SYNLETT
Spotlight

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Fluorobis(phenylsulfonyl)methane (FBSM)

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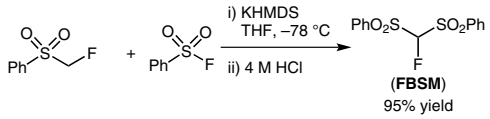
Introduction

Given the growing importance of fluorinated molecules in medicinal chemistry and chemical biology, several researchers are investigating the methods for the incorporation of fluorine into drug candidates since fluorine-containing compounds can have positive effects on the pharmacological properties of a drug. One of the most convenient ways to construct fluorine-containing organic molecules asymmetrically is the utilization of fluorobis(phenylsulfonyl)methane (FBSM), which has recently been introduced by Shibata and Hu, independently.[1] FBSM is a colorless solid, stable in air, and easily handled. It can readily be synthesized from fluoromethyl phenyl sulfone and benzenesulfonyl fluoride (Scheme 1).[2]

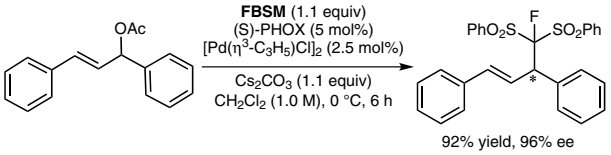
Recently, FBSM has widely been used as a potential monofluoromethide equivalent in synthetic organic transformations. For example, structurally diverse monofluorobis(phenylsulfonyl)methylated chiral adducts containing a hydroxyl-/or amino group are synthesized by means of asymmetric enamine, iminium, phase-transfer, and cooperative catalysis concepts. In particular, further reductive desulfonylation of the previous adducts can be accompanied by treatment with Mg-MeOH to give monofluoromethylated products in high yield, while keeping their enantioselectivity.



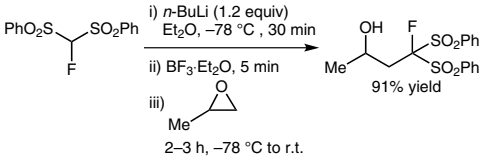
Scheme 1 Preparation of FBSM.

Abstracts

(A) Shibata, Toru and co-workers realized that FBSM is a suitable nucleophile for palladium-catalyzed enantioselective allylic monofluoromethylation of acyclic or cyclic allylic acetate.[1a] Interestingly, the authors found that incorporating a fluorine atom in the FBSM had a noticeably positive effect on the reactivity and the enantioselectivity compared to non-fluorinated bis(phenylsulfonyl)methane. In particular, biologically important molecules, such as methylfluorinated ibuprofen and 5-deoxy-5-fluoro-β-D-carbaribofuranose, were synthesized in enantiomerically pure form.



(B) Hu and co-workers reported a Lewis acid promoted non-asymmetric ring-opening reaction of epoxide with FBSM to give β-fluoroalkyl alcohols in one step.[1b] High regioselectivity is achieved by the resulting fluorinated carbanion, which is derived from FBSM and attacks at the sterically less hindered epoxide carbon.



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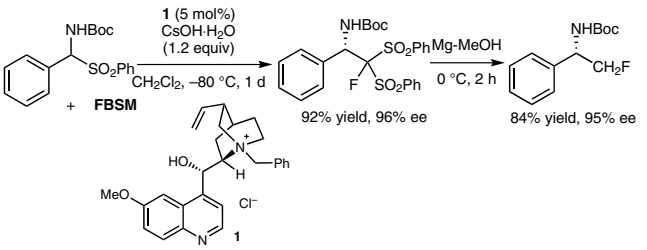
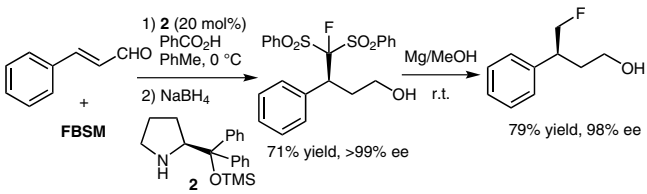
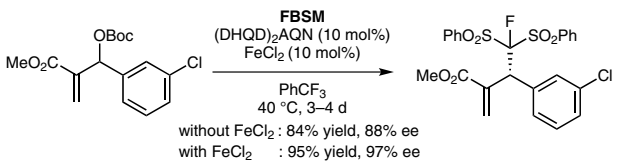
(C) Toru and co-workers developed an organocatalytic asymmetric monofluoromethylation reaction between aromatic or aliphatic α-amido sulfones and FBSM using a chiral quaternary ammonium salt derived from cinchona alkaloid, giving enantioenriched α-fluoromethyl amines via reductive desulfonylation with the Mg-MeOH system.[3] The key feature of this reaction is the in-situ generation of *N*-Boc-imines from the corresponding α-amido sulfones under basic conditions. In particular, a highly enolizable alkyl α-amido sulfone also furnished the corresponding product in excellent yield and enantioselectivity.



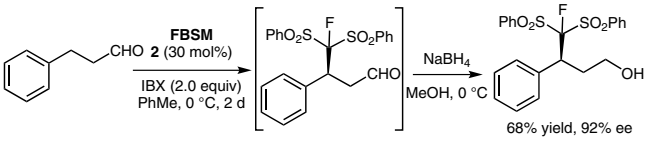
(D) Organocatalytic asymmetric Michael addition of FBSM to α,β-unsaturated aldehydes was independently developed by Moyano and Rios, Wang, and Córdova.[4] Iminium catalysis has proven to be a powerful strategy for the construction of optically active monofluoromethylated products. They observed that the chemical yield was remarkably enhanced due to the acceleration of iminium ion formation by reacting the enal with diphenylprolinol TMS-silyl ether **2** as aminocatalyst in the presence of benzoic acid.



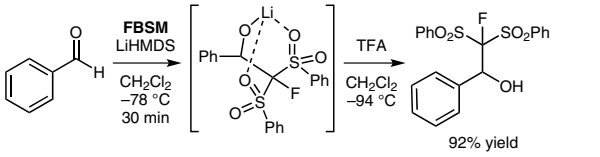
(E) A new cooperative catalytic system, consisting of $(DHQD)_2AQN$ and $FeCl_2$, promotes the enantioselective allylic monofluoromethylation of Morita–Baylis–Hillman carbonates with FBSM.[5] Interestingly, the bidentate chelating mode of FBSM with $FeCl_2$ as Lewis acid slightly enhanced the enantioselectivity of the product (maximum 10% ee) compared to without $FeCl_2$.



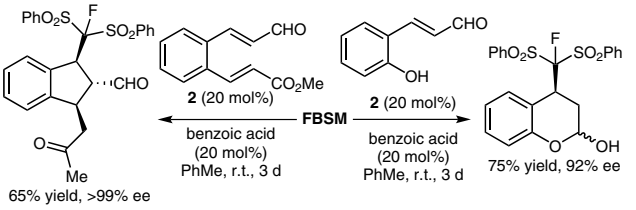
(F) Wang and co-workers developed a direct asymmetric β-functionalization of simple aldehydes with FBSM utilizing diphenylprolinol silyl ether **2** and *o*-iodoxybenzoic acid (IBX) as an oxidant via 'oxidative enamine catalysis'.[6] The enamine as the initial intermediate can be converted into an iminium species by the addition of IBX, allowing further enantioselective conjugate addition reactions to form the desired product with excellent enantioselectivity.



(G) The nucleophilic addition of FBSM to various aldehydes was performed in the presence of LiHMDS as a base.[7] Remarkable enhancement of the reactivity of FBSM could be attributed not only to the strong Li–O coordination in the carbinolate intermediate at low temperature, but also to the fluorine atom on the FBSM, which were verified by variable-temperature ^{19}F NMR spectroscopy and DFT calculations.



(H) Enantioselective cascade reactions for the synthesis of fluoroindane and fluorochromanol derivatives were achieved in moderate to good yields with high enantioselectivity by the groups of Yang and Rios.[8] The cascade reactions consist of either double Michael reaction or Michael hemiacetal formation via the addition of FBSM to α,β-unsaturated aldehydes in the presence of catalytic amounts of diphenylprolinol silyl ether **2**.



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