Practical Catalytic Enantioselective Synthesis of α,α-Dialkyl-α-amino Acids by Chiral Phase-Transfer Catalysis

Takashi Ooi, Mifune Takeuchi, Minoru Kameda, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science Hokkaido University, Sapporo 060-0810, Japan
Department of Chemistry, Graduate School of Science Kyoto University, Sakyo, Kyoto 606-8502, Japan

Received February 28, 2000

Nonproteinogenic α,α-dialkyl-α-amino acids have played a special role in the design of peptides with enhanced properties.[1] This is not only because they possess stereochemically stable quaternary carbon centers but also because their incorporation into peptides results in the significant influence on the conformational preferences, which eventually provides useful information for the elucidation of enzymatic mechanisms.[2] Furthermore, α,α-dialkyl-α-amino acids themselves are often effective enzyme inhibitors[3] and also constitute a series of interesting building blocks for the synthesis of various biologically active compounds.[4] Accordingly, development of truly efficient methods for their preparation, especially in an enantiomerically pure form, has become of great importance and numerous studies have been made for this purpose as seen in recent excellent reviews.[5] However, only a few catalytic systems have been reported with limited general applicability.[6,7] Herein we wish to disclose that α,α-dialkyl-α-amino acids can be prepared in a highly enantioselective manner by the one-pot, double alkylation of aldimine Schiff base of glycine *tert*-butyl ester **1** under phase-transfer catalytic conditions using our recently introduced C_2-symmetric chiral quaternary ammonium salts **3** as catalysts;[8] thus paved the way for practical asymmetric synthesis of α,α-dialkyl-α-amino acids from the corresponding α-amino acids.

The requisite aldimine Schiff base **1** was conveniently prepared in a similar manner as previously reported[7c] and initial studies focused on the search for the appropriate reaction conditions. Attempted sequential alkylation of **1** with allyl bromide (1 equiv) and benzyl bromide (1.2 equiv) in 50% aqueous KOH/toluene (volume ratio = 1:3) under the influence of **3a** (R = β-Naph) (1 mol %) proceeded very reluctantly at room temperature. After the solution was stirred for 12 h, hydrolysis with 0.5 M citric acid in THF afforded α-allyl phenylalanine *tert*-butyl ester (**2**; $R^1 = CH_2CH{=}CH_2$, $R^2 = CH_2Ph$) in 28% isolated yield with 83% ee. This result prompted us to examine solid−liquid phase-transfer conditions in order to attain sufficient reactivity as well as selectivity.[9] Thorough optimization of the reaction conditions eventually revealed that initial treatment of the toluene solution of **1** and **3a** (R = β-Naph) (1 mol %) with allyl bromide (1 equiv) and commercially available CsOH·H_2O (5 equiv) at −10 °C for 3.5 h and the subsequent reaction with benzyl bromide (1.2 equiv) at 0 °C for 30 min resulted in formation of the double alkylation product **2** ($R^1 = CH_2CH{=}CH_2$, $R^2 = CH_2Ph$) in 61% yield with higher enantiomeric excess (87% ee). Here, it should be particularly emphasized that tuning of electronic property of the catalyst

Scheme 1

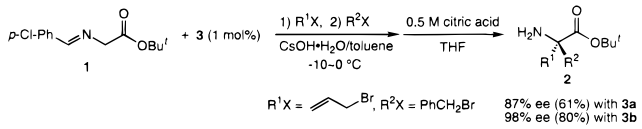
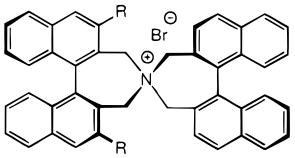


Table 1. Catalytic Enantioselective Double Alkylation of Aldimine Schiff Base Derived from Glycine under Phase-Transfer Conditions[a]

entry	R^1X	condition (°C, h)	R^2X	condition (°C, h)	% yield [b]	% ee [c] (config) [d]
1		-10, 3.5	$PhCH_2Br$	0, 0.5	80	98 (*R*)
2				0, 0.7	60	97
3				0, 0.5	58	96
4	$PhCH_2Br$	-10, 2		0, 0.3	74	92 (*S*)

[a] The reaction was performed by the sequential treatment of aldimine Schiff base **1** (0.5 mmol) with R^1X (1 equiv) and R^2X (1.2 equiv) under the indicated reaction conditions in the presence of 1 mol % of **3b** and CsOH·H_2O (5 equiv) in toluene (2 mL). [b] Isolated yield. [c] Enantiopurity was determined by HPLC analysis of the amino ester or its *N*-benzoate using a chiral column [DAICEL Chiralpak AD (for entries 1 and 4) and Chiralcel OD (for entry 2)] with hexane-2-propanol as solvent. Capillary GC analysis with a chiral column (GL Science CP-Chirasil-DEX CB) was employed for entry 3. [d] Absolute configuration was determined by cleavage of the *tert*-butyl ester (6 N HCl) and comparison of the optical rotation of the free amino acid with the literature value [Vedejs, E.; Fields, S. C.; Hayashi, R.; Hitchcock, S. R.; Powell, D. R.; Schrimpf, M. R. *J. Am. Chem. Soc.* **1999**, *121*, 2460 (for entries 1 and 4)].



3a (R = β-Naph), **3b** (R = 3,4,5-F_3-Ph)

(1) (a) Bellier, B.; McCort-Tranchenpain, I.; Ducos, B.; Danascimento, S.; Meudal, H.; Noble, F.; Garbay, C.; Roques, B. P. *J. Med. Chem.* **1997**, *40*, 3947. (b) Mossel, E.; Formaggio, F.; Crisma, M.; Toniolo, C.; Broxterman, Q. B.; Boesten, W. H. J.; Kamphuis, J.; Quaedflieg, P. J. L. M.; Temussi, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1305. (c) Dery, O.; Josien, H.; Grassi, J.; Chassaing, G.; Couraud, J. Y.; Lavielle, S. *Biopolymers* **1996**, *39*, 67. (d) Benedetti, E.; Gavuzzo, E.; Santini, A.; Kent, D. R.; Zhu, Y.-F.; Zhu, Q.; Mahr, C.; Goodman, M. *J. Pept. Sci.* **1995**, *1*, 349. (e) Toniolo, C.; Formaggio, F.; Crisma, M.; Valle, G.; Boesten, W. H. J.; Schoemaker, H. E.; Kamphuis, J.; Temussi, P. A.; Becker, E. L.; Precigoux, G. *Tetrahedron* **1993**, *49*, 3641. (f) Schiller, P. W.; Weltrowska, G.; Nguyen, T. M.-D.; Lemieux, C.; Chung, N. N.; Marsden, B. J.; Wilkes, B. C. *J. Med. Chem.* **1991**, *34*, 3125.

(2) (a) Paradisi, M. P.; Torrini, I.; Zecchini, G. P.; Lucente, G.; Gavuzzo, E.; Mazza, F.; Pochetti, G. *Tetrahedron* **1995**, *51*, 2379. (b) Burgess, K.; Ho, K.-K.; Pal, B. *J. Am. Chem. Soc.* **1995**, *117*, 3808. (c) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (d) Balaram, P. *Curr. Opin. Struct. Biol.* **1992**, *2*, 845.

(3) For example, see: (a) Zhelyaskov, D. K.; Levitt, M.; Uddenfriend, S. *Mol. Pharmacol.* **1968**, *4*, 445. (a) Sourkers, T. L. *Arch. Biochem. Biophys.* **1945**, *51*, 444.

(4) Review: Koert, U. *Nachr. Chem. Technol. Lab.* **1995**, *43*, 347.

(5) (a) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (b) Seebach, D.; Sting, A. R.; Hoffmann, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2708. (c) Wirth, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 225. (d) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517.

(6) (a) Ito, Y.; Sawamura, M.; Shirakawa, E.; Hayashizaki, K.; Hayashi, T. *Tetrahedron* **1988**, *44*, 5253. (b) Ito, Y.; Sawamura, M.; Matsuoka, M.; Matsumoto, Y.; Hayashi, T. *Tetrahedron Lett.* **1987**, *28*, 4849.

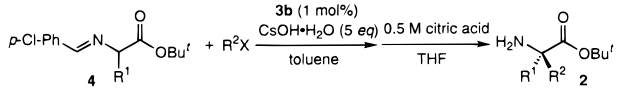
(7) For recent examples under PTC conditions, see: (a) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671. (b) Belokon, Y. N.; North, M.; Kublitski, V. S.; Ikonnikov, N. S.; Krasik, P. E.; Maleev, V. I. *Tetrahedron Lett.* **1999**, *40*, 6105. (c) Belokon, Y. N.; Kochetkov, K. A.; Churkina, T. D.; Ikonnikov, N. S.; Chesnokov, A. A.; Larionov, O. V.; Parmar, V. S.; Kumar, R.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 851. (d) O'Donnell, J. M.; Wu, S. *Tetrahedron: Asymmetry* **1992**, *3*, 591.

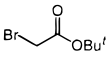
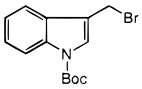
(8) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519.

(9) For recent impressive reports on solid−liquid phase-transfer reactions, see: (a) Arai, S.; Shirai, Y.; Ishida, T.; Shioiri, T. *Chem. Commun.* **1999**, 49. (b) Corey, E. J.; Bo, Y.; Busch-Petersen, J. *J. Am. Chem. Soc.* **1998**, *120*, 13000. (c) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (d) Eddine, J. J.; Cherqaoui, M. *Tetrahedron: Asymmetry* **1995**, *6*, 1225. See also ref 7.

10.1021/ja0007051 CCC: $19.00
Published on Web 05/16/2000

Table 2. Catalytic Enantioselective Synthesis of α,α-Dialkyl-α-amino Acids by Phase-Transfer Alkylation[a]



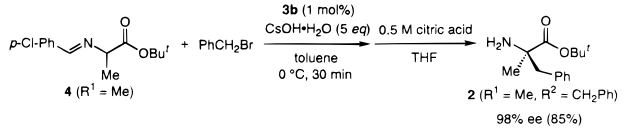
entry	R^1	R^2X	condition (°C, h)	% yield [b]	% ee [c] (config) [d]
1	Me	$PhCH_2Br$	0, 0.5	85	98 (*R*)
2			0, 0.5	73	98 (*R*)
3		EtI [e]	0, 0.3	71	99 (*R*)
4			-20, 2	60	93 (*R*)
5			-10, 0.7	78	91 (*R*)
6	$PhCH_2$		0, 0.5	71	97 (*S*)
7	*i*-Bu	$PhCH_2Br$	0, 0.5	64	92
8			0, 1	70	93

[a] Unless otherwise specified, the reaction was carried out with R^2X (1.2 equiv) in the presence of 1 mol % of **3b** and $CsOH·H_2O$ (5 equiv) in toluene (0.25 M) under the given reaction conditions. [b] Isolated yield. [c] Enantiopurity was determined by HPLC analysis of the amino ester or its *N*-benzoate using a chiral column [(DAICEL Chiralpak AD (for entries 1, 3, 5−7) and Chiralcel OD (for entries 2, 4, 8)] with hexane-2-propanol as solvent. [d] Absolute configuration was determined as noted in Table 1 [Alonso, F.; Gavies, S. G.; Elend, A. S.; Haggitt, J. L. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 257 (for entries 1 and 2), Studer, A.; Seebach, D. *Liebigs Ann.* **1995**, 217 (for entry 3), Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A.; Lapena, Y. *Tetrahedron* **1997**, *53*, 5891 (for entry 4), Gander-Coquoz, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 221 (for entry 5), See Table 1 for entry 6]. [e] Use of 5 equiv of alkyl halide.

by introducing 3,4,5-trifluorophenyl substituent on 3,3′-positions of the binaphthyl structure further enhanced the enantioselectivity, that is, the reaction in the presence of **3b** (R = 3,4,5-F_3-Ph) (1 mol %) under otherwise similar conditions gave rise to the α,α-dialkyl-α-amino acid **2** ($R^1 = CH_2CH{=}CH_2$, $R^2 = CH_2Ph$; 80%) in 98% ee (Scheme 1, entry 1 in Table 1). The distinct feature of this procedure is that it enables straightforward asymmetric synthesis of various α,α-dialkyl-α-amino acids including those otherwise inaccessible from the naturally occurring amino acids as exemplified in Table 1. Notably, in the double alkylation of **1** by the addition of the halides in a reverse order, the absolute configuration of the product **2** was confirmed to be opposite, indicating the intervention of the expected chiral ammonium enolate in the second alkylation stage (entry 1 vs 4).

Since the stereochemistry of the newly created quaternary carbon center was apparently determined in the second alkylation process, we envisaged that the core of our method should be

Scheme 2



applicable to the asymmetric alkylation of aldimine Schiff base **4** derived from the corresponding α-amino acids. Indeed, rapid benzylation of DL-alanine-derived imine **4** (R^1 = Me) occurred at 0 °C in toluene with benzyl bromide ($R^2 = CH_2Ph$) (1.2 equiv) and $CsOH·H_2O$ (5 equiv) using **3b** (R = 3,4,5-F_3-Ph) (1 mol %) as a catalyst, giving the alkylation product **2** (R^1 = Me, R^2 = CH_2Ph; 85%) (entry 1 in Table 2) in an almost enantiomerically pure form (98% ee) as illustrated in Scheme 2.[10]

Other selected examples of the alkylation of **4** using 1 mol % of catalyst **3b** (R = 3,4,5-F_3-Ph) listed in Table 2 clearly demonstrate the remarkable efficiency and generality of our approach. Not only benzylation and allylation, but also alkylation of **4** (R^1 = Me) with simple alkyl halide such as ethyl iodide proceeded smoothly at 0 °C to furnish the corresponding α,α-dialkyl-α-amino acid *tert*-butyl ester **2** (R^1 = Me, R^2 = Et) with virtually complete enantiofacial control (entry 3). Use of α-bromo *tert*-butyl acetate as an alkylating agent allows facile enantioselective access to α-methyl aspartic acid (entry 4).[11] Asymmetric synthesis of α-methyl tryptophan, an important amino acid for the design of dipeptoid with high affinity for the central cholecystokinin receptor,[12] can be realized by the present method (entry 5). Moreover, the phase-transfer catalytic alkylation of aldimine Schiff base derived from other α-amino acids such as DL-phenylalanine ($R^1 = PhCH_2$) and DL-leucine (R^1 = *i*-Bu) also appeared to be feasible with high efficiency, providing the desired noncoded amino acid esters **2**, where excellent asymmetric induction was uniformly observed (entries 6−8).

In summary, we have devised a broadly useful procedure for the asymmetric synthesis of a wide variety of α,α-dialkyl-α-amino acids based on the highly enantioselective solid−liquid phase-transfer catalytic alkylation of aldimine Schiff base of amino acid *tert*-butyl esters using structurally well-defined C_2-symmetric chiral quaternary ammonium bromides. This unprecedentedly general and practical method should have vast synthetic potential even from an industrial point of view.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

Supporting Information Available: Representative experimental procedures as well as spectroscopic characterization of catalyst **3b** and all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0007051

(10) The benzylation of either D-alanine- or L-alanine-derived imine gave almost the same results.

(11) Kiick, D. M.; Cook, P. F. *Biochemistry* **1983**, *22*, 375.
(12) Horwell, D. C.; Hughes, J.; Hunter, J. C.; Pritchard, M. C.; Richardson, R. S.; Roberts, E.; Woodruff, G. N. *J. Med. Chem.* **1991**, *34*, 404.