Phase-Transfer Catalysis

Highly Enantioselective Phase-Transfer-Catalytic Alkylation of 2-Phenyl-2-oxazoline-4-carboxylic Acid *tert*-Butyl Ester for the Asymmetric Synthesis of α-Alkyl Serines**

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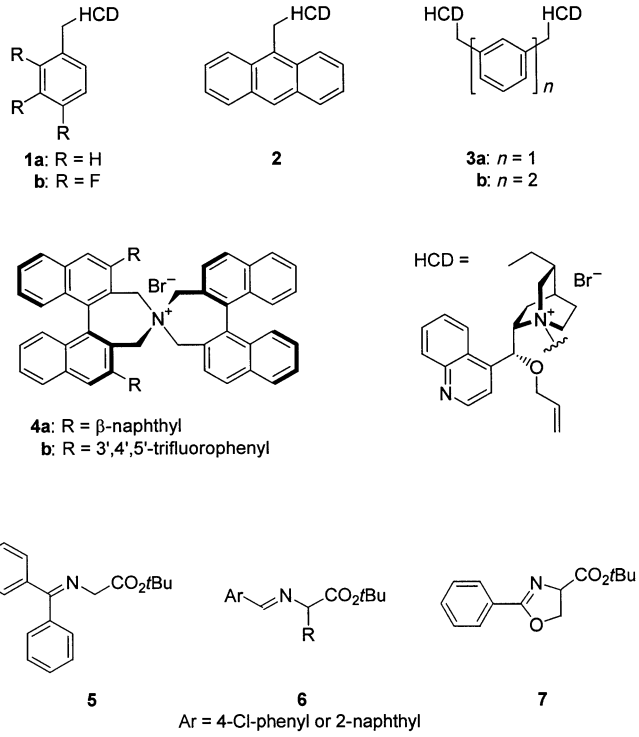
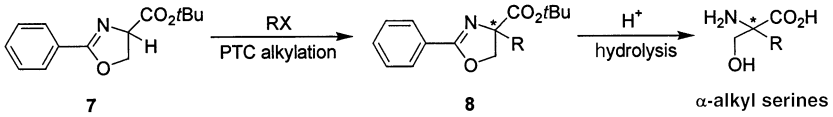


Chiral α-alkyl serines have been extensively studied owing to their important roles in synthetic and biological chemistry.[1] Their quaternary chiral moieties are frequently found in several biologically active natural products[2] and chiral α-alkyl serines themselves are useful synthetic building blocks.[1] Also, as the hydroxy group of (*S*)-serine has an important role in stabilizing the α-helical secondary structure of enzymes by hydrogen bonding with amide carbonyl groups, α-alkyl serine moieties have been employed in the design of biologically active peptidomimetics.[3] Historically, a number of enantioselective synthetic methods have been reported for chiral α-alkyl serines,[4] but only a few are practical, and only one was carried out under catalytic conditions.[4k]

Recently, several efficient chiral phase-transfer catalysts were developed from *Cinchona* alkaloids (**1**,[5] **2**,[6] **3**,[7]) and (*S*)-binaphthyl derivative (**4**[8]), and successfully applied to the asymmetric synthesis of natural and non-natural α-amino acids[5–8a] and α,α-dialkyl α-amino acids[8b,9] by the enantioselective alkylation of benzophenone imine glycine *tert*-butyl ester (**5**[10]) and aryl aldimine alanine *tert*-butyl ester (**6**[9]), respectively. As part of our program for the development of practical and synthetic methods for α-alkyl serines, we examined the use of asymmetric phase-transfer catalytic alkylation.[11]

First, we investigated the best substrate for phase-transfer catalytic alkylation. It should have an acidic proton for abstraction by mild bases, such as **5** and **6**. We chose the phenyl oxazoline derivative of serine *tert*-butyl ester, **7**. The oxazoline moiety not only enhances the acidity of the α proton of the ester, but also acts as an excellent protecting group for the both the amino and hydroxy groups in the serine ester.

As shown in the synthetic strategy in Scheme 1, the asymmetric phase-transfer alkylation of **7** with alkyl halides,



Scheme 1. Asymmetric alkylation of **7** with alkyl halides under phase-transfer catalysis (PTC) followed by acidic hydrolysis to provide chiral α-alkyl serines.

followed by acidic hydrolysis provided chiral α-alkyl serines. The methyl ester derivative was used as a substrate for the synthesis of (±)-α-alkyl serines, but it requires a strong base (such as LDA) and low temperatures (below −50 °C) otherwise β-eliminations are predominant.[4l] In the case of *n*BuLi, only the corresponding *n*-butyl ketone was obtained by substitution at −100 °C.[12] Recently, K_2CO_3[13] and DBU[14] were used for the α epimerization of oxazoline esters in a total synthesis, but these basic conditions gave neither α-alkylation nor β-elimination products in the presence of alkyl halides.[15]

Substrate **7** was easily prepared by the coupling of ethyl benzimidate and serine *tert*-butyl ester in 98% yield.[16] For the alkylation, we adapted the previously reported reaction conditions for the synthesis of α,α-dialkyl α-amino acids.[9]

To choose the optimal catalyst, the enantioselective phase-transfer-catalytic benzylation was performed in the presence of the appropriate catalysts (**1**–**4**, 10 mol%) along with 2-phenyl-2-oxazoline-4-carboxylic acid *tert*-butyl ester

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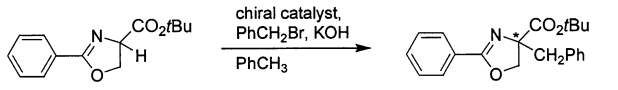
(**7**), benzyl bromide (5.0 equiv), and solid KOH (5.0 equiv) in toluene at 0 °C for 4–6 h. As shown in Table 1, the hydrocinchonidine-derived catalysts (**1**–**3**) all delivered (*R*)-**8e** with moderate enantioselectivities (42–68 % *ee*; Table 1, entries 1–5), but fortunately the commercially available (*S*)-binaphthol-derived catalyst **4b**, recently disclosed by the Maruoka group,[8b] provided (*S*)-**8e** with very high enantioselectivity (> 99 % *ee*; Table 1, entry 6). No β-eliminations or substitutions were observed. We tentatively presumed that the intermediate formed by the tight ionic binding between the quaternary ammonium cation and the corresponding enolate anion under the phase-transfer reaction conditions favors α alkylation over β elimination. As we focused our attention on optimizing this reaction for industrial processes, we decreased the amount of catalyst. Lower amounts of **4b** preserved the high enantioselectivity, but less than 2.5 mol % lowered the enantioselectivity (Table 1, entries 7–10; Figure 1).

Table 1: Enantioselective phase-transfer benzylation of **7** catalyzed by **1**–**4**.



7 **8e**

Entry	Catalyst	mol %	*T* [°C]	*t* [h]	Yield [%]	*ee* [%][c, d]
1	**1a**	10.0	0	5	85	42 (*R*)
2	**1b**	10.0	0	4	93	68 (*R*)
3	**2**	10.0	0	4	90	68 (*R*)
4	**3a**	10.0	0	6	84	50 (*R*)
5	**3b**	10.0	0	4	88	56 (*R*)
6	**4b**	10.0	0	4	99	> 99 (*S*)
7	**4b**	0.25	0	6	60	51 (*S*)
8	**4b**	0.5	0	6	74	83 (*S*)
9	**4b**	1.0	0	5	85	87 (*S*)
10	**4b**	2.0	0	5	92	98 (*S*)
11	**4b**	2.5	0	5	98	> 99 (*S*)
12	**4b**	5.0	0	4	99	> 99 (*S*)
13	**4b**	2.5	20	3	57	71 (*S*)
14	**4b**	2.5	−20	6	88	98 (*S*)
15	**4b**	2.5	−40	48	67	98 (*S*)

[a] The reaction was carried out with benzyl bromide (5.0 equiv) and solid KOH (5.0 equiv) in the presence of **1**–**4** in toluene under the given conditions. [b] Yields of isolated products. [c] The enantiopurity was determined by HPLC analysis of the benzylated oxazoline **8e** on a chiral column (DAICEL Chiralcel OD-H) with hexanes/2-propanol (500:3.0) as a solvent; in this case it was established by analysis of the racemate, of which the enantioisomers were fully resolved. [d] The configurations are given in parentheses. The absolute configurations were determined by comparison of the optical rotation of α-benzylserine from the acidic hydrolysis of **8e** with the reported value.[4m, 17]

The optimal reaction temperature was 0 °C. Higher temperatures (20 °C) decreased the enantioselectivity (Table 1, entry 12), and lower temperatures (−20, −40 °C) conserved the enantioselectivity albeit with longer reaction times and lower chemical yields than those at 0 °C (Table 1, entries 13 and 14). The hydrolysis of **8e** (> 99 % *ee*) with HCl (6 N) followed by purification through an ion-exchange resin led to the facile generation of optically pure (*S*)-(+)-α-benzylserine in 98 % yield.[4m, 17] Catalyst **4b** was chosen for further investigation of the enantioselective phase-transfer alkylation with various alkyl halides under the optimized reaction conditions. The very high *ee* values (> 93 %) shown in Table 2 indicate that this reaction is a very efficient

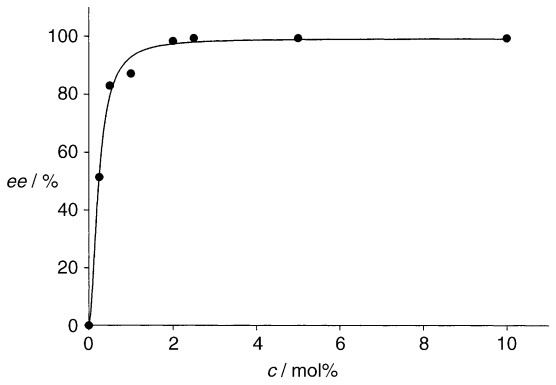
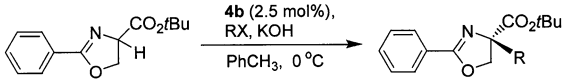
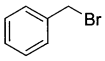
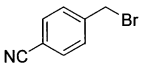
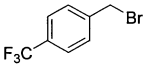
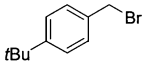
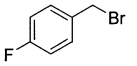
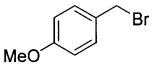
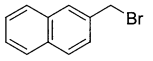


Figure 1. Relationship between the enantiomeric excess of (*S*)-**8e** and the amount of catalyst **4b** in the phase-transfer benzylation at 0 °C.

Table 2: Catalytic enantioselective phase-transfer alkylation of **7** with various alkyl halides in the presence of **4b** (1 mol %).[a]



7 **8**

RX	*t* [h]	Yield [%][b]	*ee* [%][c, d]
CH_3CH_2I	20	48	93
	3	87	97
	3	85	96
	6	86	97
	5	98	> 99
	5	99	93
	6	93	94
	3	99	> 99
	10	98	> 99
	8	90	> 99
	12	91	97

[a] The reaction was carried out with RX (5.0 equiv) and solid KOH (5.0 equiv) in the presence of **4b** (2.5 mol %) in toluene at 0 °C. [b] Yields of isolated products. [c] The enantiopurity was determined by HPLC analysis of the alkylated oxazoline **8** on a chiral column (DAICEL Chiralcel OD-H) with hexanes/2-propanol as a solvent; in this case it was established by analysis of the racemate, of which the enantioisomers were fully resolved. [d] The absolute configurations of all the products were tentatively assigned to be *S* based on the absolute configuration of **8e** (Table 1, entry 10).

enantioselective method for the preparation of α-alkyl serines.

Based on these results as well as on the reported X-ray crystal structure of **4b**,[8c] a plausible transition state in the catalytic alkylation is proposed in Figure 2. The conformation

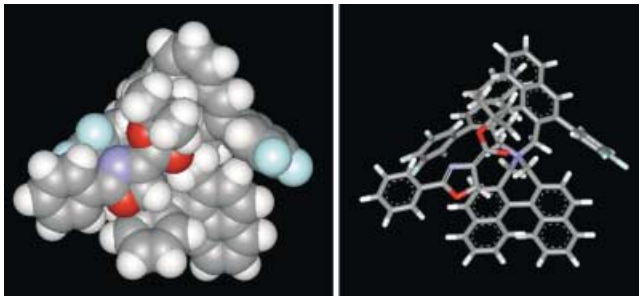


Figure 2. The plausible transition-state structure of a chiral spiro ammonium *E* enolate derived from **4b** and **7**.

of the *E* enolate of *tert*-butyl oxazoline ester **7** packs well into the molecular pocket of **4b**, and the *Si* face of the enolate is shielded by the binaphthyl and the 3′,4′,5′-trifluorophenyl moieties. Consequently, alkyl halides can only approach the *Re* face of the enolate, affording the *R* isomer **8** in accordance with the results.

In conclusion, we report the first use of an asymmetric phase-transfer-catalytic alkylation for the synthesis of chiral α-alkyl serines. The easy preparation of the substrate, the high enantioselectivity, and the very mild phase-transfer reaction conditions make this a promising method for industrial application.

Experimental Section

For the synthesis of **7**, see Supporting Information.

General procedure (alkylation of **7**): Benzyl bromide (0.12 mL, 1.00 mmol) was added to a solution of **7** (50.0 mg, 0.200 mmol), **4b** (9.55 mg, 0.005 mmol), and KOH (56.1 mg, 1.00 mmol) in toluene (0.80 mL) at 0 °C. The reaction mixture was stirred for 5 h. Upon completion of the reaction, the mixture was diluted with ethyl acetate (20 mL), washed with water (2 × 5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc 20:1) to afford **8e** (65 mg, 98 % yield) as a pale yellow oil. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD-H, hexane/2-propanol (500:3.0), flow rate = 1.0 mL min^{-1}, 23 °C, λ = 254 nm, retention times: *S* (major) 9.5 min, *R* (minor) 16.1 min, > 99 % *ee*). The absolute configuration was determined by comparison of the optical rotation of α-benzyl serine from the acid hydrolysis of **8e** with the reported value.[4m,17]

General procedure (hydrolysis of **8**): HCl (6 N; 1.5 mL) was added to a solution of **8e** (500 mg, 1.48 mmol) in ethanol (1.5 mL), and the reaction mixture was heated at reflux for 24 h. After the solvent was removed in vacuo, the residue was purified by column chromatography (15 % aqueous NH_4OH) through an ion-exchange resin (Dowex 50WX8–100[17]) to give (*S*)-(+)-α-benzyl serine as a white solid (365 mg, 98 %). $[\alpha]_D^{20} = +16.4$ ($c = 0.89$, H_2O) [lit.[4m] $[\alpha]_D^{20} = +16.4$ ($c = 0.81$, H_2O)]. Physical and spectral properties were consistent with the literature values.[4m,17]

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