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Synthesis and characterization of new amine-imine ligands based on *trans*-2,5-disubstituted pyrrolidines

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Abstract: We present a modular synthesis of a new class of chiral N,N-chelating ligands containing the C₂-symmetric trans-2,5-disubstituted pyrrolidine moiety linked to a pyridine ring. (-)-2-[(2R,5R)-2,5-Dimethylpyrrolidin-1-ylmethyl]pyridine (11, (R,R)-MePMP), (-)-2-[2-((2R,5R)-2,5-dimethylpyrrolidin-1-yl)ethyl]pyridine (12, (R,R)-MePEP), and (+)-2-[(2R,5R)-2,5-diphenylpyrrolidin-1-ylmethyl]pyridine (13, (R,R)-PhPMP) have been prepared. The X-ray structure of the $(\eta^3$ -allyl)Pd complex of (R,R)-MePMP (11) is reported. (c) 1997 Elsevier Science Ltd. All rights reserved.

The C_2 -symmetric trans-2,5-disubstituted pyrrolidine moiety 1^1 has seen wide use as a chiral auxiliary for asymmetric synthesis.²⁻⁶ Isostructural 2,5-disubstituted borolanes (**2a** and **b**) and 2,5-disubstituted phospholanes (**3a** and **b**) are also extremely effective in recognizing prochiral substrates.⁷⁻⁹ Despite this, **1** has scarcely been used in ligands for transition metal-catalyzed asymmetric synthesis. Koga and co-workers have reported ligands **4-9** for use in enantioselective palladium-catalyzed allylic alkylations,^{10,11} and Shi et al.¹² recently reported the use of ligand **10** in the alkylation of aldehydes with diethylzinc. We report here a modular synthesis of a new class of ligands which contain the trans-2,5-disubstituted pyrrolidine moiety linked to a pyridine ring. Pyridine is a strong electron donor ligand, but, because of the delocalized π -framework, also has the capacity to be a strong electron acceptor depending on ring substituents.¹³ Electronic character can play an extremely important role in ligands for transition metal-catalyzed processes, affecting both rate and stereoselectivity,^{14,15} and the presence of the pyridine moiety should allow us to alter the electronic character of these ligands.



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Successful cyclization of (2S,5S)-2,5-hexane dimesylate^{16,17} to form *N*,*N*-chelating amine–imine ligands **11** and **12** was accomplished with commercially available 2-(aminomethyl)pyridine and 2-(aminoethyl)pyridine (Scheme 1). Both ligands were synthesized using a 5:1 amine/dimesylate ratio according to the procedure reported by Masamune¹⁸ and can be purified by flash chromotography on SiO₂ (1:1 MeOH/CH₂Cl₂). In addition, pyrrolidinylethyl compound **12** can be purified by recrystallization (3:1 Et₂O/MeOH) as the HCl salt. Ligand **13**, possessing the opposite relative configuration of **11** and **12**, was prepared in a similar fashion from 2-(aminomethyl)pyridine and (1*S*,*4S*)-1,4-diphenylbutane-1,4-dimesylate² (12:1 amine/dimesylate). Ligands **11**, **12**, and **13** have been designated (*R*,*R*)-MePMP, (*R*,*R*)-MePEP, and (*R*,*R*)-PhPMP, respectively. All three ligands have been fully characterized by ¹H and ¹³C NMR and mass spectrometry.^{19,20}

Complexation of (R,R)-MePMP (11) and (R,R)-PhPMP (13) with a transition metal was achieved upon reaction with $(\eta^3$ -allyl)palladium(II) chloride dimer (Scheme 2).²¹ Of the several counterions used (BF₄⁻, ClO₄⁻, AsF₆⁻, and PF₆⁻), crystalline products were only obtained with ClO₄⁻ and PF₆⁻. (R,R)-MePEP (12) did not afford a stable complex. Analysis of (R,R)-MePMP complex 14 by ¹H NMR indicated an approximately 1:1 mixture of diastereomeric allyl complexes (π -allyl rotamers 14a and 14b) which underwent slow exchange at RT (400 MHz ¹H NMR). Four sharp doublets at 1.41, 1.27, 1.25 and 1.23 ppm of approximately equal integration indicate four inequivalent methyl groups arising from 14a and 14b. Two distinct allyl groups were also observed.²² Analysis of (R,R)-PhPMP complex 15 by ¹H NMR indicated a similar mixture of complexes (15a and 15b) in an approximately 2:1 ratio. Molecular mechanics calculations²³ on 14 and 15 yield energy differences between the allyl rotamers of <0.1 kcal/mol and 0.4 kcal/mol, respectively, which is in agreement with the observed ratios.²⁴

Yellow/orange prismatic crystals of (R,R)-MePMP complex 14 were grown from Et₂O/CH₂Cl₂ and subjected to X-ray analysis (Figure 1). The unit cell contained only one of the possible diastereomeric complexes. The structure confirms the typical face-on planar geometry of an η^3 -allyl ligand bound to a transition metal. As expected the Pd–N(sp³) bond length of 2.148Å is considerably longer than the Pd–N(sp²) bond length of 2.082Å. The Pd–N(sp³) bond length is also significantly shorter than the corresponding Pd–N(sp³) bond length (2.17–2.19Å) in 16, the only other *trans*-2,5-dimethylpyrrolidine complex in the literature.¹¹ This difference is possibly due to the steric influence of the phenyl groups on the allyl ligand in 16. In comparison to reported Pd–N(sp²) bond lengths, Pfaltz reports²⁵ the New amine-imine ligands



Figure 1. Stereoview of the X-ray structure of $[Pd(\eta^3-allyl)((R,R)-MePMP)]^+ClO_4^-$ (14).

bond lengths in a Pd complex of a C_2 -symmetric bis(oxazoline) ligand to be as shown (see structure 17). The Pd–N(sp²) bond length in our complex falls within this range. Both complexes 16 and 17, however, exhibit a significant difference in the Pd–C bond lengths to the allylic termini (2.22 and 2.18Å, 2.13 and 2.11Å), whereas we observe essentially identical bond lengths (2.124 and 2.127Å). Discrimination between allylic termini is crucial for high enantioselectivity in allylic alkylations.²⁶ We are currently investigating ligand modifications to enhance this discrimination.



Preliminary investigations indicate ligands 11–13 are active for palladium-catalyzed allylic alkylations. A full report of these investigations, the results of other metal-catalyzed reactions in the presence of these ligands, and new derivatives based on substitution of the pyridine ring will be reported in due course.

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- 19. Selected spectral data for (-)-2-[(2R,5R)-2,5-Dimethylpyrrolidin-1-ylmethylpyridine (11); ¹H NMR (400 MHz, CDCl₃) δ 8.50 (ddd, J=4.9, 1.8, 0.9 Hz, 1H), 7.60 (td, J=7.6, 1.8) Hz, 1H), 7.46 (d, J=7.8 Hz, 1H), 7.10 (m, 1H), 3.89 (d, J=14.7 Hz, 1H), 3.76 (d, J=14.8 Hz, 1H), 3.06 (m, 2H), 2.02 (m, 2H), 1.38 (m, 2H), 0.96 (d, J=6.3 Hz, 6H); ¹³C (100 MHz, CDCl₃) δ 160.8, 148.5, 135.8, 122.5, 121.2, 55.2, 53.6, 30.8, 17.0; MS (EI) m/z M⁺ 191.1551 (calcd for $C_{12}H_{18}N_2=191.1548$); $[\alpha]_D^{25}=-91.6$ (c=2.16, CH₂Cl₂). (-)-2-[2-((2R.5R)-2,5-Dimethylpyrrolidin-1-yl)ethyl]pyridine (12): ¹H NMR (400 MHz, CDCl₃) & 8.50 (ddd, J=4.9, 1.9, 0.94 Hz, 1H), 7.58 (td, J=7.7, 1.9 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.10 (ddd, J=7.5, 4.9, 1.2 Hz, 1H), 3.10 (m, 2H), 2.96 (m, 3H), 2.65 (m, 1H), 2.00 (m, 2H), 1.38 (m, 2H), 1.00 (d, J=6.3 Hz, 6H); ¹H NMR (400 MHz, MeOD- d_4) δ 8.43 (ddd, J=5.0, 1.8, 1.0 Hz, 1H), 7.75 (td, J=7.7, 1.8 Hz, 1H), 7.35 (dt, J=7.9, 1.0 Hz, 1H), 7.25 (ddd, J=7.6, 5.0, 1.1 Hz, 1H), 3.13 (m, 2H), 2.96 (m, 3H), 2.68 (m, 1H), 2.04 (m, 2H), 1.41 (m, 2H), 1.03 (d, J=6.3 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 160.8, 149.1, 136.0, 122.9, 120.9, 55.0, 47.5, 37.7, 30.7, 16.6; ¹³C NMR (100 MHz, MeOD-d₄) δ 161.4, 149.7, 138.7, 124.9, 123.0, 56.6, 48.9, 37.6, 31.4, 16.6; MS (EI)m/z (M⁺) 204.1625 (calcd for C₁₃H₂₀N₂=204.1626); $[\alpha]_D^{25} = -101.9$ (c=2.46, CH₂Cl₂). 12·HCl: mp 179–180 °C; ¹H NMR (400 MHz, MeOD-d₄) δ 8.85 (ddd, J=5.8, 1.5, 0.6 Hz, 1H), 8.64 (td, J=7.9, 1.6 Hz, 1H), 8.19 (d, J=8.1 Hz, 1H), 8.06 (ddd, 7.7, 5.9, 1.1 Hz, 1H), 4.16 (br, 1H), 3.9-3.5 (m, 5H), 2.45 (br m, 1H), 2.3 (br m, 1H), 1.9 (br m, 1H); 1.8 (br m, 1H), 1.58 (d, J =6.8 Hz, 3H), 1.43 (d, J=6.8 Hz, 3H); ¹³C NMR (100 MHz, MeOD- d_4) δ 152.5, 147.9, 142.6, 128.6, 126.7, 62.6, 60.9, 46.2, 29.98, 29.70, 29.66, 16.9, 13.6; $[\alpha]_D^{25} = -50.05$ (c=0.97, EtOH). (+)-2-[(2R,5R)-2,5-Diphenylpyrrolidin-1-ylmethyl]pyridine (13): ¹H NMR (400 MHz, CDCl₃) δ 8.45 (ddd, J=4.9, 1.8, 0.9 Hz, 1H), 7.59 (td, J=7.7, 1.8 Hz, 1H), 7.42 (d, J=7.6 Hz, 1H), 7.32-7.20 (m, 10H), 7.07 (m, 1H), 4.37 (br t, J=4.4 Hz, 2H), 3.66 (d, J=15.7 Hz, 1H), 3.39 (d, J=15.7 Hz, 1H), 2.60 (m, 2H), 2.04 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 160.3, 148.6, 143.3, 136.0, 128.2, 128.0, 127.0, 122.4, 121.2, 65.7, 53.3, 33.3; MS (EI)m/z (M+H⁺) 315.1869 (calcd for $C_{22}H_{23}N_2=315.1861$); $[\alpha]_D^{25}=+131.6$ (c=0.08, CHCl₃).
- Optical purity was established by chiral HPLC (Chiralcel OD) or 400 MHz NMR (Eu(hfc)₃ or CSA salt).
 11 and 12: >95% ee (<5% meso).
 13: >98% ee (minor isomers not detected).

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