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The role of organic fluorine in directing alkylation reactions via lithium chelation

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Abstract

The fluorine of a fluoromethyl group displays a measurable chelation effect to lithium during α-methylation of an ester with lithium diisopropylamide (LDA) and methyl iodide. A series of esters is compared with F, H and O, and the resultant diastereoselectivity is consistent with the intermediate capacity of F to chelate lithium relative to H and O. In a second system which involved comparing a tertiary organic fluorine with hydrogen, no such effect is apparent, most probably due to adverse steric effects. The absolute and relative stereochemistry of the predominant diastereoisomers are confirmed by X-ray crystallography of suitable crystalline derivatives in each case. It is concluded that there is a potential role for organic-bound fluorine to become involved in lithium chelation in well-designed enolate alkylation systems.

Keywords: Lithium enolates; Organic fluorine; Diastereoselectivity

1. Introduction

The ability of carbon-bound oxygen to chelate to lithium is a central tenet in organic chemistry and the strategy has been used widely to design pre-organisation into chemical reactions [1–6]. Of course carbon-bound hydrogen is not an obvious candidate for coordination to lithium and other metal cations and is not a useful atom for designing pre-organisation into a reaction system. In this paper, we explore the ability of organic-bound fluorine to influence the stereoselectivity of lithium enolate reactions. In this regard, an organic fluorine is an intermediate between oxygen and hydrogen, and there have been some recent reports that it performs very well as a lithium chelator in asymmetric alkylation reactions [7–11]. Of course organic bound fluorine is not an immediately obvious candidate for lithium chelation particularly as it is a moderate to poor hydrogen bonding acceptor [12,13]. Probably the most impressive results have been reported by Yamazaki et al. [14] who have demonstrated convincingly in an experimental system that the fluorine of a fluoromethyl group can induce a diastereoselectivity of 82–90% de (diastereomeric excess) in the products **5**–**7** after the methylation reactions illustrated in Scheme 1. The de's were higher for other alkylations involving benzyl bromide and allyl iodide. In the case of **1**, it is only the replacement of F for H which can account for this diastereoselectivity, and it was argued that fluorine is chelating lithium in the bicyclo[3.3.0] intermediate enolate **4** as shown in Scheme 1. The stereogenic centre in these substrates is a tertiary ether and the steric influence of this tertiary centre is clearly significant and contributes in part to the efficiency of chirality transfer in these reactions.

Prompted by these reports, and a by general focus on evaluating the experimental influence of fluorine in organic chemistry, it appeared appropriate to examine a series of enolates whereby the substrate varies only at a remote site. It was a particular focus of this study to examine the relative coordination of H, F and O in a given series. Two such studies are reported. In the first case, the substrates varied by changing the CH_2-X group attached to a secondary ether and it was envisaged that the enolate intermediates in this reaction may find stabilisation by coordination to the X group. In a second study, we report results which have

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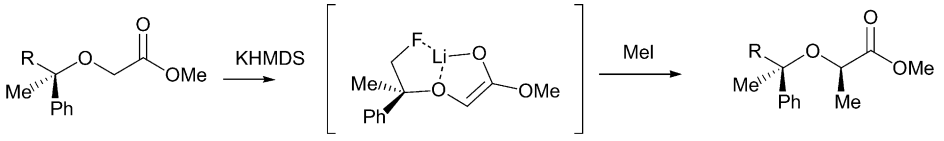


R = CH_2F, **1**
R = CF_2H, **2**
R = CF_3, **3**

4

R = CH_2F, **5**, 82% de
R = CF_2H, **6**, 88%de
R = CF_3, **7**, 90%de

Scheme 1.

X = H **8**, OMe **9**, O-*i*Pr **10**, O-*t*Bu **11**, F **12**.

13

Fig. 1. Substrate structures.

explored the ability of organic-bound fluorine, relative to hydrogen, to influence the diastereoselectivity in a much more sterically congested substrate system.

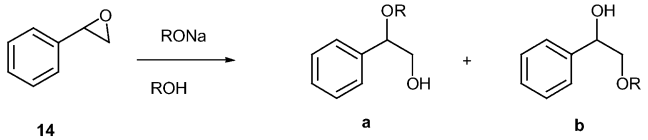
2. Results and discussion

Benzyl ethers **8–13** (Fig. 1) were selected for this study as they represented substrates which could be readily alkylated (methylated) after treatment with LDA, and as a series they allowed the exploration of the relative abilities of oxygen, hydrogen and fluorine (at the X-site) to coordinate to lithium in the intermediate enolate. Also these compounds were accessible by straightforward synthesis protocols (see Schemes 2,3 and 4).

2.1. Synthesis of benzyl ether substrates 8–13

The substrates for the study were prepared by a straightforward Williamson's ether protocol [15] between the relevant benzyl alcohol and ethyl iodoacetate. For substrates **9–11** the relevant benzyl alcohols **15–17** were prepared by alkoxide ring opening of styrene oxide [16].

These reactions gave a mixture of regioisomers **a** and **b**, as shown in Scheme 2. Regioisomer **b** was identified as a major product in all of the cases studied. The regioisomers were readily separated by chromatography and the major regioisomers **15–17** were isolated and used further in this



14

a

b

R = Me (a : b, 1 : 4) **15**
R = *i*-Pr (a : b, 1 : 9) **16**
R = *t*-Bu (a : b, 1 : 3) **17**

Scheme 2.

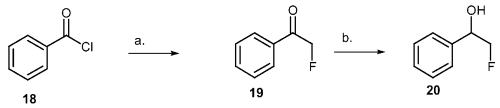
study. In order to prepare the monofluorinated substrate **12**, benzyl alcohol **20** was prepared from benzoyl chloride **18** by treatment with diazomethane and then HF–pyridine [17]. Sodium borohydride reduction of the resultant α-fluoroacetophenone **19** gave alcohol **20** as illustrated in Scheme 3.

Compounds **9–13** were then subjected to the methylation reactions. They are all α-substituted benzylic ethers, however the benzylic α-ether substituents differ in size and coordinating ability.

Benzyl ether **8** (where X = H) was used as the reference substrate in the methylation reaction as there was no expectation that hydrogen would chelate the lithium enolate during alkylation. Consistent with this, the resultant product was found to be a 1:1 mixture of diastereoisomers. On the other hand, it was anticipated that the good donor properties of oxygen would facilitate oxygen to lithium chelation and influence the diastereoselectivity. In the event, this proved to be the case and interestingly the isopropyl ether **10** displayed the highest diastereoselectivity. The smaller methyl and larger *t*-butyl ether substrates **9** and **11** were less good and it would appear that the optimal diastereoselectivity resulted due to a balance between the steric influence and coordination ability of the different ethers.

The diastereomeric excesses of the mono- and tri-fluoro benzyl ethers **12** and **13** [18] were studied and the results are shown in Table 1. In both cases, the diastereoselectivity was the same at 33% de. A direct comparison of substrates **12** and **8** indicates the influence of the F over H and clearly the incorporation of a single fluorine atom has had a significant and beneficial effect, but not as significant as the oxygen series. This is exactly in keeping with our preconceived understanding of the relative donor abilities of oxygen, fluorine and hydrogen. The result for substrate **13** indicated no apparent benefit in increasing the number of fluorine atoms at the potential coordination site (see Table 1).

In view of the high diastereoselectivity observed in the methylation of isopropyl ether **10**, an assessment of the



18

19

20

Scheme 3. (a) (i) CH_2N_2, $(CH_3CH_2)_2O$; (ii) HF Py (70/30), 39%; (b) $NaBH_4$, CH_3OH, 99%.

Table 1
Diastereoselectivities of methylation reactions with substrates **8–13**

Substrate	Product R	Diastereomeric ratio (dr): (a) NMR/(b) GC–MS	Diastereomeric excess (%de)
8	CH_3 (**21**)	1:1 (b)	–
9	CH_2OMe (**22**)	1:5 (b)	67
10	CH_2O–i-Pr (**23**)	1:15 (b)	88
11	CH_2O–*t*-Bu (**24**)	1:2.6 (a)	44
12	CH_2F (**25**)	1:2 (a)	33
13	CF_3 (**26**)	1:2 (a)	33

All de values of the methylation products **21–26** were determined by ^1H NMR/GC–MS analyses of crude reaction products.

preferred relative stereochemistry of the methylation reaction was explored by using an enantiomerically pure substrate of known absolute configuration. Sequential treatment of the styrene oxide (*R*)-**14** with sodium isopropoxide and ethyl iodoacetate furnished (*R*)-**10** as illustrated in Scheme 5. The methylated ester product (*R*,*R*)-**23** was then reduced to alcohol (*R*,*R*)-**27** by treatment with lithium aluminium hydride, followed by a Jones oxidation to access the carboxylic acid (*R*,*R*)-**28**. Preparation and recrystallisation of the major diastereoisomer of the morpholinium salt (*R*,*R*)-**29** of carboxylic acid (*R*,*R*)-**28** afforded a suitable crystal for X-ray structure analysis and this revealed the (*R*,*R*) absolute configuration of the product. The resultant structure is shown in Fig. 2.

2.2. A sterically more hindered system

In order to try to extend the lithium enolate alkylation strategy, a sterically more complex system was investigated. Thus the diastereoselectivity of the methylation of the amine esters **34** and **43**, which we envisaged may proceed via enolate intermediates **35** and **44**, respectively, as shown in Schemes 6 and 7, was explored.

The aminoester substrates **34** and **43** were prepared from the commercially available amines **30** and **39**, respectively. The routes to the hydro and fluoro analogues **34** and **43** follow each other closely and are outlined in Schemes 6 and 7, respectively. In the event, it was apparent from product analysis after the methylation reactions that the non-fluorinated aminoester **34** generated product **36** with a higher de (60%, ratio 4:1) than the fluorinated amine **41**, which gave product **43** with a diasteroisomeric ratio of 2: 1. Thus the fluorinated substrate performed less well.

The benzyl group of **36** was removed to give **37** and the hydrochloride **38** was generated after treatment with hydrochloric acid. Recrystallisation of hydrochloride **38** amplified the predominant diastereoisomer in that series and X-ray diffraction analysis of a suitable crystal of the major stereoisomer revealed the absolute and relative configuration of **38** as shown in Scheme 6 and Fig. 3.

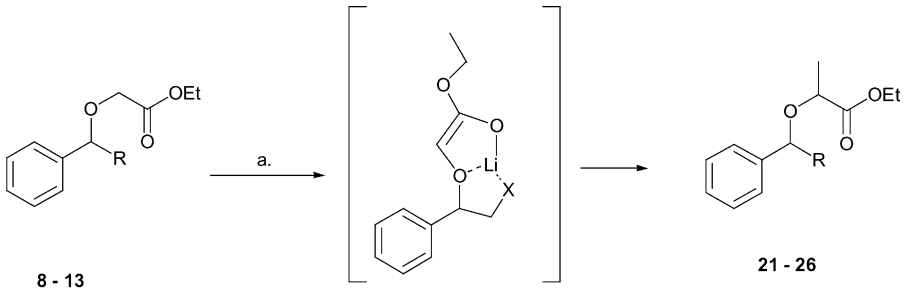
It was anticipated that the intermediate enolate **44** derived from **43** may find additional stabilisation by lithium chelation to fluorine and that this may increase the diastereoselectivity of the methylation reaction. In the event the fluorinated analogue showed a poorer diastereoselectivity when compared with **34**, the non-fluorinated analogue, although we do not know if the predominant diasteroisomer has the same relative configuration as that established for **36**.

3. Conclusions

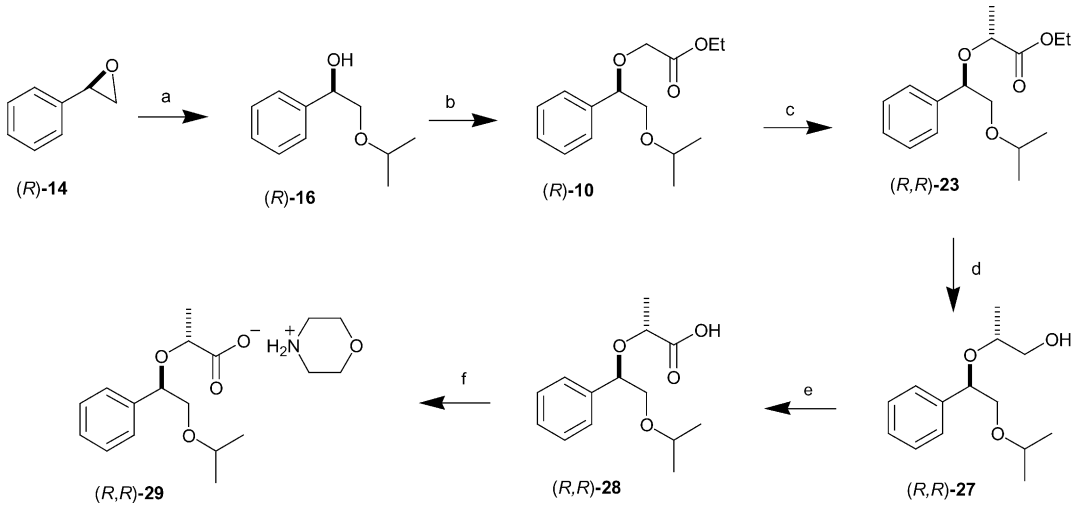
In summary, this study has shown that there is a clear fluorine effect in an alkylation model involving a fluoromethyl group as a component of a lithium enolate derived from a secondary ether functionality. The effect of the fluorine on the resultant diastereoselectivity of a methylation reaction is modest for **12** and **13** relative to the oxygen substituents in **9** and **10**. A second study with substrates **34** and **35** compared H with F at a tertiary centre and indicated a small but measurable difference in the performance of the chiral auxiliary. It is concluded that the fluorine atom can influence the efficacy of a chiral auxiliary most probably due to a coordination ability to lithium.

4. Experimental

Air- and moisture-sensitive reactions were carried out under a positive pressure of nitrogen in oven-dried (200 °C) glassware. Room temperature (RT) refers to 20–25 °C. Evaporations were carried under reduced pressure on a Büchi rotary evaporator. All reagents were of synthetic grade and were used without further purification. Solvents



Scheme 4. (a) CH_3I, LDA, THF.



Scheme 5. Reagents: (a) $(CH_3)_2CHOH$, NaH, 92%; (b) ICH_2COEt, THF, 73%; (c) MeI, LDA, THF, 87%; (d) $LiAlH_4$, THF, 100%; (e) Jones's reagent, 96%; (f) Morpholine, hexane, 100%.

and reagents were dried according to standard methods prior to use.

Optical rotations were measured using Optical Polarimeter Ltd. A-1000 as solutions in dichloromethane (CH_2Cl_2). Specific rotations are given in units of $10^{-1\circ}$ g^{-1} dm^{-1}. High-resolution mass spectra were recorded on VG AUTOSPEC and VG PLATFORM spectrometers.

Infrared spectra were recorded with Perkin Elmer 2000 FTIR instrument as a thin layer between NaCl disks. Solid materials were prepared with KBr pellets. Values were rounded to 5 cm^{-1}. Melting points were measured on a Gallenkamp Griffin MPA350.BM2.5 melting point apparatus.

Nuclear magnetic resonance (NMR) spectra were measured for $CDCl_3$ solutions on a Bruker Av-300.00 (7.0 T) operating at 300.00 MHz for ^1H, 75.45 MHz for ^{13}C and 282.4 for ^{19}F, and Varian Unity Plus 300 MHz operating at 300.00 MHz for ^1H, 75.43 MHz for ^{13}C. All chemical shifts are reported as δ values down-fielded from $(CH)_4Si$ using $CDCl_3$ as internal standard (δ_H 7.24 or δ_C 77.00 ppm, for ^1H and ^{13}C, respectively) and $CFCl_3$ (0.00 ppm) for ^{19}F. All coupling constants (J) are given in hertz (Hz). Spectral coupling patterns are designated as follows: s: singlet; d: doublet; t: triplet; q: quartet; m: multiplet; br; broad signal. The assignments of the signals in the ^1H NMR spectra are based on the first-order analysis of the spin systems and when required were confirmed by $^1H\{^1H\}$ decoupling and two-dimensional (2D) (^1H, ^1H) homonuclear chemical shift correlation (COSY) experiments. The ^{13}C chemical shifts were obtained from proton-decoupled spectra. Standard Bruker pulse sequence programs were used in these experiments.

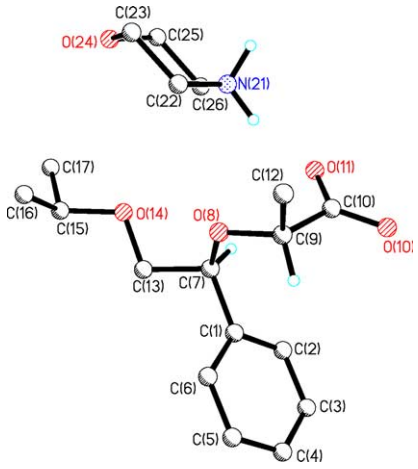


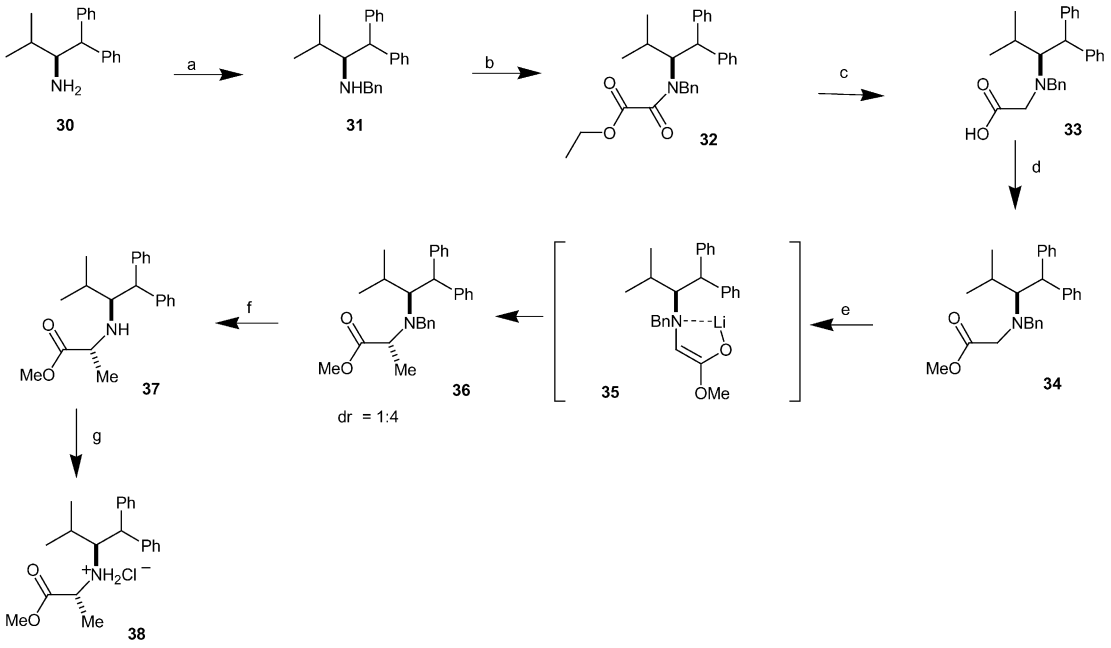
Fig. 2. ORTEP structure of (*R*,*R*)-**29** used to assess the predominant relative configuration for methylation of substrate **10**.

Reaction progress was monitored on thin-layer chromatography (TLC) using glass plates coated with silica gel 60 F_{254} (Merck). Plates were visualised under UV light (254 and 366 nm). Column chromatography was performed on Merck silica gel 60 (60–200 μm, 70–230 mesh).

Standard work-up procedure: The reaction mixture was quenched with water and the aqueous layer extracted into diethyl ether (3×). The organics were dried over $MgSO_4$, filtered and concentrated under reduced pressure. * denotes minor diastereoisomer whenever identifiable.

4.1. Procedures

General procedure for the preparation of alcohols **8**–**10** from styrene oxide followed a previously described method [16]. Yields and analytical data for the resultant products were as follows.



Scheme 6. Reagents: (a) PhCHO, $NaCNBH_3$, $CH_3OH{\cdot}HCl$, 82%; (b) $ClCOCO_2C_2H_3$, Et_3N, CH_2Cl_2, 99%; (c) (i) NaOH, ethanol, Δ; (ii). $BH_3{\cdot}THF$, Δ, AcOH, 60%; (d) CH_2N_2, Et_2O, 100%; (e) LDA, CH_3I, THF, 68%; (f) $Pd(OH)_2/C$ (20%)/CH_3OH, 100%; (g) HCl (anhydrous).

*4.1.1. 2-Methoxy-1-phenylethanol (**15**)*

The product (1.7 g, 67%) was recovered as a colourless oil. IR (neat); ν 3425, 2893, 1453, 1195, 1120; ^{1}H NMR: δ 3.22 (1H, br s, OH), 3.23 (3H, s, OCH_3), 3.35 (1H, dd, $J = 8.8$, 9.9, CH_2OCH_3), 3.45 (1H, dd, $J = 3.3$, 9.9, CH_2OCH_3), 4.79 (1H, dd, $J = 3.3$, 8.8) and 7.19–7.28 (5H, m, Ph); ^{13}C NMR: δ 59.4 (OCH_3), 73.0 (PhCH), 78.6 (CH_2OCH_3), 126.5 (C-2 of Ph), 128.2 (C-4 of Ph), 128.9 (C-3 of Ph) and 140.7 (C-1 of Ph); MS (CI) *m/z* (rel. int.): 152 $[M]^+$ (7), 135 $[M - H_2O]^+$ (100), 121 $[M - OCH_3]^+$ (7), 107 $[M - CH_2OCH_3]^+$ (8).

*4.1.2. 2-Isopropoxy-1-phenylethanol (**16**)*

The product (1.35 g, 90%) was recovered as a colourless oil. IR (neat); ν 3459, 2973, 1755, 1453, 1199, 1129; ^{1}H NMR: δ 1.21 [3H, d, $J = 6.0$, $OCH(CH_3)_2$], 1.22 [3H, d, $J = 6.0$, $OCH(CH_3)_2$], 2.99 (1H, br s, OH), 3.39 [1H, m, $OCH(CH_3)_2$], 3.62 [1H, dd, $J = 3.1$, 9.6, $CH_2OCH(CH_3)_2$], 3.69 [1H, dd, $J = 6.1$, 9.6, $CH_2OCH(CH_3)_2$], 4.86 (1H, dd, $J = 3.1$, 9.6, PhCH) and 7.27–7.42 (5H, m, Ph); ^{13}C NMR: δ 21.9 [$OCH(CH_3)_2$], 72.1 [$OCH(CH_3)_2$], 73.7 (PhCH), 73.8 [$CH_2OCH(CH_3)_2$], 126.0 (C-2 of Ph), 127.6 (C-4 of Ph), 128.2 (C-3 of Ph) and 140.3 (C-1 of Ph); MS (CI) *m/z* (rel. int.): 163 $[MH - H_2O]^+$ (100), 121 $[MH - i\text{-}PrOH]^+$ (30).

*4.1.2.1. (R)-Isopropoxy-1-phenylethanol (R)-**16**.* The product (1.20 g, 92%) was recovered as a colourless oil, $[\alpha]_D^{20} = -71.1$ (ca. 0.65, CH_2Cl_2), with identical spectroscopic data to **16**.

*4.1.3. 2-tert-Butoxy-1-phenylethanol (**17**) [19]*

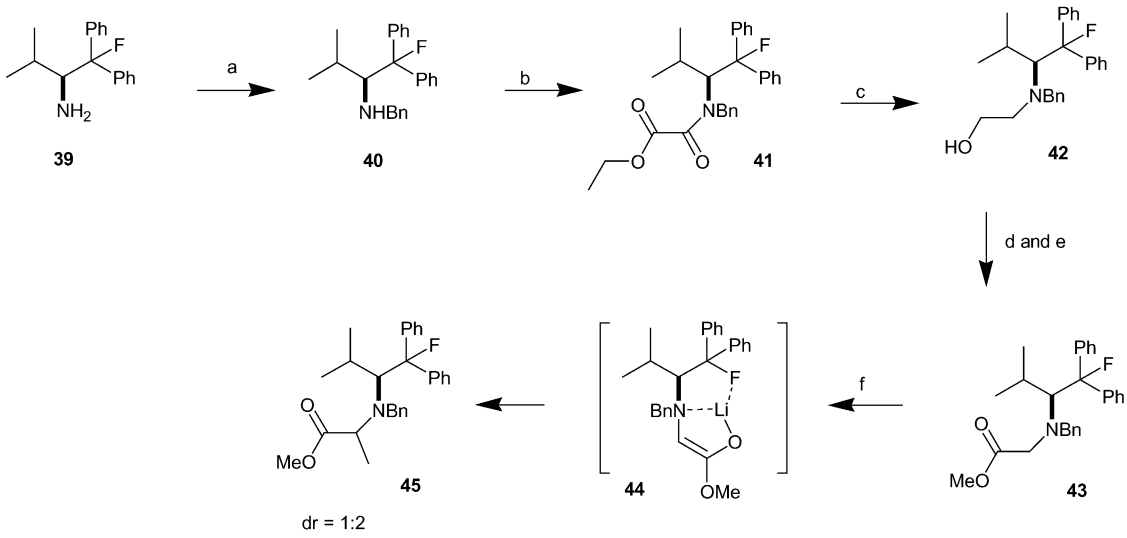
The product (1.10 g, 68%) was recovered as a colourless oil, IR (neat); ν 3452, 2975, 1453, 1364, 1199; ^{1}H NMR: δ 1.13 [9H, s, $OC(CH_3)_3$], 3.02 (1H, br s, OH), 3.24 [1H, dd, $J = 9.0$, 9.2, $CH_2OC(CH_3)_3$], 3.43 [1H, dd, $J = 3.1$, 9.0, $CH_2OC(CH_3)_3$], 4.71 (1H, dd, $J = 3.1$, 9.2, PhCH), 7.19–7.33 (5H, m, Ph); ^{13}C NMR: δ 27.5 [$OC(CH_3)_3$], 67.8 [$CH_2OC(CH_3)_3$], 73.1 (PhCH), 73.5 [$OC(CH_3)_3$], 126.1 (C-3 of Ph), 127.6 (C-4 of Ph), 128.2 (C-2 of Ph), 140.5 (C-1 of Ph), MS (EI) *m/z* (rel. int.): 216.8 $[M + Na]^+$ (100).

*4.2. General procedure A: preparation of benzyl alcohols (**8**–11)*

A stirred solution of 1-phenylethanol **15**–**17** (810 mg, 5.32 mmol) in THF (20 ml) was treated with sodium hydride (255 mg, 6.4 mmol). After 15 min, ethyl iodoacetate was added and the reaction stirred for a further 5 h at rt. The products were isolated following the standard work-up procedure. The products were recovered after silica gel chromatography.

*4.2.1. Ethyl(1-phenylethoxy)acetate (**8**)*

The product was prepared following general procedure A from 1-phenylethanol (500 mg, 4.09 mmol), sodium hydride (150 mg, 6.14 mmol) and ethyl iodoacetate (1.14 g, 5.33 mmol) in THF (15 ml) to afford the title compound as a colourless oil (830 mg, 98%). IR (neat): ν 2981, 1754, 1452, 1133, 1119; ^{1}H NMR: δ 1.25 (3H, t, $J = 7.2$, OCH_2CH_3), 1.52 (3H, d, $J = 6.4$, $OCHCH_3$), 3.87 (1H, d, $J = 16.4$, OCH_2CO), 3.96 (1H, d, $J = 16.4$, OCH_2CO), 4.18



Scheme 7. Reagents: (a) and (b) as in Scheme 5 above; (c) $LiAlH_4$/THF, Δ, 100%; (d) (i) Dess-Martin periodinate, DCM, 100% (crude), (ii) $NaOCl_2$, KH_2PO_4/H_2O, $CH_3CH{=}C(CH_3)_2$, *t*-BuOH, 30%; (e) CH_2N_2/Et_2O, 100%; (f) CH_3I, LDA/THF, 60%.

(2H, q, J = 7.2, OCH_2CH$_3$), 4.56 (1H, q, J = 6.4, PhC*H*) and 7.32–7.35 (5 H, m, Ph); ^{13}C NMR: δ 14.0 (OCH$_2$*C*H$_3$), 23.7 (OCH*C*H$_3$), 60.6 (O*C*H$_2$CH$_3$), 65.7 (O*C*H$_2$CO), 78.4 (Ph*C*H), 126.3 (C-3 of Ph), 127.7 (C-4 of Ph), 128.4 (C-2 of Ph), 142.3 (C-1 of Ph) and 170.4 (CO); MS (EI) *m*/*z* (rel. int.): 230.8 $[M + Na]^+$ (100); HRMS (EI) Calc. for $C_{12}H_{16}O_3$ + Na: 231.0997, Found 231.1001.

4.2.2. *Ethyl(2-methoxy-1-phenylethoxy)acetate (**9**)*

The product (980 mg, 77%) was recovered as a colourless oil. IR (neat): ν 2983, 1754, 1453, 1306, 1202, 1130; ^{1}H NMR: δ 1.16 (3H, dd, J = 7.2, OCH$_2$C*H*$_3$), 3.33 (3H, s, OCH$_3$), 3.42 (1H, d, J = 3.4, 10.7, C*H*$_2$OCH$_3$), 3.65 (1H, dd, J = 7.9, 10.7, C*H*$_2$OCH$_3$), 3.89 (1H, d, J = 16.4, OC*H*$_2$CO), 4.02 (1H, d, J = 16.4, OC*H*$_2$CO), 4.08 (2H, m, OC*H*$_2$CH$_3$), 4.62 (1H, dd, J = 3.4, 7.9, PhC*H*) and 7.26–7.28 (5H, m, Ph); ^{13}C NMR: δ 14.5 (OCH$_2$*C*H$_3$), 59.5 (OCH$_3$), 61.1 (O*C*H$_2$CH$_3$), 66.5 (O*C*H$_2$CO), 77.5 (*C*H$_2$OCH$_3$), 81.7 (Ph*C*H), 127.5 (C-2 of Ph), 128.7 (C-4 of Ph), 128.9 (C-3 of Ph), 138.4 (C-1 of Ph) and 170.6 (CO), MS (CI) *m*/*z* (rel. int.): 239 $[MH]^+$ (8), 207 $[MH - HOCH_3]^+$ (20), 193 $[MH - CH_3CH_3]^+$ (25), 135 $[MH - HOCH_2CO_2Et]^+$ (100); HRMS (CI) Calcd. for $C_{13}H_{19}O_4$: 239.1295, Found 239.1283.

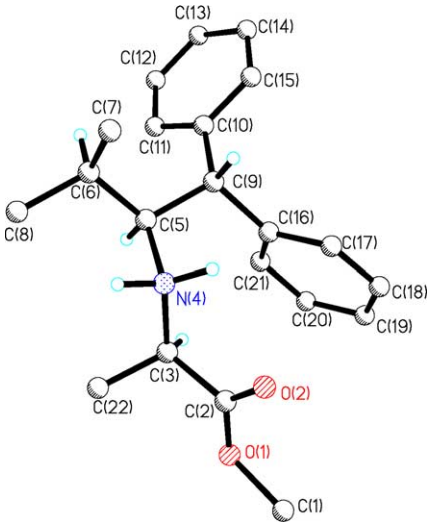


Fig. 3. ORTEP structure of hydrochloride **38**.

4.2.3. *Ethyl(2-isopropoxy-1-phenylethoxy)acetate (**10**)*

The product (400 mg, 73%) was recovered as a colourless oil. IR (neat): ν 2974, 1756, 1453, 1380, 1202, 1130; ^{1}H NMR: δ 1.04 [3H, d, J = 6.1, OCH(C*H*$_3$)$_2$], 1.08 [3H, d, J = 6.0, OCH(C*H*$_3$)$_2$], 1.17 (3H, t, J = 7.2, OCH$_2$C*H*$_3$), 3.47 [1H, dd, J = 4.1, 10.6, C*H*$_2$OCH(CH$_3$)$_2$], 3.68 [1H, dd, J = 7.4, 10.6, C*H*$_2$OCH(CH$_3$)$_2$], 3.92 (1H, d, J = 16.4, OC*H*$_2$CO), 4.06 (1H, d, J = 16.4, OC*H*$_2$CO), 4.10 (2H, q, J = 7.2, OC*H*$_2$CH$_3$), 4.54 (1H, dd, J = 4.1, 7.4, PhC*H*) and 7.19–7.29 (5 H, m, Ph); ^{13}C NMR: δ 14.1 (OCH$_2$*C*H$_3$), 21.9 [OCH(*C*H$_3$)$_2$], 22.0 [OCH(*C*H$_3$)$_2$], 60.6 (O*C*H$_2$CH$_3$), 66.5 (O*C*H$_2$CO), 72.1 [O*C*H(CH$_3$)$_2$], 72.7 [*C*H$_2$OCH(CH$_3$)$_2$], 82.0 (Ph*C*H), 127.1 (C-3 of Ph), 128.0 (C-4 of Ph), 128.3 (C-2 of Ph), 138.6 (C-1 of Ph) and 170.3 (CO); MS (CI) *m*/*z* (rel. int.): 267 $[MH]^+$ (13), 193 $[MH - CH_3CH(CH_3)_2]^+$ (22), 163 $[MH - HOCH_2CO_2Et]^+$ (100), 121 $[MH - CH_3CO_2Et - iPrOH]^+$ (45); HRMS (CI) Calc. for $C_{15}H_{23}O_4$: 267.1596, Found 267.1603.

4.2.3.1. *(R)-Ethyl(isopropoxy-1-phenylethoxy)acetate (R)-**10***

The product (700 mg, 90%) was recovered as a colourless oil $[\alpha]_D^{20} = -48.0$ (ca. 0.10, CH_2Cl_2), with identical spectroscopic data to **10**.

*4.2.4. Ethyl(2-tert-butoxy-1-phenylethoxy)acetate (**11**)*

The product (182 mg, 73%) was recovered as a colourless oil. IR (neat): ν 2976, 1732, 1307, 1198, 1133; ^{1}H NMR: δ 1.12 [9H, s, OC(CH$_3$)$_3$], 1.24 (3H, t, J = 7.2, OCH$_2$C*H*$_3$), 3.47 [1H, dd, J = 4.6, 9.9, C*H*$_2$OC(CH$_3$)$_3$], 3.71 [1H, dd, J = 6.9, 9.9, C*H*$_2$OC(CH$_3$)$_3$], 4.05 (1H, d, J = 16.4, OC*H*$_2$CO), 4.17 (1H, d, J = 16.4, OC*H*$_2$CO),4.26 (2H, q, J = 7.2, OC*H*$_2$CH$_3$), 4.54 (1H, dd, J = 4.6, 6.9, PhC*H*), 7.03–7.36 (5H, m, Ph); ^{13}C NMR: δ 14.1 (OCH$_2$*C*H$_3$), 27.3 [OC(CH$_3$)$_3$], 60.5 (OCH$_2$CH$_3$), 66.8 [*C*H$_2$OC(CH$_3$)$_3$], 67.9 (OCH$_2$CO), 73.1 [O*C*(CH$_3$)$_3$], 82.3 (Ph*C*H), 127.1 (C-3 of Ph), 128.0 (C-4 of Ph), 128.2 (C-2 of Ph), 139.0 (C-1 of Ph), 170.4 (CO); MS (CI) *m*/*z* (rel. int.): 281 [MH]$^+$ (23), 255 [MH − CH(CH$_3$)$_3$]$^+$ (66), 207 [MH − HOC(CH$_3$)$_3$]$^+$ (10), 121 [MH − CH$_3$CO$_2$Et − HOC(CH$_3$)$_3$]$^+$ (10); HRMS (CI) Calc. for C$_{16}$H$_{25}$O$_4$: 281.1753, Found 281.1755.

*4.3. General procedure B: preparation of methylated benzyl alcohols (**21** and **22**)*

A solution of LDA (2 M) in THF (49.5 mg, 0.462 mmol) was slowly added to a solution of ethyl(2-alkoxy-phenylethoxy)acetate **21**–**26** (100 mg, 420 mmol) in THF (3.0 ml) at −78 °C. The solution was stirred for 30 min before methyl iodide (72 mg, 0.507 mmol) was introduced. The reaction was allowed to warm to ambient temperature and was stirred for 12 h. The products were isolated by solvent extraction and silica gel chromatography.

*4.3.1. Ethyl-2-(2-methoxy-1-phenylethoxy)propanoate (**22**)*

The product (75 mg, 68%) was isolated as a colourless oil. IR (neat): ν 2974, 1747, 1454, 1368, 1200, 1126, 912; ^{1}H NMR: δ 1.22 (3H, t, J = 7.2, OCH$_2$C*H*$_3$), 1.31 and 1.37* (3H, d, J = 6.9, OCHC*H*$_3$), 3.32 (3H, s, OCH$_3$), 3.38 (1H, dd, J = 4.1, 10.5, C*H*$_2$OCH$_3$), 3.63 (1H, dd, J = 7.2, 10.5, C*H*$_2$OCH$_3$), 3.81 (1H, q, J = 6.9, OC*H*CH$_3$), 4.13 (2H, q, J = 7.2, OC*H*$_2$CH$_3$), 4.58 (1H, dd, J = 4.1, 7.2, PhC*H*) and 7.26–7.27 (5H, m, Ph); ^{13}C NMR: δ 14.2 (CH$_2$*C*H$_3$), 18.2* and 19.0 (O*C*HCH$_3$), 59.1 (OCH$_3$), 60.7 (O*C*H$_2$CH$_3$), 72.3 (O*C*HCH$_3$), 74.2 (*C*H$_2$OCH$_3$), 80.3 and 80.9* (Ph*C*H), 127.1 (C-2 of Ph), 128.2 (C-4 of Ph), 128.5 (C-3 of Ph), 138.9 (C-1 of Ph) and 172.2 (CO); MS (CI) *m*/*z* (rel. int.): 253 [MH]$^+$ (338), 193 [HOCH$_2$-CO$_2$Et − CH$_4$]$^+$ (100); HRMS (CI) Calc. for C$_{14}$H$_{20}$O$_4$: 253.3062, Found 253.3059.

*4.3.2. Ethyl-2-(2-isopropoxy-1-phenylethoxy)propanoate (**23**)*

The product (74 mg, 85%) was isolated as a colourless oil. IR (neat): ν 2973, 1748, 1454, 1369, 1127; ^{1}H NMR: δ 0.99 [3H, d, J = 6.1, OCH(C*H*$_3$)$_2$], 1.04 [3H, d, J = 6.1, OCH(C*H*$_3$)$_2$], 1.21 (3H, t, J = 7.2, OCH$_2$C*H*$_3$), 1.28 and 1.39* (3H, d, J = 6.9, OCHC*H*$_3$), 3.41 [1H, dd, J = 5.4, 10.5, *CH*$_2$OCH(CH$_3$)$_2$], 3.46 [1H, dd, J = 5.4, 10.5, C*H*$_2$-OCH(CH$_3$)$_2$], 3.50 [1H, dd, J = 6.1, 10.5, CH$_2$OC*H*(CH$_3$)$_2$], 3.84 (1H, q, J = 6.9, OC*H*CH$_3$), 4.13 (2H, q, J = 7.2, OC*H*$_2$CH$_3$), 4.48 (1H, dd, J = 5.4, 6.1, PhC*H*) and 7.24–7.27 (5H, m, Ph); ^{13}C NMR: δ 13.6* and 14.2 (OCH$_2$*C*H$_3$), 18.3* and 19.0 (OCH*C*H$_3$), 21.9 [OCH(*C*H$_3$)$_2$], 60.6 (O*C*H$_2$CH$_3$), 72.4 [O*C*H(CH$_3$)$_2$], 72.5 [*C*H$_2$OCH(CH$_3$)$_2$], 72.5 (O*C*H$_2$CH$_3$), 80.9 and 81.4* (Ph*C*H), 127.1 (C-2 of Ph), 127.9 (C-4 of Ph), 128.3 (C-3 of Ph), 139.5 (C-1 of Ph) and 173.3 (CO); de = 88%; MS (CI) *m*/*z* (rel. int.): 281 [MH]$^+$ (5), 207 [MH − CH$_3$OCHCH$_2$]$^+$ (10), 163 [MH − HOCH-(CH$_3$)CO$_2$Et]$^+$ (75), 121 [MH − CH$_3$CH$_2$CO$_2$Et]$^+$ (22), 58 [MH − PhCH(OH)CH$_2$OCHCH$_2$]$^+$ (100); HRMS (CI) Calc. for C$_{16}$H$_{25}$O$_4$: 281.1753, Found 281.1762.

*4.3.2.1. (R)-Ethyl-(2-isopropoxy-1-phenylethoxy)propanoate (R,R)-**23**.* The product (215 mg, 87%) was isolated as a colourless oil, $[\alpha]_D^{20}$ = −82.8 (ca. 0.83, CH$_2$Cl$_2$), and had spectroscopic data identical to **23**.

*4.3.2.2. (2R)-2-(1′R)-(2-Isopropoxy-1-phenylethyl)oxypropanol (**27**).* A solution of (*R*)-**23** (180 mg, 0.642 mmol) in THF (5 ml) was added to a suspension of lithium aluminium hydride (24 mg, 0.642 mmol) in THF (10 ml). The mixture was heated under reflux for 16 h before being quenched with ethyl acetate and water. Filtration afforded the title product (153 mg, 100%) as a colourless oil. IR (neat): ν; ^{1}H NMR: δ 1.06 (3H, d, J = 6.1, CH$_3$), 1.20 [3H, d, J = 6.1, OCH(C*H*$_3$)$_2$], 1.22 [3H, d, J = 5.9, OCH(C*H*$_3$)$_2$], 3.46–3.56 (3H, m, C*H*$_2$OH, OC*H*CH$_3$), 3.61–3.75 [3H, m, OC*H*(CH$_3$)$_2$, C*H*$_2$OCH(CH$_3$)$_2$], 4.72 (1H, dd, J = 3.6, 9.0, PhC*H*), 7.28–7.38 (5H, m, Ph); ^{13}C NMR: δ 18.0 (CH*C*H$_3$), 21.7 [OCH(*C*H$_3$)$_2$], 21.9 [OCH(*C*H$_3$)$_2$], 67.1 (CH$_2$OH), 72.5 [O*C*H(CH$_3$)$_2$], 73.6 [O*C*H$_2$(*C*H$_3$)$_2$], 77.6 (O*C*HCH$_3$), 82.3 (Ph*C*H), 126.3 (C-3 of Ph), 127.7 (C-4 of Ph), 128.3 (C-2 of Ph), 140.0 (C-1 of Ph); MS (CI) *m*/*z* (rel. int.): 239 [MH]$^+$ (12), [MH − Ph]$^+$ (100); HRMS (CI) Calc. for C$_{14}$H$_{23}$O$_3$: 239.1647, Found 239.1647.

*4.3.2.3. (2R)-2-(1′R)-2-Isopropoxy-1-phenylethyloxypropanoic acid (**28**).* Alcohol **27** (130 mg, 0.545 mmol) was oxidised with Jones's regent [CrO$_3$, H$_2$SO$_4$ (50%), acetone:water (3:1)] after stirring at ambient temperature for 5 h. Isopropanol was added and the product was isolated following solvent extraction and chromatography to give carboxylic acid **28** (132 mg, 96%) as a colourless oil. Treatment of **28** with morpholine (95 μl, 1.09 mmol) in hexane (10 ml) afforded (*R*,*R*)-**29** as a colourless crystalline solid. ^{1}H NMR: δ 1.24 [3H, d, J = 6.1, OCH(C*H*$_3$)$_2$], 1.27 [3H, d, J = 6.1, OCH(C*H*$_3$)$_2$], 1.45 (3H, d, J = 6.9, OCHC*H*$_3$), 3.50–3.61 [2H, m, OC*H*$_2$CH], 3.79 [1H, sextet, J = 6.1, OC*H*(CH$_3$)$_2$], 3.99 (OC*H*CH$_3$), 4.47 (1H, dd, J = 3.8, 9.2, PhC*H*), 7.31–7.42 (5H, m, Ph); ^{13}C NMR: δ 19.4 (OCH*C*H$_3$), 21.6 [OCH(*C*H$_3$)$_2$], 21.7 [OCH(*C*H$_3$)$_2$], 72.1 [O*C*H$_2$-CH(CH$_3$)$_2$], 73.2 [O*C*H(CH$_3$)$_2$], 75.0 (O*C*HCH$_3$), 82.9 (Ph*C*H), 126.4 (C-4 of Ph),128.7 (C-2/3 of Ph), 136.9 (C-1 of Ph), 174.8 (CO); MS (LCTOF) *m*/*z* (rel. int.): 275

$[MH + Na]^+$ (100); HRMS (CI) Calc. for $C_{14}H_{20}O_4Na$: 275.1259, Found 275.1255.

4.3.3. Ethyl-2-(2-tert-butoxy-1-phenylethoxy)propanoate (**24**)

The product (86 mg, 82%) was isolated as a colourless oil: ν 2974, 1736, 1450, 1377, 1198; ^{1}H NMR: δ 0.99 and 1.07* [9H, s, $OC(CH_3)_3$], 1.22 (3H, t, $J = 7.2$, OCH_2CH_3), 1.28 and 1.36* (3H, d, $J = 6.9$, $OCHCH_3$), 3.36 (1H, dd, $J = 4.4$, 9.5, CH_2OCH_3), 3.65 [1H, dd, $J = 7.7$, 9.5, $CH_2OC(CH_3)_3$], 3.87 (1H, q, $J = 6.9$, $OCHCH_3$), 4.14 (2H, q, $J = 7.2$, OCH_2CH_3), 4.45 (1H, dd, $J = 4.4$, 7.7, PhCH) and 7.24–7.27 (5H, m, Ph); ^{13}C NMR: δ 13.8* and 14.0 (OCH_2CH_3), 18.2* and 18.8 ($OCHCH_3$), 27.2* and 27.1 ($OC(CH_3)_3$), 60.3* and 60.4 (OCH_2CH_3), 66.3 and 67.3* (CH_2OCH_3), 72.5 and 72.9* [$OC(CH_3)_3$], 74.4 ($OCHCH_3$), 81.0 and 81.2* (PhCH), 126.7* and 127.0 (C-3 of Ph), 127.4*and 127.6 (C-4 of Ph), 127.8* and 127.9 (C-2 of Ph), 139.6* and 139.7 (C-1 of Ph) and 173.2 (CO); MS (CI) *m/z* (rel. int.): 295 $[MH]^+$ (48), 239 $[MH - CHCH_3]^+$ (91), 207 $[MH - CH_3CO_2C(CCH_3]^+$ (46), 177 $[MH - HOCH(CH_3)CO_2Et]^+$ (57), 119 $[MH - HOCH(CH_3)CO_2Et]^+$ (100); HRMS (CI) Calc. for $C_{17}H_{27}O_4$: 295.1910, Found 295.1919.

4.3.4. 2-Fluoro-1-phenylethanone (**19**) [17]

A solution of poly(hydrogen fluoride) (70/30) (3.0 ml) was added to an ethereal solution of 2-oxo-2-phenylethanediazonium at −15 °C, prepared in situ from benzoyl chloride **18** (1.0 g, 7.11 mmol) and diazomethane. The reaction was allowed to warm to room temperature and stirred for 4 h under an inert atmosphere. Water (100 ml) was added and after separation of the two phases, the aqueous layer was extracted into hexane (3× 25 ml). The organics were treated with anhydrous potassium fluoride until neutral to litmus, dried over $MgSO_4$ and concentrated under reduced pressure. Purification over silica gel afforded the product as a colourless oil (386 mg, 39%). IR (neat): ν 3065, 2938, 1707, 1598, 1451, 1318, 1286, 1234, 1089; ^{1}H NMR: δ 5.54 (2H, d, $J_{HF} = 46.8$, CH_2F), 7.46–7.96 (5H, m, Ph); ^{13}C NMR: δ 83.7 (d, $J_{CF} = 182.4$, CH_2F), 127.7 (C-3 of Ph), 128.8 (C-4 of Ph), 128.4 (C-2 of Ph), 134.1 (C-1 of Ph) and 193.3 (d, $J_{CF} = 15.3$, CO); ^{19}F NMR δ −231.5 (t, $J = 46.8$); MS (EI) *m/z* (rel. int.): 160.6 $[M + Na]^+$ (100).

4.3.5. 2-Fluoro-1-phenylethanol (**20**)

The product was prepared by treatment of 2-fluoro-1-phenylethanone **19** (300 mg, 2.14 mmol) with sodium borohydride (240 mg, 6.42 mmol) in CH_3OH (20 ml), to give the title compound (301 mg, 99%) as a colourless oil. IR (neat): ν 3406, 2893, 1495, 1454, 1101, 1012; ^{1}H NMR: δ 2.58 (1H, br s, OH), 4.32 (1H, ddd, $J = 8.0$, 9.6, $J = 46.7$, CH_2F), 4.41 (1H, ddd, $J = 3.3$, 9.6, 46.7, CH_2F), 4.91 (1H, ddd, $J = 3.3$, 8.0, 14.3, PhCH) and 7.23–7.30 (5H, m, Ph); ^{13}C NMR: δ 72.9 (d, $J_{CF} = 19.9$, PhCH), 87.1 (d, $J_{CF} = 174.2$, CH_2F), 126.3 (C-3 of Ph), 128.3 (C-4 of Ph), 128.6 (C-2 of Ph), 138.2 (C-1 of Ph); ^{19}F NMR: δ −220.8 (dt, $J = 14.3$, 46.7); MS (EI) *m/z* (rel. int.): 163.1 $[M + Na]^+$ (100).

4.3.6. Ethyl(2-fluoro-1-phenylethoxy)acetate (**12**)

The product was prepared according to general procedure A from 2-fluoro-1-phenylethanol **20** (260 mg, 1.86 mmol), sodium hydride (211 mg, 5.58 mmol) and ethyl iodoacetate (596 mg, 279 mmol) in THF (10 ml). The product (319 mg, 76%) was isolated as a colourless oil. IR (neat): ν 2983, 1755, 1455, 1135; ^{1}H NMR: δ 1.17 (3H, t, $J = 7.2$, CH_2CH_3), 3.92 (1H, d, $J = 16.4$, OCH_2CO), 4.05 (1H, d, $J = 16.4$, OCH_2CO), 4.10 (2H, q, $J = 7.2$, CH_2CH_3), 4.38 (1H, ddd, $J = 3.6$, 9.7, $J = 46.9$, CH_2F), 4.52 (1H, ddd, $J = 7.4$, 9.7, 46.9, CH_2F), 4.71 (1H, ddd, $J = 3.6$, 7.4, 15.1, PhCH) and 7.50–7.31 (5H, m, Ph); ^{13}C NMR: δ 14.0 (OCH_2CH_3), 60.7 (OCH_2CH_3), 66.1 (OCH_2CO), 80.8 (d, $J_{CF} = 19.6$, PhCH), 85.5 (d, $J_{CF} = 173.5$, CH_2F), 127.2 (C-3 of Ph), 128.6 (C-4 of Ph), 128.7 (C-2 of Ph), 135.7 (C-1 of Ph) and 169.9 (CO); ^{19}F NMR: δ −220.9 (dt, $J = 15.1$, 46.9); MS (CI) *m/z* (rel. int.): 227 $[MH]^+$ (82), 206 $[MH - HF]^+$ (16), 123 $[MH - HOCH_2CO_2Et]^+$ (63), 105 $[MH - HOCH_2$-$HOCH_2CO_2Et - HF]^+$ (100); HRMS (CI) Calc. for $C_{12}H_{16}FO_3$: 227.1083, Found 227.1080.

4.3.7. Ethyl(2,2,2-trifluoro-1-phenylethoxy)acetate (**13**) [5]

The product was prepared according to general procedure A from 2,2,2-trifluoro-1-phenylethanol (200 mg, 1.14 mmol), ethyl iodoacetate (360 mg, 1.71 mmol) and sodium hydride (55 mg, 2.28 mmol) in THF (10 ml). The product was recovered (240 mg, 80%) as a colourless oil. IR (neat): ν 2987, 1754, 1381, 1268, 1128; ^{1}H NMR: δ 1.25 (3H, t, $J = 7.2$, OCH_2CH_3), 4.03 (1H, d, $J = 16.4$, OCH_2CO), 4.19 (1H, q, $J = 7.2$, OCH_2CH_3), 4.21 (1H, d, $J = 16.4$, OCH_2CO), 4.94 (1H, q, $J_{HF} = 6.4$, PhCH) and 7.40–7.43 (5H, m, Ph); ^{13}C NMR: δ 14.0 (OCH_2CH_3), 61.1 (OCH_2CH_3), 66.0 (OCH_2CO), 78.1 (q, $J_{CF} = 31.5$, PhCH), 127.6 (q, $J_{CF} = 281.4$, CF_3), 128.4 (C-3 of Ph), 128.7 (C-2 of Ph), 129.8 (C-4 of Ph), 131.5 (C-1 of Ph) and 169.2 (CO); ^{19}F NMR: δ −76.9 (d, $J_{HF} = 6.4$, CF_3); MS (CI) *m/z* (rel. int.): 263 $[MH]^+$ (100), 159 $[MH - HOCH_2CO_2Et]^+$ (7); HRMS (CI) Calc. for $C_{15}H_{13}FO_2$: 263.0884, Found 263.0884.

4.3.8. Ethyl-2-(1-phenylethoxy)propanoate (**21**)

The product was prepared using general procedure B from ethyl(1-phenylethoxy)acetate **8** (105 mg, 0.504 mmol), LDA (2 M in THF) (64.8 mg, 0.605 mmol) and methyl iodide (79 mg, 0.554 mmol) in THF (3.0 ml) to provide the product ester as a colourless oil (78 mg, 70%). IR (neat): ν 2983, 1736, 1453, 1377, 1208, 909; ^{1}H NMR: δ 1.09 (3H, t, $J = 7.2$, OCH_2CH_3), 1.22 and 1.27 (3H, d, $J = 6.9$, $OCHCH_3$), 1.42 (3H, d, $J = 6.4$, $PhCHCH_3$), 3.92 (1H, q, $J = 6.9$, $OCHCH_3$), 4.13 (2H, q, $J = 7.2$, OCH_2CH_3), 4.82 (1H, q, $J = 6.4$, PhCH), 7.18 (5H, m, Ph); ^{13}C NMR: δ 14.0 and 14.2 (OCH_2CH_3), 18.3 and 18.9 ($OCHCH_3$), 60.6 and

61.7 (O*C*H$_2$CH$_3$), 71.9 and 72.9 (O*C*HCH$_3$), 77.2 and 77.3 (Ph*C*H), 125.3, 126.2, 127.6, 128.4, 128.5, 143.1, 173.7; MS (EI) *m/z* (rel. int.): 246 [M + Na]$^+$ (100); HRMS (EI) Calc. for $C_{13}H_{18}O_3$: 246.2802, Found 246.2715.

4.3.9. Ethyl-2-(2-fluoro-1-phenylethoxy)propanoate (25)

The product was prepared according to general procedure B from ethyl (2-fluoro-1-phenylethoxy)acetate **12** (129 mg, 0.570 mmol), LDA (2 M in THF) (67 mg, 0.628 mmol) and methyl iodide (202 mg, 3.56 mml) in THF (5.0 ml). The product (79 mg, 58%) was isolated to as a colourless oil. IR (neat): ν 2985, 1747, 1455, 1122; ^{1}H NMR: δ 1.13* and 1.29 (3H, t, J = 7.2, OCH$_2$C*H*$_3$), 1.40 and 1.46* (3H, d J = 6.9, OCHC*H*$_3$), 3.92 (1H, q, J = 6.9, OC*H*CH$_3$), 4.17* and 4.20 (1H, q, J = 7.2, OC*H*$_2$CH$_3$), 4.44 (1H, ddd, J = 3.8, 9.7, 46.9, CH$_2$F), 4.57 (1H, ddd, J = 9.7, 9.7, 46.9, CH$_2$F), 4.74 (1H, ddd, J = 3.8, 10.5, 15.6, PhC*H*) and 7.32–7.39 (5H, m, Ph); ^{13}C NMR: δ 14.0* and 14.2 (OCH$_2$*C*H$_3$), 18.2* and 18.9 (CH*C*H$_3$), 60.7* and 60.9 (O*C*H$_2$CH$_3$), 72.8 (O*C*HCH$_3$), 80.5 (d, J_{CF} = 20.7, Ph*C*H), 85.5 and 86.0* (d, J_{CF} = 177, CH$_2$F), 127.2 (C-3 of Ph), 128.4 (C-4 of Ph), 128.7 (C-2 of Ph), 136.6 (C-1 of Ph), 172.5* and 172.9 (CO); ^{19}F NMR: δ −219.1*and −221.6 (dt, J = 15.6, 46.9); MS (CI) *m/z*(rel. int.): 241 [MH]$^+$ (82), 220 [MH − HF]$^+$ (12), 123 [MH − HOCH(CH$_3$)CO$_2$Et]$^+$ (57), 119 [MH − PhCH$_2$CH$_2$F]$^+$ (100); HRMS (CI) Calc. for $C_{13}H_{18}FO_3$: 241.1239, Found 241.1239.

4.3.10. Ethyl-2-(2,2,2-trifluoro-1-phenylethoxy) propanoate (26) [5]

The product was prepared according to general procedure B from **13** (158 mg, 0.60 mmol), LDA (2 M in THF) (70.9 mg, 0.66 mmol) and methyl iodide (94 mg, 0.66 mmol) in THF (5.0 ml). The product (110 mg, 66%) was isolated as a colourless oil. IR (neat): ν 2987, 1754, 1382, 1269, 1127; ^{1}H NMR: δ 1.17 (3H, J = 7.2, OCH$_2$C*H*$_3$), 1.36 and 1.42* (3H, d, J = 6.9, OCHC*H*$_3$), 3.86 (1H, q, J = 6.9, OC*H*CH$_3$), 4.13 (2H, q, J = 7.2, OC*H*$_2$CH$_3$), 4.85 (1H, q, J_{HF} = 6.4, PhC*H*), 7.18–7.36 (5H, m, Ph); ^{13}C NMR: δ 13.9 (OCH$_2$*C*H$_3$), 31.0 (OCH*C*H$_3$), 61.0 (O*C*H$_2$CH$_3$), 65.9 (O*C*HCH$_3$), 79.26 (q, J_{CF} = 31.5, Ph*C*H), 127.1 (q, J_{CF} = 281.4, CF$_3$), 128.3 (C-2 of Ph), 128.4 (C-3 of Ph), 128.6 (C-4 of Ph), 131.5 (C-1 of Ph), 169.1 (CO); ^{19}F NMR: δ −76.9 and −78.9 (d, J_{HF} = 6.4, CF$_3$); MS (CI) *m/z* (rel. int.): 277 [MH]$^+$ (100); HRMS (CI) Calc. for $C_{13}H_{16}F_3O_3$: 277.1052, Found 277.1049.

4.4. More complex systems

4.4.1. (S)-N-Benzyl-3-methyl-1,1-diphenyl-2-butanamine (31)

Methanolic HCl was added to a solution of isopropylamine **30** (204 mg, 0.85 mmol) in methanol (3.0 ml), so as to adjust the pH to 6.3. Benzaldehyde (115 mg, 1.08 mmol) was then added followed by sodium cyanoborohydride (132 mg, 2.10 mmol). The mixture was allowed to stir for 17 h at rt. The solvent was removed under reduced pressure, before addition of water (50 ml) followed by potassium hydroxide (1 M) solution until the solution was strongly alkaline. The aqueous phase was saturated with sodium chloride before being extracted into ether (3× 20 ml). The combined ethereal extracts were washed with 20% ferrous sulfate (aq.) (2× 20 ml), dried over MgSO$_4$ and concentrated. The crude product was dissolved in hexane and purified over silica gel, yielding benzylamine **29** (230 mg, 82%) as a white amorphous solid: m.p., 114–115 °C; $[\alpha]_D^{20}$ = +64 (ca. 0.62, CH$_2$Cl$_2$); IR (KBr): ν 3319, 3026, 2952, 1491, 1451; ^{1}H NMR: δ 0.76 [3H, d, J = 6.8, CH(C*H*$_3$)$_2$]; 0.93 [3H, d, J = 6.9, CH(C*H*$_3$)$_2$]; 1.69 (1H, m, H-3), 3.19 (1H, dd, J = 6.1, 10.5, H-2), 3.20 (1H, d, J = 12.3, PhC*H*$_2$N), 3.46 (1H, d, J = 12.3, PhC*H*$_2$N), 3.70 (1H, d, J = 10.5, H-1), 6.89–7.36 (10H, m, Ph); ^{13}C NMR: δ 16.1 [CH(*C*H$_3$)$_2$], 21.8 [CH(*C*H$_3$)$_2$], 30.5 (C-3), 56.2 (Ph*C*H$_2$N), 57.4 (C-1), 66.5 (C-2), 126.6, 126.8, 127.6, 128.5, 128.6, 128.8, 129.1, 142.6, 144.1 (aromatic carbons); MS (CI) *m/z* (rel. int.): 330 [MH$^+$] (100), 240 [MH − PhCH$_2$)]$^+$ (6), 162 [MH − Ph$_2$CH$_2$]$^+$ (58); HRMS (CI) Calc. for $C_{24}H_{28}N$: 330.2222, Found 330.2217.

4.4.2. (S)-Ethyl-2-[N-benzyl-N-((1′S)-1-diphenylmethyl-2-methylpropyl)]amino-2-oxoacetate (32)

Triethylamine (158 mg, 1.56 mmol) was added to a stirred solution of *N*-benzylamine **31** (174 mg, 0.53 mmol) in CH$_2$Cl$_2$ (3.0 ml) at −78 °C. The reaction was stirred for 15 min and then ethyl oxalyl chloride (110 mg, 0.79 mmol) was added. The reaction was allowed to warm to ambient temperature and was stirred for a further 4 h. Following standard work-up, the crude product was purified over silica gel to give the title compound (890 mg, 92%) as a white crystalline solid: m.p., 117–119 °C; $[\alpha]_D^{20}$ = −9.3 (ca. 0.62, CH$_2$Cl$_2$), IR (KBr): ν 2960, 1727, 1631, 1427, 1175; ^{1}H NMR: δ 0.78 (3H, m, OCH$_2$C*H*$_3$), 0.93 [3H, d, J = 6.9, CH(C*H*$_3$)$_2$], 0.94 [3H, d, J = 6.9, CH(C*H*$_3$)$_2$], 1.79 (1H, m, H-2), 3.47 (1H, dq, J = 7.5, 10.8, OC*H*$_2$CH$_3$), 3.52 (1H, dq, J = 7.2, 10.8, OC*H*$_2$CH$_3$), 4.23 (1H, d, J = 13.5, NC*H*$_2$Ph), 4.32 (1H, d, J = 12.3, C*H*Ph$_2$), 4.28 (1H, d, J = 13.5, NC*H*$_2$Ph), 5.68 (1H, dd, J = 12.3, 12.6, H-2), 6.54–7.37 (15H, m, Ph); ^{13}C NMR: δ 13.8 (OCH$_2$*C*H$_3$), 17.8 [CH(*C*H$_3$)$_2$], 20.9 [CH(*C*H$_3$)$_2$], 31.0 (C-2), 49.67 (N*C*H$_2$Ph), 53.8 (*C*HPh$_2$), 61.9 (C-1), 62.7 (O*C*H$_2$CH$_3$), 127.2, 127.6, 128.1, 128.2, 128.6, 129.2, 129.4, 129.5, 136.7, 142.0, 142.5, 143.1 (aromatic carbons), 163.1 (N*C*OCO$_2$Et), 164.8 (NCO*C*O$_2$Et); MS (CI) *m/z* (rel. int.): 430 [MH]$^+$ (100), 75 [(CH$_3$)$_2$CHNH$_2$]$^+$ (76); HRMS (CI): Calc. for $C_{28}H_{32}NO_3$: 430.2382, Found 430.2392.

4.4.3. (S)-2-[N-Benzyl-N-((1′S)-diphenylmethyl-2-methylpropyl)]aminoethanoic acid (33)

Sodium hydroxide (25.0 mg, 0.65 mmol) was added to a solution of **32** (281 mg, 0.65 mmol) in ethanol/THF solution (1:3). The reaction was stirred at rt for 15 h, and then the

solvents were evaporated under reduced pressure, yielding the sodium carboxylate as an amorphous solid. The salt (164 mg, 0.38 mmol) was dissolved in THF (5.0 ml), and charged into a flask containing diborane (1.5 M in THF, 0.51 ml, 0.76 mmol) at 0 °C. The reaction mixture was heated under reflux for 15 h and then the mixture was cooled to rt, and subsequently quenched with glacial acetic acid (1.0 ml). The solvent was removed under reduced pressure and the crude product purified over silica gel to give carboxylic acid **33**, as a white amorphous solid; m.p.: 148–150 °C; IR (KBr): ν 3430 (COOH), 1770 (CO), 1638, 1493, 1454, 1337; ^{1}H NMR: δ 0.68 [3H, d, J = 7.2, CH(CH_3)$_2$], 0.90 [3H, d, J = 6.9, CH(CH_3)$_2$], 2.02 (H, m, NCH), 3.35 (2H, br, NCH_2CO$_2$H), 3.55 (2H, br, NCH_2Ph), 3.65 (1H, dd, J = 11.7, 11.7, H-1), 4.15 (1H, d, J = 11.7, CHPh$_2$), 7.01–7.26 (15H, m, Ph); ^{13}C NMR: δ 20.4 [CH(CH_3)$_2$], 28.9 (CHPh$_2$), 54.0 (C-1), 54.7 (NCH_2Ph), 60.7 (NCH_2CO$_2$H), 127.3, 127.6, 128.6, 128.7, 128.9, 129.1, 129.2, 129.6, 130.4, 136.1, 142.8, 143.1 (aromatic carbons), 171.8 (CH$_2$CO_2H); MS (CI) m/z (rel. int.): 388 [MH]$^+$ (100), 344 [MH − CO$_2$H]$^+$ (15), 220 [MH − Ph$_2$CH]$^+$ (48); HRMS (CI) Calc. for $C_{26}H_{30}NO_2$: 388.2277, Found 388.2283.

4.4.4. (S)-Methyl 2-[N-benzyl-N-diphenylmethyl-(2-methylpropyl)]aminoacetate (34)

A solution of diazomethane in ether was added to a solution of carboxylic acid **33** (139 mg, 0.36 mmol) in ether until the yellow diazomethane solution persisted. Glacial acetic acid was then added until the yellow solution turned colourless. The ethereal solution was evaporated in vacuo to obtain the methyl ester **34** (144 mg, 100%) as a pale yellow oil. [α]$_D^{20}$ = +4.8 (ca. 0.78, CH$_2$Cl$_2$); IR (KBr): ν 2965, 1709, 1494, 1363, 1222; ^{1}H NMR: δ 0.72 [3H, d, J = 7.2, CH(CH_3)$_2$], 0.90 [3H, d, J = 6.9, CH(CH_3)$_2$], 1.77 (1H, m, H-2), 3.13 (1H, d, J = 16.8, NCH_2CO), 3.40 (1H, d, J = 16.8, NCH_2CO), 3.41 (3H, s, OCH_3), 3.56 (1H, d, J = 13.2, PhCH_2N), 3.63 (1H, d, J = 13.2, PhCH_2N), 3.62 (1H, dd, J = 11.40, 12.0, H-1), 4.17 (1H, d, J = 11.4, CHPh$_2$), 6.95–7.99 (15H, m, Ph); ^{13}C NMR: δ 18.6 [CH(CH_3)$_2$], 21.5 [CH(CH_3)$_2$], 30.6 (C-2), 51.6 (OCH_3), 54.1 (PhCH_2N), 55.0 (NCH_2CO), 68.5 (CHPh$_2$), 126.7, 127.2, 128.2, 128.5, 128.7, 128.9, 129.0, 129.3, 130.0, 139.6, 144.5, 144.6 (aromatic carbons); 173.3 (CO); MS (CI) m/z (rel. int.): 402 [MH]$^+$ (100), [MH − Ph$_2$CH$_2$]$^+$ (46); HRMS (CI) Calc. for $C_{27}H_{32}NO_2$: 402.2433; Found 402.2445.

4.4.5. (2R)-Methyl-2-[N-benzyl-N-((1′S)-diphenylmethyl-2-methylpropyl)]aminopropanoate (36)

A solution of methyl ester **34** (119 mg, 0.30 mmol) in THF (15 ml) was added to a LDA/THF preparation: [diisopropylamine (33.1 mg, 0.33 mmol) and n-BuLi (2.5 M in hexane), 150 μl, 0.39 mmol at 0 °C solution at −50 °C]. Methyl iodide (42.2 mg, 0.30 mmol) was then added and the reaction was allowed to warm to rt over 1 h and was further stirred at ambient temperature for 8 h. The solvent was evaporated and then ether (10 ml) was added, and the products were extracted from water (30 ml). The combined ethereal layer was evaporated. The diastereoisomers were separated over silica gel and the major diastereoisomer recovered (84.3 mg, 68%). Data for the major diastereoisomer [α]$_D^{20}$ = +21 (ca. 0.81, CH$_2$Cl$_2$); IR (neat): ν 2929, 1735 (CO), 1452, 1261, 1147; ^{1}H NMR: δ 0.50 (3H, d, J = 7.2, NCHCH_3), 0.82 [3H, d, J = 7.2, CH(CH_3)$_2$], 0.89 [3H, d, J = 6.9, CH(CH_3)$_2$], 2.13 (1H, m, H-2), 3.50 (1H, q, J = 7.2, NCHCH$_3$), 3.59 (3H, s, OCH_3), 3.63 (1H, m, H-1), 3.89 (1H, d, J = 14.1, PhCH_2N), 3.96 (1H, d, J = 14.1, PhCH_2N), 4.10 (1H, d, J = 11.4, CHPh$_2$), 6.92–7.25 (15H, m, Ph); ^{13}C NMR: δ 18.5 [CH(CH_3)$_2$], 19.3 [CH(CH_3)$_2$], 23.8 (NCHCH_3), 29.3 (C-2), 51.4 (OCH_3), 51.4 (PhCH_2N), 53.9 (C-1), 54.6 (NCH_2CO), 62.5 (CHPh$_2$), 126.1, 126.7, 127.2, 128.2, 128.3, 128.7, 129.0, 129.1, 130.5, 140.1, 144.4, 144.8 (aromatics carbons), 176.7 (CO); MS (CI) m/z (rel. int.): 417 [MH]$^+$ (100), [MH − Ph$_2$CH$_2$]$^+$ (42); HRMS (CI) Calc. for $C_{28}H_{34}NO_2$: 415.5672, Found 415.5668.

4.4.6. (2R)-Methyl-2-[(1′S)-N-diphenylmethyl-2-methylpropyl]aminopropanoate (37) and hydrochloride (38)

Pearlman's catalyst (30 mg) was added to a solution of **36** (100 mg, 0.241 mmol) in methanol (50 ml). The reaction vessel was pressurised with hydrogen (10 bar). After 10 h the pressure was released and the reaction filtered and the solvent removed to afford the product (77 mg, 99%) as a colourless oil. Treatment of **37** with anhydrous HCl provided the hydrochloride salt **38** in quantitative yield. Data for **37** [α]$_D^{20}$ = +62 (ca. 0.77, CH$_2$Cl$_2$); IR (neat): ν 2963, 2947, 1714, 1495, 1451, 1214, 1152; ^{1}H NMR: δ 0.71 [3H, d, J = 6.9, CH(CH_3)$_2$], 0.89 [3H, d, J = 7.2, CH(CH_3)$_2$], 1.03 (3H, d, J = 6.9, NCHCH_3), 1.64–4.73 (1H, m, H-2), 2.94 (1H, q, J = 6.9, NCHCH$_3$), 3.20 (1H, dd, J = 2.3, 10.5, H-1), 3.45 (3H, s, OCH$_3$), 3.74 (1H, d, J = 10.5, CHPh$_2$), 7.05–7.32 (10H, m, Ph); ^{13}C NMR: δ 19.9 [CH(CH_3)$_2$], 21.2 [CH(CH_3)$_2$], 21.3 [CH(CH$_3$)$_2$], 29.3 (NCHCH_3), 55.7 (C-1), 57.2 (NCH), 63.4 (OMe), 63.4 (CHPh$_2$), 126.2, 126.4, 128.2, 128.4, 128.5, 128.6 (C of Ph), 142.8, 143.6 (C-1 of Ph), 175.6 (CO); MS (CI) m/z (rel. int.): 326 [MH]$^+$ (100), [MH − Ph$_2$CH$_2$]$^+$ (167); HRMS (CI) Calc. for $C_{21}H_{28}NO_2$: 326.2120, Found 326.2118.

4.4.7. (2S)-N-Benzyl-1-fluoro-3-methyl-1,1-diphenyl-2-butanamine (40)

Methanolic HCl was added to a solution of (*S*)-α-fluorodiphenylmethyl isopropylamine **39** (1.00 g, 3.86 mmol) in CH$_3$OH (50 ml), and the pH adjusted to 6.6. Benzaldehyde (537 mg, 5.06 mmol) was then introduced followed by sodium cyanoborohydride (733 mg, 11.7 mmol). The procedure used in Section 4.4.1 was followed. Chromatographic purification of the crude mixture yielded amine **40** (686 mg, 50%) as a white amorphous solid: m.p. = 90–92 °C; [α]$_D^{20}$ = −38 (ca. 0.80, CH$_2$Cl$_2$); IR

(KBr): ν 3314, 3026, 2956, 1494, 1449, 1326, 1098, 980, 704; ^{1}H NMR: δ 0.81 [3H, d, J = 6.9, CH(CH_3)$_2$], 0.92 [3H, d, J = 7.0, CH(CH_3)$_2$], 1.52 (1H, br NH), 1.79 (1H, m, H-3), 3.45 (1H, dd, J_{HF} = 31.9, H-2), 4.55 (2H, s, NCH_2Ph), 7.10–7.41 (15H, m, Ph); ^{13}C NMR: δ 17.0 [CH(CH_3)$_2$], 23.1 [CH(CH_3)$_2$], 29.8 (C-3), 55.2 (NCH_2Ph), 68.1 (d, J_{CF} = 21.0, C-2), 102.9 (d, J_{CF} = 183.0, C-1), 124.96, 125.0, 125.2, 126.7, 127.1, 127.2, 128.0, 128.3, 140.9, 143.1, 143.2, 143.5 (aromatic carbons); ^{19}F NMR: δ −168.2 (d, J_{HF} = 31.9); MS (CI) m/z (rel. int.): 348 [MH]$^+$ (43), 258 [MH − Ph_2CH]$^+$ (100), 72 [Ipr − CHNH_2] (58); HRMS (CI) Calc. for $C_{24}H_{27}FN$: 348.2127, Found 348.2108.

4.4.8. 2-[(1′S)-N-Benzyl-N-1-(fluorodiphenylmethyl)-2-methylpropyl]amino-2-oxoethanoate (41)

A solution of *N*-benzylamine **40** (471mg, 1.36 mmol) in CH_2Cl_2 (15 ml) was treated with triethylamine (413 mg, 4.08 mmol) and ethyl oxalylchloride (241 mg, 1.77 mmol) in CH_2Cl_2 (15 ml) as described under Section 4.4.2. Purification over silica gel afforded the title compound **41** (586 mg, 96%), as a white amorphous solid: m.p., 117–120 °C; $[\alpha]_D^{20}$ = −9.6 (ca. 0.60, CH_2Cl_2); IR (KBr): ν 2968, 1734, 1656, 1451, 1311, 1265, 1198; ^{1}H NMR: δ 0.83 [3H, d, J = 6.9, CH(CH_3)$_2$], 0.88 [3H, m, CH(CH_3)$_2$], 1.25 (3H, t, J = 7.2, OCH_2CH_3), 1.89–1.99 [1H, m, CH(CH$_3$)$_2$], 4.47 (1H, d, J = 7.2, NCH_2Ph), 4.49 (1H, d, J = 7.2, NCH_2Ph), 4.15 (1H, dq, J = 7.2, 10.2, OCH_2CH$_3$), 4.23 (1H, dq, J = 7.2, 10.2, OCH_2CH$_3$), 4.98 (1H, ddd, J = 2.2, 10.6, 35.9), 7.09–7.47 (15H, m, Ph); ^{13}C NMR: δ 14.3 (OCH$_2$CH_3), 17.3 [CH(CH_3)$_2$], 17.4 [CH(CH$_3$)$_2$], 22.5 [CH(CH_3)$_2$], 29.2 (C-3), 58.7 (d, J_{CF} = 18.6, C-2), 63.7 (OCH_2CH$_3$), 67.5 (NCH_2Ph), 102.3 (d, J = 183.3, CFPh$_2$), 124.5, 124.6, 124.8, 125.0, 126.1, 128.1, 128.4, 128.8, 129.1, 129.6, 142.0, 142.3 (aromatic carbons), 157.0 (NCOCO$_2$Et), 160.7 (NCOCO_2Et); ^{19}F NMR: δ −168.7 (d, J_{HF} = 35.9); MS (CI) m/z (rel. int.): 449 [MH]$^+$ (80), 429 [MH − HF]$^+$ (100), 263 [MH − Ph_2CHF] (16); HRMS (CI) Calc. for $C_{28}H_{29}FNO_3$: 450.2127, Found 450.2108.

4.4.9. 2-[(1′S)-N-Benzyl-N-(1-fluorodiphenylmethyl-2-methylpropyl)]aminoethanol (42)

A solution of ester **41** (350 mg, 0.78 mmol) in THF was slowly added to a suspension of lithium aluminium hydride (58 mg, 1.56 mmol) in THF at rt. The reaction was heated under reflux for 30 min. Excess hydride was quenched by the cautious addition of water. The organics were filtered and the solvent removed under reduced pressure to give alcohol **42** (306 mg, 100%) as a white amorphous solid: m.p., 90–91 °C; $[\alpha]_D^{20}$ = +5.6 (ca. 0.69, CH_2Cl_2); IR (KBr): ν 3423, 2956, 1599, 1493, 1450, 1047; ^{1}H NMR: δ 0.94 [3H, d, J = 7.2, CH(CH_3)$_2$], 0.96 [3H, dd, J = 1.5, 7.2, CH(CH_3)$_2$], 2.27 (1H, m, H-2), 2.85 (2H, m, NCH_2CH$_2$OH), 3.16–3.27 (4H, m, NCH_2Ph and NCH$_2$CH_2OH), 3.72 (1H, dd, J = 3.3, J_{HF} = 36.8, H-1), 7.09–7.36 (15H, m, Ph); ^{13}C NMR: δ 22.6 [CH(CH_3)$_2$], 23.3 [CH(CH_3)$_2$], 29.8 [CH(CH$_3$)$_2$], 57.0 (NCH_2CH$_2$OH), 59.9 (NCH$_2$CH_2OH), 67.9 (NCH_2Ph), 69.3 (d, J_{CF} = 19.3, NCH), 104.9 (d, J_{CF} = 188.5), 124.2, 124.4, 124.8, 125.0, 126.9, 127.0, 127.1, 128.1, 128.2, 144.3, 144.4, 144.7; ^{19}F NMR: δ −169.3 (d, J_{HF} = 36.8); MS (CI) m/z (rel. int.) 392 [MH]$^+$ (100), 374 [MH − H_2O]$^+$ (8), 206 [MH − Ph_2CHF]$^+$ (29); HRMS (CI) Calc. for $C_{26}H_{31}FNO$: 392.2389, Found 392.2387.

4.4.10. Methyl[(1′S)-N-benzyl-N-fluorodiphenylmethyl-2-methylpropyl]aminoethanoate (43)

A solution of alcohol **42** (95 mg, 0.245 mmol) in CH_2Cl_2 (1.0 ml) was added to a flask containing Dess-Martin periodinate (103 mg, 0.243 mmol) in CH_2Cl_2 (2.0 ml). After 20 min, a saturated solution of sodium bicarbonate was added and the organics were then washed with sodium thiosulfate solution (10%). The combined aqueous extract was washed with ether (2× 10 ml) and then evaporation of the organics under reduced pressure gave the corresponding aldehyde (95 mg, 100%), which was used directly.

To a stirred solution of the aldehyde (95 mg, 0.243 mmol) in *t*-butanol (8.0 ml) and 2-methyl-2-butene (2.0 ml) was added a solution of $NaClO_2$ (250 mg, 2.19 mmol) and NaH_2PO_4 (403 mg, 1.70 mmol) in water (2.5 ml). The reaction was allowed to stir at ambient temperature for 40 min, whereupon water (10 ml) and ethyl acetate (30 ml) were added. The phases were separated, and the organic layer was washed with saturated NaCl solution (10 ml), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was dissolved in methanol (5.0 ml) and was treated with TMS–diazomethane (2 M in hexane) (0.15 ml, 0.292 mmol). The methanol was removed under reduced pressure and the crude product purified over silica gel to give the title compound (31 mg, 30%) as a colourless oil. $[\alpha]_D^{20}$ = +5.9 (ca. 0.63, CH_2Cl_2); IR (neat): ν 2926, 1751, 1449, 1277, 1199, 1169, 1030; ^{1}H NMR: δ 0.73 [3H, d, J = 6.9, CH(CH_3)$_2$], 0.97 [3H, d, J = 6.9, CH(CH_3)$_2$], 2.10 (1H, m, H-2), 3.33 (1H, d, J =17.4, NCH_2CO), 3.44 (3H, s, OCH$_3$), 3.48 (1H, d, J = 13.3, NCH_2Ph), 3.60 (1H, d, J = 13.3, NCH_2Ph), 3.72 (1H, dd, J = 3.1, J_{HF} = 37.1, H-1), 3.84 (1H, d, J = 17.4, NCH_2CO), 7.09–7.48 (15H, m, Ph); ^{13}C NMR: δ 19.2 [CH(CH_3)$_2$], 23.0 [CH(CH_3)$_2$], 28.9 (C-2), 51.2 (OCH$_3$), 53.9 (NCH_2Ph), 58.9 (NCH_2CO), 69.3 (d, $^2J_{CF}$ = 19.4, C-2), 104.5 (d, J_{CF} = 186.9, C-1), 124.2, 124.4, 125.1, 125.3, 127.0, 127.7, 127.9, 128.0, 128.8, 130.0, 141.3, 144.6, 173.0 (CO); ^{19}F NMR: δ −168.3 (d, J_{HF} = 37.1); MS (CI) m/z (rel.): 420 [MH]$^+$ (100), 400 [MH − HF]$^+$ (8), 234 [MH − Ph_2CHF]$^+$ (14); HRMS (CI) Calc. for $C_{27}H_{31}FNO_2$: 420.2338, Found 420.2335.

4.4.11. (2R)-Methyl-2-[(1′S)-benzyl-N-(1-fluorodiphenylmethyl-2-methylpropyl)]aminopropanoate (45)

Methylation of ester **43** (54 mg, 0.129 mmol) followed the procedure outlined in Section 4.4.5. The product was purified over silica gel to give a 2:1 mixture of diastereoisomers as a colourless oil. IR (neat): ν 2930,

1738 (CO), 1493, 1384, 1262, 1148; ^{1}H NMR: δ 0.73 [d, $J = 6.9$, CH(CH_3)$_2$], 0.97 [d, $J = 6.9$, CH(CH_3)$_2$], 1.28 (d, $J = 6.7$, NCHCH_3), 1.30* (d, $J = 6.7$, NCHCH_3), 2.00 (1H, m, H-2), 3.45 (3H, s, OCH_3), 3.48 (1H, q, $J = 6.7$, NCHCH$_3$), 3.50 (1H, d, $J = 13.6$, NCH_2Ph), 3.59 (1H, d, $J = 13.6$, NCH_2Ph), 3.72 (1H, dd, $J = 3.1$, $J = 37.1$, H-1), 7.01–7.48 (15H, m, Ph); ^{13}C NMR: δ 18.1 [CH(CH_3)$_2$], 18.8 [CH(CH_3)$_2$], 23.4 (NCHCH$_3$), 28.9 (C-2), 51.0 (OCH_3), 53.9 (NCHCH$_3$), 65.8 (NCH$_2$Ph), 69.3 (d, $J_{CF} = 19.4$, C-1), 105.6 (d, $J_{CF} = 186.9$, CFPh$_2$), 124.3, 124.4, 125.1, 125.3, 127.0, 127.8, 128.4, 130.0, 139.7, 144.0, 144.3, 176.3 (CO); ^{19}F NMR: δ −168.3 (d, $J_{HF} = 37.1$); MS (CI) m/z (rel. int.): 434 [MH]$^+$ (100), 414 [MH − HF]$^+$ (10); HRMS (CI) Calc. for $C_{28}H_{32}FNO_2$: 434.5576, Found 434.5570.

4.4.11.1. Crystal structure determination of ***29*** *and* ***36***. Data for both compounds were measured on a Bruker SMART diffractometer with graphite monochromated Mo Kα radiation (λ = 0.7107) using a 0.3° width steps accumulating area detector frames spanning a hemisphere of reciprocal space for both structures; the reflections were corrected for Lorentz and polarisation effects. Absorption effects were corrected on the basis of multiple equivalent reflections. The structures were solved by direct methods and refined by full-matrix least-squares on F^2 using the program SHELXTL. All hydrogen atoms were included in calculated positions using a riding model. All non-hydrogen atoms were refined as anisotropic.

4.4.11.2. Crystal data for ***29***. $C_{18}H_{29}NO_5$, $M = 339.42$, monoclinic, space group $C2$, $a = 25.418(4)$ Å, $b = 6.5104(9)$ Å, $c = 11.3405(16)$ Å, $\beta = 101.540(2)°$, $V = 1838.7(4)$ Å^3, $T = 125(2)$ K, $Z = 4$, μ(Mo Kα) = 0.089 mm^{-1}, colourless block, crystal dimensions, 0.12 mm × 0.1 mm × 0.02 mm. Full-matrix least-squares based on F^2 gave $R1 = 0.0345$ for 3120 observed ($F > 4\sigma(F)$ and $wR2 = 0.$ 0867 for all data), GOF = 1.026 for 226 parameters.

4.4.11.3. Crystal data for ***38***. $C_{24}H_{23}N$, $M = 370.90$, tetragonal, space group $P4(1)$, $a = 10.1769(15)$ Å, $b = 10.1769(15)$ Å, $c = 40.051(9)$ Å, $V = 4148.0(12)$ Å^3, $T = 125(2)$ K, $Z = 8$, μ(Mo Kα) = 0.200 mm^{-1}, colourless block, crystal dimensions, 0.1 mm × 0.04 mm × 0.02 mm. Full-matrix least-squares based on F^2 gave $R1 = 0.1021$ for 7564 observed ($F > 4\sigma(F)$ and $wR2 = 0.2803$ for all data), GOF = 0.993 for 479 parameters.

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