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N-heterocyclic carbenes as ligands in palladium-mediated [^{11}C]radiolabelling of [^{11}C]amides for positron emission tomography

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A model palladium-mediated carbonylation reaction synthesizing *N*-benzylbenzamide from iodobenzene and benzylamine was used to investigate the potential of four *N*-heterocyclic carbenes (*N*,*N*′-bis(diisopropylphenyl)-4,5-dihydroimidazolinium chloride (I), *N*,*N*′-bis(1-mesityl)-4,5-dihydroimidazolinium chloride (II), *N*,*N*′-bis(1-mesityl)imidazolium chloride (III) and *N*,*N*′-bis(1-adamantyl)imidazolium chloride (IV)) to act as supporting ligands in combination with $Pd_2(dba)_3$. Their activities were compared with other Pd-diphosphine complexes after reaction times of 10 and 120 min. $Pd_2(dba)_3$ and III were the best performing after 10 min reaction (20%) and was used to synthesize radiolabelled [^{11}C]*N*-benzylbenzamide in good radiochemical yield (55%) and excellent radiochemical purity (99%). A Cu(Tp*) complex was used to trap the typically unreactive and insoluble [^{11}C]CO which was then released and reacted via the Pd-mediated carbonylation process. Potentially useful side products [^{11}C]*N*,*N*′-dibenzylurea and [^{11}C]benzoic acid were also observed. Increased amounts of [^{11}C]*N*,*N*′-dibenzylurea were yielded when $PdCl_2$ was the Pd precursor. Reduced yields of [^{11}C]benzoic acid and therefore improved RCP were seen for III/$Pd_2(dba)_3$ over commonly used dppp/$Pd_2(dba)_3$ making it more favourable in this case.

Keywords: 11-carbon; carbon monoxide; palladium-catalysis

Introduction

There has been a significant growth in the use of the molecular imaging technique, positron emission tomography (PET), in biological research and drug development over the last 20 years.[1,2] Radiolabelled compounds can be tracked in real time giving an insight into drug delivery as well as biochemical processes. However, significant challenges still remain in the development of new radiolabelled compounds for imaging biological processes.[3] The most commonly used positron emitters are ^{11}C, ^{18}F, ^{15}O and ^{13}N and one of the key challenges in PET is to utilize the radionuclides within approximately three half-lives in order to maintain enough radioactivity for the scan. Carbon-11 is of particular interest due to its biocompatibility; however its short half-lifetime of 20.4 min drives the need for new methods to accelerate radiolabelling methodologies. The most common method for ^{11}C incorporation is methylation using [^{11}C]methyl iodide[4] or the more reactive [^{11}C]methyl triflate[5,6] but interest in utilizing [^{11}C]carbon monoxide[7] and [^{11}C]carbon dioxide[8] is growing as new techniques open up the field[9,10].

In [^{11}C]radiolabelling, transition metal-mediated processes play an important role due to their ability to speed up incorporation via activation of [^{11}C]carbon monoxide. Pd-mediated [^{11}C]carbonylation reactions have been widely applied in Suzuki-Miyaura, Stille and carboxyamination reactions for PET radiolabelling.[11–13] Here, the picomolar amounts of [^{11}C]CO used mean that the catalyst is actually in vast excess, so the process can be considered to be Pd-mediated rather than Pd-catalysed. The amide functionality is frequently found in biologically active compounds such as DAA1106 and analogues which are potential ligands for the peripheral benzodiazepine receptor.[14] Långström *et al*. have extensively studied palladium-mediated [^{11}C]carboxyamination as a route to [^{11}C]amides, combining a wide range of organic halides and triflates with amines, utilizing a microautoclave system and high pressures.[15–19] Recent low-pressure trapping and reaction methods using either borane[10] or copper complexes[9] present certain advantages in terms of their simplicity and ease of use.

As an alternative to the commonly used organophosphines, *N*-heterocyclic carbenes (NHC) have shown potential as ancillary ligands for many palladium-catalysed cross-coupling reactions,[20–22] including Suzuki–Miyaura coupling reactions,[23]

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Sonagashira cross-coupling[24] and Buchwald–Hartwig amination.[25] Their use in the carbonylation of aryl halides is a relatively unexplored area. Some work has been carried out investigating the use of NHCs in palladium-catalysed carbonylative Suzuki–-Miyaura cross couplings[26,27] and oxidative carbonylations, employing a copper co-catalyst to synthesize ureas, carbamates and 2-oxazolidinones;[28] however, the majority of the research has been carried out on hydroformylation reactions.[29] NHCs are considered to be more catalytically robust than phosphines and are found to be generally superior under harsher conditions owing to their greater stability at higher temperatures and greater tolerances to oxygen and moisture.

Amide synthesis from palladium carbonylation using NHCs as ligands has been carried out with aryl diazonium salts and aryl boronic acids in the only reported production of amides through carbonylation using NHCs.[30] The full capability of NHCs in Pd-catalysed carbonylation reactions for the synthesis of amides – an important functional group found in many pharmaceuticals – has not yet been fully explored. In this manuscript, we illustrate the comparable ability of NHC versus commonly used mono- and bi-dentate phosphines in the synthesis of amides over the timeframes of 10 min and 2 h, and the novel utilization of these ligands in PET radiolabelling experiments using [^{11}C]carbon monoxide via the use of a carbon monoxide trapping complex recently developed in our group.

Results and discussion

Ligand/catalyst evaluation

The initial target was to find an efficient Pd-NHC system to be applied to PET radiolabelling experiments. Thus, a series of imidazolinium and imidazolium salts were tested as ligands as well as palladium catalysts with phosphine and diphosphine ligands. Diphosphines are generally favoured in carbonylation reactions to monodentate phosphines[31] and it has been suggested that the bite angle plays a key role in improving the rate of related reactions.[32] A model reaction was used in order to evaluate the effect of the catalyst system on the formation of amide. In this case iodobenzene and benzylamine (used in excess as the solvent) were combined under static 0.2 bar pressure of carbon monoxide to synthesize *N,N*-benzylbenzamide (Figure 1). Pd-NHC species were prepared *in situ* by the reaction of imidazolinium or imidazolium salts (Figure 2) with the palladium(0) precursor $Pd_2(dba)_3$ in benzylamine. Reaction of the imidazolinium and imidazolium salts in the presence of excess benzylamine base resulted in the deprotonation of the salts and dissolution of the Pd-NHC complex when heated to 150°C. The relatively high temperatures used for these reactions may be expected to enhance the yields over short time periods (10 min) compared with lower temperatures and then eventually degrade the catalyst over sustained periods at this high temperature (2 h).

A range of well-known and widely used benchmark Pd-phosphine complexes (Figure 3) were also investigated for the model carbonylation reaction. Pd-monophosphine and chelating diphosphine catalysts have been widely investigated for a range of carbonylation reactions[33,34] and as such are useful for comparative purposes with the Pd-NHC catalysts. The results from the model aminocarbonylation reactions using phosphine ligands are shown in Table 1. In the case of

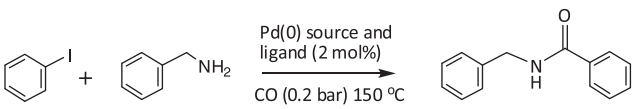


Figure 1. The model palladium-catalysed carbonylation reaction for the formation of *N*-benzylbenzamide.

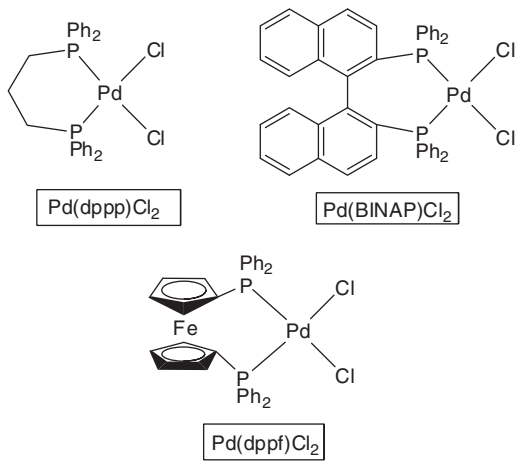


Figure 3. Palladium(II) diphosphine chloride complexes used for comparison within the model carbonylation reaction.

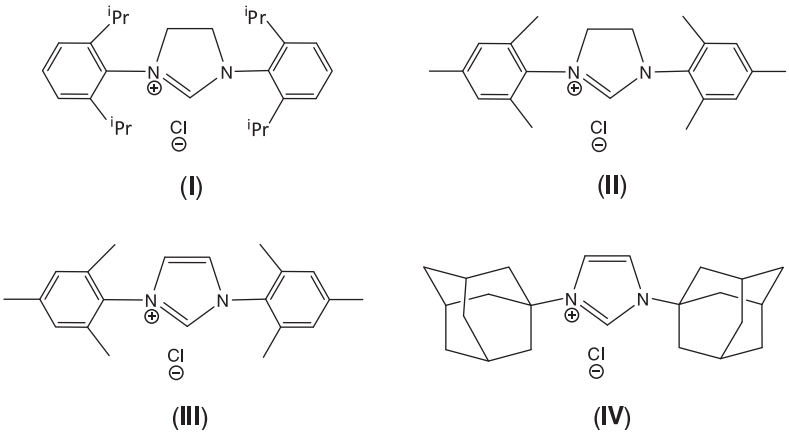


Figure 2. Structures of the four imidazolinium (**I**) and (**II**), and imidazolium (**III**) and (**IV**) salts used as NHC ligands.

tetrakis(triphenylphosphine)palladium there is no need for reduction of palladium(II) to form the catalytically active Pd(0) species prior to oxidative addition which could account for it having the highest yield after 10 min (Table 1, entry **1**). Diphosphine ligands such as bis(diphenylphosphino)propane (dppp) and bis(diphenylphosphino)ferrocene (dppf) are used extensively in catalysis and here they show moderate yields after 10 min. After 2 h, all the Pd-phoshine catalysts performed equally well giving yields of between 55 and 57%, suggesting that while the ligand–palladium system is important to the initial rate of the reaction it does not affect the yield over the longer timeframe.

Four imidazolinium and imidazolium chloride salts (*N*,*N*′-bis (diisopropylphenyl)-4,5-dihydroimidazolinium chloride (**I**), *N*,*N*′-bis(1-mesityl)-4,5-dihydroimidazolinium chloride (**II**), *N*,*N*′-bis (1-mesityl)imidazolium chloride (**III**) and *N*,*N*′-bis(1-adamantyl) imidazolium chloride (**IV**)) with varying electronic and steric properties (Figure 2) were investigated for the model carbonylation reaction. The objective was to examine the effect that the R groups and the saturated or unsaturated imidazole ring have on the reaction. It has been established that the electronic backbone of the imidazole rings can affect the rate of the oxidative addition step in the catalytic cycle.[35] Furthermore, bulky R groups such as adamantyl could aid the reductive elimination step, while the electronic effect of the R group on the system is not thought to contribute significantly.[36]

As seen previously for the phosphine ligands, similar yields in excess of 50% are observed after 2 h with the Pd-NHC catalysts; however, considerable variation is observed after 10 min (Table 2). Yields of the carbonylated product *N*-benzylbenzamide using the Pd-NHC catalysts over the 10-minute timeframe ranged from a low 4% (entry **10**) with the preformed catalyst Pd(**III**)$_2$Cl$_2$ to a reasonable 20% (entry **8**) for the *in situ* catalyst (formed from Pd$_2$(dba)$_3$ and ligand **III**). The lower yields of the preformed catalyst Pd(**III**)$_2$Cl$_2$ obtained after 10 min, initially surprising, are likely to be due to the slower reduction of this complex to the catalytically active Pd(0) species compared with its *in situ* equivalent which is prepared directly from the Pd(0) source Pd$_2$(dba)$_3$. There is evidence, however, that having two IMes moieties on the palladium can result in too strong an electron-donating effect which can prevent reductive elimination and therefore deactivation of the catalyst.[37] Pd$_2$dba$_3$ was used as the Pd source due to its good solubility in benzylamine which was used in excess as solvent. The basic environment was assumed to aid in the active complex formation although the exact structure of this is unknown. Supporting data for this assumption is shown by entry **11** in which Pd$_2$dba$_3$ on its own gives lower yields of amide after 10 min than the systems with imidazolium and imidazolinium hydrochloride salts (entries **6–9**). The Pd-NHC catalyst system with ligand **III** (Entry **8**) was chosen for subsequent radiolabelling studies using [^{11}C]carbon monoxide as it was the best performing catalyst system overall.

Table 1. Average yields of *N*-benzylbenzamide calculated by GC after 10 min and 2 h (average of three runs)

Entry	Pd source	GC Yield (%)	
		10 min	2 h
1	Pd(PPh$_3$)$_4$	18 ± 7	56 ± 2
2	Pd(PPh$_3$)$_2$Cl$_2$	13 ± 5	56 ± 1
3	Pd(dppf)Cl$_2$	14 ± 7	55 ± 2
4	Pd(dppp)Cl$_2$	15 ± 5	57 ± 2
5	Pd(BINAP)Cl$_2$	10 ± 2	57 ± 1

Table 2. Average yields of *N*-benzylbenzamide after 10 min and 2 h (average of three runs)

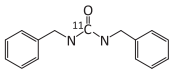
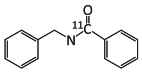
Entry	Pd source	Ligand	GC Yield (%)	
			10 min	2 h
6	Pd$_2$(dba)$_3$	I	12 ± 6	56 ± 3
7	Pd$_2$(dba)$_3$	II	16 ± 4	55 ± 1
8	Pd$_2$(dba)$_3$	III	20 ± 3	58 ± 1
9[a]	Pd$_2$(dba)$_3$	IV	11 ± 1	55 ± 0.2
10[a]	Pd(IMes)$_2$Cl$_2$	—	4 ± 0.2	57 ± 1
11[a]	Pd$_2$(dba)$_3$	—	9 ± 0.1	57 ± 2

[a]Average of two runs.

Radiolabelling experiments

Although [^{11}C]carbon monoxide is a valuable resource in radiolabelling, the low reactivity of carbon monoxide, as a result of its low solubility in most organic solvents, and high dilution in the inert carrier gas has prevented it from widespread use in PET chemistry. Previously, these issues have been overcome by the use of microautoclave systems which increase the pressure and therefore enhance the key carbon monoxide insertion step effectively but these methods require specialized equipment.[38,39] Chemical complexation can also be an effective method of improving [^{11}C]CO reactivity by increasing its solubility at low partial pressures. Such systems include BH$_3$.THF[10] and Cu(I)[9] solutions; the latter can trap [^{11}C]CO with efficiencies of over 95% compared with approximately 1% in solvent alone. The novel [^{11}C]CO chemical trapping method, exploiting a [Cu(Tp*)] complex, recently developed in our group[9] was used to test the best performing Pd-NHC catalyst system for [^{11}C] carbonylation radiolabelling. The CuTp* trapping system was chosen for the NHC carbonylation radiolabelling experiments as the trapping process can be carried out at room temperature in a one-pot process. Following formation of the Cu(Tp*)[^{11}C]CO complex, the cross coupling reagents (Pd precursor, ligand, iodobenzene, benzylamine) were added to the trapping vial and the reaction mixture heated for 10 min. The reaction was quenched and the crude product mixture analysed by analytical radio-HPLC (Table 3). The results of the [Cu(Tp*)] radiolabelling procedure for the model carbonylation reaction using the best performing NHC ligand (**III**) from the initial screening as well as the phosphine ligand dppp for comparison are shown in Table 3. Labelling reactions using **III** and Pd$_2$(dba)$_3$ *in situ* at 100°C produced three labelled products; two minor products [^{11}C]benzoic acid and [^{11}C]*N*,*N*′-dibenzylurea along with the major labelled product [^{11}C]*N*-benzylbenzamide (Table 3, entry **1**). [^{11}C]*N*,*N*′-dibenzylurea was observed in significant yield when using PdCl$_2$, which is in agreement with previous findings when a Pd(II) starting material is used[9]. Interestingly this product is not observed in the corresponding cold reactions, and the formation is attributed to the vastly different stoichiometries encountered between the 'cold' and 'hot' regimes potentially leading to an oxidative carbonylation mechanism. It is thought that the excess amount of Pd compared with [^{11}C]CO may cause this effect.

Table 3. Pd-mediated [^{11}C]carbonylation reactions using [Cu(Tp*)^{11}CO] and various Pd precursors and ligands

#	Pd source	Ligand	Temp. (°C)	RCP (%)[a]			RCY (%)[b]
				[^{11}C]benzoic acid	[^{11}C]*N*,*N*-dibenzylurea	[^{11}C]*N*,*N*-benzyl benzamide	
							
1	$Pd_2(dba)_3$	III	100	9	5	86	54 ± 10
2	$Pd_2(dba)_3$	III	120	0	1	99	55 ± 10
3	$PdCl_2$	III	120	3	59	38	11 ± 10
4	$Pd_2(dba)_3$	dppp	120	14	0	86	61 ± 5

Average of two runs for each entry.
[a]Radiochemical purity determined from radio-analytical HPLC.
[b]Radiochemical yield based on the starting radioactivity of the [Cu(Tp*)^{11}CO] complex and corrected for decay to end of bombardment.

The resultant loss of radiolabelled *N*,*N*′-benzylbenzamide at 120°C (Entry **3**) leads to a lowering of the radiochemical yield compared with the yields when using Pd_2dba_3 (Entry **2**). This could be due to the poor solubility of $PdCl_2$ in DMF, but also because the required oxidative addition of iodobenzene is suppressed owing to the slower generation of the active Pd(0) catalyst from $PdCl_2$ compared with directly using $Pd_2(dba)_3$. The copper(I) complex used for the trapping step is not thought to play a role in the oxidative carbonylation process in the case.[9]

An increase in temperature from 100 to 120°C has a significant effect on the amount of [^{11}C]benzoic acid formed from the hydrolysis of the Pd(II)-acyl complex. This indicates that less of the acyl intermediate is present at the end of the reaction before addition of the aqueous quench due to a more efficient reductive elimination at higher temperatures. Interestingly, when ligand **III** is used (Entry **2**) a significant improvement in the radiochemical purity of [^{11}C]*N*-benzylbenzamide formation is observed compared with when the chelating diphosphine 1,2-bis(diphenylphosphinopropane) is used as the ligand (Entry **4**). Almost full conversion to [^{11}C]*N*,*N*′-benzylbenzamide (99%) is observed with the NHC system whereas there is still a significant amount of [^{11}C]benzoic acid (14%) using the diphosphine which diminishes the amount of amide formed. This indicates that the reductive elimination step is slower using dppp/$Pd_2(dba)_3$ than for **III**/$Pd_2(dba)_3$ which has a noticeable impact on the yield of the desired labelled amide compound. The overall, greater efficiency may be attributed to the greater electron-donating ability of carbenes versus phosphines and their stability at higher temperatures.

Conclusion

In conclusion, NHC ligands perform similarly to a range of commonly used phosphine ligands for palladium-catalysed aminocarbonylation reactions over a 2 h reaction period. When reaction times were reduced to 10 min significant differences were observed with the *in situ* NHC catalyst system **III**/$Pd_2(dba)_3$ giving the highest yield. When applied to [^{11}C]CO palladium-mediated aminocarbonylation reactions, using the [Cu(Tp*)] trapping technique, the NHC ligand **III** proved to give good RCYs and excellent RCPs that surpassed a commonly used Pd-phosphine ligand system. Interestingly, there appears to be an enhancement of the reductive elimination step for the NHC catalyst at higher temperatures, which is evident by the suppression of [^{11}C]benzoic acid formation. We are currently investing the scope of using NHC ligands for a wider range of substrates for [^{11}C]CO Pd-mediated reactions under high-temperature reaction conditions.

Experimental

General

All carbonylation reactions were carried out on a Radley's Carousel 12 Place Reaction Station and a Heidolph heating plate fitted with a temperature probe. Quantitative analysis was carried out via gas chromatography on a Hewlett-Packard 5890 GC fitted with an Agilent 6690 autosampler and a flame ionization detection system. The products were separated on a SGE forte BP1 capillary column; length 25 m, I.D. 0.22 mm, film thickness 0.25 mm. Quantification was achieved by calculating the response factor from *N*-benzylbenzamide and diphenylether as the internal standard (purchased from Sigma-Aldrich). In all cases samples for GC analysis were made up in 1.5 mL vials using 0.2 mL of reaction mixture and 1.3 mL of diphenylether in DCM (0.0126 M) as an internal standard. All other chemicals were purchased from Sigma-Aldrich, BOC Ltd. or Strem Chemicals Inc. Further purification was carried out where stated. [$PdCl_2$(dppp)], [$PdCl_2$(dppf)] and [$PdCl_2$(BINAP)] were formed by stirring [$PdCl_2$(cod)] and 1 equivalent of corresponding diphosphine in DCM at room temperature for 30 min. The product was filtered and washed with hexane and dried *in vacuo*.

General catalyst evaluation procedures

Iodobenzene (1 mmol, 0.112 mL, 1 eq.) was added to a stirred solution of the catalyst (0.02 mmol, 2 mol%) dissolved in benzylamine (5 mL) at 150°C under an atmosphere of carbon monoxide; this was taken to be the start of the reaction. Samples (0.5 mL) were taken after 10 min and 2 h and analysed using gas chromatography.

Radiochemistry

Radiolabelled [^{11}C]CO_2 was produced on a Siemens cyclotron from a N_2 (1% O_2) target, with a beam current of 5 μA and a bombardment time of 5 min. The [^{11}C]CO_2 was converted to [^{11}C]CO via an Eckert and Ziegler modular lab system which uses

a molybdenum reductant (850°C) and delivered to the hot cell. Unconverted [^{11}C]CO_2 was collected on an ascarite trap.

General radiolabelling procedure

CuCl (11 μmol, 1.1 mg, 1 eq.) and KTp* (11 μmol, 3.7 mg, 1 eq.) was weighed into a 5 mL glass vial and placed under a N_2 atmosphere. Dry THF (1 mL) was added to form the trapping solution. A [^{11}C]CO/He gas stream was delivered to the vial, forming the CuTp*[^{11}C]CO complex. Following this, the cross-coupling reagents ($Pd_2(dba)_3$ (1.01 mg, 1.1 μmol, 20 mol %), IMes.HCl (0.75 mg, 2.2 μmol, 20 mol %), iodobenzene (2.3 mg, 11 μmol, 1 eq.), benzylamine (0.1 mL, excess) and triphenylphosphine (5.8 mg, 22 μmol, 2 eq.) in 0.9 mL DMF) were added to the vial using an Argon gas sweep. The vial was sealed and the mixture heated for 10 min after which time it was quenched by addition of 1 mL NH_4OAc (pH 4.9) under an Argon gas sweep. Finally, the radioactivity of the reaction vial was measured and the crude mixture analysed by analytical HPLC. The reaction mixture was analysed on an analytical radio HPLC (Agilent 1100, 60:40 water:acetonitrile, flow rate 1.5 mL/min, fitted with an Agilent Eclipse XDBC18, 5 μm, 4.6 × 150 mm column). During each step the radioactivity of the waste gases was measured in order to calculate incorporation of [^{11}C]CO and radiochemical yields based on the starting radioactivity of the CuTp*[^{11}C]CO solution.

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