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PAPER

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

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Palladium dimers with sterically hindered phosphines have been shown to be excellent pre-catalysts for the aminocarbonylation of aryl halides to yield amides and one of them has been successfully employed as a pre-catalyst for the synthesis of ^{11}C-radiolabelled amides for PET imaging.

Introduction

Positron emission tomography (PET) is a non-invasive imaging technique that is primarily used as a research and clinical diagnostic tool for generating an understanding of diseases such as cancer, Alzheimer's and Parkinson's.[1] Fundamentally, all PET procedures rely on the synthesis of a positron emitting tracer and its administration to a subject prior to scanning. The preparation of PET tracers is however an extremely challenging area of synthetic chemistry mainly because of the time restraints imposed by short half-lives of the commonly used positron emitting isotopes nitrogen-13 ($t_{1/2}$ = 9.96 min), oxygen-15 ($t_{1/2}$ = 2.04 min), carbon-11 ($t_{1/2}$ = 20.4 min) and fluorine-18 ($t_{1/2}$ = 110 min).[2] The rapid growth of PET imaging and its applicability for the study of a wide range of diseases and conditions has stimulated the need to develop novel approaches for labelling a new generation of PET tracers to probe underlying biological processes. Of the common PET radioisotopes ^{11}C is particularly attractive for radiotracer synthesis since carbon is the main constituent of all biological molecules which are likely to be of interest for PET studies. Although $^{11}CH_3I$ has traditionally been the precursor of choice for carbon-11 labelling, more recently [^{11}C]carbon monoxide has been demonstrated to be an attractive precursor because of its ease of production and synthetic versatility.[3] [^{11}C]carbon monoxide has been used to prepare a wide range of ^{11}C labelled molecules, such as amides, esters and carboxylic acids, that would be inaccessible using traditional $^{11}CH_3I$ labelling techniques. Synthesis with [^{11}C]carbon monoxide is generally achieved *via* metal mediated reactions using either palladium or rhodium and involves the reaction of aryl, heteroaryl or vinyl halides with a nucleophile in the presence of ^{11}CO.[2] However, besides the conventional difficulties of processing carbon-11 reactions within the necessary short timeframes (typically within 2 half-lives, *i.e.* 40 min), [^{11}C]carbon monoxide reaction processes are further hampered by its poor reactivity. This poor reactivity is a consequence of both the inherent low solubility of CO in common organic solvents and the unavoidable high molecular dilution of ^{11}CO in inert carrier gases which results in very low partial pressures of ^{11}CO. A number of methods, including high pressure reactors,[4] microfluidics[5] and solution trapping[6] have now been reported to enhance ^{11}CO labelling procedures.

The type of catalyst used for carbonylation reactions is well known to have a marked effect on the rate of reaction, product yields and selectivities.[7] Most conventional carbonylation studies are conducted over longer time periods, typically hours to days, where there is a desire to design robust and long lived catalytic species in order to maximise product yields.[8] Transition metal-mediated [^{11}C]carbonylation reactions on the other hand require catalysts that are highly active over the short timeframes typical of ^{11}C labelling reactions in order to achieve high radiochemical yields. The activity of the catalyst used for ^{11}CO labelling protocols may therefore be crucial to enhancing ^{11}C labelling methods for PET. There are indeed a very limited number of reported catalysts that can perform carbonylative coupling reactions with amines and alcohols at atmospheric pressure of CO[9] and, more importantly, over short periods of time[10] (it should be noted that most reported reactions times are over 1 h which would be too long for applications into ^{11}C labelling with ^{11}CO).

Previously our group has reported the synthesis of palladium dimeric complexes **1–4**[11] which have been demonstrated to be very effective pre-catalysts for amination reactions of aryl chlorides and bromides[11d] and for Suzuki cross-coupling reactions.[12] Importantly, extremely high conversions were observed in these reactions over short reaction times (under 10 min) which are typically desired for ^{11}C labelling protocols. Based on these observations, we hypothesised that these palladium dimers could also be effective

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Table 1 Comparison of catalysts in the aminocarbonylation of iodobenzene with benzylamine[a]

	THF (60 °C)	Toluene (100 °C)		Mesitylene (150 °C)	
Complex	Yield [%][b]	Conversion [%][b]	Yield [%][b]	Conversion [%][b]	Yield [%][b]
1	5	45	33	57	45
2	5	45	22	56	43
3	35	76	64	99	87
4	30	98	88	99	86
4	—	—	—	99[d]	84[d]
5	13	38	27	94	80
5	—	—	—	52[d]	42[d]
6	29	89	64	91	74

[a] Main product *N*-benzylbenzamide. Reaction conditions: iodobenzene (0.45 mmol), benzylamine (4.6 mmol), solvent (0.5 mL), complex (2.2 mol%), 10 min. Average of two or more reactions. For details see Supplementary Information. [b] Isolated yields and conversions determined by GC using diphenyl ether as internal standard and based on iodobenzene. A control experiment demonstrated that about 7% of iodobenzene is lost during the cannulation, thus generally leading to higher conversions and lower yields. [c] 2–3% α-ketoamide formed by double carbonylation was observed as by-product with all the complexes. [d] Reaction performed within 5 min.

pre-catalysts for carbonylative coupling reactions. Thus, herein we present our investigations on the catalytic activity of palladium dimeric complexes **1–4** (Fig. 1) for the aminocarbonylation reaction of aryl halides and present initial results on ^{11}CO labelling reactions using one of these dimers (**4**).

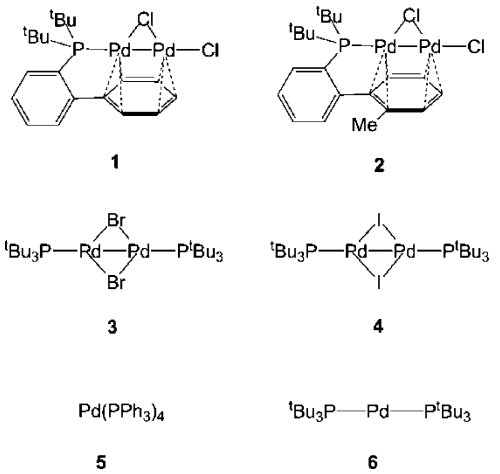
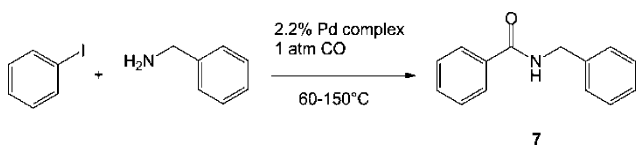


Fig. 1 Palladium complexes investigated as catalyst for carbonylative coupling reactions.

Results and discussion

Aminocarbonylation reactions mediated by Pd dimers

The well characterised aminocarbonylation of iodobenzene and benzylamine to form *N*-benzylbenzamide (**7**) (Scheme 1) was selected as an initial model reaction for our studies. Pd dimeric complexes **1–4** were investigated for their catalytic activity in this model reaction along with the benchmark Pd^0 complexes [Pd(PPh$_3$)$_4$] (**5**) and [Pd(P^{t}Bu$_3$)$_2$] (**6**) for comparative purposes.

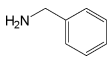
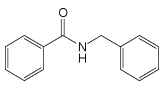
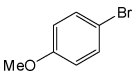
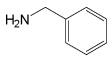
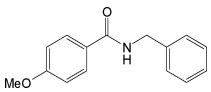
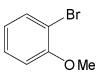
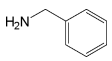
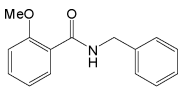
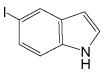
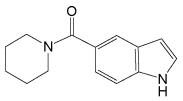
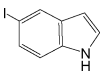
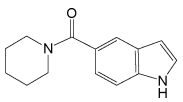


Scheme 1 Model reaction used to study the catalytic activity of complexes **1–6**.

All reactions were performed over 10 min reaction periods, to reflect the timescale of a typical ^{11}C labelling reaction, under 1 atm of carbon monoxide. Since solvent and temperature are often key parameters in catalytic reactions that greatly influence reaction rate, yield and catalyst decomposition, a series of different solvents were screened (THF, toluene and mesitylene) over a range of temperatures (60, 100 and 150 °C). The results from these screening reactions are summarised in Table 1. This aminocarbonylation reaction has previously been reported to be highly dependent on the reaction temperature;[7b,13] the results shown in Table 1 further confirm this with all catalysts giving low yields in THF at 60 °C and significantly higher yields at higher temperatures (100 °C and 150 °C using toluene and mesitylene respectively). The type of catalyst used is also observed to have a pronounced effect on product yields. The palladium bi-aryl phosphine dimeric complexes **1** and **2** were shown to have only modest catalytic activity for the aminocarbonylation reaction of iodobenzene even under the higher temperature conditions using toluene or mesitylene. In contrast, Pd^I dimers **3** and **4** exhibited excellent catalytic activities at 100 °C using toluene as solvent and were superior to the benchmark catalyst [Pd(PPh$_3$)$_4$] (**5**) but comparable in activity to [Pd(P^{t}Bu$_3$)$_2$] (**6**). Remarkably [Pd$_2$(μ-I)$_2$(P^{t}Bu$_3$)$_2$] (**4**) gave almost quantitative conversion of iodobenzene and exceptionally high isolated yields of the *N*-benzylbenzamide product (88%) at 100 °C in toluene within 10 min. Even when 1.1 mol% of **4** was used so that the Pd mol% was equal to that of the monometallic compounds (2.2 mol%), a 74% isolated yield of the amide (*cf*. 88%) was obtained. Although this is *ca*. 15% lower than the yield obtained when using 2.2 mol% of **4**, it suggests that only one of the two Pd centres from **4** is actively involved in the catalysis.

At higher temperatures of 150 °C in mesitylene over a 10 min reaction time quantitative conversions of iodobenzene were again achieved by complexes **3** and **4**. When the reaction time was reduced further to only five minutes complex **4** again gave quantitative conversions of iodobenzene (99%) and very high isolated yields (84%) of *N*-benzylbenzamide. In comparison, [Pd(PPh$_3$)$_4$] gave only modest conversions (52%) and yields (42%) under identical conditions. We believe this is a particularly interesting

Table 2 Screening of iodo- and bromo- substrates with complex **4**

Aryl halide	Amine	Product	Conditions	Conv [%][a]	Yield [%][a]
		 **7**	150 °C Mesitylene 10% (**4**)	55	46
		 **8**	150 °C Mesitylene 10% (**4**)	54	46
		 **9**	150 °C Mesitylene 10% (**4**)	48	46
		 **10**	100 °C Toluene 2.2% (**4**)	83	82
			100 °C Toluene 2.2% (**5**)	63[b]	59[b]

Reaction conditions: Aryl, heteroaryl halide (0.45 mmol), amine (4.6 mmol), solvent (0.5 mL), complex (**4**) (10 or 2.2 mol%), 10 min. Results shown are the average of two or more reactions. For details see Supplementary Information.[a] Yields and conversions determined by GC using diphenyl ether as internal standard and calculated on the aryl- or heteroaryl-halide. [b] $[Pd(PPh_3)_4]$ (**5**) employed as pre-catalyst.

finding as it demonstrates that carbonylation reactions can be very efficiently performed at low carbon monoxide pressures within remarkably short timeframes.

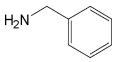
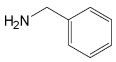
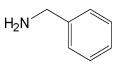
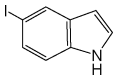
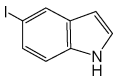
Complex **4** was selected for further catalytic evaluation because of the excellent yields obtained within short timeframes and also because of its air and moisture stability compared to complex **3**. A selection of more challenging aryl-bromides containing deactivating electron donating methoxy groups were therefore tested for the aminocarbonylation reaction with benzylamine (Table 2). Unfortunately using 2 mol% loading of complex **4** did not give satisfactory conversions within the set 10 min timeframe. Increasing the catalyst loading to 10 mol% did, however, result in a significant improvement in conversions. Bromobenzene, 4-bromoanisole and 2-bromoanisole were successfully converted at 150 °C to their corresponding *N*-benzylamides in 10 min with modest conversions ranging from 48–55%. Interestingly the deactivating methoxy groups had no significant effect on conversions or yields compared to bromobenzene over this timeframe. The scope of catalyst **4** was further investigated by performing the aminocarbonylative coupling of 5-iodoindole with piperidine at 100 °C in an attempt to synthesize the known central nervous system 5-HT_{2A} receptor ligand **10**.[14] Complex **4** was demonstrated to give high yields (82%, Table 2) of the indole amide **10** within 10 min at 1 atm of CO. In comparison, under the same reaction conditions, $[Pd(PPh_3)_4]$ (**5**) gave a modest 59% yield. Previously reported carbonylation methods for the preparation of **10** only gave high yields when CO pressures were 25 bar and reaction times exceeded 12 h,[15] however it must be noted that the more challenging 5-bromoindole substrates were used in these cases.

^{11}C-labelling *via* carbonylative cross coupling

Once we had established that dimer **4** acts as an excellent pre-catalyst for carbonylative cross-couplings under 10 min reaction times, it was of interest to investigate its applicability for radiolabelling experiments with ^{11}CO. The carbonylative coupling of iodobenzene with benzylamine to form *N*-benzylbenzamide, and of 5-iodoindole with piperidine to form **10** were selected as model reactions to test ^{11}CO labelling efficiency.

In addition to carrying out the reactions with dimer **4**, we also investigated the catalysis using $[Pd(PPh_3)_4]$ (**5**) for comparison. To overcome the problems associated with ^{11}CO radiolabelling reactions described above (low solubility and low partial pressures) a CO-trapping complex, recently reported by our group,[6b] was used to perform ^{11}CO syntheses. The copper(I) tris(3,5-dimethylpyrazolyl)-borate [CuTp*] complex was found to be a highly efficient reagent for both trapping ^{11}CO and performing palladium mediated ^{11}C carbonylative coupling reactions. In a typical radiolabelling procedure a stream of ^{11}CO in helium carrier gas was passed through a solution of [CuTp*] in toluene. On average >95% of radioactivity was found to be retained in the [CuTp*] in toluene solution. The palladium complex (**4** or **5**) and the corresponding aryl iodide (previously dissolved in anhydrous and degassed toluene) were then injected to the [CuTp*^{11}CO] solution and the vial heated to 120 °C for 2 min

Table 3 Results from [^{11}C]carbonylation reactions using complex **4** and **5** as catalyst

Entry	Aryl halide	Amine	Conditions/catalyst	Trapped radioact. [%][a]	^{11}C Amide RCP [%]	^{11}C Amide RCY [%]
1			50 eq. amine Catalyst: **4**	87	81	70
2			5 eq. amine Catalyst: **4**	72	68	47
3			5 eq. amine Catalyst: **5**	60	17	9
4			5 eq. amine Catalyst **4**	78	88	69
5			5 eq. amine Catalyst: **5**	61	36	22

Reaction conditions: Aryl/heteroaryl iodide (50 μM), amine (see table for equivalents used with respect to the aryl iodide), toluene (100 μL), palladium complex (6.4 mol% of Pd with respect to aryl iodide), 10 min reaction time. The results shown are the average of two or more reactions. For details see Supplementary Information.[a] Decay corrected radioactivity trapped in the reaction vial expressed as a fraction of total of activity (*i.e.* combination of activity in reaction and unreacted gases in the bag). [b] Decay corrected RCY (radiochemical yield) based on total radioactivity delivered to the reaction vial and corrected for RCP (radiochemical purity).

to initiate the reaction. After this time, the corresponding amine (*i.e.* benzylamine or piperidine) was injected and the reaction mixture heated for a further 8 min. The reaction was then purged with argon to remove unreacted ^{11}CO which was measured and collected in a bag in a dose calibrator. The radioactivity remaining in the reaction vial was then measured. A 20 μL aliquot was removed and analysed by analytical radio-HPLC to determine the distribution of radiolabelled products (RCP). As can be seen from Table 3, the main product from the reaction between iodobenzene and a large excess of benzylamine (50 eq. – entry 1) was the expected [*carbonyl*-^{11}C]*N*-benzylbenzamide obtained in high radiochemical yield (70%). A small amount of ^{11}C by-product (<16%) identified as [*carbonyl*-^{11}C]dibenzylurea, was also formed.

The radiochemical yields of [*carbonyl*-^{11}C]*N*-benzylbenzamide using complex **4** as a catalyst show a marked improvement compared to other phosphine or *N*-heterocyclic carbene based catalysts used for this reaction.[6b,16] We were then interested to evaluate whether the carbonylative coupling reaction with **4** as a catalyst would still proceed with only a slight excess of benzylamine (5 eq. with respect to iodobenzene – see entry 2). Although a decreased radiochemical yield (47%) is observed for this reaction (entry 2 Table 3), dimer **4** still proved far superior to the benchmark [$Pd(PPh_3)_4$] (**5**) catalyst (9% – entry 3) at these lower concentrations. To explore further the applicability of **4** in radiolabelling experiments with ^{11}CO, the aminocarbonylative coupling reaction of 5-iodoindole with piperidine to yield **10** (which is, as indicated above, a ligand for the 5-HT_{2A} receptor) was investigated. As can be seen in Table 3, entry 4, this reaction gave a high decay-corrected radiochemical yield (RCY) of the ^{11}C-labelled amide (69%) even though only 5 eq. of amine were used. This is considerably higher than the yield obtained (22%) for the same reaction when using the benchmark catalyst [$Pd(PPh_3)_4$].

Conclusions

In conclusion, it has been demonstrated that palladium dimer **4** is an excellent pre-catalyst for the carbonylative coupling of amines and aryl iodides (and bromides) giving, in some cases, practically quantitative yields of the corresponding amide. A particularly important feature of this complex in comparison to most previously reported catalytic systems is that it gives high yields within very short reactions times (under 10 min) and under atmospheric pressure of CO. These features allowed us to demonstrate the applicability of complex **4** for the synthesis of radiolabelled amides using ^{11}CO gas. The Pd dimer complex **4** (which can be readily prepared and is air stable) proved to be a clearly superior catalyst compared to the widely used [$Pd(PPh_3)_4$] benchmark both for our model [^{11}CO] aminocarbonylation and for the preparation of a biologically relevant [*carbonyl*-^{11}C]indole amide. Importantly, this was achieved even when the amine is present in only a slight excess – conditions that might be important in radiotracer synthesis where the amine may not be readily available and hence large excess quantities cannot be easily used.

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