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Asymmetric Synthesis

Recent Advances in Asymmetric Phase-Transfer Catalysis

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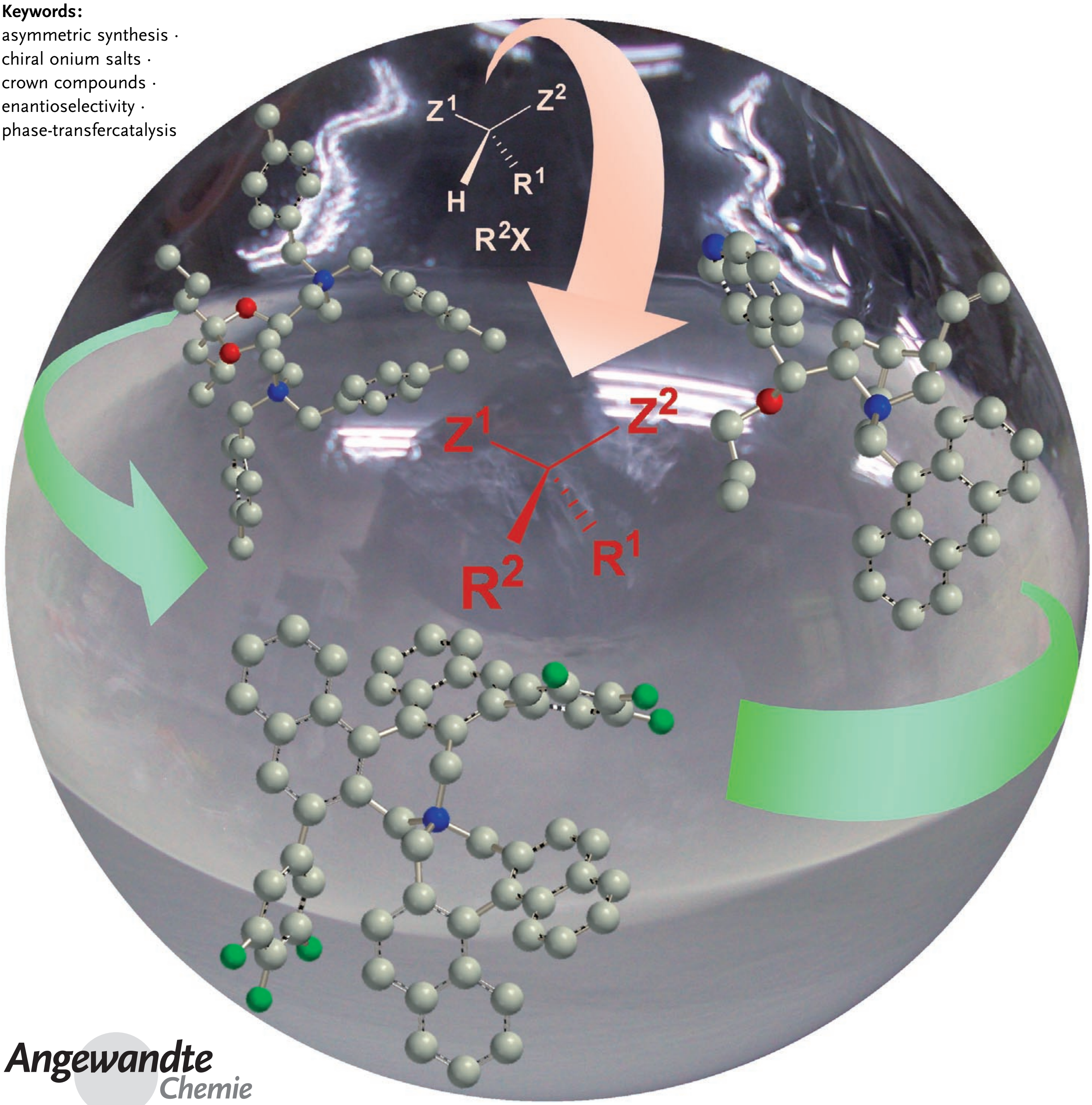

The use of chiral nonracemic onium salts and crown ethers as effective phase-transfer catalysts have been studied intensively primarily for enantioselective carbon–carbon or carbon–heteroatom bond-forming reactions under mild biphasic conditions. An essential issue for optimal asymmetric catalysis is the rational design of catalysts for targeted reaction, which allows generation of a well-defined chiral ion pair that reacts with electrophiles in a highly efficient and stereoselective manner. This concept, together with the synthetic versatility of phase-transfer catalysis, provides a reliable and general strategy for the practical asymmetric synthesis of highly valuable organic compounds.

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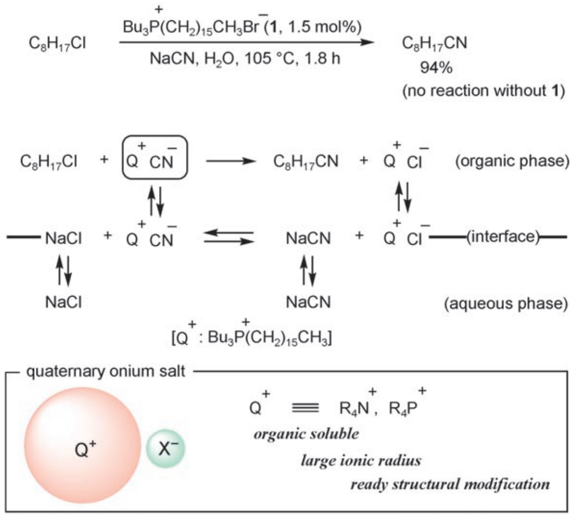
1. Introduction

In 1971, Starks introduced the term "phase-transfer catalysis" to explain the critical role of tetraalkylammonium or phosphonium salts (Q^+X^-) in the reactions between two substances located in different immiscible phases.[1] For example, the displacement reaction of 1-chlorooctane with aqueous sodium cyanide is accelerated many thousandfold by the addition of hexadecyltributylphosphonium bromide (**1**) as a phase-transfer catalyst (Scheme 1). Key to this tremendous enhancement in reactivity is the generation of a quaternary phosphonium cyanide, which makes the cyanide anion soluble in organic solvents and sufficiently nucleophilic. The high rate of displacement is mainly due to two of the three characteristic features of the pairing cation (Q^+): high lipophilicity and the large ionic radius.

Although it was not the first observation of the catalytic activity of quaternary onium salts,[2] the foundations of phase-transfer catalysis were laid by Starks together with Makosza and Brändström in the mid to late 1960s. Since then, the chemical community has witnessed an exponential growth of phase-transfer catalysis as a practical methodology for organic synthesis. The advantages of this method are its simple experimental procedures, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and the possibility of conducting large-scale preparations.[3] Nowadays, it appears to be the most important



Scheme 1. Tetraalkylonium salts as phase-transfer catalysts.

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synthetic method used in various fields of organic chemistry, and has also found widespread industrial applications.

On the other hand, the development of asymmetric phase-transfer catalysis based on the use of structurally well-defined chiral, nonracemic catalysts has progressed rather slowly, despite its potential to create a new area of asymmetric catalysis by taking full advantage of structurally and stereochemically modifiable tetraalkylonium ions (Q^+). However, recent efforts toward this direction have resulted in notable achievements, thus making it feasible to perform various bond-formation reactions under the mild conditions used in phase-transfer catalysis. This Review aims to illustrate the evolution of this active research field. Since several excellent reviews on this topic have been published,[4] the main focus will be on recent progress. It is the goal of this Review to provide a better understanding of the current situation and future perspectives of asymmetric phase-transfer catalysis.

2. General Mechanism of Asymmetric Phase-Transfer Catalysis

Two representative reaction systems can be considered for phase-transfer-catalyzed bond formations using chiral catalysts. One involves the functionalization of active methylene or methine groups, typically under basic conditions. These reactions generally follow an interfacial mechanism.[5] Most of the successful asymmetric transformations under phase-transfer conditions belong to this category. The alkylation of an active methylene group, specifically the glycinate Schiff base **2**,[4g,j,10a] is selected to illustrate the crucial parameters and key problems in such reactions. As depicted in Figure 1, the first step of the alkylation is the interfacial deprotonation of the α-proton of **2** with base (MOH) to give the corresponding metal enolate **3**, which stays at the interface of the two layers. Subsequent ion-exchange of the anion with the catalyst ($\mathbf{Q}^{*+}X^-$) generates a lipophilic chiral onium enolate **4**. This step results in the enolate going deep into the organic phase, where it reacts with an alkyl halide to afford the optically active monoalkylation product **5** with concomitant regeneration of the catalyst.[4f,10c,d] This type of reaction is only successful if the chiral onium cation ($\mathbf{Q}^{*+}$) can lead to the generation of highly reactive chiral onium enolate **4** through sufficiently fast ion-exchange and effective shielding of one of the two enantiotopic faces of the enolate anion. The former minimizes the intervention of the direct alkylation of metal enolate to give racemic **5**, and the latter rigorously controls the absolute stereochemistry. An additional important issue to be considered is the effect of the strongly basic conditions, which could primarily cause decomposition of the catalyst, although hydrolysis of the substrate (ester and imine moieties), product racemization, and dialkylation could also be problematic. Such undesirable processes associated with the starting materials and products could be prevented by appropriate choice of protecting groups. In fact, the *tert*-butyl ester of **2** resists saponification, and the benzophenone imine moiety is essential not only for facilitating the initial deprotonation but also for leaving the remaining α-proton of **5** intact. In general, the type of phase-transfer system (liquid–liquid or solid–liquid) and other reaction variables (base, solvent, temperature, substrate concentration, and stirring rate) can be tuned to optimize the reactions.

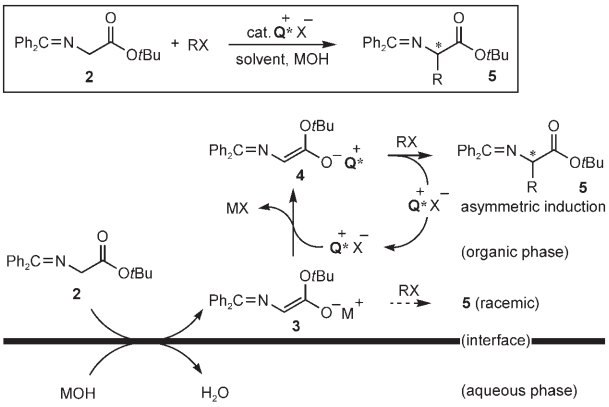
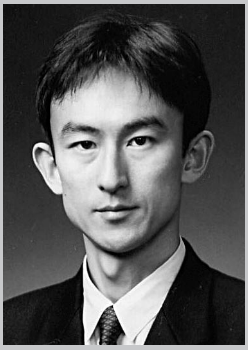


Figure 1. General mechanism for the asymmeric alkylation of active methylene compounds, with a glycine Schiff base used as an example.

Another, relatively less-studied system is the nucleophilic addition of an organic or inorganic anion lacking a prochiral center to prochiral electrophiles. In these reactions an extraction mechanism is operative.[1] The anion is used as an aqueous solution or solid of its inorganic salt, and it is transferred into the organic phase as a chiral ion pair by ion-exchange with the catalyst. It then most commonly attacks a prochiral electrophile, and a new stereogenic center is created. The asymmetric epoxidation of α,β-unsaturated



Takashi Ooi received his PhD (1994) from Nagoya University with Professor Hisashi Yamamoto, and was a postdoctoral fellow in the group of Professor Julius Rebek, Jr. at MIT (1994–1995). He was appointed as an assistant professor at Hokkaido University in 1995 and promoted to a lecturer in 1998. He moved to Kyoto University as an associate professor in 2001, and became a full professor of Nagoya University in 2006. He has been awarded the Chugai Award in Synthetic Organic Chemistry, Japan (1997), the Japan Chemical Society Award for Young Chemist (1999), and the Thieme Journal Award (2006).

Keiji Maruoka received his PhD (1980) from the University of Hawaii with Prof. Hisashi Yamamoto. He then became an assistant professor at Nagoya University and an associate professor in 1990. He moved to Hokkaido University as a full professor (1995), and since 2000 has been a professor at Kyoto University. His research interests focus on organic synthesis with bidentate Lewis acids and designer chiral organocatalysts. His awards include the Ichimura Prize for Science (2001), the Japan Synthetic Organic Chemistry Award (2003), Nagoya Silver Medal (2004), and the GSC award (2006).

ketones using an aqueous solution of sodium hypochlorite represents a typical example (Figure 2). The chiral onium hypochlorite ($\mathbf{Q}^{*+}\mathrm{OCl}^{-}$) is responsible for the enantiofacial discrimination of the prochiral enone **6**.[141,142] The pH value of the reaction is nearly neutral, so the possibility of side reactions is considerably reduced. However, an even more precise catalyst design seems to be required because the chiral cation ($\mathbf{Q}^{*+}$) should recognize the enantiotopic faces of the electrophilic reacting partner.

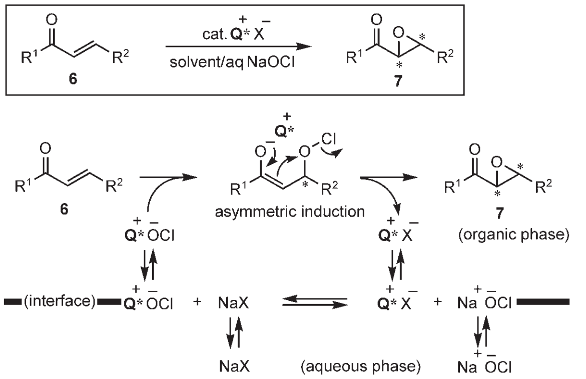


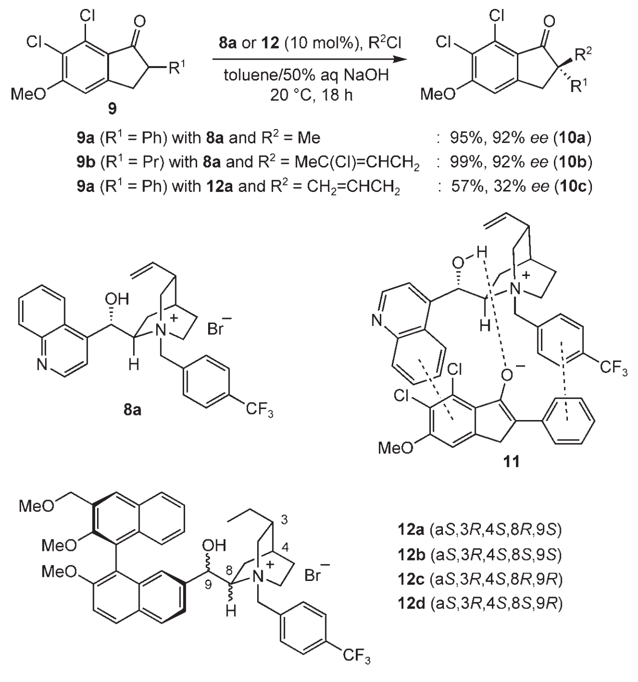
Figure 2. General mechanism for the nucleophilic addition of anions to prochiral electrophiles, with the asymmetric epoxidation of α,β-unsaturated ketones used as an example.

3. Alkylation

3.1. Pioneering Studies

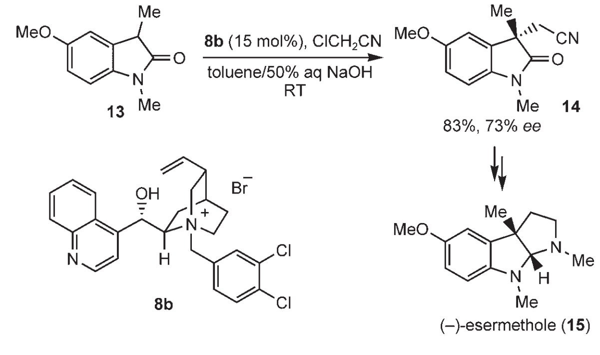
The enantioselective alkylation of active methylene compounds occupies the central position in the field of asymmetric phase-transfer catalysis, and its development was triggered by the pioneering study by a Merck research group in 1984.[6] Dolling and co-workers utilized the cinchonine-derived quaternary ammonium salt **8a** as the catalyst for the methylation of phenylindanone derivative **9a** under liquid–liquid phase-transfer conditions (toluene/50% aq NaOH solution) and succeeded in obtaining the corresponding alkylated product **10a** in excellent yield and high enantiomeric excess (Scheme 2). The authors made systematic studies of this reaction, and proposed the tight ion pair intermediate **11**, formed through hydrogen bonding as well as electrostatic and π–π stacking interactions, to account for the result. The effectiveness of the catalysis was also demonstrated in the reaction of α-propyl analogue **9b** with 1,3-dichloro-2-butene.[7]

Diederich and Ducry synthesized a series of diastereomeric chiral quaternary ammonium bromides **12a–d** which incorporated the quinuclidinemethanol fragment of cinchona alkaloids and a 1,1′-binaphthyl moiety. The ability of these compounds to function as phase-transfer catalysts in the asymmetric allylation of **9a** under similar conditions were evaluated. These studies revealed that, without any optimization, **12a** was superior to the other three diastereomeric catalysts **12b–d**, although both the chemical yield and enantiomeric excess of **10c** were unsatisfactory (Scheme 2).[8]



Scheme 2. Asymmetric phase-transfer-catalyzed alkylation of indanone derivatives.

This phase-transfer-catalyzed alkylation strategy was successfully applied to the asymmetric cyanomethylation of oxindole **13** by the use of catalyst **8b** with a 3,4-dichlorophenylmethyl group appended on the nitrogen atom. This reaction allowed a simple and stereoselective synthesis of (−)-esermethole (**15**), a precursor to the clinically useful anticholinesterase agent (−)-physostigmine (Scheme 3).[9]



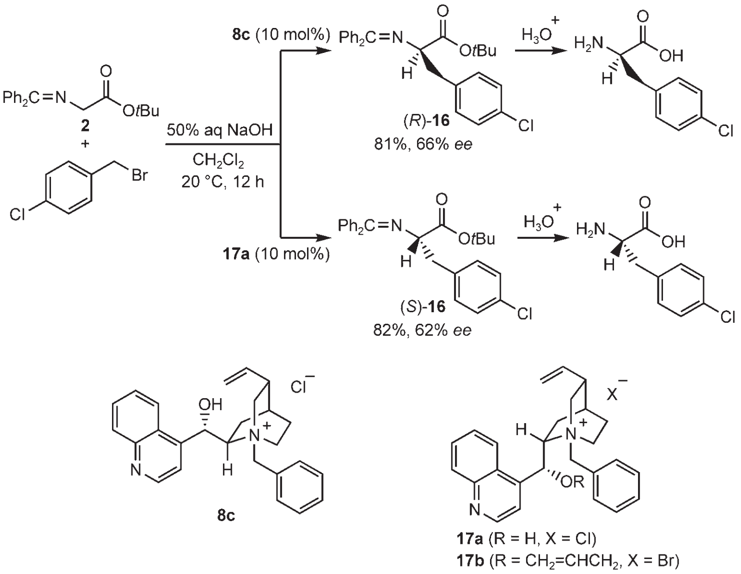
Scheme 3. Asymmetric cyanomethylation of oxindole **13** as a step in the synthesis of (−)-esermethole (**15**).

3.2. Asymmetric Synthesis of α-Amino Acids and their Derivatives

3.2.1. Monoalkylation of Schiff Bases Derived from Glycine

In 1989, five years after the pioneering work by the Merck research group, this type of catalyst was successfully utilized for the asymmetric synthesis of α-amino acids by O'Donnell et al., who used glycinate Schiff base **2** as a key substrate.[10]

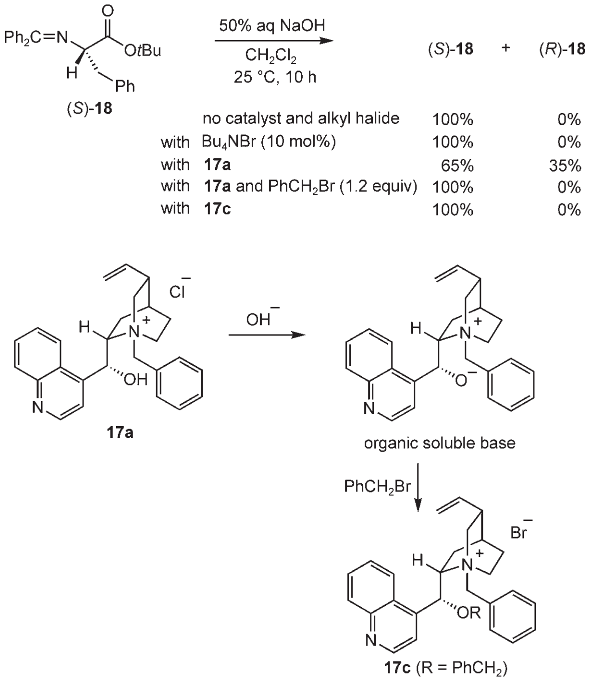
The asymmetric alkylation of **2** proceeded smoothly under mild phase-transfer conditions, with *N*-(benzyl)cinchoninium chloride (**8c**) as a catalyst, to give the alkylation product (*R*)-**16** in good yield and moderate enantioselectivity (Scheme 4).



Scheme 4. Asymmetric synthesis of α-amino acids from glycine derivative **2** by phase-transfer catalysis.

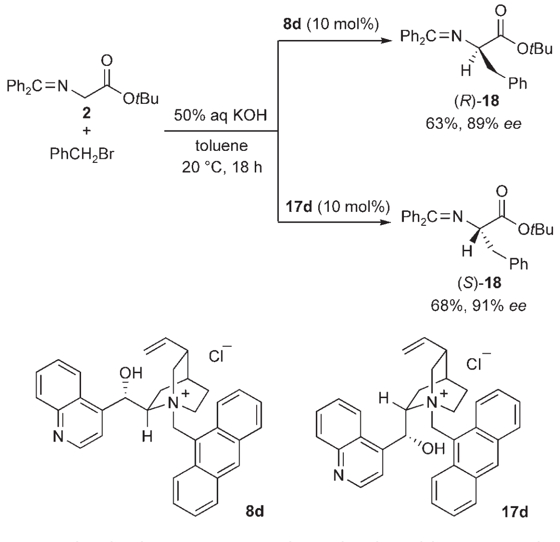
By simply switching to the cinchonidine-derived catalyst **17a**, the product could be obtained with the opposite absolute configuration (*S*) but with a similar degree of enantioselectivity. Further optimization with the hydroxy-protected catalyst **17b** (second-generation catalyst) enhanced the enantioselectivity to 81 % *ee*.[10c,11] A single recrystallization and subsequent deprotection of **16** afforded essentially optically pure α-amino acids.

An important aspect of this reaction is the selective formation of the monoalkylated product **16**, without concomitant production of the undesired dialkylated product, provided the Schiff base of benzophenone is employed as the starting material.[12] This effect results from the much lower acidity of the remaining α-proton of **16** (compared to that of **2**). This reduced acidity is also crucial for securing the configurational stability of the newly created α-stereogenic center under the reaction conditions. In fact, exposure of optically pure Schiff base (*S*)-**18** to typical alkylation conditions without alkyl halide did not cause racemization regardless of the addition of phase-transfer catalyst (Bu_4NBr; Scheme 5). Interestingly, however, a similar product racemization experiment in the presence of **17a** showed the formation of 35 % of (*R*)-**18** in two hours, and then no further racemization. Moreover, no racemization was detected if an alkyl halide such as benzyl bromide was present during the reaction with **17a**. These results suggested that the racemization of (*S*)-**18** was controlled by the organic soluble ammonium alkoxide, and its in situ benzylation generated the ammonium bromide **17c**, a possible active catalyst in the asymmetric phase-transfer-catalyzed alkylation of **2**.[11]



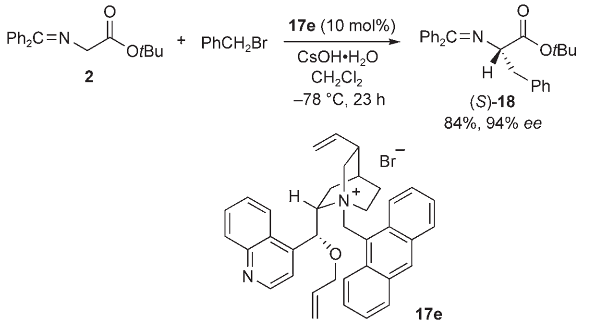
Scheme 5. Racemization experiments on (*S*)-**18**.

Although asymmetric phase-transfer alkylation of the glycinate Schiff base **2** can be achieved by using chiral phase-transfer catalysts derived from the relatively inexpensive, commercially available cinchona alkaloids, research in this area was slow. However, a new class of cinchona alkaloid derived catalysts bearing an *N*-anthracenylmethyl group (third-generation catalyst) developed by two independent research groups have opened up a new era of asymmetric phase-transfer catalysis. In 1997, Lygo et al. developed the *N*-anthracenylmethylammonium salts **8d** and **17d**, and applied them to the asymmetric phase-transfer alkylation of **2** to synthesize α-amino acids with much higher enantioselectivity (Scheme 6).[13]



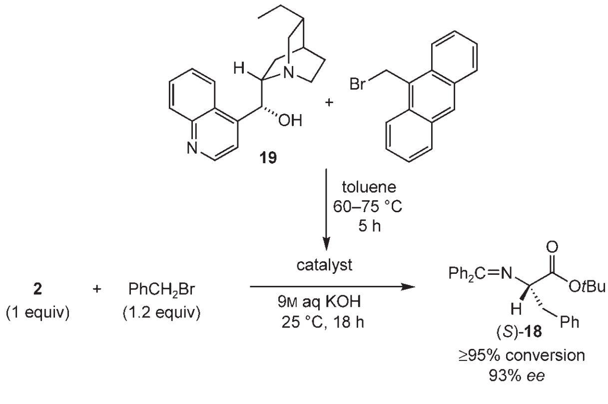
Scheme 6. The third-generation catalysts developed by Lygo et al.

At the same time Corey et al. prepared *O*-allyl-*N*-anthracenylmethyl cinchonidinium salt **17e**. By using solid cesium hydroxide monohydrate ($CsOH{\cdot}H_2O$) at very low temperature, they achieved a high asymmetric induction in the enantioselective alkylation of **2** (Scheme 7). The catalyst was characterized by X-ray analysis of *O*-allyl-*N*-anthracenylmethylcinchonidinium *p*-nitrophenoxide.[14]



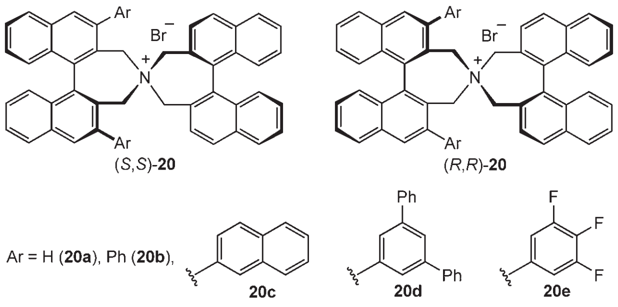
Scheme 7. The third-generation catalysts developed by Corey et al.

Recently, Lygo et al. demonstrated that this type of chiral quaternary ammonium salt can be generated in situ and directly used as a catalyst for the subsequent asymmetric alkylation of **2**. For example, treatment of dihydrocinchonine (**19**) with 9-bromomethylanthracene in toluene at 60–75 °C for 5 h followed by the addition of **2**, benzyl bromide, and aqueous KOH at room temperature and continuous stirring for 18 h afforded the desired protected phenylalanine **18** with 93 % *ee* (Scheme 8).[15] The observed enantioselectivity was comparable to that obtained with pre-prepared catalyst. This approach is likely to be useful for the identification of optimal catalyst structures for a given asymmetric transformation.



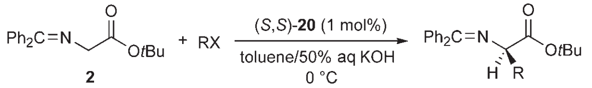
Scheme 8. In situ generation of chiral phase-transfer catalysts.

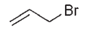
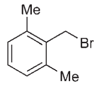
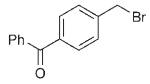
In 1999 we prepared the structurally rigid, chiral spiroammonium salts of type **20**, derived from commercially available (*S*)- or (*R*)-1,1′-bi-2-naphthol, as a new C_2-symmetric phase-transfer catalyst and successfully applied them to the highly efficient, catalytic enantioselective alkylation of **2** under mild phase-transfer conditions.[16]



The key finding was a significant effect of an aromatic substituent at the 3,3′-position of one binaphthyl subunit of the catalyst (Ar) on the enantiofacial discrimination. (*S*,*S*)-**20e** proved to be the catalyst of choice for the preparation of a variety of essentially enantiopure α-amino acids by this transformation (Table 1). In general, 1 mol % of **20e** is sufficient for the smooth alkylation, and the catalyst loading can be reduced to 0.2 mol % without loss of enantiomeric excess (entry 6). The use of aqueous cesium hydroxide (CsOH) as a basic phase at lower reaction temperature is recommended for the reaction with simple alkyl halides such as ethyl iodide (entry 7).

Table 1: Effect of aromatic substituents (Ar) and general applicability of **20e** for the phase-transfer-catalyzed alkylation of **2**.

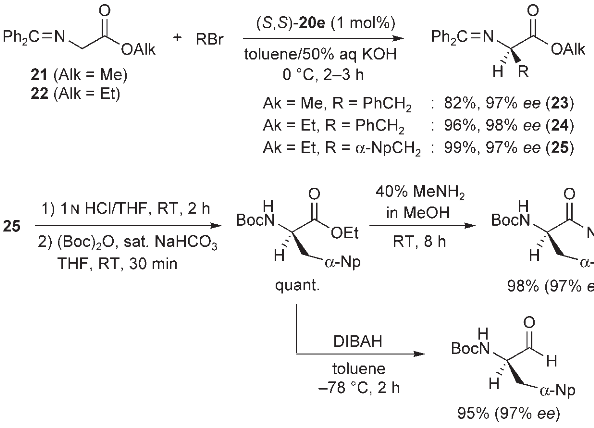


Entry	Catalyst	RX	Yield [%]	*ee* [%]
1	**20a**	$PhCH_2Br$	73	79 (*R*)
2	**20b**	$PhCH_2Br$	81	89 (*R*)
3	**20c**	$PhCH_2Br$	95	96 (*R*)
4	**20d**	$PhCH_2Br$	91	98 (*R*)
5	**20e**	$PhCH_2Br$	90	99 (*R*)
6[a]	**20e**	$PhCH_2Br$	72	99 (*R*)
7[b]	**20e**	EtI	89	98 (*R*)
8	**20e**		80	99 (*R*)
9	**20e**		98	99 (*R*)
10	**20e**		86	98 (*R*)

[a] With 0.2 mol % of (*S*,*S*)-**20e**. [b] With saturated CsOH at −15 °C.

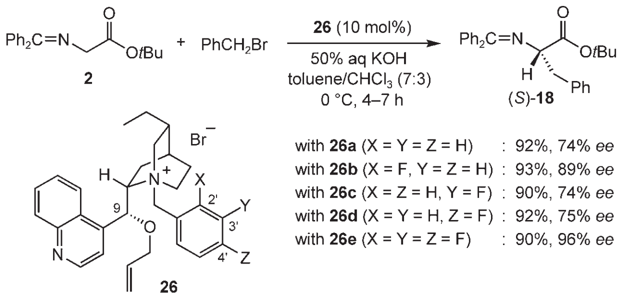
Since both enantiomers of the catalyst of type **20** can be readily assembled in exactly the same manner starting from either (*S*)- or (*R*)-1,1′-bi-2-naphthol, a wide variety of natural and unnatural α-amino acids can be synthesized in an enantiomerically pure form by the phase-transfer-catalyzed alkylation of **2**.

The salient feature of **20e** is its ability to catalyze the asymmetric alkylation of glycine methyl ester and ethyl ester derivatives **21** and **22** with excellent enantioselectivities. Since methyl and ethyl esters are certainly more susceptible toward nucleophilic additions than *tert*-butyl esters, the synthetic advantage of this process is clear, as highlighted by the facile transformation of the alkylation products (Scheme 9).[17]



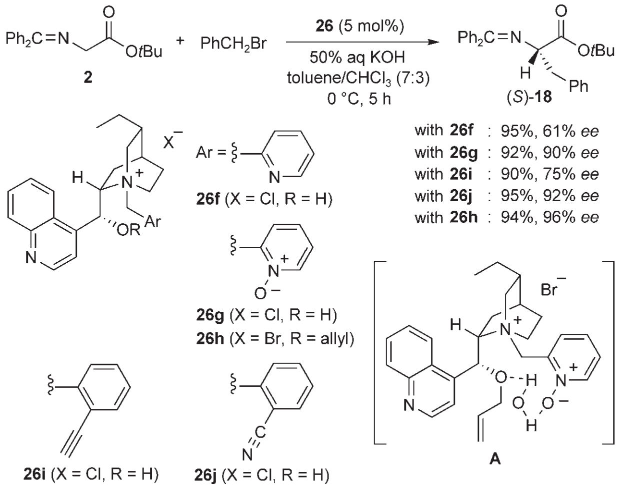
Scheme 9. Asymmetric alkylation of glycine methyl ester and glycine ethyl ester derivatives.

A similar electronic effect of fluoroaromatic substituents was utilized by Jew, Park, and co-workers for the development of efficient catalysts derived from cinchona alkaloids. Evaluation of the effect of electron-withdrawing groups on the benzylic group of dihydrocinchonidinium salt **26** revealed that an *ortho*-fluoro substituent on the aromatic ring led to dramatic enhancement of the enantioselectivity. Catalyst **26e** with a 2′,3′,4′-trifluorobenzyl group showed the highest selectivity in the transformation of a variety of alkyl halides (Scheme 10).[18]



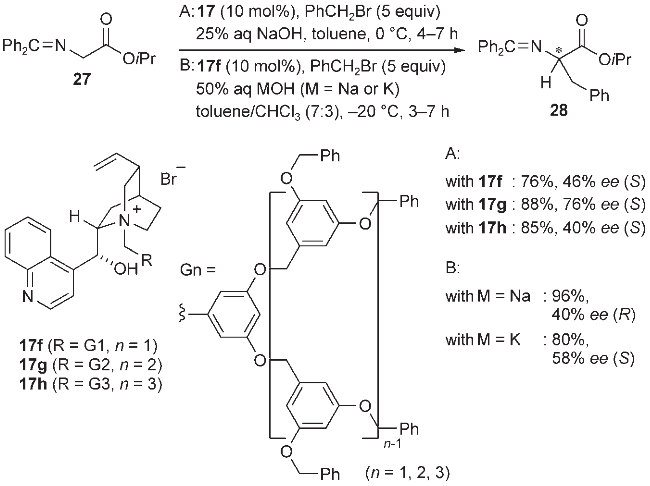
Scheme 10. Electronic effects of a fluorine-substituted benzene group on the catalyst activity.

It has been proposed that a hydrogen-bonding interaction between the oxygen atom at C9 and the fluorine atom at C2′ in **26b** might rigidify its conformation, thus leading to high enantioselectivity. Recent studies from the same research group on the evaluation of related chiral quaternary ammonium salts containing 2′-*N*-oxypyridinyl (**26g** and **26h**) and 2′-cyanophenyl groups (**26j**) strongly support this possibility. For example, **26g** and **26j** exhibited considerably higher enantioselectivity than the 2′-pyridinyl (**26f**) and 2′-ethynyl (**26i**) analogues, respectively, thus suggesting the intervention of a preorganized catalyst such as **A** (Scheme 11).[19]



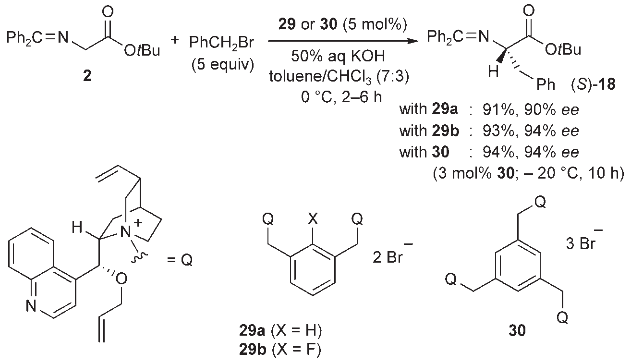
Scheme 11. Influence of hydrogen bonding in catalysts **26** on the enantioselectivity.

Nájera, van Koten, and co-workers prepared dendritic cinchonidine-derived ammonium salts **17f–h** using Fréchet dendritic wedges up to generation three.[20a] These chiral salts were used as phase-transfer catalysts in the asymmetric benzylation of glycinate Schiff base **27**. The best enantioselection was achieved with second-generation catalyst **17g**, while the the third-generation salt **17h** gave similar enantioselectivity as the first-generation salt **17f**. Interestingly, the enantioselectivity in the reaction with the first-generation catalyst **17f** was dependent on the metal base (Scheme 12).[20b]

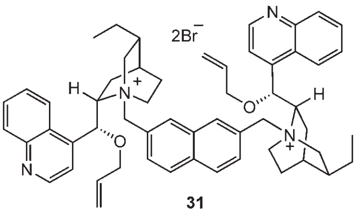


Scheme 12. Dendritic cinchonidine-derived ammonium salts **17f–h**.

During the development of the asymmetric Sharpless dihydroxylation, it was found that ligands with two cinchona alkaloid units attached to heterocyclic spacers led to a considerable increases in both the enantioselectivity and the scope of the substrate. This effect has been utilized successfully by Jew, Park, and co-workers for the design of chiral phase-transfer catalysts **29**[21] and **30**,[22] with two and three cinchona alkaloid units, respectively. These catalysts substantially enhanced the enantioselectivity of the alkylation of **2** and also expanded the range of alkyl halides that could be transformed (Scheme 13). During their search for the ideal aromatic spacer they found that the catalyst **31** consisting of 2,7-bis(bromomethyl)naphthalene and the requisite two cinchona alkaloid units exhibited remarkable catalytic and chiral efficiency.[23] Thus, 1 mol% of **31** was sufficient for the alkylation of **2** with various alkylating agents.



Scheme 13. Catalysts with two or three cinchona alkaloid groups.



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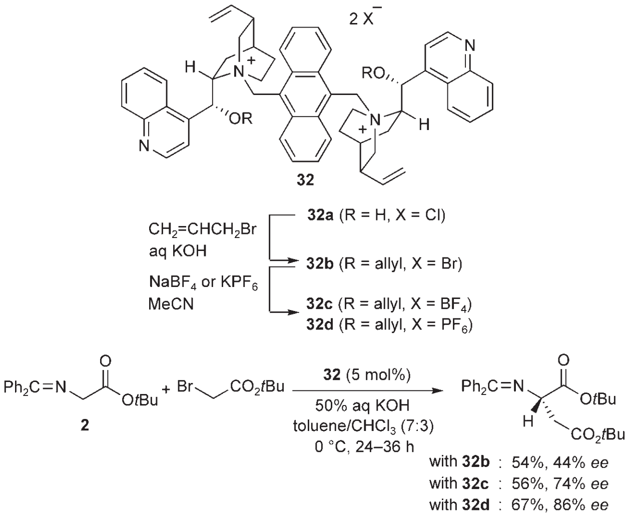
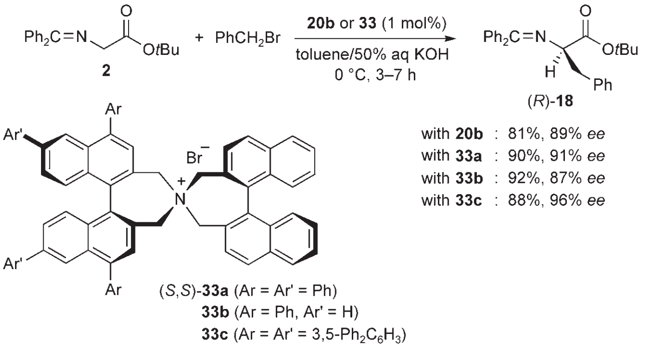
Nájera and co-workers also prepared salt **32a** which incorporates a dimethylanthracenyl bridge as a spacer. This type of catalyst was utilized for the catalytic enantioselective alkylation of **2** with different alkyl halides in a biphasic system consisting of 50% aqueous KOH and a toluene/$CHCl_3$ mixture. The α-alkyl-α-amino acids were obtained in good yields and in up to 90% *ee*.[24]

Inspired by the report by Shibasaki and co-workers on the influence of the counterion on the asymmetric alkylation of **2** using chiral bis(ammonium) salts (see Scheme 25),[36b] the bromide ion of **32b** was exchanged with tetrafluoroborate (**32c**) or hexafluorophosphate (**32d**). The counterion effect was very pronounced, with the most remarkable increase in the enantioselectivity observed in the reaction of **2** with *tert*-butyl bromoacetate (Scheme 14).[25]



Scheme 14. Anthracene-derived catalysts **32** with cinchona alkaloid substituents.

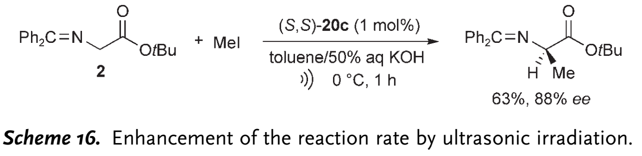
With the critical role of 3,3′-diaryl substituents of **20** in mind, we examined the effect of substituents at the 4,4′- and 6,6′-positions of one binaphthyl subunit in the phase-transfer-catalyzed alkylation of **2**. The introduction of simple aromatic groups at the 4,4′-positions led to a meaningful effect on the stereoselectivity (Scheme 15).[26]



Scheme 15. Effect of substituents on the binaphthyl N-spiro catalyst **33**.

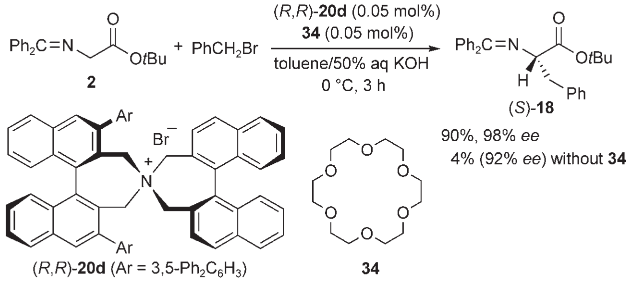
With the aim of establishing a practical method for the asymmetric synthesis of α-amino acids and their derivatives we also investigated whether the reactivity of N-spiro chiral quaternary ammonium salts could be enhanced and their structures simplified. Since ultrasonic irradiation produces homogenization, that is, very fine emulsions, it greatly increases the interfacial area over which the reaction can occur, 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*)-**20c** (1 mol%) in toluene/50% aqueous KOH at 0°C for 1 h gave rise to the corresponding alkylation product in 63% yield with 88% *ee*; the chemical yield and enantioselectivity were comparable with those from a reaction carried out by simple stirring of the mixture for eight hours (0°C, 64%, 90% *ee*; Scheme 16).[27]

To fully induce the potential catalytic activity of N-spiro chiral ammonium salts such as **20d**, we have developed binary phase-transfer catalysis using an appropriate achiral co-catalyst. For example, the phase-transfer-catalyzed alkylation of **2** with benzyl bromide in the presence of (*R*,*R*)-**20d**



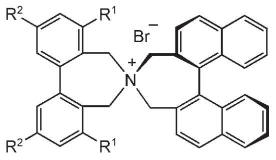
Scheme 16. Enhancement of the reaction rate by ultrasonic irradiation.

(0.05 mol %) was sluggish, and gave (*S*)-**18** in only 4 % yield (92 % *ee*). A similar benzylation of **2** in the presence of [18]crown-6 (**34**, 0.05 mol %) proceeded smoothly to furnish (*S*)-**18** in 90 % yield and 98 % *ee*. The origin of this dramatic rate enhancement is the ability of the crown ether to extract KOH into the toluene phase, thereby accelerating an otherwise slow deprotonation process (Scheme 17).[28] Indeed, the use of small crown ethers such as [15]crown-5 and [12]crown-4 dramatically lowered the chemical yield of **18**. Interestingly, tetrabutyl- and tetraoctylammonium salts also exhibited an acceleration effect.



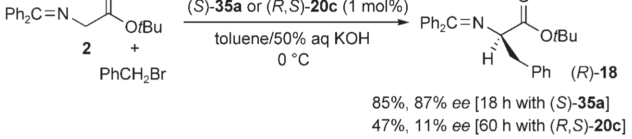
Scheme 17. Phase-transfer catalysis with the achiral co-catalyst [18]crown-6.

Although the conformationally rigid, N-spiro compound with two chiral binaphthyl subunits represents a characteristic feature of **20** and related catalyst **33**, it also imposes limitations on the catalyst design because of the need to use two different chiral binaphthyl moieties. Accordingly, we developed a new C_2-symmetric chiral quaternary ammonium bromide **35** with an achiral, conformationally flexible biphenyl subunit.[29]

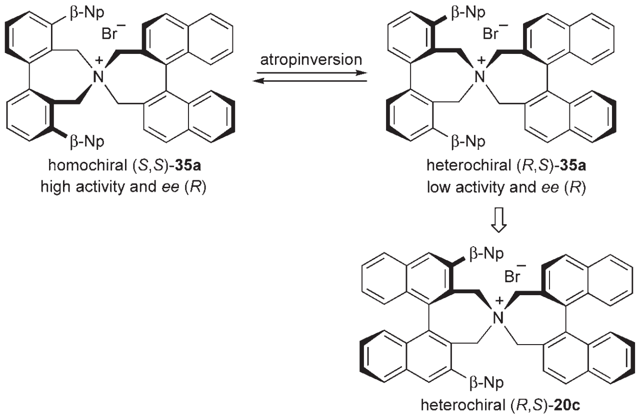


(*S*)-**35a** (R^1 = β-Np, R^2 = H)
35b (R^1 = 3,5-$Ph_2C_6H_3$, R^2 = H)
35c (R^1 = 3,5-$Ph_2C_6H_3$, R^2 = Ph)

The phase-transfer benzylation of **2** with (*S*)-**35a**, which has β-naphthyl (β-Np) groups at the 3,3′-positions of the flexible biphenyl moiety, proceeded smoothly at 0 °C to afford the corresponding alkylation product (*R*)-**18** in 85 % yield with 87 % *ee* after 18 h (Scheme 18). The enantioselectivity was ascribed to the considerable difference in the catalytic activity between the rapidly equilibrated, diastereomeric homo- and heterochiral catalysts: homochiral (*S*,*S*)-**35a** is primarily responsible for the efficient asymmetric phase-transfer catalysis to produce **18** with high enantiomeric excess, whereas heterochiral (*R*,*S*)-**35a** displays low reactivity and stereoselectivity. Supportive evidence for this hypothesis was that the benzylation with 1 mol % of conformationally rigid, heterochiral (*R*,*S*)-**20c** under similar conditions proceeded slowly, and, after 60 h, gave rise to (*R*)-**18** in 47 % yield and 11 % *ee* (Scheme 18).



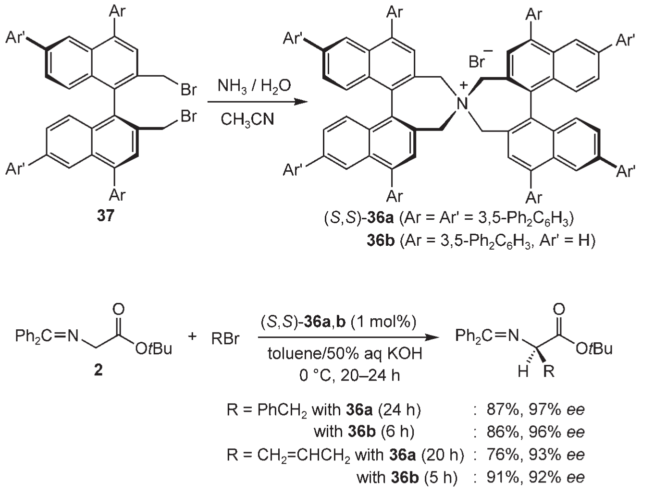
Scheme 18. Comparison of **35a** with the conformationally rigid heterochiral catalyst (*R*,*S*)-**20c**.



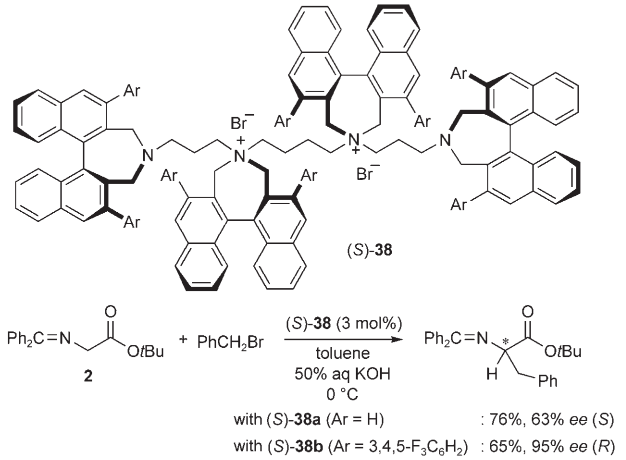
This unique phenomenon provides a powerful strategy in the molecular design of chiral catalysts: the requisite chirality can be met by the simple binaphthyl moiety, and an additional structural requirement for the fine-tuning of the reactivity and selectivity can be fulfilled by an easily modifiable achiral biphenyl structure. This approach obviates the use of two chiral units and should be useful for the synthesis of a variety of chiral catalysts with different steric and/or electronic properties. For example, quaternary ammonium bromide (*S*)-**35b** which possesses a bulky substituent can be easily prepared, and the benzylation with (*S*)-**35b** as a catalyst gave **18** in 95 % yield and 92 % *ee*. The enantioselectivity could be enhanced to 95 % *ee* when (*S*)-**35c** was used as the catalyst.

We were also intrigued by the preparation of a catalyst with a symmetrical N-spiro unit to avoid the independent synthesis of the two different binaphthyl-modified subunits required for **20**. Along this line, 4,4′,6,6′-tetraarylbinaphthyl-substituted ammonium bromide **36** was assembled through the reaction of aqueous ammonia with dibromide **37**, based on our study of the substituent effect of these types of salts.[26] Evaluation of compound **36** proved to be a highly effective chiral phase-transfer catalyst in the alkylation of **2** (Scheme 19).[30]

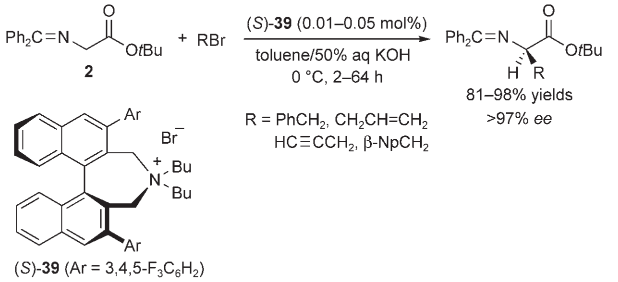
Our efforts toward the simplification of the catalyst have led to the design of new, polyamine-based chiral phase-transfer catalysts of type **38** with the expectation of the multiplicative effect of chiral auxiliaries (Scheme 20).[31] The efficiency of catalysts (*S*)-**38** was examined in the asymmetric alkylation of **2**. Among various catalysts derived from commercially available polyamines, polyammonium salts based on spermidine and spermine were found to show moderate enantioselectivity. In particular, catalyst (*S*)-**38b** with 3,4,5-trifluorophenyl groups at the 3,3′-positions of the



Scheme 19. Catalysis with the symmetrically substituted chiral N-spiroammonium bromides **36**.



Scheme 20. Activity of spermine-based chiral phase-transfer catalysts (*S*)-**38**.

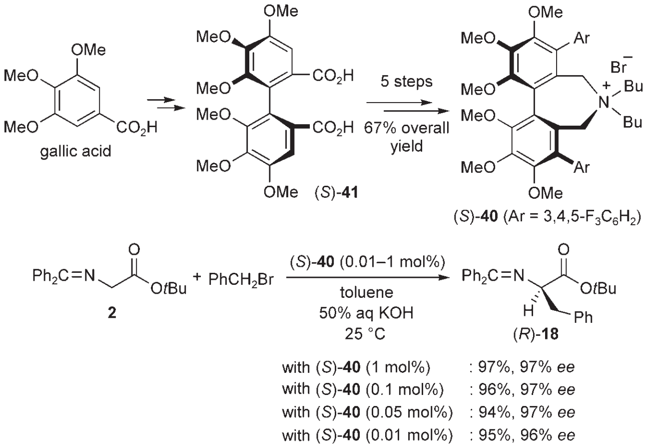


Scheme 21. Structurally simple, highly active catalyst **39**.

chiral binaphthyl moieties showed excellent asymmetric induction.

This finding led to the discovery that quaternary ammonium bromide (*S*)-**39** with flexible straight-chain alkyl groups instead of a rigid binaphthyl moiety functions as an unusually active chiral phase-transfer catalyst. Remarkably, 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% (*S*)-**39** to afford the corresponding alkylation products with excellent enantioselectivities (Scheme 21).[32]

The ready availability of starting chiral sources is crucial for the design of practical phase-transfer catalysts. Accordingly, chiral phase-transfer catalyst (*S*)-**40** was conveniently prepared from the known, readily available (*S*)-4,5,6,4′,5′,6′-hexamethoxybiphenyldicarboxylic acid (**41**) derived from gallic acid. Catalyst (*S*)-**40** (0.01–1 mol%) was very effective in the asymmetric alkylation of **2** among existing chiral phase-transfer catalysts. Thus, it provides a general and useful procedure for the highly practical enantioselective synthesis of structurally diverse natural and unnatural α-alkyl-α-amino acids (Scheme 22).[33]



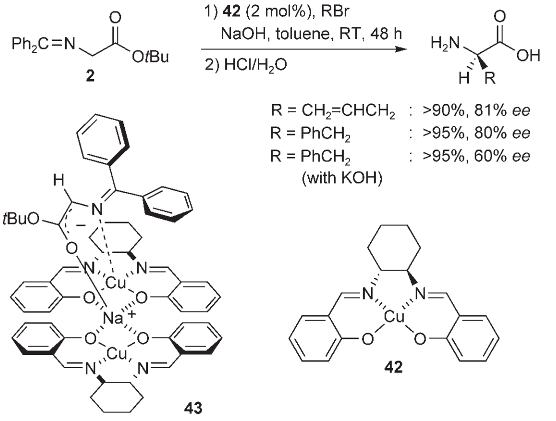
Scheme 22. Enantioselective synthesis of α-alkyl-α-amino acids with phase-transfer catalyst (*S*)-**40**.

The asymmetric monoalkylation of **2** with the chiral metal-salen complex **42** as a chiral phase-transfer catalyst was reported by Belokon et al.[80] The enantioselectivity was sensitive to the cation of the base, which was accounted for by proposing the formation of a mixed complex (**43**) of two copper(II)–salen units joined through a cation and an enolate anion (Scheme 23).[34]

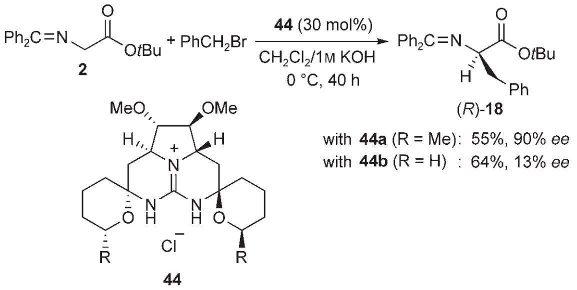
Nagasawa and co-workers reported the asymmetric alkylation of **2** with the C_2-symmetric chiral cyclic guanidines **44**. The introduction of methyl substituents is crucially important to achieve the high enantioselectivity (Scheme 24).[35] The chiral catalyst **44a** results in the alkylation of various alkyl halides in good yields and 76–90% *ee.*

Shibasaki and co-workers used the concept of two-center asymmetric catalysis to design tartrate-derived bis(ammonium) salt **45**, which resulted in the highly enantioselective alkylation of **2** (Scheme 25).[36] Interestingly, a counterion effect was observed: The enantioselectivity of the phase-transfer-catalyzed allylation of **2** with **45b** was higher than with **45a**.

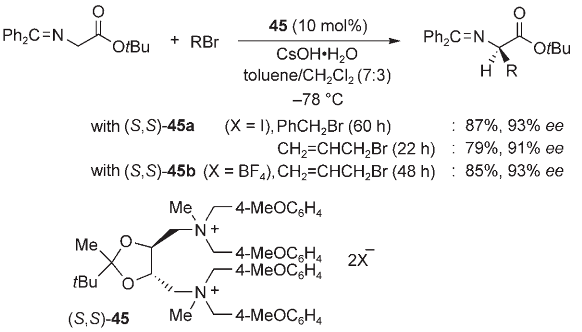
MacFarland and co-workers prepared diastereomeric bis(ammonium) salts **46** by combining a tartrate derivative and 2,5-dimethylpyrroline, and tested their ability as chiral



Scheme 23. Chiral copper–salen complex **42** as a phase-transfer catalyst.



Scheme 24. C_2-symmetric pentacyclic guanidine derivative **44** as a chiral catalyst.

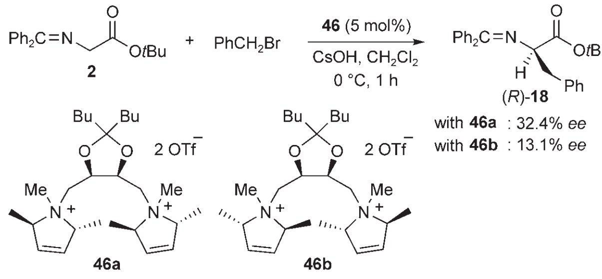


Scheme 25. Tartrate-derived chiral two-center phase-transfer catalyst **45**.

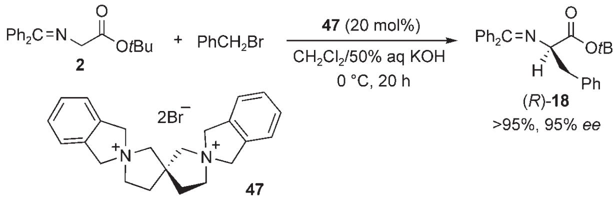
phase-transfer catalysts in the asymmetric alkylation of **2** (Scheme 26).[37]

Sasai designed bis(spiroammonium) salt **47** as a chiral phase-transfer catalyst, and applied it to a similar asymmetric alkylation reaction (Scheme 27).[38]

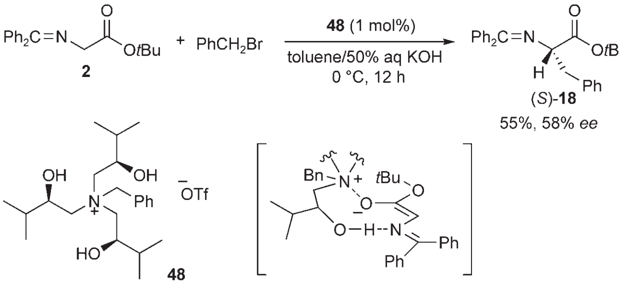
Takabe, Mase, and co-workers prepared the C_3-symmetric amine-based chiral phase-transfer catalyst **48** and applied it to the asymmetric benzylation of **2**. The observed asymmetric induction was attributed to the hydrogen-bonding interaction between the hydroxy groups of the catalyst and nitrogen atom of the *Z*-enolate in the proposed nine-membered cyclic ion pair (Scheme 28).[39]



Scheme 26. Chiral bis(ammonium) salts **46** derived from tartrate and pyrroline.



Scheme 27. Chiral bis(spiroammonium) salt **47** as a phase-transfer catalyst.

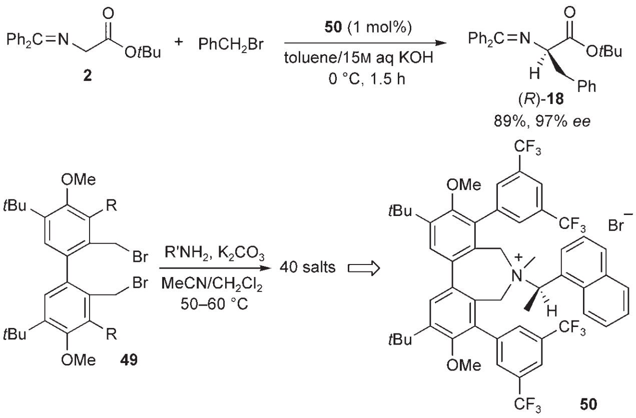


Scheme 28. C_3-symmetric chiral phase-transfer catalyst **48**.

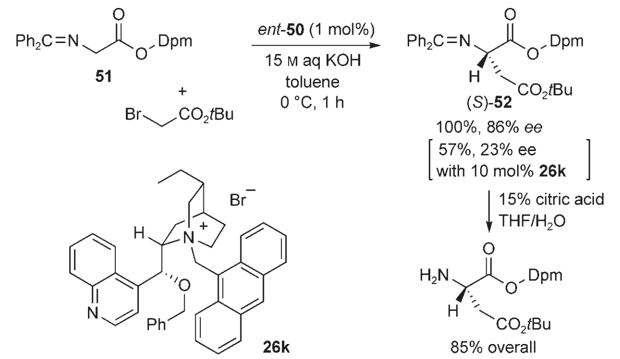
Lygo et al. constructed a library of 40 quaternary ammonium salts through the reaction of commercially available chiral secondary amines and a series of conformationally flexible biphenyl units **49** based on a similar concept as described in Scheme 18. Screening of the library against the asymmetric benzylation of **2** under liquid–liquid phase-transfer conditions led to the identification of a highly effective catalyst **50** that exhibited impressive catalytic activity and enantioselectivity (Scheme 29).[40]

Another advantage of catalyst **50** was that it allowed the use of the Schiff base **51** of glycine diphenylmethyl (Dpm) ester as an excellent alternative to **2**. For example, the alkylation of **51** with *tert*-butyl bromoacetate in the presence of *ent*-**50** under similar conditions afforded the desired **52** quantitatively with high enantiomeric excess, thus providing access to a differentially protected L-aspartic acid derivative (Scheme 30).[41] This transformation is difficult to achieve with catalysts such as **26k** derived from cinchona alkaloids.

Belokon, Vyskocil, Kagan, and co-workers introduced a substrate–catalyst combination for the asymmetric synthesis of α-amino acids. Achiral nickel(II) complex **53** undergoes highly enantioselective phase-transfer alkylation in the presence of (*R*)-2-hydroxy-2′-amino-1,1′-binaphthyl (nobin, **54**) as

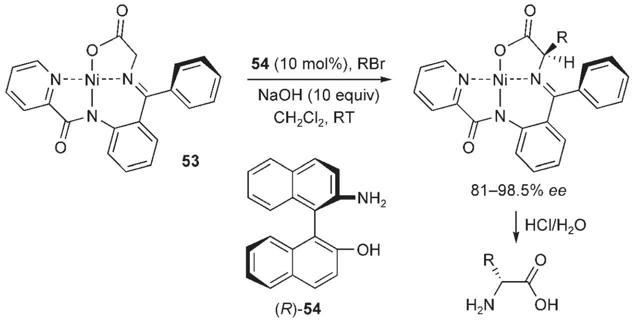


Scheme 29. Catalyst **50** consisting of a chiral secondary amine and a conformationally flexible biphenyl unit.



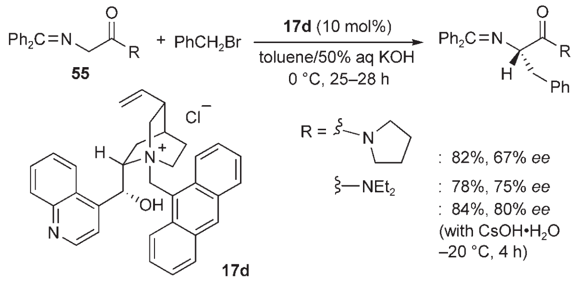
Scheme 30. Schiff base **51** of glycine diphenylmethyl ester as substrate. Dpm = $CHPh_2$.

a catalyst and NaOH or NaH as a base (Scheme 31).[42] A significant positive nonlinear effect was observed in the alkylation of **53** with benzyl bromide, thus suggesting that the ionized nobin phenolate generates heterochiral aggregates of lower reactivity (or greater stability); either homochiral aggregates or the remaining monomer are the active species.



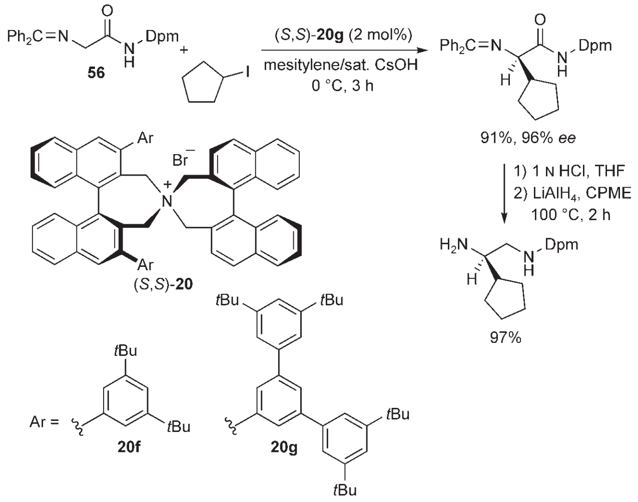
Scheme 31. Alkylation of **53** with nobin (**54**) as catalyst.

Not only esters but also amides of glycine can be used as prochiral Schiff bases for asymmetric alkylation under phase-transfer conditions. Kumar and Ramachandran demonstrated the effectiveness of cinchonidine-derived catalyst **17d** for the benzylation of various Schiff bases of tertiary glycine amides **55** (Scheme 32).[43] Generally, low enantioselectivity was observed in the reaction of substrates with secondary amide groups.



Scheme 32. Prochiral Schiff bases of glycine amides as substrates.

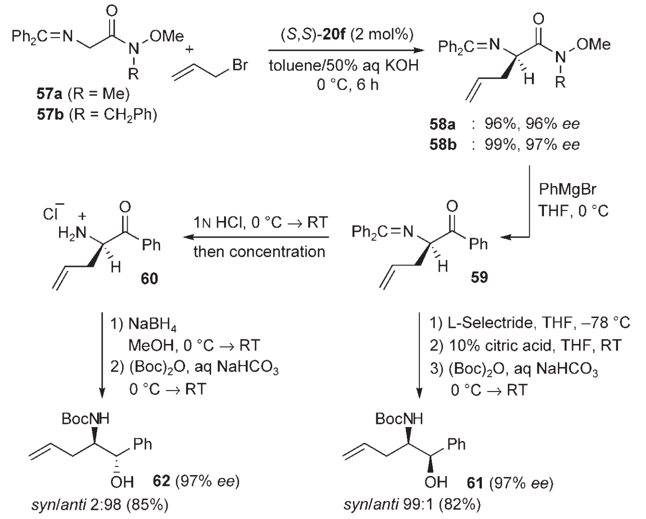
By using glycine diphenylmethyl (Dpm) amide derived Schiff base **56** as a key substrate and chiral N-spiro-ammonium bromide **20g** as an ideal catalyst, we achieved high enantioselectivity even in the alkylation with less-reactive simple secondary alkyl halides. This system offers facile access to structurally diverse optically active vicinal diamines after subsequent reduction (Scheme 33).[44]



Scheme 33. Asymmetric alkylation of glycine diphenylmethyl ester Schiff base **56**. CPME = cyclopentyl methyl ether.

Furthermore, our approach was also successful in the asymmetric alkylation of Weinreb amide derivative **57** with catalyst **20f** (Scheme 33). Optically active α-amino acid Weinreb amide **58** can be efficiently converted into the corresponding amino ketone by a simple treatment with Grignard reagents. The reduction and alkylation of the optically active α-amino ketones **59** and **60** into both *syn*- and *anti*-α-amino alcohols **61** and **62**, respectively, have been achieved with almost complete relative and absolute stereochemical control (Scheme 34).[45]

Despite numerous efforts to develop the asymmetric phase-transfer-catalyzed alkylation of **2** into a powerful method for the synthesis of natural and unnatural α-amino



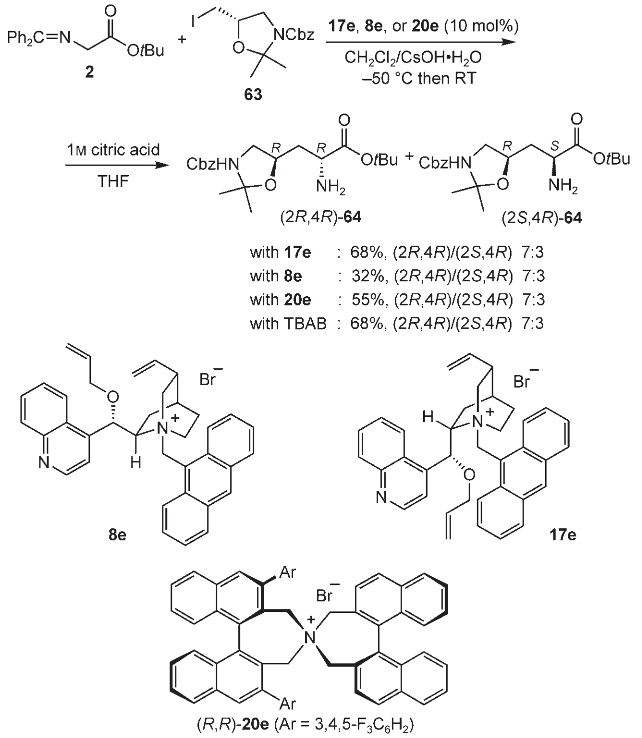
Scheme 34. Asymmetric alkylation of glycine Weinreb amide Schiff base **57**.

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-2,2-dimethyloxazolidine (**63**) in the presence of catalyst **17e** to prepare (2*S*,4*R*)-4-hydroxyornithine for the total synthesis of biphenomycin. Unexpectedly, however, product **64** with a 2*R* absolute configuration was formed as a major isomer. Furthermore, the diastereomeric ratio was not affected by the configuration and structure of the catalysts employed, thus indicating that the asymmetric alkylation was dictated by the substrate (Scheme 35).[46]

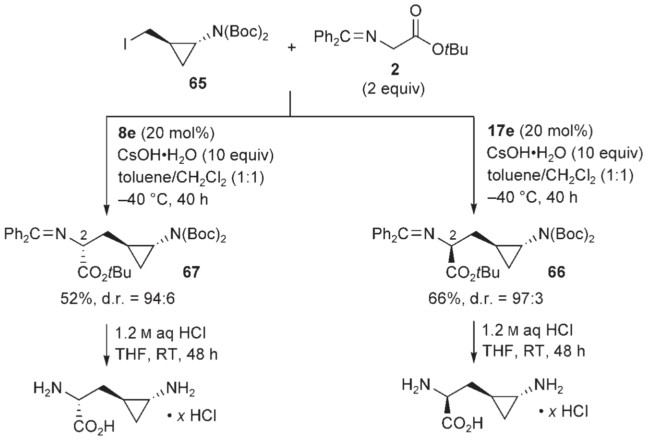
Armstrong and Scutt reported a concise synthesis of 3-(*trans*-2-aminocyclopropyl)alanine, a component of balactosin A, through the highly diastereoselective alkylation of **2** with optically pure alkyl iodide **65** under phase-transfer conditions. The desired products **66** and **67** were obtained in good yields under optimized conditions, with the C2 configuration rigorously controlled by the configuration of the catalyst (Scheme 36).[47]

During our study on the stereoselective functionalization of **56** we found that the chiral ammonium enolate generated from **20g** and **56** had the ability to recognize the configuration of chiral β-branched primary alkyl halides. Impressive levels of kinetic resolution were obtained during the alkylation of racemic halide **68**, which allowed the α- and γ-stereocenters of **69** to be built in a controlled manner (Scheme 37).[45]

Alkyl halides are typically employed as alkylation agents in the asymmetric alkylation of a prochiral protected glycine derivative such as **2** by chiral phase-transfer catalysis. Takemoto and co-workers developed a palladium-catalyzed asymmetric allylic alkylation of **2** using allylic acetates and a chiral phase-transfer catalyst such as **17i**. The choice of the achiral palladium ligand was crucial to achieve high enantioselectivity, with $(PhO)_3P$ giving the best results. Since this asymmetric allylation proceeds via a π-allylpalladium(II) intermediate, both primary and secondary allylic acetates give the same allylation products (Scheme 38).[48]



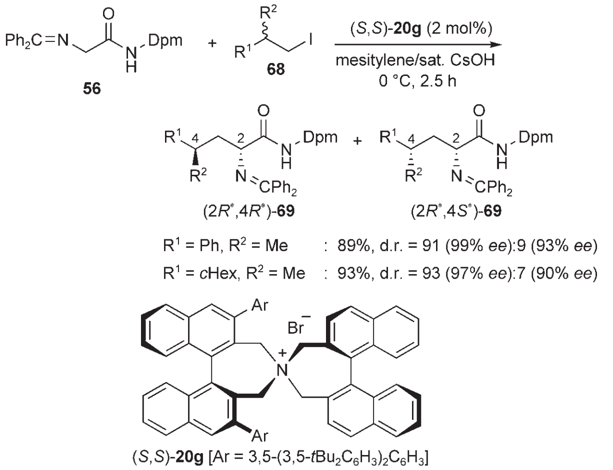
Scheme 35. Alkylation of **2** with β-chiral primary alkyl halides **63**. Cbz = benzyloxycarbonyl.



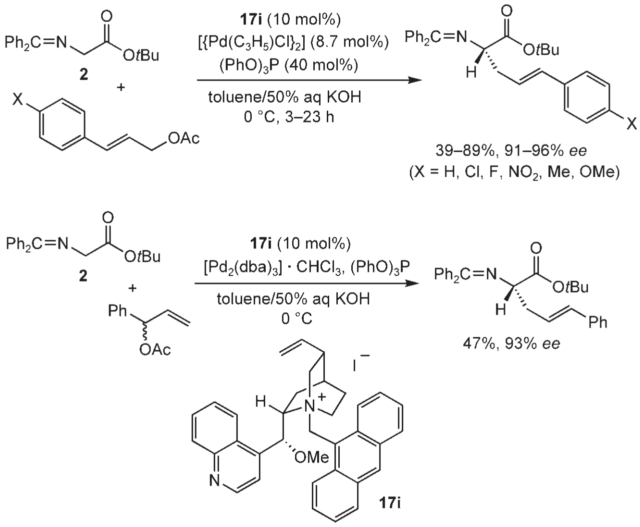
Scheme 36. Enantioselective construction of the C2 stereocenter in the alkylation of **2** with β-chiral primary alkyl halides **65**.

From a practical viewpont, a homogeneous system was desired. This goal has been realized by using an organic-soluble, non-ionic phosphazene base in combination with **17e** (Scheme 39).[49] By using either Schwesinger base BEMP or BTPP, only a small amount of the anion of **2** would be generated at equilibrium. This anion could then be removed by reaction with the alkyl halide after fast counterion exchange with **17e**. This in turn would serve to drive the formation of further enolate anion by reestablishing the acid/base equilibrium.

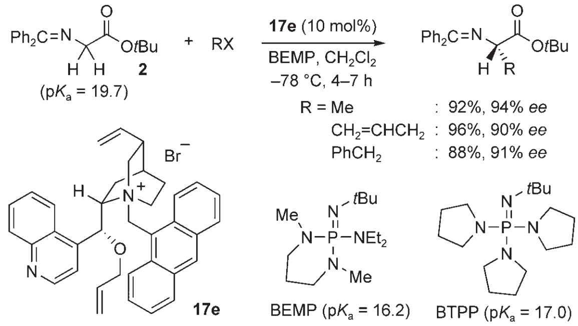
Catalytic enantioselective alkylations of **2** have been carried out with polymer-bound glycine substrates (Scheme 40) or in the presence of polymer-supported ammo-



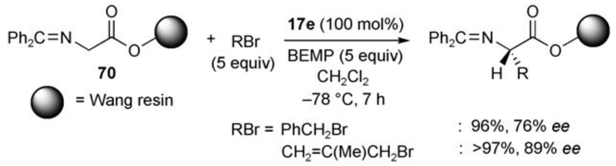
Scheme 37. Kinetic resolution in the asymmetric alkylation of **56** with racemic **68**.



Scheme 38. Palladium-catalyzed allyation with the chiral phase-transfer catalyst **17i**. dba = *trans*,*trans*-dibenzylideneacetone.



Scheme 39. Use of organic-soluble phosphazene bases BEMP and BTPP.



Scheme 40. Solid-phase synthesis with Wang-resin-bound Schiff base **70**.

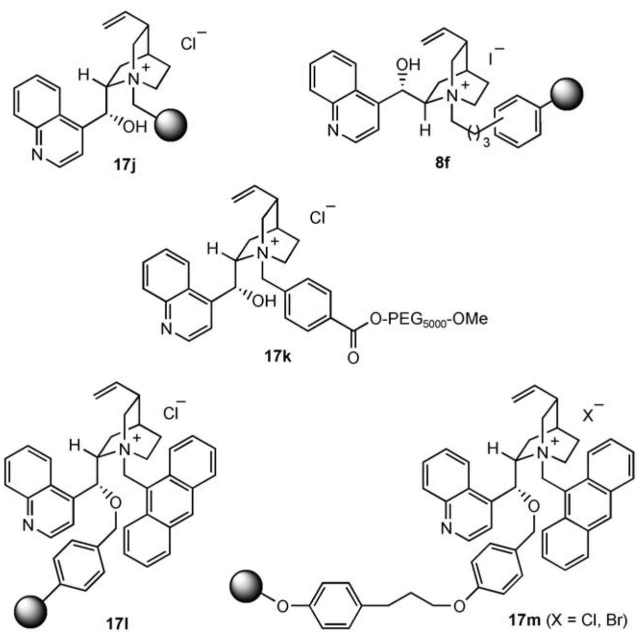
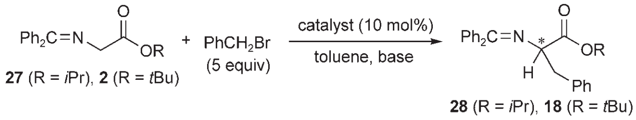


Figure 3. Polymer-supported chiral phase-transfer catalysts.

Table 2: Asymmetric benzylation of glycinate Schiff base with polymer-supported chiral phase-transfer catalysts.



Entry	Catalyst	Substrate	Base	T [°C]	t [h]	Yield [%]	*ee* [%]
1	**17j**	**27**	25% aq NaOH	0	17	90	90 (*S*)
2	**8f**	**2**	50% aq KOH	0	15	60	81 (*R*)
3	**17k**	**2**	50% aq KOH	0	15	84	81 (*S*)
4	**17l**	**2**	CsOH·H$_2$O	−50	30	67	94 (*S*)
5[a]	**17m**	**2**	CsOH·H$_2$O	−78	60	75	64 (*S*)

[a] CH$_2$Cl$_2$ was used as solvent.

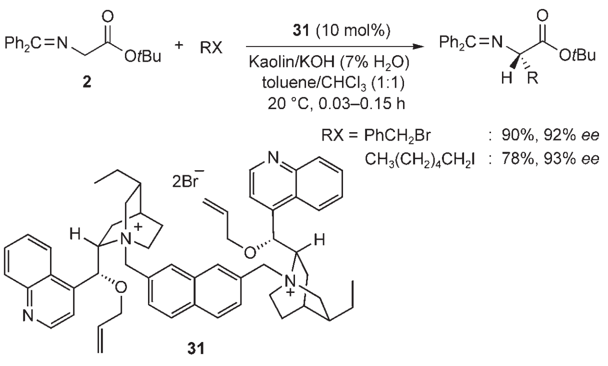
nium salts derived from cinchona alkaloids (Figure 3 and Table 2) as chiral phase-transfer catalysts. As an example of the former approach, O'Donnell et al. used Wang-resin-bound derivative **70** in combination with BEMP or BTPP and the third-generation catalyst **17e**.[50] Although the optimal conditions required a full equivalent of **17e**, the promising results created a basis for further optimization.

The importance of the second route is recognizable, since the enantioselective synthesis of α-amino acids by using readily available and reusable chiral catalysts presents clear advantages for large-scale synthesis. Nájera and co-workers prepared resin-supported ammonium salt **17j** by reaction of cross-linked chloromethylated polystyrene (Merrifield resin) and used it as a chiral phase-transfer catalyst for the alkylation of the Schiff base **27** derived from glycine isopropyl ester.[51] Optimization of the reaction parameters in the benzylation led to the formation of **28** in 90% yield and 90% *ee* (entry 1 in Table 2). Cahard and co-workers investigated the role of flexible methylene spacers between the quaternary ammonium moiety and the polystyrene backbone in the benzylation of **2**. They found that catalyst **8f** anchored to the matrix through a butyl group was optimal, and gave **18** with 81% *ee* (entry 2).[52] This research group also grafted a quaternary ammonium salt derived from cinchonidine to a poly(ethylene glycol) matrix **17k**. This catalyst was found to be efficient for the homogeneous asymmetric alkylation of **2**: up to 81% *ee* was attained in the benzylation under standard liquid–liquid phase-transfer conditions (entry 3).[53] Cahard, Plaquevent, and co-workers also succeeded in improving the enantioselectivity by attaching the Merrifield resin to the hydroxy group of catalyst **17l**, which possesses a 9-anthracenylmethyl group on the nitrogen atom (entry 4).[54] Benaglia and co-workers immobilized the third-generation catalyst on modified poly(ethylene glycol) through the alkylation of the C9 hydroxy group. The chiral ammonium salt **17m** thus obtained acts as a catalyst in the benzylation of **2** to afford **18** with a maximum of 64% *ee* (entry 5).[55]

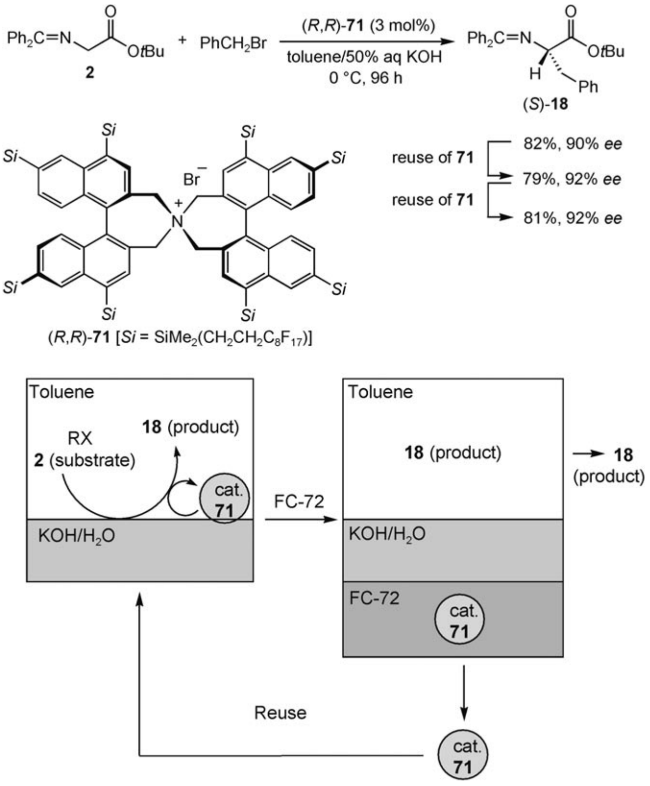
Koshima and co-workers reported the use of a solid support preloaded with base for the asymmetric alkylation of **2**. Typically, a solution of **2**, alkyl halide, and catalyst **31** in toluene/$CHCl_3$ was slowly dispersed on kaolin clay preloaded with KOH and the so-obtained solid was kept at 20°C. Residual traces of water on the support dramatically accelerated the reaction to completion within a few minutes, thus giving rise to the corresponding alkylation product in good yields and high enantioselectivities (Scheme 41).[56]

We have developed a recyclable fluorous chiral phase-transfer catalyst **71** for the highly efficient asymmetric alkylation of **2**. After the reaction, **71** could be easily recovered by simple extraction with FC-72 (perfluorohexanes) and could be reused without any loss of reactivity and selectivity (Scheme 42).[57]

In this section we have outlined the development of enantioselective monoalkylation of glycine-derived Schiff bases, particularly the Schiff base of *tert*-butyl glycinate and benzophenone (**2**), and its significant improvement in terms of reactivity and selectivity. Most of the elaborated phase-transfer catalysts have been evaluated in the asymmetric alkylation of **2**. Table 3 gives an overview of the relationship between the structure, activity, and stereoselectivity of the catalysts in this reaction.



Scheme 41. Application of a solid support preloaded with KOH.



Scheme 42. Application of the recyclable fluorous chiral phase-transfer catalyst **71**.

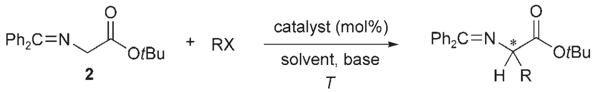
3.2.2. Asymmetric Synthesis of Valuable α-Amino Acid Derivatives and Biologically Active Compounds

The vast synthetic utility of the asymmetric phase-transfer alkylation of a prochiral protected glycine derivative **2** has been in the synthesis of various useful amino acid derivatives and natural products. Imperiali and Fisher completed the enantioselective synthesis of (*S*)-α-amino-(2,2′-bipyridin-6-yl)propanoic acid (**72**) through the asymmetric alkylation of **2** with 6-(bromomethyl)-2,2′-bipyridine in the presence of catalyst **17a** (Scheme 43).[58] Amino acid **72** has been incorporated into two model peptides to prepare unnatural metal-binding amino acids.

The research groups of Imperiali and Bowler independently prepared 2-amino-3-(2,2′-bipyridinyl)propanoic acids **73** and **74** in a similar manner. These compounds contain an unobstructed N,N′ chelation moiety and hence are expected to provide metal-binding properties complementary to those reported for **72**.[59]

The stereoselective synthesis of the pyridoxol amino acid derivative **77** has also been accomplished by Imperiali and

Table 3: Comparison of representative catalysts in their performance in the phase-transfer-catalyzed alkylation of **2**.



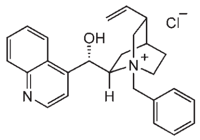
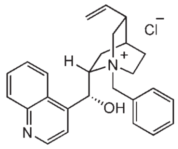
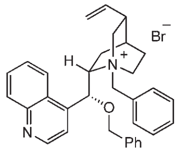
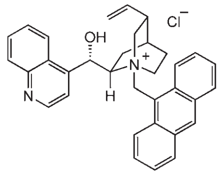
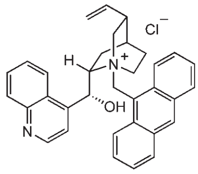
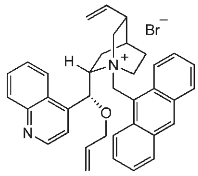
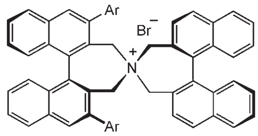
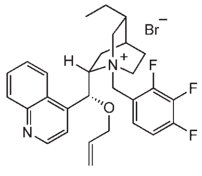
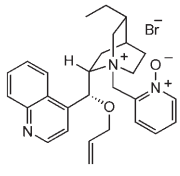
Entry		Catalyst (mol%)	Solvent Base	T [°C]	Yield, *ee* [%] with PhCH$_2$Br with CH$_2$=CHCH$_2$Br	Number of RX (or E$^+$)	Yield [%]	*ee* [%]	Ref.
1	**8c** (10)		CH$_2$Cl$_2$ 50% NaOH	25	75, 66 (*R*) 75, 66 (*R*)	6	60–82	42–66	[10a]
2	**17a** (10)		CH$_2$Cl$_2$ 50% NaOH	25	85, 64 (*S*) 78, 62 (*S*)	4	78–85	48–64	[10a]
3	**17c** (10)		toluene/CH$_2$Cl$_2$ (7:3) 50% NaOH	5	87, 81 (*S*) –	–	–	–	[10c]
4	**8d** (10)		toluene 50% KOH	25	63, 89 (*R*) 62, 88 (*R*)	7	40–86	67–89	[13a, c]
5	**17d** (10)		toluene 50% KOH	25	68, 91 (*S*) 76, 88 (*S*)	8	41–84	68–91	[13a, c]
6	**17e** (10)		CH$_2$Cl$_2$ CsOH·H$_2$O	−78 or −60	87, 94 (*S*) 89, 97 (*S*)	11	67–91	92–99.5	[14]
7	(*S*,*S*)-**20e** Ar = 3,4,5-F$_3$C$_6$H$_2$ (1)		toluene 50% KOH	0	90, 99 (*R*) 80, 99 (*R*)	14[a]	80–98	96–99	[16e]
8	**26e** (10)		toluene/CHCl$_3$ (7:3) 50% KOH	−20	96, 98 (*S*) 95, 96 (*S*)	12	60–96	94–>99	[18]
9	**26h** (5)		toluene/CHCl$_3$ (7:3) 50% KOH	−20	93, 98 (*S*) 94, 97 (*S*)	9	80–97	97–>99	[19]

Table 3: (Continued)

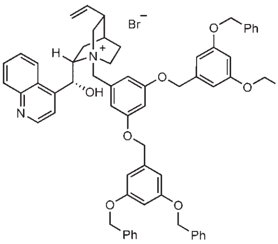
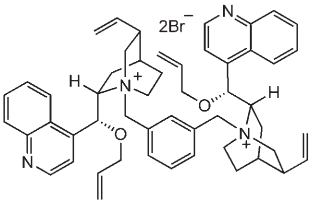
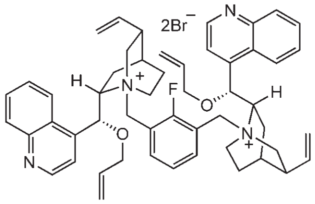
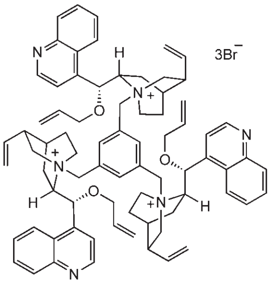
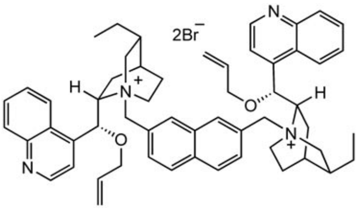
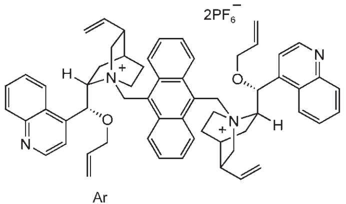
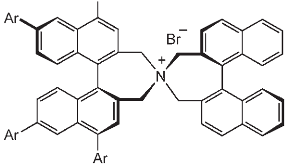
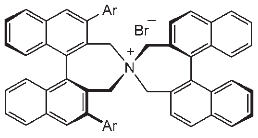
Entry	Catalyst (mol%)	Solvent Base	*T* [°C]	Yield, *ee* [%] with $PhCH_2Br$ with $CH_2{=}CHCH_2Br$	Number of RX (or E^+)	Yield [%]	*ee* [%]	Ref.
10[b]	**17g** (10) 	toluene/$CHCl_3$ (7:3) 50% KOH	−20	94, 72 (*S*) –	3	87–94	68–72	[20a]
11	**29a** (5) 	toluene/$CHCl_3$ (7:3) 50% KOH	−20	94, 95 (*S*) 86, 94 (*S*)	12	50–98	90–99	[21a]
12	**29b** (5) 	toluene/$CHCl_3$ (7:3) 50% KOH	−20	94, 98 (*S*) 92, 97 (*S*)	6	81–94	97–>99	[21b]
13	**30** (3) 	toluene/$CHCl_3$ (7:3) 50% KOH	−20	94, 94 (*S*) 90, 95 (*S*)	10	65–95	90–97	[22]
14	**31** (1) 	toluene/$CHCl_3$ (7:3) 50% KOH	0	95, 97 (*S*) 95, 97 (*S*)	13	70–95	94–>99	[23]
15	**32d** (5) 	toluene/$CHCl_3$ (7:3) 50% KOH	0	62, 84 (*S*) 70, 90 (*S*)	4	62–72	84–90	[25]
16	(*S*,*S*)-**33c** Ar = 3,5-$Ph_2C_6H_3$ (1) 	toluene 50% KOH	0	88, 96 (*R*) 92, 88 (*R*)	4	88–93	88–96	[26]
17	(*S*,*S*)-**20d** Ar = 3,5-$Ph_2C_6H_3$ + [18]crown-6 (**34**) (0.1) 	toluene 50% KOH	0	98, 98 (*S*) 87, 85 (*S*)	4[c]	70–98	85–98	[28]

Table 3: (Continued)

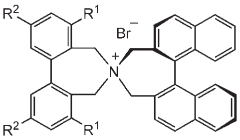
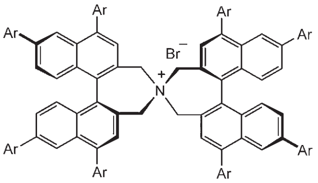
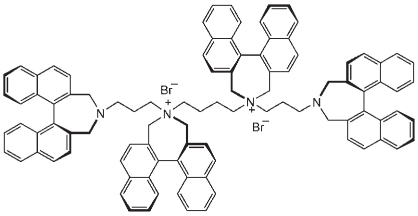
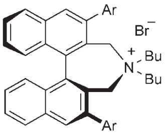
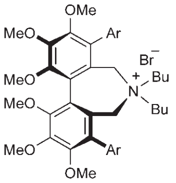
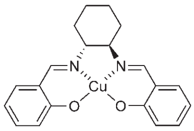
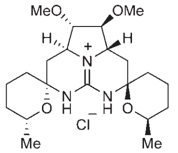
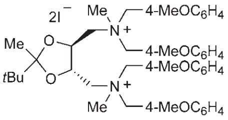
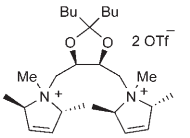
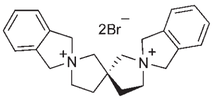
Entry	Catalyst (mol%)	Solvent Base	T [°C]	Yield, *ee* [%] with $PhCH_2Br$ with $CH_2{=}CHCH_2Br$	Number of RX (or E^+)	Yield [%]	*ee* [%]	Ref.
18	(*S*)-**35c** $R^1 = 3,5\text{-}Ph_2C_6H_3$, $R^2 = Ph$ (1) 	toluene sat. CsOH	−15	87, 94 (*R*) 85, 93 (*R*)	4	61–91	93–94	[29]
19	(*S*,*S*)-**36a** $Ar = 3,5\text{-}Ph_2C_6H_3$ (1) 	toluene 50% KOH	0	87, 97 (*R*) 76, 93 (*R*)	4	76–91	93–97	[30]
20	(*S*)-**38a** (3) 	toluene 50% KOH	0	76, 63 (*S*) –	–	–	–	[31]
21	(*S*)-**39** $Ar = 3,4,5\text{-}F_3C_6H_2$ (0.05) 	toluene 50% KOH	0	98, 99 (*R*) 87, 98 (*R*)	5[d]	67–98	97–99	[32]
22	(*S*)-**40** $Ar = 3,4,5\text{-}F_3C_6H_2$ (0.05–0.1) 	toluene 50% KOH	0–25	94, 97 (*R*) 99, 96 (*R*)	5	80–99	94–97	[33]
23	**42** (2) 	toluene NaOH (solid)	25	>95, 80 (*R*) >90, 81 (*R*)	5	12–>95	7–81[e]	[34]
24	**44** (30) 	CH_2Cl_2 1 M KOH	0	55, 90 (*R*) 61, 81 (*R*)	9	55–85	76–90	[35]
25	(*S*,*S*)-**45a** (10) 	toluene/CH_2Cl_2 (7:3) $CsOH{\cdot}H_2O$	−70	87, 93 (*R*) 79, 91 (*R*)	11	71–93	80–94	[36b]
26	**46a** (5) 	CH_2Cl_2 CsOH	−45	73,[f] 30 (*R*) 75,[f] 28 (*R*)	6	39–85[f]	−12–30	[37]
27	**47** (20) 	CH_2Cl_2 50% KOH	0	>95, 95 (*R*) –	–	–	–	[38]

Table 3: (Continued)

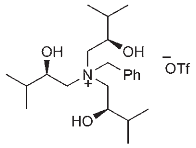
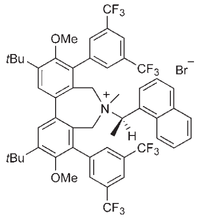
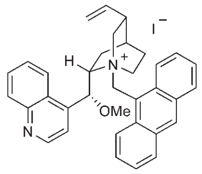
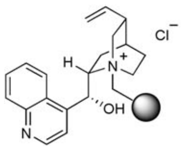
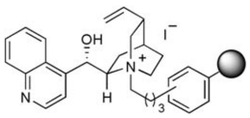
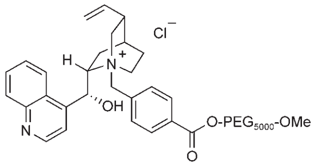
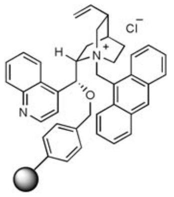
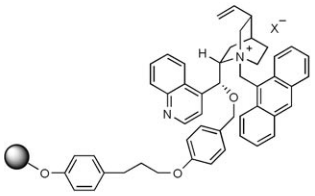
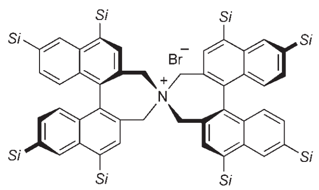
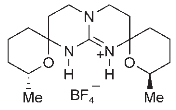
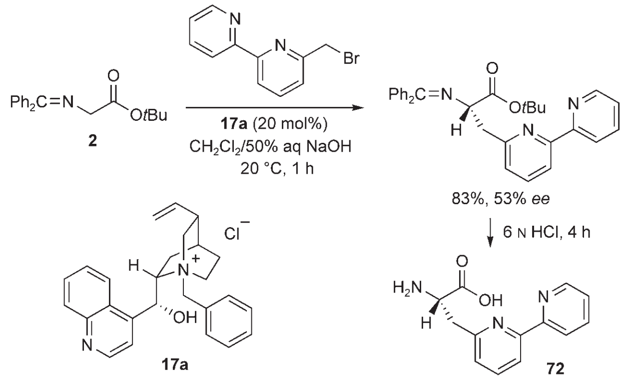
Entry	Catalyst (mol %)		Solvent Base	T [°C]	Yield, *ee* [%] with $PhCH_2Br$ with $CH_2{=}CHCH_2Br$	Number of RX (or E^+)	Yield [%]	*ee* [%]	Ref.
28	**48** (1)		toluene 50% KOH	0	55, 58 (*S*) –	–	–	–	[39]
29	**50** (1)		toluene 15 M KOH	0	89, 97 (*R*) 83, 94 (*R*)	6	71–100	89–97	[40]
30	**17i** + $[\{Pd(C_3H_5)Cl\}_2]$, $(PhO)_3P$ (10)		toluene 50% KOH	0	– –	6[g]	39–89	91–96	[48]
31[b]	**17j** (10)		toluene 25% NaOH	0	90, 90 (*S*) 75, 32 (*S*)	14	22–90	20–90	[51b]
32	**8f** (10)		toluene 50% KOH	0	60, 81 (*R*) 76, 37 (*R*)	4	60–80	37–81	[52]
33	**17k** (10)		toluene 50% KOH	0	84, 81 (*S*) –	3	63–84	20–81	[53]
34	**17l** (10)		toluene $CsOH{\cdot}H_2O$	−50	67, 94 (*S*) –	–	–	–	[54]
35	**17m** (X=Cl, Br) (10)		CH_2Cl_2 $CsOH{\cdot}H_2O$	−78	75, 64 (*S*) –	–	–	–	[55]
36	(*R*,*R*)-**71** [*Si*=$SiMe_2$ $\{(CH_2)_2C_8H_{17}\}$] (3)		toluene 50% KOH	0	82, 90 (*S*) –	5[h]	81–93	87–93	[57]

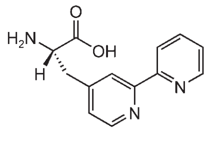
Table 3: (Continued)

Entry		Catalyst (mol %)	Solvent Base	T [°C]	Yield, *ee* [%] with $PhCH_2Br$ with $CH_2{=}CHCH_2Br$	Number of RX (or E^+)	Yield [%]	*ee* [%]	Ref.
37	**222** (10)		CH_2Cl_2 2 M NaOH	0→25	> 97,[f] 86 (*R*) –	–	–	–	[149]

[a] Use of sat. CsOH as a base at −15 °C for MeI and EtI. [b] Isopropyl glycinate benzophenone Schiff base (**27**) was employed as the substrate. [c] With 0.05 mol % each of (*S*,*S*)-**20d** and **34** for 1-(bromomethyl)naphthalene and 0.5 mol % each for EtI. [d] With 0.1 mol % of (*S*)-**39** and CsOH·H_2O as a base for EtI. [e] This system is not effective for simple RX compounds such as MeI and EtI. [f] Conversion. [g] Allylic acetates were used as electrophiles E^+. [h] With CsOH·H_2O as a base at −20 °C in α,α,α-trifluorotoluene for EtI.



Scheme 43. Stereoselective synthesis of the α-amino acid **72** incorporating a 2,2′-bipyridine unit.



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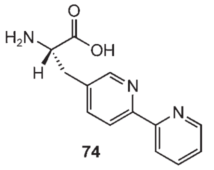

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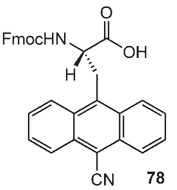
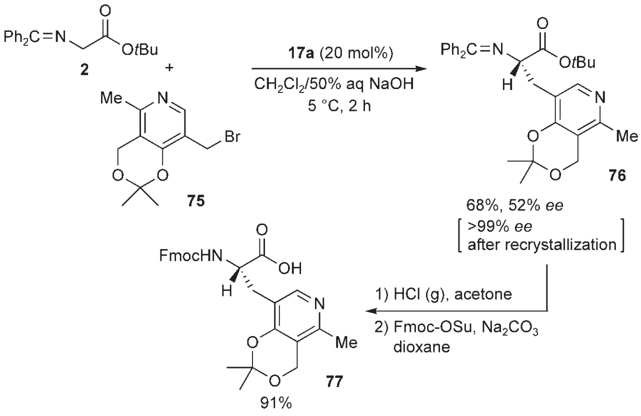
Roy, and it has been incorporated into oligopeptides and subsequently converted into reactive pyridoxal analogues. The key step involves an enantioselective alkylation of **2** with bromide **75** in the presence of catalyst **17a** to furnish **76** (52 % *ee*). One recrystallization of the enantiomerically enriched product affords essentially enantiopure (> 99 % *ee*) material (Scheme 44).[60]

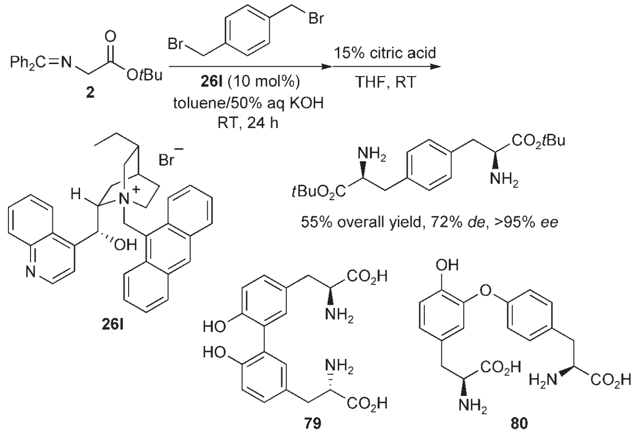
Torrado and Imperiali synthesized the novel amino acid **78** (in a similar way as that of O'Donnell), and incorporated it into peptides through solid-phase synthesis. This afforded a prototype for a chemosensor for metal ions based on photoinduced electron transfer.[61]



Lygo et al. utilized *N*-anthracenylmethyldihydrocinchonidinium bromide (**261**) for the enantio- and diastereoselective synthesis of a series of bis(α-amino esters). This approach was further extended to the enantio- and diastereoselective synthesis of dityrosine **79** and isodityrosine **80** which represent the simplest members of a group of naturally occurring tyrosine-derived α-amino acids and peptides that contain oxidatively coupled aromatic nuclei (Scheme 45).[62]



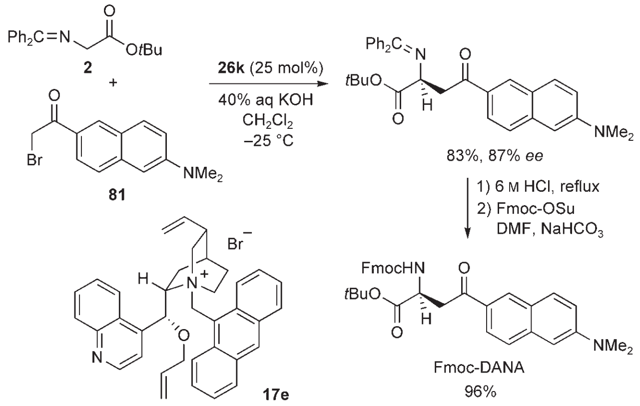
Scheme 44. Stereoselective synthesis of a pyridoxol-substituted amino acid derivative **77**. Fmoc-OSu = 9-(fluorenylmethyloxycarbonyl)succinimidyl carbonate.



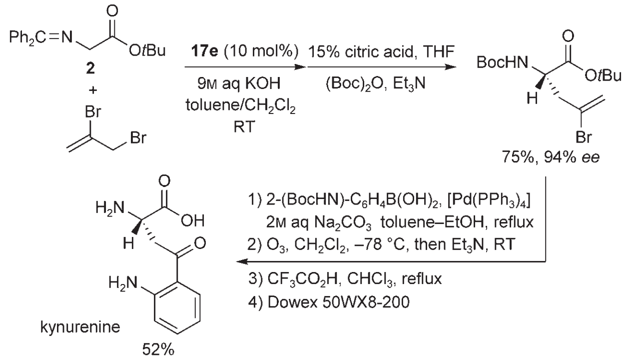
Scheme 45. Stereoselective synthesis of bis-α-amino acids.

6-(2-Dimethylaminonaphthoyl)alanine (DANA) was prepared by Imperiali and co-workers as a highly fluorescent amino acid through the asymmetric alkylation of **2** with α-bromo ketone **81** and **17e** as a phase-transfer catalyst (Scheme 46). The compound was incorporated into the S-peptide of RNase S to show peptide–protein interactions through large changes in fluorescence.[63]

Lygo and Andrews developed an alternative route to aroylalanine derivatives. They employed 2,3-dibromopropene as a masked α-halo ketone in combination with Suzuki–Miyaura coupling and ozonolysis (Scheme 47).[64]

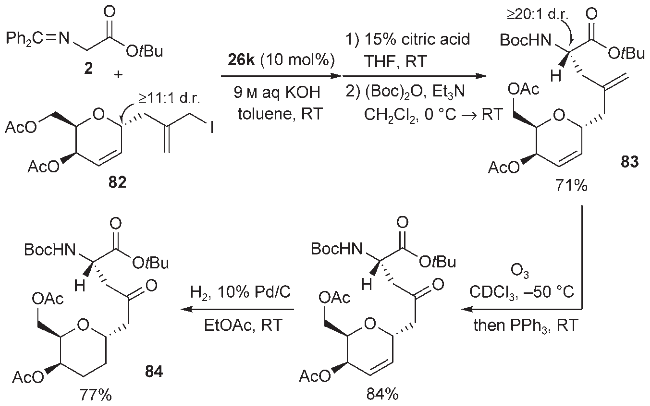


Scheme 46. Enantioselective synthesis of the Fmoc derivative of 6-(2-dimethylaminonaphthoyl)alanine (DANA). Fmoc = 9-fluorenylmethoxycarbonyl.



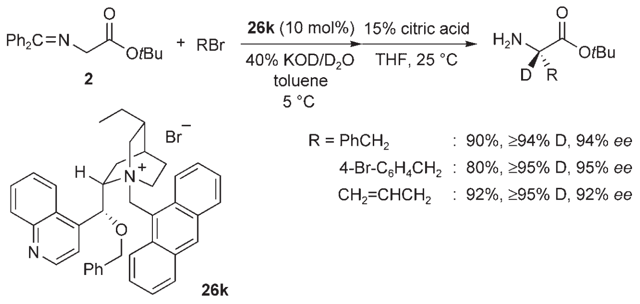
Scheme 47. Enantioselective synthesis of aroylalanine derivatives.

A similar strategy was also used for the stereoselective synthesis of C-glycosylasparagines. For example, the liquid–liquid phase-transfer alkylation of **2** with stereochemically defined allylic iodide **82** followed by imine hydrolysis and reprotection afforded **83** in 71% overall yield and high diastereoselectivity. The selective oxidative cleavage of the 1,1-disubstituted olefin and subsequent hydrogenation of the remaining double bond furnished the target compound **84** (Scheme 48).[65]



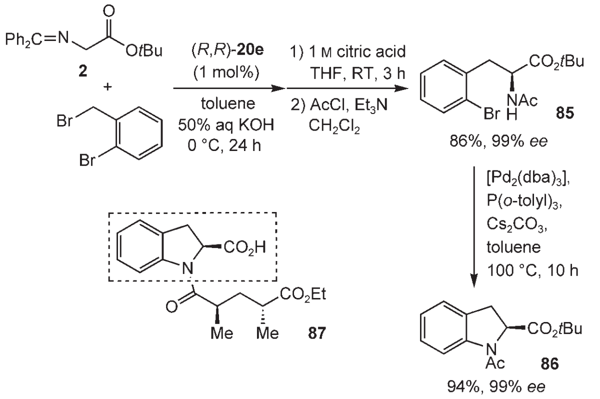
Scheme 48. Stereoselective synthesis of C-linked glycosylasparagine derivatives **84**.

Another useful feature of the phase-transfer alkylation of **2** was also demonstrated by Lygo and Humphreys: rapid H/D exchange of **2** when using KOD/D$_2$O as the aqueous phase. This method offers a convenient yet efficient means of preparing labeled α-amino acid esters (Scheme 49).[66]



Scheme 49. Enantioselective synthesis of α-deuterated α-amino acid esters.

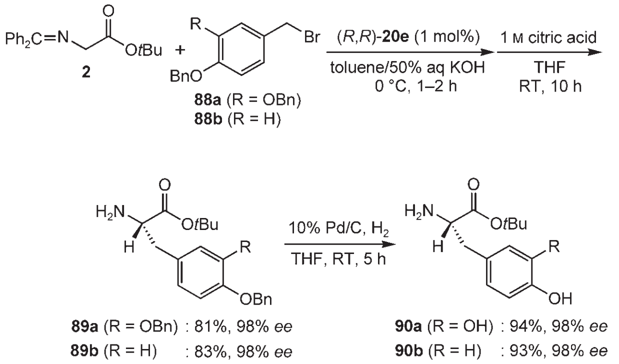
Since both enantiomers of **20e** are accessable, we carried out the asymmetric synthesis of (*S*)-*N*-acetylindoline-2-carboxylate (**86**), a key intermediate in the synthesis of the ACE inhibitor **87**. Asymmetric alkylation of **2** with *o*-bromobenzyl bromide in the presence of (*R*,*R*)-**20e**, followed by hydrolysis and N acetylation afforded **85** in 86% yield with the required configuration (99% *ee*). Almost enantiopure **85** was efficiently converted into **86** (94%, 99% *ee*) by following Buchwald's procedure (Scheme 50).[16e]



Scheme 50. Asymmetric synthesis of (*S*)-*N*-acetylindoline-2-carboxylate (**86**).

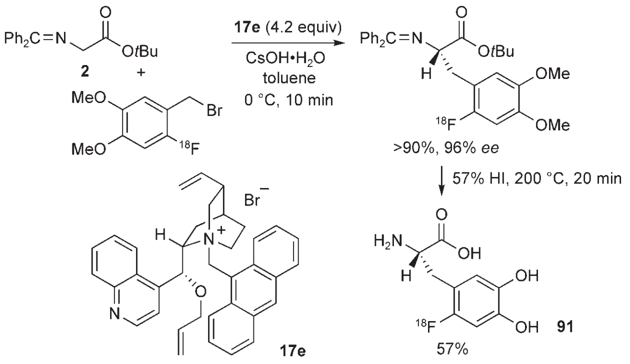
Asymmetric phase-transfer catalysis with **20e** was further applied to the facile synthesis of L-Dopa ester and its analogues, which have usually been prepared by either asymmetric hydrogenation of eneamides or enzymatic processes and tested as potential drugs for the treatment of Parkinson's disease. Phase-transfer-catalyzed alkylation of **2** with benzyl bromide **88a** in toluene/50% aqueous KOH solution proceeded smoothly at 0 °C under the influence of (*R*,*R*)-**20e** to furnish fully protected L-Dopa *tert*-butyl ester, which was subsequently hydrolyzed to afford the corresponding amino ester **89a** in 81% yield and 98% *ee*. Debenzylation of **89a** by catalytic hydrogenation produced the desired

L-Dopa *tert*-butyl ester (**90a**) in 94% yield. The successful asymmetric synthesis of the natural tyrosine *tert*-butyl ester (**90b**) in a similar manner strongly implies the feasibility of synthesizing other L-Dopa analogues in a highly enantioselective manner (Scheme 51).[16e,67]



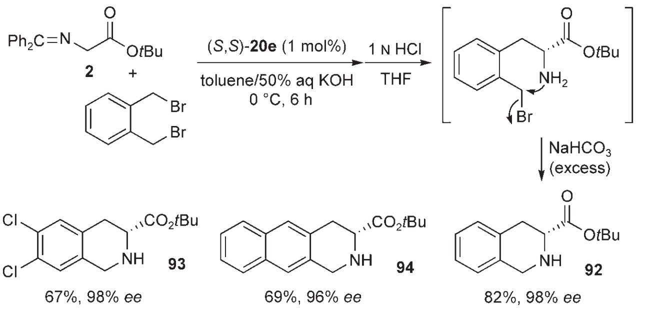
Scheme 51. Concise synthesis of L-Dopa ester **90a** and its analogue.

Lemaire et al. synthesized [^{18}F]fluoro-L-Dopa (**91**), 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 in the presence of $CsOH\cdot H_2O$ as a base and **17e** as the catalyst. Although an excess of **17e** was required, the reaction was completed within 10 min to give radiochemically and enantiomerically pure **91** after hydrolysis (Scheme 52).[68]



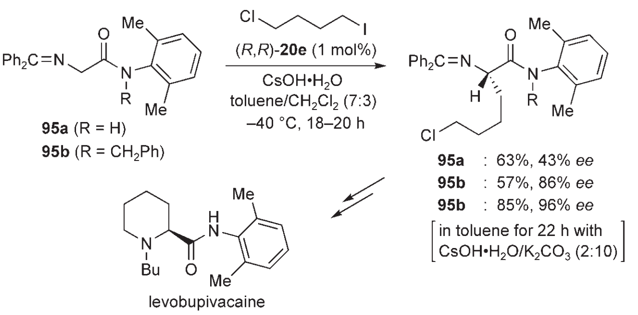
Scheme 52. Enantioselective synthesis of 6-[^{18}F]fluoro-L-Dopa (**91**).

The catalytic and chiral efficiency of (*S*,*S*)-**20e** was also used in the asymmetric synthesis of isoquinoline derivatives, which are 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*)-**20e** showed complete consumption of the starting Schiff base. Hydrolysis of the imine and subsequent treatment with excess $NaHCO_3$ facilitated intramolecular ring closure to give 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butyl ester (**92**) in 82% yield and 98% *ee*. A variety of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives, such as **93** and **94**, which have different aromatic substituents can be conveniently prepared in a similar manner in excellent enantioselectivity (Scheme 53).[69]



Scheme 53. Stereoselective entry to 1,2,3,4,-tetrahydroisoquinoline-3-carboxylate (**92**).

Kumar and Ramachandran reported an efficient catalytic route to levobupivacaine, an azacyclic amino acid amide with anaesthetic properties. The key step involves the (*R*,*R*)-**20e**-catalyzed asymmetric phase-transfer alkylation of glycine amide-derivative **95**. The N-benzylated **95b** was found to be more suitable as a substrate for attaining high selectivity (Scheme 54).[70]

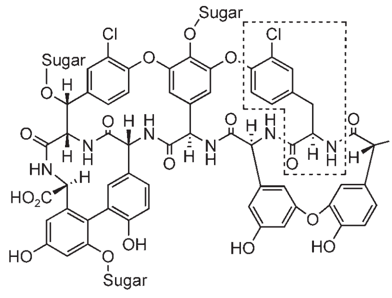


Scheme 54. Asymmetric synthesis of levobupivacaine.

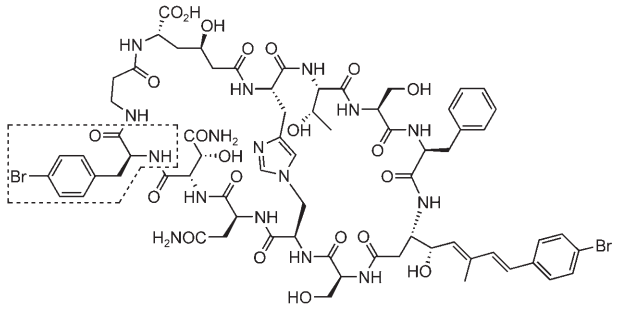
Rao et al. applied the enantioselective alkylation of **2** to the synthesis of the 16-membered cyclic tripeptide teicoplanin.[71] Shioiri and co-workers carried out the construction of theonellamide F, a bicyclic dodecapeptide of marine origin, through the asymmetric phase-transfer alkylation of **2** with *p*-bromobenzyl bromide.[72]

Castle and Srikanth showed that the alkylation of **2** with propargylic bromide **96** was catalyzed by the chiral quaternary ammonium bromide **26e** under phase-transfer conditions. The resulting enantiomerically enriched **97** was then transformed to **98**, the central tryptophan residue of celogentin C, through a palladium-catalyzed heteroannulation. This process allows the efficient assembly of tryptophan derivatives with substituents on the indole ring (Scheme 55).[73]

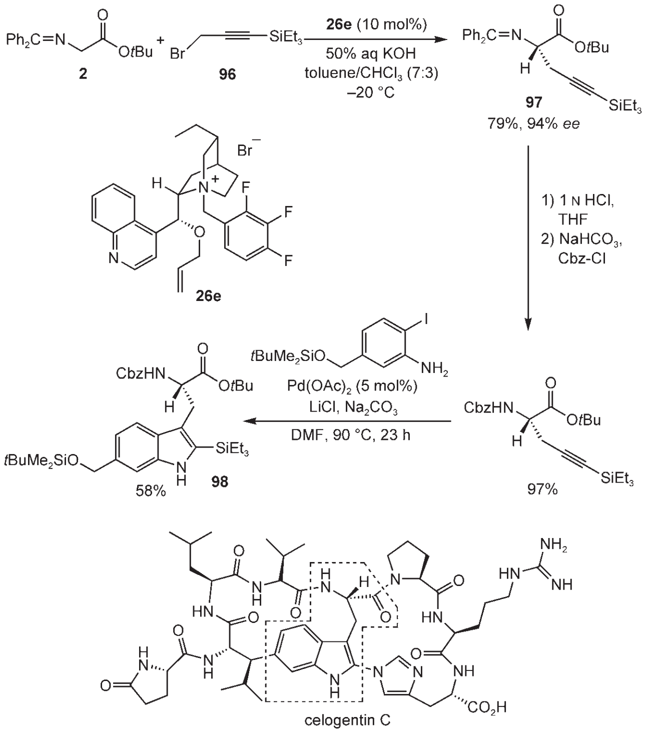
During the development of a practical enantioselective total synthesis of bengamides B, E, and Z, Boeckman et al. achieved the highly diastereoselective alkylation of **2** with optically active iodoepoxide **99** based on a protocol developed by Corey et al. Essentially diastereopure product **100** was successfully derivatized to the desired aminocaprolactam **101** (Scheme 56).[74]



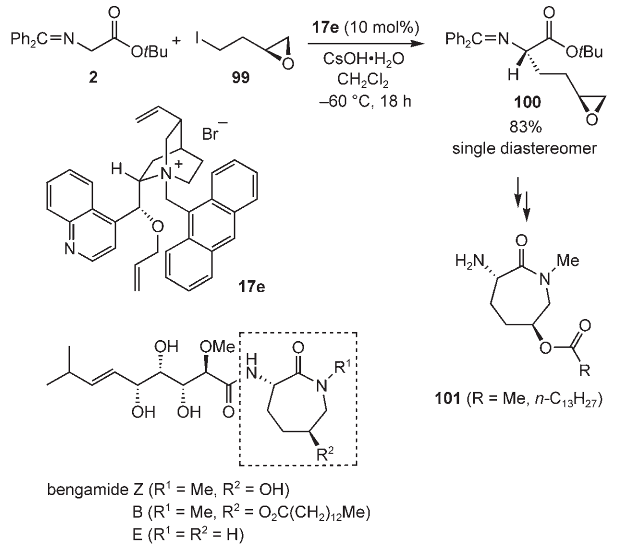
teicoplanin



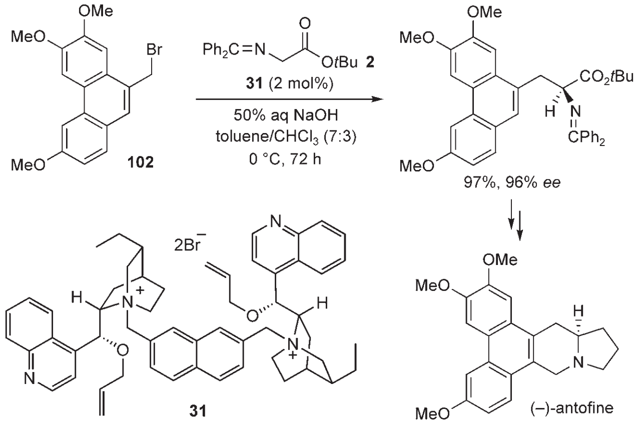
theonellamide F



Scheme 55. Asymmetric synthesis of the tryptophan residue of celogentin C.



Scheme 56. Preparation of **101**, an intermediate in the asymmetric total synthesis of bengamides B, E, and Z.



Scheme 57. A step in the total synthesis of (−)-antofine.

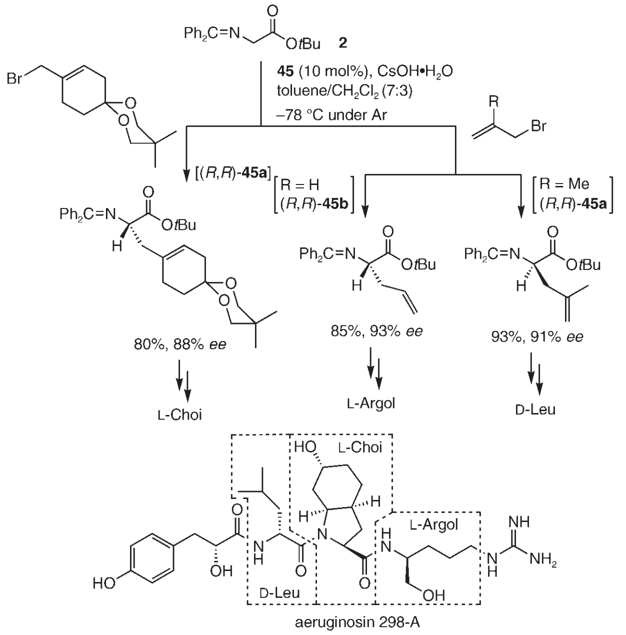
Kim et al. used the dimeric dihydrocinchonidine-derived catalyst **31** for the enantioselective alkylation of **2** with functionalized phenanthryl bromide **102**; this transformation constitutes one of the key steps in the asymmetric total synthesis of (−)-antofine (Scheme 57).[75]

Shibasaki and co-workers demonstrated the power of tartrate-derived bis(ammonium) salt **45** as a chiral phase-transfer catalyst by its application in the enantioselective synthesis of aeruginosin 298A and its analogues, which have serine protease inhibitor activity. The three characteristic amino acid components, D-Leu, L-Choi, and L-Algol, were nicely constructed with the required structure and configuration through the asymmetric alkylation of **2** with alkyl halides (Scheme 58).[36b,76]

3.2.3. Double Alkylation of Schiff Bases of α-Alkyl-α-amino Acids

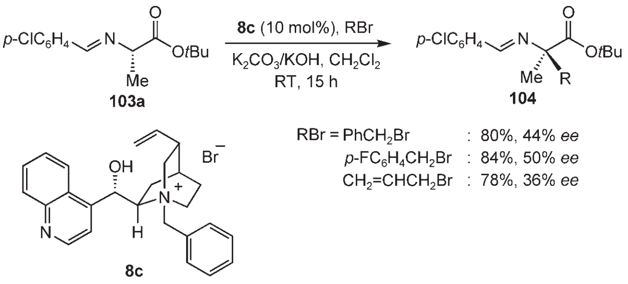
Nonproteinogenic, chiral α,α-dialkyl-α-amino acids with configurationally stable quaternary carbon centers have been significant synthetic targets for two reasons: because they are often effective enzyme inhibitors and because they are indispensable for the elucidation of enzymatic mechanisms. Accordingly, numerous studies have been conducted to develop efficient methods for their preparation,[77] and phase-transfer catalysis has made unique contributions.

In 1992, O'Donnell and Wu succeeded in obtaining optically active α-methyl-α-amino acid derivatives **104** by a



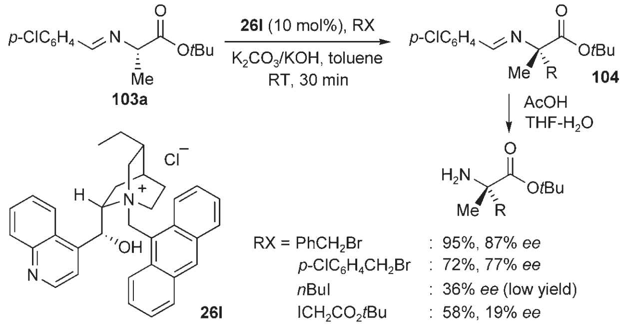
Scheme 58. Enantioselective synthesis of aeruginosin 298A.

catalytic phase-transfer alkylation of the *p*-chlorobenzaldehyde imine of alanine *tert*-butyl ester (**103a**) with catalyst **8c** (Scheme 59).[78] Examination of the effect of different base systems revealed the importance of using the mixed solid base KOH/K_2CO_3. Although the enantioselectivities are moderate, this study is the first example of preparing optically active α,α-dialkyl-α-amino acids by an asymmetric phase-transfer catalysis.



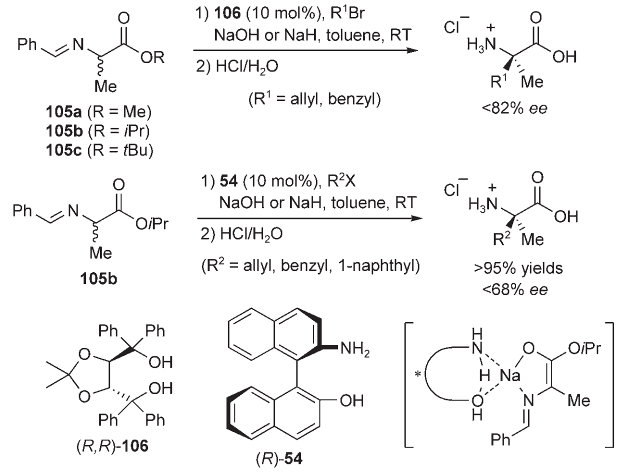
Scheme 59. The first catalytic reaction with **103a** as the substrate.

Lygo et al. demonstrated that the use of **261** significantly improved the enantioselectivity of alkylations with benzylic bromides, thus highlighting the utility of this approach for the synthesis of α,α-dialkyl-α-amino acids. They found that the solid base KOH/K_2CO_3 must be freshly prepared before use to obtain reproducible results. The lack of stereoselectivity in reactions with other electrophiles was ascribed to competing, nonselective alkylation (Scheme 60).[79]



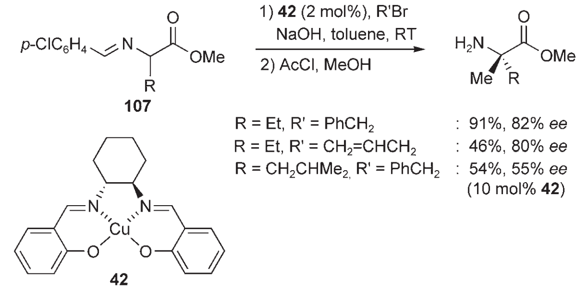
Scheme 60. Improvement in the enantioselectivity by using catalyst **261**.

Other types of chiral phase-transfer catalysts can also be employed for the enantioselective alkylation of alanine-derived imines **105**. Enantiopure (4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (**106**, taddol) and nobin (**54**), act as chiral bases upon in situ deprotonation with solid NaOH or NaH.[80] Their chelating ability toward the sodium cation is crucial for making the sodium enolate soluble in toluene as well as for achieving enantiofacial differentiation in the transition state (Scheme 61).



Scheme 61. Use of anions from taddol (**106**) or nobin (**54**) as chiral bases.

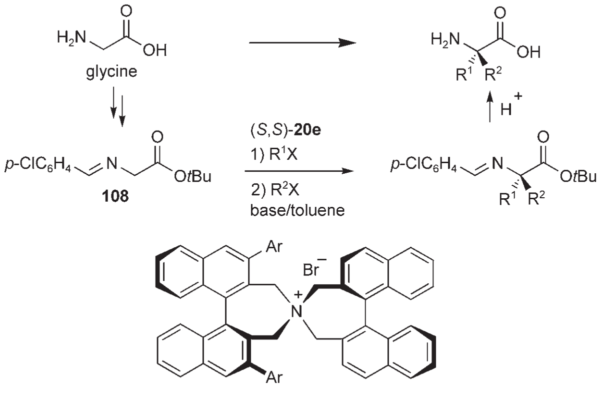
The ability of copper(II)–salen complex **42** to act as a chiral phase-transfer catalyst can be utilized for the quaternization. The aldimine Schiff bases of various α-alkyl-α-amino acid methyl esters **107** can be alkylated enantioselectively with **42** (2 mol%; Scheme 62).[34,81] Since hydrolysis of



Scheme 62. Use of copper(II)–salen complex **42** as a catalyst.

the alkylated imines occurred under the reaction conditions, a re-esterification step with methanol and acetyl chloride was introduced.

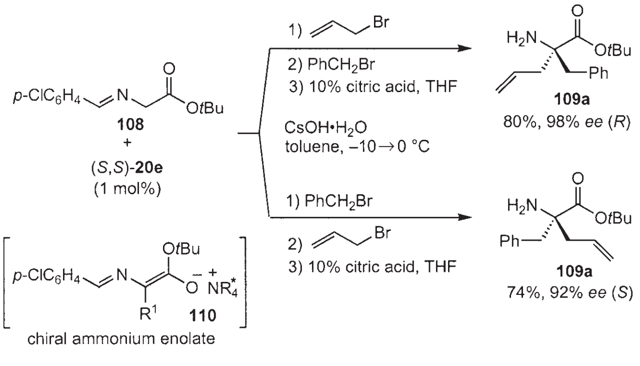
The aldimine Schiff base **108** can be readily prepared from glycine. Thus, the possibility is present for the direct stereoselective introduction of two different side chains into **108** by asymmetric phase-transfer catalysis for the synthesis of structurally diverse chiral α,α-dialkyl-α-amino acids. Such a double alkylation has been realized by using chiral quaternary *N*-spiroammonium bromide **20e** in a one-pot reaction.[82]



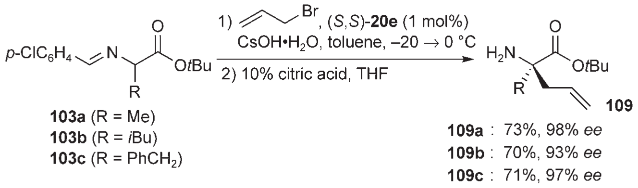
(*S*,*S*)-**20e** (Ar = 3,4,5-$F_3C_6H_2$)

A solution of **108** and (*S*,*S*)-**20e** (1 mol%) in toluene was initially treated with allyl bromide (1 equiv) and $CsOH{\cdot}H_2O$ at −10°C. Subsequent reaction with benzyl bromide (1.2 equiv) at 0°C resulted in the formation of the double alkylation product **109a** in 80% yield (98% *ee*) after hydrolysis. The absolute configuration of the product **109a** was found to be opposite when the halides were added in reverse order during the double alkylation of **108**. This finding indicates the intervention of the chiral ammonium enolate **110** in the second alkylation stage (Scheme 63).

This method should be applicable to the asymmetric alkylation of aldimines **103**, which are derived from the corresponding α-amino acids. Indeed, imines **103a–c** derived from DL-alanine, phenylalanine, and leucine can be alkylated smoothly under similar conditions to afford the desired noncoded amino acid esters **109** with excellent asymmetric induction (Scheme 64).[82]

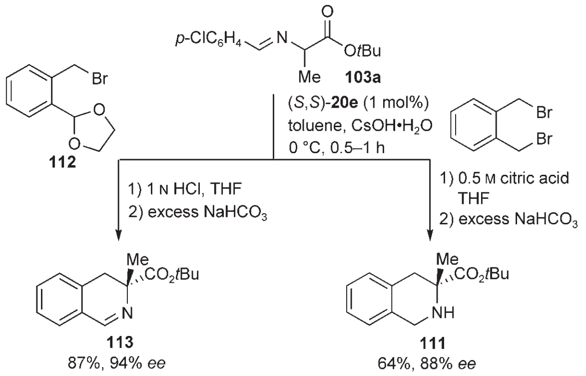


Scheme 63. A highly enantioselective, one-pot, double alkylation.



Scheme 64. Catalytic alkylation of aldimine **103** with **20e**.

This powerful method enabled the catalytic asymmetric synthesis of quaternary isoquinoline derivatives with **103a** as a substrate. Treatment of **103a** with α,α′-dibromo-*o*-xylene, $CsOH{\cdot}H_2O$, and (*S*,*S*)-**20e** (1 mol%) in toluene at 0°C resulted in the rapid generation of the monoalkylation product, which was transformed into the desired **111** (64%, 88% *ee*) during workup. Catalytic asymmetric alkylation of **103a** with functionalized benzyl bromide **112** followed by the sequential treatment with 1N HCl and then excess $NaHCO_3$ furnished the corresponding dihydroisoquinoline derivative **113** in 87% with 94% *ee* (Scheme 65).[69]

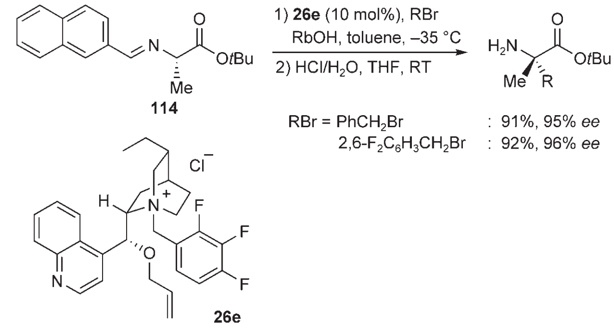


Scheme 65. Catalytic asymmetric synthesis of isoquinoline derivatives with quaternary stereocenters.

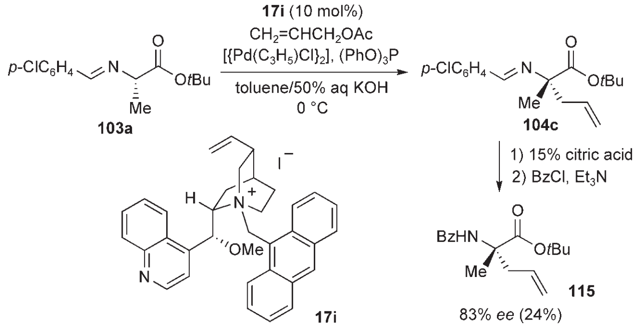
Jew, Park, and co-workers made systematic investigations to develop an efficient system for the asymmetric phase-transfer synthesis of α-alkylalanines with catalysts derived from cinchona alkaloids. Consequently, the sterically demanding 2-naphthylaldimine *tert*-butyl ester **114** was identified as a suitable substrate, and its alkylation in the presence of the strong base rubidium hydroxide (RbOH) and **26e** at −35°C led to the highest enantioselectivity (Scheme 66).[83]

Takemoto and co-workers demonstrated that the strategy of combining palladium catalysis and asymmetric phase-transfer catalysis was effective for the asymmetric allylation of **103a**. Without a chiral phosphane ligand in the palladium complex, the desired product **115** was obtained with 83% *ee* after hydrolysis of the imine moiety and subsequent benzoylation (Scheme 67).[48b]

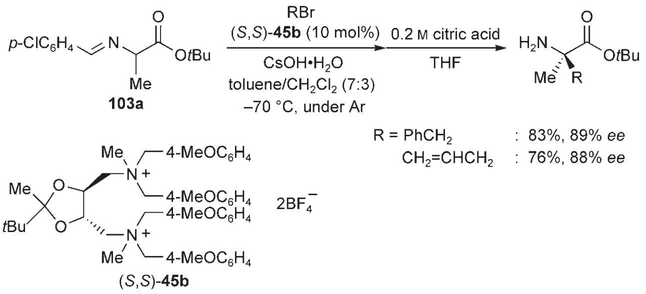
The bis(ammonium) tetrafluoroborate **45b** developed by Shibasaki and co-workers successfully promotes the alkylation of **103a**, even at low temperature, to give the corresponding α,α-dialkyl-α-amino ester in good yield and high enantioselectivity (Scheme 68).[36b] Particularly, allylation cat-



Scheme 66. Optimal combination of substrate, catalyst structure, and reaction conditions for attaining high enantioselectivity.



Scheme 67. Combination of palladium catalysis and asymmetric phase-transfer catalysis.

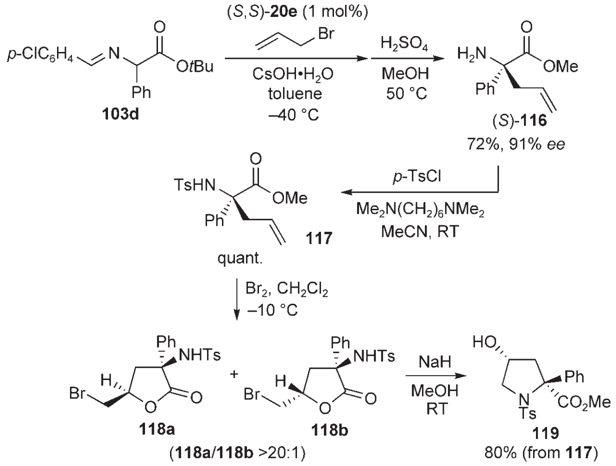


Scheme 68. Use of the chiral two-center phase-transfer catalyst (*S*,*S*)-**45b**.

alyzed by (*R*,*R*)-**45b** under the optimized conditions has been utilized for the synthesis of an aeruginosin 298A analogue.

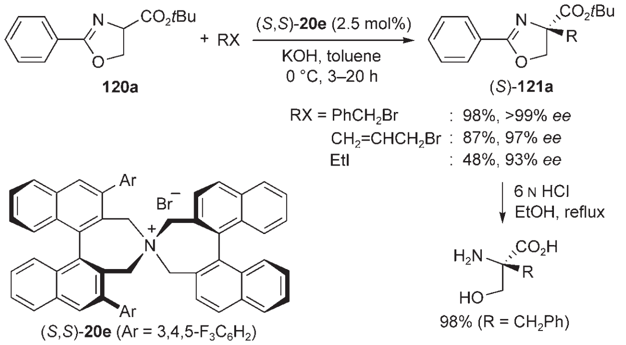
Recently, Maeda et al. utilized (*S*,*S*)-**20e** as a catalyst in the asymmetric alkylation of **103d** for the stereoselective synthesis of the 4-hydroxy-2-phenylproline framework. After hydrolysis and transesterification, the resulting (*S*)-**116** was derivatized to its tosylate **117**. Subsequent treatment of **117** with Br_2 in CH_2Cl_2 at $-10\,°C$ resulted in the formation of γ-lactones **118** with high diastereoselectivity. These were then treated with NaH in methanol to give essentially pure (2*S*,4*R*)-4-hydroxy-2-phenylproline derivative **119** (Scheme 69).[84]

This efficient phase-transfer-catalyzed alkylation strategy with **20e** was successfully applied by the research group of



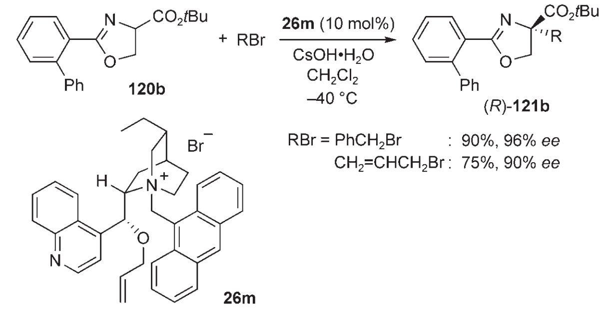
Scheme 69. Stereoselective synthesis of 4-hydroxy-2-phenylproline derivative **119**.

Jew and Park to the asymmetric synthesis of α-alkyl serines from phenyloxazoline derivative **120a**. The reaction is general and provides a practical access to a variety of optically active α-alkyl serines through acidic hydrolysis (Scheme 70).[85]



Scheme 70. Catalytic asymmetric synthesis of α-alkyl serines.

The researchers also modified the phenyl moiety of **120a** to various aromatic substituents and identified *o*-biphenyl analogue **120b** as a suitable substrate for attaining high enantioselectivity with phase-transfer catalyst **26m** (Scheme 71).[86]



Scheme 71. A highly enantioselective reaction of *o*-biphenyl analogue **120b**.

3.2.4. *Alkylation of Peptides Activated as Schiff Bases*

Naturally occurring peptides have applications in pharmaceuticals. Peptide modification is essential for efficient target screening and optimization of lead structures. The introduction of side chains directly to a peptide backbone represents a powerful method for the preparation of unnatural peptides.[87] Achiral glycine derivatives have generally been used for this purpose, and glycine enolates, radicals, as well as glycine cation equivalents have been exploited as reactive intermediates. However, control of the stereochemical outcome of these processes 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.

One reason for the difficulties in the stereoselectivity of the peptide alkylation is the presence of acidic protons in amino acid residues and amide groups, whose removal causes racemization and/or N alkylations. O'Donnell et al. compared the pK_a values of peptides activated as Schiff bases with those of model compounds (Figure 4). Their findings indicate the possibility of selective deprotonation of the terminal amino acid residue under appropriate conditions.[88]

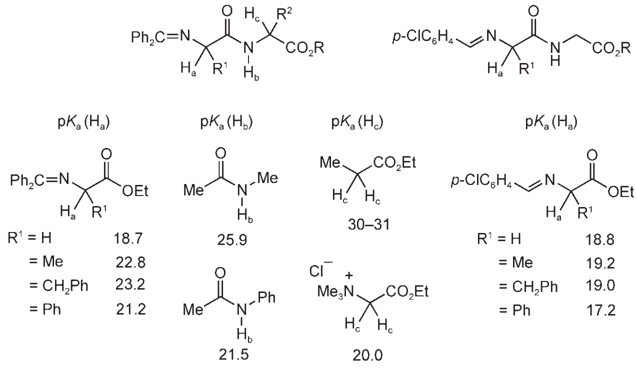
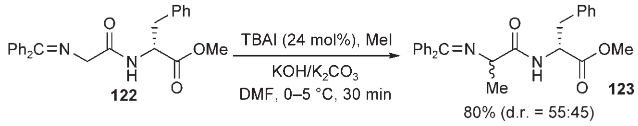


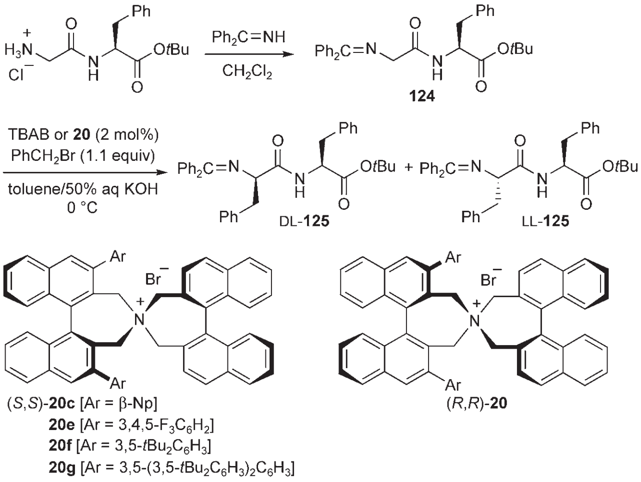
Figure 4. p*K*a values of model compounds with acidic protons (in DMSO).

Indeed, they demonstrated that N-terminal alkylation of dipeptides activated as Schiff bases could be achieved under phase-transfer conditions[10d,88] or by using non-ionic base[89] without suffering from the side reactions described above. For example, methylation of Gly-D-Phe derivative **122** with tetrabutylammonium iodide (TBAI) as a catalyst and KOH/K_2CO_3 as a base in DMF proceeded smoothly to give **123** in 80% yield; the diastereomeric ratio of the product was found to be 55:45 (Scheme 72).[88]



Scheme 72. N-terminal alkylation of dipeptide **122** (activated as a Schiff base) under phase-transfer conditions.

We envisaged that the chiral phase-transfer catalyst would play a crucial role in achieving an efficient transfer of chirality during the alkylation of the peptide, and examined the alkylation of the dipeptide Gly-L-Phe derivative **124** (Scheme 73 and Table 3). Treatment of a mixture of **124** and tetrabutylammonium bromide (TBAB, 2 mol%) in toluene with a 50% aqueous solution of KOH and benzyl bromide at 0°C for 4 h afforded the corresponding benzylation product **125** in 85% yield (entry 1 in Table 4) with a diastereomeric ratio (DL-**125**/LL-**125**) of 54:46 (8% *de*). In contrast, the reaction with chiral quaternary ammonium bromide (*S*,*S*)-**20c** under similar conditions gave rise to **125** with 55% *de* (entry 2). The preferential formation of LL-**125** in lower enantiomeric excess in the reaction with (*R*,*R*)-**20c** indicates that (*R*,*R*)-**20c** is a mismatched catalyst for this diastereofacial differentiation of **124** (entry 3). Changing the aromatic substituents in the 3,3′-position of **20** dramatically increased the stereoselectivity, and almost complete diastereocontrol was realized with (*S*,*S*)-**20g** possessing 3,5-bis(3,5-di-*tert*-butylphenyl)phenyl groups (entries 4–6).[90]



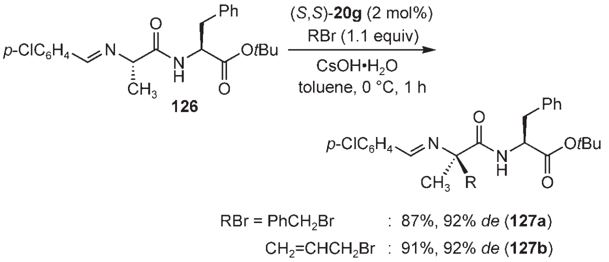
Scheme 73. Stereoselective N-terminal alkylation of dipeptide **124**.

Table 4: Diastereoselective phase-transfer benzylation of **124** in the presence of a chiral C_2-symmetric quaternary ammonium salts.

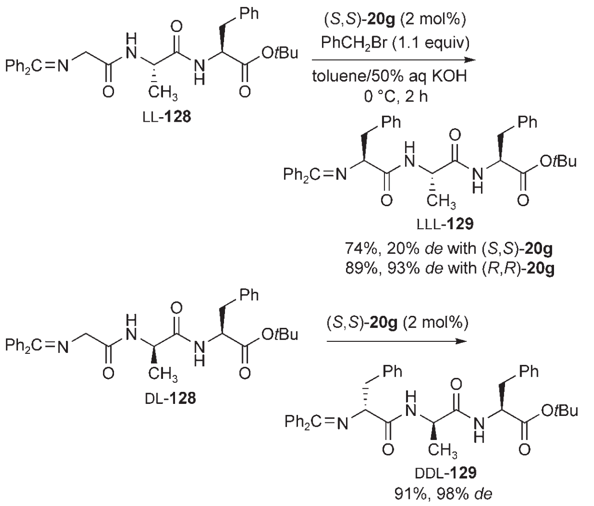
Entry	Catalyst	*t* [h]	Yield [%]	*de* [%]
1	TBAB	4	85	8
2	(*S*,*S*)-**20c**	4	88	55
3	(*R*,*R*)-**20c**	6	83	20
4	(*S*,*S*)-**20e**	8	43	81
5	(*S*,*S*)-**20f**	4	98	86
6	(*S*,*S*)-**20g**	6	97	97

A variety of alkyl halides can be employed as the electrophile in this alkylation. The efficiency of the transmission of stereochemical information was not affected by the side chains of the amino acid residues. This method allowed an asymmetric construction of noncoded α,α-dialkyl-α-amino acid residues at the peptide terminus as exemplified by the stereoselective alkylation of the dipeptide L-Ala-L-Phe derivative **126** (Scheme 74).

The asymmetric phase-transfer catalysis with (*S*,*S*)-**20g** can be successfully extended to the stereoselective alkylation of Gly-Ala-Phe derivative **128** at the N terminus. This tripeptide gave the stereoisomer with the reverse configuration (Scheme 75). The benzylation of LL-**128** with (*S*,*S*)-**20g** under the optimized conditions resulted in LLL-**129** as the major product, but with poor diastereoselectivity (20% *de*). The selectivity was enhanced to 93% *de* by using (*R*,*R*)-**20g** as the catalyst. In addition, (*S*,*S*)-**20g** turned out to be a matched catalyst for the benzylation of DL-**128** and led to the almost exclusive formation of DDL-**129**.

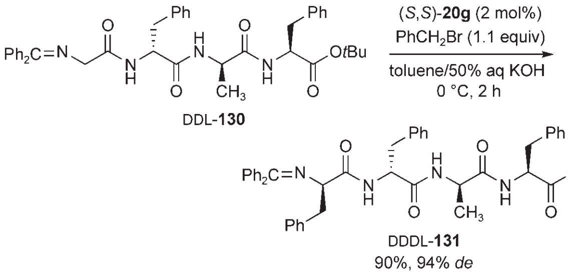


Scheme 74. Asymmetric synthesis of α,α-dialkyl-α-amino acid derivatives **127**.



Scheme 75. Diastereoselective N-terminal alkylation of tripeptide **128**.

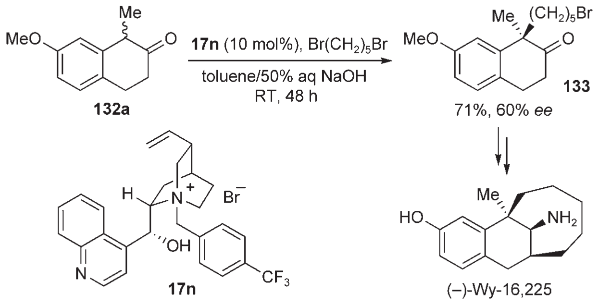
This tendency for the transfer of stereochemical information was found in the phase-transfer alkylation of DDL-**130**: the corresponding protected tetrapeptide DDDL-**131** was obtained in 90% yield with excellent stereochemical control (94% *de*) (Scheme 76).[90]



Scheme 76. Asymmetric synthesis of tetrapeptide DDDL-**131**.

3.3. Other Alkylations

The asymmetric alkylation of isotetralone derivative **132a** with 1,5-dibromopentane under phase-transfer conditions with cinchonidine-derived catalyst **17n** must be carried out under complete oxygen-free conditions because of rapid oxidation at the α-position. The involvement of an ion pair similar to **4** in Figure 1, similar to that of the indanone alkylation, was suggested by the configuration of the product **133**, which was proven to be *R* by the synthesis of (−)-Wy-16,225, a potent analgesic agent (Scheme 77).[91]

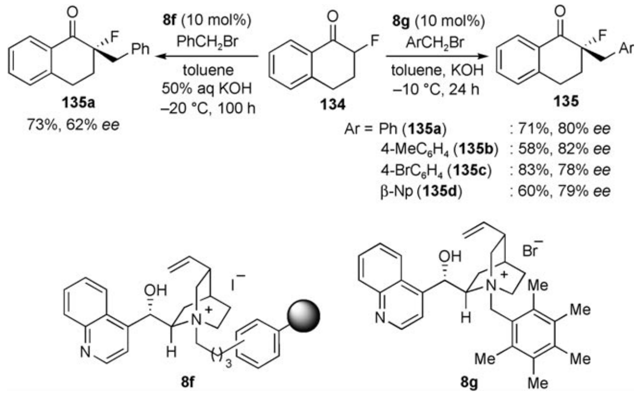


Scheme 77. Asymmetric alkylation of isotetralone derivative **132a** during the synthesis of analgesic agent (−)-Wy-16,225.

The distinctive properties of organofluorine compounds has meant that their preparation by an asymmetric synthesis has continued to be a major problem.[92] In this regard, Shioiri, Arai, and co-workers studied the asymmetric alkylation of α-fluorotetralone (**134**) under phase-transfer conditions with chiral quaternary ammonium bromide **8**. Screening of the catalyst in the benzylation of **134** by varying the arylmethyl substituent on the nitrogen atom eventually revealed that **8g** possessing a 2,3,4,5,6-pentamethylphenylmethyl group was the best catalyst. This system tolerated several benzylic bromides with substituents of different steric and electronic properties (Scheme 78).[93]

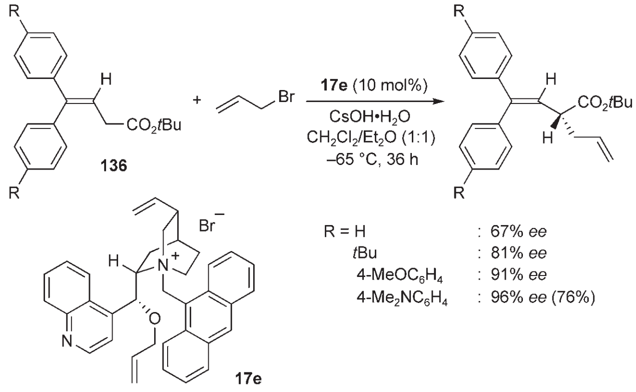
The cinchoninium iodide linked to polystyrene (**8f**) was also effective for the benzylation of **134** in toluene/50% aqueous KOH, which gave **135a** in 73% yield (62% *ee*) after stirring at −20°C for 100 h (Scheme 78).[54] Although the enantioselectivity was lower, the immobilization of the catalyst could offer several practical advantages, including the ease of catalyst recycling and product purification.

Corey et al. successfully applied catalyst **17e** to the asymmetric alkylation of β,γ-unsaturated ester **136** under phase-transfer conditions. Importantly, the enantioselectivity varied in a predictable way with the electronic effect of substituent R. This finding can be rationalized by the



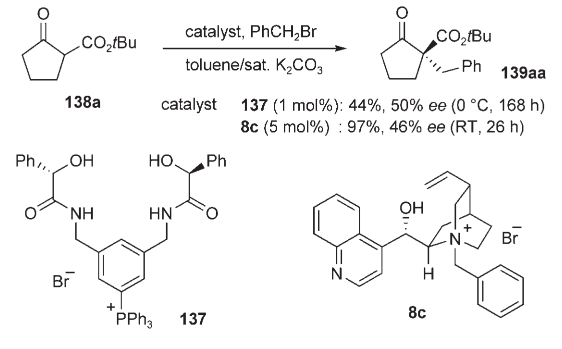
Scheme 78. Asymmetric alkylation of α-fluorotetralone **134**.

structured contact ion pair model previously postulated for the alkylation of glycinate Schiff base **2** (Scheme 79).[94]



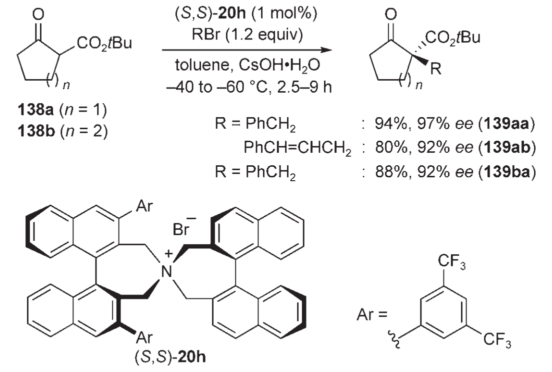
Scheme 79. Alkylation of β,γ-unsaturated ester **136**.

Manabe designed chiral phosphonium salts of type **137** that have a multiple hydrogen-bonding site. The utility of **137** as a chiral phase-transfer catalyst has been demonstrated in the asymmetric alkylation of β-keto ester **138a**, in which a quaternary carbon center was established. Although the reactivity and selectivity needed to be improved, this study provided a conceptual advance in the development of new chiral onium salts (Scheme 80).[95] The cinchona alkaloid derivative **8c** also catalyzed the benzylation of **138a** under similar conditions to give **139aa** in excellent chemical yield with 46% *ee* (Scheme 80).[96]

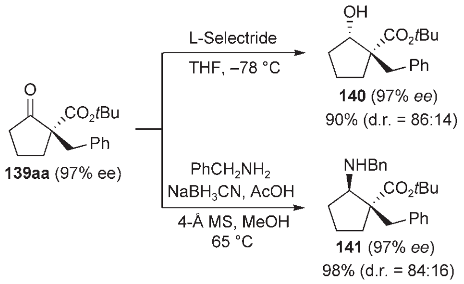


Scheme 80. Asymmetric alkylation of β-keto ester **138a**.

A highly enantioselective construction of quaternary stereocenters on β-keto esters under phase-transfer conditions has been achieved using the chiral N-spiroammonium bromide **20h** as catalyst.[97] This system has a broader generality in terms of the structure of the β-keto esters and alkyl halides (Scheme 81). The resulting alkylation products **139** can be readily converted into the corresponding β-hydroxy esters **140** and β-amino esters **141**, respectively (Scheme 82).



Scheme 81. Effectiveness of catalyst **20h** for construction of quaternary stereocenters in β-keto esters.

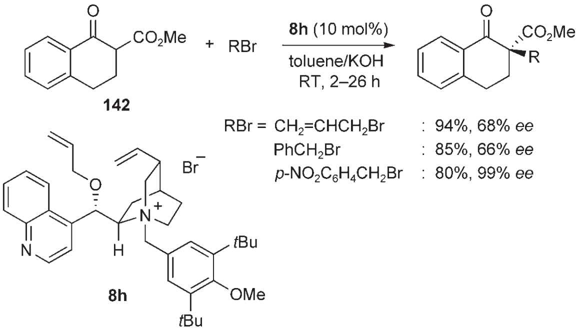


Scheme 82. Facile conversion of **139** into β-hydroxy and β-amino esters. MS = molecular sieves.

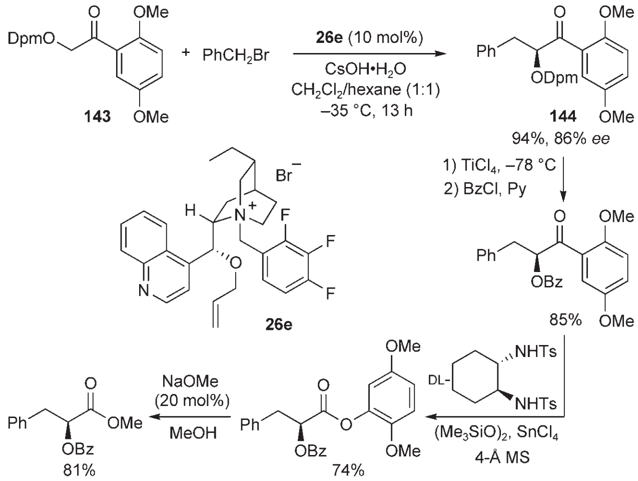
Kim and co-workers showed the effectiveness of cinchonine-derived catalyst **8h** with a bulky substituent on the bridgehead nitrogen atom for the asymmetric alkylation of β-keto esters such as **142**. The enantioselectivity was quite sensitive to the alkyl halide employed (Scheme 83).[98]

Recently, Andrus et al. introduced diphenylmethyloxy-2,5-dimethoxyacetophenone (**143**) as a useful oxygenated substrate that undergoes highly selective catalytic glycolate alkylation under phase-transfer conditions in the presence of the trifluorobenzyldihydrocinchonidinium bromide catalyst **26e** developed by Jew, Park, and co-workers. After exchange of the protecting groups of the alkylation product **144**, a subsequent Baeyer–Villiger-type oxidation and selective transesterification afforded the corresponding α-hydroxy ester derivative without loss of the enantioselectivity (Scheme 84).[99]

Jørgensen and co-workers developed a catalytic, regio- and enantioselective nucleophilic aromatic substitution reaction between activated aromatic compounds and 1,3-dicarbonyl compounds under phase-transfer conditions. Interest-

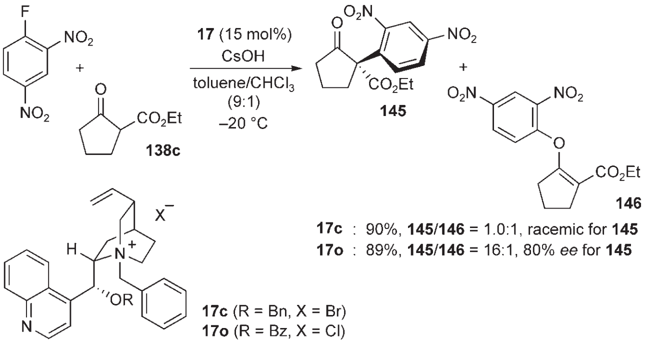


Scheme 83. Effectiveness of **8h** for the alkylation of β-keto ester **142**.



Scheme 84. Catalytic asymmetric alkylation of α-oxo compound **143**.

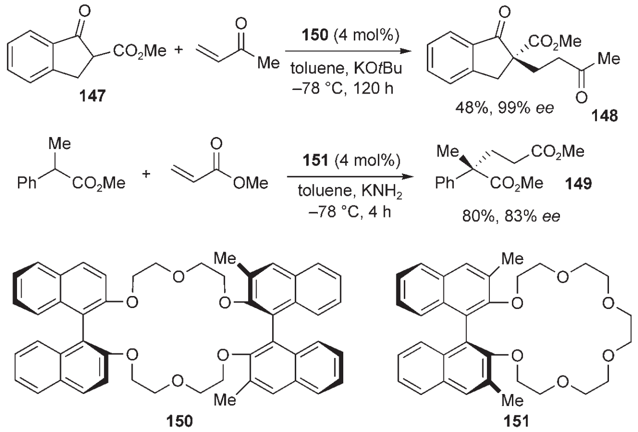
ingly, The reaction of 2,4-dinitrofluorobenzene with 2-carboethoxycyclopentanone (**138c**) in the presence of the *O*-benzoylated catalyst **17o** gave predominantly the C-arylated product **145** with high enantioselectivity (Scheme 85).[100]



Scheme 85. Catalytic regio- and enantioselective nucleophilic aromatic substitution of an activated arene.

4. Michael Addition

The asymmetric Michael addtion of compounds with active methylene or methine groups to electron-deficient olefins, particularly α,β-unsaturated carbonyl compounds, represents an important route to the construction of functionalized products.[101] The first successful Michael addition under phase-transfer catalysis was based on the use of chiral crown ethers **150** and **151** as catalysts. In the presence of **150**, β-keto ester **147** added to methyl vinyl ketone (MVK) in moderate yield but with virtually complete stereoselectivity. Crown ether **151** was shown to be efficacious for the reaction of methyl 2-phenylpropionate with methyl acrylate, and afforded the corresponding Michael adduct **149** in 80% yield and 83% *ee* (Scheme 86).[102]

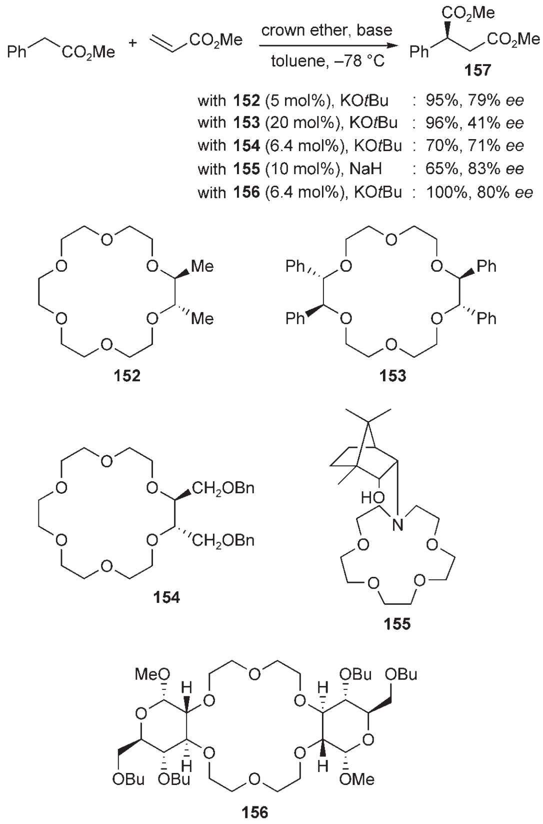


Scheme 86. Chiral crown ethers as phase-transfer catalysts.

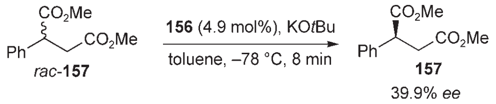
The catalytic activity of various other chiral crown ethers have been investigated in the asymmetric Michael addition of methyl phenylacetate to methyl acrylate (Scheme 87).[103–107] Since the Michael adduct **157** still has an acidic methine proton, it could undergo further deprotonation–protonation processes on longer reaction times. Tõke et al. took advantage of such phenomenon and demonstrated the feasibility of deracemizing **157** using **156** as a catalyst (Scheme 88).[107]

As part of a research effort for the stereoselective functionalization of indanone derivative **9**, a research group at Merck reported the Michael addition of **9b** to MVK catalyzed by their original catalyst **8a**. The reaction proceeded smoothly in toluene/50% aqueous NaOH to give diketone **158** in 95% yield and 80% *ee* (Scheme 89).[108] This approach can be extended to the reaction of phenylindanone derivative **9a** with MVK, although the chemical yield and enantioselectivity were moderate (Scheme 89).[109]

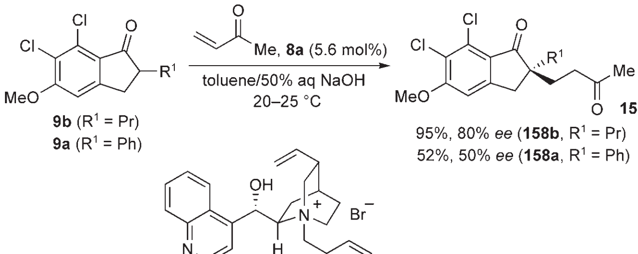
This type of catalyst has further been applied to the asymmetric Michael addition of tetralone derivatives to enones followed by a one-pot Robinson annulation. For example, the reaction of **132b** with ethyl vinyl ketone under the influence of dihydrocinchonidine-derived **26n** in toluene/60% aqueous KOH afforded the intermediary Michael adduct **159**. Subsequent addition of [18]crown-6 and continuous stirring at room temperature for 12 h furnished the cyclic enone **160** (81% yield, 81% *ee*), which can be derivatized into tricyclic enone (+)-podocarp-8(14)-en-13-one, a key intermediate in the synthesis of several diterpenes (Scheme 90).[91]



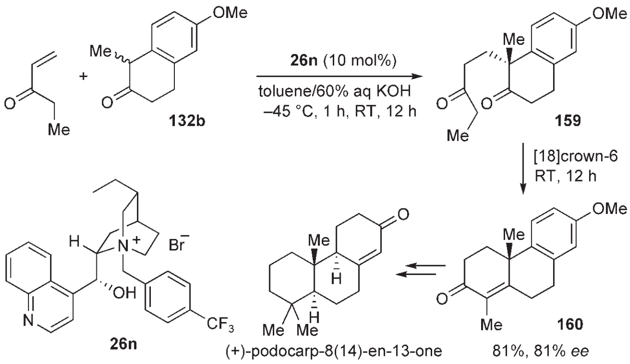
Scheme 87. Other catalytically active chiral crown ethers.



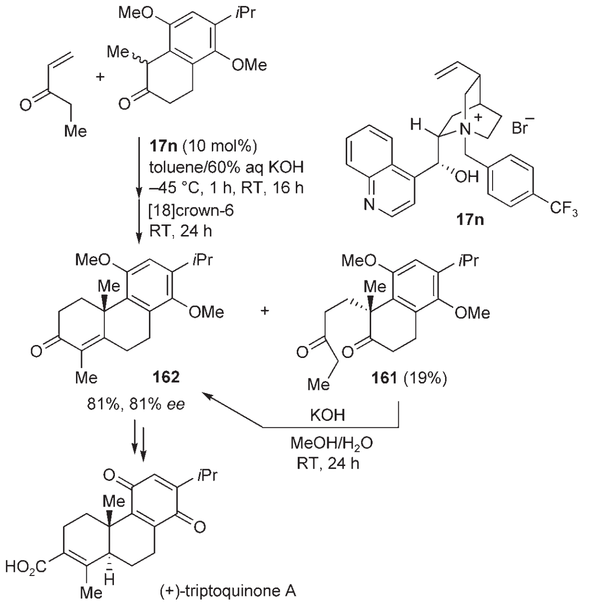
Scheme 88. Deracemization of **157**.



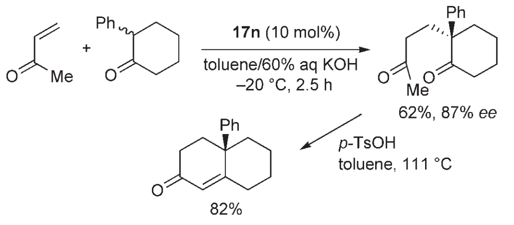
Scheme 89. Asymmetric Michael addition of indanone derivative **9** to methyl vinyl ketone (MVK).



Scheme 90. Robinson annulation to give tricycle **160**.



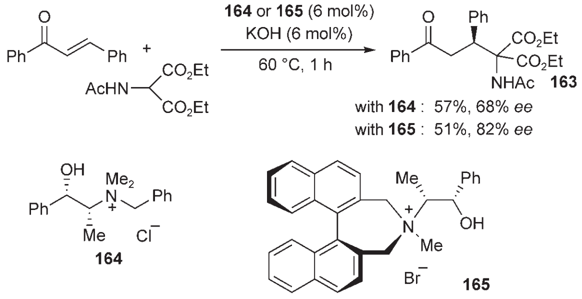
Scheme 91. Application of the reaction sequence in Scheme 90 to the asymmetric synthesis of (+)-triptoquinone A.



Scheme 92. Robinson annulation of 2-phenylcyclohexanone with MVK.

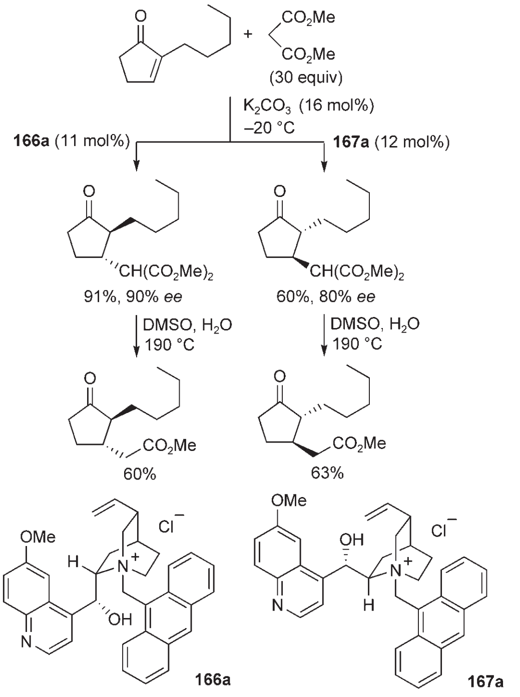
Shishido et al. utilized this strategy for the asymmetric synthesis of (+)-triptoquinone A by employing the chiral ammonium bromide **17n** as catalyst (Scheme 91).[110] The Michael adduct **161** was isolated in 19 % yield after treatment with [18]crown-6, and was converted into **162** by exposure to KOH in aqueous MeOH. A similar Michael addition/Robinson annulation sequence has also been accomplished with 2-phenylcyclohexanone and MVK in the presence of catalyst **17n** (Scheme 92).[91,109]

Loupy, Zaparucha, and co-workers reported that the reaction of diethyl acetylaminomalonate with chalcone in the presence of a catalytic amount of KOH and the ammonium salt **164** derived from (−)-*N*-methylephedrine without any solvents led to the formation of the corresponding Michael adduct **163** (57 % yield, 68 % *ee*). The enantioselectivity was enhanced to 82 % *ee* by the use of **165**, which has a chiral binaphthyl unit, as catalyst. This effect could be attributed to the increased π–π interaction between the aryl groups of the catalyst and the chalcone (Scheme 93).[111]



Scheme 93. Michael addition of diethyl acetylaminomalonate to chalcone under phase-transfer conditions without any solvents.

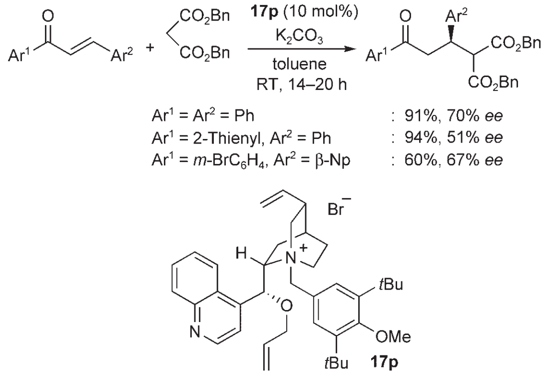
Plaquevent and co-workers achieved a highly enantioselective Michael addition of dimethyl malonate to 2-pentyl-2-cyclopentenone under phase-transfer conditions using K_2CO_3 as a base and quinine- or quinidine-derived **166a** or **167a** as the catalyst. This transformation enabled a short enantioselective synthesis of both enantiomers of methyl dihydrojasmonate (Scheme 94).[112]



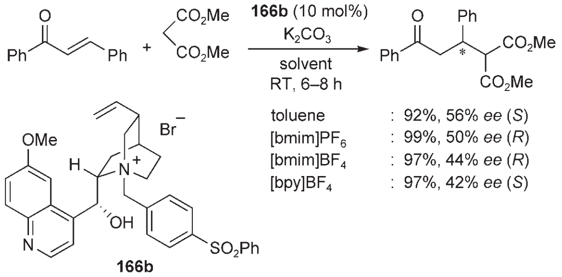
Scheme 94. Enantioselective synthesis of methyl dihydrojasmonate.

Kim et al. applied the catalyst *N*-(3,5-di-*tert*-butyl-4-methoxy)benzylcinchonidinium bromide (**17p**) to the 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 **17p** and an excess amount of K_2CO_3 (Scheme 95).[113]

Salunkhe and co-workers performed a similar phase-transfer-catalyzed Michael reaction of dimethyl malonate and chalcone with quininium bromide **166b** in an ionic liquid such as 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6), 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_6), and 1-butyl-3-pyridinium tetrafluoroborate ([bpy]BF_6). The products were obtained in excellent chemical yields in relatively short periods of time. Surprisingly, the enantioselectivity remained the same in [bpy]BF_6 as observed in toluene, while surprisingly the other enantiomer was obtained in [bmim]PF_6 and [bmim]BF_6 (Scheme 96).[114]



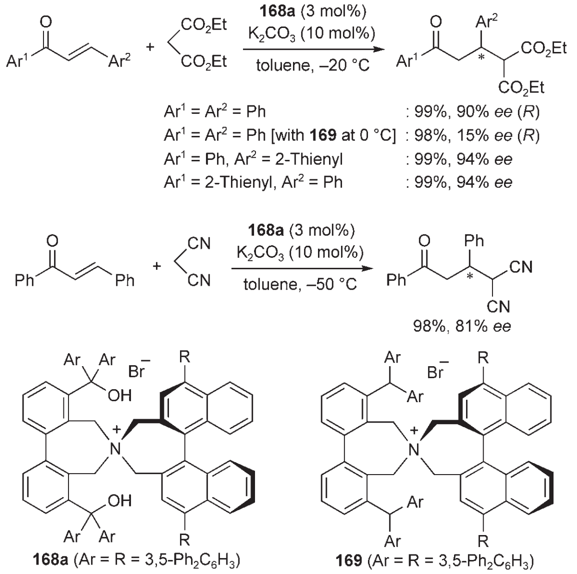
Scheme 95. Michael addition of dibenzyl malonate to chalcone derivatives under phase-transfer conditions.



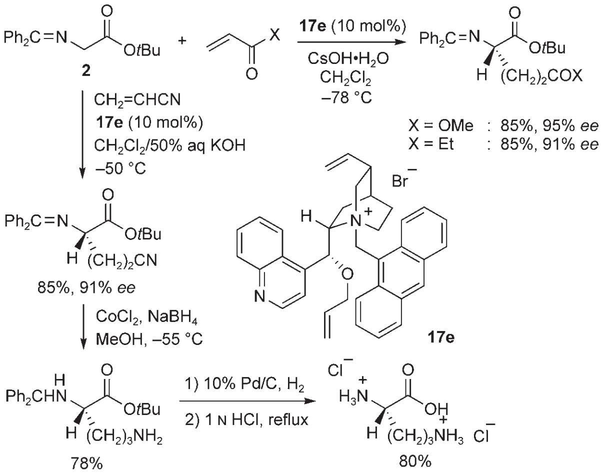
Scheme 96. Phase-transfer-catalyzed Michael addition of dimethyl malonate to chalcone in ionic liquids.

Recently, we reported that a high level of enantioselectivity is obtained in the Michael addition of malonates to chalcone derivatives when a doubly functionalized chiral phase-transfer catalyst such as **168a** is used (Scheme 97).[115] For example, the reaction of diethyl malonate with chalcone in toluene under the influence of K_2CO_3 and **168a** (3 mol%) proceeded smoothly at −20 °C with excellent enantioselectivity, while the selectivity was markedly decreased when **169** (without an OH group) was used as the catalyst. This system is applicable to the Michael addition of malononitrile (Scheme 97).

Various functionalized α-alkyl amino acids have been synthesized by the enantioselective Michael addition of glycine derivatives by chiral phase-transfer catalysis. Corey et al. utilized the cinchonidinium bromide **17e** as a catalyst for the asymmetric Michael addition of glycinate Schiff base **2** to α,β-unsaturated carbonyl substrates with high enantioselectivity (Scheme 98).[116,117] The α-*tert*-butyl γ-methyl ester of (*S*)-glutamic acid can be formed by using methyl acrylate as an acceptor. This functionalized glutamic acid derivative is highly useful for synthetic applications, as the two carboxyl



Scheme 97. Asymmetric Michael addition of diethyl malonate and malononitrile to chalcone derivatives under the influence of **168a**.

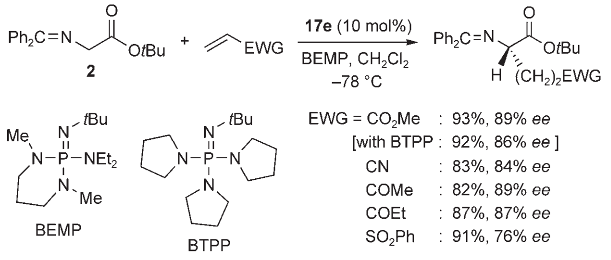


Scheme 98. Highly enantioselective Michael reactions of **2** with the third-generation catalyst **17e**.

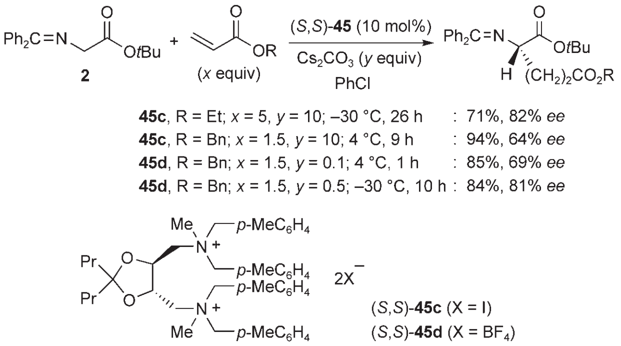
groups are differentiated. Naturally occurring (*S*)-ornithine has also been synthesized as its dihydrochloride in a concise manner by using acrylonitrile as an acceptor (Scheme 98).[117]

O'Donnell et al. carried out this type of Michael addition with the organic-soluble, non-ionic bases BEMP and BTPP. In general, the less-basic BEMP proved to be superior and tolerated several representative Michael acceptors (Scheme 99).[118] The applicability of this system to solid-phase synthesis with a resin-bound glycinate Schiff base was also demonstrated.

Shibasaki and co-workers successfully applied the tartrate-derived, C_2-symmetric bis(ammonium) salt **45** 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 100).[36]

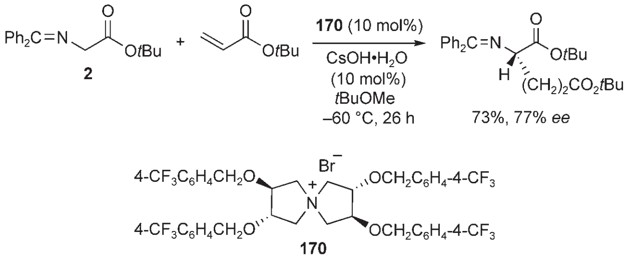


Scheme 99. Use of organic-soluble base BEMP.



Scheme 100. Effectiveness of tartrate-derived bis(ammonium) salts **45** as catalysts.

Arai, Tsuji, and Nishida also developed a similar asymmetric Michael addition by using the chiral phase-transfer catalyst **170**, which is a spiro compound with a tartrate framework (Scheme 101).[119]

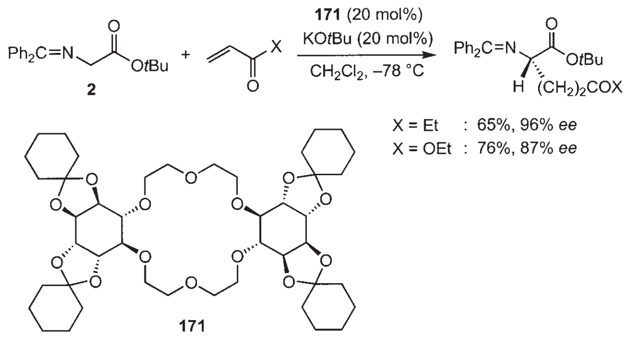


Scheme 101. Effectiveness of tartrate-derived N-spiroammonium salt **170** as a catalyst.

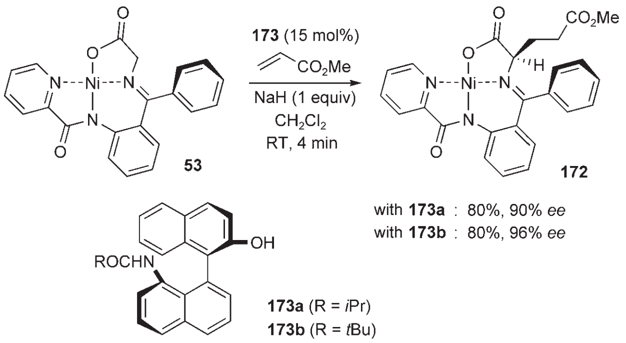
Akiyama et al. synthesized the *chiro*-inositol-derived crown ether **171** and evaluated its reactivity and selectivity in the asymmetric Michael addition of glycinate Schiff base **2**. High levels of enantioselectivity were achieved in reactions with alkyl vinyl ketones and acrylates (Scheme 102).[120]

Belokon et al. examined the asymmetric addition of nickel complex **53** to methyl acrylate under phase-transfer conditions. In addition to taddol, various nobin and *iso*-nobin derivatives were screened in combination with NaH as a base. The study revealed that *N*-pivaloyl-*iso*-nobin (**173b**) was a highly efficient catalyst and afforded the product **172** in 80% yield and 96% *ee* (Scheme 103).[42b]

Arai et al. introduced a new bis(ammonium) salt **174** derived from (*S*)-1,1′-bi-2-naphthol as an efficient chiral

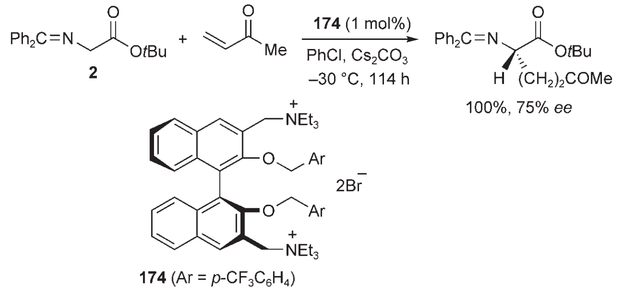


Scheme 102. *Chiro*-inositol-derived crown ether as a catalyst.



Scheme 103. Michael reaction of **53** with *iso*-nobin derivatives **173** as catalysts.

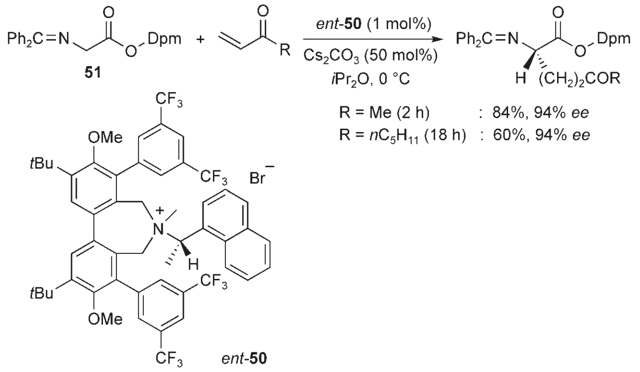
phase-transfer catalyst. For example, the reaction of **2** with methyl vinyl ketone in the presence of Cs_2CO_3 and 1 mol% of **174** in chlorobenzene proceeded quantitatively at −30 °C (75% *ee*; Scheme 104). The characteristic feature of the catalyst is that modification of the substituents on the ether and ammonium moieties appears to be advantageous.[121]



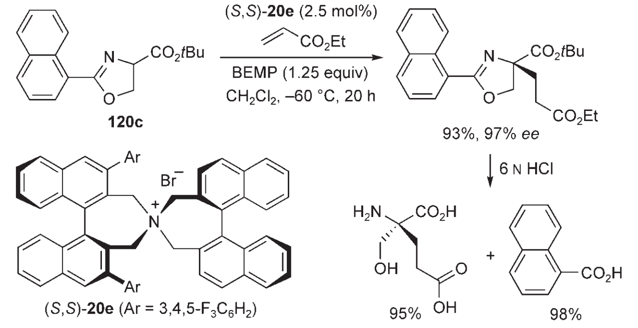
Scheme 104. Chiral binaphthyl-derived bis(ammonium) salt as catalyst.

The research group of Lygo recently reported the optimization of reaction parameters for the asymmetric Michael addition of a glycine derivative to methyl vinyl ketone with the quaternary ammonium salt *ent*-**50** derived from (α-naphthylmethyl)amine as the catalyst. This study uncovered the crucial importance of the base and solvent: high levels of enantioselectivity can be obtained by performing the addition of glycine diphenylmethyl ester Schiff base **51** to simple alkyl vinyl ketones in diisopropyl ether at 0 °C in the presence of 50 mol% Cs_2CO_3 and 1 mol% *ent*-**50** (Scheme 105).[122]

Jew, Park, and co-workers achieved the 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 (**120c**) to ethyl acrylate under phase-transfer conditions. As shown in Scheme 106, The use of BEMP as a base at −60 °C with catalyst **20e** appeared to be essential for attaining excellent selectivity.[123]



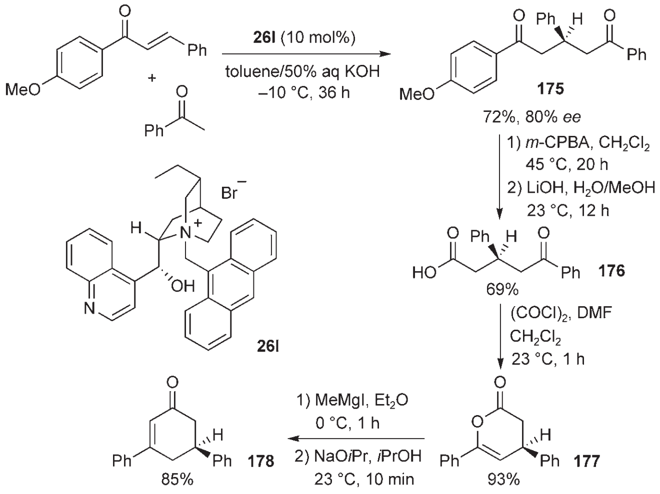
Scheme 105. α-Methylnaphthylamine-derived ammonium salt *ent*-**50** as catalyst.



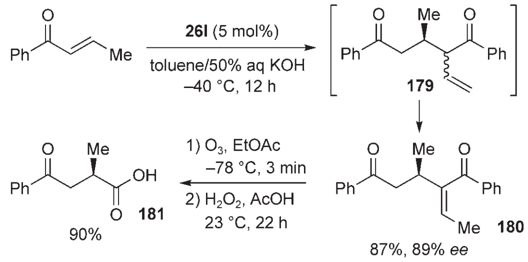
Scheme 106. Asymmetric synthesis of (2*S*)-α-(hydroxymethyl)glutamic acid.

Zhang and Corey extended the utility of the cinchona alkaloid derivative **261** to the asymmetric Michael addition of acetophenone to 4-methoxychalcone under mild phase-transfer conditions. Selective Baeyer–Villiger oxidation of the adduct **175** and subsequent saponification gave the keto acid **176**, which can be obtained in an essentially enantiopure form by a single recrystallization. Facile derivatization of **176** into optically active 2-cyclohexenone derivative **178** via enol γ-lactone **177** was also demonstrated (Scheme 107).[117]

The chiral ammonium bromide **261** also served as an effective catalyst for the enantioselective dimerization of α,β-unsaturated ketones under phase-transfer conditions. The dimerization proceeded through a Michael reaction to form **179**, followed by a base-catalyzed double-bond shift to afford chiral 1,5-dicarbonyl compound **180** (Scheme 108).[124] The



Scheme 107. Enantioselective synthesis of chiral 2-cyclohexenones **178**. *m*-CPBA = *meta*-chloroperoxybenzoic acid.



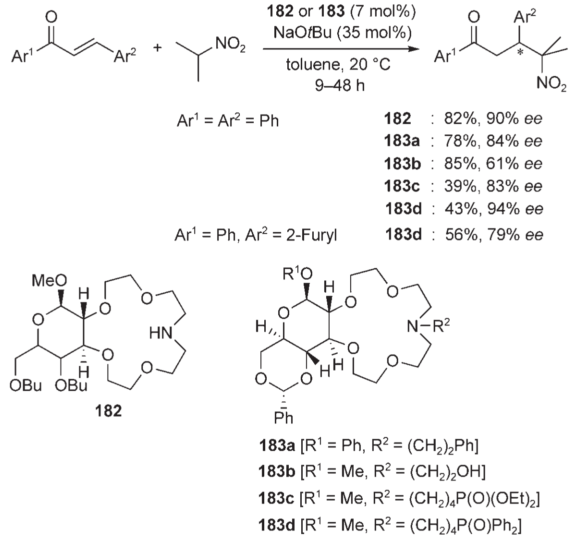
Scheme 108. Enantioselective dimerization of α,β-enones.

resulting product **180** can be readily converted into the corresponding α-alkyl-γ-keto acid **181** through ozonolysis and subsequent oxidation with H_2O_2.

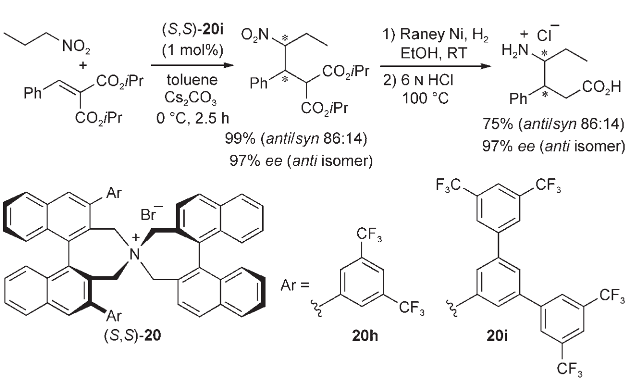
Bakó, Tõke, and co-workers synthesized a series of D-glucose-derived monoaza derivatives of [15]crown-5 ethers (**182** and **183**) and evaluated their abilities as chiral phase-transfer catalysts in the Michael addition of 2-nitropropane to chalcone derivatives. The substituents on the sugar unit and the side arms on the nitrogen atom in the crown ether ring had a significant influence on the reactivity and selectivity; the highest enantioselectivity was observed for **183d** which has a butyl side chain with phosphine oxide groups (Scheme 109).[125]

We developed the diastereo- and enantioselective conjugate addition of nitroalkanes to alkylidenemalonates under mild phase-transfer conditions by the utilization of chiral ammonium bromide **20i** as an efficient catalyst. This protocol offers a practical entry to optically active γ-amino acid derivatives (Scheme 110).[126]

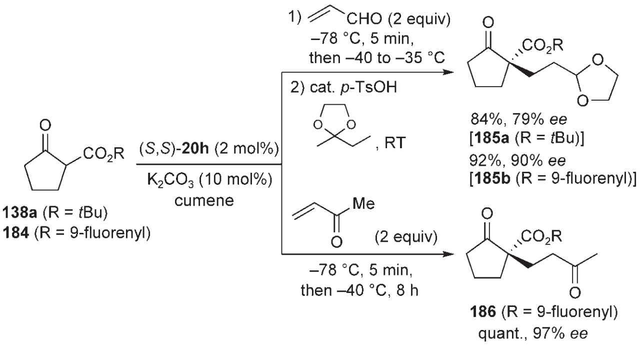
The enantioselective Michael addition of β-keto esters to α,β-unsaturated carbonyl compounds is a useful method for the construction of compounds with quaternary carbon centers. A characteristic feature of the chiral catalyst **20h** (Scheme 110) in this type of transformation is that it enables the use of α,β-unsaturated aldehydes as the acceptor, thereby leading to the construction of products with a quaternary stereocenter and three different carbonyl functionalities. An example is the reaction with 2-*tert*-butoxycarbonylcyclopentanone (**138a**). Interestingly, the use of fluorenyl ester **184** greatly improved the enantioselectivity. The addition of **184** to MVK was also feasible under similar conditions and the desired **186** was obtained quantitatively (97% *ee*, Scheme 111).[97]



Scheme 109. Michael reaction of 2-nitropropane with chalcone and a derivative.



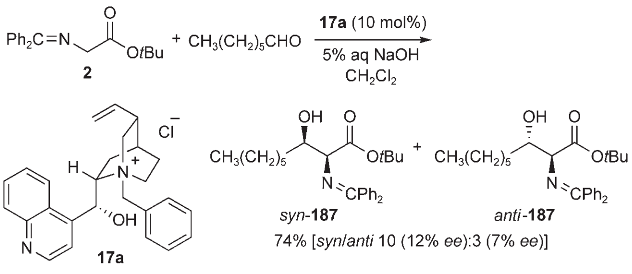
Scheme 110. Michael addition of nitropropane to an alkylidenemalonate.



Scheme 111. Asymmetric Michael addition of β-keto esters to acrolein and MVK.

5. Aldol and Related Reactions

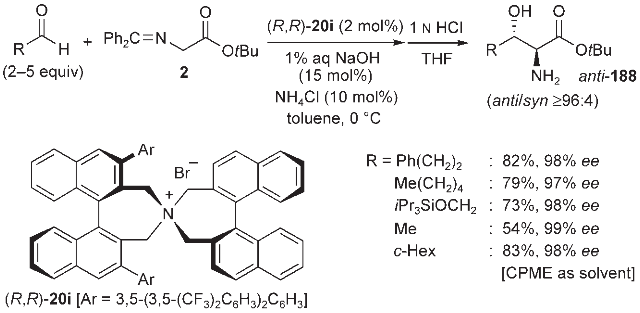
Although enantioselective direct aldol reactions of a glycine donor with an aldehyde acceptor under phase-transfer catalysis could provide an ideal method for the stereoselective construction of β-hydroxy-α-amino acids, which are extremely important chiral units, especially from a pharmaceutical viewpoint, the examples reported to date are very limited. The first catalytic asymmetric synthesis of β-hydroxy-α-amino acids by aldol condensation under phase-transfer condition was reported by Gasparski and Miller, as a synthetic variant of the α-alkylation of glycinate Schiff base **2**. The reaction of **2** with heptanal in the presence of catalyst **17a** afforded **187** in 74 % yield; unfortunately, however, the diastereo- and enantioselectivities were not satisfactory (Scheme 112).[127]



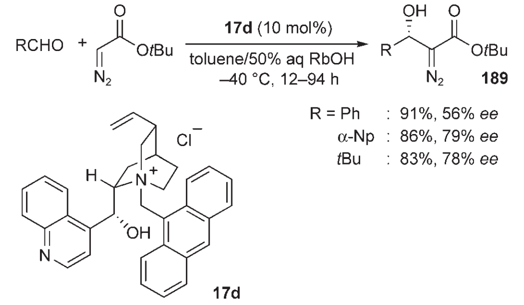
Scheme 112. First example of a phase-transfer-catalyzed direct asymmetric aldol reaction.

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 by employing the chiral N-spiroammonium salt **20i** as a catalyst. Mechanistic investigations revealed the intervention of a highly stereoselective retro-aldol reaction, which could be minimized by using a catalytic amount of 1 % NaOH aqueous solution and ammonium chloride. This approach led to the establishment of a general and practical synthesis of optically active *anti*-β-hydroxy-α-amino esters **188** (Scheme 113).[128]

Arai, Hasegawa, and Nishida investigated the catalytic asymmetric aldol reaction between *tert*-butyl diazoacetate and benzaldehyde under various liquid–liquid phase-transfer conditions with ammonium chloride **17d** as the catalyst. The reaction was found to proceed smoothly in toluene, even at −40 °C, by using 50 % aqueous solution of RbOH as a base, thereby giving rise to the desired aldol adduct **189** in 91 % yield and 56 % *ee*. The electronic properties of the substituents on the benzene ring of the aldehydes strongly influenced the enantioselectivity. This system was also effective for aliphatic aldehydes (Scheme 114).[129]

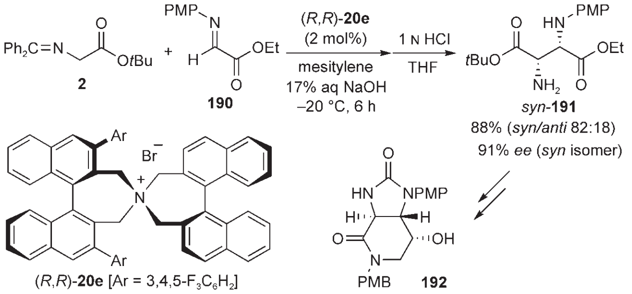


Scheme 113. Highly diastereo- and enantioselective direct aldol reaction of **2** with aliphatic aldehydes.



Scheme 114. Asymmetric aldol reactions of diazoesters.

The phase-transfer-catalyzed direct Mannich reaction of **2** with α-imino ester **190** was achieved with high enantioselectivity by using ammonium bromide **20e** as the catalyst (Scheme 115).[130] This method enables the catalytic asymmetric synthesis of differentially protected 3-aminoaspartate *syn*-**191**; this nitrogen analogue of dialkyl tartrate was converted into a precursor (**192**) of streptolidine lactam.

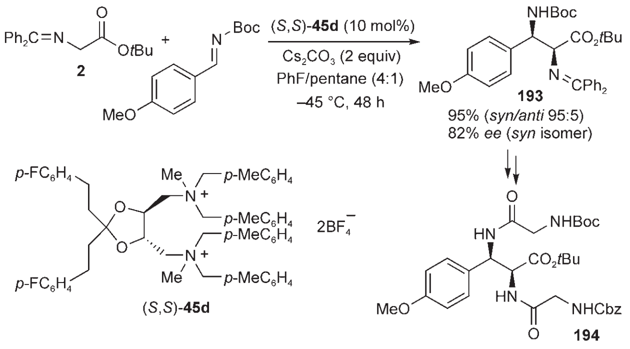


Scheme 115. Direct Mannich approach to a nitrogen analogue (*syn*-191) of dialkyl tartrate. PMB = *para*-methoxybenzyl, PMP = *para*-methoxyphenyl.

A more general and highly diastereoselective Mannich-type reaction was developed by Ohshima, Shibasaki, and coworkers. The original tartrate-derived bis(ammonium) salt **45b** was modified by introducing an aromatic ring into the acetal side chains. The 4-fluorophenyl-substituted compound **45d** was identified as an optimal catalyst for the reaction of **2** with various *N*-Boc-protected imines under solid–liquid (Cs_2CO_3–fluorobenzene/pentane) phase-transfer conditions (Scheme 116).[131] The usefulness of the Mannich adduct **193** was further demonstrated by the straightforward synthesis of the optically pure tripeptide **194**.

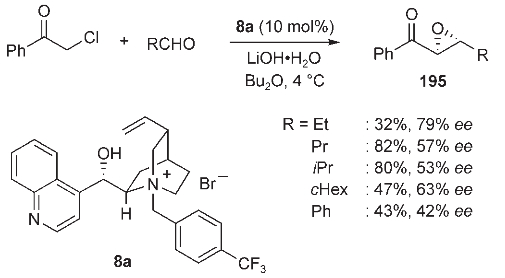
6. Darzens Reaction

The Darzens reaction represents one of the most powerful methods for the synthesis of α,β-epoxycarbonyl and related



Scheme 116. Direct Mannich reaction with *N-tert*-butoxycarbonyl imines. Boc = *tert*-butyloxycarbonyl.

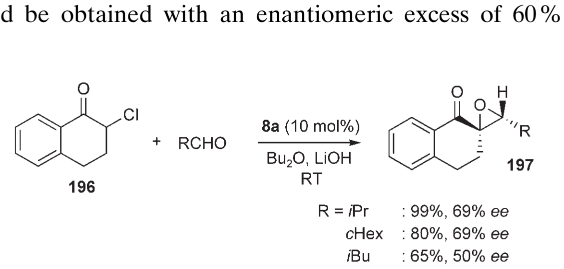
compounds. Arai and Shioiri demonstrated that phenacyl chloride underwent an asymmetric Darzens condensation with various aldehydes under phase-transfer conditions using **8a** as the catalyst and $LiOH{\cdot}H_2O$ as a base in dibutyl ether. The corresponding epoxy ketones **195** were obtained in good yield with good to moderate enantioselectivity (Scheme 117).[132]



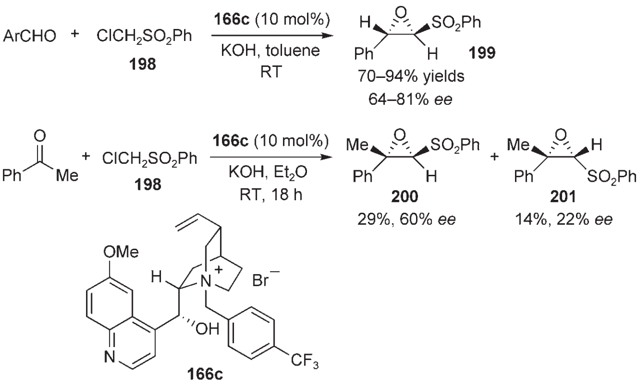
Scheme 117. Asymmetric Darzens reaction of phenacyl chloride with aldehydes.

An asymmetric Darzens condensation of cyclic α-chloro ketone **196** with various aldehydes was also carried out under similar phase-transfer conditions using **8a** as the catalyst to give enantiomerically enriched epoxy ketones **197** (Scheme 118).[132b,133]

This approach was successfully applied to the preparation of optically active α,β-epoxy sulfones through the reaction of chloromethyl phenyl sulfone (**198**) with aromatic aldehydes (Scheme 119).[134] Aryl ketones generally reacted slowly and the desired epoxides were obtained as a diastereomeric mixture, whose ratio was quite sensitive to the ketone substituent and catalyst structure. The major isomer **200** could be obtained with an enantiomeric excess of 60% *ee*



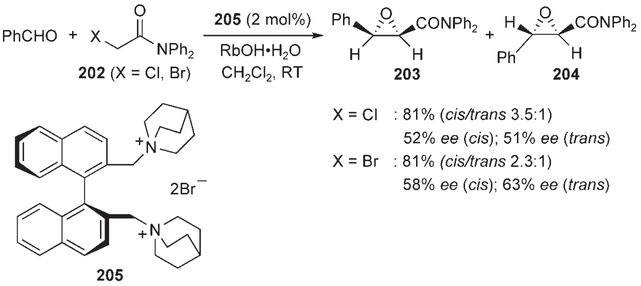
Scheme 118. Asymmetric Darzens reaction of α-chloro ketone **196** with aldehydes.



Scheme 119. Asymmetric synthesis of α,β-epoxy sulfones by a Darzens reaction.

when the quinine-derived ammonium bromide **166c** was used as the catalyst in the condensation of acetophenone and **198**.

Arai et al. designed the quaternary bis(ammonium) salt **205**, which is easily prepared from optically pure (*S*)-1,1′-bi-2-naphthol, and utilized it in the preparation of a mixture of optically active *cis* and *trans*-α,β-epoxy amides **203** and **204** by reaction of aromatic haloamides **202** with aldehydes (Scheme 120).[135]

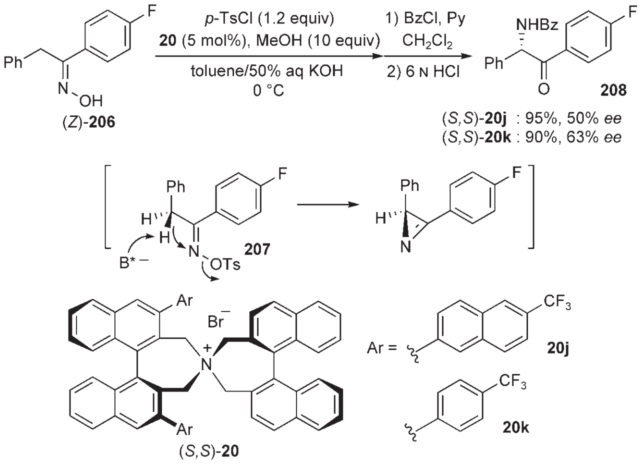


Scheme 120. Asymmetric synthesis of α,β-epoxy amides by a Darzens reaction.

7. Neber Rearrangement

The Neber rearrangement of oxime sulfonates has been considered to proceed through a nitrene or an anion pathway. If the latter mechanism is operative, the use of a certain chiral base could result in discrimination of the two enantiotopic α-protons to furnish optically active α-amino ketones. Verification of this hypothesis was provided by the asymmetric Neber rearrangement of the oxime sulfonate **207**, generated in situ from the parent oxime (*Z*)-**206**, under phase-transfer conditions using the structurally rigid, chiral N-spiro compounds **20j** or **20k** as catalysts. The protected α-amino ketone **208** was isolated in high yield and with notable enantiomeric excess (Scheme 121).[136]

The stereochemical outcome of this asymmetric Neber rearrangement can be rationalized by postulating a transition-state model in which the conformation of the catalyst–substrate ion pair would be fixed with the maximum number of possible π–π interactions (Figure 5).



Scheme 121. Asymmetric Neber rearrangement of oxime sulfonate **207**. Bz = benzoyl, Py = pyridine.

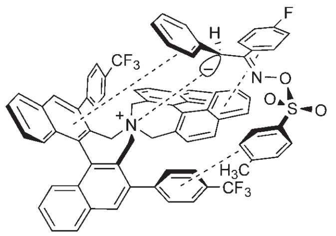
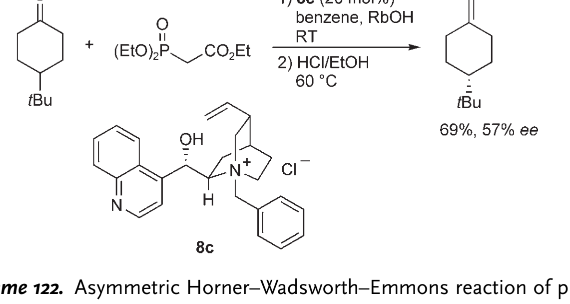


Figure 5. Transition-state model for the asymmetric Neber rearrangement of oxime sulfonate **207**.

8. Horner–Wadsworth–Emmons Reaction

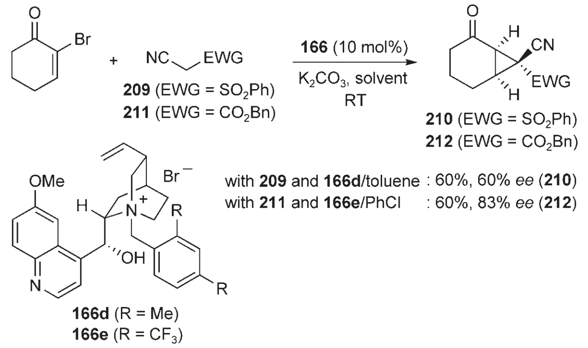
The Horner–Wadsworth–Emmons reaction is a synthetically useful method for constructing carbon–carbon double bonds. All asymmetric reactions reported so far have utilized a stoichiometric amount of a chiral source. Arai, Hamaguchi, and Shioiri reported the first catalytic example of an asymmetric Horner–Wadsworth–Emmons reaction of a prochiral ketone in the presence of the chiral phase-transfer catalyst **8c** derived from cinchona alkaloids (Scheme 122).[137]



Scheme 122. Asymmetric Horner–Wadsworth–Emmons reaction of prochiral 4-*tert*-butylcyclohexanone.

9. Cyclopropanation

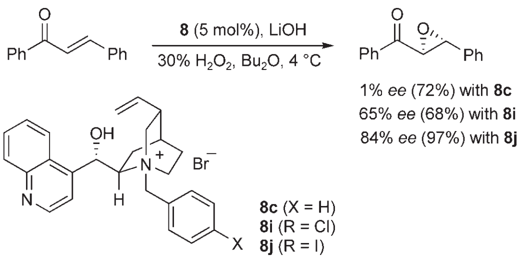
The asymmetric cyclopropanation of α-bromocyclohexenone with cyanomethyl phenyl sulfone (**209**) under phase-transfer conditions in the presence of a catalyst derived from a cinchona alkaloid affords products with stereogenic carbon atoms in the cyclopropane rings.[138] An extensive study showed that the desired product **210** could be obtained in 60% yield and 60% *ee* by performing the reaction in toluene at room temperature in the presence of **166d** (with a 2,4-dimethylphenylmethyl group) and K_2CO_3. Cyanoacetate **211** was also found to be a quite effective carbon nucleophile. In this case, chlorobenzene was an ideal solvent and the introduction of a benzyl group with an electron-withdrawing substituent on the nitrogen atom had a beneficial effect on the enantioselectivity of **212** (Scheme 123).



Scheme 123. Asymmetric cyclopropanation of α-bromocyclohexenone.

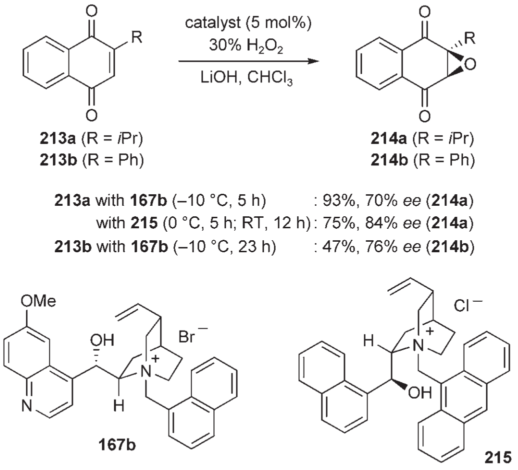
10. Epoxidation

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 developed.[139] Among these, chiral phase-transfer catalysis occupies a unique place because of its practical advantages, and it allows the highly enantioselective epoxidation of *trans*-α,β-unsaturated ketones. Arai, Shioiri, and co-workers carried out the asymmetric epoxidation of chalcone and its derivatives with 30% hydrogen peroxide using chiral ammonium salts **8** as a phase-transfer catalyst (Scheme 124).[140] The enantiomeric purity of the epoxy chalcones was found to be highly dependent on the *para* substituent in **8**.



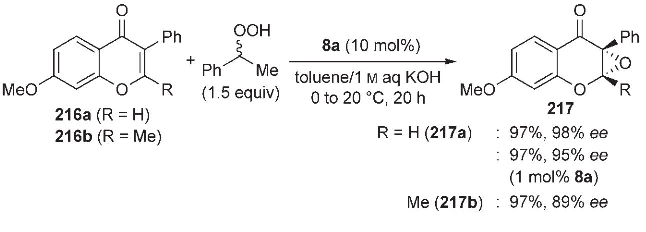
Scheme 124. Asymmetric epoxidation of chalcone.

In contrast to *trans*-enones, the enantioselective epoxidation of *cis*-enones is still a difficult task, and successful examples are limited to the epoxidation of naphthoquinones. A typical reaction for the epoxidation of naphthoquinone involves the treatment of 2-substituted naphthoquinone **213** with 30% H_2O_2 and LiOH in chloroform in the presence of a chiral ammonium bromide such as **167b** and **215** to afford the corresponding epoxides **214** with good enantiopurity.[140b] Interestingly, the use of the deaza derivative **215** as catalyst provided higher enantioselectivity (Scheme 125).[96]



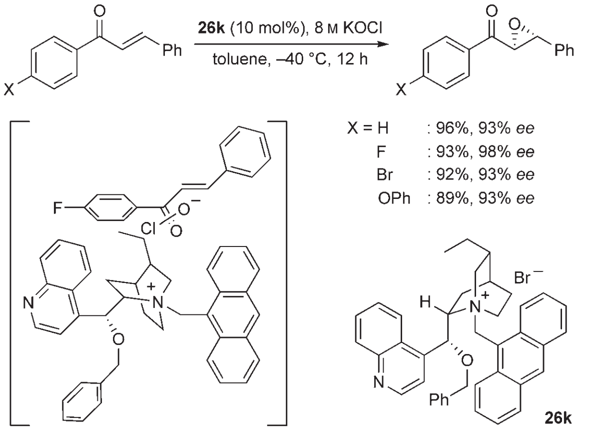
Scheme 125. Asymmetric epoxidation of naphthoquinones **213**.

The asymmetric epoxidation of chalcone is quite sensitive to the choice of oxidants. In contrast to the result obtained by Shioiri and co-workers,[140] Lygo and Wainwright found that the use of sodium hypochlorite delivered much higher stereocontrol than aqueous hydrogen peroxide,[141] and the asymmetric epoxidation proceeded with only 1 mol% of chiral catalyst derived from a cinchona alkaloid.[142] Liang and co-workers successfully utilized trichloroisocyanuric acid as a safe, inexpensive, and mild oxidant for the asymmetric epoxidations.[143] Several alkyl hydroperoxides have also been utilized for phase-transfer-catalyzed asymmetric epoxidations of conformationally flexible and fixed enone substrates with moderate to high enantioselectivity. Adam et al. achieved an asymmetric epoxidation of isoflavones **216** with cinchonine-derived **8a** as the catalyst and commercially available cumyl hydroperoxide as the oxidant (Scheme 126). Isoflavone epoxide **217a** was obtained almost quantitatively and with excellent enantioselectivity even when the catalyst loading was reduced to 1 mol%. The 2-methyl derivative **216b** afforded the corresponding epoxide **217b** which possesses two consecutive quaternary centers in 97% yield and 89% *ee*.[144]



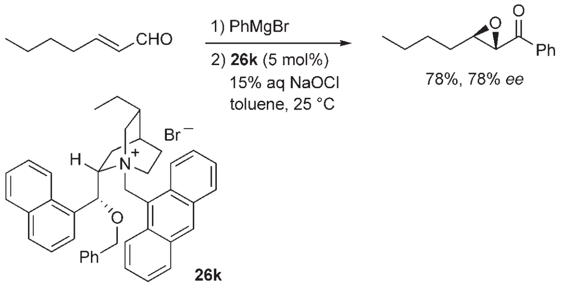
Scheme 126. Asymmetric epoxidation of isoflavones **216**.

Corey and Zhang studied the phase-transfer-catalyzed epoxidation of various α,β-enone substrates using 8 M aqueous KOCl as a stoichiometric oxidant and dihydrocinchonidine-derived, rigid quaternary ammonium salt **26k** as the catalyst, and achieved an excellent level of enantioselectivity (Scheme 127).[145] Based on a rational analysis of the reaction mechanism, they proposed a plausible transition-state structure as depicted in Scheme 127.



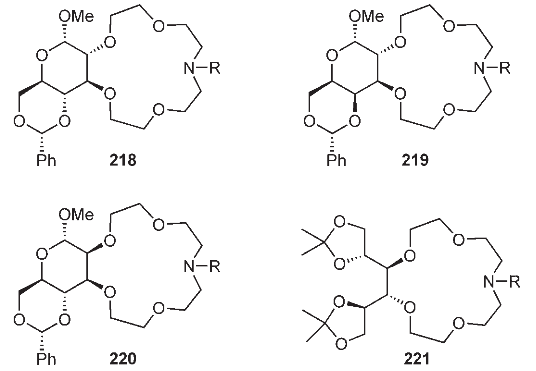
Scheme 127. Proposed transition state for the highly enantioselective epoxidation of chalcone derivatives.

Lygo and To also developed this biphasic oxidation system to the direct asymmetric transformation of allylic alcohols into α,β-epoxy ketones. 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 128).[146]



Scheme 128. Asymmetric transformation of an α,β-unsaturated aldehyde to an α,β-epoxy ketone.

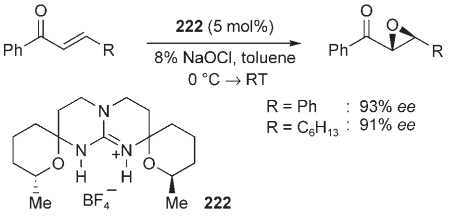
Bakó et al. reported the utility of the chiral monoaza[15]crown-5 compounds derived from D-glucose (**218**), D-galactose (**219**), D-mannose (**220**), and D-mannitol (**221**) as catalysts in the phase-transfer-catalyzed asymmetric epoxidation of chalcones with *tert*-butylhydroperoxide (Scheme 129). The highest enantioselectivity (94% *ee*) was attained with **218**.[147] Militzer and co-workers found that the



Scheme 129. Monosaccharide-based azacrown ether catalysts **218**–**221** (R = $(CH_2)_3OH$) for asymmetric epoxidations.

use of poly-L-leucine is effective for such a transformation, which is highly accelerated by combination with achiral phase-transfer catalysts.[148]

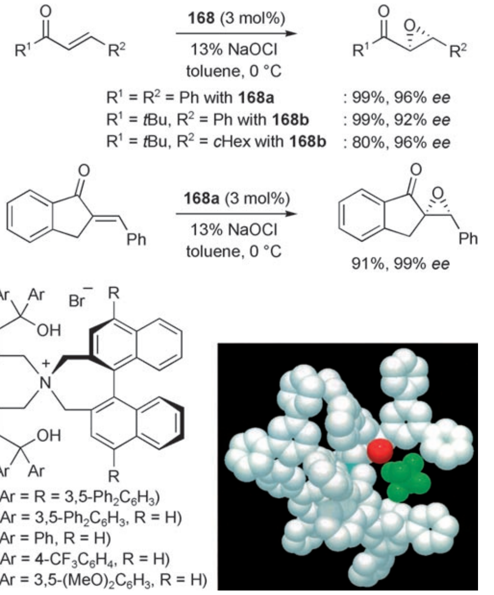
Murphy and co-workers prepared several tetracyclic C_2-symmetric guanidium salts **222** from (*S*)-malic acid, and applied them to several asymmetric transformations including the asymmetric epoxidation of chalcone derivatives (Scheme 130) and the enantioselective alkylation of glycinate Schiff base **2** (see entry 37 in Table 3).[149]



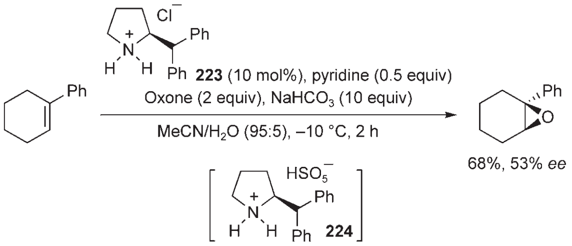
Scheme 130. Guanidine catalyst **222** for asymmetric epoxidation.

We designed the highly efficient chiral N-spiroammonium salt **168** (see Scheme 97) for the asymmetric epoxidation of various enone substrates (Scheme 131).[150] As shown in the X-ray structure of the cation of **168a** (with a PF_6 counterion), the exceedingly high asymmetric induction can be ascribed to the recognition of the catalyst by the enone substrates through the appropriately aligned hydroxy group as well as the chiral molecular cavity. Indeed, the observed enantioselectivity highly depends on the steric size and the electronic factor of both the Ar and R substituents in **168**; the use of **168c**–**168e** significantly decreased the enantioselectivity for the chalcone epoxidation (61–66 % *ee*).

Aggarwal et al. introduced the use of oxone as the oxidant for the asymmetric epoxidation of simple alkenes, in which chiral amines were used as the catalysts (Scheme 132).[151] Mechanistic investigations provided compeling evidence to support the dual role of the protonated chiral secondary ammonium salt **223**: as a phase-transfer catalyst to bring the oxidant into solution and as an activator of oxone through hydrogen bonding in the active oxidizing agent **224**.



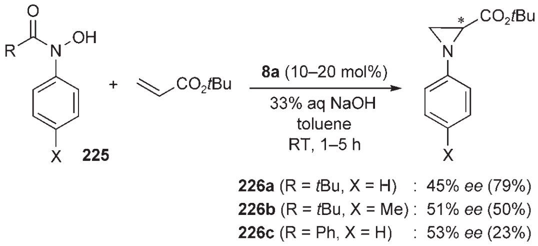
Scheme 131. The doubly functionalized N-spiro catalyst **168** for asymmetric epoxidations; CPK Model of **168a**-PF_6 (N: blue, O: red, PF_6: green).



Scheme 132. Asymmetric epoxidation of simple olefins catalyzed by chiral amines with oxone as the oxidant.

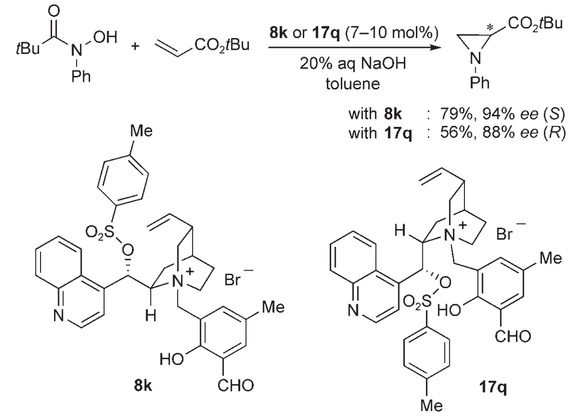
11. Aziridination

Chiral aziridines have been used as chiral auxiliaries, chiral ligands for transition metals, and chiral building blocks for the preparation of biologically active species such as amino acids, β-lactams, and alkaloids. Accordingly, Prabhakar and co-workers carried out asymmetric aziridination reactions of electron-deficient olefins such as acrylates with *O*-pivaloyl-*N*-arylhydroxylamines **225** in the presence of ammonium salt **8a** under phase-transfer conditions to furnish the corresponding chiral *N*-arylaziridines **226** with moderate enantioselectivity (Scheme 133).[152]



Scheme 133. Asymmetric aziridination of acrylates with *O*-acyl-*N*-aryl-hydroxylamine **225**.

Murugan and Siva developed a procedure for such asymmetric aziridination reactions that enabled excellent levels of enantioselectivity to be achieved by using new chiral phase-transfer catalysts **8k** and **17q** derived from cinchonidine and cinchonine, respectively (Scheme 134).[153]



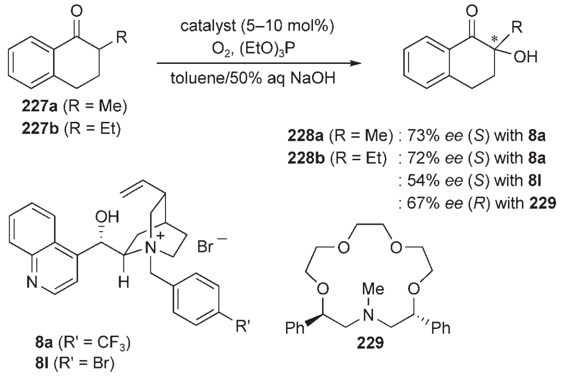
Scheme 134. Asymmetric aziridination with the chiral phase-transfer catalysts **8k** and **17q**.

12. Oxidation

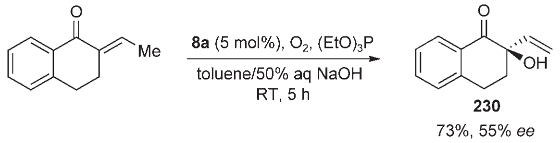
12.1. α-Hydroxylation

The catalytic enantioselective α-hydroxylation of tetralone derivatives **227a** and **227b** as well as indanone derivatives with molecular oxygen using chiral phase-transfer catalysts has been repeatedly examined since the first report by the Shioiri research group.[154] The cinchonine-derived catalysts **8a** and **8l** were employed and led to the formation of α-hydroxy ketones with quaternary carbon atoms (**228**) in more than 90% yields with good enantioselectivities. The effectiveness of the chiral crown ether **229** was also demonstrated in this oxidation process (Scheme 135).[155]

Furthermore, α,β-unsaturated ketones appeared to be good candidates for the α-hydroxylation. For example, (*E*)-2-ethylidene-1-tetralone was oxidized to the α-hydroxy ketone **230** under similar conditions in 73% yield and 55% *ee* (Scheme 136).[154a]



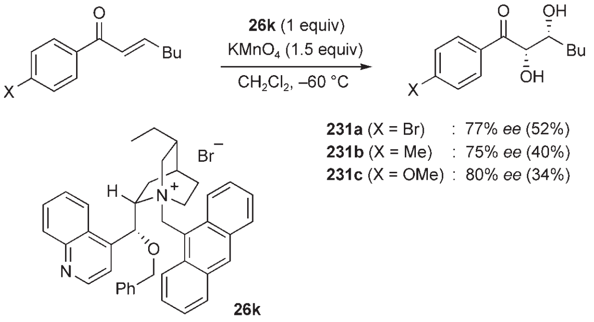
Scheme 135. Catalytic asymmetric α-hydroxylation of tetralones **227**.



Scheme 136. Asymmetric α-hydroxylation of an α,β-unsaturated ketone.

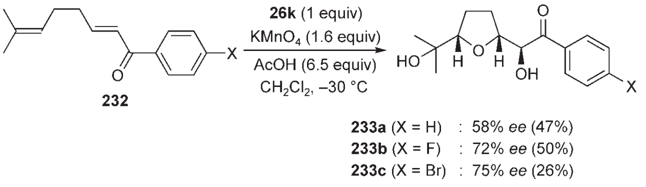
12.2. Dihydroxylation

Asymmetric phase-transfer dihydroxylation of α,β-unsaturated ketones using chiral quaternary ammonium salt **26k** as catalyst and $KMnO_4$ as oxidant has been developed by Brown and co-workers (Scheme 137).[156] Other olefins were found to give less satisfactory results; a simple olefin with a terminal double bond gave the corresponding racemic diol, and stilbene and chalcone gave over-oxidation products.



Scheme 137. Asymmetric dihydroxylation of α,β-unsaturated ketones.

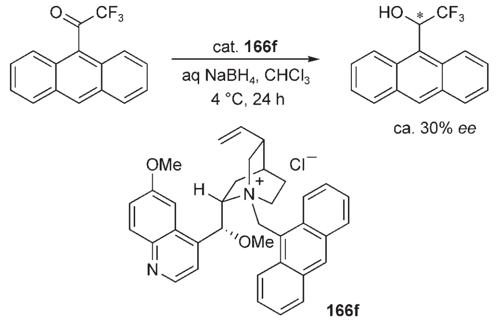
This methodology has been further extended to asymmetric oxidative cyclization of 1,5-dienes under slightly acidic conditions to promote the intramolecular ring closure. Among various 1,5-dienes investigated, those with conjugated ketone groups (**232**) gave good to high enantioselectivity (Scheme 138).[157]



Scheme 138. Asymmetric oxidative cyclization of dienone **232**.

13. Reduction

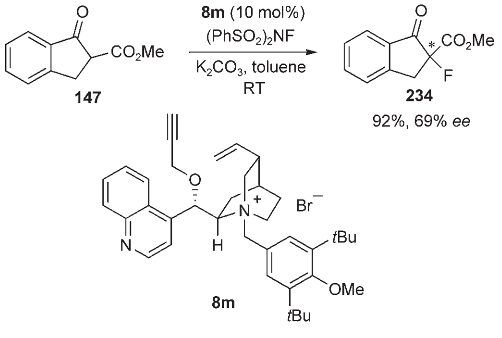
The solution structures of ion pairs formed between the cation of **166f** and the borohydride anion have been characterized by NMR methods.[158] The attempted asymmetric reduction of anthracenyl trifluoromethyl ketone under phase-transfer conditions resulted in only low levels of asymmetric induction (Scheme 139).



Scheme 139. Asymmetric phase-transfer reduction of a trifluoromethyl ketone.

14. Fluorination

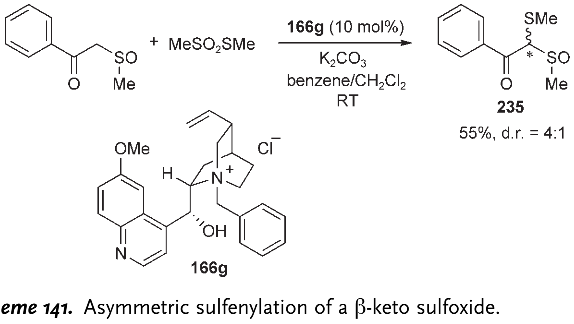
In view of the importance of optically active organofluorine compounds in various fields of chemistry, the catalytic enantioselective fluorination of carbonyl substrates was a long-awaited method. The asymmetric electrophilic fluorination of β-keto ester **147** under phase-transfer conditions certainly belongs to this category. The combined use of the modified catalyst **8m** and *N*-fluorobenzenesulfonimide as a fluorinating agent in toluene with base (K_2CO_3) afforded the desired product **234** in 92% yield and 69% *ee* (Scheme 140).[159]



Scheme 140. Catalytic asymmetric fluorination of β-keto ester **147**.

15. Sulfenylation

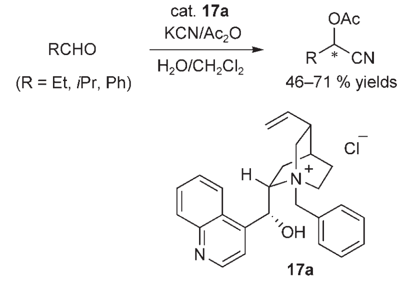
The asymmetric sulfenylation of β-keto sulfoxides has been effected in a solid–liquid biphasic system with *N*-benzylquininium chloride (**166g**) and potassium carbonate to furnish **235** in a diastereomeric ratio of 4:1 (Scheme 141).[160]



Scheme 141. Asymmetric sulfenylation of a β-keto sulfoxide.

16. Cyanation

Some asymmetric induction was observed in the cyanation of aldehydes with KCN/Ac_2O under phase-transfer conditions by using *N*-benzylcinchonidinium chloride (**17a**) as the catalyst (Scheme 142).[161]



Scheme 142. Asymmetric cyanation of aldehydes.

17. Conclusions

After the breakthrough made by the Merck research group, large numbers of naturally occurring alkaloid derivatives have been elaborated as powerful and readily available chiral phase-transfer catalysts. Purely synthetic chiral quaternary onium salts and chiral crown ethers, with their characteristic advantages, have also been developed. This catalyst manifold has certainly benefited not only in attaining considerably higher reactivity and stereoselectivity but also expanding the applicability of asymmetric phase-transfer catalysis in modern organic synthesis. In particular, the enantioselective functionalization of glycinate Schiff base introduced by O'Donnell and co-workers has been extensively utilized as a benchmark reaction to evaluate the efficiency of newly developed catalysts, through which it has been developed into a reliable and truly practical method for the synthesis of optically pure α-amino acids and their derivatives. In the meantime, the limitations of the existing systems have been highlighted, which has driven the development of new ones to extend the concept of asymmetric phase-transfer catalysis. We believe that continuous efforts should be devoted to the rational design of chiral phase-transfer catalysts and their applications to synthetically useful transformations. This would make great steps to establish genuinely sustainable chemical processes within the context of the forthcoming paradigm shift in the worldwide production of highly valuable substances in this century.

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[1] C. M. Starks, *J. Am. Chem. Soc.* **1971**, *93*, 195.
[2] Makosza's pioneering contributions are representative, see: a) M. Makosza, *Tetrahedron Lett.* **1966**, 4621; b) M. Makosza,

Tetrahedron Lett. **1966**, 5489; c) M. Makosza, *Tetrahedron Lett.* **1969**, 673; d) M. Makosza, *Tetrahedron Lett.* **1969**, 677; see also: e) A. Brändström, *Adv. Phys. Org. Chem.* **1977**, *15*, 267.

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

[4] a) T. Shioiri in *Handbook of Phase-Transfer Catalysis* (Eds.: Y. Sasson, R. Neumann), Blackie Academic & Professional, London, **1997**, chap. 14; b) M. J. O'Donnell, *Phases-The Sachem Phase Transfer Catalysis Review* **1998**, Issue 4, p. 5; c) M. J. O'Donnell, *Phases-The Sachem Phase Transfer Catalysis Review* **1999**, Issue 5, p. 5; d) A. Nelson, *Angew. Chem.* **1999**, *111*, 1685; *Angew. Chem. Int. Ed.* **1999**, *38*, 1583; e) T. Shioiri, S. Arai in *Stimulating Concepts in Chemistry* (Eds.: F. Vogtle, J. F. Stoddart, M. Shibasaki), Wiley-VCH, Weinheim, **2000**, p. 123; f) M. J. O'Donnell in *Catalytic Asymmetric Syntheses*, 2nd ed. (Ed.: I. Ojima), Wiley-VCH, New York, **2000**, chap. 10; g) M. J. O'Donnell, *Aldrichimica Acta* **2001**, *34*, 3; h) K. Maruoka, T. Ooi, *Chem. Rev.* **2003**. *103*, 3013; i) M. J. O'Donnell, *Acc. Chem. Res.* **2004**, *37*, 506; j) B. Lygo, B. I. Andrews, *Acc. Chem. Res.* **2004**, *37*, 518.

[5] a) M. Makosza, *Pure Appl. Chem.* **1975**, *43*, 439; b) H.-M. Yang, H.-S. Wu, *Catal. Rev.* **2003**, *45*, 463.

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

[7] A. Bhattacharya, U.-H. Dolling, E. J. J. Grabowski, S. Karady, K. M. Ryan, L. M. Weinstock, *Angew. Chem.* **1986**, *98*, 442; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 476.

[8] L. Ducry, F. Diederich, *Helv. Chim. Acta* **1999**, *82*, 981.

[9] T. B. K. Lee, G. S. K. Wong, *J. Org. Chem.* **1991**, *56*, 872.

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

[11] M. J. O'Donnell, S. Wu, J. C. Huffman, *Tetrahedron* **1994**, *50*, 4507.

[12] M. J. O'Donnell, W. D. Bennett, W. A. Bruder, W. N. Jacobsen, K. Knuth, B. LeClef, R. L. Polt, F. G. Boldwell, S. R. Mrozack, T. A. Cripe, *J. Am. Chem. Soc.* **1988**, *110*, 8520.

[13] a) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595; b) B. Lygo, J. Crosby, T. R. Lowdon, P. G. Wainwright, *Tetrahedron* **2001**, *57*, 2391; c) B. Lygo, J. Crosby, T. R. Lowdon, J. A. Peterson, P. G. Wainwright, *Tetrahedron* **2001**, *57*, 2403.

[14] E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414.

[15] B. Lygo, B. I. Andrews, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **2002**, *43*, 8015.

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

[17] T. Ooi, Y. Uematsu, K. Maruoka, *Tetrahedron Lett.* **2004**, *45*, 1675.

[18] S.-s. Jew, M.-S. Yoo, B.-S. Jeong II Y. Park, H.-g. Park, *Org. Lett.* **2002**, *4*, 4245.

[19] M.-S. Yoo, B.-S. Jeong, J. H. Lee, H.-g. Park, S.-s. Jew, *Org. Lett.* **2005**, *7*, 1129.

[20] a) G. Guillena, R. Kreiter, R. van de Coevering, R. J. M. Klein Gebbink, G. van Koten, P. Mazón, R. Chinchilla, C. Nájera, *Tetrahedron: Asymmetry* **2003**, *14*, 3705; b) P. Mazón, R. Chinchilla, C. Nájera, G. Guillena, R. Kreiter, R. J. M. Klein Gebbink, G. van Koten, *Tetrahedron: Asymmetry* **2002**, *13*, 2181.

[21] a) S.-s. Jew, B.-S. Jeong, M.-S. Yoo, H. Huh, H.-g. Park, *Chem. Commun.* **2001**, 1244; b) H.-g. Park, B.-S. Jeong, M.-S. Yoo, J.-H. Lee, B.-s. Park, M. G. Kim, S.-s. Jew, *Tetrahedron Lett.* **2003**, *44*, 3497.

[22] H.-g. Park, B.-S. Jeong, M.-S. Yoo, M.-k. Park, H. Huh, S.-s. Jew, *Tetrahedron Lett.* **2001**, *42*, 4645.

[23] H.-g. Park, B.-S. Jeong, M.-S. Yoo, J.-H. Lee, M.-k. Park, Y.-J. Lee, M.-J. Kim, S.-s. Jew, *Angew. Chem.* **2002**, *114*, 3162; *Angew. Chem. Int. Ed.* **2002**, *41*, 3036.

[24] R. Chinchilla, P. Mazón, C. Nájera, *Tetrahedron: Asymmetry* **2002**, *13*, 927.

[25] R. Chinchilla, P. Mazón, C. Nájera, F. J. Ortega, *Tetrahedron: Asymmetry* **2004**, *15*, 2603.

[26] T. Hashimoto, K. Maruoka, *Tetrahedron Lett.* **2003**, *44*, 3313.

[27] T. Ooi, E. Tayama, K. Doda, M. Takeuchi, K. Maruoka, *Synlett* **2000**, 1500.

[28] S. Shirakawa, K. Yamamoto, M. Kitamura, T. Ooi, K. Maruoka, *Angew. Chem.* **2005**, *117*, 631; *Angew. Chem. Int. Ed.* **2005**, *44*, 625.

[29] T. Ooi, Y. Uematsu, M. Kameda, K. Maruoka, *Angew. Chem.* **2002**, *114*, 1621; *Angew. Chem. Int. Ed.* **2002**, *41*, 1551.

[30] T. Hashimoto, Y. Tanaka, K. Maruoka, *Tetrahedron: Asymmetry* **2003**, *14*, 1599.

[31] T. Kano, S. Konishi, S. Shirakawa, K. Maruoka, *Tetrahedron: Asymmetry* **2004**, *15*, 1243.

[32] M. Kitamura, S. Shirakawa, K. Maruoka, *Angew. Chem.* **2005**, *117*, 1573; *Angew. Chem. Int. Ed.* **2005**, *44*, 1549.

[33] Z. Han, Y. Yamaguchi, M. Kitamura, K. Maruoka, *Tetrahedron Lett.* **2005**, *46*, 8555.

[34] Y. N. Belokon, M. North, T. D. Churkina, N. S. Ikonnikov, V. I. Maleev, *Tetrahedron* **2001**, *57*, 2491.

[35] T. Kita, A. Georgieva, Y. Hashimoto, T. Nakata, K. Nagasawa, *Angew. Chem.* **2002**, *114*, 2956; *Angew. Chem. Int. Ed.* **2002**, *41*, 2832.

[36] a) T. Shibuguchi, Y. Fukuta, Y. Akachi, A. Sekine, T. Ohshima, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 9539; b) T. Ohshima, T. Shibuguchi, Y. Fukuta, M. Shibasaki, *Tetrahedron* **2004**, *60*, 7743.

[37] W. E. Kowtoniuk, D. K. MacFarland, G. N. Grover, *Tetrahedron Lett.* **2005**, *46*, 5703; see also: M. E. Rueffer, L. K. Fort, D. K. MacFarland, *Tetrahedron: Asymmetry* **2004**, *15*, 3297.

[38] H. Sasai (Jpn. Kokai Tokkyo Koho), JP2003335780, **2003**.

[39] N. Mase, T. Ohno, N. Hoshikawa, K. Ohishi, H. Morimoto, H. Yoda, K. Takabe, *Tetrahedron Lett.* **2003**, *44*, 4073.

[40] B. Lygo, B. Allbutt, S. R. James, *Tetrahedron Lett.* **2003**, *44*, 5629.

[41] B. Lygo, B. Allbutt, *Synlett* **2004**, 326.

[42] a) Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, O. V. Larionov, S. R. Harutyunyan, S. Vyskocil, M. North, H. B. Kagan, *Angew. Chem.* **2001**, *113*, 2002; *Angew. Chem. Int. Ed.* **2001**, *40*, 1948; b) Y. N. Belokon, N. B. Bespalova, T. D. Churkina, I Cisarová, M. G. Ezernitskaya, S. R. Harutyunyan, R. Hrdina, H. B. Kagan, P. Kocovsky, K. A. Kochetkov, O. V. Larionov, K. A. Lyssenko, M. North, M. Polásek, A. S. Peregudov, V. V. Prisyazhnyuk, S. Vyskocil, *J. Am. Chem. Soc.* **2003**, *125*, 12860.

[43] S. Kumar, U. Ramachandran, *Tetrahedron: Asymmetry* **2003**, *14*, 2539.

[44] T. Ooi, D. Sakai, M. Takeuchi, E. Tayama, K. Maruoka, *Angew. Chem.* **2003**, *115*, 2002; *Angew. Chem. Int. Ed.*, **2003**, *42*, 5868.
[45] T. Ooi, M. Takeuchi, D. Kato, Y. Uematsu, E. Tayama, D. Sakai, K. Maruoka, *J. Am. Chem. Soc.* **2005**, *127*, 5073.
[46] R. Lépine, A.-C. Carbonnelle, J. Zhu, *Synlett* **2003**, 1455.
[47] A. Armstrong, J. N. Scutt, *Org. Lett.* **2003**, *5*, 2331.
[48] a) M. Nakoji, T. Kanayama, T. Okino, Y. Takemoto, *Org. Lett.* **2001**, *3*, 3329; b) M. Nakoji, T. Kanayama, T. Okino, Y. Takemoto, *J. Org. Chem.* **2002**, *67*, 7418.
[49] M. J. O'Donnell, F. Delgado, C. Hostettler, R. Schwesinger, *Tetrahedron Lett.* **1998**, *39*, 8775.
[50] M. J. O'Donnell, F. Delgado, R. S. Pottorf, *Tetrahedron* **1999**. *55*, 6347.
[51] a) R. Chinchilla, P. Mazón, C. Nájera, *Tetrahedron: Asymmetry* **2000**, *11*, 3277; b) R. Chinchilla, P. Mazón, C. Nájera, *Adv. Synth. Catal.* **2004**, *346*, 1186.
[52] B. Thierry, J.-C. Plaquevent, D. Cahard, *Tetrahedron: Asymmetry* **2001**, *12*, 983.
[53] B. Thierry, J.-C. Plaquevent, D. Cahard, *Tetrahedron: Asymmetry* **2003**, *14*, 1671.
[54] B. Thierry, T. Perrard, C. Audouard, J.-C. Plaquevent, D. Cahard, *Synthesis* **2001**, 1742.
[55] T. Danelli, R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, G. Tocco, *Tetrahedron: Asymmetry* **2003**, *14*, 461.
[56] a) H. Yu, H. Koshima, *Tetrahedron Lett.* **2003**, *44*, 9209; b) H. Tu, S. Takigawa, H. Koshima, *Tetrahedron* **2004**, *60*, 8405.
[57] S. Shirakawa, Y. Tanaka, K. Maruoka, *Org. Lett.* **2004**, *6*, 1429.
[58] B. Imperiali, S. L. Fisher, *J. Org. Chem.* **1992**, *57*, 757.
[59] a) B. Imperiali, T. J. Prins, S. L. Fisher, *J. Org. Chem.* **1993**, *58*, 1613; b) J. K. Kise, Jr., B. E. Bowler, *Tetrahedron: Asymmetry* **1998**, *9*, 3319.
[60] B. Imperiali, R. S. Roy, *J. Org. Chem.* **1995**, *60*, 1891.
[61] A. Torrado, B. Imperiali, *J. Org. Chem.* **1996**, *61*, 8940.
[62] a) B. Lygo, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **1999**, *40*, 1385; b) B. Lygo, *Tetrahedron Lett.* **1999**, *40*, 1389; c) B. Lygo, J. Crosby, J. A. Peterson, *Tetrahedron* **2001**, *57*, 6447.
[63] M. Nitz, A. R. Mezo, M. H. Ali, B. Imperiali, *Chem. Commun.* **2002**, 1912.
[64] B. Lygo, B. I. Andrews, *Tetrahedron Lett.* **2003**, *44*, 4499.
[65] B. Lygo, B. I. Andrews, D. Slack, *Tetrahedron Lett.* **2003**, *44*, 9039.
[66] B. Lygo, L. D. Humphreys, *Tetrahedron Lett.* **2002**, *43*, 6677.
[67] T. Ooi, M. Kameda, H. Tannai, K. Maruoka, *Tetrahedron Lett.* **2000**, *41*, 8339.
[68] C. Lemaire, S. Gillet, S. Guillouet, A. Plenevaux, J. Aerts, A. Luxen, *Eur. J. Org. Chem.* **2004**, 2899.
[69] T. Ooi, M. Takeuchi, K. Maruoka, *Synthesis* **2001**, 1716.
[70] S. Kumar, U. Ramachandran, *Tetrahedron Lett.* **2005**, *46*, 19.
[71] A. V. R. Rao, K. L. Reddy, A. S. Rao, T. V. S. K. Vittal, M. M. Reddy, P. L. Pathi, *Tetrahedron Lett.* **1996**, *37*, 3023.
[72] K. Tohdo, Y. Hamada, T. Shioiri, *Synlett* **1994**, 247.
[73] S. L. Castle, G. S. C. Srikanth, *Org. Lett.* **2003**, *5*, 3611.
[74] R. K. Boeckman, Jr., T. J. Clark, B. C. Shook, *Org. Lett.* **2002**, *4*, 2109.
[75] S. Kim, J. Lee, T. Lee, H.-g. Park, D. Kim, *Org. Lett.* **2003**, *5*, 2703.
[76] T. Ohshima, V. Gnanadesikan, T. Shibuguchi, Y. Fukuta, T. Nemoto, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 11206.
[77] a) C. Cativiela, M. D. Diaz-de-Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517; b) U. Schöllkopf, *Top. Curr. Chem.* **1983**, *109*, 65.
[78] M. J. O'Donnell, S. Wu, *Tetrahedron: Asymmetry* **1992**, *3*, 591.
[79] B. Lygo, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **1999**, *40*, 8671.
[80] a) Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, A. A. Chesnokov, O. V. Larionov, V. S. Parmar, R. Kumar, H. B. Kagan, *Tetrahedron: Asymmetry* **1998**, *9*, 851; b) Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, S. Vyskocil, H. B. Kagan, *Tetrahedron: Asymmetry* **1999**, *10*, 1723; c) Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, A. A. Chesnokov, O. V. Larionov, I. Singh, V. S. Parmar, S. Vyskocil, H. B. Kagan, *J. Org. Chem.* **2000**, *65*, 7041.
[81] a) Y. N. Belokon, M. North, V. S. Kublitski, N. S. Ikonnikov, P. E. Krasik, V. I. Maleev, *Tetrahedron Lett.* **1999**, *40*, 6105; b) Y. N. Belokon, R. G. Davies, M. North, *Tetrahedron Lett.* **2000**, *41*, 7245; c) Y. N. Belokon, R. G. Davies, J. A. Fuentes, M. North, T. Parsons, *Tetrahedron Lett.* **2001**, *42*, 8093; d) Y. N. Belokon, D. Bhave, D. D'Addario, E. Groaz, M. North, V. Tagliazucca, *Tetrahedron* **2004**, *60*, 1849; e) Y. N. Belokon, J. A. Fuentes, M. North, J. W. Steed, *Tetrahedron* **2004**, *60*, 3191.
[82] T. Ooi, M. Takeuchi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 5228.
[83] S.-s. Jew, B.-S. Jeong, J.-H. Lee, M.-S. Yoo, Y.-J. Lee, B.-s. Park, M. G. Kim, H.-g. Park, *J. Org. Chem.* **2003**, *68*, 4514.
[84] K. Maeda, R. A. Miller, R. H. Szumigala, Jr., A. Shafiee, S. Karady, J. D. Armstrong III, *Tetrahedron Lett.* **2005**, *46*, 1545.
[85] S.-s. Jew, Y.-J. Lee, J. Lee, M. J. Kang, B.-S. Jeong, J.-H. Lee, M.-S. Yoo, M.-J. Kim, S.-h. Choi, J.-M. Ku, H.-g. Park, *Angew. Chem.* **2004**, *116*, 2436; *Angew. Chem. Int. Ed.*, **2004**, *43*, 2382.
[86] Y.-J. Lee, J. Lee, M.-J. Kim, T.-S. Kim, H.-g. Park, S.-s. Jew, *Org. Lett.* **2005**, *7*, 1557.
[87] For a comprehensive review on the use of peptide enolates, see: D. Seebach, A. K. Beck, A. Studer in *Modern Synthetic Methods*, *Vol. 7* (Eds.: B. Ernst, C. Leumann), VCH, Weinheim, **1995**, p. 1.
[88] M. J. O'Donnell, T. P. Burkholder, V. V. Khau, R. W. Roeske, Z. Tian, *Pol. J. Chem.* **1994**, *68*, 2477.
[89] a) M. J. O'Donnell, C. Zhou, W. L. Scott, *J. Am. Chem. Soc.* **1996**, *118*, 6070; b) M. J. O'Donnell, M. D. Drew, R. S. Pottorf, W. L. Scott, *J. Comb. Chem.* **2000**, *2*, 172.
[90] a) T. Ooi, E. Tayama, K. Maruoka, *Angew. Chem.* **2003**, *115*, 599; *Angew. Chem. Int. Ed.* **2003**, *42*, 579; b) K. Maruoka, E. Tayama, T. Ooi, *Proc. Nat. Acad. Sci. USA* **2004**, *101*, 5824.
[91] W. Nerinckx, M. Vandewalle, *Tetrahedron: Asymmetry* **1990**, *1*, 265.
[92] a) P. Bravo, G. Resnati, *Tetrahedron: Asymmetry* **1990**, *1*, 661; b) G. S. Lal, G. P. Pez, R. G. Syvret, *Chem. Rev.* **1996**, *96*, 1737; c) *Enantiocontrolled Synthesis of Fluoro-organic Compounds* (Ed.: V. A. Soloshonok), Wiley, Chichester, **1999**.
[93] S. Arai, M. Oku, T. Ishida, T. Shioiri, *Tetrahedron Lett.* **1999**, *40*, 6785.
[94] E. J. Corey, Y. Bo, J. Busch-Petersen, *J. Am. Chem. Soc.* **1998**, *120*, 13000.
[95] a) K. Manabe, *Tetrahedron Lett.* **1998**, *39*, 5807; b) K. Manabe, *Tetrahedron* **1998**, *54*, 14465.
[96] E. V. Dehmlow, S. Düttmann, B. Neumann, H.-G. Stammler, *Eur. J. Org. Chem.* **2002**, 2087.
[97] T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi, K. Maruoka, *Angew. Chem.* **2003**, *115*, 3926; *Angew. Chem. Int. Ed.* **2003**, *42*, 3796.
[98] E. J. Park, M. H. Kim, D. Y. Kim, *J. Org. Chem.* **2004**, *69*, 6897.
[99] a) M. B. Andrus, E. J. Hicken, J. S. Stephens, *Org. Lett.* **2004**, *6*, 2289; b) M. B. Andrus, E. J. Hicken, J. S. Stephens, D. K. Bedke, *J. Org. Chem.* **2005**, *70*, 3670.
[100] M. Bella, S. Kobbelgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 3670.
[101] For reviews on catalytic asymmetric Michael reaction, see: a) N. Krause, A. Hoffmann-Röder, *Synthesis* **2001**, 171; b) M. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033; c) M. Kanai, M. Shibasaki in *Catalytic Asymmetric Synthesis*, 2nd ed. (Ed.: I. Ojima), Wiley, New York, **2000**, p. 569; d) K. Tomioka, Y. Nagaoka in *Comprehensive Asymmetric Catalysis*, *Vol. 3* (Eds.:

E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, chap. 31.1.

[102] D. J. Cram, G. D. Y. Sogah, *J. Chem. Soc. Chem. Commun.* **1981**, 625.

[103] S. Aoki, S. Sasaki, K. Koga, *Tetrahedron Lett.* **1989**, *30*, 7229.

[104] J. Crosby, J. F. Stoddart, X. Sun, M. R. W. Venner, *Synthesis* **1993**, 141.

[105] E. V. Dehmlow, V. Knufinke, *Liebigs Ann. Chem.* **1992**, 283.

[106] E. Brunet, A. M. Poveda, D. Rabasco, E. Oreja, L. M. Font, M. S. Batra, J. C. Rodrígues-Ubis, *Tetrahedron: Asymmetry* **1994**, *5*, 935.

[107] L. Tõke, P. Bakó, G. M. Keserü, M. Albert, L. Fenichel, *Tetrahedron* **1998**, *54*, 213.

[108] R. S. E. Conn, A. V. Lovell, S. Karady, L. M. Weinstock, *J. Org. Chem.* **1986**, *51*, 4710.

[109] E. Diez-Barra, A. de la Hoz, S. Merino, A. Rodríguez, P. Sánchez-Verdú, *Tetrahedron* **1998**, *54*, 1835.

[110] K. Shishido, K. Goto, S. Miyoshi, Y. Takaishi, M. Shibuya, *J. Org. Chem.* **1994**, *59*, 406.

[111] a) A. Loupy, J. Sansoulet, A. Zaparucha, C. Merienne, *Tetrahedron Lett.* **1989**, *30*, 333; b) A. Loupy, A. Zaparucha, *Tetrahedron Lett.* **1993**, *34*, 473.

[112] T. Perrard, J.-C. Plaquevent, J.-R. Desmurs, D. Hébrault, *Org. Lett.* **2000**, *2*, 2959.

[113] D. Y. Kim, S. C. Huh, S. M. Kim, *Tetrahedron Lett.* **2001**, *42*, 6299.

[114] R. T. Dere, R. R. Pal, P. S. Patil, M. M. Salunkhe, *Tetrahedron Lett.* **2003**, *44*, 5351.

[115] T. Ooi, D. Ohara, K. Fukumoto, K. Maruoka, *Org. Lett.* **2005**, *7*, 3195.

[116] E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347.

[117] F.-Y. Zhang, E. J. Corey, *Org. Lett.* **2000**, *2*, 1097; for similar Michael reactions with silyl enol ethers as a donor substrate which utilizes halogen–silicon interactions, see: F.-Y. Zhang, E. J. Corey, *Org. Lett.* **2001**, *3*, 639; this type of catalysis with chiral quaternary ammonium salts has recently been reviewed: T. Ooi, K. Maruoka, *Acc. Chem. Res.* **2004**, *37*, 526.

[118] M. J. O'Donnell, F. Delgado, E. Domínguez, J. de Blas, W. L. Scott, *Tetrahedron: Asymmetry* **2001**, *12*, 821.

[119] S. Arai, R. Tsuji, A. Nishida, *Tetrahedron Lett.* **2002**, *43*, 9535.

[120] T. Akiyama, M. Hara, K. Fuchibe, S. Sakamoto, K. Yamaguchi, *Chem. Commun.* **2003**, 1734.

[121] S. Arai, K. Tokumaru, T. Aoyama, *Chem. Parm. Bull.* **2004**, *52*, 646.

[122] B. Lygo, B. Allbutt, E. H. M. Kirton, *Tetrahedron Lett.* **2005**, *46*, 4461.

[123] Y.-J. Lee, J. Lee, M.-J. Kim, B.-S. Jeong, J.-H. Lee, T.-S. Kim, J. Lee, J.-M. Ku, S.-s. Jew, H.-g. Park, *Org. Lett.* **2005**, *7*, 3207.

[124] F.-Y. Zhang, E. J. Corey, *Org. Lett.* **2004**, *6*, 3397.

[125] a) P. Bakó, T. Kiss, L. Tõke, *Tetrahedron Lett.* **1997**, *38*, 7259; b) P. Bakó, K. Vizvárdi, Z. Bajor, L. Tõke, *Chem. Commun.* **1998**, 1193; c) P. Bakó, T. Novák, K. Ludányi, B. Pete, L. T̃ke, G. Keglevich, *Tetrahedron: Asymmetry* **1999**, *10*, 2373; d) T. Novák, J. Tatai, P. Bakó, M. Czugler, G. Keglevich, L. T̃ke, *Synlett* **2001**, 424; e) T. Novák, P. Bakó, G. Keglevich, A. Dobó, K. Vékey, L. T̃ke, *J. Inclusion Phenom. Macrocyclic Chem.* **2001**, *40*, 207; f) T. Bakó, P. Bakó, Á. Szöllõsy, M. Czugler, G. Keglevich, L. T̃ke, *Tetrahedron: Asymmetry* **2002**, *13*, 203.

[126] T. Ooi, S. Fujioka, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 11790.

[127] C. M. Gasparski, M. J. Miller, *Tetrahedron* **1991**, *47*, 5367.

[128] a) T. Ooi, M. Taniguchi, M. Kameda, K. Maruoka, *Angew. Chem.* **2002**, *114*, 4724; *Angew. Chem. Int. Ed.* **2002**, *41*, 4542; b) T. Ooi, M. Kameda, M. Taniguchi, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 9685.

[129] S. Arai, K. Hasegawa, A. Nishida, *Tetrahedron Lett.* **2004**, *45*, 1023.

[130] T. Ooi, M. Kameda, J. Fujii, K. Maruoka, *Org. Lett.* **2004**, *6*, 2397.

[131] A. Okada, T. Shibuguchi, T. Ohshima, H. Masu, K. Yamaguchi, M. Shibasaki, *Angew. Chem.* **2005**, *117*, 4640; *Angew. Chem. Int. Ed.* **2005**, *44*, 4564.

[132] a) S. Arai, T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 2145; b) S. Arai, Y. Shirai, T. Ishida, T. Shioiri, *Tetrahedron* **1999**, *55*, 6375.

[133] S. Arai, Y. Shirai, T. Ishida, T. Shioiri, *Chem. Commun.* **1999**, 49.

[134] a) S. Arai, T. Ishida, T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 8299; b) S. Arai, T. Shioiri, *Tetrahedron* **2002**, *58*, 1407.

[135] S. Arai, K. Tokumaru, T. Aoyama, *Tetrahedron Lett.* **2004**, *45*, 1845.

[136] T. Ooi, M. Takahashi, K. Doda, K. Maruoka, *J. Am. Chem. Soc.* **2002**, *124*, 7640.

[137] S. Arai, S. Hamaguchi, T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 2997.

[138] S. Arai, K. Nakayama, T. Ishida, T. Shioiri, *Tetrahedron Lett.* **1999**, *40*, 4215.

[139] a) M. J. Porter, J. Skidmore, *Chem. Commun.* **2000**, 1215; b) T. Nemoto, T. Ohshima, M. Shibasaki, *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 94.

[140] a) S. Arai, H. Tsuge, T. Shioiri, *Tetrahedron Lett.* **1998**, *39*, 7563; b) S. Arai, H. Tsuge, M. Oku, M. Miura, T. Shioiri, *Tetrahedron* **2002**, *58*, 1623.

[141] a) B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1998**, *39*, 1599; b) B. Lygo, P. G. Wainwright, *Tetrahedron* **1999**, *55*, 6289.

[142] B. Lygo, D. C. M. To, *Tetrahedron Lett.* **2001**, *42*, 1343.

[143] a) J. Ye, Y. Wang, R. Liu, G. Zhang, Q. Zhang, J. Chen, X. Liang, *Chem. Commun.* **2003**, 2714; b) J. Ye, Y. Wang, J. Chen, X. Liang, *Adv. Synth. Catal.* **2004**, *346*, 691.

[144] a) W. Adam, P. B. Rao, H.-G. Degen, C. R. Saha-Möller, *Tetrahedron: Asymmetry* **2001**, *12*, 121; b) W. Adam, P. B. Rao, H.-G. Degen, A. Levai, T. Patonay, C. R. Saha-Möller, *J. Org. Chem.* **2002**, *67*, 259.

[145] E. J. Corey, F.-Y. Zhang, *Org. Lett.* **1999**, *1*, 1287.

[146] B. Lygo, D. C. M. To, *Chem. Commun.* **2002**, 2360.

[147] a) T. Bakó, P. Bakó, G. Keglevich, P. Bombicz, M. Kubinyi, K. Pál, S. Bodor, A. Makó, L. T̃ke, *Tetrahedron: Asymmetry* **2004**, *15*, 1589; b) P. Bakó, T. Bakó, A. Mészáros, G. Keglevich, A. Szöllõsy, S. Bodor, A. Makó, L. T̃ke, *Synlett* **2004**, 643.

[148] a) T. Geller, A. Gerlach, C. M. Krüger, H.-C. Militzer, *Tetrahedron Lett.* **2004**, *45*, 5065; b) T. Geller, C. M. Krüger, H.-C. Militzer, *Tetrahedron Lett.* **2004**, *45*, 5069.

[149] M. T. Allingham, A. Howard-Jones, P. J. Murphy, D. A. Thomas, P. W. R. Caulkett, *Tetrahedron Lett.* **2003**, *44*, 8677.

[150] T. Ooi, D. Ohara, M. Tamura, K. Maruoka, *J. Am. Chem. Soc.* **2004**, *126*, 6844.

[151] V. K. Aggarwal, C. Lopin, F. Sandrinelli, *J. Am. Chem. Soc.* **2003**, *125*, 7596.

[152] J. Aires-Sousa, A. M. Lobo, S. Prabhakar, *Tetrahedron Lett.* **1996**, *37*, 3183.

[153] E. Murugan, A. Siva, *Synthesis* **2005**, 2022.

[154] a) M. Masui, A. Ando, T. Shioiri, *Tetrahedron Lett.* **1988**, *29*, 2835; b) E. V. Dehmlow, S. Wagner, A. Müller, *Tetrahedron* **1999**, *55*, 6335.

[155] E. F. J. de Vries, L. Ploeg, M. Colao, J. Brussee, A. van der Gen, *Tetrahedron: Asymmetry* **1995**, *6*, 1123.

[156] R. A. Bhunnoo, Y. Hu, D. I. Lainé. R. C. D. Brown, *Angew. Chem.* **2002**, *114*, 3629; *Angew. Chem. Int. Ed.* **2002**, *41*, 3479.

[157] R. C. D. Brown, J. F. Keily, *Angew. Chem.* **2001**, *113*, 4628; *Angew. Chem. Int. Ed.* **2001**, *40*, 4496.

[158] C. Hofstetter, P. S. Wilkinson, T. C. Pochapsky, *J. Org. Chem.* **1999**, *64*, 8794.

[159] D. Y. Kim, E. J. Park, *Org. Lett.* **2002**, *4*, 545.

[160] B. Wladislaw, L. Marzorati, F. C. Biaggio, R. R. Vargas, M. B. Bjorklund, J. Zukerman-Schpector, *Tetrahedron* **1999**, *55*, 12023.

[161] S. Juliá, A. Ginebreda, *Tetrahedron Lett.* **1979**, 2171.