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Stereospecific benzylic dehydroxyfluorination reactions using Bio's TMS-amine additive approach with challenging substrates

Stefano Bresciani, David O'Hagan *

EastCHEM and Centre for Biomolecular Sciences, School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, United Kingdom

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ABSTRACT

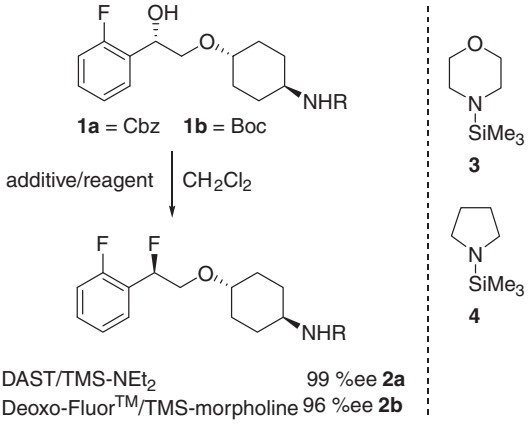
Reactions involving the conversion of a benzylic alcohol into a benzylic fluoride using RSF3 reagents are notoriously difficult to achieve with high stereochemical inversion (S_N2 reaction) due to competing dissociative S_N1 reaction processes. This Letter develops the methodology of Bio et al., and reports that the addition of a preformed 1:TMS-amine 1:RSF_3 (fluorination reagent) complex as the reagent in these reactions significantly suppresses the S_N1 process and promotes a highly stereospecific reaction generating benzylic fluorination products of high %ee.

1. Introduction

The introduction of fluorine into organic molecules is a widely recognised strategy for imparting unique properties to performance molecules,[1–3] and particularly molecules going through pharmaceutical development programmes have benefited dramatically from the introduction of fluorine.[4] An increasing range of reagents are being developed for the introduction of C–F bonds and catalytic asymmetric fluorination strategies have attracted significant attention,[5–7] however the stereospecific conversion of an enantiomerically pure alcohol into its corresponding organic fluoride remains attractive due to the wide availability of appropriate enantiopure alcohols. However, such dehydroxyfluorination reactions are a considerable challenge, particularly if the alcohol is benzylic and prone to an S_N1 reaction course. (Diethylamino)sulfur trifluoride (DAST)[8] has been widely employed for such transformations, although modified reagents of this class such as Deoxo-Fluor™,[9] have been developed which are more stable to higher reaction temperatures. Most recently, Fluolead™ has been introduced[10] for dehydroxyfluorination reactions, among other transformations. The challenging aspect of these reagents involves conducting dehydroxyfluorination reactions with high stereointegrity (inversion of configuration) from a precursor enantiopure alcohol. Very little has been achieved to address this issue. Most significantly, however Bio et al. reported[11] in 2008 that the stereospecificity of the DAST-mediated dehydroxyfluorination of **1a** and **1b** was considerably improved by the addition of *N*-(trimethylsilyl)morpholine (**3**) or *N*-(trimethylsilyl)diethylamine to the reaction as illustrated in Scheme 1.

The %ees increased from 50% ee to 96–99% ee depending on the additive. These observations were made during process development in a medicinal chemistry environment. Although mechanistic details remain speculative regarding the influence of the TMS-amines, a working hypothesis suggests that, for example, a morpholino intermediate such as **5** (Scheme 2), is less prone to an S_N1 dissociative reaction than the analogous intermediate **6** generated during a straightforward DAST reaction.

In the reaction with **1** (Scheme 1) the inductive effect of the *ortho*-aryl fluorine is anticipated to assist in suppressing a dissociative S_N1 reaction, and indeed without additive, the reaction generated a product of 50% ee, considerably higher than other benzylic alcohols.[11] We found that similar reactions of DAST with (*R*)-1-phenylethanol (**7**) and methyl (*R*)-mandelate (**9**) (Tables 1 and 2) were more prone to the S_N1 reaction course and gave the corresponding dehydroxyfluorination products with much lower %ees (7% ee and 8% ee, respectively).



Scheme 1. Previous observation of increased stereospecificity in the dehydroxyfluorination reaction of *ortho*-fluorobenzylic alcohols 1a and **1b** with TMS-amine additives.[11] TMS-amines **3** and **4** used in this study.

* Corresponding author. Tel.:+44 1334650708; fax: +44 1334463800.
E-mail address: do1@st-andrews.ac.uk (D. O'Hagan).

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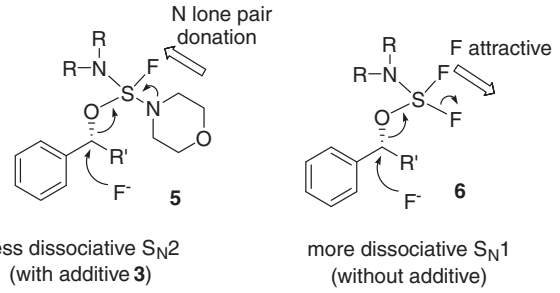
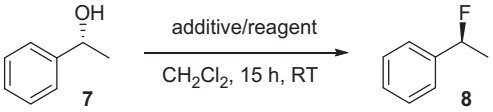


Scheme 2. Rationale for improved stereospecificity where the amine additive forms a complex and suppresses the dissociative reaction as shown in **5** against the better leaving group as illustrated in **6**.

Table 1
%Ees after reaction of (*R*)-**7** with various fluorinating reagents and the TMS-amine additives **3** and **4**



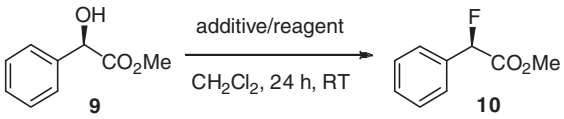
Entry	Additive:reagent (equiv)	%ee[a] (% conv)[b]
1	Fluolead™ (1)	0
2	**3**:Fluolead™ (1)	57
3	**3**:Fluolead™ (3)	92 (34)
4	**4**:Fluolead™ (1)	56
5	**4**:Fluolead™ (3)	85
6	Deoxo-Fluor™ (1)	13
7	**3**:Deoxo-Fluor™ (1)	58
8	**3**:Deoxo-Fluor™ (3)	84 (96)
9	**4**:Deoxo-Fluor™: (1)	66
10	**4**:Deoxo-Fluor™: (3)	59
11	DAST (1)	7
12	**3**:DAST (1)	74
13	**3**:DAST (2)	83
14	**3**:DAST (3)	95 (92)
15	**3**:DAST (4)	93
16	**3**:DAST (9)	93
17	**4**:DAST (1)	54
18	**4**:DAST (3)	69

[a] Determined by GC/MS.
[b] Selected conversions by GC/FID.

With this background we have now explored fluorination of these substrates (**7** and **9**) to assess if the addition of TMS-amine additives can be more generally applied to improve substantially the stereointegrity of benzylic fluoride products from enantiomerically pure benzylic alcohols. Three dehydroxyfluorination reagents of the RSF_3 class have been explored with (*R*)-1-phenylethanol (**7**) and methyl (*R*)-mandelate (**9**). In both of these cases straightforward treatment with DAST, Deoxo-Fluor™ and Fluolead™ in CH_2Cl_2 lead to fluorinated products with low enantiopurity and particularly in the case of **7** (see Table 1, entries 1, 6 and 11 for **7**, and Table 2, entries 1, 6 and 10 for **9**).

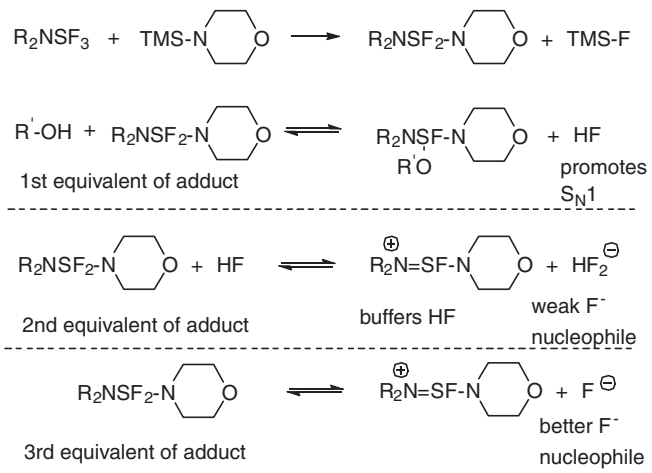
TMS-morpholine **3** and TMS-pyrrolidine **4** were explored as the additives as they are commercially available, and they were added to the reactions at various levels of equivalence. For the more challenging substrate, in terms of achieving good stereospecificity, (*R*)-1-phenylethanol (**7**) the data are presented for three reagents in Table 1. This is a poor reaction in all cases without any additive. However, in all cases, a substantial improvement in %ee is made particularly by addition of 3 equiv for either **3** or **4**. The most substantial improvement was found with TMS-morpholine addition to DAST where the reaction improved from an almost racemic product to generate (*S*)-**8** of 95% ee, and with an excellent conversion (Table 1, entry 14). The reaction with Fluolead™ under similar conditions gave a product **8** of 92% ee but with only a modest conversion (34%) (Table 1, entry 3). In the case of methyl (*R*)-mandelate (**9**) reaction conversions were significantly lower due to the electron-withdrawing nature of the ester group, and without the additive the %ees are very low. So this is a particularly challenging substrate. However, the transformations with all three reagents demonstrated a significant improvement in stereospecificity, in this case with only 1 equiv of additive/reagent with Deoxo-Fluor™ (Table 2, entry 7) and DAST (Table 2, entry 11) starting from a very low %ee (Table 2, entries 1, 6 and 10). The data is presented fully in Table 2. For Fluolead™, TMS-pyrrolidine **4** was the best additive at 3 equiv (Table 2, entry 5). The addition of one equivalent of the 1:1 complex clearly improved the %ee in these reactions, but optimal performance appeared to be at about 3 equiv, particularly for **7**, which is the more challenging substrate in terms of suppressing the S_N1 process. This may be due to the equivalent of HF that is

Table 2
%Ees after reaction of (*R*)-**9** with various fluorinating reagents and the TMS-amine additives **3** and **4**



Entry	Additive:reagent (equiv)	%ee[a] (% conv)[b]
1	Fluolead™ (1)	3
2	**3**:Fluolead™ (1)	64
3	**3**:Fluolead™ (3)	87 (20)
4	**4**:Fluolead™ (1)	89
5	**4**:Fluolead™ (3)	94
6	Deoxo-Fluor™ (1)	23
7	**3**:Deoxo-Fluor™ (1)	99 (51)
8	**3**:Deoxo-Fluor™ (3)	98 (23)
9	**3**:Deoxo-Fluor™ (4)	98
10	DAST (1)	8
11	**3**:DAST (1)	99 (31)
12	**3**:DAST (2)	98
13	**3**:DAST (3)	97 (21)
14	**3**:DAST (4)	97

[a] Determined by GC/MS.
[b] Selected conversions by GC/FID.



Scheme 3. Rationale for the improved stereospecificity at 3 equiv of adduct to benzylic alcohol. A second equivalent buffers HF produced from reaction of the alcohol. The third equivalent generates a fluoride nucleophile

produced when the adduct reacts with the alcohol as illustrated in Scheme 3. A second equivalent will buffer this HF as hydrogen bifluoride, and then the third equivalent would generate a more nucleophilic fluoride ion.

2. Experimental procedure and physical data for (*S*)-8 (95% ee, entry 14 in Table 1)

N-(Trimethylsilyl)morpholine (neat, 447 μl, 2.49 mmol) was added dropwise to a solution of DAST (312 μl, 2.43 mmol) in dry CH_2Cl_2 (0.96 ml) at −78 °C. The resulting solution was stirred at rt for 2.5 h. The reaction mixture was further cooled to −78 °C and a solution of (*R*)-(+)-1-phenylethanol (**7**) (90 μl, 0.74 mmol) in dry CH_2Cl_2 (2.24 ml) was slowly added via cannula. The resulting solution was stirred at rt for 15 h. The mixture was then slowly poured into 15 ml of saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 1.5 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (100% pentane) to afford the desired product (*S*)-**8** (65 mg, 71% yield) as a colourless oil. Chiral-phase GC/MS (EI) analysis of the product, t_R = 20.3 min for the major (*S*)-enantiomer and t_R = 21.3 min for the minor (*R*)-enantiomer, indicated that the optical purity was 95% ee; $[\alpha]_D^{22}$ +35.6 (*c* 1.0, $CHCl_3$); ν_{max} (NaCl)/cm−1 3083, 3064, 3034, 2980, 2926, 1451, 1211, 1063; δ_H (300 MHz, $CDCl_3$) 7.43–7.29 (m, 5H), 5.64 (dq, *J* = 47.6, 6.4, 1H), 1.65 (dd, *J* = 23.9, 6.4, 3H); δ_C (75.5 MHz, $CDCl_3$) 141.7 (d, *J* = 20.0, C), 128.6 (CH), 128.3 (d, *J* = 1.9, CH), 125.3 (d, *J* = 6.7, CH), 91.1 (d, *J* = 167.4, CH), 23.1 (d, *J* = 25.3, CH_3); δ_F (282 MHz, $CDCl_3$) −167.5 (dq, *J* = 47.6, 23.9, 1F); $\delta_{F\{H\}}$ (282 MHz, $CDCl_3$) −167.5 (s, 1F); GC/MS (EI, +ve) *m/z* 109, 124 [M^+]; HRMS (EI, +ve) C_8H_9F requires *m/z* 124.0688, found 124.0689.

3. Experimental procedure and physical data for (*S*)-10 (99% ee, entry 7 in Table 2)

N-(Trimethylsilyl)morpholine (neat, 298 μl, 1.66 mmol) was added dropwise to a solution of Deoxo-Fluor™ (50% in THF, 690 μl, 1.62 mmol) in dry CH_2Cl_2 (2.20 ml) at −78 °C. The resulting solution was stirred at rt for 2.5 h. The reaction mixture was further cooled to −78 °C and a solution of methyl (*R*)-(−)-mandelate (**9**) (248 mg, 1.48 mmol) in dry CH_2Cl_2 (4.48 ml) was slowly added via cannula. The resulting solution was stirred at rt for 24 h. The mixture was then slowly poured into 30 ml of saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3.0 ml). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by silica gel chromatography (9:1 hexane:EtOAc→4:1) to afford the desired product (*S*)-**10** (48 mg, 19% yield) as a colourless oil. Chiral-phase GC/MS (EI-SIM) analysis of the product, t_R = 42.2 min for the minor (*R*)-enantiomer and t_R = 42.5 min for the major (*S*)-enantiomer, indicated that the optical purity was 99% ee; $[\alpha]_D^{22}$ +117.5 (*c* 1.4, $CDCl_3$); ν_{max} (NaCl)/cm^{-1} 3083, 3062, 3027, 2972, 2937, 2877, 1761, 1714, 1448, 1350, 1091; δ_H (400 MHz, $CDCl_3$) 7.51–7.36 (m, 5H), 5.80 (d, *J* = 47.5, 1H), 3.78 (s, 3H); δ_C (75.5 MHz, $CDCl_3$) 169.1 (d, *J* = 27.7, C), 134.3 (d, *J* = 20.6, C), 129.8 (d, *J* = 2.1, CH), 128.9 (CH), 126.8 (d, *J* = 6.1, CH), 89.4 (d, *J* = 185.6, CH), 52.7 (s, CH_3); δ_F (282 MHz, $CDCl_3$) −180.3 (d, *J* = 47.5 Hz, 1F); $\delta_{F\{H\}}$ (282 MHz, $CDCl_3$) −180.3 (s, 1F); GC/MS (EI-SIM, +ve) *m/z* 168 [M^+]; HRMS (ESI, +ve) $C_9H_9FO_2Na^+$ requires *m/z* 191.0484, found 191.0482.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.104.

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