Facilitating the Design of Fluorinated Drugs

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In their recent report published in *Science*, Watson et al. (2009) describe a synthetic chemistry method to produce specifically fluorinated aryl compounds from aryl triflates under mild reaction conditions and in a single step. The strategy will likely prove useful to gain access to wider classes of fluorinated aromatic compounds.

It is now widely recognized that fluorine plays a major role in modern small-molecule drug discovery (Hagmann, 2008). The major initial focus on introducing fluorine into biologically active compounds was to reduce their in vivo metabolic turnover by blocking potential reactive positions with fluorine. Fluorine has a small atom volume, and the replacement of a hydrogen atom by fluorine is therefore often tolerated by the target protein. This strategy has been routinely employed, and many marketed drugs contain fluorine atoms that were introduced to increase the drug half-life and exposure in humans (Böhm et al., 2004).

The introduction of fluorine also significantly affects the physicochemical properties of compounds (Müller et al, 2007). Fluorine is the most electronegative atom and can therefore have strong impacts on properties such as lipophilicity and pK_a values (Morgenthaler et al., 2007). Such effects are increasingly used to tailor properties of drug candidates to improve their solubility or oral bioavailability (Filler and Saha, 2009).

The introduction of fluorine may influence the binding affinity of the fluorinated molecule to the target protein (Böhm et al., 2004; Müller et al, 2007). While covalently bound fluorine rarely acts as a hydrogen bond acceptor from hydrogen bond-donor groups in proteins (Dunitz, 2004), fluorine may efficiently interact with neighboring groups through electrostatic, di- or multipolar interactions (Paulini et al., 2005), which may result in the small but distinctly increased potency of a compound. A growing amount of data, particularly from studies including so-called fluorine scans (Olsen et al., 2004) or thermodynamic double mutant cycles (Fischer et al., 2007), suggest that favorable interactions involving C-F…H-C and C-F…C=O contacts may contribute substantially to the binding of fluorinated molecules in hydrophobic pockets of proteins. Thus, if a binding pocket contains a specific location in which a single fluorine atom can engage in several interactions of the type mentioned above, a significant increase in binding affinity can be achieved (Müller et al, 2007). However, due to its strong electronegativity, fluorine may also affect the binding affinity of a molecule indirectly by polarizing its neighboring parts (Böhm et al., 2004).

The synthetic access to fluorinated compounds was difficult in the past and largely restricted to the limited amount of commercially available fluorinated building blocks. Over the last two decades, an impressive number of novel synthetic methods for the introduction of fluorine or fluorine-containing groups have appeared, and the set of fluorine-containing building blocks that are commercially available has increased dramatically. Nevertheless, there is still room for important developments. The article by Watson et al. (2009) opens an important avenue toward specifically fluorinated aromatic compounds. While methods exist for the introduction of fluorine into aromatic compounds, the methods require relatively harsh conditions and are often not compatible with common chemical functionalities. As a consequence, fluorine introduction had to be considered early in the synthesis of a target compound or available fluorinated building blocks had to be specifically customized. Neither strategy would be amenable to the introduction of radioactive and relatively short-lived ^{18}F for positron-emission tomography (PET) studies, since this requires synthetic routes that allow facile introduction of ^{18}F at a very late stage of a multistep synthesis.

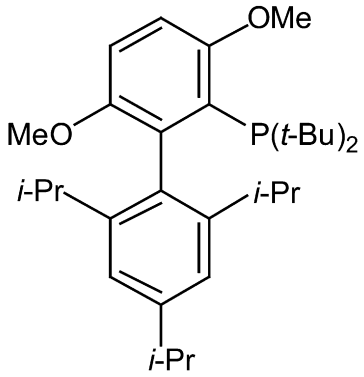

Figure 1. Chemical Structure of the Ligand *t*BuBrettPhos
This ligand was used in the studies by Watson et al. (2009).

Based on earlier observations of limited but regiospecific fluorine introduction by reductive elimination from some ligand-aryl-Pd-F intermediates, the Buchwald group undertook a focused exploration of this potentially interesting transformation (Watson et al., 2009). They identified the most suitable hydrophobic Pd-ligand, a biaryl monophosphine ligand (*t*BuBrettPhos, shown in Figure 1), the best ways to obtain the aryl-Pd-F intermediates, and optimal overall reaction conditions to provide typically high yields of the desired regiospecifically fluorinated aryl compounds in reasonably short times (Figure 2). Gratifyingly, the established standard procedure now offers a novel access to fluorinated aromatic compounds in a relatively mild and fast one-step procedure from aryl triflates; this is documented for a variety of differently substituted benzene, indole, quinoline, and other heteroaromatic substrates, and appears to work even for sterically congested cases. Many functional groups

are tolerated, except Lewis basic groups such as amines or carbonyl groups in ortho position to the triflate, possibly due to intervening Pd-coordination of these groups. Thus, there is still room for further developments. More importantly, the new procedure makes use of CsF as source of fluorine. This is particularly relevant for the incorporation of radioactive ^{18}F, as $Cs^{18}F$ can be readily prepared. Therefore, the new method presented by Watson et al. (2009) offers great potential not only for the efficient synthesis of novel fluorinated heteroaryl compounds, but also for the efficient preparation of suitable ^{18}F-labeled compounds for PET studies.

In addition to these obvious immediate benefits, this novel contribution to the synthetic armament of fluorine-organic chemistry will allow chemists to design more freely where they wish to incorporate fluorine atoms in complex molecules, thus opening the door for a broad range of new and interesting compounds that were previously not or only sporadically considered due to synthetic difficulties. This will enable specifically designed structure-property explorations. We are convinced that this will significantly contribute to a refined understanding of fluorine-modulated physicochemical properties that will have impacts much beyond medicinal chemistry.

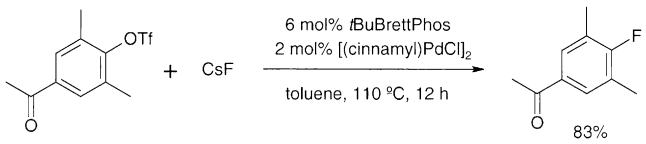

Figure 2. Typical Reaction Scheme for the Synthetic Method Developed by Watson et al. (2009).
Key advancements are the use of CsF as a source of fluorine and the biaryl monophospine *t*BuBrettPhos as a hydrophobic Pd-ligand for the regiospecific aryl fluorination by reductive elimination from ary-*t*BuBrettPhos-Pd(II)-F intermediates.

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