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2,2-Difluoro-1,3-Dimethylimidazolidine (DFI) Deoxofluorination

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Introduction

2,2-Difluoro-1,3-dimethylimidazolidine (DFI) was first reported as a novel deoxofluorination reagent by Hayashi and coworkers in 2002 [1]. It is a clear liquid with boiling point of 47 °C at 37 mmHg and melting point of −8.7 °C [1]. In terms of the chemical structure, DFI is similar to other α,α-difluoroalkylamine agents such as Yarovenko [2] and Ishikawa [3] agent. Accelerating rate calorimetry (ARC) analysis showed that thermal decomposition of DFI begins at 150 °C [1], while diethylaminosulfur trifluoride (DAST) decomposes at about 90 °C [4], indicating that DFI is much more thermally stable.

Deoxofluorination with DFI

DFI is more reactive than Yarovenko and Ishikawa agents due to the stabilizing effects endowed by the two nitrogen atoms adjacent to difluoromethylene. In addition to alcohols and carboxylic acids, aldehydes/ketones and even some phenols can be converted to the corresponding deoxofluorinated products. The reaction can be performed in acetonitrile, dichloromethane, and glyme (Scheme 1). For primary alcohols, the corresponding alkyl fluorides can be obtained in good yields under mild conditions (Scheme 1, Eq. 1). However, for some secondary alcohols, elimination products are dominant (Scheme 1, Eq. 2). At elevated temperatures, DFI reacts with non-enolizable aldehydes/ketones to afford *gem*-difluoro compounds in moderate to high yields (Scheme 1, Eq. 3); however, in the cases of enolizable carbonyl compounds, vinyl fluorides and aryl acetylene side products are generated as the main products (Scheme 1, Eqs. 4 and 5). Moreover, the hydroxy groups of phenols bearing electron-withdrawing groups can be replaced with fluorine by DFI. For example, treating 4-nitrophenol with DFI in acetonitrile at 85 °C for 15 h affords 4-fluoronitrobenzene in 62% yield (Scheme 1, Eq. 6). However, fluorobenzene cannot be obtained by the reaction of DFI with phenol; instead, 1,3-dimethyl-2-phenoxyimidazolinium hydrogen fluoride is generated [1]. Besides, unlike other deoxofluorination reagents such as SF_4 [5] and Fluolead [6], DFI cannot convert COOH into CF_3 group.

Kitazume and coworkers reported the fluorination of various alcohols, aldehydes and ketones

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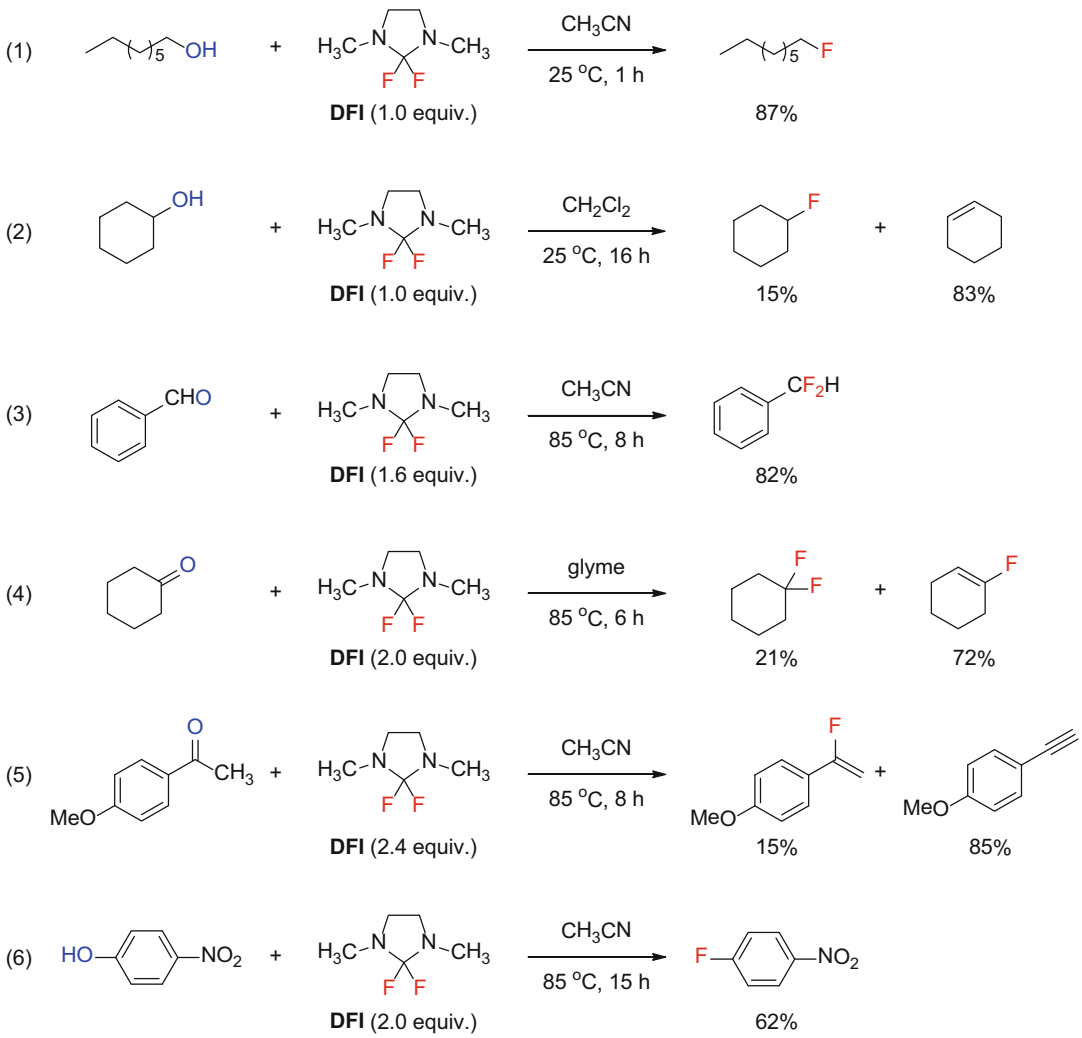
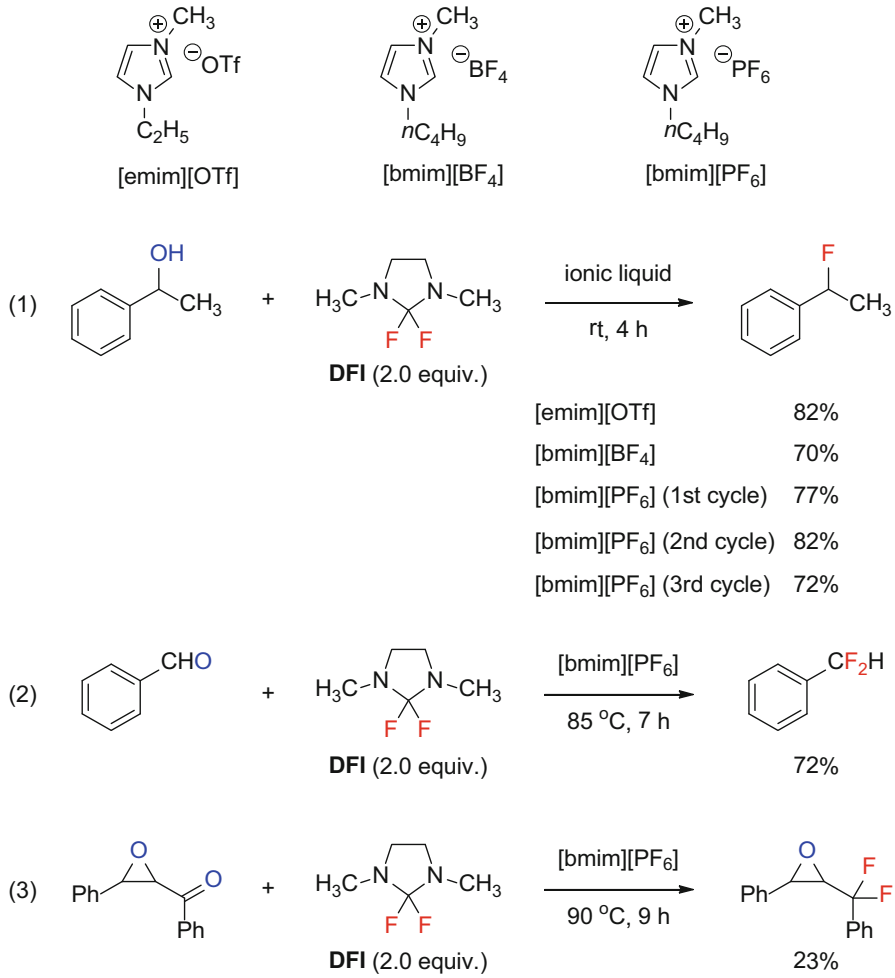


2,2-Difluoro-1,3-Dimethylimidazolidine (DFI) Deoxofluorination, Scheme 1 Fluorination of typical compounds with DFI

with DFI in ionic liquids (Scheme 2) [7]. By using ionic liquids as reaction solvent, no conventional aqueous work-up procedures are needed; moreover, the solvent can be recovered easily after extracting the fluorination products with diethyl ether. After being purified under dynamic vacuum at 70–80 °C for 1 h, the recovered ionic liquid can be reused for the fluorination process (Scheme 2, Eq. 1). In ionic liquid [bmim] [PF_6], DFI react with aldehydes/ketones affording *gem*-difluoro compounds under elevated temperatures (Scheme 2, Eqs. 2 and 3). Of note the epoxide group is kept intact during the reaction.

Regeneration of DFI

After the fluorination, DFI is transformed into 1,3-dimethyl-2-imidazolidinone (DMI), which can be recovered to regenerate DFI (Scheme 3). Firstly, DMI is converted into 2-chloro-1,3-dimethylimidazolinium chloride (CDC) via the chlorinating reaction with chlorination reagents such as phosgene and oxalyl chloride. After that, DFI is produced by the halogen exchange reaction of CDC with spray dried KF in solvents such as DMI and acetonitrile at 80–90 °C. Pure DFI can be easily obtained by filtration (to remove the



2,2-Difluoro-1,3-Dimethylimidazolidine (DFI) Deoxofluorination, Scheme 2 Deoxofluorination with DFI in ionic liquid

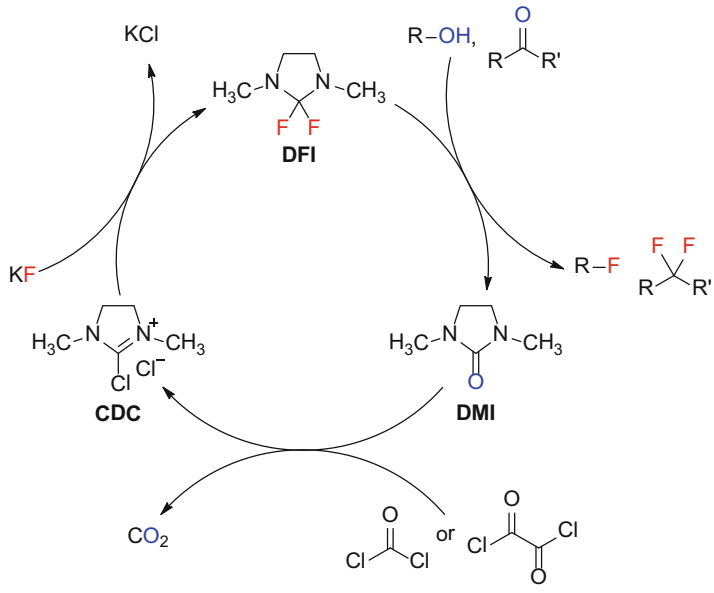
by-product KCl and excess KF) and subsequent distillation (to remove the solvent). The DFI solution obtained after filtration could also be used directly for fluorination. Comparing with DFI, DAST, and Deoxo-Fluor, all of which cannot be regenerated after the fluorinating reaction, DFI is more economical and can be used in industry [1].

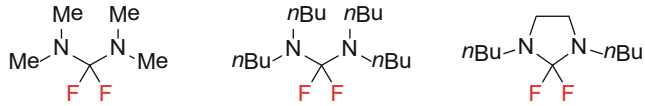
Deoxofluorination with DFI Analogues

By using the ring-opening structure or changing the substitution group on *N* atom in DFI, Hayashi and coworkers prepared several DFI analogues with varying fluorination capability and thermal stability (Scheme 4) [1].

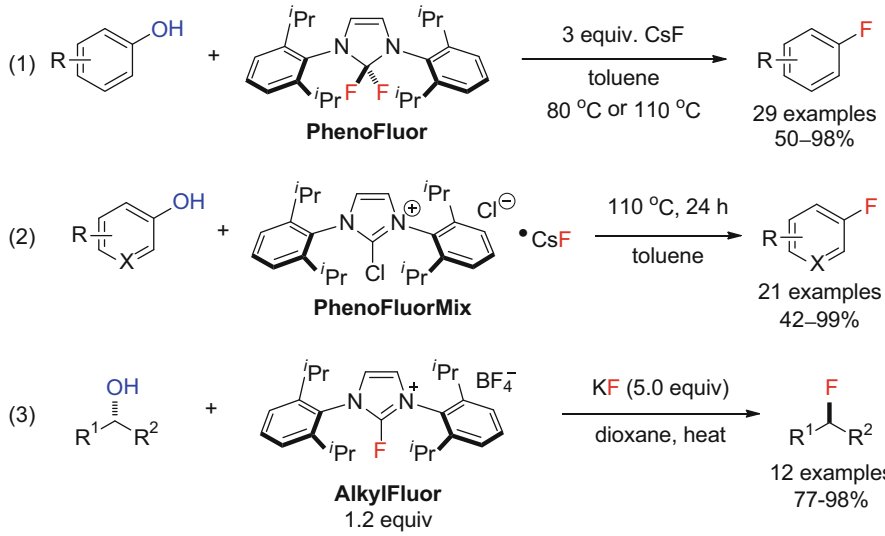
In 2011, Ritter and coworkers reported a new DFI analogue PhenoFluor [8], in which 2,6-diisopropylphenyl was used instead of methyl group and the imidazolidine ring was changed into imidazolidine ring. PhenoFluor [8–10], together with its imidazolium salt derivatives PhenoFluorMix [11] and AlkylFluor [12], have been used as powerful reagent for the deoxofluorination of various phenols and alcohols (Scheme 5).

2,2-Difluoro-1,3-Dimethylimidazolidine (DFI) Deoxofluorination, Scheme 3 Recycling of DMI in the fluorination reaction by DFI





2,2-Difluoro-1,3-Dimethylimidazolidine (DFI) Deoxofluorination, Scheme 4 DFI analogues developed by Hayashi and coworkers



2,2-Difluoro-1,3-Dimethylimidazolidine (DFI) Deoxofluorination, Scheme 5 Deoxofluorination with PhenoFluor and its derivatives

Conclusion and Future Directions

In conclusion, DFI is a thermally stable and economical deoxofluorination reagent, and the byproduct DMI can be reused to prepare DFI, which makes it practical for industry application. However, the substrate scope is limited owing to ready elimination reactions induced by DFI [13]. The development of PhenoFluor with a more complex structure has largely extended the synthetic application of this kind of "-NCF_2N-" reagents, although the cost is still much greater.

Cross-References

- α,α-Difluorobenzylamines Deoxofluorination
- Fluoroolefin-Amine Adduct Deoxofluorination
- PhenoFluor Deoxofluorination
- Tetramethylfluoroformamidinium Hexafluorophosphate (TFFH) Deoxofluorination

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