ADVANCES IN METAL-METDIATED C–F BOND FORMATION FOR THE PURPOSE OF ^{18}F POSITRON EMISSION TOMOGRAPHY

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INTRODUCTION

Unlike magnetic resonance imaging (MRI) or computed tomography (CT), which provide information on anatomical structure, positron emission tomography (PET) allows images to be made on metabolic processes in living patients. The use of exogenous molecules with positron-emitting radiolabels allows for the direct observation of physiological parameters, such as blood flow, glucose metabolism, receptor properties and drug distribution mechanisms. An annihilation event occurs when an emitted positron collides with an electron to produce detectable γ radiation. Known radioisotopes for PET imaging probes are ^{11}C, ^{13}N, ^{15}O and ^{18}F.[i] Because of rapid isotopic decay, time limits the utility of these four isotopes. ^{18}F has a half-life of 110 min (versus 20 min for ^{11}C, 10 min for ^{13}N, 2 min for ^{15}O) and is the most widely used radionuclide. Synthesis of ^{18}F, incorporation into a molecular probe, isolation, quality control, and injection into the patient must be completed within the constraints of time and toxicity. This seminar will demonstrate the traditional methodologies for rapid ^{18}[F]fluorination of physiologically active molecules and their limitations. Focus will be placed on recently developed metal–mediated processes for introducing ^{18}F into molecules and the fundamental studies on C–F bond formation that have led to these discoveries.

FLUORINATIONS WITH NUCLEOPHILIC FLUORINE

Nucleophilic ^{18}[F]fluoride is the fluorinating agent of choice for PET radiotracers. Because $^{18}F^-$ is the immediate product from a cyclotron nuclear synthesis, it has the highest possible specific activity.[ii] Aryl fluorides are prevalent in physiologically active molecules due to their metabolic stability and lipophilic character. Methodologies for Ar–F syntheses with nucleophilic fluoride are limited to arenes possessing electron-withdrawing groups (EWGs) in tandem with nitro or halo leaving groups. EWGs can be converted into electron-donating groups, but the time constraints render this synthetically feasible process undesirable. This methodological limitation has led to the study and development of metal-mediated fluorinations of arenes. Grushin reported the first Pd(II) fluoride complex[iii] in an effort to study the feasibility of C–F reductive elimination from a metal center.[iv] Yandulov later conducted computational studies to understand the Ar–F reductive elimination. It was shown that phosphine based

Pd(II) aryl fluoride complexes were more likely to undergo P–F over C–F reductive elimination.[v] A major advancement was made with the use of biaryl monophosphine ligands for the Pd-catalyzed fluorination of aryl although *meta* and *para* regioisomers are formed.[vii] Aryltrifluoroborate salts have emerged as metabolically stable and relatively nontoxic radiotracers for PET.[viii] Sequestration of a $^{18}F^-$ /$^{19}F^-$ mixture by boronic esters allows for increased specific activities over conventional fluorinations because the trifluoroborate is three times as likely to contain $^{18}F^-$ over monofluorinated arenes.

FLUORINATIONS WITH ELECTROPHILIC FLUORINE

The limitations of Pd mediated fluorinations with nucleophilic fluorine through a Pd(II) intermediate has prompted the use of electrophilic fluorine sources. Fluorination of arylboronic acids was achieved with stoichiometric Pd(II) and subsequent addition of Selectfluor.[ix] Independent work by Sanford[8c] and Ritter[x] has confirmed that C–F reductive elimination occurs through a Pd(IV) aryl fluoride complex. Electrophilic fluorinations of arylstannanes and arylboronic acids with Selectfluor were achieved in the presence of silver.[xi] The formation of a bimetallic silver complex is the proposed active catalyst that allows for the mildest and most regioselective method for the fluorination of arenes to date. Electrophilic fluorination is preferred from a synthetic standpoint, but is less useful for ^{18}F radiolabeling because of the limited number of electrophilic ^{18}F sources with high specific activity. Recently, new protocols have been developed for the synthesis of ^{18}[F]Selectfluor with high specific activities (ca. 20 GBq/μmol).[xii] Thus, advances in rapid syntheses of radiolabeled electrophilic fluorinating agents have made selective and late–stage electrophilic ^{18}[F]fluorinations of PET probes possible.

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