Modular syntheses of oxazolinylamine ligands and characterization of group 10 metal complexes

Christine A. Caputo, Florentino d.S. Carneiro, Michael C. Jennings, and Nathan D. Jones

Abstract: The syntheses of aminoalkyloxazoline and pyrrolidinyloxazoline ligands, each of which bear a pair of chiral centres, by both known and new routes are reported. Variable temperature NMR studies show that the known stepwise syntheses of the pyrrolidinyl compounds are not complicated by epimerization; however, coordination of one of the aminoalkyl derivatives to Pt(II) under conditions of prolonged heating to 80 °C does give mixtures of diastereomeric *N*,*N*′-chelated complexes that result from inversion of the chiral centre associated with the aminoalkyl fragment. A new synthesis of pyrrolidinyloxazoline ligands that involves the Zn-catalyzed cyclization of Cbz-protected 2-cyanopyrrolidine and β-amino alcohols is also reported. This procedure offers the advantages of economy, shorter time, and fewer purification steps over the previously reported synthesis. In addition, the crystal structure of an enantiopure Pd(II) complex of an *N,N*′-chelated pyrrolidinyloxazoline is disclosed. This compound has a pseudo-C_2 axis of symmetry, which may make it suitable for asymmetric catalytic applications.

Key words: chiral ligands, ligand design, oxazolines, variable temperature NMR spectroscopy, asymmetric catalysis, coordination compounds, palladium, platinum

Résumé : Faisant appel à des méthodes connues et d'autres nouvelles, on a réalisé la synthèse de ligands aminoalkyloxazolines et pyrrolidinyloxazolines qui portent une paire de centres chiraux. Des études de RMN à température variable ont permis de montrer que la méthode synthèse connue par étape pour les composés pyrrolidinyles ne sont pas compliquées par l'épimérisation; toutefois, la coordination d'un des dérivés aminoalkyles du Pt(II), dans des conditions de chauffage prolongé à 80 °C, ne conduit pas à des mélanges de complexes *N,N*′-chélatés diastéréomères résultant de l'inversion du centre chiral associé au fragment aminoalkyle. On a aussi réalisé une nouvelle synthèse des ligands pyrrolidinyloxazolines qui implique une cyclisation catalysée par le zinc de β-amino-alcools sur la 2-cyanopyrrolidine portant un groupe protecteur Cbz. Par rapport aux méthodes antérieures, cette méthode présente l'avantage d'être plus économique, d'impliquer des temps de réaction plus courts et moins d'étapes de purification. De plus, on a déterminé la structure cristalline du complexe énantiopur du Pd(II) avec une pyrrolidinyloxazoline *N,N*′-chélatée. Ce produit présente un axe de symétrie pseudo-C_2 qui pourrait le rendre susceptible d'être utilisé dans des applications de catalyse asymétrique.

Mots clés : ligands chiraux, développement de ligands, oxazolines, spectroscopie RMN à température variable, catalyse asymétrique, composés de coordination, palladium, platine.

[Traduit par la Rédaction]

Introduction

Beginning in the late 1980s and continuing to the present day, the oxazoline (4,5-dihydrooxazole) ring has featured prominently as the chiral component of a broad range of ligands that have been used to great effect in asymmetric catalytic transformations (1, 2). In particular, the C_2-symmetric bis(oxazoline) class has seen widespread and very successful application, e.g., in cycloaddition, aldol, Michael, carbonylene, and related Lewis acid-catalyzed reactions (3). More recently, C_1-symmetric compounds bearing oxazoline rings that have been elaborated with aminoalkyl functional groups predominantly in the 2-position (e.g., Chart 1, **I**) (4) have come to the fore as an important subclass of ligands in their own right and as building blocks for more elaborate ligand systems (Chart 1, **II**–**IV**) (5–7). Less common variations bearing aminomethyl groups in the 4-position have also appeared (Chart 1, **XIV**) (8).

The advantages of the ligand family **I** have been documented in a recent report by Rajaram and Sigman (4): the compounds are conveniently made in a modular manner from readily available, optically pure starting materials, bear multiple independently variable stereocentres, and are amenable to further elaboration through manipulation of the amine (e.g., to give **II**–**IV**) (5–7, 9). We also point out that the presence of N*H* protons may have important ramifications for the use of these ligands in the asymmetric hydrogenation of C=O bonds. Variations on this theme have also included oxazolines incorporating pyrrolidine (**V**) (10), quinoline (**VI**) (11), aniline (**VII**, **XIII**) (12–14),

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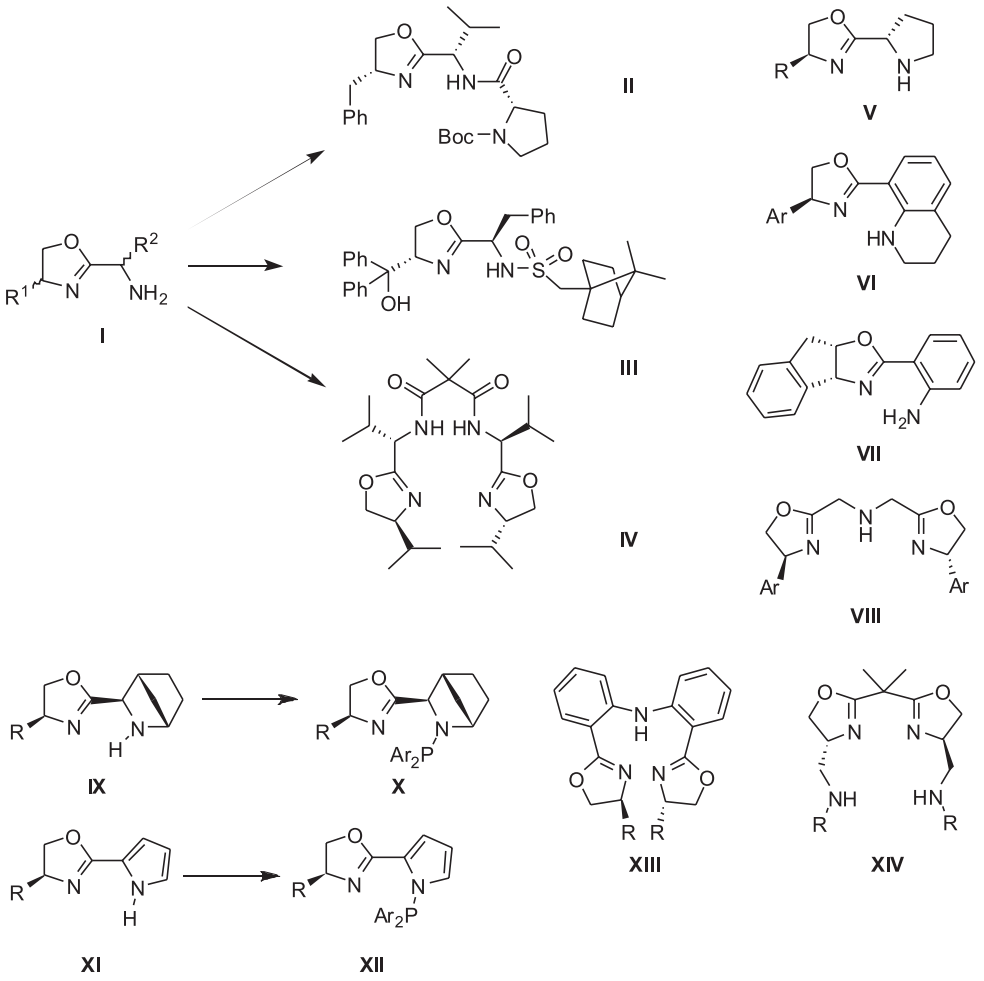
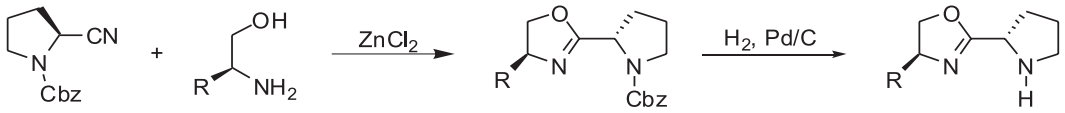
Chart 1. Examples of oxazolinylamine ligands.



Scheme 1. General synthesis of pyrrolidinyloxazolines by the Zn-catalyzed cyclization of *N*-protected 2-cyanopyrrolidine and β-amino alcohols.



azabicyclo[2.2.1]heptane (**IX**) (15), pyrrole (**XI**) (16–18), and pyridine (not shown) ring systems (21).

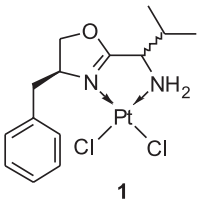
To date, access to the pyrrolidinyloxazoline ligands **V** has been limited to a stepwise synthetic route outlined by McManus et al. (10). Herein, we propose an alternate approach that involves the Zn-catalyzed cyclization of Cbz-protected 2-cyanopyrrolidine and β-amino alcohols (Scheme 1). This new approach is quicker, more economical, and requires fewer purifications. It also puts the diversification step later in the synthesis, which allows expansion of ligand libraries more easily.

Ligands in classes **I** and **V** bear two stereocentres and are, in principle, susceptible to epimerization. Through careful stepwise synthesis, we show in this report that there is no epimerization of **V** either during ligand synthesis by the McManus route or during metal complexation. However, epimerization does occur during the coordination of a ligand of type **I** to Pt(II); two diastereomers of **1** (Chart 2) result from the reaction of the appropriate ligand and $PtCl_2(SMe_2)_2$ in boiling dichloroethane.

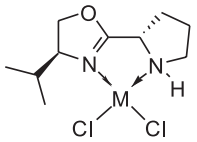
The compounds shown in Chart 1 have been used as ligands in asymmetric allylation (**II**, **XIII**) (5,13), alkylation (**IV**) (7,9), and crotylation (**XIII**) of aldehydes (13), Diels-Alder (**XI**) (16), hetero-Diels-Alder (**III**, **XI**) (6), and transfer hydrogenation (**V**, **VI VII**, **VIII** and **IX**) reactions (10–12,14,15); phosphine derivatives (**X**, **XII**) (19,20) have also been made and applied successfully in asymmetric hydrogenations.

Catalysts for these reactions have typically been generated in situ. Therefore, well-characterized examples of *N,N′*-chelated oxazolinylamine metal complexes are rare. Those *N,N′*-chelated complexes that have been structurally characterized are for the most part confined to the pyridinyloxazolines (21) and to the adducts of **VII** (12) and **XI** (16). As part of our ongoing exploration of modularly-made chiral *N,N′*-chelating ligands, we also present in this work the synthesis and

Chart 2. Group 10 metal complexes of the oxazolinylamines reported in this work.



1



M = Pt (**2**), Pd (**3**)

characterization of group 10 metal complexes of ligands of type **I** and **V**, including an X-ray structural determination of a Pd(II) complex of **V** (Chart 2, **3**).

Experimental section

General considerations

Reagents were obtained from commercial sources and used as supplied unless otherwise indicated. These were of American Chemical Society (ACS) grade or finer. Solvents were dried and deoxygenated either by N_2 purge followed by passage through alumina columns (Innovative Technology or MBraun solvent purification systems) or by distillation under N_2 from the appropriate drying agent. All reactions were carried out under N_2 atmosphere using standard Schlenk techniques unless stated otherwise. Amino alcohols were prepared by the reduction of corresponding amino acids using a standard procedure (22). The metal complexes, *trans*-$PdCl_2(PhCN)_2$ and $PtCl_2(SMe_2)_2$, were prepared according to literature procedures (23, 24).

Thin-layer chromatography was performed using 250 μm silica gel glass plates with fluorescent indicator (254 nm, Rose Scientific, Edmonton, Alberta) and viewed by exposure to UV light and (or) immersion in a staining solution (ninhydrin, $KMnO_4$, or phosphomolybdic acid) followed by heating. Flash chromatography was performed using ACP ultra pure silica gel, 60 Å, 230–400 mesh (Silicycle, Québec, Quebec), using the eluent(s) specified. All solvent mixtures are reported as volume percentages.

^1H, $^{13}C\{^1H\}$, $^{19}F\{^1H\}$, correlated spectroscopy (COSY), and heteronuclear multiple quantum coherence (HMQC) NMR data were recorded on a 400 MHz Varian Mercury (400.085 MHz for ^1H, 100.602 MHz for ^{13}C, 376.458 MHz for ^{19}F) or a 400 MHz Varian Inova spectrometer (399.762 MHz for ^1H, 100.520 MHz for ^{13}C). Unless otherwise indicated, spectra were recorded at room temperature (RT) in a $CDCl_3$ solution using residual solvent proton (relative to external $SiMe_4$, δ 0.00) or solvent carbon (relative to external $SiMe_4$, δ 0.00) as an internal reference. Downfield shifts were taken as positive. Data for the ^1H NMR spectra are reported as follows: chemical shift (δ), multiplicity, integration, assignment, and coupling constant(s). All coupling constants are reported in Hertz (Hz) and the spin multiplicities are indicated as follows: singlet (s), triplet (t), quartet (q), multiplet (m), pseudo (p), and broad (br). Peaks due to the minor geometrical (*E* or *Z* isomer) when present in ^1H or ^{13}C spectra are denoted by *. Fractional values for the ^1H NMR integrations indicate the relative concentrations of *E* and *Z* isomers in solution.

High resolution mass spectrometry data were recorded using a Finnigan MAT 8200 instrument. IR spectra were recorded using a Bruker Vector 33 FT-IR spectrometer; samples were run either neat between KCl plates or prepared as KBr pellets. Data are reported in cm^{-1}; peak intensities are given as follows: strong (s), medium (m), weak (w), very (v).

Syntheses of oxazolinylamine ligands

1-{(4S)-4-Benzyl-4,5-dihydro-oxazol-2-yl}-(2S)-2-methyl-propylamine-carbamic acid ester 9H-fluoren-9-ylmethyl (4)

The title compound was made according to the method of Rajaram and Sigman (4). ^1H NMR (DMSO-d_6, 353 K) δ: 0.89 (pt, 6H, $CH(CH_3)_2$), 2.00 (m, 1H, $CH(CH_3)_2$), 2.70 (dd, 1H, $CHH'Ph$, $^2J_{HH}$ = 13.8, $^3J_{HH}$ = 6.8), 2.85 (dd, 1H, $CHH'Ph$, $^2J_{HH}$ = 13.6, $^3J_{HH}$ = 6.4), 3.93 (pt, 1H, ox $OCHH'$), 4.03 (pt, 1H, ox $OCHH'$), 4.23–4.36 (m, 5H, Fmoc C*H*, Fmoc CH_2, NHC*H*, ox NC*H*), 7.18 (m, 1H, Ph), 7.22–7.26 (m, 4H, Ph), 7.32 (m, 2H, Fmoc Ar), 7.39 (t, 2H, Fmoc Ar, $^3J_{HH}$ = 7.6), 7.72 (pt, 2H, Fmoc Ar), 7.87 (d, 2H, Fmoc Ar, $^3J_{HH}$ = 7.6). $^{13}C\{^1H\}$ NMR δ: 18.40, 19.15, 30.17, 41.15, 46.66, 54.81, 65.66, 66.53, 71.31, 120.07, 125.32, 125.36*, 126.09, 127.01, 127.61, 128.15, 129.25, 138.23, 140.69*, 143.76*, 143.85, 156.05, 165.55*. HRMS calcd. for $C_{29}H_{30}N_2O_3$: 454.2256; found: 454.2268.

1-{(4S)-4-Benzyl-4,5-dihydro-oxazol-2-yl}-(2S)-2-methyl-propylamine (5)

The synthesis by Rajaram and Sigman (4) was modified to use Et_2NH instead of piperidine. A 50 mL round-bottomed flask was charged with **4** (0.303 g, 0.662 mol) and MeOH (6 mL) was added to give a white suspension. Et_2NH (5 mL) was added over a period of 10 min at RT. The resulting pale beige solution was stirred for 30 min. The solution was concentrated in vacuo and the residue was purified by silica gel chromatography (MeOH–CH_2Cl2 10%–20%). The title compound was obtained as a beige oil. Yield 0.154 g (97%). ^1H NMR δ: 0.91 (d, 3H, $CH(CH_3)_2$, $^3J_{HH}$ = 6.8), 0.93 (d, 3H, $CH(CH_3)_2$, $^3J_{HH}$ = 6.8), 1.77 (br s, 2H, NH_2), 1.91 (m, 2H, $CH(CH_3)_2$, $^3J_{HH}$ = 6.8), 2.62 (dd, 1H, $CHH'Ph$, $^2J_{HH}$ = 13.6, $^3J_{HH}$ = 8.4), 3.06 (dd, 1H, $CHH'Ph$, $^2J_{HH}$ = 13.6, $^3J_{HH}$ = 5.2), 3.28 (d, 1H, NH_2CH, $^3J_{HH}$ = 5.2), 3.97 (dd, 1H, $OCHH'$, $^2J_{HH}$ = 8.8, $^3J_{HH}$ = 7.2), 4.16 (pt, 1H, $OCHH'$), 4.36 (m, 1H, NC*H*), 7.16–7.29 (m, 5H, Ph). $^{13}C\{^1H\}$ NMR δ: 17.79, 19.58, 32.38, 42.02, 55.77, 67.17, 72.10, 126.74, 128.75, 129.10, 129.17, 129.30, 129.49. HRMS calcd. for $C_{14}H_{21}N_2O$: 233.1660; found: 233.1648.

Syntheses of Fmoc- and Cbz-protected pyrrolidinyloxazolines

Compounds **7** and **9** were made according to modifications to the methods reported by McManus et al. (10), who developed them for the analogous Cbz-protected pyrrolidine derivatives **8** and **10**. Room temperature spectroscopic data for **8** and **10** matched those given in the literature. However, high-temperature NMR spectroscopic data were acquired by us to ensure that the reported splitting and broadening of peaks was in fact due to *E* and *Z* isomers arising from the amide and (or) carbamate (Cbz) bonds and not instead to the presence of diastereomers resulting from epimerization. This

determination was made based on the coalescence at high temperature of the isopropyl methyl peaks from a multiplet into two doublets of equal intensity and of the benzyl CH_2 multiplet into a sharp singlet. Both sets of data (low and high temperatures) are given for comparison.

Compounds **11** and **12** were prepared by deprotection of the Cbz group using Pd–C and H_2 gas as the hydrogen source. This differed from the procedure of McManus et al. (10), which used cyclohexene as the hydrogen source.

(2S)-Chlorocarbamoyl-pyrrolidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (6)

Thionyl chloride (1.29 mL, 17.8 mmol) was added dropwise over a period of 2 min to a 100 mL round-bottomed flask charged with Fmoc-Pro-OH (3.38 g, 10.0 mmol) and dry toluene (30 mL). The mixture was heated to dissolve all solids and held at reflux for 2 h. The yellow solution was cooled to RT, then concentrated in vacuo to afford a yellow oil, which crystallized when stored at 5 °C. The product was used without further purification. IR (neat) ν: 1793 (s, C=O COCl), 1707 (s, C=O Fmoc).

(2S)-{(1S)-Hydroxylmethyl-2-methyl-propylcarbamoyl}-pyrrolidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (7)

A solution of L-valinol (0.290 g, 2.40 mmol) and NEt_3 (0.390 mL, 2.80 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise to a 100 mL Schlenk tube containing **6** (1.00 g, 2.80 mmol) and dry CH_2Cl_2 (30 mL) that had been cooled to 0 °C and flushed with N_2. The mixture was stirred at 0 °C for 20 min, warmed to RT, and stirred overnight. The mixture was concentrated to ~15 mL and washed with satd. aq. NH_4Cl (3 × 50 mL), H_2O (2 × 50 mL), and brine (50 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel chromatography (MeOH–CH_2Cl_2 2%) to afford a nearly colourless oil. Yield 0.91 g (91%). ^{1}H NMR δ: 0.87 (d, 3H, CH(CH_3)$_2$, $^3J_{HH}$ = 6.8), 0.89 (d, 3H, CH(CH_3)$_2$, $^3J_{HH}$ = 6.8), 1.81–2.02 (m, 4H, CH(CH$_3$)$_2$, pyr NCH$_2$CH_2, pyr NCHCHH'), 2.16–2.30 (m, 1H, pyr NCHCHH′), 3.41–3.66 (m, 6H, pyr NCH_2, CONHCH, CH_2OH, OH), 4.21 (pt, 1H, Fmoc CH), 4.32–4.45 (m, 4H, Fmoc OCH_2, pyr NCH), 6.37* (br s, 0.3H, CONH), 6.83 (d, 0.7H, CONH, $^3J_{HH}$ = 6.8), 7.30 (pt, 2H, Fmoc Ar), 7.39 (pt, 2H, Fmoc Ar), 7.57 (d, 2H, Fmoc Ar, $^3J_{HH}$ = 7.6), 7.75 (d, 2H, Fmoc Ar, $^3J_{HH}$ = 7.2). ^{13}C{^{1}H} NMR δ: 18.79, 19.78, 24.86, 28.78*, 29.04, 47.33, 57.57, 61.01, 63.68, 68.00, 120.24, 125.21, 127.30, 128.00, 141.49, 143.91, 156.43, 172.56. HRMS calcd. for $C_{25}H_{31}N_2O_4$: 423.2292; found: 423.2278.

(2S)-{(1S)-Hydroxylmethyl-2-methyl-propylcarbamoyl}-pyrrolidine-1-carboxylic acid benzyl ester (8)

The title compound was made according to the procedure reported by McManus et al. (10). ^{1}H NMR (298 K) δ: 0.84 (pd, 3H, CH(CH_3)$_2$), 0.87 (d, 3H, CH(CH_3)$_2$, $^3J_{HH}$ = 7.2), 1.80 (m, 1H, CH(CH$_3$)$_2$), 1.91 (m, 2H, pyr NCH$_2$CH_2), 2.17 (br s, 1H, pyr NCHCHH′), 2.32 (br s, 1H, pyr NCHCHH'), 3.46–3.66 (m, 5H, CH_2OH, NHCH, pyr NCH_2), 4.35 (m, 1H, pyr NCH), 5.06–5.20 (m, 2H, Cbz OCH_2), 6.19 (s, 0.4H, CONH), 6.75 (s, 0.6H, CONH), 7.13–7.38 (m, 5H, Cbz Ar). ^{1}H NMR (353 K) δ: 0.84 (d, 3H, CH(CH_3)$_2$, $^3J_{HH}$ = 6.8), 0.88 (d, 3H, CH(CH_3)$_2$, $^3J_{HH}$ = 6.8), 1.81 (m, 1H, CH(CH$_3$)$_2$), 1.91 (m, 3H, pyr NCH$_2$CH_2, pyr NCHCHH′), 2.28 (br s, 1H, pyr NCHCHH'), 3.49–3.68 (m, 5H, CH_2OH, NHCH, pyr NCH_2), 4.35 (m, 1H, pyr NCH), 5.15 (s, 2H, Cbz OCH_2), 7.28–7.36 (m, 5H, Cbz Ar).

(2S)-2-{(4S)-4-Isopropyl-4,5-dihydro-oxazol-2-yl}-pyrrolidine-1-carboxylic acid 9H-fluoren-9-ylmethyl ester (9)

In a 100 mL Schlenk tube, a solution of **7** (0.384 g, 95.0 mmol) in dry CH_2Cl_2 (50 mL) was cooled to –78 °C. Diethylaminosulfur trifluoride (DAST) (0.137 mL, 1.05 mmol) was added dropwise over 5 min and the resultant pale yellow solution was stirred at –78 °C for 1 h, warmed to RT over ~3 h, and stirred overnight. The mixture was poured into satd. aq. $NaHCO_3$ (70 mL). The aqueous layer was discarded and the organic layer was washed with H_2O (2 × 50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). Combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (EtOAc–hexanes 30%–50%) to afford the title compound as an off-white foam. Yield 0.31 g (85%). ^{1}H NMR δ: 0.80 (d, 3H, CH(CH_3)$_2$, $^3J_{HH}$ = 6.8), 0.84 (d, 3H, CH(CH_3)$_2$, $^3J_{HH}$ = 6.8), 1.61 (m, 1H, CH(CH$_3$)$_2$), 1.91 (m, 3H, pyr NCH$_2$CH_2, pyr NCHCHH′), 2.17 (m, 1H, pyr NCHCHH'), 3.83 (pq, 1H, Fmoc CH), 3.93 (pt, 1H, ox OCHH′), 4.17 (pt, 1H, ox OCHH'), 4.25 (m, 2H, pyr NCH_2), 4.35 (m, 1H, ox NCH), 4.45 (br d, 1H, Fmoc OCH_2, $^3J_{HH}$ = 8.8), 7.33 (pt, 2H, Fmoc Ar), 7.41 (pt, 2H, Fmoc Ar), 7.65 (d, 2H, Fmoc Ar, $^3J_{HH}$ = 7.6), 7.86 (d, 2H, Fmoc Ar, $^3J_{HH}$ = 7.2). ^{13}C{^{1}H} NMR δ: 18.12, 19.60*, 22.93*, 22.95, 28.14, 28.28*, 30.13, 31.76*, 46.49*, 46.60, 46.61, 47.25*, 55.61*, 55.62, 59.51, 59.76*, 61.30, 61.40*, 66.44, 66.99*, 120.11, 125.16, 125.31*, 125.69, 127.14*, 127.67, 127.68*, 128.21*, 128.90, 140.61*, 140.74, 143.39, 143.78*, 143.93, 143.94* 153.96, 171.65, 172.02*. HRMS calcd. for $C_{25}H_{28}N_2O_3$: 404.2100; found: 404.2107.

(2S)-2-{(4S)-4-Isopropyl-4,5-dihydro-oxazol-2-yl}-pyrrolidine-1-carboxylic acid benzyl ester (10)

The title compound was made according to the procedure reported by McManus et al. (10). ^{1}H NMR (DMSO-d_6, 298 K) δ: 0.73 (d, 3H, CH(CH_3)$_2$, $^3J_{HH}$ = 6.8), 0.80 (m, 3H, CH(CH_3)$_2$), 1.53–1.58 (m, 0.6H, CH(CH$_3$)$_2$), 1.59–1.66 (m, 0.4H, CH(CH$_3$)$_2$), 1.81–1.90 (m, 3H, pyr NCH$_2$CH_2, pyr NCHCHH′), 2.10–2.20 (m, 1H, pyr NCHCHH'), 3.73–3.78 (m, 1.2H, pyr NCH_2), 3.84–3.87 (m, 0.8H, pyr NCH_2), 3.90 (pt, 0.6H, ox OCHH'), 3.98 (pt, 0.4H, ox OCHH'), 4.07 (pt, 0.6H, ox OCHH′), 4.16 (pt, 0.4H, ox OCHH′), 4.41 (dd, 0.4H, pyr NCH, $^3J_{HH}$ = 3.2, 8.8), 4.46 (dd, 0.6H, pyr NCH, $^3J_{HH}$ = 2.8, 8.0), 4.98–5.12 (m, 2H, Cbz OCH_2), 7.29–7.36 (m, 5H, Cbz Ar). ^{1}H NMR (DMSO-d_6, 393 K) δ: 0.79 (d, 3H, CH(CH_3)$_2$, $^3J_{HH}$ = 6.8), 0.83 (d, 3H, CH(CH_3)$_2$, $^3J_{HH}$ = 6.8), 1.61 (m, 1H, CH(CH$_3$)$_2$), 1.89 (m, 3H, pyr NCH$_2$CH_2, pyr NCHCHH′), 2.17 (m, 1H, pyr NCHCHH'), 3.83 (pq, 1H, pyr NCH_2), 3.81 (pq, 1H, ox NCH), 3.92 (pt, 1H, ox OCHH'), 4.14 (m, 2H, ox OCHH′), 4.48 (pd, 1H, pyr NCH), 5.08 (s, 2H, Cbz OCH_2), 7.29–7.35 (m, 5H, Cbz Ar).

Syntheses of (4*S*)-4-isopropyl-2-pyrrolidin-(2*S*)-2-yl-4,5-dihydrooxazole (11)

By deprotection of Fmoc

A 100 mL round-bottomed flask charged with **9** (0.310 g,

0.810 mmol) and MeOH (10 mL) was cooled to 0 °C before Et_2NH (5 mL) was added dropwise. The mixture was warmed to RT with stirring over 1.5 h. Volatiles were removed in vacuo. The residue was purified by silica gel chromatography (MeOH–CH_2Cl_2 4%–10%) to afford **9** as a nearly colourless oil. Yield 0.30 g (55%). Spectroscopic data were identical to those reported by McManus et al. (10).

By deprotection of Cbz

A solution of **10** (1.0 g, 3.16 mmol) in MeOH (30 mL) was added slowly to a 100 mL Schlenk tube containing Pd–C 10% *w/w* (0.30 g, 30 wt%.). The flask was purged with H_2 and was stirred under H_2 atmosphere at RT for 24 h. The suspension was filtered through a pad of Celite that was subsequently rinsed with MeOH (30 mL). The filtrate was concentrated in vacuo to give a pale yellow oil that was purified by silica gel chromatography (MeOH–CH_2Cl_2 5%) to afford **11** as a colourless oil. Yield 0.35 g (61%). Spectroscopic data were identical to those reported by McManus et al. (10).

Synthesis of (4S)-4-Benzyl-2-pyrrolidin-(2S)-2-yl-4,5-dihydrooxazole (12)

A solution of **18** (0.990 g, 2.70 mmol) in MeOH (40 mL) was deprotected according to the method described in the immediately preceding section. Yield 0.19 g (30%). Spectroscopic data matched those reported by McManus et al. (10).

Synthesis of cyanopyrrolidine derivatives

Our syntheses of **13** and **15** are modifications of those reported by Wallén et al. (25) for the analogous Boc-protected pyrrolidines **14** and **16**. The compounds were previously made by a different route by Cobb et al. (26, 27); they are now commercially available but are very expensive. To the best of our knowledge, only RT ^{1}H NMR characterization data have been reported in the open literature.

(2S)-2-Carbamoyl-pyrrolidine-1-carboxylic acid benzyl ester (13)

Ethyl chloroformate (3.99 mL, 41.7 mmol) was added dropwise to a cooled solution (–5 °C) of Cbz-Pro-OH (4.60 g, 18.5 mmol), NEt_3 (2.57 mL, 18.5 mmol), and THF (60 mL) in a 100 mL round-bottomed flask. The resulting slurry was stirred for 20 min at –5 °C and satd. aq. NH_4OH (5 mL) was then added dropwise. The solution was stirred at RT for 18 h. Volatiles were removed in vacuo and the residue was taken up in EtOAc (60 mL). The undissolved white precipitate was filtered off and rinsed with EtOAc (30 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give an off-white amorphous solid, which was used without further purification. Yield 4.59 g (>99%). ^{1}H NMR δ: 1.87–1.99 (m, 2H, NCH_2CH_2), 2.16 (br s, 1H, NCHC*H*H′), 2.31 (br s, 1H, NCHCH*H′*), 3.44–3.54 (m, 2H, NCH_2), 4.28–4.35 (m, 1H, NC*H*), 5.10–5.18 (m, 2H, OCH_2Ar), 5.74* (br s, 0.5H, NH_2), 5.84 (br s, 0.5H, NH_2), 6.06* (br s, 0.5H, NH_2), 6.72 (br s, 0.5H, NH_2), 7.34 (m, 5H, Cbz Ar). ^{13}C{^{1}H} NMR δ: 23.39*, 24.28, 28.73, 30.97*, 46.78, 47.23*, 60.00, 60.38*, 67.04, 127.62, 127.87, 128.30, 136.20, 154.67*, 155.65, 174.63, 175.50*. HRMS calcd. for $C_{13}H_{16}N_2O_3$: 248.1161; found: 248.1169.

(2S)-2-Carbamoyl-pyrrolidine-1-carboxylic acid tert-butyl ester (14)

The title compound was made by the method of Wallén et al. (25). Yield >99%. ^{1}H NMR (DMSO-d_6, 353 K) δ: 1.39 (m, 9H, $O(CH_3)_3$), 1.72–1.87 (m, 3H, $NCH_2CH_2CH_2$, NCH_2CH_2CHH'), 2.07 (m, 1H, NCH_2CH_2CHH'), 3.28–3.40 (m, 2H, NCH_2) 4.03 (pdd, 1H, NC*H*CN). ^{13}C{^{1}H} NMR (DMSO-d_6) δ: 23.85, 24.54*, 28.68, 28.80*, 30.66*, 31.66, 46.06, 47.01, 47.22*, 59.99*, 60.20, 78.99, 79.08*, 154.00, 154.28*, 174.94*, 175.32. IR (neat) ν: 3406 (m, N-H), 1683 (s, CO amide), 1403 (m, C-N). HRMS calcd. for $C_{10}H_{18}O_3N_2$: 214.1317; found: 214.1312.

(2S)-2-Cyano-pyrrolidine-1-carboxylic acid benzyl ester (15)

A 250 mL round-bottomed flask was charged with **13** (4.37 g, 17.6 mmol) and dry THF (60 mL). The solution was cooled to 0 °C and NEt_3 (5.88 mL, 42.3 mmol) was added dropwise. Against a flow of N_2, trifluoroacetic anhydride (TFAA) (2.94 mL, 21.1 mmol) was added dropwise and the mixture was stirred for 1 h at 0 °C. The reaction was quenched by the addition of H_2O (25 mL) and all volatiles were removed in vacuo. The residue was taken up in CH_2Cl_2 (50 mL) and H_2O (20 mL) was added. The organic layer was washed with satd. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated in vacuo. The resultant yellow oil was used without further purification. Yield 2.44 g (83%). ^{1}H NMR δ: 2.04–2.31 (m, 4H, NCH_2CH_2, $NCH_2CH_2CH_2$), 3.38–3.44 (m, 1H, NCH_2), 3.55–3.62 (m, 1H, NCH_2), 4.54–4.63 (m, 1H, NC*H*CN), 5.14–5.20 (m, 2H, OCH_2), 7.26–7.43 (m, 5H, Cbz Ar). ^{1}H NMR (333 K) δ: 2.01–2.30 (m, 4H, NCH_2CH_2), 3.42–3.48 (m, 1H, NCH_2), 3.56–3.61 (m, 1H, NCH_2), 4.58 (br s, 1H, NC*H*CN), 5.20 (s, 2H, OCH_2), 7.32–7.40 (m, 5H, Cbz Ar). ^{13}C{^{1}H} NMR δ: 23.68, 24.58*, 30.72*, 31.69, 45.86*, 86.26, 46.92, 47.45*, 67.57*, 67.75, 118.63*, 118.81, 128.08, 128.22, 128.50, 135.80*, 135.99, 153.54*, 154.24. HRMS calcd. for $C_{13}H_{14}N_2O_2$: 230.1055; found: 230.1061.

(2S)-2-Cyano-pyrrolidine-1-carboxylic acid tert-butyl ester (16)

The title compound was made using the method of Wallén et al. (25). Yield 82%. ^{1}H NMR δ: 1.46–1.50 (m, 9H, $C(CH_3)_3$), 2.01–2.24 (m, 4H, NCH_2CH_2, $NCH_2CH_2CH_2$), 3.30–3.39 (m, 1H, NC*H*H′), 3.42–3.55 (m, 1H, NCH*H′*), 4.42 (pdd, 0.5H, NC*H*), 4.55 (pd, 0.5H, NC*H*). ^{1}H NMR (DMSO-d_6, 353 K) δ: 1.46 (s, 9H, $C(CH_3)_3$), 1.94 (m, 2H, NCH_2CH_2), 2.12–2.25 (m, 2H, $NCH_2CH_2CH_2$), 3.34 (m, 2H, NCH_2), 4.60 (dd, 1H, NC*H*, $^3J_{HH}$ = 3.6, 8.0). ^{13}C{^{1}H} NMR δ: 24.13, 25.01*, 28.62, 30.88*, 31.71, 46.37, 46.67*, 47.41*, 47.55, 80.65, 120.53, 153.16, 153.83*. IR (neat, cm^{-1}) ν: 2980 (m, C-H), 2240 (vw, C≡N), 1701 (vs, C=O). HRMS calcd. for $C_{10}H_{16}O_2N_2$: 196.1212; found: 196.1213.

(2S)-2-Cyano-pyrrolidine·TFA salt (17)

Via an addition funnel, TFA (34 mL) was added dropwise over a period of 10 min to a 100 mL round-bottomed flask containing a cooled (0 °C) CH_2Cl_2 (124 mL) solution of **16** (2.44 g, 12.4 mmol). The solution was stirred for 2 h at 0 °C, then concentrated in vacuo to give an off-white oil. Et_2O (30 mL) was added slowly to produce a white crystalline solid. The slurry was filtered, and the solid rinsed with Et_2O (10 mL) before being dried under vacuum to obtain the

title compound as a white crystalline solid. Yield 1.10 g (56%), mp 92–94 °C. ^{1}H NMR (CD_3OD) δ: 2.07–2.33 (m, 3H, $NHCH_2CH_2$, $NHCHCHH'$), 2.43–2.52 (m, 1H, $NHCHCHH'$), 3.35–3.47 (m, 2H, $NHCH_2$), 4.68 (pt, 1H, NHCH), 4.92 (s, 1H, NH). $^{13}C\{^1H\}$ NMR δ: 23.15, 29.65, 45.14, 45.97, 116.53. $^{19}F\{^1H\}$ NMR δ: –77.37 (s). IR (neat) ν: 2261 (vw, C≡N), 1681 (vs, C=O). HRMS calcd. for $C_5H_9N_2$: 97.0766; found 97.0760; calcd. for $C_2F_3O_2^-$: 112.9850; found: 112.9683.

Syntheses of pyrrolidinyloxazolines via 2-cyanopyrrolidines

(2S)-2-{(4S)-4-Isopropyl-4,5-dihydro-oxazol-2-yl}-pyrrolidine-1-carboxylic acid benzyl ester (10)

A solution of **15** (1.55 g, 6.70 mmol) and L-valinol (1.08 g, 10.5 mmol) in chlorobenzene (120 mL) was added to a 250 mL round-bottomed flask containing $ZnCl_2$ (1.43 g, 10.5 mmol). The mixture was heated to reflux for 24 h. Solvent was removed in vacuo and the yellow residue was purified by silica gel chromatography (EtOAc–Hexanes 30%). The title compound was obtained as a yellow oil. Yield 1.82 g (85%). Spectroscopic data for this compound matched those reported by McManus et al. (10).

(2S)-2-{(4S)-Benzyl-4,5-dihydro-oxazol-2-yl}-pyrrolidine-1-carboxylic acid benzyl ester (18)

A similar procedure to that outlined earlier was carried out using **15** (0.605 g, 2.63 mmol), L-phenylalaninol (0.665 g, 4.40 mmol), and $ZnCl_2$ (0.599 g, 4.40 mmol) to obtain **18**. Yield 0.99 g (quant.). Spectroscopic data matched those reported by McManus et al. (10).

Syntheses of oxazolinylamine metal complexes

{1-((4S)-4-Benzyl-4,5-dihydro-oxazol-2-yl)-2-methylpropylamine}dichloroplatinum(II) (1)

A 100 mL round-bottomed flask was charged with $PtCl_2(SMe_2)_2$ (0.084 g, 0.215 mmol), **5** (0.050 g, 0.215 mmol), and 1,2-dichloroethane (20 mL). The mixture was heated to reflux and held for 7 h. After cooling to RT, stirring was continued overnight (18 h). Volatiles were removed in vacuo and Et_2O (10 mL) was added. The suspension was sonicated for 5 min to produce a dark yellow powder, which was filtered and rinsed with Et_2O (10 mL). The yellow solid (isolated as a mixture of diastereomeric metal complexes) was dried under vacuum. Yield 0.10 g (95%). ^{1}H NMR δ: 0.83 (d, 3H, $CH(CH_3)_2$, $^3J_{HH}$ = 6.8), 0.95 (d, 3H, $CH(CH_3)_2$, $^3J_{HH}$ = 6.8), 1.07* (d, 6H, $CH(CH_3)_2$, $^3J_{HH}$ = 6.8), 1.13* (d, 6H, $CH(CH_3)_2$, $^3J_{HH}$ = 6.8), 2.19 (m, 1H, $CH(CH_3)_2$), 2.34* (m, 1H, $CH(CH_3)_2$), 2.68* (dd, 1H, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 10.4, $CHH'Ph$), 3.01 (dd, 2H, $CHH'Ph$, $^2J_{HH}$ = 13.6, $^3J_{HH}$ = 8.4), 3.38 (dd, 1H, $CHH'Ph$, $^2J_{HH}$ = 13.6, $^3J_{HH}$ = 2.6), 3.73* (dd, 1H, $CHH'Ph$, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 2.4), 4.03 (dd, 1H, NH_2CH, $^3J_{HH}$ = 10.4, $^3J_{HH}$ = 5.2), 4.36–4.63 (m, 6H, NH_2CH*, NCH, NCH*, $OCHH'$, $OCHH'$*, $OCHH'$*), 4.78 (pt, 1H, OCH), 5.84 (t, 2H, NH_2), 5.98* (t, 2H, NH_2), 7.13–7.39 (m, 10H, Ph, Ph*). Anal. calcd. for $C_{14}H_{20}Cl_2N_2OPt$: C 33.74, H 4.05, N 5.62; found: C 33.99, H 4.18, N, 5.32. Crystals of the title compound suitable for X-ray diffraction analysis were grown by slow diffusion of iPr_2O into a concentrated solution of **1** in CH_2Cl_2.

Dichloro{(4S)-4-isopropyl-2-pyrrolidin-(2S)-2-yl-4,5-dihydro-oxazole}platinum(II) (2)

A 50 mL round-bottomed flask was charged with $PtCl_2(SMe_2)_2$ (0.227 g, 0.580 mmol), **11** (0.107 g, 0.580 mmol), and 1,2-dichloroethane (20 mL). The mixture was heated to reflux and held for 4 h. The suspension was filtered and rinsed with Et_2O (10 mL). The yellow solid was dried under vacuum. Yield 0.11 g (42%). ^{1}H NMR (DMSO-d_6) δ: 0.74 (d, 3H, $CH(CH_3)_2$, $^3J_{HH}$ = 6.8), 0.79 (d, 3H, $CH(CH_3)_2$, $^3J_{HH}$ = 6.8), 1.68 (m, 1H, $NHCH_2CHH'$), 1.91 (m, 1H, $NHCHCHH'$), 2.00 (m, 1H, $NHCH_2CHH'$), 2.17 (m, 1H, $NHCHCHH'$), 2.47 (m, 1H, $CH(CH_3)_2$), 2.99 (m, 1H, $NHCHH'$), 3.35 (m, 1H, $NHCHH'$), 4.01 (m, 1H, NHCH), 4.27 (pq, 1H, NCH), 4.63 (t, 1H, $OCHH'$, $^2J_{HH}$ = 9.2), 4.77 (m, 1H, $OCHH'$, $^2J_{HH}$ = 9.2, $^3J_{HH}$ = 4.4), 7.29 (q, 1H, NH, $^3J_{HH}$ = 4.8). Anal. calcd. for $C_{10}H_{18}Cl_2N_2OPt$: C 26.79, H 4.05, N 6.25; found: C 26.62, H 4.04, N 6.12.

Dichloro{(4S)-4-isopropyl-2-pyrrolidin-(2S)-2-yl-4,5-dihydro-oxazole}palladium(II) (3)

A solution of **11** (87.0 mg, 0.500 mmol) in CH_2Cl_2 (20 mL) was added to a 25 mL round-bottomed flask containing *trans*-$PdCl_2(PhCN)_2$ (19.2 mg, 0.500 mmol). The resultant orange solution was stirred for 3 h at RT. An orange precipitate began to form within the first 5 min of stirring. The solid was collected by filtration and rinsed with Et_2O (20 mL), then dried under vacuum. Yield 0.12 g (66%). ^{1}H NMR (DMSO-d_6) δ: 0.71 (pt, 6H, $CH(CH_3)_2$), 1.64 (m, 1H, $NHCH_2CHH'$), 1.82–1.92 (m, 2H, $NHCHCHH'$, $NHCH_2CHH'$), 2.07 (m, 1H, $NHCHCHH'$), 2.39 (m, 1H, $CH(CH_3)_2$), 2.84 (m, 1H, $NHCHH'$), 3.23 (m, 1H, $NHCHH'$), 3.86 (m, 1H, NCH), 4.16 (m, 1H, NHCH), 4.47 (pt, 1H, $OCHH'$), 4.60 (pq, 1H, $OCHH'$), 6.58 (m, 1H, NH). Anal. calcd. for $C_{10}H_{18}Cl_2N_2OPd$: C 33.40, H 5.05, N 7.79; found: C 33.66, H 5.25, N 7.48. Crystals of the title compound suitable for X-ray diffraction analysis were grown by slow diffusion of iPr_2O into a concentrated solution of **3** in CH_2Cl_2.

Crystallography

Crystal data for **3** were collected at low temperature (150 K) using a Nonius Kappa CCD area detector diffractometer running COLLECT software (Nonius BV, Delft, The Netherlands, 1997–2002). The unit cell parameters were calculated and refined from the full data set. Crystal cell refinement and data reduction were carried out using HKL2000 DENZO-SMN (Otwinowski and Minor 1997), and absorption correction was applied using HKL2000 DENZO-SMN (SCALEPACK). The SHELXTL PC V6.14 for Windows NT (Bruker AXS Inc., Madison, Wisconsin) suite of programs was used to solve the structure by direct methods. Subsequent Fourier difference syntheses allowed the remaining atoms to be located. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atom positions were calculated geometrically and were included as riding on their respective carbon atoms. The absolute structure parameter for **3** was 0.00 (5), which indicated that the correct diastereomer had been refined and that there

Table 1. Crystal data and refinement parameters for **3**.

Empirical formula	$C_{10}H_{18}Cl_2N_2OPd$
Formula weight (g mol^{-1})	359.56
Temperature (K)	150(2)
Wavelength (Å)	0.710 73
Crystal system	Monoclinic
Space group	$P2_1$
a (Å)	6.8508(3)
b (Å)	10.0099(5)
c (Å)	9.7236(4)
α, γ (°)	90
β (°)	100.676(2)
Volume	655.26(5)
Z	2
Density (calcd., g cm^{-3})	1.822
Absorption coefficient (mm^{-1})	1.805
F(000)	360
Crystal size (mm)	0.47 × 0.20 × 0.17
Range for data collection (°)	2.95 to 27.47
Index ranges	$-8 \le h \le 8$, $-11 \le k \le 12$, $-12 \le l \le 12$
Reflections collected	8168
Independent reflections (R_{int})	2781 (0.0460)
Absorption correction	Semi-empirical from equivalents
Maximum and minimum transmission	0.7430 and 0.4810
Refinement method	Full-matrix least-squares on F^2
Data, restraints, parameters	2781, 1, 146
Goodness-of-fit on F^2	1.119
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0293, $wR2$ = 0.0723
R indices (all data)	$R1$ = 0.0317, $wR2$ = 0.0733
Absolute structure parameter	0.00(5)
Largest difference in peak and hole (e Å^{-3})	1.125 and –0.703

was no sign of racemic twinning. The crystal data and refinement parameters for **3** are listed in Table 1.[2]

Results and discussion

Aminomethyl-substituted ligands and complexes

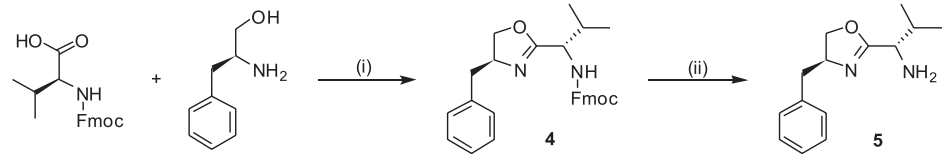
The oxazolinylamine ligand **5** was made according to a minor modification of the method by Rajaram and Sigman (4) (Scheme 2). The reaction between Fmoc-protected L-valine and L-phenylalaninol using PPh_3–CCl_4 as the activator and diisopropylethylamine (DIPEA) as the base for both the initial amide bond formation and the subsequent ring closing to install the oxazoline gave the protected precursor **4**. Deprotection by diethylamine gave the desired ligand **5** in 54% overall yield.

The Pt(II) complex **1** was made in 95% yield by the equimolar reaction of **5** and $PtCl_2(SMe_2)_2$ in a refluxing dichloroethane solution (Scheme 3). This yellow compound was soluble in moderately polar chlorinated organic solvents but insoluble in nonpolar solvents such as diethyl ether and hexanes.

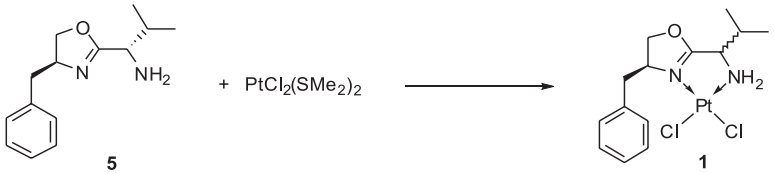
The ^{1}H NMR spectrum of the free ligand **5** was consistent, as expected from previous work (4), with a single diastereomer (e.g., the isopropyl methyl peaks appeared as the expected two doublets at δ: 0.91, 0.93). However, the ^{1}H NMR spectrum of the corresponding Pt(II) complex **1** was dependent on the time allowed for the reaction between $PtCl_2(SMe_2)_2$ and **5**. It showed a "doubling" of all of the peaks (e.g., the isopropyl methyl peaks appeared as two pairs of doublets of almost equal intensity at δ: 0.83, 0.95 and 1.07, 1.13) when the reaction time was longer than 18 h; shorter reaction times gave simpler spectra in which doubling was greatly diminished. This phenomenon was consistent with the presence of a pair of diastereomeric metal complexes, which was confirmed by X-ray crystallography. Although the structure of **1** could not be refined sufficiently well for publication, the basic atom connectivity could be determined unequivocally. The unit cell contained equal

[2] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5124. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 633044 contains the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

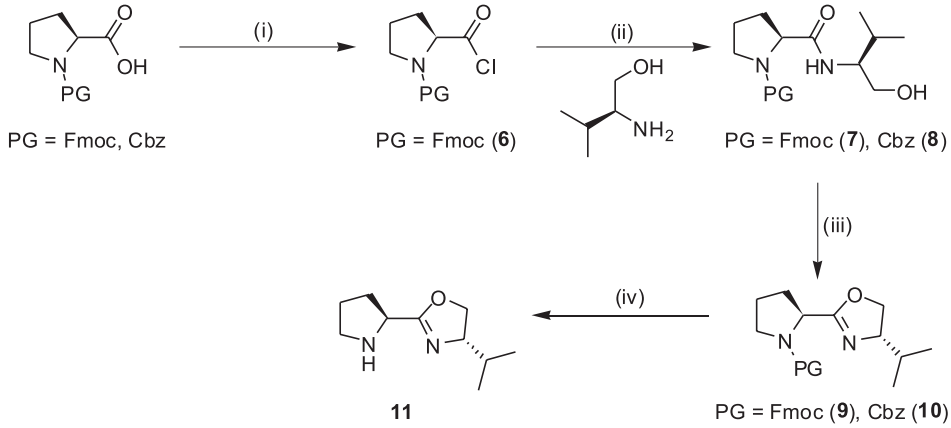
Scheme 2. Synthesis of the oxazolinylamine ligand **5** by the method of Rajaram and Sigman. (*i*) PPh_3–CCl_4–DIPEA; (*ii*) Et_2NH.



Scheme 3. Synthesis of **1**.



Scheme 4. Synthesis of pyrrolidinyloxazolines by the method of McManus et al. (*i*) $SOCl_2$, toluene, 5 h; (*ii*) NEt_3, CH_2Cl_2; (*iii*) NEt_3, DAST, CH_2Cl_2, –78 °C; (*iv*) PG = Fmoc: Et_2NH; PG = Cbz: H_2, 10% Pd–C, MeOH.



numbers of both the expected *S,S*-diastereomer and the unexpected *S,R*-diastereomer of **1**. This showed that the stereocentre associated with the aminoalkyl chain was susceptible to epimerization under the relatively harsh conditions used for the coordination reaction. ^{1}H NMR data indicated that the epimerization could be minimized (<10%) by simply reducing the reaction time to ~8 h. This result is important because catalysts incorporating ligands of this type have typically been generated in situ and have therefore generally not been well characterized; therefore, relationships drawn between the absolute configuration of the active catalyst and the observed *ee* in the product(s) of an asymmetric reaction are necessarily of limited validity. A solution of free ligand in dichloroethane was heated to reflux in the absence of metal for 24 h and, despite some decomposition, no epimerization was seen by ^{1}H NMR spectroscopy.

Pyrrolidine-substituted ligands

The pyrrolidinyloxazoline ligand **11** was made according to Scheme 4 (PG = Fmoc). This general method has been applied previously to the synthesis of **11** (and **12**, not shown) by McManus et al. (10), who instead used the Cbz-protecting group. These workers noted that the NMR spectra of their intermediates **8** and **10** were complicated by a doubling of many of the peaks but did not provide a rationale for this phenomenon.

It is well-known that the *E* and *Z* isomers of amide bonds can be seen by NMR spectroscopy at RT. These are ususally evidenced by a coalescence of some (if not all) peaks at high temperature because of rapid chemical exchange of *E* and *Z* isomers. Given our experience with **1** (vide supra), we were concerned that the doubling observed for all of the compounds **7**–**11** may have resulted not only from the presence of *E* and *Z* isomers but also from diastereomers arising at some stage during ligand synthesis. Presumably, epimerization of the pyrrolidine stereocentre could occur via the intermediate acid chloride **6** or, less likely, during the DAST-induced oxazoline ring-closing step to form **9** and **10**. It has been shown by Wipf and co-workers (28) that DAST is able to induce this cyclization with less than 1.5% racemization of sensitive substrates.

McManus et al. did not report high-temperature NMR data for their compounds. Therefore, we repeated the syntheses of the Cbz-protected compounds and examined both them and our Fmoc-protected species closely by variable temperature NMR spectroscopy. For the open chain compounds **7** and **8**, we concentrated on peaks due to the amide N*H* proton, and for the oxazolines **9** and **10**, on those due to the isopropyl methyl protons. Figure 1*a* shows the amide region of the ^{1}H NMR spectrum of **8** at RT and at 155 °C; Fig. 1*b* shows the isopropyl methyl region of the ^{1}H NMR spectrum of **10** at RT, and at 70 °C in DMSO-d_6 solution.

Scheme 5. Synthesis of pyrrolidinyloxazolines by Zn-catalyzed cyclization of 2-cyanopyrrolidine and β-amino alcohols. (*i*) EtOC(O)Cl, NEt_3; (*ii*) NH_4OH; (*iii*) TFAA, NEt_3; (*iv*) TFA; (*v*) amino alcohol, $ZnCl_2$, PhCl; (*vi*) H_2, Pd–C.

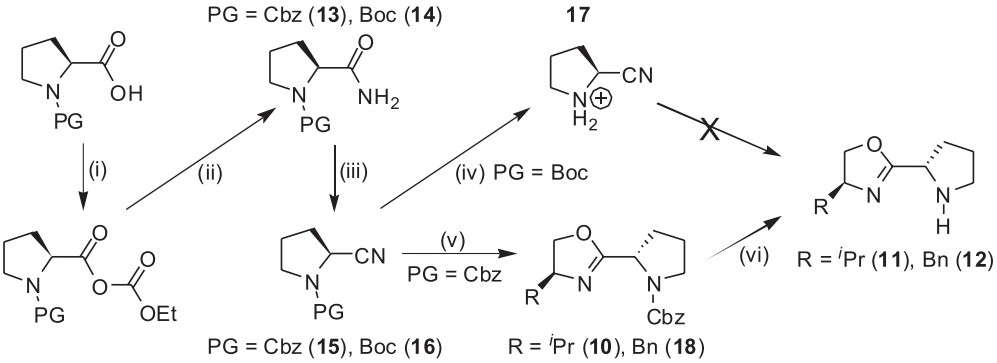
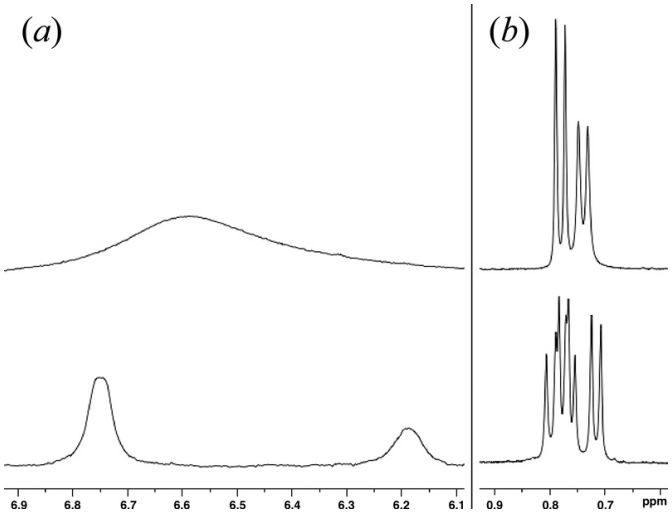


Fig. 1. (*a*) The δ 6.1–6.9 range of the ^{1}H NMR spectra of **8** at 155 °C (top) and at RT (bottom), and (*b*) the δ 0.6–0.9 range of the ^{1}H NMR spectra of **10** at 70 °C (top) and at RT (bottom) in DMSO-d_6 solution.



Coalescence of the peaks due to N*H* proton in **8** (from two broad singlets at δ: 6.18, 6.76 in the RT spectrum into a single broad peak at δ: 6.58 at 155 °C) and of those due to the isopropyl methyl protons in **10** (four doublets at δ: 0.73, 0.78, 0.79, 0.82 in the RT spectrum to two doublets at δ: 0.84, 0.88 at 70 °C) indicated that neither the acid chloride nor the DAST cyclization step were implicated in epimerization. The overall number, relative integrations, and splittings of the peaks in the high-temperature spectra were consistent with only a single diastereomer of the compound under study. These experiments implied that the likely cause of the doubling was not the presence of diastereomers but rather of *E* and *Z* isomers resulting from restricted rotation about the carbamate bond in **10** and the amide and (or) carbamate bond in **8**. The NMR spectra of our new Fmoc-protected analogues **7** and **9** were also complicated by the presence of *E* and *Z* isomers. These likewise simplified at high temperature.

Yields for the amide bond forming and cyclization steps in the Cbz- and Fmoc-protected pathways were not significantly different, being between 85% and 91%. However, differences arose in the final deprotection step. When PG = Cbz (Scheme 4), the deprotection was by hydrogenolysis; for PG = Fmoc, on the other hand, deprotection was achieved by treatment with base. These two routes gave isolated yields of 86% and 54%, respectively. The Fmoc deprotection was complicated by the decomposition of some of the intended product into an open chain peptide. The ^{1}H NMR spectra of the final products arising from the Cbz and Fmoc manifolds were identical and unequivocally consistent with the presence of only a single diastereomer.

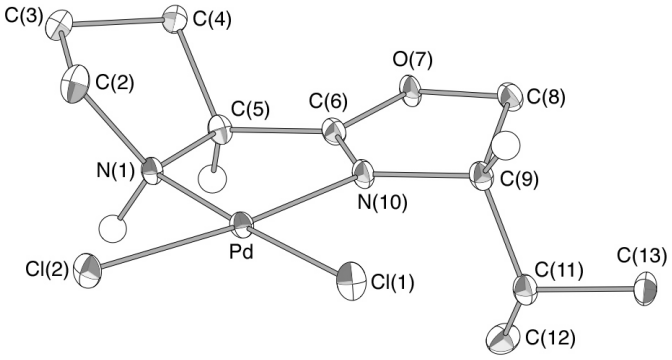
We investigated an alternate approach to the pyrrolidinyloxazolines starting from protected (2*S*)-2-cyanopyrrolidines (Scheme 5, **15** and **16**), which were made using a modification to the syntheses presented by the groups of Wállen (25) and Ley (26, 27). Judicious choice of protecting group was essential. When PG = Boc, there was no reaction between the cyanopyrrolidine **16** and the amino alcohol; moreover, given the acidic conditions, a putative Boc-protected pyrrolidinyloxazoline would be difficult to deprotect without destruction of the oxazoline ring. Cleavage of Boc prior to oxazoline formation gave the TFA salt **17**, which in our hands could not be induced to react with the amino alcohol either in the presence or absence of $ZnCl_2$ and (or) base. The Fmoc protecting group was also problematic because its corresponding cyanopyrrolidine (not shown) decomposed under the reaction conditions. Finally, we found that treatment of Cbz-protected (2*S*)-2-cyanopyrrolidine **15** with amino alcohols in the presence of $ZnCl_2$ at elevated temperature cleanly gave the intended Cbz-protected pyrrolidinyloxazolines **10** and **18**, which were easily deprotected by hydrogenolysis to give the intended products **11** and **12**.

This route had distinct advantages over the route developed by McManus et al. First, the Cbz-protected 2-cyanopyrrolidine **15** could be made quickly and in high yield (a few hours in ~83% overall yield); second, the diversity-introducing step was placed later in the synthesis; third, the overall cost was reduced by elimination of the expensive DAST reagent; and finally, the number of required purification steps was reduced (there was no need for purification until after $ZnCl_2$-mediated oxazoline formation).

Metal complexes

The Pd(II) complex **3** was made in 66% yield by the equimolar reaction of *trans*-$PdCl_2(PhCN)_2$ and **11** in CH_2Cl_2 solution at RT. The analogous Pt(II) complex **2** was also

Fig. 2. ORTEP representation of the molecular structure of **3** (ellipsoids drawn at 50% probability). Except for those associated with chiral centres, H-atoms have been omitted for clarity. All of the chiral centres have the *S*-configuration.



made in 42% yield by equimolar reaction of $PtCl_2(SMe_2)_2$ and **11** in dichloroethane at 80 °C.

The molecular structure of **3** is represented as a thermal ellipsoid plot in Fig. 2; selected bond distances and angles appear in Table 2. As expected, the coordination geometry about the metal was essentially square planar. The N(1)–Pd–N(10) and Cl(1)–Pd–Cl(2) angles were approximately 81.8° and 93.1°, respectively. Although the Pd–N(10) (Pd–oxazoline) distance (2.008(4) Å) was shorter than the Pd–N(1) (Pd–pyrrolidine) distance (2.054(4) Å), the difference was not reflected in a corresponding trans influence for the chloride ligands: the Pd–Cl bond lengths were nearly identical and approximately 2.30 Å. The Pd–N(1) distance was in the range of those typically observed for Pd(II) complexes of pyrrolidines (2.05–2.11 Å). The mean plane of the oxazoline ring was very nearly coincident with the mean coordination plane containing the metal centre and its four ligated atoms; these two planes intersected at an angle of 7.98°. The pyrrolidine ring adopted an envelope configuration in which C(3) rested 0.639 Å from the mean plane defined by C(2), N(1), C(5), and C(4). This plane made an angle of 53.68° with the mean plane of the oxazoline ring.

The absolute configurations of C(9) and C(5) were both *S*, which was consistent with the expected configurations based on the L-proline and L-valinol starting materials; no epimerization occurred either during the ligand synthesis or on coordination to the metal. These configurations allowed the quadrant analysis typically applied to chiral C_2-symmetric complexes to be superimposed on this formally C_1-symmetric compound. In the orientation shown in Fig. 2, the steric bulk of the ligand occupied the top left and bottom right quadrants; the near 180° C(11)–N(10)–N(1)–C(2) torsion angle of 172.33°, together with the similar C(11)–C(9)–N(10) and C(2)–N(1)–N(10) angles (111.67° and 127.76°, respectively), further strengthened the pseudo-C_2-symmetric approach to thinking about this ligand.

The solid-state structure of **3** featured weak intermolecular N–H...Cl interactions of 3.33 Å that were only very slightly longer than the sum of the van der Waals radii of N and Cl (3.30 Å); the N–H–Cl angle was 156.15°. These interactions in the solid state point to the possibility that the N*H* groups of coordinated pyrrolidine (as well as of oxazolidine (29) and, presumably, related nitrogen heterocycles) are noninnocent and may participate in catalytic cycles (30).

Table 2. Selected bond distances, bond angles, and torsion angles for **3** with standard deviations in parentheses.

Bond distances (Å)	
Pd–N(10)	2.008(4)
Pd–Cl(2)	2.3000(12)
Pd–N(1)	2.054(4)
Pd–Cl(1)	2.3040(13)
Bond angles (°)	
N(10)–Pd–N(1)	81.84(17)
N(1)–Pd–Cl(2)	90.50(11)
N(1)–Pd–Cl(1)	176.39(12)
N(10)–Pd–Cl(2)	172.16(13)
N(10)–Pd–Cl(1)	94.57(13)
Cl(2)–Pd–Cl(1)	93.08(5)
Torsion angles (°)	
Cl(2)–Pd–N(1)–C(2)	58.7(3)
Pd–N(10)–C(9)–C(11)	69.0(6)

Conclusion

We have successfully characterized the first simple *N,N′*-chelated Pt and Pd complexes of oxazolinylamine ligands of type **I** and **V**. Our finding that type **I** ligands may epimerize upon metal complexation illustrates the importance of proper characterization of complexes prior to their use as catalysts. We also highlight the importance of including high-temperature NMR data in the characterization of the *N*-protected intermediates to these ligands as proof of stereochemical purity. We have applied a shorter and more cost effective route to the synthesis of pyrrolidinyloxazoline ligands via the $ZnCl_2$-mediated cyclization of Cbz-protected (2*S*)-2-cyanopyrrolidine with amino alcohols. This allows for quicker and easier access to this important class of chiral ligands. The application of ligands of type **I** and **V** in the asymmetric allylic oxidation of cyclic alkenes is currently under investigation.

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