Friedel–Crafts α-Aminoacylation of Aromatic Compounds with a Chiral *N*-Carboxy-α-amino Acid Anhydride (NCA); Part 2[1]

Osamu Itoh,* Akira Amano

Department of Energy and Hydrocarbon Chemistry, Graduate School of Engineering, Kyoto University, Sakyouku Kyoto 606-8501, Japan
Fax+81(75)7535697

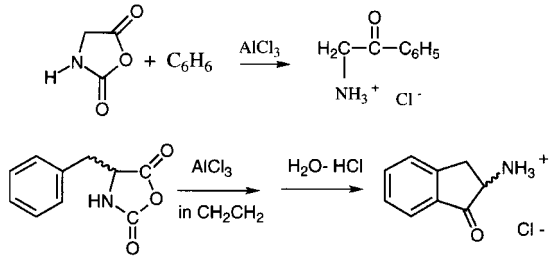
Received 17 April 1998; revised 11 September 1998

Abstract: The *N*-carboxy-α-amino acid anhydrides (NCA) derived from L-Asp(OEt), L-Glu(OMe), L-Met, and L-Pro reacted with aromatic compounds (toluene or benzene) in the presence of $AlCl_3$ to afford the corresponding α-aminoalkyl aryl ketones as hydrochloride salts in moderate yields. The β- and γ-amino acid esters, which were obtained from the reaction of the aromatic compounds with L-Asp(OEt)- and L-Glu(OMe)-NCA, were hydrolyzed by hydrochloric acid to the corresponding β- and γ-amino acids as hydrochloride salts. L-Phe-NCA did not react with benzene in the presence of $AlCl_3$, instead an intramolecular acylation occurred to afford (*S*)-2-aminoindanone hydrochloride. The chiralities of the original L-*a*-amino acids were most retained during these α-aminoacylation.

Key words: Friedel–Crafts acylation, α-aminoacylation, *N*-carboxy-α-amino acid anhydride (NCA), α-aminoalkyl aryl ketone, optically active β- and γ-amino acids

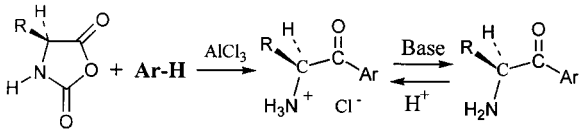
In Friedel–Crafts type α-aminoacylation with aromatic compounds, *N*-protected amino acid chlorides were generally used to afford *N*-protected α-amino ketones.[2] However, the deprotection of these *N*-protected α-aminoalkyl aryl ketones is sometimes accompanied by considerable racemization. Other methods to obtain *N*-unprotected α-aminoalkyl aryl ketones were not found in the literature, except the one using *N*-carboxy-α-amino acid anhydride (α-AA NCA).

The reaction of glycine *N*-carboxy-α-amino acetic acid anhydride (Gly-NCA) with benzene in the presence of $AlCl_3$ was first reported in 1951.[3] However, α-phenylalanine NCA was found to undergo intramolecular α-aminoacylation in the presence of $AlCl_3$ to form 2-aminoindanone (Scheme 1).[3]



Scheme 1

We have reported earlier that the *N*-carboxy-α-amino acid anhydrides (α-AA NCA) derived from L-Ala, L-Val, L-Ile, L-Leu, and L-Phe (designated as the A-group) only reacted with alkylbenzenes in the presence of $AlCl_3$ to afford chiral α-aminoalkyl aryl ketones as free bases without loss of chirality (Scheme 2).[1]

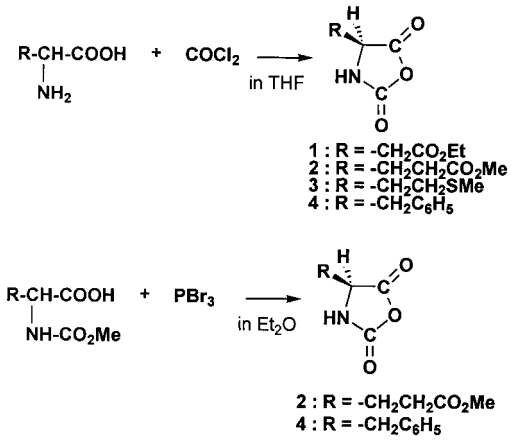


Scheme 2

However, the reaction of α-AA NCAs with benzene did not give the corresponding α-aminoalkyl aryl ketones, but instead resulted in two or three products in small yields depending on the NCAs. On the other hand, toluene and the other alkylbenzenes easily reacted with the α-AA NCAs to form α-aminoalkyl aryl ketones. The reason why both the reactions showed a different reactivity under the same Friedel–Crafts conditions, could not be explained clearly. It might be related to (a) the stability of the NCAs under the Friedel–Crafts reaction condition, and (b) the reactivity of the aromatic compounds with the acylating species.

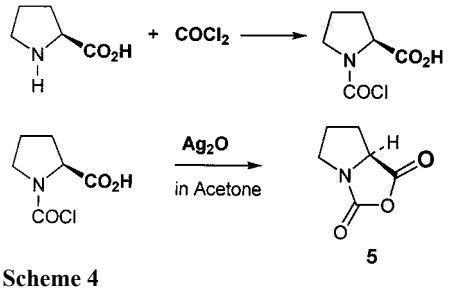
We report here the use of *N*-carboxy anhydrides of α-amino acids other than those of the A-group in the α-aminoacylation of benzene. The NCAs derived from L-Met, L-Asp(OEt), and L-Glu(OMe) (designated as the B-group) reacted with benzene in the presence of $AlCl_3$ to afford the corresponding α-aminoalkyl phenyl ketones. This might be because these NCAs are stable under the reaction conditions.

The NCAs were mainly prepared by the reaction of α-AAs with phosgene[4] or triphosgene (Scheme 3).[5] The reaction of L-*N*-methoxycarbonyl-α-amino acids with PBr_3 also afforded the corresponding NCAs **2** and **4**[6] (Scheme 3).



Scheme 3

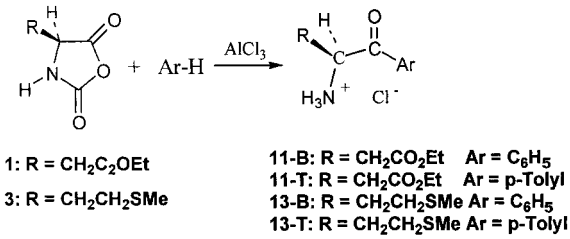
The L-Pro-NCA (**5**) was prepared in high yield by the reported method (Scheme 4).[7]



Scheme 4

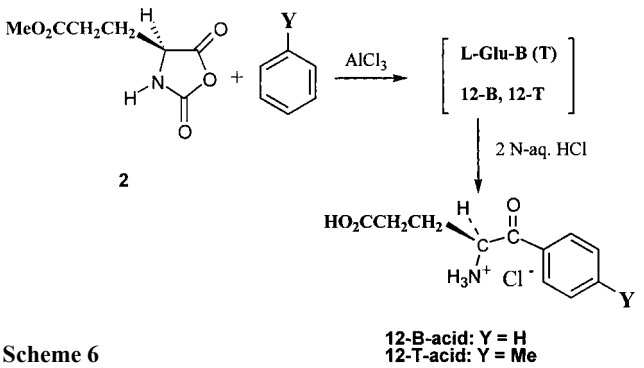
The NCAs obtained (Schemes 3 and 4) are soluble in CH_2Cl_2, and the small amount of insoluble material formed can be separated out. The $[\alpha]_D$ values of the NCAs obtained by this simple purification were measured and they were directly used in the next reaction.

NCA **1** reacted with benzene to afford **11-B** (Scheme 5) (the products are numbered in two digits with the alphabet **B** denoting that the product is derived from benzene and **T**, toluene), which was treated without purification with α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) and Et_3N to afford the MTPA-amide of **11-B**. The ee value of the MTPA-amide obtained from crude **11-B** was estimated to be 90.6% by ^1H NMR analysis. The crude **11-B** was recrystallized from EtOH. The ee value of the MTPA-amide from the recrystallized **11-B** was found to be 94% by ^1H NMR analysis.



Scheme 5

NCA **2** reacted with benzene and toluene to afford **12-B** and **12-T**, but neither of these products would crystallize. The crude products **12-B** and **12-T** were then hydrolized with aqueous 2 M hydrochloric acid at 50 °C to afford (*S*)-4-amino-4-phenylbutyric acid (**12-B**-acid, 23%) and (*S*)-4-amino-4-tolylbutyric acid (**12-T**-acid, 33%) (Scheme 6). The



Scheme 6

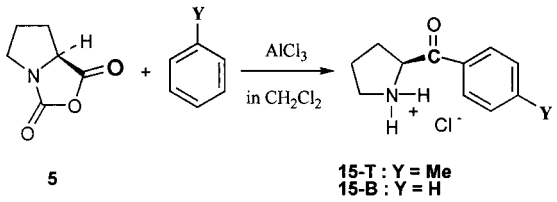
ee values of the recrystallized **12-B**-acid and **12-T**-acid were estimated to be 98 and 84 %, respectively, by ^1H NMR analysis of their MTPA-amides.

The crude products **12-B** and **12-T** obtained from another experiment were treated with MTPA-Cl and Et_3N to afford the respective MTPA-amides and analyzed by their ^1H NMR spectra. The singlets due to CH_3O-group of the (*R*)-isomer at δ = 3.48 in **12-B** and 3.49 in **12-T** were found in less than 2 and 4% intensity, respectively. Accordingly, the ee values of the crude **12-B** and **12-T** were estimated to be 96 and 92 %, respectively.

NCA **3** reacted with benzene and toluene to give **13-B** and **13-T** (Scheme 5). The crude products **13-B** and **13-T** were converted to the corresponding MTPA-amides by reacting with MTPA-Cl and Et_3N and their ee values were determined to be 88 and 94%, respectively.

The crude **13-B** and **13-T** were purified by crystallization from a small amount of EtOH and the pure compounds obtained in 9 and 27% yields had ee values of 93 and 98%, respectively. The elemental analyses of **13-B** was not coincident with the calculated values, however it gave a reasonable HRMS analysis (see experimental).

NCA **5** reacted with toluene to afford **15-T** (Scheme 7), and the ee value of this crude product could be determined by the ^1H NMR analysis of the MTPA-amide of **15-T**. The ee value of crude **15-T** was estimated to be 96%, and the $[\alpha]_D^{25}$ value of the crude product was –106.39 (*c* = 1.084, H_2O). The yield and $[\alpha]_D^{22}$ of the recrystallized product were 44% and –123.08 (*c* = 1.096, H_2O), respectively.



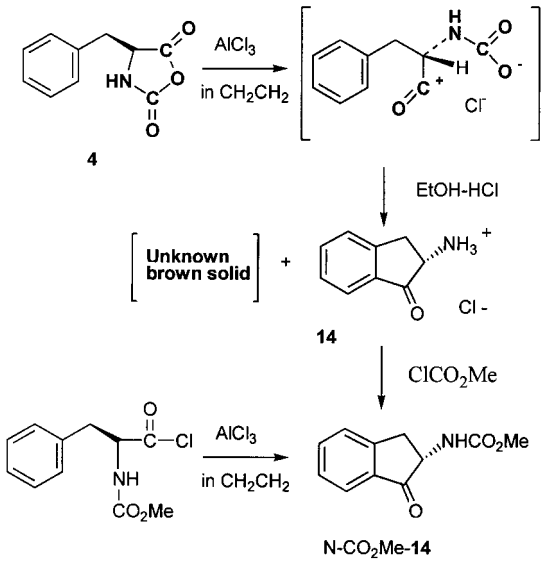
Scheme 7

Furthermore, NCA **5** can probably react with benzene (Scheme 7). A Friedel–Crafts reaction of L-proline acid chloride with benzene has already been reported,[8] but the $[\alpha]_D$ of the product was not given. This reaction might be a special case of an α-aminoacylation without racemization.

The reaction of **4** with benzene in the presence of $AlCl_3$ did not give (*S*)-2-amino-3-phenylpropiophenone hydrochloride (**14-B**). The major product was a brown solid that was not soluble in any solvents, and its IR spectrum revealed little information. However, a small amount of white solid was obtained from the aqueous layer.

NCA **4** reacted with $AlCl_3$ in CH_2Cl_2 without benzene to afford the same compound as the above white solid isolated from the aqueous layer in a 25% yield . The white solid was recrystallized from EtOH and was identified as (*S*)-2-aminoindanone hydrochloride (**14**) by elemental analyses and spectral data (Scheme 8). Although this reaction had

been reported earlier,[3] use of optically active L-Phe-NCA is reported here for the first time.



Scheme 8

The analogous compound, *N*-methoxycarbonyl-(*S*)-2-α-aminoindanone (Scheme 8) was synthesized by the reaction of *N*-methoxycarbonyl-L-phenylalanine acid chloride with benzene in the presence of $AlCl_3$ ($[\alpha]_D^{25}$ +133.70 (c = 0.54, $CHCl_3$), ee 98%.[2b]

The crude product **14** obtained by our method was treated with $ClCO_2Me$ to afford *N*-methoxycarbonyl-(*S*)-2-aminoindanone (Scheme 8) ($[\alpha]_D^{29}$ +133.80 (c = 1.012, $CHCl_3$)). The optical rotation of the *N*-CO_2Me-compound obtained from the recrystallized **14** was $[\alpha]_D^{28}$ +133.80 (c = 1.017, $CHCl_3$)

A comparison of this value with that given above in the literature[2b] showed both $[\alpha]_D$s to be almost the same. The ee values of both the crude and recrystallized product were found to be the same (98%).

In all of the α-aminoacylation reactions shown in this article, the chiralities of the original L-α-amino acids were considerably retained.

The important ^{1}H NMR spectra of the MTPA-amides of **11-B**, **12-B**,**12-T**, **13-B**, **13-T**, **15-T** are given in Table 2. The ee values could be estimated from the integration of the signals due to the methoxy hydrogens of the (*S*)- and (*R*)-isomers.

The reaction of *dl*-Pro-NCA with toluene was achieved and the obtained crude *dl*-**15-T** was treated with MTPA-Cl and Et_3N to afford the MTPA-amide of *dl*-**15-T**. Two singlets due to methoxy hydrogens were clearly identified (ee 91.2%).

Table 1 α-Aminoalkyl Aryl Ketones **11–15** Prepared

Substrate NCA	Product	Yield (%)	Optical Rotation			ee (%)[a]	^{1}H NMR (D_2O/PTS) δ, J (Hz)
			$[\alpha]_D$	Temp (°C)	(c, H_2O)		
1	**11-B**[b]	43	–6.07	19	1.020	94	–
1	**11-B**[c]	30	–5.56	19	1.067	90.6	1.20 (t, 3 H, J = 7.0), 4.13 (q, 2 H, J = 7.0), 3.17 (d, 2 H, J= 5), 5.46 (t, 1 H, J = 6)[d]
2	**12-B-acid**	23	+20.52	30	1.072	98	2.1–2.7 (m, 4 H), 5.28 (t, 1 H, J = 6.0), 7.6–7.7 (m, 2 H), 7.75–7.85 (m, 1 H), 8.0–8.1 (m, 2 H)[e]
2	**12-T-acid**	33	+23.62	31	1.091	84	2.1–2.9 (m, 4 H), 2.49 (s, 3 H), 5.30 (t, 1 H, J = 6.0), 7.48 (d, 2 H, J = 8), 7.98 (d, 2 H, J = 8)
3	**13-B**	9	–9.98	–	1.044	93	2.01 (s, 3 H), 2.1–2.4 (m, 2 H), 2.5–2.8 (m, 2 H), 5.3–5.4 (m, 1 H), 7.6–8.1 (m, 5 H)
3	**13-T**	27	–11.85	24	1.077	98	2.18 (s, 3 H), 2.20–2.45 (m, 2 H), 2.51 (s, 3 H), 2.65–2.85 (m, 2 H), 5.43 (dd, 1 H, J = 4.4, 7.7), 7.50 (d, 2 H, J = 8), 8.02 (d, 2 H, J = 8)[f]
5	**15-T**	44	–123.08	22	1.096	91.2	1.63–3.03 (m, 4 H), 2.47 (s, 3 H), 3.56 (t, 2 H, J = 7), 5.45 (t, 1 H, J = 6), 7.36 (d, 2 H, J = 8), 7.86 (d, 2 H, J = 8)[g]
4	**14**	25	+23.90	27	0.997	98	3.37 (dd, 1 H, J = 5.5, 8.1), 3.69 (dd, 1 H, J = 8.1, 16.8), 4.20 (dd, 1 H, J = 5.5, 8.1), 7.4–8.0 (m, 4 H)[h]

[a] Enantiomeric excess was determined by ^{1}H NMR analyses of the MTPA-amides of the products for **11–13** and **15**. For **14**, the ee value was determined from the $[\alpha]_D$ value (–133.80) of its *N*-methoxycarbonyl-2-aminoindanone (see Ref. 2b).

[b] Method B. L-Asp(OMe)-NCA (**1'**) was used.

[c] Method A. L-Asp(OEt)-NCA (**1'**) was used.

[d] ^{13}C NMR: δ = 14.2 (q), 40.0, 61.0 (t), 52.7 (d), 128.5, 128.9, 133.5, 134.8, 171.3, 198.7.

[e] ^{13}C NMR: δ = 28.6 (t), 31.7 (t), 57.5 (d), 131.6, 132.0, 135.5, 138.2, 178.6, 200.0.

[f] ^{13}C NMR: δ = 16.7 (q), 23.7 (q), 31.3 (t), 32.9 (t), 57.4 (d), 131.7, 132.7, 132.8, 149.9, 199.5.

[g] ^{13}C NMR: δ = 21.8 (q), 24.2 (t), 30.4 (t), 46.5 (t), 62.9 (d), 129.5, 129.7, 129.9, 146.5, 193.5.

[h] ^{13}C NMR: δ = 33.5, 56.4, 126.9, 129.5, 131.1, 135.6, 149.9, 154.3, 204.5.

Table 2 ee Values and ^{1}H NMR Spectra of MTPA-amides of α-Aminoalkyl Aryl Ketones

Aryl Ketones	ee (%)[a] (crude)	ee (%)[b] (recrystallized)	^{1}H NMR ($CDCl_3$), δ CH_3O–C–CF_3
11-B	–	94	3.33 (s)-97 % (*S*), 3.37 (s)-3% (*R*)
11-B	90.6	–	–
12-B-acid	–	98	–
12-B	96	–	3.37 (s)-98% (*S*), 3.48 (s)-2% (*R*)
12-T-acid	–	84	–
12-T	92	–	3.37 (s)-92% (*S*), 3.49 (s)-4% (*R*)[b]
13-B	–	93	–
13-B	88	–	3.38 (s)-94% (*S*), 3.40 (s)-6% (*R*)
13-T	–	98	–
13-T	94	–	3.38 (s)-97% (*S*), 3.48 (s)-3% (*R*)
15-T	91.2	–	3.70 (s)-95.6% (*S*), 3.95 (s)-4.4% (*R*)

[a] ee values were estimated by ^{1}H NMR analyses of the product MTPA-amides.

[b] ^{1}H NMR: δ = 1.81–1.91 (m, 1 H), 2.35–2.54 (m, 3 H), 2.42 (s, 3 H), 3.68 (s, 3 H), 5.69 (m, 1 H), 7.2–8.0 (m, 9 H).

L-Asp(OEt)•HCl was prepared by the reported method[9] in 46% yield; $[\alpha]_D^{25}$ +13.11 (*c* = 1.108, H_2O). L-PheNCA **(4)** was synthesized according to Ref. 1 (Scheme 3). L-Glu(OMe)•HCl was purchased from Aldrich.

(*S*)-4-Ethoxycarbonylmethyloxazolidin-2,5-dione [L-Asp(OEt)-NCA, **1**] and L-Asp(OMe)-NCA (**1'**) were prepared according to the reported method[10] in 45% yield; $[\alpha]_D^{26}$ –61.46 (*c* = 1.09, $CHCl_3$).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.26 (3 H, t, *J* = 8 Hz), 2.97 (2 H, d, *J* = 5 Hz), 4.17 (2 H, q, *J* = 8), 4.63 (1 H, t, *J* = 5), 7.24 (1 H, br s).

(*S*)-4-(2-Methoxycarbonylethyl)oxazolidine-2,5-dione (2)

Method A: To a suspension of L-Glu(OMe)•HCl (24.3 g, 150 mmol) in THF (600 mL), was bubbled gaseous phosgene over a period of 8 h at 40 °C. THF was then evaporated in vacuo at 40 °C. The residue was dissolved in CH_2Cl_2 (100 mL) and an insoluble solid was filtered. Removal of solvent gave a solid in 60% yield; $[\alpha]_D^{30}$ –24.86 (*c* = 1.034, DMSO) and used in the next reaction.

Method B: The reaction of *N*-methoxycarbonyl-L-Glu (OMe) with $(COCl)_2$ and a few drops of DMF at 50 °C gave L-Glu(OMe)-NCA (**2**) in 70% yield; $[\alpha]_D^{21}$ –25.24 (*c* = 1.07 , $CHCl_3$) and $[\alpha]_D^{20}$ –25.8 (*c* = 1.0 , CH_2Cl_2).

^{1}H NMR ($CDCl_3$): δ = 1.66–2.33 (2 H, m), 2.33–2.80 (2 H, m), 3.63 (3 H, s), 4.36 (1 H, t, *J* = 6), 8.86 (1 H, br s).

L-Met-NCA (3)

To a cooled mixture of *N*-methoxycarbonyl-*L*-methionine (25.0 g, 120 mmol) and Et_2O (45 mL) was added slowly a solution of PBr_3 (13.3 g, 49.1 mmol) in Et_2O (15 mL). The mixture was kept stirring at r.t. for 2 h, and then poured onto hexane (180 mL). To the lower layer separated from the mixture was added THF (100 mL). The precipitated solid was filtered, and the THF was evaporated. L-Met-NCA was obtained as a heavy yellow liquid; yield: 22.0 g (~100%); $[\alpha]_D^{29}$ –9.54 (*c* = 1.046, THF).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.9–2.4 (2 H, m), 2.1 (3 H, s), 2.5–2.9 (2 H, m) 4.5 (1 H, t, *J* = 7 Hz), 7.0 (1 H, br s).

L-Pro-NCA (5)

To a mixture of L-Pro (17.25 g, 150 mmol) and THF (400 mL) was bubbled gaseous phosgene over a period of 4 h at ca 30 °C. THF was evaporated from the homogeneous solution to give *N*-chlorocarbonyl-L-proline (N-COCl-L-Pro) as an yellow oil. To a solution of N-COCl-L-Pro (35.7 g, 150 mmol) in acetone (400 mL), were added Ag_2O (20.4 g, 88 mmol) and Norit A (4.5 g) and the mixture was stirred for 1 d at r.t. The mixture was filtered from the black Norit A and the THF was evaporated to afford **5**; yield: 21.1 g (ca 100%); mp 44.2–48.0 °C; $[\alpha]_D^{25}$ –99.66 (*c* = 1.002, $CHCl_3$); $[\alpha]_D^{25}$ –101.23 (*c* = 1.019, CH_2Cl_2).

^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.96 (1 H, m), 2.15 (1 H, m), 2.23 (1 H, m), 2.34 (1 H, m), 3.34 (1 H, m), 3.78 (1 H, m), 4.36 (1 H, dd, *J* = 7.7, 9.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 26.9, 27.6, 46.6, 63.1, 154.9, 168.9.

Ethyl (*S*)-3-Benzoyl-3-aminopropionate·Hydrochloride (11-B)

Method A: To a cooled mixture of **1** (4.50 g, 24.0 mmol) in benzene (11.5 mL, 128 mmol) was added $AlCl_3$ (9.80 g, 73 mmol) portionwise over a period of 25 min with vigorous stirring. The mixture was kept stirring at r.t. for 5 h, and then poured onto ice (70 g). To the filtrate was added powdered $NaHCO_3$ (22.0 g, 260 mmol) and filtered. The filtrate was concentrated in vacuo and then extracted with $CHCl_3$ (3 – 40 mL). Removal of $CHCl_3$ gave a yellow solid (3.56 g) which was washed with Et_2O (100 mL) to afford **11-B** as a white solid; yield: 2.99 g (48%); $[\alpha]_D^{18}$ –5.19 (*c* = 1.010, H_2O). A portion of **11-B** (303 mg) was treated with MTPA-Cl (310 mg) in the presence of Et_3N (220 mg). The corresponding MTPA-amide was obtained in good yield and analyzed by ^{1}H NMR spectroscopy; ee 90.6 %.

The residual **11-B** (2.32 g) was purified by recrystallization from EtOH (3 mL) to afford a white solid; mp 129.8–131.4 °C; yield: 30%; $[\alpha]_D^{19}$ –5.56 (*c* = 1.067, H_2O).

IR (neat): ν = 3400 (br), 2800 (br), 1730, 1695, 1515, 1250, 1240, 1190, 1180, 760, 690 cm^{-1}.

Anal. calcd for $C_{12}H_{16}ClNO_3$: C, 55.93; H, 6.26; N, 5.43; Cl, 13.76. Found: C, 55.83; H, 6.34; N, 5.37; Cl, 13.35.

Method B: The reaction of **1'** (11.3 g, 60.4 mmol) with benzene (23.6 g, 302 mmol) in the presence of $AlCl_3$ (24.2 g, 181 mmol) was carried out in order to prove the reproducibility. The reaction time was prolonged to 8 h in order to improve the yield. By the similar workup as given in method A above, a yellowish solid (9.20 g) was obtained as the crude product (59%). This solid (9.10 g) was recrystallized from EtOH (15 mL). The first crop amounted to 5.237 g; $[\alpha]_D$ –6.07 and the second 1.542 g; $[\alpha]_D$ –5.67; total yield: 43%.

A part of the first crop was treated with MTPA-Cl to afford the MTPA-amide. By ^{1}H NMR (270 MHz, $CDCl_3$) analysis of the MTPA-amide; ee 94%.

11-B-acid

Acidic hydrolysis of **11-B** with aq 2 N HCl often led to the formation of racemic **11-B** acid. Care must be taken during this treatment to avoid racemization. One of the hydrolysis experiment with **11-B** resulted in the formation of a solid in 9% yield, which was proved to be **11-B-acid** by ^{1}H NMR (270 MHz, D_2O-PTS as a standard); $[\alpha]_D^{19}$ –10.20 (*c* = 1.020, H_2O) (see next section for the acidic hydrolysis procedure). The ee value of **11-B-acid** was not determined.

IR (neat): ν = 3400, 1700, 1695, 760, 690 cm^{-1}.

Anal. calcd for $C_{10}H_{12}ClNO_3$: C, 52.26; H, 5.27; N, 6.10; Cl, 15.44. Found C, 51.93; H, 5.24; N, 5.99; Cl, 14.96.

(*S*)-4-Benzoyl-4-aminobutyric Acid Hydrochloride (12-B-Acid HCl)

To a cooled mixture of **2** (11.23 g, 60.0 mmol) and benzene (23.6 g), was added portionwise $AlCl_3$ (24.2 g, 181 mmol) over a period of 50 min with vigorous stirring. The mixture was kept stir-

ring at r.t. for 10 h, and then poured onto ice (150 g) and concd HCl (5 mL). The mixture was washed with Et_2O (3 × 50 mL). The aqueous layer was concentrated as much as possible on a rotary evaporater and the residue was extracted with $CHCl_3$ (3 × 30 mL). The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated. The residue was dissolved in Et_2O (30 mL) and H_2O (30 mL), and then neutralized with an aq solution of 1 N Na_2CO_3 (30 mL) until the aqueous layer reached pH 8. The mixture was extracted with Et_2O (2 × 30 mL) and the extract was treated with a satd solution of gaseous HCl in EtOH (50 mL). The solvent was evaporated to afford a red-brown liquid (10.42 g) which did not crystallize. The above red-brown liquid of **12-B** (10.26 g) was treated with aq 2 N HCl (70 mL) at 50–60 °C for 2 h, and the H_2O was evaporated. Recrystallization of the residue from hot water (20 mL) gave **12-B**-acid in two crops; first crop, 2.80 g; $[\alpha]_D^{30}$ + 20.52 (*c* = 1.070, H_2O); mp 200.9–202.2 °C; and second crop, 0.66 g; $[\alpha]_D^{30}$ + 19.72 (*c* = 1.029, H_2O); total yield: 3.46 g (23% based on **2**).

Anal. calcd for $C_{11}H_{14}ClNO_3$: C, 54.22; H, 5.79; N, 5.75; Cl, 14.55. Found C, 54.26; H, 5.99; N, 5.75; Cl, 14.32.

A part of the second crop was treated with MTPA-Cl and Et_3N to afford MTPA-amide of **12-B-acid**; ee 98% (^{1}H NMR, 270 MHz, $CDCl_3$).

12-B and MTPA-Amide of the Crude 12-B

Another α-aminoacylation of benzene with **2** was carried out in a 1.0 mmol scale. A part of the crude product **12-B** (170 mg) was treated with MTPA-Cl before the acidic hydrolysis to afford the corresponding MTPA-amide; ee 96% (^{1}H NMR, 270 MHz, $CDCl_3$).

12-B:

IR (neat): ν = 3350 (br), 2980, 1725, 1690, 1230 (br), 680 cm^{-1}.

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.32 (m,1 H), 2.47 (m,1 H), 2.62 (m,1 H), 2.97 (m,1 H), 3.56 (s, 3 H), 5.60 (d,1 H), 7.39 (t, 2 H, *J* = 8 Hz), 7.55 (t, 1 H, *J* = 8 Hz), 8.00 (d, 2H, *J* = 8 Hz), 8.9 (br s, 3 H).

HRMS of the crude **12-B**: *m*/*z* calcd for $C_{12}H_{16}NO_3$: 222.1130, found 222.1134.

(*S*)-4-*p*-Toluoyl-4-aminobutyric Acid (12-T-acid)

To a cooled mixture of **2** (3.90 g, 20.8 mmol) and toluene (9.30 g, 101 mmol) was added portionwise $AlCl_3$ (8.0 g, 60 mmol) over a period of 15 min. The mixture was stirred for 4 h at r.t. and worked up in the usual manner described above for **11-B**; yield: 3.016 g (37%); $[\alpha]_D^{28}$ + 24.62 (*c* = 1.063, H_2O). The solid (2.916 g) was treated with aq 2 N HCl (30 mL) at 60–70 °C for 1 h, and the H_2O was evaporated. The greenish white solid residue (2.60 g, 10.1 mmol, 49%) was recrystallized from a mixture of acetone (20 mL) and H_2O (5 mL); first crop, 1.32 g (5.13 mmol, 25%); $[\alpha]_D^{31}$ + 23.62 (*c* = 1.091, H_2O); mp 206.4–207.5 °C); second crop, 0.320 g (1.25 mmol); third crop, 0.122 g (0.47 mmol); total yield: 33% (6.85 mmol).

IR (neat): ν = 3430, 3000, 1700, 1680 cm^{-1}.

Anal. calcd for $C_{12}H_{16}ClNO_3$: C, 55.93; H, 6.26; N, 5.43; Cl, 13.76. Found: C, 55.76; H, 6.30; N, 5.42; Cl, 13.58.

A part of the recrystallized product **12-T**-acid (138 mg) was treated with MTPA-Cl (157 mg) in the presence of Et_3N (101 mg); ee 84% (^{1}H NMR, 270 MHz,$CDCl_3$).

12-T and MTPA-Amide of the Crude 12-T

The crude product **12-T** from the α-aminoacylation of toluene with **2** in a 1.0 mmol scale (178 mg) before acidic hydrolysis was treated with MTPA-Cl (172 mg) and Et_3N (136 mg) to afford the corresponding MTPA-amide; ee 92% (^{1}H NMR).

12-T:

^{1}H NMR (270 MHz, $CDCl_3$): δ = 2.36 (m, 3 H), 2.40 (s, 3 H), 2.52 (m,1 H), 3.63 (s, 3 H), 5.51 (br d, 1 H), 7.19 (d, 2 H, *J* = 8 Hz), 7.89 (d, 2 H, *J* = 8 Hz), 8.8 (br s, 3 H).

HRMS (crude **12-T)**: *m*/*z* calcd for $C_{13}H_{18}NO_3$: 236.1287, found 236.1286.

(*S*)-1-Benzoyl-3-methylthiopropylamine Hydrochloride (13-B•HCl)

To a cooled mixture of $AlCl_3$ (29.8 g, 223 mmol) and benzene (39.0 g, 499 mmol) was added portionwise **3** (17.6 g, 100 mmol) over a period of 1 h. The mixture was kept stirring at 40 °C for 4 h, and then poured onto ice (100 g). The aqueous layer was washed with Et_2O and then concentrated as much as possible on a rotary evaporator. To the residue was added $CHCl_3$ (30 mL) and the extraction with $CHCl_3$ was repeated (5 × 30 mL). The solvent was evaporated to afford the crude product; yield: 6.21 g (25.3 mmol); $[\alpha]_D^{30}$ –7.43 (*c* = 1.078, H_2O). A part of the crude product (3.46 g) was recrystallized from EtOH (2.5 mL). The solid obtained was washed with acetone (15 mL); yield: 1.16 g (9%); $[\alpha]_D^{28}$ –9.98 (*c* = 1.044, H_2O); mp 184.0–185.5 °C.

IR (KBr): ν = 3440, 1680, 1600 cm^{-1}.

Anal. calcd for $C_{11}H_{16}ClNOS$: C, 53.76; H,6.56; N, 5.70; S, 13.05; Cl, 14.43. Found C, 53.02; H, 6.61; N, 5.62; S,13.01; Cl, 14.18.

HRMS: *m*/*z* calcd for $C_{11}H_{16}ONS$ 210.0953, found 210.0954.

A part of the recrystallized **13-B** (131 mg, 0.53 mmol) was treated with MTPA-Cl (138 mg) and Et_3N (119 mg) in CCl_4 to afford MTPA-amide of **13-B**; ee 93% (^{1}H NMR, 270 MHz, $CDCl_3$).

The crude **13-B** obtained from the experiment in a 1.0 mmol scale (257 mg) was treated with MTPA-Cl (263 mg) and Et_3N (206 mg) to afford the corresponding MTPA-amide. By its ^{1}H NMR analysis, the ee value was estimated to be 88%.

(*S*)-1-*p*-Toluoyl-3-methylthiopropylamine Hydrochloride (13-T)

To a cooled mixture of $AlCl_3$ (17.9 g, 134 mmol) and toluene (20.4 g, 220 mmol) was added portionwise **3** (7.77 g, 44.3 mmol) with vigorous stirring over a period of 30 min. The temperature of the mixture was raised to 50 °C and then came quickly down to r.t. It was kept stirring for 4 h at r.t., and then poured onto ice-water (200 g). The aqueous layer was concentrated as much as possible on an evaporator. The residue was dissolved in $CHCl_3$ (30 mL) and dried (Na_2SO_4). The solvent was evaporated, and the yellow solid (4.99 g) obtained was characterized as **13-T** by its ^{1}H NMR spectrum. Recrystallization from EtOH gave **13-T** in 27% yield; mp 192.4–193.2 °C; $[\alpha]_D^{24}$ –11.85 (*c* = 1.007, H_2O); ee 98% (^{1}H NMR)

IR (KBr): ν = 3430, 1680, 1600 cm^{-1}.

Anal. calcd for $C_{12}H_{18}ClNOS$: C, 55.48; H, 6.98; N, 5.39; S, 12.34; Cl, 13.65. Found: C, 55.39; H, 6.87; N, 5.34; S, 12.24; Cl, 13.53.

MTPA-Amide of the Crude 13-T

The crude **13-T** obtained from the reaction of **3** with toluene in the presence of $AlCl_3$ in 1.0 mmol scale (176 mg) was treated with MTPA-Cl (172 mg) and Et_3N (136 mg) to afford the MTPA-amide of the crude **13-T**; ee: 94% (^{1}H NMR).

(*S*) 2-p-Toluoylpyrrolidine Hydrochloride [(S)-15-T]

To a cooled mixture of **5** (2.97 g, 20 mmol) and toluene (50 mL) was added portionwise $AlCl_3$ (6.20 g, 47.0 mmol) over a period of 1 h by keeping the temperature less than 3 °C. The mixture was kept stirring at 2 °C for 2 h and poured onto ice (100 g) and concd HCl (10 mL). The water layer was separated and concentrated. The residue was extracted with CH_2Cl_2 (8 × 30 mL). The solvent was evaporated and the residue (3.80 g) was recrystallized from EtOH/Et_2O

to give yellow crystals; yield: 1.98 g (44%); $[\alpha]_D^{22}$ –123.08 (*c* = 1.096, H_2O).

IR (KBr): ν = 3440 (br), 3040,1680, 1600, 1250, 1180.

Anal. calcd for $C_{12}H_{16}ClNO$: C, 63.86; H, 7.14; N,6.21; Cl, 15.71. Found: C, 63.76; H, 7.21; N, 5.98; Cl, 15.49.

MTPA-Amide of the Crude (*S*)-15-T

Compound **5** (10 mmol) was reacted with toluene in the presence of $AlCl_3$ and the crude product (**S**) **15-T** was obtained by solvent extraction from the aqueous reaction mixture as described above (1.70 g, $[\alpha]_D^{25}$ –106.39). A part of the crude product (225 mg, 1 mmol) was treated with MTPA-Cl (252 mg) and Et_3N (200 mg) in CCl_4 (10 mL); ee 91.2% (^{1}H NMR).

HRMS of the MTPA-amide of the crude (***S*)-15-T**: *m*/*z* calcd for $C_{22}H_{22}F_3O_3$: 406.1630, found 406.1638 .

(*dl*)-2p-Toluoylpyrrolidine Hydrochloride [(*dl*)-15-T] and its MTPA-Amide

dl-Proline-NCA was synthesized as an oily liquid and seemed to be more unstable than L-Pro-NCA. The reaction of dl-Pro-NCA with toluene in the presence of $AlCl_3$ gave **(*dl*)-15-T.**

HRMS (crude product): *m*/*z* calcd for $C_{12}H_{16}NO$: 190.1232, found 190.1231.

The MTPA-amide of (***dl***)-15T was synthesized in the usual manner from (***dl*)-15-T**, MTPA-Cl and Et_3N.

HRMS: *m*/*z* calcd for $C_{22}H_{22}F_3NO_3$: 406.1632, found 406.1631.

In the ^{1}H NMR spectrum of (***dl*)-15-T** MTPA-amide, two singlets due to methoxy hydrogens of (***S*)** and (***R*)-15-T** were clearly identified at 3.70 (***S***) and 3.95 (***R***), and thus the ee value of (***S*)-15-T** was estimated to be 91.2%.

2-Aminoindanone Hydrochloride (14)

To a cooled solution of **4** (3.85 g, 20.1 mmol) in CH_2Cl_2 (70 mL) was added portionwise $AlCl_3$ (5.90 g, 44.2 mmol). The mixture was kept stirring for 4 h in an ice-bath and then poured onto ice (150 g) and aq 6 N HCl (20 mL). An insoluble brown solid (1.65 g) formed was filtered which was not analysed further. The aqueous layer was separated and concentrated on a rotary evaporator. A white solid [1.466 g, $[\alpha]_D^{26}$ +23.82 (*c* = 1.003, H_2O)] was filtered from the concentrated solution. Recrystallization of the white solid (500 mg) from a small volume of EtOH afforded **14**; yield: 219 mg (25%); mp 220–221 °C; $[\alpha]_D^{27}$ +23.90 (c = 0.997, H_2O). Both $[\alpha]_D$ values of the crude and recrystallized **14** were almost identical.

IR (KBr): ν = 3550, 3500, 1725, 1610 cm^{-1}.

Anal. calcd for $C_9H_{10}ClNO$: C, 58.87; H, 5.49; N,7.63; Cl, 19.31. Found: C, 58.88; H, 5.37; N, 7.54; Cl, 19.26.

This recrystallized **14** was treated with $ClCO_2Me$ to afford *N*-CO_2Me-**14** ($[\alpha]_D^{28}$ +133.80 (*c* = 1.043, $CHCl_3$)] and the $[\alpha]_D$ value was almost the same as the literature value, $[\alpha]_D^{25}$ + 133.70 (*c* = 0.54, $CHCl_3$).[2b] Accordingly, both ee values of the recrystallized **14** and the crude **14** were determined to be 98%.

References

(1) Part 1: Itoh O.; Honnami, T.; Amano A.; Murata K.; Koichi Y.; Sugita T. *J. Org. Chem.* **1992**, *57*, 7334.
(2) (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.
(3) Statham F. S. *J. Chem. Soc.* **1951**, 213.
(4) Leuchs H. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 857.
(5) Daly W.H.; Poche D. *Tetrahedron Lett.* **1988**, *29*, 5859.
(6) Ishai D.B.; Katchalski E. *J. Am. Chem. Soc.* **1952**, *74*, 3688.
(7) Kawasaki T.; Komai T. *Polymer Journal (Tokyo)* **1983**, 743.
(8) Ookawa A.; Soai K. *J. Chem. Soc., Perkin Trans.* 1 **1987**, 1465.
(9) Goodman M.; Boardman F. *J. Am. Chem. Soc*. **1963**, *85*, 2483.
(10) Coleman D. *J. Chem. Soc.* **1951**, 2294.