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Simple Synthesis of a C_2 Symmetric Vicinal Diamine: Highly Diastereoselective Grignard Addition to a Chiral *Bis*-Imine

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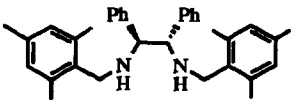
Abstract: The reaction of the enantiomerically pure *bis*-imine derived from glyoxal and (*R*)-α-methylbenzylamine with PhMgCl in diethylether is highly diastereoselective, resulting in the selective formation of the C_2 symmetric vicinal diamine **7**.

Enantiomerically pure diamines have found widespread use as chiral ligands in asymmetric reactions.[1] Vicinal diamines having C_2 symmetry have proved especially useful, for example diamines **1** and **3**, used in asymmetric dihydroxylation of alkenes by OsO_4,[2,3] and amine **2**, employed in enantioselective addition reactions of organometallics.[4] Our interests in asymmetric synthesis have centred on the use of lithium amide derivatives of certain chiral secondary amines as strong bases for enantioselective deprotonation reactions.[5] In this chemistry the simple lithium amide **4**,[6] having C_2 symmetry, has proved highly effective, although the value of additional coordination sites in chiral lithium amides such as **5** has also been demonstrated.[7]



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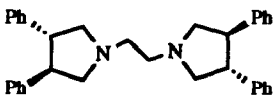

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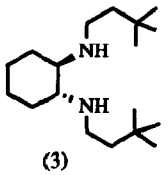

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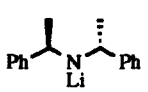

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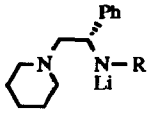
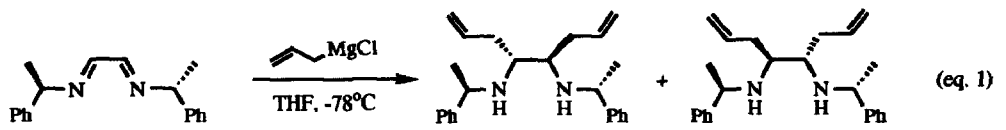


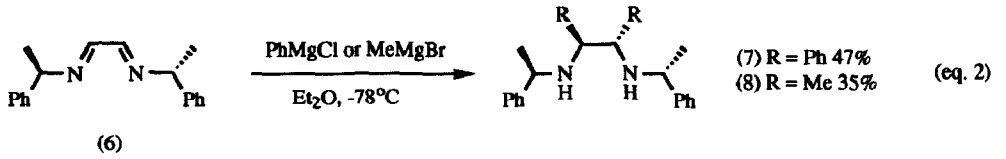
(5)

In designing new base systems of potential utility we sought to combine the features of C_2 symmetry and additional coordination site in a chiral base that was synthetically accessible. We were attracted to the report of Neumann and coworkers,[8] which described the diastereoselective addition of allylmagnesium chloride to the chiral *bis*-imine **6** derived from glyoxal and (*R*)-α-methylbenzylamine (eq. 1).



Here we show that this type of reaction is highly stereoselective with other Grignard reagents, and in particular that PhMgCl can be used to access a potentially useful new C_2 symmetric diamine in a very straightforward two-step synthesis. Furthermore, the stereochemical outcome of the reaction involving PhMgCl (as demonstrated by X-ray analysis) is *opposite* to that assigned previously for the reaction with allylmagnesium chloride.

Our initial experiments involving reaction of Grignard reagents, such as PhMgCl, or alkyllithiums, such as MeLi, with the (*R,R*)-*bis*-imine **6** in THF, were not encouraging, complex mixtures of diastereomeric products being obtained. However, by changing the reaction solvent to diethyl ether we observed smooth double addition of PhMgCl or MeMgBr to **6** to give a major diastereomeric product in each case (eq. 2).[9]



The stereochemistry of the products **7** and **8** was not readily assigned by NMR, but recrystallisation of **7** from petroleum ether gave crystals suitable for an X-ray structure determination, the result of which is shown in Fig. 1a.[10]

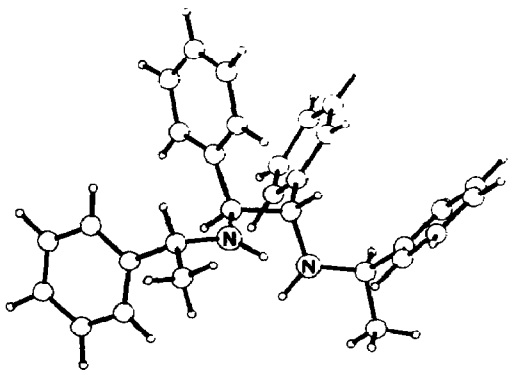


Figure 1a

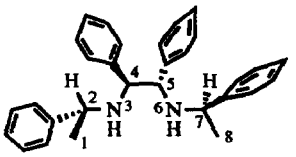


Figure 1b

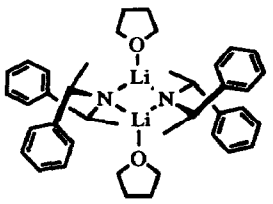
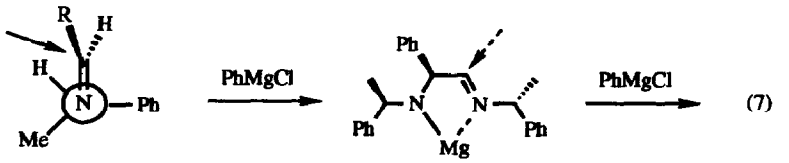


Figure 1c

The structure clearly shows the stereochemical outcome indicated in Fig. 1b, with the molecule adopting a roughly C_2 symmetric conformation in which each diethylamine portion (i.e. atoms 1–5 or 4–8) lies in a zig-zag (or W-type) array, with a staggered arrangement of the phenyl groups. The conformation of each

diethylamine portion is remarkably similar to that found recently in the crystalline dimer of lithium amide **4**, Fig. 1c.[11] Roughly the same conformation has also been observed in amine salts related to **4**,[6,12] as well as in one other dimeric lithium amide,[12] and in rationalisation of the asymmetric dihydroxylation chemistry mediated by diamine **1** an analogous staggered arrangement of aromatic groups was invoked.[2] Clearly, the arrangement shown is strongly favoured in this family of compounds. Although we have not proved the stereochemistry for the methyl-substituted analogue **8**, the assignment seems reasonable, based on the similar solvent effects seen in the organometallic additions to *bis*-imine **6** and our mechanistic rationale presented below.

We have based our explanation for the selective formation of **7** on the Cram or Felkin-Anh type model invoked by Yamamoto and Ito to explain the diastereoselectivity observed in the addition of benzylic Grignard reagents to α-imino esters derived from α-methylbenzylamine.[13] Initial addition of PhMgCl to conformer **9** is expected from the least hindered face, the stereoselectivity in the second addition presumably being enforced by both a 1,3-effect and a 1,2-effect (from the newly established asymmetric centre) in a chelated intermediate **10**.[14]



(9) (10)

Although, as noted above, this product stereochemistry is opposite to that proposed for the major product shown in eq. 1, a swap-over in stereochemical outcome on changing from allylmagnesiums to other types of Grignard reagent is well precedented in this type of imine addition reaction.[13] Therefore, the present work and the previous report of Neumann and coworkers should not be irreconcilable.

To date we have not examined the possible applications of diamine **7** in great detail, although initial results employing the dilithium diamide derivative as a chiral base give promising results (comparable or superior results to those with base **4**). The ease of synthesis of **7** from α-methylbenzylamine, which is very cheaply available in either enantiomeric form, makes it arguably the most readily available homochiral C_2 symmetric vicinal diamine to date.[15]

Acknowledgements

We are grateful to the Science and Engineering Council and Lilly Research UK for support of KB under the CASE scheme.

References and Footnotes

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9. The actual ratio of isomeric products obtained from this reaction seems to depend upon the rate of addition of the Grignard reagent (hence the need for syringe pump addition and careful monitoring of the solution temperature). Examination of the ^{1}H NMR spectrum of a crude reaction mixture from PhMgCl addition showed *ca.* 10% of an impurity tentatively assigned to another diastereomer. In the case of MeMgBr addition, the reaction is less selective, giving minor amounts (up to about 30%) of two other products, which have not been fully characterised.

   Preparation of diamine **7**: To a stirred solution of the starting *bis*-imine **6**[16] (8g, 0.03 mol) in Et_2O (100 ml) at -70°C under a nitrogen atmosphere was added by syringe pump over a period of 1h, PhMgCl (60.6 ml of a 2M solution in THF, 0.12 mol). A white precipitate formed immediately, and the mixture was then allowed to warm to room temperature over a period of 5h and then stirred for a further 2h. The mixture was then cooled to 0°C and quenched by the addition of a saturated aqueous solution of NH_4Cl (70 ml), and the organic product extracted into EtOAc (3 x 60 ml). The combined organic extract was dried ($MgSO_4$), the solvent removed under reduced pressure, and the involatile residue subjected to flash column chromatography (5% Et_2O : 95% light petroleum) to give a pale yellow solid which was recrystallised from light petroleum to give diamine **7** as large colourless crystals (6g, 47%), m.p. 119–122°C, $[\alpha]_D^{28}$ +205 (*c* 0.7 in $CHCl_3$) (Found: C, 85.7; H, 7.79; N, 6.57. $C_{30}H_{32}N_2$ requires C, 85.67; H, 7.67; N, 6.66%); ν_{max} ($CHCl_3$)/cm^{-1} 3313, 2925, 2859, 1948, 1808, 1601, 1492, 1453, 1359, 1110, 909 and 863; δ_H (250 MHz, $CDCl_3$) 1.26 (6H, d, *J* 6), 2.24 (2H, br.s, 2 x NH), 3.37 (2H, s), 3.40 (2H, q, *J* 6) and 6.92–7.25 (20H, m); δ_C (67.8 MHz) 25.2 (CH_3), 54.9 (CH), 65.7 (CH), 126.6 (CH), 127.8 (CH), 127.9 (CH), 128.3 (CH), 141.5 (C) and 145.5 (C); *m/z* (FAB) 421 (M+H, 17%). Analytically pure diamine **8** was prepared similarly, and isolated as a colourless oil $[\alpha]_D^{28}$ +128 (*c* 0.84 in $CHCl_3$).
10. Crystal data for **7**: Orthorhombic, a = 9.095(2), b = 14.403(1), c = 18.997(3) Å, space group P2, 2, 2. R =0.0544 for 1725 observed reflections. Full data deposited with Cambridge Crystallograpic Data Centre.
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14. A similar outcome is seen in reactions of α-amino imines, see Reetz, M. T.; Jaeger, R.; Drewlies, R.; Hübel, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 103.
15. Other syntheses are longer or involve less readily available starting materials. For the best alternatives see reference 14, and (a) Nantz, M. H.; Lee, D. A.; Bender, D. M.; Roohi, A. H. *J. Org. Chem.* **1992**, *57*, 6653. (b) Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 999. Simpler analogues of **7** and **8**, having R = H, are also very readily prepared, see Horner, L.; Dickerhof, K. *Liebigs Ann. Chem.* **1984**, 1240.
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