

SYNLETT Spotlight 411

N-Fluorobenzenesulfonimide

Compiled by Vincent Bizet



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

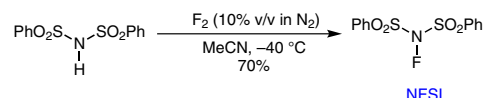
Vincent Bizet received his Master degree in 2009 from the University of Caen, France under the supervision of Professor Jacques Rouden and Professor Marie-Claire Lasne. He is currently working towards his PhD at the INSA of Rouen, France under the supervision of Dr. Dominique Cahard (CNRS Research Director). His research interest focusses on the asymmetric synthesis of fluorinated compounds and on catalysis by transition metals.

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Introduction

N-Fluorobenzenesulfonimide (NFSI) is a colorless crystalline powder with a melting point of 114–116 °C. One of the most convenient routes to prepare NFSI in high yield is the fluorination with 10% v/v F₂ in N₂ of *N*-(phenylsulfonyl)benzenesulfonamide in MeCN at –40 °C (Scheme 1).¹ NFSI can also be prepared from the corresponding sodium salt.² NFSI has been widely used as an electrophilic fluorinating agent most particularly in the field of asymmetric electrophilic fluorination.³ But NFSI

is more than an electrophilic fluorinating agent: It is also a strong oxidant for organometallic intermediates to promote reductive elimination through high-oxidation-state transition metals, an amination reagent and even a phenylsulfonyl group transfer reagent.

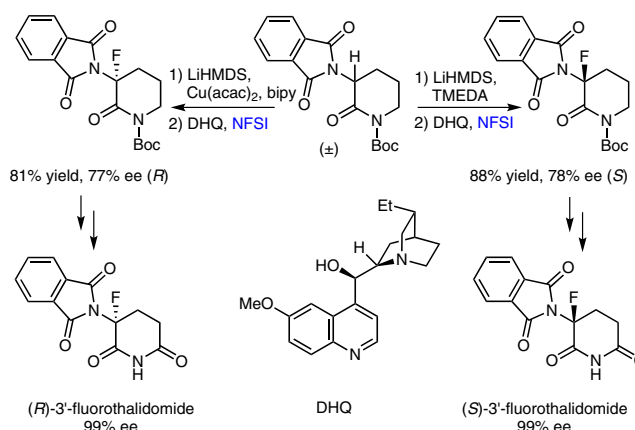


Scheme 1 Synthesis of *N*-fluorobenzenesulfonimide (NFSI)

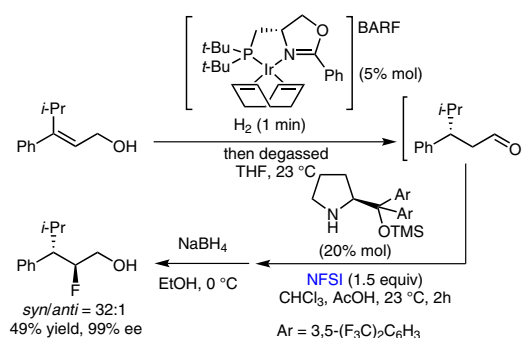
Abstracts

NFSI as Fluorinating Reagent:

(A) Shibata and co-workers reported the enantioselective synthesis of 3'-fluorothalidomide through an electrophilic fluorination using a combination of cinchona alkaloid and NFSI. The appropriate choice of additives allowed enantiodivergent fluorination using a single alkaloid; indeed, TMEDA as ligand provided the *S*-enantiomer whereas bipy–Cu(acac)₂ gave the *R*-enantiomer. Pure enantiomers were obtained after deprotection and oxidation.⁴ In the prospect of the synthesis of radiopharmaceuticals, such as ¹⁸F-fluorothalidomide, for positron emission tomography (PET) analysis, [¹⁸F]NFSI has been developed.⁵



(B) Mazet, Alexakis and co-workers have developed a sequential iridium-catalyzed redox isomerization–organocatalytic fluorination. The intermediate aldehyde, which was the result of the redox isomerization of the starting primary allylic alcohol, was submitted to the electrophilic fluorination by means of NFSI through enamine catalysis with 20 mol% of a proline derivative. A quench by NaBH₄ produced the fluoroalcohol that featured two stereogenic centers in an overall 49% yield with 99% ee for the main *syn*-diastereoisomer.⁶



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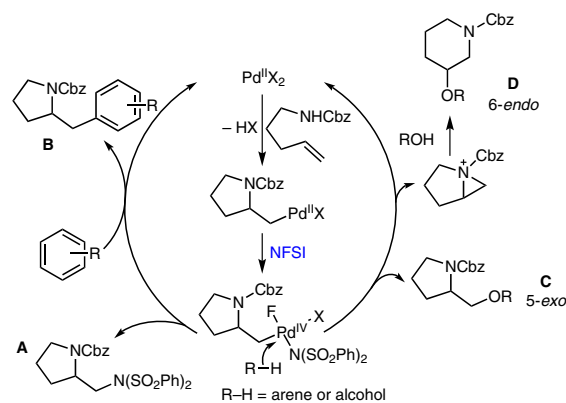
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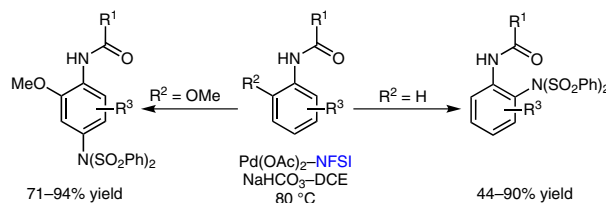
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NFSI as Oxidizing Reagent:

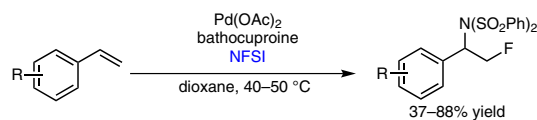
(C) NFSI has been used as a versatile oxidant in reactions that involve a Pd^{II}–Pd^{IV} catalytic cycle.⁷ Michael and co-workers described the palladium-catalyzed diamination, carboamination and alkoxyamination of unactivated alkenes using NFSI as an oxidant. The oxidative addition of NFSI allowed the formation of a Pd^{IV} intermediate; then reductive elimination led to the diamination product **A**.⁸ The Pd^{IV} intermediate could also react with nucleophilic arenes to form the carboamination product **B** through C–H activation followed by reductive elimination.⁹ When the reaction was performed in alcoholic solvents, the solvolysis of the Pd^{IV} intermediate led to the alkoxyamination 5-*exo* product **C** or through neighboring group participation to the 6-*endo* product **D** depending on solvent polarity.¹⁰

*NFSI as Amination Reagent:*

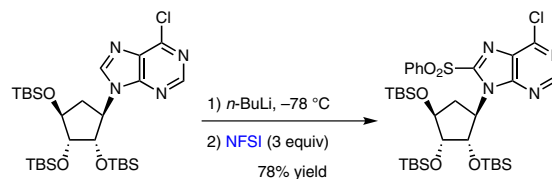
(D) NFSI has also been used to realize the selective amination of various compounds. Zhang and co-workers described the amide-directed palladium-catalyzed selective aromatic C–H amination of amides with NFSI in good yields.¹¹ In addition, it was demonstrated that NFSI is the decisive reagent for the oxidative amination of C(sp³)–H bonds at benzylic positions under palladium^{12,13} or copper catalysis.¹⁴



(E) Liu and co-workers described an intermolecular Pd-catalyzed oxidative aminofluorination of vinyl arenes with NFSI in the presence of bathocuproine. NFSI functioned not only as an amination agent but also as a fluorination and an oxidizing reagent. The reaction affords vicinal fluoroamine products with very high regioselectivity.¹⁵

*NFSI as Phenylsulfonyl Transfer Reagent:*

(F) The reaction of the purine C-8 carbanion of a protected 5'-noraristeromycin derivative with NFSI failed to give the expected 8-fluoroderivatives but gave the 8-phenylsulfonyl-5'-noraristeromycin instead. This phenylsulfonyl transfer proceeds via a single electron transfer.¹⁶



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