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 carbon electrophiles.

The incorporation of fluorne 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. In this context, monofluorinated analogues of biologically active compounds are considered to be promising isosteres of the parent molecules. 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. In recent years, fluorine incorporation has become a routine strategy for drug design. Among various monofluorinated compounds, monofluoromethylated compounds are of particular value since CH₂F functionality can mimic CH₃ and CH₂OH groups, which are often encountered in biologically active molecules. However, since the thalidomide tragedy, 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 nucleophilic fluorination of optically pure epoxides or enantioselective fluorination of racemic epoxides and enantioselective monofluoromethylation of aldehydes. However, the synthesis of optically enriched monofluoromethyl tertiary alcohols is challenging, and only a few reports are available. In 1989, Bravo and co-workers reported the addition reaction of a chiral sulfonamide substituted monofluoromethyl ketone with alkyl lithium reagents, thereby affording monofluoromethyl tertiary alcohols with low diastereomeric ratios (up to d.r. 75:25; Scheme 1a). 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 1b). In this case, although the first step gave the oxiranes in good d.r. (up to 94:6), the toxic, unstable, and explosive reagent CH₂N₂ was used. In 2000, Haufe and co-workers reported an enantioselective nucleophilic fluorination of racemic 2-methyl-2-phenyloxirane with Jacobsen/Salen catalyst, but only 20% conversion and 6% ee were obtained (Scheme 1c). 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. However, the corresponding reactions with chiral fluoroalkylation reagents designed for the synthesis of optically pure organofluorine compounds...
have been much less studied.\textsuperscript{[9,10]} In 2012, Sanz-Tejedor, Ruano, and co-workers reported an asymmetric nucleophilic monofluorobenzylzation of aromatic aldehydes that resulted in moderate to good diastereoselectivity.\textsuperscript{[10]} However, the facial selectivity and yield dramatically decreased when an aromatic ketone was used as the substrate.\textsuperscript{[9b] 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)-PhSF\textsubscript{2}NTBS\textsubscript{2}CH\textsubscript{2}F \textsuperscript{(1): NTBS = N-tert-butylmethylsilyl}, in which the stereoselectivity was facilitated by an intriguing dynamic kinetic resolution of the chiral \(\alpha\)-fluorocarbons (Scheme 1d).

Firstly, we developed an efficient synthesis of (R)-N-tert-butylidimethylsilyl-S-fluoromethyl-S-phenylsulfoximine (1). (R)-N-tosyl-S-fluoromethyl-S-phenylsulfoximine (3) was readily prepared according to reported procedures.\textsuperscript{[10b]} The tosyl group of 3 was readily removed in aqueous H\textsubscript{2}SO\textsubscript{4} (18.4 m), thus affording (R)-S-fluoromethyl-S-phenylsulfoximine (4) in 97\% yield. Silylation of 4 with tert-butyldimethylsilyl chloride (TBSCI) gave compound 1 in 98\% yield (Scheme 2).

\textbf{Scheme 2. Preparation of (R)-N-tert-butylidimethylsilyl-S-fluoromethyl-S-phenylsulfoximine (1).}

Subsequently, we investigated the addition reaction of acetophenone 5\textsubscript{a} to monofluoromethyl sulfoximine 1 by using similar conditions to those used for the addition of 5\textsubscript{a} to difluoromethyl sulfoximine 2 (Scheme 3).\textsuperscript{[10a]} Much higher 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 (RS)-PhSF\textsubscript{2}NTBS\textsubscript{2}CF\textsubscript{2} anion and the subsequent nucleophilic addition of the anion to 5\textsubscript{a} over the undesired enolization of 5\textsubscript{a} are the key factors for the satisfactory yield of the difluoromethylation reaction.\textsuperscript{[11]} In our previous study on the synthesis of 2, we found that (R\textsubscript{3})-PhSO(NTBS)CH\textsubscript{2}F possesses good thermal stability and was suitable for pregeneration.\textsuperscript{[10b,11]} We thus envisaged that pregeneration of (R\textsubscript{3})-PhSO(NTBS)CH\textsubscript{2}F could improve the yield of the monofluoromethylation reaction. When we mixed compound 1 with KH\textsubscript{2}MS at \(-78^\circ\text{C}\) for 30 min, then added 5\textsubscript{a} at the same temperature and quenched the reaction 3\textsubscript{h} later, the yield increased to 62\% without loss of facial selectivity (Table 1, entry 1).

\textbf{Scheme 3. Different reactivities of 1 and 2 towards 5\textsubscript{a}.}

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 KH\textsubscript{2}MS, 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 nBuLi 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\textsubscript{2}(NTBS)CF\textsubscript{2} and 5\textsubscript{a}.\textsuperscript{[11]} Further optimization of the reaction conditions by changing the ratio of 5\textsubscript{a}, 2, and KH\textsubscript{2}MS showed that when the ratio was 2:1:2.5, 6\textsubscript{a} 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 6\textsubscript{a–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 6\textsubscript{i} in 83\% yield, d.r. 99:1. In addition, monofluoromethylation of a heteroaryl substituted ketone was also successful, giving the tertiary alcohol 6\textsubscript{j} in 65\% yield, d.r. 94:6. Moreover, ketones 5\textsubscript{k}, 5\textsubscript{l}, 5\textsubscript{m}, and 5\textsubscript{n} were also suitable substrates for the monofluoromethylation reaction, giving the products 6\textsubscript{k} in 94\% yield with d.r. 98:2, 6\textsubscript{l} in 91\% yield with d.r. 96:4, 6\textsubscript{m} in 98\% yield with d.r. 97:3.

\begin{table}[h]
\centering
\caption{Study of reaction conditions.}
\begin{tabular}{|c|c|c|c|c|}
\hline
Entry & 5\textsubscript{a}/2 & Base & Solvent & Yield [\%] \textsuperscript{[a,b]} & d.r.\textsuperscript{[c]} \\
\hline
1 & 1.5:1:1.2 & KHMS & 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 & nBuLi & THF & 97 & \textsuperscript{[d]} 86:8:6 \\
5\textsuperscript{[d]} & 1.5:1:1.2 & KHMS & DME & 38 & 95:5 \\
6 & 1.5:1:1.2 & KHMS & PhCH\textsubscript{3} & 77 & 91:9 \\
7 & 1.5:1:1.2 & KHMS & CH\textsubscript{2}Cl\textsubscript{2} & 49 & 86:14 \\
8 & 1.5:1:1.2 & KHMS & Et\textsubscript{2}O & 64 & 87:13 \\
9 & 1.5:1:1.2 & KHMS & THF/HMPA & 15 & 99:1 \\
10 & 1.5:1:2.5 & KHMS & THF & 77 & 99:1 \\
11\textsuperscript{[e]} & 2:1:2.5 & KHMS & THF & 92\textsuperscript{(85)} & 99:1 \\
\hline
\end{tabular}
\textsuperscript{[a,b]} Total yield and diastereomeric ratio (d.r.) were determined by \textsuperscript{1}H NMR spectroscopy, and only two diastereoisomers were observed unless otherwise noted. [c] Three diastereoisomers were observed. [d] The reaction was performed at \(-70^\circ\text{C}\). [e] Yield in parentheses refers to the yield of the isolated major diastereoisomer. KHMS = potassium bis(trimethylsilyl)amide, HMPA = hexamethylphosphoramide, DME = 1,2-dimethoxy ethane.
\end{table}
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)-PhSO(NTBS)CH2F 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 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 control of the stereoselectivity at the fluorinated carbon stereogenic center results from the excellent dynamic kinetic resolution of the participating carbanions (Scheme 1d).[14d] Obviously, the chiral induction from the sulfur stereogenic center of the sulfoxime 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 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/MeOH/Na system was a good reductive desulfoximinating agent for the synthesis of difluoromethyl alcohols.[10a] However, the desulfoximination of compound 6o by using Mg/MeOH/Na 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 desulfouximation of 6. Typical procedure: under N₂ 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 ¹⁹F NMR spectroscopy.

optically enriched monofluoromethyl tertiary alcohols 8b-f were obtained in good yields without loss of optical purity at the benzylcarbon 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 bovinin B, which have interesting biological properties (Scheme 9).[13] Upon treatment with 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 H₉ was in the same plane as H₆ and H₂ (see the Supporting Information).

In conclusion, an efficient and easy-to-handle protocol for the highly stereoselective nucleophilic monofluoromethylolation 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 bovinin B demonstrated the potency of the method. The reaction showed higher facial selectivity than the corresponding difluoromethylolation reaction. In contrast to the negative effect of HMPA on the facial selectivity of the difluoromethylolation, the addition of HMPA did not influence the facial selectivity of the current monofluoromethylolation 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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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.


The K⁺ cation was proposed to be involved in the transition state of the difluoromethylation reaction between PhSO₂- (NTBS)CF₂H and acetophenone (1) and acetophenone (5a), see Ref. [10a].

In several cases, monofluoromethyl alcohol 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.