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

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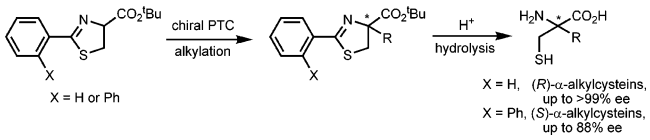

We reported efficient enantioselective synthetic methodologies for (*R*)-α-alkylcysteines and (*S*)-α-alkylcysteines. The phase-transfer catalytic alkylation of 2-phenyl-2-thiazoline-4-carboxylic acid *tert*-butyl ester and 2-*o*-biphenyl-2-thiazoline-4-carboxylic acid *tert*-butyl ester, in the presence 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 thiangazole,[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 (±)-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 transesterification[12] using $AlMe_3$ 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 cyclization[13] 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 $AlMe_3$ in 81% yield from **14** (Scheme 4).

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

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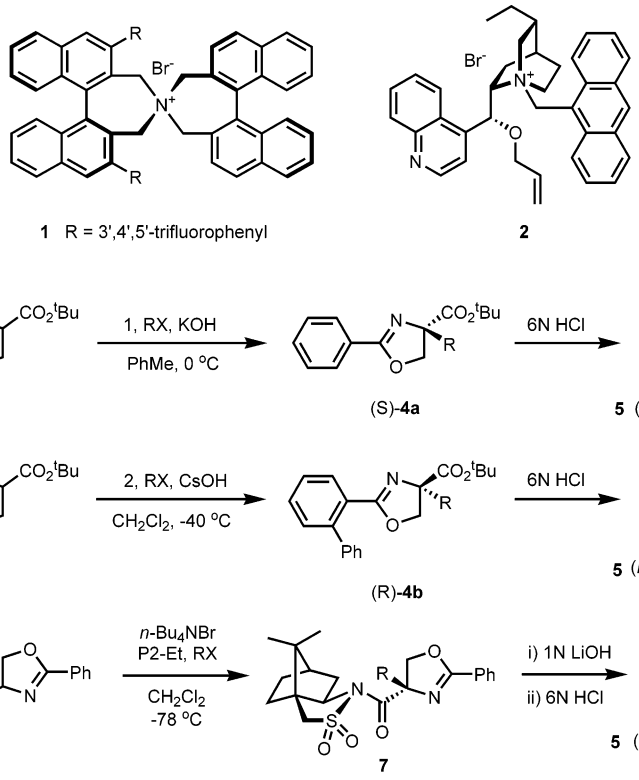
SCHEME 1



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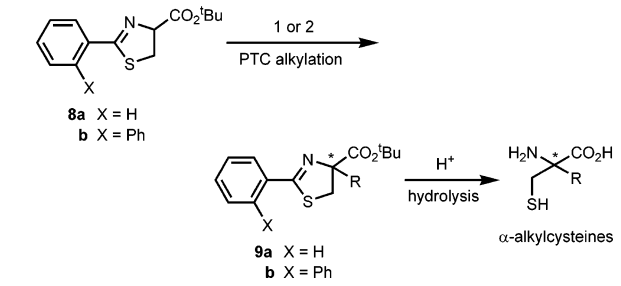

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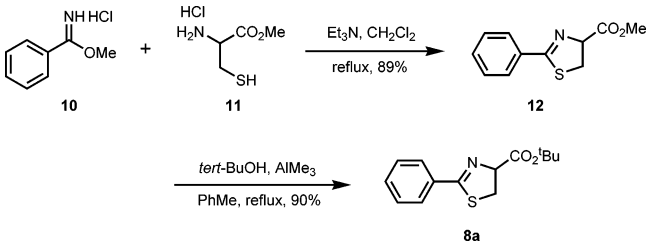

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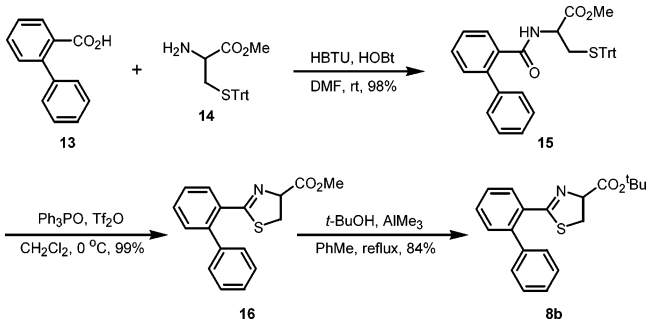


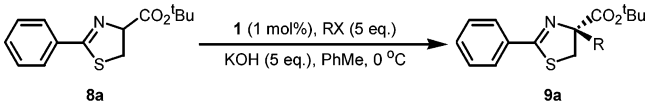
alkylation of **8a** was performed using 1 mol % of the catalyst **1** along with alkyl halides (5.0 equiv) and solid KOH (5.0 equiv) in toluene at 0 °C for 30−45 min.

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 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-biphenylthiazoline 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.

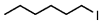
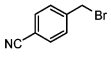
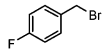
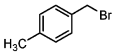
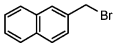
As shown in Table 2, high enantioselectivities were observed, but they were slightly less than those of substrate **8a**. Most of the activated alkyl halides showed high chemical yields at 0 °C, but no alkylation product was observed with the aliphatic halides. Relatively lower chemical yields, but comparable 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

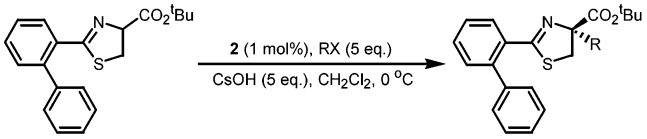


8a 9a

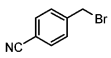
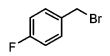
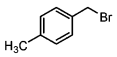
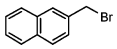
entry	RX	time (min)	yield[a] (%)	% ee[b] (config.)
a		40	42	67 (*R*)
b		30	68	96 (*R*)
c		30	67	99 (*R*)
d		35	67	97 (*R*)
e		40	90	>99 (*R*)[c]
f		45	>99	98 (*R*)
g		35	99	84 (*R*)
h		35	99	96 (*R*)
i		40	99	99 (*R*)

[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]

TABLE 2. Enantioselective Phase-Transfer Catalytic Alkylation



8b 9b

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

[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]

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 × 5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column 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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