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Asymmetric Reduction of 2-(N-Arylimino)-3,3,3trifluoropropanoic Acid Esters Leading to Enantiomerically Enriched 3,3,3-Trifluoroalanine

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A bstract: Enantiomerically enriched 3,3,3-trifluoroalanine (1) (up to 62% ee) has been synthesized by the asymmetric reduction of 2-(N-arylimino)-3,3,3-trifluoropropanoic acid esters with a chiral oxazaborolidine catalyst and subsequent oxidative removal of N-aromatic moiety with retention of the configuration. Detailed optimization studies revealed that the effects of solvents, temperature, and the structural modification of the substrate were drastic on the enantioselectivity. The absolute configuration of 1 was determined to be (R) by X-Ray crystallographic analysis of the corresponding N-(S)-(+)-camphorsulfonyl derivative.

Synthesis of fluorinated amino acids has been one of the current subjects owing to practical application to clarification of the physiological roles of specific enzymes.¹ Specifically, 3,3,3-trifluoroalanine 1 and its derivatives have received considerable attention because they act as suicide inhibitors for a number of pyridoxal enzymes.² A number of studies have been reported about the racemic trifluoroalanine 1,³ for example, *via N*-acyltrifluoroacetaldimines^{3a,b} or a trifluoromethyloxazole intermediate.^{3c,d} In contrast, studies on asymmetric synthesis of 1 are limited and the absolute configuration has not been clarified so far as known. In 1994, a patent by Kubota *et al.*⁴ reported the attempt for chiral precursor of 1 through cyanation (Me₃SiCN) to *N*-[(*S*)- α -phenylethyl]-2,2,2-trifluoroacetaldimine, but with only 33 % de. Recently, a review by Kukhar⁵ described that optically pure (>99% ee) 1 was successfully prepared by enzymatic resolution although the experimental and spectral details are not involved therein.

Our group recently reported a convenient route for racemic 1 by the reduction of 2-(N-arylimino)-3,3,3trifluoropropanoic acid esters 2 with Zn-AcOH and subsequent oxidative removal of the aromatic moiety as shown in Scheme 1.⁶ Here, we wish to report an asymmetric version of the process involving asymmetric reduction of the imine moiety of 2.



Meanwhile, asymmetric reduction of imine function to chiral amine is still a challenging subject to solve. Although wide range of studies have been devoted,⁷ generally applicable methodologies have not been established. Especially, no enantioselective reduction of imines bearing two such highly electronwithdrawing groups (CO₂R and CF₃) like in the case of **2** have been examined, so that considerable difficulties have been expected.

Asymmetric hydrogenations of imines have been attempted with a variety of chiral transition metal catalysts involving rhodium,⁸ iridium,⁹ and titanium.¹⁰ High levels of enantioselectivity can be obtained for some specially substituted imine substrates such as N-acylhyrozones or cyclic imines. Similarly. oxazaboroines-BHlid₃·THF,¹¹ dialkoxyboranes,¹² and NaBH₄-ZrCl₄-chiral amino alcohols¹³ have been used The ee value of the resulting amine of up to 90% ee was achieved in for reduction of imines and oximes. case of acetophenone O-methyloxime reduction with stoichiometric amounts of these chiral ligands. The reduction of aliphatic imines remain to afford low ee in general. Particularly, the ee decreased significantly when the reducing agent was used catalytically. Although Bolm et al.¹⁴ described the use of catalytic amounts of β -hydroxy sulfoximine (10 mol %) in reduction of aromatic ketimines with BH₃·SMe₂, the best ee Here, we examined the applicability of some reduction systems to our substrates 2 and was up to 72%. present a full account of our studies of this reduction for the enantioselective synthesis of chiral 3,3,3trifluoroalanine. 15 A detailed X-ray analysis for determination of the absolute configuration of 3,3,3trifluoroalanine 1 was also described.

Results and discussion

As summarized in Scheme 2, imino esters **2b-k** were prepared here by the previously reported method from our group.⁶ In addition, oxime ether **2a** could be readily prepared in 77% yield in a similar way through carbonylation of iodide **4a** which derived from N-(benzyloxy)-2,2,2-trifluoroacetamide **5** (Scheme 3).



Considerable efforts have been paid to optimize the reaction conditions by examining the reductants, reaction temperature, solvents, and derivatization of substrates. Table 1 summarizes the results of the reduction of typical substrates **2a** and **2f** with a variety of reductants such as Itsuno's reagents (A^{13} and B^{116}), Corey's reagents (C^{16} and E^{17}), and Pak's reagent (**D**).¹⁸ The reductant **A** was used to reduce oxime ether **2a** and imino ester **2f**, but the reductant **A** was highly reactive enough to reduce both of imine and ester groups

to amino alcohols **6a** and **6f** in 94% and 95% yields, respectively (entry 1 and 2). BH₃ THF is involved as a hydride source in the reductants **B-D** and catecholborane in **E**. Asymmetric reduction of imino ester **2f** using (S)-reductants **B-D** commonly gave amino ester (S)-**3f** together with amino alcohol (R)-**4f**, leaving the ee of the former below 32% (entry 3-5). One of the reasons of the lower ee(s) would be attributed to the formation of by-product (R)-**6f**, which also act as a ligand to give another *in situ*-formed oxazaborolizine and induce the formation of a counter enantiomer of (S)-**3f**. Use of reductant **E** with catecholborane could completely suppress such formation of amino alcohol (R)-**6f** and therefore improved the ee up to 63% with 93% yield (entry 6).

Table 1: Asymmetric Reduction of 2a and 2f with Reductants A-E

		TH	THF		CO ₂ Et CF ₃ NHR +			CF ₃ OH	
$2f: R = p - MeOC_6H_4$		4			31			6a : $R = H$ 6f : $R = p$ -MeOC ₆ H ₄	
entry	substrate	reductant	temp. (°C)		yield (%)	ee (%) ^{a)} (config.)		yield (%)	ee (%) ^{a)} (config.)
1	2a	A	rt	-	0	-	ба	94	-
2	2 f	A	rt	3f	0	-	6f	95	14 (<i>R</i>)
3	2f	В	-78~rt	3f	4 0	32 (<i>S</i>)	6f	56	46 (<i>R</i>)
4	2f	С	-78~rt	3f	42	28 (S)	6f	49	45 (<i>R</i>)
5	2f	D	-78~rt	3f	38	14 (S)	6f	45	11 (R)
6 ^{b)}	2f	E ^{c)}	rt	3f	93	63 (<i>R</i>)	6f	-	

^{a)} Determined by ¹⁹F NMR of the MTPA ester of the corresponding amino alcohol. ^{b)} The reduction was in CH₂Cl₂. ^{c)} Catalytic amount of ligand was used (10 mol %).



Table 2 shows a remarkable effect of the reaction temperature on enantioselectivity. The reduction of **2f** in CH₂Cl₂ was conducted at temperature ranging from -20 °C to 40 °C. The lower temperatures induced unexpectedly poor enantioselectivity, although Corey reported that the catecholborane procedure functions well for ketone at low temperature.¹⁷ Upon raising the temperature, the enantioselectivities gradually improved, and ee of the product **3f** was raised up to 63% at 25 °C (room temperature). The negative effect of higher temperature at under reflux in CH₂Cl₂ was observed for this reduction. At this temperature range, the chemical yield was changed little. These results suggest that the complexation of the substrate with the

entry	temp.(°C)	time (h)	yield of 3f (%)	ee (%)
1	-20	36	90	25
2	0	24	88	37
3	25	20	93	63
4	30	20	91	60
5	reflux	18	80	12

reductant may occur suitably at around 25 °C.

Table 2: Temperature Effect on the Reduction of 2f with Reductant E.^{a)}

a) CH₂Cl₂ as a solvent and 4Å molecular sieves were used in all reactions.

Then, the effect of the solvents such as hexane, aromatic compounds, THF, and halogenated hydrocarbons was examined by taking up the substrate 2f (Table 3). Due to the poor solubility of oxazaborolidine, hexane was found to be unsuitable. Reduction in THF or CHCl₃ gave amino alcohol 3f (15% yield) in addition (entry 4 and 7). In toluene, 89% yield and 43% ee were obtained as shown in entry 2. In terms of enantioselectivity, CH_2Cl_2 was the best choice of the solvent so far as examined. The yield and In particular, addition of 4Å molecular sieves ee are 85% and 55%, respectively (entry 5 in Table 3). Recently, it has been reported that trace of water in markedly affected on the selectivity (63% ee in entry 6). the reaction media lowers the ee from 95% to 50%.¹⁹ The molecular sieves would be meaningful as a desiccant in this reduction system.

entry	solvent	time (h)	yield of 3f (%)	ee (%)	
1	Hexane	72	12 ^{b)}	-	
2	Toluene	28	89	43	
3	Benzene	28	84	43	
4 ^{c)}	THF	18	72	40	
5	CH_2Cl_2	24	85	55	
6 ^{d)}	CH ₂ Cl ₂	20	93	63	
7 ^{c)}	CHCl3	20	70	15	

Table 3: Effect of Solvents on the Asymmetric Reduction of 2f with the Reductant E.^{a)}

a) Reaction at 25 °C. ^{b)} The starting 2f (82%) was recovered. ^{c)} Amino alcohol 6f was obtained about 15% yield. ^{d)} 4Å molcular seives was used.

Adjust the structure of substrates to the catalyst is further examined by changing both ester and N-aryl moieties. A series of imino esters 2 containing (L)-menthyl ester 2i and 2k were also subjected to the reduction with reductant E and the results are summarized in Table 4. The reductant E was not effective for oxime ether 2a and sterically hindered 2,6-dimethyl 2b, recovering the substrates intact. The electronic effect of N-aryl group of 2 did not affect the selectivity. Thus, both electron withdrawing (m-chloro 2c) and electron donating (p-methyl 2e and p-methoxy 2f) substituents gave the similar level of selectivities (entry 3-6). Substitution with more electron-donating substituent p-(N,N-dimethyl)amino group (2g) gave no reaction,

probably due to the substrate-catalyst complexation at p-NMe₂ nitrogen instead of at imine nitrogen. Then, the ethyl ester moiety of **2e** was changed to the bulkier benzyl (entry 10), which slightly improved the ee to 68% from 62%. The best selectivity (de) was obtained by using (L)-menthyl ester (71% de) as a result of double differentiation (entry 9).

	CO ₂ R CF ₃ NAr -		Reductant E		CO₂R		
			CH₂Cl₂, MS 4Å, 1	rt, 24 h CF	CF3 NHAr (<i>R</i>)-3		
entry		R	Ar	yield of 3 (%)	ee (%) ^{a)}	config.	
1	2a	Et	BnO	0	-		
2	2 b	Et	$2,6-Me_2C_6H_3$	0	-		
3	2 c	Et	m-ClC ₆ H ₄	94	63	R -(-) ^{b)}	
4	2d	Et	C ₆ H ₅	93	61	<i>R</i> -(-) ^{b)}	
5	2 e	Et	p-MeC ₆ H ₄	90	62	<i>R</i> -(+) ^{b)}	
6	2f	Et	p-MeOC ₆ H ₄	93	63	<i>R</i> -(-) ^{b)}	
7	2g	Et	<i>p</i> -Me ₂ NC ₆ H ₄	0	-		
8	2h	Bn	p-MeOC ₆ H ₄	91	62	<i>R</i> -(-)	
9	2i	(L)-menthyl	p-MeOC ₆ H ₄	>85	71 ^{c)}	<i>R</i> -(-) ^{b)}	
10	2ј	Bn	p-MeC ₆ H ₄	95	68	$R - (+)^{b}$	
11	2k	(L)-menthyl	p-MeC ₆ H ₄	>85	68 ^{c)}	<i>R</i> -(+) ^{b)}	

Table 4: Asymmetric Reduction of the Imino Esters 2 with Reduction (S)-E

a) Determined by ¹⁹F NMR of the MTPA ester of the corresponding amino alcohol (LiAlH₄).^{b)} Absolute configuration was assigned by comparison of ¹⁹F NMR chemical shift of the MTPA esters of the corresponding amino alcohols.^{c)} Diastereometric excess (de)

Further conversion to free 3,3,3-trifluoroalanine 1 was then accomplished. The amino ester 3i (R = Bn, $Ar = p - MeC_6H_4$) was obtained as the sole crystal in this reaction. The optically pure (R)-3j was found to be available by recrystallization of 3j (68% ee) from hexane.²⁰ However, oxidative removal of the pmethylphenyl moiety from 3 i to optically pure 1 was unsuccessful. The removal of the *p*-methoxyphenyl moiety from (R)-3h (R = Bn, Ar = p-MeOC₆H₄) by treatment with cerium (IV) diammonium nitrate at 0 °C in CH₃CN-H₂O²¹ afforded the corresponding optically active amine derivative (R)-7 in 87% yield with retention of the optical purity of (62% ee), which was confirmed by 19 F NMR analysis of the MTPA amide 8; a couple of peaks in 19 F NMR was observed at d 92.75 ppm [(R), 81%] and 92.56 ppm [(S), 19%) for CF₃ on the A simple treatment of (R)-7 with Pd / C catalyst under hydrogen atmosphere led to (R)-(+)-MTPA part. 3,3,3-trifluoroalanine 1 (62% ee, 90% yield) ($[\alpha]_D^{23}$ + 6.8, c 0.76, MeOH) as a free amine form. The optical purity was confirmed further by HPLC analysis.

The absolute configuration of amino ester **3h** was confirmed by X-ray crystallographic analysis of N-(S)-(+)-camphorsulfonyl derivative (R, S)-**9a** which was prepared by resolution of racemic amide **9a**, b. Thus,



Scheme 4

the racemic amine 7 prepared from racemic 3h was allowed to react with (S)-(+)-10-camphorsulfonyl chloride to give a 1:1 diasteromeric mixture of (R, S)-9a and (S, S)-9b, which were separated by HPLC to provide a crystalline (R, S)-9a and an oily (S, S)-9b. The former (R, S)-9a was recrystallized from ethyl acetate-hexane (1:5) to yield a white needle suitable for X-Ray analysis. An arbitrary view of (R, S)-9a is shown in Figure 1 with appropriate atomic labeling.



Figure 1. X-Ray Crystallographic Data of (R,S)-9a.

The absolute configuration of the reduction product **3h** was thus assigned to be (R) by conversion to the camphorsulfonyl derivative (R,S)-**9a** and the comparison of ¹⁹F or ¹H NMR chemical shifts with both of (R,S)-**9a** and (S,S)-**9b**.

Experimental Section

General. Melting points were measured on a capillary apparatus and are uncorrected. Infrared spectra (IR) were measured on Hitachi Model 270-30 Infrared Spectrophotometer. ¹H (200 MHz), and ¹⁹F (188 MHz) NMR spectra were recorded by Varian VXR 200 NMR apparatus in CDCl₃ or D₂O as indicated and the chemical shifts are reported in δ (ppm) values downfield from TMS (¹H NMR) or C₆F₆ (¹⁹F NMR), respectively, as internal standards. Optical rotation was measured at 23 °C in a cell with 50 mm length and 1 mL capacity using a Horiba High Sensitive Polarimeter SEPA-300. Elemental analyses were performed on Perkin Elmer series II CHNS/O Analyzer 2400.

Hexane, THF, toluene, and benzene were distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride (CH₂Cl₂) and chloroform (CHCl₃) were distilled from CaH₂. Catecholborane was distilled under reduced pressure (70 °C / 100 mmHg) and stored as 2 M CH₂Cl₂ or toluene. In all other cases, commercially available reagent grade solvents were employed without further purification. (S)-(+)-2-Amino-3-methyl-1,1-diphenylbutanol was prepared by the known method. ^{11d} (S)-2-Indoline carboxylic acid and (S)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine were purchased from TCI Tokyo Kasei Kogyo Co., Itd. (Tokyo). (S)-(+)-Methoxy- α -(trifluoromethyl)phenylacetic acid (MTPA) was obtained from the same source and converted to the acid chloride (MTPA-Cl) using the Mosher's procedure.²²

Preparation of 2-(*N*-**Arylimino**)-**3**, **3**, **3**-**trifluoropropanoates 2b-k.** The compounds **2b**, **2d-f**, **2h**, and **2j** were prepared according to the procedure reported previously from our group.⁶ Other imino esters **2c**, **2g**, **2i**, and **2k** were prepared in 30-80% yields from the corresponding imidoyl iodides **4** in a similar way and the spectral data are shown in the following. The spectral data suggest that imino esters **2b-k** have a single geometry (*E* or *Z*), however, which could not be assigned so far.

Ethyl 2-[*N*-(*p*-Chlorophenyl)imino]-3,3,3-trifluoropropanoate 2c: 80% yield; IR (neat) 1746, 1682, 858, 784, 688 cm⁻¹; ¹H NMR (CDCl₃) δ 1.12 (t, *J* = 7.2 Hz, 3H, CH₃), 4.22 (q, *J* = 7.2 Hz, 2H, CH₂), 6.79-6.98 (m, 2H, H_{arom}), 7.19-7.35 (m, 2H, H_{arom}); ¹⁹F NMR (CDCl₃) δ 91.87 (s, CF₃). Anal. Calcd for C₁₁H₉ClF₃NO₂: C, 47.25; H, 3.24; N, 5.01. Found: C, 47.19; H, 3.52; N, 5.18.

Ethyl 2-{*N*-[*p*-(*N*, *N*-Dimethylamino)phenyl]imino}-3, 3, 3-trifluoropropanoate 2g: 58% yield; IR (neat) 1738, 1582, 818 cm⁻¹; ¹H NMR (CDCl₃) δ 1.18 (t, *J* = 7.1 Hz, 6H, CH₃), 1.27 (t, *J* = 7.1 Hz, 3H, CH₃), 3.38 (q, *J* = 7.0 Hz, 4H, CH₂), 4.33 (q, *J* = 7.0 Hz, 2H, CH₂), 6.60 (d, *J* = 8.9 Hz, 2H, H_{arom}); ¹⁹F NMR (CDCl₃) δ 92.05 (s, CF₃). Anal. Calcd for C₁₅H₁₉F₃N₂O₂: C, 56.96; H, 6.05; N, 8.86. Found: C, 56.50; H, 6.48; N, 8.71.

(*L*)-Menthyl 2-[*N*-(*p*-Anisyl)imino]-3,3,3-trifluoropropanoate 2i: 35% yield; IR (neat) 1736, 1604 cm⁻¹; ¹H NMR (CDCl₃) δ 0.62 (t, *J* = 6.9 Hz, 3H, CH₃), 0.78 (t, *J* = 7.0 Hz, 3H, CH₃), 0.88 (t, *J* = 6.2 Hz, 3H, CH₃), 0.70-1.97 (m, 9H, H_{menthyl}), 3.82 (s, 3H, OCH₃), 4.76 (td, *J* = 7.1 Hz, *J* = 4.4 Hz, 1H, OCH), 6.88 (d, *J* = 9.1 Hz, 2H, H_{aron}), 7.01 (d, *J* = 8.8 Hz, 2H, H_{aron}); ¹⁹F NMR (CDCl₃) δ 92.15 (s,

CF₃). Anal. Calcd for C₂₀H₂₆F₃NO₃: C, 62.23; H, 6.80; N, 3.63. Found: C, 62.23; H, 6.67; N, 3.89. (*L*)-Menthyl 2-[*N*-(*p*-Tolyl)imino]-3,3,3-trifluoropropanoate 2k: 32% yield; IR (neat) 1736, 1662 cm⁻¹; ¹H NMR (CDCl₃) δ 0.58 (t, *J* = 6.7 Hz, 3H, CH₃), 0.75 (t, *J* = 6.8 Hz, 3H, CH₃), 0.86 (t, *J* = 6.5 Hz, 3H, CH₃), 0.75-1.90 (m, 9H, H_{menthyl}), 2.35 (s, 3H, CH₃), 4.72 (td, *J* = 10.7 Hz, *J* = 4.4 Hz, 1H, OCH), 6.87 (d, *J* = 8.3 Hz, 2H, H_{arom}), 7.01 (d, *J* = 8.1 Hz, 2H, H_{arom}); ¹⁹F NMR (CDCl₃) δ 91.97 (s, CF₃). Anal. Calcd for C₂₀H₂₆F₃NO₂: C, 65.02; H, 7.09; N, 3.79. Found: C, 64.86; H, 7.08; N, 4.15.

N-(Benzyloxy)-2, 2, 2-trifluoroacetimidoyl Iodide 4a. To a mixture of PPh₃ (3.6 g, 13.7 mmol) and *N*-(benzyloxy)-2, 2, 2-trifluoroacetamide 5 (2.0 g, 9.1 mmol) (prepared from trifluoroacetic anhydride and the *O*-benzylhydroxylamine)²³ in dry acetonitrile (15 mL) was added iodine (2.8 g, 10.9 mmol) and Et₃N (1.1 g, 10.9 mmol) at 0 °C in the dark. After warming to room temperature, the contents were stirred for 24 h. The solvent was removed under reduced pressure. The residue was diluted with hexane and the crystalline material formed was removed by filtration. The usual workup and subsequent purification by silica gel column chromatography (hexane) gave iodide 4a (2.5 g, 83% yield) as a colorless oil: IR (neat) 1590 cm⁻¹; ¹H NMR (CDCl₃) δ 5.41 (s, 2H, CH₂), 7.38 (s, 5H, C₆H₅); ¹⁹F (CDCl₃) δ 96.21 (s, CF₃). Anal. Calcd for C₉H₇F₃INO: C, 32.85; H, 2.14; N, 4.26. Found: C, 32.62; H, 2.21; N, 4.29.

Ethyl 2-(*N*-Benzyloxyimino)-3,3,3-trifluoropropanoate 2a. A two-necked flask with a septum cap and a condenser topped with CO (1 atm.) inlet was charged with $Pd_2(dba)_3 \cdot CHCl_3^{24}$ (0.16 g, 0.15 mmol) and K₂CO₃ (0.84 g, 6.0 mmol). Then, trifluoroacetimidoyl iodide 4a (1.0 g, 3.0 mmol) in toluene (10 mL) and EtOH (0.36 mL, 6.0 mmol) were added through a syringe. The mixture was stirred at room temperature for 20 h and passed through a short florisil column (hexane). Concentration followed by purification through silica gel column chromatography with ethyl acetate-hexane (1 : 50) gave 2a (0.64 g, 77% yield) as a colorless oil: IR (neat) 1750, 1632 cm⁻¹; ¹H NMR (CDCl₃) δ 1.32 (t, J = 7.1 Hz, 3H, CH₃), 4.36 (q, J = 7.1 Hz, 2H, CH₂), 5.30 (s, 2H, CH₂), 7.36 (s, 5H, C₆H₅); ¹⁹F NMR (CDCl₃) δ 95.96 (s, CF₃). Anal. Calcd for C₁₂H₁₂F₃NO₃: C, 52.37; H, 4.39; N, 5.09. Found: C, 52.44; H, 4.45; N, 5.10.

Asymmetric Reduction of 2a Using Reductant A. ¹³ To a suspension of $ZrCl_4$ (127 mg, 0.54 mmol) in THF (1.0 mL) was added NaBH₄ (82.5 mg, 2.18 mmol) at room temperature under nitrogen. After the mixture had been stirred for 20 h, a solution of (S)-(+)-2-amino-3-methyl-1, 1-diphenylbutanol (92.7 mg, 0.36 mmol) in THF (1.0 mL) was added at room temperature and the mixture was stirred for a further 20 h. To the resulting chiral reductant A was added 2a (100 mg, 0.36 mmol) and the mixture was stirred for 1 h at room temperature. Work up gave amino alcohol 6a which was isolated its acetate form in 94% yield (44 mg) as a colorless oil. ¹H NMR (CDCl₃) δ 2.09 (s, 3H, CH₃), 2.11 (s, 3H, CH₃), 4.16-4.49 (m, 2H, CH₂), 4.82-5.29 (m, 1H, CH), 5.89-5.99 (br, 1H, NH); ¹⁹F NMR (CDCl₃) δ 87.84 (d, J = 7.6 Hz, CF₃).

Asymmetric Reduction of 2f Using Reductant B.^{11d} A solution of borane (1 M in THF, 0.81 mL, 0.81 mmol) was added dropwise to (S)-(+)-2-Amino-3-methyl-1,1-diphenylbutanol (103 mg, 0.40 mmol) in THF (1.0 mL) at -78 °C. The solution was gradually warmed to 0 °C and stirred for 8 h. Imino ester 2f (100 mg, 0.36 mmol) in THF (1.0 mL) was added at -78 °C. The mixture was gradually warmed to

room temperature and stirring was continued at room temperature for 1 h. Then water was added and the mixture was extracted with ethyl acetate $(3 \times 5 \text{ mL})$. The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica gel afforded amino ester **3 f** (40 mg, 40% yield) and amino alcohol **6 f** (47.8 mg, 56% yield) as colorless oils.

Ethyl 2-[N-(p-Anisyl)]-3,3,3-trifluoropropanoate 3f: 32% ee, [α]_D²³ -11.4 (c 0.12, CHCl₃); IR (neat) 3396, 1748, 1518, 824 cm⁻¹; ¹H NMR (CDCl₃) δ 1.32 (t, J = 7.1 Hz, 3H, CH₃), 3.76 (s, 3H, OCH₃), 4.19-4.40 (m, 2H, OCH₂), 4.44 (q, J = 6.9 Hz, 1H, CH), 6.70 (d, J = 9.1 Hz, 2H, H_{arom}), 6.81 (d, J = 9.1 Hz, 2H, H_{arom}); ¹⁹F NMR (CDCl₃) δ 89.06 (d, J = 6.4 Hz, CF₃). Anal. Calcd for C₁₂H₁₄F₃NO₃: C, 51.99; H, 5.09; N, 5.05. Found: C, 52.15; H, 5.32; N, 5.15.

2-[*N*-(*p*-Anisyl)amino]-3, 3, 3-trifluoropropanol 6f: IR (neat) 3404, 1516, 824 cm⁻¹; ¹H NMR (CDCl₃) δ 3.76 (s, 3H, OCH₃), 3.79-3.97(m, 3H, CHCH₂), 6.71 (d, *J* = 9.2 Hz, 2H, H_{arom}), 6.81 (d, *J* = 9.0 Hz, 2H, H_{arom}); ¹⁹F NMR (CDCl₃) δ 88.08 (d, *J* = 6.1 Hz, CF₃). Anal. Calcd for C₁₀H₁₂F₃NO₂: C, 51.07; H, 5.14; N, 5.96. Found: C, 50.74; H, 5.01; N, 6.20.

Asymmetric Reduction of 2f with Reductants C^{16} and D.¹⁸ A similar procedure to the above experiment with reductant **B** was used.

A Typical Procedure for the Asymmetric Reduction of Imino Esters 2 with Reductant E. To a solution of imino ester 2 (0.20 mmol), (S)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (0.02 mmol), and 4Å molecular sieves in CH₂Cl₂ (1 mL) at room temperature was added catecholborane (2 M in CH₂Cl₂, 0.40 mmol) under nitrogen. After being stirred for 24 h, the reaction was quenched by addition of water and the organic layer was extracted with hexane. Usual workup followed by column chromatographic purification on silica gel with 10% benzene in hexane gave 3.

(*R*)-(-)-Ethyl 2-[*N*-(*m*-Chlorophenyl)amino]-3,3,3-trifluoropropanoate 3c: 63% ee; $[\alpha]_D^{23}$ -22.86 (*c* 0.41, CHCl₃); IR (neat) 3412, 1748, 1604, 854, 770, 682 cm⁻¹; ¹H NMR (CDCl₃) δ 1.33 (t, *J* = 7.0 Hz, 3H, CH₃), 4.22-4.45 (m, 2H, CH₂), 4.51-4.71 (m, 2H, CHNH), 6.56-6.88 (m, 3H, H_{arom}), 7.08-7.18 (m, 1H, H_{arom}); ¹⁹F NMR (CDCl₃) δ 89.23 (d, *J* = 7.0 Hz, CF₃). Anal. Calcd for C₁₁H₁₁ClF₃NO₂: C, 46.92; H, 3.94; N, 4.97. Found: C, 46.92; H, 4.02; N, 5.06.

(*R*)-(-)-Ethyl 2-(*N*-Phenylamino)-3,3,3-trifluoropropanoate 3d: 61% ee; $[\alpha]_D^{23}$ -34.60 (*c* 0.41, CHCl₃); IR (neat) 3416, 1750, 1608, 750, 682 cm⁻¹; ¹H NMR (CDCl₃) δ 1.32 (t, *J* = 7.1 Hz, 3H, CH₃), 4.20-4.43 (m, 2H, CH₂), 4.49-4.68 (m, 2H, CHNH), 6.68-6.90 (m, 3H, H_{arom}), 7.17-7.27 (m, 2H, H_{arom}); ¹⁹F NMR (CDCl₃) δ 89.10 (d, *J* = 5.8 Hz, CF₃). Anal. Calcd for C₁₁H₁₂F₃NO₂: C, 53.44; H, 4.89; N, 5.67. Found: C, 53.45; H, 4.99; N, 5.72.

(*R*)-(+)-Ethyl 3,3,3-Trifluoro-2-[*N*-(*p*-tolyl)]propanoate 3e: 62% ee; $[\alpha]_D^{23}$ +86.16 (*c* 0.10, CHCl₃); IR (neat) 3412, 1750, 1622, 810 cm⁻¹; ¹H NMR (CDCl₃) δ 1.31 (t, *J* = 7.2 Hz, 3H, CH₃), 4.18-4.38 (m, 2H, CH₂), 4.40-4.62 (m, 2H, CHNH), 6.64 (d, *J* = 8.4 Hz, 2H, H_{arom}), 7.03 (d, *J* = 8.1 Hz, 2H, H_{arom}); ¹⁹F NMR (CDCl₃) δ 89.11 (d, *J* = 6.8 Hz, CF₃). Anal. Calcd for C₁₂H₁₄F₃NO₂: C, 55.17; H, 5.40; N, 5.36. Found: C, 55.32; H, 5.48; N, 5.29.

(*R*)-(-)-Benzyl 2-[*N*-(*p*-Anisyl)]-3,3,3-trifluoropropanoate 3h: 62% ee; $[\alpha]_D^{23}$ -6.41 (*c* 0.30, CHCl₃); IR (neat) 3400, 1748, 1598, 822, 748, 698 cm⁻¹; ¹H NMR (CDCl₃) δ 3.68 (s, 3H, OCH₃), 4.23 (d,

 $J = 9.3 \text{ Hz}, 1\text{H}, \text{NH}, 4.36-4.53 \text{ (m, 1H, CH)}, 5.18 \text{ (s, 2H, CH}_2), 6.61 \text{ (d, } J = 9.1 \text{ Hz}, 2\text{H}, \text{H}_{arom}), 6.72 \text{ (d, } J = 9.2 \text{ Hz}, 2\text{H}, \text{H}_{arom}) 7.28 \text{ (m, 5H, C}_{6}\text{H}_5); {}^{19}\text{F} \text{ NMR} (\text{CDCl}_3) \delta 89.22 \text{ (d, } J = 6.8 \text{ Hz}, \text{CF}_3). \text{ Anal. Calcd for C}_{17}\text{H}_{16}\text{F}_3\text{NO}_3: \text{C}, 60.18; \text{H}, 4.75; \text{N}, 4.13. Found: C, 59.80; \text{H}, 5.09; \text{N}, 4.08.$

(*R*)-(-)-(*L*)-Menthyl 2-[*N*-(*p*-Anisyl)]-3, 3, 3-trifluoropropanoate 31: 71% ee; $[\alpha]_D^{23}$ -78.90 (*c* 0.10, CHCl₃); IR (neat) 3400, 1742, 1518, 822 cm⁻¹; ¹H NMR (CDCl₃) δ 0.68 (t, *J* = 7.0 Hz, 3H, CH₃), 0.85 (t, *J* = 7.0 Hz, 3H, CH₃), 0.91 (t, *J* = 6.5 Hz, 3H, CH₃), 0.74-2.05 (m, 9H, H_{menthyl}), 3.76 (s, 3H, OCH₃), 4.44 (q, J = 6,8 Hz, 1H, CHCF₃), 4.80 (td, *J* = 11.0 Hz, *J* = 4.5 Hz, 1H, CH), 6.70 (d, *J* = 9.2 Hz, 2H, H_{arom}); ¹⁹F NMR (CDCl₃) δ 89.23 (d, *J* = 6.8 Hz, CF₃). Anal. Calcd for C₂₀H₂₈F₃NO₃: C, 62.00; H, 7.28; N, 3.62. Found: C, 62.01; H, 7.68; N, 3.61.

(*R*)-(+)-Benzyl 3,3,3-Trifluoro-2-[*N*-(*p*-tolyl)]propanoate 3j: 68% ee; $[\alpha]_D^{23}$ +13.24 (*c* 0.20, CHCl₃); IR (neat) 3400, 1738, 1622, 810, 726, 698 cm⁻¹; ¹H NMR (CDCl₃) δ 2.25 (s, 3H, CH₃), 4.39 (br, 1H, NH), 4.52-4.65 (m, 1H, CHCF₃), 5.26 (s, 2H, CH₂),), 6.63 (d, *J* = 8.4 Hz, 2H, H_{arom}), 6.72 (d, *J* = 8.1 Hz, 2H, H_{arom}) 7.35 (s, 5H, C₆H₅); ¹⁹F NMR (CDCl₃) δ 89.11 (d, *J* = 6.8 Hz, CF₃). Anal. Calcd for C₁₇H₁₆F₃NO₂: C, 63.15; H, 4.99; N, 4.33. Found: C,63.14; H, 5.18; N, 4.26.

(*R*)-(+)-(*L*)-Menthyl 3,3,3-Trifluoro-2-[*N*-(*p*-tolyl)]propanoate 3k: 68% ee; $[\alpha]D^{23}$ +109.6 (*c* 0.15, CHCl₃); IR (neat) 3412, 1748, 1604, 810 cm⁻¹; ¹H NMR (CDCl₃) δ 0.68 (t, *J* = 6.9 Hz, 3H, CH₃), 0.86 (t, *J* = 7.0 Hz, 3H, CH₃), 0.91 (t, *J* = 6.6 Hz, 3H, CH₃), 0.80-2.05 (m, 9H, H_{menthyl}), 2.26 (s, 3H, CH₃), 4.40-4.62 (m, 2H, CHNH), 4.62 (td, *J* = 10.9 Hz, *J* = 4.5 Hz, 1H, CH),), 6.65 (d, *J* = 8.5 Hz, 2H, H_{arom}), 7.04 (d, *J* = 8.8 Hz, 2H, H_{arom}); ¹⁹F NMR (CDCl₃) δ 89.31 (d, *J* = 6.2 Hz, CF₃). Anal. Calcd for C₂₀H₂₈F₃NO₂: C, 64.67; H, 7.60; N, 3.77. Found: C, 64.32; H, 7.50; N, 4.22.

Determination of Enantiomeric Excess for Amino Esters 3. Typical procedure. Amino ester 3c (10 mg, 0.036 mmol) in THF (1.0 mL) was added dropwise to a solution of LiAlH₄ (4.0 mg, 0.11 mmol) in THF (1.0 mL) at 0 °C, and the mixture was stirred for 0.5 h. The reaction was quenched by addition of water and the organic layer was extracted with ethyl acetate. The extract was washed with brine and dried (magnesium sulfate). Upon removal of the solvent, to the residue (crude amino alcohol 6c) in benzene (1.0 mL) was directly added (S)-(-)-MTPA-Cl (14 mg, 0.055 mmol) and pyridine (14 mg, 0.18 mmol). Usual workup followed by ¹⁹F NMR analysis of the resulting MTPA ester. ¹⁹F NMR spectrum of the MTPA ester showed two doublets for CF₃ at δ 87.52 (d, J = 5.9 Hz) [(R), 81.5%] and 87.67 ppm (d, J = 5.9 Hz) [(S), 18.5%).Enantiomeric excess of other amino esters were determined by a similar method and the ¹⁹F NMR spectral data are shown in the following: **3d**: δ 87.49 (d, J = 6.2 Hz) [(R), 81.5%], 87.67 (d, J = 6.6**3e**: δ 87.54 (d, J = 6.6 Hz) [(R), 81%], 87.72 (d, J = 7.0 Hz) [(S), 19%]; **3f**: δ Hz) [(S), 18.5%]; 87.55 (d, J = 6.8 Hz) [(R), 81.5%], 87.74 (d, J = 6.9 Hz) [(S), 18.5%]; 3h: δ 87.55 (d, J = 6.8 Hz) [(R), 81%], 87.74 (d, J = 6.9 Hz) [(S), 19%]; 3i: δ 87.55 (d, J = 6.8 Hz) [(R), 85.5%], 87.74 (d, J = 6.9 Hz) **3** j: δ 87.54 (d, J = 6.6 Hz) [(R), 84%], 87.72 (d, J = 7.0 Hz) [(S), 16%]; **3** k: δ 87.54 (d, [(S), 14.5%];J = 6.6 Hz [(R), 84%], 87.72 (d, J = 7.0 Hz) [(S), 16%].

(R)-(+)-Benzyl 2-Amino-3,3,3-trifluoropropanoate 7. A solution of (R)-3h (0.2 g, 0.58 mmol) in CH₃CN (20 mL) was added to cerium ammonium nitrate (0.96 g, 1.76 mmol) in water (6.8 mL) at 0 $^{\circ}$ C over a period of 10 minutes and the whole was stirred for additional 2 h. After addition of water, the

mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. Concentration followed by purification through silica gel column chromatography with hexane-ethyl acetate (3 : 1) gave (R)-(+)-7 (0.12 g, 87% yield) as colorless oil: $[\alpha]_D^{23}$ + 4.81, (c 0.12, MeOH). IR (neat) 3432, 1752, 1616 cm⁻¹; ¹H NMR (CDCl₃) δ 1.90 (s, 2H, NH₂), 4.15 (q, J = 7.3 Hz, 1H, CH), 5.26 (s, 2H, CH₂), 7.37 (s, 5H, C₆H₅); ¹⁹F NMR (CDCl₃) δ 86.92 (d, J = 7.3 Hz, CF₃). Anal. Calcd for C₁₀H₁₀F₃NO₂: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.38; H, 4.79; N, 5.98.

Synthesis of Diastereomeric Mixture of Benzyl 2-(N-Camphorsulfonylamino)-3,3,3trifluoropropanoate 9a and 9b. To a solution of racemic 7 (0.1 g, 0.43 mmol) and (S)-(+)camphorsulfonyl chloride (0.32 g, 1.28 mmol) in benzene (2.0 mL) was added pyridine (0.34 g, 4.28 mmol) at room temperature. After the solution was stirred for 2 h, the reaction was quenched by addition of 10% aq. HCl and the organic layer was extracted with ethyl acetate. Usual workup followed by column chromatographic purification on silica gel (ethyl acetate : hexane = 1 : 3) gave a mixture of diastereomers 9a and 9b (1 : 1) which were separated by HPLC using LiChrosorb Si 60 (7 μ m) (ethyl acetate : hexane = 1 : 5; Flow rate = 2.0 ml / min) gave optically pure (R, S)-9a (white crystal) (48 min) and (S, S)-9b (oily) (44 min).

Compound (*R*,*S*)-(+)-**9a**: mp: 101-101.5 °C; $[\alpha]_D^{23}$ +6.04 (*c* 0.79, CHCl₃); IR (CH₂Cl₂) 1752, 1738 cm⁻¹; ¹H NMR (CDCl₃) δ 0.86 (s, 3H, CH₃), 0.98 (s, 3H, CH₃), 1.23-2.52 (m, 7H, H_{camphor}), 3.02, 3.43 (AB, *J* = 14.2 Hz, 2H, CH₂), 4.78-4.95 (m, 1H, CH), 5.30 (s, 2H, CH₂), 6.99 (d, *J* = 9.14 Hz, 1H, NH), 7.34 (s, 5H, C₆H₅); ¹⁹F NMR (CDCl₃) δ 89.77 (d, *J* = 7.3 Hz, CF₃). Anal. Calcd for C₂₀H₂₄F₃NO₅S: C, 53.68; H, 5.41; N, 3.13. Found: C, 53.34; H, 5.56; N, 3.36.

Compound (S, S)-(-)-**9b**: $[\alpha]_D^{23}$ -6.01 (*c* 0.94, CHCl₃); IR (CH₂Cl₂) 3284, 1752, 1738 cm⁻¹; ¹H NMR (CDCl₃) δ 0.90 (s, 3H, CH₃), 1.02 (s, 3H, CH₃), 1.24-2.54 (m, 7H, H_{camphor}), 3.08, 3.50 (AB, *J* = 14.2 Hz, 2H, CH₂), 4.82-4.99 (m, 1H, CH), 5.30 (s, 2H, CH₂), 6.53 (d, *J* = 9.14 Hz, 1H, NH), 7.37 (s, 5H, C₆H₅); ¹⁹F NMR (CDCl₃) δ 89.66 (d, *J* = 7.0 Hz, CF₃). Anal. Calcd for C₂₀H₂₄F₃NO₅S: C, 53.68; H, 5.41; N, 3.13. Found: C, 53.52; H, 5.58; N, 3.40.

(R)-(+)-3,3,3-Trifluoroalanine 1: To a suspension of 5% Pd / C (0.05 g, 0.02 mmol) in methanol (2 mL) was added (R)-7 (0.1 g, 0.43 mmol) in methanol. The mixture was stirred under an atmosphere of hydrogen for 1 h and passed through florisil column. The filtrate was evaporated to give a white crystal (R)-(+)-1 (0.06 g, 90% yield), $[\alpha]_D^{23}$ + 6.89 (c 0.76, MeOH), (decomp. above 210 °C): ¹H NMR (D₂O) δ 4.47 (q, J = 8.3 Hz, 1H, CF₃CH), 4.75 (s, 3H, NH₃+); ¹⁹F NMR (D₂O) δ 91.32 (d, J = 8.5 Hz, CF₃). Anal. Calcd for C₃H₄F₃NO₂: C, 25.19; H, 2.82; N, 9.79. Found: C, 25.37; H, 2.97; N, 9.72. Attempts for raising the % ee by recrystallization from several solvent system were unsuccessful.

The optical purity (62% ee) was determined by HPLC analysis using SUMICHIRAL OA-5000 (1 mM aqueous CuSO₄; Flow rate = 1.0 mL / min; UV Detector 254 nm), which showed a couple of peaks at 12.0 min (81%) and 24.0 min (19%).

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