SYNLETT

# Spotlight 219

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

# *N*-Fluorobenzenesulfonimide [$(PhSO_2)_2NF$] – A Neutral N–F-Containing Electrophilic Fluorinating Agent

Compiled by Amin Rostami

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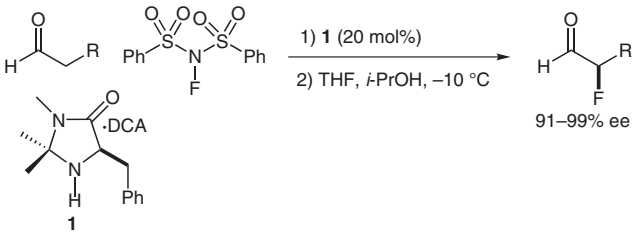
## Introduction

*N*-Fluorobenzenesulfonimide [NFSI] is a stable crystalline solid that easy to handle, non-hygroscopic, soluble in most common ethereal and chlorinated solvents, and commercially available. It is a neutral N–F-containing electrophilic fluorinating agent that permits the incorporation of fluorine into neutral and carbanionic nucleophiles ranging from very reactive organometallic species to slightly activated aromatic compounds.[1]

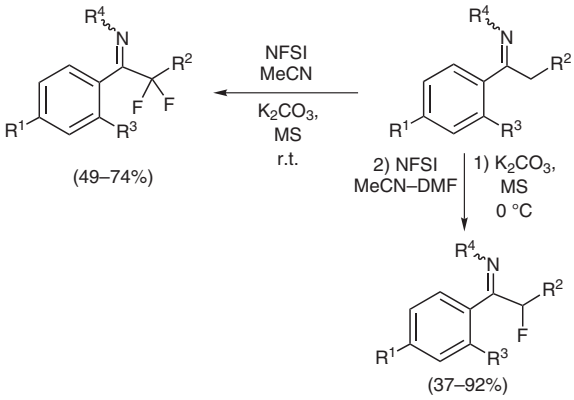
*N*-Fluorobenzenesulfonimide can be employed in the preparation of aryl (difluoromethylenephosphonates),[2] 20-deoxy-20-fluorocamptothecin,[3] *N*-fluoro sulfonamides,[4] 2-amino-5-fluorothiazole hydrochloride[5] and benzylic α,α-difluoronitriles, -tetrazoles, and -sulfonates.[6] When NFSI was associated with chiral palladium complexes an efficient method to catalytic enantioselective fluorination of β-keto esters,[7] and α-cyano acetates[8] was presented.

## Abstracts

The use of imidazolidinone **1** as the asymmetric catalyst has been found to mediate the fluorination of aldehyde substrates with *N*-fluorobenzenesulfonimide serving as the electrophilic source of fluorine. A wide range of functional groups, including olefins, esters, amines, carbamates, and aryl rings, can be readily tolerated on the aldehydic substrate.[9]




Various *N*-alkylimines derived from acetophenones were successfully monofluorinated using *N*-fluorosulfonimide (NFSI) in a mixture of acetonitrile and DMF at 0 °C. Alternatively the same procedure without DMF gave rise to diflourinated imines when performed at room temperature. The obtained α- and α,α-difluorinated imines were subsequently reduced to give the corresponding β-fluoro- and β,β-difluoroamines in good yield.[10]

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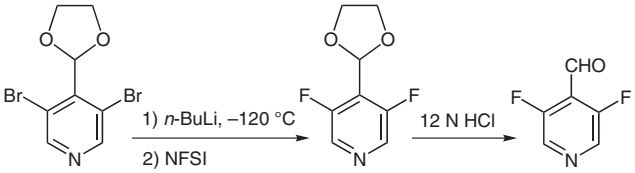
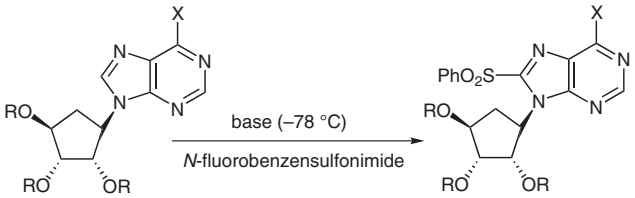
NFSI was used for synthesis of novel 3,5-difluoropyridine-4-carboxaldehyde. Difluorination was achieved through the reaction of 3,5-dibromo-1,3-dioxolane pyridine with *n*-butyllithium followed by *N*-fluorobenzenesulfonimide at –120 °C in good yield.[11]

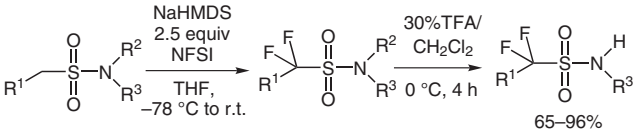



Reaction of the in situ generated purine C-8 carbanion of a protected 5′-noraristeromycin derivative with *N*-fluorobenzenesulfonimide gave 8-phenylsulfonyl-5′-noraristeromycin rather than the expected 8-fluoro derivative. A single electron transfer (SET) mechanism is proposed for this occurrence. The phenylsulfonyl product offers a structural feature common to some anti-HIV agents.[12]



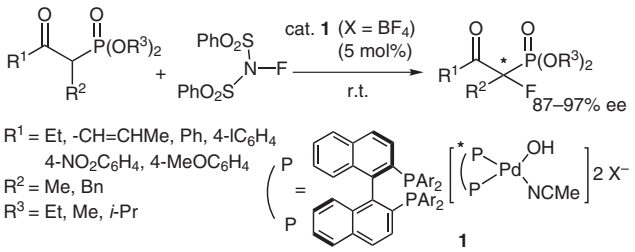

R = TBS, X = Cl, $NH_2$
base = LDA, *n*-BuLi

α-Fluorosulfonamides were prepared by electrophilic fluorination of tertiary sulfonamides using *N*-fluorobenzenesulfonimide as fluorinating agent and utilizing the dimethoxybenzyl group (DMB) as a new sulfonamide protecting group. Removal of the DMB group with TFA/$CH_2Cl_2$ gave primary and secondary α-fluorosulfonamides.[13]




$R^1$ = Ph, 4-$BrC_6H_4$, 4-$IC_6H_4$, 4-$NO_2C_6H_4$, 4-$MeC_6H_4$, 3-$BrC_6H_4$
$R^2$ = DMB
$R^3$ = Ph, Me, H

D. Y. Kim and coworkers reported the catalytic enantioselective fluorination of β-keto phosphonates catalyzed by a chiral palladium complex. Treatment of β-keto phosphonates with *N*-fluorobenzenesulfonimide (NFSI) as electrophilic fluorinating reagent under mild reaction conditions afforded the corresponding α-fluorinated β-keto phosphonates in moderate to excellent yields with excellent enantiomeric excesses.[14]




$R^1$ = Et, -CH=CHMe, Ph, 4-$IC_6H_4$, 4-$NO_2C_6H_4$, 4-$MeOC_6H_4$
$R^2$ = Me, Bn
$R^3$ = Et, Me, *i*-Pr

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