# Auxiliary-controlled diastereoselection by *N*-(1-phenylethyl) in Grignard additions to 2-*O*-benzylglyceraldehyde imines†

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**Grignard reagents add to 2-*O*-benzylglyceraldehyde *N*-(1-phenylethyl)imines in high yield at normal or high pressure (12 kbar); *threo vs. erythro* selectivity is governed by the (*R*)- or (*S*)-1-phenylethyl substituent.**

Stereoselective access to disubstituted 2-amino alcohols has become of prime importance with regard to efficient syntheses of hydroxy amino acids such as statine and congeners[1] or 3-phenylisoserine.[2] We have proposed the use of glyceraldehyde imines to that purpose, adding the requisite substituent to the C=N bond,[3–6] complementary to the common approach from amino acid derivatives.[1–3] This was based on the finding that *N,O*-dibenzylglyceraldimines add organometallic reagents RM at room temperature.[3] The stereoselectivity of this process was shown to depend on the structure of R, the solvent, and the metal cation employed. With Grignard compounds in diethyl ether, moderate to high *threo* selectivity was found (*cf.* Table 1), while $CeCl_3$ addition reversed this.[3] We now report that chiral *N*-auxiliaries (*R*)- and (*S*)-1-phenylethyl dramatically affect the diastereoselection and rate of this process. This was unexpected in view of previous results[7] of allyl additions to α- and β-alkoxyimines with a chiral *N*-auxiliary,[7a] and of related work.[8] The imines **2**–**4**‡ were prepared from 2-*O*-benzylglyceraldehyde **1**[9] and the respective amine in the presence of alumina.[10] Additions were carried out as described for the *N*-benzyl derivatives.[3] A selection of these results is given in Table 1.‡,§

With the benzhydryl imine **2**, increased *threo* formation was found, as compared to results with the *N*-benzyl substrate[3] (Table 1, entries 1,2). This led us to conclude that the more bulky *N*-substituent was responsible for this effect. However, from the (*R*)-(1-phenylethyl)imine **3** even higher proportions of *threo* diastereoisomers were observed (entries 3–9): methyl and phenyl groups were now accepted with diastereoisomeric ratios (dr) > 9 : 1 (runs 3,8), and butyl with 99 : 1 (run 4); in the crude products from *iso*-butyl, *tert*-butyl and trimethylsilylmethyl additions the *erythro* isomer was not detected (entries 5–7). Analogous reactions of methyl or butyl Grignard reagents with the (*S*)-imine **4** gave the *erythro* diastereoisomers predominantly (dr *ca.* 1 : 9, entries 10, 11), with complete conversion after less than 3 days. On the other hand, Grignard reagents with a branched alkyl group (such as *iso*-butyl, *tert*-butyl and trimethylsilylmethyl) gave rise to *ca.* 7, 50 and 5% conversion, respectively (entries 12–14). In these cases, however, high pressure (12 kbar, 50–54 °C) proved beneficial: this led to complete consumption of the imine substrate and to formation of the expected amino diols, along with minor amounts of a cyclization product (an aziridine, see runs 12–14).¶

As seen with *N*-benzylimines,[3] addition to **3** and **4** also occurred smoothly with a number of alkyl and aryl lithium reagents, with somewhat improved, albeit still moderate selectivity (see runs 16, 17 in Table 1).[11]

In order to rationalize the above phenomenon, *i.e.* auxiliary-control overriding 'substrate' induction, *N*-(1-phenylethyl)imines of 2-*O*-benzyllactaldehyde were likewise treated with several Grignard compounds.[12] In these cases, substituting *N*-benzyl by (*R*)- or (*S*)-1-phenylethyl led to slight changes with respect to the consistent *threo* preference only,[11,12] as exemplified for butylmagnesium bromide additions: the *N*-benzyl derivative gave 69% of amino diol adducts with a *threo* to *erythro* ratio of 93 : 7;[3] with the (*R*)- and (*S*)-(1-phenylethyl)imines products with a dr of > 95 : 5 (53%) and > 90 : 10 (16%) were observed. With butyllithium, similar results were recorded (dr ≥ 9 : 1 in all three cases).[12]

**Table 1** Addition of organometallic reagents to *N*-benzhydryl and *N*-(1-phenylethyl) substituted glyceraldehyde imines **2**–**4**

| Entry | Imine | RM | Product | Yield (%) | **5(7,9) : 6(8,10)**[a] *threo/erythro* | *N*-Bn[3] *threo/erythro* |
|---|---|---|---|---|---|---|
| 1 | **2** | BuMgBr | **5b/6b** | 94 | 78 : 22 | 73 : 27 |
| 2 | **2** | BnMgBr | **5g/6g** | 73 | 83 : 17 | 40 : 60 |
| 3 | **3** | MeMgBr | **7a/8a** | 67 | 92 : 8 | 63 : 37 |
| 4 | **3** | BuMgBr | **7b/8b** | 86 | 99 : 1 | 73 : 27 |
| 5 | **3** | Bu$^i$MgBr | **7c/8c** | 98 | > 99 : 1 | 88 : 12 |
| 6 | **3** | Bu$^t$MgCl | **7d/8d** | (47)[b] | > 99 : 1 | 56 : 44 |
| 7 | **3** | $Me_3SiCH_2MgCl$ | **7e/8e** | 80 | > 99 : 1 | 84 : 16 |
| 8 | **3** | PhMgBr | **7f/8f** | 90 | 91 : 9 | 76 : 24 |
| 9 | **3** | BnMgBr | **7g/8g** | 81 | 85 : 15 | 40 : 60 |
| 10 | **4** | MeMgBr | **9a/10a** | 95 | 6 : 94 | see above |
| 11 | **4** | BuMgBr | **9b/10b** | 82 | 14 : 86 | see above |
| 12 | **4** | Bu$^i$MgBr | **9c/10c** | < 7[b]; 81[c] | —[b]; 6 : 94 | see above |
| 13 | **4** | Bu$^t$MgCl | **9c/10c** | (49)[b]; 67[c] | 8 : 92[b]; < 5 : 95[c,d] | see above |
| 14 | **4** | $Me_3SiCH_2MgCl$ | **9e/10e** | < 5[b]; 41[c] | —[b]; 24 : 76[d] | see above |
| 15 | **4** | BnMgBr | **9g/10g** | 96 | 67 : 33 | see above |
| 16 | **3** | MeLi | **7a/8a** | 79 | 77 : 23 | 46 : 54 |
| 17 | **4** | MeLi | **9a/10a** | 83 | 22 : 78 | see above |

[a] Diastereoisomeric ratios (dr) are taken from $^1H$ and $^{13}C$ NMR analyses of crude reaction products and in some cases (entries 1–8, 17) also from HPLC analysis. [b] Percentage conversion for entries 6, 12, 13 and 14, after 5, 3, 4 and 3 d, respectively; crude products still containing imine. [c] High pressure reaction in diethyl ether, 12 kbar, 50–54 °C, 16–19 h; as a byproduct, 15% (with **10d**) and 26% (with **9e/10e**) of the respective aziridine was found.[11,¶] [d] Not corresponding to dr of the primary addition, since altered by partial, subsequent aziridine formation.[11,¶]

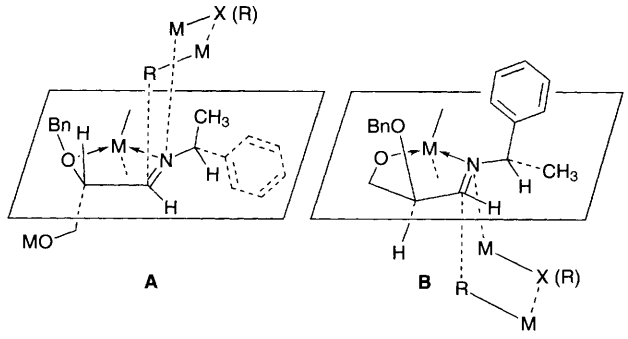
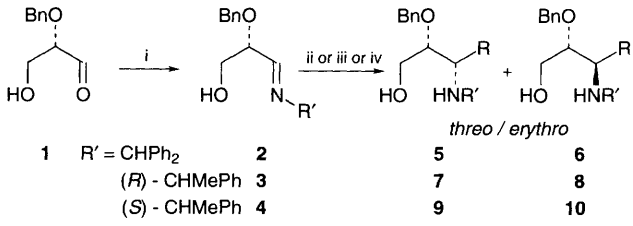



**Fig. 1** Intermediate chelate structures **A** and **B**




| | | | | |
|---|---|---|---|---|
| **1** | R' = $CHPh_2$ | **2** | **5** | **6** |
| | (*R*) - CHMePh | **3** | **7** | **8** |
| | (*S*) - CHMePh | **4** | **9** | **10** |

**Scheme 1** *Reagents and conditions*:‡,§ i, $Al_2O_3$ (neutral, activity 1, 63–200 μm, E. Merck), $R'NH_2$ (1.0 equiv.), 1 h, 25 °C, quantitative yield of **2–4**; ii, RMgX (4 equiv.), diethyl ether, 0 → 25 °C, 12 h–3 d, then $NH_4Cl$–$H_2O$; iii, RMgX (4 equiv.), 12 kbar, 25 → 50–54 °C, 16–19 h; iv, 2.5 RLi (2.5 equiv.), −78 → 25 °C

*A priori*, the (Grignard) additions to the *N*-(1-phenylethyl)-imines **3** and **4** are expected to form diastereoisomer mixtures that reflect the net directing effect of both stereogenic units present, *i.e.* 1,2-induction from the group at C-2 plus or minus 1,3-induction from the respective *N*-(1-phenylethyl) moiety. This may be correlated with the many examples of *inter*molecular reactions of two chiral (separate) species, that comply with factual $\Delta\Delta G^{\ddagger}$ additivity ('match–mismatch' relationship).[13,14] The $\Delta\Delta G^{\ddagger}$ values of the above imine reactions (*cf.* Table 1) do show a trend of this kind (passing from results with **3**, *via* the *N*-benzyl cases, to drs obtained with **4**), but the fit is far from good. Apparently, with **3** and **4** the auxiliary-controlled 1,3-induction largely overrules the 1,2-induction from the aldehyde substrate, in contrast to the results of allylmetal additions to *N*-(1-phenylethyl)imines of other alkoxy aldehydes.[7a,‖] This is not satisfactorily explained by any one of the chelate intermediates proposed so far.[4,15,16] On the basis of the above results, and on consideration of respective π-face accessibility, the competing chelate structures **A** [from (*R*)-(1-phenylethyl)imine **3**, favouring *threo*] and **B** [from (*S*)-(1-phenylethyl)imine **4**, favouring *erythro*] are proposed as intermediates.[15,16] The respective pathways are ultimately differentiated by the conformation of the 1-phenylethyl group, depicted as the one known to be preferred in related systems (due to allylic 1,3-strain).[17] A detailed discussion of this issue will be given in the full account of this work.

Although, clearly, further mechanistic studies are warranted,** facile access to amino diols—of structural variety, of both *erythro* and *threo* configuration, in either enantiomer series—is provided herewith. The utility of this concept in synthesis is demonstrated with simple routes to statine and related hydroxy amino acids.[18]

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## Footnotes

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‡ Structures and configurations of the compounds prepared were confirmed by spectroscopic data, elemental analyses and several crystal structures of derived tetrahydro-1,3-oxazin-2-ones, *cf.* ref. 3,11. *Selected data* for **2**: $[\alpha]_D^{20}$ −48.7 (*c* 1.62). For **3**: $[\alpha]_D^{20}$ +5.0 (*c* 1.34). For **4**: $[\alpha]_D^{20}$ −108 (*c* 1.51). All were colourless oils; [α] measured in $CHCl_3$.

§ *Selected data* for **7c**: $[\alpha]_D^{20}$ +134 (*c* 1.50). For **7e**: $[\alpha]_D^{20}$ +102 (*c* 1.50). For **10d**: $[\alpha]_D^{20}$ −56.2 (*c* 1.55). All were colourless oils.

¶ The structure of the *cis*-aziridine obtained with **9e**/**10e** was secured by X-ray analysis; it was also isolated in 84% yield from the reaction of **9e** and Grignard reagent as above at 12 kbar (1 bar = $10^5$ Pa), 54°C.[11]

‖ On allyl additions to 2-*O*-MOM-lactaldimines, drs of 86:14, 79:21 and 70:30 were obtained for *N*-substituents (*R*)-(1-phenylethyl), *iso*-propyl and (*S*)-(1-phenylethyl), respectively. Additions to 3-*O*-MOM-butyraldimines gave ratios of 62:38, 15:85 and 8:92.[7a]

** The slow reactions of **3** and **4** with Grignard compounds seem ideal for monitoring by NMR spectroscopy, *cf.* ref. 16. So far, experiments with methylmagnesium bromide have proved inconclusive.[11]

## References

1 S. Thaisrivongs, *Ann. Rep. Med. Chem.*, 1994, **29**, 133.
2 Review: K. C. Nicolaou, W.-M. Dai and R. K. Guy, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 15.
3 T. Franz, M. Hein, U. Veith, V. Jäger, E.-M. Peters, K. Peters and H. G. von Schnering, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1298.
4 Y. Kobayashi, T. Matsumoto, Y. Takemoto, K. Nakatani, Y. Ito, T. Kamijo, H. Harada and S. Terashima, *Chem. Pharm. Bull.*, 1991, **39**, 2550; F. L. van Delft, M. de Kort, G. A. van der Marel and J. H. van Boom, *Tetrahedron: Asymmetry*, 1994, **3**, 2261.
5 *Cf.* use of iminium salts: S. Kano, Y. Yuasa, T. Yokomatsu and S. Shibuya, *J. Org. Chem.*, 1988, **53**, 3865; J.-i. Yamada, H. Satô and Y. Yamamoto, *Tetrahedron Lett.*, 1989, **30**, 5611; W.-J. Koot, R. van Ginkel, M. Kranenburg, H. Hiemstra, S. Louwrier, M. J. Moolenaar and W. N. Speckamp, *Tetrahedron Lett.*, 1991, **32**, 401; M. Nagai, J. J. Gaudino and C. S. Wilcox, *Synthesis*, 1992, 163.
6 Addition of RM to optically active, enolizable imines, see ref. 3, 4, 7. For recent papers see, for example: T. Fujisawa, M. Nagai, Y. Koike, M. Koike and M. Shimizu, *J. Org. Chem.*, 1994, **59**, 5865; L. Cippola, L. Lay, F. Nicotra, C. Pangrazio and L. Panza, *Tetrahedron*, 1995, **51**, 4679.
7 (*a*) Y. Yamamoto, T. Komatsu and K. Maruyama, *J. Chem. Soc., Chem. Commun.*, 1985, 814; (*b*) *Cf.* methyl cuprate additions to (*S*)-(1-phenylethyl)imines of achiral aldehydes: C. Boga, D. Savoia and A. Umani-Ronchi, *Tetrahedron: Asymmetry*, 1990, **1**, 291; (*c*) additions to imines of chiral 2-amino alcohols: M. A. Scialdone and A. I. Meyers, *Tetrahedron Lett.*, 1994, **41**, 7533; use of β-alkoxy hydrazines: D. Enders, J. Schankat and M. Klatt, *Synlett*, 1994, 795; (*d*) additions to α-imino esters: D. J. Hallett and E. J. Thomas, *J. Chem. Soc., Chem. Commun.*, 1995, 657; (*e*) use of glyoxal-*bis*[(1-phenylethyl)imine]: K. Bambridge, M. J. Begley and N. S. Simpkins, *Tetrahedron Lett.*, 1994, **35**, 3391.
8 Chiral *N*-auxiliaries in other additions to imines: H. Waldmann, *Synthesis*, 1994, 535; G. I. Georg and Z. Wu, *Tetrahedron Lett.*, 1994, **35**, 381; N. Moss, J. Gauthier and J.-M. Ferland, *Synlett*, 1995, 142; S. Laschat and H. Kunz, *Synlett*, 1990, 629; R. Hamilton, B. Walker and B. J. Walker, *Tetrahedron Lett.*, 1995, **36**, 4451.
9 V. Jäger and V. Wehner, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 469.
10 F. Texier-Boullet, *Synthesis*, 1985, 679.
11 U. Veith, Dissertation, Universität Stuttgart, 1995.
12 V. Jäger, M. Hein and S. Leurs, unpublished results.
13 S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1.
14 Intramolecular cases: R. Müller, T. Leibold, M. Pätzel and V. Jäger, *Angew. Chem.*, 1994, **106**, 1305; *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1295, and examples cited therein.
15 R. A. Volkmann, in *Comprehensive Organic Synthesis*, eds. B. M. Trost and I. Fleming, Pergamon, Oxford, 1991, vol. 1, p. 355; Y. Yamamoto, S. Nishii, K. Maruyama, T. Komatsu and W. Ito, *J. Am. Chem. Soc.*, 1986, **108**, 7778; M. T. Reetz, R. Jaeger, R. Drewlies and M. Hübel, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 103.
16 M. T. Reetz, *Acc. Chem. Res.*, 1993, **26**, 462.
17 M. Klein, U. Wingen and V. Buss, *J. Am. Chem. Soc.*, 1987, **109**, 6486; R. W. Hoffmann, *Chem. Rev.*, 1989, **89**, 1841.
18 N. Meunier, U. Veith and V. Jäger, *J. Chem. Soc. Chem. Commun.*, following paper.

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