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Solvent Effects in the Enantioselective Catalytic-Phase-Transfer Alkylation of Polymer-Supported Glycine–Imine *tert*-Butyl Ester: Asymmetric Solid-Phase Synthesis of (*R*)-α-Amino Acid Derivatives

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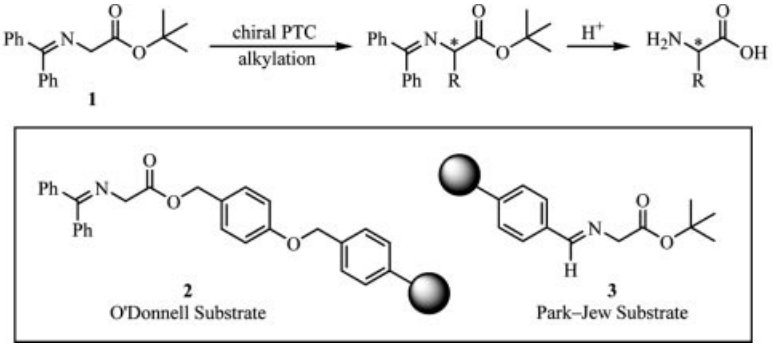
Polymer-supported glycine–imine *tert*-butyl esters (**3**, **8**) were prepared from Merrifield- or Wang-resin and used in the enantioselective synthesis of (*R*)-α-amino acid derivatives by using (*S,S*)-3,4,5-trifluorophenyl-NAS bromide (**5**) as the chiral phase-transfer catalyst. The chemical yields and enantioselectivities were found to be dramatically dependent upon the ratio of water to organic solvent. The optimal solvent was a mixture of toluene/chloroform/water (9:1:0.5). The catalytic enantioselective solid-phase phase-transfer alkylation of polymer-supported glycine–imine substrate **3** with various alkyl halides with the use of 50 % aqueous CsOH in the optimal solvent system at 0 °C followed by hydrolysis and benzoylation afforded the corresponding (*R*)-*N*-benzoyl-α-amino acid *tert*-butyl esters **11** in 60–80 % yield and with enantiomeric ratios (*er*) of 96.5:3.5 to 99.5:0.5.

Introduction

Solid-phase synthetic methods have been applied to a variety of synthetic chemistry as a result of their major benefits, which include their ease of preparation, their short overall operation time, and the possibility for automation.[1] Their efficiency has been proven in combinatorial chemistry and parallel synthesis for new drug development. A rapid growth of chiral phase-transfer catalysis for the preparation of nonnatural α-amino acids in the last decade has led to the development of polymer-supported chiral phase-transfer catalysts (PTCs),[2] as well as polymer-supported substrates for the synthesis of α-amino acid derivatives.[3]

Since the pioneering work of the O'Donnell group on unnatural peptide synthesis with the use of polymer supports,[3] we have been interested in the design and preparation of new and efficient polymer-supported glycine substrates and their application to enantioselective solid-phase catalytic-phase-transfer alkylation to afford various nonnatural α-amino acid derivatives. We recently reported an efficient solid-phase synthetic method for (*S*)-α-amino acid derivatives.[4] Generally, in solution-phase synthesis, a bulky *tert*-butyl moiety in glycine benzophenone imine *tert*-butyl ester (**1**), a representative substrate for the asymmetric catalytic-phase-transfer alkylation, has been regarded as one of



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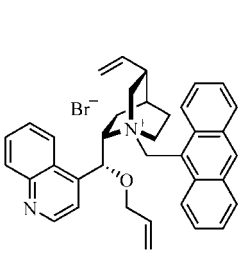
the critical factors for high enantioselectivity. This hypothesis can also be found in the case of O'Donnell polymer-supported substrate **2** in which the glycine unit is bound to a Wang resin through an ester linkage. In this case, the bulkiness of the ester group is decreased as the *tert*-butyl ester is substituted with a 4-benzyloxy benzyl ester, which led to a decrease in the enantioselectivity. These facts prompted us to devise a Merrifield resin-supported glycine derivative such as **3** in which the glycine unit is bound to the polymer through an imine linkage and the beneficial *tert*-butyl ester functional group is retained. Highly optically enriched (*S*)-α-amino acid derivatives (93.0:7.0 to 99.5:0.5 *er*) were obtained by using substrate **3** under catalytic-phase-transfer alkylation conditions, that is 50% aqueous CsOH was used as the base in a mixed solvent (toluene/chloroform, 7:3) at 0 °C and 10 mol-% of the commercially available *N*-(9-anthracenylmethyl)-*O*(9)-allylcinchonidinium bromide (**4**)[5] was employed as the chiral PTC.[6] The aldimine group in substrate **3** not only serves as a linker, but it also enhances the acidity of the α-proton enough to form the corresponding enolate in the catalytic-phase-transfer reaction.



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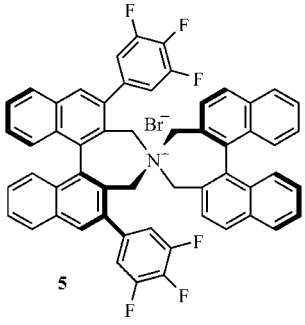

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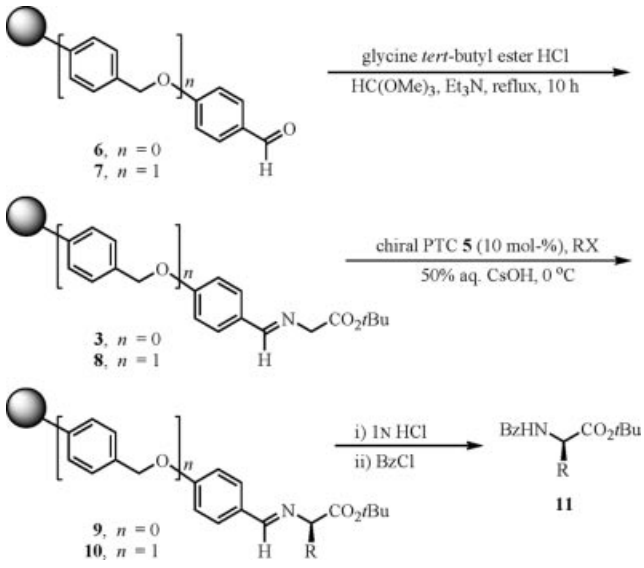
As a part of our program to construct nonnatural (*R*)-α-amino acid derivatives for incorporation into peptide libraries, we needed to optimize the enantioselective solid-phase catalytic-phase-transfer alkylation system for the synthesis of (*R*)-α-amino acid derivatives. Our previous results revealed that the catalytic-phase-transfer alkylation of the Merrifield-resin-bound glycine–imine *tert*-butyl ester **3**, with the use of 50% aqueous KOH and in the presence of the commercially available chiral PTC (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**5**),[7] gave (*R*)-α-benzyl-α-amino acid derivative (76%, 94.0:6.0 *er*).[4b] Because the reaction environment in this solid-phase system is quite different from that of the solution-phase reaction, both the chemical yields and the enantioselectivities could be affected by various factors, such as solvent polarity and reagent solubility. Moreover, the three phases (i.e. solid resin, organic solvent, and water) in the solid-phase catalytic-phase-transfer reaction system could be very sensitive to such factors. Therefore, we attempted to optimize the enantioselective solid-phase catalytic-phase-transfer alkylation conditions in the presence of (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**5**) for the preparation of (*R*)-α-amino acid derivatives.

Results and Discussion

Before we began to optimize the solid-phase PTC alkylation conditions, we first attempted to modify polymer-supported substrate **3** by extending the length of the linker (Scheme 1). We envisioned that a longer linker might be more favorable in terms of steric factors. Wang-resin-bound glycine *tert*-butyl ester **8** was prepared by the imine coupling of Wang aldehyde resin **7** and glycine *tert*-butyl ester hydrochloride by the reported method.[4]

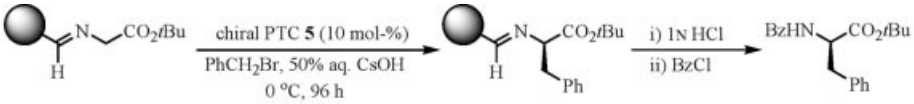


Scheme 1.

The efficiency of polymer-supported substrate **8** in the solid-phase enantioselective alkylation was examined by benzylation using 10 mol-% of chiral PTC **5** with 5 equiv. of benzyl bromide and 5 equiv. of 50% aqueous CsOH in toluene/chloroform (7:3) at 0 °C. The enantioselectivity was determined by chiral HPLC analysis of the *N*-benzoyl-α-benzylglycine *tert*-butyl ester (**11d**, R = CH_2Ph) obtained by hydrolysis of the imine of benzylated product **10** with 1 N HCl followed by benzoylation of the resulting amine. However, the observed chemical yield and enantioselectivity (65%, 86.0:14.0 *er*) were lower than those with shorter linker-bound substrate **3** (77%, 95.5:4.5 *er*). We inferred that the lower enantioselectivity might be due to the electronic effect of the benzyloxy group that is attached to the phenyl group of Wang-resin-supported substrate **8**. As the electron-donating effect of the benzyloxy moiety reduces the acidity of the α-proton of **8**, the overall reaction rate might decrease, which allows the noncatalyst-mediated reaction to take place and results in a decrease in the enantioselectivity.

Merrifield-resin-supported substrate **3** was chosen for further optimization studies of the reaction conditions for the enantioselective solid-phase alkylation. The effect of various organic solvents was examined next. Swelling of the resin is generally dependent upon the nature of the organic solvent, and we presumed that the swelling factor might

Table 1. The solvent effect.[a]



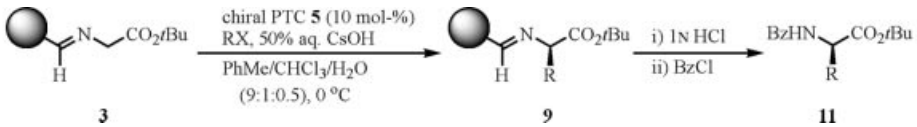
Entry	Solvent system	Yield [%][b]	*er* (*R*/*S*)[c,d]
1	PhMe/H_2O (10:1)	40	97.5:2.5
2	mesitylene/H_2O (10:1)	11	94.0:6.0
3	THF/H_2O (10:1)	75	94.5:5.5
4	DME/H_2O (10:1)	82	91.0:9.0
5	1,4-dioxane/H_2O (10:1)	57	96.0:4.0
6	CH_2Cl_2/H_2O (10:1)	12	72.0:28.0
7	$CHCl_3$/H_2O (10:1)	40	94.5:5.5
8	PhMe/$CHCl_3$/H_2O (7:3:1)	77	95.5:4.5
9	PhMe/$CHCl_3$/H_2O (8:2:1)	67	96.5:3.5
10	PhMe/$CHCl_3$/H_2O (9:1:1)	63	97.5:2.5
11	PhMe/$CHCl_3$/H_2O (9:1:0.25)	73	95.0:5.0
12	PhMe/$CHCl_3$/H_2O (9:1:0.5)	70	97.5:2.5
13	PhMe/$CHCl_3$/H_2O (9:1:2)	52	98.0:2.0
14	PhMe/$CHCl_3$/H_2O (9:1:4)	41	98.0:2.0
15	PhMe/$CHCl_3$/H_2O (9:1:0.5)[e]	45	97.5:2.5
16	PhMe/$CHCl_3$/H_2O (9:1:0.5)[f]	70	97.5:2.5
17	PhMe/$CHCl_3$/H_2O (9:1:0.5)[g]	86	96.5:3.5
18	PhMe/$CHCl_3$/H_2O (9:1:0.5)[h]	65	95.5:4.5

[a] The reaction was carried out with 5.0 equiv. of benzyl bromide and 2.5 equiv. of 50% aqueous CsOH in the presence of 10 mol-% of chiral catalyst **5** at 0 °C for 96 h in various solvent systems. [b] Isolated yield of **11d**. [c] The enantiopurity was determined by HPLC analysis of **11d** by using a chiral column (Chiralcel OD-H) with hexanes/2-propanol (98:2) as the eluent. [d] The absolute configuration was determined by comparing with the HPLC retention time of an authentic sample, which was independently prepared from α-benzyldiphenylmethylene glycine imine *tert*-butyl ester (**1**) obtained by the reported procedures.[5,7,9] [e] 1.0 equiv. of solid CsOH was added to the reaction mixture instead of 50% aqueous CsOH. [f] 2.5 equiv. of solid CsOH was added to the reaction mixture instead of 50% aqueous CsOH. [g] 5.0 equiv. of solid CsOH was added to the reaction mixture instead of 50% aqueous CsOH. [h] 10.0 equiv. of solid CsOH was added to the reaction mixture instead of 50% aqueous CsOH.

affect the catalytic efficiency of the catalyst. The solvent optimization study was performed by benzylation of substrate **3** by using 10 mol-% of chiral PTC **5** with 5 equiv. of benzyl bromide and 2.5 equiv. of 50% aqueous CsOH in various organic solvent systems at 0 °C for 96 h (Table 1). Toluene, which was the optimal solvent for the catalytic-phase-transfer alkylation of **1** with chiral PTC **5** in the solution-phase,[7] was first employed in the solid-phase synthesis (Table 1, Entry 1). Even though high enantioselectivity (97.5:2.5 *er*) was obtained in toluene/water (10:1), only a modest chemical yield (40%) was obtained.[8] Several organic solvents capable of swelling the resin were explored next. In the case of mesitylene, which has occasionally been used as an alternative for toluene, both the chemical yield and the enantioselectivity (11%, 94.0:6.0 *er*) were lower than those of toluene (Table 1, Entry 2). Improved chemical yields were obtained in the cases of tetrahydrofuran (75%) and 1,2-dimethoxyethane (82%) but the enantioselectivities observed were slightly lower (94.5:5.5 *er* and 91.0:9.0 *er*, respectively, Table 1, Entries 3 and 4).

The use of other organic solvents, such as 1,4-dioxane, dichloromethane, or chloroform did not result in an improvement in the chemical/optical yields (Entries 5–7). From the results shown in Entries 1–7, it was concluded that toluene was the best solvent in this solid-phase reaction system, particularly from the point of view of enantioselectivity. Interestingly, the chemical yields increased considerably by the addition of $CHCl_3$ to toluene, whereas the enantioselectivities decreased slightly (Entry 1 vs. Entries 8–10). The solvent system used in Entry 8 (toluene/chloroform, 7:3), which was the best system when **4** was used as the chiral PTC for the synthesis of (*S*)-α-amino acids, was not optimal for the synthesis of the (*R*)-isomers. As the proportion of chloroform was gradually increased, the chemical yields improved while the enantioselectivities decreased (Entries 8–10). The reason for the increase in the chemical yields is not clear but similar phenomena were also observed in solvent optimization studies for solution-phase catalytic-phase-transfer alkylation reactions.[9] We speculated that the polarity of the organic solvent might play an integral role in the PTC reaction. The less polar solvent in the solvent mixture might contribute to the formation of a more favorable ionic intermediate between the enolate anion of the polymer-supported glycine–imine and the ammonium cation of chiral PTC **5**. As the toluene/chloroform (9:1) system gave the highest enantioselectivity as well as an improvement in the chemical yield, it was chosen as the optimal organic solvent system for the solid-phase alkylation (Entry 10, 63%, 97.5:2.5 *er*). Attention was next focused on the effect of the amount of water. High enantioselectivities (97.5:2.5 to 98.0:2.0 *er*) were preserved until the ratio organic solvent/water reached 20:1 (Entries 10 and 12–14), but a lower amount of water showed a slight decrease in the enantioselectivity (Entry 11, organic solvent/water =

Table 2. Solid-phase enantioselective catalytic-phase-transfer alkylation of **3** to afford (*R*)-α-amino acid derivatives **11**.[a]



Entry	Alkyl halide, RX	Time [d]	Yield [%][b]	*er* (*R*/*S*)[c,d]
a	allyl bromide	5	61	96.5:3.5
b	2-methally bromide	5	65	97.5:2.5
c	propargyl bromide	5	62	96.5:3.5
d	benzyl bromide	4	70	97.5:2.5
e	4-fluorobenzyl bromide	4	60	98.0:2.0
f	4-cyanobenzyl bromide	4	80	97.5:2.5
g	4-methylbenzyl bromide	4	63	99.5:0.5
h	4-*tert*-butylbenzyl bromide	4	68	98.0:2.0
i	2-bromomethylnaphthalene	4	65	97.5:2.5

[a] The reaction was carried out with 5.0 equiv. of alkyl halide and 2.5 equiv. of 50% aqueous CsOH in the presence of 10 mol-% of chiral catalyst **5** at 0 °C in a mixture of toluene/chloroform/water (9:1:0.5). [b] Isolated yield of **11**. [c] The enantiopurity was determined by HPLC analysis of **11** by using a chiral column (Chiralcel OD-H) with hexanes/2-propanol as the eluent. [d] The absolute configuration was assigned by using the same method as that reported in Table 1.

40:1, 95.0:5.0 *er*).[10] In terms of the chemical yield, systems with less water generally gave higher chemical yields. Figure 1 shows the relationship between the chemical yields and enantioselectivities according to the ratio of organic solvent (toluene/chloroform, 9:1) to water (v/v). We assume that the higher solubility of hydrophobic PTC **5** in the solvent containing less water can promote solid-phase alkylation to afford higher chemical yields. However, the nonPTC-mediated alkylation might also be increased when the ratio organic solvent/water is lower than 20:1, which leads to a drop in the enantioselectivity. We finally chose the combination of toluene/chloroform/water (9:1:0.5) as the optimal solvent system for solid-phase asymmetric PTC alkylation.

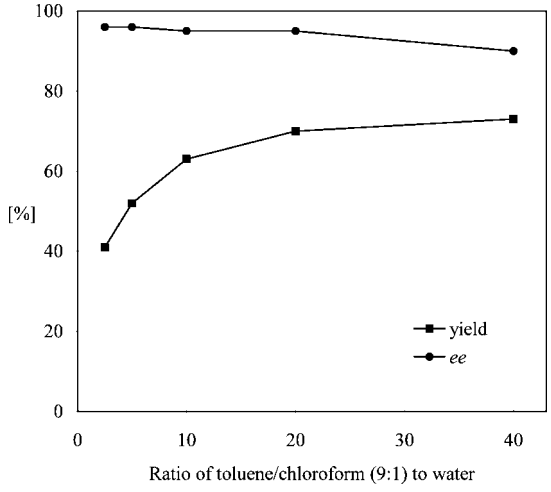


Figure 1. Relationship between chemical yields and enantioselectivities according to the ratio of organic solvent (toluene/chloroform, 9:1) to water (v/v).

Next, a fine-tuning of the amount of CsOH was performed. Four variations of the amount of CsOH (1.0, 2.5, 5.0 and 10.0 equiv. of CsOH) affected both the chemical yields and the enantioselectivities (Entries 15–18).[11] The best result, with the consideration of both the chemical and optical yields, was obtained when 2.5 equiv. of solid CsOH was used (Entry 16), which is almost the same result obtained from 2.5 equiv. of 50% aqueous CsOH (Entry 12).

For further investigation with various alkyl halides, we adopted the reaction system of Entry 12 in Table 1 from the viewpoint of ease of operation.[11–14] As shown in Table 2, very high enantioselectivities were obtained with good chemical yields, which indicates that this optimized solid-phase synthetic system is an efficient catalytic enantioselective synthetic method for the practical synthesis of highly optically enriched (*R*)-α-amino acids.

Conclusions

Optimization of the enantioselective solid-phase catalytic-phase-transfer alkylation for the synthesis of nonnatural (*R*)-α-amino acids was performed. The Merrifield-resin-supported glycine–imine *tert*-butyl ester (**3**) was chosen as the best substrate and the commercially available (*S*,*S*)-3,4,5-trifluorophenyl-NAS bromide (**5**) was employed as the chiral PTC for (*R*)-α-amino acids. High enantioselectivities with good chemical yields were achieved by optimization of the solvent system (toluene/chloroform/water, 9:1:0.5) and by fine-tuning the amount of base (2.5 equiv. of 50% aqueous CsOH).

Experimental Section

Infrared (IR) spectra were recorded on a JASCO FTIR-300E and Perkin–Elmer 1710 FT spectrometer. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were measured with a JEOL JNM-LA 300 [300 MHz (^{1}H), 75 MHz (^{13}C)] spectrometer, JEOL JNM-GSX 400 [400 MHz (^{1}H), 100 MHz (^{13}C)] spectrometer, or a Bruker AMX 500 [500 MHz (^{1}H), 125 MHz (^{13}C)] spectrometer with the use of $CHCl_3$/d as the solvents and reported relative to

$CHCl_3$ (δ = 7.26 ppm) for ^1H NMR and relative to the central $CDCl_3$ (δ = 77.23 ppm) resonance for ^{13}C NMR spectroscopy. High performance liquid chromatography (HPLC) was performed with a Hitachi L-7100 instrument by using a 4.6 mm × 250 mm Chiralcel OD-H column. Low-resolution mass spectra (MS) were recorded with a VG Trio-2 GC-MS spectrometer, and high-resolution mass spectra (HRMS) were measured with a JEOL JMS-AX 505wA, JEOL JMS-HX/HX 110A spectrometer. Melting points were measured with a Buchi B-540 melting point apparatus and are not corrected. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. For flash column chromatography, E. Merck Kieselgel 60 (70~230 mesh) was used. All solvents and commercially available chemicals were used without additional purification.

Procedure for the Preparation of 6: Merrifield resin (20 g, 0.94 mmol/g) was stirred in dimethyl sulfoxide (120 mL) with sodium hydrogen carbonate (4.0 g, 7.0 mmol) at 155 °C for 12 h. The resin was then collected on a glass filter, washed with dimethyl sulfoxide, hot water, 1,4-dioxane/water (2:1). The resin was then successively rinsed with 1,4-dioxane, acetone, ethanol, dichloromethane, and benzene. White colored resin **6** (18 g) was obtained after drying at 100 °C under high vacuum. IR (KBr): $\tilde{\nu}$ = 3440, 3022, 2913, 1698, 1602, 1489 cm^{-1}.

Procedure for the Preparation of 3: Triethylamine (8.7 g, 52 mmol) was added to a mixture of aldehyde-resin **6** (18 g, 0.96 mmol/g) and glycine *tert*-butyl ester hydrochloride (9 g, 52 mmol) in trimethyl orthoformate (140 mL), and the mixture was heated at reflux for 10 h. The resin was collected on a glass filter, washed with benzene, dichloromethane, dichloromethane/methanol (1:1), methanol, and dichloromethane. Yellow colored resin **3** (18 g, 0.26 mmol/g) was obtained after drying at 100 °C under high vacuum. IR (KBr): $\tilde{\nu}$ = 3441, 3025, 2920, 1736, 1646, 1603 cm^{-1}.

Representative Procedure for the Enantioselective Solid-Phase Catalytic-Phase-Transfer Alkylation (Benzylation): A 50% aqueous cesium hydroxide solution (0.05 mL, 0.135 mmol) and benzyl bromide (0.033 mL, 0.270 mmol) were added to a cooled (0 °C) mixture of aldimine **3** (100 mg, 0.054 mmol) and chiral catalyst **5** (4.9 mg, 0.005 mmol) in toluene/chloroform (9:1; 1.0 mL). The reaction mixture was vigorously stirred at 0 °C for 96 h. The resin was collected on a glass filter, washed with dichloromethane, a dichloromethane/methanol (1:1), methanol, and dichloromethane. Yellow colored resin **9d** was obtained after drying at 100 °C under high vacuum. Resin **9d** was suspended in THF (1 mL) and 1 N HCl (0.5 mL) was then added. The resulting mixture was stirred at room temperature for 1 h. The resulting mixture was collected on a glass filter, washed with THF, dichloromethane, a dichloromethane/methanol (1:1), methanol, and dichloromethane. The organic solvents in the combined washings were removed under reduced pressure. The residual aqueous solution was washed with hexanes (2 × 5 mL) and then basified with solid $NaHCO_3$ and extracted with dichloromethane (3 × 10 mL). The dichloromethane extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated. After the residue was dissolved in dichloromethane (0.5 mL), triethylamine (0.016 mL, 0.12 mmol) and benzoyl chloride (0.013 mL, 0.12 mmol) were successively added. The reaction mixture was stirred at room temperature for 30 min. The resulting mixture was extracted with dichloromethane (3 × 5 mL), and the combined extracts were washed with water. The dichloromethane solution was dried with anhydrous $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography on silica gel (hexanes/EtOAc, 10:1) afforded desired *N*-benzoyl derivative **11d** as a white solid. The enantiopurity was determined by chiral HPLC analysis [Chiral Technologies, Inc.; Chiralcel OD-H; hexanes/2-propanol, 98:2; flow rate = 1 mL/min, 23 °C; λ = 254 nm; t_R (*R*) isomer (major) = 11.1 min, t_R (*S*) isomer (minor) = 24.8 min, *R*/*S* = 97.5:2.5 *er*]. The absolute configuration was determined by comparison of the HPLC retention time with that of an authentic sample synthesized by the reported method.

***tert*-Butyl 2-Benzoylaminopent-4-enoate (11a) [R = allyl]:** Yield: 9 mg (61%) of a yellow solid, m.p. 56 °C ($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.8 Hz, 2 H), 7.39–7.51 (m, 3 H), 6.74 (d, *J* = 7.0 Hz, 1 H), 5.67–5.81 (m, 1 H), 5.15 (d, *J* = 4.6 Hz, 1 H), 5.11 (s, 1 H), 2.55–2.76 (m, 2 H), 1.48 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 166.8, 133.7, 132.3, 130.2, 128.6, 127.0, 119.1, 82.5, 52.4, 36.8, 28.1 ppm. IR (KBr): $\tilde{\nu}$ = 2979, 1721, 1645, 1532, 1451, 1367 cm^{-1}. MS (ESI): *m*/*z* = 298.0 [M + Na]$^+$. HRMS (FAB): calcd. for $C_{16}H_{20}NO_3$ [M + H]$^+$ 274.3349; found 275.1442. The enantioselectivity was determined by chiral HPLC analysis [Chiralcel OD-H; hexanes/2-propanol, 98:2; flow rate = 1 mL/min, 23 °C; λ = 254 nm; t_R (*R*) isomer (major) = 7.1 min, t_R (*S*) isomer (minor) = 22.7 min, *R*/*S* = 96.5:3.5 *er*].

***tert*-Butyl 2-Benzoylamino-4-methyl-pent-4-enoate (11b) [R = methallyl]:** Yield: 10 mg (65%) of a white solid, m.p. 88 °C ($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.4 Hz, 2 H), 7.38–7.51 (m, 3 H), 6.57 (d, *J* = 7.5 Hz, 1 H), 4.85 (s, 1 H), 4.74–4.81 (m. 2 H), 2.47–2.66 (m, 2 H), 1.79 (s, 3 H), 1.47 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5, 166.9, 141.0, 131.6, 130.2, 128.6, 128.4, 114.5, 51.4, 41.0, 28.0, 22.1 ppm. IR (KBr): $\tilde{\nu}$ = 3738, 2978, 1725, 1646, 1536, 1453 cm^{-1}. MS (ESI): *m*/*z* = 312.3 [M + Na]$^+$. HRMS (FAB): calcd. for [$C_{17}H_{22}NO_3$] [M + H]$^+$ 288.3615; found 289.1805. The enantioselectivity was determined by chiral HPLC analysis [Chiralcel OD-H; hexanes/2-propanol, 97:3; flow rate = 1 mL/min, 23 °C; λ = 254 nm; t_R (*R*) isomer (major) = 6.3 min, t_R (*S*) isomer (minor) = 19.4 min, *R*/*S* = 97.5:2.5 *er*].

***tert*-Butyl 2-Benzoylamino-pent-4-ynoate (11c) [R = propargyl]:** Yield: 9 mg (62%) of a yellow solid, m.p. 118 °C ($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 11.7 Hz, 2 H), 7.39–7.53 (m, 3 H), 7.01 (d, *J* = 7.0 Hz, 1 H), 4.76–4.81 (m, 1 H), 2.77–2.95 (m. 2 H), 2.01 (t, *J* = 2.8 Hz, 1 H), 1.50 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 166.9, 131.8, 130.1, 128.6, 128.4, 127.1, 83.0, 78.7, 71.4, 51.3, 27.9, 22.7 ppm. IR (KBr): $\tilde{\nu}$ = 3737, 3301, 2979, 1731, 1651, 1524 cm^{-1}. MS (ESI): *m*/*z* = 296.0 [M + Na]$^+$. HRMS (FAB): calcd. for [$C_{16}H_{18}NO_3$] [M + H]$^+$ 272.3190; found 273.1342. The enantioselectivity was determined by chiral HPLC analysis [Chiralcel OD-H; hexanes/2-propanol, 98:2; flow rate = 1 mL/min, 23 °C; λ = 254 nm; t_R (*R*) isomer (major) = 9.1 min, t_R (*S*) isomer (minor) = 26.5 min, *R*/*S* = 96.5:3.5 *er*].

***tert*-Butyl 2-Benzoylamino-3-phenylpropionate (11d) [R = benzyl]:** Yield: 12 mg (70%) of a white solid, m.p. 61 °C ($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.6 Hz, 2 H), 7.33–7.46 (m, 5 H), 7.24–7.11 (m, 2 H), 6.58 (d, *J* = 6.8 Hz, 1 H), 4.86–4.93 (m, 1 H), 3.17 (d, *J* = 5.3 Hz, 2 H), 1.37 (s, 9 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 166.8, 133.7, 131.7, 130.2, 129.6, 128.6, 128.4, 127.0, 82.7, 53.9, 38.0, 28.0 ppm. IR (KBr): $\tilde{\nu}$ = 2978, 1723, 1645, 1530, 1488, 1453 cm^{-1}. MS (ESI): *m*/*z* = 348.0 [M + Na]$^+$. HRMS (FAB): calcd. for [$C_{20}H_{22}NO_3$] [M + H]$^+$ 324.3936; found 325.1679. The enantioselectivity was determined by chiral HPLC analysis [Chiralcel OD-H; hexanes/2-propanol, 98:2; flow rate = 1 mL/min, 23 °C; λ = 254 nm; t_R (*R*) isomer (major) = 11.1 min, t_R (*S*) isomer (minor) = 24.8 min, *R*/*S* = 97.5:2.5 *er*].

***tert*-Butyl 2-Benzoylamino-3-(4-fluorophenyl)propionate (11e) [R = 4-Fluorobenzyl]:** Yield: 11 mg (60%) of a white solid, m.p. 94 °C

($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 7.1 Hz, 2 H), 7.39–7.52 (m, 3 H), 7.11–7.15 (m, 2 H), 6.95 (t, J = 8.6 Hz, 2 H), 6.64 (d, J = 7.0 Hz, 1 H), 4.87–4.94 (m. 1 H), 3.15–3.26 (m, 2 H), 1.43 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 166.7, 163.2, 134.0, 131.9, 131.9, 131.8, 131.1, 131.0, 128.6, 126.9, 115.3, 115.1, 82.8, 53.9, 37.2, 28.0 ppm. IR (KBr): $\tilde{\nu}$ = 3325, 2925, 2854, 1733, 1646, 1512 cm^{-1}. MS (ESI): m/z = 366.1 $[M + Na]^+$. HRMS (FAB): calcd. for $[C_{20}H_{21}FNO_3]$ $[M + H]^+$ 342.3840; found 343.1526. The enantioselectivity was determined by chiral HPLC analysis [Chiralcel OD-H; hexanes/2-propanol, 97:3; flow rate = 1 mL/min; 23 °C, λ = 254 nm; t_R (*R*) isomer (major) = 8.5 min, t_R (*S*) isomer (minor) = 21.2 min, *R*/*S* = 98.0:2.0 *er*].

***tert*-Butyl 2-Benzoylamino-3-(4-cyanophenyl)propionate (11f) [R = 4-cyanobenzyl]:** Yield: 15 mg (80%) of a white solid, m.p. 151 °C ($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 7.1 Hz, 2 H), 7.40–7.71 (m, 5 H), 7.29 (d, J = 8.0 Hz, 2 H), 6.70 (d, J = 6.8 Hz, 1 H), 4.90–4.96 (m, 1 H), 3.20–3.35 (m, 2 H), 1.41 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 166.7, 142.1, 133.7, 132.0, 131.9, 130.4, 128.7, 126.9, 119.2, 111.0, 83.2, 53.7, 38.2, 28.0 ppm. IR (KBr): $\tilde{\nu}$ = 3335, 2978, 2228, 1734, 1647, 1532 cm^{-1}. MS (ESI): m/z = 373.1 $[M + Na]^+$. HRMS (FAB): calcd. for $[C_{21}H_{21}N_2O_3]$ $[M + H]^+$ 349.4030; found 350.1676. The enantioselectivity was determined by chiral HPLC analysis [Chiralcel OD-H; hexanes/2-propanol, 90:10; flow rate = 1 mL/min, 23 °C; λ = 254 nm; t_R (*R*) isomer (major) = 9.2 min, t_R (*S*) isomer (minor) = 38.0 min, *R*/*S* = 97.5:2.5 *er*].

***tert*-Butyl 2-Benzoylamino-3-*p*-tolylpropionate (11g) [R = 4-methylbenzyl]:** Yield: 12 mg (63%) of a white solid, m.p. 77 °C ($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.4 Hz, 2 H), 7.38–7.51 (m, 4 H), 7.05 (s. 3 H), 6.60 (d, J = 7.4 Hz, 1 H), 3.13–3.24 (m, 2 H), 2.29 (s, 3 H), 1.43 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 166.7, 132.9, 131.6, 130.2, 129.5, 129.1, 128.6, 128.5, 127.0, 82.6, 53.9, 37.5, 28.0, 21.1 ppm. IR (KBr): $\tilde{\nu}$ = 2927, 1722, 1646, 1521, 1487, 1452 cm^{-1}. MS (ESI): m/z = 362.1$[M + Na]^+$. HRMS (FAB): calcd. for $[C_{21}H_{24}NO_3]$ $[M + H]^+$ 338.4202; found 339.1854. The enantioselectivity was determined by chiral HPLC analysis [Chiralcel OD-H; hexanes/2-propanol, 97:3; flow rate = 1 mL/min, 23 °C; λ = 254 nm; t_R (*R*) isomer (major) = 8.1 min, t_R (*S*) isomer (minor) = 18.2 min, *R*/*S* = 99.5:0.5 *er*].

***tert*-Butyl 2-Benzoylamino-3-(4-*tert*-butylphenyl)propionate (11h) [R = 4-*tert*-butylbenzyl]:** Yield: 14 mg (68%) of a yellow solid, m.p. 58 °C ($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.71 (d, J = 14.4 Hz, 2 H), 7.34–7.47 (m, 4 H), 7.21–7.26 (m, 1 H), 7.08 (d, J = 8.3 Hz, 2 H), 6.66 (d, J = 7.1 Hz, 1 H), 4.88–4.95 (m, 1 H), 3.10–3.17 (m, 2 H), 1.38 (s, 9 H), 1.25 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 149.8, 133.6, 131.6, 130.1, 129.2, 128.5, 128.4, 127.0, 125.3, 82.5, 53.9, 37.5, 31.3, 27.9 ppm. IR (KBr): $\tilde{\nu}$ = 2964, 1722, 1646, 1523, 1486, 1367 cm^{-1}. MS (ESI): m/z = 404.1 $[M + Na]^+$. HRMS (FAB): calcd. for $[C_{24}H_{30}NO_3]$ $[M + H]^+$ 380.4999; found 381.2270. The enantioselectivity was determined by chiral HPLC analysis [Chiralcel OD-H; hexanes/2-propanol, 97:3; flow rate = 1 mL/min, 23 °C; λ = 254 nm; t_R (*R*) isomer (major) = 8.0 min, t_R (*S*) isomer (minor)= 14.5 min, *R*/*S* = 98.0:2.0 *er*].

***tert*-Butyl 2-Benzoylamino-3-naphthalen-2-ylpropionate (11i) [R = 2-naphthyl]:** Yield: 13 mg (65%) of a white solid, m.p. 97 °C ($CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.64–7.74 (m, 5 H), 7.17–7.43 (m, 7 H), 6.66 (d, J = 7.0 Hz, 1 H), 4.95–5.01 (m, 1 H), 3.34 (d, J = 5.7 Hz, 2 H), 1.35 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 166.6, 133.7, 133.3, 131.7, 130.1, 128.6, 128.4, 128.3, 128.0, 127.8, 127.6, 127.4, 127.0, 126.1, 125.6, 82.7, 54.0, 38.1, 28.0 ppm. IR (KBr): $\tilde{\nu}$ = 3330, 2978, 1732, 1647, 1528, 1365 cm^{-1}. MS (ESI): m/z = 398.1 $[M + Na]^+$. HRMS (FAB): calcd. for $[C_{24}H_{24}NO_3]$ $[M + H]^+$ 374.4523; found 375.1829. The enantioselectivity was determined by chiral HPLC analysis [Chiralcel OD-H; hexanes/2-propanol, 97:3; flow rate = 1 mL/min, 23 °C; λ = 254 nm; t_R (*R*) isomer (major) = 13.8 min, t_R (*S*) isomer (minor) = 24.6 min, *R*/*S* = 97.5:2.5 *er*].

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[8] When only toluene was used without any water along with solid CsOH the chemical yield was 25% and the enantioselectivity was obtained in the ratio of (*R*)/(*S*) = 73.0:17.0.

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[10] Total amount of solvent (i.e. organic solvent + water) was fixed to 1.05 mL per 100 mg of substrate **3**.

[11] For this experiment, 1.0, 2.5, 5.0 and 10.0 equiv. of solid CsOH was added, not an aqueous solution, to a premixed solvent mixture (toluene/chloroform/water, 9:1:0.5). After CsOH was completely dissolved, the other reagents were then added.

[12] It is quite troublesome to handle solid CsOH because of its highly hygroscopic character.

[13] Results from the variation of reaction temperature (e.g. room temp. and –20 °C, the other reaction conditions were the same as that of Entry 12 in Table 1 except for the reaction temperature): i) at room temp., reaction time: 72 h, chemical yield: 73%, enantiomeric ratio: (*R*/*S*) = 91.0:9.0. ii) at –20 °C, reaction time: 144 h, chemical yield: 34%, enantiomeric ratio: (*R*/*S*) = 95.0:5.0.

[14] The aldimines have been used in the synthesis of α,α-dialkylamino acids in solution-phase systems. However, the solid-supported aldimines (**3** or **8**) gave only monoalkylation products under the reaction conditions used in this paper.

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