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Supporting Information

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

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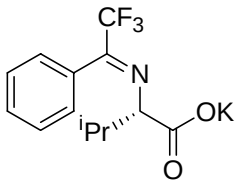
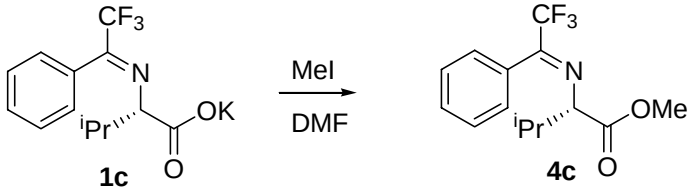
General: Unless otherwise noted all reactions were run under an inert atmosphere, and solvents and reagents were transferred by syringe. Anhydrous grade tetrahydrofuran (THF) was purchased from A&C Chemicals Ltd, anhydrous grade methanol was purchased from Acros and anhydrous acetonitrile, 1,2-dimethoxyethane (DME) and *tert*-butyl methyl ether (MTBE) were purchased from Aldrich in Sure/Seal™ bottles and used as received. Unless other wise noted, ^{1}H NMR (500 MHz), ^{13}C NMR (125 Hz) and ^{19}F NMR spectra (376.5MHz) were recorded in acetone-d_6 or methanol-d_4 purchased from CDN Isotopes. The ^{1}H and ^{13}C spectra were referenced to residual acetone (2.04 ppm) or methanol (3.30 ppm). ^{19}F 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).**

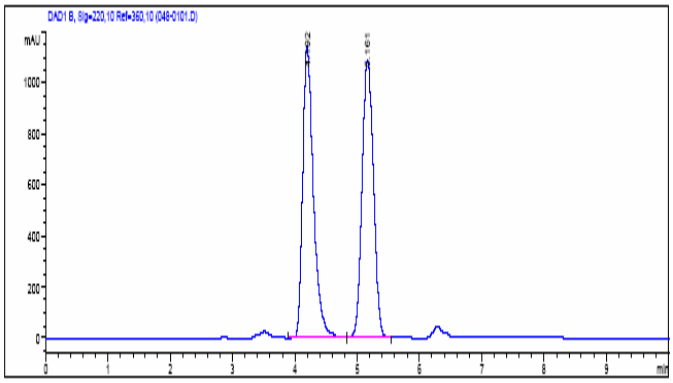


2,2,2-Trifluoroacetophenone (4.03 mL, 28.7 mmol) was added to a mixture of L-Valine methyl ester hydrochloride (5.05 g, 30.2 mmol) and potassium carbonate (9.92 g, 71.8 mmol) in MeOH (50 mL) at ambient temperature. The resulting mixture was warmed to 50 °C for 8 h, then cooled to ambient temperature 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 ^{1}H NMR analysis relative to a standard volume of mesitylene. The remaining 10 wt% is presumed to be residual $KHCO_3$ and K_2CO_3. ^{1}H NMR (CD_3OD, 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); ^{19}F NMR (CD_3OD, δ) -75.31; ^{13}C NMR (CD_3OD, 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.



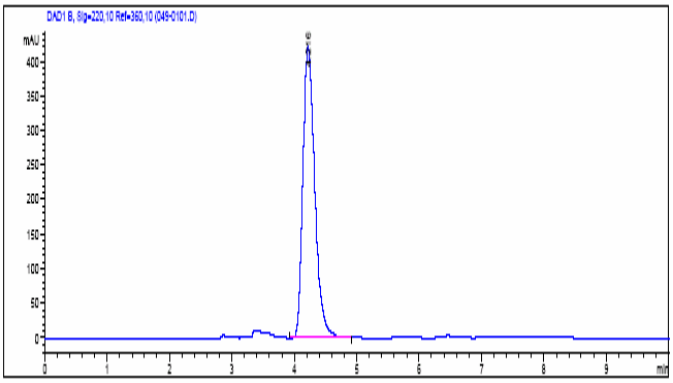
1c **4c**

The enantiomeric excess of this compound was measured by converting the potassium caboxylate 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 H_2O. The organic layer was washed twice with fresh portions of H_2O, once with brine, dried over $MgSO_4$, 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; CD_3OD) 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

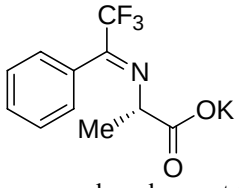
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.192	VV	0.1659	1.39118e4	1144.03723	50.0010
2	5.161	VV	0.2007	1.39113e4	1091.68005	49.9990



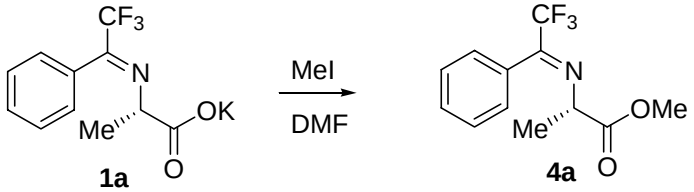
Signal 1: DAD1 B, Sig=220,10 Ref=360,10

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 accept 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 K_3PO_4 was used instead of 2.5 equiv of K_2CO_3. This afforded the desired product as a white solid assaying at ~88 wt%. ^{1}H NMR (CD_3OD, 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); ^{19}F NMR (CD_3OD, δ) -75.79; ^{13}C NMR (CD_3OD, 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.

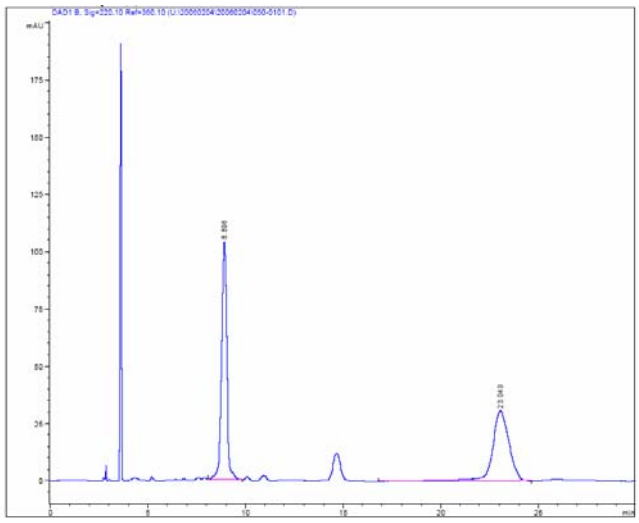


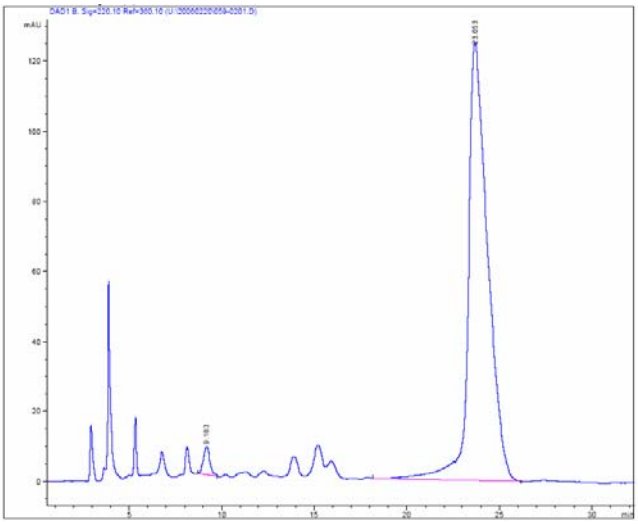
1a **4a**

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. ^{1}H NMR δH(500 MHz; CD_3COCD_3) 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**





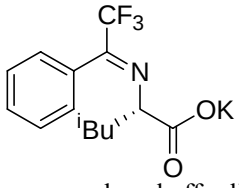
Signal 1: DAD1 B, Sig=220,10 Ref=360,10

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

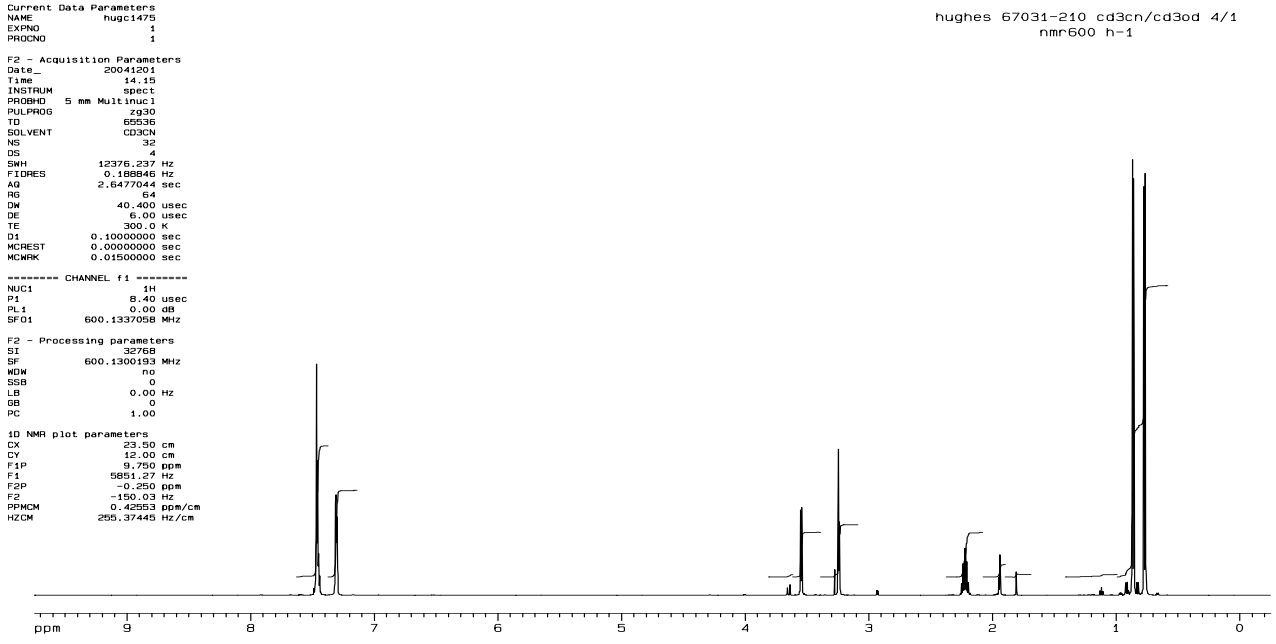
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.163	BB	0.3691	197.62823	8.08637	2.1087
2	23.653	MM	1.2213	9174.33105	125.19498	97.8913

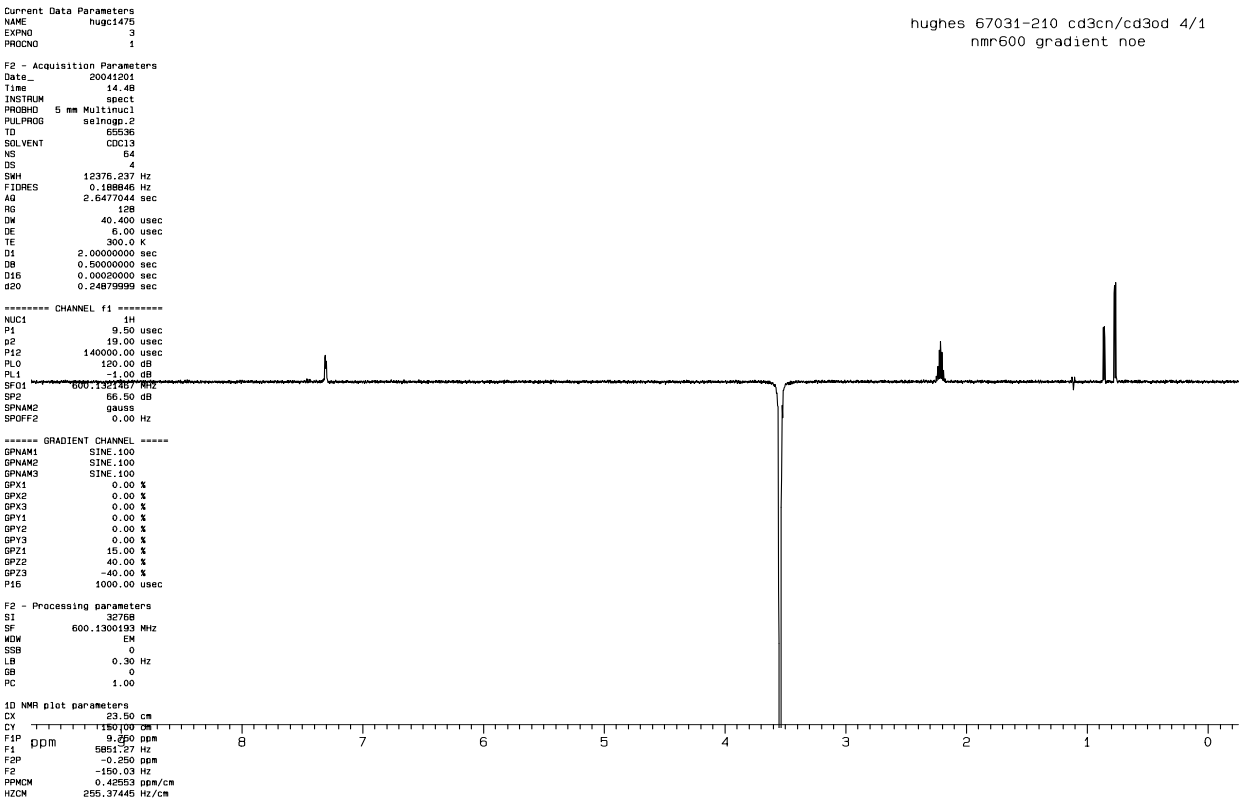
***N*-(2,2,2-Trifluoro-1-phenylethylidene)-L-leucine, potassium salt (1b).**

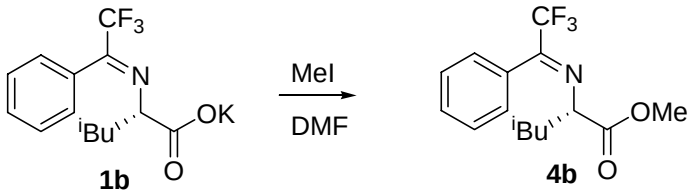


The standard imine/carboxylate formation protocol was employed affording the desired product as a white solid assaying at ~85 wt%. ^{1}H NMR (CD_3OD, δ) 0.62 (d, *J* = 7 Hz, 3H), 0.84 (d, *J* = 7Hz, 3H), 1.35-1.45 (m, 1H), 1.65-1.72 (m, 1H), 1.80-1.90 (m, 1H), 3.92 (dd, *J* = 10, 4 Hz, 1H), 7.25-7.35 (m, 2H), 3.45-3.55 (m, 3H); ^{19}F NMR (CD_3OD, δ) -75.29; ^{13}C NMR (CD_3OD, 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:



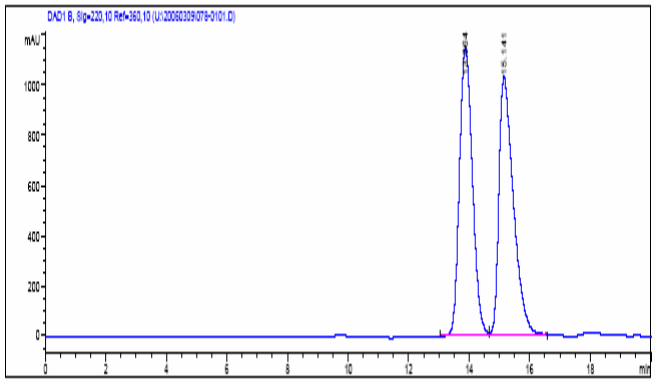




1b **4b**

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: $SOCl_2$ (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 tritureate 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. ^{1}H NMR: δH(500 MHz; CD_3OD) 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).

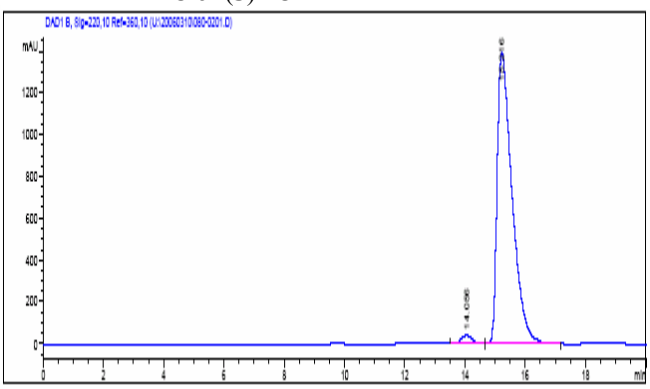
HPLC of a *rac*-**4c:**



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

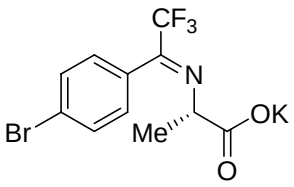
HPLC of (*S*)-**4c**



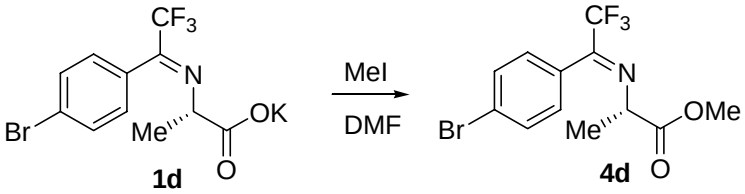
Signal 1: DAD1 B, Sig=220,10 Ref=360,10

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).**



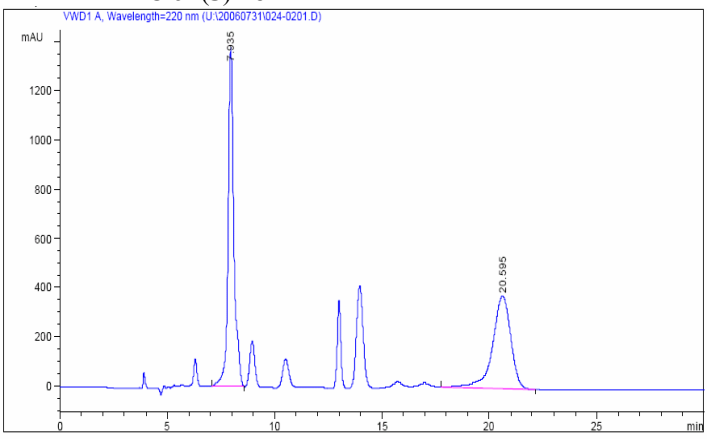
The standard imine/carboxylate formation protocol was employed accept that the reaction were run at ambient temperature instead of 50°C, 1.2 equiv of alanine methylester hydrochloride was used instead of 1.05 equiv, and 2.5 equiv of K_3PO_4 was used instead of 2.5 equiv of K_2CO_3. This afforded the desired product as a white solid. ^{1}H NMR: δH(400 MHz; CD_3OD) 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); ^{13}C NMR: δC(126 MHz; CD_3OD) 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.; ^{19}F NMR: δF(377 MHz; CD_3OD) -75.88.

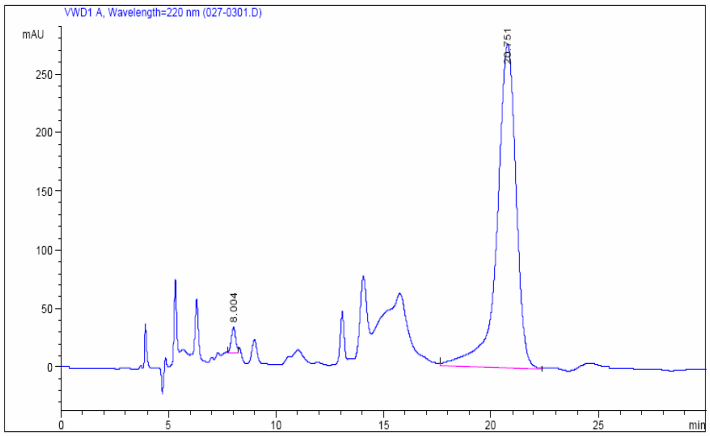


The standard protocol for ester formation was followed. A racemic reference sample was prepared from commercially available dl-alanine methylester hydrochloride. Chiral HPLC (Chiracel OJ, 10% IPA/hexanes, 0.75 ml/min, 30°C, 220nm, (R)-alanine derived imine: 9min, (S)-alanine derived imine: 23 min) showed the material to be 95.8%ee. ^{1}H NMR δH(500 MHz; CD_3COCD_3) 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**





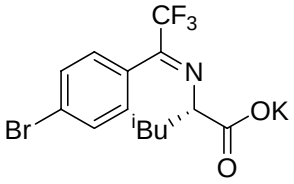
Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	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

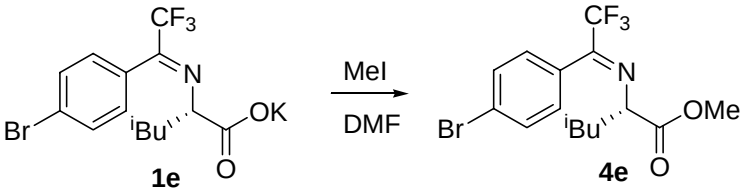
Signal 1: VWD1 A, Wavelength=220 nm

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).**

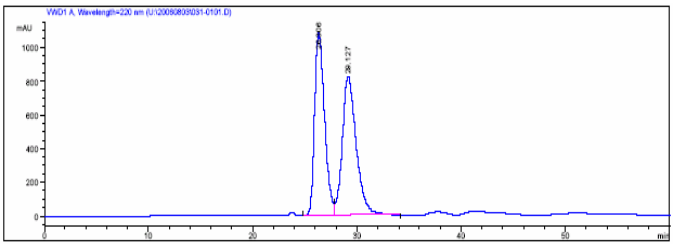


The standard imine/carboxylate formation protocol was employed affording the desired product as a white solid. ^{1}H NMR: δH(400 MHz; CD_3OD) 7.66 (2 H, d, J 8.28), 7.26 (2 H, d, J 8.15), 3.87 (1 H, dd, J 9.66 and 4.07), 1.90-1.80 (1 H, m), 1.71 (1 H, ddd, J 13.42 and 9.25 and 4.13), 1.48-1.35 (1 H, m), 0.85 (3 H, d, J 6.64), 0.64 (3 H, d, J 6.58).; ^{13}C NMR: δC(101 MHz; CD_3OD) 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. ^{19}F NMR: δF(377 MHz; CD_3OD) -75.32.; IR.

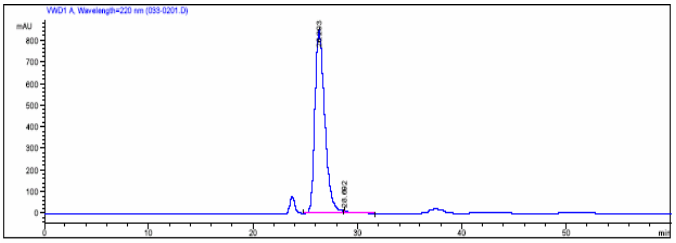


The standard protocol for ester formation was followed. A racemic reference sample was prepared from racemic dl-leucine ethylester hydrochloride. Chiral HPLC (Chiracel OJ, 0.2% IPA/hexanes, 0.2 ml/min, 30°C, 220nm, (S)-leucine derived imine: 28min, (R)-leucine derived imine: 29 min) showed the material to be 97%ee. ^{1}H 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**



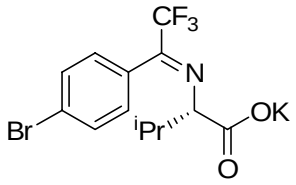
Signal 1: VWD1 A, Wavelength=220 nm

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

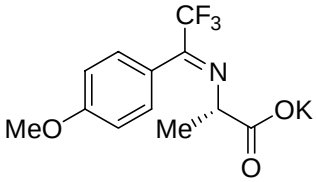
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	26.306	BV	1.0180	7.19085e4	1090.95581	48.4890
2	29.127	VB	1.3800	7.63902e4	819.59369	51.5110

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

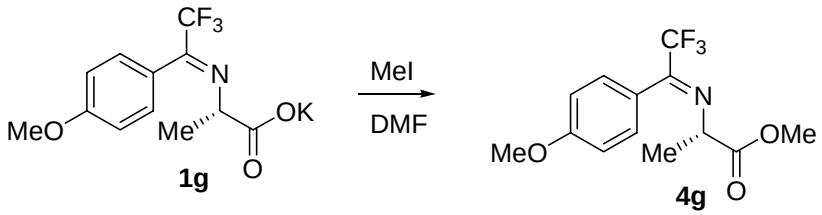


The standard imine/caboxylate formation protocol was employed affording the desired product as a white solid assaying at 95 wt%. ^{1}H NMR δ (ppm)(CD_3OD): 0.82 (d, *J* = 7 Hz, 3H), 0.92 (d, *J* = 7Hz, 3H), 2.27 (nonet, *J* = 7Hz, 1H), 3.58 (d, *J* = 6 Hz, 1H), 7.21 (d, *J* = 8Hz, 2H), 7.64 (d, *J* = 8Hz, 2H); 19F NMR (CD3OD, δ) -75.39; ^{13}C NMR (101 MHz, CD_3OD): 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).**



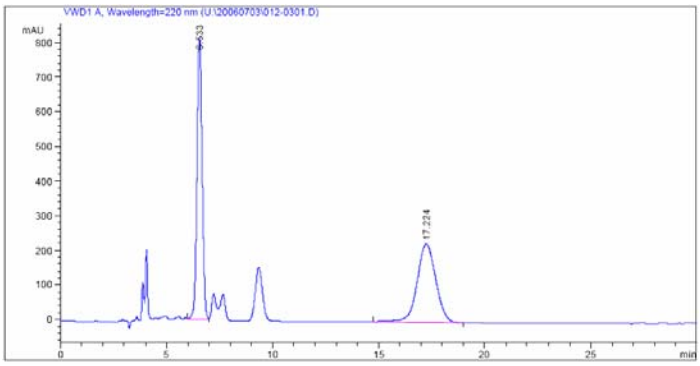
The standard imine/carboxylate formation protocol was employed accept that the reaction were run at ambient temperature instead of 50°C, 1.2 equiv of alanine methylester hydrochloride was used instead of 1.05 equiv, and 2.5 equiv of K_3PO_4 was used instead of 2.5 equiv of K_2CO_3. This afforded the desired product as a white solid. ^{1}H NMR: δH(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); ^{13}C NMR: δC(101 MHz; CD_3OD) 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.; ^{19}F NMR: δF(377 MHz; CD_3OD) -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. ^{1}H NMR δH(500 MHz; CD_3OD) 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).

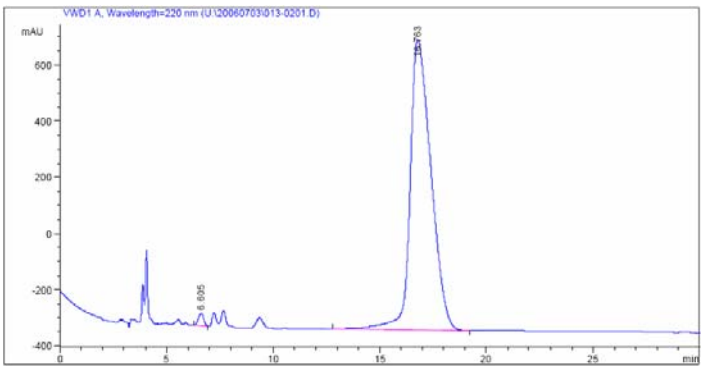
HPLC of a *rac*-**4d:**

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



Signal 1: VWD1 A, Wavelength=220 nm

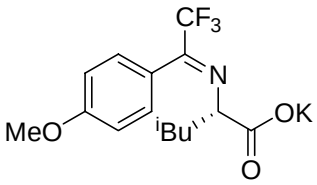
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.533	MM	0.2836	1.38107e4	811.69037	49.3644
2	17.224	VP	0.9618	1.41663e4	227.68146	50.6356



Signal 1: VWD1 A, Wavelength=220 nm

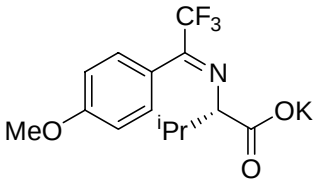
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	6.605	MM	0.2937	782.98822	44.42649	1.0888
2	16.763	VP	1.0631	7.11272e4	1034.12512	98.9112

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

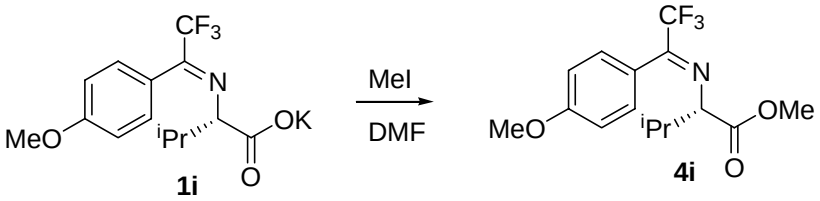


The standard imine/carboxylate formation protocol was employed affording the desired product as a white solid assaying at ~85 wt%. ^{1}H NMR: ; ^{19}F NMR (CD_3OD, δ) -75.29; ^{13}C NMR (CD_3OD, δ) 19.83, 21.98, 24.26, 42.80, 66.31, 119.60 (q, J = 278 Hz), 127.33, 128.00, 129.44, 130.06, 156.99 (q, J = 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).



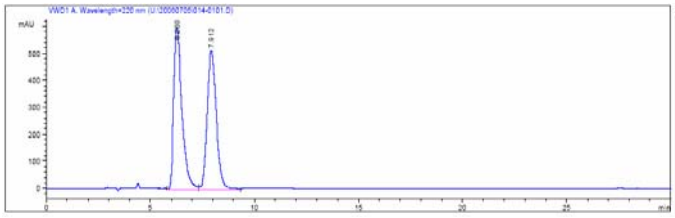
The standard imine/carboxylate formation protocol was employed affording the desired product as a white solid. ^{1}H NMR: ; ^{13}C NMR: δC(126 MHz; CD_3OD); ^{19}F NMR: δF(377 MHz; CD_3OD).



1i **4i**

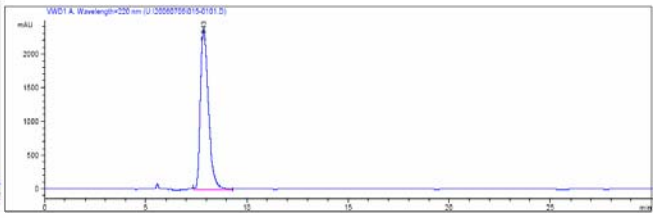
The standard protocol for ester formation was followed. A racemic reference sample was prepared from commercially available dl-alanine methylester hydrochloride. Chiral HPLC (Chiracel OJ, 40% IPA/hexanes, 1.0 ml/min, 30°C, 220nm, (R)-valnine derived imine: 6.3min, (S)-valine derived imine: 7.9 min) showed the material to be >99.5 %ee. ^{1}H NMR δH(500 MHz; CD_3OD) 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 *s	Height [mAU]	Area %
1	6.260	VV	0.4179	1.66448e4	600.73846	51.0245
2	7.912	VB	0.4806	1.59764e4	516.05994	48.9755

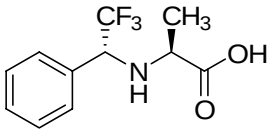


Signal 1: VWD1 A, Wavelength=220 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.843	VV	0.4352	6.74892e4	2393.54053	100.0000

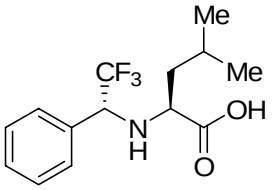
Representative procedure for the (*R*,*S*)-selective reductive amination.

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



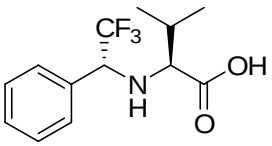
2,2,2-Trifluoroacetophenone (871 mg, 5.00 mmol) was added to a suspension of L-alanine, methyl ester hydrochloric acid salt (803 mg, 5.75 mmol) and potassium carbonate (2.25 g, 15 mmol) in MeOH (10 mL) at ambient temperature. The resulting mixture was warmed to 50 °C for 18 h. The mixture was cooled 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 $NaBH_4$ (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 $MgSO_4$, 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 ^{19}F NMR showed a 10 : 1 mixture of diastereomers. $[\alpha]_D^{23}$ = +10.5° (*c*=1.0, CH_3COCH_3); ^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); ^{19}F NMR -79.06 (d, 8Hz, minor), -79.79 (d, 8Hz, major); ^{13}C NMR (DMSO-d_6, 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 $C_{11}H_{13}F_3NO_2$ (M+H) : 248.0898; found 248.0892.

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



$[\alpha]_D^{23}$ = -11.1° (*c*=1.0, CH_3COCH_3); ^1H NMR (CD_3COCD_3, 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); ^{19}F NMR -78.81 (d, 7Hz, minor), -79.76 (d, 7Hz, major), dr = 1 : 19; ^{13}C NMR (CD_3COCD_3, 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 $C_{14}H_{19}F_3NO_2$ (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.

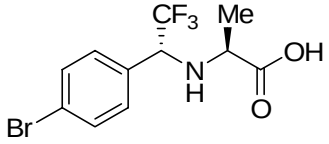
***N*-[(1*R*)-2,2,2-trifluoro-1-phenylethyl]-L-valine ((*R*,*S*)-2c)**



$[\alpha]_D$ = -11.6° (*c*=1.0, CH_3COCH_3); ^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); ^{19}F NMR -78.94 (d, 8Hz, minor), -79.82 (d, 8Hz, major), dr = 1: 25; ^{13}C NMR (CD_3COCD_3, 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,

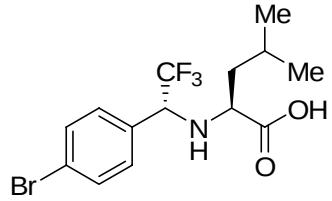
134.79, 175.49; IR (neat, cm^{-1}) 1733; HRMS: calc for $C_{13}H_{17}F_3NO_2$ (M+H) : 276.1211; found 276.1204; Elemental Analysis: calc: %C = 40.51, %H = 3.40, %N = 4.30, found %C = 40.95, %H = 3.40, %N = 4.16.

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



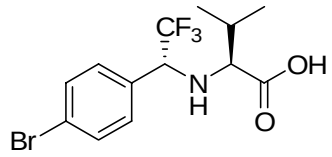
$[\square]_D^{23}$ = +7.8° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.62 (AB, d, *J* = 9Hz, 2H), 7.50 (AB, d, *J* = 8Hz, 2H), 4.53 (q, *J* = 8Hz, 1H), 3.13 (q, *J* = 7Hz, 1H), 1.29 (d, *J* = 7Hz, 3H); ^{19}F NMR -79.22 (d, 7Hz, minor), -79.89 (d, 7Hz, major), dr = 1 : 4; ^{13}C NMR (101 MHz, CD_3COCD_3, δ) 19.51, 53.77, 62.70 (q, *J* = 29 Hz), 123.64, 126.04 (q, *J* = 280 Hz), 132.01, 132.50, 134.12, 175.64; IR (neat, cm^{-1}) 1737; HRMS: calc for $C_{11}H_{10}BrF_3NO_2$ (M-H) : 323.9847; found 323.9848.

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



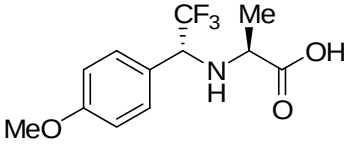
$[\square]_D^{23}$ = -9.7° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.62 (AB, d, *J* = 9Hz, 2H), 7.50 (AB, d, *J* = 9Hz, 2H), 4.45 (q, *J* = 7Hz, 1H), 2.98 (dd, *J* = 9Hz, 5Hz, 1H), 1.91 (st, *J* = 7Hz, 2Hz, 1H), 1.53 (AB, ddd, *J* = 14Hz, 9Hz, 5Hz, 1H), 1.44 (AB, ddd, *J* = 14Hz, 9Hz, 5Hz, 1H), 0.87 (d, *J* = 7Hz, 3H), 0.74 (d, *J* = 7Hz, 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 Hz), 124.22, 126.46 (q, *J* = 280 Hz), 132.66, 132.98, 134.35, 176.56; IR (neat, (cm^{-1}) 1733; HRMS: calc for $C_{14}H_{18}BrF_3NO_2$ (M+H) : 368.0473; found 368.0479.

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



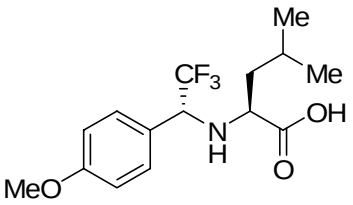
$[\square]_D^{23}$ = -10.6° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.61 (AB, d, *J* = 8Hz, 2H), 7.50 (AB, d, *J* = 8Hz, 2H), 4.38 (q, *J* = 7Hz, 1H), 2.83 (d, *J* = 5Hz, 1H), 1.97 – 2.01 (m, 1H), 0.92 (d, *J* = 7Hz, 3H); ^{19}F NMR -79.06 (d, 7Hz, minor), -79.88 (d, 7Hz, major), DR 1.0:45.8; ^{13}C NMR (CD_3COCD_3, δ) 18.55, 20.23, 32.45, 63.62 (q, *J* = 29 Hz), 64.32, 124.21, 126.50 (q, *J* = 281 Hz), 132.69, 132.97, 134.25, 175.34; IR (neat, cm^{-1}) 1733; HRMS: calc for $C_{13}H_{16}BrF_3NO_2$ (M-H) : 354.0316; found 354.0310; Chiral HPLC (Chiracel AD-H, 14% ^{i}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)**



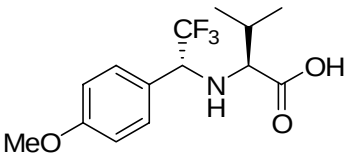
$[\square]_D^{23}$ = -1.9° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.43 (d, *J* = 8Hz, 2H), 6.96 (d, *J* = 8Hz, 2H), 4.47 (q, *J* = 7Hz, 1H), 3.80 (s, 3H), 3.51 (q, *J* = 7Hz, 1H), 1.35 (d, *J* = 7Hz, 3H); ^{19}F NMR -79.00 (d, 7Hz, major), -79.77 (d, 7Hz, minor), dr = 4 : 1; ^{13}C NMR (101 MHz, CD_3COCD_3, δ) 19.52, 53.62, 55.52, 62.71 (q, *J* = 29 Hz), 114.78, 126.16, 126.44 (q, *J* = 280 Hz), 131.11, 161.30, 175.78; IR (neat)(cm^{-1}) 1737; HRMS: calc for $C_{12}H_{15}F_3NO_3$ (M+H) : 278.1004; found 278.1004.

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



$[\square]_D^{23}$ = -10.4° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.43 (d, *J* = 9Hz, 2H), 6.97 (d, *J* = 9Hz, 2H), 4.35 (q, *J* = 8Hz, 1H), 3.81 (s, 3H), 3.02 (dd, *J* = 10Hz, 5Hz, 1H), 1.92 (septet of triplets, *J* = 7Hz, 2Hz, 1H), 1.41 – 1.56 (m, 1H), 0.87 (d, *J* = 7Hz, 3H), 0.74 (d, *J* = 7Hz, 3H); ^{19}F NMR -79.04 (d, 8Hz, minor), -80.09 (d, 8Hz, major), 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 Hz), 115.18, 126.37, 126.87 (q, *J* = 280 Hz), 131.78, 161.85, 176.37;IR (neat, cm^{-1}) 1737; HRMS: calc for $C_{15}H_{21}F_3NO_3$ (M+H) : 320.1474; found 320.1472.

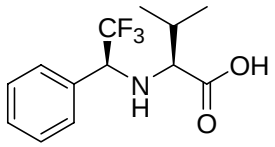
***N*-[(1*R*)-1-(4-methoxyphenyl)-2,2,2-trifluoroethyl]-L-valine ((*R*,*S*)-2i)**



$[\square]_D^{23}$ = -11.1° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.43 (AB, d, *J* = 8Hz, 2H), 6.96 (AB, d, *J* = 8Hz, 2H), 4.28 (q, *J* = 8Hz, 1H), 3.81 (s, 3H), 2.82 (d, *J* = 5Hz, 1H), 1.97 (apparent octet, *J* = 6Hz, 1H), 0.92 (d, *J* = 9Hz, 6H); ^{19}F NMR -79.14 (d, 7Hz, minor), -80.12 (d, 7Hz, major), dr = 1 : 33; ^{13}C NMR (CD_3COCD_3, δ) 18.58, 20.26, 32.40, 55.96, 63.57 (q, *J* = 28 Hz), 64.07, 115.14, 126.31, 126.92 (q, *J* = 280 Hz), 131.85, 161.81, 175.49; IR (neat, cm^{-1}) 1733; HRMS: calc for $C_{14}H_{19}F_3NO_3$ (M+H) : 306.1317; found 306.1315.

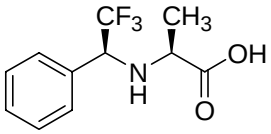
Representative procedure for the (*S*,*S*)-selective reductive amination.

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



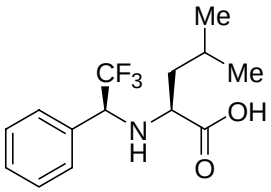
Sodium borohydride (869 mg, 23.0 mmol) was added to a 0 °C suspension of $ZnCl_2$ (1.57 g, 11.5 mmol) in DME (11.5 mL). The mixture was allowed to warm to ambient temperature and age for 18 h. In the meantime, 2,2,2-trifluoroacetophenone (1.00 g, 5.74 mmol) was added to a suspension of L-leucine methylester 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 $Zn(BH_4)_2$ 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° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.51 (d, *J* = 4Hz, 2H), 7.39 (d, *J* = 4Hz, 3H), 4.37 (q, *J* = 8Hz, 1H), 3.31 (d, *J* = 5Hz, 1H), 2.11 (apparent octet, *J* = 6Hz, 1H), 1.03 (d, *J* = 7Hz, 3H), 0.95 (d, *J* = 7Hz, 3H); ^{19}F NMR -77.98 (s, major), -78.90 (s, minor), dr = 21 : 1; ^{13}C NMR (CD_3COCD_3, δ) 18.39, 19.93, 32.77, 65.04 (q, *J* = 29 Hz), 66.45, 127.32 (q, *J* = 281 Hz), 129.73, 129.84, 130.14, 136.63, 175.92; IR (neat, cm^{-1}) 1733; HRMS: calc for $C_{13}H_{17}F_3NO_2$ (M+H) : 276.1211; found 276.1214.

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

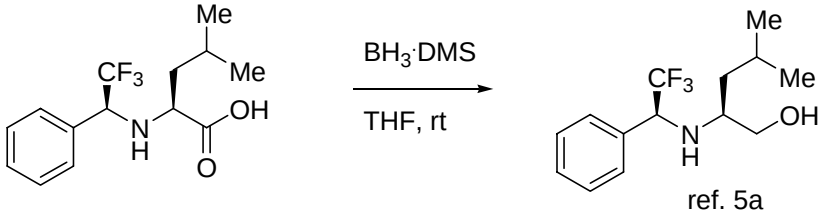


$[\alpha]_D^{23}$ = -2.5° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.44 – 7.47 (m, 2H), 7.37 – 7.41 (m, 3H), 4.43 (q, *J* = 7Hz, 1H), 3.28 (q, *J* = 7Hz, 1H), 1.23 (d, *J* = 7Hz, 3H); ^{19}F NMR -79.05 (d, 8Hz, major), -79.78 (d, 8Hz, minor), dr = 15 : 1; ^{13}C NMR (DMSO-d_6, δ) 18.76, 54.65, 61.40 (q, *J* = 28 Hz), 126.27 (q, *J* = 282 Hz), 128.79, 128.83, 129.09, 129.33, 135.10, 176.03; IR (neat, cm^{-1}) 1737; HRMS: calc for $C_{11}H_{13}F_3NO_2$ (M+H) : 248.0898; found 248.0892.

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

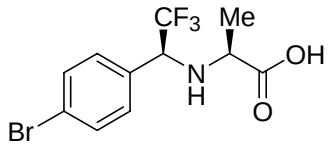


$[\alpha]_D^{23}$ = +0.74° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.47 – 7.50 (m, 2H), 7.37 – 7.40 (m, 3H), 4.33 (q, *J* = 8Hz, 1H), 3.51 (t, *J* = 7Hz, 1H), 1.98 (vs, *J* = 7Hz, 1H), 1.53 (dd, *J* = 8Hz, 7Hz, 2H), 0.95 (d, *J* = 7Hz, 3H), 0.93 (d, *J* = 7Hz, 3H); ^{19}F NMR -78.81 (d, 7Hz, major), -79.76 (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 Hz), 127.46 (q, *J* = 281 Hz), 129.78, 129.84, 130.11, 136.70, 176.83; IR (neat, cm^{-1}) 1737; HRMS: calc for $C_{14}H_{19}F_3NO_2$ (M+H) : 290.1368; found 290.1358.



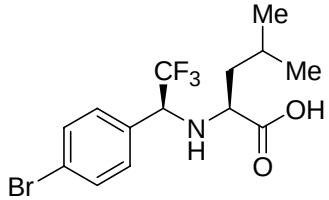
A sample of **(*S*,*S*)-2b** (289 mg, 1.00 mmol) was dissolved in THF (5 mL) and BH_3·DMS (2.0 mL, 21.0 mmol) was added. After 2h, the mixture was quenced by the careful addition of 1M HCl and TBME. The organic later was washed with brine dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by flash chromatography to afford 240mg of the desired compound whose spectral data were consistant with those reported in the supporting information of reference 5a.

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



$[\alpha]_D^{23}$ = -2.8° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.60 (AB, d, *J* = 8Hz, 2H), 7.49 (AB, d, *J* = 8Hz, 2H), 4.51 (q, *J* = 8Hz, 1H), 3.49 (q, *J* = 7Hz, 1H), 1.34 (d, *J* = 7Hz, 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 Hz), 123.33, 126.60 (q, *J* = 279 Hz), 131.47, 132.49, 135.25, 175.83; IR (neat)(cm^{-1}) 1737; HRMS: calc for $C_{11}H_{12}BrF_3NO_2$ (M+H) : 326.0003; found 325.9994.

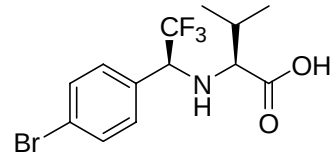
***N*-[(1*S*)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-L-leucine ((*S*,*S*)-2e)**



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

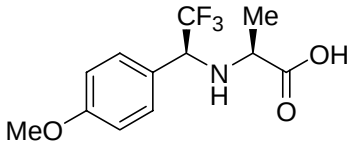
^{19}F NMR -78.93 (d, 7Hz, major), -79.82 (d, 7Hz, minor), dr = 12 : 1; ^{13}C NMR (CD_3COCD_3, δ) 22.51, 23.62, 25.79, 43.54, 59.73, 63.61 (q, *J* = 29 Hz), 123.76, 127.09 (q, *J* = 281 Hz), 131.94, 132.87, 176.53; IR (neat)(cm^{-1}) 1733; HRMS: calc for $C_{14}H_{18}BrF_3NO_2$ (M+H) : 368.0473; found 368.0473.

_N_-[(1_S_)-1-(4-bromophenyl)-2,2,2-trifluoroethyl]-L-valine ((_S_,_S_)-2f)



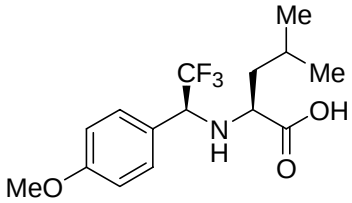
$[\alpha]_D^{23}$ = +3.9° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.58 (AB, d, *J* = 8Hz, 2H), 7.47 (AB, d, *J* = 8Hz, 2H), 4.38 (q, *J* = 7Hz, 1H), 3.26 (d, *J* = 5Hz, 1H), 2.06 – 2.08 (m, 1H), 1.02 (d, *J* = 7Hz, 3H), 0.93 (d, *J* = 7Hz, 3H); ^{19}F NMR -79.04 (d, 7Hz, major), -79.88 (d, 7Hz, minor), dr = 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 $C_{13}H_{16}BrF_3NO_2$ (M-H) : 354.0316; found 354.0316; Chiral HPLC (Chiracel AD-H, 14% ^{i}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)



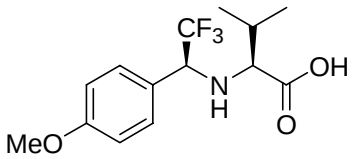
$[\alpha]_D^{23}$ = -1.9° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.43 (d, *J* = 8Hz, 2H), 6.96 (d, *J* = 8Hz, 2H), 4.47 (q, *J* = 7Hz, 1H), 3.80 (s, 3H), 3.51 (q, *J* = 7Hz, 1H), 1.35 (d, *J* = 7Hz, 3H); ^{19}F NMR -79.00 (d, 7Hz, major), -79.77 (d, 7Hz, minor), dr = 8 : 1; ^{13}C NMR (CD_3COCD_3, δ) 18.46, 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 $C_{12}H_{15}F_3NO_3$ (M+H) : 278.1004; found 278.1002.

_N_-[(1_S_)-1-(4-methoxyphenyl)-2,2,2-trifluoroethyl]-L-leucine ((_S_,_S_)-2h)



$[\alpha]_D$ = +1.2° (*c*=1.0, CH_3COCH_3); ^{1}H 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 $C_{15}H_{21}F_3NO_3$ (M+H) : 320.1474; found 320.1481.

_N_-[(1_S_)-1-(4-methoxyphenyl)-2,2,2-trifluoroethyl]-L-valine ((_S_,_S_)-2i)

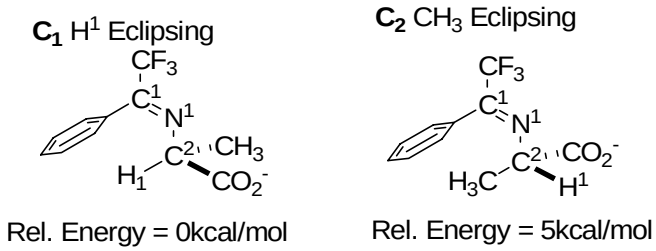


$[\alpha]_D^{23}$ = +4.5° (*c*=1.0, CH_3COCH_3); ^{1}H NMR 7.39 (d, *J* = 8Hz, 2H), 6.93 (d, *J* = 8Hz, 2H), 4.22 (q, *J* = 8Hz, 1H), 3.79 (s, 3H), 3.23 (d, *J* = 5Hz, 1H), 2.02 (apparent octet, *J* = 7Hz, 1H), 1.02 (d, *J* = 7Hz, 3H), 0.93 (d, *J* = 7Hz, 3H); ^{19}F NMR -79.08 (d, 8Hz, major), -79.81 (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 $C_{14}H_{19}F_3NO_3$ (M+H) : 306.1317; found 306.1313.

Rationale for the Observed Stereochemisty

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 preformed 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 H_1 in this conformer is eclipsing the aromatic group (***Figure 1***, **C_1**). Both of these orientations result in a minimization of $A_{1,3}$ strain between the aryl group and the substituents on C_1. A plot of ground state energies versus the torsion angle defined by C_2-N_1-C_1-H_1 shows this rotomer to be favored by ~5 kcal/mol relative to the next most stable conformer (**C_2**) in which the Methyl group is eclipsing the aromatic group.

Figure 1. Geometry optimization of the imine carboxylates.

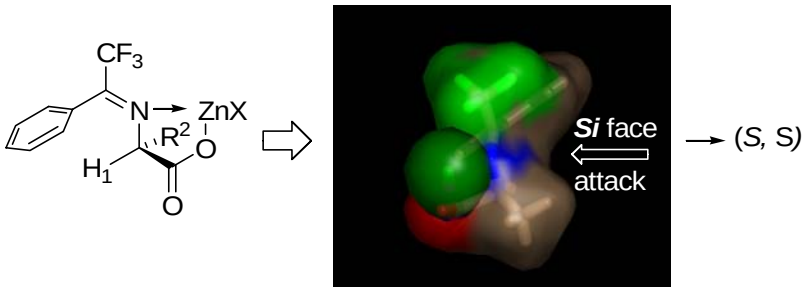


Perhaps the simplest explanation for the reversal in facial selectivity observed with $Zn(BH_4)_2$ reductions would be to invoke equilibration between the *E* to *Z* imine isomers, followed by reduction of the *Z* isomer at a rate which is faster than reduction of the *E* imine isomer. In the *Z* isomer, the s*i* 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. $ZnCl_2$, $Zn(OTf)_2$) in CD_3CN 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 preformed 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.; Schlegal, 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))



$X = Cl, R^2 = CH_3$

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.