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Anti-Selective Aldol Reactions of Pentafluorosulfanylacetic Acid Esters with Aldehydes Mediated by Dicyclohexylchloroborane

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Supporting Information

ABSTRACT: Aldol reactions of pentafluorosulfanyl (SF_5)-substituted acetic acid esters with both aromatic and aliphatic aldehydes proceeded with excellent *anti*-diastereoselectivity and good to high yields using dicyclohexylchloroborane/triethylamine. This methodology enabled the synthesis of hitherto unknown α-SF_5-β-hydroxy esters. Using a norephedrine-based auxiliary, high asymmetric induction was observed. The stereochemistry of products was assigned by NMR spectroscopy and proved by X-ray diffraction analysis. The intermediate enolate was identified as a highly unstable species.

The pentafluorosulfanyl (SF_5) group has received much research attention because of its outstanding steric and electronic properties.[1−3] In comparison to the tetrahedral trifluoromethyl (CF_3) group in 1,1,1-trifluoroethane, the pseudo octahedral SF_5 moiety in pentafluorosulfanylmethane provides a higher dipole moment alongside a higher group electronegativity between that of fluorine and chlorine.[4] Paired with a steric demand close to that of the *tert*-butyl group, the SF_5 substituent has a remarkable electronic and conformational impact on organic compounds, observed by lowered pK_a values and increased lipophilicities.[5] Consequently, promising applications of the SF_5 group in agricultural and medicinal chemistry and materials science have attracted enhanced attention.[1−3,6] Recent advances in the large-scale preparation of aromatic SF_5 containing building blocks improved the availability of the latter significantly.[7,8] A rising number of reported structure−activity relationship (SAR) studies screening SF_5-containing compounds routinely underscores this trend.[9] The incorporation of SF_5 moieties in aliphatic positions is generally based on the radical addition of SF_5X (X = Cl, Br, SF_5) to π-bonds. The forcing conditions these reactions usually require have been avoided elegantly by Dolbier et al. applying triethylborane initiation.[10] Nevertheless, only a very few cases of transformations of aliphatic SF_5 compounds have been reported so far. Representative examples are the derivatization of aliphatic 2-pentafluorosulfanyl aldehydes,[11] syntheses of 1,2,3-triazoles containing a pentafluorosulfany alkyl group via click chemistry,[12a] and the use of SF_5-bearing dienophiles in Diels−Alder reactions[12b,c] or 1,3-dipolar cycloadditions.[13] Recently, we succeeded in preparing α-SF_5 carboxylic acid derivatives by Ireland−Claisen rearrangements, which proceed via enolates of allylic SF_5 acetates.[14] Herein, we report *anti*-diastereoselective aldol reactions of SF_5-substituted acetic acid esters with both aromatic and aliphatic aldehydes.[15]

The easy to handle 2-(pentafluorosulfanyl)acetic acid (**1**), available by addition of SF_5Cl to ketene[16] or by a multistep pathway recently reported by Dolbier et al.,[17] appeared to be a suitable building block for the preparation of carboxylic esters that might undergo boron-mediated aldol reactions. This reaction is known to be powerful in the formation of C−C bonds, allowing the mild formation of β-hydroxycarbonyl compounds. Ramachandran et al. reported the use of dicyclohexylchloroborane (Cy_2BCl) in the enolization of 3,3,3-trifluoropropionates. The observed deprotonation is a result of the low pK_a value of the α-protons. Generally, chloroboranes are not suitable for the enolization of common esters.[18] Compared to its more reactive triflates, chloroboranes benefit from better availability and superior hydrolytic stability.

Since small, SF_5-containing molecules often have low boiling points, the acid **1** was first converted in good yields to the less volatile esters **2** and **3** by condensation using the DCC/DMAP[19,20] method as shown in Scheme 1.

In a first aldol reaction, octyl SF_5-acetate **2**, after enolization with Cy_2BCl/triethylamine (Et_3N) at −78 °C, was reacted with benzaldehyde (Table 1, entry 1). By increasing the number of equivalents of the reagents, prolonging the time for enolate formation from 2−4 h, and lengthening the time for the aldol reaction from 1 to 17 h, the conversion was increased from 79 to

Scheme 1. Esterification of Acid 1 with Primary Alcohols

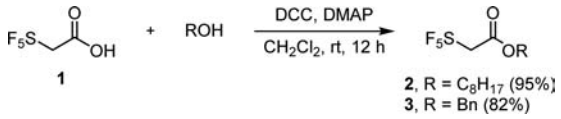

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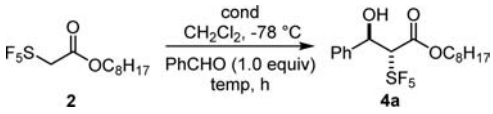
Table 1. Optimization of Aldol Reaction of Octyl Acetate 2



2 4a

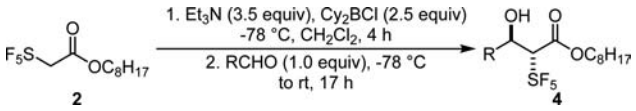
cond	temp (h)	yield[a] (%)	*anti*/*syn*[a]
Et_3N (3.0 equiv)	−78 °C, 1 h	79 (78)	95:5
Cy_2BCl (2.0 equiv), 2 h	rt, 1 h		
Et_3N (3.5 equiv)	−78 °C to rt	96 (85)	97:3
Cy_2BCl (2.5 equiv), 4 h	17 h		

[a]Determined by ^{19}F NMR of the crude product; isolated yields in parentheses.

96% as determined by ^{19}F NMR spectroscopy. The reaction was found to be highly selective (*anti*/*syn* = 97:3). Attempts to shift the selectivity to the *syn*-diastereomer by using elevated temperatures, more bulky amines, and less sterically demanding boranes failed.

Having established an efficient route to **4a**, the scope of the aldol reaction of octyl SF_5-acetate **2** with various benzaldehydes of different steric and electronic properties (Table 2, entries 1−15) was examined. The aldol products were formed in good yield and high selectivity. However, aldols of very electron-rich benzaldehydes were found to be unstable and decomposed during purification on silica or alumina (Table 2, entries 3, 4, and 6). The formation of these aldol products was established by ^{19}F NMR spectroscopy and mass spectrometry. Cinnamon aldehyde was found to react under 1,2-addition exclusively (Table 2, entry 15), whereas conversion of nonenolizable pivaldehyde amounted to 88% yield (Table 2, entry 18) and aliphatic aldehydes with acidic α-protons showed significantly lower yields (Table 2, entries 16 and 17). The enolization of these aldehydes was verified as a side reaction by ^1H NMR experiments. Lowering the equivalents of the borane and the amine or varying the reaction time could not suppress formation of side products in this reaction.

Table 2. Aldol Reaction of Ester 2 with Representative Aldehydes



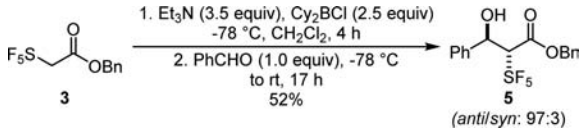
2 4

entry	RCHO	product	yield[a] (%)	*anti*/*syn*[a]
1	PhCHO	**4a**	96 (85)	97:3
2	4-$CH_3C_6H_4CHO$	**4b**	93 (71)	96:4
3	4-$CH_3OC_6H_4CHO$	**4c**	79 (−)[b]	94:6
4	3,4-$CH_3OC_6H_3CHO$	**4d**	94 (−)[b]	97:3
5	4-HO-3-$CH_3OC_6H_3CHO$	**4e**	65(25)	96:4
6	4-$(CH_3)_2NC_6H_4CHO$	**4f**	77 (−)[b]	98:2
7	4-BrC_6H_4CHO	**4g**	90 (75)	96:4
8	4-FC_6H_4CHO	**4h**	88 (84)	94:6
9	4-$SF_5C_6H_4CHO$	**4i**	94 (75)	96:4
10	2-$CH_3C_6H_4CHO$	**4j**	98 (89)	96:4
11	2-BrC_6H_4CHO	**4k**	95 (86)	>99:1
12	2-FC_6H_4CHO	**4l**	96 (89)	98:2
13	2,6-$(CH_3)_2C_6H_3CHO$	**4m**	92 (84)	>90:10[c]
14	2,6-$Cl_2C_6H_3CHO$	**4n**	>99 (82)	96:4
15	PhCH=CHCHO	**4o**	86 (75)	94:6
16	*cy*-$C_6H_{11}CHO$	**4p**	38 (29)	99:1
17	$CH_3CH_2CH_2CHO$	**4q**	45 (27)	92:8
18	^{t}BuCHO	**4r**	88 (76)	98:2

[a]Determined by ^{19}F NMR spectroscopy; isolated yields in parentheses; [b]Products were identified by mass spectrometry and ^{19}F NMR spectroscopy. [c]Three SF_5 products (90:8:2) were found.

Aldol products of SF_5-substituted esters are new, and therefore, the relative configuration could not be determined by comparing the reported NMR spectra. Since the octyl moiety caused most of the compounds in Table 2 to be obtained as oils, the benzyl ester **3** of acid **1** was prepared in order to achieve a more rigid system. The reaction of **3** with benzaldehyde resulted in the formation of a solid aldol **5** (Scheme 2).

Scheme 2. Aldol Reaction of 3 with Benzaldehyde



3 5 (*anti*/*syn*: 97:3)

Recrystallization from hexanes yielded high-quality crystals for X-ray structural analysis (Figure 1).[21] The SF_5 moiety shows the expected octahedral geometry, and its bond angles and lengths were found to be in good accordance with examples of aliphatic-bound SF_5 groups in literature.[22] The phenyl group is arranged almost *anti* to the SF_5 group with a dihedral angle S1−C2−C3−C11 of −175.9(4)°. Similarly, the plane generated by the ester functionality is almost orthogonal to the SF_5 moiety. More importantly, the configuration of the latter with respect to the hydroxyl group was found to be *anti*, leaving the conformation of the aldol moiety in a *gauche* conformation (SF_5 to OH group).

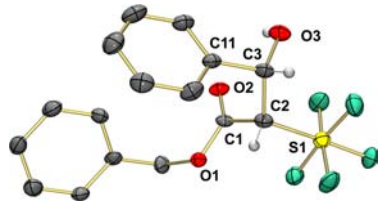


Figure 1. POV-ray diagram of compound **5**. Thermal ellipsoids shown at 50% probability; irrelevant protons omitted for clarity.

During an investigation of the scope of the substrate, aldol product **4n** was surprisingly isolated as a solid. Recrystallization from toluene gave crystals suitable for X-ray diffraction analysis (Figure 2).[21] Again, an *anti*-configuration of the aldol moiety was found.

Interestingly, the conformation of **4n** differs from compound **5**, as the dihedral angle of S1−C8−C7−C1 was −57.2(5)°.

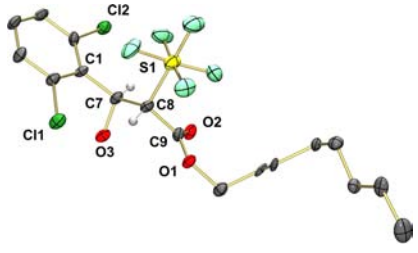


Figure 2. POV-ray diagram of compound **4n**. Thermal ellipsoids shown at 50% probability; irrelevant protons omitted for clarity.

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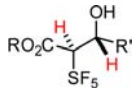
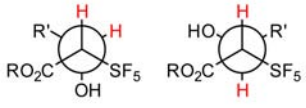
Throughout these X-ray diffraction studies, the relative configuration was proven to be *anti* in both groups of aldol products. As a consequence, the hydrogen atoms are arranged *gauche* in group A and *anti* in group B conformers leading to different coupling constants (Table 3).

Table 3. Conformational Analysis of the Aldol Products Obtained by Boron-Mediated Aldol Reaction of Ester 2



group	$J_{H,H}$ (Hz)	R	R'	Φ_{HH} (°)
A	2.4-4.0	octyl benzyl	4-XC_6H_5 (X = H, Me, OMe, F, Br, SF_5), 4-HO-3-$CH_3OC_6H_3$ *cy*-C_6H_{11} PhCH=CH	~60/120
B	9.4-9.7	octyl	2,6-$X_2C_6H_3$ (X = Cl, Me)	~0/180



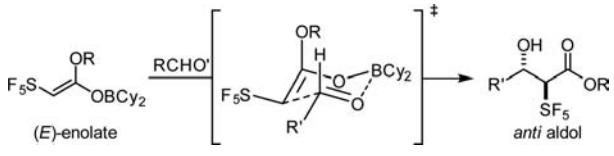
group **A** group **B**

The Karplus equation allows an estimation of the dihedral angles Φ_{HH} based on the coupling constants determined in the ^{1}H NMR spectra. A comparison of the solid-state structures of **4n** and **5** with conformers deduced from the $^3J_{H,H}$ coupling constants of the protons at C2 and C3 in the ^{1}H NMR spectra led to the hypothesis that in this particular case the preferred conformations detected by NMR in solution correspond to the conformers found in the solid state by X-ray crystallography.[23] Analysis of the coupling constants of the aldol products shown in Table 2 revealed two groups of conformers, as shown in Table 3. Aside from products with 2,6-disubstitution of the aryl ring, which result in an *anti*-conformer (regarding the protons), *gauche* conformers were generally observed. Upon the possible formation of a hydrogen bond between the hydroxyl group and the carbonyl oxygen atom a favored six-membered ring can be formed for both groups **A** and **B**. Thus, the conformational difference is the result of the introduction of a second substituent in the *ortho*′-position of the aryl moiety as confirmed by DFT calculations (see the Supporting Information).

The *anti*-configuration of aldol products is frequently a consequence of intermediate (*E*)-enolates in a Zimmerman–Traxler transition state in which both the SF_5 moiety and the R′ group of the aldehyde are located in equatorial positions as shown in Scheme 3. According to this model, less sterically demanding aldehydes lead to lower selectivity, as observed for butyraldehyde (Table 2, entry 17).

Under standard enolization conditions (CD_2Cl_2, −80 °C), a new SF_5 signal pattern (δ = 90.21 ppm (quint, $^2J_{F,F}$ = 157.4 Hz), 72.72 ppm (d, $^2J_{F,F}$ = 152.7 Hz)) was observed in the ^{19}F NMR spectra aside from that of the starting octyl SF_5-acetate **2**. Surprisingly, the ratio of starting material and enolate was only 9:1 after 4 h of enolization at −80 °C (see the SI). Although the stereochemistry could not be verified by 2D experiments, the thermal stability was tested by elevating the temperature to −40 °C. This revealed a limited stability of the formed enolate, as after 1 h at this temperature the enolate signal was no longer detectable in the ^{19}F NMR spectra.

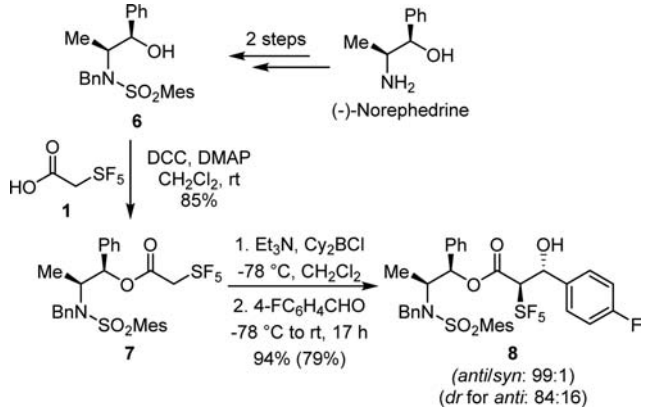
Scheme 3. Proposed Transition State for the Boron-Mediated Aldol Reaction of SF_5-Substituted Esters



(*E*)-enolate *anti* aldol

Many aldehydes showed excellent reactivity and selectivity in the boron-mediated aldol reaction. Subsequently, first asymmetric pathways have been attempted. Approaches to connect Evans oxazolidinones with the SF_5 acid **1** failed. However, the ester **7** based on Masamune's[24] norephedrine auxiliaries was used successfully as shown in Scheme 4. Ester **7** was formed by DCC/DMAP condensation[19,20] of the acid **1** with the norephedrine-based auxiliary **6**.

Scheme 4. Asymmetric Pathway for Boron-Mediated Aldol Reaction of SF_5-Substituted Acetic Acid Ester 7



The following aldol reaction with 4-fluorobenzaldehyde provided a high *anti*/*syn*-selectivity of 99:1 and a moderate dr of 84:16 for one of the *anti*-diastereomers. By lowering the reaction temperature to −90 °C, the dr was increased to 92:8, while the yield dropped to 74% (^{19}F NMR) due to solubility issues. Unfortunately, removal of the auxiliary of aldol product **8** has not yet been accomplished, since reductive ester cleavage with $LiAlH_4$ or $NaBH_4$/MeOH let to complete decomposition of the aldol moiety. The aldol reaction was found to be reversible under these conditions. Further investigations are in progress and will be communicated in due course.

In conclusion, aldol reactions of octyl and benzyl SF_5-acetates with both aromatic and aliphatic aldehydes gave α-SF_5-β-hydroxy esters with good to high yields and excellent *anti*-diastereoselectivity in the presence of excess dicyclohexylchloroborane/triethylamine. An intermediate SF_5-enolate has been identified by ^{19}F NMR spectroscopy at low temperature. Masamune's norephedrine-based auxiliary has been applied to accomplish a highly selective asymmetric aldol reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00136.

Experimental procedures and ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

X-ray crystallography data of compounds **4n** and **5** (CIF)

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Notes

The authors declare no competing financial interest.

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