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CATALYTIC STEREOSELECTIVE SYNTHESIS OF AMINOPHOSPHONIC ACID DERIVATIVES BY MICHAEL-ADDITION

Theses

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1. Introduction

Aminophosphonic acids can be considered as phosphorus analogues of amino acids. Only in recent decades has it become clear to what extent α-, β- and γ-aminophosphonates and their phosphapeptides occur in nature primarily in animal tissues and fungi. The "exchange" of the carboxyl group carbon to the phosphorus atom results in significant differences in both chemical and biological properties. Due to the tetrahedral structure of the phosphonic acid, these compounds can be considered as a stable analogue of the transient state in the construction and hydrolysis of the CONH bond in the peptides. As a result, they have many interesting uses as enzyme inhibitors, either alone or in peptide chains. Their physiological effects include modulation of brain function and antihypertensive, antibiotic and antiviral properties, and widely used herbicides.[1] Due to their biological role, it is worthwhile and necessary to prepare the individual enantiomers of the aminophosphonic acids containing the chiral carbon.

My doctoral thesis was conducted by Zsuzsa Jászay at the Department of Organic Chemistry and Technology, Budapest University of Technology and Economics.

In my research, I investigated the potential of catalytic stereoselective C-C coupling reactions to produce precursors of α- and β-aminophosphonic acids. We chose the C-C coupling because, unlike the P-C linkage at the start of our research, there were hardly any literary examples. On the other hand, by C-C coupling numerous types of functionalities of substituents could be incorporated into the molecules. The catalytic method was chosen because, if the appropriate catalyst is found, this makes for a simpler and more environmentally friendly synthesis, as if an asymmetric induction was introduced by incorporating a chiral auxiliary group.

2. Literature

By now, the literature on the synthesis and biological use of *α*-aminophosphonates is very large and the number of stereoselective syntheses is also rapidly increasing over the past decade.[2] Despite their natural occurrence and biological activity of *β*-aminophosphonates,

[1] (a) Kukhar, V. P., Hudson, H. R. (szerk.): Aminophosphonic and phosphinic acids, John Wiley & Sons, Chichester 2000. (b) Orsini, F.; Sello, G.; Sissi, M. *Current Med. Chem. J.* **2010**, 17, 264-289.

[2] (a) Ordonez, M.; Rojas-Cabrera, H.; Cativiela, C. *Tetrahedron* **2009**, *65*, 17-49. (b) Albrecht, Ł.; Albrecht, A.; Krawczyk, H.; Jorgensen, K. A. *Chem.- Eur. J.* **2010**, *16*, 28-48. (c) Ordonez, M.; Viveros-Ceballas, J.; Cativiela, C. *Curr. Org. Synth.* **2012**, *9*, 310-341.

much fewer publications were released.[3]

In the strategy for the synthesis of both α- and β-aminophosphonates, the desired compounds can be obtained by forming a C-P, C-C, C-H and C-N bond. If the target is an optically active aminophosphonate, the asymmetric induction can be achieved either by the temporary incorporation of a chiral group into one of the starting materials, which is eliminated at the end of the recovery, or by means of achiral or racemic starting compound, using chiral catalysts. The latter method provides greater variability and is more material-efficient. In this dissertation, I only dealt with this catalytic method. The chiral units of the catalysts described in the literature are most often BINOL, SALEN, monosaccharide, amino acid, cinchona derivative, more rarely a tartaric acid derivative, e.g. TADDOL. The crown ether[4] and organocatalysts[5] can be made by functionalization from the above chiral units.

3. Experimental methods

Methods of preparative organic chemistry were used to prepare aminophosphonate precursors and catalysts. The progress of the reactions was followed by thin layer chromatography. The crude products were purified by column chromatography (catalysts by preparative thin layer chromatography). The structure of the materials was confirmed by spectroscopic methods (IR, ^{1}H-, ^{13}C-, ^{31}P-NMR, MS). The enantiomeric excess was determined by HPLC containing a chiral support. The theoretical calculations were based on GAUSSIAN 09 and wB97 XD, 6-31G* packages, and the optimization of the structures was performed using the DFT method. The solvent was taken into account by the SMD method.

4. Results

Protected aminomethylenephosphonate, α-nitroethylphosphonate and cyanomethylene phosphonate were used as synthons of catalytic stereoselective Michael additions. Depending on the strength of the CH-acidity of the phosphonate, a crown ether or organocatalyst was used. To enhance the reactivity of the weakly acidic aminomethylenephosphonate, strong-base and crown ethers, while in case of strong acidic nitroethylphosphonates and medium acidic cyanomethylphosphonate organocatalysts were used.

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[3] (a) Palacios, F.; Alonzo, C.; los Santos, J. M. *Chem. Rev.*, **2005**, 105, 899-931. (b) Ma, J. A. *Chem. Soc. Rev.*, **2006**, 35, 630–636.

[4] (a) Bakó, T.; Bakó, P.; Vízvárdi, K.; Toppet, S.; Eycken, E. V. D.; Hoornaert, G. J.; Tőke, L. *Tetrahedron*, **1998**, 54, 14975-14988. (b) Jarosz, S.; Listkowski, A. *Current Org. Chem*. **2006**, *10*, 643-662.

[5] a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev*., **2007**, *107*, 5713-5743. (b) Albrecht, L.; Albrecht, A.; Krawczyk, H.; Jørgensen, K.A. *Chem. Eur. J*. **2010**, *16*, 28 – 48. (c) Singh, G. S.; Yeboah, E. MO. *Reports in Org. Chem*., **2016**, *6*, 47-75.

4.1 Enantioselective synthesis of protected, substituted α-aminophosphonic acid esters in the presence of chiral crown ether catalysts

Protected phosphoglycine ester (**3.1**) reacted with acrylic acid derivatives (**3.2**) using D-glucose (**3.3**) and BINOL-based (**3.7**) azacrown ethers and TADDOL-based linear polyether catalysts (**3.9**) in the presence of solid Na-*tert*-butylate base resulted in adduct (**3.4**) enriched in one enantiomer (Figure 1).

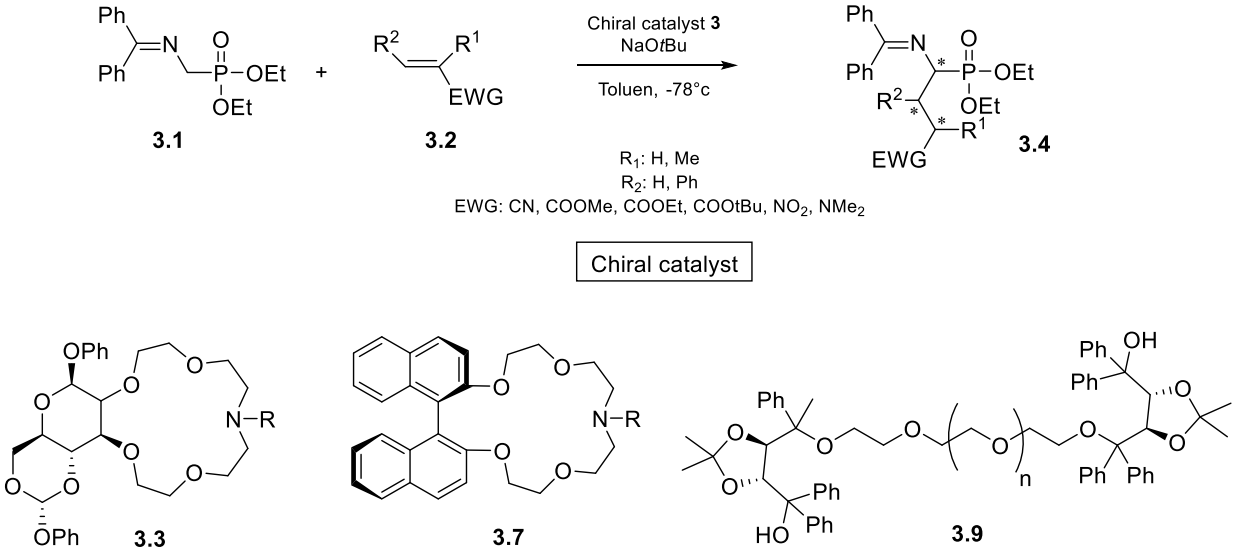

Figure 1: Michael addition of protected aminomethylene phosphonate (3.1) to acrylic derivatives (3.2) in the presence of chiral crown ethers (3.3 and 3.7) and "quasi" crown ethers (3.9)

Michael additions of 10 acrylic derivatives were investigated. Significant asymmetric induction was achieved only with the nitrile-containing Michael acceptors (mainly acrylonitrile and methacrylonitrile) (best results 96-97% ee, 18: 1 da), but non of the catalysts were selective in the reaction of acrylic esters. Cinnamic acid nitrile and nitrostyrene yielded good but not high enantioselectivity values (74-78% ee). It has been observed that for both types of crown ethers, the side chain attached to the N-atom of the ring has a fundamental role in the selectivity. It turned out, that the side arm must contain oxygen at a distance of 5-6 atoms from the ring, thus bending back effectively, which contributes to the stability of the sodium complex. The most selective catalysts were those with 3-methoxyphenylethyl and 3,4-dimethoxyphenylethyl side-arm. The Michael addition of methacrylonitrile was repeated with the best 5 D-glucose-based catalysts ending in the methoxy side-arm, with a 240 minute reaction time. To our surprise, not only the conversion has improved (typically by 5 percentage points) but also the da and ee values.

The Michael addition of the methacrylonitrile was also carried out with two D-glucose-

based azacrown-ethers (methoxyethyl side-arm and 3-methoxyphenylethyl side-arm) in the presence of a K-*tert*-butylate base, but both the enantiomeric excess and the diastereomer ratio deteriorated compared to the result obtained with Na-*tert*-butylate and the ratio of major and minor isomers also changed.

The best TADDOL-based linear polyether catalyst (**3.9d** (n=1)) resulted in superior enantioselectivity (75% ee), but conversion was unsatisfactory.

By theoretical calculations and modeling of the Michael addition, the configuration of the acrylonitrile adduct (**3.4** EWG = CN, R^1, R^2 = H) was deducted to be *S*, while that of the methacrylonitrile adduct (**3.4** EWG = CN, R^1 = Me, R^2 = H) was found to be 1*S*,3*R*. Theoretical modeling also answered why better Michael acceptors are nitriles than esters, and confirmed the assumption that the methoxyalkyl (aralkyl) side chain of the azacrown ether is needed for good catalyst selectivity [1-5].

4.2 Preparation of a new, carbethoxy group containing phosphonoglycine (3.17)

To increase the CH-acidity of the protected phosphoglycine ester (**3.1**), a ethoxycarbonyl group was incorporated into the molecule. The key step in the production of **3.17** is the diazo-transfer reaction from the phosphonoacetic acid triethyl ester (**3.19**), for which a new phase transfer catalytic method has been developed (Figure 2).

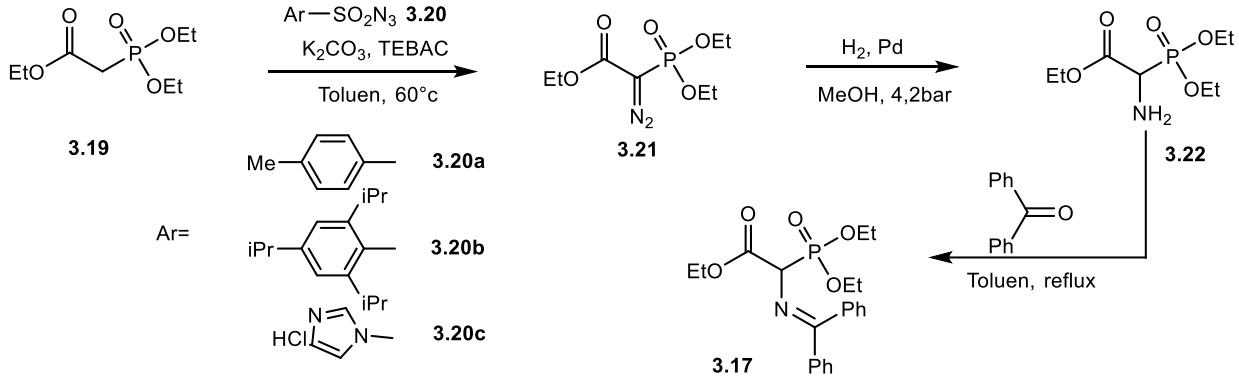

Figure 2: Synthesis of 3.17 carbethoxy-substituted protected phosphoglycine

The advantage of the method is that the reaction occurs with 100% conversion without the formation of any by-product in the presence of a solid K_2CO_3 base with aryl azides. The method is generally applicable to CH-acid compounds as illustrated in Example 8.

3.17 Synthon has not proved to be useful in Michael addition because the product decomposed under the reaction conditions [6].

4.3 Synthesis of quaternary α-aminophosphonates with organocatalysts

Novel quaternary α-aminophosphonates (**3.29**) were synthesized from α-nitroethylphosphonates (**3.26**) and aryl acrylates using bifunctional organocatalysts (**3.28**). Out of the 15 catalysts tested, the most selective was a cinchona-based squaramide derivative (**3.28l**). The bulkiest 2,6-dimethoxyphenyl acrylate was the best Michael-acceptor (ee = 96%).

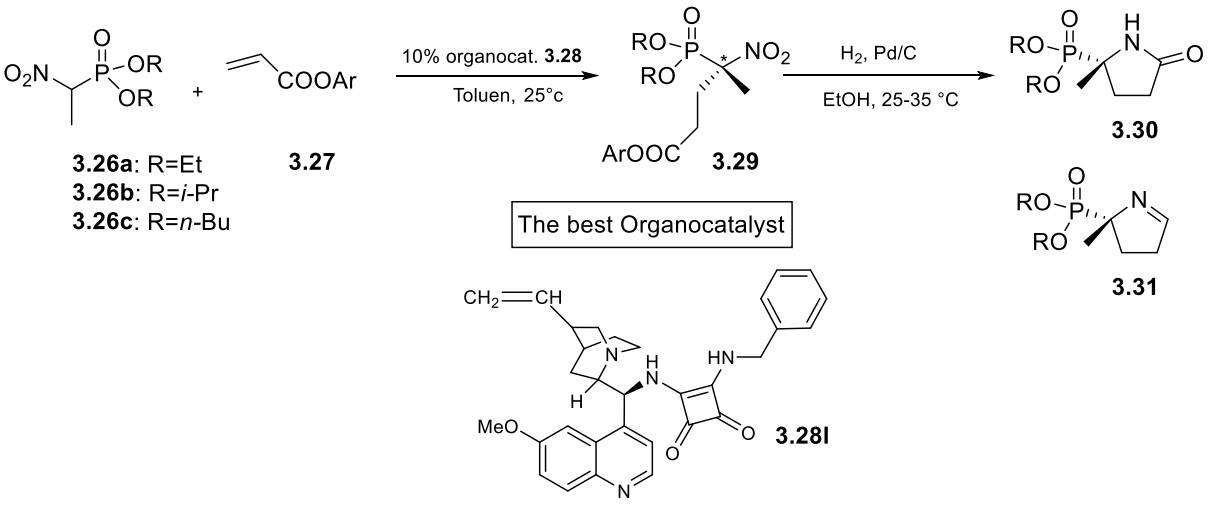

Figure 3: Stereoselective synthesis of 3.29 quaternary-nitrophosphonates with cincona-based squaramide organocatalyst(3.28l) and reduction to cyclic α-amino-,(3.30) and imino-phosphonates(3.31)

By catalytic hydrogenation of three quaternary nitrophosphonates (**3.29a** (R=Ph), **3.29j (**R=2-MeOC_6H_4) and 3.29**t** (R=2,6-diMeOC_6H_3), cyclic amino (**3.30**) and iminophosphonates (**3.31**) were obtained. It has been observed that the lactam / imine ratio depends on the substituents on the phenyl group, namely, the better the leaving group the Ar group, the higher the ratio of imine component was observed. The two reduced cyclic compounds were separable by column chromatography. In co-operation, the absolute configuration of adduct of **3.29r** was determined by CD measurement and computation and it was assigned as *S* [7].

4.4 Synthesis of substituted β-aminophosphonic acid precursors with organocatalysts

In enantioselective, catalytic Michael addition, we first synthesized new enantiomeric adducts from cyanomethyl phosphonate (**3.31**) and from 10 different substituted chalcones in the presence of 7 bifunctional organocatalysts (**3.28**).

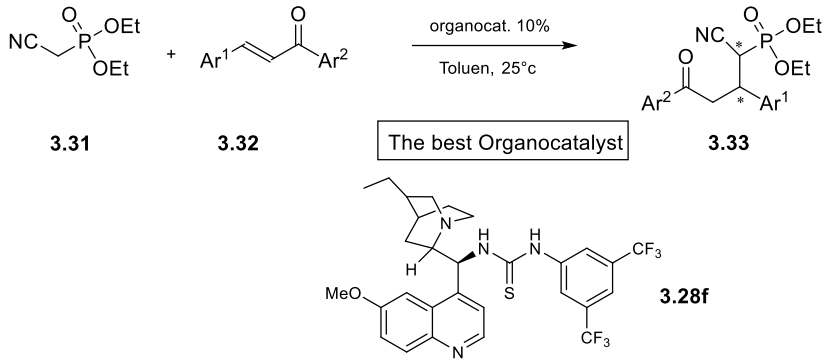

Figure 4: Michael addition of 3.31 cyanomethylphosphonate to 3.32 chalcones with cinchona-based thiourea catalyst(3.28f)

5. Thesis points

1. In enantioselective, catalytic Michael addition, for the first time we synthesized new α-aminophosphonate precursors (**3.4**) enriched in one enantiomer from protected phosphoglycine ester (**3.1**) with 10 different acrylic derivatives using D-glucopyranoside-based azacrown ether catalysts (**3.3**). We found that the most selective one (95-96% ee) of the 13 catalysts having various side-arm was the azacrown ether containing 3-methoxyphenyl ethyl (**3.3j**) and 3,4-dimethoxyphenyl ethyl (**3.3k**). Three of the catalysts (**3.3k-m**) were synthesized for the first time. The Michael acceptors were shown to have sufficient chiral induction for the nitrile-containing reagents, and not for the ester derivatives. The best Michael acceptor was methacrylonitrile. In co-operation, we calculated the abs. configuration of **3.4d** and **3.4f** adducts and modeled the structure of the transient complex, thereby interpreting the selectivity of the crown ethers used. [S1,2].

2. We found that the catalytic effect out of 9 diverse BINOL-based azacrown ethers (**3.7**) in the Michael additions of **3.1** phosphoglycine esters and 6 acrylic derivatives was best (96% ee) with methacrylonitrile and catalyst (**3.7i**) containing 3,4-dimethoxyphenyl ethyl side arm, meaning that the effect of the side arm on chiral induction was the same as that observed with D-glucopyranoside-based azacrown ethers. Experience with extending the Michael acceptors is also consistent with the results obtained with D-glucopyranoside-based azacrown ethers, i.e., chiral induction is sufficient only for the nitrile-containing reagents, not for the ester derivatives. In co-operation, using CD measurement and computation we determined the abs. configuration of **3.4e** and **3.4f** [S3].

3. We examined the catalytic effect of TADDOL-based crown ethers having two different ring-size (**3.9a, b**) and three quasi-crown ether open-chain bis-TADDOL polyether (**3.9d-f**) catalysts in the Michael addition of the phosphoglycine ester **3.1** and the four acrylic derivatives. The **3.9f** molecule was a novel catalyst. It was found that the best enantioselectivity for methacrylonitrile was achieved with the **3.9d** catalyst (75% ee) at a mean conversion. [S4,5]

4. A novel phase transfer catalytic diazotransfer method was developed for the preparation of an intermediate of the carbethoxy-substituted protected phosphoglycine ester (**3.17**) that can be interpreted as a key step for the synthesis of quaternary α-aminophosphonates. [S6]

5. In enantioselective, catalytic Michael addition, new quaternary-α-nitrophosphonates (**3.29**) were synthesized from α-nitroethylphosphonates (**3.26**) and aryl acrylates using bifunctional organocatalysts (**3.28**). We found that the most selective of the 15 catalysts tested was a cinchona-based squaramide derivative (**3.28l**), and the best of the Michael acceptors was 2,6-dimethoxyphenyl acrylate (96% ee). By catalytic hydrogenation of three quaternary nitrophosphonates (**3.29a, j, t**), cyclic amino and iminophosphonates were prepared. In co-operation, by CD measurement and computation, we determined the abs.configuration of **3.29r** adduct. [S7]

6. In enantioselective, catalytic Michael addition, for the first time we synthesized new enantiomer-rich adducts from cyanomethylphosphonate (**3.31**) and 10 different substituted chalcones in the presence of 7 bifunctional organocatalysts (**3.28**). We found that of the **3.28f** cinchona-based thiourea was the most selective catalysts. Among the chalcones, the NO_2 substituted benzylidene derivative had the best selectivity (85% ee). We found that the catalysts used in these examples were only enantioselective, while practically there was no diastereoselectivity. [S8]

6. Applications

The catalytic enantioselective Michael addition methods developed during my research work can be used to synthesize new, diverse aminophosphonate precursors. We have shown that excellent asymmetric induction can be achieved by a "tailor made" application of the catalyst and the reactants. From these nearly enantiomerically pure α- and β-aminophosphonic acid precursors potentially biologically active compounds can be achieved after hydrolysis, partial

hydrolysis, or reduction. These compounds can be useful by itself, or by coupling to amino acids, peptides, or other compounds.

7. Publication list

7.1 Own publications on which the thesis is based

[S1] Jászay, Z.; Pham, T. S.; Németh, G.; Bakó, P.; Petneházy, I.; Tőke, L.: Asymmetric Synthesis of Substituted α-alpha-Amino Phosphonates with Chiral Crown Ethers as Catalysts *Synlett* **2009**, *9*, 1429-1432. DOI: 10.1055/s-0029-1217166. IF: 2,419 (2017). Number of independent citations: 12.

[S2] Pham, T. S.; Rapi, Zs.; Bakó, P.; Petneházy, I; Stirling, A.; Jászay, Zs.: Enantioselective synthesis of substituted α-aminophosphonates catalysed by D-glucose-based crown ethers: pursuit of the origin of stereoselectivity, *New Journal of Chemistry* **2017**, *41*, 14945-14953. DOI: 10.1039/C7NJ03345A. IF: 3,201 (2017). Number of independent citations: 2.

[S3] Pham, T. S.; Czirok, J. B.; Balázs, L.; Pál, K.; Kubinyi, M.; Bitter, I.; Jászay, Zs.: BINOL-based azacrown ether catalyzed enantioselective Michael addition: asymmetric synthesis of α-aminophosphanates, *Tetrahedron: Asymmetry* **2011**, *22*, 480-486. DOI: 10.1016/j.tetasy.2011.02.002, IF: 2,126 (2015). Number of independent citations: 12.

[S4] Pham, T. S.; Gönczi, K.; Czirok, J. B.; Mátravölgyi, B.; Sólyom, S.: The synthesis and application of the new chiral catalyst in stereoselective synthesis, *Magyar Kémikusok Lapja* (The Hungarian Chemical Journal) **2011**, 51-52. IF: 0 (2017).

[S**5]** Mátravölgyi, B.; Kovács, E.; Hegedűs, L.; Jászay, Zs.; Thurner1, A.; Deák, Sz.; Erdélyi, Zs.; Pham, T. S.; Gönczi, K.; Sólyom, S.; Tőke, L.; Faigl, F.: Synthesis and application of new, optically active compounds as catalysts and ligands in enantioselective reactions, *Periodica Polytechnica Chemical Engineering* **2015**, *59*, 38-50. DOI: 10.3311/PPch.7320. IF: 0,84 (2015). Number of independent citations: 1.

[S6] Jászay, Zs.; Pham, T. S.; Gönczi, K.; Petneházy, I.; Tőke, L.: Efficient Solid/Liquid Phase-Transfer Catalytic Diazo Transfer Synthesis, *Synth. Comun.* **2010**, *40*, 1574-1579. DOI: 10.1080/00397910903100742. IF: 1,377 (2017). Number of independent citations: 3

[S7] Pham, T. S.; Gönczi, K.; Kardos, Gy.; Süle, K.; Hegedűs, L.; Kállay, M.; Kubinyi, M.; Szabó, P.; Petneházy, I.; Tőke, L.; Jászay, Zs.: Cinchona based squaramide catalysed enantioselective Michael addition of α-nitrophosphonates to aryl acrylates: enantioselective synthesis of quaternary α –aminophosphonates, *Tetrahedron: Asymmetry* **2013**, *24*, 1605–1614. DOI: 10.1016/j.tetasy.2013.10.008. IF: 2,126 (2016). Number of independent citations: 17.

[S8] Pham, T. S.; Balázs, L.; Petneházy, I.; Jászay, Zs.: Enantioselective Michael addition of diethyl cyanomethylphosphonates to chalconesusing bifunctional cinchona-derived organocatalysts synthesis of chiral precursors of α-substituted β-aminophosphonates, *Tetrahedron- Asymmetry*, **2010**, *21*, 346-351. DOI: 10.1016/j.tetasy.2010.01.006. Number of independent citations: 11.

7.2 The starting publication

[S9] Jászay, Zs. M.; Németh, G.; Pham, T. S.; Petneházy, I.; Grün, A.; Tőke, L. Catalytic enantioselective Michael addition in the synthesis of α-aminophosphonates *Tetrahedron:Asymmetry,* **2005**, 16, 3837–3840. DOI: 10.1016/j.tetasy.2005.10.020. IF: 2,126 (2016). Független idézetek száma: 32.

7.3 Conference presentations (oral)

[S10] Pham, T. S.; Jászay, Zs.; Bakó, P.; Petneházy, I.; Tőke, L.: α-Amino-foszfonátok szintézise katalitikus sztereoszelektív Michael addicióval, *13. Nemzetközi Vegyészkonferencia*, Kolozsvár, Románia, **2007.**

[S11] Pham, T. S.; Jászay, Zs.; Bakó, P.; Petneházy, I.; Tőke, L.: α-Amino-foszfonátok szintézise katalitikus sztereoszelektív Michael addicióval TADDOL származékok jelenlétében, *28. OTDK*, Szeged, **2007.**

[S12] Pham, T. S.; Jászay, Zs.; Petneházy, I.; Tőke, L.: α-, és β-Amino-foszfonátok szintézise katalitikus sztereoszelektív Michael addicióval, *Vegyészkonferencia*, Hajduszoboszló, **2008**.

[S13] Pham, T. S.; Gönczi, K.; Czirok, J. B.; Mátravölgyi, B., Jászay, Zs.: Új királis katalizátorok alkalmazása aminofoszfonsavak sztereoszelektív szintézisében, *Bruckner termi előadás,* **2010.**

[S14] Gönczi, K.; Pham, T S.; Sólyom, Sz.; Knorr, G.; Süle, K.; Jászay, Zs.: Application of TADDOL, and new TADDOL-based organocatalysts in Michael addition. 9th International Congress of Young Chemists, *9th Youngchem*, Krakkó, **2011.**

7.4 Conference presentations (poster)

[S15] Pham, T. S.; Jászay, Zs.; Németh, G.; Petneházy, I.; Tőke, L.: α-, és β-Amino-foszfonátok szintézise katalitikus sztereoszelektív Michael addicióval, *Centenáriumi Vegyészkonferencia*, Sopron, **2007**.

[S16] Pham, T. S.; Jászay, Zs.; Bakó, P.; Petneházy, I.; Tőke, L.: The synthesis of α-amino-phosphonates by catalytic stereoselective Michael addition, *9th Tetrahedron Symposium, Berkeley, CA, USA*, **2008.**)

[S17] Pham, T. S, α-Aminofoszfonátok szintézise katalitikus sztereoszelektív Michael addicióval, *Oláh György Doktori Iskola Konferenciája*, Budapest, **2008.**

[S18] Pham, T. S.; Jászay, Zs.; Petneházy, I.; Tőke, L.: The synthesis of β-amino-phosphonates by organo-catalytic stereoselective Michael addition, *10th Tetrahedron Symposium, Paris, France*, **2009**.

[S19] Gönczi, K.; Jászay, Zs.; Pham, T. S.; Süle, K.: TADDOL és új TADDOL alapú organokalatizátorok alkalmazása α-, és β-amino-foszfonátok szintézisében, V*egyészkonferencia és 53. Magyar Spektrokémiai Konferemcia*, Hajdúszoboszló, **2010.**

[S20] Czirok, J. B.; Pham, T. S.; Bitter, I.; Jászay, Zs.: Új, (*R*)-1,1'-bi-2-nafto-azakoronaéterek előállítása és alkalmazása aszimmetrikus Michael addíciókban. *Oláh György Doktori Iskola*