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Enantioselective Reduction of Prochiral Ketones by Chromium(II) Complexes with Amino Acid Ligands as the Source of Chirality

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Abstract: Prochiral ketones were reduced to enantiomerically enriched secondary alcohols by Cr(II)[*L*-amino acid] complexes in good yields and moderate enantioselectivity.

Keywords: *Amino acids, Chromans, Ketones, Reduction.*

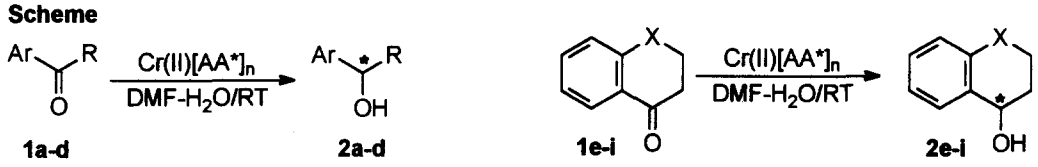
Asymmetric reduction of prochiral ketones to enantiomerically pure secondary alcohols has constituted a continuous challenge. Amino acids represent a cheap and commercially available source of chiral information but they are typically used in the form of their derivatives and amino acids themselves have been rarely used in asymmetric synthesis.[1,2] The probable reason is their poor solubility in most common organic solvents and, in turn, aqueous solutions are normally incompatible with most hydride-type reducing agents. Consequently, an enantioselective reduction where amino acid ligand(s) are utilized as sources of chirality should work in a different way to existing methods: it should employ SET processes, e.g. electrons provided by a low-valent transition metal ion followed by protonation by water.

We chose the Cr(II) ion as an electron source and complexing ion, since its usefulness in carbon-carbon bond formation reactions *via* organochromium(III) intermediates is well documented.[3-5] Our recent finding[6] that glycosyl- and morphine-chromium(III) complexes exist as *long-lived intermediates in aqueous solution* showed promise for the development of a new method for asymmetric reduction.

To test the designed system, aryl alkyl ketones **1a-d** and benzo(hetera)cyclanones **1e-i** were treated[7] with Cr(II) complexes of various *L*-amino acids in a DMF-water medium at room temperature (Scheme). Results summarized in the Table established the reducing capability of the system, the reactions generally proceeded with high conversion and moderate to good chemical yields.

The first, unoptimized experiments revealed that both yields and enantioselectivities are substrate- and ligand-specific. *L*-Alanine(Ala), *L*-histidine(His) and *L*-aspartic acid(Asp) give high conversions whereas *L*-valine(Val) and *L*-leucine(Leu) react more sluggishly. Chemical yields are high with *L*-Ala and *L*-Asp while the

Scheme



1,2	a	b	c	d
Ar	Ph	Ph	Ph	2-naphtyl
R	Et	^{i}Pr	Bn	Me

AA* = *L*-Ala, *L*-Val, *L*-Leu, *L*-His, *L*-Asp

1,2	e	f	g	h	i
X	bond	CH_2	CH_2CH_2	O	S

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Table. Enantioselective reduction of prochiral ketones **1** by chromium(II)-amino acid complexes

Subst.	Complex	pH	Conv. (%)	Yield[a] (%)	Conf.[b]	e.e.[c] (%)	Subst.	Complex	pH	Conv. (%)	Yield[a] (%)	Conf.[b]	e.e.[c] (%)
1a	Cr(*L*-Ala)$_2$	9.9	100	64	*R*	8	**1e**	Cr(*L*-Ala)$_2$	9.9	100	78	*R*	35
	Cr(*L*-Leu)$_2$	9.7	65	54	*S*	3		Cr(*L*-His)$^{\oplus}$	6.5	99	22	*S*	7
	Cr(*L*-His)$^{\oplus}$	6.5	98	33	*S*	36	**1f**	Cr(*L*-His)$^{\oplus}$	6.5	100	58	*S*	7
1b	Cr(*L*-Ala)$_2$	9.9	100	84	*R*	18	**1g**	Cr(*L*-Ala)$_2$	9.9	100	72	*R*	16
	Cr(*L*-His)$^{\oplus}$	6.5	99	44	*S*	55		Cr(*L*-His)$^{\oplus}$	6.5	94	56	*S*	25
1c	Cr(*L*-Leu)$_2$	9.7	85	34	*S*	18	**1h**	Cr(*L*-Ala)$_2$	9.9	100	67	*R*	22
	Cr(*L*-His)$^{\oplus}$	6.5	100	45	*S*	37		Cr(*L*-Val)$_2$	9.7	93	50	*R*	21
1d	Cr(*L*-Val)$_2$	9.7	76	62	*R*	39		Cr(*L*-Asp)	7.0	100	65	*R*	26
	Cr(*L*-Asp)	7.0	99	72	*S*	13	**1i**	Cr(*L*-Ala)$_2$	9.9	100	74	*R*	17
	Cr(*L*-His)$^{\oplus}$	6.5	98	61	*S*	25		Cr(*L*-His)$^{\oplus}$	6.5	100	25	*S*	8

[a] Yields refer to pure isolated products and are corrected for recovered starting material.
[b] The absolute configurations were determined by comparison of the sign of the measured specific rotation with literature values.
[c] Measured by HPLC (Chiralcel OB chiral column, hexane/2-propanol = 9/1 (for **1a,c-f,h**) or hexane/2-propanol = 95/5 (for **1g,i**).

use of *L*-Leu and *L*-His results in lower yields. Data shows a difference in the action of bi- and tridentate ligands, *L*-Ala and *L*-Val generate *R* alcohols while *L*-His leads to *S* products, *i.e.* the stereochemical outcome is tuneable not only by changing the absolute configuration, but also by the structure of the ligand used. This effect allows the use of cheaper *L*-amino acids for production of both *R* and *S* alcohols. *L*-His gave better optical yields in the aryl alkyl ketone series and in the case of the conformationally more flexible benzosuberone (**1g**) than for the more rigid benzocyclanones **1e,f,i**. The reverse effect was observed for *L*-Ala.

In summary, we demonstrated that prochiral ketones can be reduced to alcohols with moderate enantioselectivity in aqueous media, at ambient temperature, by means of Cr(II)[amino acid] complexes and that the chiral information of the amino acid ligands was successfully transferred to the substrate.

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7. *General Procedure:* *L*-Amino acid (15.00 mmol) was dissolved in a mixture of DMF (25.0 mL) and water (20.0 mL) and the pH was adjusted to the calculated value listed in the Table by 2.8 M KOH solution. The stirred solution was degassed by argon, then [Cr(OAc)$_2$H$_2$O]$_2$ (1.41 g, 7.50 mmol Cr(II) ion) was added in one portion under argon atmosphere. The colour slowly turned blue indicating the formation of the reactive Cr(II)[amino acid] complex. Ketone **1** (3.00 mmol) was added in one portion and the mixture was stirred for 18 h under a slight overpressure of argon. The mixture was extracted with dimethyl ether or dichloromethane (3x50 mL), the combined organic phases were washed with water (5x50 mL), dried (Na_2SO_4) and evaporated. Column chromatography (Silica 60, hexane/acetone = 6/1, v/v) gave pure **2**.