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Stereoretentive formylation of (*S*)-proline: new application of the self-regeneration of stereocentres (SRS) principle *via* chelation to cobalt(III)[†]

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In a Vilsmeier–Haack-type formylation reaction the α -(dihydroxymethyl)-(*S*)-prolinato complex (+)₅₇₈-*p*-[Co(tren){(*R*_C,*S*_N)-Pro[CH(OH)₂O]}Cl₂·2H₂O (**22**) was produced stereoselectively (85% ee) from the (*S*)-prolinato complex, (+)₅₇₈-*p*-[Co(tren){(*S*_C,*S*_N)-ProO}(H₃O)₂(HOEt₂)(O₃SCF₃)₇ (**18**). Similar reaction of the (*S*)-alaninato complex, (–)₅₇₈-*p*-[Co(tren)(*S*-AlaO)](H₃O)(O₃SCF₃)₃ (**13**), produced the racemate, *rac*-*p*-[Co(tren)(Ala{CH(OH)₂O})]SO₄·2H₂O (**17**). The contrasting stereochemical outcomes of the formylation reaction with **18** *versus* **13** were ascribed to the stereogenic character of the coordinated sec. amine of the (*S*)-prolinato chelate in **18**, which serves to uphold a chiral environment during reaction, whereas reaction intermediates derived from **13** lack this stereochemical feature. The stereoselective formylation of (*S*)-proline, relying on coordination to an inert metal centre, as conducted here, constitutes a novel application of the concept of Self-Regeneration of Stereocentres (SRS). The α -(hydroxymethyl)-(*S*)-prolinato complex, (+)₅₇₈-*p*-[Co(tren){(*R*_C,*S*_N)-Pro(CH₂OH)O}]Cl₂·2H₂O (**23**) resulted from borohydride reduction of **22**. The molecular structures of (+)₅₇₈-*p*-[Co(tren){(*R*_C,*S*_N)-Pro[CH(OH)₂O]}Cl₂·2H₂O (**22**), *rac*-*p*-[Co(tren)-(Ala{CH(OH)₂O})]I₂·H₂O (**17**) and (+)₅₇₈-*p*-[Co(tren){(*R*_C,*S*_N)-Pro(CH₂OH)O}]Cl₂·2H₂O (**23**) were established by X-ray crystallography.

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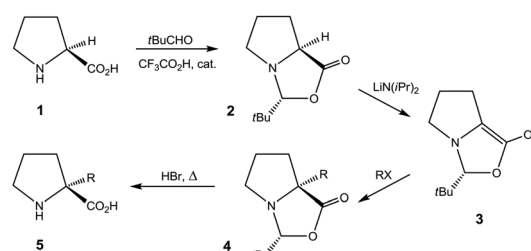
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Introduction

Proline (**1**) and derivatives play essential roles in chemistry and biology.¹ Chiral proline and analogues constitute archetypal agents in enantioselective organocatalysis.^{2,3} Prolyl segments within peptide strands impose rigid constraints on the peptide secondary structure, and in this respect proline is unique among the proteinogenic amino acids.¹ Synthetic studies have focussed on extending proline entities in order to create “proline chimeras” that mimic other peptidal amino acids with respect to side chain while retaining the conformational rigidity of the prolyl segment.⁴ This prospect has sparked interest in producing proline derivatives stereoselectively by elaboration from the α -C centre. However, modification at this, the sole stereogenic centre of proline, without loss of chirality is not straightforward.⁴ In 1981, Seebach *et al.* devised an elegant strategy which permitted α -alkylation of (*S*)-proline (**1**) to be conducted enantioselectively with a number of electrophilic reactants (Scheme 1).^{5,6} The strategy relied on temporary

incorporation of an auxiliary, stereogenic centre *via* formation of a bicyclic acetal (**2**) by condensation with pivaldehyde. The auxiliary stereogenic centre arose diastereoselectively at C-2 of the so formed 2-(*tert*-butyl)oxazolidin-5-one ring. Alkylation at the α -C centre of the lithium enolate intermediate **3** to give **4** also proceeded diastereoselectively. The inherent stereogenicity of the α -C centre in **1** was lost in the deprotonation step providing **3**, but the auxiliary stereocentre upheld an asymmetric environment for the alkylation step to yield **4** stereoselectively. Hydrolytic removal of the auxiliary centre provided **5**.⁶ This, overall, stereoretentive sequence (Scheme 1) constitutes a seminal example of the application of the



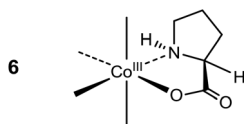
Scheme 1

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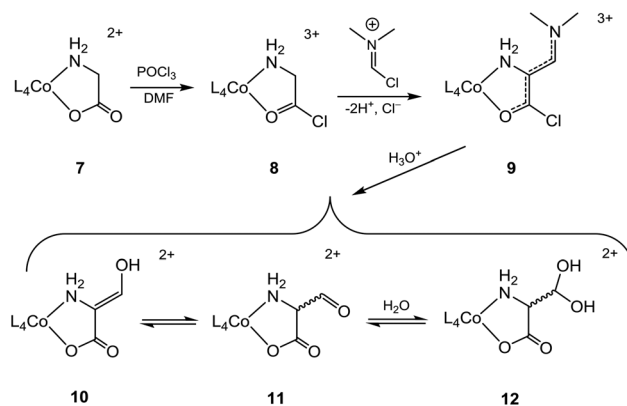


principle of Self-Regeneration of Stereocentres (SRS), due to Seebach.^{4,7}



Throughout the reaction sequence of Scheme 1 the N centre was not configurationally fixed. However, if (*S*)-proline was chelated to a metal centre (6), the configuration of the N centre (S_N) will be tied to that of the α -C centre (S_C), since the pyrrolidine ring only resides on one side of the pseudo plane defined by the chelate ring, a general feature of all reported structures of proline chelates at cobalt(III).^{8–12} In this respect the stereochemical characteristics of fragment 6 resemble those of 2 (Scheme 1). In both instances the amine and carboxylate groups are incorporated into a five-membered ring of a bicyclic system, and the absolute configuration of the parent (single) stereogenic centre of (*S*)-proline determines the configuration of the new stereocentre. Due to this similarity, proline chelates (6) may be anticipated to behave analogously to 3 with respect to stereopreferences. However, for such selectivity to operate in the case of 6 the coordinated amine would need to remain configurationally intact in the course of any reaction sequence aimed at modifying the α -C centre. Therefore, the amine should neither dissociate nor deprotonate at any point, since either event could facilitate loss of chirality by inversion, thus obviating the prospect of selectivity. These restrictions may be met by employing a substitutionally inert metal centre and applying conditions that suppress deprotonation at the amine-*N*-relative to the α -C centre. In general, bidentate coordination of an amino acidate to a cationic metal centre invariably serves to activate both of these centres, with the amine usually the most acidic, primarily due to the direct binding to the metal.¹³ However, enhanced activation of the α -C proton(s) of amino acid chelates by acid halide formation has been implicated for a number of cobalt(III) systems in reactions effecting, overall, formylation,^{14–17} oxidative imine formation^{18–23} or oxidation^{24,25} of the amino acid chelate. These reactions were typically carried out in DMF with POCl₃, SOCl₂ or PBr₃ as reagents, and were all interpreted as proceeding *via* initial conversion of the cobalt(III)-bound amino acidate to the derivative acid halide, thus enhancing activation at the α -C centre.^{14–24} However, the extent of concomitant activation of the neighbouring amine has not been elucidated. Clearly, simultaneous deprotonation at both sites would seem unlikely.

The creation of a quaternary α -C centre by introduction of a formyl group is an obvious goal, generating the basis for further elaboration. So far, successful introduction of the formyl group at the α -C centre of a cobalt(III)-bound amino acidate is only reported with glycinate (7). This was achieved by reaction with POCl₃ in DMF *via* a Vilsmeier–Haack-type reaction,²⁶ and results are summarised in Scheme 2 {L₄Co = *p*-Co(tren), *t*-Co(tren), Co(en)₂, *cis*- β -Co(trien)}.^{14–17,27} The



Scheme 2

argued mechanism assumes initial formation of a glycid chloride (8) which upon deprotonation at the α -C site is added to the *N,N*-dimethyl-chloromethyliminium ion (“Vilsmeier reagent”, generated *in situ* from reaction of POCl₃ with DMF) followed by elimination of HCl to produce the crystallographically verified 3-(dimethylamino)-2-aminoacryl chloride complex, 9 [L₄Co = *p*-Co(tren)].¹⁴ The conjugationally stabilized ligand of 9 yielded to hydrolysis in strong aqueous acid, providing^{15,16} the aldehyde complex 11, which was distributed between its hydrated (12) and enol (10) forms in water in *ca.* 9 : 1 ratio (L₄ = (en)₂).¹⁷ A published solid state structure has the aldehyde in the enol form [10, L₄Co = *cis*- β -Co(trien)].²⁷

In the sequence of Scheme 2 the site of reaction was the glycinate α -CH₂ group. However, if parallel chemistry was to be conducted with other α -amino acidates (different from GlyO[−]) with the aim of converting an α -CH group into a quaternary centre, the extensive conjugation noted for 9 would not apply. Therefore, such parallel chemistry was intuitively viewed less feasible. However, in this paper we report the successful formylation of the α -CH centres of the amino acidate ligands in (−)₅₇₈-*p*-[Co(tren)(*S*-AlaO)]²⁺ and (+)₅₇₈-*p*-[Co(tren)(*S*-ProO)]²⁺ producing the derivative aldehydes (hydrated form). While the (*S*)-alaninato complex resulted in a racemized product the reaction of the (*S*)-prolinato complex proceeded stereoselectively.

Experimental

General

Absorption spectra and optical rotations were monitored in water with a Lambda 17 spectrophotometer and a Perkin-Elmer P22 polarimeter ($\pm 0.002^\circ$), respectively; for the latter in 1 dm quartz cells at 25 °C. Within experimental error all listed values for specific rotations ($[\alpha]$, in units of 10^{−1} deg cm² g^{−1}) of chiral products did not change on further recrystallization of the product, and this was taken as evidence of optical purity. ¹³C{¹H} NMR spectra were recorded in D₂O on a (500 MHz) Bruker spectrometer (with cryoprobe) using



1,4-dioxane (^{13}C , $\delta = 69.14$ ppm relative to Me_4Si) as internal standard. When applicable, assignments of ^{13}C resonances were made on the basis of the APT technique. The cation exchange resin AG 50W-X2 (Bio-Rad, 200–400 mesh) was used throughout and resin column dimensions are given as diameter \times length. Routine concentration of solutions by removal of solvent was carried out at reduced pressure (*ca.* 20 Torr) in a Büchi rotary evaporator using a water aspirator and water bath (*ca.* 60 °C). Drying “*in vacuo*” was accomplished over P_4O_{10} . Anhydrous $\text{CF}_3\text{SO}_3\text{H}$ (3M Comp.) was used as supplied.

(–) $_{578}\text{p}[\text{Co}(\text{tren})(\text{S-AlaO})]\text{Cl}_2\cdot 5\text{H}_2\text{O}$ ([13] $\text{Cl}_2\cdot 5\text{H}_2\text{O}$). To a solution of $\text{l}(\text{S})$ -alanine (4.4 g, 50 mmol) and $\text{CoCl}_2\cdot 6\text{H}_2\text{O}$ (11.9 g, 50 mmol) in water (0.2 l) was added tris(2-aminoethyl)-amine (7.3 g, 50 mmol) and activated charcoal (4.2 g, Norit W). The magnetically stirred mixture was heated (water bath) to *ca.* 70 °C and aerated for 2 h. After cooling and acidification with 1 M HCl (10 ml) the mixture was filtered through Kieselguhr and the dark orange-coloured filtrate evaporated to near dryness. The resulting viscous oil was taken up in hot water (25 ml) and ethanol (150 ml) was gradually added, leading to crystal formation. The resulting mixture was left at 5 °C, overnight, to complete crystallisation. The product of orange crystals was collected, washed with EtOH and Et₂O and dried in the air (12.9 g, 57%). (Found: C, 23.6; H, 7.1; N, 15.2. $\text{C}_9\text{H}_{34}\text{N}_5\text{O}_7\text{Cl}_2\text{Co}$ requires C, 23.80; H, 7.54; N, 15.42%); δ_{C} (126 MHz, D_2O) 187.9 (COO); 64.2 (dbl. int.), 61.5 [$\text{N}(\text{CH}_2)_3$]; 56.5 (CH); 48.2 (dbl. int.), 47.3 [$\text{N}(\text{CH}_2\text{CH}_2)_3$]; 20.9 (CH_3); $[\alpha]_{578} -41$, $[\alpha]_{546} -34$.

(–) $_{578}\text{p}[\text{Co}(\text{tren})(\text{S-AlaO})](\text{H}_3\text{O})(\text{O}_3\text{SCF}_3)_3$ ([13] $(\text{H}_3\text{O})(\text{O}_3\text{SCF}_3)_3$). Under a N_2 blanket, anhydrous $\text{CF}_3\text{SO}_3\text{H}$ (*ca.* 25 ml) was slowly added to solid $p[\text{Co}(\text{tren})(\text{S-AlaO})]\text{Cl}_2\cdot 5\text{H}_2\text{O}$ (11.5 g, 25.3 mmol) which gradually dissolved with gas evolution (HCl). This process was completed in a vacuum (rotary evaporator) before the homogeneous orange-red solution was poured into vigorously stirred Et₂O (0.8 l). The resulting suspended orange powder (hygroscopic) was collected, washed with Et₂O and thoroughly dried *in vacuo* (19 g, 99%). (Found: C, 19.1; H, 3.0; N, 8.9. $\text{C}_{12}\text{H}_{27}\text{N}_5\text{O}_{12}\text{F}_9\text{S}_3\text{Co}$ requires C, 18.98; H, 3.58; N, 9.22%).

rac-p– $[\text{Co}(\text{tren})(\text{Ala}\{\text{CH}(\text{OH})_2\}\text{O})]\text{SO}_4\cdot 2\text{H}_2\text{O}$ ([17] $\text{SO}_4\cdot 2\text{H}_2\text{O}$). To a continuously stirred and cooled (ice bath) solution of $p[\text{Co}(\text{tren})(\text{AlaO})](\text{H}_3\text{O})(\text{O}_3\text{SCF}_3)_3$ (7.9 g, 10 mmol) in dry DMF (50 ml) was slowly added POCl_3 (30 ml) over 0.5 h. The reaction mixture was left with rapid stirring and gradually heated to 40 °C over 1 h when it became darker in colour. The reaction mixture was immediately poured into iced water (0.5 l) and the resulting orange-coloured solution adsorbed on a column of AG 50W-X2 cation exchange resin (H^+ -form, 6.5×20 cm). After washing with water the orange band was eluted with a gradient of 1–3 M HCl and the eluate concentrated to near dryness. The residue was taken up in water (30 ml) followed by addition of $\text{Na}_2\text{SO}_4\cdot 10\text{H}_2\text{O}$ (3.9 g, 12 mmol) and gradual addition of acetone (35 ml) with cooling in ice. The orange-red crystals were collected, washed with acetone, Et₂O and dried in the air (3.9 g, 80%). (Found: C, 25.6; H, 6.4; N, 14.7. $\text{C}_{10}\text{H}_{30}\text{N}_5\text{O}_{10}\text{SCo}$ requires C, 25.48; H, 6.42;

N, 14.86%); δ_{C} (126 MHz, D_2O) 187.6 (COO), 93.1 ($\text{CH}(\text{OH})_2$), 68.5 (CCH_3), 64.0, 63.5, 61.1 [$\text{N}(\text{CH}_2)_3$], 47.9, 47.3, 46.8 [$\text{N}(\text{CH}_2\text{CH}_2)_3$], 23.4 (CH_3); $[\alpha]_{578} 0$, $[\alpha]_{546} 0$.

rac-p– $[\text{Co}(\text{tren})(\text{Ala}\{\text{CH}(\text{OH})_2\}\text{O})]\text{I}_2\cdot \text{H}_2\text{O}$ ([17] $\text{I}_2\cdot \text{H}_2\text{O}$). A mixture of *rac-p*– $[\text{Co}(\text{tren})(\text{Ala}\{\text{CH}(\text{OH})_2\}\text{O})]\text{SO}_4\cdot 2\text{H}_2\text{O}$ (0.14 g, 0.30 mmol) and KI (0.21 g, 1.3 mmol) was suspended and dissolved in water (1 ml) by gentle heating. The resulting solution was left at 5 °C, whereby large orange-red, needle-shaped crystals formed. (Found: C, 19.1; H, 4.6, N 11.2. $\text{C}_{10}\text{H}_{28}\text{N}_5\text{O}_5\text{I}_2\text{Co}$ requires C, 19.65; H, 4.62; N, 11.46%).

(+) $_{578}\text{p}[\text{Co}(\text{tren})\{(\text{S}_\text{C},\text{S}_\text{N})\text{-ProO}\}]\text{Cl}_2\cdot 1.5\text{H}_2\text{O}$ ([18] $\text{Cl}_2\cdot 1.5\text{H}_2\text{O}$). To a solution of l -proline (3.45 g, 30.0 mmol) and $\text{Co}(\text{NO}_3)_2\cdot 6\text{H}_2\text{O}$ (8.73 g, 30.0 mmol) in water (100 ml) was added tris(2-aminoethyl)amine (4.39 g, 30.0 mmol) and activated charcoal catalyst (1.4 g, Norit W). The mixture was constantly aerated and stirred while maintaining the temperature at *ca.* 70 °C for 4 h. After cooling and acidification (3 M HCl, 5 ml) the reaction mixture was filtered through Kieselguhr, and the orange-coloured filtrate was sorbed on a column of AG 50W-X2 cation exchange resin (6.5×20 cm). After washing with water the single orange band was eluted with 0.5–3.0 M HCl and the eluate concentrated to almost dryness. The resulting syrupy residue was taken up in water (12 ml) followed by gradual addition of abs. EtOH (100 ml) leading to separation of orange crystals, which after cooling in ice were collected, washed with abs. EtOH, Et₂O and airdried (9.85 g, 79%). (Found: C, 31.7; H, 6.9; N, 16.5. $\text{C}_{11}\text{H}_{29}\text{N}_5\text{O}_{3.5}\text{Cl}_2\text{Co}$ requires C, 31.67; H, 7.01; N, 16.78%); δ_{C} (126 MHz, D_2O) 188.0 (COO), 67.9 (CH), 64.33, 64.28, 61.4 [$\text{N}(\text{CH}_2)_3$], 54.1 (NHCH_2), 48.0, 47.4, 47.3 [$\text{N}(\text{CH}_2\text{CH}_2)_3$], 31.6, 29.1 ($\text{CH}_2\text{CH}_2\text{CH}$). $[\alpha]_{578} 50.0$, $[\alpha]_{546} 115$; $\lambda_{\text{max}}(\text{H}_2\text{O})/\text{nm}$ 476 ($\epsilon/\text{dm}^3 \text{ mol}^{-1}$ 119) and 345 (122).

(+) $_{578}\text{p}[\text{Co}(\text{tren})\{(\text{S}_\text{C},\text{S}_\text{N})\text{-ProO}\}]_2(\text{H}_3\text{O})_2(\text{HOEt}_2)(\text{O}_3\text{SCF}_3)_7$ ([18] $_2(\text{H}_3\text{O})_2(\text{HOEt}_2)(\text{O}_3\text{SCF}_3)_7$). Anhydrous $\text{CF}_3\text{SO}_3\text{H}$ (*ca.* 25 ml) was slowly added to solid $p[\text{Co}(\text{tren})\{(\text{S}_\text{C},\text{S}_\text{N})\text{-ProO}\}]\text{Cl}_2\cdot 1.5\text{H}_2\text{O}$ (8.0 g, 19 mmol) which gradually dissolved with gas evolution (HCl). The degassing and dissolution processes were completed by applying a vacuum (rotary evaporator) before the homogeneous orange-red solution was slowly poured into vigorously stirred Et₂O (0.5 l). The resulting suspended, crude orange powder (hygroscopic) was collected, washed with Et₂O and thoroughly dried *in vacuo* (14.4 g, 84%). (Found: C, 21.9; H, 3.6; N, 7.8. $\text{C}_{33}\text{H}_{69}\text{N}_{10}\text{O}_{28}\text{S}_7\text{F}_7\text{Co}_2$ requires C, 22.08; H, 3.87; N, 7.80%); δ_{C} (126 MHz, D_2O) 188.0 (COO), 122.2 (q, CF_3), 68.5 [$\text{O}(\text{CH}_2\text{CH}_3)_2$], 67.9 (CH), 64.35, 64.25, 61.4 [$\text{N}(\text{CH}_2)_3$], 54.1 (NHCH_2), 48.0, 47.5, 47.4 [$\text{N}(\text{CH}_2\text{CH}_2)_3$], 31.5, 29.0 ($\text{CH}_2\text{CH}_2\text{CH}$), 16.7 [$\text{O}(\text{CH}_2\text{CH}_3)_2$].

(+) $_{578}\text{p}[\text{Co}(\text{tren})\{(\text{R}_\text{C},\text{S}_\text{N})\text{-Pro}\}[\text{CH}(\text{OH})_2\text{O}]]\text{Cl}_2\cdot 2\text{H}_2\text{O}$ ([22] $\text{Cl}_2\cdot 2\text{H}_2\text{O}$). To a continuously stirred and cooled (ice bath) solution of (+) $_{578}\text{p}[\text{Co}(\text{tren})\{(\text{S}_\text{C},\text{S}_\text{N})\text{-ProO}\}]_2(\text{H}_3\text{O})_2(\text{HOEt}_2)(\text{O}_3\text{SCF}_3)_7$ (5.23 g, 2.91 mmol) in dry DMF (25 ml) was slowly added POCl_3 (15 ml) over 0.5 h. The reaction mixture was left with rapid stirring at 25 °C for 1 h before it was poured into iced water (0.4 l) and the resulting orange solution adsorbed on a column of AG 50W-X2 cation exchange resin (H^+ -form, 6.5×20 cm) as an orange band. Upon washing with water the



single band was eluted with 1–3 M HCl and the eluate was concentrated to near dryness. The residue was taken up in water (10 ml) followed by addition of acetone (30 ml) and cooling in ice. The massive orange-red crystals (2.53 g, 92%) were collected, washed with gradually increasing concentrations of acetone and dried in the air. The product was recrystallized in the same manner using water (12 ml) and acetone (35 ml) to yield large orange-red crystals which were collected as above (2.20 g, 80%). (Found: C, 31.0; H, 6.7; N 14.9. $C_{12}H_{32}Cl_2CoN_5O_6$ requires C, 30.52; H, 6.83; N, 14.83%); δ_C (126 MHz, D_2O) 187.8 (COO), 93.1 ($CH(OH)_2$), 82.9 (CCOO), 64.6, 64.2, 61.8 [$N(CH_2-)_3$], 56.4 ($NHCH_2$), 47.5, 47.4, 47.0 [$N(CH_2CH_2-)_3$], 35.6, 27.4 ($NHCH_2CH_2CH_2$); $[\alpha]_{578}^{25}$ 174, $[\alpha]_{546}^{25}$ 307; $\lambda_{max}(H_2O)/nm$ 477 ($\epsilon/dm^3 mol^{-1} cm^{-1}$ 127) and 345 (128).

$(+)_578-p-[Co(tren)\{(R_C,S_N)-Pro(CH_2OH)O\}]Cl_2 \cdot 2H_2O$ ([23] $Cl_2 \cdot 2H_2O$). With stirring, $NaBH_4$ (1.0 g, 26 mmol) was slowly added to a phosphate buffer solution (0.2 M, pH 6.86, 60 ml) of $p-[Co(tren)\{(R_C,S_N)-Pro[CH(OH)_2]O\}]Cl_2 \cdot 2H_2O$ (1.48 g, 3.1 mmol), causing gas evolution. The mixture was left with stirring overnight, diluted with water (0.1 l) and the resulting solution adsorbed on a column of AG 50W-X2 cation exchange resin (Na^+ -form, 6.5×24 cm) as an orange band. After thorough washing with water the band was eluted with 1–3 M HCl and the eluate evaporated to almost dryness. The syrupy residue was dissolved in hot water (1 ml) before EtOH (80 ml) was slowly added, initiating slow deposition of crystals. After cooling (5 °C, overnight) the large crystals were collected, washed with EtOH, Et₂O and airdried (1.11 g, 78%). (Found: C, 31.5; H, 7.0; N, 15.2. $C_{12}H_{32}N_5O_5Cl_2Co$ requires C, 31.59; H, 7.07; N, 15.35%). δ_C (126 MHz, D_2O) 188.6 (COO); 80.6

(CH_2OH); 68.4 (CCOO); 64.4, 64.1, 61.8 [$N(CH_2-)_3$]; 55.4 ($NHCH_2$); 47.4, 47.2, 46.9 [$N(CH_2CH_2-)_3$]; 35.2, 28.0 ($NHCH_2CH_2CH_2$); $[\alpha]_{578}^{25}$ 131, $[\alpha]_{546}^{25}$ 242.

Crystallography

Adequate crystals of *rac-p*-[Co(tren)(Ala{CH(OH)₂}O)]I₂·H₂O ([17]I₂·H₂O), $(+)_578-p$ -[Co(tren){(*R*_C,*S*_N)-Pro[CH(OH)₂]O}]Cl₂·2H₂O ([22]Cl₂·2H₂O) and $(+)_578-p$ -[Co(tren){(*R*_C,*S*_N)-Pro(CH₂OH)O}]Cl₂·2H₂O ([23]Cl₂·2H₂O) were selected and each mounted on a glass fiber or nylon loop attached to a copper pin and placed in the N₂ stream of a Bruker D8 Venture diffractometer. Data were collected using Mo-K_α radiation ($\lambda = 0.71073$ Å). Details of the crystal structure determination and refinement are given in Table 1. The structures were solved using the charge-flipping method (olex2.solve)²⁸ and refined using the program packages SHELXL²⁹ ([17]I₂·H₂O and [23]Cl₂·2H₂O) or Olex2³⁰ ([22]Cl₂·2H₂O).

Results and discussion

The chiral (*S*)-alaninato- and (*S*)-prolinato cobalt(III) complexes were each formylated at their α -methine centres in a Vilsmeier–Haack-type reaction, essentially as done before at the α -methylene group of the analogous glycinate complexes.^{14–17} However, in the present study quaternary carbon centres were created, and the products, *rac-p*-[Co(tren)-(Ala{CH(OH)₂}O)]I₂·H₂O ([17]I₂·H₂O) and $(+)_578-p$ -[Co(tren)-{(*R*_C,*S*_N)-Pro[CH(OH)₂]O}]Cl₂·2H₂O ([22]Cl₂·2H₂O), were each isolated in their hydrated, *i.e.* α -(dihydroxymethyl) forms, and

Table 1 Summary of crystallographic data

Compound reference	[17]I ₂ ·H ₂ O	[22]Cl ₂ ·2H ₂ O	[23]Cl ₂ ·2H ₂ O
Empirical formula	C ₁₀ H ₂₈ CoI ₂ N ₅ O ₅	C ₁₂ H ₃₂ Cl ₂ CoN ₅ O ₆	C ₁₂ H ₃₂ Cl ₂ CoN ₅ O ₅
<i>M</i>	611.11	472.26	456.25
Crystal system	Monoclinic	Orthorhombic	Orthorhombic
Space group	<i>P</i> 2 ₁ / <i>n</i>	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> /Å	21.619(3)	9.6314(6)	8.9450(3)
<i>b</i> /Å	9.0014(10)	13.5664(6)	12.4236(4)
<i>c</i> /Å	22.283(3)	14.7998(8)	17.4130(6)
α /°	90	90	90
β /°	117.732(6)	90	90
γ /°	90	90	90
Unit cell volume/Å ³	3838.1(8)	1933.8(2)	1935.1(1)
Temperature/K	298(1)	122(1)	122(1)
<i>Z</i>	8	4	4
Refl. measured	35 227	14 308	30 215
Independ. refl.	6799	4259	5425
Observed refl. (<i>I</i> > 2σ(<i>I</i>))	5152	3991	4854
Parameters	427	281	233
<i>R</i> _{int}	0.051	0.0366	0.050
<i>R</i> ₁ (<i>I</i> > 2σ(<i>I</i>))	0.0550	0.0269	0.0271
<i>wR</i> (<i>F</i> ²) (<i>I</i> > 2σ(<i>I</i>))	0.1316	0.0617	0.0556
<i>R</i> ₁ (all data)	0.0765	0.0309	0.0356
<i>wR</i> (<i>F</i> ²) (all data)	0.1443	0.0662	0.0585
<i>S</i>	1.084	1.013	1.043
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å ^{−3})	1.31, −0.71	0.63, −0.37	0.63, −0.37
Flack parameter	—	0.010(13)	0.006(6)
CCDC number	1411924	1411925	1411926



their structures verified by X-ray crystallography. While the formylation of the chiral alaninato complex (**13**) gave racemic **17**, the formylation of the chiral prolinato complex (**18**) produced the chiral α -formyl (*R*)-prolinato complex (**22**) in 85% enantiomeric excess (ee).

Synthesis and characterisation

The two precursor complexes were readily produced in a “one-pot” procedure comprising aeration of a solution of cobalt(II) salt, tris(2-aminoethyl)amine (tren) and *S*-amino acid in water in the presence of activated-charcoal catalyst. Enantiopure products, $(-)_578p$ -[Co(tren)(*S*-AlaO)]Cl₂·5H₂O and $(+)_578p$ -[Co(tren)-{(S_C,S_N)-ProO}]Cl₂·1.5H₂O, respectively, were isolated in good yields. Usual cobalt(III) behaviour predicts activated charcoal to catalyse the equilibration of coordination isomers.^{31,32} Here, the *p* isomer was the sole geometrical isomer observed in both instances.^{33,34} This isomer has the carboxylate group coordinated *trans* to a primary amine of the tren ligand in the complex,³⁵ and the same single product geometry was observed in similar syntheses of the homologous glycinate, ornithinato- and sarcosinato complexes.^{33,36,37} These concurring results corroborate the suggestion that this facile strategy is generally applicable for the directed, stereoselective synthesis of *p*-[Co^{III}(tren)(amino acidato)]^{*n*+} complexes, obviating earlier (non-stereoselective) methods based on substitution of ligands of a suitable cobalt(III) complex {[Co(tren)Cl₂]Cl,^{38,39} [Co(tren)Cl₂](ClO₄)⁴⁰ or [Co(tren)(OH₂)(OH)](ClO₄)₂^{14,41,42}}. The precursor complex chlorides were converted to their DMF-soluble triflate salts, $(-)_578p$ -[Co(tren)(*S*-AlaO)](H₃O)(O₃SCF₃)₃ and $(+)_578p$ -[Co(tren){{(S_C,S_N)-ProO}}₂(H₃O)₂(HOEt₂)(O₃SCF₃)₇, and each subjected to Vilsmeier–Haack-formylation in DMF followed by chromatographic workup and crystallization of products. Thereby, the chiral (*S*)-alaninato complex (**13**) was converted to the racemic α -(dihydroxymethyl) product, *rac-p*-[Co(tren)(Ala{CH(OH)₂O})]SO₄·2H₂O (**17**), whereas the chiral (*S*)-prolinato complex (**18**) gave the product enantiomer $(+)_578p$ -[Co(tren){{(R_C,S_N)-Pro[CH(OH)₂O]}]Cl₂·2H₂O (**22**) in 85% ee (in eluate after chromatography), but recrystallization afforded enantiopure product in 80% yield. The ¹³C NMR spectra (in D₂O) of both formyl complexes (**17**, **22**) revealed the hydrated, α -(dihydroxymethyl) forms of the crystallized products to also persist in aqueous solution. With NaBH₄ in water (pH 6.9) the α -formyl-prolinato complex (**22**) was selectively reduced to the derivative alcohol complex $(+)_578p$ -[Co(tren){{(R_C,S_N)-Pro(CH₂OH)O}]Cl₂·2H₂O (**23**)Cl₂·2H₂O.

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Structures

A number of prolinato cobalt(III) complexes are reported before.^{8–12,43,44} In all instances for which a crystal structure was also reported, the five-membered pyrrolidine ring was found to reside in a *cisoid* fashion on the same side of the plane defined by the prolinato chelate ring.^{8–12} Thereby, the configurations of the α -C- and *sec*-amine-N atoms of chelated prolinato are mutually interlocked. Thus, in the published¹² structure of chiral *p*-[Co(tren){{(S_C,S_N)-ProO}]I₂·H₂O ([**18**]I₂·H₂O) the absolute configurations of these centres are S_C,S_N, and

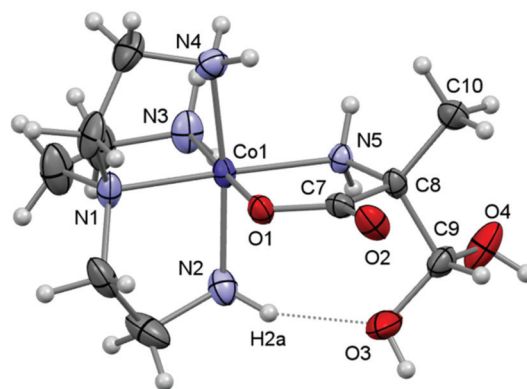


Fig. 1 A view of the molecular structure of one of the two crystallographically independent but structurally similar complex ions of [**17**]I₂·H₂O showing the atom-labelling scheme for selected atoms. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

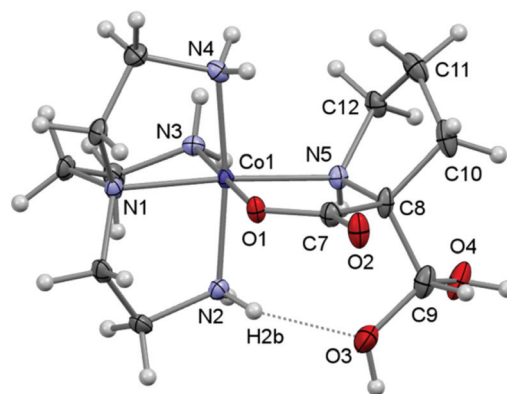


Fig. 2 A view of the molecular structure of the complex cation of [**22**]Cl₂·2H₂O showing the atom-labelling scheme for selected atoms. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

inspection of a molecular model reveals the alternative *transoid* disposition (S_C^{*}, R_N^{*}, relative configuration) to be more strained, relatively.

Here, crystal structure determinations were undertaken of product complexes *rac-p*-[Co(tren)(Ala{CH(OH)₂O})]I₂·H₂O ([**17**]I₂·H₂O), $(+)_578p$ -[Co(tren){{(R_C,S_N)-Pro[CH(OH)₂O]}]Cl₂·2H₂O ([**22**]Cl₂·2H₂O) and $(+)_578p$ -[Co(tren){{(R_C,S_N)-Pro(CH₂OH)O}]Cl₂·2H₂O ([**23**]Cl₂·2H₂O), and the complex cations of each structure are depicted in Fig. 1–3. The monoclinic crystal of racemic [**17**]I₂·H₂O contains two formula units per asymmetric unit, but since the two crystallographically independent complex ions are structurally very similar, only one of these is depicted in Fig. 1. Selected bonding parameters for all three structures appear in Table 2. Since all corresponding values of the two crystallographically independent complex cations of [**17**]I₂·H₂O are similar within a few standard deviations, only averaged values are given in Table 2 for this compound.



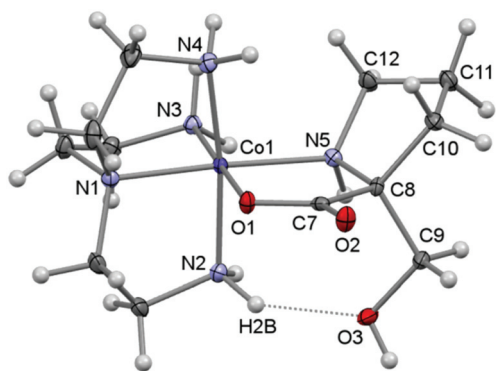


Fig. 3 A view of the molecular structure of the complex cation of [23] $\text{Cl}_2 \cdot 2\text{H}_2\text{O}$ showing the atom-labelling scheme for selected atoms. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii.

Table 2 Selected bond distances (Å) and angles (°)

Compound	[17] $\text{I}_2 \cdot \text{H}_2\text{O}^a$	[22] $\text{Cl}_2 \cdot 2\text{H}_2\text{O}$	[23] $\text{Cl}_2 \cdot 2\text{H}_2\text{O}$
Co–N1	1.938	1.956(2)	1.945(2)
Co–N2	1.948	1.969(2)	1.971(2)
Co–N3	1.934	1.940(2)	1.943(2)
Co–N4	1.944	1.971(2)	1.957(2)
Co–N5	1.952	1.973(2)	1.977(2)
Co–O1	1.885	1.902(2)	1.906(2)
N1–Co–N2	86.1	85.0(1)	86.2(1)
N1–Co–N3	87.9	86.9(1)	87.9(1)
N1–Co–N4	86.2	86.5(1)	86.5(1)
N1–Co–N5	85.3	86.0(1)	85.9(1)
N2–Co–N3	92.5	91.7(1)	92.0(1)
N3–Co–N4	91.8	92.3(1)	91.6(1)
N4–Co–O1	86.7	87.1(1)	87.0(1)
O1–Co–N2	89.1	88.8(1)	89.3(1)
N4–Co–N5	94.8	97.6(1)	96.5(1)
N2–Co–N5	92.8	90.7(1)	91.3(1)
N1–Co–N5	177.3	175.6(1)	176.8(1)
N2–Co–N4	171.1	170.4(1)	171.1(1)
N3–Co–O1	178.4	179.4(1)	178.6(1)
Co–N5–C12	—	120.1(2)	119.8(2)
Co–N5–C8	111.8	110.1(1)	109.8(1)
Co–O1–C7	116.6	117.1(2)	116.5(1)

^a Averages.

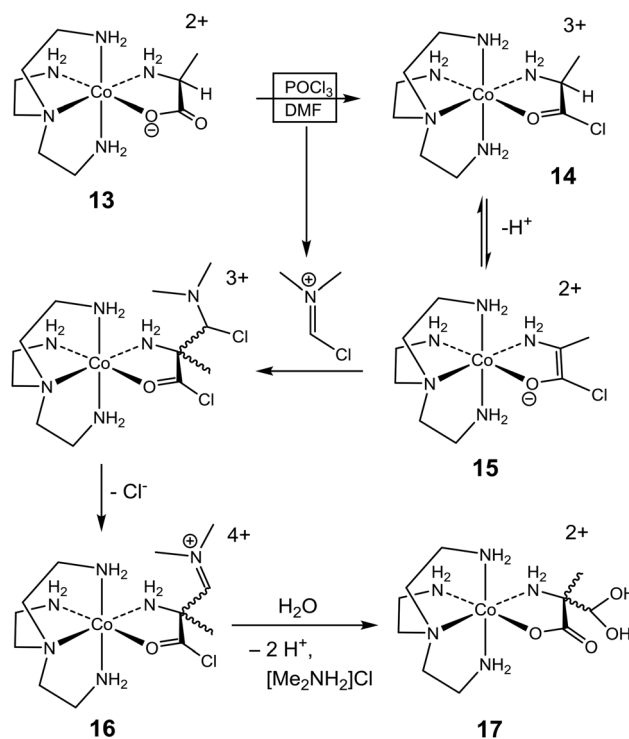
All three complex cations display very similar overall geometries. A common feature is the reduced N2–Co–N4 angle (*ca.* 171°) spanning the “meridional” segment of the tren ligand. In the formyl-alaninato complex (17) the corresponding angular increase is distributed almost equally over the angles N4–Co–N5 (94.8°) and N2–Co–N5 (92.8°). However, in the formyl-prolinato- (22) and the hydroxymethyl-prolinato (23) complexes the increase primarily affects the angle N4–Co–N5 [97.7° (22); 96.8° (23)], while the angle N2–Co–N5 [90.7° (22); 91.3° (23)] is close to the ideal octahedral value in both instances. The expanded N4–Co–N5 angles and the also enlarged Co–N5–C12 angles of 120.1° of 22 and 119.8° of 23 (>109.5°) may reflect the result of an alleviating effect arising from repulsive interactions with the pyrrolidine ring within

the complex. Nevertheless, in 22 the pyrrolidine ring adopts the envelope conformation with the flap oriented towards the complex core. This orientation contrasts with the conformation in the structure of 23 and in other structures of prolinato cobalt(III) complexes which all have the flap pointing away from the complex centre.^{8–12}

All three structures are dominated by extensive hydrogen-bonding networks. A common feature is a strong intramolecular hydrogen-bond interaction between a coordinated amine and one O atom of the α -(dihydroxymethyl) or α -hydroxymethyl groups [N2...O3: 2.799 (13) Å in 17, 2.865 (3) Å in 22 and 2.791 (3) Å in 23], a general feature in related structures.^{33,37,45}

Stereoselectivity

The contrasting stereochemical outcomes of the formylation reactions of the two amino acidate complexes of this study provide important mechanistic insight. A mechanistic proposal for the formylation (accompanied by racemization) of the (*S*)-alaninato complex (13) is depicted in Scheme 3, and the mechanism is argued on the background of the parallel reaction of the analogous glycinate system (Scheme 2).^{14–17} Thus, with POCl_3 the (*S*)-alaninato complex 13 is converted to the triply charged acid-chloride complex 14, which after proton loss and electronic readjustment provides enolate complex 15. This would be stabilized, relatively, due to the overall lower charge and electronic delocalization of the ligand with negative charge shifted towards the metal ion. The planarity of the



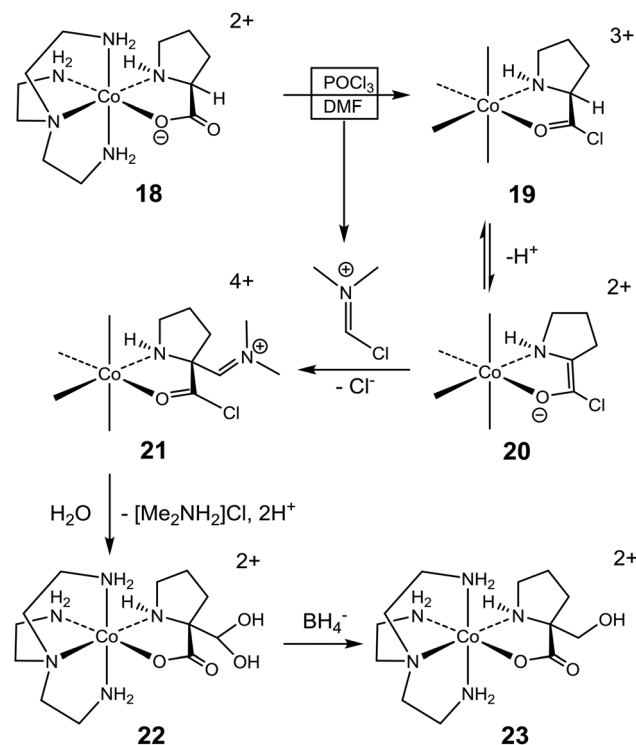
Scheme 3



enolate ligand renders **15** achiral, and any reaction which restores sp^3 -hybridization at the α -C atom would result in racemic product mixtures. Here, addition to the imine of the Vilsmeier reagent followed by elimination of Cl^- produces **16**, which after hydrolysis of the iminium- and acid chloride functionalities provides the racemic α -(dihydroxymethyl)alaninato complex **17**. Once formed, the quaternary α -C centre of this product is configurationally locked. Thus, while enantiomers of the related α -formyl-glycinato system may interconvert *via* an enol intermediate (**10**, Scheme 2),^{17,27} such path is clearly not available to the α -formyl-alaninato complex (**17**).

In the mechanistic proposal above (Scheme 3) the identity of the acid halide **14** was inferred by analogy. Thus, the formation of a chelated acid halide (**9**, Scheme 2) from p -[Co(tren)GlyO]²⁺ and POCl₃ in DMF has been verified crystallographically.¹⁴ Since **15** is achiral, re-protonation yields both enantiomers of **14** in equal proportion, and the reversible inter-conversion between **14** and **15** affects overall racemization of **14**, even though this was not verified directly. However, the same effect of activation due to acid halide formation has been noted in a related system. Thus, SOCl₂, POCl₃ and PBr₃ were each shown to induce epimerization at the α -C centre of chelated (*S*)-valinate in the Δ, Δ -[Co(en)₂(*S*-ValO)]²⁺ complex in DMF, shifting a non-equilibrium distribution of diastereoisomers ([Δ -*S*]/[Λ -*S*] = 50 : 50) towards equilibrium ([Δ -*S*, Λ -*R*]/[Δ -*R*, Λ -*S*] = 1.9, in water).^{18,23} Altogether, this evidence implies that temporary removal of the proton at the α -C centre must occur, since inversion at this centre could otherwise not occur.^{46,47} However, the fate of the removed proton is uncertain, but general base catalysis may operate, aided by dissolved PO₂Cl₂⁻ or other base. Alternatively, the proton could reside at the O atom of the chelate, which in the present system (Scheme 3) amounts to the enol tautomer of **14**.

The pronounced stereoselectivity associated with the formylation of (+)₅₇₈- p -[Co(tren){(*S*_C,*S*_N)-ProO}]²⁺ (**18**) to give (+)₅₇₈- p -[Co(tren){(*R*_C,*S*_N)-Pro[CH(OH)₂O}]²⁺ (**22**) is remarkable, not least because the “Co(tren)” backbone is achiral and chelated amino acidato ligands typically equilibrate in the conditions applied, *vide supra*.^{18,23} Nevertheless, the ee value of 85% testifies that chirality is largely retained in this instance. A mechanistic proposal, depicted in Scheme 4, assumes initial conversion of **18** to form the acid chloride **19**, as before (Scheme 3).^{14–24} The α -C centre of this triply-charged complex (**19**) is activated towards deprotonation to generate enolate intermediate **20**, stabilized by conjugation and the lower charge, but with some strain in the bound pyrrolidine ring. Most importantly, the absolute configuration of the coordinated *sec.* amine (stereogenic) is retained, and this asymmetry directs stereoselective addition to the imine of the Vilsmeier reagent to occur from the *Re* face of the enolate ligand. Subsequent loss of Cl^- (to yield **21**) followed by hydrolysis provide the α -(*R*_C,*S*_N)-di(hydroxy)methyl proline complex **22**. Effectively, the inserted formyl group occupies the position initially occupied by the α -proton, thus rendering the overall reaction “stereoretentive” even though, formally, the change of absolute configuration of the α -C site is from *S* (**18** and **19**) to



Scheme 4

R (**21** and **22**). Once formed, the quaternary α -C centre of **22** is configurationally locked.

The 85% ee for **22** implies slight racemization in the overall reaction. Conceivably, this may arise *via* either of two paths. One possibility is partial racemization of **20** prior to attack by the Vilsmeier reagent. At the molecular level such racemization requires partial inversion of the *sec.* amine of **20**, but at the inert cobalt(III) centre such event is only mechanistically feasible after prior deprotonation of the amine.^{43,44} However, further deprotonation of **20** (a product of deprotonation, itself!) would seem less probable, and this accords with the actual modest level of racemization. Alternatively, the modest degree of racemization may be explained by less than complete discrimination in the stereoselective reaction of **20** with the Vilsmeier reagent, which attacks preferentially at the *Re* face of the enolate plane to produce **21**. In the rarer event of attack at the *Si* face, the immediate product (a putative diastereoisomer of **21**) would inevitably have the pyrrolidine ring in the more strained *transoid* arrangement relative to the chelate ring. Subsequently, this situation would have to be alleviated by equilibration (*via* inversion of the *sec.* amine) in order to bring the pyrrolidine ring into the more stable *cisoid* arrangement, which was the only observed (¹³C NMR and X-ray crystallography) in the isolated product. If such equilibration is operating for the putative diastereoisomer of **21**, the mechanistically required deprotonation of the *sec.* amine would be facilitated by the high ionic charge of this complex.



Conclusions

The feasibility of conducting Vilsmeier–Haack-type formylation reactions at the α -C centre of a chelated amino acidate, hitherto only performed at the glycinate methylene group,^{14–17,27} has been expanded to also incorporate the methine groups of chelated alaninate and proline.

The highly stereoselective formylation reaction of chelated (S)-proline to give α -(R)-di(hydroxy)methyl proline (22) constitutes a novel and highly efficient example of the execution of the SRS principle.⁷ Here, the proline cobalt(III) system is unique in the sense that the combined exploitation of the activating and protecting effects of an inert metal centre, modulating the chemistry while directing the stereochemistry, has not been exemplified in this manner before. The formyl group thus introduced at the quaternary α -C centre of the chiral complex 22 makes this an ideal starting point, easily synthesized, for future controlled elaboration of the proline segment. In the complex, the amine and carboxylate functionalities remain protected by the coordination to the inert metal centre. However, product amino acids may be readily liberated at any time by gentle reduction to the labile cobalt(II) state, as demonstrated before.^{23,32,33}

Further enhancement of the stereoselectivity, and fine-tuning of reactivity, may be envisaged by the introduction of suitable steric demands in the backbone ligand sphere. Investigations along these lines are currently being pursued.

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