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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 1735–1744

Enantioselective reduction of prochiral ketones by chromium(II) amino acid complexes

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Received 18 March 2004; accepted 15 April 2004

Dedicated to Prof. Károly Lempert on the occasion of his 80th birthday

Abstract—The reduction of prochiral ketones has been performed by Cr(II) L-amino acid complexes in aqueous DMF solution under mild conditions in good yields and moderate (up to 58%) ee values. The dependence of the yield and enantioselectivity on various factors such as the structure of the ligand, pH and the solvent has also been investigated. A mechanism based on SET from the Cr(II) ion followed by protonation by water and the formation of an organochromium intermediate is also proposed.

1. Introduction

The asymmetric reduction of prochiral ketones to enantiomerically pure (or enriched) secondary alcohols represents a continuing challenge due to the importance of the products as valuable chiral building blocks. Various approaches to the chiral, nonracemic secondary alcohols have been developed over the last few decades with many excellent reviews[1,2] now available. Some prominent procedures for the reduction of the carbonyl group are (i) hydrogenation using a heterogeneous metal catalyst with a chiral modifier on its surface;[1a] (ii) homogeneous asymmetric hydrogenation using Rh, Ru or Ir complexes containing bisphosphine and more rarely mixed P,N and N,N ligands;[1b–d,3] (iii) asymmetric transfer hydrogenation, which utilizes the same metals with a wide variety of bidentate N,N, N,O or N,S or tridentate N,N,N ligands[1d–f,4] and (iv) asymmetric hydrosilylation using Rh, Pt or Ti complexes as catalysts and silanes as the hydrogen source.[1d] The most popular and productive procedures use either borane or its derivatives as the reducing agent in the presence of chiral ligands or catalysts.[1a,d,c,g–k,5] Chiral boranes themselves can be useful in the reduction of prochiral ketones, some of which are commercially available.[1k,6] Enantioselective reduction has also been achieved by sodium borohydride in the presence of cyclodextrin or chiral dendrimers even in aqueous solution.[1f,7]

Chiral, nonracemic secondary alcohols are available by other chemical protocols, too. Symmetric hydroboration/oxidation of alkenes in the presence of Rh complexes with P,P or N,P ligands using catecholborane or oxazaborolidines[1g,l,m] via asymmetric alkylation or allylation of aldehydes by the corresponding organozinc reagents in the presence of O,O, N,O or N,N ligands or even paracyclophanes and dendritic catalyst[1d,g,n,5d] are methods of overriding importance.

In addition to the chemical methods, enzyme or whole cell catalyzed protocols such as asymmetric enzymatic reduction of ketones, kinetic resolution of chiral alcohols by lipases as well as dynamic resolution and biocatalytic stereoinversion offers another attractive

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doi:10.1016/j.tetasy.2004.04.017

approach.[1o–q,8] It should be noted that an efficient (up to 99% ee) but nonenzymatic kinetic resolution has also been reported.[9]

Although many of the methods mentioned above show excellent enantioselectivity, there are drawbacks such as strong substrate specificity; high pressure and/or temperature requirements; the laborious and costly synthesis of the catalysts or chiral reagents; their sensitivity towards moisture and air and the occasional toxicity meaning there is a continuous search for new methods.

There is also the need for an inexpensive but easy commercially available source of chiral information. Amino acids represent the ideal candidates but are typically used in the form of their derivatives.[10] However, the use of unprotected amino acids as a source of chirality in asymmetric synthesis is rare. Copper(II) complexes of L-amino acids have been used as catalysts for Diels–Alder reactions in aqueous media to give ee's up to 36% using the natural compounds and up to 74% with their *N*-methylated derivatives.[11]

Amino acid modified Raney nickel and palladium catalysts were also applied in heterogeneous hydrogenation but the selectivity was only marginal (<10% ee).[1a] Ruthenium(II) proline amide-based catalysts gave ee's up to 98% in the reduction of some acetophenone derivatives in $HCOOH/Et_3N$.[12] The probable reason for the scarcity is their poor solubility in most of the common organic solvents and, in turn, the aqueous solutions are normally incompatible with most of the above-listed reducing agents. In aqueous medium amino acid modified Ru catalysts resulted in ee's of up to 86% in some ketone hydrogenation reaction.[13] At the same time, synthetic chemistry nowadays tends to replace organic solvents with the cheaper, safer and environmentally acceptable water.[14]

Keeping these facts in mind, a novel asymmetric reduction of prochiral ketones and related systems based on the use of amino acids should work in a different way to already existing methods. A plausible possibility is the use of SET processes, that is, electrons provided by a low-valent transition metal ion followed by protonation by water.

Chromium(II) compounds are widely used in organic synthesis for selective transformations of various functional groups including enantioselective C–C bond formation.[15,16] These reactions are usually performed in strictly aprotic media; although chromium(II) is the strongest metal ion soluble in water but reacts with it rather slowly. It is important to note that its redox potential, which is insufficient for the reduction of the carbonyl functionality, can be increased considerably by using donor solvents and/or polydentate nitrogen ligands.[15a] In conclusion, the ligation of chromium(II) ions with L-amino acids in a water/DMF mixture may provide a new system for the asymmetric reduction of prochiral ketones.

Based on our experience in the field of complex equilibria of transition metal ions and especially of chromium(II),[17] we have recently published several applications of chromium(II) aminocarboxylate complexes as reagents in aqueous media for various fields of synthetic organic chemistry.[18]

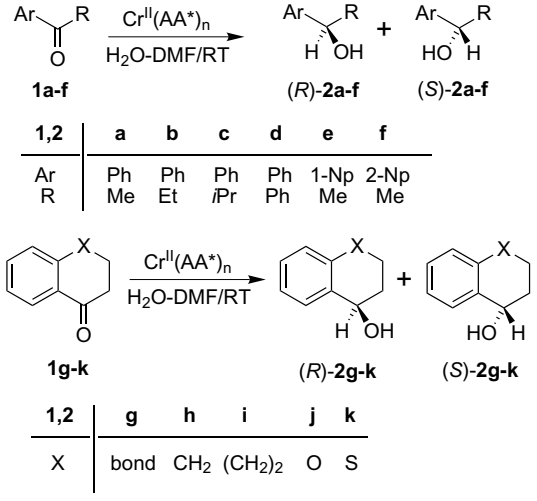
We have also reported the use of unprotected L-amino acids as ligands in the reduction of acetophenone where the chiral information was successfully transferred from the ligand sphere of the complex to the substrate resulting in 1-phenyl ethanol being formed with >95% chemoselectivity and up to 75% ee.[19]

Preliminary accounts on the successful use of our designed reducing system have already been published.[19,20] As part of this programme we extended our investigation of various prochiral ketones and describe herein our results on their enantioselective reduction by chromium(II) amino acid complexes in aqueous media.

2. Results and discussion

A wide range of prochiral aryl alkyl ketones, including the cyclic and heterocyclic ones shown in Scheme 1, has been chosen as substrate to obtain a deeper insight into the reduction. Most of them have already been used by other groups, which allows us to compare the controlling factors.

As illustrated by Tables 1–5, a wide range of ketones **1a–k** can be reduced enantioselectively by chromium(II)-natural amino acid complexes in aqueous *N*,*N*-dimethylformamide (DMF) within a 6.5–9.7 pH range at room temperature. With some exceptions, nearly complete conversions were observed giving the desired products **2a–k** in moderate-to-good yields. (Yield data given in Tables refer to pure isolated materials and normalized to



Scheme 1. Enantioselective reduction of ketones by chromium(II) amino acid complexes (AA* = amino acid, Np = naphthyl).

Table 1. Enantioselective reduction of prochiral ketones by chromium(II) L-alanine complexes

Entry	Ketone	pH	Conversion (%)	Yield (%)	Configuration	Ee (%)
1	**1b**	9.4	>95	65	*R*	8
2	**1d**	9.4	>95	81	*R*	8
3	**1e**	9.4	79	39	*R*	10
4	**1i**	9.4	>95	72	*R*	16
5	**1k**	9.4	>95	74	*R*	17
6	**1c**	9.4	>95	84	*R*	20
7	**1f**	9.4	>95	82	*R*	21
8	**1j**	9.4	>95	66	*R*	22
9	**1g**	9.4	>95	78	*R*	35
10	**1h**	9.4	>95	65	*R*	36
11	**1a**[a]	9.4	95	—	*R*	38

[a] See Ref. 19.

Table 2. Enantioselective reduction of prochiral ketones by chromium(II) L-valine complexes

Entry	Ketone	pH	Conversion (%)	Yield (%)	Configuration	Ee (%)
1	**1d**	9.5	>95	88	*R*	5
2	**1b**	9.5	>95	64	*R*	7
3	**1c**	9.5	90	50	*R*	9
4	**1k**	9.5	95	62	*R*	12
5	**1i**	9.5	>95	76	*R*	15
6	**1e**	9.5	>95	75	*R*	28
7	**1h**	9.5	>95	69	*R*	34
8	**1g**	9.5	>95	66	*R*	37
9	**1f**	9.5	76	62	*R*	39
10	**1j**	9.5	>95	55	*R*	40
11	**1a**[a]	9.5	67	—	*R*	75

[a] See Ref. 19.

Table 3. Enantioselective reduction of prochiral ketones by chromium(II) L-leucine and L-*tert*-leucine complexes

Entry	Ketone	pH	Conversion (%)	Yield (%)	Configuration	Ee (%)
1	**1k**	9.3	>95	40	*R*	1
2	**1b**	9.3	65	35	*S*	3
3	**1e**	9.3	86	47	*S*	5
4	**1j**	9.3	81	22	*S*	5
5	**1h**	9.3	59	40	*R*	11
6	**1i**	9.3	89	30	*S*	13
7	**1f**	9.3	>95	45	*R*	14
8	**1g**	9.3	56	8	*R*	14
9	**1e**[b]	9.3	84	—	*R*	14
10	**1a**[a]	9.3	55	—	*R*	17
11	**1d**	9.7	85	34	*S*	18
12	**1a**[b]	9.3	94	—	*R*	58

[a] See Ref. 19.
[b] Using L-*tert*-leucine as ligand.

100% conversion.) The enantiomeric excesses (ee's) depended on the ligand applied, the structures of the ketone **1**, the actual pH and the solvent used. For comparison, some previously reported[19] ee values have also been incorporated in the Tables.

Chromium(II) complexes of L-alanine (Ala), L-valine (Val), L-aspartic acid (Asp) and L-histidine (His) reduced the ketones with high conversion (>95%) in most cases (see Tables 1, 2, 4 and 5) while the L-leucine (Leu) resulted in lower values (Table 3). High chemical yields could be achieved especially with Ala and Asp ligands but Leu produced poorer values, again.

The highest ee values were obtained when His (Table 5) was used as the ligand (7–55%) while Ala (Table 1) and Val (Table 2) resulted in lower induction (5–38% and 5–40%, respectively). Leu (Table 3), which exerted only moderate activating effect and, hence, poorer conversions and chemical yields, also proved to be the least effective inductor (1–18% ee). Asp and L-glutamic acid (Glu) ligands resulted in similar chiral induction in accordance with their similar coordination behaviour (see Table 4, entries 6, 7 and 13, 15).

The different coordinative behaviour of the individual natural amino acids, as well as the different structure of

Table 4. Enantioselective reduction of prochiral ketones by chromium(II) L-aspartic and L-glutamic acid complexes

Entry	Ketone	pH	Conversion (%)	Yield (%)	Configuration	Ee (%)
1	**1i**	7.0	>95	46	*S*	5
2	**1b**	7.0	>95	69	*S*	7
3	**1a**[a]	7.0	64	—	*S*	12
4	**1f**	7.0	>95	72	*S*	13
5	**1g**	7.0	>95	63	*S*	14
6	**1b**	9.5	>95	82	*S*	14
7	**1b**[b]	9.5	>95	76	*S*	16
8	**1e**	7.0	79	47	*R*	16
9	**1d**	7.0	>95	89	*S*	17
10	**1k**	7.0	>95	67	*R*	17
11	**1h**	7.0	>95	65	*R*	17
12	**1j**	7.0	>95	65	*R*	26
13	**1a**	9.5	>95	—	*S*	34
14	**1k**	9.4	>95	90	*R*	35
15	**1a**[b]	9.5	>95	—	*S*	39
16	**1j**	9.4	>95	35	*R*	48

[a] See Ref. 19.
[b] Using L-glutamic acid as ligand.

Table 5. Enantioselective reduction of prochiral ketones by chromium(II) L-histidine complexes

Entry	Ketone	pH	Conversion (%)	Yield (%)	Configuration	Ee (%)
1	**1j**	9.5	90	46	*S*	3
2	**1k**	9.5	54	75	*S*	4
3	**1g**	6.6	>95	22	*S*	7
4	**1h**	6.6	>95	58	*S*	7
5	**1k**	6.6	>95	25	*S*	8
6	**1f**	6.6	>95	61	*S*	25
7	**1i**	6.6	94	56	*S*	25
8	**1e**	6.6	88	33	*S*	34
9	**1b**	6.6	>95	34	*S*	36
10	**1d**	6.6	>95	46	*S*	37
11	**1a**[a]	6.5	71	—	*S*	43
12	**1c**	6.6	>95	44	*S*	55

[a] See Ref. 19.

chromium(II) complexes formed in neutral (pH ~ 7) and mild alkaline (pH ~ 9.5) media resulted in reducing agents with diverse selectivity. The chromium(II) ion formed mono-complexes [Cr^{II}(AA*)] at pH ~ 7 and bis-complexes [Cr^{II}(AA*)$_2$] at pH ≈ 9.5.[21] At these two pH values Ala, Val and Leu coordinated as bidentates while the Asp, Glu and His act as tridentate ligands. The 1:2 complex Cr^{II}(Asp)$_2$ in each case gave higher ee values (compare entries 2 and 7, 3 and 13, 10 and 14, 12 and 16 in Table 4, entries 7 and 12 in Table 6) than the 1:1 complex formed at neutral pH. A similar effect was also found in the case of His with **1k**, although the change was less pronounced due to the low induction (see Table 5, entries 2 and 5).

The higher discriminative power of the 1:2 complexes [Cr^{II}(AA*)$_2$] was also observed in the case of the reduction of 4-chromanone **1i** with Cr(II)–L-Val reagent. By lowering the pH values, a slow decrease in the conversion and enantiomeric purity was observed first

Table 6. Enantioselective reduction of 4-chromanone **1j** by chromium(II) amino acid complexes

Entry	Amino acid	pH	Conversion (%)	Yield (%)	Configuration	Ee (%)
1	His	9.5	90	46	*S*	3
2	Leu	9.3	81	22	*S*	5
3	Lys	9.5	51	19	*R*	8
4	Phe	9.6	83	59	*R*	13
5	Trp	9.5	83	48	*R*	15
6	Ala	9.4	>95	66	*R*	22
7	Asp	7.0	>95	65	*R*	26
8	Glu	9.5	83	65	*R*	33
9	Pro	9.6	72	51	*R*	35
10	*t*-Leu	9.5	87	81	*R*	37
11	Val	9.5	>95	55	*R*	40
12	Asp	9.4	>95	35	*R*	48

(46% conversion, 30% ee at pH = 9.0, 39% conversion, 28% ee at pH = 7.9) followed by a sharp breakdown with apparently no reaction at pH = 6.9 and 6.0. Obviously, the 1:1 complex of bidentate ligands, which is the dominating form at pH ~ 7, has insufficient redox potential to reduce the ketone.

By comparing the data for bidentate ligands Ala, Val, and Leu, characteristic trends could be observed. In most cases Val induced higher ee's than Ala (see Tables 1 and 2 and Fig. 1), that is, the increasing bulkiness of the alkyl substituents on the ligand increased the chiral induction. The position of the branching in the alkyl group was crucial as when Leu had β branching, it resulted in lower ee values (Table 3). In accordance with this, the use of nonnatural L-*tert*-leucine (*t*-Leu) as the ligand gave higher ee's than those obtained with Leu (see entries 3, 9 and 10, 12 in Table 3 and also compare entry 4 in Table 3, with entry 10 in Table 6). Ee's obtained in the presence of *t*-Leu were in all cases superior to the values obtained with Ala (compare entries 9 and 12 in Table 3, entry 10 in Table 6 with entries 3, 8 and 11 in Table 1) but fell behind the data observed in the case of Val (compare entries 9 and 12 in Table 3 and entry 10 inTable 6 with entries 3, 8 and 11 in Table 2). Consequently, the first methyl group at the α-position proved advantageous in the discrimination of the diastereomeric transition states (TS's) leading to the two enantiomers, however the incorporation of a second methyl group had no beneficial effect.

The structure of the amino acid ligands influenced not only the enantioselectivity but also the absolute configuration of the product as well. As it is shown in Figure 1, Ala and Val ligands induced the (*R*)-configuration while His resulted exclusively in the (*S*)-configuration (Tables 1, 2, 5).

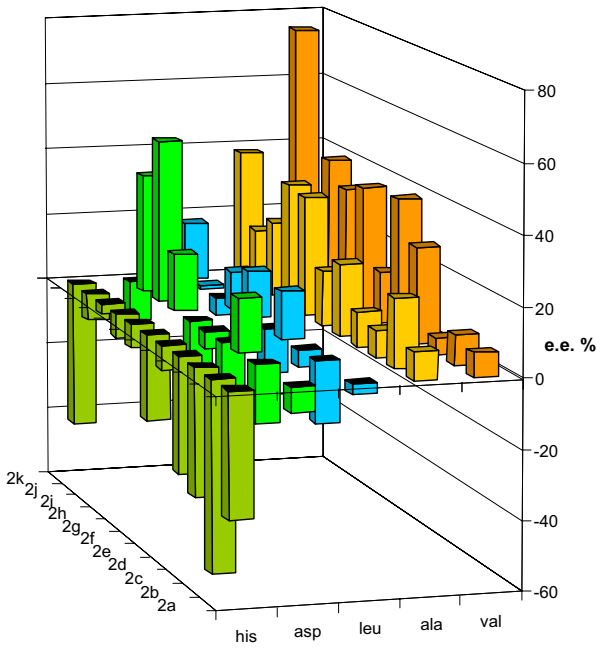


Figure 1. Enantiomeric excesses of alcohols **2a**–**k** induced by natural amino acids [ee% = (*R*–*S*)/(*R*+*S*)×100].

As a consequence, both enantiomers of the desired secondary alcohol can be synthesized by using the inexpensive and easily available natural L-amino acids and so we can choose in advance the appropriate ligand needed for the preparation of any enantiomer.

The structure of the substrate is also of great importance in determining the enantioselectivity. On the basis of our results, the prochiral ketones **1a**–**k** could be divided in two subgroups. Thus, ligand His resulted in higher ee's for reactions of aryl alkyl ketones **1a**–**f** and the conformationally flexible benzosuberone **1i** but with the more rigid benzocyclanones **1g** and **h** and benzoheteracyclanones **1j** and **k** resulted in lower ee's. Similar selectivity has also been reported for some borane reductions.[22] The opposite induction was observed when using Ala and Val, which resulted in higher ee's with the rigid ketones, especially with 1-indanone **1g** and 1-tetralone **1h**. 1-Thiochroman-4-one **1k** gave alcohol **2k** with lower enantioselectivity than the related 4-chromanone **1j** did (compare ee's of **k** and **j** in Tables 1–4; Table 1, entry 5; Table 2, entry 4; Table 3, entry 1 and Table 4, entry 10; with Table 1, entry 8; Table 2, entry 10; Table 3, entry 4 and Table 4, entry 12). Similar effects have been reported in the case of rhodium-catalyzed hydrosilylation.[23] On the other hand, the Austrian authors also found that the change of a CH_2 group to an oxygen atom in the six-membered ring had no effect on the enantioselectivity.[23] In our system the enantiopurity usually decreased in the order **1h**, **1j** and **1k** using either Ala, Val or Leu ligands (see Table 1, entries 10, 8 and 5; Table 2, entries 8, 10 and 7; Table 3, entries 5, 4 and 1).

In the alkyl phenyl ketone (PhCOR) series, the effect of the group R is rather controversial. As a typical situation, a poorer enantioselectivity was reported for the isopropyl or benzyl group in comparison with methyl or ethyl in various asymmetric reductions.[3b,5d,22–26] In contrast to the order given in literature, the ee's from our experiments varied in a narrow range (36–55%) by using Cr(II)–His complex with isobutyrophenone **1c** affording the best enantioselectivity (see Table 5, entries 9–12). In the presence of Ala or Val, the difference in selectivity was much more pronounced. Ee values of ketones **1b**–**d** fell far behind the ee of the parent acetophenone **1a**, but within the group **1b**–**d**, isobutyrophenone **1c** resulted again in better ee's than ketones **1b** or **1d** (see Table 1, entries 11, 1, 6 and 2 and Table 2, entries 11, 2, 3 and 1).

Chiral inductions in the reaction of 1-acetonaphthone **1e** and 2-acetonaphthone **1f** with chromium(II) amino acid complexes were similar to the cases of alkyl phenyl ketones. The larger steric demand of the naphthyl group does not change considerably the stereoselectivity although ee's are lower than those of acetophenone **1a** (see Tables 1–5). Previous literature data display similar enantiopurity for substrates **1a**,**e** and **1f** although 2-acetonaphthone **1f** gave lower ee's in some cases.[3b,22,23,25] Notably, the selectivity significantly depended on the structure of the amino acid ligand. Thus, bidentate Ala,

Val, Leu resulted in higher ee's with 2-acetonaphthone **1f** (see Table 1, entries 3 and 7; Table 2, entries 6 and 9; Table 3, entries 3 and 7) while the tridentate Asp and His proved to be more effective for 1-acetonaphthone **1e** (Table 4, entries 4 and 8; Table 5, entries 6 and 8). These differences could be interpreted by the different orientation of the naphthyl groups in the TS causing different steric interactions (vide infra). To interpret the above-listed tendencies a better knowledge of the TS's would be needed.

Due to the lack of quantifiable rules improvement of the enantioselectivity for a chosen substrate requires further optimization experiments. Results of such a procedure utilizing a wider range of amino acids in the reduction of 4-chromanone **1j** is shown by Table 6.

In most cases, excellent conversions and moderate-to-good yields were achieved. In accordance with our previous results[19] the chiral information of the amino acids was successfully transferred in all cases. However the ee was dependent on the ligand applied. His and Leu resulted in marginal ee's (Table 6, entries 1 and 2) in favour of the (*S*)-enantiomer while L-lysine (Lys), L-phenylalanine (Phe) and L-trytophane (Trp) induced low but *R* preference (see Table 6, entries 3, 4 and 5). The low selectivities are in accordance with the previously observed importance of an α branch on the alkyl chain. Val gave again much higher ee's than Ala (Table 6, entries 11 and 6). L-Proline (Pro) and the nonnatural *t*-Leu exerted induction similar to Val (Table 6, entries 9–11). The best ee value was obtained by Asp at pH = 9.4, a pH change from 7.0 to 9.4 doubled the enantiopurity (Table 6, entries 7 and 12). It has been pointed out that cyclic prochiral ketones or alkenes have smaller stereodiscrimination capacities giving the corresponding cyclic secondary alcohols, such as **1j**, with poorer ee's (<80%).[22,23,27]

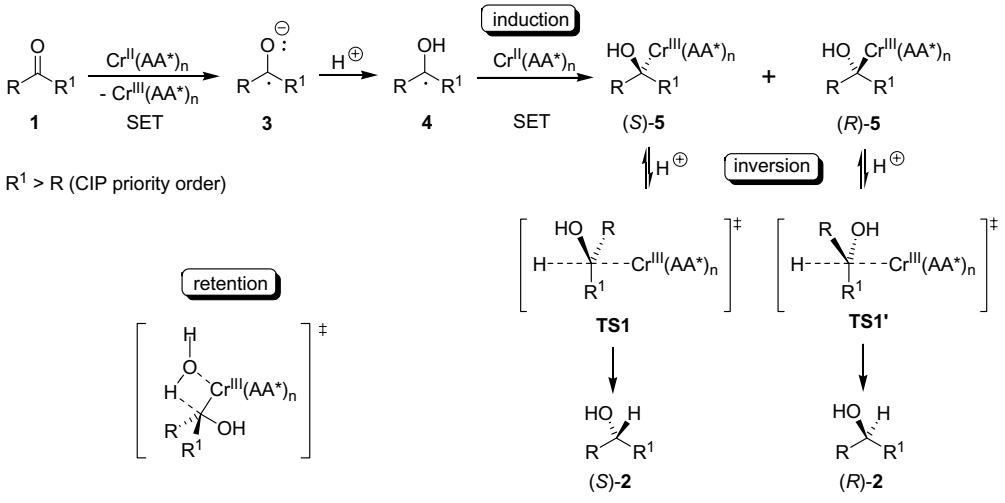
Finally, we have also investigated the effect of the solvents on the conversion and enantioselectivity by choosing 4-chromanone **1j** as the model substrate. It is well documented that donor solvents are needed to increase the reduction potential of Cr(II) ions.[15a] Thus, we tested the solvents listed in Table 7 together with 50% water using $Cr^{II}(Val)_2$ as the reducing complex at pH = 9.5. Data collected in Table 7 prove the advantage of amide type solvents; formamide nearly gave the same result as DMF (see entries 4 and 5). Surprisingly, NMP afforded poor conversion, chemical yield and enantioselectivity (entry 6). Sulfolane provided good conversion and reasonable ee but the yield was very low due to the difficulties in the extractive work-up (entry 3).

The suggested mechanism for the reduction of ketones by chromium(II) amino acid complexes in aqueous media is shown in Scheme 2. Our spectroscopic measurements (see Experimental, Section 3.4.) and literature data[28] suggest that the reduction of prochiral ketones involves the formation of radicals and then organo-

Table 7. Enantioselective reduction of 4-chromanone **1j** by chromium(II) L-valine complex in various solvents

Entry	Solvent	Conversion (%)	Yield (%)	Configuration	Ee (%)
1	Acetonitrile	50	50	*R*	24
2	Pyridine	74	3	*R*	17
3	Sulfolane	89	24	*R*	31
4	Formamide	88	41	*R*	37
5	DMF	>95	55	*R*	40
6	NMP	47	14	*R*	19

NMP: 1-methyl-2-pyrrolidone.



Scheme 2. Proposed mechanism of enantioselective reduction with Cr(II) amino acid complexes.

chromium(III) intermediates. The formation of radical intermediates has previously been proven.[18a]

According to our proposal in the first step, the ketone is reduced by one mole of chromium(II) complex in a single electron transfer (SET) process to give anionic ketyl radical **3**. The anionic centre is immediately protonated by water leading to radical **4**. In the second SET process, the organochromium(III) intermediate **5** is formed with the stereodifferentiation taking place in this crucial step. Although the carbon atom of the newly formed bond reacts readily with electrophilic reagents, its hydrolysis proceeds relatively slowly while the rate depends strongly on the structure of both the organic group and the ligand. In principle, there are two different pathways for the hydrolysis. The hydroxonium ion can attack the carbon atom from the side opposite to the chromium (transition states **TS1** and **TS1′**) with the inversion of the stereogenic centre. In this case the enantiomeric ratio generated in the C–Cr bond formation step remains unchanged. The other possibility involves protonation by a water molecule from the coordination sphere of the chromium(III). In this latter case the configuration is retained. Consequently, the enantiomeric excess of the resulting alcohol depends not only on the second SET (Cr^{II}-radical coupling) but also on the relative rate of the two controversial hydrolytic processes. According to earlier studies[29] on the mechanism of heterolysis of organochromium compounds, the first reaction route that is, the inversion of the stereogenic centre, is more probable.

If we assume that hydrolysis takes place dominantly with inversion, the enantiomeric excess of the product is dictated by steric factors during the formation intermediates **5**. However, the role of other factors such as hydrogen bonding cannot be excluded. As a rough estimation we have calculated[30] the most stable geometry of these organochromium intermediates; two of them are shown in Figures 2 and 3. The sharply different structures of the bidentate Val (Fig. 2) and the tridentate His (Fig. 3) intermediates are noteworthy and indicate different steric factors in the chiral induction step.

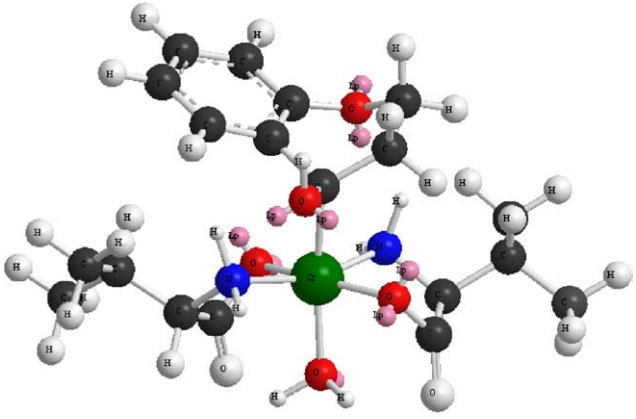


Figure 2. Calculated structure of the intermediate formed in the reaction of $Cr^{II}(Val)_2$ complex and **1j**.

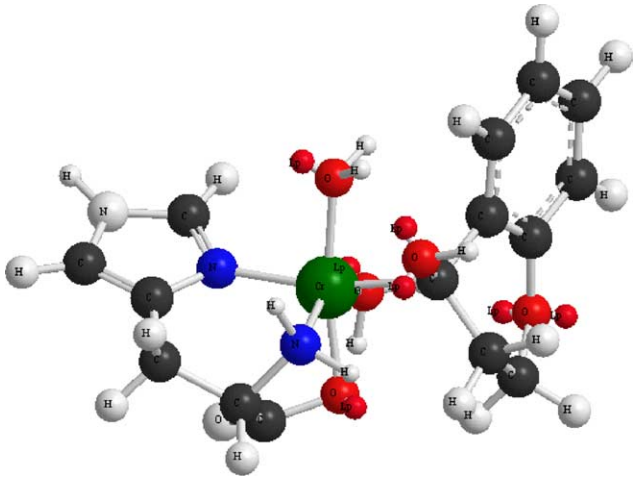


Figure 3. Calculated structure of the intermediate formed in the reaction of Cr^{II} $(His)^+$ complex and **1j**.

Taking the steric arrangement of the groups shown in Figure 2 into consideration the effect of the bulky alkyl groups of the amino acids on the enantioselectivity (vide supra) seems also reasonable. At the same time, we should emphasize that the exact characterization can only be done in possession of transition state calculations. Such efforts are currently in progress.

In conclusion, we have demonstrated that prochiral ketones can be reduced by in situ generated Cr(II) L-amino acid complexes in aqueous DMF or formamide solutions at room temperature to give the corresponding alcohols in good yields and moderate ee's. The enantioselectivity can be tuned by changing the ligand and the pH and the reaction can be optimized for any substrate. This factor together with the simplicity of the procedure and the easy availability of the source of chirality makes this new procedure promising and worth improving further.

3. Experimental

3.1. General

Preparation and reactions of Cr(II) complexes were carried out by using standard Schlenk methodology. $CrCl_3 \cdot 6H_2O$, the L-amino acids and the starting ketones **1a**–**k** of analytical grade were purchased from commercial sources. NMR spectra were recorded with a Bruker AM 360 spectrometer (^1H, 360 MHz; ^{13}C, 90 MHz). UV–vis measurements have been performed with a HP 8453 spectrophotometer.

Chiral HPLC measurements were performed using a JASCO PU-980 solvent delivery system and pressure moderator; peaks were detected using a JASCO MD-910 diode array detector. Sample solutions were filtered through a PVDF membrane filter (0.22 μm/

4 mm) prior to immediate injection of 20 μL of the obtained filtrate.

3.2. Preparation of $[Cr(OAc)_2 \cdot H_2O]_2$

$[Cr(OAc)_2 \cdot H_2O]_2$ was prepared by modification of a literature protocol.[31]

To a mixture of granulated Zn (45 g, 0.69 mol) and $CrCl_3 \cdot 6H_2O$ (75 g, 0.28 mol) distilled water (90 mL) was added under argon atmosphere. After the dissolution of $CrCl_3 \cdot 6H_2O$ the mixture was cooled with an ice bath and excess concd HCl (105 mL), added in one portion. The colour of the mixture slowly changed from green to blue as the reaction went on. Cooling was only used in the first period of the reaction. After ca. 2 h, the colour of the mixture turned to sky-blue indicating the end of the reaction. This solution was then pressed into a solution of sodium acetate (127 g, 1.55 mol in 300 mL water) and heated to 50 °C by using a slight overpressure. A red precipitate formed immediately. The warm mixture was pressed through a filter using argon. The precipitate was washed with cold deoxygenated distilled water (3 × 100 mL), cold absolute ethanol (3 × 50 mL) and cold diethyl-ether (3 × 50 mL), and dried in an argon gas flow at 40–45 °C to give 49.0 g (93%) of $[Cr(OAc)_2 \cdot H_2O]_2$.

3.3. General experimental procedure

The preparation of chromium(II) amino acid complexes was based on our previous solution equilibria studies; the actual pH of certain reactions have been calculated based on the known and/or estimated formation constants.[21]

3.3.1. General procedure for experiments with chromium(II) natural amino acid complexes. The L-amino acid (14.0 mmol) was dissolved in a mixture of DMF (25.0 mL) and water (25.0 mL). Oxygen-free conditions were provided by continuous bubbling of argon through the solution. The pH was adjusted to the calculated value listed in Tables 1–6 by adding 2.78 M KOH solution. The pH was checked potentiometrically. $[Cr(OAc)_2 \cdot H_2O]_2$ (1.32 g, 7.0 mmol Cr(II) ion) was added to the stirred solution in one portion under argon atmosphere. The colour of the solution slowly turned to blue indicating the formation of the reactive chromium(II) amino acid complex.

Ketone **1a**–**k** (3.0 mmol) was added in one portion to the solution of the complex and the mixture stirred for 18 h under a slight overpressure of argon. The mixture was extracted with diethyl ether (3 × 50 mL), the combined organic phases washed with water (5 × 50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was submitted to column chromatography (Silica 60, using toluene/ethyl acetate = 4/1, v/v; hexane/ethyl acetate = 3/1, v/v or hexane/acetone = 6/1, v/v as eluents) to give pure alcohols **2a**–**k**. The conversions have been calculated on the basis of the recovered unreacted material.

The product alcohols **2a**–**k** were assigned on the basis of their spectral characteristics and by comparison with authentic samples. Ee's have been determined by chiral HPLC using Chiralcel OJ (250 × 4.6 mm) column, eluent: hexane/2-propanol = 95:5, v/v, flow rate: 0.9 mL/min for alcohols **2e** (t_{R1} = 22.3 min, t_{R2} = 34.3 min), **2g** (t_{R1} = 11.2 min, t_{R2} = 12.6 min), **2h** (t_{R1} = 10.7 min, t_{R2} = 14.0 min), **2i** (t_{R1} = 10.9 min, t_{R2} = 13.9 min) and **2k** (t_{R1} = 21.8 min, t_{R2} = 26.3 min), Chiralcel OD (250 × 4.6 mm) column, eluent: hexane/2-propanol = 97:3, v/v, flow rate: 1.0 mL/min for alcohols **2b** (t_{R1} = 13.0 min, t_{R2} = 14.7 min) and **2d** (t_{R1} = 18.1 min, t_{R2} = 22.4 min). Alcohol **2f** (t_{R1} = 17.4 min, t_{R2} = 19.2 min) was measured on Chiralcel OB (250 × 4.6 mm) column, eluent: hexane/2-propanol = 9/1, v/v, flow rate: 0.5 mL/min. Alcohol **2c** was measured on Chiralcel OB (250 × 4.6 mm) column, eluent: hexane/2-propanol = 95:5, v/v, flow rate: 0.5 mL/min (t_{R1} = 11.9 min, t_{R2} = 12.5 min). Data for alcohol **2a** were taken from Ref. 17.

The absolute configurations were determined by comparison of the sign of the specific rotation measured in $CHCl_3$ with literature data. **2b**: *S*(−),[26,32] **2c**: *S*(−),[33] **2d**: *S*(−)[27d] but *S*(+) in EtOH,[34] **2e**: *S*(−),[26] **2f**: *S*(−),[26] **2g**: *S*(+),[32,33] **2h**: *S*(+),[25,32] **2i**: *S*(+),[35] **2j**: *S* (−),[27d,36] **2k**: *S* (−)[37] (measured in ethanol).

3.3.2. General procedure for experiments with [Cr(*t*-Leu)$_2$] complex. L-*tert*-Leucine (0.328 g, 2.50 mmol) was dissolved in a mixture of DMF (30.0 mL) and water (29.0 mL) and the pH adjusted to the calculated value listed in Tables 3 and 6 by adding KOH (1.10 mL, 2.78 M) solution. The pH was checked potentiometrically. The stirred solution was degassed by passing of argon, after which $[Cr(OAc)_2 \cdot H_2O]_2$ (0.188 g, 1.00 mmol Cr(II) ion) was added in one portion. The colour slowly turned blue indicating the formation of the reactive [Cr(*t*-Leu)$_2$] complex. Ketone **1a**,**e**,**j** (0.40 mmol) was added in one portion to the solution of the complex and the mixture stirred for 18 h under a slight overpressure of argon. The mixture was worked up according to the previous protocol.

3.4. UV–vis measurements

Deoxygenated aqueous solutions of the amino acid and the solution of the ketone **1j** in DMF were placed in a quartz tandem cell. The ionic strength was adjusted with 0.1 M KCl solution. The cell was sealed by a stopper and flushed with argon using hypodermic needles as inlets and outlets. A known volume of $CrCl_2$ solution[21a] was added through a hypodermic needle. The cell was then closed under slight overpressure. After thermostating to 25 °C, the reaction was initiated by shaking the cell; the spectra were recorded in the 190–700 nm region. A typical UV–vis spectrum of the reaction mixture is shown by Figure 4, the shoulder at 277 nm belongs to the charge transfer (CT) band[28a,b] of the organochromium(III) intermediate. The band disappears with progress of the reaction (see Fig. 5).

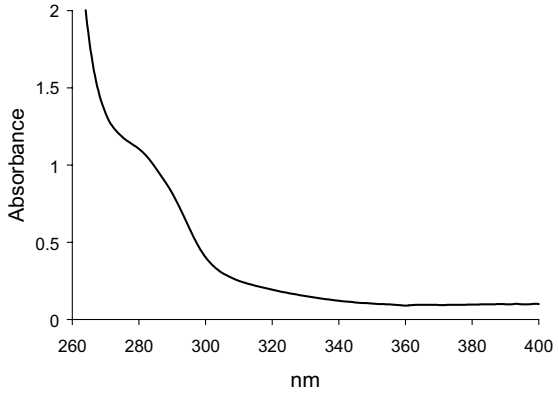


Figure 4. Typical UV–vis spectra of the R–$Cr^{III}(Val)_2$ organochromium intermediate (R = **1j**) recorded after 25 s the reaction started ($(Cr^{II}(Val)_2 = 1.59\times10^{-3}$ mol dm^{-3}, **1j** $= 6.47\times10^{-4}$ mol dm^{-3}, pH = 9.5).

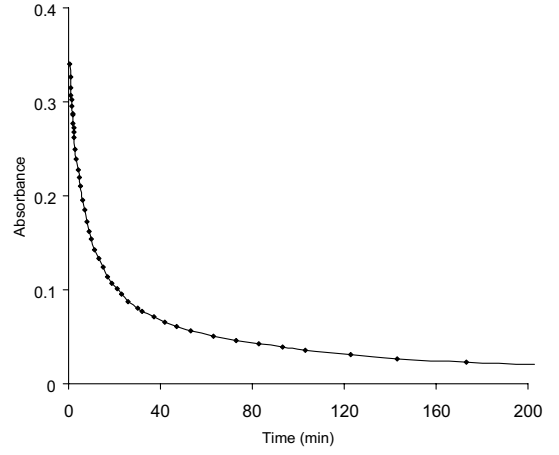


Figure 5. Typical kinetic curve recorded at 277 nm demonstrating the hydrolysis of the organochromium bond in the reaction shown by Figure 4.

Acknowledgements

Financial help is acknowledged to the Hungarian Scientific Research Foundation (Grant OTKA, No. T33130, T32429), the Hungarian Scholarship Board (MÖB) and DAAD (DAAD 48/2002-2003).

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