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Cyclometalated gold(III) iminophosphoranes which incorporate carbohydrate groups

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ABSTRACT

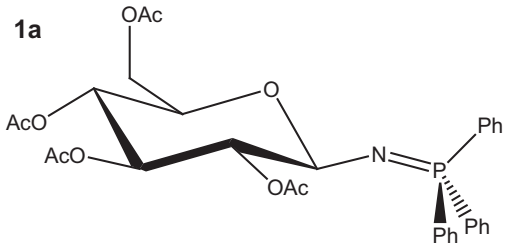
Iminophosphoranes with organic groups derived from D-glucose, D-galactose and L-arabinose have been used to prepare gold(III) dichloride complexes via mercurated intermediates, since direct cyclometallation was unsuccessful. Structures and full spectroscopic data are reported. Replacement of one or more of the chloride ligands by PPh_3, or by thiosalicylate gave new derivatives. Biological screening showed no enhanced activity relative to other alkyl or aryl analogues.

1. Introduction

Iminophosphoranes, $R_3P{=}N{-}R'$, are readily available with a wide variety of R and R′ groups [1,2]. Alper first showed that it was possible to produce cyclopalladated species by reacting $Ph_3P{=}NC_6H_4CH_3$ with $Na_2[PdCl_4]$ [3]. Direct cyclometallation has also been carried out with $Pd(OAc)_2$ or $Hg(OAc)_2$ [4] and with $PhCH_2M(CO)_5$ (M = Mn or Re) [5]. An indirect route where the iminophosphorane is initially lithiated and then transmetalated has been used to prepare gold [6,7], rhodium, iridium [8], aluminium and gallium [9] cyclometalated iminophosphoranes. We have been particularly interested in cycloaurated iminophosphoranes, since the ligand is effective at stabilising the gold(III) oxidation state.

Sugar iminophosphoranes have long been known. Acetylated glycosyl azides react with PPh_3 in Et_2O, to give species such as **1a** [10]. These sugar iminophosphoranes are useful in organic synthesis; for example they can be used to reduce azides, to produce amides or to synthesis imines via the Aza–Wittig reaction [11]. However their use as ligands has not been investigated. Since other gold(III) iminophosphoranes have been shown to be catalytically and biologically active [12], the introduction of a carbohydrate moiety is interesting, since carbohydrates not only introduce chirality but can enhance biological activity as well. This paper reports the synthesis and characterisation of some novel cycloaurated iminophosphoranes.

1a



2. Results and discussion

2.1. Complexes of glycosyl iminophosphoranes

The Staudinger reaction [13] between an azide and a phosphine seemed the best route to iminophosphoranes so sugar azides were needed. Starting from D-glucose, D-galactose and L-arabinose, literature methods [14–16] readily produced acetylated glycosyl azides **2a**–**c**, by acetylation of the sugars with acetic anhydride and catalytic amounts of iodine, bromination with HBr in acetic acid, and nucleophilic substitution with NaN_3, Scheme 1.

The reaction can be extended to many other sugars such as disaccharides but is only applicable to 1,2-*trans* sugars, so mannose with the O2 oxygen in the axial position would not produce the azide product. Azides are notorious for their explosive nature, but as the percentage of nitrogen in the azide decreases they become less explosive. The Smith rule [11] is an indication of whether an

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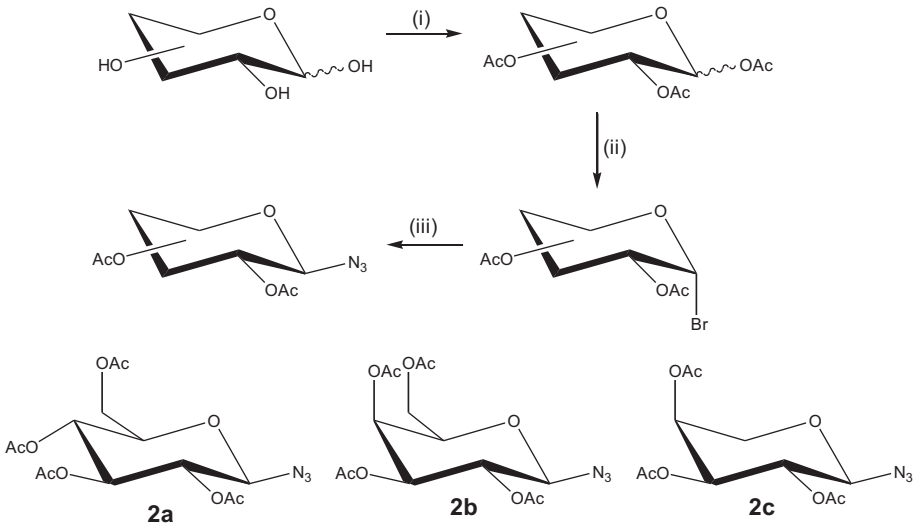


Scheme 1. General reaction scheme for the production of glycosyl azides. (i) Acetic anhydride, cat. I_2; (ii) HBr, acetic acid; (iii) NaN_3, acetone, H_2O.

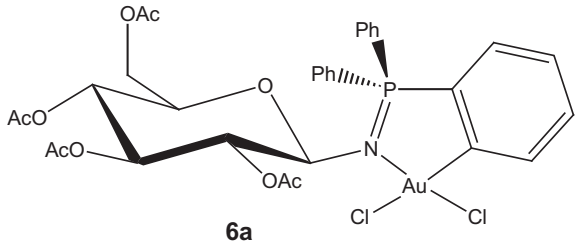
organic azide will be explosive. Since the nitrogen content of all the sugar azides was low no special precautions were taken with the manipulation of them.

Acetyl glucosyl azide was reacted with PPh_3 with a slight modification of the previous method [10] to produce **1a**, which was used without purification. The iminophosphorane $Ph_3P{=}N{-}Ph$, **3**, has been directly cyclometalated [5–7,17], so **1a** was tested to see if direct metallation was possible. $Pd(OAc)_2$, $Hg(OAc)_2$ and $PhCH_2Mn(CO)_5$ were all tried but no cyclometalated product could be isolated or detected by high resolution electrospray ionisation mass-spectrometry (ESI-MS) of an aliquot of the reaction mixture. To understand why, a structure determination of **1a** was carried out, shown in Fig. 1.

Compared with other iminophosphoranes with alkyl groups on the nitrogen the C–N (1.409(1) Å) and N=P (1.5744(10) Å) bond lengths are similar as is the C–N=P bond angle of 121.16(7)° [18,19]. The C–N=P bond angle for the aryl-substituted **3** is however larger at 130.4(3)° [20]. While the phosphorus is approximately tetrahedral there is a slight distortion in the N=P–C angles, with the carbon atoms *cis* to the nitrogen substituent having slightly larger angles. This is also seen in the structure of **3** [20] and for some other alkyl iminophosphoranes [18,19]. The torsion angle for C2–C1–N1–P1 is 176.8(1)°. The sugar portion of the molecule is as expected. A space filling model indicated that the nitrogen was sterically crowded in the solid state. Scheme 2 shows the proposed mechanism for the direct metallation by $Pd(OAc)_2$ [21–23] which starts with the coordination to the metal by the nitrogen. Presumably for **1a** the lack of availability of the nitrogen hinders the direct metallation. In support of this when **1a** was stirred with $PdCl_2$ in acetonitrile, under conditions where $Ph_3P{=}N{-}Ph$ forms the N-donor complex, $Pd[N(Ph){=}PPh_3]_2Cl_2$ [24], no product could be isolated or detected by ESI-MS. While the steric explanation for the lack of reactivity seems plausible, it should perhaps be noted that the solution NMR spectrum of **1a** does not show inequivalence of the Ph groups which would arise from hindered rotation about the C–N bond on the NMR time scale, so in solution conformations with the N exposed could be generated by twisting (c.f. Fig. 6 discussed below).

Since another route was needed, pre-metallation of the phosphine was investigated. Transmetallation from mercury to gold(I) and gold(III) has been used in a number of cases where direct auration is not feasible [25–29], and the mercurated diphosphine, **4**, was used by Kilpin et al. to produce a gold(III) iminophosphorane [30]. The phosphine was reacted with an azide to produce an intermediate mercurated iminophosphorane, which could be transmetalated with Au(III). The overall reaction is shown in Scheme 3.

The azide sugar **2a** was reacted with **4**. Monitoring of the reaction by ^{31}P NMR and ESI-MS showed that the intermediate mercurated iminophosphorane, **5a**, had fully formed after 1.5 h. Removal of the solvent gave **5a** which was used directly, after characterisation by ^{31}P NMR and ESI-MS. The ion $[AuCl_4]^-$ has been used to produce gold(III) iminophosphoranes [6,17,30]. To **5a** was added $[NMe_4][AuCl_4]$ and dry acetonitrile and the mixture stirred for several days in the dark. Monitoring by ESI-MS showed the slow disappearance of the mercurated sugar iminophosphorane and the appearance of the cyclometalated gold(III) compound. After separation of $HgCl_2$ by filtration, the solvent was removed under vacuum and recrystallisation of the residue gave air- and moisture-stable yellow crystals of **6a**.



6a

At room temperature after one month some decomposition was seen, with the development of the purple colour from colloidal elemental gold. However at −15 °C, crystals were stable for over a year. The other glycosyl azides **2b** and **2c** reacted similarly to give the analogues **6b** and **6c**.

2.1.1. ESI-MS

ESI-MS of the compounds **6a**–**c** showed several characteristic ions. The main ion was from the loss of a chloride to give $[M - Cl]^+$ with a less intense ion from $[M + Na]^+$. This is a different mode of ionisation from that seen for the mercurated intermediate **5**, which forms the ion $[M + H]^+$. This difference is because of the availability of the nitrogen to be protonated on **5**, since mercury only weakly interacts with the nitrogen while gold forms a strong bond.

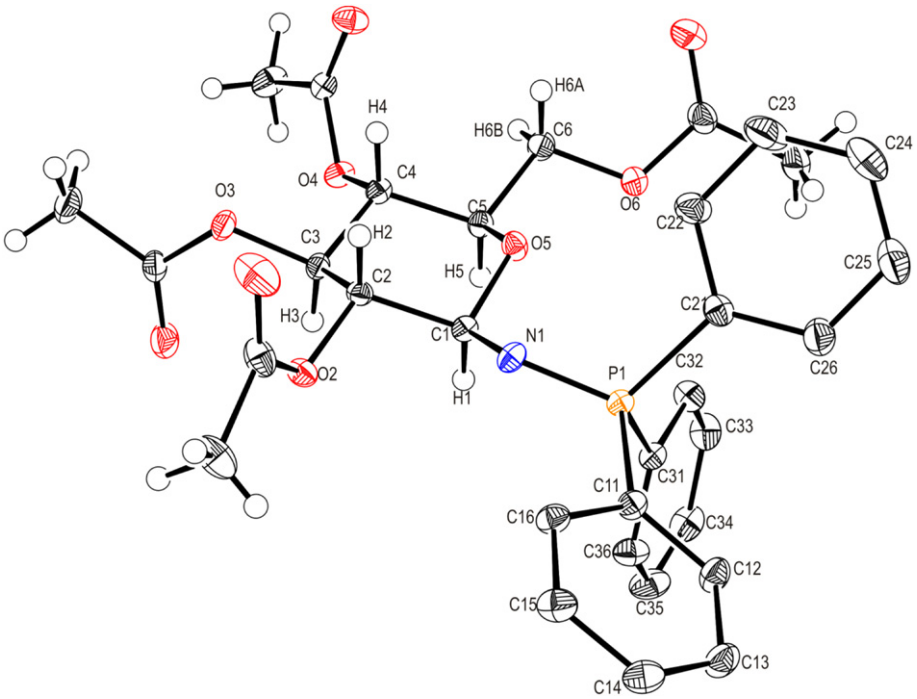


Fig. 1. The geometry of **1a** showing the atom labelling scheme and thermal ellipsoids at the 50% probability level. Phenyl hydrogen atoms have been omitted for clarity. Selected bond lengths (Å): C1–N1 1.4093(12), N1=P1 1.5744(9); bond angles (°): C1–N1=P1 121.16(7), N1=P1–C11 108.98(5), N1=P1–C21 113.33(5), N1=P1–C31 115.26(5); torsion angle (°): C2–C1–N1–P1 176.8(1).

2.1.2. ^{31}P, ^{1}H and ^{13}C NMR

Fig. 2 shows the clear changes in the ^{31}P chemical shift of the series of iminophosphoranes using the sugar azide **2a**. With the free phosphine **4** the shift is 0.38 ppm. Upon reaction with the azide to form **5a** there is a clear shift downfield to 21.2 ppm. Once the compound has been cyclometalated and the phosphorus incorporated into a cyclic system, **6a**, there is another large downfield shift to 60.3 ppm, a diagnostic indication that the phosphorus is in a 5-membered cyclic system [31,32]. For **4** and **5a** ^{199}Hg satellite peaks could be seen from $^{3}J_{Hg,P}$ coupling.

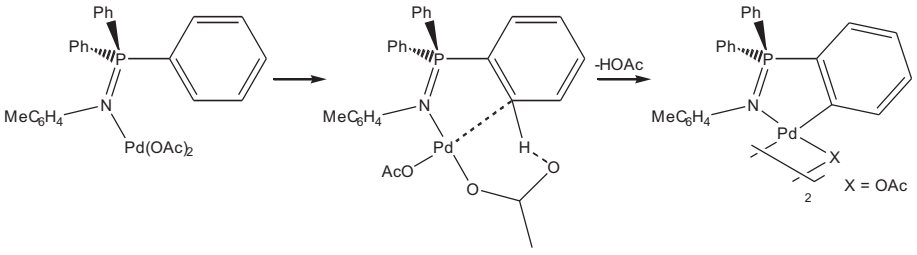
^{1}H NMR also has some diagnostic signals from the anomeric proton, H1. Fig. 3 shows a series of ^{1}H NMR spectra showing the change in the anomeric proton signal for galactose (**b**). In the gold(III) chloride iminophosphorane the normal doublet signal becomes a doublet of doublets at 6.21 ppm. This is due to the three bond coupling to the phosphorus atom and gives a $^{3}J_{H1,P}$ coupling constant of 18.1 Hz. The β anomer has been retained.

For the rest of the ^{1}H NMR spectrum the typical sugar signals are seen and could be readily assigned. The difference in the position of the hydroxyl group at C4 for glucose (**a**) and galactose (**b**), was obvious in the ^{1}H NMR spectrum. H4 in glucose is in the axial position and has a vicinal angle of 180° with H3 and H5, while for galactose it is equatorial and the vicinal angle is 60°. This smaller angle leads to small coupling constants for H3, H4 and H5. This is also seen in the ^{1}H–^{1}H COSY with no cross peak seen between H4 and H5. The spectrum for **6c** was harder to interpret since H1 and H2 were very broad signals. **6c** also has an equatorial proton at C4 and small coupling constants were also seen.

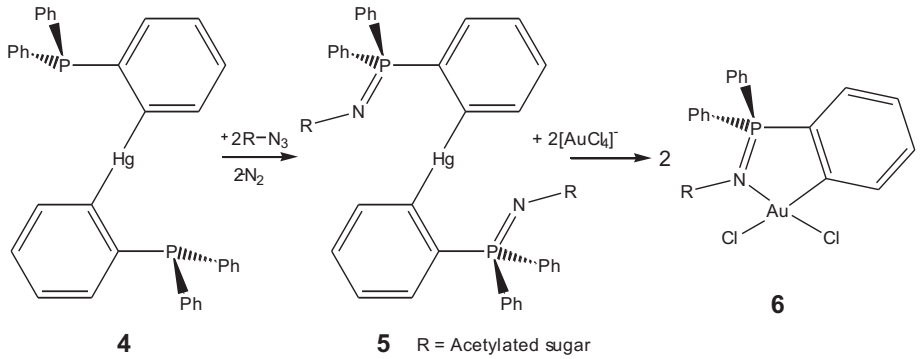
In the ^{13}C NMR spectrum the sugar signals were as expected; the anomeric carbon (C1) showed splitting from $^{2}J_{C,P}$ coupling of ~5 Hz. The aromatic region was complex with many slightly inequivalent carbon atoms, some with coupling to the phosphorus atom, and this portion was not assigned.

2.1.3. Crystal structures of the gold(III) complexes *6a* and *6c*

Recrystallisation of **6a** and **6c** by slow diffusion of hexane into solutions in dichloromethane or chloroform, respectively, produced X-ray quality crystals. Monoclinic crystals of **6c** had two independent molecules in the asymmetric unit, together with two chloroform molecules (one disordered) and a hexane molecule. Figs. 4 and 5 show the geometry of **6a** and **6c** respectively. The structure determination for **6c** was less precise than usual because of crystal quality/lattice solvent loss so the following discussion is based on the determination for **6a**, but is equally applicable to the close analogue **6c** which has the same overall conformation.



Scheme 2. Proposed mechanism for cyclometallation of $MeC_6H_4N{=}PPh_3$ by palladium acetate [21–23].



Scheme 3. General reaction scheme for the cycloaurated sugar iminophosphoranes from **4** (R = Sugar).

In both compounds the gold(III) is square planar. If a plane is calculated through Au1, Cl1, Cl2, N1 and C20, for **6a** the largest deviation is 0.065(3) Å for C20. The *trans* influence can be seen in the lengthening of the Au–Cl bond *trans* to the carbon compared with that opposite the N (2.348(2) Å compared with 2.272(2) Å) for **6a**. The bonding parameters involving Au are similar to those reported for (2-$Cl_2AuC_6H_4$)Ph_2P=N–Ph, as are the C–N and N=P bond lengths [6].

Both metallocyclic rings show a puckered envelope conformation, with the nitrogen atom out of the plane. The plane defined by Au–C–C–P is essentially planar with no atom deviating by more than 0.008(4) Å. The nitrogen is displaced from this plane by 0.411(7) Å. While there are examples of iminophosphoranes having a near-planar metallocyclic ring, such as [2-$(CO)_4MnC_6H_4$]Ph_2P=N–Ph [5], all reported Au(III) compounds give envelope conformations with the nitrogen atom out of plane [6,17].

The torsion angle of C2–C1–N1–P1 is 93.1(6)° for **6a**. For **1a** it is 176.8(1)° showing that the triphenylphosphine group has been twisted substantially which points the lone pair of electrons on the nitrogen away from the acetate group on C2 of the sugar. It is unclear why this rotation could not happen in **1a** to allow direct metallation to occur if steric hindrance of the nitrogen prevents it from happening. Fig. 6 shows this twisting with a comparison between **1a** and **6a**. This puts one of the phenyl rings above the carbohydrate ring. Despite having an axial acetate group at C4, **6c** has the phenyl ring in a similar position.

The strength of the nitrogen bond to the gold can be seen by the lengthening of the N1–P1 and C1–N1 bond as electron density is removed from the nitrogen–phosphorus bond by the gold centre. For example if **1a** and **6a** are compared N1–P1 has increased to 1.612(6) Å from 1.5744(10) Å, while C1–N1 has increased to 1.447(9) Å from 1.4093(12) Å. The C–N=P bond angle for **6a** is similar to **1a** showing little change upon cyclometallation.

The C–Au–N bite angle is 85.6(3)° for **6a**. This is comparable to known cyclometalated iminophosphoranes such as [2-$(CO)_4MnC_6H_4$]Ph_2P=N–Ph (83.5(2)° [5]) and [2-$Cl_2AuC_6H_4$]Ph_2P=N–Ph (84.9(2)° [6]).

Each of the sugar portions of the molecules show the $^4C_1$ conformation. In comparison to the D-glucose structure the L-arabinose compound lacks the hydroxymethyl group on C5 and O4 is axial instead of equatorial (As a note, even though **6c** has the same configuration as the glucose version, it is assigned the α configuration since it is an L-sugar rather the β configuration for the D-sugar of **6a**).

2.2. Reactions at the Au(III) centre

For *C,N*-cyclometalated gold(III) dichlorides, a variety of different ligands can displace the chlorides on the gold(III) atom. Two examples were examined in the present study.

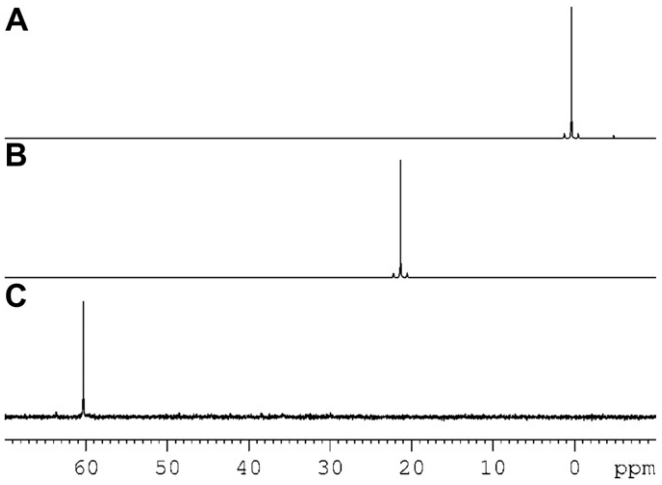


Fig. 2. ^{31}P NMR spectra comparing the changes of chemical shift for; A) mercurated diphosphine **4**; B) mercurated iminophosphorane intermediate **5a**; C) *C,N*-cycloaurated iminophosphorane **6a**.

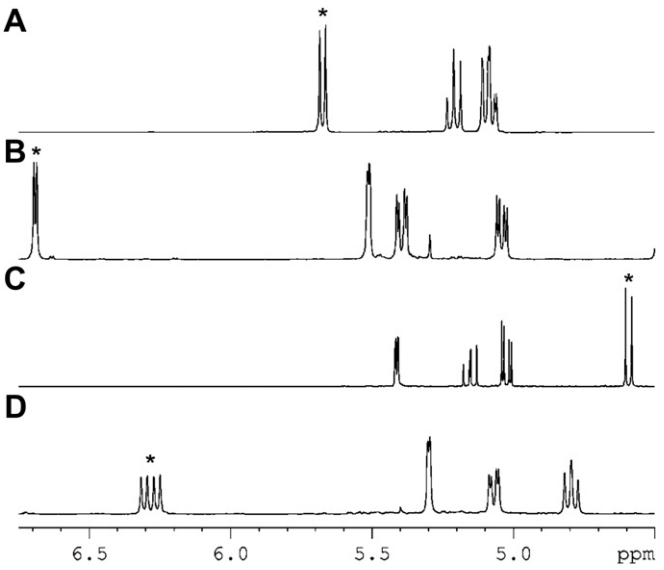


Fig. 3. ^1H NMR spectra showing the change in the anomeric proton signal by comparing; A) R–OAc; B) R–Br; C) **2b**; D) *C,N*-cycloaurated iminophosphorane **6b**. R = Per-*O*-acetyl galacosyl. The anomer proton is marked with an asterisk.

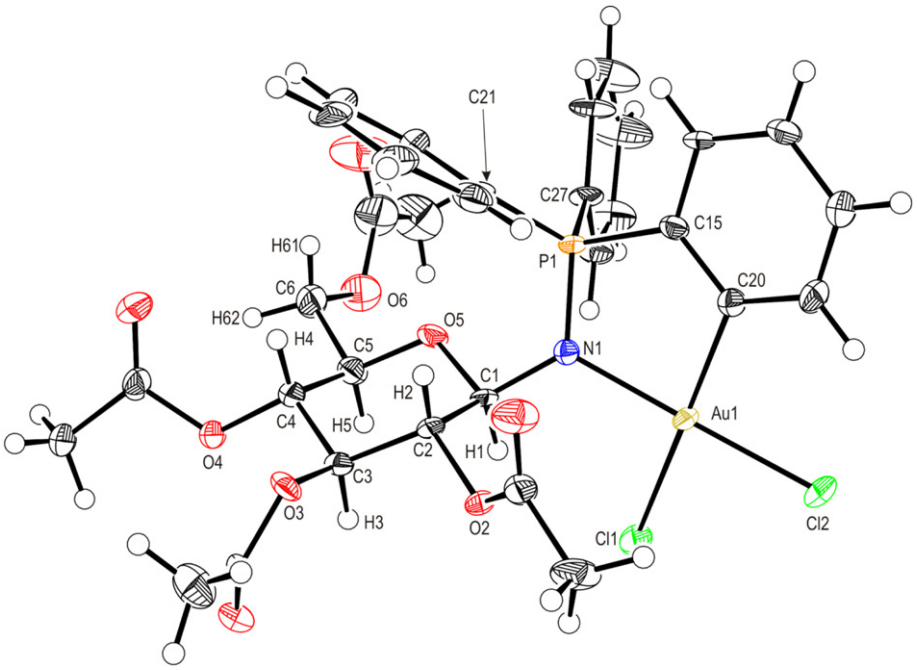


Fig. 4. The geometry of **6a** showing the atom labelling scheme and thermal ellipsoids at the 50% probability level. Selected bond lengths (Å): Au1–Cl1 2.348(2), Au1–Cl2 2.272(2), Au–C 2.073(7), Au–N1 2.040(5), C1–N1 1.447(8), N1–P1 1.612(6); bond angles (°): C–Au–N 85.6(3), C–N=P 122.2(4); torsion angles (°): P1=N1–C1–C2 93.1(6).

2.2.1. Reaction with PPh_3

There are a large number of *C,N*-cyclometalated gold(III) dichloride compounds [12]. The strength of the gold–nitrogen bond can be gauged by reaction with various reagents to see if it is a gold–chloride or the gold–nitrogen bond that is broken; PPh_3 has been used to test this [12]. Scheme 4 shows the two possible pathways; either one of the chlorides is displaced to form a cation or the nitrogen is displaced to form a neutral compound. Previous work has shown that the gold–nitrogen bond in other cyclometalated iminophosphoranes is strong and resists displacement by PPh_3 [17].

Following the reported procedure [17], the cycloaurated iminophosphorane **6a**, PPh_3 and NH_4PF_6 were stirred in CH_2Cl_2 to produce **7a**·PF_6. ESI-MS of the product showed a very intense ion corresponding to the cation. The ^{31}P NMR spectrum of **7a** confirmed the assignment. The cation showed two signals, one at 63.5 ppm from the iminophosphorane and one at 37.5 ppm from PPh_3. The high downfield position of the iminophosphorane

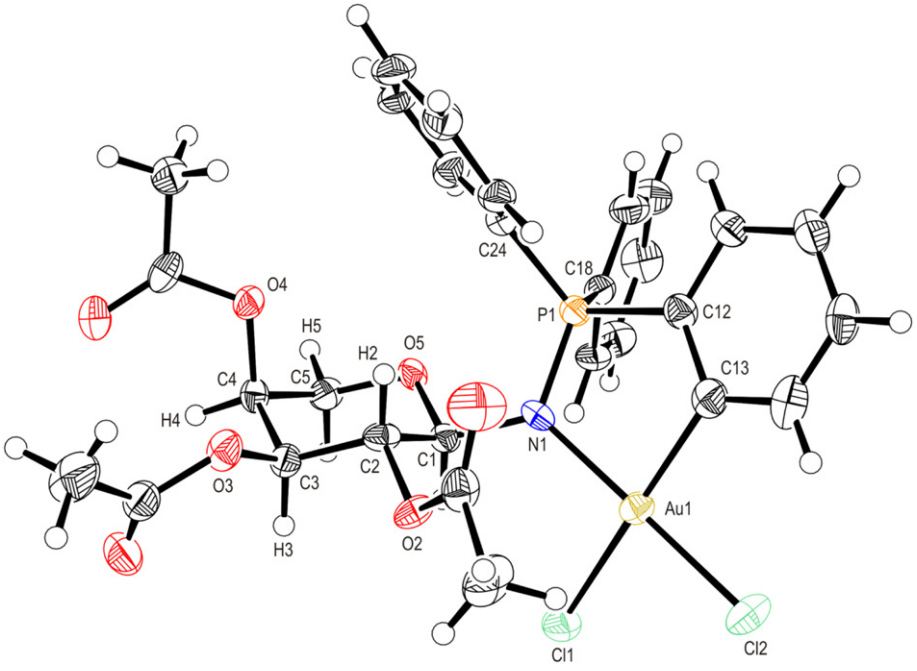


Fig. 5. The geometry of one of the independent molecules in the asymmetric unit of **6c** showing the atom labelling scheme and thermal ellipsoids at the 50% probability level.

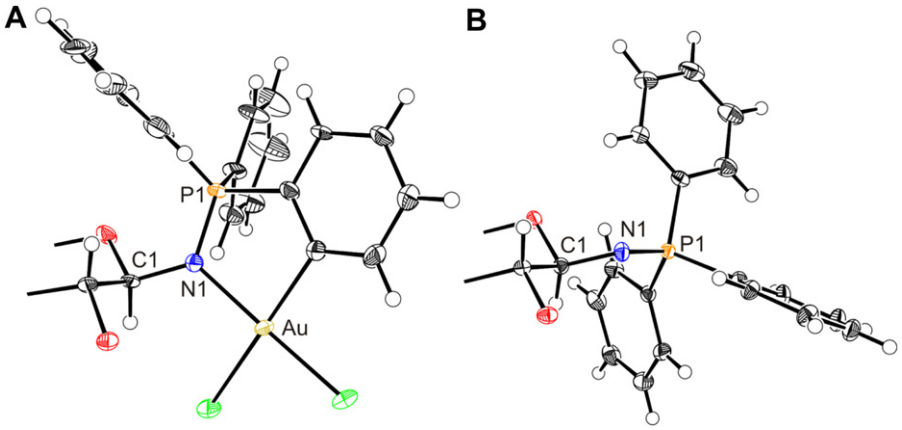


Fig. 6. Comparison of the torsion angle C2–C1–N1–P1, for *C,N*-cycloaurated iminophosphorane **6a** (A) and iminophosphorane **1a** (B), showing the twisting of the C1–N1 bond. Acetate groups have been omitted for clarity.

phosphorus indicated that it is still in a five-membered metallocyclic ring [31,32].

The ^{1}H NMR spectrum showed large changes. The carbohydrate signals were very broad so the multiplicity was difficult to determine, and the anomeric proton had been shifted upfield 1.80 ppm. In the ^{13}C NMR spectrum the anomeric carbon barely shifted, only moving 0.2 ppm downfield, it also no longer had any coupling to phosphorus. Interestingly C2 now showed ^{3}J coupling to the phosphorus (15.8 Hz for **7b**). The rest of the spectrum was similar to that of the dichloride.

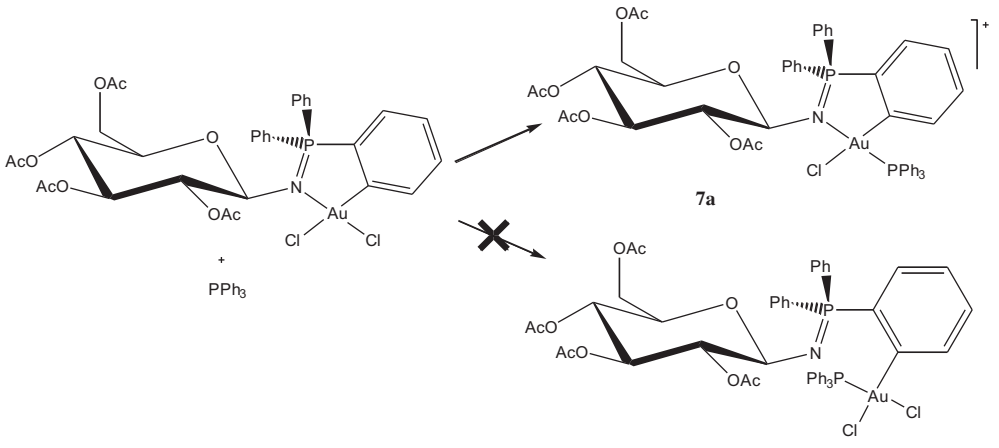
Although crystals of X-ray quality could not be grown, it was assumed that the PPh_3 was *trans* to the nitrogen as in previous examples [17]. This is caused by antisymbiosis which is the preference for a hard donor ligand *trans* to a soft ligand on a soft metal [33]. Since ligands *trans* to each other compete for the same σ and π metal orbitals, having the phosphine and carbon *trans* to each other would destabilise the complex.

2.2.2. Reaction with thiosalicylic acid

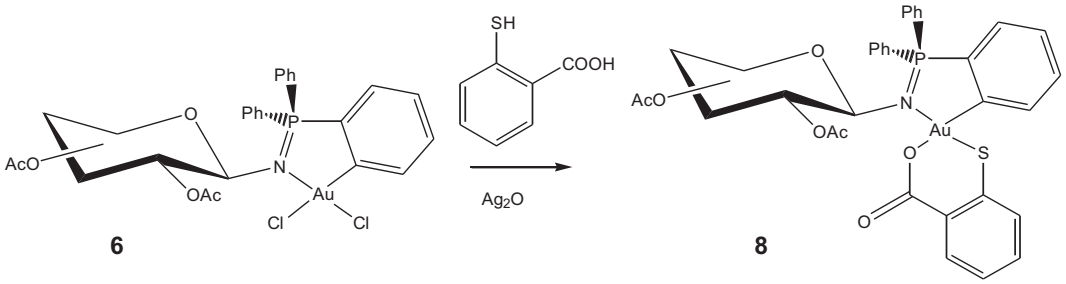
There is interest in replacing the chlorides on *C,N*-cycloaurated compounds with the dianionic thiosalicylate ligand to form a second six-membered chelate ring [34,35]. This is because such derivatives show improved anti-tumour effects [35] compared to the parent dichloride [17]. Previous reactions with other complexes were carried out in methanol with triethylamine as base [35], a process precluded in the present study because of potential cleavage of the acetate groups under these conditions. Therefore an alternative method using Ag_2O in CH_2Cl_2 [34] was chosen for the present study, and gave the products in high yields, Scheme 5. These new compounds were more stable than the dichlorides, with the thiosalicylate derivatives indefinitely stable at room temperature. ESI-MS of the compounds showed only the ions $[M + H]^+$, $[M + Na]^+$ and $[M + K]^+$. This compares with the parent dichlorides which only showed a weak $[M + Na]^+$ peak; the thiosalicylate ligand provides additional ionisation sites, and discourages alternative ionisation via anion dissociation.

The NMR spectra of the thiosalicylate complexes were similar to those of the starting dichlorides. The main changes were from the phosphorus atom signal and the anomeric proton. The anomeric proton has shifted upfield as the new ligand changes the electron density on the gold. The same effect is seen in the ^{31}P NMR, as the phosphorus signal for **8b** is 51.7 ppm compared to 60.3 ppm for **6b**. Similar shifts were seen for the other compounds. The anomeric carbon still showed coupling to phosphorus (6.1 Hz for **8b**).

Although crystals of X-ray quality could not be grown, it was assumed that the sulphur atom of the thiosalicylate was *trans* to the nitrogen because a previous structure determination of a thiosalicylate complex of a gold(III) iminophosphorane showed that configuration [17], consistent with antisymbiosis predictions.



Scheme 4. Two possible products of reacting **6a** with PPh_3.



Scheme 5. Reaction of gold(III) dichloride iminophosphoranes with thiosalicylic acid.

2.3. Biological activity

Gold(III) compounds have shown biological activity [12]. To see if the carbohydrate had any effect **6a** and its thiosalicylate derivative **8a** were tested for anti-tumour activity against a P388 Murine Leukaemia cell line. **6a** was essentially inactive with an IC_{50} value of >62,500 ng mL^{-1}, which can be compared with (2-$Cl_2AuC_6H_4$)Ph_2P=N–Ph which had an activity of 7546 ng mL^{-1} [17]. **8a** had much better activity with a value of 1665 ng mL^{-1}, although this is less than for the thiosalicylate derivative of (2-$Cl_2AuC_6H_4$)Ph_2P=N–Ph at <487 ng mL^{-1} [17]. Hence replacing the aryl substituent on the nitrogen atom with a carbohydrate moiety does not enhance the activity to the iminophosphorane, though again the thiosalicylate does boost the activity significantly, compared with the dichloride.

3. Conclusions

The reaction of acetylated sugar azides proceeded smoothly with PPh_3 to produce iminophosphoranes. All attempts at direct metallation of the iminophosphoranes failed, presumably because of steric crowding of the nitrogen atom. The pre-metallation of PPh_3 with mercury gave access to *C,N*-cycloaurated iminophosphoranes via transmetallation with [Me_4N][$AuCl_4$]. The reaction was successful with different acetylated glycosyl sugars and so it should be possible to extend this reaction to the wide range of acetylated glycosyl sugars available.

4. Experimental

4.1. General procedures

Acetylated glycosyl azides were prepared from their parent sugars [14–16]. 2-$LiC_6H_4PPh_2$ [36] and $Hg(2\text{-}C_6H_4PPh_2)_2$ [37] were prepared via literature methods. Dry CH_2Cl_2, THF, ether and hexane were produced from a Pure Solv solvent purification system [38]. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 FT NMR spectrometer at 400.13 and 100.61 MHz respectively at 300 K, while $^{31}P\{H\}$ were from a Bruker DRX 300 FT NMR spectrometer at 121.5 MHz. Samples were run in $CDCl_3$; ^1H and ^{13}C NMR spectra were referenced to the solvent line at 7.26 and 77.16 ppm respectively, while $^{31}P\{H\}$ NMR spectra were referenced using an external standard of H_3PO_4. High resolution ESI-MS was carried out on a Bruker Daltonics MicrOTOF instrument. Samples were dissolved in methanol and were infused at 180 μL min^{-1}. The instrument was calibrated over the appropriate mass range with sodium formate, and all spectra were acquired in positive ion mode. Microelemental analysis was carried out at the Campbell Microanalytical Laboratory at the University of Otago. Biological testing details have been described earlier [17].

4.2. Preparation of R–N=PPh_3 (R = per-O-acetyl glucosyl) (**1a**)

The sugar azide **2a** (200 mg, 0.536 mmol) and PPh_3 (140.5 mg, 0.536 mmol) were dissolved in dry CH_2Cl_2 (15 mL) under nitrogen and stirred for 1.5 h. Removal of the solvent gave **1a** (322.4 mg, 99%) which was used for reactions without further purification. Crystals suitable for X-ray diffraction were grown by cooling a CH_2Cl_2/hexane solution of **1a**.

^1H NMR: δ 7.67–7.10 (m, 15H, arom.), 5.93 (dd, 1H, $J_{H1,H2}$ 8.4 Hz, $J_{H1,P}$ 19.6 Hz, H1) 5.08 (t, 1H, H3), 4.25 (t, 1H, H2), 4.16 (t, 1H, H4), 3.99 (dd, 1H, $J_{H5,H6b}$ 6.3 Hz $J_{H6a,H6b}$ 12.2 Hz, H6b), 3.80 (m, br, 1H, H5), 3.70 (m, br, 1H, H6a), 2.19, 2.17, 1.93, 1.86 (s, 12H, 4× OAc) ppm. ^{13}C NMR: δ 170.5, 170.2, 169.6, 169.5 (C=O), 88.5 (d, $J_{C1,P}$ 5.8 Hz, C1), 74.7 (C5), 72.1 (C2), 72.6 (C3), 68.4 (C4), 62.2 (C6), 21.4, 20.9, 20.5 × 2 (4× CH_3) ppm. ^{31}P NMR: δ 21.1 ppm.

4.3. Preparation of (2-$Cl_2AuC_6H_4$)Ph_2P=N–R (R = per-O-acetyl glucosyl) (**6a**)

The sugar azide **2a** (200 mg, 0.536 mmol) and the diphosphine **4** (193.8 mg, 0.268 mmol) were dissolved in dry CH_2Cl_2 (15 mL) under N_2 and stirred for 2 h, solvent was removed under vacuum and [NMe_4][$AuCl_4$] (221 mg, 0.536 mmol) was added and the solids dissolved in dry acetonitrile (15 mL) and left to stir under N_2 and protected from light for 3 days. Solvent was removed under vacuum and the residue dissolved in CH_2Cl_2 and filtered through Celite. Addition of petroleum spirits and cooling to −15 °C gave yellow crystals of **6a** (397 mg, 88%). Crystals suitable for X-ray diffraction were grown by cooling a CH_2Cl_2/hexane solution of **6a**.

^1H NMR: δ 8.16–7.10 (m, 14H, arom.), 6.21 (dd, 1H, $J_{H1,H2}$ 8.7 Hz, $J_{H1,P}$ 20.4 Hz, H1) 5.09 (t, 1H, H3), 4.27 (t, 1H, H2), 4.16 (t, 1H, H4), 3.98 (dd, 1H, $J_{H5,H6b}$ 6.3 Hz $J_{H6a,H6b}$ 12.2 Hz, H6b), 3.80 (bm, 1H, H5), 3.70 (bm, 1H, H6a), 2.17, 1.93 × 2, 1.86 (s, 12H, 4× OAc) ppm. ^{13}C NMR: δ 170.4, 170.2, 169.6 × 2 (C=O), 86.9 (d, $J_{C1,P}$ 5.6 Hz, C1), 74.8 (C5), 72.9 (C2), 72.6 (C3), 68.4 (C4), 62.3 (C6), 21.3, 20.9, 20.6 × 2 (4× CH_3) ppm. ^{31}P NMR: δ 61.6 ppm. Anal. Calcd for $C_{32}H_{33}NO_9PCl_2Au$ (874.452): C, 43.95; H, 3.80; N, 1.60. Found: C, 44.07; H, 3.80; N, 1.70. ESI-MS: *m/z*: 838.122 (strong, $[M - Cl]^+$, calc. 838.124), 896.086 (weak, $[M + Na]^+$, calc. 896.083), 947.193 (weak, $[M + NMe_4]^+$, calc. 947.191).

4.4. Preparation of (2-$Cl_2AuC_6H_4$)Ph_2P=N–R (R = per-O-acetyl galacosyl) (**6b**)

C,N-Cycloaurated **6b** was made using the same method as **6a**, with the sugar azide **2b** (200 mg, 0.536 mmol), diphosphine **4** (193.8 mg, 0.268 mmol) and [NMe_4][$AuCl_4$] (221 mg, 0.536 mmol). Work up gave **6b** (378 mg, 81%).

^1H NMR: δ 8.12 (m, 1H, arom.), 8.00–7.21 (m, 12H, arom.), 7.05 (m, 1H, arom.), 6.21 (dd, 1H, $J_{H1,H2}$ 8.8 Hz, $J_{H1,P}$ 18.2 Hz, H1) 5.22 (dd, 1H, $J_{H4,H5}$ 1.4 Hz, $J_{H3,H4}$ 3.4 Hz, H4), 4.98 (dd, 1H, $J_{H3,H4}$ 3.4 Hz, $J_{H2,H3}$

10.5 Hz, H3), 4.69 (dd, 1H, $J_{H1,H2}$ 8.8 Hz, $J_{H2,H3}$ 10.5 Hz, H2), 4.06 (m, 1H, H5), 3.81 (dd, 1H, $J_{H5,H6b}$ 7.5 Hz $J_{H6a,H6b}$ 11.4 Hz, H6b), 3.65 (dd, 1H, $J_{H5,H6a}$ 5.2 Hz, $J_{H6a,H6b}$ 11.4 Hz, H6a), 2.24, 1.90, 1.87, 1.69 (s, 12H, 4× OAc) ppm. ^{13}C NMR: δ 170.8, 170.4, 169.9, 169.7 (C═O), 86.9 (d, $J_{C1,P}$ 4.9 Hz, C1), 74.2 (C5), 70.7 (C3), 70.5 (C2), 67.3 (C4), 61.4 (C6), 21.6, 20.8, 20.7, 20.6 (4× CH_3) ppm. ^{31}P NMR: δ 60.3 ppm. Anal. Calcd for $C_{32}H_{33}NO_9PCl_2Au$ (874.452): C, 43.95; H, 3.80; N, 1.60. Found: C, 44.10; H, 3.85; N, 1.84. ESI-MS: *m/z*: 838.123 (strong, $[M - Cl]^+$, calc. 838.124), 896.083 (weak, $[M + Na]^+$, calc. 896.083), 947.187 (weak, $[M + NMe_4]^+$, calc. 947.191).

4.5. Preparation of (2-$Cl_2AuC_6H_4$)Ph_2P═N–R (R = per-O-acetyl arabinosyl) (**6c**)

Similarly **6c** was made using the same method as **6a**, with the sugar azide **2c** (200 mg, 0.664 mmol), diphosphine **4** (240 mg, 0.332 mmol) and $[NMe_4][AuCl_4]$ (274 mg, 0.664 mmol). Work up gave **6c** (456 mg, 86%). Crystals suitable for X-ray diffraction were grown by cooling a CH_2Cl_2/hexane solution of **6c**.

^{1}H NMR: δ 8.15 (m, 1H, arom.), 7.99–7.54 (m, 9H, arom.), 7.42–7.25 (m, 3H, arom.), 7.04 (m, 1H, arom.), 6.06 (b, 1H, H1) 5.13 (dd, 1H, $J_{H4,H5}$ 1.7 Hz, $J_{H3,H4}$ 3.5 Hz, H4), 4.96 (dd, 1H, $J_{H3,H4}$ 3.5 Hz, $J_{H2,H3}$ 10.3 Hz, H3), 4.73 (b, 1H, H2), 3.76 (mm, 2H, H5a, H5b), 2.20, 1.89, 1.72 (s, 9H, 3× OAc) ppm. ^{13}C NMR: δ 170.3, 170.1, 169.5 (C═O), 88.7 (d, $J_{C1,P}$ 5.2 Hz, C1), 70.4 (C3), 68.7 (C2), 67.7 (C4), 65.9 (C5), 21.0, 20.8, 20.7 (3× CH_3) ppm. ^{31}P NMR: δ 60.6 ppm. Anal. Calcd for $C_{29}H_{29}NO_7PCl_2Au$ (802.389): C, 43.41; H, 3.64; N, 1.75. Found: C, 43.63; H, 3.91; N, 1.83. ESI-MS: *m/z*: 766.106 (strong, $[M - Cl]^+$, calc. 766.103), 1569.178 (weak, $[2M - Cl]^+$, calc. 1569.174).

4.6. Preparation of [(2-Cl(PPh_3)AuC_6H_4)Ph_2P═N–R]·PF_6 (R = per-O-acetyl glucosyl) (***7a***·PF_6)

The *C,N*-cycloaurated compound **6a** (50 mg, 0.0572 mmol), PPh_3 (15.0 mg, 0.0572 mmol) and $[NH_4][PF_6]$ (9.3 mg, 0.0572 mmol) were suspended in dry CH_2Cl_2 (10 mL) under N_2 and stirred for 4 h. The mixture was filtered through Celite and addition of petroleum spirits to the filtrate gave **7a**·PF_6 (47.4 mg, 67%).

^{1}H NMR: δ 8.28 (m 1H, arom.), 7.95–7.21 (m, 26H, arom.), 6.82 (m 1H, arom.), 6.66 (m 1H, arom.), 6.12 (t, 1H, H2), 5.13 (t, 1H, H4), 4.99 (t, 1H, H3), 4.61 (bd, 1H, H6b), 4.12 (m, 1H, H1), 3.85 (bd, 1H, H6a), 3.3.36 (bm, 1H, H5), 1.97, 1.94, 1.89, 1.77 (s, 12H, 4× OAc) ppm. ^{13}C NMR: δ 170.6 × 2, 170.3, 169.3 (C═O), 87.1 (C1), 73.2 (C5), 72.9 (C3), 72.4 (C2), 68.5 (C4), 61.2 (C6), 21.0, 20.8, 20.7, 20.6 (4× CH_3) ppm. ^{31}P NMR: δ 63.5, 37.5 (PPh_3), −140.4 (PF_6^-) ppm. Anal. Calcd for $C_{50}H_{48}NO_9F_6P_3ClAu$ (1246.249): C, 48.19; H, 3.88; N, 1.12. Found: C, 48.29; H, 3.91; N, 1.26. ESI-MS: *m/z*: 1101.288 (strong, [**7a**]$^+$, calc. 1101.284).

4.7. Preparation of {2-[$C_6H_4(S)CO_2$]AuC_6H_4}Ph_2P═N–R (R = per-O-acetyl glucosyl) (***8a***)

The *C,N*-cycloaurated compound **6a** (50 mg, 0.057 mmol) and thiosalicylic acid (8.8 mg, 0.057 mmol) were dissolved in CH_2Cl_2 (10 mL). Ag_2O (67.2 mg, 0.29 mmol) was added and the suspension stirred for 1 h, protected from light. The suspension was filtered through Celite and the solvent removed from the filtrate under vacuum. The residue was recrystallised from $CHCl_3$ and petroleum spirits to give **8a** (48.0 mg, 88%).

^{1}H NMR: δ 8.16–7.20 (m, 18H, arom.), 5.78 (dd, 1H, $J_{1,2}$ 8.7 Hz, $J_{1,P}$ 21.2 Hz, H1), 5.13 (t, 1H, H3), 4.25 (m, 1H, H4), 4.17 (m, 1H, H2), 3.98 (m, 1H, H6b), 3.92 (m, 1H, H5), 3.68 (dd, 1H, H6a), 1.95, 1.93, 1.81, 1.57 (4s, 12H, 4× OAc) ppm. ^{13}C NMR: δ 170.3, 170.2, 169.8, 169.7 (C═O), 169.5 (C═O, thiosalicylate), 83.8 (d, $J_{C1,P}$ 6.5 Hz, C1), 74.6 (C5), 73.1 (C2), 72.8 (C3), 68.4 (C4), 62.4 (C6), 20.9, 20.7, 20.7, 20.3 (4× CH_3) ppm. ^{31}P NMR: δ 52.8 ppm. Anal. Calcd for $C_{39}H_{37}NO_{11}PSAu$ (955.72): C, 49.01; H, 3.90; N, 1.47. Found: C, 49.04; H, 4.24; N, 1.53. ESI-MS: *m/z*: 978.141 (strong, $[M + Na]^+$, calc. 978.138), 956.159 (weak, $[M + H]^+$, calc. 956.156), 1933.289 (weak, $[2M + Na]^+$, calc. 1933.287).

4.8. Preparation of {2-[$C_6H_4(S)CO_2$]AuC_6H_4}Ph_2P═N–R (R = per-O-acetyl galacosyl) (***8b***)

Similarly *C,N*-cycloaurated **6b** (50 mg, 0.057 mmol), thiosalicylic acid (8.8 mg, 0.057 mmol) and Ag_2O (67.2 mg, 0.29 mmol) in CH_2Cl_2 (10 mL) gave **8b** (50.4 mg, 93%).

^{1}H NMR: δ 8.16 (m, 1H, arom.), 8.06–7.05 (m, 17H, arom.), 5.82 (dd, 1H, $J_{H1,H2}$ 8.6 Hz, $J_{1,P}$ 19.1 Hz, H1), 5.25 (dd, 1H, $J_{H4,H5}$ 1.4 Hz, $J_{H3,H4}$ 3.4 Hz, H4), 5.06 (dd, 1H, $J_{H3,H4}$ 3.4 Hz, $J_{H2,H3}$ 10.4 Hz, H3), 4.61 (dd, 1H, $J_{H1,H2}$ 8.6 Hz, $J_{H2,H3}$ 10.4 Hz, H2), 4.23 (ddd, 1H, $J_{H4,H5}$ 1.4 Hz, $J_{H5,H6b}$ 4.9 Hz, $J_{H5,H6a}$ 7.6 Hz, H5), 3.81 (dd, 1H, $J_{H5,H6a}$ 7.6 Hz, $J_{H6a,H6b}$ 11.4 Hz, H6a), 3.69 (dd, 1H, $J_{H5,H6b}$ 4.9 Hz, $J_{H6a,H6b}$ 11.4 Hz, H6b), 1.89, 1.82, 1.69, 1.67 (4s, 12H, 4× OAc) ppm. ^{13}C NMR: δ 170.5, 170.4, 169.4 × 2 (C═O), 169.4 (C═O, thiosalicylate), 84.0 (d, $J_{C1,P}$ 6.0 Hz, C1), 74.1 (C5), 71.0 (C2), 70.9 (C3), 67.0 (C4), 61.8 (C6), 20.8, 20.7, 20.6, 20.5 (4× CH_3) ppm. ^{31}P NMR: δ 51.7 ppm. Anal. Calcd for $C_{39}H_{37}NO_{11}PSAu$ (955.72): C, 49.01; H, 3.90; N, 1.47. Found: C, 49.14; H, 3.98; N, 1.56. ESI-MS: *m/z*: 978.140 (strong, $[M + Na]^+$, calc. 978.138), 956.160 (weak, $[M + H]^+$, calc. 956.156).

4.9. X-ray crystallography

X-ray crystallography data is summarised in Table 1. Intensity data and unit cell dimensions were collected on a Bruker APEX II CCD diffractometer. Structures were solved by the direct methods option of SHELXS97 [39]. All non-hydrogen atoms were either initially located or found in subsequent difference maps. Full-matrix least-squares refinement (SHELXL97 [40]) was based on F_o^2 with all non-hydrogen atoms anisotropic, unless otherwise stated. Hydrogen atoms were refined using a riding model. All calculations were carried out by the SHELXL97 suite of programs [40] and were run under WinGX [41]. Crystal structure graphics

Table 1
Crystal data and refinement details.

	(**1a**)	(**6a**)	(**6c**)
Formula	$C_{32}H_{34}NO_9P$	$C_{32}H_{33}NO_9PCl_2Au$ $2CH_2Cl_2$	$C_{29}H_{29}NO_7PCl_2Au$ $CHCl_3 \cdot {}^1/_2C_6H_{14}$
M_r	607.57	1044.28	1929.64
T(K)	83(2)	89(2)	89(2)
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1$	$P2_1$	$P2_1$
a (Å)	8.6161(8)	9.1905(2)	13.4315(5)
b (Å)	9.9944 (10)	12.6953(3)	13.4103(4)
c (Å)	18.1458(18)	17.4863(4)	20.9413(7)
β (deg)	90.705(1)	99.486(1)	90.785(2)
V (Å^3)	1562.5(3)	2012.34(8)	3771.6(2)
Z	2	2	4
ρ (g cm^{-3})	1.291	1.723	1.699
μ (mm^{-1})	0.142	4.145	4.343
Size (mm^3)	0.66 × 0.24 × 0.13	0.49 × 0.29 × 0.23	0.70 × 0.41 × 0.10
F (000)	640	1032	1908
θ_{max} (deg)	34.8	28.0	30.7
Refln collected	32710	32579	101907
T_{max}, min	0.982, 0.912	0.450, 0.296	0.433, 0.193
Unique reflns (R_{int})	12240(0.031)	9497(0.029)	23064(0.058)
R_1 [$I > 2\sigma(I)$]	0.0357	0.0431	0.0594
wR_2 (all data)	0.0906	0.1122	0.1675
GOF on F^2	1.028	1.134	1.035
Flack parameter	0.02(4)	0.053(7)	−0.011(7)
Final Δe (e Å^{-3})	+0.44/−0.23	+2.35/−2.94	+8.94/−2.74

were generated using ORTEP-3 [42]. The chiral compounds crystallised in non-centrosymmetric space groups and the correct absolute structures were determined using the Flack-*x* parameter [43,44] and were also confirmed from the known stereochemistry of the sugar moiety. For the refinement of **6a** the N and C atoms bonded to the Au atom were refined isotropically as their thermal ellipsoids were prolate, presumably from interference from the adjacent gold atom. The final difference map for **6c** showed one very large peak (8.9 e $Å^{-3}$) adjacent to one of the gold atoms, too close to be anything other than an artefact, perhaps associated with difficulties with the large absorption correction to the data. Some other large residual peaks (2–4 e $Å^{-3}$) were associated with the disordered $CHCl_3$ molecule.

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Appendix A. Supplementary material

CCDC 843659–843661 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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