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Organocatalytic Asymmetric Synthesis of Organophosphorus Compounds

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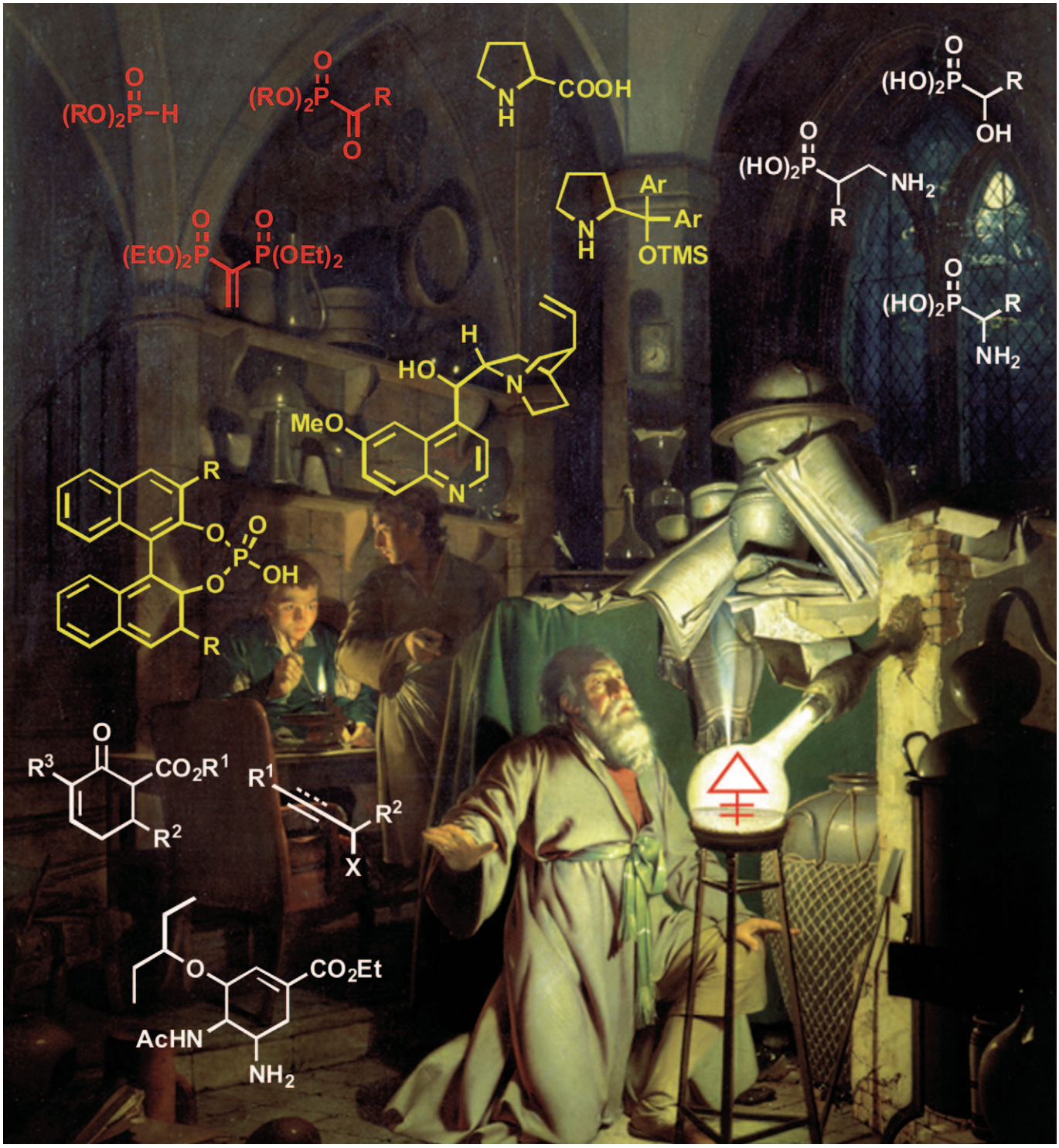

Abstract: 240 Years have passed since the discovery of elemental phosphorus. During that time organophosphorus chemistry has emerged as an interesting and exciting field of research. Recently organophosphorus chemistry has been raised to a new level. Organophosphorus compounds have found applications in asymmetric organocatalysis for the synthesis of optically active compounds of synthetic or biological importance. The aim of this review article is to present recent contributions to this developing field of chemistry and to point out synthetic advantages of methodologies developed so far.

Keywords: asymmetric synthesis · organocatalysis · organophosphorus compounds · phoshonates · phosphines

Introduction

For centuries before the chemistry was born in its modern form alchemists searched for the philosopher's stone—a substance that could turn inexpensive metals into gold. In 1669 the German alchemist Henning Brand in his quest for the philosopher's stone accidentally discovered a new element, which he named phosphorus after the Greek word meaning "light-bearing" or "light-bearer". Since then phosphorus has been found to be present in many organic compounds and the chemistry of organophosphorus compounds started to attract chemists. The extraordinary richness of organophosphorus compounds, their tremendous structural and electronic diversity, as well as specific chemical behavior makes them versatile reagents that play a very important role in modern synthetic organic chemistry.[1] For example, phosphorus ylides, phosphine oxides, and phosphonates are widely used for the stereoselective introduction of olefinic bonds into target molecules.[2] Optically active organophosphorus compounds are also valuable chiral building blocks for the synthesis of natural products.[3] Furthermore, various tri- and pentacovalent phosphorus compounds serve as ligands or catalysts in different enantioselective transformations.[4] Additionally, many organophosphorus compounds can be found in nature and possess significant, and in many cases, very specific biological activity that is often related to their absolute stereochemistry.[5] Taking into account the interesting chemical behavior and diverse biological properties of organophosphorus compounds there is a great need for the development of methods enabling their preparation in an asymmetric fashion.

Catalytic asymmetric reactions constitute one of the most potent and useful method for introduction of chirality into target molecules. Until very recently the field of enantioselective catalysis has been dominated by metal and enzyme catalysts. Since 2000 organocatalysis has emerged as a very powerful tool in modern asymmetric synthesis, being complementary to metal and enzyme catalysis. Combined efforts of different scientific groups resulted in great development of this new methodology of asymmetric synthesis.[6] As a result, asymmetric organocatalysis has become an important method of choice enabling simple and efficient approach to optically active compounds.

In recent years the increasing number of papers concerning applications of organophosphorus reagents in asymmetric organocatalysis has been published showing growing importance of this methodology. We believe that this review will deliver a comprehensive outlook on this interesting subject and will familiarize the reader with the recent advances achieved. The applications of different organocatalytic strategies for the synthesis of biologically interesting α-hydroxy- and α- or β-aminophosphonates, as well as utilization of organophosphorus compounds in organocatalytic syntheses of important organic molecules will be presented. It should also be noted that the results concerning applications of organophosphorus reagents in asymmetric organocatalysis are very rarely disclosed in reviews about organocatalysis and this topic has not been previously summarized. The material concerning applications of axially chiral phosphoric acids as Brønsted base catalysts in asymmetric organocatalysis is not covered in this review.

Modes for Catalytic Activation of Substrates in Asymmetric Organocatalysis

From a mechanistic point of view, the interactions between the substrate and the catalyst in asymmetric organocatalysis are different from mechanisms operating in classical metal-catalyzed reactions. In general, a catalyst interacting with the substrate activates it and creates the chiral environment that is essential in all enantiodifferentiating reactions. The interactions between substrate and the catalyst that are postulated to occur in asymmetric organocatalysis can be divided into three main groups:

Covalent catalysis—the catalyst binds to the substrate by a covalent bond: Aminocatalysts **2** are mainly secondary amines, such as proline and derivatives, that interact with the substrates by a covalent bond (Scheme 1). In this amino-

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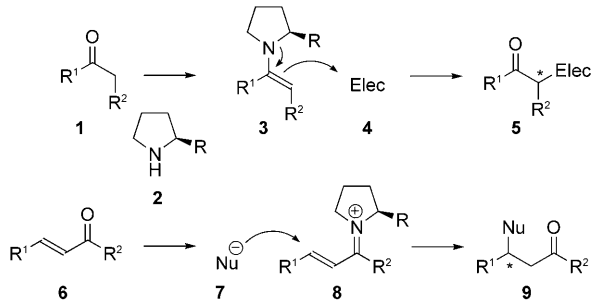
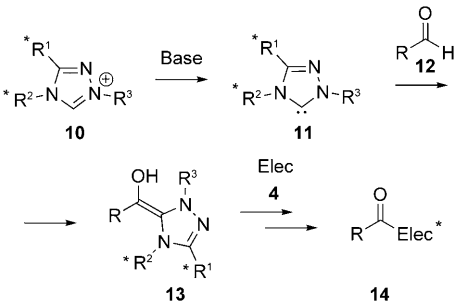


Scheme 1.

catalytic approach, carbonyl compounds, such as aldehydes or ketones and α,β-unsaturated aldehydes or enones, **1** and **6**, respectively, are activated either by the formation of enamine **3**, which in turn can react with electrophilic species **4** leading to the formation of the new bond in an enantioselective manner, or iminium ion **8**, which can act as a highly reactive electrophilic species. The stereochemical outcome of the reaction is determined by chirality located at the aminocatalyst **2**. Its ability to discriminate two diastereotopic faces of the corresponding enamine **3** or iminium ion **8** and efficiently control their geometry is crucial for obtaining high enantioselectivities.

Another important class of covalent catalysts are *N*-heterocyclic carbenes **11** (Scheme 2). In this approach triazolium salts **10** serve as precursors of in situ generated



Scheme 2.

N-heterocyclic carbenes **11**. The triazolyl proton of the salt **10** can be abstracted under basic conditions resulting in the formation of the catalyst **11**, which in turn reacts with carbonyl compound **12** and activates it. A subsequent reaction of the acyl anion equivalent **13** obtained with electrophile **4** and carbene elimination leads to the formation of optically active product **14**.

Noncovalent catalysis—the catalyst interacts with the substrate by other than covalent bond interactions, such as hydrogen or ionic bonds: The first noncovalent approach involves the activation of the substrate by a selective hydrogen bond with a chiral hydrogen-bond donor **16** leading to intermediate **17** (Scheme 3). Thiourea derivatives are most commonly used in this field of organocatalysis.

Chiral Brønsted bases constitute another important class of noncovalent catalysts (Scheme 4). Deprotonation of the pro-nucleophile **19** by such a base results in the formation of chiral ion pair **20**. This activated intermediate can be also obtained under phase-transfer catalysis (PTC) conditions in

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Henryk Krawczyk received his Ph.D. from Technical University of Łódź (Poland) in 1976. In 1979–1980 he was a postdoctoral fellow at The University of New South Wales (Australia) with Professor Michael Gallagher. From 1985 to 1989 he was a senior researcher chemist in Nufarm (Australia). In 2001 he received his Habilitation degree from Technical University of Łódź (Poland). Currently he is associate professor at the same institution. His main interests focus on the application of organophosphorus reagents in organic synthesis.

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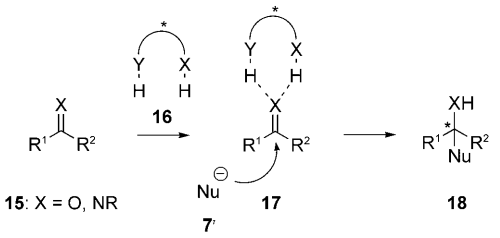
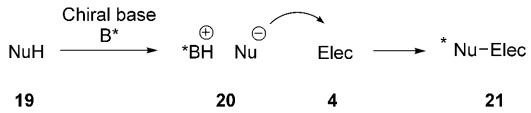


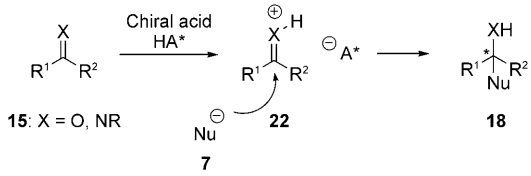
Scheme 3.



Scheme 4.

the presence of a chiral phase-transfer catalyst. In both of the cases a chiral cation is responsible for enantioselectivity of the reaction.

The chiral ion pair **22** can be also formed as a result of a protonation of carbonyl compounds or imines **15** by a chiral Brønsted acid catalyst (Scheme 5). In this approach, the



Scheme 5.

chiral anion is the factor conditioning enantioselective course of the reaction. Very recently, chiral phosphoric acids derived from binaphthol with axial chirality have emerged as a very powerful class of catalysts enabling this mode for catalytic activation of substrates.

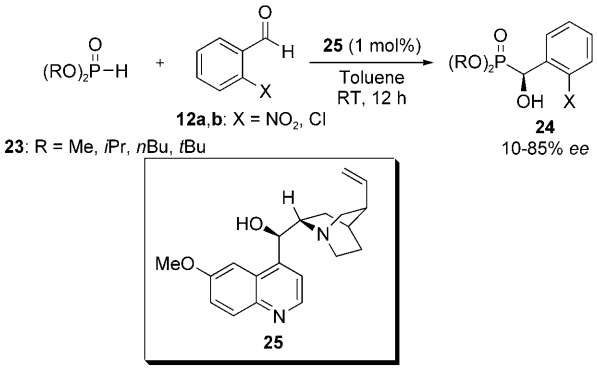
Bifunctional catalysis—the organocatalyst is designed to activate independently electrophile and nucleophile at the same time: This approach enables the reactions to proceed through a well-defined transition states and consequently to achieve high levels of stereoinduction.

The progress in particular fields of organocatalysis has been recently reviewed.[6] These accounts create the possibility for more detailed glance at the specific modes for catalytic activation of substrates in asymmetric organocatalysis and provide some mechanistic insights, as well as starting to rationalize of the stereochemical outcomes of the organocatalytic reactions.

Enantioselective, Organocatalytic Synthesis of α-Hydroxyphosphonates

α-Hydroxyphosphonic acids and α-hydroxyphosphonates constitute an interesting group of organophosphorus compounds that can be found in nature and exhibit intriguing biological properties.[7] They have been shown to possess antiviral[8] and antitumor[9] activity. Additionally, they are very potent inhibitors of enzymes such as rennin,[10] human immunodeficiency virus (HIV) protease, and polymerase.[11] α-Hydroxyphosphonates can be easily accessed by means of Pudovik reaction between carbonyl compounds and dialkyl phosphites.[12]

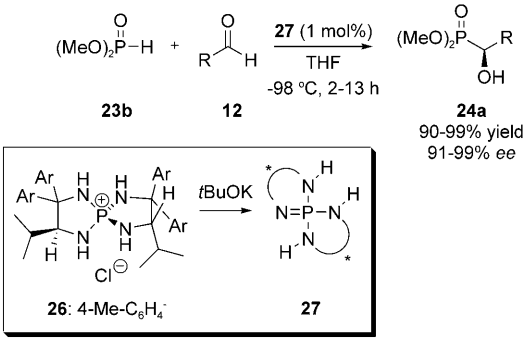
Already in 1983, when the amazing field of asymmetric organocatalysis was yet to discover, Wynberg et al. carried out enantioselective, organocatalytic Pudovik reaction for the first time (Scheme 6).[13] They used quinine **25** as a



Scheme 6.

chiral-base catalyst. However, this study is restricted to only the Pudovik reaction with aromatic aldehydes **12a**,**b** bearing electron-withdrawing substituents in the *ortho*-position of the aromatic ring, namely *o*-nitro- and *o*-chlorobenzaldehyde. It was found that the enantioselectivity of the reaction was highly dependent on the bulkiness of the phosphonate ester moiety. Good enantioselectivity was obtained only in the reaction between di-*tert*-butyl phosphite (**23a**) and *o*-nitrobenzaldehyde (**12a**). However, the reaction rate was six times slower than in the case of dimethyl phosphite (**23b**). No systematic studies on the scope or mechanism of this organocatalytic reaction were undertaken.

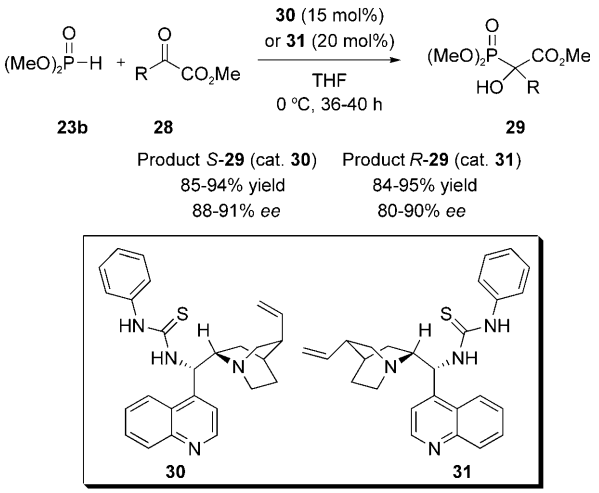
Since Wynberg's pioneering works, the enantioselective organocatalytic hydrophosphonylation of aldehydes was not a subject of detailed research until recently. In 2009 Ooi et al. identified triaminoiminophosphorane (**27**), generated in situ from the chiral *P*-spiro tetraaminophosphonium salt **26** and potassium *tert*-butoxide, as a very potent catalyst of this very important P–C bond-forming reaction (Scheme 7).[14] Among the catalysts tested, iminophosphoranes **27** with electron-donating substituents on the aromatic ring possessed the highest catalytic activity. It should be noted that the catalyst loading could be easily reduced to 1 mol% without noticeable influence on enantioselectivity. Excellent results were obtained at −98 °C yielding the corresponding α-hydroxyphosphonates **24a** in up to 99% *ee*. The reaction proved to be general, since aliphatic, heteroaromatic, and aromatic aldehydes **12** with different electronic properties were very well tolerated. The authors postulate that



Scheme 7.

the reaction proceeds through the formation of highly reactive dimethylphosphite salt with a chiral tetraaminophosphonium cation that is responsible for the stereochemical course of the addition.

Ketones are less commonly used as substrates in the Pudovik reaction. There is only one example of enantioselective organocatalytic hydrophosphonylation of ketones (Scheme 8).[15] This is the reaction between aromatic α-ke-



Scheme 8.

toesters **28** and dimethyl phosphite (**23b**) catalyzed by the cinchona alkaloid derived thioureas **30** or **31**. The ability of this type of organocatalysts to act as bifunctional promoters that can independently activate electrophile (acting as a hydrogen-bond donor) and nucleophile (acting as a Brønsted base) has been recently demonstrated by the various research groups.[16] The screening of organocatalysts revealed that cinchonidine-derived thiourea **30** gave the best results. Generality of the established synthetic protocol was confirmed by reaction of various aromatic and heteroaromatic α-ketoesters **28** with phosphite **23b**. Notably, reactions catalyzed by the cinchonine-derived thiourea **31** afforded the optically active products with slightly lower enantiomeric excesses, especially in the case of heteroaromatic and electron-withdrawing group substituted aromatic α-ketoesters **28**.

To rationalize the stereochemical outcome of the reaction, the authors proposed that in the transition state the α-ketoester is activated by double hydrogen bonding to the thiourea moiety (Figure 1). Moreover, this interaction enables

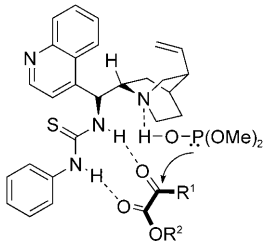
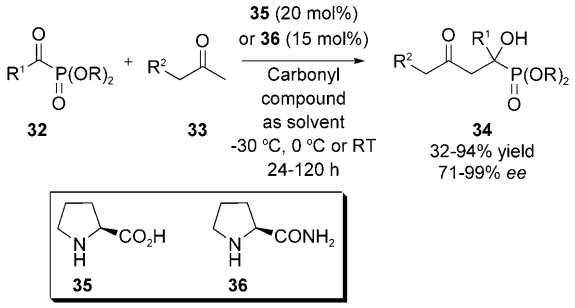


Figure 1. Transition state of the α-ketoester **28** activated by double hydrogen bonding to the thiourea moiety **30**.

sufficient discrimination of the two enantiotopic faces of the electrophile necessary in all enantiodifferentiating reactions. Additionally, due to the presence of quinuclidinic nitrogen atom, the corresponding phosphite–phosphonate equilibrium is shifted towards the phosphite form that undergoes addition to activated electrophile in an enantioselective fashion.

Acylphosphonates are another important class of organophosphorus reagents that can serve as precursors of α-hydroxyphosphonates. Their strong electrophilic character makes them excellent partners in nucleophilic additions that can lead to the formation of secondary or tertiary alcohols.

In 2006 Zhao and Samanta developed the organocatalytic cross aldol reaction between α-ketophosphonates **32** and enolizable ketones **33** (Scheme 9).[17] The reaction was found

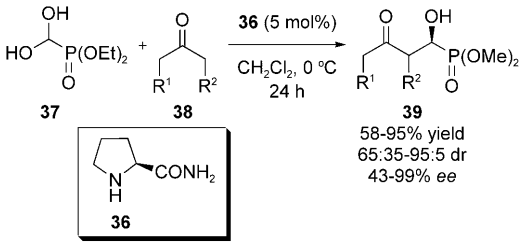


Scheme 9.

to proceed in the presence of the secondary amines as the catalyst and the formation of the corresponding enamine in the catalytic cycle is postulated. Among the catalysts tested L-proline (**35**) gave the best results in the reaction with acetone as the carbonyl compound. The influence of phosphonate ester moiety on the reaction outcome was also determined. It was found that methyl and isopropyl esters **32** performed the best affording the corresponding α-hydroxyphosphonates **34** with the highest yield and enantioselectivity. 2-Butanone and methoxyacetone could also be utilized for the synthesis of optically active phosphonates **34** when

L-prolinamide (**36**) was used as the catalyst. In this case the reactions were regioselective and less hindered nucleophilic centers of the starting ketones **33** were involved in the new C–C bond forming process.

In a similar fashion the same research group achieved an efficient synthesis of secondary α-hydroxyphosphonates, which are generally more difficult to obtain in enantiomerically enriched form (Scheme 10).[18] The authors envisioned



Scheme 10.

the reaction between diethyl formylphosphonate and ketone enamines as an efficient synthetic route to these compounds. However, because of documented instability of diethyl formylphosphonate they decided to use its hydrate **37**, which is known to be more stable and exists in equilibrium with the requisite formyl form. In this study L-prolinamide (**36**) turned out to be the best catalyst in terms of yield and enantioselectivity. Various ketones reacted smoothly under optimal reaction conditions affording highly enantioenriched secondary α-hydroxyphosphonates **39** in good yields. Additionally, in the case of unsymmetrical ketones good regio- and diastereoselectivities of the reactions were observed.

To provide an explanation of the stereochemical outcome of the reaction, the authors proposed that the addition proceeds by a nine-membered chair-like transition state in which the large phosphonate moiety occupies the pseudo-equatorial position (Figure 2). As a consequence, the corresponding enamine undergoes addition from the *Si*-face of the diethyl formylphosphonate to afford the observed stereochemistry of the product.

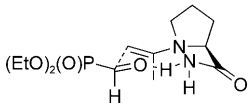
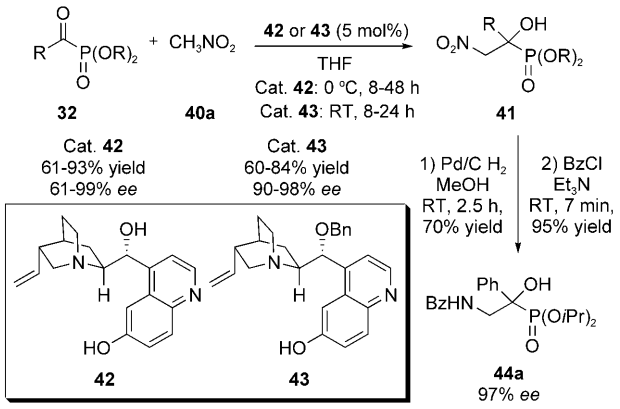


Figure 2. Proposed nine-membered chair-like transition state for the reaction of diethyl formylphosphonate and **38** catalyzed by **36**.

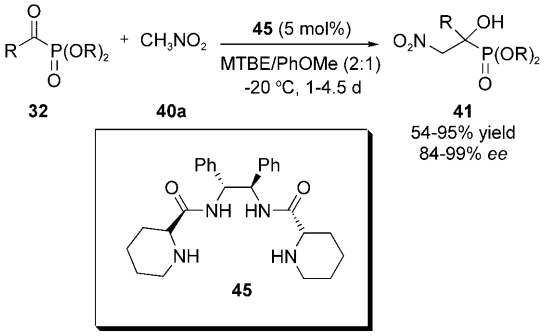
In 2007 Zhao et al. established the organocatalytic asymmetric nitroaldol reaction of acylphosphonates **32** with nitromethane (**40a**) as an entry to optically active β-nitro-α-hydroxyphosphonates **41** (Scheme 11).[19] Cupreine (**42**) and 9-*O*-benzylcupreine (**43**) have been successfully applied as the catalysts of this transformation. Catalyst **42** gave slightly better yields then **43**. However, the reactions were performed at 0 °C and were terminated after longer reaction times. Both aryl- and alkyl-substituted α-ketophosphonates



Scheme 11.

32 afforded the corresponding products with high yields and enantioselectivities. Additionally, the product **41a** could be converted into biologically important β-amino-α-hydroxyphosphonate **44a** without loss of optical purity.

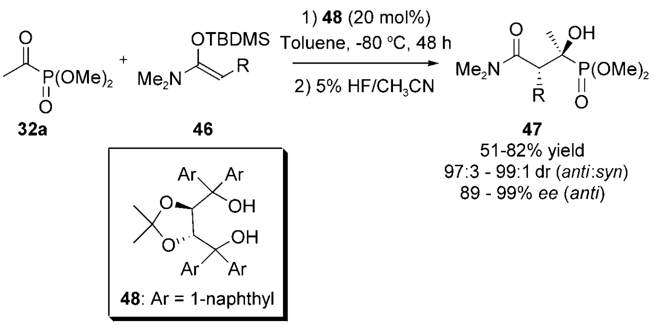
The same reaction was further studied by Feng, Hu et al. in 2008 (Scheme 12).[20] This time the reaction was catalyzed by the secondary amine amide catalyst **45**. It was found that



Scheme 12.

additive of catalytic amounts of 2,4-dinitrophenol and performing the reaction with excessive $MeNO_2$ in a mixture of *t*BuOMe and PhOMe at −20 °C was crucial to obtain high enantioselectivities. Under these conditions various aromatic, heteroaromatic and aliphatic α-ketophosphonates **32** were smoothly reacted to afford the products **41**. The authors also performed theoretical calculations in order to explain the high enantioselection achieved in the reaction. The results obtained suggest that achiral acidic additive protonates one of the piperidinic nitrogen atoms of catalyst **45** which subsequently activates the acylphosphonate **32** by hydrogen bonding. The second piperidinic nitrogen atom of **45** acts as a base and abstracts the proton from nitromethane (**40a**).

The Mukaiyama aldol reaction is a potent means of forming new C–C bond in organic synthesis.[21] In 2009 Rawal et al. reported the highly stereoselective Mukaiyama aldol reaction between dimethyl acetylphosphonate (**32a**) and various *N,O*-ketene acetals **46** (Scheme 13).[22] A range of



Scheme 13.

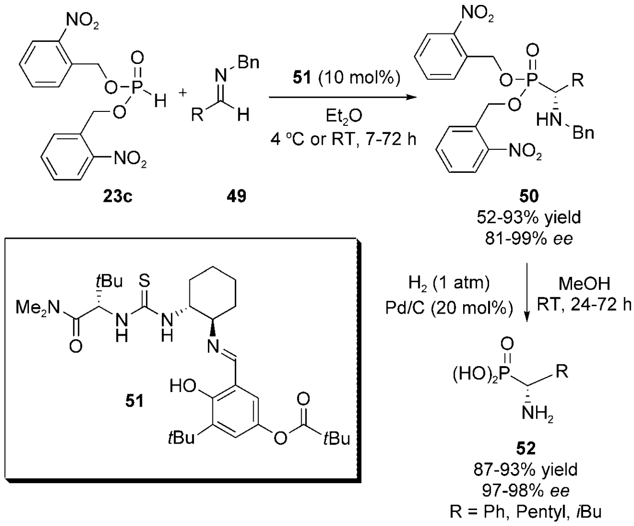
chiral hydrogen-bond donors was evaluated in this study for their ability to catalyze this transformation. Very good results were obtained with commercially available TADDOL (**48**; α,α,α′,α′-tetra(1-naphthyl)-1,3-dioxolane-4,5-dimethanol) as the catalyst. The stereoselectivity of the reaction was highly temperature dependent and increased with lowering of the reaction temperature. Additionally, the *tert*-butyldimethylsilyl (TBDMS) group could be convincingly removed from the final product by quenching the reaction mixture with 5% HF solution in CH_3CN. All tertiary alcohols **47** possessing adjacent tertiary and quaternary stereogenic centers were obtained in good yields with high enantio- and excellent diastereoselectivities. It is worth noting that β-heteroatom-substituted *N,O*-ketene acetals could be successfully utilized in this reaction. In this manner optically active α,β-dihydroxyphosphonates could be easily accessed.

Enantioselective, Organocatalytic Synthesis of α-Aminophosphonates

α-Aminophosphonates and α-aminophosphonic acids have received considerable interest over the years as an isoelectronic analogues of the corresponding α-amino acids.[23] They have been isolated from natural sources and exhibit significant biological activity such as antibacterial,[24] antiviral,[25] antifungal,[26] or anticancer.[27] Moreover, they can serve as enzyme inhibitors of many proteolytic enzymes including synthase,[28] HIV protease,[11,29] rennin,[30] or PTPases.[31] As a consequence, they have been a target of numerous synthetic endeavors and several routes for their preparation have been established.[23] Since the biological activity of α-aminophosphonic acids and their derivatives is related to the absolute configuration of the stereogenic center located at α-position to the phosphorus atom, enantioselective methods of their preparation are of great importance.[32]

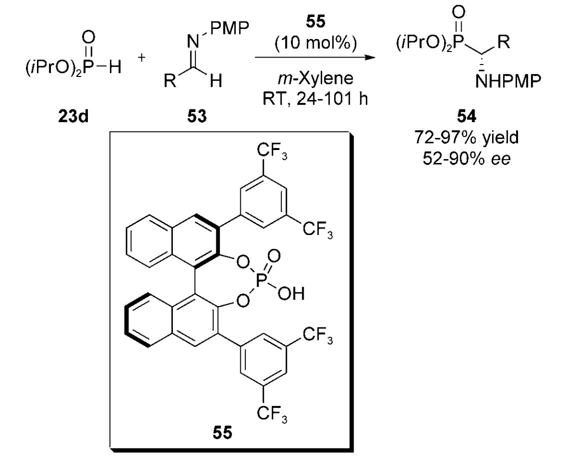
Hydrophosphonylation of imines, commonly known in the literature as the Pudovik reaction, represents an attractive approach for the synthesis of α-aminophosphonates. Enantioselective catalytic version of this reaction has been a subject of detailed studies and different chiral catalysts were found to be effective promoters of this transformation.[12]

The first synthesis of enantiomerically enriched α-aminophosphonates by means of organocatalytic Pudovik reaction was accomplished by Jacobsen and Joly (Scheme 14).[33] The authors performed the nucleophilic addition of di(*o*-nitrobenzyl) phosphite (**23c**) to *N*-benzylimines **49** in the presence of chiral thiourea derivative **51** as the catalyst. The reactions proceeded efficiently and high yields and high enantioselectivities could be obtained for imines **49** derived from both aromatic and aliphatic aldehydes. Hydrophosphinylation products **50** were readily converted into α-aminophosphonic acids **52** by global deprotection performed under mild hydrogenolytic conditions. The desired products **52** were obtained in high yields and with conservation of optical purity achieved in the organocatalytic Pudovik reaction.



Scheme 14.

In 2005 Akiyama et al. described chiral Brønsted acid catalyzed Pudovik reaction between dialkyl phosphites **23** and *N*-(*p*-methoxyphenyl)imines **53** (Scheme 15).[34] 3,3′-Bis(3,5-ditrifluoromethylphenyl)-1,1′-8-binaphtyl-2,2′-diyl hydrogenphosphate (**55**) was found to be the most effective catalyst in terms of both reactivity and enantioselectivity. The struc-



Scheme 15.

ture of the substrate was another important factor that influenced the reaction outcome. In terms of phosphite **23**, the highest enantioselectivities were obtained with diisopropyl ester **23d** as the nucleophile. Particularly good results were achieved in the reactions with aldimines **53** derived from cinnamaldehydes, especially when aromatic ring was substituted with electron-withdrawing groups in the *ortho*-position.

The authors proposed a nine-membered transition state in order to explain stereoselectivity of the reaction (Figure 3). It is anticipated that phosphoric acid serves as a bifunctional catalyst activating both the imine by hydrogen bonding and the phosphite by the phosphoryl oxygen atom acting as a Brønsted base.

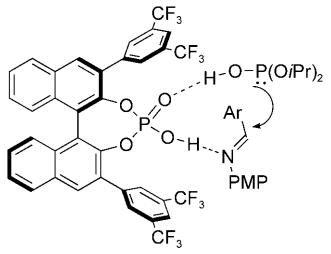
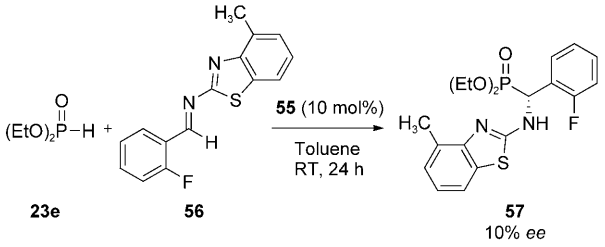


Figure 3. Proposed nine-membered transition state for the reaction of **23d** and **53** catalyzed by **55**.

Very recently two research groups independently undertook DFT studies on the hydrophosphonylation of imines catalyzed by chiral phosphoric acids in order to explain the origins of enantioselectivity in this reaction.[35] Although different model substrates were chosen for the calculations, similar results were obtained. According to the calculations, the reaction proceeds through a di-coordination pathway. It means that two different oxygen atoms of the catalyst are involved in hydrogen bonding with both of the substrates (one oxygen atom acts as a hydrogen-bond donor, the other as an acceptor). Consequent proton transfer leads to a zwitterionic intermediate. Nucleophilic addition of the activated phosphorus species and proton transfer proceed in a concerted manner and at this stage the stereochemistry of the product is determined. Furthermore, the energies of the transition states of the reaction catalyzed by different chiral phosphoric acids were calculated and the effect of the substituents in 3,3′-positions evaluated. The energy difference between transition states representing attacks from the *Si*- and *Re*-faces was highest for hydrophosphonylation reactions of aldimines catalyzed by **55** when compared to other catalysts. Additionally, the influence of substrate substitution pattern was also evaluated. In general, the difference in energy between two transition states increased with the size of the ester moiety in the dialkyl phosphite. Both observations are in accordance with the experimental results, since the highest enantioselectivities were attained using **55** as the catalyst and diisopropyl phosphite as phosphonylating reagent.

In the studies of Yamanata and Hirata the investigation on aldimine substituent effect on enantioselectivity of the reaction was conducted.[35b,c] The energy difference between transitions states leading to *R*- or *S*-configured products was higher for acrolein and cinnamaldehyde derived imines, then for the imine derived from benzaldehyde. This is in accordance with the experimental observation that the presence of an olefinic bond was crucial to obtain high enantioselectivities.

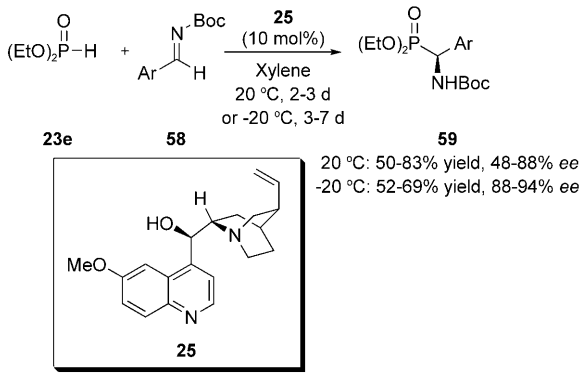
Additionally, Shi and Song demonstrated that the Brønsted acid catalyst is involved in the phosphonate–phosphite tautomerism enabling the reaction to be carried out at room temperature.[35a] Furthermore, the authors performed reactions between diethyl phosphite (**23e**) and (*E*)-*N*-benzylidene-4-methylbenzo[*d*]thiazol-2-amine (**56**) catalyzed by **55** expecting that the introduction of a heterocyclic moiety into the target α-aminophosphonate **57** might result in interesting biological properties (Scheme 16).[35a] Disappointingly,



Scheme 16.

the enantioselectivity of this reaction was very low (10% *ee*). Theoretical calculations revealed that the difference in transition-state energies accounting for the *Si*- and *Re*-face attacks in the reaction with **56** was very low (only 0.1 kcal mol^{-1}). This result explains very low enantioselectivity of this particular hydrophosphonylation.

α-Aminophosphonates were also obtained by chiral base-catalyzed reaction of *N*-Boc-protected imines **58** derived from aromatic aldehydes with diethyl phosphite (**23e**; Scheme 17).[36] Among catalysts tested quinine (**25**) was found to be the most efficient allowing the synthesis of optically active α-aryl-α-aminophosphonates **59**. The reaction



Scheme 17.

was proven to be quite general, since both electron-donating and electron-withdrawing substituents could be present at the aromatic ring of **58** without noticeable influence on reactivity and enantioselectivity. The enantioselectivity of the process could be easily enhanced by performing the reaction at −20 °C; however, longer reaction times were required to obtain the products.

The authors proposed that the free hydroxyl group at C-9 of the catalyst **25** was responsible for imine activation by hydrogen-bonding (Figure 4). On the other hand, the quinuclidinic nitrogen atom is involved in corresponding phosphite–phosphonate equilibrium and shifts it towards reactive phosphite form.

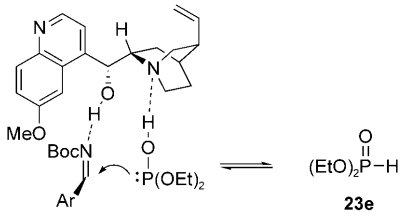
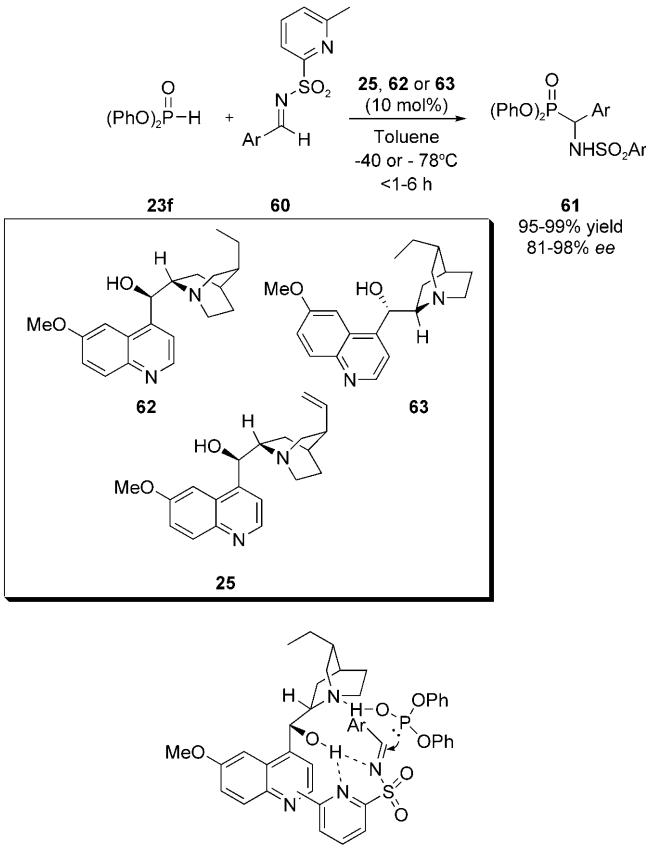


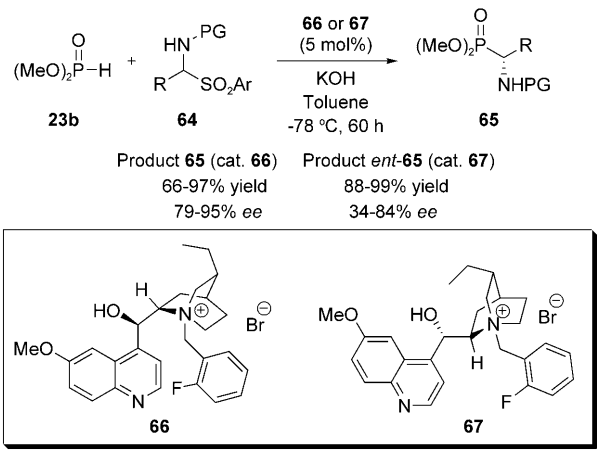
Figure 4. Transition state showing the proposed imine activation by the free hydroxyl C-9 group of catalyst **25**.

Simple cinchona alkaloids such as hydroquinine (**62**), hydroquinidine (**63**), and quinine (**25**) were also successfully employed as the catalysts of enantioselective hydrophosphonylation of aldimines **60** by Toru, Nakamura et al. (Scheme 18).[37] *N*-(6-Methyl-2-pyridylsulfonyl) imines **60** derived from aromatic aldehydes were found to be superior reagents in the reaction with diphenyl phosphite (**23 f**) yielding the products **61** with quantitative yields and high enantioselectivities. The enantiomeric excesses could be enhanced by single recrystallization. The authors postulate that the 6-methyl-2-pyridylsulfonyl group acts as efficient activating group as well as stereocontroller that enables to achieve high enantioselectivities. In the transition state (Scheme 18, bottom) the hydroxyl group at C-9 of the catalyst activates the imine **60** through a double hydrogen bond. Additionally, the quinuclidinic nitrogen atom of the catalyst as a Brønsted base activates the phosphite **23 f**. The use of pseudoenantiomeric hydroquinine (**62**) and hydroquinidine (**63**) gave access to oposite enantiomers of **61** with comparable enantioselectivity. Additionally, desulfonylation of the hydrophosphonylation products **61** and subsequent deprotection of the phosphonate moiety could be efficiently performed giving access to optically active α-aminophosphonic acids.

Asymmetric hydrophosphonylation of imines was also accomplished under PTC conditions (Scheme 19).[38] In this study α-amido sulfones **64** were used as a source of in situ generated N-protected imines. Optimization studies revealed higher efficacy of the catalysts with *ortho*-substituents on their benzylic moieties. The best results were obtained with *ortho*-fluoro-substituted catalyst **66**, derived from hydroquinine, that was used throughout the study. The reactions were performed at −78 °C in the presence of KOH



Scheme 18.

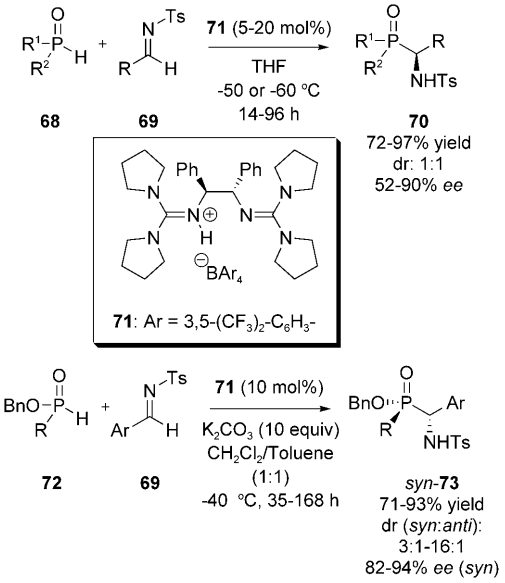


Scheme 19.

as a base using dimethyl phosphite (**23 b**) as phosphonylating agent. The reactions proceeded efficiently with β- or γ-branched and unbranched α-amido sulfones **64**. Disappointingly, the reactions with **64** derived from aromatic aldehydes led to the formation of nearly racemic products. It was also demonstrated that enantiomeric products *ent*-**65** could be accessed by using pseudoenantiomeric catalyst **67** derived from hydroquinidine, albeit with lower enantioselectivity. Importantly, the protecting groups at the nitrogen and phosphorus atoms could be convincingly removed giving access

to either the α-aminophosphonic acids or N-protected phosphonic acid monomethyl esters with conservation of optical purity.

In a very recent study the possibility of employing a phospha-Mannich reaction between phosphine oxides **68** or *H*-phosphinates **72** and *N*-tosyl imines **69** for the synthesis of α-aminophosphine oxides **70** and phosphinates **73** was established by Tan et al. (Scheme 20).[39] The guanidinium salt **71**

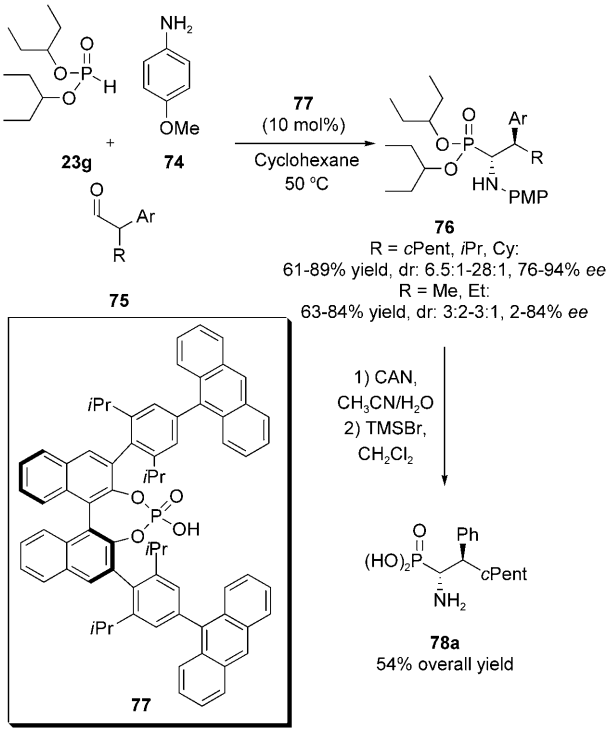


Scheme 20.

was recognized as very efficient catalyst of this P–C bond forming reaction. Various symmetric and nonsymmetric phosphine oxides **68** were evaluated in the study. The scope of the developed synthetic protocol was very broad. Imines **69** derived from aliphatic, aromatic, and heteroaromatic aldehydes were well tolerated. Reactions involving **72** as phosphorus nucleophile required the use of threefold excess of **72** and the additive of K_2CO_3 (10 equiv) in order to achieve high levels of stereoinduction and reasonable reaction rates. α-Aminophosphinates **73** bearing a stereogenic center at the phosphorus atom were formed as mixtures of two diastereoisomers in which the *syn*-isomer predominated. The reaction proceeded efficiently with aromatic and heteroaromatic imines **69**. Moreover, the authors demonstrated that different R substituents can be present in **72**, further increasing the attractiveness of this methodology.

An alternative route to α-aminophosphonates constitutes the one-pot three-component Kabachnik–Fields reaction between a carbonyl compound, an amine, and a dialkyl phosphite. This multicomponent protocol is especially attractive, since only one synthetic step is required to obtain the final product. The corresponding imine is formed in situ without the necessity of its synthesis in a separate reaction vessel.

In 2008 List et al. developed organocatalytic asymmetric variant of this interesting reaction (Scheme 21).[40] The



Scheme 21.

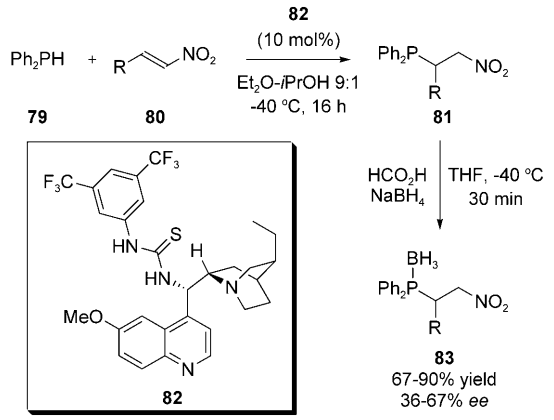
authors performed a Kabachnik–Fields reaction between *p*-anisidine (**74**), α-branched aldehydes **75**, and di(3-pentyl) phosphite (**23g**) under dynamic kinetic resolution conditions and catalyzed by chiral phosphoric acid. 3,3′-Bis(4-anthracenyl-2,6-diisopropylphenyl)-1,1′-8-binaphtyl-2,2′-diyl hydrogenphosphate (**77**) was found to be a highly effective catalyst for this transformation allowing the access to β,β-disubstituted-α-aminophosphonates **76** in an enantio- and diastereoselective manner. It was found that the bulkiness of the alkyl substituent in aldehyde **75** had a pronounced influence on the stereochemical outcome of the reaction. High levels of stereocontrol were achieved with branched isopropyl, cyclopentyl and cyclohexyl substituents. In contrast, reactions with methyl- and ethyl-substituted aldehydes **75** proceeded with modest stereoselection. The Kabachnik–Fields product was also utilized for the synthesis of α-aminophosphonic acid **78a** that was accomplished in a two-step reaction sequence involving *p*-methoxyphenyl and alkyl groups removal with cerium ammonium nitrate (CAN) and trimethylsilyl bromide (TMSBr), respectively.

Enantioselective, Organocatalytic Phospha-Michael Additions

The phospha-Michael reaction constitutes one of the most important methods for the construction of P–C bonds. An excellent review on this reaction was published in 2006.[41] Since then a few reports on organocatalytic phospha-Michael reaction appeared in the literature successfully uti-

lizing both trivalent and pentavalent phosphorus species as Michael donors.

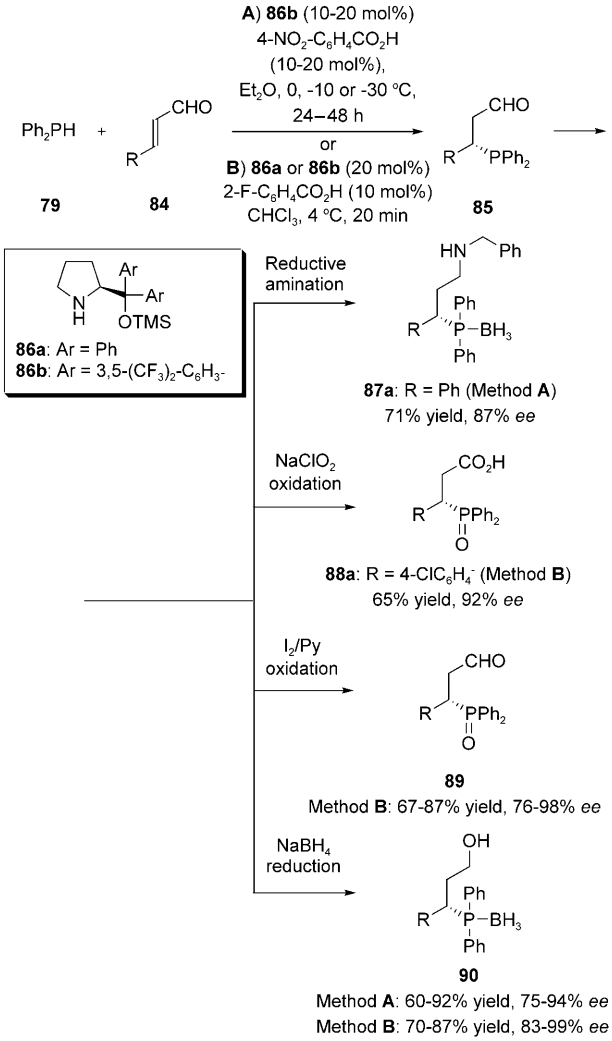
The first example of enantioselective, organocatalytic phospha-Michael addition using trivalent phosphorus species was reported by Melchiorre et al. (Scheme 22).[42] In this



Scheme 22.

work diphenylphosphine (**79**) was added in an enantioselective manner to nitroalkenes **80** in the presence of the cinchona alkaloid derived thiourea **82** as the catalyst. The originally formed β-nitrophosphines **81** were transformed in situ into the corresponding boranes **83** to facilitate the isolation and purification of the products. Solvent choice and reagent concentration turned out to be of importance. Under optimal reaction conditions hydrophospination of various nitroalkenes **80** proceeded with moderate or low enantioselectivity. In some cases, the optical purity of the products could be further enhanced with a single crystallization.

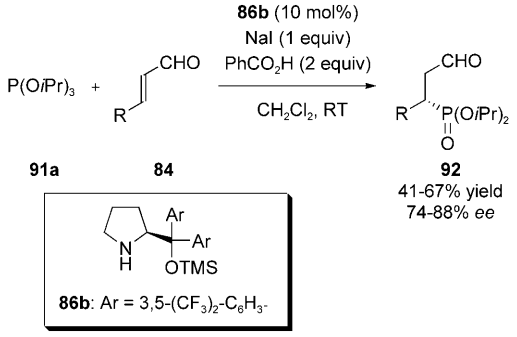
In 2007 two research groups independently described iminium-catalyzed hydrophosphination of α,β-unsaturated aldehydes **84** with diphenylphosphine (**79**) using diarylprolinol trimethylsilyl ethers **86** as the catalysts (Scheme 23).[43] In both reports, the reactions were performed in the presence of a benzoic acid derivative as co-catalyst and the originally formed adducts **85** were reduced in situ to alcohols **90**, which are stable and easier to handle. Enantioselectivities of the reactions were high and rendered from the attack of the phosphorus nucleophile on the iminium-ion activated enal from the less sterically hindered *Si*-face. Furthermore, Melchiorre et al. presented the usefulness of the optically active phospha-Michael adducts **85** for the synthesis of β-aminophosphine **87a** through reductive amination.[43a] In contrast, Córdova et al. oxidized the products into 3-(diphenylphosphoryl)alkanoic acid **88a**[43b] or phosphine oxides **89**.[43c] In further studies[43c] Córdova et al. evaluated the possibility of employing different tri- or pentavalent phosphorus nucleophiles in this reaction. However, the reactions either did not proceed or the Michael adducts were formed with low yields and enantioselectivities. The stereochemical course of the



Scheme 23.

organocatalytic hydrophosphination of α,β-unsaturated aldehydes **84** was confirmed by DFT calculations.

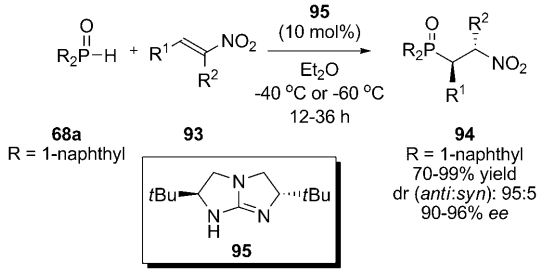
The β-phosphonylation of α,β-unsaturated aldehydes **84** by trialkyl phosphites **91** has also been developed (Scheme 24).[44] A crucial and most challenging task for the success of the envisioned synthetic protocol was the proper choice of nucleophilic additive enabling P^{III} to P^{V} oxidation by means of an S_N2-type dealkylation reaction proceeding at



Scheme 24.

one of the phosphite alkyl moiety. Optimizing experiments showed that β-phosphonylation of enals **84** proceeded with the highest efficacy in the presence of stoichiometric amounts of benzoic acid and NaI. Moreover, tri-*iso*-propyl phosphite (**91a**) was found to be an efficient phosphonylating reagent. Under these conditions chemoselective reactions proceeded with good yields and enantioselectivities. The authors also conducted DFT calculations in order to give some mechanistic insights to the reaction performed and to explain the observed absolute stereochemistry of the products. Additionally, optically active phosphonates **92** were proven to be useful precursors of various phosphonic acids, glutamic acid analogues and fosmidomycin derivatives.

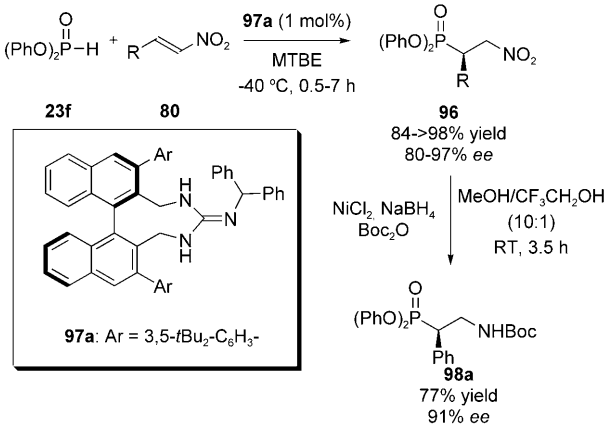
The phospha-Michael reactions using pentavalent phosphorus species in general require basic conditions. Tan et al. demonstrated that chiral bicyclic guanidine derivative **95** can act as a Brønsted base catalyst for the Michael addition of diarylphosphine oxides **68** to nitroalkenes **93** (Scheme 25).[45] Among the phosphine oxides evaluated in



Scheme 25.

this study di(1-naphthyl) phosphine oxide (**68a**) turned out to be the most useful in terms of reactivity and enantioselectivity. The generality of the developed methodology was confirmed by performing the reaction with various β-nitrostyrenes **93**, possessing either electron-withdrawing or electron-donating substituents at the aromatic ring. In all the cases, high yields and enantioselectivities were obtained. Moreover, α,β-disubstituted nitroalkenes could be successfully utilized as Michael acceptors in this reaction affording optically active β-nitrophosphine oxides **94** in a highly enantio- and diastereoselective manner. Interestingly, enantiomerically enriched phospha-Michael adducts **94** were utilized for the synthesis of potentially useful β-aminophosphine oxides and β-aminophosphines.

In a similar fashion Terada et al. accomplished the synthesis of β-nitrophosphonates (Scheme 26).[46] In this study, the axially chiral guanidine derivatives **97** were used as catalysts of a Michael addition of diphenyl phosphite (**23f**) to nitroalkenes **80**. Optimization studies revealed that the size of the aryl as well as *N*-alkyl substituents in the guanidine catalyst **97** had a pronounced impact on enantioselectivity, which improved with the increasing bulkiness of those groups. Further screening enabled the establishment of the key reaction parameters and the best results were obtained with catalyst



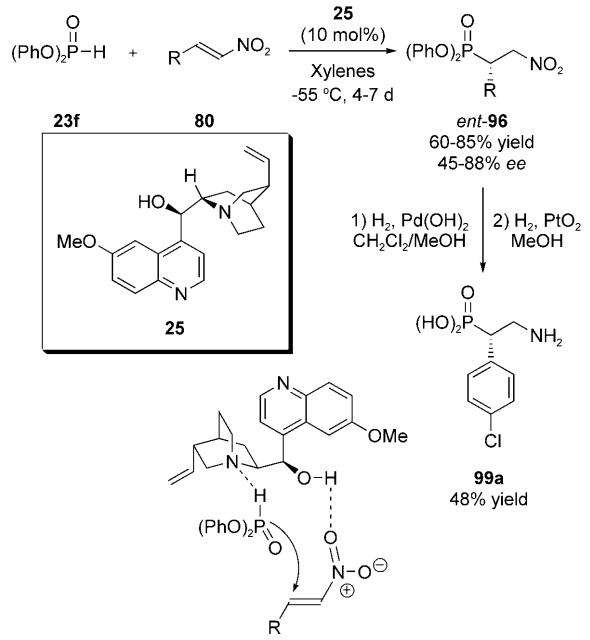
Scheme 26.

97a using methyl *tert*-butyl ether (MTBE) as the solvent at −40 °C. It is worth noting that the reaction could be easily performed in the presence of 1 mol% of the catalyst **97a** and that such a low catalyst loading did not affect enantioselectivity of the addition step. The scope of the developed phospha-Michael reaction was very broad. Aromatic, heteroaromatic, and aliphatic nitroalkenes **80** were well-tolerated and the corresponding adducts **96** were obtained with high yields and enantioselectivities. The authors also demonstrated the usefulness of the Michael adducts for the synthesis of biologically important β-aminophosphonate **98a**. The reduction of the nitro group was conducted in the presence of Boc_2O enabling in situ protection of the originally formed amine.

A complementary route leading to the formation of the opposite enantiomer of the product **96** was developed by Wang et al. (Scheme 27).[47] The authors demonstrated that the same reaction can be catalyzed by a simple cinchona alkaloid—quinine (**25**). Catalyzed by **25**, the phospha-Michael addition of diphenyl phosphite (**23f**) to aliphatic, aromatic, and heteroaromatic nitroalkenes **80** proceeded in good yields and moderate or good enantioselectivities. However, long reaction times (4–7 d) and low temperature (−55 °C) were required. The best results were obtained for heteroaromatic nitroalkenes as well as for β-nitrostyrenes substituted with electron-donating groups in the *para*-position. Notably, in this reaction, catalyst **25** serves as bifunctional catalyst activating both phosphorus nucleophile through the quinuclidinic nitrogen atom and Michael acceptor by means of hydrogen bonding to the free hydroxyl group at C-9 serving as hydrogen-bond donor (Scheme 27, bottom). Conversion of the optically active β-nitrophosphonate *ent*-**96a** into biologically important β-aminophosphonic acid **99a** was also demonstrated.

Vinylphosphonates in Asymmetric Organocatalysis

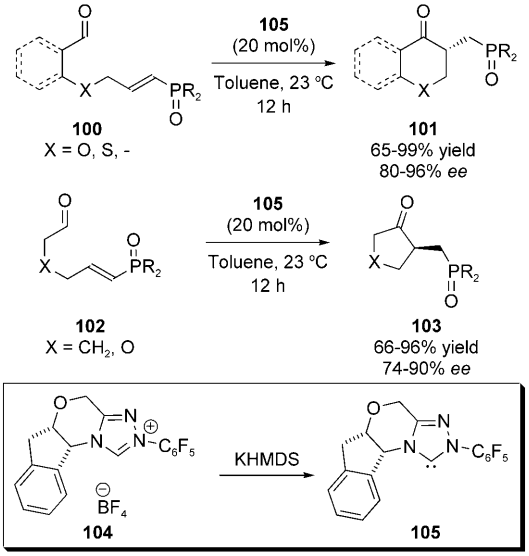
Vinylphosphonates constitute a very interesting class of organophosphorus reagents that have found widespread ap-



Scheme 27.

plications in organic synthesis.[48] These compounds have been very frequently utilized as acceptors in Michael addition. The progress in this field of chemistry has been recently reviewed.[48b]

Surprisingly, there is only one example of application of simple vinylphosphonates in asymmetric organocatalysis. It was reported in 2008 by Rovis et al. and they showed the intramolecular Stetter reaction of vinylphosphonates **100** and **102** catalyzed by N-heterocyclic carbene **105** generated in situ from triazolium salt **104** in the presence of potassium hexamethyldisilazane (KHMDS) as a base (Scheme 28).[49] Vinylphosphine oxides were also included as acceptors in this study. Intramolecular addition of acyl anion equivalent

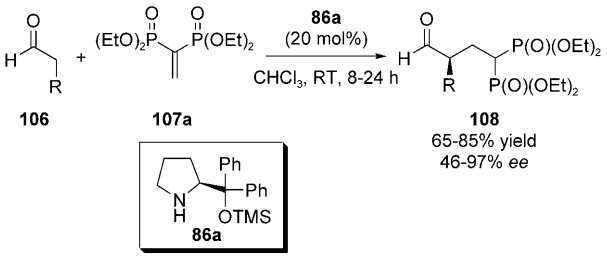


Scheme 28.

proceeded efficiently and with high levels of enantioselection, giving access to a wide range of carbo- and heterocyclic compounds **101** and **103**. Aromatic and aliphatic substrates could be successfully applied in this reaction. It is also worth noting that no racemization occurred during the reaction even though carbenes are considered as strong bases. The potential usefulness of the products was demonstrated in a few stereoselective transformations.

More attention has been devoted towards utilization of activated vinylphosphonates bearing additional electron-withdrawing group at the α-position in asymmetric organocatalysis. Four examples of asymmetric, organocatalytic Michael addition to activated vinylphosphonates can be found in the literature.[50–53] Three of them apply the Michael addition of unmodified aldehydes or ketones catalyzed by chiral secondary amines for the formation of the corresponding enamine in the catalytic cycle.[50–52] The fourth work deals with chiral base-catalyzed Michael addition of β-ketoesters.[53]

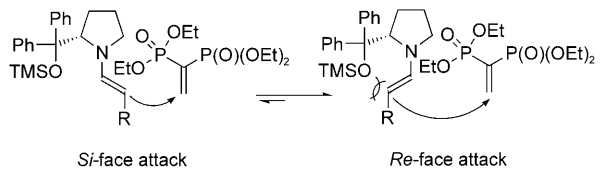
In 2007 Alexakis et al. reported that in the presence of **86a** various aldehydes **106** can be added to tetraethyl methylidenebisphosphonate **107a** in a highly asymmetric fashion leading to the formation of geminal bisphosphonates **108** (Scheme 29).[50] The Michael adducts were further converted into functionalized vinylphosphonates with conservation of optical purity achieved in the Michael addition step.



Scheme 29.

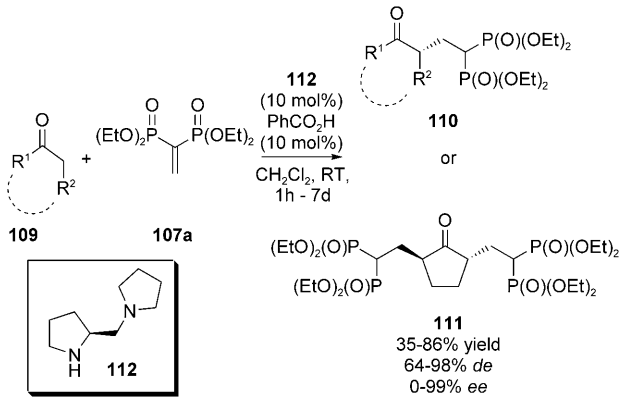
The authors suggest that high enantioselectivity is connected to the ability of the catalyst to control geometry of the corresponding enamine. The *Re*-face of thermodynamically stable enamine *anti-E* is effectively shielded by the bulky substituent present at C-2 of the catalyst **86a** (Scheme 30). As the consequence, **107a** approaches the enamine *anti-E* from less hindered *Si*-face and affords the product in a highly enantioselective manner.

The Michael addition of unmodified cyclic and acyclic ketones **109** to phosphonate **107a** was studied in details by



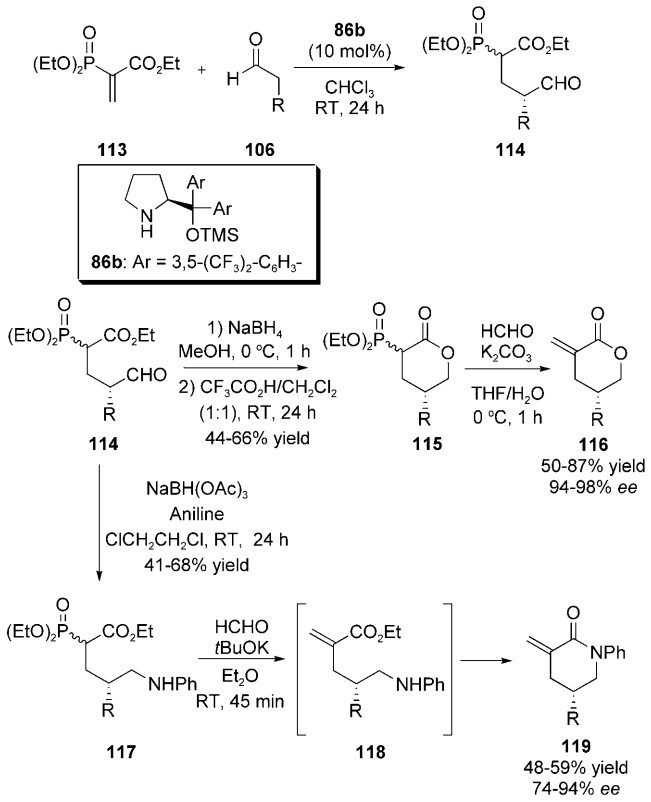
Scheme 30.

Barros and Phillips (Scheme 31).[51] The reaction was catalyzed by (*S*)-1-(2-pyrrolidynylmethyl)pyrrolidyne (**112**) and performed in the presence of benzoic acid as co-catalyst to facilitate the corresponding enamine formation. All the reactions proceeded efficiently, affording geminal bisphosphonates **110** or **111** in high yields and with good or high diastereoselectivities. However, enantioselectivities obtained varied very much. In some cases racemic products were obtained. While cyclohexanone and its derivatives afforded mono-alkylated products **110** in a highly regioselective manner, reaction with cyclopentanone gave 2,5-dialkylated derivative **111** as the only product.



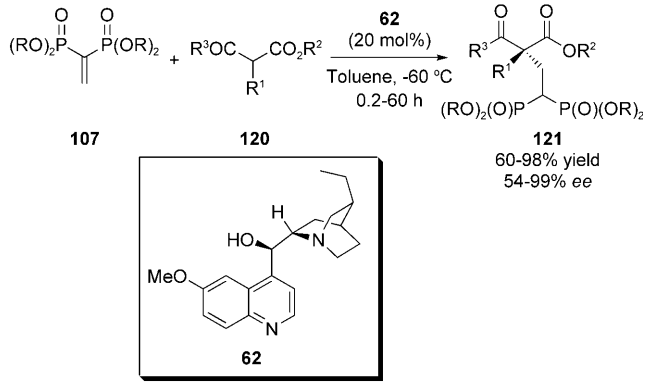
Scheme 31.

Highly enantioselective, direct, organocatalytic Michael addition of various enolizable aldehydes **106** to ethyl 2-(diethoxyphosphoryl)acrylate (**113**) catalyzed by **86b** has been reported (Scheme 32).[52] The reaction proceeded by means of the standard enamine catalytic cycle. Enantiomerically enriched adducts **114** were found to be useful precursors of γ-substituted-α-methylene-δ-lactones **116** and δ-lactams **119**. The synthesis of **116** required reduction of the carbonyl group in the originally formed adducts **114** followed by lactonization and a Horner–Wadsworth–Emmons reaction of α-diethoxyphosphoryl-δ-lactones **115** with formaldehyde. In a similar fashion the synthesis of **119** was accomplished. In the first step, reductive amination of the optically active Michael adducts **114** was performed. It is worth noting that the proper choice of aminating reagent had great influence on stereochemical outcome of the reaction. The best results were obtained when aniline was used in reductive amination step. The δ-aminoalkanoates **117** obtained were submitted to Horner–Wadsworth–Emmons reaction followed by lactamization to yield **119**.



Scheme 32.

The same research group showed that hydroquinine **62** was a very effective organocatalyst for Michael addition of various cyclic and acyclic α-substituted-β-ketoesters **120** to phosphonates **107** (Scheme 33).[53] It was found that the bulkiness of the ester substituent in starting β-ketoester **120** had a distinct impact on stereochemical outcome of the reaction. Very high enantioselectivities were obtained when *tert*-butyl esters were used as Michael donors. Notably, the use of pseudoenantiomeric hydroquinidine led to formation of opposite enantiomer of the product with comparable enantioselectivity. The standard transformation of the products obtained into functionalized optically active bisphosphonic acids or vinylphosphonates proceeded without substantial decrease in optical purity.

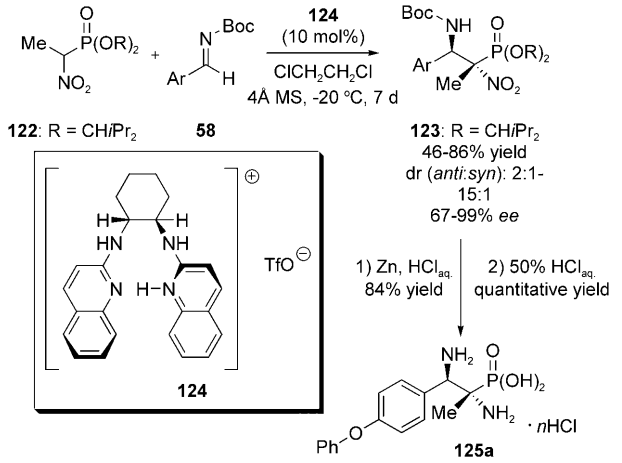


Scheme 33.

Phosphoryl-Group-Stabilized Carbanions in Asymmetric Organocatalysis

Carbanion chemistry plays a pivotal role in modern organic synthesis. The use of phosphoryl-group-stabilized carbanions

for the construction of the new C–C bond is well documented in the literature. Surprisingly, there is only one example describing their application in asymmetric organocatalysis. In 2008 Johnston et al. reported highly enantio- and diastereoselective addition of α-nitroethylphosphonate **122** to *N*-Boc imines **58** (Scheme 34).[54] The reaction was catalyzed



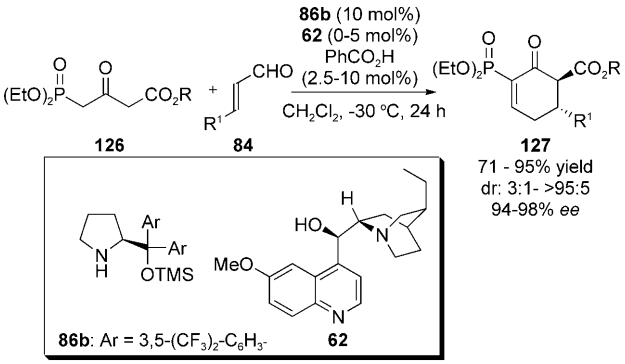
Scheme 34.

by **124** that served as bifunctional catalyst. On the one hand, catalyst **124** acted as Brønsted acid activating the imine **58** by selective hydrogen-bonding. On the other hand, its Brønsted basicity enabled deprotonation of **122** and formation of the chiral ion pair. Among the parameters tested for the influence on the reaction outcome the phosphonate ester bulkiness was crucial. 2,4-Dimethylpentane-3-yl phosphonate **122** was found superior in terms of stereoselectivity ensuring particularly high *anti* diastereoselectivities. In general both electron-rich and electron-poor aldimines **58** could be successfully applied in this reaction affording products in a highly stereoselective manner. However, yields of the reaction with electron-poor aldimines were generally lower. Furthermore, transformation of the adduct **123a** into optically active *anti*-α,β-diaminophosphonic acid **125a** was shown.

Organophosphorus Reagents in Asymmetric, Organocatalytic, Domino Reactions

Domino reactions, in which more than one bond is being formed in a multistep one-pot reaction sequence giving access to molecules of complex architecture, without isolation and purification of the intermediates, are of great importance in organic chemistry. As it has been demonstrated, organocatalysis provides a possibility to perform this type of reaction in an asymmetric fashion with high levels of stereocontrol. The immense progress in this field of organocatalysis has been recently reviewed.[55]

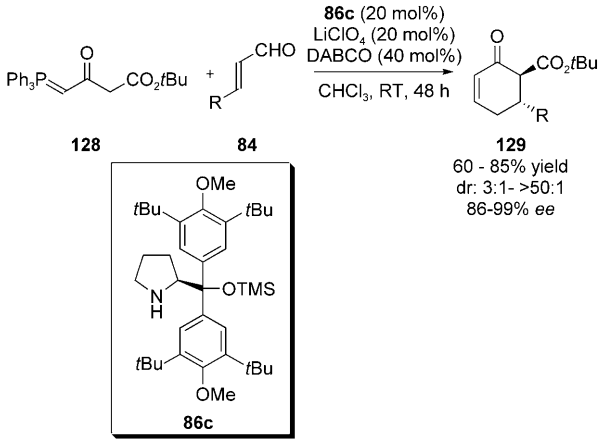
In 2009 the development of a highly stereoselective, organocatalytic Michael–Knoevenagel domino reaction of 4-diethoxyphosphoryl-3-oxobutanoates **126** with α,β-unsaturated aldehydes **84** catalyzed by **86b** leading to enantiomerically enriched 6-substituted-3-diethoxyphosphoryl-2-oxocyclohex-3-enecarboxylates **127** was presented (Scheme 35).[56] This



Scheme 35.

methodology proved to be general, since a wide range of α,β-unsaturated aldehydes **84** bearing either aromatic or aliphatic β-substituents could be easily reacted, affording the corresponding products **127** with high levels of stereocontrol. In the case of aliphatic enals, the use of hydroquinine (**62**) as a Brønsted base co-catalyst to facilitate the formation of the corresponding enol turned out to be necessary. Furthermore, the application of optically active **127** in various stereoselective transformations was demonstrated providing access to a range of cyclohexene and cyclohexane derivatives with up to four stereocenters, thus indicating the high synthetic utility of the compounds obtained.

Stabilized phosphorus ylides constitute another useful class of organophosphorus reagents widely used for the construction of new C=C double bonds.[2h] Domino Michael/Wittig reactions represent convenient and important approach for the synthesis of carbocyclic compounds.[57] In 2009 Chen et al. demonstrated the utilization of (3-carboxy-2-oxopropylidene)triphenylphosphorane[58] (**128**) in asymmetric organocatalytic Michael/Wittig domino reaction (Scheme 36).[59] The domino protocol employed aminocata-



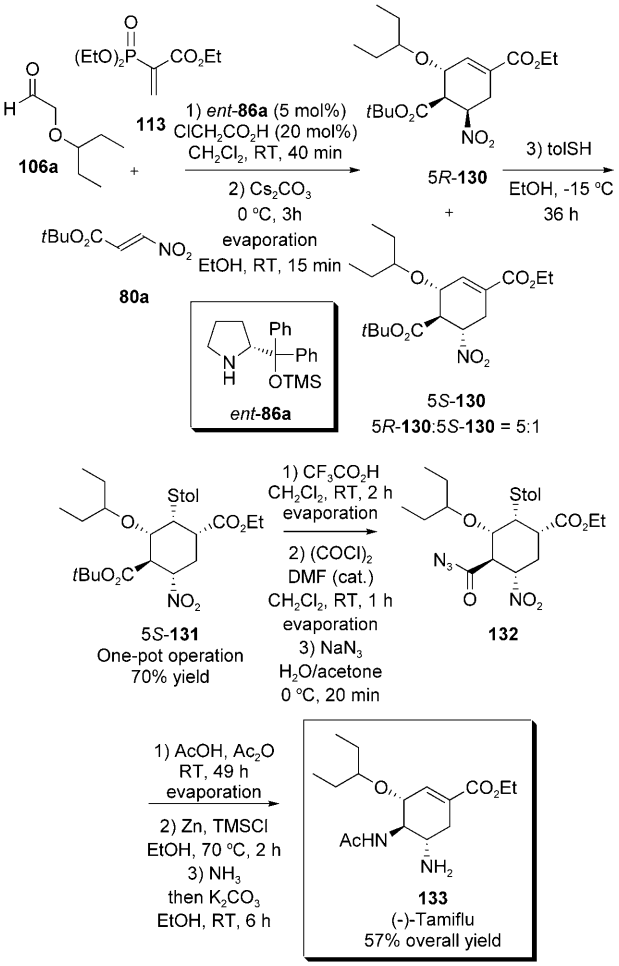
Scheme 36.

lytic Michael addition of **128** to α,β-unsaturated aldehydes **84** as the key step. It was found that the use of bulky pyrrolidine derivative **86c** was necessary to achieve particularly high levels of stereoinduction. The yield of the reaction could be enhanced by employing 1,4-diazabicyclo-[2.2.2]octane (DABCO) and $LiClO_4$ as co-catalysts. Under these reaction conditions, the originally formed Michael adducts underwent an intramolecular Wittig reaction to produce 6-substituted-2-oxocyclohex-3-enecarboxylates **129** in a highly enantio- and diastereoselective manner. It is worth noting that the aminocatalytic domino Michael/Wittig reaction could easily be performed for aromatic, heteroaromatic, and aliphatic α,β-unsaturated aldehydes **84**, confirming the high generality of the process. Additionally, various transformations of optically active cyclohexenones **129** obtained are also discussed in the paper.

Enantioselective, Organocatalytic One-Pot Procedures Involving Organophosphorus Reagents

One-pot procedures constitute an interesting alternative to domino reactions, enabling efficient synthesis of complex molecules and minimizing the number of steps and purification procedures required to obtain the product. The recent advancement of asymmetric organocatalytic reactions and their high efficiency and selectivity makes them particularly well suited for applications in one-pot transformations.

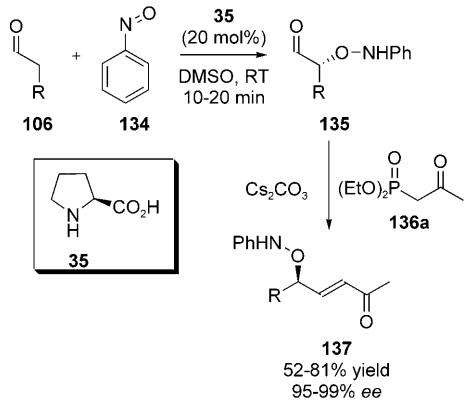
An interesting advance in the area of asymmetric organocatalytic one-pot operations was reported in 2009 by Hayashi et al., who described the total synthesis of (−)-oseltamivir phosphate (**133**; Tamiflu; Scheme 37).[60] The synthetic protocol is composed of three separate one-pot operations, with three reactions performed in each of them. The first, most important organocatalytic step started with *ent*-**86a**-catalyzed Michael addition of alkoxyaldehyde **106a** to the functionalized nitroolefin **80a**. The nitroalkane thus obtained was further reacted with acrylate **113** to produce 7-oxophosphonate, which in turn underwent intramolecular Horner–Wadsworth–Emmons reaction yielding the cyclohexene framework **130**. It is also worth noting that diester **130** was formed as a mixture of two diastereoisomers in which undesired 5*R* isomer predominated. According to the authors, (5*R*)-**130** and (5*S*)-**130** isomers are in equilibrium and Michael addition of thiol, performed in the last stage of the first one-pot procedure, proceeded to (5*R*)-**130** predominantly in a highly stereoselective manner. The originally formed Michael adduct (5*R*)-**131** isomerized under basic conditions to give the thermodynamically stable and desired (5*S*)-**131**, which was then purified by column chromatography. The second one-pot operation consisted of deprotection of *tert*-butyl ester and conversion of the acid obtained into acyl azide **132** via the corresponding acyl chloride. Notably, the azide **132** was not purified, but used as crude in the next transformations. In the final one-pot operation compound **132** was submitted to a Curtius rearrangement and subsequent protection of the thus obtained amine as its acetamide. Reduction of the nitro group and base-promoted retro-Michael reaction of the thiol afforded the target Tamiflu (**133**) with 57% overall yield. The whole process requires only one purification procedure (column chromatography) and was conducted in three separate reaction vessels.



Scheme 37.

In another interesting one-pot approach organophosphorus reagents are not involved directly in organocatalytic step. However, they are used to trap optically active α- or β-functionalized aldehydes obtained utilizing aminocatalytic approach and the whole procedure is performed in a single reaction vessel. In such a manner, double or triple bonds can be easily introduce into the molecules leading to the formation of allylic, propargylic, or homo-propargylic stereogenic centers.

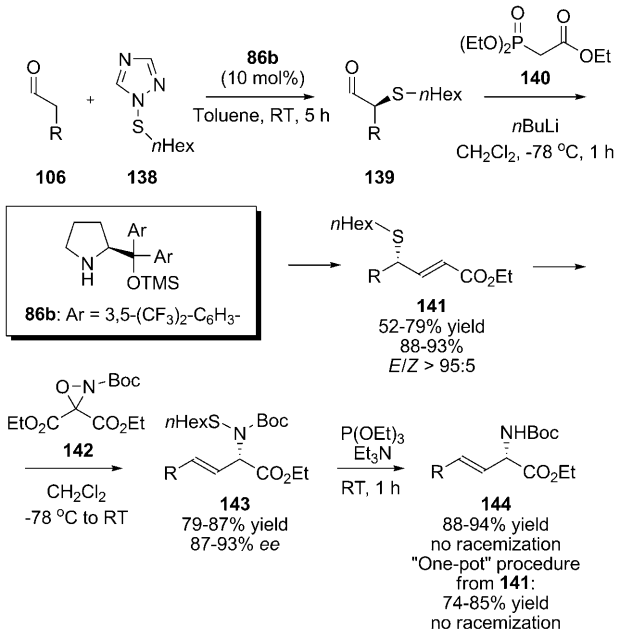
In 2004 Zhong and Yu established the possibility of employing one-pot procedure consisting of organocatalytic α-aminoxylation of aldehydes **106** and subsequent Horner–Wadsworth–Emmons olefination for the synthesis of highly enantiomerically enriched *O*-amino-substituted allylic alcohols **137** (Scheme 38).[61] Proline-catalyzed α-aminoxylation of **106** with nitrosobenzene (**134**) was performed according to the procedure developed earlier in this research group.[62] Horner–Wadsworth–Emmons olefination with diethyl (2-ox-



Scheme 38.

opropyl)phosphonate (**136a**) was accomplished by using Cs_2CO_3 as a base. Notably, no racemization occurred at this stage despite basic reaction conditions and corresponding allylic alcohols **137** were formed in high yield and in a highly enantioselective manner. Additionally, the N–O bond in the products formed could be easily cleaved to produce free allylic alcohols.

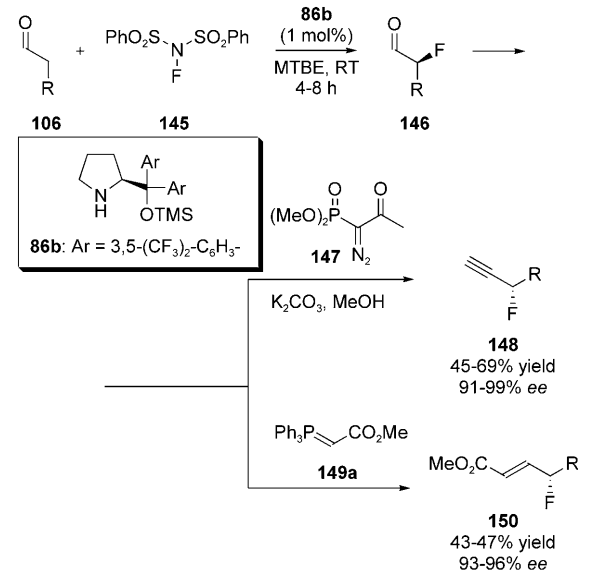
Armstrong et al. applied a one-pot α-sulfenylation/Horner–Wadsworth–Emmons olefination strategy to the synthesis of allylic sulfides **141** (Scheme 39).[63] α-Sulfenylation of aldehydes was accomplished in the presence of **86b** as the catalyst and **138** as electrophilic sulfur source according to the procedure developed earlier.[64] Subsequent Horner–Wadsworth–Emmons olefination was performed in the presence of *n*BuLi as a base and at low temperature in order to avoid racemization and achieve high *E*/*Z* selectivity. The allylic sulfides **141** thus obtained were utilized for



Scheme 39.

the synthesis of vinyl glycines **144**. The reaction sequence involving amination and [2,3]-sigmatropic rearrangement proved to be fully stereospecific affording *E*-configured product **143** with complete transfer of chirality. Additionally, the authors established the possibility of employing ethyl (diphenoxyphosphoryl)acetate in the Horner–Wadsworth–Emmons olefination step to produce (*Z*)-allylic sulfides, which underwent amination/rearrangement sequence to give enantiomeric product *ent*-**143**. Furthermore, the cleavage of the S–N bond was accomplished under mild conditions with $P(OEt)_3$ and Et_3N at room temperature to give **144**. Importantly, the transformation of **141** into **144** involving amination/rearrangement/desulfurization could be performed in "one-pot" without isolation and purification of **143**.

Very recently the organocatalytic synthesis of optically active propargylic and allylic fluorides **148** and **150** was reported (Scheme 40).[65] Both of the synthetic one-pot proce-

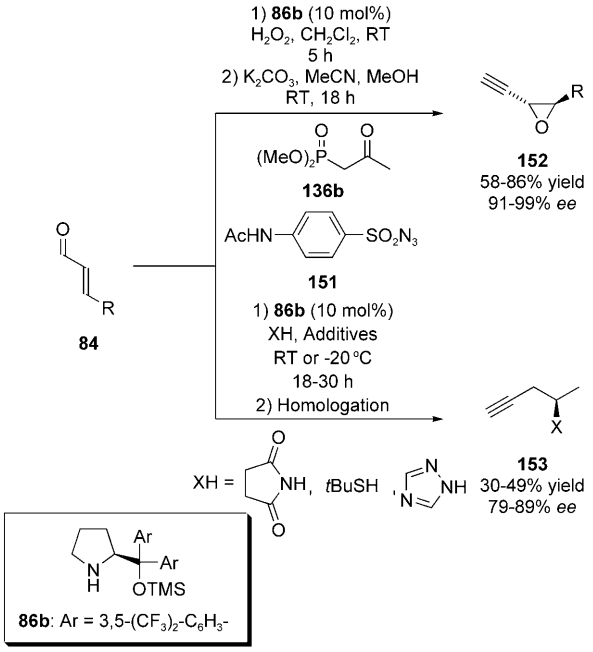


Scheme 40.

dures leading to the formation of these compounds were initialized by enantioselective organocatalytic α-fluorination of enolizable aldehydes **106** with *N*-fluoro-dibenzene-sulfonimide (**145**; NFSI) in the presence of **86b** as the catalyst. Enantiomerically enriched aldehydes **146** were transformed into **148** by reacting with Ohira–Bestmann reagent **147** (Ohira modification of the Seyferth-Gilmann homologation). Importantly, despite the basic conditions the reaction proceeded without noticeable degree of racemization. Moreover, it was demonstrated that compound **147** could be generated in situ from dimethyl 2-oxopropylphosphonate and 4-acetamidobenzenosulfonyl azide, further increasing the attractiveness of this methodology. On the other hand, the synthesis of **150** required a Wittig reaction to be performed. Again, the one-pot procedure turned out to be well suited for the developed reaction sequence, since no racemization of α-fluoro aldehydes **146** occurred. All propargylic and al-

lylic fluorides **148** and **150** were obtained with moderate to good yields and very high enantioselectivities. The potential of the optically active propargylic fluorides **148** synthesized was demonstrated in various interesting transformations.

Ohira modification of the Seyferth–Gilmann homologation was also utilized by the same research group for the construction of propargylic epoxides **152** as well as homopropargylic amines and sulfides **153** (Scheme 41).[66] Both

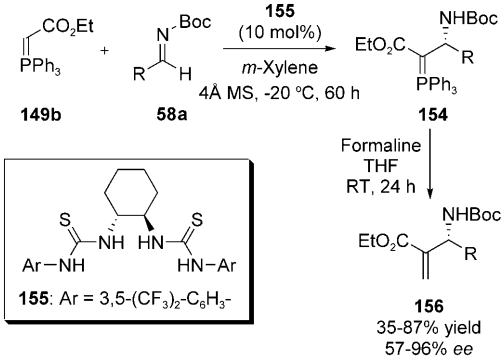


Scheme 41.

synthetic one-pot procedures started with hetero-Michael addition to iminium-activated α,β-unsaturated aldehydes **84**. Treatment of α,β-unsaturated aldehydes **84** with H_2O_2 in the presence of **86b** as the catalyst afforded *trans*-epoxy aldehydes, which were further reacted with the Ohira–Bestmann reagent prepared in situ from dimethyl 2-oxopropylphosphonate (**136b**) and 4-acetamidobenzenosulfonyl azide (**151**) to give optically active propargylic epoxides **152**. The developed synthetic protocol proceeded with good yield and excellent enantioselectivity. The synthesis of homopropargylic amines and sulfides **153** required Michael addition of succinimide or 1,2,4-triazole as nitrogen nucleophiles and *tert*-butyl sulfide as sulfur nucleophile to be performed. Subsequent trapping of the Michael adducts thus obtained with in situ generated Ohira–Bestmann reagent afforded homoproprgylic stereocenters with good enantioselectivity and moderate yield. In the case of the reaction with *tert*-butyl sulfide, a pre-prepared Ohira–Bestmann reagent was used. The scope of both approaches to propargylic and homopropargylic compounds **152** and **153** was very broad and both aliphatic and aromatic enals **84** were well tolerated. Enantiomerically enriched epoxides **152** and amines **153** were demonstrated as valuable reagents in the synthesis of allenic alcohols, bromohydrins, aminoalcohols, thiiranes, and other useful heterocycles.

Other Organocatalytic Reactions Involving Organophosphorus Reagents

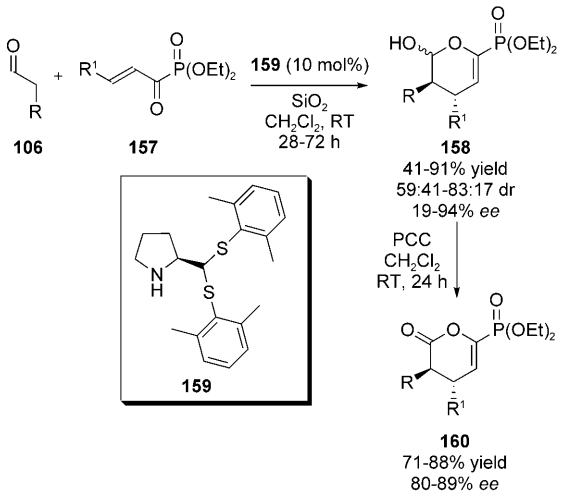
A very elegant organocatalytic approach to enantiomerically enriched *N*-Boc-β-amino-α-methylenecarboxylates **156**, products usually obtained by means of aza-Morita-Baylis–Hillman reaction, was developed by Chen et al (Scheme 42).[67] The devised methodology utilized a bis-



Scheme 42.

thiourea **155**-catalyzed Mannich-type reaction between ylide **149b** and *N*-Boc imines **58a** and subsequent olefination of **154** with formaldehyde. Imines **58a** derived from both aliphatic and aromatic aldehydes were successfully applied in this reaction sequence. Additionally, it was demonstrated that imines derived from aliphatic aldehydes could be generated in situ. Furthermore, the catalyst could be recovered by flash chromatography and reused without decrease in catalytic activity. It is worth noting that this reaction sequence could be performed without isolation of **154**; however, the final product **156** was formed with lower yield and enantioselectivity.

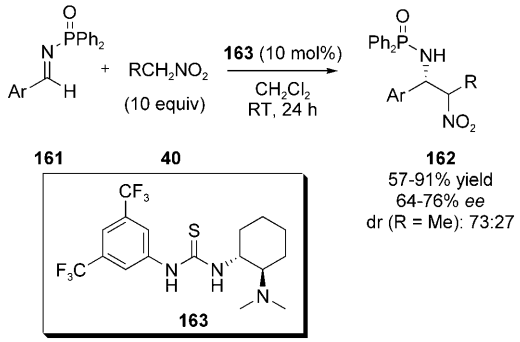
In 2007 Zhao et al. in extension to their previous studies (Scheme 9)[17] found that reaction of enolizable aldehydes with α-ketophosphonates in the presence of L-proline used as a chiral catalyst failed to give expected secondary α-hydroxyphosphonates. Surprisingly, performing the reaction of diethyl *trans*-1-oxo-2-butenylphosphonate (**157a**) with propanal **106a** led to the formation of the hetero-Diels–Alder (HDA) adduct with 38% *ee* (Scheme 43).[68] After intensive screening the proline dithioacetal **159** was found as a highly effective organocatalyst of this unexpected transformation. Under optimal reaction conditions various aldehydes **106** were reacted with β,γ-unsaturated-α-ketophosphonates **157** to give 5,6-dihydro-4H-pyran-2-ylphosphonates **158** in a highly enantioselective manner. In some of the cases, for the ease of HPLC analysis, the HDA adducts **158**, formed as mixture of two diasteroisomers with different configuration at the anomeric carbon, were oxidized to γ,δ-unsaturated-δ-lactones **160**. These products were obtained as single *trans*-diasteroisomers. The authors suggest that enamine generated in situ from the corresponding aldehyde and chiral catalyst acts as a dienophile in this inverse-elec-



Scheme 43.

tron-demanding HDA reaction and is responsible for its stereochemical outcome.

The ability of phosphoryl group to act as activating electron-withdrawing substituent as well as good acid-labile protecting group is manifested in *N*-phosphorylated imines which have found application as reactive electrophilic species in various C–C bond forming reactions. Takemoto et al. demonstrated that thiourea derivative **163** developed in their research group can serve as very efficient organocatalyst for the aza-Henry reaction between *N*-phosphorylated imines **161** and nitroalkanes **40** (Scheme 44).[69] The reactions of various imines bearing *N*-diphenylphosphoryl substituent **161** with nitromethane and nitroethane proceeded with high yields and good to moderate enantioselectivity. Diastereoselectivity attained in the reaction with nitroethane was moderate.



Scheme 44.

Summary and Outlook

In summary, applications of asymmetric organocatalysis for the synthesis of optically active organophosphorus compounds constitute an interesting and challenging field of research. The devised solutions deliver a direct and efficient approach to nonracemic phosphorus compounds of biological interest such as α-hydroxy- or α- and β-aminophosphonates. Furthermore, enantiomerically enriched phosphonic acids and phosphines can be easily accessed by means of asymmetric organocatalysis. These compounds may find applications as chiral ligands or catalysts in asymmetric synthesis. Additionally, organophosphorus compounds have been utilized in organocatalytic asymmetric syntheses of various organic molecules of importance. Particularly interesting are approaches utilizing domino and one-pot procedures. These methodologies are very similar to what nature use for natural product synthesis and can be regarded as biomimetic. Despite remarkable achievements, there is still a great demand and space for further development. We believe that in the years to come this interesting field of chemistry will further advance and new even more efficient methodologies enabling achieving higher enantioselectivities and reducing the catalysts loadings will be developed.

Acknowledgements

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