Rhodium-catalyzed addition of organozinc iodides to carbon-11 isocyanates

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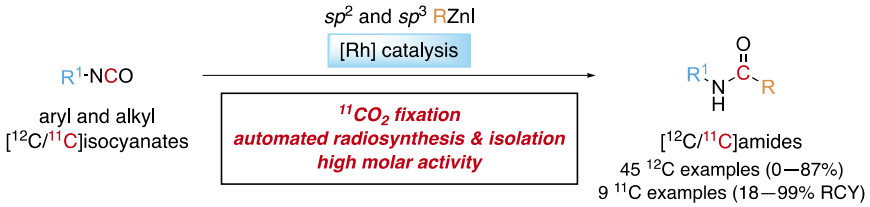
Supporting Information Placeholder



ABSTRACT: A synthetic pathway for PET-labeled amides is described using rhodium-catalyzed coupling of organozinc iodide reagents and *in situ* prepared carbon-11 isocyanates. A scope prepared using carbon-12 isocyanates yielded products from 13–87% using readily prepared sp^3 and sp^2 organozinc iodides. By manipulation of fixation, dehydration, and coupling conditions, the incorporation of [^{11}C]CO_2 into ^{11}C-amide products proceeded in moderate to strong yields, as determined by radioHPLC. Among the compounds prepared are the biologically-relevant *tert*-butyl protected [^{11}C]*N*-acetyl glutamic acid ([^{11}C]**6d**), the agrochemical [^{11}C]propanil ([^{11}C]**6f**), and a pharmaceutically-relevant [^{11}C]acetanilide ([^{11}C]**4m**). The synthetic utility of the labeling methodology was demonstrated through the isolation of [^{11}C]*N*-(4-fluorophenyl)-4-methoxybenzamide ([^{11}C]**6g**) with a molar activity of 267 GBq·μmol^{-1} and a radioactivity yield of 12%, 21 minutes after beginning of synthesis.

Positron emission tomography (PET) is a non-invasive nuclear medicine technology used for *in vivo* molecular imaging. Carbon-11 (^{11}C, $t_{1/2}$ = 20.3 min), a short-lived PET isotope, is commonly used for labeling small molecules and peptide radiotracer candidates, though its utility is limited by the availability of chemical methodologies suitable for its incorporation.[1,2] The abundance and diversity of organic frameworks in radiopharmaceuticals therefore calls for continued development of novel ^{11}C-labeling techniques to satisfy imaging needs.

Amides are a prodigious functional group in synthetic and biological molecules and amide bond formation is among the most commonly used and important reactions in drug discovery.[3,4] However, many powerful synthetic strategies using stable isotopes prove wasteful, impractical and/or ineffective when applied to carbon-11 radiochemistry. Conventional approaches to amide synthesis focus on acylation of an amine, and indeed the same can be accomplished using low molecular weight ^{11}C-acid chlorides.[5] Still, ^{11}C can only be produced in single carbon units, most frequently as [^{11}C]CO_2, and therefore more general methods directed at rapid formation of both the C–N and the C–C bonds of amides are needed to leverage existing medicinal chemistry approaches for radiotracer development.

Established methods for the preparation of ^{11}C-amides use amines and ^{11}C-carboxylic acids, the latter prepared from organolithium or Grignard reagents and [^{11}C]CO_2.[6] These syntheses require great care due to the use of reagents that can readily react with atmospheric CO_2 resulting in lower molar activity products. Recent advances using less reactive organometallic precursors for [^{11}C]CO_2-fixation[7,8] overcome this obstacle, but still require multistep activation to intermediate acid chlorides, which themselves often require purification.[9–12] Alternative synthetic approaches have been developed for ^{11}C-carbonylation with [^{11}C]carbon monoxide, using either preformed arylpalladium complexes[13] or alkyl iodide coupling mediated by nickel.[14] While these options are effective in synthesizing complex amide products, the limited availability of [^{11}C]CO curbs its widespread usage.

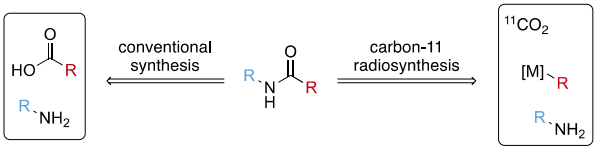


Figure 1. Strategies for stable isotope and carbon-11 amide synthesis.

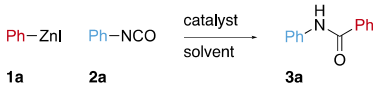
An alternative strategy toward ^{11}C-amides is to begin with ^{11}C–N formation, for example through an ^{11}C-isocyanate or ^{11}C-carbamyl chloride intermediate (Figure 1), followed by derivatization with a carbon-based nucleophile. Indeed, Grignard reagents have recently been successfully deployed in such a context for preparing ^{11}C-amides, although their elevated

reactivity and limited functional group compatibility may restrict practical applications in radiopharmaceutical synthesis.[15] Organozinc halides represent another class of organometallics offering greater stability towards many chemical moieties. Previously, a limited scope of amides had been prepared from allyl and propargyl organozinc halides and aryl isocyanates.[16] Direct addition of alkyl and benzyl organozinc halides to isocyanates did not, however, yield amides, but rather carbamates and urea byproducts. Foreseeing a potential direct route to ^{11}C-amides that could prove useful in PET radiochemistry, we set out to evaluate conditions redirecting organozinc halide reactivity with isocyanates towards selective C–N bond formation.

We herein report a transition metal-catalyzed coupling of organozinc iodides and isocyanates to produce a diverse scope of amides. This approach is effective with *in situ* prepared ^{11}C-isocyanates to generate ^{11}C-amides in suitable yields for radiotracer development.

Arylzinc iodides were the initial target for reaction discovery. First, the addition of phenylzinc iodide (**1a**) to phenyl isocyanate (**2a**) to produce benzanilide (**3a**) was used to develop coupling conditions (Table 1). Only trace product was detected in the absence of a catalyst (Table 1, entry 1). While $Pd(OAc)_2$ proved ineffective for improvement of conversion, $[Rh(Cl)(cod)]_2$ successfully yielded **3a** in 71% yield (entries 2–3). $[Rh(OH)(cod)]_2$ also demonstrated strong selectivity and conversion with a yield of 74% (entry 4). The yields were not further improved by the use of heat, which led to a slight increase in symmetrical diphenyl urea formation (entry 5). More polar solvents could also facilitate the reaction (entries 6–8), which would prove important for radiochemical applications. A significant drop in yield upon reversing the order of reactant addition indicated the importance of premixing the isocyanate with the catalyst before introducing organozinc iodides (entry 9).

Table 1. Optimization of arylzinc iodide reaction conditions.[a]

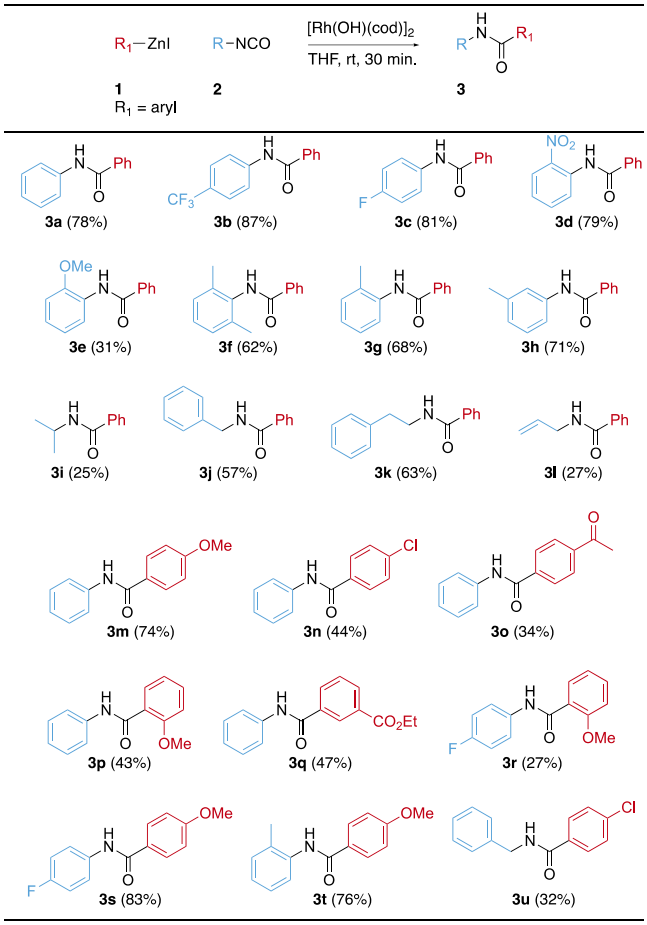


Entry	Solvent	Catalyst	Yield **3a** [%] [b]
1	THF	-	<5
2	THF	$Pd(OAc)_2$	<5
3	THF	$[Rh(Cl)(cod)]_2$	75,[c] 71
4	THF	$[Rh(OH)(cod)]_2$	78,[c] 74
5[d]	THF	$[Rh(OH)(cod)]_2$	68
6	Et_2O	$[Rh(OH)(cod)]_2$	30
7	ACN	$[Rh(OH)(cod)]_2$	62
8	DMSO	$[Rh(OH)(cod)]_2$	19
9[e]	THF	$[Rh(OH)(cod)]_2$	13

[a] Unless otherwise specified, reactions were carried out with **1a** (0.4 mmol), **2a** (0.2 mmol) in presence of 2.5 mol% catalyst in solvent (2 mL) at room temperature. [b] Yields were calculated using calibrated HPLC-UV peak integration. [c] Isolated yields. [d] Performed at 50 °C. [e] Reversed order of addition.

The scope of the reaction was evaluated for arylzinc iodides under the optimized conditions with various isocyanates (Table 2). Electron-deficient aryl isocyanates reacted smoothly, affording the products **3b–3d** in good yields. Conversely, coupling with electron-rich 2-methoxyphenyl isocyanate (**2e**) was accompanied by a reduced isolated yield (**3e**). One or more *ortho*-methyl substituents were well-tolerated on isocyanates with only slightly decreased product yields (**3f–3g**). Benzyl, phenethyl, isopropyl and allyl isocyanates could also be used to form amides **3i–3l**. Functionalized electron-rich arylzinc iodides were superior in reactivity, improving nucleophilicity of the reagent, as with **3m** compared to those with electron-withdrawing groups such as products **3n** and **3o**.

Table 2. Substrate scope with respect to arylzinc iodides.[a]

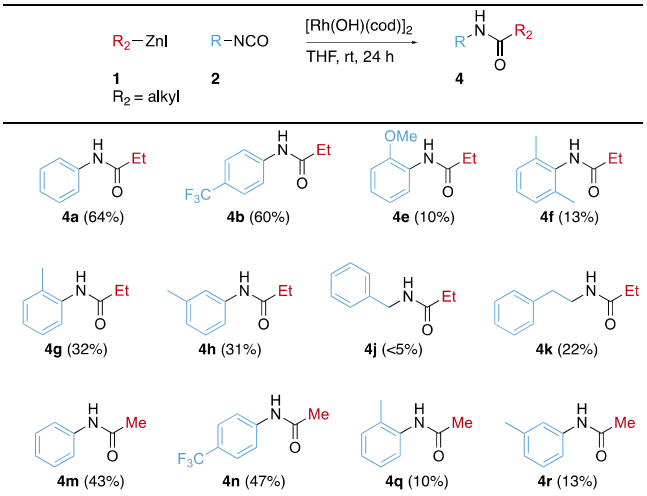


[a] Reaction conditions: **1** (2 equiv., 0.4 mmol), **2** (1 equiv., 0.2 mmol), $[Rh(OH)(cod)]_2$ (2.5 mol%, 0.005 mmol), THF (2 mL), rt, 30 min, under Ar.

Alkyl organozinc iodides were prepared[17] and successfully coupled with isocyanates under similar conditions to prepare *C*-alkyl amides. Notably, addition of $[Rh(OH)(cod)]_2$ suppresses the previously reported carbamate formation.[16] Various additives were evaluated for their effect on reaction progress. Conversions dropped with the addition of triethylamine,[18] while phenol,[19] DBU, and azo compounds were well tolerated (see ESI), suggesting the possibility of a one-pot ^{11}C-amide synthesis from $[^{11}C]CO_2$.

Similar steric and electronic trends could be observed with alkylzinc iodides as with arylzinc iodides (Table 3): more electron-poor isocyanates proceeded with useful product yields (**4b**) and *ortho*-substituents were moderately tolerated (**4f–4g**), while electron-donating groups or alkyl isocyanates fared worse (**4e,j,k**). In general, products of ethylzinc iodide were isolated in higher yields compared to those prepared from methylzinc iodide, though functionality trends were maintained throughout (for the full alkylzinc iodide reaction scope, see the supporting information).

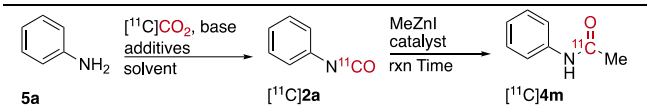
Table 3. Scope with respect to alkylzinc iodides.[a]



[a] Reaction conditions: **1** (3 equiv., 0.6 mmol), **2** (1 equiv., 0.2 mmol), $[Rh(OH)(cod)]_2$ (2.5 mol%, 0.005 mmol), THF (2 mL), rt, 24 h, under Ar.

Satisfied with this characterization of rhodium-catalyzed organozinc iodide coupling with stable isotope isocyanates, the findings provided a framework to develop a method for ^{11}C chemistry. Less reactive methylzinc iodide was selected for optimization, aiming towards [^{11}C]acetanilide due to its relevance as a parent compound to metabolic paracetamol, one of the most commonly used analgesics.[20]

Table 4. Optimization for [^{11}C]acetanilide synthesis.[a]



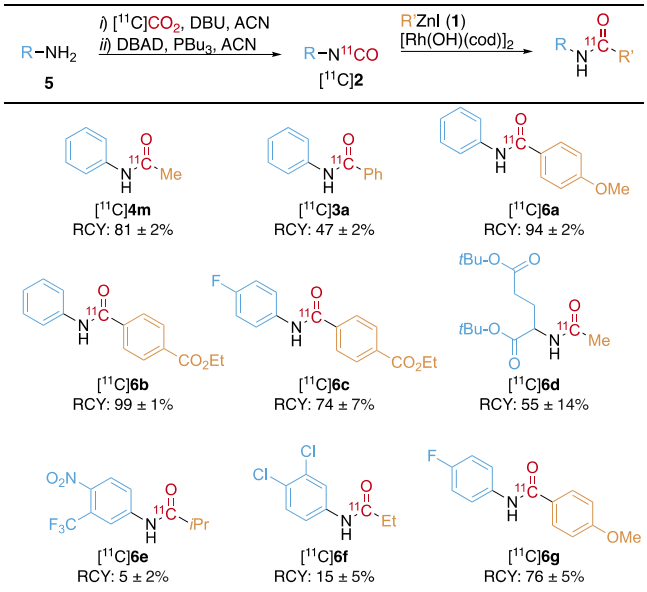
Entry	Base	Temp [°C]	TE [%] [b]	RCY [%] [c]
1	BEMP	25	98	20
2 [d]	BEMP	25	75	5
3 [e]	BEMP	25	60	11
4 [f]	DBU	25	>99	74
5 [g]	DBU	25	92	78
6	DBU	25	90	90
7	DBU	50	68	40
8	DBU	0	68	12
9 [h]	DBU	25	90	81
10 [i]	DBU	25	89	80

[a] Reaction conditions: **5a** (22.90 µmol), base (35.50 µmol), ACN (500 µL); PBu_3 (45.80 µmol) and DBAD (45.80 µmol), ACN (100 µL). (Reaction time before quench was 15 minutes after addition of MeZnI). [b] Trapping efficiency. [c] Radiochemical yield, calculated from integration of HPLC radiation signal. [d] Reaction performed in DMSO. [e] Reaction performed in DMF. [f] Coupling performed for 10 minutes. [g] $[Rh(Cl)(cod)]_2$ used as catalyst. [h] 2.0 equiv. DBU. [i] 2.5 equiv. DBU.

Initial trials using a $POCl_3$-induced dehydration procedure for the synthesis of ^{11}C-isocyanates[21,22] proved incompatible with the coupling conditions. Dehydration using Mitsunobu reagents[6,23] (tributyl phosphine and di-*tert*-butyl azodicarboxylate, DBAD) in acetonitrile provided more reliable access to [^{11}C]phenyl isocyanate and was also compatible with the subsequent rhodium-catalyzed coupling with methylzinc iodide (Table 4, entries 1–3). DBU, a base more commonly used with Mitsunobu dehydration, provided a substantial increase to both the trapping efficiency and RCY (entries 4–6). Various amounts of DBU were used to evaluate stoichiometric effect on the reaction: 1.5 equivalents yielded the best results for trapping and conversion (entries 6, 9–10).

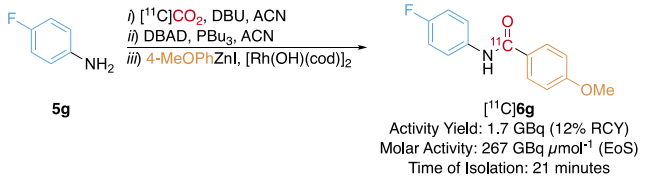
With an optimized procedure in hand, a series of biologically relevant compounds were labeled with ^{11}C using this technique (Table 5). Isocyanates were prepared *in situ* using an automated ^{11}C synthesis system before being routed to a secondary reactor containing the rhodium catalyst. The coupling reaction was commenced with the addition of organozinc iodide (0.3 mL, 3.3–9.8 equivalents), then reacted for 10–15 minutes before aqueous quenching and radioHPLC analysis. Peak integration was performed in order to derive radiochemical yields and product identities were confirmed by coinjection with nonradioactive standards of each compound. The method ensures reliable trapping conditions while also leading to moderate to strong radiochemical purity and yield. A number of compounds were prepared, including the biologically-relevant *tert*-butyl protected [^{11}C]*N*-acetyl glutamic acid ([^{11}C]**6d**), the agrochemical [^{11}C]propanil ([^{11}C]**6e**), and a pharmaceutically-relevant [^{11}C]acetanilide ([^{11}C]**4m**).

Table 5. Carbon-11 substrate scope.[a]



[a] See ESI for general procedure.

Amide [^{11}C]**6g** was selected for further isolation to demonstrate the utility of this labeling technique. A fully automated method was implemented (see ESI) with a time of synthesis of 21 minutes from delivery of $[^{11}C]CO_2$ to end of HPLC purification. The activity yield was 12% from beginning of $[^{11}C]CO_2$ delivery with a molar radioactivity of 267 GBq·µmol^{-1}. (Scheme 1).



Scheme 1. Automated synthesis and isolation of amide [^{11}C]**6g**. See ESI for details.

In conclusion, we have developed a transition metal-catalyzed synthesis of amides that can be translated for use with ^{11}C. Organozinc iodides and isocyanates can be coupled using rhodium-catalysis to synthesize a wide array of amide products under mild reaction conditions and with fast synthesis times.

^{11}C-Amide products can be derived in suitable yields and fully automated for practical radiotracer synthesis. This method will represent a new strategy for ^{11}C-labeling of biologically relevant amides.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures; characterization data; preparation of starting materials; optimization results; substrate scope; NMR spectra for compounds (PDF).

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Financial and infrastructure support for this work were provided by the University of Ottawa Heart Institute, and the Natural Sciences and Engineering Research Council of Canada (NSERC, RGPIN-2017-06167), the Canada Foundation for Innovation (CFI, 36848), and the Ontario Ministry for Research, Innovation and Science (ER17-13-119). B.A.M. was supported by the BioTalent Student Work-Integrated Learning Program. The authors are grateful to Dr. Tayebeh Hadizad, Daniel Duan, and the UOHI PET Radiochemistry Core for isotope production, and Prof. André Beauchemin for helpful discussions.

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