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Cycloauration of substituted 2-phenoxypyridine derivatives and X-ray crystal structure of gold, dichloro-[2-[[5-[(cyclopentylamino)carbonyl]-2-pyridinyl-κ*N*]oxy]phenyl-κ*C*]-, (*SP*-4-3)-

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Abstract

Direct cycloauration of 2-phenoxypyridines with different substituents at the 5-position of the pyridine ring was carried out in an CH_3CN/H_2O medium, leading to isolation of cycloaurated compounds $AuCl_2$(**L**) (**HL** = substituted 2-phenoxypyridine ligand) with alkyl, substituted alkyl, phenyl, halo, ester and amido groups. The preparation of cycloaurated compounds involves the formation of an intermediate $AuCl_3$(**HL**) via coordination reaction between the pyridine ligand and $NaAuCl_4$ at room temperature and subsequent formation of the Au−C bond at elevated temperature in an CH_3CN/H_2O medium. The presence of a bulky lipophilic group decreases the yield of cycloaurated compounds and favors the decomposition of the reaction species to Au(0). No coordination reaction was observed for ligands with a strong electron-withdrawing substituent (nitro or nitrile) in the pyridine ring. The ligand having the electron-donating dimethylamino group is oxidized by $NaAuCl_4$ at room temperature. The presence of a thienyl or an acetyl group allowed the isolation of the intermediate $AuCl_3$(**HL**), but has an adverse effect on the subsequent cycloauration. The result of direct cycloauration of methyl-substituted 2-phenoxypyridine ligands indicated that the presence of a methyl group at the 6-position in the pyridine ring closest to the Au−N(py) bond resulted in poor cycloauration and a decrease in compound stability. The X-ray crystal structure of the cycloaurated compound **25** was determined, depicting a four-coordinate Au atom located in the center of a slightly distorted square.

Keywords: Cycloauration; Coordination; Phenoxypyridine; Crystal structures

1. Introduction

Gold(III) is isoelectronic (d^8) with platinum(II) and likewise forms square-planar complexes. It is therefore tempting to speculate that such complexes would have similar anti-tumor activity to cisplatin. Although there has been significant interest in the development of gold complexes for therapeutic purposes [1,2], gold(III) complexes have not been as thoroughly investigated as gold(I) complexes, primarily because of their reactivity. To stabilize the gold(III) oxidation state in a reducing biological milieu, complexes with a bidentate ligand, damp, (2-[(dimethylamino)methyl]phenyl), were previously prepared [3,4]. The damp ligand forms part of a five-membered chelating ring in which the nitrogen of the amino group and the carbon of the aryl ring bond to the metal. The presence of the covalent Au(III)−C (aryl) bond prevents reduction of the Au(III) center by a thiol group, unlike normal coordinate Au(III) complexes. Recent studies have shown that such compounds possess anti-tumor properties [3,5,6]. It has also been shown that the gold complexes do not react in a mechanism similar to cisplatin and the true biological mechanism of action of these complexes is not yet established [6]. Possible molecular targets are biologically important thiol-containing molecules. As part of our medicinal chemistry program on the development of

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cysteine protease inhibitors, we have now synthesized and characterized six-membered cycloaurated Au(III) complexes of substituted 2-phenoxypyridines. This is the subject of this paper.

Cycloaurated complexes have been prepared by transmetallation from the corresponding organomercury(II) compounds [4,7–10], lithium reagents [11,12] or by direct cycloauration of the corresponding ligand with or without the presence of a silver(I) salt [13–21]. The transmetallation method usually involves isolation of a stable organomercury compound prepared from the corresponding organolithium or organomagnesium intermediate, which is usually obtained via metal–halogen exchange. Many functional groups are not tolerated by this method due to the use of lithium or magnesium reagents. Direct cycloauration involves C−H bond activation of a heterosubstituted ligand by an Au center to form a chelate ring containing a covalent Au−C bond, and occurs in many 2-substituted pyridines including 2-benzylpyridine [21], 2-anilinopyridine [13,17], 2-phenoxypyridine [17], 2-phenylsulfanylpyridine [17], 2-benzoylpyridine [16], 2-phenylpyridine [18], 1-ethyl-2-phenylimidazole [19], 2-phenylthiazole [14] and 2-thienylpyridine [15,20]; however, there are only two reports of cycloaurated compounds bearing a substituent on the heterocyclic ring prepared by direct cycloauration [21,22]. In many cases, the cycloaurated product is formed by heating at reflux for a set time period a suspension of the intermediate $AuCl_3$(heterosubstituted ligand) in CH_3CN/H_2O, which itself is isolated via coordination reaction between the ligand and $[AuCl_4]^-$. During our medicinal chemistry program, we investigated the feasibility of this method for the direct cycloauration of 2-phenoxypyridines containing various functional groups at the 5-position of the pyridine ring. Our goal was to determine the application of this methodology to prepare a large library of such compounds for biological screening.

2. Experimental

2.1. General information

All reactions were carried out under ambient conditions unless otherwise noted. Diethyl ether and THF were dried by refluxing over sodium in the presence of benzophenone. $NaAuCl_4 \cdot 2H_2O$ (containing 49.2–49.6% Au), $AgSO_3CF_3$, $Pd_2(dba)_3$ (dba = (dibenzylidene)acetone), $Pd(OAc)_2$, Pd/C (10% Pd in weight), Ni(dppp)Cl_2 (dppp = 1,3-bis(diphenylphosphino)propane), 1,1′-bis(diphenylphosphino) ferrocene (DPPF), 2-bromopyridine, 2-bromo-4-methylpyridine, 2-bromo-5-methylpyridine, 2-bromo-6-methylpyridine, methyl acrylate, 2,5-dichloropyridine, 2,5-dibromopyridine, methylamine (2.0 M in THF), dimethylamine (2.0 M in THF), PhMgCl (3.0 M in diethyl ether), CH_3CH_2MgBr (3.0 M in diethyl ether) and CH_3MgBr (3.0 M in diethyl ether) were all purchased from commercial sources. ^{1}H-, ^{13}C- and ^{19}F-NMR experiments were performed on a Bruker Avance 300 spectrometer. NMR spectra were referenced to residual solvent (^{1}H and ^{13}C with δ(TMS) = 0 ppm) or external CF_3COOH (^{19}F, $\delta = 0$ ppm). Mass spectra were obtained on a Bruker Esquire-LC 00052 mass spectrometer with an electrospray interface. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, GA.

2.2. Crystallographic study

Data collection and structure determination were carried out by Dr. Brian Patrick (Department of Chemistry, the University of British Columbia, Vancouver, BC, Canada). The experimental details of the X-ray structure determination and the crystallographic parameters are listed in Table 1. Single crystals of compound **25** were obtained by slow evaporation of an acetone solution. A yellow chip crystal having approximate dimensions of 0.25 mm × 0.10 mm × 0.05 mm was mounted on a glass fiber. The structure was solved by direct methods (SIR97) [23], expanded using Fourier techniques (DIRDIF94) [24] and refined by full-matrix least-squares procedure based on F^2. The non-hydrogen atoms were refined anisotropically. Some

Table 1
Crystallographic parameters and experimental details of the X-ray structure determination for compound **25**

Formula	$C_{17}H_{17}N_2O_2Cl_2Au$
Formula weight	549.21
Color, habit	yellow, chip
Dimension (mm)	0.25 × 0.10 × 0.05
Lattice type	primitive
Unit cell dimensions	
a (Å)	8.1660 (4)
b (Å)	13.3855(7)
c (Å)	15.2671(8)
V (Å^3)	1668.8 (1)
Space group	$P2_12_12_1$ (no. 19)
Z	4
μ(Mo–K$_\alpha$) (cm^{-1})	91.79
Diffractometer	Rigaku
λ(Mo–K$_\alpha$) (Å)	0.71069
temperature (°C)	−100 ± 1
ϕ($\chi = -90.0$) (°)	0.0–190.0
ω($\chi = -90.0$) (°)	−17.0–23.0
$2\theta_{max.}$ (°)	55.7
Measured reflection	15395
Unique	3735
No. of variables	221
R, R_w	0.041, 0.054
Goodness of fit	0.88
No. of observations [$I > 3\sigma(I)$]	3236
Max. peak in final diff. map (e$^-$ Å^{-1})	2.31
Min. peak in final diff. map (e$^-$ Å^{-1})	−1.55

hydrogen atoms were refined isotropically, and the rest were included in fixed positions.

3. Ligand preparation

3.1. General procedure A

A mixture of the corresponding 2-bromopyridine (20–226 mmol), phenol (1.0–1.3 eq.) and K_2CO_3 (1.1–2.0 eq.) was stirred and heated at 200 °C for 5 h. After the reaction mixture was cooled to room temperature, H_2O (20–50 ml) was added and the mixture was extracted with diethyl ether (3×50–150 ml) or CH_2Cl_2 (3×50–150 ml). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation under vacuum and the residue was purified either by distillation, flash chromatography on silica gel or recrystallization.

3.2. General procedure B

A mixture of the corresponding 2-bromopyridine, phenol (1.0–1.3 eq.) and K_2CO_3 (1.1–2.0 eq.) in DMSO (10–20 ml) was stirred and heated at 120–140 °C for a period of 5–16 h. After the reaction mixture was cooled to room temperature, H_2O (40–50 ml) was added and the mixture was extracted with diethyl ether (3×50 ml) or CH_2Cl_2 (2×20 ml). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was removed by evaporation under vacuum and the residue was purified by flash chromatography on silica gel.

3.3. General procedure C

A solution of the alkyl or aryl bromide (5–8 mmol) in dry diethyl ether (10–20 ml) was added dropwise via an addition funnel to a flask charged with Mg turnings (1.1–1.3 eq.) (pre-washed with diethyl ether and dried in vacuo) and a grain of I_2 suspended in dry diethyl ether (30 ml) under N_2. During addition of the first few drops, the mixture was heated using a heat gun to initiate the reaction. Once the addition was complete, the mixture was stirred at room temperature for 3 h. The Grignard solution was then added slowly to a mixture of the corresponding halo pyridine (4–7 mmol, 0.80–0.90 eq.) and Ni(dppp)Cl_2 (5–10 mol%) in dry diethyl ether (50 ml) via a cannula. After the addition was complete, the mixture was stirred at room temperature for 15 min, and was then heated at reflux overnight. The mixture was then cooled to room temperature, and H_2O (30 ml) was added. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×50 ml) or CH_2Cl_2 (3×30 ml). The organic extracts were combined, washed with H_2O and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum, and the residue was purified by flash chromatography on silica gel.

3.4. General procedure D

Under N_2, a suspension of **HL20** (2–5 mmol) in $SOCl_2$ (3–5 ml) was heated for 1–2 h to give a clear carbonyl chloride solution. After the excess $SOCl_2$ was removed by evaporation under vacuum the residual solid was dissolved in dry CH_2Cl_2 (10–20 ml). The CH_2Cl_2 solution was then added at room temperature to CH_3OH (10 ml) for **HL21** or a solution of excess amine (5–10 eq.) in dry THF or dry CH_2Cl_2 (5–10 ml) for the preparation of an amide. After the mixture was stirred at room temperature for 2 h, H_2O (30 ml) was added, the organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (3×30 ml). The organic extracts were combined and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum and the residue was purified either by washing with hexanes or diethyl ether, or by flash chromatography on silica gel.

3.5. General procedure E

To a solution of 6-phenoxypyridin-3-ylamine (2–5 mmol) and NEt_3 (1–2 eq.) in dry THF was added dropwise the corresponding acyl chloride or acid anhydride (1.05 eq.). After the mixture was stirred for 2 h, H_2O (30 ml) was added and the mixture was extracted with ethyl acetate (3×30 ml). The extract was collected and washed with H_2O (30 ml), and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum and the residue was purified either by washing with hexanes or diethyl ether, or by flash chromatography on silica gel.

3.6. 6-Phenoxypyridin-3-ylamine

To a flask charged with tin shot (11.9 g, 100 mmol) and **HL17** (9.85 g, 45.6 mmol) was added dropwise concentrated HCl (25 ml, $\sim$300 mmol). The mixture was then stirred and heated at 50 °C for 2 h to afford a clear solution. After the mixture was cooled to room temperature, it was neutralized with aqueous NaOH solution (10 wt.%) and extracted with CH_2Cl_2 (3×100 ml), and the extract was dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum, and the residual oil was purified by flash chromatography on silica gel (ethyl acetate–hexanes (1:3, v/v)), providing a yellow solid (5.86 g, 69%). ^{1}H-NMR ($CDCl_3$) δ 3.56 (s, broad, 2H), 6.73 (d, 1H, $J =$ 8.4 Hz), 7.01–7.15 (m, 4H), 7.30–7.36 (m, 2H), 7.69 (d, 1H, $J = 3.0$ Hz) ppm. ES-MS m/z 187 $[M+H]^+$.

3.7. 4-Methyl-2-phenoxypyridine (**HL1**)

Following general procedure A using 2-bromo-4-methylpyridine (10.0 g, 58.2 mmol), phenol (6.56 g, 69.8 mmol) and K_2CO_3 (9.63 g, 69.8 mmol). The product was extracted with diethyl ether, and a colorless oil (8.40 g, 78%) was obtained after purification by flash chromatography on silica gel (diethyl ether–hexanes (1:4, v/v)). ^{1}H-NMR ($CDCl_3$) δ 2.34 (s, 3H), 6.71 (s, 1H), 6.82 (d, 1H, $J = 5.4$ Hz), 7.11–7.14 (m, 2H), 7.16–7.22 (m, 1H), 7.36–7.43 (m, 2H), 8.07 (d, 1H, $J = 5.4$ Hz) ppm.

3.8. 5-Methyl-2-phenoxypyridine (**HL2**)

Following general procedure A using 2-bromo-5-methylpyridine (37.1 g, 0.216 mol), phenol (21.3 g, 0.226 mol) and K_2CO_3 (32.8 g, 0.237 mol). The product was extracted with diethyl ether, and a colorless oil (37.0 g, 85%) was obtained after purification by flash chromatography on silica gel (diethyl ether–hexanes (1:4, v/v)). ^{1}H-NMR ($CDCl_3$) δ 2.28 (s, 3H), 6.81 (d, 1H, $J = 8.4$ Hz), 7.10–7.20 (m, 3H), 7.34–7.41 (m, 2H), 7.48–7.51 (m, 1H), 8.02–8.03 (m, 1H) ppm.

3.9. 6-Methyl-2-phenoxypyridine (**HL3**)

Following general procedure A using 2-bromo-6-methylpyridine (3.70 g, 21.5 mmol), phenol (2.02 g, 21.5 mmol) and K_2CO_3 (3.26 g, 23.6 mmol). The product was extracted with diethyl ether, and a colorless oil (2.23 g, 56%) was obtained after purification by vacuum distillation. ^{1}H-NMR ($CDCl_3$) δ 2.47 (s, 3H), 6.57 (d, 1H, $J = 8.4$ Hz), 6.87 (d, 1H, $J = 7.5$ Hz), 7.11–7.23 (m, 3H), 7.38 (t, 2H, $J = 7.8$ Hz), 7.54 (t, 1H, $J = 7.5$ Hz) ppm.

3.10. 5-Ethyl-2-phenoxypyridine (**HL4**)

Following general procedure C using the Grignard reagent CH_3CH_2MgBr (3.0 M in diethyl ether) (1.47 ml, 4.41 mmol) and **HL15** (1.00 g, 4.00 mmol). The product was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:5, v/v)), affording a colorless oil (0.565 g, 71%). ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, 3H, $J = 7.5$ Hz), 2.61 (q, 2H, $J = 7.5$ Hz), 6.83 (d, 1H, $J = 8.4$ Hz), 7.09–7.21 (m, 3H), 7.35–7.42 (m, 2H), 7.52 (dd, 1H, $J = 2.4$, 8.4 Hz), 8.02 (d, 1H, $J = 2.4$ Hz) ppm.

3.11. 2-Phenoxy-5-propylpyridine (**HL5**)

Following general procedure C using the Grignard reagent prepared from Mg (0.134 g, 5.50 mmol) and 1-bromopropane (0.615 g, 5.00 mmol), and **HL15** (1.00 g, 4.00 mmol). The product was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:5, v/v)), affording a colorless oil (0.628 g, 74%). ^{1}H-NMR ($CDCl_3$) δ 0.94 (t, 3H, $J = 7.5$ Hz), 1.62 (sextet, 2H, $J = 7.5$ Hz), 2.54 (q, 2H, $J = 7.5$ Hz), 6.83 (d, 1H, $J = 8.1$ Hz), 7.11–7.20 (m, 3H), 7.36–7.42 (m, 2H), 7.50 (dd, 1H, $J = 2.4$, 8.1 Hz), 8.01 (d, 1H, $J = 2.4$ Hz) ppm.

3.12. 5-Butyl-2-phenoxypyridine (**HL6**)

Following general procedure C using the Grignard reagent prepared from Mg (0.180 g, 7.20 mmol) and 1-bromobutane (0.900 g, 6.60 mmol), and **HL15** (1.50 g, 6.00 mmol). The product was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:6, v/v)), affording a colorless oil (0.343 g, 25%). ^{1}H-NMR ($CDCl_3$) δ 0.93 (t, 3H, $J = 7.5$ Hz), 1.36 (sextet, 2H, $J = 7.5$ Hz), 1.52–1.62 (m, 2H), 2.56 (t, 2H, $J = 7.5$ Hz), 6.82 (d, 1H, $J = 8.1$ Hz), 7.10–7.20 (m, 3H), 7.39 (t, 2H, $J = 8.1$ Hz), 7.50 (dd, 1H, $J = 2.4$, 8.1 Hz), 8.01 (d, 1H, $J = 2.4$ Hz) ppm.

3.13. 5-Pentyl-2-phenoxypyridine (**HL7**)

Following general procedure C using the Grignard reagent prepared from Mg (0.134 g, 5.50 mmol) and 1-bromopentane (0.755 g, 5.00 mmol), and **HL15** (1.00 g, 4.00 mmol). The product was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:5, v/v)), affording a colorless oil (0.586 g, 61%). ^{1}H-NMR ($CDCl_3$) δ 0.89 (t, 3H, $J = 7.2$ Hz), 1.25–1.37 (m, 4H), 1.53–1.64 (m, 2H), 2.55 (t, 2H, $J = 7.5$ Hz), 6.83 (d, 1H, $J = 8.4$ Hz), 7.10–7.20 (m, 3H), 7.35–7.42 (m, 2H), 7.50 (dd, 1H, $J = 2.4$, 8.4 Hz), 8.01 (d, 1H, $J = 2.4$ Hz) ppm.

3.14. 3-(6-Phenoxypyridin-3-yl)propionic acid methyl ester (**HL8**) and 3-(6-phenoxypyridin-3-yl)acrylic acid methyl ester

Under N_2 to a solution of **HL15** (3.00 g, 12.0 mmol) and PPh_3 (0.126 g, 0.480 mmol) in DMF (30 ml) was added $Pd(OAc)_2$ (0.0540 g, 0.240 mmol) K_2CO_3 (3.32 g, 24.0 mmol) and methyl acrylate (1.24 g, 14.4 mmol). The mixture was heated at 105 °C for 16 h. After the reaction mixture was cooled to room temperature, H_2O (50 ml) was added. The mixture was extracted with diethyl ether (5×30 ml), and the extract was dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum, and the residual oil was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:1, v/v)), affording a white solid (2.54 g, 83%). ^{1}H-NMR ($CDCl_3$) δ 3.81 (s, 3H), 6.38 (d, 1H, $J = 15.9$ Hz), 6.94 (d, 1H, $J = 8.7$ Hz), 7.15 (d, 2H, $J = 8.1$ Hz), 7.24 (t, 1H, $J = 8.1$ Hz), 7.43 (t, 2H, $J = 8.1$ Hz), 7.64 (d, 1H, $J = 15.9$ Hz), 7.87 (dd, 1H, $J = 2.4$, 8.7 Hz), 8.29 (d, 1H, $J = 2.4$ Hz) ppm.

Under N_2, to a solution of 3-(6-phenoxypyridin-3-yl)-acrylic acid methyl ester (2.54 g, 9.95 mmol) in CH_3OH

(30 ml) was added Pd/C powder (10 wt.% Pd) (0.20 g, 0.19 mmol). A balloon of H_2 was applied to the reaction mixture, and the mixture was stirred at room temperature for 5 h. Water (50 ml) was then added to deactivate the catalyst, and CH_3OH was removed by evaporation under vacuum. The residual aqueous mixture was extracted with CH_2Cl_2 (4×30 ml), and the extract was dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum, and the residual oil was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:1, v/v)), affording a colorless oil (1.31 g, 51%). ^{1}H-NMR ($CDCl_3$) δ 2.61 (t, 2H, $J = 7.5$ Hz), 2.91 (t, 2H, $J = 7.5$ Hz), 3.68 (s, 3H), 6.83 (d, 1H, $J = 8.4$ Hz), 7.12 (d, 2H, $J = 7.8$), 7.18 (t, 1H, $J = 7.8$ Hz), 7.39 (t, 2H, $J = 7.8$ Hz), 7.54 (dd, 1H, $J = 2.4$, 8.4 Hz), 8.04 (d, 1H, $J = 2.4$ Hz) ppm.

3.15. Acetic acid 3-(6-phenoxypyridin-3-yl)propyl ester (**HL9**) and 3-(6-phenoxypyridin-3-yl)propan-1-ol

Under N_2, at 0 °C, $LiAlH_4$ (1.0 M in THF) (8.0 ml, 8.0 mmol) was added slowly to a solution of **HL8** (3.00 g, 11.7 mmol) in THF (40 ml). After the addition was complete, the reaction mixture was warmed to room temperature, and stirred for another 2 h. The reaction was then quenched by the slow addition of H_2O (20 ml). The organic layer was collected, and the aqueous layer was extracted with CH_2Cl_2 (2×20 ml). The organic layers were combined and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum, and a pale yellow oil (2.65 g, 99%) was obtained and used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ 1.82–1.91 (m, 2H), 2.68 (t, 2H, $J = 7.5$ Hz), 3.66–3.75 (m, 2H), 6.84 (d, 1H, $J = 8.4$ Hz), 7.12 (d, 2H, $J = 7.8$), 7.18 (t, 1H, $J = 7.8$ Hz), 7.39 (t, 2H, $J = 7.8$ Hz), 7.53 (dd, 1H, $J = 2.4$, 8.4 Hz), 8.04 (d, 1H, $J = 2.4$ Hz) ppm.

To a solution of the above alcohol (0.600 g, 2.62 mmol) and Et_3N (0.50 ml) in dry CH_2Cl_2 (20 ml) was added CH_3COCl (0.248 g, 3.14 mmol). After the mixture was stirred at room temperature for 2 h, H_2O (30 ml) was added, and the organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (30 ml). The organic layers were combined and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum, and the residual oil was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:1, v/v)), affording a colorless oil (0.578 g, 81%). ^{1}H-NMR ($CDCl_3$) δ 1.88–1.98 (m, 2H), 2.06 (s, 3H), 2.65 (t, 2H, $J = 7.5$ Hz), 4.09 (t, 2H, $J = 6.3$ Hz), 6.84 (d, 1H, $J = 8.4$ Hz), 7.12 (d, 2H, $J = 7.5$ H_2), 7.21 (t, 1H, $J = 7.5$ Hz), 7.39 (t, 2H, $J = 7.5$ Hz), 7.51 (dd, 1H, $J = 2.1$, 8.4 Hz), 8.03 (d, 1H, $J = 2.1$ Hz) ppm.

3.16. 4-(6-Phenoxypyridin-3-yl)butyronitrile (**HL10**) and 5-(3-chloropropyl)-2-phenoxypyridine

Under N_2, $POCl_3$ (1.27 g, 8.29 mmol) was added to a solution of 3-(6-phenoxypyridin-3-yl)propan-1-ol (1.90 g, 8.29 mmol) in dry CH_2Cl_2 (20 ml). After the mixture was stirred at room temperature for 2 h, NaOH (1 N) was added until the pH of the mixture reached ~ 10. The organic layer was collected, washed with H_2O (2×30 ml) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum, and the residual oil was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:2, v/v)), affording a colorless oil (0.631 g, 31%). ^{1}H-NMR ($CDCl_3$) δ 2.02–2.11 (m, 2H), 2.75 (t, 2H, $J = 7.5$ Hz), 3.54 (t, 2H, $J = 6.3$ Hz), 6.84–6.89 (m, 1H), 7.13 (d, 2H, $J = 7.5$ Hz), 7.22 (t, 1H, $J = 7.5$ Hz), 7.41 (t, 2H, $J = 7.5$ Hz), 7.55–7.61 (m, 1H), 8.08 (s, 1H) ppm.

A mixture of the above pyridine (0.631 g, 2.55 mmol) and NaCN (0.374 g, 7.63 mmol) in DMSO (10 ml) was heated at 90 °C for 5 h. After the solution was cooled to room temperature, H_2O (50 ml) was added, and the mixture was extracted with diethyl ether (3×50 ml). The extracts were combined, washed with H_2O (50 ml) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum to afford a colorless oil (0.560 g, 92%). ^{1}H-NMR ($CDCl_3$) δ 1.96 (quintet, 2H, $J = 7.2$ Hz), 2.36 (t, 2H, $J = 7.2$ Hz), 2.75 (t, 2H, $J = 7.2$ Hz), 6.87–6.89 (d, 1H, $J = 8.4$ Hz), 7.12 (d, 2H, $J = 7.5$ Hz), 7.20 (t, 1H, $J = 7.5$ Hz), 7.40 (t, 2H, $J = 7.5$ Hz), 7.52 (dd, 1H, $J = 2.4$, 8.4 Hz), 8.03 (d, 1H, $J = 2.4$ Hz) ppm. ES-MS m/z 239 $[M+H]^+$.

3.17. 2-Phenoxy-5-phenylpyridine (**HL11**)

Following general procedure C using the Grignard reagent PhMgCl (3.0 M in diethyl ether) (1.92 ml, 5.76 mmol) and **HL15** (1.20 g, 4.80 mmol). The product was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:6, v/v)), affording a white solid (0.363 g, 31%). ^{1}H-NMR ($CDCl_3$) δ 6.98 (d, 1H, $J = 8.4$ Hz), 7.17–7.25 (m, 3H), 7.37–7.55 (m, 7H), 7.90 (dd, 1H, $J = 2.4$, 8.4 Hz), 8.43 (d, 1H, $J = 2.4$ Hz) ppm.

3.18. 2-Phenoxy-5-thiophen-2-ylpyridine (**HL12**)

Following general procedure C using the Grignard reagent prepared from Mg (0.215 g, 8.85 mmol) and 2-bromothiophene (1.20 g, 7.36 mmol), and **HL15** (1.63 g, 6.50 mmol). The product was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:5, v/v)), affording a yellow oil (0.495 g, 30%). ^{1}H-NMR ($CDCl_3$) δ 6.94 (d, 1H, $J = 8.7$ Hz), 7.09 (dd, 1H, $J = 3.6$, 5.4 Hz), 7.15–7.19 (m, 2H), 7.22–7.26 (m, 2H), 7.31 (dd, 1H, $J = 1.2$, 5.4 Hz), 7.39–7.45 (m, 2H), 7.88 (dd, 1H, $J =$ 2.1, 8.7 Hz), 8.01 (d, 1H, $J = 2.1$ Hz) ppm.

3.19. 5-Fluoro-2-phenoxypyridine (**HL13**)

To a suspension of 6-phenoxypyridin-3-ylamine (1.00 g, 5.38 mmol) in aqueous HCl (4.5 N, 5.0 ml) cooled at ~5 °C was added $NaNO_2$ (0.414 g, 6.00 mmol) in H_2O (3.0 ml). After the addition was complete, the mixture was stirred at ~5 °C for 30 min, affording a clear solution. To the solution was added $NaBF_4$ (1.10 g, 10.0 mmol) in H_2O (7.0 ml) resulting in precipitation of a solid. The solid was collected by filtration, washed with cold water and a small amount of ethanol, and dried in vacuo overnight. The dry solid decomposed to give a brown sticky oil when it was heated up to 125 °C in a flask. After being cooled to room temperature, the oil was extracted with CH_2Cl_2 (5 ml) and purified by flash chromatography on silica gel (diethyl ether–hexanes (1:4, v/v)), affording a colorless oil (0.244 g, 24%). ^{1}H-NMR ($CDCl_3$) δ 6.91 (dd, 1H, $J = 3.3$, 8.7 Hz), 7.11–7.16 (m, 2H), 7.18–7.25 (m, 1H), 7.37–7.47 (m, 3H), 8.05 (d, 1H, $J = 3.3$ Hz) ppm.

3.20. 5-Chloro-2-phenoxypyridine (**HL14**)

Following general procedure B using 2,5-dichloropyridine (1.50 g, 10.0 mmol), phenol (1.13 g, 12.0 mmol) and K_2CO_3 (2.76 g, 20.0 mmol) in DMSO (10 ml). The product was extracted with CH_2Cl_2 (2 × 20 ml), and a colorless oil (1.44 g, 70%) was obtained after purification by flash chromatography on silica gel (diethyl ether–hexanes (1:6, v/v)). ^{1}H-NMR ($CDCl_3$) δ 6.87 (d, 1H, $J = 8.7$ Hz), 7.11–7.14 (m, 2H), 7.19–7.24 (m, 1H), 7.37–7.45 (m, 2H), 7.64 (dd, 1H, $J = 2.7$, 8.7 Hz), 8.13 (d, 1H, $J = 2.7$ Hz) ppm.

3.21. 5-Bromo-2-phenoxypyridine (**HL15**)

Following general procedure A using 2,5-dibromopyridine (8.10 g, 34.2 mmol), phenol (4.06 g, 43.2 mmol) and K_2CO_3 (6.00 g, 43.2 mmol). The product was extracted with CH_2Cl_2, and a colorless oil (7.40 g, 83%) was obtained after purification by flash chromatography on silica gel (diethyl ether–hexanes (1:9, v/v)). ^{1}H-NMR ($CDCl_3$) δ 6.83 (d, 1H, $J = 8.7$ Hz), 7.13 (d, 2H, $J = 8.1$ Hz), 7.23 (t, 1H, $J = 8.1$ Hz), 7.41 (t, 2H, $J = 8.1$ Hz), 7.77 (dd, 1H, $J = 2.4$, 8.7 Hz), 8.22 (d, 1H, $J = 2.4$ Hz) ppm.

3.22. 5-Iodo-2-phenoxypyridine (**HL16**)

To a suspension of 6-phenoxypyridin-3-ylamine (0.860 g, 4.62 mmol) in aqueous H_2SO_4 (6 N, 6.0 ml) cooled at ~5 °C was added $NaNO_2$ (0.351 g, 5.10 mmol) in H_2O (2.0 ml). After the addition was complete, the mixture was stirred at ~5 °C for 1 h, affording a clear solution. Potassium iodide (1.53 g, 9.24 mmol) in H_2O (5.0 ml) was added, and the solution was warmed to room temperature. After neutralization by adding NaOH (1 N), the solution was extracted with ethyl acetate (3 × 30 ml). The organic layers were combined, washed with H_2O (50 ml), and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum, and the brownish red residue was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:4, v/v)), affording a brown oil (0.820 g, 60%). ^{1}H-NMR ($CDCl_3$) δ 6.75 (d, 1H, $J = 8.4$ Hz), 7.11–7.14 (m, 2H), 7.19–7.25 (m, 1H), 7.38–7.44 (m, 2H), 7.91 (dd, 1H, $J = 2.1$, 8.4 Hz), 8.36 (d, 1H, $J = 2.1$ Hz) ppm.

3.23. 5-Nitro-2-phenoxypyridine (**HL17**)

Following general procedure B using 2-bromo-5-nitropyridine (10.0 g, 49.3 mmol), phenol (5.09 g, 54.1 mmol) and K_2CO_3 (8.16 g, 59.1 mmol) in DMSO. The mixture was heated at 120 °C for 4 h, and the product was extracted with diethyl ether. A pale yellow solid (9.85 g, 93%) was obtained after purification by flash chromatography on silica gel (diethyl ether–hexanes (1:2, v/v)). ^{1}H-NMR ($CDCl_3$) δ 7.03 (d, 1H, $J = 9.0$ Hz), 7.15–7.18 (m, 2H), 7.28–7.34 (m, 1H), 7.43–7.49 (m, 2H), 8.48 (dd, 1H, $J = 2.7$, 9.0 Hz), 9.04 (d, 1H, $J = 2.7$ Hz) ppm.

3.24. 5-Cyano-2-phenoxypyridine (**HL18**)

Under N_2, to a suspension of **HL15** (25.0 g, 100 mmol) and $Zn(CN)_2$ (7.05 g, 60.0 mmol) in dry DMF (80 ml) was added 1,1′-bis(diphenylphosphino)ferrocene (DPPF) (0.133 g, 0.240 mmol) and $Pd_2(dba)_3$ (0.0920 g, 0.100 mmol). After the mixture was heated at 140 °C for 40 h, the solvent was removed by evaporation under vacuum and H_2O (100 ml) was added. The aqueous suspension was extracted with CH_2Cl_2 (4 × 60 ml). The extract was washed with H_2O (100 ml), and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum, and the residual solid was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:4, v/v)), affording a white solid (15.7 g, 80%). ^{1}H-NMR ($CDCl_3$) δ 7.01 (d, 1H, $J = 8.4$ Hz), 7.12–7.16 (m, 2H), 7.26–7.31 (m, 1H), 7.42–7.49 (m, 2H), 7.92 (dd, 1H, $J = 2.4$, 8.4 Hz), 8.46 (d, 1H, $J = 2.4$ Hz) ppm.

3.25. 5-Acetyl-2-phenoxypyridine (**HL19**)

Under N_2 to a solution of **HL18** (0.785 g, 4.00 mmol) in dry THF (15 ml) was added CH_3MgBr (3.0 M in diethyl ether) (1.67 ml, 5.00 mmol) at 0 °C. After the addition was completed, the mixture was warmed to room temperature and stirred for 2 h, and then heated at reflux for 30 min. The solution was then cooled to room temperature and aqueous HCl (4 N, 16 ml) was added,

and the mixture was heated at reflux for 20 h. The solution was then neutralized with NaOH (1 N) and extracted with ethyl acetate (3 × 30 ml), and the extract was dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum, and the pale yellow liquid residue was purified by flash chromatography on silica gel (diethyl ether–hexanes (1:1, v/v)), affording a colorless liquid (0.258 g, 30%). ^{1}H-NMR ($CDCl_3$) δ 2.57 (s, 3H), 6.97 (d, 1H, $J = 8.7$ Hz), 7.14–7.18 (m, 2H), 7.24–7.30 (m, 1H), 7.41–7.47 (m, 2H), 8.26 (dd, 1H, $J = 2.4$, 8.7 Hz), 8.77 (d, 1H, $J = 2.4$ Hz) ppm.

3.26. 6-Phenoxynicotinic acid (*HL20*)

A suspension of **HL18** (10.0 g, 51.0 mmol) in aqueous NaOH (10 wt.%) was heated at reflux for 2 h, resulting in a clear solution. The solution was cooled to room temperature and neutralized with HCl (6 N), resulting in precipitation of a white solid. The white solid (14.9 g, 99%) was collected by filtration and washed with H_2O, and dried in vacuo at 60 °C overnight. ^{1}H-NMR (CD_3OD) δ 6.94 (d, 1H, $J = 8.7$ Hz), 7.12 −7.16 (m, 2H), 7.23–7.28 (m, 1H), 7.40–7.47 (m, 2H), 8.31 (dd, 1H, $J = 2.4$, 8.7 Hz), 8.71 (d, 1H, $J = 2.4$ Hz) ppm.

3.27. 6-Phenoxynicotinic acid methyl ester (*HL21*)

Following general procedure D using **HL20** (1.00 g, 4.65 mmol). A white solid (0.880 g, 83%) was obtained after purification by flash chromatography on silica gel (diethyl ether–hexanes (1:1, v/v)). ^{1}H-NMR ($CDCl_3$) δ 3.92 (s, 3H), 6.93 (d, 1H, $J = 8.7$ Hz), 7.16 (d, 2H, $J = 7.8$ Hz), 7.26 (t, 1H, $J = 7.8$ Hz), 7.46 (t, 2H, $J = 7.8$ Hz), 8.27 (dd, 1H, $J = 2.4$, 8.7 Hz), 8.82 (d, 1H, $J = 2.4$ Hz) ppm.

3.28. 6-Phenoxynicotinamide (*HL22*)

To a solution of **HL18** (1.04 g, 5.30 mmol) in CH_3OH (20 ml) was added a suspension of $NaBO_3 \cdot 4H_2O$ (1.63 g, 10.6 mmol) in H_2O (5 ml). After the mixture was heated at 60 °C for 20 h, CH_3OH was removed by evaporation under vacuum, and the residue was extracted with CH_2Cl_2 (3 × 50 ml). The extract was washed with H_2O (50 ml), and dried over anhydrous $MgSO_4$. The filtrate was concentrated, and the residue was washed with a small amount of CH_2Cl_2, affording a white solid (0.689 g, 61%). ^{1}H-NMR (CD_3OD) δ 6.98 (d, 1H, $J = 8.7$ Hz), 7.12–7.16 (m, 2H), 7.22–7.28 (m, 1H), 7.41–7.47 (m, 2H), 8.25 (dd, 1H, $J = 2.4$, 8.7 Hz), 8.63 (d, 1H, $J = 2.4$ Hz) ppm.

3.29. N-Methyl-6-phenoxynicotinamide (*HL23*)

Following general procedure D using **HL20** (1.00 g, 4.65 mmol) and methylamine (2.0 M in THF) (5.1 ml, 10 mmol). A white solid (1.03 g, 97%) was obtained. ^{1}H-NMR ($CDCl_3$) δ 3.01 (d, 3H, $J = 4.8$ Hz), 6.08 (s, broad, 1H), 6.94 (d, 1H, $J = 8.7$ Hz), 7.12–7.16 (m, 2H), 7.22–7.28 (m, 1H), 7.40–7.46 (m, 2H), 8.13 (dd, 1H, $J = 2.4$, 8.7 Hz), 8.53 (d, 1H, $J = 2.4$ Hz) ppm.

3.30. N,N-Dimethyl-6-phenoxynicotinamide (*HL24*)

Following general procedure D using **HL20** (1.00 g, 4.65 mmol) and dimethylamine (2.0 M in THF) (5.1 ml, 10 mmol). A sticky pale yellow oil (1.06 g, 94%) was obtained. ^{1}H-NMR ($CDCl_3$) δ 3.08 (s, broad, 6H), 6.94 (d, 1H, $J = 8.7$ Hz), 7.11–7.17 (m, 2H), 7.21–7.26 (m, 1H), 7.39–7.46 (m, 2H), 7.81 (dd, 1H, $J = 2.4$, 8.7 Hz), 8.28 (d, 1H, $J = 2.4$ Hz) ppm.

3.31. N-Cyclopentyl-6-phenoxynicotinamide (*HL25*)

Following general procedure D using **HL20** (0.350 g, 1.63 mmol) and cyclopentylamine (1.0 ml, 10 mmol). A white solid (0.430 g, 94%) was obtained after the crude product was washed with a small amount of diethyl ether. ^{1}H-NMR ($CDCl_3$) δ 1.44–1.52 (m, 2H), 1.61–1.74 (m, 4H), 2.05–2.13 (m, 2H), 4.33–4.44 (m, 1H), 5.95 (d, 1H, $J = 6.0$ Hz), 6.92 (d, 1H, $J = 8.7$ Hz), 7.12–7.15 (m, 2H), 7.22–7.27 (m, 1H), 7.40–7.45 (m, 2H), 8.11 (dd, 1H, $J = 2.4$, 8.7 Hz), 8.51 (d, 1H, $J = 2.4$ Hz) ppm.

3.32. Dimethyl-(6-phenoxypyridin-3-yl)amine (*HL26*)

To a solution of formic acid (1.3 ml, 33 mmol) in H_2O (1.5 ml) pre-cooled to 0 °C was added 6-phenoxypyridin-3-ylamine (1.00 g, 5.37 mmol), and the mixture was stirred until it became clear. Formaldehyde (37% in H_2O) (1.2 ml, 16 mmol) was added, and the mixture was heated in an oil bath pre-heated at 90 °C, and then at reflux for 2 h. The reaction was then cooled to room temperature, and aqueous KOH solution (1 N, 25 ml) was added. The mixture was extracted with diethyl ether (3 × 30 ml), and the extract was dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by evaporation under vacuum, and the residual oil was purified by flash chromatography on silica gel (diethyl ether–hexanes (3:2, v/v)), affording a colorless oil (0.666 g, 58%). ^{1}H-NMR ($CDCl_3$) δ 2.93 (s, 6H), 6.84 (d, 1H, $J = 9.0$ Hz), 7.03–7.07 (m, 2H), 7.08–7.17 (m, 2H), 7.32–7.38 (m, 2H), 7.75 (d, 1H, $J = 3.3$ Hz) ppm.

3.33. N-(6-Phenoxypyridin-3-yl)acetamide (**HL27**)

Following general procedure E using 6-phenoxypyridin-3-ylamine (0.500 g, 2.69 mmol) and CH_3COCl (0.222 g, 2.83 mmol). A white solid (0.605 g, 99%) was obtained after the crude product was washed with hexanes. ^{1}H-NMR ($CDCl_3$) δ 2.19 (s, 3H), 6.88–6.91 (m, 1H), 7.11 (d, 2H, $J = 7.8$ Hz), 7.19 (t, 1H, $J = 7.8$ Hz), 7.28 (s, broad, 1H), 7.39 (t, 2H, $J = 7.8$ Hz), 8.08–8.11 (m, 2H) ppm.

3.34. N-(6-Phenoxypyridin-3-yl)benzamide (**HL28**)

Following general procedure E using 6-phenoxypyridin-3-ylamine (0.516 g, 2.77 mmol) and benzoyl chloride (0.410 g, 2.92 mmol). A white solid (0.738 g, 92%) was obtained after the crude product was washed with hexanes. ^{1}H-NMR ($CDCl_3$) δ 6.95 −6.98 (m, 1H), 7.12–7.18 (m, 2H), 7.20–7.23 (m, 1H), 7.38–7.44 (m, 2H), 7.48–7.61 (m, 3H), 7.78 (s, broad, 1H), 7.87–7.90 (m, 2H), 8.24–8.28 (m, 2H) ppm.

3.35. General procedure for cycloauration

A solution of the 2-phenoxypyridine ligand (**HL**) (1.00 mmol) in CH_3CN (5 ml) was added to a solution of $NaAuCl_4$ (1.00 mmol) in H_2O (20 ml), forming a yellow suspension. The suspension was stirred at room temperature for a certain period of time (10 min to 24 h) (see Table 2), and a yellow solid was collected by filtration. After being washed with H_2O and a small amount of diethyl ether, the yellow solid was suspended in mixed CH_3CN/H_2O (50 ml; 1/5, v/v). The suspension was stirred at room temperature for 10 min, and was then heated at reflux for a certain period of time (see Table 2). The reaction mixture was cooled to room temperature, and a solid was collected by filtration and washed with H_2O. The solid was extracted with hot acetone or CH_2Cl_2, and the extract was filtered through filter paper or a celite cake. The solvent was removed by evaporation under vacuum, and the residual solid was soaked with a small amount of pre-cooled acetone, and then collected by filtration and washed with a very small amount of pre-cooled acetone and then hexanes. In some cases, the product was purified by flash chromatography on silica gel.

3.36. Gold, dichloro[2-[(4-methyl-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**1**)

^{1}H-NMR (d^6-DMSO) δ 2.52 (s, 3H), 7.18–7.24 (m, 1H), 7.30–7.39 (m, 2H), 7.53 (dd, 1H, $J = 1.5$, 6.3 Hz), 7.58 (dd, 1H, $J = 1.5$, 8.1 Hz), 7.72 (s, 1H), 8.88 (d, 1H, $J = 6.3$ Hz). ^{13}C-NMR (d^6-DMSO) δ 21.00, 116.50, 118.89, 123.31, 123.89, 126.12, 129.76, 133.45, 146.56, 148.32, 155.22, 159.77 ppm. ES-MS m/z 474 $[M+Na]^+$. Anal. Calcd. for $C_{12}H_{10}Cl_2NOAu$: C, 31.88; H, 2.23; Cl, 15.68; N, 3.10. Found: C, 31.88; H, 2.26; Cl, 15.75; N, 3.14%.

3.37. Gold, dichloro[2-[(5-methyl-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**2**)

^{1}H-NMR (d^6-DMSO) δ 2.38 (s, 3H), 7.19 (dt, 1H, $J = 1.8$, 7.5 Hz), 7.30–7.39 (m, 2H), 7.55 (d, 1H, $J = 7.8$ Hz), 7.77 (d, 1H, $J = 7.8$ Hz), 8.26 (dd, 1H, $J = 1.2$, 8.1 Hz), 8.84 (s, 1H). ^{13}C-NMR (d^6-DMSO) δ 17.17, 116.18, 118.94, 124.19, 126.11, 129.78, 132.12, 133.44, 146.77, 147.50, 148.03, 154.11 ppm. ES-MS m/z 474 $[M+Na]^+$. Anal. Calcd. for $C_{12}H_{10}Cl_2NOAu$: C, 31.88; H, 2.23; Cl, 15.68; N, 3.10. Found: C, 31.90; H, 2.20; Cl, 15.82; N, 3.03%.

3.38. Gold, dichloro[2-[(6-methyl-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**3**)

To a solution of $NaAuCl_4 \cdot 2H_2O$ (0.400 g, 1.00 mmol) and **HL3** (0.185 g, 0.100 mmol) in CH_3CH_2CN (20 ml) was added a solution of $AgSO_3CF_3$ (0.514 g, 2.00 mmol) in CH_3CH_2CN (10 ml) over a period of 8 h while the solution was being heated at reflux. The mixture was heated at reflux for an additional 16 h, then acetone (100 ml) was added and the mixture was filtered through a celite cake. The filtrate was evaporated under vacuum, and the residual solid was collected, washed with a small amount of acetone and recrystallized from CH_2Cl_2, affording the pure product (0.030 g, 6.6%). The complex was found to be unstable in both DMF and DMSO, and no ^{13}C-NMR was available due to its poor solubility in other solvents. ^{1}H-NMR (CD_2Cl_2) δ 3.11 (s, 3H), 7.19–7.26 (m, 2H), 7.28–7.36 (m, 2H), 7.48 (d, 1H, $J = 8.1$ Hz), 7.58 (dd, 1H, $J = 1.5$, 7.8 Hz), 8.04 (t, 1H, $J = 7.8$ Hz). ES-MS m/z 474 $[M+Na]^+$. Anal. Calcd. for $C_{12}H_{10}Cl_2NOAu \cdot 0.25CH_2Cl_2$: C, 31.08; H, 2.24; Cl, 18.73; N, 2.96. Found: C, 30.88; H, 2.16; Cl, 18.69; N, 3.25%.

3.39. Gold, dichloro[2-[(5-ethyl-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**4**)

^{1}H-NMR (d^6-DMSO) δ 1.19 (t, 3H, $J = 7.5$ Hz), 2.72 (q, 2H, $J = 7.5$ Hz), 7.17–7.23 (m, 1H), 7.30–7.39 (m, 2H), 7.55 (dd, 1H, $J = 1.2$, 8.1 Hz), 7.79 (d, 1H, $J = 8.1$ Hz), 8.31 (dd, 1H, $J = 2.1$, 8.7 Hz), 8.87 (d, 1H, $J = 1.2$ Hz) ppm. ^{13}C-NMR (d^6-DMSO) δ 14.69, 24.58, 116.34, 118.94, 124.09, 126.14, 129.80, 133.45, 137.68, 146.54, 146.73, 147.60, 154.19 ppm. ES-MS m/z 488 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_{12}Cl_2NOAu$: C, 33.51; H, 2.59; Cl, 15.21; N, 3.00. Found: C, 33.51; H, 2.56; Cl, 15.16; N, 2.98%.

Table 2
Cycloauration reactions of 2-phenoxypyridine derivatives

Compound	Ligand	R	Reaction time		Overall yield (%)
			Step 1	Step 2	
1	**HL1**	4-CH_3	15 min	16 h	65
				4 days	84
2	**HL2**	5-CH_3	15 min	24 h	74
3	**HL3**	6-CH_3	5 h	20 h	1
4	**HL4**	5-CH_2CH_3	2 h	20 h	42
5	**HL5**	5-$(CH_2)_2CH_3$	2 h	48 h	61
6	**HL6**	5-$(CH_2)_3CH_3$	5 h	72 h	23
	HL7	5-$(CH_2)_4CH_3$	3 h	48 h	0
8	**HL8**	5-$(CH_2)_2COOCH_3$	2 h	16 h	39
9	**HL9**	5-$(CH_2)_3OCOCH_3$	3 h	16 h	42
10	**HL10**	5-$(CH_2)_3CN$	2 h	16 h	71
11	**HL11**	5-Ph	15 min	84 h	15
	HL12	5-(2-thienyl)	15 min	16 h	0
13	**HL13**	5-F	3 h	72 h	15
14	**HL14**	5-Cl	3 h	20 h	15
15	**HL15**	5-Br	30 min	24 h	18
16	**HL16**	5-I	3 h	24 h	11
	HL17	5-NO_2	–	–	–
	HL18	5-CN	–	–	–
	HL19	5-$COCH_3$	1 h	16 h	0
	HL20	5-COOH	5 h	16 h	see text
21	**HL21**	5-$COOCH_3$	2 h	16 h	14
22	**HL22**	5-$CONH_2$	1 h	16 h	32
23	**HL23**	5-$CONHCH_3$	2 h	24 h	30
24	**HL24**	5-$CON(CH_3)_2$	2 h	48 h	36
25	**HL25**	5-$CONHC_5H_9$	24 h	24 h	6
	HL26	5-$N(CH_3)_2$	–	–	–
27	**HL27**	5-$NHCOCH_3$	4 h	16 h	21
28	**HL28**	5-NHCOPh	4 h	72 h	14

*3.40. Gold, dichloro[2-[(5-propyl-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**5**)*

^{1}H-NMR (d^6-DMSO) δ 0.89 (t, 3H, $J = 7.5$ Hz), 1.59 (sextet, 2H, $J = 7.5$ Hz), 2.66 (t, 2H, $J = 7.5$ Hz), 7.17–7.23 (m, 1H), 7.30–7.39 (m, 2H), 7.56 (dd, 1H, $J = 1.2$, 8.1 Hz), 7.77 (d, 1H, $J = 8.1$ Hz), 8.29 (dd, 1H, $J = 2.1$, 8.7 Hz), 8.85 (d, 1H, $J = 1.2$ Hz) ppm. ^{13}C-NMR (d^6-DMSO) δ 13.21, 23.27, 33.08, 116.29, 118.92, 124.03, 126.11, 129.78, 133.45, 136.13, 146.67, 146.87, 148.01, 154.16 ppm. ES-MS *m/z* 502 $[M+Na]^+$. Anal. Calcd. for $C_{14}H_{14}Cl_2NOAu$: C, 35.02; H, 2.94; Cl, 14.77; N, 2.92. Found: C, 35.02; H, 2.82; Cl, 14.99; N, 2.90%.

*3.41. Gold, dichloro[2-[(5-butyl-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**6**)*

^{1}H-NMR (CD_2Cl_2) δ 0.95 (t, 3H, $J = 7.5$ Hz), 1.39 (sextet, 2H, $J = 7.5$ Hz), 1.65 (quintet, 2H, $J = 7.5$ Hz), 2.75 (t, 2H, $J = 7.5$ Hz), 7.16–7.21 (m, 1H), 7.26 (dd, 1H, $J = 1.8$, 7.8 Hz), 7.31–7.36 (m, 1H), 7.51 (d, 1H, $J = 8.7$ Hz), 7.73 (dd, 1H, $J = 1.5$, 8.1 Hz), 7.99 (dd, 1H, $J = 2.1$, 8.7 Hz), 8.99 (d, 1H, $J = 2.1$ Hz) ppm. ^{13}C-NMR (CD_2Cl_2) δ 14.02, 22.53, 32.35, 33.26, 116.90, 119.28, 125.14, 126.68, 130.25, 134.12, 137.62, 146.26, 147.42, 148.26, 155.39 ppm. ES-MS *m/z* 516 $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{16}Cl_2NOAu$: C, 36.46; H, 3.26; Cl, 14.35; N, 2.83. Found: C, 36.62; H, 3.34; Cl, 14.51; N, 2.90%.

*3.42. Gold, dichloro[2-[[5-(3-methoxy-3-oxopropyl)-2-pyridinyl-κN]oxy]phenyl-κC]-, (SP-4-3)- (**8**)*

Direct purification by recrystallization of the crude product from acetone was unsuccessful; however, flash chromatography on silica gel (CH_2Cl_2–diethyl ether (1:1, v/v)) followed by recrystallization from cool acetone resulted in a pure solid. ^{1}H-NMR ($CDCl_3$) δ 2.72 (t, 2H, $J = 7.2$ Hz), 3.06 (t, 2H, $J = 7.2$ Hz), 3.68 (s, 3H), 7.14–7.21 (m, 2H), 7.25–7.32 (m, 1H), 7.48 (d, 1H, $J = 8.4$ Hz), 7.76 (dd, 1H, $J = 1.5$, 8.1 Hz), 8.05 (dd, 1H, $J = 2.1$, 8.4 Hz), 9.09 (d, 1H, $J = 2.1$ Hz) ppm. ^{13}C-NMR ($CDCl_3$) δ 27.26, 34.49, 52.30, 116.62, 118.85, 124.59, 126.65, 129.98, 134.02, 135.15, 146.16, 146.69, 148.34, 155.39, 172.24 ppm. ES-MS *m/z* 547 $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{14}Cl_2NO_3Au$: C, 34.37; H, 2.69; Cl, 13.53; N, 2.67. Found: C, 34.56; H, 2.69; Cl, 13.72; N, 2.69%.

3.43. Gold, [2-[[5-[3-acetyloxypropyl]-2-pyridinyl-κN]oxy]phenyl-κC]dichloro-, (SP-4-3)- (**9**)

Direct purification by recrystallization of the crude product from acetone was unsuccessful; however, flash chromatography on silica gel (CH_2Cl_2–diethyl acetate (1:1, v/v)) followed by recrystallization from cool acetone resulted in a pure solid. ^{1}H-NMR (CD_2Cl_2) δ 1.95–2.04 (m, 2H), 2.04 (s, 3H), 2.85 (t, 2H, $J = 7.5$ Hz), 4.09 (t, 2H, $J = 6.3$ Hz), 7.17–7.20 (m, 1H), 7.22–7.34 (m, 2H), 7.54 (d, 1H, $J = 8.4$ Hz), 7.73 (dd, 1H, $J = 1.5$, 8.1 Hz), 8.02 (dd, 1H, $J = 2.1$, 8.4 Hz), 9.04 (d, 1H, $J =$ 2.1 Hz) ppm. ^{13}C-NMR (CD_2Cl_2) δ 21.22, 29.17, 30.03, 63.23, 117.11, 119.28, 125.02, 126.77, 130.30, 134.13, 136.26, 146.28, 147.31, 148.43, 155.66, 171.28 ppm. ES-MS *m/z* 561 $[M+Na]^+$. Anal. Calcd. for $C_{16}H_{16}Cl_2NO_3Au$: C, 35.71; H, 3.00; Cl, 13.18; N, 2.60. Found: C, 35.70; H, 2.95; Cl, 13.25; N, 2.51%.

3.44. Gold, dichloro[2-[[5-(3-cyanopropyl)-2-pyridinyl-κN]oxy]phenyl-κC]-, (SP-4-3)- (**10**)

This compound was purified either by direct recrystallization of the crude product from acetone or by flash chromatography on silica gel (CH_2Cl_2–diethyl ether (1:1, v/v)). ^{1}H-NMR ($CDCl_3$) δ 2.05 (quintet, 2H, $J =$ 7.2 Hz), 2.48 (t, 2H, $J = 7.2$ Hz), 2.94 (t, 2H, $J = 7.2$ Hz), 7.15–7.33 (m, 3H), 7.54 (d, 1H, $J = 8.4$ Hz), 7.76 (d, 1H, $J = 7.8$ Hz), 8.01 (dd, 1H, $J = 2.1$, 8.4 Hz), 9.01 (d, 1H, $J = 2.1$ Hz) ppm. ^{13}C-NMR ($CDCl_3$) δ 15.51, 25.66, 30.08, 116.49, 118.91, 120.23, 123.92, 126.14, 129.80, 133.41, 134.64, 146.58, 146.95, 148.10, 154.41 ppm. ES-MS *m/z* 528 $[M+Na]^+$. Anal. Calcd. for $C_{15}H_{13}Cl_2N_2OAu$: C, 35.67; H, 2.59; Cl, 14.04; N, 5.55. Found: C, 35.66; H, 2.62; Cl, 13.88; N, 5.49%.

3.45. Gold, dichloro[2-[(5-phenyl-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**11**)

^{1}H-NMR (d^6-DMSO) δ 7.21–7.26 (m, 1H), 7.34–7.40 (m, 2H), 7.47–7.62 (m, 4H), 7.71–7.75 (m, 2H), 7.94 (d, 1H, $J = 8.4$ Hz), 8.72 (dd, 1H, $J = 2.1$, 8.4 Hz), 9.32 (d, 1H, $J = 2.1$ Hz) ppm. ^{13}C-NMR (d^6-DMSO) δ 116.78, 119.00, 123.58, 126.28, 126.96, 129.26, 129.55, 129.89, 133.42, 133.75, 134.07, 144.53, 146.52, 147.07, 154.83 ppm. ES-MS *m/z* 536 $[M+Na]^+$. Anal. Calcd. for $C_{17}H_{12}Cl_2NOAu$: C, 39.71; H, 2.35; Cl, 13.79; N, 2.72. Found: C, 39.79; H, 2.55; Cl, 13.92; N, 2.72%.

3.46. Gold, dichloro[2-[(5-fluoro-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**13**)

^{1}H-NMR (d^6-DMSO) δ 7.19–7.24 (m, 1H), 7.32–7.40 (m, 2H), 7.56 (d, 1H, $J = 7.8$ Hz), 7.97 (dd, 1H, $J = 4.5$, 9.3 Hz), 8.48–8.53 (m, 1H), 9.08 (s, broad, 1H) ppm. ^{13}C-NMR (d^6-DMSO) δ 118.12 (d, $^3J_{C-F} = 6.8$ Hz), 119.05, 123.89, 126.33, 129.91, 133.39, 134.98 (d, $^2J_{C-F} = 22$ Hz), 136.78 (d, $^2J_{C-F} = 38$ Hz), 146.55, 153.19, 155.63 (d, $^1J_{C-F} = 247$ Hz) ppm. ^{19}F-NMR (d^6-DMSO) δ −52.29 ppm. ES-MS *m/z* 478 $[M+Na]^+$. Anal. Calcd. for $C_{11}H_7Cl_2FNOAu$ ($0.1C_3H_6O$): C, 29.39; H, 1.66; Cl, 15.35; N, 3.03. Found: C, 29.46; H, 1.70; Cl, 15.53; N, 3.02%.

3.47. Gold, dichloro[2-[(5-chloro-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**14**)

^{1}H-NMR (d^6-DMSO) δ 7.20–7.25 (m, 1H), 7.31–7.40 (m, 2H), 7.56 (d, 1H, $J = 7.5$ Hz), 7.91 (d, 1H, $J = 8.7$ Hz), 8.56 (d, 1H, $J = 7.5$ Hz), 9.09 (s, 1H) ppm. ES-MS *m/z* 494 $[M+Na]^+$. Anal. Calcd. for $C_{11}H_7Cl_3NOAu$: C, 27.96; H, 1.49; Cl, 22.51; N, 2.96. Found: C, 28.22; H, 1.50; Cl, 22.24; N, 3.06%.

3.48. Gold, dichloro[2-[(5-bromo-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**15**)

^{1}H-NMR (d^6-DMSO) δ 7.20–7.25 (m, 1H), 7.31–7.40 (m, 2H), 7.56 (d, 1H, $J = 8.1$ Hz), 7.84 (d, 1H, $J = 8.7$ Hz), 8.63 (d, 1H, $J = 8.1$ Hz), 9.15 (s, 1H) ppm. ES-MS *m/z* 539 $[M+Na]^+$. Anal. Calcd. for $C_{11}H_7BrCl_2NOAu$: C, 25.56; H, 1.36; Cl, 13.72; N, 2.71. Found: C, 25.79; H, 1.52; Cl, 13.51; N, 2.68%.

3.49. Gold, dichloro[2-[(5-iodo-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**16**)

^{1}H-NMR (d^6-DMSO) δ 7.19–7.24 (m, 1H), 7.30–7.40 (m, 2H), 7.55 (d, 1H, $J = 7.8$ Hz), 7.68 (d, 1H, $J = 8.7$ Hz), 8.63 (d, 1H, $J = 7.8$ Hz), 9.20 (s, 1H) ppm. ES-MS *m/z* 586 $[M+Na]^+$. Anal. Calcd. for $C_{11}H_7Cl_2INOAu$ ($0.2C_3H_6O$): C, 24.21; H, 1.44; Cl, 12.32; I, 22.05; N, 2.43. Found: C, 24.10; H, 1.39; Cl, 12.07; I, 21.71; N, 2.53%.

3.50. Gold, dichloro[2-[(5-methoxy-oxomethyl-2-pyridinyl-κN)oxy]phenyl-κC]-, (SP-4-3)- (**21**)

^{1}H-NMR (CD_2Cl_2) δ 4.01 (s, 3H), 7.21–7.40 (m, 3H), 7.67 (d, 1H, $J = 8.7$ Hz), 7.77 (d, 1H, $J = 8.1$ Hz), 8.71 (dd, 1H, $J = 1.8$, 8.1 Hz), 9.83 (d, 1H, $J = 1.8$ Hz) ppm. ^{13}C-NMR (d^6-DMSO) δ 53.24, 117.20, 118.86, 122.37, 123.55, 126.53, 129.90, 133.47, 145.70, 145.86, 151.10, 157.84, 162.71 ppm. ES-MS *m/z* 518 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_{10}Cl_2NO_3Au$: C, 31.47; H, 2.03; Cl, 14.29; N, 2.82. Found: C, 31.24; H, 2.11; Cl, 14.56; N, 2.88%.

*3.51. Gold, [2-[[5-(aminocarbonyl)-2-pyridinyl-κN]oxy]phenyl-κC]dichloro-, (SP-4-3)- (**22**)*

^{1}H-NMR (d^6-DMSO) δ 7.20–7.25 (m, 1H), 7.31–7.41 (m, 2H), 7.58 (d, 1H, $J = 7.8$ Hz), 7.92–7.95 (m, 2H), 8.35 (s, 1H), 8.74 (dd, 1H, $J = 1.8$, 8.7 Hz), 9.52 (d, 1H, $J = 1.8$ Hz) ppm. ^{13}C-NMR (d^6-DMSO) δ 116.47, 118.89, 123.05, 126.41, 127.92, 129.91, 133.47, 144.27, 146.03, 150.12, 156.85, 163.31 ppm. ES-MS *m/z* 503 $[M+Na]^+$. Anal. Calcd. for $C_{12}H_9Cl_2N_2O_2Au$: C, 29.96; H, 1.89; Cl, 14.74; N, 5.82. Found: C, 30.21; H, 2.02; Cl, 14.46; N, 5.70%.

*3.52. Gold, dichloro[2-[[5-[(methylamino)carbonyl]-2-pyridinyl-κN]oxy]phenyl-κC]-, (SP-4-3)- (**23**)*

^{1}H-NMR (d^6-DMSO) δ 2.81 (d, 3H, $J = 4.5$ Hz), 7.20–7.25 (m, 1H), 7.33–7.41 (m, 2H), 7.58 (d, 1H, $J =$ 7.8 Hz), 7.94 (d, 1H, $J = 8.7$ Hz), 8.71 (dd, 1H, $J = 1.8$, 8.7 Hz), 8.85–8.88 (m, 1H), 9.50 (s, 1H) ppm. ^{13}C-NMR (d^6-DMSO) δ 26.41, 116.50, 118.87, 123.05, 126.39, 127.98, 129.89, 133.46, 143.86, 146.02, 149.68, 156.73, 162.03 ppm. ES-MS *m/z* 517 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_{11}Cl_2N_2O_2Au$: C, 31.54; H, 2.24; Cl, 14.32; N, 5.66. Found: C, 31.77; H, 2.37; Cl, 14.12; N, 5.51%.

*3.53. Gold, dichloro[2-[[5-[(dimethylamino)carbonyl]-2-pyridinyl-κN]oxy]phenyl-κC]-, (SP-4-3)- (**24**)*

^{1}H-NMR (d^6-DMSO) δ 2.97 (s, 3H), 3.01 (s, 3H), 7.20–7.26 (m, 1H), 7.33–7.41 (m, 2H), 7.58 (d, 1H, $J =$ 7.8 Hz), 7.94 (d, 1H, $J = 8.4$ Hz), 8.46 (dd, 1H, $J = 1.8$, 8.4 Hz), 9.09 (s, 1H) ppm. ^{13}C-NMR (d^6-DMSO) δ 35.19, 117.04, 118.93, 123.13, 126.34, 129.85, 133.43, 145.38, 146.10, 147.76, 155.87, 164.75 ppm. ES-MS *m/z* 531 $[M+Na]^+$. Anal. Calcd. for $C_{14}H_{13}Cl_2N_2O_2Au$: C, 33.03; H, 2.57; Cl, 13.93; N, 5.50. Found: C, 33.14; H, 2.62; Cl, 14.08; N, 5.41%.

*3.54. Gold, dichloro[2-[[5-[(cyclopentylamino)carbonyl]-2-pyridinyl-κN]oxy]phenyl-κC]-, (SP-4-3)- (**25**)*

^{1}H-NMR (d^6-DMSO) δ 1.47–1.56 (m, 4H), 1.64–1.69 (m, 2H), 1.87–1.92 (m, 2H), 4.17–4.26 (m, 1H), 7.20–7.25 (m, 1H), 7.32–7.41 (m, 2H), 7.58 (d, 1H, $J = 8.4$ Hz), 7.93 (d, 1H, $J = 8.7$ Hz), 8.69 (d, 1H, $J = 6.9$ Hz), 8.75 (dd, 1H, $J = 1.8$, 8.7 Hz), 9.49 (d, 1H, $J = 1.8$ Hz) ppm. ^{13}C-NMR (d^6-DMSO) δ 23.64, 32.08, 51.39, 116.32, 118.91, 123.11, 126.41, 128.25, 129.92, 133.45, 144.28, 146.10, 149.80, 156.71, 161.24 ppm. ES-MS *m/z* 571 $[M+Na]^+$. Anal. Calcd. for $C_{17}H_{17}Cl_2N_2O_2Au$ ($0.4H_2O$): C, 36.70; H, 3.22; Cl, 12.74; N, 5.03%. Found: C, 36.75; H, 3.16; Cl, 12.67; N, 4.97%.

*3.55. Gold, [2-[[5-(acetylamino)-2-pyridinyl-κN]oxy]phenyl-κC]dichloro-, (SP-4-3)- (**27**)*

^{1}H-NMR (d^6-DMSO) δ 2.10 (s, 3H), 7.16–7.21 (m, 1H), 7.29–7.37 (m, 2H), 7.54 (d, 1H, $J = 8.4$ Hz), 7.81 (d, 1H, $J = 9.0$ Hz), 8.48 (dd, 1H, $J = 2.1$, 8.4 Hz), 9.39 (d, 1H, $J = 2.1$, 8.7 Hz), 10.71 (s, 1H). ^{13}C-NMR (d^6-DMSO) δ 23.74, 116.64, 118.91, 124.67, 125.99, 129.71, 133.57, 134.38, 136.52, 138.88, 146.99, 151.33, 169.25 ppm. ES-MS *m/z* 517 $[M+Na]^+$. Anal. Calcd. for $C_{13}H_{11}Cl_2N_2O_2Au$: C, 31.54; H, 2.24; Cl, 14.32; N, 5.66. Found: C, 32.02; H, 2.39; Cl, 14.71; N, 5.49%.

*3.56. Gold, [2-[[5-(benzoylamino)-2-pyridinyl-κN]oxy]phenyl-κC]dichloro-, (SP-4-3)- (**28**)*

^{1}H-NMR (d^6-DMSO) δ 7.17–7.22 (m, 1H), 7.30–7.40 (m, 2H), 7.53–7.66 (m, 4H), 7.89 (d, 1H, $J = 9.0$ Hz), 7.94–8.00 (m, 2H), 8.68 (dd, 1H, $J = 2.1$, 9.0 Hz), 9.66 (d, 1H, $J = 2.1$ Hz), 11.00 (s, 1H) ppm. ^{13}C-NMR (d^6-DMSO) δ 116.57, 118.94, 124.73, 126.03, 127.91, 128.58, 129.75, 132.39, 133.45, 133.58, 134.49, 137.89, 140.08, 147.00, 151.78, 166.04 ppm. ES-MS *m/z* 579 $[M+Na]^+$. Anal. Calcd. for $C_{18}H_{13}Cl_2N_2O_2Au$ ($1.4H_2O$): C, 37.12; H, 2.73; Cl, 12.17; N, 4.81. Found: C, 37.16; H, 2.62; Cl, 12.16; N, 4.70%.

4. Results and discussion

4.1. Ligand preparation

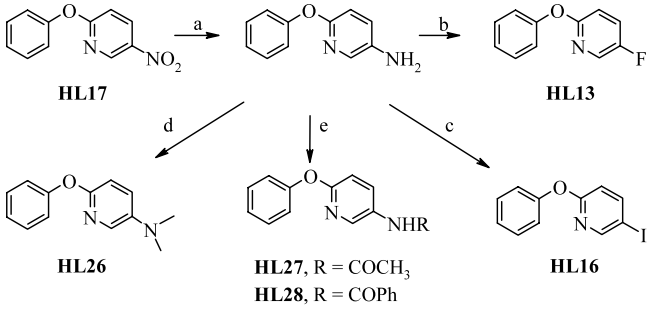
Ligands **HL1**–**HL3** and **HL15** were prepared using general procedure A, a modified literature procedure [25] involving the coupling reaction of phenol with the corresponding 2-bromopyridines in the presence of K_2CO_3 at an elevated temperature. Ligands **HL14** and **HL17** were obtained using general procedure B, similar to procedure A, but the coupling reactions were carried out in DMSO at a lower temperature. General procedure C involved the formation of a C–C bond via the Ni(II)-catalyzed coupling reaction of the C–Br bond of **HL15** with a Grignard reagent. Ligands **HL4**–**HL7**, **HL11** and **HL12** were all prepared using this procedure, with isolated yields ranging from 25 to 74%. For the preparation of ligands **HL11** and **HL12**, which involve aromatic Grignard reagents (2-thienyl- and phenylmagnesium bromide), a significant amount of 2,5-dithienylpyridine and 2,5-diphenylpyridine were also isolated, respectively, as side products, indicating that in these cases the phenoxy group acts as a leaving group.

Ligands **HL8**–**HL10** were prepared as shown in Scheme 1. Ligand **HL8** was obtained in 42% overall yield by the palladium(0)-catalyzed coupling reaction of **HL15** with methyl acrylate followed by hydrogenation on Pd/C at room temperature. Reduction of the ester

group in ligand **HL8** with $LiAlH_4$ afforded the corresponding alcohol, which was esterified with acetyl chloride to provide ligand **HL9** in 80% overall yield. Conversion of alcohol to the corresponding chloride using $POCl_3$ followed by nucleophilic substitution of the chloride with NaCN in DMSO at 90 °C afforded ligand **HL10** in 28% overall yield.

Ligands **HL13** and **HL16** were obtained from a diazo salt prepared from 6-phenoxypyridin-3-ylamine, as illustrated in Scheme 2, which was obtained from hydrogenation of ligand **HL17** using tin shot in an acidic medium at 50 °C. Ligand **HL13** was prepared in 24% yield from decomposition of the diazo salt of BF_4^- at 125 °C. Ligand **HL26** was prepared from 6-phenoxypyridin-3-ylamine treated with a mixture of formaldehyde and formic acid.

As illustrated in Scheme 3, ligand **HL18** was obtained using a modified literature method [26] as a white solid in 80% yield when a mixture of **HL15** and $Zn(CN)_2$ in dry DMF was heated at 140 °C for 40 h in the presence of $Pd_2(dba)_3$ and DPPF. Ligand **HL19** was obtained via treatment of **HL18** with CH_3MgBr followed by hydrolysis of the product under acidic conditions. The acid **HL20** was readily available from the hydrolysis of **HL18** with 10% NaOH solution, and ligand **HL22** was obtained from a mixture of **HL18** and $NaBO_3$ in mixed CH_3OH/H_2O solution heated at 50 °C for 2 h. The preparation of amides and esters **HL21**, **HL23**–**HL25**, **HL27**–**HL28** was very straightforward using general procedures D and E as illustrated in Schemes 2 and 3.



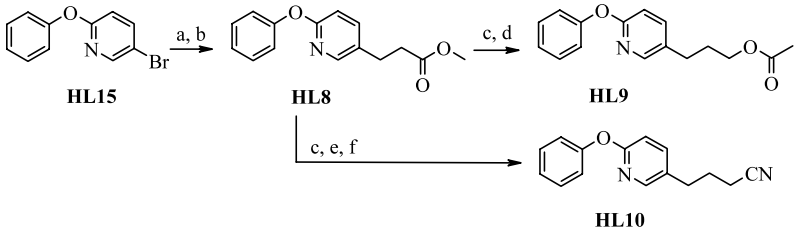
Scheme 2. (a) Sn, conc. HCl, 50 °C, 2 h, 69%; (b) (i) $NaNO_2$, HCl, 5 °C, $NaBF_4$; (ii) heated to 125 °C, 24%; (c) $NaNO_2$, H_2SO_4, 5 °C, KI, 60%; (d) HCHO, HCOOH, Δ, 2 h, 58%; (e) Et_3N, THF, acyl chloride, 92–99%.

4.2. Cycloauration

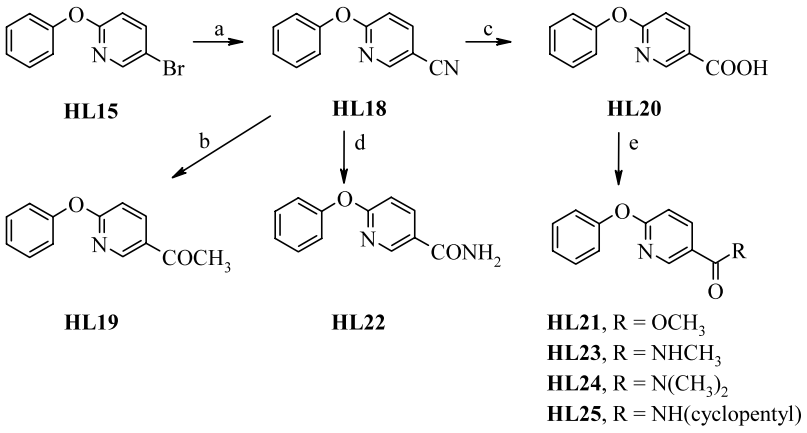
The direct cycloauration reactions were carried out as illustrated in Scheme 4, following a modified literature procedure [17]. The reaction times and isolated yields are summarized in Table 2. The intermediates with general formula $AuCl_3$(**HL**) were formed via the coordination reaction of the ligand **HL** and $Na[AuCl_4]$ in CH_3CN/H_2O (1:4, v/v) at room temperature. After being washing with H_2O and diethyl ether to remove unreacted starting materials, the intermediates were isolated as yellow solids, and the structure verified using ^{1}H-NMR spectroscopy. No further purification and characterization were performed on these intermediates. Generally, the coordination reaction was complete in a short period of time yielding a yellow solid; however, for the ligand with a bulky lipophilic group the product usually appeared as an oil floating on the reaction medium in the beginning, and solidified after the reaction mixture was stirred for a longer period of time. All cycloaurated compounds with general formula $AuCl_2$(**L**) were formed when a suspension of the intermediates $AuCl_3$(**HL**) in CH_3CN/H_2O (1:5, v/v) was heated at reflux for a certain period of time as listed in Table 2. The cycloauration time was not optimized, but was based on empirical observations such as the color of the suspending solid and the formation of Au(0) on the wall of the reaction flask. It should be noted that different substituents on the pyridine ring affect the solubility of the cycloaurated compounds in common solvents such as CH_2Cl_2, acetone and CH_3CN, but all have good solubility in high polar solvents such as DMF and DMSO with the exception of the compounds bearing a Cl (**14**), Br (**15**) or I (**16**) group at the 5-position of the pyridine ring.

4.3. Effect of methyl substituents

The effect of methyl substituents at the 4-, 5- and 6-positions of the pyridine ring on the cycloauration was examined using methyl-substituted 2-phenoxypyridine



Scheme 1. (a) Methyl acrylate, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 105 °C, 16 h, 83%; (b) Pd/C, H_2, CH_3OH, 5 h, 51%; (c) $LiAlH_4$, THF, 0–20 °C, 2 h, 99%; (d) CH_3COCl, Et_3N, CH_2Cl_2, 2 h, 81%; (e) $POCl_3$, CH_2Cl_2, 2 h, 31%; (f) NaCN, DMSO, 90 °C, 5 h, 92%.



Scheme 3. (a) $Pd_2(dba)_3$, DPPF, $Zn(CN)_2$, DMF, 140 °C, 40 h, 80%; (b) (i) CH_3MgBr, THF, Δ, 30 min, (ii) 4 N, HCl, Δ, 20 h, 30%; (c) (i) 10% NaOH, Δ, 2 h, (ii) 6 N HCl, 99%; (d) $NaBO_3$, CH_3OH/H_2O, 60 °C, 20 h, 61%; (e) (i) $SOCl_2$, Δ, 1–2 h, (ii) CH_3OH or amine in CH_2Cl_2 or THF, high yields.

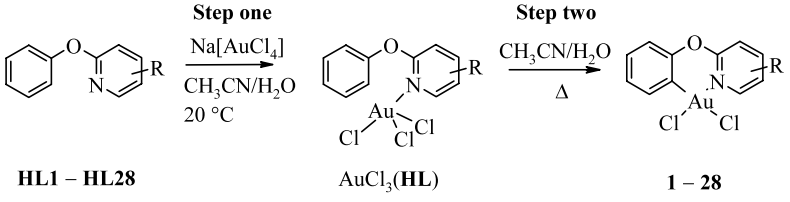
ligands (**HL1**–**HL3**). As shown in Table 2, with the methyl group at the 4- (**HL1**) or 5-positions (**HL2**), the intermediate $AuCl_3$(**HL**) species was formed and precipitated from the reaction mixture rapidly. Both the cycloaurated compounds **1** and **2** were isolated in good yields when the $AuCl_3$(**HL1** or **HL2**) intermediates were heated at reflux in mixed CH_3CN/H_2O for 16 and 24 h, respectively. The only other species observed was the starting material $AuCl_3$(**HL1** or **HL2**). The side product Au(0) was not observed, indicating that in both cases the cycloaurated products and starting materials are stable under the reaction temperature, and that prolonged reaction time could potentially result in an increase in the cycloauration yield. For instance, compound **1** was obtained in 84% isolated yield when $AuCl_3$(**HL1**) was heated at reflux in mixed CH_3CN/H_2O for 4 days. With a methyl group at the 6-position (**HL3**) of the pyridine ring, only trace amounts of the cycloaurated compound **3** were isolated from the suspension of the intermediate $AuCl_3$(**HL3**) with Au(0) as the only other gold-containing product. Compound **3** was also prepared in low yield (6.6%) from a mixture of $NaAuCl_4$, ligand **HL3** and $AgSO_3CF_3$ in CH_3CH_2CN by heating at reflux overnight. Unlike compounds **1** and **2**, compound **3** reacts with DMSO and DMF in an NMR tube at room temperature indicating it is less stable in solution. This is likely due to the steric effect of the methyl group at the 6-position.

4.4. Effect of lipophilic groups

Ligands **HL2** and **HL4**–**HL7** have a C1 to C5 alkyl group at the 5-position of the pyridine ring. Cycloauration of $AuCl_3$(**HL**) prepared from the ligands **HL2**, **HL4** and **HL5** containing a C1 to C3 group provided the cycloaurated products in good yield. Unreacted $AuCl_3$(**HL**) was also isolated, but no Au(0). In contrast, the presence of a butyl group (**HL6**) resulted in several complications. The intermediate $AuCl_3$(**HL6**) oiled out of solution when heated at reflux, and a significant amount of Au(0) was formed. As a consequence, compound **6** was isolated in a low yield of 23%. Furthermore, when the substituent was a pentyl group (**HL7**), no cycloaurated product was isolated. Au(0) was the only Au-containing product isolated when the cycloauration of the $AuCl_3$(**HL7**) intermediate was performed under the same reaction conditions. Since the direct cycloauration was performed in a highly polar medium of CH_3CN/H_2O (1:5, v/v), the presence of bulky lipophilic groups in the ligand reduces the solubility of the $AuCl_3$(**HL**) intermediate (resulting in formation of oils) thereby affecting the cycloauration.

4.5. Effects of strong electron-withdrawing and electron-donating groups

The formation and stability of the Au−N(py) bond of the intermediate $AuCl_3$(**HL**) complex was very



Scheme 4.

important for the success of the direct cycloauration. As shown in Table 2, the coordination reaction of the pyridine ligand (**HL**) with Na[$AuCl_4$] in CH_3CN/H_2O at room temperature forms a yellow intermediate $AuCl_3$(**HL**) with the exception of **HL17** and **HL18**, which contain the strong electron-withdrawing nitro and nitrile groups, and **HL26** with the electron-donating Me_2N group. For **HL17** and **HL18**, the electron-withdrawing groups decrease the electron density on the N atom of the pyridine ring, resulting in a weaker coordination tendency of the N atom to the Au(III) center. For **HL26**, the amino group was oxidized by the Au(III) center to form a black solution and Au(0), preventing the formation of the intermediate $AuCl_3$(**HL26**). For ligands **HL17** and **HL18**, no cycloaurated compound was isolated, and Au(0) metal was the main product isolated when the mixture of $NaAuCl_4$ and ligand was heated at reflux overnight in a solution of CH_3CN/H_2O (1:4, v/v).

4.6. Toleration of other functional groups

The ester and nitrile groups were well tolerated by direct cycloauration when they were attached to the pyridine ring via an alkyl chain. Compounds **8**–**10** were prepared in good yields of 39–71%. However, the efficiency of the cycloauration was lowered by the presence of the aromatic phenyl group as a substituent, and compound **11** was obtained in a low yield of 15%. Although the intermediate $AuCl_3$(**HL12**) was easily obtained from **HL12** (with a 5-(2-thienyl) substituent), only Au(0) was formed as the metal-containing product when it was heated at reflux for 16 h. Ligands **HL13**–**HL16** containing a halo substituent gave a similar result for the cycloauration, providing the corresponding products **13**–**16** with low yields of 11–18%. This result indicates that the electronegativity difference among the halo groups has a subtle effect on the cycloauration. In addition, the solubility of these compounds was poor in most organic solvents, and significantly decreases as the atomic number increases from fluoro to iodo with compound **16** having a very low solubility even in DMSO. Compounds **14**–**16** were not characterized by ^{13}C-NMR spectroscopy due to their poor solubility.

The intermediate $AuCl_3$(**HL19**) was readily prepared from a mixture of $NaAuCl_4$ and ligand **HL19** containing an acetyl group. No cycloaurated species was isolated when the intermediate was heated at reflux in CH_3CN/H_2O (5:1, v/v) overnight, the main Au-containing product isolated was Au(0), formed from either decomposition of the intermediate or the cycloaurated product. One possible explanation is that the acetyl group provided an additional Au(III)−C ($CO\mathbf{C}H_3$) interaction, resulting in the decomposition of the desired product at the elevated reaction temperature. It has previously been reported that a cycloaurated compound reacted with acetone in the presence of a silver or thallium salt at room temperature to form an Au(III)−C (acetone) bond [22,27,28].

Interestingly, the coordination reaction of **HL20** with $NaAuCl_4$ under the standard conditions afforded the intermediate $AuCl_3$(**HL20**) with an uncoordinated carboxylic group. When the intermediate was heated at reflux in CH_3CN/H_2O, an off-white material was obtained. The off-white material has an extremely poor solubility even in DMSO, and could not be characterized by ^{1}H-NMR. Its infrared spectrum (CsI) showed the presence of uncoordinated (ν(CsI) = 1708 cm^{-1}) carboxylic groups comparable to that in the free ligand **HL20** (ν(CsI) = 1701 cm^{-1}) as well as coordinated carboxylic groups (ν(CsI) = 1644 cm^{-1}). These observations and the result from elemental analysis on C (31.32%), H (1.81%), N (3.25%) and Cl (8.58%) are consistent of the formation of a poly- or oligomeric material containing Au−C, Au−Cl and Au−O bonds, the latter formed via substitution reaction of some Au−Cl bonds by the carboxylic groups.

Direct cycloauration of ligands with various amide and ester substituents at the 5-position of the pyridine ring was also examined, and the results are listed in Table 2. In all cases, the intermediates $AuCl_3$(**HL**) (**HL21**–**HL25**, **HL27** and **HL28**) were easily formed, and the cycloaurated products were obtained with yields varying from 6 to 36% with Au(0) as the major metal-containing side product.

4.7. Crystallographic study

Single crystals of compound **25** were grown from slow evaporation of an acetone solution. The experimental details of the X-ray structure determination and crystallographic parameters are listed in Table 1, and the selected bond distances and angles are summarized in Table 3. The solid structure is shown in Fig. 1, depicting a four-coordinate Au atom located in the center of a slightly distorted square with the bond distances of Au–C (2.017(6) Å), Au–N (2.053(5) Å) and Au–Cl

Table 3
Selected bond lengths and bond angles for compound **25**

Bond lengths			
Au(1)–Cl(1)	2.379(2)	Au(1)–Cl(2)	2.262(1)
Au(1)–N(1)	2.053(5)	Au(1)–C(11)	2.017(6)
Bond angles			
Cl(1)–Au(1)–Cl(2)	92.14(5)	Cl(1)–Au(1)–N(1)	90.0(1)
Cl(1)–Au(1)–C(11)	176.6(2)	Cl(2)–Au(1)–N(1)	177.8(1)
Cl(2)–Au(1)–C(11)	91.2(2)	N(1)–Au(1)–C(11)	86.6(2)
C(5)–O(1)–C(6)	115.3(4)	Au(1)–N(1)–C(1)	120.6(4)
Au(1)–N(1)–C(5)	119.4(4)	Au(1)–C(11)–C(10)	124.0(5)
Au(1)–C(11)–C(6)	116.7(5)	N(1)–C(1)–C(2)	122.0(5)

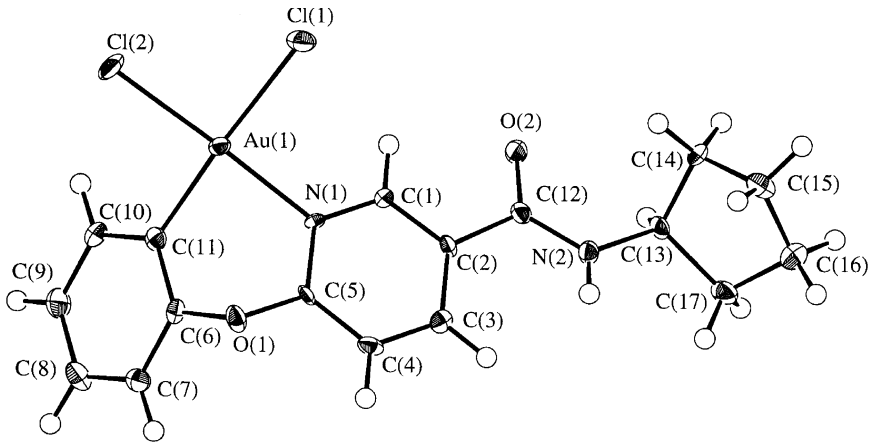


Fig. 1. ORTEP diagram of the solid-state molecular structure of compound **25**. Protons are omitted for clarity.

(2.379(2), 2.262(1) Å) and with the bond angles of Cl–Au–Cl (92.14(5)°) and N–Au–C (86.6(2)°), very similar to those of the cycloaurated compound of the unsubstituted 2-phenoxypyridine, which has the bond distances of Au–C (2.03(2) Å), Au–N (2.02(1) Å) and Au–Cl (2.275(4), 2.369(5) Å) and the bond angles of Cl–Au–Cl (92.1(2)°) and N–Au–C (86.6(6)°) [17].

5. Conclusions

Direct cycloauration of 2-phenoxypyridines with different functionalities in the pyridine ring was examined by formation of the trichloro coordinate intermediates and subsequent cycloauration at an elevated temperature in CH_3CN/H_2O. The results indicated that the cycloauration is tolerated by the presence of substituents, such as alkyl, halo, ester, amido and alkyl nitrile groups, but is not by strong electron-donating and strong electron-withdrawing groups. A methyl group at the 6-position weakens the bonding of the pyridine nitrogen atom to the Au(III) center, adversely effecting the cycloauration and compound stability. The presence of bulky lipophilic groups in the pyridine ring usually results in an increase in the decomposition of the reaction species to Au(0), and the presence of a thienyl or acetyl group in the pyridine ring totally blocks the availability of cycloaurated compounds by this method so that Au(0) is the only final product isolated.

6. Supplementary material

Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 200546 for compound **25**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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