Monofluoromethylation

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Fluorobis(phenylsulfonyl)methane: A Fluoromethide Equivalent and Palladium-Catalyzed Enantioselective Allylic Monofluoromethylation**

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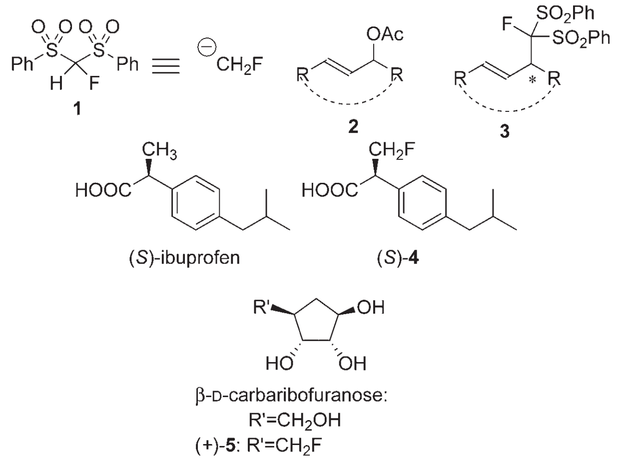
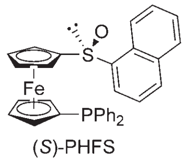
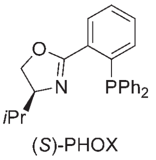
The development of efficient methodology for the synthesis of fluoroorganic compounds has attracted considerable attention particularly in the field of medicinal chemistry.[1] Owing to their unique and significant biological properties, fluorinated drugs have been commonly used in the treatment of a variety of diseases. Fluorination and fluoroalkylation reactions are two straightforward operations for the construction of fluorine-containing molecules, and their asymmetric versions are particularly useful.[2] Enantioselective electrophilic fluorination and enantioselective nucleophilic trifluoromethylation reactions probably represent the most versatile methodologies available for this purpose;[3] however, we are not aware of any reports of successful enantioselective *mono*fluoromethylation reactions.[3d] Compounds with a *mono*fluoromethyl unit are of great importance with regards to isostere-based drug design.[4] Indeed, monofluoroacetic acid is responsible for "lethal synthesis", and it blocks the tricarboxylic acid cycle (Krebs cycle).[5] Monofluoromethylated amino acids such as D-fluoroalanine are well known to act as "suicide substrates" causing inactivation of the enzyme by alkylative capture of the aminoacrylate-pyridoxal-P species.[6] In connection with our work on the asymmetric syntheses of fluorine-containing organic compounds,[7] we required a novel methodology for an enantioselective *mono*fluoromethylation reaction. Herein we disclose our first step toward achieving this goal by demonstrating that 1-fluorobis(phenylsulfonyl)methane (**1**) acts as a synthetic equivalent for the monofluoromethide species. We found that the palladium-catalyzed asymmetric allylic fluorobis(phenylsulfonyl)methylation reaction of allyl acetates **2** utilizing **1** smoothly proceed to afford the fluorobis(phenylsulfonyl)methylated compounds **3** with very high enantioselectivity up to 97 % *ee*. We also show how this methodology can be applied to the synthesis of monofluoromethylated compounds, enantiopure methyl-fluorinated ibuprofens (*S*)- and (*R*)-**4** by reductive desulfonylation and oxidation of **3a**. An efficient access to fluorinated β-D-carbaribofuranose **5** from **3f** is also described.



Inspired by the reports on difluoromethylation by the groups led by Prakash,[8a] Olah,[8a] and Hu,[8a,b] with difluorophenylsulfonylmethane,[8] we envisaged that 1-fluorobis(phenylsulfonyl)methane (**1**) would be a useful reagent for enantioselective monofluoromethylation in the palladium-catalyzed allylic substitution reaction, which has been studied in detail by us[9] and others.[10] The previously unknown compound **1** was easily prepared in good yield from bis(phenylsulfonyl)methane, $CH_2(SO_2Ph)_2$, by monofluorination with Selectfluor or molecular fluorine.[11a] Palladium-catalyzed fluorobis(phenylsulfonyl)methylation of (2*E*)-1,3-bis(4-isobutylphenyl)-2-propenyl acetate (**2a**) with **1** was carried out in the presence of catalytic amounts of $[\{Pd(C_3H_5)Cl\}_2]$ and (*S*)-1-(1′-diphenylphosphino)ferrocenyl-1″-naphthyl sulfoxide ((*S*)-PHFS)[9] or (4*S*)-2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline ((*S*)-PHOX)[10c–e] at 0 °C (Table 1).



(*S*)-PHFS



(*S*)-PHOX

First, the allylic substitution was examined under our previously optimized conditions using (*S*)-PHFS in the presence of cesium carbonate; however, the result was disappointing (Table 1, run 1). Next, (*S*)-PHOX was used as

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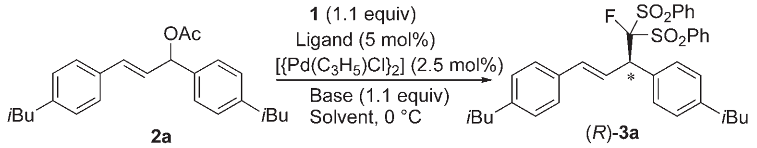
Table 1: Optimization of the palladium-catalyzed enantioselective allylic fluorobis(phenylsulfonyl)methylation of **2a**.



Run	Ligand	Base	Solvent[a]	*t* [h]	Yield [%]/*ee*[b] [%]
1	(*S*)-PHFS	Cs_2CO_3	CH_2Cl_2 (0.1 M)	6	30/9[c]
2	(*S*)-PHOX	BSA[d]	CH_2Cl_2 (0.1 M)	17	14/90
3	(*S*)-PHOX	K_2CO_3	CH_2Cl_2 (0.1 M)	14	31/94
4	(*S*)-PHOX	NaH[e]	THF (0.1 M)	9	39/96
5	(*S*)-PHOX	Cs_2CO_3	THF (0.1 M)	9	16/94
6	(*S*)-PHOX	Cs_2CO_3	CH_2Cl_2 (0.1 M)	6	12/97
7	(*S*)-PHOX	Cs_2CO_3	CH_2Cl_2 (0.1 M)	12[f]	50/94
8	(*S*)-PHOX	Cs_2CO_3	CH_2Cl_2 (0.5 M)	6	33/95
9	(*S*)-PHOX	Cs_2CO_3	CH_2Cl_2 (1.0 M)	6	83/94
10[g]	(*S*)-PHOX	Cs_2CO_3	CH_2Cl_2 (1.0 M)	24[f]	trace/65[h]
11[i]	(*S*)-PHOX	NaH[e]	dioxane (0.3 M)	48	23/89

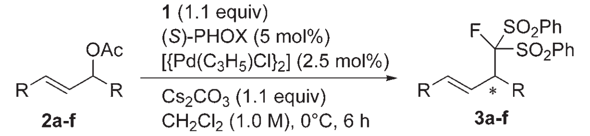
[a] The concentration refers to **2a**. [b] The *ee* value was determined by HPLC analysis using CHIRALPAK AD-H. The absolute stereochemistry was tentatively assigned by comparing the optical rotation of **3a** with that of a non-fluorinated derivative of **3a**.[10a, 13b] [c] (*S*)-**3a** was obtained. [d] The reaction was carried out in the presence of CsOAc (0.1 equiv). [e] Preformed $NaCF(SO_2Ph)_2$ was used. [f] The reaction was carried out at room temperature. [g] $CH_2(SO_2Ph)_2$ was used as a nucleophile instead of **1**. [h] A non-fluorinated analogue of (*R*)-**3a** was obtained. [i] The reaction was carried out at 73 °C.

a chiral ligand. Bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of cesium acetate were examined as promoters for the reaction according to the procedure established for palladium-catalyzed allylic substitution using bis(phenylsulfonyl)methane.[10a] After overnight stirring at 0 °C, the desired 1-fluorobis(phenylsulfonyl)methylated product (*R*)-**3a** was obtained with 90 % *ee*, while the conversion was only 14 % (Table 1, run 2). With potassium carbonate or sodium hydride as a base, the enantioselectivities increased to 96 % *ee*, but the conversion was still low (Table 1, runs 3 and 4). Then the reaction was examined using cesium carbonate as a base in the concentration range 0.1–1.0 M (Table 1, runs 5–9). The adduct (*R*)-**3a** was produced in satisfactory yield with very high enantioselectivity when the reaction was carried out with Cs_2CO_3 at a concentration of 1.0 M (Table 1, run 9).[11b] It should be noted that fluorine substitution has a striking effect on the reactivity and enantioselectivity of **1** (Table 1, cf. runs 9 and 10). As mentioned above, the allylic substitution reaction with **1** proceeds smoothly at temperatures below 0 °C within several hours and with very high enantioselectivity. In contrast, the non-fluorinated bis(phenylsulfonyl)methane, $CH_2(SO_2Ph)_2$, has rather poor reactivity in allylic substitution reaction even at room temperature over 24 h, and therefore, the corresponding addition requires heating at, for example, 73 °C for 48 h.[10a] Only trace amount of the non-fluorinated analogue of **3a** was obtained with lower enantioselectivity (65 % *ee*) (Table 1, cf. runs 9 and 10). On the other hand, when the reaction of **2a** with **1** was carried out at elevated temperatures[10a] (i.e. the optimal conditions for $CH_2(SO_2Ph)_2$), the yield and enantioselectivity decreased (Table 1, run 11). It may be possible to explain the difference in reactivity between **1** and $CH_2(SO_2Ph)_2$ in terms of the acidity of **1** relative to $CH_2(SO_2Ph)_2$ and the stability of its conjugate base. The high reactivity of **1** even at low temperatures might arise from the increased acidity of **1** as a result of the electron-withdrawing ability of fluorine. However, the effect of α-fluorine substitution on the stability of an anion generally arises from a compromise between its inductive electron-withdrawing ability and the repulsion between its electron pair and that on the carbanionic center.[12] The low stability of the conjugate base of **1** at higher temperatures could be the reason for the poor yield in run 11.

The 1-fluorobis(phenylsulfonyl)methylation reaction was also applied to a variety of allylic acetates (Table 2). Allylic acetates **2b–f** having methoxyphenyl, bromophenyl, and naphthyl groups were smoothly monofluoromethylated to furnish the desired fluorobis(phenylsulfonyl)methylated products **3b–f** in acceptable to high yields with high enantioselectivities (Table 2, entries 1–8).[13a] The reason for the loss in chemical yield for **3c**,**d** (Table 2, entries 2 and 5) is the partial decomposition of **2c**,**d**. The yield was improved when the reaction was carried out under slightly modified conditions (amounts of reagents, reaction temperature; Table 2, entries 2–6). The opposite enantiomer, (*S*)-**3a**, is accessible from **2a** when (*R*)-PHOX is used as a catalyst ligand (Table 2, entry 9).[13b]

After testing acyclic electrophiles in our enantioselective allylic 1-fluorobis(phenylsulfonyl)methylation reaction with **1**, we next examined a similar process with cyclic electrophiles. Those with five- or six-membered rings are especially interesting since the products should be useful for the synthesis of fluorinated analogues of biologically important

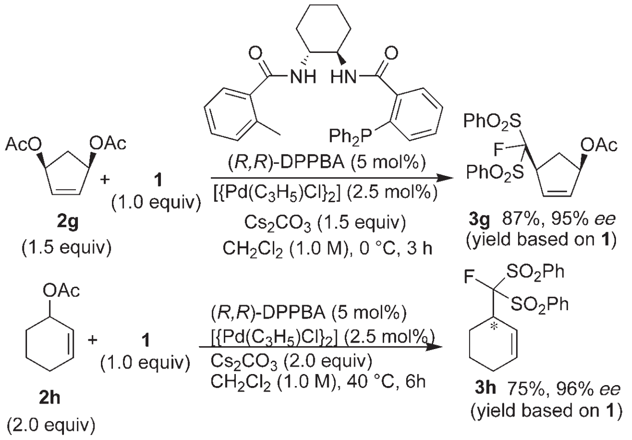
Table 2: Palladium-catalyzed enantioselective allylic fluorobis(phenylsulfonyl)methylation of allylic acetates **2a–f**.



Entry	2	Ar	3	Yield [%]	*ee* [%][a]
1	**2b**	Ph	**3b**	92	96 (*R*)[e]
2	**2c**	4-MeOC_6H_4	**3c**	58	94
3[b]	**2c**	4-MeOC_6H_4	**3c**	22[b]	97
4[c]	**2c**	4-MeOC_6H_4	**3c**	74	91
5	**2d**	4-BrC_6H_4	**3d**	54	95 (*R*)[e]
6[b]	**2d**	4-BrC_6H_4	**3d**	69[b]	94 (*R*)[e]
7	**2e**	2-naphthyl	**3e**	89	92
8	**2f**	2-(6-methoxynaphthyl)	**3f**	72	91
9[d]	**2a**	$i\text{BuC}_6H_4$	**3a**	89	91 (*S*)[e]

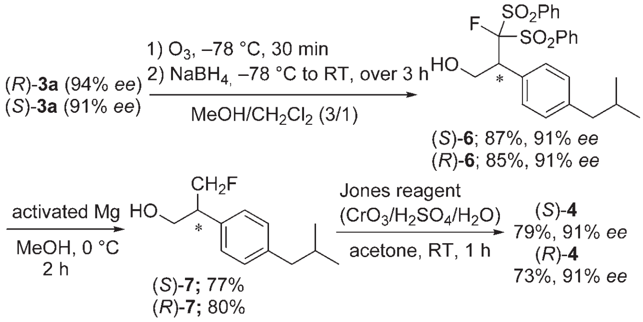
[a] Determined by HPLC analysis using CHIRALPAK AD-H or OD-H. [b] Reaction conditions: **1** (1.0 equiv), **2** (2.0 equiv), Cs_2CO_3 (2.0 equiv), 2.5 mol % [{Pd(C_3H_5)Cl}$_2$], and 5 mol % (*S*)-PHOX at room temperature for 6 h. Yield is based on **1**. [c] The reaction was carried out at room temperature for 6 h. [d] (*R*)-PHOX (5 mol %) was used instead of (*S*)-PHOX. [e] See reference [13b].

molecules.[10b] A series of chiral ligands commonly employed were examined under conditions similar to those described above. We found that (+)-1,2-bis-*N*-[2′-(diphenylphosphino)-benzoyl]-(1*R*,2*R*)-diaminocyclohexane ((*R*,*R*)-DPPBA)[10f] was effective for the desymmetrization of the meso diester **2g** with **1** in the presence of $[\{Pd(C_3H_5)Cl\}_2]$ and Cs_2CO_3 to afford the 1-fluorobis(phenylsulfonyl)methylated adduct **3g** in 87% yield with 95% *ee* (Scheme 1). Similarly, racemic acetate **2h** underwent efficient enantioselective reaction with **1** under the same conditions to provide enantioenriched **3h** in 75% with 96% *ee*.[13c]



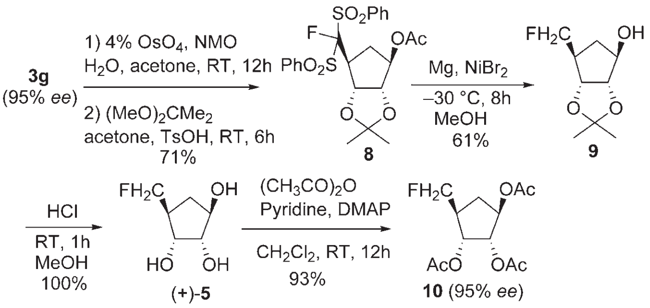
Scheme 1. Palladium-catalyzed enantioselective allylic fluorobis(phenylsulfonyl)methylation of cyclic acetates **2g**,**h**.

With facile access to this range of enantioenriched monofluorinated organic compounds, we next considered synthetic applications. Ibuprofen, a widely marketed non-steroidal anti-inflammatory drug (NSAID), is an interesting compound in terms of the pharmacokinetics of its enantiomers.[14] Ibuprofen exists as both *R* and *S* enantiomers, and it was revealed the metabolic chiral inversion of (*R*)-ibuprofen to the pharmacologically active *S* enantiomer occurs in humans. Racemic ibuprofen has been prescribed worldwide, and the *S* isomer, called dexibuprofen, is marketed in Austria and Switzerland. The physico-chemical and pharmacological properties and metabolic profiles of racemic ibuprofen and dexibuprofen are quite different, and a better understanding may be possible from studies of chiral derivatives of ibuprofen. A variety of ibuprofen derivatives have been prepared for this purpose including fluorinated ibuprofens;[15] we are interested in the previously unknown ibuprofen derivative **4**, which bears a fluoromethyl group.[16] Only the *R* enantiomer of **4** could potentially an act as a suicide substrate by β elimination of HF by the enzyme during the chiral-inversion step, and it might consequently shed new light on the study of the pharmacokinetics of the enantiomers. To show the utility of our palladium-catalyzed enantioselective fluorobis(phenylsulfonyl)methylation reaction, we next applied the method for the synthesis of the ibuprofen analogues (*S*)- and (*R*)-**4** (Scheme 2). Similar to the conventional synthesis of ibuprofen,[10a] ozonolysis of (*R*)- and (*S*)-**3a** in $MeOH/CH_2Cl_2$ (3:1) at −78 °C followed by reduction with $NaBH_4$ gave the monofluoromethylated alchohols (*S*)- and (*R*)-**6** in yields of 87% and 85%, respectively, without major loss of enantiopurity (91% *ee*). The removal of the sulfonyl group at the fluorinated carbon by reaction with activated Mg in methanol afforded the chiral monofluoromethylated compounds (*S*)- and (*R*)-**7**, and subsequent oxidation with the Jones reagent gave the *S* and *R* enantiomers of **4**,[17] which were previously unknown.[16]



Scheme 2. Enantioselective synthesis of methylfluorinated ibuprofen **4**.

Carbafuranose is a synthetic target attracting much recent interest in view of both its enzyme inhibitor activities and antiviral properties.[18] Fluorinated carbohydrates have also recently received attention for their important role in the study of enzyme–carbohydrate interactions as well as their biological activities.[19] Therefore, fluoro sugars with a carbocyclic framework have emerged as important tools in this area. We examined the synthesis of 5-deoxy-5-fluoro-β-D-carbaribofuranose (**5**). The 1-fluorobis(phenylsulfonyl)methylated adduct **3g** (Scheme 1) underwent an osmium-catalyzed diastereoselective dihydroxylation; subsequent treatment with 2,2-dimethoxypropane furnished acetonide **8** in 71% yield (Scheme 3). Reductive double-desulfonylation of **8** using $Mg/NiBr_2/MeOH$[20] gave monofluoromethylated **9** in 61% yield. Finally, the acetonide moiety on **9** was removed by acid treatment to afford (+)-**5**, a previously unknown fluoro isostere of β-D-carbaribofuranose, quantitatively.[21] The enantiopurity of (+)-**5** was determined to be 95% by chiral HPLC analysis of triacetate **10**.



Scheme 3. Enantioselective synthesis of 5-deoxy-5-fluoro-β-D-carbaribofuranose (**5**).

In conclusion, 1-fluorobis(phenylsulfonyl)methane (**1**), a newly designed synthetic equivalent for the fluoromethide species, affords the enantiopure fluoromethylated products **3** in a palladium-catalyzed allylic fluorobis(phenylsulfonyl)methylation reaction. The effect of fluorine substitution on the reactivity and enantioselectivity of the reagent **1** is remarkable. The products **3a** were readily converted to chiral methylfluorinated ibuprofens (*S*)- and (*R*)-**4** by reductive desulfonylation and oxidation. The biologically important fluoro-β-D-carbaribofuranose **5** was also synthesized from **3g** by dihydroxylation and reductive desulfonylation. The present methodology can be applicable for a wider variety of monofluoromethylated derivatives of NSAIDs and fluoro sugars. The biological activities of (*S*)- and (*R*)-**4** as NSAIDs and the pharmacokinetics of the enantiomers of **4** will be evaluated and reported in due course.

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[11] a) See the Supporting Information. b) A typical experimental procedure is given in the Supporting Information.

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[13] a) The reaction mechanism is discussed in the Supporting Information. b) Absolute stereochemistries were assigned by X-ray crystallographic analysis (for **3d**, see the Supporting Information) or tentatively determined by comparing the optical rotations of **3a** and **3b** with those of their non-fluorinated derivatives (see the Supporting Information); c) Enantiomeric excesses of **3g,h** were determined by HPLC analysis using CHIRALCEL OD-H. The absolute stereochemistry of **3g** was assigned based on the proposed reaction mechanism (see reference [10b, f] and the Supporting Information) and tentatively determined by comparing the optical rotation with that of β-D-carbaribofuranose after chemical derivatization of **3g** to 5-deoxy-5-fluoro-β-D-carbaribofuranose (**5**) (see Scheme 3).

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