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ARTICLE TYPE

N-Phosphonyl /Phosphinyl Imines and Group-Assisted Purification (GAP) Chemistry/Technology

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The development of environmentally benign, operationally simple, and economically viable synthetic methodologies has been a great challenge in organic synthesis. Group-Assisted Purification (GAP) chemistry was established to enable the synthesis of organic compounds without using traditional purification technologies, such as column chromatography and recrystallization. This concept/technology should encourage the synthetic community to make more efforts on searching for environmentally benign reagents and reactions to reduce the waste generated from silica and solvents, particularly toxic solvents; also, to reduce production/synthesis expenses, manpower, and energy. This review will discuss the GAP concept/technology and related reactions that were mainly conducted in the PI's laboratories after 2010.

1. Introduction

Synthetic organic chemistry and chemical production have been playing an important role in many disciplines such as chemical sciences and materials, biological chemistry, pharmaceuticals and medicine, etc.[1,2] Unfortunately, they have been associated with problems in regard to waste generation and pollution, energy, consumption of manpower and time, safety, etc. For example, a 15-person organic synthesis research group in academia usually uses 300-500 kg silica gels and 500-1000 liters of solvents for column chromatography; this process produces substantial amounts of waste, requires large expenses for the purchase of silica gels and toxic solvents, and includes tedious work-up. Occasionally, flash chromatography is accompanied with a serious explosion caused by the high pressure in flash columns.

Chemists in the pharmaceutical and chemical industries have been trying to find greener methodologies[1-3] and to avoid chromatography by generating solid products for purification *via* recrystallization.[3] Another strategy consists of exploring different synthetic routes based on the researchers limited empirical knowledge on solubility, hoping for the formation of solid products. So far, there has not been a general method that predicts and controls the solubility of organic products in organic chemistry. The challenging question remains, *i.e.*, can a general strategy be found in organic synthesis to *purposefully* form solid products that can be separated and purified simply by washing, without the use of chromatography and recrystallization? The concept/technology of Group-Assisted Purification (GAP) chemistry was established to address this question.

GAP chemistry is illustrated in Fig 1. The well-functionalized group (auxiliary) is first anchored onto the starting material to generate the GAP reagents for organic reactions. Generally, the GAP reagents should meet following requirements:

(1) they should have adequate stability and chemical reactivity.

(2) they should be able to result in solid products that are soluble in some solvents (*e.g.*, THF and DCM) for further reactions, but not be well soluble in some other solvents (*e.g.*, petroleum ethers, hexane and their co-solvents with EtOAc, etc) for GAP washing;

(3) if GAP reagents are chiral, then they should be able to control stereoselectivity in asymmetric reactions.

(4) they should have extensive substrate scopes;

(5) GAP auxiliaries should be readily cleaved and recycled for re-use.

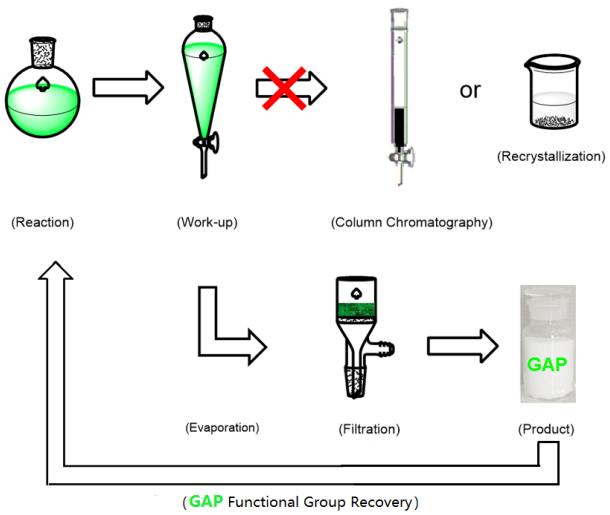


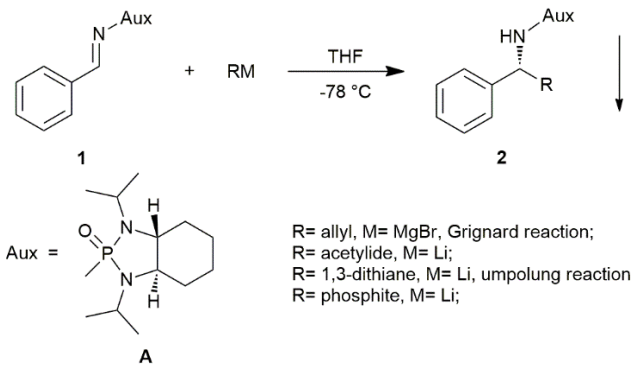
Fig. 1 GAP chemistry pictorial demonstration

After the GAP starting material is converted into the solid product, routine work-up is performed by using a separatory funnel for layer separation and extraction. Drying and evacuation lead to the formation of a crude solid mixture (unnecessary to be crystals!). The crude products are transferred into a Buchner funnel, followed by washing with solvents (and/or water) to give

an NMR pure product. The final GAP product can be subjected to deprotection for recovery of the GAP auxiliary.

This GAP concept was initially inspired by our projects in the development of new imine reagents for asymmetric synthesis by taking advantage of *N*-phosphonyl and *N*-phosphinyl functional groups. This review covers reactions and synthesis mainly based on the use of these GAP auxiliaries. Herein, we would like to define *the Group-Assisted Purification (GAP) chemistry as a chemistry for organic/medicinal synthesis that avoids traditional purification methods such as chromatography and/or recrystallization by purposely introducing well-functionalized group in starting materials or newly generated groups in precursors and products*. GAP functional groups are not limited to the *N*-phosphonyl and *N*-phosphinyl functions. Other traditional functional groups and newly generated functionalities from reactions are also covered by GAP chemistry. The GAP concept would be the first chemistry concept which combines the attributes of reagent/reaction/separation/purification together (chemical and physical aspects). We hope that the GAP chemistry concept and technology will encourage the synthetic community to *purposefully* maximize the advantages of functional groups in organic synthesis, and to directly wash the crude products from separatory funnel work-up, instead of the daily use of chromatography without any hesitation.

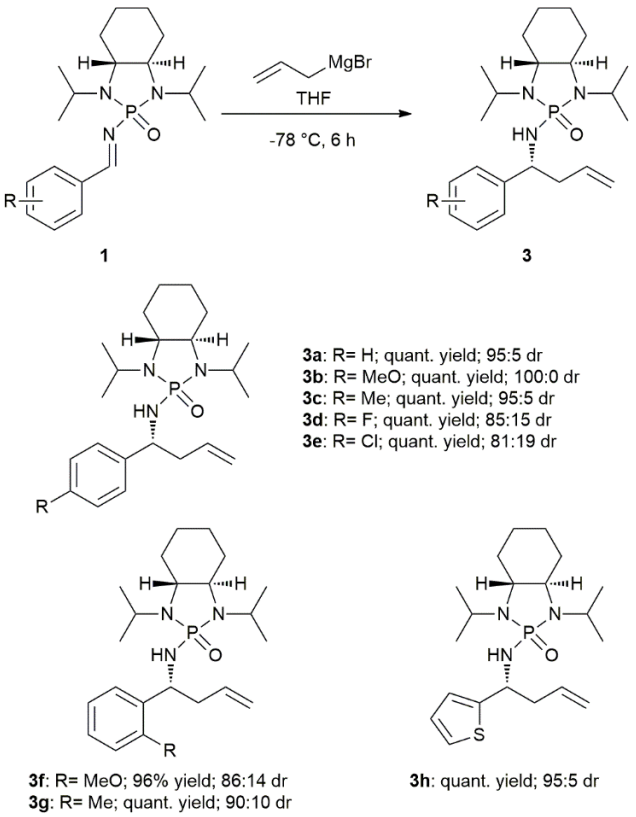
2. Reactions of *N*-phosphonyl imines with metal anion reagents



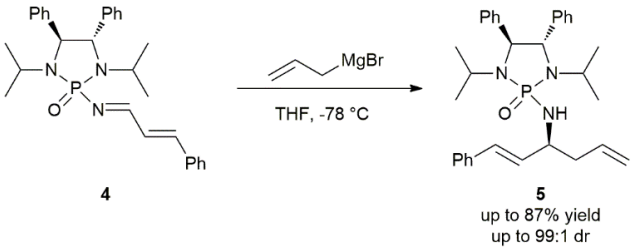
Scheme 1 Reactions of *N*-phosphonyl imines with organometallic reagents.

GAP chemistry has been realized by reacting *N*-phosphonyl imines with various metal anion reagents for the synthesis of homoallylic amines,[4] propargylamines,[5] α-amino-1,3-dithianes[6] and amino phosphonates.[7] By introducing the *N,N'*-diisopropyl-cyclohexyldiamino phosphonyl group (**A**) as the GAP auxiliary, good to excellent diastereoselectivity and yields were conveniently achieved. The resulting amino products were simply purified by washing crude products with hexanes or a mixture of hexane and ethyl acetate to give pure solid products (Scheme 1). The GAP auxiliary can be readily cleaved and recovered by a one-time extraction with *n*-butanol.

As one of the initial studies in GAP phosphonyl imine chemistry, the asymmetric addition reactions between chiral *N*-phosphonyl imines and Grignard reagents were first performed in 2008.[4a] In the case of allylmagnesium bromide as a nucleophile, the asymmetric addition reactions of aromatic *N*-phosphonyl imines **1** gave the homoallylic amines **3** (Scheme 2). Among the various C_2-symmetric chiral phosphonyl auxiliaries employed for this reaction, *N,N'*-diisopropyl-cyclohexyldiamino phosphonyl group **A** was proven to be the most efficient in controlling the stereochemistry. The high diastereoselectivity can be attributed to the increased steric bulkiness of secondary alkyl group at C_2-symmetric nitrogens of the chiral auxiliary. Different chiral *N*-phosphonyl imines were subjected to reaction conditions during examination of the substrate scope. For the *N*-phosphonyl imine derived from *para*-methoxy benzaldehyde, a single isomeric product **3b** was obtained in quantitative yield. The imines bearing *ortho*-substituents or electron-withdrawing substituents on aromatic ring gave slightly decreased diastereoselectivities (**3d**-**3g** in Scheme 2). The protocol was also accessible to chiral *N*-phosphonyl imines derived from heteroaromatic aldehydes (**3h** in Scheme 2). All of the products were washed with hexanes for purification, and the auxiliary was readily removed to afford the free amine, with the recovery of *N,N'*-diisopropyl-cyclohexyldiamine for reuse. The free amine was protected with the *t*-Boc group and compared with known compounds for assigning the absolute configuration of the newly generated chiral center as '*R*'. Subsequent investigations extended the scope to the use of chiral *N*-phosphonyl aliphatic imines as substrates.[8]

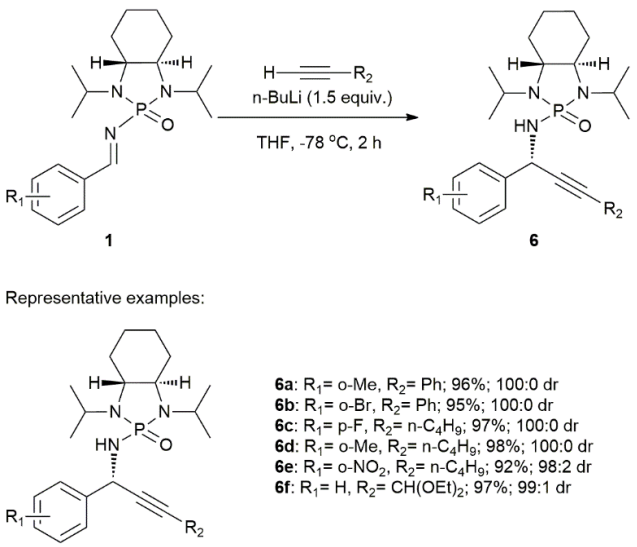


Scheme 2 Reaction of allylmagnesium bromide with chiral *N*-phosphonyl imines **1**.



Scheme 3 Reaction of allylmagnesium bromide with chiral *N*-phosphonyl imines **4**.

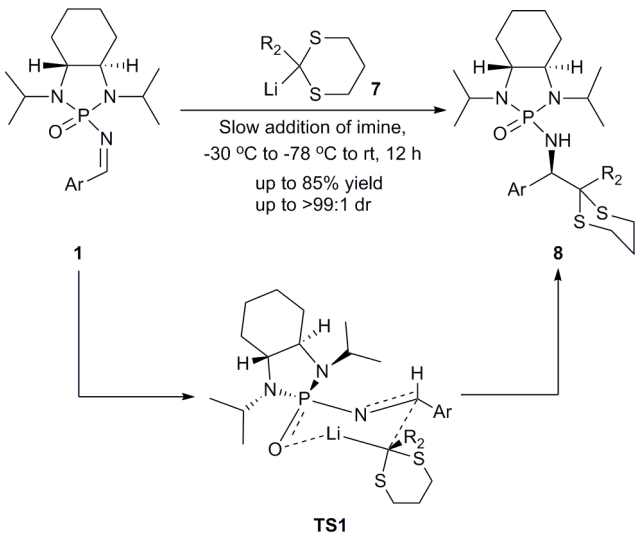
α,β-Unsaturated imines **4** anchored with the *N,N'*-diisopropyl-diphenyldiamino phosphonyl group were synthesized and subjected to the 1,2-addition reaction with allylmagnesium bromide to give the *α*-alkenyl homoallylic primary amines **5** in good yields (up to 87%) and excellent diastereselectivities (up to 99:1 dr) (Scheme 3).[4b] Given the fact that most of the products were formed as oils, due to the existence of flexible long chains in the products, new GAP groups will be explored for this reaction. This reaction is among the very few examples of a non-GAP *N*-phosphonyl imine reaction. It should be noted that column chromatography was utilized in most of our publications before 2010, when the GAP concept was proposed. However, for all cases that were re-visited, the GAP process has been proven to be efficient.



Scheme 4 GAP Synthesis chiral *N*-phosphonyl propargylamines *via* chiral *N*-phosphonyl imines.

Besides the above reactions with Grignard reagents, nucleophilic additions of lithium aryl/alkyl acetylide to chiral *N*-phosphonyl imines **1** was proven to be efficient as well (Scheme 4).[5] *N,N'*-diisopropyl-cyclohexyldiamino phosphonyl group **A** resulted in the highest diastereoselectivity, which is similar to the cases involving the Grignard reagents. It was observed that sodium, aluminum, and magnesium aryl acetylides gave lower diastereoselectivity than their lithium counterparts. A broad scope of chiral *N*-phosphonyl imines **1** and alkynes was studied for this reaction, providing the chiral *N*-phosphonyl propargylamines in up to 98% yield with excellent diastereoselectivities. As shown in Scheme 4, single isomeric products **6a**-**6d** were obtained for 4 examples. For all substrates, substitutions on the phenyl rings of the chiral *N*-phosphonyl imines had no significant effect on either the yields or the diastereoselectivities. The chiral *N*-phosphonyl imine derived from *ortho*-nitro benzaldehyde smoothly underwent the reaction as well (**6e** in Scheme 4).

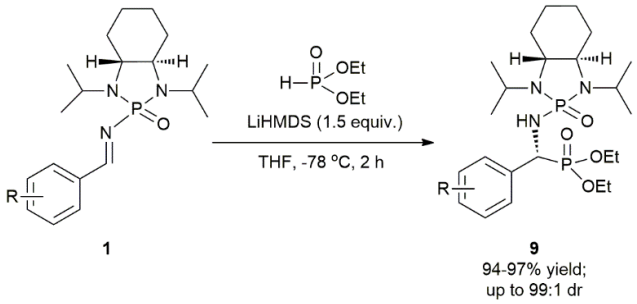
The asymmetric umpolung reaction between chiral *N*-phosphonyl imines **1** and lithio-1,3-dithianes **7** utilized the GAP process as well (Scheme 5).[6] Analogously, phosphonyl group **A** proved its efficiency for the reaction in both chemical yield and diastereoselectivity. Interestingly, the manner of adding *N*-phosphonyl imine **1** into the reaction mixture was found to be crucial for the success of this asymmetric reaction; *i.e.*, the slow addition of *N*-phosphonyl imine **1** into a solution of 2-lithio-1,3-dithiane **7** was the only efficient way to control the resulting stereochemistry. Different imines **1** and 1,3-dithianes **7** were subjected to the standard condition to afford the *α*-amino-1,3-dithianes **8** in up to 85% yield and up to >99:1 dr. The excellent diastereoselectivity was explained by the proposed six-membered transition state **TS1**. The *R*-configuration of the final product **8** was consistent with our previous results, in which the lithium cation is coordinated to the nitrogen of the *N*-phosphonyl amine reactant. However, in this reaction it is connected to the oxygen atom of the *N*-phosphonyl imine (**TS1** in Scheme 5). The pure dithiane products were obtained by simply washing the crude products with hexane or a mixture of hexane and ethyl acetate.



Scheme 5 Asymmetric GAP synthesis of *α*-amino-1,3-dithianes using chiral *N*-phosphonyl imines.

Chiral imines **1** also smoothly underwent an addition reaction with phosphites to afford *α*-aminophosphonates, which are important precursors for biologically important aminophosphonic acids.[9] The purification of the *N*-phosphonyl *α*-amino phosphonates was conducted *via* a GAP work-up (Scheme 6).[7] In this synthesis, LiHMDS was found to be more efficient than other bases such as NaHMDS, KHMDS, LDA, *n*-BuLi and *t*-BuLi for the deprotonation of phosphite substrates. In addition, chiral *N*-phosphonyl imines **1** significantly enhanced the chemical yields and diastereoselectivities over the other auxiliaries. All of the *N*-phosphonyl *α*-amino phosphonates **9** were obtained in good chemical yields and excellent diastereoselectivities; single isomeric products were obtained in the reactions of chiral *N*-phosphonyl imines derived from *p*-fluoro and *p*-methyl

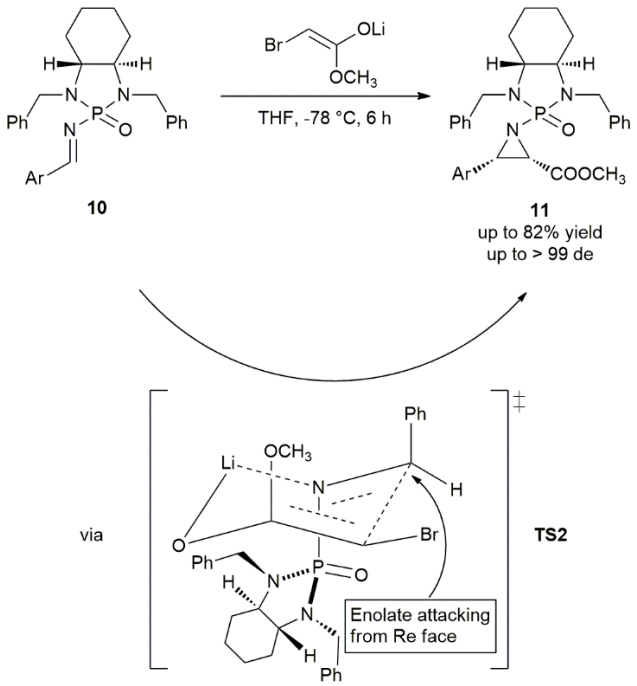
benzaldehydes. The reaction provides products in the *R*-configuration.



Scheme 6 Asymmetric hydrophosphylation of chiral *N*-phosphonyl imine.

3. Reactions of *N*-phosphonyl imines with enolates

3.1 Aziridine formation



Scheme 7 Asymmetric *aza*-Darzens reaction using *N*-phosphonyl imine.

In the initial study of chiral *N*-phosphonyl imine chemistry, chiral *N*-phosphonyl aziridines were synthesized *via* the asymmetric aza-Darzens reaction (Scheme 7).[10] The single crystal structure for phosphoramide **X** was obtained during the synthesis and shown in Fig. 2. The C_2 symmetry is clearly identified and the two benzyl groups are arranged asymmetrically, so as to participate in the asymmetric induction.

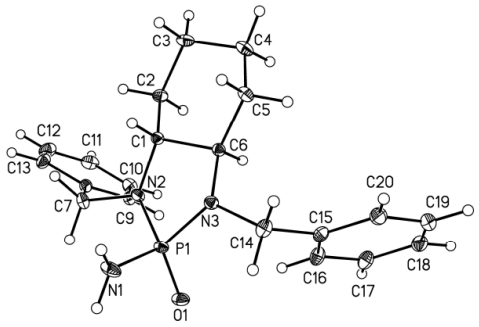
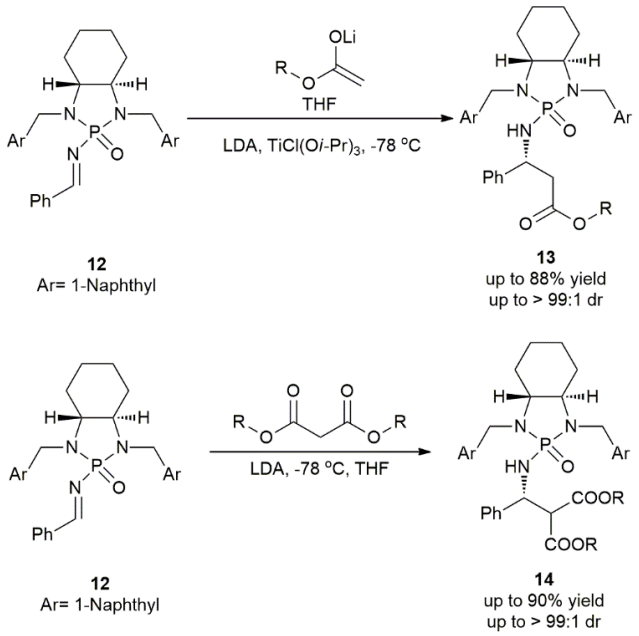


Fig. 2 Single crystal structure of phosphoramide **X**.

Imine **10** derived from phosphoramide **X** reacted with the lithium enolate of methyl 2-bromoacetate to afford *N*-phosphonyl aziridines **11** in good yields and in the complete *cis*-form, with good to excellent diastereoselectivities (Scheme 7).[10] The excellent cis/trans control was accounted for by the cyclic six-membered transition state **TS2**. Attack of the *E*-configured lithium enolate of methyl 2-bromoacetate onto the *N*-phosphonyl imine is directed onto the *Re*-face of the imine. Coordination of the phosphonyl oxygen with the lithium cation to form an additional four-membered ring is inhibited (Scheme 7). Further investigation on the aza-Darzens reaction involving the aforementioned phosphonyl group **A** improved the diastereoselectivity for most substrates.[11] The chiral *N*-phosphonyl aziridines were obtained in > 99:1 diastereoselectivity.

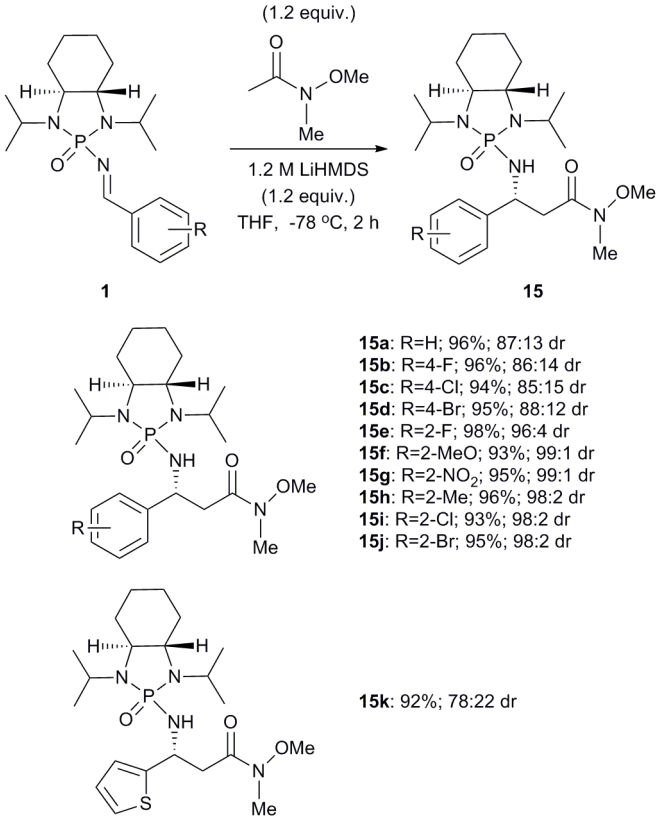
3.2 Amino ester synthesis

Chiral *N*-phosphonyl imines were subjected to asymmetric addition reactions with ester enolates (Scheme 8).[12] The aforementioned chiral *N*-phosphonyl imines **1** and **10** furnished either low diastereoselectivity or modest chemical yields, and *N,N'*-dinaphthylmethyl-cyclohexyldiamino phosphonyl imine **12** was found to be most efficient for the reaction. Among the various bases and solvents, the combination of LDA with THF gave the best results for both yield and diastereoselectivity. Triisopropoxytitanium (IV) chloride was employed as an efficient Lewis acid promoter for controlling the stereochemistry. It was found that performing the reaction in the absence of $TiCl(O\textit{i}\text{-}Pr)_3$ decreased the diastereoselectivity from 82:18 to 69:31. Under optimized conditions, different chiral *N*-phosphonyl imines **12** were used in the reaction, giving chiral *β*-amino esters **13** in good yields (70–88%) and excellent diastereoselectivities (up to >99:1 dr). For 2-substituted benzaldehyde-derived imines, slight increase in the diastereoselectivity was observed, and different acetates were proven to be suitable for this asymmetric reaction. Products **13** were readily converted into the corresponding *N*-Boc-*β*-amino esters in good chemical yields.



Scheme 8 Addition of lithium ester enolates to *N*-phosphonyl imines.

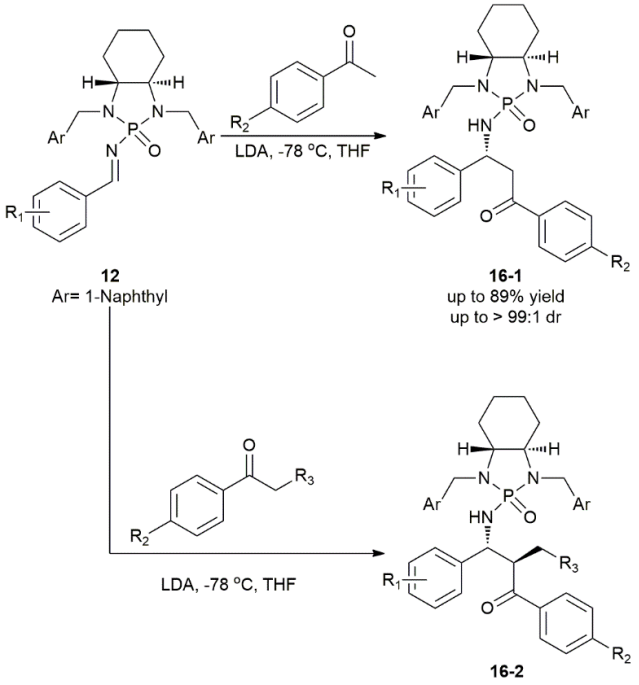
Further investigation leads to the asymmetric addition of dialkyl malonate enolates to chiral *N*-phosphonyl imines **12** (Scheme 8).[13] Imine **12** in THF with LDA as the base gave the best diastereoselectivities and good chemical yields. Unlike the previous cases for enolates of acetates,[12] the reaction requires warming to -30 °C for complete consumption of the starting materials after keeping the reaction at -78 °C for 1 h. Various imines derived from benzaldehyde derivatives bearing electron-withdrawing or electron-donating groups on their aromatic rings gave excellent diastereoselectivities (up to > 99:1 dr) and good to high yields (up to 90%). The reactions of diethyl malonates resulted in higher yields than those of dimethyl malonates, retaining diastereoselectivity at the same level.



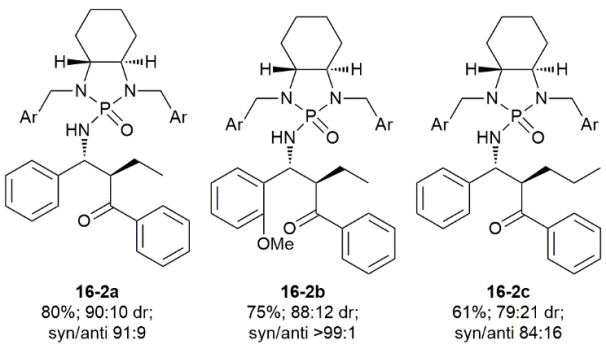
Scheme 9 Synthesis of *N*-phosphonyl-*β*-amino Weinreb amides with the use of chiral *N*-phosphonyl imines **1**.

Weinreb amides have been serving as versatile precursors in organic synthesis because they can be readily converted into ketones.[14] To achieve the successful GAP synthesis of *β*-amino Weinreb amides, lithium enolates of *N*-methoxy-*N*-methylacetamides were employed in the nucleophilic additions to chiral *N*-phosphonyl imines **1** (Scheme 9).[15] Among the various available bases for generating enolates, LiHMDS gave slightly higher diastereoselectivities and yields over KHMDS. Similar to the Grignard reactions,[4a] significant enhancement of the diastereoselectivity was achieved when a secondary alkyl group was chosen for the phosphonyl auxiliary. Eleven chiral imines **1** were subjected to the reaction under standard conditions, providing *β*-amino Weinreb amides **15** in up to 98% yield and 99:1 dr. Similar to the ester enolate-based additions,[12] *ortho*-substituted imines resulted in the highest diastereoselectivities (**15e-15j** in Scheme 9), while the imine derived from a heteroaromatic aldehyde furnished the lowest diastereoselectivity (**15k** in Scheme 9). Most of the products were purified *via* a standard GAP work-up.

3.3 Synthesis of amino ketones

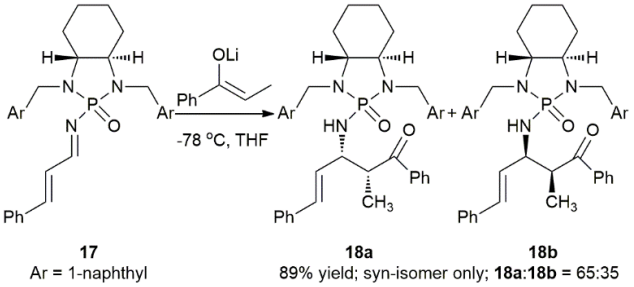


Representative examples:



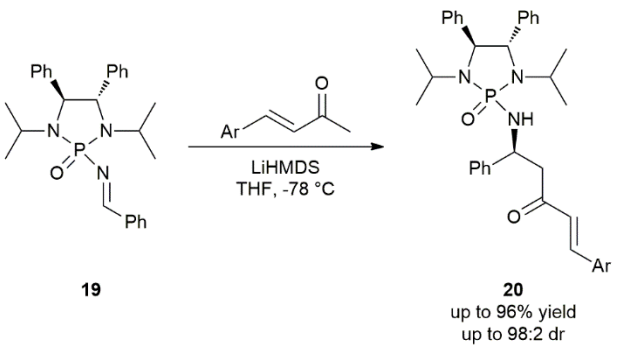
Scheme 10 Mannich-type reaction between chiral *N*-phosphonyl imines **12** and ketones.

Chiral *N*-phosphonyl imines **12** have also shown utility in reactions with various ketone enolates (Scheme 10).[16] Similar to several previous cases, LDA was found to be the best base for this Mannich-type reaction, but other bases, such as LiHMDS, KHMDS, and *n*-BuLi, decreased either the chemical yields or diastereoselectivities. Temperature was found to be crucial for the reaction, and raising the temperature to -20 °C nearly eliminated the desired reaction pathway. By employing LDA as the base and THF as the solvent, *β*-amino ketones **16-1** were obtained in good chemical yields (up to 89% yield) and excellent diastereoselectivities (up to >99:1 dr). Slightly higher diastereoselectivities were obtained for reactions of imines derived from 2-substituted benzaldehydes. The resulting chirality of the *β*-carbon center was assigned as *R*, and the asymmetric induction mechanism is believed to be similar to that of the aza-Darzens reaction [10,11] and the aza-Henry reaction (see section 5).[10, 17]

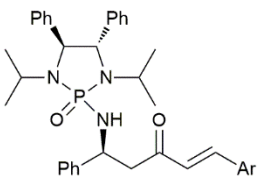


Scheme 11 Mannich-type reaction between chiral *N*-phosphonyl imines **17** and ketones.

When chiral *N*-phosphonyl imines **12** were reacted with propiophenone lithium enolates, *α*-alkyl *β*-amino ketones **16-2** with two chiral centers were generated in moderate to good chemical yields (Scheme 10).[18] The diastereoselectivities were well controlled for the major products of all substrates bearing *syn*-stereochemistry. For 2-MeO-substituted imines, the *syn*/*anti* ratio was as high as >99:1 (**16-2b** in Scheme 10). The use of butyrophenone lithium enolates reduced both yield and diastereoselectivity (**16-2c** in Scheme 10). Cinnamaldehyde-derived phosphonyl imine **17** can also react with the above anions under the standard condition, solely providing the *syn*-isomer with poor diastereoselectivity (**18a** and **18b** in Scheme 11).



Represntative examples:

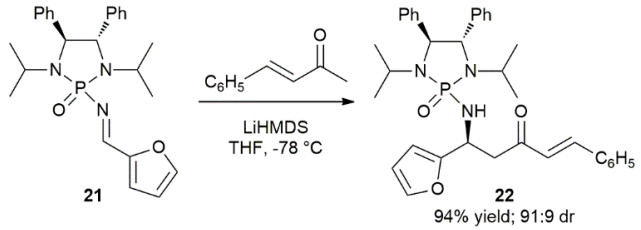


20a: Ph= 3-FC_6H_4, Ar=C_6H_5; 93%; 98:2 dr
20b: Ph= 3-$CF_3C_6H_4$, Ar=C_6H_5; 93%; 98:2 dr
20c: Ph= 1-Naphthyl, Ar=C_6H_5; 96 %; 96:4 dr
20d: Ph= 2-Naphthyl, Ar=C_6H_5; 96 %; 96:4 dr

Scheme 12 Asymmetric synthesis of *β*'-amino-*α*, *β*-enones **20**.

Subsequent investigation on addition reactions with *α*,*β*-unsaturated ketones was achieved with *N*-phosphonyl imines **19** (Scheme 12).[19] Unlike the above Mannich-type reaction of ketone enolates with imines **12**,[16,18] LiHMDS performed most efficiently as the base; other bases either gave lower yield or decreased diastereoselectivity. Raising the temperature decreased diastereoselectivities dramatically. Under the standard condition, various *N*-phosphonyl *β*-amino-*α*,*β*-enones **20** were synthesized in up to 96% chemical yield and 98:2 dr. The highest

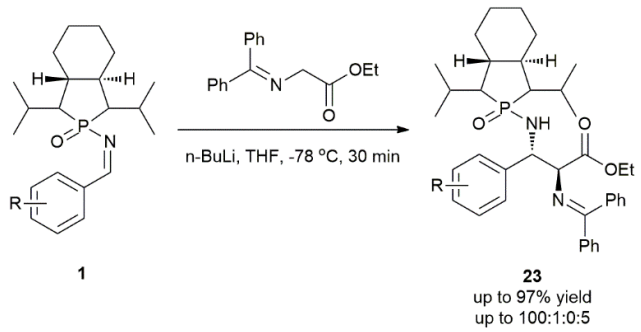
diastereoselectivities were observed in the cases of imine substrates containing a meta-substituted aromatic ring (**20a** and **20b** in Scheme 12), and the protocol was accessible to imines with a naphthyl ring (**20c** and **20d** in Scheme 12). Imine **21** with a furyl group also worked well, providing product **22** in 94% yield and 91:9 dr (Scheme 13).



Scheme 13 Synthesis of α-furyl chiral *N*-phosphonyl amine **22**.

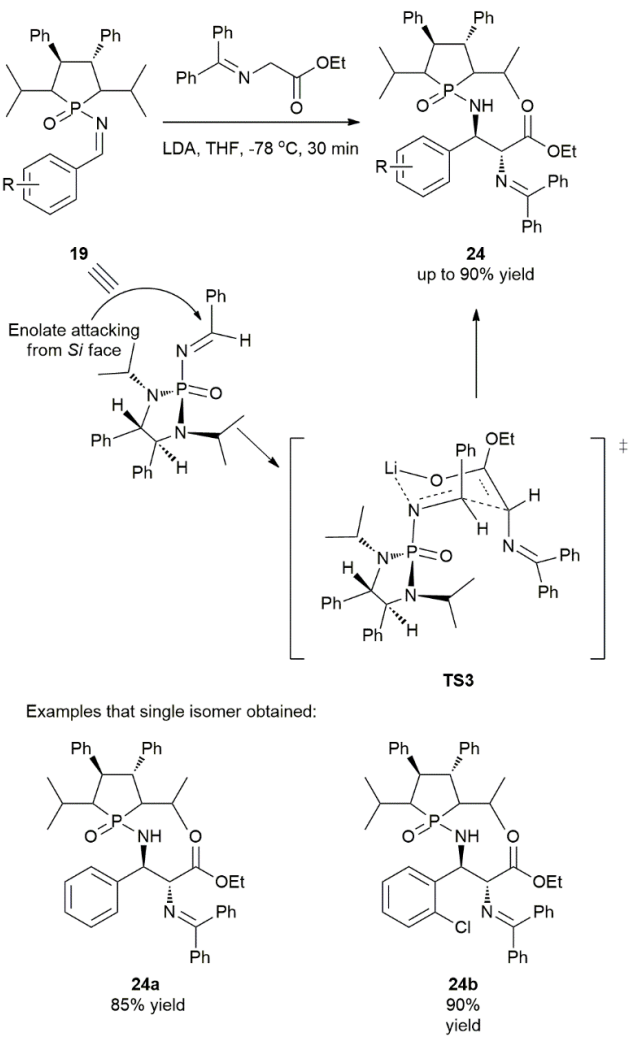
3.4 Synthesis of α, β-diamino esters

The synthesis of α,β-diamino esters, which are an important structure motif that exists in many biologically active compounds, has been extensively studied in *N*-phosphonyl imine chemistry. Both *anti* and *syn* isomers of α, β-diamino esters were obtained by using different anions.[20-22] The diamino esters **23** were synthesized from the reaction between lithium glycine enolate and phosphonyl imines **1** (Scheme 14) in excellent yields (up to 97%) and diastereoselectivities (up to 100:1:0:5)[20] Phosphonyl group **A** gave the highest diastereoselectivities and the *anti*-stereoisomer was obtained as the major product. *n*-BuLi was found as the most efficient base for the reaction, while KHMDS did not facilitate progression of the reaction, owing to the poor activation of the phosphonyl imine by the potassium cation. The reaction required the use of excess amounts of lithium glycine enolate. THF as the solvent showed the highest efficiency for both chemical yield and diastereoselectivity. The product was readily converted into free diamino ester.



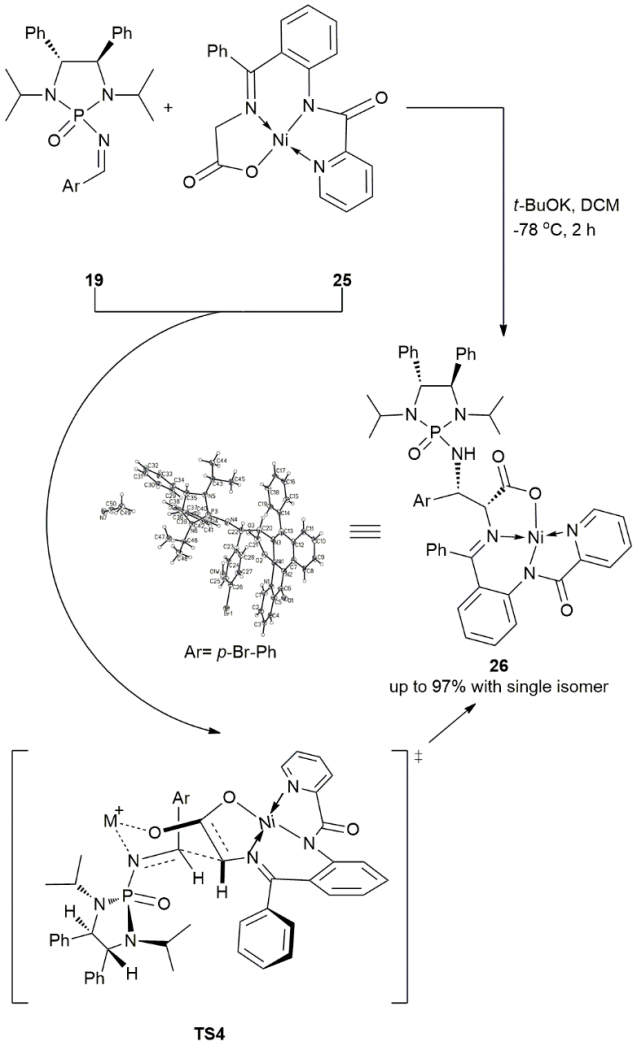
Scheme 14 Additions of glycine enolate to *N*-phosphonyl imines **1**.

Replacing phosphonyl imine **1** with **19** gave improved diastereoselectivity for the reaction between lithium glycine enolate and phosphonyl imines (Scheme 15).[21] Using LDA as the base and 5 equiv of lithium glycine enolate, the reaction ran to completion in just 30 min to afford diamino esters **24** in good chemical yields (72% - 90%). For the imines derived from non-substituted and 2-Cl-substituted benzaldehyde, a single isomeric compound was obtained (**24a** and **24b** in Scheme 15). The configuration of the products was assigned as (2*R*, 3*R*) and the excellent diastereoselectivity can be explained by a cyclic six-membered transition state **TS3** (Scheme 15). Attack of the *Z*-configured lithium enolate of the glycine ester onto the *Si*-face of the chiral phosphonyl imines resulted in the (2*R*,3*R*) configuration of diamino product **24**.



Scheme 15 Reactrion of glycine enolate with *N*-phosphonyl imines **19.**

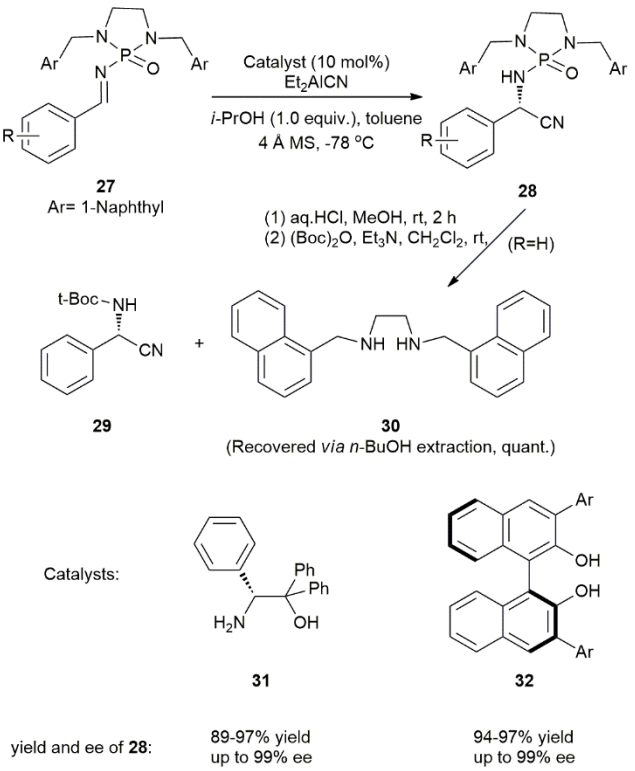
The following studies on the stereoselective GAP synthesis of (2*R*,3*S*)-α,β-diamino esters were carried out with **19** (Scheme 16).[22] To obtain the *Z*-enolate for *cis*-diamino ester formations, the Ni(II)-complex of glycine-derivative **25** was chosen as the enolate source. Different reaction conditions were examined for the reaction between **19** and **25**. Among the various organic and inorganic bases, *t*-BuOK was found to be the most effective, and the reaction reached completion within 2 h at –78 °C in CH_2Cl_2. A variety of *syn*-diamino esters were obtained in good chemical yields (91%-97%), and one single diastereoisomer was detected in each case by ^{31}P NMR spectroscopic analysis of the crude products. The reaction was proposed to proceed through a strict cyclic six-membered transition state **TS4** involving the *Z*-enolate, which accounted for the excellent diastereocontrol. All of the products were obtained through the GAP process *via* a one-time wash of the crude products with hexane/EtOAc (v/v = 2:1).



Scheme 16 The reaction of *N*-phosphonyl imines **19** with nickel(II)-complexed glycine ester enolate.

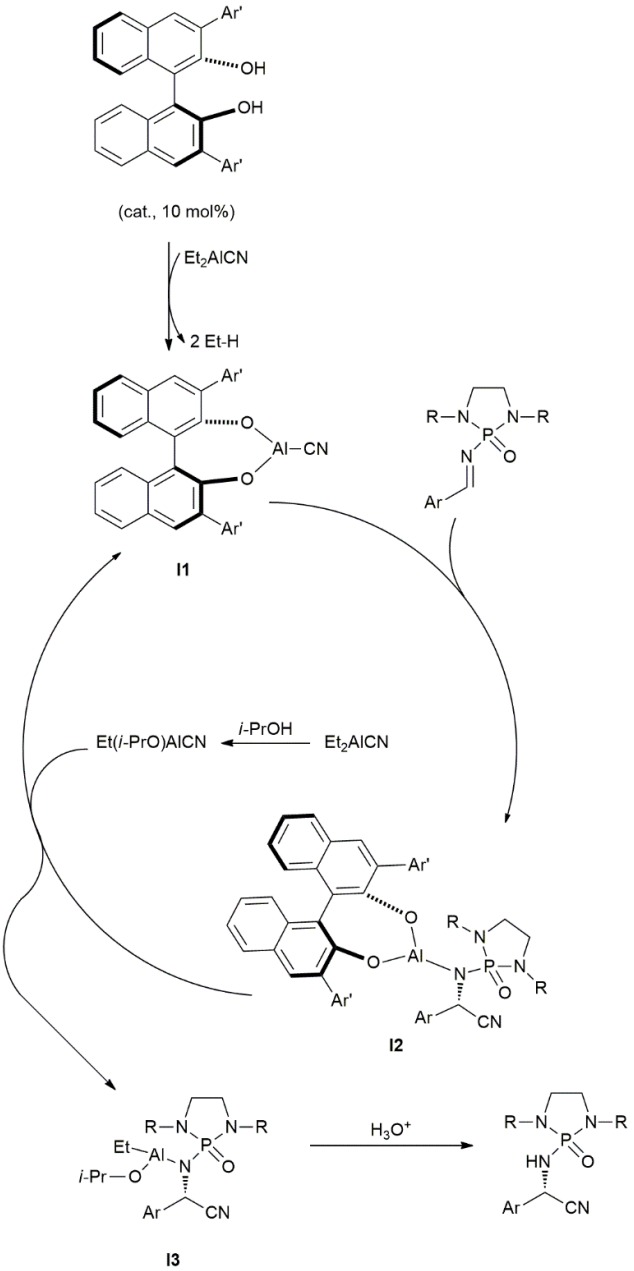
4 Strecker reaction of *N*-phosphonyl imines

Besides chiral *N*-phosphonyl imine chemistry, the asymmetric catalysis of achiral *N*-phosphonyl imines was investigated in 2010 (Scheme 17).[23-24] During the initial study, the addition of Et_2AlCN to *N*,*N*-dibenzyl *N*-phosphonyl imines by using *R*-(-)-phenylglycinol as the catalyst in presence of 4 Å MS and *i*-PrOH at low temperature (-78 °C) gave the amino cyanide in 85% yield and 47% ee. The use of *i*-propanol as an additive in toluene at -78 °C can substantially improve the reaction. It was noted that the premixing of Et_2AlCN with the aminoalcohol catalyst for at least 15 min to form the actual Al-complex species was also necessary. Further evaluation of the auxiliary groups proved that the replacement of the benzyl group with a naphthalen-1-ylmethyl group in the *N*-phosphonyl imines resulted in a higher enantioselectivity of 92% ee and yield of 89%. Additionally, the introduction of the naphthalen-1-ylmethyl group on the *N*-phosphonyl imines helped facilitate the GAP process. Among the *N*-protected and unprotected amino alcohols that were examined, (*R*)-2-amino-1,1,2-triphenylethanol **31** was proven to be most effective. Addition of Et_2AlCN to *N*-phosphonyl imines **27** derived from an aldehyde with an electron withdrawing or an electron donating group all afforded *N*-phosphonyl amino cyanides **28** in 89-97% yield and up to 99% ee (Scheme 17).



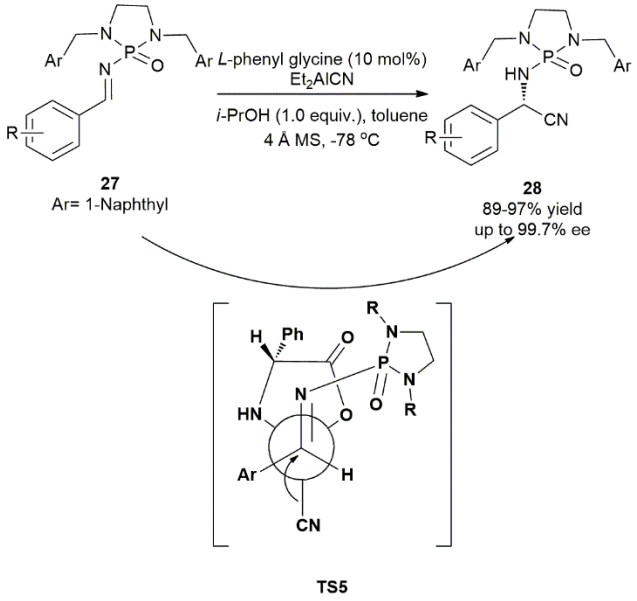
Scheme 17 Asymmetric Strecker reaction catalyzed by **31** and **32**.

The absolute configuration was determined by converting the product (R = H) to a known sample **29**, and the auxiliary **30** was readily removed and recovered quantitatively by treatment with HCl in methanol and a one-time extraction with *n*-butanol (Scheme 17). Similarly, various substituted BINOLs also showed effectiveness for this asymmetric catalytic process (Scheme 17). (*S*)-3,3'-di(*p*-Ph-phenyl)-BINOL **32** was found to substantially enhance the stereoselectivity and chemical yields. In the presence of (*S*)-3,3'-di(*p*-Ph-phenyl)- BINOL **32**, several *N*-phosphonyl imines **27** were subjected to the asymmetric Strecker reaction, providing the corresponding amino cyanide in 94-97% yield and up to 99% ee (Scheme 17). The reaction mechanism is proposed using the BINOL case for demonstration (Scheme 18). The formation of a catalytic complex **I1**, followed by cyanide anion delivery onto the C=N bond from the *Si*-face of *N*-phosphonyl imine, gave the intermediate **I2**. This intermediate is further converted to the original catalytic species **I1** *via* homo transmetallation by Et(*i*-PrO)AlCN, which was derived from the reaction of Et_2AlCN with *i*-PrOH. Adding *i*-PrOH into the system is crucial because it makes it possible to release **I1** and generate **I3**.



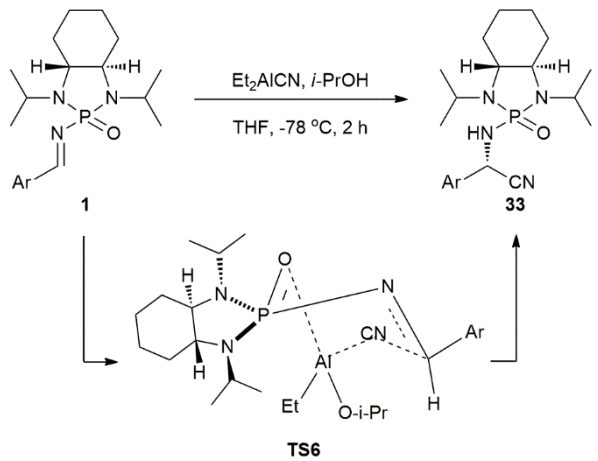
Scheme 18 Mechanism of asymmetric catalytic Strecker reactions.

Afterwards, the free natural amino acids were also found to catalyze the Strecker reaction of *N*-phosphonyl imines (Scheme 19).[24] Among the different amino acids employed in the reaction, *L*-phenyl glycine furnished the highest ee and chemical yields, and different *N*-phosphonyl imines **27** reacted with Et_2AlCN in the presence of *L*-phenyl glycine to provide amino cyanide **28** in 89-97% yield and up to 99.7% ee. A working model was proposed to explain the asymmetric induction (Scheme 19). In this model, the *N*-phosphonyl imine approaches the catalyst associated with the ^{-}CN nucleophile from the hindered side of the hydrogen, instead of the bulkier phenyl group, of the catalyst (**TS5** in Scheme 19).



Scheme 19 Asymmetric Strecker reaction catalyzed by *L*-phenyl glycine.

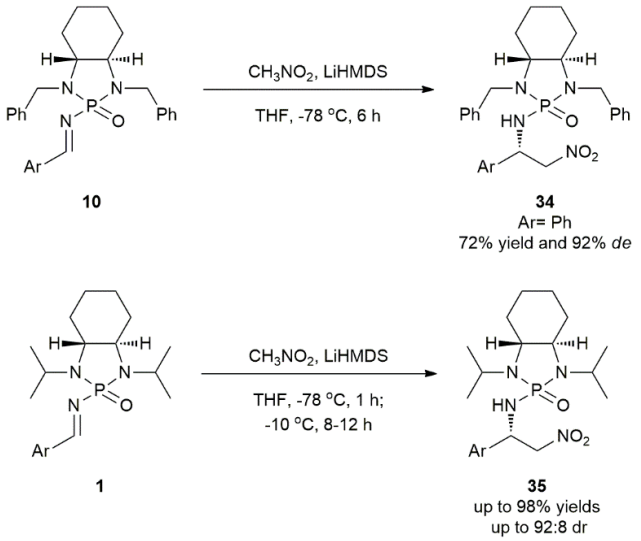
Meanwhile, the GAP Strecker reaction of chiral *N*-phosphonyl imines with Et_2AlCN as the electrophile has also been studied (Scheme 20).[25] A variety of chiral auxiliaries and solvents were examined, and chiral *N*-phosphonyl imines **1** in THF provided the best combination for achieving high yields and diastereomeric ratios. A number of chiral *N*-phosphonyl imines **1** reacted with Et_2AlCN in the presence of *i*-PrOH as additive, affording α-aminonitrile products **33** in excellent yields (94-98%) and diastereoselectivities (95:5 to >99%) (Scheme 20). The reaction underwent a GAP process.



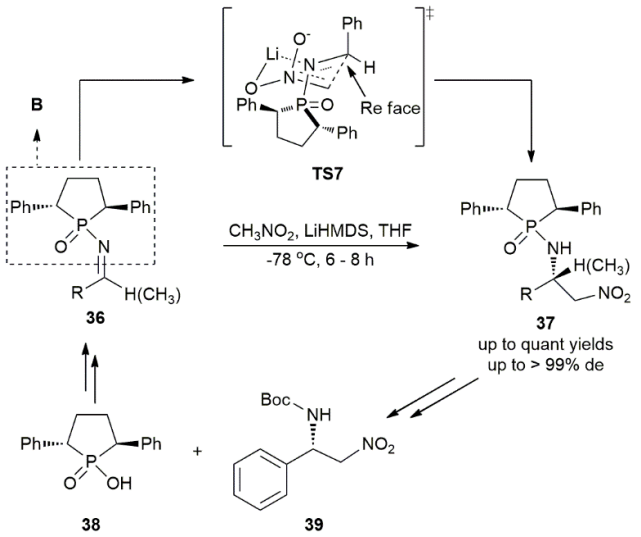
Scheme 20 Synthesis of chiral *N*-phosphonyl substituted *α*-amino nitriles.

5 GAP *N*-Phosphinyl and *N*-phosphoryl imine chemistry

The asymmetric Henry reaction of chiral *N*-phosphonyl imine chemistry using nitroalkane derived anions has been proven to be of a GAP process (Scheme 21).[10] Imines **1** underwent the aza-Henry reaction smoothly, providing an efficient protocol for the aza-Henry reaction with a broad substrate scope (Scheme 21).[17] Up to 98% yield and 92:8 dr have been achieved.

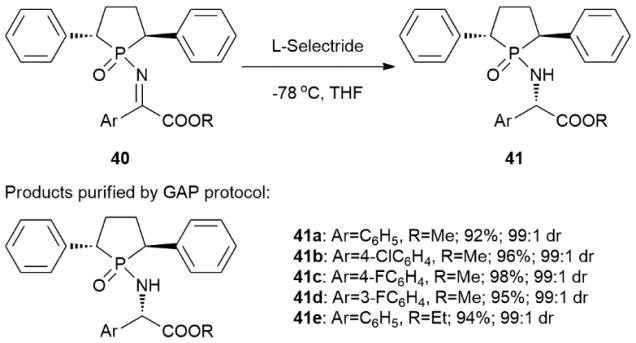


Scheme 21 aza-Henry reactions of chiral *N*-phosphonyl imines **10** and **1**.



Scheme 22 Asymmetric aza-Henry reaction using *N*-phosphinyl imines **36**.

By switching from an *N*-phosphonyl group to *N*-phosphinyl group **B**, both aromatic and aliphatic imines can readily prepared for the GAP aza-Henry reaction (Scheme 22).[26] The aza-Henry reaction between *N*-phosphinyl imine **36** and nitromethane proceeded smoothly with LiHMDS as the base at low temperature (-78 °C). Chiral *N*-phosphinyl imines showed higher reactivity toward the lithium nitronate when compared with their *N*-phosphonyl imine counterparts that required a higher reaction temperature (-10 °C) for complete consumption of the starting materials.[18] Products **37** were obtained in excellent yields and diastereoselectivities using GAP purification. This protocol can also use *N*-phosphinyl ketimines as the electrophilic substrates. The new phosphinyl auxiliary can be readily cleaved by treating the product with aqueous HBr solution to give phosphinoic acid **38**, which can be recycled for reuse. The stereoselectivity was rationalized by the cyclic transition state **TS7**, showing attack of the nitronate on the *Re* face of the *N*-phosphinyl imine (Scheme 22).

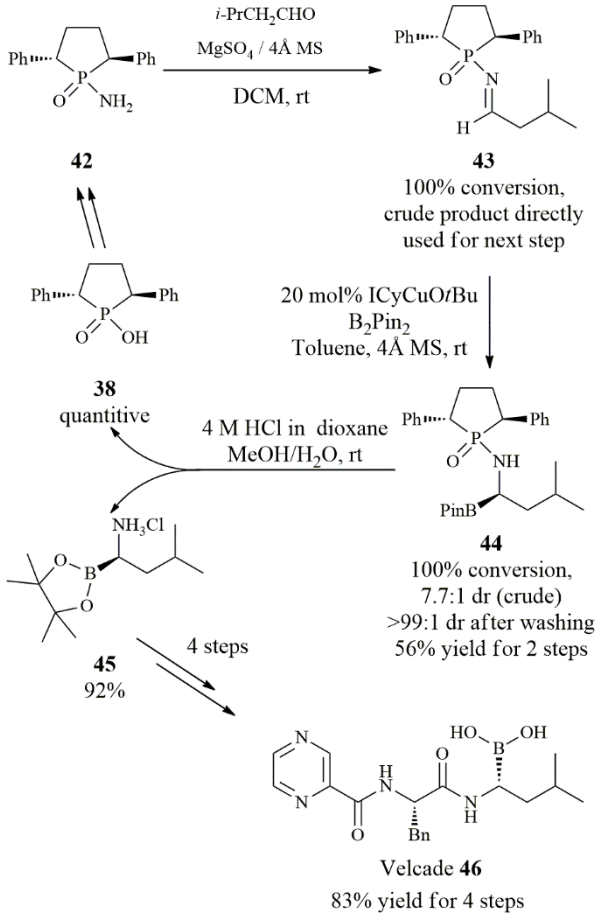


Scheme 23 Asymmetric reduction of α-imino esters **40**.

The asymmetric synthesis of α-amino esters has been performed *via* reduction of the chiral *N*-phosphinyl α-imino esters **40** (Scheme 23).[27] Among the several reduction agents, such as Hantzsch esters, silanes, DIBAL, and $NaBH_4$, L-selectride was found to be the most efficient in regard to yield and diastereocontrol when the reaction was performed in polar solvents. A series of α-amino esters **41** were obtained in excellent yields (up to 98%) and diastereoselectivities (up to 99:1 dr).

Very recently, the asymmetric borylation of *N*-phosphinyl imines **43** [28]has been studied and utilized for the synthesis of the anti-cancer drug Velcade (Scheme 24).[29] Aliphatic imine starting materials were obtained by reacting aliphatic aldehydes with *N*-phosphinyl amide in the presence of $Ti(OiPr)_4$. The crude *N*-phosphinyl imines are directly utilized for the borylation reaction. The aromatic imines can be synthesized in quantitative yield.

By replacing benzene with the less toxic toluene, complete conversion of the starting materials was achieved by using 2 equiv. of B_2Pin_2 and 20 mol% of ICyCuO^{t}Bu as the catalyst. A dr value of 7.7:1 was achieved, as revealed by crude ^{31}P NMR. The optically pure isomer (*dr* > 99:1) can be readily obtained by washing the crude mixture of the asymmetric borylation reaction with hexane to give 56% yield; the chiral *N*-phosphinyl auxiliary can be easily recovered after deprotection is finished. Several *N*-phosphinyl imines have been employed for the asymmetric borylation reaction.



Scheme 24 Asymmetric borylation of *N*-phosphinyl imines and Velacde synthesis.

The absolute configuration was determined by X-ray analysis as (*S*,*S*,*R*) (Fig. 3). After deprotection of the auxiliary by treatment with HCl, velcade **46** was synthesized by following the literature procedure[30] in 83% yield over 4 steps (Scheme 24).

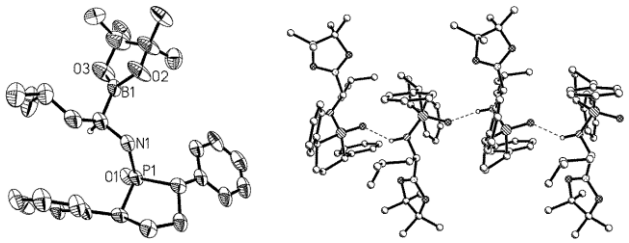
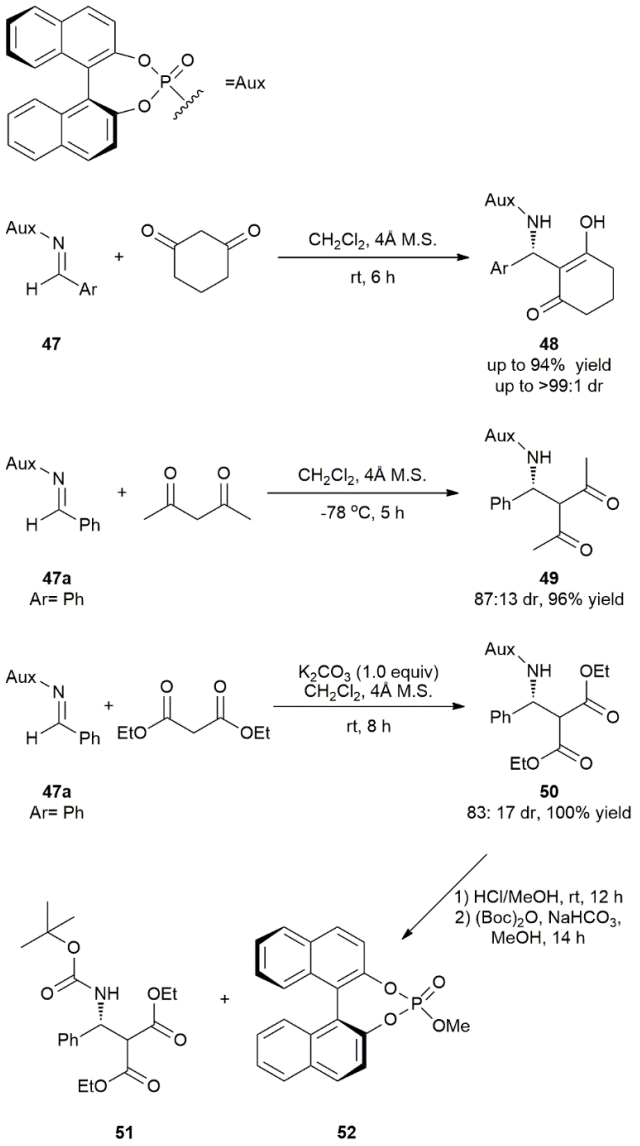
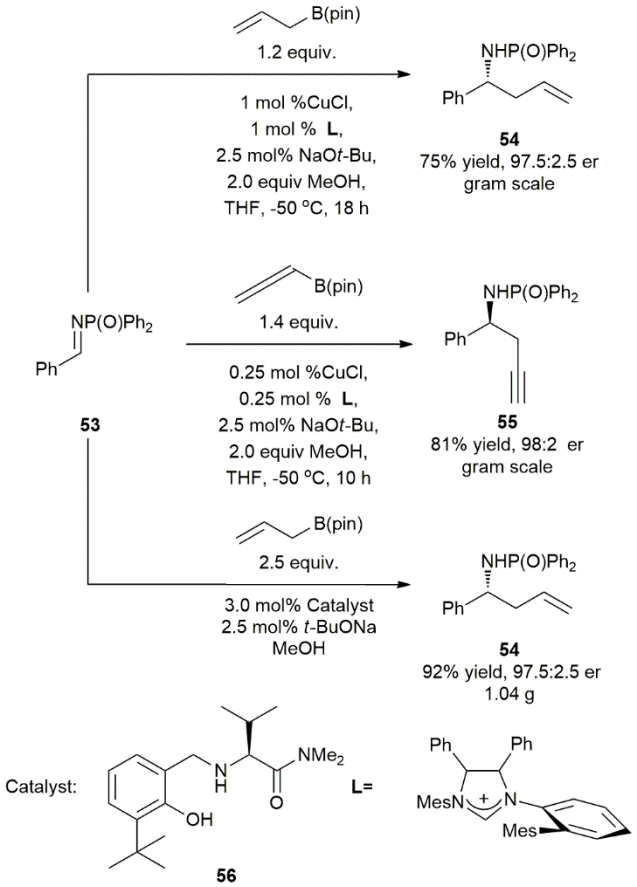


Fig. 3 X-ray structure of **44** and the intermolecular hydrogen bond in **44**.



Scheme 25 GAP Addition Reaction of *N*-phosphoryl imines.

Chiral *N*-phosphoryl imines **47** were also examined for the addition reaction with diketones to supplement *N*-phosphonyl imine chemistry (Scheme 25).[31] The reaction proceeded smoothly at rt without the use of any strong base. Different imines were subjected to the reaction with 1,3-cyclohexanedione and moderate to good yields (up to 94%) and good to excellent diastereoselectivities (up to >99:1 dr) have been achieved. Imine **47a** reacted with linear acetylacetone at -78 °C in 5 h, providing good diastereoselectivity (87: 13 dr) and an excellent yield (96%) (**49** in Scheme 25). For the reaction of diethyl malonate, K_2CO_3 was found to be necessary for good diastereoselectivity (83: 17 dr) and high yield (**50** in Scheme 25). The auxiliary was readily cleaved with HCl in MeOH to afford the phosphoric acid methyl ester **52** and the free amine. The free amine was protected with Boc_2O for determination of the absolute configuration.

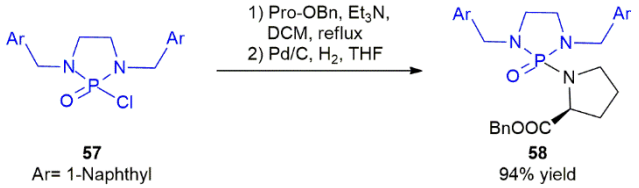


Scheme 26 Synthesis of homoallylic amines and propargylamines using *N*-phosphoryl imine **53**.

Along with the systematic investigation of GAP *N*-phosphinyl and *N*-phosphoryl imine chemistry, the catalytic enantioselective allyl addition using *N*-phosphinyl imine **53** as an electrophile has been successfully developed. The authors also found that the purification of products can be performed *via* GAP work-up without the use of column chromatography (Scheme 26).[32-34] The reaction affords propargylamines **54** on a gram-scale in good to excellent yields and enantioselectivities.

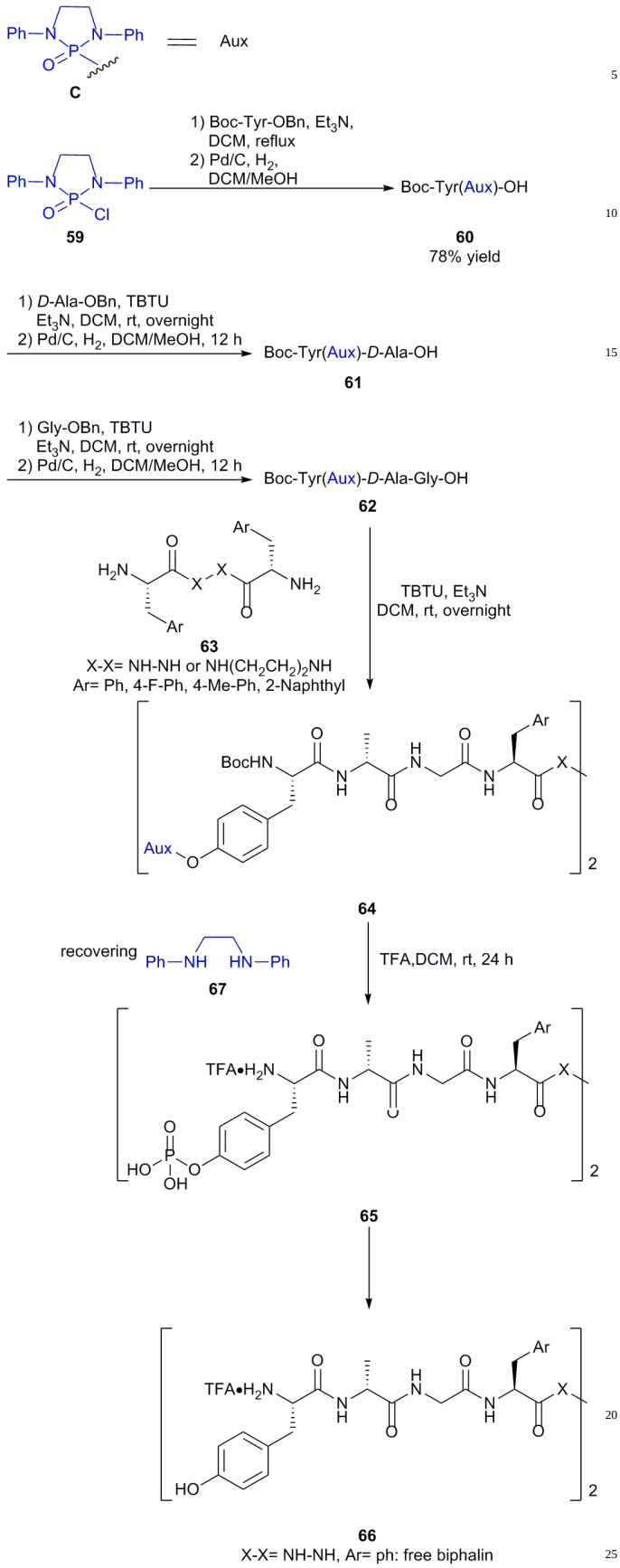
6 Peptide Synthesis

To further extend GAP chemistry, the synthesis of peptides attracted our attention. Since solid-phase-peptide synthesis (SPPS) was discovered in 1963,[35] several synthetic protocols have been developed to complement SPPS to ease the scale-up and to reduce the use of excess reagents and expensive resins for coupling reactions, particularly for synthesizing longer peptides.[36] The development of GAP peptide chemistry started with the protection of individual amino acids with phosphonyl chloride **57**.[37] The protection proceeded smoothly at 90 °C in the presence of triethyl amine and 4 Å MS in dichloromethane, affording the *N*-phosphonyl amino acid esters in good to excellent yields. The pure protected amino acid esters were obtained *via* GAP work-up by washing with hexane-DCM co-solvents (Scheme 27). The benzyl group can be readily removed by hydrogenation to provide *N*-phosphonyl amino acid **58** (Scheme 27).



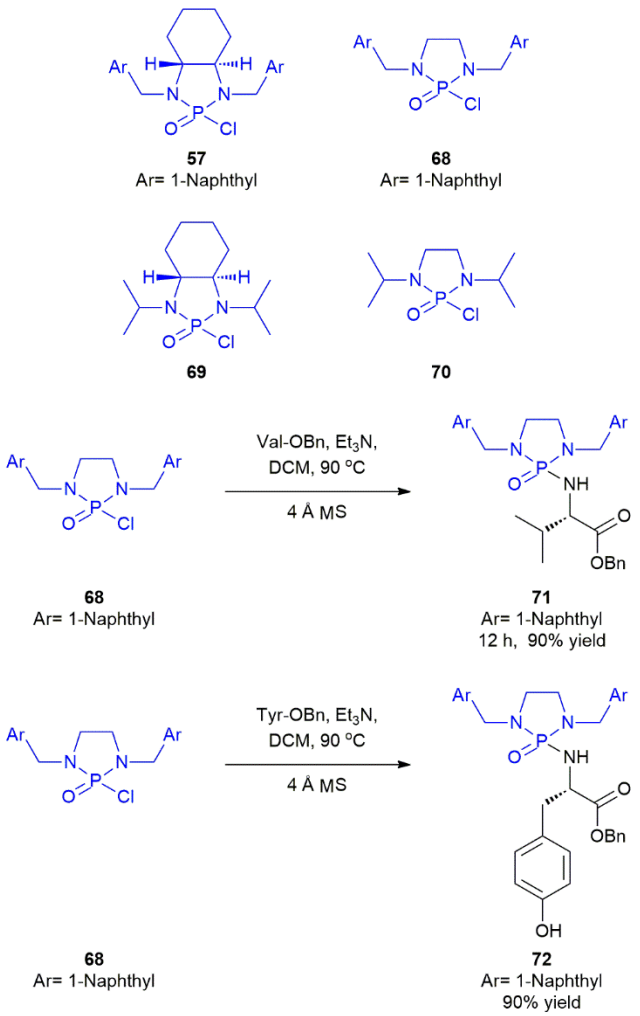
Scheme 27 GAP Protection of proline benzyl ester and its deprotection.

The protection was also performed on the hydroxy group of *L*-tyrosine with achiral phosphonyl group **C**. The resulting *O*-phosphonyl amino acid ester was then utilized in the synthesis of biphalin.[38] The protection of the above tyrosine benzyl esters with the *N*-*t*-Boc group, followed by hydrogenation gave *N*-*t*-Boc *O*-phosphonyl tyrosine **60** in 78% yield over two steps *via* GAP purification (Scheme 28). The dipeptide and tripeptide precursors **61** and **62** were obtained using standard coupling conditions (Scheme 28).[38f]



Scheme 28 GAP Synthesis of biphalin derivatives.

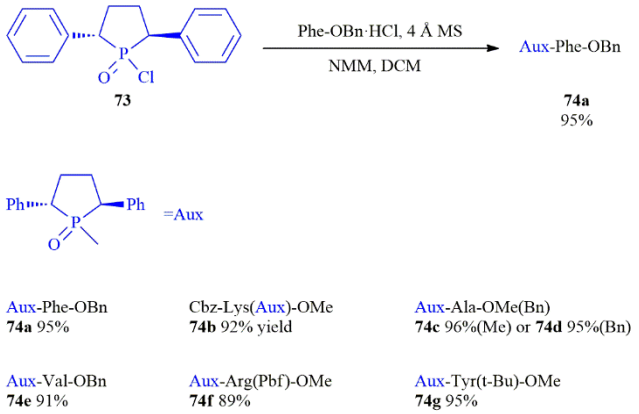
During the peptide synthesis, GAP work-up can be performed using different co-solvents such as ether, EtOAc-hexanes (v/v=1:2), and dichloromethane-hexanes (v/v, 1:100) to give pure products as white solids. The treatment of *O*-phosphonyl biphalin **64** (X-X = NH-NH, Ar = Ph) with trifluoroacetic acid (TFA) in DCM provided *O*-phosphoryl biphalin **65** (X-X = NH-NH, Ar = ph) in 88% yield with *N*,*N*'-biphenylethylenediamine auxiliary **67** recovered in 95% yield. *O*-phosphoryl biphalin derivatives **65** were obtained in good to excellent yields (78% to 92%). Removal of the phosphoryl moiety by treatment of *O*-phosphoryl biphalin with calf intestinal phosphatase (CIP) resulted in the free biphalin peptide **66** (X-X= NH-NH, Ar = Ph) in 87% chemical yield (Scheme 28).



Scheme 29 Systematic investigation of phosphonyl chloride in GAP amino acid ester protection.

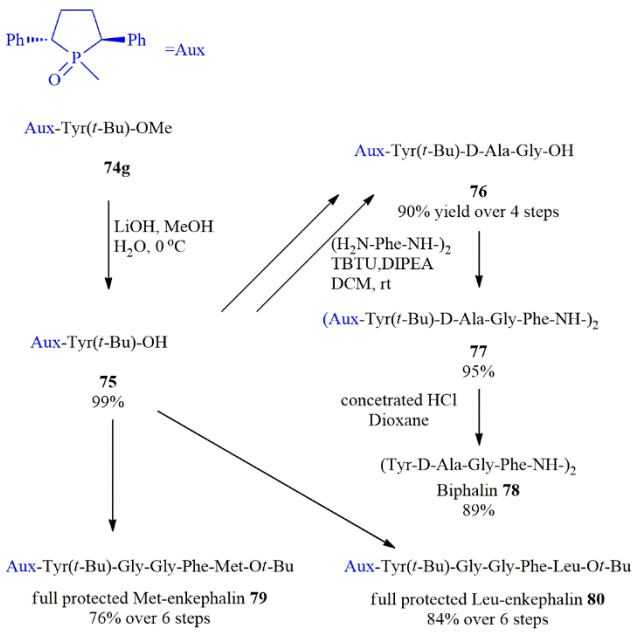
Several other phosphonyl groups have also been examined for the protection of amino acid esters.[39] Four different phosphonyl chlorides were applied for protection as shown in Scheme 29. By comparing the efficiency of different chlorides, the phosphonyl chlorides bearing a naphthyl methyl group gave higher yields than the ones with an *i*-Pr group. Interestingly, the protection of a sterically hindered amino acid, valine, proceeded more smoothly than others by treatment with chloride **68**. Using the achiral chloride **68**, the protection of the tyrosine benzyl ester at the

nitrogen atom occurred, providing *N*-phosphonyl tyrosine benzyl ester **72** in 90% yield.

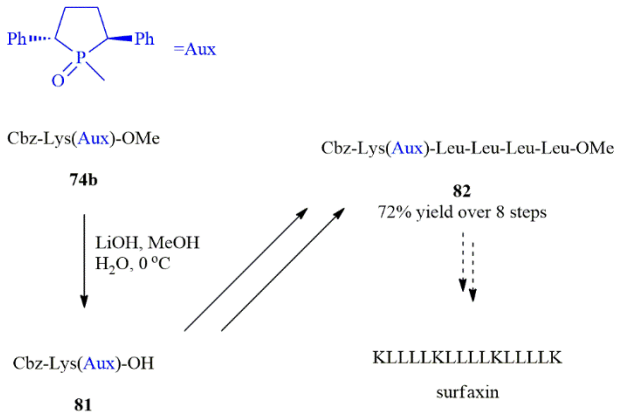


Scheme 30 GAP Protection of amino acid esters *via* phosphinyl chloride **73**.

Our chiral phosphinyl group was also applied to GAP peptide synthesis (Scheme 30).[40] The phosphinyl GAP protocol was conducted for the synthesis of biphalins, enkephalins,[41] and pentapeptide precursors for surfaxin (Scheme 31). During the biphalin synthesis, the deprotection of the GAP group occurred smoothly by treatment with concentrated HCl in dioxane. The phosphinoic acid was recovered by filtration, leaving free biphalin **78** as the only product in the aqueous phase. Analogously, the *N*-phosphinyl Leu-enkephalin **80** and the Met-enkephalin **79** were synthesized in 6 steps with 86% and 76% chemical yield, respectively. Dipeptide ester **74b** was synthesized and hydrolyzed to afford the corresponding acid. Hexapeptide methyl ester **82** was obtained using a similar procedure in 72% chemical yield over 8 steps. All of the precursors and the final peptide products of biphalin, enkephalin, and pentapeptide were purified simply by washing with either ether or a DCM/ hexane co-solvent (Scheme 32).



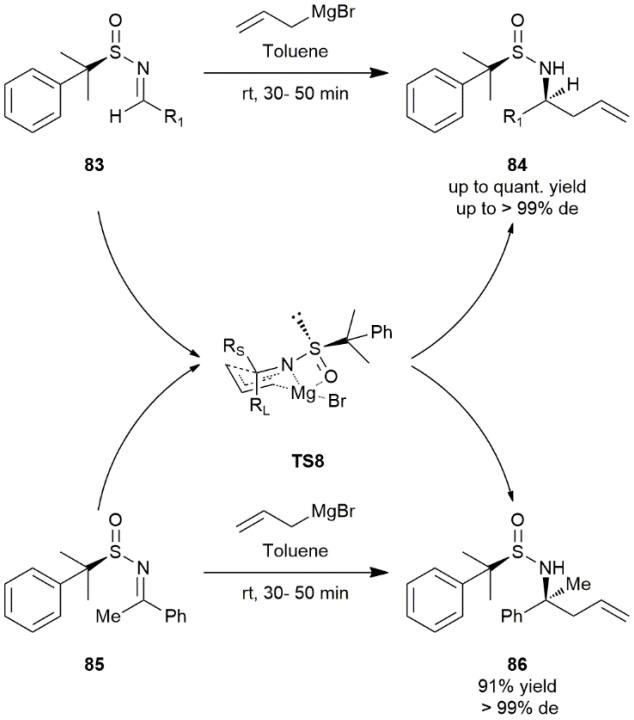
Scheme 31 GAP Synthesis of free biphalin and *N*-phosphinyl enkephalin.



Scheme 32 GAP Synthesis of pentapeptide **82**.

7 *N*-Sulfinyl GAP chemistry

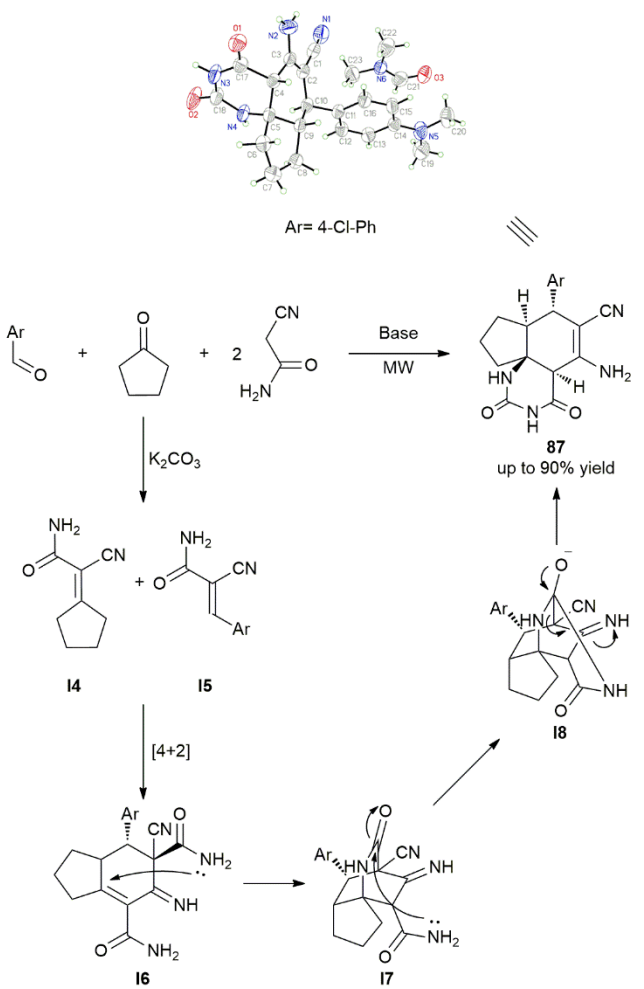
In addition to phosphonyl, phosphinyl and phosphoryl imine chemistry, GAP chemistry is also accessible to the reactions of sulfinylimines (Scheme 33).[42] Given the fact that the P=O bond polarity is responsible for solid product formation and GAP purification, a similar result was anticipated to exist for the polar S=O bond in *N*-sulfinyl products.[42] For this purpose, a new sulfinyl auxiliary was designed and synthesized to combine the advantages of *p*-tolylsulfimines (aromatic chromophore) and *t*-butylsulfimines (chemical stability) (Scheme 33). The chiral (*Rs*)-2-phenyl-2-propyl sulfinimine **83** was synthesized and first applied for its reaction with allylmagnesium bromide. Excellent yields (up to quant. yield) and diastereoselectivities (up to >99%) have been achieved at room temperature instead of -78 °C as reported in the literature. The protocol is accessible to ketimine **85** as well. The resulting homoallylic amines (**86**) bearing a tertiary carbon center were obtained in good chemical yield (91%) and excellent de (>99%). The pure homoallylic amines were obtained by washing the crude products with hexane. The '*S*' configuration of the newly generated chiral center is explained by using a chair like transition state **TS8**.



Scheme 33 Asymmetric GAP allyl addition using sulfinylimine.

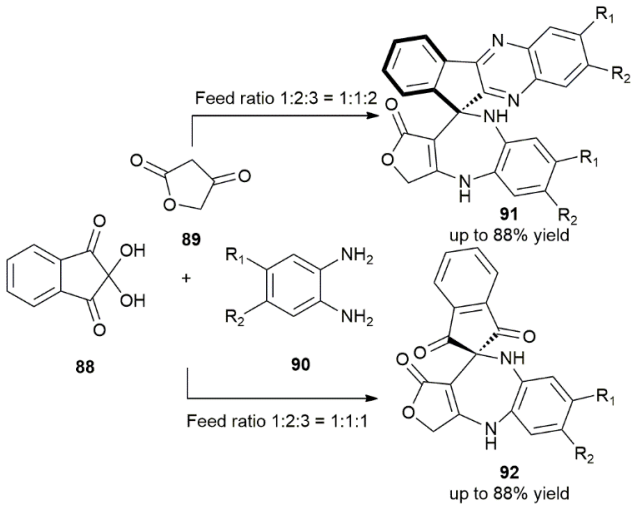
8 GAP chemistry in multicomponent reactions

As mentioned earlier, GAP chemistry is not limited to well designed groups. Newly formed functionalities which enable purification by washing without the use of column chromatography is also covered by GAP concept and technology. For example, domino multicomponent reactions for the synthesis of multi-functionalized quinazolines can be carried out *via* GAP work-up (Scheme 34).[43] As is depicted in Scheme 34, several polar functional groups, such as cynao, urea, amine, amide, and alkenyl moieties, exist in the resulting products **87** with the adequate solubility of product **87** for GAP washing.



Scheme 34 Four-component domino reaction leading to multi-functionalized quinazolines.

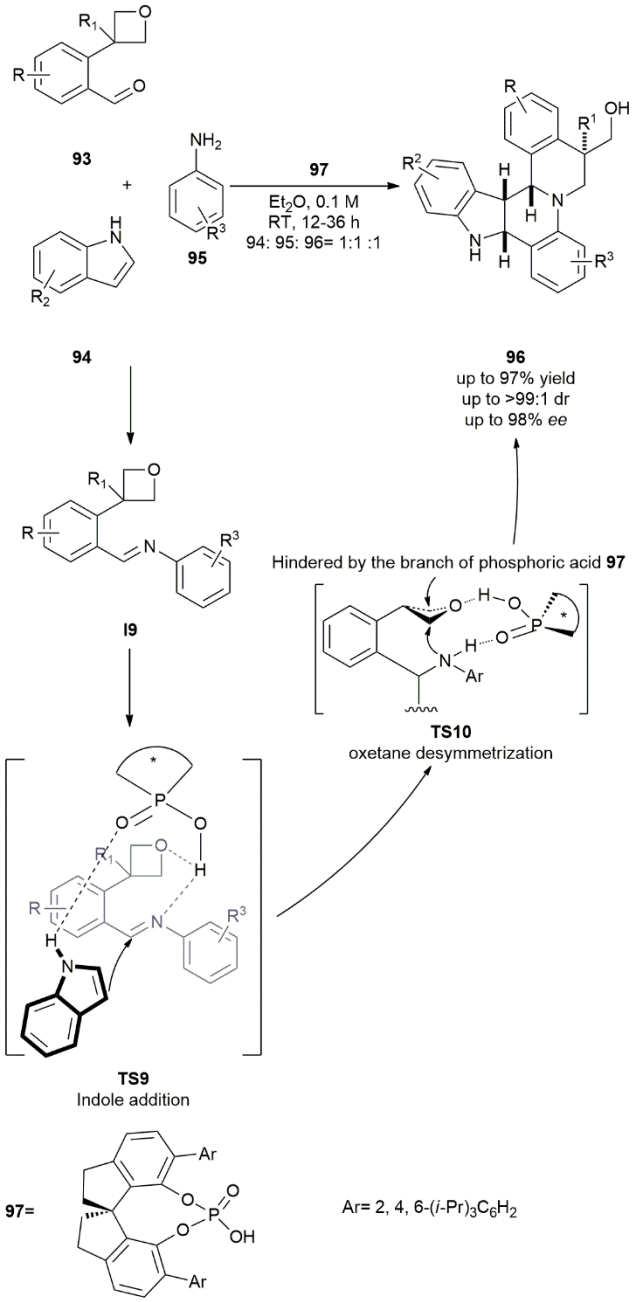
The diastereochemical control was rationalized by the proposed mechanism in Scheme 34. The key steps involve tandem formation of two different Knoevenagel intermediates **I4** and **I5**. The 4+2 addition of **I4** and **I5**, followed by sequences of intramolecular nucleophilic substitutions, gave the quinazoline as the final product. The resulting pyrido[3,4-*i*]quinazoline derivatives **87** are of importance for organic and medicinal research.



Scheme 35 GAP multicomponent reaction towards synthesis of spiro-substituted benzo[b]furo[3,4-e][1,4]diazepine derivatives **91** and **92**.

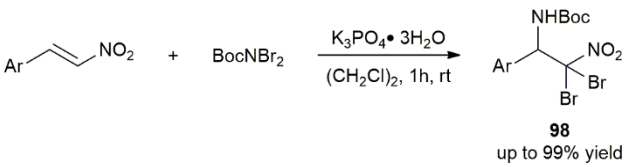
Subsequent work in GAP multicomponent reactions was achieved in the water phase. The water phase synthesis of spiro-substituted benzo[b]furo[3,4-e][1,4]diazepines in a GAP manner was developed in 2011 (Scheme 35).[44] Under microwave irradiation, the reaction of 2,2-dihydroxy-2*H*indene-1,3-dione **88** with tetronic acid **89** and benzene-1,2-diamine **90** in HOAc at 100 ^{o}C afforded products **91** in 82% yield within 15 min. Further evaluation revealed that by employing HOAc as the additive, the reaction proceeded in water in 85% yield. Under similar conditions, a variety of spiro-substituted benzo[b]furo[3,4-e][1,4]diazepine derivatives **91** were synthesized in good chemical yields(up to 88%). By changing the ratio of **88**: **89**: **90** to 1: 1: 1, a series of diazepine derivatives **92** can be obtained efficiently. As is stated in the above quinazoline synthesis, the polar functional groups lead the direct precipitation of the products, and the pure products **91** and **92** were obtained by filtration and washing with 95% EtOH.

Furthermore, the asymmetric catalytic version of a multicomponent reaction was described in a GAP manner by Zhu, Sun and co-workers (Scheme 36).[45] Chiral spiro phosphoric acid **97** was employed as the catalyst for a domino reaction. The reactants **93**, **94**, and **95** formed two rings with 4 stereogenic centers to afford polycyclic alkaloid-type products **96** in moderate to good yields (up to 97% yield) and excellent stereoselectivities (up to >99:1 dr and up to 98% *ee*). The stereochemical control was explained by the proposed 3-step mechanism. The reaction of **93** and **94** afforded imine intermediate **I9**. **I9** underwent indole addition, and oxetane desymmetrization controlled by the transition state **TS9** and **TS10** respectively, providing products **96** in good stereoselectivities. The authors reported that all of the starting materials **93**, **94**, and **95** as well as the catalyst **97** are soluble in diethyl ether with product **96** having low solubility. Product **96** directly precipitated during the reaction. Several other GAP multicomponent reactions have also been reported recently.[46]



Scheme 36 GAP synthesis of polycyclic alkaloid.

GAP chemistry has been extended to the aminohalogenation reaction (Scheme 37).[47] Given that several polar groups, like nitro, *t*-Boc, and two bromo moieties, exist in the resulting products **98**, GAP purification can be achieved efficiently. Products **98** were purified by washing the crude mixture with hexane. The various nitrostyrene derivatives were employed for the aminohalogenation reaction on a gram-scale to give excellent yields.



Scheme 37 GAP Aminohalogenation reaction of nitrostyrenes.

Conclusions

The GAP chemistry and technology is anticipated to play an increasingly important role for organic and medicinal synthesis. By utilizing the advantages of well-designed functional groups, nearly all organic reactions can be conducted *via* the GAP work-up without using column chromatography. GAP chemistry will help to solve global problems and issues that are related to waste production, pollution, energy consumption, safety, expenses, manpower and efficiency, etc. It can also greatly accelerate the process of drug discovery and development in the pharmaceutical industry.

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Notes and references

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‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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