Rapid carbonylative coupling reactions using palladium(I) dimers: applications to ^{11}CO-radiolabelling for the synthesis of PET tracers

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Supplementary Information

Experimental Details

General. All procedures were carried out under an inert atmosphere of dry nitrogen using standard Schlenk techniques. All the glassware was oven-dried at 140°C before use. Unless otherwise stated, solvents were dried using a solvent purification system (SPS, Innovative-technology) and degassed with nitrogen prior to use. Starting materials and the internal standard for GC analysis were purchased from commercial suppliers (Sigma-Aldrich Chemical Company, Strem or VWR) as high-purity products and were used as received without further purification.

Complex synthesis. $[Pd(PPh_3)_4]$ was purchased from Sigma-Aldrich Chemical Company and used without further purification. $[Pd(P^tBu_3)_2]$, $[Pd_2(\mu\text{-}Cl)Cl\{\mu\text{-}(P^tBu_2Bph\text{-}H)\}]$ (BPh-H = biphenyl), $[Pd_2(\mu\text{-}Cl)Cl\{\mu\text{-}(P^tBu_2Bph\text{-}Me)\}]$ (BPh-Me = methyl-biphenyl), $[Pd_2(\mu\text{-}Br)_2(P^tBu_3)_2]$ and $[Pd_2(\mu\text{-}I)_2(P^tBu_3)_2]$ were prepared following literature procedures.[1]

Carbonylation reactions. All reactions were carried out using Schlenk line techniques in a well ventilated fumehood and in the presence of a carbon monoxide alarm. In a typical reaction a Schlenk tube equipped with a Teflon magnetic stir bar was charged with the

complex (either 2.2 or 10 mol%), sealed with a rubber septum, evacuated and placed under an atmosphere of CO. In a separate flask a solution of the substrates arylhalide (0.45 mmol) and amine nucleophile (benzylamine or piperidine, 4.6 mmol) was prepared in the designated solvent (0.5 mL) presaturated with CO gas. This substrate solution was then transferred, via cannula, to the Schlenk tube containing the catalyst, sealed and placed in a preheated oil bath for the selected time period. After this time the reaction mixture was removed from heat source and rapidly quenched with $HCl_{(aq)}$ (4.5 mL, 1 M). The rubber septum was removed and unreacted CO vented into the fumehood. For reaction of iodobenzene (table 1) the crude product mixture was extracted with dichloromethane (2 x 5 ml) and filtered through a cotton pad prior to analysis. For reactions of the arylbromide and 5-iodoindole substrates (table 2) acidic work-up was not performed and analysis was performed on the crude product mixture after filtration through a cotton pad. Quantitative analysis was conducted by gas chromatography using the peak area of the starting material or product normalised in response to the internal diphenyl ether standard GC using a Hewlett-Packard HP5890 series II equipped with a 30 m J&W DB-5 capillary column (0.25 mm i.d., 0.25 micron film, (5%-Phenyl)-methyl-polysiloxane) and a FID detector employing helium as carrier gas; temperature was programmed from 100°C to 320°C with gradient of 12°C/min.

^{11}CO Carbonylation reactions. ^{11}CO trapping solution was prepared in a similar way to that reported in the literature.[2] A stock solution of [CuTp*] 'trapping solution' was made on the morning of the experiments and aliquots used throughout the day. Typically a 5 mL solution was made by addition of CuCl (5.5 mg, 55 μmol) and KTp* (18.5 mg, 55 μmol) to a vial and flushing with nitrogen for 10 min followed by addition of anhydrous toluene (5.0 mL).

[^{11}C]Carbon dioxide was produced using a Siemens Eclipse HP cyclotron by 11 MeV proton bombardment (2 min at 5 μA) of a target containing nitrogen and 1% oxygen.^{11}CO was produced using an Eckert and Ziegler reduction module using the following procedure: $^{11}CO_2$ was delivered from the cyclotron and trapped at room temperature in a stainless steel loop containing molecular sieves. The $^{11}CO_2$ was then released by passing a helium flow through the loop while heating to 400°C. The resultant $^{11}CO_2$/He gas stream was passed through a glass tube packed with molybdenum powder at 850°C, converting the $^{11}CO_2$ to ^{11}CO with any unreduced $^{11}CO_2$ being trapped using Ascarite. The resultant ^{11}CO/He gas stream was delivered to the [CuTp*] trapping solution at a flow rate of 20 mL/min. The time taken from end of cyclotron bombardment to complete delivery of ^{11}CO to the reaction vial was 5 to 6 min.

Synthesis of [^{11}C]*N*-benzylbenzamide (an analogous procedure was carried out for all the other ^{11}CO carbonylative coupling reactions). A 3 mL V-bottomed glass vial with a rubber septum cap was flushed with nitrogen for 10 min and loaded with [CuTp*] solution (1.0 mL, 11 μmol) and seated in a metal heater block at room temperature. The ^{11}CO/He gas stream was delivered to the vial, with the waste gases being collected in a gas bag situated inside a dose calibrator. The radioactivity of the vial was monitored using a pin diode detector situated next to the vial. Once the radioactivity of the vial had reached a steady maximum, the gas flow was stopped and a solution of iodobenzene (5.6 μ L, 50 μmol) and [Pd(μ-I)$_2$(P^{t}Bu$_3$)$_2$] (1.4 mg, 1.6 μmol, 6.4% Pd w.r.t iodobenzene) in anhydrous toluene (100 μL) was injected into the vial and the heater block set to 120°C. After 2 min the heater block had reached 120°C at which point benzylamine (27 μL, 250 μmol) in toluene (100 μL) was injected into the vial. After a further 8 min at this temperature, the crude mixture was transferred to a vial containing a solution of triphenylphosphine (5.8 mg, 22 μmol) in toluene

(200 µL) at room temperature using an argon gas sweep. The solution was purged with argon for a further two min to displace any unreacted ^{11}CO to the waste bag. The radioactivity of the vial was then measured in a dose calibrator and the radiochemical purity of the crude product measured by analytical HPLC on an Agilent 1100 equipped with UV (DAD) and radioactivity detectors, using an Agilent XDB-C18 column (5 µm, 4.6 x 150 mm), eluted with 40% acetonitrile: 60% water at a flow rate of 1.5 mL/min.

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