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Synthesis of Acyl Carbamates via Four Component Pd-Catalyzed Carbonylative Coupling of Aryl Halides, Potassium Cyanate, and Alcohols

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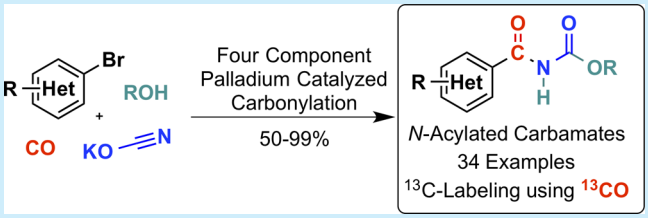
Supporting Information

ABSTRACT: A simple and mild method is demonstrated for assembling acyl carbamates through a base-free four-component Pd-catalyzed carbonylation of aryl halides in the presence of potassium cyanate and alcohols in a two-chamber system. This approach produces a wide range of aryl acyl carbamates in good to excellent yields from the corresponding aryl bromides or iodides with near-stoichiometric carbon monoxide. In addition, the method can be extended to the synthesis of primary amides thereby expanding the usefulness of cyanate as an ammonia equivalent.



N-Acyl carbamates represent a widely common functional group found in bioactive compounds such as antimalassezia agents,[1a] antibiotics,[1b] *O*-acyl-transferase inhibitors,[1c] pro-drugs,[1d] and insecticides.[1e] Furthermore, acylated carbamates are used as linkers for phototriggers due to their unique cleavage properties upon photolysis, or even as directing groups in nucleoside synthesis.[2,3]

Traditionally, *N*-acyl carbamates are obtained through the reaction of acyl halides with carbamates or from the treatment of amides with chloroformates.[4] These structures have also been obtained through the ozonolysis of substituted phenyl-oxazoles, oxidation of alkylated carbamates, and others.[5−7] Alternatively, the condensation of acyl isocyanates with alcohols has been shown to provide the desired *N*-acyl carbamates.[8] Despite these different approaches, all of them lack a broad functional group compatibility or require the synthesis of labile compounds, such as the acyl chlorides or acyl isocyanates.[9−11]

With our interest in Pd-catalyzed carbonylation reactions,[12,13] and recent reports by the laboratories of Buchwald, Baghersad, and Ma on the Pd- and Cu-catalyzed couplings of aryl halides with sodium or potassium cyanates (NaOCN or KOCN, respectively), we examined an alternative approach for the formation of acyl isocyanates.[14,15] As the moisture sensitive nature of acyl isocyanates limits their purification, possibly their *in situ* formation by the three-component coupling of aryl halides, CO, and a suitable metal cyanate would be a unique approach to these reactive intermediates. Finally, in the presence of alcohols, the acyl isocyanates would generate the desired *N*-acyl carbamates in a single reaction setup. In this letter, we report on the identification of such conditions for the coupling of aryl and heteroaryl bromides in the presence of KOCN and an alcohol. Furthermore, by introduction of water as the nucleophile, an alternative route to primary amides was secured.

For our optimization studies, 4-bromoanisole was chosen. CO (1.1−1.5 equiv) was delivered using the previously described COware/COgen setup.[16] Isopropyl alcohol was used as both the solvent and nucleophile, and the reactions were run at 80 °C for 18 h. Applying $Pd(cod)Cl_2$ in combination with BINAP as the ligand, 22% conversion into isopropyl (4-methoxybenzoyl)carbamate (**1**) was detected by ^1H NMR analysis of the crude reaction mixture (Table 1, entry 1). After a short ligand screening, Xantphos proved efficient affording **1** in an 86% isolated yield (Table 1, entries 2−4). Other Pd-sources were tested for their activity without improving the isolated yield (Table 1, entries 5−7). Lowering the reaction temperature to 70 °C provided **1** in a near-quantitative yield (Table 1, entry 8). Further reduction of the reaction temperature led to incomplete conversion, and the use of KOCN proved important (Table 1, entries 9 and 10). The reaction was complete in 8 h, whereas shorter reaction times led to incomplete transformation (Table 1, entries 11 and 12). While the amount of CO required for the reaction could be lowered to 1.1 equiv, the initial 5 mol % of both Xantphos and $Pd(cod)Cl_2$ was necessary (Table 1, entries 13−15). Finally,

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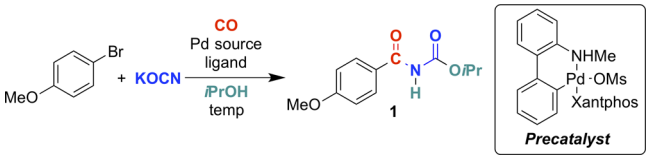
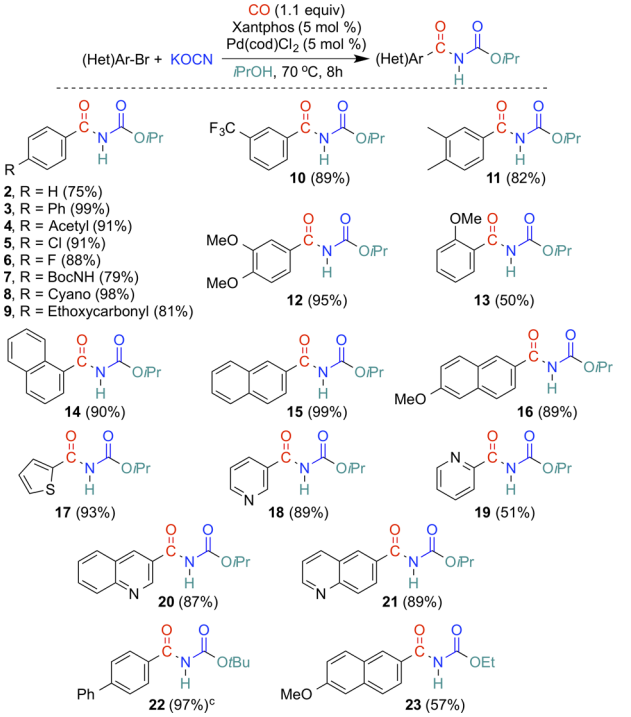
Table 1. Optimization Studies for the Synthesis of *N*-Acyl Carbamate 1[a]



entry	catalyst (mol %)	ligand (mol %)	conversion[b] (%)
1	$Pd(cod)Cl_2$ (5.0)	BINAP (5.0)	22
2	$Pd(cod)Cl_2$ (5.0)	PPh_3 (10.0)	0
3	$Pd(cod)Cl_2$ (5.0)	PPF-*t*Bu (5.0)	>95 (43)
4	$Pd(cod)Cl_2$ (5.0)	Xantphos (5.0)	>95 (86)
5	$[Pd(cinnamyl)Cl]_2$ (2.5)	Xantphos (5.0)	>95 (83)
6	$Pd(OAc)_2$ (5.0)	Xantphos (5.0)	>95 (80)
7	$Pd(dba)_2$ (5.0)	Xantphos (5.0)	50
8[c]	$Pd(cod)Cl_2$ (5.0)	Xantphos (5.0)	>95 (99)
9[d]	$Pd(cod)Cl_2$ (5.0)	Xantphos (5.0)	20
10[e]	$Pd(cod)Cl_2$ (5.0)	Xantphos (5.0)	56
11[f]	$Pd(cod)Cl_2$ (5.0)	Xantphos (5.0)	>95 (96)
12[g]	$Pd(cod)Cl_2$ (5.0)	Xantphos (5.0)	60
13[f,h]	$Pd(cod)Cl_2$ (5.0)	Xantphos (5.0)	>95 (90)
14[f,h]	$Pd(cod)Cl_2$ (2.5)	Xantphos (2.5)	>95 (72)
15[f,h]	$Pd(cod)Cl_2$ (1.0)	Xantphos (1.0)	70
16[d]	Precatalyst (2.0)	–	>95 (87)

[a]Chamber A: COgen (0.75 mmol), $HBF_4(tBu)_3P$ (1.0 mol %), $Pd(cod)Cl_2$ (1.0 mol %), Cy_2NMe (1.5 mmol) in dioxane (3.0 mL). Chamber B: 4-bromoanisole (0.50 mmol), KOCN (0.75 mmol), Pd source (*x* mol %), ligand (*y* mol %) in *i*PrOH (2.0 mL) at 80 °C for 18 h. [b]Determined by ^1H NMR, isolated yields shown in brackets. [c]Reaction performed at 70 °C. [d]Reaction performed at 50 °C. [e]0.75 mmol of NaOCN. [f]Reaction time 8 h. [g]Reaction time 5 h. [h]1.1 equiv of COgen.

Scheme 1. Scope of the Pd-Catalyzed Synthesis of Acyl Carbamates[a,b]



[a]Chamber A: COgen (0.55 mmol), $HBF_4(tBu)_3P$ (1.0 mol %), $Pd(cod)Cl_2$ (1.0 mol %), Cy_2NMe (1.1 mmol) in dioxane (3.0 mL). Chamber B: aryl bromide (0.50 mmol), KOCN (0.75 mmol), $Pd(cod)Cl_2$ (5.0 mol %), Xantphos (5.0 mol %) in *i*PrOH (2.0 mL) at 70 °C. [b]Isolated yields. [c]Catalyst **1a** (2.0 mol %) was used.

the Xantphos-precatalyst developed by Buchwald et al. proved highly reactive, even at 50 °C affording a good 87% isolated yield of **1** (Table 1, entry 16).[17]

With the identified optimal reaction conditions in hand, several substituted aromatic and heteroaromatic bromides were tested, the results of which are depicted in Scheme 1. Initially, 4-substituted aryl bromides were tested; substitutions including fluorine, Boc-protected anilines, nitriles, and others, and all products **2**–**9** were isolated in yields ranging from 75–99%.

3-Trifluoromethylphenyl bromide along with the xylyl- and the di-*O*-methyl catechol bromide afforded the desired *N*-acylated carbamates in high yields (compounds **10**–**12**, 89%, 82%, and 95%, respectively). Substituents placed *ortho* to the bromide, as with 2-bromoanisole, led to a reduction in isolated yield (**13**). Next, 1-bromo-, 2-bromo-, and 2-bromo-6-methoxynaphthalenes were tested with isolated yields ranging from 89% to 99% (compounds **14**–**16**). Heteroaromatic bromides such as thiophene, pyridines, and quinolines, all but one, provided the desired products in almost identical 90% isolated yields (compounds **17**–**21**). Only 2-bromopyridine provided a somewhat lower yield of 51% of **19**. Finally, EtOH and *t*-BuOH were tested as the solvent and nucleophile. The more bulky *tert*-butanol provided an almost quantitative yield of **22** whereas ethanol gave a 57% yield of **23**. The lower yield of **23** was related to the competing formation of the corresponding ethyl ester.

Next, the possibility of applying other alcohols as nucleophiles, though only in stoichiometric amounts, was examined. Applying the near-identical catalytic system consisting of the $Pd(cod)Cl_2$/Xantphos combination, CO (1.5 equiv), and the alcohol (2 equiv) in dioxane at 70 °C for 24 h proved effective (Scheme 2; see Supporting Information for optimization). Pentanol afforded **24** in a 91% isolated yield. Other aliphatic alcohols carrying terminal functionalities such as an alkene, chloride, trifluoromethyl group, *O*-methyl glycol, or a tetrahydrofuran moiety all proved reactive with isolated yields ranging from 62% to 92% (compounds **25**–**29**). Cyclopentanol afforded the desired *N*-acyl carbamate **30** in an excellent 97% yield. 4-Methoxybenzyl alcohol provided **31** in an 84% isolated yield.

Applying 2-iodophenol and 4-amino-3-iodobenzonitrile as the substrates yielded the heterocyclic structures **32** and **33** in 84% and 86% isolated yields, respectively, by intramolecular attack of the phenol or amine on the acyl isocyanate intermediates. Finally, with cholesterol, **34** was isolated in a good 75% yield. Substituting the alcohol for other nucleophiles, such as thiols or amines, provided either no conversion or the direct aminocarbonylated product, respectively.

As seen in Scheme 1, compound **22**, representing a Boc-protected amide, was obtained in high yield. Deprotection would lead to the primary amide, and two sets of acid promoted conditions for its deprotection were tested, namely, HCl in dioxane and TFA in CH_2Cl_2 (Scheme 3).[18] The latter provided primary amide **35** in a quantitative yield. Next, by the direct treatment of the crude carbonylation reaction mixture with TFA, **35** could be prepared in a one-pot fashion in an excellent 97% yield. By switching to iodoanisole as the electrophile, this same reaction sequence was repeated on a

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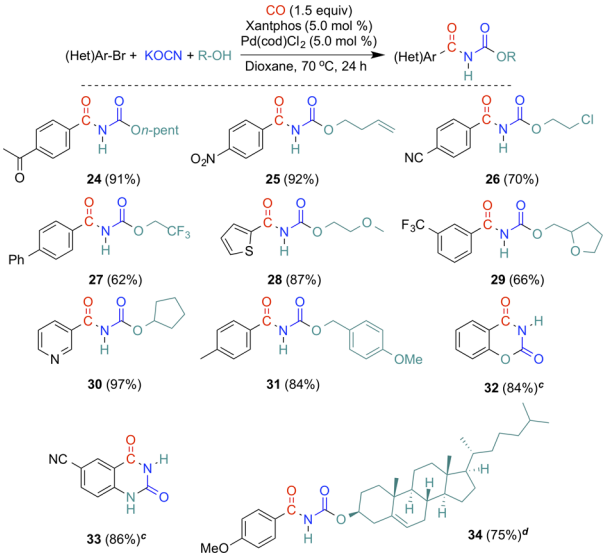
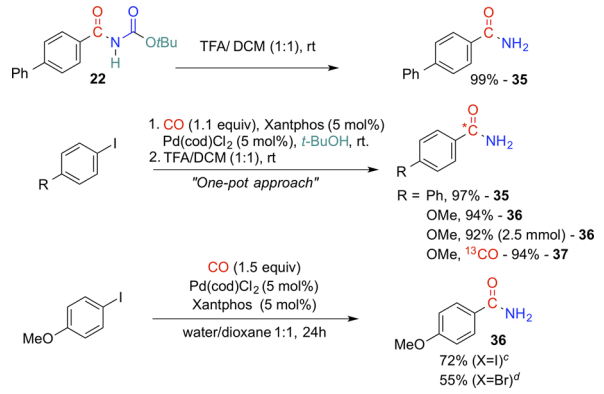
Scheme 2. Scope of the Pd-Catalyzed Synthesis of Acyl Carbamates with Different Alcohols in Dioxane[a,b]



[a]Chamber A: COgen (0.75 mmol), $HBF_4(tBu)_3P$ (1 mol %), $Pd(cod)Cl_2$ (1 mol %), Cy_2NMe (1.5 mmol) in dioxane (1.0 mL). Chamber B: aryl bromides (0.50 mmol), KOCN (0.75 mmol), $Pd(cod)Cl_2$ (5.0 mol %), Xantphos (5.0 mol %), alcohol (1 mmol) in dioxane (1 mL) at 70 °C. [b]Isolated yields. [c]Aryl iodides used as coupling partners. [d]Reaction time 48 h.

Scheme 3. Primary Amide Synthesis[a,b]



[a]Isolated yields. [b]See Supporting Information for reaction details. [c]Reaction run at rt. [d]Reaction run at 70 °C.

0.5 and 2.5 mmol scale without a decrease in yield of the desired primary amide **36**.

Applying ^{13}CO resulted in the isolation of the ^{13}C-isotope-labeled primary amide **37** in a 94% yield. Finally, it was envisioned that the implementation of water as the nucleophile, instead of *t*-BuOH, could provide the primary amide directly, by decarboxylation of the intermediately formed acylated carbamate. Indeed this proved possible and both 4-iodo- and 4-bromoanisole were transformed into **36**, however, in a slightly lower isolated yield of 72% and 55%, respectively.[19]

A mechanistic suggestion for the carbonylative transformation is depicted in Figure 1. Classical steps of oxidative addition (**A** to **B**), CO-insertion (**B** to **C**), and ligand exchange with KOCN forms complex **D**. Omitting the alcohol did not provide any aroyl cyanate, indicating that complex **D** does not undergo reductive elimination.[20] ArPd−NCO complexes have been shown to reluctantly undergo reductive elimination.[14b] Additionally, complex **D** carries two electron-withdrawing groups, thereby retarding the reductive elimination step even further.[21] Addition of an alcohol to the cyanate ligand forms the carbamate ligated complex **E**, thereby setting the stage for an efficient reductive elimination of ligands of opposed electronic nature.

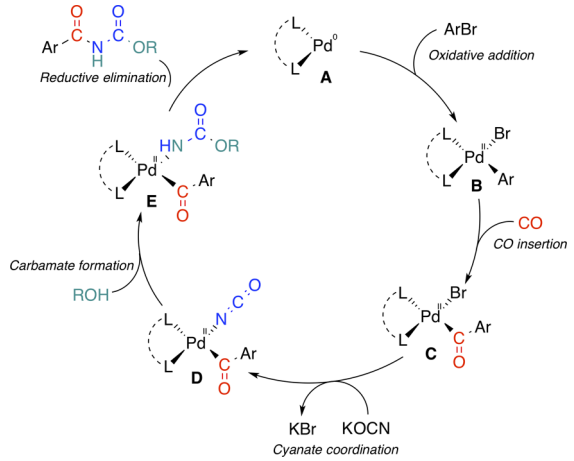


Figure 1. Proposed catalytic cycle.

In conclusion, a four-component, base-free, Pd-catalyzed carbonylative coupling of aromatic and heteroaromatic bromides with potassium cyanate in the presence of alcohols has been developed. Several alcohols proved reactive as nucleophiles, and further optimization eliminated their role as solvent. This mild and practical approach to acylated carbamates was extended to include the direct formation of primary amides, and isotope labeling thereof, in a one-pot setup.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic 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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(19) When using water as the nucleophile, the reductions in isolated yields were due to competing formation of the corresponding benzoic acid derivatives.
(20) Experiments were performed to rule out direct reaction of the potassium cyanate with the alcohol (forming $RO(CO)NH^-$ type intermediates). All attempts to trap this potential intermediate with electrophiles failed, indicating that reaction between the cyanate and the alcohol should take place on the preformed Pd-complex **D**.
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