Asymmetric Alkylation of a *tert*-Butyl Benzophenone Schiff Base Derivative in Water

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Abstract: The asymmetric alkylation of a *tert*-butyl benzophenone Schiff base derivative in water has been successfully carried out in a 'reversed-phase reaction'. The effects of chiral phase-transfer catalysts (PTCs), electrophiles, and reaction conditions (temperature, concentration, and the ratio of reagents, etc.) were investigated. Under the optimized conditions high chemical yield (99%) and good ee (up to 87%) were obtained.

Key words: alkylations, phase-transfer, asymmetric catalysis, cinchona alkoloids, amino acids

Mild reaction conditions and chiral products are an attractive and interesting objective for all synthetic chemists. Asymmetric phase-transfer catalysis (PTC) is one of the most effective tools for achieving such goals; examples include, epoxidation,[1] Michael addition,[2] cyclopropanation,[3] Darzen reaction,[4] alkylation, etc. Among these examples, the asymmetric alkylation of a *tert*-butyl benzophenone Schiff base derivative has been achieved by using N-alkylated or N,O-dialkylated cinchona alkaloid derivatives with high enantiomeric excesses.[5] This reaction is also an important method for the preparation of chiral amino acids, especially several unnatural amino acids and peptides.[6] In addition, other catalysts such as C_2-symmetric ammonium salts derived from chiral BINOL,[7] phosphonium salts,[8] TADDOL,[9] tartaric derivatives,[10] guanidinium salts,[11] and other metal–ligand catalysts[12] have also been reported.

Recently, polymer-supported chiral PTCs[13] further promoted the development of this field. Moreover, the asymmetric alkylation in non-conventional PTC reaction conditions[14] was also reported. These advances open up potential industrial applications. Meanwhile, since the concept of 'green chemistry' has been widely accepted, researchers have begun to carry out reactions in water[15] without additional organic solvents and auxiliaries. We report here the asymmetric alkylation of a *tert*-butyl benzophenone Schiff base derivative carried out in water.

Initially (Equation 1), the reaction conditions reported by Lygo et al.[5b] were used (obviously there was no need to
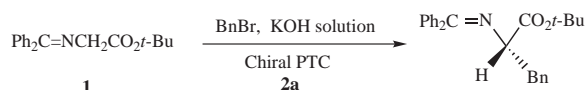
Equation 1 Asymmetric benzylation in water

remove organic solvents). The result showed that the ee was modest but the chemical yield was very low. The poor solubility of the *tert*-butyl benzophenone Schiff base derivative in a mixture of an aqueous solution of KOH and excess benzyl bromide may be responsible for the low yield. To confirm our hypothesis, experiments were designed to enhance the solubility of the starting materials. Table 1 shows that excess benzyl bromide or an aqueous solution of KOH improved the chemical yield. At the same time, a low concentration of base (1 M aqueous solution of KOH) is also beneficial to this reaction, even if it slows down the reaction. It is an interesting and valuable phenomenon since the ammonium salts, especially cinchonidium salts,[13d,14b] were reported to decompose in strong aqueous solutions of alkali (50%), which led to the use of an excess amount of expensive catalysts in the reaction. Stringent basic conditions not only hampered the industrial application but also limited the diversity of catalytic derivatives, which could be applied since many functional groups are unstable in a strong base.[13d,14b] The other factors affecting the alkylation such as the reaction temperature, the amounts of the benzyl bromide, water, and chiral PTC used were also examined. Finally, the best result was obtained when the reaction was carried out at 5 °C in a 1 M aqueous solution of KOH (13.0 equiv, 9 mL) with benzyl bromide (5.0 equiv), and PTC (1 mol%). The chemical yield obtained was 99% and the ee was up to 87%.[16]

After optimization of the conditions using chiral PTC **2a**, we studied the effects of other chiral PTCs (Figure 1) including catalyst **2b** prepared by Corey's method,[15] a new dimeric chiral catalyst **3**,[17] and a polymer-supported chiral catalyst **4**.[18] We were especially interested in the last one, since there have been few examples of asymmetric alkylation using polymer-supported catalysts in water, and such a catalyst is more applicable in industry. It was reported that this type of catalysts could not be recycled and reused by conventional conditions due to saponification.

Table 1 Asymmetric Benzylation of **1** in the Presence of Catalyst **2a**

Entry[a]	BnBr (equiv)	KOH (aq, M)	Water (mL)	**2a** (equiv)	Yield[b] (%)	ee[c] (%)
1	1.2	9	3.4	0.1	38	78
2	5.0	9	3.4	0.1	95	76.5
3	5.0	9	9.0	0.1	93	77.5
4	5.0	1	3.4	0.1	48	83
5	5.0	1	9.0	0.1	94	82
6	5.0	1	15.0	0.1	95	81
7	5.0	1	21.0	0.1	93	80
8	5.0	1	25.0	0.1	99	78.5
9	2.5	1	9.0	0.1	95	73
10	1.2	1	9.0	0.1	82	70.5
11	5.0	1	9.0	0.01	99	87
12	5.0	0.5	9.0	0.01	96	85.5
13[d]	5.0	1	9.0	0.01	53	84
14	10.0	1	9.0	0.01	87	85
15[e]	5.0	1	9.0	0.01	98	86

[a] The reactions were performed at 5 °C for 24 h except for entry 12 (48 h).

[b] The yield was determined by ^{1}H NMR spectroscopic analysis.

[c] Enantiomeric excess was determined by HPLC analysis of the alkylated imine using a chiral column (DAICEL Chiralcel OD-H) with hexane–isopropanol as solvent.

[d] The reaction was performed in an ultrasonic bath at room temperature.

[e] The reaction was performed at room temperature.

In Table 2, the reaction with catalyst **2b** afforded the best results. Although the catalytic ability of catalyst **4** was not good, both the ee and the chemical yield in water were higher than in the classic PTC system.

2a: R = H, X = Cl
2b: R = Allyl, X = Br

3

4
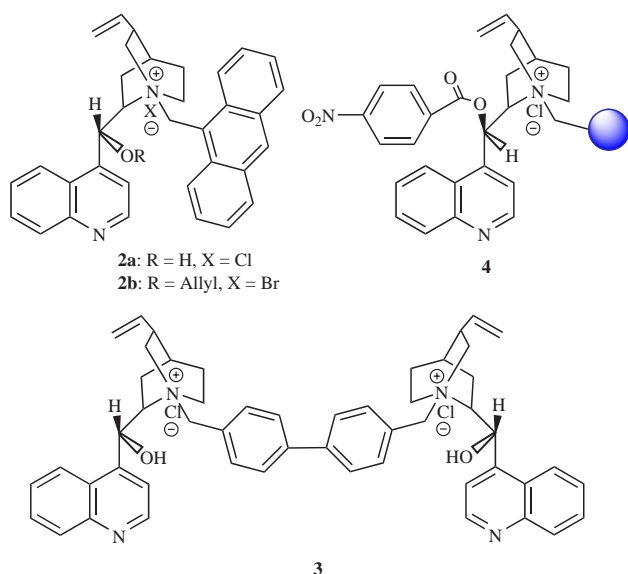
Figure 1 Several chiral phase-transfer catalysts

Table 2 Asymmetric Benzylation of **1** with Different Catalysts

Entry	Reaction Conditions	Catalyst	Yield[a] (%)	ee[b] (%)	Configuration
1	Water phase[c]	**2a**	99	87	*S*
2	Water phase[c]	**2b**	85	88	*S*
3	Classical PTC[d]	**3**	90	84	*S*
4	Water phase[c]	**3**	95	74	*S*
5	Classical PTC[d]	**4**	27	3	*R*
6	Water phase[c]	**4**	30	18	*R*

[a] The yield was determined by ^{1}H NMR spectroscopic analysis.

[b] Enantiomeric excess was determined by HPLC analysis of the alkylated imine using a chiral column (DAICEL Chiralcel OD-H) with hexane–isopropanol as solvent.

[c] The reactions were performed at 5 °C with a 1 M aqueous solution of KOH (13.0 equiv, 9 mL), benzyl bromide (5.0 equiv), and PTC (1 mol%).

[d] The reactions were performed at 0 °C in organic solvents (PhMe–CHCl₃, 7:3, 3 mL, entry 3; CH_2Cl_2, entry 5), 9 M aqueous solution of KOH (13.0 equiv, 1 mL), benzyl bromide (5.0 equiv), and PTC (10 mol%).

Finally, we tried to apply this new strategy to reactions with other electrophiles. However, the chemical yields of several electrophiles were not high, although the ees in some experiments were satisfactory. Table 3 shows that the chemical yields of several liquid halides were better than those of solid electrophiles. The low yields may be explained by the reaction mechanism, which can be described as 'reverse phase-transfer catalysis'. Under high-speed stirring, small oil droplets containing halide were dispersed in the KOH solution and the reaction occurred at the interface[19] between the water phase and the oil phase. Therefore, the ratio of oil to water in this methodology is important. On the contrary, under conventional conditions, water, not oil, was dispersed in organic solvents. Obviously, an excess of liquid halides are more effective for dispersion than solid halides.

In summary, the water-phase asymmetric alkylation of a *tert*-butyl benzophenone Schiff base derivative was accomplished with good chemical yield and high enantioselectivity.[20] The new methodology allows easy separation and purification of the products and is also environmentally friendly. In addition, the mild reaction conditions (1 M aqueous solution of KOH) make it possible to modify the chiral catalysts with other functional groups. The application of this method in other asymmetric phase-transfer reactions is being studied.

Table 3   Application of Various Alkylation Reagents

Entry[a]	Alkylation Reagents	Halide (equiv)	Yield[b] (%)	ee[c] (%)
1	BnBr	5.0	98.7	87
2	Allyl bromide	5.0	36	90
3	Allyl bromide	10.0	60	92
4	Propargyl bromide	10.0	58	84
5	CH_3I	15.0	36	69
6	9-Chloromethyl anthracene	5.0	35	49
7	4-NO_2BnBr	5.0	45	42

[a] All reactions were performed at 5 °C with a 1 M aqueous solution of KOH (13.0 equiv, 9 mL), PTC (1 mol%), and excess alkyl halide.
[b] The yield was determined by ^1H NMR analysis.
[c] Enantiomeric excess was determined by HPLC analysis of the alkylated imine using a chiral column (DAICEL Chiralcel OD-H) with hexane–isopropanol as solvent.

Acknowledgment

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(16) **Typical procedure for asymmetric alkylation**: A mixture of **1** (0.678 mmol, 200 mg), benzyl bromide (5.0 equiv, 0.4 mL) and the catalyst (0.01 equiv, 4 mg) was cooled to 5 °C and a 1 M KOH aqueous solution (13 equiv, 9.0 mL) was added. The mixture was vigorously stirred. When the reaction was finished, the mixture was extracted with ethyl acetate (4 × 20 mL). The organic extracts were combined and dried (Na_2SO_4) then evaporated in vacuo.

(17) **Synthesis of catalyst 3**: Cinchonidine (11.0 mmol, 3.234 g) and 4,4′-chloromethyl biphenyl (5.0 mmol, 1.255 g) were added to the solution of EtOH–DMF–$CHCl_3$ (2.5: 3:1, 26 mL), followed by stirring at 100 °C for 8 h. After cooling the reaction mixture to room temperature, the resulting

suspension precipitated by the addition of Et_2O. The solids were filtered, washed with Et_2O. The crude solid was recrystallized from MeOH to afford the desired product 3.566 g (85% yields) as an orange solid. The structure of sample was confirmed by a range of analytical methods.

(18) **Synthesis of catalyst 4**: A styrene–divinylbenzene copolymer (4.5 g, 7%) was swollen in DMF (100 mL) for 2 h, 9-*O*-(4-nitrobenzoyl)cinchonine (11.6 g) was added. The flask was heated at 80 °C for 60 h. During the course of the reaction the color of the copolymer beads turned dark red. After cooling, the polymer beads were separated by filtration, washed with EtOH (3 × 20 mL), DCE (3 × 20 mL), Et_2O (3 × 20 mL), and dried in vacuo. The structure of the sample was certified by several analytical methods.

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