

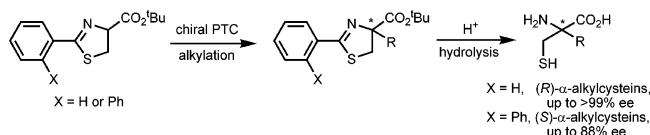
Enantioselective Synthesis of (*R*)- and (*S*)- α -Alkylcysteines via Phase-Transfer Catalytic Alkylation

Taek-Soo Kim,[†] Yeon-Ju Lee,[†] Byeong-Seon Jeong,[‡]
Hyeung-geun Park,^{*,†} and Sang-sup Jew^{*,†}

Research Institute of Pharmaceutical Science and College of Pharmacy, Seoul National University, Seoul 151-742, Korea, and College of Pharmacy, Yeungnam University, Gyeongsan 712-749, Korea

hgpk@plaza.snu.ac.kr

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We reported efficient enantioselective synthetic methodologies for (*R*)- α -alkylcysteines and (*S*)- α -alkylcysteines. The phase-transfer catalytic alkylation of 2-phenyl-2-thiazoline-4-carboxylic acid *tert*-butyl ester and 2-*o*-biphenyl-2-thiazoline-4-carboxylic acid *tert*-butyl ester, in the presence of chiral catalysts (**1** or **2**), gave the corresponding alkylated products, which could be hydrolyzed to provide (*R*)- α -alkylcysteines (67–>99% ee) and (*S*)- α -alkylcysteines (66–88% ee), respectively.

As one of the α , α -dialkyl amino acids, α -alkylcysteines are valuable building blocks for the biologically active peptidomimetics, since they can not only resist enzymatic degradation but also form the stabilized, preferred conformations of the peptide backbone.¹ In addition, they are able to form a further constrained cyclic peptide structure by disulfide bond formation. Several natural products involving α -alkylcysteine moieties exist, such as tantazoles,² mirabazoles,³ and thiagazole,⁴ which exhibit antitumor and anti-HIV-1 activities.

A number of enantioselective synthetic methods for α -alkylcysteines have been reported so far. Their main synthetic strategies can be classified as follows: (1) thiomethylation of

a bislactim ether prepared from valine as a chiral auxiliary,⁵ (2) nucleophilic ring opening of a chiral aziridine or chiral β -lactone with thiolates,⁶ (3) self-reproduction of chirality using oxazolidinone or thiazolidinone derivatives,⁷ and (4) enzymatic desymmetrization of monomethyl dimethylmalonate.⁸ However, since most of the reported methods employed chiral starting materials or chiral auxiliaries, their applications to industrial processes for the mass production of chiral α -alkylcysteines might not be straightforward. In this paper, we would like to report new and efficient synthetic methods for (*R*)- α -alkylcysteines and (*S*)- α -alkylcysteines via phase-transfer catalytic α -alkylation of thiazoline-4-carboxylates, which could be applied to industrial processes.

Quite recently, we reported a new synthetic method for (\pm)- α -alkylserines by the selective α -alkylation of *tert*-butyl 2-phenyl-2-oxazoline-4-carboxylate in phase-transfer catalytic conditions.⁹ As successive studies, the enantioselective versions using chiral phase-transfer catalysts were also disclosed (Scheme 1).¹⁰ In addition, we reported a chiral auxiliary method via phase-transfer catalytic alkylation of the oxazoline-4-carboxylate, possessing camphorsultam as a chiral auxiliary (Scheme 1).¹¹ These studies all showed that the phase-transfer catalytic conditions are very efficient for the α -alkylation of the oxazoline-4-carboxylate system. Based on our previous results, we attempted to apply the phase-transfer catalytic alkylation conditions to 2-aryl-2-thiazoline-4-carboxylate esters (**8**) for the enantioselective synthesis of chiral α -alkylcysteines (Scheme 2).

First, we prepared the thiazoline-4-carboxylate (**8a**, **8b**). The substrate **8a** was easily prepared by the coupling of ethyl benzimidate and cysteine methyl ester, followed by transesterification¹² using AlMe₃ in 80% yield from **11** (Scheme 3).

The substrate **8b** was prepared from 2-biphenylcarboxylic acid (**13**) in three steps. The coupling of **13** and **14**, followed by cyclization¹³ in the presence of triphenylphosphine oxide and trifluoromethanesulfonic anhydride, gave the thiazoline methyl ester **16**, which was converted to the corresponding *tert*-butyl ester **8b** by transesterification using AlMe₃ in 81% yield from **14** (Scheme 4).

For the phase-transfer catalytic alkylation, we adapted our previous reaction conditions.¹⁰ The phase-transfer catalytic

* To whom correspondence should be addressed. Tel: 82-2-880-7871, Fax: 82-2-872-9129.

[†] Seoul National University.

[‡] Yeungnam University.

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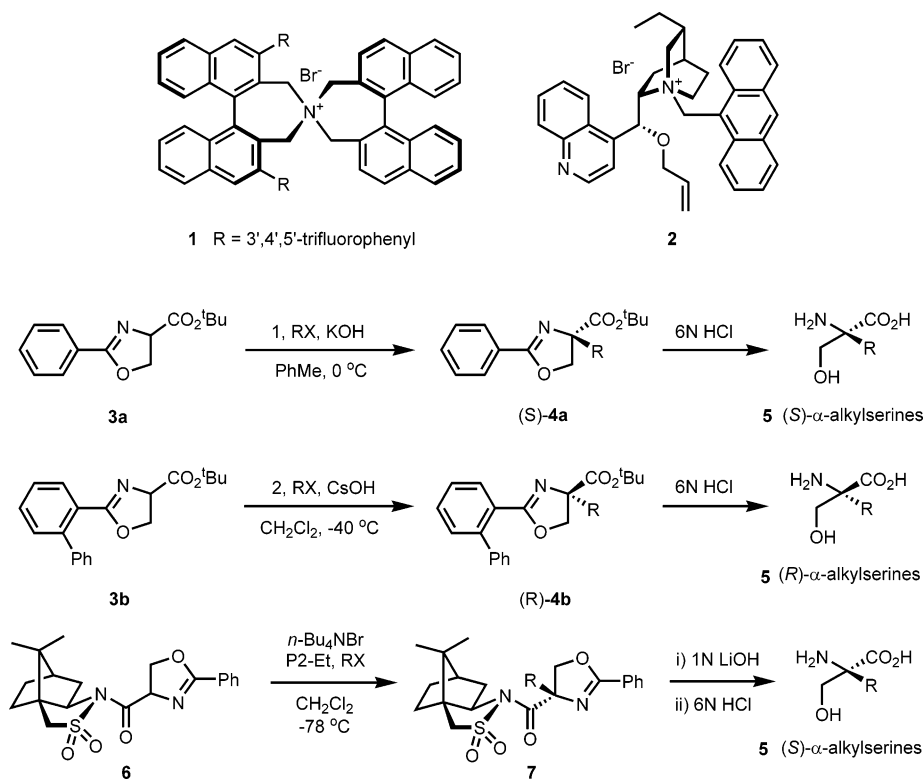
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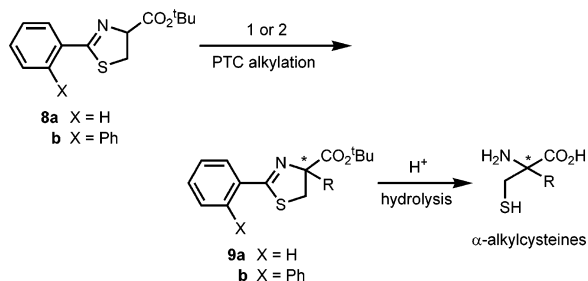
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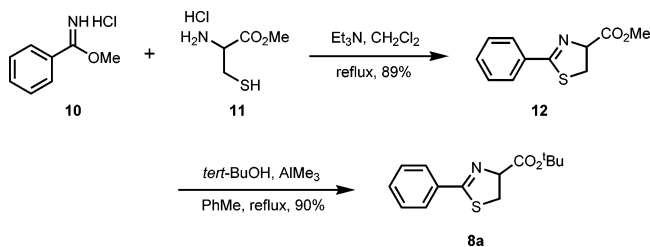
SCHEME 1



SCHEME 2



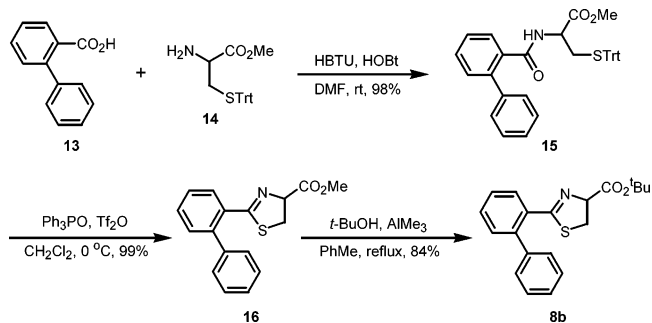
SCHEME 3



alkylation of **8a** was performed using 1 mol % of the catalyst **1** along with alkyl halides (5.0 equiv) and solid KOH (5.0 equiv) in toluene at 0 °C for 30–45 min.

As shown in Table 1, very high enantioselectivities (84–>99% ee) were observed, except with hexyl iodide (entry *a*, 67% ee). However, the chemical yields varied, depending on the reactivity of the alkyl halides. All of the benzyl halides gave high chemical yields (entry *e–i*; 90~>99%), but the allylic halides and propargylic halide gave modest chemical yields (entry *b–d*; 67–>68%). In the case of the aliphatic halide, an even lower chemical yield was observed (entry *a*; 42%). Notably, the reaction rates were 10 times faster than those of

SCHEME 4

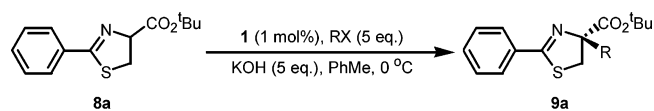


the alkylation of the oxazoline substrate **3**, even in the presence of a reduced amount of the catalyst **1** (1 mol %), instead of the 2.5 mol % of **1** used in the alkylation of the phenyloxazoline substrate **3**. In the case of the 2-biphenylthiazolidine substrate **8b**, the alkylations were performed using 10 mol % of the catalyst **2** along with **8b**, alkyl halide (5.0 equiv), and solid CsOH (5.0 equiv) in dichloromethane at 0 °C for 40–120 min.

As shown in Table 2, high enantioselectivities were observed, but they were slightly less than those of substrate **8a**. Most of the activated alkyl halides showed high chemical yields at 0 °C, but no alkylation product was observed with the aliphatic halides. Relatively lower chemical yields, but comparable enantioselectivities, were observed at –40 °C (data not shown). The reaction rates were 10 times faster than those of the alkylation of the oxazoline substrate **5**, in agreement with the alkylation of substrate **8b**. The hydrolysis of **9a–e** (>99% ee) and **9b–d** (84% ee) with 6 N HCl afforded (*R*)-(+)-benzylcysteine (98%) and (*S*)-(–)-benzylcysteine (97%), respectively.

In conclusion, we developed efficient enantioselective synthetic methodologies for (*R*)- α -alkylcysteines and (*S*)- α -alkylcysteines by the phase-transfer catalytic alkylation of 2-phenyl-

TABLE 1. Enantioselective Phase-Transfer Catalytic Alkylation



entry	RX	time (min)	yield ^a (%)	% ee ^b (config.)
<i>a</i>		40	42	67 (<i>R</i>)
<i>b</i>		30	68	96 (<i>R</i>)
<i>c</i>		30	67	99 (<i>R</i>)
<i>d</i>		35	67	97 (<i>R</i>)
<i>e</i>		40	90	>99 (<i>R</i>) ^c
<i>f</i>		45	>99	98 (<i>R</i>)
<i>g</i>		35	99	84 (<i>R</i>)
<i>h</i>		35	99	96 (<i>R</i>)
<i>i</i>		40	99	99 (<i>R</i>)

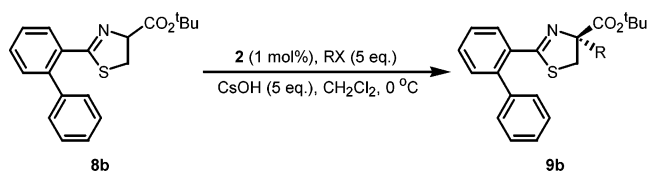
^a Isolated yields. ^b The enantiopurity was determined by HPLC analysis of the corresponding methyl esters (**9a'**) prepared from **9a** using a chiral column (Chiralcel AD or OD) with hexanes/2-propanol as eluents. ^c The absolute configuration was assigned by the comparison of the specific optical rotation value of the α -benzylcysteine prepared by the acidic hydrolysis of **9a-e** with the literature value.^{7b}

2-thiazoline-4-carboxylic acid *tert*-butyl ester (**8a**) and 2-*o*-biphenyl-2-thiazoline-4-carboxylic acid *tert*-butyl ester (**8b**), respectively. The easy preparation of the substrate, the high enantioselectivity, and the very mild reaction conditions could make this method quite practical for industrial processes involving chiral α -alkylcysteines.

Experimental Section

General Procedure for the Enantioselective Alkylation of 2-Phenyl-2-thiazoline-4-carboxylic Acid *tert*-Butyl Ester (8a**) or 2-Biphenyl-2-yl-4,5-dihydrothiazole-4-carboxylic Acid *tert*-Butyl Ester (**8b**) under Phase-Transfer Conditions (Benzylation).** To a toluene (1.0 mL) solution of 2-phenyl-2-thiazoline-4-carboxylic acid *tert*-butyl ester (**8a**, 50.0 mg, 0.2 mmol) were added the chiral catalyst **1** (1.8 mg, 0.002 mmol), KOH (56.1 mg, 1.0 mmol), and benzyl bromide (0.1 mL, 1.0 mmol) at 0 °C, and the reaction mixture was stirred for 40 min. After completion of the reaction, the reaction mixture was diluted with ethyl acetate (20 mL), washed with brine (2 \times 5 mL), dried over anhydrous MgSO₄, filtered, and concentrated in vacuo. The residue was purified by column

TABLE 2. Enantioselective Phase-Transfer Catalytic Alkylation



entry	RX	time (min)	yield ^a (%)	% ee ^b (config.)
<i>a</i>		40	90	88 (<i>S</i>)
<i>b</i>		60	95	87 (<i>S</i>)
<i>c</i>		60	92	68 (<i>S</i>)
<i>d</i>		50	>99	84 (<i>S</i>) ^c
<i>e</i>		120	>99	66 (<i>S</i>)
<i>f</i>		60	90	85 (<i>S</i>)
<i>g</i>		90	>99	75 (<i>S</i>)
<i>h</i>		120	77	76 (<i>S</i>)

^a Isolated yields. ^b The enantiopurity was determined by HPLC analysis of **9b** using a chiral column (Chiralcel AD) with hexanes/2-propanol as eluents. ^c The absolute configuration was assigned by the comparison of the specific optical rotation value of the α -benzylcysteine prepared by the acidic hydrolysis of **9b-d** with the literature value.^{7b}

chromatography (silica gel, hexanes/EtOAc = 50:1) to afford **9a-e** (63.7 mg, 90% yield) as a pale yellow oil. Because the two enantiomers of **9a-e** were not fully separated by chiral HPLC, the enantioselectivity was determined by the chiral HPLC analysis of the corresponding methyl ester, prepared from the hydrolysis of **9a-e** followed by methylation using the excess of diazomethane. The enantioselectivity was determined as >99% ee [chiral HPLC analysis (Chiralcel AD-H, hexanes:2-propanol = 99:1), flow rate = 1.0 mL/min, 23 °C, = 254 nm, retention time, *S* (minor) 12.3 min, *R* (major) 15.5 min, >99% ee]. Absolute configuration was determined by the comparison of the optical rotation of α -benzylcysteine prepared from the acidic hydrolysis of **9a-e** with the reported value.^{7b}

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Supporting Information Available: Representative experimental procedures as well as spectroscopic characterizations of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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