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Improved synthesis of phenylethylamine derivatives by Negishi cross-coupling reactions

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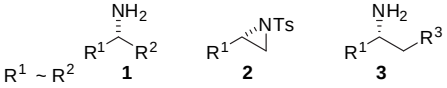
ABSTRACT

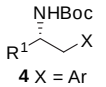
Trifluoroacetamido-protected β-aminoalkylzinc iodides undergo Negishi cross-coupling reaction with aryl iodides in moderate to excellent yields (42–84%) based on the corresponding trifluoroacetamido-protected β-aminoalkyl iodides, employing a catalyst prepared in situ from $Pd_2(dba)_3$ and SPhos (1:2 M ratio). In general, *meta*- and *para*-substituted aryl iodides give good results using relatively low levels of catalyst [0.25 mol % $Pd_2(dba)_3$], but more hindered *ortho*-substituted examples require higher catalyst loadings. The preparation of trifluoroacetamido-protected β-aminoalkyl iodides is straightforward, and the intermediates are significantly more stable than the corresponding Boc-protected derivatives.

1. Introduction

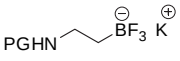
Chiral primary amines **1** continue to attract attention as synthetic targets. A very recent review highlighted approaches, which involve an asymmetric step, specifically *N*-acylenamide and enamine reduction, reductive amination and imine reduction.[1] These approaches are least effective when the two substituents are of comparable steric bulk (R^1–R^2), since facial discrimination is then more challenging. As an alternative to the asymmetric synthesis approach, methods have been developed, which rely on use of the chiral pool, for example, by reaction of carbon nucleophiles with enantiomerically pure aziridines **2**, generally prepared from enantiomerically pure amino acids, leading to amines of general structure **3**.[2,3] This method is in principle appropriate for making chiral primary amines when the two substituents are of comparable steric bulk.



Some time ago, we reported that enantiomerically pure phenylethylamines **4** could be prepared by Pd-catalysed Negishi cross-coupling of chiral non-racemic β-aminoalkylzinc iodides **5** with aryl iodides.[4,5] The protected β-aminoalkylzinc iodides are prepared from the corresponding protected β-iodoamines **6**, themselves available straightforwardly from amino acids. The yields in the Pd-catalysed Negishi cross-coupling were generally moderate,[4] although they were based on the more valuable protected β-iodoamine, and therefore also reflect the efficiency of the zinc insertion process, as well as the tendency of protected β-aminoalkylzinc iodides to undergo β-elimination.



4 X = Ar
5, X = ZnI
6, X = I



7

Related β-benzamidoethylzinc iodides had been prepared by Knochel, and converted into the corresponding zinc/copper reagents by transmetallation with CuCN·2LiCl prior to subsequent allylation.[6] More recently, Molander has shown that very stable potassium β-aminoethyltrifluoroborates **7** can undergo efficient Suzuki–Miyaura cross-coupling with aryl halides and triflates,[7,8] although this method has not yet been applied to substituted chiral potassium β-aminoalkyltrifluoroborates.

We have recently uncovered computational and (circumstantial) experimental evidence that a combination of internal coordinating groups, and Lewis basic solvents, can promote (partial) ionisation of the zinc iodine bond in alkylzinc iodides, forming tight ion pairs.[9,10] Such behaviour provides a credible explanation for the high functional group tolerance of alkylzinc iodides, as well as the (relative) stability of β-aminoalkylzinc iodides towards elimination. We have also shown that replacement of the Boc-protecting group by the more electron withdrawing TFA group results in β-aminoalkylzinc iodides that can be more reactive in Negishi cross-coupling reactions, but are also substantially more stable towards

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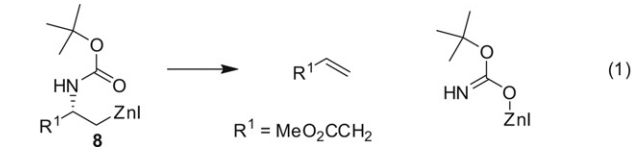
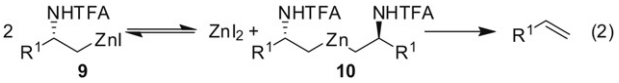
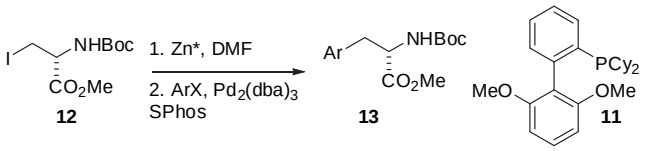
β-elimination.[11] The reason for this, at first sight, counterintuitive result is that the mechanism of the β-elimination is altered by the change in protecting group. Specifically, the Boc-protected β-aminoalkylzinc iodide **8** (derived from aspartic acid) decomposes by a first order process, which we have proposed to occur by a *syn*-elimination promoted by coordination of the electron-rich carbamate carbonyl group to zinc (Eq. 1), needed to compensate for the (partial) ionisation of the zinc–iodine bond. In contrast, the analogous TFA-protected β-aminoalkylzinc iodide **9** undergoes elimination by a second order process,[11] required because the less electron-rich TFA-carbonyl group is now unable to coordinate sufficiently strongly to the alkylzinc iodide to promote elimination, which therefore probably proceeds through the dialkylzinc reagent **10** (Eq. 2).





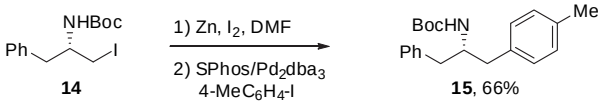
Furthermore, we have very recently established that Buchwald's biarylphosphine ligands (specifically SPhos **11**)[12] in combination with $Pd_2(dba)_3$ are effective for the Negishi cross-coupling of the serine-derived organozinc reagent **12** with aryl halides, giving high yields of phenylalanine derivatives **13**, and in many cases permitting lower levels of Pd to be used (Scheme 1).[13] It therefore appeared that an investigation of the synthesis of chiral phenylethylamines by Negishi cross-coupling of TFA-protected β-aminoalkylzinc iodides with aryl iodides, catalysed by $Pd_2(dba)_3$/SPhos would be fruitful. We report here the results of this study.



Scheme 1. Use of SPhos to prepare phenylalanine derivatives.

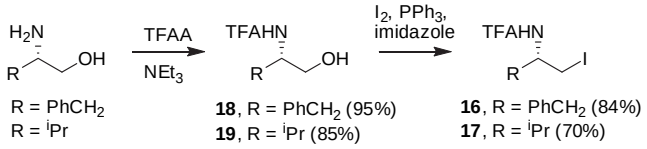
2. Results and discussion

Prior to exploring the influence of the TFA-protecting group, the application of the catalyst derived from $Pd_2(dba)_3$/SPhos to the cross-coupling of the zinc reagent derived from the Boc-protected β-aminoalkyl iodide **14** was investigated. In our previous studies, Negishi cross-coupling of this reagent with 4-iodotoluene using $Pd_2(dba)_3$/(*o*-tol)$_3$P as catalyst gave the product **15** in 59% yield.[4] Use of $Pd_2(dba)_3$/SPhos under comparable conditions showed a modest, but probably significant, improvement in yield to 66% (Scheme 2).



Scheme 2. Cross-coupling of Boc-protected β-aminoalkylzinc iodide.

The TFA-protected phenylalanine and valine-derived iodides **16** and **17** were selected to exemplify our approach, and were straightforwardly prepared from the corresponding amino alcohols by TFA-protection[14] and iodination (Scheme 3). The yields in the iodination step are consistently higher than those obtained for iodination of the corresponding Boc-protected derivatives,[4] partly because the TFA-iodides are more stable than the corresponding Boc-iodides.



Scheme 3. Preparation of trifluoroacetamido iodides.

Conversion of the iodides **16** and **17** into the organozinc reagents **20** and **21**, respectively, was carried out using zinc activated with iodine, in DMF as solvent. Although we had established that $Pd_2(dba)_3$ was superior to $Pd(OAc)_2$ in the synthesis of phenylalanine derivatives by Negishi coupling,[13] these two sources of palladium were initially compared, since Knochel had successfully used a combination of $Pd(OAc)_2$ and SPhos for related Negishi coupling reactions.[15–17] Nevertheless, as is evident from Table 1, entry 1, the use of $Pd_2(dba)_3$ (2.5 mol %) in combination with SPhos (5 mol %)

Table 1
Synthesis of *N*-TFA-protected phenylalanine derivatives **22** and **23**

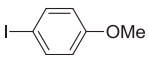
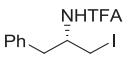
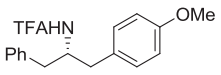
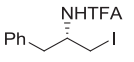
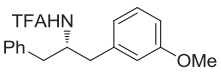
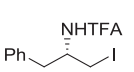
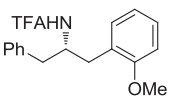
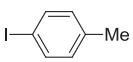
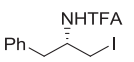
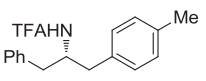
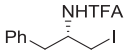
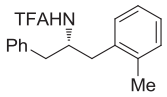
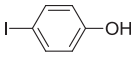
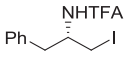
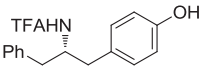
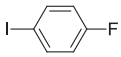
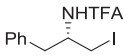
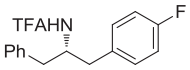
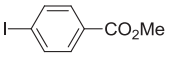
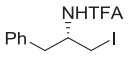
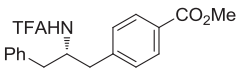
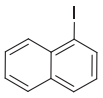
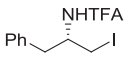
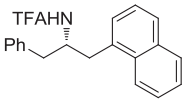
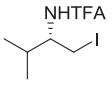
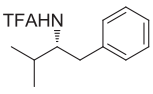
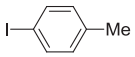
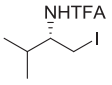
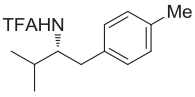
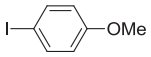
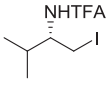
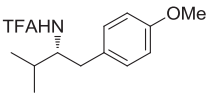
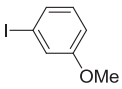
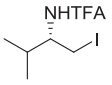
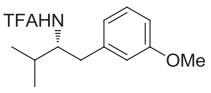
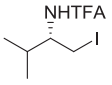
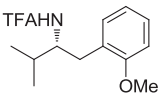
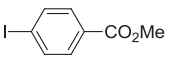
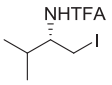
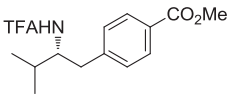
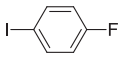
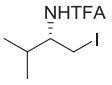
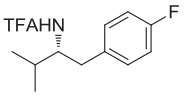
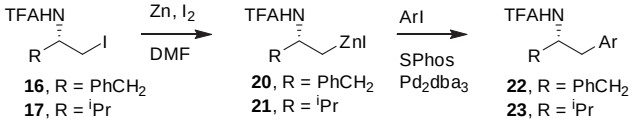
Entry	Aryl iodide	Iodoamine	Product		Yield (%) method A[a]	Yield (%) method B[b]
1				**22a**	74 (55)[c]	70
2				**22b**	72	65
3				**22c**	60	50
4				**22d**	84	72

Table 1 (*continued*)

Entry	Aryl iodide	Iodoamine	Product		Yield (%) method A[a]	Yield (%) method B[b]
5				**22e**	61	32
6				**22f**	68	35
7				**22g**	80	71
8				**22h**	70	67
9				**22i**	67	42
10				**23a**	63	58
11				**23b**	70	42
12				**23c**	57	37
13				**23d**	74	—
14				**23e**	42	—
15				**23f**	51	—
16				**23g**	61	60

[a] Method A: iodoamine (1 mmol), aryl iodide (1.3 mmol), SPhos (5 mol %), Pd_2dba_3 (2.5 mol %), Zn (3 mmol), DMF (1 mL).
[b] Method B: iodoamine (1 mmol), aryl iodide (1.3 mmol), SPhos (0.5 mol %), Pd_2dba_3 (0.25 mol %), Zn (3 mmol), DMF (0.3 mL).
[c] Using $Pd(OAc)_2$ (5 mol %) in place of Pd_2dba_3 (2.5 mol %).

gave a higher yield than was obtained with $Pd(OAc)_2$, so all subsequent reactions were conducted using $Pd_2(dba)_3$. Cross-coupling of zinc reagent **20** with a range of aryl iodides, using $Pd_2(dba)_3$ (2.5 mol %) in combination with SPhos (5 mol %) as catalyst (method A), proceeded to give the phenylethylamine derivatives **22** in good yield (Scheme 4, Table 1), representing a substantial improvement on the previous method that we have reported using Boc-protected reagents.[4] Analogous couplings of the valine-derived organozinc iodide **21** gave the products **23** (Table 1). In general, only a marginal decrease in yield was observed when the catalyst loading was reduced by a factor of 10, and the amount of solvent also substantially reduced (0.3 mL of DMF per mmol, method B). As we had previously observed, this decrease in yield was more pronounced for *ortho*-substituted aryl iodides, and also for 4-iodophenol,[18] presumably due to competitive protonation by the phenolic proton under conditions with lower catalyst concentration, and therefore a reduced rate of cross-coupling. It is appropriate to highlight that the amount of solvent employed under conditions B corresponds to approximately 4 mol of DMF for each mole of organozinc reagent. The DMF is therefore best considered as a stoichiometric reagent, acting as a ligand for zinc.



Scheme 4. Negishi cross-coupling of trifluoroacetamido zinc iodides.

3. Conclusions

TFA-protected β-aminoalkylzinc iodides are easy to prepare and react with good to excellent yields in Negishi cross-coupling reactions with aryl iodides, catalysed by a combination of $Pd_2(dba)_3$ and SPhos. In the case of 4- and 3-substituted aryl iodides, low loadings of catalyst (0.5 mol % Pd) are sufficient to achieve satisfactory results. In addition the key TFA-iodides are more efficiently prepared, and substantially more stable, than the corresponding Boc-iodides, so it is clear that TFA is an excellent choice of protecting group for the synthesis of phenylethylamines using the Negishi coupling.

4. Experimental

4.1. General

All reagents used were obtained commercially and were not purified further. The SPhos was obtained from two sources, Alfa Aesar® and Aldrich®; the SPhos obtained from Aldrich® was ground before use. All solvents used were of HPLC quality and purchased from Fischer Scientific®. Petroleum ether refers to the fraction that boils in the range of 40–60 °C. The DMF was distilled from calcium hydride and kept under an inert atmosphere over 4 Å molecular sieves. All columns were monitored using TLC, on pre-coated silica plates, TLC plates visualised by Ultra Violet light and potassium permanganate dip. Flash column chromatography was performed under pressure, using silica gel 60 from Davisil Fluorochem. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer at room temperature. Samples were dissolved in $CDCl_3$. Coupling constants are measured in Hertz and are quoted to the nearest 0.1 Hz and chemical shifts are quoted in parts per million relative to the residual chloroform peak. Melting points were determined using a Linkham HFS91 heating stage, with a TC92 controller. The temperatures are uncorrected. Optical rotations were determined using an AA-10 Automatic Polarimeter, at 589 nm. High-resolution mass spectra were recorded using a MicroMass LCT operating in electrospray (ES) mode. Infra red spectra were measured on a Perkin–Elmer Paragon RX I FT-IR spectrophotometer. Wavenumbers are quoted to the nearest whole number. The TFA-protected phenylalaninol derivative **18** was prepared by the literature method,[14] and the corresponding valinol derivative **19**[19] was prepared by a minor modification of the literature method,[14] using a smaller molar excess of trifluoroacetic anhydride (1.2 equiv rather than 1.4 equiv).

4.2. Iodination procedure

The alcohol (10.0 mmol) was added by syringe over 30 min to a stirred solution of triphenylphosphine (2.75 g, 10.5 mmol), imidazole (0.71 g, 10.5 mmol) and iodine (2.66 g, 10.5 mmol) in dry CH_2Cl_2 (30 mL) under nitrogen at room temperature and the reaction mixture was left overnight. The precipitate was removed by filtration, the filtrate concentrated under reduced pressure and the residue dissolved in ethyl acetate (150 mL). The insoluble material was removed by filtration and the filtrate was washed with saturated sodium thiosulfate solution (50 mL) and brine (50 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography.

4.2.1. (S)-(+)-2,2,2-Trifluoro-N-(1-iodo-3-phenyl-propan-2-yl)acetamide ***16***. General iodination procedure was followed using (*S*)-2,2,2-trifluoro-*N*-(1-hydroxy-3-phenylpropan-2-yl)acetamide **18** (2.35 g, 10.0 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the iodide (3.0 g, 84%) as a white solid; mp 132–133 °C; R_f 0.54 (20% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}): 3298, 3100, 2954, 1698, 1564, 1178; δ_H (400 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 14.0, 8.0, CH_AH_BPh), 2.92 (1H, dd, *J* 14.0, 6.0, CH_AH_BPh), 3.14 (1H, dd, *J* 10.5, 4.0, CH_AH_BI), 3.35 (1H, dd, *J* 10.5, 4.0, CH_AH_BI), 3.94–3.86 (1H, m, C*H*NHTFA), 6.23–6.33 (1H, br, NH), 7.16–7.30 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 10.4, 39. 9, 50.7, 115.6 (q, *J* 286), 127.5, 129.0, 129.1, 135.6, 156.5 (q, *J* 35); $[\alpha]_D^{22}$ +16.9 (*c* 1.0, $CHCl_3$); *m/z* (ES) Found: MH^+ 357.9912. $C_{11}H_{12}NOIF_3$ requires MH^+ 357.9916.

4.2.2. (S)-(−)-2,2,2-Trifluoro-N-(1-iodo-3-methylbutane-2-yl)acetamide ***17***. General iodination procedure was followed using (*S*)-2,2,2-trifluoro-*N*-(1-hydroxy-3-methylbutane-2-yl)acetamide **19** (1.99 g, 10.0 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the iodide (2.35 g, 70%) as a white solid; mp 114–116 °C; FTIR (ν_{max}/cm^{-1}): 3274, 3106, 2974, 1700, 1562; 1162; δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.6, CH_3CH), 1.05 (3H, d, *J* 6.6, CH_3CH), 1.83–1.97 (1H, m, $(CH_3)_2CH$), 3.38 (1H, dd, *J* 10.6, 4.8, CH_AH_BI), 3.46 (1H, dd, *J* 10.6, 3.5, CH_AH_BI), 3.48–3.54 (1H, m, C*H*NHTFA), 6.20–6.36 (1H, br, NH); δ_C (100 MHz, $CDCl_3$) 9.8, 18.3, 19.0, 32.3, 55.2, 115.0 (q, *J* 288), 158 (q, *J* 37); $[\alpha]_D^{22}$ −42.0 (*c* 1.0, $CHCl_3$); *m/z* (ES) Found: MH^+ 309.9918. $C_7H_{11}NOIF_3$ requires MH^+ 309.9916.

4.3. Cross-coupling reaction: method A

Zinc dust (190 mg, 3 mmol) was added to a flame dried, nitrogen purged side arm round bottom flask. Dry DMF (1 mL) was added via syringe followed by a catalytic amount of iodine (40 mg, 0.15 mmol). A colour change of the DMF was observed from colourless to yellow and back again. (*S*)-2,2,2-Trifluoro-*N*-(1-iodo-3-phenylpropan-2-yl)acetamide **16** (356 mg, 1 mmol) or (*S*)-2,2,2-trifluoro-*N*-(1-iodo-3-methylbutane-2-yl)acetamide **17** (309 mg, 1 mmol) was added immediately followed by a catalytic amount of iodine (40 mg, 0.15 mmol). The solution was stirred at room temperature and gave a noticeable exotherm. When the solution had cooled Pd_2dba_3 (22 mg, 0.025 mmol), SPhos (21 mg, 0.05 mmol) and aryl iodide (1.3 mmol) were added to the flask and left to stir at room temperature overnight, under positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column to afford the purified cross-coupled product.

4.4. Cross-coupling reaction: method B

Zinc dust (190 mg, 3 mmol) was added to a flame dried, nitrogen purged side arm round bottom flask. Dry DMF (0.3 mL) was added via syringe followed by a catalytic amount of iodine (40 mg, 0.15 mmol). A colour change of the DMF was observed from colourless to yellow and back again. (*S*)-2,2,2-Trifluoro-*N*-(1-iodo-3-phenylpropan-2-yl)acetamide **16** (356 mg, 1 mmol) or (*S*)-2,2,2-trifluoro-*N*-(1-iodo-3-methylbutane-2-yl)acetamide **17** (309 mg, 1 mmol) was added immediately followed by a catalytic amount of iodine (40 mg, 0.15 mmol). The solution was stirred at room temperature and gave a noticeable exotherm. In a separate flame dried nitrogen purged flask Pd_2dba_3 (11 mg, 0.0125 mmol), was added followed by dry DMF (0.25 mL). In a separate flame dried nitrogen purged flask, SPhos (11 mg, 0.025 mmol) was added followed by dry DMF (0.25 mL). Once the zinc insertion has cooled the palladium solution (50 μL, 0.0025 mmol) and SPhos solution (50 μL, 0.005 mmol) were added via syringe followed by aryl iodide (1.3 mmol). The reaction was allowed to stir at room temperature overnight under positive pressure of nitrogen. The crude reaction mixture was applied directly to a silica gel column to afford the purified cross-coupled product.

4.4.1. (S)-(−)-2,2,2-Trifluoro-N-(1-(4-methoxyphenyl)-3-phenylpropan-2-yl)acetamide ***22a***. General cross-coupling method A was

followed using 4-iodoanisole (304 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (249 mg, 74%) as a white solid.

General cross-coupling method B was followed using 4-iodoanisole (304 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (236 mg, 70%) as a white solid; mp 141.5–143 °C; R_f 0.44 (20% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}): 3311, 3021, 2958, 1691, 1609, 1555, 1510, 1215, 1125, 1152, 1030, 840, 808; δ_H (400 MHz, $CDCl_3$) 2.80 (1H, dd, *J* 15.0, 7.0), 2.83 (1H, dd, *J* 15.0, 7.0), 2.90 (1H, dd, *J* 14.0, 6.0), 2.95 (1H, dd, *J* 14.0, 6.0), 3.82 (3H, s, OCH_3), 4.39–4.49 (1H, m, C*H*NHTFA), 5.97–6.05 (1H, br, NH), 6.86–6.91 (2H, m, C_6H_4–OCH_3), 7.09–7.13 (2H, m, C_6H_4–OCH_3), 7.17–7.37 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 38.5, 39.3, 52.5, 55.3, 114.1, 118.6 (q, *J* 287), 127.0, 128.6, 128.7, 129.2, 130.2, 136.7, 156.6 (q, *J* 37), 158.6; $[\alpha]_D^{22}$ −2.0 (*c* 1.01, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 338.1352. $C_{18}H_{19}NO_2F_3$ requires MH^+ 338.1368.

4.4.2. (S)-(−)-2,2,2-Trifluoro-N-(1-(3-methoxyphenyl)-3-phenylpropan-2-yl)acetamide ***22b***. General cross-coupling method A was followed using 3-iodoanisole (155 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (242 mg, 72%) as a white solid.

General cross-coupling method B was followed using 3-iodoanisole (155 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (219 mg, 65%) as a white solid; mp 137.2–138.5 °C; R_f 0.46 (20% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}): 3028, 2929, 1699, 1610, 1584, 1455, 1260, 1220, 1165, 1057, 876, 782, 754; δ_H (400 MHz, $CDCl_3$) 2.75 (1H, dd, *J* 14.0, 7.0), 2.77 (1H, dd, *J* 14.0, 7.0), 2.84 (1H, dd, *J* 12.0, 6.5), 2.87 (1H, dd, *J* 12.0, 6.5), 3.73 (3H, s, OCH_3), 4.34–4.44 (1H, m, C*H*NHTFA), 5.90–5.99 (1H, br, NH), 6.63–6.65 (1H, m, C_6H_4–OCH_3), 6.67–6.76 (2H, m, C_6H_4–OCH_3), 7.09–7.29 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 39.4, 52.4, 55.2, 112.4, 114.9, 115.7 (q, *J* 286), 121.5, 127.0, 128.8, 129.2, 129.8, 136.7, 138.2, 156.6 (q, *J* 37), 159.9, one signal not observed; $[\alpha]_D^{22}$ −1.0 (*c* 1.01, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 338.1378. $C_{18}H_{19}NO_2F_3$ requires MH^+ 338.1368.

4.4.3. (S)-(−)-2,2,2-Trifluoro-N-(1-(2-methoxyphenyl)-3-phenylpropan-2-yl)acetamide ***22c***. General cross-coupling method A was followed using 2-iodoanisole (169 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (202 mg, 60%) as a white solid.

General cross-coupling method B was followed using 2-iodoanisole (169 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (167 mg, 50%) as a white solid; mp 137–139 °C; R_f 0.49 (20% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}): 3310, 3028, 2963, 1694, 1614, 1556, 1254, 1219, 1174, 1151, 1030, 837, 809, 754; δ_H (400 MHz, $CDCl_3$) 2.75–2.90 (3H, m), 3.06 (1H, dd, *J* 14.0, 5.5), 3.82 (3H, s, OCH_3), 4.21–4.32 (1H, m, C*H*NHTFA), 6.85–6.92 (2H, m, C_6H_4–OCH_3), 6.98–7.02 (1H, m, C_6H_4–OCH_3), 7.19–7.36 (m, 7H, ArH); δ_C (100 MHz, $CDCl_3$) 33.3, 40.14, 53.9, 55.2, 110.5, 115.9 (q, *J* 286), 121.2, 125.6, 126.8, 128.5, 128.6, 129.5, 131.4, 137.3, 156.7 (q, *J* 37), 157.0; $[\alpha]_D^{22}$ −24.9 (*c* 1.0, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 338.1361. $C_{18}H_{19}NO_2F_3$ requires MH^+ 338.1368.

4.4.4. (S)-(−)-2,2,2-Trifluoro-N-(1-phenyl-3-p-tolylpropan-2-yl) acetamide ***22d***. General cross-coupling method A was followed using 4-iodotoluene (283 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (270 mg, 84%) as a white solid.

General cross-coupling method B was followed using 4-iodotoluene (283 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (231 mg, 72%) as a white solid; mp 165–166.5 °C; R_f 0.58 (20% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}): 3302, 3030, 2933, 1698, 1562, 1162, 878, 757; δ_H (400 MHz, $CDCl_3$) 2.26 (3H, s, CH_3), 2.69–2.82 (3H, m), 2.86 (1H, dd, *J* 14.0, 6.5), 4.32–4.42 (1H, m, C*H*NHTFA), 5.9–5.97 (1H, br, NH), 6.99 (2H, d, *J* 8.0, C_6H_4–CH_3), 7.04–7.28 (7H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.0, 38.9, 39.3, 52.4, 115.7 (q, *J* 287), 127.0, 128.7, 129.1, 129.2, 129.4, 133.5, 136.6, 136.7, 156.6 (q, *J* 37); $[\alpha]_D^{22}$ −2.0 (*c* 1.01, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 322.14.34. $C_{18}H_{19}NOF_3$ requires MH^+ 322.1419.

4.4.5. (S)-(+)-2,2,2-Trifluoro-N-(1-phenyl-3-o-tolylpropan-2-yl) acetamide ***22e***. General cross-coupling method A was followed using 2-iodotoluene (166 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (196 mg, 61%) as a white solid.

General cross-coupling method B was followed using 2-iodotoluene (166 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (103 mg, 32%) as a white solid; mp 142.5–143.5 °C; R_f 0.57 (20% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}): 3306, 3024, 2925, 1697, 1559, 1163, 877, 749; δ_H (400 MHz, $CDCl_3$) 2.27 (3H, s, CH_3), 2.82 (1H, dd, *J* 14.0, 8.0), 2.86–3.00 (3H, m), 4.35–4.46 (1H, m, C*H*NHTFA), 6.06–6.13 (1H, br, NH), 7.05–7.35 (9H, m, ArH); δ_C (100 MHz, $CDCl_3$) 19.4, 37.3, 39.9, 51.8, 115.7 (q, *J* 287), 126.1, 127.0, 127.1, 128.8, 129.2, 129.7, 130.8, 135.1, 136.4, 136.8, 156.7 (q, *J* 37); $[\alpha]_D^{22}$ +19.1 (*c* 1.0, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 322.1414. $C_{18}H_{19}NOF_3$ requires MH^+ 322.1419.

4.4.6. (S)-(+)-2,2,2-Trifluoro-N-(1-(4-hydroxyphenyl)-3-phenylpropan-2-yl)acetamide ***22f***. General cross-coupling method A was followed using 4-iodophenol (287 mg, 1.3 mmol) and gave, after purification by silica gel column (10% ethyl acetate in petroleum ether), the title compound (220 mg, 68%) as a white solid.

General cross-coupling method B was followed using 4-iodophenol (287 mg, 1.3 mmol) and gave, after purification by silica gel column (10% ethyl acetate in petroleum ether), the title compound (113 mg, 35%) as a white solid; mp 163.0–164.5 °C; R_f 0.22 (20% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}): 3382, 3321, 3030, 2930, 1692, 1601, 1556, 1511, 1218, 1163, 1103, 825, 750, 659; δ_H (400 MHz, CD_3COCD_3) 2.80–3.04 (4H, m, PhCH_2NHTFACH_2–C_6H_4–OH), 4.32–4.43 (1H, m, C*H*NHTFA), 6.74–6.79 (2H, m, C_6H_4–OH), 7.05–7.10 (2H, m, C_6H_4–OH), 7.18–7.31 (5H, m, Ph), 8.19 (1H, s, OH), 8.22–8.30 (1H, br, NH); δ_C (100 MHz, CD_3COCD_3) 40.0, 40.6, 54.6, 116.0, 117.0 (q, *J* 287), 127.2, 129.1, 129.7, 130.0, 131.0, 139.3, 156.9, 157.0 (q, *J* 37); $[\alpha]_D^{22}$ +2.0 (*c* 1.01, acetone); *m*/*z* (ES) Found: MH^+ 324.1221. $C_{17}H_{17}NO_2F_3$ requires MH^+ 324.1211.

4.4.7. (S)-(+)-2,2,2-Trifluoro-N-(1-(4-fluorophenyl)-3-phenylpropan-2-yl)acetamide ***22g***. General cross-coupling method A was followed using 4-fluoroiodobenzene (150 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (260 mg, 80%) as a white solid.

General cross-coupling method B was followed using 4-fluoroiodobenzene (150 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (231 mg, 71%) as a white solid; mp 150.5–152 °C; R_f 0.49 (20% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}): 3304, 3031, 2934, 1697, 1561, 1509, 1223, 1159, 877, 829, 750, 724; δ_H (400 MHz, $CDCl_3$) 2.79 (1H, dd, *J* 13.5, 7.5), 2.82 (1H, dd, *J* 13.5, 7.5), 2.90 (1H, dd, *J* 14.0, 6.0), 2.92 (1H, dd, *J* 14.0, 6.0), 4.36–4.46 (1H, m, C*H*NHTFA), 6.10–6.20 (1H, br, NH), 6.96–7.36 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 38.7, 39.5, 52.6, 115.6 (d, *J* 21), 115.6 (q, *J* 286), 127.1, 128.8, 129.2, 130.6 (d, *J* 8), 132.5, 136.5, 156.7 (q, *J* 37), 161.9 (d, *J* 246); $[\alpha]_D^{22}$ +4.0 (*c* 1.0, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 326.1166. $C_{17}H_{16}NOF_4$ requires MH^+ 326.1168.

4.4.8. (S)-(−)-Methyl 4-(3-phenyl-2-(2,2,2-trifluoro-acetamido)propyl)benzoate ***22h***. General cross-coupling method A was followed

using methyl 4-iodobenzoate (340 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (255 mg, 70%) as a white solid.

General cross-coupling method B was followed using methyl 4-iodobenzoate (340 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (244 mg, 67%) as a white solid; mp 166.5–168 °C; R_f 0.32 (20% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}): 3296, 3100, 2954, 1717, 1701, 1611, 1557, 1280, 1177, 1154, 1104, 970, 880, 751; δ_H (400 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 14.0, 7.5), 2.92 (1H, dd, *J* 14.0, 7.5), 2.96 (1H, dd, *J* 14.0, 6.0), 3.02 (1H, dd, *J* 14.0, 6.0), 3.94 (3H, s, CO_2CH_3), 4.45–4.55 (1H, m, C*H*NHTFA), 5.96–6.04 (1H, br, NH), 7.16–7.20 (2H, m, C_6H_4–CO_2CH_3), 7.25–7.38 (5H, m, Ph), 8.00–8.04 (2H, m, C_6H_4–CO_2CH_3); δ_C (100 MHz, $CDCl_3$) 39.5, 39.6, 52.1, 52.3, 115.6 (q, *J* 286), 127.2, 128.8, 129.0, 129.2, 129.2, 130.0, 136.3, 142.2, 156.7 (q, *J* 35), 166.6; $[\alpha]_D^{22}$ −1.0 (*c* 1.01, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 366.1325. $C_{19}H_{19}NO_3F_3$ requires MH^+ 366.1317.

4.4.9. (S)-(−)-2,2,2-Trifluoro-N-(1-(naphthalen-1-yl)-3-phenylpropan-2-yl)acetamide ***22i***. General cross-coupling method A was followed using 1-iodonaphthalene (190 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (239 mg, 67%) as a white solid.

General cross-coupling method B was followed using 1-iodonaphthalene (190 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (150 mg, 42%) as a white solid; mp 174.0–175.5 °C; R_f 0.51 (20% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}): 3328, 3030, 2929, 1698, 1549, 1450, 1203, 1149, 913, 870, 796, 778, 700; δ_H (400 MHz, $CDCl_3$) 2.95 (1H, dd, *J* 14.0, 7.5), 3.01 (1H, dd, *J* 14.0, 6.5), 3.32–3.42 (2H, m), 4.50–4.61 (1H, m, C*H*NHTFA), 6.05–6.15 (1H, br, NH), 7.16–7.20 (2H, m, Ph), 7.24–7.36 (4H, m, Ph, Naph), 7.39–7.44 (1H, m, Naph), 7.47–7.56 (2H, m, Naph), 7.79 (1H, d, *J* 8.0, Naph), 7.85–7.89 (1H, m, Naph), 7.95–7.99 (1H, m, Naph); δ_C (100 MHz, $CDCl_3$) 36.9, 39.7, 52.4, 119.6 (q, *J* 286), 123.4, 125.3, 125.9, 126.5, 127.1, 127.5, 128.0, 128.8, 129.0, 129.2, 132.0, 133.0, 134.0, 136.7, 157.0 (q, *J* 37); $[\alpha]_D^{22}$ +25.1 (*c* 1.0, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 358.1436. $C_{21}H_{19}NOF_3$ requires MH^+ 358.1419.

4.4.10. (R)-(−)-2,2,2-Trifluoro-N-(3-methyl-1-phenylbutan-2-yl) acetamide ***23a***. General cross-coupling method A was followed using iodobenzene (145 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (163 mg, 63%) as a white solid.

General cross-coupling method B was followed using iodobenzene (145 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (151 mg, 58%) as a white solid; mp 115–117 °C; R_f 0.53 (30% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}) 3308, 3102, 2976, 2876, 1699, 1558, 1370, 1161, 851, 757; δ_H (400 MHz, $CDCl_3$) 0.98 (3H, d, *J* 6.8, CH_3CH), 1.04 (3H, d, *J* 6.8, CH_3CH), 1.81–1.95 (1H, m, $(CH_3)_2CH$), 2.75 (1H, dd, *J* 14.0, 8.3, CH_AH_BPh), 2.96 (1H, dd, *J* 14.0, 5.6, CH_AH_BPh), 4.07–4.17 (1H, m, C*H*NHTFA), 5.95–6.09 (1H, br, NH), 7.13–7.36 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 17.6, 19.5, 30.8, 37.8, 56.6, 116.0 (q, *J* 288), 126.8, 128.6, 129.0, 137.2, 158.0 (q, *J* 37); $[\alpha]_D^{22}$ −21 (*c* 1.0, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 260.1268. $C_{13}H_{17}NOF_3$ requires MH^+ 260.1262.

4.4.11. (R)-(−)-2,2,2-Trifluoro-N-(3-methyl-1-p-tolylbutan-2-yl) acetamide ***23b***. General cross-coupling method A was followed using 4-iodotoluene (283 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (191 mg, 70%) as a white solid.

General cross-coupling method B was followed using 4-iodotoluene (283 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (115 mg, 42%) as a white solid; mp 149–150 °C; R_f 0.55 (30% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}) 3308, 3102, 2979, 2879, 1699, 1558, 1370, 1161, 860, 770; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.8, CH_3CH), 0.94 (3H, d, *J* 6.8, CH_3CH), 1.71–1.83 (1H, m, $(CH_3)_2CH$), 2.25 (3H, s, PhCH_3), 2.63 (1H, dd, *J* 14.1, 8.0, CH_AH_B–Ar), 2.81 (1H, dd, *J* 14.1, 5.8, CH_AH_B–Ar), 3.95–4.05 (1H, m, C*H*NHTFA), 5.81–5.95 (1H, br, NH), 6.97 (2H, d, *J* 8.0, Ar), 7.04 (2H, d, *J* 8.0, Ar); δ_C (100 MHz, $CDCl_3$) 17.5, 19.6, 21.0, 30.6, 37.3, 56.5, 116.0 (q, *J* 288), 128.9, 129.3, 133.9, 136.4, 158.0 (q, *J* 37); $[\alpha]_D^{22}$ −27 (*c* 1.0, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 274.1412. $C_{14}H_{19}NOF_3$ requires MH^+ 274.1419.

4.4.12. (R)-(−)-2,2,2-Trifluoro-N-(1-(4-methoxyphenyl)-3-methylbutan-2-yl)acetamide ***23c***. General cross-coupling method A was followed using 4-iodoanisole (304 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (165 mg, 57%) as a white solid.

General cross-coupling method B was followed using 4-iodoanisole (304 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (106 mg, 37%) as a white solid; mp 121–123 °C; R_f 0.44 (30% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}) 3293, 3107, 2969, 2878, 1670, 1558, 1365, 1255, 1158, 858; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.8, CH_3CH), 0.94 (3H, d, *J* 6.8, CH_3CH), 1.70–1.83 (1H, m, CH_3CH), 2.61 (1H, dd, *J* 14.1, 8.0, CH_AH_B–Ar), 2.80 (1H, dd, *J* 14.1, 5.7, CH_AH_B–Ar), 3.72 (3H, s, OCH_3), 3.93–4.02 (1H, m, C*H*NHTFA), 5.81–5.93 (1H, br, NH), 6.74–6.79 (2H, m, Ar), 6.98–7.02 (2H, m, Ar), δ_C (100 MHz, $CDCl_3$) 17.6, 19.5, 30.7, 36.8, 55.2, 56.7, 114.1, 116.0 (q, *J* 288), 129.1, 130.0, 156.0 (q, *J* 37), 158.5; $[\alpha]_D^{22}$ −25 (*c* 1.0, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 290.1358. $C_{14}H_{19}NO_2F_3$ requires MH^+ 290.1368.

4.4.13. (R)-(−)-2,2,2-Trifluoro-N-(1-(3-methoxyphenyl)-3-methylbutan-2-yl)acetamide ***23d***. General cross-coupling method A was followed using 3-iodoanisole (155 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (214 mg, 74%) as a white solid; mp 102–103 °C; R_f 0.45 (30% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}) 3299, 2970, 2845, 1696, 1558, 1261, 1176, 891, 725; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.8, CH_3CH), 0.93 (3H, d, *J* 6.8, CH_3CH), 1.71–1.84 (1H, m, CH_3CH), 2.63 (1H, dd, *J* 14.1, 8.6, CH_AH_B–Ar), 2.82 (1H, dd, *J* 14.1, 5.5, CH_AH_B–Ar), 3.70 (3H, s, OCH_3), 3.96–4.05 (1H, m, C*H*NHTFA), 6.11–6.21 (1H, br, NH), 6.61–6.71 (3H, m, Ar), 7.09–7.16 (1H, m, Ar); δ_C (100 MHz, $CDCl_3$) 17.6, 19.5, 30.8, 37.7, 55.1, 56.5, 112.2, 114.7, 115.0 (q, *J* 288), 121.4, 129.6, 138.7, 156.0 (q, *J* 37), 159.8; $[\alpha]_D^{22}$ −20 (*c* 1.0, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 290.1366$C_{14}H_{19}NO_2F_3$ requires MH^+ 290.1368.

4.4.14. (R)-(−)-2,2,2-Trifluoro-N-(1-(2-methoxyphenyl)-3-methylbutan-2-yl)acetamide ***23e***. General cross-coupling method A was followed using 2-iodoanisole (169 μL, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (122 mg, 42%) as a white solid; mp 102–103 °C; R_f 0.45 (30% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}) 3297, 3107, 2973, 2845, 1696, 1564, 1261, 1167, 891, 722; δ_H (400 MHz, $CDCl_3$) 0.93 (3H, d, *J* 6.8, CH_3CH), 0.94 (3H, d, *J* 6.8, CH_3CH), 1.84–1.97 (m, 1H, CH_3CH), 2.68 (1H, dd, *J* 13.8, 4.3, CH_AH_B–Ar), 2.80 (1H, dd, *J* 13.8, 10.7, CH_AH_B–Ar), 3.77 (3H, s, OCH_3), 3.82–3.92 (m, 1H, C*H*NHTFA), 6.75–7.2 (m, 5H, NH and Ar); δ_C (100 MHz, $CDCl_3$) 18.3, 18.5, 30.9, 31.7, 55.2, 57.6, 110.3, 116.0 (q, *J* 288), 121.1, 126.1, 128.3, 131.0, 157.0 (q, *J* 37), 157.1; $[\alpha]_D^{22}$ −47.4 (*c* 1.01, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 290.1359 $C_{14}H_{19}NO_2F_3$ requires MH^+ 290.1368.

4.4.15. (R)-(−)-Methyl 4-(3-methyl-2-(2,2,2-trifluoro-acetamido)butyl)benzoate ***23f***. General cross-coupling method A was followed using methyl 4-iodobenzoate (340 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (162 mg, 51%) as a white solid; mp

129–131 °C; R_f 0.31 (10% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}) 3295, 3106, 2955, 2884, 1707, 1696, 1561, 1373, 1277, 1157, 882, 766; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.8, C*H*$_3$CH), 0.95 (3H, d, *J* 6.8, C*H*$_3$CH), 1.72–1.85 (1H, m, CH$_3$C*H*), 2.71 (1H, dd, *J* 14.1, 8.7, C*H*$_A$H$_B$–Ar), 2.93 (1H, dd, *J* 14.1, 5.6, CH$_A$*H*$_B$–Ar), 3.84 (3H, s, CO$_2$C*H*$_3$), 4.00–4.10 (1H, m, C*H*NHTFA), 5.87–5.97 (1H, br, NH), 7.15–7.19 (2H, m, Ar), 7.88–7.92 (2H, m, Ar); δ_C (100 MHz, $CHCl_3$) 17.6, 19.5, 31.3, 37.9, 52.1, 56.6, 116.0 (q, *J* 288), 128.6, 129.0, 129.9, 143.0, 158.0 (q, *J* 37), 166.9; $[\alpha]_D^{22}$ −12.2 (*c* 1.01, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 318.1318. $C_{15}H_{19}NO_3F_3$ requires MH^+ 318.1317.

4.4.16. (R)-(−)-2,2,2-Trifluoro-N-(1-(4-fluorophenyl)-3-methylbutan-2-yl)acetamide ***23g***. General cross-coupling method A was followed using 1-fluoro-4-iodobenzene (289 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (169 mg, 61%) as a white solid.

General cross-coupling method B was followed using 1-fluoro-4-iodobenzene (289 mg, 1.3 mmol) and gave, after purification by silica gel column (5% ethyl acetate in petroleum ether), the title compound (167 mg, 60%) as a white solid; mp 116–117 °C; R_f 0.47 (30% EtOAc in petrol); FTIR (ν_{max}/cm^{-1}) 3304, 3103, 2970, 2879, 1697, 1557, 1365, 1211, 1158, 861, 727; δ_H (400 MHz, $CDCl_3$) 0.88 (3H, d, *J* 6.8, C*H*$_3$CH), 0.93 (3H, d, *J* 6.8, C*H*$_3$CH), 1.70–1.83 (1H, m, CH$_3$C*H*), 2.59 (1H, dd, *J* 14.1, 8.8, C*H*$_A$H$_B$–Ar), 2.84 (1H, dd, *J* 14.1, 5.4, CH$_A$*H*$_B$–Ar), 3.91–4.01 (1H, m, C*H*NHTFA), 6.13–6.23 (1H, br, NH), 6.86–6.93 (2H, m, Ar), 7.00–7.07 (2H, m, Ar); δ_C (101 MHz, $CDCl_3$) 17.5, 19.5, 30.9, 37.0, 56.7, 115.4 (d, *J* 21), 116.0 (q, *J* 288), 130.4 (d, *J* 8), 133.0, 156.7 (q, *J* 37), 161.7 (d, *J* 245); $[\alpha]_D^{22}$ −13 (*c* 1.0, $CHCl_3$); *m*/*z* (ES) Found: MH^+ 278.1166 $C_{13}H_{16}NOF_4$ requires MH^+ 278.1168.

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