



Supporting Information

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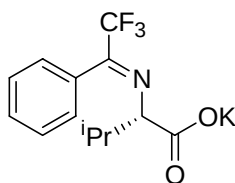
**Diastereoselective Reductive Amination of Aryl-Trifluoromethyl Ketones
and α -Amino Esters**

Greg Hughes, Paul N. Devine,* John R. Naber, Paul D. O'Shea, Bruce S. Foster, Daniel J.
McKay, R. P. Volante*

General: Unless otherwise noted all reactions were run under an inert atmosphere, and solvents and reagents were transferred by syringe. Anhydrous grade tetrahydrofuran (THF) was purchased from A&C Chemicals Ltd, anhydrous grade methanol was purchased from Acros and anhydrous acetonitrile, 1,2-dimethoxyethane (DME) and *tert*-butyl methyl ether (MTBE) were purchased from Aldrich in Sure/Seal™ bottles and used as received. Unless otherwise noted, ¹H NMR (500 MHz), ¹³C NMR (125 Hz) and ¹⁹F NMR spectra (376.5MHz) were recorded in acetone-d₆ or methanol-d₄ purchased from CDN Isotopes. The ¹H and ¹³C spectra were referenced to residual acetone (2.04 ppm) or methanol (3.30 ppm). ¹⁹F NMR spectra were referenced to added benzotrifluoride (-67.73 ppm). Coupling constants are reported in hertz (Hz). Multiplicities are as follows: s = singlet, d = doublet, t = triplet, q = quartet. Optical Rotations were recorded on a Perkin Elmer 241 polarimeter. Chiral HPLC was run on a Berger SFC system, reverse phase HPLC's were run on an Agilent 1100 series system. Infrared (IR) spectra were recorded on an Applied Systems Inc. ReactIR 1000, optics model. High resolution mass spectrometry was performed by Merck Analytical Research. Elemental analysis was performed by Prevalere Life Sciences in Whitesboro NY.

Representative Procedure for the Synthesis of Potassium Imine Carboxylates.

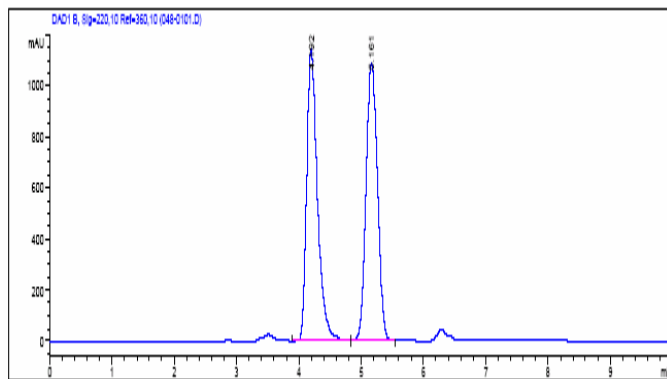
N-(2,2,2-Trifluoro-1-phenylethylidene)-L-valine, potassium salt (**1c**).



2,2,2-Trifluoroacetophenone (4.03 mL, 28.7 mmol) was added to a mixture of L-Valine methyl ester hydrochloride (5.05 g, 30.2 mmol) and potassium carbonate (9.92 g, 71.8 mmol) in MeOH (50 mL) at ambient temperature. The resulting mixture was warmed to 50 °C for 8 h, then cooled to ambient temperature and filtered through celite. The cake was rinsed with MeOH (10 mL) and the filtrate was concentrated. The residue was suspended in TBME (100 mL) and triturated for 1 h. Filtration afforded 7.84 g of a white solid. This material assayed at ~90 wt% based on the ¹H NMR analysis relative to a standard volume of mesitylene. The remaining 10 wt% is presumed to be residual KHCO₃ and K₂CO₃. ¹H NMR (CD₃OD, δ) 0.81 (d, *J* = 7 Hz, 3H), 0.91 (d, *J* = 7 Hz, 3H), 2.26 (apparent octet, *J* = 6.5 Hz, 1H), 3.64 (d, *J* = 6 Hz), 7.25-7.35 (m, 2 H), 7.40-7.50 (m, 3H); ¹⁹F NMR (CD₃OD, δ) -75.31; ¹³C NMR (CD₃OD, δ) 18.73, 20.22, 33.38, 75.89, 121.44 (q, *J* = 287 Hz), 129.23, 129.78, 131.02, 132.17, 158.81 (q, *J* = 33 Hz), 177.86; IR (2M MeOH soln, cm⁻¹) 1664, 1602, 1390, 1328, 1197, 1135, 703.

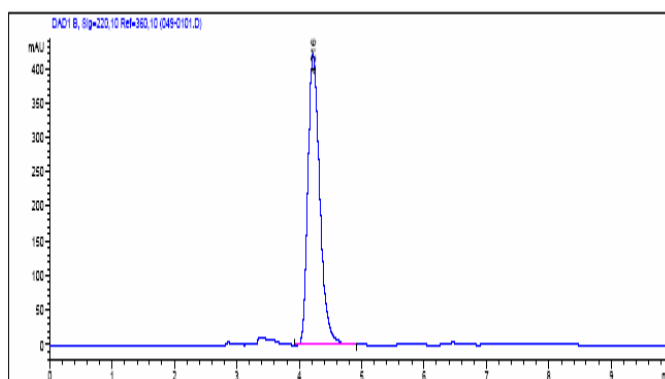


The enantiomeric excess of this compound was measured by converting the potassium carboxylate to its corresponding methyl ester **4c**. Carboxylate **1c** (1 mmol) was suspended in DMF (1mL) and MeI (1.5 mmol) was added. After 2h, the mixture was partitioned between TBME and H₂O. The organic layer was washed twice with fresh portions of H₂O, once with brine, dried over MgSO₄, filtered and concentrated. The resulting oil (1mg) was dissolved in 2ml of 2% IPA/hexanes and analyzed by chiral HPLC analysis (Chiralcel OJ, 250x4.6mm, 2% IPA/hexanes, 1.0 ml/min, 220nm, 30°C, retention times: 4.2 min for the isomer derived from (*S*)-valine, 5.2 min for the isomer derived from (*R*)-valine). None of the enantiomer could be detected. A racemic sample of the ester was prepared by an analogous sequence using commercially available (dl)-valine methylesterhydrochloride. δH(500 MHz; CD₃OD) 7.55-7.48 (3 H, m), 7.23 (2 H, d, *J* 7.12), 3.83 (1 H, d, *J* 5.85), 3.70 (3 H, s), 2.31-2.24 (1 H, m), 0.91 (3 H, d, *J* 6.78), 0.83 (3 H, d, *J* 6.86).



Signal 1: DAD1 B, Sig=220,10 Ref=360,10

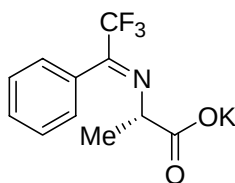
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.192	VV	0.1859	1.39118e4	1144.03723	50.0010
2	5.161	VV	0.2007	1.39113e4	1091.68005	49.9990



Signal 1: DAD1 B, Sig=220,10 Ref=360,10

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.216	VB	0.2090	5677.16309	421.88480	100.0000

***N*-(2,2,2-Trifluoro-1-phenylethylidene)-L-alanine, potassium salt (**1a**).**



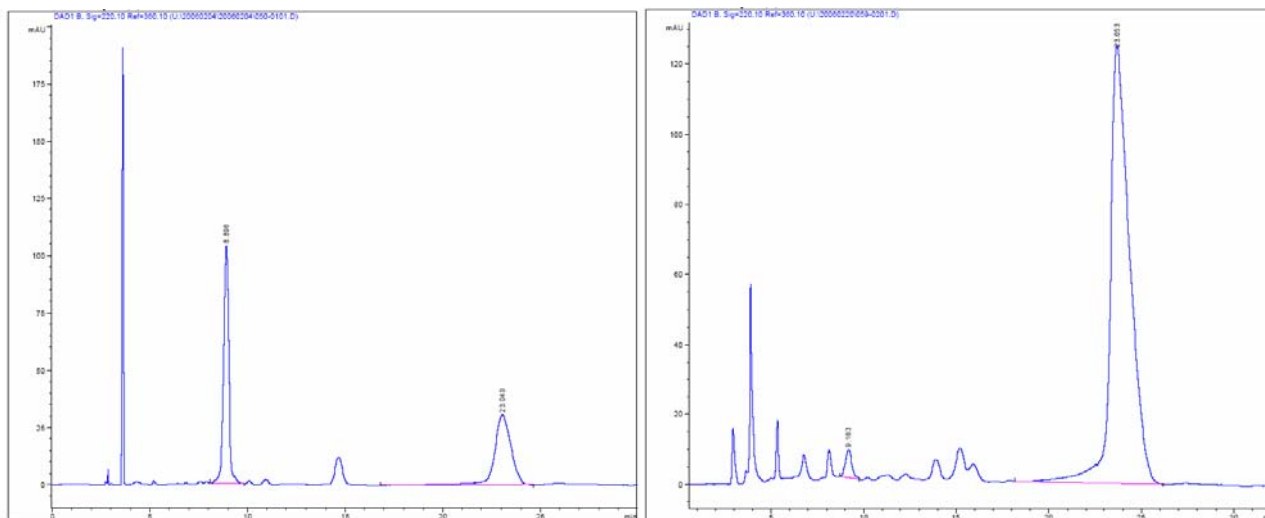
The standard imine/carboxylate formation protocol was employed except that the reaction were run at ambient temperature instead of 50°C, 1.2 equiv of alanine methylester hydrochloride was used instead of 1.05 equiv, and 2.5 equiv of K₃PO₄ was used instead of 2.5 equiv of K₂CO₃. This afforded the desired product as a white solid assaying at ~88 wt%. ¹H NMR (CD₃OD, δ) 1.36 (d, *J* = 7 Hz, 3H), 3.93 (q, *J* = 7 Hz, 1H), 7.25-7.35 (m, 2 H), 7.40-7.50 (m, 3H); ¹⁹F NMR (CD₃OD, δ) -75.79; ¹³C NMR (CD₃OD, δ) 20.60, 64.62, 121.45 (q, *J* = 287 Hz), 129.00, 129.94, 131.27, 131.76, 158.52 (q, *J* = 33 Hz), 178.98; IR (2M MeOH soln, cm⁻¹) 1664, 1602, 1390, 1328, 1197, 1135, 703.



The standard protocol for ester formation was followed. A racemic reference sample was prepared from commercially available dl-alanine methylester hydrochloride. Chiral HPLC (Chiracel OJ, 20% IPA/hexanes, 1ml/min, 30°C, 220nm, (R)-alanine derived imine: 9min, (S)-alanine derived imine: 23 min) showed the material to be 95.8%ee. ¹H NMR δH(500 MHz; CD₃COCD₃) 7.59-7.55 (3 H, m), 7.40-7.37 (2 H, m), 4.16 (1 H, q, *J* 6.68), 1.35 (3 H, d, *J* 6.69).

HPLC of a *rac*-**4a**:

HPLC of (S)-**4a**



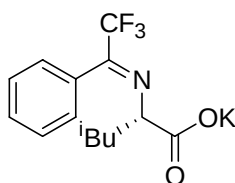
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Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.898	MM	0.3018	1875.04614	103.54388	50.0805
2	23.040	MM	1.0153	1869.02014	30.68159	49.9195

Signal 1: DAD1 B, Sig=220,10 Ref=360,10

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.163	BB	0.3691	197.62823	8.08637	2.1087
2	23.653	MM	1.2213	9174.33105	125.19498	97.8913

N-(2,2,2-Trifluoro-1-phenylethylidene)-L-leucine, potassium salt (1b).



The standard imine/carboxylate formation protocol was employed affording the desired product as a white solid assaying at ~85 wt%. ¹H NMR (CD₃OD, δ) 0.62 (d, *J* = 7 Hz, 3H), 0.84 (d, *J* = 7Hz, 3H), 1.35-1.45 (m, 1H), 1.65-1.72 (m, 1H), 1.80-1.90 (m, 1H), 3.92 (dd, *J* = 10, 4 Hz, 1H), 7.25-7.35 (m, 2H), 3.45-3.55 (m, 3H); ¹⁹F NMR (CD₃OD, δ) -75.29; ¹³C NMR (CD₃OD, δ) 19.83, 21.98, 24.26, 42.80, 66.31, 119.60 (q, *J* = 278 Hz), 127.33, 128.00, 129.44, 130.06, 156.99 (q, *J* = 33 Hz), 176.88; IR (2M MeOH soln, cm⁻¹) 1663, 1602, 1323, 1197, 1139, 707.

nOe:

Current Data Parameters
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EXPNO 1
PROCNO 1

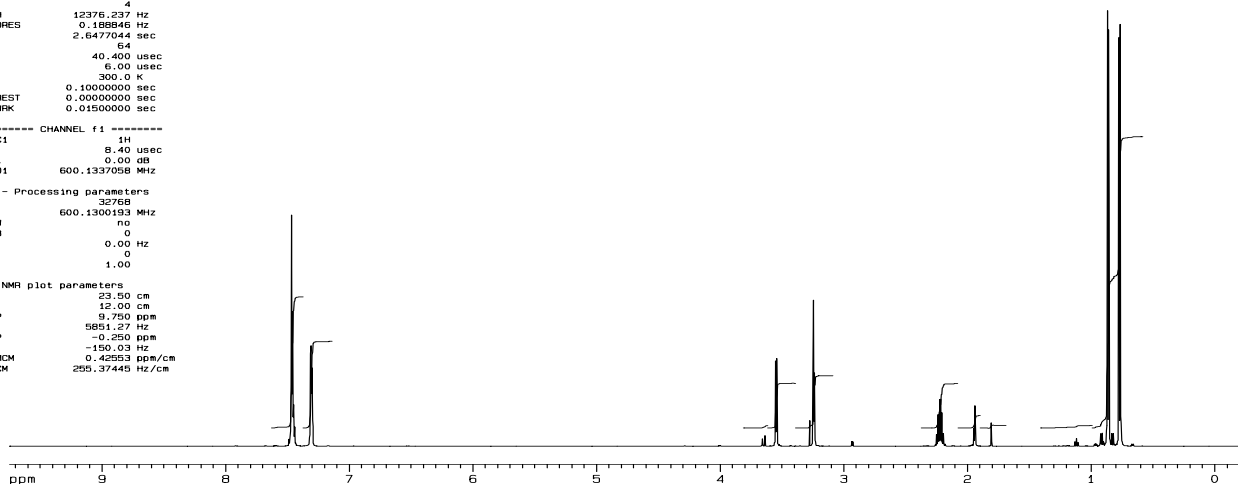
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nmr600 h-1

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TD 65536
SOLVENT CD3CN
NS 32
DS 4
SWH 12376.237 Hz
FIDRES 0.188846 Hz
AQ 2.6477044 sec
RG 64
DW 40.400 usec
DE 8.00 usec
TE 300.0 K
D1 0.10000000 sec
MCREST 0.00000000 sec
MCWPK 0.01500000 sec

----- CHANNEL f1 -----
NUC1 1H
P1 8.40 usec
PL1 0.00 dB
SF01 600.1337058 MHz

F2 - Processing parameters
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SF 600.1300193 MHz
WDW no
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 23.50 cm
CY 12.00 cm
F1P 9.750 ppm
F1 5851.27 Hz
F2P -0.250 ppm
F2 -150.03 Hz
PPHMC 0.42553 ppm/cm
HZCM 255.37445 Hz/cm



Current Data Parameters
NAME hugc1475
EXPNO 3
PROCNO 1

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nmr600 gradient noe

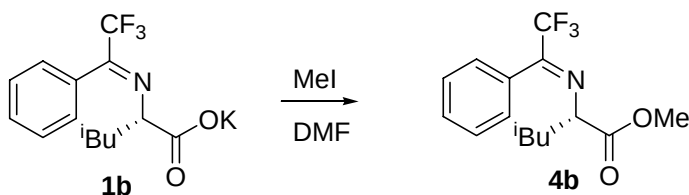
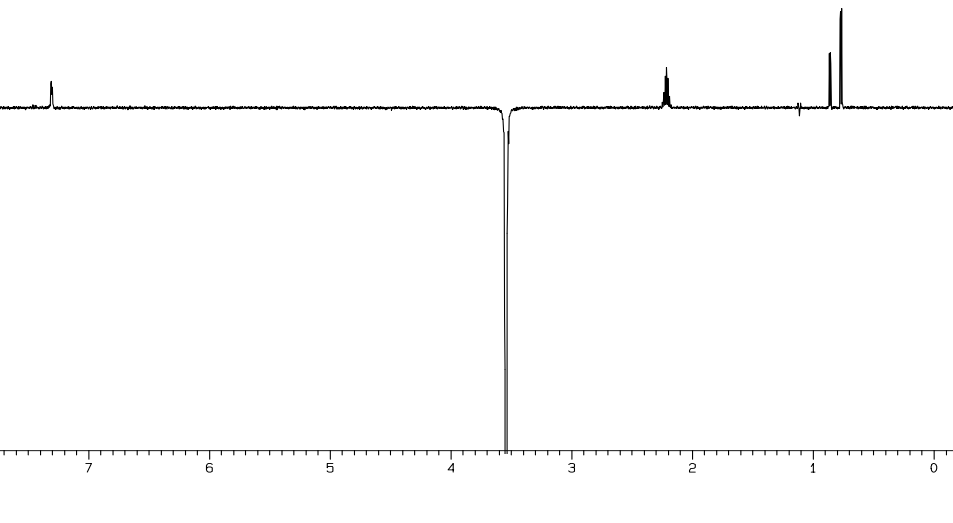
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NS 64
DS 4
SWH 12376.237 Hz
FIDRES 0.188846 Hz
AQ 2.6477044 sec
RG 128
DW 40.400 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
D8 0.50000000 sec
D16 0.00020000 sec
D20 0.24879999 sec

===== CHANNEL f1 =====
NUC1 1H
P1 9.50 usec
P2 19.00 usec
P12 14000.00 usec
PL0 120.00 dB
PL1 -1.00 dB
SFO1 600.1361887 MHz
SP2 66.50 dB
SPNAM2 gauss
SPOFF2 0.00 Hz

===== GRADIENT CHANNEL =====
GPNAM1 SINE.100
GPNAM2 SINE.100
GPNAM3 SINE.100
GPX1 0.00 %
GPX2 0.00 %
GPX3 0.00 %
GPY1 0.00 %
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GPZ2 40.00 %
GPZ3 -40.00 %
P15 1000.00 usec

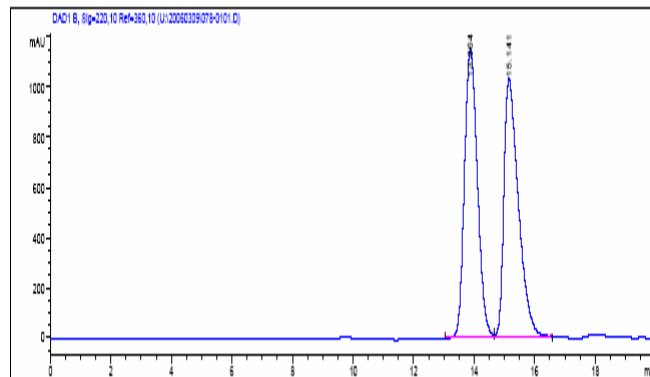
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SSB 0
LB 0.30 Hz
GB 0
PC 1.00

1D NMR plot parameters
CX 23.50 cm
CY 150.00 cm
F1 9.250 ppm
F1 5851.77 Hz
F2 -0.250 ppm
F2 -150.03 Hz
PRNCM 0.42553 ppm/cm
HZCM 255.37445 Hz/cm



The standard protocol for ester formation was followed. A racemic reference sample was prepared from racemic dl-leucine ethylester hydrochloride which was in turn prepared as follows: SOCl₂ (50 mL) was added over 1h to a suspension of dl-leucine (25g) in EtOH (250 mL). After aging 12h, the mixture was concentrated on a rotovap and the residue was triturate in TMBE (100 mL) for 1h, then filtered to afford 32g of a white solid. Chiral HPLC (Chiracel OJ, 2% IPA/hexanes, 0.3 ml/min, 30°C, 220nm, (R)-alanine derived imine: 14min, (S)-alanine derived imine: 15 min) showed the material to be 95.6%ee. ¹H NMR: δH(500 MHz; CD₃OD) 7.57-7.50 (3 H, m), 7.30 (2 H, d, J 7.23), 4.12 (1 H, dd, J 8.41 and 5.29), 3.72 (3 H, s), 1.79-1.66 (2 H, m), 1.46-1.37 (1 H, m), 0.80 (3 H, d, J 6.65), 0.64 (3 H, d, J 6.60).

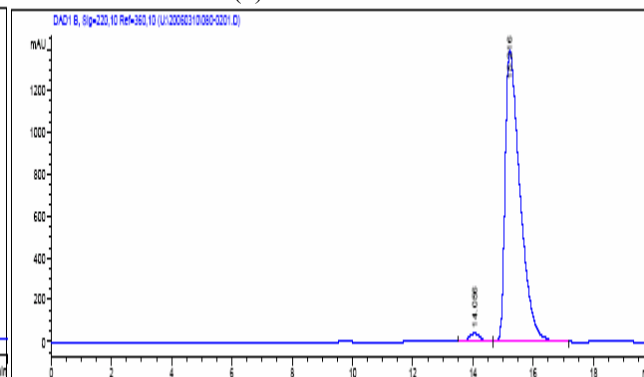
HPLC of a rac-4c:



Signal 1: DAD1 B, Sig=220,10 Ref=360,10

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.864	VV	0.4715	3.45567e4	1153.63818	50.2115
2	15.141	VB	0.5005	3.42657e4	1028.96045	49.7885

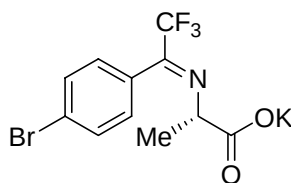
HPLC of (S)-4c



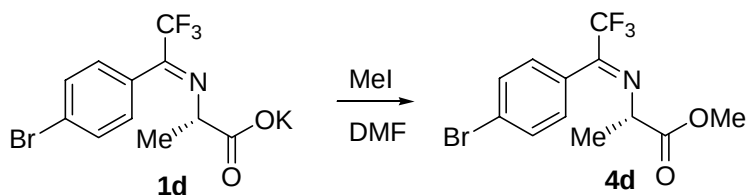
Signal 1: DAD1 B, Sig=220,10 Ref=360,10

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.056	BP	0.3683	1084.08130	45.44599	2.2086
2	15.216	VB	0.5133	4.79999e4	1395.62122	97.7914

***N*-(2,2,2-Trifluoro-1-(4-Bromophenyl)ethylidene)-L-alanine, potassium salt (1d).**



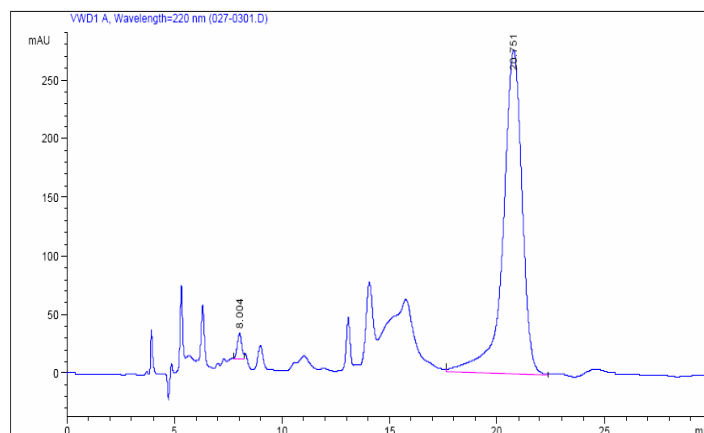
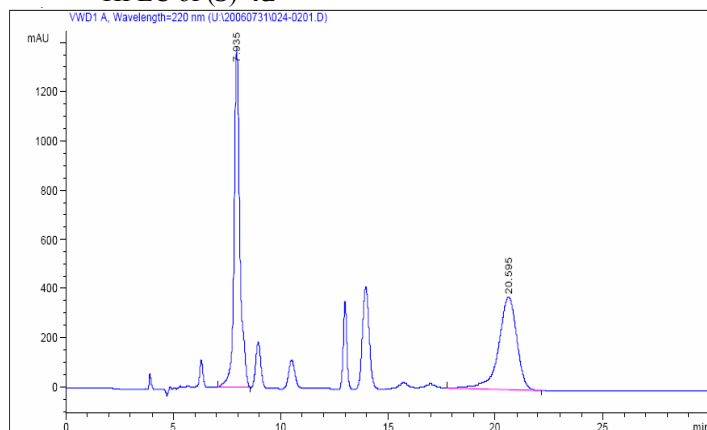
The standard imine/carboxylate formation protocol was employed except that the reaction were run at ambient temperature instead of 50°C, 1.2 equiv of alanine methylester hydrochloride was used instead of 1.05 equiv, and 2.5 equiv of K₃PO₄ was used instead of 2.5 equiv of K₂CO₃. This afforded the desired product as a white solid. ¹H NMR: δH(400 MHz; CD₃OD) 7.68-7.63 (2 H, d, J 8.20), 7.26 (2 H, d, J 8.17), 3.88 (1 H, q, J 6.77), 1.37 (3 H, d, J 6.75); ¹³C NMR: δC(126 MHz; CD₃OD) 20.47, 64.74, 121.20 (q, 125.56, J 278 Hz) 130.66, 130.94, 133.15, 157.32 (q, J 33 Hz), 178.55.; ¹⁹F NMR: δF(377 MHz; CD₃OD) -75.88.



The standard protocol for ester formation was followed. A racemic reference sample was prepared from commercially available dl-alanine methylester hydrochloride. Chiral HPLC (Chiracel OJ, 10% IPA/hexanes, 0.75 ml/min, 30°C, 220nm, (R)-alanine derived imine: 9min, (S)-alanine derived imine: 23 min) showed the material to be 95.8%ee. ¹H NMR δH(500 MHz; CD₃COCD₃) 7.59-7.55 (3 H, m), 7.40-7.37 (2 H, m), 4.16 (1 H, q, J 6.68), 1.35 (3 H, d, J 6.69).

HPLC of a *rac*-4d:

HPLC of (S)-4d



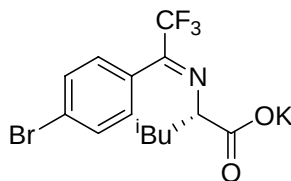
Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU	Height [mAU]	Area %
1	8.004	MM	0.2533	353.09906	23.23479	2.0342
2	20.751	MM	1.0272	1.70052e4	275.91458	97.9658

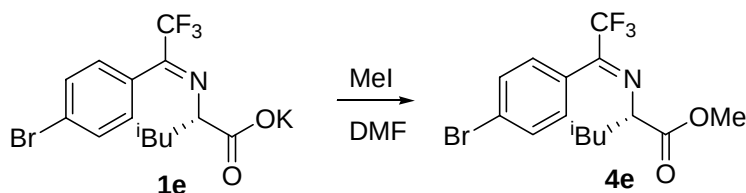
Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.935	MM	0.3101	2.55822e4	1375.03979	53.3305
2	20.595	MM	0.9911	2.23870e4	376.45303	46.6695

***N*-(2,2,2-Trifluoro-1-(4-bromophenyl)ethylidene)-L-leucine, potassium salt (1e).**



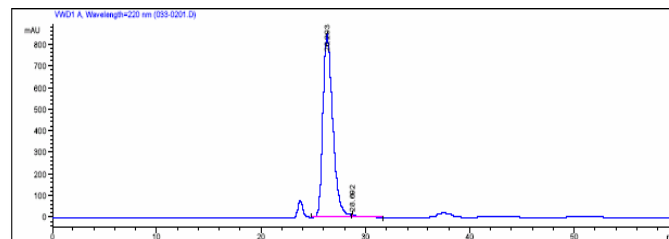
The standard imine/carboxylate formation protocol was employed affording the desired product as a white solid. ¹H NMR: δH(400 MHz; CD₃OD) 7.66 (2 H, d, J 8.28), 7.26 (2 H, d, J 8.15), 3.87 (1 H, dd, J 9.66 and 4.07), 1.90-1.80 (1 H, m), 1.71 (1 H, ddd, J 13.42 and 9.25 and 4.13), 1.48-1.35 (1 H, m), 0.85 (3 H, d, J 6.64), 0.64 (3 H, d, J 6.58).; ¹³C NMR: δC(101 MHz; CD₃OD) 21.71, 23.77, 26.12, 44.53, 68.34, 121.19 (q, J 278), 125.60, 130.84, 131.08, 133.09, 157.65 (q, J 34), 178.25. ¹⁹F NMR: δF(377 MHz; CD₃OD) -75.32.; IR.



The standard protocol for ester formation was followed. A racemic reference sample was prepared from racemic dl-leucine ethylester hydrochloride. Chiral HPLC (Chiracel OJ, 0.2% IPA/hexanes, 0.2 ml/min, 30°C, 220nm, (S)-leucine derived imine: 28min, (R)-leucine derived imine: 29 min) showed the material to be 97%ee. ¹H NMR: δH(500 MHz; Acetone) 7.78 (2 H, d, J 8.56), 7.37 (2 H, d, J 8.24), 4.12 (1 H, dd, J 8.31 and 5.30), 3.69 (3 H, s), 1.82-1.69 (2 H, m), 1.50-1.42 (1 H, m), 0.81 (3 H, d, J 6.60), 0.68 (3 H, d, J 6.59).

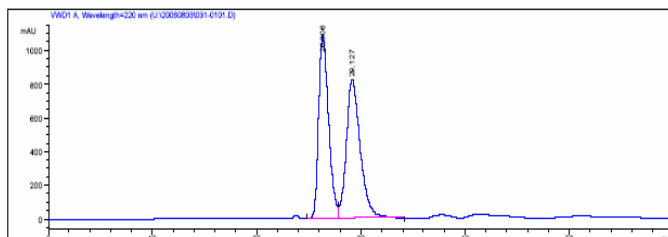
HPLC of a *rac*-4e:

HPLC of (S)-4e



Signal 1: VWD1 A, Wavelength=220 nm

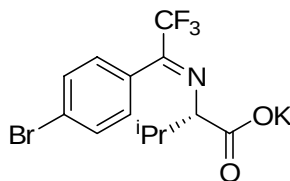
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	26.293	MM	1.0997	5.60711e4	849.82697	98.5398
2	28.692	MM	0.8745	830.85803	11.32398	1.4602



Signal 1: VWD1 A, Wavelength=220 nm

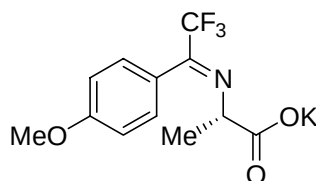
Peak #	RetTime [min]	Type	Width [min]	Area mAU	Height [mAU]	Area %
1	26.306	BV	1.0180	7.19085e4	1090.95581	48.4890
2	29.127	VB	1.3800	7.63902e4	819.59369	51.5110

***N*-(2,2,2-trifluoro-1-(4-Bromophenyl)ethylidene)-L-valine, potassium salt (1f).**

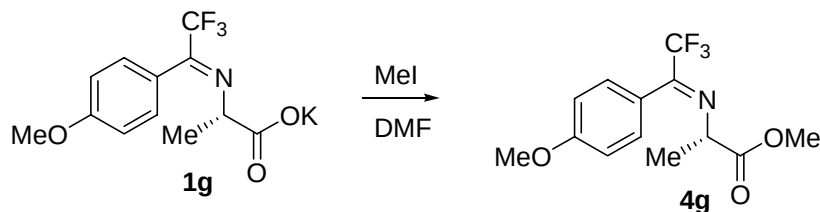


The standard imine/carboxylate formation protocol was employed affording the desired product as a white solid assaying at 95 wt%. ¹H NMR δ (ppm)(CD₃OD): 0.82 (d, *J* = 7 Hz, 3H), 0.92 (d, *J* = 7Hz, 3H), 2.27 (nonet, *J* = 7Hz, 1H), 3.58 (d, *J* = 6 Hz, 1H), 7.21 (d, *J* = 8Hz, 2H), 7.64 (d, *J* = 8Hz, 2H); ¹⁹F NMR (CD₃OD, δ) -75.39; ¹³C NMR (101 MHz, CD₃OD): δ 18.67, 20.21, 33.31, 76.02, 121.21 (q, *J* = 278 Hz), 125.35, 131.15, 133.06, 133.07, 157.69 (q, *J* = 34 Hz), 177.47; IR (2M MeOH soln, cm⁻¹) 1660, 1602, 1390, 1328, 1247, 1197, 1134. By inference from chiral HPLC analysis of the reduction product **2f**, **1f** is >99.5 % ee.

***N*-(2,2,2-Trifluoro-1-(4-Methoxyphenyl)ethylidene)-L-alanine, potassium salt (1g).**



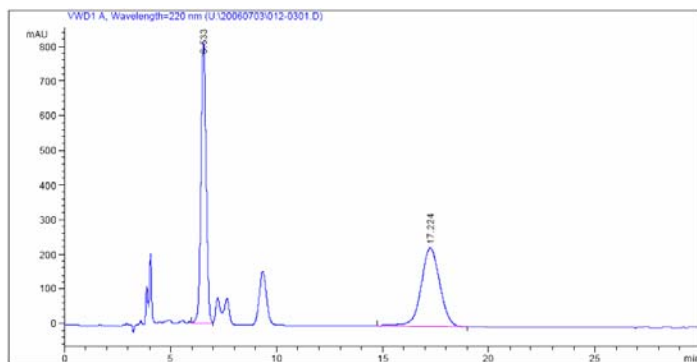
The standard imine/carboxylate formation protocol was employed except that the reaction were run at ambient temperature instead of 50°C, 1.2 equiv of alanine methylester hydrochloride was used instead of 1.05 equiv, and 2.5 equiv of K₃PO₄ was used instead of 2.5 equiv of K₂CO₃. This afforded the desired product as a white solid. ¹H NMR: δ H(500 MHz; Acetone) 7.26 (2 H, d, *J* 8.80), 7.03-6.98 (2 H, d, *J* 8.92), 3.99 (1 H, q, *J* 6.80), 3.82 (3 H, s), 1.36 (3 H, d, *J* 6.76); ¹³C NMR: δ C(101 MHz; CD₃OD) 20.61, 55.89, 64.49, 115.25, 121.53 (q, *J* 275 Hz), 123.43, 130.58, 158.39 (q, *J* 32 Hz), 162.45, 179.14.; ¹⁹F NMR: δ F(377 MHz; CD₃OD) -75.69.



The standard protocol for ester formation was followed. A racemic reference sample was prepared from commercially available dl-alanine methylester hydrochloride. Chiral HPLC (Chiracel OJ, 40% IPA/hexanes, 1.0 ml/min, 30°C, 220nm, (R)-alanine derived imine: 6.5min, (S)-alanine derived imine: 17 min) showed the material to be 97.8 %ee. ¹H NMR δ H(500 MHz; CD₃OD) 7.24 (2 H, d, *J* 8.52), 7.08-7.04 (2 H, d, *J* 8.99), 4.22 (1 H, q, *J* 6.72), 3.84 (3 H, s), 3.71 (3 H, s), 1.35 (3 H, d, *J* 6.71).

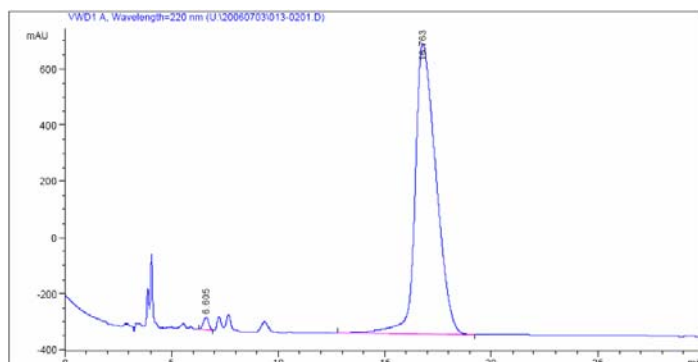
HPLC of a *rac*-**4d**:

HPLC of (*S*)-**4d**



Signal 1: VWD1 A, Wavelength=220 nm

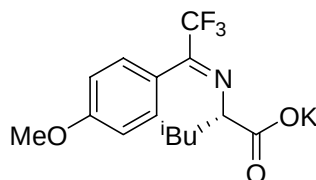
Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Height [mAU]	Area %
1	6.533	MM	0.2836	1.38107e4		811.69037	49.3644
2	17.224	VP	0.9618	1.41663e4		227.68146	50.6356



Signal 1: VWD1 A, Wavelength=220 nm

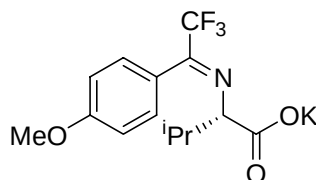
Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Height [mAU]	Area %
1	6.605	MM	0.2937	782.98822		44.42649	1.0888
2	16.763	VP	1.0631	7.11272e4		1034.12512	98.9112

***N*-(2,2,2-Trifluoro-1-(4-Methoxyphenylethylidene)-L-leucine, potassium salt (1h).**

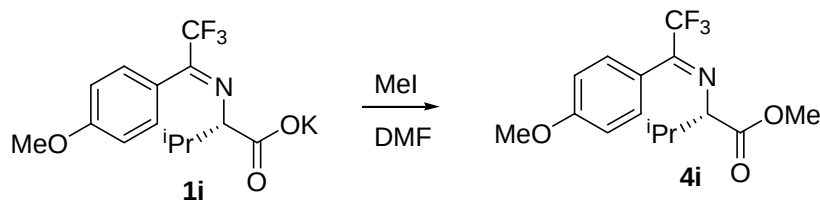


The standard imine/carboxylate formation protocol was employed affording the desired product as a white solid assaying at ~85 wt%. ¹H NMR: ; ¹⁹F NMR (CD₃OD, δ) -75.29; ¹³C NMR (CD₃OD, δ) 19.83, 21.98, 24.26, 42.80, 66.31, 119.60 (q, *J* = 278 Hz), 127.33, 128.00, 129.44, 130.06, 156.99 (q, *J* = 33 Hz), 176.88; IR (2M MeOH soln, cm⁻¹) 1663, 1602, 1323, 1197, 1139, 707.

***N*-(2,2,2-Trifluoro-1-(4-Methoxyphenyl)ethylidene)-L-valine, potassium salt (1i).**



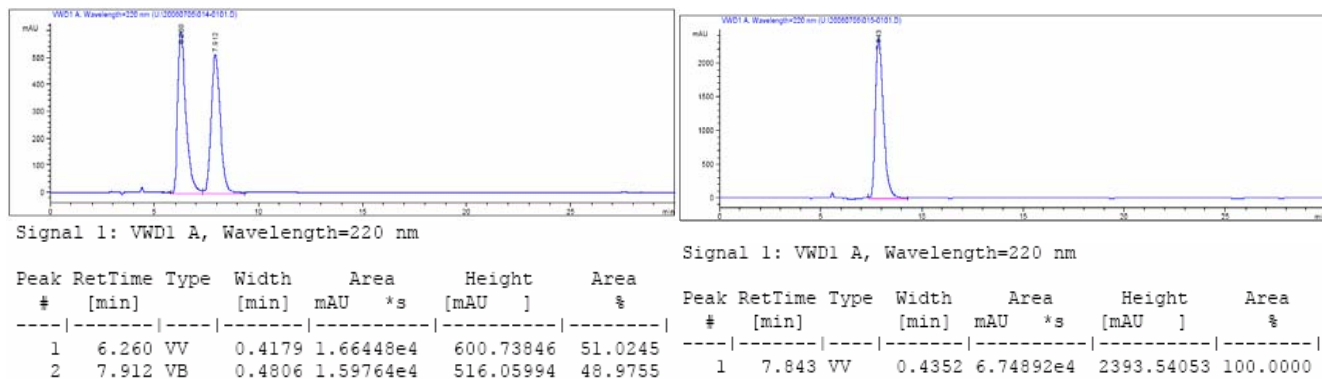
The standard imine/carboxylate formation protocol was employed affording the desired product as a white solid. ¹H NMR: ; ¹³C NMR: δC(126 MHz; CD₃OD); ¹⁹F NMR: δF(377 MHz; CD₃OD).



The standard protocol for ester formation was followed. A racemic reference sample was prepared from commercially available dl-alanine methylester hydrochloride. Chiral HPLC (Chiracel OJ, 40% IPA/hexanes, 1.0 ml/min, 30°C, 220nm, (R)-valine derived imine: 6.3min, (S)-valine derived imine: 7.9 min) showed the material to be >99.5 %ee. ¹H NMR δH(500 MHz; CD₃OD) 7.24 (2 H, d, *J* 8.52), 7.08-7.04 (2 H, d, *J* 8.99), 4.22 (1 H, q, *J* 6.72), 3.84 (3 H, s), 3.71 (3 H, s), 1.35 (3 H, d, *J* 6.71).

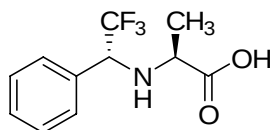
HPLC of a *rac*-**4d**:

HPLC of (*S*)-**4d**



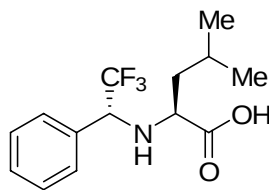
Representative procedure for the (R,S)-selective reductive amination.

N-[(1R)-2,2,2-trifluoro-1-phenylethyl]-L-alanine ((R, S)-2a)



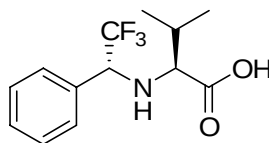
2,2,2-Trifluoroacetophenone (871 mg, 5.00 mmol) was added to a suspension of L-alanine, methyl ester hydrochloric acid salt (803 mg, 5.75 mmol) and potassium carbonate (2.25 g, 15 mmol) in MeOH (10 mL) at ambient temperature. The resulting mixture was warmed to 50 °C for 18 h. The mixture was cooled to ambient temperature and the MeOH was removed on a rotovap. The residue was suspended in THF (20 mL) and added to a 50 mL RBF which had been charged with NaBH₄ (1.51g, 40.0 mmol). A 20% (v/v) solution of water/THF was added via syringe pump over 3 h. 1N HCl (10 mL) was added and the mixture was extracted with TBME (50 mL). The TBME layer was washed with brine, dried over MgSO₄, concentrated and dissolved in a 50/50 mixture of TBME and hexanes (20 mL). This solution was extracted with 0.5M NaOH (3 x 25 mL) and acidified the aqueous layer and extracted 3 x 10 mL collected 717 mg of a white solid (58% yield). Analysis by ¹⁹F NMR showed a 10 : 1 mixture of diastereomers. [α]_D²³ = +10.5° (c=1.0, CH₃COCH₃); ¹H NMR 7.44 – 7.47 (m, 2H), 7.37 – 7.41 (m, 3H), 4.44 (q, *J* = 7Hz, 1H), 2.95 (q, *J* = 7Hz, 1H), 1.17 (d, *J* = 7Hz, 3H); ¹⁹F NMR -79.06 (d, 8Hz, minor), -79.79 (d, 8Hz, major); ¹³C NMR (DMSO-d₆, δ) 19.30, 53.19, 61.93 (q, *J* = 28 Hz), 125.76 (q, *J* = 281 Hz), 128.90, 129.23, 129.33, 134.17, 175.82; IR (neat, cm⁻¹) 1737; HRMS: calc for C₁₁H₁₃F₃NO₂ (M+H)⁺: 248.0898; found 248.0892.

N-[(1R)-2,2,2-trifluoro-1-phenylethyl]-L-leucine ((R,S)-2b)



[α]_D²³ = -11.1° (c=1.0, CH₃COCH₃); ¹H NMR (CD₃COCD₃, δ) 7.51 – 7.55 (m, 2H), 7.41 – 7.44 (m, 3H), 4.42 (q, *J* = 8Hz, 1H), 3.01 (dd, *J* = 10Hz, 5Hz, 1H), 1.92 (st, *J* = 7Hz, 2Hz, 1H), 1.54 (AB, ddd, *J* = 15Hz, 10Hz, 5Hz, 1H), 1.44 (AB, ddd, *J* = 15Hz, 10Hz, 5Hz, 1H), 0.87 (d, *J* = 7Hz, 3H), 0.72 (d, *J* = 7Hz, 3H); ¹⁹F NMR -78.81 (d, 7Hz, minor), -79.76 (d, 7Hz, major), dr = 1 : 19; ¹³C NMR (CD₃COCD₃, δ) 22.27, 23.80, 25.60, 43.81, 56.99, 63.91 (q, *J* = 29 Hz), 126.77 (q, *J* = 280 Hz), 129.84, 130.59, 130.64, 134.82, 176.33; IR (neat, cm⁻¹) 1737; HRMS: calc for C₁₄H₁₉F₃NO₂ (M+H)⁺: 290.1368; found 290.1361; Elemental Analysis: calc: %C = 58.12, %H = 6.27, %N = 4.70, found %C = 57.93, %H = 6.17, %N = 4.70.

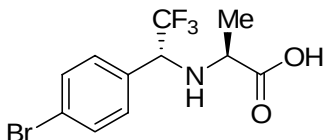
N-[(1R)-2,2,2-trifluoro-1-phenylethyl]-L-valine ((R,S)-2c)



[α]_D = -11.6° (c=1.0, CH₃COCH₃); ¹H NMR 7.52 – 7.54 (m, 2H), 7.41 – 7.43 (m, 3H), 4.36 (q, *J* = 7Hz, 1H), 2.84 (d, *J* = 5Hz, 1H), 1.99 (vo, *J* = 6Hz, 1H), 0.93 (d, *J* = 7Hz, 6H); ¹⁹F NMR -78.94 (d, 8Hz, minor), -79.82 (d, 8Hz, major), dr = 1 : 25; ¹³C NMR (CD₃COCD₃, δ) 18.57, 20.22, 32.47, 64.17, 64.28 (q, *J* = 28 Hz), 126.83 (q, *J* = 281 Hz), 129.81, 130.53, 130.68,

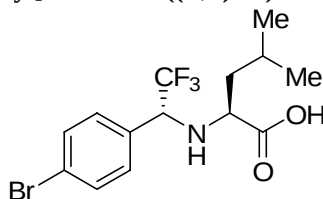
134.79, 175.49; IR (neat, cm^{-1}) 1733; HRMS: calc for $\text{C}_{13}\text{H}_{17}\text{F}_3\text{NO}_2$ (M+H) : 276.1211; found 276.1204; Elemental Analysis: calc: %C = 40.51, %H = 3.40, %N = 4.30, found %C = 40.95, %H = 3.40, %N = 4.16.

***N*-[(1*R*)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-L-alanine ((*R,S*)-2d)**



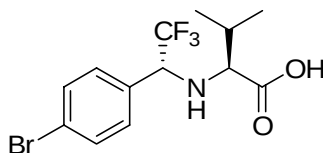
$[\alpha]_{\text{D}}^{23} = +7.8^\circ$ ($c=1.0$, CH_3COCH_3); ^1H NMR 7.62 (AB, d, $J = 9\text{Hz}$, 2H), 7.50 (AB, d, $J = 8\text{Hz}$, 2H), 4.53 (q, $J = 8\text{Hz}$, 1H), 3.13 (q, $J = 7\text{Hz}$, 1H), 1.29 (d, $J = 7\text{Hz}$, 3H); ^{19}F NMR -79.22 (d, 7Hz, minor), -79.89 (d, 7Hz, major), dr = 1 : 4; ^{13}C NMR (101 MHz, CD_3COCD_3 , δ) 19.51, 53.77, 62.70 (q, $J = 29\text{ Hz}$), 123.64, 126.04 (q, $J = 280\text{ Hz}$), 132.01, 132.50, 134.12, 175.64; IR (neat, cm^{-1}) 1737; HRMS: calc for $\text{C}_{11}\text{H}_{10}\text{BrF}_3\text{NO}_2$ (M-H) : 323.9847; found 323.9848.

***N*-[(1*R*)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-L-leucine ((*R,S*)-2e)**



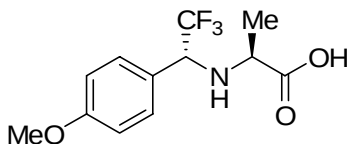
$[\alpha]_{\text{D}}^{23} = -9.7^\circ$ ($c=1.0$, CH_3COCH_3); ^1H NMR 7.62 (AB, d, $J = 9\text{Hz}$, 2H), 7.50 (AB, d, $J = 9\text{Hz}$, 2H), 4.45 (q, $J = 7\text{Hz}$, 1H), 2.98 (dd, $J = 9\text{Hz}$, 5Hz, 1H), 1.91 (st, $J = 7\text{Hz}$, 2Hz, 1H), 1.53 (AB, ddd, $J = 14\text{Hz}$, 9Hz, 5Hz, 1H), 1.44 (AB, ddd, $J = 14\text{Hz}$, 9Hz, 5Hz, 1H), 0.87 (d, $J = 7\text{Hz}$, 3H), 0.74 (d, $J = 7\text{Hz}$, 3H); ^{19}F NMR -78.97 (d, 7Hz, minor), -79.83 (d, 7Hz, major), dr = 1 : 17; ^{13}C NMR (CD_3COCD_3 , δ) 22.34, 23.82, 25.61, 43.79, 57.17, 63.27 (q, $J = 29\text{ Hz}$), 124.22, 126.46 (q, $J = 280\text{ Hz}$), 132.66, 132.98, 134.35, 176.56; IR (neat, cm^{-1}) 1733; HRMS: calc for $\text{C}_{14}\text{H}_{18}\text{BrF}_3\text{NO}_2$ (M+H) : 368.0473; found 368.0479.

***N*-[(1*R*)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-L-valine ((*R,S*)-2f)**



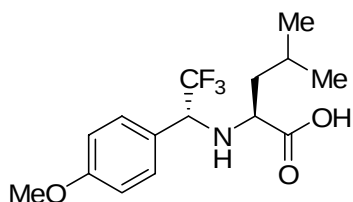
$[\alpha]_{\text{D}}^{23} = -10.6^\circ$ ($c=1.0$, CH_3COCH_3); ^1H NMR 7.61 (AB, d, $J = 8\text{Hz}$, 2H), 7.50 (AB, d, $J = 8\text{Hz}$, 2H), 4.38 (q, $J = 7\text{Hz}$, 1H), 2.83 (d, $J = 5\text{Hz}$, 1H), 1.97 – 2.01 (m, 1H), 0.92 (d, $J = 7\text{Hz}$, 3H); ^{19}F NMR -79.06 (d, 7Hz, minor), -79.88 (d, 7Hz, major), DR 1.0:45.8; ^{13}C NMR (CD_3COCD_3 , δ) 18.55, 20.23, 32.45, 63.62 (q, $J = 29\text{ Hz}$), 64.32, 124.21, 126.50 (q, $J = 281\text{ Hz}$), 132.69, 132.97, 134.25, 175.34; IR (neat, cm^{-1}) 1733; HRMS: calc for $\text{C}_{13}\text{H}_{16}\text{BrF}_3\text{NO}_2$ (M-H) : 354.0316; found 354.0310; Chiral HPLC (Chiracel AD-H, 14% $^i\text{PrOH}$ / CO_2^{sc} , 2 ml/min, 35°C , 220 nm, retention times: (S,*R*) = 2.4 min, (R,*S*) = 2.6 min, (S,*S*) = 2.9 min, (R,*R*) = 4.3 min) >99% ee.

***N*-[(1*R*)-1-(4-methoxyphenyl)-2,2,2-trifluoroethyl]-L-alanine ((*R,S*)-2g)**



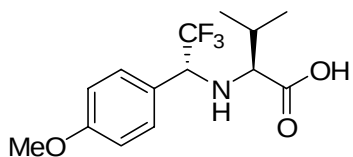
$[\alpha]_{\text{D}}^{23} = -1.9^\circ$ ($c=1.0$, CH_3COCH_3); ^1H NMR 7.43 (d, $J = 8\text{Hz}$, 2H), 6.96 (d, $J = 8\text{Hz}$, 2H), 4.47 (q, $J = 7\text{Hz}$, 1H), 3.80 (s, 3H), 3.51 (q, $J = 7\text{Hz}$, 1H), 1.35 (d, $J = 7\text{Hz}$, 3H); ^{19}F NMR -79.00 (d, 7Hz, major), -79.77 (d, 7Hz, minor), dr = 4 : 1; ^{13}C NMR (101 MHz, CD_3COCD_3 , δ) 19.52, 53.62, 55.52, 62.71 (q, $J = 29\text{ Hz}$), 114.78, 126.16, 126.44 (q, $J = 280\text{ Hz}$), 131.11, 161.30, 175.78; IR (neat)(cm^{-1}) 1737; HRMS: calc for $\text{C}_{12}\text{H}_{15}\text{F}_3\text{NO}_3$ (M+H) : 278.1004; found 278.1004.

***N*-[(1*R*)-1-(4-methoxyphenyl)-2,2,2-trifluoroethyl]-*L*-leucine ((*R,S*)-2h)**



$[\alpha]_D^{23} = -10.4^\circ$ ($c=1.0$, CH_3COCH_3); ^1H NMR 7.43 (d, $J = 9\text{Hz}$, 2H), 6.97 (d, $J = 9\text{Hz}$, 2H), 4.35 (q, $J = 8\text{Hz}$, 1H), 3.81 (s, 3H), 3.02 (dd, $J = 10\text{Hz}$, 5Hz, 1H), 1.92 (septet of triplets, $J = 7\text{Hz}$, 2Hz, 1H), 1.41 – 1.56 (m, 1H), 0.87 (d, $J = 7\text{Hz}$, 3H), 0.74 (d, $J = 7\text{Hz}$, 3H); ^{19}F NMR -79.04 (d, 8Hz, minor), -80.09 (d, 8Hz, major), $\text{dr} = 1 : 19$; ^{13}C NMR (CD_3COCD_3 , δ) 22.29, 23.82, 25.61, 43.83, 55.98, 56.90, 63.29 (q, $J = 29\text{ Hz}$), 115.18, 126.37, 126.87 (q, $J = 280\text{ Hz}$), 131.78, 161.85, 176.37; IR (neat, cm^{-1}) 1737; HRMS: calc for $\text{C}_{15}\text{H}_{21}\text{F}_3\text{NO}_3$ ($\text{M}+\text{H}$) : 320.1474; found 320.1472.

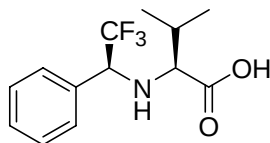
***N*-[(1*R*)-1-(4-methoxyphenyl)-2,2,2-trifluoroethyl]-*L*-valine ((*R,S*)-2i)**



$[\alpha]_D^{23} = -11.1^\circ$ ($c=1.0$, CH_3COCH_3); ^1H NMR 7.43 (AB, d, $J = 8\text{Hz}$, 2H), 6.96 (AB, d, $J = 8\text{Hz}$, 2H), 4.28 (q, $J = 8\text{Hz}$, 1H), 3.81 (s, 3H), 2.82 (d, $J = 5\text{Hz}$, 1H), 1.97 (apparent octet, $J = 6\text{Hz}$, 1H), 0.92 (d, $J = 9\text{Hz}$, 6H); ^{19}F NMR -79.14 (d, 7Hz, minor), -80.12 (d, 7Hz, major), $\text{dr} = 1 : 33$; ^{13}C NMR (CD_3COCD_3 , δ) 18.58, 20.26, 32.40, 55.96, 63.57 (q, $J = 28\text{ Hz}$), 64.07, 115.14, 126.31, 126.92 (q, $J = 280\text{ Hz}$), 131.85, 161.81, 175.49; IR (neat, cm^{-1}) 1733; HRMS: calc for $\text{C}_{14}\text{H}_{19}\text{F}_3\text{NO}_3$ ($\text{M}+\text{H}$) : 306.1317; found 306.1315.

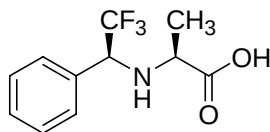
Representative procedure for the (*S,S*)-selective reductive amination.

***N*-[(1*S*)-2,2,2-trifluoro-1-phenylethyl]-*L*-valine ((*S,S*)-2c)**



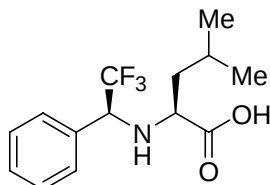
Sodium borohydride (869 mg, 23.0 mmol) was added to a 0 °C suspension of ZnCl_2 (1.57 g, 11.5 mmol) in DME (11.5 mL). The mixture was allowed to warm to ambient temperature and age for 18 h. In the meantime, 2,2,2-trifluoroacetophenone (1.00 g, 5.74 mmol) was added to a suspension of *L*-leucine methylester hydrochloride salt (1.11 g, 6.61 mmol) and potassium carbonate (1.98 g, 14.4 mmol) in MeOH (17 mL) the resulting mixture was warmed to 50 °C for 8 h, then allowed to cool to ambient temperature. The mixture was diluted with CH_3CN (170 mL) and added to the $\text{Zn}(\text{BH}_4)_2$ suspension, which had been cooled to -40 °C over 10 min. After 4 h at -40 °C, 10 mL of acetone was added and the mixture was allowed to warm to ambient temperature for 1 h. Hydrochloric acid (1M, 50 mL) was added slowly. The acetonitrile was removed on a rotovap and the mixture was extracted with TBME (3 x 30 mL). The organic fractions were washed with brine, dried over Na_2SO_4 , filtered and concentrated. ^{19}F NMR analysis of the crude mixture revealed a 21 : 1 mixture of diastereomers. The residue was dissolved in 0.5 M NaOH (50 mL) and extracted with TMBE (50 mL). The aqueous layer was acidified with 6N HCl and extracted with TBME (2x25mL). The organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated to afford 1.45 g of a white solid (92%). mp (88-89 °C); $[\alpha]_D^{23} = +3.2^\circ$ ($c=1.0$, CH_3COCH_3); ^1H NMR 7.51 (d, $J = 4\text{Hz}$, 2H), 7.39 (d, $J = 4\text{Hz}$, 3H), 4.37 (q, $J = 8\text{Hz}$, 1H), 3.31 (d, $J = 5\text{Hz}$, 1H), 2.11 (apparent octet, $J = 6\text{Hz}$, 1H), 1.03 (d, $J = 7\text{Hz}$, 3H), 0.95 (d, $J = 7\text{Hz}$, 3H); ^{19}F NMR -77.98 (s, major), -78.90 (s, minor), $\text{dr} = 21 : 1$; ^{13}C NMR (CD_3COCD_3 , δ) 18.39, 19.93, 32.77, 65.04 (q, $J = 29\text{ Hz}$), 66.45, 127.32 (q, $J = 281\text{ Hz}$), 129.73, 129.84, 130.14, 136.63, 175.92; IR (neat, cm^{-1}) 1733; HRMS: calc for $\text{C}_{13}\text{H}_{17}\text{F}_3\text{NO}_2$ ($\text{M}+\text{H}$) : 276.1211; found 276.1214.

***N*-[(1*S*)-2,2,2-trifluoro-1-phenylethyl]-*L*-alanine ((*S,S*)-2a.)**

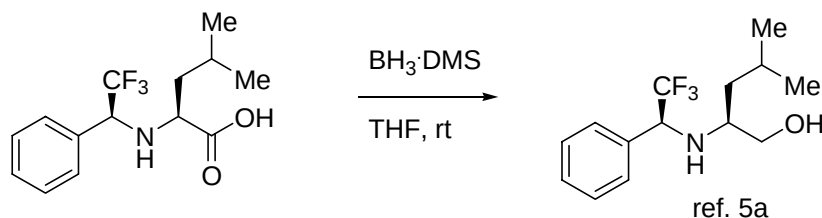


$[\alpha]_D^{23} = -2.5^\circ$ ($c=1.0$, CH_3COCH_3); ^1H NMR 7.44 – 7.47 (m, 2H), 7.37 – 7.41 (m, 3H), 4.43 (q, $J = 7\text{Hz}$, 1H), 3.28 (q, $J = 7\text{Hz}$, 1H), 1.23 (d, $J = 7\text{Hz}$, 3H); ^{19}F NMR -79.05 (d, 8Hz, major), -79.78 (d, 8Hz, minor), $dr = 15 : 1$; ^{13}C NMR (DMSO- d_6 , δ) 18.76, 54.65, 61.40 (q, $J = 28\text{ Hz}$), 126.27 (q, $J = 282\text{ Hz}$), 128.79, 128.83, 129.09, 129.33, 135.10, 176.03; IR (neat, cm^{-1}) 1737; HRMS: calc for $\text{C}_{11}\text{H}_{13}\text{F}_3\text{NO}_2$ ($M+H$) : 248.0898; found 248.0892.

N-[(1S)-2,2,2-trifluoro-1-phenylethyl]-L-leucine ((S,S)-2b)

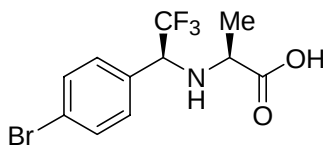


$[\alpha]_D^{23} = +0.74^\circ$ ($c=1.0$, CH_3COCH_3); ^1H NMR 7.47 – 7.50 (m, 2H), 7.37 – 7.40 (m, 3H), 4.33 (q, $J = 8\text{Hz}$, 1H), 3.51 (t, $J = 7\text{Hz}$, 1H), 1.98 (vs, $J = 7\text{Hz}$, 1H), 1.53 (dd, $J = 8\text{Hz}$, 7Hz, 2H), 0.95 (d, $J = 7\text{Hz}$, 3H), 0.93 (d, $J = 7\text{Hz}$, 3H); ^{19}F NMR -78.81 (d, 7Hz, major), -79.76 (d, 7Hz, minor), $dr = 11 : 1$; ^{13}C NMR (CD_3COCD_3 , δ) 22.56, 23.67, 25.81, 43.69, 59.76, 64.26 (q, $J = 29\text{ Hz}$), 127.46 (q, $J = 281\text{ Hz}$), 129.78, 129.84, 130.11, 136.70, 176.83; IR (neat, cm^{-1}) 1737; HRMS: calc for $\text{C}_{14}\text{H}_{19}\text{F}_3\text{NO}_2$ ($M+H$) : 290.1368; found 290.1358.



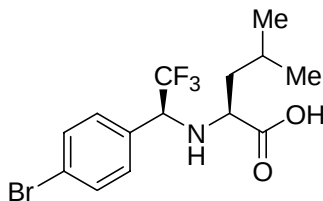
A sample of **(S,S)-2b** (289 mg, 1.00 mmol) was dissolved in THF (5 mL) and $\text{BH}_3\cdot\text{DMS}$ (2.0 mL, 21.0 mmol) was added. After 2h, the mixture was quenched by the careful addition of 1M HCl and TBME. The organic layer was washed with brine, dried over MgSO_4 , filtered and concentrated. The crude mixture was purified by flash chromatography to afford 240mg of the desired compound whose spectral data were consistent with those reported in the supporting information of reference 5a.

N-[(1S)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-L-alanine ((S,S)-2d)



$[\alpha]_D^{23} = -2.8^\circ$ ($c=1.0$, CH_3COCH_3); ^1H NMR 7.60 (AB, d, $J = 8\text{Hz}$, 2H), 7.49 (AB, d, $J = 8\text{Hz}$, 2H), 4.51 (q, $J = 8\text{Hz}$, 1H), 3.49 (q, $J = 7\text{Hz}$, 1H), 1.34 (d, $J = 7\text{Hz}$, 3H); ^{19}F NMR -79.22 (d, 7Hz, major), -79.89 (d, 7Hz, minor), $dr = 8 : 1$; ^{13}C NMR (101 MHz, CD_3COCD_3 , δ) 18.94, 55.32, 62.51 (q, $J = 29\text{ Hz}$), 123.33, 126.60 (q, $J = 279\text{ Hz}$), 131.47, 132.49, 135.25, 175.83; IR (neat)(cm^{-1}) 1737; HRMS: calc for $\text{C}_{11}\text{H}_{12}\text{BrF}_3\text{NO}_2$ ($M+H$) : 326.0003; found 325.9994.

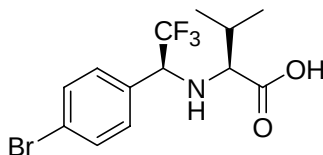
N-[(1S)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-L-leucine ((S,S)-2e)



$[\alpha]_D^{23} = +2.4^\circ$ ($c=1.0$, CH_3COCH_3); ^1H NMR 7.58 (AB, d, $J = 9\text{Hz}$, 2H), 7.47 (AB, d, $J = 9\text{Hz}$, 2H), 4.42 (q, $J = 8\text{Hz}$, 1H), 3.51 (dd, $J = 8\text{Hz}$, 6Hz, 1H), 1.95 (septet, $J = 7\text{Hz}$, 1H), 1.52 – 1.55 (m, 2H), 0.94 (d, $J = 7\text{Hz}$, 3H), 0.91 (d, $J = 7\text{Hz}$, 3H);

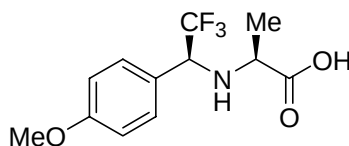
^{19}F NMR -78.93 (d, 7Hz, major), -79.82 (d, 7Hz, minor), dr = 12 : 1; ^{13}C NMR (CD_3COCD_3 , δ) 22.51, 23.62, 25.79, 43.54, 59.73, 63.61 (q, J = 29 Hz), 123.76, 127.09 (q, J = 281 Hz), 131.94, 132.87, 176.53; IR (neat)(cm^{-1}) 1733; HRMS: calc for $\text{C}_{14}\text{H}_{18}\text{BrF}_3\text{NO}_2$ (M+H) : 368.0473; found 368.0473.

***N*-[(1*S*)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-L-valine ((*S,S*)-2f)**



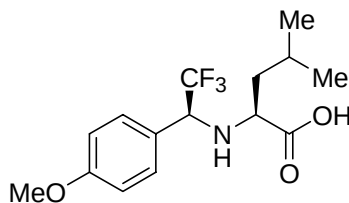
$[\alpha]_{\text{D}}^{23}$ = +3.9° (c =1.0, CH_3COCH_3); ^1H NMR 7.58 (AB, d, J = 8Hz, 2H), 7.47 (AB, d, J = 8Hz, 2H), 4.38 (q, J = 7Hz, 1H), 3.26 (d, J = 5Hz, 1H), 2.06 – 2.08 (m, 1H), 1.02 (d, J = 7Hz, 3H), 0.93 (d, J = 7Hz, 3H); ^{19}F NMR -79.04 (d, 7Hz, major), -79.88 (d, 7Hz, minor), dr = 12 : 1; ^{13}C NMR (CD_3COCD_3 , δ) 18.39, 19.88, 32.73, 64.49 (q, J = 29 Hz), 66.56, 123.77, 126.99 (q, J = 281 Hz), 131.86, 132.89, 135.92, 175.76 IR (neat, cm^{-1}) 1733; HRMS: calc for $\text{C}_{13}\text{H}_{16}\text{BrF}_3\text{NO}_2$ (M-H) : 354.0316; found 354.0316; Chiral HPLC (Chiracel AD-H, 14% $^i\text{PrOH}$ / CO_2^{sc} , 2 ml/min, 35°C, 220 nm, retention times: (*R,R*) = 2.4 min, (*S,S*) = 2.6 min, (*R,S*) = 2.9 min, (*S,R*) = 4.3 min) >99%ee.

***N*-[(1*S*)-1-(4-methoxyphenyl)-2,2,2-trifluoroethyl]-L-alanine ((*S,S*)-2g)**



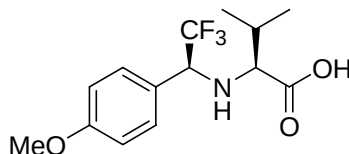
$[\alpha]_{\text{D}}^{23}$ = -1.9° (c =1.0, CH_3COCH_3); ^1H NMR 7.43 (d, J = 8Hz, 2H), 6.96 (d, J = 8Hz, 2H), 4.47 (q, J = 7Hz, 1H), 3.80 (s, 3H), 3.51 (q, J = 7Hz, 1H), 1.35 (d, J = 7Hz, 3H); ^{19}F NMR -79.00 (d, 7Hz, major), -79.77 (d, 7Hz, minor), dr = 8 : 1; ^{13}C NMR (CD_3COCD_3 , δ) 18.46, 55.55, 62.22 (q, J = 29 Hz), 114.83, 126.72 (q, J = 282 Hz), 126.75, 130.67, 161.19, 175.44; IR (neat, cm^{-1}) 1737; HRMS: calc for $\text{C}_{12}\text{H}_{15}\text{F}_3\text{NO}_3$ (M+H) : 278.1004; found 278.1002.

***N*-[(1*S*)-1-(4-methoxyphenyl)-2,2,2-trifluoroethyl]-L-leucine ((*S,S*)-2h)**



$[\alpha]_{\text{D}}^{23}$ = +1.2° (c =1.0, CH_3COCH_3); ^1H NMR 7.39 (AB, d, J = 8Hz, 2H), 6.93 (AB, d, J = 8Hz, 2H), 4.26 (q, J = 8Hz, 1H), 3.79 (s, 3H), 3.48 (dd, J = 7Hz, 7Hz, 1H), 1.92 (vs, J = 7Hz, 1H), 1.52 (t, J = 7Hz, 1H), 0.94 (d, J = 9Hz, 3H), 0.92 (d, J = 9Hz, 3H); ^{19}F NMR -79.02 (d, 7Hz, major), -80.08 (d, 7Hz, minor), dr = 16 : 1; ^{13}C NMR (CD_3COCD_3 , δ) 22.59, 23.65, 25.81, 43.72, 55.96, 59.68, 63.63 (q, J = 29 Hz), 115.11, 127.52 (q, J = 281 Hz), 128.54, 130.94, 161.44, 176.82; IR (neat, cm^{-1}) 1710; HRMS: calc for $\text{C}_{15}\text{H}_{21}\text{F}_3\text{NO}_3$ (M+H) : 320.1474; found 320.1481.

***N*-[(1*S*)-1-(4-methoxyphenyl)-2,2,2-trifluoroethyl]-L-valine ((*S,S*)-2i)**

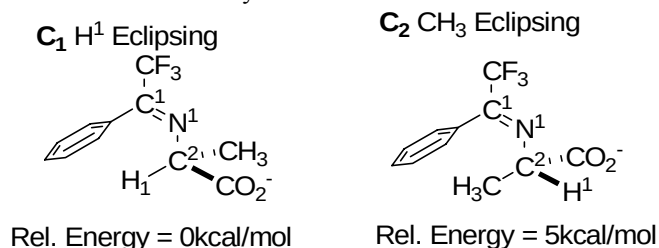


$[\alpha]_{\text{D}}^{23}$ = +4.5° (c =1.0, CH_3COCH_3); ^1H NMR 7.39 (d, J = 8Hz, 2H), 6.93 (d, J = 8Hz, 2H), 4.22 (q, J = 8Hz, 1H), 3.79 (s, 3H), 3.23 (d, J = 5Hz, 1H), 2.02 (apparent octet, J = 7Hz, 1H), 1.02 (d, J = 7Hz, 3H), 0.93 (d, J = 7Hz, 3H); ^{19}F NMR -79.08 (d, 8Hz, major), -79.81 (d, 8Hz, minor), dr = 8 : 1; ^{13}C NMR (CD_3COCD_3 , δ) 18.40, 19.90, 32.77, 55.95, 64.42 (q, J = 28 Hz), 66.38, 115.13, 127.40 (q, J = 280 Hz), 128.49, 130.89, 161.44, 175.94; IR (neat, cm^{-1}) 1733; HRMS: calc for $\text{C}_{14}\text{H}_{19}\text{F}_3\text{NO}_3$ (M+H) : 306.1317; found 306.1313.

Rationale for the Observed Stereochemistry

Ab Initio calculations on imine-carboxylate **1a** have been employed in order to strengthen our understanding of the sense of the diastereoselectivity.¹ The G03 package was used for the *ab initio* calculations. Full optimization was performed with the ROHF method. The basis set used was 6-31+G(d,p) on all atoms other than Zn. The Zn atom was treated with the LANL2DZ basis set and the LANL2 effective core potential. Geometry optimizations were performed for both the *E* and *Z* imine isomers. The *E* isomer was found to be favored by 6 kcal/mol. The lowest energy conformation shows the aromatic ring to be out of conjugation with the imine, having a dihedral angle between the imine and phenyl planes of 66°. The methine proton H₁ in this conformer is eclipsing the aromatic group (**Figure 1**, C₁). Both of these orientations result in a minimization of A_{1,3} strain between the aryl group and the substituents on C₁. A plot of ground state energies versus the torsion angle defined by C₂-N₁-C₁-H₁ shows this rotamer to be favored by ~5 kcal/mol relative to the next most stable conformer (C₂) in which the Methyl group is eclipsing the aromatic group.

Figure 1. Geometry optimization of the imine carboxylates.

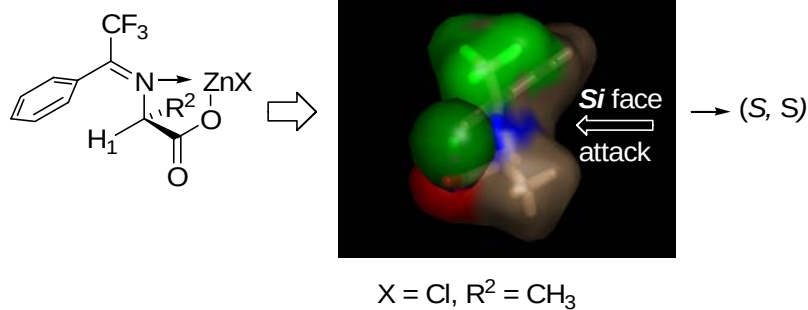


Perhaps the simplest explanation for the reversal in facial selectivity observed with Zn(BH₄)₂ reductions would be to invoke equilibration between the *E* to *Z* imine isomers, followed by reduction of the *Z* isomer at a rate which is faster than reduction of the *E* imine isomer. In the *Z* isomer, the *si* face would now be flanked by the carboxylate moiety and would be expected to afford the *S,S* isomer preferentially. While this possibility can not be ruled out completely, it seems unlikely for the following reasons: (1) Mixing the imine/ carboxylate with zinc salts (eg. ZnCl₂, Zn(OTf)₂) in CD₃CN shows a change in the ¹H NMR spectra, but the new compound was also shown by nOe to be the *E* isomer. (2) *Ab Initio* studies suggest that there is a large difference in energy between the two isomers, with the *E* isomer being strongly preferred. (3) It has been shown that similar imine substrates do not equilibrate below ambient temperature.²

¹ The Gaussian 03 package was used for the *ab initio* calculations. Full optimization was performed with the ROHF method. The basis set used was 6-31+G(d,p) on all atoms other than Zn. The Zn atom was treated with the LANL2DZ basis set and the LANL2 effective core potential. Gaussian 03, Revision C.01: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Kiu, G.; Lasshenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

² Gosselin, F.; Roy, A.; O'Shea, P.D.; Chen, C.; Volante, R.P. *Org. Lett.* **2004**, 6, 641.

Figure 2. *Ab Initio* geometry optimized orientation (6-31+G(d,p))



An association between the imine lone pair and ZnX fragment further rigidifies the geometry in the orientation having H_1 eclipsing the aryl ring (**Figure 2**). This arrangement will also significantly increase the effective steric contribution of the carboxylate moiety relative to the α -amino ester substituent. This is clearly demonstrated in the *Ab Initio* geometry optimization studies which show that the ZnCl^+ fragment has a weak affiliation with the imine lone pair.