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Revisiting optically active quaternary derivatives made from prolinol as phase transfer catalysts[1]

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Abstract

New non-racemic ammonium salts derived from prolinol have been prepared which are stereogenic both at N and at C. Absolute configurations rest on X-ray structures for **3c** and **7a**. The new compounds have been tested in a number of known enantioselective phase transfer catalytic (PTC) reactions to gain insight into steric control factors in such processes. Only very moderate e.e.s were observed. A SAMP hydrazone related catalyst (**7a**) reported by other authors was fully characterized. Racemic reaction products were obtained in two alkylations of diphenylmethylene benzylimine in the presence of this pure catalyst **7a**. Very high e.e.s reported previously by others could not be reproduced.

1. Introduction

Two years ago, J. J. Eddine and M. Cerqaoui reported in this journal enantiomeric excesses of up to 94% in C-alkylations of benzophenone benzylimine using (2S)-1-methyl-1-[N-(diphenylmethylene)]-2-hydroxymethylpyrrolidine hydrazonium iodide **7a** or the analogous derivative prepared from SAMP **7b** as a phase transfer catalysts.[2] This information met with strong interest from workers in the PTC field[3] because high e.e.s are relatively rare in PTC. They are realized most often only after very extensive optimization work (reviews: lit.[4a–d]). We paid special attention to the mentioned publication as it was closely related to our ongoing work which we shall cover here first. Generally, derivatives of cinchona alkaloids have been found to be the most promising enantioselective PT catalysts. The earlier work of our group with various substituted non-racemic catalysts was disappointing in terms of the enantioselectivity.[5] Using the cinchona catalysts as standards and L-proline as one of several

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† Stereochemical control experiments.

‡ X-Ray structural work.

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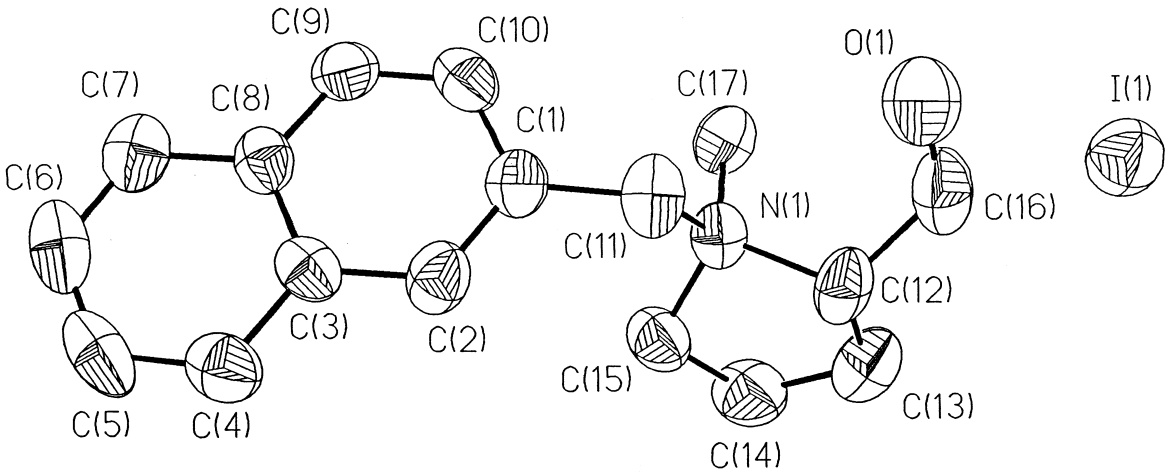


Fig. 1. ORTEP drawing of the molecular structure of **3c** in the crystal

chiral motives, we therefore tried to find out which structural elements were responsible for effective enantioselective catalysis.

2. Results and discussion

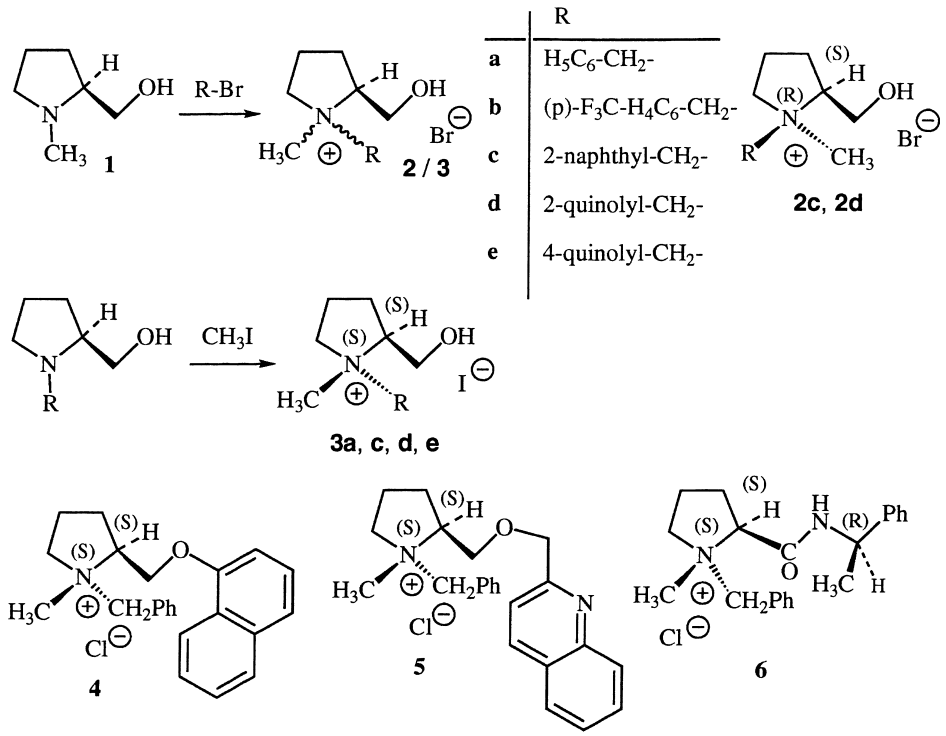
When (L)-N-methylprolinol **1** was reacted with benzyl bromide, p-trifluorobenzyl bromide, or 2-bromomethylnaphthalene, difficult to separate mixtures of epimers **2**:**3** (1:1 to 1:1.5) were obtained. Repeated recrystallization resulted in the isolation of a pure diastereoisomer **2c** only in the case of the methylnaphthyl compound. Polymerization sensitive 2-bromomethylquinoline and **1** led to a darkish oil, from which **2d** could nevertheless be crystallized. There was no indication for the epimer in the mother liquid here.

The direct preparation of the other pure isomer became possible in each case, however, when the introduction of the two groups on nitrogen was reversed. Thus, conversion of N-benzylprolinol, N-(2-methylnaphthyl)prolinol and N-(2-methylquinolinyl)prolinol with methyl iodide gave highly diastereoselective alkylations allowing the isolation of pure iodides **3a**, **3c**, and **3d**. Ion exchange transformed these into the chlorides which are more suitable as PT catalysts. Compounds **3c**,**d** proved to be the epimers of **2c**,**d** (for assignment of absolute configurations, see below).

The reaction between 4-bromomethylquinoline (which is even more sensitive than the 2-bromomethyl compound) and **1** gave a tarry mass from which a 40% yield of **3e** (R=4-methylquinolyl) could be obtained in crystalline form. N-(4-Methylquinolyl)prolinol could not be made accessible. The ether formation of benzylprolinol with 1-naphthol by a Mitsunobu type reaction and further conversion furnished **4**, and a simple etherification by 2-bromomethyl quinoline plus conventional elaboration gave **5**. These two new PTs were designed to provide additional sites for interaction with substrates in catalytic transition states.

Relative and absolute stereochemistries of compounds **2** (1R,2S) and **3**–**5** (1S,2S) rest on the known configuration of (L)-proline, an X-ray structure determination of **3c** (Fig. 1),[6] and the NMR spectroscopic correlation of this compound with the others. Chemical shifts of the two diastereomeric hydrogens of the CH_2–Ar residues are positioned 0.62–0.79 ppm apart in compounds **2** due to differential shielding by the cis hydroxymethyl group. The $\Delta\delta$ value of the respective signals in compounds **3** is much smaller, only 0.1–0.39.

It is noteworthy that methyl iodide is taken up with high preference from the same side as the hydroxymethyl group, possibly due to pre-complexation by hydrogen bonding, whereas the more voluminous alkyl groups do not exhibit much steric preference.



The 6 new catalysts were evaluated in several enantioselective PTC reactions well documented in the literature (1–5):

Reaction (1): $Ph_2C{=}N{-}CH_2{-}COOR + Br{-}CH_2{-}Ph \rightarrow Ph_2C{=}N{-}C^*H(CH_2Ph){-}COOR$ (R=Et, *t*-Bu)

Reaction (2): Ph–CO–*t*-Bu ($NaBH_4$)→Ph–CH*(OH)–*t*-Bu

Reaction (3): Phthalimid–K+Br–CH(CH_3)–COOEt→PhthN–CH*(CH_3)–COOEt

Reaction (4): Michael addition: 2-methoxycarbonyl-1-indanone+butenone

Reaction (5): Michael addition: 2-ethoxycarbonylcyclohexanone+butenone

Reaction (6): $Ph_2C{=}N{-}CH_2{-}Ph \rightarrow Ph_2C{=}N{-}CH^*(R){-}Ph \rightarrow H_2N{-}CH^*(R){-}Ph$

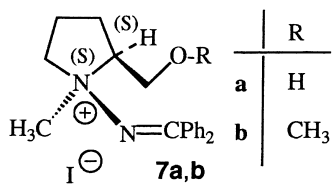
The highest previous e.e.s mostly rest on polarimetry or NMR shift reagent studies whereas most of our results were obtained by GC or HPLC on chiral columns. Reaction (1) was scrutinized by O'Donnell and gave up to 81% e.e. for the *t*-Bu ester with N,O-dibenzylcinchonidinium bromide.[7] Use of a chiral crown ether catalyst led to only 24% e.e.[8] Under the present conditions (powdered NaOH, CH_2Cl_2, 10 mol% catalyst, r.t., 24 h) the ethyl ester derivative exhibited 59% e.e. with N-benzylcinchonidinium chloride (BCDC), and 23 or 19% with **2d** and **3e**, respectively. Even lower enantiomeric excesses were found with the other catalysts.

Interestingly, the isomer formed in excess was always (S) irrespective of the stereochemistry at nitrogen. The two best catalysts contain two structural elements of the cinchona alkaloids, a flat quinoline ring region and a hydroxyl group positioned opposite to it. Such an arrangement is believed to form part of a binding pocket for substrates in cinchona catalysts.

Reaction (2) has been executed by many PTC workers.[4] Colonna reported an e.e. of 32% using N-benzylquininium chloride (QUIBEC) in benzene.[9] We found 28% in benzene and 27% in dichloromethane with the same catalyst and 23% with BCDC in toluene/CH_2Cl_2 (always with a preference for the (R) alcohol). Testing our new catalysts only **3e** reached 15% e.e., the others were even less suitable. Here the (S) alcohol was preferred. It should be noted that we reported a 39.5% e.e. of the

(S) isomer in 1994 using catalyst **6** as an inseparable diastereomeric mixture at the quaternary nitrogen.[5] Using the stereochemical information obtained in the present study we now know that the catalyst sample was 90% (S), (as drawn in **6**) and 10% (R) at the quaternary N.

Reactions (3–5) gave only negligible enantiomeric excesses with our new catalysts. Maximum e.e. values in the literature are 19.5 [reaction (3)],[10] 27 [reaction (4)][11,12] and 22 [reaction (5)].[13] We found that PT catalysts accelerate the Michael additions only moderately under most sets of reaction conditions. Thus, a simple deprotonation/addition without the help of a catalyst competes with the chiral PTC process, and (low) enantioselectivity can be achieved only in a small 'reaction window'. All in all, our results reinforce previous generalizations: enantioselective PTC is very sensitive to detailed reaction conditions and the structure of substrates. A relatively 'good' catalyst in one reaction may be worthless in another conversion.



In view of these results we turned to a reconsideration of Eddine and Cherqaoui's work.[2] Reaction (6) was described as proceeding with 91% e.e. (R=benzyl or ethyl) using a catalyst with an unspecified configuration at N (possibly **7a**) with a mixture of powdered KOH and K_2CO_3 as base in dichloromethane. Similarly, three other alkylations with allyl, butyl, and isopropyl halides were stated as proceeding with 90% or more e.e. The authors reported that no conversion occurred with normal quaternary ammonium salts. We chose the methylation as a test reaction because both enantiomers of phenethylamine are commercially available for comparison purposes. This particular reaction was not performed by Eddine and Cherqaoui. In addition, the ethylation was scrutinized.

The previous researchers did not characterize their catalyst salt by C,H,N analysis, spectral data, or even m.p. Although quaternary methyl iodides of some hydrazones are known, they are relatively unstable. In the synthesis of optical active ketones *via* the Corey–Enders SAMP hydrazones, one of the methods for regenerating the ketone is actually quaternization and subsequent hydrolysis with water, aq. $NaHCO_3$, or 1.4 N HCl.[14–16]

The cited paper does not contain a full experimental section, and thus we cannot know exactly which procedures were used by the authors. In the beginning we had difficulties in quaternizing the benzophenone-N-aminoprolinol hydrazone. The procedure of Smith and Tan[17] apparently used by Eddine and Cherqaoui (boiling with MeI in ethanol) did not work in our hands. Compound **7a** was obtained, however, after refluxing the respective hydrazone for 3 days in excess methyl iodide (52% yield). We were not successful in making **7b** from benzophenone-SAMP hydrazone in a similar way. Characterization (sharp m.p., C,H,N analysis, NMR spectra) showed that **7a** was a single epimer. To confirm the place of methylation beyond any doubt, benzophenone N,N-dimethylhydrazone was reacted with MeI.[17] The obtained salt showed the expected 9 proton singlet in its NMR spectrum. As for the configuration at N in **7a**, we expected (1R) in analogy to compound **3c**. However, X-ray structure determination (Fig. 2) showed it to be (1S).

The alkylated imines obtained in reaction (6) are sensitive and difficult to handle. They were hydrolyzed to the amines therefore before determination of the stereochemical outcome both by the previous authors and by us. Our observations are at variance with the ones of the previous workers in several respects:

(i) Whereas the authors do not mention difficulties we found hydrolysis to be slow. We saw incomplete

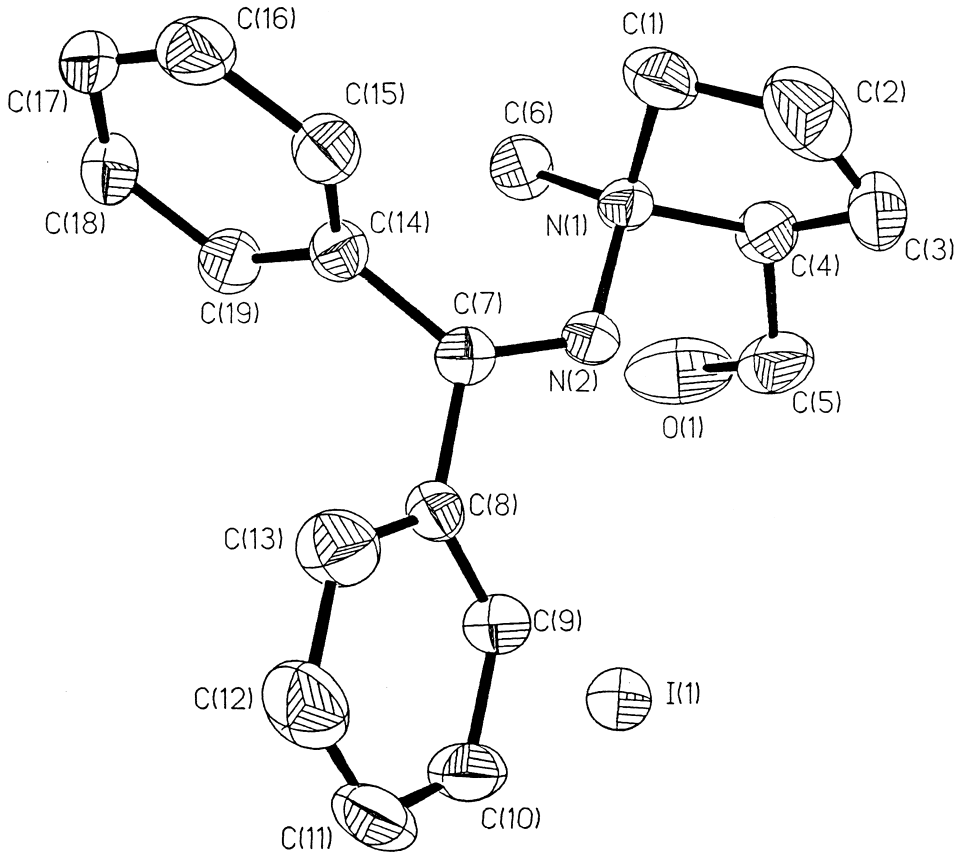


Fig. 2. ORTEP drawing of the molecular structure of **7a** in the crystal

hydrolysis after 2 days of stirring at room temperature with 10% aqueous HCl/*t*-BuOMe and still not a totally complete reaction after 15 h at 70°C. Our liberated amines were then subjected to g.c. on a chiral column. A separation of enantiomers was possible for the compounds with R=Me and Et.

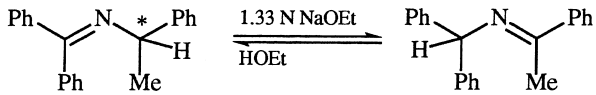
(ii) Contrary to the published statement we find that the chemical reaction as such proceeds with many achiral and chiral PT catalysts including cetyltrimethylammonium bromide, BCDC, and our new catalysts.

(iii) All catalysts gave only racemic product in methylation (Me_2SO_4) and ethylation (Et–Br). Specifically, no enantiomeric excesses were observed with **7a** as catalyst within analytical error (1–2%), and the same was true for all other tested catalysts (BCDC, BCNC, QUIBEC, **2c**, **2d**, **3a**, **3c**–**e**, **4** and **5**).

Conceivably, the discrepancies between our findings of racemic product and Eddine's high e.e.s might have been due to a racemization somewhere in the process. It is known from the literature, however, that HCl hydrolysis of optically active diphenylmethylene 1-phenethylamine does not result in racemization.[18] To test for it under the present conditions, we prepared the imine from an authentic (R) compound and hydrolyzed it again. No racemization occurred.

A second possibility consists of a racemization of the imine concurrent with its formation. This then would make a high enantiomeric excess impossible *a priori*. Scrutinizing the literature revealed a classical study on reaction mechanisms by Ingold and coworkers.[18,19] In it, rates of parallel equilibration

and racemization were measured for a number of systems, including the one of present concern at temperatures between 21 and 85°C.



Applying the alkaline conditions of the present study (powdered KOH/K_2CO_3, CH_2Cl_2, r.t., 24 h) to authentic optically active diphenylmethylene 1-phenethylamine we observed a decline in specific rotation of 45–65%. Partial racemization occured both in the absence and presence of the PT catalyst. As the alkylation reaction is comparatively slow and needs long reaction times, the generation of substantial enantiomeric excesses by the present method is impossible. This should apply not only to methylation and ethylation but similarly to all alkylations.

The earlier authors determined their reported enantioselectivities by polarimetry and reference to the highest known rotations. Considering that the used catalyst was not well characterized, we must assume that complex mixtures were submitted to polarimetry (although a chromatographic purification is mentioned in the text). Possibly compounds were involved which were impurities of the catalyst or were formed by its decomposition. A β-hydroxyhydrazonium ion can be fragmented with base to give an epoxyalkylhydrazine, for instance. Errors of this and other kinds were corrected by us before:[20–22] if the impurities have high specific rotations and if the researcher relies on polarimetry alone, an optically active reaction product may be simulated.

3. Experimental

Enantiomeric mixtures were analyzed either by GC (1 m 'Methyl-Sil' retention gap pre-column and 50 m×0.25 mm 'FS-Hydrodex-β-PM' column of Macherey & Nagel, Düren, Germany) or HPLC ('Chirasep DNBPG' 250×4 mm, 5 μm particle size of Merck, Darmstadt).

*3.1. (1R,2S)-2-Hydroxymethyl-N-methyl-N-(2-naphthylmethyl)pyrrolidinium bromide **2c***

By stirring (S)-N-methylprolinol with 2-bromomethylnaphthalene in MeCN at r.t. for 1 day, evaporation of the solvent and repeated fractional crystallization from acetonitrile gave the title compound. Yield of pure isomer: 19%; m.p. 135°C; $[\alpha]_D^{26}$=+12.7 (c=1.0, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.16–2.35 (m, 4H), 3.17 (s, 3H), 3.31–3.43 (m, 1H), 4.00–4.20 (m, 3H), 4.43–4.62 (m, 1H), 4.62 (d, J=13.0 Hz, 1H), 5.24 (d, J=13.0 Hz, 1H), 7.46–7.87 (m, 6H), 8.04 (s, 1H). Anal. calcd for $C_{17}H_{22}NOBr$ (336.27): C, 60.72; H, 6.59; N, 4.17; found: C, 59.90; H, 6.70; N 4.01.

*3.2. (1S,2S)-2-Hydroxymethyl-N-methyl-N-(2-naphthylmethyl)pyrrolidinium iodide **3c***

The compound was obtained from (S)-N-(2-naphthylmethyl)prolinol (prepared by reaction of prolinol with the bromide and $NaHCO_3$ in ethanol) with excess MeI by heating in acetonitrile for 24 h. 85% Yield; m.p. 125°C, $[\alpha]_D^{26}$=−8.9 (c=1, EtOH). ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.16–2.35 (m, 4H), 3.17 (s, 3H), 3.31–3.43 (m, 1H), 4.00–4.20 (m, 3H), 4.43–4.62 (m, 1H), 5.17 (d, J=12.9 Hz, 1H), 5.31 (d, J=12.9 Hz, 1H), 7.46–7.90 (m, 6H), 8.18 (s, 1H). ^{13}C NMR (62 MHz, CD_3OD): δ=20.4 (C-4), 24.8 (C-3), 43.8 (CH_3), 60.3 (CH_2OH), 65.25 (C-5), 69.1 (CH_2–Ar), 75.65 (C-2), 127.1, 128.0, 128.7, 128.8, 129.4, 129.5, 130.15, 134.4, 134.5, 135.25 (arom.). Anal. calcd for $C_{17}H_{22}NOI$ (383.24): C, 53.27; H, 5.79; N, 3.65; found: C, 53.26; H, 5.75; N, 3.63. The chloride was made by passing the iodide in methanol over an ion exchange column (chloride form).

3.3. (1R,2S)-2-Hydroxymethyl-N-methyl-N-(2-quinolinylmethyl)pyrrolidinium bromide **2d**

2-Bromomethylquinoline hydrobromide (m.p. 190°C (dec.)) was prepared from quinaldine by NBS bromination, extraction by dilute aq. HBr and crystallization from 2-propanol. The free base was very sensitive towards tarring. It was liberated by dilute NaOH and extracted with CH_2Cl_2 directly before reacting with N-methylprolinol (2 h boiling in MeCN). The tarry oil was crystallized from 2-propanol/*t*-BuOMe to give a 52% yield, m.p. 142°C. $[\alpha]_D^{26}=-14.7$ (c=0.9, MeCN). ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.24–2.27 (m, 2H), 2.45–2.47 (m, 2H), 3.48 (s, 3H), 3.51–3.54 (m, 1H), 4.27–4.30 (m, 2H), 4.42–4.66 (m, 2H), 4.69 (d, J=13.3 Hz, 1H), 5.47 (d, J=13.3 Hz, 1H), 7.62 (dd, J=7.3, 7.8 Hz, 1H), 7.77 (dd, J=7.2, 8.0 Hz, 1H), 7.86 (d, J=8.2 Hz, 1H), 8.04 (d, J=8.6 Hz, 1H), 8.06 (d, J=8.4 Hz, 1H), 8.27 (d, J=8.3 Hz, 1H). Anal. calcd for $C_{16}H_{21}N_2OBr$ (337.26): C, 56.98; H, 6.24; N, 8.31; found: C, 56.98; H, 6.54; N, 8.16.

3.4. (1S,2S)-2-Hydroxymethyl-N-methyl-N-(2-quinolinylmethyl)pyrrolidinium iodide **3d**

Prepared similarly from (S)-N-(quinolinylmethyl)proline, 81% yield, m.p. 135°C. $[\alpha]_D^{25}=-16.2$ (c=1.0, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ=2.01–2.04 (m, 1H), 2.15–2.17 (m, 1H), 2.22–2.26 (m, 1H), 2.37–2.38 (m, 1H), 3.37 (s, 3H), 3.73–3.77 (m, 1H), 4.17–4.19 (m, 1H), 4.23–4.29 (m, 2H), 4.52–4.57 (m, 1H), 5.16 (d, J=13.3 Hz, 1H), 5.47 (d, J=13.3 Hz), 7.61–7.64 (m, 1H), 7.75–7.79 (m, 1H), 7.87 (d, J=8.1Hz, 1H), 7.98 (d, J=8.4 Hz, 1H), 8.05 (d, J=8.4 Hz, 1H), 8.28 (d, J=8.3 Hz, 1H). ^{13}C-NMR (62 MHz, D_3COD): δ=19.45 (C-4), 23.3 (C-3), 43.1 (CH_3), 58.8 (CH_2OH), 65.0 (C-5), 68.4 (CH_2–Ar), 75.7 (C-2), 123.5 (arom. C-3), 127.60 (arom. C-5,6), 127.63 (arom. C-5,6), 127.8 (arom. C-4a), 128.9 (arom. C-7), 130.2 (arom. C-8), 137.7 (arom. C-4), 147.5 (arom. C-8a), 150.0 (arom. C-2). Anal. calcd for $C_{16}H_{21}IN_2O$ (384.26): C, 50.01; H, 5.51; N, 7.29; found: C, 49.76; H, 5.39; N, 7.20.

3.5. (1S,2S)-N-Benzyl-2-hydroxymethyl-N-methylpyrrolidinium iodide **3a**

Prepared from benzylprolinol with methyl iodide as before. 85% Yield; m.p. 112°C. $[\alpha]_D^{26}=-84.1$ (c=1, EtOH). ^{1}H NMR (250 MHz, $CDCl_3$): δ=1.26–2.36 (m, 4H), 3.03 (s, 3H), 3.23–3.29 (m, 1H), 3.96–4.15 (m, 3H), 4.28–4.40 (m, 1H), 4.91 (d, J=12.9 Hz, 1H), 5.03 (d, J=12.9 Hz, 1H), 7.43–7.65 (m, 5H). Anal. calcd for $C_{13}H_{20}INO$ (333.21): C, 46.85; H, 6.05; N, 4.20; found: C, 46.89; H, 5.98; N, 4.59.

3.6. (1S,2S)-2-Hydroxymethyl-N-methyl-N-(4-quinolinylmethyl)pyrrolidinium bromide **3e**

Prepared similarly from (S)-N-methylprolinol and the extremely sensitive 4-bromomethylquinoline. Yield: 38%, m.p. 141°C. $[\alpha]_D^{26}=-22.9$ (c=0.8, MeCN). ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.74–1.78 (m, 1H), 1.97–1.99 (m, 1H), 2.25–2.27 (m, 1H), 2.43–2.44 (m, 1H), 3.96 (s, 3H), 3.30–3.39 (m, 1H), 3.99–4.04 (m, 1H), 4.16–4.23 (m, 2H, CH_2OH), 4.69–4.72 (m, 1H), 5.47 (d, J=13.5 Hz, 1H), 5.85 (d, J=13.5 Hz, 1H), 7.76 (dd, J=7.6, 7.7 Hz, 1H), 7.81 (dd, J=7.2, 8.2 Hz, 1H), 7.91 (d, J=4.4 Hz, 1H), 8.17 (d, J=8.4 Hz, 1H), 8.43 (d, J=8.3 Hz, 1H), 8.98 (d, J=4.4 Hz, 1H). ^{13}C NMR (CD_3OD): δ=20.7 (C-4), 24.5 (C-3), 43.4 (CH_3), 60.7 (CH_2OH), 63.4 (C-5), 68.4 (CH_2–Ar), 76.4 (C-2), 125.0 (arom. C-3), 128.1 (arom. C-6), 129.4 (arom. C-4a), 129.7 (arom. C-5), 130.8 (arom. C-7), 131.6 (arom. C-8), 136.2 (arom. C-4), 149.7 (arom. C-8a), 151.1 (arom. C-2). Anal. calcd for $C_{16}H_{21}BrN_2O$ (337.26): C, 56.98; H, 6.28; N, 8.31; found: C, 56.31; H, 6.33; N, 8.86.

3.7. (1S,2S)-N-Benzyl-N-methyl-2-(1-naphthyloxymethyl)pyrrolidinium chloride **4**

(S)-N-Benzylprolinol was dissolved together with molar amounts of 1-naphthol and PPh_3 in THF and treated at 0°C with a small excess of diethyl azodicarboxylate under nitrogen. $POPh_3$ was filtered off, and the product was chromatographed over silica gel with petroleum ether (b.p. 45–60°C):ethyl acetate (4:1). The eluate was heated with excess MeI in MeCN for 24 h at 50°C, then passed in methanol over an anion exchange column (chloride form). The resultant product of a honey-like consistance could not be crystallized. ^{1}H NMR (250 MHz, $CDCl_3$): δ=2.21–2.65 (m, 4H), 3.16 (s, 3H), 3.42–3.60 (m, 1H), 3.72–3.96 (m, 1H), 4.12–4.31 (m, 1H), 4.70–4.85 (m, 2H), 5.20 (d, J=12.8 Hz, 1H), 5.37 (d, J=12.8 Hz, 1H), 7.40–7.99 (m, 12H). IR: μ=3058, 2973, 2937, 1461, 1240, 767 cm^{-1}.

3.8. (1S,2S)-N-Benzyl-2-N-methyl-2-(2-quinolyloxymethyl)pyrrolidinium chloride **5**

(S)-N-Benzylprolinol was dissolved in THF and reacted with NaH. A molar amount of 2-bromomethylquinoline dissolved in THF was dropped into the refluxing solution which was heated for 6 h. Workup gave a dark-brown oil which was purified by a fast passage through a silica gel column (ethyl acetate as eluent). The product was treated with excess MeI in MeCN at 40°C for 24 h. Passage through an anion exchange column in methanol furnished the chloride as an oil which could not be crystallized. ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.91–2.01 (m, 1H), 2.02–2.13 (m, 1H), 2.22–2.33 (m, 1H), 2.39–2.52 (m, 1H), 3.18 (s, 3H), 3.49–3.54 (m, 1H), 4.10 (s, 2H), 4.26–4.30 (m, 1H), 4.70–4.73 (m, 1H), 4.80–5.00 (m, 2H), 5.15 (d, J=12.8 Hz, 1H), 5.23 (d, J=12.8 Hz, 1H), 7.40–7.59 (m, 5H), 7.67–8.24 (m, 6H). IR: μ=3029, 3004, 2966, 2890, 1616, 1504, 1471, 1367, 1126, 829, 707 cm^{-1}.

3.9. (S)-1-(Diphenylmethyleneamino)-2-hydroxymethylpyrrolidine

Refluxing molar equivalents of (S)-1-amino-2-hydroxymethylpyrrolidine [b.p. 90°C/40 mbar (Kugelrohr), $[\alpha]_D^{26}=-51.1$ (c=1.0, C_6H_6)] and benzophenone in toluene with a few drops of BF_3 ether for 12 h under azeotropic removal of water gave the title compound. Normal workup was followed by chromatography (silica gel, petroleum ether (b.p. 50–70°):ether 1:3) to give an oil; 61% yield. $[\alpha]_D^{25}=+434.5$ (c=1.0, MeCN). High resolution MS for $C_{18}H_{20}N_2O$ calcd: 280.15755; found 280.15756. EI, 70 eV: (m/z (%)): 280 (8), 249 (62), 180 (100), 165 (13), 77 (59). ^{1}H NMR ($CDCl_3$): δ 1.62–1.88 (m, 4H), 2.41–2.48 (m, 1H), 2.68–2.78 (m, 1H), 3.43–3.88 (m, 3H), 7.24–7.81 (m, 10H). ^{13}C NMR: δ 23.2 (C-4), 25.3 (C-3), 26.9 (C-5), 54.5 (C-2), 66.5 (CH_2OH), 67.0, 127.4, 128.0, 128.1, 128.19, 128.22, 129.6, 130.1, 137.7, 140.0, 148.7.

3.10. (1R,2S)-1-(Diphenylmethyleneamino)-2-hydroxymethyl-1-methylpyrrolidinium iodide, **7a**

The respective hydrazone was refluxed for 3 days in excess methyl iodide. After removal of the reagent, the residue was crystallized from acetonitrile. M.p. 161°C; 52% yield. $[\alpha]_D^{25}=+33.7$ (c=1.0, MeCN). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.00–2.09 (m, 1H), 2.10–2.21 (m, 1H), 2.28–2.38 (m, 1H), 2.39–2.49 (m, 1H), 3.58 (s, 3H), 3.97–4.03 (m, 1H), 4.03–4.08 (m, 1H), 4.18–4.20 (m, 1H), 4.37–4.39 (m, 1H), 4.76–4.78 (m, 1H), 7.37–7.63 (m, 10H). ^{13}C NMR: δ 21.5 (C-4), 25.9 (C-3), 54.8 (CH_3), 60.9 (CH_2OH), 70.6 (C-5), 86.2 (C-2), 129.2, 129.5, 129.8, 129.9, 130.4, 130.5, 132.0, 134.1, 134.4, 138.2, 175.2. Anal. calcd for $C_{19}H_{23}IN_2O$ (422.3): C, 54.03; H, 5.49; N, 6.63; found: C, 54.00; H, 5.62; N, 6.55.

Reaction (1): 267 mg (1 mmol) of ethyl N-(diphenylmethylene)glycinate, 171 mg (1 mmol) of benzyl bromide and 0.1 mmol of catalyst were dissolved in 10 ml of CH_2Cl_2 and treated with 200 mg (5 mmol)

of powdered NaOH. The mixture was stirred at r.t. for 24 h. It was filtered and concentrated. The residue was taken up in petroleum ether:*t*-BuOMe (5:1) and filtered again. The solution was analyzed by HPLC for enantiomeric excess (hexane:2-propanol=500:1).

Reaction (2): 1.62 mg (1 mmol) of pivalophenone and 23 mg (0.6 mmol) of $NaBH_4$ were stirred with 0.1 mmol of catalyst in a mixture of 3 ml of CH_2Cl_2 and 0.5 ml of H_2O at 0°C for 3 h. Phases were separated and the aqueous layer was extracted with more CH_2Cl_2. The combined organic phases were dried (Na_2SO_4). The solvent was removed and the mixture was analyzed by HPLC on the chiral column (hexane:2-propanol=200:1).

Reaction (3): 0.5 g (2.7 mmol) of potassium phthalimide was refluxed with 2.0 g (11.04 mmol) of ethyl 2-bromopropionate in 20 ml of CH_2Cl_2 in the presence of 5 mol% catalyst for 48 h to give 95% conversion. Solvent and excess reagent were removed *in vacuo*, and the residue is purified by passage over silica gel in CH_2Cl_2, m.p. 61°C. Enantioselectivity assays were performed by polarimetry[14] showing only 2–5% e.e. When the reaction was performed in boiling THF with only a twofold excess of bromoester and BCDC as a catalyst, a maximum e.e. of 18% at 55% conversion was found.

Reaction (4): 258 mg (1.36 mmol) of 2-methoxycarbonyl-1-indanone and 100 mg (1.36 mmol) of butenone were stirred in toluene in the presence of 5% aqueous $NaHCO_3$ and 5 mol% of catalyst at r.t. or at −40°C for 24 h. Phases were separated, the aqueous layer was extracted with CH_2Cl_2. Solvents were removed, and the residue was chromatographed (silica gel, *tert*-butyl methyl ether), m.p. 104°C, yield 90–95%. Enantiomeric composition was assayed by polarimetry[15] to give a maximum e.e. of 8% with catalyst BCDC. Shorter reaction times required stronger bases, but again no useful e.e.s were observed.

Reaction (5): 200 mg (1.18 mmol) of 2-ethoxycarbonyl-1-cyclohexanone and 87 mg (1.18 mmol) of butenone were stirred in 5 ml of toluene in the presence of 165 mg (1.19 mmol) of solid K_2CO_3 and 5 mol% catalyst for 24 h at r.t. After the usual work-up, the residue was passed over silica gel in *tert*-butyl methyl ether, then distilled, b.p. 50°C/0.2 mbar. Analysis was performed by polarimetry[17] and gave a maximum e.e. of 18% with QUIBEC.

Reaction (6): 271 mg (1 mmol) of N-(diphenylmethylene)benzylamine and 127 mg (1 mmol) of dimethyl sulfate [or 109 mg (1 mmol) of ethyl bromide] were dissolved in 3 ml of dichloromethane and stirred with a mixture of 0.5 g of powdered KOH and K_2CO_3 and 10 mol% of catalyst at r.t. for 24 h. 10 ml of H_2O and 20 ml of petroleum ether were added, and the phases were separated. The aqueous phase was washed twice with 10 ml of petroleum ether. Then the combined organic phases were concentrated, and the residue was stirred with 10 ml of *t*-BuOMe and 10% aqueous HCl for 16 h at 70°C. After cooling, the organic layer was washed twice with dilute HCl. The combined aqueous phases were made alkaline by the addition of conc. NaOH and extracted three times with 10 ml of *t*-BuOMe. This extract was dried and concentrated. It contained 1-phenethylamine [or 1-phenylpropylamine] and a little unhydrolyzed alkylation product. Enantioselectivity assays were performed by g.c. on the chiral column mentioned above (111°C, 1 bar of N_2 pressure) and indicated no e.e.s in both cases.

Racemization tests: (a) 285 mg (1 mmol) of diphenylmethylene (R)-phenethylimine[19] was stirred with a mixture of 10 ml 10% aq. HCl and 10 ml of *t*-BuOMe for 2 days at r.t. or for 24 h at 70°C. Workup as described for reaction (6) furnished the amine which was subjected to g.c. on the chiral column (111°C, 1 bar pressure of N_2). Only the (R) enantiomer was present in both cases.

(b) A quantity (285 mg,1 mmol) of diphenylmethylene (R)-phenethylimine {$[\alpha]_D^{25}$=+11 (c=0.18, MeCN)} was stirred with 1.38 g of solid K_2CO_3 and 0.56 g of powdered KOH in 3 ml of CH_2Cl_2 for 24 h at r.t. In a parallel run 7 mg (0.02 mmol) of cetyltrimethylammonium bromide were present. Workup and reisolation furnished products with $[\alpha]_D^{24}$=+6 (c=0.16, MeCN) and $[\alpha]_D^{24}$=+4 (c=0.12, MeCN) respectively.

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