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Stereodivergent formation of fluorine-containing enamides

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ABSTRACT

2-Chloro-1,1,1,2-tetrafluoroethane **1** (HCFC-124) obtained as one of the major byproducts of tetrafluoroethylene synthesis were successfully employed for the stereodivergent construction of tetrafluorinated enamides **4** just by selection of a base for affecting the removal of HCl.

1. Introduction

In recent years, we have been interested in utilization of hydrochlorofluorocarbons (HCFC) as the convenient as well as versatile starting materials for construction of a variety of fluorinated compounds [1], and focused our attention to 2-chloro-1,1,1,2-tetrafluoroethane **1** (HCFC-124) obtained as one of the major byproducts during the course of the tetrafluoroethylene synthesis. Its utilization was reported by us [2] for the ready construction of α-fluoro-α,β-unsaturated acids with a variety of substituents at the β-position, usually with a high level of (*Z*)-stereoselectivity which were initiated by the condensation of the carbanion from **1** and appropriate carbonyl compounds. During our ongoing study in this area, successful employment of imines as electrophiles was realized and these products further led to stereodivergent conversion to fluorine-containing enamides as possible intermediates with pharmaceutical interests. In this article are reported synthetic details of these processes.

2. Results and discussion

First of all, with reference to the previous study [2], HCFC-124 was treated with small excess of *n*-BuLi at −80 °C for 0.5 h to generate the corresponding carbanion which was further mixed with the imine from benzaldehyde and benzylamine (Table 1, Entry 1). However, only a complex mixture was obtained whose ^{19}F NMR analysis did not show any significant amounts of fluorinated products. Then, for the purpose of effective activation of the imine function, electron-withdrawing groups were introduced as R^2 (Entries 2 and 3), and both *p*-toluenesulfonyl (Ts) and *t*-butoxycarbonyl (Boc) moieties were found to work properly to furnish the desired adducts **1ba** and **1ca** in excellent yields, respectively. The latter Boc group easier to be removed was selected for further investigation on the scope of R^1. In the case of aromatic imines with electron-donating substituents like *p*-methoxy (Entry 4) and *p*-methyl (Entry 5), nucleophilic addition occurred efficiently and the adducts **1cb** and **1cc** were successfully obtained, respectively. On the other hand, electron-withdrawing bromo and trifluoromethyl groups at the *para* position were not suitable at all in spite of their electrophilically activating nature of the C=N bond (entries 6 and 7). This phenomenon is in quite sharp contrast to the previous reaction[2)] of the same anionic species with *p*-(trifluoromethyl)benzaldehyde, attaining only slightly lower chemical yield of 72% than the ones of *p*-tolyl- (90%) and *p*-anisaldehydes (89%). In spite of no clear proof, increase of the pK_a values of the benzylic proton by these substituents would affect this tendency, leading to smooth conversion of the initial anion on nitrogen to the one at the benzylic position [3], and the following elimination of chloride would furnish enamine which might cause further undesired reactions under the conditions employed. Moderate yield was recorded by the imine with the 2-furyl moiety (Entry 8), but the one with the β-phenethyl group was not a good substrate at all. This discrepancy clearly indicated the requirement of the appropriate imine activation by R^1 for attainment of good results (Entry 9). This is also the case for the imine with a *c*-C_6H_{11} group, only 16% of the product being isolated. Although we have

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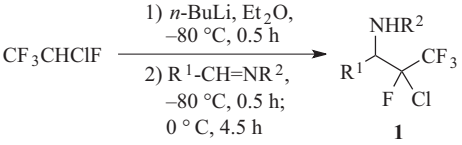
Table 1
Reaction of HCFC-124 with a variety of imines.



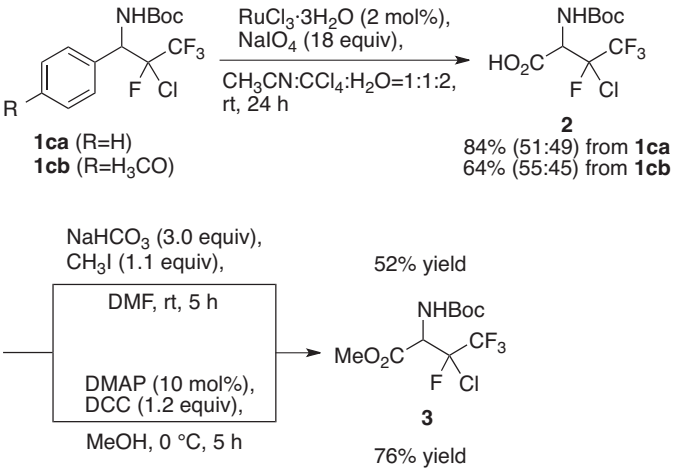
Entry	R^1	R^2	Product	Yield (%)	DR[a]
1	Ph–	$PhCH_2$–	**1aa**	Complex	–
2	Ph–	*p*-H_3C–$C_6H_4SO_2$–	**1ba**	80	53:47
3	Ph–	*t*-BuOC(O)–	**1ca**	82	52:48
4	*p*-H_3CO–C_6H_4–	*t*-BuOC(O)–	**1cb**	76	57:43
5	*p*-H_3C–C_6H_4–	*t*-BuOC(O)–	**1cc**	59	55:45
6	*p*-Br–C_6H_4–	*t*-BuOC(O)–	**1cd**	14	50:50
7	*p*-F_3C–C_6H_4–	*t*-BuOC(O)–	**1ce**	0	–
8	2-Furyl	*t*-BuOC(O)–	**1cf**	33	57:43
9	$PhCH_2CH_2$–	*t*-BuOC(O)–	**1cg**	Trace	–
10	*c*-C_6H_{11}–	*t*-BuOC(O)–	**1ch**	16	51:49
11[b]	Ph–	*t*-BuOC(O)–	**1ca**	(11)[c]	ND

[a] Diastereomeric ratios determined by ^{19}F NMR.
[b] Following to our previous report [2], to a *t*-BuOK solution of the imine in Et2O was added HCFC-124 (3 equiv.) at −20 °C and after stirring for 0.5 h, and reaction was continued at 0 °C for 4.5 h.
[c] In the parenthesis was shown the yield determined by ^{19}F NMR.

not tried yet, employment of a Lewis acids might open the way to obtain such products.

In the previous report [2], we described that *t*-BuOK was employed as the convenient alternative base specifically for aromatic electrophiles without α-proton to the carbonyl group. This protocol, direct addition of gaseous HCFC-124 to a premixed solution containing this base and a carbonyl compound, enabled acceptance of the nucleophilic attack of the CF_3CFCl anion as quickly as possible when it was generated. However, this method was unfortunately proved to be inapplicable to the present imine system, only producing the desired material in 11% yield (Entry 11). This might be attributed to the stability of the anionic species CF_3CClFK: although this modified method previously worked well for condensation with aromatic aldehydes, but its lifetime under the reaction conditions would not be long enough to react with the less reactive imine, leading to possible decomposition to KF and CF_2=CFCl due to strong intramolecular interaction of K···F [4].

It is well-known that aromatic rings can be oxidatively converted to a carboxyl group by the action of the $RuCl_3$–$NaIO_4$ combined system [5], and the selected adducts, **1ca** and **1cb** obtained above, were subjected to the reported condition (Scheme 1). Their smooth



Scheme 1. Conversion of **1ca** and **1cb** to **2** and **3**.

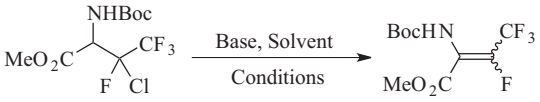
transformation into the desired carboxylic acid **2** was realized in good to excellent yields with complete retention of the Boc group for protection of the amino moiety. The lower yield of **2** from **1cb** might stem from other processes proceeding at the same moment, giving rise to formation of unidentified byproducts.

The carboxylic acid **2** thus obtained was then converted to the corresponding methyl ester **3** whose preparation was conveniently carried out in two different routes: the $NaHCO_3$-mediated methylation afforded 52% of the ester **3** which was also obtained in better yield by way of the standard DCC condensation in the presence of a catalytic amount of DMAP [6].

We have also investigated dehydrochlorination of the amino ester **3** as the promising precursor for a variety of fluorine-containing amino acids [7]. Results were summarized in Table 2. First of all, pyridine [8] was proved not to possess sufficient basicity for abstraction of the proton α to the carbonyl group and increase of the temperature to reflux affected this process only slightly (Entries 1 and 2). On the other hand, triethylamine with higher basicity worked efficiently to furnish the desired enamide **4** in a *Z* specific manner whose stereochemistry was unambiguously clarified by its ^1H–^{19}F HOESY spectrum, showing a clear cross peak between the N–*H* proton and vinylic F. It is interesting to note that change of a base to the representative lithium amide, LDA, totally altered the stereoselectivity of the product **4**, and *E* selectivity as high as 80–90% was attained. Incomplete conversion by treatment with an approximately equimolar amount of LDA (Entries 4–6) was improved by two equivalent of this base, realizing almost quantitative conversion of **3** and constructing 95% yield of **4** after 5 h stirring at −80 °C (Entry 9). Moreover, raising the reaction temperature from −80 to −40 °C recorded almost the same yield but apparently deteriorated the *E* selectivity from 87 to 63%, respectively (Entries 7 vs 8). This formal elimination of HCl was also affected by the more favorable base *t*-BuOK in terms of its handling. In this instance, in contrast to the instance of LDA, −40 °C seemed to be more suitable, and 5 h stirring at this temperature was found to be suffice to attain a similar level of chemical yield as well as stereoselectivity to LDA (Entry 11). The corresponding lithium salt formed *in situ* from *t*-BuOH and *n*-BuLi also worked quite nicely (Entry 12).

This interesting reversal of the stereoselectivity would be elucidated by the mechanism shown in Scheme 2. Circumstance at the deprotonation of **3** by LDA would be understood on the basis of

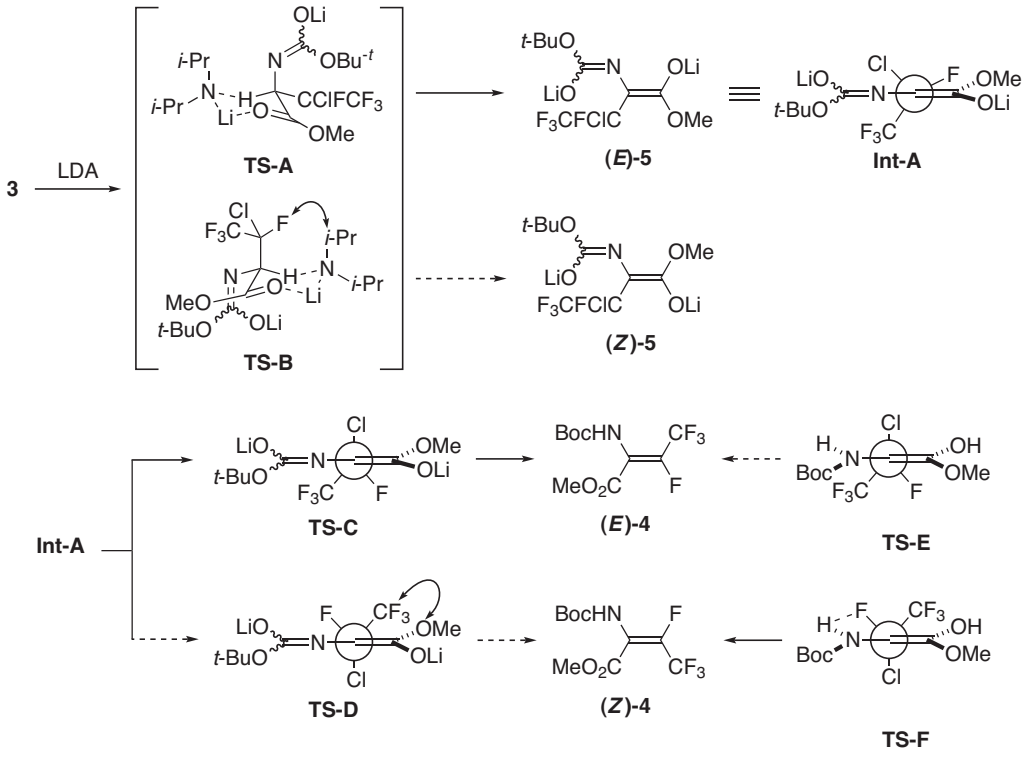
Table 2
Formal dehydrochlorination from **3**.



3 **4**

Entry	Base	Equiv.	Solvent	Conditions	Yield[a] (%)	*E*	:	*Z*
1	Pyridine	2.0	CH_2Cl_2	rt, 6 h	0		–	
2	Pyridine	2.0	CH_2Cl_2	Reflux, 6 h	13	<1	:	>99
3	Et_3N	2.0	CH_2Cl_2	rt, 3 h	[96]	<1	:	>99
4	LDA	1.1	Et_2O	−80 °C, 1 h	26 (72)	89	:	11
5	LDA	1.1	THF	−80 °C, 1 h	53 (45)	86	:	14
6	LDA	1.1	THF	−80 °C, 5 h	57 (31)	86	:	14
7	LDA	2.0	THF	−80 °C, 1 h	74	87	:	13
8	LDA	2.0	THF	−40 °C, 1 h	69	63	:	37
9	LDA	2.0	THF	−80 °C, 5 h	[95]	88	:	12
10	*t*-BuOK	2.0	THF	−80 °C, 5 h	59 (36)	87	:	13
11	*t*-BuOK	2.0	THF	−40 °C, 5 h	[90]	87	:	13
12	*t*-BuOLi	2.0	THF	−40 °C, 5 h	[92]	88	:	12

[a] Yields were determined by ^{19}F NMR using $PhCF_3$ as the internal standard. Numbers in parentheses and brackets described the recovery of **3** and isolated yields of **4**, respectively.



Scheme 2. Plausible reaction mechanism.

TS-A and **-B** when taking usual six-membered transition state models into account. In spite of seemingly similar congestion in both TSs, **TS-B** was considered to possess energetically less favorable 1,3-diaxial interaction between *i*-Pr and CF_3CClF– groups, allowing to produce the intermediary lithium enolate **5** in an *E* selective manner by way of **TS-A**. Because of expectation of the most stable conformer of **(*E*)-5** as **Int-A** [9] with the smallest fluorine atom among the three allylic substituents at the *inside* position [10], **TS-C** with the leaving chlorine atom perpendicular to the C=C π plane would be more preferable than **TS-D** in terms of inconvenient either steric (CF_3=CH_3) or electrostatic (CF_3 = pairs of O) repulsion between CF_3 and MeO groups, and thus, **(*E*)-4** was expected to be preferentially obtained. On the other hand, subjection of Et_3N to a CH_2Cl_2 solution of **3** might form thermodynamically more stable (*Z*)-enol with less steric hindrance. Thus, because **TS-F** from this enol form could avoid at least in part the undesired steric interaction which was found in **TS-D** and additional advantage by the energetically favorable hydrogen bonding with a fluorine atom and weakly acidic amide hydrogen [11] would lead to selective construction of the corresponding **(*Z*)-4**.

3. Conclusion

As an extension of the reaction of HCFC-124-based carbanion with aldehydes and ketones, some aldimines with electron-withdrawing protective groups on nitrogen were treated with

the same anionic species to successfully furnish the adducts **1** in moderate to excellent yields almost in a diastereorandom manner. Further derivatization to *N*-Boc-protected aminoester **3** led to its stereodivergent conversion to the enamide **4** with excellent stereoselectivity just by changing bases employed for the formal dehydrochlorination. Conjugate addition–elimination by a variety of nucleophiles and the following enantioselective hydrogenation are currently investigating in this laboratory whose results will be reported elsewhere.

4. Experimental

4.1. General

All reactions were carried out under an atmosphere of argon in dried glassware with magnetic stirring. Anhydrous Et_2O, THF and CH_2Cl_2 were purchased and were used without further purification. Analytical thin-layer chromatography (TLC) was routinely used for monitoring reactions by generally using a mixture of hexane and AcOEt (v/v). Spherical neutral silica gel (63–210 μm) was employed for column chromatography. ^1H (300.40 MHz), ^{13}C (75.45 Hz), and ^{19}F (282.65 Hz) NMR spectra were recorded on a JEOL AL 300 spectrometer in $CDCl_3$ unless otherwise noted and chemical shifts were recorded in parts per million (ppm), downfield from internal tetramethylsilane (Me_4Si: δ 0.00, for ^1H and ^{13}C) or hexafluorobenzene (C_6F_6: δ −163.00 for ^{19}F). Data were tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sex, sextet; m, multiplet; b, broad peak), coupling constants in Hertz. Infrared (IR) spectra were obtained on a JASCO A-302 spectrometer and reported in wave numbers (cm^{-1}). Elemental analyses were performed by Perkin-Elmer SeriesII CHNS/O analyzer. JEOL JMS-700 was used for obtaining mass spectrometry data by the positive ionization mode.

4.2. General procedure for the preparation of the adduct 1

4.2.1. N-tert-Butoxycarbonyl-2-chloro-2,3,3,3-tetrafluoro-1-phenylpropylamine (1ca)

To an Et_2O solution (5.0 mL) of HCFC-124 (0.5 mL, 5.0 mmol, 2.5 equiv.) at −80 °C was slowly added 1.7 mL of *n*-BuLi (1.4 M, 2.4 mmol, 1.2 equiv.), and after 30 min, benzaldehyde *N*-(*tert*-butoxycarbonyl)imine 0.410 g (2.0 mmol) was added to the mixture, and stirring was continued for 0.5 h at that temperature, followed by 4.5 h at 0 °C. The reaction was quenched with 1 M HCl aq (5 mL), which was extracted three times with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration and concentration in vacuo, the crude material was purified by silica gel column chromatography (EtOAc:Hexane = 1:3) to afford 0.560 g of white solid (1.64 mmol, 82%) as a 52:48 diastereomer mixture. Rf = 0.61 (EtOAc:Hexane = 1:3), mp 79.0–80.0 °C. ^1H NMR δ 1.43 (9H, s), 5.32–5.65 (2H, m), 7.39–7.40 (5H, m). ^{13}C NMR (acetone-d_6) δ 28.4, 57.7 (d, J = 26.0 Hz), 59.1 (d, J = 19.2 Hz), 80.26, 80.30, 108.1 (dq, J = 258.6, 34.1 Hz), 121.8 (qd, J = 284.7, 37.8 Hz), 121.9 (qd, J = 284.7, 31.0 Hz), 129.1, 129.2, 129.7, 129.8, 129.9, 135.1, 135.7, 155.4, 155.5. ^{19}F NMR δ −133.15 (1F, m), −127.61 (1F, m), −79.94 (3F, d, J = 6.8 Hz), −78.96 (3F, d, J = 4.5 Hz). IR (KBr) ν 621, 662, 701, 729, 754, 875, 938, 956, 1021, 1045, 1109, 1126, 1169, 1194, 1203, 1218, 1250, 1268, 1293, 1456, 1499, 1527, 1708, 2981, 3324 cm^{-1}. HRMS-FAB (*m*/*z*): $[M+Na]^+$ calcd. for $C_{14}H_{16}ClF_4NNaO_2$, 364.0703; found, 364.0664.

4.2.2. N-(2-Chloro-2,3,3,3-tetrafluoro-1-phenylpropyl)-4-methylbenzenesulfonamide (1ba)

Yield 80%, Rf = 0.40 (EtOAc:Hexane = 1:3), mp 184.5–185.5 °C, dr = 53:47. ^1H NMR δ 2.31 and 2.33 (3H, s), 5.01–5.19 (1H, m), 5.55–5.62 (1H, m), 7.03–7.23 (7H, m), 7.47–7.53 (2H, m). ^{13}C NMR (acetone-d_6) δ 21.17, 21.19, 61.0 (d, J = 27.9 Hz), 62.3 (d, J = 19.8 Hz), 108.2 (dq, J = 245.8, 32.2 Hz), 108.3 (dq, J = 234.6, 32.8 Hz), 121.4 (qd, J = 284.5, 32.0 Hz), 121.5 (qd, J = 284.9, 30.8 Hz), 127.5, 127.6, 128.8, 129.0, 129.5, 129.6, 129.8 (d, J = 3.8 Hz), 129.9 (d, J = 3.1 Hz), 133.0, 133.7 (d, J = 2.5 Hz), 138.7, 138.9, 143.76, 143.84. ^{19}F NMR δ −128.94 (1F, m), −128.04 (1F, m), −79.13 (3F, d, J = 6.8 Hz), −78.36 (3F, d, J = 4.5 Hz). IR (CH_2Cl_2) ν 669, 705, 749, 1094, 1168, 1201, 1216, 1277, 1333, 1443, 1461, 1599, 2346, 2368, 3251 cm^{-1}. Anal. Calcd. for $C_{16}H_{14}ClF_4NO_2S$: C, 48.55; H, 3.57; N, 3.54. Found: C, 48.63; H, 3.48; N, 3.52.

4.2.3. N-tert-Butoxycarbonyl-2-chloro-2,3,3,3-tetrafluoro-1-(4-methoxyphenyl)propylamine (1cb)

Yield 76%, dr = 57:43. Rf = 0.44 (EtOAc:Hexane = 1:4), mp 85.9–86.8 °C. ^1H NMR δ 1.43 (9H, s), 3.82 (3H, s), 5.25–5.58 (2H, m), 6.89–6.93 (2H, m), 7.26–7.31 (2H, m). ^{13}C NMR (acetone-d_6) δ 28.4, 55.4, 57.2 (d, J = 26.7 Hz), 58.5 (d, J = 19.8 Hz), 80.3, 108.9 (dq, J = 258.6, 12.4 Hz), 114.4, 114.5, 121.8 (qd, J = 284.1, 31.8 Hz), 121.9 (qd, J = 285.3, 31.6 Hz), 126.9, 127.5, 130.96, 131.02, 155.4 (d, J = 7.5 Hz), 160.9, 161.0. ^{19}F NMR δ −132.28 (1F, m), −127.52 (1F, m), −79.86 (3F, d, J = 7.1 Hz), −78.90 (3F, d, J = 7.1 Hz). IR (KBr) ν 623, 641, 692, 716, 734, 765, 783, 803, 843, 876, 931, 952, 979, 993, 1936, 1123, 1177, 1212, 1247, 1272, 1292, 1324, 1369, 1393, 1428, 1445, 1467, 1516, 1589, 1615, 1689, 2840, 2912, 2937, 2967, 2983, 3356 cm^{-1}. Anal. Calcd. for $C_{15}H_{18}ClF_4NO_3$: C, 48.46; H, 4.88; N, 3.77. Found: C, 48.05; H, 4.77; N, 3.67.

4.2.4. N-tert-Butoxycarbonyl-2-chloro-2,3,3,3-tetrafluoro-(4-methylphenyl)propylamine (1cc)

Yield 59%, dr = 55:45. Rf = 0.57 (EtOAc:Hexane = 1:5), mp 90.8–92.0 °C. ^1H NMR δ 1.41 (9H, s), 2.34 (3H, s), 5.45–5.64 (2H, m), 7.15–7.19 (2H, m), 7.24–7.28 (2H, m). ^{13}C NMR (acetone-d_6) δ 21.1, 28.4, 57.5 (d, J = 26.0 Hz), 58.9 (d, J = 19.8 Hz), 80.2, 108.7 (dq, J = 254.3, 33.5 Hz), 108.8 (dq, J = 259.8, 33.5 Hz), 121.7 (qd, J = 284.7, 32.2 Hz), 121.8 (qd, J = 284.7, 31.0 Hz), 129.7, 129.8, 132.1, 132.7, 139.4, 155.5 (d, J = 6.9 Hz). ^{19}F NMR δ −132.79 (1F, m), −127.80 (1F, m), −79.72 (3F, d, J = 4.5 Hz), −78.77 (3F, d, J = 6.8 Hz). IR (KBr) ν 605, 645, 690, 732, 764, 782, 796, 820, 841, 877, 935, 957, 977, 992, 1025, 1055, 1115, 1124, 1173, 1192, 1206, 1254, 1289, 1319, 1342, 1369, 1393, 1456, 1518, 1617, 1695, 1808, 1916, 2293, 2399, 2763, 2871, 2931, 2980, 3036, 3360 cm^{-1}.

4.2.5. N-tert-Butoxycarbonyl-2-chloro-2,3,3,3-tetrafluoro-4-bromopropylamine (1cd)

Yield 14%, dr = 50:50. Rf = 0.63 (EtOAc:Hexane = 1:5), mp 102.9–104.8 °C. ^1H NMR δ 1.43 (9H, s), 5.26–5.61 (2H, m), 7.23–7.27 (2H, m), 7.51–7.56 (2H, m). ^{13}C NMR (acetone-d_6) δ 28.3, 57.2 (d, J = 26.6 Hz), 58.6 (d, J = 19.9 Hz), 80.40, 80.45, 108.2 (dq, J = 259.2, 34.1 Hz), 108.3 (dq, J = 254.8, 34.1 Hz), 121.5 (qd, J = 253.1, 31.6 Hz), 121.6 (qd, J = 253.7, 31.0 Hz), 123.5, 123.6, 131.8, 131.9, 132.2, 132.4, 134.4, 135.0, 155.28, 155.34. ^{19}F NMR δ −133.44 (1F, m), −127.42 (1F, m), −79.94 (3F, d, J = 6.8 Hz), −78.89 (3F, d, J = 6.8 Hz). IR (KBr) ν 611, 656, 695, 731, 769, 798, 834, 845, 876, 935, 945, 984, 999, 1012, 1029, 1059, 1074, 1129, 1164, 1203, 1254, 1269, 1288, 1332, 1369, 1393, 1414, 1453, 1493, 1523, 1578, 1596, 1690, 1795, 1916, 2304, 2415, 2771, 2932, 2982, 3357 cm^{-1}.

4.2.6. N-tert-Butoxycarbonyl-2-chloro-2,3,3,3-tetrafluoro-1-furylpropylamine (1cf)

Yield 33%, dr = 57:43. Rf = 0.60 (EtOAc:Hexane = 1:5), mp 43.0–44.0 °C. ^1H NMR δ 1.46 (9H, s), 5.38 (1H, d, J = 10.5 Hz), 5.41 (1H, d, J = 9.6 Hz), 5.62–5.74 (1H, m), 6.38–6.44 (2H, m), 7.43 (1H, dd, J = 1.5, 0.9 Hz), 7.45 (1H, dd, J = 1.5, 0.9 Hz). ^{13}C NMR (acetone-d_6) δ 28.3, 28.4, 52.8 (m), 53.5 (m), 80.7, 107.6 (dq, J = 258.6, 33.5 Hz), 111.0 (m), 111.4 (m), 121.4 (qd, J = 279.2, 29.8 Hz), 143.9 (m),

148.0, 155.3. ^{19}F NMR δ −131.56 (1F, dq, J = 6.8, 13.6 Hz), −128.85 (1F, quint, J = 6.8 Hz), −80.40 (3F, d, J = 6.8 Hz), −79.76 (3F, d, J = 6.8 Hz). IR (KBr) ν 617, 644, 706, 726, 741, 751, 764, 785, 814, 870, 886, 930, 967, 993, 1012, 1028, 1052, 1079, 1135, 1171, 1199, 1254, 1285, 1317, 1369, 1394, 1457, 1501, 1535, 1616, 1684, 2293, 2322, 2398, 2795, 2939, 2949, 2984, 3008, 3046, 3129, 3157, 3295 cm^{-1}. Anal. Calcd. for $C_{12}H_{14}ClF_4NO_3$: C, 43.45; H, 4.25; N, 4.22. Found: C, 43.75; H, 4.37; N, 4.15.

4.2.7. N-tert-Butoxycarbonyl-2-chloro-2,3,3,3-tetrafluoro-1-cyclohexylpropylamine (1ch)

Yield 16%, dr = 51:49. Rf = 0.62 (EtOAc:Hexane = 1:5), mp 91.0–93.0 °C. ^{1}H NMR δ 0.99–1.45 (4H, m), 1.45 (9H, s), 1.62–1.92 (6H, m), 2.18 (1H, m), 4.32 (1H, m), 4.81 (1H, d, J = 11.51 Hz), 4.66 (1H, d, J = 10.8 Hz). ^{13}C NMR (acetone-d_6) δ 15.0, 21.3, 27.1, 28.3, 39.9, 40.1, 58.1 (d, J = 25.4 Hz), 58.6 (d, J = 18.6 Hz), 61.0, 80.3, 110.2 (dq, J = 214.0, 34.7 Hz), 122.2 (qd, J = 285.3, 33.5 Hz), 156.5, 156.7. ^{19}F NMR δ −132.95 (1F, m), −128.11 (1F, m), −80.91 (3F, d, J = 6.8 Hz), −79.84 (3F, d, J = 7.1 Hz). IR (KBr) ν 621, 643, 675, 696, 708, 733, 762, 782, 804, 859, 881, 897, 918, 930, 953, 965, 1011, 1040, 1059, 1086, 1134, 1175, 1186, 1200, 1212, 1252, 1272, 1284, 1300, 1310, 1339, 1369, 1392, 1452, 1531, 1687, 2408, 2857, 2932, 2974, 3306 cm^{-1}. Anal. Calcd. for $C_{13}H_{22}ClF_4NO_2$: C, 48.35; H, 6.38; N, 4.03. Found: C, 48.77; H, 6.40; N, 3.73.

4.3. Preparation of 2-(tert-butoxycarbonyl)amino-3-chloro-3,4,4,4-tetrafluorobutyric acid (2)

To a solution of CH_3CN (13.0 mL) and H_2O (26.0 mL) were added 26.09 g of $NaIO_4$ (122.0 mmol, 18.0 equiv.) and 2.317 g of **1ca** (6.779 mmol) in 13.0 mL of CCl_4 at room temperature. 0.036 g of $RuCl_3{\cdot}3H_2O$ (0.14 mmol, 2.0 mol%) was introduced to this mixture which was stirred for 1 day at room temperature. After filtration, saturated $NaHCO_3$ aq was added so as to make the pH of the solution to be 8–9, and the aqueous layer was washed with CH_2Cl_2. Then, 1 M HCl was added to this aqueous layer to adjust the pH at 2–3, which was extracted with EtOAc twice, and the organic layer was washed with brine, and dried over anhydrous Na_2SO_4. Filtration and concentration furnished 1.768 g of a crude material (5.71 mmol, 84%) as a 50:50 diastereomer mixture which was employed to the next step without further purification. ^{1}H NMR δ 1.47 (9H, s), 5.07–5.49 (2H, m), 6.13 (1H, br). ^{13}C NMR (acetone-d_6) δ 28.2, 57.0 (d, J = 26.6 Hz), 58.1 (d, J = 24.3 Hz), 81.0, 105.8 (dq, J = 260.5, 34.8 Hz), 106.3 (dq, J = 259.2, 34.7 Hz), 121.2 (qd, J = 284.7, 31.0 Hz), 155.4, 166.4, 166.9. ^{19}F NMR δ −132.54 (1F, s), −128.97 (1F, s), −80.72 (3F, d, J = 4.0 Hz), −79.85 (3F, d, J = 7.1 Hz). IR (KBr) ν 856, 943, 1222, 1372, 1509, 1706, 2980, 3376 cm^{-1}.

4.4. Preparation of methyl 2-(tert-butoxycarbonyl)amino-3-chloro-3,4,4,4-tetrafluorobutyrate (3a)

To a MeOH (20 mL) solution containing 0.877 g (2.83 mmol) of **2** were added at 0 °C DCC 0.697 g (3.38 mmol, 1.2 equiv.) and 4-DMAP 0.035 g (0.29 mmol, 10.0 mol%), and the whole mixture was stirred for 5 h at room temperature. After filtration, the usual workup and purification by silica gel column chromatography (EtOAc:Hexane = 1:4) afforded 0.699 g (2.16 mmol, 76%) of the title compound (**5a**) as a 52:48 diastereomer mixture. Rf = 0.45 (EtOAc:Hexane = 1:3). ^{1}H NMR δ 1.45 (9H, s), 3.84 (3H, s), 3.86 (3H, s), 5.17–5.45 (2H, m). ^{13}C NMR δ 28.0, 53.2, 53.4, 56.1 (d, J = 26.6 Hz), 56.9 (d, J = 21.7 Hz), 81.5, 105.3 (dq, J = 261.1, 35.9 Hz), 119.5 (qd, J = 285.4, 31.0 Hz), 154.0 (d, J = 8.7 Hz), 166.3. ^{19}F NMR δ −132.06 (1F, m), −129.57 (1F, m), −80.87 (3F, d, J = 6.8 Hz), −80.19 (3F, d, J = 7.1 Hz). IR (KBr) ν 698, 727, 776, 862, 897, 959, 987, 1026, 1054, 1161, 1217, 1252, 1281, 1327, 1370, 1395, 1439, 1456, 1504, 1729, 1757, 2937, 2982, 3342, 3447 cm^{-1}. HRMS-FAB (m/z): $[M-HF+Na]^+$ calcd. for $C_{10}H_{13}ClF_3NNaO_4$, 326.0383; found, 326.0360.

4.5. Dehydrochlorination of amino ester 3

4.5.1. Conversion to (Z)-methyl 2-(tert-butoxycarbonyl)amino-3,4,4,4-tetrafluorobut-2-enoate (Z-4)

To a CH_2Cl_2 (10.0 mL) solution of **5a** (0.699 g, 2.16 mmol) was added Et_3N (0.6 mL, 4.3 mmol, 2.0 equiv.), and the mixture was stirred for 3 h at room temperature. The usual workup and purification by silica gel column chromatography (CH_2Cl_2:Hexane = 3:1) afforded 0.594 g (2.07 mmol, 96%) of the title compound (**6a**) as a sole Z isomer. Rf = 0.41 (CH_2Cl_2:Hexane = 3:1), mp 66.0–67.0 °C. ^{1}H NMR δ 1.48 (9H, s), 3.89 (3H, s), 6.33 (1H, br). ^{13}C NMR δ 27.9, 53.3, 83.2, 118.7 (qd, J = 270.4, 36.6 Hz), 120.5 (dq, J = 9.3, 3.1 Hz), 136.2 (qd, J = 254.9, 41.6 Hz), 150.7, 160.6 (d, J = 7.4 Hz). ^{19}F NMR δ −149.46 (1F, br), −68.50 (3F, d, J = 11.3 Hz). IR (KBr) ν 711, 738, 776, 824, 876, 929, 979, 1074, 1118, 1154, 1198, 1228, 1253, 1309, 1343, 1371, 1396, 1440, 1514, 1754, 2985, 3316 cm^{-1}. Anal. Calcd. for $C_{10}H_{13}F_4NO_4$: C, 41.82; H, 4.56; N, 4.88. Found: C, 42.14; H, 4.51; N, 4.86.

4.5.2. Conversion to (E)-methyl 2-(tert-butoxycarbonyl)amino-3,4,4,4-tetrafluorobut-2-enoate (E-4)

To a THF solution (3.0 mL) of t-BuOH (0.059 g, 0.80 mmol, 2.0 equiv.) was added at −40 °C 0.53 mL of n-BuLi (1.52 M, 0.81 mmol, 2.0 equiv.) and the whole mixture was stirred for 0.5 h at that temperature. To this solution was added **5a** (0.130 g, 0.40 mmol) and 5 h stirring at that temperature was performed. The usual workup and purification by silica gel column chromatography (EtOAc:Hexane = 1:10) afforded 0.0901 g (0.314 mmol, 78%) of E isomer and 0.0154 g (0.0536 mmol, 13%) of Z isomer (The E:Z ratio of the crude material was determined as 85:15 by ^{19}F NMR). Rf = 0.39 (EtOAc:Hexane = 1:5), mp 78.0–78.4 °C. ^{1}H NMR δ 1.47 (9H, s), 3.91 (3H, s), 6.16 (1H, br). ^{13}C NMR δ 27.9, 53.2, 82.7, 118.7 (d, J = 26.0 Hz), 118.7 (qd, J = 274.2, 37.8 Hz), 143.3 (m), 152.3 (d, J = 1.9 Hz), 161.6 (d, J = 2.5 Hz). ^{19}F NMR δ −140.80 (1F, br), −69.07 (3F, d, J = 11.3 Hz). IR (KBr) ν 651, 662, 686, 772, 787, 826, 872, 896, 1005, 1030, 1065, 1153, 1194, 1236, 1283, 1303, 1371, 1394, 1451, 1518, 1686, 1739, 2751, 2810, 2851, 2955, 2986, 3183, 3229 cm^{-1}. Anal. Calcd. for $C_{10}H_{13}F_4NO_4$: C, 41.82; H, 4.56; N, 4.88. Found: C, 42.29; H, 4.56; N, 4.76.

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