SYNLETT
Spotlight 437

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

# PhenoFluor

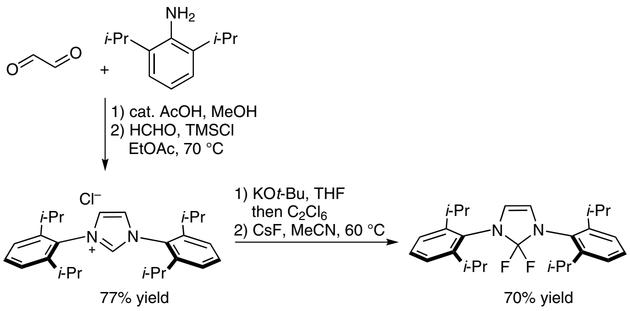
Compiled by Jana Franke

Jana Franke was born in Wolmirstedt, Germany, in 1984. She was a visiting scholar with Dr. Martin D. Smith at Oxford University, UK, in 2009 and received her diploma in chemistry from the Leibniz University of Hannover, Germany, in 2010. She is currently pursuing a Ph.D. under the supervision of Professor Dr. Andreas Kirschning at the Leibniz University of Hannover. Her current research is focused on natural product synthesis.

Department of Organic Chemistry, Leibniz University of Hannover, Schneiderberg 1B, D-30167 Hannover, Germany
E-mail: jana.franke@oci.uni-hannover.de

## Introduction

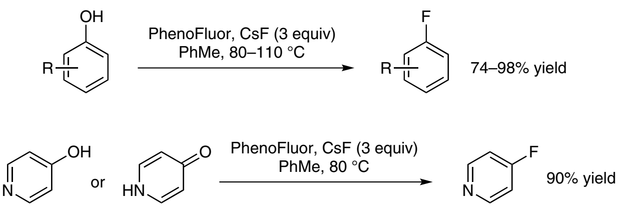
Fluorine has been demonstrated to have a dramatic impact on the physiochemical properties of organic compounds.[1,2] These effects can often lead to altered solubility and influence drug metabolism[3] making it an interesting substituent for pharmaceutical studies and drug design. The introduction of fluorine can be accomplished by deoxyfluorination. Although there are many commercially available fluorinating agents, there is still a lack of reagents for the manipulation of more complex molecules. A new nucleophilic deoxyfluorination reagent, **1,3-bis-(2,6-diisopropylphenyl)-2,2-difluoro-2,3-dihydro-1*H*-imidazole (PhenoFluor)**, has recently been developed by Ritter and co-workers.[4] It is air stable and can be stored in anhydrous toluene for about two months without detectable decomposition. The reagent is commercially available[5] (CAS: 1314657-40-3) as a crystalline, non-explosive solid. Furthermore, an exotherm of only 0.15 kcal·g$^{-1}$ was observed by differential scanning calorimetry (DSC) at PhenoFluor's decomposition temperature of 213 °C. PhenoFluor can be used in different solvents such as toluene, dioxane and dichloromethane (MeCN is not suitable). The only drawback is its high molar mass of 427 g·mol$^{-1}$ making it impractical in large-scale reactions. It can be synthesized in four steps from glyoxal and 2,6-di-*tert*-butylaniline.



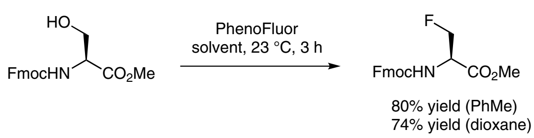

**Scheme 1** Preparation of PhenoFluor.

## Abstracts

(A) *Deoxyfluorination of Phenols:*
Fluoroarenes bearing a large variety of substitution patterns can be synthesized from their corresponding phenols using PhenoFluor. In addition to phenols that contain electron-withdrawing groups, electron-rich arenes can be fluorinated in one step in good yield.[6]




(B) *Deoxyfluorination of Primary Alcohols:*
The fluorination of primary alcohols proceeds under mild reaction conditions and is compatible with many functional groups.[7] A challenging substrate for deoxyfluorination reagents is the Fmoc-serine methyl ester that is prone to elimination of water or aziridine formation. However, fluorination of this substrate could be accomplished with PhenoFluor in high yield in dioxane (74%) and toluene (80%), while other commercially available deoxyfluorination reagents (e.g., DFI, DAST, Deoxofluor, Fluolead) failed to give the desired product.

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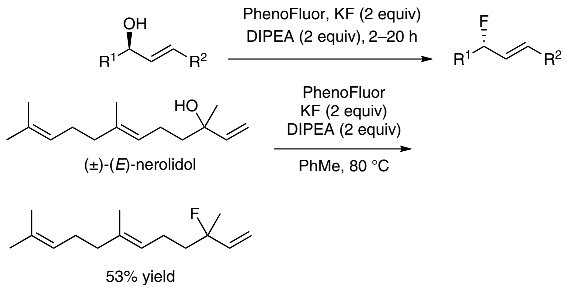
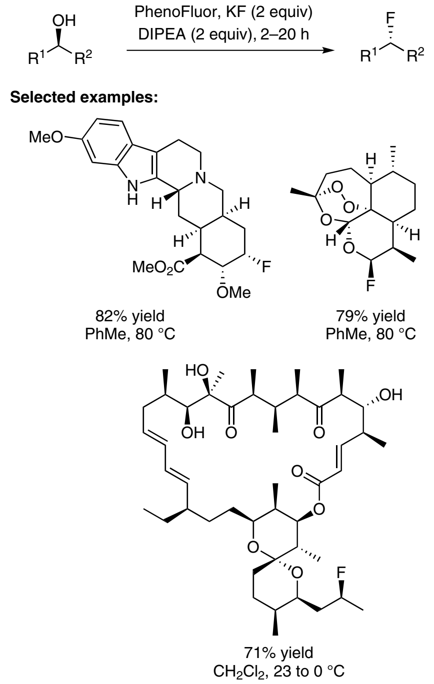
(C) *Deoxyfluorination of Allylic Alcohols:*
Allylic alcohols can be fluorinated chemoselectively in the presence of aliphatic secondary and tertiary alcohols. The reaction of allylic secondary alcohols proceeds via an $S_N2$ mechanism and only small amounts of the $S_N2'$-type product are obtained. Even tertiary allylic alcohols, as found in (±)-*(E)*-nerolidol, can be fluorinated.[7]




(D) *Deoxyfluorination of Secondary Alcohols:*
Ritter and co-workers demonstrated the potential of this fluorination method by synthesizing several fluorinated derivatives of natural products and pharmaceuticals.[7] Hydroxyl groups that participate in hydrogen bonding do not react, while secondary alcohols, including hemiacetals and hemiaminals, are substituted smoothly.




## References and Notes


(1) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.

(2) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, **2004**.

(3) Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 443.

(4) Professor Dr. Tobias Ritter, co-founder and chief scientific advisor of *SciFluor* in cooperation with *SciFluor Life Sciences LLC* in Cambridge, MA, USA.

(5) PhenoFluor$^{TM}$ is commercially available at Sigma Aldrich.

(6) Tang, P.; Wang, W.; Ritter, T. *J. Am. Chem. Soc.* **2011**, *133*, 11482.

(7) Sladojevich, F.; Arlow, S. I.; Tang, P.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 2470.

