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Enantioselective alkylation using a new C_3 symmetric amine-based chiral phase-transfer catalyst

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Abstract—A new C_3 symmetric amine-based chiral phase-transfer catalyst was synthesized. Application of the chiral PTC (1 mol%) in the alkylation of a *tert*-butyl glycinate-benzophenone Schiff base under mild reaction conditions provided an alkylated product with up to 58% enantiomeric excess.

New methods for the synthesis of chiral compounds under chiral phase-transfer conditions have been the focus of numerous studies because of the simplicity, high reactivity, safety, mild conditions, easy separation and the environmentally benign aspects of the methodology.[1] These are highly attractive advantages in the laboratory as well as industry. From the 1980s chiral phase-transfer catalysts (PTC) derived from natural alkaloids such as cinchonidine, cinchonine and quinine have induced extremely high enantioselectivity in alkylation,[2] Michael reaction,[3] epoxidation,[4] aldol reaction,[5] Darzens reaction,[6] etc.[7] Recently, Maruoka[8] and some groups[9] have reported synthesis of designed chiral PTCs, and its application to versatile enantioselective reactions. Unfortunately, halogenated solvents and low reaction temperature were needed to achieve high stereoselectivity in many cases except the Maruoka group. Moreover, it is difficult configurationally to control an ion-pair composed of chiral PTCs and a nucleophile, because Coulomb force has no directional character to fix it. As just described, chiral PTC technology involves many problems to be solved. One possible solution to this problem may be utilization of mutual interaction such as a hydrogen bond, coordination bond and others as shown in Figure 1. We have designed C_3 symmetric amine-based chiral PTCs, the structure and preparation of which are very simple as given below. There are two directions of approach of the nucleophile, that is, one is from as shown in Figure 1, and the other is from three equivalent faces of tetrahedron. If mutual interactions positively form, both fixing an ion-pair and controlling the approach of the nucleophile should be achieved. In this paper, we report an enantioselective alkylation of *tert*-butyl glycinate-benzophenone Schiff base **3** using new C_3 symmetric amine-based chiral PTCs.

C_3 symmetric amine-derived chiral PTCs were prepared in two steps as shown in Scheme 1. Stereospecific ring-opening of enantiomerically pure epoxide **1**, which was commercially available or obtained by short-step

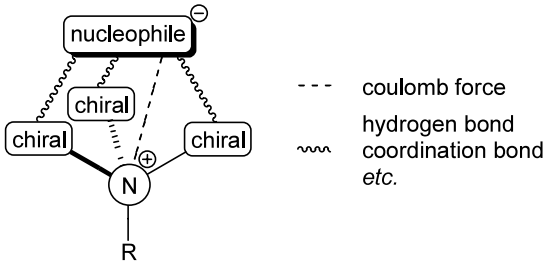
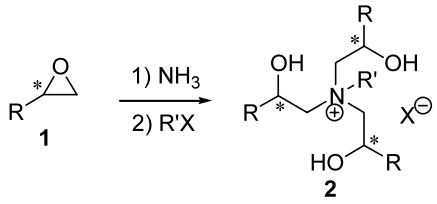


Figure 1. Configurationally control of an ion-pair.



Scheme 1. Synthesis of C_3 symmetric amine-based chiral PTCs.

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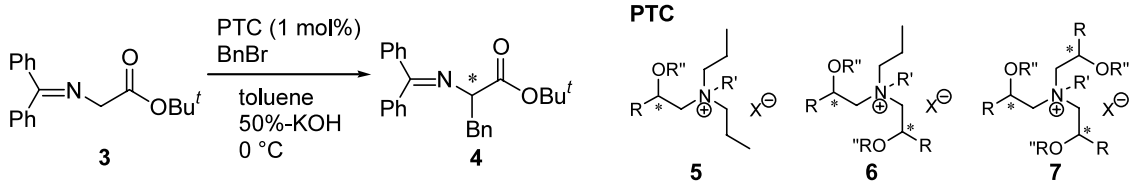
synthesis, with ammonia afforded C_3 symmetric chiral amines.[10] Quaternalization of the amine with an alkyl halide gave the chiral PTC **2**, which was purified by recrystallization or column chromatography.

We investigated eleven C_3 symmetric amine-based chiral PTCs **7** and four mono- or di-chiral group-substituted PTCs **5**,**6** for the sake of comparison. In the presence of 1 mol% of PTC, 50% KOH solution added to a toluene solution of the Schiff base **3** and benzyl bromide (1.2 equiv.) at 0°C. Reactions smoothly proceeded to give the alkylated product **4**, which was analyzed with HPLC. Results are shown in Table 1. In the beginning, PTCs derived from (*R*)-phenyl glycidyl ether were investigated. The more the number of chiral group substitution increased, the higher enantioselectivity was observed (entries 1–3). C_3 symmetric structure was needed to achieve higher enantioselectivity. Protection of the hydroxyl group with an allyl group intensively reduced the enantioselectivity (entry 4). This observation is quite different from that in reactions using the cinchona alkaloid-based PTCs, in which higher enantioselectivity and activity have been noted.[1,2] O'Donnell et al. have dug up the fact that the really active catalyst in the alkylation of **3** is *O*-alkylated cinchona alkaloid-based PTC which was formed in situ during the reaction.[11] On the other hand, our C_3 symmetric amine-based chiral PTCs **7** did not undergo *O*-protection and hence is deemed to be an active catalyst species without any protection.

Undecyloxymethyl-substituted PTC **7c** derived from (*S*)-undecyloxymethyl glycidyl ether and phenyl-substituted PTC **7d** derived from (*S*)-styrene oxide accelerated the alkylation but enantioselectivity was low (entries 5–6). Cyclohexyl-substituted PTC **7e** derived from (*S*)-cyclohexyloxirane increased the enantioselectivity up to 50% ee as well as the yield up to 75% (entry 7). Finally, we found that isopropyl-substituted PTC **7f** derived from (*S*)-isopropyloxirane was the most effective catalyst among those tested to give good enantiomeric excess (55% ee, entry 10). Mono- or di-chiral group-substituted PTCs **5b**,**6b** and *O*-protected PTC **7g** decreased the enantioselectivities (entries 8–9, 11), similarly to phenoxyethyl-substituted PTC mentioned above (entries 1–4). Electron-donating or electron-withdrawing substituents on the benzene ring were not effective (entries 12–13). A long-chain subsistent on the benzene ring such as a dodecyl group, or exchanging a counter anion from bromo to the triflate anion improved the reactivity, keeping the same level of enantioselectivity due to increasing the solubility of PTCs in toluene (58% ee, entries 14–15).

Enantioselectivity would be attributed to the hydrogen bonding between a hydroxyl group on PTC and nitrogen on the Schiff base. PTC and *E*-enolate[12] of **3** form a nine-membered ring of an ion-pair, in which the R group locates at pseudoequatorial position as shown in Figure 2. Benzyl bromide approaches from the less hindered face (*Re*-face) to afford the alkylation product **4** with *S* configuration.

Table 1. Enantioselective alkylation of *tert*-butyl glycinate-benzophenone Schiff base using C_3 symmetric amine-based chiral PTCs



Entry	PTC	R	R′	R″	X	Config. **5**,**6**,**7**	Time (h)	**4** yield[a] (%)	ee[a] (%)	Config.[b] **4**
1	**5a**	CH_2OPh	Bn	H	Br	*R*	2	67	7	*R*
2	**6a**	CH_2OPh	Bn	H	Br	*R*,*R*	4	56	19	*R*
3	**7a**	CH_2OPh	Bn	H	Br	*R*,*R*,*R*	18	29	32	*R*
4	**7b**	CH_2OPh	Bn	Allyl	Br	*R*,*R*,*R*	14	56	3	*R*
5	**7c**	$CH_2O(CH_2)_{10}CH_3$	Bn	H	Br	*R*,*R*,*R*	4	60	19	*S*
6	**7d**	Ph	Bn	H	Br	*R*,*R*,*R*	6	65	27	*S*
7	**7e**	Cyclohexyl	Bn	H	Br	*R*,*R*,*R*	7	75	50	*S*
8	**5b**	*i*-Pr	Bn	H	Br	*R*	3	79	39	*S*
9	**6b**	*i*-Pr	Bn	H	Br	*R*,*R*	5	75	23	*S*
10	**7f**	*i*-Pr	Bn	H	Br	*R*,*R*,*R*	20	62	55	*S*
11	**7g**	*i*-Pr	Bn	Bn	Br	*R*,*R*,*R*	6	91	10	*S*
12	**7h**	*i*-Pr	3,5-$(OMe)_2$Bn	H	Br	*R*,*R*,*R*	6	59	43	*S*
13	**7i**	*i*-Pr	4-BrBn	H	Br	*R*,*R*,*R*	15	29	47	*S*
14	**7j**	*i*-Pr	$CH_3(CH_2)_{11}$Bn	H	Br	*R*,*R*,*R*	10	62	57	*S*
15	**7k**	*i*-Pr	Bn	H	TfO	*R*,*R*,*R*	12	55	58	*S*

[a] The yields and the enantiomeric excesses were determined by HPLC analysis using CHIRALCEL OD with hexane/2-propanol as a solvent.
[b] The absolute configurations were determined by comparison of the HPLC retention time with the reported data.[8]

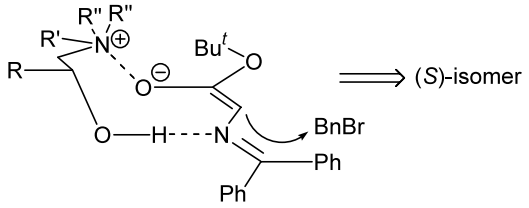


Figure 2. Proposed mechanism for enantioselectivity.

In conclusion, we have successfully designed a new C_3 symmetric amine-based chiral phase-transfer catalyst for the enantioselective alkylation of *tert*-butyl glycinate-benzophenone Schiff base under mild conditions. Research continues toward increasing the enantioselectivity and understanding the mechanism of the asymmetric induction.

Acknowledgements

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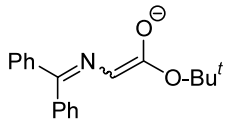

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