Review

Catalytic asymmetric synthesis of α-amino acid derivatives and peptides using chiral phase-transfer catalysts

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Abstract: Structurally rigid, chiral spiro ammonium salts of type (R,R)- or (S,S)-1 derived from commercially available (R)- or (S)-1,1'-bi-2-naphthol have been designed as new C2-symmetric chiral phase transfer catalysts and successfully applied to the highly efficient, catalytic enantioselective alkylation of tert-butyl glycinate Schiff base under mild phase transfer conditions to furnish α-alkyl-α-amino acids and α, α-dialkyl-α-amino acids with excellent enantioselectivity. These catalysts have been also utilized for the asymmetric terminal functionalization of peptides and asymmetric direct aldol reaction of glycine derivatives.

Key words: Phase transfer catalyst; asymmetric alkylation; α-amino acid; tert-butyl glycinate; aldol.

Introduction. The α-amino acids, which are usually formulated as H2NCH(R)CO2H despite their zwitterionic nature, are by far the most important, numerous, and diverse family of the naturally occurring amino acids. A wide variety of methods, which are in principle general, are available for the synthesis of α-amino acids.1) Despite the great variety of the well-tried methods, the development of new general strategies is still an active field. Accordingly, considerable effort has been paid in the development of asymmetric methodologies by certain chiral catalysts in the α-amino acid field. Our purpose in this area is the rational design of chiral phase-transfer catalysts and their practical application to the catalytic asymmetric synthesis of a wide variety of α-amino acid derivatives.2,3)

Asymmetric alkylation of glycine derivatives for α-alkyl-α-amino acid synthesis. Asymmetric synthesis of α-amino acids by phase-transfer alkylation using a chiral catalyst and a prochiral protected glycine derivative would provide a particularly attractive method for the preparation of optically active α-amino acids.4) However, most of the elaborated chiral phase-transfer catalysis for the asymmetric synthesis of amino acids using prochiral glycine derivative as a key substrate rely on the use of cinchona alkaloid derivatives, which unfortunately constitutes a major difficulty of the structural modifications, especially upon considering fine-tuning of catalysts to attain sufficient reactivity and selectivity.5) In this context, the structurally rigid, chiral spiro ammonium salts of type 1 derived from commercially available (S)- or (R)-1,1'-bi-2-naphthol have been designed as new C2-symmetric chiral phase-transfer catalysts and successfully applied to the highly efficient, catalytic asymmetric synthesis of various α-amino acids under mild phase-transfer conditions.5)
zene (volume ratio = 1:3) at room temperature and the corresponding benzyl product was obtained in 76% yield with 73% ee (R) (entry 1 in Table 1). An introduction of an aromatic substituent (Ar) on the 3,3'-position of one bismaphthyl subunit of the catalyst afforded a beneficial effect on the enantiofacial discrimination as the reaction with (S,S)-1b resulted in formation of the product in 43% yield with 81% ee (entry 2). Use of toluene as organic solvent at lower reaction temperature (0°C) led to even higher enantioselectivity (88% ee) (entry 3). Moreover, the reaction under the influence of (S,S)-1b was completed within 30 min at 0°C with 50% KOH as an aqueous base giving the product in 82% yield with 89% ee (entry 4). Switching the catalyst to (S,S)-1c and stericly more hindered (S,S)-1d further increased the enantioselectivity to 96% ee and 98% ee, respectively (entries 5 and 6), and virtually complete stereoregular control was achieved using (S,S)-1e as catalyst (entry 8). The lower chemical yield of the benzyl product with (S,S)-1e was ascribed to the intervention of enolate oxidation by aerobic oxygen and this problem was overcome by simply performing the reaction under argon atmosphere (entry 9). Notable advantage of this method is that the catalyst loading can be reduced to 0.2 mol% without loss of enantiomeric excess (entries 7 and 10).\(^6\)

(S,S)-1e is the catalyst of choice for the preparation of a variety of essentially enantiopure \(\alpha\)-amino acids by this transformation. Facile asymmetric synthesis of \(\alpha\)-amino acids usually inaccessible by enzymatic processes becomes feasible by employing appropriate electrophiles such as ortho-disubstituted benzyl bromides. In the reaction with the simple alkyl halides such as ethyl iodide, use of aqueous cesium hydroxide (CsOH) as a basic phase at lower reaction temperature is generally recommended.\(^5\)

Since both enantiomers of the catalyst of type 1 can be readily assembled in exactly the same manner starting from either (R)- or (S)-1,1'-bi-2-naphthol, a wide variety of natural and unnatural \(\alpha\)-amino acids can be synthesized in an enantiomerically pure form by the phase-transfer catalytic alkylation of \(N\)-(diphenylmethyleneglycine tert-butyl ester. The utility of such advantage has been demonstrated by asymmetric synthesis of (S)-\(N\)-acetylindoline-2-carboxylate 3, a key intermediate in the synthesis of the ACE inhibitor 4. The structure and stereochemical integrity of 2 was simultaneously constructed by the asymmetric alkylation of \(N\)-(diphenylmethyleneglycine tert-butyl ester with o-bromobenzyl bromide in the presence of the catalyst \((R,R)\)-1e, and subsequent hydrolysis with citric acid and \(N\)-acetylation afforded 2 in 86% yield with 99% ee (S). According to the Buchwald’s procedure,\(^7\) almost enantiopure 2 was efficiently converted to 3 (94%, 99% ee).\(^6\)

The synthetic utility of chiral phase-transfer catalysis using 1 was further highlighted by the facile synthesis of L-Dopa ester and its analogue, which have usually been prepared by either asymmetric hydrogenation of enamine or enzymatic processes and tested as potential drugs for the treatment of Parkinson’s disease. Catalytic phase-transfer alkylation of \(N\)-(diphenylmethyleneglycine tert-butyl ester with the requisite benzyl
bromide 5a in toluene-50% KOH aqueous solution proceeded smoothly at 0°C under the influence of (R,R)-1e (1 mol%) to furnish fully protected L-Dopa tert-butyl ester, which was subsequently hydrolyzed with 1 M citric acid in THF at room temperature for 10 h to afford the corresponding amino ester 6a in 81% yield with 99% ee. Debenzylation of 6a under catalytic hydrogenation conditions produced the desired L-Dopa tert-butyl ester (7a) in 94% yield. The successful asymmetric synthesis of natural tyrosine tert-butyl ester (7b) in a similar manner strongly implies the feasibility of highly enantioselective synthesis of various L-Dopa analogues. Furthermore, a “scale-up” experiment with 5.00 g of the starting Schiff base and 7.77 g of 5a was performed to provide 3.37 g of the desired L-Dopa tert-butyl ester (7a).^{31}

Treatment of N-(diphenylmethane)glycine tert-butyl ester with α,α′-dibromo-o-xylene (1.1 equiv) in toluene-50% KOH aqueous solution (volume ratio = 2:1) in the presence of (S,S)-1e (1 mol%) at 0°C for 6 h showed complete consumption of the starting Schiff base. Acidic hydrolysis with 1 N HCl and subsequent treatment of the in situ generated primary amine moiety with excess amount of NaHCO₃ facilitated intramolecular ring closure to give 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid tert-butyl ester (8) in 82% yield with 98% ee. A variety of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives possessing different aromatic substituents such as 9 and 10 can be conveniently prepared in a similar manner with excellent enantioselectivity.^{30}

Moreover, the catalytic and chiral efficiency of (S,S)-1e has been successfully applied to the asymmetric synthesis of isouquinoline derivatives, important conformationally constrained α-amino acids to be incorporated into peptidic or nonpeptidic structures, giving useful information for SAR analysis and, eventually, for the development of compounds with improved biological activity.

Although the conformationally rigid, N-spiro structure created by two chiral binaphthyl subunits represents a characteristic feature of 1 and seems essential for attaining sufficient reactivity and enantioselectivity, it also imposes limitations on the catalyst design due to the imperative use of the two chiral binaphthyl moieties. Accordingly, we developed a new C₂-symmetric chiral quaternary ammonium bromide 11 possessing an achiral, conformationally flexible biphenyl subunit.^{30}
The phase-transfer benzylolation of \(N\)-(diphenylmethylene)glycine \(tert\)-butyl ester with the catalyst 11a having \(\beta\)-napthyl group on 3,3'-position of the flexible biphenyl moiety was found to proceed smoothly at 0°C to afford the corresponding alkylation product in 85% yield with 87% ee (\(R\)) after 18 h. The origin of the observed chiral efficiency could be ascribed to the considerable difference of catalytic activity between the rapidly equilibrated, diastereomeric homo- and heterochiral catalysts; namely, homochiral 11a is primarily responsible for the efficient asymmetric phase-transfer catalysis to produce the alkylation product with high enantiomeric excess, whereas heterochiral 11a displays low reactivity and stereoselectivity. A supportive evidence for this hypothesis was that the benzylolation with 1 mol% of conformationally rigid, heterochiral (\(R,S\))-1c under similar conditions proceeded slowly, and, after 60 h, gave rise to the corresponding alkylation product in 47% yield with low enantiomeric excess (11% ee, \(R\)).

Asymmetric alkylation of glycine derivatives for \(\alpha,\alpha\)-dialkyl-\(\alpha\)-amino acid synthesis. Nonproteinogenic \(\alpha,\alpha\)-dialkyl-\(\alpha\)-amino acids have played a special role in the design of peptides with enhanced properties. This is not only because they possess stereochemically stable carbon centers, but their incorporation into peptides results in the significant influence on the conformational preferences, which eventually provides useful information for the elucidation of enzymatic mechanisms. Furthermore, \(\alpha,\alpha\)-dialkyl-\(\alpha\)-amino acids themselves are often effective enzyme inhibitors and also constitute a series of interesting building blocks for the synthesis of various biologically active compounds. Accordingly, development of truly efficient methods for their preparation, especially in an enantioselectively pure form, has become of great importance and numerous studies have been made for this purpose.\(^{10,11}\)

We envisioned that two different side chains could be introduced directly to the aldime Schiff base 12 derived from glycine in a highly enantioselective manner by appropriate chiral phase-transfer catalysis. This pos-
sibility of the one-pot asymmetric double alkylation has been realized by using C2-symmetric chiral quaternary ammonium bromide (S,S)-1 whose effectiveness for the asymmetric synthesis of α-alkylamino acids has already been demonstrated in the previous section.12

Initial treatment of the toluene solution of 12 and (S,S)-1c (1 mol%) with allyl bromide (1 equiv) and CsOH·H2O (5 equiv) at −10 °C for 3.5 h and the subsequent reaction with benzyl bromide (1.2 equiv) at 0 °C for 30 min resulted in formation of the double alkylation product 13 (R1 = CH2CH=CH2, R2 = CH2Ph) in 61% yield with 87% ee after hydrolysis. It is of interest that the use of (S,S)-1g as catalyst under similar conditions enhanced both chemical yield and enantioselectivity to 80% and 98% ee, respectively. The distinct feature of this procedure is that it enables straightforward asymmetric synthesis of various α,α-dialkyl-α-amino acids including those otherwise inaccessible from the naturally occurring amino acids. Notably, in the double alkylation of 12 by the addition of the halides in a reverse order, the absolute configuration of the product 13 was confirmed to be opposite, indicating the intervention of the expected chiral ammonium enolate in the second alkylation stage.

\[
\begin{align*}
\text{R}^2\text{X} & \quad \text{R}^3\text{X} \\
\text{Br} & \quad \text{Br} \\
\text{PhCH}2\text{Br} & \quad \text{Br} \\
\text{PhCH}2\text{Br} & \quad \text{PhCH}2\text{Br}
\end{align*}
\]

Since the stereochemistry of the newly created carbon center was apparently determined in the second alkylation process, the core of this method should be applicable to the asymmetric alkylation of aldazine Schiff base 14 derived from the corresponding α-amino acids. Indeed, rapid benzylolation of dl-alanine-derived imine 14a occurred at 0 °C in toluene with benzyl bromide (R1 = CH2Ph) (1.2 equiv) and CsOH·H2O (5 equiv) using (S,S)-1e (1 mol%) as a catalyst, giving the alkylation product 13 (R1 = Me, R2 = CH2Ph; 85%) in an almost enantiomerically pure form (98% ee). Other selected results illustrated below demonstrate the remarkable efficiency and generality of this method. Use of tert-butyl α-bromoacetate as an alkylation agent allows facile enantioselective access to α-methyl aspartic acid and asymmetric synthesis of α-methyl tryptophan, an important amino acid for the design of dipeptidyl with high affinity for the central cholecystokinin receptor, can also be realized. In addition, the phase-transfer catalytic alkylation of aldazine Schiff base derived from other α-amino acids such as dl-phenylalanine and dl-leucine also appeared to be feasible with high efficiency, providing the desired non-coding amino acid esters 13 with excellent asymmetric induction.13

![Diagram of chemical reaction]

This powerful method enabled the hitherto difficult catalytic asymmetric synthesis of isoquinoline derivatives with 14a as a substrate. When 14a was treated with α,α'-dibromo-o-xylene, CsOH·H2O (5 equiv) and (S,S)-1e (1 mol%) in toluene at 0 °C for 0.5 h, the transient monoalkylation product was rapidly produced, which was transformed into the desired 16a (64%, 88% ee) during workup procedure. The efficiency of this alkylation-cyclization sequence was scarcely affected by the substituent of the starting α-amino acid as demonstrated by the reactions with 14b and 14c. Catalytic asymmetric phase-transfer alkylation of 14a with functionalized benzyl bromide 15 (1.1 equiv) followed by the sequential treatment with 1 N HCl and then excess NaHCO3 furnish the corresponding dihydroisoquinoline derivative 17a in 87% with 94% ee. The sensitivity of this system involving intramolecular imine formation to the steric demand of α-substituent of the parent amino acid was implied by the decreased chemical yield and enantioselectivity observed in the reaction of 14b.15
**Diastereoselective peptide alkylation.** Peptide modification is an essential yet flexible synthetic concept for efficient target screening and optimization of lead structures in the application of naturally occurring peptides as pharmaceuticals. The introduction of side chains directly to a peptide backbone represents a powerful method for the preparation of unnatural peptides. A chiral glycine subunit has generally been used for this purpose. However, the control of the stereochemical outcome of these processes in an absolute sense is a difficult task, especially in the modification of linear peptides, and hence development of an efficient and practical approach to establish sufficient stereoselectivity and general applicability has been an issue of central importance.

We envisaged that chiral phase-transfer catalysts should play a crucial role in achieving an efficient chirality transfer, and examined the alkylation of the dipeptide, Gly-L-Phe derivative 18a as a representative system. When a mixture of 18a and tetrabutylammonium bromide (TBAB, 2 mol%) in toluene was treated with 50% KOH aqueous solution and benzyl bromide (1.1 equiv) at 0 °C for 4 h, the corresponding benzylated product 19a was obtained in 85% yield with the diastereomeric ratio (DL-19a:LL-19a) of 54:46 [8% diastereomeric excess (de)] (Fig. 1). In contrast, the reaction with chiral quaternary ammonium bromide (S, S)-1c under similar conditions gave rise to 19a with the DL/LL ratio of 77.5:22.5 (55% de, 88% yield). The preferential formation of LL-19a in lower de (20%) in the reaction with enantiomeric (R, R)-1c indicates that (R, R)-1c is a mismatched catalyst for this diastereofacial differentiation of 18a. Changing the 3,3'-aromatic substituent (Ar) of the catalyst dramatically increased the stereoselectivity and almost complete diastereoccontrol was achieved with (S, S)-1g possessing 3,5-bis(3,5-di-tert-butylphenyl)phenyl group (97% de).

A variety of alkyl halides can be employed as an electrophile in this alkylation as summarized in Table II (entries 1-5).14 The efficiency of the transmission of stereochemical information was not affected by the side chain structure of the pre-existing amino acid residues, as demonstrated in the phase-transfer benzylation of various dipeptides derived from natural α-amino acids (entries 6-9). Interestingly, sterically less demanding (S, S)-1f was found to be a suitable catalyst for the substrate possessing L-proline tert-butyl ester moiety (entry 10).

Further, this method allowed an asymmetric construction of noncoded a,a-diaryl-α-amino acid residues at the peptide terminal as exemplified by the stereoselective alkylation of the dipeptide, L-Ala-L-Phe derivative 20.
Table II. Stereoselective N-terminal alkylation of dipeptides by chiral phase-transfer catalysis

<table>
<thead>
<tr>
<th>Entry</th>
<th>AA</th>
<th>RX</th>
<th>% yield</th>
<th>% de</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phe</td>
<td>Br</td>
<td>89</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>C=Br</td>
<td>80</td>
<td>96</td>
</tr>
<tr>
<td>3*</td>
<td>CH₃CH₂I</td>
<td>90</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>Br</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td>5*</td>
<td></td>
<td>S=Br</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>Leu</td>
<td>PhCH₂Br</td>
<td>91</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>Val</td>
<td></td>
<td>85</td>
<td>93</td>
</tr>
<tr>
<td>8</td>
<td>Tyr(Bn)</td>
<td></td>
<td>90</td>
<td>98</td>
</tr>
<tr>
<td>9</td>
<td>Ala</td>
<td></td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>10</td>
<td>Pro</td>
<td></td>
<td>80</td>
<td>90**</td>
</tr>
</tbody>
</table>

* Use of sat. CsOH as an aqueous base. ** With (S,S)-1f as catalyst.

The chiral phase-transfer catalysis with (S,S)-1g can be successfully extended to the stereoselective N-terminal alkylation of Gly-Ala-Phe derivative 22, i.e., asymmetric synthesis of tripeptides, where striking reversal of the stereochemical preference was observed. The benzylolation of LL-22 with (S,S)-1g under the optimized conditions resulted in poor diastereoselectivity (20% de) with LLL-23 as a major product, and the selectivity was enhanced to 93% de (89% yield) by the use of (R,R)-1g as a catalyst. In addition, (S,S)-1g turned out to be a matched catalyst in the benzylolation of DL-22, leading to almost exclusive formation of DDL-23 under similar conditions.

This tendency for stereochemical communication was consistent in the phase-transfer alkylation of DDL-24 and the corresponding protected tetrapeptide DDDL-25 was obtained in 90% yield with excellent stereochemical control (94% de). It was also confirmed that similar alkylation of LLL-24 with (R,R)-1g as a catalyst furnished LLLLL-25 in 87%, 92% de, suggesting that (R,R)-1g is suitable for the stereoselective N-terminal alkylation of naturally occurring polypeptides.¹⁴

Fig. 1. Effect of achiral or chiral catalyst on the diastereomeric ratio.

![Graph showing diastereomeric ratio](image-url)
Asymmetric direct aldol reaction of glycine derivatives. Although phase-transfer catalytic enantioselective direct aldol reactions of glycine donor with aldehyde acceptors could provide an ideal method for the simultaneous construction of the primary structure and stereochemical integrity of β-hydroxy-α-amino acids, extremely important chiral units, especially from the pharmaceutical viewpoint, the examples reported to date are very limited.

Recently, we disclosed an efficient, highly enantioselective direct aldol reaction of glycine Schiff base with aldehydes under phase-transfer conditions using C₅-symmetric chiral quaternary ammonium salt L. Treatment of N-(diphenylmethylene)glycine tert-butyl ester with 3-phenylpropanol (2 equiv) in toluene-1% NaOH aqueous solution (volume ratio = 1.25:1; 2 equiv of base for Schiff base) in the presence of (R,R)-1h (2 mol%) at 0°C for 2 h and subsequent hydrolysis with 1 N HCl in THF resulted in the formation of the corresponding β-hydroxy-α-amino ester 26 in 76% isolated yield with the anti/syn ratio of 3:3:1, and the enantiomeric excess of the major anti isomer was determined to be 91% ee. Interestingly, use of (R,R)-1i possessing 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl substituent as a catalyst enhanced both diastereo- and enantioselectivities (anti/syn = 12:1, 96% ee for anti isomer).

The potential synthetic utility of this procedure has been demonstrated by the direct asymmetric synthesis of various useful β-hydroxy-α-amino esters. Heptanal was found to be a good candidate, indicating the feasibility of direct asymmetric synthesis of a variety of lipo β-hydroxy-α-amino acids, a useful component for the preparation of lipopholic peptides and glycopolypeptides possessing the characteristic properties of high enzymatic stability and enhanced drug transport activity. The reaction with α-trisopropylsiloxyacetaldehyde cleanly produced the desired β-hydroxy-α-amino ester in 72% yield with virtually complete stereochemical control (98% ee, anti/syn = 20:1), which parallels the L-threonine aldolase-catalyzed aldol reaction utilized for the synthesis of monobactam antibiotic carubaman and analogues. A key building block for the synthesis of carbapenem antibiotic loracarbef, previously prepared by a chemo-enzymatic process with serine hydroxymethyltransferase (SHMT), was readily assembled with 4-pentenal as acceptor, where (R,R)-1h was rather beneficial than (R,R)-1i to obtain higher enantioselectivity. It was also found that L-allo-threonine ester can be obtained by
the reaction with acetaldehyde using (R,R)-1h, confirming that the absolute configuration of the α-stereocenter newly created in this transformation is (S). Notably, this method allows a facile preparation of unnatural D-allo-threonine because of the ready availability of the enantiomeric catalyst (S,S)-1h.

**Conclusion.** Enantioselective synthesis of α-amino acids has been greatly advanced by the creation of new chiral phase-transfer catalysts, which maximize the characteristic features of the central quaternary ammonium cations. Indeed, such phase-transfer catalyzed enantioselective syntheses of α-amino acids are very useful in practical synthesis, and their applications are illustrated in numerous papers. The enantioselective reactions described in this review clearly demonstrate the high ability and great potential of chiral phase-transfer catalysis to synthesize various types of chiral α-amino acid derivatives.

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**References**


