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Coordination Compounds Based on 1,2,3,4-Tetrahydro-isoquinoline-3-carboxylic Acid †

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† *Dedicated to Professor Jaromír Kaválek in occasion of his 70th birthday.*

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Abstract: Syntheses of 2,6-bis[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine and its coordination compounds with Cu^{2+}, Co^{2+}, Co^{3+}, or Fe^{3+} are described. By means of ^{1}H- and ^{13}C-NMR spectra it was proved that 2,6-bis[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine as well as its coordination compound with Co^{3+} exist in the form of a mixture of three conformers, differing in the conformations at the two amide groups present. The prepared coordination compounds were tested in the enantioselective catalysis of the nitroaldol addition of nitromethane with 2-nitrobenzaldehyde or 4-nitrobenzaldehyde, and in the Michael addition of ethyl 2-oxocyclohexanecarboxylate to but-3-en-2-one.

Keywords: (*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid, chiral Tic acid derivatives, enantioselective catalysis, 2,6-bis[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine.

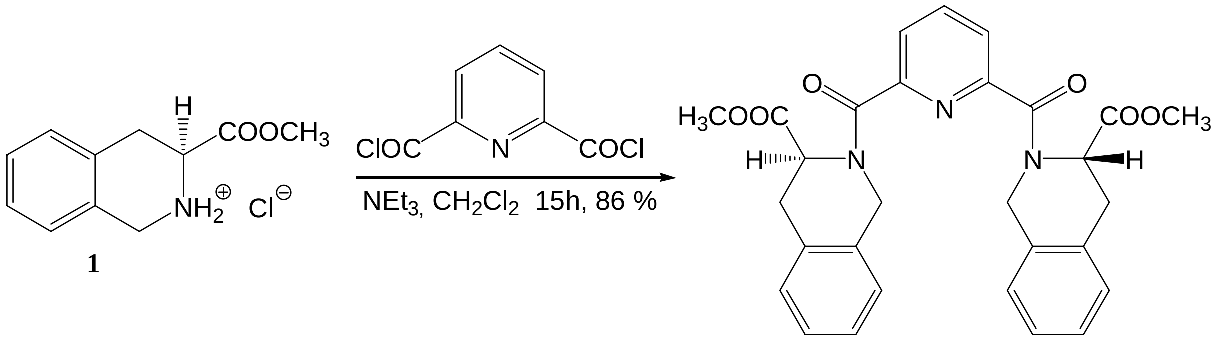
Introduction

The study of catalysis of enantioselective reactions continues to attract attention. Although the focus has shifted towards design of the optimum catalyst for carrying out a certain particular reaction, a number of papers are still being published, generally dealing with tests of chiral ligands with "potential ability" to catalyze enantioselective reactions. In particular, such ligands are taken from the "chiral pool" of natural homochiral amino acids, their derivatives and other compounds derived from them (chiral aminoalcohols, aminoamides etc.)[1-4]. The derivatives of (*S*)-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid (Tic Acid) [5, 6] (a chiral α-amino acid not found in nature) which structurally resemble anellated oxazolines [7, 8] have not been studied yet in enantioselective catalytic reactions.

Results and Discussion

2,6-bis[((3*S*)-3-(Methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine (**2**) was prepared by a reaction of hydrochloride of ester of Tic acid (**1**) and pyridine-2,6-bis-(carbonyl chloride) in the presence of triethylamine (Scheme 1).

Scheme 1



The structure of the obtained 2,6-bis[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine (**2**) was investigated by (i) quantum chemical calculations at the HF/6-31G(d,p) level [9, 10] and (ii), ^{1}H- and ^{13}C-NMR spectroscopy. Calculations showed that compound **2** can exist in three isomeric forms, namely in two symmetrical forms and one unsymmetrical one. This relatively extensive system had to be described using a simpler HF/6-31G(d,p) calculation model [9, 10]. The calculation indicates the same probabilities of formation of rotameric forms A and B (Figure 1) during formation of amide bond.

Formation of two amide bonds results in the creation of forms AA, BB, AB and BA with comparable probability. Forms AB and BA are identical and will be referred to henceforth as form AB+BA. The forms discussed are depicted in Figure 1. The unsymmetrical form AB+BA is formed in a double amount as compared with forms AA or BB. From the standpoint of symmetry, form AB+BA belongs to the point group C_1 and would exhibit two sets of signals in both ^{1}H- and ^{13}C-NMR spectra. The intensity of both sets of multiplets in the ^{1}H NMR spectrum should be comparable with the intensity of multiplets of forms AA and BB, because forms AA and BB belong to point group C_2 and will exhibit only one set of signals for each of the forms in ^{1}H-NMR spectrum. According to the quantum-chemical simulations, the ^{1}H-NMR spectrum should contain 4 sets of multiplets with similar intensities.

Figure 1. Structures of forms of compound **2** optimized at the HF/6-31G(d,p) level [9, 10].

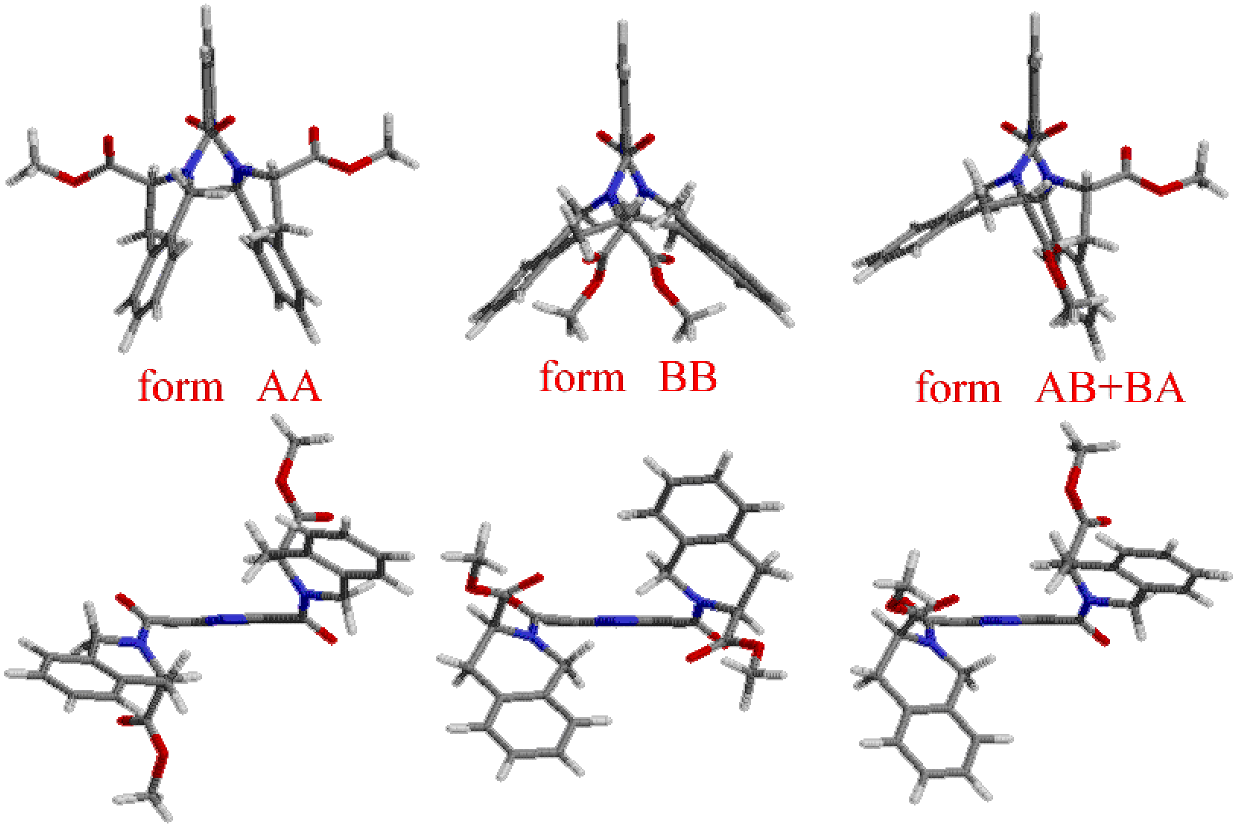
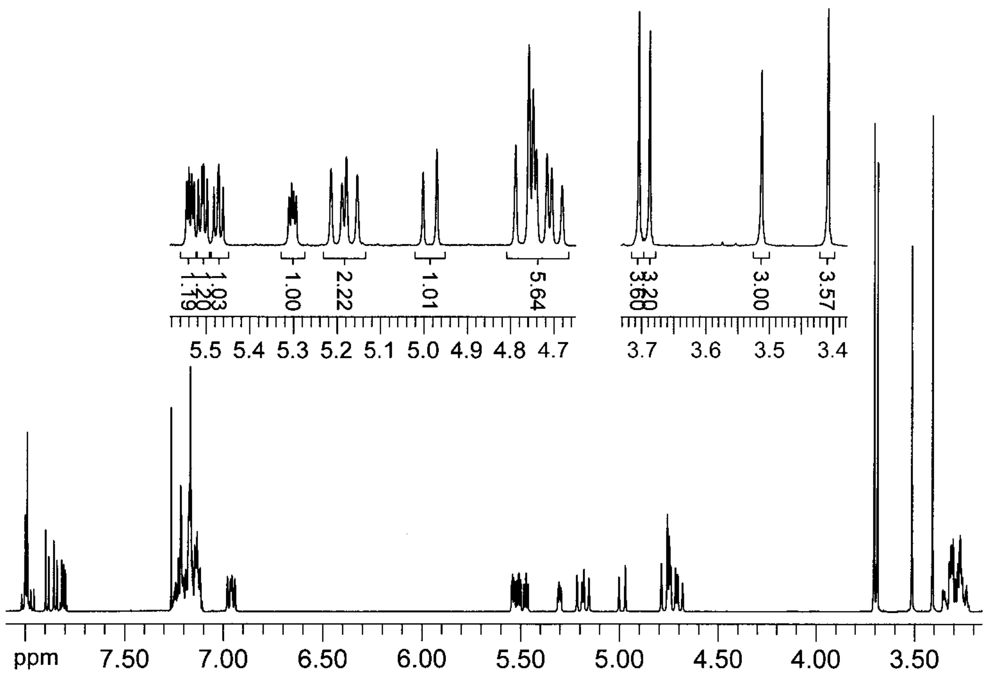


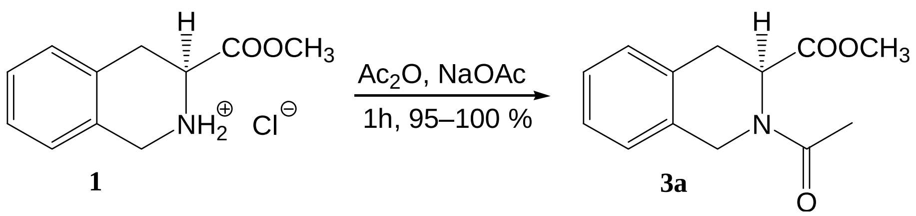
Figure 2. ^{1}H-NMR spectrum of compound **2** in $CDCl_3$ (500 MHz).



This prediction fully corresponds with the experimental NMR spectrum of compound **2** (Figure 2), in which there really are four sets of signals of comparable intensities for the individual protons. This situation can be easily observed on the multiplets of protons H(3) and H(1) of the tetrahydro-isoquinoline skeleton (δ 4.6–5.6) and the signals of the OCH_3 groups (δ 3.4–3.7). No mutual transformation of individual forms on the NMR time scale was observed up to 50 °C.

The formation of rotamers due to hindered rotation around the amide bond C–N in derivatives of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid was also observed in the case of the corresponding *N*-chlorocarbonyl [5] and *N*-acetyl derivatives. Methyl *N*-acetyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3**) was prepared from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, or from the racemic acid (Scheme 2).

Scheme 2



The optical purity of the non-racemic product determined by HPLC on chiral column by comparison with the racemic substance was 94.6 % (Figure 3). The proportion of conformers in the (*S*)-enantiomer is ca 5:2 according to the ^{1}H-NMR spectrum (Figure 4).

Figure 3. Chiral HPLC separation of the enantiomers of acetyl derivative **3**. Upper chromatogram represents separation of racemic mixture and lower the enantiomeric purity of the (*S*)-enantiomer **3a** (e.e. 94.6%). For separation conditions see Experimental.

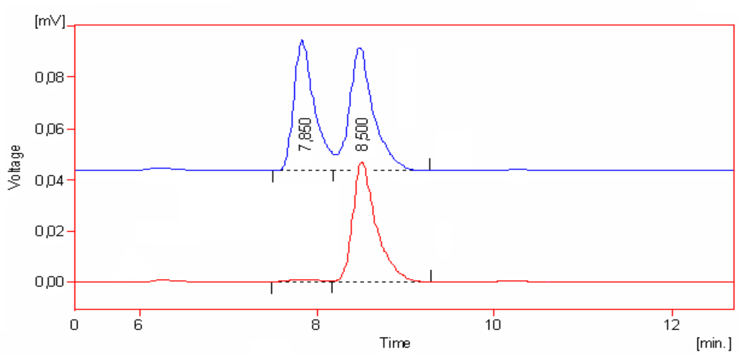
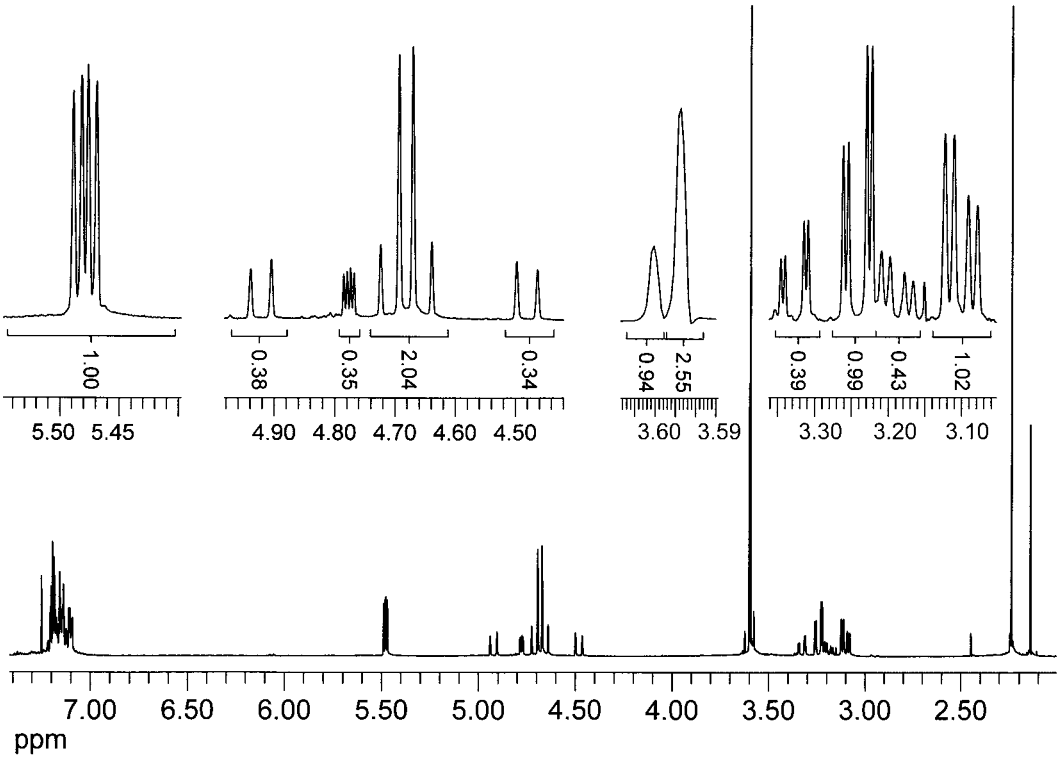
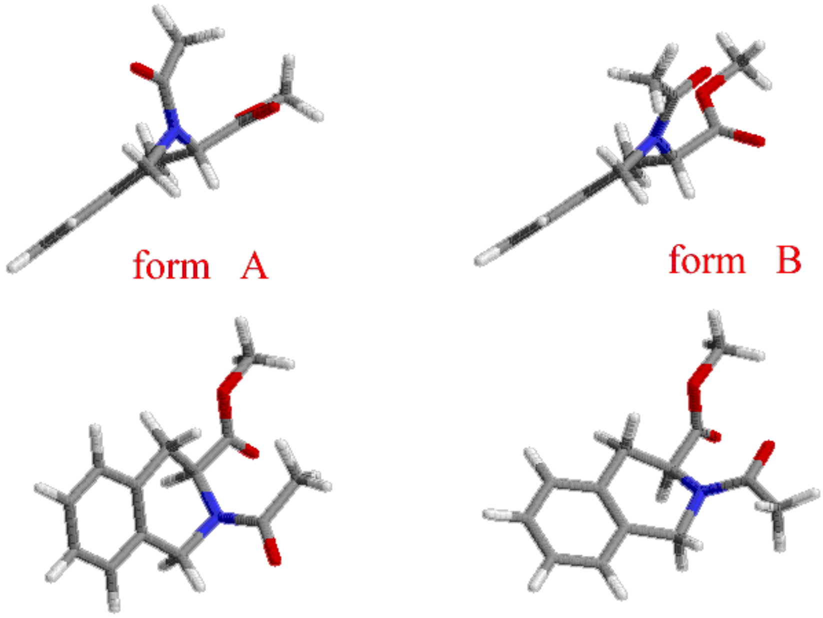


Figure 4. ¹H-NMR spectrum of compound **3a** in $CDCl_3$ (500 MHz).



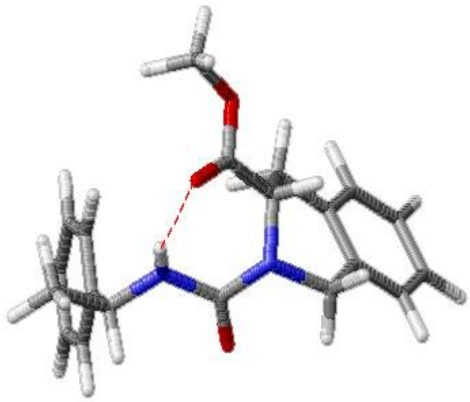
The same conclusions were obtained based on the geometry optimization of acetyl derivative carried out at the B3LYP/TZVP level [11-13] (Figure 5). In order to achieve better correlation of the results with the ¹H-NMR spectrum the calculation included the solvent (chloroform) effect by means of the polarised continuum method (PCM) [14]. Out of the pair of optimized structures (Figure 5) structure A was assigned to predominating rotameric form in NMR spectrum on the basis of calculated energies.

Figure 5. Structures of compound **3a** optimized at B3LYP/TZVP + PCM [11-14] level.



In the case of compounds having an RNHCO– group attached to nitrogen atom of tetra-hydroisoquinoline skeleton [6] the ^{1}H-NMR spectrum only exhibits the presence of only one of the two possible rotamers, due to the existence of strong intramolecular hydrogen bond (Figure 6).

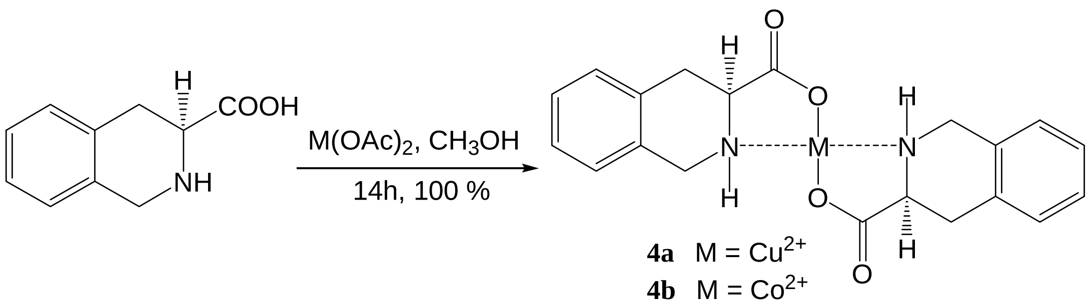
Figure 6. Structure of methyl-(3*S*)-*N*-[(1*S*)-1-methylbenzyl]carbamoyl-1,2,3,4-tetra-hydroisoquinoline-3-carboxylate [6] optimized at B3LYP/TZVP + PCM [11-14] level.



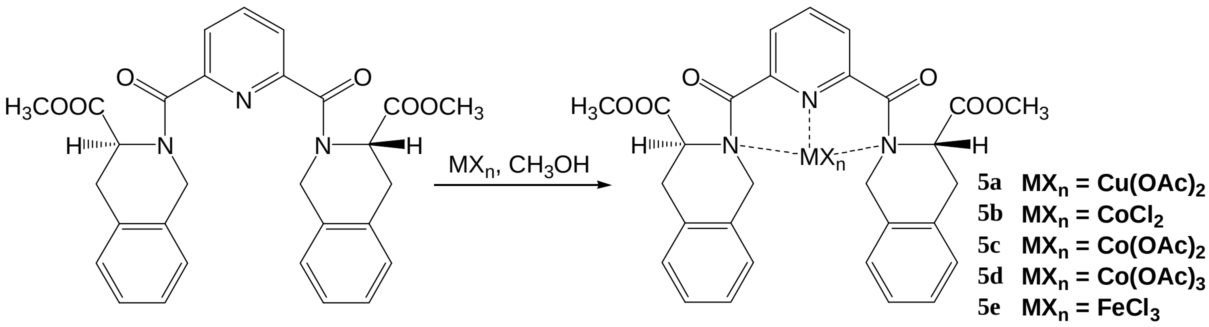
The quantum-chemical calculation results clearly indicate that the electron density at the tetra-hydroisoquinoline residue nitrogen atom is noticeably higher in the molecule of compound **2** than in that of the acetyl derivative **3a**. Due to the steric demands of the Tic residues in the molecule of **2** these residues are deviated, which disturbs the planarity and leads to partial loss of conjugation in the N-CO-Py grouping. Hence, according to these calculations compound **2** could operate as a tridentate ligand and coordinate with transition metals. This presumption was later confirmed experimentally.

The coordination compounds were prepared by a reaction of (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid or 2,6-bis[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]-pyridine (**2**) with a transition metal salt – Cu^{2+}, Co^{2+}, Co^{3+}, Fe^{3+} (chlorides, acetates) – in dry methanol (Scheme 3) [15]. The stoichiometric composition of the coordination compounds was established on the basis of elemental analyses. (*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid is an bidentate ligand and coordinates with Cu^{2+} or Co^{2+} at a ratio of 2:1. 2,6-bis[((3*S*)-3-(Methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine (**2**) is an tridentate ligand, as described for 2,6-bis-(oxazolyl)pyridines [4, 16] or 2,6-bis(imidazolyl)pyridines [17, 18], and it coordinates with Cu^{2+}, Co^{2+}, Co^{3+}, Fe^{3+} in a ratio of 1:1 (Schemes 3, 4).

Scheme 3



Scheme 4



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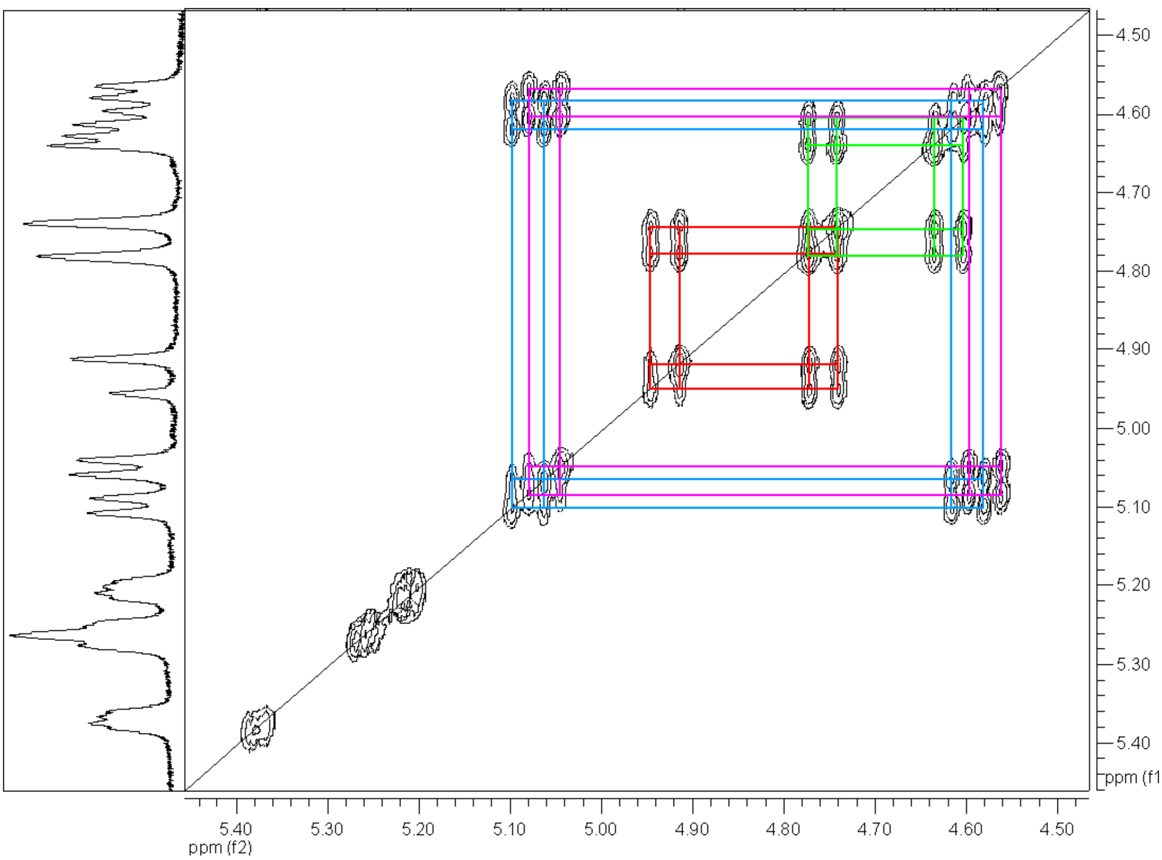
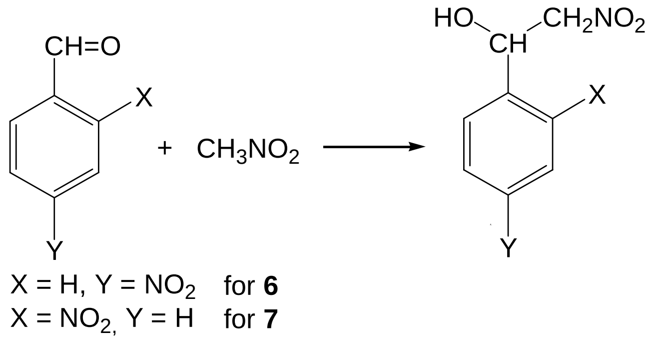
Of all the coordination compounds prepared only proved suitable for NMR measurements, namely the 2,6-bis-[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine Co^{3+} complex. Both its ^{1}H- and ^{13}C-NMR spectra were of adequate quality with slightly broadened signals (Figure 7). The ^{1}H-NMR spectrum of this coordination compound resembles that of the free ligand. From the ^{13}C-NMR spectrum it is obvious that it also corresponds to a mixture of three compounds of the types AA, BB, AB+BA, which are present at roughly equimolecular ratios (the tetrad of signals for corresponding carbons in the spectrum).

Figure 7. 500 MHz H-H COSY spectrum of the coordination compound **5d** (Co^{3+} 2,6-bis[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine) in DMSO-D_6.



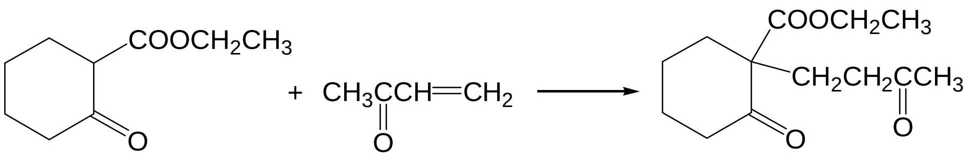
The ability of the prepared coordination compounds to catalyze enantioselective reactions was tested on the Henry nitroaldol addition of nitromethane with 2-nitro- or 4-nitrobenzaldehyde (Scheme 5), under the conditions described in [19], and on the Michael addition reaction of ethyl 2-oxocyclo-hexanecarboxylate with but-3-en-2-one (Scheme 6), under the condition described in [20-23].

Scheme 5



In the nitroaldol addition of nitromethane with 4-nitrobenzaldehyde the highest enantioselective efficiency was observed with the coordination compound **5a** containing Cu^{2+}. Application of this substance at 0 °C gave (*R*)-2-nitro-1-(4-nitrophenyl)ethanol (**6**) in an enantiomeric excess up to 61.7 % (Table 1). (*R*)-2-Nitro-1-(2-nitrophenyl)ethanol (**7**) resulted in an enantiomeric excess of only 12.3 % when using the same catalyst. The sterically more demanding nitroaldol addition with 2-nitro-benzaldehyde obviously prevents the optimum steric interaction of the chiral catalyst with the substrate. The other coordination compounds prepared exhibited only very low levels of enantioselectivity (Tables 1, 2). While the reaction of 4-nitrobenzaldehyde with nitromethane catalyzed with coordination compounds **5a** and **5c** gave a reasonable excess of (*R*)-2-nitro-1-(4-nitrophenyl)ethanol, the catalysis with coordination compound **4b** gave just a low excess, but of (*S*)-2-nitro-1-(4-nitrophenyl)ethanol.

Scheme 6



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In the Michael addition reaction of ethyl 2-oxocyclohexanecarboxylate with but-3-en-2-one catalysed by coordination compound **5e** the required product was obtained in high chemical yield but with an enantiomeric excess of only 7.2 % (Table 3). This lower efficiency is obviously due to the far higher steric demands in the surroundings of coordination centres than are those of, e.g., the catalysts based on 2,6-bis(oxazolyl)pyridines [15]. Another problem lies in the fact that the coordination compounds derived from substance **2** are present (obviously all of them) in three rotameric forms (Figure 1), and it is not quite clear whether these forms can be transformed into one another during the interaction with the molecules undergoing the catalysed reaction, neither is it known which of the forms is active in the catalysed reaction.

Table 1. Nitroaldol addition of nitromethane with 4-nitrobenzaldehyde catalysed by coordination compounds **5a, 5c** and **4a, b**.

Coordination compound	Reaction time	Temperature	Conversion	m.p. of product	Enantiomer excess (*R*)
5a	10 days	20 °C	70%	82–84 °C	54.5%
5a	15 days	0 °C	30%	82–84 °C	61.7%
5c	4 days	20 °C	100%	81–83 °C	6.1%
4a	20 days	20 °C	0%	–	–
4b	20 days	20 °C	50%	81–83 °C	7.3%*

*(*S*) enantiomer

Table 2. Nitroaldol addition of nitromethane with 2-nitrobenzaldehyde catalysed by coordination compound **5a**.

Coordination compound	Reaction time	Temperature	Conversion	m.p. of product	Enantiomer excess (*R*)
5a	15 days	20 °C	50%	80–82 °C	12.3%

Table 3. Michael addition reaction of ethyl 2-oxocyclohexanecarboxylate with but-3-en-2-one catalysed by coordination compounds **5b** and **5e**.

Coordination compound	Reaction time	Temperature	Conversion	Enantiomer excess (*S*)
5b	20 days	20 °C	0%	-
5e	1 day	20 °C	100%	7.2%
5e	20 days	–25 °C	60%	7.1%

Conclusions

Derivatives of (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid were prepared by *N*-acylation with acetic anhydride or 2,6-bis(chlorocarbonyl)pyridine. The *N*-acetyl derivative was obtained in an optical purity of 94.6 % (determined by HPLC). In solution ($CDCl_3$) it exists in the form of two rotamers, which are not mutually interconverted on the NMR time scale up to ca 50 °C. On the basis of quantum-chemical calculations it was predicted (and then confirmed by both ^{1}H- and ^{13}C-NMR spectra) that 2,6-bis[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine exists in solution as a mixture of three rotameric forms differing in the conformations at the two amide C–N bonds. The rotameric forms are not mutually interconverted on the NMR time scale, not even at 50 °C. Coordination compounds were prepared from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**4**) or 2,6-bis[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine with the cations Cu^{2+}, Co^{2+}, Co^{3+} and Fe^{3+} (**5a-e**). The stoichiometry of these substances was determined on the basis of elemental analyses. (*S*)-1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid is coordinated with metals at the ratio of 2:1 and bis[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydro-isoquinolin-2-yl)carbonyl]pyridine at the ratio of 1:1. The Co^{3+} complex of bis[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine also exists in solution as a mixture of three rotamers. The ability of the prepared coordination compounds to catalyze the enantioselective Henry reaction and Michael addition was low. The highest enantiomeric excess of 61.7 % with a conversion of only 30 % was achieved in the reaction of nitromethane with 4-nitrobenzaldehyde catalyzed with the coordination compound **5a**. Uncertainty exists as to which of the three forms of the catalyst is active, or whether the individual forms can be mutually interconverted during interaction with the substrate of reaction.

Experimental

General

The NMR spectra were measured at 298 K with a Bruker AVANCE 500 spectrometer equipped with 5 mm broadband probe at the frequencies of 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C) and with a Bruker AMX 360 spectrometer at the frequencies 360.14 MHz (^{1}H) and 90.57 MHz (^{13}C) in $CDCl_3$ and DMSO-D_6 respectively. Spectra were calibrated on TMS (in $CDCl_3$) or on the central signal of the solvent multiplet in DMSO-D_6 (δ 2.55, and 39.6 respectively). *J* values are given in Hertz. The ^{13}C NMR spectra were measured in standard way and by means of the APT pulse sequence. The proton signals were assigned with the help of H-H COSY pulse sequence. Optical purity was determined by chiral HPLC. HPLC system consisted of a Spectra Series P200 gradient pump (Fremont, CA, USA), a HP 1100 Series autosampler, a HP 1100 Series thermostated column compartment from Hewlett Packard (Waldbronn, Germany), and a SPD-10A_{VP} UV-Vis detector from Shimadzu (Prague, Czech Republic). The enantiomers of the compound **3** were measured at 209 nm (Figure 6). Data from chromatographic runs were processed using a chromatography station for Windows CSW (version 1.7) software from DataApex (Prague, Czech Republic). Separation of the respective enantiomers was performed using a 250 × 4.6 mm OD-R Chiralcel column from Daicel Chemical Industries (Tokyo, Japan). The mobile phase was prepared by mixing buffer (0.3 M sodium perchlorate, pH 3.0 set by $HClO_4$) with acetonitrile 50/50 (v/v). HPLC separation was performed at 25°C with a flow rate of 0.8 mL/min. Melting points were determined with a Kofler hot stage microscope and were not corrected. The microanalyses were performed on a FISONS EA 1108 CHNS automatic analyser. Optical rotations were measured on PERKIN ELMER 341 Polarimeter at λ 589.3 nm and 298 K, concentration *c* is given in g/100 mL. The starting material *(S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid* (CMS Chemicals LTD), mp 331 °C (decomp) was 99.1% pure, according to titration with $HClO_4$, and had $[\alpha]_D^{20}$ = –175.8° (*c* 1.1N NaOH, aq) [ref. [24] gives $[\alpha]_D^{20}$ = –177.4° (*c* 1.1N NaOH, aq)].

Hydrochloride of methyl (S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**1**)

This compound [5] was prepared from (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and $SOCl_2$ in dry methanol by a known procedure [24, 25] in practically quantitative yield; m.p. 248–250 °C (decomp), from methanol-diethyl ether; ref. [24] gives m.p. 250-255 °C (decomp.) from the same solvent mixture. The product recrystallized from a mixture of chloroform-diethyl ether melts at 261–

263 °C (decomp.); $[\alpha]_D^{20}$ = –155.1° (*c* 1, $CHCl_3$), $[\alpha]_D^{20}$ = –128.2° (*c* 1, CH_3OH); ref. [24] gives $[\alpha]_D^{20}$ = –104.1° (*c* 1, CH_3OH).

Methyl (3S)-N-acetyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3a**)

Prepared by a method analogous to one described in the literature [26]. A suspension of the hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**1**) (5 g, 22.0 mmol) and anhydrous sodium acetate (1.25 g, 15.3 mmol) in acetic anhydride (11.35 mL, 120.4 mmol) was stirred and heated at 50-60 °C for 1 h, whereupon the reaction mixture was poured into water (50 mL) and immediately extracted with $CHCl_3$ (3 × 25 mL). The chloroform extract was concentrated and the solution obtained was extracted with water (50 mL). Drying of the chloroform solution with anhydrous Na_2SO_4 and removal of the solvent by distillation gave an oily crude product, which was further purified by flash chromatography (CH_3OH - silica gel, 60 μm). Recrystallization from cyclohexane with charcoal gave 4.6 g of a white crystalline solid (90% of theory), m.p. 93–96 °C; $[\alpha]_D^{20}$ = +35.6° (c = 1, $CHCl_3$). The analysis by ^{1}H-NMR showed that the product is a mixture of two isomers (according to the integral intensities, the proportion of isomers I/II in the isolated mixture is ca 5:2). *Isomer I*: ^{1}H-NMR ($CDCl_3$): 7.22-7.11, multiplet, 4H(arom.); 4.72 H(1a), 4.66 H(1b), AB quartet, ^2J(H(1a),H(1b))=15.8 Hz, 2×1H; 5.49 H(3), 3.25 H(4a), 3.11 H(4b), AMX system, ^3J(H(3),H(4a))=3.5 Hz, ^3J(H(3),H(4b))=6.3 Hz, ^2J(H(4a),H(4b))=15.9 Hz, 3×1H; 3.61, s, OCH_3, 3H; 2.25, s, CH_3, 3H; ^{13}C-NMR ($CDCl_3$): 171.39 a 170.61 (CO), 132.10 a 131.97 (arom, 2×C_q), 128.47, 127.15, 126.88, 126.00 (arom, 4×CH), 52.26 (**C**HCO), 51.06 (OCH_3), 46.31 (Ar**C**H_2N), 30.80 (Ar**C**H_2C), 21.91 (CH_3); *Isomer II*: ^{1}H-NMR ($CDCl_3$): 7.22-7.11, multiplet, 4H(arom.); 4.93 H(1a), 4.49 H(1b), AB quartet, ^2J(H(1a),H(1b))=17.3 Hz, 2×1H; 4.78 H(3), 3.34 H(4a), 3.19 H(4b), AMX system, ^3J(H(3),H(4a))=2.8 Hz, ^3J(H(3),H(4b))=6.0 Hz, ^2J(H(4a),H(4b))=15.6 Hz, 3×1H; 3.60, s, OCH_3, 3H; 2.16, s, CH_3, 3H; ^{13}C-NMR ($CDCl_3$): 170.94 a 170.54 (CO), 132.59 a 131.00 (arom, 2×C_q), 128.00, 127.06, 126.74, 126.58 (arom, 4×CH), 55.67 (OCH_3), 52.61 (**C**HCO), 43.34 (Ar**C**H_2N), 31.82 (Ar**C**H_2C), 21.80 (CH_3); Anal. calcd. for $C_{13}H_{15}NO_3$ (233.27): C 66.94 H 6.48 N 6.00%, found: C 66.68 H 6.61 N 5.93%.

Methyl (3±)-N-acetyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3b**)

Prepared by the same procedure as **3a** from (3±)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid in a yield of 92%. After flash chromatography the product was isolated as an oily substance. Its NMR analysis showed that the product is a mixture of two isomers (according to the integral intensities, the proportion of isomers in the isolated mixture is ca 5:2). The NMR spectra of racemic compound are identical with those of methyl (3*S*)-*N*-acetyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate **(3a)**.

2,6-bis[((3S)-3-(Methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine (**2**)

Prepared in analogy with the procedure described in ref. [27] for the reaction of pyridine-2,6-bis(carbonyl chloride) with amino acids. A suspension was prepared from dry CH_2Cl_2 (200 mL) and the hydrochloride of methyl (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**1**), (2.27 g, 10 mmol). At a temperature of –25 °C the suspension was treated with dry NEt_3 (1.01 g, 10 mmol). After 5 min stirring, the mixture was treated with a solution of pyridine-2,6-bis(carbonyl chloride) (1.02 g, 5 mmol) in dry CH_2Cl_2 (50 mL) gradually added dropwise with vigorous stirring at –20 °C, whereupon another dry NEt_3 (1.01 g, 10 mmol) was added. The reaction mixture was stirred further at –20 °C for a period of 3 h, and then at r.t. for 12 h. The obtained yellowish solution was extracted with H_2O (2 × 100 mL), then with 5% aqueous hydrochloric acid (50 mL) and finally with H_2O (2 × 50 mL). After drying and removal of the solvent by distillation an oily product was isolated. Its recrystallisation from a cyclohexane-hexane mixture gave 2.19 g (86 %) of a white solid melting at 61–64 °C. Its NMR analysis showed that the product is a mixture of three isomeric forms – two symmetrical forms, and one unsymmetrical form present in a double amount, hence the NMR spectrum exhibits 4 sets of signals of comparable intensities (for the proton at the 4-position of pyridine ring only 3 multiplets for 4H). ^{1}H-NMR ($CDCl_3$) (see Figure 2): 8.02-7.78, multiplet (pyridine); 7.25-6.94, multiplet (arom.-isoquinoline); 5.55-5.29, 4 × dd (H(3)); 5.22-4.68, 4 × AB q (H(1a), H(1b)); 3.70, 3.69, 3.51 a 3.41, 4 × s, 4×(OCH_3), 3.36-3.23, multiplet (H(4a), H(4b)); ^{13}C-NMR ($CDCl_3$): 171.02, 171.00, 170.79 a 170.66 4×(C**C**OO), 168.12, 167.83, 167.69 a 167.53 4×(C**C**ON), not given 35×C(arom.), 56.17, 55.88, 52.81 a 52.14 4×(OCH_3), 52.47, 52.47, 52.43 a 52.43 4×(**C**HCO), 47.57, 47.43, 44.10 a 43.82 4×(Ar**C**H_2N), 31.49, 31.25, 30.73 a 30.64 4×(Ar**C**H_2C); Anal. calcd. for $C_{29}H_{27}N_3O_6$ (513.55): C 67.83 H 5.30 N 8.18%, found: C 67.56 H 5.45 N 7.95%.

Coordination compounds of (S)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid with transition metals

Coordination compounds **4a**,**b** were prepared according to a procedure described in ref. [15]. A suspension was prepared in methanol from equimolecular amounts of (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and the transition metal salt. After 12 h vigorous stirring, the precipitate formed was collected by suction, and then washed with methanol and ether.

Table 4. Microanalysis data for compounds **4a**,**b**

	Salt	Molecular formula (m.w)	Elemental composition - Calculated / Found C (%)	H (%)	N (%)	m.p.(°C)
4a	Cu(OAc)$_2$	$C_{20}H_{20}N_2O_4Cu$ (415.93)	57.75/57.92	4.85/4.65	6.74/6.71	360–362
4b	Co(OAc)$_2$	$C_{20}H_{20}N_2O_4Co$ (411.32)	58.40/58.26	4.90/5.15	6.81/6.62	360–361

Coordination compounds of 2,6-bis[(3S)-3-methoxycarbonyl-1,2,3,4-tetrahydroisoquinolin-2-yl)-carbonyl]pyridine with transition metals **5a**-**e**

Equimolecular amounts of 2,6-bis[((3*S*)-3-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-2-yl)carbonyl]pyridine and transition metal salt were dissolved in dry methanol. The corresponding coordination compound was obtained after evaporation of the solvent and washing with ether and hexane. Cobalt(III) acetate was prepared by oxidation of cobalt(II) acetate with aqueous solution of peroxyacetic acid [28].

Table 5. Microanalysis data for compounds **5a-e**.

	Salt	Molecular formula (m.w.)	Elemental composition - Calculated / Found C (%)	H (%)	N (%)	Cl (%)	m.p. (°C)
5a	$Cu(OAc)_2$	$C_{33}H_{33}N_3O_{10}Cu$ (695.18)	57.02/56.76	4.78/4.53	6.04/5.95	–	235–238
5b	$CoCl_2$	$C_{29}H_{27}N_3O_6Cl_2Co$ (643.39)	54.14/54.49	4.23/4.62	6.53/6.38	11.02/10.89	149–151
5c	$Co(OAc)_2$	$C_{33}H_{33}N_3O_{10}Co$ (690.57)	57.40/57.13	4.82/4.65	6.08/5.87	–	198–201
5d	$Co(OAc)_3$	$C_{35}H_{36}N_3O_{12}Co$ (749.61)	56.08/55.74	4.84/4.53	5.61/5.32	–	218–220
5e	$FeCl_3$	$C_{29}H_{27}N_3O_6Cl_3Fe$ (675.75)	51.55/51.78	4.03/4.09	6.22/6.17	15.74/15.67	280–282

The structure of coordination compound **5d** containing Co(III) can be studied by means of NMR. These spectra clearly show that the product is a mixture of three isomeric forms – two symmetrical ones, and one unsymmetrical, the latter being present in a double amount. Hence, the NMR spectrum exhibits 4 sets of signals of comparable intensities (for the proton at the 4-position of pyridine ring only 3 multiplets for 4 protons). ^{1}H-NMR (DMSO-D_6) (see Figure **7**): 8.15-7.77, multiplet (pyridine); 7.37-7.16, multiplet (arom.-isoquinoline); 5.43-5.25, 4 × multiplet (H(3)); 5.13-4.57 4 × AB q (H(1a), H(1b)); 3.68, 3.67, 3.50 a 3.50, 4 × s, (OCH_3), 3.39-3.20, multiplet (H(4a), H(4b)); 2.49, s, (CH_3COO); ^{13}C-NMR (DMSO-D_6): 184.56, (CH_3**C**OO), 171.52, 171.49, 171.40 a 171.39 4×(C**C**OO), 167.88, 167.85, 167.82 a 167.68 4×(C**C**ON), not given 35×C (arom.), 56.22, 56.12, 52.78 a 52.76 4×(OCH_3), 53.24, 53.03, 52.83 a 52.76 4×(**C**HCO), 47.51, 47.20, 43.85 a 43.74 4×(Ar**C**H_2N), 31.53, 31.37, 30.74 a 30.71 4×(Ar**C**H_2C), 26.92 (CH_3**C**OO).

2-Nitro-1-(4-nitrophenyl)ethanol (**6**)

The reaction of nitromethane with 4-nitrobenzaldehyde catalyzed by the coordination compound (Scheme 5) was carried out by the known procedure [19]: a solution of nitromethane (1.4 mL, 25 mmol) and 4-nitrobenzaldehyde (0.38 g, 2.5 mmol) in dry ethanol (2 mL) was treated with coordination compound (5 mol %, 0.125 mmol). The reaction course was monitored by means of TLC (silica gel – ethyl acetate-hexane 1:4 by vol.). After keeping at the chosen temperature for a chosen time interval, the reaction was stopped by evaporating the solvent in vacuum without heating. The evaporation residue was treated with $CoCl_2$ (0.05 g, 0.385 mmol) in ethanol (10 mL) in order to transform any possible uncoordinated ligand present into the coordination compound. Methanol was evaporated under vacuum, and the residue was dissolved in ether. The coordination compounds and the unreacted $CoCl_2$ were removed from the ether solution by flash chromatography (silica gel 60 μm – ether). The ethereal filtrate was then extracted with 10% aqueous solution of sodium sulphite (2 × 20 mL) and with H_2O (1 × 10 mL). This procedure removed all unreacted aldehyde. Drying and removal of ether by evaporation without heating gave pure *2-nitro-1-(4-nitrophenyl)ethanol*; m.p. 82–84 °C. The enantiomeric excess was then calculated from chemical purity and optical rotation. The reaction of nitromethane with 2-nitrobenzaldehyde was carried out in the same way as that with 4-nitrobenzaldehyde above to afford *2-nitro-1-(2-nitrophenyl)ethanol* (**7**); m.p. 80–82 °C, o.r. +31.4 (c = 1, CH_2Cl_2).

Ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate (**8**)

The reaction of ethyl 2-oxocyclohexanecarboxylate with but-3-en-2-one catalyzed with the coordination compounds (Scheme 6) was carried out by known procedures [20-23]. A solution (or suspension) of ethyl 2-oxocyclohexanecarboxylate (0.16 mL, 1 mmol) and coordination compound (5 mol %, 0.05 mmol) in CH_2Cl_2 (1 mL) was vigorously stirred and treated with but-3-en-2-one (0.20 mL, 2 mmol). The reaction course was monitored by means of TLC (silica gel – ether-hexane 1:2 by vol.). After keeping at the chosen temperature for a chosen time interval, the reaction was stopped by evaporation of solvent without heating, whereupon the evaporation residue was dissolved in ether. The coordination compound was removed from the resulting ethereal solution by means of flash chromatography (silica gel 60 μm – ether). The ether solvent was evaporated without heating to give pure ethyl 2-oxo-1-(3-oxobutyl)cyclohexanecarboxylate as an oily substance. Its chemical purity was checked by means of liquid chromatography and its enantiomeric purity by measuring optical rotation of the product. The enantiomeric excess was then calculated from chemical purity and optical rotation.

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Sample availability: Contact the author (P.J.).