Asymmetric synthesis of unusual α-amino acids

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The synthesis of enantiomerically pure non-proteinogenic bis and cyclic amino acids 3a,b and achiral amino acid 3c using chiral Ni^{II} complex 1 and α,α′-dibromo-*o*-xylene as a bifunctional agent of alkylation is presented.

The synthesis of non-proteinogenic chiral α-amino acids is of considerable interest.[1,2] Previously, we introduced **1**, a chiral Ni^{II} complex of Schiff's base of glycine and (*S*)-*o*-[*N*-(*N*′-benzylprolyl)amino]benzophenone (BPB), as a useful substrate for the asymmetric synthesis of α-amino acids by different reactions of C–C bond formation.[3,4] This approach has significant advantages including the simplicity of preparation of complex **1**,[5] a wide range of alkylating reagents and high reactant concentration and reaction rates at room temperatures.[3,4] At the same time, dihalogen alkyls were used in asymmetric alkylation only casually.[6,7]

The aim of this work was to introduce a bifunctional agent into **1** and thus to develop the synthesis of either chiral mono or bis α,α′-amino acids by simply changing the reaction conditions (Scheme 1). We supposed that the preparation of amino acids **3a–c** by the alkylation of **1** with a bifunctional agent, α,α′-dibromo-*o*-xylene **2**, could be performed. Varying the ratio of **1** and **2** and reaction conditions, we intended to achieve selective alkylation of the complex, as a result of which amino acids **3a–c** could be obtained according to Scheme 1. Pipecoline analogues (such as **3a**) and α,α′-diaminodicarboxylic acid **3b** are of importance in peptide chemistry[8–10] and in the design of chiral ligands used in asymmetric catalysis.[11,12] Therefore, amino acid **3b** is a cysteine isostere,[8(a)] the disulfide bridge being substituted by an ethylene unit, and it can act as a substitute for cysteine in biologically active substrates.[13]

The alkylation of **1** with alkyl dihalide **2** (Scheme 1) always gave a mixture of monomeric and dimeric complexes **4** and **5** with their ratio depending on the reaction conditions.† The reaction was monitored by TLC (SiO_2, $CHCl_3$–acetone); 96% conversion was observed after 1 h. To optimise the conditions of formation of each of the complexes, comparative experiments were carried out at different ratios between **1** and **2**. We found that monoalkylation product **4** is mainly (72%) formed under a routine alkylation and a ratio of **1** to **2** equal to 1:1. A decrease in the quantity of the alkylating agent up to 0.5 equiv. and the heating of a reaction mixture (50 °C, 2 h) resulted in another product **5** in 62% yield. In this case, **2** reacted with two molecules of **1** linking them and producing **5**.

The reaction mixture was quenched with aqueous acetic acid, and **4** or **5** precipitated as a red solid. The separation of the main (*S*,*S*)-diastereoisomers was carried out by preparative TLC according to a standard procedure.[3,4] The structures of (*S*,*S*)-**4**‡ and (*S*,*S*,*S*,*S*)-**5**§ were confirmed by ^{1}H NMR spectroscopy and elemental analysis.

After the decomposition¶ of pure (*S*,*S*)-**4** with aqueous HCl, the intramolecular ring formation of the liberated amino acid resulted in the intramolecular alkylation of the free amino group with the formation of cyclic amino acid (*S*)-**3a**.†† Previously, amino acid **3a** was obtained by the diastereoselective alkylation of chiral cyclic derivatives of glycine with a small yield and *ee* of only 66%.[7(a)] Dimeric complex **5** is less stable as compared to other monomeric complexes,[3–5] and it decomposed on heating to 100 °C. The decomposition of complex (*S*,*S*,*S*,*S*)-**5** by aqueous HCl according to the routine procedure[3,4] gave bis(amino acid) (*S*,*S*)-**3b**.‡‡ The hydrochloride of (*S*)-BPB was removed by filtration in almost quantitative yield as usual.[3,4] $NiCl_2$ and the amino acid were easily separated by the ion-exchange technique.

It was important that the product of intramolecular bis-alkylation, complex (*S*)-**6**, was not formed under routine alkylation, by virtue of various factors. However, complex **4** under the action of MeONa in MeOH§§ was found to undergo intramolecular alkylation to form (*S*)-**6**,¶¶ from which achiral 2-aminoindane-2-carboxylic acid **3c**††† (synthesis of other aminoindancarboxylic acids see in ref. 14) was recovered in a usual way.

Thus, we propose a simple procedure for the synthesis of three non-proteinogenic α-amino acids using a single alkylating agent and a single Ni^{II} complex.

† *General procedure.* To a solution of **1** (100 mg, 0.2 mmol) [or 200 mg (0.4 mmol) of **1** for the main preparation of complex **5**] and **2** (52.8 mg, 0.2 mmol) in MeCN (3 ml), powdered NaOH (80 mg, 2 mmol) was added, and the reaction mixture was stirred under argon for 40 min at 20 °C [2 h at 50 °C for the preparation of **5**]. The mixture was quenched with AcOH (1.5 ml), and the precipitate was extracted with $CHCl_3$. Complexes **4** and **5** were separated by TLC or column chromatography on SiO_2 ($CHCl_3$–Me_2CO, 3:1).

‡ Ni^{II} complex of a Schiff's base of (*S*)-BPB and (2*S*)-2-amino-3-[2-(bromomethyl)phenyl]propanoic acid **4**. Yield 72%, dark-red crystals, mp 134–136 °C (decomp., MeOH), $[\alpha]_D^{25}$ +1800 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.9–3.3 (m, 7H, Pro), 3.42 (d, 1H, NBn, *J* 18 Hz), 3.44 (d, 2H, C*H*$_2$C$_6$H$_4$CH$_2$Br, *J* 10 Hz), 4.19 (t, 1H, α-H, *J* 6 Hz), 4.24 (d, 1H, CH$_2$Br, *J* 9 Hz), 4.29 (d, 1H, NBn, *J* 18 Hz), 4.38 (d, 1H, CH$_2$Br, *J* 9 Hz), 6.45–8.4 (m, 18 H, ArH). Found (%): C, 60.42; H, 4.73; N, 5.85. Calc. for $C_{35}H_{32}N_3NiO_3Br·H_2O$ (%): C, 60.12; H, 4.90; N, 6.01.

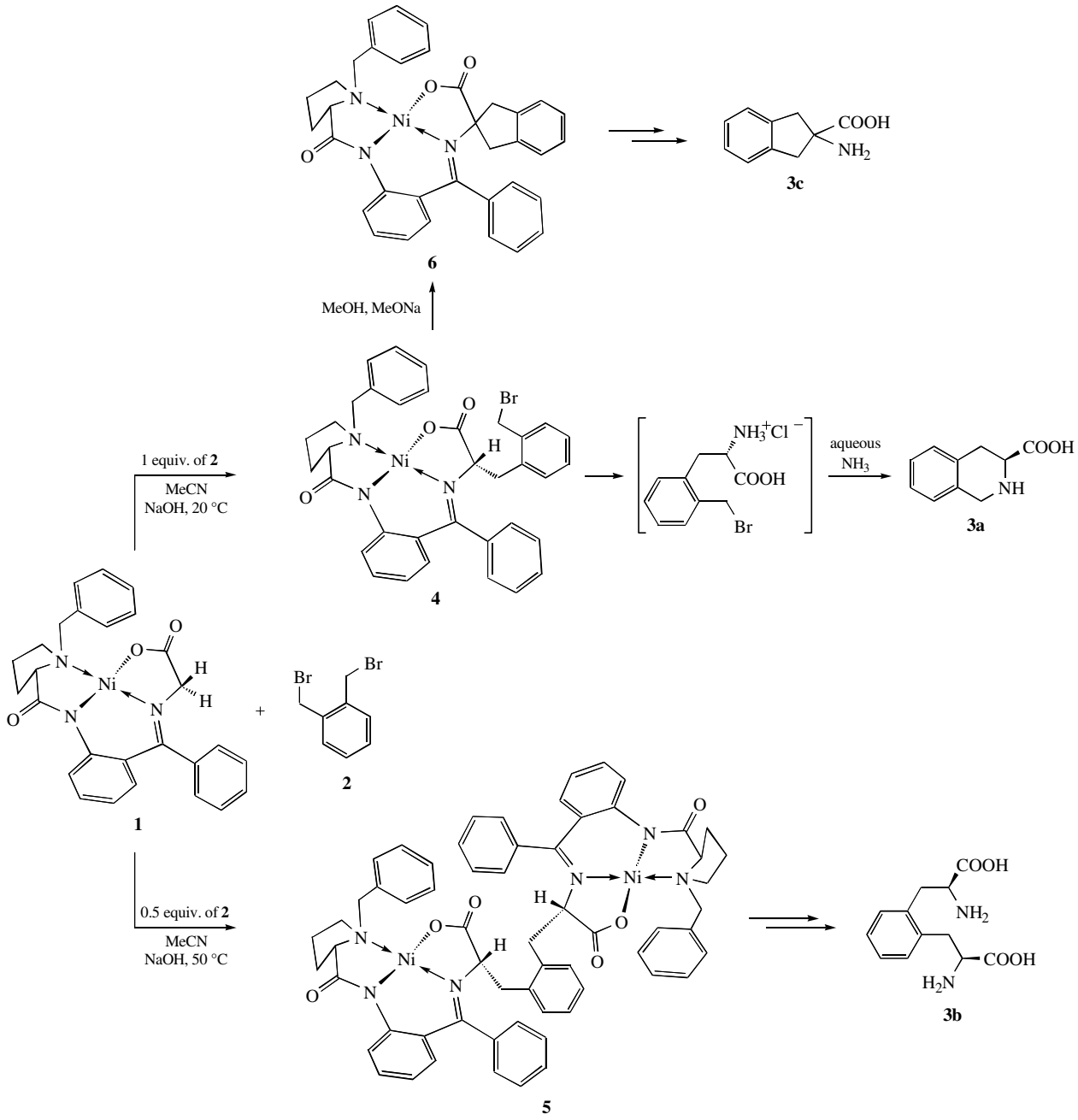
§ Bis-[Ni^{II} complex of Schiff's base of (*S*)-BPB] and (2*S*)-2-amino-3-{2-[(2*S*)-2-amino-2-carboxyethyl]phenyl}propanoic acid **5**. Dark-red crystals, mp 97 ° (decomp., MeOH), $[\alpha]_D^{25}$ +2248 (*c* 1, $CHCl_3$). The ^{1}H NMR spectrum was not interpreted because of low resolution, which can be explained by changing the Ni^{II} configuration from a square-planar arrangement and paramagnetic admixtures. Found (%): C, 67.63; H, 5.32; N, 6.98. Calc. for $C_{62}H_{56}N_6Ni_2O_6$ (%): C, 67.79; H, 5.14; N, 7.65.

¶ The isolation of the amino acid **3a** is different from the usual method.[3–5] The mixture of complex **4** (500 mg, 0.73 mmol) in MeOH (3 ml) and a 6 M HCl solution (3.5 ml) was agitated for 20 min at 50 °C and evaporated to dryness. The residue was diluted with a minimum quantity of water (0.5 ml) to dissolve $Ni(NO_3)_2$, and the solution was filtered. The pH of the residue was brought to 9 by the addition of aqueous NH_3 and BPB was extracted with $CHCl_3$. Finally, the solution of the amino acid was evaporated.

†† (3*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid **3a**. The white crystals, mp > 300 °C, $[\alpha]_D^{25}$ –165.5 (*c* 2, NaOH, 1 M) {lit.,[16] $[\alpha]_D^{25}$ –167 (*c* 2, NaOH, 1 M)}. ^{1}H NMR (400 MHz, D_2O) δ: 3.5 (d, 1H, ArC*H*$_2$CH, *J* 15.9 Hz), 3.85 (t, 1H, ArCH$_2$C*H*, *J* 2.2 Hz), 3.91 (d, 1H, ArC*H*$_2$CH, *J* 15.9 Hz), 4.64 (d, 1H, ArC*H*$_2$NH, *J* 12.8 Hz), 4.87 (d, 1H, ArC*H*$_2$NH, *J* 12.8 Hz), 7.63 (d, 1H, ArH, *J* 7.5 Hz), 7.73 (t, 1H, ArH, *J* 7.2 Hz), 7.82 (d, 1H, ArH, *J* 7.2 Hz), 8.1 (t, 1H, ArH, *J* 7.2 Hz). Found (%): C, 67.54; H, 6.36; N, 7.63. Calc. for $C_{10}H_{11}NO_2$ (%): C, 67.78; H, 6.26; N, 7.90.

‡‡ (2*S*)-2-Amino-3-{2-[(2*S*)-2-amino-2-carboxyethyl]phenyl}propanoic acid **3b**. White crystals, mp 223 °C, $[\alpha]_D^{25}$ –17.65 (*c* 2, H_2O). ^{1}H NMR (400 MHz, D_2O) δ: 2.85 (dd, 2H, ArC*H*$_2$, *J* 7 Hz, *J* 3 Hz), 3.06 (dd, 2H, ArC*H*$_2$, *J* 7 Hz, *J* 3 Hz), 3.63 (t, 2H, 2C*H*NH$_2$, *J* 3 Hz), 7.05 (m, 4H, ArH). Found (%): C, 57.54; H, 6.35; N, 10.85. Calc. for $C_{12}H_{16}N_2O_4$ (%): C, 57.13; H, 6.39; N, 11.10.

§§ *Preparation of complex* **6** *from* **4**. The mixture of complex **4** (0.4 mmol) in MeOH (3 ml) and a 4.44 M MeONa solution in MeOH (0.2 ml) was stirred for 1 h and then quenched with acetic acid (1 ml). The red precipitate of **6** was extracted with $CHCl_3$, and the solution was evaporated.



Scheme 1

We believe that this procedure can be performed catalytically with the use of an achiral substrate/chiral catalyst pair by a new method[15] proposed for the asymmetric synthesis of α-amino acids.

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¶¶ Ni^{II} complex of Schiff's base of (*S*)-BPB and 2-aminoindane-2-carboxylic acid **6**. Dark-red crystals, mp 187 °C (decomp., MeOH), $[\alpha]_D^{25}$ +1224 (*c* 1, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ: 2.0–3.52 (m, 7H, Pro), 3.40 (d, 1H, CBn, *J* 18 Hz), 3.60 (d, 1H, NBn, *J* 14 Hz), 3.70 (d, 1H, CBn, *J* 18 Hz), 3.77 (d, 1H, Bn, *J* 17 Hz), 3.92 (d, 1H, CBn, *J* 17 Hz), 4.49 (d, 1H, NBn, *J* 14 Hz), 6.5–8.15 (m, 18H, ArH). Found (%): C, 69.97; H, 5.09; N, 7.12. Calc. for $C_{35}H_{31}N_3NiO_3$ (%): C, 70.02; H, 5.20; N, 7.00.

††† 2-Aminoindane-2-carboxylic acid **3c**. Colourless crystals, mp 178 °C. ^1H NMR (400 MHz, D_2O) δ: 3.41 (d, 2H, $ArCH_2$, *J* 15 Hz), 3.56 (d, 2H, $ArCH_2$, *J* 15 Hz), 7.80 (d, 2H, ArH, *J* 7 Hz, *J* 3 Hz), 8.1 (dd, 2H, ArH, *J* 7.2 Hz, *J* 3.2 Hz). Found (%): C, 68.04; H, 6.14; N, 7.45. Calc. for $C_{10}H_{11}NO_2$ (%): C, 67.78; H, 6.26; N, 7.90.

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