Department of Organic and Nuclear Chemistry
Faculty of Science
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Ph.D. Thesis

Chiral metallocomplex synthons of α-amino acids. Synthesis, physical-chemical properties and applications

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This work (or its substantial part) has never been submitted as a PhD Thesis anywhere else except for the Faculty of Science, Charles University.

Contents

"... ultraviolet radiation, which is common in interstellar space, can interact with icy mixtures of water and other simple molecules found there at temperatures of less then 15K to produce amino acids"

Chem. Eng. News **2002**, *80* (13), 14

1. INTRODUCTION

Chiral stoichiometric α-amino acid synthons are often the optimal choice for preparation of small batches of new α-amino acids [1-15] and for special applications like the preparation of radiolabelled α-amino acids [16-19]. While efficient catalytic approaches have been suggested for a number of α-amino acids, [20-21] development of such catalytic syntheses often requires time-consuming screening for an optimal catalyst, precursor and reaction conditions. Application of nickel(II) complexes of Schiff bases of (*S*)-*N*-benzylproline (2-benzoylphenyl)amide (BPB) and α-amino acids for asymmetric synthesis of α-amino acids has become a popular synthetic method due to cheap starting compounds, easy chromatographic detection (λ=330 nm) of both starting and alkylated complexes and re-usage of BPB without any loss of enantiomeric purity of its chiral centre after several turnovers (Scheme 1) [22-24][i]. The complexes provide the easy generation of an

[i] Paper XI

intermediate carbanion due to high acidity of α-hydrogen of an amino acid fragment ($pK_a \approx 19$) [25].

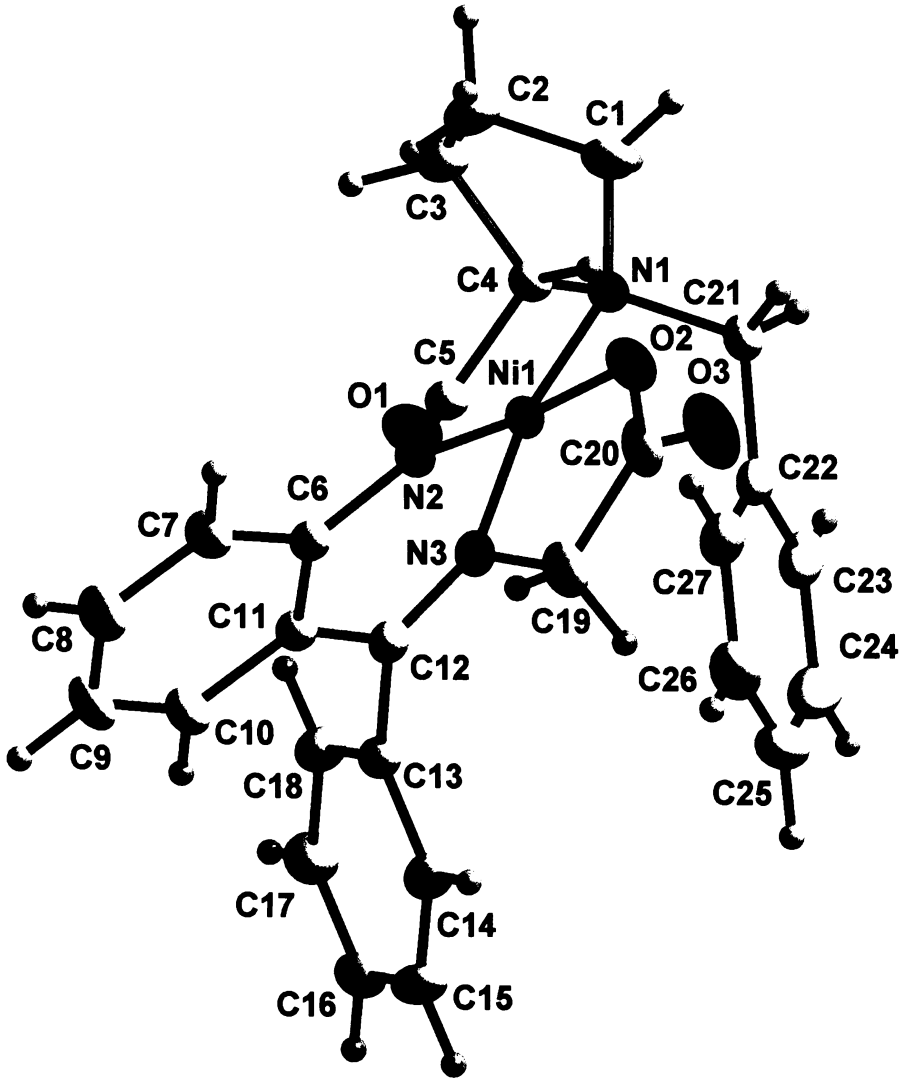


Figure 1. Nickel(II) complex of the Schiff base of BPB and glycine (**2**). Numbering scheme.

Two decades of worldwide research dealing with this chemistry have resulted in a number of synthetic applications [26-42]. A Moscow group led by Professor Belokon suggested the core structure (**2**, Figure 1). The group developed main synthetic applications as well. They include reaction of glycine synthon with:

1 aldehydes leading to α-amino-β-hydroxy acids [22, 43];

2 α,β-unsaturated esters leading to β- or γ-substituted glutamic acids [44];

3 α,β-unsaturated aldehydes and ketones leading to β-, γ- or δ-substituted prolines [45];

Alkylation of glycine or alanine synthons with alkyl-, benzyl- or allylhalides leads to analogues of aromatic α-amino acids or α-amino acids with aliphatic side chains [46]. Original procedures were further developed by a group led by Professor Soloshonok. They prepared a number of fluoro-substitured analogues of phenylalanine [47] and β,β-disubstituted serine [48] and some phosphorus-containing α-amino acids [49, 50] This group proposed a procedure for a gentle control of stereochemistry of both chiral centres of α-amino-β-hydroxy acids [22]. Application of the second chiral auxiliary attached to α,β-unsaturated electrophile allowed them to improve significantly the control of stereochemistry of β- and γ-carbons of resulting pyroglutamic acids (they did not suggest a procedure for preparation of similarly substituted glutamic acids) [31, 42]. A group led by Professor Danion [35] suggested an original one-pot formation of a cyclic core of a quaternary amino acid containing two chiral centres. This approach was further developed by the Moscow group [51]. The most common application of nickel complexes as chiral amino acid synthons for preparation of analogues of aromatic α-amino acids or α-amino acids with aliphatic side chains consists of several standard steps (Scheme 1):

1 Template preparation of the starting complex **2** from glycine, nickel salt and re-usable chiral auxiliary BPB.

2 Alkylation of complex **2** with an electrophile in an aprotic solvent.

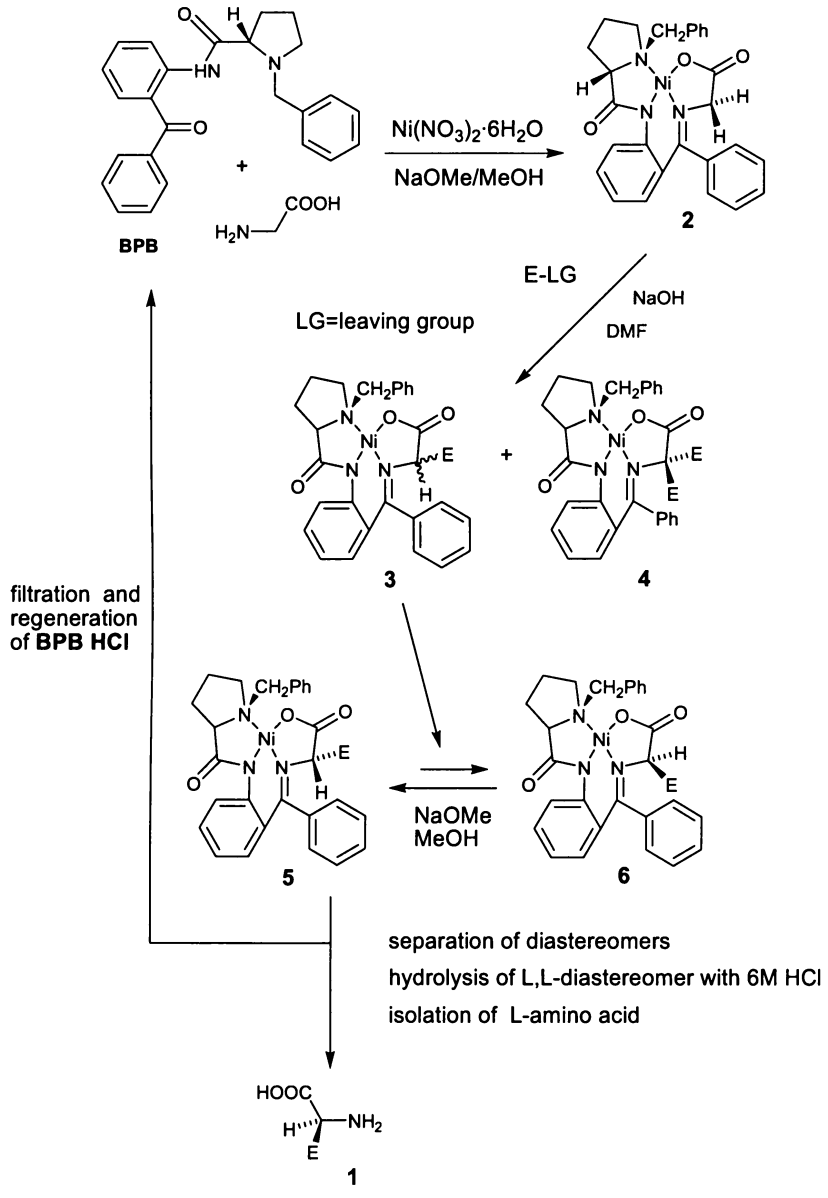
3 Epimerization of **3** in the reaction mixture in MeONa/MeOH [46].

4 Separation of diastereomers of the alkylated complex **5** and **6**, starting

complex **2** and a minor amount of a product of bis-alkylation **4**.

5 Optional epimerization of the undesired diastereomer **6** in MeONa/MeOH.

6 Acid hydrolysis of diastereomerically pure complex **5**, isolation of the amino acid **1** and regeneration of BPB.



Scheme 1 Asymmetric synthesis of α-amino acids via nickel complexes. Regeneration of the chiral auxiliary BPB.

Less attention has been paid to a deep physical-chemical investigation of the complexes. Scientific curiosity is a good reason for such research; properties of neutral chiral complexes of nickel (d^8) constitute an interesting research subject due to their compatibility with various NMR techniques, chiroptical techniques like circular dichroism and frequently successful preparation of single crystals for X-ray structure determination. While at the beginning of my interest in this topic, the complexes were purely a curiosity, the confrontation of my own results with detected problems that arose during application of the complexes for synthesis of various non-coded α-amino acids led to an understanding of the importance of structure determination tools. In many cases organic chemists applied naive mechanistic ideas of how the predominant formation of one diastereomer during alkylation of the complexes could be achieved. Insight from colleagues with different backgrounds (neurologists, oncologists, toxicologists, radiochemists, spectroscopists, theoretical chemists) shifted our specific interest to structures of α-substituted complexes (Scheme 1, compounds **5** and **6**), for very challenging applications as evaluation of applicability of the complexes for preparation of [^{11}C]substances for positron emission tomography or disclosure of structures of unstable electrophilic synthons of α-amino acids.

2. AIMS

The principal aims of the work presented in this Thesis are:

1 to increase stereochemical output of alkylation of the complexes in order to avoid or at least simplify separation of diastereomeric products of alkylation;

2 to elucidate analytical methods for determination of stereochemistry of chiral centres of the complexes;

3 to develop an environmentally-friendly procedure for multikilogram-scale preparation of starting metallocomplex chiral synthons of α-amino acids;

4 to re-evaluate applicability of metallocomplex chiral synthons of α-amino acids for asymmetric synthesis of ^{11}C-labeled α-methyl amino acids (as a more challenging goal).

3. OUTLINE OF THIS THESIS

This Thesis is based on twelve papers published by the author and co-workers. Their contents are briefly characterised in the following text with the aim to emphasize the main ideas of the papers. More details are given in Chapter 4 and copies of these papers are in Chapter 9.

Paper I (*Collect. Czech. Chem. Commun.* **1995**, *60*, 990) discloses conformations of three model complexes in their $CDCl_3$ solutions. Proximity of *ortho*-protons of the benzyl group to both the α-proton of the proline residue and substituents in α-position of the amino acid fragment leads to formulation of the first hypothesis about structure of the improved synthon – it should carry substituents in *ortho*-positions of the benzyl group.

Paper II (*Transition Metal Chem.* **2003**, *28*, 475) describes the influence of a polar solvent to spin-spin interactions observed in ^{13}C-NMR spectra of the complex derived from glycine. The high-quality X-ray structure of the complex is presented. MP2 single-point modelling of the complex clearly shows that available computers are too poor for realistic modelling of the structure of the complex in a vacuum.

In the *Paper III* (*Acta Crystallogr. A* **2004**, *60*, 510) the same complex is studied, now with experimental synchrotron X-ray measurement of electron density and MP2 modelling followed by topologic analysis. The polarisation of electron density in an aromatic electron cloud of the benzyl group towards positively charged nickel atoms is proved by experiment. The crystallographic data and results of quantum-chemical modelling described in Chapter 3 are used.

Paper IV (*Polyhedron* **2007**, *26*, 911) continues with crystallographic and NMR studies of the complexes bearing substituents. Observed influence of two methyl substituents in α-position of the amino acid fragment to spin-spin interactions in a ^{13}C-NMR spectrum and the conformation of the complex in solid state are in good agreement with expectations. The complex with two methyl substituents is a lead compound for synthetic intermediates for preparation of enantiomerically pure α-[^{11}C]methyl amino acids.

Paper V (*Chem. Heterocycl. Comp.* **2000**, *36*, 544) describes the preparation of substituted *N*-benzylprolines, one of witch is used for the synthesis of new glycine and alanin synthons.

Paper VI (*Transition Metal Chem.* **2002**, *27*, 884) continues with the preparation of new glycine and alanin synthons. Their stereodiscrimative properties are compared with previously published structures and found to be superior. Model reactions and spectroscopic analytical methods are suggested aimed to eliminate possible error in determination of the ratio of diastereomers characteristic for HPLC analyses. All measurements of *d.e.*'s are done in an NMR tube.

Paper VII (*Collect. Czech. Chem. Commun.* **2005**, *70*, 1397) contains a description of the preparation of the non-coded amino acid (*S*)-2-naphthyl-β-alanine via a chiral complex. Synthetic steps and analytical methods used for structure elucidation and determination of stereochemistry of a newly created chiral centre (circular dichroism, NMR, crystallography) are described in detail in order to enable quick introduction into standard methodology for novices.

Paper VIII (*Magn. Reson. Chem.* **1998**, *36*, 351) describes the preparation of complexes derived from selectively isotopically labelled

glycines and long-range spin-spin interactions observed in ^{13}C-NMR and ^{15}N-NMR spectra of the complexes.

In the *Paper IX* (*Collect. Czech. Chem. Commun.* **1998**, *63*, 990) the search for long-range intramolecular interactions continues; the effect of H ... Br interactions to ^{1}H-NMR spectra is described.

Paper X (*Arkivoc* **2006**, 92) gives one more example of a crystal structure of a complex derived from a non-coded amino acid which is unstable in a free form.

Paper XI (*Green Chem.* **2002**, *4*, 71) addresses the environmental dimension of the application of the complexes. An improved procedure is suggested which allows a significant decreased amount of nickel in waste water.

Paper XII (*Czech. J. Phys.* **2006**, *56,* D689) contains a description of the first synthetic steps towards the asymmetric preparation of enantiomerically pure α-[^{11}C]methyl amino acids.

4 RESULTS AND DISCUSSION

4.1 Stereochemical output of alkylation of nickel(II) complexes of Schiff bases of α-amino acids and (*S*)-*N*-benzylproline (2-benzoylphenyl)amide or its analogues with alkyl halides[i]

During a long period of development of chiral nickel complexes, sporadic attempts were made to understand the mechanism and facilitate the control of the stereochemical output of the alkylation of the complexes by alkyl halides [22, 43, 46, 52, 53]. In this chapter, I will present a short overview of current understanding of factors that affect stereochemistry at the α-carbon atom of the amino acid fragment of the complex (C–19) in such reactions. There are two common cases – (i) thermodynamically controlled synthesis of α-amino acids (α-monoalkylated glycines) and (ii) kinetically controlled synthesis of α-alkyl amino acids (non-symmetrically α-bisalkylated glycines) [46]. Realisation of thermodynamic control requires a two-step procedure (Scheme 2):

1 Alkylation of a carbanion generated from the nickel(II) complex of the Schiff base of BPB and glycine 1. This step usually led to moderate diastereomeric excess of the *4S,19S* diastereomer.

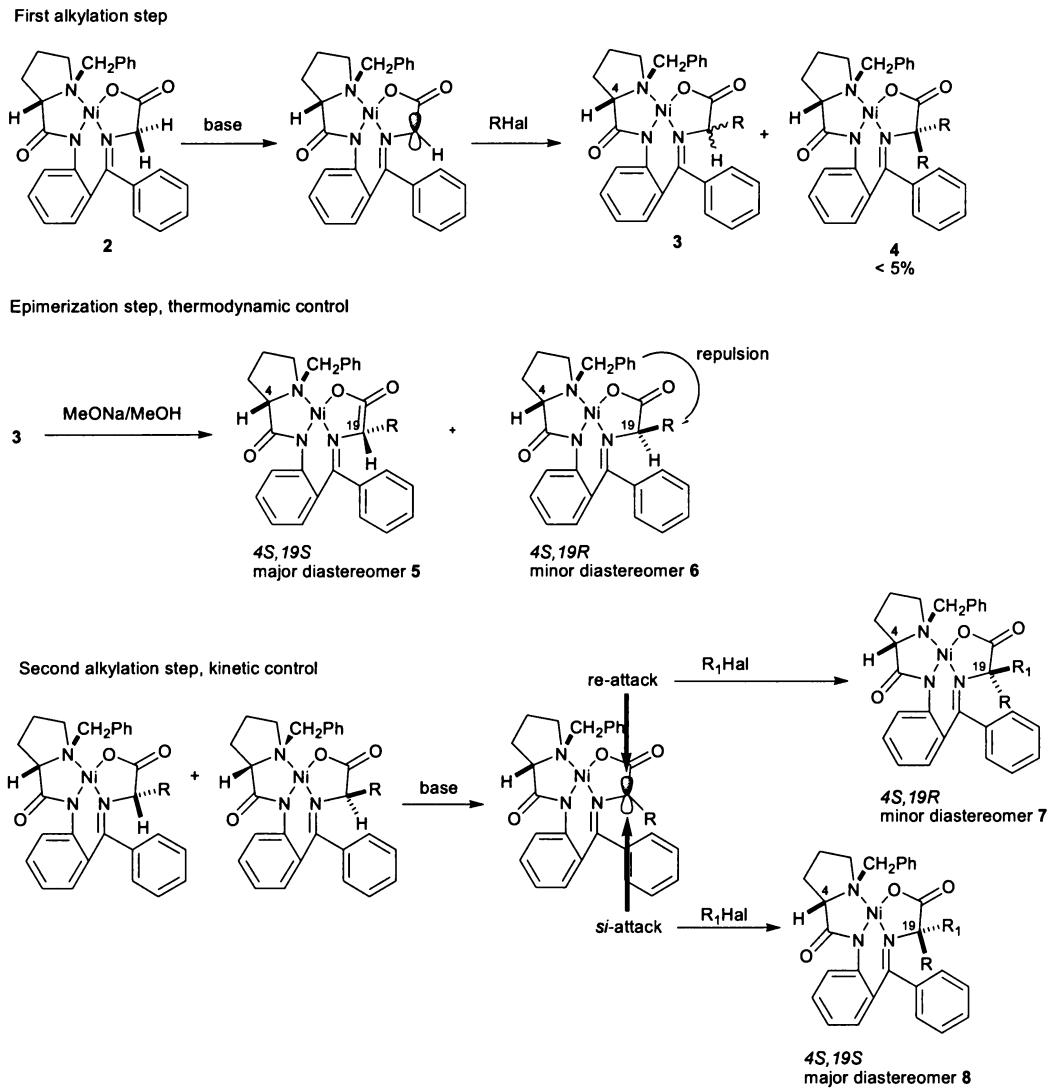
2 Epimerization of the reaction mixture could be achieved by application of an excess of base (*e. g.* KOH, KOBu-*t*) during the alkylation step or as a separate step when a crude reaction product is dissolved in MeONa/MeOH [46]. It was observed that the application of the excess of base during the alkylation step in an aprotic solvent usually leads to a lower diastereomeric excess than that one achieved in the separate

[i] Full citations of Papers I-XII are given in Chapter 7

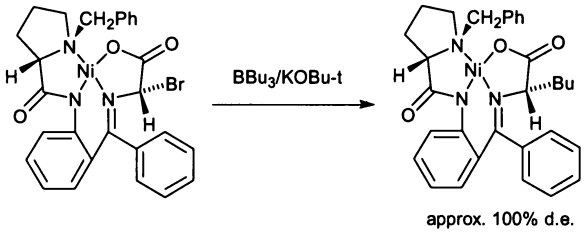
MeONa/MeOH step, with one important exception. It was found that the reaction of the nickel(II) complex of the Schiff base of BPB and (*S*)-α-bromoglycine with BBu_3/KOBu-*t* in MeCN leads to the formation of the only diastereomer of the nickel(II) complex of the Schiff base of BPB and 2-aminohexanoic acid (norleucine) (Scheme 3).[i] This finding was further applied for epimerization of the nickel(II) complex of the Schiff base of BPB and [^{11}C]alanine in KOBu-*t*/MeCN leading to a diastereomerically pure complex [54]. In the case of incomplete shift of the equilibrium during epimerization, the procedure might be applied one more time to the minor *SR* diastereomer after its separation by crystallisation or chromatography.

A purely kinetic control is realised in the case of the formation of the quaternary chiral centre during alkylation of nickel (II) complexes of Schiff bases of BPB and α-monoalkylated glycines (Scheme 2). The lack of acidic α-H (H–19) in the amino acid fragment of the resulting complex 3 makes thermodynamic control by epimerization impossible.

[i] Popkov, Saporovskaya, Belokon, *unpublished results*.



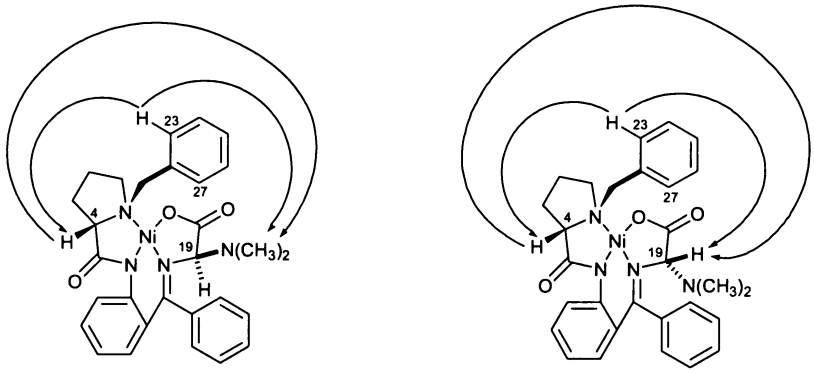
Scheme 2 Thermodynamic and kinetic control of diastereoselectivity of alkylation of the complexes



Scheme 3 Diastereospecific alkylation with BBu_3

4.2 Modification of the synthon structure in order to achieve higher asymmetric induction

In an early work, *Belokon et al.* hypothesised that the introduction of a trimethylamino electron-withdrawal substituent into the *para*-position of the benzyl group would result in a donation of electron density from nickel orbitals to an electron cloud of the benzyl group and the formation of a charge-transfer complex, thus resulting in additional stabilisation of the 4*S*,19*S* diastereomer of the complex [53]. In the 4*S*,19*R* diastereomer, steric repulsion of the bulky *para*-substituent of the benzyl group and a substituent of C–19 should disable this kind of stabilisation. A following experiment did not confirm the hypothesis. The complex with the electron-withdrawal substituent demonstrated lower asymmetric induction, than did a similar complex with smaller dimethylamino electron-donor substituents in the *para*-position [53]. The same negative results were obtained in the case when electron-withdrawal picolyl groups replaced the benzyl group of the complex [28]. In the solid state no coordination of picolinic nitrogen to nickel was observed [55].



Scheme 4 NOE interactions

Our comparison of partially interpreted solid-state ^{1}H–NMR and ^{13}C–NMR spectra of the nickel(II) complex of Schiff bases of (*S*)-*N*-

benzylproline (2-benzoyl-4-methylphenyl)amide and glycine with the same spectra recorded in $CDCl_3$ solution indicated that conformation of the complex is similar in both $CDCl_3$ solution and in solid-state.[i] NOESY investigation of the nickel(II) complex of Schiff bases of BPB and glycine and both diastereomers of nickel(II) complexes of Schiff bases of BPB and 2-amino-2-dimethylaminoacetic acid (α-dimethylaminoglycine, *R* and *S* enantiomers) demonstrated that in any complex the *ortho*-protons of the benzyl group (H–23 and H–27) give the cross-peak with both α-proton of the proline fragment (H–4) and α-proton of the amino acid fragment (H–19) or the dimethylamino group protons (Scheme 4).[ii] In the NMR time scale protons H–23 and H–27 are indistinguishable. Similar NOE interactions were confirmed by a number of other complexes of α-monosubstituted glycines[iii] (H-4 to H-19 NOE interactions or H-23 to H-19 NOE interactions were not observed in the spectra of complexes derived from α-methyl-α-amino acids[iv]). In several cases direct NOE interactions between H–4 and H–19 or a side chain attached to C–19 were observed. We draw two practical conclusions based on the observations:

1 NOE interactions between H–23 (H–27) and H–19 or a side chain attached to C–19 allow absolute configuration determination for C–19 in many cases.

2 For both thermodynamic and kinetic control of C–19 stereochemistry, substitution of H–23 and H–27 with bulkier substituents should increase diastereoselectivity of alkylation of C–19 with alkyl halides (followed by epimerization for complexes derived from α-monoalkylated glycines). Mechanisms of action of the *ortho*-substituents in these two cases are different:

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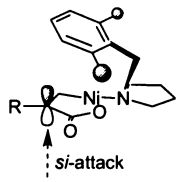
[i] Jakobsen, Popkov, *unpublished results*
[ii] Paper I
[iii] a) Paper I, b) Jirman, Lycka, Nadvornik, Popkov, *unpublished results*
[iv] a) Paper IV, b) Jirman, Lycka, Popkov, *unpublished results.*

a) under thermodynamically controlled conditions, when interconversion of the diastereomers is possible, free energy of the *4S,19R* diastereomer is higher due to steric repulsion between the *ortho*-substituents of the benzyl group and the amino acid side chain attached to C–19 (Scheme 1);

b) under kinetically controlled conditions higher steric shielding of C–19 by the substituted benzyl group leads to higher preference of *si*-attack over *re*-attack (Scheme 5). Such a control requires a conformation of the complex when the benzyl group is rotated towards the nickel atom.

In both cases 4S,19S/4S,19R ratio[i] should be higher in the case of complex carrying bulky substituents at C–23 and C–27.



Scheme 5 *Si*-attack (part of the complex structure is omitted for clarity).

We studied the influence of electronic factors. X-Ray structure determination of **2** (Figure 1) followed by static electron density mapping proved an electrostatic interaction between nickel orbitals and the aromatic system of the benzyl group. A partial positive charge on the nickel atom leads to polarisation of the benzyl group π-electron density towards the nickel atom (Figures 2, 3).

[i] In assumption that R_2 has priority over R_1 according to Cahn-Ingold-Prelog rules.

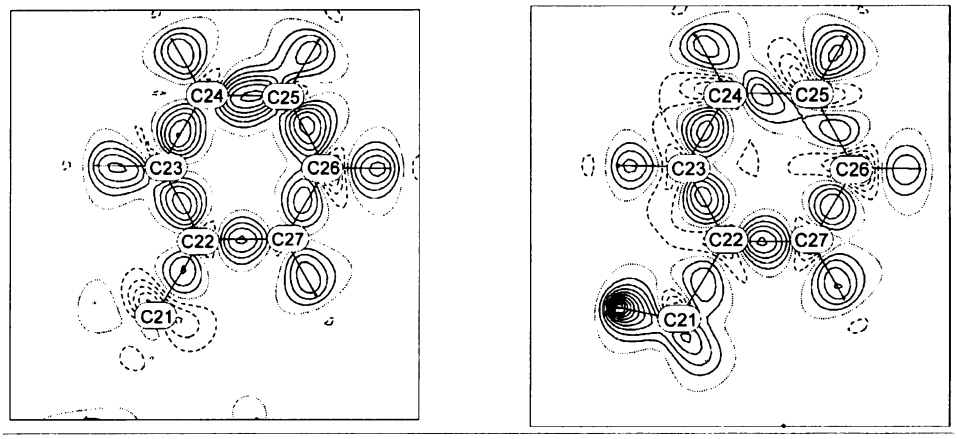


Figure 2 Polarisation of electron density towards one of the *ortho*-carbons which is the closest to the nickel atom (static electron deformation densities 0.3 Å below (closer to the nickel atom) and 0.3 Å above the plane defined by the atoms C(22), C(27) and C(23); positive, negative, and zero contours are represented by solid, dashed and dotted curves; contour spacing 0.05 e/Å^3).

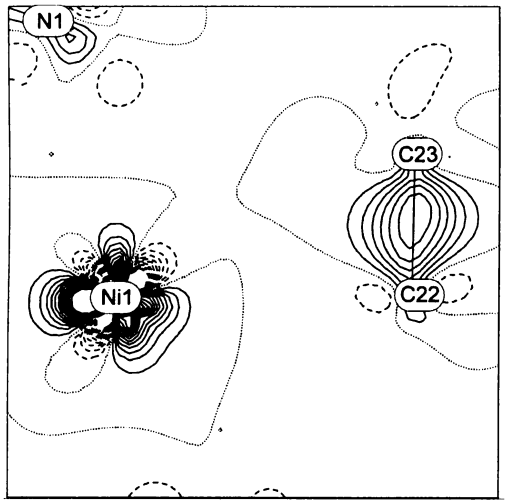
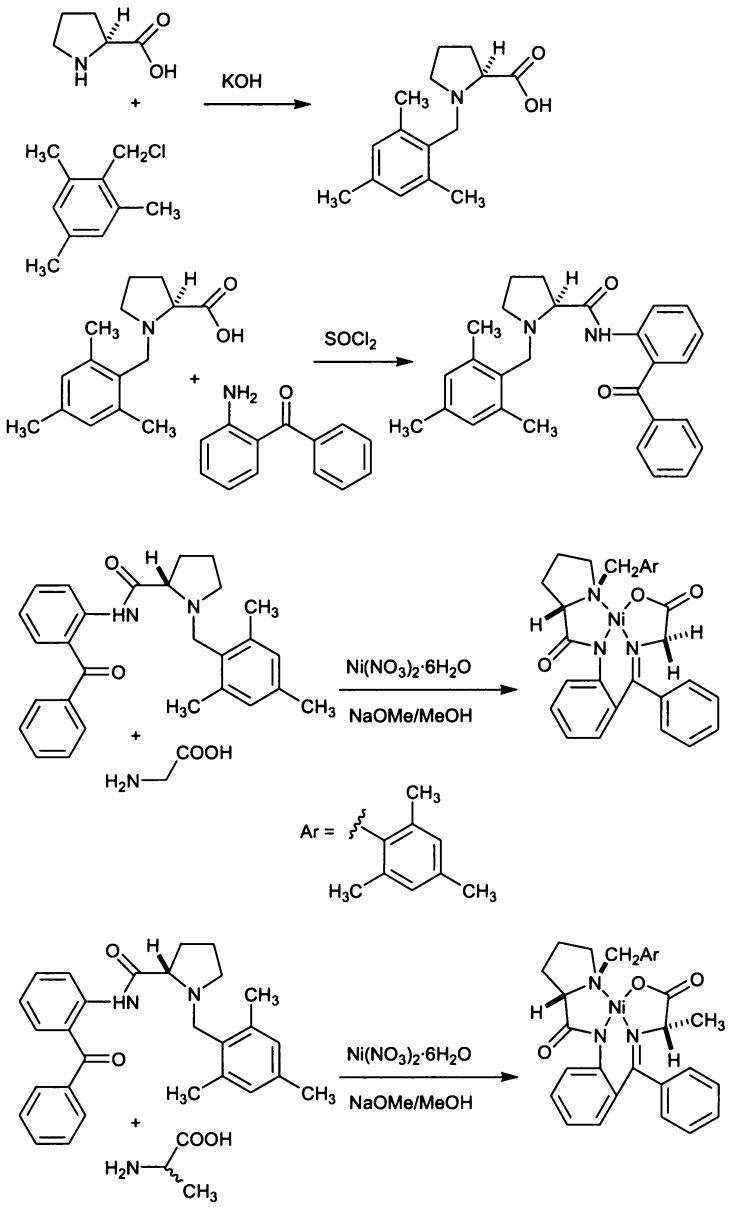


Figure 3. Absence of covalent bonding between π-system of the benzyl ring and the nickel atom (static electron deformation densities in the plane defined by the atoms Ni(1), C(22) and C(23); positive, negative, and zero contours are represented by solid, dashed and dotted curves; contour spacing 0.05 e/Å^3).

The interaction between the induced dipole and the nickel atom is partially responsible for stabilisation of a conformation when the benzyl group is rotated towards nickel, thus enabling steric shielding of the *re*-side of C–19 by the benzyl group. Such an interaction was also confirmed by distortion of the "tetrahedral" N - C–21 - C–22 angle to 113.95(3)°. In spite of strong steric repulsion between the nickel atom and the benzyl group, leading to the distortion, impact of electrostatic

interaction overcompensates the repulsion thus preventing the benzyl group from rotation outside the nickel atom.[i]



Scheme 6 Preparation of the nickel (II) complexes bearing methyl substituents on the benzyl ring

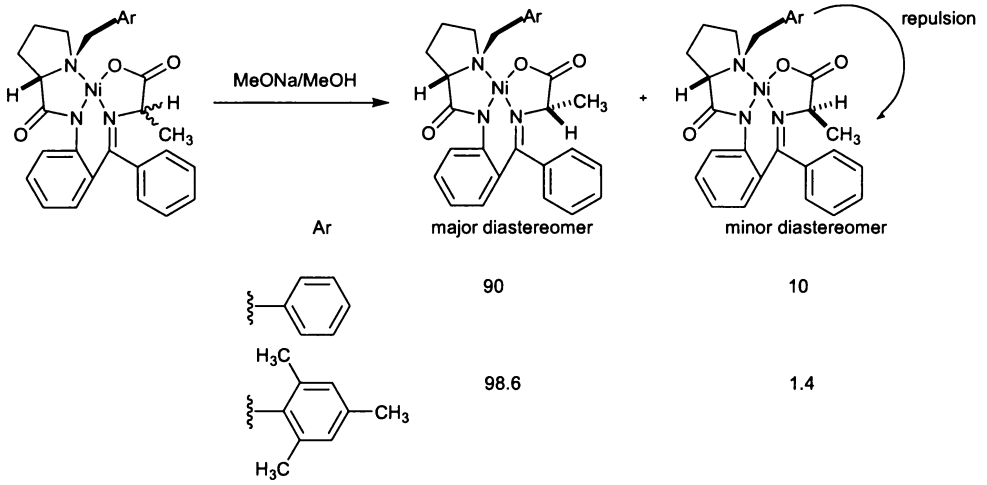
Our quantum-chemical modelling at both MP2[ii] and DFT [56] levels was unable to reveal fine details of nickel-benzyl group orbital interactions. Bader's AIM analysis of strong covalent bonds gave good agreement

[i] Paper III.
[ii] Papers II and III

with experimental data; for possible weak interactions no new information was disclosed.[i] Future application of more extended basis sets for MP2 calculations will probably improve the quality of modelling.

The application of knowledge obtained by physical chemical methods led me to prepare nickel complexes bearing electron-donating substituents on the benzyl ring (Scheme 6).[ii]

The introduction of three methyl groups allowed achievement of > 97% *d. e.* after epimerization of a corresponding alanine complex (Scheme 7).[iii] Under the same conditions, epimerization of the non-substituted alanine complex led to 80% *d. e.* only (Scheme 7).

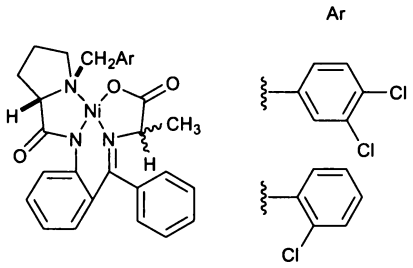


Scheme 7 Epimerization of the alanine complexes

To ensure the correct measurement of ratios of the diastereomers by integration of intensities of CH_2Ph protons, we compared the integral intensity of protons of the minor diastereomer with integral intensity of satellite signals of protons of the major diastereomer. Satellite signals originate from ^{1}H-^{13}C coupling, thus their intensity is 1.13%/2=0.565% of the intensity of the main peak. The integration of signals of similar

[i] Paper II.
[ii] Paper V, Paper VI
[iii] Paper VI.

intensity allows more accurate ratio determination.[i] For integration of intensities of CH_2Ph protons, crude reaction mixtures after epimerization were quenched by aqueous citric acid followed by chloroform extraction. Extracts were evaporated, dissolved in $CDCl_3$ and measured. No chromatographic purification steps were applied in order to prevent unequal loss of diastereomers due to irreversible sorption on chromatographic sorbent.

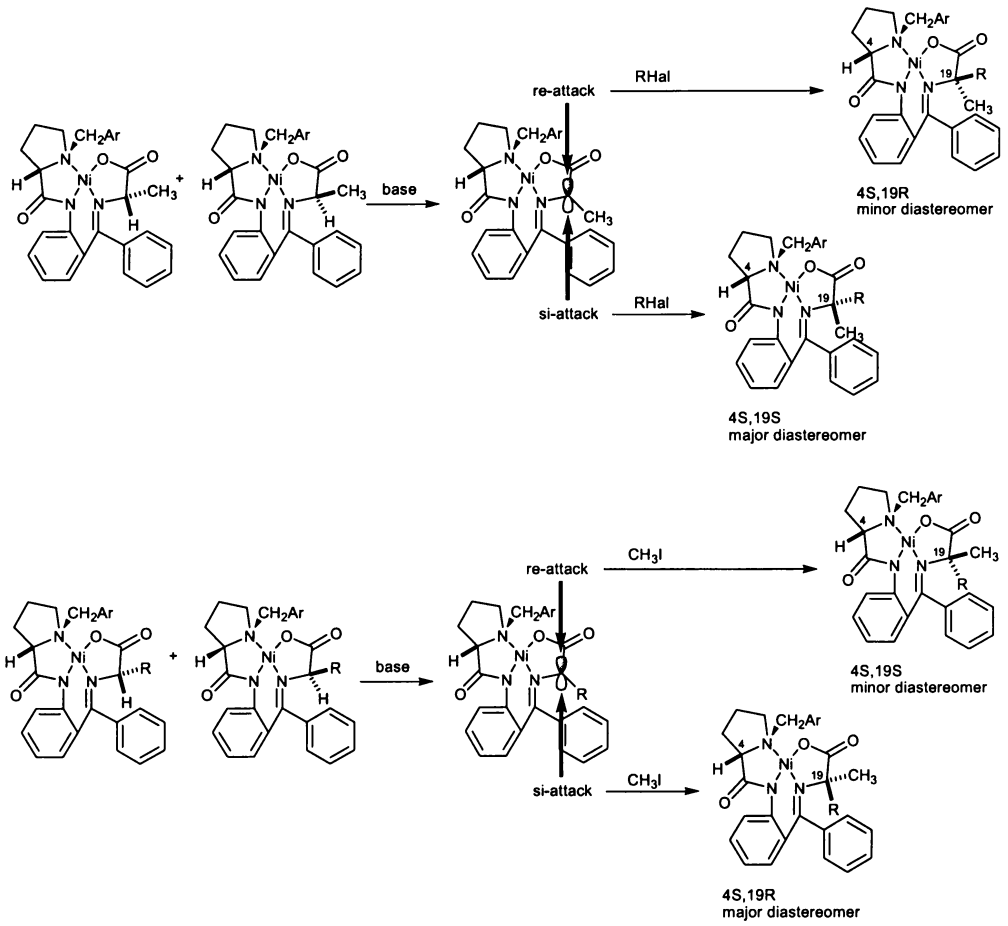


Scheme 8 Complexes bearing the 3,4-dichlorosubstituted or 2-chloro-substituted benzyl group

Promising results were also obtained with complexes bearing the 3,4-dichlorosubstituted or 2-chrorosubstituted benzyl group (Scheme 8) [57, 58]. For the alanine complex, *Belokon et al.* claimed stereospecific epimerization [59]. These authors hydrolysed the epimerized complex, isolated alanine on cation-exchanger and afterwards derivatised the amino acid with a chiral regent and determined the ratio of the enantiomers by HPLC with UV-VIS detector [59]. A number of chromatographic steps and the possible discrimination of the enantiomers during the derivatisation step renders this result less reliable.

We also tested the complex bearing 2,4,6-trimethylgroup in kinetically controlled alkylation. From a practical point of view there are two different synthetically relevant cases:

[i] Paper VI



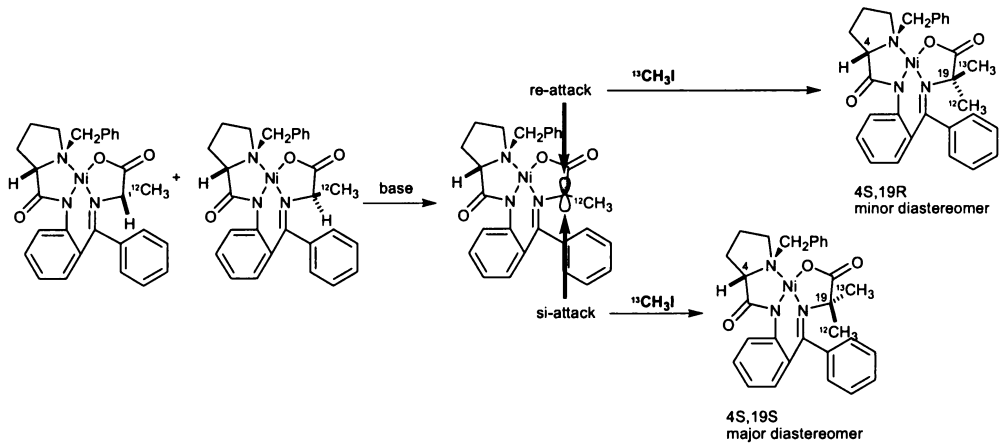
Scheme 9 Stereochemistry of alkylation of alanine complexes with alkyl halides and alkylation of complexes derived from amino acids bearing a longer side-chain with methyliodide

1 alkylation of an alanine synthon with bulky alkyl halide suitable for the preparative synthesis of α-methyl amino acids (Scheme 2, Scheme 9) [40, 46]. In this case the asymmetric induction is relatively high;

2 alkylation of an amino acid synthon (*e. g.* derivatives of protected tyrosine or DOPA) with methyl iodide (Scheme 9).[i] The asymmetric induction is very low due to the low steric volume of methyl iodide compared with some bulky alkyl halide in the first case. However, such synthesis is of practical

[i] Paper XII

importance in the case of a radiolabelled α-methyl amino acids preparation.[i] [^{11}C]Methyliodide or [^{14}C]methyliodide are much easier to prepare compared to more sophisticated radiolabelled alkyl halides.



Scheme 10 Designed model reaction for elucidation of the stereodiscriminative power of different alanine complexes (kinetic control of diastereoselectivity)

Designed model reaction conditions cover both cases. The alanine complex is alkylated with (^{13}C)methyliodide/KOH (Scheme 10) in 1,3-dimethylimidasolidin-2-one.[ii] The resulting diastereomers are indistinguishable by chromatography, crystallisation or extraction because the chirality of C–19 originates from a different number of neutrons in otherwise the same methyl substituents. This unique property allows chromatographic purification of the reaction mixture before ^{13}C-NMR integration of the diastereomeric ratio. Such purification is necessary due to partial decomposition of the reaction mixture during alkylation of tertiary C–19. The presence of a low amount of ^{13}C in the starting complex and some ^{12}C in commercial $^{13}CH_3I$ required recalculation of the observed ratios of the integral intensities of the $^{13}CH_3$- signals in the ^{13}C-NMR spectra of the mixtures of the

[i] Paper XII
[ii] Paper VI.

diastereomers into diastereomeric excesses. I derived the following equation:

d. e. = 100-200·(a·[*S, R*]/[*S, S*]*-b)/(a-b)·(1+[*S, R*]/[*S, S*]*)

where [*S, R*]/[*S, S*]* is the ratio of the integral intensities of the ^{13}C-signals of the diastereomers

a is the abundance of ^{13}C in starting $^{13}CH_3I$

b is the natural abundance of ^{13}C

The complex bearing 2,4,6-trimethylgroup demonstrated a much higher prevalence of the *4S,19S* diastereomer over the *4S,19R* diastereomer (66% *d. e.*) than it was in the case of the original alanine complex (41% *d. e.*).

The introduction of electron-donating or electron-withdrawing substituents into position 9 (see Figure 1) has little effect on the stereochemical outcome. Their steric influence is negligible, the electronic effects are realised probably by pulling on or off the electron density around the nickel atom followed by changes in polarisation of an electron cloud belonging to the benzyl group. Methylation of such complexes bearing the methyl group, hydrogen or a chlorine atom in position 9 led to very similar ratios of diastereomers[i] [38].

For wider discussion see Papers I – VII and Paper XII.

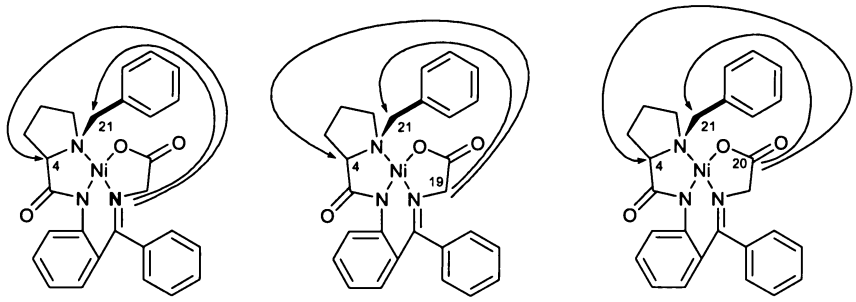
[i] Paper VI.

4.3 Determination of stereochemistry of newly created chiral centres. The existence of unique long-range spin-spin through space interactions in ^{13}C-NMR and ^{15}N-NMR spectra of some complexes

For determination of the stereochemistry of C–19, X-ray crystal structure determination is the superior method. I have grown single crystals of fourteen complexes from their benzene or acetone solutions and the structures have been solved. Five structures have been published to date. NOE interactions between H–23 (H–27) and H–19 or a side chain attached to C–19 (see above) allow quick determination of C–19 stereochemistry when there is no time to grow a single crystal for X-ray structure determination. Circular dichroism (CD) and optical rotation dispersion (ORD) spectra were employed for routine determination of the configuration of C–19 of complexes derived from α-monoalkylated glycines [46, 60, 61]. Differences between CD or ORD spectra of the nickel(II) complex of the Schiff base of BPB and glycine and spectra of diastereomers of nickel(II) complexes of Schiff bases of BPB and α-monoalkylated glycines are due to chromophore distortion introduced by C–19 substituents. It was empirically found that the methanolic solution of *4S,19S* diastereomers demonstrate a positive Cotton effect in the range of approximately 610 - 480 nm and a negative Cotton effect in the range of approximately 370 - 480 nm. *4S,19R* diastereomers demonstrate very different CD spectra from those of *4S,19S* diastereomers. Determination of the C–19 configuration of quaternary C–19 by NMR, CD or ORD spectroscopy is not always reliable, [40] X-ray crystallography is necessary in such cases.

Universal chiral synthons of (1-^{13}C)glycine, (2-^{13}C)glycine and (^{15}N)glycine of the same structure as unlabelled **2** were prepared as intermediates for selectively labelled peptides. We observed long-range spin-spin through space interactions $^{n}J(^{13}C; ^{13}C)$ and $^{n}J(^{13}C; ^{15}N)$ in their

^{13}C-NMR and ^{15}N-NMR spectra in $CDCl_3$ during investigation of the synthons (Scheme 11).[i]



Scheme 11 The long-range spin-spin through space interactions $^{n}J(^{13}C; ^{13}C)$ and $^{n}J(^{13}C; ^{15}N)$ in the ^{13}C-NMR and ^{15}N-NMR spectra of $CDCl_3$ solutions of **2** prepared from (1-^{13}C)glycine, (2-^{13}C)glycine and (^{15}N)glycine

Similar phenomena – long-range intramolecular H ... Br bonding is present in complexes derived from α-(*S*)-bromoglycine.[ii] Fellow theoreticians have been running quantum-chemical modelling of the complexes on supercomputers abroad aiming to explain the observations.

For concrete examples and relevant discussion see Papers I, IV, VII, VIII, IX.

[i] Paper VIII
[ii] Paper IX

4.4 Development of an environmentally-friendly procedure for multikilogram-scale preparation of starting metallocomplex chiral synthons of α-amino acids

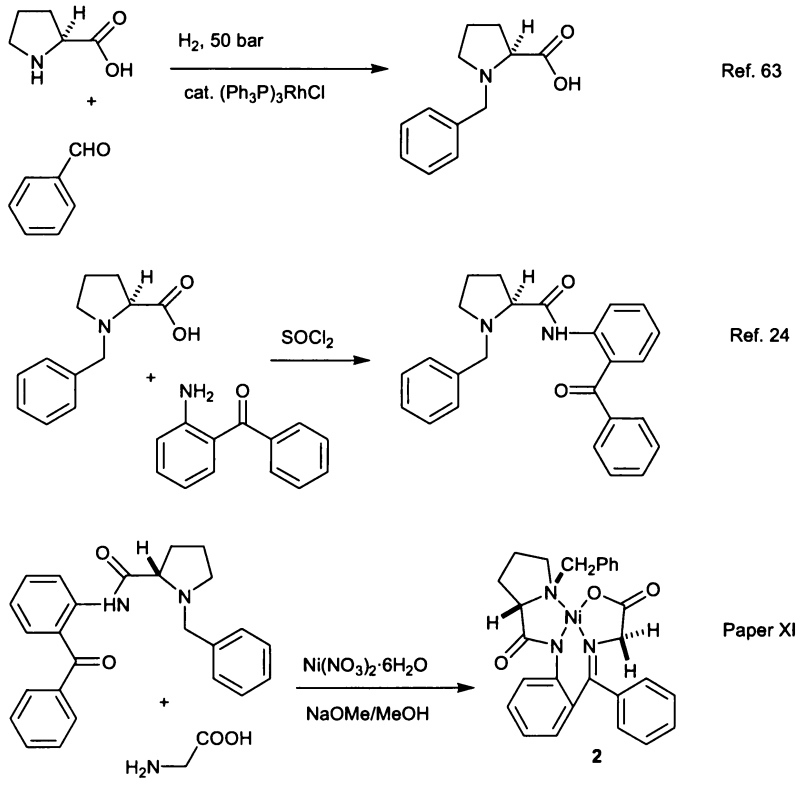
Significant steps were taken to reduce the environmental impact of the complexes' high-scale application. The most important feature is that BPB itself was initially designed as a re-usable enzyme-like auxiliary [62]. In the synthesis of BPB no chromatographic steps are used [24]. Recently, an improved synthesis of BPB was published where work with the lacrymatory alkylating agent benzylchloride was avoided. In a catalytic process less toxic benzaldehyde was used without any reduction of isolated yield (Scheme 12) [63]. Preparation of the complexes from BPB, nickel nitrate, sodium methoxide and various α-amino acids results in release of nickel to waste water. For the most often used complex derived from the simplest α-amino acid glycine we developed a modified procedure. It allowed a significant decrease in the amount of nickel in waste water.[i]

The most optimal ratio of BPB : glycine : nickel nitrate was found to be 1 : 2: 1.2. This is in a strong contrast to the previously used ratio of 1 : 5: 2 when solid nickel oxide/hydroxide was formed in the reaction mixture which could reduce the yield of the complex due to absorption of starting BPB. A big excess of glycine could also lead to the complexation of nickel cations in waste water thus lowering the efficiency of removal of nickel from waste water.

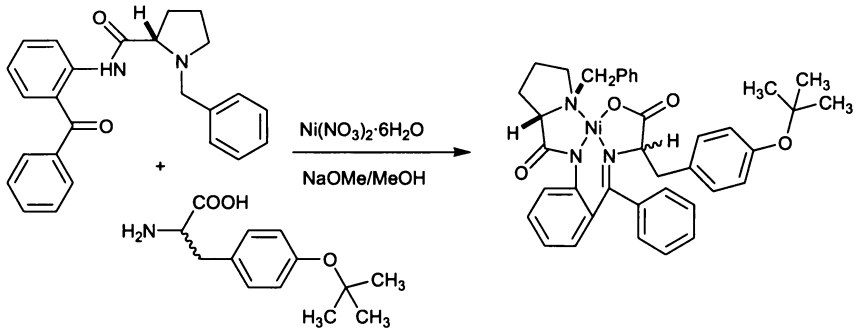
Complexes derived from other proteinogenic α-amino acids are prepared in lower amounts than the complex derived from glycine but their consumption is increasing, *e. g.* for preparation of α-methyl amino acids for positron emission tomography[ii] or other quaternary α-amino acids [12, 13, 46]. As an example, I chose a complex derived from a side-

[i] Paper XI.
[ii] Paper XII.

chain *tert*-Bu-protected tyrosine as an attractive goal for optimization (Scheme 13).



Scheme 12 The environmentally-friendly preparation of **2**



Scheme 13 Preparation of the complex derived from a side-chain *tert*-Bu-protected tyrosine (MeTyrK(OBu-t))

The compatibility of this standard side chain protective group for Fmoc-strategy of peptide synthesis with reaction conditions used for preparation of complexes was also checked. The ratio of starting compounds for the complex preparation was chosen with respect to previous optimisation of the ratio of starting compounds for the preparation of the complex derived from glycine. Twenty percent excess of nickel nitrate to BPB was expected to be optimal for both maximisation of the yield of the complex and the minimisation of the amount of nickel in waste water. A five and fifty percent excess were also tested (Table 1). Unlike glycine, side-chain protected amino acids are relatively expensive. Thus the previously applied two-fold excess of the amino acid was considered to be uneconomical. Ten, twenty and forty percent excess of amino acid to BPB were tested (Table 1).

$Ni(NO_3)_2 \cdot 6H_2O$ excess	Amino acid excess	BPB	Yield of complex (sum of diastereomers)
1.05	1.1	1	57
1.2	1.2	1	79
1.2	1.4	1	83
1.5	1.4	1	87

Table 1 Yields of the Ni(II) complex of Schiff base of BPB and MeTyrK(OBu-*t*) depending on excess of the nickel salt and the excess of the amino acid

Twenty percent excess of both protected amino acid and nickel nitrate seems to be the best ratio. This result could be the most important for optimization of preparation of complexes from other amino acids.[i]

A more detailed desctription is given in Paper XI, see also Paper XII.

[i] Nádvorník, Popkov, *unpublished results*.

4.5 Development of metallocomplex chiral synthons of α-amino acids for asymmetric synthesis of ^{13}C or ^{11}C-labeled α-methyl amino acids

α-Amino acids bearing α-methyl group instead of α-hydrogen [10, 13] are widely used for replacement of proteinogenic amino acids with their α-methylated analogues in peptides. Such modification of peptides introduces restriction to conformational freedom and increase stability of the peptides towards various enzymes [64, 65]. I expect that in PET (positron emission tomography) α-[^{11}C]methyl amino acids could play a dual role:

1 Precursors of neurotransmitters, both metabolised and non-metabolised (analogues of serotonin and, in some extend, dopamine) for study of neurodegenerative deseases.

2 Non-metabolised analogues of proteinogenic amino acids (*e. g.* tyrosine [66]) for study of amino acids uptake into normal and cancer cells. The difference in the uptake rates during a PET scan could visualise cancer cells in a human body.

Evaluation of clinical usefulness of such amino acids is limited by lack of reliable preparative approaches to these compounds. An industrial procedure was adopted for the synthesis of the only enantiomerically pure ^{11}C-labelled α-methyl amino acid, α-[^{11}C]methyltryptophan [9, 18, 67]. All attempts to prepare enantiomerically pure α-[^{11}C]methylated tyrosine failed [68, 69]. The only published synthesis of ^{11}C-methyl labelled α-metyltyrosine has been done using a very original combined chemical and enzymatic approach [68]. The amino acid core was built by malonic esters chemistry; dimethyl 2-(4-methoxybenzyl)malonate was methylated with [^{11}C]methyliodide. Hydrolysis of the prochiral diester using pig liver esterase (EC 3.1.1.1) led to the enantiomerically enriched monoester. After transformation of the free carboxylic group into an

amino group via isocyanate and deprotection, the labelled α-metyltyrosine was obtained in 62 % *e. e.* The decay-corrected radiochemical yield was 12-20% in a synthesis time of 45-50 min. However, low enantiomeric excess and long synthesis does not allow the use of this approach for rutine clinical production of the amino acid.

Except of ^{11}C-labelled α-methyltryptophan and several ^{14}C-labelled α-methyl amino acids (α-methyltyrosine [70], α-methylDOPA) no other enantiomerically pure radiolabelled α-methyl amino acid was used for *in vivo* investigation of human being (α-[^{11}C]methyltryptophan) or laboratory animals. Among published procedures for asymmetric synthesis of non-labelled α-methyl amino acids, none could be used without modification for preparation of ^{11}C-labelled α-methyl amino acids [10-13].

My efforts concentrated on the application of the metallocomplex amino acids synthons which do not require low temperature work with organolithium compounds. Such a synthetic sequence is difficult to automate in a reliable way. Previously, [^{11}C]methylation of metallocomplex synthon of alalnine and the Ni(II) complex of the Schiff base of BPB and α-phenylalanine was tested [71]. In my hands methylation with $^{11}CH_3I$/NaOH in 1,3-dimethylimidazolidin-2-one at 25°C led to a 9% radiochemical yield (decay corrected) of a mixture of the diastereomeric α-[^{11}C]methylDOPA complexes and a 7% radiochemical yield of a mixture of the diastereomeric α-[^{11}C]methyltyrosine complexes.[i] Individual diastereomers were quickly separated by preparative HPLC, diluted with excess of water and extracted on C_{18} cartridges.

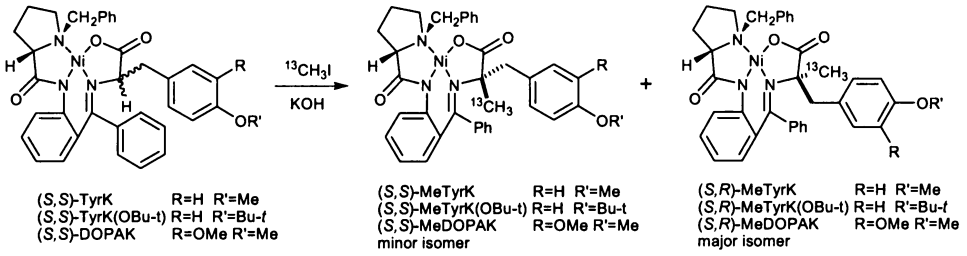
Low radiochemical yield was observed due to two reasons:

1 *(4S,19S)*-α-[^{11}C]MeDOPAK is a minor diastereomer. Sterically preferred *si*-attack leads to unwanted *(4S,19R)*-α-

[i] The second generation synthon with *tert*-Bu protective group on the phenolic oxygen (see Chapter 4.4)

[^{11}C]MeDOPAK (Scheme 1, scheme 5, scheme 9). This disadvantage might be overcame by application of (*4R,19R*)-dastereomer of the starting synthon instead of (*4S,19S*)-diastereomer. Usage of the complex bearing methyl substituents on the benzyl group attached to the proline residue should further increase the yield of the desired diastereomer;

2 slow alkylation of the sterically hindered α-carbon allows [^{11}C]methyl iodide to be mostly hydrolysed by KOH.



Scheme 14 (^{13}C)Methylation (or [^{11}C]methylation) of tyrosine or DOPA synthons.

I used (^{13}C)methylation of sterically hindered complexes (*S,S*)-TyrK and (*S,S*)-DOPAK as a model reactions (Scheme 14). Chromatographic properties of (*S,S*)-α-MeTyrK and (*S,R*)-α-MeTyrK are very similar. Their separation on a 4 x 150 mm C_{18} column takes 50 min, too long time for preparation of ^{11}C-labelled compounds ($t_{1/2}$ of ^{11}C is 20.4 minutes). It was necessary to prepare analogous complex bearing *tert*-Bu protective group on the phenolic oxygen in order to separate α-methylated tyrosine synthons. At the same time *tert*-Bu protective group is much more sensitive to acidic cleavage then Me protective group. This makes final deprotection easier and requires application of carbocation scavengers during deprotection procedure. Diastereomers of α-MeDOPAK are easily separable. The retention times of (*S,S*)-α-MeDOPAK and starting (*S,S*)-DOPAK are so close that the mixture of these compounds appears

as a single peak on a chromatogram. This fact was discovered by application of the reconstructed ion current technique during HPLC-ESI-MS separation of a mixture of starting (*S,S*)-DOPAK and both *(S,R)*-α-(^{13}C)MeDOPAK and *(S,S)*-α-(^{13}C)MeDOPAK (Figure 4).

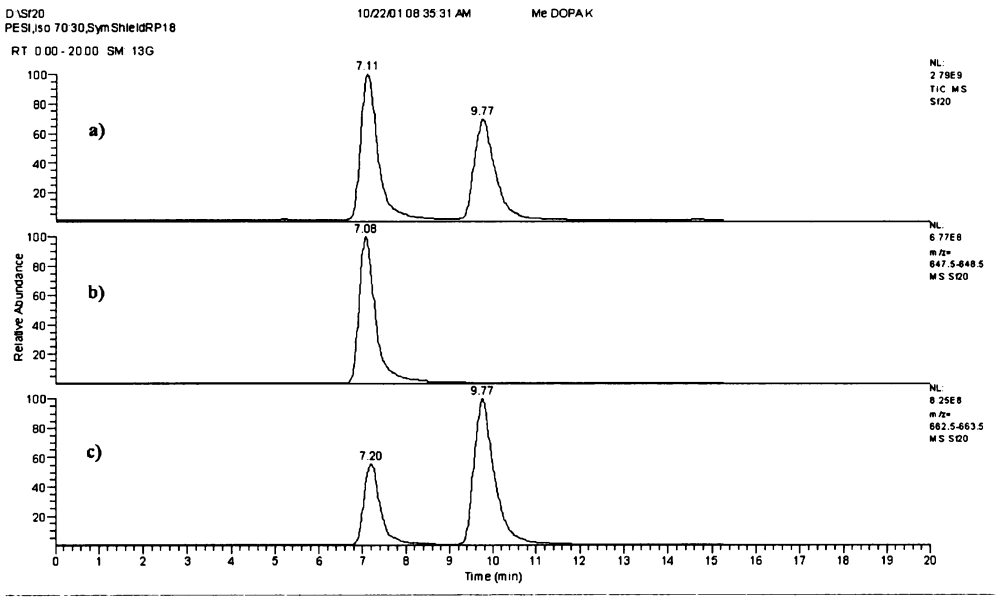


Figure 4 Reconstructed ion current (RIC) chromatogram during HPLC-ESI-MS separation of (*S,S*)-DOPAK ($[M]^+$=647) and both diastereomers of α-[^{13}C]MeDOPAK ($[M]^+$=663):

a) total ion current chromatogram (similar to HPLC analysis with UV-VIS detection);

b) RIC chromatogram (M=647.5-648.5). Retention time 7.08 min corresponds to (*S,S*)-DOPAK;

c) RIC chromatogram (M=662.5-663.5). Retention time 7.20 min corresponds to (*S,S*)- α-[^{13}C]MeDOPAK; retention time 9.77 min corresponds to (*S,R*)-α-[^{13}C]MeDOPAK.

We disclosed the stereochemistry of the diastereomers of α-[^{13}C]MeTyrK by combined application ^{13}C NMR and circular dichroism (CD) spectroscopy:

1 the reaction mixture after alkylation of (*S,S*)-TyrK with $^{13}CH_3I$ gave two predominant peaks in the ^{13}C NMR spectrum: minor at 29.3 ppm and major at 28.5 ppm. The diastereomeric excess was 6.9 %;

2 preparative TLC separation of the reaction mixture gave two fractions. In the ^{13}C NMR spectrum of the first fraction a single predominant peak at 29.3 ppm was recorded. The first fraction was associated with minor diastereomer. Similarly, in the ^{13}C NMR spectrum of the second fraction a single predominant peak at 28.5 ppm was recorded. The second fraction was associated with the major diastereomer;

3 circular dichroism spectra of starting (*S,S*)-TyrK and both fractions (diastereomers) of α-(^{13}C)MeTyrK were recorded. Cotton effects in the spectra of both (*S,S*)-TyrK and the first fraction (minor diastereomer) were similar in both areas (650-480 nm and 480-360 nm). Cotton effect in the spectrum of the second fraction (major diastereomer) in the range 480-360 nm had an opposite sign (Figure 5). Based on these CD data, the *SS* configuration was assigned to the first fraction (minor diastereomer) and the *SR* configuration was assigned to the second fraction (major diastereomer). This assignment is consistent with proposed predominance of *Si*-alkylation leading to major formation of (*S,R*)-α-(^{13}C)MeTyrK (Scheme 9).

Assignment of predominant signals in ^{13}C NMR spectra of diastereomers of α-(^{13}C)MeDOPAK was done using analogy. The major peak at 28.9 ppm was assigned to (*S,R*)-α-(^{13}C)MeDOPAK, the minor peak at 27.7 ppm was assigned to (*S,S*)-α-(^{13}C)MeDOPAK. The diastereomeric excess of the methylation reaction was 12.3 %. Higher diastereomeric excess is probably due to additional steric hindrance introduced by the second methoxygroup in the amino acid part of the complex.

Diastereomeric excess (*d.e.*) calculations were based on the ratio of the integral intensities of the $^{13}CH_3$-signals in the ^{13}C-NMR spectra of the mixtures of the diastereomers.

Optimisation of the procedure followed by hydrolysis of the complexes and purification of the enantiomers of α-[^{11}C]methylDOPA and α-[^{11}C]methyltyrosine is underway.

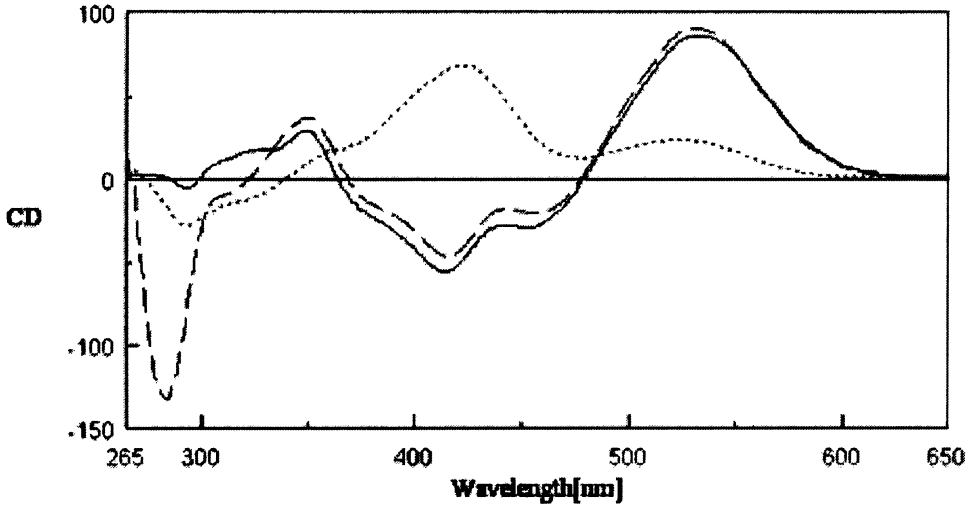


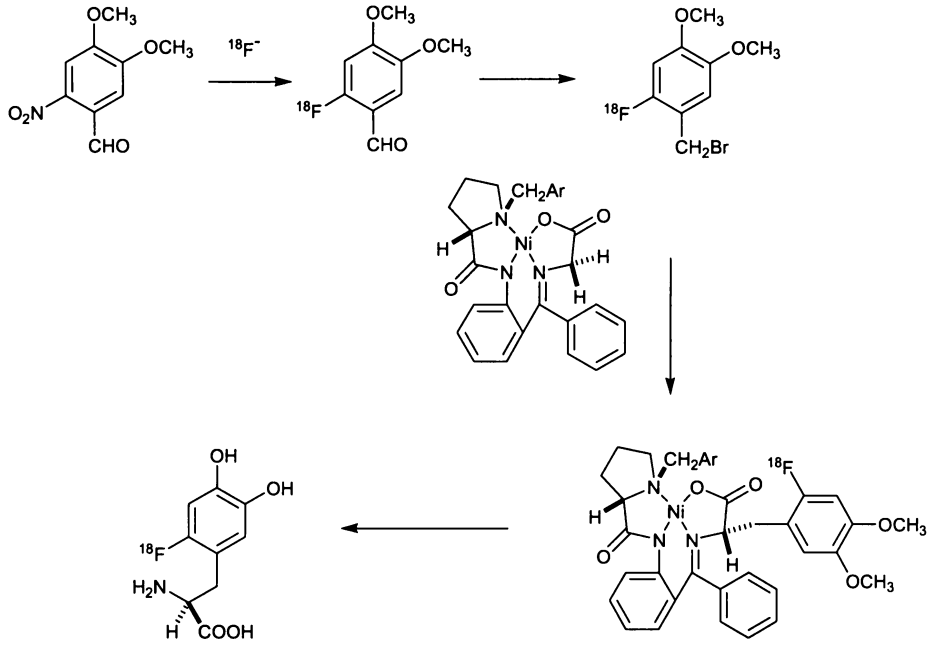
Figure 5 CD spectra of (*S,S*)-TyrK (————), the first fraction, (*S,S*)-α-(^{13}C)methylTyrK (—— —— ——) and the second fraction (*S,R*)-α-(^{13}C)methylTyrK (• • • • • • •).

A description of the experiments is given in Paper XII.

5 CURRENT RESEARCH AND FUTURE PERSPECTIVES

There are three main research directions that I consider the most promising ones for future development:

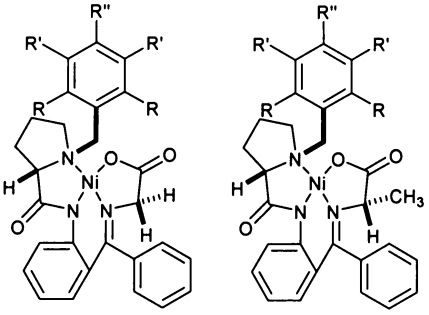
1 The application of the newly developed glycin synthon for the preparation of enantiomerically pure 6-[^{18}F]fluoroDOPA (FDOPA) via 6-[^{18}F]fluoro-3,4-dimethyoxybenzaldehyde (Scheme 15) [72-75]. FDOPA is a very popular PET radiotracer for the diagnosis of neuroendocrine tumours [76-77] and for study of dopamine metabolism *in vivo* [78-79]. Its current preparation via $^{18}F_2$ suffers from low reliability of the corresponding cyclotron ion target and low chemical yields leading to long waiting lists for cancer patients.



Scheme 15. Possible synthetic approach to 6-[^{18}F]fluoroDOPA

2 Analogous α-amino acids synthons carrying C_2-symetrically substituted benzyl group are being developed and their

behaviour in alkylation reactions is being studied (Scheme 16). Further progress in the stereodiscriminative power of the synthons is necessary for the convenient preparation of enantiomerically pure α-[^{11}C]methyl amino acids. The higher difference in retention factors during HPLC separation of individual diastereomers of the complexes derived from α-[^{11}C]methyl amino acids and new chiral auxiliaries will also make the whole procedure quicker and more reliable.



Scheme 16. The Ni(II) complexes carrying C_2-symetrically substituted benzyl groups

3 Search for suitable indole *N*-protective group for the complexes derived from tryptophan will enable preparation of L-α-[^{11}C]methyltryptophan which is a promising radiotracer for quantification of serotonin metabolism in the human brain and differential diagnostics of epilepsy [80-87]. The existing procedure for the preparation of L-α-[^{11}C]methyltryptophan requires application of a micromolar amount of air-sensitive organolithium compound in a robotic synthesis, which is not reliable enough [9, 18].

6 CONCLUSIONS

Our study of chiral amino acids synthons resulted in:

1 a deeper understanding of the intramolecular interactions affecting the stereochemistry of alkylation of the metallocomplex α-amino acids synthons. The interactions are a valuable tool for evaluation of the stereochemistry of the complexes;

2 the disclosure of new phenomena in NMR spectroscopy (unexpected long-range couplings);

3 synthesis of the stereospecific synthon of glycine;

4 the continuing development of diagnostic tools for the clinical diagnostic of some tumours.

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