INTRODUCTION

Fluorine has been prevalent in pharmaceuticals and agrochemicals for several decades, and its ability to tune the pharmacology of bioactive molecules has been applied in increasingly sophisticated ways. These advances have been enabled by the development of new synthetic methodologies that can introduce previously inaccessible fluorinated functional groups and substitution patterns. One such example is the difluoromethyl group. This substituent has highly desirable pharmacological properties yet limited synthetic accessibility until the last decade.

The difluoromethyl group can introduce to drugs many of the same advantages common to other fluorinated functional groups. These include a unique steric profile, increased membrane permeability, increased metabolic stability, and inductive effects on proximal functional groups.\(^1\) Unique to this group, however, is its ability to serve as a lipophilic hydrogen bond donor (Figure 1),\(^2\) thereby avoiding the decreased membrane permeability and metabolic stability that other hydrogen bond donors can introduce.

Despite these valuable properties, FDA-approved drugs with this functionality are sparse. The two dominant methods for introducing difluoromethyl substituents are via *de novo* synthesis starting from small building blocks—typically difluoroacetic acid derivatives—or deoxyfluorination of an aldehyde using a S(IV) fluorinating agent. The former presents obvious limitations in the range of efficiently accessible structures while the latter involves hazardous reagents with poor functional group tolerance while necessitating a preinstalled formyl group. Less common strategies utilize the electrophilic difluorocarbene typically generated from ozone-depleting gases and are limited to functionalizing heteroatoms and soft carbon nucleophiles.\(^3\)

MODERN APPROACHES

In 2012, two seminal papers introduced complementary methods for direct C(sp\(^2\)) difluoromethylation. The Hartwig group reported a Cu(I)-mediated cross-coupling of aryl iodides with (difluoromethyl)trimethylsilane (TMSCF\(_2\)H)\(^4\) while the Baran group reported the synthesis of zinc difluoromethanesulfinate—a bench-stable precursor for radical difluoromethylation.\(^5\) The following

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**Figure 1.**\(^2\) Dimeric crystal structures of *o*-nitrophenol and...
decade has seen rapid development of new methodologies and difluoromethylating reagents expanding the range of difluoromethylated scaffolds available to medicinal chemists.

Cross-coupling methods have been developed mediated by Cu, Pd, and Ni. Each of these metals present unique advantages and disadvantages in difluoromethylation. Cu(I) salts are the least expensive and undergo facile transmetalation with TMSCF\textsubscript{2}H, the only commercially available difluoromethyl nucleophile amenable to cross-couplings. However, subsequent oxidative addition to generate the Cu(III) intermediate has a high energy barrier which largely limits the scope of the cross-coupling to electron-poor aryl and heteroaryl iodides and often requires stoichiometric Cu(I). Additionally, the thermal instability of the presumed active species—CuCF\textsubscript{2}H—presents unique synthetic challenges and has complicated mechanistic understanding. Pd(0), on the other hand, undergoes facile oxidative addition to a more electronically diverse range of aryl halides, but usually requires co-catalysts or non-commercially available M-CF\textsubscript{2}H nucleophiles due to more sluggish transmetalation. Pd and Ni are also capable of coupling aryl boronic acids with more commercially available X-CF\textsubscript{2}H electrophiles. The availability of both 1- and 2-electron pathways to Ni catalysts facilitates cross-electrophile couplings between aryl halides and X-CF\textsubscript{2}H electrophiles.\textsuperscript{3}

Radical methods enable direct C–H difluoromethylation of building blocks and late-stage intermediates without the need for preinstalled functional handles, although regio- and site-selectivity limit the scope of these methods. Much of the recent advancements in this field enable the use of inexpensive and commercially available radical precursors and transition metal-free photocatalytic methods. Alkene difunctionalization via difluoromethyl radicals can access a wide array of C(sp\textsuperscript{3})-CF\textsubscript{2}H-containing structures relevant to medicinal chemistry.\textsuperscript{3}

CONCLUSION

The need for more economical and efficient methods for introducing the difluoromethyl group is clear upon review of recently published industry literature. Direct C(sp\textsuperscript{2}) difluoromethylation is already being adopted in drug discovery, and scalable syntheses of the necessary precursors are active areas of research that may enable industrial-scale applications in the near future. Success in this endeavor will accelerate the development of new pharmaceuticals benefiting from the unique pharmacological properties conferred by difluoromethylation.

REFERENCES