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Palladium-Mediated [^{11}C]Carbonylation at Atmospheric Pressure: A General Method Using Xantphos as Supporting Ligand

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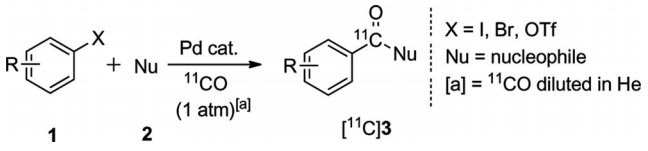
The palladium-catalyzed [^{11}C]carbonylation of aryl halides and triflates was achieved at atmospheric pressure by employing xantphos as the supporting ligand. Aryl halides were converted into their corresponding [^{11}C]amides in good to excellent yields. The conditions were also successfully employed in the radiolabeling of an [^{11}C]ester, a [^{11}C]carboxylic acid, an [^{11}C]aldehyde, and a [^{11}C]ketone.

Introduction

Of the available radionuclides for use in positron emission tomography (PET), the most interesting is arguably ^{11}C ($t_{1/2}$ = 20.4 min), as carbon is the main constituent in nearly all biologically active compounds.[1] Herein we describe a novel methodology for the incorporation of ^{11}C through transition-metal-mediated [^{11}C]carbonylation that is general, simple, and robust (Scheme 1). The method has the potential to bring wide access to the highly attractive but elusive synthon [^{11}C]carbon monoxide.



Scheme 1. Three-component Pd-mediated carbonylation to form an [^{11}C]carbonyl containing product.

Although many of the methods developed for synthetic organic chemistry can also be applied to the radiochemistry of ^{11}C, its properties impose several challenges. First of all, its short half-life precludes lengthy reactions and its high-energy radioactive emission requires that syntheses be carried out in lead-shielded fume hoods (hot cells). Furthermore, ^{11}C is initially delivered from the cyclotron in simple chemical forms, such as $^{11}CO_2$ or $^{11}CH_4$, and in minute amounts. This means that reactions may not be driven by access of the radiolabeled precursor.[1]

[^{11}C]Carbon monoxide (^{11}CO) has many attractive features as a synthon in PET chemistry, including its facile production and high versatility in transition-metal-mediated [^{11}C]carbonylation.[2] Despite the great potential of ^{11}CO, its widespread use has since long been hampered by the lack of a simple method for its introduction. It is believed that efficient radiolabeling with ^{11}CO is impossible without the use of high-pressure devices[3] (e.g., microautoclaves) or chemical ^{11}CO fixation reagents[4] (e.g., boron [^{11}C]carbonyl, CuTp^{11}CO, etc.) as a result of the low solubility of ^{11}CO in organic solvents.[5] However, recently two approaches were reported in which [^{11}C]carbonylation was achieved at near atmospheric pressure. Eriksson et al. elegantly demonstrated that ^{11}CO can be transferred to a sealed reaction vial without noticeable pressure increase by use of xenon gas.[6] However, only a few substrates were radiolabeled in that study. Concomitant with this work being finalized, Suzuki et al. reported on an oxidant-assisted methoxy[^{11}C]carbonylation of aryl boronates under atmospheric pressure.[7] This method produced a number of [^{11}C]esters in low to moderated yields but appears to be limited to the syntheses of [^{11}C]carboxylic acids and their methyl esters, as the reaction solvent mixture of methanol/dimethylformamide was essential for the reaction to proceed.

In an effort to develop a simple and versatile low-pressure method for the radiolabeling of molecules with ^{11}CO, we initiated a study focused on establishing a palladium–ligand complex in which the ^{11}CO is trapped as a part of the ^{11}CO insertion procedure. Recently, Buchwald et al. showed that lower CO pressures (1 bar) can be used in aminocarbonylation reactions when using the wider bite angle bidentate phosphane ligand xantphos as a supporting ligand.[8] Although the partial pressure of ^{11}CO in the reactor is expected to be much lower than 1 bar, we hoped the

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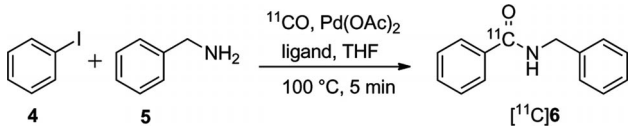
wider bite angle would enhance the reactivity enough to allow the [^{11}C]carbonylation to occur.[9] We were thus led to investigate a series of ligands in the amino[^{11}C]-carbonylation of iodobenzene.

Results and Discussion

The initial target was to discover a palladium complex that allowed the efficient trapping of ^{11}CO in solution. Thus, a series of bidentate phosphane ligands with ranging neutral bite angles from 78 to 110° (Table 1, entries 1–8) was tested by using *N*-benzyl-[carbonyl-^{11}C]benzamide ([^{11}C]**6**) as a model compound for the reaction. The monophosphane ligand PPh_3 and the biaryl monophosphane ligand Sphos were also included, as these ligands are frequently employed in carbonylation chemistry.[10] Despite the success of biaryl monophosphanes in Pd-catalyzed C–N bond-formation reactions,[11] Sphos was shown to be inefficient (Table 1, entry 9). Furthermore, the standard ligand for Pd-catalyzed [^{11}C]carbonylation reactions,[2] PPh_3, showed poor trapping efficiency (21%) and gave a low radiochemical yield (RCY) of the desired [^{11}C]benzamide (7.4%), which is in accord with earlier studies conducted with a similar design.[12]

Table 1. Effect of the ligand on the ^{11}CO trapping efficiency and the analytical radiochemical yield of *N*-benzyl-[carbonyl-^{11}C]-benzamide.[a]



4 **5** [^{11}C]**6**

Entry	Ligand[b]	Bite angle[c]	Trapped ^{11}CO[d] [%]	RCP[e] [%]	RCY[f] [%]
1	dppe	78	31	67	21
2	(*S*)-BINAP	92	18	17	3
3	dppp	95	63	49	31
4	dppb	99	40	24	10
5	dppf	106	85	35	30
6	DPEphos	108	55	34	19
7	xantphos	110	>99	54 ± 1[g]	54
8	dcpp	–	11	0	0
9	PPh_3	145	21	35	7
10	Sphos	217	9	42	4
11	*t*Bu-xantphos	140	12	18	2
12	EA-xantphos	–	34	35	12

[a] Conditions: Iodobenzene (20 μmol), benzylamine (100 μL), ligand (14–48 μmol), Pd source (14 μmol), THF (0.7 mL), 100 °C, 5 min. [b] Ligand abbreviations are given in the Supporting Information. [c] See ref.[8,13] [d] Decay corrected; the fraction of radioactivity left in the crude product after purging with nitrogen. [e] Radiochemical purity determined by radioanalytical HPLC. [f] Radiochemical yield based on the total radioactivity delivered to the reaction vial. [g] Average of three runs.

A number of bidentate ligands with previously demonstrated utility in Pd-catalyzed processes gave low to moderate yields (Table 1, entries 1, 2, 4 and 8), although dppp and dppf showed some promise, with fairly high trapping efficiency (TE) and RCYs near 30% (Table 1, entries 3 and 5). To our delight, xantphos provided a highly active catalyst and produced *N*-benzyl-[carbonyl-^{11}C]benzamide in 54 ± 1%, with an almost quantitative TE (Table 1, entry 7). This result is notable, as DPEphos and dppf have neutral bite angles that are similar to that of xantphos, but these ligands generated catalysts with quite disparate activity. The flexible backbone structure of xantphos (bite angle: 97–133°) may partly account for this phenomenon, as it is believed to induce a dynamic coordination environment that may be of importance for catalyst activity in transition-metal-catalyzed processes.[13] Further investigations using *t*Bu-xantphos and EA-xantphos (Table 1, entries 11 and 12) did not improve the catalytic system.

We continued our study by exploring whether $Pd(OAc)_2$ was the preferred palladium catalyst source for this reaction. A series of palladium(0) and palladium(II) catalysts was tested (Table 2). $PdCl_2$, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$ all formed active Pd–ligand complexes, with RCYs in the range of 78–92%. Remarkably, when using the palladium(II) catalyst, $Pd_2(\pi\text{-cinnamyl})Cl_2$, an almost quantitative conversion to *N*-benzyl-[carbonyl-^{11}C]benzamide was obtained. $Pd_2(\pi\text{-cinnamyl})Cl_2$ was therefore established as the preferred Pd source for the Pd-catalyzed [^{11}C]carbonylation.

Table 2. Effect of the Pd source on the ^{11}CO trapping efficiency and the analytical RCY of *N*-benzyl-[carbonyl-^{11}C]benzamide.[a]

Entry	Pd source	Trapped ^{11}CO [%]	RCP [%]	RCY [%]
1	$Pd(OAc)_2$	>99	54	54
2	$PdCl_2$	82	96	79
3	$Pd_2(dba)_3$	>99	93	92
4	$Pd(PPh_3)_4$	96	85	82
5	$Pd_2[\pi\text{-cinnamyl}]Cl_2$	>99	99 ± 1[c]	98
6	$Pd_2[\pi\text{-cinnamyl}]Cl_2$	61[b]	–	–

[a] Conditions: iodobenzene (20 μmol), benzylamine (100 μL), xantphos (14 μmol), Pd source (14 μmol), THF (0.7 mL), 100 °C, 5 min. [b] Test was conducted in a solution mixture of the Pd catalyst and xantphos without the aryl halide or benzylamine present. [c] Average of three runs.

To investigate the utility of this methodology with regard to solvent compatibility, some commonly used solvents were tested. To our delight, low-pressure [^{11}C]carbonylation proceeded in good yields in all examined solvents with RCYs above 76% (Table 3, entries 1 and 6–10). In addition,

Table 3. Effect of the solvent and reaction temperature on the analytical RCY of *N*-benzyl-[carbonyl-^{11}C]benzamide.[a]

Entry	Solvent	Temp. [°C]	Trapped ^{11}CO [%]	RCP [%]	RCY [%]
1	THF	100	>99	99.6	99
2	THF	80	98	98.3	97
3	THF	60	>99	96.4	95
4	THF	40	>99	92.5	92
5	THF	r.t.	98	88.6	87
6	1,4-dioxane	100	>99	99.4	98
7	toluene	100	>99	96.1	95
8	CH_3CN	100	>99	96.3	95
9	DMF	100	>99	85.6	85
10	DMSO	100	>99	77.6	77

[a] Conditions: iodobenzene (20 μmol), benzylamine (100 μL), xantphos (14 μmol), $Pd_2[\pi\text{-cinnamyl}]Cl_2$ (14 μmol), solvent (0.7 mL), r.t. to 100 °C, 5 min.

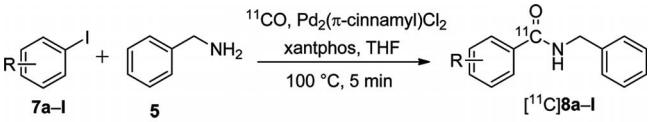
we also investigated the reaction at lower temperatures by using THF as the solvent (Table 3, entries 1–5). Notably, no obvious difference in TE was observed in the examined temperature range, but we did see a difference in product distribution with a 10% decrease in product formation at room temperature relative to that obtained at 100 °C. The RCY at 100 °C (99%; Table 3, entry 1) is, to the best of our knowledge, the best reported for *N*-benzyl-[carbonyl-^{11}C]-benzylamide. Although other solvents may be useful for carbonylation cross-coupling reactions other than aminocarbonylations,[10] THF was chosen for our continued study on the aminocarbonylation of some functionalized arenes.

With the optimized reaction conditions in hand (Table 2, entry 5), a series of aryl halides was successfully converted into their corresponding benzylamides (Table 4). Excellent RCYs (>96%) were obtained when using iodo- and bromobenzene (Table 4, entries 1 and 2) under the optimized conditions. Chlorobenzene, in contrast (Table 4, entry 3), was shown to be ineffective as a substrate under these conditions. Phenyl triflate was also included in the investigation (Table 4, entry 4) and produced *N*-benzyl-[carbonyl-^{11}C]-benzamide in good RCY. As expected, aryl iodides with electron-donating substituents gave excellent RCYs (Table 4, entries 9 and 10), whereas electron-withdrawing groups in the *ortho* position were more or less well tolerated (Table 4, entries 5–8). For example, the less deactivated substrate *o*-chloroiodobenzene gave an RCY of 82% (Table 4, entry 5), whereas *o*-dinitroiodobenzene only generated the desired product in 13% yield (Table 4, entry 8). Product yields were good to excellent when substrates containing electron-withdrawing groups were situated in the *para* position (Table 4, entries 11 and 12). As anticipated, the RCYs are strongly dependent on the nature of the substrate and its tendency to engage in oxidative addition with the Pd^0 complex.

To further test the scope of this methodology, we decided to apply this method to functional groups other than amides. Thus, an ester, a carboxylic acid, a ketone, and an aldehyde were prepared by using the conditions for the aminocarbonylation reaction with only minor modifications (Scheme 2). All investigated reactions showed high TEs and the products were formed in moderate to good yields. Although this shows that the scope extends beyond aminocarbonylation, there may be room for substantial improvements in the RCY of these compounds if conditions were optimized accordingly. In addition, microwave heating, with its well-known advantages over conventional heating could be an ideal improvement for this novel method.[14] Further investigations on the application of palladium-mediated [^{11}C]carbonylation are currently ongoing.

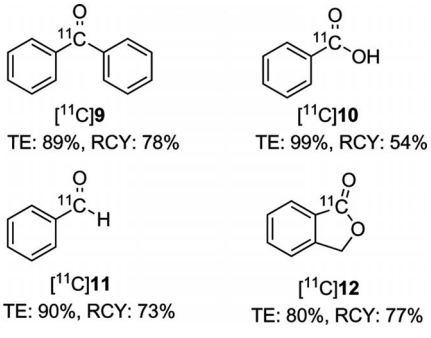
As a final testament to the utility of this method, a candidate radioligand for the histamine type-3 receptor, [^{11}C]**15**, was prepared by using the optimized conditions (Scheme 3). Compound [^{11}C]**15** was obtained with a RCY of 95% with a TE over 99%. In a preparative run, 4170 MBq (112.8 mCi) isolated product ([^{11}C]**15**) was obtained in a 88% decay-corrected RCY calculated from ^{11}CO delivered to reaction vessel. The RCP was greater than 97% and the specific radioactivity was 121 GBq μmol^{-1} (3280 Ci mmol^{-1}). The product identity was confirmed by co-elution on HPLC with UV and radioactive detection and LC–MS/MS.

Table 4. Effect of the nature of the substrate on the ^{11}CO trapping efficiency and the analytical RCY of the corresponding benzyl-[carbonyl-^{11}C]benzamide.[a]

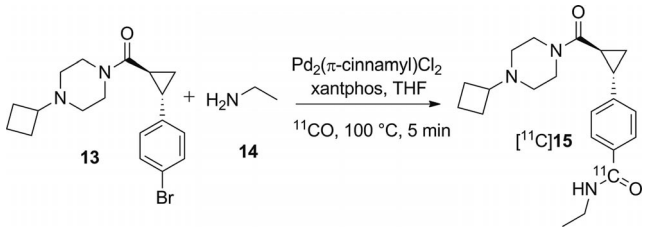


Entry	Substrate	Trapped ^{11}CO [%]	RCP[b] [%]	RCY [%]
1	**7a**	>99	99±1	98
2	**7b**	>99	97±1	96
3	**7c**	98	<1	<1
4	**7d**	>99	78±3	77
5	**7e**	98	84±4	82
6	**7f**	73	64±3	46
7	**7g**	61	70±5	43
8	**7h**	23	57±4	13
9	**7i**	>99	97±2	96
10	**7j**	>99	98±3	97
11	**7k**	>99	91±5	91
12	**7l**	66	72±3	48

[a] Conditions: substrate (20 μmol), benzylamine (100 μL), xantphos (14 μmol), Pd_2[π-cinnamyl]Cl_2 (14 μmol), THF (0.7 mL), 100 °C, 5 min. [b] Average of three runs.



Scheme 2. Structures, TEs and RCYs of prepared [^{11}C]ketone, [^{11}C]carboxylic acid, [^{11}C]aldehyde, and [^{11}C]ester.



Scheme 3. Radiosynthesis of the histamine type-3 receptor radioligand [^{11}C]**15**.

Conclusions

In summary, we herein described the development of a Pd-mediated [^{11}C]carbonylation protocol employing xantphos as the supporting ligand. The reaction proceeds at close to atmospheric pressure and at moderate temperatures with aryl halides or aryl triflates as substrates. In addition to the labeling of [^{11}C]amides, the protocol also demonstrated its utility in the radiosynthesis of an [^{11}C]ester, a [^{11}C]carboxylic acid, an [^{11}C]aldehyde, and a [^{11}C]ketone. Given the simplicity and efficiency of this method, it has great potential to allow [^{11}C]carbonylation reactions to be performed in a routine fashion with similar ease as [^{11}C]-methylations,[15] and we expect this novel method to be widely adapted in PET radiopharmaceutical research and development.

Experimental Section

General Procedure for the Low-Pressure [^{11}C]Carbonylation Reaction: $^{11}CO_2$ was reduced online to ^{11}CO by using a preheated quartz column (850 °C) charged with Mo powder. Unreacted $^{11}CO_2$ was subsequently removed by an ascarite trap, and the ^{11}CO was concentrated on a silica gel trap immersed in liquid nitrogen. After complete entrapment, the trap was heated to release the ^{11}CO into a vial (4 mL) containing the coupling reagents (aryl halide, Pd source, ligand, and amine dissolved in anhydrous THF) equipped with a rubber septum. The vial was heated at the desired temperature for 5 min, after which the vial was cooled to room temperature. The radioactivity was measured before and after the vial was purged with nitrogen. RCP of the crude reaction mixture was established with radio-HPLC. For a more detailed description of the reaction procedure see the Supporting Information.

Supporting Information (see footnote on the first page of this article): General methods, experimental procedures, spectroscopic data for new compounds. No NMR spectroscopic analysis was performed during this study, as all radioactive products were produced in insufficient quantities.

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