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Synthesis of Morita–Baylis–Hillman-fluorides using 1,1,2,2-tetrafluoroethyl-*N*,*N*-dimethylamine

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ABSTRACT

Morita–Baylis–Hillman (MBH)-fluorides are valuable platforms for asymmetric allylic substitution reactions. However, the preparation of MBH-fluorides requires the use of an explosive fluorinating reagent, namely (diethylamino)sulfur trifluoride (DAST). Thus, we herein report a safe, alternative method for the preparation of MBH-fluorides via the deoxyfluorination of MBH-alcohols using 1,1,2,2-tetrafluoroethyl-*N*,*N*-dimethylamine (TFEDMA). Accordingly, a variety of MBH-alcohols were smoothly converted to their corresponding MBH-fluorides in moderate to good yields without the requirement for an activator. This fluorination reaction was found to proceed via an S_N1 process involving a stable allylic cation intermediate.

1. Introduction

Morita–Baylis–Hillman (MBH) adducts are valuable multifunctional synthetic building blocks for various complex molecules, including heterocyclic compounds [1]. Significantly, under asymmetric organocatalysis using chiral amines and phosphines, MBH adducts react smoothly with various nucleophiles via S_N2' or dual S_N2' pathways to enantioselectively provide allylic substitution products bearing a stereogenic C–C, C–O, C–S, C–N, or C–P bond [2]. Among the numerous synthetic transformations of MBH adducts reported to date, MBH-acetates and carbonates are critical in the context of asymmetric allylic substitution (AAS) reactions. On the other hand, MBH-halides such as bromides are known, but have rarely been used in such applications, likely due to their inherent instability [3]. However, in 2014, MBH-fluorides emerged as an alternative platform for the AAS reaction [4a]. As shown in Fig. 1a, MBH-fluorides possess an allylic carbon center bearing a fluorine atom. In contrast to the other MBH-halides, the MBH-fluorides are stable due to the presence of a strong C_{sp3}-F bond. Notably, in the presence of silicon-containing nucleophiles, the MBH-fluorides are efficiently activated, and can be converted into their corresponding allylic substitution products via a selective C–F bond activation process induced by silicon [4]. Moreover, in the presence of catalytic amounts of cinchona alkaloids, various AAS reactions between the MBH-fluorides and silylated nucleophiles have been reported, including trifluoromethylation [4a], alkynylation [4b], difluoromethylation [4c,d], and tetrazole-methylation reactions [4e], among others [4f–h]. In addition, C–H-containing substrates, such as $HCCl_3$, HC_6F_5, $CHF(SO_2Ph)$, are also directly applicable as nucleophiles in the presence of trifluoromethyl trimethyl silane, CF_3SiMe_3 (Fig. 1b) [4f].

The preparation of MBH-fluorides, however, is somewhat tedious. As previously reported, they can be prepared from their corresponding MBH-alcohols via a deoxy-fluorination with (diethylamino)sulfur trifluoride (DAST) in low to moderate yields [4]. Although DAST has been widely used for various deoxyfluorination reactions, DAST is unstable toward moisture and is highly explosive under heating conditions (>90 °C) (Fig. 1c) [5]. Without an alternative method for their preparation, these issues could restrict the use of the MBH-fluorides as platforms for AAS reactions. Thus, we became interested in the use of 1,1,2,2-tetrafluoroethyl-*N*,*N*-dimethylamine (TFEDMA) for the deoxyfluorination of MBH-

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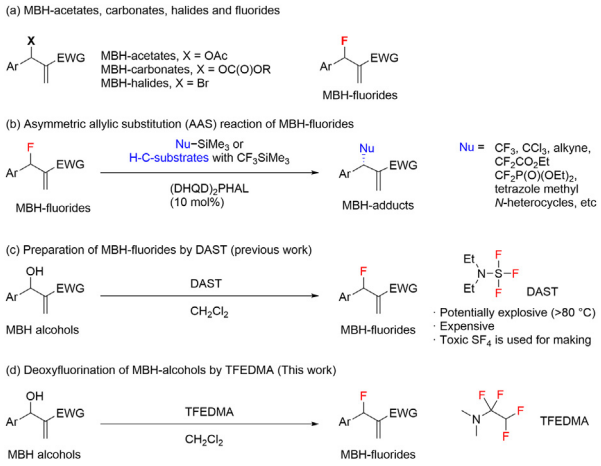


Fig. 1. MBH-adducts. (a) Structures of the MBH-acetates, carbonates, halides, and fluorides. (b) Examples of the asymmetric allylic substitution reactions of MBH-fluorides. (c) Preparation of the MBH-fluorides using DAST. (d) Deoxyfluorination of MBH-alcohols using TFEDMA (this work).

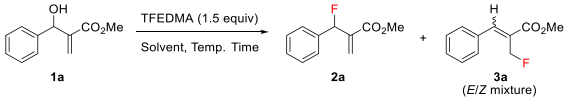
alcohols to yield MBH-fluorides. TFEDMA is a commercially available, inexpensive, thermally stable fluorinating reagent, and was developed by Petrov et al., in 2001 [6]. TFEDMA can be quantitatively prepared by mixing *N*,*N*-dimethylamine and tetrafluoroethylene (TFE, a component of Teflon®), and so can be considered a promising fluorinating reagent for industrial applications [7]. However, the utility of TFEDMA for deoxyfluorination processes has yet to be examined in detail [6,7].

Thus, to address the above issues, we herein report the efficient and straightforward synthesis of MBH-fluorides from MBH-alcohols using TFEDMA (Fig. 1d). For this purpose, a variety of MBH-alcohols are converted into their corresponding MBH-fluorides using a solution of TFEDMA in dichloromethane at temperatures ranging from 0 °C to rt (17–24 °C) over a relatively short reaction time (i.e., 30 min). The application of a chiral MBH-alcohol to this system is also investigated to reveal the reaction pathway.

2. Results and discussion

For optimization of the deoxyfluorination reaction of MBH-alcohols **1** using TFEDMA, methyl 2-(hydroxy(phenyl)methyl) acrylate (**1a**) was initially employed as a model substrate (Table 1). More specifically, the deoxyfluorination of **1a** was carried out using 1.5 equivalents of TFEDMA in CH_2Cl_2 (0.1 M) at rt. After a reaction completed, the desired MBH-fluoride (**2a**) was obtained in 56 % yield, along with the regioisomeric allylic fluoride **3a** in 16 % yield as an *E*/*Z* mixture (entry 1). Heating the reaction was not found to have any beneficial effect on the yield (entries 2 and 3), and a similar result was obtained when a temperature of 0 °C was employed (entry 4). However, a slightly increased yield of 62 % (59 % isolated yield) was obtained when the TFEDMA reagent was added at 0 °C and the reaction was conducted at rt (entry 5). Lowering the reaction temperature further (i.e., to −20 and −40 °C) reduced the yield further (entries 6 and 7), and neither solvent screening (entries 8–11) nor variation in the amount of TFEDMA employed (entries 12–14) improved the reaction outcome. Interestingly, we also found that carrying out the reaction in a Teflon® bottle was preferable; otherwise, the yield was slightly compromised (entries 5 *vs* 15). Furthermore, for comparison, we attempted the use of Deoxo-Fluor® for the transformation of **1a** to **2a**. Deoxo-Fluor®, i.e., bis(2-methoxyethyl)aminosulfur trifluoride, was developed as a thermally stable alternative to DAST [8]. However, in this test reaction, only 10 % of the desired **2a** was obtained (entry 16). The starting materials almost disappeared in all the cases, and additional byproducts were observed while we couldn't identify them.

Table 1
Optimization of the deoxyfluorination reaction of MBH-alcohol **1a** using TFEDMA[a].



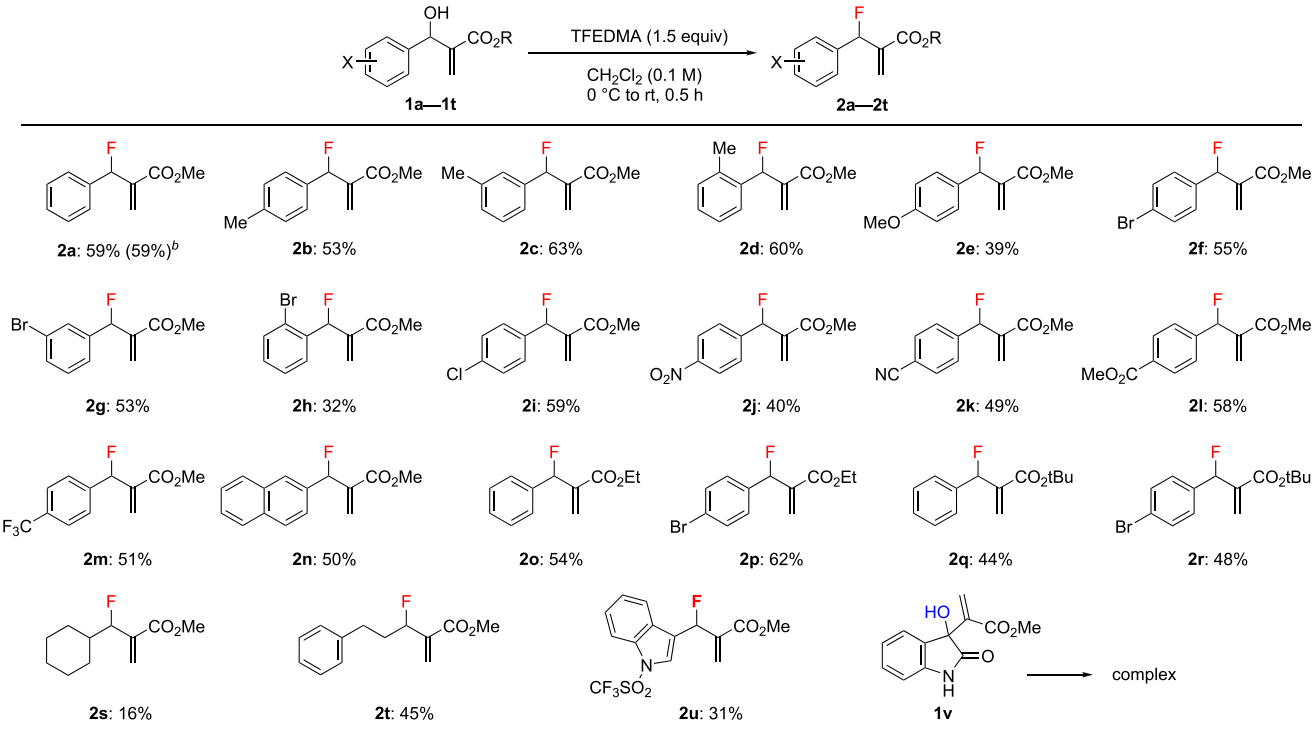
entry	solvent	temp	time	**2a** yield (%)[b]	**3a** yield (%)[b]
1	CH_2Cl_2	rt	40 min	56	16
2	CH_2Cl_2	40 °C	20 min	56	16
3	$CHCl_3$	60 °C	5 min	52	10
4	CH_2Cl_2	0 °C	1 h	57	15
5	CH_2Cl_2	0 °C-rt	10 min	62 (59[c])	16 (16[c])
6	CH_2Cl_2	−20 °C	2 h	51	13
7	CH_2Cl_2	−40 °C	12 h	48	11
8	THF	0 °C–rt	24 h	trace	–
9	$ClCH_2CH_2Cl$	0 °C–rt	10 min	57	14
10	MeCN	0 °C–rt	11 h	15	5
11	Toluene	0 °C–rt	1 h	40	16
12[d]	CH_2Cl_2	0 °C–rt	40 min	55	15
13[e]	CH_2Cl_2	0 °C–rt	20 min	59	15
14[f]	CH_2Cl_2	0 °C–rt	10 min	59	15
15[g]	CH_2Cl_2	0 °C–rt	20 min	53	14
16[h]	CH_2Cl_2	rt	3 h	10	–

[a] Reaction conditions: TFEDMA (1.5 equiv) was added to a solution of MBH-alcohol (0.2 mmol, 1.0 equiv) in dry solvent (2.0 mL, 0.1 M) in a Teflon® bottle at 0 °C, and the reaction mixture was stirred at the desired temperature (rt: 17–24 °C).
[b] Yields were determined by ^{19}F NMR spectroscopic analysis of the crude product using trifluorotoluene as an internal standard.
[c] Isolated yield.
[d] TFEDMA (1.0 equiv).
[e] TFEDMA (1.2 equiv).
[f] TFEDMA (2.0 equiv).
[g] The reaction was performed in a glass bottle.
[h] Deoxo-Fluor® (1.5 equiv) was used instead of TFEDMA.

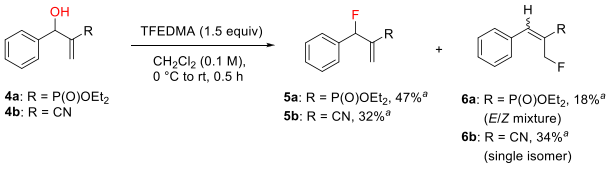
With the optimized conditions in hand, we examined the substrate scope of the TFEDMA-mediated deoxyfluorination reaction using a variety of MBH-alcohols (Table 2). It was found that substrates bearing an electron-donating Me, OMe, or halogen substituent on the benzene ring (**1b**–**1i**) provided the corresponding MBH-fluorides **2b**–**2i** in moderate to good yields (39–63 % yields), while the sterically demanding *o*-Br-phenyl MBH-alcohol **1h** was converted to **2h** in a lower yield of 32 %. In addition, substrates **1j**–**1m**, which bear electron-withdrawing groups (i.e., NO_2, CN, CO_2Me, and CF_3) were also readily converted into their corresponding MBH-fluorides (**2j**–**2m**) in good yields (40–58 %). Furthermore, naphthalene-substituted MBH-alcohol (**1n**) gave the desired product **2n** in 50 % yield, and the reaction of ethyl and sterically bulky *tert*-butyl esters (**1o**–**1r**) also proceeded to give the corresponding MBH-fluorides (**2o**–**2r**) in good yield (44–62 %). Subsequently, the conversion of MBH-alcohols bearing aliphatic substituents (i.e., cyclohexyl-containing **1s** and phenylethyl-containing **1t**) produced the desired MBH-fluorides in yields of 16 % (**2s**) and 45 % (**2t**). The indole-derived substrate **1u** also gave the desired product **2u** in 31 %. Unfortunately, the isatin-derived MBH adduct **1v** having a tertiary alcohol was not converted ideally.

We next examined the deoxyfluorination of MBH-phosphonate alcohol **4a** and MBH-acrylonitrile alcohol **4b** using TFEDMA under the optimal conditions determined above. As indicated in Scheme 1, the desired fluorides **5a** (47 %) and **5b** (32 %) were obtained as inseparable mixtures with their regioisomers **6a** (18 %, *E*/*Z* mixture) and **6b** (34 %).

Table 2
Substrate scope for the deoxyfluorination reaction of MBH-alcohols using TFEDMA[a].



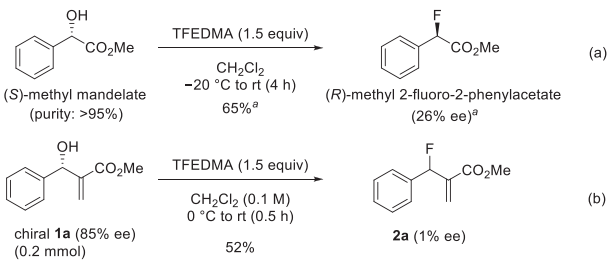
[a]Reaction conditions: TFEDMA (0.3 mmol, 1.5 equiv) was added to a solution of MBH-alcohol (0.2 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) in a Teflon® bottle at 0 °C, and the reaction mixture was stirred at rt for 30 min. [b]1.0 g of **1a** was used.



Scheme 1. Deoxyfluorination of MBH-phosphonate alcohol **4a** and MBH-acrylonitrile alcohol **4b** using TFEDMA. [a]Yields were determined by ^{19}F NMR spectroscopic analyses of the crude products using trifluorotoluene as an internal standard.

Previously, Petrov et al. reported that (*S*)-methyl mandelate can be converted into the desired methyl (*R*)-2-fluoro-2-phenylacetate in 65 % yield with inversion of stereochemistry *via* cyclic S_N2 process, while the enantiopurity of the fluoride is low (26 % ee) (Scheme 2a) [6,7a]. We therefore examined the deoxyfluorination reaction using chiral, non-racemic **1a** (85 % ee) under the optimized reaction conditions (Scheme 2b), and found that **1a** was smoothly transformed into the corresponding racemic MBH-fluoride **2a** in 43 % yield (1 % ee).

The above result indicated that the deoxyfluorination of MBH-alcohol **1** using TFEDMA proceeds *via* an S_N1 process rather than the previously reported S_N2 process. We therefore considered that during this reaction, MBH-alcohol **1** reacts with TFEDMA to give an intermediate **I** with the loss of HF. This HF then activates intermediate **I** *via* hydrogen bonding to provide a stable allyl cation intermediate **II** with the elimination of difluoroacetamide **7** via an S_N1 process. Such activation of **I** by HF is key due to the fact that we found that the reaction is slightly hampered by the use of standard glassware instead of a Teflon® bottle (Table 1, entry 15) [9]. Finally, fluoride attacks at the more stable benzylic cation (route a) rather than terminal cation (route b) to give MBH-fluoride **2** as the major product, along with the regioisomer **3**. The difluoroacetamide **7**, presumably as a complex with HF was also released [10] (Fig. 2).



Scheme 2. Deoxyfluorination reaction of chiral alcohols using TFEDMA. [a]See reference 7a.

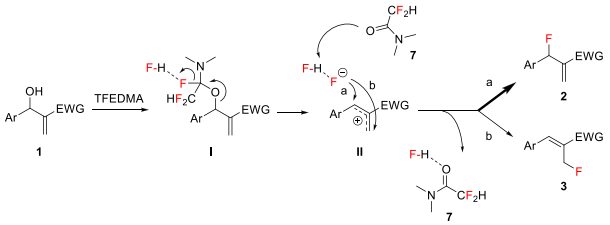


Fig. 2. Proposed reaction mechanism for the deoxyfluorination of MBH-alcohols using TFEDMA.

3. Conclusion

We herein report the development of a safe, alternative synthetic route to Morita–Baylis–Hillman (MBH)-fluorides from MBH-alcohols using 1,1,2,2-tetrafluoroethyl-*N*,*N*-dimethylamine (TFEDMA) instead of the explosive (diethylamino)sulfur trifluoride (DAST). Using this procedure, various MBH-alcohols were smoothly converted into their corresponding MBH-fluorides in moderate to good yields within 30 min. Since our described route avoids the necessity to employ DAST, we expect that it will expand the utility of MBH-fluorides as valuable platforms for various asymmetric allylic substitution reactions. Moreover, due to the fact that MBH-adducts are considered a new class of bioactive compounds [11], and the fact that fluorine-containing compounds have shown significant potential in the pharmaceutical [12a] and agrochemical industries [12b], we expect that the MBH-fluorides will also be valuable in the design of novel biologically active molecules. The further application of the MBH-fluorides in this direction is ongoing.

4. Experimental section

4.1. General information

Reactions were performed under anhydrous conditions with flame dried glassware under a positive pressure of nitrogen. All reaction mixtures were stirred magnetically. Room temperature was in the range of 17–24 °C. Solvents were transferred via syringes and were introduced into the reaction vessels through rubber septa. All reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel (60-F_{254}) (Merck). The TLC plates were visualized using 254 nm UV light or heating following treatment with an aqueous solution of 7 % phosphomolybdic acid or $KMnO_4$. Column chromatography was carried out on a column packed with 60 N spherical neutral size 40–50 μm (Kanto Chemical) or 63–210 μm (FUJIFILM Wako) silica-gel. NMR spectra were recorded on a Varian Mercury 300 spectrometer for the ^{1}H NMR (300 MHz) and ^{19}F NMR (282 MHz) spectra, and a Bruker Avance 500 spectrometer for the ^{1}H NMR (500 MHz) and ^{13}C{^{1}H} NMR (125 MHz) spectra. The chemical shifts (δ) were measured in parts per million with respect to the solvent (^{1}H: $CDCl_3$, $\delta = 7.26$ ppm; ^{13}C{^{1}H}: $CDCl_3$, $\delta = 77.16$ ppm) or an internal standard (^{19}F: C_6F_6, $\delta = -162.2$ ppm in $CDCl_3$) and the coupling constants (J) are given in hertz. The following abbreviations denote the corresponding peak multiplicities: s, singlet; d, doublet; t, triplet; q, quadruplet; dd, doublet of doublets; td, triplet of doublets; dt, doublet of triplets; m, multiplet; br, broad. Mass spectra were recorded using a JEOL JMS-Q1050GC (EI-MS) and a SHIMADZU LCMS-2020 (ESI-MS) system. Fourier transform infrared (FT-IR) spectra were recorded on a JASCO FT/IR-4100 spectrometer. High-resolution mass spectrometry (HR-MS) was performed on a Waters Synapt G2 HDMS (ESI-MS). MBH-alcohols **2**,**4** were prepared according to reported method [4a,4d,4g,13]. TFEDMA (86 % purity) was available from Tosoh Finechem Corporation.

4.2. General procedure for deoxyfluorination of the MBH-alcohols using TFEDMA

TFEDMA (36.5 μL, 0.3 mmol, 1.5 equiv) was added to a solution of the prepared MBH-alcohol (0.2 mmol, 1.0 equiv) in dry CH_2Cl_2 (2.0 mL) in a Teflon® bottle at 0 °C, and the reaction mixture was stirred at room temperature for 30 min. After this time, the mixture was cooled to 0 °C, saturated aqueous $NaHCO_3$ was added to the mixture, and the resulting mixture was extracted with CH_2Cl_2. The combined organic layer was then washed with brine, dried over anhydrous Na_2SO_4, and the filtrate was concentrated under reduced pressure to give the crude product. Purification was by column chromatography (hexane/EtOAc, hexane/Et_2O or hexane/DCM) to give the corresponding MBH-fluoride.

4.2.1. Methyl 2-(fluoro(phenyl)methyl)acrylate (**2a**)

Following the general deoxyfluorination procedure using allylic alcohol **1a** (38.4 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/Et_2O (20:1) to give the desired product **2a** (21.8 mg, 59 %) as a colorless oil and regioisomeric allylic fluoride **3a** (6.2 mg, 16 %, *E*/*Z* mixture (major:minor = 6.5:1)) as a colorless oil. **2a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44–7.32 (m, 5H), 6.47–6.45 (m, 1H), 6.29 (d, $J = 45.9$ Hz, 1H), 6.03 (br s, 1H), 3.72 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −171.27 (d, $J = 46.6$ Hz, 1F) ppm. MS (EI) *m*/*z*: $[M]^+$ 193. Analytical data are consistent with reported values.[4a] **3a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, $J = 4.0$ Hz, 0.87H), 7.51–7.50 (m, 1.74H), 7.46–7.42 (m, 2.61H), 7.35 (br s, 0.65H), 7.07 (d, $J = 3.7$ Hz, 0.13H), 5.23 (d, $J = 47.6$ Hz, 1.74H), 5.16 (d, $J = 47.0$ Hz, 0.28H), 3.88 (s, 2.6H), 3.71 (s, 0.4H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −205.3 (td, $J = 47.4$, 3.4 Hz, 2.6F), −211.6 (td, $J = 47.4$, 3.4 Hz, 0.4F) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 167.4, 147.7 (d, $J = 7.3$ Hz), 139.6 (d, $J = 10.9$ Hz), 134.1 (d, $J = 3.6$ Hz), 130.2, 130.0 (d, $J = 3.6$ Hz), 129.1, 128.9, 128.6 (d, $J = 16.3$ Hz), 128.4, 126.7 (d, $J = 14.5$ Hz), 84.2 (d, $J = 169.9$ Hz), 77.2 (d, $J = 161.7$ Hz), 52.6, 52.0 ppm. MS (EI) *m*/*z*: $[M]^+$ 193. Analytical data of *Z* isomer of **3a** are consistent with reported values [14].

4.2.2. Methyl 2-(fluoro(p-tolyl)methyl)acrylate (**2b**)

Following the general deoxyfluorination procedure using allylic alcohol **1b** (41.2 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (20:1) to give the desired product **2b** (21.9 mg, 53 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28 (d, $J = 9.1$ Hz, 2H), 7.18 (d, $J = 7.6$ Hz, 2H), 6.45–6.44 (m, 1H), 6.25 (d, $J = 46.2$ Hz, 1H), 6.03 (d, $J = 1.0$ Hz, 1H), 3.71 (s, 3H), 2.36 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −169.75 (d, $J = 44.8$ Hz, 1F) ppm. MS (EI) *m*/*z*: $[M]^+$ 208. Analytical data are consistent with reported values [4a].

4.2.3. Methyl 2-(fluoro(m-tolyl)methyl)acrylate (**2c**)

Following the general deoxyfluorination procedure using allylic alcohol **1c** (41.2 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (45:1) to give the desired product **2c** (26.2 mg, 63 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.28–7.17 (m, 4H), 6.45 (s, 1H), 6.25 (d, $J = 45.9$ Hz, 1H), 6.02 (s, 1H), 3.72 (s, 3H), 2.36 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −170.86 (d, $J = 46.6$ Hz, 1F) ppm. MS (EI) *m*/*z*: $[M]^+$ 208. Analytical data are consistent with reported values [4a].

4.2.4. Methyl 2-(fluoro(o-tolyl)methyl)acrylate (**2d**)

Following the general deoxyfluorination procedure using allylic alcohol **1d** (41.2 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (35:1) to give the desired product **2d** (24.6 mg, 60 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.33 (d, $J = 7.9$ Hz, 1H), 7.29–7.18 (m, 3H), 6.55 (d, $J = 45.9$ Hz, 2H), 6.49 (s, 1H), 5.88 (d, $J = 0.9$ Hz, 1H), 3.75 (s, 3H), 2.40 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −173.22 (d, $J = 44.8$ Hz, 1F) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 165.6 (d, $J = 4.5$ Hz), 139.0 (d, $J = 22.7$ Hz), 136.5 (d, $J = 4.5$ Hz), 135.3 (d, $J = 19.1$ Hz), 130.8, 129.1 (d, $J = 2.7$ Hz), 127.3 (d, $J = 8.2$ Hz), 126.8 (d, $J = 6.4$ Hz), 126.2, 87.9 (d, $J = 171.7$ Hz), 52.2, 19.1 ppm. MS (EI) *m*/*z*: $[M]^+$ 208. Analytical data are consistent with reported values [4a].

4.2.5. Methyl 2-(fluoro(4-methoxyphenyl)methyl)acrylate (**2e**)

Following the general deoxyfluorination procedure using allylic

alcohol **1e** (44.4 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (25:1) to give the desired product **2e** (17.3 mg, 39 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.32 (dd, J = 8.5, 1.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.43–6.43 (m, 1H), 6.22 (d, J = 46.2 Hz, 1H), 6.05 (s, 1H), 3.81 (s, 3H), 3.70 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −167.63 (d, J = 46.0 Hz, 1F) ppm. MS (ESI) m/z: $[M]^+$ 224. Analytical data are consistent with reported values [4g].

4.2.6. Methyl 2-((4-bromophenyl)fluoromethyl)acrylate (**2f**)

Following the general deoxyfluorination procedure using allylic alcohol **1f** (54.2 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (20:1) to give the desired product **2f** (30.0 mg, 55 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 (d, J = 7.9 Hz, 2H), 7.27 (dd, J = 7.6, 1.8 Hz, 2H), 6.46 (d, J = 2.9 Hz, 1H), 6.23 (d, J = 45.9 Hz, 1H), 6.04 (s, 1H), 3.72 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −172.39 (d, J = 44.8 Hz, 1F) ppm. MS (EI) m/z: $[M]^+$ 272. Analytical data are consistent with reported values [4a].

4.2.7. Methyl 2-((3-bromophenyl)fluoromethyl)acrylate (**2g**)

Following the general deoxyfluorination procedure using allylic alcohol **1g** (54.2 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (35:1) to give the desired product **2g** (54.6 mg, 53 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 (s, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.34–7.32 (m, 1H), 7.27–7.22 (m, 1H), 6.48 (d, J = 2.9 Hz, 1H), 6.23 (d, J = 45.9 Hz, 1H), 6.05 (s, 1H), 3.73 (s, 4H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −172.73 (d, J = 46.6 Hz, 1F) ppm. MS (EI) m/z: $[M]^+$ 272. Analytical data are consistent with reported values [4a].

4.2.8. Methyl 2-((2-bromophenyl)fluoromethyl)acrylate (**2h**)

Following the general deoxyfluorination procedure with allylic alcohol **1h** (54.2 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (30:1) to give the desired product **2h** (54.6 mg, 32 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 (d-like, J = 7.9 Hz, 1H), 7.46 (dd, J = 7.8, 1.6 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 6.67 (d, J = 45.0 Hz, 1H), 6.52 (s, 1H), 5.78 (s, 1H), 3.78 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −173.57 (d, J = 44.8 Hz, 1F) ppm. MS (EI) m/z: $[M-Br]^+$ 193. Analytical data are consistent with reported values [4a].

4.2.9. Methyl 2-((4-chlorophenyl)fluoromethyl)acrylate (**2i**)

Following the general deoxyfluorination procedure using allylic alcohol **1i** (45.3 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (20:1) to give the desired product **2i** (27.0 mg, 59 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37–7.31 (m, 4H), 6.46 (d-like, J = 2.1 Hz, 1H), 6.24 (d, J = 45.9 Hz, 1H), 6.04 (s, 1H), 3.72 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −171.96 (d, J = 44.8 Hz, 1F) ppm. MS (EI) m/z: $[M]^+$ 228. Analytical data are consistent with reported values [4a].

4.2.10. Methyl 2-(fluoro(4-nitrophenyl)methyl)acrylate (**2j**)

Following the general deoxyfluorination procedure using allylic alcohol **1j** (47.4 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (20:1) to give the desired product **2j** (19.2 mg, 40 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 6.51 (d, J = 2.6 Hz, 1H), 6.36 (d, J = 45.6 Hz, 1H), 6.09 (s, 1H), 3.74 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −176.11 (d, J = 44.8 Hz, 1F) ppm. MS (EI) m/z: $[M]^+$ 238. Analytical data are consistent with reported values [4a].

4.2.11. Methyl 2-((4-cyanophenyl)fluoromethyl)acrylate (**2k**)

Following the general deoxyfluorination procedure using allylic alcohol **1k** (43.4 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (18:1) to give the desired product **2k** (21.4 mg, 49 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.68 (d, J = 7.9 Hz, 2H), 7.52 (d, J = 8.2 Hz, 2H), 6.50 (d, J = 2.6 Hz, 1H), 6.31 (d, J = 45.6 Hz, 1H), 6.07 (s, 1H), 3.73 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −175.98 (d, J = 44.8 Hz, 1F) ppm. MS (EI) m/z: $[M]^+$ 218. Analytical data are consistent with reported values [4g].

4.2.12. Methyl 4-(1-fluoro-2-(methoxycarbonyl)allyl)benzoate (**2l**)

Following the general deoxyfluorination procedure using allylic alcohol **1l** (50.1 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (15:1) to give the desired product **2l** (29.0 mg, 58 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, J = 7.9 Hz, 2H), 7.46 (d, J = 7.9 Hz, 2H), 6.47 (d, J = 2.4 Hz, 1H), 6.32 (d, J = 45.9 Hz, 1H), 6.03 (s, 1H), 3.91 (s, 3H), 3.72 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −174.43 (d, J = 46.6 Hz, 1F) ppm. MS (EI) m/z: $[M]^+$ 252. Analytical data are consistent with reported values [4g].

4.2.13. Methyl 2-(fluoro(4-(trifluoromethyl)phenyl)methyl)acrylate (**2m**)

Following the general deoxyfluorination procedure using allylic alcohol **1m** (52.0 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (30:1) to give the desired product **2m** (26.9 mg, 51 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.64 (d-like, J = 7.9 Hz, 2H), 7.52 (d-like, J = 7.9 Hz, 2H), 6.49 (s, 1H), 6.33 (d, J = 45.9 Hz, 1H), 6.06 (s, 1H), 3.74 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −63.23 (s, 3F), −174.79 (d, J = 44.8 Hz, 1F) ppm. Analytical data are consistent with reported values [4f].

4.2.14. Methyl 2-(fluoro(naphthalen-2-yl)methyl)acrylate (**2n**)

Following the general deoxyfluorination procedure using allylic alcohol **1n** (48.5 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (30:1) to give the desired product **2n** (24.2 mg, 50 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88–7.85 (m, 4H), 7.53–7.48 (m, 3H), 6.47 (d, J = 45.9 Hz, 2H), 6.51 (d, J = 2.4 Hz, 1H), 6.10 (s, 1H), 3.72 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −171.15 (d, J = 44.8 Hz, 1F) ppm. MS (EI) m/z: $[M]^+$ 244. Analytical data are consistent with reported values [4a].

4.2.15. Ethyl 2-(fluoro(phenyl)methyl)acrylate (**2o**)

Following the general deoxyfluorination procedure using allylic alcohol **1o** (41.2 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (30:1) to give the desired product **2o** (22.6 mg, 54 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44–7.33 (m, 5H), 6.46 (d, J = 2.6 Hz, 1H), 6.29 (d, J = 45.9 Hz, 1H), 6.02 (s, 1H), 4.22–4.11 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −171.22 (d, J = 46.6 Hz, 1F) ppm. MS (EI) m/z: $[M]^+$ 208. Analytical data are consistent with reported values [4d].

4.2.16. Ethyl 2-((4-bromophenyl)fluoromethyl)acrylate (**2p**)

Following the general deoxyfluorination procedure with allylic alcohol **1p** (57.0 mg, 0.2 mmol), the obtained crude product was

purified by silica gel column chromatography with hexane/EtOAc (30:1) to give the desired product **2p** (35.6 mg, 62 %) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 (d, J = 8.2 Hz, 2H), 7.27 (d, J = 6.5 Hz, 2H), 6.45 (d-like, J = 1.5 Hz, 1H), 6.23 (d, J = 45.9 Hz, 1H), 6.03 (s, 1H), 4.22–4.11 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −172.31 (d, J = 44.8 Hz, 1F) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 164.6 (d, J = 6.4 Hz), 139.3 (d, J = 22.7 Hz), 136.7 (d, J = 20.9 Hz), 131.8, 129.0 (d, J = 5.4 Hz), 125.9 (d, J = 9.1 Hz), 123.2 (d, J = 3.6 Hz), 90.3 (d, J = 175.3 Hz), 61.2, 14.2 ppm. MS (EI) m/z: $[M]^+$ 286. Analytical data are consistent with reported values [4d].

4.2.17. *tert*-Butyl 2-(fluoro(phenyl)methyl)acrylate (**2q**)

Following the general deoxyfluorination procedure with allylic alcohol **1q** (46.9 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (55:1) to give the desired product **2q** (21.0 mg, 44 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 (brd, 5H), 6.39–6.37 (m, 1H), 6.22 (dd, J = 46.3, 1.0 Hz, 1H), 5.97–5.94 (m, 1H), 1.37 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −170.30 (d, J = 46.6 Hz, 1F) ppm. MS (EI) m/z: $[M-t\text{Bu} + H]^+$ 180. Analytical data are consistent with reported values [4a].

4.2.18. *tert*-Butyl 2-((4-bromophenyl)fluoromethyl)acrylate (**2r**)

Following the general deoxyfluorination procedure using allylic alcohol **1r** (62.6 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (55:1) to give the desired product **2r** (30.4 mg, 48 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 (d, J = 7.9 Hz, 2H), 7.25 (d, J = 5.0 Hz, 2H), 6.38 (s, 1H), 6.17 (d, J = 46.2 Hz, 1H), 5.95 (s, 1H), 1.39 (s, 9H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −171.36 (d, J = 46.6 Hz, 1F) ppm. MS (EI) m/z: $[M-t\text{-Bu} + H]^+$ 258. Analytical data are consistent with reported values [4a].

4.2.19. Methyl 2-(cyclohexylfluoromethyl)acrylate (**2s**)

Following the general deoxyfluorination procedure with allylic alcohol **1s** (39.6 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/DCM (3:1) to give the desired product **2s** (6.4 mg, 16 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.38 (s, 1H), 5.86 (s, 1H), 5.12 (dd, J = 46.8, 3.8 Hz, 1H), 3.77 (s, 3H), 1.75–1.63 (m, 6H), 1.25–0.97 (m, 5H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −192.34 (dd, J = 46.6, 24.1 Hz, 1F) ppm. MS (EI) m/z: $[M-C_6H_{11}]^+$ 118. Analytical data are consistent with reported values [4a].

4.2.20. Methyl 3-fluoro-2-methylene-5-phenylpentanoate (**2t**)

Following the general deoxyfluorination procedure using allylic alcohol **1t** (44.1 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (45:1) to give the desired product **2t** (20.2 mg, 45 %) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36–7.31 (m, 2H), 7.26–7.24 (m, 3H), 6.40 (s, 1H), 6.01 (s, 1H), 5.37 (dd, J = 47.2, 7.8 Hz, 1H), 3.80 (s, 3H), 2.95–2.73 (m, 2H), 2.33–1.93 (m, 2H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −186.38 to −186.73 (m, 1F) ppm. MS (EI) m/z: $[M-HF]^+$ 202, $[M-HF-CO_2H]^+$ 143. Analytical data are consistent with reported values [4g].

4.2.21. Methyl 2-(fluoro(1-((trifluoromethyl)sulfonyl)-1H-indol-3-yl)methyl)acrylate (**2u**)

Following the general deoxyfluorination procedure using allylic alcohol **1u** (72.7 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (25:1) to give the desired product **2u** (22.8 mg, 31 %) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, J = 7.9 Hz, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.47–7.36 (m, 3H), 6.59 (s, 1H), 6.58 (d, J = 45.6 Hz, 1H), 6.17 (s, 1H), 3.77 (s, 3H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −75.76 (s, 3F), −177.26 (d, J = 46.6 Hz, 1F) ppm. MS (EI) m/z: $[M]^+$ 365. Analytical data are consistent with reported values [4g].

4.3. Deoxyfluorination of MBH-phosphonate alcohol (**4a**) using TFEDMA

Following the general deoxyfluorination procedure using MBH-phosphonate alcohol **4a** (54.0 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (1:2) to give the desired fluoride product (37.7 mg) as inseparable mixture of regio-isomers (**5a**: 47 %, **6a**:18 %). The yield was determined by ^{19}F NMR with trifluorotoluene as internal standard. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (dd, J = 23.2, 3.7 Hz, 0.1H), 7.59–7.30 (m, 5.2H), 6.33–6.28 (m, 0.7H), 6.16 (dq, J = 45.0, 1.5 Hz, 0.7H), 6.09 (dd, J = 46.2, 6.0 Hz, 0.7H), 5.21–5.04 (m, 0.6H), 4.18–4.12 (m, 0.4H), 4.02–3.88 (m, 2.9H), 3.82–3.74 (m, 0.7H), 1.35 (t, J = 7.2 Hz, 0.5H), 1.24–1.20 (m, 2.4H), 1.14–1.10 (m, 3.1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −168.23 (dd, J = 45.7, 16.4 Hz, 0.72F), −203.18 (t, J = 48.3 Hz, 0.1F), −207.91 to −207.53 (m, 0.18F) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 151.6 (dd, J = 10.9, 7.3 Hz), 147.2 (dd, J = 12.7, 6.4 Hz), 139.7 (d, J = 21.8 Hz), 138.3 (d, J = 21.8 Hz), 137.0 (dd, J = 20.9, 2.7 Hz), 134.9 (d, J = 6.4 Hz), 134.0 (dd, J = 21.3, 3.2 Hz), 130.9 (dd, J = 10.4, 5.9 Hz), 130.1, 130.0, 129.8 (d, J = 3.6 Hz), 129.6, 129.3, 129.2 (d, J = 2.7 Hz), 128.9, 128.5, 128.3, 128.1, 127.3 (d, J = 5.4 Hz), 125.9 (dd, J = 178.9, 13.6 Hz), 124.7 (dd, J = 183.0, 14.1 Hz), 124.0, 123.9, 91.8 (dd, J = 178.9, 19.1 Hz), 85.0 (dd, J = 173.5, 16.3 Hz), 77.3 (dd, J = 166.2, 10.0 Hz), 62.4–62.2 (m), 16.4 (d, J = 6.4 Hz), 16.3 (d, J = 6.4 Hz), 16.1 (d, J = 7.3 Hz) ppm. IR (KBr): 3468, 2984, 1721, 1619, 1391, 1251, 1024, 970, 799, 734, 699 cm^{-1}.

4.4. Deoxyfluorination of MBH-acrylonitrile alcohol (**4b**) using TFEDMA

Following the general deoxyfluorination procedure using MBH-acrylonitrile alcohol **4b** (31.8 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/EtOAc (6:1) to give the desired fluoride product (19.3 mg) as inseparable mixture of regio-isomers (**5b**: 32 %, **6b**: 34 %). The yield was determined by ^{19}F NMR with trifluorotoluene as internal standard. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83–7.81 (m, 1.1H), 7.48–7.42 (m, 3.0H), 7.42–7.38 (m, 0.9H), 7.26 (d, J = 4.0 Hz, 0.55H), 6.16 (dd, J = 2.0, 1.1 Hz, 0.45H), 6.13 (t, J = 1.7 Hz, 0.45H), 5.93 (d, J = 45.8 Hz, 0.45H), 5.07 (dd, J = 47.0, 0.9 Hz, 1.1H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: −172.0 (d, J = 44.8 Hz, 0.45F), −209.4 (t, J = 46.6 Hz, 0.55F) ppm. ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ: 147.3 (d, J = 8.2 Hz), 135.1 (d, J = 20.9 Hz), 132.5, 131.7 (d, J = 7.3 Hz), 131.5, 130.0, 129.4, 129.2, 129.1, 126.6 (d, J = 6.4 Hz), 123.1 (d, J = 27.2 Hz), 116.8 (d, J = 2.7 Hz), 115.8 (d, J = 4.5 Hz), 106.2 (d, J = 18.2 Hz), 91.6 (d, J = 181.6 Hz), 83.2 (d, J = 177.1 Hz) ppm. IR (KBr): 3446, 3063, 2219, 1626, 1452, 1368, 1294, 1170, 996, 933, 693 cm^{-1}.

4.5. Deoxyfluorination of the MBH-alcohols using DAST

DAST (39.3 μL, 0.3 mmol, 1.5 equiv) was added to a solution of desired the MBH-alcohol (0.2 mmol, 1.0 equiv) in dry CH_2Cl_2 (2.0 mL) in a Teflon® bottle at −78 °C, and the reaction mixture was stirred at −78 °C for 20–50 min. After this time, a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The combined organic layer was then washed with brine, dried over anhydrous Na_2SO_4, filtered, and the

filtrate was concentrated to give the corresponding crude product. The yield was determined by ^{19}F NMR analysis of the crude product using trifluorotoluene as an internal standard.

4.6. Deoxyfluorination of the MBH-alcohols using DeoxoFluor

DeoxoFluor (52.7 μL, 0.3 mmol, 1.5 equiv) was added to a solution of the desired MBH-alcohol (0.2 mmol, 1.0 equiv) in dry CH_2Cl_2 (2.0 mL) in a Teflon® bottle at 0 °C, and the resulting mixture was stirred at room temperature for 3 h. After subsequent cooling to 0 °C, a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with CH_2Cl_2. The combined organic layer was then washed with brine, dried over anhydrous Na_2SO_4, and the filtrate was concentrated under reduced pressure to give the corresponding crude product. The yield was determined by ^{19}F NMR spectroscopy of the crude product using trifluorotoluene as an internal standard.

4.7. Preparation of chiral MBH-alcohol **1a**

DMAP (0.156 mmol, 10 mol%) was added to a to a solution of MBH-alcohol **1a** (300 mg, 1.56 mmol, 1.0 equiv) and $(Boc)_2O$ (0.37 mL, 1.63 mmol, 1.05 equiv) in dry CH_2Cl_2 (7.8 mL) at rt, and the resulting mixture was stirred at rt for 10 h. After this time, the reaction mixture was concentrated under reduced pressure to give the crude product, which was purified by column chromatography (hexane/CH_2Cl_2 = 2:1) to give *O*-Boc MBH-alcohol (325 mg, 71 % yield). The *O*-Boc-MBH-alcohol (282 mg, 0.965 mmol, 1.0 equiv) was then dissolved in *N*,*N*-dimethylacetamide (9.7 mL), and CaF_2 (377 mg, 4.83 mmol, 5.0 equiv), H_2O (35 μL, 1.93 mmol, 2.0 equiv), and $(DHQD)_2AQN$ (82.7 mg, 0.0965 mmol, 10 mol%) were added to the mixture at 0 °C. After stirring the resulting mixture at 0 °C for 72 h, H_2O was added, and extractions were carried out using hexane and EtOAc. The combined organic layer was then washed with brine, dried over anhydrous Na_2SO_4, and the filtrate was concentrated to give the crude product. Purification was by column chromatography (hexane/EtOAc = 3:1) to give the chiral MBH-alcohol (85 % ee, 152 mg, 82 % yield). The enantiomeric excess was determined by HPLC analysis (column: CHIRALPAK IH, *n*-hexane/isopropanol = 90:10, flow rate: 0.8 mL/min, λ = 220 nm), t (major) = 25.6 min, t (minor) = 18.6 min). All other analytical data were consistent with that of the racemic **1a** [4a].

4.8. Deoxyfluorination of chiral MBH-alcohol **1a** using TFEDMA

Following the general deoxyfluorination procedure using chiral allylic alcohol **1a** (85 % ee, 38.4 mg, 0.2 mmol), the obtained crude product was purified by silica gel column chromatography with hexane/Et_2O (20:1) to give the desired product **2a** (20.1 mg, 52 %, 1 % ee) as a colorless oil. The enantiomeric excess was determined by HPLC analysis (column: CHIRALPAK IH, *n*-hexane/isopropanol = 99:1, flow rate: 0.5 mL/min, λ = 220 nm), t (major) = 19.6 min, t (minor) = 21.1 min). All other analytical data were consistent with that of the racemic **2a** [4a].

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Norio Shibata reports financial support was provided by Japan Society for the Promotion of Science.

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