Synthesis of tertiary alkyl fluorides and chlorides by site-selective nucleophilic ring-opening reaction of α-aryl azetidinium salts†

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Site-selective nucleophilic ring-opening reactions of 2-arylazetidine-2-carboxylic acid ester-derived tetraalkyl ammonium salts with tetrabutylammonium halides (Bu4NX) to give tertiary alkyl halides are successfully demonstrated. For example, a nucleophilic ring-opening reaction of 2-(o-tolyl) derivative 2a with 1.2 equivalents of tetrabutylammonium fluoride (Bu4NF) in THF at 60 °C preferentially proceeded at a more substituted carbon atom (2-position) compared to a less-substituted carbon atom (4-position) and afforded tert-butyl 4-(dimethylamino)-2-fluoro-2-(o-tolyl)butanoate 3aa in 71% yield as the corresponding tertiary alkyl fluoride. This result was applied to synthesize optically active organofluorine compounds starting from commercially available (R)-1-phenylethylamine.

Introduction

Ring-strained four-membered N-heterocycle azetidines are valuable building blocks in organic synthesis. Although they are chemically stable without any additives, nucleophilic ring-opening reactions proceed to give various types of functionalized nitrogen-containing compounds by electrophilic activation of the nitrogen atom by N-quaternization, 1,2 or addition of Bronsted acid (H+) 3 or Lewis acids 4 (Scheme 1). These transformations are applicable for the synthesis of amino acids, alkaloids, and biologically active drugs.

The initial studies of this ring-opening reaction were mainly performed by Couty’s group using tetraalkylazetidinium salts as substrates. 1 One point to consider in this reaction is site-selectivity at the 2- and 4-positions, which reacts with a nucleophile (Nu). In many cases, a less-substituted and/or electron-deficient carbon atom is attacked by a nucleophile because of the SN2 process. For example, a reaction of a substrate with a nucleophile in Scheme 1 proceeded at the 4-position preferentially to afford the corresponding product. However, some nucleophiles do not act according to this tendency, and the reaction occurs at the 2-position, which is a much-substituted carbon atom. Although these phenomena are currently difficult to explain, the site selectivity at the 2- and 4-positions can be determined based on the properties of nucleophiles, substituents at the 2- and 4-positions, and reaction conditions. 5,6,8,9 Previously, our group reported that the site-selective nucleophilic ring-opening reaction of α-azetidin-2-carboxylic acid ester-derived tetraalkylammonium salt (S)-2b prepared from 95% ee of (S)-1b (Scheme 2, Our previous work). 6 Cesium acetate (AcOCs) and dimethylamine (Me2NH) as nucleophiles reacted at the 4-position. In contrast, sodium azide (NaN3) reacted at the 2-position with inversion of the configuration. This result shows that the Sn2 substitution at the tertiary carbon atom (2-position) proceeded. 7 With the results, our group started to further investigate the scope of this reaction, since some nucleophiles such as fluoride (F-) provide valuable compounds. Furthermore, previous examples of the ring-opening reaction of azetidine derivatives with F- to give organofluorine compounds are rare 8,9 compared to the reaction of three-membered N-heterocycle aziridine derivatives. 9 Herein, we wish to report the site-selective nucleophilic ring-opening reaction of α-aryl azetidinium salts 2 with halides to afford α-aryl-α-halo-carboxylic acid esters 3 (Scheme 2, this work). Further synthetic applications of the resulting products 3, e.g., asymmetric synthesis of organofluorine compounds, are also demonstrated.

Scheme 1 Nucleophilic ring-opening of azetidine derivatives.

† Electronic supplementary information (ESI) available: Copies of 1H, 13C, and 19F NMR spectra of substrates and products, preparation of substrates, and copies of chiral HPLC chromatogram of chiral compounds. See DOI: 10.1039/d1ra08706a
Results and discussion

We started investigating the nucleophilic ring-opening reaction of 2a with a halide source (Table 1). First, the reaction of 2a with sodium fluoride (NaF) as an F⁻ source in DMF at room temperature for 2 h was examined to obtain the corresponding organofluorine compounds 3aa and 4aa; however, no products were obtained (entry 1). Although a reaction with potassium fluoride (KF) gave the same result (entry 2), the use of cesium fluoride (CsF) afforded 3aa in 13% yield (entry 3). We expected that tetrabutylammonium fluoride (Bu₄NF) might be more reactive, and its solubility in organic solvents would improve the yields of 3aa and 4aa. In addition, Ghorai et al. reported the Lewis acid-promoted nucleophilic ring-opening reaction of N-tosylazetidines with tetrabutylammonium chloride (Bu₄NCl) and bromide (Bu₄NBr). Thus, we attempted a reaction with a THF solution of Bu₄NF, and the desired 3aa was obtained in 33% yield with trace amounts of 4aa (<4% yield) (entry 4). The use of THF as a solvent and other F⁻ sources, such as Bu₄NBr/3H₂O, did not show any improvements (entries 5 and 6). We found that the yield of 3aa could be improved to 71% with minimization of the formation of 4aa (7% yield) when the reaction was performed at 60 °C (entry 7).

Next, we examined the same reaction with other tetrabutylammonium salts (Bu₄NX) to define the scope of this site-selective ring-opening reaction. Reactions with Bu₄NCl in THF, DMF and CH₂Cl₂ proceeded even at room temperature, and similar yields of 3ab (69–76% yields) and 4ab (14–23% yields) were observed (entries 8–10). At 0 °C, the yields of 3ab (34% yield) and 4ab (10% yield) decreased (entry 11). When the reaction was performed at 60 °C, the yield of undesired 4ab was slightly improved (27% yield) (entry 12). The use of Bu₄NBr is also applicable; however, the selectivity between 3ac (61% yield) and 4ac (21% yield) was insufficient (entry 13). Additionally, the resulting isolated bromo products 3ac and 4ac were unstable because of the self-N-quanternization. Therefore, a reaction with tetrabutylammonium iodide (Bu₄NI) did not give 3ad and 4ad (entry 14). Finally, we applied this reaction for pseudohalogen salts (MCN) to provide α-cyano derivative 3ae with an all-carbon quaternary stereocentre (entries 15 and 16). Unfortunately, both reactions with potassium cyanide (KCN) and tetrabutylammonium cyanide (Bu₄NHCN) gave similar results to provide 3ae and 4ae without selectivities.¹¹

The ring-opening products 3 and 4 in Table 1 were assigned by NMR analyses, and their representative results are shown in Fig. 1. Fluorine derivatives 3aa and 4aa were clearly identified by the ¹⁹F NMR analysis. Tertiary alkyl fluoride 3aa showed a chemical shift of −157 ppm. Primary alkyl fluoride 4aa showed a chemical shift of −222 ppm. These values are reasonable for the corresponding alkyl fluorides. In contrast, chlorine derivatives 3ab and 4ab did not show clear differences in ¹H and ¹³C NMR analyses. Consequently, we assigned these

| Entry | MX (equiv.) | Solvent | Temp., time | ³F (%) | ⁴F (%) |
|-------|------------|---------|-------------|--------|--------|
| 1     | NaF (5)    | DMF     | rt, 2 h     | 0      | 0      |
| 2     | KF (5)     | DMF     | rt, 2 h     | 0      | 0      |
| 3     | CsF (5)    | DMF     | rt, 2 h     | 13     | 0      |
| 4     | Bu₄NF in THF (1.2) | DMF | rt, 2 h | 33     | <4    |
| 5     | Bu₄NF in THF (1.2) | THF   | rt, 2 h     | 35     | 2      |
| 6     | Bu₄NF:3H₂O (1.2) | THF   | rt, 2 h     | 41     | <3    |
| 7     | Bu₄NF in THF (1.2) | THF   | 60 °C, 1 h | 71     | 7      |
| 8     | Bu₄NCl (1.2) | DMF | rt, 2 h     | 74     | 14     |
| 9     | Bu₄NCl (1.2) | THF | rt, 2 h     | 76     | 23     |
| 10    | Bu₄NCl (1.2) | CH₂Cl₂ | rt, 2 h | 69     | 14     |
| 11    | Bu₄NCl (1.2) | THF | 0 °C, 2 h   | 34     | 10     |
| 12    | Bu₄NCl (1.2) | THF | 60 °C, 2 h | 70     | 27     |
| 13    | Bu₄NBr (1.2) | THF | rt, 1 h     | 61     | 21     |
| 14    | Bu₄NI (1.2) | THF | rt, 1 h     | 0      | 0      |
| 15    | KCN (5)    | DMF     | rt, 2 h     | 42     | 55     |
| 16    | Bu₄NHCN (1.2) | THF | rt, 2 h     | 38     | 62     |

a Isolated yield.
by comparison of $^1$H NMR chemical shifts of methylene protons. Primary alkyl chloride 4\textit{ab} had low-field chemical shifts due to an electron-withdrawing effect of chloride. One of the two products (3\textit{ab} or 4\textit{ab}) with chemical shifts of 3.27 and 2.98 ppm was assigned to 4\textit{ab}. Another product was assigned to tertiary alkyl chloride 3\textit{ab}, which showed chemical shifts of 2.73–2.33 ppm. Bromine derivatives 3\textit{ac} and 4\textit{ac} were assigned by analogy to 3\textit{ab} and 4\textit{ab}. Meanwhile, nitrile derivatives 3\textit{ae} and 4\textit{ae} could be clearly identified by $^{13}$C NMR analysis. 4\textit{ae} showed a chemical shift of 12.1 ppm, which is a reasonable value as a primary nitrile.

To define the scope and limitations of this site-selective ring-opening reaction to produce tertiary alkyl halides 3, we prepared various azetidinium salts 2\textit{b–h} and examined their reactions with Bu$_4$NF or Bu$_4$NCl under identical conditions (Table 2). First, we attempted the reactions of 5-substituted aryl derivatives 2\textit{a–e} with Bu$_4$NF and obtained the corresponding organofluorine compounds 3\textit{ba–ea} in moderate yields (entries 1–4). The minor products 4\textit{a} were not isolated (N.D.), although their formations were observed by TLC analysis. The pure products of these organofluorine 4 for spectroscopic characterizations were difficult to isolate because of small amounts (ca. 5% yield). Electron-withdrawing substituents on the \(\alpha\)-aryl substituent, such as bromo (2\textit{b}) and trifluoromethyl (2\textit{c}), might be desirable to yield 3 (entries 1 and 2, approximately 75%). Reactions of methyl (2\textit{d}) and methoxy (2\textit{e}) derivatives resulted in lower yields of 3 (entries 3 and 4, approximately 60%). Thus, we next examined the reactions of 4-bromo (2\textit{f}) and 4-trifluoromethyl (2\textit{g}) derivatives and obtained 3\textit{fa–ga} in approximately 70% yields (entries 5 and 6). However, the reaction of 3-bromo derivative 2\textit{h} was resulted in a 58% yield of 3\textit{ha} (entry 7).

The use of Bu$_4$NCl for the reactions of 2\textit{b, d, f, and h} provided the corresponding organochlorine compounds 3\textit{bb–hb} (entries 8–11) with a similar tendency to the reaction with Bu$_4$NF. In these cases, the minor products 4\textit{bb–hb} could be isolated as a pure form to perform their spectroscopic characterizations.

We confirmed the chemical stability of products 3 and 4 (Scheme 3) because a transformation between 3 and 4 might proceed via the formation of ammonium salts generated from the alkyl halides and dimethylamino substituents as in the products (self-N-quaternization). A THF solution of tertiary alkyl

![Fig. 1](image1.png)

**Table 2** Substrate scope of the site-selective ring-opening of 2 with Bu$_4$NX

| Entry | X   | R     | 3\textit{a} (%) | 4\textit{a,b} (%) |
|-------|-----|-------|-----------------|------------------|
| 1     | F   | 5-Br  | 2b              | 77 (3ba)         |
| 2     | F   | 5-CF$_3$ | 2c         | 75 (3ca)         |
| 3     | F   | 5-Me  | 2d              | 59 (3da)         |
| 4     | F   | 5-OMe | 2e              | 61 (3ea)         |
| 5     | F   | 4-Br  | 2f              | 72 (3fa)         |
| 6     | F   | 4-CF$_3$ | 2g      | 68 (3ga)         |
| 7     | F   | 3-Br  | 2h              | 58 (3ha)         |
| 8     | Cl  | 5-Br  | 2b              | 82 (3bb)         |
| 9     | Cl  | 5-Me  | 2d              | 53 (3db)         |
| 10    | Cl  | 4-Br  | 2f              | 83 (3fb)         |
| 11    | Cl  | 3-Br  | 2h              | 65 (3hb)         |

\^ Isolated yields. \(\text{b} \) N.D. = not determined.
halides 3aa (X = F) or 3ab (X = Cl) was subjected to the reaction temperature depicted in Table 1. The removal of THF by evaporation and $^1$H NMR analysis of the residue did not show any formation of 4aa or 4ab, respectively (eqn (1)). Similarly, a stirring at room temperature of a THF solution of primary alkyl chloride 4ab did not afford 3ab (eqn (2)).

The N,N-dimethylamino substituent, as in product 3, is not synthetically valuable because of the impossibility of removing the N-methyl substituents. One N-methyl substituent could be changed into an N-allyl, which would be removable via Rh-catalysed isomerization, by N-quaternization of 1 with allyl triflate$^{15}$ (Scheme 4). For example, azetidinium salt 5 was prepared from 1b in 70% yield as an 8/2 mixture of diastereomers followed by ring-opening with Bu$_4$NF to provide N-allyl derivative 6 in 82% yield. Rh-catalyzed deallylation of 6 gave secondary amine 7 in 84% yield.

To demonstrate the utility of this ring-opening reaction, we attempted further synthetic transformations of organofluorine product 3aa. First, Hofmann elimination of 3aa to produce aryl-β-fluoro-α-vinylacetic acid ester 9 was examined (Scheme 5). N-Quaternization with iodomethane (Mel) or methyl trifluoromethanesulfonate (MeOTf) gave 8-I or 8-OTf in good yields (8-I: 91% yield, 8-OTf: quant.). Treatment of iodide salt 8-I with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing toluene for 1 day gave desired 9 in 36% yield. We expected that the iodide ion in the reaction mixture might cause undesirable side reactions such as nucleophilic substitutions, and the reaction resulted in a low yield. Thus, we examined the same reaction using triflate salt 8-OTf. As expected, the yield of 9 was improved to 57%.

Next, the synthesis of optically active tertiary organofluorine compounds from chiral (R)-1-phenylethylamine, which is one of the least expensive chiral sources, was examined (Scheme 6). 93% ee of (S)-1a was prepared according to our previous work.$^{6,11}$ N-Quaternization of (S)-1a with MeOTf to prepare (S)-2a (quant.) followed by the ring-opening reaction with Bu$_4$NF under the conditions in Table 1 afforded (R)-3aa (68% yield). The ee of the obtained 3aa was determined after conversion into (R)-11 because of the low sensitivity of 3aa towards a UV/vis detector in chiral HPLC analysis. Reduction of (R)-3aa with LiAlH$_4$ to amino alcohol (R)-10 (73% yield) followed by O-benzoylation gave benzoate (R)-11 (95% yield). The ee of (R)-11 was determined to be 93% ee by the chiral HPLC analysis. No lack of the ee was confirmed during the transformations from (S)-1a into (R)-11. This result indicates that the Bu$_4$NF-promoted ring-opening reaction of (S)-2a affording (R)-3aa proceeds by inverting the tertiary carbon configuration (S$_2$2) in the same manner as the reaction of (S)-2b with NaN$_3$, which was previously reported by our group.* Therefore, the absolute configuration of 3aa was determined to be (R).

To clarify that the aryl substituent as in 2 is necessary for this site-selective ring-opening reaction to produce 3, we investigated a reaction α-ethyl derivative 12 with Bu$_4$NF (Scheme 7). As expected, the reaction proceeded at 4-position preferentially to give γ-fluoro product 14 in 62% yield. Identifiable amount of the corresponding α-fluoro product 13 was not

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Scheme 4 Synthesis of N-allyl derivative 5 and 6 and deallylation into 7.

Scheme 5 Synthesis of α-aryl-β-fluoro-α-vinylacetic acid ester 9 from 3aa by Hofmann elimination.

Scheme 6 Synthesis of optically active organofluorine compound (R)-3aa starting from (R)-1-phenylethylamine.
obtained. Instead, α-hydroxy derivative 15, which might be derived from 13, was isolated in 7% yield.

Couby’s group described in the previous literature⁴ that the nucleophilic ring-opening of α,α-disubstituted azetidinium ions at the quaternary α-carbon (2-position) is intrinsically favoured. Steric repulsions generated by substituents as in the azetidine ring affect the site-selectivity. The highly nucleophilic azide anion (N₃⁻) reacts at 2-position, the less nucleophilic cyanide anion (CN⁻) reacts at 2- and 4-positions, and the poor nucleophilic acetate anion (AcO⁻) reacts at 4-position. The exact reason of the site-selective ring-opening reaction to produce 3 demonstrated by our group are difficult to explain at present, a size of the nucleophiles might affect the site-selectivity. F⁻ and Cl⁻ are small and enable to react at the quaternary α-carbon (2-position) although they are poor nucleophilic anion. Further experimental studies are needed to discuss.

Conclusions

In conclusion, we described that the site-selective nucleophilic ring-opening reaction of 2-arylazetidine-2-carboxylic acid ester-derived ammonium salts 2 with Bu₄NF or Bu₄NCl proceeded at a much-substituted 2-position preferentially over a less-substituted 4-position and produced the corresponding tertiary alkyl fluorides and chlorides 3. Our result is a rare successful example of the fluoride ion-promoted ring-opening reaction of azetidine derivatives that yields organofluorine compounds. Further synthetic transformations of the product 3 were also successfully demonstrated. Our protocol enables the production of optically active organofluorine compound (R)-3aa starting from commercially available chiral (R)-1-phenylethylamine, which is an inexpensive chiral compound.

Representative procedure for ring-opening of 2a with Bu₄NF in THF to afford 3aa and 4aa (Table 1, entry 7)

A solution of 2-( tert-butoxycarbonyl)-1,1-dimethyl-2-( o-tolyl) azetidin-1-ium trifluoromethanesulfonate (2a) (62.3 mg, 0.146 mmol) in THF (0.55 mL) was stirred at 60 °C under an Ar atmosphere and treated with a 1 M Bu₄NF THF solution (175 µL, 0.175 mmol). After stirring for 1 h at 60 °C, the resulting mixture was cooled to room temperature and diluted with H₂O. The mixture was extracted with cyclohexane and the combined extracts were washed with H₂O. The organic solution was dried over Na₂SO₄ and concentrated by evaporation. The residue was purified by chromatography on silica gel (Wakosil 60, 64–210 µm) purchased from FUJIFILM Wako Chemical Corporation. For strong basic compound such as (5)-10, NH TLC plates and amino-functionalized silica gel (Chromatorex NH-DM1020) purchased from Fuji Silysis Chemical Ltd. (Japan) were used.

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RSC Adv., 2021, 11, 39607–39618 | 39611

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RSC Adv., 2021, 11, 39607–39618 | 39611
1305, 1289, 1240, 1207, 1153, 1130, 1080, 1049, 1011, 986, 950, 883, 844, 814, 752, 749; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.43–7.37 (1H, m, ArH), 7.18–7.08 (3H, m, ArH), 4.24 (1H, ddd, \(J_{HF} = 47.2\) Hz, \(J = 9.4, 9.2, 5.4\) Hz, 4H), 4.06 (1H, ddd, \(J_{HF} = 46.8\) Hz, \(J = 9.6, 9.2, 5.6\) Hz, 4H), 2.66 (1H, ddd, \(J_{HF} = 15.3\) Hz, \(J = 14.2, 9.6, 5.4\) Hz, 3H), 2.42–2.24 (1H, m, 3H), 2.36 (6H, s, N(CH\(_3\))\(_2\)), 2.35 (3H, s, ArCH\(_3\)), 1.54 (9H, s, tBu); \(^{13}\)C\({^1}\)H NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.5, 137.8, 136.2, 132.2, 128.1, 127.0, 124.9, 81.9, 81.5 (d, \(J_{FC} = 161\) Hz), 71.4 (d, \(J_{FC} = 11\) Hz), 40.0, 34.5 (d, \(J_{FC} = 21\) Hz), 28.5, 21.1; \(^1\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) –222; HRMS (ESI): calcd for C\(_{17}\)H\(_{27}\)FNO\(_2\) [M + H\(^+\)] 312.1725, found 312.1715.

Representative procedure for ring-opening of 2a with Bu\(_4\)NCl in THF to afford 3ab and 4ab (Table 1, entry 9)

Bu\(_4\)NCl (230 mg, 0.828 mmol) was added to a solution of the eluent, \(R_c\), to obtain tert-butyl 2-chloro-4-(dimethylamino)-2-(o-toly)butanoate (3ab) (163 mg, 76% yield) as a pale yellow oil and tert-butyl 4-chloro-2-(dimethylamino)-2-(o-toly)butanoate (4ab) (49.8 mg, 23% yield) as a colourless oil.

Ring-opening of 2a with KCN in DMF to afford 3ae and 4ae (Table 1, entry 15)

KCN (50.5 mg, 0.775 mmol) was added to a solution of 2a (67.0 mg, 0.157 mmol) in DMF (0.8 mL) at room temperature. The mixture was degassed under reduced pressure and filtered with Ar. After stirring for 2 h, the resulting mixture was diluted with H\(_2\)O. The mixture was extracted with n-hexane/EtOAc = 3/1 mixed solvent and the combined extracts were washed with H\(_2\)O. The organic solution was dried over Na\(_2\)SO\(_4\) and concentrated by evaporation. The residue was purified by chromatography on silica gel (CH\(_2\)Cl\(_2\)/MeOH = 100/0 to 30/1 as the eluent, \(R_c\), for 3ab and 4ab) to obtain tert-butyl 4-bromo-2-(dimethylamino)-2-(o-toly)butanoate (4ac) (12.1 mg, 21% yield) as a colourless oil. 3ac: IR (ATR) \(\nu_{\text{max}}/\text{cm}^{-1}\) 3062, 2975, 2938, 2860, 2818, 2765, 1726, 1681, 1457, 1392, 1367, 1252, 1144, 1078, 1040, 1028, 965, 889, 843, 791, 751, 721, 689; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.68–7.61 (1H, m, ArH), 7.24–7.10 (3H, m, ArH), 2.72 (1H, ddd, \(J = 14.0, 11.0, 4.8\) Hz, 2CH\(_3\)), 2.64 (1H, ddd, \(J = 14.0, 10.8, 4.8\) Hz, CH\(_2\)), 2.44 (1H, ddd, \(J = 12.0, 10.8, 4.8\) Hz, CH\(_2\)), 2.38–2.28 (1H, m, CH\(_3\)), 2.33 (3H, s, ArCH\(_3\)), 2.25 (6H, s, N(CH\(_3\))\(_2\)), 1.45 (9H, s, tBu); \(^{13}\)C\({^1}\)H NMR (101 MHz, CDCl\(_3\)) \(\delta\) 169.3, 130.5, 134.1, 129.2, 127.8, 125.8, 83.0, 56.2, 54.5, 38.7, 27.5, 20.7; HRMS (ESI): calcd for C\(_{17}\)H\(_{27}\)BrNO\(_2\) [M + H\(^+\)] \(356.1220\), found 356.1218.

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**tert-Butyl 2-(5-bromo-2-methylphenyl)-4-(dimethylamino)-2-fluorobutanoate (3ba) (Table 2, entry 1)**

Obtained from 2b (76.0 mg, 0.151 mmol) by the same procedure with 3aa. Purification by chromatography on silica gel (CH2Cl2/MeOH = 30/1 to 20/1 as the eluent) gave 3ba (43.3 mg, 77% yield) as a pale yellow oil. IR (ATR) \( \nu_{\text{max}} \text{cm}^{-1} = 2976, 2938, 2861, 2818, 2767, 1749, 1731, 1592, 1565, 1481, 1459, 1391, 1368, 1283, 1251, 1218, 1149, 1104, 1092, 984, 949, 876, 842, 809, 769, 738, 704; ^1H NMR (400 MHz, CDCl3) \( \delta \) 7.53 (1H, dd, \( J = 1.6, 1.8 \) Hz, ArH), 7.35 (1H, dd, \( J = 8.0, 1.8 \) Hz, ArH), 7.03 (1H, d, \( J = 8.0 \) Hz, ArH), 2.73–2.30 (4H, m, CH2), 2.37 (3H, d, \( J_{\text{F–H}} = 3.6 \) Hz, ArCH3), 2.27 (6H, s, N(CH3)2), 1.43 (9H, s, tBu). ^13C{1H} NMR (101 MHz, CDCl3) \( \delta \) 168.4 (d, \( J_{\text{C–F}} = 27 \) Hz), 138.3 (d, \( J_{\text{C–F}} = 21 \) Hz), 135.5 (d, \( J_{\text{C–F}} = 27 \) Hz), 133.7, 131.4, 129.1 (d, \( J_{\text{C–F}} = 9 \) Hz), 119.3, 95.8 (d, \( J_{\text{C–F}} = 190 \) Hz), 83.1, 53.4 (d, \( J_{\text{C–F}} = 5 \) Hz), 45.4, 34.4 (d, \( J_{\text{C–F}} = 22 \) Hz), 27.7, 20.2 (d, \( J_{\text{C–F}} = 7 \) Hz); HRMS (ESI): calcd for C18H27N2O2 [M + H]^+ 303.2067, found 303.2058.

**tert-Butyl 4-(dimethylamino)-2-fluoro-2-(2-methyl-5-(trifluoromethyl)phenyl)butanoate (3ca) (Table 2, entry 2)**

Obtained from 2c (167 mg, 0.338 mmol) by the same procedure with 3aa. Purification by chromatography on silica gel (CH2Cl2/MeOH = 30/1 to 20/1 as the eluent) gave 3ca (92.2 mg, 75% yield) as a pale yellow oil. IR (ATR) \( \nu_{\text{max}} \text{cm}^{-1} = 2979, 2942, 2864, 2821, 2769, 1752, 1732, 1621, 1460, 1393, 1370, 1311, 1286, 1252, 1151, 1209, 1040, 1046, 990, 948, 896, 842, 829, 771, 748, 721; ^1H NMR (400 MHz, CDCl3) \( \delta \) 7.49 (1H, d, \( J = 8.0 \) Hz, ArH), 7.29 (1H, d, \( J = 8.0 \) Hz, ArH), 2.78–2.31 (4H, m, CH2), 2.49 (3H, d, \( J_{\text{F–H}} = 3.2 \) Hz, ArCH3), 2.28 (6H, s, N(CH3)2), 1.43 (9H, s, tBu). ^13C{1H} NMR (101 MHz, CDCl3) \( \delta \) 168.4 (d, \( J_{\text{C–F}} = 27 \) Hz), 140.9 (d, \( J_{\text{C–F}} = 2 \) Hz), 137.2 (d, \( J_{\text{C–F}} = 22 \) Hz), 132.6, 128.1 (d, \( J_{\text{C–F}} = 33 \) Hz), 125.3–125.0 (m), 124.1 (d, \( J_{\text{C–F}} = 273 \) Hz), 123.2 (dq, \( J_{\text{F–C}} = 8 \) Hz, 96.0 (d, \( J_{\text{C–F}} = 190 \) Hz), 83.1, 53.4 (d, \( J_{\text{C–F}} = 5 \) Hz), 45.4, 34.7 (d, \( J_{\text{C–F}} = 22 \) Hz), 27.6, 20.7 (d, \( J_{\text{C–F}} = 8 \) Hz); HRMS (ESI): calcd for C18H29FNO2 [M + H]^+ 310.2176, found 310.2163.

**t2er-Butyl 2-(4-bromo-2-methylphenyl)-4-(dimethylamino)-2-fluorobutanoate (3fa) (Table 2, entry 5)**

Obtained from 2f (318 mg, 0.631 mmol) by the same procedure with 3aa. Purification by chromatography on silica gel (CH2Cl2/MeOH = 30/1 to 20/1 as the eluent) gave 3fa (170 mg, 72% yield) as a pale yellow oil. IR (ATR) \( \nu_{\text{max}} \text{cm}^{-1} = 2976, 2938, 2862, 2818, 2769, 1749, 1731, 1590, 1480, 1459, 1391, 1368, 1275, 1250, 1216, 1158, 1092, 1042, 988, 960, 940, 900, 844, 811, 768, 747, 704; ^1H NMR (400 MHz, CDCl3) \( \delta \) 7.35–7.29 (2H, m, ArH), 7.29–7.23 (1H, m, ArH), 2.66–2.30 (4H, m, CH2), 2.40 (3H, d, \( J_{\text{F–H}} = 3.6 \) Hz, ArCH3), 2.26 (6H, s, N(CH3)2), 1.42 (9H, s, tBu). ^13C{1H} NMR (101 MHz, CDCl3) \( \delta \) 168.6 (d, \( J_{\text{C–F}} = 27 \) Hz), 139.0 (d, \( J_{\text{C–F}} = 22 \) Hz), 135.3 (d, \( J_{\text{C–F}} = 21 \) Hz), 134.7, 128.6, 127.8 (d, \( J_{\text{C–F}} = 8 \) Hz), 122.4 (d, \( J_{\text{C–F}} = 2 \) Hz), 96.0 (d, \( J_{\text{C–F}} = 189 \) Hz), 88.2, 53.4 (d, \( J_{\text{C–F}} = 5 \) Hz), 45.4, 34.6 (d, \( J_{\text{C–F}} = 22 \) Hz), 27.6, 20.4 (d, \( J_{\text{C–F}} = 8 \) Hz); HRMS (ESI): calcd for C17H28BrFNO2 [M + H]^+ 326.2126, found 326.2115.
tert-Butyl 2-(3-bromo-2-methylphenyl)-2-chloro-4-(dimethylamino)butanoate (3bb) and tert-butyl 2-(5-bromo-2-methylphenyl)-4-chloro-2-(dimethylamino)butanoate (4bb) (Table 2, entry 8)

Obtained from 2b (135 mg, 0.268 mmol) by the same procedure with 3ab and 4ab. Purification by chromatography on silica gel (CH₂Cl₂/MeOH = 100/0 to 30/1 as the eluent Rₖ: 3bb < 4bb) gave 3bb (85.5 mg, 82% yield) as colourless crystals and 4bb (18.0 mg, 17% yield) as a colourless oil. HRMS (ESI): calcd for C₁₇H₂₆BrFNO₂ [M + H]+ 374.1125, found 374.1120.

tert-Butyl 2-chloro-4-(dimethylamino)-2-(5-dimethylphenyl)butanoate (3db) and tert-butyl 4-chloro-2-(dimethylamino)-2-(5-dimethylphenyl)butanoate (4db) (Table 2, entry 9)

Obtained from 2d (85.8 mg, 0.195 mmol) by the same procedure with 3ab and 4ab. Purification by chromatography on silica gel (CH₂Cl₂/MeOH = 100/0 to 30/1 as the eluent Rₖ: 3db < 4db) gave 3db (33.9 mg, 53% yield) as colourless crystals and 4db (12.3 mg, 19% yield) as a colourless oil. 3db: mp 41–42 °C; IR (ATR) ν/cm⁻¹ 2976, 2938, 2861, 715, 1732, 3165, 1497, 1458, 1392, 1367, 1252, 1146, 1080, 1039, 992, 928, 911, 846, 809, 771, 745, 718, 700; ¹H NMR (400 MHz, CDCl₃) δ 7.40 (1H, s, ArH), 7.07–7.99 (2H, m, ArH), 2.71–2.52 (2H, m, CH₂), 2.47–2.35 (2H, m, CH₂), 2.34 (3H, s, ArCH₃), 2.30 (3H, s, ArCH₃), 2.26 (6H, s, N(CH₃)₂), 1.44 (9H, s, tBu); ¹³C [¹H] NMR (101 MHz, CDCl₃) δ 169.3, 137.8, 135.0, 132.6, 131.9, 128.8, 82.9, 73.8, 55.1, 45.6, 37.9, 27.6, 21.2, 20.0; HRMS (ESI): calcd for C₁₉H₂₈BrFNO₂ [M + H]+ 326.1881, found 326.1873.

tert-Butyl 2-(4-bromo-2-methylphenyl)-2-chloro-4-(dimethylamino)butanoate (3fb) and tert-butyl 2-(4-bromo-5-methylphenyl)-4-chloro-2-(dimethylamino)butanoate (4fb) (Table 2, entry 10)

Obtained from 2f (95.6 mg, 0.190 mmol) by the same procedure with 3ab and 4ab. Purification by chromatography on silica gel (CH₂Cl₂/MeOH = 100/0 to 30/1 as the eluent Rₖ: 3fb < 4fb) gave 3fb (61.4 mg, 83% yield) as a pale yellow oil and 4fb (12.9 mg, 17% yield) as colourless crystals. 3fb: mp 57–59 °C; IR (ATR) ν/cm⁻¹ 2975, 2939, 2861, 2818, 2766, 1734, 1589, 1560, 1458, 1391, 1368, 1345, 1362, 1357, 1354, 1346, 1288, 1236, 1232, 1179, 1143, 1130, 1080, 1063, 1041, 920, 875, 849, 811, 796, 768, 755, 722; ¹H NMR (400 MHz, CDCl₃) δ 7.74 (1H, d, J = 2.0 Hz, ArH), 7.35 (1H, ddd, J = 8.2, 2.0, 2.0 Hz, ArH), 7.03 (1H, d, J = 8.2 Hz, ArH), 2.63 (1H, ddd, J = 13.5, 10.1, 5.6 Hz, CH₂), 2.52 (1H, ddd, J = 13.5, 9.6, 5.8 Hz, CH₂), 2.44–2.31 (2H, m, CH₂), 2.29 (3H, s, ArCH₃), 2.25 (6H, s, N(CH₃)₂), 1.44 (9H, s, tBu); ¹³C [¹H] NMR (101 MHz, CDCl₃) δ 168.6, 140.1, 134.8, 135.3, 131.1, 129.5, 119.4, 83.4, 72.8, 54.9, 45.6, 37.8, 27.6, 20.0; HRMS (ESI): calcd for C₁₇H₂₉BrClNO₂ [M + H]+ 390.0830, found 390.0822.

Obtained from 2b (155 mg, 0.307 mmol) by the same procedure with 3aa. Purification by chromatography on silica gel (CH₂Cl₂/MeOH = 30/1 to 20/1 as the eluent) gave 3aa (66.7 mg, 58% yield) as a pale yellow oil. IR (ATR) ν/cm⁻¹ 2976, 2938, 2861, 2818, 2766, 1748, 1732, 1562, 1459, 1432, 1392, 1368, 1283, 1250, 1148, 1092, 1076, 1033, 1005, 965, 944, 903, 842, 783, 763, 742, 715; ¹H NMR (400 MHz, CDCl₃) δ 7.57 (1H, d, J = 8.0 Hz, ArH), 7.38 (1H, d, J = 8.0 Hz, ArH), 7.06 (1H, ddd, J = 8.0, 8.0, 0.5 Hz, ArH), 2.66–2.34 (4H, m, CH₂), 2.47 (3H, d, J = 2.8 Hz, ArCH₃), 2.26 (6H, s, N(CH₃)₂), 1.43 (9H, s, tBu); ¹³C [¹H] NMR (101 MHz, CDCl₃) δ 169.0 (d, 14.3 Hz, ArCH₃), 138.4 (d, 2.4 Hz = 26.4 Hz), 138.4 (d, 14.3 Hz), 136.4, 133.1 (d, 14.3 Hz = 2 Hz), 127.7 (d, J = 2 Hz), 126.6, 125.3 (d, 4.3 Hz = 8 Hz), 96.0 (d, 14.3 Hz = 190 Hz), 83.0, 53.5 (d, 14.3 Hz = 5 Hz), 45.3, 34.9 (d, 14.3 Hz = 22 Hz), 27.7, 20.3 (d, 14.3 Hz = 7 Hz); HRMS (ESI): calcd for C₁₇H₂₆BrFNO₂ [M + H]+ 374.1125, found 374.1120.
MHZ, CDCl3) δ 167.6, 138.4, 136.8, 134.9, 130.2, 128.0, 120.9, 82.4, 71.9, 40.3, 40.0, 37.3, 28.4, 20.9; HRMS (ESI): caleld for C12H18BrClINO2 [M + H]+ 390.0830, found 390.0824.

tert-Butyl 2-(3-bromo-2-methylphenyl)-2-chloro-4-(dimethylamino)butanoate (3hb) and tert-butyl 2-(3-bromo-2-methylphenyl)-4-chloro-2-(dimethylamino)butanoate (4hb) (Table 2, entry 11)

Obtained from 2h (149 mg, 0.295 mmol) by the same procedure with 3aa and 4aa. Purification by chromatography on silica gel (CH2Cl2/MeOH = 100/0 to 30/1 as the eluent Rf: 3hb < 4hb) gave 3hb (74.7 mg, 65% yield) as colourless crystals and 4hb (37.5 mg, 33% yield) as a colourless oil. 3hb: mp 45–47°C; IR (ATR) νmax/cm−1 2976, 2940, 2872, 2818, 2766, 1733, 1561, 1459, 1427, 1368, 1304, 1251, 1146, 1078, 1031, 997, 967, 939, 912, 841, 783, 765, 742, 714; 1H NMR (400 MHz, CDCl3) 5.79 (1H, dd, J = 8.1, 1.0 Hz, ArH), 7.55 (1H, dd, J = 8.0, 1.0 Hz, ArH), 7.07 (1H, dd, J = 8.1, 8.0 Hz, ArH), 2.66 (1H, dd, J = 13.4, 11.1, 4.8 Hz, CH2), 2.52 (1H, dd, J = 12.3, 10.4, 4.8 Hz, CH2), 2.41 (1H, dd, J = 12.0, 10.4, 4.8 Hz, CH2), 2.38 (3H, s, ArCH3), 2.34 (1H, dd, J = 12.0, 11.1, 4.8 Hz, CH2), 2.24 (6H, s, N(CH3)2), 1.44 (9H, s, tBu); 13C[1H] NMR (101 MHz, CDCl3) 5.69 t (1H, dd, J = 169.1, 140.1, 153.6, 132.7, 127.5, 126.6, 125.7, 83.4, 73.5, 54.9, 45.6, 38.3, 27.5, 21.1; HRMS (ESI): caleld for C17H26BrClNO2 [M + H]+ 380.0830, found 380.0823. 4hb: IR (ATR) νmax/cm−1 2976, 2930, 2872, 2837, 2797, 1713, 1560, 1455, 1428, 1392, 1366, 1329, 1233, 1151, 1098, 1081, 1048, 986, 962, 875, 842, 821, 789, 736, 719; 1H NMR (400 MHz, CDCl3) 5.70 (1H, dd, J = 7.9, 1.0 Hz, ArH), 7.46 (1H, br, d, J = 8.0 Hz, ArH), 7.01 (1H, dd, J = 8.0, 0.4 Hz, ArH), 3.33 (1H, dd, J = 11.6, 10.8, 3.7 Hz, CH2), 2.92 (1H, dd, J = 12.1, 10.8, 5.2 Hz, CH2), 2.71 (1H, dd, J = 14.2, 12.1, 3.7 Hz, CH2), 2.40–2.15 (1H, m, CH2), 2.35 (3H, s, ArCH3), 2.33 (6H, s, N(CH3)2), 1.53 (9H, s, tBu); 13C[1H] NMR (101 MHz, CDCl3) 5.67 t (1H, dd, J = 167.4, 139.8, 153.6, 131.7, 127.8, 127.6, 126.0, 82.4, 72.4, 40.3, 40.1, 37.5, 28.4, 21.8; HRMS (ESI): caleld for C17H26BrClNO2 [M + H]+ 380.0826.

1-Allyl-2-(5-bromo-2-methylphenyl)-2-(tert-butoxycarbonyl)-1-methylazetidin-1-ium trifluoromethanesulfonate (5)

A solution of allyl alcohol (50 µL, 0.74 mmol) and pyridine (55 µL, 0.68 mmol) in CCl4 (1.7 mL) was treated with trifluoromethanesulfonic anhydride (0.11 mL, 0.65 mmol) at 0 °C. The mixture was stirred for 20 min at the same temperature to precipitate a pale-brown solid. The generated allyl tri

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RSC Adv., 2021, 11, 39607–39618 | 39615

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m, CH$_3$), 2.45 (3H, s, NCH$_3$), 2.36 (3H, d, $^3$J$_{FH}$ = 3.6 Hz, ArCH$_3$), 1.59 (1H, br, NH), 1.44 (9H, s, tBu); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.5 (d, $^3$J$_{FC}$ = 27 Hz), 138.3 (d, $^2$J$_{FC}$ = 21 Hz), 135.5 (d, $^2$J$_{FC}$ = 2 Hz), 133.7, 131.4 (d, $^2$J$_{FC}$ = 2 Hz), 129.1 (d, $^3$J$_{FC}$ = 9 Hz), 119.3, 96.2 (d, $^1$J$_{FC}$ = 189 Hz), 83.2, 46.2 (d, $^1$J$_{FC}$ = 5 Hz), 36.43 (d, $^2$J$_{FC}$ = 22 Hz), 36.36, 27.7, 20.2 (d, $^4$J$_{FC}$ = 7 Hz); HRMS (ESI): calcd for C$_{16}$H$_{24}$BrFNO$_2$ [M + H]$^+$ 360.0969, found 360.0964.

4-(tert-Butoxy)-3-fluoro-N,N,N-trimethyl-4-oxo-3-(o-tolyl)butan-1-aminium iodide (8-I)

A mixture of 3aa (67.0 mg, 0.227 mmol) and MeI (21 mL, 0.34 mmol) in MeCN (1.1 mL) was stirred for 2 h at room temperature. The resulting mixture was concentrated by evaporation and the residue was concentrated by chromatography on silica gel (CH$_2$Cl$_2$/MeOH = 20/1 to 10/1 as the eluent) to obtain 8-I (90.3 mg, 91% yield) as a yellow solid, mp 162–164 °C. IR (ATR) $v_{max}$/cm$^{-1}$ 3002, 2978, 2932, 1738, 1484, 1455, 1418, 1394, 1368, 1335, 1294, 1259, 1243, 1215, 1145, 1089, 1062, 1009, 992, 975, 934, 912, 838, 777, 748; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.51–7.44 (1H, m, ArH), 7.32–7.23 (2H, m, ArH), 7.22–7.15 (1H, m, ArH), 3.70 (1H, ddd, $^3$J$_{FH}$ = 13.1, 8.7, 7.3 Hz, CH$_3$), 3.60–3.40 (1H, m, CH$_3$), 3.52 [9H, s, N(Ch$_3$)$_3$], 2.93–2.76 (2H, m, CH$_2$), 2.41 [3H, d, $^3$J$_{FH}$ = 3.6 Hz, ArCH$_3$], 1.43 [9H, s, tBu]; $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.7 (d, $^3$J$_{FC}$ = 25 Hz), 135.7 (d, $^3$J$_{FC}$ = 2 Hz), 133.8 (d, $^2$J$_{FC}$ = 21 Hz), 132.5, 129.2 (d, $^1$J$_{FC}$ = 2 Hz), 126.4 (d, $^2$J$_{FC}$ = 2 Hz), 126.1 (d, $^3$J$_{FC}$ = 9 Hz), 96.1 (d, $^1$J$_{FC}$ = 190 Hz), 84.4, 62.7–62.4 (m), 54.0, 30.3 (d, $^4$J$_{FC}$ = 22 Hz), 27.8, 20.7 (d, $^4$J$_{FC}$ = 7 Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ –157; HRMS (ESI): calcd for C$_{14}$H$_{28}$NO$_2$ [M – I]$^+$ 310.2177, found 310.2166.

4-(tert-Butoxy)-3-fluoro-N,N,N-trimethyl-4-oxo-3-(o-tolyl)butan-1-aminium trifluoromethanesulfonate (8-OTf)

A mixture of 3aa (91.3 mg, 0.309 mmol) and NaHCO$_3$ (82 mg, 1.28 mmol) in CH$_2$Cl$_2$ (1.5 mL) was treated with methyl trifluoromethanesulfonate (52 µL, 0.46 mmol) at 0 °C and stirred for 2 h at room temperature. The resulting mixture was purified by chromatography on silica gel (CH$_2$Cl$_2$/MeOH = 20/1 to 10/1 as the eluent) to obtain 8-OTf (143 mg, quant.) as a white solid, mp 140–142 °C. IR (ATR) $v_{max}$/cm$^{-1}$ 3039, 2979, 2936, 1760, 1733, 1484, 1459, 1420, 1395, 1371, 1257, 1227, 1155, 1084, 1030, 1008, 976, 933, 841, 793, 746; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.42–7.35 (1H, m, ArH), 7.30–7.21 (2H, m, ArH), 7.21–7.13 (1H, m, ArH), 3.55–3.43 (1H, m, CH$_3$), 3.41–3.27 (1H, m, CH$_3$), 3.21 [9H, s, N(Ch$_3$)$_3$], 2.86–2.69 (2H, m, CH$_2$), 2.38 (3H, d, $^3$J$_{FH}$ = 3.6 Hz, ArCH$_3$), 1.41 [9H, s, tBu]; $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.8 (d, $^3$J$_{FC}$ = 26 Hz), 135.9 (d, $^3$J$_{FC}$ = 2 Hz), 134.0 (d, $^2$J$_{FC}$ = 21 Hz), 132.4, 129.2, 126.3, 125.9 (d, $^3$J$_{FC}$ = 9 Hz), 120.5 [q, $^2$J$_{FC}$ = 321 Hz], 95.9 (d, $^1$J$_{FC}$ = 190 Hz), 84.3, 62.1 (d, $^1$J$_{FC}$ = 5 Hz), 53.3, 30.0 (d, $^4$J$_{FC}$ = 22 Hz), 27.6, 20.5 (d, $^4$J$_{FC}$ = 8 Hz); $^{35}$F NMR (376 MHz, CDCl$_3$) $\delta$ –80, –157; HRMS (ESI): calcd for C$_{16}$H$_{24}$F$_3$O$_2$NO$_2$ [M – OTf]$^+$ 376.0958, found 376.0955.

(R)-4-(dimethylamino)-2-fluoro-2-(o-tolyl)butanoate ([R]-3aa)

Obtained from (S)-2a (277 mg, 0.651 mmol) by the same procedure with 3aa. Purification by chromatography on silica gel (CH$_2$Cl$_2$/MeOH = 20/1 to 10/1 as the eluent) gave [R]-3aa (131 mg, 68% yield) as a colourless oil. [$^3$H$_{max}$/cm$^{-1}$ 9.6, 9.4, 2.4 Hz, 4H), 3.90 (1H, ddd, $^3$J$_{FH}$ = 12.4, 10.6, 9.6 Hz, 3H), 3.63 (3H, s, NCH$_3$), 3.02–2.84 (1H, br m, 3H), 2.97 (3H, s, NCH$_3$), 2.33 (3H, s, ArCH$_3$), 1.39 [9H, s, tBu]; $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 164.6, 153.9, 132.5, 130.6, 129.7, 128.5, 126.9, 120.6 (q, $^3$J$_{FC}$ = 322 Hz), 86.8, 86.3, 62.7, 50.9, 50.7, 27.4, 27.1, 20.7; HRMS (ESI): calcd for C$_{17}$H$_{24}$F$_2$NO$_2$ [M – OTf]$^+$ 376.0958, found 376.0955.
0 °C by addition of H2O (35 µL), 15 wt% NaOH-H2O solution (35 µL), and H2O (105 µL). The suspension was diluted with EtOH (4 mL) and stirred for 12 h at room temperature. The resulting mixture was filtered through a pad of Celite and the filtrate was concentrated by evaporation. The residue was purified by chromatography on amino-functionalized silica gel (Chromatorex NH-DM1020, n-hexane/EtOAc = 2/1 to 1/1 as the eluent) to obtain (R)-10 (73.0 mg, 73% yield) as a colourless oil. [α]D5 9.9 (c 1.0 in EtOH); IR (ATR) rmax/cm−1 3339, 3061, 3020, 2974, 2863, 2825, 2778, 1462, 1385, 1290, 1258, 1217, 1180, 1163, 1095, 1057, 1038, 1000, 944, 878, 846, 800, 757, 726; 1H NMR (400 MHz, CDCl3) δ 7.47–7.40 (1H, m, ArH), 7.23–7.10 (3H, m, ArH), 3.92 (1H, dd, JFH = 26.8 Hz, J = 12.8 Hz, 1H), 3.88 (1H, dd, JFH = 20.2 Hz, J = 12.8 Hz, 1H), 2.87–2.76 (1H, m, OH), 2.48 (3H, d, JFH = 4.4 Hz, ArCH3), 2.45–2.13 (4H, m, CH2), 2.31 (6H, s, N(CH3)2), 13C{1H} NMR (101 MHz, CDCl3) δ 139.9 (d, JFC = 20 Hz), 135.2 (d, JFC = 2 Hz), 132.5, 127.7, 125.7 (d, JFC = 2 Hz), 125.5 (d, JFC = 11 Hz), 99.4 (d, JFC = 179 Hz), 67.6 (d, JFC = 28 Hz), 53.5 (d, JFC = 6 Hz), 44.9, 35.2 (d, JFC = 25 Hz), 21.8 (d, JFC = 9 Hz); 19F NMR (376 MHz, CDCl3) δ −161; HRMS (ESI): calcd for C18H30NO3 [M + H]+ 316.2260, found 316.2260.

(R)-4-(Dimethylamino)-2-fluoro-2-(o-tolyl)butyl benzoate [(R)-11]

A solution of (R)-10 (73.0 mg, 0.324 mmol) and Et3N (135 µL, 0.969 mmol) in CH2Cl2 (3.2 mL) was treated with benzyl chloroide (45 µL, 0.39 mmol) at 0 °C and stirred for 2 h at room temperature. The resulting mixture was diluted with H2O and extracted with EtOAc. The combined extracts were washed with H2O, dried over Na2SO4, and concentrated by evaporation. Purification by chromatography on silica gel (CH2Cl2/Methanol = 20/1 to 10/1 as the eluent) gave (R)-11 (101 mg, 95% yield) as a colourless oil. 93% ee [determined by HPLC analysis: Daicel Chiralcel AD-H column (25 cm), n-hexane/EtOH/0.01% EtNH2 = 100/0.2 as the eluent, flow rate: 0.50 mL/min, tR = 14.7 min for (R)-11 (96.5%) and 19.1 min for (S)-11 (3.5%)]. [α]D5 66.6 (c 1.0 in EtOH); IR (ATR) rmax/cm−1 3062, 3022, 2970, 2944, 2861, 2818, 2765, 1719, 1602, 1584, 1491, 1450, 1377, 1314, 1265, 1176, 1156, 1111, 1095, 1068, 1042, 1026, 936, 893, 849, 802, 760, 727, 708; 1H NMR (400 MHz, CDCl3) δ 7.98–7.93 (2H, m, ArH), 7.54 (1H, tt, J = 7.6, 1.3 Hz, ArH), 7.43–7.35 (3H, m, ArH), 7.25–7.15 (3H, m, ArH), 4.73 (1H, dd, JFH = 17.4 Hz, J = 12.6 Hz, 1H), 4.67 (1H, dd, JFH = 15.8 Hz, J = 12.6 Hz, 1H), 2.50 (3H, d, JFH = 3.6 Hz, ArCH3), 2.50–2.33 (3H, m, CH3), 2.25–2.09 (1H, m, CH3), 2.20 (6H, s, N(CH3)2), 13C{1H} NMR (101 MHz, CDCl3) δ 166.1, 135.6 (d, JFC = 21 Hz), 134.8 (d, JFC = 2 Hz), 133.1, 132.6, 129.7, 129.6, 128.3, 128.1, 126.1 (d, JFC = 14 Hz), 125.9 (d, JFC = 2 Hz), 98.8 (d, JFC = 180 Hz), 68.4 (d, JFC = 25 Hz), 53.7 (d, JFC = 3 Hz), 45.5, 33.7 (d, JFC = 24 Hz), 21.8 (d, JFC = 8 Hz); 19F NMR (376 MHz, CDCl3) δ −157; HRMS (ESI): calcd for C30H32F3O2N [M + H]+ 320.2220, found 320.2214.

**Author contributions**

E. T. was supervisor of this project and conducted all area of this work, idea, development of the methodology, a part of experiments and writing the manuscript. K. K. performed the main experiments and compounds analyses.

**Conflicts of interest**

There are no conflicts to declare.

**Notes and references**

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