Chiral template amino acid syntheses using a 2-iminoacetatocobalt(III) chelate as a synthon

Lars Bendahl,[a] Anders Hammershøi,[a] Dan Kjærgaard Jensen,[a] Elisabeth Kaifer,[b] Alan M. Sargeson[b] and Anthony C. Willis[b]

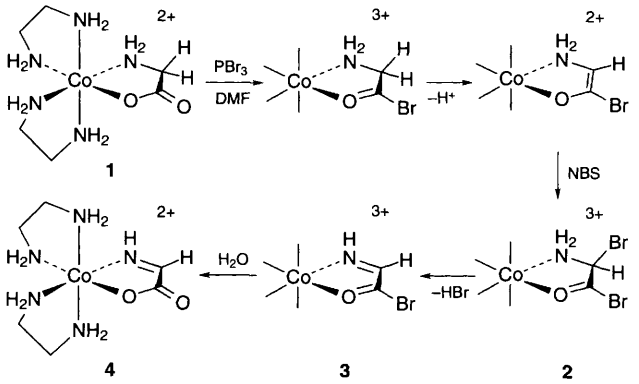
[a] *Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark*
[b] *Research School of Chemistry, Australian National University, Canberra, A.C.T. 0200, Australia*

Chelated glycinate on cobalt(III) is readily oxidized to 2-iminoacetate to give a useful synthon for stereoselective syntheses of α-amino acids by the addition of carbanions and through asymmetric transformations of the second kind.

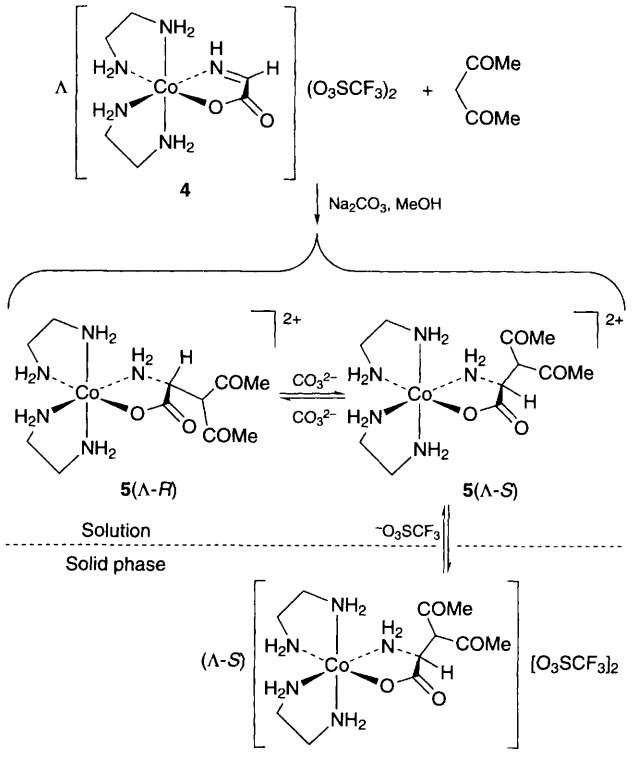
The increasing importance of nonprotein α-amino acids has triggered new general procedures for asymmetric synthesis of such compounds.[1] In this connection, the prospect of employing kinetically inert metal ions for specific binding, activation and protection of organic reactants is far from full exploitation. Here, a strategy based on a 2-iminoacetate–metal ion chelate is elaborated.

Reported chiral cobalt(III) complexes, qualifying as 'chiral glycine equivalents' for derivative syntheses, typically contain chelated glycinate or chelated glycine acid halide as the reacting ligand. In these systems, carbanion formation at the α-carbon is facilitated, and nucleophilic reactivity of this centre towards aldehydes and more powerful electrophiles is well documented.[2] However, attempts to perform alkylation reactions employing alkyl halides (or equivalents) have not been fruitful, and this limits the scope for amino acid synthesis.[3] In contrast, readily produced[4–6] 2-iminocarboxylatocobalt(III) complexes have proved useful starting points for asymmetric syntheses of various amino acids.[4] The bis(ethane-1,2-diamine)(2-iminopropanoato)cobalt(III) ion,[7] $[(en)_2Co(O_2CC(Me)=NH)]^{2+}$, and derivatives thereof, substituted at the imine nitrogen atom and/or at the methyl group, have been produced.[4,8] Carbanion addition reactions to the imine resulted in chelated 2,2-dialkyl-2-aminoacetates, and direct reduction of modified imines has provided 2-monoalkyl derivatives. Subsequent intramolecular condensation reactions of addition products may also occur.[4] Altogether, this illustrates the synthetic potential of such 2-iminocarboxylate complexes. The 2-iminoacetatocobalt(III) complex, which has remained synthetically elusive,[9] is now added to this class of complexes. Chiral $\Lambda(+)_D$-$[(en)_2Co(O_2CCH=NH)]Br_2\cdot H_2O$† **4**, was obtained (75% isolated yield) from $\Lambda(+)_{578}$-$[(en)_2Co(GlyO)][O_3SCF_3]_2$[10] **1** in dry dmf with *N*-bromosuccinimide (NBS) and PBr_3 (Scheme 1). The overall reaction is remarkably selective. The glycinate α-carbon is oxidized to the imine **4** and not further to the carboxamide level as observed in other oxidations.[3] The mechanism is proposed to involve acid bromide formation followed by α-bromination in a Hell–Vollhard–Zelinskii type reaction.[11] The activated intermediate **2** produced eliminates HBr forming the 2-iminoacetylbromide **3** and finally **4** with water. The strategy is general: the *N*-methyl derivative, $[(en)_2Co(O_2CCH=N\text{-}Me)]Br_2$, and the 2-iminopropanato complex, $[(en)_2Co(O_2CC(Me)=NH)]Cl_2\cdot H_2O$, were each obtained in the same way from the corresponding sarcosinato and alaninato complexes, respectively.

The imine **4** is sufficiently stable to hydration under basic conditions that nucleophilic attack by carbanionic reagents competes effectively. In water (pH ≈ 10), pentane-2,4-dione adds to the imine yielding a diastereomeric mixture of the 3-acetyl-2-amino-4-oxovalerato complex **5**. An organic (achiral) parallel is offered by addition reactions to *N*-acyliminoacetates.[12] The diastereomeric ratio‡ of **5**(Λ-*S*)/**5**(Λ-*R*) ≈ 2.5 is comparable to known equilibrium ratios for structurally related amino acidato complexes. For the aspartato system, $[(en)_2Co(AspO)]^+$, the (Λ-*S*)/(Λ-*R*) ratio is 1.5, but for the analogous valinato system, $[(en)_2Co(ValO)]^{2+}$, it is 0.50 after base-



Scheme 1



Scheme 2

catalysed epimerization at the α-carbon centre (25 °C, 0.05 mol dm^{-3}, 0.1 mol dm^{-3} NaCl).[13] These values reflect the rather low thermodynamic stereoselectivities in solution which are usually displayed with such complexes. However, when the addition reaction was carried out in absolute MeOH with $\Lambda(+)_{578}$-$[(en)_2Co(O_2CCH{=}NH)][O_3SCF_3]_2$ **4** and solid Na_2CO_3 as a basic catalyst, much higher diastereomer ratios resulted (Scheme 2). The overall **5**(Λ-*S*)/**5**(Λ-*R*) isomer distribution changed with time and the **5**(Λ-*S*) isomer, preferentially, precipitated as the triflate salt. Thus, even after the addition reaction was over, the proportion of the **5**(Λ-*S*) isomer gradually increased at the expense of the **5**(Λ-*R*) isomer, and after 6 days of stirring the diastereomeric excess (de) of the **5**(Λ-*S*) complex§ was 92%.

This behaviour manifests an 'asymmetric transformation of the second kind'.[15] While the diastereomers interconvert in solution by base-catalysed epimerization, the liquid phase is depleted of the **5**(Λ-*S*) isomer by crystallization, due to the lower solubility of its triflate salt compared with that of the **5**(Λ-*R*) isomer. Effectively, this crystallisation-induced transformation results in the formation of one diastereomer in a yield far in excess of what has hitherto been observed in solution for such complexes.

Analogous behaviour was found with the racemic complex, *rac*-$[(en)_2Co(O_2CCH{=}NH)][O_3SCF_3]_2$. A single diastereomer dominated‡ in the isolated products (> 80% yield) for additions with pentane-2,4-dione (86% de), diethylmalonate (88% de) and ethylacetoacetate (98% de). Clearly, the high selectivity in these instances rests on the serendipitous solubility difference of diastereomeric salts, and, thus, cannot be expected to hold in a general way. Nevertheless, with the present complexes some generality evidently obtains, and the strategy offers a simple stereoselective avenue to a range of amino acids.

Footnotes

† ^{13}C NMR (D_2O): δ 179.7, 175.7, 48.5, 48.0, 47.2, 46.6. [α] (λ/nm), (1.2 mol dm^{-3} $HClO_4$): 500 (578), 874 (546), −1074 (436).

‡ Determined by ion-exchange chromatography (Pharmacia Mono-S HR 5/5 column, Na_2H citrate/Na_3 citrate eluent).

§ Isolated as Λ-$[(en)_2Co\{NH_2(S)CH[CH(COMe)_2]CO_2\}][O_3SCF_3]_2{\cdot}0.5NaO_3SCF_3$ (74% yield): ^{13}C NMR (D_2O): δ 209.5, 209.1, 185.5, 58.6, 48.1, 47.5, 47.4, 46.2, 33.6, 32.6. [α] (λ/nm), (0.1 mol dm^{-3} HCl): 329 (578), 544 (546), −570 (436). Structural assignment based on X-ray crystallography[14] of racemic perchlorate salt [giving identical ^{13}C NMR (D_2O) spectrum, different from the diastereomer] and assuming the precursor (Λ-**4**) absolute configuration.

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