Stereoselective Fluoroalkylation

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Stereoselective Monofluoromethylation of Primary and Secondary Alcohols by Using a Fluorocarbon Nucleophile in a Mitsunobu Reaction**

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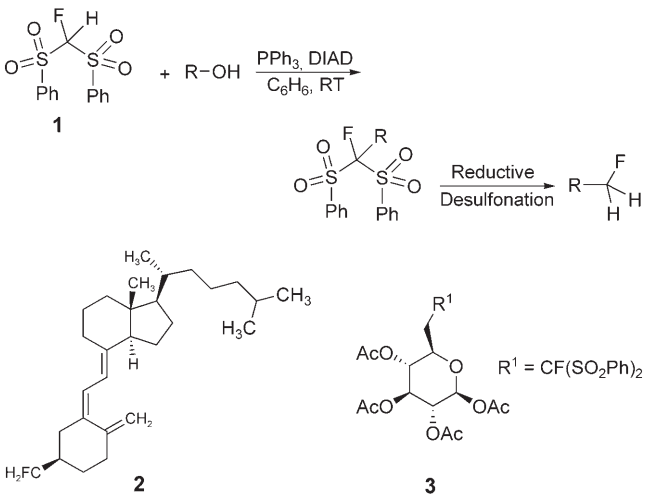
Stereoselective monofluoromethylation is one of the major areas of interest to life scientists as fluoromethyl-substituted compounds carry great importance in biological systems, in medical treatments, and in healthcare.[1] Sevoflurane, a new generation of fluoromethylated anaesthetics is found to have fast uptake and elimination properties.[2] The selective peripheral activity of α-monofluoromethyl-dopa (dopa = 3,4-dihydroxyphenylalanine) is attributed to the presence of a monofluoromethyl group at the α-carbon atom.[3] Fluoromethylglutamic acid is found to inhibit glutamic acid decarboxylase, and 4-amino-5-fluoropentanoic acid is found to be effective in blocking γ-aminobutyric acid (GABA) transaminase and is recognized as potential anticonvulsant.[4] The biomedical toxic defensive mechanism of the shrub *Dichapetalum cymosum* towards mammals is due to the presence of fluoroacetate.[5] Monofluoroacetic acid has been found to be an inhibitor for the Krebs cycle.[6]

An effective method for the diastereoselective monofluoromethylation of imines by using fluoromethyl phenyl sulfone has been reported recently by Hu and co-workers.[7] Palladium-catalyzed stereoselective monofluoralkylation reported by Shibata and co-workers requires the generation of the long-lived fluoroalkyl anion, longer reaction times, and low temperature, and is only applicable for the fluoroalkylation of allylic acetates.[8] On the other hand, the Mitsunobu reaction[9] is widely used in organic synthesis owing to its mild reaction conditions, stereospecificity, and versatility. There has been significant progress made in recent years in the reagent modification and in the application of the Mitsunobu reaction.[10] Nucleophilic fluoroalkylation has been one of the major interests in our group for a decade and significant progress has been made.[11] In continuation of our work on efficient nucleophilic fluoroalkylation methodologies, we have carried out monofluoroalkylation of alcohols by using the Mitsunobu reaction and found that the reaction is simple, efficient, and highly stereoselective. 1-Fluoro-bis(phenylsulfonyl)methane (**1**) was used as the pronucleophile for the Mitsunobu reaction, which is the synthetic equivalent of the monofluoromethide species. Triphenylphosphine (PPh_3) and diisopropyl azodicarboxylate (DIAD) were used as the redox couple in benzene at room temperature to give products in good yields under neutral conditions. The methodology works efficiently for a wide variety of alcohols including primary, secondary, allylic, alicyclic, and benzylic alcohols. The reaction proceeds through a typical S_N2-type pathway leading to stereochemical inversion. With chiral alcohols, the inverted adducts were obtained with a high enantiomeric excess of up to 98%. The Mitsunobu reaction followed by reductive desulfonation has been applied for the synthesis of monofluoromethylated vitamin D_3 (**2**). The monofluro-bis(phenylsulfonyl) derivative of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (**3**) was also synthesized by this protocol.



The Mitsunobu reaction has been studied by using a variety of substrates under different reaction conditions, and it provides an efficient protocol towards the formation of C–O, C–N, C–S, C–X, and C–C bonds and the synthesis of aryl ethers, etc. The most prominent feature we noticed is the inversion of configuration in the case of secondary alcohols. To the best of our knowledge, there has been no report on the Mitsunobu reaction with fluorocarbon nucleophiles. In spite of all the improvements in the redox system, the selection of the acidic component is limited by the pK_a value of the

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pronucleophile for satisfactory results.[12] Falck and co-workers have fine-tuned the acidity of the α-hydrogen atom in carbon nucleophiles with various electron-withdrawing groups to satisfy the requirement for this reaction.[13] Failure of the alkylation of monofluoromethyl derivatives of similar systems by alkyl halides was reported by Takeuchi et al.[14] During our study on stereoselective nucleophilic fluoromethylation, we found that bis(phenylsulfonyl)-substituted fluorocarbon nucleophiles facilitate the reaction at room temperature. The presence of a phenylsulfonyl group was effective in stabilizing the carbanion as well as in counteracting the so-called negative "fluorine effect".[15]

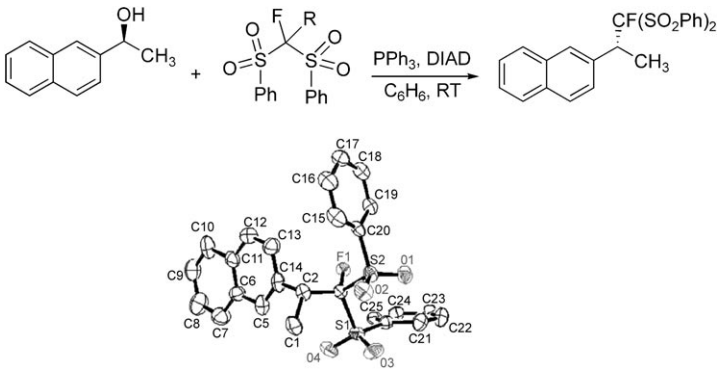
The reactions of 1-fluoro-bis(phenylsulfonyl)methane with primary, secondary, allylic, benzylic, and alicyclic alcohols were found to produce the corresponding 1-fluoro-bis(phenylsulfonyl) derivatives under suitable reaction conditions. The reaction was carried out under inert atmosphere by adding DIAD slowly to the reaction flask containing a mixture of alcohol, 1-fluoro-bis(phenylsulfonyl)methane, and PPh_3 in benzene. The reaction was monitored by ^{19}F NMR spectroscopy and found to be complete in 1 hour. The highest yields were obtained when 1 equivalent of 1-fluoro-bis(phenylsulfonyl)methane was treated with 1.1 equivalents of alcohol and 1.5 equivalents of the redox couple at room temperature. Primary and benzylic systems were found to react faster and give the products in excellent yields (Table 1), whereas the reactions with secondary alcohols and crowded systems were slightly sluggish.

Mitsunobu reaction proceeded through activation of the alcohol by the redox couple to form the oxophosphonium intermediate and displacement of the activated oxophosphonium group by the nucleophile. It has been reported that the enantiospecificity of the Mitsunobu reaction by Walden inversion of secondary chiral alcohols varies by up to 99% *ee*.[9] The yield of the inverted product depends on the pK_a value of the pronucleophile and the steric environment of the reacting alcohols.[16] To estimate the enantiospecificity in the reaction in benzene at room temperature, we have chosen three different chiral alcohols as representative examples and found that the reaction proceeded through a stereochemical inversion of configuration that gave *ee* values up to 98% (Table 2), as determined by chiral HPLC analysis. The inversion of the chiral center has been confirmed by X-ray crystallographic analysis of the product obtained from the Mitsunobu reaction of (*S*)-(−)-α-methyl-2-naphthalenemethanol with 1-fluoro-bis(phenylsulfonyl)methane . The product is found to have an *R* absolute configuration as evident from the crystal structure (Scheme 1).

Table 2: Walden inversion of chiral alcohols using the Mitsunobu reaction.

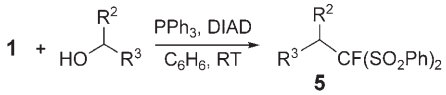
Entry	ROH	% *ee*[a]	$RCF(SO_2Ph)_2$	% *ee*[b]
1	(*S*)-2-octanol	>96	$CH_3(CH_2)_5CH(CH_3)CF(SO_2Ph)_2$	96
2	(*R*)-2-octanol	>96	$CH_3(CH_2)_5CH(CH_3)CF(SO_2Ph)_2$	96
3	(*S*)-$PhCH(OH)CH_3$	>98	$PhCH(CH_3)CF(SO_2Ph)_2$	98

[a] The *ee* value of the commercially available starting material. [b] Determined by HPLC analysis by using a CHIRALPAK AD-H column with hexane and 2-propanol in an 80:20 ratio.



Scheme 1. Crystal structure of the monofluoromethyl adduct of (*S*)-(−)-α-methyl-2-naphthalenemethanol.

Table 1: Mitsunobu reaction of various alcohols with 1-fluoro-bis(phenylsulfonyl)methane.



Entry[a]	R^2	R^3	Prod.	Yield [%][b]
1	*p*-tolyl	H	**5a**	90
2	$CH_3(CH_2)_7$	H	**5b**	73
3	Ph_2CHCH_2	H	**5c**	73
4	Ph	CH_3	**5d**	81
5	Ph	CH_2Ph	**5e**	67
6	$CH_3(CH_2)_5$	CH_3	**5f**	60
7	2-naphthyl	CH_3	**5g**	75
8	Ph-CH=CH	H	**5h**	80
9	$(CH_3)_2C{=}CH$	H	**5i**	75
10	$-(CH_2)_5-$		**5j**	60

[a] In all cases, DIAD (1.5 equiv) in dry benzene was added to a mixture of **1** (1 equiv), PPh_3 (1.5 equiv), and alcohol (1.1 equiv) in benzene at room temperature. [b] Yield of the isolated product.

Inspired by the excellent stereospecificity of this reaction, we continued our study by subjecting the products to reductive desulfonation reaction. It was found that the use of activated magnesium in methanol at 0 °C[17] produced selectively the desulfonated monofluoromethyl derivatives and that the methodology works well for primary, secondary, and even allylic systems (Table 3).

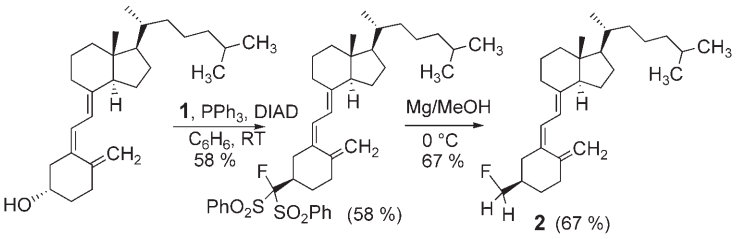
Table 3: Reductive desulfonation by using activated magnesium and methanol.

Entry[a]	$RCF(SO_2Ph)_2$	$RCFH_2$	Yield [%][b]
1	$Ph_2CH(CH_2)_2CF(SO_2Ph)_2$	$Ph_2CH(CH_2)_2CFH_2$	81
2	$PhCH\{CF(SO_2Ph)_2\}CH_2Ph$	$PhCH(CFH_2)CH_2Ph$	76
3	$PhCH{=}CH\text{-}CH_2CF(SO_2Ph)_2$	$PhCH{=}CH\text{-}CH_2CFH_2$	74

[a] In all cases, the reaction was carried out in methanol by using activated magnesium at 0 °C. [b] Yield of the isolated product.

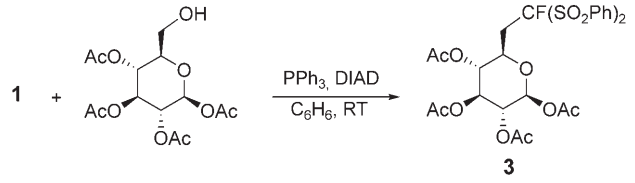
After establishing an easy route to generate chiral monofluoromethyl derivatives, we applied this methodology to the synthesis of biologically important molecules, sugars, etc. Vitamin D_3 and its fluoro derivatives are used as molecular probes for metabolites of vitamin D and their target molecules. Various synthetic analogues of vitamin D (deltanoids) are being recognized for their potent antiproliferative, prodifferentiative, and immunomodulatory activities.[18] By using our methodology, we were successful in synthesizing steroselectively monofluoromethylated vitamin D_3 under very mild conditions (Scheme 2).

Fluorinated carbohydrates are found to be very important in enzyme–carbohydrate interaction studies owing to their intrinsic biological activities.[19] The bioisosteric properties of



Scheme 2. Monofluoromethylation of vitamin D_3.

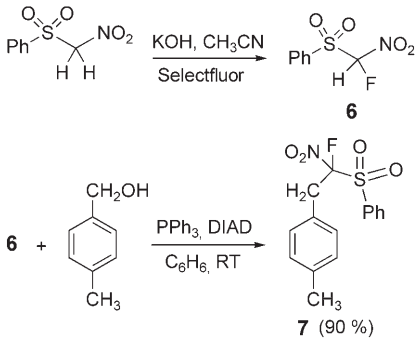
a C–F bond with a C–OH bond and its ability to participate in hydrogen bonding make some of the fluorinated sugars suitable as glycosylation inhibitors. This methodology has been used for the synthesis of monofluoro-bis(phenylsulfonyl)-1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (**3**). The parent compound is found to be important in the study of substrates for inositol synthase and also in the preparation of anionic surfactants (Scheme 3).[20]



Scheme 3. Mitsunobu reaction of 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose.

This reaction is found to be applicable to other monofluoro systems with the appropriate pK_a value. We have synthesized monofluorophenylsulfonylnitromethane (**6**) from phenylsulfonylnitromethane by the electrophilic fluorination by using selectfluor.[21] It smoothly underwent a Mitsunobu reaction under the described reaction conditions, giving the adduct **7** in high yields. This expands the versatility and scope of this reaction to produce a range of synthetically important monofluoroorganics (Scheme 4).

In conclusion, we have reported a new, efficient Mitsunobu reaction by using fluorinated carbon pronucleophile for the facile synthesis of monofluoromethyl derivatives of alcohols. This reaction can be performed under mild conditions and is highly feasible for primary, secondary, allylic, benzylic, and alicyclic alcohols. Excellent enantiospecificity is observed for chiral alcohols. The versatile synthetic utility of this method has been manifested by the synthesis of monofluoromethylated vitamin D_3 and the monofluoromethyl adduct of glucopyranose. Therefore, this methodology extends promise for a convenient synthetic protocol for the preparation of many organofluorine compounds.



Scheme 4. Monofluoronitromethylation of alcohols by using a Mitsunobu reaction.

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