16 h. The reaction mixture was partitioned between 110 mL of additional dichloromethane and 150 mL of water. The organic phase was dried and concentrated to give the crude mesylate, which was used as such for the next reaction.

A solution of the crude mesylate in 60 mL of 1:1 methanol/tetrahydrofuran was treated with 23 mL of 1 M methanolic sodium methoxide, and the reaction was stirred at 23 °C for 1 h. The reaction mixture was neutralized with Amberlite IR-120 (H^+) resin, concentrated, and then chromatographed with 1:1 and then 3:2 petroleum ether/ethyl acetate as the eluant to give 1.87 g (88%) of the Cerny epoxide **32** with mp 60–62 °C (lit.[21] mp 66–67 °C): $[\alpha]_D$ +30.6° (c = 0.16, H_2O) (lit.[21] $[\alpha]_D$ +30°, c = 1.8, H_2O); NMR (200 MHz) 1.70 (dd, J = 15.6, 5.3, H-4_{eq}), 2.46 (dd, J = 15.6, 5.0, H-4_{ax}), 2.98 (d, J = 4.3, H-2), 3.15 (ddd, J = 0.5, 5.3, 4.3, H-3), 3.74 (dd, J = 7.4, 1.6, H-6_{endo}), 3.91 (dd, J = 7.4, 5.8, H-6_{exo}), 4.40 (m, H-5), 5.58 (s, H-1); ^{13}C NMR (50 MHz) 33.0 (C-4), 47.6, 48.5 (2 oxirane C), 68.8, 71.1, 97.1 (C-1).

1,6-Anhydro-2-*O*-benzoyl-β-D-galactopyranose (34). 1,6-Anhydro-3,4-*O*-(dimethyl)methylene-β-D-galactopyranose was prepared according to the literature procedure[31] from 23.85 g of β-D-galactose pentaacetate. Chromatography with 2:1 and then 1:1 petroleum ether/ethyl acetate as the eluant and crystallization from 100 mL of 1:1 petroleum ether/dichloromethane afforded 5.83 g (45%) of the anhydrosugar, mp 143–144 °C. This material (28.86 mmol) was 2-*O*-benzoylated with 4 mL (34.46 mmol) of benzoyl chloride and 35 mg (0.29 mmol) of 4-(*N*,*N*-dimethylamino)pyridine in pyridine solution (30 mL) at 23 °C for 30 min. The reaction mixture was partitioned between ether and 1 N aqueous hydrochloric acid, and the organic phase was dried and concentrated to a syrup. The acetonide was removed by treatment with 25 mL of 4 N aqueous hydrochloric acid in 60 mL of 5:1 methanol/dichloromethane at 50 °C for 6 h. The reaction mixture was cooled, quenched by addition of triethylamine, concentrated, and chromatographed with 1:1 petroleum ether/ethyl acetate as the eluant to afford 7.01 g (91% overall yield) of diol **34**, mp 154–157 °C (lit.[30] mp 164–165 °C), $[\alpha]_D$ + 45.5° (c = 0.15, $CHCl_3$) (lit.[30] $[\alpha]_D$ + 47.2°, c = 0.8, $CHCl_3$).

1,6-Anhydro-2-*O*-benzoyl-4-deoxy-4-iodo-β-D-glucopyranose (36). Trifluoromethanesulfonic anhydride (4.7 mL, 27.94 mmol) was added to a stirred solution of 6.45 g (24.25 mmol) of 1,6-anhydro-2-*O*-benzoyl-β-D-galactopyranose[30,31] (**34**) in 19.7 mL (243.6 mmol) of pyridine and 300 mL of dichloromethane at −20 °C. The mixture was stirred at −20 °C for 4 h, −10 °C for 2 h, and then quenched by adding 300 mL of water. The organic phase was dried and concentrated to give a residue containing the 4-triflate **35**. The crude triflate was dissolved in 200 mL of dimethylformamide and treated with 14.30 g (38.71 mmol) of tetra-*n*-butylammonium iodide. The solution was stirred for 21 h at 23 °C, and then quenched with 500 mL of 10% aqueous sodium thiosulfate. The aqueous phase was back-extracted with ether (950 mL total), and the combined organic extracts were dried and concentrated. Chromatography with 4:1 and then 3:1 petroleum ether/ethyl acetate as the eluant afforded 7.11 g (78%) of iodide **36** with mp 97–99 °C: $[\alpha]_D$ + 7.8° (c = 1.5, $CHCl_3$); NMR (200 MHz) 3.61 (d, J = 5.5, OH), 3.66 (dd, J = 7.8, 4.8, H-6_{exo}), 4.23 (s, H-4), 4.28 (d, J = 7.8, H-6_{endo}), 4.38 (d, J = 5.5, H-3), 4.81 (d, J = 4.8, H-5), 4.90 (s, H-2), 5.64 (s, H-1), 7.39–8.18 (m, 5 H_{arom}); ^{13}C NMR (50 MHz) 24.6 (C-4), 67.6, 71.4, 73.5, 78.1, 99.7 (C-1), 128.4, 129.0, 130.2, 133.5 (4 C_{arom}), 165.8 (C=O); FT-IR (film) 3457 (OH), 2963, 1723 (OBz), 1269, 1113, 1026. Anal. Calcd for $C_{13}H_{13}O_5I$: C, 41.51; H, 3.48; I, 33.74. Found: C, 41.65; H, 3.31; I, 33.71.

1,6-Anhydro-2-*O*-benzoyl-4-deoxy-β-D-glucopyranose (37). A solution of 6.40 mL (23.79 mmol) of tri-*n*-butyltin hydride, 25 mg of azobis(isobutyronitrile), and 7.11 g (18.91 mmol) of iodide **36** in 60 mL of toluene was heated at 90 °C for 40 min. The reaction mixture was cooled, concentrated, and chromatographed with 3:1 and then 2:1 petroleum ether/ether as the eluant to give 4.13 g (87%) of deoxysugar **37** with mp 89–92 °C: $[\alpha]_D$ +23.1° (c = 0.75, $CHCl_3$); NMR (200 MHz), 1.81 (d, J = 14.8, H-4_{eq}), 2.36 (dt, J = 14.8, 4.6, H-4_{ax}), 3.06 (d, J = 4.9, OH), 3.74 (dd, J = 6.8, 5.5, H-6_{exo}), 3.97 (dd, J = 4.9, 4.6, H-3), 4.25 (d, J = 6.8, H-6_{endo}), 4.59 (dd, J = 5.5, 4.6, H-5), 4.83 (s, H-2), 5.58 (s, H-1), 7.38–8.06 (m, 5 H_{arom}); ^{13}C NMR (50 MHz) 33.0 (C-4), 66.3, 67.5, 71.7, 72.1, 99.5 (C-1), 128.4, 129.4, 129.8, 133.4 (4 C_{arom}), 165.7 (C=O); FT-IR (film) 3462 (OH), 2961, 2899, 1718 (OBz), 1265, 1115, 997. Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.19; H, 5.52.

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Friedel–Crafts α-Aminoacylation of Alkylbenzene with a Chiral *N*-Carboxy-α-amino Acid Anhydride without Loss of Chirality

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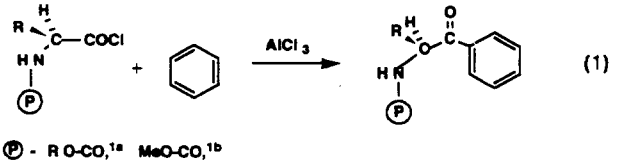
A Friedel–Crafts-type α-aminoacylation of alkylbenzene with *N*-carboxy anhydrides of five L-α-amino acids was developed. Five new α-aminoalkyl *p*-methylphenyl ketones and other α-aminoalkyl aryl ketones were obtained and isolated as free bases or hydrochloride salts. The chiralities of the original L-α-amino acids were retained during this acylation.

A Freidel–Crafts-type α-aminoacylation of benzene with N-protected α-amino acid chlorides has recently been developed by several chemists[1a–c] (eq 1). The reaction affords α-aminoalkyl phenyl ketones, which have been used as precursors of biologically active medicines such as ephedrine.[1a] The optically active N-protected α-amino ketones obtained from the reaction shown in eq 1 cannot be easily converted to the corresponding α-amino ketone free bases (abbreviated as F-B) without loss of chirality.



(1)

P - R O-CO,[1a] MeO-CO,[1b] and CF_3CO,[1c]

(1) (a) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1981**, *103*, 6157. (b) McClure, D. E.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1985**, *46*, 2431. (c) Nordlander, J. E.; Njoroge, F. G.; Payne, M. J.; Warman, D. *J. Org. Chem.* **1985**, *50*, 3481.

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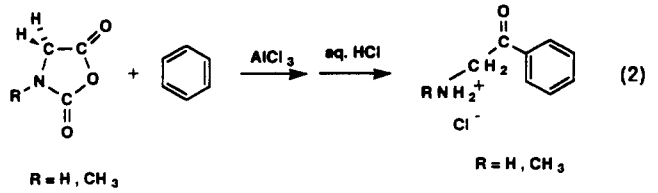
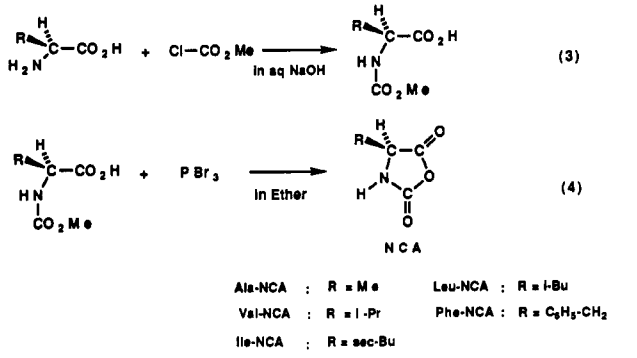
However, when an *N*-carboxy-α-amino acid anhydride (abbreviated as NCA) is employed as an acylating agent, it is possible to obtain the α-aminoalkyl phenyl ketones without a N-protective group. This reaction was first reported in 1951 by Statham using the NCAs of glycines (eq 2).[2]



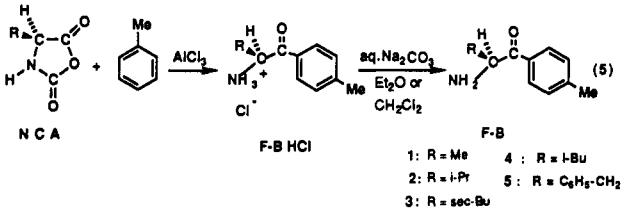
(2)

Although NCAs could potentially be used as optically active α-amino acylating agents without being racemized, the reaction of benzene and NCAs derived from α-amino acids other than glycines in the presence of $AlCl_3$ did not give such α-aminoalkyl phenyl ketones. For example, the reaction of Ala-NCA with benzene gave only a small amount of the expected α-aminopropiophenone.[1a] We also confirmed this result.

A lot of NCAs, which are familiar compounds in the field of peptide chemistry, can be synthesized readily either by Leuchs' method,[3a] by direct phosgenation of α-amino acid,[3b] or by an improved Leuch's method that uses PBr_3 (eqs 3 and 4).[3c] We synthesized a number of NCAs by



means of the improved version of Leuchs' method. All of the NCAs retained the chirality of the original α-amino acid almost completely. We then attempted to use these compounds as chiral acylating agents of aromatic compounds other than benzene to obtain unprotected chiral α-aminoalkyl aryl ketones (eq 5). In this paper, we de-



scribed the details of the syntheses of several chiral amino ketones from toluene, xylenes, and mesitylene. These chiral compounds may be useful as precursors of the corresponding chiral amino alcohols and Schiff bases.

Results and Discussion

The Reaction of NCAs with Alkylbenzene in the Presence of $AlCl_3$. The Friedel–Crafts reaction of NCAs with alkylbenzenes in the presence of $AlCl_3$ gave the corresponding α-aminoalkyl aryl ketones (F-Bs) in moderate yields. The ketones were also isolated as their hydrochlorides (F-B-HCl) after treatment with ethanol–HCl. Detailed studies of the reaction of Val-NCA (NCA of L-valine) under various conditions revealed that, in order to obtain the best yields of α-aminoalkyl aryl ketones, the reaction should be carried out below 10 °C with a $AlCl_3$ to NCAs ratio of 2–3:1 in alkylbenzene itself as the solvent. When CH_2Cl_2 was used as the solvent, the expected reaction occurred only a small amount. When CH_3NO_2 was used as the solvent, the expected reaction did not occur. Lewis acids such as $FeCl_3$, $TiCl_4$, and BF_3·OEt_2 did not work as catalysts in this reaction.

Table I. The Effect of the Reactant Ratio upon the Product Yield in the Reaction of Val-NCA with Toluene

run no.	NCA (mmol)	$AlCl_3$ (mmol)	toluene (mmol)	yield (%)	$[\alpha]^t_D$	T (°C)	(c, solv)
1	20	43	470	54	76.78	23	(1.070, $CHCl_3$)
2	20	20	470	25			
3	112	247	560	57	77.20	24	(1.027, $CHCl_3$)
4	51	151	253	56	77.58	23	(1.053, $CHCl_3$)
5	20	61	100	65	76.82	23	(1.027, $CHCl_3$)
6	20	62	100	69	77.11	18	(1.053, $CHCl_3$)

Several examples of reactions of Val-NCA with toluene in the presence of $AlCl_3$ are shown in Table I. The only product was only a para-substituted compound, which was isolated and identified as 3-methyl-2-amino-1-(*p*-methylphenyl)-1-butanone (2) or 2-HCl. As shown in Table I, the ratio of Val-NCA to $AlCl_3$ strongly affected the product yield. The optimum ratio of the reactants seemed to be Val-NCA:$AlCl_3$:toluene = 1:2–3:5. The amount of toluene did not affect the yield.

The reaction was normally carried out as follows. To a suspension of Val-NCA (20 mmol) in toluene (9.2 g, ca. 11 mL, 100 mmol) was added 2–3 equiv of solid $AlCl_3$ (8.0 g, 60 mmol) carefully, keeping the temperature under 10 °C. After all of $AlCl_3$ was added over a period of 0.5–1.0 h, the mixture was kept stirring at room temperature for 4–5 h. The reaction mixture was not homogeneous at the first stage, but at the end of the reaction it had became a dark brown, homogeneous oil. Then the mixture was treated with ice and dilute HCl, and the organic phase and/or a solid, if there was one, were separated. The aqueous layer was concentrated as much as possible by means of a rotary evaporator to give a solid residue, which was filtered and dried. The solid was dissolved in a small amount of water and neutralized with an aqueous 1 N Na_2CO_3 solution. Ether or CH_2Cl_2 extraction of the neutral or slightly basic solution and evaporation of the solvent left a pale yellow oil which was almost chemically as well as optically pure α-aminoalkyl aryl ketone. Reverse addition (run 6), that is, the addition of Val-NCA to a mixture of $AlCl_3$ and toluene, gave a result similar to that of run 5.

Unlike the reaction of Val-NCA with toluene, the reaction of Leu-NCA with toluene gave a mixture of 2-amino-4-methyl-1-(*p*-methylphenyl)-1-pentanone (4) (more than 97%) and the ortho-substituted product (less than 3%) as determined by ^1H NMR analysis. The elemental analysis of the mixture was coincident with the calculated value. The products were not isolated, but ^1H NMR analysis of the methyl proton of the tolyl group revealed the isomers to be the para- and ortho-substituted ones. In the case of Ala-NCA, it is possible that the product, obtained in 12.5% yield, was also a mixture of ortho- and para-isomers. However, the structure of the product could not be assigned as (−)-α-aminopropionyl *p*-methylphenyl ketone (F-B-1) by ^1H NMR because the product was very unstable and changed rapidly. The F-B derived from 8-HCl (cited below) was also chemically unstable.

(2) Statham, F. S. *J. Chem. Soc.* **1951**, *213*.
(3) (a) Leuchs, H. *Ber.* **1906**, *39*, 857. (b) Fuchs, F. *Ber* **1922**, *55*, 2943. (c) Ishai, D. B.; Katchalski, E. *J. Am. Chem. Soc.* **1952**, *74*, 3688.

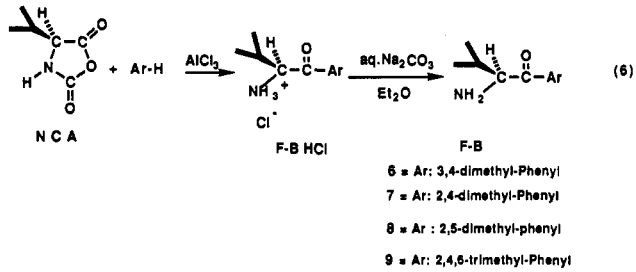
Table II. Preparation of α-Aminoalkyl Aryl Ketones, F-B 2–9. Yields and Analytical Data

product yield[a] (%)	$[\alpha]^t_D$ (c, $CHCl_3$)	T (°C)	ee[b] (%)	found C	found H	found N	calcd C	calcd H	calcd N
2, 54.4[c]	+76.78 (1.026)	23	98	75.28	9.04	7.29	75.36	8.96	7.32
2, 69.1	+77.11 (1.020)	18							
3, 55.4	+63.43 (1.000)	17	65 (96)	75.68	9.40	6.72	76.06	9.33	6.82
4, 74.8	+9.55 (1.050)	18	– (96)	76.51	9.05	6.74	76.06	9.33	6.82
5, 64.9	+65.46 (1.029)	29	95	80.56	7.08	5.72	80.30	7.16	5.85
6, 52.5	+69.70 (1.010)	28	96	75.65	9.60	6.58	76.06	9.33	6.82
6, 62.1	+60.70 (1.009)	23							
7, 55.0	+53.31 (1.023)	27	94	75.89	9.46	6.72	76.06	9.33	6.82
8, 17.7	+41.12 (1.004)	26	d	75.20	8.71	6.28	76.06	9.33	6.82
9, 79.2	+114.58 (1.068)	21	98	76.43	9.66	6.37	76.67	9.65	6.39

[a] Isolated yields. [b] Estimated by ^1H NMR of MTPA-amide. The values in parentheses are those of MTPA-amides derived from the HCl salts of 3 and 4. [c] Toluene was used as a solvent (50 mL). [d] Too unstable to measure.

In the reaction of Val-, Ile-, and Phe-NCA with toluene, only para-substituted products 2, 3, and 5 were obtained. The products of the reactions of Ile- and Leu-NCA, 3 and 4, respectively, were optically unstable to the neutralization conditions; 4 was more unstable than 3. Under the acidic reaction conditions, both compounds seemed to retain completely the optical activities of the original amino acids. When the HCl salts of 3 and 4, which were extracted from the crude reaction products with $CHCl_3$, were directly treated with Mosher's chloride (MTPA-Cl),[4] good yields of MTPA-amides were obtained. Both amides retained more than 96% of the optical activity of the original amino acids. Therefore, we believe that F-B-3 and F-B-4, after neutralization of the crude reaction products, underwent considerable racemization in the neutralization step (Table II).

This α-aminoacylation was applied to the other alkylbenzenes. *o*-, *m*- and *p*-xylene and mesitylene also reacted with Val-NCA to form the expected products 6–9, respectively. Each product was composed of only one isomer as determined by ^1H NMR spectra (eq 6). However, in



(6)

the case of *p*-xylene, the product yield was low, and a satisfactory elemental analysis was not obtained. We were able to assign the configuration of 2-amino-3-methyl-1-(2,5-dimethylphenyl)-1-butanone (8) as that shown by means of all of the spectral data. However, 8 was too unstable to measure a reproducible value of $[\alpha]_D$.

The HCl salts, which were extracted from the crude reaction products with $CHCl_3$, were hardly purified by the usual recrystallization to the grade of an analytically pure. But we were able to purify 1-, 2-, 5-, 6-, 7-, and 9-HCl by the method described here (see the Experimental Section). Unfortunately, 3- and 4-HCl racemized in the neutralization step, 3 to a slight extent and 4 to a large extent.

The *dl*-isomer of 2 was synthesized by the same method from *dl*-Val-NCA. By treating 2 and *dl*-2 with MTPA-Cl, we obtained the corresponding amides, and the ^1H NMR (270 MHz) spectral analysis of the amides were performed. Only one singlet (δ 3.4) for the CH_3O group was found in the spectrum of the former (98% ee), whereas two singlets appeared in the spectrum of the latter. Furthermore, in the latter spectrum, two pairs of two doublets for the *i*-Pr methyl groups were found. One pair of doublets at lower field (0.83 and 1.06 ppm) was assigned to the *i*-Pr methyl groups of the (*S*)-isomer and the other (0.63 and 0.95 ppm) to the *i*-Pr methyl groups of the (*R*)-isomer. From the results of ^1H NMR spectral analyses of many MTPA-amides, we believe that the α-aminoalkyl aryl ketones (F-Bs) are optically pure, although some of them are unstable and very sensitive to the isolation conditions. This result means that the optical purities of the starting α-amino acids are completely retained in our acylation.

Experimental Section

General Procedure. Melting points were determined on a SHIMADZU melting point apparatus. GC analyses were performed with a SHIMADZU GC-3AH gas chromatograph with a column of 10% OV-17 on Shimalite. Infrared spectra were determined on a HITACHI EPI-G2 spectrophotometer. NMR spectra were recorded with JEOL-GSX-270 and FX-100 spectrophotometers in $CDCl_3$ with Me_4Si as an internal standard or in D_2O with sodium 3-(trimethylsilyl)propylsulfonate as an internal standard. Optical rotations were measured on a JASCO DIP-360 polarimeter with a 10-cm cell. Column chromatography (5% EtOAc–95% *n*-hexane) was employed to separate and purify all products.

***N*-Carboxy-α-amino Acid Anhydride (NCA).** L-*N*-(Methoxycarbonyl)-α-amino acids were synthesized according to the literature method.[1a] The NCAs were synthesized from L-*N*-(methoxycarbonyl)-α-amino acids by the improved Leuchs' method.[3c]

L-*N*-Carboxyalanine Anhydride (Ala-NCA). L-*N*-(Methoxycarbonyl)alanine was synthesized according to the literature method. Ala-NCA: yield 36.7%; $[\alpha]^{21}_D$ +5.13° (*c* 1.039, CH_2Cl_2) (lit.[5] $[\alpha]^{25}_D$ –2.70° (c 6.4, dioxane)); IR (neat) ν C=O 1860, 1840, 1790, 1760 cm^{-1}; ^1H NMR δ 1.58 (d, 3 H), 4.42 (q, 1 H), 6.57 (br s, 1 H); ^{13}C NMR (DMSO-d_6) δ 17.0, 53.0, 151.8, 172.5.

L-*N*-Carboxyvaline Anhydride (Val-NCA). L-*N*-(Methoxycarbonyl)valine was prepared in 75.2% by the same method as L-*N*-(methoxycarbonyl)alanine: $[\alpha]^{33}_D$ +16.83° (*c* 1.033, $CHCl_3$).

Val-NCA: yield 67.2%; $[\alpha]^{22}_D$ –41.63° (*c* 1.100, CH_2Cl_2). Val-NCA prepared from $COCl_2$ method in our laboratory: $[\alpha]^{26}_D$ –42.08° (*c* 1.036, CH_2Cl_2), $[\alpha]^{27}_{589}$ –44.4° (*c* 4.476, acetone).[6]

L-*N*-Carboxyisoleucine Anhydride (Ile-NCA). L-*N*-(Methoxycarbonyl)isoleucine was prepared in 97% yield by the same method as L-*N*-(methoxycarbonyl)alanine: $[\alpha]^{20}_D$ +22.1° (*c* 1.00, $CHCl_3$).

Ile-NCA: yield 85.4%; $[\alpha]^{27}_D$ –31.68° (*c* 0.995, CH_2Cl_2); IR (KBr) ν C=O 1850 (s), 1770 (br s) cm^{-1}; ^1H NMR δ 0.97 (t, 3 H), 1.06 (d, 3 H), 1.40 (m, 1 H), 1.48 (m, 1 H), 1.97 (m, 1 H), 4.29 (d, 1 H), 7.2 (br s, 1 H); ^{13}C NMR δ 11.4, 14.8, 24.3, 37.3, 62.5, 153.6,

(4) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(5) Du Pont de Nemours & Co., U.S.P. 2789973, 1950.

(6) Hirshmann, R.; Schwam, H.; Strachan, R. G.; Schoenewaldt, E. F.; Barkemeyer, H.; Miller, S. M.; Conn, J. B.; Garsky, V.; Veber, P. F.; Denkewalter, R. G. *J. Am. Chem. Soc.* **1971**, *93*, 2746.

169.0. Anal. Calcd for $C_7H_{11}NO_3$: C, 53.50; H, 7.05; N, 8.91. Obsd: C, 53.59; H, 7.10; N, 8.74.

L-*N*-Carboxyleucine Anhydride (Leu-NCA). L-(Methoxycarbonyl)leucine was prepared quantitatively as an oil by the same method as L-(methoxycarbonyl)alanine: $[\alpha]^{26}_D$ −13.06° (*c* 1.002, CH_2Cl_2).

Leu-NCA: yield 59%; $[\alpha]^{24}_D$ −38.42 (*c* 1.052, CH_2Cl_2); $[\alpha]^{24}_D$ −42.02° (*c* 1.015, $CHCl_3$) (lit.[7] $[\alpha]^{rt}_D$ −37.40 (*c* 1.0, $CHCl_3$)); IR (neat) ν C=O 1860 (s), 1820 (s), 1760 (s) cm^{-1}; ^1H NMR δ 0.98 (d, 3 H), 1.00 (d, 3 H), 1.70 (q, 1 H), 1.77–1.90 (m, 1 H), 1.80 (m, 1 H), 4.37 (d d, 1 H), 7.24 (br s, 1 H); ^{13}C NMR δ 21.5, 22.7, 25.0, 40.8, 56.3, 153.3, 170.2.

L-*N*-Carboxyphenylalanine Anhyride (Phe-NCA). L-*N*-(Methoxycarbonyl)phenylalanine was prepared quantitatively by the same method as L-(methoxycarbonyl)alanine. Recrystallization of the raw product from EtOAc and *n*-hexane (1:5) gave a pure product: yield 76%; $[\alpha]^{22}_D$ +38.45° (*c* 1.024, EtOH).

Phe-NCA: yield 66.8%; $[\alpha]^{23}_D$ −100.49° (*c* 1.009, CH_2Cl_2); $[\alpha]^{25}_D$ −108.57 (*c* 1.004, $CHCl_3$) (lit.[7] $[\alpha]^{rt}_D$ −108.30° (*c* 1.0, $CHCl_3$), (lit.[8] $[\alpha]^{20}_D$ −110.4° (*c* 1, THF)).

(*S*)-2-Amino-3-methyl-1-(*p*-methylphenyl)-1-butanone (2). 1 (Run 1 in Table I). To a cooled mixture of Val-NCA (2.93 g, 20.4 mmol) in toluene (50 mL) was added $AlCl_3$ (5.8 g, 43.0 mmol) portion by portion over a period of 1.5 h with vigorous stirring. The reaction mixture was kept stirring at room temperature for 4 h and then poured onto ice (100 g) and extracted with toluene (20 mL × 2). From the toluene solution a small amount of organic products (0.50 g) was obtained. The product was a mixture, which had two main peaks by GC. The aqueous filtrate was concentrated in vacuo to about 40 mL. A white solid (2.57 g) was obtained and was designated as B_1. The fitrate was concentrated again to 25 mL, and a second solid (1.76 g), designated as B_2, was obtained. $[\alpha]^{22}_D$ of B_1 and B_2 were +52.44° and +41.60°, respectively. An aqueous solution of B_1 (2.09 g) was neutralized with an aqueous 1 N Na_2CO_3 solution (11 mL), and ether extraction gave a yellow solid (1.294 g, 40.68%): $[\alpha]^{23}_D$ +76.78° (*c* 1.026, $CHCl_3$). From solid B_2 (1.190 g) was obtained the same compound (0.362 g, 13.66%): $[\alpha]^{23}_D$ +75.43° (*c* 1.065, $CHCl_3$). The total yield was 54.5%: ^1H NMR δ 0.75 (s, 3 H), 1.07 (s, 3 H), 2.08 (m, 1 H), 2.41 (s, 3 H), 4.28 (d, 1 H), 7.26 (d, 2 H), 7.82 (d, 2 H); ^{13}C NMR δ 15.5, 20.5, 21.6, 31.9, 60.7, 128.4, 129.4, 133.4, 144.0, 202.6. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.28; H, 9.04; N, 7.29. Obsd: C, 75.36; H, 8.96; N, 7.32.

(*S*)-2-Amino-3-methyl-1-(*p*-methylphenyl)-1-butanone (2)). 2 (6 in Table I, Second 2 in Table II). To a cooled mixture of $AlCl_3$ (8.3 g, 62 mmol) and toluene (9.5 g, 100 mmol) was added Val-NCA (2.91 g, 20.3 mmol) portion by portion over a period of 1 h at under 10 °C. The reaction mixture was kept stirring at room temperature for 5 h and then added onto ice (100 g). A white solid (0.97 g), designated as A, was isolated and washed with 40 mL of ether. The aqueous solution was concentrated to about 15 mL. A white solid (4.15 g), designated as B, was separated, and it was filtered and washed with 40 mL of ether. A portion of solid B (2.28 g) was dissolved in H_2O (10 mL) and ether (40 mL), and then an aqueous 1 N $NaHCO_3$ solution (8 mL) was added. Extraction with ether (40 mL × 2) gave 0.43 g (2.27 mmol) of a yellow solid. Then 5 mL of an aqueous 1 N $NaHCO_3$ solution was added to the above aqueous solution. A second extraction afforded 0.72 g (3.76 mmol) of a yellow solid, and the third one afforded 29 mg. The total amount of **2** obtained was 1.18 g (6.17 mmol, yield 69.1%, 99% ee). $[\alpha]^{18}_D$ of the second one was +77.11° (*c* 1.036, $CHCl_3$).

(*S*)-2-Amino-3-methyl-1-(*p*-methylphenyl)-1-pentanone (3) (3 in Table II). To a cooled mixture of Ile-NCA (3.23 g, 20.5 mmol) and toluene (9.8 g, 110 mmol) was added $AlCl_3$ (8.0 g, 60 mmol) portionwise over a period of 1 h at 10 °C. Solids A and B were obtained in amounts of 2.11 and 2.83 g, respectively. The workup used for **2** gave **3** (55.4% yield, 65% ee): $[\alpha]^{17}_D$ +63.43° (*c* 1.000, $CHCl_3$); ^1H NMR δ 0.79 (t, 3 H), 1.04 (d, 3 H), 1.05 (m, 1 H), 1.25 (m, 1 H), 1.8 (m, 1 H), 2.42 (s, 3 H), 4.30 (d, 1 H), 7.28 (d, 2 H), 7.83 (d, 2 H); ^{13}C NMR δ 11.7, 16.8, 21.6, 23.0, 38.9, 60.6, 128.3, 129.8, 133.6, 143.8, 202.8. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Obsd: C, 75.68; H, 9.40; N, 6.72.

The Reaction of Crude 3-HCl with MTPA-Cl. A part of the crude A (5.73 g), which was obtained from an another experiment, was dissolved in $CHCl_3$, and an insoluble solid was filtered off. The filtrate was dried over Na_2SO_4, and the solvents were removed to yield a white solid. ^1H NMR analysis of the solid obtained from the filtrate indicated that it was 3-HCl contaminated with inorganic aluminum salts. To a mixture of 3-HCl above (110 mg, 47 mmol) and MTPA-Cl (120 mg, 48 mmol) in CCl_4 (5 ml) was added a solution of Et_3N (97 mg, 96 mmol) in CCl_4 (2 mL). The reaction mixture was kept stirring for 1 day. The solution was diluted with ether and washed successively with an aqueous 1 N HCl solution, an aqueous saturated $NaHCO_3$ solution, and water. After drying over Na_2SO_4, all solvents were removed by rotary evaporation to yield the MTPA-amide. The amides was analyzed by 270-MHz ^1H NMR, and the ee value of the crude 3-HCl was estimated to be 96%. The $[\alpha]^{28}_D$ of the crude 3-HCl was −78.5° (*c* 1.020, $CHCl_3$).

(*S*)-2-Amino-4-methyl-1-(*p*-methylphenyl)-1-pentanone (4). To a cooled mixture of Leu-NCA (2.99 g, 19.0 mmol) and toluene (9.0 g, 98 mmol) was added $AlCl_3$ (7.9 g, 59 mmol) portion by portion at under 10 °C over a period of 45 min. The reaction mixture was kept stirring at room temperature for 5 h. Solids A and B were obtained in amounts of 2.98 and 3.02 g, respectively. The usual workup gave a yellow liquid (**4**) in 74.8% yield: $[\alpha]^{18}_D$ +9.55° (*c* 1.050, $CHCl_3$). The ee value could not be obtained: ^1H NMR δ 0.92 (d, 3 H), 1.04 (d, 3 H), 1.34 (q, 1 H), 1.37 (q, 1 H), 1.54 (m, 1 H), 1.9 (br s, 2 H), 2.42 (s, 3 H), 4.44 (m, 1 H), 7.28 (d, 2 H), 7.83 (d, 2 H); ^{13}C NMR δ 21.4, 21.6, 23.6, 25.1, 44.8, 54.2, 128.4, 129.4, 132.7, 144.1, 203.0. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Obsd: C, 76.51; H, 9.05; N, 6.74.

The Reaction of Crude 4-HCl with MTPA-Cl. The crude product A (5.17 g), which was obtained from another experiment under the reaction conditions described above, was dissolved in $CHCl_3$ (50 mL × 2), and an insoluble solid was filtered off. ^1H NMR analysis of the solid obtained from the filtrate indicated that it was 4-HCl contaminated with inorganic aluminum salts. This solid (110 mg, 50 mmol) was treated with MTPA-Cl (126 mg, 50 mmol) in the presence of Et_3N (96 mg, 95 mmol). The corresponding MTPA-amide was obtained in a good yield and was analyzed by ^1H NMR. The ee value of this solid was determined to be 96%.

(*S*)-2-Amino-3-phenyl-1-(*p*-methylphenyl)-1-propanone (5). To a cooled mixture of Phe-NCA (3.90 g, 20.4 mmol) and toluene (9.50 g, 100 mmol) was added $AlCl_3$ (8.3 g, 62 mmol) portion by portion at under 2 °C over a period of 2 h. The reaction mixture was kept stirring at room temperature for 5 h and then was poured on to ice (100 g). A yellow solid (A, 5.32 g) was filtered and washed with ether (80 mL). Half of the solid A (2.54 g) was added to a mixture of ether (40 mL) and water (10 mL). Portions of an aqueous solution of 1 N Na_2CO_3 solution were added with a brief shake until the aqueous layer reached pH 8. The ether layer was separated. The aqueous phase was extracted with two additional portions of ether (30 mL × 2). The combined ether extracts were dried over Na_2SO_4 and evaporated. The total yield of product was 1.53 g (6.40 mmol, 64.9%), and the ee value of the product was determined to be 95%: $[\alpha]^{29}_D$ +65.46° (*c* 1.029, $CHCl_3$); ^1H NMR δ 2.43 (s, 3 H), 2.70 (dd, 1 H), 3.16 (dd, 1 H), 4.64 (m, 1 H), 7.2–7.4 (m, 5 H + 2 H), 7.88 (d, 2 H). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Obsd: C, 80.56; H, 7.08; N, 5.72.

(*S*)-2-Amino-1-(*p*-methylphenyl)-1-propanone (1-HCl). 1. To a cooled mixture of Ala-NCA (5.87 g, 51 mmol) and toluene (120 mL) was added $AlCl_3$ (10.0 g, 75 mmol) portion by portion over a period of 1 h at under 10 °C. The reaction mixture was kept stirring at room temperature for 3.5 h and then poured onto ice (150 g) and 30 mL of 1 N HCl. From the organic layer, a brown liquid was obtained. The liquid was determined to be 1,1-ditolylethane (yield, 15.1%) by GC and ^1H NMR analysis. The aqueous layer was concentrated as much as possible on a rotary evaporator. A white solid (B, 6.42 g) was obtained and dried: $[\alpha]^{22}_D$ −25.57° (*c* 1.046, H_2O). An aqueous solution of solid B (3.91 g) was neutralized with 20 mL of an aqueous 1 N $NaHCO_3$ solution. At the same time, CH_2Cl_2 (80 mL) was added, and the mixture was vigorously shaken. The CH_2Cl_2 layer separated and was dried with Na_2SO_4. To the dried CH_2Cl_2 solution was added EtOH (80 mL) saturated with HCl gas. After all of the solvent

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was evaporated, an orange solid was obtained (1.92 g; 29.4% yield). Recrystallization of this solid from EtOH (9 mL) gave 1-HCl in two crops, first crop, 0.60 g, and second crop, 0.31 g (total yield 14.6%): $[\alpha]^{18}_D$ −38.88° (*c* 1.050, H_2O); IR ν C=O 1690 and ν N–H 3400 cm^{-1}. First crop: mp 203.0–203.9 °C; ^1H NMR (D_2O) δ 1.63 (d, 3 H), 2.42 (s, 3 H), 5.23 (q, 1 H), 7.42 (d, 2 H), 7.98 (d, 2 H); ^{13}C NMR (D_2O) δ 17.8, 21.9, 52.7, 129.9, 130.7, 130.5, 147.9, 198.3. Anal. Calcd for $C_{10}H_{14}NOCl$: C, 60.15; H, 7.07; N, 7.01; Cl, 17.15. Obsd: C, 59.85; H, 7.15; N, 7.02; Cl, 17.77. F-B-1 could be obtained, but it changed rapidly. We were unable to assign the isolated product as 1 from the NMR spectrum. It might be possible to isolate F-B-1 and assign its structure by NMR if the workup was done at a lower temperature.

The Reaction of 1-HCl with MTPA-Cl. The above 1-HCl and *dl*-1-HCl, which was obtained from the reaction of *dl*-Ala-NCA with toluene, were treated with MTPA-Cl in the same way, and the MTPA-amides obtained were analyzed. The ee value of 1-HCl was determined to be 99%.

(*S*)-2-Amino 1-(*p*-methylphenyl)-1-propanone (1-HCl). 2. To a cooled mixture of Ala-NCA (2.31 g, 20.0 mmol) and toluene (9.3 g, 100 mmol), was added $AlCl_3$ (8.2 g, 61 mmol) at under 10 °C over a period of 45 min. The reaction mixture was kept stirring at room temperature for 4 h and then poured onto ice (100 g). No solid precipitated. The aqueous layer was washed with ether (40 mL × 2). After evaporation of the aqueous layer by a rotary evaporator, a white solid precipitated. The solid B (6.44 g) was filtered and dried: $[\alpha]^{17}_D$ −15.80° (*c* 1.027, H_2O). Half of solid B (3.2 g) was added to water (30 mL) and ether (40 mL). To the mixture was added an aqueous 1 N Na_2CO_3 solution (5 mL). Ether extraction (40 mL × 2) gave a yellow liquid (0.202 g, 1.01 mmol). We were unable to assign this as 1.

Another portion of B (2.20 g) was dissolved in a mixture of water (10 mL) and CH_2Cl_2 (40 mL). An aqueous 1 N Na_2CO_3 solution (10 mL) was added until the pH of the solution became 8. The CH_2Cl_2 solution was separated and dried over Na_2SO_4. To this solution was added EtOH saturated with HCl gas (50 mL). Rotary evaporation of the solvent afforded an orange crystalline solid (0.49 g, 24 mmol): $[\alpha]^{19}_D$ −37.49° (*c* 1.045, H_2O). A second extraction of the aqueous basic solution with CH_2Cl_2 gave a little more crystalline solid (0.19 g, 0.95 mmol). Recrystallization of the combined solid (0.57 g) from EtOH (4 mL) gave three crops: first crop, 270 mg; second crop, 170 mg; third crop, 84 mg. The total yield of 1-HCl (0.524 mg, 2.63 mmol) was 38.3%, and the ee value was determined to be 99%.

(*S*)-2-Amino-3-methyl-1-(3,4-dimethylphenyl)-1-butanone (6). To a cooled mixture of Val-NCA (2.86 g, 20 mmol) and *o*-xylene (10.6 g, 100 mmol) was added $AlCl_3$ (8.31 g, 62.3 mmol) portion by portion over a period of 45 min keeping the temperature at under 10 °C. The mixture was kept stirring at room temperature for 4 h. It was added to ice (50 g), and a gray solid was filtered off. The gray solid was washed with petroleum ether (100 mL) and dried (4.93 g). The solid (3.10 g) was added to a mixture of water (30 mL) and *n*-hexane (50 mL) in a separatory funnel. To the mixture were added portions of an aqueous solution of 1 N Na_2CO_3 with a brief shake until the aqueous layer reached pH 9. The hexane layer was separated, and then the aqueous layer was extracted with two additional portions (50 mL) of hexane. The hexane extracts were dried over Na_2SO_4. (Hexane was the best solvent to isolate the free base in a pure state.) The solvent was evaporated to yield a yellow liquid (2.58 g, 12.6 mmol): yield 62.1%, 96% ee; $[\alpha]^{25}_D$ 67.80° (*c* 1.009, $CHCl_3$); ^1H NMR δ 0.77 (d, 3 H), 1.07 (d, 3 H), 1.68 (br s, 2 H), 2.09 (m, 1 H), 2.32 (s, 3 H × 2), 4.28 (d, 1 H), 7.22 (d, 1 H), 7.64 (d, 1 H), 7.70 (s, 1 H); ^{13}C NMR δ 15.4, 19.7, 19.9, 20.3, 31.8, 60.5, 125.8, 129.1, 129.7, 133.7, 137.0, 142.6, 202.7. Anal. Calcd for $C_{13}H_{19}NO$: C, 76.06; H, 9.33; N, 6.82. Obsd: C, 75.65; H, 9.46; N, 6.72.

(*S*)-2-Amino-3-methyl-1-(2,4-dimethylphenyl)-1-butanone (7). To a cooled mixture of Val-NCA (20.2 mmol) and *m*-xylene (100 mmol) was added $AlCl_3$ (60.5 mmol) at under 10 °C over a period of 45 min. The usual reaction conditions and workup gave a yellow liquid in 55.0% yield and 95% ee: $[\alpha]^{26}_D$ 53.31° (*c* 1.020, $CHCl_3$). ^1H NMR δ 0.77 (d, 3 H), 1.02 (d, 3 H), 1.77 (br s, 2 H), 2.06 (m, 1 H), 2.35 (s, 3 H), 2.45 (s, 3 H), 4.19 (d, 1 H), 7.06 (d, 1 H), 7.08 (s, 1 H), 7.47 (d, 1 H); ^{13}C NMR δ 15.6, 20.6, 21.0, 21.4, 31.4, 62.8, 126.3, 128.4, 133.0, 134.2, 138.6, 141.8, 206.3. Anal. Calcd for $C_{13}H_{19}NO$: C, 26.06; H, 9.33; N, 6.82. Obsd: C, 75.89; H, 9.46; N, 6.56.

(*S*)-2-Amino-3-methyl-1-(2,5-dimethylphenyl)-1-butanone (8). To a cooled mixture of Val-NCA (2.88 g, 20.1 mmol) and *p*-xylene (10.6 g, 100 mmol) was added $AlCl_3$ (8.28 g, 62.1 mmol) portion by portion at under 10 °C over a period of 45 min. The mixture was kept stirring on an ice bath for 2 h and then poured on to ice (100 g). No solid precipitated. The aqueous layer was washed with ether (50 mL × 2). The aqueous layer was concentrated as much as possible on an evaporator, and a white solid was obtained (15.6 g). The solid was dissolved in $CHCl_3$, and an insoluble solid was filtered off. The $CHCl_3$ solution was dried over Na_2SO_4 and then evaporated. The white solid obtained (1.26 g) was assigned as 8-HCl by ^1H- and ^{13}C-NMR analyses.

A part of the solid (0.95 g) was dissolved in a mixture of water (5 mL) and ether (10 mL) in a separatory funnel. To the mixture were added portions of an aqueous 1 N Na_2CO_3 solution with a brief shake until the aqueous layer reached pH 9. The ether was separated, and then the aqueous layer was extracted with two additional portions (30 mL) of ether. The ether extracts were dried over Na_2SO_4. Evaporation afforded a yellow liquid (0.55 g, 2.7 mmol). We were able to assign the liquid as 2-amino-3-methyl-1-(2,5-dimethylphenyl)-1-butanone by ^1H- and ^{13}C-NMR analysis: $[\alpha]^{26}_D$ 41.12° (*c* 1.004, $CHCl_3$). Anal. Calcd for $C_{18}H_{19}O$: C, 76.06; H, 9.33; N, 6.82. Obsd: C, 75.20; H, 8.71; N, 6.28. This value was obtained 1 h after the sample had been removed from a refrigerator. Obsd (after 2 h): C, 74.16; H, 8.91. Obsd (after 3 h): C, 72.15; H, 8.41. The fluctuation of the combustion analysis shows that this compound is unstable at room temperature. The ^1H NMR spectrum of the sample after 2 days was too complicated to assign. Spectral data: ^1H NMR δ 0.75 (d, 3 H), 1.03 (d, 3 H), 2.01 (m, 1 H), 2.01 (m, 1 H), 2.35 (s, 3 H), 2.41 (s, 3 H), 4.17 (d, 1 H), 7.13 (d, 1 H), 7.18 (d, 1 H), 7.32 (s, 1 H); ^{13}C NMR δ 15.5, 20.4, 20.6, 21.1, 31.1, 63.2; 128.4, 131.9 (2C), 134.8, 135.2, 137.3, 207.1.

(*S*)-2-Amino-3-methyl-1-(2,4,6-trimethylphenyl)-1-butanone (9). The usual reaction conditions (2, 10 mmol) and the usual workup gave a yellow liquid (1.93 g, 8.80 mmol): yield 79.2%, 98% ee; $[\alpha]^{21}_D$ 114.58° (*c* 1.068, $CHCl_3$); ^1H NMR δ 0.86 (d, 3 H), 1.03 (d, 3 H), 1.6 (br s, 2 H), 2.02 (m, 1 H), 2.23 (s, 6 H), 2.28 (s, 3 H), 3.79 (d, 1 H), 6.5 (br s, 2 H); ^{13}C NMR δ 15.2, 19.7 (2 C), 21.0, 21.4, 29.0, 66.6, 128.9 (2 C), 134.1 (2 C), 137.7, 138.9, 211.9. Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Obsd: C, 76.43; H, 9.66; N, 6.37.

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