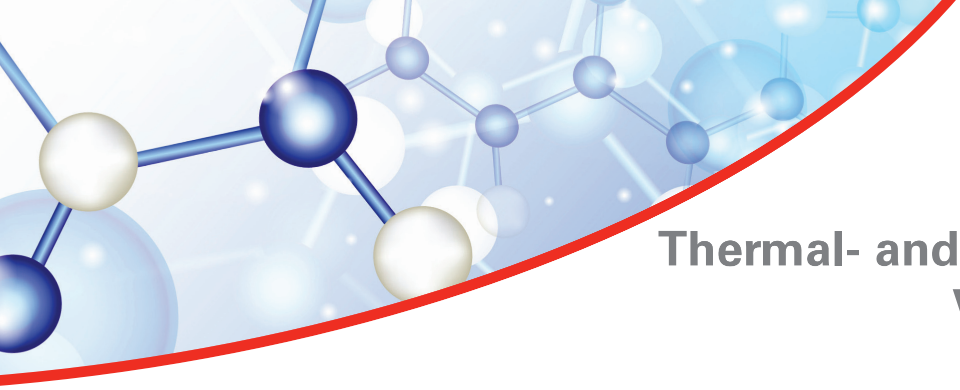
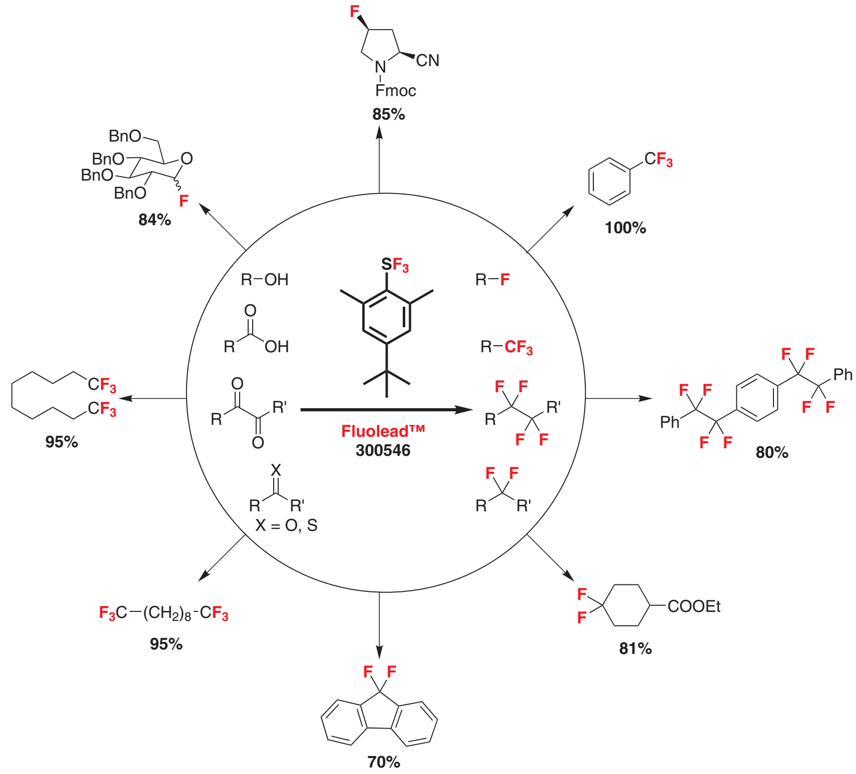


Fluolead™

Thermal- and Air-Stable DAST Alternative with Enhanced Performance

In the past 10 years, researchers have been devising methods to introduce fluorine into molecules. The presence of fluorine has been recognized to enhance the molecular properties and functionality of target molecules.[1] A plethora of molecules were synthesized with fluorine moiety for various industries such as pharmaceutical, agrochemical, and organic electronic.[2] Currently, a wide variety of fluorinating reagents are commercially available.[3] However, most of them are very reactive and require drastic air-free conditions to be effective and safe.[3]

Recently, Umemoto et al. developed Fluolead™, an air-stable alternative to common fluorinating reagents such as DAST for the transformation of hydroxyl and carbonyl groups.[4] This reagent has proved to be very versatile reacting with a variety of hydroxyl and carbonyl groups yielding the corresponding fluorinated products in good to high yields. Moreover, Fluolead™ exhibited enhanced performance by converting carboxyl groups directly to trifluoromethyl groups and also undergoing deoxofluorination with non-enolizable ketones under mild conditions. Finally, Fluolead™ showed high thermal stability and high resistance to aqueous hydrolysis, making this novel reagent the optimal choice in terms of safety and ease-of-handling.



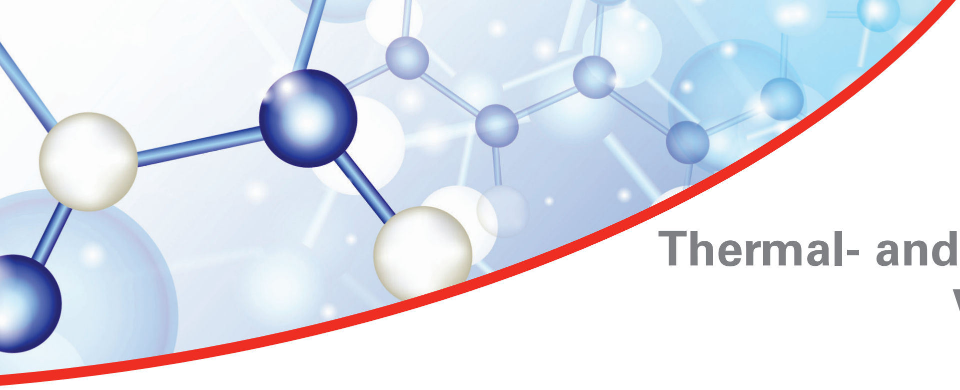
- Easy-to-handle; thermal- and air-stable
- Broad substrate scope including carboxyl and thiocarbonyl groups
- Shelf-stable and available in competitive g-to-kg pricing

Product Number: **300546**
1 g, 5 g, 25 g

For bulk inquiries,
please contact bulk@aspirasci.com.

References

(1) (a) Cho, E. J. et al. Science 2010, 328, 1679. (b) Grushin, V. V. et al. J. Am. Chem. Soc. 2006, 128, 12644. (c) Kitazume, T. Chem. Lett. 1982, 137. (d) Monnier, F. et al. Angew. Chem. Int. Ed. 2009, 48, 6954.
(2) Kirk, K. L. et al. Org. Proc. Res. Dev. 2008, 12, 305.
(3) (a) Kirsch, P. Modern Fluoroorganic Chemistry; Wiley-VCH: Weinheim, Germany, 2004. (b) Uneyama, K. Organofluorine Chemistry; Blackwell: Oxford, U.K., 2006. (c) Ojima, I. Fluorine in Medicinal Chemistry and Chemical Biology; Wiley-Blackwell: Chichester, U.K., 2009.
(4) Umemoto, T. et al. J. Am. Chem. Soc. 2010, 132, 18199.
(5) (a) G. S. Lal et al. J. Org. Chem. 1999, 64, 7048. (b) G. S. Lal et al. Chem. Commun. 1999, 215.



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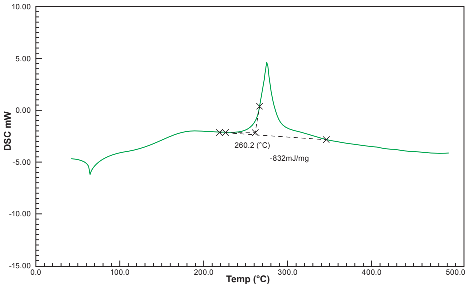
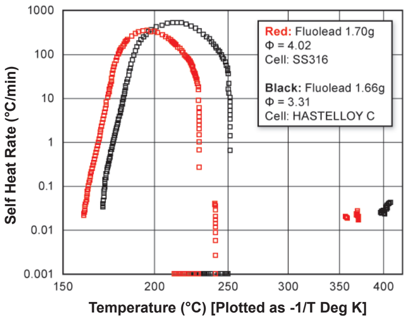
Thermal Stability

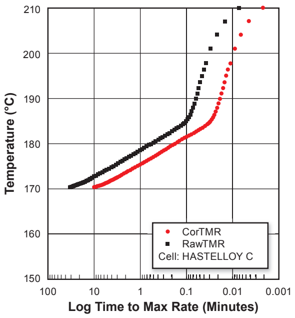
Fluolead™ has greater thermal stability than common deoxofluorinating reagents such as DAST and Deoxo-Fluor®. In Differential Scanning Calorimetry (DSC) study, the thermal decomposition of Fluolead™ started at 260 °C (Gold Plated Cell) and the released energy was 832 J/g (**Graph 1**). For DAST and Deoxo-Fluor®, the decomposition started at 140 °C (both in Gold Cell) and the released energy were 1700 J/g and 1100 J/g, respectively.[5]



Graph 1. DSC Thermogram of Fluolead (Gold Plated Cell)



Graph 2. SHR Thermograms of Fluolead (SS316 and Hastelloy C Cells)



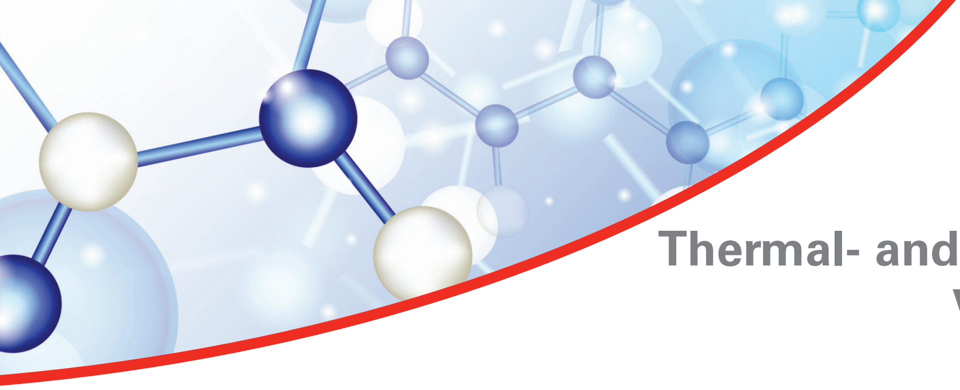
Graph 2. TMR Measurement of Fluolead (Hastelloy C Cell)

The assessment of the thermal hazards of Fluolead™ in process, storage, and transportation was evaluated by Accelerated Rate Calorimetry (ARC). From Self Heat Rate (SHR) measurement (**Graph 2**), the onset temperature of self-heated decomposition was 170 °C (Hastelloy C). From Time to Maximum Rate (TMR) measurement (**Graph 3**), the TMR value was approximately 10 minutes if Fluolead™ was kept at 170 °C. From a series of ARC tests, the Temperature of No Return (TNR) values were measured for 25L and 210L scale and recorded in **Table 1** to assess the thermal hazard in process. Similarly, the Self Accelerating Decomposition Temperature (SADT) values were measured to assess the thermal hazard in storage and transportation and recorded also in **Table 1**.

	25L Drum		210L Drum	
TNR	158.5°C	(Hastelloy C)	157.3°C	(Hastelloy C)
	152.6°C	(SS316)	151.5°C	(SS316)
SADT	157°C	(Hastelloy C)	155°C	(Hastelloy C)
	151°C	(SS316)	150°C	(SS316)

Table 1. Estimated TNR and SADT Values of Fluolead Obtained by ARC

In general, TNR and SADT values indicate the maximum safe temperature for the handling of Fluolead™ in process, storage, and transportation is 150 °C; this is well above those for other deoxofluorination reagents on the market today. This high thermal stability allows Fluolead™ to be used in applications requiring temperatures in excess of 100 °C, such as the direct transformation of carboxyl group to trifluoromethyl group. In addition, this high thermal stability demonstrates the applicability of Fluolead™ for deoxofluorination reactions in large scale industrial production.



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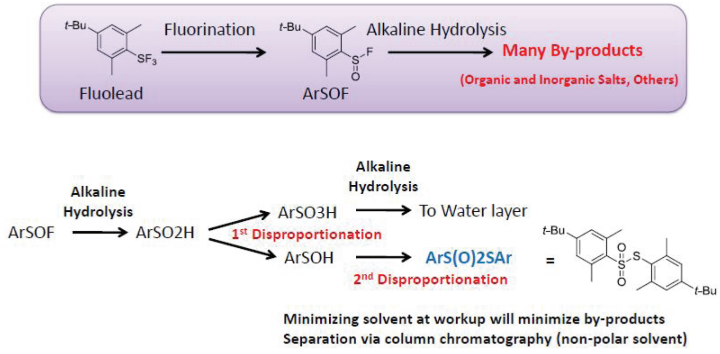
Experimental Conditions

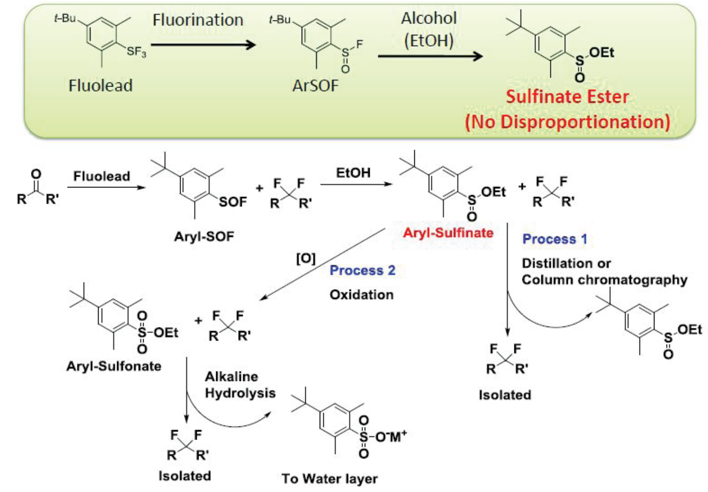
Representative Reaction: Fluorination of *p*-Bromobenzyl alcohol

To a solution of Fluolead (7.51 g, 30 mmol, 1.5 eq.) in 20 mL of dry dichloromethane cooled on an ice batch was added slowly a solution of *p*-Bromobenzyl alchohol (3.74 g, 20 mmol) in 15 mL of dry dichloromethane. After 0.5 h, the ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was poured into cooled 100 mL of 5% NaOH aqueous solution and the mixture was stirred at room temperature for 1 h. The product was extracted with dichloromethane and washed with water [note: most of the by-products from ArS(O)F was removed by this alkaline treatment]. The removal of solvent *in vacuo* gave the crude product which was further purified by chromatography to give 3.0 g (80%) of *p*-Bromobenzyl fluoride.

Scheme 1: Alkaline Hydrolysis



Scheme 2: Alcohol Addition



Work-Up Method A: Alkaline Hydrolysis

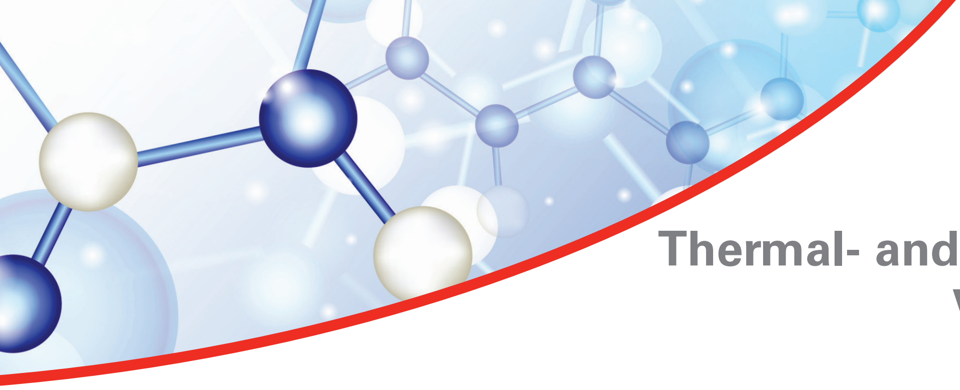
A standard method for removal of the ArS(O)F by-product (Ar = 4-*t*-Butyl-2,5-dimethylphenyl) is to use alkaline hydrolysis as shown in **Scheme 1**. However, because of possible disproportionation reactions, various by-products could be generated. Separation of the desired fluorinated product could be achieved with column chromatography but the purification process is highly dependent on the extend of by-product formation.

Work-Up Method B: Alcohol Addition

A newly developed method consists of the addition of an alchohol such as ethanol to the reaction mixture as shown in **Scheme 2**. Disporportionation reactions are avoided in this approach leading to a "controlled" by-product removal process.

Other Important Notes

1) Optimal solvents were found to be non-polar hydrocarbons (hexane, heptane, toluene, etc.) and halogenated hydrocarbons (dichloromethane, dichloroethane, etc.). With polar solvents (acetonitrile, ethyl acetate, etc.), fluorination does not proceed in many cases.
2) Pyridine-HF was found to be the most optimal additive.
3) The fluorination reaction should be performed in fluoropolymer vessel.
4) For fluorination reactions requiring temperature higher than room temperature, a "closed" system is preferred.



Fluolead™

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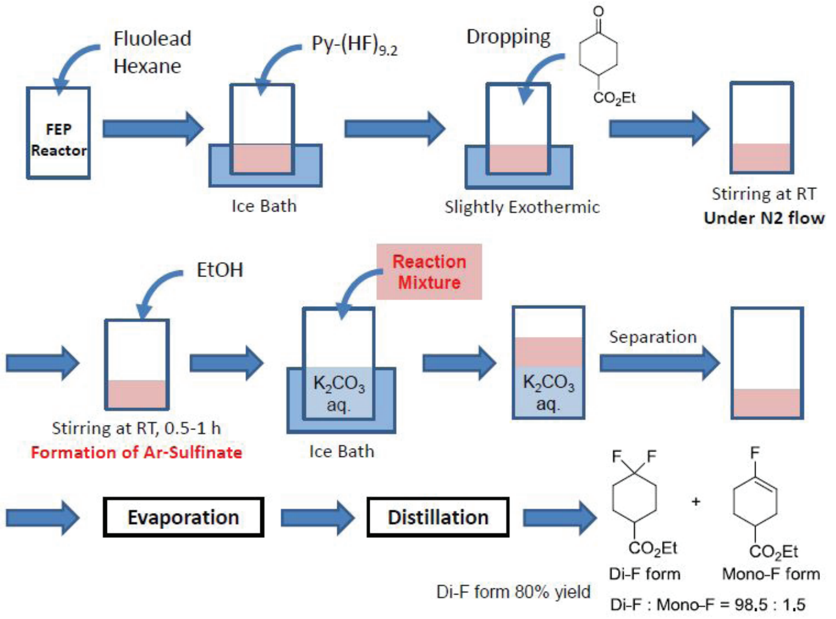
Experimental Conditions

Representative Workflow: Deoxofluorination of 4-Ethoxycarbonylcychohexanone / Alcohol Work-up, Process 1



Representative Workflow: Deoxofluorination of Fluorenone / Alcohol Work-up, Process 2