



Fluorination Chemistry

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Let Sigma-Aldrich Assist You With All of Your Fluorination Needs

Fluorine has a profound ability to alter the biological properties of a compound due to its electronegativity and small size. In pharmaceutical research, fluorine is often introduced into the target compound to improve bioavailability and enhance the metabolic stability profile.

However, the general and practical fluorination of functionalized molecules continues to be a highly researched area.

We are pleased to feature an ever-expanding portfolio of fluorination reagents and fluorinated building blocks to assist fluorination, difluoromethylation and trifluoromethylation.

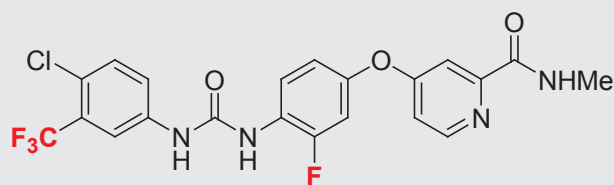
Did you know?

At least 8 out of the 39 FDA approved drugs in 2012 were small molecules containing fluorine?

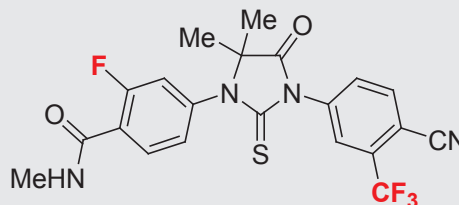
.... and that Sigma-Aldrich is your trusted resource for reagents and building blocks to incorporate fluorine to assist in obtaining your next hit?

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Fluorination

The high toxicity/corrosivity of HF renders any fluorination technology that precludes its use or generation highly valuable to synthetic chemists. With this in mind, Aldrich Chemistry provides a versatile toolbox of fluorine reagents for both nucleophilic and electrophilic methods.

In the mode of nucleophilic fluorination, we provide fluoride sources for direct displacement of alcohols, additions to aldehydes, ketones and carboxylic acids in highly chemoselective fashions for small molecule synthesis as well as poly-fluorination for materials synthesis.

Classically, the source of electrophilic fluorine has been fluorine gas, which is highly toxic and a strong oxidizer. The Aldrich catalog has a growing portfolio of milder, safer and highly stable alternatives for electrophilic fluorination. These reagents have shown excellent utility in several applications, ranging from electrophilic aromatic substitution to formation of α -fluoro-keto species.

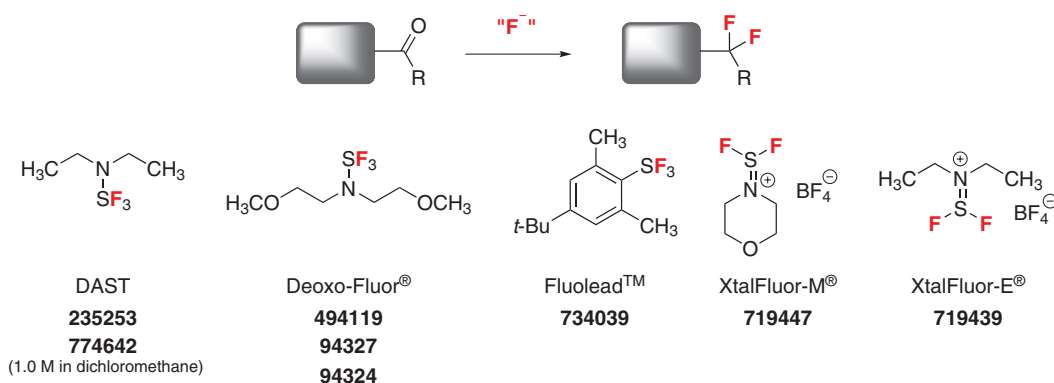


Figure 1. Nucleophilic Fluorination

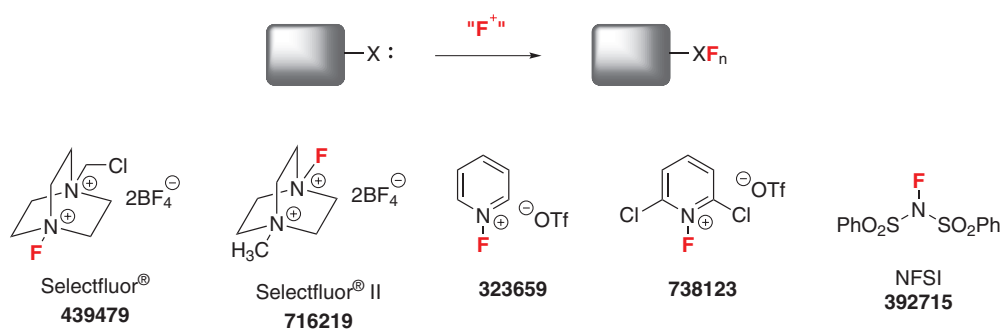
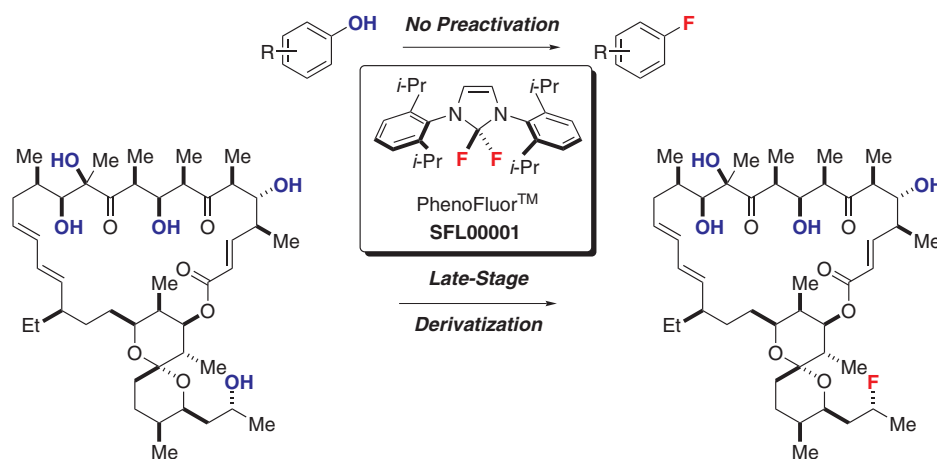


Figure 2. Electrophilic Fluorination

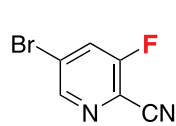
Aldrich Chemistry now features an innovative fluorinating reagent, PhenoFluor™ (SFL00001), which is capable of producing a wide range of aryl fluorides directly from the corresponding phenol (tolerant of several aryl functional group), without requiring functionalization of the free alcohol through common approaches, e.g. sulfonylation.¹

PhenoFluor was also shown to accomplish late-stage fluorination of highly functionalized free alcohols. This unprecedented display of regioselectivity further demonstrates the value of this reagent in late-stage derivatization.

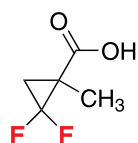


References: (1) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482. (2) Sladojevich, F.; Arlow, S. L.; Tang, P.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 2470.

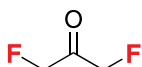
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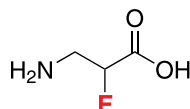
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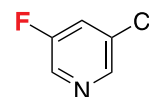
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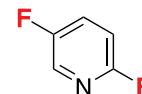
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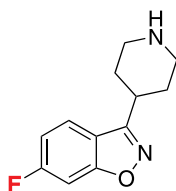
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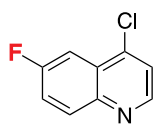
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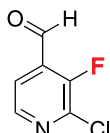
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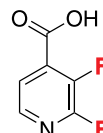
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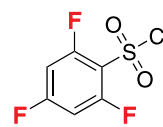
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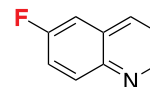
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Difluoromethylation

The difluoromethyl group (R-CF₂H) has recently garnered much attention in drug, agrochemical and material research since it is isosteric to a carbinol group (CH₂OH). The Aldrich catalog has innovative sources for installing the difluoromethyl group through nucleophilic addition and radical functionalization of C-H bonds. Nucleophilic difluoromethylation of carbonyls and imines using (Difluoromethyl)trimethylsilane (744050) and Difluoromethyl phenyl sulfone (742600) was developed by Jinbo Hu and coworkers.

Zinc difluoromethanesulfinate (DFMS, 767840), developed in the Baran lab, can directly add CF₂H to heterocycles under open flask conditions making it very operationally simple to carry out difluoromethylation. A wide range of heteroaromatic substrates are compatible (namely nitrogen-containing heterocycles) and several functional groups are tolerated in presence of DFMS.

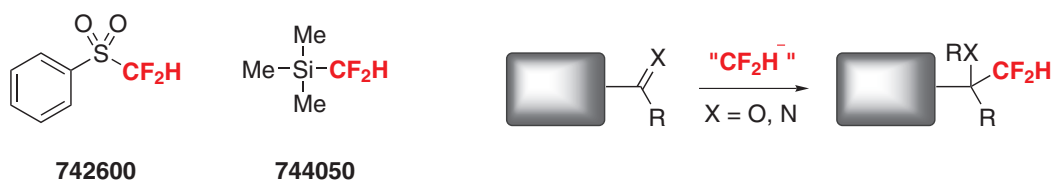
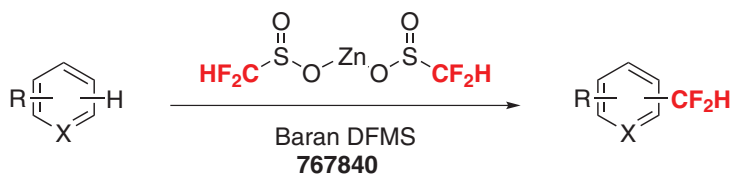


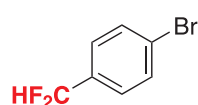
Figure 3. Nucleophilic Difluoromethylation

References: (1) Shen, X.; Ni, C.; Hu, J. *Helv. Chim. Acta* **2012**, *95*, 6606-6610. (2) Zhao, Y.; Huang, W.; Zheng, J.; Hu, J. *Org. Lett.* **2011**, *13*, 5342-5345.

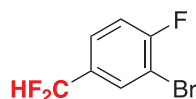


Reference: Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95-100.

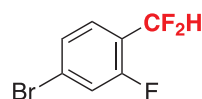
Additional Difluoromethyl Building Blocks:



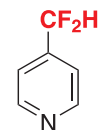
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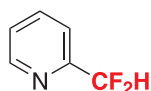
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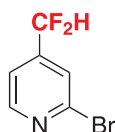
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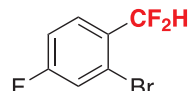
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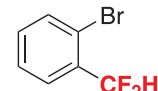
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Trifluoromethylation

Trifluoromethylation has been a rapidly growing field in chemical research, one that has interfaced elegantly with catalysis in crafting new chemical methodologies for placing trifluoromethyl groups onto molecules. In the arena of stoichiometric reagents, Aldrich offers three classes of reagents amenable to trifluoromethylation.

For nucleophilic trifluoromethylation, the Ruppert-Prakash reagent (488712, 819062) has long been a staple for adding CF_3 to carbonyls and imines. This reagent has also been featured in several publications in tandem with transition metal catalysis to install CF_3 to several motifs.

A new nucleophilic trifluoromethylation source was developed by the Colby group. The Colby Trifluoromethylation Reagent (L511315) is an air-stable solid that adds CF_3 to ketones and thiols under mildly basic conditions. The major by-products from this reaction are DBU and trifluoroacetate, which are both considered benign.

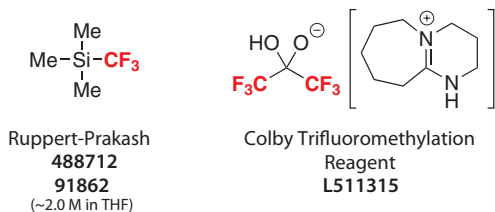
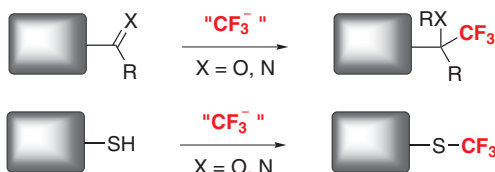


Figure 4. Nucleophilic Fluorination

More recently, trifluoromethylation by a radical process has been developed in the Baran (771406) and Hartwig (777692) groups. The Baran TFMS reagent, like the DFMS reagent, can be used to convert aryl and heteroaryl C-H bonds directly into C- CF_3 bonds under mild conditions. Trifluoromethylator® is one of the more robust reagents used to form C- CF_3 bonds from aryl and vinylogous iodides.

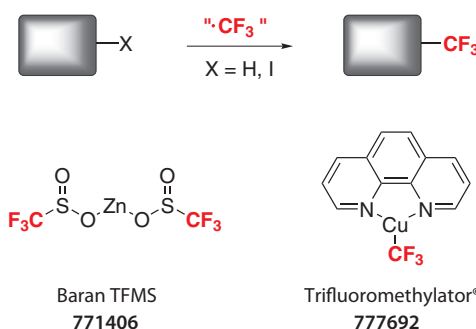


Figure 5. Radical Trifluoromethylation

The Aldrich portfolio also offers electrophilic sources of trifluoromethyl groups. Notably, the Togni I (696641, 754218) and Togni II (771147) reagents can provide highly selective trifluoromethylation of a wide range of substrates. The Togni II reagent is offered as a safer alternative for shipping and storage, available as a mixdown formulation with Celatom® that can either be easily isolated by washing away the adsorbent or even used directly.

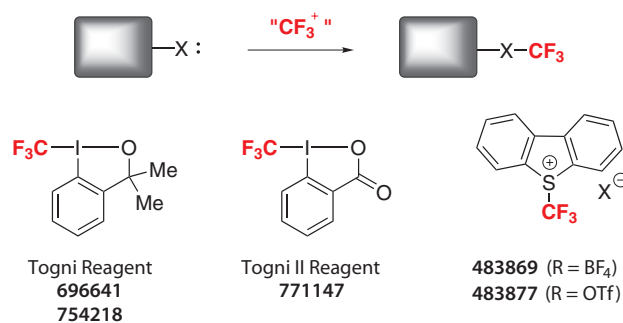


Figure 6. Electrophilic Trifluoromethylation

Reference: Fiederling, N.; Hallar, J.; Schramm, H. *Org. Process Res. Dev.*, 2013, 17, 318.

For a complete listing of the Baran Reagents, which promote innate C-H functionalization of aryl and heteroaryl motifs, visit Aldrich.com/baranreagents

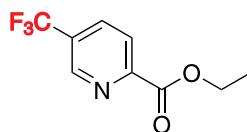
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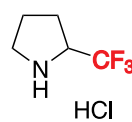
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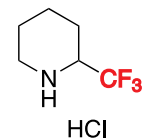
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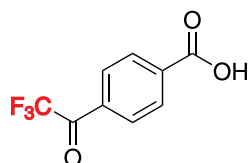
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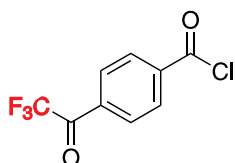
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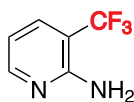
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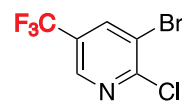
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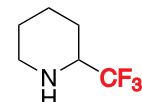
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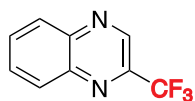
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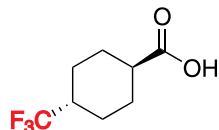
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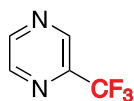
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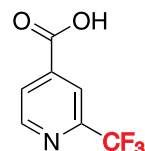
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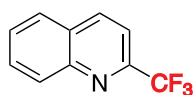
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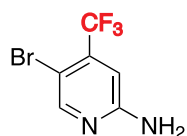
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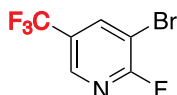
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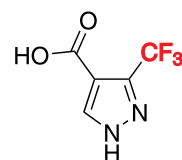
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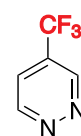
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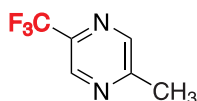
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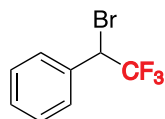
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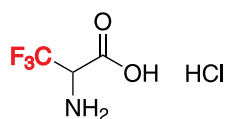
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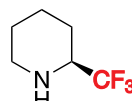
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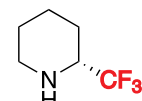
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