(s, 3 H, C-2 CH_3); MS, m/z 208 (M^+), 164 (M – 44), 98 (base), 69.

Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.98; H, 8.03.

Acid 13: IR (film) 3400 (br), 2950, 1720, 1050, 890 cm^{-1}; ^1H NMR, δ 5.23 (s, D_2O exchangeable, 1 H, COOH), 4.87 (s, 2 H, vinyl H), 4.0 (d of d, J_{AX} = 5 Hz, J_{BX} = 10 Hz, 1 H, -CH_2CHOH-), 3.0–2.0 (m, 7 H), 1.78 (s, 3 H, vinyl CH_3), 1.18 (s, 3 H, C-2 CH_3).

Acid 14: IR (film) 3400 (br), 2950, 1720, 1050, 890 cm^{-1}; ^1H NMR, δ 5.38 (br s, D_2O exchangeable 1 H, COOH), 4.81 (d, 2 H, vinyl H), 4.17 (t, J = 6 Hz, 1 H, -CH_2CHOH-), 3.0–2.0 (m, 7 H), 1.80 (s, 3 H, vinyl CH_3), 1.23 (s, 3 H, C-2 CH_3).

Lactone 15. Acid **13** (0.056 g, 0.25 mM) was dissolved in dioxane (8 mL). Dicyclohexylcarbodiimide (0.049 g, 0.24 mM) was added, and the reaction was stirred at 25 °C for 66 h during which time a white precipitate (dicyclohexylurea) formed. The precipitate was filtered, and the resultant dioxane solution was concentrated to give an oil. The oil was dissolved in acetone (4 mL) and filtered through a short silica gel column. The acetone solution was then dried (Na_2SO_4) and concentrated in vacuo to give an oil (0.040 g). Pure **15** (0.0167 g) was isolated as an oil by preparative TLC on silica gel with ethyl acetate/hexane (1:3) as the eluent: IR ($CHCl_3$) 3000, 1795, 1730, 1190, 910 cm^{-1}; ^1H NMR, δ 4.87 (s, 2 H, vinyl H), 4.0 (d of d, J_{AX} = 5 Hz, J_{BX} = 11 Hz, 1 H, -CHO-), 3.0–2.0 (m, 7 H), 1.81 (s, 3 H, vinyl CH_3), 1.32 (s, 3 H, C-2 CH_3); MS, m/z 208 (M^+), 164 (M – 44), 98, 69 (base).

Keto Ester 16. Acid **13** (0.0161 g, 0.06 mM) was dissolved in ether (5 mL) and cooled to 0 °C. A solution of diazomethane (ca. 0.6 mM) in ether (7 mL) was added and stirred for 2 h as the temperature gradually warmed to 25 °C. The solvent was removed in vacuo to afford **16** (0.0198 g) as an oil. TLC (ethyl acetate/hexane 1:4) showed one spot, R_f 0.28. GC (3% Carbowax 20M, 185 °C) showed one peak with a retention time (flow rate ca. 30 cc/min) of 8 min 50 s: IR ($CHCl_3$) 3000, 1740, 1710, 900 cm^{-1}; ^1H NMR, δ 4.75 (s, 2 H, vinyl H), 4.27 (d of d, J_{AX} = 5 Hz, J_{BX} = 9 Hz, 1 H, -CHOH-), 3.65 (s, 3 H, -OCH_3), 3.0–2.0 (m, 7 H), 1.77 (br s, 3 H, vinyl CH_3), 1.17 (s, 3 H, C-2 CH_3).

Keto Ester 17. The same procedure as for **16** was used. Acid **14** (0.0309 g, 0.13 mM) afforded ester **17** (0.028 g) as an oil. TLC (ethyl acetate/hexane (1:4) showed one spot, R_f 0.20. GC (3% Carbowax 20M, 195 °C) showed one peak with a retention time (flow rate ca. 30 cc/min) of 11 min 10 s. A sample of **10** showed identical TLC and GC and spectral properties.

1α,4aβ-Dimethyl-1β,10aβ-epoxy-1,4,4a,9,10,10a-hexahydro-2(3*H*)-phenanthrone (19a) and 1β,4aβ-Dimethyl-1α,10aα-epoxy-1,4,4a,9,10,10a-hexahydro-2(3*H*)-phenathrone (19b). A modification of the method of Plattner[15] was used. Ketone **18**[14b] (4.82 g, 21.3 mM) was dissolved in methanol (450 mL) along with 4 N NaOH (20 mL). Hydrogen peroxide (37 mL of 30% aqueous) was added, and the reaction mixture was stirred at 30–33 °C for 24 h and then at 25 °C for 4 h until the IR of an aliquot showed no more unsaturated carbonyl. The reaction mixture was extracted with hexane (4 × 100 mL). The methanol phase was concentrated to ca. 100 mL and extracted with hexane (4 × 50 mL). All the hexane layers were combined, dried (Na_2SO_4), and concentrated to give a pale yellow solid (4.24 g, 83%) which GC analysis (10 ft 6% SE-30 240 °C) showed to be a mixture of **19a** (38%), **19b** (59%), and **18** (3%) at 7:00, 7:25, and 8:15, respectively. The yellow solid was recrystallized 2× from methanol to afford pure **19b**: mp 116 °C; IR (KBr) 2980, 2940, 1705, 780 cm^{-1}; ^1H NMR, δ 7.3–7.0 (m, 4 H, Ar), 3.3–1.7 (m, 8 H), 1.48 (s, 3 H, C-1α CH_3), 1.30 (s, 3 H, C-4aβ CH_3); MS, m/z 242 (M^+), 224, 157 (base).

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.29; H, 7.49. Found: C, 79.49; H, 7.60.

Pure **19a** could be obtained by pressure-assisted column chromatography of the mother liquor from above with ethyl acetate (0–5%)/hexane (100–95%) as the eluent: mp 81–82 °C; IR (KBr) 2980, 2940, 1705, 780 cm^{-1}; ^1H NMR, δ 7.3–7.0 (m, 4 H, Ar), 3.0–1.7 (m, 8 H), 1.5 (s, 3 H, C-4aβ CH_3), 1.45 (s, 3 H, C-1α CH_3); MS, m/z 242 (M^+), 224, 157 (base).

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.29; H, 7.49. Found: C, 79.58; H, 7.38.

Registry No. 1, 6485-40-1; **2a**, 36616-60-1; **2b**, 18383-49-8; **3**, 97643-04-4; **4**, 97643-05-5; **5a**, 97570-23-5; **5b**, 97570-28-0; **6**, 69153-92-0; **7a**, 74290-94-1; **7b**, 97643-06-6; **10**, 97570-24-6; **11**, 97570-25-7; **12**, 88580-84-1; **13**, 97591-81-6; **14**, 97591-82-7; **15**, 97570-26-8; **16**, 97591-83-8; **17**, 97570-24-6; (±)-**18**, 97643-07-7; (±)-**19a**, 97570-27-9; (±)-**19b**, 97643-08-8; CD_3I, 865-50-9; $BrCH_2CO_2CH_3$, 96-32-2.

N-(Trifluoroacetyl)-α-amino Acid Chlorides as Chiral Reagents for Friedel–Crafts Synthesis

J. Eric Nordlander,*[1] F. George Njoroge, Mark J. Payne, and Dhiraj Warman

Departments of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106, and Cleveland State University, Cleveland, Ohio 44115

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Chiral *N*-(trifluoroacetyl)-α-amino acid chlorides undergo Friedel–Crafts reaction with benzene and 1,2-dimethoxybenzene under mild conditions commonly with complete (>99%) preservation of configurational identity. The resultant (trifluoroacetyl)amino ketones may be deoxygenated with Et_3SiH or H_2/Pd–C in acidic media to the corresponding *N*-(trifluoroacetyl)-β-arylalkylamines likewise without loss of configurational purity.

Recently we described the advantageous use of achiral and racemic *N*-(trifluoroacetyl)-α-amino acid chlorides in Friedel–Crafts acylations of benzene, anisole, and veratrole.[2] The resultant ketones could be reduced conveniently to the corresponding *N*-(trifluoroacetyl)-β-hydroxy-β-arylalkylamines or *N*-(trifluoroacetyl)-β-arylalkylamines.[2] Here we report that representative chiral *N*-(trifluoroacetyl)-α-amino acid chlorides can be converted in this manner to aryl α-[(trifluoroacetyl)amino]alkyl ketones and *N*-(trifluoroacetyl)-β-arylalkylamines with complete (>99%) preservation of configurational identity.

Results

Friedel–Crafts Acylations and Configurational Analysis of *N*-(Trifluoroacetyl)amino Ketones. L-

(1) Current address: Department of Chemistry, Cleveland State University, Cleveland, OH 44115.
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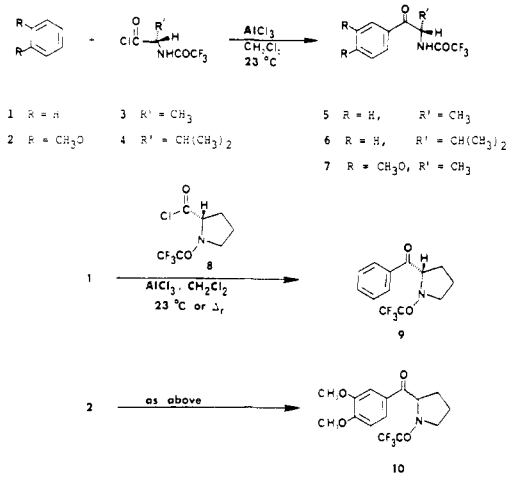
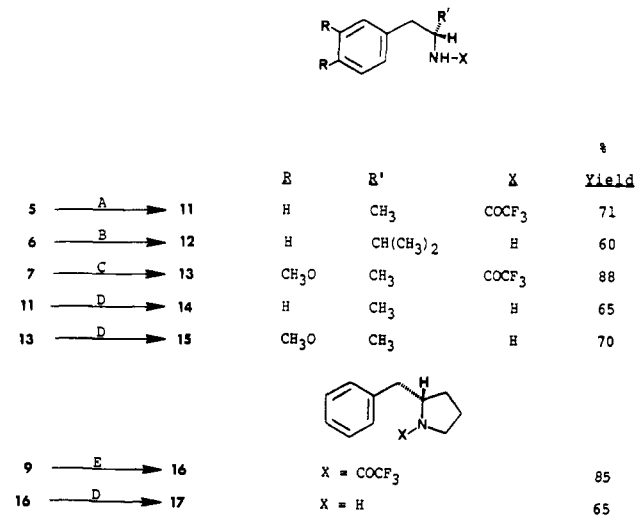
0022-3263/85/1950-3481$01.50/0

Scheme I. Friedel-Crafts Acylations



Scheme II. Ketone Deoxygenations and Amide Hydrolyses[a]



		R	R'	X	% Yield
5	A → 11	H	CH_3	$COCF_3$	71
6	B → 12	H	$CH(CH_3)_2$	H	60
7	C → 13	CH_3O	CH_3	$COCF_3$	88
11	D → 14	H	CH_3	H	65
13	D → 15	CH_3O	CH_3	H	70
9	E → 16			$X = COCF_3$	85
16	D → 17			X = H	65

[a] Reagents: (A) H_2/Pd-C, CF_3CO_2H; (B) (i) $NaBH_4$, EtOH (96%), (ii) PBr_5, dioxane, then H_2/Pd-C, EtOH (62%); (C) Et_3SiH, CF_3CO_2H; (D) K_2CO_3, MeOH, H_2O; (E) H_2/Pd-C, EtOH, Et_2O·HCl.

Alanine was *N*-trifluoroacetylated with ethyl trifluoroacetate in the presence of *N,N,N',N'*-tetramethylguanidine,[3] and the resultant amido acid was treated with oxalyl chloride[2] to generate the acid chloride **3** (Scheme I). Reaction of **3** in CH_2Cl_2 with a large excess of benzene (**1**) in the presence of 2.1 equiv of anhydrous $AlCl_3$ under dry N_2 with efficient stirring at 22 °C for 12 h produced after standard workup (*S*)-(trifluoroacetyl)amino ketone **5** in 68% yield. The configurational purity of the crude product was determined to be >99.7% from the 200-MHz ^1H NMR spectrum of its complex with chiral shift reagent Eu(hfbc)$_3$.[4] A single doublet was observed for the CH_3 protons, whereas the racemic ketone[2] under the same conditions gave rise to two separate CH_3 doublets. Control experiments showed that as little as 0.3% of the *R* enantiomer could have been detected in an admixture with **5**.

Likewise, *N*-(trifluoroacetyl)-L-valyl chloride (**4**) was reacted with benzene to give (*S*)-amido ketone **6** in 35% yield. NMR analysis again with Eu(hfbc)$_3$ showed the product to be ≥99.5% enantiomerically pure.

Acid chloride **3** was next used to acylate 1.1 equiv of veratrole (**2**) under catalysis by 1.1 equiv of $AlCl_3$.[5] (*S*)-(Trifluoroacetyl)amino ketone **7** was obtained in 32% yield. This product was shown to have high optical purity by configurational analysis after reduction (see below).

If the preceding acylations were conducted at reflux temperature, the respective ketones were obtained in approximately the same yields but were now wholly racemic.

N-(Trifluoroacetyl)-L-prolyl chloride (**8**) reacted with excess benzene and 2.1 equiv of $AlCl_3$ in CH_2Cl_2 at 23 °C to give the corresponding ketone **9** in 85% yield (Scheme I). High configurational purity was also demonstrated for this product following reduction (see below). The optical result in this case was unaffected by carrying out the acylation in boiling solvent. Reaction of **8** with 1.1 equiv of veratrole (**2**) and 1.1 equiv of $AlCl_3$ in CH_2Cl_2 at either 23 °C or reflux temperature gave only racemic ketone **10**,[2] in 55–65% yield. At 0 °C the product yield was no better than 8% after 24 h, and configurational analysis was not pursued.

Ketone Deoxygenations. Several methods were used to deoxygenate ketones **5–7** and **9** to the corresponding *N*-(trifluoroacetyl)-β-arylalkylamines, as outlined in Scheme II. The stereochemistries were determined after reduction or hydrolysis to the free amines. L-Alanine-derived ketone **5** was hydrogenolyzed over 10% palladium-on-carbon in trifluoroacetic acid in a Parr low-pressure shaking apparatus for 54 h to give the desired **11**.[2] At shorter reaction times the mixture was found to contain the intermediate alcohol and its corresponding ester, which were subsequently fully consumed.

Ketone **6** from L-valine was reduced in two steps with a procedure developed by Buckley and Rapoport.[6] After treatment with $NaBH_4$ in EtOH the resultant mixture of amino alcohols was converted to bromo amines by means of PBr_5, and debromination was then effected by catalytic hydrogenolysis, affording **12**.

Treatment of ketone **7** with Et_3SiH in CF_3CO_2H[7] resulted in smooth transformation to the methylene compound **13**.

Ketone **9** was readily deoxygenated to **16** by direct hydrogenolysis over 10% Pd–C in acidified ethanol.

Hydrolysis of Trifluoroacetamides and Configurational Analysis of β-Arylalkylamines. Trifluoroacetamides **11**, **13**, and **16** were hydrolyzed under mild basic conditions[2] to the corresponding amines **14**, **15**, and **17**, respectively (Scheme II).

For configurational analysis amines **12**, **14**, **15**, and **17** were converted to the carboxamides derived from (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid),[8] **18–21**, respectively. The 200-MHz ^1H NMR spectrum of amide **19** contained one sharp doublet for the CH_3 protons. In contrast, the CH_3 absorptions for the diastereomeric amides prepared from the corresponding racemic amine consisted of two adjacent doublets. A more precise analysis was obtained by HPLC of amide **19**. Only

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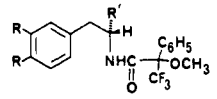

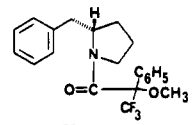

21

18 R = H, R' = $CH(CH_3)_2$

19 R = H, R' = CH_3

20 R = CH_3O, R' = CH_3

one peak was observed, whereas control experiments showed that as little as 2% of the other diastereomer could have been detected in admixture. Thus amine **14** was shown to be ≥98% enantiomerically pure.

The same methods applied to amides **18**, **20**, and **21** indicated the following enantiomeric purities for the precursor amines: **12**, 95%; **15**, ≥99%; **17**, ≥98%.

Discussion

N-Trifluoroacetylation allows the conversion sequence α-amino acid → acid chloride → aromatic α-amino ketone → β-arylalkylamine to be carried out in representative cases with essentially complete preservation of configuration at the original α-position. The present results cap a series of earlier efforts toward the same end[2,6,9] and open a new route to enantiospecific synthesis of a number of biologically interesting amines. This chemistry builds on an auspicious original reaction reported by Pines and coworkers.[10]

Our aromatic acylations with *N*-(trifluoroacetyl)amino acid chlorides[2] have produced a range of chemical yields (22–87%), typical of the Friedel–Crafts reaction in general.[11] We used $AlCl_3$ in the proportions optimized by Buckley and Rapoport.[5]

Among the ketone reduction methods we explored, one showed minor (5%) stereochemical leakage, the conversion of **6** to **12** (Scheme II) via the amino alcohol and amino bromide.[6] It would appear that the first-step reaction with $NaBH_4$ effects some enolization in competition with reduction.[12]

Under even strongly acidic conditions, however, the *N*-(trifluoroacetyl)-α-aminoacyl moiety typically maintains configurational integrity through aromatic acylation and deketonization. A single exception occurred here in the preparation of ketone **10**, the enolization of which is evidently particularly favored.

Experimental Section

General. Capillary melting points are uncorrected. Infrared spectra were obtained with a Beckman IR-8 or IR-10 spectrophotometer. ^1H NMR spectra were recorded at 60 MHz on a Varian EM-360A spectrometer and at 200 MHz on a Varian XL-200 Fourier-transform spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. High performance liquid chromatography utilized a Varian 8500 dual-pump system accompanied by a Varian Vari-Chrom detector. $Eu(hfbc)_3$ was purchased from Norell, Inc., and stored in a desiccator over P_2O_5. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

***N*-(Trifluoroacetyl)amino Acids and *N*-(Trifluoroacetyl)amino Acid Chlorides.** *N*-(Trifluoroacetyl)alanine, -valine, and -proline and their respective acid chlorides were prepared according to previously described methods.[2]

(*S*)-*N*-(Trifluoroacetyl)-α-aminopropiophenone (5). To a magnetically stirred solution of 4.0 g (21.6 mmol) of (*S*)-*N*-(trifluoroacetyl)alanine in 100 mL of CH_2Cl_2 under N_2 at 0 °C were added 4 drops of dry pyridine and 4 mL (5.82 g, 45.9 mmol) of oxalyl chloride (Aldrich) in one portion. The reaction mixture was allowed to warm to room temperature and stirred for an additional 2 h. After concentration of the mixture by rotary evaporation (temperature kept below 30 °C) the residue was diluted with 40 mL of CH_2Cl_2 and 250 mL of benzene and cooled to 0 °C. In one portion 5.8 g (4.35 mmol) of anhydrous $AlCl_3$ was added, and the mixture was stirred at room temperature for 12 h. The solution was quenched with 60 mL of cold 1 M HCl and diluted with 40 mL of cold water. The phases were separated, and the organic layer was washed successively with 2 × 40 mL of cold 1 M HCl, 60 mL of H_2O, and 2 × 40 mL of saturated $NaHCO_3$ solution. The organic phase was dried over $MgSO_4$ and concentrated by rotary evaporation to afford **5**, which was recrystallized from petroleum ether to yield 3.2 g (68%) of pure product:[2] mp 48–49 °C; IR and ^1H NMR spectral data for all racemic ketones can be found in ref 2. Proton NMR chiral shift analysis indicated the configurational purity to be >99.7% *S* (see text).

(*S*)-*N*-(Trifluoroacetyl)-α-aminoisovalerophenone (6). Following the procedure described for the preparation of **5** and substitution of (*S*)-*N*-(trifluoroacetyl)valine as the starting material, **6** was obtained in 35% yield. Recrystallization from hexanes gave pure **6**:[2] mp 86–88 °C. Chiral shift analysis again indicated the product to be >99.5% configurationally pure.

(*S*)-*N*-(Trifluoroacetyl)-α-amino-3′,4′-dimethoxypropiophenone (7). (*S*)-*N*-(Trifluoroacetyl)alanyl chloride, 1.1 equiv of veratrole, and 1.1 equiv of $AlCl_3$ were reacted at room temperature according to the procedure described for the preparation of **5** to afford, after recrystallization from hexane, pure **7**[2] in 32% yield: mp 89–90 °C.

(*S*)-[*N*-(Trifluoroacetyl)prolyl]benzene (9). (*S*)-*N*-(Trifluoroacetyl)prolyl chloride was reacted with benzene as for the preparation of **5** at both room temperature and under reflux. In both cases, **9**[2] was obtained in 85% yield after recrystallization from toluene/heptane: mp 102–104 °C.

(*S*)-[*N*-(Trifluoroacetyl)prolyl]-3,4-dimethoxybenzene (10). (*S*)-*N*-(Trifluoroacetyl)prolyl chloride (**8**) was reacted with veratrole following the procedure described for the preparation of **7** at 0 °C to give pure **10**[2] in 8% yield: mp 78–80 °C. However, when the reaction was carried out at either room temperature or at reflux, the product ketone had undergone complete racemization.

Racemic *N*-(trifluoroacetyl)-α-aminopropiophenone [(±)-5], *N*-(trifluoroacetyl)-α-aminoisovalerophenone [(±)-6], *N*-(trifluoroacetyl)-α-amino-3,4-dimethoxypropiophenone [(±)-7], and [*N*-(trifluoroacetyl)prolyl]benzene [(±)-9] were prepared by a method analogous to that described for **5**. Detailed procedures have been previously reported.[2]

(*S*)-2-[*N*-(Trifluoroacetyl)amino]-1-phenylpropane (11). To a 250-mL hydrogenation bottle was added 1.0 g (4.08 mmol) of ketone **5** in 15 mL of trifluoroacetic acid (doubly distilled over P_2O_5). To this solution was added 0.2 g of 10% Pd–C, and the mixture was shaken under H_2 (55 psig) for 54 h. The solution was filtered and diluted with H_2O. The acid was neutralized with solid K_2CO_3, and the product was extracted with CH_2Cl_2. Silica gel chromatography using hexanes and CH_2Cl_2 afforded, following recrystallization from hexanes, 0.6 g (71%) of pure **11**: mp 79–81 °C (lit.[13] mp 82–84 °C); ^1H NMR δ 1.20 (d, *J* = 6 Hz, 3 H, CH_3), 2.80 (d, *J* = 6 Hz, 2 H, $ArCH_2$), 4.25 (m, *J* = 6 Hz, 1 H, CHNH), 6.30 (br s, 1 H, NH), 7.20 (m, 5 H, Ar).

(*S*)-2-Amino-3-methyl-1-phenylbutane (12). To a magnetically stirred solution of 0.24 g (0.87 mmol) of ketone **6** in 10 mL of absolute ethanol was added 0.20 g (5.2 mmol) of $NaBH_4$.[2] The mixture was stirred under N_2 for 12 h, and the EtOH was removed by rotary evaporation. The resulting solid was suspended in 2 mL of H_2O, and the product was extracted into Et_2O. The Et_2O was dried and rotary evaporated to afford a mixture of amino alcohols. The amino alcohols (0.72 mmol) were dissolved in 3 mL

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Table I. ^{1}H NMR Data[a] for α-Methoxy-α-(trifluoromethyl)phenylacetamides

compd	δ
18	0.85 (d, J = 7.8, 6 H, CH_3), 1.80 (m, 1 H, $CH(CH_3)_2$), 2.68 and 2.88 (q_{AB}, 2 H, J_{gem} = 8, $ArCH_2$), 3.35 (s, 3 H, CH_3OCCO), 4.18 (m, 1 H, CHNH), 6.40 (d, J = 6.5, 1 H, NH), 7.15-7.75 (m, 10 H, Ar). For the corresponding diastereomeric mixture from racemic amine 12: 0.85 (d, J = 7.8, 6 H, CH_3), 1.00 (t, J = 7.0, 6 H, CH_3), 1.80 (m, 4 H, $CH(CH_3)_2$), 2.65 and 2.93 (2 q_{AB}, J_{gem} = 5.2, J_{gem} = 8, 4 H, $ArCH_2$), 3.35 (s, 6 H, CH_3OCCO), 4.18 (m, 2 H, CHNH), 6.40 (d, J = 6.5, 1 H, NH), 6.78 (d J = 6.5, 1 H, NH), 7.00-7.65 (m, 20 H, Ar)
19	1.15 (d, J = 8, 3 H, CH_3), 2.75 (d, J = 6, 2 H, $ArCH_2$), 3.25 (s, 3 H, CH_3OCCO), 4.39 (m, J = 8, 1 H, CHNH), 6.65 (d, J = 8, 1 H, NH), 7.13-7.65 (m, 10 H, Ar). For the corresponding diastereomeric mixture from racemic amine 14: 1.15 (d, J = 8, 3 H, CH_3), 1.20 (d, J = 8, 3 H, CH_3), 2.88 (dd, J = 6, 4 H, $ArCH_2$), 3.25 (s, 6 H, CH_3OCCO), 4.39 (m, J = 8, 2 H, CHNH), 6.65 (d, J = 8, 1 H, NH), 6.80 (d, J = 8, 1 H, NH), 7.08-7.75 (m, 20 H, Ar)
20	1.05 (d, J = 6, 3 H, CH_3), 2.64 (d, J = 8, 2 H, $ArCH_2$), 3.20 (s, 3 H, CH_3OCCO), 3.74 (s, 6 H, CH_3OAr), 4.15 (m, 1 H, CHNH), 6.50 (br m, 1 H, NH), 6.60 (s, 3 H, $(CH_3O)_2Ar$), 7.10-7.60 (m, 5 H, Ar). For the corresponding diastereomeric mixture from racemic amine 15: 1.05 (d, J = 6, 3 H, CH_3), 1.20 (d, J = 6, 3 H, CH_3), 2.64 (d, J = 8, 2 H, $ArCH_2$), 2.75 (d, J = 8, 2 H, $ArCH_2$), 3.25 (dd, 6 H, CH_3OCCO), 3.75 (s, 12 H, CH_3OAr), 4.25 (m, 2 H, CHNH), 6.50 (br m, 2 H, NH), 6.60 (d, J = 4, 6 H, $(CH_3O)_2Ar$), 7.10-7.70 (m, 10 H, Ar)
21	1.20-2.00 (m, 4 H, $CH_2CH_2CH_2N$), 2.38 and 2.42 (d, J = 11, 2 H, $ArCH_2$), 2.78 and 3.28 (dt, J = 7, 2 H, $NCH_2CH_2CH_2$), 3.40 (s, 3 H, CH_3OCCO), 4.43 (m, 1 H, $ArCH_2CH$), 7.15-7.75 (m, 10 H, Ar). For the corresponding diastereomeric mixture from racemic amine 17: 1.10-2.00 (m, 8 H, $CH_2CH_2CH_2N$), 2.25 and 3.30 (d, J = 11, 2 H, $ArCH_2$), 2.38 and 2.42 (d, J = 11, 2 H, $ArCH_2$), 2.55 (dt, J = 7, 2 H, $NCH_2CH_2CH_2$), 2.78-3.28 (dt, J = 7, 2 H, $NCH_2CH_2CH_2$), 3.38 (s, 6 H, CH_3OCCO), 4.45 (m, 2 H, $ArCH_2CH$), 7.15-7.75 (m, 20 H, Ar)

[a] Spectra were run in $CDCl_3$. Chemical shifts are reported as ppm from Me_4Si. J values are in Hz.

of CH_2Cl_2, and ethereal HCl was added to the solution. The solvents were removed by rotary evaporation to yield the hydrochloride salts. These salts were dissolved in 4 mL of dioxane, heated to 95 °C with magnetic stirring, and treated with 0.31 g (100 mol %) of PBr_5 in one portion.[6] After 2 h the volatiles were evaporated. The residue was cooled to 0 °C, dissolved in 10 mL of absolute ethanol to which was added 36 mg of 10% Pd–C, and shaken under H_2 (55 psig) for 6 h. The EtOH was removed by rotary evaporation, and the residue was partitioned between CH_2Cl_2 (15 mL) and 1 N NaOH (10 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried and concentrated by rotary evaporation to give 85 mg (60%) of the free amine **12** as a light yellow oil: ^{1}H NMR δ 0.92 (d, J = 7 Hz, 6 H, CH_3), 1.50 (br s, 2 H, NH_2), 1.10–1.99 (m, 1 H, $CH(CH_3)_2$), 2.20–2.92 (m, 2 H, $ArCH_2$), 3.42–3.84 (m, 1 H, CHNH), 7.24 (s, 5 H, Ar).

(*S*)-2-[*N*-(Trifluoroacetyl)amino]-1-(3,4-dimethoxyphenyl)propane (13). Ketone **7** was deoxygenated with Et_3SiH in trifluoroacetic acid by the method of Doyle and co-workers[7] to provide **13**:[2] mp 128–129 °C.

(*S*)-*N*-(Trifluoroacetyl)-2-benzylpyrrolidine (16). Ketone **9** was reduced by catalytic hydrogenolysis using 10% Pd–C in a solution of ethanol containing ethereal HCl as previously described,[2] to yield compound **16**[2] as a light yellow oil.

(*S*)-2-Amino-1-phenylpropane (14). (*S*)-2-[*N*-(Trifluoroacetyl)amino]-1-phenylpropane (**11**) was detrifluoroacetylated[2] to yield the free amine **14** as a colorless oil: ^{1}H NMR δ 1.01 (d, J = 6 Hz, 3 H, CH_3), 1.67 (br s, 2 H, NH_2), 2.50 (dd, J = 5 Hz, 2 H, $ArCH_2$), 3.00 (m, 1 H, CHNH), 7.06 (s, 5 H, Ar).[14]

(*S*)-2-Amino-1-(3,4-dimethoxyphenyl)propane (15). The free amine was prepared from **13** as previously reported.[2]

(*S*)-2-Benzylpyrrolidine (17). Saponification was effected as previously described[2] to afford amine **17**: ^{1}H NMR δ 1.20–2.00 (m, 4 H, $CH_2CH_2CH_2N$), 2.10 (s, 1 H, NH), 2.69 (d, J = 6 Hz, 2 H, $ArCH_2$), 2.70–3.36 (m, 3 H, $CHNCH_2$), 7.23 (s, 5 H, Ar).[15]

General Procedure for the Preparation and Analysis of α-Methoxy-α-(trifluoromethyl)phenylacetamides. Method A.[16] To a magnetically stirred solution of 0.26 mmol of the amine in 3 mL of CH_2Cl_2 at room temperature under N_2 was added 0.26 mmol of (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, (−)-MTPA, followed by 0.26 mmol each of *N*-hydroxybenzotriazole and *N*,*N*′-dicyclohexylcarbodiimide. After 12 h the precipitated *N*,*N*′-dicyclohexylurea was removed by filtration. The solution was then diluted with CH_2Cl_2 and 1 N HCl, the phases were separated, and the organic layer was washed with saturated $NaHCO_3$ and evaporated to a white crystalline solid.

Method B. To a solution of 0.14 mmol of the acid chloride[8] of (−)-MTPA in 200 μL of CCl_4 containing 300 μL of dry pyridine was added a solution of 0.1 mmol of the amine in 100 μL of CCl_4. Pyridinium chloride precipitated immediately. After the reaction was complete, as evidenced by the lack of further pyridinium chloride precipitation, the solution was diluted with CH_2Cl_2 and washed successively with 1 N HCl, saturated $NaHCO_3$, and saturated NaCl. After drying over $MgSO_4$, the solvents were removed by rotary evaporation to yield the carboxamide.

The diastereomeric carboxamides prepared by either method above were dissolved in CH_3CN and analyzed by reversed-phase HPLC. In addition, 200-MHz ^{1}H NMR spectra were obtained for the amides. For ^{1}H NMR spectral data for **18–21** and the corresponding racemic carboxamides, see Table I.

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Registry No. **1**, 71-43-2; **2**, 91-16-7; (*S*)-**3**, 56271-78-4; (*S*)-**4**, 56236-38-5; (*S*)-**5**, 97589-52-1; (*S*)-**6**, 97589-53-2; (*S*)-**7**, 97590-48-2; (*S*)-**8**, 36724-68-2; (*S*)-**9**, 97589-54-3; (*S*)-**10**, 97589-55-4; (*S*)-**11**, 62840-99-7; (*S*)-**12**, 97589-56-5; (±)-**12**, 84524-59-4; (*S*)-**13**, 97589-57-6; (*S*)-**14**, 51-64-9; (±)-**14**, 300-62-9; (*S*)-**15**, 17279-41-3; (±)-15, 2936-29-0; (*S*)-**16**, 97589-58-7; (*S*)-**17**, 97522-31-1; (±)-17, 97589-59-8; **18** (isomer 1), 97522-32-2; **18** (isomer 2), 97522-33-3; **19** (isomer 1), 97522-34-4; **19** (isomer 2), 39532-57-5; **20** (isomer 1), 97550-88-4; **20** (isomer 2), 97550-89-5; **21** (isomer 1), 97522-35-5; **21** (isomer 2), 97522-36-6; (S)-(−)-MTPA, 17257-71-5; (*R*)-(−)-MTPA acid chloride, 20445-33-4; (*S*)-*N*-(trifluoroacetyl)alanine, 407-23-8; (*S*)-*N*-(trifluoroacetyl)valine, 349-00-8.

(14) The spectrum was the same as that recorded in: Pouchert, C. J.; Campbell, J. R. "The Aldrich Library of NMR Spectra"; Aldrich Chemical Co.: Milwaukee, WI, 1974; Vol. 5, p 104.

(15) This report is closely similar to that of: Tseng, C. C.; Terashima, S.; Yamada, S.-I. *Chem. Pharm. Bull.* **1977**, *25*, 29.

(16) Windridge, G. C.; Jorgensen, E. C. *J. Am. Chem. Soc.* **1971**, *93*, 6318.