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A simple enantioselective preparation of (2*S*,5*S*)-2,5-diphenylpyrrolidine and related diaryl amines

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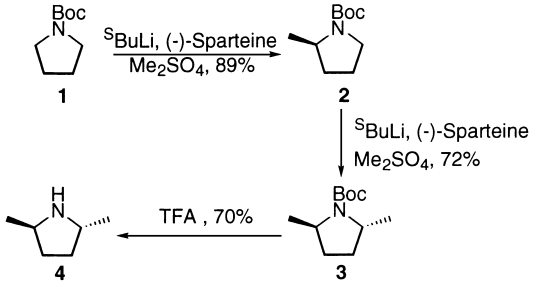
Abstract

A short efficient catalytic asymmetric route to the preparation of C_2-symmetric diaryl cyclic amines is described.

1. Introduction

The use of C_2-symmetric chiral auxiliaries is an area of considerable importance in current asymmetric synthesis.[1] One of the most popular and useful classes of these reagents are the *trans* 2,5-disubstituted pyrrolidines pioneered by Whitesell[2] and subsequently by many others. When, in the course of another project, we sought to examine the use of a C_2-symmetric diamine chiral auxiliary we explored the preparation of the 2,5-dimethyl derivative **4** using the enantioselective deprotonation strategy developed by Beak, Scheme 1.[3]



Scheme 1.

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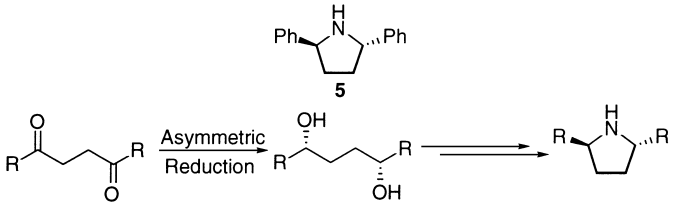
Whilst this approach was successful we had difficulties in scaling up the procedure and in the recovery and recycling of the chiral auxiliary. This problem can be overcome through the use of the corresponding diphenyl analogue **5**; a non-volatile, stable crystalline compound which can be prepared following a strategy of enantioselective reduction of 1,4-diphenyl-1,4-butanedione and cyclisation of the resultant diol, Scheme 2.[4,5]



Scheme 2.

Partly due to the need to generate such C_2-symmetric species there has been considerable effort directed towards the stereoselective reduction of diketones.[6–12] With a view towards the preparation of the diphenylpyrrolidine, two procedures involving either the asymmetric reduction with diisopinocampheylchloroborane[4] or the reduction with borane and an oxazaborolidine catalyst, have been reported.[5] However, neither process is ideal. Although the former can be easily adapted to prepare either enantiomer, the reagent must be prepared (or purchased) and the removal of the chiral auxiliary from the product mixture is non-trivial and requires considerable time. The oxazaborolidine method requires considerable care and time in the preparation of the chiral catalyst to achieve good selectivities.[13] Although this is simplified through the in situ procedure developed by Quallich et al.[14] it is still necessary to premix the chiral auxiliary and borane for 18 h to generate the catalyst. Furthermore, good diastereoselectivity (84:16) and enantioselectivity ($>99:<1$) is only obtained with the use of stoichiometric amounts of oxazaborolidine.

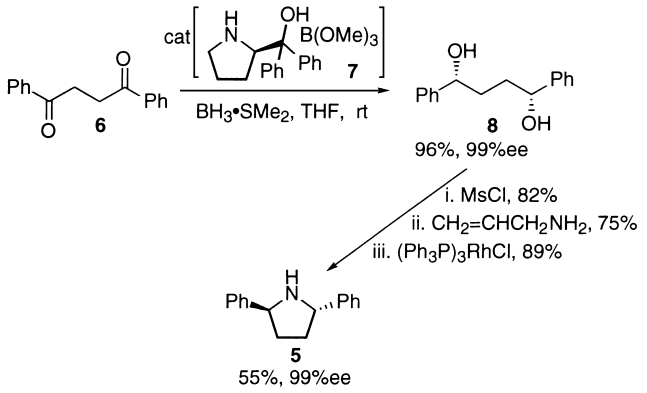
We sought a simpler more effective protocol and were attracted by a report from Masui and Shioiri that indicated that extremely effective oxazaborolidine catalysts can be easily and rapidly generated in situ from an aminoalcohol and trimethyl borate (1 h at room temperature).[15] They reported that these catalysts were effective in the reduction of simple arylketones. In this paper we report that they also represent an extremely attractive option for the selective reduction of related diketones and hence the preparation of 2,5-diarylpyrrolidines.

2. Results and discussion

The required diphenylbutanedione **6** can be easily prepared following established protocols by Friedel–Crafts acylation of benzene with fumaroyl chloride and subsequent reduction of the alkene with sodium dithionate.[16,17] The use of benzene may be avoided by an equally efficient procedure involving ceric ammonium nitrate mediated oxidative coupling of the silylenol ether of acetophenone.[18]

Following the procedure of Masui, slow addition of this dione to a solution of in situ prepared *B*-methoxy oxazaborolidine (0.1 equiv.) derived from diphenylprolinol **7** and borane dimethylsulfide complex (1 equiv.) afforded, after a further 1 h at room temperature and aqueous work up, the desired diol in excellent yield (96%) and stereoselectivity (>95% de and 99% ee), Scheme 3.

The process is simple and amenable to scale up—we have repeated the procedure using up to 10 g of dione without any loss in yield or selectivity. With the diol in hand we were able to convert this to the desired pyrrolidine using the efficient methodology reported by Chong.

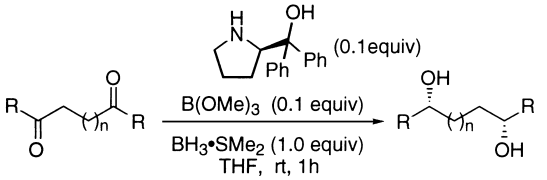


Scheme 3.

The diastereoselectivity is noteworthy in that it is considerably higher than that obtained with the related oxazaborolidines used by other workers in the reduction of diones (B-H, B-alkyl, B-aryl). This can possibly be attributed to the increased Lewis acidity of the boron centre allowing the catalyst to more effectively overcome substrate controlled selectivity which leads to the *meso* isomer.[19]

We were curious to see if this would provide a general method for the prepartion of these C_2-symmetric diamines and examined the reduction of a number of other simple diones varying the nature of the substituents. Those substrates which are not readily available were prepared in an analogous fashion to that described above. All the reductions were carried out in an identical fashion and we have made no attempt to significantly optimise the yields of these reactions, Table 1. As can be seen from Table 1, 2,5-hexanedione (R = Me) **9** is not a viable substrate for selective reduction. This is consistent with Quallich's observations for the B-H oxazaborolidines although in this case the opposite sense of asymmetric induction is observed as ascertained by a comparison

Table 1
Catalytic enantioselective reduction of diones **9**–**12**



Dione		Diol	(yield %de, %ee)
R = Me **9**	n = 1	**13**	74%, 22%de, 33%ee[a,b]
R = ^{t}Bu **10**	n = 1	**14**	57%, 72% de, 86%ee[a]
R = 2-naphthyl **11**	n = 1	**15**	no reaction
R = Ph **12**	n = 2	**16**	91%, 96%de, 98%ee[c]

a Determined by comparison of $[\alpha]_D$ values with literature; b(S,S) isomer obtained
c Determined by HPLC using Chiracel OD column

of $[\alpha]_D$ values. The reason for this change is not obvious at the present time. As with these earlier reports, increasing the tether length has little effect on the selectivity; 1,5-diphenylpentane-1,5-diol **16** being produced with both good de and ee.

Interestingly, 1,4-di-2′-naphthylbutane-1,4-dione **11** proved to be resistant to reduction. Given that 2-acetonaphthone is an excellent substrate for asymmetric reduction (>99% ee) with this procedure, we attribute this to interactions (π-stacking) between the aromatic nucleus and the carbonyl group which inhibits binding of the catalyst and shields the carbonyl group from attack by the borane. Evidence for this arises from the ^{13}C NMR spectra in which the carbonyl carbon appears at $\delta = 198$ for acetonapthone and $\delta = 209$ for the dione **11**.

With the exception of the bis *tert* butyl diol **15**, which proved resitant to nucleophilic displacement, all the diols could be efficiently converted to the C_2-symmetric cyclic diamines by the same sequence of mesylation, double displacement with allylamine and final deprotection using Wilkinson's catalyst. In the case of the piperidine derivative a small amount of the corresponding *meso* isomer was detected after the cyclisation step. We presume that this arises through the intermediacy of a benzylic cation.

In conclusion, the catalytic enantioselective reduction of α,ω-diaryldiones to the corresponding diol can be simply and rapidly achieved using the Masui protocol. This allows an efficient catalytic asymmetric synthesis of C_2-symmetric diaryl cyclic amines to be easily realised. Aliphatic ketones are less satisfactory substrates and the corresponding diols are best accessed via the reduction of the corresponding unsaturated species[20] or via enzymatic reduction.[21]

3. Experimental

All air and/or moisture sensitive reactions were carried out under an argon atmosphere. Solvents were purified following established protocols.[22] Petrol refers to petroleum spirit boiling in the 40–60°C range. Ether refers to diethyl ether. Commercially available reagents were used as received unless otherwise stated. Diones were prepared following established literature procedures. Yields refer to isolated yields of products of greater than 95% purity as determined by ^1H and ^{13}C NMR spectroscopy or elemental analysis (Durham University, Microanalytical Laboratory).

Infrared (IR) spectra were recorded on a Perkin–Elmer FT-IR 1720X spectrophotometer, in a liquid film (NaCl plates), solution cell ($CHCl_3$), KBr disk, or on the above machine fitted with Graseby Specac Single Reflection Diamond ATR (10500 series) 'Golden Gate' accessory, as specified in the text. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian VXR-400 (^1H at 399.968 MHz, ^{13}C at 100.572 MHz), Varian Oxford Unity 300 (^1H at 299.908 MHz, ^{13}C at 75.412 MHz) and a Varian Oxford Mercury 200 (^1H at 199.975 MHz, ^{13}C at 50.289 MHz) spectrometer with deuterochloroform as solvent. Chemical shifts are recorded in ppm (δ units) relative to residual $CHCl_3$ ($\delta(^1H) = 7.26$, $\delta(^{13}C) = 77.0$), unless otherwise stated. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Coupling constants were recorded in hertz. All ^{13}C spectra were proton decoupled. Mass spectra (EI and CI) were recorded on either a VG Analytical 7070E or a Micromass Autospec mass spectrometer. GC–MS was performed using a Hewlett–Packard 5890 Series II GC, equipped with a 25 m SE30 column, connected to a VG Mass Lab Trio 1000. Chiral HPLC was carried out using a Varian Star HPLC system using a Chiracel OD column. Optical rotations were measured on an Optical Activity LTD AA-10 Automatic Polarimeter. Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected.

Reactions were followed by gas chromatography (GC) using Perkin–Elmer 8410 GC with a SA50 column or by thin-layer chromatography (TLC). Flash column chromatography was performed according to the method of Still et al. using 200–400 mesh silica.[23]

3.1. General dione reduction procedure

3.1.1. (1R,4R)-1,4-Diphenylbutan-1,4-diol **8**

To a stirred solution of α,α-diphenyl-2-pyrrolidine methanol **7** (2 g, 8 mmol) in THF (50 ml) at room temperature, trimethyl borate ($B(OMe)_3$) (1.15 ml, 10 mmol) was added and stirred for 1 h. After borane–dimethyl sulfide complex (9.27 ml, 98 mmol) was added, a solution of the diketone 1,2-dibenzoylethane **6** (11 g, 46.2 mmol) in THF (100 ml) was added over an hour. After a further hour, the resulting mixture was slowly quenched with 2N HCl (69 ml). The aqueous layer was extracted with ether (3×100 ml) before the combined organic extracts were washed with H_2O and brine, dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was purified by flash chromatography (eluting with 35% ethyl acetate in petrol) to give the title diol **8**, as a colourless oil (10.7 g, 96%). $[\alpha]_D^{25}=+58$ (*c* 1.02, $CHCl_3$) (lit.[4] –58.5 (*c* 1.01, $CHCl_3$, >98% ee) for *S*,*S* isomer). ν_{max} (thin film); 3339 (OH), 3025 (Ar), 1207 (CH), 990 cm^{-1}. δ_H (300 MHz); 7.3–7.1 (10H, m, Ph), 4.58 (2H, br s, C*H*OH), 3.0 (2H, br s, O*H*), 1.84–1.6 (4H, m, CH_2). δ_C (75 MHz); 144.6, 128.1, 127.0, 125.6 (Ar), 74.3 (H*C*OH), 35.1 (CH_2). *m*/*z* (EI); 242 (M^+), 224, 118 (100%), 107, 79.

3.1.2. (2R,5R)-Hexan-2,5-diol **13**

In an identical fashion to that described above hexan-2,5-dione **9** (3 g, 26 mmol) was reduced to give, following flash chromatography (eluting with 40% ethyl acetate in petrol), hexandiol **13**, as a colourless oil which solidified on standing (2.27 g, 74%). *dl*:*meso* 61:39 (GC/^{13}C NMR). Mp (48–51°C, lit.[21] 53.0–53.3°C). $[\alpha]_D^{25}=-7$ (*c* 1, $CHCl_3$) (lit.[21] +34.9 (*c* 9.48, $CHCl_3$ for (2*S*,5*S*)-hexan-2,5-diol >98% ee). ν_{max} (thin film); 3346 (OH), 3003 (CH), 1378, 1307, 1052 cm^{-1}. δ_H (400 MHz); 3.77 (2H, m, C*H*OH), 2.58 (2H, br, O*H*), 1.48 (4H, m, CH_2), 1.13 (6H, d, 2 Hz, CH_3). δ_C (75 MHz); 68.37 (0.39C, *meso*-H*C*OH), 67.87 (0.61C, *dl*-H*C*OH), 35.97 (0.78C, *meso*-CH_2), 34.98 (1.22C, *dl*-CH_2), 23.80 (0.39C, *meso*-CH_3), 23.46 (0.61C, *dl*-CH_3).

3.1.3. (3R,6R)-2,2,7,7-Tetramethyloctan-3,6-diol **14**

In an identical fashion to that described above 2,2,7,7-tetramethyloctan-3,6-dione **10** (396 mg, 0.2 mmol) was reduced to give, following flash chromatography (eluting with 40% ethyl acetate in petrol), diol **14**, as a white crystalline solid (230 mg, 57%). *dl*:*meso* 86:14 (^{13}C NMR). Mp 142–143°C. $[\alpha]_D^{25}=+37$ (*c* 1, CH_3OH) (lit.[5] –34.3 (*c* 1, CH_3OH, 97% ee), lit.[20] –44.4 (*c* 0.94, CH_3OH, 99% ee) for the (*S*,*S*) isomer). CHN: (found: C, 71.29; H, 13.01; $C_{12}H_{26}O_2$ requires: C, 71.23; H, 12.95). ν_{max} (solution); 3417 (OH), 2962, 2869 (CH), 1478, 1383, 928 cm^{-1}. δ_H (300 MHz); 3.20 (2H, d, 10 Hz, C*H*OH), 2.35 (2H, br, O*H*), 1.7–1.3 (4H, m, CH_2), 0.90 (18H, s, CH_3). δ_C (75 MHz, CD_3OD); 81.4 (0.14C, *meso*-H*C*OH), 80.2 (0.86C, *dl*-H*C*OH), 36.0 (*C*Me_3), 30.4 (0.14C, *meso*-CH_2), 29.3 (0.86C, *dl*-CH_2), 26.4 (CH_3). *m*/*z* (CI); 203 (M^++H), 185, 167, 127, 111, 97 (100%), 83.

3.1.4. (1R,5R)-1,5-Diphenylpentan-1,5-diol **16**

In an identical fashion to that described above 1,2-dibenzoylpropane **12** (5 g, 20 mmol) was reduced to give, following flash chromatography (eluting with 35% ethyl acetate in petrol), the title diol **16**, as a crystalline solid (4.6 g, 91%). *dl*:*meso* 98:2 (HPLC). Mp 101–102°C. $[\alpha]_D^{25}=+18$ (*c* 1.0, methanol), +20 (*c* 2.0, methanol) (lit.[5] –22.8 (*c* 1.0, CH_3OH, 99% ee)). CHN: (found: C,

79.63; H, 7.94; $C_{17}H_{20}O_2$ requires: C, 79.56; H, 7.86). ν_{max} (thin film); 3321 (OH), 2935 (Ar), 2855 (CH), 1454, 1013 cm^{-1}. δ_H (400 MHz); 7.3–7.1 (10H, m, Ph), 4.59 (2H, m, CHOH), 2.1 (2H, br, OH), 1.84–1.6 (4H, m, 2-H_2, 4-H_2), 1.4 (2H, m, 3-H_2). δ_C (100 MHz); 144.7, 128.4, 127.5, 125.8 (Ar), 74.4 (HCOH), 38.8 (C(2), C(4)), 22.2 (C(3)). *m*/*z* (CI); 239 (M^+-OH), 221, 161, 117 (100%).

3.2. General procedure for cyclic amine synthesis

3.2.1. (2S,5S)-N-*Allyl-2,5-diphenylpyrrolidine*

To a solution of methanesulfonyl chloride (400 μl, 5.3 mmol) in DCM (20 ml) at –20°C was added a solution of (1*R*,4*R*)-1,4-diphenylbutan-1,4-diol **8** (500 mg, 2.06 mmol) and triethylamine (870 μl, 6.2 mmol) in DCM (20 ml). The mixture was stirred for 105 min at –20°C and then quenched with satd NH_4Cl (2 ml). The mixture was warmed to room temperature and solvent removed in vacuo to approximately 17 ml. The solution was then diluted with ethyl acetate (80 ml) and washed with water:brine:satd $NaHCO_3$ (1:2:1) (4×20 ml), and satd $NaHCO_3$ (2×20 ml), before being dried ($MgSO_4$), filtered through Celite and concentrated in vacuo to approximately 8 ml. The solution was then cooled to 0°C, set to stir and the crude dimesylate was precipitated out by dropwise addition of hexane (80 ml). The resulting solid was recrystallized from ethyl acetate by addition of hexane at 0°C to yield the desired dimesylate, (1*R*,4*R*)-1,4-bis(methanesulfonyloxy)-1,4-diphenylbutane, (680 mg, 82%) as a moderately unstable compound which was used directly in the next step. δ_H (200 MHz, C_6D_6); 7.21–7.00 (10H, m, Ph), 5.74–5.70 (2H, m, CHOMs), 2.05–1.84 (4H, m, CH_2), 2.01 (6H, s, SO_2CH_3).

Allyl amine (25 ml, 0.33 mol) was added to a cooled flask (0°C) containing the dimesylate (670 mg, 1.68 mmol) and the resultant solution stirred at this temperature for 14 h. After warming to room temperature, the excess allyl amine was removed in vacuo and the residue dissolved in ether (70 ml) and washed with satd $NaHCO_3$ (2×25 ml) and brine (25 ml), dried ($MgSO_4$) and concentrated to afford the crude product as a yellow oil. Flash chromatography (eluting with 3% ether/petrol) yielded the diastereomerically pure title amine as a colourless oil (330 mg, 75% yield). $[\alpha]_D = -115$ (*c* 0.56, $CHCl_3$) (lit.[4] +115.1 (*c* 1.40, $CHCl_3$) for (*R*,*R*) isomer). CHN: (found: C, 86.38; H, 7.93; N, 5.57; $C_{19}H_{21}N$ requires: C, 86.65; H, 8.04; N, 5.32). ν_{max} (thin film); 3070, 2967, 2817, 1640, 1071, 916 cm^{-1}. δ_H (300 MHz); 7.41–7.20 (10H, m, Ph), 5.7–5.55 (1H, m, C*H*=CH_2), 4.92–4.87 (2H, m, CH=CH_2), 4.32–4.30 (2H, m, C*H*Ph), 2.95–2.68 (2H, m, NCH_2), 2.60–2.45 (2H, br, m, 3,4-C*H*), 2.01–1.90 (2H, br m, 3,4-C*H*′). δ_C (75 MHz); 144.6, 137.2, 128.5, 128.2, 127.1 (Ar, H*C*=CH_2), 115.9 (HC=*C*H_2), 65.9 (Ph*C*HN), 50.2 (N*C*H_2CH=), 33.5 (*C*H_2*C*H_2). *m*/*z* (EI); 263 (M^+, 30%), 262, 186 (100%), 91.

3.2.2. (2S,5S)-2,5-*Diphenylpyrrolidine* **5**

(*S*,*S*)-*N*-Allyl-*trans*-2,5-diphenylpyrrolidine (2.56 g, 9.72 mmol) and $(Ph_3P)_3RhCl$ (Wilkinson's catalyst, 44 mg, 0.047 mmol) was dissolved in 25 ml of 84:16 w/w acetonitrile:water mixture and placed in a 50 ml three-necked flask fitted with distillation head and dropping funnel. The mixture was purged with nitrogen gas and heated to boiling. The solvent level was maintained via the dropping funnel and the reaction heated for 5 h. The reaction was then cooled to room temperature and diluted with 40 ml ether. The layers were separated and the organic layer washed with brine (2×20 ml), and the combined aqueous washes were back extracted with ether (10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The resulting oil was purified by flash chromatography (eluting with 33% ethyl acetate in petrol) to yield the desired amine **5** (192 mg, 89%) as a yellow oil which solidified overnight. Mp 43.0°C. $[\alpha]_D = -108.2$ (*c* 0.45, $CHCl_3$)

(lit.[4] +104.5 (*c* 1.00, $CHCl_3$) >98% ee). CHN: (found: C, 86.23; H, 7.63; N, 6.17; $C_{16}H_{17}N$ requires: C, 86.05; H, 7.67; N, 6.27). ν_{max} (thin film); 3360, 3055, 2962, 2867, 1598, 1489, 1450, 1402 cm^{-1}. δ_H (200 MHz); 7.5–7.1 (10H, m, Ar), 4.5 (2H, t, PhC*H*N), 2.4–2.3 (2H, m, 3,4-C*H*), 2.3 (1H, br N*H*), 1.9–1.8 (2H, m, 3,4-C*H*′). δ_C (75 MHz); 145.7, 128.2, 126.5, 126.1 (Ar), 62.1 (N*C*HPh), 35.3 (CH_2CH_2). *m*/*z* (EI); 223 (M^+, 31%), 222, 195 (100%).

3.2.3. (2S,6S)-N-*Allyl-2,6-diphenylpiperidine*

In an identical fashion to that described above (1*R*,5*R*)-1,5-diphenylpentan-1,5-diol **17** was converted to (*R*,*R*)-1,5-bis(methanesulfonyloxy)-1,5-diphenylpentane, δ_H (300 MHz); 7.42–7.2 (10H, m, Ph), 5.42 (2H, m, C*H*OMs), 2.02 (6H, s, SO_2CH_3), 1.81–1.67 (4H, m, CH_2), 1.38 (2H, m, CH_2), and subsequently cyclised with allyl amine to give, following flash chromatography (eluting with 3% ethyl acetate in petrol), (2*S*,6*S*)-*N*-allyl-2,6-diphenylpiperidine as a colourless oil (2.13 g, 72%) accompanied by a small amount of the *meso* isomer (*R*,*S*/*S*,*R*)-*N*-allyl-2,6-diphenylpiperidine (GC ratios, 94.3:5.7%). $[\alpha]_D = -80$ (*c* 0.56, $CHCl_3$). CHN: (found: C, 86.45; H, 8.29; N, 4.94; $C_{20}H_{23}N$ requires: C, 86.59; H, 8.36; N, 5.05). ν_{max} (thin film); 3059, 2932, 2862, 1640, 1600, 1492, 1448, 915 cm^{-1}. δ_H (400 MHz); 7.4–7.1 (10H, m, Ph), 5.8–5.6 (1H, m, C*H*=CH_2), 4.98 (1H, d, 6 Hz, CH=CH_2), 4.94 (1H, s, CH=CH_2), 4.10 (2H, dd, 6.5 Hz, 4.5 Hz, C*H*Ph), 3.05–2.8 (2H, m, NCH_2), 1.8–1.6 (2H, m, 4-CH_2), 2.01–1.90 (br m, 4H, 3,5-CH_2). δ_C (100 MHz); 144.3, 137.5, 128.3, 128.2, 128.0, 126.3 (Ar, H*C*=CH_2), 115.8 (HC=*C*H_2), 58.6 (Ph*C*HN), 50.9 (N*C*H_2CH=), 27.7 (*C*(3)H_2), 19.8 (*C*(4)H_2); *m*/*z* (GC–MS, EI) (*cis*: rt 21.48 min; 277 (M+), 200 (100%), 144, 117, 91, 77) (*trans*: rt 22.28 min; 277 (M+), 200 (100%), 144, 117, 104, 91, 77).

3.2.4. (2S,6S)-trans-*2,6-Diphenylpiperidine*

In an identical fashion to that described above (2*S*,6*S*)-*N*-allyl-*trans*-2,6-diphenylpiperidine (1 g, 3.6 mmol) was treated with $(Ph_3P)_3RhCl$ (166 mg, 0.18 mmol) to give, following flash chromatography (eluting with 33% ethyl acetate in petrol), the title amine (642 mg, 75%) as a yellow solid. Mp 45–46°C. $[\alpha]_D = -81.2$ (*c* 5, EtOH) (lit.[24] +70.1 *c* 4.63, EtOH (*c* 4.63, EtOH) for the (*R*,*R*) isomer). CHN: (found: C, 85.82; H, 8.97; N, 6.04; $C_{17}H_{19}N$ requires: C, 86.03; H, 9.07; N, 5.90). ν_{max} (Golden Gate); 3359, 3058, 2951, 2867, 1486, 1448, 1401 cm^{-1}. δ_H (300 MHz); 7.3–7.1 (10H, m, Ar), 3.99 (2H, bt, PhC*H*N), 2.2 (1H, br N*H*), 1.9–1.75 (4H, m, 3,5-CH_2), 1.6 (2H, m, 4-CH_2). δ_C (75 MHz); 144.9, 128.1, 126.8, 126.3 (Ar), 59.4 (N*C*HPh), 28.3 (*C*(2,4)H_2), 18.7 (CH_2). *m*/*z* (EI); 237 (M^+, 31%), 160, 181 (100%).

Acknowledgements

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