# Phase Transfer Catalyst (PTC) Catalyzed Alkylations of Glycinamides for Asymmetric Syntheses of α-Amino Acid Derivatives

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The chiral amine auxiliary mediated stereoselective alkylation reactions of glycinamides **1**-**6** and **15**-**17** using phase transfer catalyst (PTC) for liquid-solid extraction are described. The secondary *N*-(diphenylmethylene) glycinamides **1**, **2** and **3** give better selectivities and yields than tertiary *N*-(diphenylmethylene) glycinamides **4**, **5** and **6**. Alkylation of the glycinamide **1** and **2** using 18-Crown-6 as a PTC in toluene at –40 °C gives best selectivities and yields. Alkylations of *N*-(4-chlorophenylmethylene)glycinamides **15**, **16** and **17** under same PTC conditions give α,α-disubstituted amino acid derivatives **18**, **19** and **20** with low diastereoselectivities.

**Keywords :** Phase transfer catalyst, Amino acids, Chiral auxiliary, Crown ether, Alkylation.

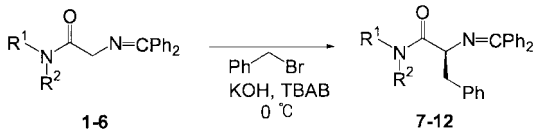
## Intoduction

Preparation of peptides modified with nonproteinogenic amino acids has become increasingly important area in organic syntheses, because nonproteinogenic amino acid plays special role in peptidomimetics with enhanced properties. Accordingly, development of efficient methods for the asymmetric syntheses of unnatural α-amino acids has become of great importance and numerous studies have been made for this purpose as seen in recent reviews.[1] One of the most useful and efficient methods is the electrophilic alkylation of enolates generated by the deprotonation of α-hydrogen of glycine derivatives.[1d] The reactions of enolates generated by deprotonation represent a widely exploited part of phase transfer catalysis (PTC) applications. Such enolates are obtained using concentrated alkaline solutions or solid bases (NaOH, KOH etc.) instead of expensive and very strong organometallic bases, metal amides and metal alkoxides in strictly dry media of which extreme reaction conditions are not compatible with economical large-scale syntheses. PTC offers many advantages as a process technology; high yield, environmental aspects, safety, lower costs, and simple reaction procedures.[2] For PTC catalyzed asymmetric organic syntheses, an intensive progress has been made recently, as there has been only a limited number of successful examples, most of which use ammonium salts derived from cinchona alkaloids as a chiral PTC.[3,4] Also, although asymmetric induction using chiral auxilliary is still efficient and has some advantages,[5] chiral auxiliary mediated reaction using PTC remains poorly studied due to the possibility of hydrolysis under basic conditions to give the chiral auxiliary and the amino acid moiety. In this paper, we describe the chiral auxiliary mediated stereoselective alkylation reactions of glycinamides using phase transfer catalyst (PTC) for the asymmetric syntheses of nonproteinogenic α-mono-, α,α-disubstituted amino acid derivatives.

## Results and Discussion

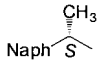
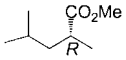
Aldimines and ketimines of glycine ester have been successfully used under PTC condition for asymmetric syntheses of amino acid derivatives.[3,4] However, those of glycinamide have not been much used in PTC catalyzed reaction, even though glycinamide offer advantages over glycine ester due to the better stability under PTC condition. We have recently reported the stereoselective alkylation of *N*'-((*S*)-phenylethyl)-*N*-(diphenylmethylene)glycinamide (**1**) for the asymmetric syntheses of α-amino acids under PTC conditions.[6] In connection with the previous work, we here report the results on the stereoselective mono- and dialkylation reactions of glycinamides **1**-**6** and **15**-**17** using phase transfer catalyst (PTC) for asymmetric syntheses of amino acids derivatives.

As a first step toward finding more efficient chiral inducer which is inexpensive and available in quantity in both enantiomeric forms, we chose to investigate six different chiral amine auxiliaries as shown in Table 1. Initial attempts to alkylate the glycinamides **1**-**6** were carried out with powered KOH (3 equiv), benzyl bromide (1.5 equiv) and tertrabutyl ammonium bromide (TBAB, 30 mol%) in toluene at 0 °C to provide the benzylated product **7**-**12** as shown in Table 1. Because two diastereomers of the products **7**-**12** were not clearly distinguishable by $^1$H-NMR (400 MHz), the stereochemical outcome of these alkylation processes was determined using chiral HPLC after acidic hydrolysis of **7**-**12** removing chiral auxiliary and diphenylmethylene moiety. Two diastereomeric mixture of **7**-**12** was converted to methyl *N*-(diphenylmethylene) glycinate in 80-90% yield under conventional acidic cleavage condition and both $NH_2$ and $CO_2H$ protections. Glycinamide **1** gave the benzylated product **7** with 68 : 32 dr (diastereomeric ratio) in 52% yield, while in methylene chloride **7** was obtained in 47% yield with 64 : 36 dr with *S*-configuration as a major at newly




**1-6** **7-12**

**Table 1**. Asymmetric Benzylations of *N*-(diphenylmethylene)-glycinamides **1-6**

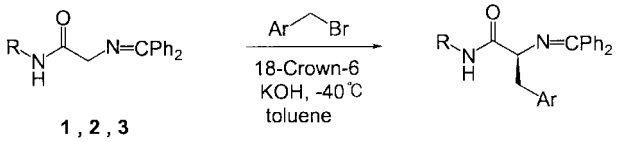
| Glycinamide | $R^1$ | $R^2$ | Solvent | %Yield[a] (product) | Dr[b] (*S*:*R*)[c] |
|---|---|---|---|---|---|
| **1** |  | H | Toluene<br>$CH_2Cl_2$ | 52 (**7**)<br>47 (**7**) | 68 : 32<br>64 : 36 |
| **2** |  | H | Toluene | 57 (**8**) | 67 : 33 |
| **3** |  | H | Toluene | 30 (**9**) | 55 : 45 |
| **4** |  | $CH_3$ | Toluene | 18 (**10**) | 48 : 52 |
| **5** |  | $CH_3$ | Toluene<br>$CH_2Cl_2$ | 16 (**11**)<br>21 (**11**) | 41 : 59<br>33 : 67 |
| **6** |  | $CH_3$ | Toluene<br>$CH_2Cl_2$ | 12 (**12**)<br>19 (**12**) | 43 : 57<br>32 : 68 |

[a]The yields are not optimized, and trace amount of imine moiety deprotected product was observed during purification by column chromatography. [b]The drs are determined after hydrolysis of crude reaction mixture by CSP-HPLC (Chiralcel-OD) with hexane and 2-propanol as solvent. [c]Configuration at $\alpha$-position

generated chiral center. *N*′-((*S*)-(1-naphtyl)ethyl)-*N*-(diphenylmethylene)glycinamide (**2**) gave **8** in 57% yield and 67 : 33 dr. When methyl leucinate was used as chiral auxiliary for the alkylation, the modification of dipeptide **4** gave **10** in 30% yield with 55 : 45 dr. It is well known that the N-H proton in secondary amide should have a p$K_a$ in the range of 21-26 (in DMSO), while $\alpha$-protons of glycine ketimines have a p$K_a$ of approximately 18-20 (in DMSO).[8] From this assessment of acidities of protons, the selective alkylation at the $\alpha$-carbon of Schiff base could be expected under above PTC conditions with no detection of *N*-alkylated product. To understand the effect of acidic N-H bond of secondary glycinamide **1-3**, the alkyation of the tertiary amide **4-6** bearing N-$CH_3$ bond was also investigated. The alkylation of *N*′-Methyl-*N*′-((*S*)-phenylethyl)-*N*-(diphenylmethylene) glycinamide (**4**) provided the product **10** in only 18% yield with 48 : 52 dr. The reactions of (*S*,*S*)-Pseudoephedrine-*N*-(diphenylmethylene)glycinamide (**5**) and (*R*,*S*)-Ephedrine-*N*-(diphenylmethylene)glycinamide (**6**) under the same PTC condition gave the benzylated products **11** and **12** in 16% and 12% yields respectively.[7] Some *O*-alkylated products were observed in both reactions of **5** and **6**. The drs of **11** and **12** are 41 : 59 and 43 : 57 respectively with *R*-configuration as a major at newly generated chiral center. In methylene chloride, drs were improved to 33 : 67 and 32 : 68 respectively. As shown in Table 1, the reactions of tertiary amides **4**, **5** and **6** give low yields and low stereoselectivities with *R*-configuration as a major, while the reactions of the secondary amides **1**, **2** and **3** gave better yields and selectivities with *S*-configuration as a major. The presence of N-H bond is crucial for high yield and selectivity.

A number of experiments was conducted for the improvement of the stereoselective benzylation reaction of glycinamide **1**. Variations were made in the solvent first. Other solvents such as *n*-Hexane, diethyl ether, THF, Xylene, $CH_3CN$ and $CHCl_3$ were attempted, but in most cases the obtained drs were a little lower and in $CHCl_3$ the reaction did not provide the product. A variety of bases was used for the alkylation reactions, in which NaOH, CsOH, RbOH and $Rb_2CO_3$ as a solid base did not give better selectivities than the reaction with KOH. (entry 1-5) The reactions with $K_2CO_3$ and LiOH did not give the benzylated product **7**. The diastereoselectivity of the reaction did not depend on solvent and base significantly. Introduction of chiral PTC such as *N*-benzyl Cinconidinium bromide and *N*-benzyl Quininium chloride in combination with the chiral auxiliary (double asymmetric induction) showed better selectivities. (entry 8 and 9) When 18-Crown-6 was used with NaOH or KOH at room temp., the reaction gave significantly improved drs. (entry 10 and 11) The reactions which use CsOH and RbOH as a solid base with 18-Crown-6 gave lower selectivities than the reaction with KOH (entry 12 and 13). The reactions with LiOH, $K_2CO_3$ and $Rb_2CO_3$ using 18-crown-6 as a PTC did not give the benzylated product **7**. At −40 °C with KOH for 3 h, the product **7** was obtained in 63% yield with 80 : 20 dr (entry 19), while the reaction with NaOH at −20 °C was too slow to be completed within several days. At −78 °C for 10 h, the dr and yield of **7** dropped to 66 : 34 dr and 32% yield (entry 20).

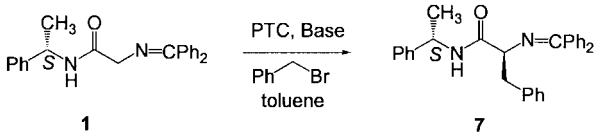
Attention had been turned to scale up of the reaction of **1** with *m*-iodobenzyl bromide for the synthesis of *meta*-substituted phenylalanine derivatives, because large scale preparation of unnatural amino acids was a key goal in the industrial process. The reaction condition which gave best results in Table 2 (entry 19) was used for gram scale reaction of **1**. The reaction of **1** (1.1 g) with *m*-iodobenzyl bromide gave the product **13** with 79 : 21 dr in 66% yield which was comparable results to the result (83 : 17 dr, 65% yield) of small scale reaction of **1** (30 mg).[6] The secondary glycinamide **2** was treated with *m*-iodobenzyl bromide to provide **14** in 52% yield with 77 : 23 dr. Also, the secondary glycinamide **2** and **3** were benzylated with 18-Crown-6 at −40 °C to give **8** and **9**, which gave better results compared to the results shown in Table 1.




**1 , 2 , 3**

**13** R = (*S*)-phenylethyl, Ar = *m*-I-Ph
66% yield, 79:21 dr
**14** R = (*S*)-naphtylethyl, Ar = *m*-I-Ph
52% yield, 77:23 dr
**8** R = (*S*)-naphtylethyl, Ar = Ph
70% yield, 74:26 dr
**9** R = (*R*)-methyl leucyl, Ar = Ph
50% yield, 60:40 dr

An extension of this alkylation methodology to preparation of $\alpha,\alpha$-disubstituted amino acid derivatives was investigated.




**1** **7**

**Table 2**. Reactions of **1** under various conditions

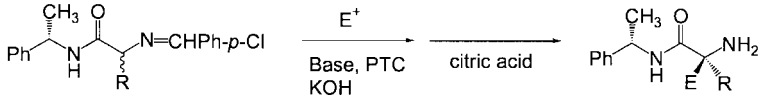
| Entry | PTC | Base | Temp | %Yield[a] | Dr[b](*S:R*)[c] |
|---|---|---|---|---|---|
| 1 | TBAB | NaOH | rt | 53 | 62 : 38 |
| 2 | TBAB | KOH | rt | 63 | 68 : 32 |
| 3 | TBAB | RbOH | rt | 44 | 64 : 36 |
| 4 | TBAB | CsOH | rt | 47 | 67 : 33 |
| 5 | TBAB | $Rb_2CO_3$ | rt | 33 | 60 : 40 |
| 6 | TBAB | $K_2CO_3$ | rt | N.R. | – |
| 7 | TBAB | LiOH | rt | N.R. | – |
| 8 | *N*-Benzyl Quininium Chloride | KOH | rt | 61 | 71 : 29 |
| 9 | *N*-Benzyl Cinconidinium Bromide | KOH | rt | 58 | 80 : 20 |
| 10 | 18-crown-6 | NaOH | rt | 68 | 76 : 24 |
| 11 | 18-crown-6 | KOH | rt | 64 | 74 : 26 |
| 12 | 18-crown-6 | RbOH | rt | 40 | 68 : 32 |
| 13 | 18-crown-6 | CsOH | rt | 37 | 54 : 46 |
| 14 | 18-crown-6 | $Rb_2CO_3$ | rt | N.R. | – |
| 15 | 18-crown-6 | $K_2CO_3$ | rt | N.R. | – |
| 16 | 18-crown-6 | LiOH | rt | N.R. | – |
| 17 | 18-crown-6 | KOH | 0 (0.5 h) | 53 | 77 : 23 |
| 18 | 18-crown-6 | KOH | -20 (2 h) | 57 | 78 : 22 |
| 19 | 18-crown-6 | KOH | -40 (3 h) | 63 | 80 : 20 |
| 20 | 18-crown-6 | KOH | -78 (10 h) | 32 | 66 : 34 |

[a]The yields are not optimized, and trace amount of imine moiety deprotected product was observed during purification by column chromatography. [b]The drs are determined after hydrolysis of crude reaction mixture by CSP-HPLC (Chiralcel-OD) with hexane and 2-propanol as solvent. [c]Configuration at $\alpha$-position.

Further alkylation of *N*-(diphenylmethylene) glycinamide **7** had been examined under above PTC condition, but the reaction did not give the dialkylated product. It is well known that there is a large difference in acidity between $\alpha$-hydrogen of glycine ketimines (p$K_a$=18-20) and that of $\alpha$-monosubstituted glycine ketimines (p$K_a$=21-24) due to the steric crowding.[8] Also, it has been reported that steric crowding could be less severe in $\alpha$-monosubstituted aldimines prepared using 4-chlorobenzaldehyde and the aldimine has enough aicidity for the alkylation under PTC conditions.[8,3b] Thus, 4-chlorobenzaldehyde Schiff base of phenylalanine **15** was prepared for the second alkylation and the initial studies focused on the search for the appropriate reaction conditions as shown in Table 3. Attempted allylation of **15** with allyl bromide (1.5 equiv) and 18-Crown-6 (30 mol%) in toluene proceeded slowly at −40 °C. Stirring for 2 h and hydrolysis with 0.5 M citric acid in THF afforded the dialkylated product **18** in 26% isolated yield with 56 : 44 dr. (entry 1) In methylene chloride at room temp, **18** was obtained in 36% yield with 56 : 44 dr. (entry 2) The level of diastereoselectivity and yield observed here were lower than those obtained in first alkylation of glycine ketimine **1**. Allylation of 4-chlorobenzaldehyde Schiff base of phenylglycine **16** gave **19** with 57 : 43 dr in 33% yield. (entry 3) When the alanine derived aldimine **17** was treated with benzyl bromide and 15-Crown-5 in methylene chloride, the benzylated product **20** was obtained in 76% yield with 55 : 45 yield. (entry 10) With tetrabutylphosphonium bromide (TBPB) as a PTC, **20** was obtained with 60 : 40 dr (entry 12).

## Experimental Section

**General Procedure for the Asymmetric Alkylation of *N*-(diphenylmethylene) glycinamides 1, 2, 3, 4, 5 and 6**. To a solution of ketimimes (**1**, **2**, **3**, **4**, **5** and **6**) in toluene (*ca*. 0.1 M) at a given temperature were added 18-crown-6 (or TBAB, 30 mol%), electrophile (1.2 equiv) and powered




**15, 16, 17** **18, 19, 20**

**Table 3**. Asymmetric syntheses of $\alpha,\alpha$-Disubstituted Amino Acids Derivatives

| Entry | R | $E^+$ | PTC | Solvent | Temp | % Yield[a] | Dr[b] |
|---|---|---|---|---|---|---|---|
| 1 | Bn (**15**) | Allyl-Br | 18-Crown-6 | Toluene | -40 | 26 (**18**) | 56 : 44 |
| 2 | Bn (**15**) | Allyl-Br | 18-Crown-6 | MC | rt | 36 (**18**) | 56 : 44 |
| 3 | Ph (**16**) | Allyl-Br | 18-Crown-6 | Toluene | -40 | 33 (**19**) | 57 : 43 |
| 4 | Ph (**16**) | Allyl-Br | 18-Crown-6 | MC | rt | 37 (**19**) | 57 : 43 |
| 5 | Me (**17**) | Bn-Br | 18-Crown-6 | Toluene | -40 | 54 (**20**) | 52 : 48 |
| 6 | Me (**17**) | Bn-Br | 18-Crown-6 | Toluene | rt | 44 (**20**) | 54 : 46 |
| 7 | Me (**17**) | Bn-Br | 18-Crown-6 | MC | rt | 38 (**20**) | 57 : 43 |
| 8 | Me (**17**) | Bn-Br | 18-Crown-6 | THF | rt | 54 (**20**) | 56 : 44 |
| 9 | Me (**17**) | Bn-Br | 18-Crown-6 | Hexane | rt | 42 (**20**) | 54 : 46 |
| 10 | Me (**17**) | Bn-Br | 15-Crown-5 | MC | rt | 76 (**20**) | 55 : 45 |
| 11 | Me (**17**) | Bn-Br | TBAB | MC | rt | 53 (**20**) | 57 : 43 |
| 12 | Me (**17**) | Bn-Br | TBPB | MC | rt | 59 (**20**) | 60 : 40 |

[a]The yields are not optimized. [b]The drs are determined by $^1$H-NMR (400 MHz) of crude products.

KOH (3 equiv.) The resulting reaction mixture was stirred for 0.5-3 h, and then 20 mL of ether was poured into the mixture. The solid was removed from the mixture by filteration and the filterate was evaporated to give crude alkylated product mixture. The crude material was purified by column chromatography to give the product.

***N'*-((*S*)-Phenylethyl)-*N*-(diphenylmethylene) phenylalaninamide (7)**. From 80 mg of **1**, 63 mg (63% isolated yield) of mixture of two diastereomers of **7** was obtained as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.55-6.44 (m, 21H), 5.19 (m, 1H), 4.16 (dd, $J$ = 3.5 and 8.7 Hz, 1H), 3.20-2.90 (m, 2H) 1.45 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz, major diastereomer) 172.1, 170.4, 143.9, 143.7, 138.2, 135.9, 130.9, 129.1, 129.0, 128.8, 128.6, 128.5, 127.8, 127.6, 126.7, 126.3, 115.1, 68.1, 48.6, 42.0, 22.6. An aqueous solution of HCl (6 M, 4 mL) was added to **7** and the resulting solution was heated at reflux for 24 h. The acidic solution was washed with 20 mL portions of $CH_2Cl_2$ and the aqueous layer was concentrated *in vacuo*. The crude deprotected amino acid was treated with acetyl chloride (1 mL) and $CH_3OH$ (3 mL) at room temperature and concentrated *in vacuo* to give methyl ester amino acid hydrochloride. The resulting material was treated with benzophenone imine (1.0 equiv) in $CH_2Cl_2$ for 8 h followed by regular extractive workup and column chromatography to give the ester as a colorless oil in 82% yield. $^1$H NMR ($CDCl_3$, 400 MHz) 7.58-6.59 (m, 15H), 4.26 (dd, $J$ = 4.4 and 8.6 Hz, 1H), 3.73 (s, 3H), 3.30-3.15 (m, 2H). The enantiomeric ratio of **7** was determined to be 80 : 20 in favor of the *S* enantiomer by chiral HPLC using racemic material as a standard and the absolute configuration was assigned by comparison of CSP-HPLC retention time with authentic material prepared from commercially available (*S*)-Phenylalanine. (Chiralcel OD column; 10% 2-propanol in hexane; 0.5 mL/min; The *S*-enantiomer (major) had a retention time of 18 min, and the *R*-enantiomer (minor) had a retention time of 9 min).

***N'*-((*S*)-Naphtylethyl)-*N*-(diphenylmethylene) phenylalaninamide (8)**. From 81 mg of **2**, 58 mg (57% isolated yield) of mixture of two diastereomers of **8** was obtained as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz, major diastereomer) 8.10-6.28 (m, 23H), 5.95 (m, 1H), 4.17 (dd, $J$ = 3.2 and 8.8 Hz, 1H), 3.27-3.08 (m, 2H) 1.45 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz, major diastereomer) 172.6, 171.6, 139.1, 136.7, 135.2, 131.7, 131.5, 130.1, 129.8, 129.6, 129.57, 129.5, 129.47, 129.33, 129.3, 128.5, 127.6, 127.0, 126.5, 124.8, 123.8, 68.9, 45.9, 42.7, 22.4. The diastereomeric ratio of **8** was determined to be 67 : 33 by the same method as in the determination of dr of **7**.

**Methyl *N*-[*N*-(diphenylmethylene)phenylalanyl] leucinate (9)**. From 64 mg of **3**, 24 mg (30% isolated yield) of mixture of two diastereomers of **9** was obtained as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.63-6.39 (m, 16H), 4.64 (m, 1H), 4.20 (m, 1H), 3.71 (s, 3H), 3.38-3.07 (m, 2H), 1.65 (m, 3H), 0.90 (m, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz, major diastereomer) 173.5, 130.5, 128.8, 128.7, 128.6, 128.0, 127.0, 126.8, 68.0, 52.6, 51.5, 41.8, 30.1, 25.4, 23.2, 22.4. The diastereomeric ratio of **9** was determined to be 55 : 45 by the same method as in the determination of dr of **7**.

***N'*-Methyl-*N'*-((*S*)-phenylethyl)-*N*-(diphenylmethylene) phenylalaninamide (10)**. From 72 mg of **4**, 16 mg (18% isolated yield) of mixture of two diastereomers of **10** was obtained as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz, major diastereomer, major rotamer) 7.79-6.58 (m, 20H), 6.05 (m, 1H), 4.49 (m, 1H), 3.40-3.11 (m, 2H), 2.09 (s, 3H), 1.41 (d, $J$ = 5.7 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz, major diastereomer, major rotamer) 172.1, 169.9, 140.9, 139.7, 138.6, 130.7, 130.2, 130.1, 129.3, 129.0, 128.9, 128.7, 128.66, 128.4, 127.9, 127.6, 127.58, 127.4, 126.7, 66.2, 50.7, 41.3, 29.2, 18.5. The diastereomeric ratio of **10** was determined to be 48 : 52 by the same method as in the determination of dr of **7**.

**(*S,S*)-Pseudoephedrine-*N*-(diphenylmethylene) glycinamide (11)**. From 59 mg of **5**, 12 mg (16% isolated yield) of mixture of two diastereomers of **11** was obtained as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz, major diastereomer, major rotamer) 7.81-6.67 (m, 20H), 4.80 (m, 1H), 4.57 (m, 1H), 4.38 (m, 1H), 4.25 (m, 1H), 3.35 (m, 1H), 3.05 (m, 1H), 2.42 (s, 3H), 1.03 (d, $J$ = 6.7 Hz, 3H). The diastereomeric ratio of **11** was determined to be 41 : 59 by the same method as in the determination of dr of **7**.

**(*R,S*)-Ephedrine-*N*-(diphenylmethylene) glycinamide (12)**. From 55 mg of **6**, 8 mg (12% isolated yield) of mixture of two diastereomers of **12** was obtained as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz, major diastereomer, major rotamer) 7.63-6.73 (m, 20H), 4.77 (m, 1H), 4.43 (m, 1H), 4.24 (m, 1H), 3.77 (m, 1H), 3.27 (m, 1H), 3.08 (m, 1H), 2.26 (s, 3H), 1.09 (d, $J$ = 6.1 Hz, 3H). The diastereomeric ratio of **12** was determined to be 43 : 57 by the same method as in the determination of dr of **7**.

***N'*-((*S*)-Phenylethyl)-*N*-(diphenylmethylene) *m*-iodophenylalaninamide (13)**. From 1.11 g of **1**, 1.20 g (66% isolated yield) of mixture of two diastereomers of **13** was obtained as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.56-6.52 (m, 19H), 5.17 (m, 1H), 4.16 (m, 1H), 3.12-2.95 (m, 2H) 1.46 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz, major diastereomer) 171.7, 171.0, 143.8, 140.7, 139.5, 135.8, 131.1, 130.2, 129.9, 129.1, 129.0, 127.7, 127.6, 126.4, 126.3, 67.5, 48.7, 41.4, 22.7. The diastereomeric ratio of **13** was determined to be 79 : 21 by the same method as in the determination of dr of **7**.

***N'*-((*S*)-Naphtylethyl)-*N*-(diphenylmethylene) *m*-iodophenylalaninamide (14)**. From 57 mg of **2**, 47 mg (52% isolated yield) of mixture of two diastereomers of **14** was obtained as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz, major diastereomer) 8.05-6.36 (m, 22H), 5.95 (m, 1H), 4.17 (m, 1H), 3.17-3.03 (m, 2H) 1.46 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz, major diastereomer) 171.4, 140.7, 139.5, 139.2, 135.8, 135.7, 131.0, 130.2, 129.9, 129.3, 129.0, 128.9, 128.7, 128.5, 127.6, 126.8, 126.1, 125.6, 123.9, 123.1 67.5, 45.2, 41.3, 21.6. The diastereomeric ratio of **14** was determined to be 77 : 23 by the same method as in the determination of dr of **7**.

**General Procedure for the Asymmetric Alkylation of *N*-(4-Chlorophenylmehylene) glycinamides 15, 16 and 17**. To a solution of aldimimes (**15**, **16** and **17**) in toluene (*ca.* 0.1 M) at a given temperature were added 18-crown-6 (or

TBAB, 30 mol%), electrophile (1.2 equiv) and powered KOH (3 equiv.) The resulting reaction mixture was stirred for 10-30 min, and then 10 mL of water was added and the extraction was performed with $CH_2Cl_2$. Solvents were evaporated and the residue was dissolved into THF (10 mL). A 0.5 M citric acid (5 mL) was added and the mixture was stirred at room temperature for 1 h. The aqueous phase was separated and washed with ether. It was then basified by the addition of solid $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic extracts were dried over $MgSO_4$ and concentrated. Purification of the residual oil by column chromatography on silica gel gave the dialkylated product.

***N'*-((*S*)-Phenylethyl)-*N*-(4-chlorophenylmethylene) α-allylphenylalaninamide (18)**. From 60 mg of **15**, 12 mg (26% isolated yield) of mixture of two diastereomers of **18** was obtained as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.77-7.05 (m, 11H), 5.79 (m, 1H), 5.18-5.01 (m, 3H), 3.40 (d, $J$ = 13.2 Hz, 1H), 2.80 (m, 1H), 2.59 (d, $J$ = 13.2 Hz, 1H), 2.18 (m, 1H), 1.43 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz, major diastereomer) 174.5, 144.0, 143.7, 137.0, 136.9, 133.6, 130.8, 128.9, 128.7, 127.5, 127.4, 127.3, 127.1, 126.5, 119.8, 60.9, 48.7, 45.9, 45.6, 22.2. The diastereomeric ratio of **18** was determined to be 56 : 44 by $^1$H-NMR of crude mixture.

***N'*-((*S*)-Phenylethyl)-*N*-(4-chlorophenylmethylene) α-allylphenylglycinamide (19)**. From 119 mg of **16**, 30 mg (33% isolated yield) of mixture of two diastereomers of **19** was obtained as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.82-7.05 (m, 11H), 5.72 (m, 1H), 5.21-4.92 (m, 3H), 3.21 (m, 1H), 2.65 (m, 1H), 1.86 (br, 2H), 1.48 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz, major diastereomer) 173.6, 143.7, 143.3, 134.2, 129.0, 128.9, 127.8, 127.7, 127.6, 127.4, 126.5, 126.3, 125.9, 120.5, 62.6, 48.9, 45.6, 22.5. The diastereomeric ratio of **19** was determined to be 57 : 43 by $^1$H-NMR of crude mixture.

***N'*-((*S*)-Phenylethyl)-*N*-(4-chlorophenylmethylene) α-benzylalaninamide (20)**. From 83 mg of **17**, 70 mg (59% isolated yield) of mixture of two diastereomers of **20** was obtained as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz, major diastereomer) 7.82-7.05 (m, 11H), 5.04 (m, 1H), 3.40 (d, $J$ = 13.3 Hz, 1H), 2.62 (d, $J$ = 13.3 Hz, 1H) 1.79 (br, 1H), 1.34 (d, $J$ = 6.9 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz, major diastereomer) 175.7, 143.9, 137.3, 130.7, 128.9, 128.8, 127.5, 127.2, 126.6, 58.6, 48.7, 47.2, 28.4, 22.4. The diastereomeric ratio of **20** was determined to be 60 : 40 by $^1$H-NMR of crude mixture.

## Conclusions

We have investigated the development of new chiral glycine reagents for the asymmetric syntheses of α-amino acids under PTC conditions amenable to easily scalable processes. The secondary glycinamides **1**, **2** and **3** give better selectivities and yields than tertiary glycinamides **4**, **5** and **6**. Alkylation of the glycinamide **1** and **2** using 18-Crown-6 as a PTC in toluene at −40 °C gives best selectivities and yields. We conclude that (*S*)-phenylethylamine is practical and effective chiral inducer for the asymmetric syntheses of α-monosubstituted amino acids derivatives, not much effective for the asymmetric syntheses of α,α-disubstituted amino acids derivatives.

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