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Asymmetric Nucleophilic Monofluorobenzylation of Carbonyl Compounds: Synthesis of Enantiopure *vic*-Fluorohydrins and α-Fluorobenzylketones

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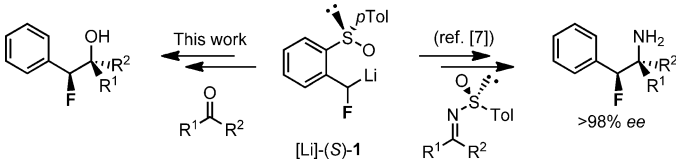
Abstract: Asymmetric nucleophilic monofluoroalkylation of a broad range of aldehydes with an α-fluoro-γ-sulfinylbenzyl carbanion takes place with complete control of the facial selectivity at the carbanion and good to high *anti*-diastereoselectivity to give easily separable mixtures of two optically pure 1,2-fluorohydrin derivatives (up to 24:1 *anti*/*syn*). Separation and removal of the *p*-tolylsulfinyl group with *t*BuLi provides enantiomerically pure *anti*-1,2-disubstituted-1,2-fluorohydrins, whereas α-fluorobenzylketones can be obtained by desulfinylation of the mixture followed by pyridinium chlorochromate oxidation (one-pot process).

Keywords: asymmetric synthesis · fluorine · fluorohydrins · fluoroketones · sulfoxides

Introduction

Fluorine-containing organic compounds occupy a significant place in pharmaceutical, agrochemical, and materials sciences because of the ability of the fluorine atom to modulate molecular properties, such as metabolic stability or binding affinity.[1] Particularly, monofluorinated analogues of biologically active compounds are of great importance with regards to isostere-based drug design.[2] Electrophilic fluorination and nucleophilic monofluoroalkylation reactions of carbonyl compounds are two straightforward operations for the construction of monofluorinated compounds and their asymmetric versions are particularly useful. The former allows to access to α-fluorocarbonyl compounds and allylic fluorides in high enantiomeric excess (*ee*).[3] On the other hand, nucleophilic fluorination strategies for the synthesis of monofluoroalkyl derivatives have only recently emerged, with important contributions from the groups of Prakash and Olah,[4] Hu,[5] and Shibata and Toru.[6] They proved that fluoromethylcarbanions with removable electron-withdrawing group(s)—usually a sulfonyl functionality—possess significant thermal stability and they are effective nucleophilic monofluoromethylating reagents of wide scope. Nevertheless, this strategy places the fluorine atom in the primary position after the removal of the sulfonyl group(s), therefore, does not allow introduction of the fluorine atom on a stereogenic center. To overcome this limitation, we recently developed 1-(fluoromethyl)-2-((*S*)-*p*-tolylsulfinyl)benzene ((*S*)-**1**) as a chiral monofluorinated reagent. The reactions of (*S*)-**1** with *N*-sulfinyl aldimines were completely stereoselective and yielded enantiomerically pure β-fluorinated β-phenylethylamines[7] (Scheme 1). These results encouraged us to study the monofluoroalkylation of carbonyl compounds with the carbanion of (*S*)-**1** as an easy route to 1,2-fluorohydrins in which both the fluorine and hydroxyl groups are attached to a chiral center (Scheme 1).



Scheme 1. Reactions of prochiral fluoride synthon [Li]-(*S*)-**1** with *N*-sulfinylimines and carbonyl compounds.

1,2-Fluorohydrins are versatile building blocks and key intermediates for the synthesis of monofluorinated analogues of many bioactive compounds[8] and they find application as derivatizing agents for the determination of enantiomeric composition by ^{19}F NMR spectroscopy.[9] Additionally, important new materials, such as liquid crystals, contain this functional group relationship.[10] Despite this great interest, there is no simple and direct method to obtain optically active 1,2-fluorohydrins and their synthesis is even more challenging when the fluorine atom occupies a benzylic posi-

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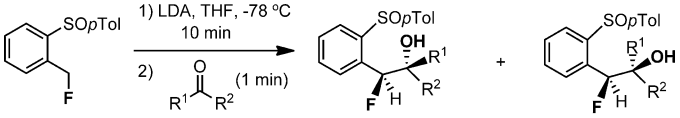
tion. The most often applied approach for preparation of 1,2-fluorohydrins is the ring opening of enantiopure epoxides with nucleophilic fluorine reagents.[11] However, the synthetic usefulness of this strategy is mainly restricted by the incomplete regio- and stereoselectivity of the process. Desymmetrization of *meso* epoxides has also been studied;[12] only recently, high enantiodifferentiation (up to 95% *ee*) was achieved in the fluoride ring-opening of epoxides by using a chiral amine and chiral Lewis acid as cooperative catalysts.[13] Alternatively, α-fluoroaldols have been prepared by asymmetric aldol reaction either with fluoroketene silyl acetal as a donor with Masamunes's catalyst[14] or from fluoroacetone in the presence of a variety of organocatalysts.[15] High enantioselectivities were usually achieved but with low diastereo and/or regioselectivity. Finally, 1,2-fluorohydrins have been prepared through deracemization by classical or enzymatic processes,[16] and through catalytic transfer hydrogenation of α-fluoroketones by dynamic kinetic resolution (DKR).[17] In any case, all of the reported methods for the preparation of stereodefined 1,2-fluorohydrins in enantiopure form present severe limitations, so additional synthetic efforts in this field are necessary. Herein, we present our results for the asymmetric monofluoroalkylation of a broad range of carbonyl compounds with the α-fluoro-γ-sulfinylbenzyl carbanion derived from (*S*)-**1**, which allows the synthesis of *vic*-fluorohydrins with two adjacent stereogenic centers.

Results and Discussion

Compound (*S*)-**1** is readily available from 2-bromobenzylic alcohol in a three-step sequence (sulfinylation, tosylation, and fluorination with CsF) in high yield by our previously reported procedure.[7] The aldehydes and ketones used in this study were commercially available. We studied the reaction of (*S*)-**1** with aldehydes **2a–o**. We found that optimal reaction conditions involved quick addition of the electrophile to the carbanion (generated by treatment with lithium diisopropylamine (LDA)) at −78°C. In all cases, the reactions were complete in less than one minute. As summarized in Table 1, this process generally provided a mixture of only two fluorhydrins, *anti*-**3** and *syn*-**4**, that differ in the configuration at the hydroxylic carbon atom. The major isomer had the *anti* configuration. In all cases, both diastereoisomers were readily separated by column chromatography. The reaction of benzaldehyde (**2a**) evolved with high *anti*-diastereoselectivity to afford a 92:8 mixture of *anti*-**3a**/*syn*-**4a**. The major isomer *anti*-**3a** was isolated in 80% yield (Table 1, entry 1).

Reactions carried out with arylaldehydes **2b–e**, with electron-donating groups at the *para* and/or *meta* positions, showed similar behavior. *Anti*/*syn* ratios ranged from 10:1 to 24:1 (Table 1, entries 2–5). A slight improvement of the *anti* selectivity was observed when the aromatic ring was activated by several electron-donating groups, as in the case of **2e** (diastereomeric excess (*de*) = 92%, Table 1, entry 5). The reactions of sterically demanding naphthyl aldehydes **2f** and **2g** also proceeded with high *anti* diastereoselectivity (86 and 84% *de*, respectively; Table 1, entries 6 and 7). Aldehydes **2h–i**, with a substituent at the *ortho* position, provided lower diastereoselectivity than those with the same substituent at the *para* or *meta* position (Table 1, entries 8 and 9 versus 2 and 3). Aldehydes **2j** and **2k**, which contain the weakly electron-withdrawing group chlorine at the *meta* or *para* position, respectively, also evolved with good *anti* diastereoselectivity, although a small amount of a third diastereoisomer was also detected in the ^{1}H NMR spectrum of the reaction mixture (Table 1, entries 10 and 11). Unfortunately, reactions with arylaldehydes that contained electron-withdrawing groups *p*-CF_3 or *p*-CN were less successful and mixtures of four fluorohydrins were formed with low diastereoselectivity (36:26:20:18 and 36:31:24:9, respectively). The method was also found to be successful for aliphatic aldehydes **2l–n**, to furnish *anti* fluorohydrins **3l–n** as the major isomers with moderate diastereoselectivity. The *anti*/*syn* ratio ranged from 3:1 to 4:1; the stereoselectivity slightly increased with the size of the R group (Table 1, entries 12–14). Conjugate aldehyde **2o** was also compatible with the reaction conditions and afforded 1,2-addition products *anti*-**3o** and *syn*-**4o** in a 6:1 ratio (Table 1, entry 15). It is remarkable that despite the moderate stereoselectivity observed in these

Table 1. Monofluorobenzylation of carbonyl compounds **2a–s** with (*S*)-**1** by a single asymmetric-induction procedure.[a]



(*S*)-**1** **2a-s** *anti*-**3** *syn*-**4**

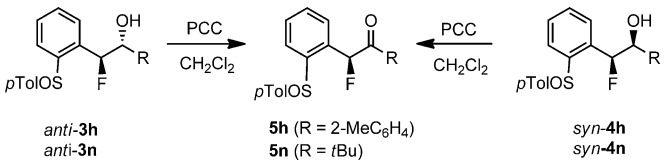
Entry	Carbonyl compound	R^1	R^2	d.r. (*anti*-**3**/*syn*-**4**)[b]	Yield of *anti*-**3**[%][c]
1	**2a**	H	C_6H_5	92:8	80
2	**2b**	H	4-Me−C_6H_4	91:9	79
3	**2c**	H	4-MeO−C_6H_4	92:8	79
4	**2d**	H	3-MeO−C_6H_4	93:7	81
5	**2e**	H	3,4,5-tri-MeO−C_6H_2	96:4	79
6	**2f**	H	2-naphthyl	93[d]:7	78
7	**2g**	H	1-naphthyl	92:8	78
8	**2h**	H	2-Me−C_6H_4	80:20	66
9	**2i**	H	2-MeO−C_6H_4	81:19	63
10	**2j**	H	3-Cl−C_6H_4	86:14[e]	69
11	**2k**	H	4-Cl−C_6H_4	84:16[f]	62
12	**2l**	H	*n*-butyl	75:25	59
13	**2m**	H	*i*Pr	76:24	63
14	**2n**	H	*t*Bu	80:20[d]	69
15	**2o**	H	*trans* PhCH=CH	86:14	70
16	**2p**	Ph	Ph	–[g]	91
17	**2q**	CH_3	CH_3	–[g]	89
18	**2r**	CH_3	4-OMe−C_6H_4	70:30	50
19	**2s**	CH_3	*t*Bu	89:11	75

[a] All reactions were performed on a 0.5 mmol scale. [b] Diastereomeric ratio (d.r.) determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c] Yield of isolated product. [d] ORTEP representations of *anti*-**3f** and *syn*-**4n** can be found in the Supporting Information. [e] A 84:14:2 mixture of three fluorohydrins was observed. [f] A 81:15:4 mixture of three fluorohydrins was observed. [g] Single enantiomer.

latter reactions, the isolated yield of the major *anti*-**3** isomers is typically higher than 60%.

To broaden the scope of this strategy, we also studied the behavior of (*S*)-**1** with ketones to afford α,α-dibranched-β-fluoroalcohols. The exclusive formation of fluorohydrins **3p** and **3q** in high yield from symmetrical ketones **2p** and **2q**, respectively, was observed (*ee* > 98%; Table 1, entries 16 and 17). Furthermore, the method was found to be applicable to nonsymmetrical ketones **2r** and **2s**, although only **2s** gave high *anti* diastereoselectivity (Table 1, entries 18 and 19). The full scope of the reaction of (*S*)-**1** with ketones is currently being investigated.

Taking into account that all of the reactions of electrophiles with γ-sulfinylbenzyl carbanions studied so far evolved with a complete control of the stereoselectivity at the benzylic position,[18] we first assumed that compounds *anti*-**3** and *syn*-**4** were epimers at the hydroxylic carbon atom, C1. To confirm this assumption, the independent oxidation of pure compounds *anti*-**3h** and *syn*-**4h** with pyridinium chlorochromate (PCC) was performed. Both reactions afforded the same α-fluoroketone, **5h** (Scheme 2), indicative that the epimers only differ in the configuration at C1. Similar conclusions could be established for *anti*-**3n** and *syn*-**4n**, which were both oxidized with PCC into **5n**.

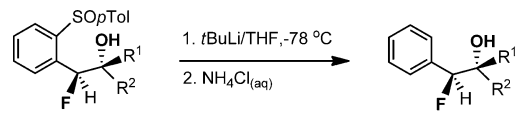


Scheme 2. PCC oxidations of *anti*- and *syn*-1,2-fluorohydrins **3** and **4**.

These results prove that the remote sulfinyl group on the nucleophile completely controls the configuration at the α-fluorobenzylic carbon atom through a 1,4-asymmetric-induction process.

Configurational assignment of compounds **3** and **4** was tentatively made from the NMR spectroscopic data (significant differences between the diastereoisomers) and later unequivocally confirmed by X-ray analysis of *anti*-**3f** and *syn*-**4n** (see the Supporting Information). The fact that all of the reactions evolved similarly, with complete control of the configuration at the α-fluorobenzylic carbon atom and good to high *anti*/*syn* diastereoselectivity, suggests that the absolute configuration is (1*R*,2*S*) for fluorohydrins *anti*-**3a–o**, *anti*-**3r**, and *anti*-**3s** and (2*S*) for **3p** and **3q**. Likewise, the minor isomers *syn*-**4a–o**, *syn*-**4r**, and *syn*-**4s** should exhibit a (1*S*,2*S*) configuration.

Compounds **3** could be easily transformed into 1,2-fluorohydrins **6** by C-desulfinylation with *t*BuLi at −78°C (Scheme 3). We checked the efficiency of this procedure in the cases of **3a**, **3e**, and **3n–p**. The corresponding 1,2-fluorohydrins **6** were obtained in good yields as pure compounds. The *ee* values of *anti*-**6a** and *anti*-**6e** were established as higher than 98% from a ^{1}H NMR study of their Mosher's



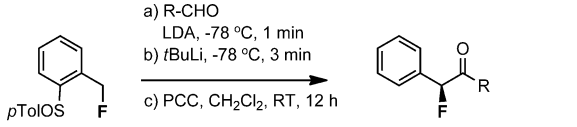
anti-**3a** (R^1 = H; R^2 = C_6H_5) — *anti*-**6a** (90 %)
anti-**3e** (R^1 = H; R^2 =3,4,5-tri-O-MeC_6H_2) — *anti*-**6e** (93 %)
anti-**3n** (R^1 = H; R^2 =*t*Bu) — *anti*-**6n** (88 %)
anti-**3o** (R^1 = H; R^2 =*trans*-C_6H_5CH=CH) — *anti*-**6o** (92 %)
anti-**3p** (R^1 =; R^2 = C_6H_5) — *anti*-**6p** (88 %)

Scheme 3. Desulfinylation of 1,2-fluorohydrins *anti*-**3** with *t*BuLi.

esters, which allowed us to conclude that the desulfinylation process proceeded without epimerization at the chiral carbon atoms.[19]

Chiral, nonracemic α-fluoroketones are valuable building blocks for the construction of active compounds[1,2] and, in recent years, they have become promising reagents for the asymmetric epoxidation of alkenes.[20] Most strategies to prepare simple α-fluoroketones are based on enolate or enamine methodologies, but only a few examples yield high *ee* values.[3] Thus, high diastereoselectivity has been achieved starting from chiral α-silylketones[21] but harsh conditions are required to remove the (*S*)-1-amino-2-(methoxymethyl)-pyrrolidine (SAMP) hydrazone auxiliary used in the preparation of the silylketone. Alternatively, an oxazolidinone was used as a chiral auxiliary to direct the addition of a fluorine atom in the preparation of α-fluoroketones via Weinreb *N*-methoxy-*N*-methyl amides.[22] Enantioselective fluorination by transition-metal catalysis or organocatalysis has been widely used but this approach is limited to the fluorination of β-ketoesters and, only very recently, a highly enantioselective α-fluorination of cyclic ketones by enamine organocatalysis has been reported.[23]

The results presented in Schemes 2 and 3 suggest that any product mixture obtained from the reaction of (*S*)-**1** with aldehydes **2** could be desulfinylated and subsequently oxidized into α-fluorobenzylketones. Given that the conditions of the PCC oxidation are not overly favorable for epimerization of the fluorinated carbon atom, we thought this procedure could provide enantiomerically pure α-fluoroketones. To confirm this assumption, we prepared compounds **7a** and **7e** by reaction of (*S*)-**1** with aldehydes **2a** and **2e**, respectively, further treatment of the resulting fluorohydrins with *t*BuLi, and finally oxidation with PCC (Scheme 4). We also checked that the conditions of these reactions were efficient when they were applied to the crude mixture of the reaction of (*S*)-**1** with **2**, which allowed the direct synthesis of de-



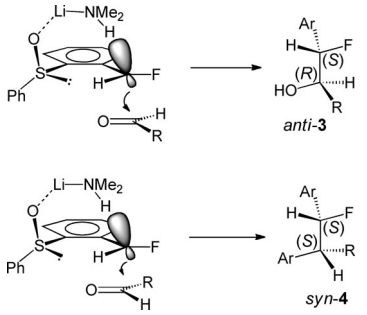
(*S*)-**1**

7a (R = C_6H_5)
7e (R = 3,4,5-tri-OMe-C_6H_2)

Scheme 4. One-pot conversion of (*S*)-**1** and aldehyde **2a** or **2e** into desulfinylated α-fluoroketones **7a** and **7e**.

sulfinylated α-fluoroketones **7** (neither the fluorohydrins **3**, nor the sulfinyl derivatives **6** were isolated). Under the conditions of the one-pot process, α-fluoroketones **7a** and **7e** were isolated in good yield (54 and 63%, respectively) and complete control of the configuration at the fluorinated chiral carbon atom was achieved (*ee* > 98%; see the Supporting Information).

The stereochemical results of the reactions described in Table 1 can be explained by the assumption that the free carbanion (Scheme 5) stabilized by hydrogen bonds to N–H



Scheme 5. Diastereoselective control in the formation of fluorohydrins **3** and **4**.

is the most stable form for benzylic carbanions derived from (*S*)-**1** (supported by theoretical calculations).[7] Because the amine blocks the upper face of the carbanion, electrophilic attack can only take place from the bottom face to yield compounds with the *S* configuration at the benzylic carbon atom (C–F). Nevertheless, the formation of mixtures of epimers at the hydroxylic carbon atom in these reactions indicates that the approach of the α-fluoro-γ-sulfinylbenzyl carbanion to the electrophile can take place at either of its two diastereotopic faces, with the antiperiplanar arrangement of the C–F and C=O bonds maintained to minimize their dipolar repulsion. Stronger steric interactions in the approach that yields *syn*-**4** ($(Ar/R)_{gauche}+(R/F)_{gauche}$) justifies the observed *anti* stereoselectivity.

Conclusion

We have described the first asymmetric monofluoroalkylation of a broad range of aldehydes with the α-fluoro-γ-sulfinylbenzyl carbanion derived from (*S*)-**1** to generate *anti*-1,2-fluorohydrins with two contiguous stereogenic centers in high isolated yields. The sulfinyl group exerts complete control of the facial selectivity at the benzylic carbon atom. The observed *anti* diastereoselectivity ranges from 3:1 to 24:1, dependent on the starting aldehyde (higher ratios are observed in the presence of larger substituents). Furthermore, this protocol also provides α-fluorobenzyl ketones in a one-pot fluorobenzylation/desulfinylation/PCC oxidation sequence.

Acknowledgements

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