

Asymmetric Synthesis by Chromium(II) Amino Acid Complexes

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Chiral molecules play an essential role in the chemistry of biological processes. In the biosynthesis of natural products amino acids are used as chiral inductors as they build up enzymes, the catalysts of these processes.

Here we describe a system consisting of chromium(II) as reducing agent and amino acid ligands as chiral inductors which proved to be an effective reagent in enantiomeric reduction of prochiral functional groups in aqueous medium.

In our earlier work we found that acetophenone was reduced by chromium(II) amino acid complexes with excellent chemoselectivity (>95%) and enantioselectivities up to 75% e.e. In order to study the effect of the structure of various prochiral substrates, aryl alkyl ketones and benzo(hetera)cyclanones were treated with chromium(II) amino acid complexes in a DMF-water solvent mixture at room temperature. We found that that both yields and enantioselectivities strongly depend on the substrates and ligands. L-alanine, L-histidine and L-aspartic acid gave high conversions while L-valine and L-leucine reacted more sluggishly. The highest enantioselectivities were achieved using L-histidine (up to 55% e.e.). Data show a difference in the action of bi- and tridentate ligands: L-alanine and L-valine generated *R* alcohols while L-histidine and L-aspartic acid lead mostly to *S* products. The structure of the substrates also affects the obtained optical purity.

Enantioselective synthesis of ferrocenyl alcohols is questionable in many cases. Formerly it was found that by reduction of ferrocenyl ketones with chromium(II) complexes stable ferrocenylketyl radicals were obtained instead of the alcohols. By modification of the conditions, we could bring the reaction towards the formation of the alcohol. Thus, using amino acid complexes, it was possible to reduce monobenzoyl ferrocene with 2-25% e.e. The low stereochemical outcome can be explained by the formation of the stable radical that allows racemization processes.

Selective transformation of α -diketones plays an important role in synthesis of natural products. We reduced benzil with chromium(II) amino acid complexes in order to obtain the corresponding products selectively. In these reactions the enantioselectivities remained under 30%.

Some recent works support that the studied ketone reductions occur via organochromium(III) complex intermediates. We monitored the reaction of several ketones with chromium(II) amino acid complexes using UV-VIS spectrophotometry, detecting the absorption band in the 250-290 nm region, characteristic for C–Cr bonds. We found that the intermediates form with all studied substrates and complexes and proposed a mechanism for enantioselective ketone reduction.

The reduction of oximes has a more complicated mechanism. In reduction of acetophenone oxime with chromium(II) complexes, our first experiments lead to unwanted side products like acetophenone, 1-phenyl-ethanol and several coupling products. After optimization of the reaction it was possible to obtain the 1-phenyl-ethyl-amine with >95% chemoselectivity. The application of several amino acids as ligands the amine formed with enantiomeric excesses up to 50%.

Considering the essential role of amino acids in life phenomena, the asymmetric synthesis of amino acids using also amino acids as chiral inductors, might have special importance. We performed reduction of the C=N double bond of oxime precursors of α -amino acids in aqueous medium by chromium(II) complexes of amino acids, using the reaction conditions developed formerly for the aromatic oximes. 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. Our UV-VIS spectrophotometric measurements demonstrated the presence of the organochromium(III) intermediate. This means that the reaction undergoes mostly through the basic steps unveiled formerly for the ketones.

We performed the diastereoselective pinacol coupling of several aromatic aldehydes. The most effective ligand was L-histidine that gave much better chemo- and enantioselectivity (e.e. = 67%) than other amino acids. We investigated the behavior of other aromatic aldehydes with chromium(II) L-histidine complex. In most cases we obtained conversions above 90% and enantiomeric excesses between 30-62%. We suppose that in an enantioselective coupling reaction the formation of the carbon-carbon bond occurs inside the common (chiral) coordination sphere of two associated organometallic intermediates.

List of Publications

Articles in English

1. J. Gyarmati, C. Hajdu, Z. Dinya, K. Micskei, C. Zucchi, G. Pályi:
Asymmetric Induction by Amino Acid Ligands in Chromium(II)-Assisted Reduction of Ketones
J. Organomet. Chem., **1999**, 586, 106-109.
2. T. Patonay, C. Hajdu, J. Jekő, A. Lévai, K. Micskei, C. Zucchi:
Enantioselective Reduction of Prochiral Ketones by Chromium(II) Complexes with Amino Acid Ligands as the Source of Chirality
Tetrahedron Letters, **1999**, 40, 1373-1374.
3. K. Micskei, A. Kiss-Szikszai, J. Gyarmati, C. Hajdu:
Carbon-Carbon Bond Formation in Neutral Aqueous Medium: Modification of the Nozaki-Hiyama Reaction
Tetrahedron Letters, **2001**, 42, 7711-7713.
4. K. Micskei, O. Holczknecht, C. Hajdu, T. Patonay, V. Marchis, M. Meo, C. Zucchi, G. Pályi, :
Asymmetric Synthesis of Amino Acids by Cr(II) Complexes of Natural Amino Acids
J. Organomet. Chem., **2003**, 682, 143-148.
5. K. Micskei, C. Hajdu, L. A. Wessjohann, L. Mercs, A. Kiss-Szikszai, T. Patonay:
Enantioselective reduction of prochiral ketones by chromium(II) amino acid complexes
Tetrahedron Asymmetry, **2004**, 15, 1735-1744.
6. K. Micskei, A. Mona, C. Hajdu, L. A. Wessjohann, A. Kiss-Szikszai, T. Patonay:
Enantioselective pinacol coupling with chromium(II) amino acid complexes
2004, in preparation.

Reviews in English

1. G. Pályi, C. Zucchi, C. Hajdu:
Theories on the origin(s) of life
Acc. Naz. Sci. Lett. Arti (Modena), **2000**, 316, [8/2], 457-478.
2. C. Hajdu, L. Keszthelyi:
Origin of Biomolecules – Origin of Homochirality
in: G. Pályi, C. Zucchi, L. Caglioti (Eds.), *Advances in BioChirality*, Elsevier, Amsterdam, **2004**, in press.
3. K. Micskei, C. Hajdu, T. Patonay, L. Caglioti, C. Zucchi, G. Pályi:
Evolution of the Chiral Information of Natural Amino Acids in Biomimetic Organic Synthesis
in: G. Pályi, C. Zucchi, L. Caglioti (Eds.), *Advances in BioChirality*, Elsevier, Amsterdam, **2004**, in press.

Presentations at scientific meetings in English

1. J. Gyarmati, C. Zucchi, G. Kovács, C. Hajdu, G. Pályi, K. Micskei: Asymmetric Synthesis with Cr(II)Amino Acid Complexes: New Chiral Organometallic Complex Intermediates. XXIIth FEChem Conference on Organometallic Chemistry, Prague, Czech Republic, 1997 (poster).
2. T. Patonay, J. Gyarmati, C. Hajdu, J. Jekő, A. Lévai, K. Micskei: Enantioselective Reductions of Ketones to Alcohols by Chromium(II)-amino acid Complexes. 7th Belgian Organic Synthesis Symposium, Louvain-la Neuve, Belgium, 1998.
3. K. Micskei, C. Hajdu, J. Gyarmati, T. Patonay, A. Lévai, C. Zucchi, Pályi, G.: Transformation of the Chiral Information in a Biomimetic Medium with Chromium(II) Amino Acid Complexes. International Conference on Coordination Chemistry, Florence, Italy, 1998.
4. C. Hajdu, J. Gyarmati, S. Makleit, C. Simon, Z. Szabó, K. Micskei: Diastereoselective Transformation of Natural Product Derivatives in a Biomimetic Medium. Interdisciplinary Symp. on Biological Homochirality, Serramazzoni, Italy, 1998 (poster PS4, p. 36.).
5. T. Patonay, C. Hajdu, J. Jekő, A. Lévai, K. Micskei: Chemo- and Stereoselective Reduction of Carbon-Heteroatom Double Bonds by Chromium(II) Complexes under Biomimetic Conditions. 11th European Symposium on Organic Chemistry, Göteborg, Sweden, 1999.
6. C. Hajdu, K. Micskei, T. Patonay, G. Pályi: Asymmetric Induction by Chromium(II) Amino Acid Complexes in a Biomimetic Medium. Symposium on Biological Chirality, Szeged, 2000 (poster P8).
7. K. Micskei, C. Hajdu, J. Jekő, T. Patonay, A. Lévai: Enantioselective Reduction of Prochiral Ketones and Oximes by Chromium(II) Complexes with Amino Acid Ligands as the Source of Chirality. "Stereoselective Transformations of Heterocyclic Compounds" (COST D12 Symposium), Debrecen, 2002.
8. G. Pályi, O. Holzknecht, C. Hajdu, M. Meo, C. Zucchi K. Micskei: Asymmetric synthesis of amino acids by Cr(II) complexes of natural amino acids. 10th International Conference on the Origin of Life (ISSOL-02) Oaxaca, Mexico, 2002.
9. C. Zucchi, O. Holzknecht, C. Hajdu, M. Meo, K. Micskei G. Pályi: Natural amino acids as ligands in the enantioselective reductions of oximes by Cr(II). 3rd Italian-French Meeting on Organic Chemistry, Organic Chemistry Toward Interface, Pisa, Italy, 2002.
10. C. Hajdu, K. Micskei, O. Holczknecht, A. Mona, T. Patonay, C. Zucchi: Preparation and application of chiral complex reagents in aqueous medium, 3rd Interdisciplinary Symposium on Biological Chirality, Modena, Italy, 2003.
11. C. Hajdu, K. Micskei: Theories of chiral evolution. 3rd Interdisciplinary Symposium on Biological Chirality, Modena, Italy, 2003 (poster, p. 56.).

12. K. Micskei, C. Hajdu, O. Holczknecht, A. Mona, T. Patonay, C. Zucchi: Evolution of the chiral information of natural amino acids in organic synthesis. 3rd Interdisciplinary Symposium on Biological Chirality, Modena, Italy, 2003.

Presentations at Hungarian scientific meetings

1. Gyarmati J.; Hajdu Cs.; Pályi Gy.; Micskei K.: Aszimmetrikus szintézis a biológiai aktivitás körülményei között koordinációs kémiai szabályozással. MKE XXXII. Komplexkémiai Kollokvium, Kecskemét, 1997.
2. Hajdu, Cs.; Gyarmati, J.; Micskei, K.; Patonay, T.; Lévai, A.; Zucchi, A.; Pályi, Gy.: Aminosavak által indukált aszimmetrikus információ továbbítása fémorganikus kötésen keresztül koordinációs kémiai szabályozással. MKE XXXIII. Komplexkémiai Kollokvium, Paks, 1998.
3. Hajdu Cs., Marchis V., Micskei K., Patonay T., Pályi Gy.: A természetes aminosavak királis információjának továbbítása: királis aminosavak előállítása átmenetifém-aminosav komplexekkel. MKE XXXIV. Komplexkémiai Kollokvium, Tata, 1999.
4. Hajdu Cs., Marchis V., Patonay T., Pályi Gy., Micskei K.: A biológiai homokiraliás kialakulásának kémiai modellezése. MKE XXXV. Komplexkémiai Kollokvium, Kecskemét, 2000.
5. Kövér A., Kiss-Szikszai A., Hajdu Cs., Micskei K.: Természetes aminosavak mint kiralitásforrások alkalmazása: szén-szén kötés enantioszelektív kialakítása. MKE XXXV. Komplexkémiai Kollokvium, Pécs, 2001.
6. Hajdu Cs., Z. Ratkovic, Nagy I., Micskei K.: Ferrocenilketil-gyökök előállítása és jellemzése. MKE XXXVII. Komplexkémiai Kollokvium, Mátraháza, 2002.

Other scientific publications

1. H. S. Schrekker, K. Micskei, C. Hajdu, T. Patonay, M. W. G. de Bolster, L. A. Wessjohann:
Involvement of an Oxidation-Reduction Equilibrium in Chromium- Mediated Enantioselective Nozaki-Hiyama Reactions
Adv. Synth. Catal., **2004**, in press.
2. L. Caglioti, C. Hajdu, L. Zékány, C. Zucchi, K. Micskei, G. Pályi:
A Consequence of the Soai-Reaction: Re-evaluation of Racemates
Chirality, **2004**, submitted.