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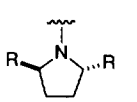
Synthesis and characterization of new amine–imine ligands based on *trans*-2,5-disubstituted pyrrolidines

James A. Sweet,[a] Jennifer M. Cavallari,[a] William A. Price,[b] Joseph W. Ziller[c] and Dominic V. McGrath[a,*]

[a] Department of Chemistry, University of Connecticut, Storrs, CT 06269-4060, USA
[b] Department of Chemistry, La Salle University, Philadelphia, PA 19141, USA
[c] Department of Chemistry, University of California, Irvine, CA 92717-2025, USA

Abstract: We present a modular synthesis of a new class of chiral *N,N*-chelating ligands containing the C_2-symmetric *trans*-2,5-disubstituted pyrrolidine moiety linked to a pyridine ring. (−)-2-[(2*R*,5*R*)-2,5-Dimethylpyrrolidin-1-ylmethyl]pyridine (**11**, (*R,R*)-MePMP), (−)-2-[2-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)ethyl]pyridine (**12**, (*R,R*)-MePEP), and (+)-2-[(2*R*,5*R*)-2,5-diphenylpyrrolidin-1-ylmethyl]pyridine (**13**, (*R,R*)-PhPMP) have been prepared. The X-ray structure of the (η^3-allyl)Pd complex of (*R,R*)-MePMP (**11**) is reported.

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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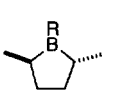
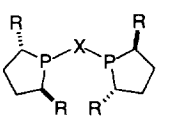
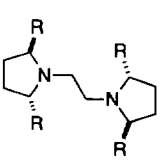


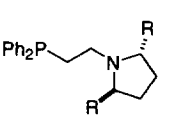
2a: (R = H)
b: (R = CF_3SO_3)



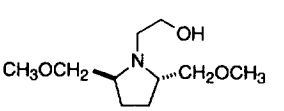
3a: (X = CH_2CH_2)
b: (X = *o*-C_6H_4)



4: (R = CH_3)
5: (R = Et, ent)
6: (R = Bn, ent)



7: (R = CH_3)
8: (R = Et, ent)
9: (R = Bn, ent)



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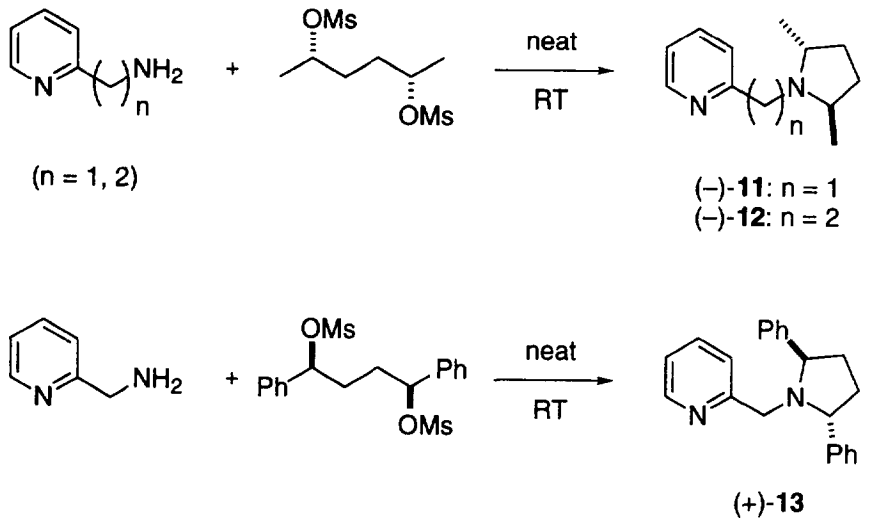
* Corresponding author. Email: DMCGRATH@nucleus.chem.uconn.edu

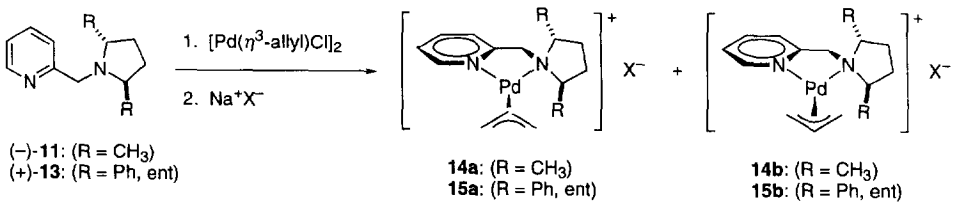


Scheme 1.

Successful cyclization of (2*S*,5*S*)-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 Masamune[18] and can be purified by flash chromotography on SiO_2 (1:1 MeOH/CH_2Cl_2). In addition, pyrrolidinylethyl compound **12** can be purified by recrystallization (3:1 Et_2O/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*,4*S*)-1,4-diphenylbutane-1,4-dimesylate[2] (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 ^{13}C 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 (η^3-allyl)palladium(II) chloride dimer (Scheme 2).[21] Of the several counterions used (BF_4^-, ClO_4^-, AsF_6^-, and PF_6^-), crystalline products were only obtained with ClO_4^- and PF_6^-. (*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 calculations[23] 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 Et_2O/CH_2Cl_2 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(sp^3) bond length of 2.148Å is considerably longer than the Pd–N(sp^2) bond length of 2.082Å. The Pd–N(sp^3) bond length is also significantly shorter than the corresponding Pd–N(sp^3) 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(sp^2) bond lengths, Pfaltz reports[25] the



Scheme 2.

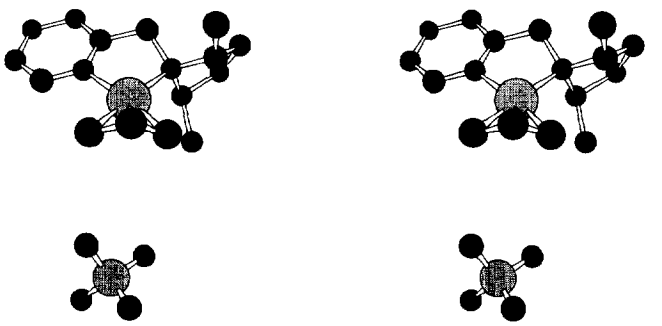
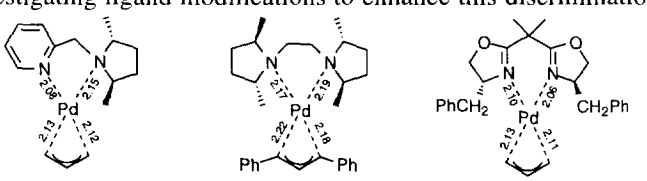


Figure 1. Stereoview of the X-ray structure of $[Pd(\eta^3\text{-allyl})((R,R)\text{-MePMP})]^+ClO_4^-$ (**14**).

bond lengths in a Pd complex of a C_2-symmetric bis(oxazoline) ligand to be as shown (see structure **17**). The Pd–N(sp^2) 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.



14 **16** **17**

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.

Acknowledgements

We are grateful to Per-Ola Norrby and Mark Burk for helpful discussions. Acknowledgement is made to the donors of The Petroleum Research Fund, administered by the ACS, and the University of Connecticut Research Foundation for support of this research. J.M.C. was the recipient of a Pfizer Summer Undergraduate Research Fellowship, for which she is grateful.

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19. Selected spectral data for **(−)-2-[(2*R*,5*R*)-2,5-Dimethylpyrrolidin-1-ylmethyl]pyridine (11)**: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C (100 MHz, $CDCl_3$) 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, CH_2Cl_2). **(−)-2-[2-((2*R*,5*R*)-2,5-Dimethylpyrrolidin-1-yl)ethyl]pyridine (12)**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{1}H 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8, 149.1, 136.0, 122.9, 120.9, 55.0, 47.5, 37.7, 30.7, 16.6; ^{13}C NMR (100 MHz, MeOD-d_4) 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 $C_{13}H_{20}N_2$=204.1626); $[\alpha]_D^{25}$=−101.9 (*c*=2.46, CH_2Cl_2). **12·HCl**: mp 179–180 °C; ^{1}H NMR (400 MHz, MeOD-d_4) 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); ^{13}C 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-[(2*R*,5*R*)-2,5-Diphenylpyrrolidin-1-ylmethyl]pyridine (13)**: ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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, $CHCl_3$).
20. 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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