Copper-Mediated Oxidative Fluorination of Aryl Stannanes with Fluoride

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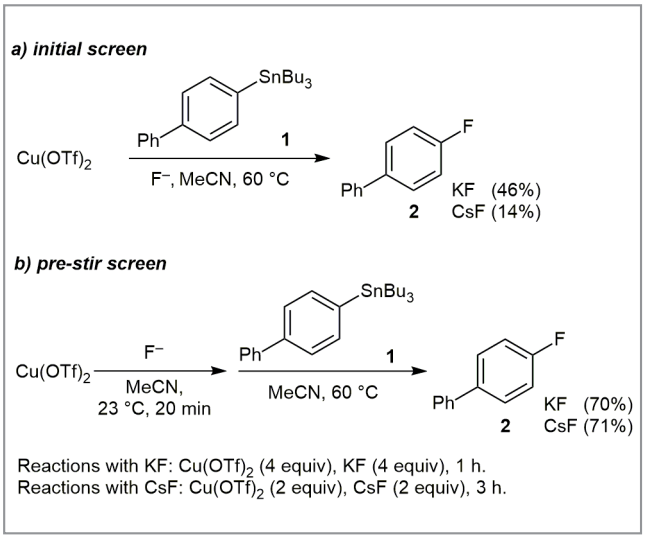
The importance of fluorinated organic molecules in applications such as pharmaceuticals, agrochemicals, new materials and imaging agents for positron-emission tomography (PET) has become well understood within the scientific community. While carbon–fluorine bond construction is a challenging chemical transformation that, until recently, was limited to simple substrates that could tolerate harsh conditions, a remarkable number of novel synthetic methodologies for C–F bond construction has been reported in the past decade.[1–3] Notable improvements in aryl fluoride bond formation have involved the use of transition metals to facilitate this transformation.[4–6] While these methods have considerably improved the accessibility of fluorinated arenes, many of them require the use of electrophilic fluorinating sources (e.g., Selectfluor, *N*-fluoropyridinium salts) which are not useful for applications in PET, a powerful noninvasive imaging technique that can provide information about molecular targets *in vivo*. The positron-emitting radioisotope fluorine-18 (^{18}F) is generated as nucleophilic fluoride and thus fluorination methods using electrophilic fluorine sources are not broadly useful for PET molecular imaging applications.

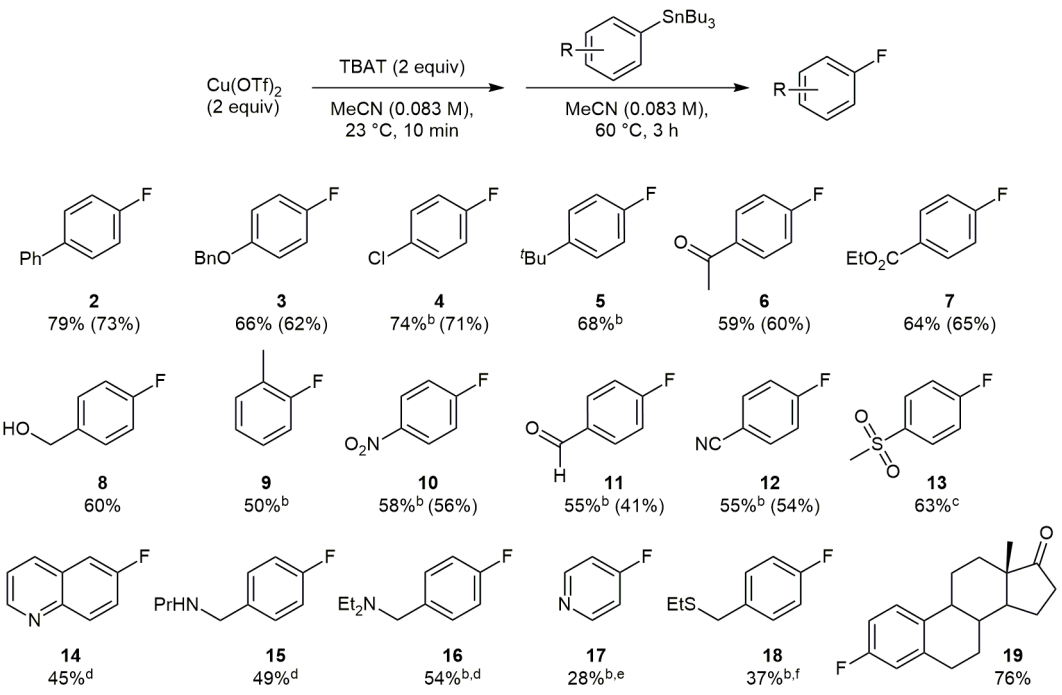


Scheme 1 Effects of pre-stir towards oxidative fluorination of aryl stannanes (Yields were determined by ^{19}F NMR spectroscopy with 1-fluoro-3-nitrobenzene as an internal standard.)

The group of Professor Jennifer Murphy at the University of California Los Angeles (UCLA, USA) was interested in expanding the methods available for ^{18}F-radiofluorination towards applications in PET and this led them to investigate oxidative fluorination chemistry. "Oxidative fluorination transformations, which utilize a nucleophilic fluoride source and an external oxidant, are conceptually challenging due to the fact that fluorine is the most oxidizing element known. Such oxidative fluorination transformations have been reported, yet they require the synthesis of complex starting materials, use of directing groups, long reaction times or a large excess of transition metal,[7–11]" said Professor Murphy, who explained: "Our group sought to develop a mild, relatively quick, oxidative fluorination reaction using nucleophilic fluoride and synthetically accessible starting materials. Aryl stannanes are highly stable and can be readily obtained with a wide range of complex functionality, attracting our attention to their use over other starting materials. In addition, reports confirming reductive elimination of high-valent Cu(III) species initiated our interest in evaluating this transition metal to facilitate C–F bond formation with nucleophilic fluoride."

Copper-based methods for C–F bond formation are known[11,12] and mechanistic studies suggest that copper plays a dual role of transition-metal mediator for aryl–F coupling as well as the oxidant to access a Cu(III) intermediate, requiring excess copper reagent. "In agreement with the proposed dual role of copper, our initial experiments screening the fluorination of aryl stannanes required upwards of four equivalents of copper to obtain moderate yields, which dramatically dropped off when less than two equivalents were used," said Professor Murphy. She continued: "We hypothesized that initial formation of a Cu(II)(OTf)(F) complex might facilitate the transmetalation more efficiently and tested this hypothesis by pre-stirring the fluoride source and copper(II) triflate before adding the stannane to the reaction mixture. Gratifyingly, this stepwise protocol resulted in significant improvement in yield of the aryl fluoride, 70% compared to 46% obtained from single addition (Scheme 1). Of note, these effects were more apparent with CsF as the fluoride source, which enabled the reaction to proceed with only two equivalents of copper(II) triflate."

In their evaluation of solvent effects on the reaction, the authors of this study found that the presence of acetonitrile



[a] Isolated yields are reported unless noted otherwise. Yields using CsF (2 equiv) as fluoride source are reported in parentheses and determined by ^{19}F NMR.
[b] Yields were determined by ^{19}F NMR spectroscopy with 1-fluoro-3-nitrobenzene as an internal standard added after the reaction. Pre-stir was conducted at 60 °C.
[c] Stirred for 5 h.
[d] $Cu(OTf)_2$ (4 equiv).
[e] 80 °C, 3 h.
[f] $Cu(OTf)_2$ (3 equiv), TBAT (3 equiv).

Scheme 2 Oxidative fluorination of aryl stannanes with $Cu(OTf)_2$ and TBAT.[a]

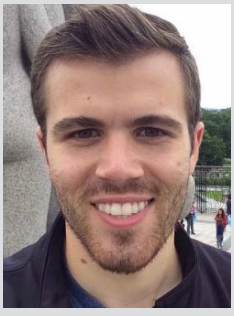
was required for efficient fluorination to proceed. The use of various other solvents provided no detectable fluorinated products; however, when these solvents were spiked with as little as 10% acetonitrile, the fluorination proceeded in moderate to good yields. Professor Murphy remarked: "We hypothesize that acetonitrile plays a key role as a ligand for copper, perhaps to stabilize the copper center to promote rapid transmetalation and to support reductive elimination of the arylcopper(III) intermediate. Further evaluation of fluoride sources revealed tetrabutylammonium triphenyldifluorosilicate (TBAT) gave the highest yields while, in the context of alkali metal fluoride sources, CsF gave comparable yields."

This reaction demonstrates broad compatibility and a large functional group tolerance (Scheme 2). Common functionality including esters, nitriles, aldehydes, ketones, ethers, sulfones and alcohols survive the reaction conditions and provide the corresponding arylfluorides in good yields (Scheme 2). Notably, arenes bearing protic groups or nucleophilic moieties, such as amines or thioethers, also participated in fluorination in modest yields. Professor Murphy concluded: "Given the versatility of this method, we expect other oxidative fluorination methods such as this one to become more prevalent amongst the broad chemistry community. Translation of this methodology into ^{18}F-radiofluorination for applications in PET is currently being investigated in our laboratory."

About the authors

Prof. J. M. Murphy

Jennifer M. Murphy received her B.S. degree in chemistry (cum laude) from Santa Clara University in Northern California (USA). In 2010, she obtained her Ph.D. working under the direction of Professor Michael E. Jung at UCLA (USA). She then became a Scholar in Oncologic Molecular Imaging (SOMI) postdoctoral fellow in the Ahmanson Translational Imaging Division at the David Geffen School of Medicine at UCLA. In 2012, Jennifer joined Professor Tobias Ritter's research laboratory as a visiting scholar at Harvard University (USA). In 2013, she was appointed as Assistant Professor in the Department of Molecular and Medical Pharmacology at the Crump Institute for Molecular Imaging at UCLA. Her lab resides in the California NanoSystems Institute building and she is also a member of the Jonsson Comprehensive Cancer Center at UCLA.



R. Gamache

Raymond Gamache was born in Burlington, VT (USA) and raised in King George, VA (USA). In 2013, he received his B.S. degree in chemistry from Christopher Newport University (CNU, USA). At CNU he worked under the supervision of Professor Jeffrey Carney researching the synthesis of heterocycles using the Hosami–Sakurai reaction. Raymond also participated in several internships at the Naval Research Laboratories with Dr. Mike Roland where he studied the physical attributes of polyurea rubber. After graduating from CNU, Raymond began his Ph.D. studies in organic chemistry at the University of California Los Angeles (UCLA, USA). In 2014, Raymond joined Professor Jennifer Murphy's laboratory where his research involves the development of new fluorination methods, rapid bioorthogonal reactions and approaches for [^{18}F]-radiolabeling of proteins for molecular imaging applications.

Dr. C. Waldmann

Christopher Waldmann was born in Tübingen (Germany) and received his M.S. in chemistry from the University of Cologne (Germany) in 2009. At the same university, he performed undergraduate research with Professor Hans-Günther Schmalz. He obtained his Ph.D. in organic synthesis and radiochemistry working with Professor Günter Haufe as well as Professor Klaus Kopka at the University of Münster (Germany) in 2013. He then moved to Los Angeles and worked under the mentorship of Professor Jennifer Murphy as a postdoctoral scholar in the Crump Institute for Molecular Imaging at UCLA (USA). In 2016, Christopher joined the laboratory of Professor Saman Sadeghi as a postdoctoral scholar. His research interests include the synthesis and radiolabeling of small organic molecules as imaging probes for positron emission tomography (PET).

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