Inorganic Chemistry

Communication

pubs.acs.org/IC

Structure and Properties of Neutral and Cationic Gold(III) Complexes from Substituted 2-(2′-Pyridyl)quinoline Ligands

Edward M. Laguna,[†] Pauline M. Olsen,[†] Michael D. Sterling,[†] Jack F. Eichler,[†] Arnold L. Rheingold,[‡] and Catharine H. Larsen*,[†]

[†]Department of Chemistry, University of California, Riverside, California 92521, United States

[‡]Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, California 92093, United States

Supporting Information

ABSTRACT: A one-step catalytic synthesis of 6-substituted 4-phenyl-2-(2′-pyridyl)quinolines provides electronically differentiated ligands without solvent, inert atmosphere, metal contamination, or chromatography. Gold(III) complexes formed from these bidentate PyQuin ligands were characterized and studied by single-crystal X-ray diffraction. The cationic gold(III) chloride synthesized from 6-methoxy-4-phenyl-2-(2′-pyridyl)quinoline has a distorted square-planar ligand environment. Diamagnetic neutral gold(III) complexes from methoxy-, methyl-, and phenyl-PyQuin ligands exhibit a long axial Au−N2 interaction.

Gold compounds have long been valued for their catalytic power and therapeutic effects.[1−7] Gold(III) chloride complexes of pyridyl-based ligands combat cancer, including cisplatin-resistant cell lines.[3] Metal complexes of various bidentate 2-(2′-pyridyl)quinoline ligands have been studied as potential drug therapies and catalysts.[7−9] Precise ligand tuning requires the ability to install substituents that range from electron-donating to electron-withdrawing. Classic syntheses of 2-(2′-pyridyl)quinoline continue to be applied but are not readily adapted for additional functional groups.[8−10]

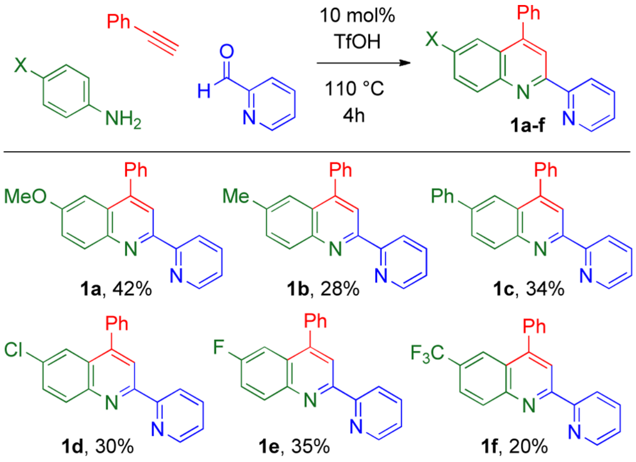
Friëdlander cyclization of *o*-aminobenzaldehyde and 2-acetylpyridine forms 2-(2′-pyridyl)quinoline.[9,10] Stille cross-coupling of the appropriate 2-bromoquinoline and 2-stannylpyridine is another strategy employed to synthesize substituted variants of these ligands.[8a] Because *o*-aminobenzaldehyde for the Friëdlander cyclization and substituted 2-bromoquinolines for cross-coupling cost hundreds of dollars per gram,[11] these starting materials are generally synthesized.[7,8]

For accelerated testing of the relationship between the ligand structure and catalytic or biomedical activity, a one-step ligand synthesis would ideally employ inexpensive starting materials bearing a range of substituents. Multicomponent reactions present many advantages for the synthesis of quinolines.[12−14] One disadvantage when attempting to expand known metal-catalyzed methods to produce 2-(2′-pyridyl)quinoline ligands is that both the imine intermediate and product are bidentate and can inhibit the catalyst activity.[12,13]

Herein we report that electronically diverse ligands are obtained by heating anilines, 2-pyridinecarboxaldehyde, and phenylacetylene with trifluoromethanesulfonic (triflic) acid as the catalyst, bypassing metal contamination. Highlighting the utility of this PyQuin ligand synthesis, the first neutral and cationic gold(III) complexes of these substituted 4-phenyl-2-(2′-pyridyl)quinoline ligands have been synthesized and characterized.

The one-step method in Table 1 is not affected by air or moisture: the reactions are set up on the benchtop in disposable vials closed with screw caps. Each substituted aniline is combined with 2-pyridinecarboxaldehyde and phenylacetylene, treated with 10 mol % triflic acid, and heated for 4 h. Vacuum filtration of the crude reaction mixture through alumina and washing with cold hexanes provides these bidentate heteroaromatic ligands.

Table 1. One-Step Synthesis of PyQuin Ligands with Electron-Rich to Electron-Poor Substituents



1a, 42% **1b**, 28% **1c**, 34%

1d, 30% **1e**, 35% **1f**, 20%

Anilines from electron-rich 4-methoxyaniline to electron-poor 4-(trifluoromethyl)aniline convert to PyQuins **1a**−**1f** (Table 1). On a 2 mmol scale, *p*-anisidine converts to 0.27 g (42% yield) of MeO-PyQuin (**1a**). In 4 h on a 10 mmol scale (less than 6 USD of starting materials and catalyst), 0.97 g (31% yield) of ligand **1a** is isolated. Cl-PyQuin (**1d**) provides a handle for cross-coupling[8d] or other elaborations of the PyQuin core.

Neutral gold(III) complexes (MeO-PyQuin)$AuCl_3$ (**2a**), (Me-PyQuin)$AuCl_3$ (**2b**), and (Ph-PyQuin)$AuCl_3$ (**2c**) are synthesized from PyQuin ligands **1a**−**1c** using a method reported for phenanthrolines.[6] Deep-red solutions filtered

Received: August 14, 2014
Published: November 12, 2014

dx.doi.org/10.1021/ic501965m | *Inorg. Chem.* 2014, 53, 12231−12233

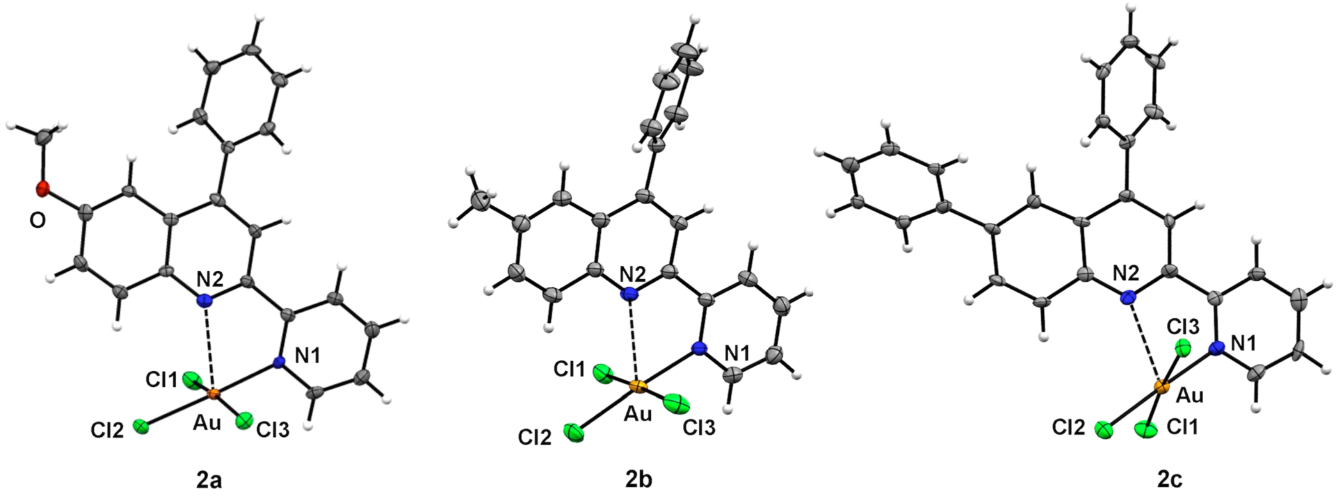
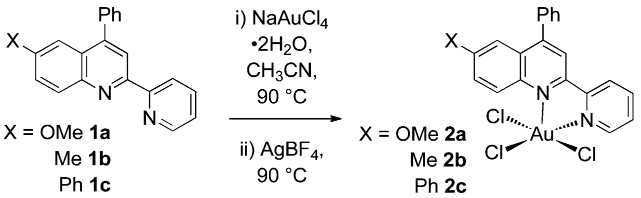
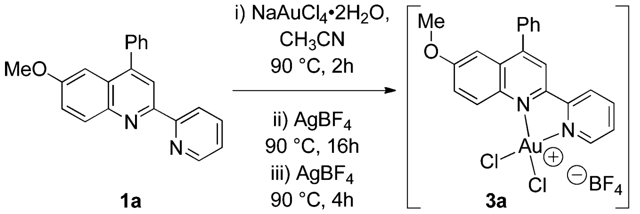


Figure 1. Solid-state structures of **2a**−**2c** with ellipsoids at 50% probability. Color code: C, gray; N, blue; Au, orange; Cl, green; O, red. CH_3CN solvent was omitted for clarity in **2a**. **2a** bond lengths (Å): Au−N1, 2.039(3); Au−N2, 2.633(3); Au−Cl1, 2.2886(8); Au−Cl2, 2.2745(8); Au−Cl3, 2.2910(8). **2b** bond lengths (Å): Au−N1, 2.063(3); Au−N2, 2.639(3); Au−Cl1, 2.2948(12); Au−Cl2, 2.2608(12); Au−Cl3, 2.2790(12). **2c** bond lengths (Å): Au−N1, 2.061(5); Au−N2, 2.736(5); Au−Cl1, 2.2884(16); Au−Cl2, 2.2727(17); Au−Cl3, 2.2850(15).

through Celite produce red-orange crystals in 43−72% yield. Red solutions form using the same procedure as that with F-PyQuin (**1e**) and CF_3-PyQuin (**1f**). However, gold(III) complexes of fluorinated ligands **1e** and **1f** do not precipitate even when cooled. The main issue is incomplete conversion of **1e** to the corresponding gold(III) complex. ^1H NMR analysis of the crude reaction mixture shows a 58:42 ratio of the gold complex to the free ligand. Gold(III) complexes of similar heteroaromatic ligands are also known to be more soluble than those of other metals.[4,8]



The corresponding cationic complex can be synthesized by refluxing **1a** with $NaAuCl_4{\cdot}2H_2O$ and 2 equiv of $AgBF_4$. Deep-black-red crystals of tetrafluoroboratogold(III) complex (**3a**) are isolated in 6% yield because neutral complex **2a** remains the major constituent of the reaction mixture. Heating the starting materials to 120 °C in toluene did not improve conversion from **2a** to **3a**. By allowing the first 1 equiv of $AgBF_4$ to form neutral complex **2a** before adding the second 1 equiv of $AgBF_4$, a 27% yield of cationic gold(III) complex **3a** is isolated.



As shown in Figure 1, all three neutral gold complexes (**2a**−**2c**) display bond lengths and angles that are consistent with those reported by O'Connor and Sinn for trichloro[2-(2′-pyridyl)quinoline]gold(III): Au−N1 = 2.11(2) Å, Au−N2 = 2.68(2) Å, and N1−Au−N2 = 68.0°.[4b] For substituted PyQuin complexes **2a**−**2c**, Au−N1 is 2.039(3)−2.063(3) Å, Au−N2 is 2.633(3)−2.736(5) Å, and the N1−Au−N2 angle is 69.5−72.2°. Although the axial Au−N2 bonds are weaker (covalent Au−N = 1.40 + 0.74 = 2.04 Å), they are markedly shorter than the van der Waals radii (nonbonded Au−N = 2.2 + 1.5 = 3.7 Å).

Steric crowding at gold(III) from 2-(2′-pyridyl)quinoline, 2,2′-biquinoline, and 2,9-dimethylphenanthroline ligands is believed to force halides out of the bidentate ligand plane, forming neutral five-coordinate species.[4−6] The possible effect of intermolecular packing forces in the solid-state lattice has not been given much consideration. The geometry of such gold(III) complexes has been labeled as distorted square pyramidal, credited with increased stability, and labeled as the origin of different modes of action compared to square-planar platinum(II) and gold(III) complexes.[3,6] However, in the absence of charge density, X-ray analysis, or high-level density functional theory calculations, the ligand arrangement around the gold nucleus of **2a**−**2c** is most accurately described as square-planar with an axial metal-to-nitrogen electrostatic interaction.

In contrast with the ligand-face view in Figure 1 of neutral complex **2a** formed from **1a**, Figure 2 displays cationic complex **3a** from the bottom for a clear view of the metal plane. Each Au−Cl bond bends away from the ligand plane.[4−6] The N1−Au−N2

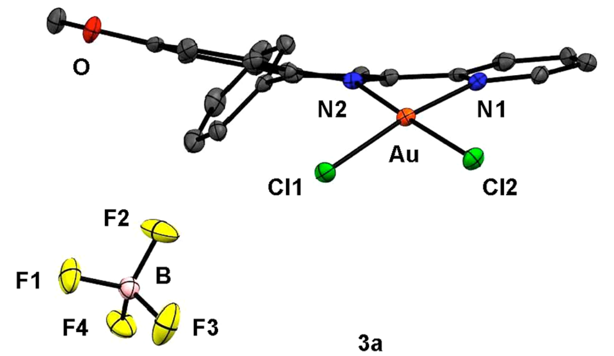


Figure 2. Solid-state structure of square-planar **3a** (bottom view) with ellipsoids drawn at 50% probability. Hydrogen atoms and CH_2Cl_2 solvent are omitted for clarity. Color code: C, gray; N, blue; Au, orange; Cl, green; O, red; B, pink; F, yellow. Bond lengths (Å) for **3a**: Au−N1, 2.030(4); Au−N2, 2.048(4); Au−Cl1, 2.2669(12); Au−Cl2, 2.2627(11).

angle of square-planar **3a** is 79.9° (10° distortion versus the 18−20° deviation from 90° in neutral complexes **2a**−**2c**). Gold tetrafluoroborate salt **3a** has Au−N1 = 2.030(4) Å and Au−N2 = 2.048(4) Å. These bond lengths are nearly equal to the sum of the covalent radii, 2.04 Å, and are in the expected range for cationic square-planar gold(III) complexes.[3a−d] The Au−Cl bond lengths for neutral and cationic complexes **2a**−**2c** and **3a** are all between 2.26 and 2.29 Å.[3−6]

A one-step synthesis of 4-phenyl-2-(2′-pyridyl)quinolines bearing electron-rich to electron-poor substituents will streamline the study of electronic effects of ligands on a range of metal centers.[7,8] This green procedure[15] proceeds efficiently without inert atmosphere, solvent, additives, or column chromatography. In one air- and water-tolerant step, inexpensive starting materials are combined with the triflic acid catalyst to provide 1 g of bidentate ligand.

X-ray crystallographic analysis illustrates that four-coordinate cationic gold(III) complex **3a** has a distorted square-planar configuration. Neutral gold(III) complexes **2a**−**2c** display an additional axial interaction. The synthesis of PyQuin ligands with additional substituents and their corresponding gold(III) complexes for ligand-exchange studies and biological testing is underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic data in CIF format, experimental procedures and characterization including ^{1}H and ^{13}C NMR, IR, HRMS, and X-ray data, ^{1}H and ^{13}C NMR spectra for **1a**−**1f**, and ^{1}H NMR spectra for **2a**−**2c** and **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: catharine.larsen@ucr.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by University of California Cancer Research Coordinating Committee Funds. The authors thank Prof. Vincent LaVallo for helpful discussions.

■ REFERENCES

(1) (a) Höffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *23*, 387. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.

(2) General medicinal gold(III) reviews: (a) Shaw, C. F., III. *Chem. Rev.* **1999**, *99*, 2589. (b) Ott, I. *Coord. Chem. Rev.* **2009**, *253*, 1670.

(3) For recent examples of medicinal chemistry with heteroaromatic gold(III) complexes, see: (a) Cinellu, M. A.; Maiore, L.; Manassero, M.; Casini, A.; Arca, M.; Fiebig, H.-H.; Kuelter, G.; Michelucci, E.; Pieraccini, G.; Gabbiani, C.; Messori, L. *ACS Med. Chem. Lett.* **2010**, *1*, 336. (b) Casini, A.; Diawara, M. C.; Scopelliti, R.; Zakeeruddin, S. M.; Grätzel, M.; Dyson, P. J. *Dalton Trans.* **2010**, *39*, 2239. (c) Wein, A. N.; Stockhausen, A. T.; Hardcastle, K. I.; Saadein, M. R.; Peng, S. B.; Wang, D.; Shin, D. M.; Chen, Z. G.; Eichler, J. F. *J. Inorg. Biochem.* **2011**, *105*, 663. (d) Che, C.-M.; Sun, R. W.-Y. *Chem. Commun.* **2011**, *47*, 9554. (e) Sanghvi, C. D.; Olsen, P. M.; Elix, C.; Peng, S. B.; Wang, D.; Chen, Z. G.; Shin, D. M.; Hardcastle, K. I.; MacBeth, C. E.; Eichler, J. F. *J. Inorg. Biochem.* **2013**, *128*, 68.

(4) (a) Charlton, R. J.; Harris, C. M.; Patil, H.; Stephenson, N. C. *Inorg. Nucl. Chem. Lett.* **1960**, *2*, 409. (b) O'Connor, C. J.; Sinn, E. *Inorg. Chem.* **1978**, *17*, 2067.

(5) Robinson, W. T.; Sinn, E. *J. Chem. Soc., Dalton Trans.* **1975**, 726.

(6) Hudson, Z. D.; Sanghvi, C. D.; Rhine, M. A.; Ng, J. J.; Bunge, S. D.; Hardcastle, K. I.; Saadein, M. R.; MacBeth, C. E.; Eichler, J. F. *Dalton Trans.* **2009**, 7473.

(7) (a) Sadiq, M. F.; Zaghal, M. H. *Polyhedron* **1997**, *16*, 1483. (b) Dahal, U. P.; Joswig-Jones, C.; Jones, J. P. *J. Med. Chem.* **2012**, *55*, 280. (c) Tsoupras, A. B.; Papakyriakou, A.; Demopoulos, C. A.; Philippopoulos, A. I. *J. Inorg. Biochem.* **2013**, *120*, 63.

(8) For recent 2-(2′-pyridyl)quinoline metal complexes, see: (a) Michel, B. W.; Steffens, L. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 8317. (b) El Ojaimi, M.; Thummel, R. P. *Inorg. Chem.* **2011**, *50*, 10966. (c) Ali, B. F.; Zaghal, M. H.; Mhaidat, R. M.; Qaseer, H. A.; El-Qisiari, A. K. *Polyhedron* **2013**, *54*, 237. (d) Vougioukalakis, G. C.; Stergiopoulos, T.; Kontos, A. G.; Pefkianakis, E. K.; Papadopoulos, K.; Falaras, P. *Dalton Trans.* **2013**, *42*, 6582. (e) Zucca, A.; Cordeschi, D.; Maidich, L.; Pilo, M. I.; Masolo, E.; Stoccoro, S.; Cinellu, M. A.; Galli, S. *Inorg. Chem.* **2013**, *52*, 7717.

(9) (a) Harris, C. M.; Kokot, S.; Patil, H. R. H.; Sinn, E.; Wong, H. *Aust. J. Chem.* **1972**, *25*, 1631. (b) Campagna, S.; Mamo, A.; Stille, J. K. *J. Chem. Soc., Dalton Trans.* **1991**, 2545.

(10) Smirnoff, A. P. *Helv. Chim. Acta* **1921**, *4*, 802.

(11) *o*-Aminobenzaldehyde at Sigma-Aldrich: 176.50 USD/g.

(12) Khusnutdinov, R. I.; Bayguzina, A. R.; Dzhemilev, U. M. *J. Organomet. Chem.* **2014**, *768*, 75.

(13) Meyet, C. E.; Larsen, C. H. *J. Org. Chem.* **2014**, *79*, 9835.

(14) For multicomponent quinoline synthesis via aza-Diels−Alder, see: Majumdar, K. C.; Ponra, S.; Ghosh, D.; Taher, A. *Synlett* **2011**, 104.

(15) (a) Li, C.-J.; Trost, B. M. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 13197. (b) Sheldon, R. A. *Chem. Commun.* **2008**, 3352. (c) Noyori, R. *Chem. Commun.* **2005**, 1807.