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Polymeric chiral phase-transfer catalysts derived from cinchona alkaloids for enantioselective synthesis of α-amino acids

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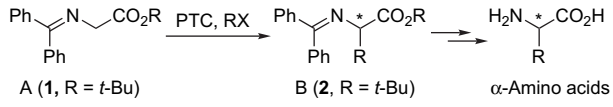
Abstract—A series of dimeric/trimeric chiral quaternary ammonium salts derived from cinchona alkaloids were designed as efficient and practical chiral phase-transfer catalysts (PTCs). Presented are the details on the development of the dimeric PTCs for the synthesis of optically active α-amino acid derivatives and the optimization of the reaction variables suitable for the dimeric PTCs. The 1,3-phenyl- and the 2,7-naphthyl-linked dimeric PTCs showed excellent catalytic capability on the reactivity and enantioselectivity in the catalytic phase-transfer alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (**1**). A variety of α-amino acid derivatives were obtained with high enantiopurities using the dimeric PTCs, especially the 2,7-naphthyl-dimer **41**, in a very practical manner.

1. Introduction

Optically active amino acids play a key role in the area of design and preparation of pharmaceutical and agrochemical targets, such as peptides, proteins, and many other natural products.[1] Moreover, amino acids themselves are useful sources of chiral substrates, auxiliaries, and catalysts in various fields of modern organic chemistry.[2] Therefore, the development of efficient and practical synthetic method of optically active both natural and non-natural α-amino acids is one of the most important areas in organic chemistry.[3] Tremendous amounts of efforts are known in literature for the asymmetric synthesis of optically active amino acids, which can be categorized into four main approaches, using chiral substrates, chiral reagents, chiral auxiliaries, and chiral catalysts. Among the four synthetic approaches, the asymmetric synthesis using chiral catalysts has more advantages over the other synthetic methods, since a catalytic amount of chiral material can produce large quantities of enantiomerically enriched or enantiopure products. Much attention has been paid to chiral catalysts from the viewpoints of efficiency and practical concern so far.

Phase-transfer catalysis has been recognized as a practical methodology for organic synthesis due to its operational simplicity, high yield process, mild reaction conditions, use of safe and inexpensive reagents and solvents, safety considerations, environmental concerns, and possibility to conduct reactions on large scale.[4] In addition, when a chiral phase-transfer catalyst (PTC) is employed in reactions producing new stereogenic centers, reactions may proceed stereoselectively to give optically active products.

One of the most successful utilization of asymmetric phase-transfer catalysis to date is the preparation of optically active α-amino acid derivatives as depicted in Scheme 1.[5] The use of benzophenone imine of glycine derivatives **A** as substrates in enantioselective alkylation under catalytic phase-transfer condition has been developed toward an excellent method for preparation of a wide range of optically active α-amino acids with high chemical yield and enantioselectivity.[6,7]



Scheme 1. Synthesis of α-alkyl-α-amino acids via asymmetric phase-transfer catalytic alkylation of benzophenone imine glycine ester (**A**).

The cinchona alkaloids have been used extensively in designing chiral PTCs because they are inexpensive, are available in both pseudoenantiomeric forms, and can be easily converted to many different chiral PTCs (Fig. 1). The monumental first employment of the cinchona-derived quaternary ammonium salts to the asymmetric synthesis of α-amino acids under catalytic phase-transfer conditions

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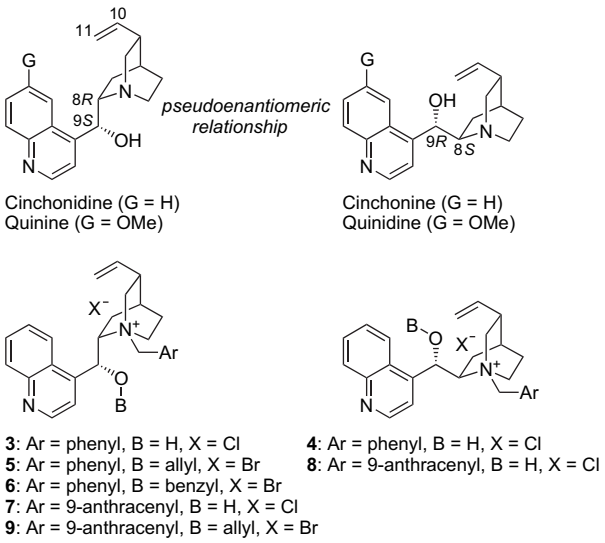


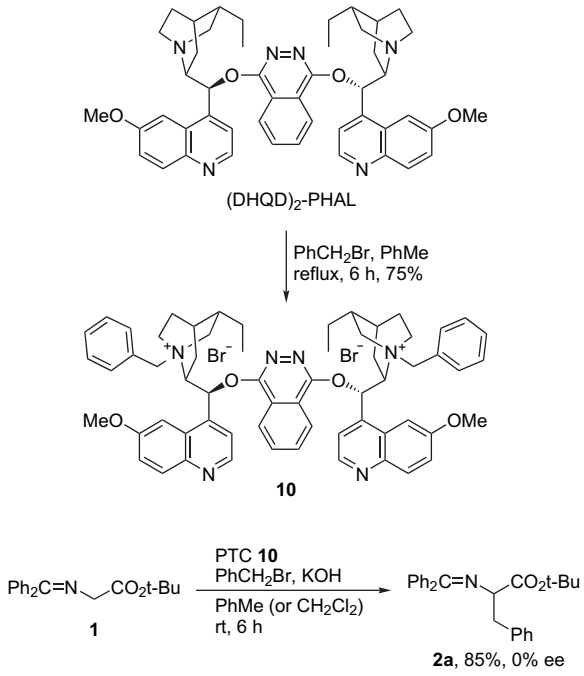
Figure 1. The representative cinchona alkaloids (top) and the reported cinchona-derived phase-transfer catalysts (bottom).

was done by the O'Donnell group in 1989.[8] They obtained optically enriched α-amino acid derivatives by the monoalkylation of **1** using (*N*-alkyl)cinchoni(di)nium halides (**3**–**6**) as chiral PTCs with moderate enantiomeric excess. In 1997, the Lygo group and the Corey group accomplished remarkable progress in the cinchona-derived PTCs by introduction of the bulkier 9-anthracenylmethyl group at the bridgehead nitrogen, as shown in **7**–**9**, leading to huge enhancement of the level of enantioselectivity.[9,10] Besides the cinchona-derived chiral PTCs, several efficient non-cinchona-derived, purely synthetic chiral quaternary ammonium salts have also been developed. The Maruoka group has designed and prepared a series of highly efficient, structurally rigid, C_2-symmetric, chiral spiro ammonium salts, and successfully applied them to the synthesis of α-amino acids with excellent stereoselectivities.[11] The Nagasawa group[12] and the Shibasaki group[13] reported the efficient chiral PTCs, C_2-symmetric guanidine-derived ammonium salt and tartrate-derived bis-ammonium salt, respectively.

Despite having all these successful results, some problems still remain to be worked out in this area, such as long reaction times, low chemical and optical yields, impractical reaction conditions unavoidably used to obtain better results and inaccessible PTCs to common users. With all these perspectives, we set out to address our efforts to the development of more efficient and practical PTCs to break through the problems observed so far. In the course of this study, we have paid attention to the fact that the cinchona alkaloids have shown their great utility in the Sharpless asymmetric dihydroxylation. Especially, we have noticed that a significant improvement in both stereoselectivity and scope of this methodology was achieved when the dimeric ligands of two independent cinchona alkaloid units attached to heterocyclic spacers were used, such as $(DHQ)_2$-PHAL or $(DHQD)_2$-PHAL.[14] This dramatic dimerization effect prompted us to apply it to the design of dimeric cinchona-derived quaternary ammonium salts as new chiral PTCs. This article describes our efforts toward the design and preparation of a series of novel dimeric/trimeric chiral PTCs derived from cinchona alkaloids and optimization of the catalytic phase-transfer alkylation conditions suitable for the newly prepared dimeric chiral PTCs and finally their applications to the asymmetric alkylation of the benzophenone imine of glycine *tert*-butyl ester (**1**) affording optically active α-amino acid derivatives.[15]

2. Results and discussion

In the beginning, the dimeric catalyst **10** was tentatively designed and prepared, which was easily derived from commercially available $(DHQD)_2$-PHAL in one step. The two tertiary amines in $(DHQD)_2$-PHAL were quaternarized by the simple benzylation with 2 equiv of benzyl bromide in refluxing toluene, giving the dimeric quaternary ammonium salt **10** in 75% yield (Scheme 2).



Scheme 2. Preparation and evaluation of Bn_2-$(DHQD)_2$-PHAL $2Br^-$ (**10**).

The ammonium salt **10** was then employed in the alkylation of **1** with benzyl bromide and 50% aqueous KOH to evaluate its catalytic ability (Scheme 2). This particular assay reaction was chosen because it was very well known that the enantiopurity of the benzylated imine **2a** could be readily evaluated by chiral HPLC, and because the absolute stereochemistry of **2a** was already known.[8–13] Although the tentatively designed quaternary ammonium salt **10** was found to be able to catalyze this reaction, giving complete consumption of starting material within 6 h at room temperature, it failed to give any optical purity for **2a** in the alkylation.

It is generally thought that a quaternary ammonium salt derived from cinchona alkaloid has an imaginary tetrahedron composed of four carbons adjacent to the bridgehead nitrogen. As demonstrated in Figure 2, in order to be an efficient catalyst in this alkylation, the cinchona-derived PTC should be designed to provide effective steric screening that can inhibit an approach of the enolate of imine **1** to three faces

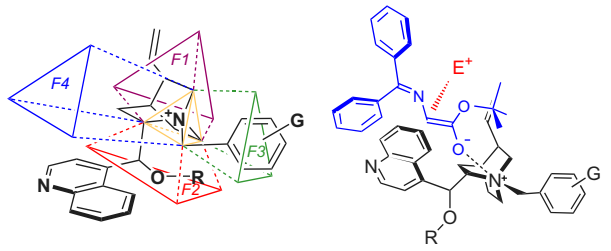
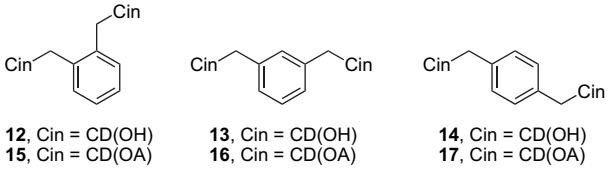


Figure 2. Origin of stereoselectivity of cinchona-derived quaternary ammonium salts.

(F1–F3) of this tetrahedron, while the remaining face (F4) should be sufficiently open to allow close contact between the enolate anion and the ammonium cation.

On the basis of this background information, we designed novel dimeric quaternary ammonium salts **11**, as depicted in Figure 3, by attaching an appropriate linker (e.g., aromatic rings) to bridgehead nitrogen of the two cinchona units. The first series of the dimeric quaternary ammonium salts (**12**–**17**) having a phenyl ring as a linker was designed to look into the primary effect according to the relationship of the attached position. One of the two independent cinchona alkaloid units can be located at *ortho*-, *meta*-, or *para*-position against the other, respectively. We envisaged that both chemical yield and enantioselectivity of the asymmetric alkylation of imine **1** should be affected by the direction of each cinchona unit.

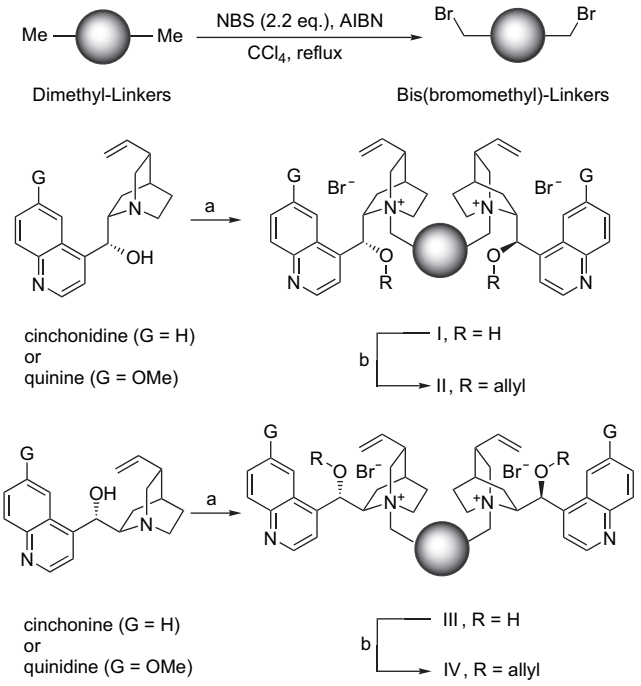


12, Cin = CD(OH)
15, Cin = CD(OA)

13, Cin = CD(OH)
16, Cin = CD(OA)

14, Cin = CD(OH)
17, Cin = CD(OA)

Quaternary ammonium salts **12**–**14** were readily prepared from (−)-cinchonidine and the commercially available 1,2-, 1,3-, or 1,4-bis(bromomethyl)benzene, respectively (Scheme 3). One of the distinguished advantages of our catalysts is that most of the dimeric/trimeric cinchona-derived ammonium salts introduced in this article can be prepared in short steps in good chemical yields and generally high purities of the prepared salts can be achieved by simple recrystallization process. We would first prepare dimeric ammonium salts derived from (−)-cinchonidine because it has been reported that cinchonidine-derived ammonium salts have been mainly used as chiral PTCs in this asymmetric alkylation of glycine imines and have generally shown better results than those of the others [e.g., derived from (+)-cinchonine, (−)-quinine, and (+)-quinidine].[9a] (−)-Cinchonidine and 1,2-, 1,3-, or 1,4-bis(bromomethyl)-benzene were reacted at room temperature (or occasionally elevated reaction temperature in case of need) in ethanol–DMF–chloroform (volume ratio=5:6:2) to give the corresponding dimeric ammonium salts **12**–**14** in 94–97% yields.[16]



Scheme 3. General synthetic scheme for cinchona-derived dimeric ammonium salts (**I**–**IV**). *Reagents and conditions*: (a) bis(bromomethyl)-linkers (0.5 equiv), EtOH–DMF–$CHCl_3$ (5:6:2), rt or reflux; (b) allyl bromide (6.0 equiv), 50% KOH (10.0 equiv), CH_2Cl_2, rt.

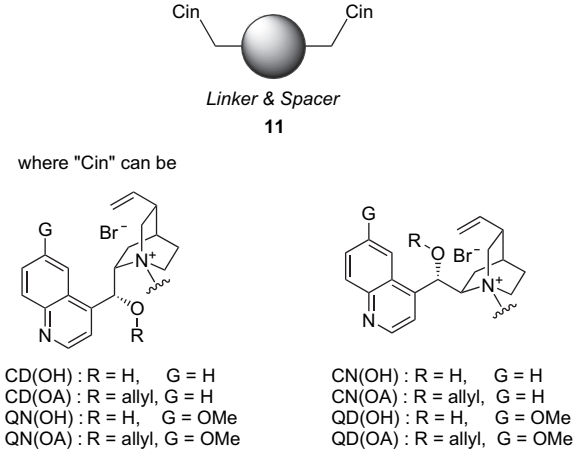
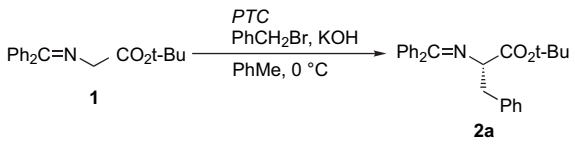


Figure 3. Newly designed structure of cinchona-derived dimeric PTCs.

The catalytic efficiency of the ammonium salts **12**–**14** was examined by the standard benzylation of **1** under phase-transfer conditions. 5 mol % of the newly prepared dimeric ammonium salts were used as chiral PTCs, and 50% aqueous KOH was used as a base in toluene at 0 °C. It was found that all of the quaternary ammonium salts **12**–**14** have the ability to catalyze this phase-transfer benzylation and in all cases the (*S*)-isomer of the benzylated imine **2a** was formed in excess (Table 1). The 1,3-phenyl-linked dimeric PTC **13** showed the highest enantioselectivity among the three dimeric PTCs. The order of enantioselectivity of the three PTCs along with the monomeric PTC **3** was as follows: the 1,3-dimeric PTC **13**>the 1,4-dimeric PTC **14**≒the monomeric PTC **3**≫the 1,2-dimeric PTC **12**. The lack of a difference in the enantioselectivity between the 1,4-phenyl-dimeric PTC **14** and the monomeric PTC **3** implies that the two cinchona alkaloid units of the 1,4-phenyl-dimeric

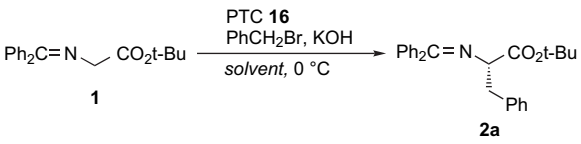
Table 1. Evaluation of the catalytic efficiency of the PTCs **12**–**17**[a]



Entry	PTC	Time (h)	Yield[b] (%)	ee[c,d] (%)
1	**3**	20	80	64 (*S*)
2	**12**	20	75	33 (*S*)
3	**13**	20	81	81 (*S*)
4	**14**	20	80	68 (*S*)
5	**15**	18	78	25 (*S*)
6	**16**	12	87	84 (*S*)
7	**17**	19	85	72 (*S*)

[a] The reaction was carried out with 5.0 equiv of benzyl bromide and 50% aqueous KOH in the presence of either 10.0 mol % (for **3**) or 5.0 mol % (for the others) of catalyst in toluene at 0 °C.
[b] Isolated yield of **2a**.
[c] The enantiopurity was determined by HPLC analysis of the benzylated imine **2a** using a chiral column (Chiralcel OD) with hexanes–2-propanol (500:2.5) as the solvent.
[d] The absolute configuration was determined by comparing with the HPLC retention time of an authentic sample, which was independently prepared by the reported procedures.[9a,10a,11a]

Table 2. Effect of solvent[a]



Entry	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	Toluene	12	87	84
2	CH_2Cl_2	5	93	80
3	$CHCl_3$	5	92	86
4	$(CH_2Cl)_2$	3	95	80
5	Chlorobenzene	10	92	83
6	Anisole	20	86	81
7	Toluene–CH_2Cl_2 (5:5)	3	94	86
8	Toluene–CH_2Cl_2 (9:1)	5	90	86
9	Toluene–CH_2Cl_2 (7:3)	2	91	88
10	Toluene–CH_2Cl_2 (3:7)	2	94	85
11	Toluene–$CHCl_3$ (7:3)	2	91	90
12	Toluene–$(CH_2Cl)_2$ (7:3)	3	91	85
13	Chlorobenzene–CH_2Cl_2 (7:3)	3	93	84
14	Anisole–CH_2Cl_2 (7:3)	6	89	83

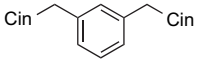
[a] The reaction was carried out with 5.0 equiv of benzyl bromide and 50% aqueous KOH in the presence of 5.0 mol % of the PTC **16** in the given solvent at 0 °C.
[b] Isolated yield of **2a**.
[c] The enantiopurity was determined by HPLC analysis of the benzylated imine **2a** using a chiral column (Chiralcel OD) with hexanes–2-propanol (500:2.5) as the solvent.

PTC do not sterically affect each other. In the case of the 1,2-phenyl-dimeric PTC **12**, the severe steric repulsion between the two cinchona alkaloid units may lead to an unfavorable conformation affording the poor enantioselectivity.

We then prepared the *O*(9)-allyl catalysts by allylation of the two 9-hydroxyl groups in the PTCs **12**–**14**, because it has been known that the *O*(9)-allylated PTCs showed both higher chemical yield and enantioselectivity than non-allylated ones in the asymmetric alkylation of the glycine imines.[8c] The advantages of the *O*(9)-allyl moiety might come from a more effective screening capability in view of enantioselectivity as well as from the improved solubility of the catalyst in organic solvents commonly used in this alkylation affording faster reaction rates and higher chemical yields. Allylation of **12**–**14** with allyl bromide in the biphasic system composed of 50% aqueous KOH and dichloromethane at room temperature afforded the allylated ammonium salts **15**–**17** in 92–95% yields (Scheme 3). These allylated ammonium salts (**15**–**17**) were then subjected to the assay reaction and the results are listed in Table 1. As expected, the chemical and optical yields obtained by using the allylated PTCs were generally higher than the non-allyl PTCs under the same reaction conditions. In the case of the 1,2-dimeric catalysts (**12** vs **15**), however, decrease in enantioselectivity occurred. It could be explained by the more severe steric repulsion between the two cinchona alkaloid units that resulted from the *O*(9)-allylation.

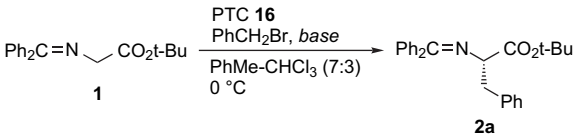
In order to establish the optimal reaction conditions for our dimeric chiral PTCs, a solvent screening was attempted at first. Benzenes and haloalkanes were mainly used as single or mixed forms. Table 2 summarizes the results obtained from the benzylation of **1** with the 1,3-dimeric PTC **16** at 0 °C in various solvent systems. Although the reaction smoothly proceeded to afford the desired product in any solvent, the use of chloroform only (entry 3) and the mixed solvent of toluene–haloalkane (entries 7–12) gave generally high optical yields. As shown in entries 1 and 11, the result obtained from the mixed solvent of toluene–chloroform (7:3) was better than that from toluene only in terms of both reaction rate and chemical/optical yield, which indicates that chloroform plays a critical role in using the dimeric catalysts. Whereas the catalyst **16** is basically insoluble in toluene, chloroform can dissolve catalyst **16** to some extent. The difference in capability of dissolving the catalyst **16** might be deeply associated with the reaction rate as well as the chemical/optical yield. However, the single use of chloroform turned out to be insufficient to be selected for further experiments (entry 3). From the solvent screening experiments, the mixed solvent system of toluene–chloroform (7:3) was selected as the best solvent condition especially suitable for the dimeric PTCs.

The effect of inorganic bases on both the enantioselectivity and the catalytic activity was then investigated. The results summarized in Table 3 show that the best enantioselectivity with good chemical yield was accomplished when 50% aqueous potassium hydroxide was used (entry 4). When sodium hydroxide was employed either as solid form or as 50% aqueous solution, the reaction proceeded sluggishly to give lower chemical and optical yields than those with potassium hydroxide (entries 1 and 2). A similar level of enantioselectivity was obtained in the cases of employing rubidium or cesium hydroxide (entries 5–8), but the chemical yields considerably dropped. The decrease in chemical



13, Cin = CD(OH)
16, Cin = CD(OA)
20, Cin = QN(OH)
21, Cin = QN(OA)
18, Cin = CN(OH)
19, Cin = CN(OA)
22, Cin = QD(OH)
23, Cin = QD(OA)

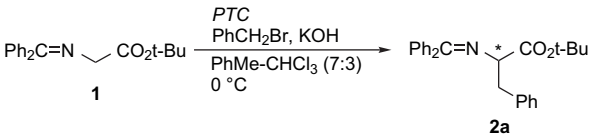
Table 3. Effect of base[a]



Entry	Base	Time (h)	Yield[b] (%)	ee[c] (%)
1	Solid NaOH	5	73	86
2	50% NaOH	10	68	88
3	Solid KOH	0.5	92	88
4	50% KOH	2	91	90
5	Solid RbOH	0.5	86	86
6	50% RbOH	2	79	88
7	Solid CsOH	0.5	82	84
8	50% CsOH	2	62	87

[a] The reaction was carried out with 5.0 equiv of benzyl bromide and the given base in the presence of 5.0 mol % of the PTC **16** in toluene–chloroform (7:3) at 0 °C.
[b] Isolated yield of **2a**.
[c] The enantiopurity was determined by HPLC analysis of the benzylated imine **2a** using a chiral column (Chiralcel OD) with hexanes–2-propanol (500:2.5) as the solvent.

Table 4. Effect of the nature of cinchona alkaloids[a]



Entry	PTC	Time (h)	Yield[b] (%)	ee[c,d] (%)
1	**13**	4	90	84 (*S*)
2	**16**	2	91	90 (*S*)
3	**18**	10	88	74 (*R*)
4	**19**	6	89	84 (*R*)
5	**20**	8	91	65 (*S*)
6	**21**	5	92	78 (*S*)
7	**22**	8	87	70 (*R*)
8	**23**	5	90	81 (*R*)

[a] The reaction was carried out with 5.0 equiv of benzyl bromide and 50% aqueous KOH in the presence of 5.0 mol % of the given PTC in toluene–chloroform (7:3) at 0 °C.
[b] Isolated yield of **2a**.
[c] The enantiopurity was determined by HPLC analysis of the benzylated imine **2a** using a chiral column (Chiralcel OD) with hexanes–2-propanol (500:2.5) as the solvent.
[d] The absolute configuration was determined by comparing with the HPLC retention time of an authentic sample, which was independently prepared by the reported procedures.[9a,10a,11a]

yield might be due to the decomposition of the starting imine **1** or the benzylated imine **2a** under the strongly basic conditions. As a result, 50% aqueous KOH was finally selected as the base of choice.

On the basis of these results, we then probed the effect of the nature of cinchona alkaloid component on the catalytic phase-transfer alkylation using the catalysts derived from other cinchona alkaloids (e.g., cinchonine, quinine, and quinidine). The 1,3-phenyl-dimeric ammonium salts **18**–**23** were prepared with cinchonine (**18**, **19**), quinine (**20**, **21**), and quinidine (**22**, **23**) by the same method as mentioned above. The cinchonine-derived catalysts (**18** and **19**), which are in pseudoenantiomeric relationship to the cinchonidine-derived ones (**13** and **16**) gave the opposite enantioselectivity, despite the enantiomeric excess being somewhat low in the alkylation reaction (Table 4). The quinine and quinidine derivatives (**20**, **21** and **22**, **23**) gave poorer results.

Figure 4 shows the probable structure of the 1,3-phenyl-dimeric catalyst **13** on the basis of X-ray crystallographic study[20b] in which the conformation is such that the two cinchona alkaloid units are placed in an *anti*-relationship to each other. And it also displays that each cinchona alkaloid unit has the same conformation and is situated in an identical environment. Therefore, the same result will be obtained even if an anion such as an enolate of imine **A** approaches either of the two ammonium sites of the dimeric catalyst. Unlike the monomeric catalyst **3**, the rotations of phenyl ring in the dimeric catalyst **13** get restricted, especially when two cinchona alkaloid units are connected through phenyl spacer in the *meta*-orientation. The bulkiness of cinchona alkaloid unit can obstruct free rotation of both N^+–CH_2 (benzylic) bond and CH_2 (benzylic)–C (phenyl) bond. This can make the whole conformation of the dimeric catalyst **13** rigid providing an efficient blocking of one face among the four faces of an imaginary tetrahedron from an access of enolate to bridgehead nitrogen cation. Moreover another face around the ammonium cation (N^+) can be

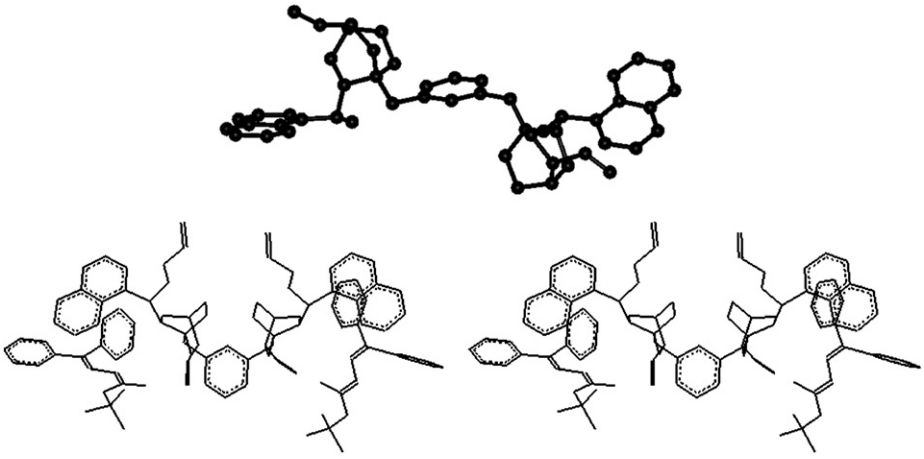


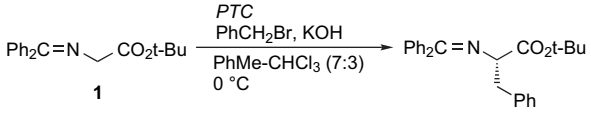
Figure 4. The plausible structure of the dimeric PTC **13** (top) and stereoview of plausible model of the preferred three-dimensional arrangement of the ion pair from **16** and one (or two) *E*-enolate(s) of **1** for understanding the enantioselectivity (bottom).

effectively screened by the quinuclidine ring system itself and the *O*(9)-allyl moiety also provides an effective additional screening of another face in the case of the *O*(9)-allylated catalyst, such as **16**. Consequently, the remaining face can be open to approach of the enolate of **1** to N^+ to make ion pair resulting in enantioselective alkylation. Taking account of all of the above results, the presumed transition state is presented as shown in Figure 4, which was calculated by the energy minimization using the SYBYL program.[17] Electrophile can approach only the *si* face of the enolate due to steric reasons, leading to the high enantioselectivity.

We next turned our attention to explore other linkers besides phenyl moiety on purpose to develop more efficient and practical catalysts, such as biphenyls (**24–26**), alkenes and alkyne (**27–29**), naphthalenes (**30–35**), anthracene (**36**), phenanthrene (**37**), and trimeric catalyst (**38**). All the newly designed catalysts were easily prepared in good yields using the same method in Scheme 3. Efficacy of these catalysts was tested in the optimized reaction condition of phase-transfer benzylation of **1** and the results are summarized in Table 5.

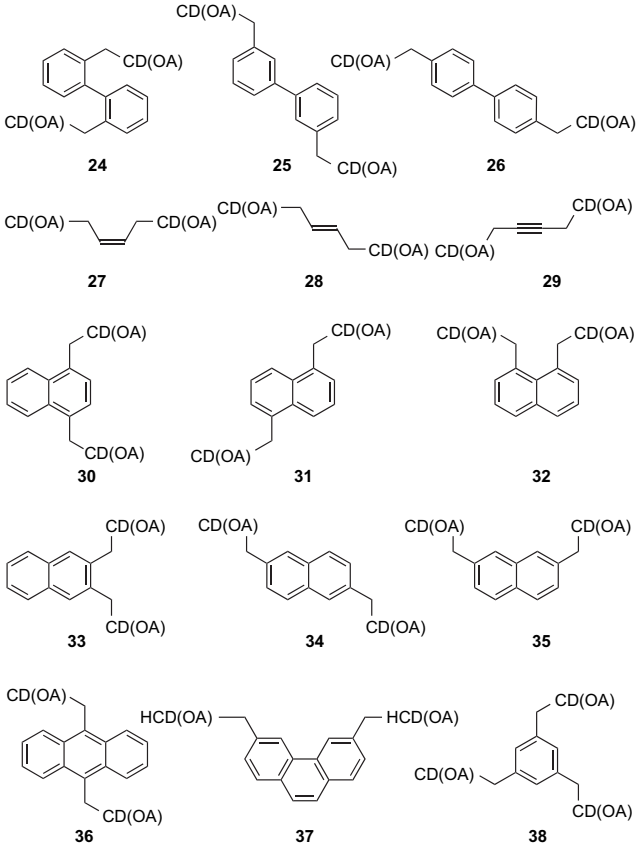
Catalysts containing symmetric biphenyl linkers (**24–26**) showed dramatic differences according to the substituted position of cinchona alkaloid moieties to the linker (entries 5–7). The sterically hindered 2,2′-biphenyl-linked catalyst **24** showed poor activity while the 3,3′- and the 4,4′-biphenyl-linked catalysts **25** and **26** were able to effectively catalyze the reaction with moderate enantiomeric excesses. Generally low enantioselectivities were obtained when employing acyclic linkers as in **27–29** (entries 8–10). In the cases of the catalysts containing naphthalene linker (entries 11–16), the 1,4-, 1,5- and 2,7-substituted catalysts **30**, **31**, and **35** gave good enantioselectivities. Whereas the 2,6-substituted catalyst **34** yielded moderate result, the sterically hindered catalysts **32** and **33** showed poor enantioselectivities. Especially, the 2,7-naphthalene-linked catalyst **35** was found to possess excellent catalytic activity for this alkylation from the viewpoints of enantioselectivity as well as chemical yield. We also envisaged that good result could be obtained if 9,10-anthracenyl moiety, as in **36**, was employed as a linker on the analogy of Lygo's and Corey's improvements.[9a,10a] However, contrary to our expectation, the level of enantiomeric excess of the benzylated imine **2a** was not satisfactory (entry 17).[18] The catalyst **37** having a similar shape to the catalyst **35**, but for the distance between the two cinchona units, was prepared and tested. But a drop in enantiomeric excess was observed (entry 18). On the ground of the fact that the *meta*-relationship in the catalyst **16** showed good activity in asymmetric alkylation, the same concept was applied to the 1,3,5-trimeric catalyst **38** in which all cinchona units on the phenyl ring are placed in *meta*-position to each other, and it would be expected that this relationship could increase or maintain the catalytic efficiency of the *meta*-dimeric effect. Compared with the result from **16** (entry 3), the effect of the trimerization shown in entry 19 could be regarded as quite similar to that of the *meta*-directing-dimerization in chemical and optical yields.

Table 5. Results from the screening of the PTCs for the catalytic enantioselective phase-transfer benzylation[a]



Entry	PTC	Time (h)	Yield[b] (%)	ee[c] (%)
1	**5**	2	92	75
2	**15**	3	90	31
3	**16**	2	91	90
4	**17**	4	92	80
5	**24**	10	80	25
6	**25**	3	85	80
7	**26**	4	87	82
8	**27**	3	92	19
9	**28**	7	90	24
10	**29**	12	86	10
11	**30**	2	94	91
12	**31**	12	94	89
13	**32**	10	85	27
14	**33**	10	90	22
15	**34**	4	89	70
16	**35**	1	94	94
17	**36**	2	84	78
18	**37**	4	85	69
19	**38**	8	95	91

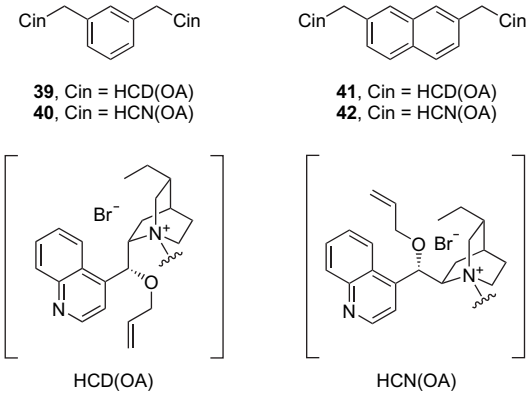
[a] The reaction was carried out with 5.0 equiv of benzyl bromide and 50% aqueous KOH in the presence of either 10.0 mol % (for **5**) or 5.0 mol % (for the others) of catalyst in toluene–chloroform (7:3) at 0 °C.
[b] Isolated yield of **2a**.
[c] The enantiopurity was determined by HPLC analysis of the benzylated imine **2a** using a chiral column (Chiralcel OD) with hexanes–2-propanol (500:2.5) as the solvent.



So far, through the systematic examination, two types of catalysts, the 1,3-phenyl- and 2,7-naphthyl-based dimeric ammonium salts, were selected as efficient chiral PTCs for

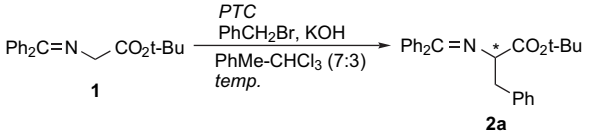
the catalytic asymmetric phase-transfer alkylation of the benzophenone imine of glycine derivative **1**. 10,11-Hydroderivatives were adopted in order to obtain the maximum results.[9a] In addition, antipodal *R*-amino acid derivatives were expected to be obtained in excess by simply changing cinchona alkaloid to hydrocinchoninium component. Using the selected catalysts (**39**–**42**), further studies on the reaction conditions were performed by varying reaction temperature and loading amount of PTC to find the optimal reaction condition (Table 6). The use of the naphthalene-linked catalysts (**41**, **42**) compared with the benzene-linked ones (**39**, **40**) and the lower reaction temperature provided slightly higher enantioselectivities. Optically enriched (*R*)-α-amino acid derivatives could be obtained using hydrocinchoninium derivatives (**40** or **42**) with satisfactory enantiomeric excesses, up to 96%. Especially when the 2,7-naphthalene-linked dimeric catalyst **41** was employed at 0 °C, very high enantioselectivity (98% ee) as well as high chemical yield (95%) was obtained within short reaction time (30 min) (entry 12). Notably, all of the catalysts can conserve their high catalytic efficiency in terms of both reactivity and enantioselectivity, even when present in a smaller quantity (1 mol %).

Interestingly, the molecular structure of the 2,7-naphthyl catalysts **41** and **42** markedly resembles that of the 1,3-phenyl catalysts **39** and **40**, respectively. The only difference is the distance between the two cinchona alkaloid units. The naphthalene linker is about 2.4 Å longer than the benzene linker. The reason for the higher enantioselectivity of the 2,7-naphthyl catalyst is not clear at the moment, but it is thought that the 2,7-naphthalene linker confers a spatial benefit to form a more favorable conformation by decreasing the steric hindrance between the two cinchona units compared to that in the 1,3-benzene linker.



Having optimized the catalytic enantioselective phase-transfer alkylation system, we explored the scope and limitations to demonstrate the superiority of our reaction system. A variety of electrophiles were reacted with the benzophenone imine glycine *tert*-butyl ester **1** catalyzed by the chiral dimeric PTC **41** (5.0 mol %) at a convenient reaction temperature (0 °C). As demonstrated in Table 7, highly optically

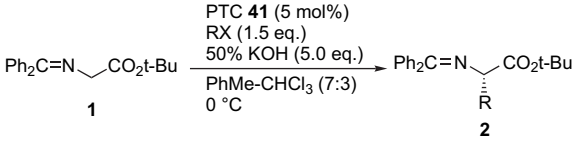
Table 6. Searching for the optimal reaction conditions[a]



Entry	PTC	Temp (°C)	Time (h)	Yield[b] (%)	ee[c,d] (%)
1	**39**	rt	2	95	90 (*S*)
2	**39**	0	4	94	93 (*S*)
3[e]	**39**	0	10	92	93 (*S*)
4	**39**	−20	6	94	96 (*S*)
5	**39**	−40	18	90	98 (*S*)
6	**40**	rt	3	94	83 (*R*)
7	**40**	0	3	93	86 (*R*)
8[e]	**40**	0	12	90	86 (*R*)
9	**40**	−20	10	92	92 (*R*)
10	**40**	−40	30	85	94 (*R*)
11	**41**	rt	0.05	95	92 (*S*)
12	**41**	0	0.5	95	98 (*S*)
13[e]	**41**	0	10	95	98 (*S*)
14	**41**	−20	6	93	99 (*S*)
15	**41**	−40	20	90	>99 (*S*)
16	**42**	rt	2	94	91 (*R*)
17	**42**	0	3	92	93 (*R*)
18[e]	**42**	0	10	91	93 (*R*)
19	**42**	−20	8	92	95 (*R*)
20	**42**	−40	20	88	96 (*R*)

[a] The reaction was carried out with 5.0 equiv of benzyl bromide and 50% aqueous KOH in the presence of 5.0 mol % of the catalysts in toluene–chloroform (7:3) at the given temperature.
[b] Isolated yield of **2a**.
[c] The enantiopurity was determined by HPLC analysis of the benzylated imine **2a** using a chiral column (Chiralcel OD) with hexanes–2-propanol (500:2.5) as the solvent.
[d] The absolute configuration was determined by comparing with the HPLC retention time of an authentic sample, which was independently prepared by the reported procedures.[9a,10a,11a]
[e] 1 mol % of the PTC was used.

Table 7. Catalytic enantioselective phase-transfer alkylation of **1**[a]



Entry	RX	Time (h)	Yield[b] (%)	ee[c] (%)
a	Benzyl bromide	0.5	95	98
b	Dimethyl sulfate	4	80	94
c	Iodoethane	5	85	97
d	1-Iodohexane	5	82	99
e	Allyl bromide	0.5	96	97
f	Methallyl bromide	1	96	96
g	Propargyl bromide	1	92	98
h	2-Nitrobenzyl bromide	1	92	95
i	3-Iodobenzyl bromide	2	91	95
j	4-Fluorobenzyl bromide	1	95	98
k	4-Cyanobenzyl bromide	1	91	96
l	4-Methylbenzyl bromide	2	95	97
m	4-Nitrobenzyl bromide	0.5	94	99
n	4-(*tert*-Butyl)benzyl bromide	1	93	98
o	4-(Trifluoromethyl)benzyl bromide	0.5	98	95
p	3,4-Bis(benzyloxy)benzyl bromide	0.5	95	98
q	Cinnamyl bromide	1.5	92	96
r	1-(Chloromethyl)naphthalene	1	91	97
s	2-(Bromomethyl)naphthalene	1	95	96
t	9-(Chloromethyl)anthracene	0.5	96	99

[a] The reaction was carried out with 1.5 equiv of alkyl halide (RX) and 5.0 equiv of 50% aqueous KOH in the presence of 5.0 mol % of the chiral PTC **41** in toluene–chloroform (7:3) at 0 °C.
[b] Isolated yield of **2**.
[c] The enantiopurity was determined by HPLC analysis of the benzylated imine **2** using a chiral column (Chiralcel OD) with hexanes–2-propanol as the solvent.

active α-amino acid derivatives were obtained in short reaction times with high chemical yields indicating that our new reaction system deserves to be thought of as the primary choice for an efficient and practical asymmetric synthetic method for α-amino acid derivatives.

3. Conclusion

We designed a series of novel dimeric/trimeric ammonium salts derived from cinchona alkaloids as chiral phase-transfer catalysts, and applied them to the phase-transfer catalytic alkylation of the glycine anion equivalent **1**, which has been recognized as a very powerful way of preparing α-amino acids. We found out the optimal reaction conditions for the synthesis of optically active α-amino acid derivatives under phase-transfer catalytic conditions by the fine-tuning of various reaction parameters and by the delicate structural modification of the cinchona-derived ammonium salts. Through the screening of the dimeric chiral catalysts under the optimized reaction conditions, classes of the 1,3-phenyl- and the 2,7-naphthyl-linked dimeric PTCs were found that possess distinguished catalytic capabilities. Mechanistic investigations were also carried out with the 1,3-phenyl dimers (**13**, **16**) on the basis of X-ray crystallography and molecular modeling. The 10,11-hydrocinchonidinium salt of the 2,7-naphthyl-linked dimeric PTC **41** turned out to be an extremely efficient catalyst for the enantioselective phase-transfer catalytic alkylation.[19] Our new reaction system guarantees that both natural and non-natural α-amino acid derivatives can be obtained in a very practical manner with excellent chemical yield and enantiopurity. Moreover, our new reaction system does not require long steps for the preparation of the catalysts and also does not need inconvenient reaction conditions, such as very low temperature and long reaction time, any more. The high accessibility of our cinchona-derived dimeric PTCs with low cost, the practical reaction conditions, and guarantee on the high chemical/optical yields could make our reaction system a very helpful choice in the field of synthesis of optically active α-amino acid derivatives.[20]

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on JASCO FT/IR-300E and Perkin–Elmer 1710 FT spectrometers. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were measured on a JEOL JNM-LA 300 [300 MHz (^{1}H), 75 MHz (^{13}C)] spectrometer, JEOL JNM-GSX 400 [400 MHz (^{1}H), 100 MHz (^{13}C)] spectrometer, and Bruker AMX 500 [500 MHz (^{1}H), 125 MHz (^{13}C)] spectrometer, using DMSO-d_6 or $CHCl_3$-*d* as a solvent, and were reported in parts per million relative to DMSO (δ 2.50) or $CHCl_3$ (δ 7.26) for ^{1}H NMR and relative to the central DMSO-d_6 (δ 39.51) or $CHCl_3$-*d* (δ 77.23) resonance for ^{13}C NMR. Coupling constants (*J*) in ^{1}H NMR are in hertz. High performance liquid chromatography (HPLC) was performed on Hitachi L-7100 instruments using 4.6 mm×25 cm Daicel Chiralcel OD. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Low-resolution mass spectra (MS) were recorded on a VG Trio-2 GC–MS spectrometer, and high-resolution mass spectra (HRMS) were measured on JEOL JMS-AX 505wA, JEOL JMS-HX/HX 110A spectrometers. Melting points were measured on a Buchi B-540 melting point apparatus and were not corrected. For thin-layer chromatography (TLC) analysis, Merck precoated TLC plate (silica gel 60 GF_{254}, 0.25 mm) was used. For flash column chromatography, E. Merck Kieselgel 60 (70–230 mesh) was used. All solvents and commercially available chemicals were used without additional purification.

4.1.1. Representative procedure for the synthesis of chiral phase-transfer catalyst (41).

4.1.1.1. (−)-Hydrocinchonidine. A mixture of (−)-cinchonidine (5.0 g, 16.98 mmol) and 10% Pd/C (1.0 g) in methanol (130 mL) was stirred under hydrogen atmosphere at room temperature for 10 h. The reaction mixture was filtered through Celite pad and the filtrate was concentrated in vacuo. The residue was suspended in hexane (200 mL) and stirred at room temperature for 1 h and then filtered. The solids were collected to afford 4.6 g (92% yield) of the desired product as a white solid.

4.1.1.2. 2,7-Bis(bromomethyl)naphthalene. A mixture of 2,7-dimethylnaphthalene (2.00 g, 12.80 mmol), *N*-bromosuccinimide (5.00 g, 28.16 mmol), and 2,2′-azobisisobutyronitrile (190 mg, 1.15 mmol) in carbon tetrachloride (160 mL) was stirred at reflux for 10 min after which the mixture was cooled to 0 °C. The precipitated succinimide was filtered off and the filtrate evaporated under reduced pressure. The residue was recrystallized from chloroform to give 3.50 g (88% yield) of the desired product as a white solid.

4.1.1.3. 2,7-Bis(hydrocinchonidinium-*N*-methyl)naphthalene dibromide. A mixture of (−)-hydrocinchonidine (2.00 g, 6.75 mmol) with 2,7-bis(bromomethyl)naphthalene (1.04 g, 3.31 mmol) in a mixture of ethanol (5 mL), DMF (6 mL), and chloroform (2 mL) was stirred at 100 °C for 6 h. After cooling the reaction mixture to room temperature, the resulting suspension was diluted with methanol (20 mL) and ether (60 mL) and stirred for 1 h. The solids were filtered and washed with ether. The crude solid was recrystallized from methanol–ether to afford 2.90 g (97% yield) of desired product as a pink solid. Mp 248 °C (decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.00 (d, *J*=4.4 Hz, 2H), 8.37–8.31 (m, 4H), 8.21 (d, *J*=8.6 Hz, 2H), 8.12 (d, *J*=8.6 Hz, 2H), 7.93 (d, *J*=7.8 Hz, 2H), 7.88–7.82 (m, 4H), 7.76–7.71 (m, 2H), 6.77 (d, *J*=4.6 Hz, 2H), 6.63 (s, 2H), 5.36 (d, *J*=12.4 Hz, 2H), 5.15 (d, *J*=12.7 Hz, 2H), 4.43–4.32 (m, 2H), 4.02–3.96 (m, 2H), 3.54–3.41 (m, 2H), 3.39–3.27 (m, 4H), 2.20–2.05 (m, 4H), 2.01–1.92 (m, 2H), 1.73–1.61 (m, 4H), 1.48–1.36 (m, 2H), 1.31–1.23 (m, 4H), 0.71 (t, *J*=7.3 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.6, 148.1, 145.7, 136.2, 134.7, 132.6, 132.1, 130.4, 129.9, 128.8, 127.7, 127.0, 124.9, 124.2, 120.6, 68.2, 64.6, 63.2, 62.3, 51.4, 49.5, 35.6, 25.9, 24.1, 11.7; IR (KBr) 3855, 3434, 2960, 1629, 1509, 1458, 1059, 779, 489, 458 cm^{-1}; $[\alpha]_D^{25}$ −127 (*c* 0.57, MeOH); MS (ESI): 746 $[M-2Br]^{2+}$; HRMS (ESI) calcd for $[C_{50}H_{58}N_4O_2]^{2+}$: 746.4560, found: 746.4736.

4.1.1.4. 2,7-Bis[*O*(9)-allylhydrocinchonidinium-*N*-methyl]naphthalene dibromide (41). To a suspension of

2,7-bis(hydrocinchonidinium-*N*-methyl)naphthalene dibromide (1.80 g, 1.99 mmol) in dichloromethane (10 mL) was added allyl bromide (1.03 mL, 11.90 mmol) and 50% aqueous KOH (2.23 mL, 19.90 mmol). The resulting mixture was stirred vigorously at room temperature for 4 h, during which time all of the solids dissolved. The mixture was diluted with water (20 mL) and was extracted with dichloromethane (2×50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude solid was recrystallized from dichloromethane–hexane to yield 1.95 g (95% yield) of desired product as a light yellow solid. Mp 194 °C (decomp.); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.05 (d, J=4.3 Hz, 2H), 8.45 (s, 2H), 8.34 (d, J=7.9 Hz, 2H), 8.25 (d, J=8.2 Hz, 2H), 8.17 (d, J=7.8 Hz, 2H), 7.97 (d, J=7.6 Hz, 2H), 7.90 (t, J=7.2 Hz, 2H), 7.80 (t, J=7.0 Hz, 2H), 7.74 (d, J=4.1 Hz, 2H), 6.54 (s, 2H), 6.25–6.18 (m, 2H), 5.53 (d, J=17.2 Hz, 2H), 5.38–5.33 (m, 4H), 5.14 (d, J=12.2 Hz, 2H), 4.46 (d, J=7.8 Hz, 2H), 4.20–4.12 (m, 2H), 4.09–4.01 (m, 4H), 3.60–3.52 (m, 2H), 3.42–3.39 (m, 2H), 2.33–2.29 (m, 2H), 2.17–2.10 (m, 2H), 2.07–1.99 (m, 2H), 1.81–1.76 (m, 4H), 1.56–1.48 (m, 2H), 1.29–1.16 (m, 6H), 0.72 (t, J=7.1 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 150.7, 148.5, 141.7, 134.9, 134.8, 132.6, 132.2, 130.4, 130.1, 128.8, 127.9, 126.8, 125.5, 124.2, 120.2, 117.9, 72.5, 69.7, 68.2, 63.9, 61.9, 51.7, 35.4, 25.6, 25.3, 24.1, 21.1, 11.7; IR (KBr) 3434, 2959, 1634, 1509, 1459, 1068, 859, 524 cm^{-1}; $[\alpha]_D^{25}$ −196 (*c* 0.62, $CHCl_3$); MS (ESI): 826 $[M-2Br]^{2+}$; HRMS (ESI) calcd for $[C_{56}H_{66}N_4O_2]^{2+}$: 826.5186, found: 826.5240.

*The pseudoenantiomeric hydrocinchoninium catalyst **42** was prepared by the similar synthetic procedure of **41** from (+)-hydrocinchonine.*

4.1.1.5. 2,7-Bis(hydrocinchoninium-*N*-methyl)naphthalene dibromide. Yield 94%; pink solid; mp 223 °C (MeOH–Et_2O, decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.00 (d, J=4.4 Hz, 2H), 8.50 (s, 2H), 8.37 (d, J=8.5 Hz, 2H), 8.22 (d, J=8.5 Hz, 2H), 8.12 (d, J=8.3 Hz, 2H), 8.01 (d, J=8.0 Hz, 2H), 7.81–7.92 (m, 4H), 7.71–7.79 (m, 2H), 6.84 (d, J=3.9 Hz, 2H), 6.57 (s, 2H), 5.33 (d, J=12.9 Hz, 2H), 5.12 (d, J=12.1 Hz, 2H), 3.97–4.09 (m, 6H), 3.56–3.60 (m, 2H), 2.97–3.00 (m, 2H), 2.25–2.29 (m, 2H), 1.60–1.89 (m, 8H), 1.42–1.58 (m, 4H), 0.96–1.15 (m, 2H), 0.85 (t, J=7.3 Hz, 6H); IR (KBr) 3431, 2959, 1629, 1509, 1460, 1388, 1125, 1051, 933, 859, 777, 482, 428 cm^{-1}; $[\alpha]_D^{25}$ +152 (*c* 0.14, MeOH); MS (FAB): 825 $[M-Br]^+$.

4.1.1.6. 2,7-Bis[*O*(9)-allylhydrocinchoninium-*N*-methyl]naphthalene dibromide (42). Yield 92%; light yellow solid; mp 172 °C (CH_2Cl_2–hexanes, decomp.); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.03 (d, J=4.2 Hz, 2H), 8.13–8.46 (m, 8H), 7.73–8.10 (m, 8H), 6.41–6.44 (m, 2H), 6.12–6.24 (m, 2H), 5.27–5.50 (m, 8H), 4.26–4.40 (m, 2H), 3.79–4.15 (m, 8H), 3.57–3.69 (m, 2H), 2.85–3.05 (m, 2H), 2.26–2.41 (m, 2H), 1.61–1.92 (m, 8H), 1.45–1.58 (m, 4H), 1.17–1.30 (m, 2H), 0.84 (t, J=7.3 Hz, 6H); ^{13}C NMR (75 MHz, $CHCl_3$-*d*) δ 149.0, 147.9, 140.5, 136.8, 133.8, 132.5, 131.9, 130.5, 129.1, 128.6, 127.4, 125.8, 125.1, 124.4, 119.7, 119.2, 71.7, 70.2, 68.3, 64.0, 56.5, 49.5, 35.8, 24.7, 24.2, 23.9, 21.6, 11.4; IR (KBr) 3210, 1590, 1405, 1110, 858, 750, 661, 618, 454 cm^{-1}; $[\alpha]_D^{25}$ +102 (*c* 0.24, $CHCl_3$); MS (FAB): 905 $[M-Br]^+$.

4.1.2. Representative procedure for enantioselective catalytic alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester (1) under phase-transfer conditions (benzylation). To a mixture of *N*-(diphenylmethylene)glycine *tert*-butyl ester **1** (50.0 mg, 0.17 mmol) and chiral catalyst **41** (8.4 mg, 0.0085 mmol) in toluene–chloroform (volume ratio=7:3, 0.5 mL) was added benzyl bromide (0.03 mL, 0.255 mmol). The reaction mixture was then cooled (0 °C), 50% aqueous KOH (0.1 mL) was added, and the reaction mixture was stirred at 0 °C until the starting material had been consumed (0.5 h). The suspension was diluted with ether (20 mL), washed with water (2×5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography on silica gel (hexanes–EtOAc=50:1) afforded the desired product **2a** (62 mg, 95% yield) as a colorless oil. The enantioselectivity was determined by chiral HPLC analysis (DAICEL Chiralcel OD, hexanes:2-propanol=500:2.5, flow rate=1.0 mL/min, 23 °C, λ=254 nm, retention times: *R* (minor) 12.2 min, *S* (major) 22.5 min, 98% ee) The absolute configuration was determined by comparison of the HPLC retention time with the authentic sample synthesized by the reported procedure.

Acknowledgements

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Supplementary data

The spectroscopic data of the selected polymeric phase-transfer catalysts and the chiral HPLC conditions for the alkylated imines **2** are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.05.076.

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