aza-Darzens reaction for chiral aziridine synthesis (Scheme 19):[31],[45] magnesium proved to be the best counterion, providing the best yields (up to 78%) and enantiomeric excess (up to 92%). Thanks to the presence of the magnesium, the catalyst can simultaneously stabilize the nucleophile and the electrophile, while providing the chiral environment for asymmetric induction. As the imine coordinates with the catalyst, its aryl rings align perpendicular to the plane of the catalyst, while crossing the center to minimize the steric interactions with the phenanthrenes.



Scheme 19. Asymmetric aza-Darzens reaction towards chiral aziridines.

A remarkable use of chiral phosphate magnesium salts was described by the group of Antilla in 2013 in the enantioselective synthesis of chiral spirooxindoles using a magnesium salt derived from **[PA-16]$_2$-Mg** (Scheme 20);[53] indeed, the magnesium cation is able to coordinate to the carbonyl protecting group of the indole to induce enantioselectivity, providing a rigid six-membered ring transition state (Scheme 21).



Scheme 20. Antilla's enantioselective Diels-Alder reaction towards chiral spirooxindoles.

The authors also found that this formal Diels-Alder reaction is moisture-sensitive, since water molecules can coordinate to magnesium cation, decreasing its Lewis acidity and changing its coordination geometry from tetrahedral to octahedral,[54] resulting in lower reactivity and even reversed stereoselectivity. Based on these outcomes, they also proposed a possible transition state: in the presence of chiral Mg(II) phosphate, the imide group of the oxindole coordinates with the metal cation, forming a tetrahedral intermediate in which the top face of the C=C bond is blocked by the 9-phenylanthryl group, while leaving the bottom face open for the diene **61** to form the endo adduct **62a**. Meanwhile, the *t*-butoxycarbonyl (Boc) group holds one of the other 9-phenylanthryl groups in position by steric hindrance. Another successful application of magnesium phosphate salts in an enantioselective Diels-Alder reaction was described in 2019, once again by Antilla and coworkers, starting from benzoquinones and vinylindoles to give the pentacyclic compounds **65** with excellent yields and enantioselectivity (up to 96%) (Scheme 22).[55]

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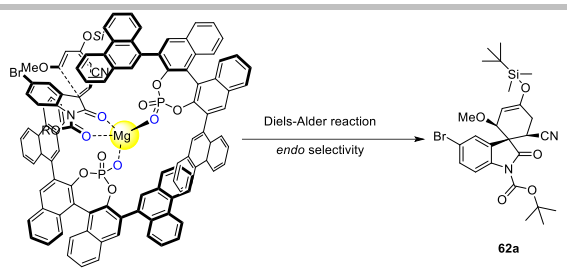
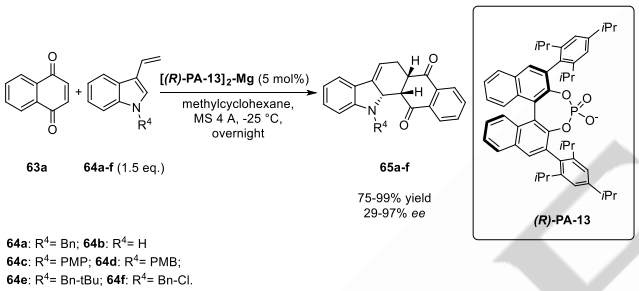


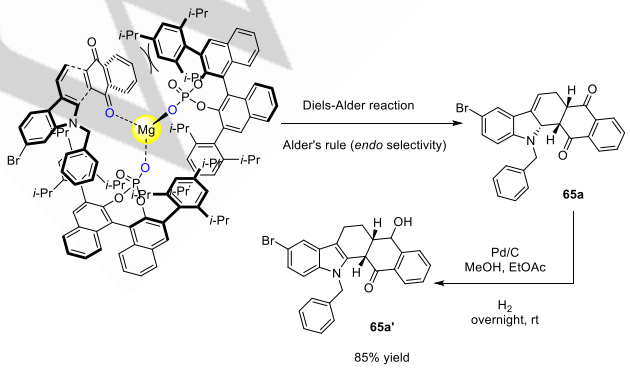
Scheme 21. Role of the Mg(II) cation in the possible transition state of the spirooxindoles synthesis.

Through the screening of the protecting groups on the indole nitrogen, the authors highlighted their important role in the interaction with the catalyst. Indeed, influencing the steric hindrance (even dramatically as in case of the PMP (*p*-methoxy-phenyl) protecting group **65c**, in which the *ee* drops down to 5%), while in case of the free indole nitrogen (**65b**, 48% *ee*) such interaction is due to hydrogen bonding between the catalyst and the indole substrate.



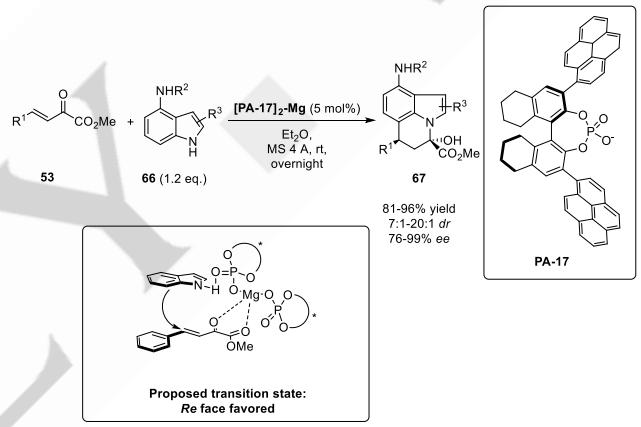
Scheme 22. Asymmetric Diels-Alder from benzoquinones and vinylindoles by Antilla and coworkers.

The carbonyl group of the benzoquinone is presumed to be coordinated with Mg(II) forming the tetrahydrocarbazole intermediate, in which the benzene ring of the dienophile is shielded by the TRIP group, leaving the C=C bond to be attacked by the vinylindole to form the *endo* product (Scheme 23).



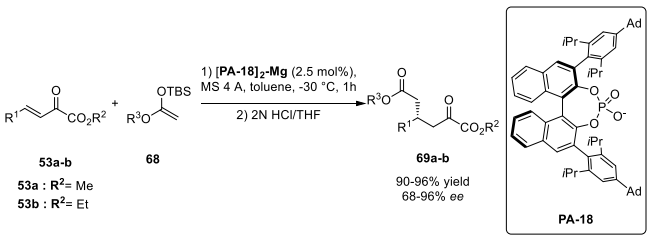
Scheme 23. Role of the Mg(II) cation explained in the transition state towards the pentacyclic molecule **65a**.

On the basis of the aforementioned findings, Antilla and coworkers reported two additional applications of a chiral phosphate magnesium salt. The first one, in 2021 (Scheme 24), concerns a C7 Friedel-Crafts alkylation of 4-aminoindoles using β,γ-unsaturated-α-keto esters, followed by a *N*-hemiacetalization.[56] In this case, they proposed a dual activation mode in which the Mg(II) of the chiral magnesium phosphate **[PA-17]$_2$-Mg** acts a Lewis acid, activating the carbonyl group of the β,γ-unsaturated-α-keto ester. Meanwhile the P=O moiety can activate the 4-aminoindole through hydrogen bonding. The indole can give the 1,4-adduct by attacking the C=C bond from the *Re*-face and subsequently the *N*-hemiacetalization can then occur spontaneously affording the related 1,7-annulated indole derivatives in high yield and enantioselectivity (up to 99% *ee*).



Scheme 24. Antilla's C7 asymmetric Friedel-Craft alkylation of 4-aminoindoles.

In 2023 (Scheme 25), Antilla's group provided an enantioselective Mukayama-Michael reaction on β,γ-unsaturated-α-keto esters with silyl enol ethers, in high selectivity (up to 96% yield and 96% *ee*).[57]



Scheme 25. Enantioselective Mukayama-Michael reaction on β,γ-unsaturated-α-keto esters from Antilla's group.

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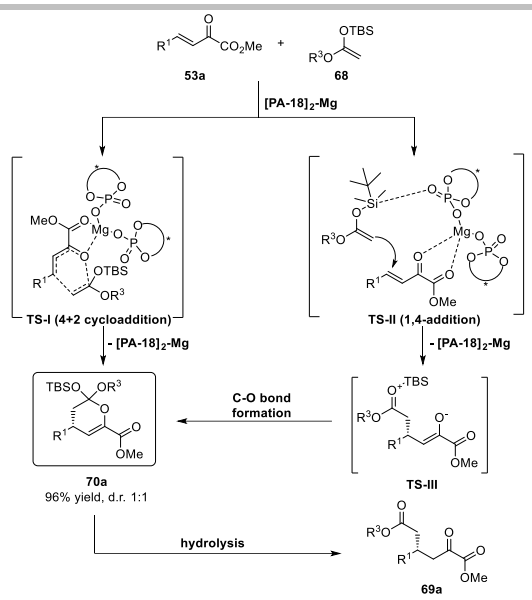
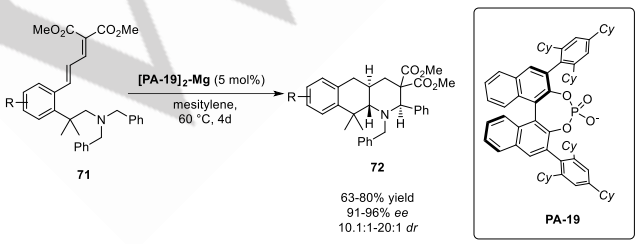


Scheme 26. The two possible pathways of the asymmetric Mukayama-Michael reaction on β,γ-unsaturated-α-keto esters.

According to the proposed mechanisms, two pathways are possible (Scheme 26). In the first one, the Mg(II) acts as a Lewis acid while the P=O exerts its Lewis base character, therefore the silicon interacts with the basic site of the catalyst, while the β,γ-unsaturated-α-keto ester is activated by coordination by the magnesium cation (**TS-II**). The Michael addition then proceeds by the reaction of the silyl enol ether to the unsaturated double bond of **53a** passing through **TS-III** leading to **70a**. Finally, the compound **69a** is obtained after hydrolysis. In the second pathway, the magnesium cation coordinates the two carbonyl groups of the β,γ-unsaturated-α-keto ester catalysing the Michael addition of the silyl enol ether providing product **70a** *via* **TS-I**. Treatment with HCl then allows the hydrolysis of the TBS group, leading to **69a**. Akiyama and coworkers described also a powerful and elegant application of a chiral magnesium di-phosphate, **[PA-19]$_2$-Mg**, in the asymmetric double C(sp3)−H bond functionalization via sequential hydride shift/intramolecular processes between the dibenzyl amine and the vinylogous moieties (Scheme 27).[58] This approach showed a powerful synthetic potential for the construction of complex tricyclic structures in an enantioselective and diastereoselective fashion, with up to 80% yields, 96% *ee*, 20:1 d.r..

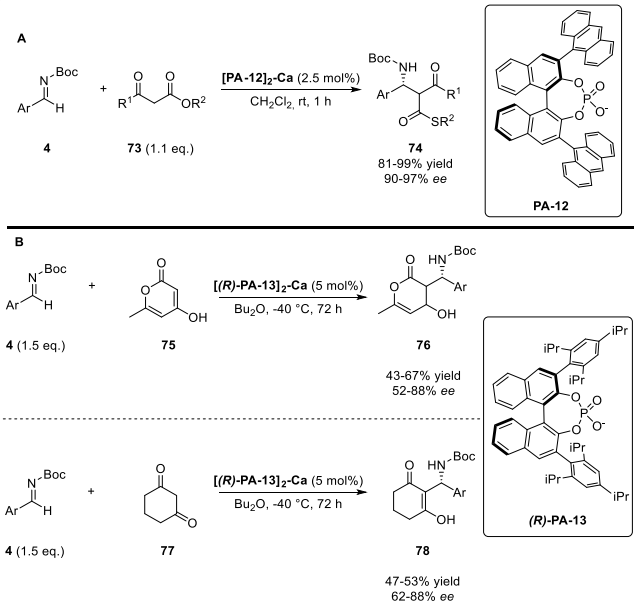


Scheme 27. Asymmetric double C(sp3)-H bond functionalization via hydride shift developed by Akiyama's group.

In conclusion, chiral magnesium phosphates proved to be efficient and solid catalysts, even though the number of reactions catalysed is not large, limiting their application to a niche of substrates.

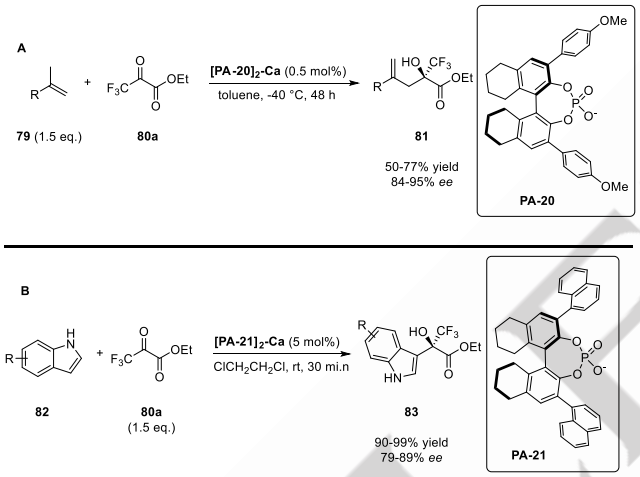
3.6. Calcium phosphates (Ca)

Coming immediately after Magnesium and being one the most widely used alkaline earth metals, many examples of Ca(II) as the counterion of chiral phosphates were reported. These salts were among the first studied, proving that phosphoric acids are obtained as salts with a different reactivity than the acids themselves immediately after chromatographic purification.[25], [26] Compared to magnesium salts, chiral calcium phosphates seem to catalyze a wider number of reactions, making them more versatile. One of the first examples of chiral phosphate calcium salts was reported by Ishihara and co-workers[25] in the enantioselective direct Mannich-type reaction of aldimines with 1,3-dicarbonyl compounds. In particular, **[PA-12]$_2$-Ca** showed a high effectiveness in presence of less acidic 1,3 dicarbonyl compounds such as β ketothioesters and thiomalonates, affording the product in up to quantitative yields and up to 97% *ee*. (Scheme 28 A). Other pioneering works were reported by Rueping and his group. In the first one a chiral calcium phosphate salt, **[*(R)*-PA-13]$_2$-Ca**, was used in the asymmetric Mannich reaction of aldimines with cyclic 1,3-diketones and 1,3-ketolactones with moderate to good yields (up to 67%) and good enantioselectivity (up to 88% ee) (Scheme 28 B).[59] Even though the authors did not provide a mechanistic explanation, the fundamental role of the Ca(II) as coordinating agent can be deduced by the fact that performing the reaction using the corresponding free acid the enantiomeric excess drops sensitively of 20%. The second one proved the efficacy of the two chiral phosphate calcium salts **[PA-20]$_2$-Ca** and **[PA-21]$_2$-Ca** in the enantioselective carbonyl-ene reaction (Scheme 29 A) and the enantioselective Friedel-Craft alkylation (Scheme 29 B), respectively, using trifluoromethyl α-keto ethyl ester **80a** as the electrophile.[60]

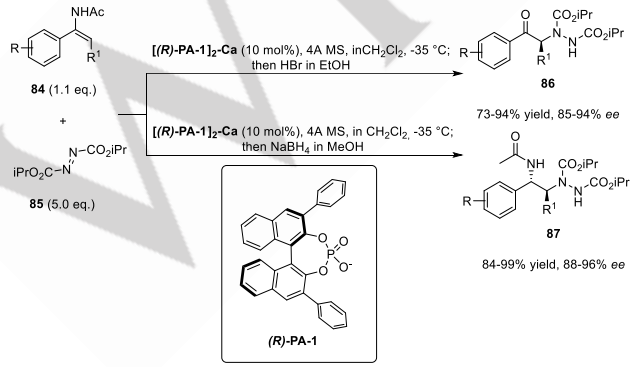


Scheme 28. A: Ishihara's enantioselective Mannich-type reaction of aldimines with 1,3-dicarbonyl compounds; **B:** Rueping's asymmetric Mannich reaction of aldimines with 1,3-diketones or 1,3-ketolactones.

Due to the nature of the substrates, that leads to by-products and, in certain cases, to dimerisations, as in case of styrenes, in acidic environment, chiral calcium phosphates proved to be a better option compared to the corresponding triflylphosphoramides. The carbonyl-ene reaction performed well, both in terms of yield (up to 77%) and enantioselectivity (up to 95% *ee*), while the Friedel-Craft showed better yields (up to 99%) but slightly lower enantioselectivity, not exceeding 89% *ee*. Early reliable applications of chiral phosphate calcium salts have been reported by Zhu and Masson: Zhu and coworkers reported the use of the calcium phosphate salt [*(R)*-PA-1]$_2$-Ca in the enantioselective electrophilic amination of aryl enamides with high yields (up to 94%) and enantioselectivity (up to 94% *ee*) (Scheme 30),[61a, 62b] while Masson's group showed how the TRIP-Ca(II) salt [*(R)*-PA-13]$_2$-Ca was able to catalyze the α-bromination of enecarbamates, in up to 98% *ee* (Scheme 31).[62] While in the first case [*(R)*-PA-1]$_2$-Ca performed better than its corresponding free acid, in the reaction from 89 to 90 the only difference between the use of [*(R)*-PA-13]$_2$-Ca and its free acid (*(R)*-PA-13-H) was the enantioselectivity reversal.

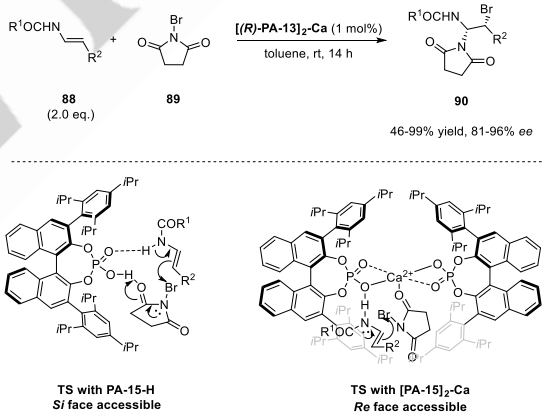


Scheme 29 A:. Rueping's enantioselective carbonyl-ene reaction, **B:** Rueping's enantioselective Firedel-Craft type alkylation of indoles.



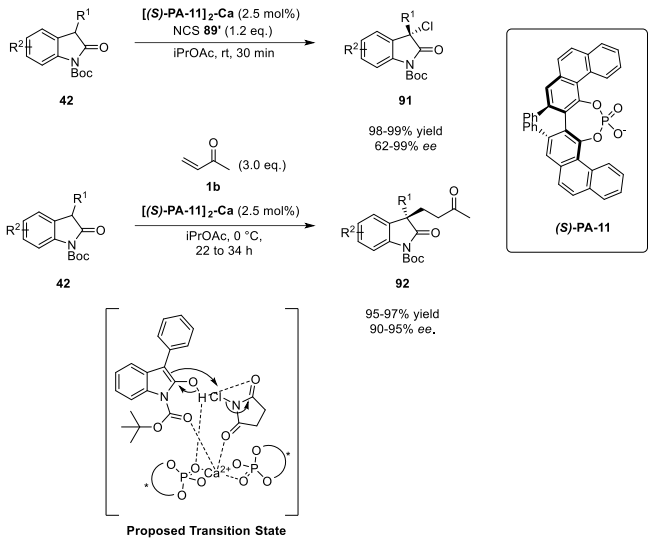
Scheme 30. Asymmetric amination of aryl enamides developed by Zhu's group.

This outcome can be explained by the fact that while ***(R)*-PA-13-H** hinders the *Re* face of **89**, forcing the enecarbamate to attack from the Si face. Another great contribution to the study of chiral phosphate calcium salts can be ascribed to Antilla's group. In 2011 they proved the use of the VAPOL derived phosphate calcium salt **[*(S)*-PA-11]$_2$-Ca** in the asymmetric chlorination of 3 substituted oxindoles with *N*-Chloro-succinimide (NCS) and the asymmetric Michael reaction of the same substrates with methyl vinyl ketone (Scheme 32): both reactions performed extremely well (up to 99% yield and *ee*).[63] Attending to their proposed mechanism, highlighting the bifunctional nature of the catalyst in the activation of both the nucleophile and the electrophile, the calcium ion can chelate to both the carbonyl group of the Boc and the NCS, generating a more compact reaction sphere, while the Lewis basicity of the phosphate can activate the oxindole tautomer. The enantioselectivity can be then enhanced by the hydrogen bonding interactions between the oxindole tautomer and the NCS, alongside with the coordination between the carbonyl oxygens and the calcium cation. On the other hand, if the corresponding free acid was used, no enantioselectivity was detected. Building up on these outcomes, the same group reported also a VAPOL-derived calcium phosphate (**[*(S)*-PA-11]$_2$-Ca**) catalyzed double asymmetric cascade reaction, in which the enantioselective chlorination of oxindoles is combined with the asymmetric formation of geminal diamines from *N*-Boc imines as the electrophiles, in the presence of NCS (Scheme 33), providing the final product 97 in excellent yields and up to 96%.[64]

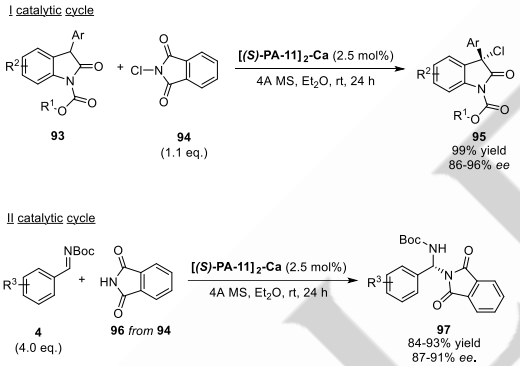


Scheme 31. Masson's enantioselective α-bromination of enecarbamates.

Attending to their suggested mechanism, the chiral calcium phosphate simultaneously activates both the nucleophile and the electrophiles. Indeed, the cation coordinates to the oxygen of the Moc group (R^1 = Me in Scheme 34) and the chlorine atom belonging to NCS, increasing the basicity of the chiral phosphate, while allowing the activation of the oxindole tautomer. These interactions, alongside with the hydrogen bonding interactions of the oxindole tautomer OH group and the P=O group of the catalyst can drive the enantioselectivity of the reaction. The imide formed from the NCS can then participate to the subsequent aminal formation after the calcium in the catalyst activates the imine nitrogen (Scheme 34).

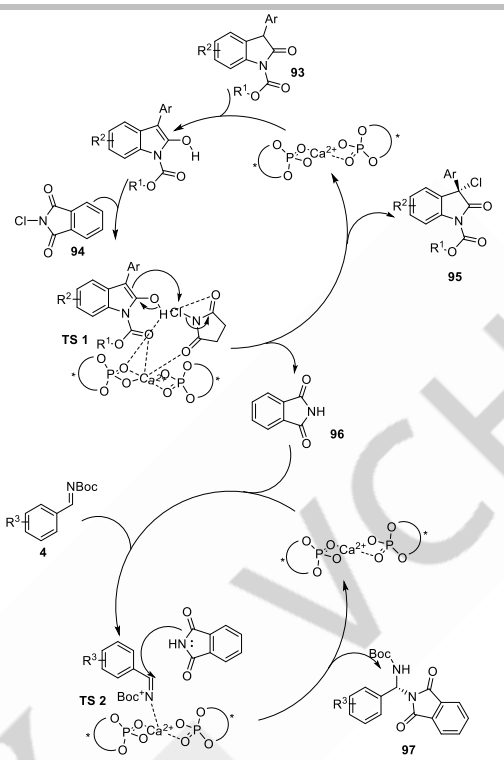


Scheme 32. Antilla's asymmetric chlorination (above) and asymmetric Michael reaction (below) of 3-substituted oxindoles.



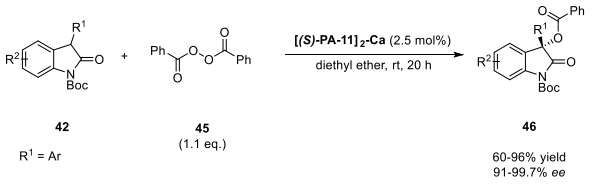
Scheme 33. Antilla's double asymmetric cascade reaction on oxindoles with *N*-Boc-protected imines and NCS.

The catalytic efficiency of VAPOL-derived phosphate calcium salts was proved in several asymmetric reactions. The same [*(S)*-PA-11]$_2$-Ca species showed a good performance in the benzoyloxylation of 3-aryl-oxindoles with benzoyl peroxide (Scheme 35), giving even more than 99% *ee* and up to 96% yield.[48]

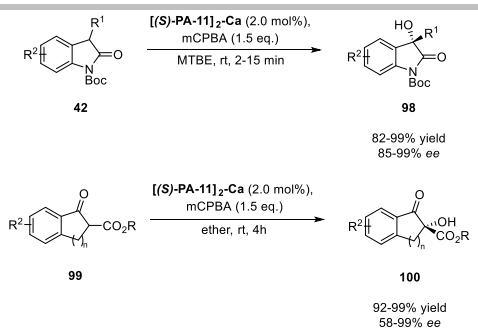


Scheme 34. Proposed mechanism for the double asymmetric cascade reaction on oxindoles.

Even the asymmetric Rubottom-type oxidation on oxindoles and β-keto esters was straightforwardly promoted by 2 mol% **[*(S)*-PA-11]$_2$-Ca**, using *m*-CPBA as the oxidant (Scheme 36). The reaction gave up to 99% yield and *ee* on both the substrate types.[65] In all the examples reported, the coordination of the carbonyl groups and the oxidants driven by the Ca(II) was the key behind the enantioselectivity of the system.

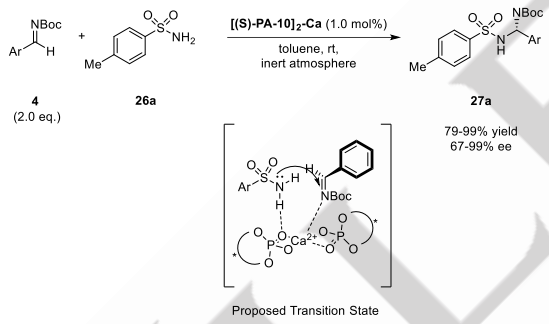


Scheme 35. Enantioselective benzoyloxylation of 3-aryl-oxindoles.



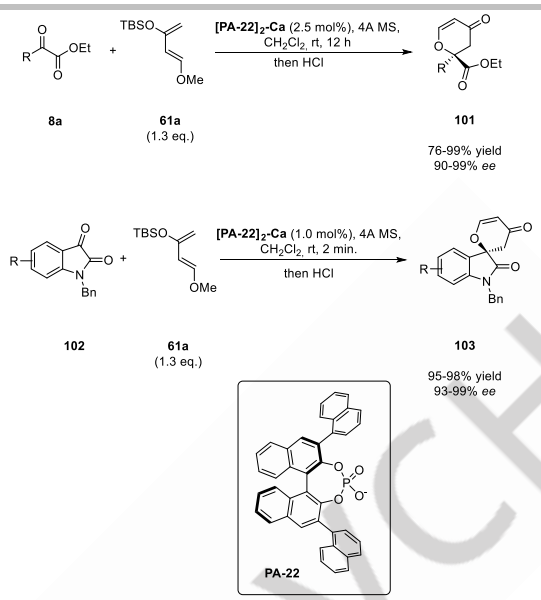
Scheme 36. Asymmetric Rubottom-type oxidation of oxindoles and β-keto esters.

Antilla's group found the VAPOL-Calcium Phosphate **[*(S)*-PA-11]$_2$-Ca** was an efficient catalyst in the enantioselective imine amidation reaction with sulfonamides, reaching up to 99% *ee* alongside a quantitative yield (Scheme 37),[44] proposing a possible transition state in which the calcium ion activates the nitrogen of the imine group while the phosphate is able to act as a Lewis base in hydrogen bonding the sulfonamide (indeed, little reaction was found when the free acid was used, while other cations gave good yield but mediocre *ee*). In the meanwhile, the sulfonamide acts as a nucleophile, attacking the carbonyl electrophilic carbon of the imine.

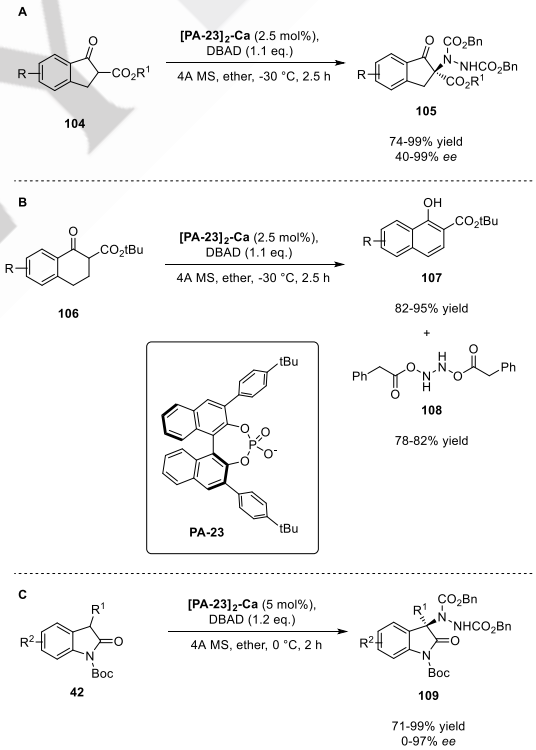


Scheme 37. Enantioselective amidation of imines developed by Antilla.

With respect to chiral BINOL-derived calcium phosphate salts, a highly remarkable application is the enantioselective Diels-Alder reaction. Antilla and coworkers reported an enantioselective hetero Diels-Alder reaction on 1,2-dicarbonyl compounds using Danishefsky's diene and catalyst **[PA-22]$_2$-Ca**.[66] The methodology proved to be excellent, providing up to 99% yield and *ee* (Scheme 38). A little clarification has to be done on the role of molecular sieves when the reaction was carried out on *N*-benzyl protected isatins **102**: they are necessary to activate the catalyst *in situ*. Indeed, if molecular sieves were added without the catalyst, little conversion only was obtained (alongside no enantioselectivity), while in presence of the catalyst alone the reaction time was prolonged.



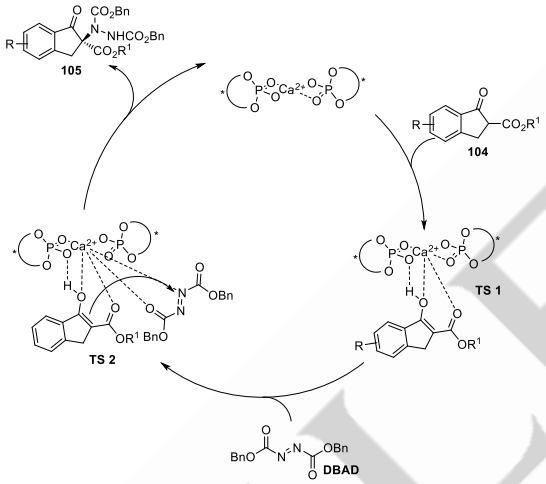
Scheme 38. Antilla's hetero Diels-Alder reaction on 1,2-dicarbonyl compounds using Danishefsky's diene



Scheme 39. Antilla's threefold application of the DBAD in presence of the calcium phosphate **[PA-23]$_2$-Ca**: **A:** enantioselective amination of β-keto esters; **B:** oxidation of 1-tetralone-derived β-keto esters; **C:** enantioselective amination of 3-substituted-2-oxindoles

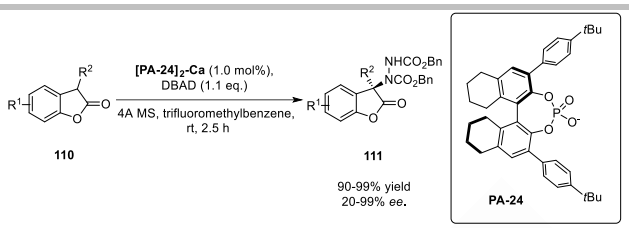
Other reactions that have made a successful use of a chiral BINOL-derived calcium phosphate catalyst are the

enantioselective amination of β-keto esters and the α-amination of 3-substituted-2-oxindoles **42**. Indeed, Antilla's group has developed a catalytic approach using catalyst **[PA-23]$_2$-Ca** in the presence of dibenzyl azodicarboxylate (DBAD) (Scheme 39).[51], [67] With regard to the amination of β-keto esters **104** (Scheme 39 A), the reaction proceeds with high enantioselectivity (up to 99% *ee*) and yields (up to 99%). However, when the substrate was switched to 1-tetralone-derived β-keto esters **106**, the reaction did not work, giving a reaction system in which the DBAD oxidises the substrate instead (Scheme 39 B). In the amination of 3-aryl-2-oxindoles (Scheme 39 C) instead, high yields and *ee* are observed (both up to 99%) when an aromatic group is present in position 3 (R^1= aromatic) of the 2-oxindole. However, when R^1 is a benzyl, an allyl or an *o*-phenyl group, the *ee* decreases dramatically, obtaining a racemate in case of the 3-(*o*-methyl-phenyl)-2-oxindole. Even though the precise mechanism has not been identified yet, as for previous chiral calcium phosphate salts, it has been envisioned that the calcium acts as a Lewis acid activating the β-keto esters while the enol proton interacts with the phosphate through hydrogen bonding and giving rise to the chiral induction and directing the approach of the DBAD (Scheme 40).



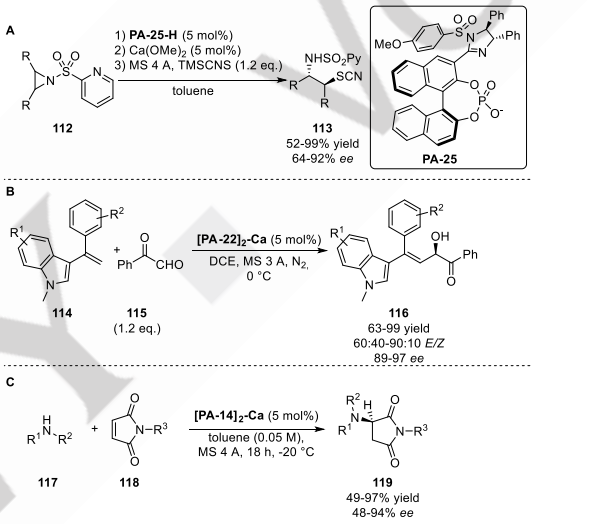
Scheme 40. Proposed mechanism for the selective amination of β-keto esters.

Similarly to the previous example, Antilla's group showed that chiral calcium phosphate salts can be an efficient catalyst in the enantioselective amination of benzofuranones: the catalyst **[PA-24]$_2$-Ca** , used in a 1% loading, allowed the efficient amination of 3-Aryl-2-benzofuranones, providing the products in high yields and enantioselectivities (up to 99% *ee*) using dibenzyl azodicarboxylate as the aminating source, as depicted in Scheme 41.[68] They also found the reaction can work on a larger scale (5 mmol).



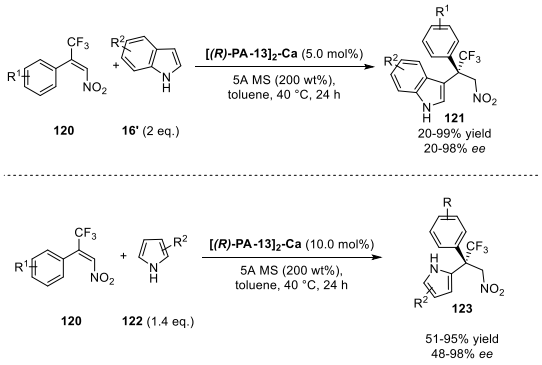
Scheme 41. Antilla's asymmetric amination of benzofuranones.

Other elegant applications of chiral phosphate calcium salts have been reported by Funahashi,[69] Guo[70] and Schneidt[71] (Summarised in Scheme 42) .



Scheme 42: A) Funahashi's desymmetrisation of *meso*-aziridines using TMSC; **B)** Guo's asymmetric alkenylation of arylglyoxals with 3-vinylindoles; **C)** Schneidt's enantioselective conjugate additions of amines.

The last successful application, in terms of complete synthetic methodologies, of a chiral phosphate calcium salt to be described herein belongs to the findings by Akiyama and co-workers. The BINOL-derived species **[*(R)*-PA-13]$_2$-Ca** proved to be an efficient catalyst in the Friedel-Craft alkylation of pyrroles and indoles using β-trifluoromethyl nitrostyrenes (Scheme 43).[50, 72] The reaction proceeds with good yields (up to 99%) and enantioselectivities (up to 98% *ee*), even though it did not work in presence of an alkyl group on the pyrrole or indole nitrogen (the hydrogen bonding between the the pyrrole NH group and the phosphoryl hydrogen is crucial to the outcome of the reaction) and when an *ortho*-substituted nitrostyrene is employed, probably due to steric reasons.

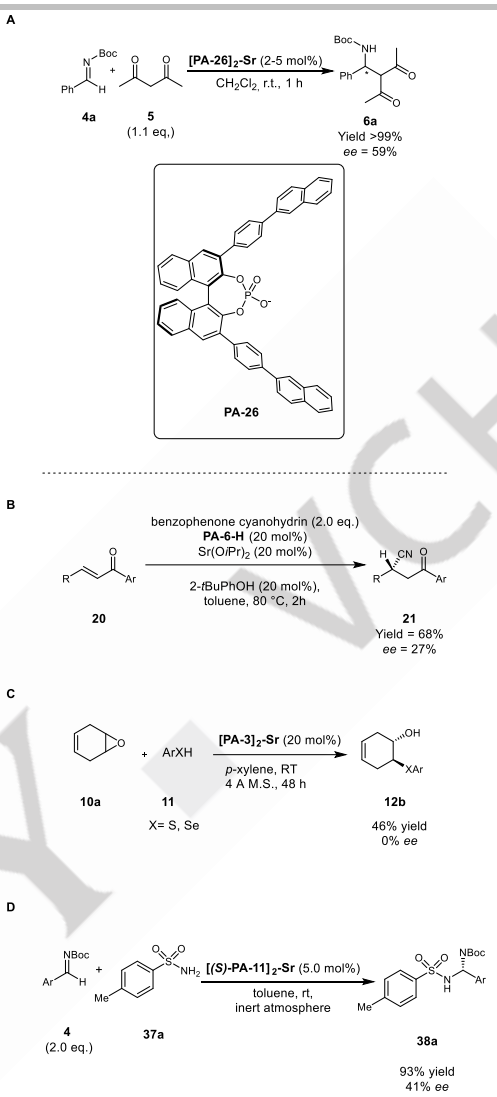


Scheme 43. Akiyama's asymmetric Friedel-Craft alkylation of pyrroles and indoles with β-trifluoromethyl nitrostyrenes.

In conclusion, calcium has been the most exploited counterion for chiral phosphates between all alkali and alkali-earth metals, in contrast with the magnesium, whose chiral phosphate salts have only been used in a restricted niche of reactions. Among all the chiral phosphates, calcium salts a proved to be the most versatile and useful, being able to catalyze several and different reactions, even though the presence of a functional group able to coordinate to the calcium cation generally appears to be required in the substrate. Being calcium the most exploited counterion in the family of chiral alkali and alkaline earth metal phosphates, all of those examples in which calcium salts are employed within the framework of a catalyst screening, even though not being selected as the privileged catalyst, will not be taken into account.

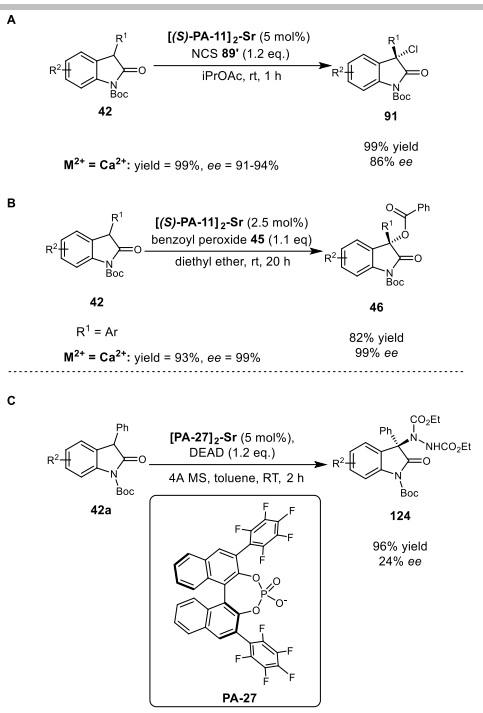
3.7. Strontium phosphates (Sr)

Chiral strontium phosphates have not found pretty much space in the development of catalytic asymmetric methodologies. This may be due to the relatively high ionic radius of this cation, associated with weaker Lewis's acidity. In any case, only scattered examples of the employment of strontium phosphate catalysts can be found in the literature. Starting from the beginning, from a chronological point of view, the first work in which strontium has been tested as a Lewis acidic counterion for axially chiral phosphates is the one by Ishihara deeply facing for the first time the dualism between phosphoric acids and their alkali/alkaline earth metal salts. In particular, the Mannich reaction of acetylacetone and *N*-Boc benzaldimine was the test reaction, the strontium-based catalyst (derived from 3,3'-di-(2-naphthyl) BPA) affording the product in quantitative yield and 59% *ee* (Scheme 44 A).[25], [27c] Similar outcomes involving the use of chiral strontium phosphates were obtained: in the asymmetric conjugate addition of cyanide to *E*-chalcone (Scheme 44 B; 63% yield and -6% *ee*), the catalyst being generated *in situ* from equimolar amounts of the acid and Sr(O*i*-Pr)$_2$;[32] in the desymmetrization of epoxycyclohexane with thiophenol (Scheme 44 C; 46% yield, no enantioselectivity)[34] and in the asymmetric imine amidation of *N*-Boc benzaldimine with p-toluenesulfonamide (Scheme 44 D; 93% yield and 41% *ee*).[44]



Scheme 44. Some examples of chiral strontium phosphate applications: A) Mannich reaction between acetylacetone and benzaldymine; B) asymmetric conjugate cyanide addition on chalchones; C) desymmetrisation of epoxycyclohexane with thiophenols and arylselenols; D) asymmetric imine amidation of *N*-Boc benzaldimine with *p*-toluenesulfonamide.

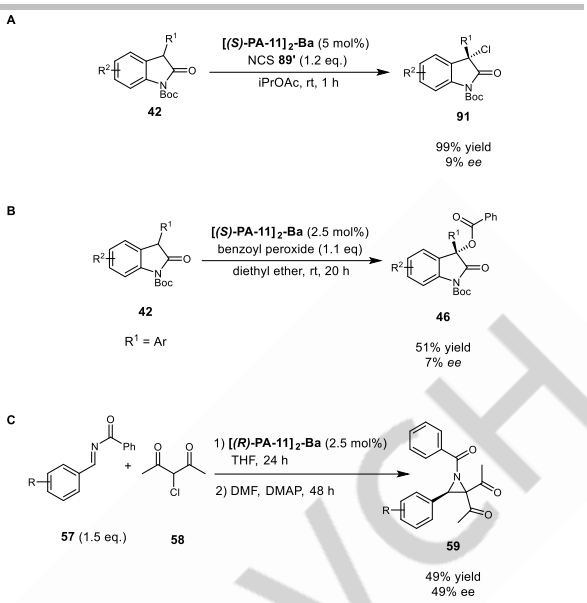
Promising results were obtained by Antilla in the chlorination[47] and benzoyloxylation[48] of *N*-Boc-3-phenyl-2-oxindole. In both the cases, the strontium *(S)*-VAPOL phosphate performed very similarly to the privileged calcium salt: in the case of asymmetric chlorination (Scheme 45 A), 99% yield and 86% *ee* versus 99% yield and 91% *ee* is the result of the comparative outcome Sr versus Ca; on the other side, in the asymmetric benzoyloxylation (Scheme 45 B), the obtained *ee* was higher than 99% in both cases, even the yield being nearly the same (82% for Sr, 83% for Ca). The same substrate was later on explored once again by Antilla, in the asymmetric addition to diethylazodicarboxylate, for which 5 mol% of strontium 3,3'-di-pentafluorophenyl BNP (10 minutes in toluene, with 4 Å molecular sieves, at room temperature) allowed to isolate the diamino functionalized adduct in 96% yield and 24% *ee* (See Scheme 45 C).[51]



Scheme 45. A) Asymmetric chlorination of *N*-Boc-3-phenylindoles; B) asymmetric benzoyloxylation of *N*-Boc-3-phenyl-2-oxindoles; C) Asymmetric addition of diethylazodicarboxylate on *N*-Boc-3-phenyl-2-oxindoles.

3.8. Barium phosphates (Ba)

As well as for strontium, the use of chiral barium phosphates in asymmetric catalysis is doubtless underdeveloped. Indeed, to the best of our knowledge, only three sporadic uses within a catalyst screening are reported in the literature, all of them being related to barium *(S)*-VAPOL phosphate. Moreover, only in a single case, namely asymmetric chlorination of *N*-Boc-3-phenyloxindole (2.5 mol% catalyst loading, 1 h at room temperature in i-PrOAc), a quantitative yield was obtained, against an unsatisfactory 9% *ee*.[47] A similar outcome, in terms of enantioselectivity, was registered in the asymmetric benzoyloxylation of *N*-Boc-3-phenyloxindole (2.5 mol% catalyst loading, 20 h at room temperature in diethyl ether), allowing to afford the product in only 51% yield and 7% *ee*.[48] The last example, being the one with the highest enantioselectivity achieved by a chiral barium phosphate so far, is the already mentioned aza-Darzens aziridination of *N*-benzoyl 3-methoxybenzaldimine and 2-chlorobutan-1,3-dione, where the aziridine product was isolated in 49% yield and 49% *ee* (2.5 mol% catalyst loading, reaction conditions in Scheme 46).[31]



Scheme 46. Some examples of chiral barium phosphates: Asymmetric chlorination of *N*-Boc-3-phenyl-2-oxindoles; B) asymmetric benzoyloxylation of *N*-Boc-3-phenyl-2-oxindoles; C) asymmetric aza-Darzens aziridination.

Room for improvement could be offered, as a future perspective, by the reliable synthesis and purification of barium cGPAs,[73] whose employment in asymmetric synthesis is totally unprecedented.

4. Conclusions

The employment of alkali and alkaline earth metal phosphates in asymmetric catalysis, even though strictly not classifiable as asymmetric organocatalysis, displays many of its advantages, namely fully biodegradability and handiness of the catalyst, absence of costly and toxic heavy transition metals and easiness of preparation from the corresponding phosphoric acids. Sometimes, these salts even allow reactive pathways on complementary substrates with respect to those successfully reacted in the presence of the free acid, following proper “organocatalytic” activation modes. Calcium and magnesium dominate the scene, while most of the other metal belonging to the first and second group have been quite limited in the application to particular reactivities (*i.e.,* sodium phosphates for cyanide direct and conjugate addition to carbonyl compounds) or neglected. Being the metal catalytically active in an ACDC mechanistic fashion, the role of the chiral anion is generally aimed at pursuing the stereoselectivity, and the bivalence of alkaline earth can allow to better address this task, as the corresponding metal phosphates are likely C_2-symmetric and may displace confinement, to some extent.[38] Nevertheless, additional effort both on an experimental and mechanistic perspective in the future will hopefully led to a more widespread use of such species in asymmetric catalysis and to a deeper insight into the related mechanistic rationale.

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Keywords: chiral phosphoric acids • asymmetric catalysis • asymmetric counteranion directed catalysis (ACDC) • alkali and alkaline earth salts • organic synthesis

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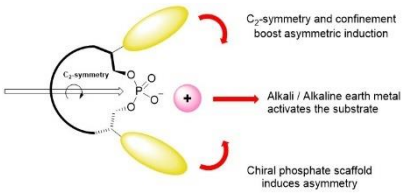

A comprehensive overview on asymmetric organic reactions catalyzed by alkali and alkaline earth metal phosphates following ACDC mechanistic pathways. The lower toxicity associated to such metal species, with respect to transition metals, offers food for thought to their further employment in asymmetric synthesis, also giving a nod to green chemistry.

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