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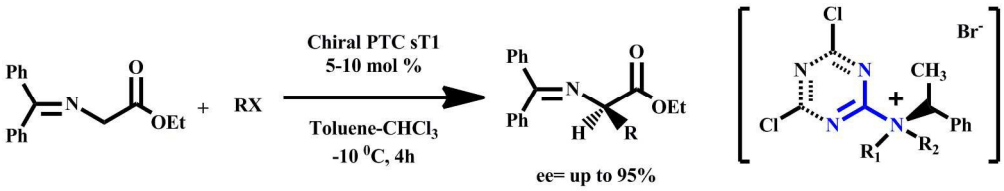

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Design and Synthesis of *s*-Triazene based Asymmetric Organocatalysis and its Application in Enantioselective Alkylation

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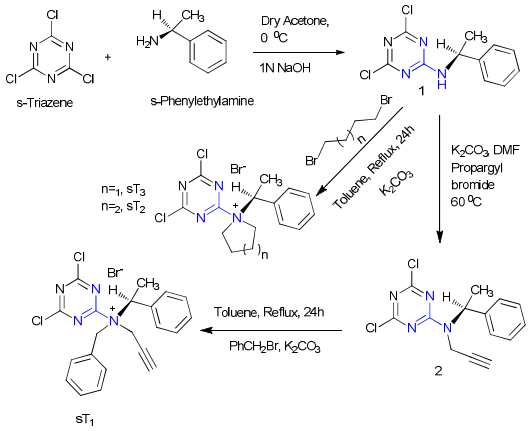
A very efficient chiral organocatalyst was prepared from the easily available cyanuric chloride. The asymmetric catalyst exhibited the high enantioselective catalytic performance in the alkylation of glycinate Schiff base, which allows useful procedure for enantioselective synthesis of structurally diverse natural and unnatural α-alkyl-α-amino acids.

The development of enantioselective C-C bond formation is a topic of great interest in organic synthesis.[1] Recent advances highlights the benefits/significance of environmental friendly and efficient catalyst for such enantioselective transformations. Among others, phase transfer catalysts (PTCs) are known to play a pivotal role in enantioselective modifications in organic synthesis. Within PTCs, usage of several nitrogen and phosphorous containing quaternary centres is much frequent as chiral PTCs.[2] Such chiral PTCs have broad spectrum of applications owing to their diverse catalytically active structural motifs and high catalytic potential.[3] It is well acknowledged that chiral PTCs are non-metal containing environmental friendly organocatalysts.[4] Additionally, chiral PTCs have many advantages over homogenous reactions, due to their high catalytic potential and broad spectrum of applications.[5] Use of Cinchona alkaloid salts have been reported as catalysts under biphasic conditions initially for the enantioselective alkylation of glycinate Schiff base by O'Donell *et al.* in 1989.[6] Subsequently, *o*-alkylation of the Cinchona alkaloids resulted high enantiomeric excess.[7] Later, a chiral C_2-symmetric quaternary ammonium salts, a new PTC class was introduced by Maruoka *et al.* in 1999 with a binaphthyl structure for alkylation of glycinate derivative.[8] Shortly, the Maruoka catalysts were found to be very efficient for variety of asymmetric transformations even at very low catalyst loadings (<1 mol%). In addition, Shibasaki's tartaric acid-derived bidentate PTCs,[9] Lygo's spirocyclic catalysts[10] and guanidine type catalysts[11] were found to be highly efficient in asymmetric synthesis. The novel chiral quaternary catalysts have drawn attention of many scientists because of easy accessibility from sufficiently available chiral starting materials. Literature survey reveals that guanidines and amidines as asymmetric organocatalysts have shown several synthetic applications in organic synthesis.[12-14] Indeed, guanidine group containing molecules more often form stabilized complex salts via parallel interactions including hydrogen bonding with anionic compounds.[15]

Our research group is highly active within the field of catalytic-organic-transformations and designing *s*-triazene based effective catalytic systems for the synthesis of biologically active molecules.[16] We diversified our idea by targeting the use of *s*-triazene as starting materials for the synthesis of a new class of quaternary ammonium salts. It is well documented that *s*-triazene show excellent catalytic property for organic transformation reactions such as C-C and C-N bond formations.[17] Literature survey revealed that the nature of the guanidine and thiourea containing groups of the catalyst have a strong influence on the catalytic performance for the alkylation of α-amino acids.[18] In view of various studies, we designed three different chiral PTCs based on *s*-triazine for alkylation of prochiral substrate 3 to produce optically active α-amino acids in good yields. The overall synthesis of three different chiral PTCs are mentioned in scheme 1. In the first step, chloro group of *s*-triazene was substituted by chiral amine (s)-phenylethylamine to give compound 1, containing guanidine type moiety. Then compound 1 was reacted with propargyl bromide to produce compound 2, which on further reaction with benzyl bromide in toluene yielded chiral quaternary ammonium salt sT1. After successful synthesis of chiral PTC sT1, we further investigated the chemistry and designed two new catalyst based on pyrrolidine and piperidine containing quaternary salts sT2 and sT3 shown in scheme 1. For the synthesis of chiral quaternary salts sT2 and sT3, compound 1 was reacted with 1,5-dibromopentane and 1,4-dibromobutane, respectively. The structures of the chiral quaternary salts were confirmed by ^1H, ^{13}C NMR and mass spectrometry (see the supporting information).

Herein, we show the enantioselective alkylation of glycinate Schiff base using newly developed chiral catalysts sT1, sT2 and sT3 to produce

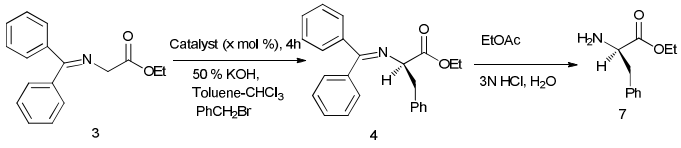
optically active α-amino acids, which are frequently used in peptide and peptidomimetics synthesis.



Scheme 1. Synthesis of chiral PTCs sT1, sT2 and sT3.

Based on this, we began with the synthesis of prochiral substrate benzophenone imine glycinate **3** for the asymmetric alkylation study.[19] To optimize the enantioselective potential of synthesized quaternary salts in the asymmetric alkylations, we performed alkylation with excess of benzyl bromide as shown in scheme **2**. All reactions were carried out under biphasic conditions to get maximum yield and high enantioselectivity, using different mol % of catalyst and varying temperature ranges for the scope of C-C bond forming practice.

It is observed that at room temperature with 2 mol % catalyst loading, the alkylated product showed lower enantioselectivity (**Table 1, Entry 1**). Subsequently, increase of catalyst loading from 2 mol % to 5 and 10 mol % catalyst at room temperature resulted in increase in enantioselectivity (**Table 1, Entries 2, 3**). Further, lowering of temperature from room temperature to -10 °C increased the enantioselectivities of the compounds as shown in Table 1. The alkylated product showed better enantioselectivity at 10 mol % of catalyst loading (**Table 1, Entries 3, 6, 9, 12**). The reaction was also performed in liquid-solid state (**Table 1, Entry 13**) and showed poor enantioselectivity, therefore remaining two catalyst sT2 & sT3 were not evaluted in liquid-solid phase.



Scheme 2. Optimization of catalysts.

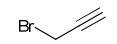
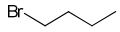
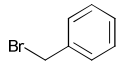
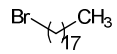
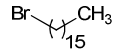
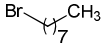
Table 1. Screening of chiral catalysts for enantioselectivity

Entry	Temp (°C)	50% Base[a] in water (w/v)	Catalyst	Mol % of Catalyst	Yield[b] (%)	ee[c] (%)
1	rt	0.5 ml	sT1	2	74	22
2	rt	"	sT1	5	76	28
3	rt	"	sT1	10	76	46
4	10	"	sT1	2	72	48
5	10	"	sT1	5	68	52
6	10	"	sT1	10	58	60
7	0	"	sT1	2	74	48
8	0	"	sT1	5	60	60
9	0	"	sT1	10	85	70
10	-10	"	sT1	2	53	72
11	-10	"	sT1	5	58	76
12	**-10**	"	**sT1**	**10**	**90**	**82**
13	-10	0.24 gm pallates	sT1	10	40	50
14	-10	"	sT2	2	59	26
15	-10	"	sT2	5	70	38
16	-10	"	sT2	10	65	39
17	-10	"	sT3	2	58	28
18	-10	"	sT3	5	68	50
19	-10	"	sT3	10	68	38
20	-10	"	------	------	52	rac[e]

[a] 50% KOH aqueous solution (5 gm dissolved in water and make up 10 ml KOH solution) [b]Experimental yield, [c]Determined by HPLC using CHIRALCEL OD-H column. [e]Racemic Mixture chromatogram shown in supporting information **S26**

Then, we investigated the affect of other two chiral ammonium quaternary salts **sT2** and **sT3** (**Table 1**, **Entries 14-19**) under the similar reaction conditions. It is noticed that piperidine and pyrrolidine derived catalysts **sT2** and **sT3** using 10 mol % at -10 °C gave a reduced enantiomeric excess (ee) in comparison to *N*-alkyne and *N*-benzyl derived catalyst **sT1.** It is obvious from the analysis of table **1** that the chiral ammonium salt **sT1** was found most promising PTC among all. In conclusion, the reaction performed with an excess of electrophile in the presence of 10 mol % of **sT1** at -10 °C was found to be the suitable condition for asymmetric alkylation of glycinate Schiff base (**Table 1**, **Entry 12**). This optimized reaction condition were used (**Table 1, Entry 12**) for the alkylation of glycinate Schiff base **3** with different electrophiles and hydrolyzed alkylated product 4 to get corresponding products (**5-14**) in better enantioselectivity given in table **2**.

Table 2. Scope of the α-alkylation of benzophenone glycinate Schiff base using different electrophiles

Entry	Electrophile (RBr)	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1		5	3.5	75	95
2		6	3.5	85	89
3		7	4.5	90	82
4		8	6.0	67	81
5		9	4.5	55	75
6		10	5.5	85	85
7		11	5.5	80	77
8		12	4.5	76	68
9		13	4.5	90	83
10		14	4.5	85	90

[a]Reaction of prochiral substrate 3 with electrophiles, [b]Experimental yield, [c]Determined by HPLC using CHIRALCEL OD-H column.

The possible role of new catalyst in asymmetric synthesis is presented in figure **1**. It is stipulated that PTC's (sT1) s-triazene nitrogen is hydrogen bonded with hydrogen of hydroxyl group of the E-enolate (glycinate Schiff base). *s*-Triazene form guanidine type moiety with cationic nitrogen and stabilize this complex. The benzylic groups of the catalyst lie in one plane which possibly get coordinated to the phenyl rings of the benzophenone Schiff base through π-π interactions.[20] Hydrogen atom of alkyne is then bonded with the nitrogen of Schiff base that stabilized transition state. Formation of this transition state allow the electrophile to attack the prochiral centre in a 'trans' direction to generate asymmetric centre. Thus, the choice of benzyl group and alkyne group are crucial in designing of newer catalyst with respect to enantioselectivity.

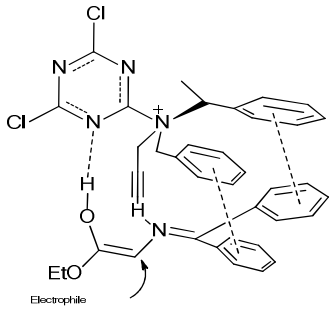


Figure 1. Proposed transition state of catalyst with substrate 3.

Conclusions

In conclusion, we designed and synthesized new efficient s-triazene based N-quaternary ammonium salts sT1, sT2 and sT3 as phase transfer catalysts (PTCs) and used efficiently to alkylate glycinate Schiff base to produce natural and unnatural α-amino acids. The asymmetric catalytic potential of these compounds in the asymmetric α-alkylation of glycinate Schiff base depends on their substituent's and reaction conditions. Under optimized conditions, the α-alkylated products could be obtained in excellent yields and up to 95% ee. More enantioselective applications of catalysts are under progress.

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Notes and references

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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