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# Asymmetric synthesis of amino acids by Cr(II) complexes of natural amino acids

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## Abstract

Stoichiometric reduction of the C,N double bond of oxime precursors of α-amino acids was performed in aqueous media by Cr(II) complexes of natural amino acids. The reduction of oximes of α-ketophenylacetic, α-keto-β-phenylpropionic and α-ketopropionic acids proceeded up to $>90\%$ conversion and 2–30% enantiomeric excess. 1:2 complexes of Cr(II) with L-alanine, L-valine, L-aspartic acid, L-histidine and L-phenylalanine were used as reducing agents. The reduction of α-(oximino)phenylacetic acid showed increasing e.e. (and decreasing conversion) with increasing temperature.


*Keywords:* Oxime reduction; α-Amino acids; Synthesis; Chromium(II); Amino acid complexes

## 1. Introduction

Induction of chirality in chemical transformations is a very important issue in preparative organic chemistry [1,2]. One of the strategies leading to chiral products is the use of transition metal reagents with chiral ligands [3]. In spite of the easy accessibility of natural amino acids, which are also excellent di- or tridentate ligands [4], their transition metal complexes were seldom used as chiral reagents or catalysts in enantioselective syntheses [5].

Considering the essential role of amino acids in life phenomena and the possibility that transition metal ions might have played a key role in the prebiotic as well as in the early biotic phase of the origin of life [6], the reactions of amino acid/transition metal complexes with organic substrates could merit special attention.

These arguments prompted us to study the reactions with Cr(II)/amino acid complexes. In the course of this project enantioselective reductions of ketones to the corresponding secondary alcohols were achieved recently [7]. We report here on the reduction of α-amino acid precursor oximes with these reagents.

## 2. Experimental

All compounds were of commercial origin with the exception of the oximes which were prepared according to literature procedures. α-(Oximino)phenylacetic acid (**1**) was obtained by treating phenylglyoxylic acid by hydroxylamine, while α-oximino-β-phenylpropionic acid (**2**) and α-oximinopropionic acid (**3**) were synthesised by nitrosation of the corresponding substituted malonic acids with amyl nitrite [8].

The amino acid/Cr(II) reagents were prepared in situ, using parameters calculated by PSEQUAD program [9].

Spectroscopic measurements were performed using the following instruments: FTIR: spectrointerferometer

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Perkin–Elmer 1600; $^{1}$H- and $^{13}$C-NMR: Bruker AMX 400; UV–vis: spectrophotometer Perkin–Elmer Lambda Bio 20 and CD (UV region): spectropolarimeter JASCO J-710.

The products of the reductions were analysed by HPLC (JASCO, pump PU-980; gradient LG-900-02; detector UV-975; column: 250 mm × 4.6 mm Supelco RP-C18 5 μm; at 1.00 ml min$^{-1}$, 20 °C; with acetonitrile–phosphate-buffer-[0.05 M $H_2PO_4^-/HPO_4^{2-}$, 1/1]-methanol eluents) in derivatized form, with Marfey's reagent L-2-[(1′-fluoro-2′,4′-dinitrophenyl-5′)amino]-propionamide [10], using standards prepared from pure L, D and DL-amino acids.

The reactions were carried out using standard Schlenk technique under deoxygenated Ar atmosphere [11].

## 3. Reductions

The parameters and results of the reduction experiments are shown in Table 1. We describe below the details of a few characteristic experiments.

### 3.1. Reaction of α-(oximino)phenylacetic acid with Cr(II)/L-histidine (1:2) complex

Into a 3-necked 50 ml reaction vessel was filled 0.80 ml of 2.15 M aqueous KOH and 9.2 ml water then this solution was deoxygenated by bubbling Ar gas for 15 min. To this solution, at 25 °C, while stirred by an external magnetic stirrer, L-histidine (0.310 g, 2 mmol) and [$Cr(OAc)_2 \cdot H_2O$] (0.125 g, 0.667 mmol) were added in one portion each. Upon the addition of the Cr(II) salt, almost immediately blue–violet colour developed, indicating the formation of the histidine/Cr(II) complex [4a,7,12,13] while the pH of the reaction mixture was 9.3. The stirring of the solution was continued and subsequently α-(oximino)phenylacetic acid (41 mg, 0.25 mmol) was added in one portion. Then the reaction vessel was closed under a slight overpressure of Ar and the magnetic stirring was continued for an additional 18 h.

After this period an 0.20 ml sample was taken to 5 ml tube and to this solution 1.60 ml of 1.0 M aqueous $NaHCO_3$ was added. After mixing these solutions by shaking the vessel for a few times, from this solution an 0.20 ml portion was taken, and to this portion 0.25 ml of

Table 1

| No | Oxime | L-Amino acid | Oxime (mmol) | Cr(II) (mmol) | Amino acid (mmol) | pH | e.e. [a] % |
|---|---|---|---|---|---|---|---|
| 1 | **1** | asp | 0.25 | 1 | 2 | 8.9 | −1.2 |
| 2 | **1** | asp | 0.25 | 0.667 | 2 | 9.3 | −4.5 |
| 3 | **1** | val | 0.25 | 1 | 2 | 9.5 | −7.3 |
| 4 | **1** | val | 0.25 | 0.667 | 2 | 9.1 | −4.8 |
| 5 | **1** | ala | 0.25 | 1 | 2 | 9.1 | −6.7 |
| 6 | **1** | ala | 0.25 | 0.667 | 2 | 9.3 | −11.7 |
| 7 | **1** | his | 0.25 | 1 | 2 | 9.4 | −2.2 |
| 8 | **1** | his | 0.25 | 0.667 | 2 | 9.4 | −4.5 |
| 9 | **1** | phe | 0.25 | 1 | 2 | 9.5 | −23.3 |
| 10 | **1** | phe | 0.25 | 0.667 | 2 | 9.4 | −30.5 |
| 11 | **2** | asp | 0.25 | 1 | 2 | 9.5 | 6.4 |
| 12 | **2** | val | 0.25 | 1 | 2 | 9.4 | 0.7 |
| 13 | **2** | ala | 0.25 | 1 | 2 | 9.4 | 10.4 |
| 14 | **2** | his | 0.25 | 1 | 2 | 9.4 | −5.2 |
| 15 | **2** | phe | 0.25 | 1 | 2 | 9.4 | – [b] |
| 16 | **3** | asp | 0.25 | 1 | 2 | 9.3 | 8.2 |
| 17 | **3** | val | 0.25 | 1 | 2 | 9.3 | 2.4 |
| 18 | **3** | ala | 0.25 | 1 | 2 | 9.3 | – [b] |
| 19 | **3** | his | 0.25 | 1 | 2 | 9.3 | −3.6 |
| 20 | **3** | phe | 0.25 | 1 | 2 | 9.3 | 2.5 |

[a]

$$\text{e.e.\%} = \frac{A_R - A_S}{A_R + A_S} \times 100$$

For **1** α-oximinophenylacetic acid (this is not natural), negative values refer to S-isomer.

$$\text{e.e.\%} = \frac{A_D - A_L}{A_D + A_L} \times 100$$

For **2** and **3** (these are natural), negative values refer to L-isomer.

[b] Could not be measured (see text).

the 0.02 M solution of Marfey's reagent, in acetone, was added. The tube containing the mixture of the sample with Marfey's solution was closed and it was immersed into a 40 °C water bath for 90 min then the reaction mixture cooled to r.t. and the pH of the solution was adjusted to ~2 by adding 65 μl 2.52 M aqueous HCl solution. This sample was then diluted with 1:19 v/v ratio with the eluent and analysed by HPLC.

The HPLC measurement was calibrated (for this sample) by a standard solution prepared as follows.

In a 50 ml flask L-histidine (0.620 g, 4 mmol) and DL-phenylglycine (0.076 g, 0.5 mmol) was dissolved in 10 ml of water. An 0.20 ml portion of this solution was mixed with 0.25 ml of 0.02 M solution of Marfey's reagent in acetone, allowed to react and worked-up as described above. This solution was diluted with the eluent 1:19 v/v ratio before used as standard for the HPLC measurement.

### *3.2. Reaction of α-oximino-β-phenylpropionic acid with Cr(II)/L-valine (1:2) complex*

Essentially the procedure described above was followed. The pH of the L-valine/Cr(II) (2:1) complex solution was 9.4. The α-oximino-β-phenylpropionic acid (0.045 g, 0.25 mmol) was dissolved in 3 ml water solution of NaOAc (0.381 g, 4.65 mmol). The reduction, the analysis/derivatisation, and the preparation of the L-valine/DL-phenylalanine standard was performed as described above.

### *3.3. Reaction of α-(oximino)phenylacetic acid with Cr(II)/L-alanine (1:2) complex at −10 °C*

Essentially the procedure described above was followed. The reduction was performed in a (deoxygenated) mixture of 4.3 ml water and 5 ml DMF as solvent, the reaction mixture was cooled (−10 °C) by (external) ice/NaCl. α-(Oximino)phenylacetic acid (0.041 g, 0.25 mmol) dissolved in 1 ml DMF cooled to −10 °C, was added in one portion to the solution of this Cr(II)/L-alanine reagent and allowed to react for 48 h at that temperature. Preparation of the derivatized sample for HPLC and of the L-valine/DL-phenylglycine standard was performed as described above.

### *3.4. Reaction of (α-oximino)phenylacetic acid with Cr(II)/L-phenylalanine complex at 90 °C*

The general procedure described above was followed. Water was used as solvent. The colour of the Cr(II)/L-phenylalanine complex was blue. The reaction time was 18 h at 90 °C (oil bath). Preparation of the derivatized sample and of the L-phenylalanine/DL-phenylglycine standard was performed as described above.

## 4. Results and discussion

α-Amino acids were prepared from the corresponding oximes (α-oximinocarboxylic acids) by reduction of the C,N double bond with complexes of Cr(II) ion and natural L-amino acids in aqueous solution. The results of these experiments are summarized in Table 1.

The reduction of the oximes proceeds under mild conditions with conversions >90%. The reactions show also partial enantioselectivity (Fig. 1), resulting in low to medium e.e. values of the products. The most important result of this study is *that the chirality of natural amino acids as ligands could be transmitted to chiral α-amino acids, prepared from achiral precursors*. Natural amino acids were rarely used as ligands in transition metal mediated reactions [5,9,13], but neither products in these studies was an amino acid. To our best knowledge this is the very first example in which a C=N double bond was enantioselectively reduced to C–N single bond by means of an amino acid complex of a transition metal ion. Attempts to optimise the enantiomeric excesses, as well as at finding a catalytic variant [14] are in course in our laboratories.

Beyond the obvious biological significance [6,15] of results of this study, it is an important "practical" feature, that the reduction proceeds in aqueous media (with the exception of the model experiment at −10 °C). The use of water as solvent facilitates to find direct biological connections of the results (that is the reaction proceeds under "bioimitating" [16] conditions). In the perspective of eventual future catalytic practical applications water counts as the most "green" solvent [17], which could be desired.

Only L-amino acids were used as ligands. It is noteworthy that enantiomeric preference varied in a wide range (Table 1), independently of the bidentate (Ala, Val, Phe) or tridentate (His, Asp) character of the ligand. This result indicates that the main governing factor controlling the "nascent" stereochemistry is the *relative* interaction, bulkiness, etc. *of the ligand and the substrate.* This interaction is mainly responsible for the self-organization of the very sensitive transition state/intermediate *conformations* [7c,18] which are governing the stereochemical outcome of the reaction. This can be discussed on the basis of the supposed mechanism.

The mechanism is much more complicated than in the case of the reduction of prochiral ketones [7,13], as is depicted in Scheme 1. In aqueous media oximes first undergo (through N-radical) reductive dehydroxylation (reactions (1)–(3)) [19]. The resulting unstable imine is supposed to give a C-centred radical (4) [7,12,13], which reacts with a second Cr(II) ion resulting in the corresponding (and stereochemically decisive) σ-alkylchromium intermediate (5). We made an attempt to identity this intermediate through UV–vis and CD spectroscopy (Fig. 1).

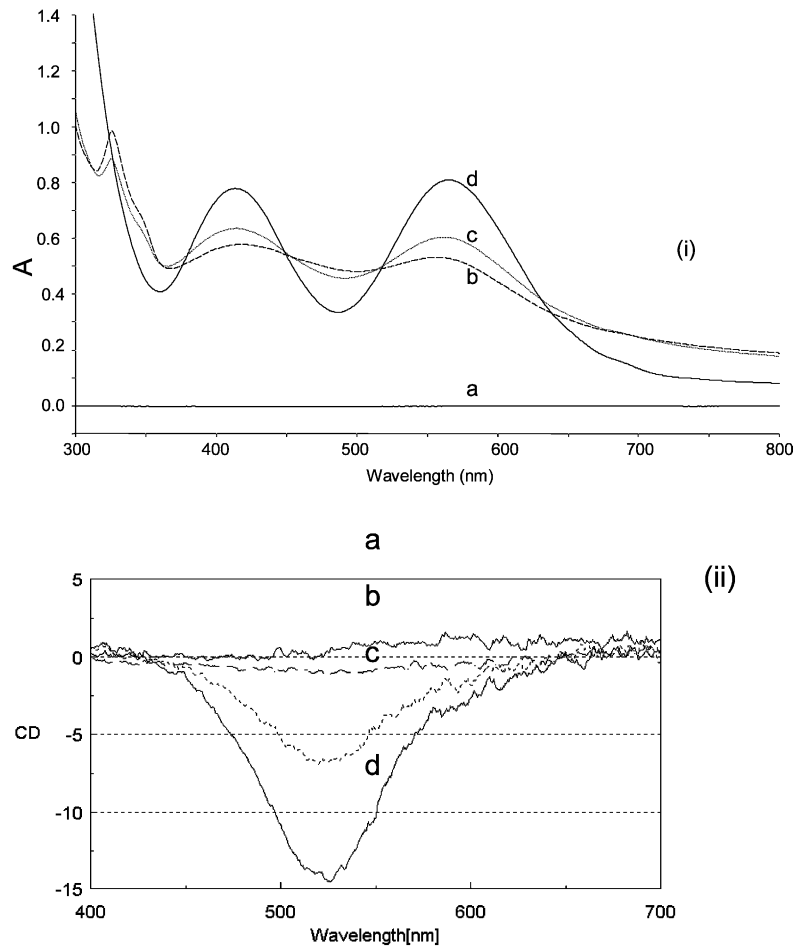
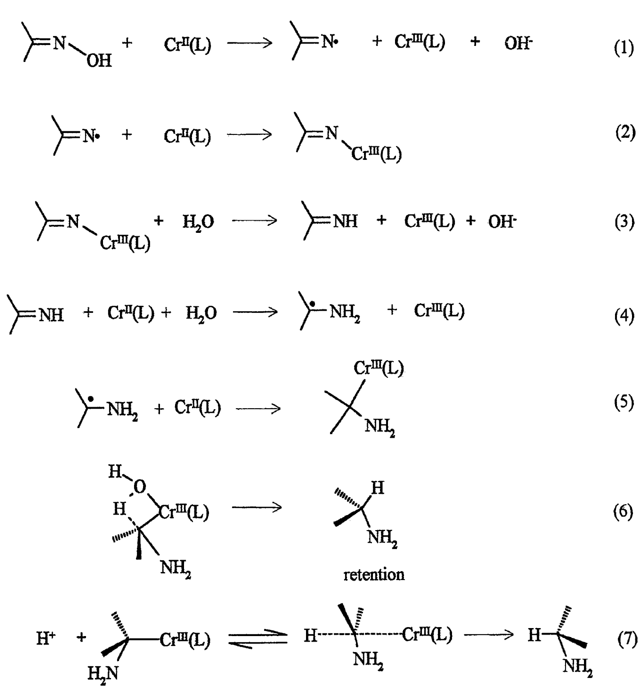



Fig. 1. (i) UV and (ii) CD spectra of (a) L-Ala; (b) Cr(II); (c) Cr(II)+L-Ala, (d) Cr(II)+L-Ala+α-(oximino)phenylacetic acid in water solution.




Scheme 1.

The UV–vis/CD spectra indicate:

a) Inner sphere coordination of the ligand amino acids before the addition of the substrate verified by the appearance of low-energy d–d bands [4,9a,13c].
b) Formation of the *chiral* σ-alkylchromium intermediate upon addition of the substrate oxime [7,12,13].
c) Chiral perturbation of the central metal ion [20] itself in both cases (but differently), as indicated by the presence of the low energy CD bands.

The final step is the protonation of the organometallic bond where either retention or inversion is possible (see Eqs. (6) and (7)), similarly to the ketone reduction discussed earlier [7].

Since the completion of the reaction needs an excess of the reducing agent due to chemical reasons, analysis of those samples where the ligand and the (expected) product amino acids is the *same* became highly unreliable. From the disappearance of the oxime substrate formation of high amount of product amino acids could be suspected but no quantitative statements are possible at the moment. This is an important research goal for

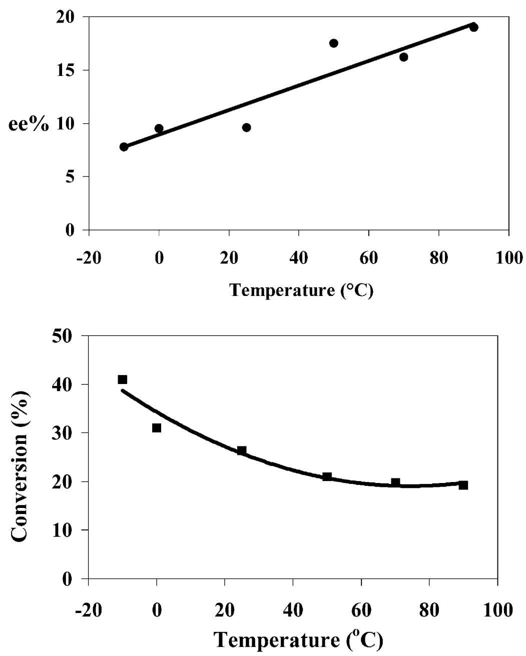



Fig. 2. Temperature dependence of the e.e. and of the conversion of the reduction of α-(oximino)phenylacetic acid with C(II)/L-Ala (1:2) reagent.

the future since in this way even a system with chiral autocatalysis [21] could be eventually hoped, for *amino acid chirality*.

A highly interesting feature of the present system was observed when attempts were made to study the behaviour of the reaction mixture at temperatures lower or higher than r.t. Our experiments clearly show that the *enantiomeric excess increases with increasing temperature* (Fig. 2). This rare behaviour [22] is reflecting to a complicated mechanism of typically non-linear character [23]—an outstanding characteristic of life phenomena [24]. This aspect merits further exploration, as well.

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## References

[1] (a) S. Hanessian, Total Synthesis of Natural Products: The Chiron Approach, Pergamon, Oxford, 1983;
(b) R.E. Gawley, J. Aubé, Principles of Asymmetric Synthesis, Pergamon-Elsevier, Oxford, 1996;
(c) G.R. Stephenson (Ed.), Advanced Asymmetric Synthesis, Blackie Academic & Professional, London, 1996.

[2] (a) S.C. Stinson, Chem. Eng. News, Sept. 21 (1998) 83; Oct. 11 (1999) 101; May 8 (2000) 59; July 10 (2000) 63; Oct. 23 ( 2000) 55; Oct. 1 (2001) 79;
(b) M. Jacoby, Chem. Eng. News, March 25 (2002) 43;
(c) A.M. Rouhi, Chem. Eng. News, June 10 (2002) 43; June 10 (2002) 51.

[3] (a) H. Brunner, W. Zettlmeier, Handbook of Enantioselective Catalysis, vol. I–II, VCH, Weinheim, 1993;
(b) R.A. Sheldon, Chirotechnology, M. Dekker, New York, 1993;
(c) J. Ojima (Ed.), Catalytic Asymmetric Synthesis, Pergamon-Elsevier, Oxford, 1993.

[4] (a) K. Burger (Ed.), Biocoordination Chemistry: Coordination Equilibria in Biologically Active Systems, E. Horwood, New York, 1990;
(b) A. Iakovidis, N. Hadjiliadi, Coord. Chem. Rev. 135/136 (1994) 17.

[5] (a) M. Nakagawa, H. Nakao, K. Watanabe, Chem. Lett. (1985) 391;
(b) G. Wilkinson, R.D. Gillard, J.A. Mc Cleverty (Eds.), Comprehensive Coordination Chemistry, Pergamon, Oxford, 1987, Vol. 2, pp. 739;
(c) K. Harada, T. Munegumi, in: B.M. Trost, I. Fleming (Eds.), Comprehensive Organic Synthesis, vol. 8, Pergamon, London, 1991, pp. 139–158;
(d) D. Carmona, F.J. Lahoz, R. Atencio, L.A. Oro, L.P. Lamata, E.S. José, Tetrahedron: Asymmetry 4 (1993) 1425;
(e) J.-i. Kikuchi, Z.Y. Zhang, Y. Murakami, J. Am. Chem. Soc. 117 (1995) 5383.

[6] (a) G. Wächterchäuser, Proc. Natl. Acad. Sci. USA 87 (1990) 200;
(b) G. Wächterchäuser, Progr. Biophys. Mol. Biol. 58 (1992) 85;
(c) G. Wächterchäuser, Science 289 (2000) 1307;
(d) C. Huber, G. Wächterchäuser, Science 276 (1997) 245;
(e) C. Huber, G. Wächterchäuser, Science 281 (1998) 670;
(f) R.H. Crabtree, Science 276 (1997) 222;
(g) G.D. Cody, N.Z. Boctor, T.R. Filley, R.M. Hazen, J.H. Scott, A. Sharma, H.S. Yoder, Jr., Science 289 (2000) 1337.

[7] (a) J. Gyarmati, C. Hajdu, Z. Dinya, K. Micskei, C. Zucchi, G. Pályi, J. Organomet. Chem. 586 (1999) 106;
(b) T. Patonay, C. Hajdu, J. Jekö, A. Lévai, K. Micskei, C. Zucchi, Tetrahedron Lett. 40 (1999) 1373;
(c) G. Pályi, L. Bencze, K. Micskei, C. Zucchi, Atti Accad. Nazl. Sci. Lett. Arti (Modena) 317 (8/3) (2001) 457.

[8] (a) V. Marchis, Diploma (MSc) Thesis, University of Debrecen, Debrecen, 2001;
(b) A. Ahmad, I.D. Spenser, Can. J. Chem. 39 (1961) 1349.

[9] (a) K. Micskei, F. Debreczeni, I. Nagypál, J. Chem. Soc. Dalton Trans. (1983) 1335;
(b) L. Zékány, J. Nagypál, in: D.G. Leggett (Ed.), Computational Methods for the Determination of Formation Constants, Plenum, New York, 1985, pp. 291–353;
(c) K. Micskei, I. Nagypál, J. Chem. Soc. Dalton Trans. (1986) 2721; see also T. Kiss, in Ref. [4a], pp. 56.

[10] (a) P. Marfey, Carlsberg Res. Commun. 49 (1984) 591;
(b) G. Szókán, S. Hadfi, K. Krizsán, A. Liembeck, M. Almás, C. Somlai, J. Liquid Chromatogr. 17 (1994) 2759.

[11] D.F. Shriver, M.A. Drezdzon, Manipulation of Air Sensitive Compounds, 2nd ed, Wiley, New York, 1986.

[12] J.H. Espenson, Acc. Chem. Res. 25 (1992) 222.

[13] (a) G. Kovács, J. Gyarmati, L. Somsák, K. Micskei, Tetrahedron Lett. 37 (1996) 1293;
(b) G. Kovács, K. Micskei, Tetrahedron Lett. 38 (1997) 9055;
(c) K. Micskei, J. Gyarmati, G. Kovács, S. Makleit, C. Simon, Z. Szabó, J. Marton, S. Hosztafi, H. Reineke, H.J. Drexler, Eur. J. Org. Chem. (1999) 149.
[14] A. Fürstner, Chem. Rev. 99 (1999) 991.
[15] A. Lazcano, S.L. Miller, Cell 85 (1996) 793.
[16] (a) B. Honig, K. Sharp, A.S. Yang, J. Phys. Chem. 97 (1993) 1101;
(b) A. Lubineau, J. Augé, Y. Queneau, Synthesis (1994) 741.
[17] (a) K. Barta, M. Csékei, S. Csihony, H. Mehdi, I.T. Horváth, Z. Pusztai, G. Vlád, Magy. Kém. Lapja 55 (2000) 173;
(b) M. Poliakoff, J.M. Fitzpatrick, T.R. Farren, P.T. Anastas, Science 297 (2002) 807.
[18] (a) G. Pályi, K. Alberts, T. Bartik, R. Boese, G. Fráter, T. Herbrich, A. Herfurth, C. Kriebel, A. Sorkau, C.M. Tschoerner, C. Zucchi, Organometallics 15 (1996) 3253;
(b) M. Szabó, R. Szilágyi, L. Bencze, R. Boese, C. Zucchi, L. Caglioti, G. Pályi, Enantiomer 5 (2000) 549;
(c) C. Zucchi, R. Boese, K. Alberts, T. Herbrich, G. Tóth, L. Bencze, G. Pályi, Eur. J. Inorg. Chem. (2001) 2297.
[19] (a) G.H. Timms, E. Wildsmith, Tetrahedron Lett. (1971) 195;
(b) K. Takai, N. Katsura, Y. Kunisada, Chem. Commun. (2001) 1724.
[20] (a) V. Galamb, G. Pályi, M. Kajtár, Inorg. Chim. Acta 55 (1981) L113;
(b) C. Zucchi, S. Tiddia, R. Boese, C.M. Tschoerner, L. Bencze, G. Pályi, Chirality 13 (2001) 458.
[21] (a) K. Soai, H. Morioka, K. Choji, Nature 378 (1995) 767;
(b) K. Soai, T. Shibata, in: G. Pályi, C. Zucchi, L. Caglioti (Eds.), Advances in BioChirality, Elsevier, Amsterdam, 1999, pp. 125–136;
(c) K. Soai, T. Shibata, I. Sato, Acc. Chem. Res. 33 (2000) 382;
(d) K. Soai, I. Sato, T. Shibata, S. Komiya, M. Hayashi, Y. Matsueda, H. Imamura, T. Hayase, H. Morioka, H. Tabira, J. Yamamoto, Y. Kowata, Tetrahedron Asymmetry 14 (2003) 185;
(e) I. Sato, H. Urabe, S. Ishiguro, T. Shibata, K. Soai, Angew. Chem. Int. Ed. 42 (2003) 315.
[22] (a) R. Ueoka, Y. Matsumoto, T. Nagamatsu, S. Hirohata, Chem. Lett. (1984) 583;
(b) K. Borszéky, T. Mallat, R. Aeschiman, W.B. Schiweizer, A. Baiker, J. Catal. 161 (1996) 451;
(c) T. Nishida, A. Miyafuji, Y.N. Ito, T. Katsuki, Tetrahedron Lett. 41 (2000) 7053.
[23] C. Girard, H.B. Kagan, Angew. Chem. Int. Ed. 37 (1998) 2922.
[24] G. von Kiedrowski, in: G. Pályi, C. Zucchi, L. Caglioti (Eds.), Fundamentals of Life, Elsevier, Paris, 2002, p. 38.