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First enantioselective reductive amination of α-fluoroenones

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Abstract

From α-fluoroenones **2**, a synthesis of (*E*) ketone oxime *O*-alkyl ethers **5** is reported with good to excellent yields. Then the first enantioselective reduction of these ketimines, via oxazaborolidine, is described with moderate to good enantiomeric excesses, leading to valuable chiral fluoroallylic amines **1**.

Keywords: Fluoroalkene; Fluoroenone; Ketone oxime ether; Oxazaborolidine; Enantioselective reductive amination

1. Introduction

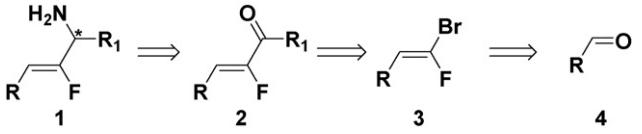
In the last few decades, fluorinated compounds gained high interest due to relevant influence of fluorine atom. Indeed, the incorporation of fluorine substituent in a molecule alters chemical, physical and physiological properties [1] of these compounds leading to materials with highly desirable properties [2]. Among them, functionalized fluoroolefins are particularly important, with current applications in the field of biology where fluoroolefins could be used in the synthesis of biologically active materials such as peptide isosteres [3].

In our ongoing fluorine project devoted to the organic synthesis of new functionalized fluoroolefins, we needed to reach chiral α-alkylated-β-fluorinated allylic amines **1**. These compounds should be obtained from any aldehydes following the sequence described in Scheme 1.

We already described efficient access to bromofluoroolefins **3** via a Wittig-type reaction [4] and, more recently, to compounds **2** via a Negishi coupling reaction [5]. At this stage, we were therefore interested in short sequences allowing the transformation from unsaturated ketones **2** to chiral allylic primary amines **1**. To our knowledge, no reductive aminations were described from α-fluoro-α,β-unsaturated ketones **2** and only few racemic methods were described to reach molecules type **1** [3d,6]. Moreover, the racemic [7] as well as the asymmetric [8] amination reactions of enones are extremely rare in the literature. Herein, we report the first enantioselective reductive amination of α-fluoroenones **2** via oxazaborolidine reduction of oxime ether intermediates **5**.

1.1. Enantiomeric access to α,β-unsaturated amines from enones

Essentially three different hydride donor families were developed to reduce α,β-unsaturated imine derivatives: the NADH mimics [9], the silylated compounds such as trichlorosilane [10], dimethylphenylsilane [8b] and polymethylhydrosiloxane (PMHS) [11] and the borane reductions of activated ketimines [12]. However, the two first classes needed long catalyst's synthesis and led to secondary (alkyl, phenyl or protected) amines. We therefore chose to examine the borane reductions of activated ketimines via chiral oxazaborolidines which are easily obtained and allow the direct access to enantio enriched primary amines. Among these activated ketimines, we decided to study the reduction of ketone oxime *O*-alkylated ethers **5** (Scheme 2) which seemed to provide better results, in terms of imine access, reaction yield and/or stereoselectivity, than *N*-silylimines [13], *N*-tosyl and *N*-diphenylphosphinylimines [8,14].



Scheme 1. Strategy to access to α-alkylated-β-fluorinated allylic amines **1**.

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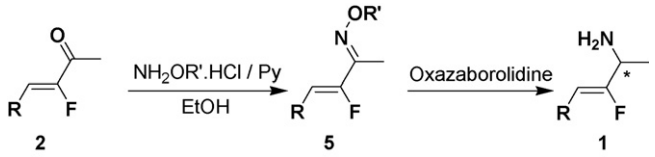


Scheme 2. Access to chiral allylic amines via oxazaborolidines.

2. Results and discussion

2.1. Synthesis of β-fluoro-β,γ-unsaturated oxime ethers 5

The desired ketoxime *O*-ethers **5** were obtained from a solution of α-fluoroenones **2** (with *Z* configuration of double bond) in ethanol reacting with 1.2 equiv. of *O*-alkylhydroxylamine hydrochloride, in presence of 1.2 equiv. of pyridine at room temperature [14a] (Table 1).

After 1 h reaction time, this reaction gave high yield in oxime methyl or benzyl ethers **5**. In each case only the (*E*) isomer was obtained as probed by ^{1}H, ^{13}C and ^{19}F NMR [15].

2.2. Oxazaborolidine reduction

As we mentioned in Section 1, fluorine substituent modifies molecules properties, so we first tested achiral reduction conditions of oxime ether on our fluorinated oxime ether **5a**. BH_3 allowed the obtention of the desired primary amines in 56% yield. All the others conditions tried led to double bond reduction [16].

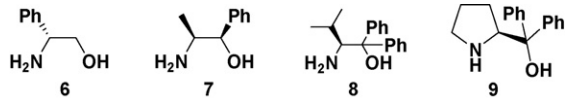
Then we investigated the asymmetric part of the reduction using four aminoalcohols and BH_3 to react with β-fluoro-β,γ-unsaturated oxime ethers **5** (Scheme 3).

(*R*) Phenylglycinol **6** and (−) norephedrine **7** were commercial products, while diphenylvalinol **8** [17] and diphenylprolinol **9** [18] were synthesized from known procedures. We chose the reduction of **5a** as reaction model (Scheme 4). It has to be noted that the reaction could afford hydroxylamine ether **10a** along with expected amine **1a**. The enantiomeric excesses of the hydroxylamine ether **10a** and amine **1a** should be the same since the amine is formed by the reduction of hydroxylamine ether not affecting the stereogenic centre [19].

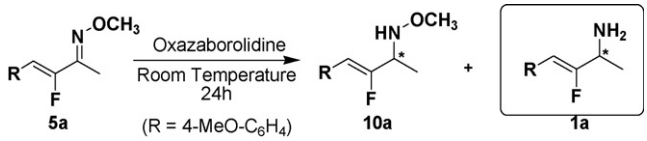
From oxazaborolidines formed with (*S*) aminoalcools, Bolm and Felder [14] and Sakito et al. [20] reported that the absolute configuration of the amines formed are dependent of the geometry of the oxime ethers: (*E*) oxime led to (*S*) amine, while (*Z*) oxime gave rise to (*R*) amine. Our results are in accordance with these rules proving that the fluorinated atom did not affect reduction process.

Table 1
Reaction of alkylhydroxylamine hydrochloride with α-fluoroenones **2**

Entry	*R* (**2***i*)	*R*′	Product yield (%)
1	4-MeO-C_6H_4 (**2a**)	CH_3	**5a**(*E*) 94
2	4-MeO-C_6H_4 (**2a**)	Bn	**5a**′(*E*) 89
3	2-Naphthyl (**2b**)	CH_3	**5b**(*E*) 99
4	4-MeO_2C-C_6H_4 (**2c**)	CH_3	**5c**(*E*) 67
5	4-NC-C_6H_4 (**2d**)	CH_3	**5d**(*E*) 79
6	4-Br-C_6H_4 (**2e**)	CH_3	**5e**(*E*) 97
7	4-O_2N-C_6H_4 (**2f**)	CH_3	**5f**(*E*) 81
8	$PhCH_2CH_2$ (**2g**)	CH_3	**5g**(*E*) 92
9	$TBDPSOCH_2CH_2$ (**2h**)	CH_3	**5h**(*E*) 91



Scheme 3. Aminoalcohols used in the reduction reaction.



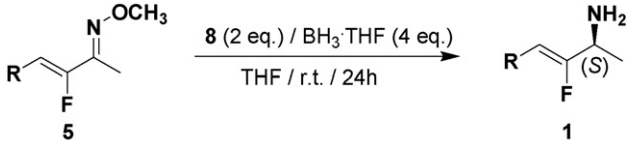
Scheme 4. Reduction of oxime methyl ethers **5a**: reaction model.

Each oxazaborolidine was formed in 2 h at room temperature in presence of two equivalents of borane reagent. Indeed, we first found that best ratio between aminoalcohol and borane for the efficient conversion of **5a** to **1a** were 1:2, respectively, using borane–THF complex as borane source. Reduction reaction results are described in Table 2. The geometry of the fluorinated double bond is not affected during the reaction as followed by NMR coupling constant measurement.

Table 2
Enantiomeric reduction of **5a** and **5a**′ using different aminoalcohols

Entry	Substrate	Aminoalcohol	Amount (equiv.)	Conversion (%)[a,b]		% e.e.[c] (config)[d]
				10a	**1a**	
1	**5a**	**6**	1.1	0	0	–
2	**5a**	**6**	2.5	0	0	–
3	**5a**	**7**	1.1	17	25	–
4	**5a**	**7**	2.5	30 (5)	48 (21)	62 (*S*)
5	**5a**	**7**	3	31	50	–
6	**5a**	**7**	4	33 (16)	51 (42)	66 (*S*)
7	**5a**	**7**	5	32 (8)	50 (41)	70 (*S*)
8	**5a**	**8**	1.1	46 (32)	22 (12)	59 (*S*)
9	**5a**	**8**	2	59 (45)	18	61 (*S*)
10	**5a**	**8**	2.5	56	19	–
11	**5a**	**8**	3	54 (38)	23	76 (*S*)
12	**5a**	**8**	0.25	49 (28)	20 (11)	37 (*S*)
13[e]	**5a**	**8**	1.25	48 (35)	25	53 (*S*)
14	**5a**	**9**	2.5	26 (12)	27 (22)	28 (*S*)
15	**5a**′	**7**	2	34 (13)	46	70 (*S*)
16	**5a**′	**8**	2	53 (18)	22	75 (*S*)

[a] Conversion were determined in ^{19}F NMR.
[b] The number in parentheses refers to isolated yields.
[c] e.e. was determined for amine **1a**; HPLC: Chiralcel OD 250 mm × 4.6 mm; 10 mm; 1 mL min^{-1}; λ = 254 nm; 9/1/0.1%: Hept/IPA/DEA.
[d] Absolute configuration was determined by HPLC by comparison with related compound from which X-ray structure has been determined.
[e] $ZrCl_4/NaBH_4$ instead of BH_3 as reducing agent (Itsuno's conditions [21]).



Scheme 5. Reduction of compounds **5**.

We first tried (*R*) phenylglycinol **6** without any reaction (entries 1 and 2). (−) Norephedrine **7** reduction gave better results but the reduction of hydroxylamine **10a** to amine **1a** was incomplete as described by Fontaine et al. [17b] and Krzeminski and Zaidlewitz [19]. However, the products could be easily separated by flash chromatography. The best excesses with compound **7** were obtained using 5 equiv. increasing e.e. up to 70% but the yields in amine **1a** was very low, 8% (entry 7). Diphenylprolinol **9** did not improve results (entry 14). Only diphenylvalinol **8** gave good results: the better isolated yield was reached with two equivalents furnishing 45% yield with 61% e.e. (entry 9). The use of 3 equiv. allowed the obtention of the higher e.e. up to 76% with a slightly lower yield (entry 11). It is important to note that the e.e. was linked to the aminoalcohol amount. This observation was already shown by Demir et al. [22] and confirmed by experimentation with aminoalcohol **8**: the excesses obtained, with 3 equiv., i.e. 76% e.e. (entry 11), decreased to 61, 59 and 37% e.e. with 2, 1.1 and 0.25 equiv., respectively (entries 9, 8 and 12).

We then tried to improve the results with other reduction conditions reaction described by Itsuno et al. [21], using zirconium tetrachloride/$NaBH_4$ complex instead of borane. In our case, best result was obtained with 1.25 equiv. of aminoalcohol **8** in 24 h leading to **1a** and **10a** in 48 and 25% conversion, respectively, and 53% e.e. (entry 13). Using more than 1.25 equiv. of aminoalcohol involved the degradation of compounds.

We also tried to use benzylated oxime ether **5a′** in order to increase yields and enantiomeric excesses, as described by Fontaine et al. [17b] and Demir et al. [22]. The reduction of **5a′** with oxazaborolidine led to 13% of **1a** in 70% e.e. with aminoalcohol **7** and to 18% yield in 75% e.e. with aminoalcohol **8** (entries 15 and 16).

Table 3
Oxazaborolidine reduction of compounds **5**

Entry	Oxime methyl ethers **5**	Product **1** yield (%)	% e.e. (config)[a]
1	**5a** (R = 4-MeO-C_6H_4)	**1a** 45[b]	61[c] (*S*)
2	**5b** (R = 2-Naphthyl)	**1b** 40[b]	71[c] (*S*)
3	**5c** (R = 4-MeO_2C-C_6H_4)	**1c** 27[d]	n.d.
4	**5d** (R = 4-NC-C_6H_4)	**1d** 36[d]	n.d.
5	**5e** (R = 4-Br-C_6H_4)	**1e** 39[b]	49[c] (*S*)
6	**5f** (R = 4-O_2N-C_6H_4)	**1f** 37[b]	88[e] (*S*)

[a] Absolute configuration was determined by HPLC by comparison with related compound from which X-ray structure has been determined.
[b] Isolated yields.
[c] e.e. was measured by HPLC: Chiralcel OD 250 mm × 4.6 mm; 10 mm; 1 mL min^{-1}; λ = 254 nm; 9/1/0.1%: Hept/IPA/DEA.
[d] Yields based on NMR analysis of crude mixture.
[e] e.e. was determined by HPLC: Chiralcel OD 250 mm × 4.6 mm; 10 mm; 1 mL min^{-1}; λ = 254 nm; 99.5/0.5/0.1%: Hept/IPA/DEA 25 min, then 98/2/0.1%.

Finally, we decided to apply our best reaction conditions to reduce different oxime methyl ether derivatives **5** (Scheme 5 and Table 3). In aliphatic series, chiral allylic amines could not be reached because of degradation of fluorinated double bond during the reaction course.

In aromatic series, compounds bearing reducible substituent, such as ester and nitrile aromatic derivatives **5c** and **5d** revealed to be unstable under our reaction conditions. Indeed in these cases, complex reaction mixtures were obtained; e.e. could not be determined and yields were calculated based on NMR analysis of crude mixture (entries 3 and 4). The compound **5b** gave higher e.e. (71%) than reference compound **5a** (61%) with quite equivalent yield (entries 1 and 2). While surprisingly **5e** just reached 49% e.e., **5f** allowed to get the best e.e. up to 88% (entries 5 and 6).

3. Conclusion

In summary, we reported the first enantioselective reductive amination of β-fluoro-β,γ-unsaturated ketones **2**. The first synthesis of β-fluoro-β,γ-unsaturated oxime ethers **5** with excellents yields is also described. Then asymmetric reaction were effected via oxazaborolidine reduction of oxime methyl ethers **5**. This reaction furnished moderate yields and moderate-to-good enantiomeric excesses for aromatic compounds while it remains unsuccessful with aliphatic compounds. It is important to note that fluorinated double bond remained untouched during reduction process of aromatic derivatives. We are still working on asymmetric methods to improve the access to this kind of allylic amines.

4. Experimental

4.1. General

All commercial solvents were distilled before using: THF and Et_2O were distilled from sodium benzophenone ketyl under nitrogen atmosphere, DMF and DMSO over BaO and CH_2Cl_2 over P_2O_5. TLC were performed on Merck 60F-250 silica gel plates and column chromatography over silica gel SI 60 (230–240 mesh). Flash column chromatography purifications were carried out using silica gel (70–230 mesh). ^1H NMR, ^{13}C NMR and ^{19}F NMR ($CFCl_3$ as external reference) were recorded at 300.13, 75.47 and 282.40 MHz, respectively on a Bruker DXP 300. Abbreviations used for peak multiplicity are s: singlet, b: broad singlet, d: doublet, t: triplet, q: quadriplet, m: multiplet. *J* was used to indicate coupling constant in Hertz. IR spectra were recorded on a Perkin-Elmer 1420. GC–MS were performed on a Thermoquest Finnigan. The enantiomeric excess were determined by chiral HPLC, using a SpectraThermoPhysic equipped with a CHIRACEL-OD column (DAICEL).

4.2. General procedure for obtaining of (Z) oxime alkyl ethers (5)

A mixture of enone **2** (1 equiv.), alkoxyamine hydrochloride (1.2 equiv.) and pyridine (1.2 equiv.) in EtOH (5 mL $mmol^{-1}$

of ketone) was stirred at room temperature for 1 h. After the reaction was completed, controlled by monitoring ^{19}F NMR signal of the reaction mixture, the mixture was concentrated under reduced pressure and purified by chromatography on silica gel (eluent: 5% AcOEt in cyclohexane), affording (*Z*) oxime alkyl ether.

*(Z) 3-Fluoro-4-(4-methoxyphenyl)but-3-en-2-one oxime methyl ether (**5a**)*. White power (mp 100–102 °C). IR (KBr): 3018, 2944, 2841, 2370, 1606, 1513, 1254, 1188, 1045, 1030, 908, 863, 830, 549 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.5 (d, $J = 8.7$ Hz, 2H), 6.9 (d, $J = 9.0$ Hz, 2H), 6.1 (d, $^3J_{H–F} = 38.7$ Hz, 1H), 4.0 (s, 3H), 3.8 (s, 3H), 2.0 (d, $^4J_{H–F} = 1.0$ Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −122.8 (d, $^3J_{H–F} = 38.7$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 159.4 (d, $^3J_{C–F} = 3$ Hz), 152.5 (d, $^1J_{C–F} = 257$ Hz), 149.4 (d, $^2J_{C–F} = 21$ Hz), 130.9 (d, $J = 8$ Hz), 125.6 (d, $^3J_{C–F} = 3$ Hz), 114.2, 110.2 (d, $^2J_{C–F} = 9$ Hz), 62.5, 55.3, 10.7 (d, $^3J_{C–F} = 2$ Hz). MS (EI): 223 (M^+), 192 ($M^+ - OCH_3$), 177 ($M^+ - HNOCH_3$), 149. Anal. Calcd. for $C_{12}H_{14}FNO_2$: C, 64.56; H, 6.32; N, 6.27. Found: C, 64.23; H, 6.41; N, 6.32.

*(Z) 3-Fluoro-4-(4-methoxyphenyl)but-3-en-2-one oxime benzyl ether (**5a′**)*. White power (mp 84–86 °C). IR (KBr): 3038, 2947, 2849, 2373, 1608, 1516, 1258, 1180, 1034, 946, 856, 816, 699, 535 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.4 (d, $J = 8.8$ Hz, 2H), 7.3–7.1 (m, 5H), 6.8 (d, $J = 8.8$ Hz, 2H), 6.0 (d, $^3J_{H–F} = 38.6$ Hz, 1H), 5.2 (s, 2H), 3.7 (s, 3H), 2.0 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −122.5 (d, $^3J_{H–F} = 38.7$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 159.5 (d, $J = 3$ Hz), 152.6 (d, $^1J_{C–F} = 257$ Hz), 149.9 (d, $^2J_{C–F} = 21$ Hz), 137.5, 131.0 (d, $J = 9$ Hz), 128.5, 128.3, 128.1, 125.6 (d, $^3J_{C–F} = 3$ Hz), 114.2, 110.2 (d, $^2J_{C–F} = 9$ Hz), 76.9, 55.3, 11.1 (d, $^3J_{C–F} = 2$ Hz). MS (EI): 299 (M^+), 91 ($PhCH_2^+$). Anal. Calcd. for $C_{18}H_{18}FNO_2$: C, 72.22; H, 6.06; N, 4.68. Found: C, 72.27; H, 5.98; N, 4.71.

*(Z) 3-Fluoro-4-(naphtalen-3-yl)but-3-en-2-one oxime methyl ether (**5b**)*. White power (mp 94–96 °C). IR (KBr): 3055, 2940, 2819, 2364, 1641, 1343, 1051, 886, 827, 742, 486 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 8.0 (s, 1H), 7.8–7.7 (m, 4H), 7.5–7.4 (m, 2H), 6.3 (d, $^3J_{H–F} = 38.2$ Hz), 4.0 (s, 3H), 2.1 (d, $^4J_{H–F} = 1.0$ Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −119.6 (d, $^3J_{H–F} = 37.6$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 154.0 (d, $^1J_{C–F} = 260$ Hz), 149.3 (d, $^1J_{C–F} = 21$ Hz), 133.8, 133.3, 130.8, 129.4–126.8 ($7CH_{arom}$), 110.5 (d, $^2J_{C–F} = 68$ Hz), 62.7, 10.8. MS (EI): 243 (M^+), 212 ($M^+ - OCH_3$), 170 ($M^+ - CH_3C{=}NOCH_3$). Anal. Calcd. for $C_{15}H_{14}FNO$: C, 74.06; H, 5.80; N, 5.76. Found: C, 74.09; H, 5.75; N, 5.83.

*(Z) 3-Fluoro-4-(4-ethylbenzoate)but-3-en-2-one oxime methyl ether (**5c**)*. Yellow solid (mp 96–98 °C). IR (KBr): 3056, 2942, 1723, 1439, 1348, 1279, 1117, 1055, 870, 841 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 8.0 (d, $J = 8.5$ Hz, 2H), 7.6 (d, $J = 8.5$ Hz, 2H), 6.2 (d, $^3J_{H–F} = 37.6$ Hz, 1H), 4.0 (s, 3H), 3.9 (s, 3H), 2.0 (d, $^4J_{H–F} = 1.3$ Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −116.6 (d, $^3J_{H–F} = 37.6$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 166.7, 156.8 (d, $^1J_{C–F} = 263$ Hz, 149.0 (d, $^2J_{C–F} = 22$ Hz), 137.3 (d, $J = 4$ Hz), 129.9, 129.3, 129.2, 109.1 (d, $^2J_{C–F} = 8$ Hz), 62.7, 52.2, 10.7. MS (EI): 251 (M^+), 250, 220 ($M^+ - OCH_3$), 188, 176, 161, 160, 59 (CH_3OCO^+). Anal. Calcd. for $C_{13}H_{14}FNO_3$: C, 62.14; H, 5.62; N, 5.57. Found: C, 62.18; H, 5.44; N, 5.49.

*(Z) 3-Fluoro-4-(4-cyanophenyl)but-3-en-2-one oxime methyl ether (**5d**)*. White powder (mp 117–119 °C). IR (KBr): 3045, 2987, 1681, 1510, 1418, 1351, 1281, 1089, 834, 595 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.6–7.5 (m, 2H), 6.1 (d, $^3J_{H–F} = 37.1$ Hz, 1H), 3.9 (s, 3H), 2.0 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −115.1 (d, $^3J_{H–F} = 37.6$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 155.5 (d, $^1J_{C–F} = 264$ Hz), 148.6 (d, $^2J_{C–F} = 22$ Hz), 137.3 (d, $J = 3$ Hz), 132.2 (d, $J = 8$ Hz), 129.6 (d, $J = 9$ Hz), 118.7, 111.0 (d, $J = 3$ Hz, 108.1 (d, $^2J_{C–F} = 8$ Hz), 62.7, 10.5. MS (EI): 218 (M^+), 217, 187 ($M^+ - OCH_3$), 186, 134. Anal. Calcd. for $C_{12}H_{11}FN_2O$: C, 66.05; H, 5.08; N, 12.84. Found: C, 66.07; H, 4.95; N, 12.73.

*(Z) 3-Fluoro-4-(4-bromophenyl)but-3-en-2-one oxime methyl ether (**5e**)*. White solid (mp 81–83 °C). IR (KBr): 3026, 2933, 1643, 1404, 1346, 1054, 843, 522 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.5–7.4 (m, 4H), 6.1 (d, $^3J_{H–F} = 37.8$ Hz, 1H), 4.0 (s, 3H), 2.0 (s, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −118.7 (d, $^3J_{H–F} = 37.6$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 154.2 (d, $^1J_{C–F} = 261$ Hz), 149.1 (d, $^2J_{C–F} = 22$ Hz), 131.9, 131.8, 130.8 (d, $J = 9$ Hz), 122.1 (d, $^3J_{C–F} = 4$ Hz), 109.1 (d, $^2J_{C–F} = 9$ Hz), 62.7, 10.7. MS (EI): 271–273 (M^+), 240–242 ($M^+ - OCH_3$), 161 ($M^+ - (Br + OCH_3)$), 120. Anal. Calcd. for $C_{11}H_{11}BrFNO$: C, 48.55; H, 4.07; N, 5.15. Found: C, 48.59; H, 4.09; N, 5.11.

*(Z) 3-Fluoro-4-(4-nitrophenyl)but-3-en-2-one oxime methyl ether (**5f**)*. Yellow solid (mp 152–154 °C). IR (KBr): 3032, 2940, 1646, 1600, 1512, 1340, 1056, 919, 862, 843 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 8.2 (d, $J = 8.9$ Hz, 2H), 7.7 (d, $J = 8.9$ Hz, 2H), 6.2 (d, $^3J_{H–F} = 36.9$ Hz, 1H), 4.0 (s, 3H), 2.0 (d, $^4J_{H–F} = 1.2$ Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −114.3 (d, $^3J_{H–F} = 37.6$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 156.1 (d, $^1J_{C–F} = 265$ Hz), 148.8 (d, $^2J_{C–F} = 23$ Hz), 146.7 (d, $J = 3$ Hz), 139.4 (d, $J = 3$ Hz), 129.8 (d, $J = 5$ Hz), 124.0, 107.7 (d, $^2J_{C–F} = 8$ Hz), 62.9, 10.7. MS (EI): 238 (M^+), 221, 191 ($M^+ - HNO_2$), 161 ($M^+ - (NO_2 + OCH_3)$). Anal. Calcd. for $C_{11}H_{11}FN_2O_3$: C, 55.46; H, 4.65; N, 11.76. Found: C, 55.49; H, 4.76; N, 11.59.

*(Z) 3-Fluoro-6-phenylhex-3-en-2-one oxime methyl ether (**5g**)*. Pale yellow oil. IR (neat): 3028, 2938, 1667, 1497, 1455, 1394, 1102, 1055, 900, 748, 700 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.3–7.2 (m, 5H), 5.3 (dt, $^3J_{H–F} = 35.7$ Hz, $^3J_{H–H} = 7.4$ Hz, 1H), 4.0 (s, 3H), 2.8–2.7 (m, 2H), 2.6–2.5 (m, 2H), 1.9 (d, $^4J_{H–F} = 1.0$ Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −125.0 (d, $^3J_{H–F} = 35.5$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 154.0 (d, $^1J_{C–F} = 249$ Hz), 148.7 (d, $^2J_{C–F} = 21$ Hz), 141.2, 128.5, 128.4, 126.2, 111.2 (d, $^2J_{C–F} = 16$ Hz), 62.4, 35.3, 26.0 (d, $^3J_{C–F} = 4$ Hz), 10.7. MS (EI): 221 (M^+), 190 ($M^+ - OCH_3$), 130, 91 ($PhCH_2^+$). Anal. Calcd. for $C_{13}H_{16}FNO$: C, 70.57; H, 7.29; N, 6.33. Found: C, 70.38; H, 7.66; N, 6.39.

*(Z) 3-Fluoro-6-(oxytert-butyldiphenylsilyl)hex-3-en-2-one oxime methyl ether (**5h**)*. Colourless oil. IR (neat): 3071, 3022, 2932, 2858, 1670, 1590, 1472, 1428, 1112, 1054, 702, 505 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.6–7.5 (m, 4H), 7.4–7.3 (m, 6H), 5.3 (d, $^3J_{H–F} = 35.9$ Hz, 1H), 3.9 (s, 3H), 3.6 (m, 2H),

2.5–2.4 (m, 2H), 1.8 (s, 3H), 1.0 (s, 9H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −124.6 (d, $^3J_{H-F}$ = 36.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 154.4 (d, $^1J_{C-F}$ = 249 Hz), 148.7 (d, $^2J_{C-F}$ = 20 Hz), 135.7, 133.8, 129.8, 127.8, 108.9 (d, $^2J_{C-F}$ = 16 Hz), 62.9, 62.4, 27.9 (d, J = 5 Hz), 26.9, 19.3, 10.7. MS (CI^+): 400 (MH^+), 370 ($M^+ - OCH_3$). Anal. Calcd. for $C_{23}H_{30}FNO_2Si$: C, 69.14; H, 7.57; N, 3.51. Found: C, 68.96; H, 7.17; N, 3.37.

4.3. General procedure for the obtention of diphenylaminoalcohol from amino ester hydrochloride

To a solution of (*S*) amino methyl ester hydrochloride (1 equiv.) in Et_2O (4 mL mmol^{-1} of amino acid derivative) at 0 °C was added dropwise phenylmagnesiumbromide in Et_2O (3 M, 8 equiv.). The mixture was heated at reflux for 7 h and then poured into ice (4 mL mmol^{-1} of amino acid derivative). Concentrated HCl aq. was added slowly at 0 °C (0.1 mL mmol^{-1} of amino acid derivative) and the mixture was stirred at room temperature for 1 h. The etheral layer was separated and the aqueous phase was basified until pH reached 10 with NH_3 aq. (20%) and then extracted with Et_2O (3×). The combined organic phases were dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by chromatography on silica gel (eluent: 5% MeOH in CH_2Cl_2), affording desired diphenylaminoalcohol.

*(S) α,α-Diphenylvalinol (**8**)*. Yellow solid (mp 90–92 °C). IR (KBr): 3339, 3086, 3022, 2937, 2927, 2875, 1594, 1491, 1448, 1366, 1174, 1050, 966, 943, 893, 753, 704, 638 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.7 (m, 2H), 7.6 (m, 2H), 7.5–7.3 (m, 6H), 4.0 (d, J = 1.9 Hz, 1H), 2.0–1.9 (m, 1H), 1.1 (2s, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$): 147.8, 144.9, 128.3, 127.9, 126.5, 126.1, 125.8, 125.4, 79.7, 60.1, 27.7, 22.9, 16.1. MS (ESI^+): 256 (MH^+), 238 ($MH^+ - H_2O$), 196, 179, 167. Anal. Calcd. for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.72; H, 8.45; N, 5.46. In accordance with Ref. [17].

*(S) α,α-Diphenylprolinol (**9**)*. Orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): 7.5 (d, J = 7.5 Hz, 2H), 7.4 (d, J = 7.5 Hz, 2H), 7.2–7.0 (m, 6H), 4.2 (t, J = 7.3 Hz, 1H), 4.0 (b, 2H), 2.9–2.8 (m, 2H), 1.7–1.4 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$): 148.0, 145.4, 128.8, 128.5, 127.1, 126.9, 126.4, 125.9, 77.2, 65.1, 47.2, 26.8, 25.8. In accordance with Ref. [18].

4.4. General procedure for the obtention of chiral amines **1** from oxime alkyl ethers **5**

To a solution of (*S*) α,α-diphenylvalinol (2 equiv.) in THF (2 mL mmol^{-1} of aminoalcohol) at 0 °C under argon was added BH_3·THF (4.08 equiv.) slowly. The mixture was stirred at room temperature for 2 h and then added to a solution of oxime ether **5** (1 equiv.) in THF (2 mL mmol^{-1} of oxime ether) at 0 °C. The reaction mixture was then stirred for 18 h at room temperature. After no more conversion was observed, controlled by monitoring ^{19}F NMR signal of the reaction mixture, HCl aq. (1 M) was added at 0 °C until the pH reached 1. The solution was stirred for 5 h at room temperature and KOH aq. (2 M) was then added at 0 °C until the pH reached 10. The mixture was stirred for 1 h at room temperature and extracted with AcOEt (3×). The combined organic layers were dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by chromatography on silica gel (eluent: 10% AcOEt in cyclohexane), affording starting oxime alkyl ether **5**, alkoxyamine **10** (*S*) α,α-diphenylvalinol **8** and desired amine **1**.

*(Z) 2-Amino-3-fluoro-4-(4-methoxyphenyl)but-3-ene (**1a**)*. Yellow oil. IR (neat): 3369, 3024, 2972, 2934, 2838, 1690, 1609, 1513, 1464, 1302, 1251, 1180, 1034, 858, 826, 533 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.4 (d, J = 8.7 Hz, 2H), 6.8 (d, J = 9.0 Hz, 2H), 5.5 (d, $^3J_{H-F}$ = 40.2 Hz, 1H), 3.7 (s, 3H), 3.6 (m, 1H), 1.7 (b, 2H), 1.3 (d, $^4J_{H-F}$ = 6.7 Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −118.5 (dd, $^3J_{H-F}$ = 40.8 Hz, $^4J_{H-F}$ = 15.0 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 162.3 (d, $^1J_{C-F}$ = 266 Hz), 158.4 (d, J = 3 Hz), 129.7 (d, J = 7 Hz), 125.9 (d, $^3J_{C-F}$ = 2 Hz), 113.8, 103.2 (d, $^2J_{C-F}$ = 9 Hz), 55.1, 48.8 (d, J = 29 Hz), 20.5. MS (EI): 195 (M^+), 180 ($M^+ - CH_3$), 174, 163. Anal. Calcd. for $C_{11}H_{14}FNO$: C, 67.67; H, 7.23; N, 7.17. Found: C, 67.27; H, 7.53; N, 7.21.

*(Z) 3-Fluoro-2-methoxyamino-4-(4-methoxyphenyl)but-3-ene (**10a**)*. Colourless oil. IR (KBr): 3331, 3256, 3018, 2929, 2854, 1609, 1513, 1251, 1179, 1054 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.4 (d, J = 8.7 Hz, 2H), 6.9 (d, J = 9.0 Hz, 2H), 5.6 (b, 1H), 5.5 (d, $^3J_{H-F}$ = 40.2 Hz, 1H), 3.8 (s, 3H), 3.8–3.7 (m, 1H), 3.6 (s, 3H), 1.3 (d, $^3J_{H-H}$ = 6.9 Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −121.0 (dd, $^3J_{H-F}$ = 39.8 Hz, $^3J'_{H-F}$ = 19.3 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 158.7 (d, J = 3 Hz), 158.0 (d, $^1J_{C-F}$ = 266 Hz), 130.1 (d, J = 7 Hz), 125.9 (d, $^3J_{C-F}$ = 3 Hz), 114.0, 106.9 (d, $^2J_{C-F}$ = 8 Hz), 62.6, 58.1 (d, $^2J_{C-F}$ = 27 Hz), 55.4, 15.5 (d, $^3J_{C-F}$ = 2 Hz). MS (EI): 225 (M^+), 210 ($M^+ - CH_3$), 179 ($M^+ - HNOCH_3$), 159, 144. Anal. Calcd. for $C_{12}H_{16}FNO_2$: C, 63.98; H, 7.16; N, 6.22. Found: C, 64.04; H, 7.26; N, 6.32.

*(Z) 2-Amino-3-fluoro-4-(naphthalen-7-yl)but-3-ene (**1b**)*. Colourless oil. IR (neat): 3359, 3054, 2976, 2933, 1682, 1594, 1372, 1293, 1021, 904, 868, 826, 749, 482 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.6 (s, 1H), 7.4 (m, 3H), 7.4 (m, 1H), 7.4–7.3 (m, 2H), 5.7 (d, $^3J_{H-F}$ = 39.8 Hz, 1H), 4.1–3.6 (m, 1H), 1.9 (b, 2H), 1.3 (d, $^4J_{H-F}$ = 6.8 Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −115.2 (dd, $^3J_{H-F}$ = 39.8 Hz, $^3J_{H-F}$ = 15.0 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 164.1 (d, $^1J_{C-F}$ = 269 Hz), 133.6, 132.5, 130.9, 128.1, 127.7, 127.6, 126.8, 126.6, 126.2, 126.0, 104.1 (d, $^2J_{C-F}$ = 7 Hz), 49.1 (d, $^3J_{C-F}$ = 29 Hz), 20.7. MS (EI): 215 (M^+), 194, 183. Anal. Calcd. for $C_{14}H_{14}FN$: C, 78.11; H, 6.56; N, 6.51. Found: C, 77.92; H, 6.17; N, 6.33.

*(Z) 2-Amino-4-(4-bromophenyl)-3-fluorobut-3-ene (**1e**)*. Yellow oil. IR (neat): 3374, 2974, 2931, 1694, 1588, 1488, 1402, 1074, 1010, 858, 812, 515 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 7.3 (d, J = 8.6 Hz, 2H), 7.2 (d, J = 8.6 Hz, 2H), 5.5 (d, $^3J_{H-F}$ = 39.3 Hz, 1H), 3.5–3.7 (m, 1H), 2.4 (b, 2H), 1.2 (d, $^4J_{H-F}$ = 6.7 Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −114.2 (dd, $^3J_{H-F}$ = 39.2 Hz, $^3J_{H-F}$ = 15.5 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 163.7 (d, $^1J_{C-F}$ = 270 Hz), 132.2 (d, J = 3 Hz), 131.6, 130.1 (d, J = 7 Hz), 120.8 (d, J = 3 Hz), 103.3 (d, $^2J_{C-F}$ = 8 Hz), 48.8 (d, $^2J_{C-F}$ = 29 Hz), 20.4. MS (EI): 243–245 (M^+), 230–228 ($M^+ - CH_3$), 222–224, 147–148. Anal. Calcd.

for $C_{10}H_{11}BrFN$: C, 49.20; H, 4.54; N, 5.74. Found: C, 49.12; H, 4.63; N, 5.78.

*(Z) 2-Amino-3-fluoro-4-(4-nitrophenyl)but-3-ene (**If**)*. Yellow oil. IR (neat): 3295, 3056, 2980, 2931, 1686, 1596, 1516, 1344, 1110, 750, 694, 542 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 8.2 (d, $J = 9.0$ Hz, 2H), 7.6 (d, $J = 9.0$ Hz, 2H), 5.8 (d, $^3J_{H–F} = 38.5$ Hz, 1H), 3.6–3.8 (m, 1H), 2.4 (b, 2H), 1.4 (d, $^4J_{H–F} = 6.7$ Hz, 3H). ^{19}F NMR (282.5 MHz, $CDCl_3$): −108.5 (dd, $^3J_{H–F} = 38.2$ Hz, $^3J_{H–F} = 14.5$ Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): 166.6 (d, $^1J_{C–F} = 275$ Hz), 141.2, 132.1 (d, $^3J_{C–F} = 8$ Hz), 128.9 (d, $J = 8$ Hz), 123.8, 102.6 (d, $^2J_{C–F} = 7$ Hz), 49.0 (d, $^2J_{C–F} = 29$ Hz), 20.8. MS (CI^+): 211 (MH^+), 194 ($MH^+ - NH_3$), 181 ($MH^+ - NO$), 164 ($MH^+ - HNO_2$). Anal. Calcd. for $C_{10}H_{11}FN_2O_2$: C, 57.14; H, 5.27; N, 13.33. Found: C, 57.46; H, 5.62; N, 13.03.

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