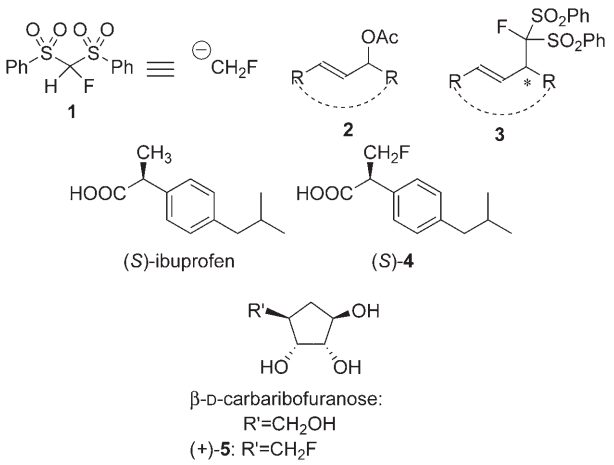
Monofluoromethylation

DOI: 10.1002/anie.200600625

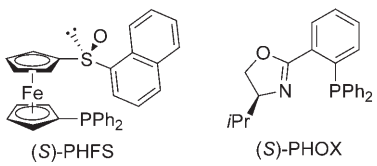
Fluorobis(phenylsulfonyl)methane: A Fluoromethide Equivalent and Palladium-Catalyzed Enantioselective Allylic Monofluoromethylation**

Takeo Fukuzumi, Norio Shibata, Masayoshi Sugiura, Hiroyuki Yasui, Shuichi Nakamura, and Takeshi Toru**

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).



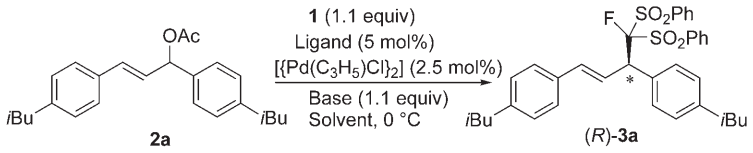
First, the allylic substitution was examined under our previously optimized conditions using (*S*)-PHFS in the presence of cesium carbonate; however, the result was disappointing (Table 1, run 1). Next, (*S*)-PHOX was used as

[*] Prof. Dr. N. Shibata, Prof. Dr. T. Toru
Department of Applied Chemistry
Graduate School of Engineering, Nagoya Institute of Technology
Gokiso, Showa, Nagoya 466-8555 (Japan)
Fax: (+81) 52-735-5442
E-mail: nozshiba@nitech.ac.jp
toru@nitech.ac.jp
T. Fukuzumi, M. Sugiura, H. Yasui, Dr. S. Nakamura
Department of Applied Chemistry
Graduate School of Engineering, Nagoya Institute of Technology
Gokiso, Showa, Nagoya 466-8555 (Japan)

[**] This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan (17350047, 17590087) and by Japan Science & Technology (JST) Agency, Innovation Plaza Tokai. T.F. is grateful for research fellowships from JSPS. We thank Dr. Jon Bordner, Shinichi Sakemi, and Dr. Masami Nakane, Pfizer Inc., for X-ray crystallographic analysis.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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

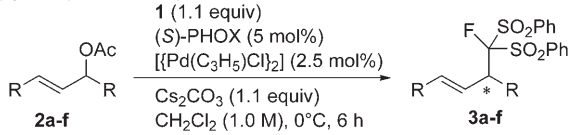
[a] The concentration refers to **2a**. [b] The *ee* value was determined by HPLC analysis using CHIRALPAK AD-H. The absolute stereochemistry was tentatively assigned by comparing the optical rotation of **3a** with that of a non-fluorinated derivative of **3a**.[10a,13b] [c] (*S*)-**3a** was obtained. [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

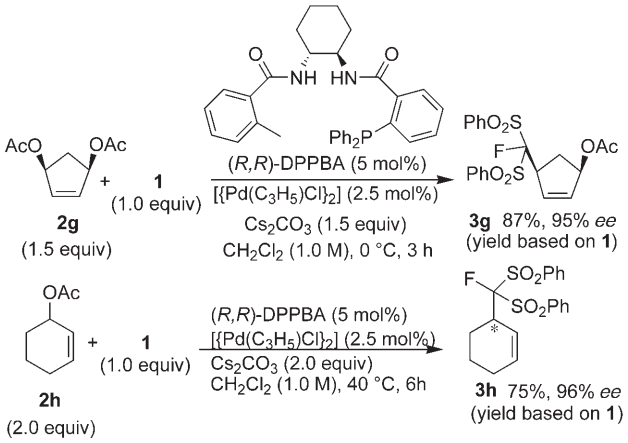
Table 2: Palladium-catalyzed enantioselective allylic fluorobis(phenylsulfonyl)methylation of allylic acetates **2a–f**.



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*BuC_6H_4	**3a**	89	91 (*S*)[e]

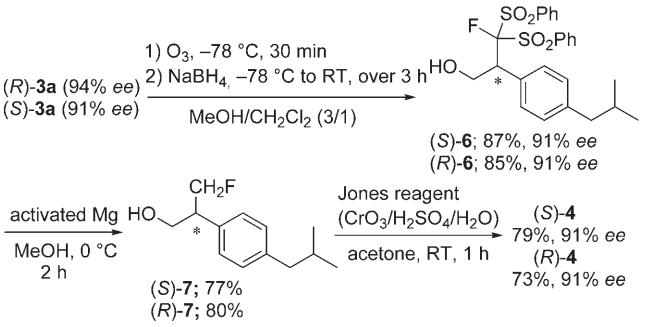
[a] Determined by HPLC analysis using CHIRALPAK AD-H or OD-H. [b] Reaction conditions: **1** (1.0 equiv), **2** (2.0 equiv), Cs_2CO_3 (2.0 equiv), 2.5 mol % [{$Pd(C_3H_5)Cl$}$_2$], and 5 mol % (*S*)-PHOX at room temperature for 6 h. Yield is based on **1**. [c] The reaction was carried out at room temperature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

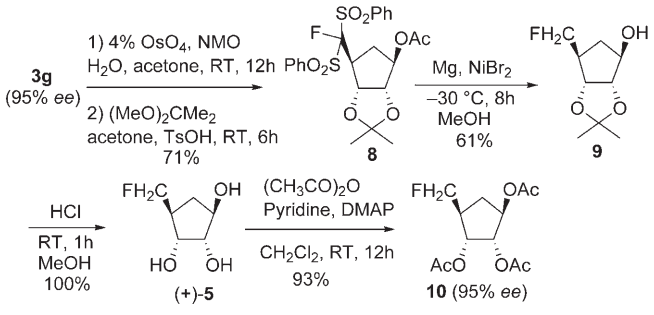
With facile access to this range of enantioenriched monofluorinated organic compounds, we next considered synthetic applications. Ibuprofen, a widely marketed non-steroidal anti-inflammatory drug (NSAID), is an interesting compound in terms of the pharmacokinetics of its enantiomers.[14] Ibuprofen exists 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



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

$NaBH_4$ 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]

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**



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

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**.

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.

Received: February 16, 2006
Revised: May 15, 2006
Published online: July 4, 2006

Keywords: asymmetric synthesis · drug design · fluorine · fluoromethylation · palladium

[1] a) *Biomedicinal Aspects of Fluorine Chemistry* (Eds.: R. Filler, Y. Kobayashi), Elsevier Biomedical Press and Kodansha Ltd, New York, **1982**; b) "Biomedical Frontiers of Fluorine Chemistry": *ACS Symp. Ser.* **1996**, *639*; c) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications* (Eds.: R. Filler, Y. Kobayashi, L. M. Yagupolskii), Elsevier, Amsterdam, **1993**.

[2] a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets* (Ed.: V. A. Soloshonok), Wiley, Chichester, **1999**; b) "Asymmetric Fluoroorganic Chemistry. Synthesis, Applications, and Future Directions": *ACS Symp. Ser.* **2000**, *746*; c) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell Publishing, Oxford, UK, **2004**; d) P. Kitsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**.

[3] a) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147 – 1155; b) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119 – 6146; c) G. K. S. Prakash, A. K. Yudin, *Chem. Rev.* **1997**, *97*, 757 – 786; d) After submission of this manuscript, the diastereoselective nucleophilic monofluoromethylation of imines with fluoromethyl phenyl sulfone was described: Y. Li, C. Ni, J. Liu, L. Zhang, J. Zheng, L. Zhu, J. Hu, *Org. Lett.* **2006**, *8*, 1693 – 1696.

[4] a) *Fusso Yakugaku* (Eds.: Y. Kobayashi, I. Kumadaki, T. Taguchi), Hirokawa, Tokyo, **1992**; b) *Organofluorine Chemistry: Principles and Commercial Applications* (Eds.: R. E. Banks, B. E. Smart, J. C. Tatlow), Plenum, New York, **1994**, chap. 3; c) B. E. Smart, *J. Fluorine Chem.* **2001**, *109*, 3 – 11.

[5] a) G. W. Gribble, *J. Chem. Educ.* **1973**, *50*, 460 – 462; b) R. Peters, R. W. Wakelin, *Proc. R. Soc. London Ser. B* **1953**, *140*, 497 – 507; c) E. Kun, R. J. Dummel, *Methods Enzymol.* **1969**, *13*, 623 – 672.

[6] a) D. O'Hagan, H. S. Rzepa, *Chem. Commun.* **1997**, 645 – 652; b) J. Kollonitsch in *Biomedicinal Aspects of Fluorine Chemistry*, (Eds.: R. Filler, Y. Kobayashi), Elsevier Biomedical Press and Kodansha Ltd, New York, Tokyo, **1982**, pp. 93 – 122; c) R. H. Abeles, A. L. Maycock, *Acc. Chem. Res.* **1976**, *9*, 313 – 319; d) R. B. Silverman, S. M. Nanavati, *J. Med. Chem.* **1990**, *33*, 931 – 936; e) J. Kollonitsch, A. A. Patchett, S. Marburg, A. L. Maycock, L. M. Perkins, G. A. Doldouras, D. E. Duggan, S. D. Aster, *Nature* **1978**, *274*, 906 – 908.

[7] a) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem.* **2005**, *117*, 4276 – 4279; *Angew. Chem. Int. Ed.* **2005**, *44*, 4204 – 4207; b) N. Shibata, E. Suzuki, Y. Takeuchi, *J. Am. Chem. Soc.* **2000**, *122*, 10728 – 10729; c) N. Shibata, E. Suzuki, T. Asahi, M. Shiro, *J. Am. Chem. Soc.* **2001**, *123*, 7001 – 7009; d) N. Shibata, T. Ishimaru, E. Suzuki, K. L. Kirk, *J. Org. Chem.* **2003**, *68*, 2494 – 2497; e) N. Shibata, T. Ishimaru, T. Nagai, J. Kohno, T. Toru, *Synlett* **2004**, 1703 – 1706; f) N. Shibata, T. Ishimaru, M. Nakamura, T. Toru, *Synlett* **2004**, 2509 – 2512; g) N. Shibata, T. Tarui, Y. Doi, K. L. Kirk, *Angew. Chem.* **2001**, *113*, 4593 – 4595; *Angew. Chem. Int. Ed.* **2001**, *40*, 4461 – 4463; .

[8] a) G. K. S. Prakash, J. Hu, G. A. Olah, *J. Org. Chem.* **2003**, *68* 4457 – 4463; b) Y. Li, J. Hu, *Angew. Chem.* **2005**, *117*, 6032 – 6036; *Angew. Chem. Int. Ed.* **2005**, *44*, 5882 – 5886.

[9] S. Nakamura, T. Fukuzumi, T. Toru, *Chirality* **2004**, *16*, 10 – 12.

[10] a) L. Acemoglu, J. M. J. Williams, *J. Mol. Catal. A* **2003**, *196*, 3 – 11; b) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, *103*, 2921 – 2944; c) P. V. Matt, A. Pfaltz, *Angew. Chem.* **1993**, *105*, 614 – 615; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 566 – 568; d) J. Sprinz, G. Helmchen, *Tetrahedron Lett.* **1993**, *34*, 1769 – 1772; e) G. J. Dawson, C. G. Frost, J. M. J. Williams, S. J. Coote, *Tetrahedron Lett.* **1993**, *34*, 3149 – 3150; f) B. M. Trost, D. L. V. Vranken, C. Bingel, *J. Am. Chem. Soc.* **1992**, *114*, 9327 – 9343.

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

[12] H. J. Castejon, K. B. Wiberg, *J. Org. Chem.* **1998**, *63*, 3937 – 3942.

[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).

[14] H. Hao, G. Wang, J. Sun, *Drug Metab. Rev.* **2005**, *37*, 215 – 234.

[15] a) O. Goj, S. Kotila, G. Haufe, *Tetrahedron* **1996**, *52*, 12761 – 12774; b) W. J. Middleton, E. M. Bingham, *J. Fluorine Chem.* **1983**, *22*, 561 – 574; c) Y. Yamazaki, S. Yusa, Y. Kageyama, H. Tsue, K. Hirao, H. Okuno, *J. Fluorine Chem.* **1996**, *79*, 167 – 171; d) M. Schlosser, D. Michel, Z. Guo, C. J. Sih, *Tetrahedron* **1996**, *52*, 8257 – 8262; e) M. Villa, N. J. Smeyers, M. -L. Senent, Y. G. Smeyers, *THEOCHEM* **2001**, *537*, 265 – 269; f) Y. Takeuchi, H. Fujisawa, T. Fujiwara, M. Matsuura, H. Komatsu, S. Ueno, T. Matsuzaki, *Chem. Pharm. Bull.* **2005**, *53*, 1062 – 1064.

[16] Other monofluoromethylarylpropionic acid derivatives besides **4** have been reported: a) D. Haigh, L. J. Jefcott, K. Magee, H. McNab, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2895 – 2900; b) M. C. Lu, L. B. Shih, H. S. Jae, J. E. Gearien, E. B. Thompson, *J. Med. Chem.* **1987**, *30*, 424 – 427; c) S. Hamman, C. G. Beguin, *Tetrahedron Lett.* **1983**, *24*, 57 – 60; d) J. Barker, R. Keck, J. Rétey, *Tetrahedron Lett.* **1982**, *23*, 1549 – 1552; e) F. Faustini, S. D. Munari, A. Panzeri, V. Villa, C. A. Gandolfi, *Tetrahedron Lett.* **1981**, *22*, 4533 – 4536; f) G. A. Olah, G. K. S. Prakash, Y. L. Chao, *Helv. Chim. Acta* **1981**, *64*, 2528 – 2530; g) R. Keck, J. Rétey, *Helv. Chim. Acta* **1980**, *63*, 769 – 772; h) Y. Yamazaki, S. Yusa, Y. Kageyama, H. Tsue, K. Hirao, H. Okuno, *J. Fluorine Chem.* **1996**, *79*, 167 – 171.

[17] Absolute stereochemistries were determined by comparing the optical rotations of **4** with those of ibuprofen. (*S*)-**4** (91% *ee*): $[\alpha]_D^{30} = +50.1$ ($c = 0.57$ in EtOH); (*R*)-**4** (91% *ee*): $[\alpha]_D^{30} = -50.1$ ($c = 0.68$, EtOH); (*S*)-ibuprofen (91% *ee*): $[\alpha]_D^{30} = +60$ ($c = 2$ in EtOH), see D. G. Kaiser, G. J. Vangiessen, R. J. Reischer, W. J. Weckter, *J. Pharm. Sci.* **1976**, *65*, 269 – 273.

[18] For example: a) M. T. Crimmins, *Tetrahedron* **1998**, *54*, 9229–9272; b) E. De Clercq, *Nucleosides Nucleotides* **1998**, *17*, 625–634; c) V. E. Marquez, *Adv. Antiviral Drug Des.* **1996**, *2*, 89–146; d) T. S. Mansour, R. Storer, *Curr. Pharm. Des.* **1997**, *3*, 227–264; e) G. Rassu, L. Auzzas, L. Pinna, V. Zambrano, L. Battistini, F. Zanardi, L. Marzocchi, D. Acquotti, G. Casiraghi, *J. Org. Chem.* **2001**, *66*, 8070–8075.

[19] For example: a) P. Hadwiger, P. Mayr, B. Nidetzky, A. E. Stütz, A. Tauss, *Tetrahedron: Asymmetry* **2000**, *11*, 607–620; b) C. Schaffrath, S. L. Cobb, D. O'Hagan, *Angew. Chem.* **2002**, *114*, 4069–4071; *Angew. Chem. Int. Ed.* **2002**, *41*, 3913–3915; c) E. P. J. Boot, G. A. Koning, G. Storm, J. P. A. Wagenaar-Hilbers, W. van Eden, L. A. Everse, M. H. M. Wauben, *Arthritis Res. Ther.* **2005**, *7*, R604–R615.

[20] I. Das, T. Pathak, *Org. Lett.* **2006**, *8*, 1303–1306.

[21] (+)-**5** (95% *ee*): $[\alpha]_D^{30} = +10.6$ ($c = 0.98$ in MeOH). β-D-carbaribofuranose: $[\alpha]_D^{20} = +10.0$ ($c = 1.1$ in MeOH). See reference [18e].

