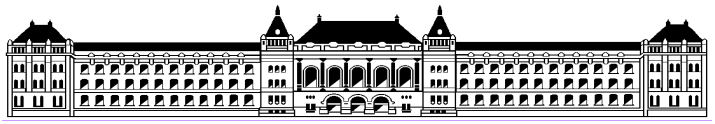

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Stereoselective synthesis of α-aminophosphinic acids and derivatives

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Ph.D. Tesis

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1. Antecedents and aims

In the past twenty years, considerable attention has been paid to the synthesis of α-aminophosphonic and α-aminophosphinic acids (Figure 1), because the phosphonic and phosphinic acids are the phosphorous analogues of α-aminocarboxylic acids, and therefore have biological importance both in itself and as a building block for peptides. Despite of its importance, there is no enantioselective synthesis for α-aminophosphinic acids in the literature.

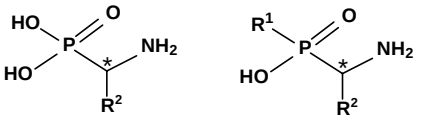
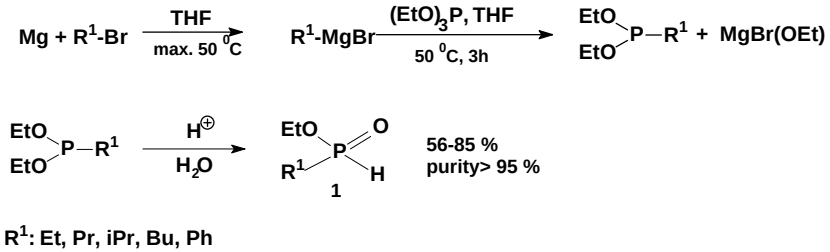


Figure 1

2. Results

2.1 A simple, generally applicable method was elaborated for the synthesis of **1** H-phosphinates, which are the precursors of α-aminophosphinic acids (Scheme 1).

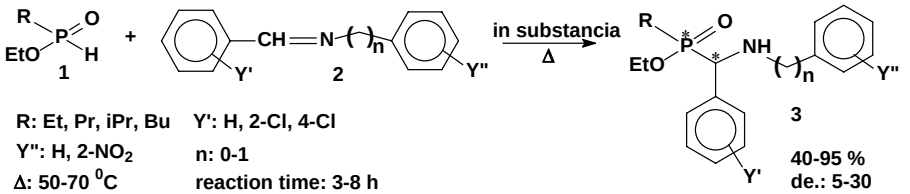


Scheme 1

2.2 The **3** α-aminophospinates were synthesised by the reaction of the **2** achiral imine with the **1** H-phosphinate (Scheme 2).

The ratio of diastereomers was established by means of ^{31}P-NMR measurements. The results demonstrate in all cases a slight extent of diastereoselectivity, some tendencies can, however, be observed. Comparing the effect on the diastereoselectivity of substituted imines **2**, I found that the imines having orto chloro-substituent on the α-benzene ring gave better selectivity than para- or unsubstituted ones, probably due to

the steric effects during the addition. The *N*-substituent of the imine (benzyl or phenyl) exerts only a small effect on the diastereoselectivity.

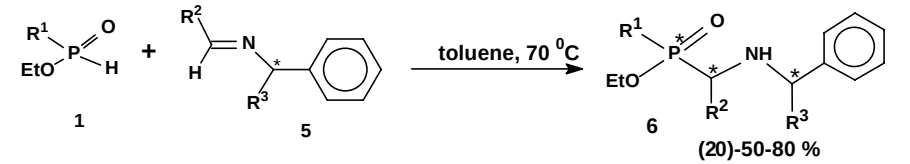


Scheme 2

In conclusion, I observed, there is no need catalyst or lithium salt to formation of diastereoselectivity and it can be affect slightly with type of solvents.

2.3 In further part of my work, numerous **6** amiphosphinates were synthesised by the reaction of **1** H-phosphinates and **5** chiral imines. The chiral imines were prepared from aldehyde and chiral amines, such as phenylethyl amine, phenylglycinol methylether and phenylglycinol benzylether (Scheme 3).

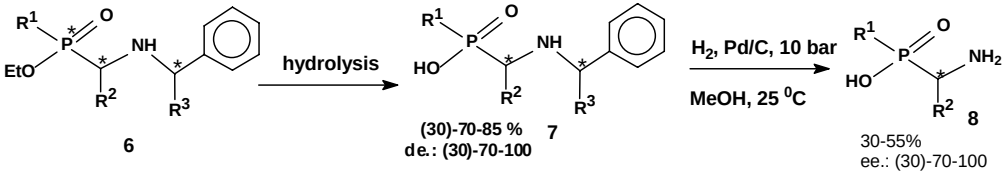
I found that the addition results in mixture of four diastereomeric pairs due to the attack of the prochiral phosphinate to the prochiral C-centre of the C=N bond forming two new stereo centres and the configuration of the carbon atom in the chiral auxiliary is fixed (namely *S*).



Scheme 3

2.4 The desired **8** free aminophosphinic acid was obtained in two steps. The removal of ethyl ester was performed by hydrolysis using hydrochlorid acid (R^3: Me) or hydrobromide acid in glacial acetic acid (R^3: CH_2OMe, CH_2OBz). The stereodirecting

group was removed by hydrogenolysis. The yield and the enantiomer excess varies from modest to excellent (Scheme 4).



Hydrolysis: R^3=Me: cc. HCl, reflux, 8 h; R^3=CH_2OMe, CH_2OBz: HBr in glacial acetic acid, 1 day, 25 ^{0}C

Scheme 4

Starting from phenylethylamine, phenylglycinol methyl or benzylether, the enantiomeric excess are excellent in **8** phenylphosphinic acids having aromatic substituents on the α-carbon atom, but having aliphatic substituents the ee. values are lower. Using propyl-H-phosphinate in the addition, the ee. values was modest except isobuthyl group on the α-carbon atom.

The only known compound is the **8a** (R^1, R^2: Ph) α-phenylphosphinic acid having a negative sign of optical rotation, which was prepared by us as well, and its absolute configuration is also known, namely *R*. I assumed that the others also having a negative sign of optical rotation have *R* configuration, too, so the *S* configuration in both type of chiral auxiliary induces *R* configuration on the α-carbon atom.

2.5 A new analytical method was elaborated. Running the ^{31}P-NMR spectra of the reaction mixture of the addition I always found four peaks, two major and two minor. After the hydrolysis of the **6** ester only two isomers can be observed due to the loss of chirality on the phosphorus atom. Therefore the ratio of the two peaks consist of the enantomeric ratio of free aminophosphinic acid, which is similar to the sum of the two major peaks in **6** aminophosphinates. It means that the enantiomeric excess can be calculated directly from the ^{31}P-NMR spectra of the addition reaction mixture. To control this calculation, I removed the protecting group from the NH, and methylated the free acid by means of diazomethane. The diastereomeric ratio of the methyl ester is very similar that of the **7** *N*-protected acid. It also means that there is no racemization via the hydrolysis and the hydrogenolysis. A slight improvement in the

ee was also observed that occurs during the working up processes of the hydrolysis and hydrogenolysis.

2.6 I found correlation between the diastereomeric ratio and electronic or steric effects of the substituents (Figure 2). Only a few curiosity was observed, according to a calculation by the ee. for all model compound as the method was mentioned above. As one can see on the figure, the oxigen containing chiral auxiliaries caused smaller chiral induction than the α-methylbenzylamine chiral auxiliary both in the case of phenyl- and propylphosphinates. Moreover that in the case of α-methylbenzylamine the chiral induction does not depend on the substituent of the α-carbon atom when there is a phenyl substituent on the phosphorus, while the chiral induction strongly depends on the substituent of the α-carbon atom when there is a propyl substituent on the phosphorusatom.

Comparison of the enantiomer excess

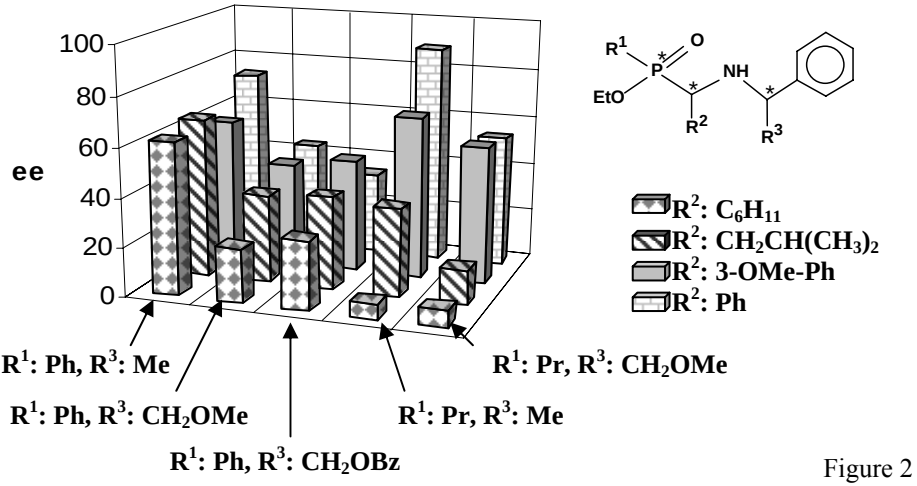
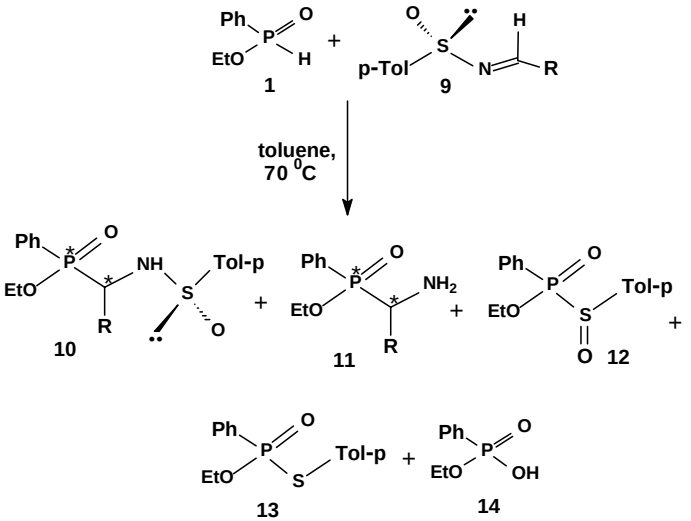


Figure 2

2.7 Using enantiopure **9** sulfinimines as chiral auxiliary I observed the formation of thiophosphonic acid ester **13,** phenylphosphonic acid monoethyl ester **14,** phosphonyl p-tolylsulfoxide **12,** and unprotected aminophosphinic acid ester **11** beside the desired α-aminophosphinate **10** (Scheme 5)**.**

The mechanism of products formation was assumed as well.

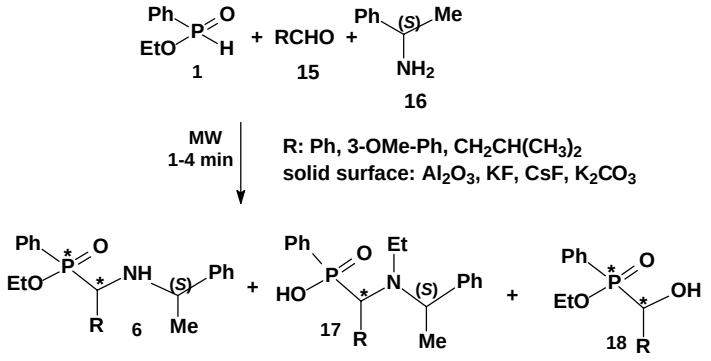
Removal of the N-sulfinyl auxiliary and hydrolysis of the ethyl esters from the diastereomers of **10** was achieved in one step resulting in **8** α-aminophosphinic acid in modest enantiomeric excess (ee. 20-40).



Scheme 5

2.8 Henceforward, the aminophosphinate forming reaction was studied under microwave circumstances as well. Because addition of H-phosphinates to imines resulted only low diastereoselectivity, I tried three component Kabachnik-Field reaction of H-phosphinate, aldehyde and (*S*)-phenylethylamine on solid surface, at 235 MW, which resulted two by product, namely **18** α-hydroxy-phosphinate and an **17** *N*-ethylated compound (Scheme 6).

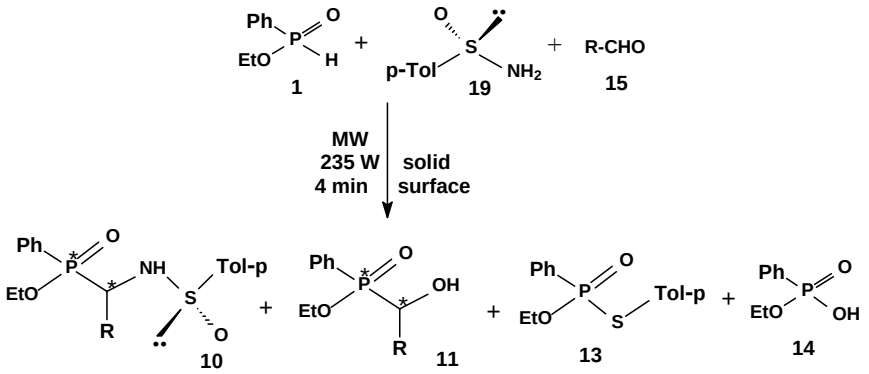
I found that on the surface of alumina or potassium-fluoride, the ratio of **17** derivative was grown with accession of reaction time and on higher efficiency of microwave, simultaneously the diastereoselectivity was decreased. In the presence of cesium-fluoride, the four diastereomer of aminophosphinate was nearly the same. Using potassium-carbonate as a solid surface, only the **17** derivative arose with high conversion. Interestingly, in case of aliphatic substituent of the α-carbon atom, this type of by product was not observed.



Scheme 6

The effect of the chiral induction on the carbon atom was determined after hydrolysis, the de. of the N-protected aminophosphinic acids was modest to good, so the diastereoselectivity was only slightly decreased compared to the diastereoselectivity in toluene.

2.9 Starting from **19** (*S*)-sulfinamines, **15** aldehyde and **1** phenyl-H-phosphinates in microwave reactor, **10** aminophosphinates was obtained in case both aliphatic and aromatic aldehyde (Scheme 7).



R: Ph, 2-Cl-Ph, 3-OMe-Ph, $CH_2CH(CH_3)_2$, c-C_6H_{11}; solid surface: Al_2O_3, KF, K_2CO_3

Scheme 7

On the surface of alumina, only **13** thiophosphonic acid ester and **10** aminophosphinates was observed with modest conversion and good diastereoselectivity. Staring from isovaleraldehyde, tiophosphonic acid ester was

obtained, such as earlier in case of toluene. In the presence of potassium-carbonate, **13** derivate was not arisen, even aliphatic aldehyde. This type of carrier caused the best result in diastereoselectivity and conversion, because only two diastereomer of **10** was observed from the possible four. These aminophosphinates was work-up and deprotected resulting **8** aminophosphinic acids moderate yield and low/moderate enantiomeric excess (ee.: 5-30). It means that the chiral induction affect on the phosphorus atom, the diastereoselectivity on the carbon atom is low.

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