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Synthesis of new C_{60} based phosphines

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Abstract—Two series of new phosphine derivatives based on C_{60} protected by borane have been synthesized and characterized. These phosphines were used for two preliminary complexation trials with $[RhCl(COD)]_2$ and $[Re(S_3CPh)_2(S_2CPh)]$ to afford, respectively, the corresponding complexes $[RhCl(COD)(PRPh_2)]$ and $[Re(S_2CPh)_3(PRPh_2)]$.

Fullerenes, especially C_{60}, have received increasing attention since their discovery in 1985.[1] Their derivatives show a large range of promising applications in many domains due to their remarkable electronic,[2] magnetic[3] and charge-transfer[4] properties. In biomedical fields, various potential areas of application have been investigated such as neuroprotection,[5] apoptosis,[6] inhibition of HIV-protease,[7] photodynamic therapy[8]or X-ray contrast agents.[9] Among potential domains, radiomedicine and diagnostic purposes appear to be another interesting field of possible development for both empty or endohedral metallofullerene derivatives.

As part of our work on the synthesis of radiopharmaceuticals, we have reported recently the synthesis of oxorhenium(V) complexes carrying the C_{60} moiety,[10] using a new SNO/SN coordination system around the metal. Tertiary phosphines are able to stabilize various transition metals in a variety of oxidation states and coordination geometries, mainly due to π backbonding. This approach has been used for the design of various radiopharmaceuticals. In this paper, we present the synthesis of phosphine ligands bearing C_{60}. To connect C_{60} to phosphine, we chose the well-known cyclopropanation of Bingel[11] and 1,3-dipolar addition of azomethine ylides[12] for fullerene functionalization. Fullerene derivatives are well known to sensitize the formation of singlet oxygen through their triplet excited state.[13] This property is discordant with the high sensitivity of alkylphosphines to oxidation. Thus, with the aim of making fullerene derivatives easy to handle, purify and characterize, we alternatively used phosphine–borane complexes which are very stable and not sensitive to chemical oxidation.[14] Finally, the first attempts at fullerene–phosphine ligand coordination were carried out on rhodium and rhenium complexes.

The general synthetic pathway for the preparation of fullerene phosphine ligands is presented in Scheme 1. Starting from diols **1**, monotosylated compounds **2a** and **2c** were obtained by treatment with tosyl chloride and triethylamine in dichloromethane; the monobrominated derivative **2b** was prepared by refluxing 1,8-octanediol **1b** with aqueous HBr (48%) in cyclohexane. Then two routes leading to fullerene adducts were possible through the key building blocks **5**. Derivatives **5b** and **5c** were obtained in two steps: first, the triphenylphosphine–borane complex was stirred with lithium metal in dry THF, then compound **2b** or **2c** was added in dry THF to the non-isolated intermediate $[Ph_2P(BH_3)Li]$ complex to afford building blocks **5b** and **5c** in 43 and 65% yields, respectively.

Malonate derivatives **3** and **6** were conveniently available by esterification reactions between alcohols **2** and **5** and ethyl malonyl chloride in CH_2Cl_2. Malonates **6** could also be obtained from the corresponding tosylated derivatives **3** by reaction with $[Ph_2P(BH_3)Li]$ in dry THF. Bingel reactions with C_{60}, diiodine, DBU and malonates **6** led to the first fullerene-protected phosphine ligands **7**. Fullerene derivative **4a** prepared by the Bingel reaction from **3a** did not allow the preparation of the corresponding phosphine ligand.

From key building blocks **5**, the corresponding aldehyde derivatives **8** were prepared through classical PCC

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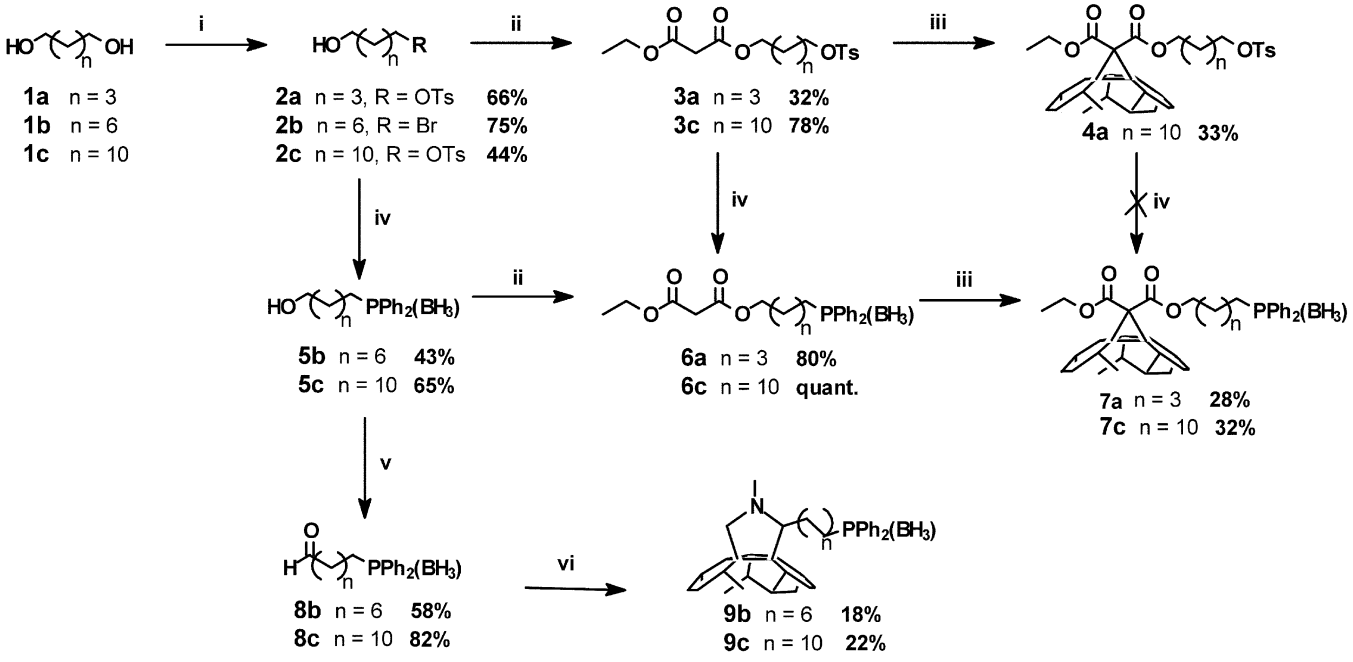
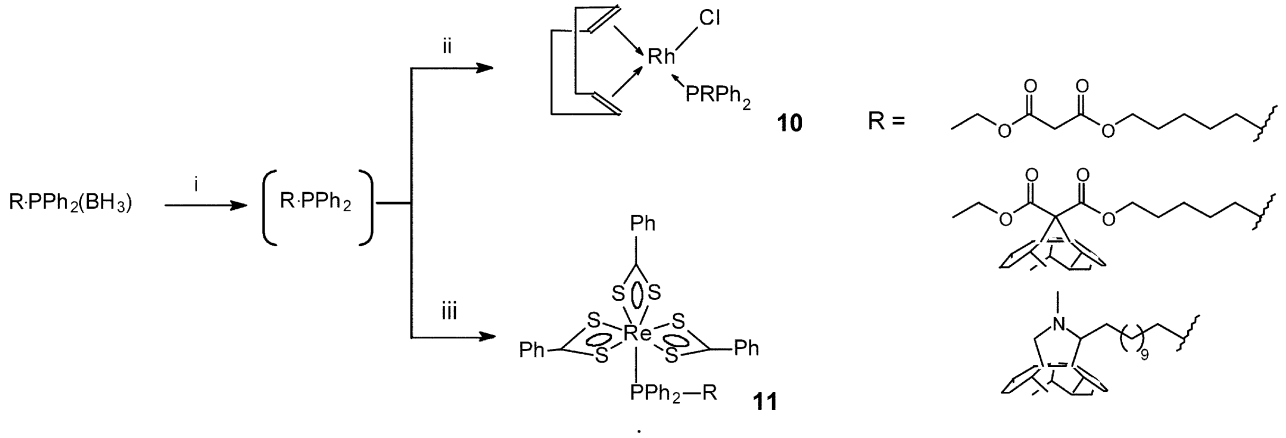
oxidation in dichloromethane (58 and 82% yields). Fulleropyrrolidines **9** were finally obtained by 1,3-dipolar addition of azomethine ylides prepared in situ from *N*-methylglycine and the latter aldehydes **8** in 18 and 22% yields, respectively. Deprotection of the phosphine–borane complexes occurred using tertiary amines such as diazabicyclooctane (DABCO)[15] in dry toluene for 4 h at 50–60°C under an atmosphere of argon (Scheme 2). The complex solution was then added and stirred overnight under an argon atmosphere at room temperature or 60°C.[16]

Preliminary complexation experiments with rhodium utilized chloro(1,5-cyclooctadiene)rhodium(I) dimer, whereas complexation with rhenium was carried out with bis(perthiobenzoato)(dithiobenzoato)rhenium(III) (Scheme 2).

The spectroscopic data for the novel fullerene phosphine ligands (**7a**, **7c**, **9b** and **9c**) are in agreement with the proposed structures.[17] Thus, the ^{1}H NMR spectra of the methanofullerene **7a** and fulleropyrrolidine **9c** showed the presence of the aromatic protons in the region between δ 7.7 and 7.4 ppm as two multiplets of 4 and 6 protons and the methylene close to phosphorus as an ill-defined signal between 2.2 and 2.1 ppm. The ^{1}H NMR spectrum of **9c** showed the characteristic signals of a fulleropyrrolidine with the two doublets of one proton each at 4.8 and 4.1 ppm for the CH_2N group, the triplet of one proton at 3.9 ppm for the

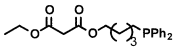
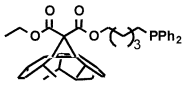
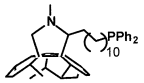


Scheme 1. *Reagents and conditions*: (i) TsCl, Et_3N, CH_2Cl_2, room temperature or HBr, cyclohexane, Δ; (ii) ethyl malonyl chloride, Et_3N, CH_2Cl_2, room temperature; (iii) C_{60}, I_2, DBU, toluene, room temperature; (iv) $[Ph_2P(BH_3)Li]$, THF, room temperature; (v) PCC, CH_2Cl_2, room temperature; (vi) C_{60}, *N*-methylglycine, toluene, Δ.



Scheme 2. *Reagents and conditions*: (i) DABCO, toluene, 50–60°C; (ii) $[Rh(COD)Cl]_2$, toluene, room temperature; (iii) $[Re(S_3CPh)_2(S_2CPh)]$, toluene, room temperature.

Table 1. Selected ^{31}P NMR ($CDCl_3$, 161.98 MHz) data for free ligands and complexes

Ligands	 **6a**	 **7a**	 **9c**
Free Ligand	bs	bs	bs
$P(BH_3)$ shift (ppm)	16.89	16.79	16.96
Complex **10**	d (J = 148.2 Hz)	d (J = 148.2 Hz)	d (J = 147.1 Hz)
P-Rh shift (ppm)	27.29	27.26	27.48
Complex **11**	s	s	s
P-Re shift (ppm)	-9.28	-7.27	-5.79

CHN group and the singlet of three protons at 3 ppm for NCH_3. The ^{13}C NMR spectra of the two fullerene derivatives were also in agreement with the proposed structures. The CH_2–CH_2–P group was characterized by two doublets: at 20.6 and 31.2 ppm for CH_2–CH_2–P and 25.7 and 25.6 ppm for CH_2–CH_2–P in the methanofullerene and fulleropyrrolidine, respectively with coupling constants of 14 and 37 Hz for CH_2–CH_2–P and CH_2–CH_2–P, respectively. Finally, all the protected ligands were characterized by ^{31}P NMR with a singlet at about 17 ppm. This signal was very broad due to borane complexation.

Resulting rhodium and rhenium complexes were obtained after organophosphorus compound deprotection as shown by ^{31}P NMR (Table 1). These complexes could not be isolated because of the high sensitivity of the phosphine derivatives (only phosphine oxide was isolated by column chromatography).

Thus, the ^{31}P NMR data of the rhodium complexes in Table 1 showed doublets at 27.3, 27.3 and 27.5 ppm with characteristic coupling constants of 148, 148 and 147 Hz, respectively for the corresponding ligands **6a**, **7a** and **9c**. These signals attributed to P–Rh bonding were in agreement with the proposed structures shown in Scheme 2 with only one phosphine for one rhodium metal. Indeed, a large amount of deprotected phosphine was recovered as phosphine oxide (singlet at 33.7 ppm).

Phosphine complexation was achieved with rhenium complex $[Re(S_3CPh)_2(S_2CPh)]$ to the corresponding $[Re(S_2CPh)_3(PRPh_2)]$ complexes.[18] ^{31}P NMR spectra of the reaction media showed three different sets of signals: the complex as a singlet at −5.8 ppm, the phosphine oxide as a singlet at 33.7 ppm and a major signal (singlet) at 43.9 ppm corresponding to the phosphine thiooxide (P=S). The latter signal is due to the reduction of two perthiobenzoates of the $[Re(S_3CPh)_2(S_2CPh)]$ complex, establishing again that complex **11** had been synthesized.

In conclusion, diphenylalkylphosphine ligands carrying the C_{60} moiety have been synthesized and well characterized in their protected forms. These phosphines were used for two preliminary complexation trials with $[RhCl(COD)]_2$ and $[Re(S_3CPh)_2(S_2CPh)]$ to afford, respectively, the corresponding complexes, $[RhCl(COD)(PRPh_2)]$ and $[Re(S_2CPh)_3(PRPh_2)]$.

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16. General procedure: Under an argon atmosphere, protected phosphine (4 equiv.) and DABCO (4 equiv.) were refluxed in dry toluene for 4 h. After cooling to room temperature, the rhenium or rhodium complex (1 equiv.) dissolved in dry toluene was added under an Ar atmosphere and the mixture was stirred overnight (at room temperature or 60°C). After evaporation of solvent under vacuum, NMR spectroscopy was carried out under argon.
17. Selected spectroscopic data for compound **7a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69–7.64 (m, 4H, arom), 7.49–7.42 (m, 6H, arom), 4.54 (q, $J=7.1$ Hz, 2H, CH_2OCO), 4.46 (t, $J=6.5$ Hz, 2H, $COOCH_2$), 2.24–2.17 (m, 2H, CH_2P), 1.86–1.80 (m, 2H, CH_2), 1.66–1.52 (m, 4H, $2CH_2$), 1.47 (t, $J=7.1$ Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 163.70, 163.61 (*C*OO), 145.46, 145.33, 145.26, 145.23, 145.19, 144.95, 144.76, 144.74, 144.68, 143.95, 143.93, 143.15, 143.09, 143.00, 142.27, 142.24, 141.96, 141.91, 141.02, 141.00, 139.24, 138.84, 137.94 (*C* C_{60}), 132.21, 132.12, 131.32, 131.30, 129.67, 129.12, 129.10, 129.00, 128.90, 128.29, 125.36 (*C* arom), 77.30, 71.62 (Csp^3 C_{60}), 67.00 ($COOCH_2$), 63.55 (CH_2COO), 52.28 (CO*C*–CO), 28.21 (CH_2), 27.70, 27.55 (CH_2CH_2P, $J=14$ Hz), 25.93, 25.57 (CH_2P, $J=37$ Hz), 22.73 (CH_2), 14.27 (CH_3); ^{31}P NMR ($CDCl_3$, 161.98 MHz) δ 16.79 (broad s). Anal. calcd for $C_{82}H_{28}O_4BP$ (1118.91) : C, 88.02 ; H, 2.52%. Found: C, 87.0; H 2.7%
Compound **9c**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69–7.59 (m, 4H, arom), 7.50–7.38 (m, 6H, arom), 4.80 (d, $J=9.6$ Hz, 1H, CH_2N), 4.15 (d, $J=9.6$ Hz, 1H, CH_2N), 3.88 (t, $J=5.2$ Hz, 1H, CHN), 2.97 (s, 3H, NCH_3), 2.56–2.47 (m, 1H, NCH–CH_2), 2.40–2.31 (m, 1H, NCH–CH_2), 2.20–2.13 (m, 2H, CH_2P), 1.95–1.82 (m, 2H, CH_2), 1.54–1.11 (m, 16H, 8 CH_2); ^{13}C NMR ($CDCl_3$, 100.62 MHz) δ 156.57, 154.58, 154.49, 153.57, 147.29, 147.25, 146.88, 146.62, 146.46, 146.35, 146.30, 146.23, 146.21, 146.14, 146.10, 146.02, 146.00, 145.87, 145.63, 145.57, 145.46, 145.37, 145.35, 145.28, 145.23, 144.80, 144.63, 144.47, 144.40, 143.25, 143.10, 142.74, 142.70, 142.69, 142.66, 142.25, 142.23, 142.21, 142.12, 141.87, 141.79, 141.72, 140.32, 140.24, 139.80, 139.65, 137.23, 136.31, 135.92, 135.60 (*C* C_{60}), 132.22, 132.13, 131.15, 131.12, 129.99, 129.44, 128.89, 128.79 (*C* arom), 78.24 (N*C*H), 76.35 (Csp^3 C_{60}), 70.48, 70.18 (CH_2N, Csp^3 C_{60}), 40.16 (NCH_3), 31.32, 31.19 (CH_2CH_2P, $J=13.6$ Hz), 31.11 ($NCHCH_2$), 30.25, 29.53, 29.50, 29.43, 29.10, 27.49, 23.03 (CH_2), 25.86, 25.50 (CH_2P, $J=36.9$ Hz); ^{31}P NMR ($CDCl_3$, 161.98 MHz) δ 16.96 (broad s). Anal. calcd for $C_{89}H_{42}O_4BP$ (1217.10): C, 87.83; H, 3.48%. Found: C, 87.6; H 3.5%.
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