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Enantioselective reactions of *tert*-butyl glycinate–benzophenone Schiff base catalyzed by chiral phase-transfer catalyst in aqueous media without any organic solvent

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Abstract—Chiral phase-transfer catalyzed enantioselective alkylations of *tert*-butyl glycinate–benzophenone Schiff base were investigated in aqueous media without any organic solvent. Reactions in aqueous media smoothly proceeded to give the desired product in higher yield than under standard liquid–liquid biphasic conditions. In aqueous media the formation of benzophenone, which was caused by in situ hydrolysis of Schiff base, was depressed.

Enantioselective alkylations of *tert*-butyl glycinate–benzophenone Schiff base **1** catalyzed by chiral phase-transfer catalyst (chiral PTC) have become an important approach to the synthesis of α-amino acids in organic chemistry.[1] Since the 1980s chiral PTC derived from natural cinchona alkaloids such as cinchonidine, cinchonine, and quinine have induced extremely high enantioselectivity.[2–5] Recently, Maruoka and co-workers[6] and other groups[7] have reported synthesis of non-natural and designed chiral PTCs, and their application to versatile enantioselective reactions. However, environmentally undesirable media such as chlorinated solvents and impractical low temperatures were often needed to achieve high enantioselectivity. It is reasonable to consider that chiral PTC-catalyzed alkylation in aqueous media without any organic solvent might be feasible. This would provide a cheaper, safer, and more industrial organic synthesis.

Recently, we communicated enantioselective alkylations of Schiff base **1** in the presence of a designed C_3 symmetric amine-based chiral PTC **2** under mild conditions.[8] The C_3 symmetric structure was a key to enhancing higher enantioselectivity, yet isolated yield of desired product (*S*)-**4a** was low because of hydrolysis of **1** to give benzophenone (**5**) (Table 1, entry 1). Therefore, we investigated the alkylation of **1** in 50% KOH aqueous solution without any organic solvent. The reaction smoothly proceeded to give the desired product (*S*)-**4a** in quantitative yield within a period of hours (entry 2). Interestingly, in aqueous media (*S*)-**4a** was obtained in higher yield than in standard liquid–liquid biphasic condition. Unfortunately, enantioselectivity was lower in aqueous media than in liquid–liquid condition, because the hydrogen bonding between the hydroxyl group on PTC **2** and nitrogen on **1** played an important role for increasing enantioselectivity in our PTC system.[8] Encouraged by these primary results, we investigated chiral PTC-catalyzed enantioselective alkylation of **1** in aqueous media without any organic solvent.[9]

We chose *N*-alkyl cinchonidinium salts **6**, which are well known as chiral PTCs to give various and valuable compounds under mild biphasic conditions.[1] Results are shown in Table 2. Without PTC **6** and organic solvent, the reaction slowly proceeded to give the racemic alkylated product **4a** and benzophenone **5** in 71% and 20% yield, respectively (entry 1). While in the presence of *N*-benzylcinchonidinium bromide (**6a**) the reaction was finished within 3 h, and (*S*)-**4a** was obtained in quantitative yield as similar to Table 1 (entry 2 vs 3). When concentration of potassium hydroxide was decreased to 5%, no significant change was observed in terms of yield and

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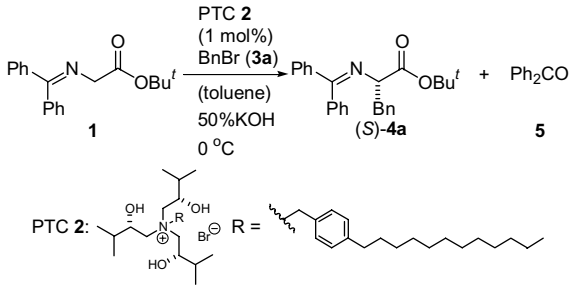
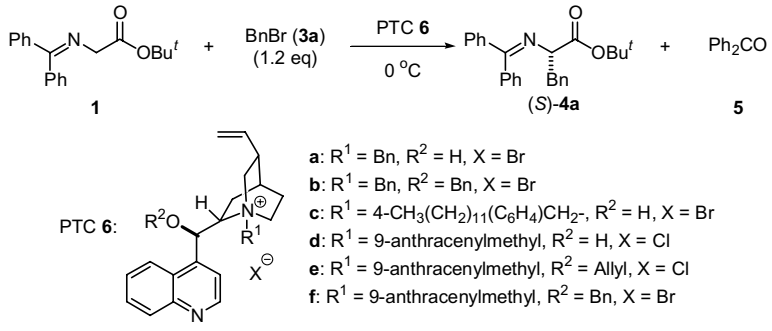
Table 1. Enantioselective alkylation of **1** using PTC **2**



Entry	Toluene	Time (h)	**4** Yield (%)	Ee[a] (%)	**4**:**5**[a]
1	Yes	10	62	57	62:38
2	No	3	98	10	99:1

[a] Determined by HPLC analysis using Chiralcel OD-H with hexane/2-propanol as an eluent. The absolute configuration was determined by comparison of the HPLC retention time with the reported data.

Table 2. Enantioselective alkylation of **1** using PTC **6** in aqueous media



Entry	PTC **6** (mol %)	Condition	Time (h)	**4** Yield (%)	Ee[a] (%)	**4**:**5**[a]
1	—	50% KOH	50	71	—	78:22
2	**6a** (10)	Toluene–50% KOH	6	82	74	84:16
3	**6a** (10)	50% KOH	3	97	56	98:2
4	**6a** (10)	10% KOH	5	99	56	99:1
5	**6a** (10)	5% KOH	96	96	53	97:3
6	**6a** (1)	50% KOH	19	82	70	93:7
7	**6b** (1)	50% KOH	29	98	67	98:2
8	**6c** (1)	Toluene–50% KOH	10	62	57	62:38
9	**6c** (10)	50% KOH	4	96	52	97:3
10	**6c** (1)	50% KOH	32	92	35	94:6
11	**6d** (1)	Toluene–50% KOH	4	81	96	82:18
12	**6d** (1)	50% KOH	30	96	85	98:2
13[b]	**6d** (1)	50% KOH	2	98	81	98:2
14	**6e** (1)	50% KOH	19	94	83	99:1
15	**6f** (1)	50% KOH	7	94	82	97:3

[a] Determined by HPLC analysis using Chiralcel OD-H with hexane/2-propanol as an eluent.
[b] The reaction was carried out under ultrasonic irradiation at 25 °C.

chemoselectivity (entries 3–5). The catalyst *N*-alkyl cinchonidinium bromide (**6c**) containing a long chain alkyl group showed similar results with catalyst **6a** (entries 8–10). Unfortunately, PTCs **6a** and **6c** showed only moderate enantioselectivities. In 1997, Lygo et al. reported alkylation of **1** using *N*-anthracenylmethylcinchonidinium chloride (**6d**) under liquid–liquid conditions, which gave (*S*)-**4a** in over 68% yield and 91% ee after 18 h stirring at room temperature.[2g] Indeed, (*S*)-**4a** was obtained in 81% yield with 96% ee after 4 h stirring at 0 °C, however benzophenone (**5**) was also obtained in 18% yield (entry 11). Formation of **5** was depressed by using aqueous media without any organic solvent. Alkylation of **1** using PTC **6d** in 50% KOH aq afforded (*S*)-**4a** in 96% yield with 85% ee (entry 12). Furthermore, reaction time was improved by using an ultrasonic irradiation (entry 13). *O*-Alkyl-*N*-alkyl cinchonidinium salts (**6b**, **6e**–**f**) showed a similar yield and ee compared with *N*-alkyl cinchonidinium salts **6a** and **6d**, respectively (entries 6, 12 vs 7, 14, 15). These results suggest that the active cat-

alyst in the alkylation of **1** using **6a** or **6d** is *O*-alkyl-*N*-alkyl cinchonidinium salts, which is formed in situ during the reaction as O'Donnell et al. reported.[2e]

We further examined the scope of this class of alkylations with a series of alkyl halides **3a–g** using PTC **6d** under the same reaction conditions (Table 3). Alkylations with allylic bromide, arylmethyl bromide, and alkyl iodide provided the corresponding alkylated products **4a–f** in high yields (81–96%) and enantioselectivities (82–92% ee) (entries 1–6). Conversely, alkylation with 4-chlorobenzyl bromide (**3g**) was very slow, giving the desired product **4g** in unacceptable yields and ee (entry 7). Usually in alkylation of **1** with **3** under aqueous media Schiff base **1** was not soluble but floating on the water phase at first, and then gradually changed to liquid as the reaction proceeded. In the case of alkylation with **3g** Schiff base **1** was not consumed after 2 days. We put forward that alkyl halide **3** plays an important role as a kind of organic solvent; because alkyl halides **3a–f** are liquid but alkyl halide **3g** is a solid. Therefore, we added 1% toluene to the reaction mixture; the desired product (*S*)-**4g** was obtained in 97% yield with 91% ee (entry 8). These reaction conditions were readily scaled up. To study a gram-scale synthesis, PTC **6d** (1 mol %) was added to a suspension of Schiff base **1** (1.0 g) and alkyl halide **3g** (1.2 equiv) in 50% KOH (10 mL) and toluene (0.1 mL) at 0 °C. The reaction mixture was stirred for several hours, then removed aqueous layer and washed with water. The crude product (y. 88%, 80% ee) was directly purified by recrystallization to afford alkylation product **4g** (y. 78%, 93% ee). In all reactions carried out in aqueous media, the absolute configuration of the products **4** were *S* configuration, the same as under organic-aqueous two-phase conditions.

The exact reason for improvement of chemical yield is not clear at this stage, but we propose that hydrophobic interaction is a key to depressing hydrolysis of Schiff base **1**. A small amount of hydrophobic alkyl halide **3** assembles in aqueous media, and then Schiff base **1** gradually dissolves in the alkyl halide phase.[10] Alkylation quickly occurred in high concentrated alkyl halide phase in the presence of 1 mol % chiral PTC, therefore, hydrolysis of Schiff base **1** is depressed.[11]

In summary, a system employing aqueous media without any organic solvent demonstrated good reactivity and enantioselectivity in this class of chiral PTC-catalyzed alkylation of Schiff base **1**. This approach could be carried out under simple and mild reaction conditions with easy handling, and could be applied to multi-gram reactions to give chiral usual and unusual α-amino acids. Further studies focusing on the full scope of this condition system are currently under investigation and will be reported in due course.

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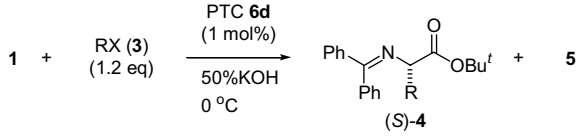
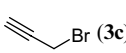
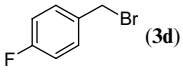
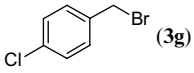
Table 3. Enantioselective alkylation of **1** with various alkyl halides **3** using PTC **6d** in aqueous media



Entry	RX	Time (h)	**4** Yield (%)	Ee[a] (%)	Ratio[a] **4**:**5**
1	BnBr (**3a**)	30	96	85	98:2
2	 (**3b**)	12	87	82	96:4
3	(**3c**)	12	87	90	96:4
4	 (**3d**)	24	84	83	92:8
5	MeI (**3e**)	31	83	84	89:11
6	EtI (**3f**)	40	81	92	87:13
7	 (**3g**)	48	51[b]	0	76:24
8[c]	**3g**	22	97	91	96:4

[a] Determined by HPLC analysis using Chiralcel OD-H with hexane/2-propanol as an eluent. The absolute configurations were determined by comparison of the HPLC retention time with the reported data.
[b] Schiff base **1** was recovered in 34% yield.
[c] The reaction was carried out in 50% KOH aq/toluene = 99/1 (v/v).

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9. Recently, Okino and Takemoto reported chiral PTC-catalyzed alkylation of **1** under micellar conditions. They also reported that yield of the desired product was low in aqueous media using *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (33% yield, 78% ee) Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 1515–1517.
10. A small amount of Schiff base **1** (5.9 mg, 0.02 mmol) was soluble in benzyl bromide (102.6 mg, 0.6 mmol), though **1** (147.7 mg, 0.5 mmol) did not completely dissolve. All of *N*-alkyl cinchonidinium salts (PTC **6**, 0.005 mmol) were soluble in benzyl bromide (102.6 mg, 0.6 mmol). These solubility data would support that the ion-exchange process between potassium enolate and catalyst following the alkylation proceeded in alkyl halide phase.
11. Schiff base **1** was easily hydrolyzed to give benzophenone in toluene–50% KOH aq in the presence of PTC **6f** (1 mol %) after 24 h, while hydrolysis of the alkylated product **4a** was not observed under same condition. Therefore, benzophenone obtained by alkylation in 50% KOH aq should be derived from Schiff base **1**.