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Relativistic Functional Groups: Aryl Carbon–Gold Bond Formation by Selective Transmetalation of Boronic Acids**

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The rational design of triplet-state sensitizers for the photodynamic therapy of cancers[1–3] and other diseases[4] remains an obdurate challenge. A prominent strategy[5–7] is the modification of existing photosensitizers with bromine ($Z=35$) or iodine ($Z=53$); the resulting heavy-atom effects potentiate the generation of therapeutic $^1\Delta_g$ O_2. The (phosphane)gold(I) fragment is σ-isolobal with the proton. Terminal substitution of aromatic organic molecules with gold ($Z=79$) has clear desirability for developing phototherapy mediators. What is missing are mild means of carbon–gold bond formation in the presence of sensitive functional groups. We describe here a selective protocol that installs gold(I)–carbon bonds along the peripheries of organic molecules. Reducible, polar moieties are tolerated, including nitro groups, aldehydes, ketones, and esters. The organometallic compounds described here withstand air and water indefinitely. The ability to modify organic fluorophores with gold raises immediate opportunities in metallopharmaceuticals design.[8–10] Finally, the new protocol affords organogold(I) compounds more rapidly and in higher yield than by traditional methods[11] of arylating gold.

In the palladium-catalyzed Suzuki–Miyaura cross-coupling,[12,13] carbon–carbon bond formation is believed to follow transmetalation from boron to palladium. The reaction often requires an auxiliary base, which is thought to quaternize boron and promote transmetalation.[14] Related precedents include observations by the groups of Schmidbaur[15] and Fackler[16] of phenyl-group transfer from BPh_4^- to gold(I) in aqueous and non-aqueous media.

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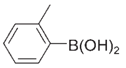
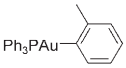
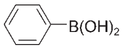
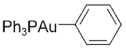
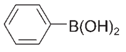
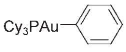
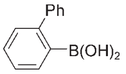
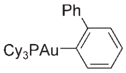
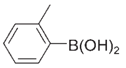
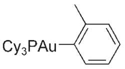
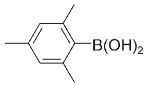
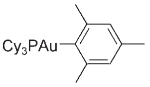
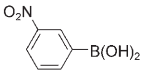
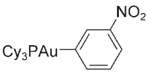
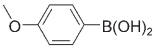
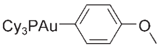
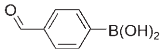
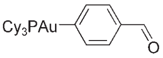
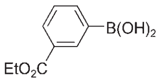
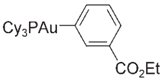
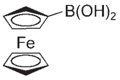
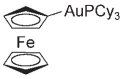
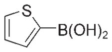
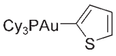
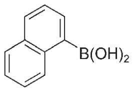
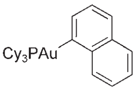
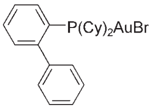
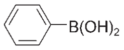
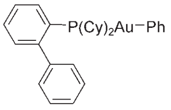
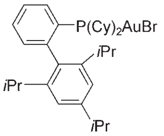
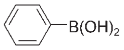
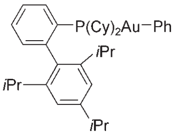
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Transmetalation of (triphenylphosphane)gold(I) bromide with *o*-tolylboronic acid in isopropyl alcohol in the presence of cesium carbonate causes disappearance over 24 h of the ^{31}P NMR resonance at $\delta = 35.2$ ppm, with concomitant growth of a singlet at $\delta = 44.4$ ppm attributable to **1** (Scheme 1). No other products were discernible by ^{31}P NMR spectroscopy. For comparison, an independent synthesis of **1** from Ph_3PAuBr and (*o*-tol)MgBr in toluene achieved less than 50% conversion after 3 days. Similar reactions proceed for a range of arylboronic acids, all in moderate to excellent yields. Gold(I) bromide complexes of triaryl, trialkyl, and mixed alkyl-aryl phosphanes transmetalate effectively. The reaction tolerates steric bulk and accommodates *o*-biphenyl, *o*-tolyl, and mesityl substituents, affording gold aryls in 61% (**4**), 79% (**5**), and 65% (**6**) yields upon isolation (Table 1). Transmetalation also proceeds for substrates bearing electron-withdrawing groups (**7**, **9**, and **10**). The protocol is not limited to substituted phenylboronic acids as witnessed by transmetalation of ferrocenyl and 2-thienyl boronic acids (**11** and **12**). Control experiments found no reaction in the absence of base. The new organogold(I) compounds are stable to air, water, and laboratory lighting over periods of months.

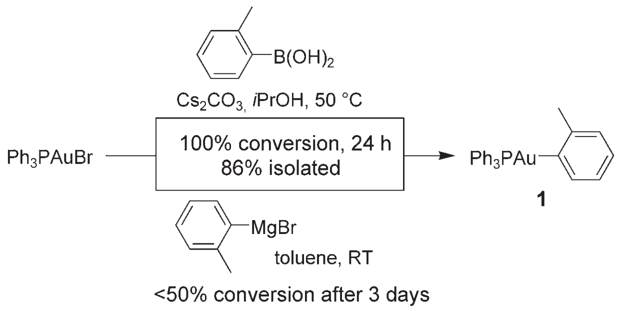
Products were characterized by multinuclear NMR spectroscopy and elemental analysis. Figure 1 depicts crystal structures of representative organogold(I) species.[17,18] In complex **11** an expected two-coordination about gold is found. The P-Au-$C_{\sigma\text{-aryl}}$ angle is 173.74(10)°; the gold–carbon bond length is 2.040(3) Å; and the gold–phosphorus separation is 2.2970(9) Å. No intermolecular contacts between gold atoms are observed.

Complexes of sterically imposing phosphane ligands transmetalate efficiently. Dia-

Table 1: Arylgold(I) products, reaction conditions, and isolated yields.

Gold(I) precursor	Arylboronic acid	Boronic acid [equiv]	*t* [h]	Product		Yield [%][a]
Ph_3PAuBr		1.8	24		**1**	86
Ph_3PAuBr		1.9	24		**2**	59
Cy_3PAuBr		1.9	24		**3**	89
Cy_3PAuBr		1.8	24		**4**	61
Cy_3PAuBr		1.9	24		**5**	79
Cy_3PAuBr		2.6	48		**6**	65
Cy_3PAuBr		2.5	36		**7**	94
Cy_3PAuBr		2.5	30		**8**	85
Cy_3PAuBr		2.0	36		**9**	90
Cy_3PAuBr[b]		2.2	36		**10**	80
Cy_3PAuBr		2.3	48		**11**	85
Cy_3PAuBr		1.8	24		**12**	86
Cy_3PAuBr		1.9	24		**13**	86
		2.0	30		**14**	84
		2.3	30		**15**	74

[a] Isolated material of ≥ 95% purity. [b] Reaction run in ethanol. Cy = cyclohexyl.



Scheme 1. Syntheses of **1** from boronic acid and Grignard reagent precursors.

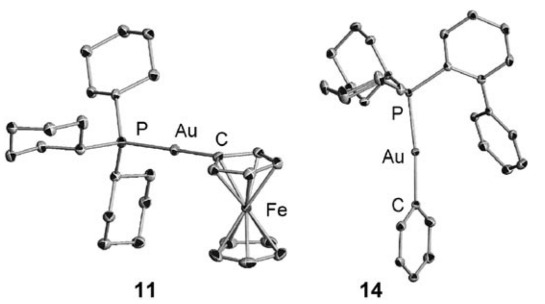


Figure 1. Crystal structures of **11** and **14** (50% probability ellipsoids shown).

lkylbiarylphosphanes[19,20] undergo widespread use in palladium-catalyzed reactions; they are increasingly applied in gold(I) catalysis.[21] Transmetalation of biarylphosphane complexes with phenylboronic acid proceeded smoothly and in high yields; reaction times are comparable to those of other entries in Table 1. The crystal structure of **14** is shown in Figure 1. Close approaches occur between gold and two carbon atoms of the pendant aryl ring (non-phosphorus-bound) of each biarylphosphane: 3.3063(18) Å (Au−C_{ipso}) and 3.2469 (19) Å (Au−C_{ortho}). The P-Au-$C_{\sigma\text{-aryl}}$ bond angle is a modestly nonlinear 174.18(6)°.

The new organogold(I) compounds do not significantly absorb visible light except for ferrocenyl complex **11** (orange) and **13** (pale yellow). Complex **13** is luminescent in THF solution upon excitation with UV light. A conflated absorption and emission spectrum of **13** is shown in Figure 2.

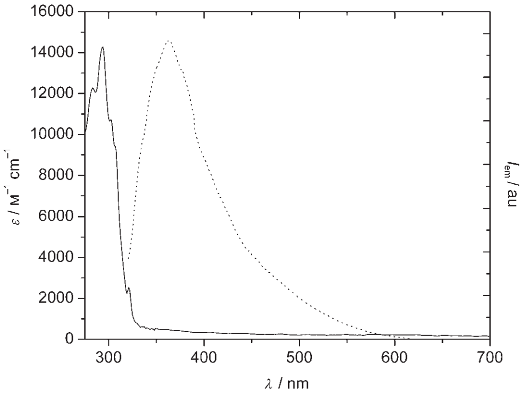


Figure 2. Room-temperature absorption (——) and emission (-----) spectra of **13** in THF (10^{-8} M, $\lambda_{ex}=310$ nm).

Absorption extends from ca. 340 nm to the solvent limit of THF. Vibronic structure is apparent in the absorption at 293 nm, with an average spacing of 1050 cm^{-1} (9.57 nm). Room-temperature emission of **13** extends from ca. 350–600 nm. The absorption cutoff of **13**, but not the emission maximum, is red-shifted relative to that of the parent hydrocarbon.[22] Upon increasing the sample concentration to 10^{-6} M, emission features appear between 480–560 nm that have no counterpart in the fluorescence (Supporting Information). We attribute these emissions to oligomeric gold species. Time-dependent characterization of new arylgold(I) complexes is in progress.

Static and time-dependent density functional theory (DFT) calculations were conducted on Me_3PAu(1-naphthyl), **13′**[23,24] (see the Supporting Information for full details). Implicit THF solvation was included with the polarizable continuum model of Tomasi and co-workers.[25–27] The calculated (observed) Au–C bond length is 2.066 (2.030(4)) Å, the Au–P distance is 2.367 (2.3008(10)) Å, and the P-Au-C angle is 178.9 (176.52(12))°. A Kohn–Sham orbital energy diagram of **13′** appears in the Supporting Information (Figure S2). Images of selected orbitals are inset. The energy gap between the highest occupied and lowest unoccupied Kohn–Sham orbitals (HOMO and LUMO, respectively) is calculated to be 3.290 eV, and the LUMO←HOMO transition is optically allowed. Both orbitals have predominant naphthyl character. A fragment orbital calculation finds the LUMO of **13′** to be 87.5 % derived from the LUMO of the naphthyl monoanion, and the HOMO is 93.2 % composed of naphthyl anion HOMO−1. The HOMO−1 of **13′** is the primary C–Au σ-bonding combination. This orbital carries a 42.4 % contribution from the a_1 LUMO of Me_3PAu^+, which is an sd hybrid orbital of σ symmetry.[28] The lower energy of the gold-heavy HOMO−1 (of **13′**), 0.63 eV below the HOMO, effectively precludes luminescence deactivation by electron transfer from Au^I. A Dapprich–Frenking charge decomposition analysis[29,30] finds a net charge donation of 0.33e from the naphthyl ligand to the (phosphane)gold fragment. The Au–C Wiberg bond order[31] in the Löwdin basis is 0.970; that of the Au−P bond is 0.984.

Time-dependent DFT calculation[32] of the low-lying singlet excited states of **13′** indicates an allowed excitation at 324.3 nm of mixed parentage, deriving mainly from a LUMO←HOMO transition with an admixed LUMO+1←HOMO excitation; both are π*←π transitions. The calculated oscillator strength is $f=0.209$. Weaker absorption transitions are calculated at 258 and 254 nm, with $f=0.0201$ and 0.0489, respectively. No other singlet–singlet transitions of significant oscillator strength were calculated in the absorption window of THF. The lowest-energy triplet state (computed for the singlet geometry) is calculated at 452.1 nm.

To summarize, a general protocol for creating gold(I) carbon bonds is presented. The reaction entails transmetalation from boronic acids to (phosphane)gold(I) bromides in the presence of base. Significant steric encumbrance is supported, both in the phosphane and the transmetalating aryl group. The gold(I) products are robust compounds that are stable in air and water for prolonged periods. Terminal (phosphane)gold(I) functionality is compatible with luminescence of the aromatic parent compound. The ability to tether gold(I) fragments to organic skeletons invites syntheses of more potent photodynamic therapy mediators that operate at reduced dosages. Gold(I) compounds that can be prepared by the new method hold added potential as rheumatoid arthritis prodrugs. Lipophilicity and cell permeability are adjustable in principle through the ancillary phosphane. Transmetalation from boronic acids proffers gold compounds bearing Grignard- and organolithium-incompatible functional groups. Further investigations of this process and applications to photoactive organic species are ongoing.

Experimental Section

13: Cs_2CO_3 (98 mg, 0.30 mmol) and 1-naphthylboronic acid (53 mg, 0.31 mmol) were suspended in isopropyl alcohol (5 mL). Cy_3PAuBr (88 mg, 0.16 mmol) was added to the suspension, and the mixture was stirred at 50 °C for 24 h. After cooling, the solvent was evaporated in vacuo, the residue was extracted into benzene, the solution was filtered through celite, and the filtrate was concentrated by rotary evaporation. The residue was triturated with pentane, and the pentane was removed by rotary evaporation. The pale yellow solid was washed with pentane, dried, and extracted into benzene. Then the solution was filtered through celite and concentrated to saturation. Vapor diffusion of pentane caused separation of a colorless crystalline mass, which was washed with cold methanol and pentane, dried, and collected. Yield: 82 mg (86 %). ^{1}H NMR (C_6D_6): $\delta = 9.10$ (d, 1H, 1-naphthyl), 8.21 (td, 1H, 1-naphthyl), 7.89 (d, 1H, 1-naphthyl), 7.77 (d, 1H, 1-naphthyl), 7.65–7.58 (m, 2H, 1-naphthyl), 7.41–7.36 (m, 1H, 1-naphthyl), 1.95–0.94 ppm (m, 33H, C_6H_{11}); ^{31}P NMR (C_6D_6): $\delta = 58.0$ ppm; UV/Vis (THF, 10^{-6} M): λ (ε) = 283 (11800), 293 (13500), 302 (10000), 321 nm (2300 cm^{-1}M^{-1}); emission (THF, 10^{-8} M, $\lambda_{ex} =$ 310 nm): $\lambda = 363$ nm; emission (THF, 10^{-6} M, $\lambda_{ex} = 310$ nm): $\lambda = 363$, 483, 494 (sh), 520, 560 nm. Elemental analysis (%) calcd for $C_{28}H_{40}AuP$: C 55.63, H 6.67; found: C 55.60, H 6.83.

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Keywords: boron · gold · phosphane ligands · photodynamic therapy · transmetalation

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[17] CCDC 616180 and 616190 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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