C_2-Symmetric Chiral Pentacyclic Guanidine: A Phase-Transfer Catalyst for the Asymmetric Alkylation of *tert*-Butyl Glycinate Schiff Base**

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Phase-transfer catalysts (PTCs) have been recognized as useful reagents in synthetic organic chemistry. Since reactions that involved the use of PTCs have many advantages over homogeneous reactions, and PTCs are environmentally friendly as non-metal-containing organocatalysts, many efficient PTCs and related reaction systems have been explored.[1] In particular, the development of enantioselective reactions that use effective chiral PTCs is an important and challenging issue in synthetic organic chemistry.[2] Several chiral PTCs have been reported so far, most of which were developed from the cinchona alkaloid structure. The enantioselective alkylation of the *tert*-butyl glycinate benzophenone Schiff base **2** (Table 1) under biphasic conditions with *N*-benzylcinchonium salt catalyst was first reported in 1989 by O'Donnell et al.[3] They improved the catalyst by using O-alkyl derivatives of the cinchona alkaloid,[4] and recently, Corey et al.[5] and Lygo et al.[6] independently reported so-called third-generation catalysts in which a 9-anthracenylmethyl group was introduced to mask the nitrogen face, thus inducing a high enantiomeric excess. In 1999, Maruoka and co-workers introduced a new PTC, a chiral C_2-symmetric ammonium salt with a binaphthyl structure, for alkylation of glycine derivative.[7] This catalyst afforded a high enantiomeric excess of alkylated compounds under mild conditions (0 °C), with a short reaction time.

The guanidine group, which contributes to the stabilization of three-dimensional structures in proteins, is a superbase[8] that forms stabilized complex salts with anionic compounds through parallel interactions, including hydrogen bonding. These features suggest that the guanidine-containing molecules can be used use as new "reaction vessels". Indeed, several synthetic applications have been reported with guanidines and amidines as catalysts.[9–13] In the course of our studies aimed at the development of new organocatalysts, we recently reported the novel C_2-symmetric chiral cyclic guanidine compounds **1a**–**c** as hetero Michael reaction catalysts (Figure 1).[14] The structures of these catalysts **1a**–**c** are based on the parent skeleton of the marine natural product ptilomycalin A[15] and related compounds,[16] and were designed rationally to have a C_2-symmetric chiral reaction cavity around the substrate recognition/activation site (guanidine function). These catalysts **1a**–**c** effectively accelerated the hetero Michael reaction, depending on their cavity size,[14] although no asymmetric inductions were observed. Since these results suggested the involvement of complex formation between guanidine salts **1a**–**c** and the substrate under these reaction conditions, possible applications of these new chiral catalysts **1a**–**c** in organic synthesis were intriguing. Herein, we wish to describe the first example of the enantioselective alkylation of the *tert*-butyl glycinate benzophenone Schiff base **2** in the presence of chiral pentacyclic guanidines **1a**–**c** as novel chiral PTCs.

The chiral pentacyclic guanidines **1a**–**c**, which have different cavity sizes around the central guanidine group, were prepared as described before.[14, 17] Previous X-ray crystallographic analysis of **1a**–**c** (Figure 1) revealed that the **1a** and **1b** have a closed-type cavity, whereas **1c** has an open-type cavity (top views).[14] The spiro ether rings of **1a**–**c** and the methyl substituents on the spiro ether rings of **1a** and **1c** are directed vertically up and/or down with respect to the guanidine plane (side views).[14] Thus, these catalysts are expected to show some asymmetric induction through steric

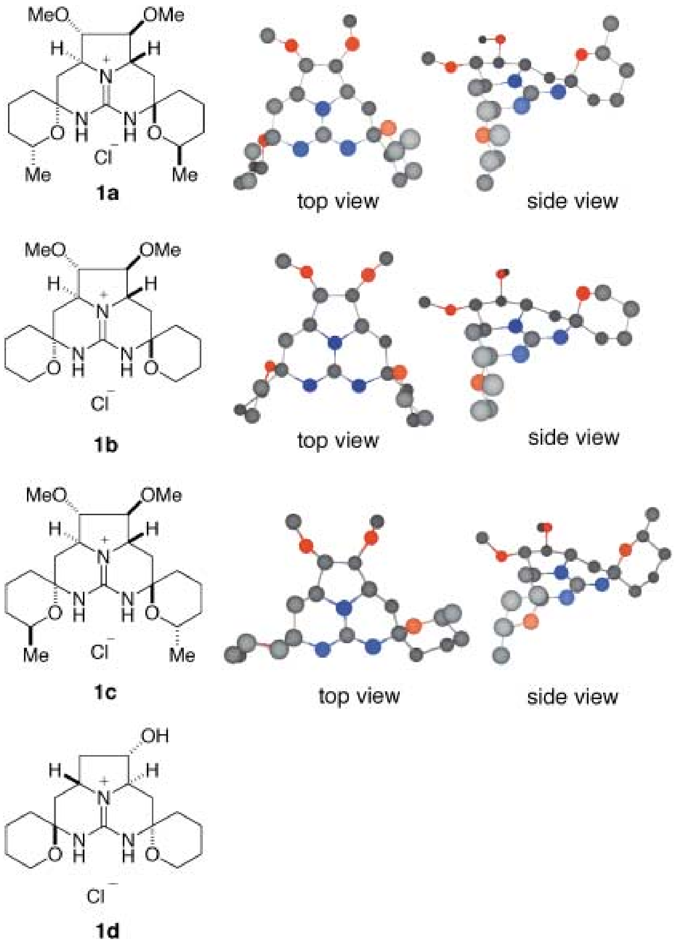

Figure 1. Novel guanidine-type PTCs and their X-ray structures.

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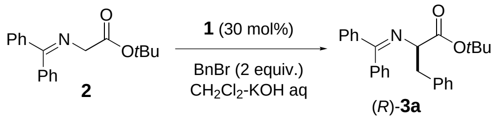
hindrance at this cavity if the reaction proceeds at the substrate-activation site, that is, the guanidine moiety.

Firstly, alkylation of **2** with benzyl bromide (2 equiv) in the presence of a catalytic amount of **1a–d** was examined in an aqueous 1M KOH/dichloromethane (volume ratio 1:1) biphasic solution system at room temperature (Table 1). In the presence of catalyst **1a** (10 mol %), the alkylation product **3a** was obtained in 70 % yield and 75 % *ee*, with the *R* isomer as the major component. An increase in the amount of catalyst **1a** to 30 mol % resulted in a higher yield (90 %) and *ee* value (81 % *ee*). A decrease in the temperature to 0 °C improved the asymmetric induction of (*R*)-**3a** to 90 % *ee*.[18] The use of cesium hydroxide[5a] or more concentrated aqueous KOH instead of 1M KOH solution caused decomposition of the catalysts. Alkylation reactions of **2** in the presence of the structurally related PTCs **1b–d**[14] under the optimized conditions (30 mol % of **1** at 0 °C), were then examined, and the results are summarized in Table 1. The use of catalysts **1b** and **1c** led to the formation of (*R*)-**3a** with 13 % and 12 % *ee*, respectively. Catalyst **1d**, which has exactly the same type of cavity as **1b** but with the opposite stereochemical configurations around the guanidine moiety, led to the formation of (*S*)-**3a** with 7 % *ee*.

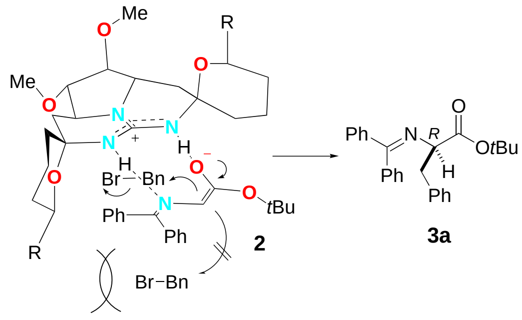
Table 1. Alkylation of the Schiff base **2** with BnBr in the presence of PTC **1**.



PTC	*T* [°C]	*t* [h]	Yield [%]	*ee* [%][a]
1a	RT	140	90	81
1a	0	160	55	90
1b	0	140	64	13
1c	0	140	65	12
1d	0	140	50	7 (*S*)

[a] The enantiomeric excess of **3a** was determined by HPLC analysis of the alkylated imine with a chiral column (DAICEL Chiralcel OD) with hexane/2-propanol as the solvent. The absolute configuration was determined by comparison of the HPLC retention time and $[\alpha]_D$ value with the reported data of an authentic sample.[5a]

These observations indicate that the newly generated stereochemistry of the alkylated product **3a** is controlled by the configuration of the spiro ether rings of the pentacyclic guanidine core structure of the PTC **1** (**1b** versus **1d**). Furthermore, the substituent (methyl group) on the spiro ether rings of PTC **1** plays a critical role in effective asymmetric induction of (*R*)-**3a** (**1a** versus **1b**). As shown in Figure 2, the transition state of this alkylation reaction can be considered to arise as follows: the base form of the PTC **1a** or **1b**, generated from the corresponding guanidium salt in aqueous potassium hydroxide, forms a complex with the *Z* enolate of **2** through ionic and hydrogen-bonding interactions, and the electrophile (benzyl bromide) approaches from the less hindered face (upper surface in this case) of this complex to give the alkylation product **3a**. Thus, (*R*)-**3a** was generated as the major alkylated product (Figure 2).[19] The methyl groups on the spiro ether rings of **1a** are remarkably effective as sterically hindering groups to control the electrophile approach, which results in a very high level of asymmetric induction. Moreover, the closed-type cavity of **1a** is also important for the high asymmetric induction of the alkylated product **3a** (**1a** versus **1c**). Thus, for high asymmetric induction in this alkylation reaction, both closed-type cavity structure and substituents at suitable positions on the spiro ether rings of the pentacyclic guanidine PTC **1** seem to be mandatory.

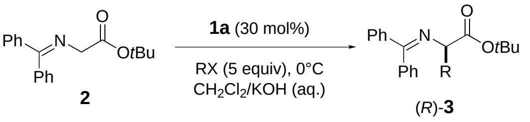


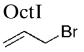
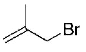
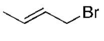
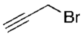
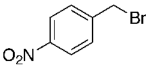
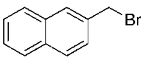
1a: R = Me
1b: R = H

Figure 2. Alkylation mechanism of **2** with benzyl bromide in the presence of pentacyclic guanidine catalysts **1a** and **1b**.

The results of the alkylation of **2** with various alkyl halides (5 equiv) in the presence of PTC **1a** are summarized in Table 2. In all cases examined, the alkylation products **3** were obtained with high enantiomeric excesses (76–90 % *ee*), which indicates the general applicability of this asymmetric reaction system. It should also be noted that these PTCs can be recovered easily in almost quantitative yield by the use of silica-gel column chromatography.

Table 2. Alkylation of the Schiff base **2** with electrophiles in the presence of PTC **1a**.



RX	*t* [h]	Product	Yield [%]	*ee* [%][a]
MeI	145	**3b**	80	76
OctI	145	**3c**	83	80
	140	**3d**	61	81
	145	**3e**	85	81
	160	**3f**	72	79
	145	**3g**	84	81
	40	**3h**	80	82
	95	**3i**	81	90

[a] The enantiomeric excesses of **3** were determined by HPLC analysis of the alkylated imine with a chiral column (DAICEL Chiralcel OD) with hexane/2-propanol as the solvent. The absolute configurations were determined by comparison of the HPLC retention time and $[\alpha]_D$ value with the reported data of an authentic sample.[5a, 20]

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In conclusion, we have successfully employed the new type of chiral guanidine PTC **1** for the enantioselective alkylation reaction of the glycinate benzophenone Schiff base **2**, and high asymmetric induction was obtained in the case of **1a**. This catalyst can be modified easily by changing the stereochemistries and the positions of the substituents on the spiro ether rings to provide appropriate cavity sizes for other reaction substrates, and therefore should be applicable to the alkylation of other substrates or to other asymmetric reactions. Our studies into these reactions will be reported in due course.

Experimental Section

Typical procedure: A solution of the glycine imine **2** (0.03 mmol) in dichloromethane (0.15 mL) was treated sequentially with the guanidine catalyst **1** (0.01 mmol), alkylating agent (0.06 mmol), and an aqueous solution of potassium hydroxide (1M, 0.15 mL). The resulting mixture was stirred vigorously at 0 °C for 140 h. The aqueous layer was then extracted with dichloromethane (3 × 2 mL), and the combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes 1:12) to give **3**. The enantiomeric excess of **3** was determined by the use of chiral HPLC analysis (DAICEL CHIRALCEL OD-H, 0.46 cm (∅) × 25 cm (L), *n*-hexane/2-propanol 100:1, flow rate = 0.5 mL min^{-1}).[5a, 20]

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[18] The use of toluene instead of dichloromethane led to an increase in the enantiomeric excess of **3** to 95 %, although the chemical yield was 20 %, even after 160 h.

[19] The asymmetric induction of the alkylation reaction with the cinchona-alkaloid-type or binaphthyl-type PTCs is explained by the complex with the *E* enolate of Schiff base **2**.[5a,7] In our case, the *Z* enolate of **2** would be generated by forming the complex with the guanidine-type PTC **1** through the two parallel ionic and hydrogen-bonding attractions. The asymmetric alkylation results of **2** also support this hypothesis. More detailed investigations are currently underway in our laboratories.

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