SYNTHESIS OF OCTAHYDROBENZO-1,2,3-DIAZAPHOSPHOLIDINE-2-OXIDES AND THEIR DERIVATIVES: APPLICATIONS IN ASYMMETRIC SYNTHESIS

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Abstract. *This chapter outlines recent efforts devoted to the synthesis of heterocycles that include the octahydrobenzo-1,3,2-diazaphospholidine-2-oxide fragment, as well as their application in asymmetric synthesis. The first part of this review provides a brief discussion of the general structural characteristics of this phosphorus-containing heterocyclic scaffold. The second part describes the synthetic paths that were undertaken to synthesize the desired heterocycles, as well as some relevant considerations pertaining the spectroscopic characterization of the phosphorus-containing heterocycles of interest. The third part provides several illustrative examples where the novel chiral heterocycles were employed in enantioselective synthesis. The new phosphorus-containing heterocycles proved useful: i) as chiral auxiliaries in nucleophilic addition reactions, as well as as imine activators in electrophilic addition reactions; ii) as chiral ligands in nucleophilic allylation and crotonylation of prochiral aldehydes, and iii) as chiral organocatalysts in enantioselective aldol, Michael, and cascade reactions.*

Contents

1. Introduction

In order to be successful, organic synthesis must take into consideration several crucial selectivity factors for the preparation of a given molecule. Most importantly, chemo-, regio- and stereoselectivity must be securely planned.[1] In this regard proper stereoselectivity is a very important factor for the synthesis of biological active molecules as their activity on living organisms is directly dependent of their relative and absolute configuration.[2] Indeed, enantiomeric isomers can be differentiated by their pharmacodynamic properties (stereospecific interactions in the living organism and the corresponding effects they induce) and pharmacokinetic behavior (distinctive absorption, distribution and elimination properties), and therefore represent two different active ingredients. For this reason, the organic chemist dedicated to the synthesis of pharmacologically active substances must develop stereoselective synthetic strategies affording a single enantiomer of any chiral target.

There exist several useful methodologies to obtain pure enantiomers that can be loosely subdivided in two major categories: 1) chiral resolution of racemic mixtures and 2) asymmetric synthesis of chiral compounds.[3] The former strategy consists in the separation of a racemic mixture of enantiomers by physical methodologies such as fractional distillation, recrystallization, chiral phase chromatography, etc. These

techniques usually require the use of chiral resolving agents to generate diastereomeric derivatives (that present different physical and chemical behavior) from the enantiomeric substrates (that exhibit identical behavior).[3]

As it is the case with resolution methods, asymmetric synthesis requires the use of enantiopure chiral reagents in order to give rise to different kinetic profiles during the reaction.[3] A popular strategy consists in the employment of natural products, as many of them are chiral and abundant so that can be isolated in high yield and high enantiopurity; this is the so-called chiral pool. In particular, natural products have been successfully used for the development of chiral auxiliaries and catalysts. In the case of employment of chiral auxiliaries, the prochiral substrate is first covalently bonded to the chiral auxiliary so that subsequent reactions with non-chiral reagents will be stereoselective as a consequence of diastereomeric transition states with different activation energies. Eventually the auxiliary must be removed, thus the insertion and removal of the chiral auxiliary must be a simple and high yielding process allowing when possible to recover such valuable chiral molecule.[3]

Unlike chiral auxiliaries that are used in stoichiometric quantities, catalytic reagents are employed in sub-stoichiometric amounts to induce the formation of enantiopure or enantioenriched products. Asymmetric catalytic methods may be further subdivided in three major types, biocatalysis, catalysis induced by chiral metal complexes, and chiral organocatalysis.

In the present overview we will describe the use of the chiral heterocycle octahydrobenzo-1,3,2-diazaphospholidine-2-oxide **I** as chiral inductor in asymmetric organic synthesis. This moiety has been previously used as chiral auxiliary by Hanessian, Li, and others. Furthermore, it has also been employed as chiral Lewis base by Denmark in the asymmetric activation of silicon species through hypervalent silicon nucleophiles. Finally, chiral scaffold **I** has been applied in asymmetric organocatalysis by Juaristi and co-workers (Figure 1).

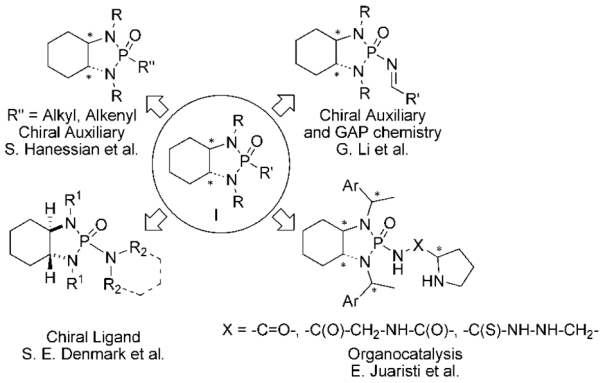


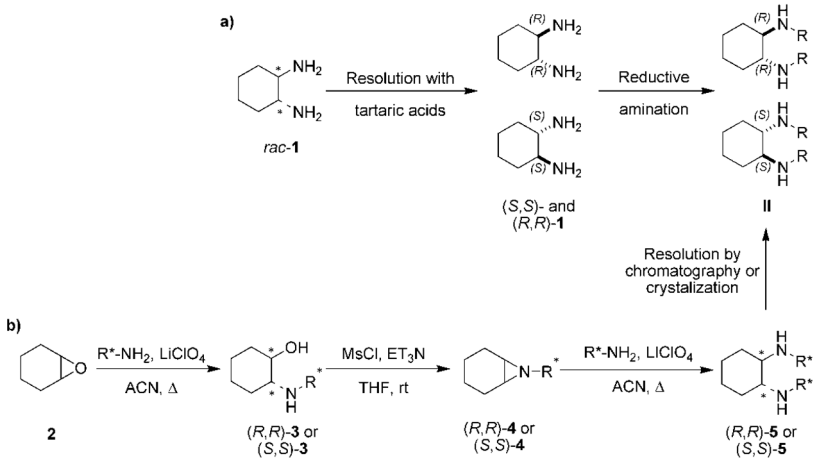
Figure 1. Applications of octahydrobenzo-1,3,2-diazaphospholidine-2-oxide in asymmetric synthesis.

It can be appreciated that the octahydrobenzo-1,3,2-diazaphospholidine-2-oxide moiety exhibits C_2 symmetry as the result of the *trans*-cyclohexane diamine segment. The bicyclic core adopts an anchored conformation with the alkyl groups at nitrogen oriented in a *trans*-diequatorial relationship that appears to be responsible for the observed diastereofacial selectivity.[4] It will be demonstrated that these structural characteristics make **I** and derivatives excellent chiral inductors (*vide infra*).

2. Synthesis of the octahydrobenzo-1,3,2-diazaphospholidine-2-oxides

The synthesis of the octahydrobenzo-1,3,2-diazaphospholidine-2-oxide **I** residue was carried out by the condensation of the corresponding enantiopure *trans*-cyclohexanediamine **II** with several electrophilic phosphorous reagents such as phosphorus oxychloride, phosphorous trichloride, etc. Thus, resolution of commercially available *rac-trans*-cyclohexanediamine *rac*-**1** with tartaric acid,[5] followed by alkylation with carbonyl compounds *via* reductive amination afforded alkylated diamines (*R*,*R*)-**II** and (*S*,*S*)-**II** (Scheme 1a).[6] On the other hand, *trans*-diamines **II** could also be prepared from cyclohexene oxide **2** as shown in

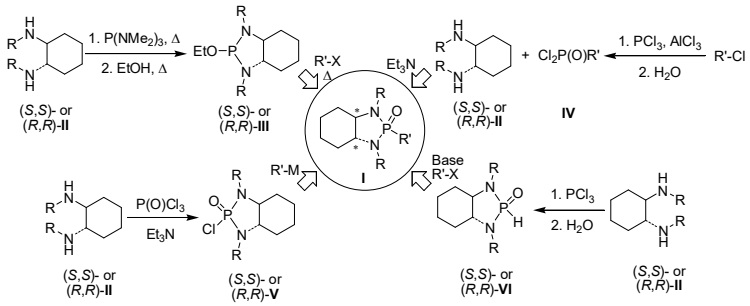
Scheme 1b, employing enantiopure amines (*S*)- or (*R*)-phenylethylamine[7,8] and (*R*)-2-naphthylethylamine.[9] These reactions provide diastereomeric derivatives, which could be separated by fractional crystallization of the corresponding di-chlorhydrates,[8,10] or by flash column chromatography.[7]



Scheme 1. General approaches for the synthesis of substituted secondary *trans*-1,2-cyclohexanediamines **II**.

The next step in the synthesis of the octahydrobenzo-1,3,2-diazaphospholidine-2-oxide **I** residue consisted in the condensation of the enantiopure (*S*,*S*)- or (*R*,*R*)-diamines **II** with electrophilic phosphorus reagents as shown in Scheme 2. Relevantly, Hanessian and co-workers have carried out this reaction in the presence of hexamethylphosphorotriamine [$P(NMe_2)_3$] in refluxing benzene to obtain the anticipated phospholane, which was subjected to a nucleophilic substitution reaction in refluxing ethanol to give compound **III**. Finally, an Arbuzov type reaction with alkyl halides afforded the desired diazaphospholidine-2-oxide derivative in good yields.[11]

Alkyl phosphinic dichlorides **IV** were employed in order to incorporate allyl or crotyl *P*-substituents. Condensation with diamine **II** in the presence of base gave the desired product **I**.[12] An alternative method developed by Denmark,[13] Li,[14] and Juaristi[8,9] consists in the condensation of the chiral amines with phosphorous oxychloride in refluxing toluene in the presence of triethylamine or pyridine as base. The resulting *P*-chloro derivatives **V** were treated with nucleophilic organometallic reagents such as Grignard reagents, sodium azide, and others to afford the desired phosphoramide **I**. Finally, phosphinic acids **VI** could be deprotonated with strong bases such as LDA or *n*-BuLi and then trapped with alkyl halides to give the desired products **I**.[15]



Scheme 2. Synthesis of octahydrobenzo-1,3,2-diazaphosphorinane-2-oxide moiety.

2.1. Conformational and configurational assignments

As in the case of most organic compounds, the octahydrobenzo-1,3,2-diazaphospholidine-2-oxide derivatives are characterized by traditional techniques such as infrared, mass spectrometry, and proton and carbon-13 nuclear magnetic resonance (NMR). Furthermore, the presence of phosphorus allows the use of P-31 NMR spectroscopy.

One important characteristic of derivatives **I** is that this moiety promotes the formation of solid compounds which could afford good quality crystals for X-ray crystal diffraction structural analysis. In fact, Hanessian and co-workers reported over a dozen crystallographic structures which permit the correct assignment of the stereochemistry in these heterocycles (Figure 2).[16-22]

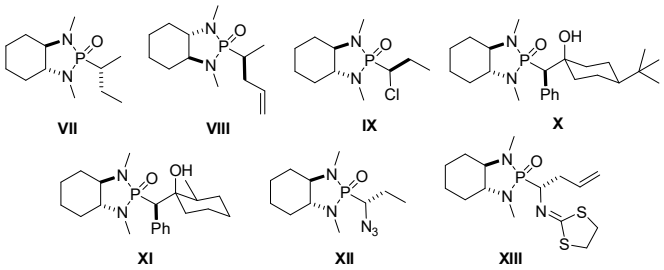


Figure 2. Examples of structurally related phosphoramides with reported X-ray diffraction crystallographic structures.[16-22]

From the analysis of the crystallographic structures, together with appropriate computational calculations, Hanessian and co-workers established that the octahydrobenzo-1,3,2-diazaphospholidine-2-oxide moiety adopts a conformationally fixed structure where the cyclohexane ring is anchored in a chair conformation,[22] with a *pseudo trans* relationship between the *N*-methyl groups (Figure 3).

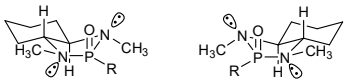


Figure 3. Conformation of bicyclic phosphoramides (*R*,*R*)-**I** and (*S*,*S*)-**I** adopted in the solid state.

In this context, we recently reported seven X-ray crystallographic structures,[8,9,23] which present similar characteristics relative to those observed by Hanessian (Figure 4).

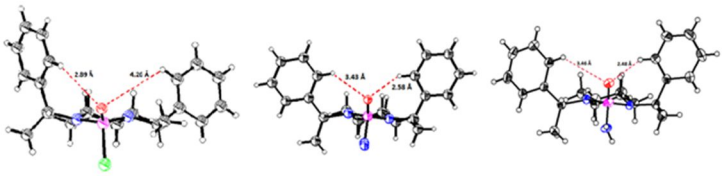


Figure 4. X-ray crystallographic structures of some phosphoramide derivatives of type **I** obtained in our laboratory

3. Applications in asymmetric synthesis

This section presents several asymmetric strategies based on the application of the octahydrobenzo-1,3,2-diazaphospholidine-2-oxide segment. As the result of its C_2-symmetry, this

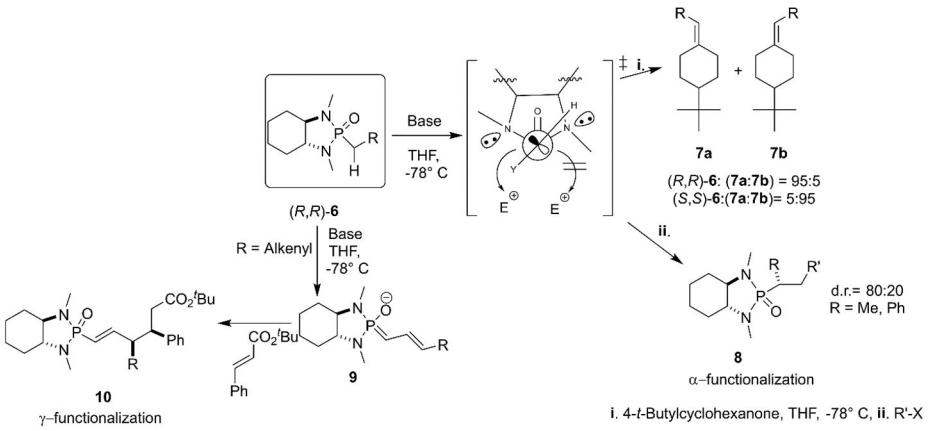
heterocyclic moiety plays a key role in the control of stereochemical reaction outcomes, such as diastereoselectivity.

3.1. Octahydrobenzo-1,3,2-diazaphospholidine-2-oxide as chiral auxiliary

In the previous section we briefly discussed some conformational characteristics of the octahydrobenzo-1,3,2-diazaphospholidine-2-oxide segment, although nothing has been said about the chemical properties that in fact make this and related structures containing the phosphoryl group, a very good activator agent in chemical synthesis. In one hand, the phosphoryl group helps stabilize α-carbanions by both inductive and hyperconjugative mechanisms. Such stabilized carbanions have been frequently utilized in synthesis, for example in the famous Horner-Wadsworth-Emmons reaction. On the other hand, the phosphoryl group can activate imines for electrophilic addition *via* inductive effects. This dichotomy in reactivity of phosphoryl containing compounds make possible the α- and γ-functionalization when acting as nucleophile, and β-functionalization when acting as electrophile (*vide infra*).

3.1.1. Phosphoryl group as a carbanion stabilizer in α- and γ-functionalization

The use of chiral organophosphorus compounds in asymmetric syntheses has been reported extensively.[24-26] This section will be focused in applications of chiral phosphoramides containing the general framework **I**. The first report for the synthesis and application of the bicyclic octahydrobenzo-1,3,2-diazaphospholidine-2-oxide moiety was made by Hanessian and co-workers;[11] nevertheless, it must be mentioned that Denmark and Chen[27] and Hua, et al.[28] worked with structurally related heterocycles but using chiral oxazaphosphorinane and oxazaphospholidine moieties, respectively. In the present system of interest, compounds **6** can be deprotonated with strong bases such as LDA and *n*-BuLi to afford the corresponding lithium salts before reaction with various electrophiles. For example, in reaction with carbonyl compounds Wittig olefination produces alkenes with excellent diastereoselectivities (up to 95:5) (Scheme 3).[11] In a complementary fashion, treatment with alkyl halides provides α-functionalized derivatives *via* an S_N2 reaction.[29] Furthermore, in the presence of unsaturated substituents such as in **9**, then γ-functionalization becomes possible.[12,30,31] Interesting variations of this methodology have been described in the synthesis of natural products as it can give rise up to four new chiral centers.[32]



Scheme 3. Application of Hanessian´s auxiliary in the Wittig olefination, and in α- and γ-functionalization.

The selectivity achieved in these processes is explained in terms of the transition state depicted in Scheme 3, where the electrophile is attacked from the less hindered side, that is the face closer to the lone pair of electrons at nitrogen. Nevertheless, this preference can change depending on the type of electrophile and the nature of the R group.[12,22,29]

3.1.2. Phosphoryl moiety as activating group for electrophilic addition in β-functionalization

Since 2008, in their search for novel chiral auxiliaries Li and co-workers have been developing the so-called *N*-phosphonyl chemistry.[33] The general molecular structure that is representative of this series of studies is depicted in Figure 5. Salient features of chiral *N,N*-disubstituted-*N*-phosphonyl imines include the C_2-symmetric structure that can be easily modified by varying the *N*-protecting groups (R_1=isopropyl, benzyl, 1-naphthyl, *t*-butyl, etc.). By the same token, the steric hindrance and the nature of the substituent groups (R_2) can be readily modified, either with electron withdrawing groups (EWG) or electron donating groups (EDG). Additionally, the oxygen atom of the phosphoryl group (P=O) can be substituted by sulfur to give a thiophosphoryl group (P=S). Thanks to all this, the steric and electronic properties of the *N*-phosphonyl group can be modulated to improve the reactivity and stereoselectivity in various applications.[24]

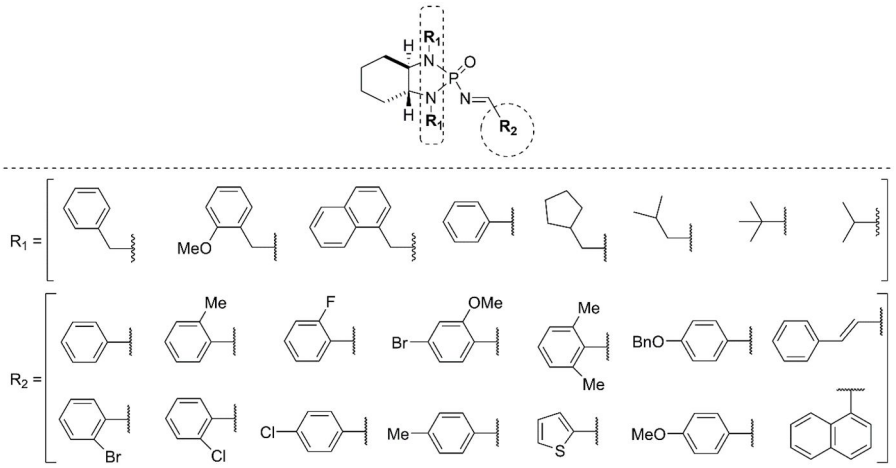
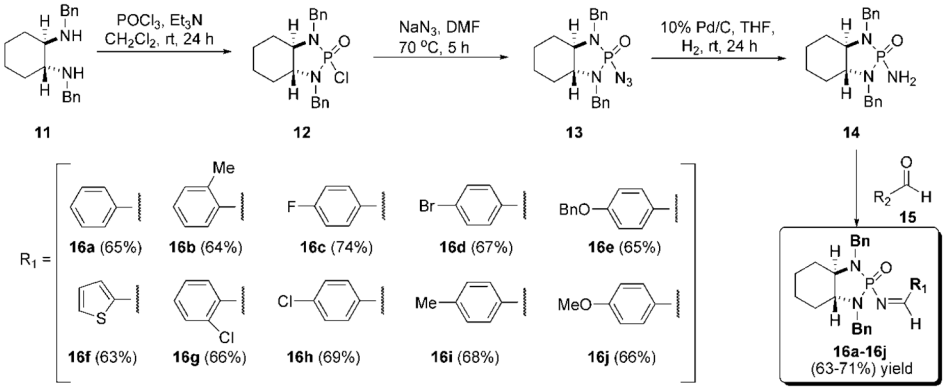


Figure 5 General structure of chiral *N,N'*-disubstituted-*N''*-phosphonyl imines.

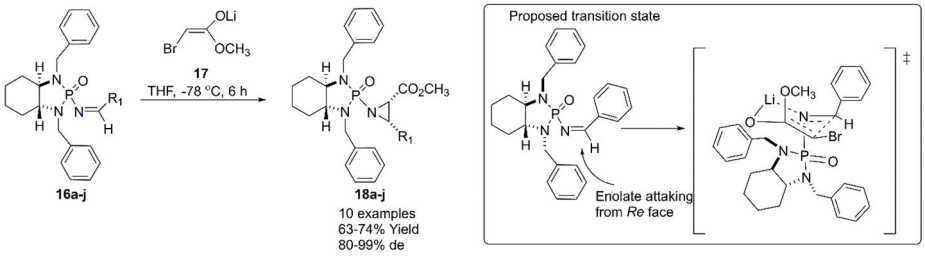
The synthesis of a new family of *N,N'*-dibenzyl-*N''*-phosphonylaldimines was achieved according to the general methodology summarized in Scheme 4.[14,33]



Scheme 4 General synthesis of *N,N*-disubstituted-*N*-phosphoryl imines.

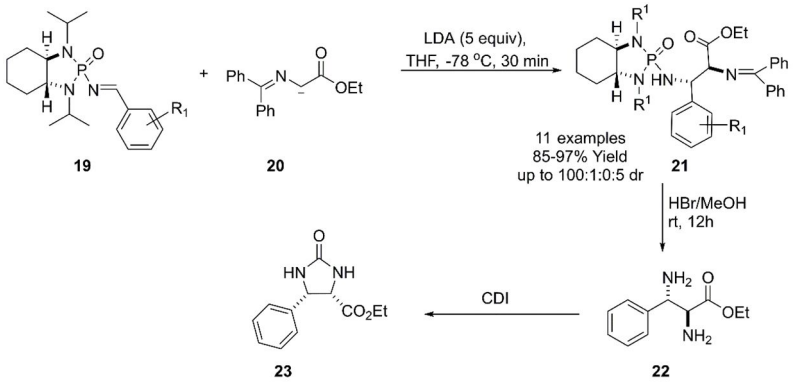
In a representative application of chiral *N*-phosphonyl imines where the octahydrobenzo-1,3,2-diazaphospholidine-2-oxide moiety is acting as chiral auxiliary, Kattuboina and Li evaluated asymmetric aza-Darzens and aza-Henry reactions. As it can be appreciated in Scheme 5,

N-phosphoramide **14** reacted with aromatic carbaldehydes **15** in the presence of *N,N*-diisopropylethylamine (DIPEA) and $TiCl_4$, to afford chiral imines **16a-16j** in moderate yields (63%-74%).[33] Subsequently, an asymmetric aza-Darzens reaction was developed with *N*-phosphonyl imines **16** and the preformed lithium enolate of methyl 2-bromoacetate **17** to give new aziridines **18a-j** with good to excellent diastereoselectivity and moderate to good yields (59-82%) (Scheme 5). The absolute configuration of *N*-phosphonyl aziridine **18a** was determined by ring opening under acidic conditions (TFA, acetone/water at rt), affording β-hydroxyl-α-amino acid methyl esters of (*S*)-configuration. Based on this result, a cyclic six-membered transition state was proposed (Scheme 5), where the *Re* face of *N*-phosphonyl imine is attacked by the *Z*-configured lithium enolate **17**.



Scheme 5 Synthesis of aziridines via asymmetric aza-Darzens reaction.

Motivated by the rather high diastereoselectivity induced by the *N*-chiral phosphoryl fragment, Li *et al*. extended its application to the synthesis of α,β-diamino esters (Scheme 6).[34]



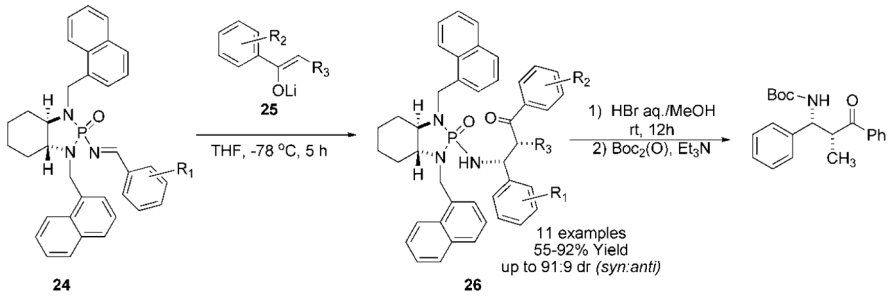
Scheme 6 Asymmetric synthesis of α,β-diamino esters.

Furthermore, Ai *et al*. demonstrated the applicability of chiral *N,N*-disubstituted-*N*-phosphonyl imines for the synthesis of α-alkyl-β-amino ketones (Scheme 7).[35] In this work the 1-naphthylmethyl group affords the highest diastereoselectivity for the major *syn* stereoisomer (90:10 dr).

Additional applications of so-called *N*-phosphonyl chemistry examined by Li *et al*.[14,33-48] include the synthesis of α-amino amides[36] and Weinreb β-amino amide,[37] propargyamines,[38] α-alkyl-β-amino nitriles,[39] homoallylic amines,[40] α-alkyl-α,β-diamino,[41] α-amine-phosphonates,[42] β-nitro amines,[14,33] β-amino esters,[43] a,β-diamino esters,[34] β-amino malonates,[44] α-amino-1,3-dithianyl derivatives,[45] β-amino ketones,[46] α-alkyl-β-amino ketone,[35] 2-imidazolines,[47] and α-quaternary-α,β-diamines[48] (Figure 6).

3.2. Chiral phosphoramides as Lewis bases

A Lewis base (LB) catalyzed reaction is defined as an accelerated reaction where a Lewis acid (LA) or electron-acceptor is activated by the action of electron donor species.



Scheme 7 Asymmetric synthesis of α-alkyl-β-amino carbonyl derivatives.

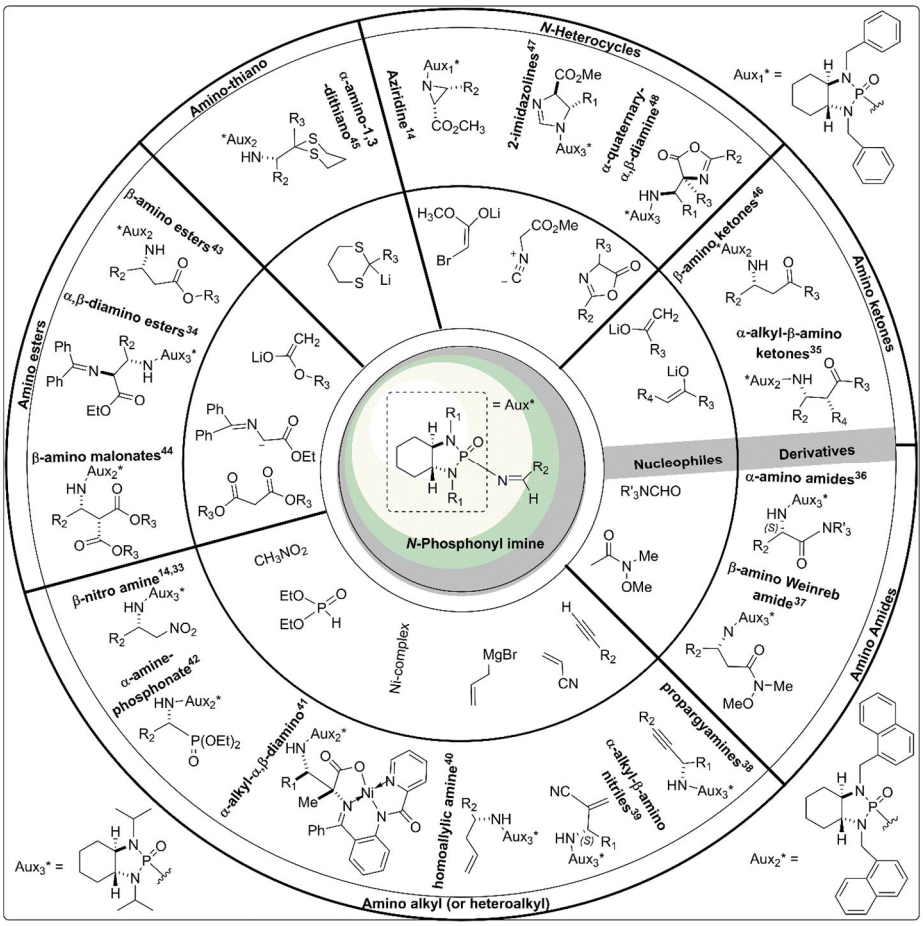
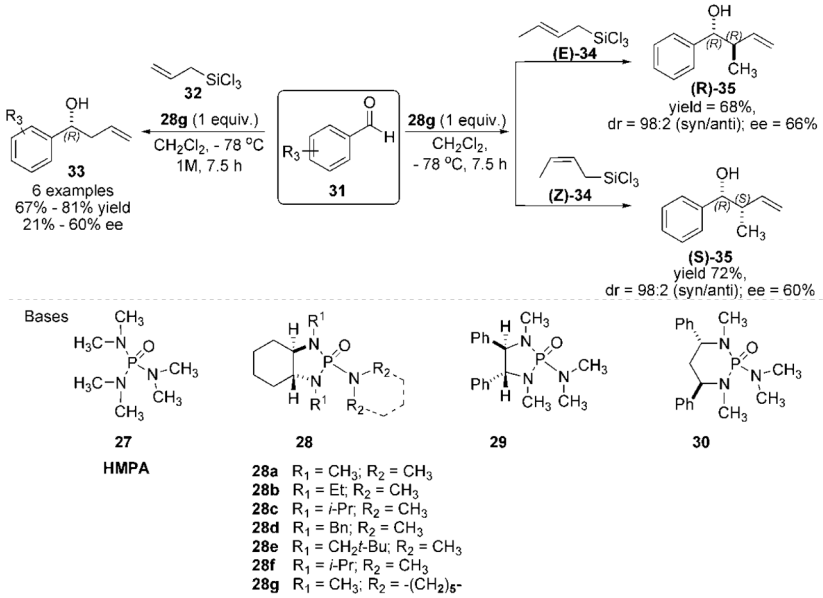


Figure 6 Asymmetric reactions with *N,N'*-disubstituted-*N*-phosphonyl imine.

In this regard, Denmark and Gutmann noticed a significant increase in electron density present in the fragment of the acceptor when an acid-base adduct is generated.[49,50] Such increased electron density around the acceptor atom is distributed to the most electronegative peripheral atoms; therefore, a consequence of this interaction is that the acceptor atom becomes more electrophilic, while one of its ligands becomes more

nucleophilic, allowing dual activation of the substrates. In line with the above, silicon atom exhibits this type of behavior, which can expand its sphere of coordination thanks to its empty 3d orbitals, giving rise to stable "hypervalent silicates" (*e.g.* penta- or hexacoordinated species).[51]

In 1994, Denmark developed asymmetrical allylation and crotylation reactions of prochiral aldehydes using phosphoramides as chiral Lewis bases in the presence of allyl- and crotyl-trichlorosilanes (Scheme 8).[13] This protocol affords the corresponding chiral allylation and crotylation products in moderate to good yields, excellent diastereoselectivities, and moderate enantioselectivity, as shown in Scheme 8. Several solvents and both achiral and chiral phosphoramides were assayed. The results show no significant solvent effect in the reaction's enantioselectivity, although hexamethylphosphoramide (HMPA, **27**) affords the product as racemic mixture in 80% of yield. The presence of chiral substituents in derivatives of *N,N*-phosphoramide results in higher stereoselectivity.



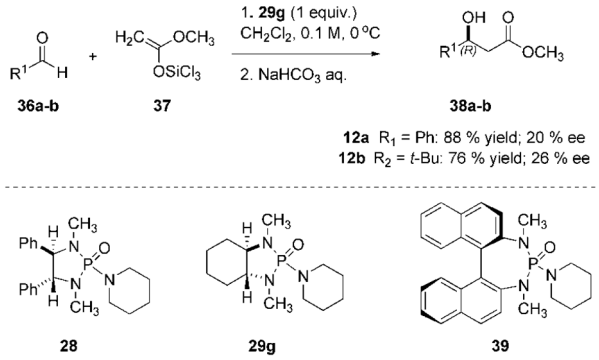
Scheme 8 Allylation and crotonylation of aldehydes **31** using chiral *N,N*-phosphoryl amides **27**-**30**.

Denmark's group envisioned the use of chiral *N,N*-dimethyl-*N*-phosphoramides as chiral Lewis bases in asymmetric aldol addition reactions between aldehydes and preformed trichlorosilyl enolates (Scheme 9).[52] Preliminary optimization was conducted in HMPA solvent, affording the aldol product in good to excellent yields. When trichlorosilylacetate **37** reacts with benzaldehyde **36a** or pivalaldehyde **36b** in the presence of **27**, **28g**, or **39**, the reaction proceeded with good yields (76-88%) but low enantioselectivity (<27% ee).

Subsequently, Denmark *et al.* extended this methodology to other ketone enolate derivatives;[53-58] the authors propose the formation of hexacoordinated and pentacoordinate silicon species in the transition state to explain the diastereo- and enantioselectivity (Figure 7).

3.3. Phosphoramides as chiral organocatalysts

Organocatalysis has emerged as an important methodology for asymmetric synthesis and complements enzymatic catalysis, as well as that mediated by transition metals in coordination compounds. In this regard, organocatalysis presents certain practical advantages since for example their preparation is easy and generally cheaper; furthermore, its use does not require special reaction conditions because organocatalysts tend to be more stable to moisture and oxygen.[59]



Scheme 9 Asymmetric aldol addition of enolates to aldehydes using chiral *N,N*-phosphoryl amides.

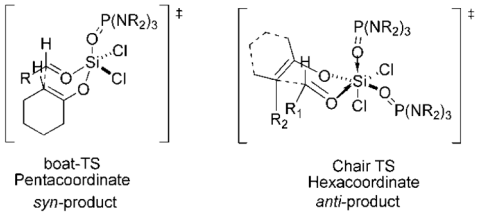


Figure 7 Proposed transition states for *syn*- and *anti*-product in the Mukaiyama type aldol reaction.

Advances in organocatalysis have made it possible to identify the specific molecular characteristics necessary for the effective role of organic compounds as catalysts, as well as the development of various activation modes according to the substrate and the type of reaction.[60] In addition, the search for environmentally friendlier reaction conditions has led to the development of procedures that can be used for example, under solvent-free conditions with ball mill activation,[61] in water solvent,[62] under *neat* reaction conditions,[63] or involving ionic liquids,[64] which facilitates their recovery and recycling.

Thus, our work in this area has been focused in the development of several novel catalysts with hydrophobic characteristics for their use in processes in the presence of water, that is a cheap, safe and low environmental impact solvent.[9] The design of these new catalysts was based on the understanding of the various forms of activation in organocatalysis, from non-covalent interactions such as hydrogen bonding in Brønsted acid type catalysis[65] to covalent catalysis via enamine and other Lewis-base catalysts.[66]

3.3.1. Asymmetric aldol reactions

The aldol reaction constitutes an important strategy in organic synthesis for C–C bond formation with the concomitant creation of up to two new stereogenic centers. Two of the first reports of organocatalytic reactions were made independently by Hajos and co-workers[67] and by Eder and co-workers[68] in the 1970s, when reporting the Robinson annulation reaction catalyzed by (*S*)-proline. Nevertheless, it was not until the year 2000 that the seminal works of List an co-workers[69] in the aldol reaction catalyzed by (*S*)-proline, and MacMillan and co-workers in the Diels-Alder cycloaddition reaction catalyzed by chiral oxazolidinones,[70] triggered the rapid development of asymmetric organocatalysis. Indeed, following this pioneering work organocatalysis grew forcefully to include several kinds of activation modes to catalyze different transformations. In this regard, our efforts in the field were devoted to the design of new organocatalysts with hydrophobic characteristics, that could be employed in aldol addition reactions. Three important factors were taken into consideration:[8,23] 1) the essential incorporation of the pyrrolidine ring derived from chiral prolinamide to ensure chiral enamine chemistry;[66] 2) the presence of a group that increases the acidity of the amide hydrogen in order to activate the corresponding electrophile via hydrogen bonding;[65] 3) the incorporation of a chiral framework that generates the asymmetric environment and also confers the desired hydrophobic characteristics (Figure 8).[62,71]

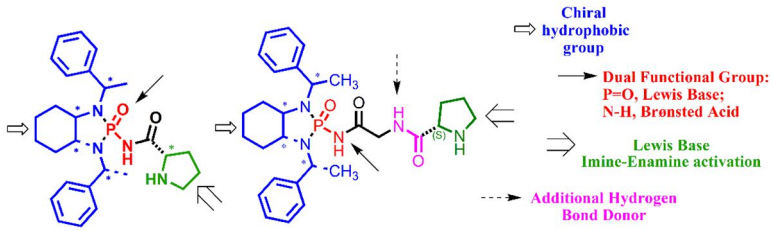
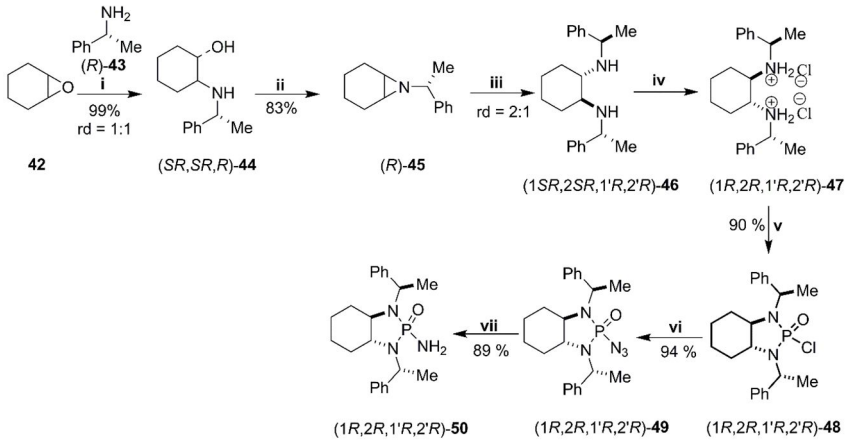


Figure 8. Organocatalysts **40** and **41** developed by Juaristi and co-workers[8,23] for the asymmetric aldol reaction.

Both catalysts **40** and **41** present the octahydrobenzo-1,3,2-diazaphospholidine-2-oxide moiety as a unique framework, that was synthesized as shown in Scheme 10.



i. $LiClO_4$, CH_3CN, reflux, 20 h. **ii**. MsCl, Et_3N, THF, rt 24h. **iii**. (*R*)- or (*S*)-FEA, $LiClO_4$, CH_3CN, reflux, 60 h.
iv. HCl, AcOEt, Recristalization (MeOH/AcOEt (1:3)). **v**. 1. NaOH 1M Et_2O, rt 30 min 2. $P(O)Cl_3$, Et_3N Tol. reflux, 16 h.
vi. NaN_3, DMF/DMSO 9:1, MW, 40 watts, 55° C 1h. **vii**. Pd/C, H_2 (1 atm), MeOH, rt

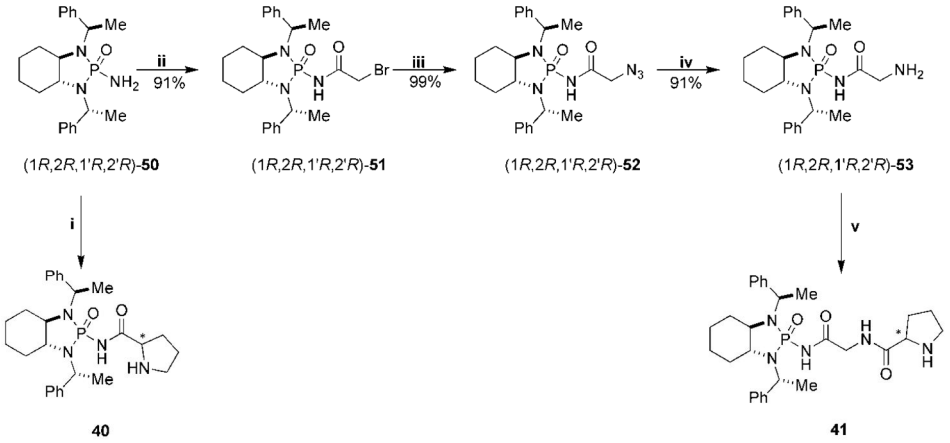
Scheme 10. Synthesis of the chiral phosphoramide framework of interest.

The coupling of (*S*)- or (*R*)-proline methyl ester with phosphoramide **50** was made through the phosphoramide lithium salt.[8] In the case of catalyst **41** the lithium phosphoramide was reacted with benzyl 2-bromoacetate to afford bromide **51**, and then the bromo was substituted by an amino NH_2 group trough the reduction of the corresponding azide **52**, that was obtained by an S_N2 reaction. Finally, the phosphoramide-glycine adduct was coupled with *N*-Boc protected (*S*)- or (*R*)-proline, employing T3P® as coupling reagent (Scheme 11).[23]

Novel organocatalysts **40** and **41** were evaluated in the aldol reaction between cyclohexanone and 4-nitrobenzaldehyde. Although catalyst **40** provided the aldol products with moderate selectivity, it proved rather effective in enantioselective additions to isatin; a transformation that until now has been more commonly explored with primary amines as catalysts.[72] Finally, it could be established that the stereochemistry of the product is controlled by the configuration of the (*S*)-proline moiety (Scheme 12). As anticipated, the isomeric catalyst with the (*R*)-configuration at proline segment gave the enantiomeric products.[8]

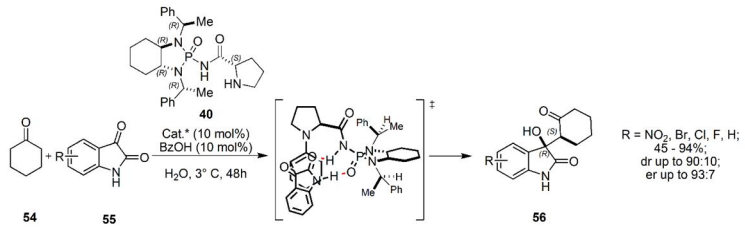
Several structural modifications of the organocatalyst were performed with the aim of improving the selectivity in the addition of cyclohexanone to arylcarbaldehydes. In particular, the effect of the incorporation of a spacer group in **41** was carried out by means of the use of (*S*)- or (*R*)-Pro-Gly dipeptide (Scheme 13).[73] This modification had two consequences: 1) an increase in the organocatalyst's reactive "cavity" during incorporation of the electrophile; 2) the presence of an additional hydrogen bond donor

group.[74] With this modification, it was indeed possible to improve the asymmetric induction in reactions involving arylaldehydes as substrate for the aldol addition with cyclohexanone.[23] Furthermore, the catalytic activity using isatins as the substrate was maintained, and the product's configuration is again dependent on the configuration of the proline segment; that is, the presence of an additional chiral center on the dipeptidic segment does not affect significantly the reaction's stereochemical course.[23]

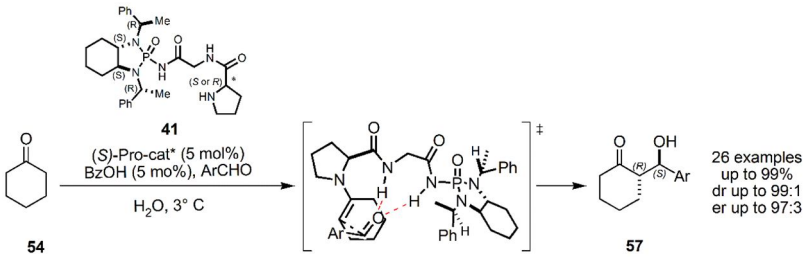


i. 1) *n*-BuLi, THF, 0° C, 20 min. 2) (*S*) - or (*R*)-proline methyl ester, THF, rt, 24 h. **ii**. 1) *n*-BuLi, THF, 0° C, 20 min. 2) methylbromoacetate, THF, 0° C - rt, 24 h. **iii**. NaN_3, DMSO-DMF 9:1, rt, 24 h. **iv**. H_2, Pd/C, MeOH, rt, 12 h. **v**. 1) T3P, NMM, ACN, 0° C, 30 min. 2) *N*-Boc (*S*) - or (*R*)-proline,THF, 0° C - t.a., 24 h **ii**. 3) CF_3CO_2H, DCM, 0° C - rt 48 h. 4) NH_4OH, AcOEt.

Scheme 11. Synthesis of catalysts **40** and **41**.[8,23]



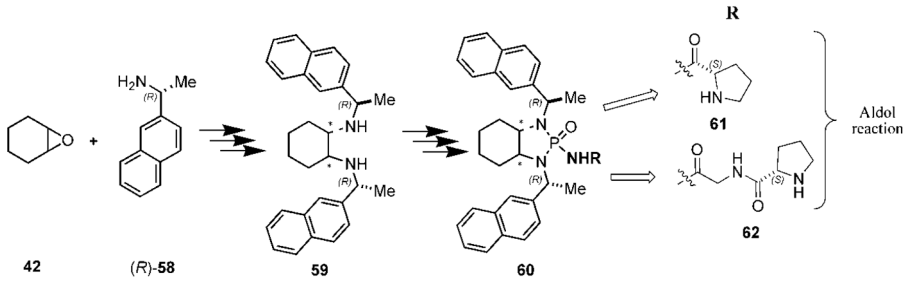
Scheme 12. Asymmetric organocatalyzed aldol reaction between cyclohexanone and isatins.



Scheme 13. Application of the improved catalyst **41** in asymmetric aldol reactions.

Inspired by the finding made by Jørgensen, Hayashi, and co-workers regarding the fact that some organocatalysts efficiency depends substantially on steric interactions,[75,76] it was decided to perform the synthesis of catalysts with *N*-(2*R*)-2-naphthylethylamine substituents instead of *N*-(2*R*)-2-phenylethylamino

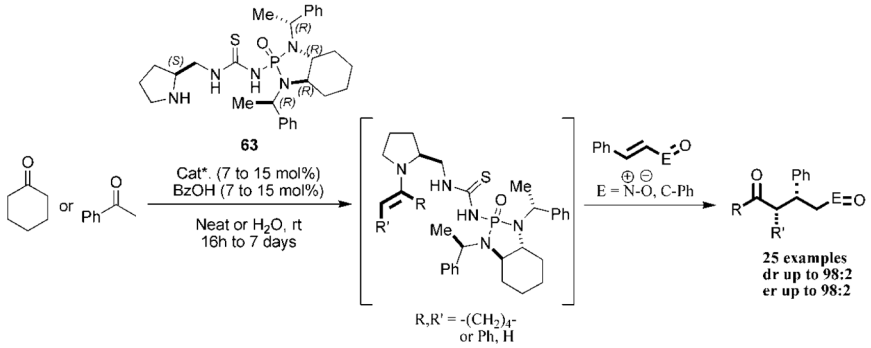
groups (Scheme 14).[9] The synthesis followed similar strategy to those reported above.[8,23] The new catalysts **61** and **62** were very efficient in the enantioselective aldol addition of cyclohexanone to arylcarbaldehydes as well as isatins, although the difference in size of the aryl moiety did not affect significantly the extent of chiral induction.[9]



Scheme 14. Synthesis of new catalysts **61** and **62** incorporating sterically larger aryl groups.

3.3.2. Asymmetric Michael addition reactions

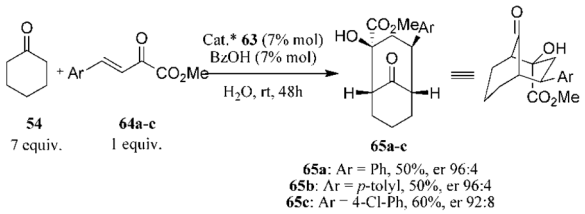
Seeking to expand the range of application of the novel organocatalytic system to other C–C bond forming reactions, the new organocatalyst **63** incorporating both a thiourea segment and the prolinamine residue was synthesized and evaluated in the Michael addition of enolizable carbonyl substrates compounds such as cyclohexanone and acetophenone to nitrostyrenes and chalcones. This new organocatalyst presents features which are attractive for the enantioselective Michael addition reaction. In particular, the thiourea moiety helps activate and bring into proximity potential Michael acceptors by means of hydrogen bonding. Furthermore, the phosphoramide group directly bound to the urea segment enhances the acidity of the adjacent N–H bond, that should become a better hydrogen bond donor. Indeed, the Michael products of interest where obtained in good yield and enantioselectivity up to 98:2 (Scheme 15).[77]



Scheme 15. Application of novel urea-containing organocatalyst **63** in asymmetric organocatalyzed Michael addition.[77]

3.3.3. Asymmetric cascade processes

Because of the mechanism involved, an important characteristic of the Michael addition reaction is that it offers the possibility of performing cascade processes that give rise to the formation of new C–C bonds as well as additional centers of chirality in more complex structures. This feature was elegantly demonstrated by Hanessian[30,31] and more recently by Tang and co-workers.[78] Thus, it was deemed of interest to evaluate the potential of organocatalyst **63** in the [3+3] formal cyclization reaction, arising from a cascade process between cyclohexanone **54** and arylidenepyruvate methyl esters **64a-c**. The cascade process involves the Michael addition-proton transfer-aldol addition to produce bicyclic products in good selectivity (Scheme 16).[77]



Scheme 16. Enantioselective organocatalyzed cascade reaction with organocatalyst **63**.[77]

4. Conclusions

In summary, four reported approaches for the preparation of chiral heterocycles containing the octahydro-1,3,2-diazaphospholidine-2-oxide framework are revised in the present overview. More relevantly, selected examples of their application in asymmetric synthesis are presented. In particular, their employment as chiral ligands in natural product synthesis and Wittig and aziridination reactions proceeded with good to excellent stereoselectivity. Furthermore, the use of the diazaphosphol-2-oxide framework as chiral auxiliary in imines gives rise to *N*-phosphonyl imine chemistry that is especially successful for the asymmetric synthesis of amino esters, aziridines, amino ketones, α,β-diamino esters, propargylamines and homoallylic amines. Finally, application in asymmetric organocatalysis provides interesting examples of enantioselective Michael, aldol and cascade reactions, affording products with good to excellent stereoselectivity. With all this evidence it can be anticipated that heterocycles containing the *N*-phosphoryl moiety will be continuously developed, playing a key role in modern organic synthesis.

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