Recent Development and Application of Chiral Phase-Transfer Catalysts

Takuya Hashimoto and Keiji Maruoka*

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

Received April 23, 2007

Contents

1. Introduction

Phase-transfer catalysis has long been recognized as a versatile methodology for organic synthesis in both industrial and academic laboratories, featuring its simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and possibility to conduct large-scale preparations.[1] In particular, during more than the last two decades, asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral, nonracemic catalysts has become a topic of great scientific interest, and recent enormous efforts have resulted in notable achievements, making it feasible to perform various bond-formation reactions under mild phase-transfer-catalyzed conditions.[2] This review focuses on the recent progress on asymmetric reactions with various types of chiral quaternary ammonium salts as phase-transfer catalysts reported between 2000 and 2006, showcasing the variations of their molecular designs and synthetic applications. For literature coverage prior to this period, the reader should consult the excellent published reviews of asymmetric phase-transfer catalysis.[2]

2. Alkylation

2.1. Asymmetric Synthesis of α-Alkyl-α-Amino Acids and their Derivatives

2.1.1. Binaphthyl-Modified Phase-Transfer Catalyst for the Asymmetric Monoalkylation of Glycine Schiff Base

In 1989, after 5 years of the groundbreaking work by the Merck group,[3] *N*-benzyl cinchoninium halide as a chiral phase-transfer catalyst has been successfully utilized for the asymmetric alkylation of glycine Schiff base **2** as a key substrate by O'Donnell and co-workers.[4] Although asymmetric phase-transfer alkylation of glycine Schiff base **2** can be achieved by using chiral phase-transfer catalysts derived from relatively inexpensive, commercially available cinchona alkaloid, the research in this area had made little progress for some time after O'Donnell and co-workers' milestone reports. However, a new class of cinchona alkaloid-derived catalysts bearing an *N*-anthracenylmethyl function (third-generation catalyst) developed by Lygo and co-workers and Corey et al. independently[5,6] has opened a new era of asymmetric phase-transfer catalysis.

In 1999, we designed and prepared the structurally rigid, chiral spiro ammonium salts of type **1** derived from commercially available (*S*)- or (*R*)-1,1′-bi-2-naphthol as a new C_2-symmetric chiral phase-transfer catalyst and successfully applied it to the highly efficient, catalytic enantioselective alkylation of **2** under mild phase-transfer conditions (Scheme 1).[7]

The key finding was a significant effect of an aromatic substituent (Ar) at the 3,3′-position of one binaphthyl subunit of the catalyst **1** on the enantiofacial discrimination, and (*S*,*S*)-**1e** was revealed to be the catalyst of choice for the preparation of a variety of essentially enantiopure α-amino

* To whom correspondence should be addressed. Phone: +81-75-753-4041. Fax: +81-75-753-4041. E-mail: maruoka@kuchem.kyoto-u.ac.jp.

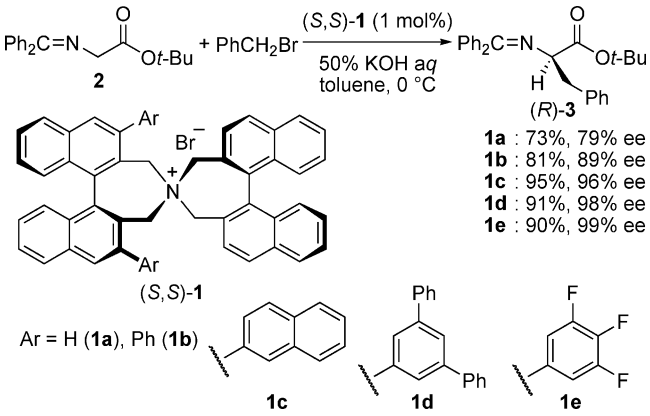
10.1021/cr068368n CCC: $65.00
Published on Web 12/12/2007

Takuya Hashimoto was born in Osaka, Japan. He received his Ph.D. degree (2006) from Kyoto University under the direction of Professor Keiji Maruoka. After spending one year as a postdoctoral researcher, he was appointed as an assistant professor at Kyoto University in 2007. His research interests include the design of chiral acid and base catalysts for the development of new synthetic methodologies and the use of diazo compounds in organic synthesis.

Keiji Maruoka was born in 1953 in Mie, Japan. He graduated from Kyoto University (1976) and received his Ph.D. (1980) from University of Hawaii (Thesis Director: Prof. H. Yamamoto). He became an assistant professor of Nagoya University (1980) and was promoted to a lecturer (1985) and an associate professor (1990) there. He moved to Hokkaido University as a full professor (1995–2001), and he currently is a professor of chemistry in Kyoto University since 2000. Recently, he was awarded the Inoue Prize for Science (2000), the Ichimura Prize for Science (2002), the Synthetic Organic Chemistry Award of Japan (2003), the Nagoya Silver Medal (2004), the Green and Sustainable Chemistry Award (2006), the Award by the Minister of Education, Culture, Sports, Science and Technology (2006), the Japan Chemical Society Award (2007), the Molecular Chirality Award (2007), and the Novartis Lectureship Award (2007/2008). He is a board member of *Chem. Commun.* and is a member of the international advisory editorial board of *Org. Biomol. Chem.* and *Chem. Asian J.* His current research interests include bidentate Lewis acids in organic synthesis and practical asymmetric synthesis with chiral C_2-symmetric phase-transfer catalysts and chiral bifunctional organocatalysts. He is now a leader of the group research project "Advanced Molecular Transformations of Carbon Resources" consisting of 100 university professors.

acids by this transformation. Generally, 1 mol % of **1e** is sufficient for the smooth alkylation, and the catalyst loading can be reduced to 0.2 mol % without loss of enantiomeric excess. 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 (−15 °C) is recommended. Since both enantiomers of the catalyst of type **1** can be readily assembled in exactly the same manner starting from either (*S*)- or (*R*)-1,1′-bi-2-naphthol, a wide

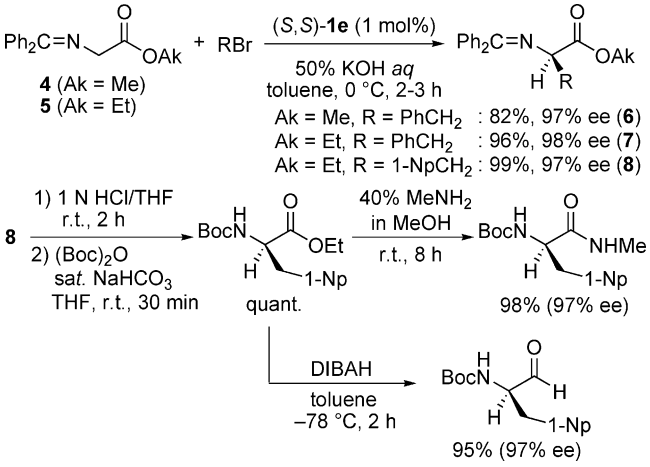
Scheme 1



variety of natural and unnatural α-amino acids can be synthesized in an enantiomerically pure form by the phase-transfer catalytic alkylation of **2**.

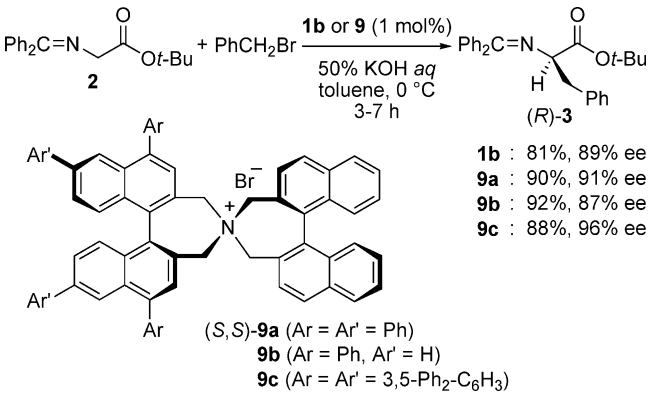
The salient feature of **1e** as a chiral phase-transfer catalyst is its ability to catalyze the asymmetric alkylation of glycine methyl and ethyl ester derivatives **4** and **5** with excellent enantioselectivities. Since methyl and ethyl esters are certainly more susceptible toward nucleophilic additions than *tert*-butyl ester, the synthetic advantage of this process is quite obvious and highlighted by the facile transformation of the alkylation products (Scheme 2).[8]

Scheme 2



With the critical role of 3,3′-diaryl substituents of **1** in mind, we examined the effect of 4,4′- and 6,6′-substituents of one binaphthyl subunit. As shown in Scheme 3, introduc-

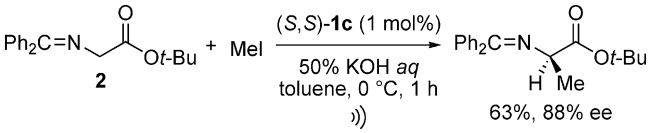
Scheme 3



tion of simple aromatic groups even at 4,4′-position leads to the exhibition of a meaningful effect on the stereoselectivity of the phase-transfer-catalyzed alkylation of **2**.[9a]

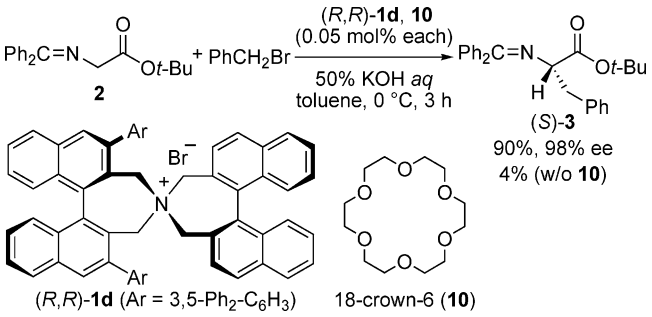
We also made research efforts aiming at the substantial reactivity enhancement of *N*-spiro chiral quaternary ammonium salt and the simplification of its structure in view of establishing a truly practical method for the asymmetric synthesis of α-amino acids and their derivatives. Since ultrasonic irradiation produces homogenization, i.e., very fine emulsions, it greatly increases the reactive interfacial area, which could deliver substantial rate acceleration in the liquid−liquid phase-transfer reactions. Indeed, sonication of the reaction mixture of **2**, methyl iodide, and (*S*,*S*)-**1c** (1 mol %) in toluene−50% KOH aqueous solution at 0 °C for 1 h gave rise to the corresponding alkylation product in 63% yield with 88% ee (enantiomeric excess), demonstrating that the reaction was sped up markedly, and the chemical yield and enantioselectivity were comparable with those of the reaction with simple stirring (0 °C for 8 h; 64%, 90% ee) (Scheme 4).[10]

Scheme 4



To fully induce the potential catalytic activity of *N*-spiro chiral ammonium salt such as **1d**, we have developed binary phase-transfer catalysis using an appropriate achiral cocatalyst. For instance, the phase-transfer-catalyzed alkylation of **2** with benzyl bromide under the influence of **1d** (0.05 mol %) turned out to be sluggish to give **3** 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 **3** in 90% yield with 98% ee. The origin of this dramatic rate enhancement would be the ability of the crown ether to extract KOH into the toluene phase, accelerating the otherwise slow deprotonation process (Scheme 5).[11] Indeed, use

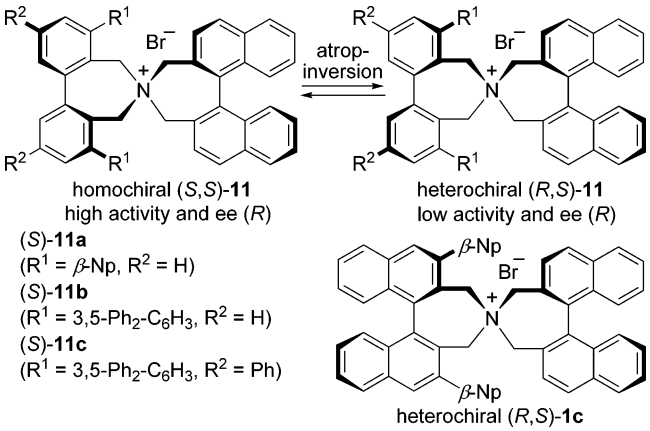
Scheme 5



of small-sized crown ethers such as 15-crown-5 and 12-crown-4 dramatically lowered the chemical yield of **3**. Interestingly, tetrabutyl- and tetraoctylammonium salts also exhibited similar acceleration effects.

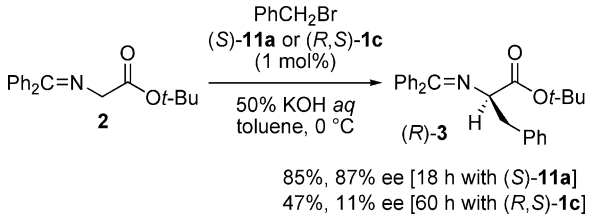
Although the conformationally rigid, *N*-spiro structure created by two chiral binaphthyl subunits represents a characteristic feature of **1** and related catalyst **9**, it also imposes limitations on the catalyst design due to the imperative use of the two different chiral binaphthyl moieties. Accordingly, we developed a new C_2-symmetric chiral quaternary ammonium bromide **11** incorporating an achiral, conformationally flexible biphenyl subunit (Scheme 6).[12]

Scheme 6



The phase-transfer benzylation of **2** with the catalyst (*S*)-**11a** having a β-naphthyl group on the 3,3′-position of the flexible biphenyl moiety proceeded smoothly at 0 °C to afford the corresponding alkylation product **3** in 85% yield with 87% ee (*R*) after 18 h (Scheme 7). The origin of the

Scheme 7



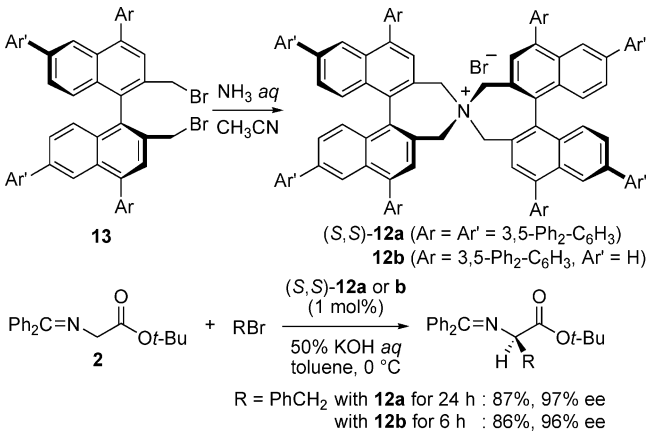
observed chiral efficiency could be ascribed to the considerable difference of catalytic activity between the rapidly equilibrated, diastereomeric homo- and heterochiral catalysts; namely, homochiral (*S*,*S*)-**11a** is primarily responsible for the efficient asymmetric phase-transfer catalysis (PTC) to produce **3** with high enantiomeric excess, whereas heterochiral (*R*,*S*)-**11a** displays low reactivity and stereoselectivity. 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, even after 60 h, gave rise to **3** in 47% yield with 11% ee (*R*), as also shown in Scheme 7.

This unique phenomenon provides a 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 appreciated in the synthesis of a variety of chiral catalysts with different steric and/or electronic properties. Actually, quaternary ammonium bromide possessing a sterically demanding substituent such as (*S*)-**11b** can be easily prepared, and the benzylation of **2** with (*S*)-**11b** as a catalyst gave **3** in 95% yield with 92% ee. Further, the enantioselectivity was enhanced to 95% ee with (*S*)-**11c** as a catalyst.

On the other hand, we were intrigued with the preparation of symmetrical *N*-spiro type catalyst 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

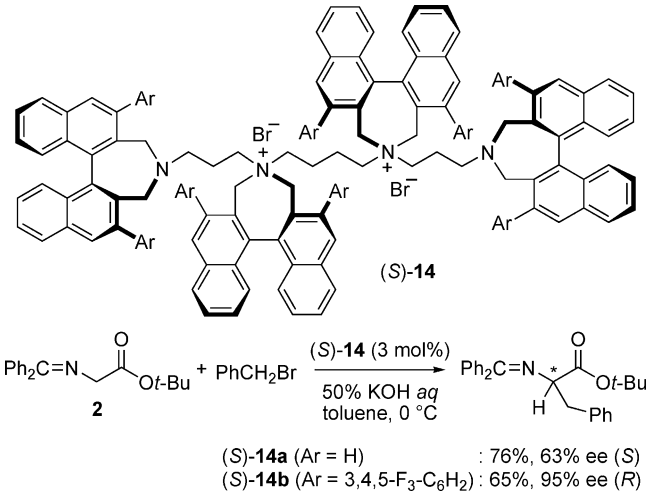
of salts. Evaluation of **12** as a chiral phase-transfer catalyst in the alkylation of **2** uncovered its high catalytic and chiral efficiency (Scheme 8).[9b]

Scheme 8



Our further efforts toward the simplification of the catalyst have led to the design of new, polyamine-based chiral phase-transfer catalysts of type **14** with the expectation of the multiplier effect of chiral auxiliaries as illustrated in Scheme 9.[13] The chiral efficiency of such polyamine-based chiral

Scheme 9

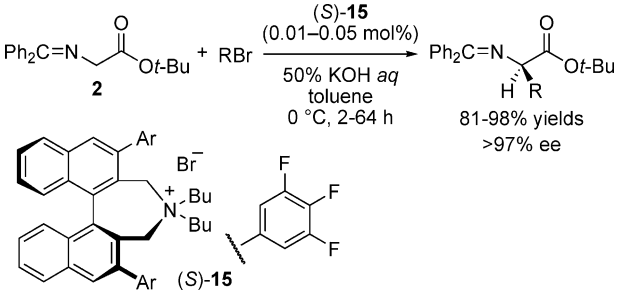


phase-transfer catalysts (*S*)-**14** was examined by carrying out asymmetric alkylation of glycine derivative under phase-transfer conditions. Among various commercially available polyamines, spermidine- and spermine-based polyammonium salts were found to show moderate enantioselectivity. In particular, introduction of the 3,4,5-trifluorophenyl group at 3,3′-positions of chiral binaphthyl moieties (**14b**) showed excellent asymmetric induction.

This finding 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 unusually active chiral phase-transfer catalyst. Most notably, the reaction of **2** with various alkyl halides proceeded smoothly under mild phase-transfer conditions in the presence of only 0.01−0.05 mol % of (*S*)-**15** to afford the corresponding alkylation products with excellent enantioselectivities (Scheme 10).[14]

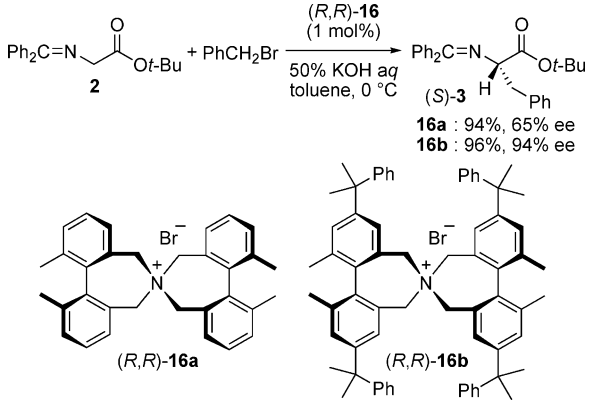
We have been interested in the development of C_2-symmetric phase-transfer catalysts, which consist of two

Scheme 10



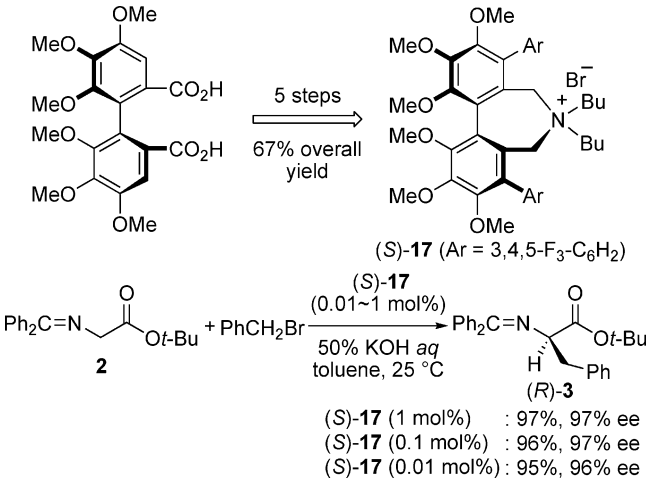
chiral biphenyl units, as a new, easily modifiable subunit for further elaboration. To this end, chiral phase-transfer catalyst **16** was synthesized and evaluated in the asymmetric alkylation of glycine Schiff base **2** (Scheme 11).[15]

Scheme 11

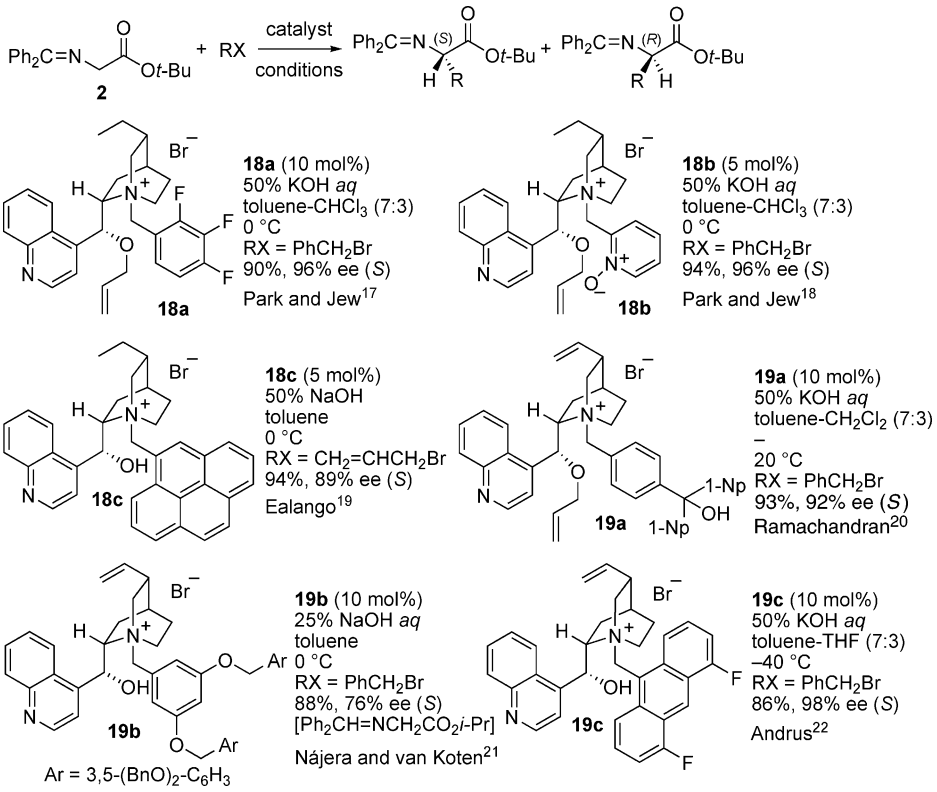


In designing practical phase-transfer catalysts, the ready availability of starting chiral sources is crucial. Accordingly, a highly practical, chiral phase-transfer catalyst **17** was conveniently prepared from the known, readily available (*S*)-4,5,6,4′,5′,6′-hexamethoxybiphenyldicarboxylic acid derived from gallic acid. This catalyst (*S*)-**17** 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).[16]

Scheme 12



Scheme 13. Cinchona Alkaloid Derived Monoammonium Salts



2.1.2. Other Chiral Phase-Transfer Catalysts for the Alkylation of Glycine Schiff Base

Some pioneering works and our research have prompted the development of various chiral phase-transfer catalysts in the past decade. They are classified into three groups: (1) cinchona alkaloid derivatives (Schemes 13 and 14),[17−27] (2) tartrate derivatives (Scheme 15),[28−30] and (3) others (Scheme 16).[31−35] According to this classification, the catalytic activities of these catalysts are summarized in the following schemes. Among these, the development of bis- and tris-ammonium phase-transfer catalysts represented by Park, Jew, and co-workers[23−25] and Shibasaki and co-workers[28] is especially noteworthy. Intriguingly, these bis- and tris-ammonium salts generally exhibit higher reactivity and selectivity compared to the corresponding monoammonium salts.

2.1.3. Effect of the Counterions in the Asymmetric Alkylation of Glycine Schiff Base

Taking the reaction pathway of the phase-transfer catalysts into consideration, it is quite interesting that the counterion affects the enantioselectivity of the process in some cases. This observation was revealed by Shibasaki and co-workers for the first time during their research on phase-transfer catalyzed allylation of **2** with **24b**. Thus, the reaction catalyzed by **24b** that contains tetrafluoroborate as counterions provided the alkylated compound in better enantiomeric excess than the reaction catalyzed by **24a** (Scheme 15). Further, inspired by Shibasaki's report, Nájera prepared dimeric salts **22a** with bromide, **22b** with tetrafluoroborate, and **22c** with hexafluorophosphate, respectively, and the counterion effect was examined. Consequently, a most remarkable increment in the enantioselectivity was observed in the reaction of **2** with *tert*-butyl bromoacetate (Scheme 14). The counterion effect was also investigated in the monomeric chiral phase-trasnfer catalyst by Nájera and co-workers.[37]

2.1.4. Organic Solvent-Free Condition

Phase-transfer alkylation of glycine Schiff base under organic solvent free conditions was investigated by Takabe and co-workers.[38] As salient features of the organic solvent free condition, the higher chemical yield and the depression of the imine hydrolysis are described. Zhang and co-workers also reported the organic solvent-free reaction separately.[39] In both cases, Lygo's *N*-anthracenylmethyl cinchonidinium chloride **19d** was found to be optimal (Scheme 17).

2.1.5. Other Glycine Esters

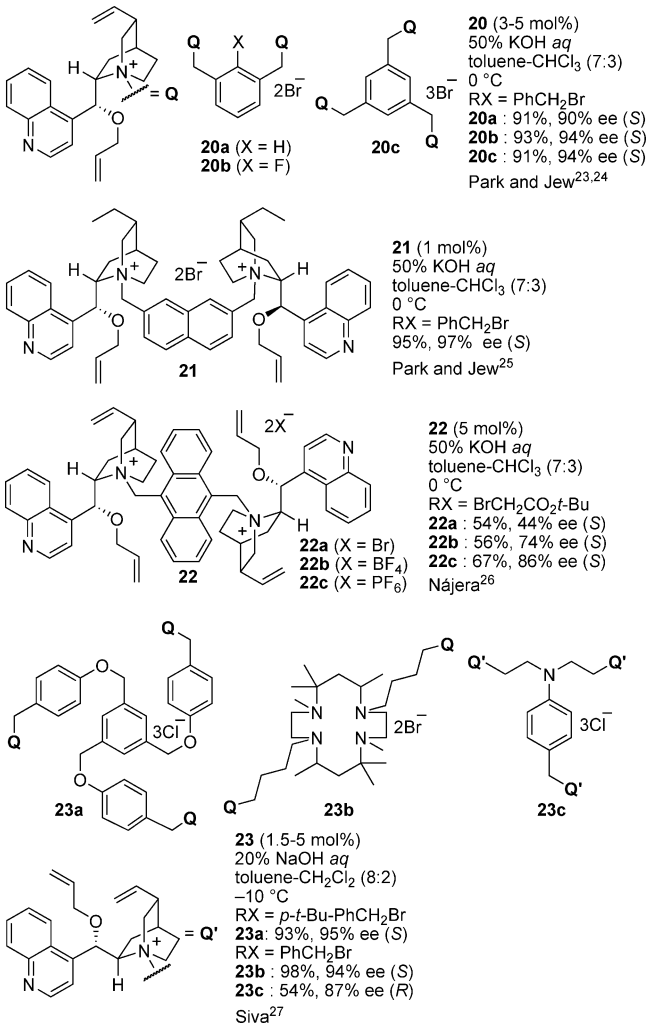
As described above, benzophenone imine glycine Schiff base was successfully applied to the asymmetric α-amino acid synthesis. However, the rather difficult procedure for its synthesis is considered to be the major drawback for its industrial application. At this point, we disclosed that glycine *tert*-butyl ester aldimine Schiff base **32**, which is normally employed for the synthesis of α,α-dialkyl-α-amino acids, can be also utilized for α-alkyl-α-amino acids under the influence of **1e** or **15**. This finding demonstrated the possibility to use glycine *tert*-butyl ester aldimine Schiff base instead of benzophenone Schiff base as a cost-effective way to obtain optically active α-alkyl-α-amino acids (Scheme 18).[40]

Use of glyoxylic acid ester imines, such as **33**, as unique glycine Schiff base equivalents was reported by DSM research group.[41] Imine isomerization prior to the alkylation provides the reactive glycine Schiff base in the reaction system. This approach may have an advantage considering the facile preparation of these glyoxylic acid ester imines compared to glycine Shiff bases (Scheme 19).

2.1.6. Glycine Amides

As prochiral glycine-derived Schiff bases, not only esters but also amides can be used as suitable substrates for the

Scheme 14. Cinchona Alkaloid Derived Bis- and Tris-Ammonium Salts

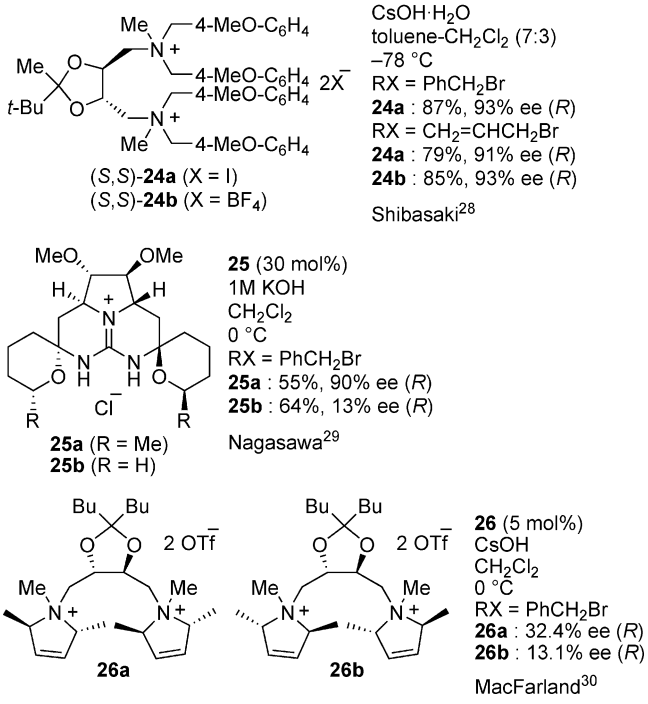


asymmetric alkylation under phase-transfer conditions. Kumar and Ramachandran demonstrated the effectiveness of *N*-anthracenylmethyl cinchonidinium chloride **19d** for the benzylation of various Schiff bases of tertiary glycine amides **34** (Scheme 20).[42] Generally, low enantioselectivity was observed in the reaction with substrates having secondary amide moiety.

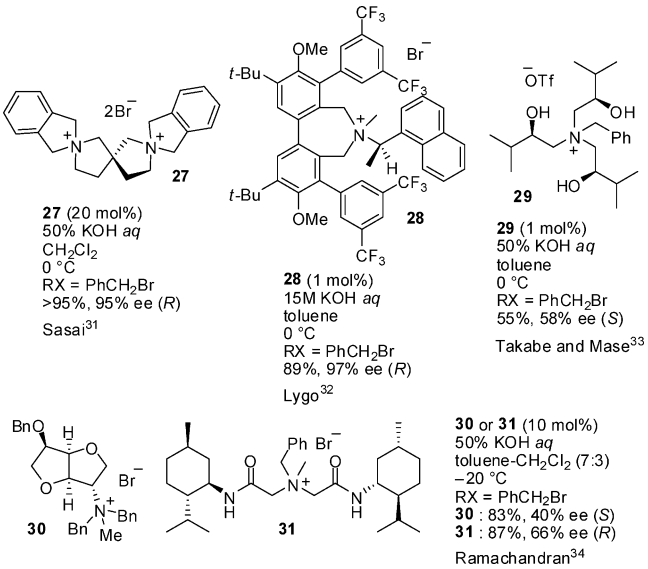
Using glycine diphenylmethyl (Dpm) amide-derived Schiff base **35** as a key substrate and *N*-spiro chiral quaternary ammonium bromide **1g** as an ideal catalyst, we achieved high enantioselectivity even in the alkylation with less-reactive simple secondary alkyl halides. This system offers a facile access to structurally diverse optically active vicinal diamines in combination with the subsequent reduction (Scheme 21).[43]

Furthermore, our approach was found to be successfully applicable to the asymmetric alkylation of Weinreb amide derivative **36** utilizing **1f** as a catalyst. Optically active α-amino acid Weinreb amide **37** can be efficiently converted to the corresponding aminoketone by a simple treatment with Grignard reagents. In addition, reduction and alkylation of the optically active α-aminoketones **38** and **39** into both *syn*- and *anti*-α-amino alcohols with almost complete relative and absolute stereochemical control have been achieved (Scheme 22).[44]

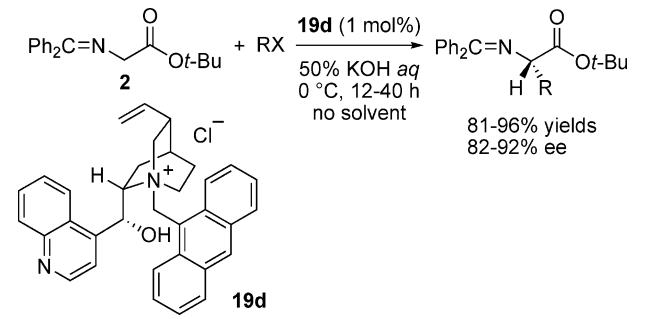
Scheme 15. Tartrate Derived Ammonium Salts



Scheme 16. Other Phase-Transfer Catalysts



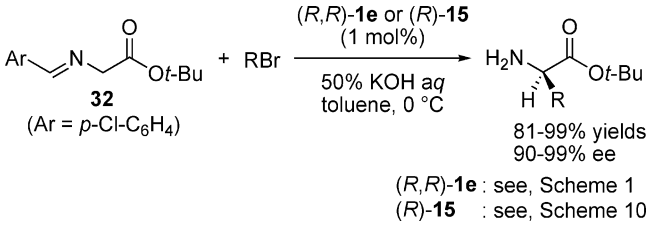
Scheme 17



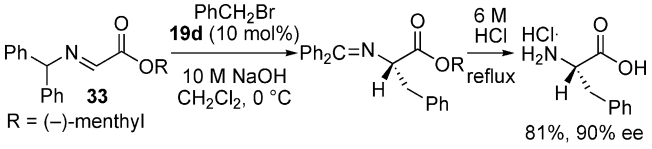
2.1.7. Diastereoselectvie Alkylation of Glycine Schiff Base with Optically Enriched Alkyl Halides

Despite numerous efforts for the development of the asymmetric phase-transfer catalyzed alkylation of **2** into a

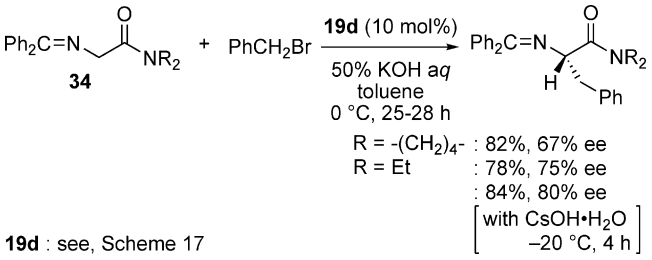
Scheme 18



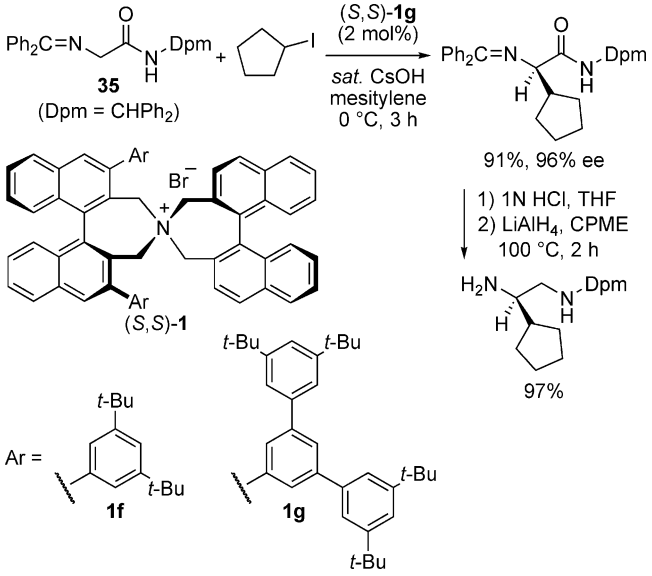
Scheme 19



Scheme 20

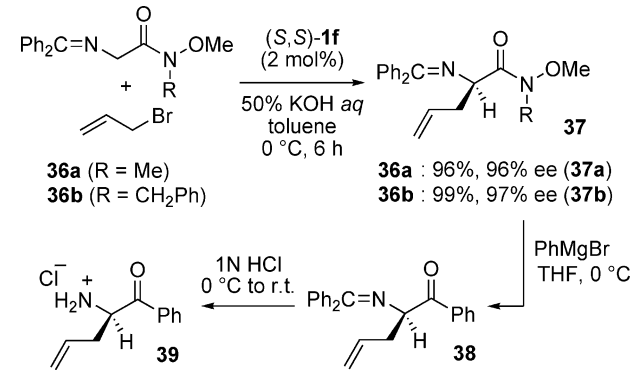


Scheme 21

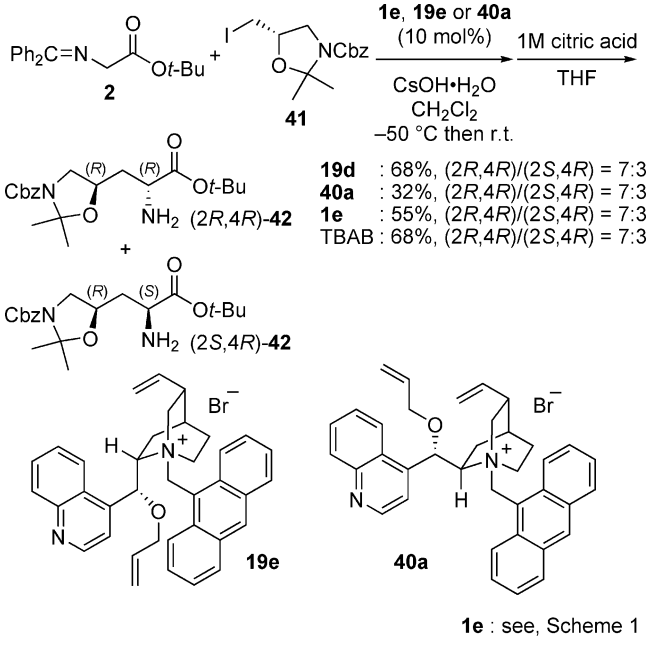


powerful method for the synthesis of natural and unnatural α-amino acids, the stereochemistry of the alkylation of **2** with chiral electrophiles has scarcely been addressed. Zhu and co-workers investigated the reaction of **2** with stereochemically defined (5*S*)-*N*-benzyloxycarbonyl-5-iodomethyl oxazolidine **41** using Corey's *O*-allyl-*N*-anthracenylmethyl cinchonidinium bromide **19e** to prepare (2*S*,4*R*)-4-hydroxyornithine for the total synthesis of biphenomycin. Unexpectedly, however, product **42** with a 2*R* absolute configuration was formed as a major isomer. Further, the diastereomeric ratio was not affected by the chirality and structure of the catalysts employed, indicating that the asymmetric induction during the alkylation was dictated by the substrate (Scheme 23).[45]

Scheme 22

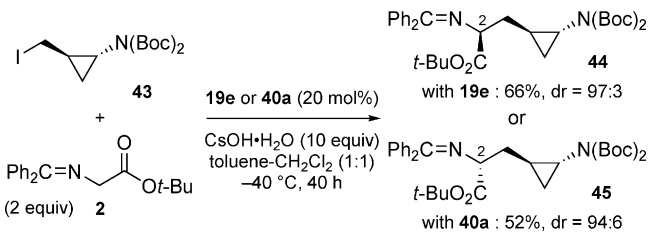


Scheme 23



Armstrong and Scutt reported a concise synthesis of 3-(*trans*-2-aminocyclopropyl)alanine, a component of belactosin A, through the highly diastereoselective alkylation of **2** with optically pure alkyl iodide **43** under phase-transfer conditions. Under thoroughly optimized conditions, the desired products **44** and **45** were obtained in good yields and the C(2) configuration was rigorously controlled by changing the chirality of the cinchona alkaloid-derived catalyst (Scheme 24).[46]

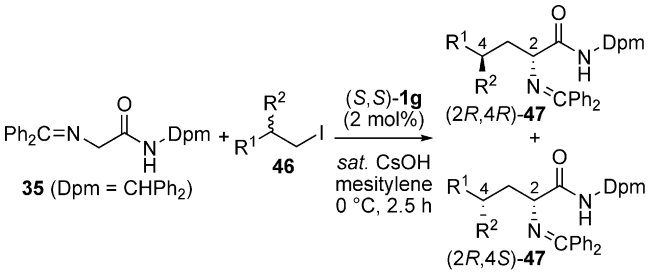
Scheme 24



In connection with our study on the stereoselective functionalization of prochiral glycine Dpm amide derivative **35**, we found that chiral ammonium enolate generated from **1g** and **35** had an ability to recognize the chirality of β-branched primary alkyl halides, which provides impressive levels of kinetic resolution during the alkylation with racemic

halide **46**, allowing for two α- and γ-stereocenters of **47** to be controlled, as exemplified in Scheme 25.[44]

Scheme 25



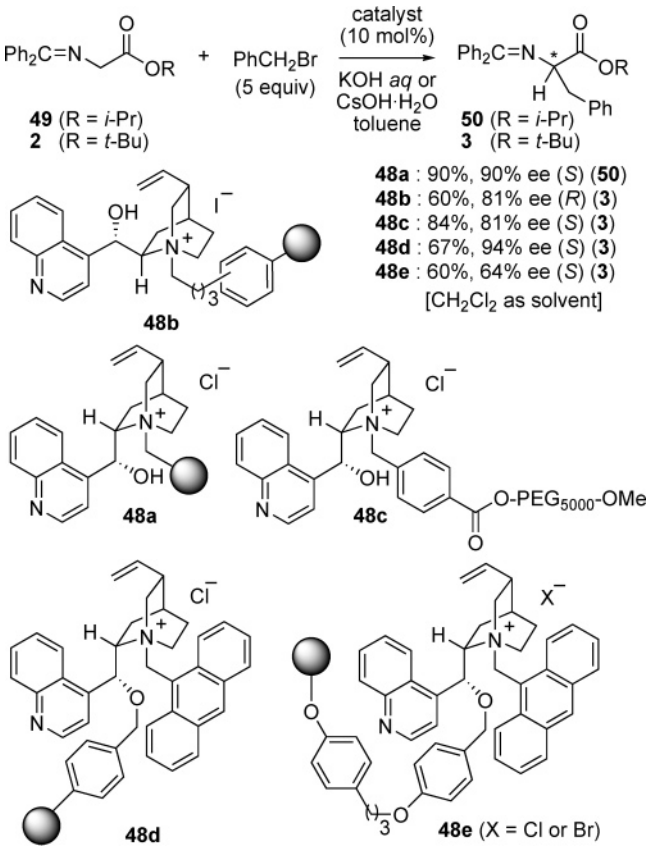
2.1.8. Recyclable Catalysts and Reagents and Solid-Phase Synthesis

The enantioselective synthesis of α-amino acids employing easily available and reusable chiral catalysts or reagents presents clear advantages for large-scale application. Nájera and co-workers prepared resin-supported ammonium salt **48a** by reaction of cross-linked chloromethylated polystyrene (Merrifield resin) and employed it as a chiral phase-transfer catalyst for the alkylation of glycine isopropyl ester-derived Schiff base **49**.[47] Optimization of the reaction parameters in the benzylation led to the formation of **50** in 90% yield with 90% ee. Cahard and co-workers investigated the role of flexible methylene spacer between the quaternary ammonium moiety and the polystyrene backbone in the similar benzylation of **2**, and they found that catalyst **48b** anchored to the matrix through the four lengths of carbon spacers was optimal, giving **3** with 81% ee.[48] Cahard and co-workers also introduced cinchonidine-derived quaternary ammonium salt grafted to a poly(ethylene glycol) matrix **48c** as an efficient homogeneous catalyst for the asymmetric alkylation of **2**, and up to 81% ee was attained in the benzylation under standard liquid−liquid phase-transfer conditions.[49] Meanwhile, Cahard, Plaquevent, and co-workers succeeded in improving the enantioselectivity by attaching Merrifield resin on the hydroxy moiety of cinchonidine-derived catalyst possessing a 9-anthracenylmethyl group on nitrogen **48d**.[50] Benaglia and co-workers immobilized the third-generation catalyst on modified poly(ethylene glycol) through the alkylation of C(9) hydroxy functionality. The chiral ammonium salt **48e** thus obtained acts as a homogeneous catalyst in the benzylation of **2** to afford **3** with a maximum ee of 64%).[51] These results are showcased in Scheme 26.

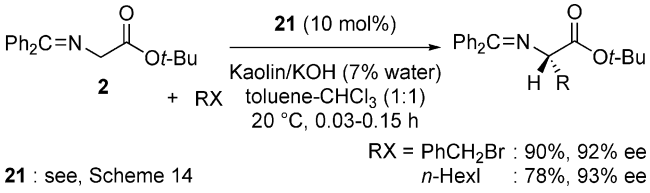
Yu and Koshima reported a utility of solid support preloaded with base for the asymmetric alkylation of **2**. Typically, a solution of **2**, alkyl halide, and catalyst **21** in toluene/$CHCl_3$ was slowly dispersed on kaolin clay-preloaded KOH, and the so-obtained solid was just stirred at 20 °C. Here, residual traces of water on the support dramatically accelerated the reaction to complete within a few minutes, giving rise to the corresponding alkylation product in good yields with high enantioselectivities (Scheme 27).[52]

A recyclable fluorous chiral phase-transfer catalyst **51** has been developed in our group, and its high chiral efficiency and reusability have been demonstrated in the asymmetric alkylation of **2**. After the reaction, **51** could be easily recovered by the simple extraction with FC-72 (perfluorohexanes) as a fluorous solvent and could be used for the next run without any loss of reactivity and selectivity (Scheme 28).[53]

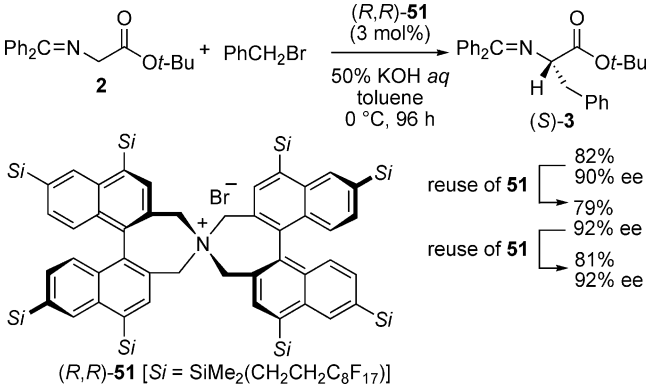
Scheme 26



Scheme 27



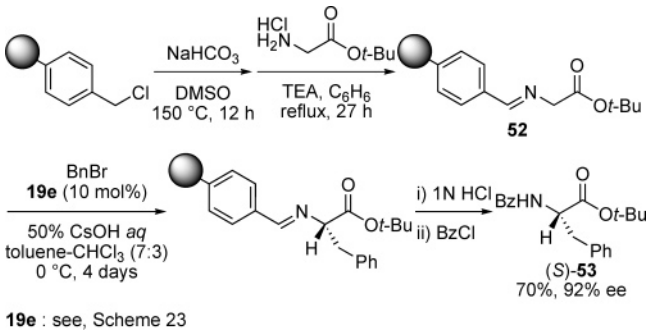
Scheme 28



Solid-phase synthesis, in which polymer-bound substrates are utilized, has some advantages over liquid-phase synthesis, such as easy purification and application to combinatorial chemistry. Park, Jew, and co-workers utilized Merrifield-resin-supported glycine Schiff base **52** for asymmetric alkylation under PTC conditions. Considering the sensitivity

of the ester groups for the enantioselectivity, aldimine linker was chosen and asymmetric alkylation was performed by use of 10 mol % *O*-allyl *N*-anthracenylmethyl cinchonidinium bromide **19e**. *N*-Benzoyl-α-amino acid *tert*-butyl ester **53** could be isolated after treating the solid-bound products with aqueous hydrochloric acid and protection with benzoyl chloride (Scheme 29).[54]

Scheme 29

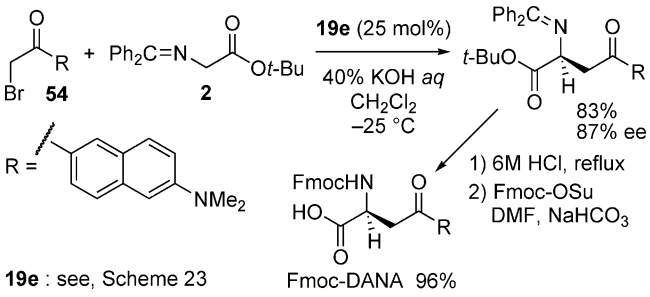


2.1.9. Applications of the Asymmetric Synthesis of α-Amino Acids

The vast synthetic utility of the asymmetric phase-transfer alkylation of glycine Schiff base **2** has been visualized by its successful application to synthesize various types of useful amino acid derivatives and natural products.

6-(2-Dimethylaminonaphthoyl)alanine (DANA) was prepared by Imperiali as a highly fluorescent amino acid through the asymmetric alkylation of **2** with α-bromoketone **54** using **19e** as a phase-transfer catalyst, and incorporated into the *S*-peptide of RNase S, establishing the large changes in fluorescence that can occur upon peptide−protein interaction (Scheme 30).[55]

Scheme 30

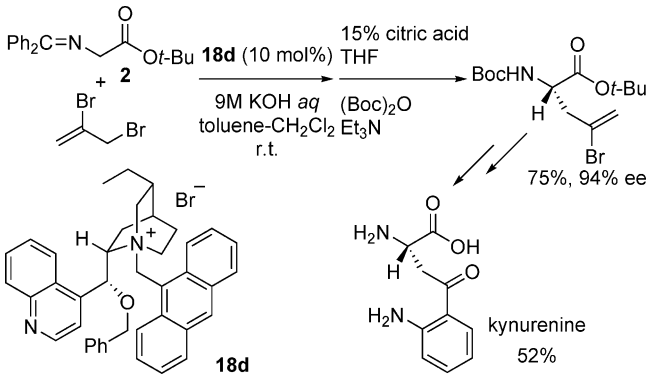


Lygo and Andrews employed 2,3-dibromopropene as a masked α-haloketone and, in combination with Suzuki-Miyaura coupling and ozonolysis, provided an alternative access to various aroylalanine derivatives, as exemplified in Scheme 31.[56]

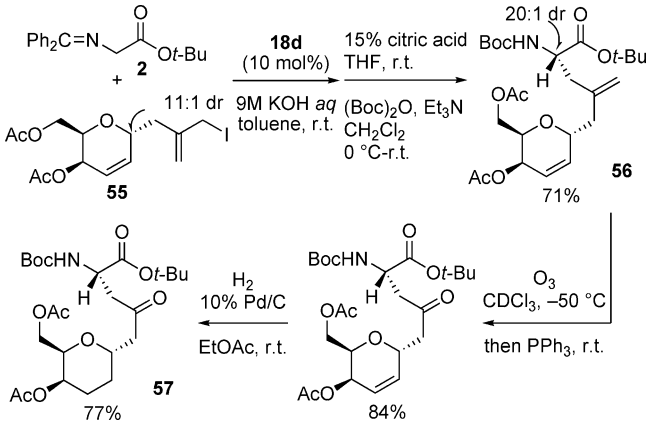
Lygo et al. utilized a similar strategy for the stereoselective synthesis of *C*-glycosylasparagines. For instance, the liquid−liquid phase-transfer alkylation of **2** with stereochemically defined allylic iodide **55** followed by the imine hydrolysis and reprotection afforded **56** in 71% overall yield with high diastereoselectivity. The selective oxidative cleavage of the 1,1-disubstituted olefin and subsequent hydrogenation of the remaining double bond furnished the target **57** (Scheme 32).[57]

Another useful feature of the phase-transfer alkylation of **2** was also demonstrated by Lygo and Humphreys, that is, rapid H/D exchange of **2** upon using KOD/D_2O as the

Scheme 31

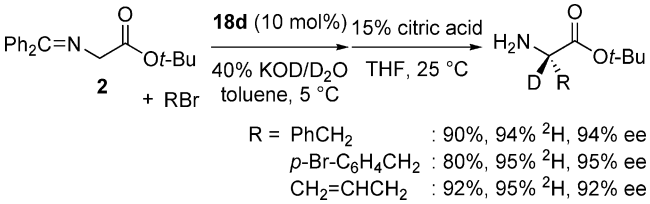


Scheme 32



aqueous phase. This offers a convenient yet efficient means of preparing labeled α-amino acid esters as shown in Scheme 33.[58]

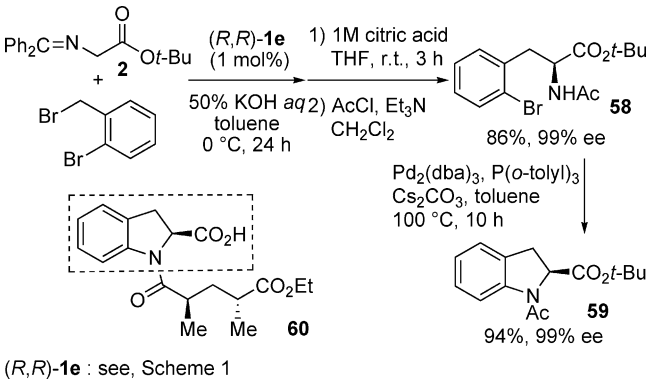
Scheme 33



With both enantiomers of **1e** in hand, we carried out asymmetric synthesis of (*S*)-*N*-acetylindoline-2-carboxylate **59**, a key intermediate in the synthesis of the ACE inhibitor **60**. The structure and stereochemical integrity of **59** was simultaneously constructed by the asymmetric alkylation of **2** with *o*-bromobenzyl bromide in the presence of (*R*,*R*)-**1e**, and subsequent hydrolysis and *N*-acetylation afforded **58** in 86% yield with 99% ee. According to Buchwald's procedure, almost enantiopure **58** was efficiently converted to **59** (94%, 99% ee) (Scheme 34).[7e]

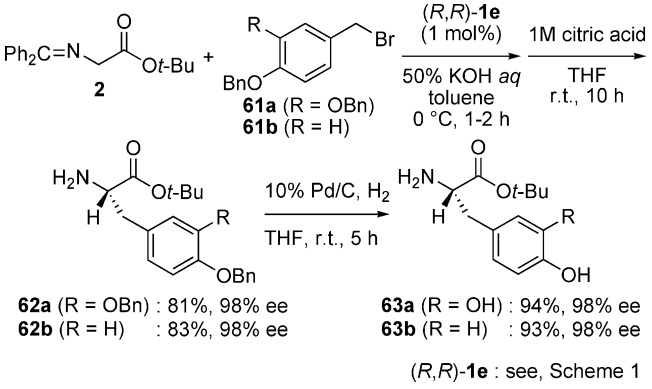
The chiral phase-transfer catalysis of **1e** was further applied to the facile synthesis of L-Dopa ester and its analogue, which have usually been prepared by either asymmetric hydrogenation of eneamides or enzymatic processes and tested as potential drugs for the treatment of Parkinson's disease. Phase-transfer-catalyzed alkylation of **2** with the requisite benzyl bromide **61a** in toluene−50% KOH aqueous solution proceeded smoothly at 0 °C under the influence of (*R*,*R*)-**1e** to furnish fully protected L-Dopa *tert*-butyl ester, which was subsequently hydrolyzed to afford

Scheme 34



the corresponding amino ester **62a** in 81% yield with 98% ee. Debenzylation of **62a** under catalytic hydrogenation conditions produced the desired L-Dopa *tert*-butyl ester **63a** in 94% yield. The successful asymmetric synthesis of natural tyrosine *tert*-butyl ester **63b** in a similar manner strongly implies the feasibility of highly enantioselective synthesis of various L-Dopa analogues (Scheme 35).[7e,59]

Scheme 35

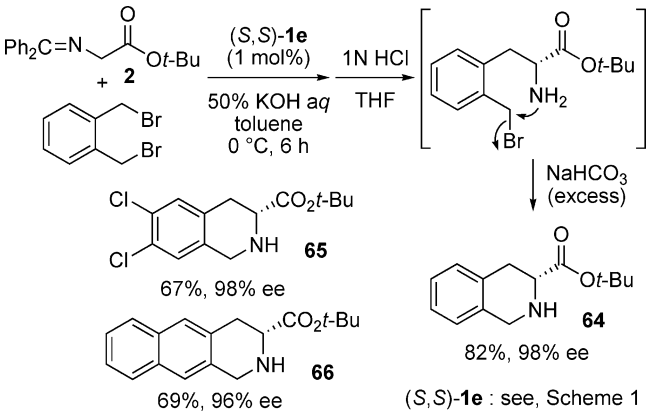


The catalytic and chiral efficiency of (*S*,*S*)-**1e** was also appreciated in the asymmetric synthesis of isoquinoline derivatives, important conformationally constrained α-amino acids. Treatment of **2** with α,α′-dibromo-*o*-xylene under liquid−liquid phase-transfer conditions in the presence of (*S*,*S*)-**1e** showed complete consumption of the starting Schiff base. Imine hydrolysis and subsequent treatment with an excess amount of $NaHCO_3$ facilitated intramolecular ring closure to give 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butyl ester **64** in 82% yield with 98% ee. A variety of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives possessing different aromatic substituents such as **65** and **66** can be conveniently prepared in a similar manner with excellent enantioselectivity (Scheme 36).[60]

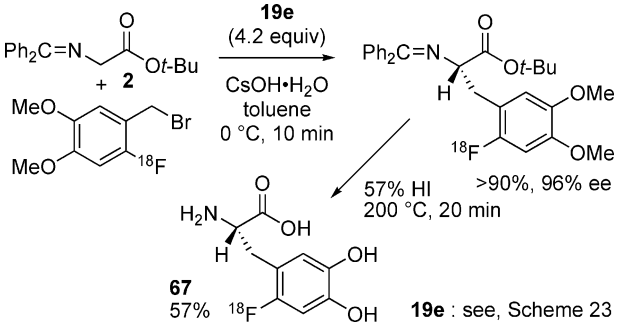
Lemaire et al. synthesized [^{18}F]fluoro-L-Dopa **67**, an important radiopharmaceutical for positron emission tomography (PET), by the asymmetric alkylation of **2** with 2-[^{18}F]-fluoro-4,5-dimethoxybenzyl bromide under phase-transfer conditions using $CsOH{\cdot}H_2O$ as a base and *O*-allyl-*N*-anthracenylmethyl cinchonidinium bromide **19e** as a stereocontroller. Although an excess amount of **19e** was required, the reaction completed within 10 min to give radiochemically and enantiomerically pure **67** after hydrolysis (Scheme 37).[61]

Kuman and Ramachandran reported an efficient catalytic route to levobupivacaine, an azacyclic amino acid amide showing anesthetic activity. The key step involves the (*R*,*R*)-

Scheme 36

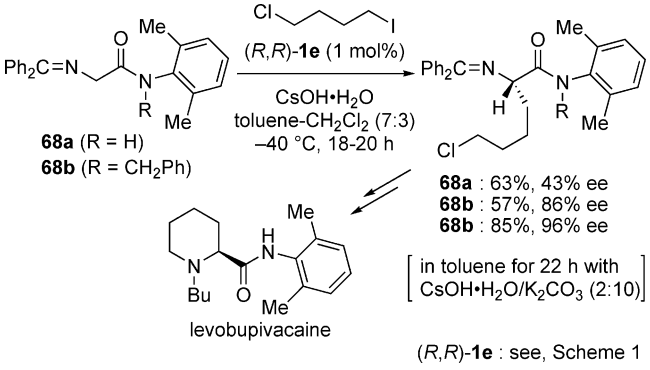


Scheme 37



1e-catalyzed asymmetric phase-transfer alkylation of glycine amide-derived Schiff base **68**, where the *N*-benzylated **68b** was found to be more suitable as a substrate for attaining high selectivity (Scheme 38).[62]

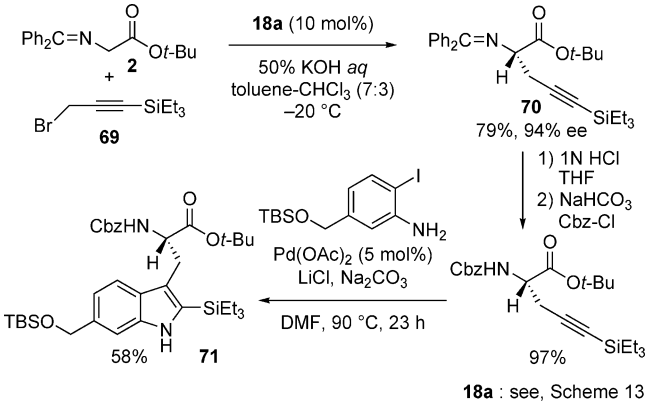
Scheme 38



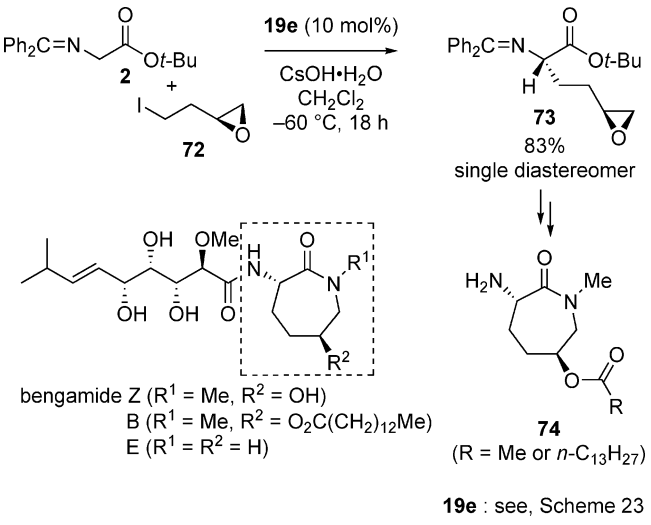
Castle and Srikanth showed that the alkylation of **2** with propargylic bromide **69** was catalyzed by the chiral quaternary ammonium bromide **18a** under phase-transfer conditions. The resulting enantiomerically enriched **70** was then transformed to **71**, the central tryptophan residue of celogentin C, through the palladium-catalyzed heteroannulation. This process allows an efficient assembly of tryptophan derivatives having substituent on the indole ring (Scheme 39).[63]

For establishing a practical enantioselective total synthesis of the bengamides B, E, and Z, Boeckman et al. achieved the highly diastereoselective alkylation of **2** with optically active iodoepoxide **72** based on Corey's protocol. Essentially diastereopure product **73** was successfully derivatized to the desired amino caprolactam **74** (Scheme 40).[64]

Scheme 39

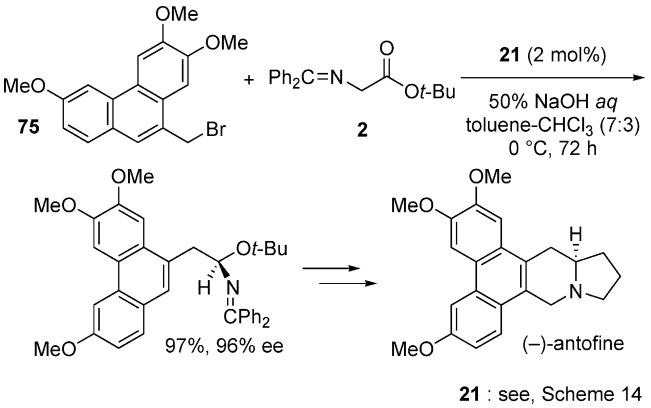


Scheme 40



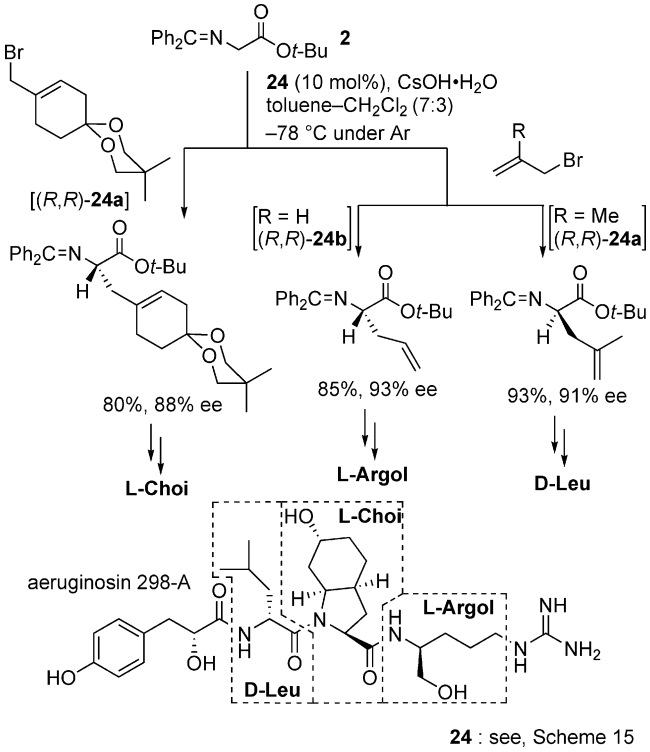
Kim et al. used cinchonidine-derived dimeric catalyst **21** for the enantioselective alkylation of **2** with appropriately functionalized phenanthryl bromide **75,** which constitutes one of the key steps of the asymmetric total synthesis of (−)-antofine (Scheme 41).[65]

Scheme 41



Shibasaki and co-workers demonstrated the power of tartrate-derived bis-ammonium salt **24** as a chiral phase-transfer catalyst by the application to enantioselective synthesis of aeruginosin 298-A and its analogues, which have serine protease inhibitor activity. The structure and stereochemistry of the three characteristic amino acid components, D-Leu, L-Choi, and L-Algol, were nicely constructed through

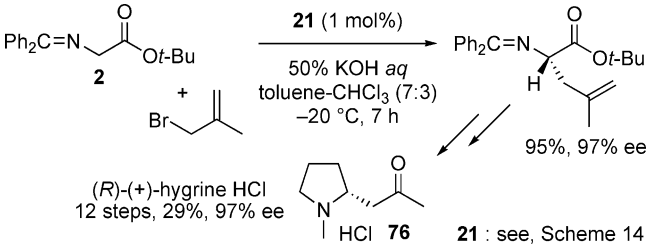
Scheme 42



the asymmetric alkylation of **2** with requisite alkyl halides, as illustrated in Scheme 42.[28b,66]

Park, Jew, and co-workers applied their dimeric dihydrocinchonidinium salt **21** to the synthesis of hygrine hydrochloride salt **76.** Asymmetric methallylation of glycine Schiff base **2** was chosen as a key step and completed the synthesis with 12 steps in overall 29% yield. They also succeeded in the determination of the absolute configuration of the (+)-hygrine as *R* (Scheme 43).[67]

Scheme 43

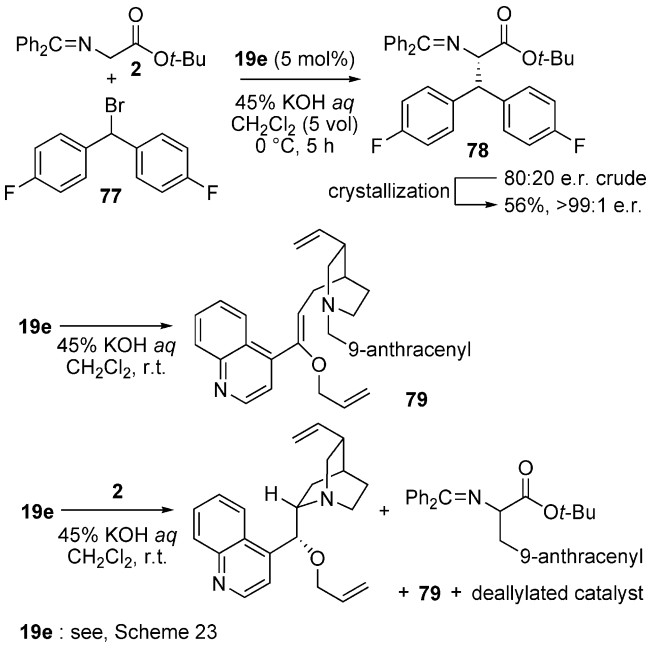


GlaxoSmithKline group synthesized 4-fluoro-β-(4-fluorophenyl)-L-phenylalanine **78** as a key intermediate for a lead drug candidate by phase-transfer catalyzed alkylation of glycine Schiff base **2.** Their report described the detailed study of the catalyst decomposition, which disclosed the vulnerability of cinchonidinium salt under phase-transfer conditions in the absence of **77** and/or **2** (Scheme 44).[68]

2.1.10. Use of Allyl Acetates in the Asymmetric Alkylation of Glycine Schiff Base

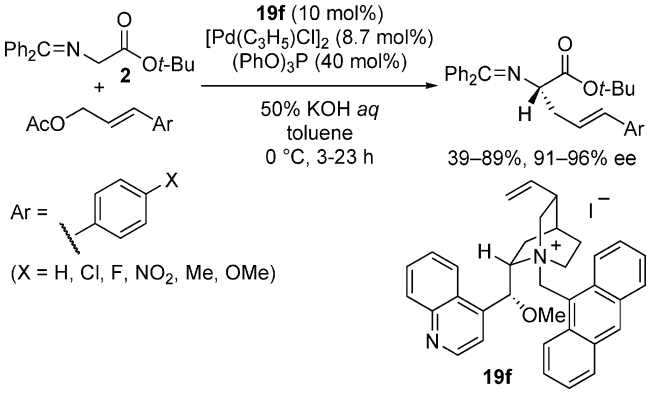
In the asymmetric alkylation of prochiral protected glycine derivatives such as **2** by chiral phase-transfer catalysis, alkyl halides are typically employed as alkylation agents. Takemoto and co-workers developed the palladium-catalyzed asymmetric allylic alkylation of **2** using allylic acetates and chiral phase-transfer catalysts such as **19f**. The proper choice

Scheme 44



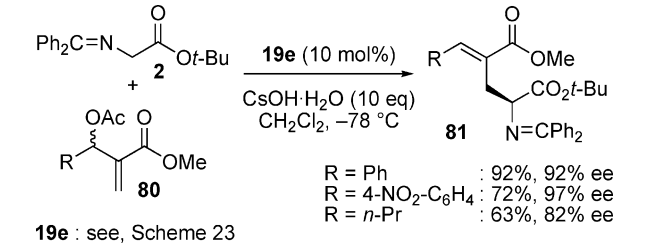
of the achiral palladium ligand, $(PhO)_3P$, was crucial to achieve high enantioselectivity (Scheme 45).[69]

Scheme 45



Ramachandran et al. reported an asymmetric conjugate addition−elimination reaction of activated allylic acetates **80** and glycine Schiff base **2**. Use of *O*-allyl-*N*-anthracenylmethyl cinchonidinium salt **19e** developed by Corey gave the glutamic acid derivatives **81** with the enantiomeric excesses ranging from 80 to 97% (Scheme 46).[70]

Scheme 46

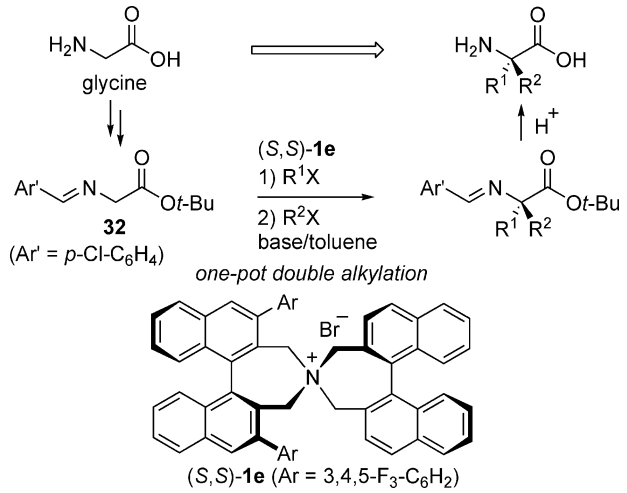


2.2. Asymmetric Synthesis of α,α-Dialkyl-α-amino Acids

Nonproteinogenic, chiral α,α-dialkyl-α-amino acids possessing stereochemically stable quaternary carbon centers have been significant synthetic targets not only because they are often effective enzyme inhibitors but also because they are indispensable for the elucidation of enzymatic mechanisms. Accordingly, numerous studies have been conducted to develop truly efficient methods for their preparation,[71] and phase-transfer catalysis has made unique contributions.

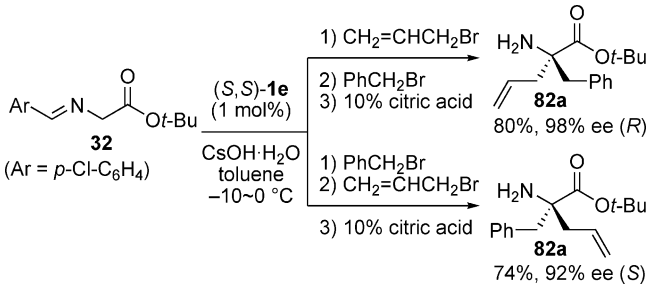
Since the aldimine Schiff base **32** can be readily prepared from glycine, direct stereoselective introduction of two different side chains to **32** by appropriate chiral phase-transfer catalysis would provide an attractive yet powerful strategy for the asymmetric synthesis of structurally diverse α,α-dialkyl-α-amino acids. This possibility of the one-pot asymmetric double alkylation has been realized by using *N*-spiro chiral quaternary ammonium bromide **1e** (Scheme 47).[72]

Scheme 47



Initial treatment of the toluene solution of **32** and (*S*,*S*)-**1e** (1 mol %) with allyl bromide (1 equiv) and $CsOH\cdot H_2O$ at −10 °C and the subsequent reaction with benzyl bromide (1.2 equiv) at 0 °C resulted in formation of the double alkylation product **82a** in 80% yield with 98% ee after hydrolysis. Notably, in the double alkylation of **32** by the addition of the halides in a reverse order, the absolute configuration of the product **82a** was confirmed to be the opposite (Scheme 48).

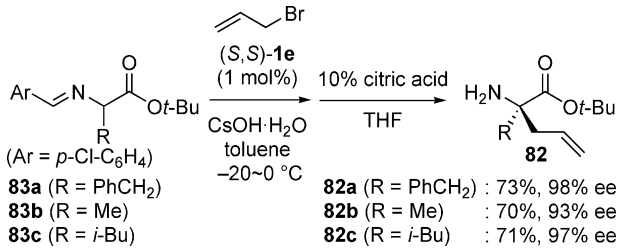
Scheme 48



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 **83** derived from the corresponding α-amino acids. Indeed, phenylalanine-, alanine-, and leucine-derived imines **83a**−**c** can be alkylated smoothly under similar conditions, affording the desired noncoded amino acid esters **82** with excellent asymmetric induction, as exemplified in Scheme 49.[72]

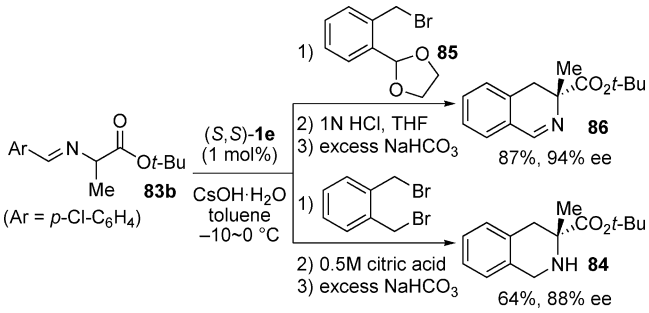
This powerful quaternization method enabled the catalytic asymmetric synthesis of quaternary isoquinoline derivatives

Scheme 49



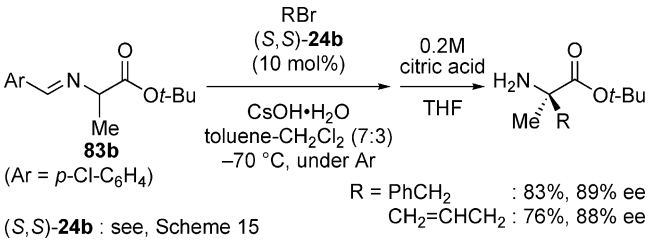
with **83b** as a substrate. When **83b** was treated with α,α′-dibromo-*o*-xylene, $CsOH·H_2O$, and (*S*,*S*)-**1e** (1 mol %) in toluene at 0 °C, the transient alkylation product was rapidly produced, which was transformed into the desired **84** (64%, 88% ee) during workup procedure. Catalytic asymmetric alkylation of **83b** with functionalized benzyl bromide **85** followed by the sequential treatment with 1 N HCl and then excess $NaHCO_3$ furnished the corresponding dihydroisoquinoline derivative **86** in 87% with 94% ee (Scheme 50).[60]

Scheme 50



Bis-ammonium tetrafluoroborate **24b** developed by Shibasaki and co-workers successfully promotes the alkylation of **83b** even at low temperature to give the corresponding α,α-dialkyl-α-amino ester in good yield with high enantioselectivity (Scheme 51).[28b] Particularly, (*R*,*R*)-**24b**-catalyzed

Scheme 51



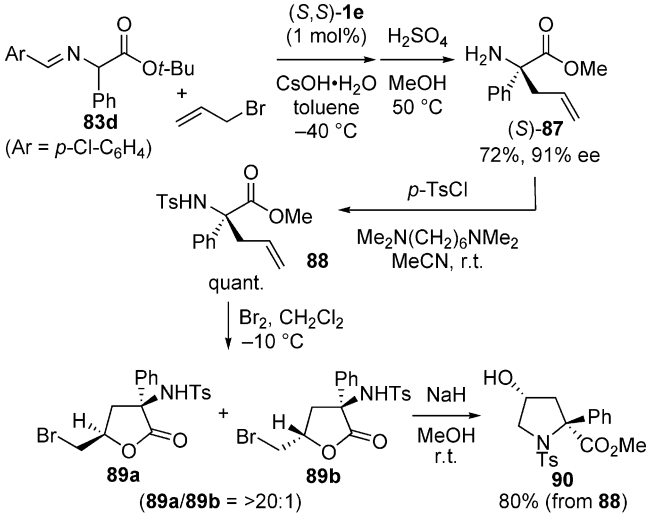
(*S*,*S*)-**24b** : see, Scheme 15

allylation under the optimized conditions has been utilized for the synthesis of aeruginosin 298-A analogue.

Recently, Maeda and co-workers utilized the (*S*,*S*)-**1e** catalyzed asymmetric alkylation of phenylglycine-derived Schiff base **83d** for the stereoselective synthesis of 4-hydroxy-2-phenylproline framework. After hydrolysis and transesterification, the resulting (*S*)-**87** was derivatized to its *N*-tosylate **88**. Subsequent treatment of **88** with Br_2 in CH_2Cl_2 at −10 °C resulted in the formation of γ-lactones **89** with high diastereoselectivity, which was then treated with NaH in methanol to give essentially pure (2*S*,4*R*)-4-hydroxy-2-phenylproline derivative **90** in 80% yield from **88** (Scheme 52).[73]

Takemoto and co-workers demonstrated that the strategy of combining achiral palladium catalysis and chiral phase-transfer catalysis was effective for the asymmetric allylation

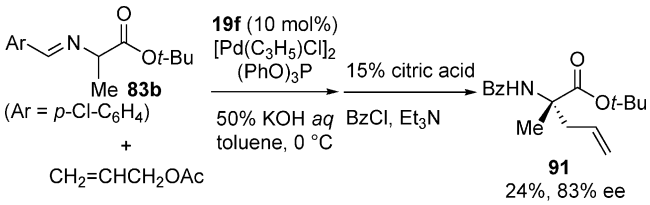
Scheme 52



(*S*,*S*)-**1e** : see, Scheme 47

of **83b**. Without chiral phosphine ligand on palladium, the desired product **91** was obtained with 83% ee after hydrolysis of the imine moiety and subsequent benzoylation, as depicted in Scheme 53.[69b]

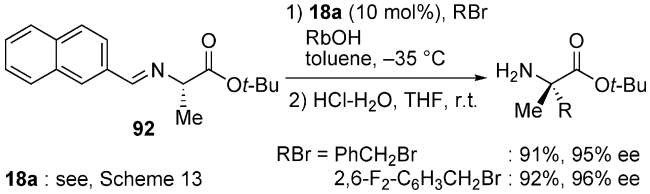
Scheme 53



19f : see, Scheme 45

Jew, Park, and co-workers made systematic investigations to develop an efficient system for the asymmetric synthesis of α-alkylalanines by chiral phase-transfer catalysis of cinchona alkaloid-derived catalysts. Consequently, sterically more demanding 2-naphthyl aldimine *tert*-butyl ester **92** was identified as a suitable substrate, and its alkylation in the presence of stronger base rubidium hydroxide (RbOH) and **18a** at lower reaction temperature (−35 °C) led to the highest enantioselectivity (Scheme 54).[74]

Scheme 54

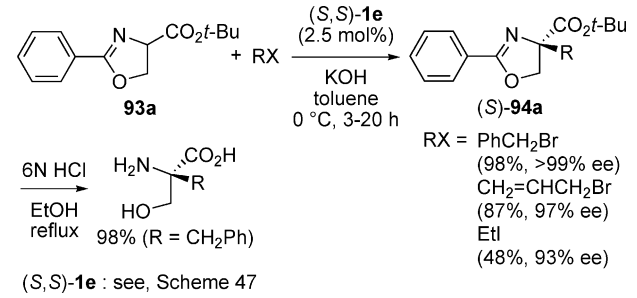


18a : see, Scheme 13

The efficient phase-transfer-catalyzed alkylation strategy with **1e** was successfully applied by Jew and Park to the asymmetric synthesis of α-alkyl serines using phenyl oxazoline derivative **93a** as a requisite substrate. The reaction is general and provides a practical access to a variety of optically active α-alkyl serines through acidic hydrolysis of **94a**, as exemplified in Scheme 55.[75]

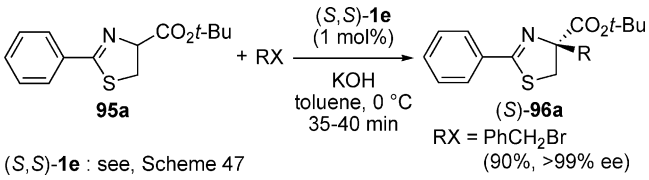
They also succeeded in expanding their methodology to the similar asymmetric alkylation of 2-phenyl-2-thiazoline-

Scheme 55



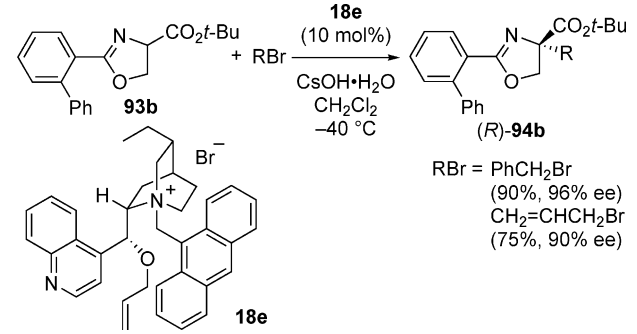
4-carboxylic acid ester **95a** to furnish optically enriched α-alkyl cystein derivatives **96a** (Scheme 56).[77]

Scheme 56



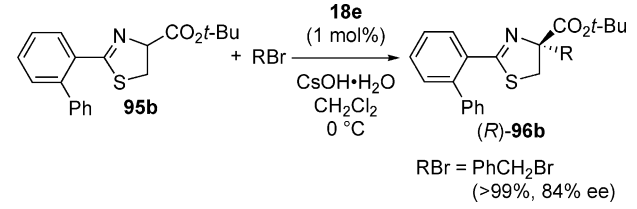
Further, they undertook the modification of the phenyl moiety of **93a** to various aromatic groups and identified *o*-biphenyl analogue **93b** as a suitable substrate for attaining high enantioselectivity with *O*-allyl-*N*-anthracenymethyl dihydrocinchonidinium bromide **18e** as phase-transfer catalyst (Scheme 57).[76]

Scheme 57



In a following report, the applicability of this approach to the synthesis of α-alkyl cysteins was disclosed by the same authors (Scheme 58).[77]

Scheme 58

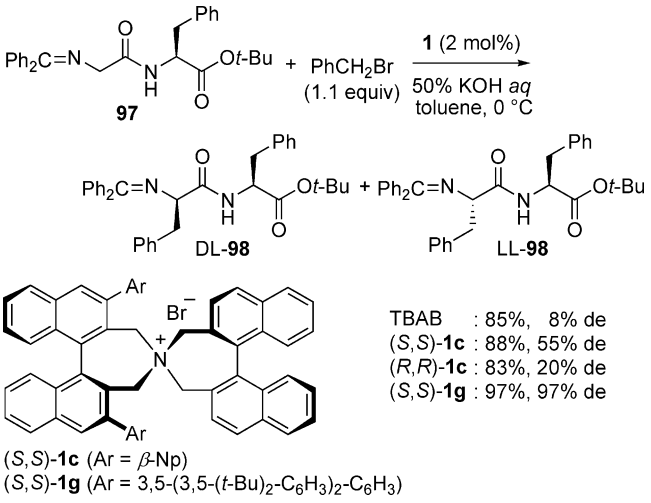


2.3. Alkylation of Schiff Base-Activated Peptides

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.[78] Achiral glycine subunit has generally been used for this purpose, and glycine enolates, radicals, and glycine cation equivalents have been exploited as reactive intermediates. However, 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.

Upon facing the difficulty of the stereochemical control in the peptide alkylation event, we envisaged that chiral phase-transfer catalyst should play a crucial role in achieving an efficient chirality transfer and examined the alkylation of the dipeptide, Gly-L-Phe derivative **97** (Scheme 59). When

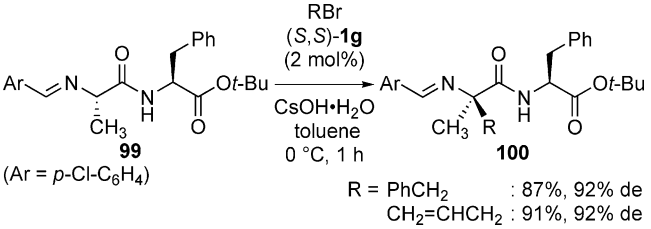
Scheme 59



a mixture of **97** and tetrabutylammonium bromide (TBAB, 2 mol %) in toluene was treated with 50% KOH aqueous solution and benzyl bromide at 0 °C for 4 h, the corresponding benzylation product **98** was obtained in 85% yield with the diastereomeric ratio (DL-**98**/LL-**98**) of 54:46 (8% de). In contrast, the reaction with chiral quaternary ammonium bromide (*S*,*S*)-**1c** under similar conditions gave rise to **98** with 55% de. The preferential formation of LL-**98** in lower diastereomeric excess (de) in the reaction with (*R*,*R*)-**1c** indicates that (*R*,*R*)-**1c** is a mismatched catalyst for this diastereofacial differentiation of **97**. Changing the 3,3′-aromatic substituent (Ar) of **1** dramatically increased the stereoselectivity, and almost complete diastereocontrol was realized with (*S*,*S*)-**1g**.[79]

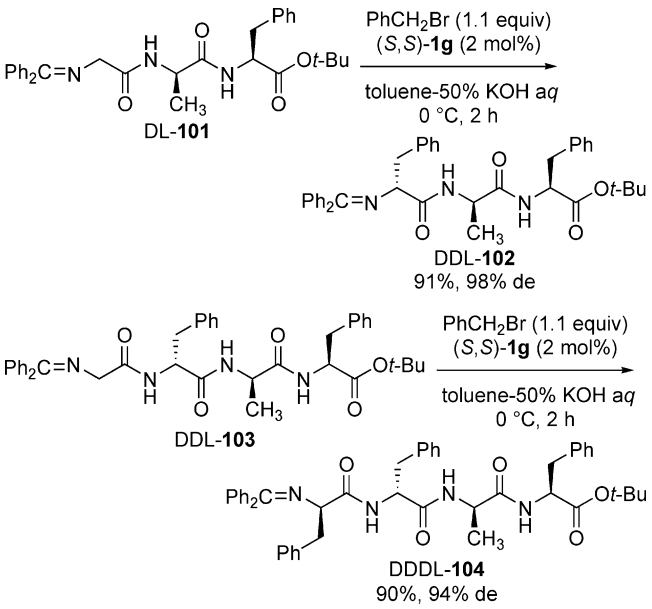
A variety of alkyl halides can be employed as an electrophile in this alkylation, and the efficiency of the transmission of stereochemical information was not affected by the side-chain structure of the pre-existing amino acid residues. Further, this method allowed an asymmetric construction of noncoded α,α-dialkyl-α-amino acid residues at the peptide terminal as exemplified by the stereoselective alkylation of the dipeptide, L-Ala-L-Phe derivative **99** (Scheme 60).

Scheme 60



The chiral phase-transfer catalysis with (*S*,*S*)-**1g** can be successfully extended to the stereoselective *N*-terminal alkylation of Gly-Ala-Phe derivative **101**, i.e., asymmetric synthesis of tripeptides, where (*S*,*S*)-**1g** turned out to be a matched catalyst in the benzylation of DL-**101**, leading to almost exclusive formation of DDL-**102**. This tendency for stereochemical communication was consistent in the phase-transfer alkylation of DDL-**103**, and the corresponding protected tetrapeptide DDDL-**104** was obtained in 90% yield with excellent stereochemical control (94% de) (Scheme 61).[79]

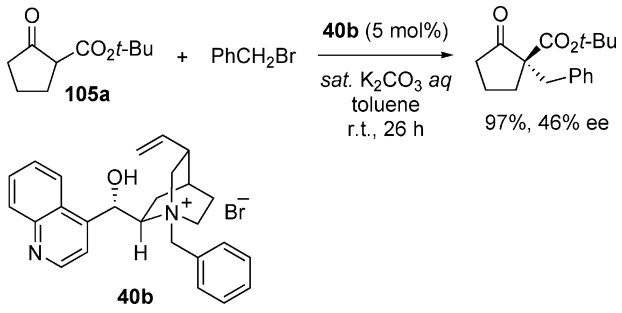
Scheme 61



2.4. Other Alkylations

Asymmetric alkylation of β-keto ester under phase-transfer conditions can be a unique tool to construct an all-carbon chiral quaternary carbon center easily. Dehmlow and co-workers reported that *N*-benzyl cinchoninium bromide **40b** catalyzed the asymmetric alkylation of β-keto ester **105a** to give the benzylated compound in an excellent chemical yield with 46% ee, as included in Scheme 62.[80]

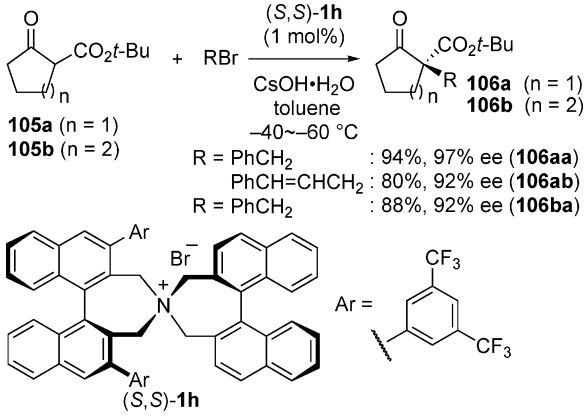
Scheme 62



Efficient, highly enantioselective construction of a quaternary stereocenter on β-keto esters under phase-transfer conditions has been achieved using *N*-spiro chiral quaternary ammonium bromide **1h** as catalyst.[81] This system has a broad generality in terms of the structure of β-keto esters **105** and alkyl halides (Scheme 63). The resulting alkylation products **106** can be easily converted into the corresponding β-hydroxy esters and β-amino esters, respectively.

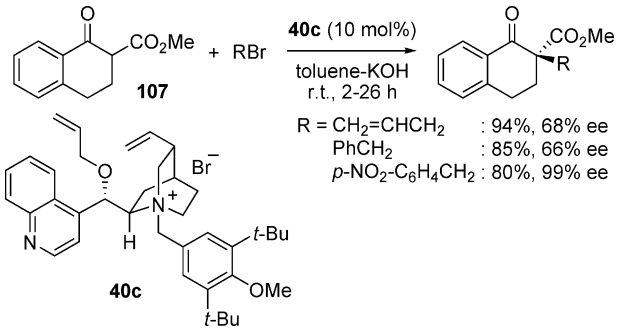
Kim and co-workers showed the effectiveness of cinchonine-derived catalyst **40c** with a specific bulky substituent

Scheme 63



on the bridgehead nitrogen for the asymmetric alkylation of β-keto esters such as **107**. The enantioselectivity seems to be quite sensitive to the alkyl halide employed, and virtually complete stereochemical control can be achieved in the reaction with *p*-nitrobenzyl bromide (Scheme 64).[82]

Scheme 64



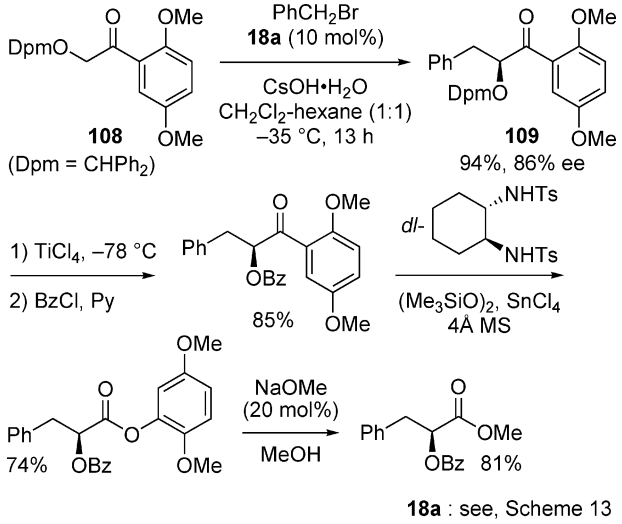
Recently, Andrus et al. introduced diphenylmethyloxy-2,5-dimethoxyacetophenone **108** as a useful oxygenated substrate that undergoes highly selective catalytic glycolate alkylation under phase-transfer conditions in the presence of *N*-(3,4,5-trifluorobenzyl)dihydrocinchonidinium bromide **18a** developed by Jew, Park, and co-workers. After deprotection and reprotection of the alkylation product **109**, subsequent Baeyer−Villiger-type oxidation and selective transesterification afforded the corresponding α-hydroxyester derivative without losing the enantioselectivity (Scheme 65).[83a]

Two applications of this asymmetric glycolate alkylation were reported by the same group using *p*-(4-bromomethyl)-phenyl pivalate **110** as an alkylating partner. The anti-diabetes drug (−)-ragaglitazar was synthesized in 6 steps from the alkylated compound **111**. The synthesis of farnesyltransferase inhibitor kurasoin A was also achieved in 6 steps starting from **111** (Scheme 66).[83b,83c]

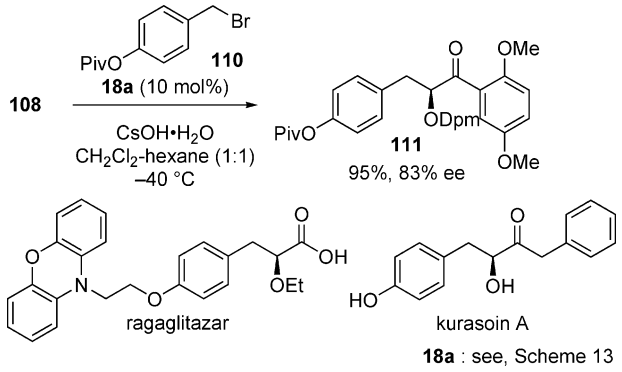
Accessing enantioenriched carbonyl compounds of high value, which possess quaternary α-carbon stereocenters containing heterofunctionalities, is one of the most challenging tasks in the phase-transfer catalyzed asymmetric alkylation. In due course, we devised the asymmetric alkylation of cyclic α-amino-β-keto ester **112** with C_2-symmetric phase-transfer catalyst **1h** as a means of obtaining azacyclic amino acids with quaternary stereocenters (Scheme 67).[84]

Our other approach toward this largely unsolved problem utilizes 3,5-diaryloxazolidin-2,4-diones **114** that undergo

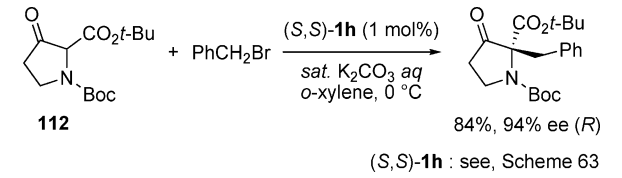
Scheme 65



Scheme 66



Scheme 67

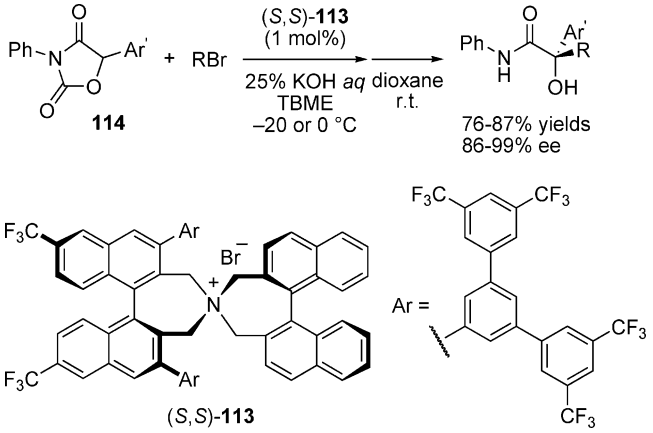


highly enantioselective alkylation under mild phase-transfer conditions in the presence of *N*-spiro chiral quaternary ammonium bromide **113**. With this methodology in hand, a wide range of tertiary-α-hydroxy-α-aryl carboxylic acid derivatives can be easily obtained in good yields and high enantiomeric excesses (Scheme 68).[85]

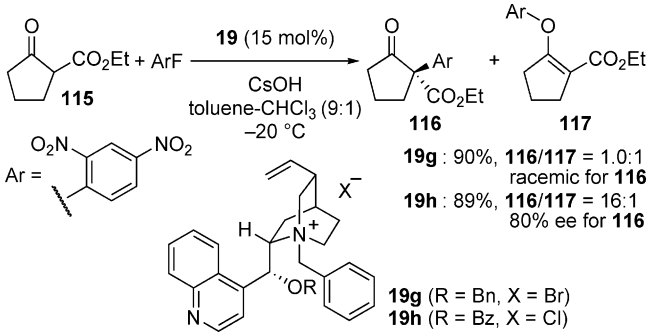
Jørgensen and co-workers developed the catalytic, regioselective, and enantioselective nucleophilic aromatic substitution reaction between activated aromatic compounds and 1,3-dicarbonyl compounds under phase-transfer conditions. Interestingly, examination of the addition of 2,4-dinitrofluorobenzene to 2-carboethoxycyclopentanone **115** revealed that the use of *O*-benzoylated cinchonidine-derived catalyst **19h** was crucial for obtaining *C*-arylated product **116** predominantly with high enantioselectivity (Scheme 69).[86]

Jørgensen and co-workers reported asymmetric vinylic substitution reaction of β-keto esters catalyzed by dihydrocinchonine-derived phase-transfer catalyst **118a** incorporating 1-adamantoyl group. As vinyl sources, activated β-haloalkenes, which participate in the substitution reaction via an addition−elimination sequence, were utilized. Starting from (*Z*)-vinyl halide **119**, a *Z*-configured double bond could be incorporated into the product **120** (Scheme 70).[87]

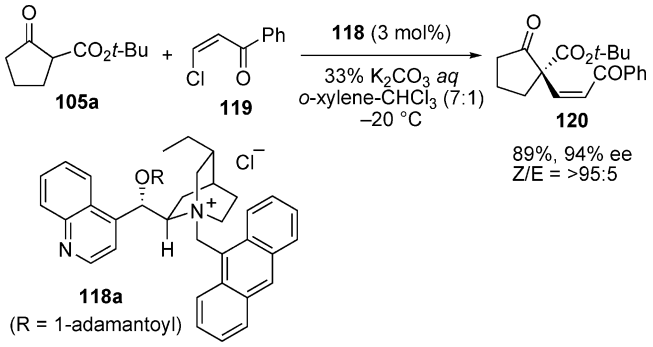
Scheme 68



Scheme 69

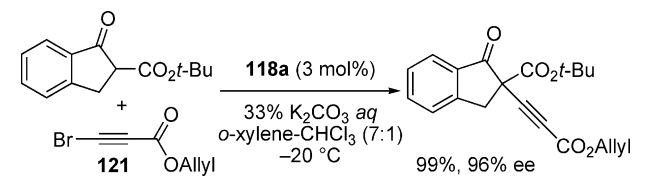


Scheme 70



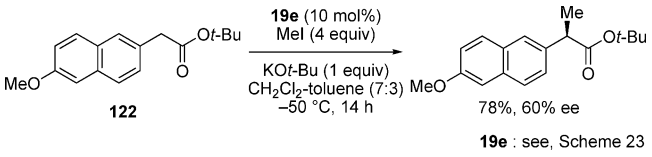
As an extension of this research, Jørgensen and co-workers succeeded in the asymmetric alkynylation of cyclic β-keto esters employing activated β-halo-alkyne **121** catalyzed by **118a** (Scheme 71).[88]

Scheme 71



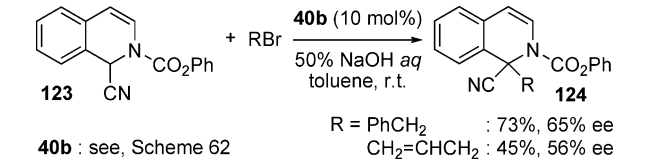
Asymmeric alkylation of simple aliphatic or arylacetic acid esters under phase-transfer conditions is a difficult task because of their low pK_a values. Kumar and Ramachandran reported the asymmetric alkylation of 2-(6-methoxynaphthalen-2-yl)acetic acid ester **122** by use of strong base potassium *tert*-butoxide, as a means of an efficient synthesis of naproxen (Scheme 72).[89]

Scheme 72



Rozwadowska and co-workers reported the asymmetric alkylation of Reissert compounds **123**. *N*-Benzyl cinchoninium bromide **40b** catalyzed phase-transfer alkylation of *N*-phenoxycarbonyl dihydroisoquinoline provided the benzylated compound **124** containing a quaternary stereocenter with 65% ee (Scheme 73).[90]

Scheme 73

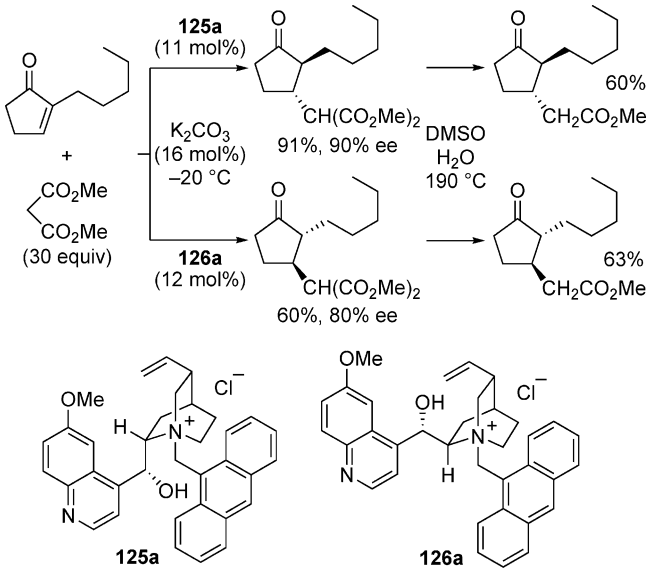


3. Michael Addition

The asymmetric Michael addtion of active methylene or methine compounds to electron-deficient olefins, particularly α,β-unsaturated carbonyl compounds, represents a fundamental yet useful approach to construct functionalized carbon frameworks.[91]

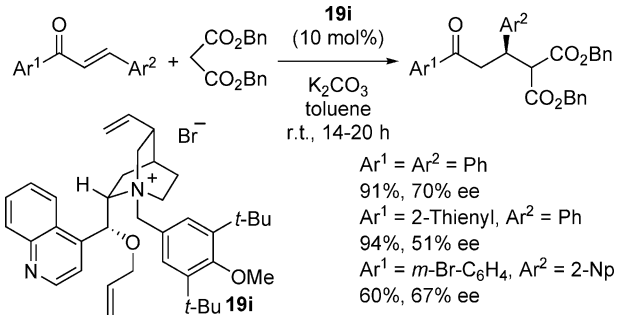
Plaquevent and co-workers achieved highly enantioselective Michael addition of simple dimethyl malonate to 2-pentyl-2-cyclopentenone under phase-transfer conditions using K_2CO_3 as a base and quinine- or quinidine-derived **125a** or **126b** as catalyst: this enabled a short enantioselective synthesis of both enantiomers of methyl dihydrojasmonate, as illustrated in Scheme 74.[92]

Scheme 74



Kim and co-workers applied *N*-(3,5-di-*tert*-butyl-4-methoxy)benzyl cinchonidinium bromide **19i** to asymmetric Michael addition of malonates to chalcone derivatives. The reactions of dibenzyl malonate with differently substituted chalcone derivatives in toluene were found to proceed at room temperature with moderate enantioselectivities in the

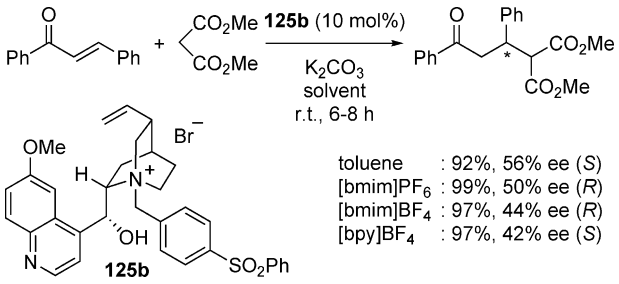
Scheme 75



presence of 10 mol % of **19i** and an excess amount of K_2CO_3 (Scheme 75).[93]

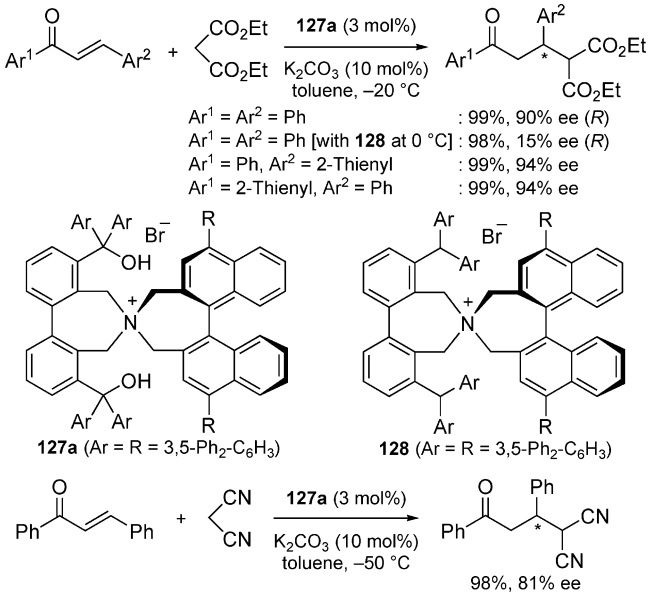
Salunkhe and co-workers performed the similar phase-transfer catalyzed Michael reaction of dimethyl malonate and chalcone with newly devised quininium bromide **125b** in ionic liquid such as 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6, tetrafluoroborate [bmim]BF_4, and 1-butyl-3-pyridinium tetrafluoroborate [bpy]BF_4. The reactions afforded the product in excellent chemical yields in relatively short periods of time, and surprisingly, the enantioselectivity was reversed in the reactions in [bmim]PF_6 and [bmim]BF_4, while it remained the same in [bpy]BF_4, versus that observed in toluene (Scheme 76).[94]

Scheme 76



Recently, we addressed the importance of dual-functioning chiral phase-transfer catalyst such as **127a** for obtaining a high level of enantioselectivity in the Michael addition of malonates to chalcone derivatives (Scheme 77).[95] For

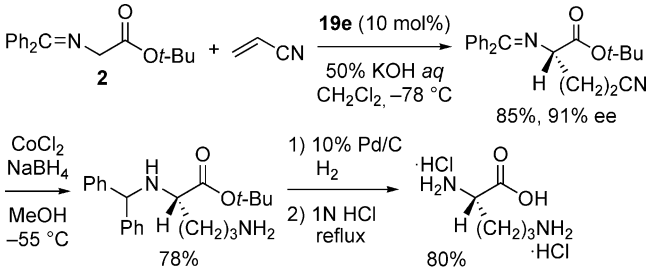
Scheme 77



instance, reaction of diethyl malonate with chalcone in toluene under the influence of K_2CO_3 and **127a** (3 mol %) proceeded smoothly at −20 °C with excellent enantioselectivity, while the selectivity was markedly decreased when **128** possessing no hydroxy functionality was used as catalyst. This system is applicable to the Michael addition of malononitrile as included in Scheme 77.

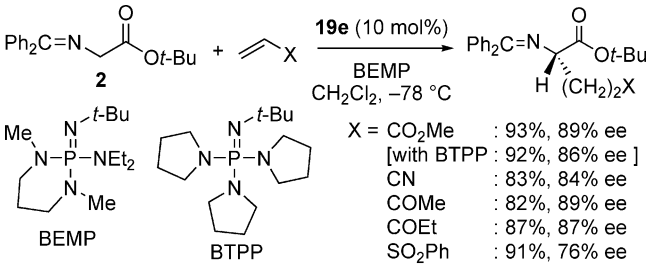
Enantioselective Michael addition of glycine derivatives by means of chiral phase-transfer catalysis has been developed to synthesize various functionalized α-alkyl-α-amino acids. Zhang and Corey utilized *O*-allyl *N*-anthracenylmethyl cinchonidinium bromide **19e** as catalyst for asymmetric Michael addition of glycine Schiff base **2** to acrylonitrile with high enantioselectivity. Naturally occurring (*S*)-ornithine has been synthesized as its dihydrochloride in a concise manner, as included in Scheme 78.[96]

Scheme 78



O'Donnell et al. carried out this type of Michael addition by the use of organic soluble, non-ionic bases BEMP and BTPP. In general, the less-basic BEMP proved to be superior and tolerated several representative Michael acceptors, as shown in Scheme 79.[97] The applicability of this system to

Scheme 79



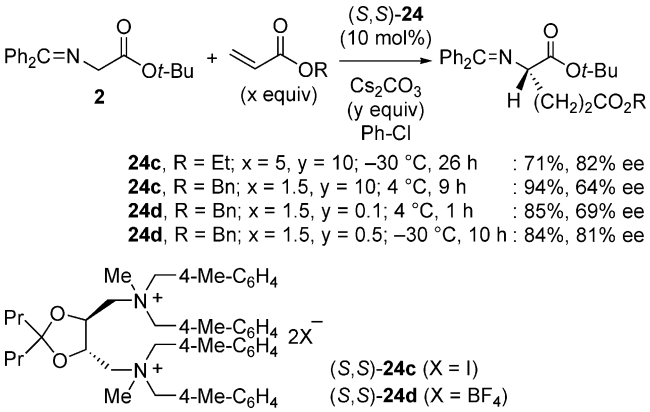
the solid-phase synthesis with resin-bound glycine Schiff base was also demonstrated.

Shibasaki and co-workers successfully applied the tartrate-derived, C_2-symmetric bis-ammonium salt **24** to the asymmetric Michael addition of **2** to acrylates. Exchange of the counterion from iodide to tetrafluoroborate using the corresponding silver salt dramatically accelerated the reaction even in the case of a catalytic amount of base (Scheme 80).[28]

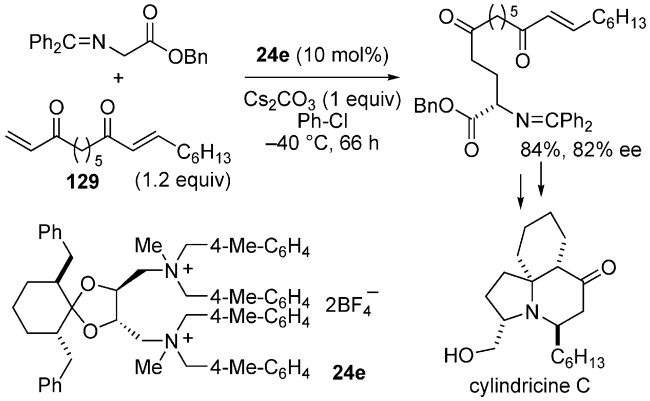
By employing the asymmetric Michael addition catalyzed by C_2-symmetric bis-ammonium salt **24e**, Shibasaki and coworkers succeeded in the total synthesis of cylindricine C. The Michael acceptor **129** was designed to include the appropriate functionalities for the following acid-catalyzed tandem cyclization (Scheme 81).[98]

Arai et al. designed tartrate-derived spiro-type chiral phase-transfer catalyst **130** and applied it to the similar asymmetric Michael addition (Scheme 82).[99] Arai introduced a new bis-

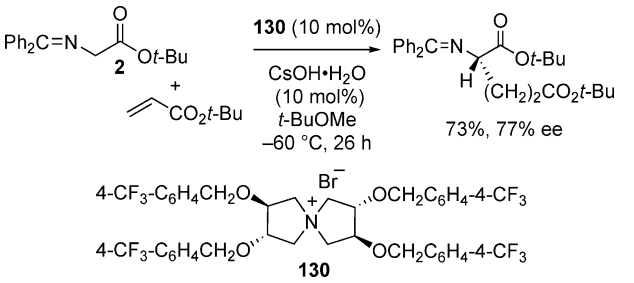
Scheme 80



Scheme 81

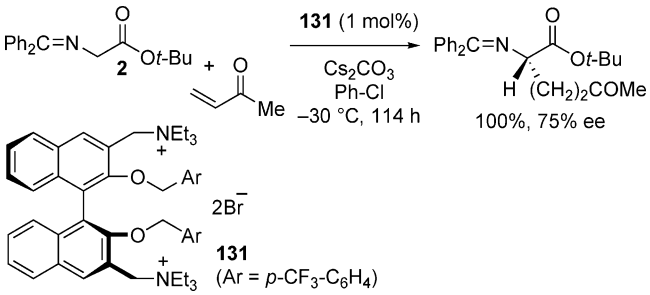


Scheme 82



ammonium salt **131** derived from (*S*)-1,1′-bi-2-naphthol as an efficient chiral phase-transfer catalyst. For instance, reaction of **2** with methyl vinyl ketone in the presence of Cs_2CO_3 and 1 mol % of **131** in chlorobenzene proceeded at −30 °C quantitatively with 75% ee (Scheme 83). The

Scheme 83

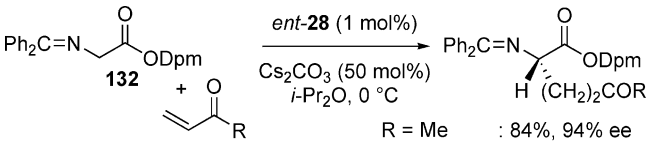


flexibility of the catalyst modification on the substituents of the ether and the ammonium moieties appears to be advantageous.[100]

Lygo et al. recently reported the optimization of reaction parameters for the asymmetric Michael addition of glycine

derivative to methyl vinyl ketone with the α-methylnaphthylamine-derived quaternary ammonium salt *ent*-**28** as catalyst. This uncovered the crucial importance of base and solvent, and high levels of enantioselectivity can be obtained by performing the addition of glycine diphenylmethyl ester Schiff base **132** to simple alkyl vinyl ketones in diisopropyl ether at 0 °C in the presence of 50 mol % of Cs_2CO_3 and 1 mol % of *ent*-**28** (Scheme 84).[101]

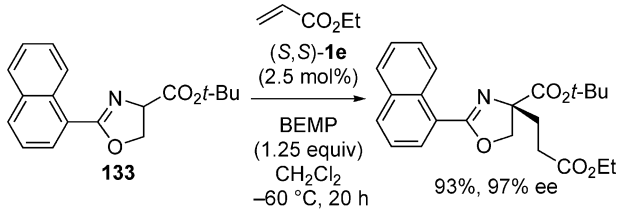
Scheme 84



ent-**28** : see, Scheme 16

Jew, Park, and co-workers achieved highly enantioselective synthesis of (2*S*)-α-(hydroxymethyl)glutamic acid, a potent metabotropic receptor ligand, through the Michael addition of 2-naphthalen-1-yl-2-oxazoline-4-carboxylic acid *tert*-butyl ester **133** to ethyl acrylate under phase-transfer conditions. As shown in Scheme 85, use of BEMP as a base at −60 °C

Scheme 85



(*S*,*S*)-**1e** : see, Scheme 47
BEMP : see, Scheme 79

with the catalysis of *N*-spiro chiral quaternary ammonium bromide **1e** appeared to be essential for attaining an excellent selectivity.[102]

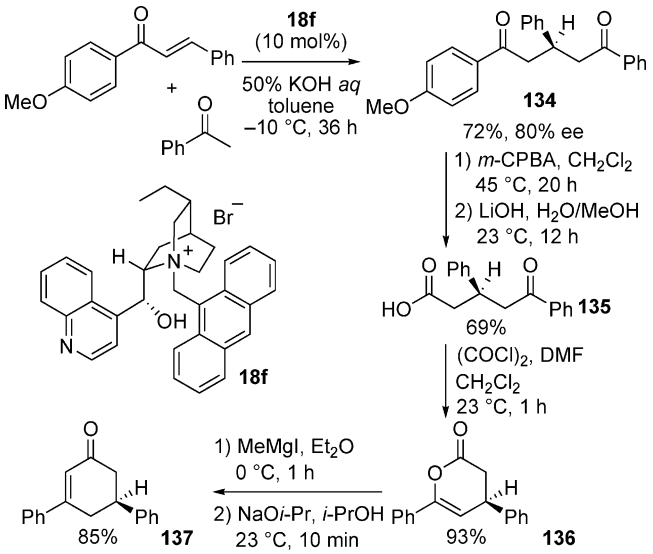
Zhang and Corey extended the utility of *N*-anthracenylmethyl dihydrocinchonidinium bromide **18f** to the asymmetric Michael addition of acetophenone to 4-methoxychalcone under mild phase-transfer conditions. Selective Baeyer−Villiger oxidation of the adduct **134** and subsequent saponification gave the keto acid **135**, which can be obtained in an essentially enantiopure form by a single recrystallization. In addition, facile derivatization of **135** into optically active 2-cyclohexenone derivative **137** via enol γ-lactone **136** was demonstrated (Scheme 86).[96]

Furthermore, chiral quaternary ammonium bromide **18f** served as an effective catalyst for the enantioselective dimerization of α,β-unsaturated ketones under phase-transfer conditions, which proceeded through Michael reaction to form **138**, followed by base-catalyzed double-bond transposition to afford chiral 1,5-dicarbonyl compound **139**, as exemplified in Scheme 87.[103] The resulting **139** can be readily converted to the corresponding α-alkyl-γ-keto acid **140** through ozonolysis and subsequent oxidation with H_2O_2.

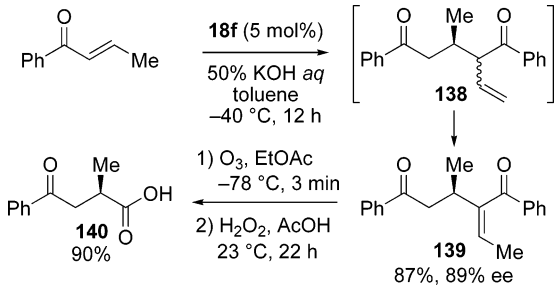
Bella and co-workers recently reported the similar asymmetric dimerization of cyclic enones catalyzed by *N*-3,4,5-tribenzyloxybenzyl cinchoninium bromide **40d** (Scheme 88).[104]

We developed the diastereo- and enantioselective conjugate addition of nitroalkanes to alkylidenemalonates under mild phase-transfer conditions by the utilization of appropriately designed chiral quaternary ammonium bromide

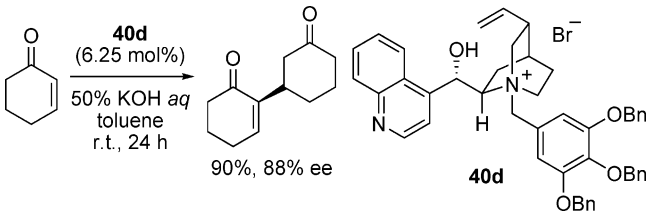
Scheme 86



Scheme 87

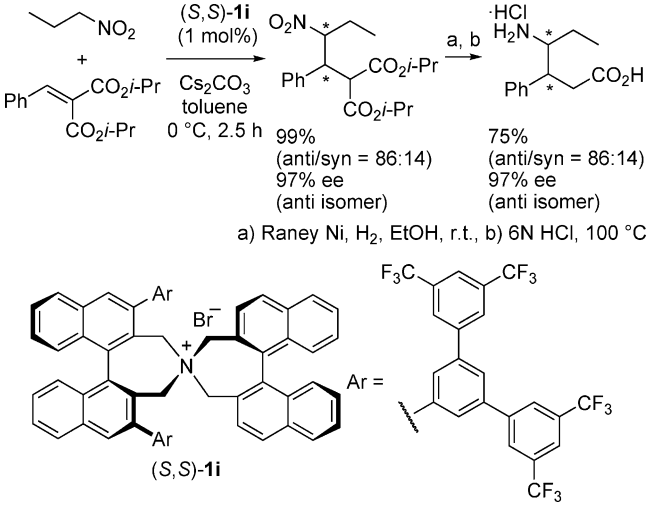


Scheme 88



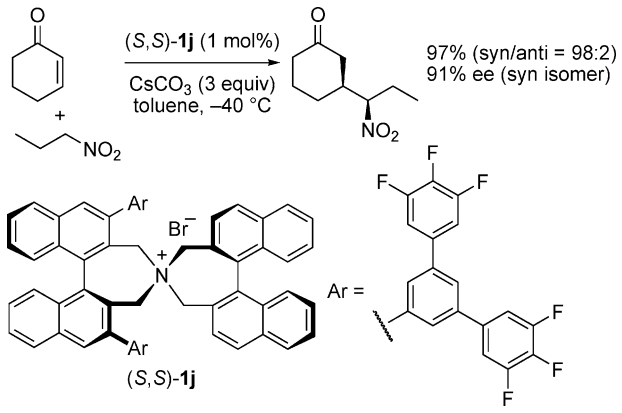
1i as an efficient catalyst. This new protocol offers a practical entry to optically active γ-amino acid derivatives, as shown in Scheme 89.[105a]

Scheme 89



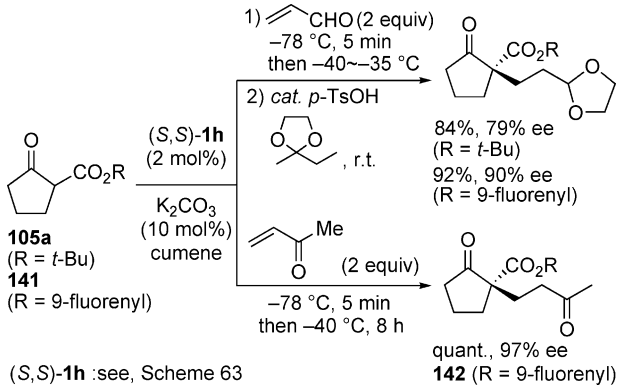
As an extension of this research, we succeeded in the catalytic asymmetric conjugate addition of nitroalkanes to cyclic α,β-unsaturated ketones under phase-transfer condition (Scheme 90).[105b]

Scheme 90



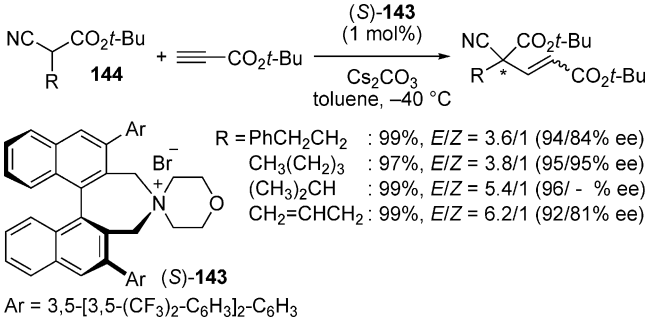
As already addressed in this section, enantioselective Michael addition of β-keto esters to α,β-unsaturated carbonyl compounds is a useful method for the construction of densely functionalized chiral quaternary carbon centers. A characteristic feature of designer chiral phase-transfer catalyst **1h** in this type of transformation is that it enables the use of α,β-unsaturated aldehydes as an acceptor, leading to the construction of a quaternary stereocenter having three different functionalities of carbonyl origin as demonstrated in the reaction with 2-*tert*-butoxycarbonylcyclopentanone **105a**. It is of interest that the use of fluorenyl ester **141** greatly improved the enantioselectivity. The addition of **141** to MVK was also feasible under similar conditions, and the desired **142** was obtained quantitatively with 97% ee (Scheme 91).[81a]

Scheme 91



Asymmetric conjugate addition of α-substituted-α-cyanoacetates **144** to acetylenic esters under phase-transfer conditions 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 developed a new morpholine-derived phase-transfer catalyst (*S*)-**143** and applied it to the asymmetric conjugate additions of α-alkyl-α-cyanoacetates **144** to acetylenic esters. In this asymmetric transformation, an all-carbon quaternary stereocenter can be constructed in a high enantiomeric purity (Scheme 92).[106]

Scheme 92

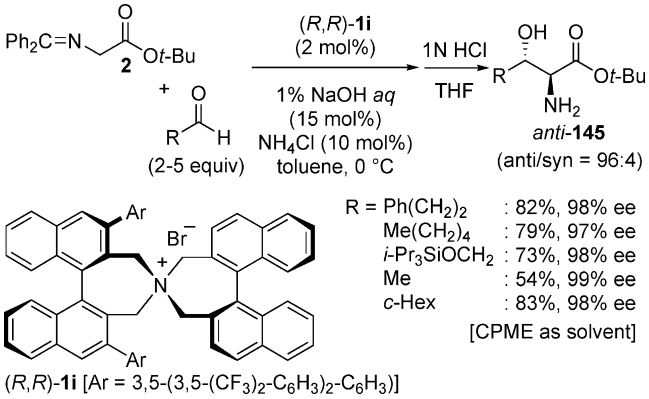


4. Aldol Reaction

Although phase-transfer catalyzed enantioselective direct aldol reactions of glycine donors 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, which are extremely important chiral units, especially from the pharmaceutical viewpoint, the examples reported to date are very limited.

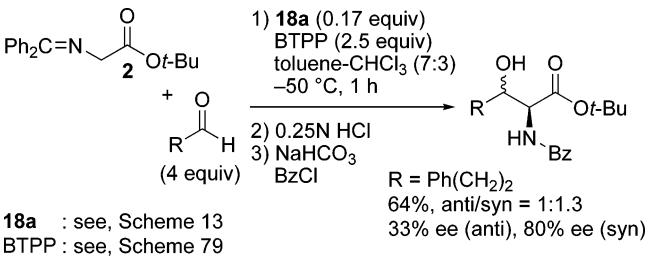
We recently developed an efficient, highly diastereo- and enantioselective direct aldol reaction of **2** with a wide range of aliphatic aldehydes under mild phase-transfer conditions employing *N*-spiro chiral quaternary ammonium salt **1i** as a key catalyst, leading to the establishment of a general and practical chemical process for the synthesis of optically active *anti*-β-hydroxy-α-amino esters **145** (Scheme 93).[107]

Scheme 93



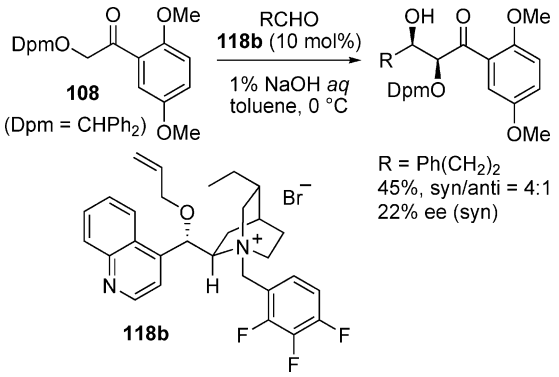
Castle and co-workers revealed that this type of aldol reaction could be performed in the presence of BTPP as an organic base under homogeneous conditions. Use of quaternary ammonium salt **18a** developed by Park and Jew was found to be optimal, giving the aldol adduct as a mixture of diastereomers in moderate-to-high enantioselectivities (Scheme 94).[108]

Scheme 94



Andrus et al. utilized their glycolate template to the phase-transfer catalyzed asymmetric aldol reaction to give 1,2-dihydroxyester. The reaction of glycolate **108** and 3-phenylpropionaldehyde catalyzed by dihydrocinchoninium bromide **118b** afforded the aldol adduct in moderate yield with low enantioselectivity (Scheme 95).[109] To improve the

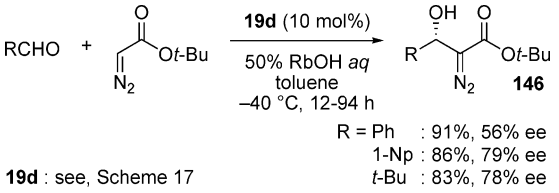
Scheme 95



reactivity and selectivity of this reaction system, Andrus et al. employed silyl enol ether of **108** and hydrogen bifluoride salt of **118b** to achieve high yields and selectivities.[110]

Arai et al. investigated the catalytic asymmetric aldol reaction between *tert*-butyl diazoacetate and benzaldehyde under various liquid−liquid phase-transfer conditions with *N*-anthracenylmethyl cinchonidinium chloride **19d** as catalyst. The reaction was found to proceed smoothly in toluene even at −40 °C using 50% RbOH aqueous solution as a base, giving rise to the desired aldol adduct **146** in 91% yield with 56% ee. Further experiments to probe the substrate scope revealed that the electronic property of the substituents on the benzene ring in aldehydes strongly influenced the enantioselectivity, and this system was also effective for aliphatic aldehydes (Scheme 96).[111]

Scheme 96

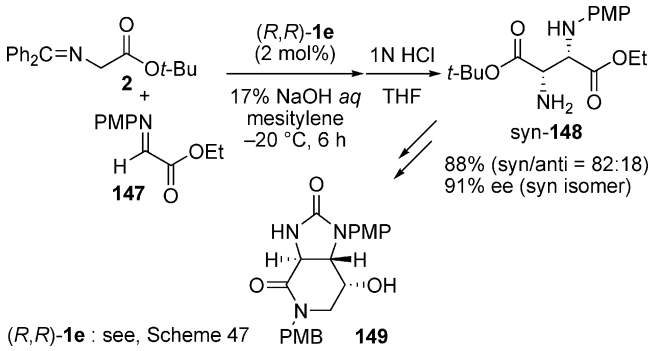


5. Mannich Reaction

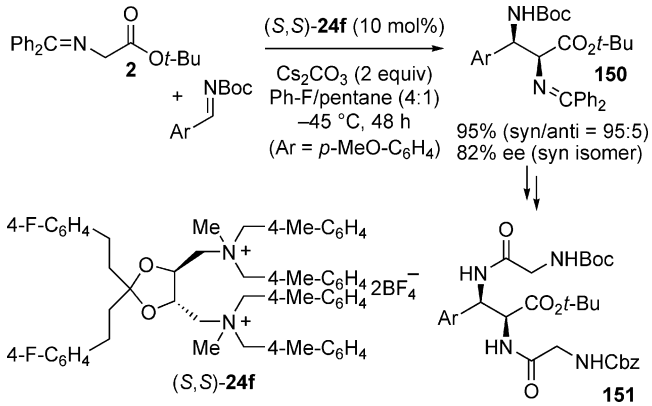
Phase-transfer catalyzed direct Mannich reaction of glycine Schiff base **2** with α-imino ester **147** was achieved with high enantioselectivity by the utilization of *N*-spiro chiral quaternary ammonium bromide **1e** as catalyst (Scheme 97).[112] This method enables the catalytic asymmetric synthesis of differentially protected 3-aminoaspartate, a nitrogen analog of dialkyltartrate, whose utility was demonstrated by the product *syn*-**148** being converted into a precursor **149** of streptolidine lactam.

A more general and highly diastereoselective Mannich-type reaction was developed by Ohshima, Shibasaki, and co-workers. The original tartrate-derived diammonium salt **24b** was modified by introducing an aromatic ring at the acetal side chains, and 4-fluorophenyl-substituted **24f** was identified as an optimal catalyst for the reaction of **2** with various *N*-Boc imines under solid (Cs_2CO_3)−liquid (fluorobenzene) phase-transfer conditions, as exemplified in Scheme 98.[113]

Scheme 97



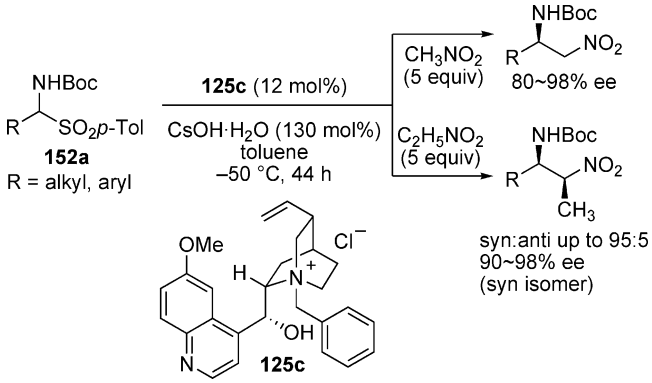
Scheme 98



The usefulness of the Mannich adduct **150** was further demonstrated by the straightforward synthesis of the optically pure tripeptide **151**.

Palomo et al. reported that *N*-benzyl quininium chloride **125c** acted as a promising catalyst for the asymmetric aza-Henry reaction under solid−liquid phase-transfer conditions utilizing cesium hydroxide as a base. α-Amido sulfones **152** were used to generate reactive *N*-carbamoyl imines in situ and succeeded in aza-Henry reactions of not only aromatic imines but also aliphatic imines (Scheme 99). Unprotected

Scheme 99

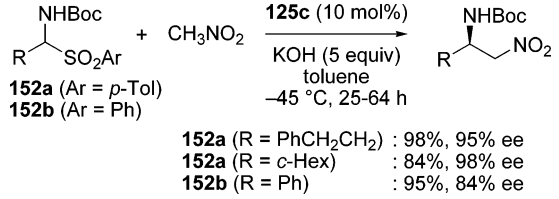


hydroxyl group on *N*-benzyl quininium chloride **125c** was found to be crucial to obtain high enantioselectivities.[114]

At the same time, Herrera, Bernardi, and co-workers reported the same asymmetric aza-Henry reaction catalyzed by *N*-benzylquininium chloride **125c** separately. In their report, freshly ground potassium hydroxide was utilized as a base (Scheme 100).[115]

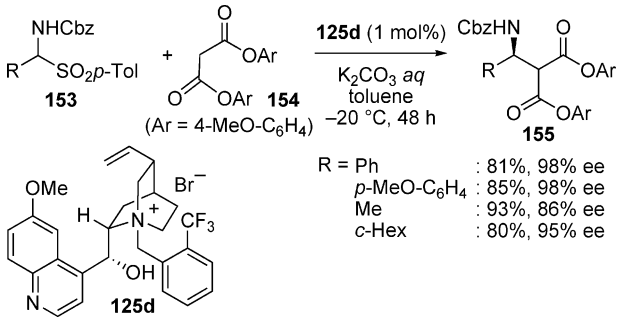
Ricci and co-workers reported Mannich reaction of in situ generated *N*-Cbz imines from α-amido sulfones **153** and bis-

Scheme 100



(4-methoxyphenyl) malonate **154** under the liquid−liquid phase-transfer condition. Via decarboxylation/transesterification sequence, the Mannich adduct **155** could be converted to the optically enriched β-amino acid ester (Scheme 101).[116]

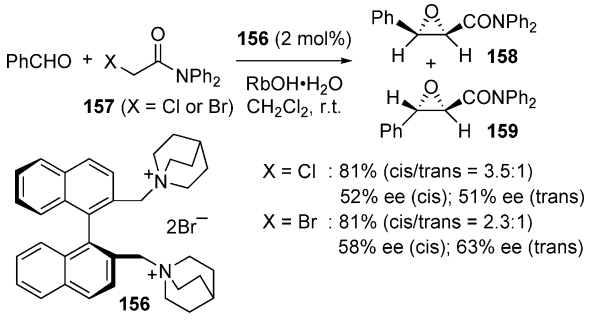
Scheme 101



6. Darzens Reaction

The Darzens reaction represents one of the most powerful methods for the synthesis of α,β-epoxy carbonyl and related compounds.[117] Arai et al. designed a new quaternary bis-ammonium salt **156** easily prepared from optically pure (*S*)-1,1′-bi-2-naphthol and utilized it for the preparation of optically active α,β-epoxy amides as a mixture of cis and trans isomers **158** and **159** by reaction of aromatic haloamides **157** with aldehydes (Scheme 102).[118]

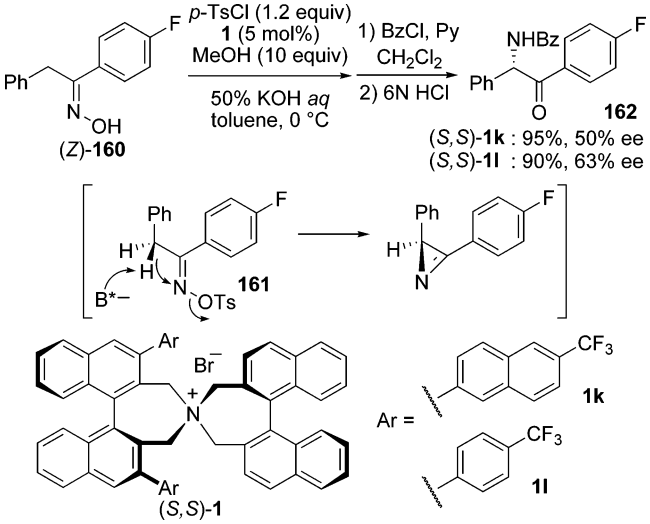
Scheme 102



7. Neber Rearrangement

The Neber rearrangement of oxime sulfonates has been considered to proceed via a nitrene pathway or an anion pathway. If the latter mechanism is operative, use of a certain chiral base could result in the discrimination of two enantiotropic α-protons to furnish optically active α-aminoketones. Verification of this hypothesis was provided by realizing the asymmetric Neber rearrangement of simple oxime sulfonate **161**, generated in situ from the parent oxime (*Z*)-**160**, under phase-transfer conditions using the structurally rigid, *N*-spiro-type chiral quaternary ammonium bromide **1k** or **1l** as catalyst, and the corresponding protected α-amino ketone **162** was isolated in high yield with notable enantiomeric excess (Scheme 103).[119]

Scheme 103

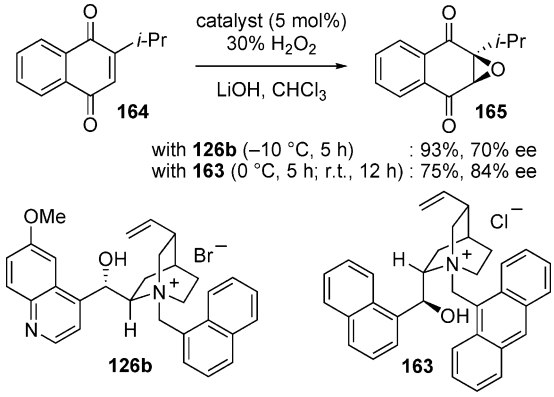


8. Epoxidation

The catalytic asymmetric epoxidation of electron-deficient olefins, particularly α,β-unsaturated ketones, has been the subject of numerous investigations, and a number of useful methodologies have been elaborated.[120] Among these, the method utilizing chiral phase-transfer catalysis occupies a unique place featuring its practical advantages, and it allows highly enantioselective epoxidation of *trans*-α,β-unsaturated ketones, particularly chalcone.

In contrast to *trans*-enone substrates, the enantiocontrol in the epoxidation of *cis*-enones is still a difficult task, and successful examples are limited to the epoxidation of naphthoquinones. A typical reaction recipe for the naphthoquinone epoxidation involves a treatment of 2-substituted naphthoquinone **164** with 30% H_2O_2 and LiOH in chloroform in the presence of chiral ammonium bromide such as **126b**, affording the corresponding epoxide **165** with a quaternary carbon center with a good enantioselectivity.[121] Interestingly, use of the deaza derivative **163** as catalyst provided the enhanced enantioselectivity (Scheme 104).[80]

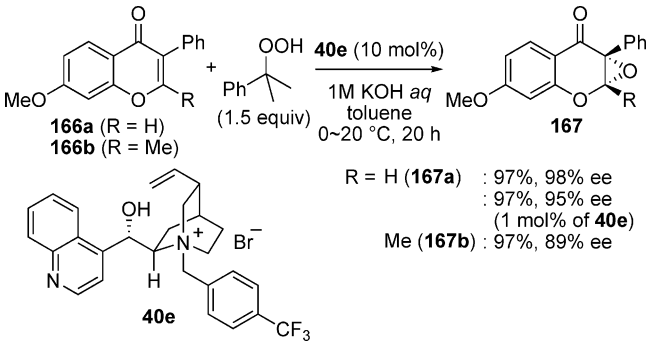
Scheme 104



The asymmetric epoxidation of chalcone is quite sensitive to the choice of oxidants. In contrast to Shioiri and co-workers' result,[121] Lygo and To found that the use of sodium hypochlorite delivered much higher stereocontrol than aqueous hydrogen peroxide, and the asymmetric epoxidation proceeded with only 1 mol % of a cinchona alkaloid−derived chiral phase-transfer catalyst.[122] Liang and co-workers successfully utilized trichloroisocyanuric acid as

a safe, inexpensive, and mild oxidant for the asymmetric epoxidations.[123] Several alkyl hydroperoxides were also utilized for phase-transfer-catalyzed asymmetric epoxidations of conformationally flexible and fixed enone substrates with moderate-to-high enantioselectivity. Adam et al. realized asymmetric epoxidation of isoflavones **166** with (4-trifluoromethyl)benzyl cinchoninium bromide **40e** developed by Merck group as catalyst and commercially available cumene hydroperoxide as oxidant (Scheme 105). Upon reducing the

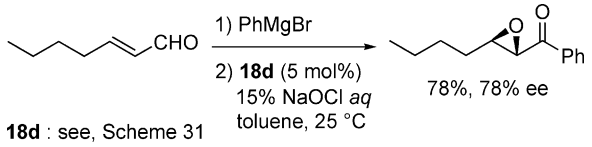
Scheme 105



catalyst loading to 1 mol %, isoflavone epoxide **167a** was obtained almost quantitatively with excellent enantioselectivity. The 2-methyl derivative **166b** afforded the corresponding epoxide **167b** possessing two consecutive quaternary stereogenic centers in 97% yield with 89% ee.[124]

Lygo and To also developed the direct asymmetric transformation of allylic alcohols into α,β-epoxyketones based on the biphasic oxidation system catalyzed by *N*-anthracenylmethyl-*O*-benzyldihydrocinchonidinium bromide **18d**. In combination with an ordinary carbonyl alkylation procedure, an α,β-unsaturated aldehyde is smoothly transformed to a chiral epoxyketone with good enantioselectivity (Scheme 106).[125]

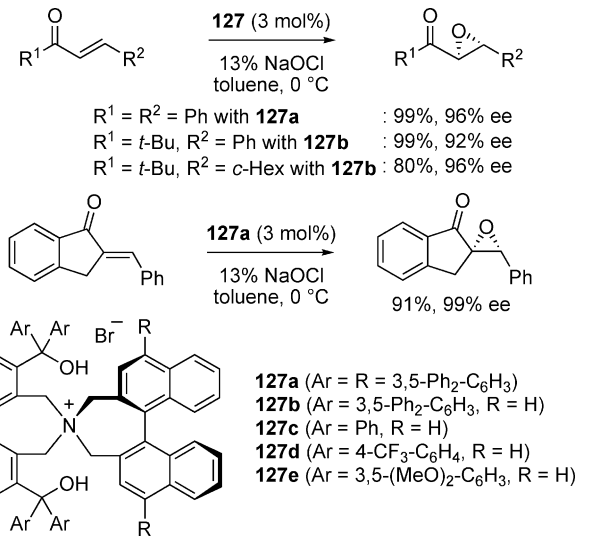
Scheme 106



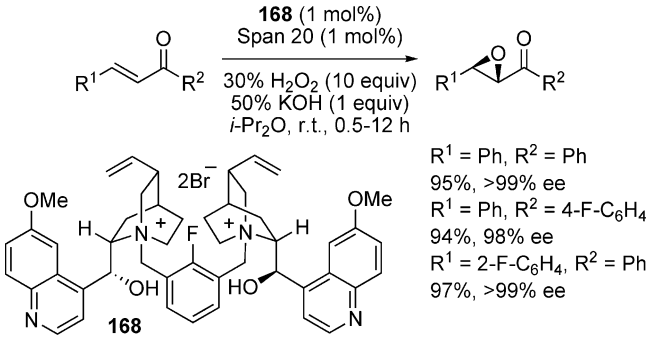
We designed a new and highly efficient chiral *N*-spiro-type quaternary ammonium salt **127** with dual functions for asymmetric epoxidation of various enone substrates (Scheme 107).[126] The exceedingly high asymmetric induction is ascribable to the molecular-recognition ability of the catalyst toward enone substrates by virtue of the appropriately aligned hydroxy functionality as well as the chiral molecular cavity. Indeed, the observed enantioselectivity highly depends on the steric size and the electronic factor of both Ar and R substituents in **127**, and use of **127c**−**127e** significantly decreased the enantioselection (61−66% ee for chalcone epoxidation).

Park, Jew, and co-workers applied chiral dimeric cinchona phase-transfer catalyst **168** for the catalytic asymmetric epoxidation of 2,4-diarylenones, providing the corresponding epoxide in excellent yields and selectivies. Their crucial point was the introduction of surfactant, such as Span 20, in the reaction system, which is neseccary to realize both high yields and enantioselectivities (Scheme 108).[127]

Scheme 107

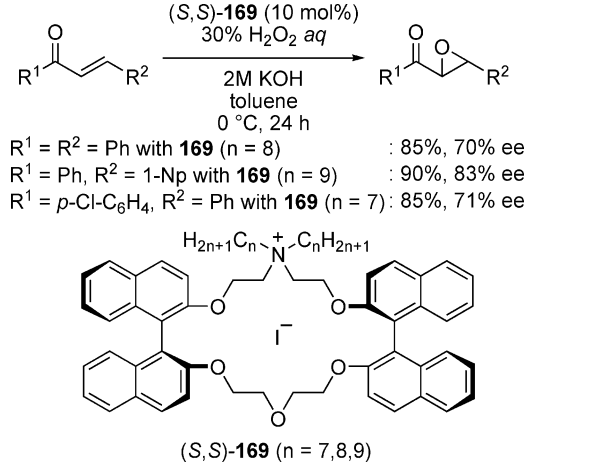


Scheme 108



Hori et al. designed phase-transfer catalysts **169** containing a quaternary ammonium salt moiety and a crown ether moiety, expecting that the ammonium salt would act as surfactant and the crown ether moiety would be for molecular recognition. The ability of the catalyst was demonstrated in the asymmetric epoxidation of diarylenones, furnishing the epoxides in moderate enantioselectivity. The length of the aliphatic chain was adjusted to achieve good selectivity depending on the enones (Scheme 109).[128]

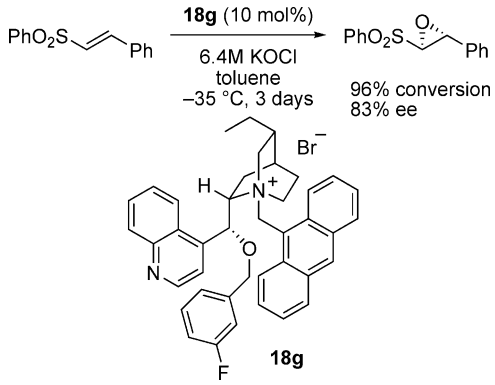
Scheme 109



The Pfizer group reported the scalemic asymmetric epoxidation of α,β-unsaturated sulfones. Among the screening of several parameters, they examined the effect of the ether

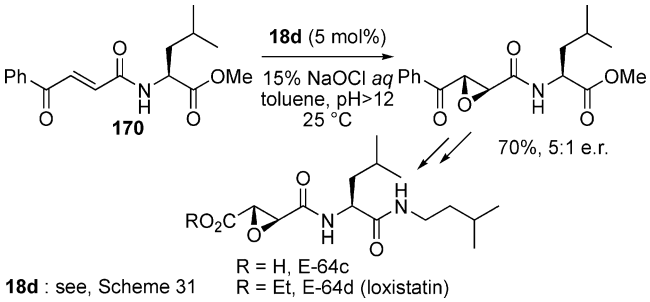
moiety of the dihydrocinchonidinium salt, leading to the use of (3-fluorophenyl)methyl ether **18g** as an optimal catalyst design (Scheme 110).[129]

Scheme 110



Lygo et al. utilized the chiral phase-transfer catalyzed epoxidation in the stereoselective synthesis of E-64c and E-64d (loxistatin). In the key step of these syntheses, the diastereoselective epoxidation of the enone **170** bearing leucine ester moiety was employed. The diastereomeric ratio was highly dependent on the phase-transfer catalyst, and they succeeded in achieving moderate diastereoselectivity by the use of *N*-anthracenylmethyl-*O*-benzyldihydrocinchonidinium bromide **18d** (Scheme 111).[130]

Scheme 111



9. Aziridination

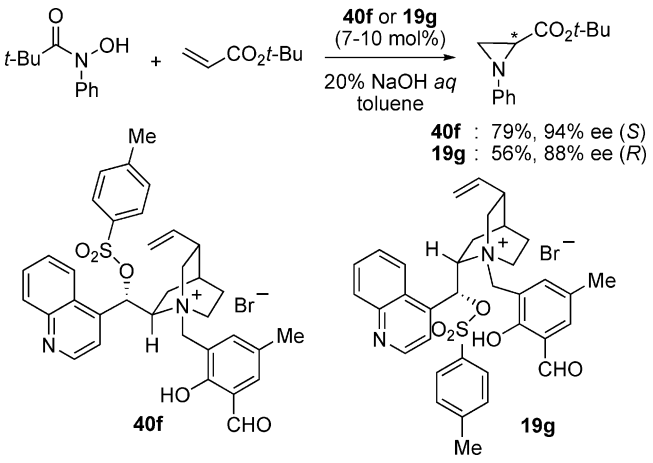
Chiral aziridines have been used as chiral auxiliaries, chiral ligands for transition metals, and chiral building blocks for preparation of biologically active species such as amino acids, β-lactams, and alkaloids.[131] Murugan and Siva developed a new procedure for asymmetric aziridination reactions to achieve an excellent level of enantioselectivity using new chiral phase-transfer catalysts **40f** and **19g** derived from cinchonine and cinchonidine, respectively (Scheme 112).[132]

10. Dihydroxylation

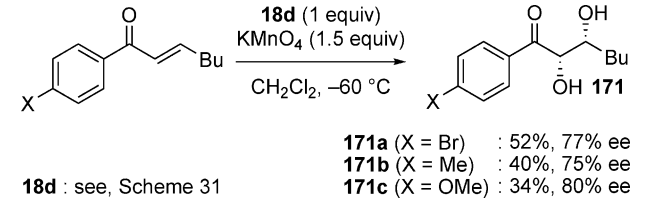
Asymmetric phase-transfer dihydroxylation of α,β-unsaturated ketones has been developed by Brown using *N*-anthracenylmethyl-*O*-benzyldihydrocinchonidinium bromide **18d** as catalyst and $KMnO_4$ as oxidant (Scheme 113).[133] Other types of olefins were found to be less rewarding; a simple terminal olefin gave the corresponding diol without detectable enantiomeric excess, and stilbene and chalcone gave over oxidation products.

This methodology stems from the study on the asymmetric oxidative cyclization of 1,5-dienes under slightly acidic conditions to promote the intramolecular ring closure. Among

Scheme 112

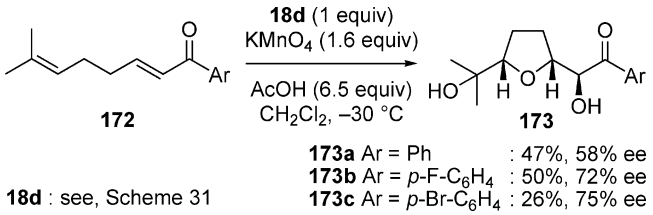


Scheme 113



various 1,5-dienes, those with conjugated ketones **172** showed good-to-high enantioselectivity (Scheme 114).[134]

Scheme 114



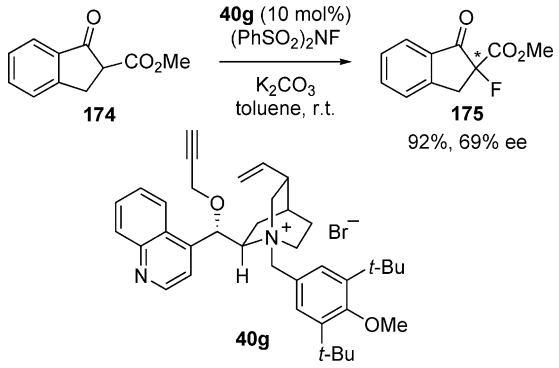
11. Fluorination

In view of the importance of optically active organofluorine compounds in various fields of chemistry, catalytic enantioselective fluorination of carbonyl substrates has emerged as an ever-awaited method, and the asymmetric electrophilic fluorination of β-keto ester **174** under phase-transfer conditions certainly belongs in this category. By the combined use of appropriately modified catalyst **40g** and *N*-fluorobenzenesulfonimide as a fluorinating agent in toluene with base (K_2CO_3), the desired **175** was isolated in 92% yield with 69% ee (Scheme 115).[135]

12. Strecker Reaction

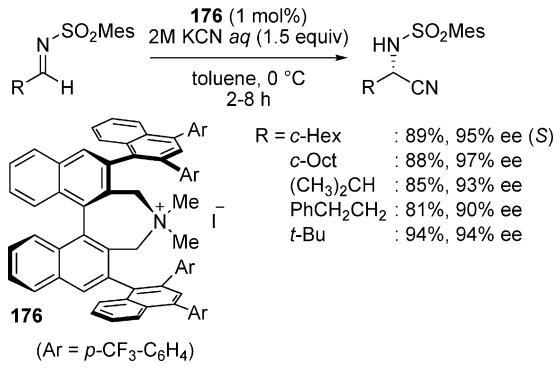
The catalytic asymmetric cyanation of imines, Strecker reaction, represents one of the most direct and viable methods for the asymmetric synthesis of α-amino acids and their derivatives. Numerous recent efforts in this field have resulted in the establishment of highly efficient and general protocols, although the use of either alkylmetal cyanide or anhydrous hydrogen cyanide, generally at low temperature, is inevitable. In this regard, we disclose the first example of phase-transfer-catalyzed, highly enantioselective Strecker reaction of aldimines using aqueous KCN based on the molecular design of chiral quaternary ammonium salts **176**

Scheme 115



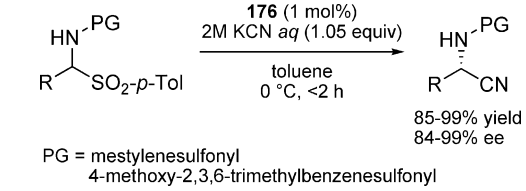
bearing the tetranaphthyl backbone as a remarkably efficient catalyst (Scheme 116).[136a]

Scheme 116



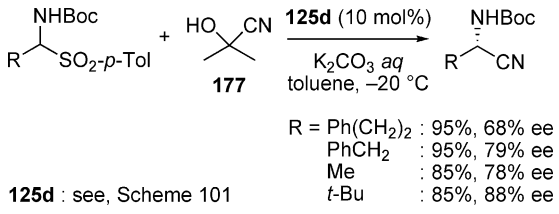
This phase-transfer-catalyzed asymmetric Strecker reaction is further elaborated by use of α-amidosulfone as a precursor of *N*-arylsulfonyl imine. In this system, the reaction can be conducted with a slight excess of potassium cyanide (1.05 equiv), and the reaction leads to completion within 2 h (Scheme 117).[136b]

Scheme 117



Herrera, Ricci, and co-workers utilized acetone cyanohydrin **177** as a cyanide source for the phase-transfer-catalyzed Strecker reaction. The intermediacy of the conjugate base of acetone cyanohydrin was suggested, since use of potassium cyanide as a cyanide source led to a lower enantioselectivity (Scheme 118).[137]

Scheme 118



13. Conclusion

The development of various types of chiral phase-transfer catalysts largely relies on the molecular design of both natural product-derived and purely synthetic chiral quaternary ammonium salts, which often delivers not only higher reactivity and stereoselectivity but also new synthetic opportunities, expanding the applicability of asymmetric phase-transfer catalysis in modern organic synthesis. Continuous efforts should be made toward the understanding of the relationship between the structure of the catalyst and its activity and stereocontrolling ability. Systematic accumulation of such knowledge would allow us to conduct even more rational catalyst design for pursuing selective chemical synthesis in a manner of reliable and practical elegance, thereby allowing us to establish genuinely sustainable chemical processes within the context of the forthcoming paradigm shift in worldwide production of highly valuable substances in this century.

14. Acknowledgments

We thank colleagues at Hokkaido University and Kyoto University for the personal and scientific collaborations, whose names appear in the references. Without their enthusiasm for organic chemistry, our research in the field of asymmetric phase-transfer catalysis would not have been achieved.

15. References

(1) (a) Dehmlow, E. V.; Dehmlow, S. S. *Phase Transfer Catalysis*, 3rd ed.; VCH: Weinheim, Germany, 1993. (b) Starks, C. M.; Liotta, C. L.; Halpern, M. *Phase−Transfer Catalysis*; Chapman & Hall: New York, 1994. (c) Sasson, Y., Neumann, R., Eds. *Handbook of Phase−Transfer Catalysis*; Blackie Academic & Professional: London, 1997. (d) Halpern, M. E., Ed. *Phase−Transfer Catalysis*; ACS Symposium Series 659; American Chemical Society: Washington, DC, 1997.

(2) (a) Shioiri, T. In *Handbook of Phase−Transfer Catalysis*; Sasson, Y., Neumann, R., Eds.; Blackie Academic & Professional: London, 1997; Chapter 14. (b) Nelson, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1583. (c) Shioiri, T.; Arai, S. In *Stimulating Concepts in Chemistry*; Vögtle, F., Stoddart, J. F., Shibasaki, M., Eds.; Wiley-VCH: Weinheim, Germany, 2000; p 123. (d) O'Donnell, M. J. In *Catalytic Asymmetric Syntheses*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 10. (e) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3. (f) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (g) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (h) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (i) Vachon, J.; Lacour, J. *Chimia* **2006**, *60*, 266.

(3) (a) Dolling, U.-H.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (b) Hughes, D. L.; Dolling, U.-H.; Ryan, K. M.; Schoenewaldt, E. F.; Grabowski, E. J. J. *J. Org. Chem.* **1987**, *52*, 4745.

(4) (a) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. (b) Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem.* **1991**, *56*, 5181. (c) Esikova, I. A.; Nahreini, T. S.; O'Donnell, M. J. In *Phase−Transfer Catalysis*; ACS Symposium Series 659; Halpern, M. E., Ed.; American Chemical Society: Washington, DC, 1997; Chapter 7. (d) O'Donnell, M. J.; Esikova, I. A.; Shullenberger, D. F.; Wu, S. In *Phase-Transfer Catalysis*; ACS Symposium Series 659; Halpern, M. E., Ed.; American Chemical Society: Washington, DC, 1997; Chapter 10.

(5) (a) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1997**, *38*, 8595. (b) Lygo, B.; Crosby, J.; Lowdon, T. R.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2391. (c) Lygo, B.; Crosby, J.; Lowdon, T. R.; Peterson, J. A.; Wainwright, P. G. *Tetrahedron* **2001**, *57*, 2403. (d) Lygo, B.; Andrews, B. I.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **2002**, *43*, 8015.

(6) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.

(7) (a) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **1999**, *121*, 6519. (b) Maruoka, K. *J. Fluorine Chem.* **2001**, *112*, 95. (c) Ooi, T.; Uematsu, Y.; Maruoka, K. *Adv. Synth. Catal.* **2002**, *344*, 288. (d) Ooi, T.; Uematsu, Y.; Maruoka, K. *J. Org. Chem.* **2003**, *68*, 4576. (e) Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.

(8) Ooi, T.; Uematsu, Y.; Maruoka, K. *Tetrahedron Lett.* **2004**, *45*, 1675.

(9) (a) Hashimoto, T.; Maruoka, K. *Tetrahedron Lett.* **2003**, *44*, 3313. (b) Hashimoto, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron: Asymmetry* **2003**, *14*, 1599.
(10) Ooi, T.; Tayama, E.; Doda, K.; Takeuchi, M.; Maruoka, K. *Synlett* **2000**, 1500.
(11) Shirakawa, S.; Yamamoto, K.; Kitamura, M.; Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 625.
(12) (a) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 1551. (b) Ooi, T.; Uematsu, Y.; Kameda, M.; Maruoka, K. *Tetrahedron* **2006**, *62*, 11425.
(13) Kano, T.; Konishi, S.; Shirakawa, S.; Maruoka, K. *Tetrahedron: Asymmetry* **2004**, *15*, 1243.
(14) Kitamura, M.; Shirakawa, S.; Maruoka, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549.
(15) Ooi, T.; Kubota, Y.; Maruoka, K. *Synlett* **2003**, 1931.
(16) Han, Z.; Yamaguchi, Y.; Kitamura, M.; Maruoka, K. *Tetrahedron Lett.* **2005**, *46*, 8555.
(17) Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, I. Y.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245.
(18) Yoo, M.-S.; Jeong, B.-S.; Lee, J.-H.; Park, H.-g.; Jew, S.-s. *Org. Lett.* **2005**, *7*, 1129.
(19) Elango, S.; Venugopal, M.; Suresh, P. S.; Eni *Tetrahedron* **2005**, *61*, 1443.
(20) Kumar, S.; Ramachandran, U. *Tetrahedron* **2005**, *61*, 7022.
(21) (a) Guillena, G.; Kreiter, R.; van de Coevering, R.; Klein Gebbink, R. J. M.; van Koten, G.; Mazón, P.; Chinchilla, R.; Nájera, C. *Tetrahedron: Asymmetry* **2003**, *14*, 3705. (b) Mazón, P.; Chinchilla, R.; Nájera, C.; Guillena, G.; Kreiter, R.; Klein Gebbink, R. J. M.; van Koten, G. *Tetrahedron: Asymmetry* **2002**, *13*, 2181.
(22) Andrus, M. B.; Ye, Z.; Zhang, J. *Tetrahedron Lett.* **2005**, *46*, 3839.
(23) (a) Jew, S.-s.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244. (b) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, B.-s.; Kim, M. G.; Jew, S.-s. *Tetrahedron Lett.* **2003**, *44*, 3497.
(24) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* **2001**, *42*, 4645.
(25) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036.
(26) (a) Chinchilla, R.; Mazón, P.; Nájera, C.; Ortega, F. J. *Tetrahedron: Asymmetry* **2004**, *15*, 2603. (b) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2002**, *13*, 927.
(27) (a) Siva, A.; Murugan, E. *Synthesis* **2005**, 2927. (b) Siva, A.; Murugan, E. *J. Mol. Catal. A: Chem.* **2005**, *241*, 111. (c) Siva, A.; Murugan, E. *J. Mol. Catal. A: Chem.* **2006**, *248*, 1.
(28) (a) Shibuguchi, T.; Fukuta, Y.; Akachi, Y.; Sekine, A.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 9539. (b) Ohshima, T.; Shibuguchi, T.; Fukuta, Y.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 7743.
(29) Kita, T.; Georgieva, A.; Hashimoto, Y.; Nakata, T.; Nagasawa, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 2832.
(30) (a) Kowtoniuk, W. E.; MacFarland, D. K.; Grover, G. N. *Tetrahedron Lett.* **2005**, *46*, 5703. See also: (b) Rueffer, M. E.; Fort, L. K.; MacFarland, D. K. *Tetrahedron: Asymmetry* **2004**, *15*, 3297. See also ref 35.
(31) Sasai, H. *Jpn. Kokai Tokkyo Koho* **2003**, JP2003335780.
(32) (a) Lygo, B.; Allbutt, B.; James, S. R. *Tetrahedron Lett.* **2003**, *44*, 5629. (b) Lygo, B.; Allbutt, B. *Synlett* **2004**, 326.
(33) Mase, N.; Ohno, T.; Hoshikawa, N.; Ohishi, K.; Morimoto, H.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 4073.
(34) (a) Kumar, S.; Ramachandran, U. *Tetrahedron* **2005**, *61*, 4141. (b) Kumar, S.; Sobhia, M. E.; Ramachandran, U. *Tetrahedron: Asymmetry* **2005**, *16*, 2599.
(35) Grover, G. N.; Kowtoniuk, W. E.; MacFarland, D. K. *Tetrahedron Lett.* **2006**, *47*, 57.
(36) Deleted in proof.
(37) Chinchilla, R.; Nájera, C.; Ortega, F. J. *Tetrahedron: Asymmetry* **2006**, *17*, 3423.
(38) Mase, N.; Ohno, T.; Morimoto, H.; Nitta, F.; Yoda, H.; Takabe, K. *Tetrahedron Lett.* **2005**, *46*, 3213.
(39) Li, L.; Zhang, Z.; Zhu, X.; Popa, A. Wang, S. *Synlett* **2005**, 1869.
(40) Ooi, T.; Arimura, Y.; Hiraiwa, Y.; Yuan, L. M.; Kano, T.; Inoue, T.; Matsumoto, J.; Maruoka, K. *Tetrahedron: Asymmetry* **2006**, *17*, 603.
(41) Hyett, D. J.; Didonè, M.; Milcent, T. J. A.; Broxterman, Q. B.; Kaptein, B. *Tetrahedron Lett.* **2006**, *47*, 7771.
(42) Kumar, S.; Ramachandran, U. *Tetrahedron: Asymmetry* **2003**, *14*, 2539.
(43) Ooi, T.; Sakai, D.; Takeuchi, M.; Tayama, E.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 5868.
(44) Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073.
(45) Lépine, R.; Carbonnelle, A.-C.; Zhu, J. *Synlett* **2003**, 1455.
(46) Armstrong, A.; Scutt, J. N. *Org. Lett.* **2003**, *5*, 2331.
(47) (a) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3277. (b) Chinchilla, R.; Mazón, P.; Nájera, C. *Adv. Synth. Catal.* **2004**, *346*, 1186.
(48) Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Tetrahedron: Asymmetry* **2001**, *12*, 983.
(49) Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Tetrahedron: Asymmetry* **2003**, *14*, 1671.
(50) Thierry, B.; Perrard, T.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Synthesis* **2001**, 1742.
(51) Danelli, T.; Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. *Tetrahedron: Asymmetry* **2003**, *14*, 461.
(52) (a) Yu, H.; Koshima, H. *Tetrahedron Lett.* **2003**, *44*, 9209. (b) Yu, H.; Takigawa, S.; Koshima, H. *Tetrahedron* **2004**, *60*, 8405.
(53) Shirakawa, S.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2004**, *6*, 1429.
(54) Park, H.-g.; Kim, M.-J.; Park, M.-K.; Jung, H.-J.; Lee, J.; Choi, S.-h.; Lee, Y.-J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Ku, J.-M.; Jew, S.-s. *J. Org. Chem.* **2005**, *70*, 1904.
(55) Nitz, M.; Mezo, A. R.; Ali, M. H.; Imperiali, B. *Chem. Commun.* **2002**, 1912.
(56) Lygo, B.; Andrews, B. I. *Tetrahedron Lett.* **2003**, *44*, 4499.
(57) Lygo, B.; Andrews, B. I.; Slack, D. *Tetrahedron Lett.* **2003**, *44*, 9039.
(58) Lygo, B.; Humphreys, L. D. *Tetrahedron Lett.* **2002**, *43*, 6677.
(59) Ooi, T.; Kameda, M.; Tannai, H.; Maruoka, K. *Tetrahedron Lett.* **2000**, *41*, 8339.
(60) Ooi, T.; Takeuchi, M.; Maruoka, K. *Synthesis* **2001**, 1716.
(61) Lemaire, C.; Gillet, S.; Guillouet, S.; Plenevaux, A.; Aerts, J.; Luxen, A. *Eur. J. Org. Chem.* **2004**, 2899.
(62) Kumar, S.; Ramachandran, U. *Tetrahedron Lett.* **2005**, *46*, 19.
(63) Castle, S. L.; Srikanth, G. S. C. *Org. Lett.* **2003**, *5*, 3611.
(64) Boeckman, R. K., Jr.; Clark, T. J.; Shook, B. C. *Org. Lett.* **2002**, *4*, 2109.
(65) Kim, S.; Lee, J.; Lee, T.; Park, H.-g.; Kim, D. *Org. Lett.* **2003**, *5*, 2703.
(66) (a) Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Fukuta, Y.; Nemoto, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 11206. (b) Fukuta, Y.; Ohshima, T.; Gnanadesikan, V.; Shibuguchi, T.; Nemoto, T.; Kisugi, T.; Okino, T.; Shibasaki, M. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5433.
(67) Lee, J.-H.; Jeong, B.-S.; Ku, J.-M.; Jew, S.-s.; Park, H.-g. *J. Org. Chem.* **2006**, *71*, 6690.
(68) Patterson, D. E.; Xie, S.; Jones, L. A.; Osterhout, M. H.; Henry, C. G.; Roper, T. D. *Org. Process Res. Dev.* **2007**, *11*, 624.
(69) (a) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 3329. (b) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *J. Org. Chem.* **2002**, *67*, 7418.
(70) Ramachandran, P. V.; Madhi, S.; Bland-Berry, L.; Ram Reddy, M. V.; O'Donnell, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 13450.
(71) (a) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406. (b) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127. (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517. (d) Schöllkopf, U. *Top. Curr. Chem.* **1983**, *109*, 65.
(72) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.
(73) Maeda, K.; Miller, R. A.; Szumigala, R. H., Jr.; Shafiee, A.; Karady, S.; Armstrong, J. D., III *Tetrahedron Lett.* **2005**, *46*, 1545.
(74) Jew, S.-s.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Lee, Y.-J.; Park, B.-s.; Kim, M. G.; Park, H.-g. *J. Org. Chem.* **2003**, *68*, 4514.
(75) Jew, S.-s.; Lee, Y.-J.; Lee, J.; Kang, M. J.; Jeong, B.-S.; Lee, J.-H.; Yoo, M.-S.; Kim, M.-J.; Choi, S.-h.; Ku, J.-M.; Park, H.-g. *Angew. Chem., Int. Ed.* **2004**, *43*, 2382.
(76) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Kim, T.-S.; Park, H.-g.; Jew, S.-s. *Org. Lett.* **2005**, *7*, 1557.
(77) Kim, T.-S.; Lee, Y.-J.; Jeong, B.-S.; Park, H.-g.; Jew, S.-s. *J. Org. Chem.* **2006**, *71*, 8276.
(78) For a comprehensive review on the use of peptide enolates, see: Seebach, D.; Beck, A. K.; Studer, A. In *Modern Synthetic Methods*; Ernst, B., Leumann, C., Eds.; VCH: Weinheim, Germany, 1995; Vol. 7, p 1.
(79) (a) Ooi, T.; Tayama, E.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 579. (b) Maruoka, K.; Tayama, E.; Ooi, T. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 5824.
(80) Dehmlow, E. V.; Düttmann, S.; Neumann, B.; Stammler, H.-G. *Eur. J. Org. Chem.* **2002**, 2087.

(81) (a) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796. (b) Ooi, T.; Miki, T.; Fukumoto, K.; Maruoka, K. *Adv. Synth. Catal.* **2006**, *348*, 1539.
(82) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897.
(83) (a) Andrus, M. B.; Hicken, E. J.; Stephens, J. C. *Org. Lett.* **2004**, *6*, 2289. (b) Andrus, M. B.; Hicken, E. J.; Stephens, J. C.; Bedke, D. K. *J. Org. Chem.* **2005**, *70*, 9470. (c) Andrus, M. B.; Hicken, E. J.; Stephens, J. C.; Bedke, D. K. *J. Org. Chem.* **2006**, *71*, 8651.
(84) Ooi, T.; Miki, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 191.
(85) Ooi, T.; Fukumoto, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3839.
(86) (a) Bella, M.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670. (b) Kobbelgaard, S.; Bella, M.; Jørgensen, K. A. *J. Org. Chem.* **2006**, *71*, 4980.
(87) Poulsen, T. B.; Bernardi, L.; Bell, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6551.
(88) Poulsen, T. B.; Bernardi, L.; Alemán, J.; Overgaard, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 441.
(89) Kumar, S.; Ramachandran, U. *Tetrahedron: Asymmetry* **2005**, *16*, 647.
(90) Brózda, D.; Hoffman, K.; Rozwadowska, M. D. *Heterocycles* **2006**, *69*, 119.
(91) For recent reviews on catalytic asymmetric Michael reactions, see: (a) Krause, N.; Hoffman-Röder, A. *Synthesis* **2001**, 171. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (c) Kanai, M.; Shibasaki M. In *Catalytic Asymmetric Synthesis*, second ed.; Ojima, I., Ed.; Wiley: New York, 2000; p 569. (d) Tomioka, K.; Nagaoka Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, Chapter 31.1.
(92) Perrard, T.; Plaquevent, J.-C.; Desmurs, J.-R.; Hébrault, D. *Org. Lett.* **2000**, *2*, 2959.
(93) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299.
(94) Dere, R. T.; Pal, R. R.; Patil, P. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2003**, *44*, 5351.
(95) Ooi, T.; Ohara, D.; Fukumoto, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 3195.
(96) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.
(97) O'Donnell, M. J.; Delgado, F.; Domínguez, E.; de Blas, J.; Scott, W. L. *Tetrahedron: Asymmetry* **2001**, *12*, 821.
(98) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakuraba, S.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4635.
(99) (a) Arai, S.; Tsuji, R.; Nishida, A. *Tetrahedron Lett.* **2002**, *43*, 9535. (b) Arai, S.; Takahashi, F.; Tsuji, R.; Nishida, A. *Heterocycles* **2006**, *67*, 495.
(100) Arai, S.; Tokumaru, K.; Aoyama, T. *Chem. Pharm. Bull.* **2004**, *52*, 646.
(101) Lygo, B.; Allbutt, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461.
(102) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Jeong, B.-S.; Lee, J.-H.; Kim, T.-S.; Lee, J.; Ku, J.-M.; Jew, S.-s.; Park, H.-g. *Org. Lett.* **2005**, *7*, 3207.
(103) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3397.
(104) Ceccarelli, R.; Insogna, S.; Bella, M. *Org. Biomol. Chem.* **2006**, *4*, 4281.
(105) (a) Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 11790. (b) Ooi, T.; Takada, S.; Fujioka, S.; Maruoka, K. *Org. Lett.* **2005**, *7*, 5143.
(106) Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 1038.
(107) (a) Ooi, T.; Taniguchi, M.; Kameda, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2002**, *41*, 4542. (b) Ooi, T.; Kameda, M.; Taniguchi, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 9685.
(108) Mettath, S.; Srikanth, G. S. C.; Dangerfield, B. S.; Castle, S. L. *J. Org. Chem.* **2004**, *69*, 6489.
(109) Andrus, M. B.; Liu, J.; Ye. Z.; Cannon, J. F. *Org. Lett.* **2005**, *7*, 3861.
(110) For a general review on asymmetric catalysis with quaternary ammonium fluoride, see: Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526.
(111) (a) Arai, S.; Hasegawa, K.; Nishida, A. *Tetrahedron Lett.* **2004**, *45*, 1023. (b) Hasegawa, K.; Arai, S.; Nishida, A. *Tetrahedron* **2006**, *62*, 1390.
(112) Ooi, T.; Kameda, M.; Fujii, J.-i.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397.
(113) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564.
(114) Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622.
(115) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975.
(116) Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sgarzani, V. *Adv. Synth. Catal.* **2006**, *348*, 2043.
(117) For a review, see: Rosen, T. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 2, p 409.
(118) Arai, S.; Tokumaru, K.; Aoyama, T. *Tetrahedron Lett.* **2004**, *45*, 1845.
(119) Ooi, T.; Takahashi, M.; Doda, K.; Maruoka, K. *J. Am. Chem. Soc.* **2002**, *124*, 7640.
(120) For reviews, see: (a) Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215. (b) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 94.
(121) Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron* **2002**, *58*, 1623.
(122) Lygo, B.; To, D. C. M. *Tetrahedron Lett.* **2001**, *42*, 1343.
(123) (a) Ye, J.; Wang, Y.; Liu, R.; Zhang, G.; Zhang, Q.; Chen, J.; Liang, X. *Chem. Commun.* **2003**, 2714. (b) Ye, J.; Wang, Y.; Chen, J.; Liang, X. *Adv. Synth. Catal.* **2004**, *346*, 691.
(124) (a) Adam, W.; Rao, P. B.; Degen, H.-G.; Saha-Möller, C. R. *Tetrahedron: Asymmetry* **2001**, *12*, 121. (b) Adam, W.; Rao, P. B.; Degen, H.-G.; Levai, A.; Patonay, T.; Saha-Möller, C. R. *J. Org. Chem.* **2002**, *67*, 259.
(125) Lygo, B.; To, D. C. M. *Chem. Commun.* **2002**, 2360.
(126) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844.
(127) Jew, S.-s.; Lee, J.-H.; Jeong, B.-S.; Yoo, M.-S.; Kim, M.-J.; Lee, Y.-J.; Lee, J.; Choi, S.-h.; Lee, K.; Lah, M. S.; Park, H.-g. *Angew. Chem., Int. Ed.* **2005**, *44*, 1383.
(128) Hori, K.; Tamura, M.; Tani, K.; Nishiwaki, N.; Ariga, M.; Tohda, Y. *Tetrahedron Lett.* **2006**, *47*, 3115.
(129) Dorow, R. L.; Tymonko, S. A. *Tetrahedron Lett.* **2006**, *47*, 2493.
(130) Lygo, B.; Gardiner, S. D.; To, D. C. M. *Synlett* **2006**, 2063.
(131) For reviews, see: (a) Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347.
(132) Murugan, E.; Siva, A. *Synthesis* **2005**, 2022.
(133) Bhunnoo, R. A.; Hu, Y.; Lainé. D. I.; Brown, R. C. D. *Angew. Chem., Int. Ed.* **2002**, *41*, 3479.
(134) Brown, R. C. D.; Keily, J. F. *Angew. Chem., Int. Ed.* **2001**, *40*, 4496.
(135) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545.
(136) (a) Ooi, T.; Uematsu, U.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2548. (b) Ooi, T.; Uematsu, Y.; Fujimoto, J.; Fukumoto, K.; Maruoka, K. *Tetrahedron Lett.* **2007**, *48*, 1337.
(137) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Fini, F.; Pettersen, D.; Ricci, A. *J. Org. Chem.* **2006**, *71*, 9869.

CR068368N