OL | Organic Letters

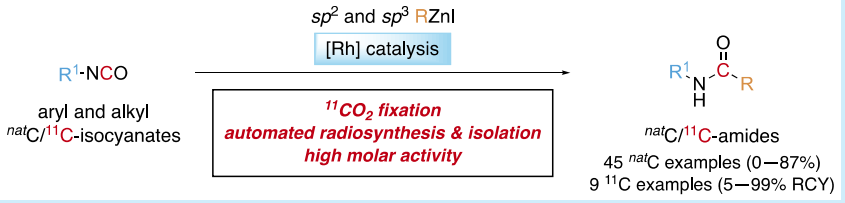
pubs.acs.org/OrgLett Letter

Rhodium-Catalyzed Addition of Organozinc Iodides to Carbon-11 Isocyanates

Braeden A. Mair, Moustafa H. Fouad, Uzair S. Ismailani, Maxime Munch, and Benjamin H. Rotstein*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c00729 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Amides were prepared using rhodium-catalyzed coupling of organozinc iodides and carbon-11 (^{11}C, $t_{1/2}$ = 20.4 min) isocyanates. Nonradioactive isocyanates and sp^3 or sp^2 organozinc iodides generated amides in yields of 13%−87%. Incorporation of cyclotron-produced [^{11}C]CO_2 into ^{11}C-amide products proceeded in yields of 5%−99%. The synthetic utility of the 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 12% radiochemical yield in 21 min from the beginning of synthesis.

Positron emission tomography (PET) is a noninvasive nuclear medicine technology used for in vivo molecular imaging. Carbon-11 (^{11}C, $t_{1/2}$ = 20.4 min), which is a short-lived PET isotope, is commonly used for labeling small molecules and peptide radiotracer candidates, although its utility is limited by the availability of chemical methodologies suitable for its incorporation.[1,2] Therefore, the abundance and diversity of organic frameworks in radiopharmaceuticals 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. These syntheses require great care, because of 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[6,7] overcome this obstacle but still require multistep activation to intermediate acid chlorides, which themselves often require purification.[8−11] Alternative synthetic approaches have been developed for ^{11}C-carbonylation with [^{11}C]carbon monoxide, using either preformed arylpalladium complexes[12] or alkyl iodide coupling mediated by nickel.[13] While these options are effective in synthesizing complex amide products, only a few laboratories prepare [^{11}C]CO.[14]

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

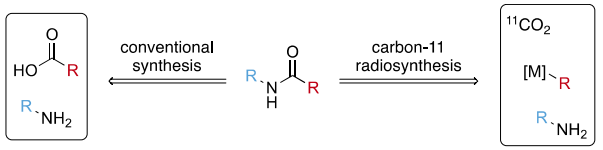


Figure 1. Strategies for stable isotope and carbon-11 amide synthesis.

Received: February 25, 2020

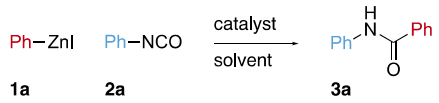
https://dx.doi.org/10.1021/acs.orglett.0c00729
Org. Lett. XXXX, XXX, XXX−XXX

synthesis.[15] Organozinc halides represent another class of organometallics offering greater stability toward many chemical moieties. Previously, a limited scope of amides had been prepared from allyl and propargyl organozinc halides and aryl isocyanates.[16] However, direct addition of alkyl and benzyl organozinc halides to isocyanates did not 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 toward 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 (see Table 1). Only a trace amount of 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 (Table 1, entries 2 and 3). $[Rh(OH)(cod)]_2$ also demonstrated strong selectivity and conversion with a yield of 74% (Table 1, entry 4). The yields were not further improved by the use of heat, which led to a slight increase in the formation of symmetrical diphenyl urea (Table 1, entry 5). More polar solvents could also facilitate the reaction (Table 1, entries 6−8), which would prove important for radiochemical applications. A significant decrease in yield upon reversing the order of reactant addition indicated the importance of premixing the isocyanate with the catalyst before introducing organozinc iodides (Table 1, entry 9).

Table 1. Optimization of Arylzinc Iodide Reaction Conditions[a]



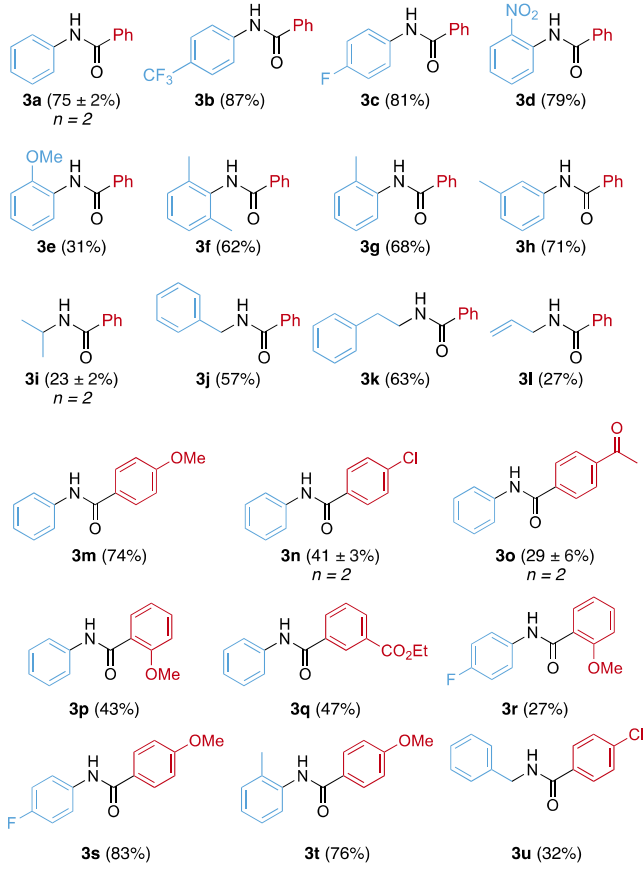
1a **2a** **3a**

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 performed with **1a** (0.4 mmol), **2a** (0.2 mmol), and 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]50 °C. [e]Reversed order of addition.

The scope of the reaction was evaluated for arylzinc iodides under the optimized conditions with various isocyanates (see Scheme 1). 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** and **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**.

Scheme 1. Substrate Scope with Respect to Arylzinc Iodides[a]



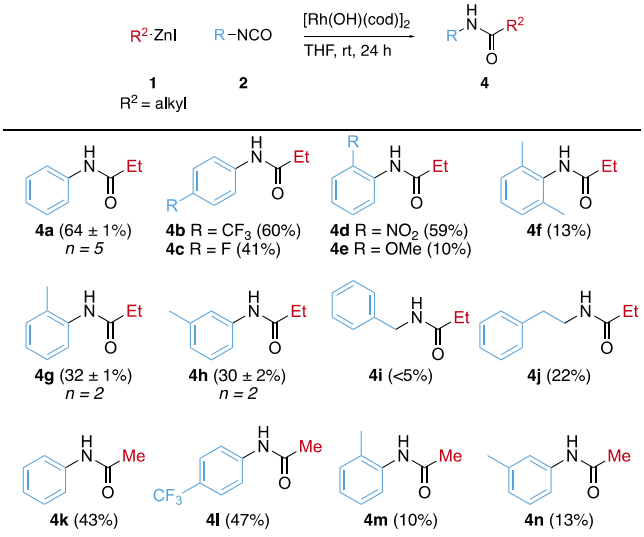
[a]Reaction conditions: **1** (2 equiv, 0.4 mmol), **2** (1 equiv, 0.2 mmol), $[Rh(OH)(cod)]_2$ (2.5 mol %, 0.005 mmol), THF (2 mL), rt, 30 min, under Ar.

Alkyl organozinc iodides were prepared[17] and successfully coupled with isocyanates under similar conditions to prepare C-alkyl amides, with longer reaction times required for complete conversion. 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 decreased with the addition of triethylamine,[18] while phenol,[19] DBU, and azo compounds were well-tolerated (see the Electronic Supporting Information (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 (see Scheme 2): more electron-poor isocyanates proceeded with useful product yields (**4b** and **4c**) and *ortho*-substituents were moderately tolerated (**4e**−**4g**), while electron-donating groups or alkyl isocyanates fared worse (**4e**, **4i**, **4j**). Generally, products of ethylzinc iodide were isolated in higher yields, compared to those prepared

https://dx.doi.org/10.1021/acs.orglett.0c00729
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. 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.

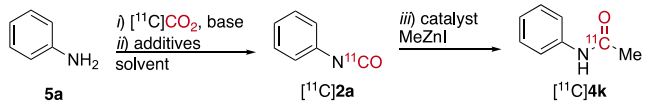
from methylzinc iodide, although functionality trends were maintained throughout (for the full zinc iodide reaction scope, including additional compounds, see the ESI).

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 toward [^{11}C]acetanilide due to its relevance as a parent compound to metabolic paracetamol, one of the most commonly used analgesics.[20]

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[23,24] (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 2, entries 1−3). DBU, which is a base more commonly used with Mitsunobu dehydration, provided a substantial increase to both the trapping efficiency (TE) and radiochemical yield (RCY) (Table 2, entries 4−6). Various amounts of DBU were used to evaluate stoichiometric effect on the reaction: 1.5 equiv yielded the best results for trapping and conversion (Table 2, entries 6, 9, and 10).

With an optimized procedure in hand, a series of biologically relevant compounds were labeled with ^{11}C using this technique (Scheme 3). 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 commenced with the addition of organozinc iodide (0.3 mL, 3.3−9.8 equiv), then was reacted for 10−15 min 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. Many compounds were prepared, including the biologically relevant *tert*-butyl protected [^{11}C]*N*-acetyl glutamic acid ([^{11}C]**6d**), the

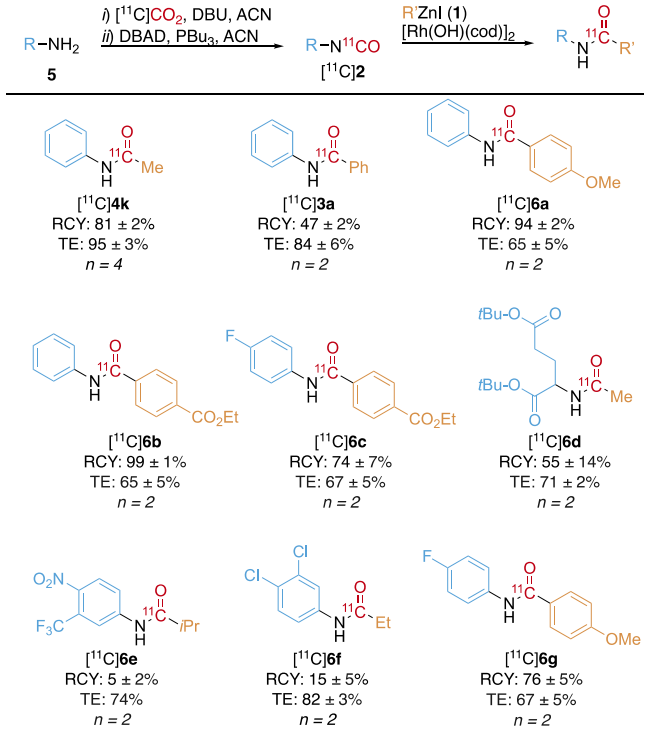
Table 2. Optimization for [^{11}C]Acetanilide Synthesis[a]



entry	base	trapping efficiency, TE [%]	radiochemical yield, RCY[b] [%]	TE × RCY [%]
1 (n = 2)	BEMP	99 ± 1	15 ± 1	20
2[c]	BEMP	75	5	4
3[d]	BEMP	60	11	7
4[e]	DBU	>99	74	74
5[f]	DBU	92	78	72
6 (n = 4)	DBU	95 ± 3	81 ± 2	77
7[g]	DBU	68	40	27
8[h]	DBU	68	12	8
9[i]	DBU	90	81	73
10[j]	DBU	89	80	71

[a]Reaction conditions: (i) **5a** (22.90 μmol), base (35.50 μmol), ACN (500 μL), <2 min; (ii) PBu_3 (45.80 μmol) and DBAD (45.80 μmol), ACN (100 μL), 1 min; and (iii) 15 min. [b]Calculated from integration of radioHPLC signal. [c]DMSO. [d]DMF. [e]Coupling performed for 10 min. [f]$[Rh(Cl)(cod)]_2$ used as a catalyst. [g]50 °C. [h]0 °C. [i]2.0 equiv DBU. [j]2.5 equiv DBU.

Scheme 3. Carbon-11 Substrate Scope[a]



[a]See the ESI for general procedure (P5). Standard error given for all reactions.

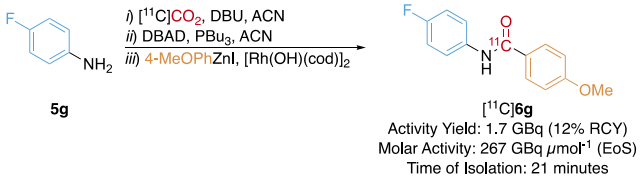
agrochemical [^{11}C]propanil ([^{11}C]**6e**), and a pharmaceutically relevant [^{11}C]acetanilide ([^{11}C]**4k**).

Amide [^{11}C]**6g** was selected for further isolation to demonstrate the utility of this labeling technique. A fully automated method was implemented (see the ESI) with a total time of 21 min from delivery of [^{11}C]CO_2 to end of semipreparative HPLC purification (C18, aqueous acetonitrile mobile phase). The decay-corrected radiochemical yield was

https://dx.doi.org/10.1021/acs.orglett.0c00729
Org. Lett. XXXX, XXX, XXX−XXX

12% from [^{11}C]CO_2 delivery with a molar activity of 267 GBq μmol^{-1} (see Scheme 4).

Scheme 4. Automated Synthesis and Isolation of Amide [^{11}C]6g[a]



[a]See the 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 at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00729.

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

■ AUTHOR INFORMATION

Corresponding Author

Benjamin H. Rotstein − *Departments of Biochemistry, Microbiology and Immunology and Departments of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario, Canada K1H 8M5; University of Ottawa Heart Institute, Ottawa, Ontario, Canada K1Y 4W7;* orcid.org/0000-0001-9707-9357; Email: benjamin.rotstein@uottawa.ca

Authors

Braeden A. Mair − *Departments of Chemistry and Biomolecular Sciences, University of Ottawa, Ottawa, Ontario, Canada K1H 8M5; University of Ottawa Heart Institute, Ottawa, Ontario, Canada K1Y 4W7*

Moustafa H. Fouad − *Departments of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Ontario, Canada K1H 8M5; University of Ottawa Heart Institute, Ottawa, Ontario, Canada K1Y 4W7*

Uzair S. Ismailani − *Departments of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Ontario, Canada K1H 8M5; University of Ottawa Heart Institute, Ottawa, Ontario, Canada K1Y 4W7*

Maxime Munch − *Departments of Biochemistry, Microbiology and Immunology, University of Ottawa, Ottawa, Ontario, Canada K1H 8M5; University of Ottawa Heart Institute, Ottawa, Ontario, Canada K1Y 4W7*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00729

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial and infrastructure support for this work were provided by the University of Ottawa Heart Institute (UOHI), 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 and Daniel Duan (UOHI PET Radiochemistry Core) for isotope production, and Prof. André Beauchemin (University of Ottawa) for helpful discussions.

■ REFERENCES

(1) Deng, X.; Rong, J.; Wang, L.; Vasdev, N.; Zhang, L.; Josephson, L.; Liang, S. H. Chemistry for Positron Emission Tomography: Recent Advances in ^{11}C-, ^{18}F-, ^{13}N-, and ^{15}O-Labeling Reactions. *Angew. Chem., Int. Ed.* **2019**, *58* (9), 2580−2605.

(2) Miller, P. W.; Long, N. J.; Vilar, R.; Gee, A. D. Synthesis of ^{11}C, ^{18}F, ^{15}O, and ^{13}N Radiolabels for Positron Emission Tomography. *Angew. Chem., Int. Ed.* **2008**, *47* (47), 8998−9033.

(3) Boström, J.; Brown, D. G.; Young, R. J.; Keserü, G. M. Expanding the Medicinal Chemistry Synthetic Toolbox. *Nat. Rev. Drug Discovery* **2018**, *17*, 709−727.

(4) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54* (10), 3451−3479.

(5) Luthra, S. K.; Pike, V. W.; Brady, F. Preparation of Some NCA [1-^{11}C]Acid Chlorides as Labelling Agents. *Int. J. Rad. Appl. Instrum. [A]* **1990**, *41* (5), 471−476.

(6) Rotstein, B. H.; Liang, S. H.; Placzek, M. S.; Hooker, J. M.; Gee, A. D.; Dollé, F.; Wilson, A. A.; Vasdev, N. ^{11}C = O Bonds Made Easily for Positron Emission Tomography Radiopharmaceuticals. *Chem. Soc. Rev.* **2016**, *45* (17), 4708−4726.

(7) Rotstein, B. H.; Liang, S. H.; Holland, J. P.; Collier, T. L.; Hooker, J. M.; Wilson, A. A.; Vasdev, N. $^{11}CO_2$ Fixation: A Renaissance in PET Radiochemistry. *Chem. Commun.* **2013**, *49* (50), 5621.

(8) Aubert, C.; Huard-Perrio, C.; Lasne, M.-C. Rapid Synthesis of Aliphatic Amides by Reaction of Carboxylic Acids, Grignard Reagent and Amines: Application to the Preparation of [^{11}C]Amides. *J. Chem. Soc., Perkin Trans. 1* **1997**, *19*, 2837−2842.

(9) McCarron, J. A.; Turton, D. R.; Pike, V. W.; Poole, K. G. Remotely-Controlled Production of the 5-HT1A Receptor Radioligand, [*Carbonyl*-^{11}C]WAY-100635, via ^{11}C-Carboxylation of an Immobilized Grignard Reagent. *J. Labelled Compd. Radiopharm.* **1996**, *38* (10), 941−953.

(10) Luthra, S. K.; Pike, V. W.; Brady, F. The Preparation of Carbon-11 Labelled Diprenorphine: A New Radioligand for the Study of the Opiate Receptor System in Vivo. *J. Chem. Soc., Chem. Commun.* **1985**, *20*, 1423−1425.

(11) Riss, P. J.; Lu, S.; Telu, S.; Aigbirhio, F. I.; Pike, V. W. CuI-Catalyzed ^{11}C Carboxylation of Boronic Acid Esters: A Rapid and Convenient Entry to ^{11}C-Labeled Carboxylic Acids, Esters, and Amides. *Angew. Chem., Int. Ed.* **2012**, *51* (11), 2698−2702.

(12) Andersen, T. L.; Friis, S. D.; Audrain, H.; Nordeman, P.; Antoni, G.; Skrydstrup, T. Efficient ^{11}C-Carbonylation of Isolated Aryl Palladium Complexes for PET: Application to Challenging Radiopharmaceutical Synthesis. *J. Am. Chem. Soc.* **2015**, *137* (4), 1548−1555.

(13) Rahman, O.; Långström, B.; Halldin, C. Alkyl Iodides and [^{11}C]CO in Nickel-Mediated Cross-Coupling Reactions: Successful Use of Alkyl Electrophiles Containing a β Hydrogen Atom in Metal-

Mediated [^{11}C]Carbonylation. *ChemistrySelect* **2016**, *1* (10), 2498−2501.
(14) Taddei, C.; Pike, V. W. [^{11}C]Carbon Monoxide: Advances in Production and Application to PET Radiotracer Development over the Past 15 Years. *EJNMMI Radiopharm. Chem.* **2019**, *4* (1), 25.
(15) Bongarzone, S.; Runser, A.; Taddei, C.; Dheere, A. K. H.; Gee, A. D. From [^{11}C]CO_2 to [^{11}C]Amides: A Rapid One-Pot Synthesis via the Mitsunobu Reaction. *Chem. Commun.* **2017**, *53* (38), 5334−5337.
(16) Yang, H.; Huang, D.; Wang, K.-H.; Xu, C.; Niu, T.; Hu, Y. Reaction of Organozinc Halides with Aryl Isocyanates. *Tetrahedron* **2013**, *69* (12), 2588−2593.
(17) Edeson, S. J.; Maduli, E. J. M.; Swanson, S.; Procopiou, P. A.; Harrity, J. P. A. Investigation of a Late-Stage Derivatization Approach to Isatogens: Discovery of New Reaction Pathways: Late-Stage Derivatization Approach to Isatogens. *Eur. J. Org. Chem.* **2016**, *2016* (1), 83−86.
(18) Vinogradova, E. V.; Fors, B. P.; Buchwald, S. L. Palladium-Catalyzed Cross-Coupling of Aryl Chlorides and Triflates with Sodium Cyanate: A Practical Synthesis of Unsymmetrical Ureas. *J. Am. Chem. Soc.* **2012**, *134* (27), 11132−11135.
(19) Koike, T.; Takahashi, M.; Arai, N.; Mori, A. Addition of Organostannanes to Isocyanate Catalyzed by a Rhodium Complex. *Chem. Lett.* **2004**, *33* (10), 1364−1365.
(20) Lester, D.; Greenberg, L. A.; Carroll, R. P. The Metabolic Fate of Acetanilid and Other Aniline Derivatives: II. Major Metabolites of Acetanilid Appearing in the Blood. *J. Pharmacol. Exp. Ther.* **1947**, *90* (1), 68−75.
(21) Schirbel, A.; Holschbach, M. H.; Coenen, H. H. N.C.A. [^{11}C]CO_2 as a Safe Substitute for Phosgene in the Carbonylation of Primary Amines. *J. Labelled Compd. Radiopharm.* **1999**, *42* (6), 537−551.
(22) Wilson, A. A.; Garcia, A.; Houle, S.; Sadovski, O.; Vasdev, N. Synthesis and Application of Isocyanates Radiolabeled with Carbon-11. *Chem. - Eur. J.* **2011**, *17* (1), 259−264.
(23) Haji Dheere, A. K.; Yusuf, N.; Gee, A. Rapid and Efficient Synthesis of [^{11}C]Ureas via the Incorporation of [^{11}C]CO_2 into Aliphatic and Aromatic Amines. *Chem. Commun.* **2013**, *49* (74), 8193−8195.
(24) Horvath, M. J.; Saylik, D.; Elmes, P. S.; Jackson, W. R.; Lovel, C. G.; Moody, K. A Mitsunobu-Based Procedure for the Preparation of Alkyl and Hindered Aryl Isocyanates from Primary Amines and Carbon Dioxide under Mild Conditions. *Tetrahedron Lett.* **1999**, *40* (2), 363−366.

https://dx.doi.org/10.1021/acs.orglett.0c00729
Org. Lett. XXXX, XXX, XXX−XXX