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Reviews

Practical Aspects of Recent Asymmetric Phase-Transfer Catalysis

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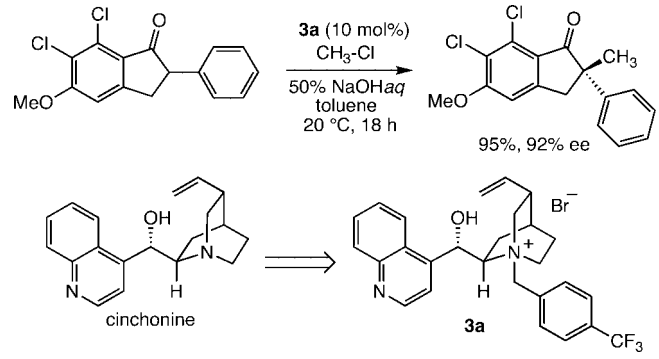
Abstract:

This review article outlines the recent practical aspects of asymmetric phase-transfer catalysis including (1) asymmetric alkylation of glycine and α-substituted amino acid derivatives as well as other substrates, (2) asymmetric Michael addition, (3) asymmetric aldol reaction, (4) asymmetric Mannich reaction, (5) asymmetric epoxidation, (6) asymmetric aziridination, (7) and the asymmetric Strecker reaction.

1. Introduction

Phase-transfer catalysis has long been recognized as a versatile methodology for organic synthesis in both industry and academia, featuring simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility to conduct large-scale preparations in process chemistry.[1] In particular, over the recent past, 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 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 practical aspects of asymmetric transformations using various types of chiral phase-transfer catalysts since 2000, showcasing the variations of their molecular designs and synthetic applications from a practical point of view, including (1) economy of the catalysts, (2) stability of catalysts and handling issues, and (3) separation of biphasic system and recycling issues. For literature coverage prior to this period, the reader should consult the existing excellent reviews of asymmetric phase-transfer catalysis.[2a–g] Other recent reviews of asymmetric phase-transfer catalysis are also useful.[2h–n]

Scheme 1



2. Asymmetric Alkylation

2.1. Asymmetric Synthesis of α-Alkyl-α-amino Acids. *2.1.1. Binaphthyl-Modified Phase Transfer Catalysts for the Asymmetric Monoalkylation of Glycine Schiff Bases.* Although initial study on asymmetric alkylation of carbonyl compounds by chiral phase-transfer catalyst has shown only disappointing results, a first efficient chiral phase-transfer catalyst, *N*-(*p*-(trifluoromethyl)benzyl)cinchonidium bromide (**3a**) has been devised in 1984 by the Merck group for asymmetric alkylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone, giving the corresponding methylation product with 92% ee in this particular case (Scheme 1).[3]

After 5 years of this successful endeavor, similar *N*-benzyl cinchoninium halide **3b** has been successfully utilized by O'Donnell as a chiral phase-transfer catalyst for the asymmetric alkylation of glycine Schiff base **1a**. This produced the alkylation product (*R*)-**2a** in good yield and moderate enantio-

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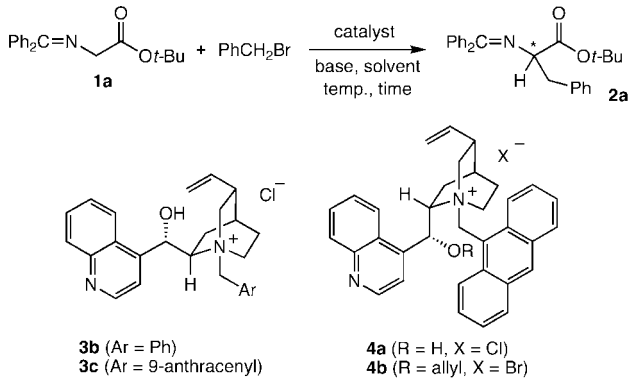
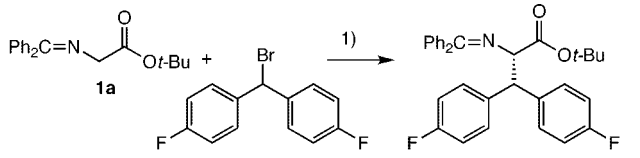
Scheme 2



75%, 66% *ee* (*R*)	63%, 89% *ee* (*R*)	68%, 91% *ee* (*S*)	84%, 94% *ee* (*S*)
3b (10 mol%)	**3c** (10 mol%)	**4a** (10 mol%)	**4b** (10 mol%)
50% NaOH *aq*	50% KOH *aq*	50% KOH *aq*	$CsOH{\cdot}H_2O$
CH_2Cl_2	Ph-Me	Ph-Me	CH_2Cl_2
20 °C, 12 h	20 °C, 18 h	20 °C, 18 h	–78 °C, 23 h
Ref. 4	Ref. 5	Ref. 5	Ref. 6

Scheme 3

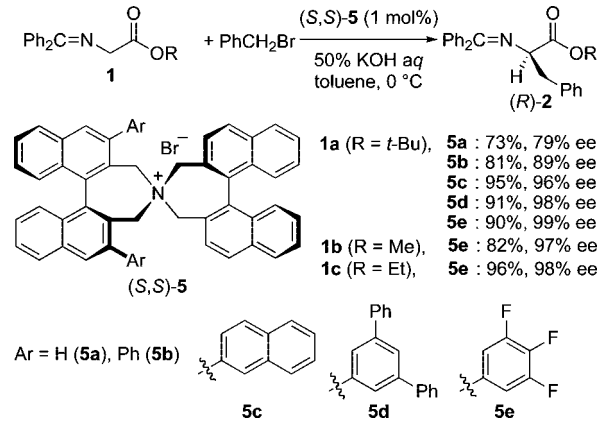


1) **4b** (5 mol%), CH_2Cl_2 (5 vol); then alkyl bromide (1.5 eq); then 45% KOH *aq*.

selectivity (Scheme 2).[4] Although asymmetric phase-transfer alkylation of glycine Schiff base **1** can be achieved by using chiral phase-transfer catalysts derived from the relatively inexpensive, commercially available cinchona alkaloid, research in this area had made little progress until recently after O'Donnell's milestone reports. However, new class of cinchona alkaloid-derived catalysts **3c** and **4a**,**b** bearing an *N*-anthracenylmethyl function developed by Corey and Lygo independently[5,6] have opened a new era of asymmetric phase-transfer catalysis.

Large-scale application of such cinchona-derived chiral phase-transfer catalysts is very limited, although the great progress was made these several years by academic scientists. Very recently, the GSK group successfully applied the catalyst **4b** to the asymmetric synthesis of 4-fluoro-β-(4-fluorophenyl)-L-phenylalanine by asymmetric phase-transfer alkylation (Scheme 3).[7] Addition order of the catalyst or base is found to be

Scheme 4



extremely critical for their kg-scale experiments, and after modification of their process, 1.72 kg product was obtained in 99% ee.

In 1999, we designed and prepared the structurally rigid, chiral spiro ammonium salts of type **5** 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 **1** under mild phase-transfer conditions (Scheme 4).[8]

A significant effect of aromatic substitution (Ar) at the 3,3′-position of one binaphthyl subunit of the catalyst **5** was observed for enantiofacial discrimination. (*S*,*S*)-**5e** was revealed to be the catalyst of choice for the preparation of a variety of essentially enantiopure α-amino acids by this transformation. Compared to cinchona-alkaloid derived phase-transfer catalysts, 1 mol % of **5e** is sufficient for smooth alkylation. Since both enantiomers of the catalyst of type **5** can be readily assembled starting from either (*S*)- or (*R*)-1,1′-bi-2-naphthol, a wide variety of natural and unnatural α-amino acids can be synthesized in enantiomerically pure form by the phase-transfer catalytic alkylation of **1**. The salient feature of **5e** as a chiral phase-transfer catalyst is its ability to catalyze the asymmetric alkylation of glycine methyl and ethyl ester derivatives **1b** and **1c** with excellent enantioselectivities (Scheme 4). Since methyl and ethyl esters are more susceptible toward nucleophilic additions as compared to *tert*-butyl ester, the synthetic advantage of this process is quite obvious by the facile transformation of the ester moiety such as hydrolysis and amidation.[9]

With the critical role of 3,3′-diaryl substituents of **5** in mind, we examined the effect of 4,4′- and 6,6′-substituents of one binaphthyl subunit as shown in catalyst (*S*,*S*)-**6** (Scheme 5). Introduction of simple aromatic groups at the 4,4′-positions led to a meaningful effect on the stereoselectivity of the phase-transfer-catalyzed alkylation of **1**.[10a] On the other hand, we were intrigued with the preparation of symmetrical *N*-spiro type catalyst to avoid the tedious independent synthesis of the two

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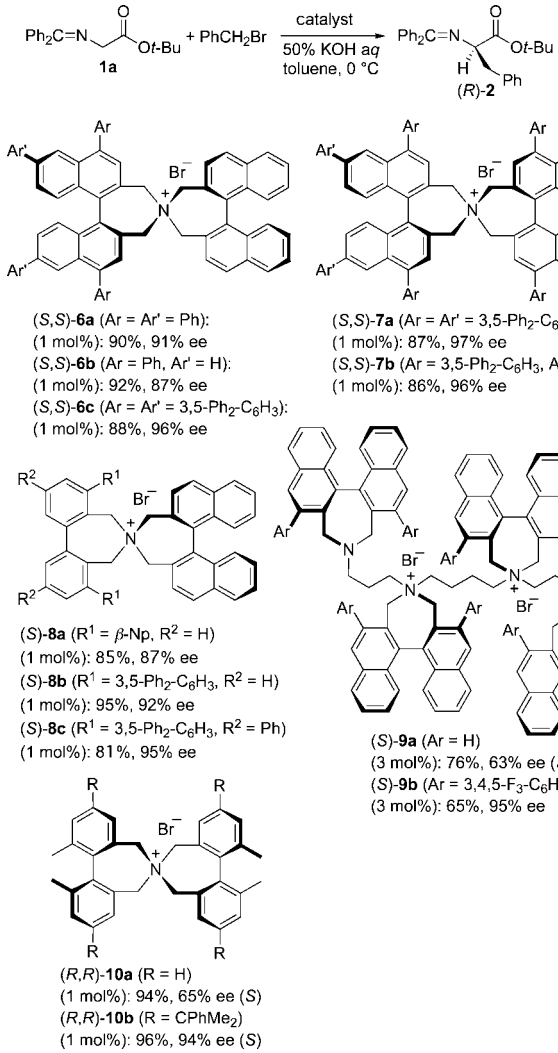
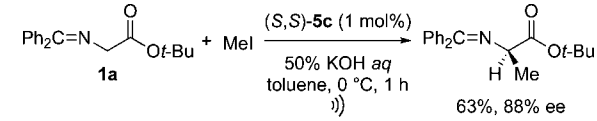
Scheme 5



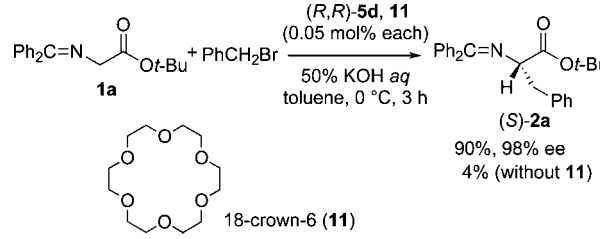
different binaphthyl-modified subunits required for **5**. Along this line, 4,4′,6,6′-tetraarylbinaphthyl-substituted ammonium bromide **7** was assembled through the reaction of aqueous ammonia with bis-bromide on the basis of our study on the substituent effect of this type of salt. Evaluation of **7** as a chiral phase-transfer catalyst in the alkylation of **1** uncovered its high catalytic and chiral efficiency (Scheme 5).[10b] Although the conformationally rigid, *N*-spiro structure created by two chiral binaphthyl subunits represents a characteristic feature of **5** and related catalyst **6**, it also imposes limitations on the catalyst design due to the use of the two different chiral binaphthyl moieties. Accordingly, we developed a new C_2-symmetric chiral quaternary ammonium bromide **8** by incorporating an achiral, conformationally flexible biphenyl subunit (Scheme 5).[11]

Our further efforts toward the simplification of the catalyst have led to the design of new, polyamine-based chiral phase-transfer catalysts of type **9** with the expectation of the multiplier effect of chiral auxiliaries (Scheme 5).[12] The chiral efficiency of such polyamine-based chiral phase-transfer catalysts (*S*)-**9**

Scheme 6



Scheme 7



was examined by carriying out the asymmetric alkylation of glycine derivatives under phase-transfer conditions. Among various commercially available polyamines, spermidine- and spermine-based polyammonium salts showed moderate enantioselectivity. In particular, introduction of the 3,4,5-trifluorophenyl group at the 3,3′-positions of chiral binaphthyl moieties (**9b**) displayed excellent asymmetric induction. We have also been interested in the development of other C_2-symmetric phase-transfer catalysts, which consist of two chiral biphenyl units as a new, easily modifiable subunit for further elaboration. To this end, chiral phase-transfer catalyst **10** was synthesized and evaluated in the asymmetric alkylation of glycine Schiff base **1** (Scheme 5).[13]

We attempted to enhance the reactivity of the *N*-spiro chiral quaternary ammonium salt and simplification of its structure in view of establishing a truly practical method for the asymmetric synthesis of α-amino acids and their derivatives. Since sonication produces homogenization, i.e., very fine emulsions, it greatly increases the reactive interfacial area, which could deliver substantial rate acceleration under liquid−liquid phase-transfer reactions. Indeed, sonication of the reaction mixture of **1**, methyl iodide and (*S,S*)-**5c** (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, demonstrating that the reaction rate increased markedly (cf. 0 °C for 8 h stirring; 64%, 90% ee) (Scheme 6).[14]

In order to fully induce the potential catalytic activity of *N*-spiro chiral ammonium salt such as **5d**, we have developed binary phase-transfer catalysis using an appropriate achiral cocatalyst. For instance, the phase-transfer-catalyzed alkylation of **1a** with benzyl bromide under the influence of **5d** (0.05 mol %) turned out to be sluggish as (*S*)-**2a** formed in only 4% yield (92% ee), while a similar benzylation of **1a** in the presence of 18-crown-6 (**11**, 0.05 mol %) proceeded smoothly to furnish (*S*)-**2a** 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 toluene phase, accelerating the otherwise slow deprotonation process (Scheme 7).[15] Indeed, use of small-sized crown ethers such as 15-crown-5 and 12-crown-4 dramatically

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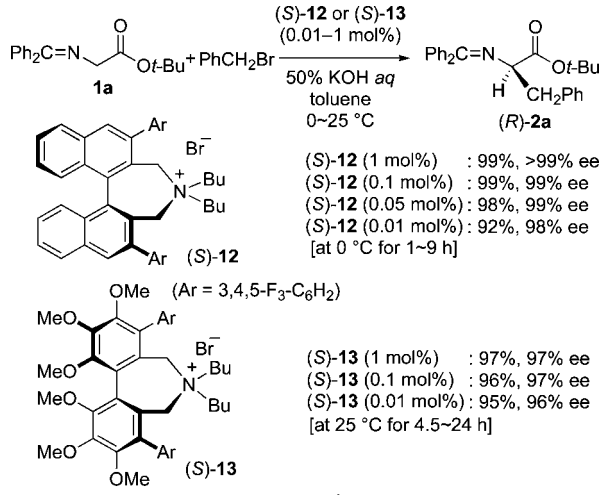
Scheme 8



lowered the chemical yield of (*S*)-**2a**. Interestingly, tetrabutyl- and tetraoctylammonium salts also exhibited similar acceleration effects.

We recently discovered the very powerful chiral quaternary ammonium bromide **12** 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 **1a** with various alkyl halides proceeded smoothly under mild phase-transfer conditions in the presence of only 0.01−0.05 mol % of (*S*)-**12** to afford the corresponding alkylation products with excellent enantioselectivities (Scheme 8).[16]

In designing practical phase-transfer catalysts, the ready availability of chiral starting materials is crucial. Accordingly, a highly practical, chiral phase-transfer catalyst **13** was conveniently prepared from the known, readily available (*S*)-4,5,6,4′,5′,6′-hexamethoxybiphenyldicarboxylic acid derived from gallic acid. This catalyst (*S*)-**13** also exhibited high catalytic performance (0.01−1 mol %) in the asymmetric alkylation of **1a** compared to existing chiral phase-transfer catalysts, thereby providing a general and useful procedure for highly practical enantioselective synthesis of structurally diverse natural and unnatural α-alkyl-α-amino acids (Scheme 8).[17]

2.1.2. Other Chiral Phase-Transfer Catalysts for the Alkylation of Glycine Schiff Base. Pioneering work by us and other groups have led to the development of particularly effective chiral phase-transfer catalysts in the past decade. They are classified into three groups: (1) cinchona alkaloid derivatives (Schemes 9 and 10), (2) tartrate derivatives (Scheme 11), and (3) other derivatives (Scheme 12). Among these, the development of bis- and tris-ammonium phase-transfer catalysts represented by Park, Jew, and Shibasaki is especially noteworthy, since these bis- and tris-ammonium salts generally exhibit higher reactivity and selectivity compared to the corresponding monoammonium salts.

2.1.3. Other Glycine Derivatives. As described above, benzophenone imine glycine Schiff base was successfully applied to asymmetric synthesis of α-amino acids. However, the rather difficult preparation is considered to be a major drawback for industrial application. This problem could be solved by the use of glycine *tert*-butyl ester aldimine Schiff base **28a**, which is normally employed for the synthesis of α,α-dialkyl-α-amino acids. It may also be utilized for α-alkyl-α-amino acids under the influence of **5e** or **12**. This finding demonstrated the possibility to use glycine *tert*-butyl ester aldimine Schiff base instead of the benzophenone Schiff base as a cost-effective way to obtain optically active α-alkyl-α-amino acids (Scheme 13).[36]

As prochiral glycine-derived Schiff bases, not only esters but also amides can be used as suitable substrates for asymmetric alkylation under phase-transfer conditions. Using glycine diphenylmethyl (Dpm) amide-derived Schiff base **29** as substrate and *N*-spiro chiral quaternary ammonium bromide **5g** as catalyst, we achieved high enantioselectivity even for alkylation with unreactive secondary alkyl halides. This system offers a facile access to structurally diverse optically active vicinal diamines in combination after the subsequent reduction (Scheme 14).[37]

Furthermore, this approach was found to be applicable to the asymmetric alkylation of Weinreb amide derivative **30**,

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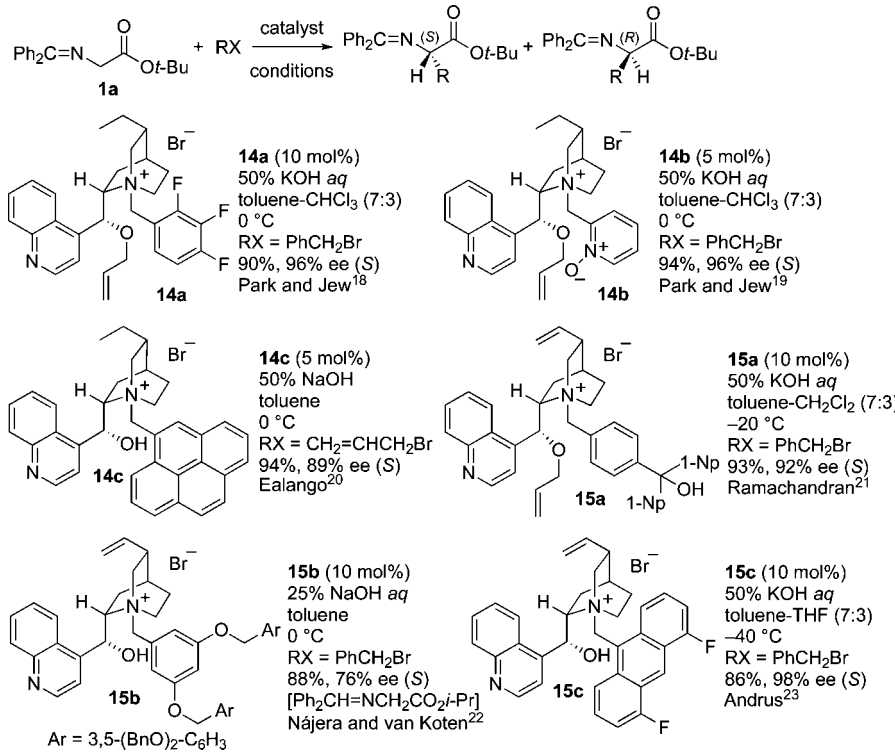
Scheme 9. **Cinchona alkaloid-derived mono-ammonium salts**



utilizing **5f** as catalyst. Optically active α-amino acid Weinreb amide **31** can be efficiently converted to the corresponding amino ketone by a simple treatment with Grignard reagents. In addition, reduction and alkylation of the optically active α-amino ketones **32** and **33** into both *syn* and *anti* α-amino alcohols with almost complete relative and absolute stereochemical control have been achieved (Scheme 15).[38]

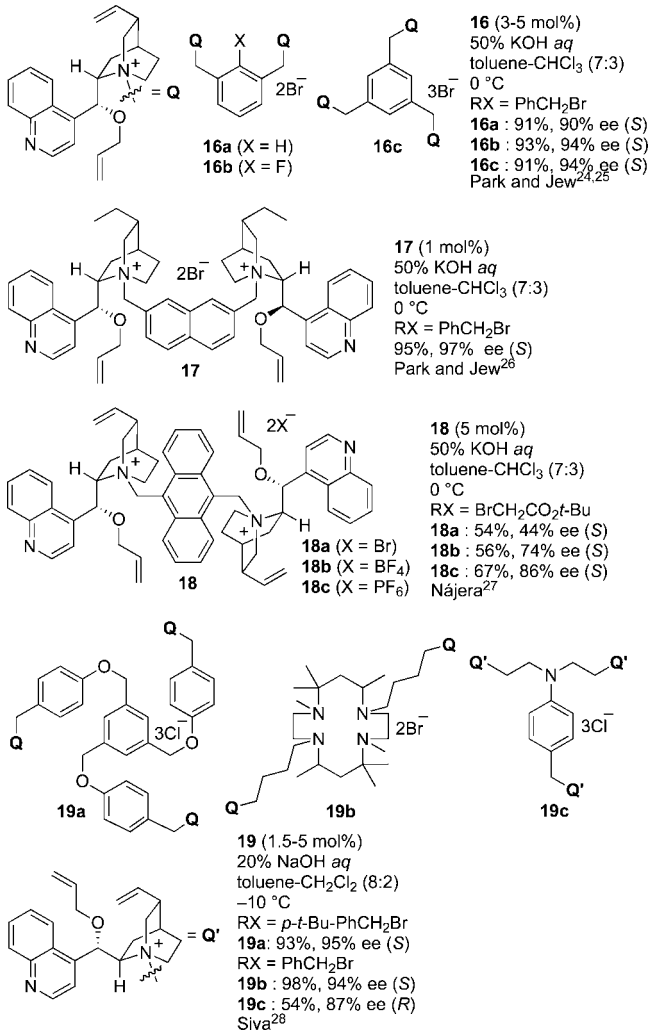
2.1.4. Recyclable Catalysts and Reagents and Solid-Phase Synthesis. The enantioselective synthesis of α-amino acids by employing easily available and reusable chiral catalysts or reagents presents clear advantages for large-scale application. Nájera prepared resin-supported ammonium salt **34a** by reaction 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 **1d**.[39] Optimization of the reaction parameters for the benzylation led to the formation of **2d** in 90% yield with 90% ee (Scheme 16). Cahard investigated the role of a flexible methylene spacer between the quaternary ammonium moiety and the polystyrene backbone in a similar benzylation of **1a**, and found that catalyst **34b** anchored to the matrix through four carbon spacers was optimal, giving **2a** with 81% ee.[40] He also introduced the idea of cinchonidine-derived quaternary ammonium salt grafted to a poly(ethylene glycol) matrix (**34c**) as an efficient homogeneous catalyst for the asymmetric alkylation of **1a**. Up to 81% ee was attained for benzylation under standard liquid−liquid phase-transfer conditions.[41] Meanwhile, Cahard and Plaquevent succeeded in improving the enantioselectivity by attaching Merrifield resin on the hydroxy moiety of cinchonidine-derived catalyst possessing the 9-anthracenylmethyl group on nitrogen (**34d**).[42] Benaglia immobilized the third-generation catalyst onto modified poly(ethylene glycol) through the alkylation of the C(9) hydroxy functionality. The chiral ammonium salt **34e** thus obtained acts as a homogeneous catalyst in the benzylation of **1a** to afford **2a** with a maximum ee of 64%.[43]

Koshima has reported the benefit of solid support preloaded with base for the asymmetric alkylation of **1a**. A solution of **1a**, alkyl halide, and catalyst **17** in toluene/$CHCl_3$ was slowly added to Kaolin clay preloaded with KOH, and this solid was stirred at 20 °C. Residual traces of water on the support dramatically accelerated the reaction to completion within a few minutes, giving rise to the corresponding alkylation product in good yields with high enantioselectivities (Scheme 17).[44]

A recyclable chiral phase-transfer catalyst **35** has been developed in our group, and its high chiral efficiency and ability to recycle have been demonstrated in the asymmetric alkylation of **1a**. Following the reaction, **35** could be easily recovered by simple extraction with perfluorohexanes and could be used in the next run without loss of reactivity or selectivity (Scheme 18).[45]

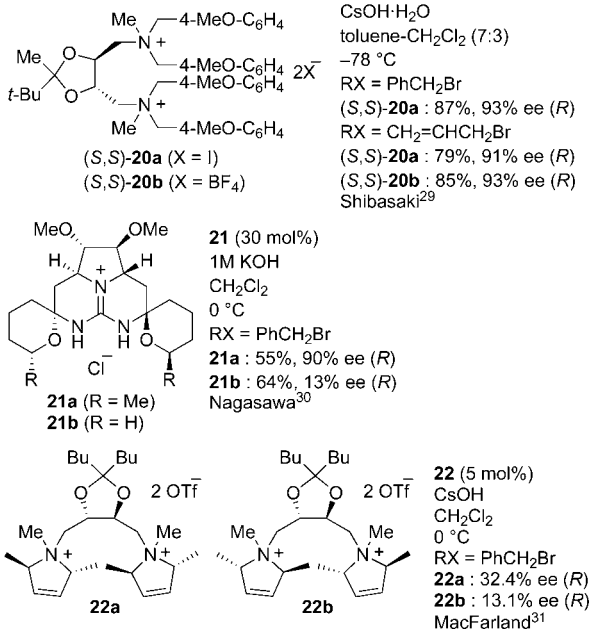
(38) Ooi, T.; Takeuchi, M.; Kato, D.; Uematsu, Y.; Tayama, E.; Sakai, D.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 5073.
(39) (a) Chinchilla, R.; Mazón, P.; Nájera, C. *Tetrahedron: Asymmetry* **2000**, *11*, 3277. (b) Chinchilla, R.; Mazón, P.; Nájera, C. *Adv. Synth. Catal.* **2004**, *346*, 1186.
(40) Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Tetrahedron: Asymmetry* **2001**, *12*, 983.
(41) Thierry, B.; Plaquevent, J.-C.; Cahard, D. *Tetrahedron: Asymmetry* **2003**, *14*, 1671.
(42) Thierry, B.; Perrard, T.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Synthesis* **2001**, 1742.
(43) Danelli, T.; Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. *Tetrahedron: Asymmetry* **2003**, *14*, 461.
(44) (a) Yu, H.; Koshima, H. *Tetrahedron Lett.* **2003**, *44*, 9209. (b) Yu, H.; Takigawa, S.; Koshima, H. *Tetrahedron* **2004**, *60*, 8405.
(45) Shirakawa, S.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2004**, *6*, 1429.

Scheme 10. **Cinchona alkaloid-derived bis- and tris-ammonium salts**

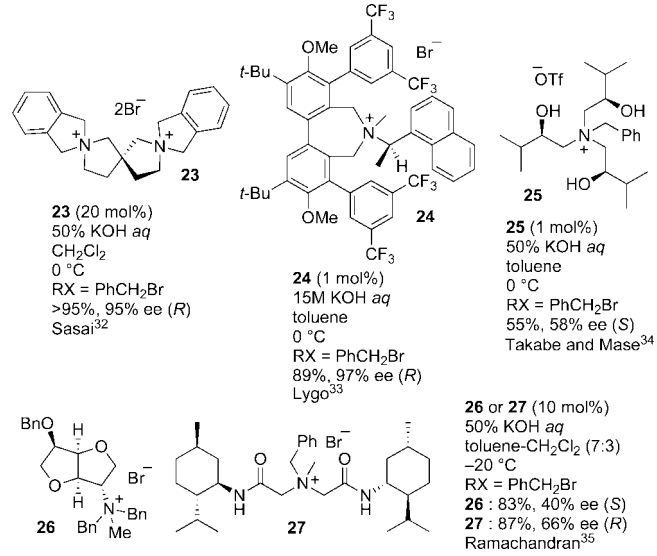


Solid-phase synthesis, in which polymer-bound substrates are utilized, has advantages over liquid-phase synthesis, such as easy purification and application to combinatorial chemistry. Park and Jew utilized the Merrifield resin-supported glycine Schiff base **36** for asymmetric alkylation under PTC conditions. Considering the influence of the ester groups for the enantioselectivity, an aldimine linker was chosen, and asymmetric alkylation was performed by the use of 10 mol % *O*-allyl *N*-anthracenylmethyl cinchonidinium bromide, **15e**. *N*-Benzoyl α-amino acid *tert*-butyl ester **37** could be isolated after treating the bound product with aqueous hydrochloric acid followed by protection with benzoyl chloride (Scheme 19).[46]

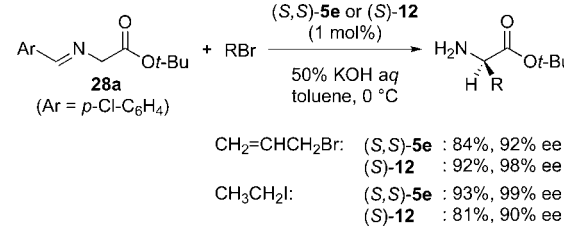
Scheme 11. **Tartrate-derived ammonium salts**



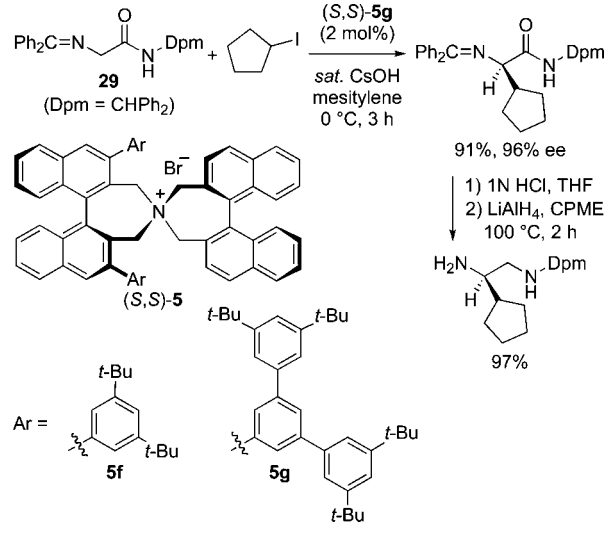
Scheme 12. **Other phase-transfer catalysts**



Scheme 13

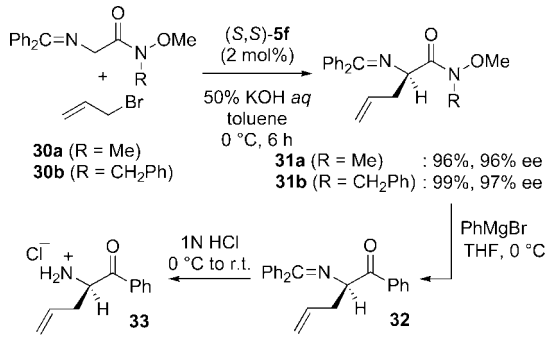


Scheme 14

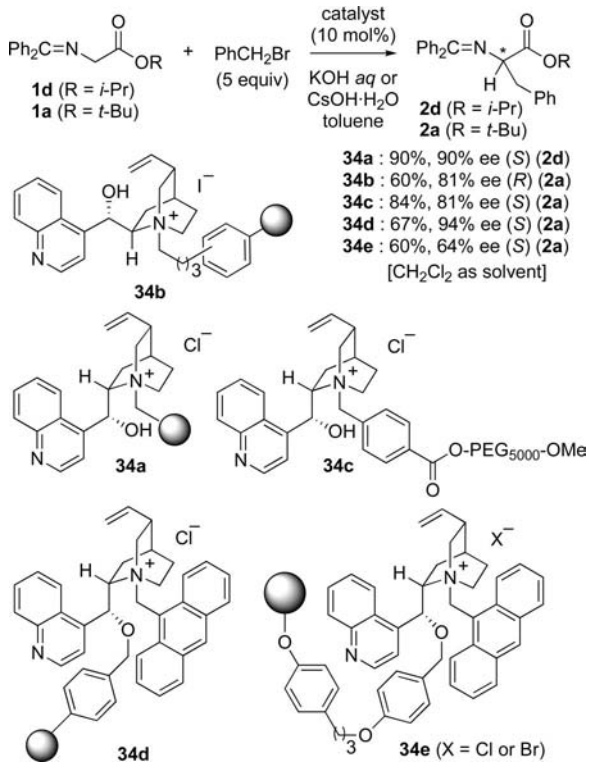


(46) Lygo, B.; Humphreys, L. D. *Tetrahedron Lett.* **2002**, *43*, 6677.

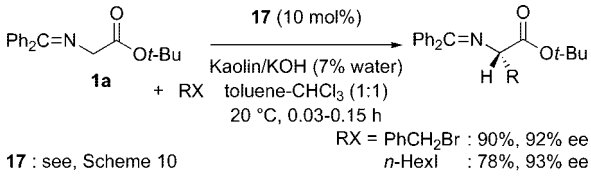
Scheme 15



Scheme 16



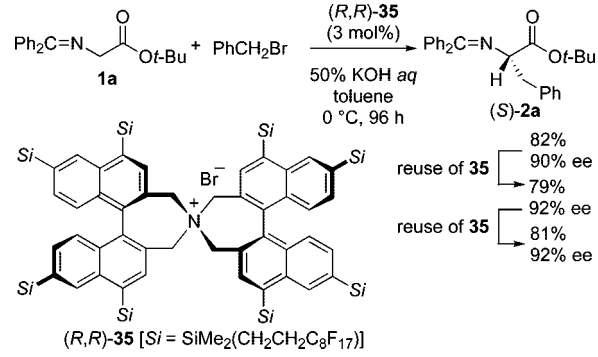
Scheme 17



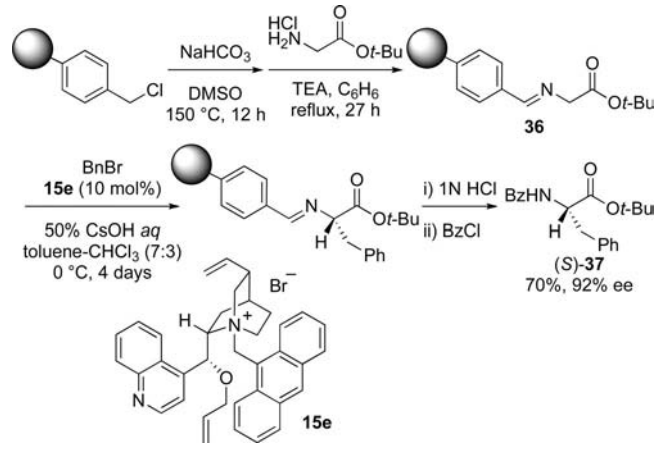
2.2. Asymmetric Synthesis of α,α-Dialkyl-α-amino Acids. Nonproteinogenic, chiral α,α-dialkyl-α-amino acids possessing stereochemically stable quaternary carbon centers have been significant synthetic targets since they are often effective enzyme inhibitors and can be indispensable for the elucidation of enzymatic mechanisms. Accordingly, numerous studies have been conducted to develop truly efficient methods for their preparation,[47] and phase-transfer catalysis has made unique contributions.

(47) (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.

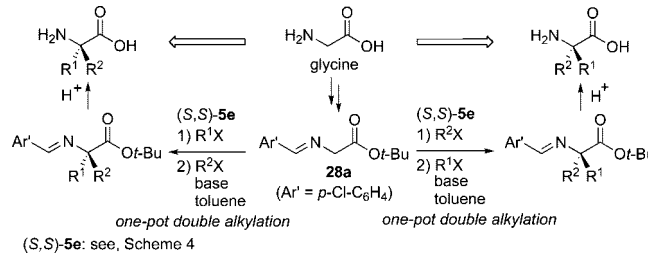
Scheme 18



Scheme 19



Scheme 20

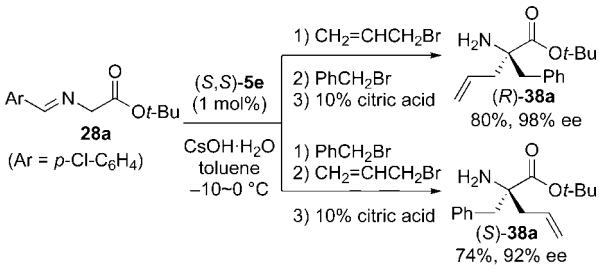


Since the aldimine Schiff base **28a** can be readily prepared from glycine, the controlled stereoselective introduction of two different side chains to **28a** by appropriate chiral phase-transfer catalysis would provide an attractive and powerful strategy for the asymmetric synthesis of structurally diverse α,α-dialkyl-α-amino acids. A one-pot asymmetric double alkylation has been realized by using *N*-spiro chiral quaternary ammonium bromide **5e** (Scheme 20).[48] Of course, by changing the addition sequence of two different alkyl halides (R^1X and R^2X), an enantiomeric product is obtainable in the presence of the same catalyst.

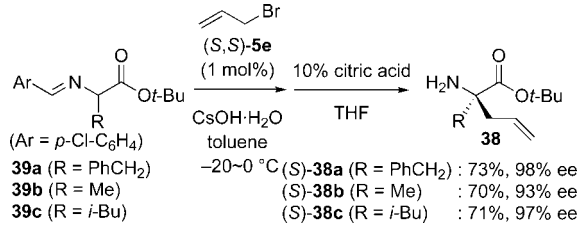
Initial treatment of the toluene solution of **28a** and (*S*,*S*)-**5e** (1 mol %) with allyl bromide (1 equiv) and $CsOH \cdot H_2O$ at −10 °C and the subsequent reaction with benzyl bromide (1.2 equiv) at 0 °C resulted in formation of the double alkylation product (*R*)-**38a** in 80% yield with 98% ee after hydrolysis. Notably, if the halide addition was inverted, the absolute configuration of the product (*R*)-**38a** was opposite (Scheme 21).

(48) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228.

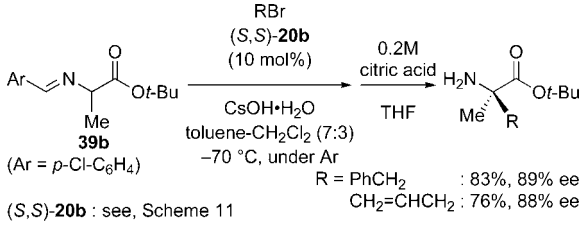
Scheme 21



Scheme 22



Scheme 23



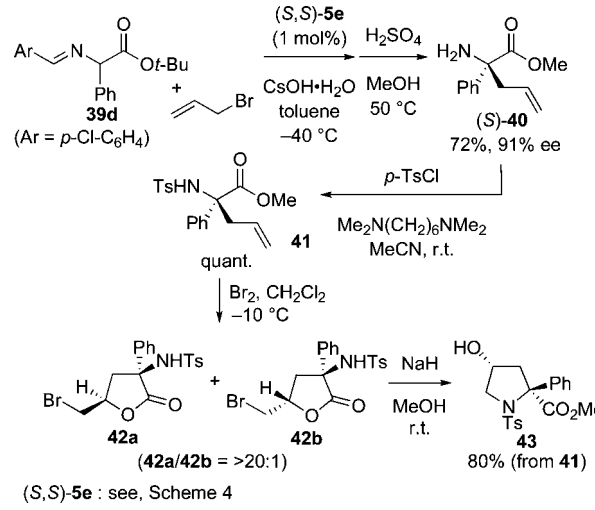
Since the stereochemistry of the newly created quaternary carbon center was determined in the second alkylation process, this method should be applicable to the asymmetric alkylation of the aldimine Schiff bases **39** derived from the corresponding α-amino acids. Indeed, phenylalanine-, alanine-, and leucine-derived imines **39a**−**c** can be alkylated smoothly under similar conditions, affording the desired amino acid esters **38** with excellent asymmetric induction (Scheme 22).[48]

The bis-ammonium tetrafluoroborate catalyst **20b** developed by Shibasaki successfully promotes the alkylation of **39b** even at low temperature to give the corresponding α,α-dialkyl-α-amino ester in good yield with high enantioselectivity (Scheme 23).[29b]

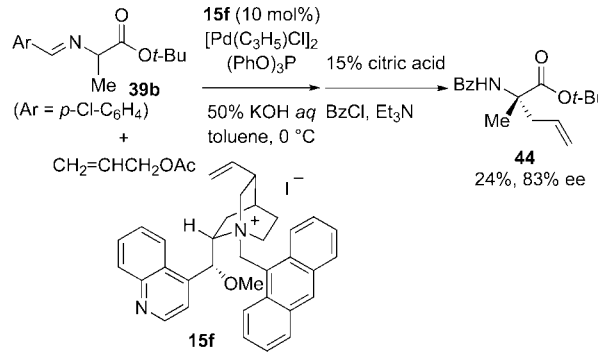
Recently, Maeda and co-workers utilized the (*S*,*S*)-**5e**-catalyzed asymmetric alkylation of phenylglycine-derived Schiff base **39d** for the stereoselective synthesis of 4-hydroxy-2-phenylproline. After hydrolysis and transesterification, the resulting (*S*)-**40** was derivatized to its *N*-tosylate **41**. Subsequent treatment of **41** with Br_2 in CH_2Cl_2 at −10 °C resulted in the formation of γ-lactones **42** in high diastereoselectivity, which were then treated with NaH to produce essentially pure (2*S*,4*R*)-4-hydroxy-2-phenylproline derivative **43** in 80% yield from **41** (Scheme 24).[49]

Takemoto demonstrated the strategy of combining achiral palladium catalysis and chiral phase-transfer catalysis for the asymmetric allylation of **39b**. Even without a chiral phosphine ligand on palladium, **44** was

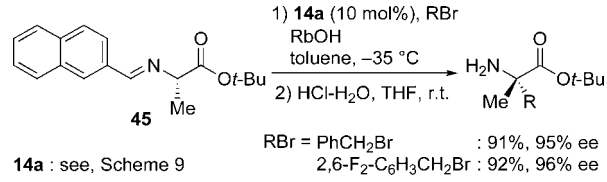
Scheme 24



Scheme 25



Scheme 26



obtained in 83% ee after hydrolysis of the imine moiety and subsequent benzoylation (Scheme 25).[50]

Jew and Park have developed an efficient system for the asymmetric synthesis of α-alkylalanines by chiral phase-transfer catalysis of cinchona alkaloid-derived catalysts. This was used for the sterically more demanding 2-naphthyl aldimine *tert*-butyl ester **45**. Its alkylation in the presence of rubidium hydroxide (RbOH) and **14a** at −35 °C led to the highest enantioselectivity (Scheme 26).[51]

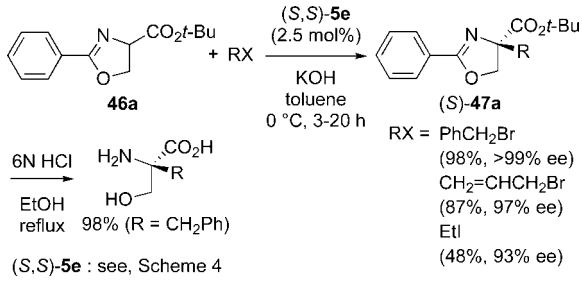
The efficient phase-transfer-catalyzed alkylation strategy with **5e** was successfully applied by Jew and Park to the asymmetric synthesis of α-alkyl serines using phenyl oxazoline derivative **46a** as a requisite substrate. The reaction is general and provides a practical access to a variety of optically active α-alkyl serines through acidic hydrolysis of **47a** as exemplified in Scheme 27.[52]

(49) Maeda, K.; Miller, R. A.; Szumigala, R. H.; Shafiee, A.; Karady, S.; Armstrong, J. D., III. *Tetrahedron Lett.* **2005**, *46*, 1545.

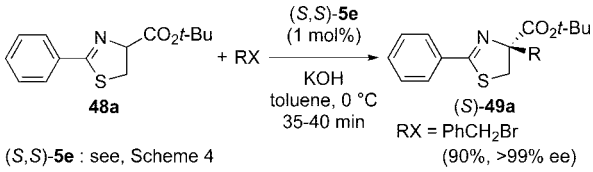
(50) (a) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 3329. (b) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *J. Org. Chem.* **2002**, *67*, 7418.

(51) 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.

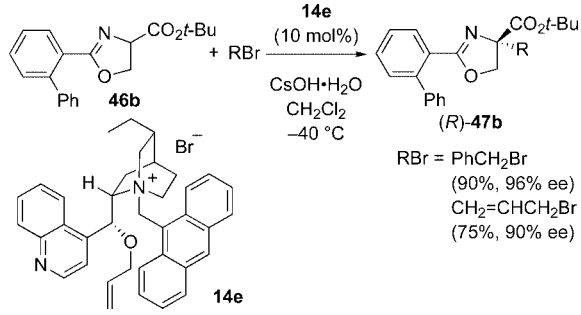
Scheme 27



Scheme 28



Scheme 29



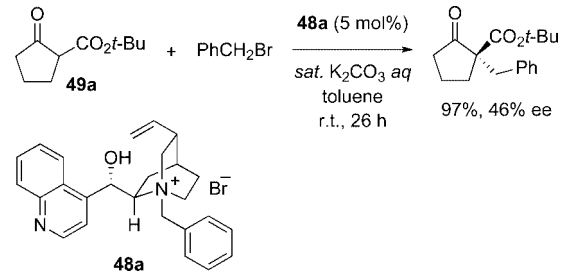
They also succeeded in expanding this methodology to thio analogue **48a** to furnish the optically enriched α-alkyl cysteine derivative **49a** (Scheme 28).[53]

They also modified the phenyl moiety of **46a** and identified *o*-biphenyl analogue **46b** as a suitable substrate for attaining high enantioselectivity with *O*-allyl *N*-anthracenylmethyl dihydrocinchonidinium bromide **14e** as a phase-transfer catalyst (Scheme 29).[54] The applicability of this approach for the synthesis of α-alkyl cysteines was also successful. [53]

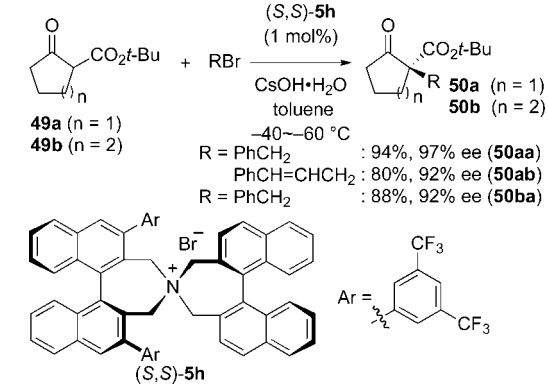
2.3. Other Asymmetric Alkylations. Asymmetric alkylation of *β*-keto ester under phase-transfer condition can be a unique tool to construct an all-carbon chiral quaternary carbon center easily. *N*-Benzyl cinchoninium bromide **48a** catalyzed the asymmetric alkylation of *β*-keto ester **49a** to give the benzylated compound in an excellent chemical yield with 46% ee as included in Scheme 30.[55]

Efficient, highly enantioselective construction of quaternary stereocenter on *β*-keto esters under phase-transfer conditions has been achieved using *N*-spiro chiral quaternary ammonium

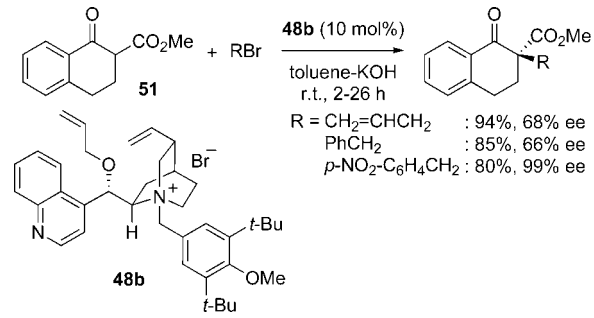
Scheme 30



Scheme 31



Scheme 32



bromide **5h** as catalyst.[56] This system has a broad generality in terms of the structure of *β*-keto esters **49** and alkyl halides (Scheme 31). The resulting alkylation products **50** can be easily converted into the corresponding *β*-hydroxy esters and *β*-amino esters, respectively.

Kim showed the effectiveness of cinchonine-derived catalyst **48b** with a specific bulky substituent on the bridgehead nitrogen for the asymmetric alkylation of *β*-keto esters such as **51**. 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 32).[57]

Recently, Andrus introduced diphenylmethyloxy-2,5-dimethoxyacetophenone **52** 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 **14a** developed by Jew and Park. After deprotection and reprotection of the

(52) 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.

(53) Kim, T.-S.; Lee, Y.-J.; Jeong, B.-S.; Park, H.-G.; Jew, S.-s. *J. Org. Chem.* **2006**, *71*, 8276.

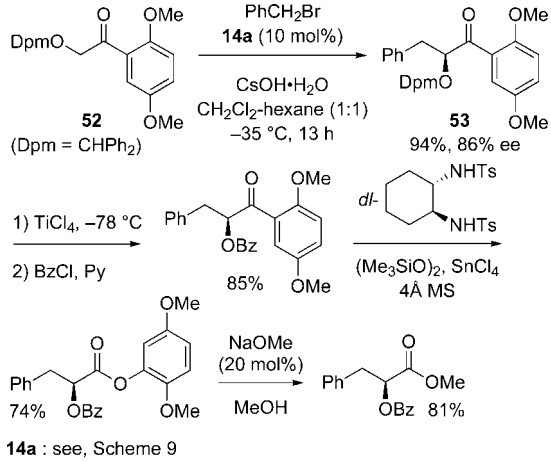
(54) Lee, Y.-J.; Lee, J.; Kim, M.-J.; Kim, T.-S.; Park, H.-G.; Jew, S.-s. *Org. Lett.* **2005**, *7*, 1557.

(55) Dehmlow, E. V.; Düttmann, S.; Neumann, B.; Stammler, H.-G. *Eur. J. Org. Chem.* **2002**, 2087.

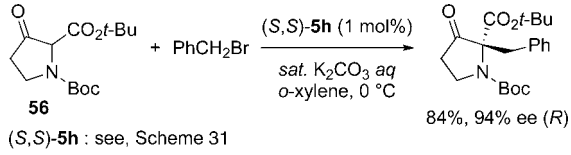
(56) (a) Ooi, T.; Miki, T.; Taniguchi, M.; Shiraishi, M.; Takeuchi, M.; Maruoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 3796. (b) Ooi, T.; Miki, T.; Fukumoto, K.; Maruoka, K. *Adv. Synth. Catal.* **2006**, *348*, 1539.

(57) Park, E. J.; Kim, M. H.; Kim, D. Y. *J. Org. Chem.* **2004**, *69*, 6897.

Scheme 33



Scheme 34



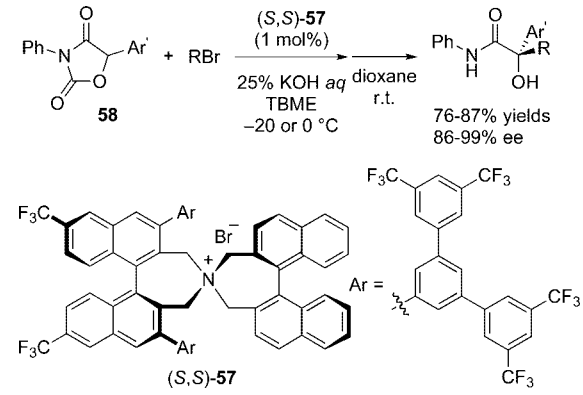
alkylation product **53**, subsequent Baeyer−Villiger-type oxidation and selective transesterification afforded the corresponding α-hydroxy ester derivative without losing the enantioselectivity (Scheme 33).[58]

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 esters **56** with C_2-symmetric phase-transfer catalyst **5h** as a means of obtaining aza-cyclic amino acids with quaternary stereocenters (Scheme 34).[59]

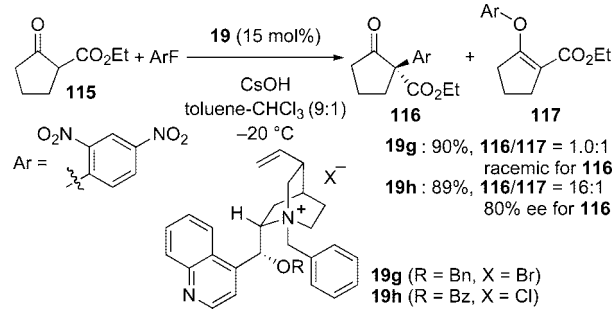
Our other approach toward this largely unsolved problem utilizes 3,5-diaryloxazolidin-2,4-diones **58** that undergo highly enantioselective alkylation under mild phase-transfer conditions in the presence of *N*-spiro chiral quaternary ammonium bromide **57**. With this methodology in hand, a wide range of tertiary-α-hydroxy-α-aryl carboxylic acid derivatives can be easily obtained in good yields and high enantiomeric excesses (Scheme 35).[60]

Jørgensen developed the catalytic, regio- and enantioselective nucleophilic aromatic substitution reaction between activated aromatic compounds and 1,3-dicarbonyl compounds under phase-transfer conditions. Interestingly, examination on the addition of 2,4-dinitrofluorobenzene to 2-carboethoxycyclopentanone **59** revealed that the use of *O*-benzoylated cinchonidine-derived catalyst **19h** was crucial for obtaining *C*-arylated product **60** predominantly with high enantioselectivity (Scheme 36).[61]

Scheme 35



Scheme 36



Jørgensen also reported asymmetric vinylic substitution reaction of β-keto esters catalyzed by dihydrocinchonine derived phase-transfer catalyst **62a** incorporating 1-adamantoyl group. Utilized as vinyl sources were activated β-haloalkenes, which participate in the substitution reaction via an addition−elimination sequence. Starting from (*Z*)-vinyl halides **63**, a *Z*-configured double bond could be incorporated into the product **64** (Scheme 37).[61] As an extension of this research, Jørgensen succeeded in the asymmetric alkynylation of cyclic β-keto esters by employing activated β-halo-alkyne **65** catalyzed by **62a** (Scheme 37).[63]

Asymmeric alkylation of simple aliphatic or arylacetic acid esters under phase-transfer conditions is a difficult task due to their low pK_a values. Ramachandran reported the asymmetric alkylation of 2-(6-methoxynaphthalen-2-yl)acetic acid ester **66** by use of strong base potassium *tert*-butoxide, as a means of an efficient synthesis of naproxen (Scheme 38).[64]

Rozwadowska reported the asymmetric alkylation of Reissert compounds **67**. *N*-Benzyl cinchoninium bromide (**48a**)-catalyzed phase-transfer alkylation of *N*-phenoxycarbonyl dihydroisoquinoline provided the benzylated compound **68** containing a quaternary stereocenter with 65% ee (Scheme 39).[65]

(58) (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.

(59) Ooi, T.; Miki, T.; Maruoka, K. *Org. Lett.* **2005**, *7*, 191.

(60) Ooi, T.; Fukumoto, K.; Maruoka, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3839.

(61) (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.

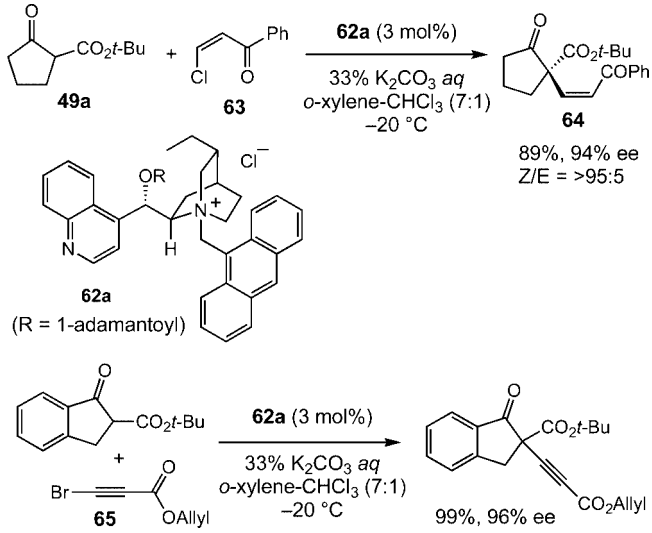
(62) Poulsen, T. B.; Bernardi, L.; Bell, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6551.

(63) Poulsen, T. B.; Bernardi, L.; Alemán, J.; Overgaard, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 441.

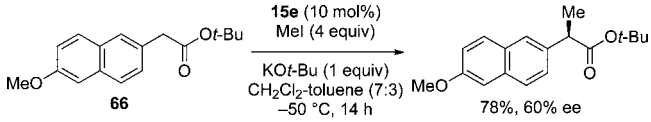
(64) Kumar, S.; Ramachandran, U. *Tetrahedron: Asymmetry* **2005**, *16*, 647.

(65) Brózda, D.; Hoffman, K.; Rozwadowska, M. D. *Heterocycles* **2006**, *69*, 119.

Scheme 37

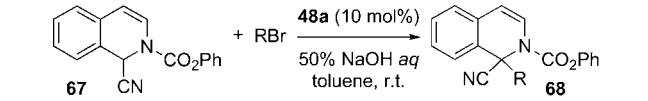


Scheme 38



15e : see, Scheme 19

Scheme 39



48a : see, Scheme30

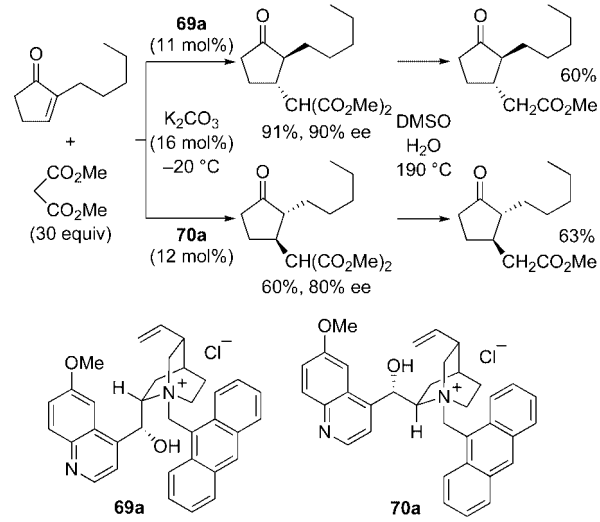
3. Asymmetric Michael Addition

The asymmetric Michael addition 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.[66]

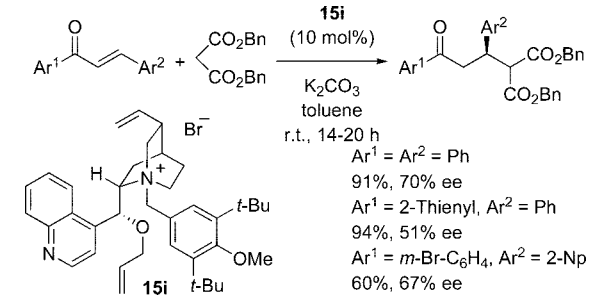
Plaquevent achieved highly enantioselective Michael addition of simple dimethyl malonate to 2-pentyl-2-cyclopentenone under phase-transfer conditions using K_2CO_3 as a base and quinine- or quinidine-derived **69a** or **70a** as catalyst: this enabled a short enantioselective synthesis of both enantiomers of methyl dihydrojasmonate as illustrated in Scheme 40.[67]

Kim applied *N*-(3,5-di-*tert*-butyl-4-methoxy)benzyl cinchonidinium bromide **15i** 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 presence of 10 mol % of **15i** and an excess amount of K_2CO_3 (Scheme 41).[94]

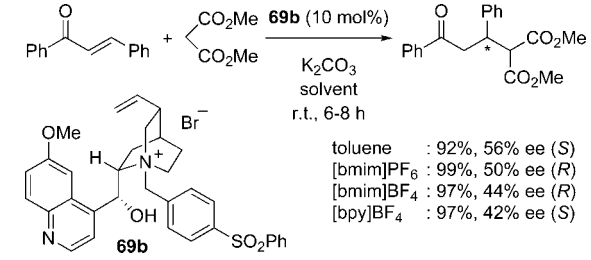
Scheme 40



Scheme 41



Scheme 42



Salunkhe performed the similar phase-transfer-catalyzed Michael reaction of dimethyl malonate and chalcone with newly devised quininium bromide **69b** in ionic liquid such as 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6, tetrafluoroborate [bmim]BF_6, and 1-butyl-3-pyridinium tetrafluoroborate [bpy]BF_6. 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_6, while it remained the same in [bpy]BF_6 as that observed in toluene (Scheme 42).[69]

Recently, we addressed the importance of dual-functioning chiral phase-transfer catalyst such as **71a** for obtaining a high level of enantioselectivity in the Michael addition of malonates to chalcone derivatives (Scheme 43).[70] For instance, reaction

(66) (a) For recent reviews on catalytic asymmetric Michael reactions, see: 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*,2nd 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; Chapter 31.1.

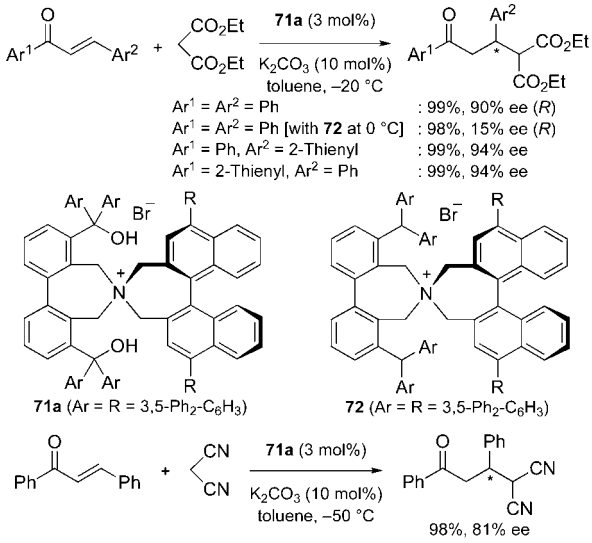
(67) Perrard, T.; Plaquevent, J.-C.; Desmurs, J.-R.; Hébrault, D. *Org. Lett.* **2000**, *2*, 2959.

(68) Kim, D. Y.; Huh, S. C.; Kim, S. M. *Tetrahedron Lett.* **2001**, *42*, 6299.

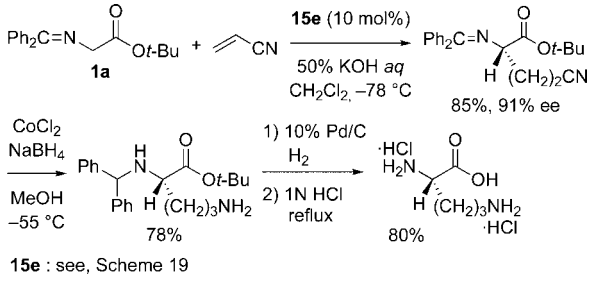
(69) Dere, R. T.; Pal, R. R.; Patil, P. S.; Salunkhe, M. M. *Tetrahedron Lett.* **2003**, *44*, 5351.

(70) Ooi, T.; Ohara, D.; Fukumoto, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 3195.

Scheme 43



Scheme 44



of diethyl malonate with chalcone in toluene under the influence of K_2CO_3 and **71a** (3 mol %) proceeded smoothly at −20 °C with excellent enantioselectivity, while the selectivity was markedly decreased when **72** possessing no hydroxy functionality was used as catalyst. This system is applicable to the Michael addition of malononitrile as included in Scheme 43.

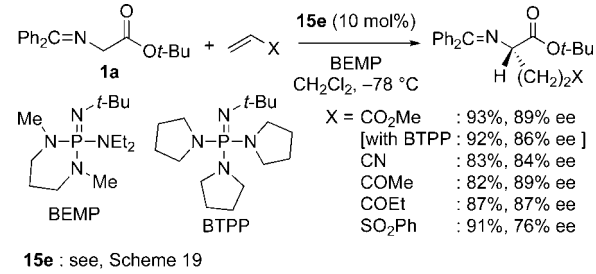
Enantioselective Michael addition of glycine derivatives by means of chiral phase-transfer catalysis has been developed to synthesize various functionalized α-alkyl-α-amino acids. Corey utilized *O*-allyl *N*-anthracenylmethyl cinchonidinium bromide **15e** as catalyst for asymmetric Michael addition of glycine Schiff base **1a** to acrylonitrile with high enantioselectivity. Naturally occurring (*S*)-ornithine has been synthesized as its dihydrochloride in a concise manner (Scheme 44).[71]

O'Donnell carried out this type of Michael addition by the use of organic soluble, nonionic bases BEMP and BTPP. In general, the less basic BEMP proved to be superior and tolerated several representative Michael acceptors (Scheme 45).[72] The applicability of this system to the solid-phase synthesis with resin-bound glycine Schiff base was also demonstrated.

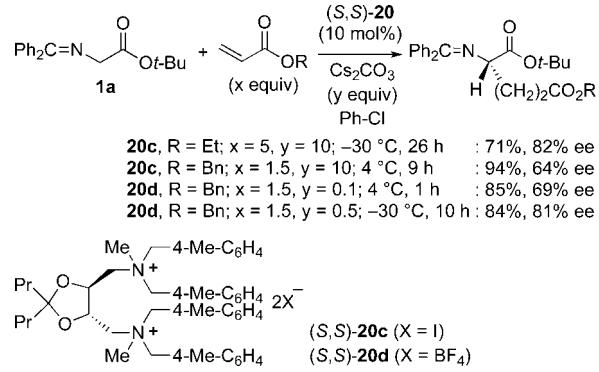
Shibasaki successfully applied the tartrate-derived, C_2-symmetric bis-ammonium salt **20** to the asymmetric Michael addition of **1a** to acrylates. Exchange of the counterion from iodide to tetrafluoroborate using the corresponding silver salt dramatically accelerated the reaction even in the case of a catalytic amount of base (Scheme 46).[29]

(71) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2000**, *2*, 1097.
(72) O'Donnell, M. J.; Delgado, F.; Domínguez, E.; de Blas, J.; Scott, W. L. *Tetrahedron: Asymmetry* **2001**, *12*, 821.

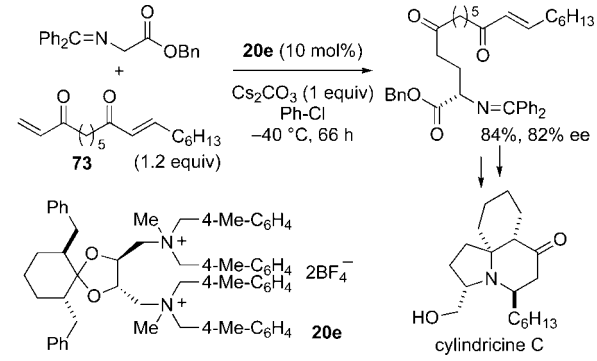
Scheme 45



Scheme 46



Scheme 47

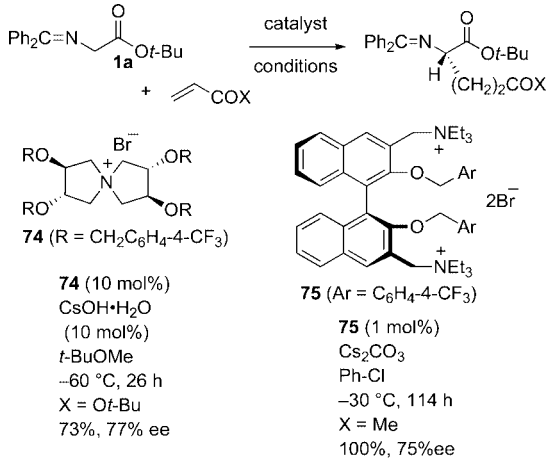


By employing the asymmetric Michael addition catalyzed by C_2-symmetric bis-ammonium salt **20e**, Shibasaki succeeded in the total synthesis of cylindricine C. The Michael acceptor **73** was designed to include the appropriate functionalities for the acid-catalyzed tandem cyclization shown in Scheme 47.[73]

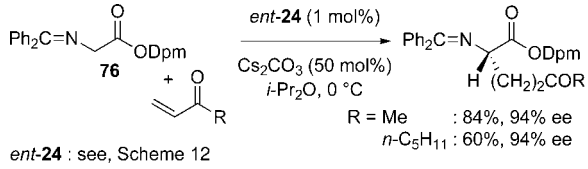
Arai and Nishida designed tartrate-derived spiro-type chiral phase-transfer catalyst **74** and applied it to the similar asymmetric Michael addition (Scheme 48).[74] Arai also introduced a new bis-ammonium salt **75** derived from (*S*)-1,1′-bi-2-naphthol as an efficient chiral phase-transfer catalyst. For instance, reaction of **1a** with methyl vinyl ketone in the presence of Cs_2CO_3 and 1 mol % of **75** in chlorobenzene proceeded at −30 °C quantitatively with 75% ee. The flexibility of the catalyst modification on the substituents of the ether and the ammonium moieties appears to be advantageous.[75]

(73) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Sakuraba, S.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4635.
(74) (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.
(75) Arai, S.; Tokumaru, K.; Aoyama, T. *Chem. Pharm. Bull.* **2004**, *52*, 646.

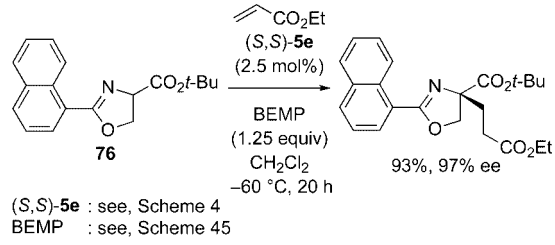
Scheme 48



Scheme 49



Scheme 50



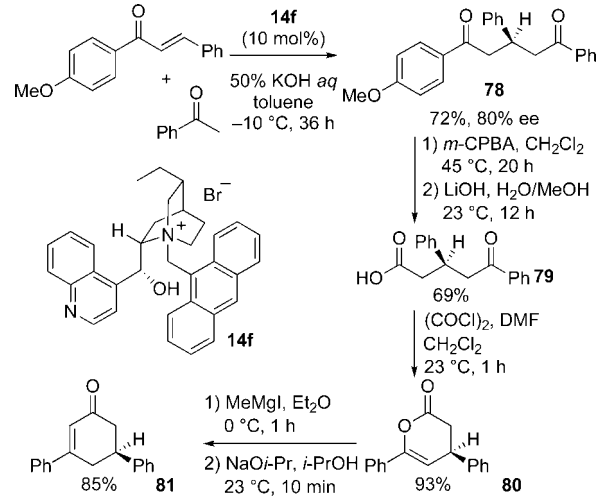
Lygo recently reported the optimization of reaction parameters for the asymmetric Michael addition of glycine derivative to methyl vinyl ketone with the α-methylnaphthylamine-derived quaternary ammonium salt *ent*-**24** as catalyst. This uncovered the crucial importance of base and solvent, and high levels of enantioselectivity can be obtained by performing the addition of glycine diphenylmethyl ester Schiff base **76** 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*-**24** (Scheme 49).[76]

Jew and Park 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 **77** to ethyl acrylate under phase-transfer conditions. As shown in Scheme 50, use of BEMP as a base with the catalysis of *N*-spiro chiral quaternary ammonium bromide **5e** appeared to be essential for attaining an excellent selectivity.[77]

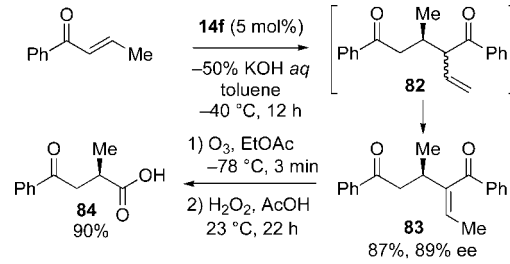
Corey and Zhang extended the utility of *N*-anthracenylmethyl dihydrocinchonidinium bromide **14f** to the asymmetric Michael addition of acetophenone to 4-methoxychalcone under mild phase-transfer conditions. Selective Baeyer−Villiger oxidation of the adduct **78** and subsequent saponification gave the keto

(76) Lygo, B.; Allbutt, B.; Kirton, E. H. M. *Tetrahedron Lett.* **2005**, *46*, 4461.
(77) 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.

Scheme 51



Scheme 52



acid **79**, which can be obtained in an essentially enantiopure form by a single recrystallization. In addition, facile derivatization of **79** into optically active 2-cyclohexenone derivative **81** via enol γ-lactone **80** was demonstrated (Scheme 51).[71]

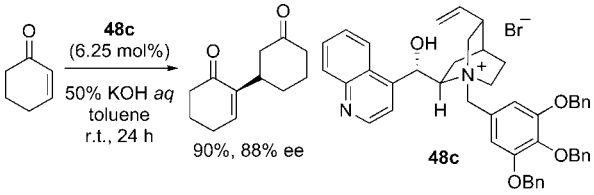
Furthermore, chiral quaternary ammonium bromide **14f** served as an effective catalyst for the enantioselective dimerization of α,β-unsaturated ketones under phase-transfer conditions, which proceeded through Michael reaction to form **82**, followed by base-catalyzed double bond transposition to afford chiral 1,5-dicarbonyl compound **83** (Scheme 52).[78] The resulting **83** can be readily converted to the corresponding α-alkyl-γ-keto acid **84** through ozonolysis and subsequent oxidation with H_2O_2.

Bella recently reported the similar asymmetric dimerization of cyclic enones catalyzed by *N*-3,4,5-tribenzyloxybenzyl cinchoninium bromide **48c** (Scheme 53).[79]

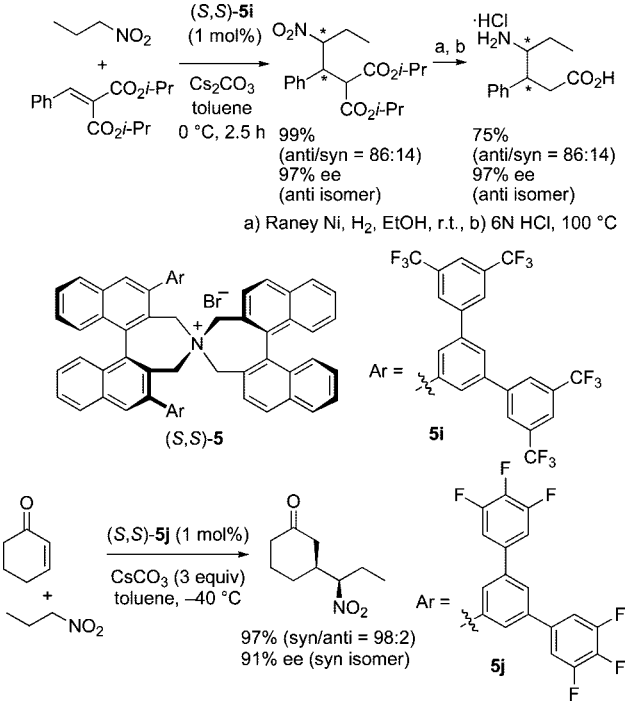
We developed the diastereo- and enantioselective conjugate addition of nitroalkanes to alkylidenemalonates under mild phase-transfer conditions by the utilization of appropriately designed chiral quaternary ammonium bromide **5i** as an efficient catalyst. This new protocol offers a practical entry to optically active γ-amino acid derivatives as shown in Scheme 52.[80a] As an extension of this research, catalytic asymmetric conjugate addition of

(78) Zhang, F.-Y.; Corey, E. J. *Org. Lett.* **2004**, *6*, 3397.
(79) Ceccarelli, R.; Insogna, S.; Bella, M. *Org. Biomol. Chem.* **2006**, *4*, 4281.
(80) (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.
(81) (a) Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 1038. (b) Lan, Q.; Wang, X.; Maruoka, K. *Tetrahedron Lett.* **2007**, *48*, 4675.

Scheme 53



Scheme 54

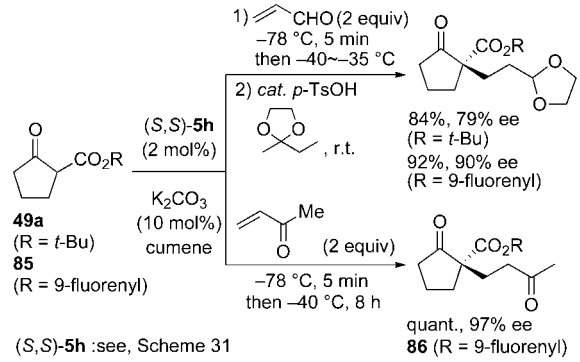


nitroalkanes to cyclic α,β-unsaturated ketones was also realized under phase-transfer condition (Scheme 54).[80b]

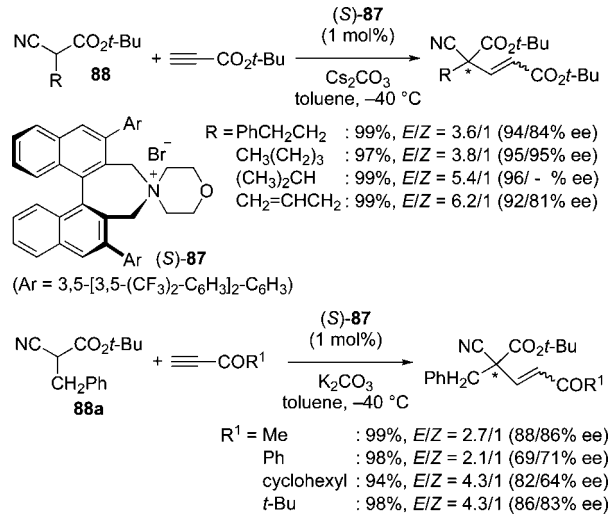
As already addressed in this section, enantioselective Michael addition of β-keto esters to α,β-unsaturated carbonyl compounds is a useful method for the construction of densely functionalized chiral quaternary carbon centers. A characteristic feature of designer chiral phase-transfer catalyst **5h** 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 **49a**. It is of interest that the use of fluorenyl ester **85** greatly improved the enantioselectivity. The addition of **85** to MVK was also feasible under similar conditions, and the desired **86** was obtained quantitatively with 97% ee (Scheme 55).[56]

Asymmetric conjugate addition of α-substituted-α-cyanoacetates **88** to acetylenic esters under phase-transfer condition is quite challenging because of the difficulty to control the stereochemistry of the product. In addition, despite numerous examples of the conjugate additions to alkenoic esters, so far there is no successful asymmetric conjugate addition to acetylenic esters. In this context, we recently developed a new morpholine-derived phase-transfer catalyst (*S*)-**87** and applied it to the asymmetric conjugate additions of α-alkyl-α-cyanoacetates **88** to acetylenic esters. In this asymmetric transformatioan,

Scheme 55



Scheme 56



an all-carbon quaternary stereocenter can be constructed in a high enantiomeric purity (Scheme 56).[81a] This approach is also applicable to alkenoic ketones.[81b]

4. Asymmetric Aldol Reaction

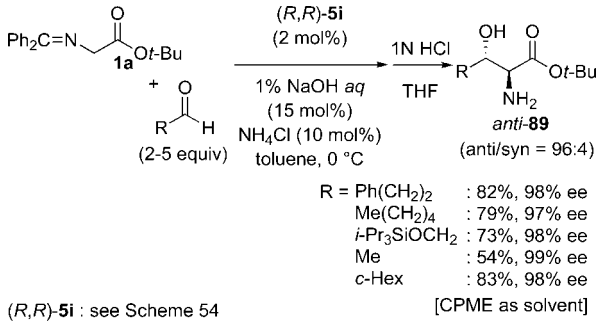
Although phase-transfer-catalyzed enantioselective direct aldol reactions of glycine donors with aldehyde acceptors could provide an ideal method for the simultaneous construction of the primary structure and stereochemical integrity of β-hydroxy-α-amino acids (extremely important chiral units, especially 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 **1a** with a wide range of aliphatic aldehydes under mild phase-transfer conditions employing *N*-spiro chiral quaternary ammonium salt **5i** as a key catalyst, leading to the establishment of general and practical chemical process for the synthesis of optically active *anti*-β-hydroxy-α-amino esters **89** (Scheme 57).[82]

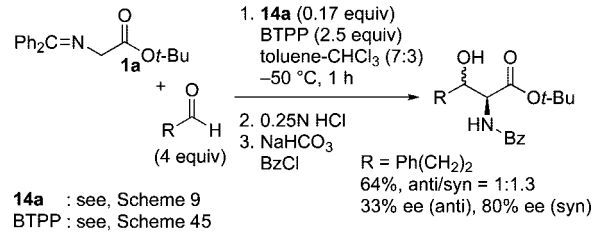
Castle revealed that this type of aldol reaction could be performed in the presence of BTPP as an organic base under homogeneous condition. Use of quaternary ammonium salt **14a** developed by Park and Jew was found to be optimal, giving

(82) (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.

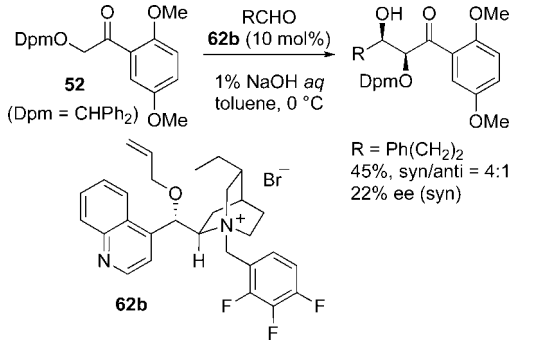
Scheme 57



Scheme 58



Scheme 59

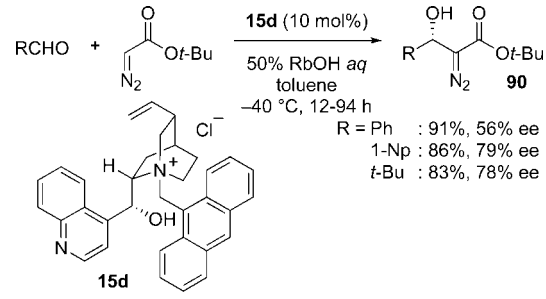


the aldol adduct as a mixture of diastereomers with moderate to high enantioselectivities (Scheme 58).[83]

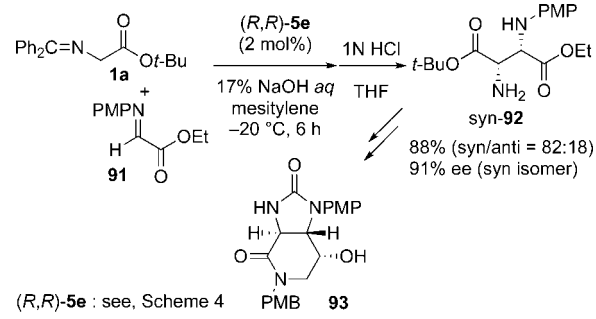
Andrus utilized their glycolate template to the phase-transfer-catalyzed asymmetric aldol reaction to give 1,2-dihydroxy ester. The reaction of glycolate **52** and 3-phenylpropionaldehyde catalyzed by dihydrocinchoninium bromide **62b** afforded the aldol adduct in moderate yield with low enantioselectivity (Scheme 59).[84] To improve the reactivity and selectivity of this reaction system, Andrus employed silyl enol ether of **52** and hydrogen bifluoride salt of **62b** to achieve high yields and selectivities.[85]

Arai and Nishida investigated the catalytic asymmetric aldol reaction between *tert*-butyl diazoacetate and benzaldehyde under various liquid−liquid phase-transfer conditions with *N*-anthracenylmethyl cinchonidinium chloride **15d** 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 **90** in 91% yield with 56% ee. Further experiments to probe the substrate scope revealed that the

Scheme 60



Scheme 61



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 60).[86]

5. Asymmetric Mannich Reactions

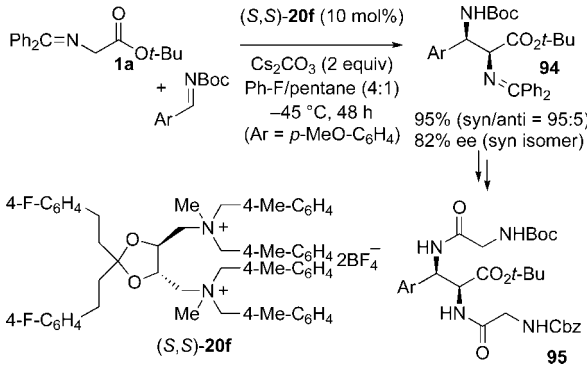
Phase-transfer-catalyzed direct Mannich reaction of glycine Schiff base **1a** with α-imino ester **91** was achieved with high enantioselectivity by the utilization of *N*-spiro chiral quaternary ammonium bromide **5e** as catalyst (Scheme 61).[87] This method enables the catalytic asymmetric synthesis of differentially protected 3-aminoaspartate, a nitrogen analogue of dialkyl tartrate, whose utility was demonstrated when the product *syn*-**92** was converted into a precursor **93** of streptolidine lactam.

A more general and highly diastereoselective Mannich-type reaction was developed by Ohshima and Shibasaki. The original tartrate-derived diammonium salt **20b** was modified by introducing an aromatic ring at the acetal side chains, and 4-fluorophenyl-substituted **20f** was identified as an optimal catalyst for the reaction of **1a** with various *N*-Boc imines under solid (Cs_2CO_3)−liquid (fluorobenzene) phase-transfer conditions as exemplified in Scheme 62.[88] The usefulness of the Mannich adduct **94** was further demonstrated by the straightforward synthesis of the optically pure tripeptide **95**.

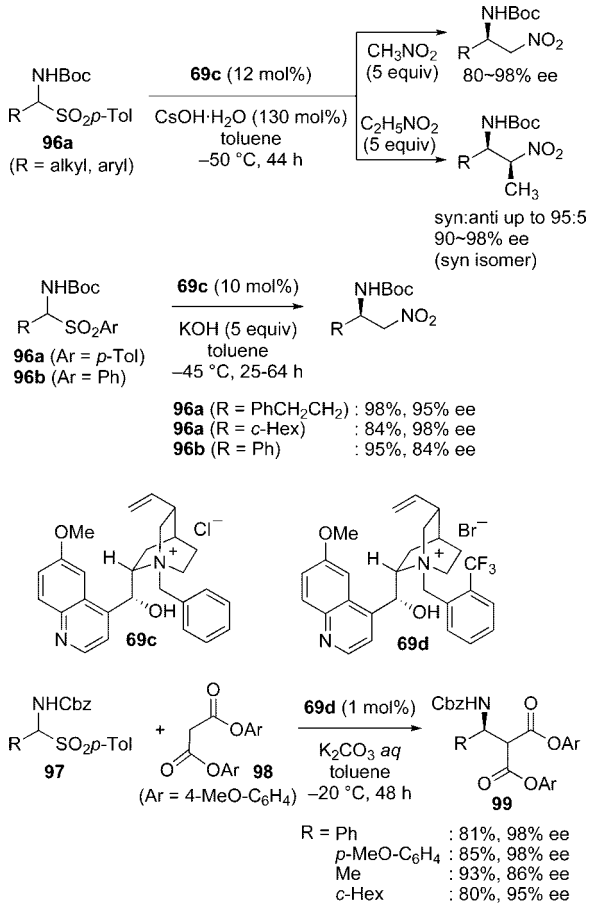
Palomo reported that *N*-benzyl quininium chloride **69c** acted as a promising catalyst for the asymmetric aza-Henry reaction under solid−liquid phase-transfer conditions utlizing cesium hydroxide as a base. α-Amido sulfones **96** were used to generate reactive *N*-carbamoyl imines in situ and succeeded in aza-Henry reactions of not only aromatic imines but also aliphatic imines (Scheme 63). The unprotected hydroxyl group on *N*-benzyl

(83) Mettath, S.; Srikanth, G. S. C.; Dangerfield, B. S.; Castle, S. L. *J. Org. Chem.* **2004**, *69*, 6489.
(84) Andrus, M. B.; Liu, J.; Ye., Z.; Cannon, J. F. *Org. Lett.* **2005**, *7*, 3861.
(85) For a general review on asymmetric catalysis with quaternary ammonium fluoride, see: Ooi, T.; Maruoka, K. *Acc. Chem. Res.* **2004**, *37*, 526.
(86) (a) Arai, S.; Hasegawa, K.; Nishida, A. *Tetrahedron Lett.* **2004**, *45*, 1023. (b) Hasegawa, K.; Arai, S.; Nishida, A. *Tetrahedron* **2006**, *62*, 1390.
(87) Ooi, T.; Kameda, M.; Fujii, J.-i.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397.
(88) Okada, A.; Shibuguchi, T.; Ohshima, T.; Masu, H.; Yamaguchi, K.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4564.

Scheme 62



Scheme 63

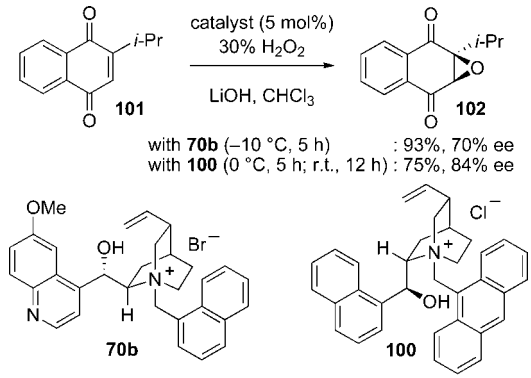


quininium chloride **69c** was found to be crucial to obtain high enantioselectivities.[89] At the same time, Herrera and Bernardi reported separately the same asymmetric aza-Henry reaction catalyzed by *N*-benzylquininium chloride **69c**. In their report, freshly ground potassium hydroxide was utilized as a base (Scheme 63).[90]

Ricci reported a Mannich reaction of *N*-Cbz imines generated in situ from α-amido sulfones **97** and bis(4-methoxyphenyl) malonate **98** under the liquid−liquid phase-transfer conditions. Via a decarboxylation/transesterification sequence, the Mannich

(89) Palomo, C.; Oiarbide, M.; Laso, A.; López, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622.
(90) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975.

Scheme 64



adduct **99** could be converted to the optically enriched β-amino acid ester (Scheme 63).[91]

6. Epoxidation

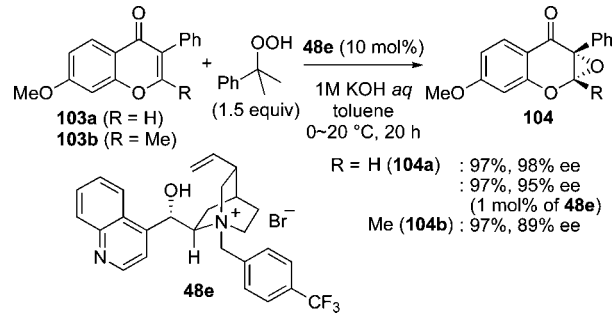
The catalytic asymmetric epoxidation of electron-deficient olefins, particularly α,β-unsaturated ketones, has been the subject of numerous investigations, and a number of useful methodologies have been elaborated.[92] Among these, the method utilizing chiral phase-transfer catalysis occupies a unique 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 **101** with 30% H_2O_2 and LiOH in chloroform in the presence of chiral ammonium bromide such as **70b**, affording the corresponding epoxide **102** with a quaternary carbon center with a good enantioselectivity.[93] Interestingly, use of the deaza derivative **100** as catalyst provided the enhanced enantioselectivity (Scheme 64).[55]

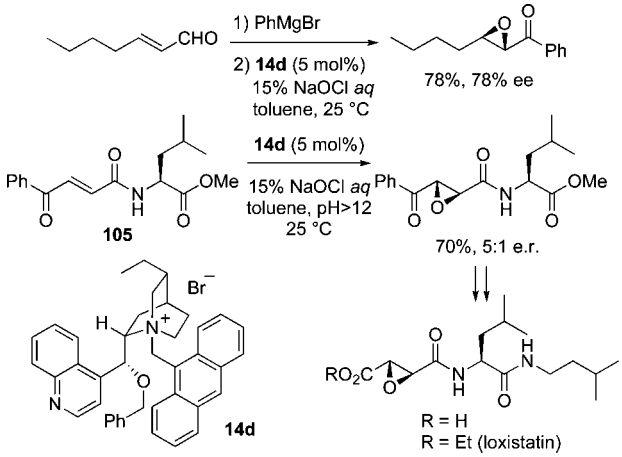
The asymmetric epoxidation of chalcone is quite sensitive to the choice of oxidants. In contrast to Shioiri's result, [93] Lygo found that the use of sodium hypochlorite delivered much higher stereocontrol than aqueous hydrogen peroxide, and the asymmetric epoxidation proceeded with only 1 mol % of a cinchona alkaloid-derived chiral phase-transfer catalyst.[94] Liang successfully utilized trichloroisocyanuric acid as a safe, inexpensive, and mild oxidant for the asymmetric epoxidations.[95] 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 realized asymmetric epoxidation of isoflavones **103** with (4-trifluoromethyl)benzyl cinchoninium bromide **48e**

(91) Fini, F.; Bernardi, L.; Herrera, R. P.; Pettersen, D.; Ricci, A.; Sgarzani, V. *Adv. Synth. Catal.* **2006**, *348*, 2043.
(92) (a) For reviews, see: Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215. (b) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 94.
(93) Arai, S.; Tsuge, H.; Oku, M.; Miura, M.; Shioiri, T. *Tetrahedron* **2002**, *58*, 1623.
(94) Lygo, B.; To, D. C. M. *Tetrahedron Lett.* **2001**, *42*, 1343.
(95) (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.

Scheme 65



Scheme 66

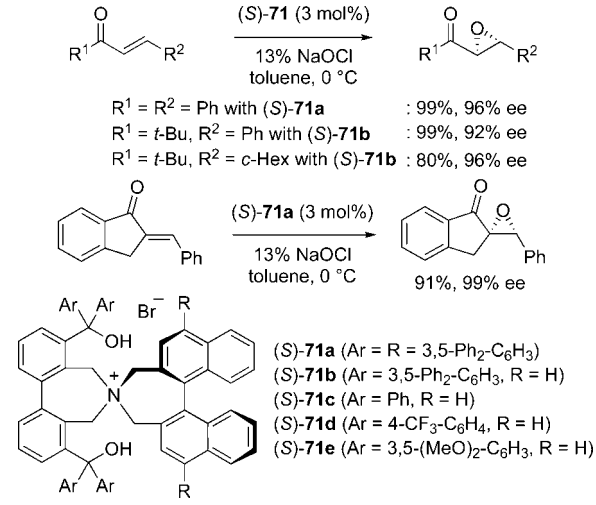


(developed by the Merck group) as catalyst and commercially available cumene hydroperoxide as oxidant (Scheme 65). Upon reducing the catalyst loading to 1 mol %, isoflavone epoxide **104a** was obtained almost quantitatively with excellent enantioselectivity. The 2-methyl derivative **103b** afforded the corresponding epoxide **104b** possessing two consecutive quaternary stereogenic centers in 97% yield with 89% ee.[96]

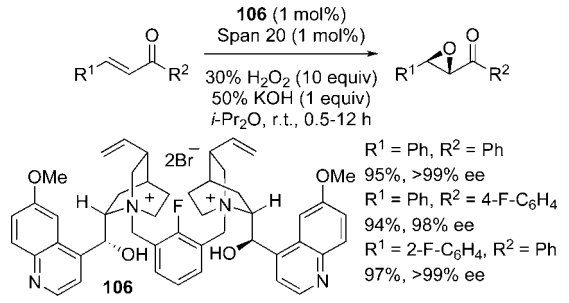
Lygo developed the direct asymmetric transformation of allylic alcohols into α,β-epoxy ketones based on the biphasic oxidation system catalyzed by *N*-anthracenylmethyl *O*-benzyl dihydrocinchonidinium bromide **14d**. In combination with an ordinary carbonyl alkylation procedure, an α,β-unsaturated aldehyde is smoothly transformed to a chiral epoxy ketone with good enantioselectivity (Scheme 66).[97] Lygo also utilized the chiral phase-transfer-catalyzed epoxidation in the stereoselective synthesis of loxistatin. In the key step of these syntheses, the diastereoselective epoxidation of the enone **105** 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*-benzyl dihydrocinchonidinium bromide **14d** (Scheme 66).[98]

We designed a new and highly efficient chiral *N*-spiro-type quaternary ammonium salt **71** with dual functions for asymmetric epoxidation of various enone substrates (Scheme 67).[99] 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 **71**, and use of **71c**−**71e** significantly decreased the enantioselection (61−66% ee for chalcone epoxidation).

Scheme 67



Scheme 68



Park and Jew applied chiral dimeric cinchona phase-transfer catalyst **106** 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 a surfactant, such as Span 20, in the reaction system, which is necessary to realize both high yields and enantioselectivities (Scheme 68).[100]

Hori designed phase-transfer catalysts **107** 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 function in molecular recognition. The ability of the catalyst was demonstrated in the asymmetric epoxidation of diarylenones, furnishing the epoxides in moderate

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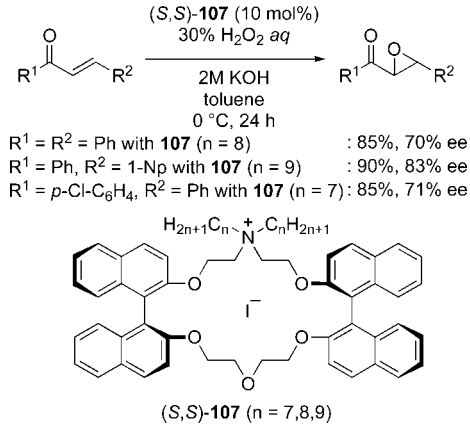
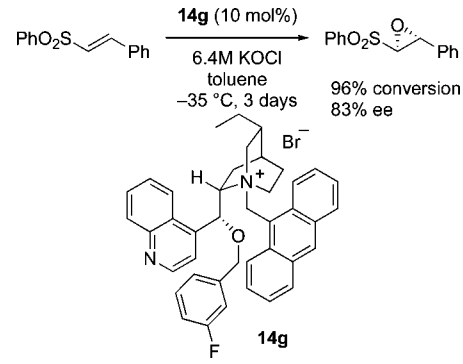
(97) Lygo, B.; To, D. C. M. *Chem. Commun.* **2002**, 2360.
(98) Lygo, B.; Gardiner, S. D.; To, D. C. M. *Synlett* **2006**, 2063.
(99) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844.
(100) Jew, S.-s.; Lee, J.-H.; Jeong, B.-S.; Yoo, M.-S.; Kim, M.-J.; Lee, Y.-J.; Lee, J.; Choi, S.-h.; Lee, K.; Lah, M. S.; Park, H.-G. *Angew. Chem., Int. Ed.* **2005**, *44*, 1383.

Scheme 69



Scheme 70



enantioselectivity. The length of the aliphatic chain was adjusted to achieve good selectivity, depending on the enones (Scheme 69).[101]

The Pfizer group reported the scalemic asymmetric epoxidation of α,β-unsaturated sulfones. Among the screening of several parameters the effect of the ether moiety of the dihydrocinchonidinium salt was examined, leading to the use of (3-fluorophenyl)methyl ether **14 g** as an optimal catalyst design (Scheme 70).[102]

7. Aziridination

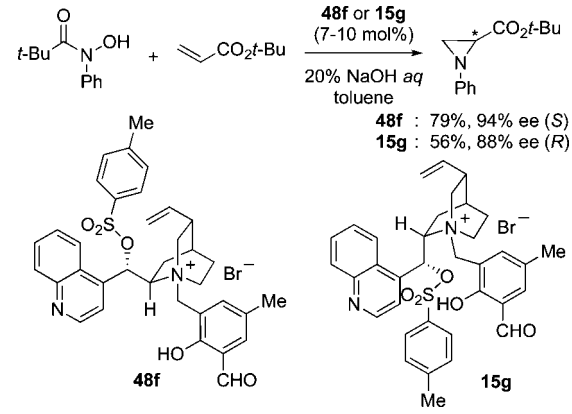
Chiral aziridines have been used as chiral auxiliaries, chiral ligands for transition metals, and chiral building blocks for preparation of biologically active species such as amino acids, β-lactams, and alkaloids.[103]

Murugan developed a new procedure for asymmetric aziridination reactions to achieve excellent levels of enantioselectivity using new chiral phase-transfer catalysts **48f** and **15 g** derived from cinchonine and cinchonidine, respectively (Scheme 71).[104]

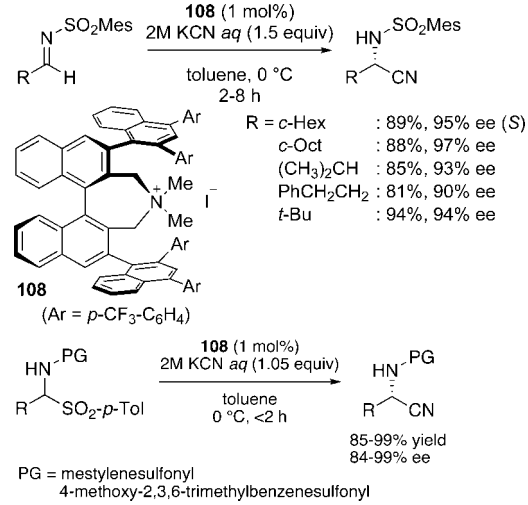
8. Strecker Reaction

The catalytic asymmetric cyanation of imines, Strecker reaction, represents one of the most direct and viable methods

Scheme 71



Scheme 72



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 **108** bearing the tetranaphthyl backbone as a remarkably efficient catalyst (Scheme 72).[105a]

This phase-transfer catalyzed asymmetric Strecker reaction is further elaborated by use of α-amido sulfone 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 72).[105b]

9. Conclusion

The study of chiral phase-transfer catalysis is certainly one of the hottest research area in asymmetric organocatalysis. The use of chiral phase-transfer catalysis to introduce chirality is significantly different compared with ordinary chiral transition metal complexes, and such a metal-free process or asymmetric organocatalysis is extremely valuable for pharmaceutical process due to the nontoxicity of metal without the need of the cost and effort to remove trace of metal.

(101) Hori, K.; Tamura, M.; Tani, K.; Nishiwaki, N.; Ariga, M.; Tohda, Y. *Tetrahedron Lett.* **2006**, *47*, 3115.
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(103) (a) For reviews, see Tanner, D. *Angew. Chem., Int. Ed.* **1994**, *33*, 599. (b) McCoull, W.; Davis, F. A. *Synyhesis* **2000**, 1347.
(104) Murugan, E.; Siva, A. *Synthesis* **2005**, 2022.
(105) (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.

The recent 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 practical 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 as well as stereocontrolling ability. Systematic accumulation of such knowledge will allow further rational catalyst design for pursuing selective chemical syntheses in reliable and elegant fashion.

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