High Diastereoselectivity in the Reaction of α-Aminonitriles bearing an (*S*)-(+)-2-Methoxymethylpyrrolidine Group with Grignard Reagents

Nicole Maigrot, Jean-Paul Mazaleyrat,* and Zoltan Welvart

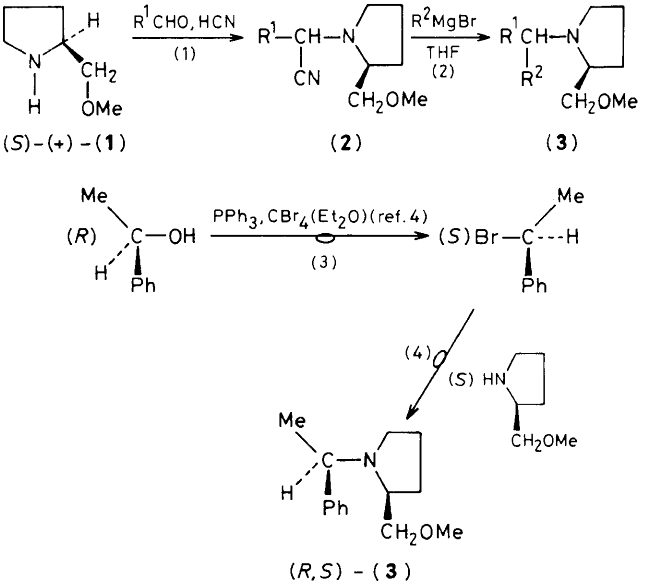
Groupe de Recherche n^o 12, CNRS, 2, rue H. Dunant, 94320 Thiais, France

(*S*)-(+)-2-Methoxymethylpyrrolidine induces high diastereoselectivities (80% diastereoisomeric excess) in the reaction of α-aminonitriles with Grignard reagents.

Natural (*S*)-proline and its derivatives are widely used as auxiliary reagents in asymmetric synthesis.[1,2] We report here our preliminary results which show that (*S*)-(+)-2-methoxymethylpyrrolidine (**1**),[2] incorporated as the amino group of α-aminonitriles (**2**), induces a high diastereoselectivity in the reaction of these compounds with Grignard reagents (Bruylants reaction[3]).

(*S*)-(+)-2-Methoxymethylpyrrolidine (**1**), reacts with various aldehydes and hydrocyanic acid to give two diastereoisomeric α-aminonitriles (**2**) [reaction (1)], which after reaction with a Grignard reagent lead to a mixture of two diastereoisomeric amines (**3**) [reaction (2)].

In order to determine the absolute configuration of the amines (**3**) (R^1 = Me, R^2 = Ph), we used reactions (3) and (4) which both involve inversion of configuration. Thus, starting from (*R*)-(+)-α-phenylethanol (optical purity 55%),[5] the major isomer (**3**) obtained must have the (*R*,*S*) configuration.†



The results obtained in reactions (1) and (2) are reported in Table 1 and show the following. i, The formation of the α-aminonitriles (**2**) [reaction (1)] is highly stereoselective; one isomer is largely predominant whatever the R^1 group (Table 1, exps. 1 and 2). This selectivity may result, at least for R^1 = Ph, from thermodynamic control: when the 90:10 mixture of

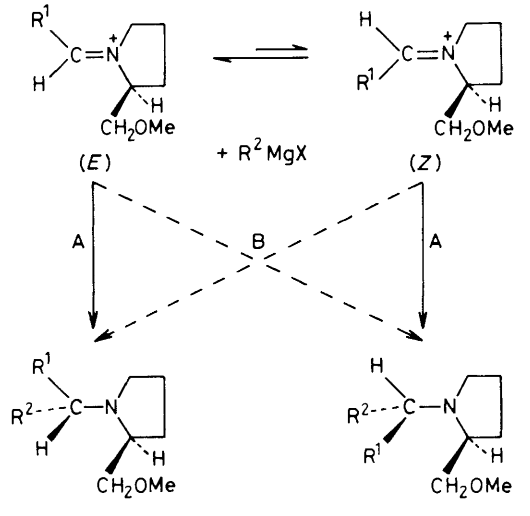
---

† The crude product from reaction (3) was treated with an excess of (*S*)-(+)-2-methoxymethylpyrrolidine, in benzene at room temperature for 24 h, leading to a diastereoisomeric mixture of amines (*R*,*S*)-(**3**):(*S*,*S*)-(**3**) 65:35, with 10% overall yield. The observed enrichment in the isomer (*R*,*S*)-(**3**) could be due to kinetic resolution of the enantiomerically impure bromide in reaction (4); however we ruled this out by starting with racemic α-phenylethanol, which after the same reaction sequence leads to an equimolecular mixture (*R*,*S*)-(**3**):(*S*,*S*)-(**3**) 50:50 (10% yield).

Table 1. The results obtained from reaction (1) and (2).

Exp.	R^1	R^2	Aminonitrile (**2**) (diastereoisomeric ratio)	Amine (**3**) Yield (%)[d]	Amine (**3**) $(R,S):(S,S)$[e]
1	Me	Ph	90 : 10[a,c]	88	10 : 90
2	Ph	Me	90 : 10[a,c]	89	90 : 10
3	Ph	Me	63 : 35[b,c]	60	90 : 10

[a] Prepared from (*S*)-(+)-2-methoxymethylpyrrolidine, by treatment with the corresponding aldehyde R^1CHO and hydrocyanic acid [R^1 = Me (ref. 6): 94% yield; $t_{0.07\,\mathrm{mm}}$ 45 °C. R^1 = Ph: 73% yield; $t_{0.1\,\mathrm{mm}}$ 100 °C]. [b] Obtained by reaction of a 90 : 10 mixture of (**2**) with lithium di-isopropylamide in THF (−78 °C), followed by protonation with water. [c] Determined by gas chromatography (column SIL SC, 10 m) and/or by ^1H n.m.r. spectroscopy. For R^1 = Ph, the OMe singlets corresponding to the two isomers appear at δ 3.38 (major) and δ 3.08 (minor); the Cα–H singlets appear at δ 5.55 (major) and δ 5.17 (minor). For R^1 = Me, only one OMe singlet is visible at δ 3.32. [d] Relative to the aminonitrile (**2**), which was stirred overnight at room temperature, with a large excess of Grignard reagent in THF. Acid base extraction led to pure samples of amines (**3**). The two isomers (**3**) can be separated by gas chromatography (column SIL SC 26.7 m) and have analytical and spectral data in agreement with the reported structures. [e] The diastereoisomeric ratio is determined by gas chromatography and/or ^1H n.m.r. spectroscopy. The OMe singlet appears at δ 3.13 for (*R,S*)-(**3**) and at δ 3.37 for (*S,S*)-(**3**). The optical rotations of the mixtures are $[\alpha]^{25}_{546}$ −74.5° (*c* 1; abs. EtOH) for (*R,S*) : (*S,S*) 10 : 90 and −28° for (*R,S*) : (*S,S*) 90 : 10, which allow the calculation of the absolute rotations $[\alpha]_{546}$ of the pure diastereoisomers (*R,S*)-(**3**) : −22°; (*S,S*)-(**3**) : −80°.



(**3**) (major) (**3**) (minor)

Scheme 1. A, Main attack of R^2MgX at the less hindered side (back). B, Main attack of R^2MgX at the more hindered side (front).

aminonitriles (**2**) (R^1 = Ph) resulting from reaction (1) is stirred with LiOD in D_2O–tetrahydrofuran (THF) at room temperature for 24 h, the recovered aminonitrile is fully deuteriated at the Cα position, showing that equilibration has occurred, and the mixture of isomers is still in the same ratio 90 : 10. ii, The Grignard reaction (2) also shows a similar high selectivity (which results from kinetic control); the isomer (*S,S*)-(**3**) is largely predominant when R^1 = Me, R^2 = Ph (diastereoisomeric excess, d.e., 80%) whereas the isomer (*R,S*)-(**3**) is the major product (d.e. 80%) when R^1 = Ph, R^2 = Me. Thus, the ratio of the two amines may be reversed by an appropriate choice of the order of introduction of the R^1 and R^2 groups (Table 1, exps. 1 and 2). It should also be noted that the diastereoselectivity of reaction (2) is independent of the diastereoisomeric ratio of the aminonitrile (Table 1, exps. 2 and 3).

The simplest rationalization of our stereochemical results concerning the Grignard reaction (2), is depicted in Scheme 1. According to this scheme, the high diastereoselectivity results not only from the selective addition of the nucleophile R^2MgX at the less hindered side of the $C{=}N^+$ double bond, but also from the predominant formation of the more stable iminium ion of configuration (*E*).

Iminium ions were previously proposed as intermediates in the Bruylants reaction,[7] in the formation of α-aminonitriles,[8] and may be involved in other reactions in which asymmetric induction occurs.[9,10]

Similar schemes, showing the important role of the geometry of the double bond in asymmetric induction were previously proposed for the reduction of aldimines[11] and for the conjugate addition of Grignard reagents to chiral α,β ethylenic esters.[12] The double bond geometry must also be an important factor in the high induction observed in the addition of organometallics to chiral arylsulphinylcyclopentenones.[13]

The diastereoselectivity observed here, induced by (*S*)-2-methoxymethylpyrrolidine, demonstrates the possibility of high asymmetric inductions by chiral amines in Grignard reactions involving iminium ion intermediates. We are investigating further the usefulness of these types of reactions in asymmetric synthesis.

Received, 30th September 1983; Com. 1303

References

1 S. Yamada, K. Hiroi, and K. Achiwa, *Tetrahedron Lett.*, 1969, 4233; S. Yamada and G. Otani, *ibid.*, p. 4237; D. Enders and H. Eichenauer, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 397; 1976, **15**, 549; H. Eichenauer, E. F. Friedrich, W. Lutz, and D. Enders, *ibid.*, 1978, **17**, 206; M. Kolb and J. Barth, *ibid.*, 1980, **19**, 725; T. Mukaiyama, *Tetrahedron*, 1981, **37**, 4111.

2 D. Enders and H. Eichenauer, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 549; D. Seebach, H. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nüssler, H. Oei, and M. Schmidt, *Helv. Chim. Acta*, 1977, **60**, 301.

3 P. Bruylants, *Bull. Soc. Chim. Belg.*, 1924, **33**, 467; 1926, **35**, 139.

4 D. Brett, I. M. Downie, J. B. Lee, and M. H. F. Matough, *Chem. Ind. (London)*, 1969, 1017.

5 J. P. Vigneron and J. Jacquet, *Tetrahedron*, 1976, **32**, 939; we are grateful to Dr. D. Cabaret for the gift of a sample.

6 D. Enders and H. Lotter, *Tetrahedron Lett.*, 1982, 639.

7 G. Chauviere, B. Tchoubar, and Z. Welvart, *Bull. Soc. Chim. Fr.*, 1963, 1423; D. Cabaret, G. Chauviere, and Z. Welvart, *ibid.*, 1969, 4463.

8 H. G. Reiber and J. Erway, *J. Am. Chem. Soc.*, 1950, **72**, 1881; J. Taillades and A. Commeyras, *Tetrahedron*, 1974, **30**, 127; 2493; 3407.

9 J. D. Morrison and H. S. Mosher, 'Asymmetric Organic Reactions,' Prentice Hall, Englewood Cliffs, New Jersey, 1971, p. 328 and references therein.

10 H. P. Husson, *Bull. Soc. Chim. Belg.*, 1982, **91**, 985.

11 J. P. Charles, H. Christol, and G. Solladié, *Bull. Soc. Chim. Fr.*, 1970, 4439.

12 D. Cabaret and Z. Welvart, *J. Organomet. Chem.*, 1974, **80**, 185.

13 G. H. Posner, J. P. Mallamo, M. Hulce, and L. L. Frye, *J. Am. Chem. Soc.*, 1982, **104**, 4180.