Design of chiral organocatalysts for practical asymmetric synthesis of amino acid derivatives

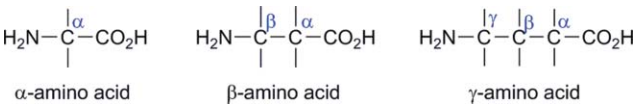
Keiji Maruoka,* Takashi Ooi and Taichi Kano

Received (in Cambridge, UK) 8th September 2006, Accepted 22nd November 2006
First published as an Advance Article on the web 8th December 2006
DOI: 10.1039/b613049f

A series of structurally rigid, chiral quaternary ammonium salts and several chiral *sec*-amine catalysts derived from commercially available (*R*)- or (*S*)-binaphthol have been designed as new C_2-symmetric chiral phase-transfer catalysts and chiral bifunctional amino-catalysts. These chiral organocatalysts have been successfully applied to the highly practical asymmetric synthesis of various amino acid derivatives.

1 Introduction

Amino acids represent compounds possessing both amino and carboxyl functionalities, and they generally include α-amino acids, β-amino acids, γ-amino acids, *etc*.[1] An investigation has shown that ~18% of the top 500 best selling drug products in the world use α-amino acids as pharmaceutical intermediates. In addition, some of the drugs originate from β-amino acids, γ-amino acids, *etc*. Accordingly, amino acids are indispensable for the preparation of drugs, and have become the mainstream of medicinal products.



Among these, α-alkyl-α-amino acids are by far the most important, numerous, and diverse family of the naturally occurring amino acids. Although a set of only 20 amino acids comprises polypeptide chains under genetic control, the total number of α-amino acids identified as occurring free or incorporated in natural products of animals, plants and microorganisms is estimated in hundreds, and the list of such α-amino acids grows all the time. The majority of these naturally found α-alkyl-α-amino acids have the L configuration at the α-carbon. Many natural α-alkyl-α-amino acids of the D series are also encountered in non-protein compounds of plants, fungi and microorganisms, but not generally in animals and never in any protein. In contrast to these α-alkyl-α-amino acids, nonproteinogenic α,α-dialkyl-α-amino acids have played a special role in the design of peptides with enhanced properties. This is not only because they possess stereochemically stable quaternary carbon centers, but their incorporation into peptides results in a significant influence in conformational preferences. Furthermore, α,α-dialkyl-α-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 the preparation of various α-amino acids as well as β- and γ-amino

Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502, Japan.
E-mail: maruoka@kuchem.kyoto-u.ac.jp;
Fax: 081 75-753-4041; Tel: 081 75-753-4041

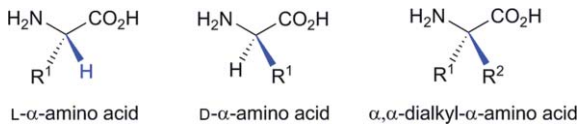
Keiji Maruoka

Keiji Maruoka was born in 1953 in Mie, Japan. He graduated from Kyoto University (1976) and received his PhD (1980) from University of Hawaii. He became an Assistant Professor of Nagoya University (1980) and an Associate Professor (1990) there. He moved to Hokkaido University as a Full Professor (1995–2001), and currently is a Professor of Chemistry in Kyoto University since 2000. He has a wide range of research interests in synthetic organic chemistry. His current research interests include bidentate Lewis acids in organic synthesis and practical asymmetric synthesis with designer chiral organocatalysts including chiral C_2-symmetric phase-transfer catalysts and chiral amino-catalysts.

Takashi Ooi

Takashi Ooi was born in 1965 in Nagoya, Japan. He received his PhD (1994) from Nagoya University and spent his post-doctoral period at MIT (1994–1995). He was appointed as an Assistant Professor at Hokkaido University in 1995 and promoted to a Lecturer (1998). In 2001 he moved to Kyoto University as an Associate Professor, and is currently a Full Professor of Chemistry at Nagoya University since 2006. His research interests are focused on the development of new and useful synthetic methodologies based on the design of organic molecular catalysts including chiral C_2-symmetric quaternary ammonium salts.

acids, especially in an enantiomerically pure form, has become of great importance. However, despite numerous studies only a few catalytic systems have been reported with limited general applicability. In this context, we were interested for some time in the possibility of effecting the practical asymmetric synthesis of these useful amino acids and their derivatives. In this article, we wish to review our recent achievements on this subject on the design of certain chiral organocatalysts which possess environmentally benign properties. Among various organocatalysts, our attention has been particularly focused on the design of a series of novel phase-transfer catalysts and bifunctional amino-catalysts.

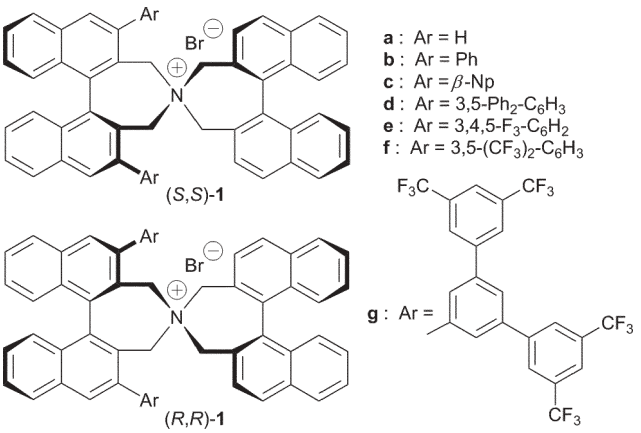


2 Design of spiro-type chiral phase-transfer catalysts

2.1 Asymmetric synthesis of α-alkyl-α-amino acids

Since the initial work of O'Donnell *et al.* in 1989,[2] asymmetric synthesis of α-amino acids by phase-transfer enantioselective alkylation of prochiral protected glycine derivatives using a chiral catalyst has become an attractive method for the preparation of both natural and unnatural amino acids.[3] However, when we started asymmetric phase-transfer chemistry in 1998, almost all the elaborated chiral phase-transfer catalysts had been restricted to *cinchona* alkaloid derivatives, which unfortunately constituted a major difficulty in rationally designing and fine-tuning of catalysts to attain sufficient reactivity and selectivity. 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 by our group as a new C_2-symmetric chiral phase-transfer catalyst (Scheme 1) and successfully applied to the highly efficient, catalytic enantioselective synthesis of various α-amino acids under mild phase-transfer conditions.[4]

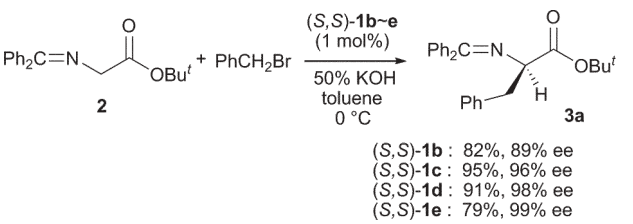
An initial attempt was made on the benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester **2** with 1 mol% of symmetric (*S*,*S*)-**1a** in 50% aqueous NaOH–benzene



Scheme 1 Designer chiral phase-transfer catalysts.

(volume ratio = 1 : 3) at room temperature and the corresponding benzylation product **3a** was obtained in 76% yield with 73% ee. Introduction of aromatic substituents (Ar) on the 3,3′-position of one binaphthyl subunit of the catalyst afforded a beneficial effect on the enantiofacial discrimination since the reaction of **2** with (*S*,*S*)-**1b** resulted in formation of **3a** in 43% yield with 81% ee. Moreover, the reaction in toluene as organic solvent 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 **3a** in 82% yield with 89% ee (Scheme 2). Switching the catalyst to (*S*,*S*)-**1c** and sterically more hindered (*S*,*S*)-**1d** further increased the enantioselectivity to 96 and 98% ee, respectively, and virtually complete stereochemical control was achieved using (*S*,*S*)-**1e** as catalyst.[5,6] The lower chemical yield (79%) with (*S*,*S*)-**1e** was ascribed to the intervention of enolate oxidation by aerobic oxygen and was improved to 90% by simply performing the reaction under argon atmosphere. A notable advantage of this method is that in the case of a reactive alkyl halide, the catalyst loading can be reduced to 0.2 mol% without loss of enantiomeric excess.[6] (*S*,*S*)-**1e** is the catalyst of choice for the preparation of a variety of essentially enantiopure α-amino acids by this transformation as shown in Scheme 3. Facile asymmetric synthesis of α-amino acids, usually inaccessible by enzymatic processes, becomes feasible by employing appropriate electrophiles such as *ortho*-disubstituted benzyl bromides. In the reaction with simple alkyl halides such as ethyl iodide, use of aqueous caesium hydroxide (CsOH) as a basic phase at lower reaction temperature is generally recommended.[6]

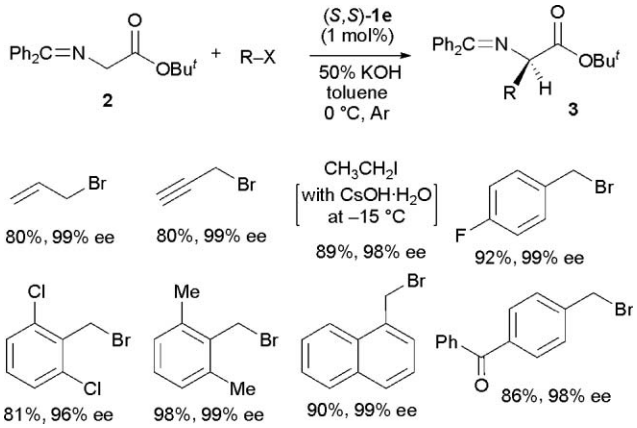
Since both enantiomers of the catalyst of type **1** can be readily assembled in exactly the same manner starting from



Scheme 2 Asymmetric benzylation of glycine derivative **2** with (*S*,*S*)-**1b–e**.

Taichi Kano

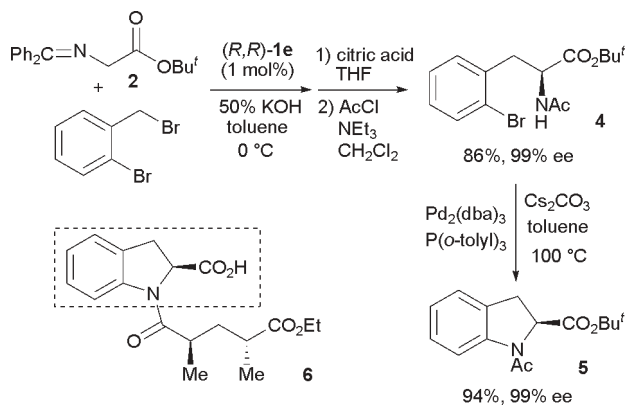
Taichi Kano was born in 1974 in Aichi, Japan. He received his PhD from Nagoya University in 2001 under the supervision of Prof. H. Yamamoto, and carried out postdoctoral research at Caltech with Prof. B. M. Stoltz. He has been an Assistant Professor at Kyoto University since 2003, working in the research group of Prof. K. Maruoka. His research interests include asymmetric synthesis with designer chiral Lewis acid catalysts and organocatalysts.



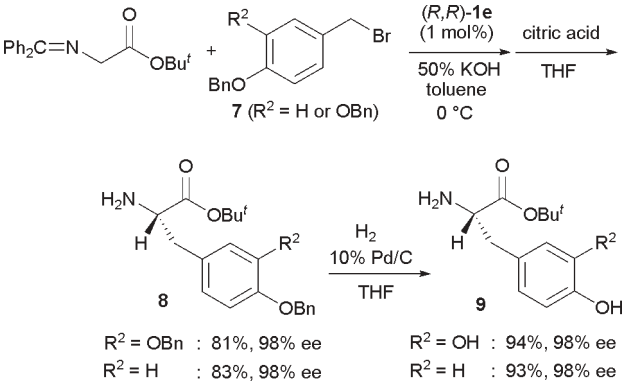
Scheme 3 Generality in the asymmetric alkylation of glycine derivative **2** with (*S*,*S*)-**1e**.

either (*R*)- or (*S*)-1,1′-bi-2-naphthol, a wide variety of natural and unnatural α-amino acids can be synthesized in an enantiomerically pure form by the catalytic phase-transfer alkylation of **2**. The utility of such an advantage has been demonstrated by the asymmetric synthesis of (*S*)-*N*-acetylindoline-2-carboxylate **5**, a key intermediate in the synthesis of the ACE inhibitor **6** (Scheme 4). The structure and stereochemical integrity of **4** was simultaneously constructed by the asymmetric alkylation of **2** with *o*-bromobenzyl bromide in the presence of the catalyst (*R*,*R*)-**1e**, and subsequent hydrolysis with citric acid and *N*-acetylation afforded **4** in 86% yield with 99% ee. According to the procedure of Buchwald and co-workers[7] almost enantiopure **4** was efficiently converted to **5** (94%, 99% ee).[6]

The synthetic utility of chiral phase-transfer catalysis of **1** was further highlighted by the facile synthesis of L-Dopa esters and analogues, which have usually been prepared by either asymmetric hydrogenation of eneamides or enzymatic processes and tested as potential drugs for the treatment of Parkinson's disease. Catalytic phase-transfer alkylation of **2** with the requisite benzyl bromide **7** (R^2 = OBn) 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 to



Scheme 4 Asymmetric synthesis of **5**, a key intermediate for the synthesis of the ACE inhibitor **6**.

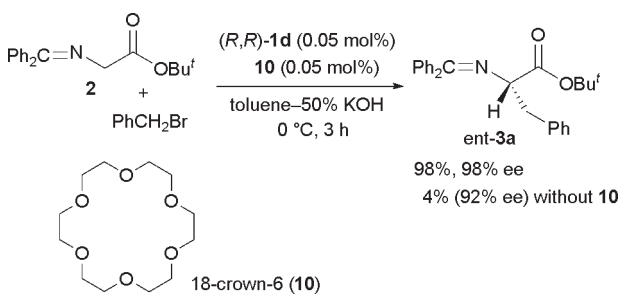


Scheme 5 Asymmetric synthesis of L-Dopa ester **9** (R^2 = OH).

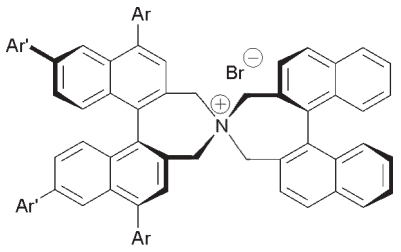
afford the corresponding amino ester **8** (R^2 = OBn) in 81% yield with 98% ee (Scheme 5). Debenzylation of **8** (R^2 = OBn) under catalytic hydrogenation conditions produced the desired L-Dopa *tert*-butyl ester **9** (R^2 = OH) in 94% yield. The successful asymmetric synthesis of natural tyrosine *tert*-butyl ester **9** (R^2 = H) in a similar manner strongly implies the feasibility of highly enantioselective synthesis of various L-Dopa analogues.[8]

To fully induce the potential catalytic activity of *N*-spiro chiral ammonium salts such as **1d**, we have developed binary phase-transfer catalysis using an appropriate achiral co-catalyst. For instance, the phase-transfer-catalyzed alkylation of **2** with benzyl bromide under the influence of (*R*,*R*)-**1d** (0.05 mol%) turned out to be sluggish to give **3a** in only 4% yield (92% ee), while similar benzylation of **2** in the presence of 18-crown-6 (**10**) (0.05 mol%) proceeded smoothly to furnish **3a** in 98% yield with 98% ee.[9] The origin of this dramatic rate enhancement would be the ability of the crown ether to extract KOH into the toluene phase, thereby accelerating otherwise slow deprotonation process (Scheme 6).

In the series of this work, introduction of 3,3′-diaryl substituents to the parent symmetrical ammonium bromide **1a** is found to be crucially important for obtaining high enantioselectivity. In this regard, we have been interested in the possibility of examining the effect of adjacent 4,4′-substituents of the catalyst rather than 3,3′-substituents in asymmetric phase-transfer alkylations.[10] Interestingly, even 4,4′-diaryl substituents of the catalysts of type **11** (Scheme 7) exhibited unexpectedly high asymmetric induction on such asymmetric phase-transfer alkylations. For example, reaction of **2** with benzyl bromide in toluene–50% aqueous KOH under the



Scheme 6 Binary phase-transfer catalysis.



(*S*,*S*)-**11a** (Ar = Ar' = Ph)
(*S*,*S*)-**11b** (Ar = Ph; Ar' = H))
(*S*,*S*)-**11c** (Ar = Ar' = 3,5-Ph_2-C_6H_3)

Scheme 7

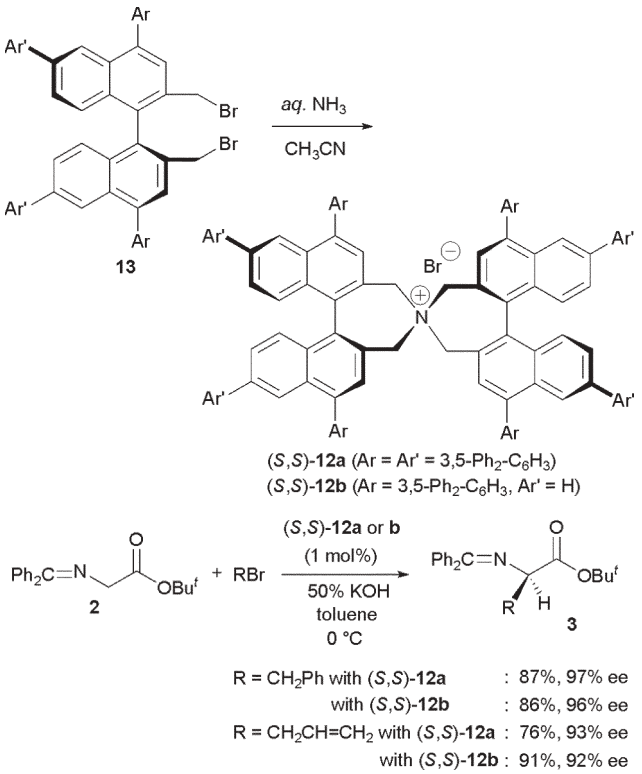
influence of 1 mol% of catalyst (*S*,*S*)-**11a** at 0 °C gave rise to benzylation product **3a** in 90% yield with 91% ee. The observed enantioselectivity is rather surprising compared to that (89% ee) using 3,3′-diphenyl-substituted **1b** under similar reaction conditions.

The 4,4′-diphenylbinaphthyl derivative (*S*,*S*)-**11b** was found to exhibit similar reactivity and a little lower selectivity compared to (*S*,*S*)-**11a** in the asymmetric alkylation of glycine derivative **2**. We also prepared the sterically more hindered 4,4′,6,6′-tetrakis(3,5-diphenylphenyl)binaphthyl analogue (*S*,*S*)-**11c** and applied it to the asymmetric alkylation of **2** to furnish the alkylation product **3** with slightly higher enantioselectivity (96% ee) and shorter reaction time (*cf.* 98% ee in the asymmetric benzylation of **2** with **1d** under similar phase-transfer conditions).

On the other hand, we were intrigued with the preparation of symmetrical *N*-spiro type catalysts to avoid the independent synthesis of two different binaphthyl-modified subunits required for **1**. Along this line, 4,4′,6,6′-tetraarylbinaphthyl-substituted ammonium bromide **12** was assembled through the reaction of aqueous ammonia with bis-bromide **13** on the basis of our study on the substituent effect of this type of salts. Evaluation of **12** as a chiral phase-transfer catalyst in the alkylation of **2** uncovered its high catalytic and chiral efficiency (Scheme 8).[11]

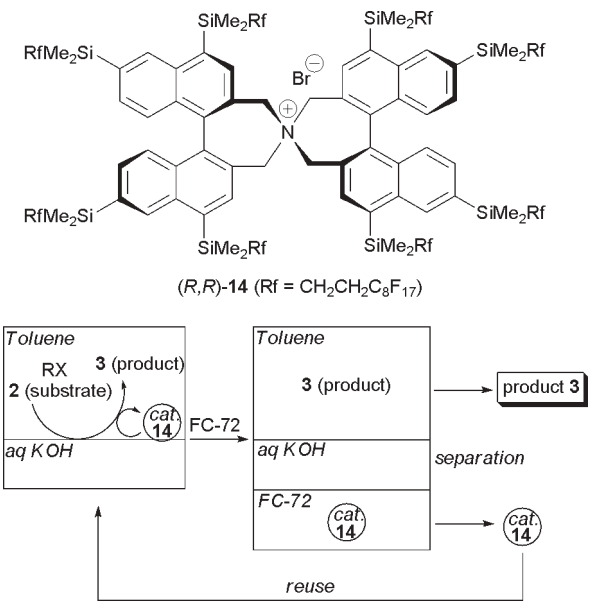
A further useful advance in the field of chiral phase-transfer chemistry would involve the design of easily recyclable catalysts. Few examples of polymer supported chiral phase-transfer catalysts derived from *cinchona* alkaloid have been reported for this purpose, however and unfortunately, almost all of these systems seriously reduced the enantioselection of the product compared with non-supported catalyst systems. In this context, we were interested in the development of fluorous chiral phase-transfer catalyst (*R*,*R*)-**14** as a recyclable catalyst (Scheme 9), since fluorous phase separation techniques for the recovery of fluorinated catalyst have been found as a most useful method in recently advanced catalyst recovery strategies. Indeed, (*R*,*R*)-**14** can be successfully applied to the catalytic asymmetric synthesis of both natural and unnatural α-amino acids, based on the asymmetric alkylation of glycine derivative, followed by extractive recovery of chiral phase-transfer catalyst by using fluorous solvent (Scheme 9).[12] The observed enantioselectivity is somewhat lower compared to the corresponding non-fluoro catalysts.

Although the conformationally rigid, *N*-spiro structure created by two chiral binaphthyl subunits represents a

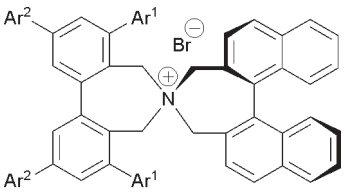


Scheme 8 Synthetic utility of symmetrical chiral *N*-spiro ammonium bromides.

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 C_2-symmetric chiral quaternary ammonium bromide **15** possessing an achiral, conformationally flexible biphenyl subunit (Scheme 10).[13]



Scheme 9 Fluorous chiral phase-transfer catalyst (*R*,*R*)-**14** as a recyclable catalyst.

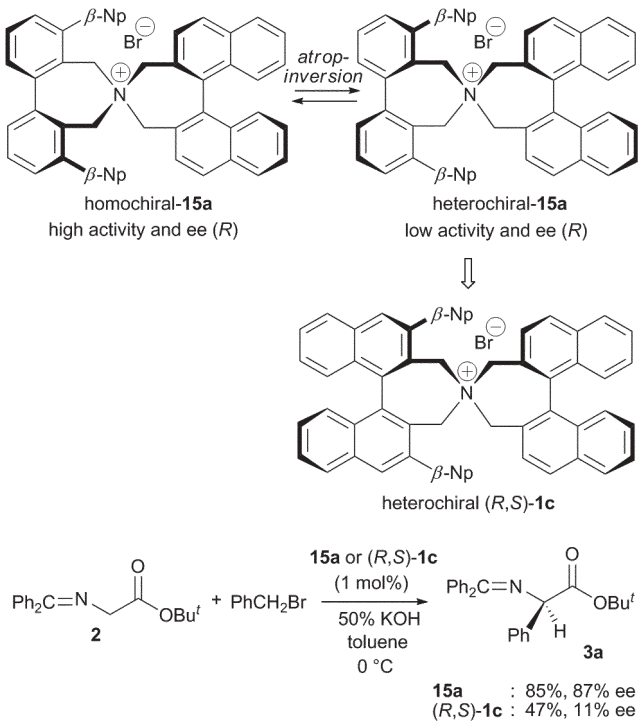


(*S*)-**15a** : Ar^1 = β-Np, R^2 = H
(*S*)-**15b** : Ar^1 = 3,5-Ph_2-C_6H_3, Ar^2 = H
(*S*)-**15c** : Ar^1 = 3,5-Ph_2-C_6H_3, Ar^2 = Ph

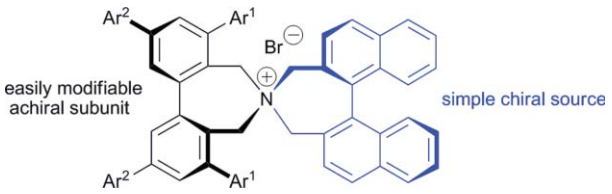
Scheme 10

The phase-transfer benzylation of **2** with the catalyst (*S*)-**15a** having a β-naphthyl group on 3,3′-position of the flexible biphenyl moiety was found to proceed smoothly at 0 °C to afford **3a** in 85% yield with 87% ee (*R*) after 18 h (Scheme 11). 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-**15a** is primarily responsible for the efficient asymmetric phase-transfer catalysis to produce the alkylation product with high enantiomeric excess, whereas heterochiral-**15a** displays low reactivity and stereoselectivity. A supportive evidence for this hypothesis was that the benzylation with 1 mol% of conformationally rigid, heterochiral (*R*,*S*)-**1c** under similar conditions proceeded slowly, and, after 60 h, gave rise to **3a** in 47% yield with low enantiomeric excess (11% ee, *R*) as also shown in Scheme 11.

This unique phenomenon provides a new, yet powerful strategy in the molecular design of chiral catalysts; *i.e.*, the requisite chirality can be served by the simple binaphthyl moiety and an additional structural requirement for fine-tuning of reactivity and selectivity can be fulfilled by an easily modifiable achiral biphenyl structure. This certainly obviates the use of two chiral units and should be greatly appreciated in the synthesis of a variety of chiral catalysts with different steric and/or electronic properties. Actually, quaternary ammonium bromides possessing a sterically demanding substituent such as (*S*)-**15b** can be easily prepared, and the benzylation of **2** with (*S*)-**15b** as a catalyst gave the alkylation product **3a** in 95% yield with 92% ee. Further, the enantioselectivity was enhanced to 95% ee when (*S*)-**15c** was used as a catalyst.[15]



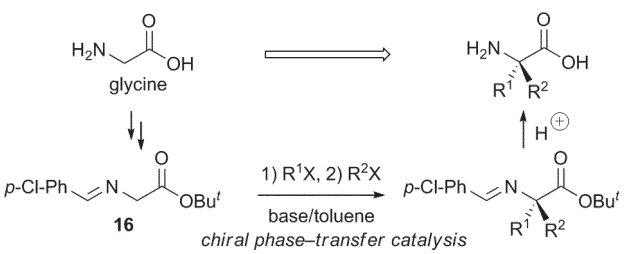
Scheme 11



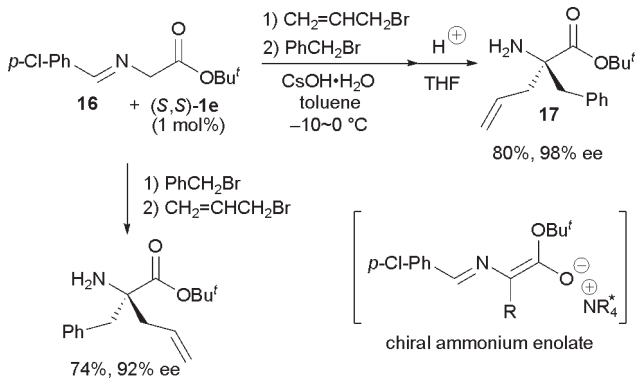
2.2 Asymmetric synthesis of α,α-dialkyl-α-amino acids

With this basic information at hand, our attention has been focused on α,α-dialkyl-α-amino acid synthesis. As already mentioned in the introductory part of the review, development of truly efficient methods for their preparation, especially in an enantiomerically pure form, has become of great importance. Accordingly, we envisioned that two different side chains could be introduced directly to the aldimine Schiff base **16** derived from glycine in a highly enantioselective manner by appropriate chiral phase-transfer catalysis (Scheme 12). This possibility of one-pot asymmetric double alkylation has been realized by using C_2-symmetric chiral quaternary ammonium bromide (*S*,*S*)-**1**.[14]

Initial treatment of a toluene solution of **16** and (*S*,*S*)-**1c** (1 mol%) with allyl bromide (1 equiv.) and $CsOH \cdot H_2O$ (5 equiv) at −10 °C and the subsequent reaction with benzyl bromide (1.2 equiv.) at 0 °C for 30 min resulted in formation of the double alkylation product **17** in 61% yield with 87% ee after hydrolysis. It is of interest that the use of (*S*,*S*)-**1e** as catalyst under similar conditions enhanced both the chemical yield and the enantioselectivity to 80 and 98% ee, respectively.[14] 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 **16** by the addition of the halides in a reverse order, the absolute configuration of the product was confirmed to be opposite, indicating the intervention of the expected



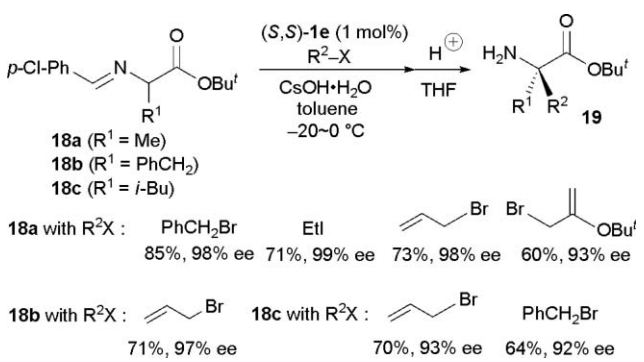
Scheme 12 New strategy for α,α-dialkyl amino acid synthesis.



Scheme 13 One-pot asymmetric double alkylation of glycine derivative **16**.

chiral ammonium enolate in the second alkylation stage (Scheme 13). This double alkylation procedure works well only for reactive alkyl halides.

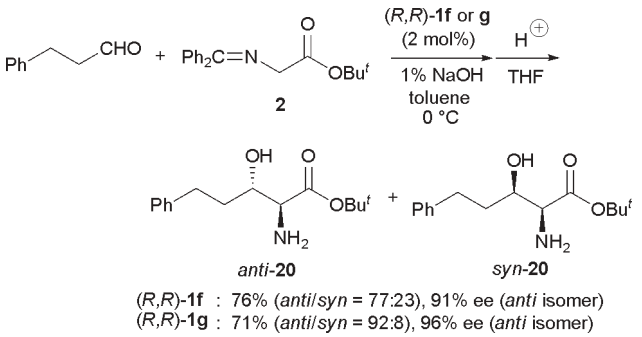
Since the stereochemistry of the newly created quaternary carbon center was apparently determined in the second alkylation process, the core of this method should be applicable to the asymmetric alkylation of aldimine Schiff base **18** derived from the corresponding α-amino acids. Indeed, rapid benzylation of DL-alanine-derived imine **18a** occurred at 0 °C in toluene with benzyl bromide (1.2 equiv.) and $CsOH·H_2O$ (5 equiv.) using (*S*,*S*)-**1e** (1 mol%) as a catalyst, giving the alkylation product **19** (R^1 = Me, R^2 = CH_2Ph; 85%) in an almost enantiomerically pure form (98% ee). Other selected results illustrated in Scheme 14 demonstrate the remarkable efficiency and generality of this method.[14] Use of *tert*-butyl α-bromoacetate as an alkylating agent allows facile enantioselective access to α-methyl aspartic acid and asymmetric synthesis of α-methyltryptophan, an important amino acid for the design of dipeptoids with high affinity for the central cholecystokinin receptor, can also be realized. In addition, the phase-transfer catalytic alkylation of the aldimine Schiff base derived from other α-amino acids such as DL-phenylalanine (**18b**) and DL-leucine (**18c**) also appeared to be feasible with high efficiency, providing the desired non-coded amino acid esters **19** with excellent asymmetric induction (Scheme 14).[14]



Scheme 14 Dialkylamino acid synthesis from α-substituted amino acid derivatives **18a–c**.

2.3 Asymmetric synthesis of β-hydroxy-α-amino acids

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. In this context, we were successfully able to realize an efficient, highly enantioselective direct aldol reaction of glycine Schiff base with aldehydes under phase-transfer conditions using the C_2-symmetric chiral quaternary ammonium salt **1**. Treatment of **2** with 3-phenylpropanal in toluene–1% NaOH aqueous solution in the presence of (*R*,*R*)-**1f** (2 mol%) at 0 °C for 2 h and subsequent hydrolysis with 1 M HCl in THF resulted in the formation of the corresponding β-hydroxy-α-amino ester **20** in 76% isolated yield with an *anti*/*syn* ratio of 77 : 23, and the enantiomeric excess of the major *anti* isomer was determined to be 91% ee. Interestingly, use of (*R*,*R*)-**1g** possessing a 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl substituent as catalyst enhanced both diastereo- and enantioselectivities (*anti*/*syn* = 92 : 8, 96% ee for *anti* isomer) (Scheme 15).[15]

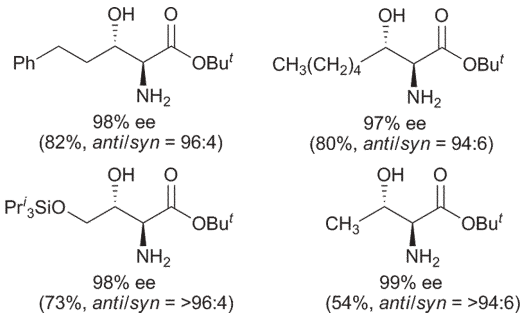


Scheme 15 Asymmetric synthesis of β-hydroxy-α-amino esters **20** by direct asymmetric aldol reaction.

The initially developed reaction conditions using 2 equiv. of aqueous base (1% NaOH aq) exhibited inexplicably limited general applicability in terms of aldehyde acceptors. For example, reaction of glycine derivative **2** with 4-benzyloxybutanal gave the aldol product with low diastereoselectivity (*anti*/*syn* = 58 : 42; 82% ee for *anti* isomer). The mechanistic investigation revealed the intervention of an unfavorable yet inevitable retro-aldol process involving chiral catalyst **1**. Based on this information, a reliable procedure has been established by use of the catalyst **1g** (2 mol%) with a catalytic amount of 1% NaOH (15 mol%) and ammonium chloride (10 mol%), which tolerates a wide range of aldehydes to afford the corresponding *anti*-β-hydroxy-α-amino esters almost exclusively in an essentially optically pure form (Scheme 16).[16]

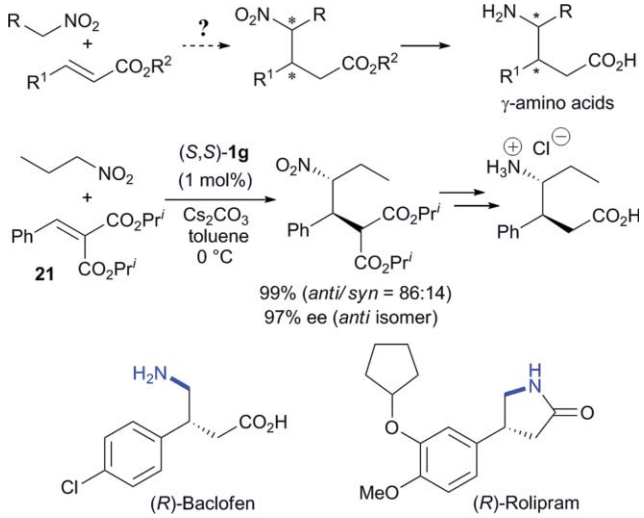
2.4 Asymmetric synthesis of γ-amino acid derivatives

Asymmetric conjugate addition of α-anions of nitroalkanes to α,β-unsaturated esters provides a useful method of preparing γ-amino acids by way of the hydrogenation of the nitro group and hydrolysis of ester moiety. However, the direct conjugate addition of α-anions of nitroalkanes to α,β-unsaturated esters



Scheme 16

is not an easy task. Accordingly, we developed the diastereo- and enantioselective conjugate addition of nitroalkanes to alkylidenemalonates **21** under mild phase-transfer conditions by using chiral quaternary ammonium bromide **1g** as an efficient catalyst (Scheme 17).[17] This new protocol offers a practical entry to the facile synthesis of optically active γ-amino acid derivatives such as (*R*)-Baclofen and (*R*)-Rolipram.

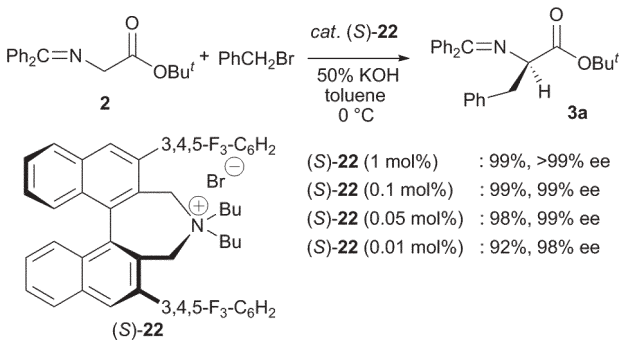


Scheme 17 Asymmetric conjugate addition of nitroalkanes to α,β-unsaturated malonates.

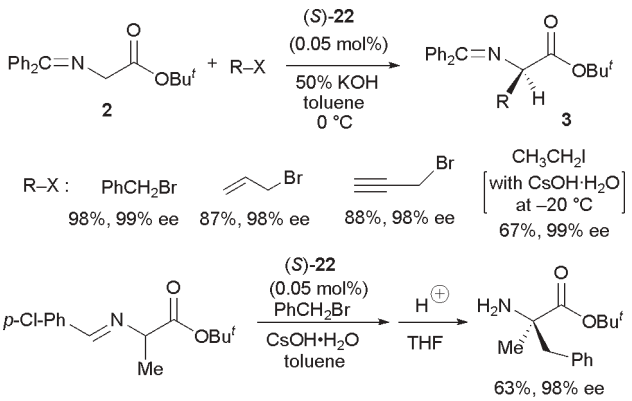
3 Design of simplified, yet very efficient, chiral phase-transfer catalysts

Our further efforts toward the simplification of catalysts have led to the discovery that chiral quaternary ammonium bromide **22**, possessing flexible straight-chain alkyl groups instead of a rigid binaphthyl moiety, functions as an efficient chiral phase-transfer catalyst. Most notably, the asymmetric alkylation of **2** with various alkyl halides proceeded smoothly under mild phase-transfer conditions in the presence of only 0.01–0.05 mol% of **22** to afford the corresponding alkylation products with excellent enantioselectivities (Scheme 18).[18] Various alkyl halides are employable for the practical synthesis of α-alkyl- αnd α,α-dialkyl-α-amino acids (Scheme 19).

In designing practical phase-transfer catalysts, the ready availability of starting chiral sources is crucial. Accordingly, chiral phase-transfer catalyst **23** was conveniently prepared



Scheme 18 Structurally simplified, highly reactive catalyst **22**.



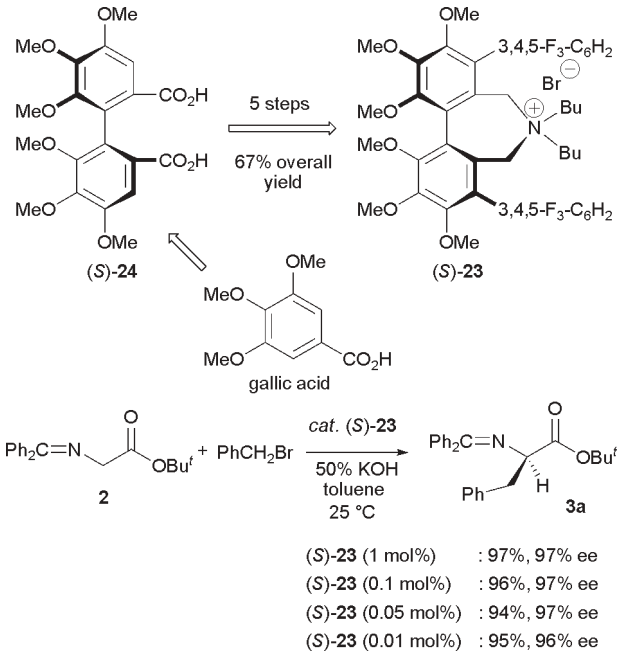
Scheme 19 Practical synthesis of α-alkylamino acids and α,α-dialkyl-amino acids.

from the known, readily available (*S*)-4,5,6,4′,5′,6′-hexamethoxybiphenyldicarboxylic acid (**24**) derived from gallic acid. This catalyst (*S*)-**23** exhibited the high catalytic performance (0.01–1 mol%) in the asymmetric alkylation of **2** compared to existing chiral phase-transfer catalysts, thereby providing a general and useful procedure for highly practical enantioselective synthesis of structurally diverse natural and unnatural α-alkyl-α-amino acids (Scheme 20).[19]

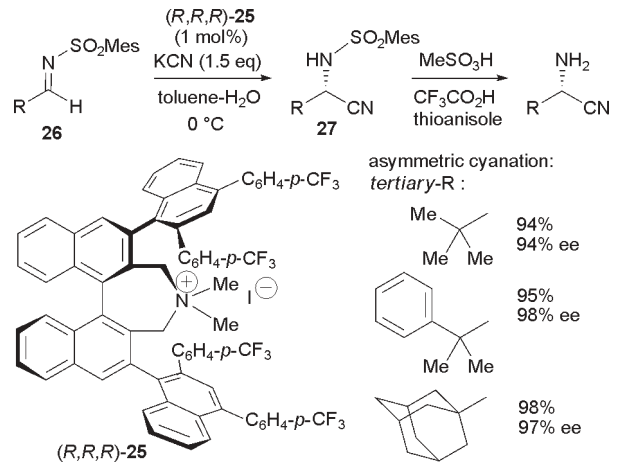
4 Design of chiral helical phase-transfer catalysts

4.1 Asymmetric synthesis of sterically hindered α-alkyl-α-amino acids

One disadvantage of the asymmetric phase-transfer alkylation of glycine derivative **2** for the synthesis of α-alkyl-α-amino acids is the difficulty of preparing sterically hindered α-alkyl-α-amino acids. In this context, we are intrigued for the development of asymmetric Strecker reactions under phase-transfer conditions. The Strecker reaction, catalytic asymmetric cyanation of imines represents one of the most direct and viable methods for the asymmetric synthesis of α-amino acids and their derivatives. However, there are no examples of asymmetric Strecker reactions under phase-transfer conditions. By designing helical chiral phase-transfer catalysts of type **25**, asymmetric phase-transfer catalyzed cyanation of sulfonyl imines **26** can be realized under phase-transfer conditions to furnish protected amino nitriles **27** with excellent enantioselectivity (Scheme 21).[20] Deprotection of



Scheme 20 Practical phase-transfer catalyst (*S*)-**23** for the enantioselective synthesis of α-alkyl-α-amino acids.



Scheme 21 Asymmetric Strecker reaction of **26** under phase-transfer conditions.

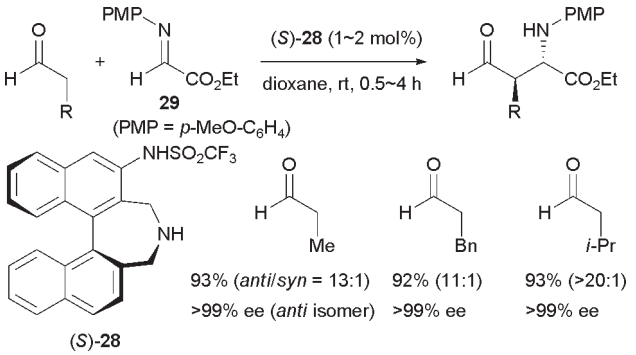
the sulfonamide moiety is effected under acidic conditions with $MeSO_3H$ and CF_3CO_2H.

5 Design of binaphthyl-based chiral secondary amine catalysts

In addition to such promising, chiral phase-transfer catalysts, we also developed several types of new bifunctional aminocatalysts for the synthesis of α- and β-amino acid derivatives.

5.1 Asymmetric synthesis of β-formyl-α-amino acids and β-amino acids

The asymmetric direct Mannich reaction was also developed to prepare optically enriched β-formyl-α-amino acids.[21] Proline and its derivatives are known to catalyze the asymmetric direct

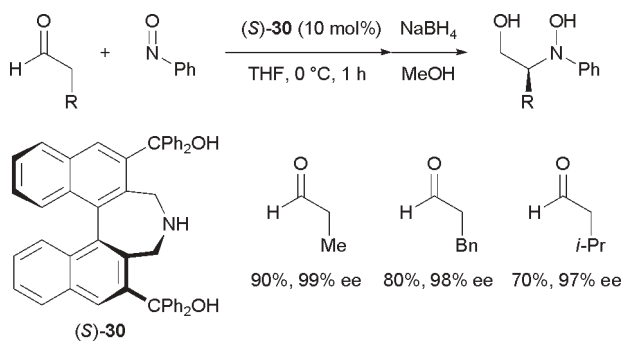


Scheme 22 *Anti*-selective asymmetric direct Mannich reaction catalyzed by (*S*)-**28**.

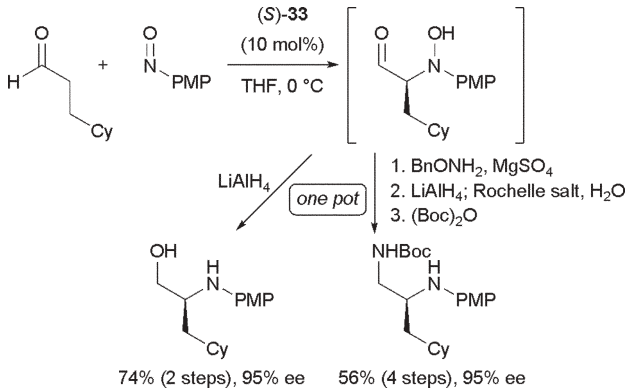
Mannich reaction between α-imino esters and aldehydes through the enamine intermediate to give the *syn*-product predominantly. Thus, we designed a novel axially chiral amino sulfonamide (*S*)-**28**, which is structurally different from the proline derivatives and has a chemically stable binaphthyl backbone, to obtain the *anti*-product (Scheme 22). The reaction between propanal and α-imino ester **29** with the catalyst (*S*)-**28** (1 mol%) in dioxane was found to proceed smoothly at room temperature to give the corresponding Mannich product in 93% isolated yield with excellent stereoselectivities (*anti*/*syn* = 13 : 1, >99% ee for *anti*-isomer). Additionally, other aldehydes with a primary or secondary alkyl group at the α-position proved to be suitable substrates in the *anti*-selective direct asymmetric Mannich reaction, and selected results are shown in Scheme 22. Of course, this asymmetric Mannich reaction is also employable for the asymmetric synthesis of β-amino acids by simple oxidation of the aldehyde moiety of the Mannich product.

5.2 Asymmetric synthesis of α-amino aldehyde derivatives

The asymmetric direct hydroxyamination reaction of aldehydes, which would give the α-amino aldehyde derivative, was realized by a related axially chiral secondary amine catalyst (*S*)-**30**.[22] Thus, treatment of propanal with nitrosobenzene in the presence of 10 mol% of (*S*)-**30** in THF at 0 °C and subsequent reduction with $NaBH_4$ in THF–MeOH, furnished the corresponding *N*-hydroxy-β-amino alcohol in 90% yield with 99% ee (Scheme 23). The reaction with other aldehydes



Scheme 23 Asymmetric direct hydroxyamination reaction catalyzed by (*S*)-**30**.



Scheme 24 One-pot asymmetric synthesis of β-amino alcohol and 1,2-diamine.

such as 3-phenylpropanal and 3-methylbutanal also proceeded to completion in 1 h at 0 °C to give *N*-hydroxy-β-amino alcohols in good yield with excellent enantioselectivity.

In order to enhance the synthetic utility of this methodology, *p*-methoxynitrosobenzene was employed instead of nitrosobenzene, and by using the resulting hydroxyamination product, one-pot procedures to prepare the β-amino alcohol or the 1,2-diamine were also developed (Scheme 24).

Conclusions

This review overviews our recent development on the practical asymmetric synthesis of various amino acid derivatives, particularly α-amino acids, by designing several chiral organocatalysts. Such achievements certainly provide valuable tools for the production of a wide variety of pharmaceutical intermediates. For example, the enantioselective functionalization of glycinate Schiff bases introduced by O'Donnell has been extensively utilized to evaluate the efficiency of the newly devised catalysts, through which it has been developed into several reliable and truly practical methods for the synthesis of optically pure α-amino acids and their derivatives. We believe that continuous efforts should be devoted for the rational design of various chiral organocatalysts including chiral phase-transfer catalysts and chiral bifunctional amino-catalysts and their applications to synthetically useful transformations, which would make great contributions to establish genuinely sustainable chemical processes within the context of the forthcoming paradigm shift in worldwide production of highly valuable pharmaceutical substances in this century.

References

1 G. C. Barrett, *Chemistry and Biochemistry of the Amino Acids*, Chapman and Hall, London, 1985; *Amino Acids, Peptides and Proteins, Specialist Periodical Reports*, The Royal Society of Chemistry, London, 1969–1985, vol. 1–16; *Amino Acids and Peptides, Specialist Periodical Reports*, The Royal Society of Chemistry, London, 1984–1987, vol. 17–20.
2 M. J. O'Donnell, D. W. Bennett and S. Wu, *J. Am. Chem. Soc.*, 1989, **111**, 2353.
3 K. Maruoka and T. Ooi, *Chem. Rev.*, 2003, **103**, 3013.
4 K. Maruoka, *J. Fluorine Chem.*, 2001, **112**, 95.
5 T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 1999, **121**, 6519.
6 T. Ooi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 2003, **125**, 5139.
7 S. Wagaw, R. A. Rennels and S. L. Buchwald, *J. Am. Chem. Soc.*, 1997, **119**, 8451.
8 T. Ooi, M. Kameda, H. Tannai and K. Maruoka, *Tetrahedron Lett.*, 2000, **41**, 8339.
9 S. Shirakawa, K. Yamamoto, M. Kitamura, T. Ooi and K. Maruoka, *Angew. Chem., Int. Ed.*, 2005, **44**, 625.
10 T. Hashimoto and K. Maruoka, *Tetrahedron Lett.*, 2003, **44**, 3313.
11 T. Hashimoto, Y. Tanaka and K. Maruoka, *Tetrahedron: Asymmetry*, 2003, **14**, 1599.
12 S. Shirakawa, Y. Tanaka and K. Maruoka, *Org. Lett.*, 2004, **6**, 1429.
13 T. Ooi, Y. Uematsu, M. Kameda and K. Maruoka, *Angew. Chem., Int. Ed.*, 2002, **41**, 1621.
14 T. Ooi, M. Takeuchi, M. Kameda and K. Maruoka, *J. Am. Chem. Soc.*, 2000, **122**, 5228.
15 T. Ooi, M. Taniguchi, M. Kameda and K. Maruoka, *Angew. Chem., Int. Ed.*, 2002, **41**, 4542.
16 T. Ooi, M. Kameda, M. Taniguchi and K. Maruoka, *J. Am. Chem. Soc.*, 2004, **126**, 9685.
17 T. Ooi, S. Fujioka and K. Maruoka, *J. Am. Chem. Soc.*, 2004, **126**, 11790.
18 M. Kitamura, S. Shirakawa and K. Maruoka, *Angew. Chem., Int. Ed.*, 2005, **44**, 1549.
19 Z. Han, Y. Yamaguchi, M. Kitamura and K. Maruoka, *Tetrahedron Lett.*, 2005, **46**, 8555.
20 T. Ooi, Y. Uematsu and K. Maruoka, *J. Am. Chem. Soc.*, 2006, **128**, 2548.
21 T. Kano, Y. Yamaguchi, O. Tokuda and K. Maruoka, *J. Am. Chem. Soc.*, 2005, **127**, 16408.
22 T. Kano, M. Ueda, J. Takai and K. Maruoka, *J. Am. Chem. Soc.*, 2006, **128**, 6046.