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Efficient ^{11}C-Carbonylation of Isolated Aryl Palladium Complexes for PET: Application to Challenging Radiopharmaceutical Synthesis

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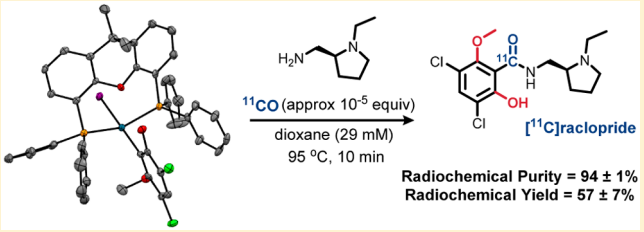
Supporting Information

ABSTRACT: We describe the successful implementation of palladium-aryl oxidative addition complexes as stoichiometric reagents in carbonylation reactions with ^{11}CO to produce structurally challenging, pharmaceutically relevant compounds. This method enables the first ^{11}C-carbonyl labeling of an approved PET tracer, [^{11}C]raclopride, for the dopamine D2/D3 receptor by carbonylation with excellent radiochemical purity and yield. Two other molecules, [^{11}C]olaparib and [^{11}C]JNJ 31020028, were efficiently labeled in this manner. The technique distinguishes itself from existing methods by the markedly improved purity profiles of the tracer molecules produced and provides access to complex structures in synthetically useful yields, hereby offering a viable alternative to other ^{11}C-labeling strategies.



INTRODUCTION

Positron Emission Tomography (PET) has established itself among the primary biomedical imaging techniques and serves today as a routine tool in disease diagnostics, drug development research, and molecular imaging in general.[1,2] The field is expanding fast and combination techniques have been developed, including PET-MR and PET-CT, to further increase the resolution and information available from a scan. Consequently, there is an ever-increasing demand for the development of novel radiotracers and reliable labeling techniques. Yet, considering this demand, ^{18}F-labeled neuraceq, a ligand for the estimation of β-amyloid neuritic density in the brain of patients being evaluated for Alzheimer's disease, remains the only PET tracer which has been approved for clinical use by the FDA in 2014. Altogether, only a handful of approved PET-tracers exist. This discrepancy is due in part to a continued need to develop new and improve existing labeling techniques.

^{18}F remains the most widely used radionuclide for the labeling of tracer molecules for PET. This is partly due to a more convenient half-life of 110 min, when compared to for example ^{11}C, being only 20 min. Nonetheless, from a future perspective, ^{11}C remains an interesting radionuclide for PET tracer production as all organic-based endogenous ligands of protein receptors contain carbon but not necessarily fluorine. Introduction of ^{18}F to nonfluorine containing ligands could lead to changes in biological properties, such as binding efficiency and receptor selectivity. Only in isolated cases can the incorporation of a fluorine atom be expected to directly benefit the biological properties of the ligands. Moreover, if marketed pharmaceuticals can be labeled as their parent structures, little additional efforts are necessary for approval of the ^{11}C-labeled structure for PET applications, thus reducing the development costs of the tracers.

^{11}C is routinely produced in high yielding reactions as either $^{11}CH_4$ through proton bombardment of a N_2/H_2 target gas, or as $^{11}CO_2$ generated by using a N_2/O_2 target gas. Through online processes, these primary products can be transformed into a number of ^{11}C-labeled building blocks. Thus, ^{11}C-cyanations starting from H^{11}CN, carboxylations employing $^{11}CO_2$, and reactions with ^{11}C-phosgene are common ways to introduce a ^{11}C-label.[3] However, the majority of ^{11}C-radiolabeling is confined to ^{11}C-methylating agents ($^{11}CH_3I$, $^{11}CH_3OTf$) because of their simplicity and efficiency as electrophiles in nucleophilic substitution reactions with functional groups such as alcohols, amines, and thiols.[4] These methylating protocols are firmly established and include automated tracer synthesis in one-pot procedures. On the downside, this ^{11}C-carbon labeling technique necessitates that the parent bioactive molecule displays a heteroatom-bound methyl group. Hence, it would be useful to identify other general and efficient protocols not only for ^{11}C-carbon isotope labeling to increase the breadth of potential tracers but also for

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investigations into the importance of the positioning of the isotope-label on the chemical structure of interest.[5]

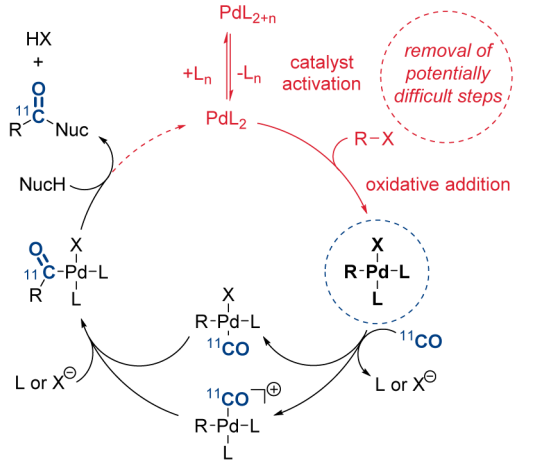
Over the past decade, a rising interest in the use of ^{11}CO as a C1-building block in labeling strategies has emerged. The advantages of this strategy include (i) the facile production of ^{11}CO from $^{11}CO_2$, (ii) a diverse array of developed carbonylation reactions,[6−13] (iii) high selectivity of the labeling position, (iv) the generally high functional group tolerance, and (v) the high specific activity of the labeled tracers as very low contamination with $^{12}CO_2$ is usually observed. Furthermore, the possibility of labeling both known and novel radiotracers and pharmaceuticals at an internal position, for example the carbonyl group of an amide, could be useful for shedding light on the metabolic fate of such molecules. Finally, where it is applicable, future work to develop new tracer molecules will not be complicated by the requirement of installing certain functional groups in the target molecule for late stage radiolabeling, for example free hydroxyl groups or primary/secondary amines.

The quantities of $^{11}CO_2$, and thereby the ^{11}CO produced by the cyclotron, amounts to only pico- to nanomoles. Furthermore, reaction times must be kept short in order to produce useful amounts of the radiotracer at the end of synthesis. These features differentiate ^{11}C-carbonylation from ordinary transition-metal-catalyzed carbonylation reactions considerably, and direct extrapolation of established conditions is generally not possible. Several strategies have been employed to promote trapping of ^{11}CO in the reaction container and ensure a fast reaction, including the use of microautoclaves,[14−16] microfluidics,[17] and low-pressure chemical trapping. Thus, carbonylation reactions can now be conducted to produce ^{11}C-carbonyl labeled esters,[18] carboxylic acids,[19] amides,[20−22] (hydroxyl)ureas,[23,24] and malonates[25] in respectable radiochemical purity and yield. However, despite this apparent success, *no examples of routine uses of carbonylation for tracer production exist*. This lack of routine carbonylation for ^{11}C-isotope labeling is mainly due to the fact that the existing techniques function only for less sophisticated molecules rather than for more complex and pharmaceutically relevant substrates.

Hence, if carbonylation is to find a useful place in PET, more efficient carbonylation techniques are required for the synthesis of medicinally relevant but synthetically challenging motifs.

One common feature of the transition-metal-mediated carbonylation reactions listed above is the necessity of the aryl halide starting material to undergo a number of reaction steps approaching one full catalytic cycle of, for example, aminocarbonylation, disregarding catalyst regeneration, in order to provide one radiolabeled molecule. When sterically or electronically demanding substrates are required, oxidative addition may be slow, thus resulting in the inefficient radiolabeling of more challenging compounds within the PET-time scale (Scheme 1). To circumvent this difficulty, we envisioned the utilization of pregenerated (Aryl)Pd(X)L_n oxidative addition complexes as a potential solution. These complexes would already have undergone the potentially challenging oxidative addition prior to their employment in carbonylative ^{11}C-labeling. Additionally, the steps involved for the formation of a phosphine ligated, catalytically active palladium complex would also be eliminated, thereby effectively eliminating two potentially slow reaction steps. The use of transition metal complexes as PET-labeling mediators has recently been elegantly illustrated on several occasions in late stage ^{18}F-fluorinations by the Doyle and Ritter groups.[26−28] On a similar note, the general notion of employing preformed aryl palladium complexes to mediate challenging couplings has previously been investigated by the Myers group.[29] The use of Pd-complexes for the detection of CO in living cells has also recently been demonstrated.[30] No similar initiative has so far been reported with regards to ^{11}C-carbon labeling.

Scheme 1. Advantages of Using Aryl Palladium Complexes in ^{11}C-Radiolabeling



Potential advantages of using pregenerated aryl palladium complex:
reaction less dependent on the nature of R
more clean conversion / less byproduct formation
faster product formation / higher radiochemical yield

Herein, we wish to report on the finding that the use of pregenerated aryl palladium complexes in ^{11}C-carbonylation reactions greatly improves the radiochemical purity and yield in the preparation of ^{11}C-labeled pharmaceutically relevant molecules. Furthermore, this strategy significantly broadens the scope of ^{11}C-carbonylations, exemplified by the production of three synthetically challenging molecules, [^{11}C]raclopride, [^{11}C]olaparib, and the neuropeptide Y Y_2 receptor antagonist, [^{11}C]JNJ-31020028, in good to excellent purities and all in synthetically useful yields.

RESULTS AND DISCUSSION

Initial work was undertaken to assess the ability of phosphine ligated aryl palladium complexes to absorb CO from the gas phase. This property is essential, considering the minute amount of ^{11}CO, which is available during radiolabeling. In order to investigate the effect which the halide counterion exerts on the CO-uptake ability of phosphine ligated aryl palladium complexes, oxidative addition complexes of iodo- and bromobenzene were prepared with triphenylphosphine as the supporting ligand. These complexes were then treated with 2.05 equiv of ^{13}CO at room temperature by applying a two-chamber system setup. ^{13}CO was generated in the other chamber from ^{13}C-labeled methyldiphenylsilacarboxylic acid by treatment with KF.[31,32] The bromobenzene complex **1** was first subjected to these conditions for 60 min in $CDCl_3$. Subsequent ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy indicated full conversion of the oxidative addition complex into the corresponding ^{13}C-labeled acyl complex ^{13}CO-**1** (Table 1, entry 1). Shortening the reaction time to 20 min led to only a 59% conversion to the acyl complex ^{13}CO-**1** (entry 2). Reaction of complex **2** under similar conditions led to full conversion into the acyl complex,

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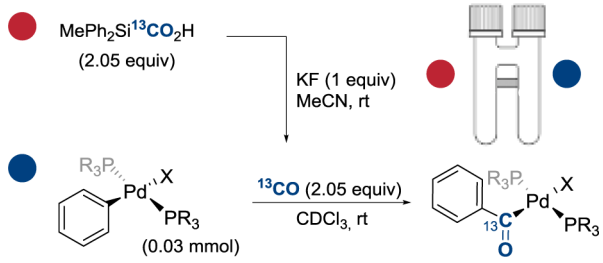
Table 1. CO-Uptake by Phosphine Ligated Palladium Oxidative Addition Complexes[a]



entry	X	ligand (complex)	time [min]	conversion [%][b] (^{13}CO-complex)
1	−Br	PPh_3 (**1**)	60	100 (^{13}CO-**1**)
2	−Br	PPh_3 (**1**)	20	59 (^{13}CO-**1**)
3	−I	PPh_3 (**2**)	20	100 (^{13}CO-**2**)
4	−I	PPh_3 (**2**)	8	50 (^{13}CO-**2**)
5	−I	XPhos (**3**)	8	63 (^{13}CO-**3**)
6	−I	dppf (**4**)	8	72 (^{13}CO-**4**)
7	−I	XantPhos (**5**)	8	100 (^{13}CO-**5**)
8	−Br	XantPhos (**6**)	8	100 (^{13}CO-**6**)
9	−I	P(*t*-Bu)$_3$ (**7**)	8	100 (^{13}CO-**7**)
10	−I	cataCXium A (**8**)	8	100 (^{13}CO-**8**)

[a]Reaction conditions: Ar−Pd complex (**1**−**8**) (0.03 mmol) and $CDCl_3$ (0.5 mL) in chamber 1. $MePh_2{}^{13}CO_2H$ (0.62 mmol), KF (0.65 mmol), and MeCN (0.5 mL) in chamber 2. Room temperature. [b]Conversion to the acyl complex was established by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy.

thereby demonstrating an enhanced ability of iodide-coordinated complexes toward CO capture (entry 3). By reducing the reaction time to 8 min only a 50% conversion of the oxidative addition complex **2** was observed (entry 4). This time frame proved suitable for comparison with a number of supporting ligands. The Buchwald-type biaryl ligand, XPhos, led to slightly improved CO-uptake, with a 63% conversion of **3** (entry 5), while the bidentate ligand dppf showed a 72% conversion of **4** into ^{13}CO-**4** (entry 6). Conversely, when XantPhos was employed, full conversion to acyl complex ^{13}CO-**5** was observed after only 8 min (entry 7). This remarkably high CO-uptake ability of XantPhos ligated complexes was further underlined when the analog complex originating from bromobenzene showed equally fast conversion to the acyl complex, ^{13}CO-**6** (entry 8).[33,34] On a similar time scale, trialkylphosphine ligated palladium complexes **7** and **8** also displayed full conversion to their corresponding acyl complexes ^{13}CO-**7** and ^{13}CO-**8**, respectively (entries 9 and 10).[35,36]

Most importantly, Table 1 serves as a simple guideline for which oxidative addition complexes will have the highest probability of undergoing ^{11}CO coordination and insertion to form the ^{11}CO-acyl complexes within a time frame suitable for PET chemistry. Not only does this study identify a number of ligands suitable for coordinating CO, it also indicates that iodide is a better choice as a counterion than bromide for the production of radiotracers, as CO uptake is faster in these complexes.

Next the oxidative addition complex strategy was applied for the introduction of the ^{11}C-carbonyl radiolabel into structurally different but pharmaceutically relevant molecules. To this end, a simple ^{11}CO trapping system derived from a setup recently reported by Eriksson and co-workers was employed as depicted in Figure 1.[37] Upon reduction of $^{11}CO_2$ over a preheated molybdenum catalyst, concentration of the ^{11}CO gas was effected by condensation on a silica trap immersed in liquid nitrogen. Subsequent release of the trapped ^{11}CO into the reaction vial was then achieved by simply heating the trap.

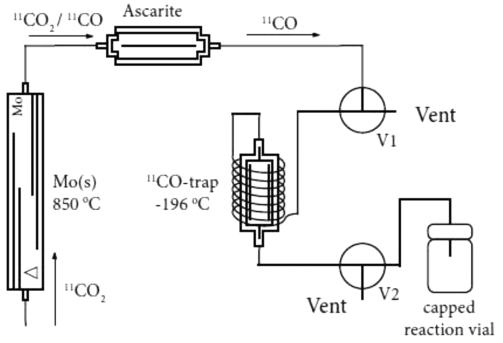


Figure 1. Fixation of ^{11}CO gas and delivery to reaction vial.

[^{11}C]raclopride. Initial attempts to employ aryl palladium complexes for ^{11}C-labeling purposes were directed toward the ^{11}C-carbonyl radiolabeling of raclopride. This dopamine D2/D3 receptor antagonist is commonly used as a PET tracer to assess the degree of dopamine binding to the D2-dopamine receptor, and is produced in PET-facilities as its ^{11}C-methyl labeled analog. Two *ortho*-substituents flank the central halide of a potential coupling partner, **9**, thereby hampering oxidative addition.[33,38]

Furthermore, previous attempts by us to produce this radiotracer by aminocarbonylation employing nonlabeled CO on a submillimole scale led to decomposition of the aryl iodide under the basic conditions commonly required in aminocarbonylations. Similar attempts starting from the aryl bromide gave only low conversion to raclopride in a slow reaction unsuitable for the PET time scale.

The oxidative addition complex **10** bearing XantPhos was prepared from the corresponding aryl iodide **9** and isolated by trituration and filtration. X-ray data confirmed the proposed structure (Scheme 2) and demonstrated XantPhos to form a *trans*-complex as has been previously observed with other aryl XantPhos−Pd complexes.[39] This finding was also consistent with the ^{31}P NMR spectrum displaying a singlet at 4.9 ppm.

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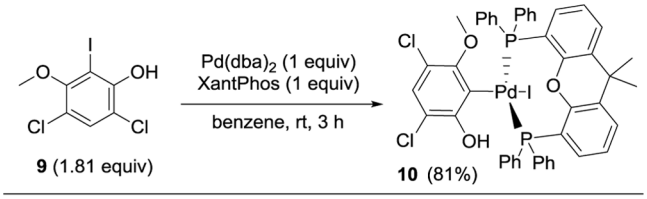
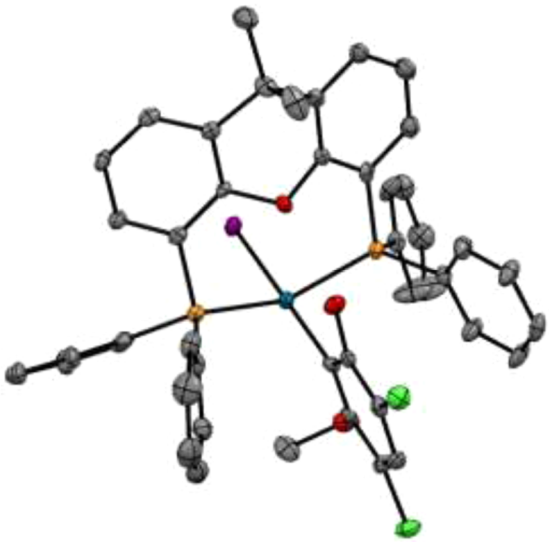
Scheme 2. Preparation of XantPhos Ligated Aryl Palladium Complex 10 and Its X-ray Structure[a]





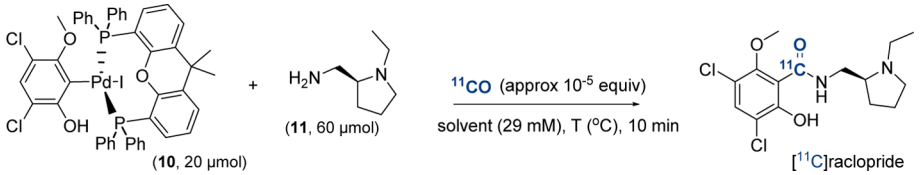
[a]For full details, see Supporting Information. ORTEP representation of **10**, 50% probability level.

After initials tests, it was found that combining complex **10** with (*S*)-(1-ethylpyrrolidin-2-yl)methanamine (**11**) in DMF for 10 min at 95 °C after delivery of ^{11}CO, radioanalytical HPLC analysis of the crude mixture indicated a remarkably clean transformation into ^{11}C-labeled raclopride. Furthermore, measuring the radioactivity in the reaction vial before and after flushing of the vial headspace proved that the complex did indeed fixate the available ^{11}CO efficiently (Table 2, entry 1). No additional base was necessary. Further investigation of the reaction conditions demonstrated that alternative solvents performed equally well (entries 2 and 3). Dioxane was maintained as the solvent for further examinations due to the excellent radiochemical purity observed (entry 4). The trapping efficiency could be increased by conducting the reaction at 120 °C, which nevertheless resulted in a lower radiochemical purity (entry 5). Conversely, reducing the reaction temperature to 85 °C led to a drop in the trapping efficiency (entry 6). Employing more of the reactants only decreased the radiochemical purity (entry 7), whereas lowering the amount of **10** slightly impeded the trapping efficiency, while the radiochemical purity was essentially unchanged (entry 8). The same observation was made when the reaction time was shortened to 6 min. This is an interesting feature, considering the short half-life of the ^{11}C-isotope (entry 9). Lastly, repeating the reaction conditions employed in entry 9, but using the free aryl iodide **9** along with $Pd(dba)_2$ and XantPhos in place of the pregenerated complex **10**, led to formation of ^{11}C-carbonyl labeled raclopride in a significantly reduced radiochemical purity of 39% and in a radiochemical yield of 13% (entry 10).

In order to test the reproducibility of the enclosed method, the results displayed in entry 4 were reproduced by different researchers at two separate PET-facilities at Aarhus, Denmark and Uppsala, Sweden. In all cases, the high radiochemical purity and yield were consistently obtained. Moreover, preparative HPLC purification of the product was successfully undertaken to isolate 29−43 mCi (n = 3) of [^{11}C]raclopride as a radiochemically pure sample with a decay corrected yield of 38−44% after 8 min of target irradiation. The specific activity was determined to be 9−11 Ci/μmol^{-1}, thus demonstrating one of the advantages of radiolabeling with ^{11}CO as very little dilution by atmospheric ^{12}CO is possible. These results constitute the first ^{11}C-labeling of an approved PET tracer by carbonylation with ^{11}CO gas.[40]

[^{11}C]olaparib. To further probe the applicability of the aryl palladium complex strategy, we next investigated the ^{11}C-

Table 2. Raclopride ^{11}C-Carbonyl Labeling[a]



entry	solvent	temp [°C]	trapping efficiency [%]	radiochemical purity [%]	radiochemical yield [%]
1	DMF	95	64	75	48
2	toluene	95	65	88	57
3	THF	95	64	88	56
4[b]	**1,4-dioxane**	**95**	**62 ± 8**	**94 ± 1**	**57 ± 7 (n = 3)**
5	1,4-dioxane	120	86	80	69
6	1,4-dioxane	85	57	93	53
7[c]	1,4-dioxane	95	64	80	51
8[d]	1,4-dioxane	95	50	94	47
9[e]	1,4-dioxane	95	45	94	42
10[f]	1,4-dioxane	95	33	39	13

[a]Reaction conditions: **10** (20 mg, 20 μmol), solvent (0.7 mL), **11** (7 mg, 60 μmol) in a 5 mL crimp-cap vial under argon. Upon delivery of ^{11}CO, the reaction was heated for 10 min. See Supporting Information for full details. [b]Average of three reactions. [c]**10** (40 μmol), **11** (120 μmol). [d]**10** (10 μmol). [e]Reaction time 6 min. [f]Aryl halide **9** (6.4 mg, 20 μmol), $Pd(dba)_2$ (11.5 mg, 20 μmol), XantPhos (11.5 mg, 20 μmol), **11** (7 mg, 60 μmol), and Et_3N (10 μL, 71 μmol) in dioxane (0.7 mL), 95 °C for 6 min with ^{11}CO.

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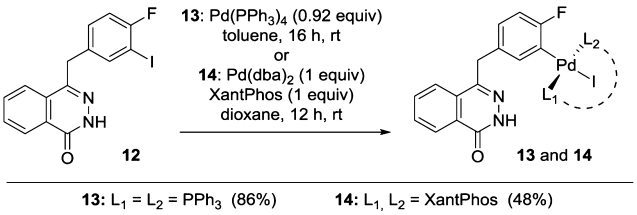
labeling of the PARP inhibitor, olaparib. This chemotherapeutic agent from AstraZeneca has recently been approved in the EU for the treatment of women with BRCA-mutated ovarian cancer. The radiochemical ^{11}C-labeling of this structural motif is inherently challenging as the parent compound contains no functional groups, which can be readily methylated to produce a ^{11}C-methyl analog.

Preparation of the XantPhos ligated oxidative addition complex from aryl iodide **12**, by reaction with $Pd(dba)_2$ and XantPhos in dioxane at room temperature, yielded complex **14** in a respectable yield (Scheme 3). When this complex was

Scheme 3. Preparation of the PPh_3 and XantPhos Ligated Aryl Palladium Complexes 13 and 14[a]



[a]For full details, see Supporting Information section.

subjected to the conditions identified in Table 2, analytical HPLC of the crude reaction mixture indicated formation of one major radioactive species. However, upon coinjection with olaparib, it was clear that the product was not the desired amide (Table 3, entry 1). The same unwanted product was observed when substituting XantPhos for PPh_3 with complex **13**, albeit with a low trapping efficiency. To confirm the identity of this side product, a range of possible structural candidates were prepared and coinjected with an analytical amount of freshly prepared reaction mixture. In this way, formation of the corresponding ^{11}C-labeled carboxylic acid was confirmed, however only in minor quantities. The identity of the major product was determined when the cold amide ^{12}C-**17** was synthesized and coinjected as a reference.

The origin of this product is suggested to arise from aryl scrambling of the phenyl groups from the supporting XantPhos ligand onto the aryl palladium complex. Such findings have precedence in the literature although the quantitative nature of this scrambling was surprising.[41] To demonstrate whether this aryl scrambling had occurred during the carbonylation reaction, or if the complex isolated and used as the starting material was actually the phenyl palladium complex, a crystal structure of **14** was required. Unfortunately, crystals of the XantPhos ligated palladium complex **14** suitable for X-ray diffraction studies could not be isolated in our hands. However, inspection of the crystal structure of **13** showed that no phenyl group migration had occurred prior to the carbonylation reaction (Figure 2). We suggest that this result can be extrapolated to the XantPhos ligated complex **14**, as **13** also produces exclusively the scrambled product ^{11}C-**17**.

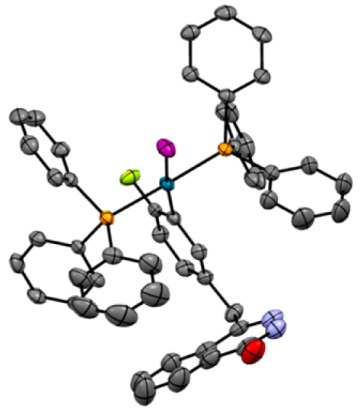
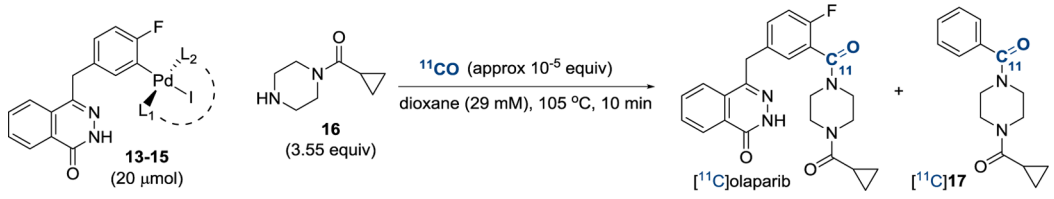


Figure 2. ORTEP representation of **13**, 50% probability level.

Increasing the reaction temperature only served to provide better trapping of ^{11}CO, but did not improve the selectivity (Table 3, entry 2). Consequently, nonaryl based phosphine ligands were considered. $P(t\text{-Bu})_3$ ligated oxidative addition complex **15** could be prepared by reacting the appropriate aryl halide with $Pd(cod)(CH_2TMS)_2$ (Scheme 4).[42,43]

Attempts to prepare this complex starting from $Pd(dba)_2$/$P(t\text{-Bu})_3$ or $Pd(P(t\text{-Bu})_3)_2$ only led to complex product mixtures, which proved difficult to purify. The reaction of complex **15** with ^{11}CO and amine **16** at 105 °C for 10 min in

Table 3. Olaparib ^{11}C-Carbonyl Labeling[a]



entry (complex)	ligand	trapping efficiency [%]	radiochemical purity [%]		radiochemical yield [%]	
			[^{11}C]olaparib	[^{11}C]**17**	[^{11}C]olaparib	[^{11}C]**17**
1	L_1, L_2 = XantPhos (**14**)	36	<1	99	<1	36
2[b]	L_1, L_2 = XantPhos (**14**)	51	<1	99	<1	51
3	$L_1 = L_2 = PPh_3$ (**13**)	4	<1	99	<1	4
4[c]	**L_1 = P(*t*-Bu)$_3$ (15) (L_2 = open site)**	**76 ± 10**	**99 ± < 1**	**<1**	**75 ± 10 (n = 3)**	**<1**
5[d]	$P(t\text{-Bu})_3$ (**12**)	74	74	<1	54	<1

[a]Reaction conditions: **13**−**15** (20 μmol), **16** (10 μL, 71 μmol), and dioxane (0.7 mL) in a 5 mL crimp-cap vial under argon. Upon delivery of ^{11}CO, the reaction was heated to 105 °C for 10 min. See Supporting Information for full details. [b]120 °C, [c]Average of three reactions. [d]Aryl iodide **12** (7.6 mg, 20 μmol), $Pd(dba)_2$ (11.5 mg, 20 μmol), $P(t\text{-Bu})_3$ (11.5 mg, 20 μmol), and **16** (10 μL, 71 μmol) in dioxane (0.7 mL), 105 °C for 10 min with ^{11}CO.

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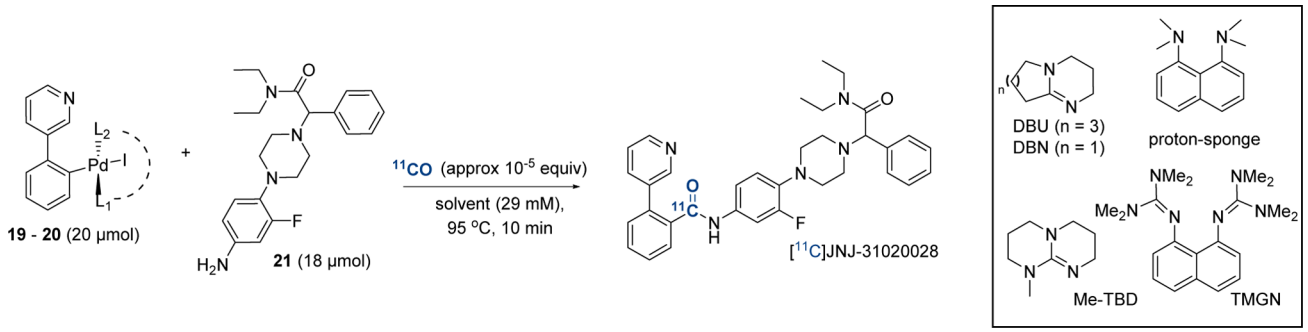
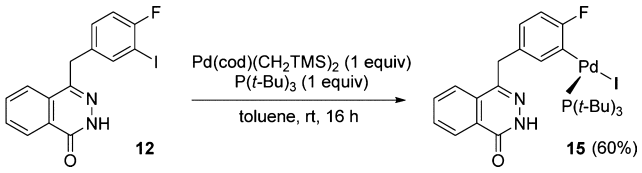
Table 4. JNJ-31020028 ^{11}C-Carbonyl Labeling[a]



entry	ligand (complex)	base (equiv)	trapping efficiency (%)	radiochemical purity (%)	radiochemical yield (%)
1	$L_1 = L_2 = PPh_3$ (**19**)	TEA (1)	–	–	–
2[b]	L_1, L_2 = XantPhos (**20**)	DBU (4)	16	23	4
3[c]	L_1, L_2 = XantPhos (**20**)	DBU (4)	36	10	4
4[d]	L_1, L_2 = XantPhos (**20**)	–	–	–	–
5	L_1, L_2 = XantPhos (**20**)	DBN (4)	15	3	0.5
6	L_1, L_2 = XantPhos (**20**)	Proton-sponge (4)	6	–	–
7	L_1, L_2 = XantPhos (**20**)	TMGN (4)	22	–	–
8	L_1, L_2 = XantPhos (**20**)	Me-TBD (4)	38	55	21
9[e]	L_1, L_2 = XantPhos (**20**)	Me-TBD (4)	42	25	11
10[f]	**L_1, L_2 = XantPhos (20)**	**Me-TBD (6)**	**48 ± 7**	**55 ± 7**	**25 ± 4 (n = 3)**
11[g]	XantPhos (**18**)	Me-TBD (6)	21	<5	<1

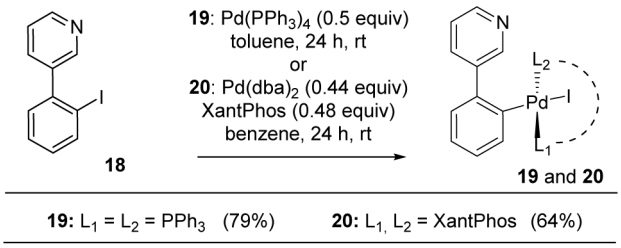
[a]Reaction conditions: **19**–**20** (22 mg, 20 μmol), **21** (7 mg, 18 μmol), and dioxane (0.7 mL) in a 5 mL crimp-cap vial under argon. Upon delivery of ^{11}CO, the reaction was heated to 95 °C for 10 min. See Supporting Information for full details. [b]90 °C. [c]100 °C. [d]The lithium amide of **21** (14 mg, 36 μmol) was used. See Supporting Information for full details. [e]115 °C. [f]Average of three reactions. [g]Aryl iodide **18** (5.6 mg, 20 μmol), $Pd(dba)_2$ (11.5 mg, 20 μmol), XantPhos (11.5 mg, 20 μmol), **21** (7.0 mg, 18 μmol), and Me-TBD (18 μL, 125 μmol) in dioxane (0.7 mL), 95 °C for 10 min with ^{11}CO.

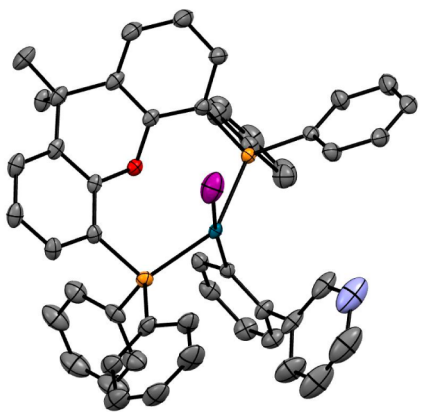
Scheme 4. Preparation of the P(t-Bu)$_3$ Ligated Aryl Palladium Complex 15[a]



[a]For full details, see Supporting Information.

Scheme 5. Preparation of the PPh_3 and XantPhos Ligated Aryl Palladium Complexes 19 and 20[a]





[a]For full details, see Supporting Information. ORTEP representation of **20**, 50% probability level.

dioxane led to remarkably clean conversion into ^{11}C-carbonyl labeled olaparib in a 99% radiochemical purity. Furthermore, in accordance with the findings in Table 1, the complex exhibited excellent trapping efficiency. Employing these conditions but starting from the corresponding aryl iodide **12** led to product formation in reduced radiochemical yield, mainly caused by inferior radiochemical purity (Table 3, entry 5).

[^{11}C]JNJ-31020028. Finally, ^{11}C-carbonyl labeling of the brain-penetrant human neuropeptide Y Y_2 receptor antagonist JNJ-31020028 was undertaken.[44] Labeling of this tracer is currently achieved through ^{11}C-methylation of the amide nitrogen to form the *N*-methylated analog.[45] Pd-catalyzed carbonylative assembly of this molecule from a nitrogen nucleophile **21** and a biaryl halide is complicated both by the *ortho*-pyridyl substituent on aryl halide **18** resulting in increased sterical hindrance and the poor nucleophilicity of the aniline. To this end, complexes **19** and **20** were synthesized. Attempts to prepare the P(t-Bu)$_3$ or cataCXium A ligated complexes unfortunately only led to decomposition of the starting material (Scheme 5).

Initial attempts on the aminocarbonylation with **19** and ^{12}CO demonstrated that the addition of base was essential for

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useful turnover. Therefore, Et_3N was applied, when complex **19** was reacted with amine **21** in the PET-setup. However, no ^{11}CO trapping was observed (Table 4, entry 1). On the other hand, the XantPhos ligated palladium complex **20** afforded product as determined by analytical HPLC, when DBU was used as the base, albeit not in a synthetically useful yield (entry 2). Increasing the reaction temperature only led to a trade-off with the trapping efficiency and the radiochemical purity (entry 3). Upon speculation of whether the low turnover could be related to the poor reactivity of the aniline coupling partner, an attempt was made to prepare the more reactive lithium amide by treatment of **21** with *t*-BuLi.[46] However, this approach again led to no improvement (entry 4). On the other hand, a profound effect of reactivity was observed when a series of other organobases were tested. With the bases DBN, proton-sponge, and TMGN only low trapping of the ^{11}CO gas was observed. But with the guanidine base Me-TBD, both the trapping efficiency and the radiochemical purity of the product increased dramatically (entry 8).

Raising the temperature had no beneficial effect (entry 9), but a slight improvement was brought about by increasing the amount of base to 6 equiv, thereby affording [^{11}C]JNJ-31020028 with a good purity profile and in a synthetically useful radiochemical yield of 25 ± 4% (entry 10) on an average of three reproducible reactions. Employing these conditions but starting from the corresponding aryl iodide **18** led to a poor trapping efficiency, and product formation was only observed in trace amounts (entry 11).

CONCLUSION

In conclusion, we have reported on the development of an oxidative addition complex strategy suitable for efficient ^{11}C-carbonyl labeling of structurally demanding motifs by means of aminocarbonylation employing ^{11}CO in a simple low pressure setup. This is a promising method, and in some cases, the use of pregenerated oxidative addition complexes was crucial for successfully producing the radiolabeled target structure in a synthetically useful yield. It is our belief that this strategy will pave the way for the use of transition metal mediated carbonylations employing ^{11}CO as a future labeling strategy for PET-tracers with clear benefits for diagnostic and drug development use.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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