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Development of a novel highly anti-proliferative family of gold complexes: Au(I)-phosphonium-phosphines†

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A family of gold(I)-phosphonium-phosphine complexes was synthesized thanks to an efficient 5-step strategy, which involves a phospha-Fries rearrangement. It enables the facile variation of the phosphonium moiety. All the complexes along with a synthetic intermediate were fully characterized (a crystal structure was obtained for two of them). The antiproliferative properties of the six novel complexes were evaluated on three human cancer cell lines (A549, MDA-MB-231, and SW480) and compared to those of three benchmark anticancer drugs used in clinics (**oxaliplatin**, 5-fluorouracil, and **paclitaxel**) and to a phosphonium-free gold(I) complex [Au(PPh_3)Br]. All the gold(I) complexes, containing a phosphonium, displayed strong anti-proliferative properties. They were more efficient than **oxaliplatin** and 5-fluorouracil, and one of the complexes was even more efficient than **paclitaxel**.

Introduction

Phosphonium-phosphines are a class of compounds, which are not so common. They were mainly used as ligands – chiral or not – for catalysis or as Wittig intermediates.[1–5] They were also used to give humidity-sensitive properties to polyelectrolyte copolymers.[6] However, in the present study, we are interested in their biological applications. Phosphonium is known to be a good vector to target mitochondria, especially in cancer cells.[7] Indeed, it was reported that phosphonium can accumulate ten times more in cancer cells than in healthy ones, because the negative potential of cancer cell mitochondria is higher than that of healthy ones (163 mV *vs.* 104).[8] Moreover, the association of the water solubility brought by the positive charge and the lipophilicity due to its delocalization facilitate the crossing of the cell membrane of phosphonium derivatives.[7] These are some of the reasons why phosphoniums were used for vectorizing antioxidant,[9] antibacterial,[10] or anti-cancer[11] agents. Concerning phosphonium-phosphine, Nakagawa and coll. reported an elegant study, in which they developed an OFF/ON smart probe for detecting reactive oxygen species (ROS) in mitochondria.[12] Bagherjeri and coll. chose to use the coordination properties of phosphine to develop a zwitterionic Hg(II)-based antibacterial complex, where they took advantage of phosphonium to counterbalance the negative charge of the mercury complex.[13]

In the present study, we decided to combine the vectorization properties of phosphonium with the ability of phosphine to coordinate gold(I) in order to develop novel anti-cancer agents. Among the metal-based complexes, Au(I)-phosphine complexes attract increasing interest since the repurposing of auranofin – an anti-rheumatoid drug – for anticancer applications.[14] Gold(I) complexes were extensively studied by many researchers including our group.[15–26] In contrast to platinum derivatives, the main hypothesis concerning the mechanism of action of gold(I)-based phosphine complexes is the inhibition of thio and/or seleno-cysteine enzymes, such as thioredoxine reductases (TrxRs), *via* the coordination of the gold center to thiols or selenols. TrxRs are in charge of the regulation of oxidative stress and their inhibition leads to the increase of ROS and to apoptosis.[27–29] Based on this observation, we wanted to take advantage of the phosphonium to vectorise the Au(I)-phosphine complex to the mitochondria, where TrxR2 is located. Moreover, the presence of the phosphonium will improve the solubility of the gold complexes in biological media (Fig. 1).

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†Electronic supplementary information (ESI) available: ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra of compounds **2**, **3**, **4**, **5a-f**, and **Ia-g**, stability study, water solubility evaluation of the complexes, biological experimental data, crystal structure and table of crystal data of compound **Ie** and **If**. CCDC 2036897 and 2036898. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0dt03708g

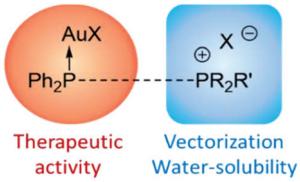


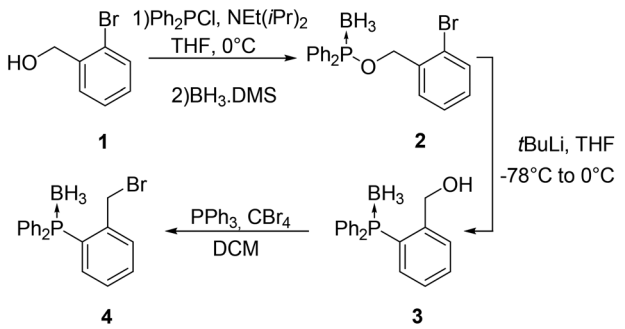
Fig. 1 General structure of the targeted complexes.

Results and discussion

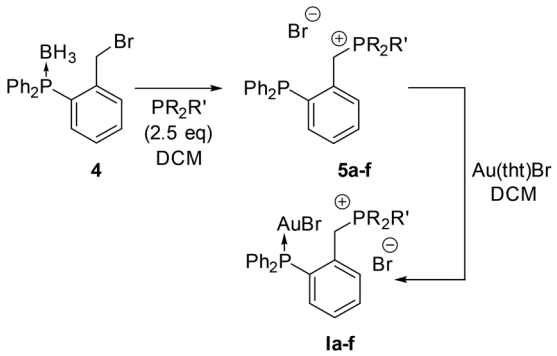
Synthesis of gold-phosphonium-phosphine complexes Ia-f

The synthesis of the phosphonium-phosphine ligands is based on the quaternisation reaction of various phosphines with [(2-bromo methyl)phenyl]diphenylphosphine borane **4**. This halogenated intermediate was prepared *via* a three-step synthetic route starting from the commercially available 2-bromobenzyl alcohol (**1**) (Scheme 1). In the first step, the reaction of **1** with chlorodiphenylphosphine in the presence of ethyldiisopropylamine followed by BH_3·DMS addition gave the 2-bromobenzyl phosphinite borane derivative **2** in 83% yield. Its ^{31}P NMR spectrum presents a signal at 107.2 ppm in CD_2Cl_2 the characteristic region for phosphinite borane derivatives. Metal-halogen exchange takes place when *t*BuLi is added to **2** to further give, by an elegant phospha-Fries rearrangement, the (2-hydroxymethylphenyl)phosphine borane derivative **3** in 77% yield. This rearrangement is based on the reaction described by Melvin[30] in 1991 with aryl phosphates and further developed by Beak[31] or Jugé[32] with phosphinite borane derivatives. A significant change is observed in the ^{31}P NMR spectrum with the appearance of a signal at 18.3 ppm. In the last step, the Appel reaction allowed conversion of the alcohol **3** in the corresponding alkyl halide **4** in 83% yield using triphenylphosphine and tetrabromomethane at room temperature. A minor shift in the ^{31}P NMR spectrum was observed for this step (**4**: δ = 19.9 ppm). In the ^{1}H NMR spectrum, the doublet corresponding to the methylene of compound **3** (δ = 4.54 ppm, J = 5.7 Hz) is transformed into a singlet for compound **4** due to the loss of coupling with the hydroxyl proton.

The halogenated phosphine borane derivative **4** was further reacted with various phosphines to give the corresponding



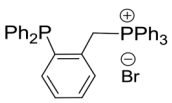
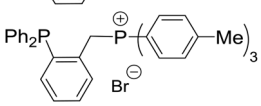
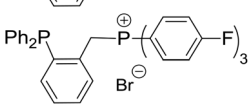
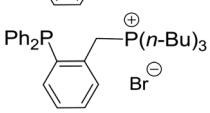
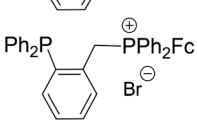
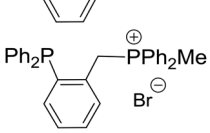
Scheme 1 Synthesis of (*o*-bromomethylphenyl) phosphine borane **4**.



Scheme 2 Synthesis of ligand **5** by phosphine quaternization.

phosphonium-phosphine ligands **5** (Scheme 2). 2.5 equivalents of the phosphine PR_2R' were necessary to enable the nucleophilic substitution on the bromomethyl moiety and the decoordination of the borane group in one single step. This methodology avoids the homoleptic quaternisation of bromo derivative **4** and gives the desired phosphonium phosphine ligands **5** with yields up to 91%. Six different phosphines bearing an alkyl or aryl group with electron withdrawing or electron donating groups were used for this study. The ^{31}P NMR spectra of the ligands **5** present a signal ranging from −14 to −17 ppm for the phosphine moiety and a second one ranging from 20 to 26 ppm for the phosphonium group (Table 1) except ligand **5d** which gives a signal at +32.6 ppm for the phosphonium group. This chemical shift is very similar to that described in the literature for methyltributylphosphonium tetrafluoroborate at +32.8 ppm.[33]

Table 1 Structures, ^{31}P NMR data and yields for phosphonium-phosphines **5a-f**

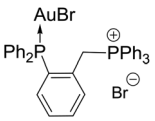
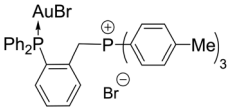
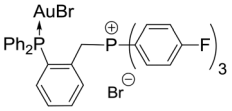
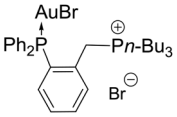
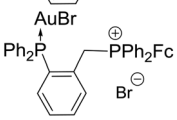
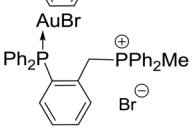
No	Structure	^{31}P NMR (ppm)		Yield
5a		−15.12	+22.97	87%
5b		−15.62	+22.08	91%
5c		−17.24	+20.72	82%
5d		−14.57	+32.60	67%
5e		−14.13	+26.29	90%
5f		−15.53	+21.75	80%

Gold complexes **Ia-f** were readily synthesized by reacting the phosphonium-phosphines **5a-f** with the bromo(tetrahydrothiophene) gold(I) precursor in dichloromethane at room temperature (Scheme 2). The reaction was monitored by ^{31}P NMR and a significant shift for the phosphine moiety could be observed from −15 ppm to 24–28 ppm (Table 2). After one hour at room temperature, the reaction is completed, and the corresponding gold complexes **Ia-f** were obtained with yields up to 94%. It is worth noting that the use of [Au(tht)Br] instead of [Au(tht)Cl] prevents the formation of a mixture of complexes. Indeed, when using [Au(tht)Cl], the bromide counter anion of **5** can exchange with the chlorido ligand of the gold complex leading to the formation of "P–Au–Cl" and "P–Au–Br" complexes.

The stability of the complexes **Ia-If** was investigated thanks to NMR studies. They were stable at least 72 h in DMSO and in the presence of water (see the ESI† for details).

Single crystals suitable for DRX analysis were obtained for **Ie** and **If** from a biphasic dichloromethane/cyclohexane mixture. The structures determined by X-ray diffraction are presented in Fig. 2 and 3. The structures of the two gold complexes **Ie** (ferrocenyl substituent on phosphonium) and **If** (methyl substituent on phosphonium) show similar data. The geometry around the gold atom is almost linear, characteristic of a phosphine-AuX complex.[34] Nevertheless, the more bulky ferrocenyl group leads to a different organization of the phosphonium moiety. The bond lengths around the gold atom in complexes **Ie** and **If** are similar to those of the PPh_3AuBr complex (P–Au: 2.252(6); Au–Br: 2.407 (2)). In **Ie**, intermolecular interactions in the crystal lead to a P–Au–Br angle of 172.73°.

Table 2 Structures, ^{31}P NMR data and yields for gold(I) complexes **Ia-f**

No	Structure	^{31}P NMR (ppm)		Yield
Ia		+22.66	+25.98	80%
Ib		+21.76	+26.07	94%
Ic		+21.71	+26.03	64%
Id		+26.91	+33.43	80%
Ie		+26.43	+27.88	78%
If		+21.80	+24.91	87%

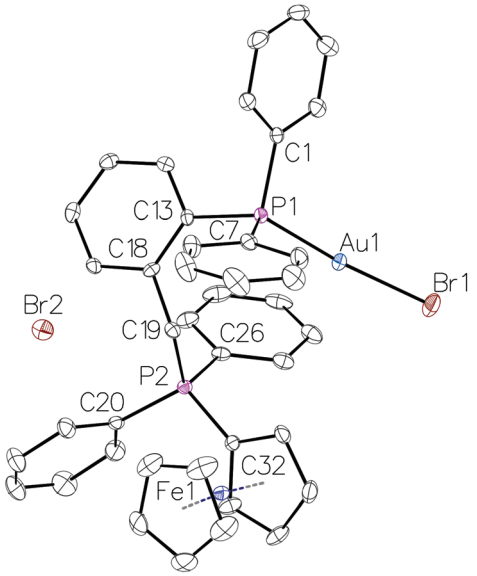


Fig. 2 ORTEP view of complex **Ie** Au1–Br1: 2.4026(4); Au1–P1: 2.2373 (9); P1–Au1–Br1: 172.73(2). Thermal ellipsoids are drawn at the 50% probability plot. Hydrogen atoms and DCM solvent are omitted for clarity.

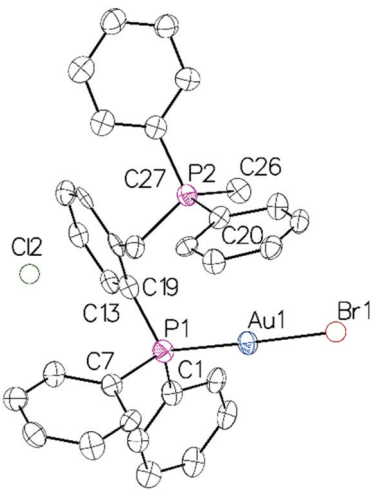


Fig. 3 ORTEP view of complex **If** Au1–Br1: 2.371(5); Au1–P1: 2.250(5); P1–Au1–Br1: 178.3(3). Thermal ellipsoids are drawn at the 30% probability plot. Hydrogen atoms and DCM solvent are omitted for clarity. The complex was obtained with a mixture of Br/Cl, and the minor disordered part was omitted for clarity. See the ESI† for more details.

Anti-proliferative properties

The anti-proliferative properties of the different gold(I) complexes **Ia-f** were evaluated on three human cancer cell lines: A549 (lung carcinoma), MDA-MB-231 (breast adenocarcinoma), and SW480 (colorectal adenocarcinoma) (Table 3). Their IC_{50} values were compared to those of three clinically used drugs:

Table 3 Antiproliferative activity of our complexes **Ia-g**, **oxaliplatin**, **5-FU**, and **paclitaxel** on three cancer cell lines (A549, MDA-MB-231, and SW480)

	IC_{50} (μM)		
Compound	A549	MDA-MB-231	SW480
Ia	0.89 ± 0.03	1.81 ± 1.20	4.1 ± 1.30
Ib	0.34 ± 0.02	0.47 ± 0.02	0.44 ± 0.04
Ic	3.17 ± 0.50	4.04 ± 0.55	9.36 ± 1.75
Id	0.86 ± 0.13	3.18 ± 1.07	4.2 ± 0.30
Ie	0.68 ± 0.20	1.72 ± 0.20	5.08 ± 0.90
If	2.44 ± 0.73	4.28 ± 0.34	4.46 ± 0.20
Ig	38.1 ± 7.79	3.5 ± 1.26	14.2 ± 2.20
Oxaliplatin	7.5 ± 0.40	14.4 ± 1.90	9.2 ± 1.40
5-FU	9.1 ± 0.90	22.3 ± 0.60	52.5 ± 8.40
Paclitaxel	0.33 ± 0.04	0.39 ± 0.02	2.0 ± 0.74

oxaliplatin used for the treatment of colorectal cancer, 5-fluorouracil (**5-FU**) used for colorectal, breast, and ovarian cancers, and **paclitaxel** used for lung, breast, and ovarian cancers, and to a common Au(I)-phosphine complex [$Au(PPh_3)Br$] **Ig**. All the tested complexes displayed strong anti-proliferative properties on the three cell lines. Their activities are in the range of **paclitaxel** but significantly better than **oxaliplatin** (up to 30 times more efficient) and **5-FU** (up to 120 times more efficient) (Fig. 4). It is worth noting that **Ig** displays an efficacy 10 to 100 times lower than the best complexes, which highlights the positive impact of the presence of the phosphonium moiety on anti-proliferative activity. This can be explained by the fact that introducing a phosphonium greatly improves the water solubility of the complexes compared to the gold complexes not containing phosphonium (by about a factor of 100 compared to [$Au(PPh_3)Br$], see the ESI† for details).

Their anti-proliferative properties were always better onto A549 than onto the other cell lines and most of the time lower onto SW480, except for complex **Ib**, which displays submicromolar IC_{50} for all the tested cancer cell lines. The results highlight a significant impact of the substituents of the phosphonium on anti-proliferative properties of the compounds. They can be qualitatively ranked as follows: $-P^+(p\text{-Tol})_3 \gg -P^+(Ph)_2Fc \approx -P^+(Ph)_3 > -P^+(Bu)_3 > -P^+(Ph)_2Me > -P^+(p\text{-fluorophenyl})_3$. Thus, there is no obvious correlation between anti-proliferative properties of the complexes and either the electron donating character of the substituents or their steric hindrance. It seems that the best results were obtained, when the positive charge of phosphonium can be delocalized on several aromatic substituents and when these aromatic rings are substituted with electron donating groups. The negative impact of *p*-fluorophenyl groups with respect to phenyl substituents on anti-proliferative properties was also observed by Bricklebank and coll.[35]

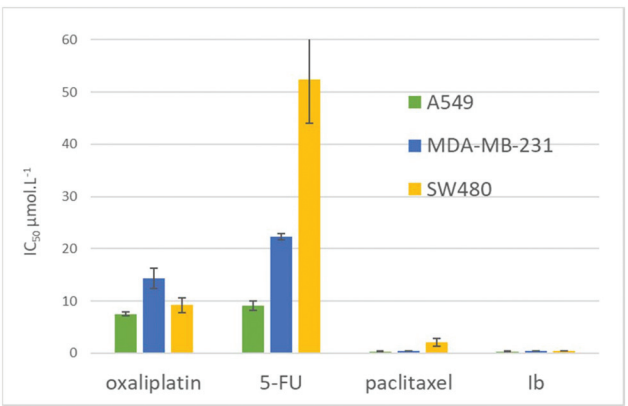


Fig. 4 Comparison of the antiproliferative activity of our most active complex **Ib** on three cancer cell lines with clinically used anticancer agents.

Conclusions

We reported an efficient strategy to synthesize phosphonium-phosphine ligands and their corresponding gold(I) complexes. This strategy enables the facile introduction of different types of phosphoniums. The gold(I) complexes displayed IC_{50} in the low micromolar to the submicromolar range, which is better than that of **5-FU** and **oxaliplatin**, and in the range of **paclitaxel**. These results are promising for future *in vivo* applications; even it would be interesting to synthesize analogues with phosphonium bearing other electron donating substituted aromatic rings to improve again their anti-proliferative properties. Moreover, it will be interesting to evaluate the impact of tethering a vector on biological properties in order to obtain selective therapeutic agents (*i.e.* it could be introduced *via* substitution of the gold bromido ligand[36]).

Experimental

Materials and methods

All synthetic manipulations were carried out using standard Schlenk techniques. All reagents were purchased either from Acros Organics, Sigma-Aldrich, Fischer Scientific, Alfa Aesar, TCI or ABCR and used without further purification. THF and dichloromethane were dried over alumina cartridges using a solvent purification system MB-SPS-800 model from M. BRAUN. Column chromatography was conducted on silica gel 60–200 μm or 40–63 μm purchased from Sigma-Aldrich. NMR spectra (^1H, ^{13}C, ^{13}C–J_{mod}, ^{19}F, ^{31}P) were recorded with Bruker 300 MHz, 500 MHz or 600 MHz apparatus, using tetramethylsilane as the internal reference for ^1H, ^{13}C NMR, and phosphoric acid (85%) as the external reference for ^{31}P NMR. Abbreviations used to describe the multiplicity of the signal are: s (singlet), d (doublet), t (triplet), q (quartet), bs (broad signal), and m (multiplet). Mass spectra were recorded under electrospray ionization conditions (ESI) with a Thermo LTQ Orbitrap XP.

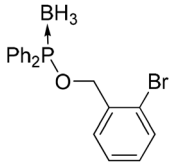
Single crystal X-ray diffraction

All experimental data procedures and refinement are detailed in the ESI.† Data CCDC 2036897 and 2036898† for compounds

Ie and **If** contain the supplementary crystallographic data for this paper.

Synthesis of the ligand precursor 4

(2-Bromobenzyl)diphenylphosphinite borane (2).

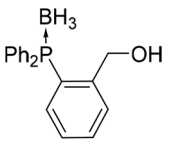


Chemical Formula: $C_{19}H_{19}BBrOP$
Molecular Weight: 385.05 g/mol

To a solution of 2-bromobenzyl alcohol (1.6 g, 8.5 mmol) in anhydrous THF (50 mL) was added ethyldiisopropylamine (5.0 mL, 28.7 mmol). The mixture was cooled at 0 °C, and then chlorodiphenylphosphine (1.8 mL, 10.0 mmol) was added. After 30 min of stirring at 0 °C, the precipitate was removed by filtration using millipore and the solvent was evaporated. The resulting white solid was dissolved in anhydrous THF (50 mL), and then BH_3·DMS (2 mL, 21.0 mmol) was added at RT. After 2 h of stirring, the resulting mixture was hydrolyzed by adding distilled water (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL). The organic phase was dried over $MgSO_4$. After removal of the solvent, the residue was purified by recrystallization in methanol.

Yield = 83%, m = 2.72 g, n = 7.1 mmol; white crystals. ^{1}H NMR (300 MHz, chloroform-d) δ 7.81–7.72 (m, 4H, H_{aro}), 7.58–7.41 (m, 8H, H_{aro}), 7.30 (td, J = 7.5, 1.3 Hz, 1H, H_{aro}), 7.17 (td, J = 7.7, 1.8 Hz, 1H, H_{aro}), 5.09 (d, J = 6.7 Hz, 2H, CH_2), 1.50–0.15 (m, 3H, BH_3); ^{13}C{^{1}H} NMR (75 MHz, chloroform-d) δ 136.22 (d, J = 8.3 Hz, C_{aro}), 132.50 (d, J = 53.5 Hz, C_{aro}), 132.26 (C_{aro}), 132.11 (C_{aro}), 131.49 (d, J = 11.4 Hz, C_{aro}), 129.84 (d, J = 1.5 Hz, C_{aro}), 128.81 (d, J = 10.6 Hz, C_{aro}), 127.65 (C_{aro}), 123.06 (C_{aro}), 68.43 (CH_2); one carbon signal is not seen. ^{31}P{^{1}H} NMR (202 MHz, methylene chloride-d_2) δ 107.20 (br.s).

[(2-Hydroxymethyl)phenyl]diphenylphosphine borane (3).

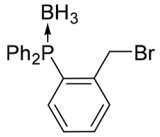


Chemical Formula: $C_{19}H_{20}BOP$
Molecular Weight: 306.15 g/mol

To a solution of phosphinite **2** (2.37 g, 6.2 mmol) in THF (10 mL) was added dropwise t-BuLi (9.1 mL, 15.4 mmol, 1.7 M) at −78 °C under argon. After 2 h 30 of stirring, the temperature was allowed to reach 0 °C, and the resulting mixture was hydrolyzed by adding distilled water (5 mL). The aqueous phase was extracted with DCM (3 × 10 mL), and then the organic phase was dried over $MgSO_4$. After removal of the solvent, the residue was purified over silica gel using EA/PE 1 : 1 as the eluent.

Yield = 77%, m = 1.46 g, n = 4.8 mmol; white solid. ^{1}H NMR (500 MHz, methylene chloride-d_2) δ 7.64 (ddd, J = 7.7, 4.2, 1.4 Hz, 1H, H_{aro}), 7.59–7.53 (m, 7H, H_{aro}), 7.50–7.44 (m, 4H, H_{aro}), 7.28–7.23 (m, 1H, H_{aro}), 6.96 (ddd, J = 11.7, 7.8, 1.3 Hz, 1H, H_{aro}), 4.54 (d, J = 5.7 Hz, 2H, CH_2), 2.32–2.24 (m, 1H, OH), 1.71–0.98 (m, 3H, BH_3); ^{13}C{^{1}H} NMR (75 MHz, chloroform-d) δ 145.38 (d, J = 11.5 Hz, C_{aro}), 134.22 (d, J = 6.2 Hz, C_{aro}), 133.33 (d, J = 9.0 Hz, C_{aro}), 132.11 (d, J = 2.4 Hz, C_{aro}), 131.66 (d, J = 2.4 Hz, C_{aro}), 131.22 (d, J = 8.8 Hz, C_{aro}), 129.14 (d, J = 10.3 Hz, C_{aro}), 129.08 (d, J = 58.5 Hz, C_{aro}), 127.89 (d, J = 8.8 Hz, C_{aro}), 127.33 (d, J = 53.9 Hz, C_{aro}), 63.29 (d, J = 6.1 Hz, CH_2); ^{31}P {^{1}H} NMR (202 MHz, methylene chloride-d_2) δ 18.30 (br.s).

[(2-Bromomethyl)phenyl]diphenylphosphine borane (4).



Chemical Formula: $C_{19}H_{19}BBrP$
Molecular Weight: 369.05 g/mol

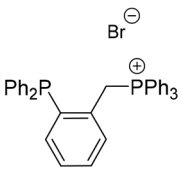
To a solution of [(2-hydroxymethyl)phenyl]diphenylphosphine borane **3** (1.44 g, 4.7 mmol) in DCM (5 mL), CBr_4 (2.85 g, 8.6 mmol) and PPh_3 (2.47 g, 9.4 mmol) were successively added under argon. After two hours of stirring at RT, the solvent was removed and the residue was purified on silica gel using DCM/PE 1 : 1 as the eluent.

Yield = 83%, m = 1.44 g, n = 3.9 mmol; white solid. ^{1}H NMR (500 MHz, methylene chloride-d_2) δ 7.67 (ddd, J = 7.8, 4.2, 1.2 Hz, 1H, H_{aro}), 7.63–7.44 (m, 11H, H_{aro}), 7.28–7.22 (m, 1H, H_{aro}), 7.00 (ddd, J = 11.6, 7.9, 1.3 Hz, 1H, H_{aro}), 4.63 (s, 2H, H_{aro}), 1.78–0.85 (m, 3H, BH_3); ^{13}C{^{1}H} NMR (75 MHz, chloroform-d) δ 138.71 (d, J = 10.4 Hz, C_{aro}), 133.45 (d, J = 10.6 Hz, C_{aro}), 133.28 (d, J = 9.7 Hz, C_{aro}), 133.19 (d, J = 8.9 Hz, C_{aro}), 132.13 (d, J = 2.5 Hz, C_{aro}), 131.54 (d, J = 2.5 Hz, C_{aro}), 130.26 (d, J = 57.0 Hz, C_{aro}), 129.38 (d, J = 10.2 Hz, C_{aro}), 128.98 (d, J = 10.3 Hz, C_{aro}), 128.84 (d, J = 58.0 Hz, C_{aro}), 32.58 (CH_2); ^{31}P{^{1}H} NMR (202 MHz, methylene chloride-d_2) δ 19.90 (br.s); IR (cm^{-1}): 3059, 2389, 2354, 1478, 1434, 1214, 1102, 1058, 1027, 998, 761, 751, 691, 622, 604, 562, 511, 493, 483, 457, 427; HR-MS (ESI): m/z calcd for $C_{19}H_{19}BBrPNa$ $[M + Na]^+$: 391.03930 Da; found: 391.04037 Da.

General synthesis of the phosphonium-phosphine ligands 5a–f

All the phosphonium phosphines are prepared using the following procedure: To a solution of [(2-bromomethyl)phenyl] diphenyl phosphine borane **4** (0.5 mmol) in DCM (2 mL) was added the tertiary phosphine (1.25 mmol, 2.5 equivalents). The reaction mixture was stirred until completion (24–48 h). After removing most of the solvent, Et_2O (5 mL) was added and a precipitate appeared which was filtered and purified on silica gel using MeOH/DCM 1 : 10 as the eluent.

[(2-Diphenylphosphanyl)phenyl]methyl-triphenylphosphonium bromide (5a).

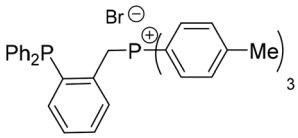


Chemical Formula: $C_{37}H_{31}BrP_2$
Molecular Weight: 617.51 g/mol

Stopped after 36 hours of reaction. Yield = 87%, m = 0.27 g, n = 0.44 mmol; white solid, Mp >250 °C. ^{1}H NMR (500 MHz, methylene chloride-d_2) δ 7.91–7.83 (m, 3H, H_{aro}), 7.71–7.62 (m,

6H, H_{aro}), 7.59–7.50 (m, 6H, H_{aro}), 7.39–7.34 (m, 2H, H_{aro}), 7.34–7.28 (m, 6H, H_{aro}), 7.29–7.21 (m, 1H, H_{aro}), 6.94–6.88 (m, 4H, H_{aro}), 6.87–6.81 (m, 1H, H_{aro}), 5.09 (d, J = 13.9 Hz, 2H, CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, methylene chloride-d_2) δ 138.6 (dd, J = 6.4, 12.8 Hz, C_{aro}), 135.4 (d, J = 3.1 Hz, C_{aro}), 134.8 (d, J = 3.1 Hz, C_{aro}), 134.5 (d, J = 9.7 Hz, C_{aro}), 134.1 (d, J = 8.1 Hz, C_{aro}), 133.7 (d, J = 19.3 Hz, C_{aro}), 132.0 (dd, J = 8.4, 25.2 Hz, C_{aro}), 131.1 (d, J = 4.6 Hz, C_{aro}), 130.3 (d, J = 13.0 Hz, C_{aro}), 130.0 (d, J = 3.1 Hz, C_{aro}), 129.5 (d, J = 3.8 Hz, C_{aro}), 129.4 (C_{aro}), 128.8 (d, J = 6.9 Hz, C_{aro}), 117.4 (d, J = 92.2 Hz, C_{aro}), 29.9 (dd, J = 24.0, 48.0 Hz, CH_2); $^{31}P\{^1H\}$ NMR (202 MHz, methylene chloride-d_2) δ 22.97 (s), −15.12 (s); IR (cm^{-1}): 3052, 3006, 2818, 2758, 1476, 1433, 1343, 1184, 1107, 1027, 994, 823, 787, 748, 722, 690; HR-MS (ESI): m/z calcd for $C_{37}H_{31}P_2$ $[M - Br]^+$: 537.1896 Da; found: 537.1904 Da.

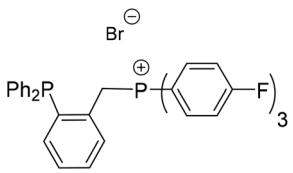
[(2-Diphenylphosphanyl)phenyl]methyl-tri(*p*-tolyl)phosphonium bromide (5b).



Chemical Formula: $C_{40}H_{37}BrP_2$
Molecular Weight: 659.59 g/mol

Stopped after 24 hours of reaction. Yield = 91%, m = 0.30 g, n = 0.45 mmol; white solid. ^1H NMR (500 MHz, methylene chloride-d_2) δ 7.47–7.41 (m, 6H, H_{aro}), 7.38–7.19 (m, 14H, H_{aro}), 7.20–7.15 (m, 1H, H_{aro}), 6.92–6.85 (m, 5H, H_{aro}), 4.88 (dd, J = 13.8, 1.0 Hz, 2H, CH_2), 2.52 (s, 9H, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, methylene chloride-d_2) δ 147.30 (d, J = 3.2 Hz, C_{aro}), 139.03–138.65 (m, C_{aro}), 135.19 (d, J = 3.1 Hz, C_{aro}), 134.73 (C_{aro}), 134.63 (d, J = 10.3 Hz, C_{aro}), 134.63 (m, C_{aro}), 134.14 (C_{aro}), 133.98 (C_{aro}), 132.79 (dd, J = 8.2, 25.8 Hz, C_{aro}), 131.38 (C_{aro}), 131.33 (C_{aro}), 131.28 (C_{aro}), 130.41 (d, J = 3.5 Hz, C_{aro}), 129.83 (d, J = 3.7 Hz, C_{aro}), 129.74 (C_{aro}), 129.17 (d, J = 7.2 Hz, C_{aro}), 114.52 (d, J = 88.8 Hz, C_{aro}), 30.59 (dd, J = 49.3, 24.7 Hz, CH_2), 22.01 (CH_3); $^{31}P\{^1H\}$ NMR (202 MHz, methylene chloride-d_2) δ 22.08 (s), −15.62 (s); IR (cm^{-1}): 3403, 2867, 1594, 1433, 1399, 11 312, 1190, 1158, 1107, 802, 773, 746, 721, 697, 656, 524, 498, 473, 448, 436; HR-MS (ESI): m/z calcd for $C_{40}H_{37}P_2$ $[M - Br]^+$: 579.23650 Da; found: 579.23605 Da.

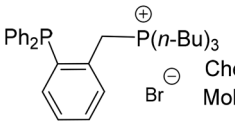
[(2-Diphenylphosphanyl)phenyl]methyltri(*p*-fluorophenyl) phosphonium bromide (5c).



Chemical Formula: $C_{37}H_{28}BrF_3P_2$
Molecular Weight: 671.48 g/mol

Stopped after 48 hours of reaction. Yield = 82%, m = 0.27 g, n = 0.41 mmol; white solid, Mp: 134 °C (dec). ^1H NMR (500 MHz, methylene chloride-d_2) δ 7.71 (ddd, J = 11.8, 8.6, 4.9 Hz, 6H, H_{aro}), 7.57–7.52 (m, 1H, H_{aro}), 7.36–7.23 (m, 14H, H_{aro}), 6.92–6.82 (m, 5H, H_{aro}), 5.63 (d, J = 14.2 Hz, 2H, CH_2); $^{13}C\{^1H\}$ NMR (75 MHz, methylene chloride-d_2) δ 167.0 (dd, J = 260.5, 3.9 Hz, C_{aro}), 138.2 (dd, J = 12.7, 7.2 Hz, C_{aro}), 137.5 (t, J = 10.9 Hz, C_{aro}), 135.0 (d, J = 3.6 Hz, C_{aro}), 134.2 (d, J = 7.2 Hz, C_{aro}), 133.5 (d, J = 19.9 Hz, C_{aro}), 132.1 (dd, J = 27.1, 7.2 Hz, C_{aro}), 131.6 (t, J = 3.6 Hz, C_{aro}), 130.2 (d, J = 3.6 Hz, C_{aro}), 129.5 (d, J = 3.6 Hz, C_{aro}), 129.4 (C_{aro}), 128.8 (d, J = 7.2 Hz, C_{aro}), 118.0 (dd, J = 22.1, 13.6 Hz, C_{aro}), 113.4 (dd, J = 90.1, 3.4 Hz, C_{aro}), 30.0 (dd, J = 68.0, 23.4 Hz, CH_2); $^{31}P\{^1H\}$ NMR (202 MHz, methylene chloride-d_2) δ 20.72 (s), −17.24 (s); IR (cm^{-1}): 3053, 2973, 1589, 1498, 1434, 1399, 1310, 1239, 1164, 1108, 1010, 828, 778, 746, 697; HR-MS (ESI): m/z calcd for $C_{37}H_{28}F_3P_2$ $[M - Br]^+$: 591.1613 Da; found: 591.1617 Da.

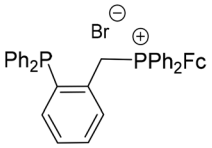
[(2-Diphenylphosphanyl)phenyl]methyltributyl-phosphonium bromide (5d).



Chemical Formula: $C_{31}H_{43}BrP_2$
Molecular Weight: 557.54 g/mol

Stopped after 24 hours of reaction. Yield = 67%, m = 0.19 g, n = 0.33 mmol; yellow viscous solid. ^1H NMR (500 MHz, methylene chloride-d_2) δ 7.80–7.75 (m, 1H, H_{aro}), 7.47–7.34 (m, 7H, H_{aro}), 7.31–7.27 (m, 1H, H_{aro}), 7.26–7.21 (m, 4H, H_{aro}), 7.02–6.96 (m, 1H, H_{aro}), 4.30 (d, J = 15.4 Hz, 2H, CH_2), 2.55–2.43 (m, 6H, PCH_2), 1.50–1.36 (m, 12H, CH_2CH_2), 0.93 (t, J = 6.8 Hz, 9H, CH_3); $^{13}C\{^1H\}$ NMR (75 MHz, methylene chloride-d_2) δ 136.8 (dd, J = 13.3, 5.8 Hz, C_{aro}), 134.8 (d, J = 2.5 Hz, C_{aro}), 134.7 (d, J = 7.5 Hz, C_{aro}), 133.7 (d, J = 20.2 Hz, C_{aro}), 133.7 (d, J = 35.8 Hz, C_{aro}), 131.9 (d, J = 4.2 Hz, C_{aro}), 130.1 (d, J = 3.1 Hz, C_{aro}), 129.5 (C_{aro}), 129.0 (d, J = 7.7 Hz, C_{aro}), 128.8 (d, J = 3.5 Hz, C_{aro}), 25.2 (dd, J = 45.0, 21.4 Hz; CH_2), 24.0 (d, J = 14.6 Hz, CH_2), 23.5 (d, J = 4.5 Hz, CH_2), 19.3 (dd, J = 3.5, 45.5 Hz, CH_2), 13.2 (CH_3); $^{31}P\{^1H\}$ NMR (202 MHz, methylene chloride-d_2) δ 32.60 (s), −14.57 (s); IR (cm^{-1}) 2959, 2931, 2871, 1621, 1586, 1464, 1434, 1403, 1381, 1344, 1234, 1186, 1093, 1000, 968, 909, 746, 697; HR-MS (ESI): m/z calcd for $C_{31}H_{43}P_2$ $[M - Br]^+$: 477.2835 Da; found: 477.2812 Da.

[(2-Diphenylphosphanyl)phenyl]methyldiphenylferrocenyl phosphonium bromide (5e).

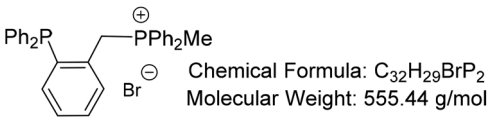


Chemical Formula: $C_{41}H_{35}BrFeP_2$
Molecular Weight: 725.43 g/mol

Stopped after 48 hours of reaction. Yield = 90%, m = 0.33 g, n = 0.45 mmol; orange solid, Mp: 130 °C (dec). ^1H NMR (500 MHz, methylene chloride-d_2) δ 7.85–7.82 (m, 2H, H_{aro}), 7.68–7.62 (m, 8H, H_{aro}), 7.49–7.24 (m, 9H, H_{aro}), 7.02 (t, J = 7.5 Hz, 4H, H_{aro}), 6.78–6.76 (m, 1H, H_{aro}), 5.07 (d, J = 13.8 Hz, 2H, CH_2), 4.92 (s, 2H, Cp), 4.55 (s, 2H, Cp), 4.39 (s, 5H, Cp); $^{13}C\{^1H\}$ NMR (75 MHz, methylene chloride-d_2) δ 137.8 (dd, J = 12.7, 6.1 Hz, C_{aro}), 134.8 (d, J = 2.8 Hz, C_{aro}), 134.3 (C_{aro}), 134.2 (C_{aro}), 134.1 (d, J = 9.9 Hz, C_{aro}), 133.7 (d, J = 19.9 Hz, C_{aro}), 132.7 (dd, J = 24.8, 7.8 Hz, C_{aro}), 131.5 (t, J = 4.4 Hz, C_{aro}), 129.8 (d, J = 3.5 Hz, C_{aro}), 129.7 (d, J = 12.6 Hz, C_{aro}), 129.4 (C_{aro}), 129.1 (d, J = 3.8 Hz, C_{aro}), 128.9 (d, J = 7.2 Hz, C_{aro}), 119.3 (d, J = 87.7 Hz, C_{aro}), 74.8 (Cp), 74.7 (Cp), 73.2 (d, J = 3.1 Hz, Cp), 73.1 (d, J = 3.5 Hz, Cp), 70.9 (Cp), 60.8 (d, J = 100.9 Hz, Cp), 29.7 (dd, J =

51.3, 22.3 Hz, CH_2); $^{31}P\{^1H\}$ NMR (202 MHz, methylene chloride-d_2) δ 26.29 (s), −14.13 (s); IR (cm^{-1}): 3052, 2853, 1587, 1478, 1434, 1413, 1392, 1181, 1107, 1029, 998, 829, 781, 745, 726, 691; HR-MS (ESI): m/z calcd for $C_{41}H_{35}FeP_2$ $[M - Br]^+$: 645.1557 Da; found: 645.1552 Da.

[(2-Diphenylphosphanyl)phenyl]methyldiphenylmethyl phosphonium bromide (5f).

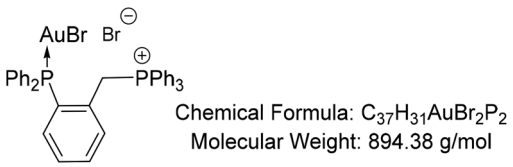


Stopped after 24 hours of reaction. Yield = 80%, m = 0.22 g, n = 0.4 mmol; white solid, Mp: 122 °C (dec). ^1H NMR (500 MHz, methylene chloride-d_2) δ 7.86–7.78 (m, 6H, H_{aro}), 7.68–7.62 (m, 5H, H_{aro}), 7.41–7.30 (m, 8H, H_{aro}), 7.05–6.92 (m, 5H, H_{aro}), 5.10 (dd, J = 15.7, 1.2 Hz, 2H, CH_2), 2.83 (d, J = 13.4 Hz, 3H, CH_3); $^{13}C\{^1H\}$ NMR (126 MHz, methylene chloride-d_2) δ 137.6 (dd, J = 13.8, 6.9 Hz, C_{aro}), 135.0 (d, J = 2.6 Hz, C_{aro}), 134.8 (C_{aro}), 134.8 (d, J = 2.5 Hz, C_{aro}), 133.6 (d, J = 20.2 Hz, C_{aro}), 133.1 (d, J = 10.4 Hz, C_{aro}), 132.6 (dd, J = 26.7, 8.5 Hz, C_{aro}), 131.6 (t, J = 4.6 Hz, C_{aro}), 130.0 (d, J = 3.7 Hz, C_{aro}), 129.9 (d, J = 12.5 Hz, C_{aro}), 129.2 (C_{aro}), 129.0 (d, J = 3.6 Hz, C_{aro}), 128.8 (d, J = 7.3 Hz, C_{aro}), 118.9 (d, J = 84.3 Hz, C_{aro}), 28.7 (dd, J = 47.8, 23.4 Hz, CH_2), 8.3 (dd, J = 56.1, 3.4 Hz, CH_3). One carbon signal is not seen. $^{31}P\{^1H\}$ NMR (202 MHz, methylene chloride-d_2) δ 21.75 (s), −15.53 (s); IR (cm^{-1}): 3053, 2882, 1618, 1588, 1476, 1434, 1186, 1161, 1116, 1027, 997, 900, 841, 743, 689; HR-MS (ESI): m/z calcd for $C_{32}H_{29}P_2$ $[M - Br]^+$: 475.1739 Da; found: 475.1733 Da.

General synthesis of the phosphonium phosphine gold complexes Ia-f

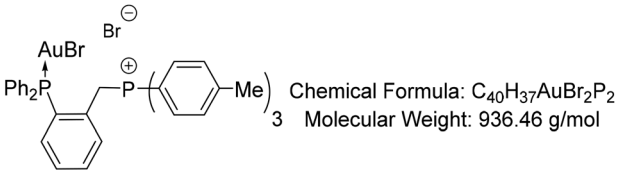
To a solution of phosphonium phosphine **5a-f** (0.1 mmol) in DCM (4 mL), bromo(tetrahydrothiophene)Au(I) (0.1 mmol) was added under argon at RT. The reaction mixture was stirred until completion, as determined by ^{31}P NMR (one hour). Then the resulting mixture was concentrated and the product was precipitated using pentane and washed twice with a mixture of pentane/DCM 10 : 1.

{[(2-Diphenylphosphanyl)phenyl]methyltriphenylphosphonium bromide} AuBr (Ia).



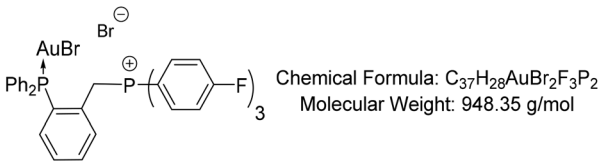
Yield = 80%, m = 0.07 g, n = 0.08 mmol; white solid, Mp: 150 °C (dec). ^1H NMR (500 MHz, methylene chloride-d_2) δ 7.90–7.86 (m, 3H, H_{aro}), 7.70–7.64 (m, 6H, H_{aro}), 7.63–7.55 (m, 8H, H_{aro}), 7.50 (bs, 4H, H_{aro}), 7.41 (s, 3H, H_{aro}), 7.33 (bs, 3H, H_{aro}), 7.28–7.23 (m, 1H, H_{aro}), 6.93–6.86 (m, 1H, H_{aro}), 5.55–5.43 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (151 MHz, methylene chloride-d_2) δ 135.94 (d, J = 3.0 Hz, C_{aro}), 135.73 (d, J = 6.7 Hz, C_{aro}), 135.20 (C_{aro}), 135.13 (C_{aro}), 134.78 (d, J = 14.5 Hz, C_{aro}), 132.89 (m, C_{aro}), 132.10 (d, J = 9.9 Hz, C_{aro}), 130.95 (C_{aro}), 130.87 (C_{aro}), 130.54 (d, J = 12.6 Hz, C_{aro}), 130.17 (d, J = 11.7 Hz, C_{aro}), 130.06–129.98 (m), 129.12 (d, J = 12.3 Hz, C_{aro}), 117.50 (d, J = 86.3 Hz, C_{aro}), 29.79 (dd, J = 48.9, 13.5 Hz, CH_2). $^{31}P\{^1H\}$ NMR (202 MHz, methylene chloride-d_2) δ 25.98 (s), 22.66 (bs); IR (cm^{-1}): 3341, 3051, 1585, 1478, 1434, 1161, 1098, 995, 822, 780, 744, 687, 546, 494; m/z calcd for $C_{37}H_{31}AuBrP_2$ $[M - Br]^+$: 813.0744 Da; found: 813.0739 Da. Elemental analysis calculated for $C_{37}H_{31}AuBr_2P_2$: C% 49.69, H% 3.49; obtained: C% 49.82, H% 3.51.

{[(2-Diphenylphosphanyl)phenyl]methyltri(*p*-tolyl)phosphonium bromide} AuBr (Ib).



Yield = 94%, m = 0.088 g, n = 0.094 mmol; white solid, Mp >250 °C. ^1H NMR (500 MHz, methylene chloride-d_2) δ 7.57 (bs, 3H, H_{aro}), 7.54–7.28 (m, 21H, H_{aro}), 7.22–7.16 (m, 1H, H_{aro}), 6.95–6.87 (m, 1H, H_{aro}), 5.25–5.17 (m, 2H, CH_2), 2.51 (s, 9H, CH_3); $^{13}C\{^1H\}$ NMR (151 MHz, methylene chloride-d_2) δ 147.51 (d, J = 2.9 Hz, C_{aro}), 135.70 (d, J = 6.5 Hz, C_{aro}), 134.86 (d, J = 10.5 Hz, C_{aro}), 134.76 (d, J = 14.4 Hz, C_{aro}), 132.95 (dd, J = 11.1, 6.8 Hz, C_{aro}), 132.82–132.53 (m, C_{aro}), 131.63 (C_{aro}), 131.54 (C_{aro}), 130.11 (d, J = 11.7 Hz, C_{aro}), 129.95 (d, J = 3.2 Hz, C_{aro}), 129.90 (d, J = 3.2 Hz, C_{aro}), 114.25 (d, J = 89.0 Hz, C_{aro}), 30.22 (dd, J = 50.5, 13.6 Hz, CH_2), 22.10 (CH_3); $^{31}P\{^1H\}$ NMR (202 MHz, methylene chloride-d_2) δ 26.07 (s), 21.76 (s); IR (cm^{-1}): 3353, 2917, 1596, 1498, 1476, 1434, 1399, 1190, 1099, 801, 749, 692, 652, 541, 499; m/z calcd for $C_{40}H_{37}AuBrP_2$ $[M - Br]^+$: 855.1214 Da; found: 855.1208 Da. Elemental analysis calculated for $C_{40}H_{37}AuBr_2P_2$: C% 51.30, H% 3.98; obtained: C% 51.04, H% 4.36.

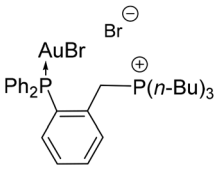
{[(2-Diphenylphosphanyl)phenyl]methyltri(*p*-fluorophenyl) phosphonium bromide}AuBr (Ic).



Yield = 64%, m = 0.061 g, n = 0.064 mmol; white solid, Mp: 140 °C. ^1H NMR (600 MHz, methylene chloride-d_2) δ 7.69–7.59 (m, 8H, H_{aro}), 7.58–7.50 (m, 4H, H_{aro}), 7.49 (t, J = 7.6 Hz, 1H, H_{aro}), 7.48–7.32 (m, 11H, H_{aro}), 7.23 (t, J = 6.4 Hz, 1H, H_{aro}), 6.92 (dd, J = 12.4, 7.8 Hz, 1H, H_{aro}), 5.52 (d, J = 14.8 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (151 MHz, methylene chloride-d_2) δ 167.63 (dd, J = 261.2, 3.0 Hz, C_{aro}), 138.15 (d, J = 10.2 Hz, C_{aro}), 138.07 (d, J = 10.2 Hz, C_{aro}), 135.92 (d, J = 7.3 Hz, C_{aro}), 134.86 (d, J = 14.3 Hz, C_{aro}), 133.26 (m, C_{aro}), 133.02 (C_{aro}), 132.06 (d, J = 9.1 Hz, C_{aro}), 130.36 (d, J = 12.2 Hz, C_{aro}), 127.33 (dd, J = 63.3, 3.5 Hz, C_{aro}), 119.07 (d, J = 14.2 Hz, C_{aro}), 118.96 (d, J = 14.3 Hz, C_{aro}), 112.92 (d, J = 90.7 Hz, C_{aro}), 30.29

(dd, J = 50.4, 12.7 Hz, CH_2), one carbon is not seen. $^{31}P\{^1H\}$ NMR (243 MHz, methylene chloride-d_2) δ 26.07 (s), 21.71 (s); IR (cm^{-1}): 3054, 1588, 1497, 1435, 1398, 1308, 1241, 1162, 1099, 1009, 828, 773, 747, 691, 661, 542, 515, 482, 443; m/z calcd for $C_{37}H_{28}AuBrF_3P_2$ $[M - Br]^+$: 867.0462 Da; found: 867.0464 Da. Elemental analysis calculated for $C_{37}H_{28}AuBr_2F_3P_2$: C% 46.86; H% 2.98; obtained: C% 47.09, H% 3.23.

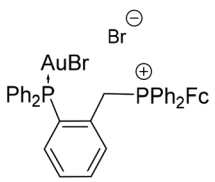
{[(2-Diphenylphosphany)lphenyl]methyltributyl-phosphonium bromide}AuBr (Id).



Chemical Formula: $C_{31}H_{43}AuBr_2P_2$
Molecular Weight: 834.41 g/mol

Yield = 80%, m = 0.067 g, n = 0.08 mmol, white solid, Mp: 152 °C. ^1H NMR (500 MHz, methylene chloride-d_2) δ 7.90 (t, J = 6.6 Hz, 1H, H_{aro}), 7.70 (t, J = 7.6 Hz, 1H, H_{aro}), 7.67–7.61 (m, 2H, H_{aro}), 7.60–7.48 (m, 8H, H_{aro}), 7.40 (t, J = 7.7 Hz, 1H, H_{aro}), 6.95 (ddd, J = 12.5, 7.8, 1.1 Hz, 1H, H_{aro}), 4.58 (d, J = 15.5 Hz, 2H, CH_2), 2.62–2.51 (m, 6H), 1.52–1.27 (m, 12H), 0.93 (t, J = 6.9 Hz, 9H); $^{13}C\{^1H\}$ NMR (151 MHz, methylene chloride-d_2) δ 135.60 (d, J = 7.6 Hz, C_{aro}), 134.85 (d, J = 14.0 Hz, C_{aro}), 133.97–133.65 (m, C_{aro}), 133.42 (t, J = 3.5 Hz, C_{aro}), 133.30 (d, J = 2.6 Hz, C_{aro}), 132.14 (d, J = 10.0 Hz, C_{aro}), 130.32 (d, J = 12.2 Hz, C_{aro}), 129.36 (dd, J = 9.5, 2.8 Hz, C_{aro}), 127.94 (dd, J = 57.9, 6.6 Hz, C_{aro}), 127.63 (d, J = 63.1 Hz, C_{aro}), 26.33 (dd, J = 45.5, 12.1 Hz, CH_2), 24.37 (CH_2), 24.30 (d, J = 11.7 Hz, CH_2), 20.49 (d, J = 45.5 Hz, CH_2), 13.66 (CH_3). $^{31}P\{^1H\}$ NMR (202 MHz, methylene chloride-d_2) δ 33.43 (s), 26.91 (s); IR (cm^{-1}): 2866, 1463, 1434, 1309, 1193, 1119, 911, 746, 691, 541, 500, 474; m/z calcd for $C_{31}H_{43}AuBrP_2$ $[M - Br]^+$: 753.16834 Da; found: 753.16567 Da. Elemental analysis calculated for $C_{31}H_{43}AuBr_2P_2$: C% 44.62, H% 5.19; obtained: C% 44.98, H% 5.35.

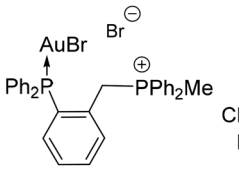
{[(2-Diphenylphosphanyl)phenyl]methyldiphenylferrocenyl phosphonium bromide}AuBr (Ie).



Chemical Formula: $C_{41}H_{35}AuBr_2FeP_2$
Molecular Weight: 1002.30 g/mol

The product was recrystallized by vapor diffusion of cyclohexane in DCM. Yield = 78%, m = 0.078 g, n = 0.078 mmol; orange solid, Mp: 190 °C. ^1H NMR (600 MHz, methylene chloride-d_2) δ 7.81 (bs, 2H, H_{aro}), 7.75–7.67 (m, 4H, H_{aro}), 7.66–7.50 (m, 15H, H_{aro}), 7.49 (bs, 1H, H_{aro}), 7.34 (bs, 1H, H_{aro}), 6.77 (dd, J = 12.9, 7.0 Hz, 1H, H_{aro}), 5.19 (d, J = 15.3 Hz, 2H, CH_2), 4.82 (s, 2H, Cp), 4.44 (s, 2H, Cp), 4.27 (s, 5H, Cp); $^{13}C\{^1H\}$ NMR (151 MHz, methylene chloride-d_2) δ 135.47 (d, J = 3.0 Hz, C_{aro}), 135.23 (d, J = 6.4 Hz, C_{aro}), 135.18 (d, J = 14.2 Hz, C_{aro}), 134.81 (d, J = 10.2 Hz, C_{aro}), 133.25 (d, J = 6.7 Hz, C_{aro}), 133.17 (d, J = 2.6 Hz, C_{aro}), 132.72 (C_{aro}), 130.60 (d, J = 12.7 Hz, C_{aro}), 130.47 (d, J = 12.2 Hz, C_{aro}), 129.59 (dd, J = 9.3, 2.6 Hz, C_{aro}), 128.85 (dd, J = 57.9, 7.7 Hz, C_{aro}), 127.75 (d, J = 63.0 Hz, C_{aro}), 118.86 (d, J = 87.7 Hz, C_{aro}), 75.09 (d, J = 10.7 Hz, Cp), 73.77 (d, J = 13.0 Hz, Cp), 71.39 (Cp), 60.73 (d, J = 102.8 Hz, Cp_{aro}), 31.06 (dd, J = 53.9, 11.8 Hz, CH_2); one quaternary carbon signal is not seen. $^{31}P\{^1H\}$ NMR (243 MHz, methylene chloride-d_2) δ 27.88 (s), 26.43 (s); IR (cm^{-1}): 3388, 3054, 1586, 1478, 1434, 1180, 1106, 1033, 996, 838, 781, 744, 726, 691, 598, 547, 469; m/z calcd for $C_{41}H_{35}AuBrFeP_2$ $[M - Br]^+$: 921.0409 Da; found: 921.0433 Da. Elemental analysis calculated for $C_{41}H_{35}AuBr_2FeP_2$: C% 49.13, H% 3.52; obtained: C% 48.92, H% 3.52.

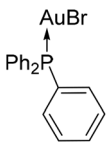
{[(2-Diphenylphosphanyl)phenyl]methyldiphenylmethyl phosphonium bromide}AuBr (If).



Chemical Formula: $C_{32}H_{29}AuBr_2P_2$
Molecular Weight: 832.31 g/mol

The product was recrystallized by vapor diffusion of cyclohexane in DCM. Yield = 87%, m = 0.072 g, n = 0.087 mmol; white solid, Mp: 158 °C. ^1H NMR (500 MHz, methylene chloride-d_2) δ 7.85–7.77 (m, 6H, H_{aro}), 7.68–7.62 (m, 4H, H_{aro}), 7.61–7.56 (m, 2H, H_{aro}), 7.54–7.45 (m, 6H, H_{aro}), 7.39 (ddd, J = 7.6, 6.1, 1.8 Hz, 1H, H_{aro}), 7.33–7.25 (m, 4H, H_{aro}), 6.93 (ddd, J = 12.1, 7.8, 1.3 Hz, 1H, H_{aro}), 5.50 (d, J = 15.6 Hz, 2H, CH_2), 2.90 (d, J = 13.4 Hz, 3H, Me); $^{13}C\{^1H\}$ NMR (151 MHz, methylene chloride-d_2) δ 135.95 (d, J = 6.4 Hz, C_{aro}), 135.47 (d, J = 3.1 Hz, C_{aro}), 134.69 (d, J = 14.1 Hz, C_{aro}), 134.09 (d, J = 10.0 Hz, C_{aro}), 133.44–133.59 (m, C_{aro}), 133.13 (C_{aro}), 132.93–132.91 (m, C_{aro}), 130.60 (d, J = 12.4 Hz, C_{aro}), 130.11 (d, J = 12.1 Hz, C_{aro}), 129.68 (dd, J = 9.1, 3.2 Hz, C_{aro}), 127.83 (d, J = 61.8 Hz, C_{aro}), 118.70 (d, J = 84.5 Hz, C_{aro}), 30.10 (dd, J = 48.7, 12.9 Hz, CH_2), 9.67 (d, J = 55.4 Hz, Me). $^{31}P\{^1H\}$ NMR (202 MHz, methylene chloride-d_2) δ 24.91 (s), 21.80 (s); IR (cm^{-1}): 3380, 2824, 1586, 1435, 1307, 1189, 1099, 996, 902, 744, 689, 540, 499, 473, 452; m/z calcd for $C_{32}H_{29}AuBrP_2$ $[M - Br]^+$: 751.0588 Da; found: 751.0594 Da. Elemental analysis calculated for $C_{32}H_{29}AuBr_2P_2$: C% 46.18, H% 3.51; obtained: C% 46.36, H% 3.88.

TriphenylphosphineAuBr (Ig).



Chemical Formula: $C_{18}H_{15}AuBrP$
Molecular Weight: 539.16 g/mol

To a solution of triphenylphosphine (26 mg, 0.1 mmol) in DCM (2 mL), bromo(tetrahydrothiophene)Au(I) (36.5 mg, 0.1 mmol) was added under argon at RT. The reaction mixture was stirred until completion, as determined by ^{31}P NMR (one hour). Then the resulting mixture was concentrated and the product was precipitated using pentane and washed twice with 5 mL of pentane to give **Ig** as a white powder.

Yield = 69%, m = 0.037 g, n = 0.069 mmol. ^1H NMR (500 MHz, methylene chloride-d_2) δ 7.61–7.52 (m, 3H, H_{aro}),

7.52–7.46 (m, 2H, H_{aro}), $^{31}P\{^{1}H\}$ NMR (202 MHz, methylene chloride-d_2) δ 35.19 (s). Elemental analysis calculated for $C_{18}H_{15}AuBrP$: C% 40.10, H% 2.80; obtained: C% 39.92, H% 2.68.

Biological experimental procedures

Cell lines and culture conditions. Human colon cancer (SW 480), human breast cancer (MDA-MB-231), and human lung cancer (A-549) cell lines were obtained from the American Type Culture Collections (Manassas, VA, United States). They were cultured in RPMI 1640 medium (Biowhittaker, France) supplemented with 10% fetal bovine serum (Biowhittaker, France) at 37 °C under a humidified atmosphere containing 5% CO_2. All cell lines were maintained as exponentially growing monolayers under mycoplasma free culture conditions checked by polymerase chain reaction (PCR) analysis (PCR Mycoplasma Test Kit I/C, PromoKine, PromoCell France).

Drug solutions. The newly synthesized derivatives were diluted into dimethylsulfoxide (DMSO) (Sigma, France). Reference molecules, approved in clinics for colon, breast or lung cancer, were obtained from commercial solutions: **oxaliplatin** (Oxaliplatine Dakota Pharm® 5 mg mL^{-1}), 5-fluorouracil (Fluorouracil Accord® 50 mg mL^{-1}) and **paclitaxel** (Paclitaxel Kabi® 6 mg mL^{-1}). In cell culture, the maximum concentration of DMSO did not exceed 3% in the medium.

Assay of cytotoxicity in cancer cell lines. SW 480, MDA-MB-231 and A-549 were seeded in 96-well plates at a density of 10 000 cells per well. Twenty four hours later, cells were treated for 48 hours with increasing concentrations (from 0 to 500 μM or from 0 to 25 μM according to the drug) of the newly synthesized or reference molecules. After treatment, cytotoxicity was assessed by crystal violet staining: cells were washed in Phosphate Buffered Saline (PBS) 1×, fixed in pure ethanol, stained with 1% crystal violet, and eluted in 33% acetic acid. The intensity of coloration was determined by the measurement of absorbance by spectrophotometry (UVM 340, Bioserv) at λ = 570 nm. Each concentration measurement was conducted in *triplicate* from three independent experiments.

Results were expressed as concentration-response curves, representing the percentage of cytotoxicity according to the concentration of the drug. From these curves, the 50% Inhibitory Concentration (IC50), representing the concentration which inhibits 50% of cell growth, was calculated for each compound.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 R. Zurawinski, B. Donnadieu, M. Mikolajczyk and R. Chauvin, *Organometallics*, 2003, **22**, 4810–4817.
2 P. Leglaye, B. Donnadieu, J.-J. Brunet and R. Chauvin, *Tetrahedron Lett.*, 1998, **39**, 9179–9182.
3 E. Ranaud, R. B. Russell, S. Fortier, S. J. Brown and M. C. Baird, *J. Organomet. Chem.*, 1991, **419**, 403–415.
4 I. J. B. Lin, H. C. Shy, C. W. Liu, L.-K. Liu and S.-K. Yeh, *J. Chem. Soc., Dalton Trans.*, 1990, 2509–2514.
5 R. Usón, J. Forniés, R. Navarro and A. M. Ortega, *J. Organomet. Chem.*, 1987, **334**, 389–397.
6 C.-W. Lee, O. Kim and M.-S. Gong, *J. Appl. Polym. Sci.*, 2003, **89**, 1062–1070.
7 M. P. Murphy, *Biochim. Biophys. Acta, Bioenerg.*, 2008, **1777**, 1028–1031.
8 J. Wang, C.-T. Yang, Y.-S. Kim, S. G. Sreerama, Q. Cao, Z.-B. Li, Z. He, X. Chen and S. Liu, *J. Med. Chem.*, 2007, **50**, 5057–5069.
9 R. A. J. Smith, C. M. Porteous, A. M. Gane and M. P. Murphy, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 5407–5412.
10 S. Kumari, S. Jayakumar, G. D. Gupta, S. C. Bihani, D. Sharma, V. K. Kutala, S. K. Sandur and V. Kumar, *Free Radicals Biol. Med.*, 2019, **143**, 140–145.
11 S. Jayakumar, R. S. Patwardhan, D. Pal, B. Singh, D. Sharma, V. K. Kutala and S. K. Sandur, *Free Radicals Biol. Med.*, 2017, **113**, 530–538.
12 K. Shioji, Y. Oyama, K. Okuma and H. Nakagawa, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3911–3915.
13 S. Samiee, N. Kooti, H. Motamedi, R. W. Gable and F. A. Bagherjeri, *Polyhedron*, 2015, **98**, 120–130.
14 C. Roder and M. J. Thomson, *Drugs*, 2015, **15**, 13–20.
15 T. Zou, C. T. Lum, C.-N. Lok, J.-J. Zhang and C.-M. Che, *Chem. Soc. Rev.*, 2015, **44**, 8786–8801.
16 P. J. Barnard, M. V. Baker, S. J. Berners-Price and D. A. Day, *J. Inorg. Biochem.*, 2004, **98**, 1642–1647.
17 R. Rubbiani, I. Kitanovic, H. Alborzinia, S. Can, A. Kitanovic, L. A. Onambele, M. Stefanopoulou, Y. Geldmacher, W. S. Sheldrick, G. Wolber, A. Prokop, S. Wölfl and I. Ott, *J. Med. Chem.*, 2010, **53**, 8608–8618.
18 R. Rubbiani, S. Can, I. Kitanovic, H. Alborzinia, M. Stefanopoulou, M. Kokoschka, S. Mönchgesang, W. S. Sheldrick, S. Wölfl and I. Ott, *J. Med. Chem.*, 2011, **54**, 8646–8657.

19 J. Ceramella, A. Mariconda, D. Iacopetta, C. Saturnino, A. Barbarossa, A. Caruso, C. Rosano, M. S. Sinicropi and P. Longo, *Bioorg. Med. Chem. Lett.*, 2020, **30**, 126905.
20 C. Yeo, K. Ooi and E. Tiekink, *Molecules*, 2018, **23**, 1410.
21 *Metallo-Drugs: Development and Action of Anticancer Agents*, ed. A. Sigel, H. Sigel, E. Freisinger and R. K. O. Sigel, De Gruyter, Berlin, Boston, 2018.
22 B. Bertrand, M. R. M. Williams and M. Bochmann, *Chem. – Eur. J.*, 2018, **24**, 11840–11851.
23 C. Nardon, N. Pettenuzzo and D. Fregona, *Curr. Med. Chem.*, 2016, **23**, 3374–3403.
24 A. Trommenschlager, F. Chotard, B. Bertrand, S. Amor, P. Richard, A. Bettaïeb, C. Paul, J.-L. Connat, P. Le Gendre and E. Bodio, *ChemMedChem*, 2018, **13**, 2408–2414.
25 A. Trommenschlager, F. Chotard, B. Bertrand, S. Amor, L. Dondaine, M. Picquet, P. Richard, A. Bettaïeb, P. L. Gendre, C. Paul, C. Goze and E. Bodio, *Dalton Trans.*, 2017, **46**, 8051–8056.
26 J. Pliquett, S. Amor, M. Ponce-Vargas, M. Laly, C. Racoeur, Y. Rousselin, F. Denat, A. Bettaeib, P. Fleurat-Lessard, C. Paul, C. Goze and E. Bodio, *Dalton Trans.*, 2018, **47**, 11203–11218.
27 T. Onodera, I. Momose and M. Kawada, *Chem. Pharm. Bull.*, 2019, **67**, 186–191.
28 B. Bertrand and A. Casini, *Dalton Trans.*, 2014, **43**, 4209–4219.
29 L. Ortego, F. Cardoso, S. Martins, M. F. Fillat, A. Laguna, M. Meireles, M. D. Villacampa and M. C. Gimeno, *J. Inorg. Biochem.*, 2014, **130**, 32–37.
30 L. S. Melvin, *Tetrahedron Lett.*, 1981, **22**, 3375–3376.
31 M. B. Tollefson, J. J. Li and P. Beak, *J. Am. Chem. Soc.*, 1996, **118**, 9052–9061.
32 D. Moulin, S. Bago, C. Bauduin, C. Darcel and S. Jugé, *Tetrahedron: Asymmetry*, 2000, **11**, 3939–3956.
33 M. Picquet, S. Stutzmann, I. Tkatchenko, I. Tommasi, J. Zimmermann and P. Wasserscheid, *Green Chem.*, 2003, **5**, 153–162.
34 P. Barron, L. Engelhardt, P. Healy, J. Oddy and A. White, *Aust. J. Chem.*, 1987, **40**, 1545.
35 Y.-S. Chen, D. W. Allen, G. J. Tizzard, M. B. Pitak, S. J. Coles, N. A. Cross and N. Bricklebank, *Eur. J. Med. Chem.*, 2017, **125**, 528–537.
36 P.-E. Doulain, R. Decréau, C. Racoeur, V. Goncalves, L. Dubrez, A. Bettaieb, P. L. Gendre, F. Denat, C. Paul, C. Goze and E. Bodio, *Dalton Trans.*, 2015, **44**, 4874–4883.