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Designer chiral phase-transfer catalysts for green sustainable chemistry*

Keiji Maruoka

Department of Chemistry, Graduate School of Science, Kyoto University, Kyoto 606-8502, Japan

Abstract: A series of chiral quaternary ammonium salts derived from commercially available (*R*)- or (*S*)-binaphthol have been designed as new C_2-symmetric chiral phase-transfer catalysts. In order to realize the flexible design of these phase-transfer catalysts, the combinatorial design approach has been developed. Chiral high-performance organocatalysts, thus obtained, have been successfully applied to the highly practical asymmetric synthesis of various amino acid derivatives, including α-alkyl and α,α-dialkyl-α-amino acids in addition to alkaloids. Furthermore, several chiral bifunctional phase-transfer catalysts have been designed and synthesized for effecting base-free phase-transfer reactions under essentially neutral conditions in order to realize green sustainable chemistry.

Keywords: alkaloid synthesis; alkylation; amino acids; asymmetric synthesis; bifunctional catalysis; green sustainable chemistry; phase-transfer catalysis; organocatalyst.

INTRODUCTION

Phase-transfer catalysis has long been recognized as a versatile methodology for organic synthesis in both industry and academia, featuring simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility to conduct large-scale preparations [1]. It appears to be a prime synthetic tool that is 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 in creating a new domain in modern asymmetric catalysis by taking full advantage of structurally and stereochemically modifiable tetraalkylonium cations. However, recent enormous efforts toward this direction have resulted in notable achievements, making it feasible to perform various bond formation reactions under mild phase-transfer-catalyzed conditions [2]. This article illustrates our recent development on the flexible design of various types of chiral phase-transfer catalysts, which possess the high environmentally benign property, and applied them to practical asymmetric synthesis of useful organic molecules such as amino acid and alkaloid derivatives [3,4]. In particular, the design of several chiral bifunctional phase-transfer catalysts allows base-free phase-transfer reactions under essentially neutral conditions in order to realize green sustainable chemistry.

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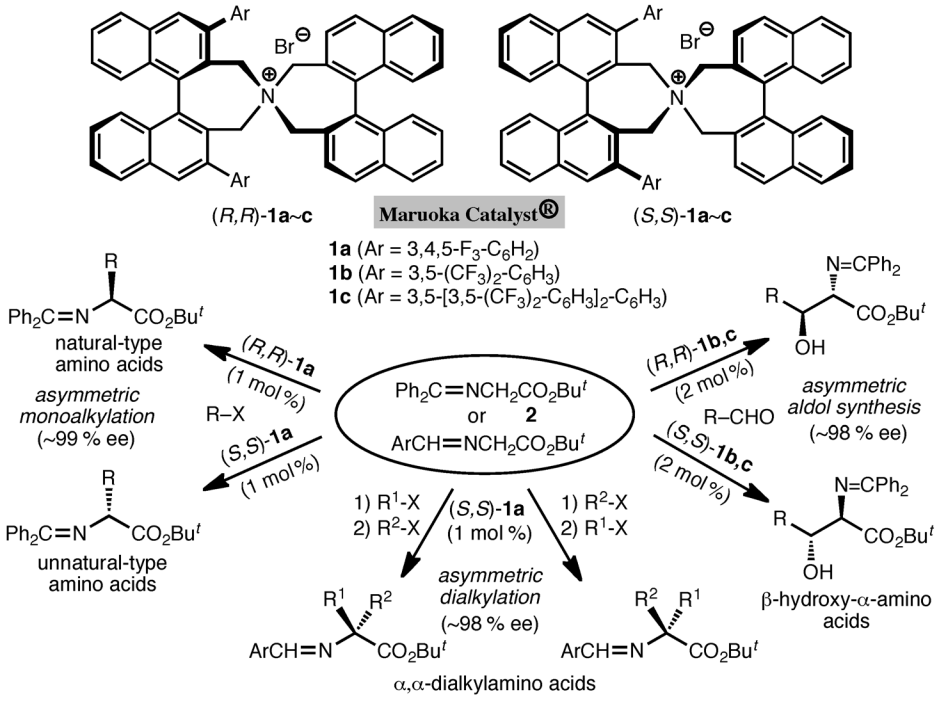
DESIGN OF SPIRO-TYPE CHIRAL PHASE-TRANSFER CATALYSTS

Asymmetric synthesis of α-substituted α-amino acids by enantioselective alkylation of a prochiral protected glycine derivative using a chiral phase-transfer catalyst has provided an attractive method for the preparation of both natural and unnatural amino acids [5]. However, when we initiated asymmetric phase-transfer chemistry in 1998, almost all the elaborated chiral phase-transfer catalysts reported so far had been restricted to *cinchona* alkaloid derivatives, which unfortunately constitutes a major difficulty in rationally designing and fine-tuning catalysts to attain sufficient reactivity and selectivity [2]. 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 C_2-symmetric chiral phase-transfer catalysts and successfully applied to the highly efficient, catalytic enantioselective synthesis of various α-amino acids under mild phase-transfer conditions (Scheme 1) [6–8]. These catalysts (*R*,*R*)-**1** and (*S*,*S*)-**1** are now called "Maruoka catalyst®".

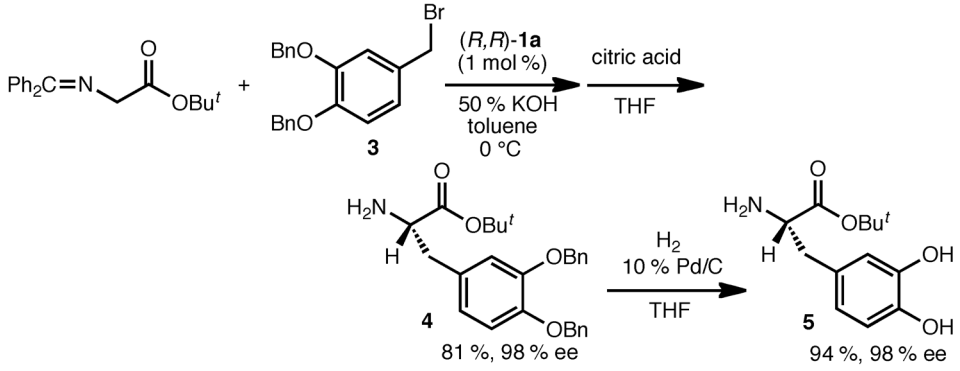


Scheme 1 Asymmetric transformation of glycine derivatives with Maruoka catalyst.

For example, catalyst (*R*,*R*)-**1a** or (*S*,*S*)-**1a** is found to be the catalyst of choice for the preparation of a variety of essentially enantiopure natural-type and unnatural-type α-alkyl-α-amino acids by asymmetric alkylation of glycine derivative **2** as shown in Scheme 1 [8]. In addition, facile and direct asymmetric synthesis of α,α-dialkyl-α-amino acids becomes feasible by employing two different alkyl halides [7]. Of course, by simply changing the addition sequence of two different alkyl halides, the enantiomeric α,α-dialkyl-α-amino acids are available by using the same catalyst (*S*,*S*)-**1a**. 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 derived from the corresponding α-alkyl-α-amino acids. Furthermore, 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 (*R*,*R*)-**1b** or (*S*,*S*)-**1b** [9]. Interestingly, use of (*R*,*R*)-**1c** or (*S*,*S*)-**1c** possessing 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl substituent as a catalyst enhanced both diastereo- and enantioselectivities [10]. 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 α-amino acids can be synthesized in an enantiomerically pure form by the catalytic phase-transfer alkylation of glycine derivative **2**.

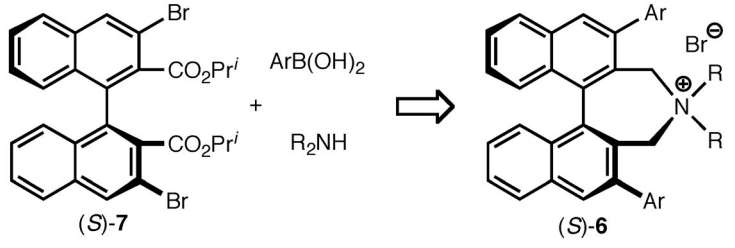
The synthetic utility of chiral phase-transfer catalysis of **1** was highlighted by the facile synthesis of L-DOPA ester, which has usually been prepared by either asymmetric hydrogenation of eneamides or enzymatic processes and tested as potential drugs for the treatment of Parkinson's disease. Thus, catalytic enantioselective phase-transfer alkylation of glycine derivative **2** with the requisite benzyl bromide **3** proceeded smoothly under the influence of (*R*,*R*)-**1a** (1 mol %) to furnish fully protected L-DOPA *tert*-butyl ester, which was subsequently hydrolyzed with aqueous citric acid to afford the corresponding amino ester **4** with high enantioselectivity. Debenzylation of **4** under catalytic hydrogenation conditions produced the desired L-DOPA *tert*-butyl ester **5** (Scheme 2) [11].



Scheme 2 Asymmetric synthesis of L-DOPA ester **5** from glycine derivative.

DESIGN OF SIMPLIFIED, HIGH-PERFORMANCE CHIRAL PHASE-TRANSFER CATALYSTS

In order to simplify the structure of the original catalyst (*S*,*S*)-**1**, we chose the fundamental structure **6** as a simplified chiral phase-transfer catalyst. Because the catalyst (*S*)-**6** can be readily prepared from three components, a chiral binaphthyl part (*S*)-**7**, an arylboronic acid [$ArB(OH)_2$], and a secondary amine (R_2NH) as shown in Scheme 3, the appropriate modification of the $ArB(OH)_2$ and R_2NH portions should give a series of newly designed catalysts [12]. Hence, we studied the substituent effects of



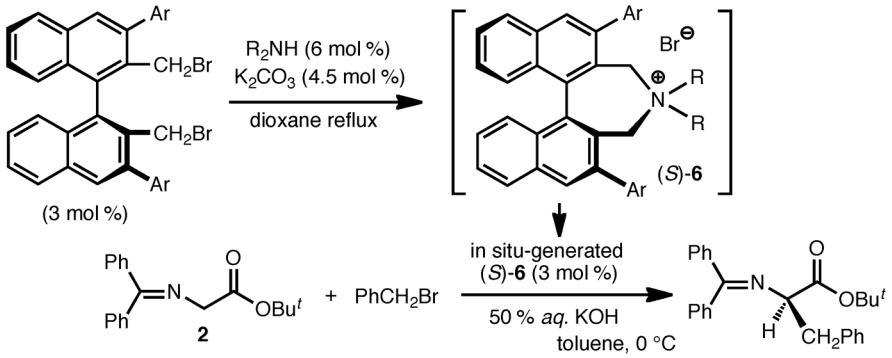
Scheme 3 Combinatorial design approach for new chiral phase-transfer catalysts.

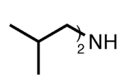
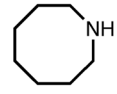
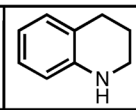
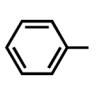
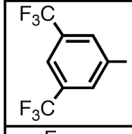
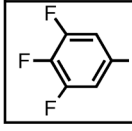
Ar and R moieties in detail by using combinatorial chemistry, as variation of the substituents Ar and R would allow facile generation of large libraries of structures (Scheme 3).

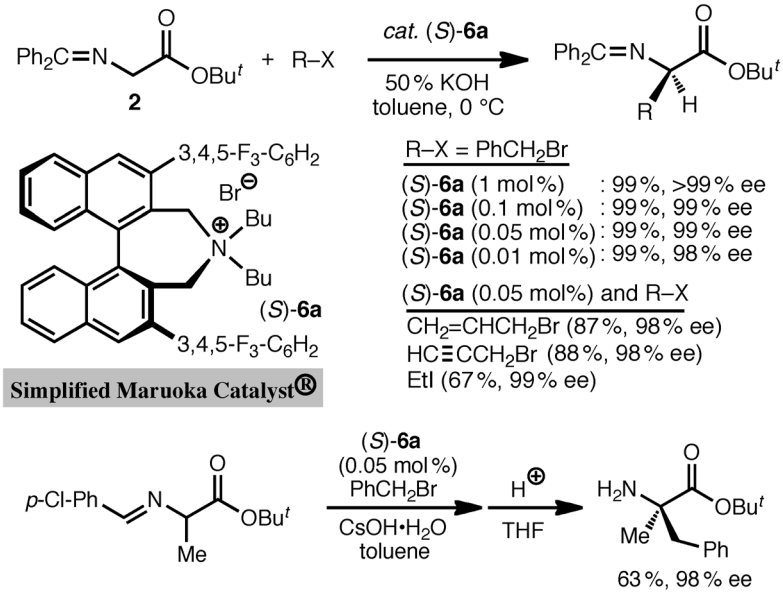
The initial rough screening of catalyst (*S*)-**6** on the variation of substituents, Ar and R revealed that the combination of Ar = 3,5-bis(trifluoromethyl)phenyl and 3,4,5-trifluorophenyl with R = Bu and decyl exhibited high enantioselectivity in the asymmetric alkylation of glycine derivative **2** (Table 1).

As a result, we discovered that chiral quaternary ammonium bromide **6** possessing 3,4,5-trifluorophenyl group (as Ar) and flexible straight-chain alkyl groups (R) instead of a rigid binaphthyl moiety functions as chiral high-performance phase-transfer catalyst. In case of R = Bu, we call it "simplified Maruoka catalyst". Most notably, the asymmetric alkylation of glycine derivative **2** with benzyl bromide proceeded smoothly under mild phase-transfer conditions in the presence of only 0.01–0.05 mol % of simplified Maruoka catalyst to afford the corresponding alkylation products with excellent enantioselectivities (Scheme 4) [13]. Various types of alkyl halides are employable for the practical synthesis of α-alkyl- and α,α-dialkyl-α-amino acids.

Table 1 Screening of in situ-generated catalyst (*S*)-**6** in asymmetric phase-transfer alkylation of glycine derivative **2**.

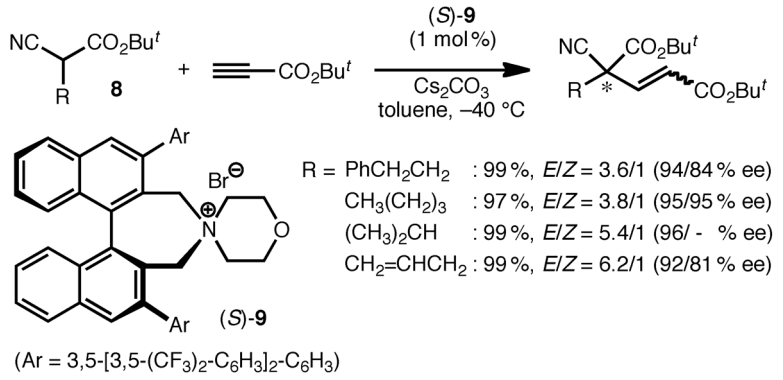


Ar \ R_2NH	Me_2NH	Bu_2NH	$(C_{10}H_{21})_2NH$				
H	12% ee	–27% ee	–17% ee	–9% ee	–7% ee	–23% ee	–19% ee
	26% ee	43% ee	58% ee	22% ee	5% ee	33% ee	26% ee
	1% ee	93% ee	96% ee	44% ee	31% ee	41% ee	78% ee
	7% ee	97% ee	97% ee	7% ee	43% ee	20% ee	81% ee



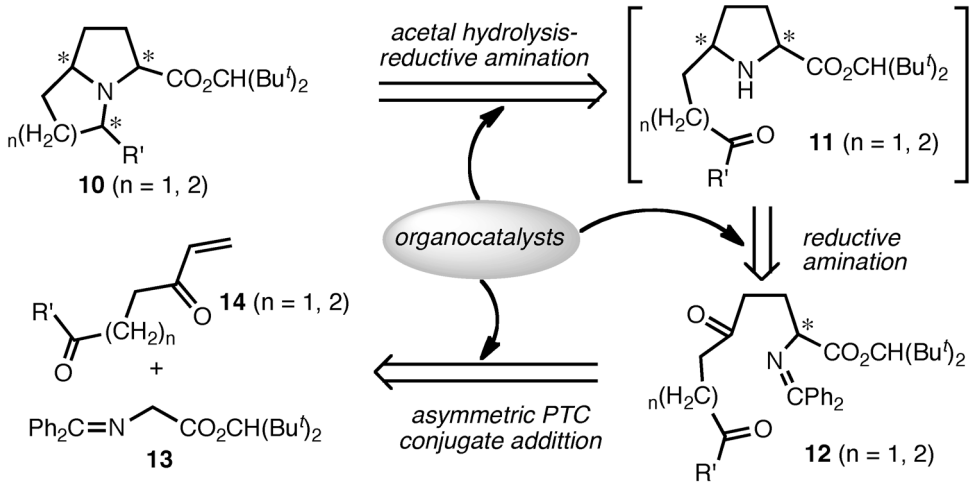
Scheme 4 Practical synthesis of α-amino acids with simplified Maruoka catalyst.

Our combinatorial design approach is found to be quite useful to develop hitherto difficult asymmetric transformatons. For example, asymmetric conjugate addition of α-substituted-α-cyanoacetates **8** to acetylenic esters under phase-transfer condition is quite challenging, because of the difficulty to control the stereochemistry of the product. In addition, despite numerous examples of the conjugate additions to alkenoic esters, so far there is no successful asymmetric conjugate addition to acetylenic esters. In this context, we recently found that a new morpholine-derived phase-transfer catalyst (*S*)-**9** is highly useful for asymmetric conjugate additions of α-alkyl-α-cyanoacetates **8** to acetylenic esters. In this asymmetric transformation, an all-carbon quaternary stereocenter can be constructed in a high enantiomeric purity (Scheme 5) [14]. This approach is also applicable to alkynoic ketones [15].



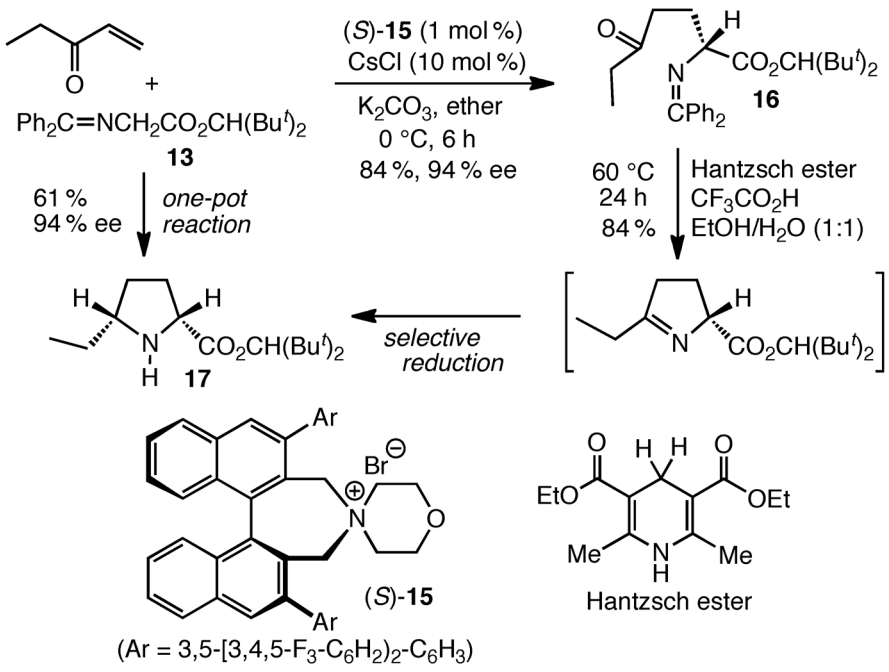
Scheme 5 Asymmetric conjugate addition of α-cyano esters with new chiral phase-transfer catalyst (*S*)-**9**.

With this information at hand, an enantioselective organocatalytic, one-pot synthesis of hexahydropyrrolizine and octahydroindolizine core structures **10** (n = 1 or 2) would be considered starting from readily available glycine esters **13** in combination with several different organocatalytic reactions (Scheme 6). Our key strategy is based on the development of asymmetric conjugate addition of *N*-(diphenylmethylene)glycine ester **13** and α,β-enones **14** (n = 1 or 2) by using a chiral phase-transfer catalyst of type (*S*)-**9** (Scheme 6). Organocatalytic intramolecular reductive amination of conjugate adduct **12** (n = 1 or 2) with Hantzsch ester would proceed in a stereoselective manner to give pyrrolidine derivative **11** (n = 1 or 2) as an intermediate, which is susceptible to the subsequent cyclization with iminium ion formation and reductively aminated to furnish a hexahydropyrrolizine or octahydroindolizine core structure **10** (n = 1 or 2), respectively.



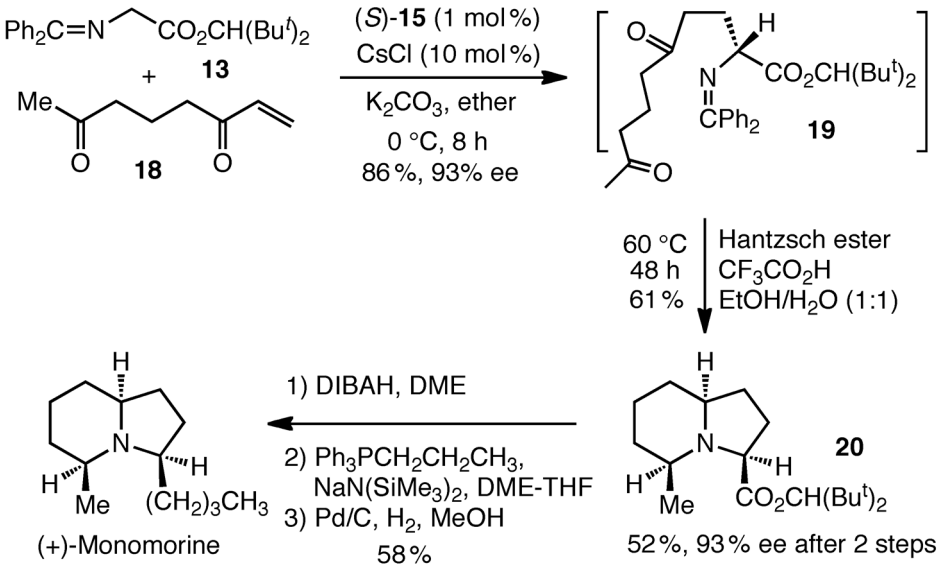
Scheme 6 Retrosynthetic pathway on alkaloid core structures.

We first examined asymmetric conjugate addition of *N*-(diphenylmethylene)glycine di(*tert*-butyl)methyl ester **13** and ethyl vinyl ketone with K_2CO_3 under the influence of chiral phase-transfer catalyst (*S*)-**9** to furnish conjugate adduct **16** with low enantioselectivity. However, use of chiral phase-transfer catalyst of type (*S*)-**15** and 10 mol % of CsCl in ether at 0 °C gave conjugate adduct **16** in 84 % yield with 94 % ee (Scheme 7) [16]. With the optimal reaction condition for asymmetric conjugate addition at hand, we carried out intramolecular reductive amination of **16** with Hantzsch ester (2 equiv) and CF_3CO_2H (1 equiv) in aqueous EtOH at 60 °C to furnish 2,5-disubstituted *cis*-pyrrolidine **17** stereospecifically in 84 % yield [17]. Of course, one-pot synthesis of *cis*-pyrrolidine **17** without isolation of adduct **16** was realized in a reasonable yield.



Scheme 7 One-pot synthesis of optically active pyrrolidine alkaloid core structures.

This information led us to develop a facile and short asymmetric synthesis of physiologically active (+)-monomorine in a highly stereoselective manner by way of key octahydroindolizine core structure **20** (Scheme 8). Accordingly, we carried out asymmetric conjugate addition of glycine ester **13** with α,β-enone **18** (2.0 equiv) and K_2CO_3 (5 equiv) under the influence of chiral phase-transfer catalyst (*S*)-**15** and catalytic CsCl in ether at 0 °C for 8 h to give conjugate adduct **19** in 86 % yield with

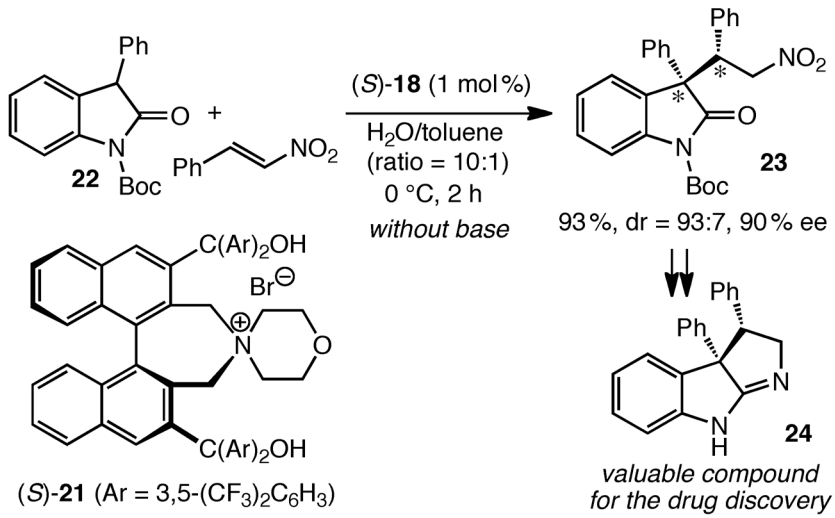


Scheme 8 Short-step synthesis of natural alkaloid, (+)-monomorine.

93 % ee. Intramolecular reductive amination of the adduct **19** and subsequent iminium ion formation followed by second reductive amination were effected with Hantzsch ester (5 equiv) and CF_3CO_2H in aqueous EtOH at 60 °C for 48 h to furnish octahydroindolizine core structure **20** in 61 % yield without loss of enantioselectivity. The absolute configuration of **20** was unambiguously confirmed by X-ray crystallographic analysis after reduction and subsequent *p*-bromobenzoate formation. The one-pot reaction of the whole reaction sequence was also realized without any difficulty by sequentially adding several different reagents to afford **20** in 48% overall yield. The transformation of the key intermediate **20** to (+)-monomorine was realized in a three-step sequence as shown in Scheme 8.

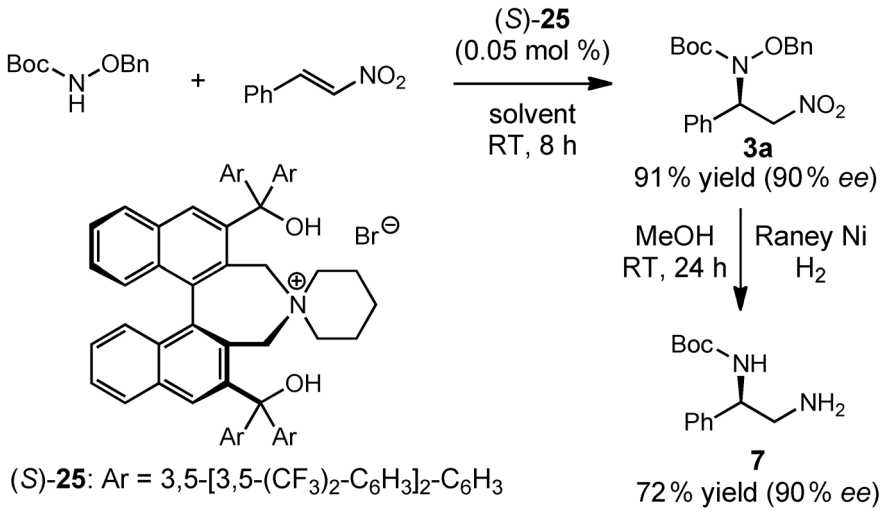
DESIGN OF CHIRAL BIFUNCTIONAL PHASE TRANSFER CATALYSTS

The development of new, catalytic asymmetric transformations by using a chiral metal-free catalyst in water solvent under neutral conditions with excellent atom economy is one of the most ideal approaches in current asymmetric synthesis from the viewpoint of green sustainable chemistry. Accordingly, we are interested in the possibility of realizing such an ideal transformation, and hence study to develop an environmentally benign asymmetric conjugate addition to nitroolefins under essentially neutral conditions in order to fulfill the four important keywords (i.e., metal-free, water, neutral, and atom economy) as described above. Although quaternary ammonium salts as phase-transfer catalysts are generally believed to require base additives for phase-transfer reactions, we discovered that even without any base additives the enantioselective phase-transfer conjugate addition of 3-phenyl oxindole **22** to β-nitrostyrene proceeded smoothly in the presence of chiral bifunctional ammonium bromide (*S*)-**21** under neutral conditions in water-rich solvent (i.e., H_2O/toluene = 10:1) with both high diastereomeric and enantiomeric ratios (Scheme 9) [17]. *Our finding is a very surprising and unusual result in the long-standing phase-transfer chemistry, and is quite desirable in green sustainable chemistry*. Importantly, both racemic and optically active conjugate adducts derived from 3-aryl oxindoles can be readily transformed into valuable natural products and their analogues as exemplified by the transformation of optically active conjugate adduct **23** (90 % ee) to the corresponding cyclization product **24**, which comprises a similar core structure with many important natural products such as flustramines and flustramides, etc. [18]. These natural product analogues might possess the important biological activity and hence are valuable for drug discovery.



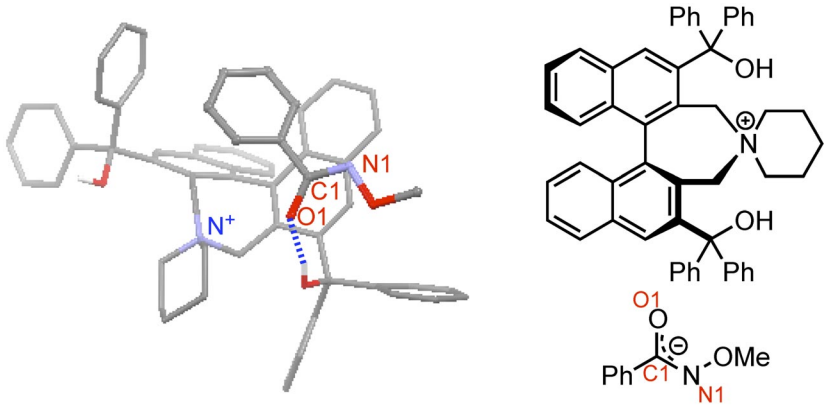
Scheme 9 Asymmetric base-free phase-transfer reaction in water-rich solvent.

We are also interested in the development of an environmentally benign asymmetric conjugate amination to nitroolefins under essentially neutral conditions. This transformation allows the efficient asymmetric synthesis of chiral 1,2-diamino compounds as a useful chiral building block in pharmaceutical areas. After various screeing of reaction conditions, an asymmetric neutral amination to nitroolefins was found to be catalyzed by chiral bifunctional tetraalkylammonium salts of type **25** with very low catalyst loading (0.05 mol %) in water-rich biphasic solvent (Scheme 10) [19]. Here, piperidine-derived catalysts (*S*)-**25** is found to be superior to morphorine-derived catalyst (*S*)-**21** in terms of enantioselectivity. It should be noted that asymmetric conjugate amination does not work well under the ordinary phase-transfer reaction conditions using aqueous base solutions, such as aqueous KOH, K_2CO_3, and PhCOOK solutions, and under the homogeneous reaction conditions without aqueous solution. Hence, the highly enantioselective conjugate amination of nitroolefins was only achieved when the reaction was performed under the base-free neutral phase-transfer conditions in water-rich biphasic solvent. The resulting amination products can be readily transformed by the catalytic hydrogenation with Raney Ni catalyst to the corresponding 1,2-diamines, which are versatile chiral building blocks from synthetic as well as pharmaceutical viewpoints.



Scheme 10 Asymmetric conjugate amination to nitrostyrene with (*S*)-**2c** under neutral phase-transfer conditions.

The X-ray crystal structure of chiral ammonium amide (*S*)-**26** provides important structural information. The bond lengths of amide moiety indicate that the negative charge of amide anion is delocalized on the nitrogen–carbon–oxygen atoms as shown in Scheme 11 [19]. Importantly, the hydrogen-bonding interaction between the hydroxy group in the binaphthyl unit and the oxygen of amide anion is clearly observed in the crystal structure of (*S*)-**26**.



Scheme 11 X-ray crystal structure of chiral ammonium amide (*S*)-**26**.

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