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Highly Enantioselective Synthesis of (*R*)-α-Alkylserines via Phase-Transfer Catalytic Alkylation of *o*-Biphenyl-2-oxazoline-4-carboxylic Acid *tert*-Butyl Ester Using *Cinchona*-Derived Catalysts

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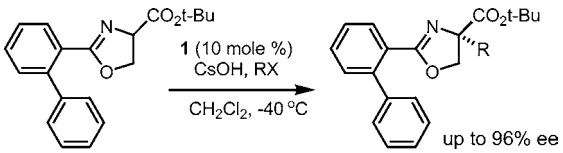
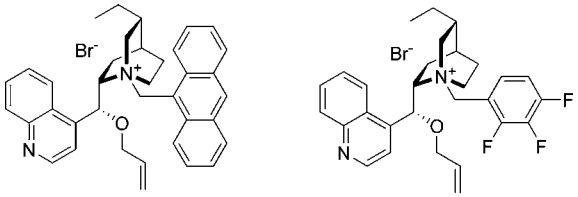
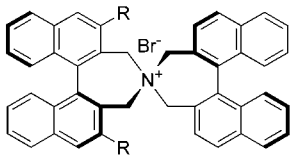
ABSTRACT



A highly enantioselective synthetic method for (*R*)-α-alkylserines was developed by the phase-transfer catalytic alkylation of *o*-biphenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester (4i) using *cinchona*-derived phase-transfer catalyst *N*(1)-(9-anthracenylmethyl)-*O*(9)-allyl-dihydrocinchonidinium bromide (up to 96% ee).

Chiral α-alkylserines have been regarded as important components in the areas of the both synthetic and medicinal chemistry.[1] Their hydroxyl groups contribute to stabilize the secondary structure in peptides by hydrogen bonding with amide carbonyl groups, which makes α-alkylserines useful in peptidomimetic drug design.[2] There are also several biologically active natural products, possessing chiral α-alkylserine moieties.[3] In addition, chiral α-alkylserines could be converted to various useful synthetic building blocks via chemical transformations.[1] So far, a number of enantioselective synthetic methods have been developed for chiral α-alkylserines, but only a few are practical.[4]





3 R = 3′,4′,5′-trifluorophenyl

(1) (a) Wilson, E. M.; Snell, E. E. *J. Biol. Chem.* **1962**, *237*, 3180. (b) Flynn, E. H.; Hinman, J. W.; Caron, E. L.; Woolf, D. O., Jr. *J. Am. Chem. Soc.* **1953**, *75*, 5867. (c) Hanessian, S.; Haskell, T. H. *Tetrahedron Lett.* **1964**, *5*, 2451. (d) Wirth, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 225. (e) Cativiela, C.; Diaz-de-Villegas, M. D. T. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (f) Cativiela, C.; Diaz-de-Villegas, M. D. T. *Tetrahedron: Asymmetry* **2000**, *11*, 645.

(2) (a) Barrett, G. C. *Amino Acids, Peptides and Proteins*; The Chemical Society: London, 1980; Vol. 13, p 1. (b) Hunt, S. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; p 55. (c) Richardson, J. S. *Biophysik. J.* **1992**, *63*, 1186.

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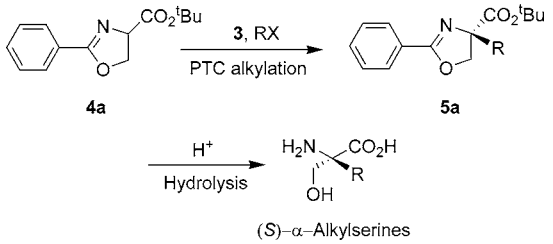
Very recently, we reported a very efficient enantioselective synthetic method for (*S*)-α-alkylserines by the phase-transfer catalytic alkylation[5] of 2-phenyl-2-oxazoline-4-carboxylate *tert*-butyl ester (**4a**) using chiral quaternary ammonium salts (**1**,[6] **2**,[7] and **3**[8]).[9] The previous study revealed that (*S*)-binaphthyl quaternary ammonium salt **3** showed enantioselectivity quite superior to that of the *cinchona*-derived catalysts (**1** and **2**) (Scheme 1).[9] Regardless of the excellent

Scheme 1. Enantioselective PTC Alkylation for (*S*)-α-Alkylserines Using **3**

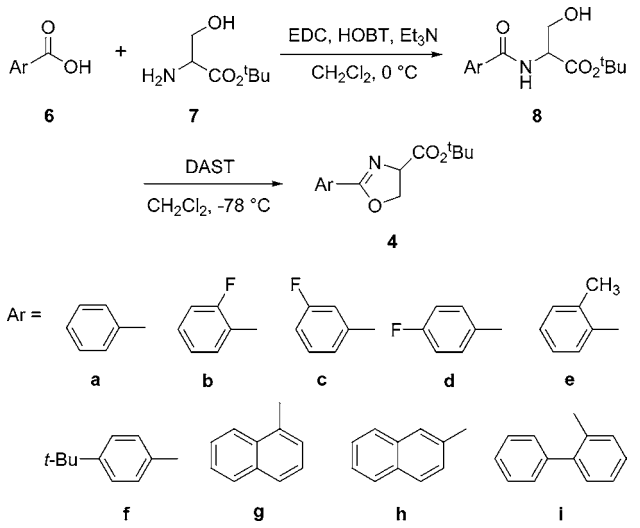


enantioselective catalytic efficiency of **3**, the high cost and several steps involved in the preparation of **3** might make this method less practical for industrial application. In this letter, we report a new synthetic method for (*R*)-α-alkylserine using *cinchona*-derived catalysts (**1** and **2**) by the modification of oxazoline ester substrate **4a**.

It was assumed that the enantioselectivity in phase-transfer catalytic alkylation might depend on the favorable ionic binding between quaternary ammonium salt catalysts and the enolate of **4a**. As shown in the previous studies, the *cinchona*-derived catalysts (**1** and **2**) have a limit in enantioselectivity compared to (*S*)-binaphthyl quaternary ammonium salt **3**.

As part of our program for the practical synthesis of (*R*)-α-alkylserine, we attempted to design new oxazoline ester substrates to form favorable binding intermediate with *cinchona*-derived catalysts by the modification of **4a**. As the *tert*-butyl ester group of **4a** was known as an essential group for high enantioselectivity, the *tert*-butyl ester group was retained and the phenyl group of **4a** was modified to various aromatic groups. Nine oxazoline *tert*-butyl esters (**4a**−**i**) were prepared in two steps from the corresponding aromatic acids (Scheme 2).

Scheme 2. Preparation of the Oxazoline *tert*-Butyl Ester Substrates



The coupling of the aromatic acids and serine *tert*-butyl ester by EDC, followed by the cyclization using DAST, gave the corresponding oxazoline *tert*-butyl esters (**4a**−**i**) in high yields (75−92%).

For the alkylation, we adapted the previous reaction conditions except for solvent. The enantioselective phase-transfer catalytic benzylation was performed using 10 mol % catalyst (**1** or **2**) along with the prepared oxazoline *tert*-butyl esters (**4a**−**i**), benzyl bromide (5.0 equiv), and solid KOH (5.0 equiv) in methylene chloride at 0 °C for 2−8 h. As shown in Table 1, the enantioselectivity dramatically depended on the aromatic groups. There was no significant electronic effect on the phenyl group, but the enantioselectivity was variable with the position of substituents. The ortho-substituted derivatives (entries 3 and 4, **4b**; entries 9 and 10, **4e**) still retained the enantioselectivity, but quite a drop in enantioselectivity was observed in meta- and para-substituted derivatives in both cases of electron-donating (**4f**) and -withdrawing groups (**4c** and **4d**). However, the bulky aromatic analogues showed variable enantioselectivity. The α-naphthyl derivative **4g** (entries 13 and 14) exhibited much higher enantioselectivity than **4a**, but moderate enantioselectivity was observed in the *β*-naphthyl analogue **4h** (entries 15 and 16). The *o*-biphenyl analogue **4i** (entry 17) showed the highest enantioselectivity among the prepared oxazoline esters. In the case of catalysts, catalyst **1** gave relatively lower enantioselectivity than catalyst **2** in phenyl analogues (**4a**−**f**) and *β*-naphthyl analogue (**4h**), but α-naphthyl (**4g**)

(3) (a) Fujita, T.; Inoue, K.; Yamamoto, S.; Ikumoto, T.; Sasaki, S.; Toyama, R.; Yoneta, M.; Chiba, K.; Hosino, Y.; Okumoto, T. *J. Antibiotics* **1994**, *47*, 216. (b) Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. *J. Antibiotics* **1991**, *44*, 113. (c) Omura, S.; Matsuzaki, K.; Fujimoto, T.; Kosuge, K.; Furuya, T.; Fujita, S.; Nakagawa, A *J. Antibiotics* **1991**, *44*, 117. (d) Yamashita, T.; Iijima, M.; Nakamura, H.; Isshiki, K.; Naganawa, H.; Hattori, S.; Hamada, M.; Ishizuka, M.; Takeuchi, T. *J. Antibiotics* **1991**, *44*, 557. (e) Kawatsu, M.; Yamashita, T.; Ishizuka, M.; Takeuchi, T. *J. Antibiotics* **1995**, *48*, 222.

(4) Previous synthetic methods of chiral α-alkylserines are cited in ref 9.

(5) For recent reports for asymmetric phase-transfer catalytic reactions, see: (a) Shioiri, T.; Arai, S. In *Stimulating Concepts in Chemistry*; Vogtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Germany, 2000; pp 123−143. (b) O'Donnell, M. J. In *Catalytic Asymmetric Synthesis*; Ojima, I.; Wiley-VCH: New York, 2000; Chapter 10. (c) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3.

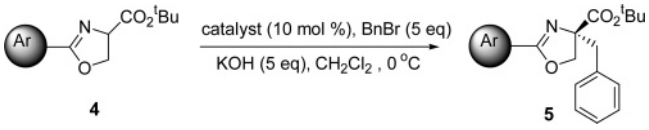
(6) (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

(7) Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245.

(8) (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.

(9) 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.

Table 1. Enantioselective Phase-Transfer Catalytic Benzylation[a]



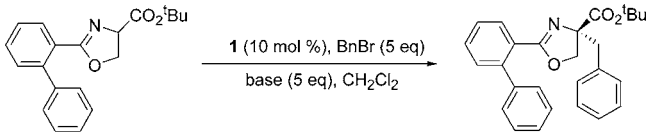
entry	substrate	catalyst	time (h)	yield[b] (%)	% ee[c] (configuration[d])
1	**4a**	1	4	90	49 (*R*)
2	**4a**	2	3	94	69 (*R*)
3	**4b**	1	3	90	41 (*R*)
4	**4b**	2	3	91	81 (*R*)
5	**4c**	1	4	82	10 (*R*)
6	**4c**	2	3	83	28 (*R*)
7	**4d**	1	3	87	12 (*R*)
8	**4d**	2	4	85	20 (*R*)
9	**4e**	1	5	82	45 (*R*)
10	**4e**	2	8	80	74 (*R*)
11	**4f**	1	2	86	41 (*R*)
12	**4f**	2	5	87	47 (*R*)
13	**4g**	1	6	85	90 (*R*)
14	**4g**	2	3	88	81 (*R*)
15	**4h**	1	6	92	43 (*R*)
16	**4h**	2	3	90	66 (*R*)
17	**4i**	1	6	91	93 (*R*)
18	**4i**	2	7	88	91 (*R*)
19	**4i**	3	8	62	41 (*S*)

[a] Reaction was carried out with 5.0 equiv of benzyl bromide and 5.0 equiv of solid KOH in the presence of catalyst (10 mol %) in methylene chloride at 0 °C. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis of the benzylated oxazoline *tert*-butyl ester **5** using a chiral column (DAICEL Chiralcel OD) with hexanes/2-propanol as a solvent; in this case, the enantiopurity was established by analysis of the racemate, of which the enantioisomers were fully resolved. [d] Absolute configuration was determined by comparison of the optical rotation of α-benzylserine from the acidic hydrolysis of **5** with the reported value.[9]

and *o*-biphenyl analogues (**4i**) showed higher enantioselectivity with catalyst **1** compared to catalyst **2**. Notably, the best catalyst in the previous report,[9] **3**, gave poor enantioselectivity in the alkylation of **4i**, suggesting that the enolate of **4i** and **3** could not form a favorable binding intermediate in phase-transfer catalytic alkylation. On the basis of the cumulative results, the general tendency could be summarized as follows: (1) The ortho substituents on the phenyl group play a more important role for high enantioselectivity than the corresponding meta and para substituents, but their electronic properties are not important. (2) The ortho aromatic moieties afford high enantioselectivity, and the increase of enantioselectivity might be due to the enhanced favorable binding affinity by the π,π-stacking interaction with catalysts. (3) The sterically hindered oxazoline substrates gave higher enantioselectivity in the presence of catalyst **1**, but catalyst **2** shows higher enantioselectivity in relatively less hindered oxazoline substrates.

Next, we focused our attention toward finding on optimal base conditions using the best substrate, **4i**. As shown in Table 2, KOH gave the highest enantioselectivity (entry 2, 93% ee) among the alkali bases used at 0 °C, but the lower reaction temperature gave lower enantioselectivity with a

Table 2. Optimization of Phase-Transfer Catalytic Benzylation[a]

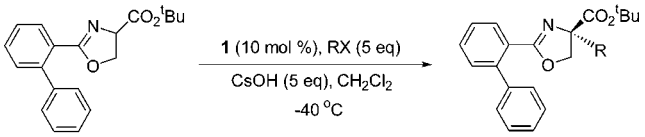


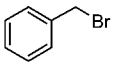
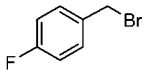
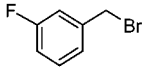
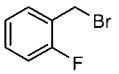
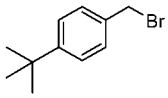
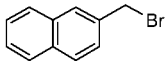
entry	base	temp (°C)	time (h)	yield[b] (%)	% ee[c] (configuration[d])
1	NaOH	0	16	90	32 (*R*)
2	KOH	0	6	91	93 (*R*)
3	KOH	−20	20	87	90 (*R*)
4	KOH	−40	120	86	80 (*R*)
5	CsOH	0	2	79	68 (*R*)
6	CsOH	−20	4	83	84 (*R*)
7	CsOH	−40	8	90	96 (*R*)

[a] Reaction conditions were the same as those in Table 1 except for the base and reaction temperature. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis of the benzylated oxazoline *tert*-butyl ester **5i-*b*** using a chiral column (DAICEL Chiralcel OD) with hexanes/2-propanol (volume ratio = 500:2.5) as a solvent; in this case, the enantiopurity was established by analysis of the racemate, of which the enantioisomers were fully resolved. [d] Absolute configuration was determined by comparison of the optical rotation of α-benzylserine from the acidic hydrolysis of **5i-*b*** with the reported value.[9]

longer reaction time. This might be due to the slow reaction rate at low temperature, which enhanced the non-PTC

Table 3. Enantioselective Phase-Transfer Catalytic Alkylation[a]



entry	RX	time (h)	yield[b] (%)	% ee[c] (config.[d])
a		12	75	90 (*R*)
b		8	90	96 (*R*)
c		16	85	94 (*R*)
d		12	75	94 (*R*)
e		12	82	90 (*R*)
f		18	83	92 (*R*)
g		12	84	92 (*R*)

[a] Reaction conditions were same as those for entry **7** of Table 2 except for alkyl halides. [b] Isolated yields. [c] Enantiopurity was determined by HPLC analysis of **5i** using a chiral column (Chiralcel OD) with hexanes/2-propanol as eluents. [d] Absolute configuration was assigned by the relative retention times of both enantiomers determined previously.[1−3]

intermediate reaction pathway. In contrast, the decrease of reaction temperature under CsOH base conditions could increase the enantioselectivity, and the optimal temperature was −40 °C. **4i** and the above optimal reaction conditions were chosen for further investigation of the enantioselective phase-transfer catalytic alkylation with various alkyl halides. As shown in Table 3, very high enantioselectivities (90−96% ee) were observed in the case of activated alkyl halides, but unfortunately nonactivated alkyl halides did not afford alkylation. The hydrolysis of **5i-*b*** (96% ee) with 12 N HCl afforded optically active (*R*)-(+)-benzylserine in 98% yield.[9,10] As a merit for practicality, **6i** could be recovered (99%) after hydrolysis of **5i** and recycled to prepare the substrate **4i**.

In conclusion, we prepared new oxazoline *tert*-butyl esters for the enantioselective synthesis of (*R*)-α-alkylserines by the asymmetric phase-transfer catalytic alkylation using *cinchona*-derived catalysts. Among the prepared oxazoline substrates, *o*-biphenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester showed the highest enantioselectivity using catalyst **1**. The easy preparation of substrate **4i**, the high enantioselectivity, and the very mild reaction conditions could make this method very practical for (*R*)-α-alkylserines.

Acknowledgment. This work was supported by a grant (R01-2002-000-0005-0) from the Basic Research Program of the KOSEF (2004).

Supporting Information Available: Experimental procedures and spectroscopic characterizations of the new catalysts. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Clerici, F.; Gelmi, M. L.; Gambini, A. *J. Org. Chem*. **1999**, *64*, 5764.