JOC*Note*

Highly Enantioselective Phase-Transfer Catalytic Alkylation in the Preparation of Non-natural α-Amino Acids via Solid Phase Synthesis Using Aldimine Linker

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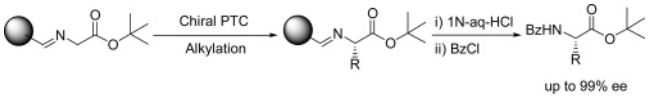
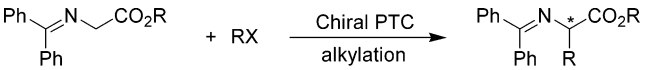


A new Merrifield-resin-derived glycinimine *tert*-butyl ester (**9**) was prepared and applied to the enantioselective synthesis of non-natural α-amino acids. High enantioselectivities (86 to >99% ee) were accomplished by employing the aldimine linker under phase-transfer alkylation conditions, using 50% aqueous CsOH in toluene/chloroform (7:3) at 0 °C in the presence of *N*-(9-anthracenylmethyl)-*O*(9)-allylcinchonidium bromide (10 mol %).

Since the pioneering work by Merrifield in 1963, the applications of solid-phase synthesis to synthetic chemistry have expanded greatly.[1] The major benefits, such as easy purification, lower synthesis time, and the availability for automation, have contributed to the development of combinatorial chemistry, which plays an important role in new drug development. Generally, newly developed solution-phase synthetic methods are adapted to solid-phase synthesis for application to combinatorial synthesis. Recently, the asymmetric phase-transfer alkylation of the diphenylmethyleneglycinimine ester **1** in the presence of *cinchona*-derived ammonium salts was developed and successfully applied to the enantioselective synthesis of natural and non-natural α-amino acids (Scheme 1).[2]

On the basis of this method, O'Donnell and Scott reported very efficient solid-phase synthetic methods for α-amino acids and peptides by using a resin-bound diphenylmethyleneglycinimine ester (Scheme 2).[3] However, the enantioselectivities (51−89% ee) were generally lower than those obtained from the solution-phase synthesis. In this note, we report a highly enantioselective solid-phase synthetic method for non-natural α-amino acids by a modification of the linker.

SCHEME 1

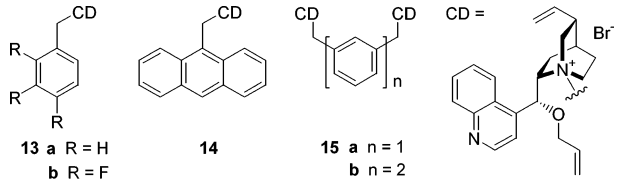


1 **2**

Structure−enantioselectivity relationship studies on the phase-transfer alkylation of diphenylmethyleneglycinimine ester (**1**) revealed that the ester group was quite sensitive for enantioselectivity and that the *tert*-butyl ester was the best group.[4] It was presumed that the relatively lower enantioselectivies of O'Donnell's solid-phase synthetic method compared to the solution-phase synthesis might be due to the less effective ester group, bound to the resin. Imines have not been popular linkers in solid-phase synthesis on account of their instability in acidic conditions. However, solid-supported aromatic imines are stable enough to prevent hydrolysis under the basic condition of phase-transfer alkylation. Therefore, the linker was changed from an ester group to an imine group, and the *tert*-butyl ester group was retained, as shown in Scheme 3.

The resin-bound glycinimine *tert*-butyl ester **9** was prepared from a Merrifield resin in two steps (Scheme 4). The Merrifield resin was oxidized by dimethyl sulfoxide in the presence of $NaHCO_3$ to the corresponding aldehyde **8**, which was followed by condensation with glycine *tert*-butyl ester to give the imine **9**.[5]

The optimal catalyst and reaction conditions for phase-transfer alkylation were examined by the enantioselective benzylation using 10 mol % of the reported catalysts (catalysts **13**,[6] **14**,[7] **15**,[8] and **16**[9]) with benzyl bromide (5 equiv) and 50% aqueous KOH (10 equiv) in toluene/chloroform (volume ratio = 7:3) at 0 °C. The enantioselectivities were determined using *N*-benzoyl-α-benzylglycine *tert*-butyl ester (**12e**),[10] which was obtained from the hydrolysis of **10** with 1 N aq HCl followed by benzoylation.



13 a R = H
b R = F

14

15 a n = 1
b n = 2

16 R = 3',4',5'-trifluorophenyl

As shown in Table 1, both catalysts **14** (88% ee, entry 3) and **16** (88% ee, entry 6) showed the highest enantioselectivities among the evaluated catalysts, but the *N*-benzyl type catalysts (**13a** and **13b**) and dimeric

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(1) (a) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149. (b) Merrifield, R. B. *Science* **1986**, *232*, 341. (c) Terrett, N. K. *Combinatorial Chemistry*; Oxford University Press: Oxford, 1998. (d) Dörwald, F. Z. *Organic Synthesis on Solid Phase*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2000. (e) Bannwarth, W.; Felder, E. *Combinatorial Chemistry*; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2000. (f) Seneci, P. *Solid-Phase Synthesis and Combinatorial Technologies*; John Wiley and Sons: New York, 2000.

(2) For the reviews, see: (a) Nelson, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1583. (b) Shioiri, T.; Arai, S. In *Stimulating Concepts in Chemistry*; Vogtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, Germany, 2000; pp 123−143. (c) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 10. (d) O'Donnell, M. J. *Aldrichimica Acta* **2001**, *34*, 3. (e) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013.

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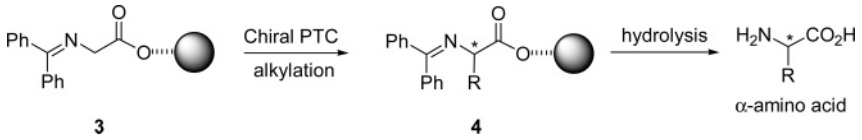
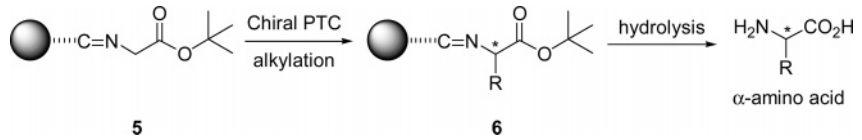
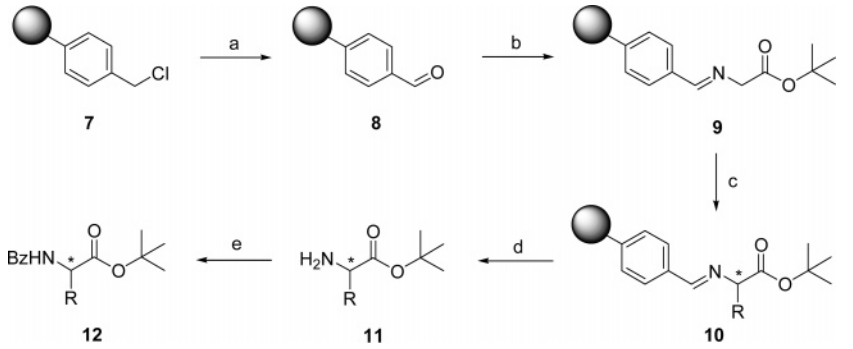
SCHEME 2



SCHEME 3

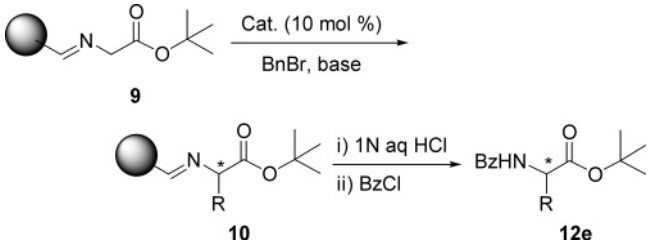


SCHEME 4[a]



[a] Reagents and conditions: (a) $NaHCO_3$, DMSO, 150 °C, 12 h; (b) glycine *tert*-butyl ester·HCl, Et_3N, C_6H_6, reflux, 27 h; (c) 50% aq CsOH, RX, toluene/$CHCl_3$ (7:3), 0 °C; (d) 1 N aq HCl, THF, 0 °C; (e) BzCl, Et_3N, CH_2Cl_2, 0 °C, 50−82% from **9**.

TABLE 1. Optimal Conditions for Phase-Transfer Alkylation[a]



no.	cat.	base	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	**13a**	50% aq KOH	0	72	80	42 (*S*)[d]
2	**13b**	50% aq KOH	0	72	72	34 (*S*)
3	**14**	50% aq KOH	0	72	76	88 (*S*)
4	**15a**	50% aq KOH	0	72	65	45 (*S*)
5	**15b**	50% aq KOH	0	72	75	50 (*S*)
6	**16**	50% aq KOH	0	72	80	88 (*R*)
7	**14**	50% aq CsOH	rt	48	84	80 (*S*)
8	**14**	50% aq CsOH	0	96	80	92 (*S*)
9	**14**	50% aq CsOH	−20	144	30	90 (*S*)

[a] The reaction was carried out with 5.0 equiv of benzyl bromide and 10.0 equiv of base in the presence of 10.0 mol % of catalyst in toluene/chloroform (7:3) under the temperature conditions. [b] Isolated yield (**12e**). [c] The enantiopurity was determined by HPLC analysis of the benzoylate **12e** using a chiral column (Chiralcel OD) with hexanes/2-propanol (98:2) as the solvent. [d] The absolute configuration was determined by comparison with the HPLC retention time of an authentic sample, which was independently prepared from α-benzyl-diphenylmethyleneglycinimine *tert*-butyl ester obtained by the reported procedures.[6−9]

catalysts (**15a** and **15b**) gave poor enantioselectivities. In the case of basic conditions, 50% aq CsOH provided a slightly higher enantioselectivity than 50% aq KOH. The optimal reaction temperature was 0 °C. The higher temperature (20 °C, entry 7) decreased the enantioselectivity, and the lower temperatures (−20 °C, entry 9) conserved the enantioselectivity with a longer reaction time and a lower chemical yield than those at 0 °C. In particular, the α,α-dibenzylated product was not detected

(3) (a) O'Donnell, M. J.; Zhou, C.; Scott, W. L. *J. Am. Chem. Soc.* **1996**, *118*, 6070. (b) Scott, W. L.; Zhou, C.; Fang, Z.; O'Donnell, M. J. *Tetrahedron Lett*. **1997**, *38*, 3695. (c) O'Donnell, M. J.; Lugar, C. W.; Pottorf, R. S.; Zhou, C. *Tetrahedron Lett*. **1997**, *38*, 7163. (d) Griffith, D. L.; O'Donnell, M. J.; Pottorf, R. S.; Scott, W. L.; Porco, J. A., Jr. *Tetrahedron Lett*. **1997**, *38*, 8821. (e) Dorminguez, E.; O'Donnell, M. J.; Scott, W. L. *Tetrahedron Lett*. **1998**, *39*, 2167. (f) O'Donnell, M. J.; Delgado, F.; Pottorf, R. S. *Tetrahedron* **1999**, *55*, 6347. (g) O'Donnell, M. J.; Delgado, F.; Drew, M.; Pottorf, R. S.; Zhou, C.; Scott, W. L. *Tetrahedron Lett*. **1999**, *40*, 5831. (h) O'Donnell, M. J.; Delgado, F.; Dorminguez, E.; Blas, J. D.; Scott, W. L. *Tetrahedron: Asymmetry* **2001**, *12*, 821. (i) Scott, W. L.; Delgado, F.; Lobb, K.; Pottorf, R. S.; O'Donnell, M. J. *Tetrahedron Lett*. **2001**, *42*, 2073. (j) O'Donnell, M. J.; Alsiana, J.; Scott, W. L. *Tetrahedron Lett*. **2003**, *44*, 8403.

(4) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353.

(5) Frechet, J. M.; Schuerch, C. *J. Am. Chem. Soc.* **1971**, *93*, 492.

(6) (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc*. **1984**, *106*, 446. (b) Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245.

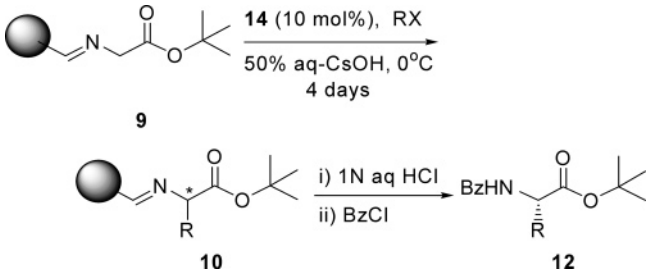
(7) (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett*. **1997**, *38*, 8595. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc*. **1997**, *119*, 12414.

(8) (a) Jew, S.-s.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun*. **2001**, 1244. (b) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* **2001**, *42*, 4645. (c) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-K.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036. (d) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, B.-s.; Kim, M. G.; Jew, S.-s. *Tetrahedron Lett.* **2003**, *44*, 3497.

(9) (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc*. **1999**, *121*, 6519. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (c) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc*. **2003**, *125*, 5139. (d) Jew, S.-s.; Lee, Y.-J.; Lee, J.; Kang, M. J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Kim, M.-J.; Choi, S.-h.; Ku, J.-M.; Park, H.-g. *Angew. Chem., Int. Ed.* **2004**, *43*, 2382.

(10) Adger, B.; Berens, U.; Griffiths, M. J.; Kelly, M. J.; McCague, R.; Miller, J. A.; Palmer, C. F.; Roberts, S. M.; Selke, R.; Vitinius, U.; Ward, G. *Chem. Commun*. **1997**, 1713.

TABLE 2. Phase-Transfer Catalytic Alkylation[a]



entry	RX	yield[b] (%)	ee[c] (%)
a	hexyl bromide	50	92 (*S*)[d]
b	allyl bromide	54	88 (*S*)
c	2-methylallyl bromide	62	92 (*S*)
d	propargyl bromide	50	86 (*S*)
e	benzyl bromide	70	92 (*S*)
f	4-fluorobenzyl bromide	73	>99 (*S*)
g	4-cyanobenzyl bromide	80	94 (*S*)
h	4-methylbenzyl bromide	75	92 (*S*)
i	4-*tert*-butylbenzyl bromide	82	92 (*S*)
j	2-bromomethylnaphthalene	72	97 (*S*)
k	9-chloromethylanthracene	82	93 (*S*)

[a] The reaction conditions were the same as in Table 1 except for the reaction temperature and alkyl halides. [b] Isolated yield (**12**). [c] The enantiopurity was determined by HPLC analysis of the benzoate **12** using a chiral column (Chiralcel OD) with hexanes/2-propanol as the solvent. [d] The absolute configuration was assigned using the same method reported in Table 1.

in excessive basic conditions, which generally caused the second alkylation in the solution-phase system of the aldimine substrates.[11] It was presumed that the steric hindrance in the solid-supported polymer itself might contribute to the inhibition of the second alkylation. Catalyst **14** was chosen for further investigation with various alkyl halides, using the above optimal reaction conditions. The very high enantioselectivities (86 to >99% ee) shown in Table 2 indicate that this solid-phase phase-transfer catalytic method is an efficient enantioselective synthetic method for non-natural α-amino acids.

In conclusion, we developed a highly efficient enantioselective solid-phase synthetic methodology for non-natural α-amino acids using a phase-transfer catalytic alkylation of a resin-bound diphenylmethyleneglycinimine *tert*-butyl ester (**9**). Quite high enhancements in enantioselectivity were accomplished by employing aldimine linker. The easy preparation of the solid-supported substrate **9**, the high enantioselectivity, and the very mild reaction conditions make this method very practical for the construction of the chiral non-natural α-amino acid library via combinatorial synthesis or parallel synthesis.

(11) (a) O'Donnell, M. J.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591. (b) Lygo, B.; Crosby, J.; Perterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671. (c) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (d) Jew, S.-s.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Lee, Y.-J.; Park, B.-s.; Park, H.-g. *J. Org. Chem.* **2003**, *68*, 4514.

Experimental Section

Representative Procedure for the Catalytic Enantioselective Phase-Transfer Alkylation of 9 (Benzylation). To a mixture of aldimine **9** (300 mg, 0.077 mmol) and chiral catalyst **14** (4.6 mg, 0.008 mmol) in a 7:3 mixture of toluene and chloroform (2 mL) was added 50% aqueous cesium hydroxide (0.34 mL, 0.77 mmol) and benzyl bromide (0.045 mL, 0.38 mmol). The reaction mixture was stirred vigorously at 0 °C for 4 days. The resin (**10e**) was filtered, washed with methylene chloride and methanol, and dried at 100 °C under vacuum. To the resin **10e** in tetrahydrofuran (1 mL) was added 1 N aq HCl (0.5 mL), and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered and washed with tetrahydrofuran, methylene chloride, and methanol. The organic solvent was removed under vacuum, basified with saturated aq $NaHCO_3$ (3 mL), and extracted with methylene chloride (6 × 10 mL). The combined methylene chloride was dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford **11e**. To **11e** in methylene chloride (0.5 mL) was added triethylamine (0.032 mL, 0.24 mmol) and benzoyl chloride (0.013 mL, 0.12 mmol) successively at 0 °C. The reaction mixture was stirred for 0.5 h and extracted with methylene chloride (3 × 5 mL). The combined methylene chloride was washed with water, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc = 10:1) to afford the desired product **12e** as a white solid (70%). The enantioselectivity was determined by chiral HPLC analysis of **12e. Conditions:** Chiral Technologies, Inc., DIACEL Chiralcel OD-H; Hexanes/2-propanol = 98:2; Flow rate = 1 mL/min; 23 °C; λ = 254 nm. Retention times: *R* (minor), 11.1; *S* (major), 24.8; 92% ee. The absolute configuration was determined by comparison with the HPLC retention time of an authentic sample, which was independently prepared from the α-benzyldiphenylmethyleneglycinimine *tert*-butyl ester obtained by reported procedures.[6–9] Physical and spectral properties of **12e** were consistent with the literature values.[10]

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Note Added after ASAP Publication. This paper posted ASAP on January 21, 2005. A change was made to the column head of Table 1. The paper was reposted on January 26, 2005.

Supporting Information Available: General experimental methods, procedures for the preparation of **8** and **9**, and spectroscopic characterizations of **12a**−**k** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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