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Design of C_2-Symmetric Chiral Phase-transfer Catalysts for Practical Asymmetric Synthesis

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Abstract: A series of structurally rigid, chiral quaternary ammonium salts derived from commercially available (*S*)- or (*R*)-1,1'-bi-2-naphthol have been designed as new C_2-symmetric chiral phase-transfer catalysts. These chiral organocatalysts have been successfully applied to the highly practical asymmetric synthesis of useful organic molecules including amino acid derivatives.

Keywords: Alkylation · Ammonium salts · Asymmetry · Catalyst · Phase transfer

1. Introduction

The chemical community has witnessed the exponential growth of phase-transfer catalysis as a practical methodology for organic synthesis, featuring its simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility to conduct large-scale preparations.[1] Nowadays, it appears to be a prime synthetic tool appreciated in various fields of organic chemistry, and also finds widespread industrial applications. On the other hand, the development of asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral, non-racemic catalysts has progressed rather slowly, despite its great importance to create a new domain in modern asymmetric catalysis by taking full advantage of structurally and stereochemically modifiable tetraalkylonium cations. However, recent enormous efforts toward this goal have resulted in notable achievements, making it feasible to perform various bond formation reactions under mild phase transfer-catalyzed conditions.[2] This review illustrates our recent development on the design of various types of chiral phase-transfer catalysts, which possess the high environmentally benign properties, and applied them to practical asymmetric synthesis of useful organic molecules, mainly amino acid derivatives.

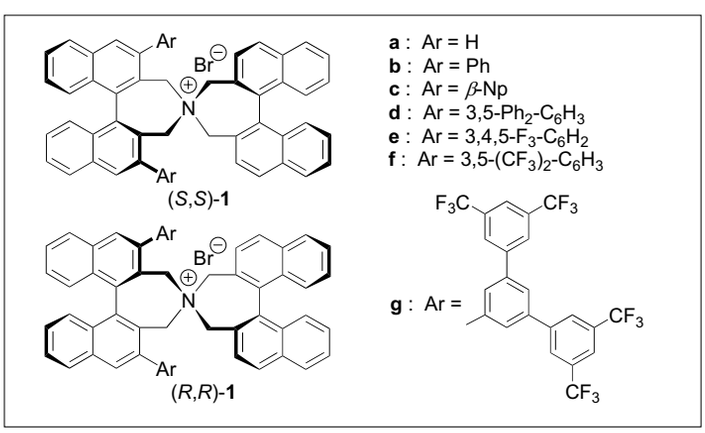

Fig. 1. C_2-Symmetric chiral phase-transfer catalysts derived from BINOL

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,[3] asymmetric synthesis of α-alkyl-α-amino acids by asymmetric phase-transfer alkylation of a prochiral protected glycine derivative using a chiral catalyst has become an attractive method for the preparation of both natural and unnatural amino acids.[4] 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 were designed as a new C_2-symmetric chiral phase-transfer catalyst (Fig. 1) and successfully applied to the highly efficient, catalytic asymmetric synthesis of various α-alkyl-α-amino acids under mild phase-transfer conditions.[5]

Attempted benzylation of N-(diphenylmethylene)glycine *tert*-butyl ester (**2**) with 1 mol% of symmetric (*S,S*)-**1a** in 50%

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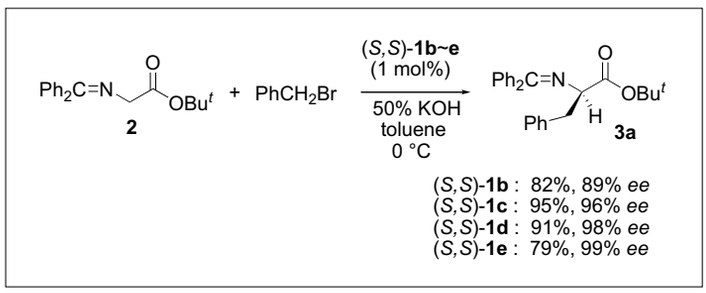
aqueous NaOH/benzene (volume ratio = 1:3) at room temperature afforded the corresponding benzylation product **3a** in 76% yield with 73% *ee*. Introduction of aromatic substituents (Ar) on the 3,3'-position of one binaphthyl subunit of the catalyst afforded a beneficial effect on the enantiofacial discrimination, and the similar reaction in toluene under the influence of (*S*,*S*)-**1b** gave the product **3a** in 82% yield with 89% *ee* (Scheme 1). Switching the catalyst to (*S*,*S*)-**1c** and sterically more hindered (*S*,*S*)-**1d** further increased the enantioselectivity to 96% *ee* and 98% *ee*, respectively, and virtually complete stereochemical control was achieved using (*S*,*S*)-**1e** as catalyst.[6,7] 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. In the case of a reactive alkyl halide, the catalyst loading can be reduced to 0.2 mol% without loss of enantiomeric excess.[7]

(*S*,*S*)-**1e** is the catalyst of choice for the preparation of a variety of essentially enantiopure α-alkyl-α-amino acids by this transformation (Scheme 2). Facile asymmetric synthesis of α-alkyl-α-amino acids, which is 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.[7] Since both enantiomers of the catalyst of type **1** are readily available from either (*R*)- or (*S*)-1,1'-bi-2-naphthol, a wide variety of natural and unnatural α-alkyl-α-amino acids can be synthesized in an enantiomerically pure form by the catalytic phase-transfer alkylation of **2**.

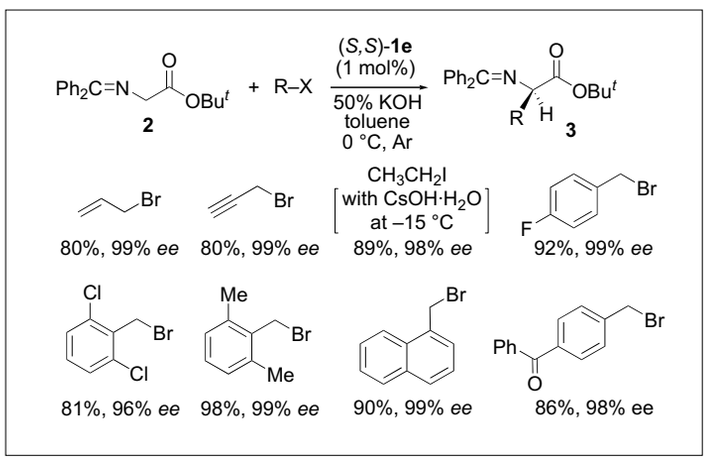
The synthetic utility of chiral phase-transfer catalysis of **1** was highlighted by the facile synthesis of L-Dopa ester **4** (R^2 = OH) and its analogue (Scheme 3), which are usually prepared by either asymmetric hydrogenation of eneamides or enzymatic processes and tested as potential drugs for the treatment of Parkinson's disease. The successful asymmetric synthesis of natural tyrosine *tert*-butyl ester **4** (R^2 = H) in a similar manner strongly implies the feasibility of highly enantioselective synthesis of various L-Dopa analogues.[8]

In order 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 benzylation of **2** in the presence of 18-crown-6 (**5**) (0.05 mol%) under similar conditions proceeded smoothly to furnish **3a** in 98% yield with 98% *ee* (Scheme 4).[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 the otherwise slow deprotonation process. Interestingly, achiral tetrabutyl- and tetraoctylammonium bromides are also employable for this purpose.

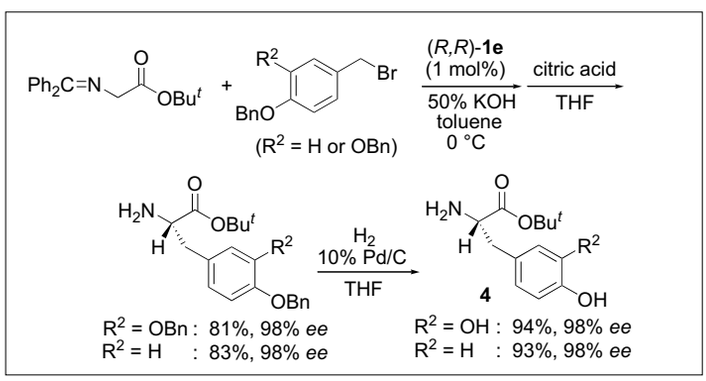
In this series, introduction of 3,3'-diaryl substituents to the parent symmetrical



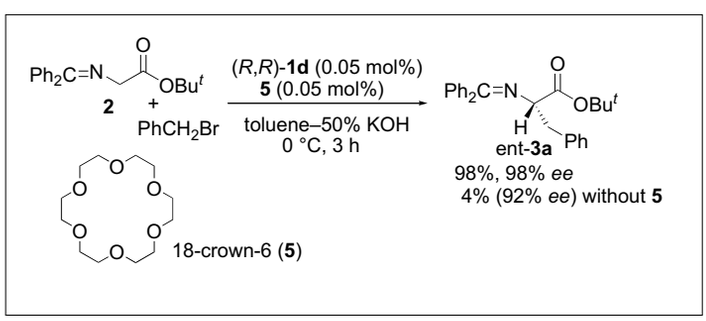
Scheme 1. Asymmetric benzylation of glycine derivative **2** with (*S*,*S*)-**1b–e**



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



Scheme 3. Asymmetric synthesis of L-Dopa ester **4** (R^2 = OH)



Scheme 4. Binary phase-transfer catalysis

ammonium bromide **1a** is found to be crucially important for high enantioselectivity. In this regard, we were interested in the possibility of examining the effect of adjacent 4,4'-substituents of the catalyst rather than 3,3'-substituents in the asymmetric phase-transfer alkylations.[10] Interestingly, even 4,4'-diaryl substituents of the catalysts of type **6** (Fig. 2) exhibited unexpectedly high asymmetric induction on such asymmetric phase-transfer alkylations. For example, asymmetric alkylation of **2** with benzyl bromide in toluene/50% aqueous KOH under the influence of 1 mol% of catalyst (*S*,*S*)-**6** gave rise to benzylation product **3a** in 90% yield with 91% *ee*. The observed enantioselectivity is rather surprising compared to that obtained (89% *ee*) using 3,3'-diphenyl-substituted **1b** under similar reaction conditions. The sterically more hindered 4,4',6,6'-tetrakis(3,5-diphenylphenyl)binaphthyl analogue (*S*,*S*)-**6b** was also prepared and applied 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).

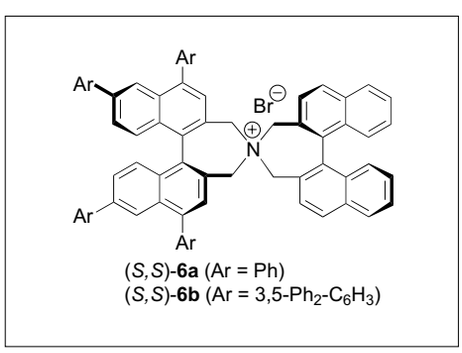
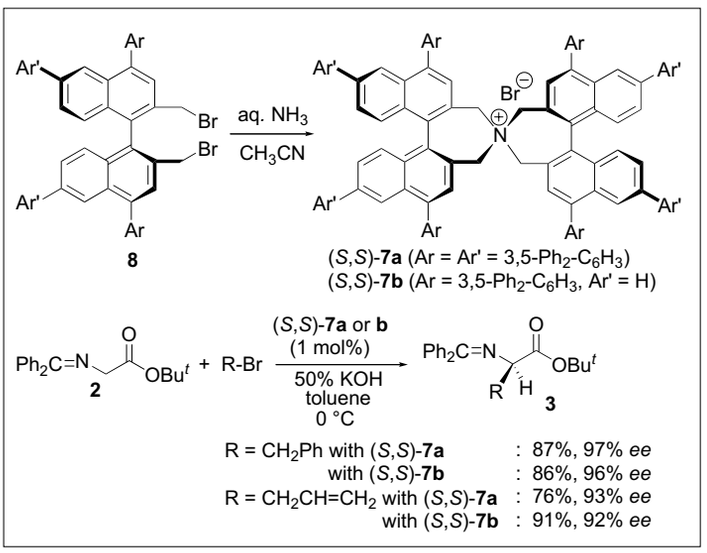
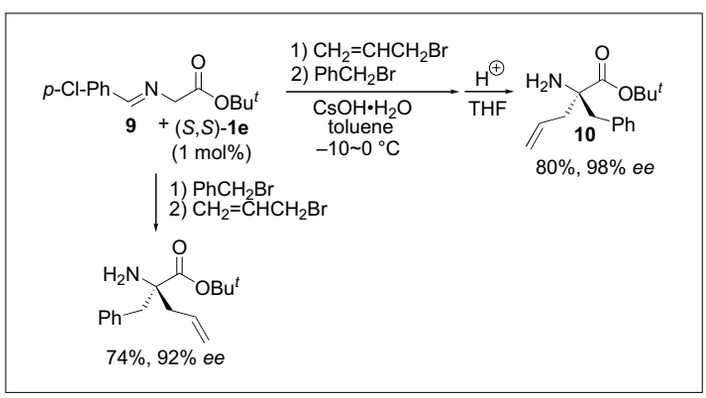


Fig. 2. Synthesis of 4,4'-diaryl-substituted catalysts (*S*,*S*)-**6**

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 **7** was assembled through the reaction of aqueous ammonia with bis-bromide **8** on the basis of our study on the substituent effect of this type of salt. Evaluation of **7** as a chiral phase-transfer catalyst in the alkylation of **2** uncovered its high catalytic and chiral efficiency (Scheme 5).[11]



Scheme 5. Synthetic utility of symmetrical chiral N-spiral ammonium bromides (*S*,*S*)-**7**



Scheme 6. One-pot asymmetric double alkylation of glycine derivative **9**

2.2. *Asymmetric Synthesis of α,α-Dialkyl-α-amino Acids*

With this basic information at hand, our attention was focused on the α,α-dialkyl-α-amino acid synthesis. We envisioned that two different side chains could be introduced directly to the aldimine Schiff base **9** derived from glycine in a highly enantioselective manner by appropriate chiral phase-transfer catalysis (Scheme 6). This possibility of a one-pot asymmetric double alkylation was realized by using the C_2-symmetric chiral quaternary ammonium bromide (*S*,*S*)-**1**.[12] Initial treatment of the toluene solution of **9** and (*S*,*S*)-**1c** (1 mol%) with allyl bromide and CsOH•H$_2$O and the subsequent reaction with benzyl bromide resulted in formation of the double alkylation product **10** 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.[12] 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 **9** by the addition of the halides in a reverse order, the absolute configuration of the product was confirmed to be the opposite, indicating the intervention of the expected chiral ammonium enolate in the second alkylation stage (Scheme 6). 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 **11** derived from the corresponding α-amino acids. Indeed, rapid benzylation of *dl*-alanine-derived imine **11a** occurred in toluene with benzyl bromide and CsOH•H$_2$O using (*S*,*S*)-**1e** (1 mol%) as a catalyst, giving the alkylation product **12** (R^1 = Me, R^2 = CH$_2$Ph; 85%) in an almost enantiomerically pure form (98% *ee*). Other selected results illustrated in Scheme 7 demonstrate the remarkable efficiency and generality of this method.[12] Use of *tert*-butyl α-bromoacetate as an alkylating 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 dipeptoids with high affinity for the central cholecystokinin receptor, can also be realized. In addition, the phase-transfer catalytic alkylation of

aldimine Schiff bases **11b** and **11c** derived from other α-alkyl-α-amino acids such as *dl*-phenylalanine and *dl*-leucine also appeared to be feasible with high efficiency, providing the desired non-coded amino acid esters **12** with excellent asymmetric induction (Scheme 7).

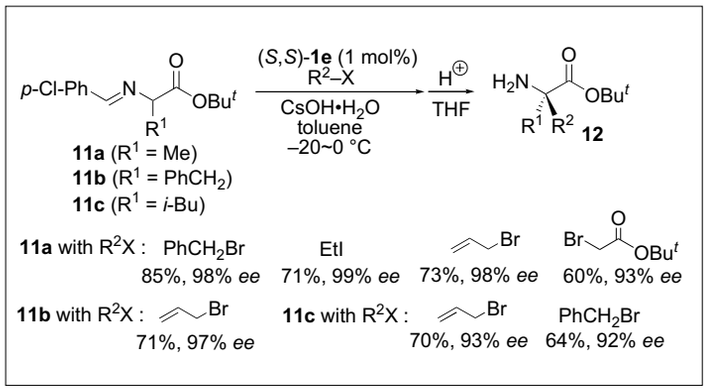
2.3. *Asymmetric Synthesis of β-Hydroxy-α-amino Acids*

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 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%) and subsequent hydrolysis with 1 N HCl in THF resulted in the formation of the corresponding β-hydroxy-α-amino ester **13** in 76% isolated yield with the *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 the 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl substituent as a catalyst enhanced both diastereo- and enantioselectivities (*anti*/*syn* = 92:8, 96% *ee* for the *anti* isomer) (Scheme 8).[13]

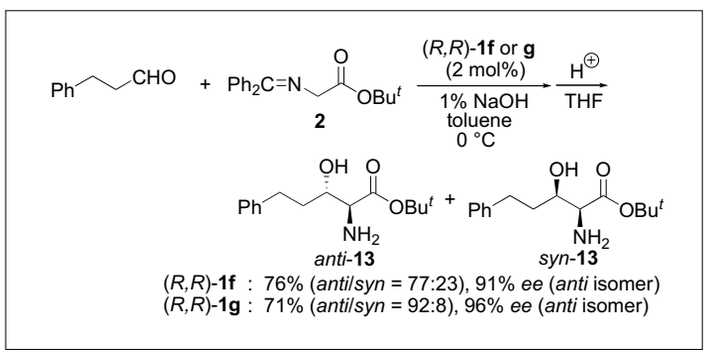
The initially developed reaction conditions using 2 equiv. of aqueous base (1% NaOH aq) exhibited inexplicably limited general applicability in terms of aldehyde acceptors. For example, reaction of glycine derivative **2** with 4-benzyloxybutanal gave the aldol product with low diastereoselectivity (*anti*/*syn* = 58:42; 82% *ee* for the *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 (Fig. 3).[14]

2.4. *Asymmetric Conjugate Addition of Nitroalkanes*

Asymmetric conjugate addition of α-anions of nitroalkanes to α,β-unsaturated esters is not an easy task. Accordingly, we developed the diastereo- and enantioselective conjugate addition of nitroalkanes to alkylidenemalonates **14** under mild phase-transfer conditions by using chiral quaternary ammonium bromide **1g** as an efficient catalyst (Scheme 9).[15] 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 7. Dialkylamino acid synthesis from α-substituted amino acid derivatives **11a–c**



Scheme 8. Asymmetric synthesis of β-hydroxy-α-amino acids **13** by direct asymmetric aldol reaction

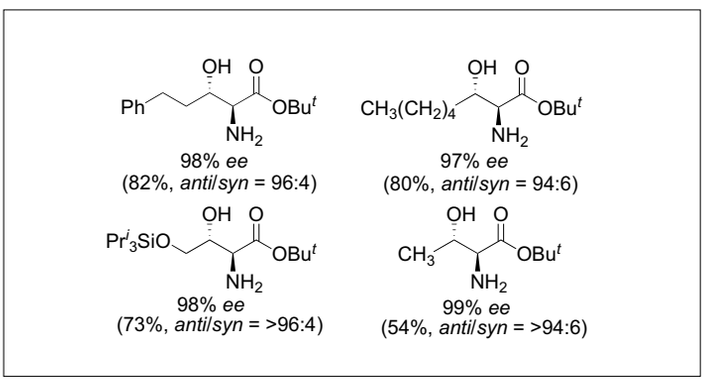


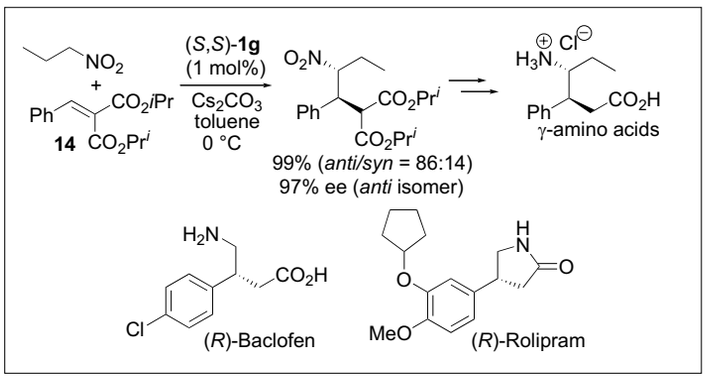
Fig. 3. Asymmetric direct aldol synthesis under phase-transfer conditions

3. Design of Simplified, Yet Very Efficient Chiral Phase-transfer Catalysts

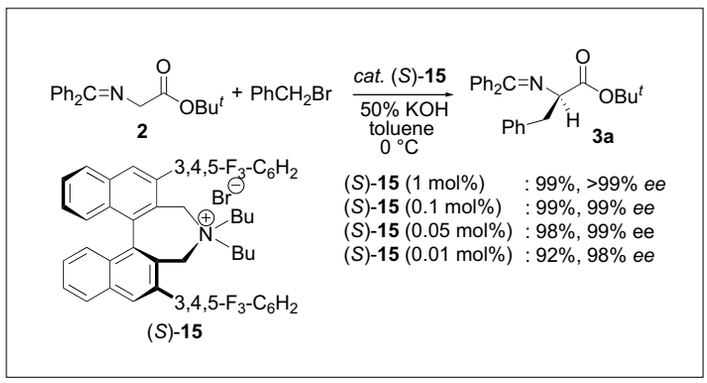
Our further efforts toward the design of very efficient, chiral phase-transfer catalyst have led to the discovery that chiral quaternary ammonium bromide **15** possessing flexible straight-chain alkyl groups instead of a rigid binaphthyl moiety functions as an efficient chiral phase-transfer catalyst. 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 **15** to afford the corresponding alkylation products with excellent enantioselectivities (Scheme 10).[16]

Various alkyl halides are employable for the practical synthesis of α-alkyl- and α,α-dialkyl-α-amino acids (Scheme 11).

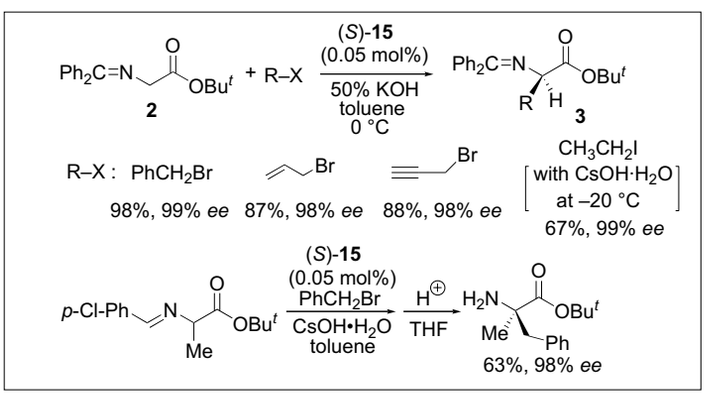
In designing practical phase-transfer catalysts, the ready availability of starting chiral sources is crucial. Accordingly, chiral phase-transfer catalyst **16** was conveniently



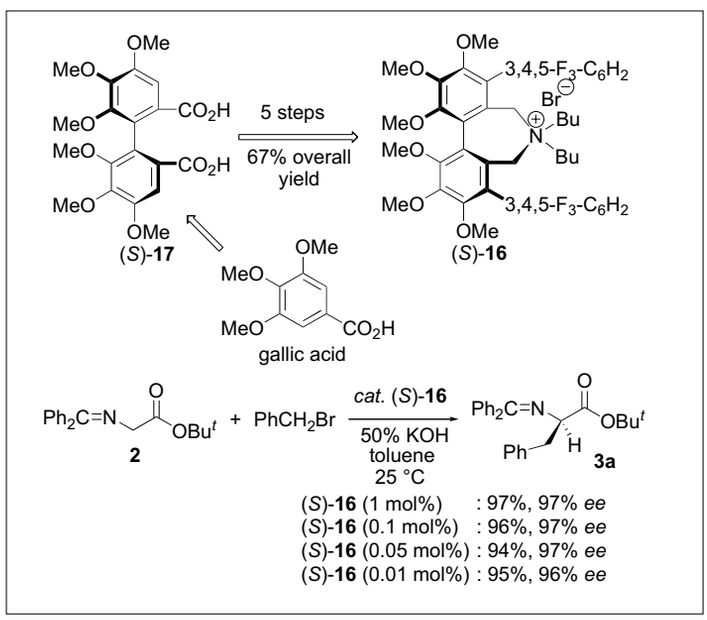
Scheme 9. Asymmetric conjugate addition of nitroalkanes to α,β-unsaturated malonates under phase-transfer conditions



Scheme 10. Structurally simplified, highly reactive catalyst **15**

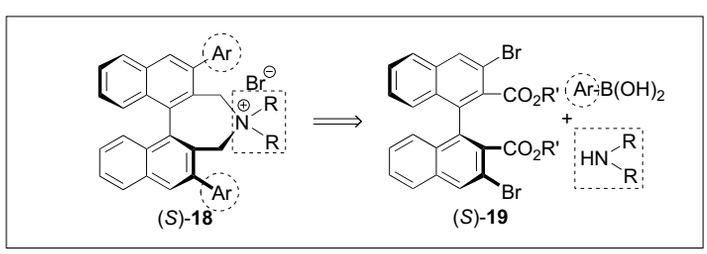


Scheme 11. Practical synthesis of α-alkylamino acids and α,α-dialkylamino acids



Scheme 12. Practical phase-transfer catalyst (*S*)-**16** for the enantioselective synthesis of α-alkyl-α-amino acids

prepared from the known, readily available (*S*)-4,5,6,4',5',6'-hexamethoxybiphenyldicarboxylic acid (**17**) derived from gallic acid. This catalyst, (*S*)-**16**, exhibited the high catalytic performance (0.01~1 mol%) in the asymmetric alkylation of **2** compared to the 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 12).[17]



Scheme 13. Retrosynthesis of chiral phase-transfer catalyst (*S*)-**16**

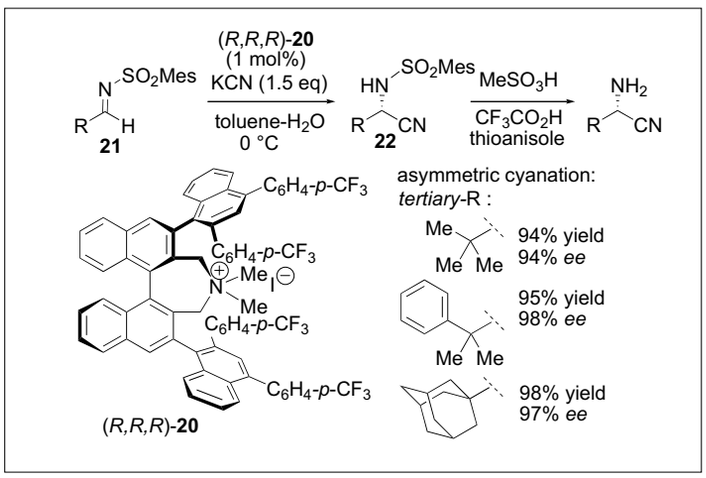
4. Design of New, Chiral Phase-Transfer Catalysts

4.1. *Asymmetric Strecker Reaction for Sterically Hindered α-Alkyl-α-amino Acid Synthesis*

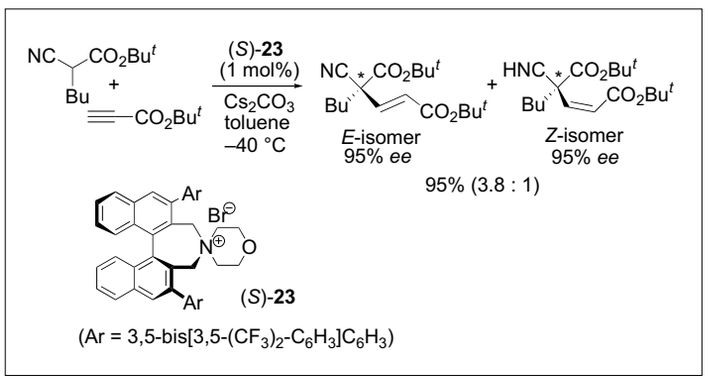
One disadvantage of the asymmetric phase-transfer alkylation of glycine derivative **2** for the synthesis of α-alkyl-α-amino acids is the difficulty of preparing sterically hindered α-alkyl-α-amino acids. In this context, we are interested in the development of asymmetric Strecker reactions under phase-transfer conditions. The Strecker reaction, the 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 is no example of asymmetric Strecker reaction under phase-transfer conditions.

Our strategy is based on our recent findings of a very active, chiral phase-transfer catalyst of type (*S*)-**18** (Ar = 3,4,5-F_3-C_6H_2; R = Bu) for the asymmetric alkylation of N-(diphenylmethylene)glycine *tert*-butyl ester.[16] Since the catalyst (*S*)-**18** can be readily prepared from three components, *i.e.* a chiral binaphthyl part (*S*)-**19**, an arylboronic acid ($ArB(OH)_2$), and a secondary amine (R_2NH) (Scheme 13),[18] the appropriate modification of $ArB(OH)_2$ and R_2NH parts should give a newly designed catalyst for the development of a novel asymmetric transformation.

Accordingly, by designing helical chiral phase-transfer catalysts of type **20**, asymmetric phase-transfer catalyzed cyanation of sulfonyl imines **21** can be realized under phase-transfer conditions to furnish protected amino nitriles **22** with excellent enantioselectivity (Scheme 14).[19] Deprotection of sulfonamide moiety is effected under acidic conditions with $MeSO_3H$ and CF_3CO_2H.



Scheme 14. Asymmetric Strecker reaction of **21** under phase-transfer conditions



Scheme 15. Asymmetric conjugate additions of α-substituted-α-cyanoacetates to acetylenic esters

4.2. *Asymmetric Conjugate Additions of α-Substituted-α-cyanoacetates to Acetylenic Esters*

Our second example on the design of a new phase-transfer catalysts is illustrated by the development of a hitherto unknown asymmetric conjugate addition of α-substituted-α-cyanoacetates to acetylenic esters (Scheme 15). The combination of these substrates is quite appealing, because both α-substituted-α-cyanoacetates and acetylenic esters have been a difficult class of nucleophiles and electrophiles, respectively, in current asymmetric stereochemical control. Accordingly, we succeeded in designing a new, chiral phase-transfer catalyst of type (*S*)-**23** to realize a general and useful procedure for the asymmetric conjugate addition of various *tert*-butyl α-substituted-α-cyanoacetates to *tert*-butyl propiolate with high enantioselectivity.[20]

5. Conclusions

This review overviews our recent developments on the practical asymmetric synthesis of various useful organic molecules, particularly α-amino acids, by designing several chiral phase-transfer catalysts. Such achievements certainly provide valuable tools for the production of a wide variety of pharmaceutical intermediates. We believe that continuous efforts should be devoted for the rational design of various chiral organocatalysts including chiral phase-transfer catalysts and their applications to synthetically useful transformations, which would make great contributions to establish genuinely sustainable chemical processes within the context of forthcoming paradigm shift in worldwide production of highly valuable pharmaceutical substances in this century.

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