

Stereoselective Nucleophilic Fluoromethylation of Aryl Ketones: Dynamic Kinetic Resolution of Chiral α -Fluoro Carbanions**

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Abstract: Although many methods are available for the synthesis of optically enriched monofluoromethyl secondary alcohols, synthesizing optically enriched monofluoromethyl tertiary alcohols remains a challenge. An efficient and easy-to-handle nucleophilic fluoromethylation protocol was developed. The current monofluoromethylation showed much higher facial selectivity than the corresponding difluoromethylation and proceeded via a different type of transition state. Excellent stereoselective control at the fluorinated carbon chiral center was found, an effect believed to be facilitated by the dynamic kinetic resolution of the chiral α -fluoro carbanions.

The incorporation of fluorine into a bioactive molecule can often impart desirable chemical and biological properties with minimal steric alterations. These properties include stability, lipophilicity, and bioavailability, and can favorably affect in vivo drug transport and absorption.^[1] In this context, monofluorinated analogues of biologically active compounds are considered to be promising isosteres of the parent molecules.^[2] In 1954, Fried and Sabo successfully synthesized 9- α -fluorohydrocortisone acetate and demonstrated that it possessed ten to twelve times the activity of cortisone acetate in the rat liver glycogen assay; this was one of the early examples that showed improved bioavailability of a bioactive molecule through the selective incorporation of fluorine.^[3] In recent years, fluorine incorporation has become a routine strategy for drug design.^[1] Among various monofluorinated compounds, monofluoromethylated compounds are of particular value since CH_2F functionality can mimic CH_3 and CH_2OH groups, which are often encountered in biologically active molecules.^[4] However, since the thalidomide tragedy,^[5] there has been more awareness of the potential dangers of using racemic drugs. Therefore, the development of new methods for the synthesis of optically pure monofluoromethyl compounds would be highly desirable for drug development.

In the past decades, several strategies have been reported for the synthesis of optically enriched monofluoromethyl secondary alcohols, including asymmetric reduction of monofluoromethyl ketones,^[6a-c] nucleophilic fluorination of optically pure epoxides or enantioselective fluorination of racemic epoxides,^[6d-f] and enantioselective monofluoromethylation of aldehydes.^[6g] However, the synthesis of optically enriched monofluoromethyl tertiary alcohols is challenging, and only a few reports are available.^[6f,7] In 1989, Bravo and co-workers reported the addition reaction of a chiral sulfoxide substituted monofluoromethyl ketone with alkyl lithium reagents, thereby affording monofluoromethyl tertiary alcohols with low diastereomeric ratios (up to d.r. 75:25; Scheme 1 a).^[7a] In 1995, the same group reported a stereoselective oxirane formation from chiral 1-fluoro-3-arylsulfinyl-2-propanone with diazomethane, and monofluoromethyl tertiary alcohols were obtained after the ring-opening reaction (Scheme 1 b).^[7b] In this case, although the first step gave the oxiranes in good d.r. (up to 94:6), the toxic, unstable, and explosive reagent CH_2N_2 was used. In 2000, Haufe and co-workers reported an enantioselective nucleophilic fluorination of racemic 2-methyl-2-phenyloxirane with Jacobsen's (S,S)-(+)-(salen)chromium catalyst, but only 20 % conversion and 6 % ee were obtained (Scheme 1 c).^[6f] Therefore, the development of a new, efficient and easy-to-handle protocol for the stereoselective synthesis of optically pure monofluoromethyl tertiary alcohols is highly desired.

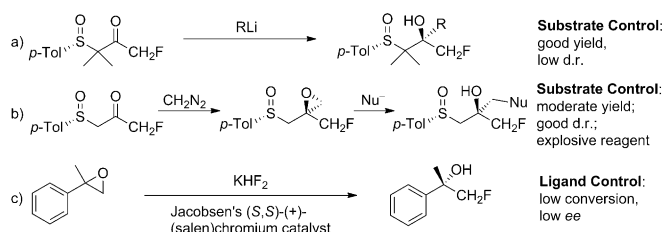
Nucleophilic fluoroalkylation with a racemic fluorinated carbanion or carbanion equivalent has proven to be one of the most important and efficient methods for synthesizing fluorinated organic molecules.^[8] However, the corresponding reactions with chiral fluoroalkylation reagents designed for the synthesis of optically pure organofluorine compounds

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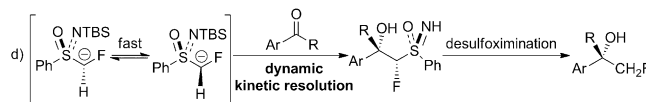
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Previous work



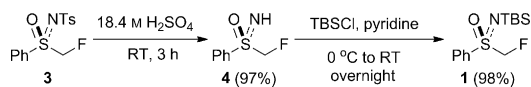
This work (Reagent Control: good yield, excellent d.r., easy-to-handle reagents)



Scheme 1. Strategies for the synthesis of optically enriched monofluoromethyl tertiary alcohols.

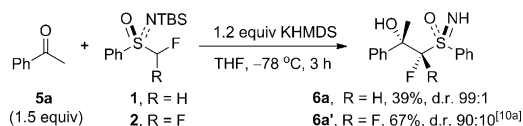
have been much less studied.^[9,10] In 2012, Sanz-Tejedor, Ruano, and co-workers reported an asymmetric nucleophilic monofluoromethylation of aromatic aldehydes that resulted in moderate to good diastereoselectivity.^[9a] However, the facial selectivity and yield dramatically decreased when an aromatic ketone was used as the substrate.^[9a] Herein, we report our recent success in the synthesis of optically enriched monofluoromethyl tertiary alcohols through a highly stereoselective nucleophilic fluoromethylation of aryl ketones with (*R*)-PhSO(NTBS)CH₂F (**1**; NTBS = *N*-tert-butyldimethylsilyl), in which the stereoselectivity was facilitated by an intriguing dynamic kinetic resolution of the chiral α -fluoro carbanions (Scheme 1d).

Firstly, we developed an efficient synthesis of (*R*)-*N*-tert-butyldimethylsilyl-*S*-fluoromethyl-*S*-phenylsulfoximine (**1**). (*R*)-*N*-tosyl-*S*-fluoromethyl-*S*-phenylsulfoximine (**3**) was readily prepared according to reported procedures.^[10b] The tosyl group of **3** was readily removed in aqueous H₂SO₄ (18.4 M), thus affording (*R*)-*S*-fluoromethyl-*S*-phenylsulfoximine (**4**) in 97% yield. Silylation of **4** with *tert*-butyldimethylsilyl chloride (TBSCl) gave compound **1** in 98% yield (Scheme 2).



Scheme 2. Preparation of (*R*)-*N*-tert-butyldimethylsilyl-*S*-fluoromethyl-*S*-phenylsulfoximine (**1**).

Subsequently, we investigated the addition reaction of acetophenone **5a** to monofluoromethyl sulfoximine **1** by using similar conditions to those used for the addition of **5a** to difluoromethyl sulfoximine **2** (Scheme 3).^[10a] Much higher



Scheme 3. Different reactivities of **1** and **2** towards **5a**.

facial selectivity was obtained for the monofluoromethylation reaction (d.r. 99:1) than for the difluoromethylation reaction (d.r. 90:10), although the yield was lower for the monofluoromethylation. We suppose that both the kinetically preferred generation of the (*R*)-PhSO(NTBS)CF₂[−] anion and the subsequent nucleophilic addition of the anion to **5a** over the undesired enolization of **5a** are the key factors for the satisfactory yield of the difluoromethylation reaction.^[11] In our previous study on the synthesis of **2**, it was found that (*R*_s)-PhSO(NTBS)CHF[−] possesses good thermal stability and was suitable for pregeneration.^[10a,12] We thus envisaged that pregeneration of (*R*_s)-PhSO(NTBS)CHF[−] could improve the yield of the monofluoromethylation reaction. When we mixed compound **1** with KHMDS at −78 °C for 30 min, then added **5a** at the same temperature and quenched the reaction 3 h later, the yield increased to 62% without loss of facial selectivity (Table 1, entry 1).

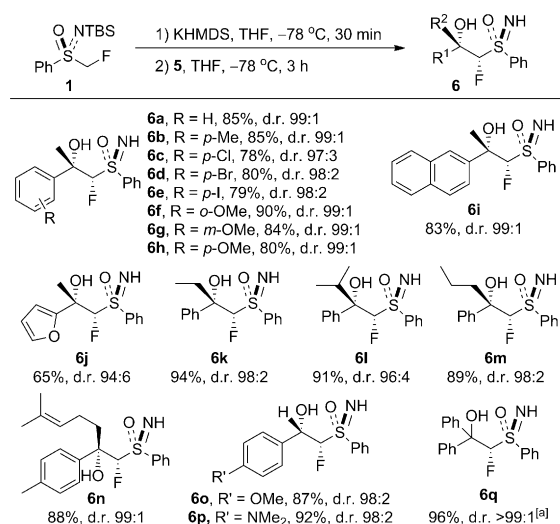
Table 1: Study of reaction conditions.

Entry	5a /2/Base	Base	Solvent	Yield [%] ^[a]	d.r. ^[b]
1	1.5:1:1.2	KHMDS	THF	62	99:1
2	1.5:1:1.2	NaHMDS	THF	55	99:1
3	1.5:1:1.2	LiHMDS	THF	9	80:20
4	1.5:1:1.2	<i>n</i> BuLi	THF	97	86:8:6 ^[c]
5 ^[d]	1.5:1:1.2	KHMDS	DME	38	95:5
6	1.5:1:1.2	KHMDS	PhCH ₃	77	91:9
7	1.5:1:1.2	KHMDS	CH ₂ Cl ₂	49	86:14
8	1.5:1:1.2	KHMDS	Et ₂ O	64	87:13
9	1.5:1:1.2	KHMDS	THF/HMPA (v/v=10:1)	15	99:1
10	1.5:1:2.5	KHMDS	THF	77	99:1
11 ^[e]	2:1:2.5	KHMDS	THF	92(85)	99:1

[a,b] Total yield and diastereomeric ratio (d.r.) were determined by ¹⁹F NMR spectroscopy, and only two diastereoisomers were observed unless otherwise noted. [c] Three diastereoisomers were observed. [d] The reaction was performed at −70 °C. [e] Yield in parentheses refers to the yield of the isolated major diastereoisomer. KHMDS = potassium bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide, DME = 1,2-dimethoxy ethane.

Encouraged by the above results, we further investigated the stereoselective synthesis of optically pure monofluoromethyl tertiary alcohols through the chiral monofluoromethylation reagent strategy. It was found that when NaHMDS was used as the base instead of KHMDS, the yield decreased slightly but excellent facial selectivity was still observed (Table 1, entry 2). When the base was changed to LiHMDS, both yield and d.r. decreased dramatically (9% yield, d.r. 80:20; Table 1, entry 3). However, when *n*BuLi was used as the base, a yield of 97% was obtained with the observation of three diastereoisomers (d.r. 86:8:6). A screening of solvents showed that THF was the best solvent in terms of stereoselectivity (Table 1, entries 1, 5–8). Although the yield decreased to 15%, the addition of HMPA did not reduce the diastereoselectivity, a result in sharp contrast to the influence of HMPA on the reaction of (*R*)-PhSO(NTBS)CF₂H and **5a**.^[10a] Further optimization of the reaction conditions by changing the ratio of **5a**, **2**, and KHMDS showed that when the ratio was 2:1:2.5, **6a** was obtained in 92% yield with d.r. 99:1 (Table 1, entry 11).

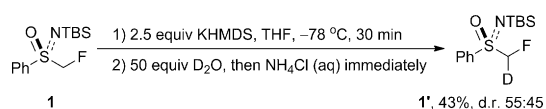
With the optimized conditions, the substrate scope of the reaction between **5** and **1** was examined (Scheme 4). Reaction with various aryl methyl ketones gives the corresponding enantiomerically enriched monofluoromethyl tertiary alcohols **6a–h** in good to excellent yields (78–90%) and with excellent facial selectivity (d.r. 97:3–99:1). The reaction tolerates many substituents such as methyl, chloro, bromo, iodo, and methoxy groups. A naphthyl-substituted ketone also reacted with reagent **1** to afford the product **6i** in 83% yield, d.r. 99:1. In addition, monofluoromethylation of a heteroaryl substituted ketone was also successful, giving the tertiary alcohol **6j** in 65% yield, d.r. 94:6. Moreover, ketones **5k**, **5l**, **5m**, and **5n** were also suitable substrates for the monofluoromethylation reaction, giving the products **6k** in 94% yield with d.r. 98:2, **6l** in 91% yield with d.r. 96:4, **6m**



Scheme 4. Stereoselective monofluoromethylation of ketones and aldehydes with sulfoximine **1**. General procedures: under N₂, KHMDS (1 mmol in THF, 2.5 mL, 2.5 mmol) was added to the solution of **1** (287 mg, 1 mmol) in THF (5 mL) at –78 °C; 30 min later, a solution of **5** (2 mmol) in THF (1 mL) was added, and 3 hours later, the reaction was quenched with 5 mL of 3 M HCl (aq). The d.r. value was determined by ¹⁹F NMR spectroscopy before silica gel column chromatography and refers to the facial selectivity unless otherwise noted. Yield refers to the yield of the isolated major diastereoisomer. [a] The d.r. value results from the sulfur and fluorinated carbon stereogenic centers.

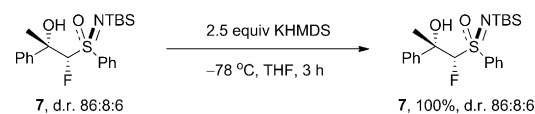
in 89 % yield with d.r. 98:2, and **6n** in 88 % yield with d.r. 99:1, respectively. The reaction could also be applied to the synthesis of enantiomerically enriched monofluoromethyl secondary alcohols. Products **6o** and **6p** were obtained in 87 % yield with d.r. 98:2, and 92 % yield with d.r. 98:2, respectively. The exclusive formation of monofluoromethyl tertiary alcohol **6q** in 96 % yield with d.r. >99:1 from symmetrical ketone **5q** shows excellent control of the stereoselectivity at the fluorinated carbon stereogenic center in the current monofluoromethylation reaction. The absolute configurations of **6d** and **6o** were confirmed by X-ray crystal-structure analysis (see the Supporting Information),^[13] and those of the other products were assigned by analogy.

To probe the mechanism of the current monofluoromethylation reaction, we performed several experiments. Firstly, a reaction of (*R*_S)-PhSO(NTBS)CHF[–] with D₂O was conducted. Very low diastereoselectivity (d.r. 55:45) was observed for monodeuterated product **1'** (Scheme 5), thus indicating that carbanions in both *R* and *S* configurations at the fluorinated carbon were formed.^[14a–c] Secondly, we examined whether the addition reaction is reversible. After being treated with KHMDS at –78 °C for 3 h, compound **7**



Scheme 5. Reaction of (*R*)-PhSO(NTBS)CH₂F (**1**) with D₂O.

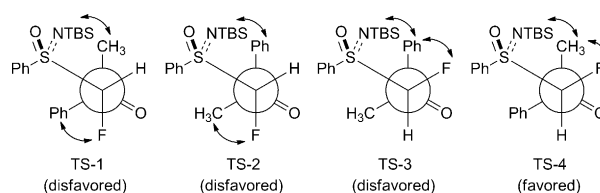
was recovered in 100 % yield without a change in d.r. (Scheme 6), thus suggesting that the addition reaction was irreversible. Based on these results, we propose that complete



Scheme 6. Investigation of the stability of compound **7** in the presence of KHMDS.

control of the stereoselectivity at the fluorinated carbon stereogenic center results from the excellent dynamic kinetic resolution of the participating carbanions (Scheme 1 d).^[14d] Obviously, the chiral induction from the sulfur stereogenic center of the sulfoximine to the fluorinated carbon stereogenic center has a beneficial effect on the facial selectivity of the monofluoromethylation reaction.

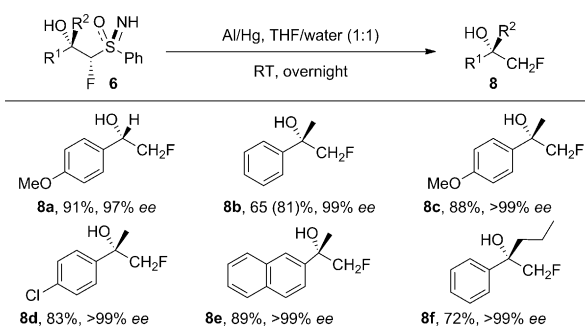
Based on the fact that the addition of HMPA did not obviously influence the diastereoselectivity of the monofluoromethylation of **5a** with **1**, we propose that the cation might not participate in the transition state.^[15] One can envisage several possible nonchelated transition states, such as TS-1, TS-2, TS-3, and TS-4 shown in Scheme 7. Since the Ph...F



Scheme 7. Proposed transition states. Repulsive interactions are indicated by curved arrows.

repulsive interaction is stronger than the CH₃...F interaction, TS-1 is less favored than TS-4. Given that the repulsive interaction of PhSO(NTBS)...Ph is stronger than that of PhSO(NTBS)...CH₃, TS-2 is also less favored than TS-4. Finally, TS-3 is less favored than TS-4 because of the stronger repulsive interactions of Ph...F and PhSO(NTBS)...Ph compared to those of the CH₃...F and PhSO(NTBS)...CH₃.

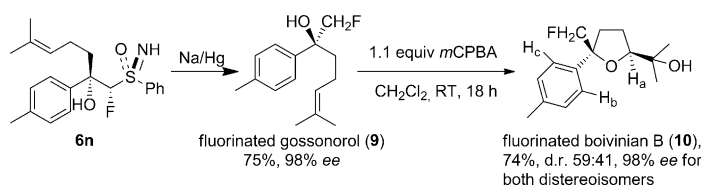
In a previous study, we found that the Mg/AcOH/AcONa system was a good reductive desulfoximinating agent for the synthesis of difluoromethyl alcohols.^[10a] However, the desulfoximation of compound **6o** by using Mg/AcOH/AcONa was found to be inefficient, giving monofluoromethyl alcohol **8a** in only 37 % yield (for details, see Table S-1 in the Supporting Information). In 1988, Boys and co-workers reported that the adducts of PhSO(NMe)CH₂F and aldehydes could be converted into monofluoroalkenes in the presence of Al/Hg.^[16] However, we found that monofluoromethyl alcohol **8a** was obtained in 91 % yield with 97 % *ee* from **6o** (a mixture of diastereoisomers with d.r. 99:1) without the formation of monofluoroalkene compounds in the presence of Al/Hg (Scheme 8). Under similar reaction conditions,



Scheme 8. Synthesis of optically enriched monofluoromethyl alcohols through reductive desulfoximation of **6**. Typical procedure: under N_2 atmosphere, the newly prepared Al/Hg (405 mg of Al) was added to the solution of **6** (d.r. 99:1, 0.5 mmol) in THF/water (5 mL:5 mL) at room temperature in several portions and stirred overnight. Substrates **6** were diastereomerically pure except for **6a**. The yield refers to the yield of isolated product and the yield in parentheses was determined by ^{19}F NMR spectroscopy.

optically enriched monofluoromethyl tertiary alcohols **8b–f** were obtained in good yields without loss of optical purity at the benzylic carbon stereogenic centers.

To show the potential value of our present monofluoromethylation reaction in organic synthesis, the product **6n** was transformed into fluorinated analogues of the natural products gossonorol and boivinian B, which have interesting biological properties (Scheme 9).^[17] Upon treatment with



Scheme 9. Synthesis of natural-product analogues.

Na/Hg, compound **6n** was converted into product **9** in 75% yield, 98% ee. Compound **10** was afforded in 74% yield, d.r. 59:41 through epoxidation/ring-opening cascade reaction of compound **9** by using *meta*-chloroperoxybenzoic acid (mCPBA). Both diastereoisomers of compound **10** were obtained in 98% ee. The NOE spectrum of the major diastereoisomer showed that H_a was in the same plane as H_b and H_c (see the Supporting Information).

In conclusion, an efficient and easy-to-handle protocol for the highly stereoselective nucleophilic monofluoromethylation of ketones with large substrate scope was developed. To our knowledge, this is the first report on the synthesis of optically pure monofluoromethyl tertiary alcohols through a nucleophilic fluoroalkylation strategy. The synthesis of fluorinated analogues of the natural products gossonorol and boivinian B demonstrated the potency of the method. The reaction showed higher facial selectivity than the corresponding difluoromethylation reaction. In contrast to the negative effect of HMPA on the facial selectivity of the difluoromethylation,^[10a] the addition of HMPA did not influence the facial

selectivity of the current monofluoromethylation reaction, a result that indicates that different transition states were involved in the two reactions. Excellent stereoselective control at the fluorinated carbon stereogenic center was found, an effect believed to be facilitated by the dynamic kinetic resolution of the chiral α -fluoro carbanions.

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- [1] a) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, 37, 320; b) K. Mueller, C. Faeh, F. Diederich, *Science* **2007**, 317, 1881; c) H. J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, 5, 637; d) M. Sani, A. Volonterio, M. Zanda, *ChemMedChem* **2007**, 2, 1693; e) C. Fäh, R. Mathys, L. A. Hardegger, S. Meyer, D. Bur, F. Diederich, *Eur. J. Org. Chem.* **2010**, 4617.
- [2] a) R. E. Banks, B. E. Smart, J. C. Tatlow, Eds. *Organofluorine Chemistry, Principles and Commercial Applications*, Plenum, New York, **1994**, chap. 3; b) D. O'Hagan, H. S. Rzepa, *Chem. Commun.* **1997**, 645; c) R. E. Banks, *J. Fluorine Chem.* **2001**, 109, 3; d) J. R. McCarthy, *Fluorine in Drug Design: A Tutorial Review*, 17th Winter Fluorine Conference, St. Pete Beach, FL, **2005**; e) K. L. Kirk, *J. Fluorine Chem.* **2006**, 127, 1013.
- [3] J. Fried, E. F. Sabo, *J. Am. Chem. Soc.* **1953**, 75, 1455.
- [4] Selected examples: a) 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; b) P. Bey, F. Gerhart, V. V. Dorselaer, C. Danzin, *J. Med. Chem.* **1983**, 26, 1551; c) R. B. Silverman, S. M. Nanavati, *J. Med. Chem.* **1990**, 33, 931; d) M. K. Bhattacharjee, E. E. Snell, *J. Biol. Chem.* **1990**, 265, 6664; e) G. L. Grunewald, T. M. Caldwell, Q. Li, M. Slavica, K. R. Criscione, R. T. Borchardt, W. Wang, *J. Med. Chem.* **1999**, 42, 3588; f) G. L. Grunewald, M. R. Seim, R. C. Regier, G. L. Martin, L. Gee, N. Drinkwater, K. R. Criscione, *J. Med. Chem.* **2006**, 49, 5424; g) K. Mckeage, S. J. Keam, *Drugs* **2009**, 69, 1799; h) R. A. Rojas, I. Paluga, C. H. Goldfrad, M. T. Duggan, N. Barnes, *J. Asthma* **2007**, 44, 437; i) G. K. S. Prakash, S. C. Istvan, G. A. Olah, *Org. Lett.* **2008**, 10, 557.
- [5] J. H. Kim, A. R. Scialli, *Toxicol. Sci.* **2011**, 122, 1.
- [6] a) B. Barkakaty, Y. Takaguchi, S. Tsuboi, *Tetrahedron* **2007**, 63, 970; b) P. V. Ramachandran, A. V. Teodorovic, B. Q. Gong, H. C. Brown, *Tetrahedron: Asymmetry* **1994**, 5, 1075; c) P. Veeraraghavan Ramachandran, B. Gong, A. V. Teodorovic, *J. Fluorine Chem.* **2007**, 128, 844; d) J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc.* **2011**, 133, 16001; e) J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc.* **2010**, 132, 3268; f) S. Bruns, G. Haufe, *J. Fluorine Chem.* **2000**, 104, 247; g) H. Ma, K. Matsuzaki, Y.-D. Yang, E. Tokunaga, D. Nakane, T. Ozawa, H. Masuda, N. Shibata, *Chem. Commun.* **2013**, 49, 11206.
- [7] a) P. Bravo, F. Ganazzoli, E. Piovosi, G. Resnati, *Gazz. Chim. Ital.* **1989**, 119, 323; b) A. Arnone, P. Bravo, M. Frigerio, G. Salani, F. Viani, C. Zappala, G. Cavicchio, M. Crucianelli, *Tetrahedron* **1995**, 51, 8289.
- [8] Reviews: a) W. Zhang, C. Ni, J. Hu, *Top. Curr. Chem.* **2012**, 308, 25; b) C. Ni, J. Hu, *Synlett* **2011**, 770; c) J. Hu, *J. Fluorine Chem.* **2009**, 130, 1130; d) J. Hu, W. Zhang, F. Wang, *Chem. Commun.* **2009**, 7465; e) G. K. S. Prakash, J. Hu, *Acc. Chem. Res.* **2007**, 40, 921; Selected examples: f) Y. Li, J. Hu, *Angew. Chem.* **2005**, 117, 6032; *Angew. Chem. Int. Ed.* **2005**, 44, 5882; g) G. K. S. Prakash, S. Chacko, S. Alconcel, T. Stewart, T. Mathew, G. A. Olah, *Angew. Chem.* **2007**, 119, 5021; *Angew. Chem. Int. Ed.* **2007**, 46,

- 4933; h) W. Zhang, W. Huang, J. Hu, *Angew. Chem.* **2009**, *121*, 10042; *Angew. Chem. Int. Ed.* **2009**, *48*, 9858; i) T. Fukuzumi, N. Shibata, M. Sugiura, H. Yasui, S. Nakamura, T. Toru, *Angew. Chem.* **2006**, *118*, 5095; *Angew. Chem. Int. Ed.* **2006**, *45*, 4973; j) X. Shen, L. Zhang, Y. Zhao, L. Zhu, G. Li, J. Hu, *Angew. Chem.* **2011**, *123*, 2636; *Angew. Chem. Int. Ed.* **2011**, *50*, 2588; k) G. K. S. Prakash, N. Shao, Z. Zhang, C. Ni, F. Wang, R. Haiges, G. A. Olah, *J. Fluorine Chem.* **2012**, *133*, 27; l) X. Shen, C. Ni, J. Hu, *Helv. Chim. Acta* **2012**, *95*, 2043; m) X. Shen, C. Ni, J. Hu, *Chin. J. Chem.* **2013**, *31*, 878.
- [9] a) Y. Arroyo, M. A. Sanz-Tejedor, A. Parra, J. L. García Ruano, *Chem. Eur. J.* **2012**, *18*, 5314; b) J. L. García Ruano, A. Parra, I. Alonso, S. Fustero, C. del Pozo, Y. Arroyo, A. Sanz-Tejedor, *Chem. Eur. J.* **2011**, *17*, 6142; c) J. L. García Ruano, J. A. Fernández-Salas, M. C. Maestro, *J. Org. Chem.* **2012**, *77*, 2893.
- [10] For chiral fluorinated sulfoximine as fluoroalkylation reagents, see a) X. Shen, W. Zhang, C. Ni, Y. Gu, J. Hu, *J. Am. Chem. Soc.* **2012**, *134*, 16999; b) X. Shen, W. Zhang, L. Zhang, T. Luo, X. Wan, Y. Gu, J. Hu, *Angew. Chem.* **2012**, *124*, 7072; *Angew. Chem. Int. Ed.* **2012**, *51*, 6966; reviews on the application of sulfoximine in synthesis: c) C. R. Johnson, *Aldrichimica Acta* **1985**, *18*, 3; d) C. R. Johnson, *Acc. Chem. Res.* **1973**, *6*, 341; e) M. Reggelin, C. Zur, *Synthesis* **2000**, 1; f) Y. Macé, E. Magnier, *Eur. J. Org. Chem.* **2012**, 2479; recent examples on the application of sulfoximine in synthesis: g) W. Dong, L. Wang, K. Parthasarathy, F. Pan, C. Bolm, *Angew. Chem.* **2013**, *125*, 11787; *Angew. Chem. Int. Ed.* **2013**, *52*, 11573; h) L. Wang, H. Huang, D. L. Priebe, F.-F. Pan, C. Bolm, *Angew. Chem.* **2013**, *125*, 3562; *Angew. Chem. Int. Ed.* **2013**, *52*, 3478; i) M. R. Yadav, R. K. Rit, A. K. Sahoo, *Org. Lett.* **2013**, *15*, 1638; j) X. Shen, M. Zhou, C. Ni, W. Zhang, J. Hu, *Chem. Sci.* **2014**, *5*, 117.
- [11] J. Liu, J. Hu, *Chem. Eur. J.* **2010**, *16*, 11443.
- [12] J. Liu, L. Zhang, J. Hu, *Org. Lett.* **2008**, *10*, 5377.
- [13] CCDC 959109 (**6d**) and CCDC 959110 (**6o**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [14] Deuteration of chiral carbanions: a) J. M. Concellón, J. R. Suarez, S. Garcia-Granda, M. R. Diaz, *Angew. Chem.* **2004**, *116*, 4433; *Angew. Chem. Int. Ed.* **2004**, *43*, 4333; b) R. Luisi, V. Capriati, C. Carlucci, L. Degennaro, S. Florio, *Tetrahedron* **2003**, *59*, 9707; c) F. Hammerschmidt, A. Hanninger, H. Völlenke, *Chem. Eur. J.* **1997**, *3*, 1728; An excellent review on dynamic resolution of the chiral organolithium compounds: d) In *Top. Stereochem.* **2010**, *26*: *Stereochemical Aspects of Organolithium Compounds*. (Ed.: R. E. Gawley), Verlag Helvetica Chimica Acta, Zurich, **2010**.
- [15] The K⁺ cation was proposed to be involved in the transition state of the difluoromethylation reaction between PhSO-(NTBS)CF₂H (**1**) and acetophenone (**5a**), see Ref. [10a].
- [16] In several cases, monofluoromethyl alcohols were obtained as the by-products, see: M. L. Boys, E. W. Collington, H. Finch, S. Swanson, J. F. Whitehead, *Tetrahedron Lett.* **1988**, *29*, 3365.
- [17] a) G. W. Elzen, J. Williams, S. B. Vinson, *J. Chem. Ecol.* **1984**, *10*, 1251; b) P. Weyerstahl, S. Schneider, H. Marschall, A. Rustaiyan, *Liebigs Ann. Chem.* **1993**, 111; c) P. Magiatis, A. Michaelakis, A.-L. Skaltsounis, S. A. Haroutounian, *Nat. Prod. Lett.* **2001**, *13*, 125; d) J. Sun, D. Shi, M. Ma, S. Li, S. Wang, L. Han, Y. Yang, X. Fan, J. Shi, L. He, *J. Nat. Prod.* **2005**, *68*, 915; e) A. Cakir, S. Kordali, H. Kilic, E. Kaya, *Biochem. Syst. Ecol.* **2005**, *33*, 245; f) M. Sylvestre, A. Pichette, A. Longtin, F. Nagau, J. Legault, *J. Ethnopharmacol.* **2006**, *103*, 99; g) N. Kartal, M. Sokmen, B. Tepe, D. Daferera, M. Polissiou, A. Sokmen, *Food Chem.* **2007**, *100*, 584; h) V. Saroglou, M. Arfan, A. Shabir, D. Hadjipavlou-Litina, H. Skaltsa, *Flavour Fragrance J.* **2007**, *22*, 154; i) T.-L. Ho, S.-H. Liu, *Synth. Commun.* **1983**, *13*, 463; j) K. Abecassis, S. E. Gibson, *Eur. J. Org. Chem.* **2010**, 2938; k) J. Boukouvalas, R. Pouliot, Y. Fréchette, *Tetrahedron Lett.* **1995**, *36*, 4167.