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Asymmetric Synthesis of *trans*-2,5-Diphenylpyrrolidine: A C_2-Symmetric Chiral Amine

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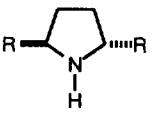
Abstract: (*R,R*)-2,5-Diphenylpyrrolidine of high enantiomeric purity (>98% e.e.) may be prepared from 1,4-diphenyl-1,4-butanedione in 4 steps and 64% overall yield. A key step is asymmetric reduction of the dione with Ipc_2BCl.

C_2-Symmetric chiral amines are useful reagents for asymmetric synthesis.[1] Notable examples of such amines include *trans*-2,5-dimethylpyrrolidine (**1**),[2-4] *trans*-2,5-bis(methoxymethyl)-pyrrolidine (**2**),[5,6] α,α'-dimethyldibenzylamine (**3**),[7] binaphthylamine **4**,[8] piperidine **5**,[9] and aziridine **6**.[10] Other amines that have been prepared are *trans*-1,3-dibenzylisoindoline (**7**)[11] and "tricyclamine" (**8**).[12]



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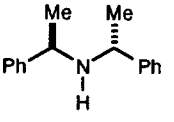
2: R = CH_2OCH_3



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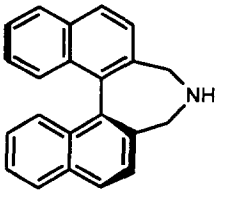

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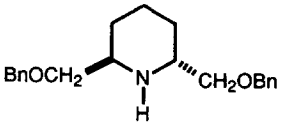

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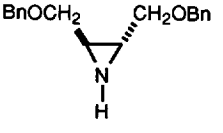

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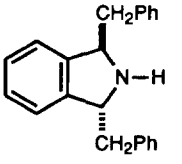

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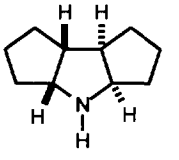

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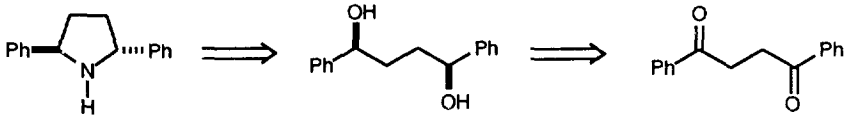
Of these amines, the most popular have been the pyrrolidines **1** and **2**. The C_2-symmetric pyrrolidine **1**, initially introduced by Whitesell in 1977,[2a] has been used in a variety of transformations including alkylations of vinylogous urethanes,[4a-c] radical cyclizations[4d,e] and (intermolecular) additions,[4f-j] Michael additions,[4k] enantioselective deprotonations,[4l] Claisen rearrangements,[4m] cycloaddition reactions,[4n,o] and additions to arene-manganese complexes.[4p] Pyrrolidine **2** (or the corresponding OMOM derivative), introduced by Katsuki in 1984,[5a] has been used as a chiral auxiliary in many asymmetric processes including various amide alkylations and acylations,[5a-f] radical additions,[5g] and Diels-Alder reactions.[6a] While excellent diastereoselectivities have been achieved with these pyrrolidines, they have some disadvantages. For example,

1 has a low boiling point (106 °C) which can make recovery of the auxiliary difficult. Pyrrolidine **2** has not been routinely accessible until recently because of the long original synthesis (11 steps)[5a] involving a resolution of a carboxylic acid with a chiral amine that is not readily available. A number of improved syntheses of **2** that require fewer steps have been introduced,[6a-e] and it is now commercially available but quite expensive.[6f]

We felt that the structurally-similar amine **9** bearing phenyl groups at the 2 and 5 positions might be a useful new addition to this class of C_2-symmetric pyrrolidine ligands. 2,5-Diphenylpyrrolidine has been prepared previously as a mixture of *cis* and *trans* isomers[13a] but there have been no reports of preparations of pure enantiomers by resolution of the *trans* isomer or by asymmetric synthesis. We targeted **9** for several reasons. First, with larger phenyl groups in place of methyl groups, one might expect better facial discrimination in some cases when **9** is used as a chiral auxiliary. Second, volatility would no longer be a problem for recovering the auxiliary. Finally, and perhaps most importantly, we thought that **9** could be easily prepared in a few steps from readily available dione **11** via asymmetric reduction followed by simple functional group manipulations (Scheme 1).

Scheme 1



9 **10** **11**

Since dione **11** may be thought of as two alkyl aryl ketones linked together, chiral reducing agents capable of reducing alkyl aryl ketones such as acetophenone with high selectivities should also work well to give the desired diol **10**. In fact, with two functional groups to reduce, one might expect multiplicative selectivities since most of the minor isomer formed in the initial reduction becomes a diastereomer. For example, if the selectivity in the reduction of each carbonyl group is 100:1 in favour of the *R* isomer, and if the facial selectivity remains the same for the second reduction, the diols would be formed in a ratio of approximately 10,000:200:1 (*RR:RS:SS*) and the ee of the desired diastereomer would be 99.98%. Given that many of the chiral reducing agents that have been developed work best with alkyl aryl ketones,[14] we were confident of finding a suitable reagent.

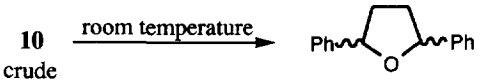
We now report that amine **9** is indeed easily prepared in high enantiomeric purity from dione **11**.

RESULTS AND DISCUSSIONS

Dione **11** was easily prepared in large quantities by Friedel-Crafts acylation of benzene with fumaryl chloride followed by reduction ($SnCl_2$/HCl) of the double bond.[13] While there have been many reducing agents developed which provide high enantioselectivities with alkyl aryl ketones,[14] we chose to examine those which might be readily amenable for large-scale synthesis. The borane-based reagents developed by Itsuno[15] and Corey[16] were especially attractive since the chiral auxiliary could be employed in catalytic amounts.

However, reduction of dione **11** using these reagents gave mixtures of diastereomeric diols in only modest ratios ranging from 3:1 to 14:1, dl:meso.[17]

Fortunately, (–)-diisopinocampheylchloroborane Ipc_2BCl[18] [derived from (+)-pinene and now marketed by Aldrich as DIP-Chloride™[19]] reacted with dione **11** to give diol **10** with only small (≤2%) amounts of the meso isomer. The meso isomer could be removed by recrystallization from CH_2Cl_2-hexanes. The diol appears to isomerize slowly (over a period of several days) in this solvent so that the fraction of meso isomer increased if the mixture was allowed to stand too long. The diol, once isolated as a crystalline solid, is quite stable with no isomerization observed for samples that have been stored at RT for several years. Samples of diol which were not crystallized were not stable and formed a mixture of *cis*- and *trans*-2,5-diphenyltetrahydrofuran (**12**) (presumably via a benzylic carbocation intermediate) on standing at room temperature.



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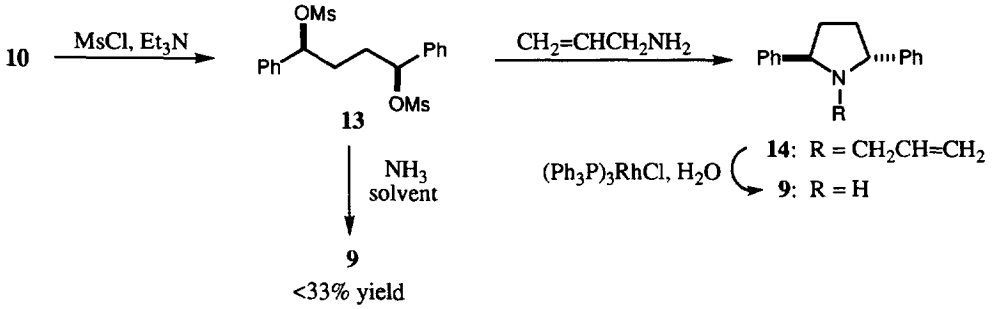
We expected to be able to easily establish that the diol produced was of high enantiomeric purity (given the high diastereoselectivity observed), but analysis of the enantiomeric purity of diol **10** proved to be more challenging than anticipated. The bis-3,5-dinitrophenylcarbamates were not separable by HPLC on a Pirkle covalent D-Naphthylalanine column,[20,21] and the bis-MTPA esters[22] were also not separable by HPLC. Analysis of the bis-MTPA esters by ^1H NMR spectroscopy was also not useful due to poor signal separation. Eventually, it was found that ^{19}F NMR analysis of the bis-MTPA esters works very well; in the $^{19}F\{^1H\}$ spectrum, there are 4 baseline-resolved singlets: one for the (*SS*) isomer, two for the (*RS*) (meso) isomer, and one for the (*RR*) isomer. In addition, there are ^{13}C satellites associated with the major (*SS*) isomer that are clearly visible; these satellites are very useful for quantitation of minor signals since it is known that the natural abundance of ^{13}C is 1.108%.[23] The major isomer was tentatively assigned as (*SS*) based on the established propensity of (–)-Ipc_2BCl to give *S* alcohols from *n*-alkyl aryl ketones.[18] Since the signal for the (*RR*) isomer was smaller than the ^{13}C satellites of the (*SS*) isomer, we concluded that there was no more than 0.5% of the minor (*RR*) isomer present.[24]

A search of the literature revealed that the dimesylate of (racemic) diol **10**[25] had been previously prepared by J.M. Brown.[26] Attempts to prepare the dimesylate of *S,S*-diol **10** under the conditions (MsCl, Et_3N, Et_2O, -20 °C) described by Brown gave only poor (<10%) yields of the desired product. With a small amount of dimesylate **13** in hand, it was possible to determine that it is only sparingly soluble in ether. Since the dimesylate is much more soluble in CH_2Cl_2, diol **10** was treated under standard mesylation conditions and the reaction was worked-up using EtOAc as solvent. The mesylate was isolated as a white crystalline solid in excellent (80→90%) yield. However, this material was quite capricious and sometimes spontaneously decomposed exothermically to give a thick orange or black oil during final removal of solvent on a vacuum line or on standing. To overcome this extremely annoying propensity of the mesylate towards decomposition, a protocol was developed to minimize complete removal of solvent from the crystals. Thus, precipitation of the mesylate from EtOAc using hexanes followed by decantation of the supernatant and washing with hexanes gave samples of dimesylate (containing some hexanes) suitable for use in the next step.

In principle, the most direct route to the desired pyrrolidine would be to treat dimesylate **13** with NH_3 (Scheme 2). Addition of dimesylate **13** to liquid ammonia at –78 °C and allowing the colourless solution to slowly warm to RT returned only crystalline dimesylate. Addition of a solvent to keep NH_3 (bp –33 °C) from evaporating prior to reaction seemed to be necessary. A variety of solvents [dimethylethyleneurea (DMEU), DMF, DMSO, THF, 2-butanol] were tried and cyclization was observed in most cases, but the pyrrolidine was often contaminated with diphenyltetrahydrofuran **12**. Pyrrolidine **9** could be purified by recrystallization of its hydrochloride salt, but the best yield of **9** obtained by this route was 33%.

Scheme 2



At this stage, the absolute configuration of the diphenylpyrrolidine was verified by X-ray diffraction on the hydrochloride salt. It was expected that reduction of dione **11** with (–)-Ipc_2BCl would produce the *SS*-diol which, after cyclization, would give the (*R*,*R*)-pyrrolidine. This was found to be the case (Figure 1).

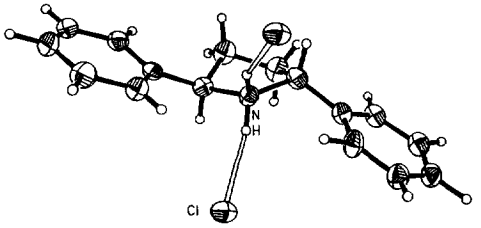


Figure 1. X-ray crystal structure of **9•HCl**

The relatively low yield of the desired amine obtained by direct cyclization prompted us to examine other routes involving cyclization/deprotection. Benzylamine has been used previously to form *N*-benzylpyrrolidines and piperidines which could be subsequently hydrogenolyzed to the parent secondary amine.[3c,9a] In our case, hydrogenolysis was expected to be problematic since the amine would be tribenzylic. We chose to use allylamine since the allyl group should be easily removed via Rh-catalyzed isomerization/hydrolysis[27] or other methods.[28] Addition of allylamine to crude dimesylate **13** gave a reasonable yield of *N*-allylpyrrolidine **14** (71% from diol **10**). Deprotection under the Ganem conditions (cat. $(Ph_3P)_3RhCl$, CH_3CN-H_2O, N_2 stream)[27b] followed by flash chromatography gave the desired pyrrolidine **9** in 98% yield (Scheme 2). Analysis of the product by chiral stationary phase HPLC (Chiracel OD) showed that it was of >98% ee.[29]

In summary, we have developed a short (4 steps from dione **11**, 64% overall yield), stereoselective (>98% ee) synthesis of *trans*-2,5-diphenylpyrrolidine (**9**). The (*R,R*) isomer is produced using (–)-Ipc_2BCl (DIP-Cl™) in the initial reduction of dione **11**; use of (+)-Ipc_2BCl, which is also commercially available, should provide (*S,S*)-**9**. Now that pyrrolidine **9** is readily accessible, it may find a multitude of uses in asymmetric synthesis as have its congeners **1** and **2**.[30]

EXPERIMENTAL

General

All reactions involving air or moisture sensitive reagents were performed under argon using oven-dried glassware. THF and ether were distilled from Na/benzophenone; hexanes, CH_2Cl_2, DMF, and Et_3N were distilled from CaH_2. Melting points were determined in an open capillary using a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained using a Perkin-Elmer 983 spectrophotometer as neat liquids (NaCl plates) or as KBr pellets. NMR spectra were recorded using Bruker AM-250 or AC-200 spectrometers as $CDCl_3$ solutions with Me_4Si (^1H δ 0.0) or $CDCl_3$ (^{13}C δ 77.0) as internal standards unless otherwise noted. For ^{19}F NMR spectra, CF_3COOH was used as an external standard (76.53 ppm upfield from $CFCl_3$) and peak positions are reported in ppm upfield from $CFCl_3$. Mass spectra were recorded on a Kratos MA980 mass spectrometer using electron impact (EI, 20-50 eV) ionization. Optical rotations were determined on a JASCO DIP-360 digital polarimeter. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. Dione **11** was prepared as previously described.[13]

(*S,S*)-1,4-Diphenylbutan-1,4-diol (10)

This compound was prepared using a modification of the procedure developed by Brown for reductions of alkyl aryl ketones with Ipc_2BCl.[18a] Thus, THF (390 mL) was added slowly to a mixture of 1,4-diphenylbutan-1,4-dione (**11**, 20.0 g, 84 mmol) and (–)-Ipc_2BCl (56.5 g, 176 mmol) at -78 °C. The solution was stirred at –78 °C for 2 h, and then allowed to slowly warm to RT, and stirred at RT for 10 h. The solvent was removed *in vacuo* and the resulting pale yellow oil was stirred under vacuum (0.5 torr) at 40 °C for 24 h to remove excess pinene. Dry ether (600 mL) and diethanolamine (20.4 g, 194 mmol) were then added to the mixture at 0 °C and the mixture was stirred vigorously for 30 min at 0 °C and for 12 h at RT. The white solid was removed by filtration through a pad of Celite. The yellow filtrate was concentrated and the resulting oil was chromatographed on silica gel (650 g) using hexanes:ether 1:1 followed by hexanes:ether 1:3 as eluents. Solvent removal gave 18.9 g (93%) of an oil that slowly crystallized to a colourless solid. This material could be used in the next step without further purification.

Recrystallization from CH_2Cl_2/hexanes gave analytically-pure colourless needles. mp 74.6-75.2 °C; IR (KBr) 3339, 3026, 1208, 990 cm^{-1}; ^1H NMR δ 7.25-7.15 (m, 10 H), 4.44 (br, 2 H), 4.03 (d, J = 3.4 Hz, 2 H), 1.84-1.6 (m, 4 H); ^{13}C NMR δ 144.6, 128.2, 127.1, 125.7, 74.2, 35.7; MS m/e (rel intensity) 242 (0.1, M^+), 224 (23), 118 (100), 107 (75), 79 (57), 77 (26); $[\alpha]_D^{25}$ –58.5 (c 1.013, $CHCl_3$). Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H. 7.49. Found: C, 79.14; H, 7.37.

Derivatization of a small sample of the crude reaction product with (+)-MTPA-Cl [prepared from (*R*)-(+)-MTPA] provided diastereomeric MTPA esters. Analysis by ^{19}F NMR spectroscopy (188 Mz) showed

signals at δ –70.41 (*S,S*), –70.49 and –70.60 (*R,S*), and –70.69 (*S,S*). The intensity of the signal at δ –70.41 was comparable to that of the ^{13}C satellites (δ –70.07, –71.60) of the major (δ –70.69) signal.

The meso isomer (obtained as the major product by reduction of dione **11** with $LiAlH_4$) showed ^{13}C NMR signals at δ 144.5, 128.3, 127.3, 125.8, 74.0, and 35.0.

(*S,S*)-1,4-Bis(methanesulphonyloxy)-1,4-diphenylbutane (13).

To a cold (–20 °C) stirred solution of methanesulfonyl chloride (1.2 mL, 16 mmol) in CH_2Cl_2 (60 mL) was added a solution of (*S,S*)-1,4-diphenylbutan-1,4-diol (1.50 g, 6.18 mmol) and triethylamine (2.6 mL, 19 mmol) in CH_2Cl_2 (60 mL). The mixture was stirred at –20 °C for 1.75 h, then quenched with saturated NH_4Cl (5 mL). The mixture was warmed to room temperature, and the solvent was removed *in vacuo* to approx. 50 mL volume. The residue was diluted with ethyl acetate (250 mL) and washed with 1:2:1 water:brine:sat. $NaHCO_3$ (4 x 50 mL) and with sat. $NaHCO_3$ (2 x 50 mL). The solution was dried ($MgSO_4$), filtered through Celite, and the solution was evaporated to approx. 25 mL volume. The solution was cooled to 0 °C, and the dimesylate was precipitated by the dropwise addition of 250 mL of hexane with stirring. The solvent was decanted, and the damp white crystals were dissolved in a minimum of ethyl acetate. The solution was evaporated to 25 mL volume again, and hexane was added to induce precipitation as before. The crystals were collected by suction filtration to yield 2.05 g of the desired product (5.15 mmol, 83% yield) as a white powder. The product was stored under argon at –60 °C to prevent decomposition. mp ~50 °C (dec); ^1H NMR (200 MHz, C_6D_6) δ 7.21-7.00 (m, 10 H, Ph), 5.74-5.70 (m, 2 H, C<u>H</u>OMs), 2.05-1.84 (m, 4 H, C<u>H</u>$_2$), 2.01 (s, 6 H, $SO_2C\underline{H}_3$); ^{13}C NMR (50 MHz, C_6D_6) δ 139.0, 129.0, 128.9, 126.7, 82.8, 38.3, 33.4; $[\alpha]_D^{25}$ –91.6 (c 1.10, EtOAc). Satisfactory mass spectral data and combustion analysis of this compound could not be obtained due to its instability.

(*R,R*)-*N*-allyl-*trans*-2,5-diphenylpyrrolidine (14).

Dimesylate **13** was prepared as above from 2.0 mL (26 mmol) of mesyl chloride, 2.53 g (10.5 mmol) of (*S,S*)-1,4-diphenylbutan-1,4-diol (**10**) and 5.0 mL (36 mmol) of triethylamine. After the second crystallization, the solvent was decanted, and the damp crystals were cooled to 0 °C. Allylamine (75 mL, 1.0 mol) was added, and the mixture was stirred overnight and allowed to warm slowly to room temperature. The allylamine was removed *in vacuo*, and the residue was dissolved in 300 mL of ether. The ether solution was washed with sat. $NaHCO_3$ (2 x 75 mL) and brine (75 mL), dried ($MgSO_4$), and filtered through Celite. Solvent removal *in vacuo* gave the crude product as a yellow oil. Column chromatography of the crude product (136 g silica, 30:1 hexane:ether) gave a small forerun (0.05 g) and a small mixed fraction, followed by diastereomerically pure amine **14** (1.94 g, 71% from **10**) as a colourless oil. IR (neat, NaCl) 3070, 2964, 2818, 1641, 1070, 916, 860, 753, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.4-7.2 (m, 10 H), 5.75-5.53 (m, 1 H), 4.95-4.83 (m, 2 H), 4.33-4.30 (m, 2 H), 3.02-2.92 (m, 1 H), 2.76-2.55 (m, 1 H), 2.6-2.4 (br m, 2 H), 2.1-1.8 (br m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2, 136.7, 128.3, 127.9, 126.8, 115.6, 65.6, 49.9, 33.1; MS (EI) *m/e* 263 (M^+, 36), 262 (27), 194 (17), 187 (14), 186 (100), 144 (17), 104 (29), 41 (22); $[\alpha]_D^{25}$ +115.1 (c 1.40, $CHCl_3$); Anal. Calcd for $C_{19}H_{21}N$: C, 86.64; H, 8.04; N, 5.32. Found: C, 86.60; H, 7.85; N, 5.16.

The small forerun mentioned above was determined to be the *cis* isomer. ^{1}H NMR (250 MHz, C_6D_6) δ 7.51-7.48 (m, 4 H), 7.3-7.1 (m, 6 H), 5.78-5.62 (m, 1 H), 4.88-4.75 (m, 2 H), 3.70 (br t, J = 5.5 Hz, 2 H), 3.1 (d, J = 6.9 Hz, 2 H), 2.1-1.7 (m, 4 H,); ^{13}C NMR (63 MHz, C_6D_6) δ 145.2, 134.2, 128.6, 127.8, 127.2, 117.3, 67.3, 53.1, 34.7.

(*R,R*)-*Trans*-2,5-diphenylpyrrolidine (9).

(*R,R*)-*N*-allyl-*trans*-2,5-diphenylpyrrolidine (**14**, 2.56 g, 9.72 mmol) was placed in a 500 mL 3-necked flask fitted with a dropping funnel and a distillation head. The material was dissolved in 250 mL of 84:16 w/w acetonitrile/water mixture, and $(Ph_3P)_3RhCl$ (Wilkinson's catalyst, 0.411 g, 0.477 mmol) was added. The mixture was purged with a stream of nitrogen gas and heated to boiling. The solvent level was maintained by additions from the funnel, and the reaction was monitored by TLC until all starting material had been consumed (approx. 3 h). The reaction mixture was cooled to room temperature and diluted with 400 mL of ether. The layers were separated, the organic layer was washed (2 x 200 mL brine), and the combined aqueous washes were back-extracted (100 mL ether). The combined organic layers were dried ($MgSO_4$) and filtered through Celite. The solvent was removed *in vacuo* to give 3.0 g of a red-brown oil. This material was purified by flash chromatography (75 g silica gel, 1:1 hexane:ether) to give 2.12 g (98% yield) of product as a yellow oil which solidified slowly. mp 43.0-44.4 °C; IR (neat, NaCl) 3360, 3055, 3026, 2965, 2939, 2868, 1599, 1487, 1450, 1402, 1359, 1095, 1067 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.5-7.1 (m, 10 H), 4.50 (t, 2 H), 2.4-2.3 (m, 2 H), 2.3 (br s, 1 H), 1.9-1.8 (m, 2 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 145.7, 128.3, 126.6, 126.2, 62.1, 35.4; MS m/e (relative intensity) 223 (M^+, 30), 222 (38), 195 (100), 146 (21),117 (23), 104 (25), 91 (24); $[\alpha]_D^{25}$ +104.5 (c 1.00, $CHCl_3$). Anal. Calcd for $C_{16}H_{17}N$: C, 86.06; H, 7.67; N, 6.26. Found: C, 86.33; H, 7.82; N, 6.32.

HPLC Analysis of *Trans*-2,5-diphenylpyrrolidine. Determination of the enantiomeric excess was carried out with a Chiracel OD column. The eluent was 98.5:1.5:0.1 hexanes:isopropanol:diethylamine, with a flow rate of 0.5 mL/min. Samples were prepared by dissolving approx. 10 mg of the material to be analyzed in 2 mL of hexane, and injecting 2 μL of the sample solution. The (*R,R*) enantiomer was found to have a retention time of 17.1 min, while the (*S,S*) isomer had a retention time of 18.6 min. All samples of (*R,R*) isomer tested showed no detectable signal due to the (*S,S*) isomer.

X-ray diffraction analysis of 9•HCl.[31] The HCl salt of pyrrolidine **9** was prepared by bubbling HCl gas through a solution of **9** in ether. The resulting precipitate was recrystallized from CH_2Cl_2/ether to give crystals suitable for x-ray diffraction studies. A single crystal measuring 0.56 x 0.18 x 0.20 mm was chosen. Intensity data were collected at 200 K with graphite-monochromated MoKα radiation using a Siemens R3m/V diffractometer. The structure was solved by direct methods (SHELXTL PLUS) and refined through full-matrix least-squares calculations, anisotropically for non-hydrogen atoms and isotropically for hydrogen atoms, to a final R = 3.25% and R_w = 4.50%. Crystal system: monoclinic. Space group: $P2_1$. Lattice parameters: a = 10.042(2) Å, b = 7.5550(10) Å, c = 18.221(4) Å, β = 90.72(2)°. The *trans*- orientation of the phenyl groups, and the absolute configuration (*R,R*) were readily apparent.

The HCl salt of **9** showed the following properties: mp 183.4-184.2 °C; IR (KBr) 3623, 3429, 2940 (v br), 2527, 1569, 1492, 1455, 1382, 1024 cm-1; ^{1}H NMR (250 MHz) δ 9.94 (br s, 2 H), 7.5-7.3 and 7.2-7.1 (m, 10 H), 4.69 (br s, 2 H), 2.5-2.3 (m, 2 H), 2.3-2.1 (m, 2 H); ^{13}C NMR (63 MHz) δ 134.3, 128.5, 128.4, 128.0, 62.7, 31.6; MS m/e (relative intensity) 223 (38, M-36), 222 (40), 195 (100), 146 (28), 129 (15), 117 (23), 104 (27), 91 (19); $[\alpha]_D^{25}$ +69.6 (c 1.01, $CHCl_3$). Anal. Calcd for $C_{16}H_{18}ClN$: C, 73.98; H, 6.98; N, 5.39. Found: C, 74.11, H, 6.85; N, 5.35.

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