Development of new precursors for asymmetric preparation of α-[11C]methyl amino acids for PET
Popkov, Alexander

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Chapter 3.1

Synthesis of derivatives of (S)-proline with alkylated N-benzyl substituents. Benzylation of (S)-indoline-2-carboxylic acid

Alexander Popkov

Laboratory of Biomembranes, University of South Bohemia, České Budějovice, Czech Republic

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Summary
The synthesis is reported of (S)-proline derivatives which contain a 2,4,6-trimethyl-, 4-tert-butyl-, or pentamethylbenzyl substituents on the nitrogen atom. Under similar conditions the benzylation of indoline-2-carboxylic acid was unsuccessful. Treatment of indoline-2-carboxylic acid with benzyl chloride in the presence of KOH in dimethylacetamide gave the benzyl ester of N-benzyldindoline-2-carboxylic acid which is unstable on light.

Keywords
N-benzylproline, proline, chiral synthon, asymmetric synthesis.

Tightening up of environmental standards has stimulated the development of highly selective catalysts for organic process syntheses. In particular, they are of great interest for the synthesis of enantiomerically pure medicines with the aim of eliminating the side effects of the racemic form [1].

N-Benzylproline derivatives are used as chiral catalysts and chiral inductors in various reactions [2-9]. On the basis of a study of the conformation of several chiral synthons which contained an N-benzyl residue, a higher degree of asymmetric induction was anticipated for similar compounds containing substituents in the ortho positions of the benzyl group [10]. In this connection it was of interest to study N-benzylprolines substituted in the aromatic ring as potential chiral inductors.

N-Benzylprolines, having alkyl substituents in the benzene ring have not been reported before. In this work we describe the synthesis of novel (S)-prolines which contain a 2,4,6-trimethyl-, 4-tert-butyl-, or pentamethylbenzyl substituent on the nitrogen atom (1-3 respectively) and also the methyl esters of the first two amino acids (4, 5 respectively). For the preparation of compounds 1-3 there was used a method previously reported for the reaction of proline with benzyl chloride [11]. In this way, products 1-3 were synthesized in 32-60% yields (Scheme 3.1.1). The reaction conditions were not optimized. Methylation of the acids l and 3 with excess of diazomethane solution gave the corresponding esters 4 and 5 in quantitative yield. Compound 1 was used for the preparation of the recoverable chiral reagent (S)-2-[N-(2,4,6-trimethylbenzyl)prolyl]aminobenzophenone, thus permitting the synthesis of (S)-[11C]alanine with a 97% enantiomeric excess (e.e.) [12]. From the unsubstituted (S)-2-(N-benzylproplyl)aminobenzophenone the (S)-[11C]alanine was obtained with 80% e.e.

Scheme 3.1.1 Preparation of N-benzylprolines substituted in the aromatic ring

1. R=Me, R'=H, R''=Me
2. R=R'=H, R''=Bu-t
3. R=R'=R''=Me
We also studied the possible benzylation of a proline analogue, indoline-2-carboxylic acid. The racemic ethyl ester of N-benzylindoline-2-carboxylic acid has previously been used for design of the skeleton of \( \alpha_2 \)-adrenoblockers [14]. However, the material obtained by reduction of the corresponding indole-2-carboxylic acid was used without purification in a reaction with the trimethylaluminium ethylenediamine complex. Hence no characterisation was presented for the compound.

The reaction of indoline-2-carboxylic acid with benzyl chloride in the conditions reported in [11] did not lead to N-benzylindoline-2-carboxylic acid. Using a similar reaction in dimethylacetamide (DMAA) we obtained the benzyl ester of N-benzylindoline-2-carboxylic acid (6) in 23% yield (according to GC-MS) based on the identified compounds with an indoline/indole skeleton (see Scheme 3.1.2). The content of product 6 in neutral chloroform solution in the reaction mixture decreased to 11% over 16 h at +4°C. The ester is light sensitive and can hardly be used for preparative purposes as an intermediate compound. This is in agreement with published data concerning the light sensitivity of N-benzylindoline [15]. Attempts to lower it by addition of base or acid or by removal of solvent were unsuccessful. A chloroform solution of compound 6 or an amorphous powder prepared by addition of dry ether to this solution became intensely purple or violet on ambient light.

\[
\begin{align*}
\text{NH}-\text{COOH} + \text{Cl} & \xrightarrow{\text{KOH, dimethylacetamide}} \text{NH}-\text{COO}^+ \text{H}^+ \\
& + \text{COOH} + \text{C}_6\text{H}_5\text{N}^+ \text{COO}^-
\end{align*}
\]

**Scheme 3.1.2** Benzylation of indoline-2-carboxylic acid with benzyl chloride

**Experimental**

Analytical samples of the synthesized compounds were prepared using preparative TLC on silica gel (methylchloroform-acetone gradient from 10:1 to 2:1). \(^1\)H-NMR spectra were recorded on a Varian Gemini 200 spectrometer using CDCl\(_3\) solvent and TMS internal standard. Optical rotations were measured on a Schmidt-Haenich Polatronic NH 8 polarimeter using a 5 cm cuvette. GC-MS spectra were obtained on a Kratos MS25RPA instrument (70 eV) combined with a Hewlett-Packard 5890 capillary gas chromatograph using an Ultra-2 column (25 m x 0.22 mm, 5% loading, phenylmethyl silicone, layer thickness 0.11 mm). The sample was introduced into the column. Ionization current 100 \(\mu\)A. Low resolution \((R_{10\%}) = 600\), calibration 28-480 daltons. The temperature of the ion source, the column inlet into the ion
source and the injector were 220°C and the temperature program 2 min at 80°C followed by 10°C/min to 280°C.

High resolution mass spectra were obtained on a VG analytical ZAB-SEQ instrument. (S)-Proline derivatives (1-3) were synthesized by a known method [11]. The substituted benzyl chloride (100 mmol) was added to a solution of (S)-proline (11.6 g, 100 mmol) and KOH (14 g, 250 mmol) in isopropanol (250 ml) over 30 min with vigorous stirring at 60°C. The reaction mixture was then stirred for 30 min and evaporated in vacuo. Water (50 ml) was added to the residue which was filtered, 10% HCl added with stirring to the filtrate to pH 6-7, and the precipitate formed was washed on the filter with water (200 ml) and dried in vacuo. The dry precipitate was dissolved in a minimum amount of MeOH at 40-50°C, filtered, and added dropwise to diethyl ether (500 ml) with vigorous stirring. The precipitated product 1-3 was then washed on the filter with diethyl ether (200 ml) and dried in vacuo.

(S)-N-(2,4,6-Trimethylbenzyl)proline (1). Yield 41%; mp 150-152°C. [α]_576^25 = - 44º, [α]_546^25 = - 40º (c 0.005, CHCl_3). _1^H NMR spectrum: 1.90-3.70 (6H, m, H_α-Pro); 2.23 (3H, s, 4-CH_3); 2.41 (6H, s, 2- and 6-CH_3); 4.00-4.20 (1H, m, α-H_Pro); 4.36 and 4.52 (2H, AB, J = 13.6 Hz, CH_2-Ar); 6.89 ppm (2H, s, H_Ar). Found: [M+H]^+: 248.1613 (FAB-MS). C_{15}H_{21}NO_2. Calculated 248.1651.

(S)-N-(4-tert-Butylbenzyl)proline (2). Yield 32%; mp 171-173°C. [α]_576^25 = - 24º, [α]_546^25 = - 32º (c 0.005, CHCl_3). _1^H NMR spectrum: (9H, s, -C(CH_3)_3); 1.90-3.70 (6H, m, H_α-Pro); 3.95-4.10 (1H, m, α-H_Pro); 4.33 and 4.45 (2H, AB, J = 12.8 Hz, CH_2-Ar); 7.41 ppm (4H, s, H_Ar). Found [M+H]^+: 262.1776 (FAB-MS). C_{16}H_{23}NO_2. Calculated 262.1807.

(S)-N-(Pentamethylbenzyl)proline (3). Yield 60%; mp 142-146°C. [α]_576^25 = - 39º, [α]_546^25 = - 47º (c 0.005, CHCl_3). _1^H NMR spectrum: 1.95-3.6 (6H, m, H_α-Pro); 2.22 (6H, s, 3- and 5-CH_3); 2.36 (6H, s, 2- and 6-CH_3); 3.40-3.60 (1H, m, α-H_Pro); 4.30 and 4.35 ppm (2H, AB, J = 7.0 Hz, CH_2-Ar). Found [M+H]^+: 276.1888 (FAB-MS). C_{17}H_{25}NO_2. Calculated 276.1963.

The methyl ethers of the substituted (S)-prolines 4 and 5 were prepared by a known method [16] by treatment of compounds 1 and 2 with an excess of diazomethane solution in diethyl ether.

Methyl ester of (S)-N-(2,4,6-trimethylbenzyl)proline (4). Yield ~ 100%; oil. _1^H NMR spectrum: 1.70-3.80 (7H, m, H_α-Pro); 2.24 (3H, s, 4-CH_3); 2.36 (6H, s, 2- and 6-CH_3); 3.59 (3H, s, OCH_3); 3.63 and 3.82 (2H, AB, J = 12.5 Hz, CH_2-Ar); 6.81 ppm (2H, s, H_Ar). Found M^+: 261,1642 (EI-MS). C_{16}H_{23}NO_2. Calculated: 261,1729.

Methyl ester of (S)-N-(4-tert-butylbenzyl)proline (5). Yield ~ 100%. Oil. _1^H NMR spectrum: 1.30 (9H, s, 3-CH_3); 1.70-3.70 (7H, m, H_α-Pro); 3.62 (3H, s, OCH_3); 3.62 and 3.88 (2H, AB, J = 13.4 Hz, CH_2-Ar); 7.10-7.50 ppm (4H, m, AA'BB', H_Ar). Found M^+: 275,1865 (EI-MS). C_{17}H_{25}NO_2. Calculated: 275,1885.

Benzyl ester of N-benzylindoline-2-carboxylic Acid (6). Under argon benzyl chloride (2 ml, 17.4 mmol) was added dropwise with vigorous stirring over 30 min at 60°C to a solution of N-benzylindoline-2-carboxylic acid (1 g, 6.13 mmol) and KOH (2 g, 35.7 mmol) in DMAA (15 ml) which had been placed to a flask covered by black paper. The reaction mixture was stirred for 30 min, an aqueous solution of citric acid (20%, 70 ml) added, and the product extracted with chloroform (3 x 10 ml). The combined extract was immediately analyzed by GC-MS. The mass spectrum identified product 6 (13.3%) in the mixture with m/z: 344 (M+).
10, 208 (M-\text{COOCH}_2\text{C}_6\text{H}_5^+) 63, 91 (\text{CH}_2\text{C}_6\text{H}_5^+) 100. The remaining components of the mixture were, %: \text{N}-benzylindoline 3.6, \text{N}-benzylindole 22.1, \text{N}-benzylindole-2-carboxylic acid 1.1, benzyl chloride 19.7, and benzyl alcohol 33.3.

Acknowledgements
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References
Chapter 3.2

Chiral nucleophilic glycine and alanine synthons: Ni(II) complexes of Schiff bases of (S)-2-[N-(2, 4, 6-trimethylbenzyl)-prolyl]aminobenzophenone and glycine or alanine

Alexander Popkov\textsuperscript{1,2}, Milan Nádvorník\textsuperscript{3}, Antonín Lyčka\textsuperscript{4} and Antony Gee\textsuperscript{1,5}

\textsuperscript{1} Positron Emission Tomography Centre, Aarhus University Hospital, Denmark, \textsuperscript{2} Present address: University of South Bohemia, Nové Hrady, Czech Republic, \textsuperscript{3} Department of General and Inorganic Chemistry, University of Pardubice, Czech Republic, \textsuperscript{4} Research Institute for Organic Syntheses, Pardubice - Rybitví, Czech Republic, \textsuperscript{5} Present address: GlaxoSmithKline, Addenbrooke's Centre for Clinical Investigation, Cambridge CB2 2GG, UK

*Transition Metal Chem.* \textbf{2002}, \textit{27}, 884
Abstract
A new chiral auxiliary (S)-2-[N-(2,4,6-trimethylbenzyl)prolyl]aminobenzophenone has been synthesised as a potential building block for preparation of chiral synthons of amino acids. Nickel (II) complex of its Schiff base derivative with glycine has been methylated with 97% d.e. (diastereomeric access); whilst nickel(II) complex of its Schiff base derivative with (RS)alanine has been 13C-methylated with 66% d.e..

Keywords
α-amino acids, DFT, enantiospecific synthesis, nickel complexes, positron emission tomography.

Introduction
In spite of the fact that the development of catalytic asymmetric synthesis of α-amino acids is necessary for multi-ton industrial production [1-6], stoichiometric chiral synthons [7-13] are still in use for special applications such as preparation of labelled amino acids. Our efforts in this area have concentrated on nickel(II) complexes of Schiff bases of (S)-2-(N-benzylprolyl)aminobenzophenone (BPB) and α-amino acids [14-19]. Two groups reported several attempts to increase asymmetric induction by the complexes by introducing various substituents into the benzyl group [20-22], but these experiments met with little success. Previously, we used a combination of solution NMR [23], solid state NMR, X-ray crystallography [24] and DFT calculations [25] to disclose the nature of the asymmetric induction achieved with chiral nickel complexes. In this communication a successful design of a stereospecific glycine synthon synthon and a stereoselective alanine synthon is described.

Results and discussion
Two factors were identified which might be used for creation of synthons with higher asymmetric induction, as follows. The first concerns the conformations of the complexes. Based on NOE interactions, it was found that the ortho protons of the benzyl group are situated closest to =N-CHR-CO- fragment of the complex [23]. Hence, we hypothesize that the degree of asymmetric induction of these nickel complexes can be improved by increasing the steric hindrance of the benzyl group through the introduction of methyl substituents in the ortho-positions. The second factor concerns the donation of electron density from the π-system of the benzyl ring to nickel orbitals. We inferred such a donation of electrons in complex 4 (see Scheme 2). Quantum chemical calculations confirmed a weak interaction, which decreases the distance between the plane of the benzyl group and the nickel atom [25]. This effect influences the stereocchemical result of alkylation of the complexes under thermodynamically controlled conditions. In addition, two examples supporting our hypothesis can be found in the literature: the replacement of the benzyl group in the complex by an electron-rich naphthylmethy group led to higher asymmetric induction [20], whereas the replacement of the benzyl group by various picoly groups in many cases decreased the induction [22]. We therefore hypothesized that the distance of the benzyl group to the nickel atom will be reduced by the introduction of alkyl substituents in any position on the benzyl group. Replacement of the N-benzyl group by an N-(2,4,6-trimethylbenzyl) group should also result in steric hindrance of 'ring-edge' bonding (between the η2-bonded aromatic ring and the metal atom), compared to 'ring-centre' bonding where the 2,4,6-trimethylbenzyl group is a η6-ligand. The polyalkyl-substituted benzyl group
may also increase steric hindrance with respect to alkylation of the α-carbon of the glycine or the alanine fragment, thereby enhancing the diastereoselectivity of the reaction. Based on this reasoning, we prepared (S)-2-[N-(2,4,6-trimethylbenzyl)prolyl]amino-benzophenone 1, starting from (S)-N-(2,4,6-trimethylbenzyl)proline [26], for the synthesis of sterically hindered nickel complexes 2 and 3 (Scheme 3.2.1). In our hands, the only successful method for amide bond formation to give 1, was via activation of the carboxylic acid with thionyl chloride.

![Scheme 3.2.1. Template synthesis of 2 and 3.]

In order to evaluate these potential chiral auxiliaries, two model sequences were created for both thermodynamic and kinetic control of alkylation diastereoselectivity, as follows. Monoalkylation of glycine synthons led to complexes containing α-alkylglycine residues (for example, α-alanine residue in case of monomethylation) [27]. The diastereomeric purity of the resulting complexes depends on the reaction conditions used. Two hours equilibration of any monomethylated complex in 1M NaOMe/MeOH at 22°C led to thermodynamically controlled ratios of the diastereomers regardless of the starting diastereomeric ratio. The same equilibration conditions were applied to the previously described complex 4, new complex 3 and two analogs of the complex 4 bearing an electron donating or electron withdrawing substituent, available to us from previous work (5 and 6) (Scheme 3.2.2) [28]. The observed diastereoselectivities (Table 3.2.1) support our hypothesis. Thus, the complex containing two ortho-methyl groups and one para-methyl group 3, providing both donation of electron density to nickel orbitals and steric hindrance, led to almost exclusive formation of the S,S-3 diastereomer.

**Table 3.2.1.** Epimerisation of alanine complexes in 1M MeONa/MeOH; thermodynamic control

<table>
<thead>
<tr>
<th>Complex</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>R'</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>Cl</td>
</tr>
<tr>
<td>D.e. of the S,S diastereomer (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>97</td>
<td>83</td>
<td>83</td>
<td>86</td>
</tr>
</tbody>
</table>

<sup>a</sup>D.e.’s were determined by integration of <sup>1</sup>H NMR spectra of the mixtures of the diastereomers.
Scheme 3.2.2. Epimerisation of alanine complexes; thermodynamic control.

Alkylation of the alanine complexes led to the corresponding α-methyl-α-amino acids complexes 7 - 9 (Scheme 3.2.3). As these new complexes contain no α-proton, the stereochemistry of the amino acid fragment's α-carbon is controlled kinetically [27]. Methylation with $^{13}$CH$_3$I in 1,3-dimethyl-imidazolidin-2-one (DMI) (Scheme 3.2.3, Table 3.2.2) has been chosen as the most challenging model reaction (the methyl iodide molecule is relatively small, and the observed diastereoselectivity of methylation is lower than in alkylation by bulkier electrophiles). Chromatographic purification of the methylated products on silica gel should not affect the ratio of the diastereomers because $^{12}$CH$_3$ and $^{13}$CH$_3$ are chromatographically undistinguishable.

### Table 3.2.2 Asymmetric induction of methylation of alanine synthons by $^{13}$CH$_3$I; kinetic control

<table>
<thead>
<tr>
<th>Complex</th>
<th>3 → 7</th>
<th>4 → 8</th>
<th>5 → 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>R'</td>
<td>H</td>
<td>H</td>
<td>Me</td>
</tr>
<tr>
<td>D.e. of the S, S diastereomer (%)</td>
<td>66</td>
<td>43</td>
<td>41</td>
</tr>
</tbody>
</table>

Scheme 3.2.3 Methylation of alanine complexes; kinetic control.

Complex 2 has been used for stereospecific preparation of $[^{11}\text{C}]$alanine for positron emission tomography [29].

**Experimental**

$^1\text{H}$ and $^{13}\text{C}$ NMR spectra were recorded on a Bruker AMX 360 spectrometer using TMS as internal standard. High-resolution EI-mass spectra were recorded on a Finnigan MAT 90 spectrometer.

Preparation of 2

SOCl$_2$ (0.95 ml, 13.2 mmol) was added dropwise to a stirred suspension of ($S$)-N-(2,4,6-trimethylbenzyl)proline [26] (2.13 g, 8.62 mmol) in CH$_2$Cl$_2$ (20 ml) at -78ºC. The reaction mixture was warmed to -5ºC for 10 min, then cooled to -78ºC and a solution of 2-aminobenzophenone (2.24 g, 11.4 mmol) in CH$_2$Cl$_2$ (20 ml) was added dropwise. The reaction mixture was warmed to +5ºC, stirred for 30 min, quenched with 15% aqueous Na$_2$CO$_3$ (15 ml) and extracted with CH$_2$Cl$_2$ (3x30 ml). Combined extracts were evaporated in vacuo and were used for the next step without purification.

Under an atmosphere of Ar a suspension of glycine (1.5 g, 20 mmol) in 2N MeONa/MeOH (50 ml) was added dropwise to a stirred solution of the product from the previous step and nickel nitrate hexahydrate (1.16 g, 4 mmol) in MeOH (30 ml) at 50ºC. After 30 min the reaction mixture was poured into 5% aqueous citric acid (200 ml), stirred and extracted with CH$_2$Cl$_2$ (4x50 ml). Combined extracts were evaporated in vacuo and the residue was purified by chromatography on silica gel with CH$_2$Cl$_2$. The first red fraction containing the reaction product was collected. The obtained complex 2 was then purified by chromatography on Sephadex LH-20 with toluene:MeOH=2:1 as a red, non-crystalline solid. Yield 137 mg (3%).

$^1\text{H}$ NMR (360.13 MHz, CDCl$_3$): 8.20 (d, 1H), 7.45 (m, 3H), 7.20 (t, 1H), 7.08 (d, 1H), 6.91 (m, 1H), 6.82 (s, 2H), 6.79 (d, 1H), 6.68 (s, 1H), 4.87 (d, 1H) and 4.21 (d, 1H) (AB system of -CH$_2$Ar, $^2$J(H, H) = 14.1 Hz), 3.76 (d, 1H) and 3.63 (d, 1H) (AB system of -CH$_2$COO-, $^2$J(H, H) = 20.2 Hz), 3.44 (m, 1H), 3.32 (m, 2H), 3.00 - 2.20 (very broad signal of two methyl groups, 6H), 2.70 (m, 1H), 2.34 (m, 1H), 2.14 (s, 3H), 2.00 (m, 1H), 1.84 (m, 1H). High resolution EI-MS (70 eV): for C$_{30}$H$_{31}$N$_3$O$_3$Ni [M$^+$] calculated 539.1711, observed 539.1710.

Preparation of 3

Complex 3 (10 mg) was prepared in the same way as described for complex 2 starting from racemic alanine instead of glycine. $^1\text{H}$ NMR (360.13 MHz, CDCl$_3$): 8.02 (d, 1H), 7.44 (m, 3H), 7.20 (m, 2H), 6.90 (m, 1H), 6.80 (m, 2H), 6.63 (s, 2H), 4.66 (d, 1H) and 3.99 (d, 1H) (AB system of -CH$_2$Ar, $^2$J(H, H) = 14.3 Hz), 3.88 (q, $^3$J(H, H) = 8.7 Hz, 1H), 3.68 (m, 1H), 3.32 (m, 2H), 3.06 (broad s, 3H), 2.92 (m, 1H), 2.48 (m, 1H), 2.37 (broad s, 3H), 2.13 (m, 1H), 2.11 (broad s, 3H), 1.88 (m, 1H), 1.53 (d, $^3$J(H, H) = 8.7 Hz, 3H). High resolution EI-MS (70 eV): for C$_{31}$H$_{33}$N$_3$O$_3$Ni [M$^+$] calculated 553.1875, observed 553.1889; for C$_{30}$H$_{33}$N$_3$ONi [M-CO$_2$]$^+$ calculated 553.1875, observed 553.1889.

Methylation of alanine synthons by $^{13}\text{CH}_3$I

At 20ºC to a 0.05 M solution of a complex, excess of KOH and a fivefold excess of $^{13}\text{CH}_3$I were added and the reaction mixture was stirred for 30 min. Yields are quantitative. D.e.'s
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;

$$d.e. = 100-200 \cdot \frac{(a \cdot [S, R]/[S, S]* - b)}{(a-b) \cdot (1+ [S, R]/[S, S]*)}$$

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$_3$I

$b$ is the natural abundance of $^{13}$C

Acknowledgement

A. P. thanks IAESTE Denmark and IAESTE Czech Republic for managing of radiochemical training at Aarhus PET Centre.

References

Chapter 3.3

Development of a universal approach to enantiomerically pure $\alpha$-amino acids by stereospecific introduction of a side chain. Evaluation of metallocomplex synthons of glycine and alanine employing efficient shielding of the $re$-side of $\alpha$-carbon of the amino acid residue

Alexander Popkov, Jiří Hanusek, Jiří Čermák, Vratislav Langer, Robert Jirásko, Michal Holčapek and Milan Nádvorník

1Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, The Netherlands, 2Department of Organic Chemistry, University of Pardubice, Czech Republic, 3Research Institute for Organic Syntheses, Rybitví, Czech Republic, 4Chalmers University of Technology, Göteborg, Sweden, 5Department of Analytical Chemistry, University of Pardubice, Czech Republic, 6Department of General and Inorganic Chemistry, University of Pardubice, Czech Republic

Submitted for publication
Abstract
Newly prepared amino acids synthons 3-5 and 8 demonstrate a very high level of stereocontrol in both thermodynamically and kinetically controlled alkylation reactions; they are promising leads for further development of stereospecific.

Keywords
Amino acids, Diastereoselectivity, Nickel, Schiff bases, Template synthesis

Introduction
In industry bulk amounts of α-amino acids are usually prepared by biotechnological or asymmetric catalytic approaches. Catalysts exist for stereospecific introduction of a bulky side chain into α-position of glycine or alanine synthons. No efficient chiral catalyst is known for introduction of small electrophiles (e.g. methyl group) into α-position of proteinogenic α-amino acids synthons. Stoichiometric asymmetric syntheses are better suited for research purposes and for the synthesis of small batches of non-coded α-amino acids for drug design, where simplicity of the experimental procedures is of great importance. Radiolabelling with short-lived isotopes for in vivo diagnostic imaging is another growing field for application of these synthons. Until recently, Ni(II) complexes of Schiff bases of (S)-N-(2-benzoylphenyl)-1-benzylpyrrolidine-2-carboxamide (BPB) and α-amino acids were not an attractive tool for large scale preparation of α-amino acids due to contamination of waste water with nickel and use of lacrymatory benzylchloride in the production of BPB. Both disadvantages were overcome in newly developed procedures. As the synthetic pathway via Ni(II) complexes brings important advantages, like complete regeneration and re-use of BPB or no need for very strong bases for generation of the intermediate carbanion, considerable attention was paid to improvement of the stereochemical output of alkylation of the complexes (Scheme 1).

Our approach was based on disclosure of factors influencing intramolecular interactions in the complexes and shielding of one side of prochiral or asymmetric centre. Data from X-ray structure determinations and mapping of differential electron density, NMR studies of conformations of the complexes in solutions and solid state, ab initio MP2 modeling followed by topological analysis let to a lead structure: a complex carrying a C2-symmetric benzyl group with electron-donating groups in both ortho-positions. The application of this concept immediately bore fruit. The first structures prepared were Ni(II) complexes of modified BPB and glycine or α-alanine. Both structures were tested in methylation reactions in order to create the most challenging conditions by use of a small electrophile molecule. Methylation of the glycine derivative followed by epimerisation was practically stereospecific; NMR analysis of the reaction mixture gave 97% d.e. During HPLC purification of the complex no traces of the minor isomer were observed. Methylation of the alanine derivative led to 66% d.e. The large difference in the observed diastereoselectivities was due to different control of the stereochemical output. Methylation of the glycine derivative (or preparation of a complex from racemic alanine) followed by epimerisation in 1N MeONa/McOH runs under thermodynamic control of stereochemistry whilst (13)Cmethylation of the alanine derivative runs under kinetic control. Thus, a stereospecific metallocomplex glycine synthon was successfully developed, but it is still necessary to improve stereodiscriminative properties of the metallocomplex synthons of alanine and other α-amino acids. In this communication the evaluation of eleven new synthons bearing C2-symmetric benzyl groups with electron-donating and electron-withdrawing substituents is described (Table 1, Scheme 1). Glycine
complexes were evaluated alongside alanine complexes in order to obtain a deeper understanding of the relationship between their structures and the equilibrium stereochemistry of monoalkylated products.

![Chemical structures](image)

Scheme 3.3.1. Methylation and epimerization of alanine complexes.

### Table 3.3.1 Methylation and epimerization of alanine complexes.

<table>
<thead>
<tr>
<th>No</th>
<th>ortho-substituents</th>
<th>meta-substituents</th>
<th>para-substituent</th>
<th>Epimerization, d.e. (%)</th>
<th>Epimerization, d.e. (%)</th>
</tr>
</thead>
<tbody>
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- a for the experimental details, see ref.¹²;
- b based on ratio of integral intensities of CH₂Ar quadruplet or CH₃ doublet of the minor isomer to corresponding peaks of ¹H-¹³C satellites of the major isomer in ¹H-NMR spectra of reaction mixtures;
- c based on measurement of integral intensities of methyl group peaks in ¹³C-NMR spectra recorded with relaxation time 20 s;
- d data from ref.¹²;

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no signal of the minor diastereomer was found in the $^1$H-NMR spectrum of the reaction mixture;

preparation of this alanine complex was described earlier, but no epimerization or $(^{13}$C)methylation measurements were done.\textsuperscript{10}

**Results and Discussion**

The first hypothesis was to increase the steric hindrance of the substituted benzyl group by introduction of bigger (and/or more) substituents. This should also to increase electron density donated to the aromatic ring, thus increasing polarisation of its electron cloud towards the positively charged nickel atom, followed by stronger electrostatic interactions between the aromatic ring and nickel.\textsuperscript{11} With the exception of three complexes carrying ortho-substituents: 3 bearing pentamethylbenzyl group, 4 bearing (9-anthracenyl)methyl group and 9 with 2,6-difluorobenzyl group; all other newly synthesised compounds have meta-disubstituted or para-monosubstituted benzyl groups in order to compare the influence of the same substituents in ortho-, meta- and para- positions. It is possible to introduce very bulky tert-butyl substituents to para- and meta-positions only. Syntheses and evaluation of complexes with electron-withdrawing fluoro or trifluoromethyl substituents was necessary for separation of the steric and electronic influence of the substituents; there was a published report about highly stereoselective alkylation of a complex carrying one chlorine substituent in ortho-position.\textsuperscript{9}

Behaviour of complex 3, where the lead structure 2 was modified by addition of two meta-methyl substituents into the benzyl group, supported the initial hypothesis – both thermodynamically controlled epimerisation and kinetically controlled $(^{13}$C)methylation ran more efficiently. Diastereomeric excess of methylation increased from 66\% to 75\%. Complex 7 bearing only two meta-methyl substituents is not so efficient as complex 3, probably due to an important steric role played by the ortho-methyl substituents. This is also confirmed by methylation of complex 9, where smaller planar –CH=CH substiuents in the ortho- and meta-positions are not as efficient as ortho-methyl substituents in complex 3. Compound 5 bears very bulky tert-Bu substituents in meta-positions. Its stereodiscriminativeness efficiency is even more than complex 3. Results of both epimerization and methylation of complex 6 confirm the importance of electronic control. Its methoxy groups donate more electron density to the aromatic system than the methyl groups in complex 7. This leads to stronger interaction of the polarised electron cloud with partial positive charge of the nickel atom, and more efficient shielding of the re-side of the intermediate carbanion during methylation. Stronger repulsion between the (substituted) benzyl group and the equatorial methyl group during epimerization may also play a role. Electron-withdrawing CF\textsubscript{3} substituents in meta-positions of the benzyl group gave a very efficient synthon, probably due to formation of hydrogen bonds between fluorine atoms and the hydrogens on the benzophenone part of the ligand. This explanation is consistent with results observed with para-substituted complexes 10-13, where compounds carrying CF\textsubscript{3} or OCF\textsubscript{3} substituents overperform similar complexes with bulky tert-Bu or electron-rich OCH\textsubscript{3} substituents. Fluorine atoms in ortho-positions of the benzyl group improve the results of compound 9 compared to complex 1. In solid state one of the fluorine atoms is situated in apical position of the complex (Fig. 3.3.1), thus confirming strong electrostatic interaction between this negatively charged atom and the positively charged nickel, similar to weaker intramolecular interactions observed in 1.\textsuperscript{11} Hydrogen bond C4-H4...F2 observed in solid state of compound 9 is also responsible for stabilisation of a conformation where the 2,6-difluorobenzyl group efficiently shields the re-side of carbanion
formed from complex 9. These interactions lead to higher efficiency of epimerization of this complex compared to its steric analogue 1. Kinetically controlled (13C)methylation is not very much affected by the interaction; this corresponds to quick rotation of the benzyl groups around their axis of symmetry in both 1 and 9 revealed by NMR spectra in CDCl3. Similar electrostatic interactions possibly play their role in behaviour of analogous complexes bearing ortho-Cl or poly-F substituents of benzyl group.9,16

Figure 3.3.1 Full-color in appendix. X-ray structure of 9. Numbering scheme with atomic displacement ellipsoids drawn at 30% probability level.

Conclusions
Newly prepared amino acids synths 3-5 and 8 demonstrate a very high level of stereocontrol in both thermodynamically and kinetically controlled alkylation reactions. They are promising leads for further development of stereospecific synths of α-amino acids and for preparation of helically chiral precursors of nanostructures.17

Experimental section
General procedure for the template synthesis of the alanine complexes
2 M MeONa/MeOH (5 ml, 10 mmol) was added to a stirred suspension of a chiral auxilliary (0.65 mmol), alanine (195 mg, 1.3 mmol) and nickel nitrate hexahydrate (227 mg, 0.78 mmol) in dry MeOH (5 ml) under argon at 55 °C. After stirring at 55 °C for 30 min, the mixture was poured into 3% aqueous citric acid (150 ml), stirred and the resulting precipitate was filtered off and dried in air. The dry red precipitates (or red solidified oils) was purified by preparative TLC on silica gel eluted with chloroform followed by gel chromatography on Sephadex LH-20 (eluent toluene/methanol=2:1) and characterised by 1H-NMR, 13C-NMR, ESI full-scan and
MS/MS spectra measured with ion trap and high-resolution QqTOF analyzers providing information on the elemental composition of protonated complexes and fragment ions as well.

**Methylation of alanine synthons by CH$_3$I**

At 20 °C to a 0.05 M solution of a complex, an excess of KOH and a fivefold excess of $^{13}$CH$_3$I were added and the reaction mixture was stirred for 30 min. Yields are quantitative. Diastereomeric excess calculations were based on the ratio of the integral intensities of the $^{13}$C-signals in the $^{13}$C NMR spectra of the mixtures of the diastereomers;

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

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$_3$I; $b$ is the natural abundance of $^{13}$C.

**Acknowledgements**

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**References**


15 Symmetry of all used benzyl groups was higher ($C_{2v}$), $C_2$-symmetry is a minimum requirement for elimination of influence of the group rotation to intramolecular interactions.

