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γ-Fluorophenyl-GABA derivatives from fluorobenzonitriles in high diastereomeric and enantiomeric excess

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ABSTRACT

An enantioselective synthesis of α-fluoroaryl homoallylic amines in 52–71% yields and 76–93% enantioselectivities has been achieved *via* the allylboration of the corresponding fluorinated *N*-aluminobenzaldimines with *B*-allyldiisopinocampheylborane in the presence of methanol, followed by alkaline hydrogen peroxide workup. Crotylboration of these aluminobenzaldimines with potassium *B*-methoxy *B*-*E*- or -*Z*-crotyldiisopinocampheylborinate provided the corresponding β-*anti*- or -*syn*-methyl α-fluoroarylhomoallylamines, respectively in high de and ee. Similarly, alkoxyallylboration with lithium *B*-methoxy *B*-γ-OMEMallyldiisopinocampheylborinate provided the corresponding β-*syn*-alkoxyhomoallylamines in excellent de and ee. Representatives of these amino alkenes were converted to the corresponding optically active *N*-Boc-protected fluorinated amino alcohols *via* hydroboration-oxidation. Further chromium-mediated oxidation provided *N*-Boc-protected γ-fluorophenyl-γ-aminobutyric acids, which upon deprotection provided the corresponding γ-lactams.

1. Introduction

Appropriate substitution of a hydrogen atom or hydroxyl group with a fluorine atom is commonplace in medicinal and biological studies [1]. Synthesis of unnatural amino acids and peptidomimetics are important for biomedical research [2]. Fluorinated amino acids and peptides often create altered physical, chemical, and biological properties [3]. Gamma-aminobutyric acid (GABA) is a ubiquitous neurotransmitter that modulates neuronal activity throughout the central and peripheral nervous system [4] and GABA-associated receptors play a vital role in numerous central nervous system (CNS) disorders [5]. The major effect of GABA is to inhibit neuronal activity *via* its action on the GABA-A receptors [6]. A second type of GABA receptor, GABA-B receptor, a G-protein-coupled receptor, also plays an important role in the physiological actions of GABA [7]. The neuro-modulatory role of GABA and GABA-A receptors has led to the development of drugs designed to enhance the action of GABA for the treatment of disorders that stem from abnormal neuronal activity such as epilepsy and neuropathic pain [8]. A number of drugs currently available for their treatment include GABA analogs, such as Tiagabine (Gabitril®) [9], Gabapentin (Neurontin®) [10], Pregabalin (Lyrica®) [11], and Vigabatrin (Sabril®) [12]. Though related in structure, these drugs target several different proteins involved in modulation of neuronal excitability. For example, Tiagabine inhibits the re-uptake of GABA from the synaptic cleft by the GABA transporters (GATs), prolonging the action of endogenously released GABA. Vigabatrin inhibits the breakdown of endogenous GABA by inhibiting GABA transaminase. Finally, Gabapentin and Pregabalin bind to the $\alpha_2\delta_1$ subunit of voltage-dependent Ca^{2+} channels, and may inhibit the release of excitatory neurotransmitters by inhibiting Ca^{2+} current. Interestingly, none of the currently available GABA-derived drugs is an agonist at the GABA-A receptors. The antispastic drug baclofen (Lioresal®) is a GABA-B receptor agonist [13]. As part of our program on the application of organoboranes for biologically active molecules [14], we were interested in developing agonists and antagonists for GABA receptors. Recently, we accomplished the synthesis of a series of β- and γ-substituted GABA derivatives *via* the "allyl" boration of *N*-metaloimines Scheme 1 [15]. Owing to our interest in fluoroorganic chemistry [16–18], we turned our attention to the development of fluorinated analogs of this primary class of

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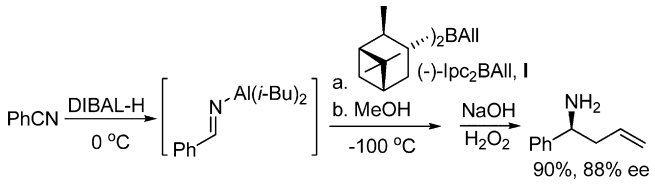
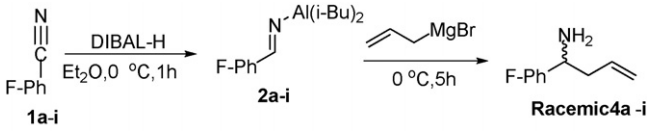


Scheme 1.



Scheme 4.

biomolecules for structure–activity relationship (SAR) studies and therapy. Although several classes of fluorinated amino acids have been synthesized [19], the preparation of optically active γ-fluoroalkyl and -aryl substituted GABA has not been examined thoroughly [20]. We have recently reported a few fluoroaryl-GABA *via* the allylboration of imine–borane complexes (Scheme 2) [21]. We wished to include crotyl- and alkoxyallylboration of fluroarylimines to prepare the β,γ-disubstituted GABA derivatives. For feasible and cost-effective large-scale synthesis, we now examined the allyl-, crotyl-, and alkoxyallylboration of the corresponding fluoroaryl aluminoimines [15]. Our results are summarized herein.

2. Results and discussion

2.1. Allylboration

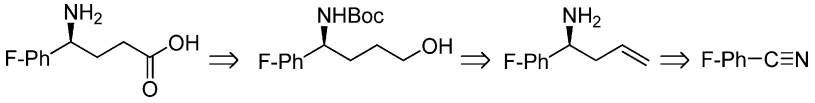
Initially, we examined the preparation of the homoallylic amine from 2-fluorobenzonitrile (**1a**) *via* allylboration. The required fluorinated *N*-alumino-benzaldimine (**2a**) was prepared from the corresponding benzonitrile *via* the reduction using diisobutylaluminum hydride (DIBAL-H) according to the reported procedure [22]. Consistent with our earlier observation in the case of non-fluorinated *N*-aluminoimines, treatment of **2a** with **I**, prepared from (−)-*B*-methoxydiisopinocampheylborane and allylmagnesium bromide [23], in THF failed to react, even at room temperature (RT), over several days, as revealed by ^{11}B NMR spectroscopy. This was, however, overcome by the addition of 1 equiv. of water or methanol, which released the free aldimine, as an allylborane complex [24,25]. The reaction now proceeded within 4–5 h at −78 °C, as was shown by the chemical shift in the ^{11}B NMR spectrum (change from δ 79 ppm for reagent **I** to δ 47 ppm for the intermediate **3a**, Scheme 3).

Alkaline hydrogen peroxide workup provided the corresponding homoallylamine (**4a**) in 71% yield. Analysis of the corresponding α-methoxy α-(trifluoromethyl)phenylacetamides (MTPA-amides, Mosher amides) [26] using ^{19}F NMR spectroscopy revealed 76% enantiomeric excess. The racemic homoallylamine was prepared by the reaction of allyl Grignard reagent with the corresponding aluminoimine (Scheme 4) for comparison of the MTPA amide and the determination of the enantiomeric excess. On the basis of our earlier results from the non-fluorinated benzaldimines, we believe that we have obtained the *S* isomer.

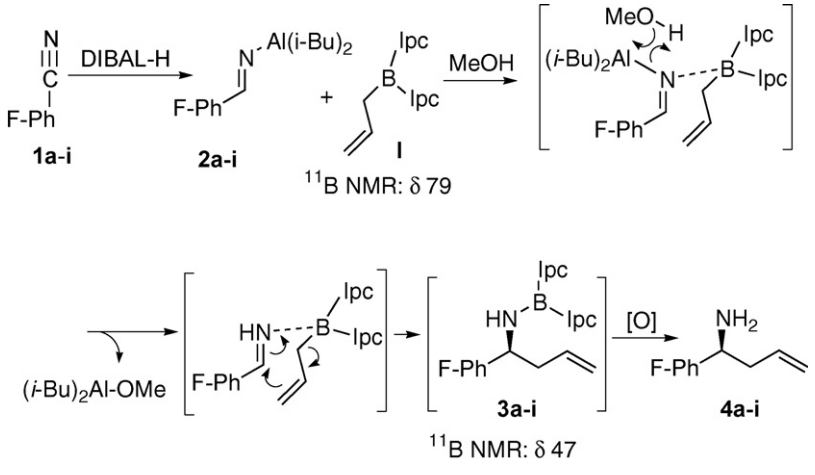
Encouraged by this result, we examined a series of ring-fluorinated *N*-alumino-benzaldimines, prepared by the reduction of the corresponding benzonitriles with DIBAL-H. Accordingly, 3-fluorobenzonitrile (**1b**), 4-fluorobenzonitrile (**1c**), 2,3-difluoro- (**1d**), 2,4-difluoro- (**1e**), 2,5-difluoro- (**1f**), 2,6-difluoro- (**1g**), 3,4-difluoro- (**1h**) and 3,5-difluorobenzonitrile (**1i**) were subjected to DIBAL-H reduction for further allylboration reaction in the presence of methanol. In all of the cases, the allylboration of the corresponding *N*-alumino-fluorobenzaldimines **2b**–**2i** were performed at −78 °C and were complete within 4–5 h. Alkaline hydrogen peroxide workup provided the corresponding homoallylic amines **4b**–**4i** in 52–69% yield and 76–93% ee (Scheme 3, Table 1). In general, the yields of the fluorinated homoallylic amines were slightly lower than the corresponding non-fluorinated derivatives [21]. The % enantiomeric excesses were consistently high, as is the norm with the allylborating agent **I** [23].

2.2. Crotylboration

Having achieved the allylboration of ring-fluorinated benzaldimines, we turned our attention to the crotylboration reaction, with the aim of preparing β-methyl-α-fluoroarylhomoallylamines that can be further converted to the corresponding δ-amino alcohols

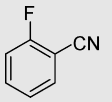
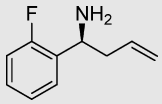
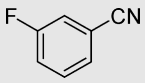
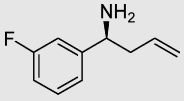
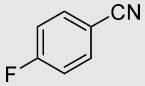
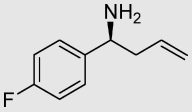
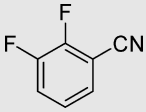
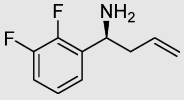
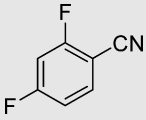
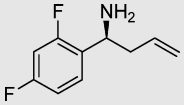
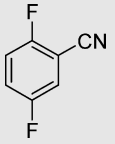
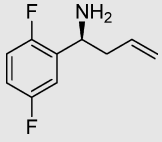
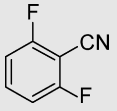
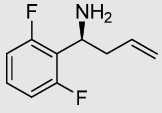
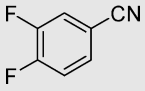
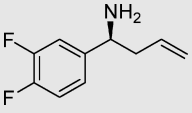
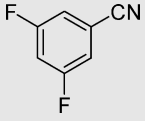
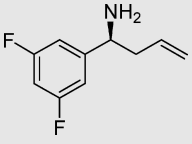


Scheme 2.



Scheme 3.

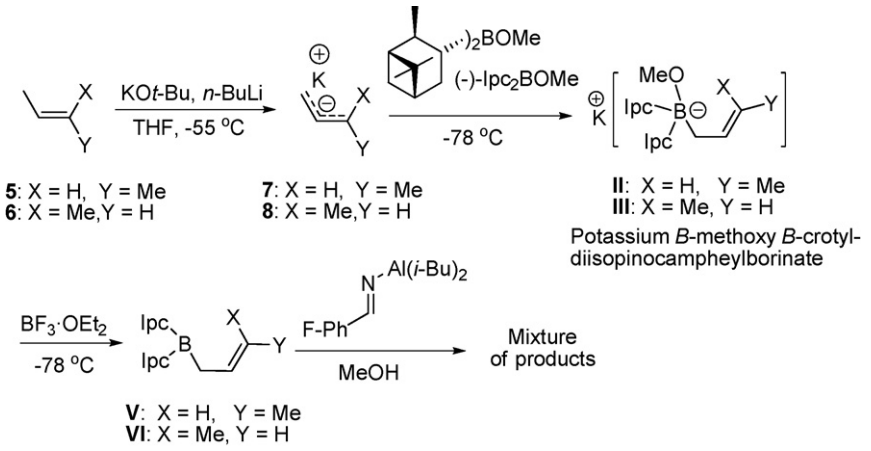
Table 1
Preparation of α-fluorophenylhomoallylamines from fluorobenzonitriles[a].

Entry	Benzonitrile		Homoallylic amine		Yield, %[b]	ee, %[c]
	#	Structure	#	Structure		
1	**1a**		**4a**		71	76
2	**1b**		**4b**		63	88
3	**1c**		**4c**		69	90
4	**1d**		**4d**		55	82
5	**1e**		**4e**		52	80
6	**1f**		**4f**		59	76
7	**1g**		**4g**		57	93
8	**1h**		**4h**		60	90
9	**1i**		**4i**		62	89

[a] Reactions were carried out in Et_2O at −78 °C for 4–5 h.
[b] Isolated yield after chromatography.
[c] Determined from the ^{19}F NMR spectra of Mosher (MTPA) amides. In all of the cases, we assign the (*S*)-configuration of homoallylic amines for the major isomer, see text.

and γ-aminobutyric acids. The crotylborane reagents **V** and **VI** were prepared from *E*- and *Z*-2-butene (**5** and **6**) (Scheme 5) and attempted crotylboration in the presence of methanol gave a complex mixture of products difficult to separate. Boron trifluoride diethyl etherate used to free the reagents from the 'ate' complexes **II** and **III** was found to be detrimental to the free imine [15]. However, for the non-fluorinated aluminoimines, we had shown that the reaction proceeded well with **II** and **III**. Accordingly, we extended this reaction to *N*-aluminofluorobenzaldimines with **II** and **III** (Scheme 6).

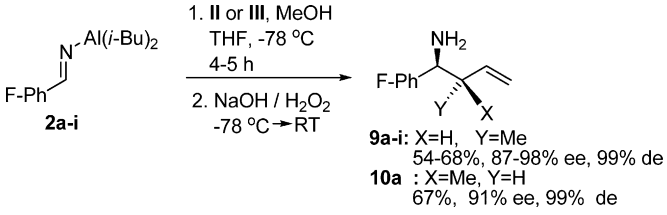
Potassium *B*-methoxy *B*-*E*- or -*Z*-crotyldiisopinocampheylborinates (**II** and **III**) were prepared from *E*- or *Z*-2-butenylpotassium (**7** and **8**) respectively and (−)-*B*-methoxydiisopinocampheylborane as reported earlier [27] and the imine **2a**, obtained from 2-fluorobenzonitrile **1a**, was reacted in THF at −78 °C after the addition of 1 equiv. of methanol. The reaction was complete within 4–5 h and the usual workup provided the expected amines **9a** and **10a**, respectively, in 71% and 73% yields and very high de and 92% ee. The diastereomeric excess was determined from the ^1H NMR of the crude product. The



Scheme 5.

enantiomeric excess was determined using the ^{19}F NMR of the MTPA (Mosher) amide.

We then chose **II** as the representative reagent for the crotylboration of aluminoimines **2b–2i** and the corresponding *anti*-β-methylhomoallylamines were obtained in very high de and 87–98% ee (Scheme 6; Table 2, Entries 3–10). The stereochemistry of the products was assigned based on analogy of the non-fluorinated benzaldimines. The racemic products were prepared by the reaction of corresponding aluminoimines in presence of methanol with the 'ate' complexes obtained from *E*- or *Z*-2-butenylpotassium (**7** and **8**) and *B*-methoxy-9-BBN (Scheme 7).



Scheme 6.

2.3. Alkoxyallylboration

Having completed the crotylboration successfully with the 'ate' complexes **II** and **III**, we now proceeded to the alkoxyallylboration. As in the case of crotylboration, the reaction gave a mixture of products with the free reagent **VII** (Scheme 8). However, the reaction proceeded well with the 'ate' complex. **IV**. Imine **2a** was mixed with **IV** [28], followed by the addition of 1 equiv. of methanol and the reaction was monitored with ^{11}B NMR spectroscopy. Upon completion (4–5 h), alkaline oxidative workup

Table 2
Preparation of γ-fluorophenyl-β-methylhomoallylamines from fluorobenzonitriles[a].

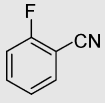
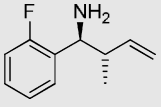
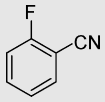
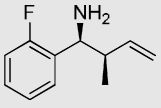
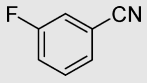
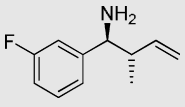
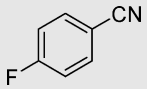
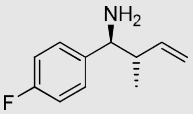
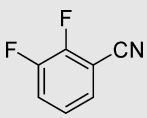
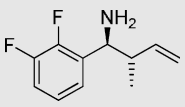
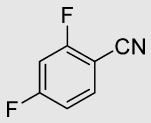
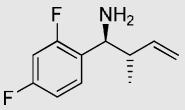
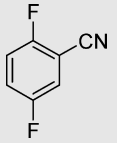
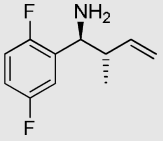
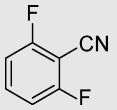
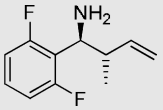
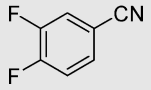
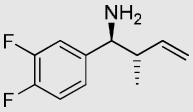
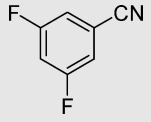
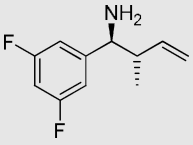
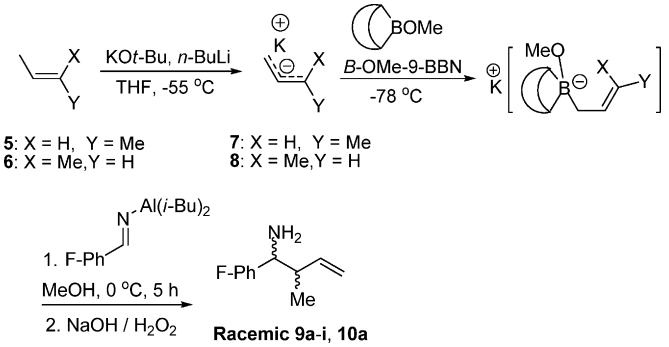
Entry	Benzonitrile		Homoallylic amine		Yield, %[b]	ee, %[c]	de, %[d]
	#	Structure	#	Structure			
1	**1a**		**9a**		71	92	99
2	**1a**		**10a**		73	92	99
3	**1b**		**9b**		75	92	99
4	**1c**		**9c**		69	91	99
5	**1d**		**9d**		63	88	99

Table 2 (*Continued*)

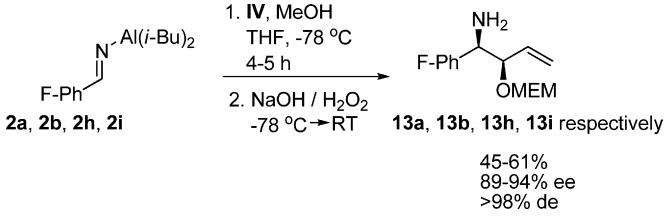
Entry	Benzonitrile		Homoallylic amine		Yield, %[b]	ee, %[c]	de, %[d]
	#	Structure	#	Structure			
6	**1e**		**9e**		66	90	99
7	**1f**		**9f**		60	87	99
8	**1g**		**9g**		54	88	99
9	**1h**		**9h**		66	95	99
10	**1i**		**9i**		68	98	99

[a] Reactions were carried out in THF at −78 °C for 4–5 h.
[b] Isolated yield after chromatography.
[c] Determined from the ^{19}F NMR spectra of Mosher (MTPA) amides. In all of the cases, we assign the (*S*)-configuration of homoallylic amines for the major isomer, see text.
[d] Determined by analysis of ^{1}H NMR of crude product.

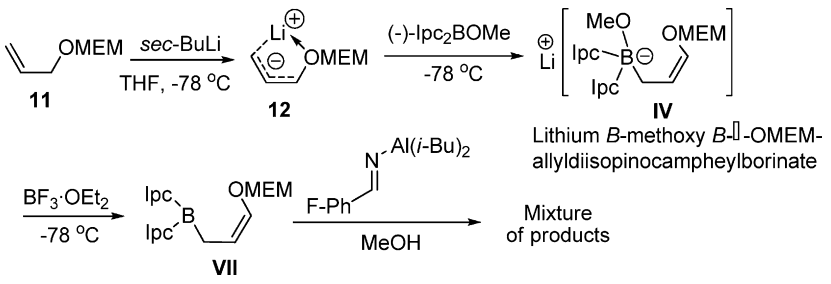


Scheme 7.

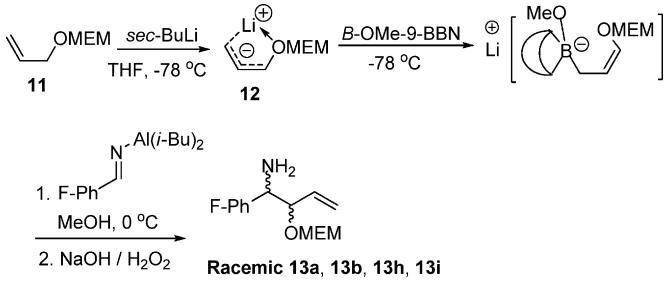
furnished the *syn*-β-alkoxy homoallylic amine **13a** with the results (51%, 91% ee and 99% de) comparable with those obtained from the crotylboration (Scheme 9; Table 2, Entry 1). As in the case of the crotylboration, the de was determined from the ^{1}H NMR of the crude product mixture and the ee was determined from the ^{19}F NMR of the MTPA amide. The racemic products were prepared by



Scheme 9.



Scheme 8.



Scheme 10.

the reaction of corresponding aluminoimines in presence of methanol with the 'ate' complex obtained from lithiated *Z*-allylOMEM (**12**) and *B*-methoxy-9-BBN (Scheme 10). Additional examples of fluorobenzaldimines were also subjected to alkoxyallylboration and consistent results (45–61% yields, >98% de, and 89–94% ee) were obtained, which are summarized in Scheme 9.

2.4. Preparation of δ-amino alcohols and γ-lactams

Having achieved the preparation of the homoallylic amines in very high de and ee, we attempted their conversion to the corresponding amino alcohols, and eventually to the γ-amino acids. First, we selected four representative examples of fluorophenyl homoallylamines for this purpose. The homoallylic amines **4a**, **4b**, **4g**, and **4i** were protected using di-*tert*-butyldicarbonate and the hydroboration of the alkenes was examined using various hydroborating agents, such as borane-THF, borane-methyl sulfide, dicyclohexylborane (Chx_2BH), and 9-borabicyclo[3.3.1]nonane (9-BBN). Both Chx_2BH and 9-BBN were found to be superior for the hydroboration, which was complete within 24 h at RT (^{11}B NMR δ 80 ppm). Oxidation using alkaline hydrogen peroxide provided the corresponding Boc-protected δ-amino alcohols, **14a**, **14b**, **14g**, and **14i**, respectively, in 75–79% yields. On the basis of our earlier work on the hydroboration-oxidation of homoallylic alcohols [18b], we believe that there is no loss of optical activity during the preparation of **14**. Further oxidation of the above *N*-Boc protected amino alcohols using pyridinium dichromate (PDC) gave the Boc-protected γ-fluorophenyl GABA derivatives, **15a**, **15b**, **15g**, and **15i**, respectively, in 76–84% yields. Boc-deprotection using 30% trifluoroacetic acid in dichloromethane lactamized the amino acids instantly to provide the γ-lactams, **16a**, **16b**, **16g**, and **16i**, respectively, in 94–98% isolated yields. All of these results are summarized in Table 3 (Scheme 11).

This methodology was now extended to include representative examples of β-substituted-γ-(fluorophenyl)-γ-aminobutyric acid. Thus **9a**, **9b**, **9g**, **9i**, and **13a** were protected using di-*tert*-

Table 3
Preparation of δ-amino alcohols, GABA derivatives, and γ-lactams.

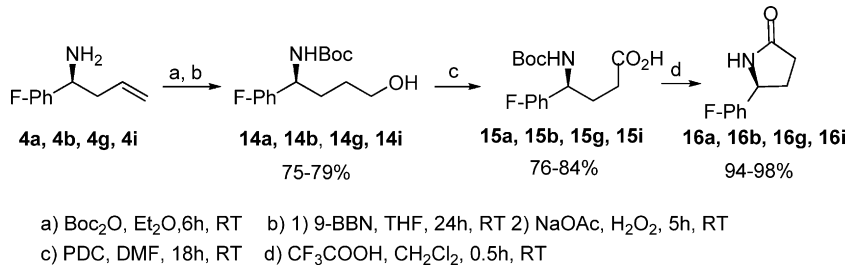
Entry	Homoallylamines		δ-Amino alcohols		γ-F-Ph-GABA		γ-Lactam	
	#	F-Ph	#	Yield, %[a]	#	Yield, %[a]	#	Yield, %[a]
1	**4a**	2-F-Ph	**14a**	75	**15a**	78	**16a**	94
2	**4b**	3-F-Ph	**14b**	78	**15b**	84	**16b**	98
3	**4g**	2,6-F_2-Ph	**14g**	76	**15g**	76	**16g**	95
4	**4i**	3,5-F_2-Ph	**14i**	79	**15i**	83	**16i**	98

[a] Isolated yields of pure products, after chromatography.

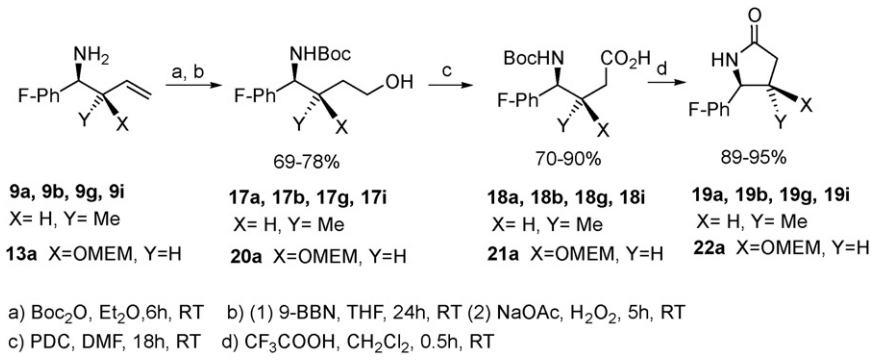
Table 4
Preparation of γ-methyl-δ-amino alcohols, β-methyl-GABA derivatives, and β-methyl-γ-lactams.

Entry	Homoallylamines		δ-Amino alcohols		γ-F-Ph-GABA		γ-Lactam	
	#	F-Ph	#	Yield, %[a]	#	Yield, %[a]	#	Yield, %[a]
1	**9a**	2-F-Ph	**17a**	71	**18a**	77	**19a**	90
2	**9b**	3-F-Ph	**17b**	69	**18b**	90	**19b**	97
3	**9g**	2,6-F_2-Ph	**17g**	78	**18g**	70	**19g**	89
4	**9i**	3,5-F_2-Ph	**17i**	70	**18i**	81	**19i**	95
5	**13a**	2-F-Ph	**20a**	72	**21a**	79	**22a**	91

[a] Isolated yields of pure products, after chromatography.



Scheme 11.



Scheme 12.

butyldicarbonate and subjected to hydroboration with 9-BBN, followed by alkaline hydrogen peroxide oxidation to obtain the corresponding δ-amino alcohols **17a**, **17b**, **17g**, **17i**, and **20a** in 69–78% yield. Further PDC oxidation of the above *N*-Boc protected amino alcohols gave the *N*-Boc-protected β-substituted-γ-fluorophenyl GABA **18a**, **18b**, **18g**, **18i**, and **21a** in 70–90% yields. Boc-deprotection using 30% trifluoroacetic acid in dichloromethane lactamized the amino acids instantly to provide the β-substituted γ-lactams, **19a**, **19b**, **19g**, **19i**, and **22a** in 89–97% isolated yields (Table 4, Scheme 12).

3. Conclusion

In summary, we have examined the isopinocampheyl-mediated enantioselective allyl-, crotyl-, and alkoxyallylboration of *N*-alumino fluorobenzaldimines, prepared by the reduction of the corresponding fluorobenzonitriles with DIBAL-H. The homoallylic amines were prepared in 52–71% yields and in 76–93% ee for the allylboration, in 54–75% yields and in 87–98% ee for the crotylboration, and in 45–61% yields and in 89–94% ee for the alkoxyallylboration. The diastereoselectivity achieved for the crotyl- and alkoxy-allylboration was consistently >98%. A representative series of the fluoroaryl homoallylamines achieved from the above reactions were converted to δ-amino alcohols and the corresponding γ-fluorophenyl γ-amino acids and γ-lactams as well as β-substituted γ-fluorophenyl γ-amino acids and β-substituted γ-lactams without any loss of optical activity. The γ-fluoroaryl GABA derivatives are currently being screened for the ability to activate Cl^- currents via GABA-A receptors composed of several different combinations of GABA-A subunits. The results from this study will be reported in due course.

4. Experimental

Unless otherwise noted, all manipulations were carried out under an inert atmosphere using flame-dried glassware. Tetrahydrofuran (THF) was freshly distilled before use from sodium benzophenone ketyl and anhydrous diethyl ether was purchased from Mallinckrodt Chemicals. The fluorinated benzonitriles, *E*- and *Z*-2-butene, DIBAL-H, 9-borabicyclo-[3.3.1]nonane (9-BBN), *B*-methoxydiisopinocampheylborane, *B*-methoxy-9-BBN, allylmagnesium bromide, (*R*)-(+)-α-methoxy α-(trifluoromethyl)phenylacetic acid, dicyclohexylcarbodiimide (DCC), *N*,*N*-dimethylaminopyridine (DMAP), pyridinium dichromate (PDC) and trifluoroacetic acid were purchased from commercial sources and were used without further purification, unless otherwise noted. (−)-*B*-allyldiisopinocampheylborane (**I**) was prepared according to Brown's procedure by the treatment of (−)-*B*-methoxydiisopinocampheylborane with allylmagnesium bromide [23]. The 'ate' complexes **II** and **III** were prepared by the treatment of (−)-*B*-methoxydiisopinocampheylborane with *E*- or *Z*-2-butenylpotassium, respectively [27] and 'ate' complex **IV** was produced by the treatment of (−)-*B*-methoxydiisopinocampheylborane with lithiated *Z*-allylOMEM [28]. The ^1H, ^{13}C and ^{19}F nuclear magnetic resonance (NMR) spectra were plotted on a Varian Gemini-300 spectrometer (300, 75 and 282 MHz, respectively) with a Nalorac-quad probe. ^1H NMR spectra were obtained using $CDCl_3$ as the solvent with either tetramethylsilane (TMS: δ 0 ppm) or chloroform ($CHCl_3$: δ 7.2 ppm) as the internal standard. ^{19}F NMR spectra were recorded in $CDCl_3$ using $CFCl_3$ as the internal standard. ^1H NMR data are reported as chemical shifts (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), and integration. Enantiomeric excesses (% ee) were measured using ^{19}F NMR spectroscopy of the corresponding Mosher amides. Mass spectra were recorded using a Hewlett Packard 5989B mass spectrometer/5890 series II gas chromatograph or a Finnigan mass spectrometer model 4000. The chemical ionization gas used was isobutene. Flash chromatography was performed on 40–63 μm silica gel (230–400 mesh).

Preparation of (*1S*)-1-(3-fluorophenyl)-but-3-en-1-amine (**4b**) is representative for the allylboration reaction. Preparation of (*1S,2S*)-1-(3-fluorophenyl)-2-methylbut-3-en-1-amine (**9b**) is representative for the crotylboration reaction and the preparation of (*1R,2R*)-1-(2-fluorophenyl)-2-((2-methoxyethoxy)methoxy)-but-3-en-1-amine (**13a**) is representative of the alkoxyallylboration reaction. The preparation of (*S*)-*tert*-butyl-1-(3-fluorophenyl)-4-hydroxybutylcarbamate (**14b**), (*S*)-4-(*tert*-butoxycarbonylamino)-4-(3-fluorophenyl)butanoic acid (**15b**), and (*S*)-5-(3-fluorophenyl)-pyrrolidin-2-one (**16b**) from 3-fluorobenzonitrile (**1b**) are representatives of the protection-hydroboration-oxidation of the homoallylamine, the oxidation of the amino alcohol, and the deprotection of the Boc-derivative. The same procedures were adopted for all of the other fluoro-benzonitriles.

5. Experimental procedure and analytical data for products

5.1. (1S)-1-(3-fluorophenyl)-but-3-en-1-amine (4b)

DIBAL-H (0.89 mL, 5 mmol) was added to a solution of 3-fluorobenzonitrile (**1b**; 0.54 mL, 5.05 mmol) in Et_2O (5 mL) cooled to 0 °C and the mixture was stirred for 1 h to obtain the corresponding *N*-aluminoimine (**2b**). This was transferred *via* cannula to a solution of (−)-*B*-allyldiisopinocampheylborane (**I**, 1*M* in pentane; 7 mL, 7 mmol) diluted with Et_2O (7 mL) and cooled to −78 °C, followed by a slow addition of 0.20 mL (5.0 mmol) of methanol. The mixture was then stirred for 4 h when the reaction was complete (^{11}B NMR spectral peak shift from δ 79 ppm to 47 ppm). The mixture was now slowly oxidized with H_2O_2 (30% in H_2O; 1.5 mL) in presence of aqueous NaOH (3*M*, 3 mL) and was left stirring under positive N_2 pressure while it slowly warmed to RT. The product was then extracted with Et_2O (3× 50 mL), treated with HCl (20% in H_2O; 5 mL), and stirred for 0.2 h. Water (50 mL) was added to the mixture and the organics removed. The aqueous solution of the homoallylamine hydrochloride was extracted thrice with ether (3× 25 mL), and neutralized with NaOH until pH ~8 and the resulting amine was extracted with Et_2O (3× 50 mL). The solvent was removed under reduced pressure, and the material was purified on silica gel (hexanes/ethyl acetate/triethylamine 84.5:15:0.5) to afford the product (*1S*)-1-(3-fluorophenyl)-but-3-en-1-amine (**4b**) (0.52 g, 3.15 mmol, 63%). The Mosher amide of **4b** was made using DCC condensation in the presence of DMAP [26]. Analysis of the ^{19}F NMR spectrum of the MTPA amide revealed an enantiomeric ratio of 94% and 6% favoring the *S*-isomer.

^1H NMR: (300 MHz, $CDCl_3$) δ 7.33–7.22 (m, 1H), 7.15–7.04 (m, 2H), 6.97–6.88 (m, 1H), 5.83–5.63 (m, 1H), 5.16–5.07 (m, 2H), 4.01 (dd, *J* = 7.6 Hz, *J* = 5.4 Hz, 1H), 2.57–2.26 (m, 2H), 1.66 (br s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −135.4 (s, 1F); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 162.7 (d, J_{C-F} = 240.2 Hz), 148.2, 134.8, 129.9 (d, J_{C-F} = 8.1 Hz), 122.1, 118.2, 113.9 (d, J_{C-F} = 28.1 Hz), 113.3 (d, J_{C-F} = 21.3 Hz), 54.9, 43.8; MS (EI): *m*/*z*: 146 $[M-F]^+$, 124; (CI): *m*/*z*: 166 $[M+H]^+$, 149 $[(M+H)-NH_3]^+$, 124 $[M-C_3H_5]^+$.

5.2. (1S)-1-(2-fluorophenyl)-but-3-en-1-amine (4a)

^1H NMR (300 MHz, $CDCl_3$): δ 7.43–6.98 (m, 4H), 5.81–5.69 (m, 1H), 5.14–5.07 (m, 2H), 4.29 (dd, *J* = 7.3 Hz, *J* = 5.9 Hz, 1H), 2.54–2.35 (m, 2H), 1.74 (br s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −133.1 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8 (d, J_{C-F} = 258.0 Hz), 135.2, 128.7, 128.3, 127.6 (d, J_{C-F} = 21.0 Hz), 124.2, 117.9, 115.4 (d, J_{C-F} = 21.0 Hz), 49.2, 42.7; MS (EI): *m*/*z*: 146 $[M-F]^+$, 124; (CI): *m*/*z*: 166 $[M+H]^+$, 149 $[(M+H)-NH_3]^+$, 124 $[M-C_3H_5]^+$.

*5.3. (1S)-1-(4-fluorophenyl)-but-3-en-1-amine (**4c**)*

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.33–7.26 (m, 2H), 7.0 (t, J = 8.6 Hz, 2H), 5.83–5.62 (m, 1H), 5.15–5.06 (m, 2H), 3.99 (dd, J = 7.5 Hz, J = 5.7 Hz, 1H), 2.47–2.25 (m, 2H), 1.61 (br s, 2H); ^{19}F NMR (282 MHz, CDCl3): δ −134.2 (s, 1F); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 161.8 (d, J_{C-F} = 242.1 Hz), 141.6, 135.2, 127.8 (d, J_{C-F} = 8.5 Hz), 117.8, 115.1 (d, J_{C-F} = 21 Hz), 54.7, 44.4; MS (EI): m/z: 146 $[M-F]^+$, 124; (CI): m/z: 166 $[M+H]^+$, 149 $[(M+H)-NH_3]^+$, 124 $[M-C_3H_5]^+$.

*5.4. (S)-1-(2,3-difluorophenyl)but-3-en-1-amine (**4d**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18–7.15 (m, 1H), 7.06–7.02 (m, 2H), 5.79–5.67 (m, 1H), 5.14–5.08 (m, 2H), 4.32 (dd, J = 7.6 Hz, J = 5.8 Hz, 1H), 2.54–2.34 (m, 2H), 1.69 (br s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −152.4 (m, 1F), −158.4 (d, J = 21 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.7 (dd, J_{C-F} = 247.5 Hz, J_{C-F} = 13.9 Hz), 146.5 (dd, J_{C-F} = 246.5 Hz, J_{C-F} = 10.4 Hz), 134.5, 128.1, 118.4, 109.3 (d, J_{C-F} = 7.3 Hz), 109.0 (d, J_{C-F} = 7.7 Hz), 102.3 (t, J_{C-F} = 25.1 Hz), 54.8, 34.9; MS (EI): m/z: 164 $[M-F]^+$, 142; (CI): m/z: 184 $[M+H]^+$, 167 $[(M+H)-NH_3]^+$, 142 $[M-C_3H_5]^+$.

*5.5. (S)-1-(2,4-difluorophenyl)but-3-en-1-amine (**4e**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.36 (m, 1H), 6.88–6.74 (m, 2H), 5.78–5.69 (m, 1H), 5.13–5.07 (m, 2H), 4.28 (m, 1H), 2.51–2.37 (m, 2H), 1.98 (br s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −126.3 (s, 1F), −129.1 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.8 (dd, J_{C-F} = 246.4 Hz, J_{C-F} = 12.7 Hz), 160.3 (dd, J_{C-F} = 246.5 Hz, J_{C-F} = 12.7 Hz), 134.9, 128.3 (d, J_{C-F} = 8.4 Hz); 118.1, 111.2 (t, J_{C-F} = 12.6 Hz), 103.9 (d, J_{C-F} = 25.2 Hz), 103.3 (d, J_{C-F} = 25.3 Hz), 48.6, 42.9; MS (EI): m/z: 164 $[M-F]^+$, 142; (CI): m/z: 184 $[M+H]^+$, 167 $[(M+H)-NH_3]^+$, 142 $[M-C_3H_5]^+$.

*5.6. (S)-1-(2,5-difluorophenyl)but-3-en-1-amine (**4f**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14–7.09 (m, 1H), 6.91–6.82 (m, 2H), 5.77–5.63 (s, 1H), 5.09–5.03 (m, 2H), 4.24 (dd, J = 6.8 Hz, J = 6.0 Hz, 1H), 2.48–2.24 (m, 2H), 1.55 (br s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −139.1 (m, 1F), −132.2 (m, 1F) ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9 (dd, J_{C-F} = 240.3 Hz, J_{C-F} = 14.7 Hz), 156.1 (dd, J_{C-F} = 239.4 Hz, J_{C-F} = 2.1 Hz), 134.6, 118.1, 116.3 (d, J_{C-F} = 8.3 Hz), 116.0 (d, J_{C-F} = 8.6 Hz), 114.4 (d, J_{C-F} = 23.6 Hz), 114.0 (d, J_{C-F} = 19.2 Hz), 48.6, 42.5; MS (EI): m/z: 164 $[M-F]^+$, 142; (CI): m/z: 184 $[M+H]^+$, 167 $[(M+H)-NH_3]^+$, 142 $[M-C_3H_5]^+$.

*5.7. (S)-1-(2,6-difluorophenyl)but-3-en-1-amine (**4g**)*

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.17–7.09 (m, 1H), 6.89–6.78 (m, 2H), 5.79–5.66 (m, 1H), 5.08–4.99 (m, 2H), 4.30 (t, J = 7.4 Hz, 1H), 2.59–2.51 (m, 2H), 1.77 (br s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −128.6 (m, 2F); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 161.1 (dd, J_{C-F} = 245.1 Hz, J_{C-F} = 9.1 Hz), 135.1, 128.3 (d, J_{C-F} = 10.4 Hz), 117.6, 111.7 (d, J_{C-F} = 17.7 Hz), 111.5 (d, J_{C-F} = 17.8 Hz), 47.2, 42.1; MS (EI): m/z: 164 $[M-F]^+$, 142; (CI): m/z: 184 $[M+H]^+$, 167 $[(M+H)-NH_3]^+$, 142 $[M-C_3H_5]^+$.

*5.8. (S)-1-(3,4-difluorophenyl)but-3-en-1-amine (**4h**)*

^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.17–6.96 (m, 3H), 5.71–5.58 (m, 1H), 5.06–4.99 (m, 2H), 3.90 (dd, J = 5.4 Hz, J = 8.4 Hz, 1H), 2.36–2.15 (m, 2H), 1.53 (br s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −138.0 (m, 1F), −140.9 (m, 1F); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 150.0 (dd, J_{C-F} = 246.0 Hz, J_{C-F} = 12.6 Hz), 149.3 (dd, J_{C-F} = 245.1 Hz, J_{C-F} = 12.6 Hz), 142.9 (t, J_{C-F} = 4.1 Hz), 134.8, 122.2 (d, J_{C-F} = 9.5 Hz), 118.2, 117.1 (d, J_{C-F} = 11.1 Hz), 115.0 (d, J_{C-F} = 18.9 Hz), 54.4, 44.2; MS (EI): m/z: 164 $[M-F]^+$, 142; (CI): m/z: 184 $[M+H]^+$, 167 $[(M+H)-NH_3]^+$, 142 $[M-C_3H_5]^+$.

*5.9. (S)-1-(3,5-difluorophenyl)but-3-en-1-amine (**4i**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90–6.87 (m, 2H), 6.70–6.63 (m, 1H), 5.78–5.64 (m, 1H), 5.15–5.05 (m, 2H), 3.99 (dd, J = 7.7 Hz, J = 7.6 Hz, 1H), 2.27–2.48 (m, 2H), 1.95 (br s, 2H), ^{19}F NMR (282 MHz, $CDCl_3$): δ −123.5 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1 (dd, J_{C-F} = 246.5 Hz, J_{C-F} = 12.7 Hz), 149.6, 134.4, 118.5, 109.2 (d, J_{C-F} = 24.5 Hz), 102.4 (t, J_{C-F} = 25.4 Hz), 54.8, 43.8; MS (EI): m/z: 164 [M-F]$^+$, 142; (CI): m/z: 184 $[M+H]^+$, 167 $[(M+H)-NH_3]^+$, 142 $[M-C_3H_5]^+$.

*5.10. (1S,2S)-1-(3-fluorophenyl)-2-methylbut-3-en-1-amine (**9b**)*

Trans-butene (**5**, 1 mL, 10 mmol) and *n*-butyllithium (2.5 M in hexanes; 2.8 mL, 7.0 mmol) were added to potassium *tert*-butoxide (1 M in THF; 7 mL, 7 mmol) diluted with 7 ml of THF and cooled to −78 °C. The mixture was stirred for 0.1 h at −78 °C, followed by 0.3 h at −55 °C, and cooled again to −78 °C, when a solution of (−)-*B*-methoxydiisopinocampheylborane (2.36 g, 7.4 mmol) in 8 mL THF was added and the reaction mixture was stirred for 1 h at −78 °C. To thus generated **II** was added via cannula a solution of **2b** [prepared as follows: to a solution of 3-fluorobenzonitrile (**1b**; 0.54 mL, 5.05 mmol) in 5 mL THF cooled to 0 °C was added DIBAL-H (0.89 mL, 5 mmol) and the mixture was stirred for 1 h], followed by slow addition of methanol (0.20 mL, 5 mmol) and the mixture was stirred for 4 h at −78 °C when it was slowly oxidized with H_2O_2 (30% in H_2O; 1.5 mL) in presence of aqueous NaOH (3 M; 3 mL) and was left stirring under positive N_2 pressure while it slowly warmed to RT. The product was extracted with Et_2O (3× 50 mL) after the acid–base manipulation, the solvent was removed under reduced pressure, and the crude material was purified on silica gel (hexanes/ethyl acetate/triethylamine 84.5:15:0.5) to afford (*1S,2S*)-1-(3-fluorophenyl)-2-methylbut-3-en-1-amine (**9b**) (0.68 g, 3.9 mmol, 68%) in >98% *de* as determined by ^{1}H NMR analysis of the crude product. The Mosher amide of **9b** was made using DCC condensation in the presence of DMAP [26]. Analysis of the ^{19}F NMR spectrum of the MTPA amide revealed an enantiomeric ratio of 96% and 4%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.21 (m, 1H), 7.06–7.0 (m, 2H), 6.92–6.86 (m, 1H), 5.74–5.62 (m, 1H), 5.14–5.06 (m, 2H), 3.6 (d, J = 8.1 Hz, 1H), 2.30 (q, J = 7.6 Hz, 1H), 1.52 (br s, 2H), 0.80 (d, J = 6.7 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −127.0 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9 (d, J_{C-F} = 210 Hz), 141.3, 131.8, 128.4 (d, J_{C-F} = 4.8 Hz), 128.2 (d, J_{C-F} = 8.4 Hz), 124.1 (d, J_{C-F} = 3.2), 116.1, 115.3 (d, J_{C-F} = 22.5 Hz), 53.9, 45.6, 17.5; MS (EI): 163 $[M-NH_2]^+$, 124; (CI): 180 $[M+H]^+$, 163 $[(M+H)-NH_2]^+$, 124 $[M-C_4H_7]^+$.

*5.11. (1S,2S)-1-(2-fluorophenyl)-2-methylbut-3-en-1-amine (**9a**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39–7.34 (m, 1H), 7.20–7.08 (m, 2H), 7.0–6.94 (m, 1H), 5.78–5.66 (m, 1H), 5.14–5.07 (m, 2H), 3.95 (d, J = 8.3 Hz, 1H), 2.4 (q, J = 7.4 Hz, 1H), 1.56 (br s, 2H), 0.85 (d, J = 6.7 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −132.3 (s, 1F); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 160.7 (d, J_{C-F} = 248 Hz), 141.3, 131.5 (d, J_{C-F} = 13.2 Hz), 128.4 (d, J_{C-F} = 14.6 Hz), 128.1 (d, J_{C-F} = 15.0 Hz), 124.1, 116.0, 115.2 (d, J_{C-F} = 22.7 Hz), 53.8, 45.6, 17.5; MS (EI): 163 $[M-NH_2]^+$, 124; (CI): 180 $[M+H]^+$, 163 $[(M+H)-NH_2]^+$, 124 $[M-C_4H_7]^+$.

*5.12. (1S,2R)-1-(2-fluorophenyl)-2-methylbut-3-en-1-amine (**10a**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.19 (m, 1H), 7.06–7.01 (m, 2H), 6.92–6.86 (m, 1H), 5.74–5.62 (m, 1H), 5.14–5.06 (m, 2H), 3.61

(d, J = 8.13 Hz, 1H), 2.29 (q, J = 7.4 Hz, 1H), 1.52 (br s, 2H), 0.80 (d, J = 7.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −134.6 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9 (d, J_{C-F} = 242.0 Hz), 147.2, 141.2, 129.5 (d, J_{C-F} = 8.1 Hz), 123.0 (d, J_{C-F} = 2.6 Hz), 116.1, 114.1 (d, J_{C-F} = 21.1), 113.8 (d, J_{C-F} = 15.0 Hz), 60.3, 46.3, 17.5; MS (EI): 163 [M–NH_2]$^+$, 124; (CI): 180 [M+H]$^+$, 163 [(M+H)–NH_2]$^+$, 124 [M–C_4H_7]$^+$.

5.13. (1S,2S)-1-(4-fluorophenyl)-2-methylbut-3-en-1-amine (9c)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.33 (m, 2H), 7.10–7.05 (m, 2H), 5.85–5.73 (m, 1H), 5.20–5.16 (m, 2H), 3.7 (d, J = 8.1 Hz, 1H), 2.38 (q, J = 6.9 Hz, 1H), 1.76 (br s, 2H), 0.87 (d, J = 6.6 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −131.9 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.1 (d, J_{C-F} = 248.0 Hz), 141.6, 140.2, 128.7 (d, J_{C-F} = 8.4 Hz), 116.1, 115.0 (d, J_{C-F} = 21.0 Hz), 60.0, 46.4, 17.6; MS (EI): 163 [M–NH_2]$^+$, 124; (CI): 180 [M+H]$^+$, 163 [(M+H)–NH_2]$^+$, 124 [M–C_4H_7]$^+$.

5.14. (1S,2S)-1-(2,3-difluorophenyl)-2-methylbut-3-en-1-amine (9d)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16–7.11 (m, 1H), 7.04–6.99 (m, 2H), 5.77–5.65 (m, 1H), 5.15–5.09 (m, 2H), 3.9 (d, J = 8.4 Hz, 1H), 2.38 (q, J = 7.5 Hz, 1H), 1.58 (br s, 2H), 0.86 (d, J = 6.7 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −157.6 (d, J = 21.3 Hz, 1F), −152.4 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.4 (dd, J_{C-F} = 255.0 Hz, J_{C-F} = 14.1 Hz), 148.8 (dd, J_{C-F} = 195.0 Hz, J_{C-F} = 13.2 Hz), 140.9, 134.0 (d, J_{C-F} = 10.4 Hz), 123.9 (d, J_{C-F} = 4.6 Hz), 123.0 (d, J_{C-F} = 3.5 Hz), 116.4, 115.4 (d, J_{C-F} = 17.2 Hz), 53.6, 45.6, 17.4; MS (EI): 180 [M–NH_3]$^+$, 142; (CI): 198 [M+H]$^+$, 181 [(M+H)–NH_3]$^+$, 142 [M–C_4H_7]$^+$.

5.15. (1S,2S)-1-(2,4-difluorophenyl)-2-methylbut-3-en-1-amine (9e)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.33 (m, 1H), 6.87–6.71 (m, 2H), 5.77–5.66 (m, 1H), 5.15–5.09 (m, 2H), 3.95 (d, J = 8.3 Hz, 1H), 2.37 (q, J = 7.3 Hz, 1H), 1.49 (br s, 2H), 0.87 (d, J = 6.7 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −128.5 (m, 1F), −126.3 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.7 (dd, J_{C-F} = 255 Hz, J_{C-F} = 12.1 Hz), 160.7 (dd, J_{C-F} = 225.0 Hz, J_{C-F} = 11.1 Hz), 141.1, 129.2 (d, J_{C-F} = 16.1 Hz), 127.4 (d, J_{C-F} = 10.1 Hz), 116.3, 111.2 (d, J_{C-F} = 17.3 Hz), 103.5 (t, J_{C-F} = 25.8 Hz), 53.2, 45.7, 17.4; MS (EI): 180 [M–NH_3]$^+$, 142; (CI): 198 [M+H]$^+$, 181 [(M+H)–NH_3]$^+$, 142 [M–C_4H_7]$^+$.

5.16. (1S,2S)-1-(2,5-difluorophenyl)-2-methylbut-3-en-1-amine (9f)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14–7.08 (m, 1H), 6.98–6.83 (m, 2H), 5.76–5.64 (m, 1H), 5.14–5.08 (m, 2H), 3.96 (d, J = 8.1 Hz, 1H), 2.35 (q, J = 7.4 Hz, 1H), 1.66 (br s, 2H), 0.87 (d, J = 6.7 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −138.3 (m, 1F), −132.2 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9 (dd, J_{C-F} = 240.4 Hz, J_{C-F} = 4.2 Hz), 156.5 (dd, J_{C-F} = 239.2 Hz, J_{C-F} = 5.1 Hz), 140.7, 133.7 (dd, J_{C-F} = 15.8 Hz, J_{C-F} = 6.6 Hz), 116.4, 116.3, 116.0 (d, J_{C-F} = 8.7 Hz), 114.2 (t, J_{C-F} = 22.2 Hz), 53.4, 45.5, 17.3; MS (EI): 180 [M–NH_3]$^+$, 142; (CI): 198 [M+H]$^+$, 181 [(M+H)–NH_3]$^+$, 142 [M–C_4H_7]$^+$.

5.17. (1S,2S)-1-(2,6-difluorophenyl)-2-methylbut-3-en-1-amine (9g)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.16–7.08 (m, 1H), 6.84–6.78 (m, 2H), 5.81–5.69 (m, 1H), 5.16–5.08 (m, 2H), 3.93 (d, J = 9.6 Hz, 1H), 2.54 (q, J = 7.4 Hz, 1H), 1.7 (br s, 2H), 0.81 (d, J = 6.7 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −127.5 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.3 (dd, J_{C-F} = 245.3 Hz, J_{C-F} = 9.0 Hz), 141.9, 128.3 (t, J_{C-F} = 10.8 Hz), 119.6 (t, J_{C-F} = 13.1 Hz), 116.1, 111.4 (dd, J_{C-F} = 20.7 Hz, J_{C-F} = 11.9 Hz)), 51.9, 45.2, 17.9; MS (EI): 180 [M–NH_3]$^+$, 142; (CI): 198 [M+H]$^+$, 181 [(M+H)–NH_3]$^+$, 142 [M–C_4H_7]$^+$.

5.18. (1S,2S)-1-(3,4-difluorophenyl)-2-methylbut-3-en-1-amine (9h)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18–6.97 (m, 3H), 5.71–5.60 (m, 1H), 5.14–5.06 (m, 2H), 3.6 (d, J = 8.1 Hz, 1H), 2.24 (q, J = 7.2 Hz, 1H), 1.5 (br s, 2H), 0.78 (d, J = 6.7 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −154.1 (m, 1F), −151.7 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.2 (dd, J_{C-F} = 246.0 Hz, J_{C-F} = 12.6 Hz), 149.3 (dd, J_{C-F} = 245.0 Hz, J_{C-F} = 12.5 Hz), 141.8, 141.6 (d, J_{C-F} = 4.12 Hz), 123.2 (d, J_{C-F} = 3.5 Hz), 116.7 (d, J_{C-F} = 17.1 Hz), 116.3, 115.9 (d, J_{C-F} = 17.0 Hz), 59.8, 46.3, 17.4; MS (EI): 180 [M–NH_3]$^+$, 142; (CI): 198 [M+H]$^+$, 181 [(M+H)–NH_3]$^+$, 142 [M–C_4H_7]$^+$.

5.19. (1S,2S)-1-(3,5-difluorophenyl)-2-methylbut-3-en-1-amine (9i)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.85 (d, J = 6.5 1H), 6.69–6.63 (m, 2H), 5.73–5.61 (m, 1H), 5.16–5.09 (m, 2H), 3.64 (d, J = 7.8 Hz, 1H), 2.30 (q, J = 7.2 Hz, 1H), 1.63 (br s, 2H), 0.84 (d, J = 6.7 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −123.9 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.0 (dd, J_{C-F} = 246.5 Hz, J_{C-F} = 12.5 Hz), 148.9, 140.7, 116.5, 110.1 (d, J_{C-F} = 9.4 Hz), 102.4 (t, J_{C-F} = 25.2 Hz), 60.1, 46.1, 17.4; MS (EI): 180 [M–NH_3]$^+$, 142; (CI): 198 [M+H]$^+$, 181 [(M+H)–NH_3]$^+$, 142 [M–C_4H_7]$^+$.

5.20. (1R,2R)-1-(2-fluorophenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-amine (13a)

sec-Butyllithium (1.4 M in cyclohexane; 5.4 mL, 7.5 mmol) was added to 3-[(2-methoxyethoxy)-methoxy]prop-1-ene (**11**; 1.10 g, 7.6 mmol) diluted with THF (8 mL) and cooled to −78 °C and the mixture was stirred for 0.5 h at −78 °C. Then, a solution of (−)-*B*-methoxydiisopinocampheylborane (2.84 g, 9.0 mmol) in THF (10 mL) was added and the mixture was stirred for 1 h. To thus generated **IV** was added *via* cannula a solution of **2a** [prepared as follows: to a solution of 2-fluorobenzonitrile (**1a**; 0.55 mL, 5.05 mmol) in 5 mL THF and cooled to 0 °C was added DIBAL-H (0.89 mL, 5 mmol) and the mixture was stirred for 1 h], followed by methanol (0.20 mL, 5 mmol). The reaction mixture was stirred for 4 h at −78 °C and was slowly oxidized with H_2O_2 (30% in H_2O; 1.5 mL) in presence of aqueous NaOH (3M; 3 mL) and was left stirring under positive N_2 pressure while it slowly warmed to RT. The product was extracted with Et_2O (3× 50 mL) after the acid–base manipulation, the solvent was removed under reduced pressure, and the crude material was purified on silica gel (hexanes/ethyl acetate/triethylamine 84.5:15:0.5) to afford (*1R,2R*)-1-(2-fluorophenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-amine (**13a**) (0.69 g, 2.57 mmol, 51%) in 99% *de* as determined by ^{1}H NMR analysis of the crude product. The Mosher amide of **13a** was made using DCC condensation in the presence of DMAP [25]. Analysis of the ^{19}F NMR spectrum of the MTPA amide revealed an enantiomeric ratio of 95.5% and 4.5%.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.36 (m, 1H), 7.14–7.10 (m, 1H), 7.06–7.0 (m, 1H), 6.95–6.89 (m, 1H), 5.71–5.60 (m, 1H), 5.13–5.07 (m, 2H), 4.23–4.13 (m, 2H), 4.66 (d, J = 7.0 Hz, 1H), 4.53 (d, J = 6.9 Hz, 1H), 4.23–4.16 (m, 2H), 3.39–3.30 (m, 4H), 3.26 (s, 3H), 1.71 (br s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −131.6 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3 (d, J_{C-F} = 243.7 Hz), 135.3, 129.6 (d, J_{C-F} = 13.1 Hz), 128.7 (d, J_{C-F} = 4.6 Hz), 128.4 (d, J_{C-F} = 8.3 Hz), 123.8 (d, J_{C-F} = 3.3 Hz), 118.9, 115.1 (d, J_{C-F} = 22.1 Hz), 92.8, 80.7, 71.6, 66.8, 58.8, 53.1; MS (EI): 194 [M–$OCH_2CH_2OCH_3$]$^+$, 124; (CI): 270 [M+H]$^+$, 194 [M+H–$CH_2OCH_2CH_2OH$]$^+$, 124.

5.21. (1R,2R)-1-(3-fluorophenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-amine (13b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.19 (m, 1H), 7.09–7.04 (m, 2H), 6.92–6.85 (m, 1H), 5.66–5.55 (m, 1H), 5.18–5.10 (m, 2H), 4.70

(d, J = 6.8 Hz, 1H), 4.57 (d, J = 6.9 Hz, 1H), 4.13 (t, J = 6.4 Hz, 1H), 3.94 (d, J = 5.8 Hz, 1H), 3.47–3.36 (m, 4H), 3.31 (s, 3H), 1.76 (br s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −127.1 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.8 (d, J_{C-F} = 243.8 Hz), 145.3 (d, J_{C-F} = 6.7 Hz), 135.1, 129.4 (d, J_{C-F} = 8.2 Hz), 123.2, 119.1, 114.4 (d, J_{C-F} = 21.3 Hz), 113.9 (d, J_{C-F} = 20.9 Hz), 92.8, 81.4, 71.6, 67.0, 59.3, 58.9; MS (EI): 194 $[M-OCH_2CH_2OCH_3]^+$, 124; (CI): 270 $[M+H]^+$, 194 $[M+H-CH_2OCH_2CH_2OH]^+$, 124.

5.22. (1R,2R)-1-(3,4-difluorophenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-amine (13h)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.0 (m, 3H), 5.63–5.51 (m, 1H), 5.18–5.09 (m, 2H), 4.71 (d, J = 6.8 Hz, 1H), 4.59 (d, J = 6.8 Hz, 1H), 4.08 (t, J = 6.7 Hz, 1H), 3.92 (d, J = 6.1 Hz, 1H), 3.53–3.40 (m, 4H), 3.34 (s, 3H), 1.77 (br s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −153.8 (s, 1F), −151.7 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.2 (dd, J_{C-F} = 246.2 Hz, J_{C-F} = 12.7 Hz), 149.5 (dd, J_{C-F} = 245.4 Hz, J_{C-F} = 12.8 Hz), 139.6 (q, J_{C-F} = 4.3 Hz), 134.8, 123.4 (d, J_{C-F} = 6.1 Hz), 120.3, 119.5, 116.5 (t, J_{C-F} = 17.7 Hz), 92.9, 81.5, 71.6, 67.1, 58.9, 58.8; MS (EI): 194 $[M-OCH_2CH_2OCH_3]^+$, 124; (CI): 270 $[M+H]^+$, 194 $[M+H-CH_2OCH_2CH_2OH]^+$, 124.

5.23. (1R,2R)-1-(3,5-difluorophenyl)-2-((2-methoxyethoxy)methoxy)but-3-en-1-amine (13i)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.90–6.81 (m, 2H), 6.69–6.61 (m, 1H), 5.66–5.55 (m, 1H), 5.22–5.13 (m, 2H), 4.70 (d, J = 7.0 Hz, 1H), 4.58 (d, J = 6.9 Hz, 1H), 4.12 (t, J = 6.7 Hz, 1H), 3.93 (d, J = 5.7 Hz, 1H), 3.50–3.39 (m, 4H), 3.33 (s, 3H), 1.67 (br s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −123.8 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7 (dd, J_{C-F} = 246.5 Hz, J_{C-F} = 13.1 Hz), 146.9, 134.8, 119.5, 110.4 (d, J_{C-F} = 16.9 Hz), 102.4 (t, J_{C-F} = 25.3 Hz), 92.8, 81.1, 71.6, 67.1, 56.1, 58.9; MS (EI): 194 $[M-OCH_2CH_2OCH_3]^+$, 124; (CI): 270 $[M+H]^+$, 194 $[M+H-CH_2OCH_2CH_2OH]^+$.

5.24. (S)-tert-butyl-1-(3-fluorophenyl)-4-hydroxybutylcarbamate (14b)

Di-*tert*-butyl dicarbonate (0.68 g, 3.1 mmol) was added to the above (1*S*)-1-(3-fluorophenyl)-but-3-en-1-amine (**4b**; 0.46 g, 2.8 mmol) dissolved in Et_2O (30 mL) and the reaction was stirred for 6 h at RT, after which time the solvent was removed under reduced pressure. The crude material was dissolved in THF (7 mL) and treated with 9-BBN (0.5 M in THF; 13 mL, 6.5 mmol) for 24 h at RT, followed by oxidation with sodium acetate (20% in H_2O, 20 mL) and, slowly, H_2O_2 (30% in H_2O; 6 mL) for 5 h at RT. The product was extracted with Et_2O (3× 30 mL), and after evaporation of the solvents purified on silica gel (hexanes/ethyl acetate 2:1) to furnish (*S*)-*tert*-butyl-1-(3-fluorophenyl)-4-hydroxybutylcarbamate (**14b**) (0.60 g, 2.13 mmol, 76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.21 (m, 1H), 7.04–6.87 (m, 3H), 5.18 (br s, 1H), 4.62 (br s, 1H), 3.61 (t, J = 6.9 Hz, 2H), 2.53 (br s, 1H), 1.86–1.77 (m, 1H), 1.58–1.47 (m, 3H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −169.2 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9 (d, J_{C-F} = 244.2 Hz), 155.6, 145.6, 130.1 (d, J_{C-F} = 6.2 Hz), 122.1, 114.0 (d, J_{C-F} = 21.2 Hz), 113.2 (d, J_{C-F} = 21.8 Hz), 79.8, 62.1, 54.2, 33.1, 28.9 and 28.4.

5.25. (S)-tert-butyl-1-(2-fluorophenyl)-4-hydroxybutylcarbamate (14a)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.21 (m, 2H), 7.14–7.02 (m, 2H), 5.42 (d, J = 8.1 Hz, 1H), 4.85 (d, J = 7.5 Hz, 1H), 3.64 (t, J = 6.6 Hz, 2H), 3.06 (br s, 1H), 1.91–1.79 (m, 2H), 1.65–1.51 (m, 2H), 1.45 (m, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −134.3 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.6 (d, J_{C-F} = 244.0 Hz), 155.5, 129.7 (d, J_{C-F} = 12.8 Hz), 128.5 (d, J_{C-F} = 21.1 Hz), 127.5 (d, J_{C-F} = 23.1 Hz), 124.3, 115.8 (d, J_{C-F} = 21.1 Hz), 79.6, 61.9, 50.7, 32.5, 29.2 and 28.4.

5.26. (S)-tert-butyl-1-(2,6-difluorophenyl)-4-hydroxybutylcarbamate (14g)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27–7.17 (m, 1H), 6.93–6.85 (m, 2H), 5.40 (d, J = 9.9 Hz, 1H), 5.19 (q, J = 7.5 Hz, 1H), 3.65 (t, J = 5.7 Hz, 2H), 2.86 (br s, 1H), 2.01–1.79 (m, 2H), 1.69–1.49 (m, 2H), 1.44 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −114.8 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.9 (dd, J_{C-F} = 246.3 Hz, J_{C-F} = 8.4 Hz), 155.4, 128.8 (t, J_{C-F} = 10.5 Hz), 118.4 (t, J_{C-F} = 13.4 Hz), 111.7 (d, J_{C-F} = 25.3 Hz), 79.9, 61.9, 45.7, 31.9, 29.3 and 28.4.

5.27. (S)-tert-butyl-1-(3,5-difluorophenyl)-4-hydroxybutylcarbamate (14i)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.13–7.0 (m, 3H), 5.58 (d, J = 5.1 Hz, 1H), 4.56 (d, J = 6.0 Hz, 1H), 3.59 (t, J = 5.1 Hz, 2H), 2.01 (br s, 1H), 1.83–1.70 (m, 2H), 1.63–1.46 (m, 2H), 1.39 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −123.1 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.3 (dd, J_{C-F} = 246.3 Hz, J_{C-F} = 12.6 Hz), 147.5, 140.6, 117.0 (d, J_{C-F} = 16.8 Hz), 115.1 (d, J_{C-F} = 16.3 Hz), 79.6, 61.6, 53.9, 33.1, 29.0, 28.3.

5.28. tert-Butyl-1-(1S,2S)-1-(3-fluorophenyl)-4-hydroxy-2-methylbutylcarbamate (17b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36–7.29 (m, 1H), 7.08–6.95 (m, 3H), 5.49 (d, J = 7.8 Hz, 1H), 4.53 (t, J = 7.2 Hz, 1H), 3.83–3.61 (m, 2H), 2.61 (br s, 1H), 2.21–2.01 (m, 1H), 1.98–1.89 (m, 1H), 1.73–1.62 (m, 1H), 1.46 (s, 9H), 0.90 (d, J = 7.2 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −113.05 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.9 (d, J_{C-F} = 246.9 Hz), 155.8, 144.8, 129.8, 122.5 (d, J_{C-F} = 27.3 Hz), 113.9 (d, J_{C-F} = 21.1 Hz), 113.4 (J_{C-F} = 16.8 Hz), 79.8, 60.4, 59.3, 36.3, 35.2, 28.4 and 16.6.

5.29. (S)-4-(tert-butoxycarbonylamino)-4-(3-fluorophenyl)butanoic acid (15b)

The above *N*-Boc protected alcohol (**14b**; 0.23 g, 0.8 mmol) in DMF (10 mL) was added to a stirring solution of pyridinium dichromate (1.13 g, 3.0 mmol) in DMF (20 mL) and the mixture was stirred for 18 h at RT. The reaction was quenched with H_2O (5 mL), the product was extracted with Et_2O (3× 50 mL), the combined ether layers were washed with H_2O (3× 50 mL), the solvent was removed and the obtained material was purified on silica gel (flash; hexanes/ethyl acetate 2:1) to afford (*S*)-4-(*tert*-butoxycarbonylamino)-4-(3-fluorophenyl)butanoic acid (**15b**) (0.19 g, 0.64 mmol, 80%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.26 (m, 1H), 6.98–6.87 (m, 3H), 5.10 (t, J = 3.7 Hz, 1H), 2.66–2.42 (m, 2H), 1.87–1.80 (m, 1H), 1.25 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −125.9 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 163.2 (d, J_{C-F} = 226.7 Hz), 149.4, 145.2 (d, J_{C-F} = 6.8 Hz), 130.4 (d, J_{C-F} = 8.2 Hz), 120.6 (d, J_{C-F} = 2.8 Hz), 114.4 (d, J_{C-F} = 21.1 Hz), 112.1 (d, J_{C-F} = 22.1 Hz), 83.1, 61.1, 31.2, 27.7 and 27.2.

5.30. (S)-4-(tert-butoxycarbonylamino)-4-(2-fluorophenyl)butanoic acid (15a)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.02 (m, 4H), 5.43 (dd, J = 6.4 Hz, J = 8.3 Hz, 1H), 2.67–2.44 (m, 3H), 1.93–1.86 (m, 1H),

1.26 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −133.4 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.7, 159.7 (d, J_{C-F} = 244.7 Hz), 149.3, 129.4 (d, J_{C-F} = 13.1 Hz), 129.2 (d, J_{C-F} = 8.3 Hz), 125.9 (d, J_{C-F} = 3.8 Hz), 124.3, 115.7 (d, J_{C-F} = 21.2 Hz), 83.0, 55.5, 31.2, 27.7 and 25.9.

*5.31. (S)-4-(tert-butoxycarbonylamino)-4-(2,6-difluorophenyl)butanoic acid (**15g**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.20 (m, 1H), 6.91–6.85 (m, 2H), 5.52 (dd, J = 4.0 Hz, J = 9.3 Hz, 1H), 2.88–2.43 (m, 3H), 2.07–1.97 (m, 1H), 1.29 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −128.9 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5, 160.7 (dd, J_{C-F} = 247.1 Hz, J_{C-F} = 10.9 Hz), 149.2, 129.4 (d, J_{C-F} = 10.9 Hz), 118.6 (d, J_{C-F} = 7.2 Hz), 111.7 (d, J_{C-F} = 17.6 Hz), 83.0, 51.9, 31.6, 27.7 and 23.9.

*5.32. (S)-4-(tert-butoxycarbonylamino)-4-(3,5-difluorophenyl)butanoic acid (**15i**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.89–6.62 (m, 3H), 5.08 (dd, J = 3.8 Hz, J = 7.5 Hz, 1H), 2.62–2.42 (m, 3H), 1.94–1.78 (m, 1H), 1.27 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −122.1 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 163.4 (dd, J_{C-F} = 248.3 Hz, J_{C-F} = 12.4 Hz), 149.3, 1146.8, 108.1 (d, J_{C-F} = 9.2 Hz), 103.0 (t, J_{C-F} = 25.1 Hz), 83.4, 60.8, 31.0, 27.7 and 26.9.

*5.33. (3S,4S)-4-(tert-butoxycarbonylamino)-4-(3-fluorophenyl)-3-methylbutanoic acid (**18b**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34–7.28 (m, 1H), 7.01–6.81 (m, 3H), 5.09 (d, J = 8.1 Hz, 1H), 2.78–2.68 (m, 1H), 2.59–2.51 (m, 1H), 2.36–2.1 (m, 1H), 1.25 (s, 9H), 0.67 (d, J = 6.9 Hz, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −112.5 (m, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 162.9 (d, J_{C-F} = 246.3 Hz), 149.3, 140.0 (d, J_{C-F} = 6.3 Hz), 130.2 (d, J_{C-F} = 16.9 Hz), 121.0, 114.5 (d, J_{C-F} = 18.9 Hz), 113.4 (d, J_{C-F} = 23.2 Hz), 82.8, 65.1, 38.7, 30.1, 27.6 and 15.7.

*5.34. (S)-5-(3-fluorophenyl)-pyrrolidin-2-one (**16b**)*

The above *N*-Boc protected γ-amino acid **16b** (0.15 g, 0.5 mmol) dissolved in CH_2Cl_2 (3 mL) was treated with CF_3COOH (0.1 mL) for 0.5 h at RT, the solvents were removed and the obtained material was purified on silica gel (flash; hexanes/ethyl acetate 1:1) to obtain (*S*)-5-(3-fluorophenyl)-pyrrolidin-2-one (**16b**) (0.09 g, 0.48 mmol, 96%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.26 (m, 2H), 7.22 (br s, 1H), 7.07–6.93 (m, 2H), 4.74 (t, J = 6.9 Hz, 1H), 2.59–2.36 (m, 3H), 1.98–1.89 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −125.7 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0, 163.2 (d, J_{C-F} = 245.5 Hz), 145.3 (d, J_{C-F} = 6.5 Hz), 130.4 (d, J_{C-F} = 8.1 Hz), 121.1 (d, J_{C-F} = 2.6 Hz), 114.7 (d, J_{C-F} = 20.9 Hz), 112.5 (d, J_{C-F} = 22.2 Hz), 57.7, 31.1, 30.4; MS (EI): 179 $[M]^+$, 159, 135; (CI): 180 $[M+H]^+$.

*5.35. (S)-5-(2-fluorophenyl)pyrrolidin-2-one (**16a**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.23 (m, 2H), 7.17–7.12 (m, 1H), 7.08–7.01 (m, 1H), 6.92 (br s, 1H), 5.06 (t, J = 6.5 Hz, 1H), 2.69–2.58 (m, 1H), 2.48–2.38 (m, 2H), 2.04–1.93 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −133.0 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.0, 160.0 (d, J_{C-F} = 257.4 Hz), 129.6 (d, J_{C-F} = 12.8 Hz), 129.3 (d, J_{C-F} = 8.2 Hz), 126.2 (d, J_{C-F} = 4.1 Hz), 124.5 (d, J_{C-F} = 3.3 Hz), 115.6 (d, J_{C-F} = 21.1 Hz), 51.9, 29.9, 29.5; MS (EI): 179 $[M]^+$, 159, 135; (CI): 180 $[M+H]^+$.

*5.36. (S)-5-(2,6-difluorophenyl)pyrrolidin-2-one (**16g**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.19 (m, 1H), 6.91–6.83 (m, 2H), 6.66 (br s, 1H), 5.17 (dd, J = 4.8 Hz, J = 8.1 Hz, 1H), 2.66–2.37 (m, 3H), 2.26–2.16 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −128.5 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.5, 161.1 (dd, J_{C-F} = 255.9 Hz, J_{C-F} = 14.6 Hz), 129.7 (t, J_{C-F} = 10.7 Hz), 117.7, 111.9 (d, J_{C-F} = 17.6 Hz), 47.9, 29.9, 27.3; MS (EI): 197 $[M]^+$, 177, 142 (CI): 198 $[M+H]^+$.

*5.37. (S)-5-(3,5-difluorophenyl)pyrrolidin-2-one (**16i**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (br s, 1H), 6.84–6.69 (m, 3H), 4.73 (t, J = 6.9 Hz, 1H), 2.61–2.35 (m, 3H), 1.98–1.89 (m, 1H); ^{19}F NMR (282 MHz, $CDCl_3$): δ −122.0 (s, 2F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.9, 163.4 (dd, J_{C-F} = 248.3 Hz, J_{C-F} = 11.1 Hz), 146.9, 108.5 (d, J_{C-F} = 17.2 Hz), 103.3 (d, J_{C-F} = 25.4 Hz), 57.5, 30.9, 30.0; MS (EI): 197 $[M]^+$, 177, 142 (CI): 198 $[M+H]^+$.

*5.38. (4S,5S)-5-(3-fluorophenyl)-4-methylpyrrolidin-2-one (**19b**)*

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38–7.31 (m, 1H), 7.11–6.99 (m, 3H), 6.10 (br s, 1H), 4.22 (d, J = 7.1 Hz, 1H), 2.65–2.57 (m, 1H), 2.30–2.08 (m, 2H), 1.17 (d, J = 6.5, 3H); ^{19}F NMR (282 MHz, $CDCl_3$): d −125.6 (s, 1F); ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.7, 162.9 (d, J_{C-F} = 240.5 Hz), 143.7 (d, J_{C-F} = 6.5 Hz), 130.4 (d, J_{C-F} = 8.3 Hz), 121.8, 115.1 (d, J_{C-F} = 20.9 Hz), 113.1 (d, J_{C-F} = 21.9 Hz), 65.5, 40.3, 38.9, 17.8; MS (EI): 193 $[M]^+$, 173, 149; (CI): 194 $[M+H]^+$.

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