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Asymmetric Alkylation of *tert*-Butyl Glycinate Schiff Base with Chiral Quaternary Ammonium Salt under Micellar Conditions

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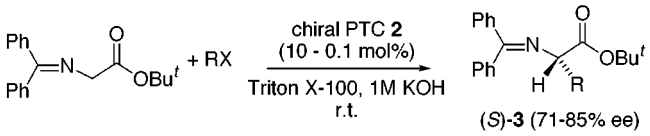
ABSTRACT



The asymmetric alkylation of the *tert*-butyl glycinate–benzophenone Schiff base 1 with various arylmethyl bromides catalyzed by *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (2) proceeded smoothly under micellar conditions (5 equiv of 1 M KOH and 0.4 equiv of Triton X-100) to give the alkylated products in good yields and with good enantioselectivity (72–85% ee), depending on the electrophiles.

The development of environmentally friendly catalysts for organic transformation is becoming an area of growing importance.[1] From economical and environmental points of view, catalytic use of nonmetallic catalysts such as a chiral phase transfer catalyst (PTC) is very promising.[2] Until recently, there have been no successful applications of PTC reaction to catalytic asymmetric synthesis.[3] However, quite recently, the highly enantioselective alkylation of the *tert*-butyl glycinate−benzophenone Schiff base **1** has been achieved under PTC conditions using *N*-alkylated cinchonidinium salts[4,5] and C_2-symmetric ammonium salts[6] derived from chiral binaphthol. These excellent results provided an efficient tool for the preparation of both natural and unnatural amino acids.[7] To further improve the asymmetric alkylation with these new chiral PTC's, several problems must be solved. Since these catalysts, in particular cinchonidium salts, are reported to be unstable under basic conditions, the asymmetric alkylation usually demands the addition of more than 10 mol % of the chiral catalyst to attain high enantioselectivity. In addition, all of the chiral PTC reactions reported so far have been carried out in organic solvents such as toluene and methylene chloride or a water/toluene two-phase system. It is desirable to develop the PTC-catalyzed asymmetric reaction without the use of

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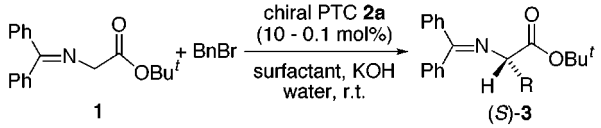
any organic solvents, because of the inherent advantages of using water as the only solvent. For developing an ideal PTC which satisfies these conditions (active, stable, cheap, and recoverable), extensive efforts are being continued.[8] In this Letter, we wish to describe a novel strategy, which has not been reported, for overcoming these problems concurrently, i.e., the asymmetric alkylation of **1** with *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**2**) in a micellar medium (a mixture of water and a neutral surfactant). Using this method we successfully carried out a highly efficient PTC-catalyzed enantioselective alkylation in water; we also found that the amount of the chiral PTC can be reduced up to 0.1 mol % without a serious decrease in the enantiomeric excess.

We first examined the standard asymmetric alkylation of **1** with benzyl bromide without an organic solvent. The benzylation of **1** proceeded very reluctantly without the organic solvent, giving the desired product **3** in low yield but with good enantioselectivity (Table 1, entry 1). Recently,

Table 1. Catalytic Enantioselective Alkylation of **1** with BnBr in the Presence of **2a** under Micellar Conditions[a]



1 (*S*)-**3**

entry	surfactant	BnBr (equiv)	**2a** (mol %)	% yield[b]	% ee[c]
1	*d*	1.2	10	33	78
2	Triton X-100[d]	1.2	10	24	<5
3	Triton X-100[e]	1.2	10	59	78
4	SDS[f]	1.2	10	30	63
5	CTAB[g]	1.2	10	34	39
6	Triton X-100	2.4	10	91	84
7	Triton X-100	2.4	1	92	85
8	Triton X-100	2.4	0.1	81	80

[a] The reaction was carried out with BnBr (1.2−2.4 equiv), **2a** (0.1−10 mol %), and 1.0 M aqueous KOH (5 equiv) in the presence of several surfactants (0.4 equiv) at room temperature. [b] Isolated yield. [c] Enantiomeric excess of **3** was determined by HPLC analysis of the alkylated imine using a chiral column (DAICEL Chiralcel OD) with hexane/2-propanol as solvent. [d] The reaction was performed with 50% KOH. [e] $Me_3CCH_2C(Me)_2C_6H_4$-$(OCH_2CH_2)_nOH$ (n = 10). [f] Sodium dodecyl sulfate. [g] Cetyltrimethylammonium bromide.

the remarkable effects of surfactants were demonstrated in transition metal- and Lewis acid-mediated reactions.[9,10] Only a few attempts of application of surfactants to asymmetric synthesis have been successful and only in a limited area.[11,12] However, a serious problem that may be incurred is that the addition of a surfactant may promote a racemic reaction because surfactants are known as PTC catalysts.[13] In fact, treatment of **1** with BnBr and 50% KOH in the presence of the chiral PTC **2** and Triton X-100 gave the nearly racemic product **3** in 24% yield (entry 2). Then, with the expectation of improving the enantioselectivity, several reaction conditions, including the base and surfactant, were investigated (entries 3−5). Consequently, use of a 1.0 M KOH solution as a base dramatically improved the ee of **3**. Among the examined surfactants, neutral surfactants such as Triton X-100 were revealed to efficiently promote the alkylation, giving the desired product **3** in good yield and with good enantioselectivity. On the other hand, neither an anionic nor a cationic surfactant was effective in terms of the chemical yield and enantioselectivity. In addition, it was revealed that the addition of 2.4 equiv of BnBr to the reaction mixture improved both the chemical yield and enantiomeric excess (entry 6). To our surprise, the reduction of the amount of **2** from 10 to 1 mol % did not affect the asymmetric alkylation, giving the same result (entry 7). It should be emphasized that the alkylation can be carried out with only 0.1 mol % of **2** without a serious decrease of the chemical yield and ee (entry 8). The same reactions with various neutral surfactants bearing different PEG lengths such as Triton X-114, Targitol NP-40, and Triton X-405[14] showed that these surfactants affected only the chemical yield of **3** but not their enantioselectivities [Triton X-114 (76%, 84% ee), Targitol NP-40 (63%, 85% ee), and Triton X-405 (57%, 84% ee)].

Since the optimal reaction conditions could be found for the asymmetric benzylation, we next examined the influence of various chiral PTC's other than **2a** on the enantioselectivity of **3** (Table 2). The alkylation of **1** using other *N*-alkylated cinchonidium salts **2b**−**d**[4,5] bearing a different alkyl group afforded the same product (*S*)-**3** with similar enantioselectivity (entries 1−3). Therefore, the alkyl groups of **2** have only a marginal effect in terms of the chemical yield and enantiomeric excess. Furthermore, the C_2-symmetric ammonium salt **4**,[6] recently developed by Maruoka,

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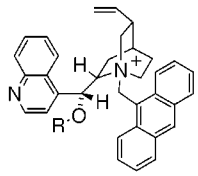
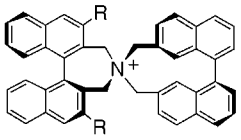
(14) These surfactants were purchased from Nacalai tesque.

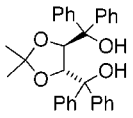
Table 2. Enantioselective Benzylation of **1** with Various PTC's under Micellar Conditions[a]



2a (R = allyl)
2b (R = H)
2c (R = Me)
2d (R = Bn)



4 (R = 3,4,5-F_3-Ph)



5

entry	catalyst	% yield[b]	% ee[c]
1	**2b** (R = H)	82	84
2	**2c** (R = Me)	92	76
3	**2d** (R = Bn)	89	85
4	**4**	78	72
5	**5**	20	3

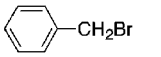
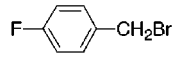
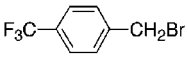
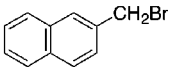
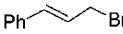
[a] The reaction was carried out with BnBr (2.4 equiv), PTC (1 mol %), and Triton X-100 (0.5 equiv) in a 1.0 M aqueous KOH (5 equiv) solution at room temperature. [b] Isolated yield. [c] Enantiomeric excess of **3** was determined by HPLC analysis of the alkylated imine using a chiral column (DAICEL Chiralcel OD) with hexane/2-propanol as solvent.

was less effective under the micellar conditions, resulting in a slight decrease of the enantiomeric excess (entry 4). In contrast with these results, the reaction of **1** with (−)-TADDOL, which is known as a chiral metal-chelator,[8] gave the racemic product in poor yield (entry 5). From these results, we selected the allyl ether **2a** as the best chiral PTC.

We finally investigated whether our new method could be applied to **1** with other electrophiles (Table 3). Indeed, the alkylation with several arylmethyl bromides and allylic bromides proceeded smoothly to give rise to the corresponding monoalkylated products **3** in good enantioselectivity (72−85% ee), even though, in the latter cases, the reaction required 10 equiv of electrophiles to achieve good chemical yields (entries 1−7). In contrast to these entries, alkylations with methyl iodide and ethyl iodide were very sluggish, resulting in the alkylated products in poor yield or low enantioselectivity (entries 8 and 9). In any event, the configurations of the products **3** were the same as those of products obtained by the liquid−liquid and liquid−solid two-phase reactions using **2**.[4−6]

These results suggest that the surfactants only provide a hydrophobic area for the interaction of the reactants and the catalyst. The surfactants have no effect on determining the stereochemistry of the products, despite the fact they are known as phase-transfer catalysts. The exact role of the surfactant is not clear at this stage, but because the chiral PTC would be protected from exposure of the aqueous base by the incorporation in the PEG moiety of the surfactant, the asymmetric alkylation in micellar conditions proceeded effectively with less than 1 mol % of the chiral catalyst **2**. Besides the mild basic conditions and independence of the substrate solubility in the solvent, the surfactant-aided asymmetric alkylation may have practical consequences in

Table 3. Catalytic Enantioselective Alkylation of **1** with Several Alkyl Halides in the Presence of **2a** and Triton X-100 in Water[a]

entry	RX (equiv.)		% yield[b]	% ee[c] (config.)[d]
1		(2.4)	92	85 (*S*)
2		(2.4)	87	81 (*S*)
3		(2.4)	80	74 (-)[e]
4		(2.4)	83	80 (*S*)
5		(10)	85	82 (*S*)
6		(10)	90	72 (*S*)
7		(10)	60	77 (-)[e]
8	MeI	(20)	43	64 (*S*)
9	EtI	(20)	28	82 (*S*)

[a] The reaction was carried out with RX (2.4 equiv), **2a** (1 mol %), and 1.0 M aqueous KOH (5 equiv) in the presence of Triton X-100 (0.4 equiv) at room temperature. [b] Isolated yield. [c] Enantiomeric excess of **3** was determined by HPLC analysis of the alkylated imine using a chiral column (DAICEL Chiralcel OD) with hexane/2-propanol as solvent. [d] Absolute configuration was determined by comparison of the HPLC retention time with that of an authentic sample. [e] Not determined.

organic synthesis in light of the increased demand for reduction of organic solvents. In addition, the enantiomeric excess shown here might be further enhanced by using a more suitably designed PTC.

In conclusion, we have devised a useful and environmentally benign procedure for the catalytic asymmetric alkylation of the aldimine Schiff base of an amino acid *tert*-butyl ester using the micellar system. This method is the first asymmetric reaction using a micellar system other than the transition metal-promoted asymmetric reaction. We are now investigating other applications in nonmetallic catalyst-promoted asymmetric reactions.

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Supporting Information Available: Experimental details and characterization of all compounds. This material is available free of charge via the Internet at http://pubs.acs.

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