Bioorganic & Medicinal Chemistry Letters 19 (2009) 3795–3797

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Catalytic asymmetric synthesis of cyclic α-alkyl-amino acid derivatives having a tetrasubstituted α-carbon

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A R T I C L E I N F O

Article history:
Received 26 March 2009
Revised 8 April 2009
Accepted 9 April 2009
Available online 14 April 2009

Keywords:
Asymmetric synthesis
Amino acid
Phase-transfer
Alkylation
Cyclic

A B S T R A C T

Catalytic asymmetric synthesis of various cyclic α-alkyl-amino acid derivatives having a tetrasubstituted α-carbon has been accomplished by the utilization of phase-transfer alkylation of α-alkyl-amino acid derivatives.

α,α-Dialkyl-α-amino acids are conformationally constrained and they play an important role in designing a novel peptide.[1] Among them, cyclic α-alkyl-α-amino acids with the amine group inside the cyclic system such as α-methyl proline are applied not only to peptide chemistry but also to organocatalytic reactions as catalyst,[2] and development of their synthetic method has become a research area of great importance in medicinal and synthetic chemistry (Fig. 1). While a number of asymmetric syntheses of such cyclic amino acids via construction of tetrasubstituted α-carbon have been reported to date,[3–9] general methods for their preparation based on the catalytic asymmetric construction of tetra-substituted carbon are scarce.[7–9] In this context, we have been interested in utilization of enantioselective phase-transfer alkylation of α-amino acid derivatives to prepare cyclic α-alkyl-α-amino acids.[8,9] Here we wish to report the efficient asymmetric synthesis of α-alkylproline, α-alkylpipecolic acid and α-alkylaziridine-2-carboxylic acid derivatives based on the enantioselective phase-transfer alkylation.

We first examined the synthesis of α-alkylproline *t*-butyl esters by C,N-double alkylation of *C*-alkyl-substituted-*N*-(4-chlorobenzylidene)glycine esters **2** using 1-chloro-3-iodopropane as an alkylating agent. The reaction of **2** (R = Me) with 1-chloro-3-iodopropane (2 equiv) in toluene in the presence of a chiral phase transfer catalyst (*S*)-**1**[10] (1 mol %) and $CsOH·H_2O$ (5 equiv) at 0 °C proceeded smoothly to afford the corresponding α-alkylated alanine derivative. Acidic hydrolysis with 1 N HCl and subsequent ring closure with an excess amount of Na_2CO_3 gave α-methylproline *t*-butyl ester **3** (R = Me) in 87% yield. The enantiomeric excess of **3** (R = Me) was determined to be 99% ee by chiral HPLC analysis of its *N*-benzoyl adduct (Table 1, entry 1). Other α-amino acid derivatives **2** (R = *i*-Bu, allyl, and Bn) were also applicable to this reaction sequence, and the corresponding α-alkylproline *t*-butyl esters **3** (R = *i*-Bu, allyl, and Bn) were obtained in good yield with excellent enantioselectivity (entries 2–4). The catalyst loading could be reduced without significant loss of enantioselectivity, and moderate to good yields of **3** (R = Bn) were obtained with prolonged reaction time (entries 5 and 6).

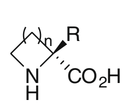
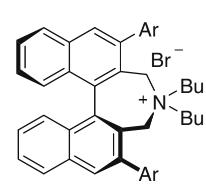


Figure 1. Cyclic α-alkyl-α-amino acid.



(*S*)-**1**
(Ar = 3,4,5-$F_3C_6H_2$)

In a similar manner, using 1,3-dichloro-2-methylenepropane instead of 1-chloro-3-iodopropane, a variety of α-alkyl-4-methyle-

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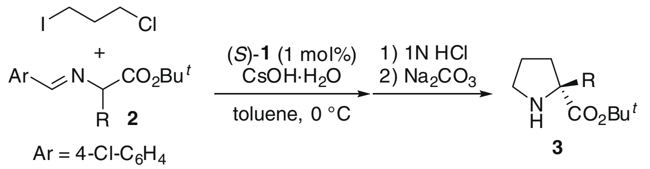
doi:10.1016/j.bmcl.2009.04.025

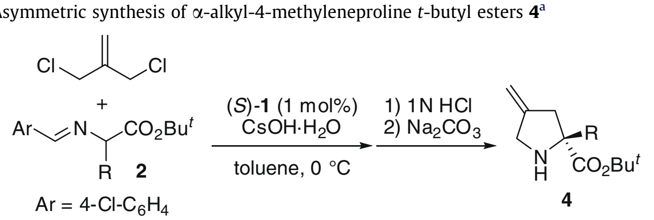
Table 1
Asymmetric synthesis of α-alkylproline *t*-butyl esters **3**[a]



Entry	R	Time (h)	Yield[b] (%)	ee[c] (%) (config)
1[d]	Me	6	87	99[e] (*R*)
2	*i*-Bu	12	94	99[e]
3	Allyl	8	76	98[e]
4	Bn	6	91	99
5[f]	Bn	24	81	99
6[g]	Bn	40	75	98

[a] The reaction of **2** (1 equiv) with 1-chloro-3-iodopropane (3 equiv) was carried out in toluene in the presence of catalyst (*S*)-**1** (0.01 equiv) and CsOH·H_2O (5 equiv) at 0 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral column (Chiralpak AD-H or Chiralcel OD-H, Daicel Chemical Industries, Ltd).
[d] 2 equiv of 1-chloro-3-iodopropane was used.
[e] ee of the corresponding *N*-benzoyl adduct.
[f] 0.5 mol % of (*S*)-**1**.
[g] 0.1 mol % of (*S*)-**1**.

Table 2
Asymmetric synthesis of α-alkyl-4-methyleneproline *t*-butyl esters **4**[a]



Entry	R	Time (h)	Yield[b] (%)	ee[c] (%)
1	Me	2	44	97[d]
2	*i*-Bu	1	48	96[d]
3	Allyl	0.7	64	96[d]
4	Bn	0.75	56	97

[a] The reaction of **2** (1 equiv) with 1,3-dichloro-2-methylenepropane (2 equiv) was carried out in toluene in the presence of catalyst (*S*)-**1** (0.01 equiv) and CsOH·H_2O (5 equiv) at 0 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral column (Chiralpak AD-H or Chiralcel OD-H, Daicel Chemical Industries, Ltd).
[d] ee of the corresponding *N*-benzoyl adduct.

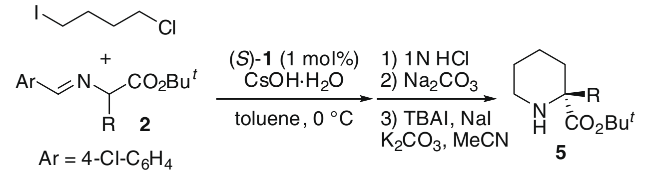
neproline *t*-butyl esters **4** could be synthesized in moderate yield with excellent enantioselectivity (Table 2).

Based on the above results, we then examined the catalytic asymmetric synthesis of α-alkylpipecolic acid *t*-butyl esters using 1-chloro-4-iodobutane. Under similar conditions the ring-closing N-alkylation did not proceed. When the cyclization was performed in the presence of TBAI (0.1 equiv), NaI (5.0 equiv) and K_2CO_3 (2.0 equiv) in MeCN under reflux overnight, the desired α-alkylpipecolic acid *t*-butyl esters **5** were obtained in good yield with excellent enantioselectivity (Table 3).[11]

While the attempted synthesis of α-alkylazetidine-2-carboxylic acid derivative using 1,2-diiodoethane as an alkylating agent failed, probably due to the decomposition of 1,2-diiodoethane under basic alkylation conditions, α-alkylaziridine-2-carboxylic acid derivatives **6** were effectively prepared using diiodomethane (Table 4).

To enhance the utility of this methodology we further examined the synthesis of an α-alkylproline derivative through the one-pot

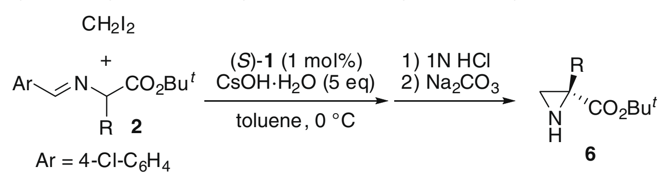
Table 3
Asymmetric synthesis of α-alkyl-pipecolic acid *t*-butyl esters **5**[a]



Entry	R	Time (h)	Yield[b] (%)	ee[c] (%)
1	Me	12	83	99[d]
2	Allyl	8	81	98[d]
3	Bn	8	84	99

[a] The reaction of **2** (1 equiv) with 1-chloro-4-iodobutane (3 equiv) was carried out in toluene in the presence of catalyst (*S*)-**1** (0.01 equiv) and CsOH·H_2O (5 equiv) at 0 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral column (Chiralpak AS-H or Chiralcel OD-H, Daicel Chemical Industries, Ltd).
[d] ee of the corresponding *N*-benzoyl adduct.

Table 4
Asymmetric synthesis of α-alkylaziridine-2-carboxylic acid *t*-butyl esters **6**[a]

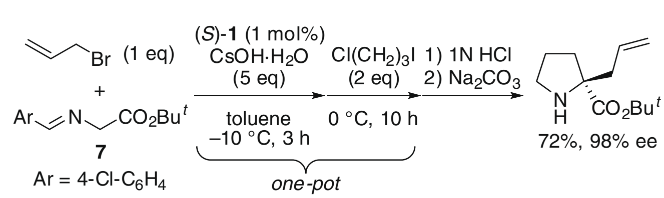


Entry	R	Time (h)	Yield[b] (%)	ee[c] (%)
1	*i*-Bu	6	89	97[d]
2	Bn	6	91	83[d]
3[e]	Bn	12	87	98

[a] The reaction of **2** (1 equiv) with diiodomethane (3 equiv) was carried out in toluene in the presence of catalyst (*S*)-**1** (0.01 equiv) and CsOH·H_2O (5 equiv) at 0 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral column (Chiralcel OJ-H, Daicel Chemical Industries, Ltd).
[d] ee of the corresponding *N*-benzoyl adduct.
[e] The reaction was performed at −20 °C.

double alkylation of *N*-(4-chlorobenzylidene)glycine ester **7**.[12] Using α-unsubstituted glycine derivative **7**, sequential alkylations were performed with allyl bromide (1.0 equiv) and 1-chloro-3-iodopropane (2.0 equiv) in one-pot, and the cyclization of the resulting α,α-dialkylated product gave the α-allylproline *t*-butyl ester in 72% yield with 98% ee (Scheme 1).

In summary, we have demonstrated an efficient asymmetric synthesis of α-alkylproline, α-alkylpipecolic acid and α-alkylaziridine-2-carboxylic acid derivatives by the highly enantioselective phase-transfer alkylation. Further investigations for utilizing these amino acid derivatives as attractive chiral building blocks are in progress in our laboratory.



Scheme 1.

Acknowledgments

This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas 'Advanced Molecular Transformation of Carbon Resources' from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. H.M. is grateful to the Japan Society for the Promotion of Science for Young Scientists for a research fellowship.

References and notes

1. For reviews, see: (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645; (b) Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629; (c) Calaza, M. I.; Cativiela, C. *Eur. J. Org. Chem.* **2008**, 3427.
2. (a) Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem.* **2003**, *68*, 3844; (b) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450; (c) Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914.
3. (a) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390; (b) Wang, H.; Germanas, J. P. *Synlett* **1999**, 33; (c) Ferey, V.; Vedrenne, P.; Toupet, L.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **1996**, *61*, 7244; (d) Matsumura, Y.; Kinoshita, T.; Yanagihara, Y.; Kanemoto, N.; Watanabe, M. *Tetrahedron Lett.* **1996**, *37*, 8395; (e) Berrien, J.-F.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1994**, *59*, 3769; (f) Hou, D.-R.; Hung, S.-Y.; Hu, C.-C. *Tetrahedron: Asymmetry* **2005**, *16*, 3858.
4. (a) Bajgrowicz, J.; Achquar, A. E.; Roumestant, M.-L.; Pigière, C.; Viallefont, P. *Heterocycles* **1986**, *24*, 2165; (b) Chinchilla, R.; Galindo, N.; Nájera, C. *Tetrahedron: Asymmetry* **1998**, *9*, 2769; (c) Chinchilla, R.; Galindo, N.; Nájera, C. *Synthesis* **1999**, 704; (d) Kedrowski, B. L.; Heathcock, C. H. *Heterocycles* **2002**, *58*, 601; (e) Balducci, D.; Grandi, A.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **2005**, *16*, 1453; (f) Schöllkopf, U.; Hinrichs, R.; Lonsky, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 143.
5. (a) Kawabata, T.; Kawakami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012; (b) MacQuarrie-Hunter, S.; Carlier, P. R. *Org. Lett.* **2005**, *7*, 5305.
6. (a) Davis, F. A.; Liu, H.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 5473; (b) Risberg, E.; Fischerb, A.; Somfai, P. *Chem. Commun.* **2004**, 2088.
7. (a) Shao, H.; Zhu, Q.; Goodman, M. *J. Org. Chem.* **1995**, *60*, 790; (b) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400; (c) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732.
8. (a) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347; (b) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett.* **1999**, *40*, 3843.
9. Ooi, T.; Takeuchi, M.; Maruoka, K. *Synthesis* **2001**, 1716.
10. Kitamura, K.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549.
11. *Typical procedure for the asymmetric synthesis of α-methylpipecolic acid t-butyl ester* **5** (R = Me): To a mixture of *N*-(4-chlorobenzylidene)glycine ester **2** (60 mg, 0.22 mmol), (*S*)-**1** (1.7 mg, 0.0022 mmol) and $Cl(CH_2)_4I$ (82 μL, 0.67 mmol) in toluene (2.0 mL) was added $CsOH{\cdot}H_2O$ (188 mg, 1.1 mmol) at 0 °C under an argon atmosphere. After vigorous stirring for 12 h at 0 °C, the resulting mixture was poured into water and extracted with Et_2O twice. The combined extracts were dried over Na_2SO_4 and concentrated. The residue was dissolved into EtOAc (5 mL). After stirred with 1 N HCl (5 mL) at room temperature for 1 h, the aqueous phase was separated. The organic phase was washed with H_2O (3 mL × 2). The combined aqueous phase was adjusted to pH 9–10 by addition of Na_2CO_3 and extracted by CH_2Cl_2 for three times. The combined organic extracts were dried over Na_2SO_4, and concentrated. The residual oil was used for the next reaction without further purification. To a solution of the crude mixture obtained above in MeCN (5.0 mL) were added TBAI (8.3 mg, 0.022 mmol), NaI (168 mg, 1.1 mmol) and K_2CO_3 (62 mg, 0.45 mmol). The resulting mixture was refluxed overnight and cooled to room temperature. The reaction mixture was then filtered through a pad of Celite with EtOAc. The filtrate was concentrated and the residue was purified by column chromatography on silica gel (EtOAc/hexane) to furnish α-methylpipecolic acid *t*-butyl ester **5** (R = Me) (37 mg, 0.19 mmol, 83% yield). The enantiomeric excess was determined by HPLC analysis of the corresponding *N*-benzoyl adduct (Daicel Chiralpak AS-H, hexane/2-propanol = 20:1, flow rate 0.5 mL/min, retention time: 8.6 min (major) and 9.0 min).
12. Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.