

Cationic gold(i) heteroleptic complexes bearing a pyrazole-derived *N*-heterocyclic carbene: syntheses, characterizations, and cytotoxic activities†Haresh Sivaram,^a Jackie Tan^b and Han Vinh Huynh^{*a}Cite this: *Dalton Trans.*, 2013, **42**, 12421

A series of cationic gold(i) heteroleptic complexes bearing the pyrazole-derived *N*-heterocyclic carbene (NHC) FPyr (1,2,3,4,6,7,8,9-octahydropyridazino[1,2-*a*]indazolin-11-ylidene), and either a 1,3-disubstituted benzimidazole-derived NHC of the type RR'-bimy (**3**: R = R' = CHPh₂; **4**: R = CHPh₂, R' = ⁱPr; **5**: R = R' = CH₂Ph; **6**: R = R' = ^tBu; **7**: R = R' = *n*-Pr; **8**: R = R' = Et; **9**: R = R' = 2-propenyl) or a non-NHC co-ligand L (**10**: L = PPh₃; **11**: L = P(OPh)₃; **12**: L = DMAP) (DMAP = 4-dimethylaminopyridine) have been synthesized from [AuCl(FPyr)] (**1**). Complexes **3–12** have been characterized using multinuclei NMR spectroscopies, ESI mass spectrometry, and elemental analysis. X-ray diffraction analyses have been performed on complexes **5**, **6**, and **9–11**. To the best of our knowledge, **11** represents the first gold–NHC complex to bear the P(OPh)₃ ligand. The cytotoxic activities of complexes **3–12** have been studied *in vitro* with the NCI-H1666 non-small cell lung cancer cell line.

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Introduction

Interest in the cytotoxic activities of gold complexes has grown tremendously over the years.^{1,2} In particular, gold complexes bearing *N*-heterocyclic carbenes (NHCs) have been gaining much attention,³ given the ease with which NHC precursors can be tuned, both electronically and sterically, by varying the *N*-substituents.⁴ This in turn allows for synthetic control of the hydro- and lipophilic properties of the resultant complexes; properties that have been shown to be important factors in the development of gold-based anti-cancer agents.^{2,3} However, only gold mono- and homo-bis(carbene) complexes bearing imidazolin-2-ylidenes have been extensively studied,^{2,3} whereas complexes bearing other types of NHCs, as well as heteroleptic complexes, have been scarcely considered.⁵

Therefore, as our maiden contribution to this field of research, we had recently published the cytotoxic activities of a range of gold(i) and gold(III) mono-, homo-bis- and hetero-bis(carbene) complexes bearing benzimidazole- and/or pyrazole-derived NHC ligands on the NCI-H1666 non-small cell lung cancer cell line.⁶ The preliminary study revealed that the

cationic bis(carbene) complexes are far more active as cytotoxic agents when compared with the neutral monocarbene complexes. The gold(i) hetero-bis(carbene) complex **2** (Fig. 1), in particular, shows superior performance with an IC₅₀ value of 0.241 μM. Based on these findings, it was proposed that a heteroleptic system in which a strongly donating ligand is situated *trans* to a relatively weaker donating ligand was necessary for the labilization of the latter. This would create a vacant coordination site that may be essential for the cytotoxic activity of the complex. For example, donor atoms on target proteins, such as thioredoxin reductase,^{2,5,7} could bind to the complex fragment when a free coordination site is made available.

Spurred by the findings of our initial study, we have extended the investigation to consider a range of other cationic gold(i) heteroleptic complexes bearing the strongly donating pyrazole-derived FPyr (1,2,3,4,6,7,8,9-octahydropyridazino[1,2-*a*]indazolin-11-ylidene) ligand, and either a 1,3-disubstituted benzimidazole-derived NHC, or a non-NHC co-ligand. Benzimidazolin-2-ylidenes bearing a variety of *N*-substituents have

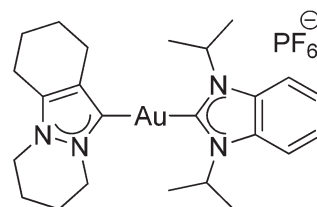


Fig. 1 Gold(i) hetero-bis(carbene) complex [Au(FPyr)(ⁱPr₂-bimy)]PF₆ (**2**).

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been considered, in an effort to study the effect on the cytotoxicity of the resultant complexes. For the purpose of comparison with our previous work, the cytotoxic activities of the complexes were studied *in vitro* with the NCI-H1666 non-small cell lung cancer cell line. We herein report on the syntheses, characterizations, and cytotoxic activities of the aforementioned complexes.

Results and discussion

Syntheses and characterizations

The gold(i) chlorido-monocarbene complex $[\text{AuCl}(\text{FPyr})]$ (**1**) was synthesized according to the previously reported procedure.⁶ Reaction of **1** with the appropriate 1,3-disubstituted benzimidazolium salts in the presence of K_2CO_3 afforded the gold(i) hetero-bis(carbene) complexes **3–9** in very good yields ranging from 72 to 82% (Scheme 1). The heteroleptic complexes **10–12**, which bear non-NHC co-ligands, were synthesized *via* straightforward ligand exchange reactions. Complex **1** was reacted with the appropriate pro-ligand in the presence of a large excess of KPF_6 in acetone, and the products were obtained in very good yields of 77 to 94% (Scheme 1). All ten complexes were obtained as white powders, and are soluble in most polar organic solvents. It should be noted that **11** represents the first gold–NHC complex to bear a phosphite co-ligand.

Complexes **3–12** were characterized using MS (ESI) and multinuclei NMR spectroscopies. The MS (ESI) spectra of the complexes were particularly useful in confirming the formation of the compounds, given that the base peak observed in all cases corresponds to the $[\text{M} - \text{PF}_6]^+$ fragment. ^1H NMR spectroscopy corroborated the successful formation of the complexes, whereby signals from both ligands are observed in the respective spectra. For complexes **3–9**, the ^{13}C NMR spectra correspondingly featured two downfield signals as a result of the presence of two carbene carbon atoms in the molecules. These two signals were assigned to their respective carbene carbon atoms by using the previously reported complex **2** as a

reference.⁶ The chemical shift(s) of the carbene carbon atom(s) in complexes **3–12** are presented in Table 1.

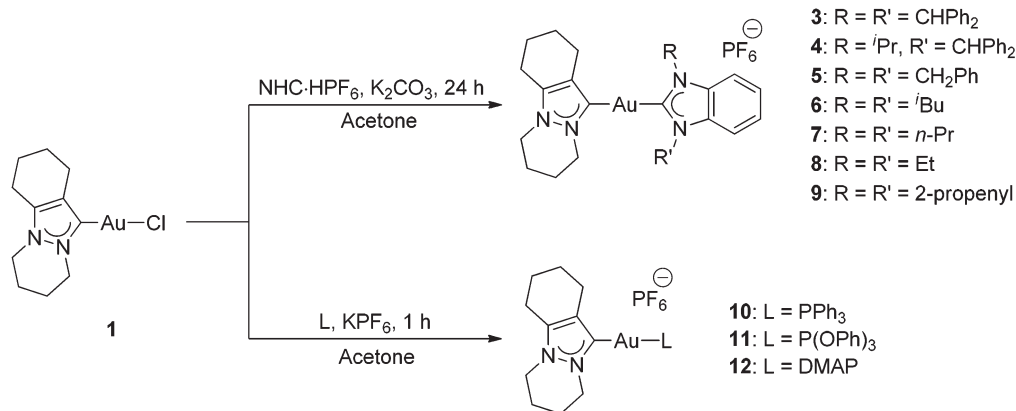
Considering the chemical shift of the FPyr carbene carbon, it is overt that as compared to the gold(i) chlorido monocarbene complex **1** (*cf.* 167.8 ppm),⁶ the FPyr carbene carbon in complexes **3–11**, resonate at a much more downfield region, ranging from 178.8–182.4 ppm. This is due to the replacement of the chlorido co-ligand in **1** with a stronger donating ligand situated *trans* to the FPyr ligand in the mentioned complexes, leading to the observed downfield shift of the signal.^{6,8} On the other hand, complex **12**, with its DMAP co-ligand, shows a more upfield FPyr carbene carbon resonance as compared to **1**, which is the result of DMAP being a weaker donating ligand as compared to the chlorido ligand.

The changes in the chemical shift of the FPyr carbene carbon also reveal other interesting, albeit unexpected, findings. For example, when focusing on the relevant data for hetero-bis(carbene) complexes **3–9**, it is noteworthy that no real correlation can be drawn between the chemical shift of the FPyr carbene carbon and the *N*-substituents of the RR' -bimy ligands, where the latter would inadvertently influence the overall donating ability of said RR' -bimy ligands. This is

Table 1 Chemical shift(s) of the carbene carbon atom(s) in complexes of the type $[\text{Au}(\text{FPyr})(\text{L})]\text{PF}_6$ (**3–12**)^a

Complex	L	FPyr	RR' -bimy
3	$(\text{CHPh}_2)_2$ -bimy	178.8	197.8
4	$(^i\text{Pr}_2)(\text{CHPh}_2)$ -bimy	179.2	195.1
5	$(\text{CH}_2\text{Ph})_2$ -bimy	179.9	195.7
6	$^i\text{Bu}_2$ -bimy	180.2	194.8
7	<i>n</i> - Pr_2 -bimy	180.0	194.8
8	Et_2 -bimy	180.7	194.1
9	$(2\text{-Propenyl})_2$ -bimy	179.9	196.0
10	PPh_3	182.4	—
11	$\text{P}(\text{OPh})_3$	179.6 ^b	—
12	DMAP	161.0	—

^a All ^{13}C NMR spectra were measured in CDCl_3 , except for complexes **7**, **9** and **12**, which were measured in CD_3CN due to poor solubility in chloroform. ^b Doublet, $^2J(\text{C},\text{P}) = 178$ Hz.



Scheme 1 Syntheses of cationic gold(i) hetero-bis(carbene) complexes of the type $[\text{Au}(\text{FPyr})(\text{RR}'\text{-bimy})]\text{PF}_6$ (**3–9**), and heteroleptic complexes of the type $[\text{Au}(\text{FPyr})(\text{L})]\text{PF}_6$ (**10–12**).



unlike the ^{13}C NMR spectroscopic methodology for determining ligand donor strengths that has been reported by our group, wherein even small changes to the *N*-substituents of various NHCs are shown to affect the donating ability of the ligands, and can be detected by the $^1\text{Pr}_2\text{-bimy}$ probe in complexes of the type $[\text{PdBr}_2(^1\text{Pr}_2\text{-bimy})(\text{NHC})]$.^{4a} Therefore, the data presented in this work seems to suggest that the Au(I) system is less sensitive than the Pd(II) system when it comes to detecting small changes in donor strength. Furthermore, while the Pd(II) system is able to confirm the stronger donating ability of NHCs as compared to phosphines, the Au(I) system studied in this work suggests the reverse, with the FPyr carbene carbon in $[\text{Au}(\text{FPyr})(\text{PPh}_3)]\text{PF}_6$ (**10**) resonating at 182.4 ppm, which is significantly more downfield as compared to the hetero-bis(carbene) complexes **3–9**. This may be due to some unique interactions that the phosphorus donor in PPh_3 has with the electron-rich gold(I) metal center, and warrants further investigation.

Single crystals suitable for X-ray diffraction analysis were obtained for complexes **5**, **6**, and **9–11** via vapour diffusion of diethyl ether into solutions of the compounds in either CHCl_3 or CH_2Cl_2 . The determined molecular structures were as expected, with all complexes adopting a linear geometry about the gold(I) metal center (Fig. 2). Complex **5** crystallised as the chloroform solvate, while all other complexes crystallised unsolvated. It is interesting to note that unlike **5**, where both the benzyl *N*-substituents are arranged in an *anti* arrangement across the benzimidazole plane, the *N*-substituents in **6** and **9**

are arranged in a *syn* arrangement, which is a result of achieving optimum packing in the unit cell. Two of the carbon atoms (C29 and C30) in the alicyclic ring of the FPyr ligand in **5** were also disordered into two positions, with an occupancy ratio of 50 : 50. The molecular structure of complex **11** is particularly interesting, in that two of the phenyl rings of the $\text{P}(\text{OPh})_3$ ligand are pointed towards the gold metal center. The remaining one is pointed away as a result of the close proximity of a PF_6^- anion. The potential steric shielding of the metal center accorded by the phenyl rings is unique to this ligand, and could prove beneficial for the overall stability of the complex. Furthermore, it is worth noting that none of the complexes showed evidence for intermolecular aurophilic interactions in the solid state.⁹

Cytotoxicity study

The cytotoxic activities of complexes **3–12** were investigated through a cell proliferation assay conducted on the NCI-H1666 non-small cell lung cancer cell line, and IC_{50} values were obtained from best-fit dose response curves (see ESI†). The performance of each complex in comparison to the previously reported complex **2**, as well as cisplatin, is tabulated in Table 2.

Considering the hetero-bis(carbene) complexes **3–9**, it is noted that they do not perform as well as the previously reported complex **2**, although **3** does come close with an IC_{50} value of 0.346 μM . Also, there seems to be no consistent relationship between the nature and length of the

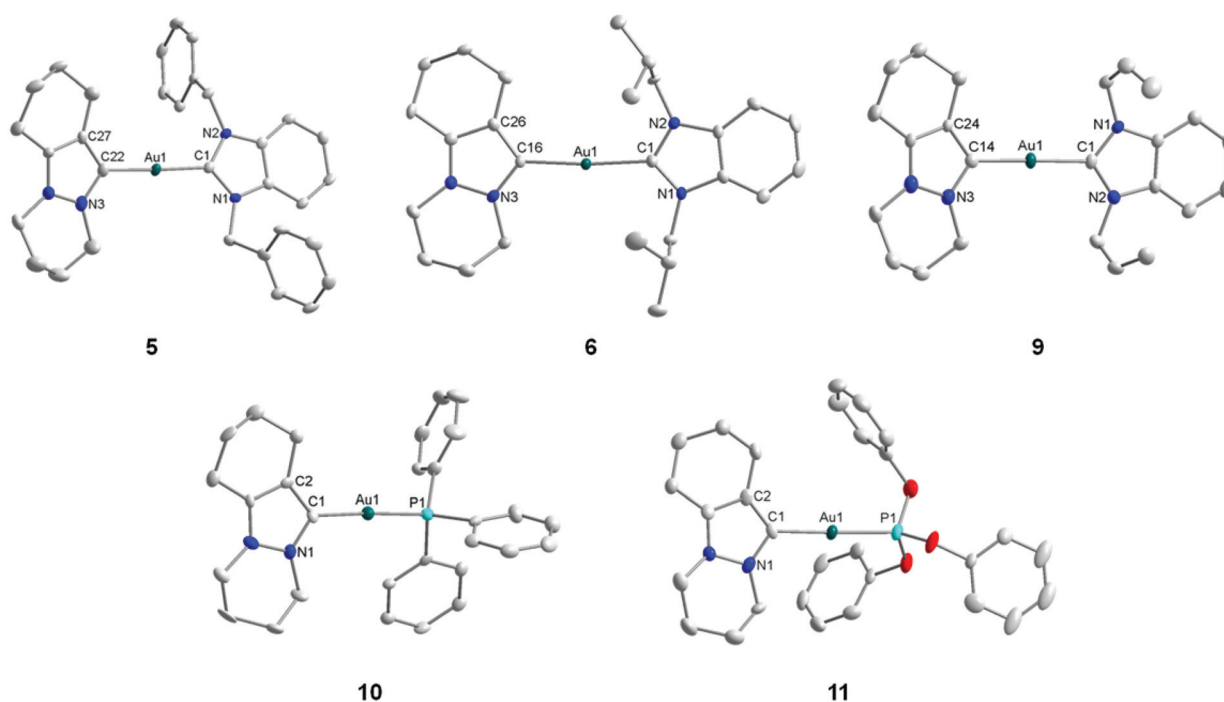


Fig. 2 Molecular structures of complexes **5**- CHCl_3 , **6**, and **9–11** showing 50% probability ellipsoids; hydrogen atoms, PF_6^- anions, and solvent molecules (if any) are omitted for clarity. Selected bond lengths [Å] and angles [°]: **5**- CHCl_3 : Au1–C1 2.017(5), Au1–C22 2.015(5); C1–Au1–C22 177.7(2); **6**: Au1–C1 2.027(5), Au1–C16 2.013(5); C1–Au1–C16 174.85(19); **9**: Au1–C1 2.020(3), Au1–C14 2.018(3); C1–Au1–C14 176.81(12); **10**: Au1–C1 2.035(6), Au1–P1 2.2843(17); C1–Au1–P1 175.43(17); **11**: Au1–C1 2.030(6), Au1–P1 2.2426(18); C1–Au1–P1 177.17(18).



Table 2 Cytotoxicity of complexes of the type [Au(FPyr)(L)]PF₆ (**2–12**) and cisplatin expressed as IC₅₀ values

Complex	L	IC ₅₀ (μM)
2 ⁶	ⁱ Pr ₂ -bimy	0.241 ± 0.01
3	(CHPh ₂) ₂ -bimy	0.346 ± 0.03
4	(ⁱ Pr)(CHPh ₂)-bimy	2.01 ± 0.20
5	(CH ₂ Ph) ₂ -bimy	0.720 ± 0.18
6	ⁱ Bu ₂ -bimy	0.964 ± 0.06
7	<i>n</i> -Pr ₂ -bimy	1.91 ± 0.40
8	Et ₂ -bimy	0.747 ± 0.08
9	(2-Propenyl) ₂ -bimy	5.10 ± 0.10
10	PPh ₃	2.15 ± 0.22
11	P(OPh) ₃	3.04 ± 0.27
12	DMAP	>10
Cisplatin ⁶	—	2.51 ± 0.11

N-substituents on the benzimidazole-derived NHC and the activity of the complexes. However, it is worth noting that complexes **2** and **3**, which both bear symmetrically substituted benzimidazole-derived NHCs, with both *N*-substituents being 2° carbon atoms, show superior performance as compared to complexes that bear benzimidazole-derived NHCs with either asymmetric *N*-substituents (*i.e.* complex **4**), or 1° carbon atom *N*-substituents (*i.e.* complexes **5–9**). This does suggest some form of structure–activity relationship, although further studies would be necessary to better understand the relative performance. Among the hetero-bis(carbene) complexes, **9** is an exception, and this may be attributed to the presence of reactive allyl moieties that make the complex more susceptible to addition and redox reactions, possibly degrading and/or deactivating the complex.

While the presence of a labile ligand seems necessary for the superior activity of these gold(i) complexes, it is apparently also important that the ligand *trans* to the FPyr ligand is not too weakly bound to the metal center. Evidence for this is found when considering complexes **10–12**. As we progress from the stronger donating PPh₃ to the much weaker donating DMAP, there is an increase in the IC₅₀ values. Since the mode of action of other cationic gold–NHC complexes has been reported to involve permeation into the mitochondria,^{1,2,7} it is possible that in the case of complex **12**, for example, the DMAP ligand detaches from the complex cation prematurely and prior to entering the mitochondria. This may potentially deactivate the compound even before it reaches its target site. Therefore, a fine balancing of these various properties seems necessary for the development of an optimum complex.

Conclusion

We have reported on the syntheses and characterizations of a series of cationic gold(i) heteroleptic complexes bearing the pyrazole-derived FPyr ligand, and either a benzimidazole-derived NHC of the type RR'-bimy (**3–9**), or a non-NHC co-ligand L (**10–12**). Complexes **3–9** were synthesized using [AuCl(FPyr)] (**1**) and the appropriate disubstituted benzimidazolium salt in the presence of K₂CO₃. **10–12**, on the other hand, were

synthesized using **1** and the necessary pro-ligand in the presence of an excess of KPF₆. The cytotoxic activities of all ten complexes were studied with the NCI-H1666 non-small cell lung cancer cell line, and their performances were compared with the previously reported activity of the gold(i) hetero-bis(carbene) complex [Au(FPyr)(ⁱPr₂-bimy)]PF₆ (**2**), and cisplatin. While the complexes reported in this work are not as cytotoxic as **2**, some do show comparable performance, and most complexes perform better than cisplatin. Our lab is currently in the midst of further investigations of some of the complexes, focussing primarily on their physiochemical and pharmacokinetic properties, as well as their *in vitro* toxicities to healthy cell lines. We look forward to reporting our findings from these studies in the near future.

Experimental

General considerations

All operations were performed without taking precautions to exclude air and moisture, and all solvents and chemicals were used as received. ¹H, ¹³C, ¹⁹F and ³¹P NMR spectra were recorded on a Bruker ACF 300 spectrometer or a Bruker AMX 500 spectrometer. The chemical shifts (δ) were internally referenced to the residual solvent signals relative to tetramethylsilane (¹H and ¹³C), or externally to CF₃CO₂H (¹⁹F) and 85% H₃PO₄ (³¹P). ESI mass spectra were measured using a Finnigan LCQ spectrometer. Elemental analyses were performed on an Elementar Vario Micro Cube elemental analyser at the Department of Chemistry, National University of Singapore. Complex **1** was synthesized as previously reported.⁶ The azolium salts 1,3-dibenzhydrylbenzimidazolium bromide,¹⁰ 1,3-dibenzylbenzimidazolium bromide,¹⁰ 1,3-diisobutylbenzimidazolium bromide,¹⁰ 1,3-dipropylbenzimidazolium bromide,¹¹ 1,3-diethylbenzimidazolium bromide,¹² and 1,3-di(2-propenyl)benzimidazolium bromide¹³ were synthesized according to literature procedures, albeit with slight modifications. 1-Benzhydryl-3-isopropylbenzimidazolium bromide was synthesized from 1-benzhydrylbenzimidazole, and the procedures for the syntheses of both are reported in this section. All azolium salts were converted to their hexafluorophosphate analogues *via* salt metathesis reaction with KPF₆ in acetone, stirred overnight at ambient temperature.

1-Benzhydrylbenzimidazole. Benzimidazole (1.18 g, 10 mmol) was suspended in CH₃CN (20 mL). NaOH (1.60 mL, 10 mmol, 6.25 M) was added to the suspension, and the reaction mixture was stirred for 30 min before a solution of benzhydryl bromide (2.47 g, 10 mmol) dissolved in CH₃CN (10 mL) was added. The reaction mixture was heated under reflux overnight, following which it was filtered through Celite. The filtrate was dried over anhydrous Na₂SO₄, filtered, and all volatiles were removed under vacuum affording a beige oil. The crude product was purified by flash column chromatography (silica gel, ether) (1.45 g, 5.1 mmol, 51%). ¹H NMR (300 MHz, CDCl₃): δ 7.84 (d, 1 H, Ar-H), 7.63 (s, 1 H, NCHN), 7.38–7.14 (m, 13 H, Ar-H), 6.76 (s, 1 H, NCHPh₂). ¹³C{¹H}



NMR (75.5 MHz, CDCl₃): δ 144.0 (Ar-C), 142.5 (NCHN), 138.0, 134.0, 129.0, 128.5, 128.2, 123.0, 122.4, 120.3, 110.7 (Ar-C), 63.6 (NCHPh₂).

1-Benzhydryl-3-isopropylbenzimidazolium bromide. 1-Benzhydrylbenzimidazole (1.42 g, 5.0 mmol) was suspended in CH₃CN (2 mL). Isopropyl bromide (0.5 mL, 5.3 mmol) was added to the suspension, and the reaction mixture was refluxed for 24 h. After cooling to ambient temperature, all volatiles were removed under vacuum. The crude product was washed several times with ethyl acetate and dried under vacuum to yield a white solid (1.58 g, 3.9 mmol, 78%). ¹H NMR (300 MHz, CDCl₃): δ 11.32 (s, 1 H, NCHN), 7.99 (s, 1 H, NCHPh₂), 7.80–7.17 (m, 14 H, Ar-H), 5.18–5.04 (m, 1 H, NCH(CH₃)₂), 1.83 (d, 6 H, CH₃). ¹³C{¹H} NMR (75.5 MHz, CDCl₃): δ 147.9 (NCHN), 141.9, 135.6, 131.3, 131.0, 129.2, 129.1, 128.6, 126.82, 126.76, 115.8, 113.7 (Ar-C), 66.5 (NCHPh₂), 52.2 (NCH(CH₃)₂), 22.2 (CH₃). MS (ESI): m/z = 327 [M – Br]⁺.

General procedure for the synthesis of gold(i) hetero-bis(carbene) complexes 3–9

Complex 1 (1 equiv.) and the appropriate azolium hexafluorophosphate salt (1 equiv.) were dissolved in acetone. K₂CO₃ (1.3 equiv.) was added to the solution, and the resulting mixture was stirred for 24 h at ambient temperature. The solvent of the reaction mixture was then removed under vacuum. The residue was suspended in CH₂Cl₂ and filtered over Celite. The solvent of the filtrate was removed under vacuum, and the resulting residue was washed thrice with ethyl acetate or diethyl ether. The crude product was purified by crystallization *via* vapour diffusion of diethyl ether into a solution of the compound in CHCl₃ or CH₂Cl₂. All complexes were obtained as colourless crystals.

[Au(FPyr)((CHPh₂)₂-bimy)]PF₆ (3). Yield: 82%. ¹H NMR (500 MHz, CDCl₃): δ 7.66 (s, 2 H, NCH), 7.40–7.38 (m, 12 H, Ar-H), 7.28–7.27 (m, 8 H, Ar-H), 7.17 (dd, 2 H, Ar-H), 7.05 (dd, 2 H, Ar-H), 4.02 (t, 2 H, ³J(H,H) = 5.70 Hz, NCH₂), 3.88 (t, 2 H, ³J(H,H) = 5.70 Hz, NCH₂), 2.56 (t, 2 H, ³J(H,H) = 6.30 Hz, CH₂), 2.34 (t, 2 H, ³J(H,H) = 5.70 Hz, CH₂), 2.12 (m, 2 H, CH₂), 2.01 (m, 2 H, CH₂), 1.82 (m, 2 H, CH₂), 1.70 (m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 197.8 (C_{carbene} ((CHPh₂)₂-bimy)), 178.8 (C_{carbene} (FPyr)), 144.4, 137.9, 134.5, 129.7, 129.5, 129.0, 126.3, 125.3, 114.6 (Ar-C), 68.8 (NCH), 51.5, 46.5 (NCH₂), 23.3, 22.9, 22.5, 21.9, 21.2, 21.0 (CH₂). ³¹P{¹H} NMR (202.4 MHz, CDCl₃): δ –143.8 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CDCl₃): δ 2.30 (d, PF₆). Anal. Calc. for C₄₄H₄₂N₄AuPF₆: C, 54.55; H, 4.37; N, 5.78. Found: C, 54.54; H, 4.26; N, 5.61%. MS (ESI): m/z = 823 [M – PF₆]⁺.

[Au(FPyr)((ⁱPr)(CHPh₂)-bimy)]PF₆ (4). Yield: 76%. ¹H NMR (500 MHz, CDCl₃): δ 7.73 (d, 1 H, Ar-H), 7.68 (s, 1 H, NCHPh₂), 7.42–7.28 (m, 11 H, Ar-H), 7.22 (t, 1 H, Ar-H), 7.03 (d, 1 H, Ar-H), 5.40 (m, 1 H, ³J(H,H) = 6.30 Hz, NCH(CH₃)₂), 4.20 (br t, 2 H, NCH₂), 4.09 (br t, 2 H, NCH₂), 2.62 (br t, 2 H, CH₂), 2.52 (br t, 2 H, CH₂), 2.16 (br m, 4 H, CH₂), 1.88 (d, 6 H, ³J(H,H) = 6.30 Hz, CH₃), 1.77 (br m, 2 H, CH₂), 1.31 (br m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 195.1 (C_{carbene} ((ⁱPr)(CHPh₂)-bimy)), 179.2 (C_{carbene} (FPyr)), 144.4, 138.0, 134.2, 133.4, 129.7,

129.6, 129.3, 129.0, 126.4, 125.13, 125.07, 114.6, 113.5 (Ar-C), 68.8 (NCHPh₂), 54.0 (NCH(CH₃)₂), 51.7, 46.6 (NCH₂), 23.31 (CH₂), 23.29 (CH₃), 23.0, 22.5, 21.9, 21.2, 21.0 (CH₂). ³¹P{¹H} NMR (202.4 MHz, CDCl₃): δ –143.8 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CDCl₃): δ 2.34 (d, PF₆). Anal. Calc. for C₃₄H₃₈N₄AuPF₆·0.3CH₂Cl₂·0.6Et₂O: C, 48.20; H, 4.92; N, 6.13. Found: C, 48.29; H, 4.71; N, 6.01%. MS (ESI): m/z = 699 [M – PF₆]⁺.

[Au(FPyr)((CH₂Ph)₂-bimy)]PF₆ (5). Yield: 80%. ¹H NMR (500 MHz, CDCl₃): δ 7.44–7.31 (m, 14 H, Ar-H), 5.77 (s, 4 H, NCH₂Ph), 4.22 (t, 2 H, ³J(H,H) = 5.70 Hz, NCH₂), 4.03 (t, 2 H, ³J(H,H) = 5.70 Hz, NCH₂), 2.57 (t, 2 H, ³J(H,H) = 6.30 Hz, CH₂), 2.50 (t, 2 H, ³J(H,H) = 6.30 Hz, CH₂), 2.09 (m, 4 H, CH₂), 1.83 (m, 2 H, CH₂), 1.72 (m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 195.7 (C_{carbene} ((CH₂Ph)₂-bimy)), 179.9 (C_{carbene} (FPyr)), 144.4, 135.8, 134.2, 129.8, 129.2, 127.9, 126.7, 125.6, 112.8 (Ar-C), 52.9 (NCH₂Ph), 51.7, 46.6 (NCH₂), 23.3, 22.9, 22.5, 21.9, 21.3, 21.1 (CH₂). ³¹P{¹H} NMR (202.4 MHz, CDCl₃): δ –143.7 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CDCl₃): δ 2.59 (d, PF₆). Anal. Calc. for C₃₂H₃₄N₄AuPF₆: C, 47.07; H, 4.20; N, 6.86. Found: C, 47.15; H, 4.25; N, 6.87%. MS (ESI): m/z = 671 [M – PF₆]⁺.

[Au(FPyr)(ⁱBu₂-bimy)]PF₆ (6). Yield: 74%. ¹H NMR (500 MHz, CDCl₃): δ 7.52 (dd, 2 H, Ar-H), 7.44 (dd, 2 H, Ar-H), 4.40 (br t, 2 H, NCH₂), 4.31 (d, 4 H, ³J(H,H) = 7.55 Hz, NCH₂CH(CH₃)₂), 4.10 (br t, 2 H, NCH₂), 2.62 (t, 2 H, ³J(H,H) = 6.30 Hz, CH₂), 2.59 (t, 2 H, ³J(H,H) = 6.30 Hz, CH₂), 2.44 (m, 2 H, NCH₂CH(CH₃)₂), 2.19 (br t, 4 H, CH₂), 1.87 (m, 2 H, CH₂), 1.79 (m, 2 H, CH₂), 1.03 (d, 12 H, ³J(H,H) = 6.30 Hz, CH₃). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 194.8 (C_{carbene} (ⁱBu₂-bimy)), 180.2 (C_{carbene} (FPyr)), 144.5, 134.3, 126.6, 125.3, 112.5 (Ar-C), 56.4 (NCH₂CH(CH₃)₂), 51.8, 46.6 (NCH₂), 30.2 (NCH₂CH(CH₃)₂), 23.4, 23.0, 22.5, 22.0, 21.3, 21.1 (CH₂), 21.0 (CH₃). ³¹P{¹H} NMR (202.4 MHz, CDCl₃): δ –143.7 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CDCl₃): δ 2.49 (d, PF₆). Anal. Calc. for C₂₆H₃₈N₄AuPF₆: C, 41.72; H, 5.12; N, 7.48. Found: C, 41.52; H, 5.10; N, 7.31%. MS (ESI): m/z = 603 [M – PF₆]⁺.

[Au(FPyr)(*n*-Pr₂-bimy)]PF₆ (7). Yield: 79%. ¹H NMR (500 MHz, CD₃CN): δ 7.67 (dd, 2 H, Ar-H), 7.47 (dd, 2 H, Ar-H), 4.49 (t, 4 H, ³J(H,H) = 6.90 Hz, NCH₂CH₂CH₃), 4.41 (br t, 2 H, NCH₂), 4.04 (br t, 2 H, NCH₂), 2.60 (m, 4 H, CH₂), 2.10 (br t, 4 H, CH₂), 1.99 (m, 4 H, CH₂), 1.84 (m, 2 H, CH₂), 1.76 (m, 2 H, CH₂), 0.98 (t, 6 H, ³J(H,H) = 7.60 Hz, CH₃). ¹³C{¹H} NMR (125.8 MHz, CD₃CN): δ 194.8 (C_{carbene} (*n*-Pr₂-bimy)), 180.0 (C_{carbene} (FPyr)), 144.5, 134.2, 126.3, 125.1, 112.7 (Ar-C), 51.8 (NCH₂), 50.6 (NCH₂CH₂CH₃), 46.6 (NCH₂), 24.2 (NCH₂CH₂CH₃), 23.4, 22.8, 22.5, 21.7, 21.1, 20.8 (CH₂), 11.5 (CH₃). ³¹P{¹H} NMR (202.4 MHz, CD₃CN): δ –143.2 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CD₃CN): δ 3.43 (d, PF₆). Anal. Calc. for C₂₄H₃₄N₄AuPF₆: C, 40.01; H, 4.76; N, 7.78. Found: C, 40.04; H, 4.40; N, 7.73%. MS (ESI): m/z = 575 [M – PF₆]⁺.

[Au(FPyr)(Et₂-bimy)]PF₆ (8). Yield: 72%. ¹H NMR (500 MHz, CDCl₃): δ 7.53 (dd, 2 H, Ar-H), 7.46 (dd, 2 H, Ar-H), 4.57 (m, 4 H, ³J(H,H) = 7.55 Hz, NCH₂CH₃), 4.47 (t, 2 H, ³J(H,H) = 5.65 Hz, NCH₂), 4.09 (t, 2 H, ³J(H,H) = 6.30 Hz, NCH₂), 2.62 (t, 4 H, ³J(H,H) = 6.30 Hz, CH₂), 2.21 (m, 4 H, CH₂), 1.89 (m, 2 H,



CH₂), 1.80 (m, 2 H, CH₂), 1.60 (t, 6 H, ³J(H,H) = 7.60 Hz, CH₃). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 194.1 (C_{carbene} (Et₂-bimy)), 180.7 (C_{carbene} (FPyr)), 144.3, 133.7, 126.7, 125.3, 112.1 (Ar-C), 52.0, 46.7 (NCH₂), 44.4 (NCH₂CH₃), 23.4, 23.0, 22.6, 22.0, 21.4, 21.2 (CH₂), 16.6 (CH₃). ³¹P{¹H} NMR (202.4 MHz, CDCl₃): δ -143.8 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CDCl₃): δ 2.27 (d, PF₆). Anal. Calc. for C₂₂H₃₀N₄AuPF₆: C, 38.16; H, 4.37; N, 8.09. Found: C, 38.38; H, 4.04; N, 8.09%. MS (ESI): *m/z* = 547 [M - PF₆]⁺.

[Au(FPyr)((2-propenyl)₂-bimy)]PF₆ (9). Yield: 75%. ¹H NMR (500 MHz, CD₃CN): δ 7.63 (dd, 2 H, Ar-H), 7.47 (dd, 2 H, Ar-H), 6.14 (m, 2 H, NCH₂CH=CH₂), 5.28 (dm, 2 H, ³J(H,H) = 10.10 Hz, NCH₂CH=CH_{trans}), 5.16–5.19 (m, 6 H, NCH₂CH=CH₂ and NCH₂CH=CH_{cis}), 4.39 (t, 2 H, ³J(H,H) = 5.70 Hz, NCH₂), 4.04 (t, 2 H, ³J(H,H) = 5.70 Hz, NCH₂), 2.59 (m, 4 H, CH₂), 2.09 (br t, 4 H, CH₂), 1.84 (m, 2 H, CH₂), 1.76 (m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, CD₃CN): δ 196.0 (C_{carbene} ((2-propenyl)₂-bimy)), 179.9 (C_{carbene} (FPyr)), 144.7, 134.4, 133.7, 126.5, 125.6, 118.6, 113.1 (Ar-C and vinylic-C), 52.0 (NCH₂), 51.5 (NCH₂CH=CH₂), 46.8 (NCH₂), 23.6, 23.0, 22.7, 21.9, 21.3, 21.0 (CH₂). ³¹P{¹H} NMR (202.4 MHz, CD₃CN): δ -144.0 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CD₃CN): δ 3.46 (d, PF₆). Anal. Calc. for C₂₄H₃₀N₄AuPF₆: C, 40.23; H, 4.22; N, 7.82. Found: C, 40.14; H, 4.36; N, 7.64%. MS (ESI): *m/z* = 571 [M - PF₆]⁺.

General procedure for the synthesis of gold(i) heteroleptic complexes 10–12

Complex 1 (1 equiv.) and the appropriate pro-ligand (1.2 equiv.) were dissolved in acetone. KPF₆ (3 equiv.) dissolved in acetone was added to the solution, and the resulting mixture was stirred for 1 h at ambient temperature. The solvent of the reaction mixture was then removed under vacuum. The residue was suspended in CH₂Cl₂ and filtered over Celite. The solvent of the filtrate was removed under vacuum, and the resulting residue was washed thrice with diethyl ether. The crude product was purified by crystallization *via* vapour diffusion of diethyl ether into a solution of the compound in CH₂Cl₂. All complexes were obtained as colourless crystals.

[Au(FPyr)(PPh₃)₃]PF₆ (10). Yield: 94%. ¹H NMR (500 MHz, CDCl₃): δ 7.54–7.41 (m, 15 H, Ar-H), 4.41 (br t, 2 H, NCH₂), 4.12 (br t, 2 H, NCH₂), 2.60 (m, 4 H, CH₂), 2.18 (br m, 4 H, CH₂), 1.86 (br m, 2 H, CH₂), 1.77 (br m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 182.4 (C_{carbene}), 144.7 (Ar-C), 134.6, 132.5, 130.1, 130.0 (d, Ar-C), 126.4 (Ar-C), 52.0, 46.7 (NCH₂), 23.2, 22.9, 22.5, 21.8, 21.2, 20.9 (CH₂). ³¹P{¹H} NMR (202.4 MHz, CDCl₃): δ 41.3 (PPh₃), -143.8 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CDCl₃): δ 2.32 (d, PF₆). Anal. Calc. for C₂₉H₃₁N₂AuP₂F₆: C, 44.63; H, 4.00; N, 3.59. Found: C, 44.88; H, 3.89; N, 3.40%. MS (ESI): *m/z* = 635 [M - PF₆]⁺.

[Au(FPyr)(P(OPh)₃)]PF₆ (11). Yield: 77%. ¹H NMR (500 MHz, CDCl₃): δ 7.48–7.27 (m, 15 H, Ar-H), 4.02 (t, 2 H, ³J(H,H) = 5.70 Hz, NCH₂), 3.79 (t, 2 H, ³J(H,H) = 6.30 Hz, NCH₂), 2.52 (t, 2 H, ³J(H,H) = 6.30 Hz, CH₂), 2.20 (t, 2 H, ³J(H,H) = 6.30 Hz, CH₂), 2.10 (m, 2 H, CH₂), 2.00 (m, 2 H, CH₂), 1.78 (m, 2 H, CH₂), 1.65 (m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ 179.6

(d, ²J(C,P) = 178 Hz, C_{carbene}), 150.1, 144.6, 131.3, 127.5, 126.6, 121.9 (d, Ar-C), 51.5, 46.6 (NCH₂), 23.1, 22.4, 22.3, 21.4, 21.2, 20.7 (CH₂). ³¹P{¹H} NMR (202.4 MHz, CDCl₃): δ 139.3 (P(OPh)₃), -143.8 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CDCl₃): δ 2.35 (d, PF₆). Anal. Calc. for C₂₉H₃₁N₂O₃AuP₂F₆: C, 42.04; H, 3.77; N, 3.38. Found: C, 42.30; H, 3.77; N, 3.62%. MS (ESI): *m/z* = 683 [M - PF₆]⁺.

[Au(FPyr)(DMP)]PF₆ (12). Yield: 81%. ¹H NMR (500 MHz, CD₃CN): δ 7.99 (d, 2 H, Ar-H), 6.68 (d, 2 H, Ar-H), 4.37 (br t, 2 H, NCH₂), 4.00 (br t, 2 H, NCH₂), 3.05 (s, 6 H, NCH₃), 2.54 (m, 4 H, CH₂), 2.06 (m, 4 H, CH₂), 1.82 (br m, 2 H, CH₂), 1.73 (br m, 2 H, CH₂). ¹³C{¹H} NMR (125.8 MHz, CD₃CN): δ 161.0 (C_{carbene}), 156.1, 150.4, 144.7, 125.9, 108.3 (Ar-C), 52.1, 46.7 (NCH₂), 39.5 (NCH₃), 23.3, 23.0, 22.5, 21.7, 21.1, 20.9 (CH₂). ³¹P{¹H} NMR (202.4 MHz, CD₃CN): δ -143.1 (m, PF₆). ¹⁹F{¹H} NMR (282.4 MHz, CD₃CN): δ 3.46 (d, PF₆). Anal. Calc. for C₁₈H₂₆N₄AuPF₆: C, 33.76; H, 4.09; N, 8.75. Found: C, 33.85; H, 4.10; N, 8.51%. MS (ESI): *m/z* = 405 [M - PF₆ - DMAP + CH₃OH]⁺, 495 [M - PF₆]⁺.

X-ray diffraction studies

X-ray data for 5-CHCl₃, 6, and 9–11 were collected with a Bruker AXS SMART APEX diffractometer, using Mo Kα radiation at 100(2) K with the SMART suite of programs.¹⁴ Data were processed and corrected for Lorentz and polarization effects with SAINT,¹⁵ and for absorption effect with SADABS.¹⁶ Structural solution and refinement were carried out with the SHELXTL suite of programs.¹⁷ The structures were solved by direct methods to locate the heavy atoms, followed by difference maps for the light, non-hydrogen atoms. All hydrogen atoms were placed in calculated positions. All non-hydrogen atoms were generally given anisotropic displacement parameters in the final model. A summary of the most important crystallographic data is provided in Table 3.

Cytotoxicity studies

In vitro toxicities of 3–12 were determined by CellTiter 96 Aqueous Non-Radioactive Cell Proliferation Assay (MTS). NCI-H1666 cells were maintained in complete RPMI medium with 10% FBS and 1% PenStrep. Standard DMSO solutions of 3–12 were diluted with complete RPMI medium, with the final concentration of DMSO in each diluted solution being less than 0.5%. The cells were seeded in 96-well plates at a density of 2000 cells per well in 100 μL of complete RPMI medium without antibiotics and cultured overnight at 37 °C in a humidified atmosphere containing 5% CO₂. A 100 μL portion of media containing different concentrations of 3–12 was added in the wells to a final concentration from 0.0005 to 50 μM. Compound-free solvent controls were also included. After a 72-hour incubation period, 20 μL of CellTiter 96 Aqueous One Reagent containing the tetrazolium compound MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt) was added to each well. After incubation for about 3 h, the absorbance was measured at 490 nm using a Tecan Infinite M200 plate reader. Nonlinear regression analysis was performed using GraphPad



Table 3 Selected X-ray crystallographic data for complexes 5-CHCl₃, 6, 9, 10 and 11

	5-CHCl ₃	6	9	10	11
Formula	C ₃₃ H ₃₅ N ₄ AuCl ₃ PF ₆	C ₂₆ H ₃₈ N ₄ AuPF ₆	C ₂₄ H ₃₀ N ₄ AuPF ₆	C ₂₉ H ₃₁ N ₂ AuP ₂ F ₆	C ₂₉ H ₃₁ N ₂ O ₃ AuP ₂ F ₆
fw	935.94	748.54	716.46	780.46	828.46
Colour, habit	Colourless, block	Colourless, block	Colourless, block	Colourless, block	Colourless, block
Crystal size (mm)	0.13 × 0.11 × 0.04	0.27 × 0.11 × 0.05	0.36 × 0.26 × 0.10	0.28 × 0.08 × 0.06	0.17 × 0.11 × 0.08
Temp (K)	100(2)	100(2)	100(2)	100(2)	100(2)
Cryst syst	Triclinic	Triclinic	Triclinic	Orthorhombic	Orthorhombic
Space group	P1	P1	P1	Pna2 ₁	P2 ₁ 2 ₁ 2 ₁
a (Å)	8.5921(10)	11.000(3)	9.7407(7)	20.319(4)	10.5523(6)
b (Å)	11.9088(14)	12.126(3)	12.5859(9)	13.683(3)	14.9858(8)
c (Å)	17.348(2)	12.426(3)	12.8314(9)	10.2795(19)	19.0095(10)
α (°)	87.324(2)	109.051(5)	60.9630(10)	90	90
β (°)	87.300(2)	98.373(5)	73.3970(10)	90	90
γ (°)	80.596(2)	108.802(5)	68.0160(10)	90	90
V (Å ³)	1747.9(4)	1423.7(6)	1264.80(16)	2857.9(9)	3006.1(3)
Z	2	2	2	4	4
D _c (g cm ⁻³)	1.778	1.746	1.881	1.814	1.831
Radiation used	Mo Kα	Mo Kα	Mo Kα	Mo Kα	Mo Kα
μ (mm ⁻¹)	4.546	5.285	5.944	5.321	5.072
θ (°)	1.18–27.50	2.04–27.49	1.83–27.50	2.48–27.50	2.14–27.50
No. of unique data	8012	6505	5813	6506	6905
Max, min transmission	0.8391, 0.5895	0.7456, 0.5412	0.5879, 0.2234	0.7407, 0.3173	0.6871, 0.4793
Final R indices	R ₁ = 0.0400, wR ₂ = 0.0890	R ₁ = 0.0384, wR ₂ = 0.0850	R ₁ = 0.0244, wR ₂ = 0.0622	R ₁ = 0.0373, wR ₂ = 0.0764	R ₁ = 0.0452, wR ₂ = 0.0847
[I > 2σ(I)]	R ₁ = 0.0469, wR ₂ = 0.1057	R ₁ = 0.0449, wR ₂ = 0.0873	R ₁ = 0.0263, wR ₂ = 0.0703	R ₁ = 0.0494, wR ₂ = 0.0816	R ₁ = 0.0514, wR ₂ = 0.0869
Goodness-of-fit on F ²	1.132	1.068	1.266	0.973	1.004
Peak/hole (e Å ⁻³)	1.687/–2.077	2.285/–2.254	1.227/–0.647	2.555/–0.638	2.037/–1.176

Prism version 5.00 for Windows to calculate the IC₅₀ value of each compound.

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