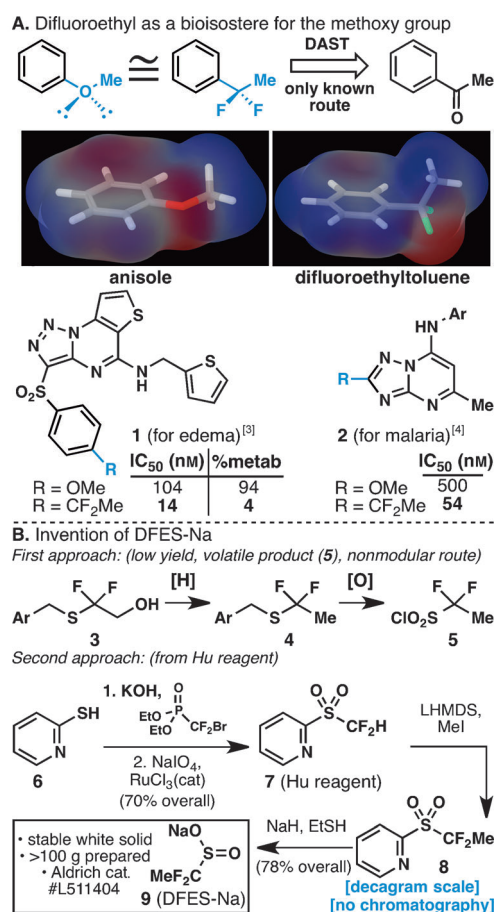


Direct Synthesis of Fluorinated Heteroarylether Bioisosteres**

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Medicinal chemists have a love–hate relationship with aryl ethers, which are generally enlisted to explore SAR and to modulate the properties of bioactive scaffolds. Yet, aryl ethers (such as methoxy aryls) represent a metabolic liability and thus much effort is expended to replace such moieties with metabolically stable derivatives or bioisosteres.^[1] The goal of this work was to develop a rapid and direct means for medicinal chemists to introduce stable, fluorinated mimics of alkoxy ethers into scaffolds. A tried-and-true method to achieve this is a point mutation of the oxygen atom to a difluorinated carbon atom. As shown in Scheme 1 A for the case of a methoxy ether, the difluoroethyl group mimics the steric and electronic features of a methoxy group, albeit with a conformational preference of the former that places the methyl group out of the plane of the aromatic ring.^[2] Numerous applications of difluoroethyl as a methoxy replacement can be found in the literature. For example, in two recent reports (**1**^[3] and **2**^[4]) the remarkable advantage that such a modification can have on both potency and metabolic stability have been demonstrated. Unfortunately, the only known route to such compounds uses fluorinating agents such as DAST (diethylaminosulfur trifluoride) or its derivatives to convert a ketone into the corresponding difluoroalkyl group, thus requiring a significant investment of resources since direct methods for late-stage appendage are not known. Even programmed approaches involving cross-coupling are unprecedented, thus rendering routes to these types of compounds a serious unmet need that could have an immediate impact in the synthesis of medicines. Herein, the invention of reagents and methods for the direct installation of fluorinated heteroarylether bioisosteric replacements is reported.



Scheme 1. A) The difluoroethyl group mimics a methoxy group and improves the bioactivity and metabolic stability of medically important molecules. B) Invention of DFES-Na and a modular approach to difluoroalkylsulfonate preparation. LHMDS = lithium hexamethyldisilazide, %metab = % of parent compound metabolized after 30 min of incubation with rat liver microsomes.^[3]

Sulfonate salts have recently emerged as promising reagents for the direct incorporation of alkyl groups onto heteroaromatic systems by a formal C–H functionalization through a radical addition process.^[5,6] Thus, the synthesis of a difluoroethylsulfonate salt was pursued as shown in Scheme 1 B. Analogous to the synthesis of the difluoromethylsulfonate salt (which is prepared from the corresponding sulfonyl chloride),^[6b] **5** was targeted. After extensive experimentation and evaluation of numerous routes, a multistep path to **5** via **3** and **4** was devised only to find that this material was a low-boiling liquid that, in our hands, was problematic to manipulate. Furthermore, this approach is not modular and would require a lengthy synthesis for each difluoroalkyl group

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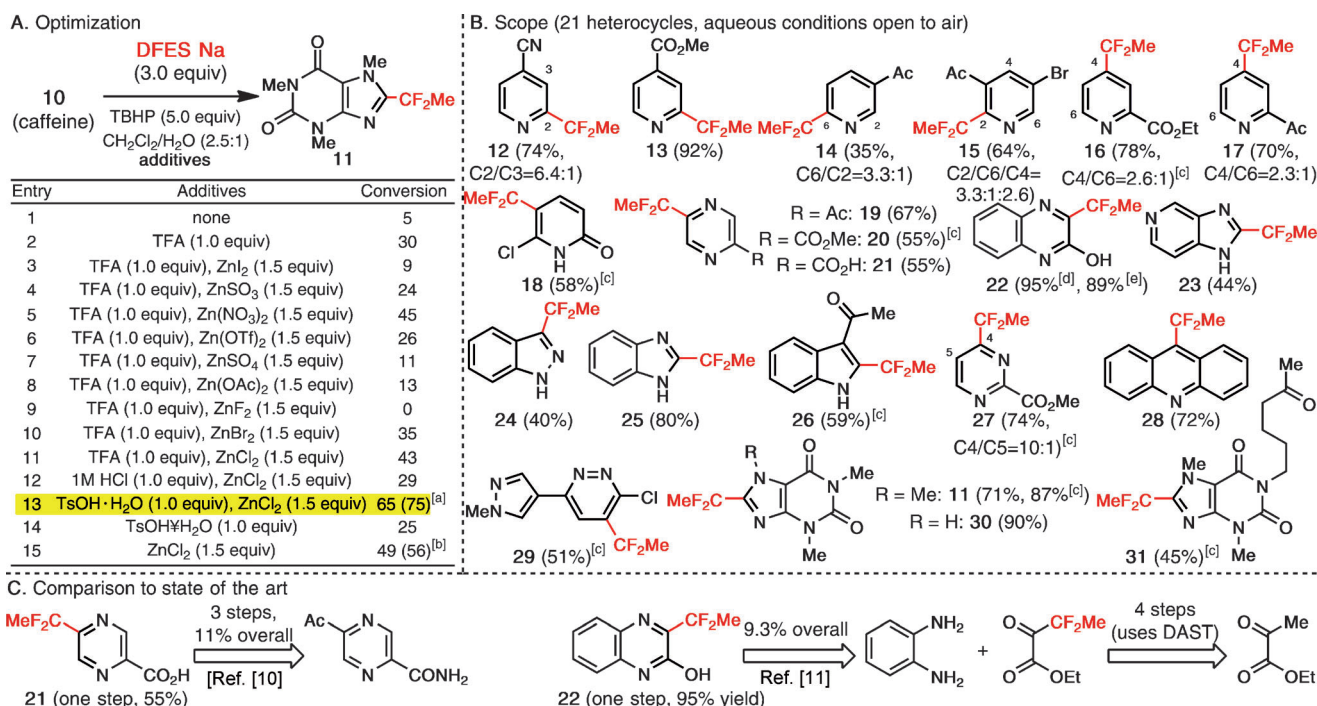
that one wishes to transfer. Inspiration was thus drawn from two independent reports, one from the Prakash, Olah, and co-workers^[7] and one from Hu and co-workers.^[8] The former group elegantly demonstrated that Hu's reagent (**7**) could be efficiently alkylated and cleaved to liberate sodium sulfinate salts (which were immediately oxidized to sulfonates). This route was adapted for the scalable preparation^[9] of sodium difluoroethylsulfinate (**9**, DFES-Na, a new chemical entity), a stable white solid that is now commercially available (Sigma-Aldrich).

With a reliable synthesis of the requisite sulfinate salt (**9**) established, optimization of the C–H alkylation was conducted as shown in Scheme 2A. Using caffeine (**10**), in a 2.5:1 mixture of CH₂Cl₂/H₂O with TBHP as oxidant, and in the absence of any additives, only trace amounts of the desired product **11** were observed (entry 1). Although Brønsted acids such as TFA improved the conversion (entry 2), zinc-based Lewis acids (entries 3–13) dramatically enhanced the reaction. Ultimately, ZnCl₂ was identified as the optimal additive along with TsOH·H₂O (entry 13).

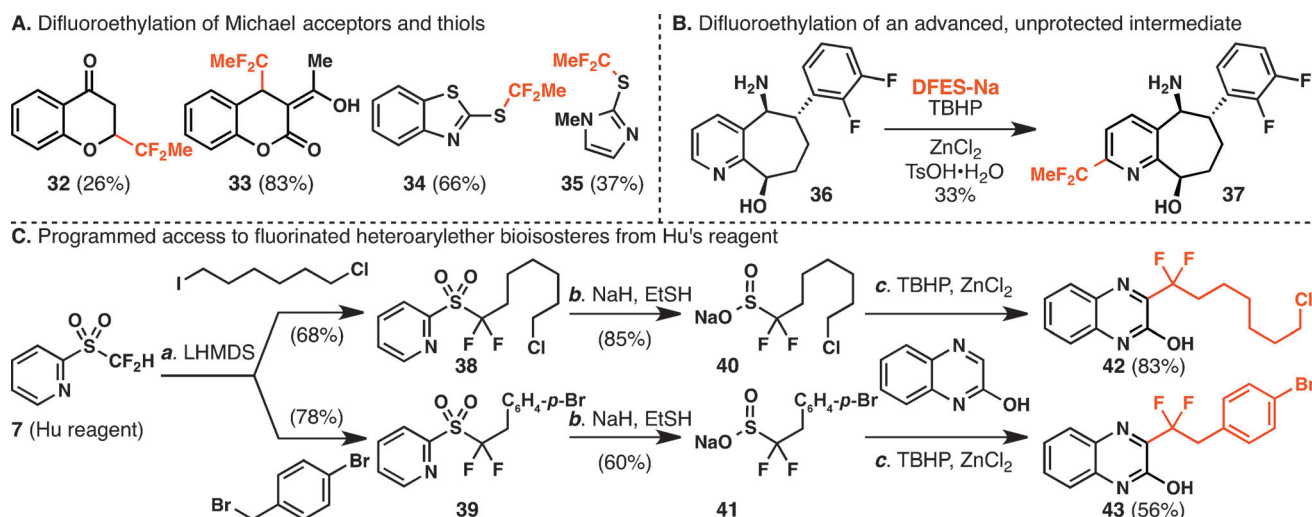
Using these optimized conditions, a wide range of heterocycles were examined as depicted in Scheme 2B. The scope, site selectivity, and functional-group tolerance are notable aspects of the method. Thus, pyridines (**12–17**), pyridones (**18**), pyrazines (**19–21**), quinoxalines (**22**), azabenzimidazoles (**23**), indazoles (**24**), benzimidazoles (**25**), indoles (**26**), pyrimidines (**27**), benzoquinolines (**28**), pyridazines (**29**),

and xanthenes (**11**, **30**, **31**) are all amenable to fluoroalkylation. Out of the 21 examples shown, 18 could potentially result in mixtures of regioisomers. Remarkably, 12 of these react with DFES-Na to deliver a single regioisomer, two react with good regioselectivity (6.4:1 or higher), and four achieve modest but synthetically useful selectivity (2.3:1 or higher). Particularly notable examples are **18**, **23**, and **29**, the precursors of which have three or more C–H bonds that could conceivably be substituted. The functional group tolerance of this reaction, which is conducted with water as a co-solvent and open to the air if desired, is also notable. Ketones, esters, nitriles, chlorides, bromides, heterocycles containing free N–H, and even free carboxylic acids are tolerated, as well as free amines and alcohols (see above). These reactions are also scalable, with heterocycle **22** being difluoroethylated on a gram scale in 89% yield upon isolation.

Cursory analysis of the patent literature indicates that the current method can dramatically simplify the way such fluoroalkylated compounds are prepared. As shown in Scheme 2C, the known route to pyrazine **21**^[10] involves a three-step procedure proceeding in 11% overall yield, all of which involve laborious functional group manipulations (and DAST). The known route to **22**^[11] requires a 5-step sequence (using DAST and KCN) proceeding in 9.3% overall yield. In contrast, the one-step routes to **21** and **22** proceed in



Scheme 2. A) Optimization of the reaction. Reactions performed on 0.05 mmol scale. B) Scope of C–H difluoroethylation of heteroarene substrates. Reactions performed on 0.2 mmol scale. Reaction conditions: Heterocycle (1.0 equiv), DFES-Na (3.0 equiv), *tert*-butyl hydroperoxide (TBHP, 5.0 equiv), TsOH·H₂O (1.0 equiv), ZnCl₂ (1.5 equiv), 0 to 23 °C. C) Comparison to current state-of-the-art methods. Yields of chromatographically pure products are displayed, unless otherwise noted. [a] Conversion on 0.2 mmol scale, yield 71%. [b] Conversion on 0.2 mmol scale, yield 51%. [c] Reaction showed incomplete conversion after 12–24 h, and a second addition of DFES-Na (3.0 equiv), ZnCl₂ (1.5 equiv), and TBHP (5.0 equiv) was performed. [d] DFES-Na (2.0 equiv), ZnCl₂ (1.0 equiv), TsOH·H₂O (1.0 equiv), TBHP (5.0 equiv), 0 to 23 °C, reaction completed in 10 h. [e] Gram-scale reaction: DFES-Na (2.5 equiv), ZnCl₂ (1.25 equiv), TsOH·H₂O (1.0 equiv), TBHP (5.0 equiv), 0 to 23 °C, 8 h, then 15 h with O₂ balloon. TBHP = *tert*-butyl hydroperoxide, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid, Ts = *p*-toluenesulfonyl.



Scheme 3. A) Direct difluoroethylation of heteroaromatic Michael acceptors and thiols. B) Direct difluoroethylation of an advanced intermediate from the Bristol-Myers Squibb compound library. C) A general synthesis of fluorinated heteroarylether bioisosteric reagents and a proof of concept on 2-quinoxalinol. Reagents and conditions for heterocycle functionalization using sulfinate reagents **40** and **41**: for **40**, reaction performed on 0.2 mmol scale, **40** (2.0 equiv), TBHP (5.0 equiv), TsOH·H₂O (1.0 equiv), ZnCl₂ (1.0 equiv), 0 to 23 °C, reaction completed in 24 h; for **41**, reaction performed on 0.1 mmol scale, **41** (1.5 equiv), TBHP (5.0 equiv), TsOH·H₂O (1.0 equiv), ZnCl₂ (1.5 equiv), reaction completed in 4 h at 0 °C after second addition of **41** (1.5 equiv), TBHP (5.0 equiv).

55 and 95% yields, respectively, and represent ideal^[12] syntheses.

Difluoroethyl radicals generated from DFES-Na (**9**) are also capable of adding to Michael acceptors and thiols as shown in Scheme 3A. In an extreme example (Scheme 3B) of site specificity and functional-group tolerance, an advanced intermediate from a program at Bristol-Myers Squibb (**36**) can be directly difluoroethylated to deliver **37** without protecting the reactive and oxidizable benzylic alcohol and amine groups.

Perhaps the most significant finding of this work is that the current strategy for introducing a difluoroethyl group (methoxy bioisostere) can also be enlisted for the synthesis of virtually any difluoroalkyl group (alkoxy bioisostere) of interest. As shown in Scheme 3C, the same approach used to create **9** (Scheme 1B) could be used for the synthesis of sulfinate salts **40** and **41**. Thus, subjecting Hu's sulfone (**7**) to the Olah–Prakash alkylation conditions delivered **38** and **39**. Subsequent cleavage furnished **40** and **41**, which were used to accomplish the direct difluoroalkylation of 2-quinoxalinol to deliver the alkyl ether and benzyl ether bioisosteres **42** and **43** in 83 and 56% yields, respectively. There are currently no other known methods for making compounds of this sort.

This research establishes a simple, reliable, and scalable platform for the direct synthesis of fluorinated bioisosteres of alkoxy ethers. Such moieties are highly sought after in the context of drug discovery and agrosience but difficulties in the chemical synthesis of such compounds severely hampers their incorporation. Recognition that Hu's reagent **7** can be employed in concert with the Olah–Prakash protocol led to a programmable synthesis of sulfinate reagents such as **9** (DFES-Na), **40**, and **41**. Aside from direct radical functionalization, sulfinate reagents have already begun to find use in other types of useful transformations.^[13] The addition of zinc chloride was critical for the success of the radical alkylation

method that, in the case of **9**, demonstrates admirable conversion, site selectivity, functional-group tolerance, and extreme operational simplicity. While caveats to this work involve the use of excess reagent, the use of inexpensive but stoichiometric additives, as well as a reliance on innate selectivity, the features of this work bode well for the widespread adoption of this chemistry in a medicinal chemistry setting.

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