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Synthesis and Application of New, Optically Active Compounds as Catalysts and Ligands in Enantioselective Reactions

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RESEARCH ARTICLE

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Abstract

New methods for efficient preparation of optically active compounds developed recently are reported. Combination of selective organometallic, organocatalytic, phase transfer catalytic and catalytic hydrogenation reactions provided numerous new optically active members of the families of atropisomeric 1-phenylpyrrole derivatives, 4-aminobutan-1-ol and 3,4-disubstituted pyrrolidine derivatives and optically active α- and β-aminophosphonic acids. The products can be used as valuable new chiral ligands or organocatalysts and can serve as building blocks of practically important biologically active compounds.

Keywords

enantioseletive reaction, organocatalysis, atropisomerism, selective hydrogenolysis, amino phosphonates, chiral amino alcohols

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1 Introduction

The steric arrangement of compounds has crucial role in the formation of molecular interactions. Receptor-drug interactions are illustrative examples of this fact, because the most of the biological targets are chiral. In these cases, the different stereoisomers of a compound may cause diverse biological responses. This observation has initiated numerous research programs in order to find efficient synthetic methods for preparation of the useful pure enantiomer of biologically active ingredients. Such expectation resulted in the development of the basic methods of asymmetric synthesis. In the last fifty years dozens of chiral organometallic complexes and organocatalysts (chiral organic molecules without coordinated metal atom) have been developed and applied successfully [1,2]. Reports on preparations of enantiomerically enriched chiral compounds frequently contain data on development of new chiral catalysts or ligands with the aim of finding the optimum preparation method for the target compounds. On the other hand, optically active intermediates of biologically active compounds may serve as chiral auxiliaries or precursors of chiral ligands or catalysts. Such a synergistic combination of research work was acomplished in our laboratory in the last decade. Systematic development of special diastereo- and enantioselective reactions has been carried out in order to find new methods for preparation of the following groups of compound:

A) multifuctionalised atropisomeric 1-phenylpyrrole derivatives,

B) optically active 4-aminobutan-1-ol and 3,4-disubstituted pyrrolidine derivatives,

C) optically active α- and β-aminophosphonic acids.

Each group of compounds can be treated as intermediates of biologically active entities. In addition the members of group **A** were tested as chiral ligands while the members of group **B** can be used as precursors of biologically active compounds or chiral catalysts. Members of group **C** were prepared as important surrogates of natural α- and β-amino acids. In this short review we summarize our recent results achieved in the above mentioned projects.

2 Synthesis and application of optically active 1-phenylpyrrole derivatives

In case of compounds type **A**, development of an organometallic synthetic route for the preparation of a biologically active 4*H*,6*H*pyrrolo-[1,2*a*][4,1]benzoxazepine derivative initiated the research project in our group with the aim of investigating organometallic reactions of 1-arylpyrroles [3]. Detailed investigations on regioselective metalation possibilities of 1-(substituted phenyl)-1*H*-pyrroles were accomplished since that time [4-10]. Fine tuning of the reaction conditions resulted in novel, highly regioselective mono- and dimetalation methods. For instance, simultaneous metalation of the pyrrole Cα and phenyl *ortho* positions (followed by carboxylation) provided new, atropisomeric dicarboxylic acid derivatives. The first enantiomerically pure member of the new family of atropisomeric 1-phenylpyrrole derivatives, namely optically active 1-(6-carboxy-2-trifluoromethylphenyl)-1*H*-pyrrole-2-carboxylic acid was prepared by consecutive dimetallation and carboxylation of 1-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole followed by optical resolution [7]. This compound was used as starting material in the synthesis of numerous new atropisomeric amino alcohol type ligands.

Enantioselective addition of organozinc reagents to aldehydes is one of the most important synthetic methods for the preparation of enantioenriched secondary alcohols, [11,12] which are key intermediates in the preparation of valuable chiral biologically active compounds [13]. Therefore this reaction was choosen as a test of the efficiency of our new-found atropisomeric amino alcohol ligands.

Noyori and his coworkers published the successful application of DAIB [14] in the above mentioned enantioselective addition to produce optically active 1-arylpropanols (Fig. 1).

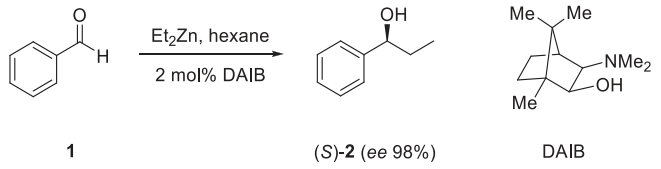

Fig. 1 Synthesis of optically active 1-phenyl-1-propanol (**2**).

Since then numerous optically active β-aminoalcohol dertivatives [15,16] were described in the literature. Even though axially chiral ligands have had huge success in other enantioselective reactions, only a few examples of amino alcohols with 1,1'-biaryl backbone (atropisomeric phenol or naphtol derivatives) have been reported for the addition of organozincs to aldehydes [17-19]. Therefore, our primary aim was to elaborate efficient methods for the synthesis of enantiomerically pure, new atropisomeric amino alcohol derivatives having 1-phenyl-1*H*-pyrrole backbone.

2.1 Resolution of 1-phenyl-1*H*-pyrrole dicarboxylic acids

Optically active 1-(6-carboxy-2-substituted phenyl)-1*H*-pyrrole-2-carboxylic acids can be suitable starting materials of the planned amino alcohol synthesis. In order to get such compounds, preparation of the racemic dicarboxylic acids was accomplished on the basis of our previous achivements.

Two decades ago, mechanism of the lithiation of 1-phenyl-1*H*-pyrrole was investigated [20] and it was postulated that dilithiation of 1-phenyl-1*H*-pyrrole is a kinetically controlled process. These findings were used during dimetalation of several 1-(substituted phenyl)-1*H*-pyrroles and the consecutive carboxylation led us to prepare several new dicarboxylic acid derivatives (**3a-d**). These dicarboxylic acids exist as stereochemically stable (until 100–150 °C) mixtures of atropisomers. Separation of the optical isomers was accomplished due to our experience in the field of optical resolution [21] using optically active 1-phenylethylamine ((*S*)-PhEA) resolving agent under different conditions (Fig. 2) [7,22-24]. The absolute configurations of the pure optical isomers of **3a-d** were determined by combined application of CD spectroscopy and quantum chemical calculations or X-ray diffraction measurements [7,22-24].

A highly efficient resolution process was also developed for **3a** dicarboxylic acid using (*R*)-phenylglycine methyl ester ((*R*)-**4**) as new resolving agent and the optimum parameters of the diastereoisomeric salt crystallization were experimentally determined [25]. It was found that the salt contains the practically pure diacid enantiomer ((*S*)-**3a**) after short (2–4 h)

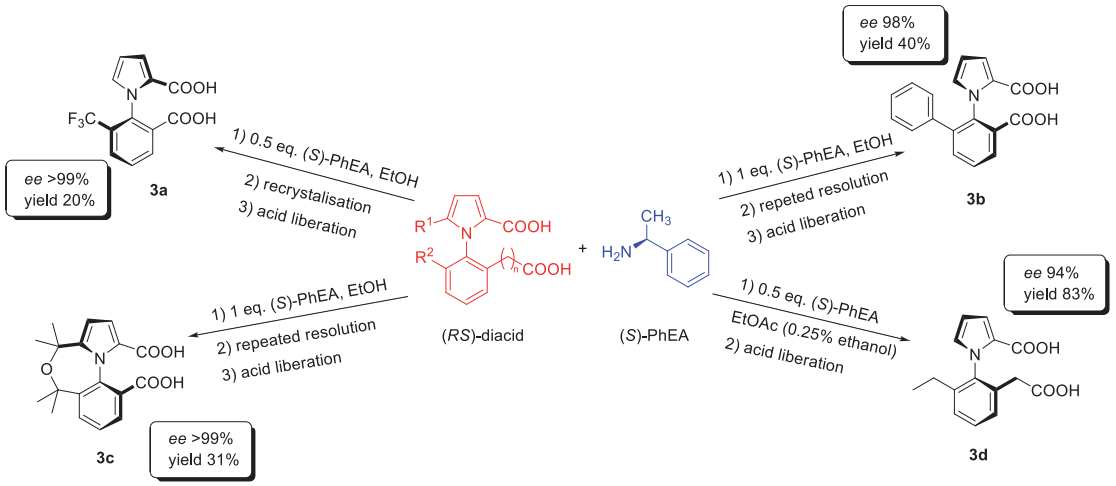

Fig. 2 Optical resolution methods of atropisomeric dicarboxylic acids (**3a-d**).

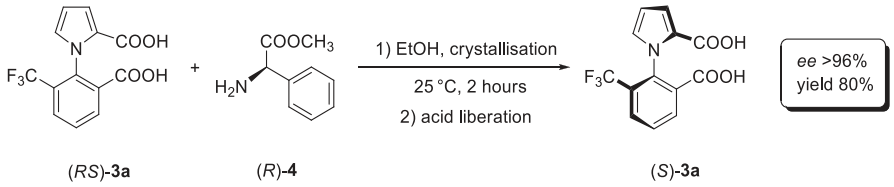

Fig. 3 Optical resolution of 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxylic acid (**3a**).

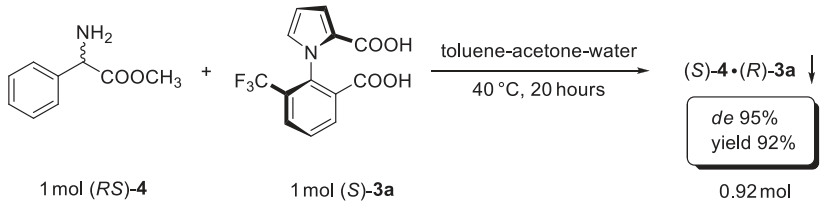

Fig. 4 Second order asymmetric transformation of (*RS*)-**4** with (*S*)-**3a**.

crystallization time (Fig. 3), but the enantiomer content of the salt gradually decreases during longer crystallization because of the slow racemization of the resolving agent.

On the basis of this observation a new second order asymmetric transformation of (*RS*)-**4** was accomplished in a toluene/acetone/water mixture using (*S*)-**3a** as resolving agent. This way practically the whole amount (92%) of racemic (*RS*)-**4** was transformed into (*R*)-**4** enantiomer (*ee* 95%, Fig. 4) [25].

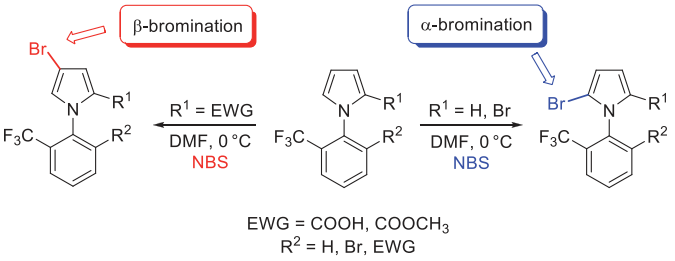

Fig. 5 Selective Cα' and Cβ' bromination of the Cα–, *orto*-substituted 1-[2-(trifluoromethyl)phenyl]-1*H*-pyrrole derivatives, and preparation of new carboxylic acids via bromine/lithium exchange reactions.

2.2 Regioselective bromination of 1-arylsubstituted pyrroles

Mono- and dimetalation reactions are convenient methods for functionalization of 1-aryl-1*H*-pyrroles, however, organometallic 1-aryl-1*H*-pyrrole derivatives can also be prepared via halogen/metal interconversion between halogenated 1-aryl-1*H*-pyrroles and organometallic reagents. Therefore a new functionalization method has been developed in our group using sequential bromination and halogen/metal exchange reactions [26]. Optimal conditions of the selective brominations were experimentally determined. It was found that the most selective reactions can be carried out with *N*-bromosuccinimide (NBS) in dimethylformamide. Under such conditions, selective bromination of the pyrrole Cα' or Cβ' positions was achieved (Fig. 5). Further bromination of **3a** and its 2-bromo derivative provided Cα' brominated product, exclusively. However, clean Cβ' bromination of the pyrrole moiety was observed when the heteroaromatic ring contained an electron withdrawing substituent in Cα (pyrrole C2) position (Fig. 5). The positions of the bromine atoms were confirmed by single crystal X-ray diffraction measurements.

Combination of the new, regioselective bromination methods and organometallic reactions led us to prepare the Cα' (**5**) and Cβ' (**6**) brominated regioisomers of 1-[2-carboxy-6-(trifluoromethyl)-phenyl]-1*H*-pyrrole-2-carboxylic acid (**3a**, Fig. 6) [26]. Further bromine/lithium exchange reactions or other C-C coupling reactions can be used for diverse functionalization of the pyrrole ring. Thus, the electronic and steric behaviours of the amino alcohol type target compounds can easily be modified in order to provide stereochemically more stable and more active new catalysts and ligands.

2.3 Synthesis and application of amino alcohols

Starting from (*S*)-**3a**, new amino alcohol type products were prepared with primary and tertiary alcohol moieties ((*S*)-**10**). (Fig. 7) [27].

As it was mentioned above, addition of diethylzinc to benzaldehyde was choosen to test the utility of the prepared new chiral amino alcohols as enantioselective catalysts. Amino alcohol (*S*)-**9** (R^1 = H, R^2 = 2-Pr, R^3 = Ph) proved an efficient

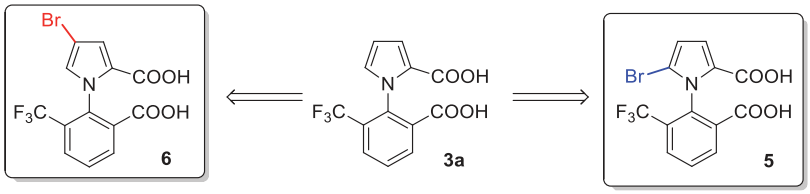

Fig. 6 Cα' (**5**) and Cβ' (**6**) brominated regioisomers of **3a**.

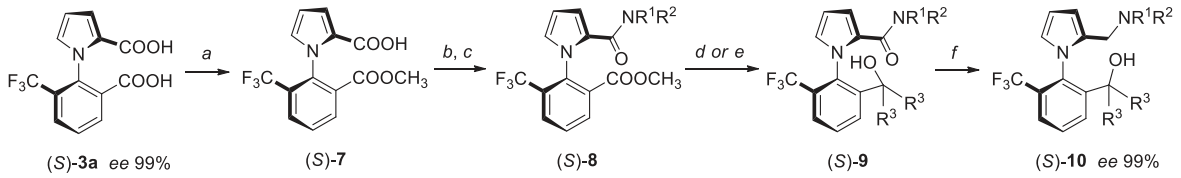

Fig. 7 Synthesis of (*S*)-**10**. a) $SOCl_2$, MeOH 80%, b) $SOCl_2$, toluene, 80 °C, 2 h, c) amine, toluene, 0 °C, 92–98%, d) PhMgCl, Et_2O, 0 °C → r.t., 93–97%, e) $NaBH_4$, 10% EtOH/THF, 25 °C, 48h, 92–96%, f) BH_3SMe_2, toluene, 60-80 °C, 24 h; MeOH, NaOH, 50 °C, 24h, 65–82%, R^1 = H, Et, 2-Pr, R^2 = H, Et, 2-Pr, Bn, (*R*)-1-phenylethyl, R^3 = H, Ph.

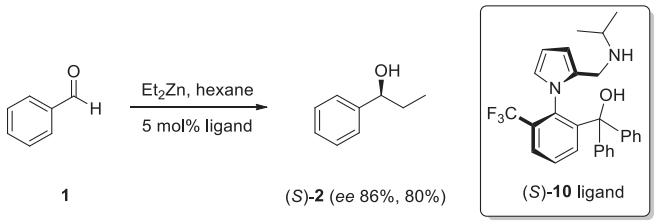

Fig. 8 Application of (*S*)-**10** amino alcohol as ligand in enantioselective reaction.

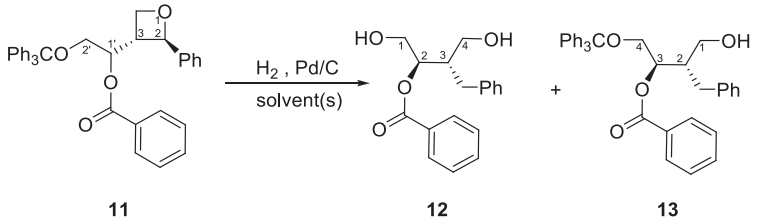

Fig. 9 Hydrogenolysis of (+)-(2*R*,3*R*,1'*R*)-3-[1'-benzoyloxy-2'-(triphenylmethoxy)ethyl]-2-phenyloxetane (**11**).

catalyst ligand in the addition reaction. The (*S*)-enantiomer of 1-phenylpropanol (**2**) was obtained in good (80%) yield and 86% enantiomeric excess by loading 5 mol% ligand. Consequently, the first, efficient member of a new, atropisomeric, 1-aryl-1*H*-pyrrole type family of chiral catalyst precursors was synthesized and tested by our group for asymmetric catalytic reaction (Fig. 8) [27]. The prepared compounds probably also catalyse the addition reactions of other organozinc reagents to aromatic aldehydes and can be used in other known enantioselective reactions as catalysts.

3 Synthesis of optically active 2,3-disubstituted 1,4-dihydroxybutane and 4-aminobutan-1-ol derivatives *via* hydrogenolysis of *O*-protected hydroxyoxetanes over palladium

Optically active 1,4-diols are useful intermediates for the synthesis of biologically active heterocycles. Ring closure reaction between the two hydroxyl groups is a well known route to produce non-racemic tetrahydrofurans and pyrrolidines [28]. During the heterogeneous catalytic hydrogenolysis of (+)-(2*R*,3*R*,1'*R*)-3-[1'-benzoyloxy-2'-(triphenylmethoxy)ethyl]-2-phenyloxetane (**11**) to (+)-(2*R*,3*S*)-2-benzoyloxy-3-benzylbutane-1,4-diol (**12**) a potential starting material, which can be used for preparing optically active, practically important tetrahydrofuran or pyrrolidine derivatives, was formed (Fig. 9).

Compound **11** was synthesized from (+)-(2*R*,3*R*,1'*R*)-3-[1'-hydroxy-2'-(triphenyl-methoxy)ethyl]-2-phenyloxetane, prepared according to our procedure described in [29], with benzoyl chloride, in the presence of butyllithium, in tetrahydrofuran (Fig. 10) [30].

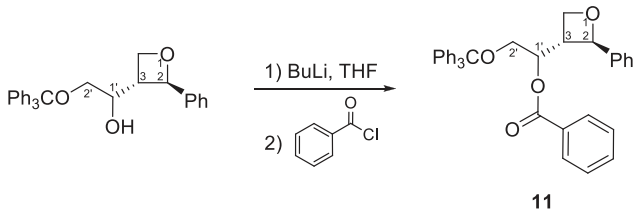

Fig. 10 Synthesis of (+)-(2*R*,3*R*,1'*R*)-3-[1'-benzoyloxy-2'-(triphenylmethoxy)-ethyl]-2-phenyloxetane (**11**).

3.1 Effect of solvents

As known [31], in the catalytic hydrogenations both the selectivity of a reaction and the activity of a catalyst can be influenced by using appropriate solvents. The results of the hydrogenolysis of **11** in different organic solvents, over 10% Pd/C (Selcat Q) catalyst are summarized in Table 1.

In methanol, only compound **13** was formed at atmospheric pressure and 30 °C in a fast reaction (1 h), but even at higher pressure (10 bar) and after longer reaction time (8 h) no changes were observed in the course of the hydrogenation

Table 1 Hydrogenolysis of **11** in different solvents

No.	Solvents	Pressure (bar)	Reaction time (h)	Conversion of 11 (%)	Yield (%) compound 12	Yield (%) compound 13
1	Methanol	1	1.0	100	0	100
		10	8.0	100	0	100
2	Tetrahydrofuran	10	8.0	100	0	100
3	Ethyl acetate	10	24.0	100	0	100
4	Dichloromethane	1	4.0	87	15	85
		10	16.0	100	70	30
5[a]	Dichloromethane	10	8.0	100	56	0
6[b]	Methanol + HCl	10	4.0	100	61	0
7[c]	Dichloromethane + *p*-TsOH	10	4.0	100	80	0

Conditions: 0.3 g (0.55 mmol) substrate, 0.06 g 10% Pd/C catalyst (Selcat Q), 30 mL solvent, 30 °C.

[a] 50 °C. [b] 0.02 mL cc. HCl. [c] 0.02 g *p*-toluenesulphonic acid (*p*-TsOH).

of **11**, i.e. the oxetane ring was opened selectively. Using tetrahydrofuran or ethyl acetate similar results were obtained as in methanol, but the complete conversion of **11** required longer reaction time (8 and 24 h). In dichloromethane, however, the formation of compound **12** was also observed beside that of compound **13**. After 4 h reaction time, at atmospheric pressure and 30 °C, the conversion of **11** was 87% and the yields of compound **12** and **13** were 15 and 85%, respectively. On the basis of these results, we were led to the conclusion that there are traces of acid in dichloromethane which could catalyse the removal of trityl group, because acidic conditions are favourable for the detritylation reaction [32]. Further hydrogenation of **11** at higher pressure (10 bar), after 16 h, provided complete conversion of **11**, but compound **12** was achieved with 70% yield only. When the temperature was raised to 50 °C, no compound **13** was detected after 8 h, i.e. the cleavage of trityl group took place completely, but the yield of **12** decreased to 56%. This was, presumably, due to side-reactions, such as hydrolysis of the benzoyl group, which can be attributed to the higher temperature. Using catalytic amount of mineral acid (HCl) in methanol or that of a weaker organic one (*p*-TsOH) in dichloromethane, the hydrogenation of **11** at 10 bar and 30 °C, after 4 h reaction time, resulted in similar lower yields of **12** (61 and 80%, respectively) as it was observed under the aforementioned conditions (dichloromethane, 50 °C). These were also due to side-reactions (e.g. hydrolysis of the ester bond), which can be ascribed to the strong acidic conditions.

To avoid the unwanted side-reactions, a mixture of dichloromethane and methanol was applied in the hydrogenation of **11**. Both the 50:50 (v/v%) and the 20:80 (v/v%) dichloromethane/methanol mixtures provided the same results, i.e. compound **12** was selectively formed with 100% yield (by complete conversion of **11**), over palladium on carbon, at 10 bar and 30 °C, after 8 h reaction time.

On the basis of these results, it can be stated that methanol, similarly to other protic and polar solvents, is very efficient in the hydrogenolysis of oxetane ring and provides high reaction rate, while dichloromethane makes acidic conditions which are advantageous for the removal of trityl protecting group by the cleavage of carbon–oxygen bond.

3.2 Mechanistic considerations

To clarify the role of acids in the reductive cleavage of trityl group, two experiments were carried out starting from the alcohol **13**. First, a hydrolytic reaction was performed, when the alcohol was dissolved in dichloromethane containing catalytic amount of *p*-toluenesulphonic acid (5%), but no Pd/C catalyst was added to the reaction mixture. Under these conditions slow formation of (+)-(3*R*,4*S*)-3-benzoyloxy-4-benzyltetrahydrofuran (**14**), triphenylmethanol and only trace amounts of **12** were observed (Fig. 11). Compound **14** was isolated with 50% yield. Formation of **14** can be explained by the protonation of the primary hydroxyl group of **13** (intermediate **A**) followed by an intramolecular nucleophilic reaction. Alternatively, consecutive protonation of the oxygen atom situated in the trityloxymethyl group (intermediate **B**) and intramolecular nucleophilic reaction may result in the same product (compound **14**) and triphenylmethanol. In a second experiment compound **13** was hydrogenated in the same solvent, over 10% Pd/C catalyst, in the presence of *p*-toluenesulphonic acid. In this case a fast reductive cleavage of the triphenylmethyl group was observed yielding a 5:1 mixture of the diol (**12**) and the tetrahydrofuran derivative (**14**).

These experiments demonstrated that an acid catalyst is essential for efficient, fast reductive cleavage of the trityl group. Without Pd/C, a slow hydrolytic reaction takes place providing compound **14** as a main product, while it is only a side-product of the catalytic reduction. It has to be emphasized, these chemical transformations have no influence on the configurations of the stereogenic carbon atoms, therefore, starting from optically active **11**, the products (**12**, **13** and **14**) were obtained with the same ee.

3.3 Hydrogenolysis of *N*-protected aminooxetanes over palladium

Chiral 1,4-amino alcohols can also be useful intermediates for the synthesis of biologically active *N*-heterocycles. Ring closure reaction between the amino and hydroxyl groups,

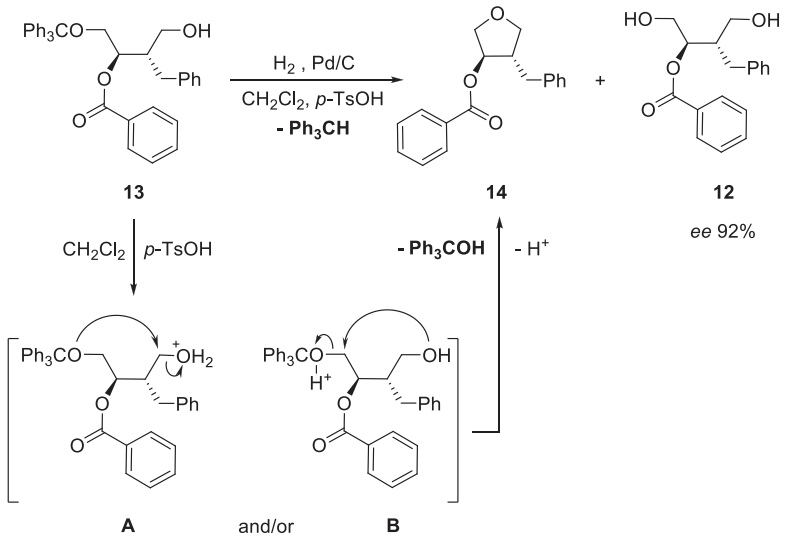

Fig. 11 Hydrolytic *vs*. reductive cleavage of the trityl group from compound **13**.

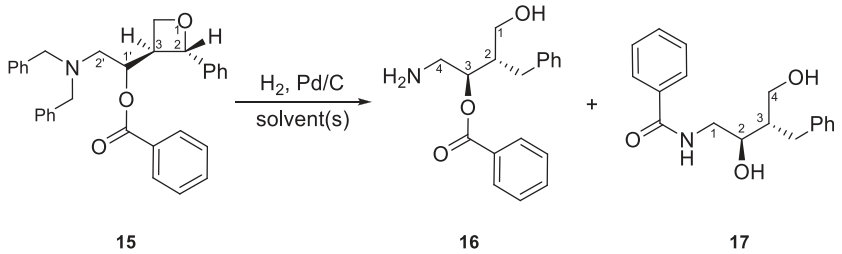

Fig. 12 Hydrogenolysis of (–)-(2*S*,3*S*,1'*S*)-3-[1'-benzoyloxy-2'-(dibenzylamino)ethyl]-2-phenyloxetane (**15**).

under the Mitsunobu protocol [33], is an alternative route to produce non-racemic pyrrolidines. Adopting the aforementioned hydrogenation method (Section 3.1), the heterogeneous catalytic hydrogenolysis of (–)-(2*S*,3*S*,1'*S*)-3-[1'-benzoyloxy-2'-(dibenzylamino)ethyl]-2-phenyloxetane (**15**) resulted in (2*S,*3*R*)-4-amino-3-benzoyloxy-2-benzylbutan-1-ol (**16**), which can also be a potential starting material for preparing optically active, practically important pyrrolidine derivatives.

Compound **15** was synthesized from (–)-(2*S*,3*S*,1'*S*)-3-[1'-hydroxy-2'-(dibenzylamino)ethyl]-2-phenyloxetane, prepared according to our procedure described in [34], with benzoyl chloride, in the presence of butyllithium, in tetrahydrofuran (Fig. 13) [35].

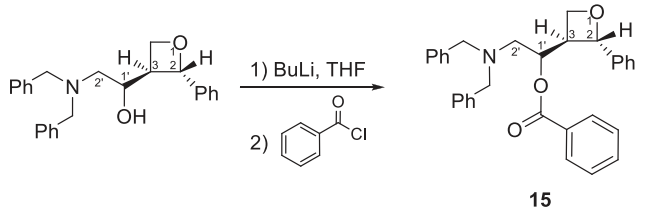

Fig. 13 Synthesis of (–)-(2*S*,3*S*,1'*S*)-3-[1'-benzoyloxy-2'-(dibenzylamino) ethyl]-2-phenyloxetane (**15**).

As well known, debenzylation is a common method to obtain the active forms of amines or alcohols from the corresponding *N*- or *O*-protected derivatives [36,37]. Removing the benzyl group attached to nitrogen, however, does not readily take place as its cleavage from oxygen does [38,39]. Moreover, the products of hydrogenolysis are strongly basic amines which can deactivate the supported precious metal catalysts due to their poisoning effects [40-42], therefore a higher amount of catalyst or adding acids are necessary to complete the reaction.

3.3.1 Effect of solvents

The results of the hydrogenolysis of **15** in different organic solvents, over 10% Pd/C (Selcat Q) catalyst are summarized in Table 2. In methanol, the conversion of compound **15** was complete at atmospheric pressure and 30 °C after 4 h reaction time, but the wanted compound **16** was not formed. Surprisingly a side-product, (2*R,*3*S*)-*N*-(3-benzyl-2,4-dihydroxybutyl)benzamide (**17**), was isolated from the reaction mixture with 20% yield. Further hydrogenation of **15** also provided compound **17** with a higher isolated yield (52%). It means that after opening the oxetane ring, the two benzyl groups were removed already at atmospheric pressure and room temperature, but hydrogenolysis of secondary amines, in general, requires higher pressure (>4 bar) and temperature (>40 °C) [43]. Using tetrahydrofuran or dichloromethane no conversion of **15** was observed even after 12–24 h reaction time and at 10 bar and 30 °C. In dichloromethane, however, compound **16** was obtained with 70% yield after 24 h, when the temperature was raised to 45 °C, but it was isolated in a form of hydrogen chloride salt (**16.HCl**). Moreover,

Table 2 Hydrogenolysis of **5** in different solvents

No.	Solvents	Pressure (bar)	Reaction time (h)	Conversion of 15 (%)	Isolated yield (%) compound 16	Isolated yield (%) compound 17
1	Methanol	1	4.0	100	0	20
			72.0	100	0	52
2	Tetrahydrofuran	10	24.0	0	—	—
3	Dichloromethane	10	12.0	0	—	—
4[a]	Dichloromethane	10	24.0	100	70[b]	0[c]

Conditions: 0.3 g (0.63 mmol) substrate, 0.15 g 10% Pd/C catalyst (Selcat Q), 30 mL solvent, 30 °C.
[a] 45 °C. [b] Prepared in a form of **16.HCl** salt. [c] No formation of compound **13** was observed.

Table 3 Hydrogenolysis of **15** in the mixture of dichloromethane (CH_2Cl_2) and methanol (MeOH)

No.	CH_2Cl_2/MeOH (v/v %)	Reaction time for complete conversion of 15 (h)	Isolated yield of compound 16[a] (%)
1	50:50	4.0	50
2	80:20	20.0	54
3	70:30	16.0	79
4[b]	70:30	16.0	87

Conditions: 0.3 g (0.63 mmol) substrate, 0.15 g 10% Pd/C catalyst (Selcat Q), 30 mL solvent, 30 °C, 10 bar.
[a] No formation of compound **13** was observed. [b] 2.85 g (5.98 mmol) substrate, 1.42 g 10% Pd/C catalyst (Selcat Q), 50 mL solvent.

no compound **13** was detected. This was due to the hydrodehalogenating ability of palladium [44], i.e. under such conditions palladium is able to hydrogenolyse dichloromethane, and the hydrogen chloride formed gives a salt with compound **16**.

To avoid the unwanted side-reactions, a mixture of dichloromethane and methanol was applied in the hydrogenation of **15**, similarly to our previous results concerning the hydrogenolysis of *O*-protected hydroxyoxetanes [30]. The effect of solvent mixtures with different composition on the conversion of **11** and the isolated yield of **16** is given in Table 3.

As seen, in the 50:50 (v/v%) dichloromethane/methanol mixture compound **16** was isolated with 50% yield (by complete conversion of **15**), over palladium on carbon, at 10 bar and 30 °C, after 4 h reaction time. Similarly to dichloromethane used by itself, no formation of compound **13** was observed, but compound **16** was in a form of free base. Using a 80:20 (v/v%) mixture the complete conversion of **15** required longer reaction time (20 h), moreover the isolated yield of **16** became slightly better (50 → 54%). Whereas, increasing the amount of methanol to 30 (v/v%) the rate of hydrogenolysis also increased, namely 16 h reaction time was sufficient to complete the hydrogenation of **15**, as well as compound **16** was achieved with 79% isolated yield. Further increase in isolated yield of **16** was obtained (87%), when this reaction was repeated using about ten times higher amount of starting material (0.3 → 2.85 g), presumably due to the smaller loss of **16** suffered during the working-up procedure.

According to our results, it can be stated that methanol, similarly to other protic and polar solvents, is very efficient in the hydrogenolysis of oxetane ring and the removal of benzyl protecting group, as well as providing a high reaction rate, while dichloromethane prevents the possibility of side-reactions (e.g. hydrolysis of the ester bond).

3.3.2 Possible reaction mechanism for the formation of side-product (**17**)

To explain the formation of side-product benzamide derivative **17** we suggested the following mechanism shown in Fig. 14. First, the oxetane ring was opened and a benzyl group was removed by the cleavage of carbon–nitrogen bond in a fast reaction. Then methanol, which was present as a solvent in large excess, could initiate transesterification of the benzoyl ester moiety of **18** in a slow reaction to form methyl benzoate, which could acylate fast the secondary *N*-monobenzyl aminodiol derivative. Since this *N*-benzoyl-*N*-benzyl aminodiol became a tertiary amine again, the hydrogenolysis of benzyl group could take place already at atmospheric pressure and room temperature, over palladium. The appearance of methyl benzoate was proved by GC–MS measurements which gives an indirect evidence of the proposed mechanism.

To demonstrate the practical usefulness of the prepared 1,4-amino alcohol derivative **16**, a ring closure reaction was carried out using the Mitsunobu conditions (Fig. 15). Product **19** was isolated in pure form which can also be used as a key intermediate in the synthesis of Balanol analogues [45].

It has to be emphasized, these chemical transformations have no influence on the configurations of the stereogenic carbon atoms, therefore, starting from optically active **15**, the products (**16** and **19**) were obtained with the same ee. Furthermore, these solvent effects also gave evidence that selectivity, yield and rate of the catalytic hydrogenation reactions can be influenced by changing solvents or solvent mixtures.

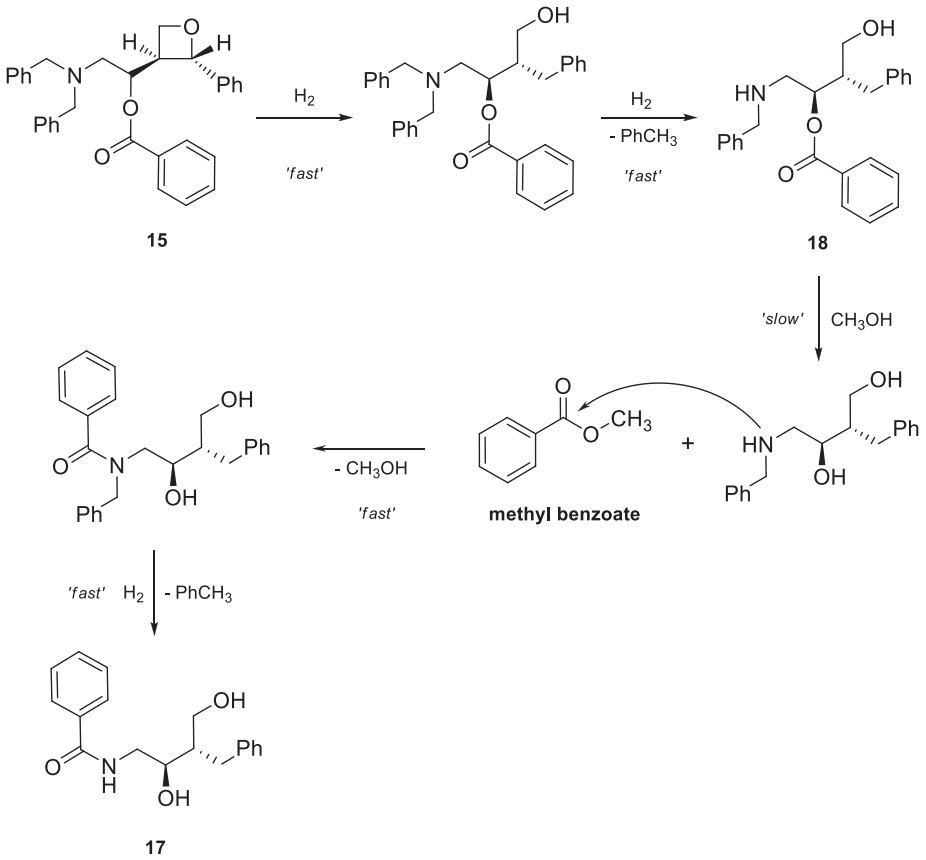

Fig. 14 Proposed mechanism of the formation of compound **17**.

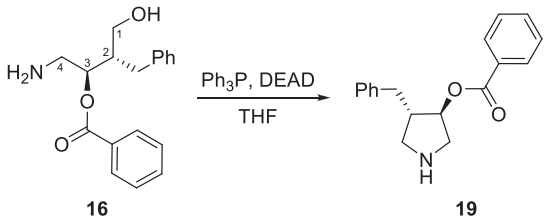

Fig. 15 Synthesis of (–)-(3*R*,4*S*)-3-benzoyloxy-4-benzylpyrrolidine (**19**).

4 Catalytic enantioselective synthesis of α- and β-aminophosphonates via CC coupling reactions

Optically active α- and β-aminophosphonic acids (**20a-c**) have potential importance as surrogates of natural α- and β-amino acids [46-48]. Due to the tetrahedral structure of the phosphonic moiety (versus planar structure of the carboxylic group), they act as "transition state analogues" either in themselves, or as constituents of phosphonopeptides [49,50]. Therefore, they can serve as proteinase inhibitors, such as antibacterial agents [51], antihypertensive agents [52], anti-HIV agents [53], herbicides [54] and haptens for catalytic antibodies [55].

Since biological activity is strongly influenced by the configuration of the carbon atom adjacent to phosphorus, there is a great demand for the development of methods enabling their preparation in an enantioselective fashion. Catalytic asymmetric reactions constitute one of the most potent and environmentally-friendly methods for introduction of chirality into target molecules. Various efforts using chiral catalysts providing non-racemic α- and β-aminophosphonates were developed in the last decade and have recently been reviewed [56-59]. Among them, stereoselective P-C and C-C coupling approaches can be considered the most preferred methods.

Our aim was to investigate the applicability of α-substituted phosphonates of various CH acidity (**21a-21c**) as precursors and the proper selection of chiral catalysts of different type (**23a-23g**) in the synthesis of α- and β-aminophosphonates. We summarize here our recently explored methods of introduction of reactive functional groups in the α-position of the prochiral (**21a** and **21c**) and racemic (**21b**) aminophosphonate precursor molecules by catalytic enantioselective Michael addition. *N*-protected aminomethylenephosphonate (**21a**), α-nitroethylphosphonate (**21b**) and cyanomethylphosphonate (**21c**) were chosen as easily accessible starting compounds. As the Michael adducts (**22**) in hand, **20a** could be readily obtained by hydrolysis, **20b** and **20c** by reduction followed by hydrolysis (Fig. 16).

Asymmetric induction was generated by chiral diols (**23a** and **23b**), by chiral azacrown ethers (**23c** and **23d**) and by bifunctional organocatalysts (**23e-23g**) respectively (Fig. 17). Applicability of these catalysts depended on the acidity of the carbon atom next to the phosphorus in **21** and the reactivity of the Michael acceptors (**23**). The chiral backbone of the catalysts involved *R,R*-TADDOLs (α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols) (**23a** and **23f**) derived from the natural L-tartaric acid, D-glucose (**23c**) and chincona moiety (**23e-23g**), all obtained from easily available natural sources,

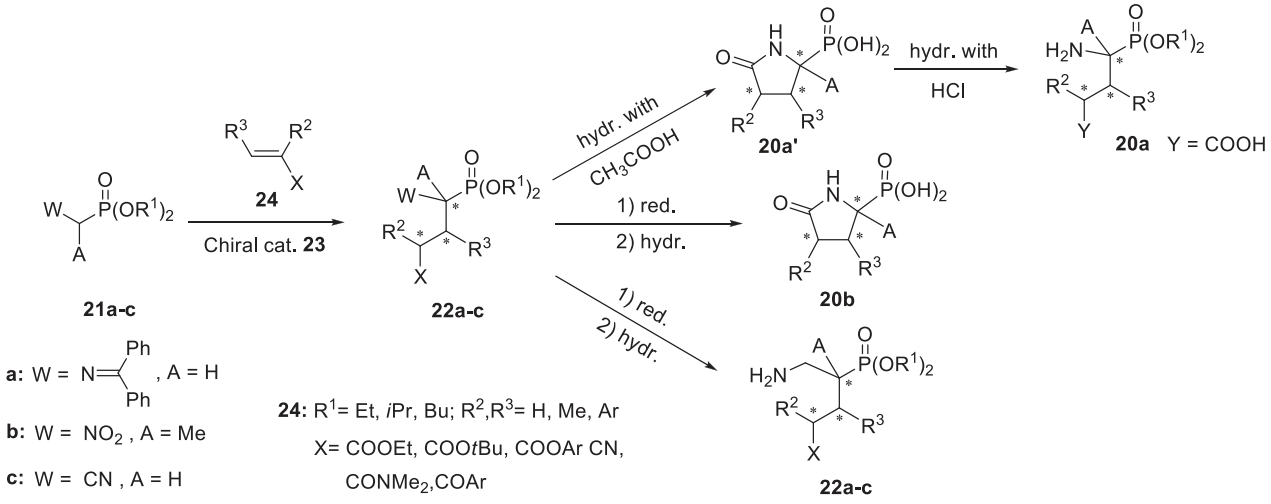

Fig. 16 Synthetic routes to optically active α- and β-aminophosphonic acids by catalytic Michael addition.

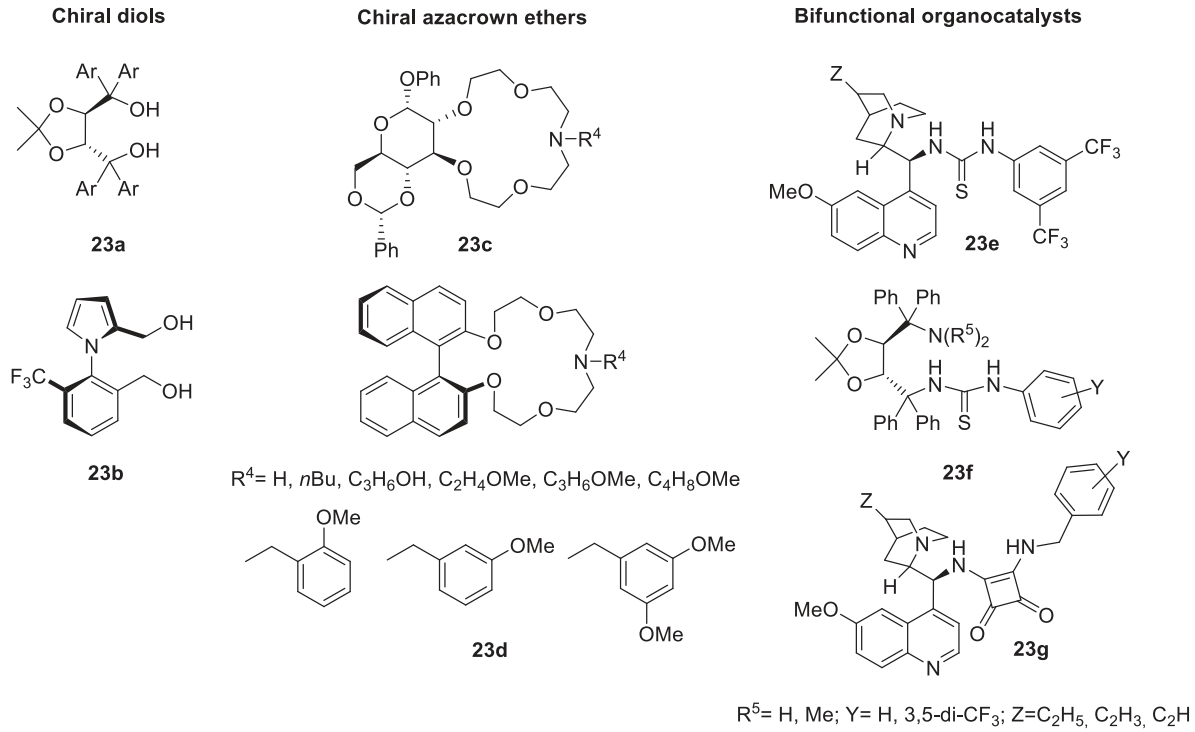

Fig. 17 Choice of chiral catalysts used in Michael additions.

while the 1-phenylpyrrole based diol (**23b**) and 1,1'-bi-2-naphthol (BINOL) catalysts were derived synthetically (**23d**). According to the mode of action of the catalysts chiral diols (**23a** and **23b**) and chiral azacrown ethers (**23c** and **23d**) act as phase transfer catalysts in a solid-liquid phase reaction. As bifunctional organocatalysts, they are small molecules having enzyme like activity capable of H-bonding with both the substrate and the reagent molecule. Organocatalysis is a relatively new and ever growing field in asymmetric catalysis because of their high selectivity, low toxicity and relative insensivity to the reaction conditions. At present cinchona based thiourea (**23e**) and squaramide (**23g**) catalysts are the most successful group of the organocatalysts [60].

4.1 Synthesis of α-aminophosphonates (**20a**) starting from *N*-protected phosphonoglycine (**21a**)

4.1.1 Applying chiral diol catalysts (**23a** and **23b**)

Though **21a** seems to be an obvious starting compound to introduce a functional group in the α-position a deprotonation by a strong base is required in the Michael addition due to its low CH acidity (pK_a~23 in DMSO). Thus, chiral diols (**23a** and **23b**) and chiral crown ethers were applied as ligands to generate a chiral transition complex in the process. According to our first method the Michael addition reactions of *N*-protected phosphonoglycine (**21a**) to alkyl acrylates and acrylonitrile (**24** R^1 = H, R^2 = Me, X = COOEt, COO*t*Bu, CN) were performed. TADDOL (**23a)** and atropisomer chiral diol (**23b**) were used as

catalysts in the presence of solid potassium, sodium and lithium *tert*-butylate as base, respectively. The reaction was conducted in dry toluene at low temperature under argon atmosphere and quenched with ammonium chloride after 15 min. The best enantiomeric excess (*ee* 72%) and chemical yield (88%) were obtained when the bulky *tert*-butyl acrylate as Michael acceptor, 1.2 equivalent of NaO*t*Bu as base and one equivalent of TADDOL (Ar = Ph) as catalyst were applied. Using the bulkier isopropyl phosphonate esters (**21a**, R^1 = *i*Pr) did not affect reaction rate, but decreased enantioselectivity. The atropisomer diol catalyst (**23b**) proved to be less selective (*ee* 58%) than TADDOL (**23a**) probably due to its looser structure. To get a better insight into the catalytic process the dependence of the enantiomeric excess of product **22** (X = COO*t*Bu) of the Michael addition reaction on the enantiomeric purity of catalyst **23a** was also determined. A positive nonlinear effect ((+)-NLE) was observed indicating that not only a transition complex involving the substrate **21a** and TADDOL of 1:1 ratio might be present, but some associations occurs. Hydrolysis of **22** by a weak acid resulted in a cyclic phosphonate (**20a'**), which could be further hydrolyzed by means of a strong acid to optically active phosphonoglutaminic acid (**20a**), a biologically active *P*-analogue of glutaminic acid. The absolute configuration of **20a** was found to be *S* by comparison of the signs of optical rotation with literature value [61].

4.1.2 Applying chiral azacrown ether catalysts (**23c** and **23d**)

Sugar based azacrown ethers (**23a**) were synthesised and checked in numerous C-C coupling reactions at our department [62], while similar azacrown ethers bearing BINOL scaffold were designed in our research group and tested first time in the above mentioned aminophosphonate synthesis. We found that both (**23c** and **23d**) efficiently catalyzed the Michael addition of **21a** synthon onto a broad variety of Michael acceptors **5** (X = COOEt, COO*t*Bu, CN, $CONMe_2$, R^2 = H, Me, R^3 = H, Ph). The reactions were performed in toluene at a temperature of –75 °C in the presence of NaO*t*Bu (1.5 equivalent) and with 10 mol% of catalyst loading. In these experiments catalysts (**23c** and **23d**) bearing 2-methoxyphenylethyl and 3,4-dimethoxyphenylethyl side-arm proved to be the most effective. It seems that the presence of an oxygen atom in an appropriate (5–6 atom) distance in the enfolding podand arm significantly enhanced the stereoselectivity, presumably due to the formation of a three dimensional binding site for the sodium cation. Excellent enantioselectivity was obtained in those cases when the electron withdrawing group of the Michael acceptors was cyano group (**24**, X = CN), such as in acrylonitrile (*ee* 75–95%), methacrylonitrile (*ee* 86–96% for the major diastereomer) and *trans*-cinnamonitrile (*ee* 71% for the major diastereomer), but the selectivity of all of the catalysts was low in cases of Michael acceptors bearing carboxylic ester groups (**24,** X = COOEt, COO*t*Bu). The same selectivity could be observed for the diastereoselectivities (99.3/0.7 for the methacrylonitrile, but only 68/32 for *t*Bu methacrylate). It is noteworthy that the accelerating effects of the *R*-BINOL- and the D-glucose-azacrown ethers on these Michael reactions are similar, while the selectivity of the *R*-BINOL based family (**23d**) is somewhat superior to that of the crown ethers with sugar backbone (**23c)**. Hydrolysis of **22** (X = CN, R^2 = Me, R^3 = H) results in methyl substituted optically active phosphonoglutaminic acid (**20a,** X = COOH, R^2 = Me, R^3 = H). Moreover, the absolute configuration of **22** (X = CN, R^2 = Me, R^3 = H) could be deduced to be (1*S*,3*R*) by comparing the experimental CD spectrum with the quantum chemically calculated CD spectra of the four possible optical isomers [63,64].

4.2 Synthesis of quaternary α-aminophosphonates (**20b**) starting from α-nitroethylphosphonates (**21b**)

Quaternary α-aminophosphonates could be useful for biomimetic research, because the incorporation of them into peptides may lend them increased rigidity and resistance to proteases. α-nitroethylphosphonates (**21b**, W = NO_2, A = Me) in accordance with our expectations proved to be good synthons, because they can be easily deprotonated by weak bases due to the strong acidity of the α-CH group (pK_a~12 in DMSO). Bifunctional organocatalysts seemed to be the best choice to promote the Michael addition of α-nitroethylphosphonates (**21b**) to acrylic acid aryl esters (**24**, X = COOAr, R^2, R^3 = H). The reaction ran smoothly with a catalyst loading of 10 mol% in toluene at room remperature resulting in **22**. All of catalysts **23e** and **23**g were active and selective, the highest ee (96%) was obtained with benzyl substituted squaramide catalyst (**23g**, Y = H, Z = vinyl) in the reaction of the bulky 2,6-dimethoxyphenyl acrylate (**24**). Catalytic hydrogenation of **22** over a Pd/C catalyst was performed resulting in the cyclic quaternary α-aminophosphonate (**20b**, A = Me). The absolute configuration of a representative example (**22**, X= $COOC_6H_4$(*m*-OMe), A = Me, R^2, R^3 = H) was deduced as *S* by comparing the experimental and quantum chemically calculated CD spectra [65].

4.3 Synthesis of precursors of β-aminophosphonates (**20c**) starting from cyanomethylphosphonates (**21c**)

As the CH acidity of **21c** is in the medium range (pK_a~17 in DMSO), its Michael addition could be catalyzed by all chiral diols (**23a** and **23b**), azacrown ethers (**23c**) and organocatalysts (**23e** and **23f**), but in cases of **23a** and **23b** only diastereoselectivity, and in the case of **23c** neither diastereoselectivity, nor enantioselectivity was observed with the Michael acceptors screened. Using cinchona based thiourea organocatalysts (**23e**) *trans*-chalcones (**24**, X = COAr, R^2 = H, R^3= Ar) proved to be excellent Michael acceptors of diethyl cyanomethyl phosphonate (**21c**). According to the optimized conditions the reaction was run in toluene at room temperature using 10 mol% catalyst

resulting in **22** adduct (W = CN, A = H, X = COAr, R^3 = Ar) in high chemical yield and good enantioselectivity (the best *ee* 85%, when X = COPh, R^3 = 4-NO_2Ph). It is noteworthy that the diastereoselection was very modest for all the catalysts and chalcones (typical diastereometric ratio (*dr*) 55/45). Recently our group designed a new thiourea type organocatalyst having TADDOL backbone (**23f**) and tested in the above mentioned Michael addition. An improved enantioselectivity (*ee* 91%) and diastereoselectivity (*dr* 94/6) was observed with *trans*-chalcone (**24**, X = COPh, R^2 = H, R^3 = Ph), but the scope of the reaction seems to be limited, namely all of the other chalcones examined provided medium or low enantioselectivity in a slow reaction. The relative configuration of adducts **22** (W = CN, A = H, X = COAr, R^3 = Ar) could also be deduced from their ^{13}C NMR spectra. According to the preferred conformations (generated by HyperChem® 7.5) the large (*transoid*) coupling for the PCH_2 and the small (*cisoid*) coupling for the PC_{Ar1} would correspond to the major (*anti:* 2*S*,3*S* and 2*R*,3*R*) isomer, and *vice versa*. [66].

5 Conclusions

The above described brief summary of the scientific results achieved recently by our group demonstrates our succesful efforts to find new methods for efficient preparation of optically active compounds. Very first synthesis and application of atropiosomeric 1-phenylpyrrole derivatives and highly selective hydrogenolysis of optically active oxetane and azetidine derivatives provided numerous new chiral compounds. Systematic investigation of optically active TADDOL, chincona alkaloid and atropisomeric biaryl derivatives as catalysts led us to prepare several new, optically active α-amino- and β-aminophosphonates. Some part of the synthesized new products showed excellent properties as chiral ligands or catalysts in different enantioselective reactions. It has to be mentioned, these products can also be used as valuable building blocks of practically important compounds and the products of the enantioselective Michael additions may be applied in drug synthesis as valuable phosphonic acid analogs of aminocarboxylic acids.

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References

[1] Jacobsen, E. N., Pfaltz, A., Yamamoto, H. (eds). "*Comprehensive Asymmetric Catalysis I-III*." Berlin: Springer. 1999. DOI: 10.1007/978-3-642-58571-5

[2] Walsh, P. J., Kozlowski, M. C. (eds). "*Fundamentals of Asymmetric Catalysis*." Palgrave Macmillan. 2009.

[3] Schlooser, M., Faigl, F. "Pyrrolobenzoxazepine ring construction through metalation and electrophilic substitution of *N*-(2-hydroxymethylphenyl)pyrrole." *Tetrahedron.* 50 (7). pp. 2071-2076. 1994. DOI: 10.1016/S0040-4020(01)85069-9

[4] Faigl, F., Fogassy, K., Thurner, A., Tőke, L. "Competition and co-operation between *ortho* directing groups and activating agents: Regioselective metallation of 1(methoxyphenyl)pyrroles." *Tetrahedron.* 53 (13). pp. 4883-4888. 1997. DOI: 10.1016/S0040-4020(97)00183-X

[5] Faigl, F., Fogassy, K., Szántó, Z., Lopata, A., Tőke, L. "The special directing effect of fluorine: Ligand independent *ortho* lithiation of 1-(fluorophenyl)pyrroles." *Tetrahedron.* 54 (17). pp. 4367-4374. 1998. DOI: 10.1016/S0040-4020(98)00150-1

[6] Faigl, F., Fogassy, K., Szűcs, E., Kovács, K., Keserű, G. M., Harmat, V., Böcskei, Z., Tőke, L. "Effect of a trifluoromethyl group on molecular structure: Competitive mono- and dilithiation of 1-[(trifluoromethyl)phenyl]pyrroles." *Tetrahedron.* 55 (25). pp. 7881-7892. 1999. DOI: 10.1016/S0040-4020(99)00398-1

[7] Fogassy, K., Harmat, V., Böcskei, Z., Tárkányi, G., Tőke, L., Faigl, F. "Efficient synthesis and resolution of (±)-1-[2-carboxy-6-(trifluoromethyl)phenyl]pyrrole-2-carboxylic acid." *Tetrahedron: Asymmetry.* 11 (23). pp. 4771-4780. 2000. DOI: 10.1016/S0957-4166(00)00449-3

[8] Fogassy, K., Kovács, K., Keserű, G. M., Tőke, L., Faigl, F. "Solvent and ligand effects on selective mono- and dilithiation of 1-(chlorophenyl)pyrroles and 1(methoxyphenyl)pyrroles." *Journal of the Chemical Society, Perkin Transactions. 1*. 2001 (9). pp. 1039-1043. 2001. DOI: 10.1039/B100008J

[9] Faigl, F., Thurner, A., Vass, B. "Efficient methods for optional metalation of 1(methylphenyl)pyrroles in or benzylic positions." *Journal of Chemical Research (Synopses)*. 2003 (3). pp. 132-133. 2003. DOI: 10.3184/030823403103173228

[10] Faigl, F., Vas Feldhoffer, B., Thurner, A. "Organometallic Approach to the Functionalization of Alkyl Groups Containing 1-Phenylpyrroles." *Synthetic Communications.* 36 (19). pp. 2841-2849. 2006. DOI: 10.1080/00397910600770672

[11] Soai, K., Niwa, S. "Enantioselective addition of organozinc reagents to aldehydes." *Chemical Reviews*. 92 (5). pp. 833-856. 1992. DOI: 10.1021/cr00013a004

[12] Zhu, H. J., Jiang, J. X. , Ren, J., Yan, Y. M., Pittman, C. U. "Recently Developed Organometallic Complexes of Zn, Cu(Zn, Li), Fe, Ru and Less-used Ions. Use in Selective 1,2-or 1,4-Additions, Transfer Hydrogenations, Aldol Reactions and Diels-Alder Reactions." *Current Organic Synthesis*. 2 (4). pp. 547-587. 2005. DOI: 10.2174/157017905774322677

[13] Stivala, C. E., Zakarian, A. "Total Synthesis of (+)-Pinnatoxin A." *Journal of the American Chemical Society.* 130 (12). pp. 3774-3776. 2008. DOI: 10.1021/ja800435j

[14] Kitamura, M., Okada, S., Suga, S., Noyori, R. "Enantioselective addition of dialkylzincs to aldehydes promoted by chiral amino alcohols. Mechanism and nonlinear effect." *Journal of the American Chemical Society.* 111 (11). pp. 4028-4036. 1989. DOI: 10.1021/ja00193a040

[15] Tasgin, D. I., Unaleroglu, C. "Enantioselective addition of diethylzinc to aldehydes catalyzed by β-amino alcohols derived from (1*R*,2*S*)-norephedrine." *Applied Organometallic Chemistry*. 24 (1). pp. 33-37. 2010. DOI: 10.1002/aoc.1583

[16] Wang, M.-C., Wang, Y.-H., Li, G.-W., Sun, P.-P., Tian, J.-X., Lu, H.-J. "Applications of conformational design: rational design of chiral ligands derived from a common chiral source for highly enantioselective preparations of (*R*)- and (*S*)-enantiomers of secondary alcohols." *Tetrahedron: Asymmetry.* 22 (7). pp. 761-768. 2011. DOI: 10.1016/j.tetasy.2011.04.013

[17] Vyskocil, S., Jaracz, S., Smrcina, M., Sticha, M., Hanus, V., Polasek, M., Kocovsky, P. "Synthesis of N-Alkylated and N-Arylated Derivatives of 2-Amino-2‘-hydroxy-1,1‘-binaphthyl (NOBIN) and 2,2‘-Diamino-1,1‘-binaphthyl and Their Application in the Enantioselective Addition of Diethylzinc to Aromatic Aldehydes." *Journal of Organic Chemistry.* 63 (22). pp. 7727-7737. 1998.
DOI: 10.1021/jo9807565

[18] Bringmann, G., Breuning, M. "Enantioselective addition of diethylzinc to aldehydes using novel axially chiral 2-aminomethyl-1-(2′-hydroxyphenyl)naphthalene catalysts." *Tertahedron: Asymmetry*. 9 (4). pp. 667-679. 1998.
DOI: 10.1016/s0957-4166(98)00020-2

[19] Ko, D.-H., Kim, K.-H., Ha, D.-C. "Enantioselective Additions of Diethylzinc and Diphenylzinc to Aldehydes Using 2-Dialkyl-aminomethyl-2‘-hydroxy- 1,1‘-binaphthyls. *Organic Letters.* 4 (21). pp. 3759-3762. 2002.
DOI: 10.1021/ol026761j

[20] Faigl, F., Schlosser, M. "*N*-phenylpyrrole: A kinetic, though not thermodynamic preference for dilithiation." *Tetrahedron.* 49 (45). pp. 10271-10278. 1993.
DOI: 10.1016/s0040-4020(01)80556-1

[21] Fogassy, E., Ács, M., Tőke, L. "*Optikai izomerek előállítása*, *A kémia legújabb eredményei 65.*" Budapest: Akadémiai Kiadó. 1987.

[22] Faigl, F., Vas-Feldhoffer, B., Kudar, V., Czugler, M., Pál, K., Kubinyi, M. "Synthesis and optical resolution of 1-[(3-carboxy-1,1′-biphenyl)-2-yl]-1*H*-pyrrole-2-carboxylic acid." *Chirality*. 21 (10). pp. 905-910. 2009.
DOI: 10.1002/chir.20686

[23] Faigl, F., Vas-Feldhoffer, B., Kubinyi, M., Pál, K., Tárkányi, G., Czugler, M. "Efficient synthesis of optically active 1-(2-carboxymethyl-6-ethylphenyl)-1H-pyrrole-2-carboxylic acid: a novel atropisomeric 1-arylpyrrole derivative." *Tetrahedron: Asymmetry.* 20 (1). pp. 98-103. 2009.
DOI: 10.1016/j.tetasy.2009.01.010

[24] Faigl, F., Mátravölgyi, B., Erdélyi, Zs., Pál, K., Hessz, D., Kubinyi, M. "Synthesis and resolution of 4,4,6,6-tetramethyl-4*H*,6*H*-pyrrolo[1,2-*a*][4,1]benzoxazepine-1,10-dicarboxylic acid." *Tetrahedron: Asymmetry*. 21 (24). pp. 2920-2924. 2010.
DOI: 10.1016/j.tetasy.2010.12.005

[25] Faigl, F., Mátravölgyi, B., Holczbauer, T., Czugler, M., Madarász, J. "Resolution of 1[2-carboxy-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxylic acid with methyl (*R*)2phenylglycinate, reciprocal resolution and second order asymmetric transformation." *Tetrahedron: Asymmetry.* 22 (20-22). pp. 1879-1884. 2011.
DOI: 10.1016/j.tetasy.2011.10.021

[26] Faigl, F., Mátravölgyi, B., Deák, Sz., Holczbauer, T., Czugler, M., Balázs, L., Hermecz, I. "Useful, regioflexible methods for functionalization of 1-phenylpyrrole derivative." *Tetrahedron*. 68 (22). pp. 4259-4266. 2012.
DOI: 10.1016/j.tet.2012.03.070

[27] Faigl, F., Mátravölgyi, B., Szöllősy, Á., Czugler, M., Tárkányi, G., Vékey, K., Kubinyi, M. "Synthesis of atropisomeric 1-phenylpyrrole-derived amino alcohols: New chiral ligands." *Chirality*. 24 (7). pp. 532-542. 2012.
DOI: 10.1002/chir.22049

[28] Ding, Z., Tufariello, J. J. "A Facile Synthesis of 3-Pyrrolines." *Synthetic Communications*. 20 (2). pp. 227-230. 1990.
DOI: 10.1080/00397919008052287

[29] Faigl, F., Thurner, A., Farkas, F., Battancs, M., Poppe, L. "Synthesis and enantioselective rearrangement of (Z)-4-triphenylmethoxy-2,3-epoxybutan-1-ol enantiomers." *Chirality*. 19 (3). pp. 197-202. 2007.
DOI: 10.1002/chir.20361

[30] Farkas, F., Thurner, A., Kovács, E., Faigl, F., Hegedűs, L. "Hydrogenolysis of *O*-protected hydroxyoxetanes over palladium: An efficient method for a one-step ring opening and detritylation reaction." *Catalysis Communications.* 10 (5). pp. 635-639. 2009.
DOI: 10.1016/j.catcom.2008.11.007

[31] Rylander, P. N. "Solvents in catalytic hydrogenation." In: Jones, W. H. (ed) *Catalysis in Organic Syntheses*. New York: Academic Press. 1980.
DOI: 10.1016/b978-0-12-389050-4.50015-9

[32] Stegerhoek, L. J., Verkade, P. E. "Esters derived from batyl alcohol." *Recueil des Travaux Chimiques des Pays-Bas*. 75 (2). pp. 143-163. 1956.
DOI: 10.1002/recl.19560750203

[33] Mitsunobu, O. "The Use of Diethyl Azodicarboxylate and Triphenylphosphine in Synthesis and Transformation of Natural Products." *Synthesis.* 1981 (1). pp. 1-28. 1981.
DOI: 10.1055/s-1981-29317

[34] Faigl, F., Thurner, A., Battancs, M., Farkas, F., Poppe, L., Bódai, V., Kmecz, I., Simándi, B. "Efficient, scalable kinetic resolution of *cis*-4-benzyloxy-2,3-epoxybutanol." *Tetrahedron: Asymmetry.* 16 (23). pp. 3841-3847. 2005.
DOI: 10.1016/j.tetasy.2005.09.029

[35] Kovács, E., Thurner, A., Farkas, F., Faigl, F., Hegedűs, L. "Hydrogenolysis of *N*-protected aminooxetanes over palladium: An efficient method for a one-step ring opening and debenzylation reaction." *Journal of Molecular Catalysis A: Chemical.* 339 (1-2). pp. 32-36. 2011.
DOI: 10.1016/j.molcata.2011.02.008

[36] Rylander, P. N. "*Catalytic Hydrogenation over Platinum Metals*." New York: Academic Press. 1967.

[37] Freifelder, M. "*Practical Catalytic Hydrogenation*." New York: Wiley. 1971.

[38] Birkofer, L. "Gesetzmäßigkeiten bei der hydrierenden Spaltung von *N*-Benzyl-Verbindungen." *Berichte der deutschen chemischen Gesellschaft*. 75 (4). pp. 429-441. 1942.
DOI: 10.1002/cber.19420750420

[39] Baltzly, R., Buck, J. S. "Catalytic Debenzylation. The Effect of Substitution on the Strength of the O-Benzyl and N-Benzyl Linkages." *Journal of the American Chemical Society*. 65 (10). pp. 1984-1992. 1943.
DOI: 10.1021/ja01250a048

[40] Maxted, E. B., Biggs, M. S. "The catalytic toxicity of nitrogen compounds. Part I. Toxicity of ammonia and of amines." *Journal of the Chemical Society.* pp. 3844-3847. 1957.
DOI: 10.1039/JR9570003844

[41] Hegedűs, L., Máthé, T. "Hydrogenation of pyrrole derivatives. Part V. Poisoning effect of nitrogen on precious metal on carbon catalysts." *Applied Catalysis A: General.* 226 (1-2). pp. 319-322. 2002.
DOI: 10.1016/S0926-860X(01)00898-5

[42] Hegedűs, L. "Katalizátorok mérgeződése, katalizátorméreg típusú vegyületek hidrogénezése." *Magyar Kémiai Folyóirat.* 113 (4). pp. 139-144. 2007.
http://www.mkf.mke.org.hu/images/stories/docs/2007_4/139_144_4-2007.pdf

[43] Baltzly, R., Russell, P. B. "Catalytic Debenzylation. III. The Influence of α-Substitution on the Ease of Hydrogenolysis." *Journal of the American Chemical Society.* 75 (22). pp. 5598-5602. 1953.
DOI: 10.1021/ja01118a036

[44] Rylander, P. N. "*Catalytic Hydrogenation in Organic Syntheses.*" New York: Academic Press. 1979.

[45] Defauw, J. M., Murphy M. M., Jagdmann G. E., Hu H., Lampe J. W., Hollinshead S. P., Mitchell T. J., Crane H. M., Heerding J. M., Mendoza J. S., Davis J. E., Darges J. W., Hubbard F. R., Hall S. E. "Synthesis and Protein Kinase C Inhibitory Activities of Acyclic Balanol Analogs That Are Highly Selective for Protein Kinase C over Protein Kinase A." *Journal of Medicinal Chemistry*. 39 (26). pp. 5215-5227. 1996. DOI: 10.1021/jm960581w

[46] Oleksyszyn, J. "Aminophosphonic and Aminophosphinic Acid Derivatives in the Design of Transition State Analogue Inhibitors: Biomedical Opportunities and Limitations." In: Kukhar, V. P., Hudson, H. R. (eds).: *Aminophosphonic and Aminophosphinic Acids*. Chichester: John Wiley and Sons. 2000.

[47] Palacios, F., Alonso, C., de los Santos, J. M. "Synthesis of β-Aminophosphonates and -Phosphinates." *Chemical Reviews*. 105 (3). pp. 899-932. 2005. DOI: 10.1021/cr040672y

[48] Kudzin, Z. H., Kudzin, M. H., Drabowicz, J., Stevens, C. V. "Aminophosphonic Acids-Phosphorus Analogues of Natural Amino Acids. Part 1: Synthesis of α-aminophosphonic Acids." *Current Organic Chemistry*. 15 (12). pp. 2015-2071. 2011. DOI: 10.2174/138527211795703612

[49] Orsini, F., Sello, G., Sisti, M. "Aminophosphonic Acids and Derivatives. Synthesis and Biological Application." *Current Medicinal Chemistry*. 17 (3). pp. 264-289. 2010. DOI: 10.2174/092986710790149729

[50] Mucha, A., Kafarski, P., Berlicki, Ł. "Remarkable Potential of the α-Aminophosphonate/Phosphinate Structural Motif in Medicinal Chemistry." *Journal of Medicinal Chemistry*. 54 (17). pp. 5955-5980. 2011. DOI: 10.1021/jm200587f

[51] Atherton, F. R., Hassall, C. H., Lambert, R. W. "Synthesis and structure-activity relationships of antibacterial phosphonopeptides incorporating (1-aminoethyl)phosphonic acid and (aminomethyl)phosphonic acid." *Journal of Medicinal Chemistry*. 29 (1). pp. 29-40. 1986. DOI: 10.1021/jm00151a005

[52] Rozenfeld, R., Iturrioz, X., Okada, M., Maigret, B., Llorens-Cortes, C. "Contribution of Molecular Modeling and Site-Directed Mutagenesis to the Identification of a New Residue, Glutamate 215, Involved in the Exopeptidase Specificity of Aminopeptidase A." *Biochemistry*. 42 (50). pp. 14785-14793. 2003. DOI: 10.1021/bi034358u

[53] Sherin, S. A-M., Zhao, B., Murthy, K. H. M., Winborne, E., Choi, J. K., DesJarlais, R. L., Minnich, M. D., Culp, J. S., Debouck, C. "Inhibition of human immunodeficiency virus-1 protease by a C2-symmetric phosphinate. Synthesis and crystallographic analysis." *Biochemistry*. 32 (31). pp 7972-7980. 1993. DOI: 10.1021/bi00082a019

[54] Hudson, H. "Aminophosphonic and Aminophosphinic Acids and their Derivatives as Agrochemicals." In: Kukhar, V. P., Hudson, H. R. (eds) *Aminophosphonic and Aminophosphinic Acids*. Chichester: John Wiley and Sons. 2000.

[55] Tanaka, F., Kinoshita, K., Tanimura, R., Fujii, I. "Relaxing Substrate Specificity in Antibody-Catalyzed Reactions: Enantioselective Hydrolysis of *N*-Cbz-Amino Acid Esters." *Journal of the American Chemical Society*. 118 (10). pp. 2332-2339. 1996. DOI: 10.1021/ja952220w

[56] Palacios, F., Alonso, C., de los Santos, J. M. "Asymmetric Synthesis of α-Substituted-β-Amino Phosphonates and Phosphinates and β-Amino Sulfur Analogs." In: Juaristi, E., Soloshonok, V. A. (eds).: *Enantioselective Synthesis of* β*-Amino Acids 2*. John Wiley and Sons. 2005.

[57] Ordóñez, M., Rojas-Cabrera, H., Cativiela, C. "An overview of stereoselective synthesis of α-aminophosphonates." *Tetrahedron*. 65 (1). pp. 17-49. 2009. DOI: 10.1016/j.tet.2008.09.083

[58] Albrecht, Ł., Albrecht, A., Krawczyk, H., Jørgensen, K. A. "Organocatalytic Asymmetric Synthesis of Organophosphorous Compounds." *Chemistry – A European Journal*. 16 (1). pp. 28-48. 2010. DOI: 10.1002/chem.200902634

[59] Ordóñez, M., Viveros-Ceballos, J. L., Cativiela, C., Arizpe, A. "Stereoselective Synthesis of α-Aminophosphonic acids Analogs of the 20 Proteinogenic α-Amino acids." *Current Organic Synthesis*. 9 (3). pp. 310-341. 2012. DOI: 10.2174/157017912801270595

[60] Song, C. E. (ed) "*Cinchona Alkaloids in Synthesis and Catalysis*." Weinheim: WILEY-VCH Verlag GmbH & Co. KgaA. 2009.

[61] 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*. 16 (23). pp. 3837-3840. 2005. DOI: 10.1016/j.tetasy.2005.10.020

[62] Bakó, P., Vizvárdi, K., Bajor, Z., Tőke, L. "Synthesis and application in asymmetric synthesis of azacrown ethers derived from D-glucose." *Chemical Communications*. (11). p. 1193-1194. 1998. DOI: 10.1039/a802098a

[63] Jászay, Zs., Pham, T. S., Németh, G., Bakó, P., Petneházy, I., Tőke, L. "Asymmetric Synthesis of Substituted α-Amino Phosphonates with Chiral Crown Ethers as Catalysts." *Synlett*. 2009 (9). pp. 1429-1432. 2009. DOI: 10.1055/s-0029-1217166

[64] 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-aminophosphonates." *Tetrahedron: Asymmetry*. 22 (4). pp. 480-486. 2011. DOI: 10.1016/j.tetasy.2011.02.002

[65] 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*. 24 (24). pp. 1605-1614. 2013. DOI: 10.1016/j.tetasy.2013.10.008

[66] Pham, T. S., Balázs, L., Petneházy, I., Jászay, Zs. "Enantioselective Michael addition of diethyl cyanomethyl phosphonate to chalcones using bifunctional cinchona derived organocatalysts: Synthesis of chiral precursors of α-substituted β-aminophosphonates." *Tetrahedron: Asymmetry*. 21 (3). pp. 346-351. 2010. DOI: 10.1016/j.tetasy.2010.01.006