ORGANIC LETTERS

2005
Vol. 7, No. 2
191−193

Asymmetric Synthesis of Functionalized Aza-Cyclic Amino Acids with Quaternary Stereocenters by a Phase-Transfer-Catalyzed Alkylation Strategy

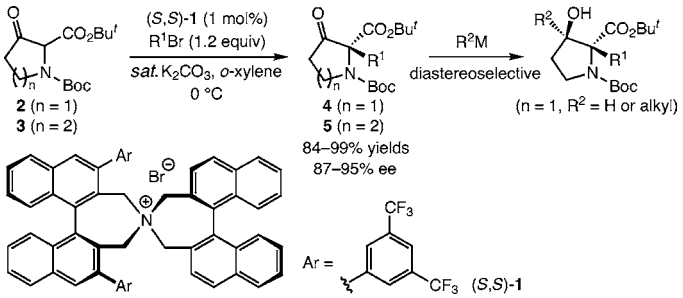
Takashi Ooi, Takashi Miki, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

maruoka@kuchem.kyoto-u.ac.jp

Received October 8, 2004 *(Revised Manuscript Received December 6, 2004)*

ABSTRACT



Practical asymmetric synthesis of functionalized aza-cyclic α-amino acid derivatives possessing quaternary stereocenters has been achieved by the phase-transfer-catalyzed alkylation of 2 or 3 using chiral quaternary ammonium bromide 1 as catalyst. Subsequent reduction and alkylation of the 3-keto carbonyl moiety of 4 proceeded with complete diastereochemical control to afford the corresponding *β*-hydroxy aza-cyclic α-amino acid derivatives having stereochemically defined consecutive quaternary carbon centers.

As a family of nonproteinogenic amino acids, aza-cyclic α-amino acids with quaternary stereogenic carbon centers have attracted a particular interest in the various fields of science, mainly for the following reasons: (1) their conformational constraints offer an important tool for evaluating the relationship between peptide conformation and biological activity,[1] (2) they are found as a component of biologically active natural products with therapeutic potential,[2] and (3) they serve as valuable chiral building blocks in organic synthesis and also constitute a core structure of effective catalysts for asymmetric bond formation reactions.[3] Since these amino acids are not available from natural sources, considerable research efforts have been made to develop useful methods for their synthesis,[4−6] and the recently introduced asymmetric intramolecular ring-closure of protected α-amino acids utilizing memory of chirality is a representative example.[7] Unfortunately, however, almost all the previous studies have relied on the use of stoichiometric amount of external/internal chirality,[4,5,7] and hence, catalytic asymmetric construction of the requisite stereocenters of aza-

(1) For example, see: (a) Ward, P.; Ewan, G. B.; Jordan, C. C.; Ireland, S. J.; Hagan, R. M.; Brown, J. R. *J. Med. Chem.* **1990**, *33*, 1848. (b) Bisang, C.; Weber, C.; Inglis, J.; Schiffer, C. A.; van Gunsteren, W. F.; Jelesarov, I.; Bosshard, H. R.; Robinson, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7904.

(2) (a) Long, R. D.; Moeller, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 12394. (b) Trancard, D.; Tout, J.-B.; Giard, T.; Chichaoui, I.; Cahard, D.; Plaquevent, J.-C. *Tetrahedron Lett.* **2000**, *41*, 3843. (c) Gutiérrez-Rodríguez, M.; García-López, M. T.; Herranz, R. *Tetrahedron* **2004**, *60*, 5177.

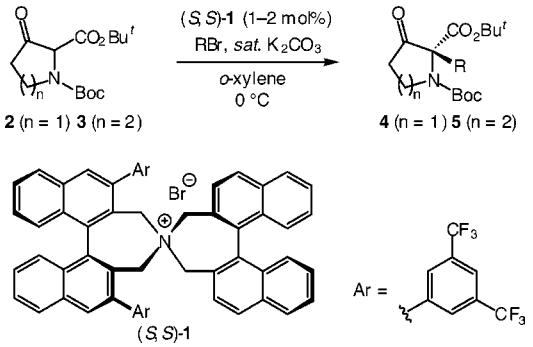
(3) (a) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450. (b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790.

(4) For a comprehensive review, see: Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645 and valuable sets of references therein.

10.1021/ol047921p CCC: $30.25
Published on Web 12/30/2004

cyclic α-amino acids remains to be investigated.[6] We report herein our own approach to this problem based on the phase-transfer-catalyzed, highly enantioselective alkylation of cyclic α-amino-*β*-keto esters **2** or **3** with C_2-symmetric chiral quaternary ammonium salt **1**[8] as catalyst (Scheme 1). This

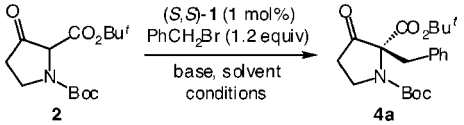
Scheme 1



enables the preparation of various optically active 3-oxoproline− and 3-oxopipecolic acid−chimeras **4** and **5**, which can further be functionalized onto the 3-keto carbonyl to give 3-hydroxy aza-cyclic α-amino acid derivatives possessing stereochemically defined consecutive quaternary carbon centers.

Initially, we chose 3-oxoproline derivative **2** as a representative substrate and examined its benzylation under phase-transfer conditions using chiral quaternary ammonium bromide (*S*,*S*)-**1**, a promising catalyst for the alkylation of simple *β*-keto esters.[8a] Attempted reaction of **2** with benzyl bromide (1.2 equiv) in the presence of powdered KOH (5 equiv) and 1 mol % of (*S*,*S*)-**1** in toluene at room temperature resulted in nearly instantaneous consumption of the starting **2**, but the desired alkylation product **4a** was obtained in only 31% isolated yield with 87% ee (entry 1 in Table 1). Although promising enantioselectivity was observed, this result apparently indicated the instability of **2** under strongly basic

Table 1. Optimization of the Reaction Conditions in the Phase-Transfer-Catalyzed Benzylation of **2** with (*S*,*S*)-**1** as Catalyst[a]



entry	base	solvent	conditions	% yield[b]	% ee[c] (config)[d]
1	KOH[e]	toluene	rt, 40 min	31[f]	87 (*R*)
2	K_2CO_3		rt, 40 h	88	88 (*R*)
3	*sat.* K_2CO_3[g]		rt, 6 h	94	88 (*R*)
4		mesitylene	rt, 26 h	89	84 (*R*)
5		*m*-xylene	rt, 7 h	91	87 (*R*)
6		*o*-xylene	rt, 2 h	92	89 (*R*)
7		*o*-xylene	0 °C, 3 h	84	94 (*R*)

[a] Unless otherwise specified, the reaction was carried out on a 0.3 mmol scale with 1.2 equiv of benzyl bromide and 5 equiv of base in the presence of 1 mol % of (*S*,*S*)-**1** in 2 mL of solvent under the given reaction conditions. [b] Isolated yield. [c] Enantiopurity of **4a** was determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD) with hexane-2-propanol as solvent. [d] For determination of the absolute configuration, see the Supporting Information. [e] Finely powdered. [f] **2** was partially decomposed. [g] 1.5 mL of saturated aqueous K_2CO_3 was used.

conditions. Thus, we changed the base to K_2CO_3 and found that the benzylation of **2** under otherwise similar conditions afforded **4a** in 88% yield after stirring for 40 h and its enantiomeric excess was revealed to be 88% ee (entry 2). Here, use of saturated aqueous K_2CO_3 was also effective and the reaction in toluene-saturated K_2CO_3 (volume ratio = 4:3) at room temperature reached completion in 6 h without sacrificing the chemical yield and the enantioselectivity (entry 3). We then examined the solvent effect, and interestingly, *o*-xylene was identified as a solvent of choice for this system, providing a substantial enhancement of the reaction rate (entries 4−6). This observation prompted us to conduct the reaction at 0 °C, where **2** was consumed within 3 h and **4a** was obtained in 84% yield with 94% ee (entry 7).

This optimized reaction condition was used to further investigate the applicability of the present method for the synthesis of various aza-cyclic quaternary amino acid derivatives. As shown in Table 2, a series of benzylic bromides with substituents of different electronic properties were employable, allowing the preparation of diverse chimeras of 3-oxoproline and phenylalanine derivatives (entries 1−4). Construction of quaternary carbon centers having allylic substituents on **2** can also be achieved in a similar manner (entries 5 and 6). The catalytic asymmetric quaternization of homologous substrate **3**, 3-oxopipecolic acid derivative, appeared feasible with 2 mol % of (*S*,*S*)-**1**, and a uniformly high level of enantioselectivity was attained (entries 7−10).

The optically active α-alkyl-α-amino-*β*-keto ester **4** thus obtained can further be functionalized by taking advantage of the presence of the 3-keto carbonyl moiety. For instance, simple treatment of **4a** with $NaBH_4$ in MeOH gave rise to **6**, a protected chimera of 3-hydroxyproline and phenylalanine, as a single diastereomer in a quantitative yield

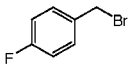
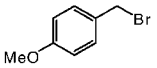
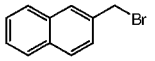
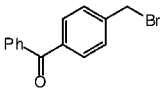
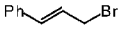
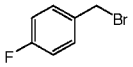
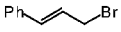
(5) Recent representative examples: (a) Glaeske, K. W.; West, F. G. *Org. Lett.* **1999**, *1*, 31. (b) Abellán, T.; Mancheño, B.; Nájera, C.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 6627. (c) Gil, A. M.; Buñuel, E.; Díaz-de-Villegas, M. D.; Cativiela, C. *Tetrahedron: Asymmetry* **2003**, *14*, 1479. (d) Tamura, O.; Yanagimachi, T.; Ishibashi, H. *Tetrahedron: Asymmetry* **2003**, *14*, 3033. (e) Le Nguyen, B. K.; Langlois, N. *Tetrahedron Lett.* **2003**, *44*, 5961. (f) Andrei, M.; Efskind, J.; Viljugrein, T.; Römming, C.; Undheim, K. *Tetrahedron: Asymmetry* **2004**, *15*, 1301. (g) Bashiardes, G.; Safir, I.; Barbot, F.; Laduranty, J. *Tetrahedron Lett.* **2004**, *45*, 1567. (h) Khasanov, A. B.; Ramirez-Weinhouse, M. M.; Webb, T. R.; Thiruvazhi, M. *J. Org. Chem.* **2004**, *69*, 5766.

(6) For rare examples involving catalytic asymmetric bond formation, see: (a) multistep synthesis via Sharpless epoxidation: Brennan, C. J.; Pattenden, G.; Rescourio, G. *Tetrahedron Lett.* **2003**, *44*, 8757. (b) based on phase-transfer-catalyzed alkylation of α-amino acid Schiff base (enantiomeric excess was not determined): Belokon, Y. N.; Bhave, D.; D'Addario, D.; Groaz, E.; North, M.; Tagliazucca, V. *Tetrahedron* **2004**, *60*, 1849.

(7) (a) Kawabata, T.; Kawakami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012. See also: (b) Brewster, A. G.; Jayatissa, J.; Mitchell, M. B.; Schofield, A.; Stoodley, R. J. *Tetrahedron Lett.* **2002**, *43*, 3919.

(8) (a) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, 42, 3796. See also: (b) Ooi, T.; Doda, K.; Maruoka, K. *Org. Lett.* **2001**, *3*, 1273. (c) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542.

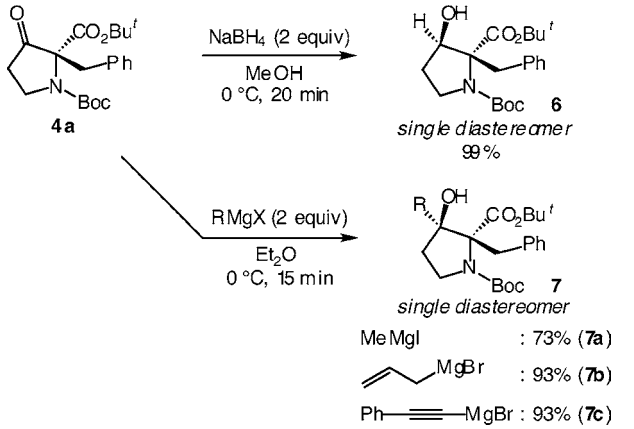
Table 2. Phase-Transfer-Catalyzed Asymmetric Quaternization of **2** and **3**[a]

entry	substrate	**1** (mol%)	RBr	react. time (h)	% yield[b]	% ee[c] (config)[d]
1	**2**	1		4	94	95
2		1		24	99	94
3		1		8	94	93
4		1		9	85	95
5[e]		2		9	84	90
6		1		24	92	89
7	**3**	2	$PhCH_2Br$	4	96	91 (*R*)
8		2		3	87	93
9[e]		2		9	91	87
10		2		4	91	90

[a] Unless otherwise noted, the reaction was carried out with 1.2 equiv of RBr in the presence of 1−2 mol % of (*S*,*S*)-**1** in *o*-xylene-saturated K_2CO_3 (volume ratio = 4:3) at 0 °C for the given reaction time. [b] Isolated yield. [c] Enantiopurity of products was determined by HPLC analysis using a chiral column. [d] For determination of the absolute configuration, see the Supporting Information. [e] With 3 equiv of allyl bromide.

(Scheme 2). Moreover, selective alkylation with various Grignard reagents was found to proceed smoothly to furnish **7** with complete stereochemical control, thereby allowing the construction of two consecutive stereochemically defined quaternary stereocenters. The observed diastereoselectivity could be accounted for by the chelate formation with the magnesium cation with both the ester and ketone group, and nucleophilic attack occurs from the side opposite the benzylic side chain, resulting in the *cis*-disposition of the hydroxy and benzyl group.[9]

Scheme 2



In summary, a concise, catalytic asymmetric synthesis of functionalized aza-cyclic α-amino acid derivatives possessing quaternary stereocenters has been accomplished by the phase-transfer-catalyzed alkylation using chiral quaternary ammonium bromide **1** as catalyst. Subsequent reduction and alkylation of the 3-keto carbonyl moiety proceeded with high diastereoselectivity to afford the corresponding densely functionalized *β*-hydroxy-α-amino esters. Further application of this method to the asymmetric synthesis of biologically intriguing compounds is being investigated in our laboratory.

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

Supporting Information Available: Detailed experimental procedure, spectroscopic characterization of new compounds and stereochemical assignment. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047921P

(9) (a) Van Emelen, K.; De Wit, T.; Hoornaert, G. J.; Compernolle, F. *Org. Lett.* **2000**, *2*, 3083. (b) Van Emelen, K.; De Wit, T.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron* **2002**, *58*, 4225.