Copper(I) scorpionate complexes and their application in palladium-mediated [^{11}C]carbonylation reactions

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Received (in Cambridge, UK) 30th March 2009, Accepted 23rd April 2009
First published as an Advance Article on the web 7th May 2009
DOI: 10.1039/b906166e

Solutions of copper(I) tris(pyrazolyl)borate complexes have been used to greatly improve the solubility of [^{11}C]carbon monoxide, enabling it to be used in low-pressure, 'one-pot' palladium-mediated carbonylation reactions to form ^{11}C-radiolabelled amides and ureas for use in positron emission tomography.

Positron emission tomography (PET) is a powerful imaging technique that uses radiolabelled compounds as molecular probes to study biological processes *in vivo*. In addition to its well-established role in disease diagnostics,[1] PET can benefit the drug development process by providing valuable biodistribution and receptor occupancy data using sub-pharmacological doses of radiolabelled drug candidates.[2] Despite the great wealth of information that PET tracers can provide, their preparation is not trivial.[3] ^{11}C, for example, is an important positron-emitting radionuclide due to the ubiquity of carbon in biologically-active compounds. However, its use is hindered by its short radioactive half-life (20 minutes), compounded by the handling restrictions imposed when working with ionising radiation.

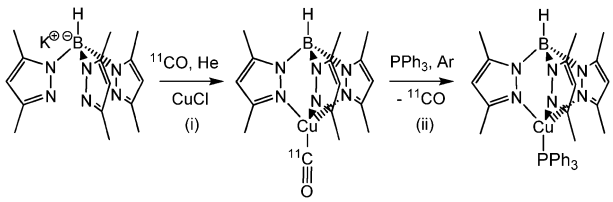
[^{11}C]carbon monoxide is an appealing ^{11}C labelling reagent as it can be incorporated into a range of biologically-relevant molecules, usually through metal-catalysed [^{11}C]carbonylation reactions.[4] However, the widespread use of this gas has been restricted by poor reactivity as a consequence of low solubility in organic solvents and its high dilution in inert carrier gases. The last decade has seen ^{11}CO emerge as a viable labelling reagent through the use of microautoclave reactors which enhance the reactivity of the gas using high pressures (>350 bar).[5,6] In order to broaden the scope of [^{11}C]carbonylation reactions we have been exploring low-pressure techniques which could enhance the reactivity of ^{11}CO by increasing its solubility through a process of chemical complexation.[7] Here we present a simple one-pot procedure for efficient ^{11}CO trapping using a copper(I) tris(pyrazolyl)borate solution, and its applications in palladium-mediated [^{11}C]carbonylation reactions to form [^{11}C-*carbonyl*]amides as well as a new pathway to [^{11}C-*carbonyl*]ureas.

Solutions of copper(I) halides have a history of reversible CO absorption, and typically rely on a weakly-bound carbonyl ligand which allows dissociation to be achieved through lowering the pressure or purging the solution with an inert gas.[8] Such systems would not be suitable for trapping ^{11}CO at high dilution in an inert carrier gas stream as it might be prone to undesired ^{11}CO loss. In order to achieve a high trapping efficiency without the need for time consuming recirculation of the gases, our studies focussed on complexes that could bind ^{11}CO relatively strongly, such that subsequent decarbonylation could only be triggered by a chemical means, for example, the introduction of a competing ligand.

Tris(pyrazolyl)borate (Tp) ligands[9,10] were deemed an ideal partner for copper(I) in our studies due to their electron-releasing properties which serve to strengthen the copper–carbonyl bond through backbonding. Indeed, the Tp ligand was used to form the first stable[11] and crystallographically characterised[12] copper(I) carbonyl complex, Cu[Tp]CO. Commercially-available potassium tris(3,5-dimethylpyrazolyl)-borate (K[Tp*]) was employed in our studies due to its increased organic solubility over its non-methylated analogue. Importantly, the negative charge of the Tp* ligand results in a neutral copper(I) complex thus eliminating the need for non-coordinating counter ions which may interfere with reactivity and reduce organic solubility.

While it has been reported that Cu[Tp*]CO could be formed by prolonged bubbling of unlabelled CO through an acetone solution of K[Tp*] and CuCl,[13] this would not be acceptable for use with ^{11}CO due to the very small quantities of the gas produced (picomoles) and the short radioactive half-life of ^{11}C. Such small quantities of ^{11}CO might benefit the trapping process as there will be a large excess of the copper complex in solution. In our experiments,† 11 μmol of K[Tp*] and CuCl in 1 ml THF was used as the ^{11}CO trap, providing approximately a 10^5 fold excess of trapping reagents (Scheme 1) over ^{11}CO.

Control reactions were performed initially, to observe the extent of ^{11}CO trapping in solvent alone, or with only one component (CuCl or K[Tp*]) in solution. As expected, the solubility of ^{11}CO in THF was extremely poor, with $<1\%$ of the ^{11}CO remaining in the vial after a single sweep of the



Scheme 1 (i) Trapping of ^{11}CO *via* the formation of Cu[Tp*]^{11}CO. (ii) ^{11}CO release by addition of triphenylphosphine.

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Table 1 ^{11}CO trapping and release reactions

Entry	Trapping reagents[a]	CO trapping[b] (%)	CO release[b] (%)
1	THF only	<1[c]	—
2	CuCl	<1[c]	—
3	K[Tp*]	<1[c]	—
4	CuCl + K[Tp*]	96 ± 6[d]	99 ± 1[c]

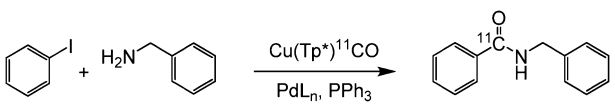
[a] 11 μmol of reagents in 1.0 ml THF. [b] Calculated as a fraction of the radioactivity of the vial at the end of the reaction compared to the untrapped waste gases. [c] Average of 3 runs. [d] Average of 14 runs.

^{11}CO–He gas stream (Table 1, entry 1). Using CuCl produced a suspension which displayed similarly poor trapping (entry 2). In the last of the control experiments, a K[Tp*] solution was used, again showing minimal trapping of ^{11}CO (entry 3). Solutions of CuCl and K[Tp*] produced an average trapping efficiency of 96% (entry 4)—a vast improvement over the control reactions, thus showing suitability of this system for efficient ^{11}CO trapping.

Since displacement of the carbonyl ligand in Cu[Tp*]CO is known to occur by addition of a competing phosphine donor (which favourably binds to copper(I)),[11,14] we proceeded to examine this reaction in our setup by addition of triphenylphosphine (two equivalents with respect to CuCl) to the solution of Cu[Tp*]^{11}CO whilst passing a stream of argon through the solution. This resulted in almost complete (99%) displacement of the radioactivity from the vial to waste in one minute, indicating that ^{11}CO release occurs rapidly, without the need to heat the solution.

Having successfully used the CuCl–K[Tp*] system for efficient ^{11}CO capture and release, we sought to use the ^{11}CO for *in situ* [^{11}C]carbonylation reactions, rather than displacing it from the vial. Our studies focused on palladium-catalysed carbonylation reactions between aryl halides and amines to produce [^{11}C-*carbonyl*]amides—a functional group found in many important drug targets and natural products. We selected the synthesis of [^{11}C]*N*-benzylbenzamide from iodobenzene and benzylamine as a model reaction to test the Cu[Tp*]^{11}CO system. These reactions were performed by addition of the carbonylation reagents (iodobenzene, benzylamine, palladium catalyst and triphenylphosphine) to a solution of Cu[Tp*]^{11}CO, followed by heating the sealed vial for 10 minutes (Scheme 2).† Following this, the reaction was quenched by addition of water, and the crude product analysed by high performance liquid chromatography (HPLC).

Use of an *in situ* catalytic species generated from $Pd_2(dba)_3$ and 1,3-bis(diphenylphosphino)propane (dppp) obtained the best results, producing [^{11}C]*N*-benzylbenzamide in 84% radiochemical purity and decay-corrected radiochemical yield of 67% (Table 2, entry 1). In these reactions, the radiochemical purity was reduced due to the formation of small amounts (<15%) of [^{11}C]benzoic acid, presumably

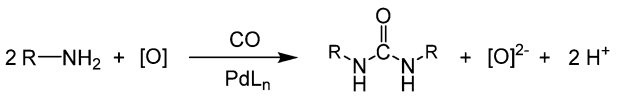


Scheme 2 [^{11}C]carbonylation reaction between iodobenzene and benzylamine, using a solution of Cu[Tp*]^{11}CO as the source of ^{11}CO.

Table 2 Palladium-mediated [^{11}C]carbonylation reactions using Cu[Tp*]^{11}CO solutions: formation of [^{11}C]*N*-benzylbenzamide and [^{11}C]dibenzylurea

			RCP[ac] (%)		RCY[bc] (%)	
Entry	Catalyst species	Temp./°C	Amide	Urea	Amide	Urea
1	$Pd_2(dba)_3$ + dppp	100	84 ± 6	2 ± 1	67 ± 2	2 ± 1
2	$Pd(dppp)Cl_2$	100	20 ± 3	70 ± 9	13 ± 2	45 ± 6
3	$Pd(dppp)Cl_2$	100	0	92 ± 7	0	47 ± 6
4	—	100	0	0	0	0

[a] Radiochemical purity determined by radio-analytic HPLC. [b] Radiochemical yield based on total radioactivity delivered to the vial and corrected for decay to end of bombardment. [c] Average of 3 runs.



Scheme 3 Urea formation *via* palladium(II)-catalysed oxidative carbonylation of amines. [O] = co-oxidant.

formed from hydrolysis of small amounts of Pd(II) acyl intermediate present at the end of the reaction. Using the palladium(II) species, $Pd(dppp)Cl_2$, however, resulted in the formation of significant amounts (70%) of a ^{11}C-labelled side product which dramatically reduced the amide yield as evidenced by radio-HPLC (entry 2). Given the limited number of possible radiolabelled products which could form, it was proposed that this species might be [^{11}C]dibenzylurea, formed *via* the oxidative carbonylation of two benzylamine molecules. The identity of this product was confirmed by its co-elution with an unlabelled reference sample of dibenzylurea.[15] While oxidative carbonylation of amines has been reported as an effective means of synthesising ureas using unlabelled CO (Scheme 3),[16–25] to our knowledge, this pathway has not been reported for use in ^{11}C radiolabelling experiments.

Since the urea functionality features in many pharmaceuticals, versatile radiolabelling approaches to these compounds are highly sought after. Most commonly, ^{11}C-labelling of ureas has been achieved using [^{11}C]phosgene,[26–28] a method which is hindered by synthetic difficulties and poor reproducibility. In order to explore the viability of this new radiolabelling method, attempts were made to improve the purity of [^{11}C]dibenzylurea in our setup. In these experiments, iodobenzene was removed from the reagent mixture thus excluding amide–acid formation. This led to the formation of [^{11}C]dibenzylurea in high radiochemical purity (92%) and moderate radiochemical yield (Table 2, entry 3) in the crude reaction mixture. Since previous studies into Pd(II)-mediated [^{11}C]carbonylation reactions[7,29] had not reported urea formation, we explored the possibility of a copper-mediated process occurring in our experiments. In order to test this hypothesis, control reactions were performed in the absence of any palladium species and in otherwise identical conditions (entry 4). These reactions resulted in no formation of radiolabelled products, suggesting that [^{11}C]dibenzylurea formation is palladium-mediated, although a tandem palladium/copper-mediated process cannot be ruled out. Further investigations are currently underway to elucidate the precise nature of the

co-oxidant species, and to examine the scope of this reaction towards a range of amine substrates including the formation of unsymmetrical ureas.

In summary, we have used a copper(I) tris(pyrazolyl)borate complex to significantly improve the solubility of ^{11}CO at room temperature and pressure. These ^{11}CO solutions open up a new means of performing [^{11}C]carbonylation reactions for PET tracer synthesis. The application of this system in palladium-mediated [^{11}C]carbonylation reactions has led to an efficient and versatile method of synthesising either ^{11}C-labelled amides or ureas, depending on the choice of palladium catalyst used. This new approach to ^{11}C-labelled ureas may prove to be an important tool in the synthesis of radiopharmaceuticals. We are currently examining the use of ^{11}CO solutions for rapid [^{11}C]carbonylation reactions performed on microfluidic devices.

Notes and references

† Experimental procedure: [^{11}C]carbon dioxide was produced using a Siemens Eclipse HP cyclotron by 11 MeV proton bombardment of a target containing nitrogen and 1% oxygen. ^{11}CO was produced using an Eckert and Ziegler reduction module by passing $^{11}CO_2$ over a molybdenum reductant at 850 °C. In a typical experiment, the trapping solution was prepared by addition of CuCl (1.1 mg, 11 μmol) and K[Tp*] (3.7 mg, 11 μmol) to a 5 mL V-bottomed glass vial, flushing with nitrogen for 15 min followed by addition of anhydrous THF (1.0 mL). The carbonylation reagents were prepared by addition of Pd(dppp)Cl_2 (1.3 mg, 2 μmol), PPh_3 (5.8 mg, 22 μmol) and iodobenzene (2.3 mg, 11 μmol) to a second vial, flushing with nitrogen for 15 min, followed by addition of benzylamine (0.1 ml) and anhydrous dimethylformamide (0.4 ml). The aqueous quench, a pH 4 ammonium formate buffer solution (0.5 ml), was added to the third vial. [^{11}C]Carbon monoxide was delivered to the trapping solution in a helium carrier gas stream where it was bubbled through the solution at a flow rate of 20 mL min^{-1}. All waste gases were collected in a bag and their radioactivity monitored in dose calibrator. Following delivery of the ^{11}CO to the vial, the carbonylation reagents were added and the vial sealed and heated at 100 °C in a heating block. After 10 min at this temperature the vial was allowed to cool for one minute at which point the quench was added under a stream of argon, causing any unreacted CO to be pushed from the vial into the waste bag. The vial was then removed from the hot cell, its radioactivity measured and a 20 μL aliquot was removed for analytical HPLC analysis (solvent: 60 : 40 H_2O–acetonitrile, flow: 1.5 mL min^{-1}, column: Agilent XDB C_{18} {5 μm, 4.6 × 150 mm}).

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