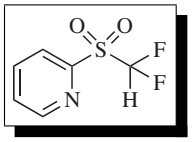
Difluoromethyl 2-Pyridyl Sulfone

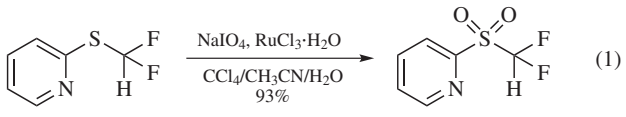


[1219454-89-3] $C_6H_5F_2NO_2S$ (MW 193.17)
InChI = 1S/C6H5F2NO2S/c7-6(8)12(10,11)5-3-1-2-4-9-5/h1-4,6H
InChIKey = YRQNSTAWTLXCEZ-UHFFFAOYSA-N

(*gem*-difluoroolefination reagent;[1,7,9] nucleophilic difluoro (sulfonato)methylation reagent[2–4])

Physical Data: mp 45–47 °C.[1]
Solubility: insoluble in H_2O; soluble in organic solvents.
Form Supplied in: white solid or colorless crystal.
Preparative Method: prepared by oxidation of 2-[(difluoromethyl)thio]pyridine with sodium metaperiodate/ruthenium(III) chloride hydrate or sodium tungstate dihydrate/hydrogen peroxide.[1,2]
Handling, Storage, and Precautions: moisture and air stable, not sensitive to visible light.[9]

Preparation of Difluoromethyl 2-Pyridyl Sulfone. Difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$) is prepared from 2-[(difluoromethyl)thio]pyridine (2-$PySCF_2H$) and sodium metaperiodate ($NaIO_4$) in the presence of ruthenium(III) chloride hydrate ($RuCl_3 \cdot xH_2O$) (eq 1).[1] Other oxidative conditions include mixing 2-[(difluoromethyl)thio]pyridine (2-$PySCF_2H$) and hydrogen peroxide (H_2O_2) in the presence of sodium tungstate dihydrate ($Na_2WO_4 \cdot 2H_2O$) (eq 2).[2] Unlike the use of superstoichiometric sodium metaperiodate (eq 1), low-cost hydrogen peroxide is added as the oxidant in the latter case (eq 2). Moreover, the residual hydrogen peroxide should be removed during the workup and/or purification process.



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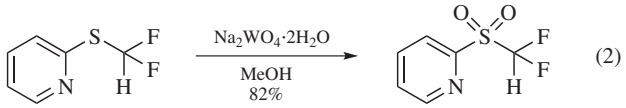
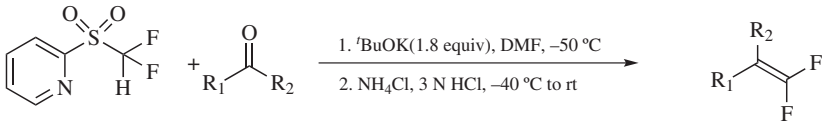


(2)

***gem*-Difluoroolefination Reaction with Aldehydes and Ketones.** 2-$PySO_2CF_2H$ can be used as a Julia–Kocienski-type *gem*-difluoroolefination reagent for aldehydes and ketones. In general, an excess amount of potassium *tert*-butoxide (^{t}BuOK) is added to a *N*,*N*-dimethylformamide (DMF) solution of 2-$PySO_2CF_2H$ and the substrate at −50 °C, then the reaction mixture is warmed to −40 °C, and subsequently quenched with hydrochloric acid (HCl) (eq 3).[1] 2-$PySO_2CF_2H$ can be used in the *gem*-difluoroolefination of aldehydes and ketones containing various functional groups, and the reaction is amenable to



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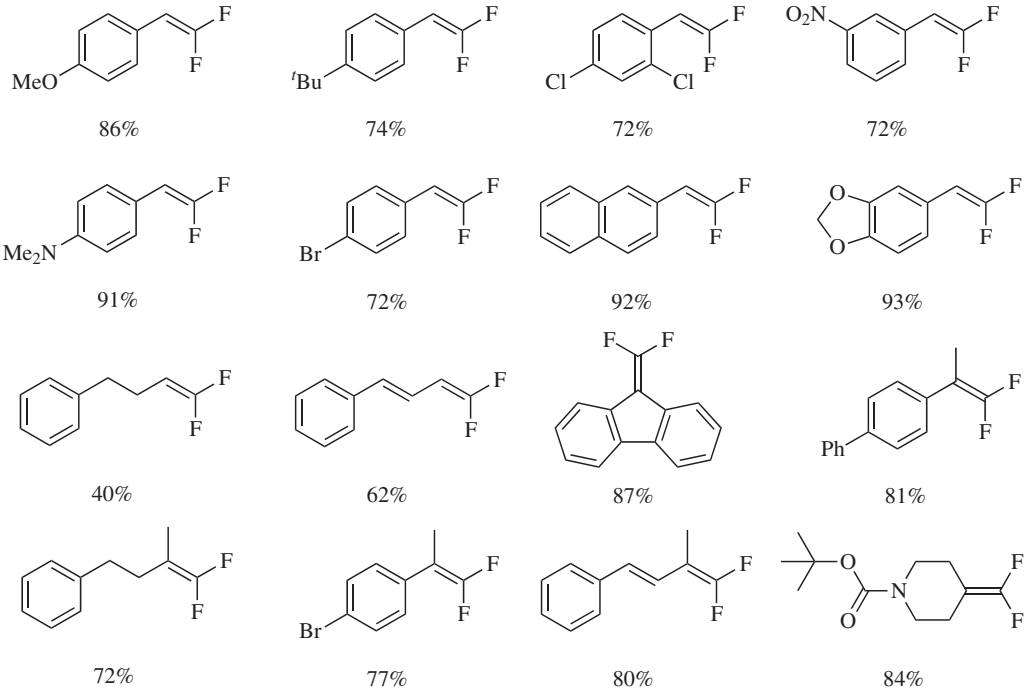
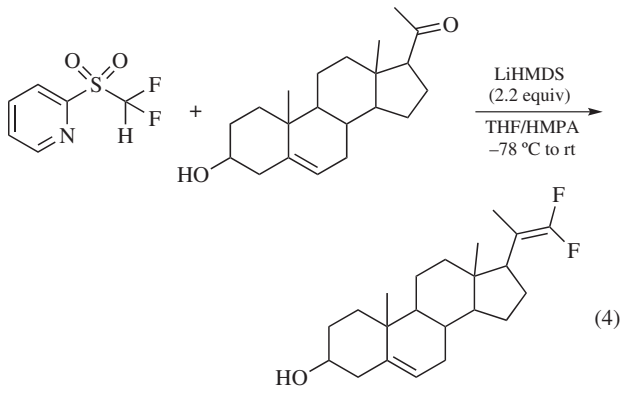


aromatic carbonyl compounds. Furthermore, this *gem*-difluoroolefination reaction is also successfully applied to the synthesis of 21,21-difluoro-3-hydroxy-20-methylpregna-5, 20-diene (eq 4).[1]



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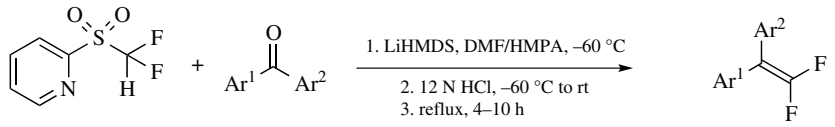
Later on, this *gem*-difluoroolefination reaction is modified to be more amenable to diaryl ketones and enolizable aldehydes. For diaryl ketones, *N*,*N*-dimethylformamide and hexamethylphosphoramide (HMPA) are used as cosolvents to dissolve 2-$PySO_2CF_2H$ and the substrate. A solution of lithium hexamethyldisilazide (LiHMDS) is injected into the solution at −60 °C (eq 5).[7] For enolizable aldehydes, catalytic amounts of tris(trimethylsilyl)amine [$N(TMS)_3$] and cesium fluoride (CsF) are added, and the in situ generated base $N(TMS)_2^-$ promotes the *gem*-difluoroolefination reaction (eq 6).[7] These modified procedures are able to extend the substrate scope to base-sensitive or sterically hindered carbonyl compounds.



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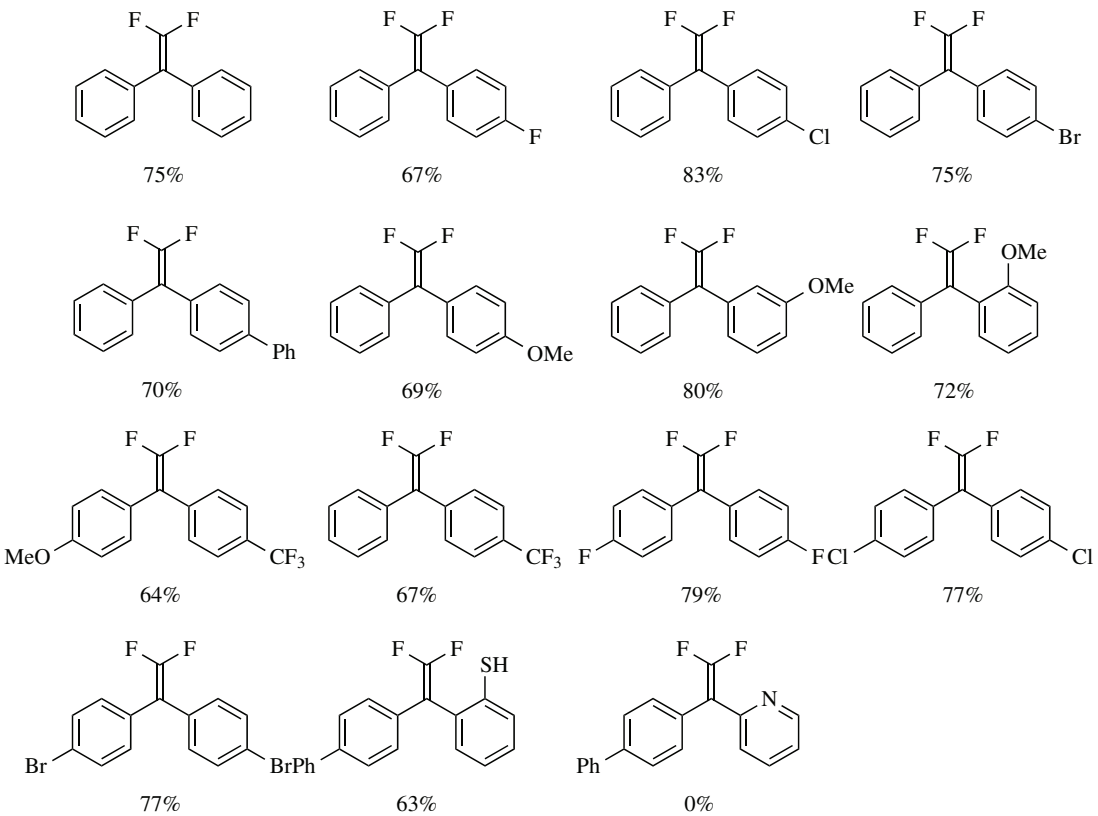
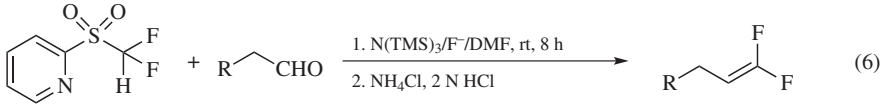
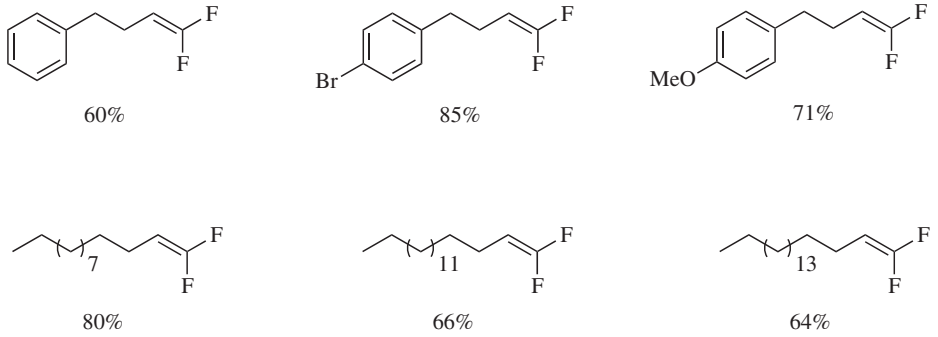
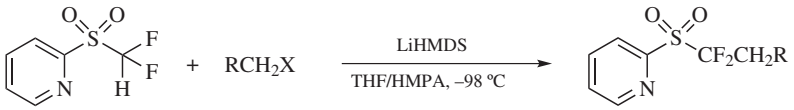
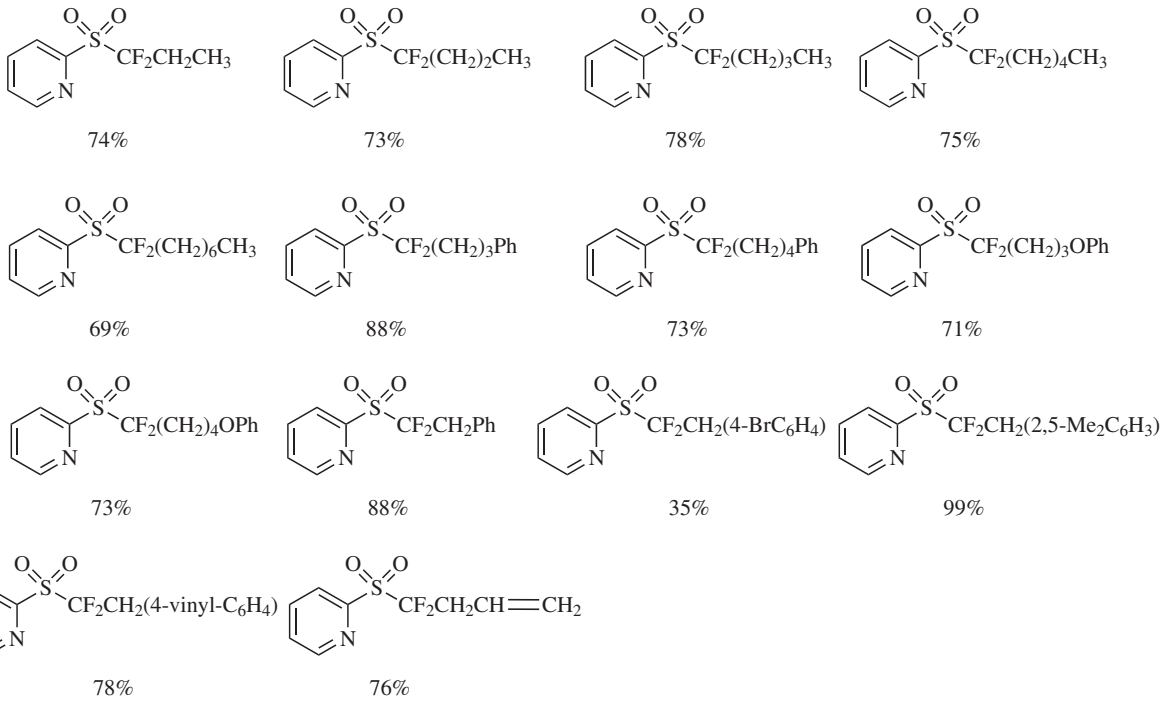


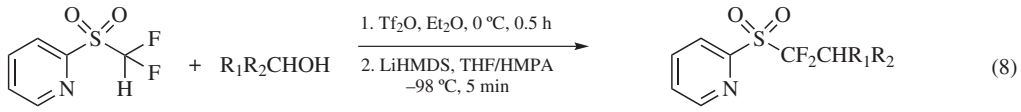




Nucleophilic Difluoro(sulfonato)methylation of Halides and Alcohols. The title reagent can also difluoro(sulfonato)methylate alkyl halides to give substituted difluoromethyl sulfones. A low reaction temperature (−98 °C) is required. The reaction is compatible with various iodides or bromides (eq 7).[2] Alcohols can be first transformed into the corresponding **/trifluoromethanesulfonates, and the latter species** are subjected to the difluoro(sulfonato)methylation in a one-pot process (eq 8).[2] After the reaction with halides, the pyridyl group can be removed with sodium ethylthiolate (EtSNa)/ethanethiol (EtSH) to provide the corresponding 1,1-difluoroalkanesulfinates. Further oxidation with hydrogen peroxide (H_2O_2) will give various difluorinated sulfonates (eq 9).[2]







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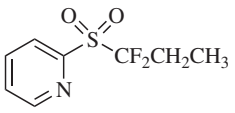

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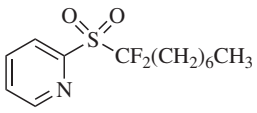

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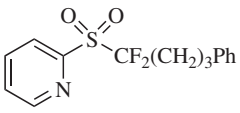

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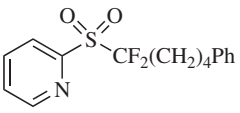

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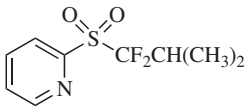

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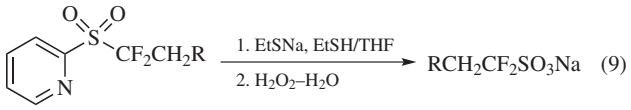
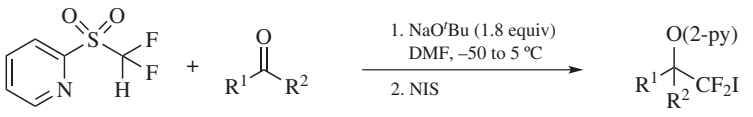


(9)

Formal Nucleophilic Iodo- and Bromodifluoromethylation of Carbonyl Compounds. The 2-$PySO_2CF_2H$ reagent can react with carbonyl compounds to provide the in situ generated sulfinate intermediates from the Julia–Kocienski pathway. Subsequently, these intermediates undergo halogenation in the presence of *N*-iodosuccinimide (NIS) (eq 10)[3,10] or trimethylphenylammonium tribromide ($PhMe_3NBr_3$) (eq 11)[3,10] to give the corresponding halodifluoromethylated products. The overall transformation represents a formal nucleophilic iodo- and bromodifluoromethylation reaction for carbonyl compounds. The pyridinoxyl group in the products can be removed at elevated temperature, and CF_3COOH is added to promote the hydrolysis of the pyridinoxyl group to a hydroxyl group (eq 12).[3]



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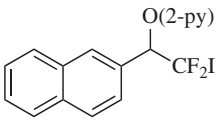

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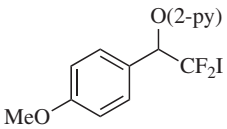

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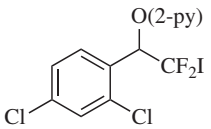

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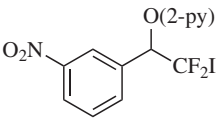

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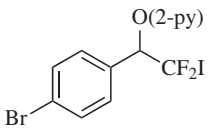

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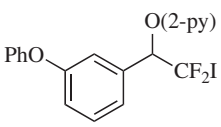

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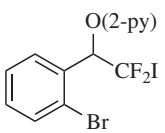

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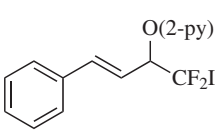

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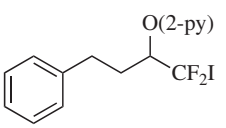

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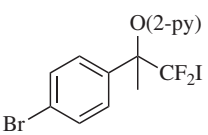

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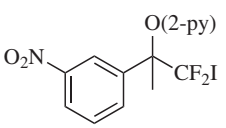

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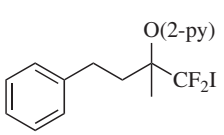

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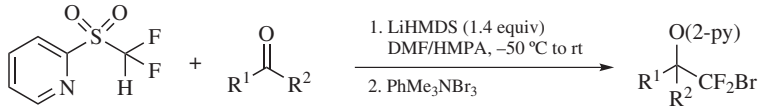

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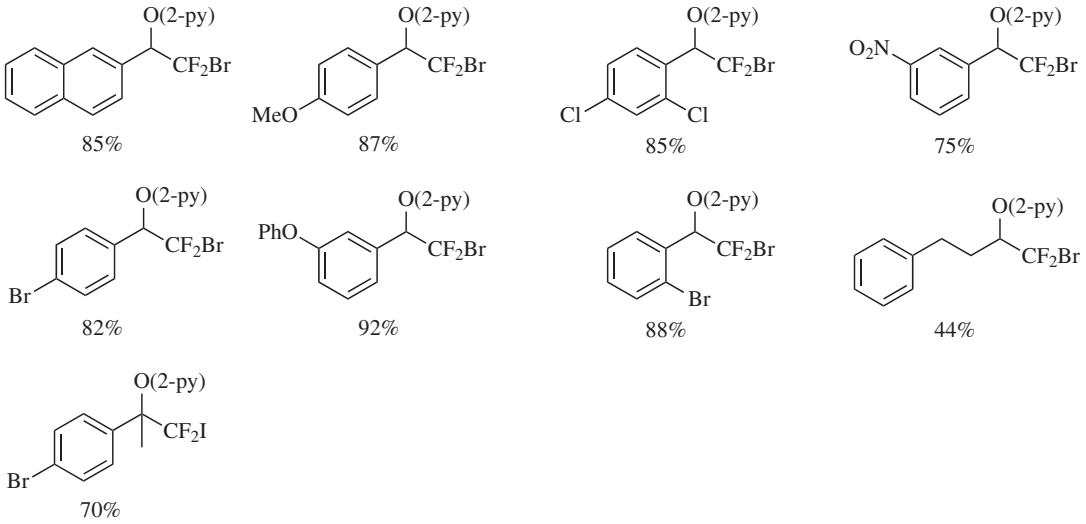

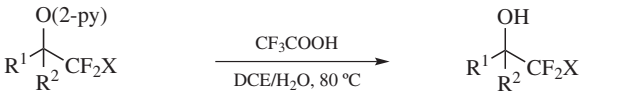

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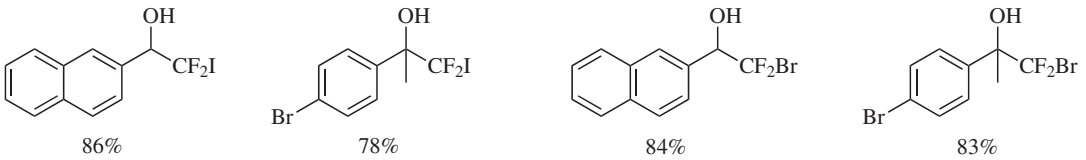
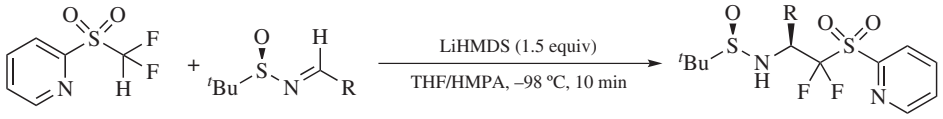


Nucleophilic Difluoro(sulfonato)methylation of *N*-Sulfinyl Imines. *β*-Amino sulfones can be prepared by the nucleophilic addition of the title reagent to the *N*-sulfinyl imines. A variety of (*R*)-*tert*-butanesulfinyl imines have been investigated. Both aryl- and alkyl-substituted aldimines are smoothly converted into the amino sulfones with high diastereoselectivity (eq 13).[4]



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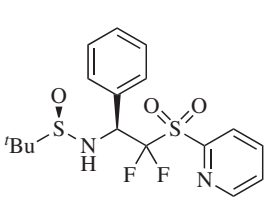

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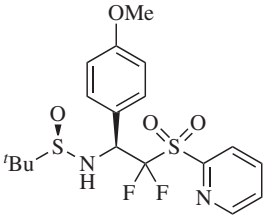

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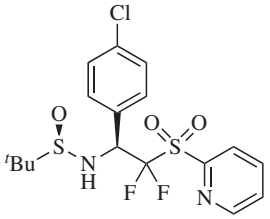

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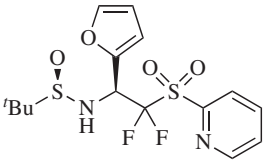

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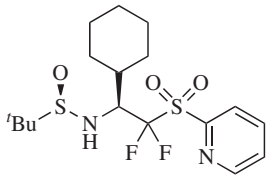

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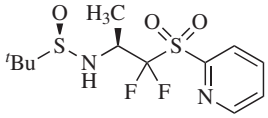

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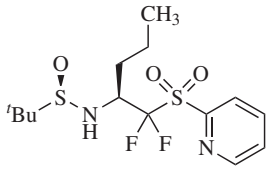

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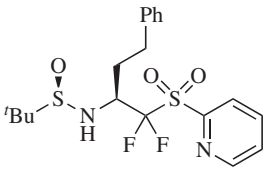

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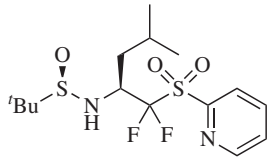

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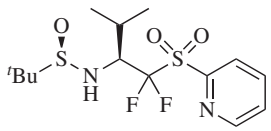

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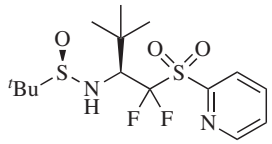
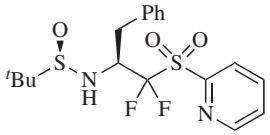
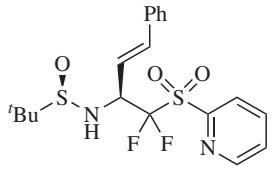


94%, dr > 99:1

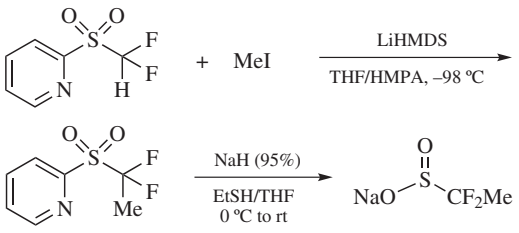


51%, dr > 99:1



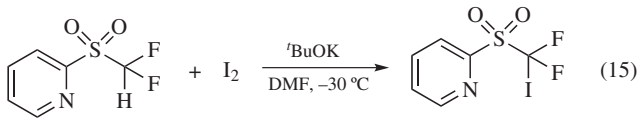
69%, dr = 95:5

Preparation of Sodium Difluoroethylsulfinate (DFES-Na). The 2-$PySO_2CF_2H$ reagent can be also applied to prepare sodium difluoroethylsulfinate (DFES-Na). Methyl iodide (MeI) was added to the tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA) solution of 2-$PySO_2CF_2H$ at a low temperature of −98 °C. A tetrahydrofuran (THF) solution of lithium hexamethyldisilazide (LiHMDS) is injected dropwise to give 2-[(1,1-difluoroethyl)sulfonyl]pyridine (2-$PySO_2CF_2Me$). This intermediate is mixed with the in situ generated sodium ethylthiolate (EtSNa) to provide sodium difluoroethylsulfinate (DFES-Na), which is a useful difluoroethylation reagent for a series of substrates such as heterocycles, Michael acceptors, and thiols (eq 14).[5]



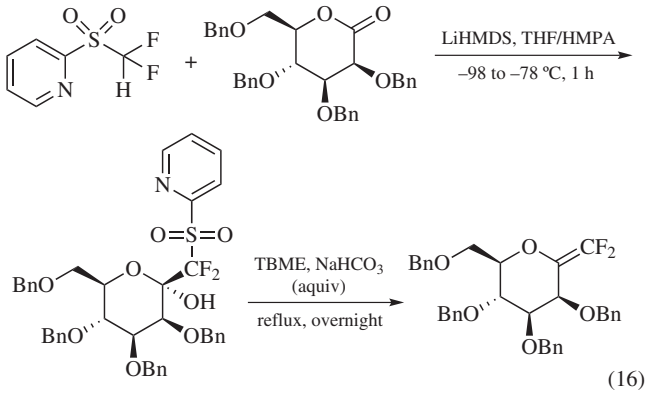
(14)

Preparation of Iododifluoromethyl 2-Pyridyl Sulfone (2-$PySO_2CF_2I$). Iododifluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2I$) can be prepared by the iodization of 2-$PySO_2CF_2H$ with iodine (eq 15).[6] A radical atom-transfer reaction between 2-$PySO_2CF_2I$ and terminal alkenes in the presence of triethyl borane (Et_3B) and oxygen will afford the difluoro(sulfonato)methylated alkanes.

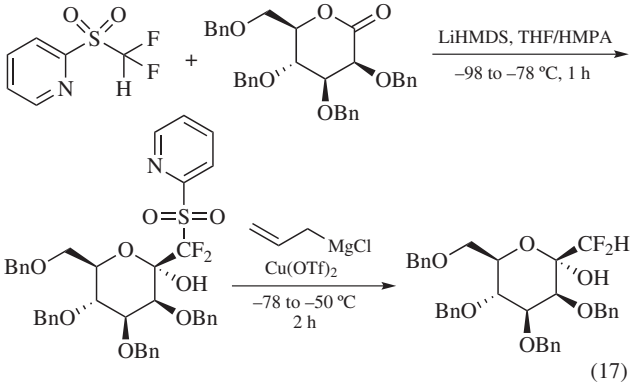


(15)

Nucleophilic Addition to Sugar Lactones. 2-$PySO_2CF_2H$ is also used for nucleophilic additions to sugar lactones. These intermediates can undergo two types of transformation. One is the formal elimination of the sulfonyl group and the anomeric hydroxyl group to provide 1-deoxy-1-difluoromethylene mannopyranose derivative (eq 16).[8] The other is a one-pot reduction of the sugar lactones with Grignard reagents, affording fluorinated 2-ketone analogs (eq 17). These corresponding products promise to be useful for organic and medicinal chemists.[8]



(16)



(17)

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