A General ^{11}C-Labeling Approach Enabled by Fluoride-Mediated Desilylation of Organosilanes

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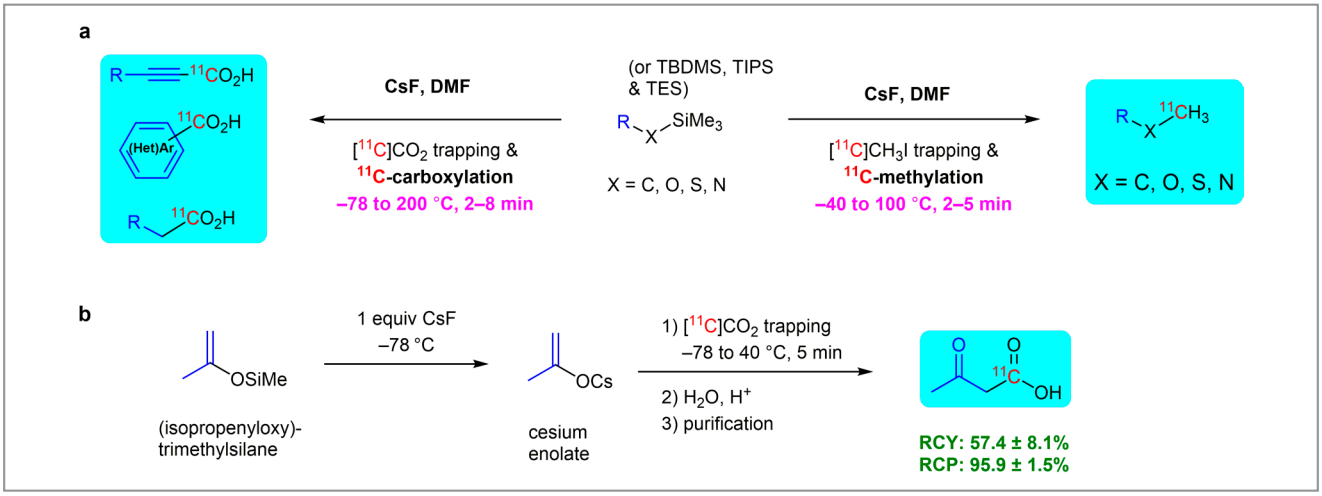
Positron emission tomography (PET) is an important imaging modality for the non-invasive investigation of biochemical and molecular events in living organisms. Because of the ubiquitous presence of carbon atoms in organic molecules, carbon-11 (^{11}C, $t_{1/2}$ = 20.4 min, $E_{\beta+}$ = 1.98 MeV) labeled organic compounds with well-characterized biological and pharmacological properties (i.e., metabolism, drug pharmacokinetics, receptor binding affinity, enzyme substrate affinity, etc.) could be used for clinical and pre-clinical studies with much fewer hurdles, compared with compounds labeled with other radioisotopes (such as fluorine-18, iodine-123 and bromine-76). In addition, the short half-life of ^{11}C allows the performance of multiple studies on the same subject in a single site visit, which represents a great advantage in clinical studies. To produce the desired ^{11}C-labeled compounds in high radiochemical and chemical purities, as well as with high molecular activity, there is a still unmet demand to develop fast and reliable approaches for introducing ^{11}C into molecules with diversified structures. Among them, the development of a new ^{11}C-carboxylation approach for the direct use of [^{11}C]CO_2 as radiosynthon would be especially attractive. Recently, Professor Wenhao Qu at Stony Brook University (USA) and his colleagues reported a general ^{11}C-labeling strategy using a fluoride-mediated desilylation (FMDS) process to generate reactive nucleophiles for nucleophilic ^{11}C-carboxylation and ^{11}C-methylation (Scheme 1, a).

In early 2017, during the development of a protocol for preparing [^{11}C]acetoacetic acid to support a clinical imaging study, Professor Qu and his colleagues occasionally noticed an unexpected amount of chemical impurities when they used an existing literature method for the lithium enolate ^{11}C-carboxylation. "To circumvent this problem, we explored alternative methods and eventually identified conditions for enolate formation mediated by fluoride ion desilylation that could represent a milder and general [^{11}C]CO_2 incorporation method," explained Professor Qu. He continued: "The optimal reaction conditions were obtained following careful and extensive modifications and this updated synthesis method led to the formation of [^{11}C]acetoacetic acid with good radiochemical and chemical purities, and also dramatically improved radiochemical yield in a similar production time frame (Scheme 1, b)."

This success triggered the group's interest in employing this FMDS approach for ^{11}C-carboxylation further, with different organosilanes as labeling precursors. "It turned out that a variety of organosilanes with trialkylsilyl group attached at sp-, sp^2-, and sp^3-carbon atoms could all afford the corresponding ^{11}C-carboxylic acids with fair to excellent yields,"



Scheme 1 Fluoride-mediated desilylation for (a) ^{11}C-carboxylation and ^{11}C-methylation of organic molecules and (b) FMDS ^{11}C-carboxylation for synthesizing [^{11}C]acetoacetic acid.

remarked Professor Qu. He continued: "The presence of different reactivities among these organosilane substrates was readily explained by the pK_a values of the conjugate acids of these anionic nucleophiles generated by the fluoride-desilylation. In addition, we also found that the newly formed ^{11}C-carboxylic acids could be converted into the corresponding ester or amide in a simple and fast manner (Figure 1, a)."

Encouraged by the success of using the FMDS ^{11}C-labeling strategy to afford various ^{11}C-carboxylic acids, which was even more remarkable considering that previously many of them could be prepared only with difficulty, Professor Qu and his co-workers further extended their FMDS approach for ^{11}C-methylation. "We found that the [^{11}C]CH_3- group could be attached to specific positions (oxygen, sulfur, nitrogen and carbon atoms) of organic molecules through a FMDS ^{11}C-methylation process under very mild reaction conditions in a straightforward manner (Figure 1, b)," explained Professor Qu.

Professor Qu commented: "This FMDS ^{11}C-labeling approach not only provides radiochemists with a fast and easy access to various ^{11}C-carboxylic acids, but also presents itself as an ideal alternative for ^{11}C-methylation of organic molecules with attractive biological activities." He concluded: "In the end, I expect that our group will apply this newly established ^{11}C-labeling approach to develop synthetic protocols for radiotracers of high clinical interest where regular production is very difficult using currently reported methods."

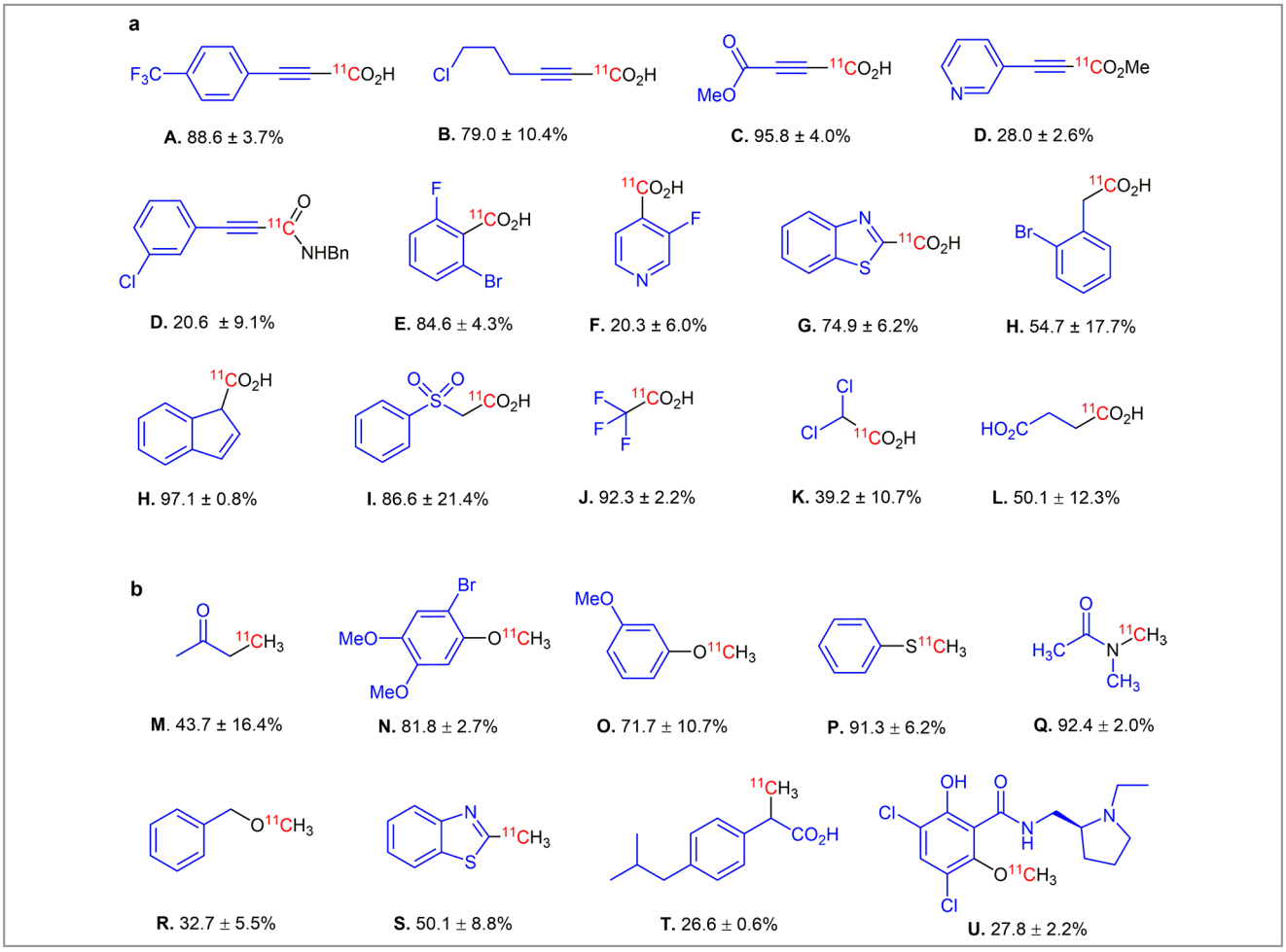
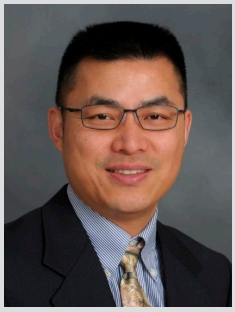


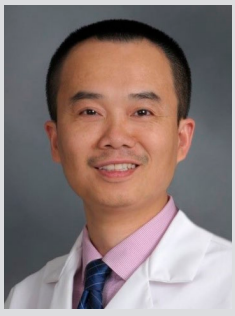
Figure 1 Selected ^{11}C-labeling examples and the radiochemical yields (RCYs, n = 3).

About the authors



Prof. W. Qu

Wenchao Qu was trained as a synthetic organic chemist and obtained his Ph.D. from the University of Akron, Ohio (USA) in 2006. After a postdoctoral fellowship in Dr. Hank F. Kung's radiopharmaceutical chemistry group at University of Pennsylvania (Upenn, USA) and later a research track assistant professorship at the same university, he joined Dr. Joanna Folwer's PET chemistry program at Brookhaven National Laboratory (USA) as an associate chemist in 2012. Three years later, he moved to Citigroup Biomedical Imaging Center at Weill Cornell Medicine (USA) and become a senior radiochemist and associate professor in radiopharmaceutical sciences research. In November 2019, he started his current position as associate professor and deputy director of PET chemistry at Psychiatry Department, Stony Brook University (SBU, USA). In addition to supervising regular radiotracer productions for supporting clinical and preclinical imaging studies at SBU, he is highly interested in developing novel radiopharmaceuticals for diagnosis and treatment of chronic diseases, as well as developing new radiochemistry methodologies for facile and fast incorporation of short half-life radioisotopes (carbon-11, fluorine-18, and other radiohalides) into bioactive molecules.



Dr. B. Hu

Bao Hu was born in Hunan, P. R. of China in 1982. He completed his B.E. from Hunan University of Science and Technology (P. R. of China) in 2005. After gaining his PhD with Prof. Zhongwen Wang at Nankai University (P. R. of China) in 2010, he joined Zhejiang University of Technology (ZJUT, P. R. of China) as an Assistant Professor. After a short period of independent research at ZJUT, he moved to the USA in 2012 as a postdoctoral fellow with Prof. Stephen DiMagno at the University of Nebraska-Lincoln (UNL, USA). He then became a Research Assistant Professor at UNL and University of Illinois at Chicago (USA). In 2017, he moved his family to New York City and joined Weill Cornell Medicine (USA) as an Instructor, where he worked with Prof. John Babich and Prof. Wenchao Qu in the field of radiochemistry. Since early 2020, he has served as an Assistant Professor of Research Psychiatry and the Director of Radiotracer Production at Stony Brook University (USA). His current work at SBU includes cGMP production of ^{11}C- and ^{18}F-labeled tracers for human and animal studies, development of novel radiotracers for imaging and therapeutic applications, and clinical translation of these new radiopharmaceutical candidates.

Dr. J. W. Babich

John W. Babich is a native of New York City (USA) where he received his early education before attending St. John's University (USA) for his B.S. in pharmaceutical sciences. He received his Master's degree in radiopharmacy from the University of Southern California in Los Angeles (USA) and his doctoral degree in radiopharmaceutical chemistry from The Institute of Cancer Research (ICR) of the University of London (UK), under the supervision of Prof. R. J. Ott. He began his research career at Brookhaven National Laboratory (USA) working with Powel Richards and Suresh Srivastava on technetium-99m labeling of red blood cells. He then joined NASA in Houston, TX (USA), where he was developing a Tungtsen-178/Tantalum-178 radionuclide generator for cardiovascular imaging in humans and later joined the faculty at Baylor College of Medicine (USA). He moved to the UK in 1984 to pursue his PhD at the ICR and also worked full time in the Department of Physics where he was responsible for the radiopharmaceutical research program which focused on the use of monoclonal antibodies for cancer imaging, radiometals for positron emission tomography and targeted radiotherapy of neuroblastoma. In 1990 he moved to Boston to take a position at Massachusetts General Hospital (USA) and joined the faculty of Harvard Medical School (USA) where he was Assistant Professor of Radiology. Here he developed his interest in Techentium-99m labeled peptides for disease detection focusing on infection and breast cancer imaging. In 1998 he co-founded Molecular Insight Pharmaceuticals (MIP) where he was CSO and head of Research and Development until the company was acquired in January 2013. At MIP he oversaw the clinical development of seven novel radiopharmaceuticals, including the world's first imaging and therapy of human prostate cancer using small-molecule inhibitors of PSMA. In 2013 he joined the faculty at Weill Cornell Medical College (USA) where he is currently Chief of Radiopharmaceutical Sciences in Radiology. Babich's research interests include the design of molecular imaging probes and metabolic substrates for unmet needs in cancer, heart disease and neurological disease. Dr. Babich's contributions are reported in 220 peer-reviewed articles and 40 issued patents.

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N. Waterhouse

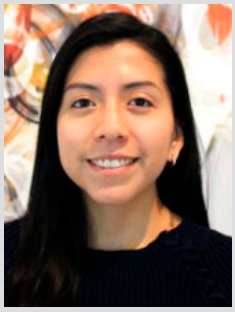
Nicole Waterhouse was born in 1993 in Markham, Ontario (Canada), and grew up in nearby Richmond Hill, before moving to Ho-Ho-Kus, New Jersey (USA). She graduated with a BSc degree in chemistry from Manhattan College (USA) in 2016. Currently, she is enjoying working in radiochemistry at Weill Cornell Medicine (USA) under Dr. John Babich, while studying to earn her MS in chemistry from New Jersey Institute of Technology (USA).

M. Dooley

Marybeth Dooley was born in 1993 in Queens, New York (USA) and lived there before moving to Rockland County, NY (USA) where she grew up. She graduated from Manhattan College (USA) with a BS in chemistry in 2015. Having previously worked as a Research Technician for four years at Weill Cornell Medicine (USA), she is now working in the pharmaceutical industry as a QC Chemist.

Dr. S. Ponnala

Shashikanth Ponnala earned his doctoral degree from Central Drug Research Institute (CDRI, India) under the supervision of Dr. Devi Prasad Sahu and received his Ph.D. in 2009. He worked as an Associate Scientist at GVK Biosciences (India) before moving to the USA to pursue his postdoctoral studies in 2010 with Prof. Wayne Harding (Hunter College, CUNY, USA) and Prof. Jason Lewis (Memorial Sloan Kettering Cancer Center, USA). He subsequently joined Dr. John Babich's group at Weill Cornell Medicine, NY (USA) as a Research Associate, where he worked on the design and synthesis of PSMA-targeting ligands in prostate cancer PET imaging and therapy. At present he is working as a Senior Scientist at Angion Biomedica Corp, NY (USA) on small-molecule therapy for liver and kidney fibrosis.



J. Urgiles

Julie Urgiles received her BA degree in chemistry in 2017 from Cornell University (USA) where she worked under Prof. Justin J. Wilson. She then worked as a research assistant for a year under Dr. John Babich at Weill Cornell Medicine (USA). She is currently enrolled in Harvard Medical School (USA) where she completed a research assistantship in Dr. Angela Koehler's lab at MIT in 2019.