Enantioselective Amino Acid Synthesis by Chiral Phase-Transfer Catalysis

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I. Introduction

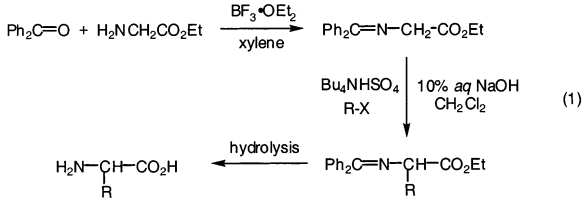
The α-amino acids, which are usually formulated as $H_2NCH(R)CO_2H$ despite their zwitterionic nature, are by far the most important, numerous, and diverse family of the naturally occurring amino acids. Although a set of only 19 together with the heterocyclic amino acid proline comprises the building blocks from which polypeptide chains are assembled under genetic control, the total number of α-amino acids identified as occurring free or incorporated in natural products of animals, plants, and microorganisms is estimated in the hundreds, and the list of such α-amino acids grows all the time. The majority of these naturally found α-amino acids have the L configuration at the α-carbon. Many natural α-amino acids of the D series are also encountered in nonprotein compounds of plants, fungi, and microorganisms but not generally in animals and never in any protein.

A wide variety of methods, which are in principle general, are available for the synthesis of α-amino acids.[1] Some of them include the amination of α-halo acids, the Strecker synthesis, and approaches through hydantoins and oxazolones, which were developed in the early days of amino acid chemistry but still retain their importance. Several modern elaborations of these routes have been developed. Syntheses in which the amino group is introduced by reduction or rearrangement have also been available for a long time. Despite the great variety of the well-tried methods, the development of new general strategies is still an active field. In addition, considerable effort has been paid in the development of asymmetric methodologies by certain chiral catalysts in the α-amino acid field. Our main concern in this review has been to illustrate the range of asymmetric approaches available for the laboratory preparation of optically active amino acids by using chiral phase-transfer catalysts.[2,3]

II. Amino Acid Synthesis with Achiral Phase-Transfer Catalysts

Phase-transfer catalysis is a very useful approach that typically involves simple experimental operations, mild reaction conditions, inexpensive and environmentally benign reagents and solvents, and large-scale reactions. Initially, achiral phase-transfer catalysts can be utilized to synthesize various types of α-amino acids. For example, azide anion or trifluoroacetamide reacts with α-bromo esters under phase-transfer conditions to furnish α-amino acid precursors.[4,5] Achiral phase-transfer catalysts are also employable for conversion of α-amino acids to the corresponding esters,[6,7] amides,[8,9] and didehydroamino acid derivatives.[10−12]

Alkylation of glycine derivatives is a very powerful way of preparing α-alkyl-α-amino acids. Benzophenone imines of glycine esters and aminoacetonitrile are frequently utilized as protected glycine derivatives for phase-transfer alkylations. A stable Schiff base was derived from glycine ester and benzophenone under forcing conditions (toluene or xylene reflux with catalytic $BF_3{\cdot}OEt_2$).[13,14] Phase-transfer alkylation of such a Schiff base with tetrabutylammonium hydrogensulfate and alkyl halide in 10% aqueous sodium hydroxide/methylene chloride and subsequent acid hydrolysis of the resulting alkylated Schiff base provides the corresponding amino acid (eq 1). This approach is applicable to the polyhalophenylalanine synthesis.[15] Benzophenone imines and benzaldehyde imines of glycine esters can be utilized for monoalkylation, dialkylation, Michael addition, and aldol reaction under solid−liquid phase-transfer catalysis.[16,17]



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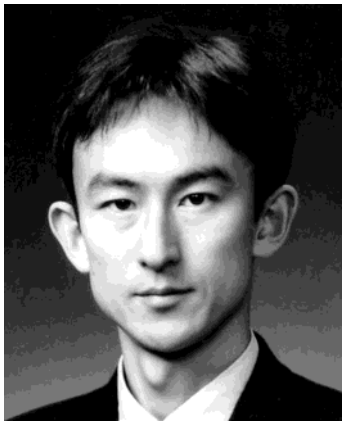
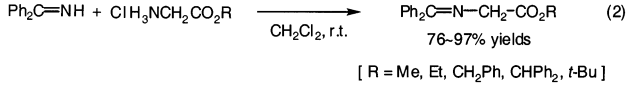
Keiji Maruoka was born in 1953 in Mie, Japan. He graduated from Kyoto University (1976) and received his Ph.D. degree (1980) from the University of Hawaii (Thesis Director: Professor. H. Yamamoto). He became an assistant professor of Nagoya University (1980) and was promoted to a lecturer (1985) and an associate professor (1990) there. He moved to Hokkaido University as a full professor (1995–2001), and he has been a professor of chemistry at Kyoto University since 2000. He was awarded the Japan Chemical Society Award for Young Chemist (1985), the Inoue Prize for Science (2000), and the Ichimura Prize for Science (2001). He is an associate editor of *Chemistry Letters* and is a member of the international advisory editorial board of *Organic & Biomolecular Chemistry*. He has a wide range of research interests in synthetic organic chemistry. His current research interests include bidentate Lewis acids in organic synthesis, molecular recognition with bowl-shaped molecules, and practical asymmetric synthesis with chiral C_2-symmetric spiro-type phase-transfer catalysts.



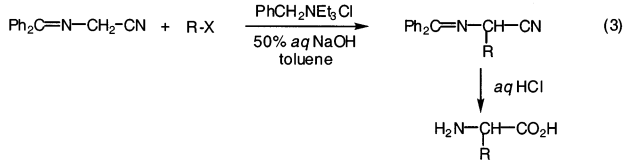
Takashi Ooi was born in 1965 in Nagoya, Japan. He received his Ph.D. degree (1994) from Nagoya University under the direction of Professor Hisashi Yamamoto. He has been granted a Fellowship of the Japan Society for the Promotion of Sciences (JSPS) for Japanese Junior Scientists (1992–1995), during which he joined the group of Professor Julius Rebek, Jr. at MIT as a postdoctoral fellow (1994–1995). He was appointed as an assistant professor at Hokkaido University in 1995 and promoted to a lecturer (1998). In 2001 he moved to Kyoto University and currently is an associate professor of chemistry. He was awarded the Japan Chemical Society Award for Young Chemist (1999). His current research interests are focused on the development of new and useful synthetic methodologies by designing main-group metal and organic catalysts including chiral C_2-symmetric ammonium salts.

Later, the transimination of glycine ester with benzophenone imine as a highly reactive benzophenone equivalent has been developed (eq 2). This mild procedure is employable for the preparation of various types of benzophenone imine derivatives.[15]



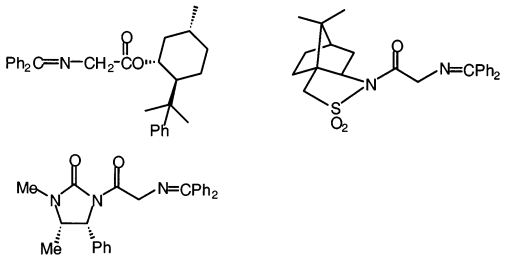
(2)

Benzophenone imine of aminoacetonitrile is also utilized as a protected glycine derivative. The catalytic phase-transfer alkylation of the Schiff base is carried out with benzyltriethylammonium chloride (BTEAC) as the phase-transfer catalyst and 50% aqueous NaOH as the aqueous phase (eq 3).[18]

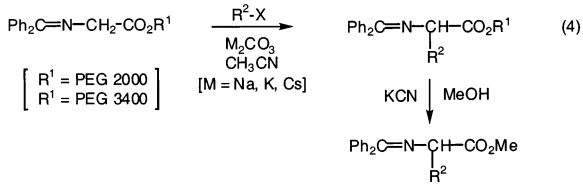


(3)

Synthesis of optically active α-amino acids has been realized with chiral substrates such as chiral imines of glycine esters, benzophenone imine of chiral glycine esters, amides and imides derived from chiral alcohols, chiral amines, and chiral imidazolidinones.[19,20]



Benzophenone imines of glycine derivative supported on a soluble poly(ethylene glycol) (PEG) was smoothly alkylated with various electrophiles in the presence of a carbonate base in acetonitrile (eq 4).[21] The presence of the polymer provided a phase-transfer catalysis environment which markedly accelerates the reaction. After cleavage from the polymer, α-amino methyl esters can be generated in good yields.



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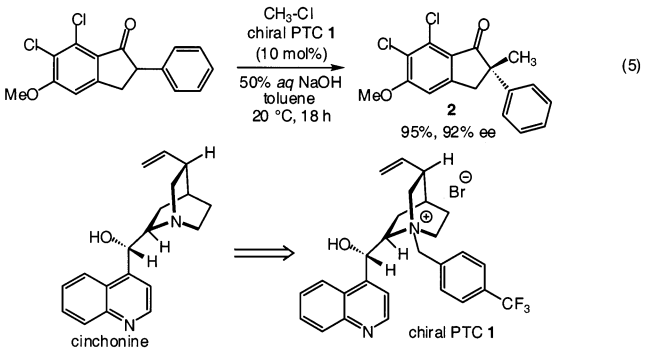
III. Enantioselective Alkylation of Glycine Derivatives for α-Alkyl-α-amino Acid Synthesis

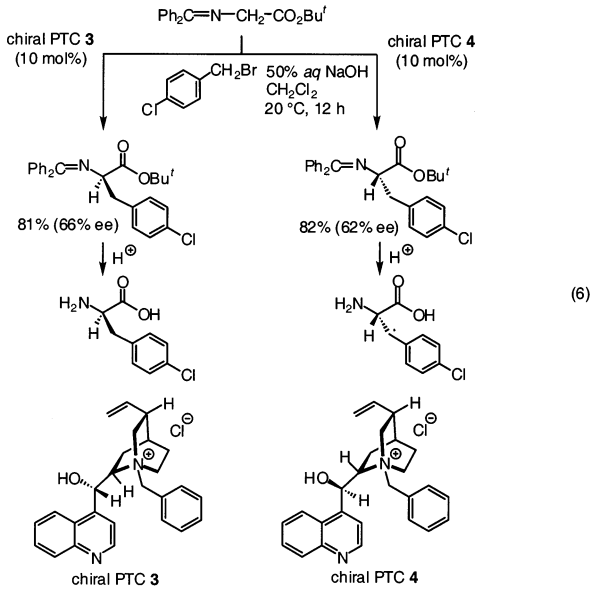
Asymmetric synthesis of α-amino acids by phase-transfer alkylation using a chiral catalyst and a prochiral protected glycine derivative would provide a particularly attractive method for the preparation of optically active α-amino acids. However, initial study on asymmetric alkylation of carbonyl compounds by chiral phase-transfer catalyst showed only disappointing results.[22] In 1984, the first efficient chiral phase-transfer catalyst, *N*-(*p*-(trifluoromethyl)-benzyl)cinchonidium bromide (**1**), was devised by the Merck group for asymmetric methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone, giving **2** with 92% ee in this particular case (eq 5).[23] After 5 years of this successful endeavor, similar *N*-(benzyl)cinchonidium chloride **3** has been applied by O'Donnell

to asymmetric alkylation of *N*-(diphenylmethylene)-glycine *tert*-butyl ester. In contrast to 6,7-dichloro-



(5)

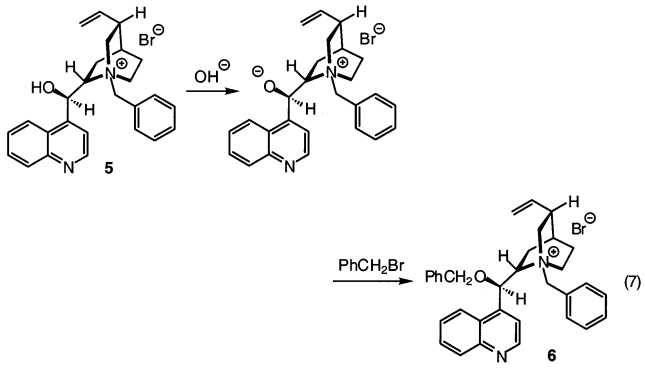
5-methoxy-2-phenyl-1-indanone substrate, two potentially complicating factors should be considered. First, a prochiral protected glycine derivative is acyclic, and hence the enantiocontrol seems to be difficult. Second, the selective monoalkylation of a glycine derivative gives rise to an active methine product which should not be racemized under phase-transfer conditions. Despite these potential difficulties, the first practical asymmetric synthesis of α-amino acids has been developed by using phase-transfer catalysis (eq 6).[24]



(6)

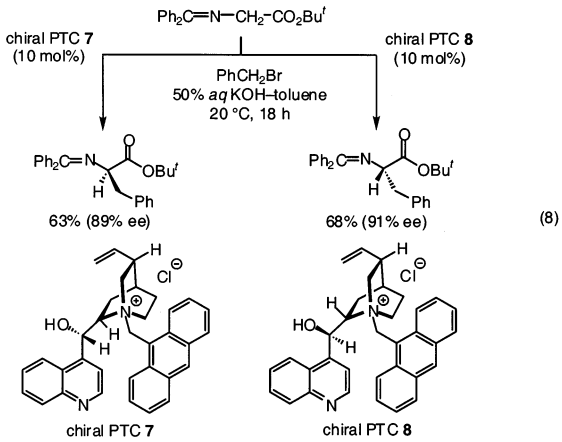
In the presence of *N*-(benzyl)cinchonidium bromide, *R* enantiomer can be generated with moderate enantioselectivity, and by simply switching the catalyst from the cinchonine to cinchonidine series, the absolute configuration of the product turned out to be opposite (*S* enantiomer) with similar enantioselectivity. A single recrystallization and subsequent deprotection afforded essentially optically pure α-amino acids.

A theoretical and mechanistic study has been carried out on the asymmetric alkylation of a prochiral protected glycine derivative with chiral *N*-(benzyl)-cinchonidium chloride **3**. In a theoretical study, molecular-recognition techniques are used to examine the complexes formed between *N*-(diphenylmethylene)glycine *tert*-butyl ester enolate and *N*-(benzyl)-cinchonidium chloride **3**.[25] Consideration of a general mechanistic scheme for the monoalkylation of a prochiral protected glycine derivative under phase-transfer catalysis invoked that a number of undesirable processes can occur in competition with the formation of the optically active product. As a result of these mechanistic studies, it is necessary to consider the possibility that the active catalyst in the asymmetric PTC alkylation of *N*-(benzyl)cinchonidinium bromide **5** is the *N*-alkyl-*O*-alkyl cinchona salt **6** which is formed in situ during the alkylation reaction (eq 7).[26]



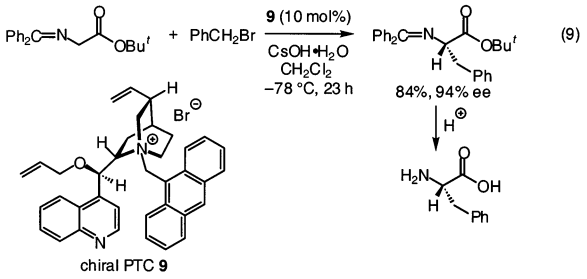
(7)

Although asymmetric phase-transfer alkylation of a prochiral glycine derivative can be achieved by using chiral phase-transfer catalysts derived from relatively cheap, commercially available cinchona alkaloids, the only drawback of this approach is the moderate enantioselectivity of α-alkyl-α-amino acid products. These products can often be obtained in optically pure form by recrystallization, but the material losses detract from the overall efficiency of this process. Clearly, if the enantioselectivity of the alkylation process could be significantly improved, this would substantially enhance the appeal of this approach. Accordingly, a new class of cinchona alkaloid-derived quaternary ammonium phase-transfer catalysts bearing a *N*-anthracenylmethyl function have been developed by two independent research groups. Lygo designed *N*-anthracenylmethylammonium salts **7** and **8** and applied to the asymmetric phase-transfer alkylation of *N*-(diphenylmethylene)-glycine *tert*-butyl ester to synthesize α-alkyl-α-amino acids with much higher enantioselectivity (89−92% ee) (eq 8).[27]



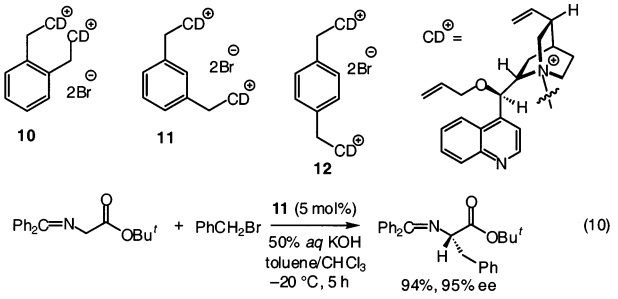
(8)

On the other hand, Corey prepared *O*-allyl-*N*-anthracenylmethyl cinchonidium salt **9**. By using solid $CsOH \cdot H_2O$ and very low temperature, they achieved high asymmetric induction in the asymmetric phase-transfer alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (eq 9).[28] The structure of the catalyst is confirmed by X-ray analysis after crystallization of *O*-allyl-*N*-anthracenylmethyl cinchonidium *p*-nitrophenoxide.



(9)

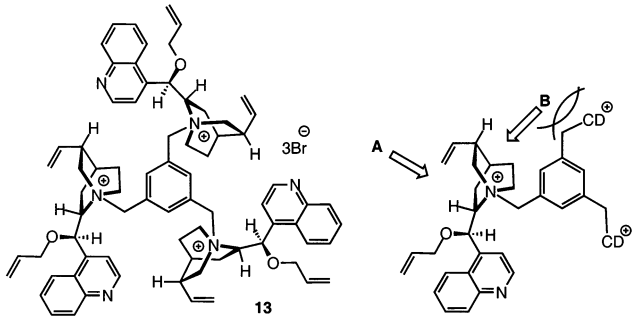
In connection with the development of Sharpless asymmetric dihydroxylation, the discovery of ligands with two independent cinchona alkaloid units attached to heterocyclic spacers led to considerable increases in both the enantioselectivity and the scope of the substrate. This dimerization concept has been successfully introduced to the new design of dimeric cinchona alkaloid-derived chiral phase-transfer catalysts. Accordingly, Jew prepared several dimeric ammonium salts **10**, **11**, and **12** from cinchonidine and α,α′-dibromo-*o*-xylene, α,α′-dibromo-*m*-xylene, and α,α′-dibromo-*p*-xylene, respectively. The enantioselective efficiency of these catalysts was evaluated by asymmetric phase-transfer alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester using 5 mol % of catalysts **10**−**12**, and among these the *meta*-dimeric catalyst **11** showed the highest enantioselectivity (eq 10).[29]

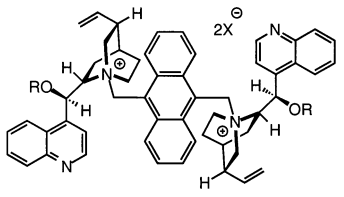


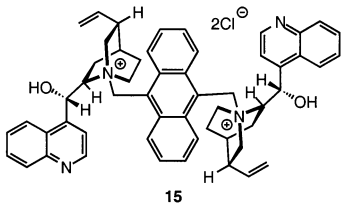
(10)

Jew further developed this strategy to synthesize triply oriented cinchona alkaloid-derived chiral phase-transfer catalyst **13** from α,α′,α″-tribromomesitylene and 3 equiv of cinchonidine. The catalytic enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with the trimeric catalyst **13** exhibited the high enantioselectivity by combination with various types of alkyl halides.[30] Since the direction **B** is blocked by two *meta*-substituted cinchona units in **13**, glycine ester enolate can form an ion pair with **13** from the less hindered direction **A**.

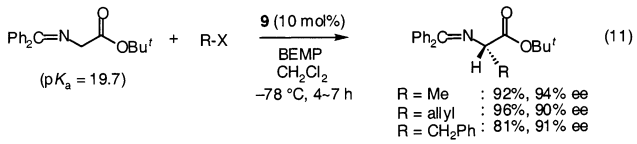
Nájera also prepared new dimeric cinchonidine- and cinchonine-derived ammonium salts **14** and **15** which incorporate a dimethylanthracenyl bridge as a spacer. These catalysts are utilized for the catalytic enantioselective alkylation of *N*-(diphenylmethylene)-glycine *tert*-butyl ester with different alkyl halides in a biphasic system consisting of 50% aqueous KOH and toluene/$CHCl_3$ mixture to furnish α-alkyl-α-amino acids in good yields and up to 90% ee.[31]







From a practical viewpoint, the need for efficient stirring can be problematic in heterogeneous reactions such as phase-transfer reaction processes. To realize a homogeneous system in the asymmetric alkylations, the organic soluble, nonionic phosphazene base (BEMP or BTPP) is successfully utilized by combination with the chiral quaternary ammonium catalysts (eq 11).[32] Using either Schwesinger base BEMP or BTPP, only a small amount of the anion of *N*-(diphenylmethylene)glycine *tert*-butyl ester would be generated at equilibrium. This anion could then be removed by reaction with alkyl halide, which in turn would serve to drive the formation of further enolate anion by reestablishing the acid/base equilibrium.



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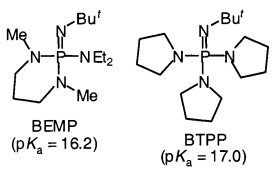
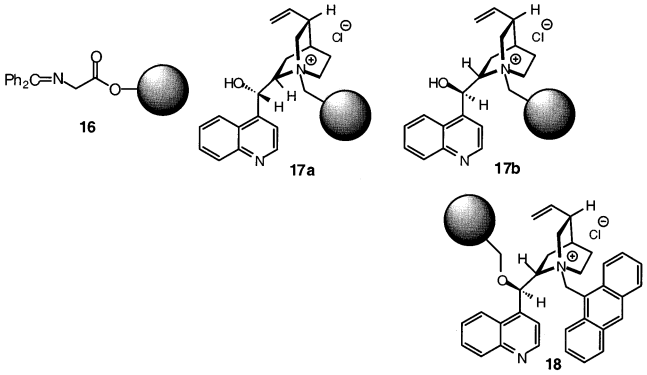
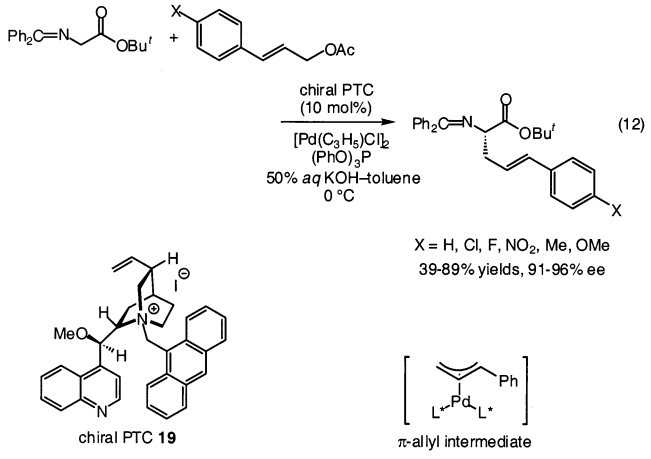


Catalytic enantioselective alkylations of *N*-(diphenylmethylene)glycine ester have been carried out with

polymer-bound glycine substrates **16** or in the presence of polymer-supported cinchona alkaloid-derived ammonium salts **17** and **18** as chiral phase-transfer catalysts. The latter attempt seems to be important since the enantioselective synthesis of α-amino acids employing easily available and re-usable chiral catalysts presents clear advantages for large-scale synthesis. O'Donnell used Wang-resin-bound derivatives of *N*-(diphenylmethylene)glycine esters by combination with organic soluble Schwesinger base (BEMP or BTPP).[33] Nájera carried out *N*-alkylation of cinchona alkaloids with Merrifield resin and employed them as chiral phase-transfer catalysts.[34] In both cases, the observed enantioselectivity is not very impressive. However, Cahard and Plaquevent greatly improved the stereoselectivity by attaching Merrifield resin on the hydroxy moiety of cinchonidine derivative.[35]

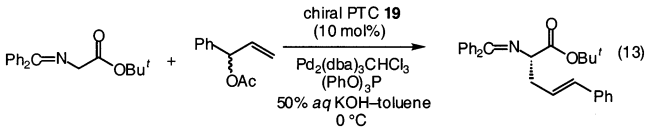


In the asymmetric alkylation of a prochiral protected glycine derivative by chiral phase-transfer catalysis, so far alkyl halides are typically utilized as alkylation agents. Recently, Takemoto found that allylic acetates by combination with palladium catalysts are employable for such asymmetric alkylation (eq 12).[36] Since this asymmetric allylation proceeds

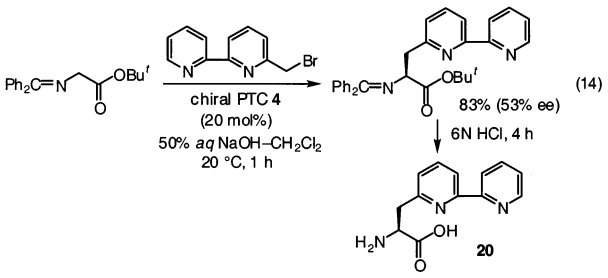


via π-allyl palladium(II) intermediate, both *primary* and *secondary* allylic acetates give the same allylation products (eq 13).

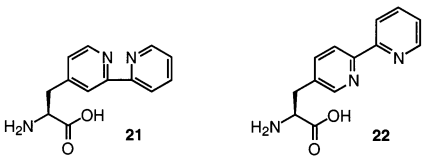
Several researchers apply the asymmetric phase-transfer alkylation of a prochiral protected glycine derivative to synthesize various types of useful amino acid derivatives. Imperiali carried out the enantioselective synthesis of (*S*)-α-amino-(2,2′-bipyridin-6-



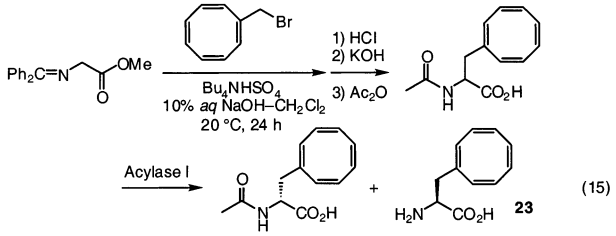
yl)propanoic acid **20** through the asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with 6-(bromomethyl)-2,2′-bipyridine using the chiral phase-transfer catalyst *N*-benzylchinchonidium chloride **4** (eq 14).[37] Although the alkylation proceeds with modest asymmetric induction (53% ee), one recrystallization of the alkylation product from hexane gives essentially pure material (>99% ee). The amino acid **20** is incorporated into two model peptides to synthesize unnatural metal-binding amino acids.



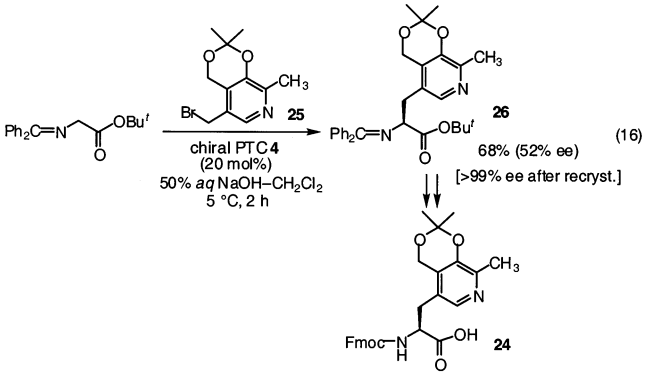
Imperiali and Bowler independently prepared a series of 2-amino-3-(2,2′-bipyridinyl)propanoic acids **21** and **22** in a similar manner, which contain an unobstructed N−N′ chelation moiety and are expected to provide metal-binding properties complementary to those reported for **20**.[38]



Pirrung synthesized cyclooctatetraene amino acid **23** in racemic forms with the following expectations: (1) meaningful conformational changes with barriers comparable to those for amide rotation, potentially providing both structural limitation and flexibility; (ii) potent excited-state quenchers and efficient electron acceptor, which are useful for studies of light- and redox-activated processes; (iii) to bind transition metals and actinides effectively. This material is subjected to kinetic resolution with Acylase I to furnish (*S*)-**23** in 43% yield (eq 15).[39]



Imperiali accomplished a stereoselective synthesis of a pyridoxol amino acid **24** which has been incorporated into oligopeptides and subsequently converted to reactive pyridoxal analogues. The key step involves an enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with the bromide **25** using the chiral phase-transfer catalyst *N*-benzylchinchonidium chloride (**4**) to furnish **26** in 52% ee (eq 16).[40] One recrystallization of the optically enriched product affords enantiomerically pure (>99% ee) material.



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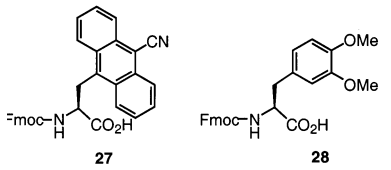
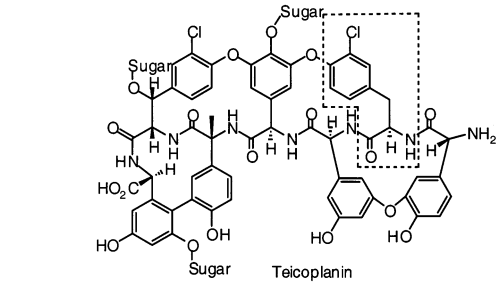
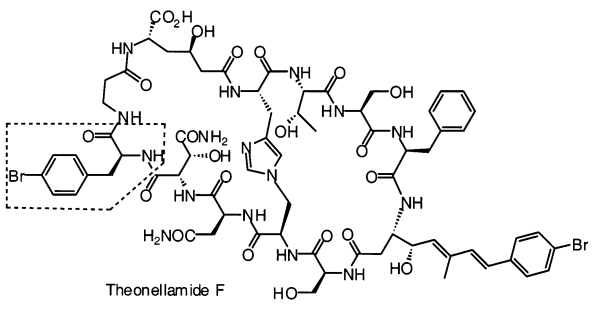
Two new nonstandard amino acids **27** and **28** are synthesized according to O'Donnell's procedure and incorporated into peptides via solid-phase synthesis to afford the prototype for a photoinduced electron transfer-based metal ion chemosensor.[41]

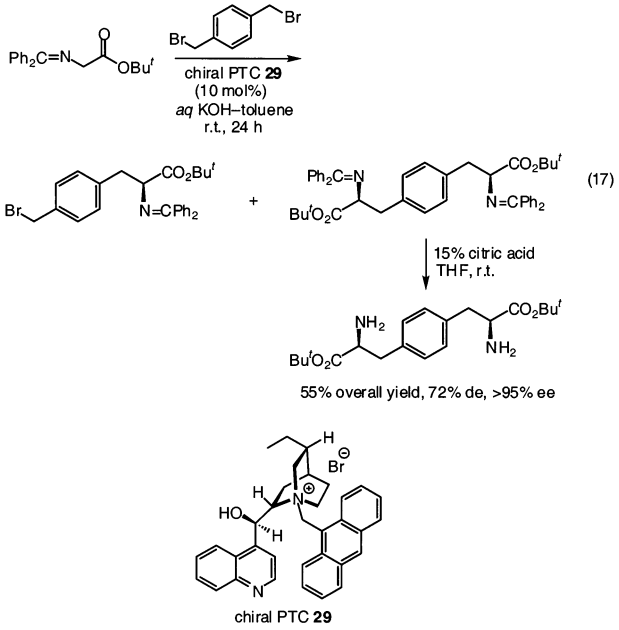


Asymmetric phase-transfer alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester by chiral phase-transfer catalyst *N*-benzylchinchonidium chloride (**4**) can be applied to natural product synthesis as demonstrated by the synthesis of glycopeptide antibiotics Teicoplanin and Theonellamide F.[42,43]



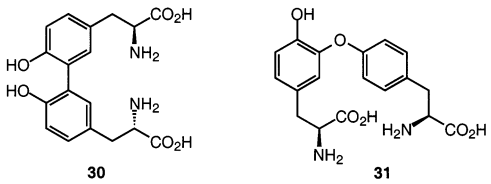


Lygo applied a phase-transfer catalyst *N*-anthracenylmethyl dihydrocinchonidium bromide **29** to the enantio- and diastereoselective synthesis of a series of bis-α-amino esters (eq 17).[44]



(17)

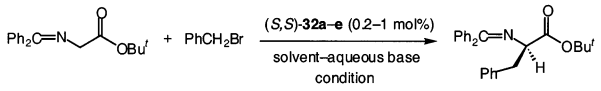
This approach is further extended to the enantio- and diastereoselective synthesis of dityrosine **30** and isodityrosine **31**, which represent the simplest members of a group of naturally occurring tyrosine-derived α-amino acids and peptides that contain oxidatively coupled aromatic nuclei.[45]



As clearly outlined in this section, most of the elaborated chiral phase-transfer catalysis for the asymmetric synthesis of amino acids using prochiral glycine derivative as a key substrate rely on the use of cinchona alkaloid derivatives, which unfortunately constitutes a major difficulty of the structural modifications, especially upon considering fine-tuning of catalysts to attain sufficient reactivity and selectivity. In this context, the structurally rigid, chiral spiro ammonium salts of type **32** derived from commercially available (*S*)- or (*R*)-1,1′-bi-2-naphthol have been designed by the authors as a new C_2-symmetric chiral phase-transfer catalyst and successfully applied to the highly efficient, catalytic enantioselective synthesis of various α-amino acids under mild phase-transfer conditions.[46]

Initial attempt was made on the benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with 1 mol % of symmetric (*S*,*S*)-**32a** in 50% aqueous NaOH−benzene (volume ratio = 1:3) at room temperature, and the corresponding benzylation product

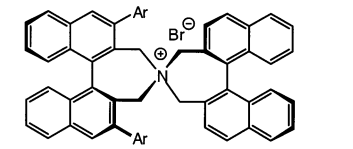
Table 1. Effect of Catalyst Structure, Solvent, and Aqueous Base on the Reactivity and Selectivity of Phase-Transfer Benzylation



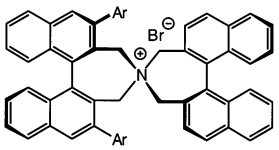
entry	catalyst (mol %)	solvent	base	condition (°C, h)	% yield	% ee
1	**32a** (1)	benzene	50% NaOH	r.t.; 10	76	73 (*R*)
2	**32b** (1)			r.t.; 10	43	81 (*R*)
3		toluene		0; 5	62	88 (*R*)
4			50% KOH	0; 0.5	82	89 (*R*)
5	**32c** (1)			0; 0.5	95	96 (*R*)
6	**32d** (1)			0; 0.5	91	98 (*R*)
7	**32d** (0.2)			0; 12	81	98 (*R*)
8	**32e** (1)			0; 2	79	99 (*R*)
9	**32e** (1)			0; 12	90	99 (*R*)[a]
10	**32e** (0.2)			0; 48	72	99 (*R*)[a]

[a] Under argon atmosphere.

was obtained in 76% yield with 73% ee (*R*) (entry 1 in Table 1). Introduction of an aromatic substituent on the 3,3′-position of one binaphthyl subunit of the catalyst (Ar) afforded a beneficial effect on the enantiofacial discrimination as the reaction with (*S*,*S*)-**32b** resulted in formation of the product in 43%



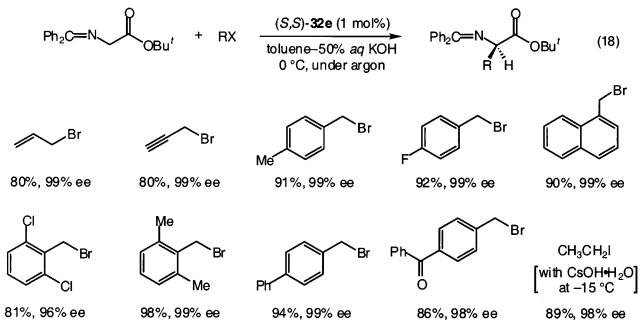
(*S*,*S*)-**32a** (Ar = H), **b** (Ar = Ph), **c** (Ar = β-Np)
d (Ar = 3,5-Ph_2-Ph), **e** (Ar = 3,4,5-F_3-Ph)



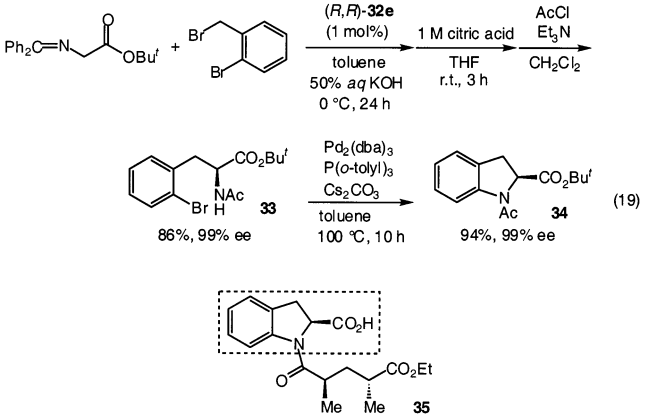
(*R*,*R*)-**32**

yield with 81% ee (entry 2). Use of toluene as organic solvent at lower reaction temperature (0 °C) led to even higher enantioselectivity (88% ee) (entry 3). Moreover, the reaction under the influence of (*S*,*S*)-**32b** was completed within 30 min at 0 °C with 50% KOH as an aqueous base, giving the product in 81% yield with 89% ee (entry 4). Switching the catalyst to (*S*,*S*)-**32c** and sterically more hindered (*S*,*S*)-**32d** further increased the enantioselectivity to 96% ee and 98% ee, respectively (entries 5 and 6), and virtually complete stereochemical control was achieved using (*S*,*S*)-**32e** as catalyst (entry 8). The lower chemical yield of the benzylation with (*S*,*S*)-**32e** was ascribed to the intervention of enolate oxidation by aerobic oxygen, and this problem was overcome by simply performing the reaction under argon atmosphere (entry 9). Notable advantage of this method is that the catalyst loading can be reduced to 0.2 mol % without loss of enantiomeric excess (entries 7 and 10).[47]

(*S*,*S*)-**32e** is the catalyst of choice for the preparation of a variety of essentially enantiopure α-amino acids by this transformation as shown in eq 18. Facile asymmetric synthesis of α-amino acids usually inaccessible by enzymatic processes becomes feasible by employing appropriate electrophiles such as *ortho*-disubstituted benzyl bromides. In the reaction with the simple alkyl halides such as ethyl iodide, use of aqueous cesium hydroxide (CsOH) as a basic phase at lower reaction temperature is generally recommended.[47]

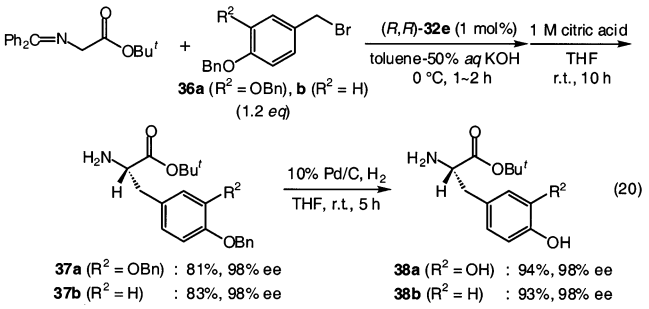


Since both enantiomers of the catalyst of type **32** can be readily assembled in exactly the same manner starting from either (*R*)- or (*S*)-1,1′-bi-2-naphthol, a wide variety of natural and unnatural α-amino acids can be synthesized in an enantiomerically pure form by the phase-transfer catalytic alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester. The utility of such advantage has been demonstrated by asymmetric synthesis of (*S*)-*N*-acetylindoline-2-carboxylate **34**, a key intermediate in the synthesis of the ACE inhibitor **35**. The structure and stereochemical integrity of **33** were simultaneously constructed by the asymmetric alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with *o*-bromobenzyl bromide in the presence of the catalyst (*R*,*R*)-**32e**, and subsequent hydrolysis with citric acid and *N*-acetylation afforded **33** in 86% yield with 99% ee (*S*). According to the Buchwald's procedure,[48] almost enantiopure **33** was efficiently converted to **34** (94%, 99% ee) (eq 19).[47]



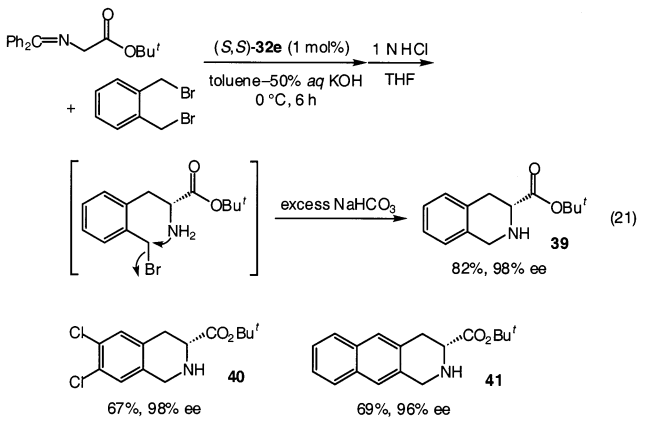
The synthetic utility of chiral phase-transfer catalysis using **32** was further highlighted by the facile synthesis of L-Dopa ester and its analogue, which have usually been prepared by either asymmetric

hydrogenation of eneamides or enzymatic processes and tested as potential drugs for the treatment of Parkinson's disease. Catalytic phase-transfer alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with the requisite benzyl bromide **36a** in toluene-50% KOH aqueous solution proceeded smoothly at 0 °C under the influence of (*R*,*R*)-**32e** (1 mol %) to furnish fully protected L-Dopa *tert*-butyl ester, which was subsequently hydrolyzed with a 1 M citric acid in THF at room temperature for 10 h to afford the corresponding amino ester **37a** in 81% yield with 98% ee. Debenzylation of **37a** under catalytic hydrogenation conditions produced the desired L-Dopa *tert*-butyl ester (**38a**) in 94% yield. The successful asymmetric synthesis of natural tyrosine *tert*-butyl ester (**38b**) in a similar manner strongly implies the feasibility of highly enantioselective synthesis of various L-Dopa analogues (eq 20). Furthermore, a "scale-up" experiment with 5.00 g of the starting Schiff base and 7.77 g of **36a** was performed to provide 3.37 g of the desired L-Dopa *tert*-butyl ester (**38a**).[49]

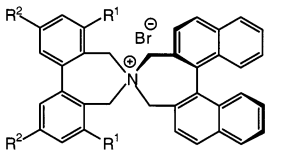


Moreover, the catalytic and chiral efficiency of (*S*,*S*)-**32e** has been successfully applied to the asymmetric synthesis of isoquinoline derivatives, important conformationally constrained α-amino acids to be incorporated into peptidic or nonpeptidic structures, giving useful information for SAR analysis and, eventually, for the development of compounds with improved biological activity.

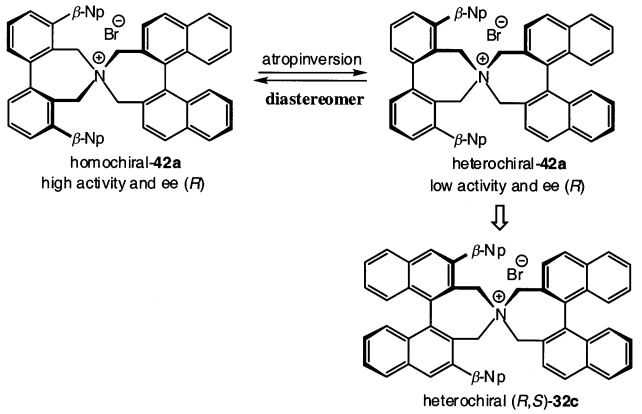
Treatment of *N*-(diphenylmethylene)glycine *tert*-butyl ester with α,α′-dibromo-*o*-xylene (1.1 equiv) in toluene−50% KOH aqueous solution (volume ratio = 2:1) in the presence of (*S*,*S*)-**32e** (1 mol %) at 0 °C for 6 h showed complete consumption of the starting Schiff base. Acidic hydrolysis with 1 N HCl and subsequent treatment of the in situ generated *primary* amine moiety with an excess amount of $NaHCO_3$ facilitated intramolecular ring closure to give 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid *tert*-butyl ester (**39**) in 82% yield with 98% ee. A variety of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives possessing different aromatic substituents such as **40** and **41** can be conveniently prepared in a similar manner with excellent enantioselectivity (eq 21).[50]

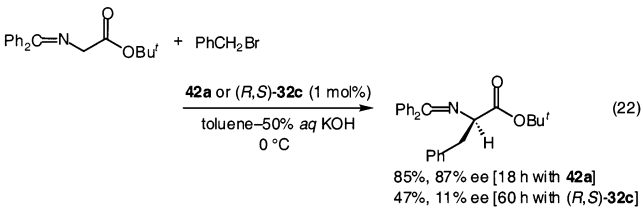


Although the conformationally rigid *N*-spiro structure created by two chiral binaphthyl subunits represents a characteristic feature of **32** and seems essential for attaining sufficient reactivity and enantioselectivity, it also imposes limitations on the catalyst design due to the imperative use of the two chiral binaphthyl moieties. Accordingly, the authors developed a new C_2-symmetric chiral quaternary ammonium bromide **42** possessing an achiral, conformationally flexible biphenyl subunit.[51]

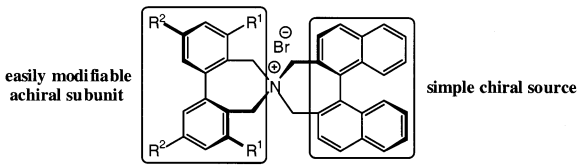


The phase-transfer benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with the catalyst **42a** having β-naphthyl group on 3,3′-position of the flexible biphenyl moiety was found to proceed smoothly at 0 °C to afford the corresponding alkylation product in 85% yield with 87% ee (*R*) after 18 h (eq 22). The origin of the observed chiral efficiency could be ascribed to the considerable difference of catalytic activity between the rapidly equilibrated, diastereomeric homo- and heterochiral catalysts; namely, homochiral-**42a** is primarily responsible for the efficient asymmetric phase-transfer catalysis to produce the alkylation product with high enantiomeric excess, whereas heterochiral-**42a** displays low reactivity and stereoselectivity. Supportive evidence for this hypothesis was that the benzylation with 1 mol % of conformationally rigid, heterochiral (*R*,*S*)-**32c** under similar conditions proceeded slowly and, after 60 h, gave rise to the corresponding alkylation product in 47% yield with low enantiomeric excess (11% ee, *R*) as also shown in eq 22.



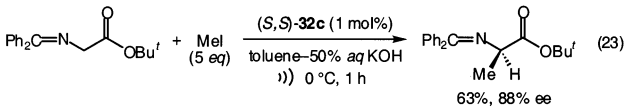


This unique phenomenon provides a new yet powerful strategy in the molecular design of chiral catalysts, i.e., the requisite chirality can be served by the simple binaphthyl moiety and an additional structural requirement for fine-tuning of reactivity and selectivity can be fulfilled by an easily modifiable achiral biphenyl structure; this certainly obviates the use of two chiral units and should be greatly appreciated in the synthesis of a variety of chiral catalysts with different steric and/or electronic properties.

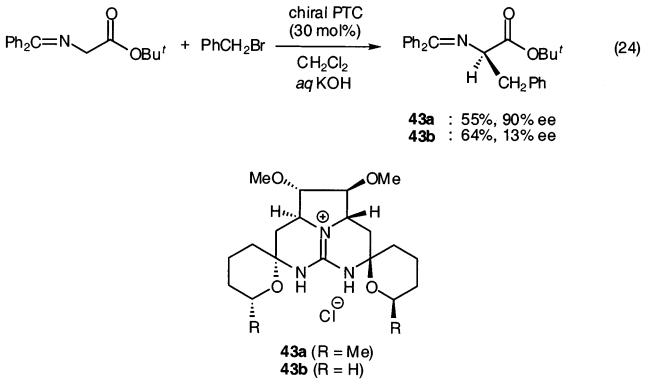


Actually, quaternary ammonium bromide possessing a sterically demanding substituent such as **42b** can be easily prepared, and the benzylation with **42b** as a catalyst gave the alkylation product in 95% yield with 92% ee. Further, the enantioselectivity was enhanced to 95% ee when **42c** was used as a catalyst.[51]

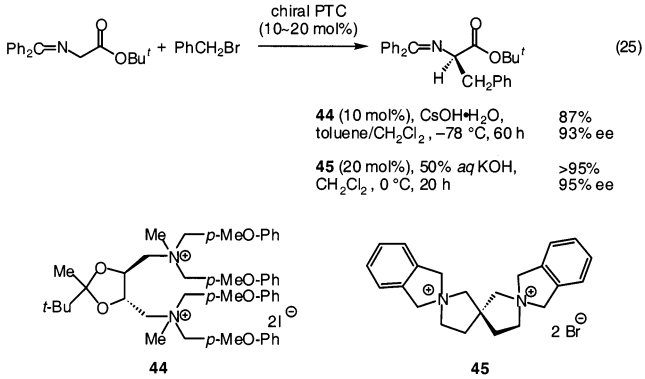
The common phase-transfer reactions are carried out using a mechanical stirrer, and vigorous stirring is usually necessary to attain a sufficient reaction rate, which sometimes results in unfortunate unreproducibility and inefficiency, especially in preparative large-scale reactions. In this respect, the combined use of ultrasonic irradiation has gained recognition and a number of studies have been performed especially in solid−liquid phase-transfer reactions. Liquid (organic)−liquid (aqueous) phase-transfer reaction also benefits from the use of ultrasound because sonication produces homogenization, i.e., very fine emulsions, which greatly increase the reactive interfacial area. Indeed, sonication of the reaction mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester, methyl iodide (5 equiv), and (*S*,*S*)-**32c** (1 mol %) in toluene−50% KOH aqueous solution (volume ratio = 3:1) at 0 °C for 1 h gave rise to the corresponding alkylation product in 63% yield with 88% ee (eq 23), demonstrating that the reaction was speeded up markedly, and the chemical yield and enantioselectivity were comparable with those of the reaction with simple stirring (0 °C for 8 h; 64%, 90% ee).[52]



Quite recently, several new types of chiral phase-transfer catalysts have been developed for asymmetric phase-transfer alkylation of prochiral glycine derivatives. Nagasawa reported a novel C_2-symmetric chiral cyclic guanidine of type **43**, which was originally utilized for a hetero Michael reaction, for asymmetric benzylation of *N*-(diphenylmethylene)-glycine *tert*-butyl ester (eq 24).[53] Here, introduction of methyl substituents is crucially important to achieve the high enantioselectivity. By using chiral catalyst **43a**, asymmetric alkylation with various alkyl halides gives ∼80% ee's.



Shibasaki designed tartrate-derived bis-ammonium salt **44** as a two-center catalyst and achieved high enantioselectivity in asymmetric benzylation at low temperature (eq 25).[54] Sasai also designed spiro-type bis-ammonium salt **45** as a chiral phase-transfer catalyst and applied it to similar asymmetric alkylation reaction (eq 25).[55] In both cases, the observed enantioselectivity is highly dependent on the structural modification of catalysts.

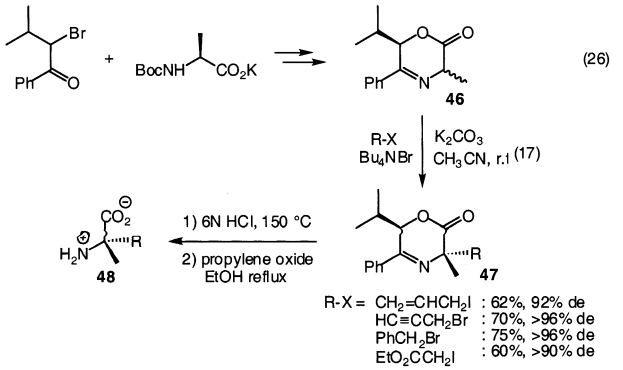


IV. Enantioselective Alkylation of Glycine and α-Alkyl-α-amino Acid Derivatives for α,α-Dialkyl-α-amino Acid Synthesis

Nonproteinogenic α,α-dialkyl-α-amino acids have played a special role in the design of peptides with enhanced properties. This is not only because they possess stereochemically stable quaternary carbon centers, but their incorporation into peptides results in the significant influence on the conformational preferences, which eventually provides useful information for the elucidation of enzymatic mechanisms. Furthermore, α,α-dialkyl-α-amino acids themselves are often effective enzyme inhibitors and also constitute a series of interesting building blocks for the synthesis of various biologically active compounds. Accordingly, development of truly efficient methods

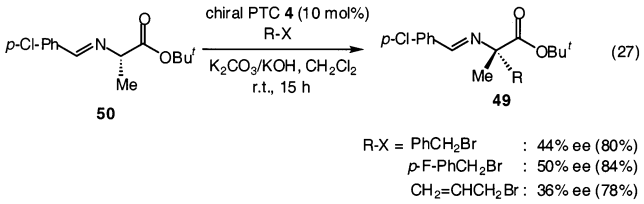
for their preparation, especially in an enantiomerically pure form, has become of great importance, and numerous studies have been made for this purpose.[1e,56]

Chiral 3,6-dihydro-2*H*-1,4-oxazin-2-ones **46** act as very reactive chiral cyclic alanine equivalents and can be diastereoselectively alkylated and allylated under solid−liquid phase-transfer conditions with K_2CO_3 as base. Hydrolysis of the resulting alkylated or allylated oxazinones **47** allows the preparation of enantiomerically enriched (*S*)-α-methyl α-amino acids **48** (eq 26).[57]



(26)

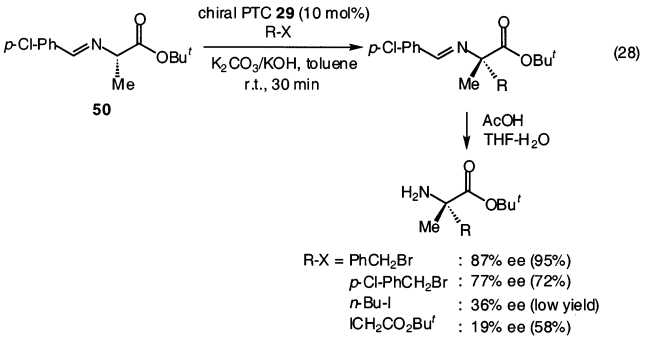
O'Donnell already reported the asymmetric synthesis of monoalkylated α-amino acids from protected glycine derivatives by liquid−liquid phase-transfer reaction in the presence of cinchona alkaloid-derived quaternary ammonium salts. On the basis of this finding, he developed the asymmetric synthesis of α-methyl-α-amino acids **49** from the Schiff base derivative **50** of aromatic aldehyde and alanine *tert*-butyl ester using solid−liquid phase-transfer catalytic alkylations (eq 27).[58] Examination on the effect of different base systems revealed the importance of using the mixed base KOH/K_2CO_3.



(27)

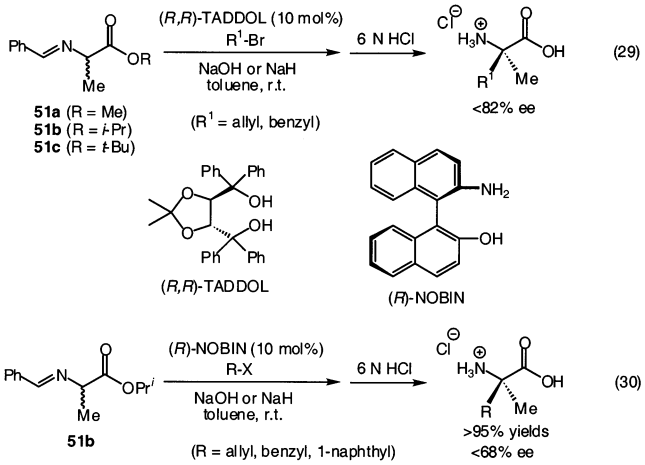
Lygo also applied his catalyst, *N*-anthracenylmethyl dihydrocinchonidium bromide **29**, to the enantioselective alkylation of a series of alanine-derived imine **50**. Again, use of solid KOH/K_2CO_3 as the stoichiometric base allows such alkylation with enantiomeric excesses up to 87% ee. This transformation realized rapid access to the synthesis of α,α-dialkyl-α-amino acids (eq 28).[59]

Other types of chiral phase-transfer catalysts are also employable for the enantioselective alkylation of alanine-derived imines **51**. Enantiopure (4*R*,5*R*)- or (4*S*,5*S*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL) and 2-hydroxy-2′-amino-1,1′-binaphthyl (NOBIN) are shown to catalyze such enantioselective alkylations with solid NaOH or NaH at room temperature under the influence of 10 mol % catalysts (eqs 29 and 30).[60,61]



(28)

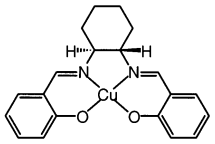
In general, stoichiometric use of TADDOL is necessary to achieve high asymmetric induction.



(29)

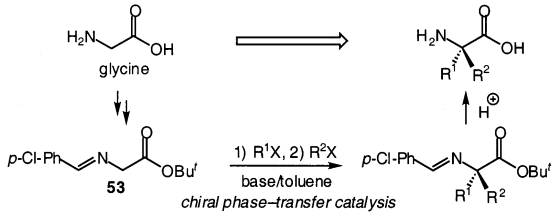
(30)

Nickel(II)− or optimally copper(II)−salen complexes **52** functioned as asymmetric phase-transfer catalysts, with just 1 mol % of the catalyst being sufficient to produce α,α-dialkyl-α-amino acids with >90% enantiomeric excess in certain cases.[62]

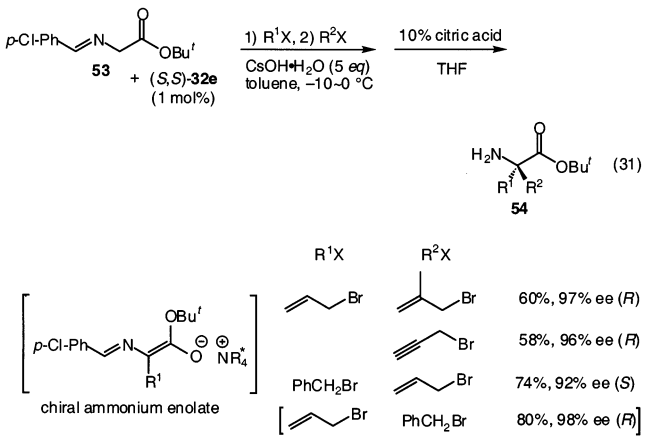


52

With the limited generality in mind, the authors envisioned that two different side chains could be introduced directly to the aldimine Schiff base **53** derived from glycine in a highly enantioselective manner by appropriate chiral phase-transfer catalysis. This possibility of one-pot asymmetric double alkylation has been realized by using C_2-symmetric chiral quaternary ammonium bromide (*S*,*S*)-**32** whose effectiveness for the asymmetric synthesis of α-alkylamino acids has already been demonstrated in the previous section.[63]

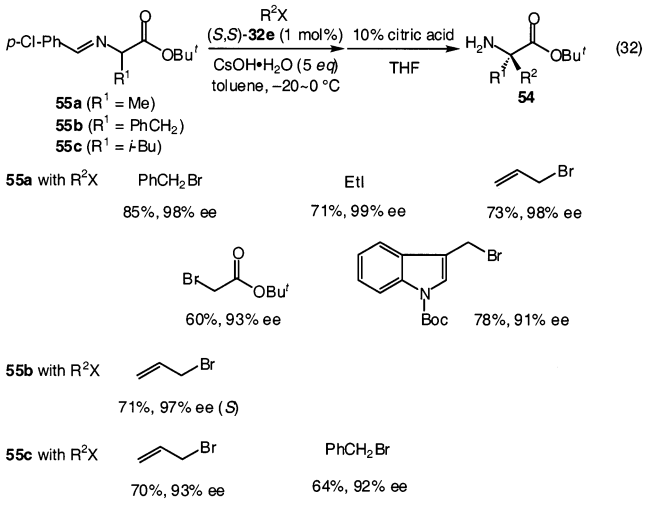


Initial treatment of the toluene solution of **53** and (*S*,*S*)-**32c** (1 mol %) with allyl bromide (1 equiv) and CsOH·H_2O (5 equiv) at −10 °C for 3.5 h and the subsequent reaction with benzyl bromide (1.2 equiv) at 0 °C for 30 min resulted in formation of the double-alkylation product **54** ($R^1 = CH_2CH{=}CH_2$, $R^2 = CH_2$-Ph) in 61% yield with 87% ee after hydrolysis. It is of interest that the use of (*S*,*S*)-**32e** as catalyst under similar conditions enhanced both chemical yield and the enantioselectivity to 80% and 98% ee, respectively. The distinct feature of this procedure is that it enables straightforward asymmetric synthesis of various α,α-dialkyl-α-amino acids, including those otherwise inaccessible from the naturally occurring amino acids as exemplified in eq 31. Notably, in the double alkylation of **53** by the addition of the halides in a reverse order, the absolute configuration of the product **54** was confirmed to be opposite, indicating the intervention of the expected chiral ammonium enolate in the second alkylation stage (eq 31).

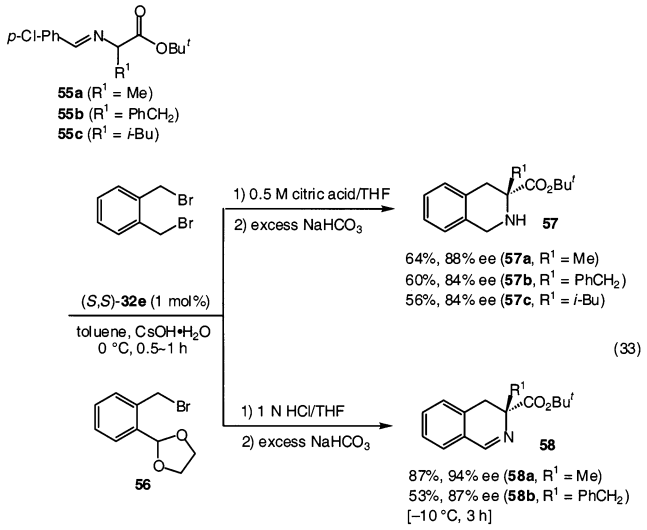


Since the stereochemistry of the newly created quaternary carbon center was apparently determined in the second alkylation process, the core of this method should be applicable to the asymmetric alkylation of aldimine Schiff base **55** derived from the corresponding α-amino acids. Indeed, rapid benzylation of DL-alanine-derived imine **55a** occurred at 0 °C in toluene with benzyl bromide ($R^2 = CH_2Ph$) (1.2 equiv) and CsOH·H_2O (5 equiv) using (*S*,*S*)-**32e** (1 mol %) as a catalyst, giving the alkylation product **54** (R^1 = Me, $R^2 = CH_2Ph$; 85%) in an almost enantiomerically pure form (98% ee). Other selected results illustrated in eq 32 demonstrate the remarkable efficiency and generality of this method. Use of *tert*-butyl α-bromoacetate as an alkylating agent allows facile enantioselective access to α-methyl aspartic acid, and asymmetric synthesis of α-methyl tryptophan, an important amino acid for the design of dipeptoid with high affinity for the central cholecystokinin receptor, can also be realized. In addition, the phase-transfer catalytic alkylation of aldimine Schiff base derived from other α-amino acids such as DL-phenylalanine (**55b**) and DL-leucine (**55c**) also appeared to be feasible with high efficiency, providing the desired noncoded amino acid esters **54** with excellent asymmetric induction.[63]

This powerful quaternization method enabled the hitherto difficult catalytic asymmetric synthesis of



quaternary isoquinoline derivatives with **55a** as a substrate. When **55a** was treated with α,α′-dibromo-*o*-xylene, CsOH·H_2O (5 equiv), and (*S*,*S*)-**32e** (1 mol %) in toluene at 0 °C for 0.5 h, the transient monoalkylation product was rapidly produced, which was transformed into the desired **57a** (64%, 88% ee) during workup procedure. The efficiency of this alkylation−cyclization sequence was scarcely affected by the substituent of the starting α-amino acid as demonstrated by the reactions with **55b** and **55c**. Catalytic asymmetric phase-transfer alkylation of **55a** with functionalized benzyl bromide **56** (1.1 equiv) followed by the sequential treatment with 1 N HCl and then excess $NaHCO_3$ furnished the corresponding dihydroisoquinoline derivative **58a** in 87% with 94% ee. The sensitivity of this system involving intramolecular imine formation to the steric demand of α-substituent of the parent amino acid was implied by the decreased chemical yield and enantioselectivity observed in the reaction of **55b** (eq 33).[50]



V. Diastereoselective Peptide Alkylation

Peptide modification is an essential yet flexible synthetic concept for efficient target screening and optimization of lead structures in the application of naturally occurring peptides as pharmaceuticals. The introduction of side chains directly to a peptide

backbone represents a powerful method for the preparation of unnatural peptides.[64] Achiral glycine subunit has generally been used for this purpose, and glycine enolates, radicals, as well as glycine cation equivalents have been exploited as reactive intermediates. However, the control of the stereochemical outcome of these processes in an absolute sense is a difficult task, especially in the modification of linear peptides, and hence, development of an efficient and practical approach to establish sufficient stereoselectivity and general applicability has been an issue of central importance.

One of the reasons for the difficulties in controlling the peptide alkylation is the presence of acidic protons of amino acid residues and amide functionalities, whose deprotonation causes racemization and/or *N*-alkylations. O'Donnell et al. reported pK_a values of Schiff base-activated peptides with those of model compounds (Figure 1), which indicate the possibility of selective deprotonation of the terminal amino acid residue by choosing appropriate conditions.[65]

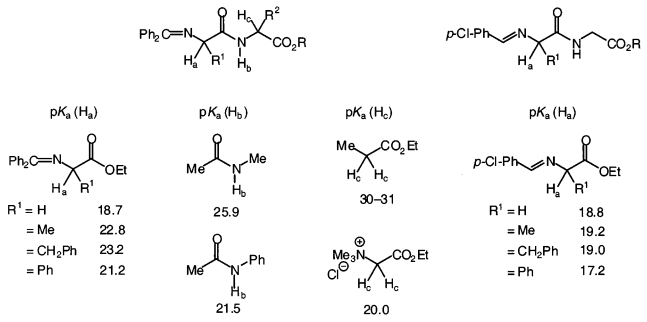
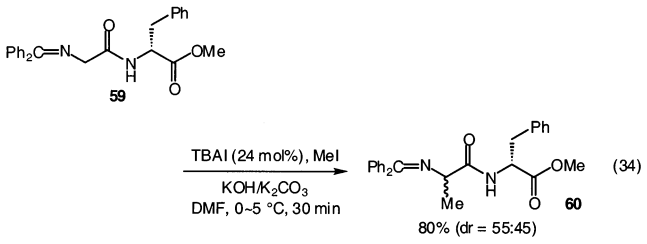


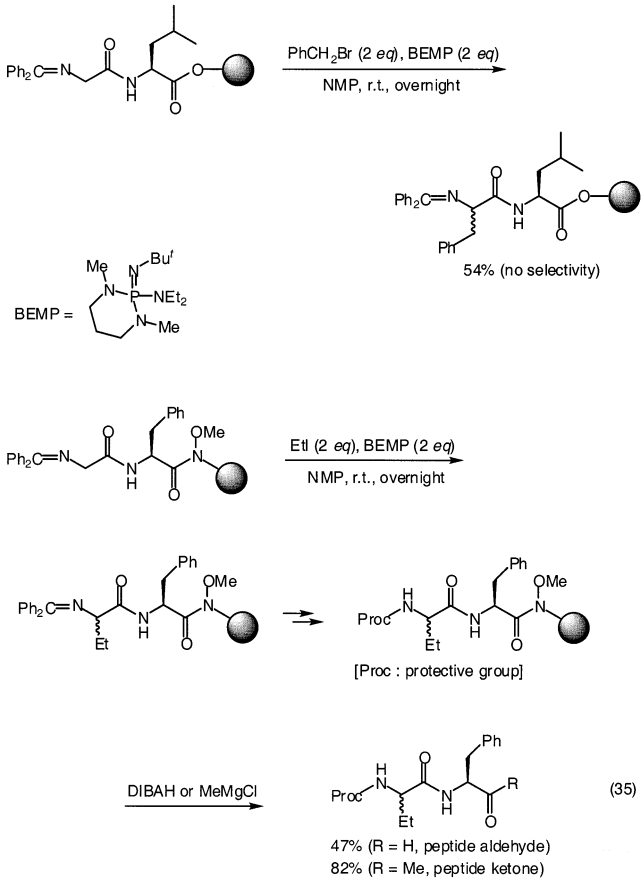
Figure 1. pK_a values (in DMSO) of acidic protons of model compounds.

Indeed, they demonstrated that the terminal alkylation of Schiff base-activated small peptides could be achieved under phase-transfer conditions[65] or by using nonionic base[66] without suffering from the side reactions addressed above. For instance, methylation of Gly-D-Phe derivative **59** with tetrabutylammonium iodide (TBAI) as a catalyst and KOH/K_2CO_3 as a base in DMF proceeded smoothly to give **60** in 80% yield, though its diastereomeric ratio was found to be 55:45 (eq 34).[65]



Nonionic base such as BEMP is quite effective for the solid-phase terminal alkylation of small peptides. This method is practical and allows the preparation of various peptide esters, amides, ketones, and aldehydes, but in all cases problems regarding the diastereofacial differentiation remains unsolved (eq 35).[66]

Upon facing such formidable difficulty of the stereochemical control in the peptide alkylation event,



the authors envisaged that chiral phase-transfer catalyst should play a crucial role in achieving an efficient chirality transfer and examined the alkylation of the dipeptide Gly-L-Phe derivative **61a** as a representative system. When a mixture of **61a** and tetrabutylammonium bromide (TBAB, 2 mol %) in toluene was treated with 50% KOH aqueous solution and benzyl bromide (1.1 equiv) at 0 °C for 4 h, the corresponding benzylation product **62a** was obtained in 85% yield with the diastereomeric ratio (DL-**62a**:LL-**62a**) of 54:46 [8% diastereomeric excess (de)] (eq 36 and Figure 2). In contrast, the reaction with chiral

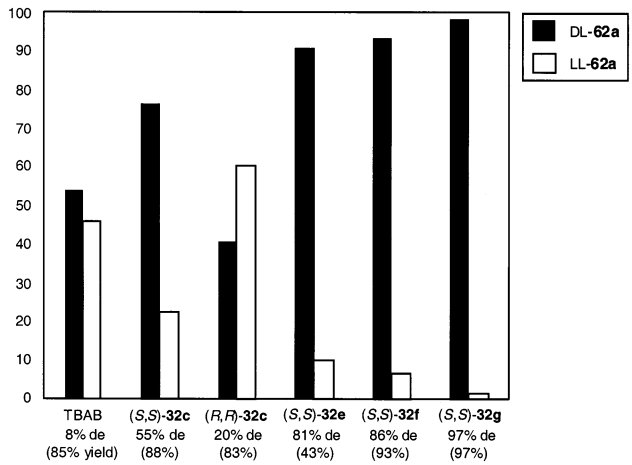
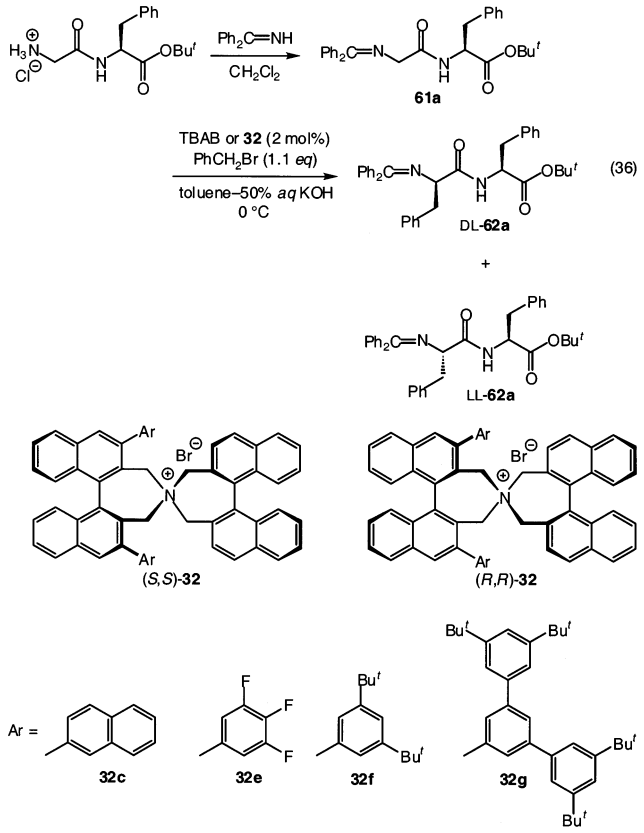


Figure 2. Effect of achiral or chiral catalyst on the diastereomer ratio.

quaternary ammonium bromide (*S*,*S*)-**32c** under similar conditions gave rise to **62a** with the DL/LL

ratio of 77.5:22.5 (55% de, 88% yield). The preferential formation of LL-**62a** in lower de (20%) in the reaction with enantiomeric (*R*,*R*)-**32c** indicates that (*R*,*R*)-**32c** is a mismatched catalyst for this diastereofacial differentiation of **61a**. Changing the 3,3′-aromatic substituent (Ar) of the catalyst dramatically increased the stereoselectivity, and almost complete diastereocontrol was achieved with (*S*,*S*)-**32g** possessing 3,5-bis(3,5-di-*tert*-butylphenyl)phenyl group (97% de).



A variety of alkyl halides can be employed as an electrophile in this alkylation as summarized in Table 2 (entries 1−5).[67] The efficiency of the transmission of stereochemical information was not affected by the side chain structure of the preexisting amino acid residues, as demonstrated in the phase-transfer benzylation of various dipeptides derived from natural α-amino acids (entries 6−9). Interestingly, sterically less demanding (*S*,*S*)-**32f** was found to be a suitable catalyst for the substrate possessing L-proline *tert*-butyl ester moiety (entry 10).

Further, this method allowed an asymmetric construction of noncoded α,α-dialkyl-α-amino acid residues at the peptide terminal as exemplified by the

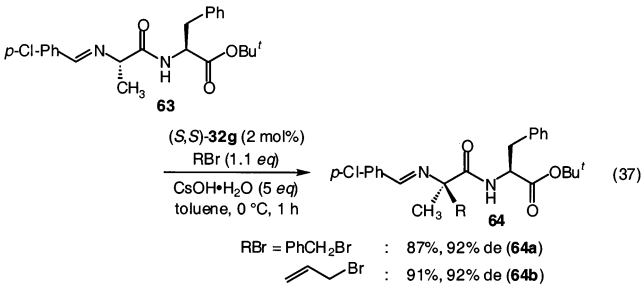
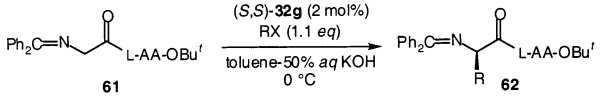
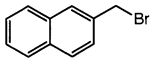
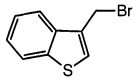


Table 2. Stereoselective *N*-Terminal Alkylation of Dipeptides by Chiral Phase-Transfer Catalysis

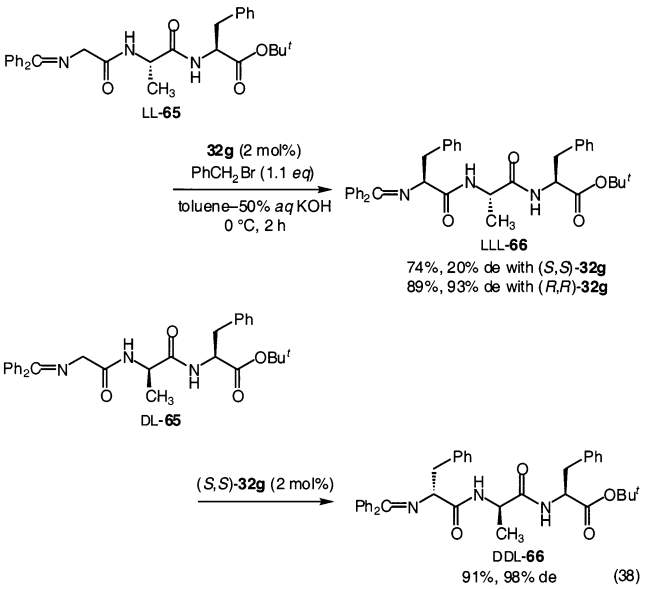


entry	AA	RX	% yield	% de
1	Phe		89	98
2			80	96
3[a]		CH_3CH_2I	90	98
4			92	96
5[a]			95	91
6	Leu	$PhCH_2Br$	91	96
7	Val		85	93
8	Tyr(Bn)		90	98
9	Ala		92	93
10	Pro		80	90[b]

[a] Use of *sat.* CsOH as an aqueous base. [b] With (*S*,*S*)-**32f** as catalyst.

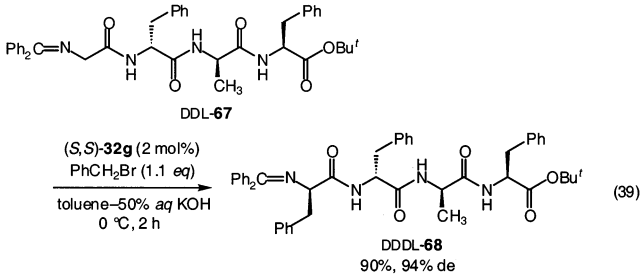
stereoselective alkylation of the dipeptide L-Ala-L-Phe derivative **63** (eq 37).

The chiral phase-transfer catalysis with (*S*,*S*)-**32g** can be successfully extended to the stereoselective *N*-terminal alkylation of Gly-Ala-Phe derivative **65**, i.e., asymmetric synthesis of tripeptides, where striking reversal of the stereochemical preference was observed (eq 38). The benzylation of LL-**65** with (*S*,*S*)-**32g** under the optimized conditions resulted in poor diastereoselectivity (20% de) with LLL-**66** as a major product, and the selectivity was enhanced to 93% de



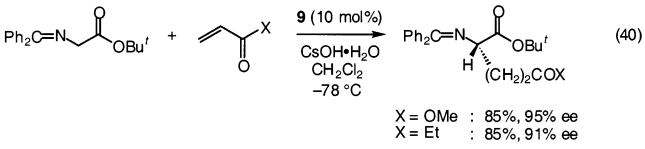
(89% yield) by the use of (*R*,*R*)-**32g** as a catalyst. In addition, (*S*,*S*)-**32g** turned out to be a matched catalyst in the benzylation of DL-**65**, leading to almost exclusive formation of DDL-**66** under similar conditions.

This tendency for stereochemical communication was consistent in the phase-transfer alkylation of DDL-**67**, and the corresponding protected tetrapeptide DDDL-**68** was obtained in 90% yield with excellent stereochemical control (94% de) (eq 39). It was also confirmed that similar alkylation of LLL-**67** with (*R*,*R*)-**32g** as a catalyst furnished LLLL-**68** in 87%, 92% de, suggesting that (*R*,*R*)-**32g** is suitable for the stereoselective *N*-terminal alkylation of naturally occurring polypeptides.[67]

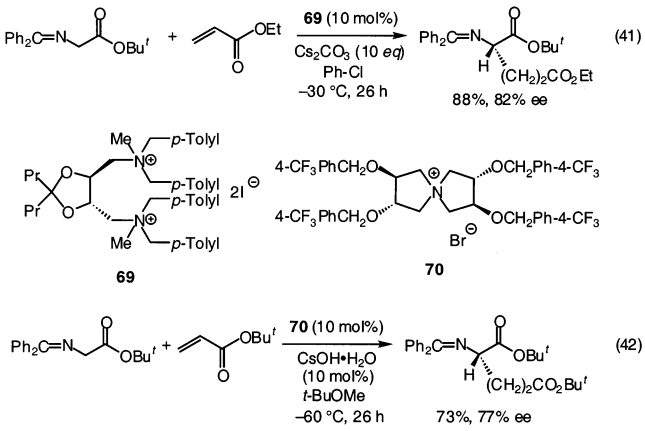


VI. Enantioselective Michael Addition of Glycine Derivatives

Enantioselective Michael addition of glycine derivatives by means of chiral phase-transfer catalysis has been developed by several researchers to synthesize various functionalized α-alkylamino acids. Corey utilized *O*(9)-allyl-*N*-9-anthracenylmethylcinchonidium bromide (**9**) as a chiral phase-transfer catalyst for asymmetric Michael addition of *N*-(diphenylmethylene)glycine *tert*-butyl ester to α,*β*-unsaturated carbonyl substrates with high enantioselectivity (eq 40).[68] With methyl acrylate as the Michael acceptor, α-*tert*-butyl *γ*-methyl ester of (*S*)-glutamic acid can be formed, and this functionalized glutamic acid derivative is highly useful for synthetic applications because the two carboxyl groups are differentiated. Notably, the enantioselectivity of the Michael addition of glycine enolate is the same as that for alkylation.



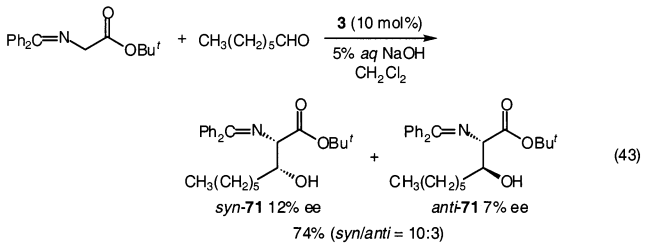
Quite recently, new tartrate-derived chiral phase-transfer catalysts have been developed. Shibasaki designed tartrate-derived bis-ammonium salt **69** for asymmetric alkylation of glycine derivative and also applied it to asymmetric Michael addition of *N*-(diphenylmethylene)glycine *tert*-butyl ester to methyl acrylate (eq 41).[54] Arai and Nishida also designed tartrate-derived spiro-type chiral phase-transfer catalyst **70** and applied it to similar asymmetric Michael addition (eq 42).[69]



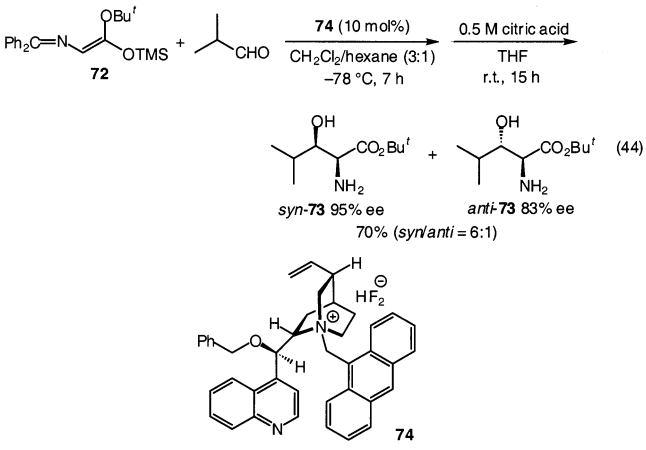
VII. Enantioselective Direct Aldol Reaction of Glycine Derivatives

Although phase-transfer catalytic enantioselective direct aldol reactions of glycine donor with aldehyde acceptors could provide an ideal method for the simultaneous construction of the primary structure and stereochemical integrity of *β*-hydroxy-α-amino acids, extremely important chiral units, especially from the pharmaceutical viewpoint, reported to date are very limited.

As a synthetic variety of α-alkylation of glycine Schiff base, the first catalytic asymmetric synthesis of *β*-hydroxy-α-amino acids by aldol condensation under phase-transfer condition has been described by Miller's group. The reaction of *N*-(diphenylmethylene)glycine *tert*-butyl ester with heptanal in the presence of *N*-benzyl cinchonidinium chloride **3** as a catalyst afforded **71** in 74% yield. Unfortunately, however, the diastereo- and enantioselectivities were not satisfactory (eq 43).[70]

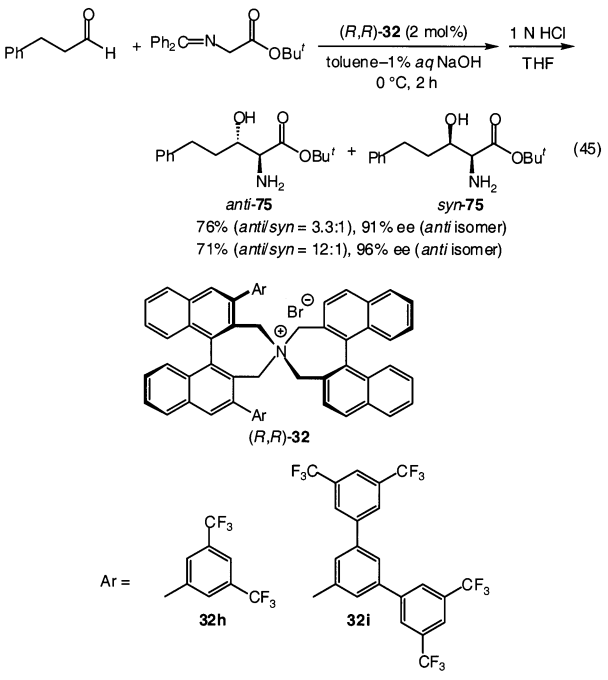


On the other hand, Corey et al. developed a Mukaiyama-type aldol reaction of ketene silyl acetal



72 as an alternative method. The reaction catalyzed by cinchonidine-derived ammonium bifluoride **74** gave mostly syn-β-hydroxy-α-amino esters **73** as the major diastereomer with good to excellent enantiomeric excesses (eq 44).[71]

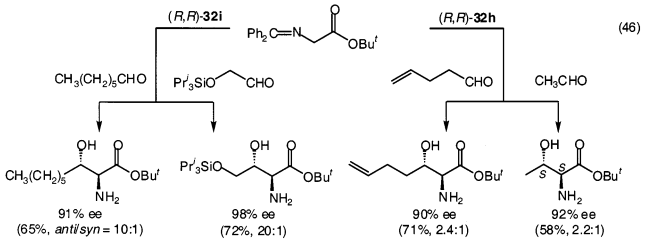
Very recently, the authors disclosed an efficient, highly enantioselective direct aldol reaction of glycine Schiff base with aldehydes under phase-transfer conditions using C_2-symmetric chiral quaternary ammonium salt **32**.[72] Treatment of *N*-(diphenylmethylene)glycine *tert*-butyl ester with 3-phenylpropanal (2 equiv) in toluene−1% NaOH aqueous solution (volume ratio = 1.25:1; 2 equiv of base for Schiff base) in the presence of (*R*,*R*)-**32h** (2 mol %) at 0 °C for 2 h and subsequent hydrolysis with 1 N HCl in THF resulted in the formation of the corresponding β-hydroxy-α-amino ester **75** in 76% isolated yield with the anti/syn ratio of 3.3:1, and the enantiomeric excess of the major anti isomer was determined to be 91% ee. Interestingly, use of (*R*,*R*)-**32i** possessing 3,5-bis[3,5-bis(trifluoromethyl)phenyl]phenyl substituent as a catalyst enhanced both diastereo- and enantioselectivities (anti/syn = 12:1, 96% ee for anti isomer) (eq 45).



(45)

The potential synthetic utility of this procedure has been demonstrated by the direct asymmetric synthesis of various useful β-hydroxy-α-amino esters (eq 46). Heptanal was found to be a good candidate, indicating the feasibility of direct asymmetric synthesis of a variety of lipo β-hydroxy-α-amino acids, a useful component for the preparation of lipophilic peptides and glycopeptides possessing the characteristic properties of high enzymatic stability and enhanced drug transport activity. The reaction with α-triisopropylsiloxyacetaldehyde cleanly produced the desired β-hydroxy-α-amino ester in 72% yield with virtually complete stereochemical control (98% ee, anti/syn = 20:1), which parallels the L-threonine aldolase-catalyzed aldol reaction utilized for the synthesis of monobactam antibiotic Carunoman and analogues.[73]

A key building block for the synthesis of carbacephem antibiotic Loracarbef, previously prepared by a chemoenzymatic process with serine hydroxymethyltransferase (SHMT),[74] was readily assembled with 4-pentenal as acceptor, where (*R*,*R*)-**32h** was more beneficial than (*R*,*R*)-**32i** to obtain higher enantioselectivity. It was also found that L-*allo*-threonine ester can be obtained by the reaction with acetaldehyde using (*R*,*R*)-**32h**, confirming that the absolute configuration of the α-stereocenter newly created in this transformation is (*S*). Notably, this method allows a facile preparation of unnatural D-*allo*-threonine because of the ready availability of the enantiomeric catalyst (*S*,*S*)-**32h**.



(46)

VIII. Conclusion

Enantioselective synthesis of α-amino acids has been greatly advanced by the creation of new chiral phase-transfer catalysts, which maximize the characteristic features of the central quaternary ammonium cations. Indeed, such phase-transfer-catalyzed enantioselective syntheses of α-amino acids are very useful in practical synthesis, and their applications are illustrated in numerous papers. The enantioselective reactions described in this review clearly demonstrate the high ability and great potential of chiral phase-transfer catalysis to synthesize various types of chiral α-amino acid derivatives.

Phase-transfer-catalyzed enantioselective synthesis of α-amino acids is still a developing filed of chemistry, and after submission of the manuscript, several studies of relevance to the field appeared in print.[75] As a continuing effort to this field, rational design of chiral phase-transfer catalysts minimizing the catalyst loading is crucially important from a practical point of view. However, some of the reported methods are somewhat limited in the range of applicable reactions. If these problems were overcome and recyclable use were to be established, development of a series of chiral, nontoxic, and nonharmful quaternary ammonium salts would certainly play an important role in the future green chemistry, considering the importance of chiral phase-transfer catalysts in the vast field of basic and applied chemistry.

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