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

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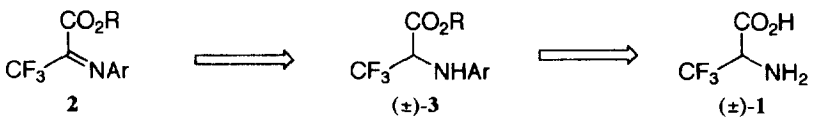
Abstract: Enantiomerically enriched 3,3,3-trifluoroalanine (1) (up to 62 % ee) has been synthesized by the asymmetric reduction of 2-(*N*-arylimino)-3,3,3-trifluoropropanoic acid esters with a chiral oxazaborolidine catalyst and subsequent oxidative removal of *N*-aromatic moiety with retention of the 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 (Me_3SiCN) to *N*-[(*S*)-α-phenylethyl]-2,2,2-trifluoroacetaldimine, but with only 33 % de. Recently, a review by Kukhar[5] 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)-3,3,3-trifluoropropanoic 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**.



Scheme 1

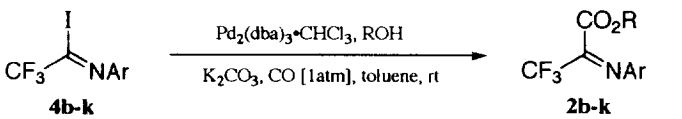
Meanwhile, asymmetric reduction of imine function to chiral amine is still a challenging subject to solve. Although wide range of studies have been devoted,[7] generally applicable methodologies have not been established. Especially, no enantioselective reduction of imines bearing two such highly electron-withdrawing groups (CO_2R and CF_3) 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-$BHlid_3 \cdot THF$,[11] dialkoxyboranes,[12] and $NaBH_4$-$ZrCl_4$-chiral amino alcohols[13] have been used for reduction of imines and oximes. The ee value of the resulting amine of up to 90% ee was achieved in 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 $BH_3 \cdot SMe_2$, the best ee was up to 72%. Here, we examined the applicability of some reduction systems to our substrates **2** and present a full account of our studies of this reduction for the enantioselective synthesis of chiral 3,3,3-trifluoroalanine.[15] A detailed X-ray analysis for determination of the absolute configuration of 3,3,3-trifluoroalanine **1** was also described.

Results and discussion

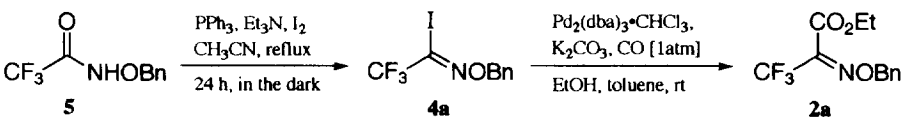
As summarized in Scheme 2, imino esters **2b-k** were prepared here by the previously reported method from our group.[6] In addition, oxime ether **2a** could be readily prepared in 77% yield in a similar way through carbonylation of iodide **4a** which derived from *N*-(benzyloxy)-2,2,2-trifluoroacetamide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



4b-k **2b-k**

b	R = Et, Ar = 2,6-$Me_2C_6H_3$	**g**	R = Et, Ar = *p*-$Me_2NC_6H_4$
c	R = Et, Ar = *m*-ClC_6H_4	**h**	R = Bn, Ar = *p*-$MeOC_6H_4$
d	R = Et, Ar = C_6H_5	**i**	R = (*L*)-menthyl, Ar = *p*-$MeOC_6H_4$
e	R = Et, Ar = *p*-MeC_6H_4	**j**	R = Bn, Ar = *p*-MeC_6H_4
f	R = Et, Ar = *p*-$MeOC_6H_4$	**k**	R = (*L*)-menthyl, Ar = *p*-MeC_6H_4

Scheme 2



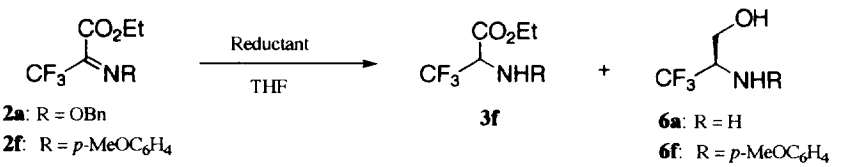
5 **4a** **2a**

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**[11d]), 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). BH_3·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**



2a: R = OBn
2f: R = *p*-$MeOC_6H_4$

3f

6a: R = H
6f: R = *p*-$MeOC_6H_4$

entry	substrate	reductant	temp. (°C)		yield (%)	ee (%)[a] (config.)		yield (%)	ee (%)[a] (config.)
1	**2a**	**A**	rt	-	0	-	**6a**	94	-
2	**2f**	**A**	rt	**3f**	0	-	**6f**	95	14 (*R*)
3	**2f**	**B**	-78~rt	**3f**	40	32 (*S*)	**6f**	56	46 (*R*)
4	**2f**	**C**	-78~rt	**3f**	42	28 (*S*)	**6f**	49	45 (*R*)
5	**2f**	**D**	-78~rt	**3f**	38	14 (*S*)	**6f**	45	11 (*R*)
6[b]	**2f**	**E**[c]	rt	**3f**	93	63 (*R*)	**6f**	-	-

[a] Determined by ^{19}F NMR of the MTPA ester of the corresponding amino alcohol. [b] The reduction was in CH_2Cl_2. [c] Catalytic amount of ligand was used (10 mol %).

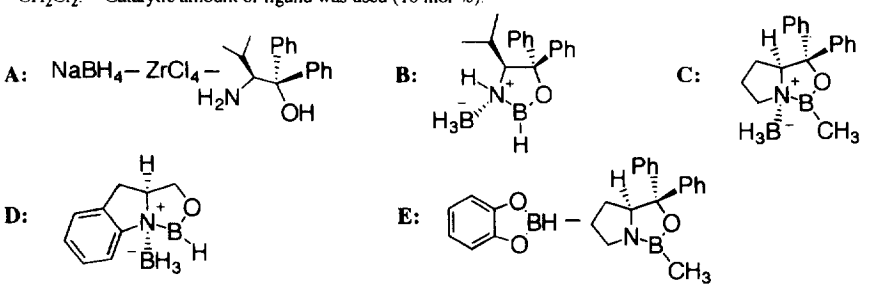


Table 2 shows a remarkable effect of the reaction temperature on enantioselectivity. The reduction of **2f** in CH_2Cl_2 was conducted at temperature ranging from -20 °C to 40 °C. The lower temperatures induced unexpectedly poor enantioselectivity, although Corey reported that the catecholborane procedure 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 CH_2Cl_2 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

reductant may occur suitably at around 25 °C.

Table 2: Temperature Effect on the Reduction of **2f** with Reductant **E**. [a]

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

[a] CH_2Cl_2 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 $CHCl_3$ 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 ee are 85% and 55%, respectively (entry 5 in Table 3). In particular, addition of 4Å molecular sieves markedly affected on the selectivity (63% ee in entry 6). Recently, it has been reported that trace of water in the reaction media lowers the ee from 95% to 50%.[19] The molecular sieves would be meaningful as a desiccant in this reduction system.

Table 3: Effect of Solvents on the Asymmetric Reduction of **2f** with the Reductant **E**.[a]

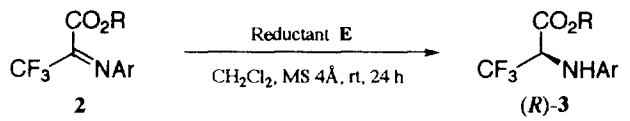
entry	solvent	time (h)	yield of **3f** (%)	ee (%)
1	Hexane	72	12[b]	-
2	Toluene	28	89	43
3	Benzene	28	84	43
4[c]	THF	18	72	40
5	CH_2Cl_2	24	85	55
6[d]	CH_2Cl_2	20	93	63
7[c]	$CHCl_3$	20	70	15

[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*-NMe_2 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).

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



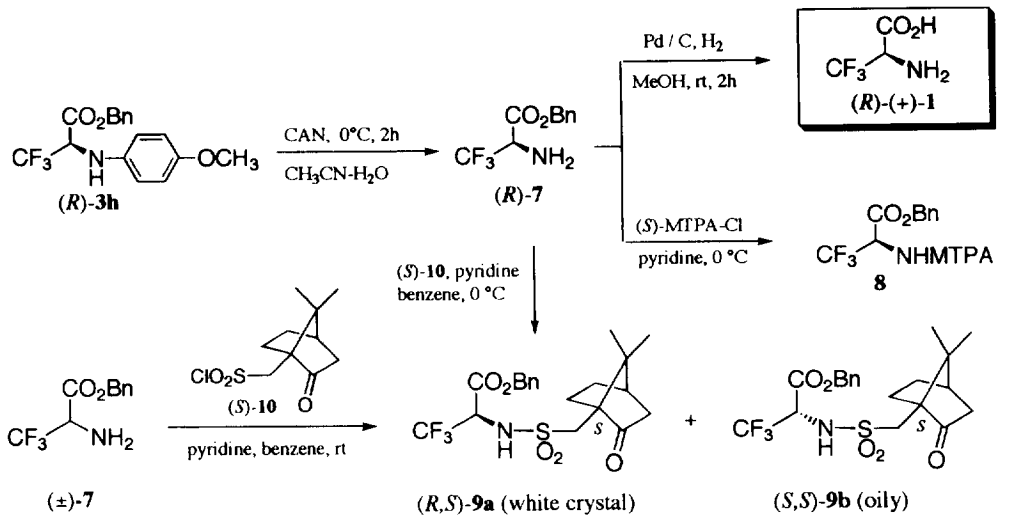
2 (*R*)-**3**

entry		R	Ar	yield of **3** (%)	ee (%)[a]	config.
1	**2a**	Et	BnO	0	-	
2	**2b**	Et	2,6-$Me_2C_6H_3$	0	-	
3	**2c**	Et	*m*-ClC_6H_4	94	63	*R*-(-)[b]
4	**2d**	Et	C_6H_5	93	61	*R*-(-)[b]
5	**2e**	Et	*p*-MeC_6H_4	90	62	*R*-(+)[b]
6	**2f**	Et	*p*-$MeOC_6H_4$	93	63	*R*-(-)[b]
7	**2g**	Et	*p*-$Me_2NC_6H_4$	0	-	
8	**2h**	Bn	*p*-$MeOC_6H_4$	91	62	*R*-(-)
9	**2i**	(*L*)-menthyl	*p*-$MeOC_6H_4$	>85	71[c]	*R*-(-)[b]
10	**2j**	Bn	*p*-MeC_6H_4	95	68	*R*-(+)[b]
11	**2k**	(*L*)-menthyl	*p*-MeC_6H_4	>85	68[c]	*R*-(+)[b]

[a] Determined by ^{19}F NMR of the MTPA ester of the corresponding amino alcohol ($LiAlH_4$). [b] Absolute configuration was assigned by comparison of ^{19}F NMR chemical shift of the MTPA esters of the corresponding amino alcohols. [c] Diastereomeric excess (de)

Further conversion to free 3,3,3-trifluoroalanine **1** was then accomplished. The amino ester **3j** (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 *p*-methylphenyl moiety from **3j** to optically pure **1** was unsuccessful. The removal of the *p*-methoxyphenyl moiety from (*R*)-**3h** (R = Bn, Ar = *p*-$MeOC_6H_4$) by treatment with cerium (IV) diammonium nitrate at 0 °C in CH_3CN-H_2O[21] 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 CF_3 on the MTPA part. A simple treatment of (*R*)-**7** with Pd / C catalyst under hydrogen atmosphere led to (*R*)-(+)-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.

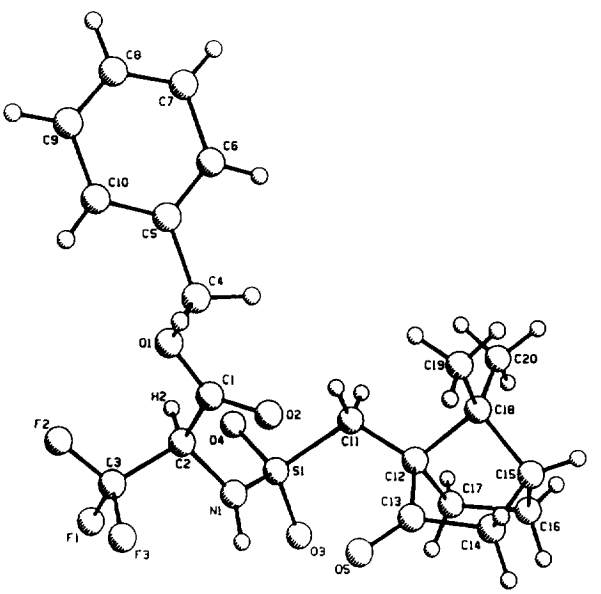


Figure 1. X-Ray Crystallographic Data of (*R*,*S*)-**9a**.

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 ^{19}F or ^{1}H 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. ^{1}H (200 MHz), and ^{19}F (188 MHz) NMR spectra were recorded by Varian VXR 200 NMR apparatus in $CDCl_3$ or D_2O as indicated and the chemical shifts are reported in δ (ppm) values downfield from TMS (^{1}H NMR) or C_6F_6 (^{19}F 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 (CH_2Cl_2) and chloroform ($CHCl_3$) were distilled from CaH_2. Catecholborane was distilled under reduced pressure (70 °C / 100 mmHg) and stored as 2 M CH_2Cl_2 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}; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, *J* = 7.2 Hz, 3H, CH_3), 4.22 (q, *J* = 7.2 Hz, 2H, CH_2), 6.79-6.98 (m, 2H, H_{arom}), 7.19-7.35 (m, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 91.87 (s, CF_3). Anal. Calcd for $C_{11}H_9ClF_3NO_2$: 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}; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, *J* = 7.1 Hz, 6H, CH_3), 1.27 (t, *J* = 7.1 Hz, 3H, CH_3), 3.38 (q, *J* = 7.0 Hz, 4H, CH_2), 4.33 (q, *J* = 7.0 Hz, 2H, CH_2), 6.60 (d, *J* = 8.9 Hz, 2H, H_{arom}), 7.08 (d, *J* = 8.9 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 92.05 (s, CF_3). Anal. Calcd for $C_{15}H_{19}F_3N_2O_2$: 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}; ^{1}H NMR ($CDCl_3$) δ 0.62 (t, *J* = 6.9 Hz, 3H, CH_3), 0.78 (t, *J* = 7.0 Hz, 3H, CH_3), 0.88 (t, *J* = 6.2 Hz, 3H, CH_3), 0.70-1.97 (m, 9H, $H_{menthyl}$), 3.82 (s, 3H, OCH_3), 4.76 (td, *J* = 7.1 Hz, *J* = 4.4 Hz, 1H, OCH), 6.88 (d, *J* = 9.1 Hz, 2H, H_{arom}), 7.01 (d, *J* = 8.8 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 92.15 (s,

CF_3). Anal. Calcd for $C_{20}H_{26}F_3NO_3$: 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 ($CDCl_3$) δ 0.58 (t, J = 6.7 Hz, 3H, CH_3), 0.75 (t, J = 6.8 Hz, 3H, CH_3), 0.86 (t, J = 6.5 Hz, 3H, CH_3), 0.75-1.90 (m, 9H, $H_{menthyl}$), 2.35 (s, 3H, CH_3), 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}); ^{19}F NMR ($CDCl_3$) δ 91.97 (s, CF_3). Anal. Calcd for $C_{20}H_{26}F_3NO_2$: 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 PPh_3 (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 Et_3N (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 ($CDCl_3$) δ 5.41 (s, 2H, CH_2), 7.38 (s, 5H, C_6H_5); ^{19}F ($CDCl_3$) δ 96.21 (s, CF_3). Anal. Calcd for $C_9H_7F_3INO$: 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 K_2CO_3 (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 ($CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H, CH_3), 4.36 (q, J = 7.1 Hz, 2H, CH_2), 5.30 (s, 2H, CH_2), 7.36 (s, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 95.96 (s, CF_3). Anal. Calcd for $C_{12}H_{12}F_3NO_3$: 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 $NaBH_4$ (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 ($CDCl_3$) δ 2.09 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 4.16-4.49 (m, 2H, CH_2), 4.82-5.29 (m, 1H, CH), 5.89-5.99 (br, 1H, NH); ^{19}F NMR ($CDCl_3$) δ 87.84 (d, J = 7.6 Hz, CF_3).

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 × 5 mL). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica gel afforded amino ester **3f** (40 mg, 40% yield) and amino alcohol **6f** (47.8 mg, 56% yield) as colorless oils.

Ethyl 2-[*N*-(*p*-Anisyl)]-3,3,3-trifluoropropanoate 3f: 32% ee, $[\alpha]_D^{23}$ -11.4 (*c* 0.12, $CHCl_3$); IR (neat) 3396, 1748, 1518, 824 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.19-4.40 (m, 2H, OCH_2), 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}); ^{19}F NMR ($CDCl_3$) δ 89.06 (d, *J* = 6.4 Hz, CF_3). Anal. Calcd for $C_{12}H_{14}F_3NO_3$: 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 ($CDCl_3$) δ 3.76 (s, 3H, OCH_3), 3.79-3.97(m, 3H, $CHCH_2$), 6.71 (d, *J* = 9.2 Hz, 2H, H_{arom}), 6.81 (d, *J* = 9.0 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 88.08 (d, *J* = 6.1 Hz, CF_3). Anal. Calcd for $C_{10}H_{12}F_3NO_2$: 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 CH_2Cl_2 (1 mL) at room temperature was added catecholborane (2 M in CH_2Cl_2, 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, $CHCl_3$); IR (neat) 3412, 1748, 1604, 854, 770, 682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (t, *J* = 7.0 Hz, 3H, CH_3), 4.22-4.45 (m, 2H, CH_2), 4.51-4.71 (m, 2H, CHNH), 6.56-6.88 (m, 3H, H_{arom}), 7.08-7.18 (m, 1H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 89.23 (d, *J* = 7.0 Hz, CF_3). Anal. Calcd for $C_{11}H_{11}ClF_3NO_2$: 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, $CHCl_3$); IR (neat) 3416, 1750, 1608, 750, 682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3H, CH_3), 4.20-4.43 (m, 2H, CH_2), 4.49-4.68 (m, 2H, CHNH), 6.68-6.90 (m, 3H, H_{arom}), 7.17-7.27 (m, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 89.10 (d, *J* = 5.8 Hz, CF_3). Anal. Calcd for $C_{11}H_{12}F_3NO_2$: 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, $CHCl_3$); IR (neat) 3412, 1750, 1622, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, *J* = 7.2 Hz, 3H, CH_3), 4.18-4.38 (m, 2H, CH_2), 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}); ^{19}F NMR ($CDCl_3$) δ 89.11 (d, *J* = 6.8 Hz, CF_3). Anal. Calcd for $C_{12}H_{14}F_3NO_2$: 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, $CHCl_3$); IR (neat) 3400, 1748, 1598, 822, 748, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (s, 3H, OCH_3), 4.23 (d,

J = 9.3 Hz, 1H, NH), 4.36-4.53 (m, 1H, CH), 5.18 (s, 2H, CH_2), 6.61 (d, J = 9.1 Hz, 2H, H_{arom}), 6.72 (d, J = 9.2 Hz, 2H, H_{arom}) 7.28 (m, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 89.22 (d, J = 6.8 Hz, CF_3). Anal. Calcd for $C_{17}H_{16}F_3NO_3$: C, 60.18; H, 4.75; N, 4.13. Found: C, 59.80; H, 5.09; N, 4.08.

(*R*)-(-)-(*L*)-Menthyl 2-[*N*-(*p*-Anisyl)]-3,3,3-trifluoropropanoate 3i: 71% ee; $[\alpha]_D^{23}$ -78.90 (*c* 0.10, $CHCl_3$); IR (neat) 3400, 1742, 1518, 822 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (t, J = 7.0 Hz, 3H, CH_3), 0.85 (t, J = 7.0 Hz, 3H, CH_3), 0.91 (t, J = 6.5 Hz, 3H, CH_3), 0.74-2.05 (m, 9H, $H_{menthyl}$), 3.76 (s, 3H, OCH_3), 4.44 (q, J = 6,8 Hz, 1H, $CHCF_3$), 4.80 (td, J = 11.0 Hz, J = 4.5 Hz, 1H, CH), 6.70 (d, J = 9.2 Hz, 2H, H_{arom}), 6.81 (d, J = 9.2 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 89.23 (d, J = 6.8 Hz, CF_3). Anal. Calcd for $C_{20}H_{28}F_3NO_3$: 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, $CHCl_3$); IR (neat) 3400, 1738, 1622, 810, 726, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H, CH_3), 4.39 (br, 1H, NH), 4.52-4.65 (m, 1H, $CHCF_3$), 5.26 (s, 2H, CH_2),), 6.63 (d, J = 8.4 Hz, 2H, H_{arom}), 6.72 (d, J = 8.1 Hz, 2H, H_{arom}) 7.35 (s, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 89.11 (d, J = 6.8 Hz, CF_3). Anal. Calcd for $C_{17}H_{16}F_3NO_2$: 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, $CHCl_3$); IR (neat) 3412, 1748, 1604, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (t, J = 6.9 Hz, 3H, CH_3), 0.86 (t, J = 7.0 Hz, 3H, CH_3), 0.91 (t, J = 6.6 Hz, 3H, CH_3), 0.80-2.05 (m, 9H, $H_{menthyl}$), 2.26 (s, 3H, CH_3), 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}); ^{19}F NMR ($CDCl_3$) δ 89.31 (d, J = 6.2 Hz, CF_3). Anal. Calcd for $C_{20}H_{28}F_3NO_2$: 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 $LiAlH_4$ (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 ^{19}F NMR analysis of the resulting MTPA ester. ^{19}F NMR spectrum of the MTPA ester showed two doublets for CF_3 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 ^{19}F 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 Hz) [(*S*), 18.5%]; **3e**: δ 87.54 (d, J = 6.6 Hz) [(*R*), 81%], 87.72 (d, J = 7.0 Hz) [(*S*), 19%]; **3f**: δ 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) [(*S*), 14.5 %]; **3j**: δ 87.54 (d, J = 6.6 Hz) [(*R*), 84%], 87.72 (d, J = 7.0 Hz) [(*S*), 16%]; **3k**: δ 87.54 (d, 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 CH_3CN (20 mL) was added to cerium ammonium nitrate (0.96 g, 1.76 mmol) in water (6.8 mL) at 0 °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 ($CDCl_3$) δ 1.90 (s, 2H, NH_2), 4.15 (q, *J* = 7.3 Hz, 1H, CH), 5.26 (s, 2H, CH_2), 7.37 (s, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 86.92 (d, *J* = 7.3 Hz, CF_3). Anal. Calcd for $C_{10}H_{10}F_3NO_2$: 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)-3,3,3-trifluoropropanoate 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 μm) (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, $CHCl_3$); IR (CH_2Cl_2) 1752, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.23-2.52 (m, 7H, $H_{camphor}$), 3.02, 3.43 (AB, *J* = 14.2 Hz, 2H, CH_2), 4.78-4.95 (m, 1H, CH), 5.30 (s, 2H, CH_2), 6.99 (d, *J* = 9.14 Hz, 1H, NH), 7.34 (s, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 89.77 (d, *J* = 7.3 Hz, CF_3). Anal. Calcd for $C_{20}H_{24}F_3NO_5S$: 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, $CHCl_3$); IR (CH_2Cl_2) 3284, 1752, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.24-2.54 (m, 7H, $H_{camphor}$), 3.08, 3.50 (AB, *J* = 14.2 Hz, 2H, CH_2), 4.82-4.99 (m, 1H, CH), 5.30 (s, 2H, CH_2), 6.53 (d, *J* = 9.14 Hz, 1H, NH), 7.37 (s, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 89.66 (d, *J* = 7.0 Hz, CF_3). Anal. Calcd for $C_{20}H_{24}F_3NO_5S$: 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 (D_2O) δ 4.47 (q, *J* = 8.3 Hz, 1H, CF_3CH), 4.75 (s, 3H, NH_3^+); ^{19}F NMR (D_2O) δ 91.32 (d, *J* = 8.5 Hz, CF_3). Anal. Calcd for $C_3H_4F_3NO_2$: 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 $CuSO_4$; 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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