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Synthesis and Resolution of a Chiral Analogue of 2,2,6,6-Tetramethylpiperidine and of its Corresponding Nitroxide

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Abstract : The novel C_2 symmetric chiral amine *trans*-2,6-dimethyl-2,6-diphenylpiperidine has been synthesized via two successive nitrone nucleophilic addition-oxidation sequences, followed by reduction of the intermediate nitroxide. Pure enantiomers have been obtained via resolution with mandelic acid.

Highly sterically hindered C_2-symmetric amines are of increasing importance for enantioselective synthesis and catalysis. For example, their lithium amides are used as chiral equivalents of LDA for enantioselective deprotonations.[1] Lithium 2,2,6,6-tetramethylpiperidide (LiTMP) or the corresponding magnesium amides (TMPMgX) are non nucleophilic strong bases which possess, in some cases, decisive advantages over LDA.[2] Chiral equivalents of LiTMP or TMPMgX are, therefore, valuable synthetic targets with interesting potential applications. Moreover, the stable nitroxides derived from the corresponding amines would themselves be of geat interest: Recently chiral nitroxides have emerged as promising tools in various fields of chemistry, for example as enantioselective oxidation catalysts,[3] for the development of paramagnetic chiral liquid crystals,[4] in stereoselective coupling reactions with prochiral radicals[5] or in the control of living free-radical polymerisation processes.[6,7] We report here the synthesis of the novel, C_2 symmetric chiral amine *trans*-2,6-dimethyl-2,6-diphenylpiperidine **5** (Scheme 1) and of the corresponding nitroxide **4**, as well as the obtention of optically active **5** and **4** via resolution of amine **5**.

Our synthetic approach is based on tandem nucleophilic addition-oxidation sequences on nitrone **2** obtained by oxidation of piperidine **1**, allowing the sequential introduction of the phenyl substituents. Such an approach has originally been developped by Keana for the synthesis of various pyrrolidinyl nitroxides. He has demonstrated that it allows a high stereochemical control of the newly created stereocenters.[8] Müllen et al.[9] have applied this methodology for the synthesis of *trans*-2,5-dimethyl-2,5-diphenylpyrrolidine-1-oxyl and have carried out its resolution by preparative chiral HPLC. Recently, we have described an enantioselective approach to the same compound and its reduction to the corresponding amine.[10] To our knowledge, Keana's methodology has not been applied previously in the piperidine series.

As outlined in scheme 1, commercial *cis*-2,6-dimethylpiperidine **1** was first oxidized to nitrone **2** by the complex urea-hydrogen peroxide catalysed by methyltrioxorhenium.[11] Nitrone **2** was reacted with phenylmagnesium bromide in THF, followed by oxidation of the crude reaction product with molecular oxygen in the presence of ammoniacal cupric acetate,[8] leading to nitrone **3**. As nitrone **3** has a low stability it was used

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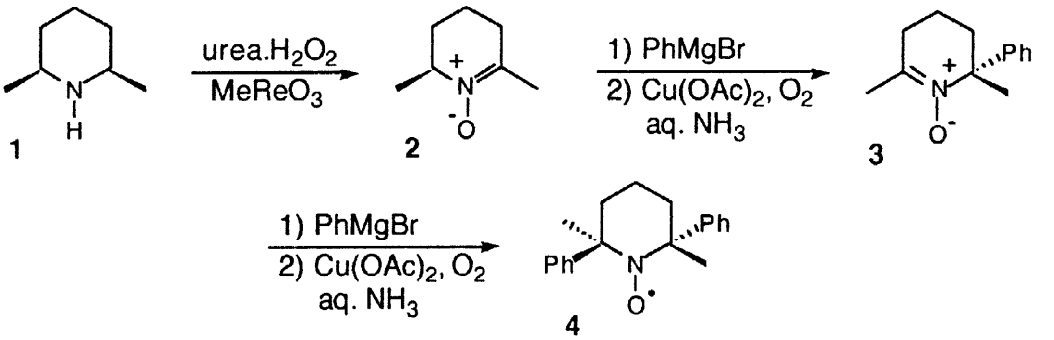
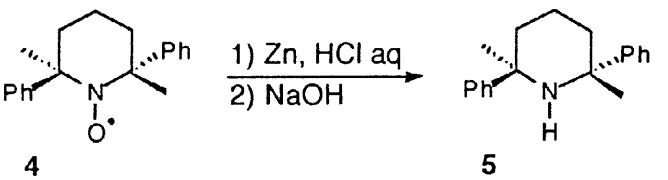
without purification: the same Grignard addition-oxidation sequence furnished nitroxide **4**, isolated as yellow crystals after column chromatography purification (yield 8% from **2**, unoptimized).[12] Only one diastereomer was obtained. X-ray crystallography revealed the trans relationship of the methyl and of the phenyl groups respectively (Fig. 1).[13]



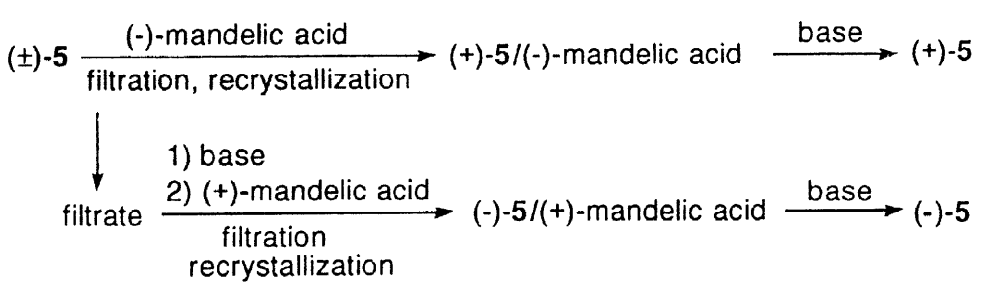
Scheme 1 Synthesis of (+)-*trans*-2,6-dimethyl-2,6-diphenylpiperidin-1-oxyl **4**

Nitroxide **4** was next reduced by treatment with zinc powder in aqueous hydrochloric acid, followed by alkaline work-up.[14] Amine **5** was isolated with a 86% yield (Scheme 2).[15]



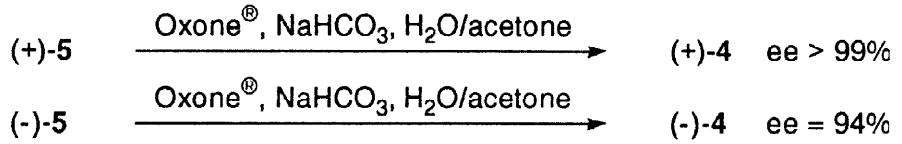
Scheme 2 Reduction of nitroxide **4** to amine **5**

(±)-Amine **5** has been resolved by fractional crystallization of its diastereomeric salts formed with mandelic acid (Scheme 3) : *(R)*-(-)-mandelic acid gives a crystalline salt with (±)-**5** from ether/ethanol, 3:1. After one recrystallization of this salt from ethyl acetate and alkaline treatment, (+)-**5** was obtained in 26% yield (theoretical yield 50%), with $[\alpha]_D^{21}$ +77 (c 1.03, EtOAc). The filtrate from the isolation of the salt (+)-**5**/ (-)-mandelic acid furnished, after alkaline treatment, amine **5** enriched in the (-) enantiomer. This sample was treated with 1 equivalent of *(S)*-(+)-mandelic acid, furnishing the crystalline salt (-)-**5**/(+)-mandelic acid from ether/ethanol, 3:1. One recrystallization of this salt from ethyl acetate, followed by alkaline work-up gave amine (-)-**5** in 24% yield, $[\alpha]_D^{21}$ -82 (c 1.18, EtOAc).



Scheme 3 Resolution of racemic **5**

Both enantiomers of amine **5** were finally reoxidized into enantiomeric nitroxides **4**, using Oxone®(Scheme 4).[16] (-)-**5** (with $[\alpha]_D^{21}$ -82) gave nitroxide (-)-**4** in 85% yield : $[\alpha]_D^{21}$ -140 (c 1.11, EtOAc); ee > 99%.[17] Enantiomeric purity of (-)-**4** was measured after column chromatography purification and without recrystallization. Therefore its value can be assumed to reflect the enantiomeric purity of amine (-)-**5**.[18] Likewise amine (+)-**5** ($[\alpha]_D^{21}$ +27) was oxidized into (+)-**4** with $[\alpha]_D^{21}$ +132 (c 1.09, EtOAc), ee = 94%. Since the molecule does not contain any heavy atoms the direct determination of the absolute configuration by X-ray was not possible. Efforts to crystallize derivatives of **5** containing heavy atoms or additional asymmetric centers of known configuration for X-ray diffraction are in progress.



Scheme 4 Obtention of optically active 4

In summary, we have demonstrated that the methodology originally developed by Keana for the synthesis of pyrrolidinyl nitroxides can also be applied in the piperidine series, with a similar degree of diastereoselectivity. Thus, it offers a new access to C_2 symmetric chiral piperidines and to the corresponding nitroxides. Optically active amines and, subsequently, nitroxides can be obtained via resolution. Synthetic applications of both class of compounds are under investigation.

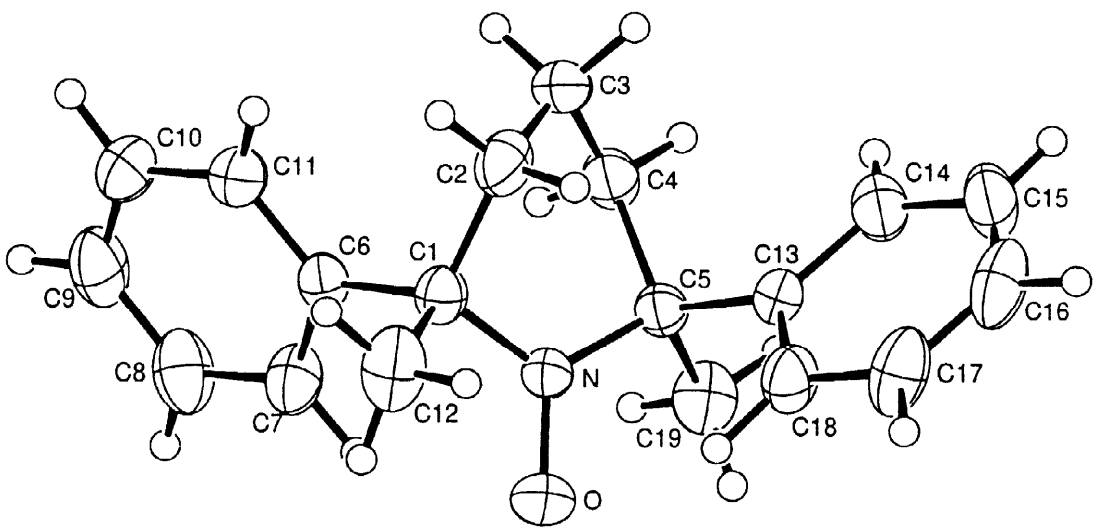


Fig. 1 Crystal structure of nitroxide 4. Selected bond lengths (Å) and angles (°): N-O 1.271(4), N-C(1) 1.482(4), N-C(5) 1.481(2), C(1)-N-O 119.5(1), C(5)-N-O 118.6(1), C(1)-N-C(5) 121.9. Dihedral angle between the planes of the two phenyl rings: 71.5(1)°.

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12. Nitroxide **4** is stable and could be stored at room temperature for several weeks without noticeable decomposition. It melts at 127 - 127.5°C after recrystallization from hexane. Its ESR spectrum exhibits a characteristic triplet hyperfine structure (g = 2.0066, a_N = 14.06). The ^{1}H-NMR spectrum consists of only unresolved, very broad signals. IR (KBr) 3088, 3063, 3026, 2979, 2959, 2945, 1494, 1448, 1371, 1266, 1029 cm^{-1}. UV-vis 242 nm (ε = 2705), 446 nm (ε = 2). DCI-MS (NH_3 + isobutane) : m/z(%) = 281 (100), 266 (9), 250 (15). Anal. calcd for $C_{19}H_{22}NO$: C, 81.39; H, 7.91; N, 5.00. Found: C, 81.59; H, 7.83; N, 5.04.
13. X-ray crystal data for racemic nitroxide **4**: $C_{19}H_{22}NO$, M_r = 280.39, monoclinic, space group $P2_1/c$ N° 14), a = 8.843(2), b = 18.315(4), c = 10.731(3) Å, β = 114.17(2)°, V = 1585.6(7) Å^3, Z = 4, ρcalcd = 1.174 gcm^{-3}, R = 0.034, R_w = 0.038, for 1306 reflections with $I > 3\sigma(I)$ and 191 variables. Data were recorded on a Nonius CAD4 diffractometer with Mo-Kα radiation. The structure was solved by direct methods (Sir 92) and refined using full-matrix least squares methods. Hydrogen atoms were included, but not refined. Full data will be deposited at the Cambridge Crystallographic Data Center (CCDC). For a comparison with the X-ray data of the homologous pyrrolidinyl nitroxide, see ref. 9.
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15. Selected data for amine **5** : Colorless oil; b.p. 165°C (0.15 mm). IR (neat) 3308, 3092, 3067, 3024, 2931, 2869, 1603, 1492, 1239, 1078, 1035 cm^{-1}; ^{1}H-NMR (250 MHz) δ (ppm) 1.03 (s, 6H) 1.54 (bs, 1H), 1.61 - 1.71 (m, 2H), 1.81 - 1.88 (m, 2H), 2.10 - 2.20 (m, 2H), 7.18 - 7.67 (m, 10H); ^{13}C NMR (62.5 MHz) δ (ppm) 18.6, 33.1, 36.6, 54.9, 125.5, 125.9, 127.8, 150.4; DCI-MS (NH_3 + isobutane) : m/z (%) = 266 (100), 250 (19.5).
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17. Enantiomeric composition of optically active **4** have been determined by HPLC on a chiracel OD-H column, elution : isopropanol/hexane (1: 9), 0.5 mL min^{-1}.
18. Attemps to determine the enantiomeric purity of amine **5** directly by chiral HPLC or by using NMR techniques have failed so far.