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Asymmetric Synthesis of Uncommon α-Amino Acids by Diastereoselective Alkylations of a Chiral Glycine Equivalent

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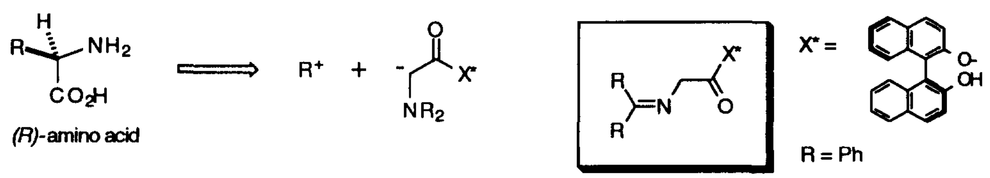
Abstract: For the purpose of practical preparations of a variety of enantiomerically pure uncommon α-amino acids, alkylations of the chiral glycine equivalent **5**, which possesses axially chiral binaphthol as an auxiliary, with several electrophiles were investigated. The alkylation proceeded smoothly in satisfactory chemical yield with high diastereoselectivities to give protected α-amino acid derivatives. The free hydroxyl group of the auxiliary played an important role for the induction of diastereoselectivity. Using *(S)*-1,1'-binaphthalene-2,2'-diol as a chiral auxiliary, D-α-amino acid derivatives having the unnatural (*R*)-configuration were predominantly obtained. Some of the alkylated products were converted into free non-proteinogenic D-α-amino acids.

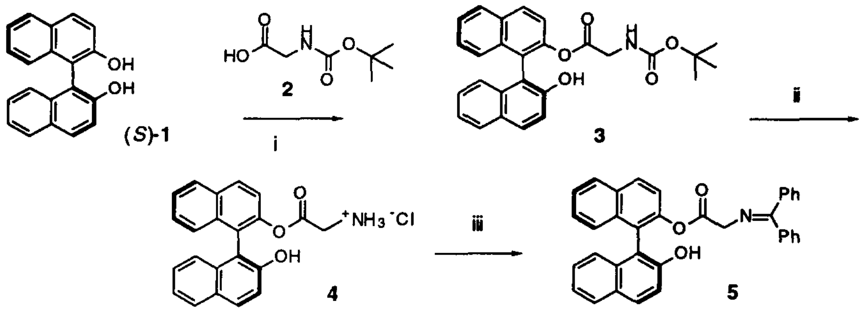
Optically active non-proteinogenic amino acids[1] are useful compounds of great interest not only because of their biological activities but also for their role for as an investigative topographic probe for bioactive conformations of peptides and the mechanisms of enzyme reactions.[2] There is a growing demand for optically active - ideally enantiomerically pure - uncommon amino acids in conjunction with the recent revolution in molecular biology and protein engineering technologies. Asymmetric synthesis is one of the most economic and direct ways to these kinds of organic molecules. Even though a large number of methods to prepare such compounds is known,[3] the development of versatile new methodology is still a challenging and important synthetic endeavor. Thus, both nucleophilic and electrophilic aminations[2e,4] of optically active carbonyl compounds have led to non-racemic α-amino acids, but the amine sources are quite limited and tedious transformation to the free amino group is necessary. Furthermore, the classical approaches involving the asymmetric hydrogenation[5] of prochiral dehydro amino acid derivatives also suffer from restrictions and the limited range of substituents of α-alkyl groups, albeit that high enantiomeric excess is obtained.



It is unquestionable that asymmetric derivatization of glycine equivalents or templates is the most promising and general approach to a wide range of α-amino acid derivatives.[3,6] In this regard, several preparatively useful methods to homologate glycine derivatives into a variety of optically active α-amino acids have been so far exploited. These are classified into alkylation of carbanion and electrophilic carbocation reactions, such as nucleophilic 1,2-addition to the CN double bond or a related bond.[7] Straightforward alkylations of glycine enolate derivatives are, however, relatively scarce, and perhaps most notable among the former methods reported to date are deprotonation/alkylation of sultam-derived compounds,[8] bis-lactim ethers,[3,9] imidazolidinones and oxazolidinones[10] reported by Seebach (self-reproduction of chirality), diphenyloxazinones,[11] pseudoephedrine amide and paracyclophane.[12]

Using 1,1'-binaphthalene-2,2'-diol as a chiral auxiliary we recently reported highly diastereoselective alkylations giving optically active α-alkylated carboxylic acid derivatives.[13] This alkylation was successfully used to prepare clinically important drugs.[13a,c] As an extension of this investigation to the application for the asymmetric synthesis of α-amino acids, this paper describes some results achieved with diastereoselective alkylations of the chirally modified glycine equivalent **5** with various electrophiles.

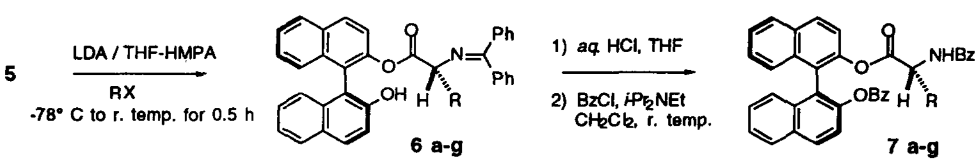
Scheme I. Preparation of the Glycine Equivalent **5**.[a]



[a] Key: i) WSC, DMAP, CH_2Cl_2, r. temp., for 1.5 h, 95% ; ii) c-HCl, EtOAc, r. temp., for 1.5 h, 90% ; iii) benzophenone imine, CH_2Cl_2, r. temp., for 2 h, 96%.

Since O'Donnell and his coworkers first reported benzophenone Schiff base substrates in 1978,[14] these protected and activated synthons have been frequently employed as a source for α-anionic amino acid equivalents.[15] We also used this convenient protecting group for the amino group, and the chiral glycine equivalent **5** was prepared as follows (Scheme I). Thus, condensation of *N*-(*t*-butoxycarbonyl)glycine **2** with (*S*)-(-)-1,1'-binaphthalene-2,2'-diol **1** in the presence of a condensing agent gave (*S*)-2'-hydroxy-1,1'-binaphthalene 2-yl-*N*-(*t*-butoxycarbonyl)glycinate **3**, which was converted to (*S*)-2'-hydroxy-1,1'-binaphthalene-2-yl-*N*-(diphenylmethylene)glycinate **5** by successive treatment with hydrochloric acid and benzophenone imine.[16]

Scheme II. Diastereoselective Alkylation of the Anion of Chirally Modified Glycine Equivalent **5**.



The alkylation of the anion of **5** was examined with methyl iodide as a standard electrophile under various reaction conditions. The methylation proceeded satisfactorily with the anion generated with 2.2 eq of LDA, at low temperature in THF containing 10 eq of HMPA by using excess methyl iodide. For completion of the reaction, the temperature was allowed to rise to room temperature for 0.5 h. It was observed that *n*-BuLi played an important role as a base due to the complex-induced proximity effect (CIPE)[17] in enolate formation of the related compounds;[13a-d] however, the alkylation of the anion generated with *n*-BuLi resulted in poorer yields of alkylated products. HMPA was found to be an essential additive responsible for both high chemical yield and diastereoselectivity.

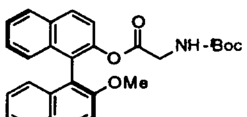
Alkylation of the anion of **5** with seven different electrophiles was carried out. Since the alkylated products **6** with diphenyl imine groups turned out to be rather unstable compounds, the corresponding alkylated products **6** were directly converted to *N*-benzoyl derivatives **7** without isolation or purification procedures (Scheme II). The isolated chemical yield for the *N*-benzoyl derivatives **7** as well as their diastereoselectivity, which was determined by both HPLC and ^{1}H NMR analyses, are listed in Table 1.

Table 1. Diastereoselective Alkylation[a] of Glycine Equivalent *(S)*-**5**.

entry	electrophile	conditions (°C, h)	product[b]	% yield[c]	de (%)[d]	configuration[e]
1	methyl iodide	-78 to r. temp., 0.5	**7a**	62[f]	82	*R*
2	allyl bromide	-78 to r. temp., 0.5	**7b**	66[f]	72	*R*
3	propargyl bromide	-78 to r. temp., 0.5	**7c**	69[f]	78[g]	*R*
4	benzyl bromide	-78 to r. temp., 0.5	**7d**	70[f]	70	*R*
5	2-(bromomethyl)naphthalene	-78 to r. temp., 0.5	**7e**	71[f]	69[g]	*R*
6	methyl bromoacetate	-78, 1.7	**6f**	71	86	--[h]
7	iodoacetonitrile	-78, 1.7	**6g**	77	80	--[h]

[a] All reactions were carried out in THF-HMPA. [b] Isolable products, **6** or **7**. [c] Isolated yield. [d] Determined by HPLC analysis of **6** or **7**. [e] Configuration at α-carbon. [f] Isolated yield of *N,O*-dibenzoylated products **7**. [g] From specific rotation. [h] Not specified.

A previous paper from our laboratories described the importance and the neighbouring group participation of the free 2'-hydroxyl group for induction of diastereoselectivity in closely related reactions.[13] It was also suggested in the above alkylations that the presence of a free hydroxy group at 2' position of the chiral auxiliary was responsible for the high induction of diastereoselectivity. Thus, for example, the allylation of 2'-methoxy-1,1'-binaphthalene-*N*-(diphenylmethylene)glycinate **9**, derived from the methyl ether **8** in a similar way, with allyl bromide under the same reaction conditions afforded the product **10** with the lower diastereoselectivity of 36% de. Furthermore, the configuration of the carbon α to the carbonyl was found to be natural *S*-configuration by the chemical transformation to ***ent*-12b** and by comparison with an authentic sample in HPLC on the chiral stationary phase (*vide infra*).



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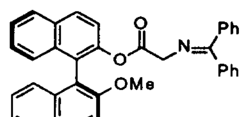

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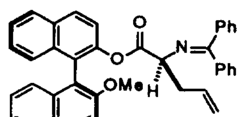

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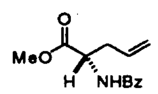
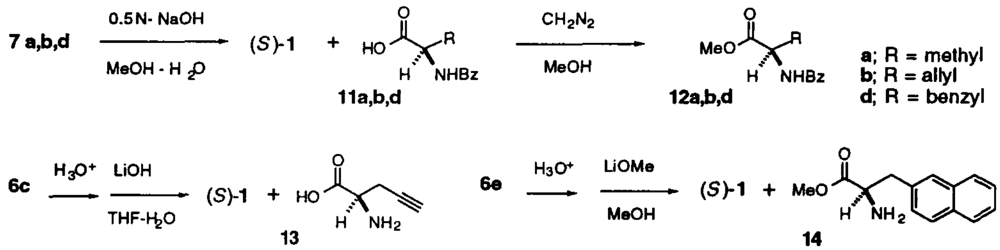


***ent*-12b**

In order to obtain α-amino acid as well as to determine the configuration at the α-carbon, the alkylated products **7** were first transformed into *N*-benzoyl α-amino acid methyl ester derivatives **12**, whose HPLC behavior was comparable to that of authentic samples on the chiral stationary phase. Comparison of the specific rotation also substantiated this finding. Although the recovered 1,1'-binaphthalene-2,2'-diol preserved its enantiomeric purity completely, racemization was observed to some extent during the alkaline hydrolysis procedure (Table 2 in Experimental section). For the propargyl derivative, the alkylated product **6c** was directly hydrolyzed by the successive treatment with N HCl and LiOH to give free propargyl glycine **13** whose specific rotation was compared with that of the authentic sample.[18] The specific rotation was also employed for determination of the stereochemistry of β-naphthylalaninate derivative. Thus, after the acidic deprotection of the imine group of **6e**, the ester exchange reaction with LiOMe was carried out to give methyl 2-naphthylalaninate **14**[19](Scheme III).

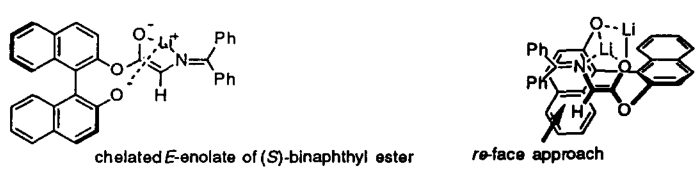
Scheme III. Conversion of the Alkylated Products **6** and **7** to α-Amino Acid Derivatives.



In the present study, the unnatural D-α-amino acids were produced by use of the *S*-enantiomer of binaphthol. There is no doubt that alkylation of the chirally modified glycine **5** with *R*-binaphthol could give the natural type of both common and uncommon α-amino acids.

Taking the crucial role of the intramolecular phenolic 2'-hydroxyl and the possible π–π stacking between the phenyl of the protective group and the naphthalene ring into account, the observed stereochemistry in the alkylation of the lithium enolate of **5** with electrophiles can be explained by consideration of a plausible transition state model, where the lithium metal forms a rigid tridentate complex and the electrophile approaches from the less hindered *re* side of the π-face of the *E*-enolate of **5** (Figure 1).

Figure 1. Proposed Conformation and Alkylation of the Chelated *E*-enolate of (*S*)-**5** Leading to D-α-Amino Acid Derivatives.



Since both enantiomers of 1,1'-binaphthalene-2,2'-diol are commercially available, the reaction sequence presented in this paper allows for practical synthesis of a wide variety of common as well as uncommon α-amino acid derivatives with predicted stereochemistry.

Experimental

General Aspects. Melting points are uncorrected. Otherwise specified, the proton nuclear magnetic resonance (^1H NMR) spectra were taken at 200 MHz in $CDCl_3$ with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard, and couplings are expressed in hertz. Infrared (IR) spectra were measured in $CHCl_3$. THF was distilled from sodium benzophenone ketyl, and CH_2Cl_2 was from calcium hydride. Hexamethylphosphoramide (HMPA) was freshly distilled from calcium hydride under reduced pressure before use. Lithium diisopropylamide (LDA) was generated by treatment of diisopropylamide (1.1 eq) in THF with *n*-BuLi (1.0 eq of 1.68M in hexane) at -78 °C under argon and by stirring for 15 min at 0 °C. Unless otherwise noted, all reaction were run under an argon or nitrogen atmosphere. All extractive organic solution were dried over anhydrous magnesium sulfate. Flash column chromatography was carried out with silica gel 60 spherical (150-325 mesh) and silica gel 60 F254 plates (Merck) were used for preparative TLC (pTLC). Diastereomeric excess (de) of the alkylated products (**7a-e, 6g**) was determined by HPLC analysis on the Shimpak Silica prepacked column (Shimadzu Co.) with a solvent system of hexane:*i*PrOH = 99.4:0.6 and the Puresil C_{18} column (Waters Co.) was used for **6e** and **6f** with $MeOH:CH_3CN:H_2O$ = 3:2:1 and $MeOH:H_2O$ = 75:25, respectively. Enantiomeric excess (ee) of α-amino acid methyl esters was determined by HPLC analysis on a Chiralpak AD column (Daicel Co.) with hexane:*i*PrOH = 90:10, and a Chiralpak AS column (hexane:*i*PrOH = 80:20, Daicel Co.) was used for analysis of the recovered *S*-(-)-binaphthol.

2'-Hydroxy-1,1'-binaphthalene-2-yl-*N*-(*t*-butoxycarbonyl)glycinate 3. A solution of *N*-(*t*-butoxycarbonyl)glycine (514 mg, 2.94 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of *S*-(-)-binaphthol (1.0 g, 3.53 mmol, 1.2 eq), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (846 mg, 4.4 mmol, 1.5 eq) and 4-dimethylaminopyridine (36 mg, 0.29 mmol, 0.1 eq) in 30 mL of CH_2Cl_2 at 0 °C and the mixture was stirred for 1.5 h at the same temperature. The reaction mixture was poured into cold 5 % HCl solution and extracted with CH_2Cl_2. The extract was washed with water, dried and evaporated. The residual product was purified by flash column chromatography with hexane:EtOAc = 3:1 to give **3** (1.23g) as colorless powder in 95% yield.

3: mp 82-83 °C; $[\alpha]_D^{18}$ -76.7 (c 1.0, $CHCl_3$); IR 3520, 3450, 3080-2920, 1770, 1710, 1150 cm^{-1}; ^1H NMR δ 1.39 (s, 9H), 3.49 (dd, 1H, *J* = 18.7, 5.8) 3.70 (dd, 1H, *J* = 18.7, 6.2), 4.78 (brt, 1H, *J* = 5.4), 5.73 (s, 1H), 6.98-8.05 (m, 12H); MS *m/z* 443 (M^+); HRMS *m/z* calcd for $C_{27}H_{27}NO_5$ (M^+) 443.1734, found 443.1714. Anal. Calcd for $C_{27}H_{27}NO_5$: C, 73.12; H, 5.68; N, 3.16. Found: C, 72.38, H, 5.67; N, 3.09.

2'-Hydroxy-1,1'-binaphthalene-2-yl-glycinate Hydrochloride 4. To a stirred solution of **3** (111 mg, 0.25 mmol) in EtOAc (3 mL), c-HCl (0.2 mL) was added at room temperature and the mixture was stirred for 1.5 h. The solvent was evaporated, and the precipitated products were collected by filtration, washed with cold EtOAc several times, and finally dried *in vacuo* to give **4** (94 mg) in 90% yield as off-white amorphous powder, which were purified by recrystallization from EtOH-H_2O to give colorless crystals.

4: mp 156-158 °C (plates from EtOH-H_2O). Anal. Calcd for $C_{22}H_{18}NClO_3{\cdot}2H_2O$: C, 63.53; H, 5.33; N, 3,37. Found: C, 63.45; H, 5.25; N, 3.36.

2-Hydroxy-1,1'-binaphthalene-2-yl-*N*-(diphenylmethylene)glycinate 5. To a stirred solution of **4** (208 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) at room temperature, benzophenone imine (101 mg, 0,56 mmol) was added and the mixture was stirred for 2 h, and then poured into water. The mixture was extracted with CH_2Cl_2 and the extracts were dried, and evaporated. The residual product was purified by preparative recycle HPLC on a direct connection of H-1 and H-2 JAIGEL columns (JAI Co.) with $CHCl_3$ to give **5** (243 mg) as colorless powder in 96% yield.

5: mp 68 °C; $[\alpha]_D^{18}$ -77.5 (c 1.1, $CHCl_3$); IR 3350, 3080-2900, 1760, 1140 cm^{-1}; ^1H NMR δ 3.93 (d, 1H, *J* = 17.2), 4.09 (d, 1H, *J* = 17.2), 6.78-8.06 (m, 22H); MS *m/z* 507 (M^+); HRMS calcd for $C_{35}H_{25}NO_3$ (M^+) 507.1836, Found 507.1816. Anal. Calcd for $C_{35}H_{25}NO_3$: C, 82.82; H, 4.96; N, 2.76. Found: C, 81.24, H, 4.76; N, 2.82.

General Procedure for Alkylation of (*S*)-5. The methylation of (*S*)-**5** is typical. To a stirred solution of **5** (121 mg, 0.24 mmol) in dry THF (4 mL), the LDA solution (0.25 mmol, 2,2 eq) was added at -78 °C. Then, HMPA (415 μL, 2.4 mmol, 10 eq) and methyl iodide (1.48 μL, 2.4 mmol, 10 eq) were added, and the mixture was allowed to room temperature with stirring by removal of the cooling bath. Stirring was continued for 0.5 h and the reaction mixture was poured into water, extracted with EtOAc. The organic layer was dried, and evaporated. The crude product **6a** was used in next step without further purification. N HCl solution (3 mL) was added to a solution of **6a** in 4 mL of THF at room temperature, and the mixture was stirred for 0.5 h, then made alkaline with 25% NH_4OH to pH 10. The extraction with EtOAc, drying and evaporation of the solvent left the crude residue of the mixture, which was separated by flash column chromatography with a short column using hexane : EtOAc = 3:2 as a first eluent and $CHCl_3$: MeOH = 3:1 as a second eluent. The $CHCl_3$-MeOH fractions were collected and evaporated. The product in CH_2Cl_2 (5 mL) was treated with benzoyl chloride (111 μL, 0.96 mmol, 4 eq) and diisopropylethylamine (167 μL, 0.96 mmol, 4 eq) at 0 °C and stirred at room temperature for 2 h. The reaction mixture was poured into cold diluted HCl, extracted with EtOAc and washed with water. The organic layer was dried, and evaporated. The residue was purified by pTLC (hexane:CH_2Cl_2:acetone = 4:1:1) to give **7a** (83 mg, 82% de) in 62% yield as amorphous solids.

2'-Hydroxy-1,1'-binaphthalene-2-yl-*N*-(diphenylmethylene)alaninate 6a: IR 3550, 3150-2850, 1760, 1200-1100 cm^{-1}; ^1H NMR δ 1.06 (d, 3H, *J* = 6.6), 3.98 (q, 1H, *J* = 6.7), 6.68-8.08 (m, 22H); MS *m/z* 521 (M^+); HRMS *m/z* calcd for $C_{36}H_{27}NO_3$ (M^+) 521.1990, found 521.1954.

2'-Benzoyloxy-1,1'-binaphthalene-2-yl-*N*-benzoyl-alaninate 7a: $[\alpha]_D^{17}$ -0.79 (c 1.0, $CHCl_3$, 89% de); IR 3450, 3050-2900, 1760-1730, 1200-1150 cm^{-1}; ^1H NMR δ 0.91 (d, 3H, *J* = 7.1), 4.78 (m, 1H), 6.50 (d, 1H, *J* = 8.1), 7.15-8.08 (m, 22H); MS *m/z* 565 (M^+); HRMS *m/z* calcd for $C_{37}H_{27}NO_5$ (M^+) 565.1888, found 565.1888.

2'-Hydroxy-1,1'-binaphthalene-2-yl-*N*-(diphenylmethylene)allylglycinate 6b: IR 3550, 3080-2850, 1740, 1150 cm^{-1}; ^1H NMR δ 2.28-2.50 (m, 2H), 3.97 (dd, 1H, *J* = 7.6, 5.9), 4.88-4.96 (m, 2H), 5.39 (m, 1H), 6.51 (d, 2H, *J* = 7.1) 6.09-8.07 (m, 22H); MS *m/z* 547 (M^+); HRMS *m/z* calcd for $C_{38}H_{29}NO_3$ (M^+) 547.2148, found 547.2162.

2'-Benzoyloxy-1,1'-binaphthalene-2-yl-*N*-benzoyl-allylglycinate 7b: mp 136-137 °C (colorless powder); $[\alpha]_D^{16}$ +18.9 (c 1.2, $CHCl_3$, 66% de); IR 3440-3350, 3080-2920, 1760-1740, 1280-1140 cm^{-1}; ^1H NMR δ 1.93 (m, 1H), 2.25 (m, 1H), 4.70-5.15 (m, 4H), 6.46 (d, 1H, *J* = 8.4) 7.05-8.10

(m, 22H); MS *m/z* 591 (M^+), 390, 105, 77; HRMS *m/z* calcd for $C_{39}H_{29}NO_5$ (M^+) 591.2045, found 591.2008.

2'-Hydroxy-1,1'-binaphthalene-2-yl-*N*-(diphenylmethylene)propargylglycinate 6c: mp 78 °C (colorless powder); IR 3550, 3310, 3070-2920, 1750, 1150 cm^{-1}; ^1H NMR δ 1.87 (t, 1H, *J* = 2.6), 2.42-2.67 (m, 2H), 4.16 (dd, 1H, *J* = 7.8, 5.9), 6.55 (d, 2H, *J* = 7.0), 7.0-8.1 (m, 20H); MS *m/z* 545 (M^+); HRMS *m/z* calcd for $C_{38}H_{27}NO_3$ (M^+) 545.1990, found 545.1978.

2'-Benzoyloxy-1,1'-binaphthalene-2-yl-*N*-benzoyl-propargylglycinate 7c: mp 151-153 °C (colorless powder); 78% de by HPLC; IR 3440, 3320, 3060-2920, 1760-1740, 1180 cm^{-1}; ^1H NMR δ 1.56 (t, 1H, *J* = 2.6), 2.40 (ddd, 1H, *J* = 17.0, 5.3, 2.6), 2.60 (ddd, 1H, *J* = 17.1, 5.5, 2.6), 4.90 (dt, 1H, *J* = 8.3, 5.4), 6.80 (d, 1H, *J* = 8.2), 7.14-8.1 (m, 22H); MS *m/z* 589 (M^+); HRMS *m/z* calcd for $C_{39}H_{27}NO_5$ (M^+) 589.1889, found 589.1859.

2'-Hydroxy-1,1'-binaphthalene-2-yl-*N*-(diphenylmethylene)phenylalaninate 6d: IR 3550, 3080-2920, 1750, 1150 cm^{-1}; ^1H NMR δ 2.90 (d, 2H, *J* = 7.0), 4.03 (t, 1H, *J* = 6.8), 5.83 (d, 2H, *J* = 7.0), 6.83-8.03 (m, 20H); MS *m/z* 597 (M^+); HRMS *m/z* calcd for $C_{42}H_{31}NO_3$ (M^+) 597.2304, found 597.2308.

2'-Benzoyloxy-1,1'-binaphthalene-2-yl-*N*-benzoyl-phenylalaninate 7d: mp 76-78 °C (colorless powder); $[\alpha]_D^{16}$ -62.5 (c 1.1, $CHCl_3$, 57% de); IR 3440-3360, 3080-2920, 1760-1730, 1280-1140 cm^{-1}; ^1H NMR δ 2.57 (dd, 1H, *J* = 14.0, 7.4), 2.91(dd, 1H, *J* = 14.0, 6.4), 4.96 (m, 1H), 6.52 (d, 1H, *J* = 8.1), 6.85-7.95 (m, 27H); MS *m/z* 641 (M^+); HRMS *m/z* calcd for $C_{43}H_{31}NO_5$ (M^+) 641.2203, found 641.2229.

2'-Hydroxy-1,1'-binaphthalene-2-y-*N*-(diphenylmethylene)-2-naphthylalaninate 6e: mp 84-87 °C (colorless powder); IR 3550, 3080-2850, 1750, 1150 cm^{-1}; ^1H NMR δ 3.04-3.08 (m, 2H), 4.16 (dd, 1H, *J* = 8.2, 5.7), 5.75 (d, 2H, *J* = 7.0), 6.79-8.05 (m, 27H); MS *m/z* 647 (M^+); HRMS *m/z* calcd for $C_{46}H_{33}NO_3$ (M^+) 647.2459, found 647.2434.

2'-Benzoyloxy-1,1'-binaphthalene-2-yl-*N*-benzoyl-2-naphthylalaninate 7e: mp 78-79 °C (colorless powder); $[\alpha]_D^{16}$ +30.1 (c 0.95, $CHCl_3$, 71% de); IR 3450-3350, 3050-2920, 1760-1730, 1200-1150 cm^{-1}; ^1H NMR δ 2.75 (dd, 1H, *J* = 14.0, 7.1), 3.05 (dd, 1H, *J* = 14.0, 6.4), 5.01 (m, 1H), 6.56 (d, 1H, *J* = 8.1), 7.03-8.10 (m, 29H); MS *m/z* 494 (M^+-197), 390, 141, 105, 77.

2'-Hydroxy-1,1'-binaphthalene-2-yl-*N*-(diphenylmethylene)acetoxylalaninate 6f: $[\alpha]_D^{17}$ +89.5 (c 1.0, $CHCl_3$, 86% de); IR 3540, 3080-2850, 1740, 1170-1150 cm^{-1}; ^1H NMR δ 2.51 (dd, 1H, *J* = 16.7, 6.4), 2.94 (dd, 1H, *J* = 16.6, 7.2), 3.59 (s, 3H), 4.34 (t, 1H, *J* = 6.7), 6.48-8.09 (m, 22H); MS *m/z* 579 (M^+); HRMS *m/z* calcd for $C_{38}H_{29}NO_5$ (M^+) 579.2045, found 579.2024

2'-Benzoyloxy-1,1'-binaphthalene-2-yl-*N*-benzoyl-acetoxylalaninate 7f: 44% yield from **6f**; $[\alpha]_D^{17}$ -36.7 (c 0.8, $CHCl_3$); IR 3440, 3080-2880, 1760-1730, 1250-1160 cm^{-1}; ^1H NMR δ 2.71 (dd, 1H, *J* = 16.6, 5.1), 2.81 (dd, 1H, *J* = 16.9, 5.5), 5.02 (m, 1H), 7.06 (d, 1H, *J* = 8.1), 7.19-8.14 (m, 22H); MS *m/z* 494 (M^+-129), 390, 105, 77.

2'-Hydroxy-1,1'-binaphthalene-2-yl-*N*-(diphenylmethylene)cyanoalaninate 6g: mp 87-89 °C (colorless powder); $[\alpha]_D^{17}$ +87.6 (c 1.1, $CHCl_3$, 80% de); IR 3560, 3070-2920, 2360, 1760, 1150 cm-1; ^1H NMR δ 2.50 (dd, 1H, *J* = 16.6, 4.4), 2.67 (dd, 1H, *J* = 16.7, 8.9), 4.23 (dd, 1H, *J* = 8.9, 4.5), 6.89-8.10 (m, 22H); MS *m/z* 546 (M^+); HRMS *m/z* calcd for $C_{37}H_{26}N_2O_3$ (M^+) 546.1943, found 546.1933.

2'-Benzoyloxy-1,1'-binaphthalene-2-yl-*N*-benzoyl-cyanoalaninate 7g: 44% yield from **6g**; $[\alpha]_D^{17}$ -61.5 (c 1.9, $CHCl_3$); IR 3440, 3080-2880, 1760-1730, 1250-1160 cm^{-1}; ^1H NMR δ 2.67 (dd, 1H, *J* = 17.0, 6.0), 2.87 (dd, 1H, *J* = 17.0, 5.9), 4.96 (dt, 1H, *J* = 8.0, 6.0), 7.04-8.14 (m, 23H); MS *m/z* 494 (M^+-96), 390, 105, 77.

2'-Methoxy-1,1'-binaphthalene-2-yl-*N*-(*t*-butoxycarbonyl)glycinate 8. The methyl ether **8** was prepared in the same manner as the preparation of **3** described above. Thus, starting from (*S*)-2'-methoxy-1,1'-binaphthalene-2-ol (540 mg, 1.8 mmol) **8** (676 mg) was obtained in 82% yield after purification by flash column chromatography with hexane:EtOAc (4:1) as amorphous solids.
8: mp 67-68 °C (colorless powder); $[\alpha]_D^{18}$ +13.4 (c 1.1, $CHCl_3$); IR 3450, 3070-2840, 1770, 1720, 1270-1150 cm^{-1}; ^1H NMR δ 1.38 (s, 9H), 3.47 (dd, 1H, *J* = 18.4, 5.1), 3.69 (dd, 1H, *J* = 18.4, 6.2), 3.74 (s, 3H), 4.68 (brs, 1H), 7.06-8.00 (m, 12H); MS *m/z* 457 (M^+); HRMS *m/z* calcd for $C_{28}H_{27}NO_5$ (M^+) 457.1890, found 457.1892.

2'-Methoxy-1,1'-binaphthalene-2-yl-*N*-(diphenylmethylene)glycinate 9. The compound **9** (518 mg) was obtained in the same procedures as those for **4** and **5** in 87% yield from **8** (520 mg, 1.14 mmol), after purification by flash column chromatography with hexane:EtOAc (5:1) as amorphous solids.
9: mp 55-56 °C (colorless powder); $[\alpha]_D^{18}$ +22.3 (c 1.2, $CHCl_3$); IR 3080-2840, 1760, 1150 cm-1; ^1H NMR δ 3.64 (s, 3H), 4.02 (s, 2H), 6.70-8.00 (m, 22H); MS *m/z* 521 (M^+); HRMS *m/z* calcd for $C_{36}H_{27}NO_3$ (M^+) 521.1990, found 521.1956.

2'-Methoxy-1,1'-binaphthalene-2-yl-*N*-(diphenylmethylene)allylglycinate 10.
Following the general procedure for alkylation described above, **9** (102 mg, 0.20 mmol) gave **10** (78 mg, 36% de) in 71% yield after purification by flash column chromatography with hexane:EtOAc (4:1). In this case, the diastereomeric excess (de) was determined by ^1H NMR.
10: $[\alpha]_D^{18}$ -36.7 (c 1.0, $CHCl_3$); IR 3070-2840, 1760, 1200-1120 cm^{-1}; ^1H NMR δ 2.16-2.40 (m, 2H), 3.60 (s, 3H), 3.91 (dd, 1H, *J* = 7.6, 5.5), 3.95-4.77 (m, 2H), 5.33 (m, 1H), 6.34-7.99 (m, 22H); MS *m/z* 561 (M^+); HRMS *m/z* calcd for $C_{39}H_{31}NO_3$ (M^+) 561.23 04, found 561.2307.

General Procedure for Hydrolysis of Alkylated Products. The alkaline hydrolysis of **7a** is typical. To a stirred solution of **7a** (72.4 mg, 0.13 mmol, 89 % de) in aq. 10% MeOH (10 mL), 0.5 M solution of NaOH (1 mL) was added and the mixture was stirred for 0.5 h at room temperature and then poured into water. The whole was extracted with EtOAc. The organic layer was washed with water, dried, and evaporated to leave the residual product, which was purified by pTLC (hexane : EtOAc = 3:1) to give *S*-(-)-binaphthol (28.5 mg, 78%, >99% ee). The aqueous layers were combined and acidified with N HCl solution to pH 2 and the resulting mixture was extracted with EtOAc. The extract was dried, and evaporated to give the residue, which was methylated with CH_2N_2 without purification. Thus, the residue in MeOH was treated with ethereal CH_2N_2 at 0 °C. The resulting methyl ester was purified by pTLC (hexane: EtOAc = 3:2) to give **12a** (22.4 mg) in 85 % yield (Table 2).

***N*-Benzoylalanine Methyl Ester 12a:** $[\alpha]_D^{17}$ -21.9 (c 1.1, $CHCl_3$, 81% ee); IR 3680, 3440, 3080-2840, 1740, 1660, 1240-1160 cm^{-1}; ^1H NMR δ 1.51 (d, 2H, *J* = 7.2), 3.78 (s, 3H), 4.80 (q, 1H, *J* = 7.2), 6.92 (brd, 1H, *J* = 6.9), 7.39-7.84 (m, 5H); MS *m/z* 207 (M^+), 148, 105, 77.

***N*-Benzoylallylglycine Methyl Ester 12b:** 72% yield; $[\alpha]_D^{16}$ -31.0 (c 1.2, $CHCl_3$, 61% ee); IR 3440, 3080-2840, 1740, 1660, 1280-1160 cm^{-1}; ^1H NMR δ 2.66 (m, 2H), 3.78 (s, 3H), 4.88 (m, 1H), 5.15 (m, 2H), 5.74 (m, 1H), 6.73 (brd, 1H, *J* = 6.8), 7.28-7.82 (m, 5H); MS *m/z* 233 (M^+), 192, 174, 112, 105, 77.

***N*-Benzoylphenylalanine Methyl Ester 12d:** 89% yield; $[\alpha]_D^{16}$ -62.5 (c 1.1, $CHCl_3$, 57% ee); IR 3440, 3080-2840, 1740, 1660, 1230-1180 cm^{-1}; ^1H NMR δ 3.22 (dd, 1H, *J* = 13.8 , 5.4), 3.32 (dd, 1H *J* = 13.6, 5.6), 5.08 (dt, 1H, *J* = 7.5, 5.7), 6.59 (brd, 1H, *J* = 7.4), 7.12-7.76 (m, 10H); MS *m/z* 283 (M^+), 224, 162, 105, 77.

***N*-Benzoyl-acetoxylalanine Methyl Ester 12f:** 94% yield; $[\alpha]_D^{18}$ -33.2 (c 2.1, $CHCl_3$, 54% ee); IR 3440, 3040-2850, 1740, 1660, 1240-1180 cm^{-1}; ^1H NMR δ 2.97 (dd, 1H, *J* = 17.3, 4.6), 3.15 (dd, 1H, *J* = 17.3, 4.2), 3.71 (s, 3H), 3.80 (s, 3H), 5.08 (dt, 1H, *J* = 8.4, 4.4), 7.28-7.84 (m, 6H); MS *m/z* 265 (M^+); HRMS *m/z* calcd for $C_{13}H_{15}NO_5$ (M^+) 265.0949, found 265.0942.

***N*-Benzoyl-cyanoalanine Methyl Ester 12g:** 48% yield; IR 3430, 3040-2850, 2350, 1750, 1670, 1230 cm^{-1}; ^1H NMR δ 3.07 (dd, 1H, *J* = 17.0, 4.3), 3.26 (dd, 1H, *J* = 17.0, 5.3), 3.91 (s, 3H), 4.96 (dt, 1H, *J* = 6.4, 5.2), 7.12 (brd, 1H, *J* = 7.0), 7.28-7.84 (m, 5H); MS *m/z* 232 (M^+); HRMS *m/z* calcd for $C_{12}H_{12}N_2O_3$ (M^+) 232.0847, found 232.0821.

***N*-Benzoylallylglycine Methyl Ester *ent*-12b from 10.** The benzoylation of **10** (20 mg, 0.04 mmol) was carried out by the same procedure as above. Without purification, the crude product was subjected to alkaline hydrolysis and methylation with ethereal CH_2N_2 in a similar way to the preparation of **12b**. The *N*-benzoyl methyl ester ***ent*-12b** (8.0 mg, 32% ee) was obtained in 96% yield.

Propargylglycine 13. To a stirred solution of **6c** (159.4 mg, 0.29 mmol) in THF (10 mL), N HCl solution (5 mL) was added and the mixture was stirred for 20 min at room temperature. The resulting mixture was made alkaline with 25% NH_4OH to pH 10 and extracted with EtOAc. The extract was dried, and evaporated to leave the residue, which was dissolved in THF-H_2O (7.5 mL, 2:1) without purification. $LiOH{\bullet}H_2O$ (49 mg, 1.17 mmol, 4 eq) was added and the mixture was stirred at room temperature. After 2.5 h, the mixture was made acidic with N HCl solution to pH 2 and extracted with CH_2Cl_2. The organic layer was washed with water, dried, and evaporated. The residue was purified with pTLC (hexane/EtOAc (3:1)) to give *S*-(-)-binaphthol (77.4 mg, 93%, > 99% ee). The aqueous layer was adsorpted on ion exchange resin (Dowex 50w x 8, H^+ form) and desorpted with aqueoùs NH_4OH to furnish **13** (33 mg) in 94% yield. The crude amino acid thus obtained was purified by recrystallization from EtOH-H_2O.
13: $[\alpha]_D^{18}$ +20.6 (c 1.0, H_2O, 66% ee); ^1H NMR (D_2O) δ 2.53 (t, 1H, *J* = 2.6), 2.86 (dd, 1H, *J* = 5.4, 2.6), 3.92 (t, 1H, *J* = 5.4).

2-Naphthylalanine Methyl Ester 14. The benzophenone imine group of **6e** (285 mg, 0.44 mmol) was removed by the same procedure as above for **13** to give the crude product, which, without purification, was dissolved in MeOH (10 mL). A solution of LiOMe in MeOH (4 mL, 1.2 M) added at 0 °C, and the mixture was stirred for 1 h and then for 1 h at room temperature. The resulting mixture was poured

into water and worked up as usual. The crude product was purified by pTLC (hexane:CH_2Cl_2:acetone = 4:1:1) to give **14** (67 mg, 66%) and *S*-(-)-binaphthol (107 mg, 85%, > 99% ee).
14: $[\alpha]_D^{21}$ -13.5 (c 1.1, EtOH, 80% ee); IR 3380, 3080-2840, 1740, 1280-1160 cm^{-1}; ^1H NMR δ 2.99 (dd, 1H, *J* = 13.5, 8.0), 3.25 (dd, 1H, *J* =13.5, 5.2) 3.72 (s, 3H), 3.82 (dd, 1H, *J* = 8.1, 5.1), 7.29-7.84 (m, 7H); MS *m/z* 229 (M^+), 170, 141, 115, 88.

Table 2. Conditions for Removal of Chiral Auxiliary to α-Amino Acid Derivatives.

naphthyl esters (% de)	conditions (% yield)	α-amino acid derivatives (% ee)
7a (89)	0.5N NaOH/MeOH-H_2O at r. temp. for 15 min (85[a])	**12a** (81[b])
7b (64)	0.5N KOH/MeOH-H_2O at r. temp. for 30 min (72[a])	**12b** (59[b])
7d (60)	0.5N NaOH/MeOH-H_2O at r. temp. for 30 min (89[a])	**12d** (55[b])
7f (86)	0.5N NaOH/MeOH-H_2O at r. temp. for 30 min (94[a])	**12f** (54[b])
7g (74)	LiOMe/MeOH at r. temp. for 2 h (48)	**12g** (2[b])
6c (--)	1) HCl 2) LiOH/THF-H_2O at r. temp. for 2.5 h (94)	**13** (66[c])
6e (81)	1) HCl 2) LiOMe/MeOH at r. temp. for 2 h (66)	**14** (80[c])

[a] Isolated yield after methylation with CH_2N_2. [b] Determined by HPLC. [c] Determined by $[\alpha]_D$.

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