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Asymmetric Synthesis by Chromium(II) Amino Acid Complexes

Summary

Chiral molecules play an essential role in the chemistry of biological processes and because of this reason all biochemical reactions are highly enantioselective. 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. The most remarkable conclusion of these results was that the obtained chiral induction is highly variable with the structure of the ligands.

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. Our experiments revealed 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.), while L-leucine gave significantly worse (maximum 18% 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. This finding allows the use of natural amino acids for production of both R and S alcohols. The structure of the substrates also affects the obtained optical purity. We observed that aryl alkyl ketones usually gave higher enantioselectivities than the conformationally more rigid benzo(hetera)cyclanones.
Chiral ferrocene derivatives as ligands play crucial role in homogeneous catalysis. Ferrocenyl ketones and alcohols are key intermediates for various transformations of racemates of ferrocene derivatives with configurational chirality. Enantioselective synthesis of ferrocenyl alcohols under mild conditions is questionable in many cases. Formerly it was found in our group that by reduction of ferrocenyl ketones with chromium(II) complexes stable ferrocenylketyl radicals were obtained instead of the expected alcohols. By modification of the conditions, using an excess of the reagent 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. Numerous terpenes, pheromones and steroids contain chiral α-hydroxy-ketone and vicinal diol groups. We reduced benzil with chromium(II) amino acid complexes in order to obtain the corresponding products selectively. In these reactions low conversion of the starting material was observed, unless an excess of the reducing agent was used. The enantioselectivities remained under 30%. Considering the presence of the chromium(III) as Lewis acid, it was likely that a tautomerization equilibrium leads to racemization of the product. Our control experiments, however, didn’t support this assumption.

Some recent works support that the studied reactions occur via organochromium(III) complex intermediates. Using them as reagents in chemical synthesis requires more details about the kinetics of their formation and lifetime in aqueous medium. The formation of the intermediates was demonstrated by UV-VIS spectrophotometry. We monitored the reaction of several ketones with chromium(II) amino acid complexes 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. The formation is fairly rapid (we could not detect an initial ascending section of the curves using classical UV-VIS technique) and the rate of decomposition is determined by the structure of the amino acid ligand. The complex of the valine showed the fastest decomposition and the reaction was much slower using aspartic acid and histidine. We found that organochromium(III) compounds can be prepared in aqueous medium with considerable stability and the lifetime of the intermediates depends on the ligand and the substrate.
We propose the following mechanism for reduction of ketones with chromium(II) amino acid complexes. The first step is a single electron transfer process when a radical anion (ketyl) is formed and it is rapidly protonated by water:

\[ \text{O} + \text{Cr}^{II}(L^*) \rightarrow \text{O}^- + \text{Cr}^{III}(L^*) \]

\[ \text{O}^- + \text{H}^+ \rightarrow \text{OH} \]

In the following step the radical reacts with the chromium(II) complex and forms the organochromium(III) intermediate:

\[ \text{OH} + \text{Cr}^{II}(L^*) \rightleftharpoons \text{Cr}^{III}(L^*) \text{OH} \]

When the carbon-metal bond is formed the chiral complex approaches the planar radical at one of its enantiotopic surfaces. The configuration of the intermediate is determined when the organometallic bond is formed. The carbon atom in the C–Cr bond reacts readily with electrophilic agents. However, the bond is hydrolyzed slowly by the oxonium ion and because of this reason the intermediates have a long lifetime in aqueous medium. The last step of the reduction of ketones is the heterolysis of the C–Cr bond when the final product, an alcohol is formed.

\[ \text{OH} + \text{Cr}^{III}(L^*) \rightleftharpoons \text{Cr}^{III}(L^*) \text{OH} \]

\[ \text{H}^+ + \text{Cr}^{III}(L^*) \rightarrow \text{H} \cdots \text{Cr}^{III}(L^*) \rightarrow \text{HO} + \text{Cr}^{III}(L^*) \]

The intermediate can be hydrolyzed either by bulk water (see above) or by one in the coordination sphere of the chromium(III) as shown below. Thus, these two mechanisms of the hydrolysis may result in retention or inversion of the asymmetric center.
The reduction of oximes proved to be more difficult than the one of the ketones because it requires four electrons, that is, a more complicated mechanism. In reduction of acetophenone oxime with chromium(II) complexes, our first experiments lead to unwanted side products like acetophenone (formed from hydrolysis of the oxime), 1-phenyl-ethanol and several coupling products. After optimization of the reaction (using excess of the reagent and adding the substrate dropwise to the complex) 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%. Comparing these results with those obtained in case of the ketones we found that the chiral induction is basically affected by the reduced functional group, too.

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, 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. As reducing agents CrL_2 type complexes of L-alanine, L-valine L-aspartic acid, L-histidine and L-phenylalanine were used. The mechanism of the reaction is probably much more complicated than in the case of the prochiral ketones. Our UV-VIS spectrophotometric measurements demonstrated the presence of the organochromium(III) intermediate in the reduction of the amino acid oximes as well. This means that the reaction undergoes mostly through the basic steps unveiled formerly for the ketones. The reduction of α-ketophenylacetic acid showed increasing enantioselectivity and decreasing conversion with increasing temperature. This rare behavior is reflecting to a complicated mechanism of typically non-linear character — an outstanding characteristic of life phenomena.
Our research group already developed an effective method for carbon-carbon bond formation with chromium(II) complexes in aqueous medium. In this work we performed the diastereoselective pinacol coupling of several aromatic aldehydes. Our results showed that in carbon-carbon bond formation reaction starting from benzaldehyde the conversion and the asymmetric induction strongly depends on the amino acid ligand. The most effective one 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%. Starting from literature data and our preparative results 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.

In this work we demonstrated that the chiral information of natural amino acids can be transferred to prochiral molecules using their chromium(II) complexes. Choosing the appropriate amino acid and preparing different complexes we achieved the enantioselective reduction of various functional groups and formation of C-C bonds. With this method amino acids can be used also in the design and synthesis of drugs and biomaterials. Due to the nature of the reagent and the applied conditions this reaction system can be a model of biochemical processes that transfer and multiply chiral information.