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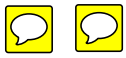
Mini-Reviews in Organic Chemistry, 2014, *11*, 000-000

Organocatalytic Asymmetric Synthesis of Chiral Phosphonates



Ana Maria Faísca Phillips*

Department of Chemistry, Faculty of Sciences and Technology, Universidade Nova de Lisboa, Campus de Caparica, Quinta da Torre, 2829-516 Caparica, Portugal

Abstract: Chiral phosphonates find many applications in medicine, agriculture, materials science and also in organic synthesis. The rapid growth of asymmetric organocatalysis in the last decade has sparkled the interest of organophosphorus chemists, and a wealth of new methodologies to obtain chiral phosphonic acid derivatives has been developed in recent years. This review surveys the last five years, and it includes methodology to synthesize hydroxyphosphonates, aminophosphonates, asymmetric aldol reactions and Michael addition reactions, cycloadditions and domino processes, as well as applications in target-oriented synthesis involving the Horner-Wadsworth-Emmons olefination reaction and the use of chiral phosphonates as acylating agents.

Keywords: Aldol reaction, asymmetric synthesis, domino reactions, enantioselective catalysis, hydrophosphonylation, Michael addition, organocatalysis, phosphonates.

1. INTRODUCTION

Phosphonates have a wide range of applications in medicine, agriculture, materials science, and in synthetic chemistry. Their bioactivity derives from their close structural similarity to the phosphates that occur widely in living organisms, in RNA and DNA, in proteins, in the energy carriers ATP and ADP, in phospholipids, and also to their similarity to carboxylic acids of which they are isosters. When there is a chiral centre present in the molecule, its configuration is often crucial for activity [1]. The presence of a C-P bond makes these compounds very stable to acidic and basic hydrolysis and to enzymatic cleavage. Many phosphonates have antiviral, antimicrobial, or antitumor activity, they are potent enzyme inhibitors, they serve as substrates for the preparation of catalytic antibodies, they are pesticides or herbicides [2]. For all these reasons there is always a rising interest in the production of chiral phosphonates. Organocatalysis is still a young branch of asymmetric synthesis, but the mild conditions and energy savings, *i.e.* the possibility of operating frequently at or near room temperature, the frequent insensitivity to moisture and oxygen, the ease of availability of catalysts and the low toxicity which make organocatalyzed processes environmentally friendly have contributed to an ever increasing popularity. In addition, the high asymmetric inductions which are frequently obtained, and the fact that the catalysts are able to promote many different types of reactions leading to the development of domino processes which allow rapid assembly of complex structures in a highly stereocontrolled fashion, have all contributed to the popularity of this field of research [3]. Phosphorus chemists have not remained indifferent, and the large number of publications that appeared in the last few years is good proof.

*Address correspondence to this author at the Department of Chemistry, Faculty of Sciences and Technology, Universidade Nova de Lisboa, Campus de Caparica, Quinta da Torre, 2829-516 Caparica, Portugal;
Tel: +351 212949647; Fax: +351 212948550;
E-mails: ana.faisca@fct.unl.pt, and amfp@fct.unl.pt

The last very comprehensive review covering organocatalyzed asymmetric synthesis of organophosphorus compounds was published at the end of 2009 [4]. The present review consists of a survey of recent strategies that use organocatalysts to synthesise phosphonates or the closely related phosphinates published in the last five years. The review is divided into different sections according to the type of bond that is being formed in the organocatalyzed step of the reaction. It covers the hydrophosphonylation of imines and carbonyl compounds, aldol reactions and Michael additions with phosphonates as acceptors or donors, cycloaddition reactions, domino processes and more. It also includes applications of phosphonates in synthesis which rely on the Horner-Wadsworth-Emmons olefination reaction and the use of phosphonates as acylating agents. The information is divided into the following sections:

2. Carbon-phosphorus bond forming reactions

3. Carbon-carbon bond forming reactions

4. Carbon-sulphur bond forming reactions

2. CARBON-PHOSPHORUS BOND FORMING REACTIONS

2.1. Hydrophosphonylation

2.1.1. Hydrophosphonylation of Imines

The hydrophosphonylation of imines, also referred to as the aza-Pudovic reaction, is the nucleophilic addition of a phosphite to an imine (Scheme **1**) [5]. In the enantioselective hydrophosphonylation, chiral α-amino phosphonic acids are produced. Many of these substances are useful building blocks for pharmaceutical targets such as alafosfalin, anti-HIV agents, phosphatase enzyme inhibitors, antifungal compounds or even peptidic components with unique properties [6, 7].

A few organocatalysts have now been used to promote this reaction (**5-12**, Fig. **1**). In the first organocatalyzed version, developed by Joly and Jacobsen in 2004, chiral

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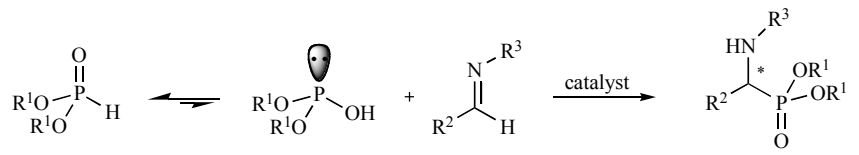


1: Phosphonate form **2:** Phosphite form **3** **4**

Scheme 1.

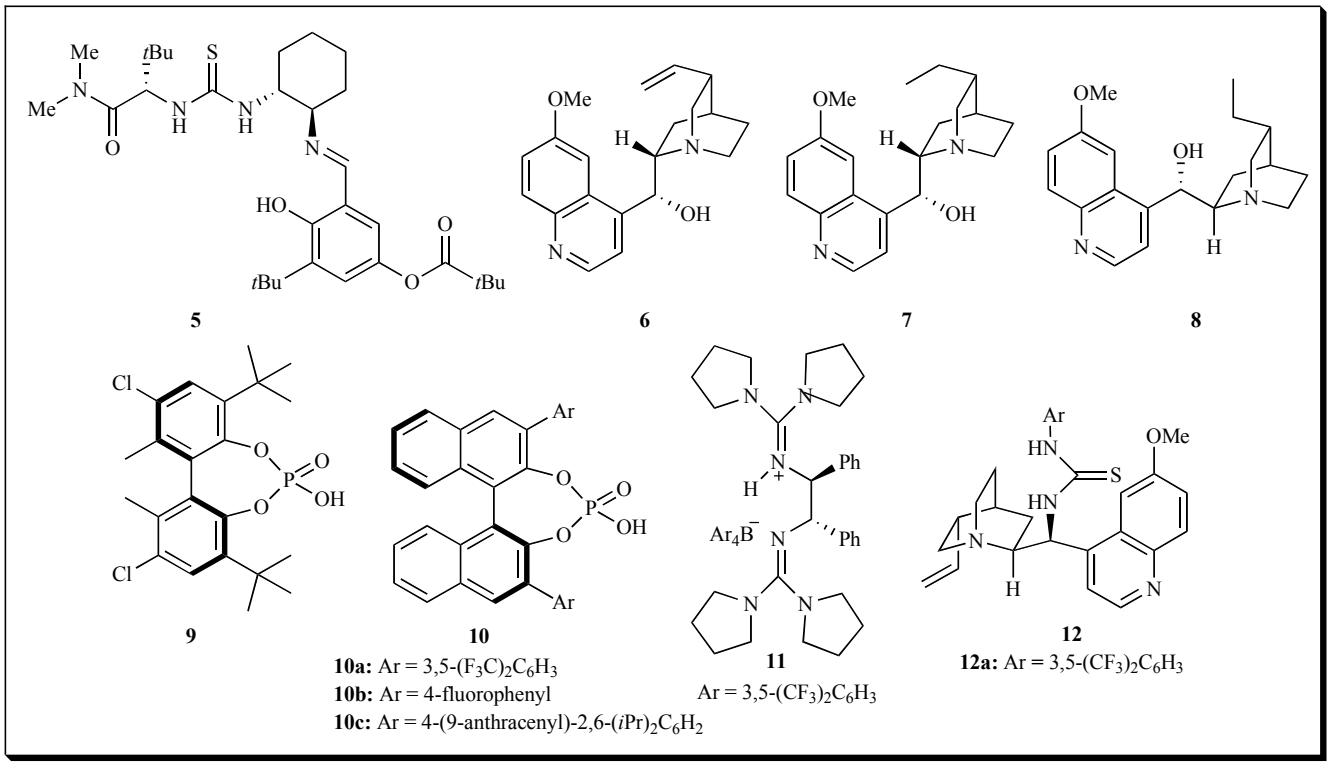


Fig. (1). Organocatalysts used in the hydrophosphonylation of imines.

thiourea **5** was used to catalyze the synthesis of chiral α-aminophosphonates from dialkyl phosphites and *N*-benzylaldimines in high yields and ees of up to 99% [6]. Chiral thioureas like **5** are bifunctional catalysts. The basic nitrogen is capable of activating the nucleophilic component of the reaction, and the thiourea group, with two coplanar protons available for hydrogen bonding, can activate the electrophilic reaction component. The two sites are in close proximity and act in synergy, they can bring the reaction partners closer and provide high levels of chiral induction (Fig. **2**) [8].

The developments during the last five years have centred on new catalyst design and on the development of new substrate combinations. Nakamura *et al.* used commercially available quinine **6**, or hydroquinine **7** and its pseudo-enantiomer **8**, for the base-promoted addition of diethyl and diphenylphosphite to *N*-sulfonylimines derived from aromatic aldehydes [7]. The use of a heteroarenesulfonyl nitrogen protecting group allowed the formation of products in >95% yield and 82-98% ee (83-99% after recry-stallization), an improvement on a previous report in which the tosyl protecting group was used [9]. Nakamura *et al.* also reported the first enantioselective addition of phosphites to ketimines [10] (Scheme **2**). Although these substrates are less reactive and enantiofacial discrimination is more challenging, hydroquinine **7** and its pseudoenantiomer

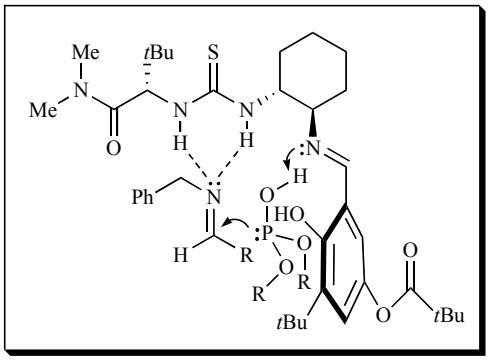
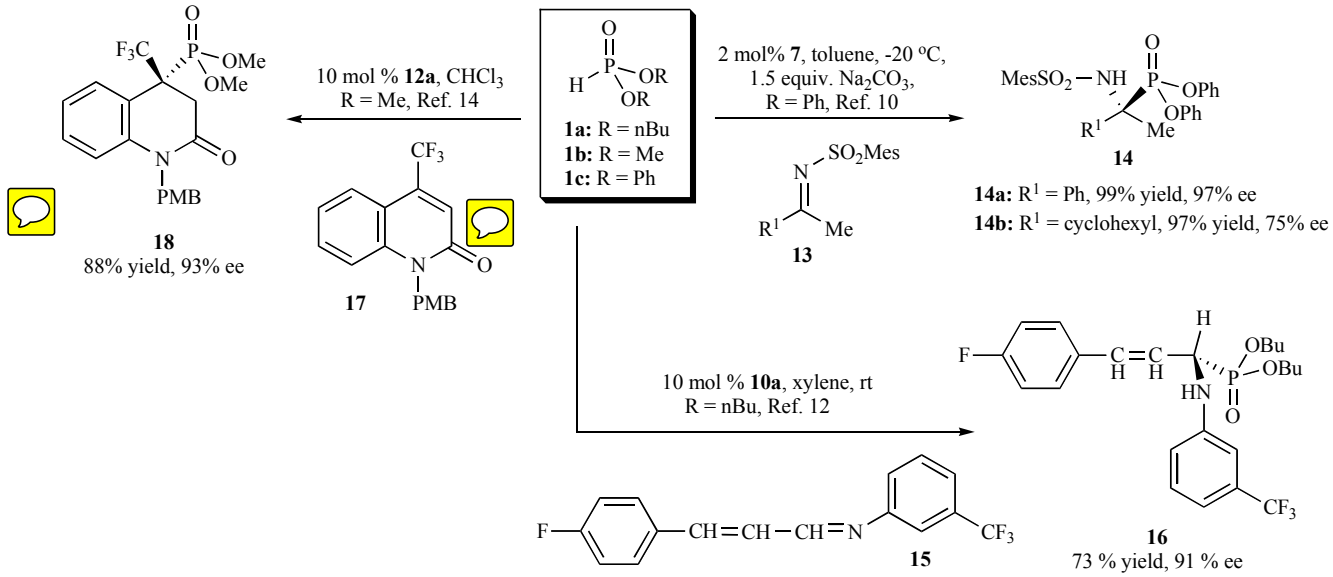


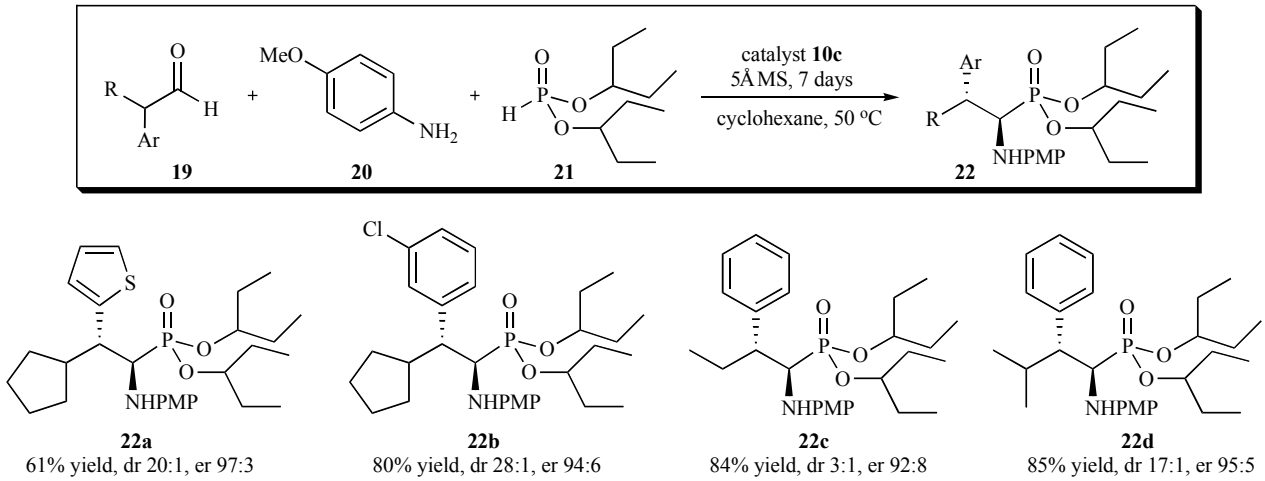
Fig. (2). NMR and computational data for other reactions of imines catalyzed by **5** showed that imines hydrogen-bonded to both urea hydrogen atoms [8].

hydroquinidine **8** proved to be suitable activators, although the reaction only proceeded in the presence of an extra inorganic base like Na_2CO_3. Low temperatures (-20 °C) were necessary to obtain high ees.

Brønsted acid catalysis has also been used successfully to promote the enantioselective hydrophosphonylation of imines. Although with axially chiral biphenyl-2,2'-diyl hydrogen phosphate **9** only 40% ee was obtained in the addition of diisopropylphosphite to N-benzylidene-2-



Scheme 2.



Scheme 3.

methoxyaniline [11], axially chiral 1,1-binaphthol phosphates **10a** provided high levels of stereoinduction in the hydrophosphonylation of imines **15** derived from cinnamaldehydes (Scheme **2**). These substrates may be troublesome, since the presence of a free conjugated olefinic functionality may promote Michael addition of the nucleophile instead of the desired reaction; they usually require reaction conditions that are highly substrate specific [12]. Nevertheless, Song and coworkers reported in 2009 the successful hydrophosphonylation of a range of α,β-unsaturated imines promoted by 10 mol% of catalyst **10a** (Scheme **2**). However, when the same methodology was applied to benzotriazole substituted imines, using **10b** as catalyst, the products obtained were nearly racemic [13]. In the same year Wang and coworkers reported the first organocatalyzed hydrophosphonylation of cyclic imines, ketimines **17** (Scheme **2**) [14]. Simultaneous activation of the nucleophilic phosphite through acid-base interactions with thiourea catalyst **12a**, and of the electrophilic imine *via* H-bonding, provided a rigid transition state which led to the formation of the desired dihydroquinazolinones in high yields and ees.

If H-phosphinates are used as nucleophiles, P-chiral phosphinate esters may be produced. This was achieved by Tan and coworkers in the hydrophosphonylation of *N*-tosylated imines with chiral guanidinium salts **11** as activators [15]. Although the diasteroselectivities of the reactions were not very high (3:1 to 7:1), the ees varied from 90 to 94% in favour of the *syn* stereoisomer.

Further developments in organocatalyzed hydrophosphonylation of imines included three-component reactions, in which instead of a pre-formed imine, an *in situ*-generated imine was used (Scheme **3**). This variation is generally known as the Kabachnik-Fields reaction. The first report of an organocatalyzed version was made by List and coworkers in 2008 [16]. Chiral BINOL derived phosphoric acid **10c** was the best catalyst. The presence of bulky substituents in the α-branched aldehyde was found to have a significant effect on the enantiomeric ratio of the products, which was as high as 97:3 in favour of the *R*,*R*-diastereoisomer, even when the reaction was run at 50 °C. The Kabachnik-Fields reaction was also studied by Ma and coworkers who found that aromatic or cinnamic aldehydes gave good yields of α-

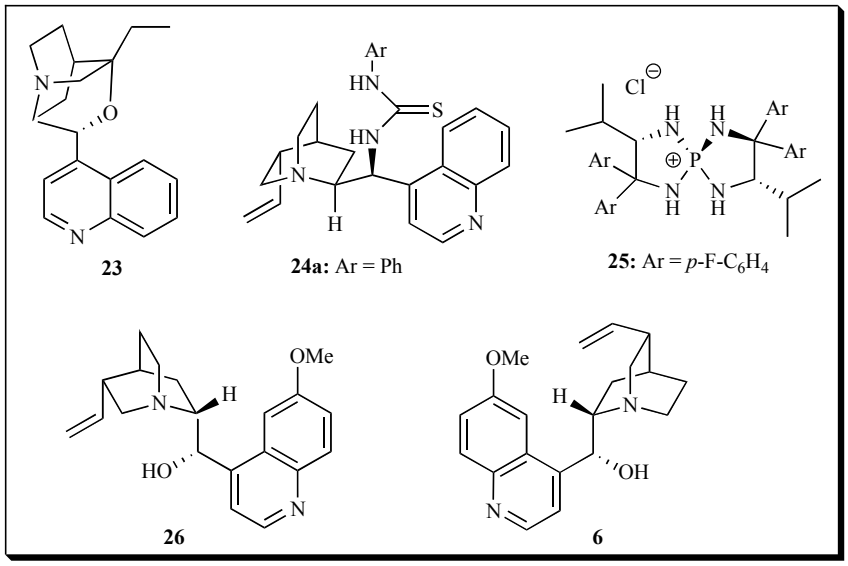


Fig. (3). Organocatalysts used in the hydrophosphonylation of carbonyl compounds.

aminophosphonic acids in the presence of catalyst **10a** and 4Å molecular sieves, when the reaction was run at 40 °C for 7 days [17]. Ees varied between 31 and 87%. The nature of the substituents on the ring did not influence the enantioselectivity, but the presence of substituents on the *o*-position favoured enantiofacial discrimination.

2.1.2. Hydrophosphonylation of Carbonyl Compounds

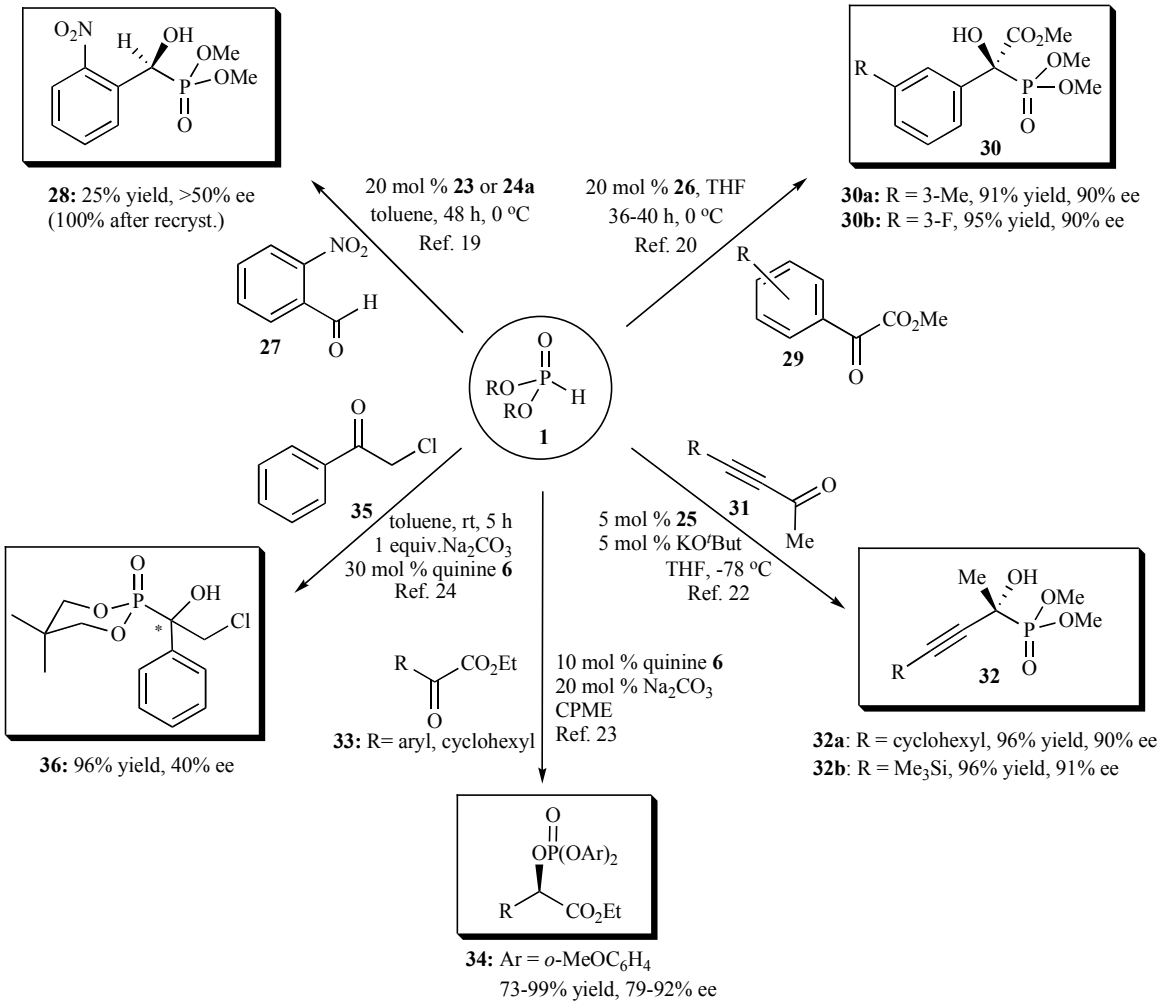
The enantioselective reaction between a phosphite and a carbonyl compound provides chiral α-hydroxy phosphonic acid derivatives. These compounds are mimics of hydroxy-carboxylic acids, and many have important biological properties: antibacterial, antiviral, antibiotic, pesticidal, anticancer and enzyme inhibitor properties [18]. The hydrophosphonylation of carbonyl compounds, due to its analogy to the aldol reaction, is also known as the phospha-aldol reaction. Some authors refer to it as the Pudovik reaction. The best catalysts used in the hydrophosphonylation of carbonyl compounds are represented in Fig. **3**.

Kolodyazhnaya *et al.* studied the reaction of dimethyl phosphite **1b** with aromatic aldehydes in the presence of cinchona alkaloids and derivatives (Scheme **4**) [19]. Although the yields and ees were only moderate, optically pure products could be obtained after recrystallization from certain solvents. Feng and coworkers used thiourea derived cinchona alkaloids for the reaction of **1b** with α-ketoesters [20]. Cinchonidine derived thioureas gave (*S*) compounds and cinchonine derived ones (*R*) compounds, in both cases in high yields and ees (Scheme **4**). Since the enantioselective construction of quaternary carbon centres is notoriously difficult to achieve [21], the present methodology may provide a useful entry into otherwise difficult to obtain α-tertiary hydroxyphosphonates. Ooi and coworkers showed that ynones could also be hydrophosphonylated with dimethyl phosphite when nucleophilic P-spiro chiral ammonium phosphonium chloride salt **25** was used as catalyst [22]. The resulting phosphonates, obtained in high yields and ees, have a propargylic alcohol functionality which allows further synthetic elaboration into a wide variety of useful compounds (Scheme **4**).

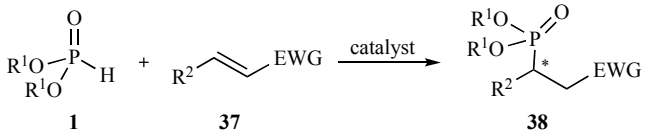
The reaction of phosphites with ketones may give rise to α-hydroxyphosphonates (the hydrophosphonylation reaction) or it may follow a different path and a phospha-Brook rearrangement may take place after the initial phosphite addition reaction, depending on the structure of the reacting molecules and the reaction conditions. The second option was explored by Hayashi and Nakamura in 2011 [23]. They found that when α-ketoesters were treated with arylphosphites in the presence of Na_2CO_3 and quinine or quinidine, the α-phosphonyloxy enolate/enol produced in the phosphite addition step underwent rearrangement to give the correspoding phosphate ester (Scheme **4**). The reactions were highly enantioselective and the products were obtained in high yields and in 79-92% ee. They attributed the high stereoinduction obtained to an enantioselective protonation of the prochiral enolates by the protonated cinchona alkaloids, acting as proton transfer agents. Hydrogen bonding with the chiral catalyst then allows the highly stereoselective phospha-Brook rearrangement to take place. In the presence of quinine (*S*) products were obtained, and with quinidine (*R*) products [23]. The hydrophosphonylation of α-chloroketones was reported by us [24]. When quinine was used to catalyse the reaction of cyclic phosphite **1d** (R = $-CH_2C(CH_3)_2CH_2-$) in the presence of an inorganic base like Na_2CO_3, α-tertiary hydroxyphosphonate **36** was obtained with ees of up to 40% (Scheme **4**). Some vinylphosphate resulting from the phospha-Brook rearrangement of the initial alkoxide anion was also obtained. When the reaction was carried out in toluene in the presence of proton sponge or pyridine as additives, without Na_2CO_3, several tertiary hydroxyphosphonates with α-aliphatic, cyclic or aromatic substituents could be obtained in high yields, but the ees dropped and in many cases the products were almost racemic.

2.1.3. The Phospha-Michael Reaction

The addition of a phosphorus nucleophile to an alkene substituted by an electron withdrawing group which can act as a charge acceptor, the phospha-Michael addition (Scheme **5**), is another versatile reaction to produce compounds having a P-C bond [25].



Scheme 4. The hydrophosphonylation of carbonyl compounds.



Scheme 5. The phospha-Michael reaction.

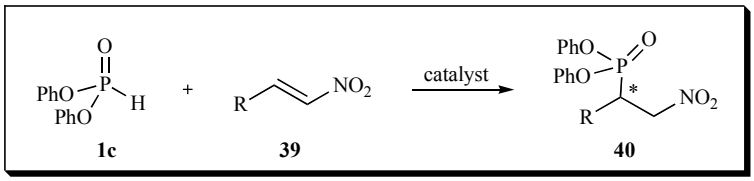
The first report of an organocatalytic enantioselective version of this reaction dates back to 2007, when Wang and coworkers showed that 10 mol% of quinine promoted the conjugate addition of phosphites to β-nitroolefins, giving the corresponding β-nitrophosphonates in high yields and ees ranging from 45 to 88% [26]. The presence of β-aromatic or heteroaromatic substituents gave higher enantiofacial discrimination, whereas the presence of aliphatic substituents resulted in a less marked differentiation of the two faces. Since the nitro group may be reduced easily to an amino group leading to the production of β-aminosubstituted phosphonates, compounds which have found increasing applications in peptide and medicinal chemistry, this reaction has attracted the attention of many research groups. During the last five years it has been studied a few times as a test for the performance of several organocatalysts (Scheme **6**). Catalysts **41** [27], **42** [28], **12a** [29] and **43** [30] were found to perform the best in each study. Equimolar proportions of reagents gave high yields of products. The ees ranged from high to excellent, with **41** and conformationally flexible **43** giving the best induction. The performance of these two catalysts was also unaltered in terms of induction when branched aliphatic substituents were present on the nitroolefin.

3. CARBON-CARBON BOND FORMING REACTIONS

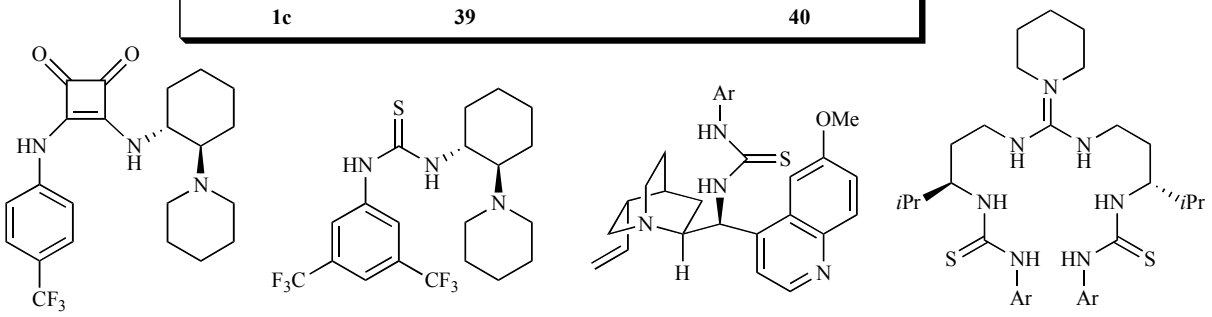
3.1. The Aldol Reaction

3.1.1. The Cross Aldol Reaction

The reaction between two carbonyl compounds, one in the enol/enolate form reacting as the nucleophile, and the other in the keto form reacting as the electrophile, to produce a β-hydroxy carbonyl compound, the aldol reaction, has been one of the reactions mediated by organocatalysts most widely studied. The product may subsequently dehydrate under certain reaction conditions to give a α,β-unsaturated carbonyl compound and the process is then referred to as the aldol condensation, although some authors refer to this reaction as such even when there is no dehydration. Without dehydration, enantioselective processes lead to the formation of polyoxygenated compounds with one or two new chiral centres. Organocatalysts, mimicking aldolase enzymes, but without suffering from their substrate specificity, have become very poweful tools for the development of this



1c **39** **40**



41 **42** **12a:** Ar = 3,5-$(CF_3)_2C_6H_3$ **43•HCl:** Ar = 3,5-$(CF_3)_2C_6H_3$

R	Catalyst	Catalyst load (%)	Solvent + Additives	Yield (%)	ee (%)	Reference
Ph	**41**	10	DCM	99	97	27
4-$MeOC_6H_4$	**41**			98	99	27
4-BrC_6H_4	**41**			94	97	27
*i*Pr	**41**	20	DCM	89	95	27
Ph	**42**	10	DCM	95	76	28
4-$MeOC_6H_4$	**42**			79	78	28
4-BrC_6H_4	**42**			79	76	28
Ph	**12a**	10	DCM, 4Å MS	91	79	29
4-$MeOC_6H_4$	**12a**			89	80	29
4-BrC_6H_4	**12a**			90	80	29
*i*Pr	**12a**			60	64	29
Ph	**43**	5	tol/H_2O, K_2CO_3	99	88	30
4-$MeOC_6H_4$	**43**			90	96	30
4-ClC_6H_4	**43**			88	90	30
*t*Bu	**43**			95	92	30

Scheme 6.

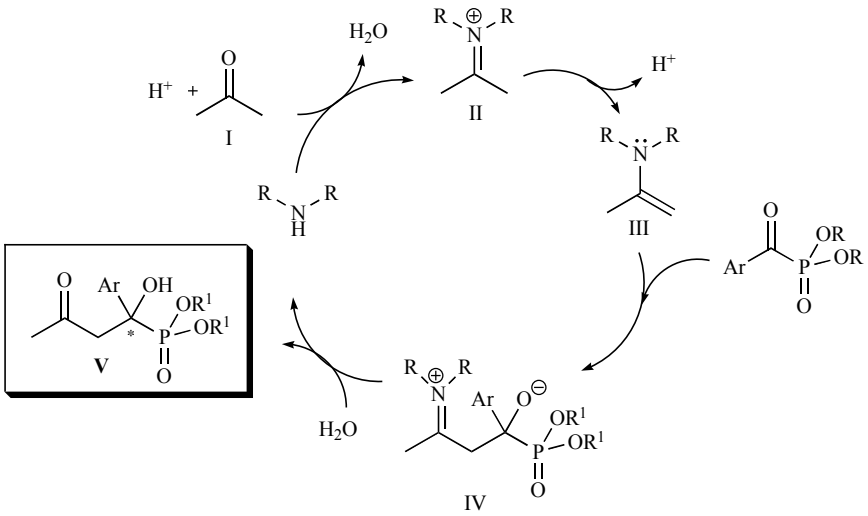
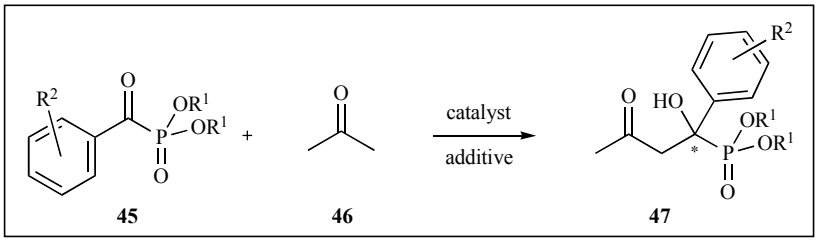


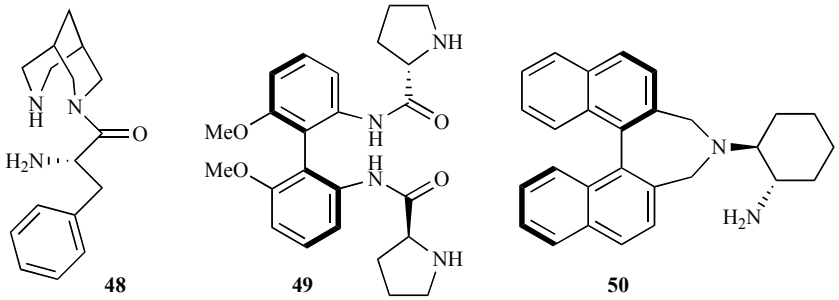
Fig. (4). Reaction mechanism for the enamine-catalysed aldol reaction.

reaction, in that they allow the interaction of substrates in their native forms, without the need of protection or the use of pre-formed enolates to overcome the characteristic side reactions of self-condensation, polymerization and dehydration followed by Michael addition, which may otherwise occur in the presence of acidic and basic catalysts [31-33].

The first report of an aldol reaction applied to phosphonate chemistry was by Samanta and Zhao in 2006 [34]. They found that proline and derivatives promoted the addition of ketophosphonates to acetone, resulting in the formation of tertiary α-hydroxyphosphonates in good to high yields and very high ees. Even enolisable ketophosphonates could be used successfully in the presence of 20 mol % l-proline. Acetone was present in large excess, being both a reagent and the solvent for the reaction. Methoxyacetone and 2-butanone could also be used when l-prolinamide **44** was used as catalyst. In addition, they found that prolinamide also catalyzes the cross aldol between ketones and diethyl



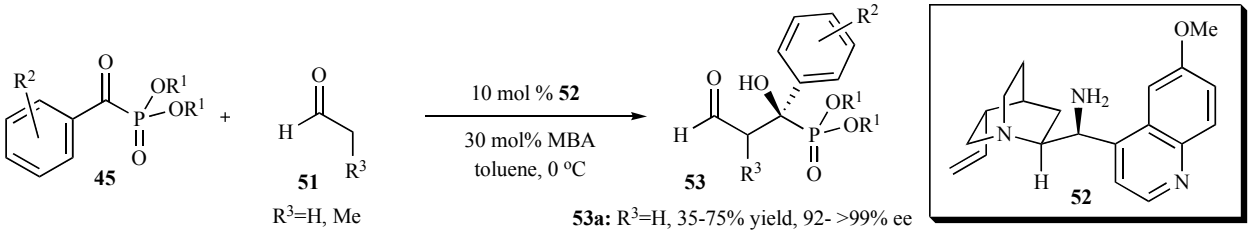
45 **46** **47**



48 **49** **50**

Catalyst	R^1	R^2	Catalyst load (mol %)	Additive	Yield (%)	ee (%)	Ref.
48	*p*Me	Et	5	HCOOH	72	96	36
48	*p*Me	*i*Pr	5	HCOOH	93	97	36
49	*p*Me	Et	10	TFA	69	94	36
49	Ph	Et	10	TFA	89	94	37
49	Ph	*i*Pr	10	TFA	74	97	37
50	*p*Me	Et	20	$pNO_2C_6H_4COOH$	80	79	38
50	*p*Me	*i*Pr	20	$pNO_2C_6H_4COOH$	78	95	38
50	Et	Et	20	$pNO_2C_6H_4COOH$	71	87	38

Scheme 7. The cross aldol between acetone and aromatic α-ketophosphonates.



45 **51** **53** **52**

R^3=H, Me

MBA = $pMeOC_6H_4COOH$

53a: R^3=H, 35-75% yield, 92- >99% ee

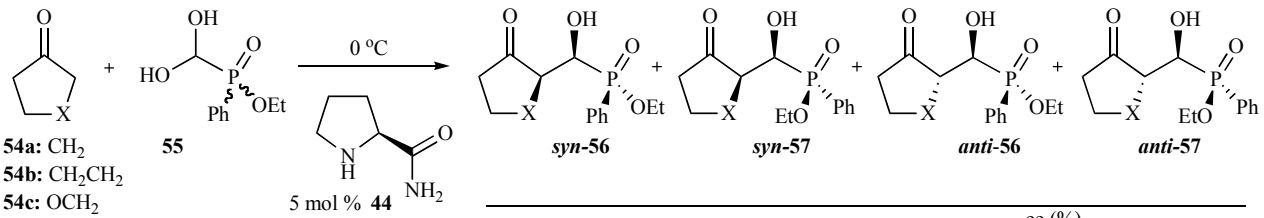
53b: R^3=Me, R^2=Ph, 44% yield, dr (*anti*:*syn*) 7:5, ee (major) 68%, ee (minor) 73%

Scheme 8.

formylphosphonate hydrate. Secondary α-hydroxyphosphonates could be obtained in a highly enantioselective manner (up to > 99% ee) and with good diastereoselectivities [35]. Fig. **4** illustrates a possible mechanism for the amine catalyzed aldol reaction, a form of covalent catalysis. During the last 5 years a number of diamine catalysts have been tested using the cross aldol reaction between acetone and aromatic ketophosphonates as a model reaction [36-38]. A few selected examples are shown in (Scheme **7**). In every case acidic additives were necessary for very high ees to be obtained. Acetone was present in large excess, being both a reagent and the solvent or part of it, for the reaction. High yields of products were also obtained. Bispidine **48** allowed the reaction to run with catalyst loads as low as 5 mol % without a drop in ee [36]. Slightly lower ees were obtained with chiral diamine **49**, but this catalyst also allowed a cross aldol between an aliphatic ketophosphonate, diethyl 1-oxopropanephosphonate and acetone to occur [38].

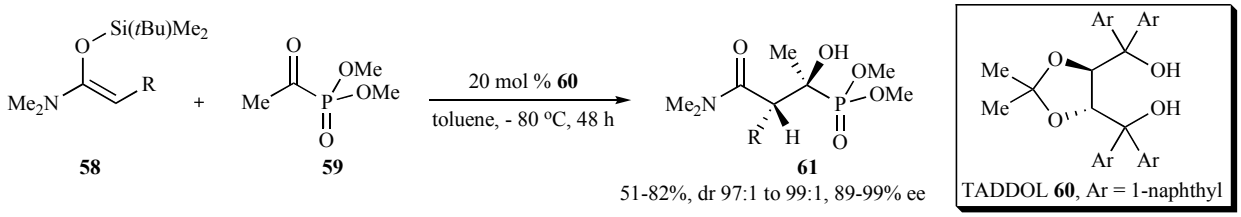
In 2011 Zhao and coworkers reported the first example of a highly enantioselective organocatalyzed direct cross-aldol between enolizable aldehydes and α-ketophosphonates [39]. Hence, the reaction between acetaldehyde and aromatic α-ketophosphonates in toluene, catalyzed by diamine **52** derived from quinine, gave β-formyl-α-hydroxyphosphonates **53** in good yields and excellent ees (Scheme **8**). The aldehyde was used in five-fold excess only in toluene. Propanal could also be used in this reaction (Scheme **8**). Some of the products were found to have anticancer activity, inhibiting the proliferation of immortalized cell line foreskin fibroblasts (HFF) and ovarian cancer cells (ID8). Phosphonate **53a** (R^1=Et, R^2=R^3=H) was the most active, displaying ≥ 50% inhibition at a concentration of 50 μM in both cases.

The same group has also reported the l-proline catalyzed cross aldol between racemic α-acylphosphinates and ketones

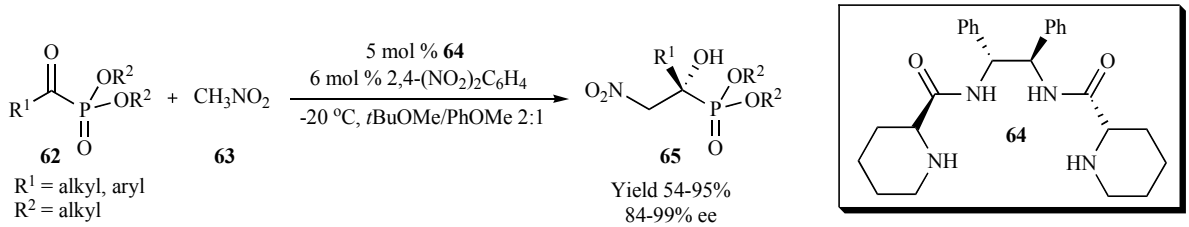


54	Yield (%)	56/57	*syn/anti*	ee (%)			
				syn-**56**	*syn*-**57**	*anti*-**56**	*anti*-**57**
a	83	50:50	99:1	96	87		
b	88	50:50	35:65	98	95	89	93
c	91	50:50	40:60	99	94	26	99

Scheme 9. l-prolinamide catalyzed cross aldol between racemic formylphosphinate hydrate and ketones.



Scheme 10. The Mukaiyama aldol reaction.



Scheme 11.

[40]. The products were obtained with high ees. In reactions with acetone the diastereoselectivities were low. The reaction was also attempted with racemic formylphosphinate hydrate **55**, but no products were obtained, presumably because the high acidity of l-proline was incompatible with the acetal. However, when cyclic ketones were made to react in the presence of l-prolinamide, products with good to excellent *syn* to *anti* ratios of the two newly formed carbon centres were obtained (Scheme **9**).

3.1.2. The Mukaiyama Aldol Reaction

In 2009 Rawal and coworkers showed that it was possible to use hydrogen bond catalysis to promote a Mukayama aldol reaction for the synthesis of chiral γ-keto-α-hydroxyphosphonates with two contiguous chiral centres [41]. The reaction between *N,O*-ketene acetals **58** and acetyl phosphonate **59**, catalyzed by a TADDOL derivative, gave preferentially *anti*-products with excellent drs and ees (Scheme **10**).

3.1.3. The Nitro Aldol Reaction

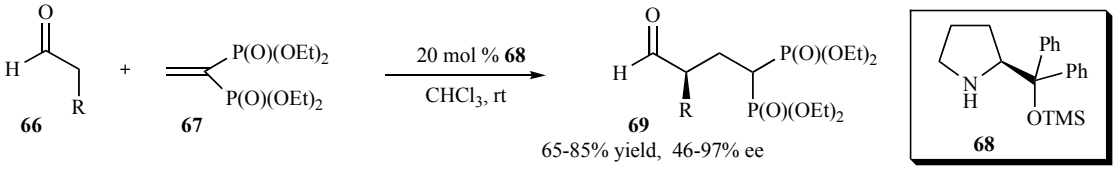
An example of an organocatalyzed version of the nitro aldol reaction (the Henry reaction), applied to phosphonate chemistry, to give chiral β-nitro-α-hydroxyphosphonates, was also reported in this period. The first example of this reaction dates back to 2007, when Zhao and coworkers used cupreine or 9-O-benzyl cupreine to obtain tertiary α-hydroxy phosphonates in high yields and excellent ees of > 91 to 99% [42]. The authors also showed with one example that the products could be reduced with Pd-C to give the corresponding β-aminophosphonates with complete retention of configuration, after hydroxy protection with BzCl. In the latter work, Feng, Hu and coworkers demonstrated that chiral secondary amines also catalyze the nitroaldol reaction between nitromethane and α-ketophosphonates **62** [43]. In the presence of an additive, 2,4-dinitrophenol, very high ees could be obtained (Scheme **11**).

3.2. The Michael Addition Reaction

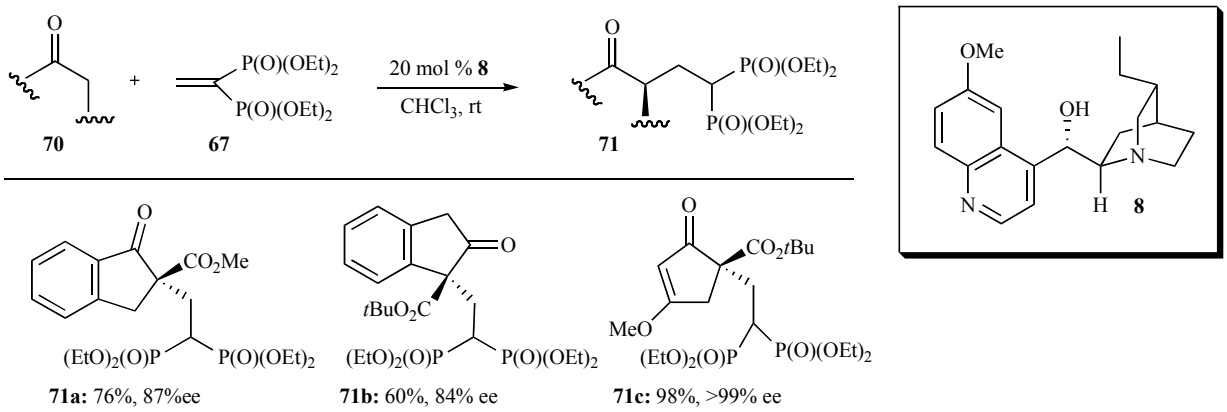
The 1,4-addition of a nucleophile to an olefin activated by an electron withdrawing group, generally known as the Michael addition reaction, is one of the most fundamental processes for C-C bond formation [44-46]. A few examples of enantioselective organocatalyzed Michael addition reactions applied to phosphonate chemistry have now been reported, in which the phosphonate was the Michael acceptor molecule or the Michael donor. Domino processes which involve Michael addition are discussed in section 2.5.

3.2.1. Phosphonates as Michael Acceptors

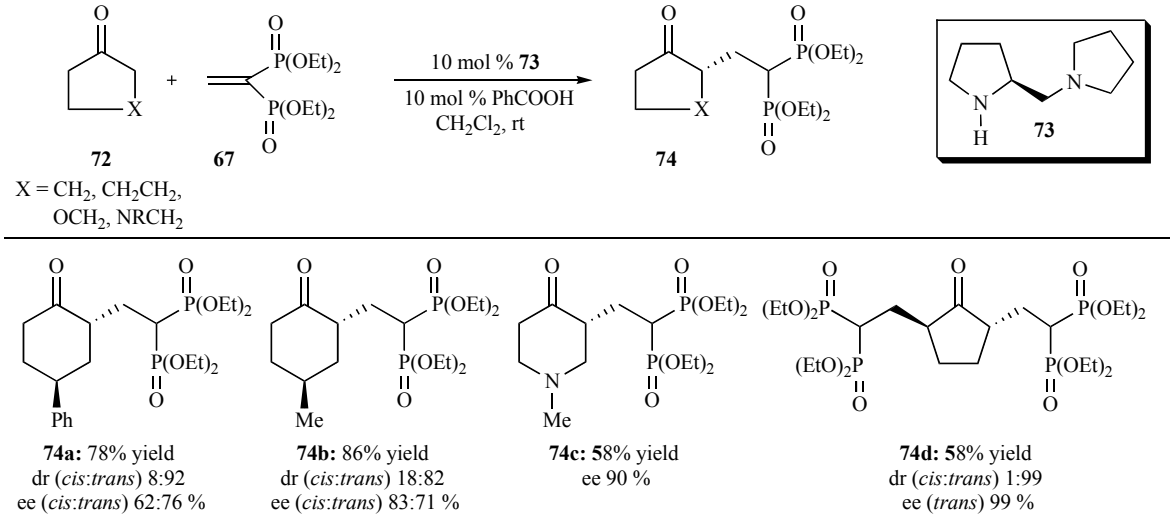
The first report of an organocatalyzed Michael addition reaction to vinyl phosphonates was by Alexakis and coworkers in 2007. They found that although aldehydes did not react with diethyl vinylphosphonate in the presence of chiral diamines or diphenylprolinol silyl ether **68**, when an



Scheme 12.



Scheme 13.



Scheme 14.

additional phosphonate moiety was added to the geminal position, smooth addition took place to give γ-geminal phosphonate aldehydes in high yields and ees [47, 48]. A 10-fold excess of aldehyde was used in this reaction. Catalyst **68** provided the best results (Scheme **12**).

Many gem-bisphosphonates have important biological activities, being currently used for the prevention and treatment of several bone disorders, such as osteoporosis, Paget's disease of the bone, bone metastasis resulting from multiple myeloma or certain forms of cancer, rheumatoid arthritis, periodontal disease and inflamation. More recently some have also been shown to inhibit the growth of protozoa responsible for major tropical diseases such as malaria, sleeping sickness and Chagas' disease, and also to inhibit the growth of several cancer cell lines [49]. Novel synthetic methodology aimed at the preparation of novel bisphosphonates is therefore highly desirable. Soon after the first report of this Michael addition reaction, Jørgensen and coworkers reported methodology for the addition of cyclic β-ketoesters to diethyl vinylphosphonate **67** [50]. When the two reaction partners were used in nearly equivalent amounts, dihydroquinine **12** (Scheme **13**) promoted the formation of products in high yields and ees of up to 99%. The reaction was also applied to one linear ketoester, and product was obtained in good yield, but with a moderate ee of 54%.

A novel example of enamine catalysis was reported by us shortly after, in which diamine **73** was used to catalyse the addition of ketones to vinylidene bisphosphonate **67** [49]. Although both linear and cyclic substrates gave Michael adducts, only the addition of cyclic ketones was enantioselective, and products were obtained in high yields, high drs and ees of up to >99% (Scheme **14**). A 10-fold excess of ketone was used in this reaction. Cyclopentanone was very reactive, and in this case double addition took place to give a C_2-symmetric product.

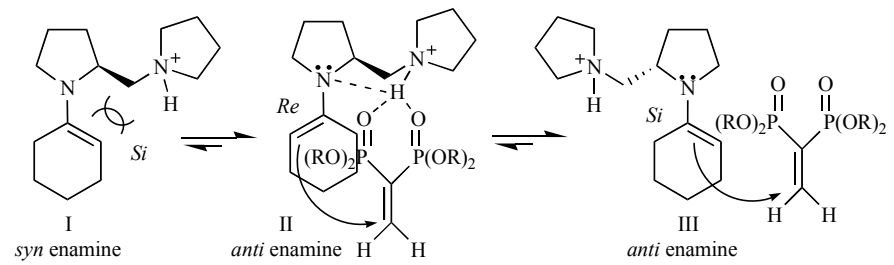
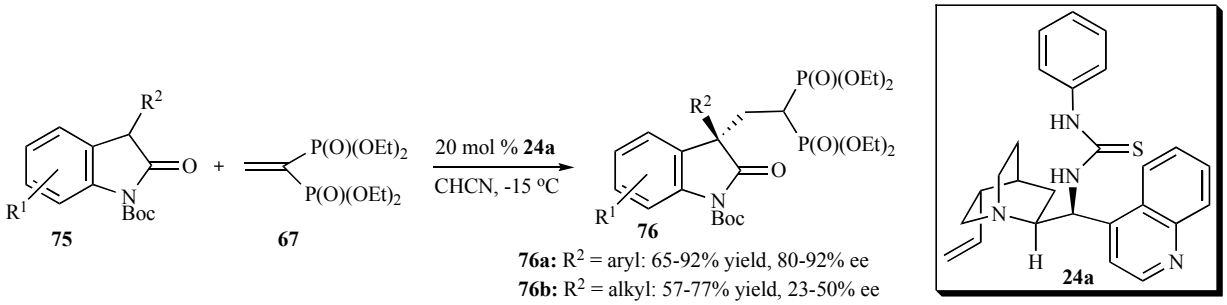
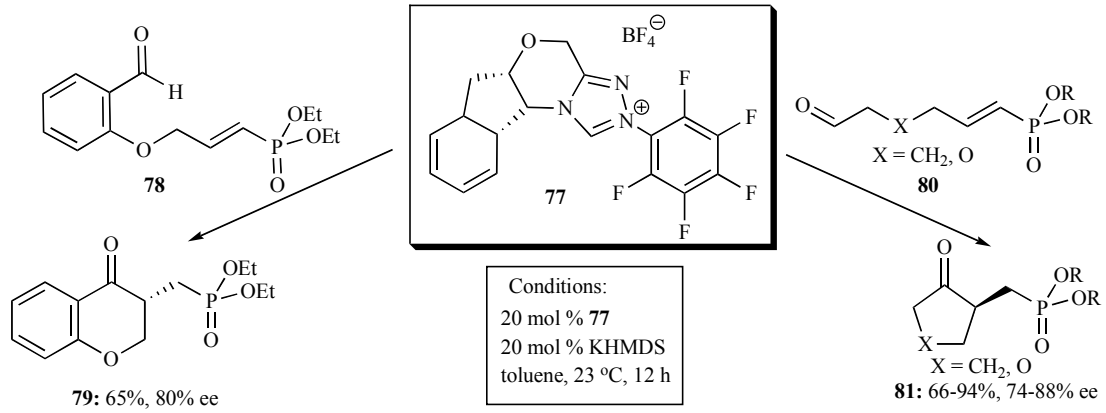


Fig. (5). Proposed facial selectivity for the transition state.



Scheme 15.



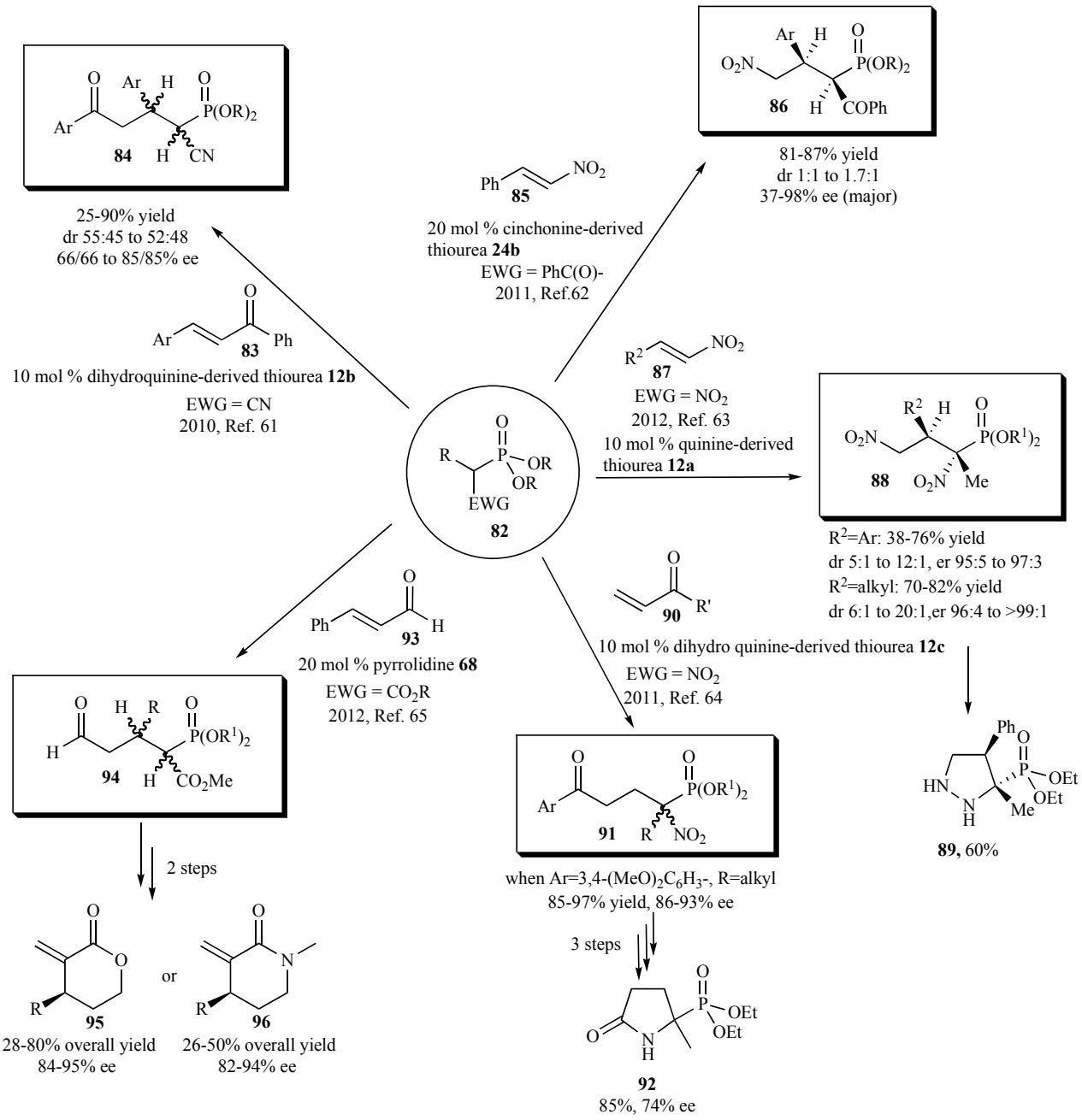
Scheme 16.

The absolute configuration at position 2 was determined by ^{13}C NMR spectroscopy after conversion of the products into their acetals with (2*S*,3*S*)-2,3-butanediol [51, 52]. The configuration was consistent with the preferential formation of an *anti* enamine (Fig. **5**) in which the double bond is oriented away from the bulky substituent at position 2 of the pyrrolidine ring, with the subsequent reaction taking place at the *Re* face. In this manner the reacting partners can be held in close proximity by hydrogen-bonding interactions in the transition state (Fig. **5**). The results agree with what is generally observed in Michael addition reactions of ketones catalyzed by pyrrolidines [53]. The phosphonates synthesized were analogues of those compounds that are known to have potent anti-arthritic and anti-inflammatory activities in their racemic forms [54].

In 2012 we reported the extension of this methodology to the synthesis of chiral tetrahydropyranone and 4-piperidones containing a methylene(bis)phosphonate moiety (Scheme **14**) [55]. Not only do piperidones often display biological activities, but they are also frequently used as advanced intermediates in the synthesis of biologically active piperidines [56]. The piperidine ring itself is a structural feature of many alkaloid natural products and prospective drugs and new methods for the production of these valuable intermediates could prove to be useful.

Shi and coworkers developed a highly enantioselective Michael addition reaction of 3-aryloxindoles to vinyl bisphosphonates [57]. Hydrogen bonding cinchonine derived thiourea **24a** provided the enantiofacial discrimination needed in the oxindole enolate. While Boc-substituted aryl oxindoles with several substitution patterns gave both high yields and high ees, the presence of aliphatic substituents at position 3 lowered the yield and ees considerably. This appears to be related to steric factors, since with R^2 = *ortho*-Me-C_6H_4 only trace amounts of product were obtained (Scheme **15**).

An intramolecular version of the Stetter reaction onto vinylphosphonates was also reported within this period. In the Stetter reaction, a 1,4-addition of an aldehyde to an α,β-unsaturated carbonyl compound takes place in the presence of a nucleophilic catalyst [58]. Cullen and Rovis reported an organocatalyzed extension of this reaction, in which vinylphosphine and vinylphosphonate moieties acted as the Michael acceptors [59]. Five- and six-membered rings could be assembled in a highly enantioselective fashion when a chiral carbene, generated *in situ* from chiral triazolium salt **77**, was used to catalyse the reaction (Scheme **16**). The yields of products were high.



Scheme 17. Phosphonates as Michael donors in organocatalyzed Michael addition reactions.

3.2.2. Phosphonates as Michael Donors

During the last five years there were a few reports of novel synthetic methods using Michael addition reactions in which a phosphonate was the nucleophile (Scheme **17**). The best catalysts used to promote these reactions are compiled in Fig. **6**. Hydrogen bonding catalysis with cinchona alkaloid derived thioureas provided the best option in most cases [60]. In the first report, in 2010, Jászay and coworkers described methodology for the enantioselective synthesis of γ-oxo-α-cyanophosphonates **84**, which may be chiral precursors of α-substituted β-aminophosphonates, structural analogues of β-amino acids, and potential inhibitors of proteolytic enzymes, with potential applications in peptidic medicinal chemistry and agriculture [61]. The addition of diethyl cyanomethylphosphonate to *trans*-chalcones gave mixtures of diastereoisomers with moderate dr and good to high ees. One year later Zhou and coworkers showed that nitroolefins could be good Michael acceptors for β-oxophosphonates, providing high yields of γ-nitro-β-oxophosphonates **86** with moderate diastereoselectivity, and moderate to very high ees, in the presence of cinchonine-based bifunctional thiourea **24b** [62]. The reaction was only applicable to aromatic nitroolefins (Scheme **17**). When an aliphatic olefin, **(***E***)**-1-nitrobut-1-ene, was used, there was no addition. The authors suggest that the catalyst plays a dual role activating the β-oxophosphonate for nucleophilic attack by deprotonation brought about by the tertiary amine moiety, and activating the nitroolefin by hydrogen bonding interactions between the thiourea subunit and the nitro group. In this way nucleophilic attack at the *Re* face of the

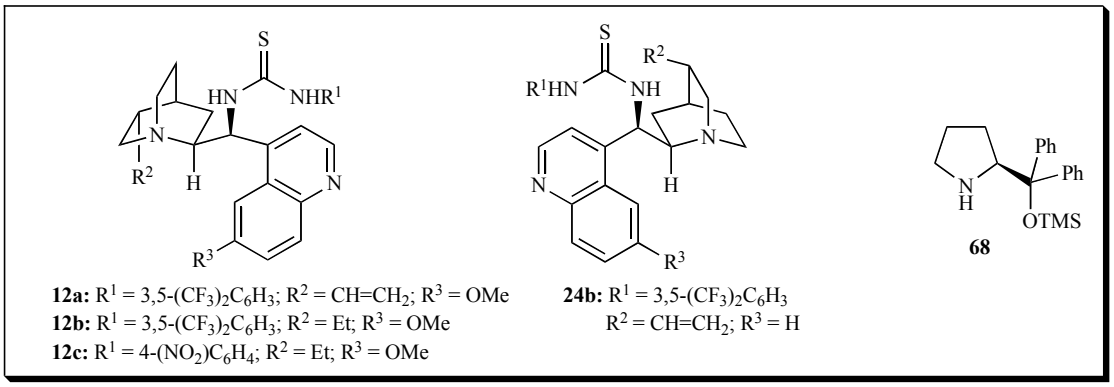
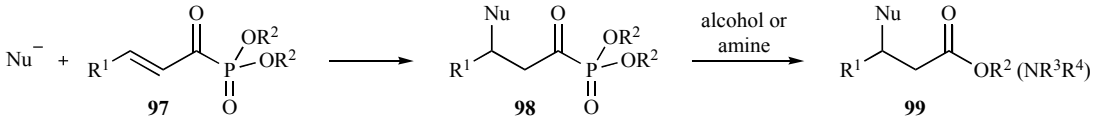


Fig. (6). Catalysts used in the Michael addition of phosphonates to various Michael acceptors.



Scheme 18. α-Ketophosphonates as acyl transfer agents.

nitro olefin is favoured to give the product obtained (Fig. **7**). The results were confirmed by X-ray analysis.

In 2012 Michael addition to nitrostyrenes was studied again, this time with α-nitrophosphonates as the Michael donors [63]. Hence Mukherjee and coworkers succeeded in synthesizing α,γ-nitrophosphonates with high drs and ees. Thiourea **12a** also allowed the use of aliphatic nitroolefins as Michael acceptors, and the products were also obtained in high ees and diastereoselectivity. A possible synthetic application was exemplified with the formation of a pyrazolidinyl phosphonate after treatment of a reaction product with $NaBH_4$ /$NiCl_2$.

The addition of α-nitrophosphonates to enones, described by Bera and Namboothiri in 2011, gave chiral quaternary α-nitrophosphonates in high yields [64]. The enantioselectivity was strongly influenced by the electronic properties of the enone substituents. The best ees were obtained with aromatic enones having strong electron-donating substituents (Scheme **17**). The authors showed that the products could be converted to chiral pyrrolidinylphosphonates like **92** with complete retention of configuration.

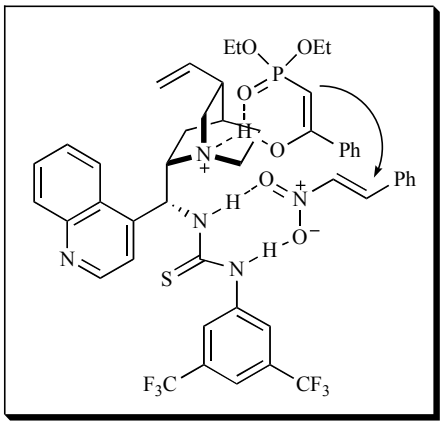


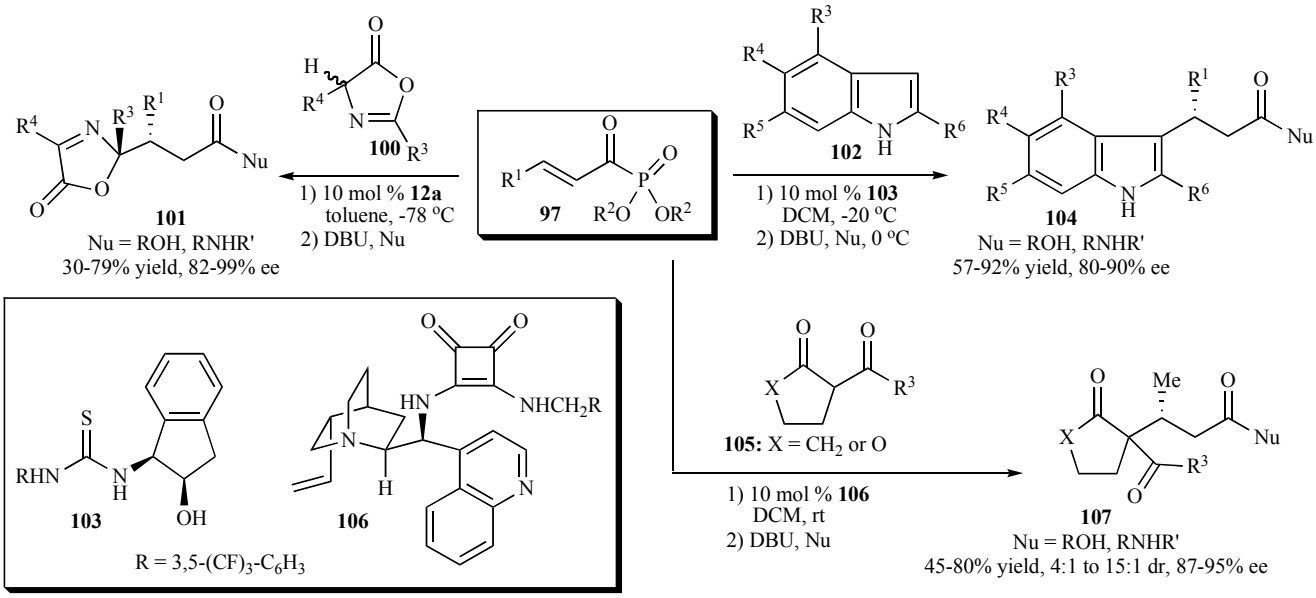
Fig. (7). Dual activation of the phosphonate and the nitroolefin through hydrogen bonding with catalyst **24b** provides the required enantiofacial discrimination in the synthesis of γ-nitro-β-oxophosphonates **86**.

Aromatic enals also proved to be good Michael acceptors for phosphoryl stabilized anions (Scheme **17**). Hence chiral pyrrolidine **68** was found by Jørgensen and coworkers to promote the smooth addition of trimethyl phosphonoacetate to cinnamaldehydes, giving products in good yields and very high ees [65], *via* iminium catalysis. Aliphatic aldehydes did not react. The authors used the newly developed methodology as a key step for the synthesis of α-methylene-δ-lactones and δ-lactams, which are important heterocyclic frameworks present in many biologically active compounds and natural products. Hence they applied the Michael addition reaction to the synthesis compounds having an indolo-[2,3-a]quinolizine framework, through a sequence of Pictet-Spengler reactions with tryptamine followed by Horner-Wadsworth-Emmons olefination, with complete preservation of enantioselectivity throughout.

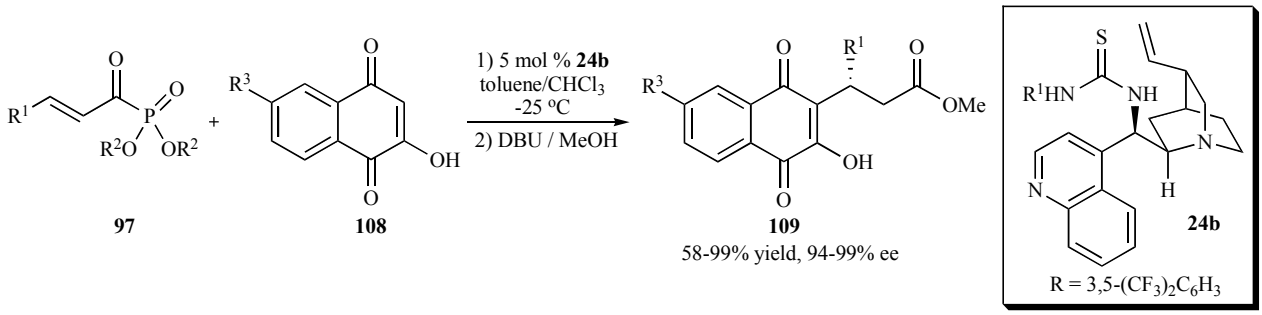
3.2.3. Phosphonates as Acylating Agents

Acyl phosphonates may be used as effective activated esters in acyl transfer reactions (Scheme **18**) [66, 67]. Jørgensen and coworkers were the first to apply this concept to organocatalysis [68]. They showed that α,β-unsaturated acyl phosphonates behave as Michael acceptors towards nucleophiles, and that the adducts may be converted into simple esters or amides when a second nucleophile is added. In the presence of suitable chiral hydrogen-bonding organocatalysts, chirality is transferred to the activated acylphosphonate in the addition step, from which it is efficiently transferred to the final ester or amide.

This concept was successfully applied to a few reactions. Hence, in the 1,4-addition of oxazolones **101** to acylphosphonates **97** catalyzed by quinine derived thiourea **12a**, when the reaction was quenched by DBU followed by an alcohol or an amine, the oxazolone was alkylated at position 2, and the corresponding 3-oxazonyl substitued esters or amides were obtained in good yields and very high ees (Scheme **19**). Similarly, when indoles **102** were added to acylphosphonates **97** in the presence of chiral thiourea **103**, quenching the reaction with DBU followed by an alcohol or an amine, resulted in indole alkylation at position 3, and the



Scheme 19.



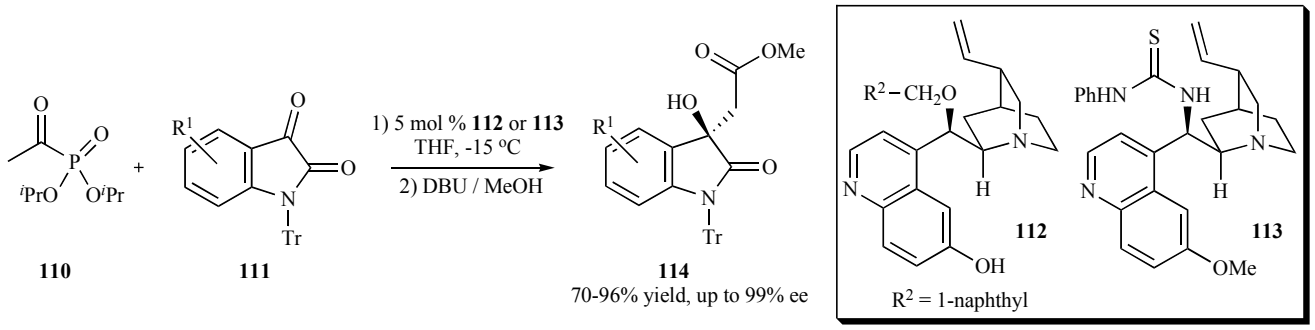
Scheme 20.

corresponding 3-indonyl esters or amides were obtained in high yields and ees (Scheme **19**). The presence of a N-H bond at position 1 of the indole was crucial for enantioinduction. When a methyl substituent was present, the products were racemic, suggesting that this hydrogen atom is probably involved in hydrogen-bonding interactions with the catalyst in the transition state. Application of the methodology to the alkylation of 1,3-dicarbonyl compounds, resulted in the formation of cyclic ketones or esters containing a α-quaternary carbon centre in good to high yields and very high ees, when cinchonine-derived squaramide **106** as used as catalyst (Scheme **19**). The analogous quinidine-derived thiourea gave products having the opposite configuration at the chiral centre.

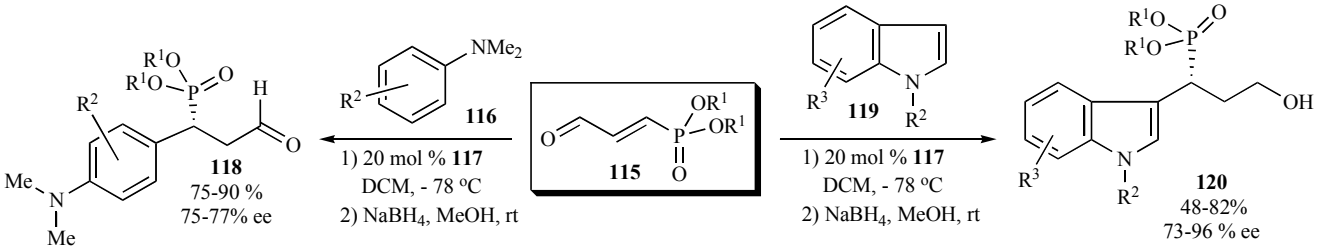
Almost at the same time, but days later, Bachu and Akiyama published a method for the Friedel-Crafts alkylation of indoles with α,β-unsaturated acyl phosphonates, in which the products were quenched *in situ* with DBU followed by MeOH or morpholine to give the corresponding 3-indonyl esters or amides [69]. Hence, in the presence of chiral phosphoric acid **10c**, the products were obtained in moderate to good yields (31-73%) and high ees (64-92%). In this case aromatic α,β-unsaturated acyl phosphonates were used, whereas in the study of Jørgensen and coworkers, aliphatic α,β-unsaturated acyl phosphonates were the substrates.

In 2011 Wang, Zhou and coworkers applied the acyl transfer properties of acylphosphonates to the synthesis of chiral 3-substituted 2-hydroxy-1,4-naphthoquinones [70]. Naphthoquinones are thought of as privileged structures in medicinal chemistry [71], and methodology directed at functionalization of these compounds to give chiral derivatives could lead to materials with important biological activity. Cinchonine-based chiral thiourea **24b** promoted the asymmetric Michael addition reaction giving adducts in good yields and excellent ees, once the reaction was quenched with DBU followed by methanol or ethanol (Scheme **20**).

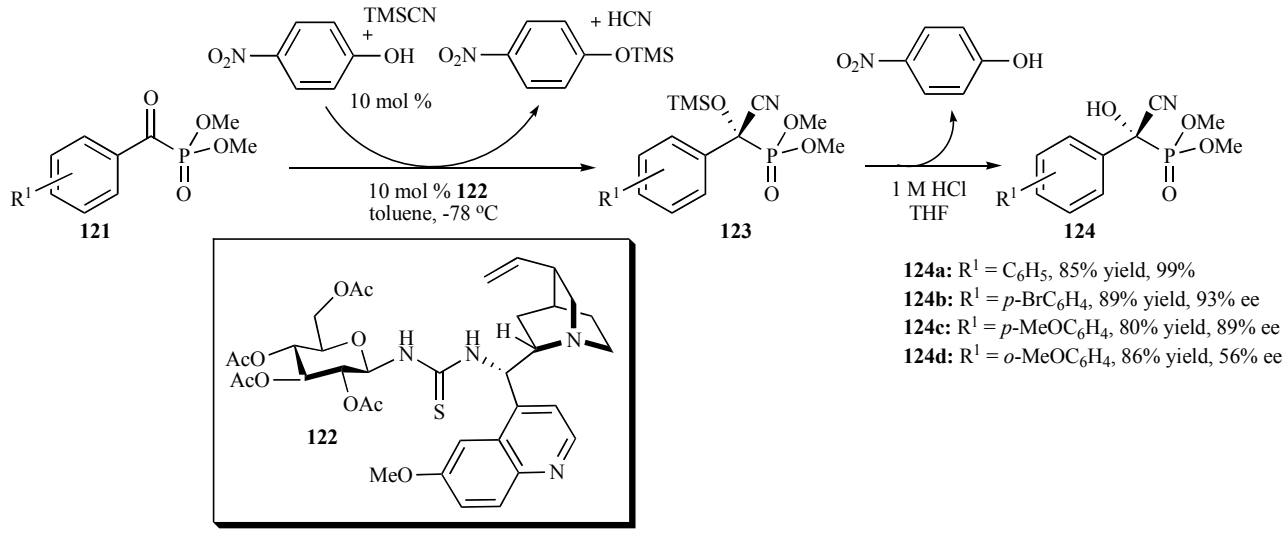
The lability of α-acyl phosphonates was further explored by Zhao and co-workers for another novel application. They used enolizable acetylphosphonates **110** as nucleophiles in organocatalyzed enantioselective aldol reactions with isatins **111**. When the reactions were quenched with DBU and methanol, 3-chiral 2-indanone derivatives **114** were obtained in very high yields and ees, if either **112** or **113** were used as catalysts (Scheme **21**) [72]. This was in effect an example of a formal organocatalyzed direct acetate aldol reaction, since compound **110** acts as a surrogate of acetate in this process. This transformation is rather difficult to achieve by other means, the only other examples of enantioselective acetate aldol reactions reported so far beeing Mukaiyama aldol reactions, in which preformed silyl ketenes acetals were used



Scheme 21.



Scheme 22.



Scheme 23.

[72]. Phenylglyoxals and α-keto esters could also be used as substrates for the reaction.

3.3. Friedel-Crafts Alkylation and α-Cyanation

A Friedel-Crafts alkylation reaction leading to α-aryl substituted phosphonates was developed by Xiao and coworkers in 2009 (Scheme **22**) [73]. Using imminium catalysis mediated by MacMillan's imidazolidinone catalyst **117** (Fig. **8**), and equimolar amounts of reagents, they achieved the Friedel Crafts alkylation of indoles and substituted anilines with 3-oxoprop-1-enylphosphonates in good yields and high ees. The products were reduced *in situ* to the corresponding carbinols.

Recently Miao and coworkers developed novel catalysts consisting of combinations of thiourea derived cinchona alkaloids and sugar moieties [74]. They found that, in the presence of *p*-nitrophenol, diethyl and dimethyl benzoylphosphonates could be cyanosilylated in very high yields and high enantioselectivities (Scheme **23**). Aliphatic acylphosphonates also gave products in high yields but only with moderate enantioselectivities. They found that steric effects played a significant role, since *ortho* substitution in the aromatic ring lowered the ee considerably, *e.g.* from 89% in the *p*MeO-substituted ring to 58% in the *o*MeO-substituted one, and also with an increase in the steric bulk of the phosphonate ester substituent. The crude TMSCN adducts produced initially were subsequently hydrolyzed to the corresponding α-hydroxyphosphonates, for which ees were reported. The absolute configuration of the products was determined by X-ray crystallography.

3.4. Cycloaddition Reactions

Cycloaddition reactions leading to five- and six-membered rings were reported during this period [75].

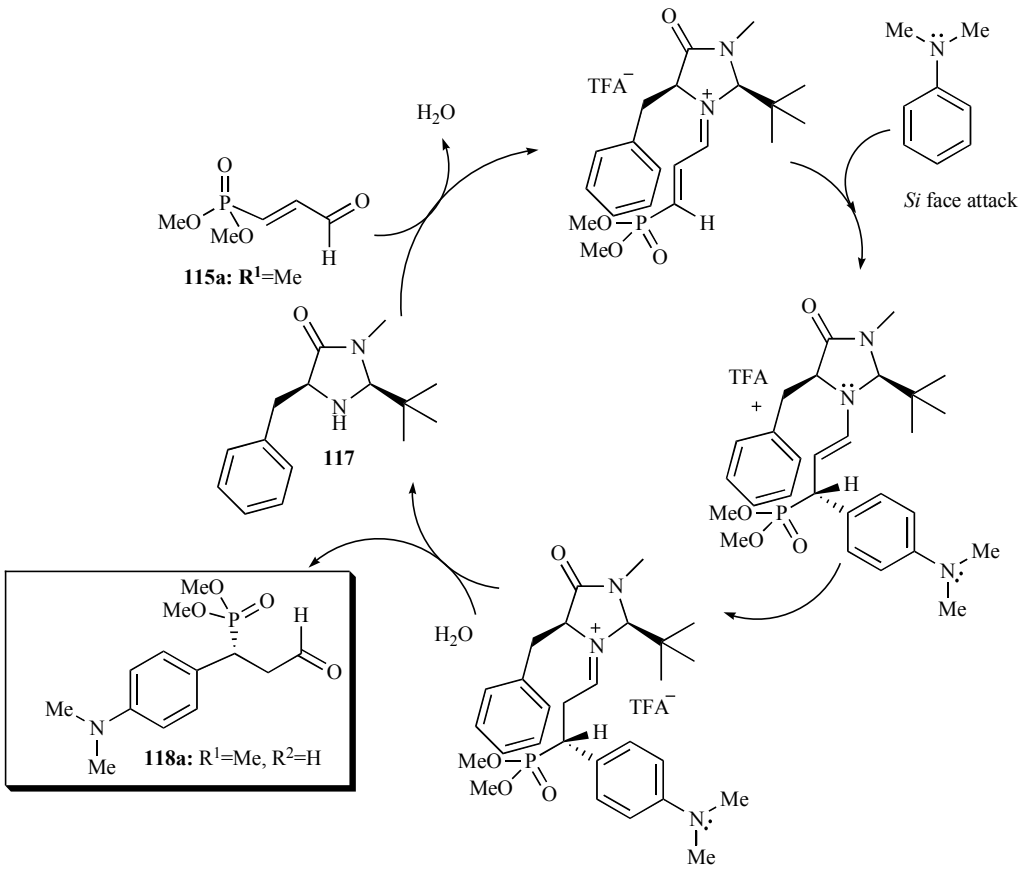
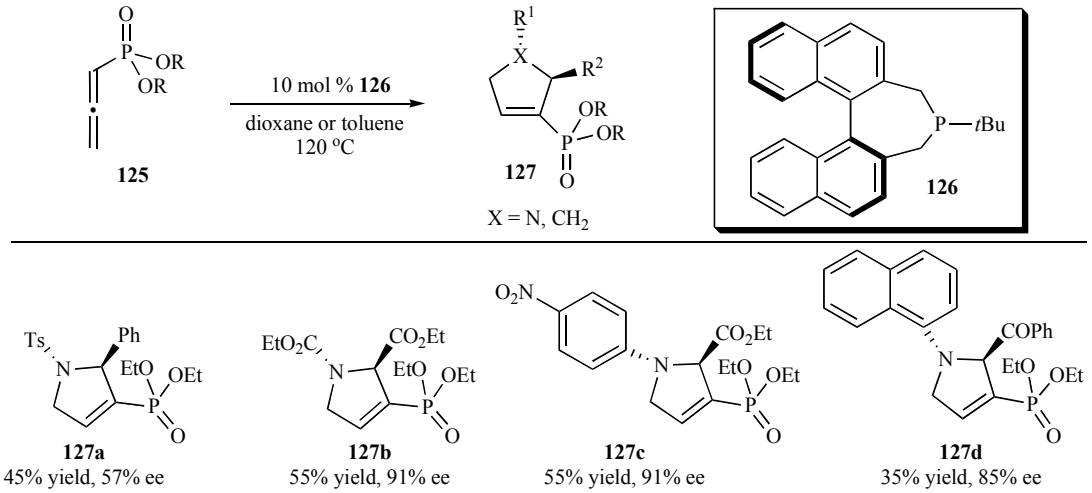


Fig. (8).

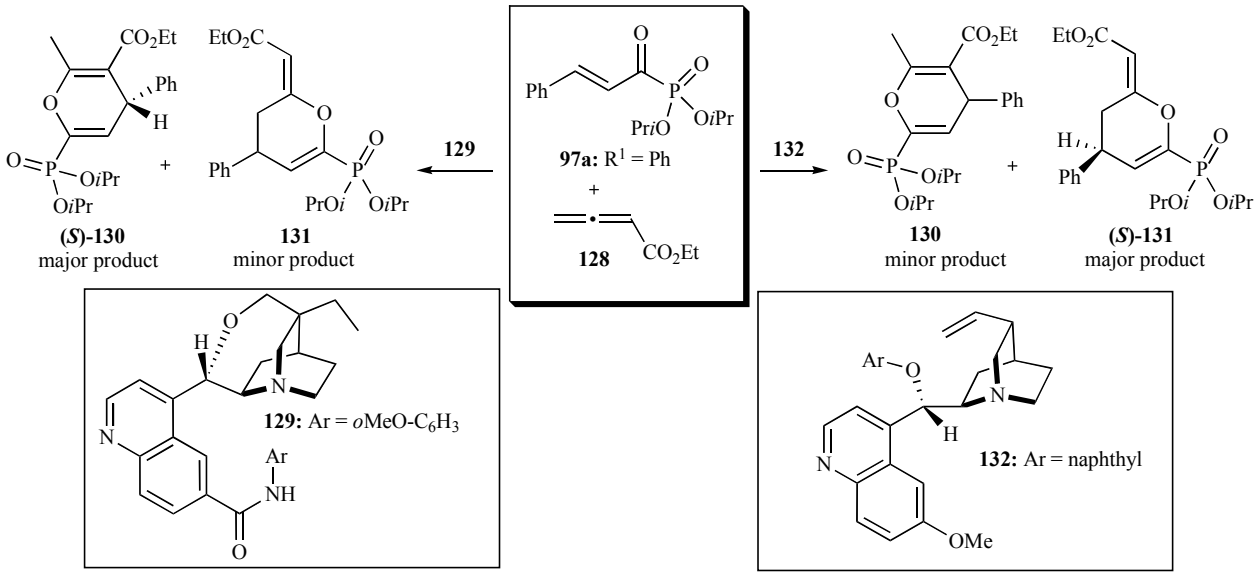


Scheme 24.

Marinetti and coworkers showed that electron-deficient allenes bearing a phosphoryl group can participate in [3+2] cycloaddition reactions with imines and electron-deficient alkenes when a phosphine is added to the reaction mixture [76]. Although phosphines have been known for a number of years to promote cycloaddition reactions between allenes and electron deficient alkenes by Lewis base activation or nucleophilic catalysis [77], this appears to be the first report on the use of phosphines to catalyse cycloaddition reactions of allenylphosphonates.

Highly substituted pyrrolines and cyclopentenes were obtained (Scheme **24**). The reactions were regioselective and diastereoselective in favour of the *trans* product. Although conversions were generally low to moderate, due to a competitive isomerization of the allenylphosphonate to the corresponding alkyne, enantioinduction was high in the presence of phosphine **126**. In the reaction with diethyl fumarate, the product was obtained in 55% yield and 91% ee. In the presence of electron-richer substituents on the olefin there was no reaction, and with methyl substitution α to phosphorus, [4+2] cycloaddition was the favoured reaction, but an asymmetric version was not explored in this case.

Pyrans and dehydropyrans bearing phosphoryl substituents are structural components of many natural products,



Scheme 25.

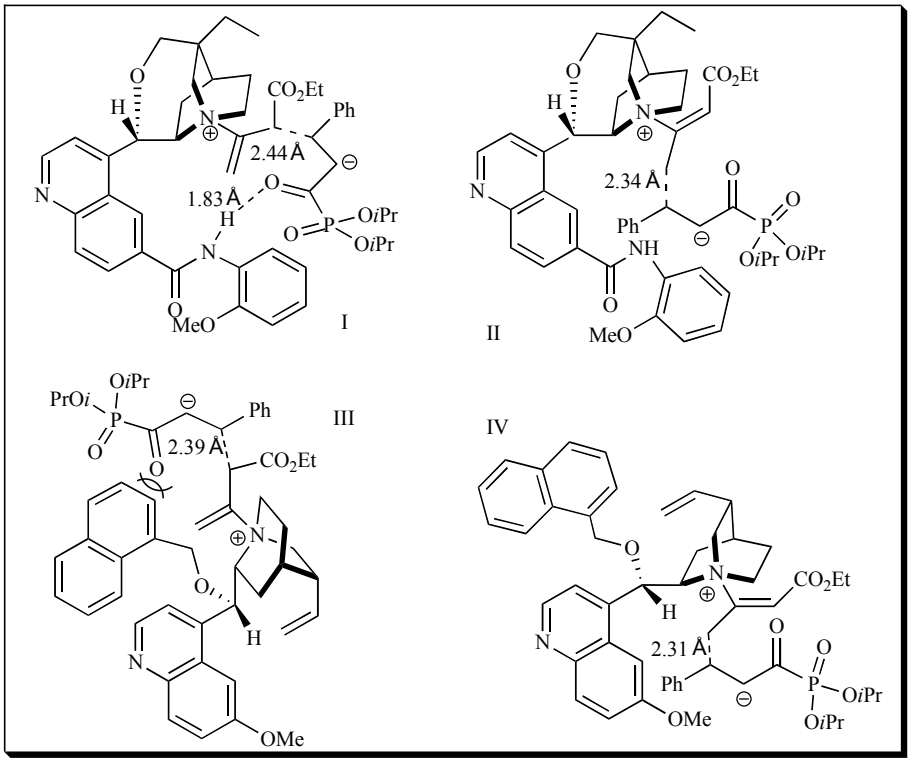
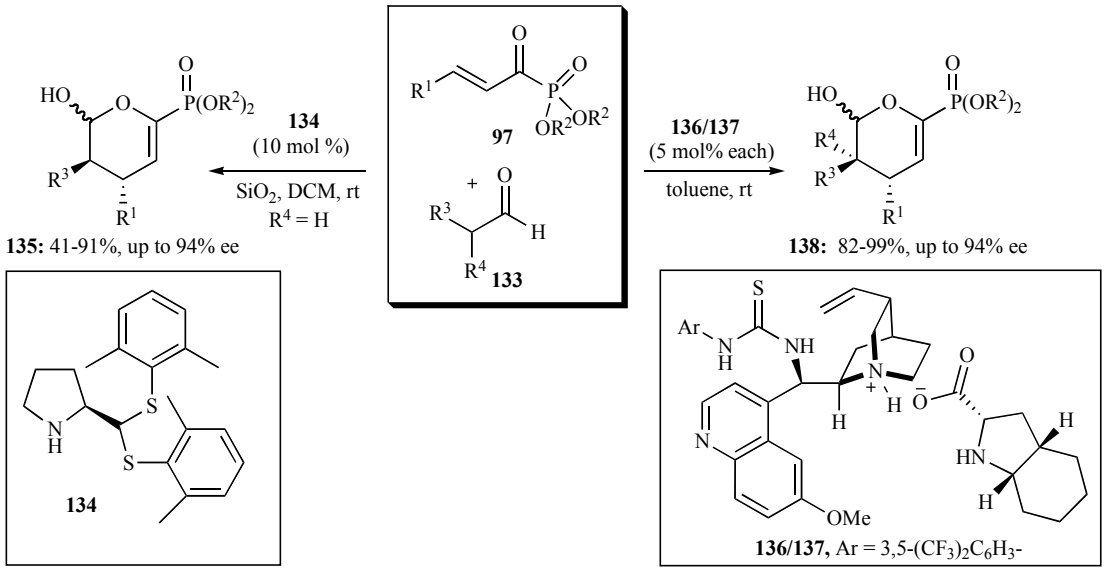


Fig. (9). The relative energies of the key transition state models were calculated and optimized at the mPW1K/6-31 + G(2d)//mPW1K/6-31G(d) level of theory: ΔH_{298}(kJmol^{-1}): **I** 0.0, **II** 18.2, **III** 6.4, **IV** 0.0 [79]. Transition state **I** gives rise to **(*S*)-130 (major)** and transition state **IV** gives rise to **(*S*)-131 (major)**.

drugs, and biologically active molecules. Examples are, for instance, phosphono-Zanamivir, a potent inhibitor of the neuraminidases of avian and human influenza viruses [78], and phosphorus chromones, which are important intermediates in the synthesis of platelet-aggregation inhibitors [79]. Recently Shi and coworkers reported a method for the enantioselective synthesis of pyrans and dehydropyrans based on the organocatalyzed [4+2] cycloaddition of allenic esters with β,γ-unsaturated α-ketophosphonates [79]. In the presence of suitable cinchona alkaloid derivatives, they could obtain a mixture of these two compounds.

Further optimization showed that it was possible to obtain either of them in a highly regioselective manner, by small variations in catalyst structure. Hence, when derivative **129** was used as catalyst, the pyran was obtained in an excess of 3:1 to 7:1, in good yields of up to 77% and very high ees of 83-92%. When **132** was used, the dihydropyran was the major product, obtained in up to 92% yield and 91-95% ee (Scheme **25**). Theoretical calculations showed that with **129**, hydrogen bonding between the CONH moiety in the catalyst and the carbonyl and phosphonate groups in the substrates lowers the energy of the key transition state (Fig.



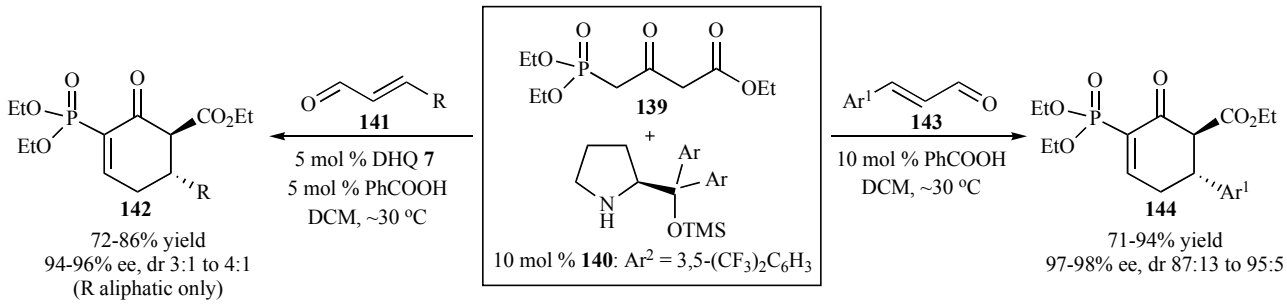
Scheme 26.

9). When catalyst **132** which lacks a H-bonding donor atom is used, H-bonding cannot occur, and steric interactions between the reagents and the naphthyl group of the catalyst control the orientation of approach of the reagents. Hence different produts are obtained in majority in each case (Fig. **9**).

In 2007 Zhao and co-workers developed the first inverse-electron-demand hetero-Diels-Alder reaction mediated by organocatalysts in which a phosphonate was one of the reaction partners [80]. Hence β,γ-unsaturated α-keto-phosphonates were reacted with α-enolisable aldehydes to produce 5,6-dihydro-4H-pyran-2-ylphosphonates in high yields and ees (Scheme **26**). Although three stereogenic centres were produced, only two diastereoisomers were obtained, in anomeric ratios varying from 76:24 to 83:17. When R^1 = Ph in **97**, the results were very different, with a low chiral induction of 19% only, probably due to electronic effects. Since the diastereoisomers were difficult to separate by HPLC, the authors oxidized the products to the corresponding lactones, obtaining only one product. This was an indication that the diastereoisomerism was due to the stereochemistry of the hydroxyl group, whereas the formation of the carbon stereogenic centres was completely diastereoselective. This enamine catalyzed process was conducted in the presence of silica gel, whose function was to speed-up the reaction and to improve yields, presumably by catalyzing the cleavage of the catalyst from the primary Diels-Alder product. More recently, in 2013, Zhao and co-workers revisited this reaction, employing a different methodology for catalysis [81]. Self-assembled organo-catalysts, consisting of an amino acid and a cinchona alkaloid derived thiourea, held together by ionic interactions, were used in this case. Modularly designed organocatalysts were introduced to organocatalysis by Clark and co-workers in 2007 [82], but only a few applications of this methodology have been developed so far. Self-assembly is a powerful way to modify and fine-tune catalyst structure, since no actual synthetic steps are involved in the final step of catalyst formation, when the different units assemble together. In the presence of a catalyst resulting from the *in situ* self-assembly of quinidine thiourea **136** with (2*S*,3a*S*,7a*S*)-octahydro-1*H*-indole-2-carboxylic acid **137**, the reaction of β,γ-unsaturated α-ketophosphonates or β,γ-unsaturated α-ketoesters with α-branched aldehydes led to the formation of products in very high yields and ees (Scheme **26**). If the thiourea or the amino acid proline were used alone, poor results were obtained, which showed that the combination of both was crucial. A NOESY study revealed the probable structure of the self-assembled catalyst.

3.5. Domino Processes

Domino reactions are one of the most powerful and versatile developments of organocatalysis. They allow the rapid assembly of complex molecules in one pot without the need for isolation and purification of individual reaction products before the next reaction occurs. One catalyst promotes several reactions. In most organocatalytic domino processes developed so far, the products are obtained with very high diastereo- and enantioselectivities [83-85]. A few examples have appeared in phosphonate chemistry. Jørgen-sen and coworkers reported an organocatalytic domino Michael-Knoevenagel condensation which led to the for-mation of optically active highly substituted cyclohexenones bearing a phosphoryl substituent from 6-substituted-3-diethoxyphosphoryl-2-oxocyclohex-3-enecarboxylates and α,β-unsaturated aldehydes (Scheme **27**) [86]. Activation of the aldehyde by chiral diarylprolinol ether **140** resulted in the formation of an imminium ion, which was attacked preferentially from the less hindered *re* face by the enol of **139** avoiding steric interactions with the bulky substituent at C-2 (Fig. **10**). Spontaneous hydrolysis releases the adduct, which undergoes spontaneous Knoevenagel condensation to the cyclic phosphonate. Reactions with aromatic α,β-unsaturated aldehydes were highly diastereoselective and cyclohexenones were obtained in excellent ees too. The yields were improved when benzoic acid was used as an additive. Surprisingly, when aliphatic aldehydes were tried under the same conditions, no reaction took place. The authors overcame the problem adding small amounts (5 mol %) of a second catalyst, dihydroquinine, which may facilitate



Scheme 27.

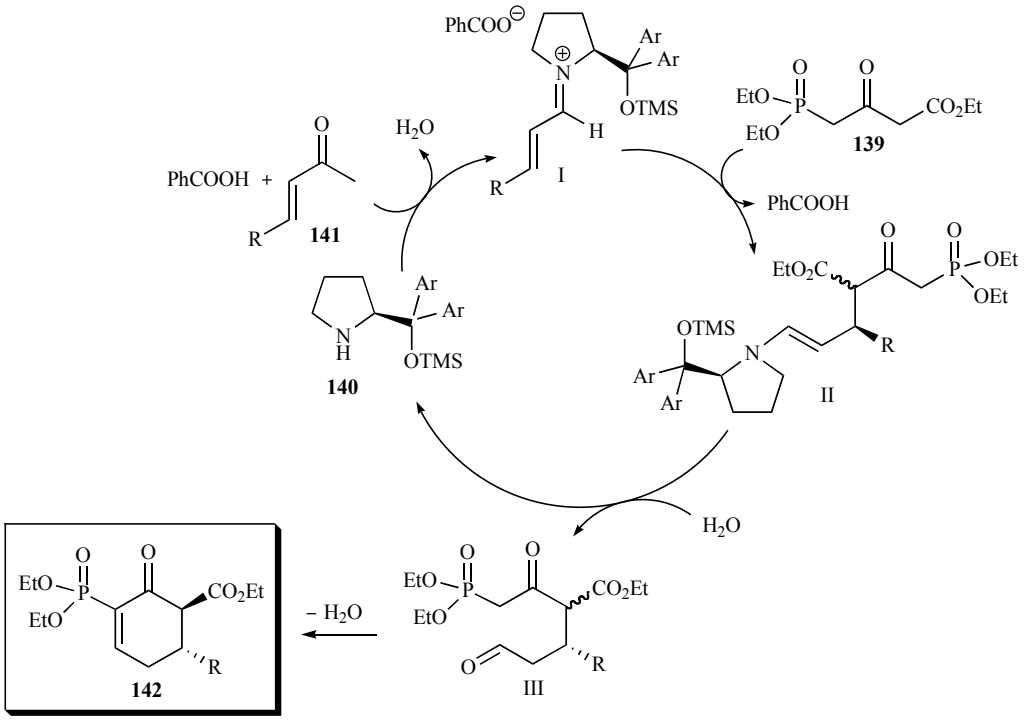
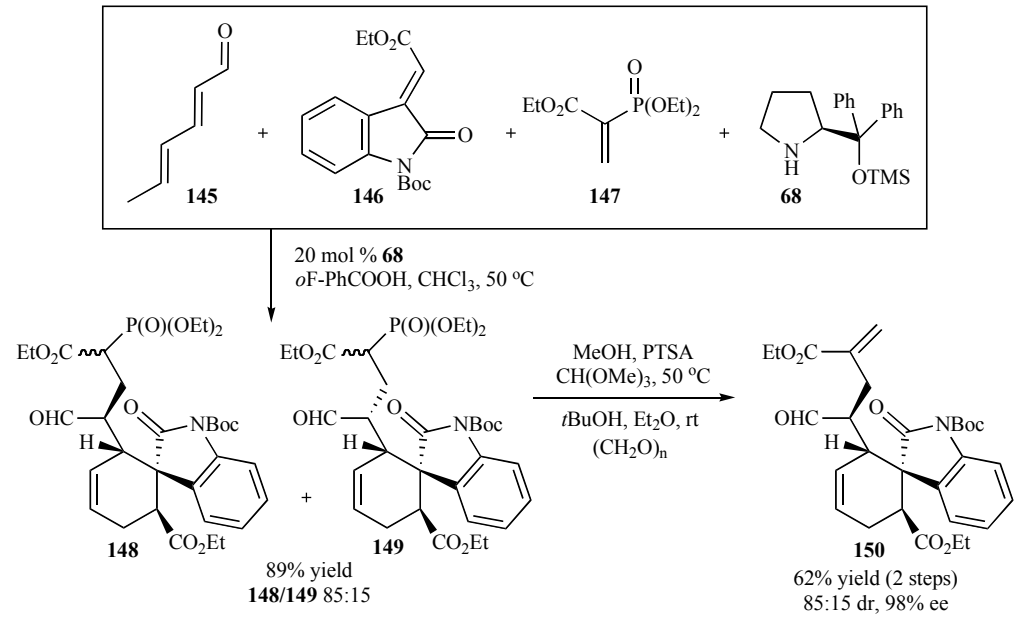


Fig. (10).

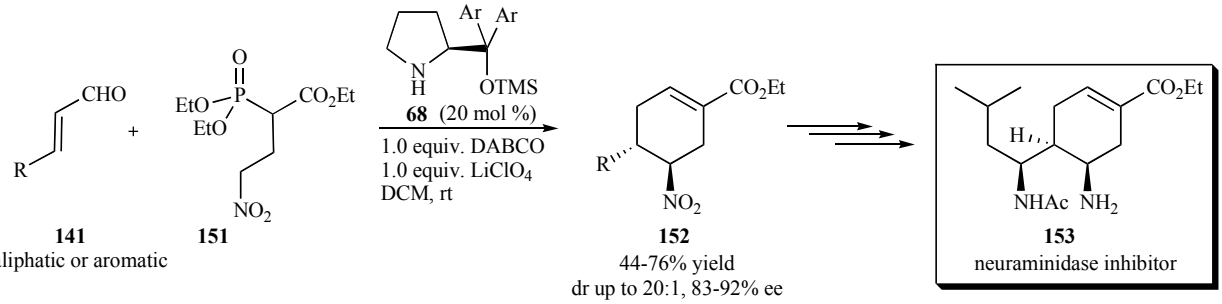
the enolisation process, and the respective products were then obtained in excellent ees, albeit with lower diastereoselectivity.

The same group developed the first example of an organocatalytic trienamine-enamine multicomponent tandem process, an organocatalyzed Diels-Alder-Michael addition domino reaction [87]. They found that 2,4-dienals could be used in organocatalytic reactions as reactive trienamine intermediates after reaction with a chiral pyrrolidine. In this way, a substrate in which a HOMO with both the γ and the ε-carbon atoms activated is obtained. Enantioselective reactions at these atoms imply a relay of chirality over a distance of up to eight bonds. Hence, when they mixed 2,4-dienal **145**, ethyl-2-(diethoxyphosphoryl)acrylate and 3-olefinic oxindole **146**, in the presence of chiral pyrrolidine **68** and ortho-fluorobenzoic acid as additive, a domino Diels-Alder-Michael addition reaction took place to give a spirocycle oxindole with a substituent bearing a phosphoryl group which could be subsequently used in Wadsworth-Horner-Emmons reactions after suitable protection without epimerization (Scheme **28**). The spirocycle oxindole was obtained in high yield and good diastereoselectivity. The final product was obtained with 98% ee. To discard the possibility that the product resulted from double conjugate addition rather then the proposed Diels-Alder-Michael addition domino reaction proposed, the reaction was monitored by NMR spectroscopy. They concluded that the lack of observable monoaddition intermediates and the high diastereo- and enantioselectivity of the reaction pointed to the second hypothesis, since with the double Michael mechanism the reaction could also occur from the all trans enamine where steric-shielding by the catalyst is minimal and a low ee would be obtained.

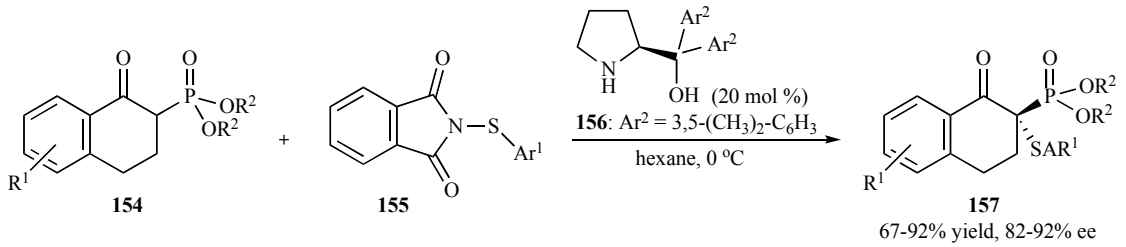
Phosphonate chemistry was applied to another asymmetric domino process. Lu and coworkers found that chiral prolinol **68** promoted an asymmetric domino nitro-Michael-Horner-Wadsworth-Emmons reaction involving α,β-unsaturated aldehydes and γ-nitrophosphonates leading to tri-substituted cyclohexenecarboxylates [88]. The products were obtained in good yields and very high ees and high diastereoselectivities, with aromatic α,β-unsaturated aldehydes (Scheme **29**). The same conditions could be used with aliphatic α,β-unsaturated aldehydes, but both the yield and the ees were more moderate, although asymmetric



Scheme 28.



Scheme 29.



Scheme 30.

induction remained high. Subsequent elaboration of the reaction products in a few steps led to pharmaceutically useful compounds like dipeptidyl peptidase IV inhibitor ABT-341 and an influenza neuraminidase inhibitor **153**, analogous to tamiflu, with an IC_{50} of 1.9 μM, hinting at the enormous potential of asymmetric organocatalysis for future target-oriented synthesis.

4. CARBON-SULPHUR BOND FORMING REACTIONS

Heterofunctionalization of phosphonates leading to the formation of C-S bonds can give rise to molecules useful on their own right or which may be useful synthetic intermediates. For example, bacteria produce β-lactamases to withstand β-lactam antibiotics, and although the emergence of carbapenem-resistant bacteria is a growing concern, clinically there are still no useful inhibitors of metallo-β-lactamases [89, 90]. Certain mercaptophosphonates have been shown to be potent broad spectrum inhibitors of the metallo-β-lactamases [90]. Research in this area may lead to novel compounds useful for pharmaceutical applications.

Recently Zhu, Cheng and coworkers developed methodology for the α-sulfenylation of β-ketophosphonates, obtaining in a highly asymmetric fashion products with a α-quaternary carbon centre, notoriously difficult to obtain [91, 92]. They found that various α,α-diaryl-l-prolinols could be used as catalysts. As sulfur sources, *N*-(aryl-thio)phthalimides proved to be efficient (Scheme **30**). Good yields of products with very high ees were obtained with 3,4-dihydro-(2*H*)-1-naphthalenones bearing a 2-phosphoryl substituent, but in a reaction with diethyl 2-cyclopentanonephosphonate, although the induction remained high, the yield was

moderate. Aliphatic substrates gave almost no reaction. The authors suggest that the catalyst activates the substrate, in the enol form, for reaction, *via* the formation of hydrogen bonds.

In summary, the wealth and variety of the methodology developed during the last five years using organocatalytic approaches for the synthesis of chiral phosphonates will no doubt give rise to many applications in synthesis and let one barely guess the potential that exists for future developments.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

The financial support from Fundação para a Ciência e a Tecnologia, Ministério da Educação e Ciência, is gratefully acknowledged.

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Received: May 15, 2013 **Revised: June 16, 2013** **Accepted: June 16, 2013**