

Asymmetric induction by amino acid ligands in chromium(II)-assisted reduction of ketones[☆]

Julianna Gyarmati^{a,1}, Csongor Hajdu^a, Zoltán Dinya^{a,c}, Károly Micskei^{a,*},
Claudia Zucchi^b, Gyula Pályi^{b,2}

^a Department of Inorganic and Analytical Chemistry, Lajos Kossuth University, Egyetem tér 1, H-4010 Debrecen, Hungary

^b Department of Chemistry, University of Modena, Via Campi, 183, I-41100 Modena, Italy

^c Research Group for Antibiotics of the Hungarian Academy of Sciences, H-4010 Debrecen, Hungary

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Dedicated to: Professor Dr László Markó (Veszprém, Hungary) on the occasion of his 70th birthday.

Abstract

Asymmetric reduction of acetophenone by Cr(II)/amino acid/water/DMF system is reported. Chemical yields up to 94%, enantiomeric excesses up to 74% were observed. The relevance to the Nozaki–Hiyama–Kishi reaction is discussed. © 1999 Elsevier Science S.A. All rights reserved.

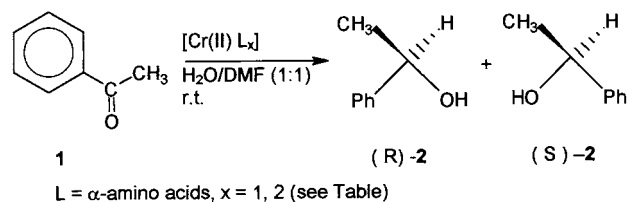
Keywords: Asymmetric reduction; Nozaki–Hiyama–Kishi reaction; Ketones; Chromium

Asymmetric induction by transition metal complexes is one of the most active fields in organic chemistry [1]. The so-called Nozaki–Hiyama–Kishi (N–H–K) reductive C,C-bond coupling, which uses in situ generated organochromium reagents, is one of the most versatile new methods in transition metal-assisted organic chemistry [2]. This reaction recently was commented on as follows [3]: “An efficient enantioselective version of the Nozaki–Hiyama–Kishi reaction—although highly desirable—is still missing”.

Here we describe a chromium(II)/amino acid/water/DMF system for enantioselective ketone reduction

which represents the first breakthrough in this respect, being correlated with the reductive step in the N–H–K reaction.

The reagent used in this work was planned on the basis of earlier solution equilibria studies [4]. Acetophenone, **1**, was added to this system and it has been observed [5] that methylphenylcarbinol, **2**, was formed (see Eq. (1) and Table 1) with > 95% chemoselectivity (conversion max. 94%).



(1)

Keeping the reaction time constant, the influence of the amino acids and pH (also used for tuning of the coordination number) can be compared as shown in Fig. 1. These data provide some remarkable hints at the chemistry and eventual further development:

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* Corresponding author. Tel.: +36-52-316-666/2757; fax: +36-52-489-667.

E-mail addresses: kmicskei@tigris.klte.hu (K. Micskei), palyi@unimo.it (G. Pályi)

¹ Work partly done at the University of Modena.

² Also corresponding author. Tel.: +39-59-378-443; fax: +39-09-373-543.

- Asymmetric induction, observed up to 75% ee, is highly variable with the structure of the ligands. Chemical yields are near quantitative (up to 94%) in some cases.
- Generally higher ee values are observed with combinations where CrL₂ type complexes are formed [4]. This hints at the cooperativity of some of the amino acid ligands (Val, Leu, Phe, Asn). Tridentate ligands such as Asp and His behave differently. These show a change in the sense of chirality of the product [6] at Cr:L = 1:1 ratio, while the ee decreases with Cr:L = 1:2 ('anti-cooperativity').
- The effects of D-amino acids were equal to those of the L-enantiomers with opposite sign—as expected.

Mechanistic background [7] of the N–H–K reaction indicate that the reduction described in this paper proceeds through an oxyalkylchromium(III) complex intermediate (**A**). Current research in our laboratories showed that this intermediate might be used for asymmetric C,C-coupling [8], which is the final goal of this work.

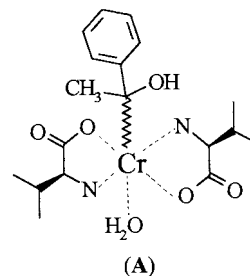


Table 1

No.	Ligand ^a	L/D/DL	Cr(II) (mmol)	Ligand (mmol)	1 (mmol)	V (cm ³)	pH	Reactive complex	2 ^b (%)	ee ^c (% (R)/(S))
1	–	–	9	–	4	30	5.0	Cr(H ₂ O) ²⁺	0.0	0
2	IDA	–	15	15	7	50	6.5	Cr(IDA)	71.2	0
3	Ala	L	15	7.5	2	50	6.4	Cr(Ala) ⁺	43.7	40.5 (R)
4		L	7.5	15	3.5	50	9.5	Cr(Ala) ₂	75.0	40.9 (R)
5		L	7.5	15	3.5	50	9.5	Cr(Ala) ₂	95.3	37.8 (R)
6		D	7.5	15	3.5	50	9.5	Cr(Ala) ₂	72.9	35.7 (S)
7	Val	L	15	7.5	2	50	6.1	Cr(Val) ⁺	35.0	60.6 (R)
8		L	7.5	15	3.4	50	9.2	Cr(Val) ₂	78.9	72.9 (R)
9		L	7.5	15	3.5	50	9.2	Cr(Val) ₂	78.3	73.1 (R)
10		L	7.5	15	3.6	50 ^d	9.2	Cr(Val) ₂	67.4	74.6 (R)
11		L	7.5	15	3.6	50 ^e	9.2	Cr(Val) ₂	44.7	69.1 (R)
12		L	5 ^{f,g}	10	1	30	10.2	Cr(Val) ₂	81.0	47.2 (R)
13		L	5 ^{f,h}	10	3.8 ^h	50	10.2	Cr(Val) ₂	18.4	29.9 (R)
14	Leu	L	12.5	7.5	2.2	50	7.4	Cr(Leu) ⁺	58.4	10.2 (R)
15		L	5	15.1	2.3	50	8.8	Cr(Leu) ₂	54.9	16.9 (R)
16	Met	L	12.5	7.5	2.1	50	6.6	Cr(Met) ⁺	17.6	12.5 (R)
17	Phe	L	6	9	2.8	60	5.5	Cr(Phe) ⁺	23.2	16.2 (R)
18		L	6	13.2	2.8	60	9.0	Cr(Phe) ₂	91.9	32.4 (R)
19		D	3	6.6	1.4	30	9.0	Cr(Phe) ₂	85.2	31.0 (S)
20		DL	6	13.2	2.8	60	9.0	Cr(Phe) ₂	82.2	0
21	Tyr	L	12.5	7.5	2.8	50	9.2	Cr(Tyr) ⁺	84.2	17.9 (R)
22	Trp	L	10	7.5	1.3	50	6.7	Cr(Trp) ⁺	66.7	21.6 (R)
23	Pro	L	12.5	7.5	2.1	50	7.4	Cr(Pro) ⁺	51.4	28.3 (R)
24	Hypro	L	9.5	7.5	1.2	50	6.6	Cr(Hypro) ⁺	68.0	24.4 (R)
25	Asp	L	12.5	7.5	2.2	50	6.9	Cr(Asp)	64.2	12.1 (S)
26		L	6.4	14.8	2.62	50	8.6	Cr(Asp) ₂ ²⁻	41.8	11.0 (S)
27	Asn	L	15	7.5	2.2	50	5.9	Cr(Asn) ⁺	11.1	16.1 (R)
28		L	7.5	15	3.5	50	9.0	Cr(Asn) ₂	35.3	34.5 (R)
29	Lys	L	12.5	7.5	2.8	50	9.2	Cr(Lys) ⁺	85.5	18.1 (R)
30	His	L	15	15	7	50	6.5	Cr(His) ⁺	71.1	43.2 (S)
31		L	7.5	7.5	3.5	50	8.5	Cr(His) ⁺	69.4	38.2 (S)
32		L	6	12	2.8	60	9.5	Cr(His) ₂	93.6	19.1 (S)
33		D	7.5	7.5	3.5	50	6.5	Cr(His) ⁺	73.8	39.7 (R)
34		L	5 ^f	5	1	30	6.5	Cr(His) ⁺	89.4	18.9 (S)

^a Iminodiacetate (IDA), alanine (Ala), valine (Val), leucine (Leu), methionine (Met), phenylalanine (Phe), tyrosine (Tyr), tryptophane (Trp), proline (Pro), hydroxyproline (Hypro), aspartic acid (Asp), asparagine (Asn) lysine (Lys), histidine (His).

^b ¹H-NMR yields.

^c Polarimetric and chiral GLC yields.

^d After 30 s the reaction mixture was quenched by 5 cm³ 5 mol dm⁻³ CH₃COOH.

^e After 30 s the reaction mixture was quenched by 5 cm³ 5 mol dm⁻³ HCl.

^f Aqueous CrCl₂ solution was used for preparation.

^g The solution of the complex was added dropwise to the solution of **1** within 60 min.

^h The solution of **1** was added dropwise to the solution of the complex within 60 min.

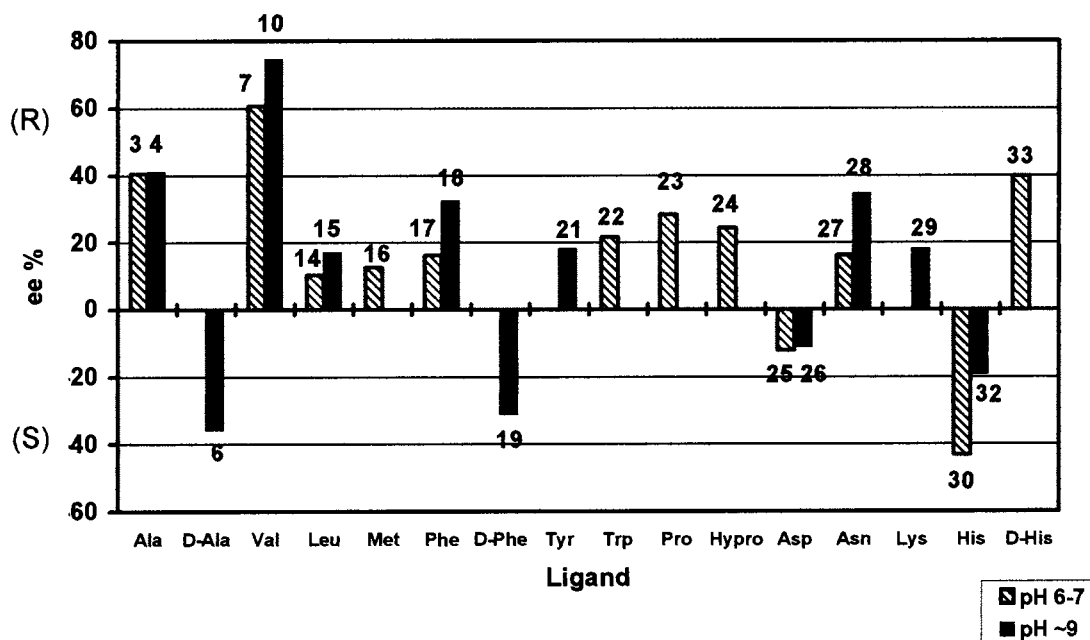


Fig. 1. Comparison of optical yields (ee%) obtained with some amino acids. (Numbers correspond to serial numbers of Table 1.)

It should be pointed out that in spite of the fact that natural amino acids are easily accessible sources of chirality [9], they are rarely used as chirogenic ligands in transition metal-assisted or catalyzed reactions [1,10], most probably due to the solubility problems.

Cr(II)-assisted organic reactions became important in the synthesis of complex biogenic organic molecules [2] but under non-biogenic conditions (solvents, ligands). Our system represents the first step towards a biomimetic [11] set-up, by using a high percentage of water as solvent and natural amino acids as sources of chirality.

Acknowledgements

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- [Cr(OAc)₂H₂O]₂ (1.41 g, 7.5 mmol Cr(II) ion) was added, in one portion, under an argon atmosphere. The color of the solution slowly turned blue indicating [4] the formation of the reactive complex [Cr(L-Val)₂]. Acetophenone (0.42 g, 3.5 mmol) was added in one portion to the reaction mixture and then the color of the mixture gradually turned to deep-violet. The reaction vessel was then closed under a slight overpressure of argon, and (external) stirring was continued for 18 h. After this period the solution was extracted (3 ×) with diethylether, the organic phase was washed (3 ×) with water, then dried with anhydrous Na₂SO₄, subsequently the solvent was evaporated under reduced pressure. The product was obtained in the form of a dense oil which was analyzed by GLC (Perkin–Elmer Autosystem-XL; Cyclodex-B fused silica column (30 m, 0.32 mm); injector temp. 200°C; detector: FID, 300°C; oven temp. 100°C.) and polarimetry (Perkin–Elmer 241), **2**, (*R*)-(+)- α -phenylethyl alcohol; $[\alpha]_{\text{D}}^{20}$: +42°, (*S*)-(–)- α -phenylethyl alcohol; $[\alpha]_{\text{D}}^{23}$: –41.3° (Aldrich Catalog 1999/2000, p. 1353). The differences between results obtained by these methods were less than 5%. The analyses were also controlled by isolating **2**: the main product was separated using column chromatography, (Kieselgel 60, 6:1 hexane–acetone) and was identified by elemental analyses (Found: C, 78.5; H, 8.2%. C₈H₁₀O, 122.17, Calc: C, 78.64; H, 8.26%) and ¹H- and ¹³C-NMR spectra. The isolated products all had characteristics identical with that of an authentic sample. Chemical (GLC, ¹H-NMR and isolated) yields were within 5% range, optical (polarimetric and chiral GLC, ee) yields were within 7% range.
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