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A New Active Catalyst Species for Enantioselective Alkylation by Phase-Transfer Catalysis

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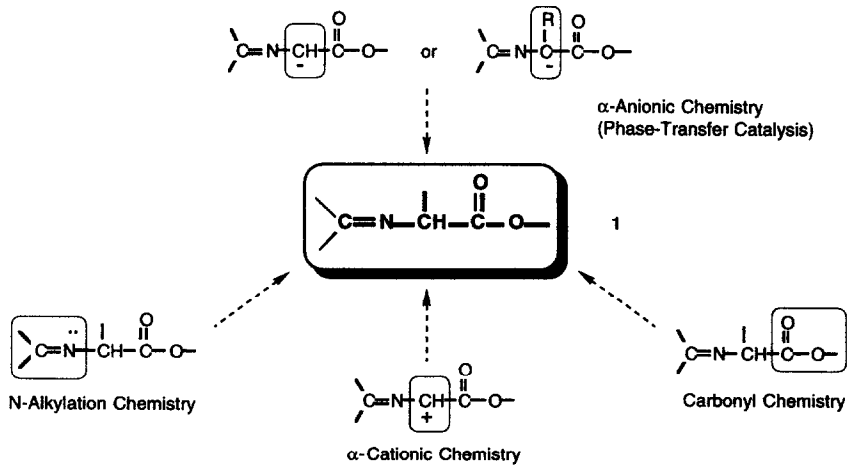
Abstract: This paper briefly reviews the use of Schiff base substrates in amino acid synthesis. Recent studies lead to the proposal of a *new active catalyst species* (**12**) for the asymmetric PTC alkylation of active methylene compounds (**2**). Mechanistic implications are detailed.

INTRODUCTION

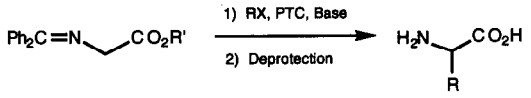
Amino Acid Synthesis from Benzophenone Schiff Base Substrates

Since 1978 we have made use of the acyclic structural subunit **1** for the synthesis of α-amino acid derivatives. Synthetic methodology has been developed for carbon-carbon bond constructions, by either anionic[1] or cationic[2] amino acid equivalents, as well as processes which establish carbon-nitrogen[3] and carbon-oxygen bonds.[4,5]



Racemic Alkylations by Phase-Transfer Catalysis (PTC)

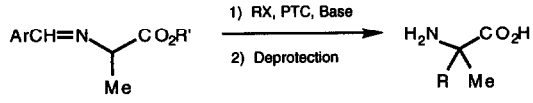
In the area of carbon-carbon bond formation involving the reaction of α-anionic synthons of glycine or higher amino acids, a practical synthesis of α-monoalkyl amino acids was developed using catalytic phase-transfer (PTC) alkylations of the benzophenone imine of glycine alkyl esters (**2**) and other glycine synthons.[1a-c, 1e-i] In contrast to known anhydrous alkylative routes,[6] the PTC method involves a simple reaction



2 (±)-**3**

PTC Monoalkylation (1)

procedure, mild conditions, inexpensive and safe reagents and solvents, commercially available starting substrates and the ability to easily scale-up the reaction. Since there was no chirality control element used in these early reactions, the product **3** is a racemic mixture. The method has been extended to the alkylation of aldimine derivatives **4** as a route to α,α-dialkyl amino acids, here exemplified by a racemic synthesis of the



4 (±)-**5**

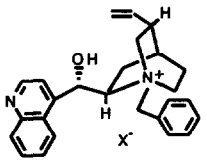
PTC Dialkylation (2)

important α-methyl amino acids **5**.[1d-g,1m] These phase transfer alkylations have been conducted under a variety of mild, basic conditions[1a-c,1e-f] and other interesting amino acids, such as 1-aminocyclopropane-1-carboxylic acid,[1g] and 3-fluorophenylalanine[1h] have been prepared using this procedure.

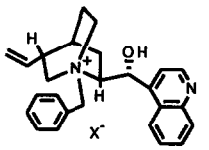
Catalytic Enantioselective Synthesis of α-Amino Acids by PTC

The preparation of chiral, non-racemic compounds from prochiral substrates with chiral catalysts under phase-transfer conditions is potentially a powerful synthetic method for asymmetric bond construction[7] in which there have been several notable successes.[8-12]

The first practical asymmetric synthesis of α-amino acids by phase-transfer catalysis (PTC) was reported from our laboratory in 1989.[11] The methodology developed allowed preparation of either enantiomer of a variety of types of target amino acids in up to 66% ee (83:17 mixture of enantiomers) by a simple and straightforward procedure at room temperature from readily available starting materials. The method uses catalytic amounts of the enantiocontrol element and both pseudoenantiomeric phase-transfer catalysts **6** and **7**, as well as the catalyst precursors, cinchonine (**Cn**) and cinchonidine (**Cd**), respectively, are inexpensive

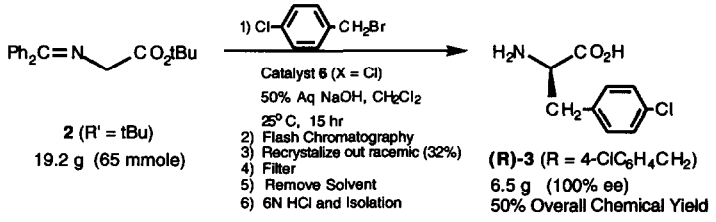


6
(from cinchonine, **Cn**)



7a
(from cinchonidine, **Cd**)

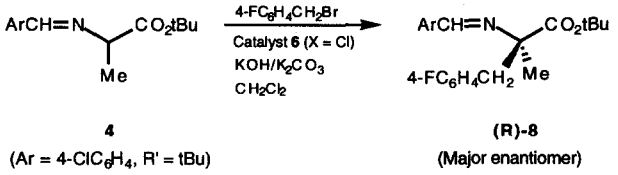
and commercially available. The ability to scale the reaction up and the possibility of preparing α-amino acids in high optical purity were demonstrated by the synthesis of 6.5 g of optically pure non-natural 4-chloro-D-phenylalanine (**R-3**, R = 4-$ClC_6H_4CH_2$) from the starting substrate **2** (R' = tBu).[11] By simply changing from



Catalytic Enantioselective PTC Monoalkylation (3)

the cinchonine- (**6**) to the cinchonidine-derived catalyst series (**7**), the optically pure enantiomeric product (**S-3**, R = 4-$ClC_6H_4CH_2$) can also be prepared by this procedure. This method for preparing optically pure α-alkyl amino acid derivatives has also been used by others.[13-15]

The PTC methodology has recently been extended to the synthesis of α-methyl amino acids,[1n] an important class of unnatural amino acid derivatives. For example, **4** (Ar = 4-ClC_6H_4, R' = tBu) was alkylated with 4-fluorobenzyl bromide in the presence of a catalytic amount of N-benzylcinchoninium



4
(Ar = 4-ClC_6H_4, R' = tBu)

(R)-8
(Major enantiomer)

Catalytic Enantioselective PTC Dialkylation (4)

chloride (**6**, X = Cl) to give the α-methyl-4-fluoro-R-phenylalanine derivative **R-8** (a protected **R-5**) in 50% enantioselectivity (75:25 mixture of enantiomers).[1n]

Further in-depth understanding of the mechanisms of these complex reactions, the nature of the active catalyst species, and the molecular recognition processes involved in the asymmetric induction step of asymmetric PTC reactions are needed to fully realize the potential of this important process. This paper details some recent studies which suggest the presence of a new active catalyst in asymmetric PTC alkylation reactions.

RESULTS AND DISCUSSION

Mechanistic Scheme for PTC Alkylation

A general mechanistic scheme (Figure 1) for the monoalkylation of active methylene compounds such as **2** illustrates the variables common to many of the systems studied and helps define key problems which need to be addressed in such reactions.[7] Three main steps have been proposed in this process:[16] (1) deprotonation of the active methylene compound with base, which generally occurs at the interface between the two layers (liquid-liquid (L/L) or solid-liquid (S/L) PTC); (2) extraction of the anion ($\mathbf{A}^-$) into the bulk organic phase by ion-exchange with the cation of the chiral quaternary ammonium salt to form a lipophilic ion-pair (**D**); and (3) creation of the new chiral center in product **P*** by alkylation of the ion-pair (**D**) with concomitant regeneration of the catalyst.

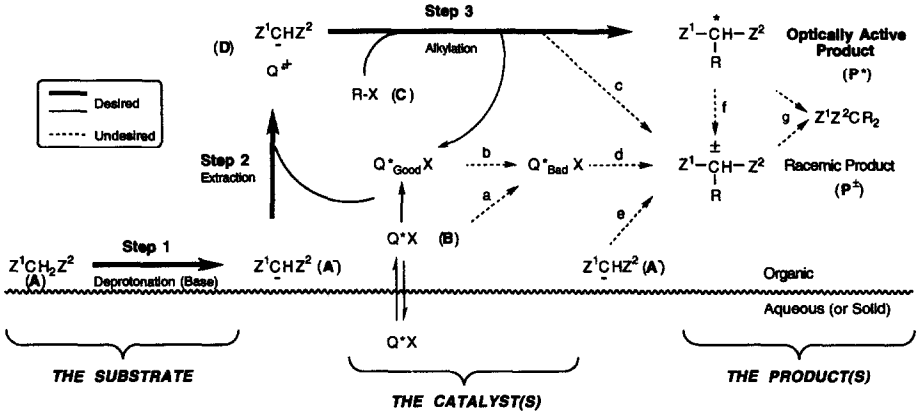
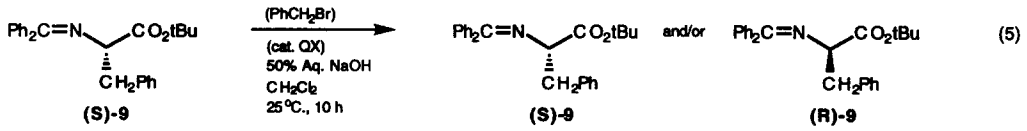


Figure 1. Mechanistic Scheme for the Asymmetric Alkylation of an Active Methylene Compound by PTC.

A number of undesirable processes can occur in competition with the formation of the optically active product: (1) alkylation of the "wrong" ion-pair leading to the enantiomer of the desired product (step c); (2) side-reactions of either the starting substrate (e.g. ester saponification or imine hydrolysis of starting materials such as **2** or the reaction product (racemization (step f) and/or dialkylation (step g) following product formation as well as the hydrolyses reactions mentioned above for the starting material); (3) interfacial alkylation (step e) of substrate anion ($\mathbf{A}^-$) in the absence of the chiral quat cation which necessarily yields racemic product; (4) reaction of the chiral quat (**B**) to form a new organic compound which could function either as the reactive catalyst species ($\mathbf{Q^*_{Good}X}$) or as a compound ($\mathbf{Q^*_{Bad}X}$) (steps a or b) which is either an ineffective catalyst or one which leads to racemic product.

Product Racemization Studies and a New Active Catalyst

Studies concerned with racemization of the monoalkylation product (step f in Figure 1) have resulted in several interesting observations concerning the nature of the active catalyst species in these reactions (eq 5 and Table I). At the outset of these studies, racemization and/or dialkylation were expected to be minimal since the product **9** from the monoalkylation is considerably less acidic than the starting active methylene compound **2**.[17,18] In the event, when the optically pure benzophenone imine ((**S**)-**9**) (prepared independently by transimination of S-phenylalanine t-butyl ester hydrochloride with benzophenone imine[19]) was subjected to conditions typical of those following a phase-transfer alkylation (no alkyl halide, 50% aqueous NaOH, CH_2Cl_2



(5)

Table 1. Racemization Studies of Monoalkylation Product **(S)-9**.

Experiment	QX	$PhCH_2Br$?	Product (%S)	% Racemization
1	nBu_4NBr	No	100	0
2	None	No	100	0
3	**6** (X=Br)	No	64	72
4	**7a** (X=Br)	No	65	70
5	**7a** (X=Br)	Yes	100	0
6	**12a**	No	100	0

at room temperature for ten hours either in the presence (exp. 1) or absence (exp. 2) of the phase-transfer catalyst tetrabutylammonium bromide) no racemization of **(S)-9** was observed. Surprisingly, when the cinchonine- or cinchonidine-derived chiral catalysts (**6** or **7a**, X=Br) were used under the above conditions, 36% and 35%, respectively, of **(R)-9** was observed in two hours and then no further racemization occurred (exp. 3 & 4). However, when benzyl bromide was present during the reaction with catalyst **7a**, no racemization of **(S)-9** occurred (exp. 5).

These seemingly disparate results can be explained by invoking a catalyst-degradation mechanism (Figure 2) similar to that proposed by the Merck group.[20] Deprotonation of the initial catalyst (**7a**) leads to the zwitterionic alkoxide **10**[21] which could serve as an effective lipophilic base capable of deprotonation of **(S)-9**. It was proposed that decomposition of such an alkoxide can occur by two pathways, a slow fragmentation to form epoxide **11** and a faster O-alkylation to **12**[22] followed by Hofmann elimination to **13**.[23] In the present study, in the absence of alkyl halide (Table 1, exp. 3 & 4), the latter pathway for destruction of the alkoxide would not be possible, however the slow fragmentation to **11** could still occur, thus accounting for the partial racemization of **(S)-9** which stopped after two hours. When alkyl halide was added (exp. 5), rapid O-alkylation of zwitterion **10** to form **12** would remove the alkoxide as soon as it was formed and, thereby, minimize base-promoted racemization. It is noted that during the normal PTC alkylation of **2** there is always sufficient alkyl halide present to form **12** since RX is used in excess (1.2-5 eq of RX with respect to **2**, 12-50 eq of RX with respect to catalyst **7**). As a result of these racemization studies, it is necessary to consider the possibility that *the active catalyst in the asymmetric PTC alkylation of* **2** *is the N-alkyl-O-alkyl cinchona salt (***12***) which is formed in situ during the reaction!*

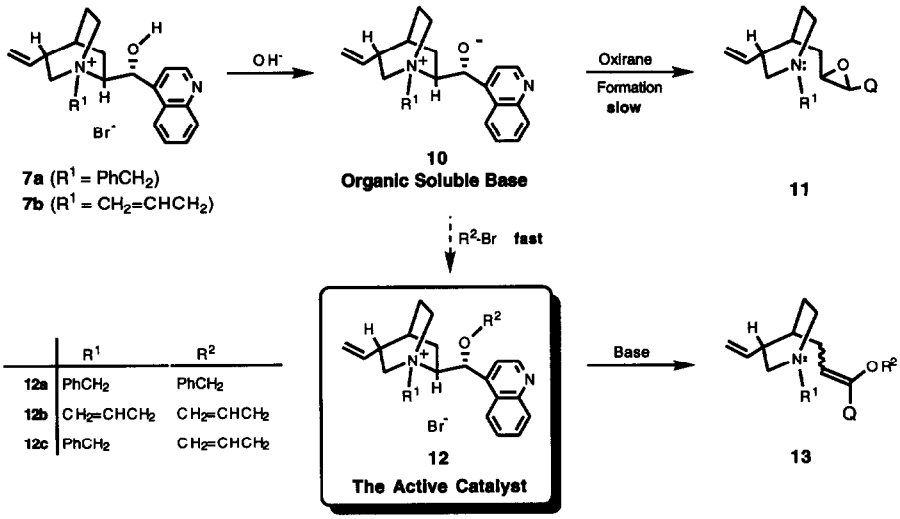


Figure 2. Catalyst Decomposition Studies and Identification of the Active Phase-Transfer Catalyst.

To test this hypothesis, catalyst **12a** was prepared independently either by reacting cinchonidine with two equivalents of benzyl bromide in CH_2Cl_2 in the presence of 50% aqueous NaOH or by O-benzylation of

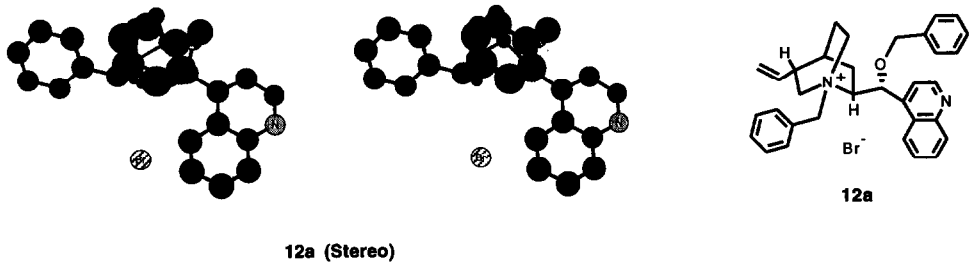
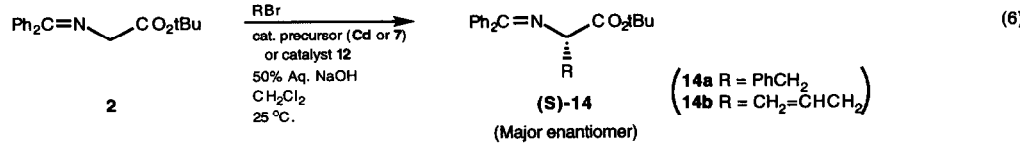


Figure 3. X-Ray Structure of New Catalyst **12a**.

quaternary ammonium bromide **7a** with benzyl bromide. The structure of the product, N,O-dibenzylcinchonidinium bromide (**12a**) was confirmed by the crystal structure[24] (Figure 3).

Three separate benzylations of **2** (eq 6, RBr = benzyl bromide) using different catalyst precursors or catalysts [cinchonidine (**Cd**), N-benzyl cinchonidinium bromide (**7a**) and N,O-dibenzylcinchonidinium



(6)

bromide (**12a**)] were carried out. The observed % enantiomeric excesses of product **(S)-14a** were identical (61, 60 and 60% ee, respectively) with all three catalytic species, which provides supporting evidence that compound **12** is the active catalyst in these PTC alkylations.

A similar series of experiments involving allylation of **2** (eq 6, RBr = allyl bromide) provided further insight into these processes. When the allylation was carried out using cinchonidine (**Cd**) as the catalyst precursor, the monoallylated product **(S)-14b** was formed in only 36% ee. This result is not unexpected since the catalyst formed *in-situ* from cinchonidine *via* **7b** would be N,O-diallylcinchonidinium bromide (**12b**). This experiment supports previous studies[25] that indicate an aromatic unit at the quaternary ammonium site is much preferable to an alkyl group. Allylation of **2** in the presence of a catalytic amount of either N-benzylcinchonidinium bromide (**7a**) or independently prepared N-benzyl-O-allylcinchonidinium bromide (**12c**) gave the product in 59% ee whereas allylation using N,O-dibenzylcinchonidinium bromide (**12a**) resulted in 54% ee of **(S)-14b**. These last three experiments show that an O-allyl group is slightly preferable to an O-benzyl group.

As expected, when new catalyst **12a** was used in the product racemization study described earlier (eq 5 and Table I, exp 6) no racemization of **(S)-9** was observed. In this experiment, a base such as **10**, capable of racemizing **(S)-9**, would not be formed since the oxygen of the catalyst is already alkylated. In contrast, in the earlier example (eq 5 and Table 1, exp 4), where the catalyst **12a** is formed *in situ* from the catalyst precursor **7** by O-alkylation, the zwitterion **10** would be an intermediate. In this case, as long as alkyl halide was absent, the organic soluble base **10** could racemize **(S)-9**.

A key tenet in the folklore of asymmetric PTC reactions is the pivotal role of the β-hydroxyammonium ion in the chiral catalyst.[26,27] The importance of the hydroxyl group in the catalyst dates from the very early literature in asymmetric PTC,[21a-b,25a] which in most cases resulted in, at best, only low inductions. Also some of this early research has either been retracted or disputed, due in large part to the use of optical rotations for the determination of levels of induction. It has been noted[25b] that phase-transfer catalysts can, under basic conditions, decompose to compounds which themselves have high optical rotations. Thus, crude or even purified reaction products which contain a small amount of a decomposition product from the catalyst can have non-zero rotations and lead to erroneous interpretation of results. Furthermore, a variety of different reactions (reductions, epoxidations, alkylations, Michael additions, etc.) conducted under various basic or neutral reaction conditions as well as the related use of the free alkaloids[28] in catalytic systems seem to have been classified together in an attempt to provide a single, broad and all-encompassing interpretation of the mode origin of the asymmetric induction in these various reactions. Finally, previous studies using catalysts with a modified hydroxyl group (OR where R = alkyl[22] or acyl[29]) or catalysts in which the hydroxyl has been replaced by hydrogen[30] have, for the most part, not been systematic, have resulted in only low inductions or were conducted under conditions in which the catalyst would not be stable (e.g. OR where R = acyl).[21c]

The studies presented here further demonstrate the need for careful scrutiny of both past and future results in the area of asymmetric PTC. Although these results do not prove that the active catalysts in the alkylation reaction studied are O-alkylated compounds such as **12**, they provide necessary support for this proposal. This opens the door to a whole new family of modified catalysts for this and possibly other PTC reactions. Kinetic and structural studies to further probe the mechanism of this reaction and the origin of the chiral induction step are in progress.

EXPERIMENTAL SECTION

General. Nuclear magnetic resonance (NMR) spectra were determined on a GE QE-300 300-MHz NMR spectrometer with $CDCl_3$ as solvent and Me_4Si (TMS) as internal standard unless otherwise specified. Chemical shifts are reported as δ values in parts per million (ppm). Proton NMR spectra are recorded in order: chemical shift, number of protons and multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; bs, broad singlet; m, multiplet; J, coupling constant). Melting points were obtained by using a Thomas Hoover Capillary melting

point apparatus and are uncorrected. High resolution mass spectral (HRMS) analyses were done in the School of Pharmacy, Purdue University, West Lafayette. HPLC analyses were done on Varian Model 360 and Water's model 500 HPLC instruments using a Baker Bond Chiral Phase DNBPG (Covalent) column (5 u, 4.6 x 250 mm) (product No. RP-7113-0) (Serial No. 503115-17) with hexane/dioxane (100/0.5 or 200/3, v/v) or hexane/isopropanol (350/1). Thin layer chromatography (TLC) was performed using 5 x 10 cm precoated TLC plates of 0.25 nm thick silica gel 60F-254 on glass (EM reagent) and analyzed under ultraviolet light (model UVG-11 mineral light lamp, short wave UV-254 nm, Ultra-Violet Products Inc.). Flash chromatographic separations and purifications were carried out on various columns filled with silica gel 60 (230-400 mesh) from Aldrich Chemical Co. Unless otherwise noted, chemicals were reagent grade and used without further purification.

1,1-Dimethylethyl N-(diphenylmethylene)-(S)-phenylalaninate (S-9). Benzophenone imine (0.34 g, 1.9 mmol), (S)-phenylalanine t-butyl ester hydrochloride (0.50 g, 1.9 mmol) and CH_2Cl_2 (10 mL) were added to a 25 mL flask containing a stirring bar and a drying tube ($CaCl_2$). The mixture was stirred at room temperature for 24 h, filtered to remove NH_4Cl and the filtrate was evaporated to dryness on a rotary evaporator. Ether (15 mL) was added to the residue and the resulting solution was washed with H_2O (3 x 10 mL), dried ($MgSO_4$), filtered and evaporated *in vacuo* to give crude product (0.628 g, 86%). The crude product could be purified further by flash chromatography (hexane/EtOAc, 8/2); oil; ^{1}H-NMR: δ (ppm) 1.45 (9H, s), 3.17 (1H, dd, J = 9.1, 13.3 Hz), 3.25 (1H, dd, J = 4.5, 13.3 Hz), 4.12 (1H, dd, J = 4.5, 9.1 Hz), 6.58-7.58 (15H, m); ^{13}C-NMR: δ (ppm) 28.03, 39.56, 67.91, 81.11, 126.13, 127.63, 127.91, 128.02, 128.05, 128.17, 128.25, 128.69, 129.85, 130.06, 136.33, 138.32, 139.52, 170.28, 170.81; Anal. Calcd for $C_{26}H_{27}NO_2$: C, 81.01, H, 7.06, N, 3.63. Found: C, 80.73, H, 6.85, N, 3.43.

Product Racemization Studies Using Various Combinations of Reagents and Types of Catalysts. General procedure. 1,1-Dimethylethyl N-(diphenylmethylene)-L-phenylalaninate [**(S)-9**][19] (pure S, 0.385 g, 1 mmole.), CH_2Cl_2 (6.5 mL), catalyst (0.1 mmol) or no catalyst and benzyl bromide (0.21 g, 1.2 mmol) or no benzyl bromide were added to a 25 mL round-bottom flask equipped with a magnetic stirring bar. 50% Aqueous NaOH (1.6 g, 20 mmole) was added in one portion and the resulting mixture was stirred vigorously for 10 h at room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), the CH_2Cl_2 solution was washed with water (10 mL) and the CH_2Cl_2 was evaporated *in vacuo*. The residue was taken up in ether (20 mL), washed with water (2 x 10 mL), the layers were separated and the ether layer was dried with anhydrous $MgSO_4$, filtered and evaporated *in vacuo*. The product samples were analyzed for % racemization by HPLC using a chiral Pirkle column with hexane/dioxane (100/0.5, v/v) at a flow rate of 0.5 mL/min and UV detection at 254 nm.

- **(a) Experiment 1:** tetrabutylammonium bromide (catalyst) and no benzyl bromide. 0 % racemization, (100% S, 0% R).
- **(b) Experiment 2:** no catalyst and no benzyl bromide. 0 % racemization, (100% S, 0% R).
- **(c) Experiment 3:** N-benzylcinchoninium bromide (**6**) (catalyst) and no benzyl bromide. 72 % racemization (64% S, 36% R).
- **(d) Experiment 4:** N-benzylcinchonidinium bromide (**7a**) (catalyst) and no benzyl bromide. 70 % racemization (65% S, 35% R).
- **(e) Experiment 5:** N-benzylcinchonidinium bromide (**7a**) (catalyst) and benzyl bromide. 0 % racemization, (100% S, 0% R).
- **(f) Experiment 6:** N,O-dibenzylcinchonidinium bromide (**12a**) (catalyst) and no benzyl bromide. 0 % racemization, (100% S, 0% R).

N,O-Dibenzylcinchonidinium Bromide (12a). Cinchonidine (1.18 g, 4 mmole) and methylene chloride (40 mL) were added to a 100 round-bottom flask equipped with a magnetic stirring bar. Benzyl bromide (2.05

g, 12 mmole) was added followed by 50% aqueous NaOH (6.4 g, 80 mmole) in one portion and the resulting mixture was stirred vigorously at room temperature for 4 h. The mixture was transferred to a separatory funnel, the layers were separated and the methylene chloride layer was washed with water (2 x 10 mL), dried ($MgSO_4$), filtered and evaporate *in vacuo*. The crude product was suspended in ether (40 mL), stirred for 4 h and filtered again. After recrystallization from methylene chloride-acetone, 1.90 g (85%) of white crystalline product was obtained; mp 214-215 °C; ^{1}H-NMR: δ (ppm) 1.48 (1H, m), 1.82 (1H, m), 2.05 (1H, bs), 2.11-2.25 (2H, m), 2.57 (1H, m), 3.16 (2H, m), 4.11 (1H, d, J=11.8 Hz), 4.18 (1H, m), 4.40 (1H, d, J=11.6 Hz), 4.62 (1H, m), 4.87 (1H, d, J=11.6 Hz), 4.92 (1H, m), 4.94 (1H, d, J=10.45 Hz), 5.30 (1H, d, J=17.2 Hz), 5.62-5.70 (1H, m), 6.19 (1H, d, J=11.7 Hz), 6.25 (1H, bs), 7.37-7.65 (8H, m), 7.76 (2H, d, J=6.5 Hz), 7.80 (2H, t, J=7.7 Hz), 7.93 (1H, m), 8.15 (1H, d, J=8.4 Hz), 8.76 (1H, d, J=8.15 Hz); 9.02 (1H, d, J=4.2 Hz); ^{13}C-NMR: δ (ppm) 22.51, 25.19, 26.93, 37.71, 51.10, 59.90, 61.80, 66.01, 71.44, 72.63, 118.30, 119.44, 119.66, 124.69, 125.35, 126.96, 128.98, 129.23, 129.33, 129.40, 129.99, 130.40, 134.02, 135.56, 136.23, 139.88, 148.57, 149.54; Anal. Calcd for $C_{33}H_{35}BrN_2O$: C, 71.35, H, 6.31, N, 5.04, Br, 14.41. Found: C, 71.17, H, 6.24, N, 4.93, Br, 14.53.

O-Alkylation of N-Benzylcinchonidinium Bromide. General Procedure. N-Benzyl cinchonidinium bromide (**7a**) (0.93 g, 2 mmole) and methylene chloride (20 mL) were added to a 50 mL round-bottom flask equipped with a magnetic stirring bar. Alkyl bromide (6 mmole) then was added followed by 50% aqueous NaOH (3.2 g, 4 mmole) in one portion. The reaction mixture was stirred for 3-4 h at room temperature. The mixture was separated and the aqueous layer was extracted by methylene chloride (2 x 5 mL). The combined methylene chloride layers were washed with water (2 x 10 mL), and dried over magnesium sulfate, filtered and evaporated *in vacuo*. The crude product was suspended in ether (30 mL), stirred for 4 h and filtered again. The product was washed with ether (3 x 10 mL) and further purified by recrystallization or chromatography.

(a) Synthesis of N,O-Dibenzylcinchonidinium Bromide (12a). 78%; mp 215-216 °C; HRMS: Calcd for $C_{33}H_{35}N_2O$ (Cation): 475.2749, Anion=Br. Found: 475.2744.

(b) Synthesis of N-Benzyl-O-allylcinchonidinium Bromide (12c). 75%; mp 165-167 °C; ^{1}H-NMR: δ (ppm) 1.43 (1H, m), 1.86 (1H, m), 2.09 (1H, bs), 2.13-2.23 (2H, m), 2.63 (1H, bs), 3.25 (1H, t, J=12.0 Hz), 2.42 (1H, t, J=9.0 Hz), 4.05 (1H, dd, J=6.7 Hz, J=6.7 Hz), 4.27 (1H, dd, J=5.0 Hz, J=4.7 Hz), 4.33 (1H, m), 4.66 (1H, d, J=10.5 Hz), 4.70 (1H, m), 4.90 (1H, m), 4.95 (1H, d, J=10.5 Hz), 5.34-5.43 (3H, m), 5.64-5.75 (1H, m), 6.08-6.17 (1H, m), 6.24 (1H, bs), 6.52 (1H, d, J=11.7 Hz), 7.47-7.49 (3H, m), 7.68-7.70 (1H, m), 7.75 (1H, t, J=7.6 Hz), 7.86-7.94 (3H, m), 8.11 (1H, d, J=8.4 Hz), 8.85 (1H, d, J=8.4 Hz), 8.98 (1H, d, J=4.2 Hz); ^{13}C-NMR: δ (ppm) 22.64, 25.22, 26.89, 37.71, 51.37, 59.58, 62.35, 66.36, 70.35, 74.16, 118.16, 119.52, 119.58, 119.72, 120.02, 124.73, 125.30, 127.16, 128.87, 129.20, 129.95, 130.04, 130.56, 132.59, 134.23, 136.35, 140.07, 148.48, 149.67; HRMS: Calcd for $C_{29}H_{33}N_2O$ (Cation): 425.2593, Anion=Br. Found: 425.2584.

Alkylation Studies using Catalyst Precursors or New Catalysts. General Procedure. 1,1-Dimethylethyl N-(diphenylmethylene)glycinate (**2**)[19] (0.295 g, 1 mmol), benzyl bromide (0.208 g, 1.2 mmole) or allyl bromide (0.6 g, 5 mmole), catalyst or catalyst precursor (0.1 mmole) and CH_2Cl_2 (6.5 mL) followed by 50% aqueous NaOH (20 mmole) were added to a reaction flask. The mixture was stirred vigorously by magnetic stirring for 10 h (benzylation) or 5 h (allylation) at room temperature. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined CH_2Cl_2 layers were washed with water (2 x 10 mL) and evaporated. The residue was taken up in ether (30 mL) and washed with water (2 x 10 mL), dried with anhydrous $MgSO_4$, filtered, and the filtrate was evaporated *in vacuo*. The product was obtained as an oil. For analysis, product (50 mg) was dissolved in isopropanol or hexane (1 mL) and the % ee was obtained by HPLC on a Pirkle column: eluent hexane/dioxane (100/0.5), flow rate 0.5 ml/min.

(a) **Benzylation:** 61% ee was obtained using cinchonidine (**Cd**) as catalyst precursor and 60% ee was obtained using either N-benzylcinchonidinium bromide (**7a**) as catalyst precursor or N,O-dibenzylcinchonidinium bromide (**12a**) as catalyst. All three reactions gave **(S)-14a** as the major enantiomer.

(b) **Allylation:** 36% ee was obtained using cinchonidine (**Cd**), 59% ee was obtained using N-benzylcinchonidinium bromide (**7a**) or N-benzyl-O-allylcinchonidinium bromide (**12c**) and 54% ee was obtained using N,O-dibenzylcinchonidinium bromide (**12a**), respectively. All four reactions gave **(S)-14b** as the major enantiomer.

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