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1,13 and 1,14 Asymmetric Induction: Remote Control

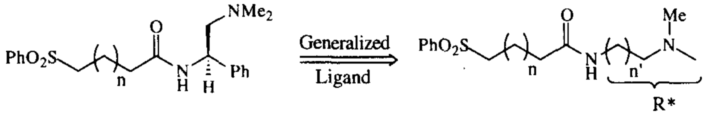
Nicholas Magnus and Philip Magnus

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712

Abstract: Treatment of the acyclic sulfones **6** (n = 1, 2, 3 and 4) with *n*-BuLI/THF/-100°C followed by PhCHO gave only two diastereomeric β-hydroxysulfones **7**. The selection of two out of a possible four diastereomers is observed even though the chiral inducing entity is 10, 11, 12 and 13 atoms from the reaction locus. These results represent the illustration of long range asymmetric induction (LAI) controlled by supramolecular interactions. © 1997 Elsevier Science Ltd.

Recently, we have discovered some long-range asymmetric induction (LAI) reactions that operate over as many as nine achiral connecting atoms to give predominantly one diastereomer of a possible four. Furthermore, through systematically increasing the distance between the chiral auxiliary and the reaction locus, we observed an alternating behavior in the diastereoselectivity.[1,2]

The best substrate (to-date) has been **1**, which for n = 2, gave very high diastereoselectivity when the derived dianion was treated with PhCHO. The stereogenic inducing center in **1** is adjacent to the *sec*-amide. A more generalized version of this ligand involves changing the number of atoms between the *sec*-amide and the terminal *tert*-amine, and varying the position of the stereogenic center within the ligand, as shown in **3**, **Eqn 1**.



Eqn 1

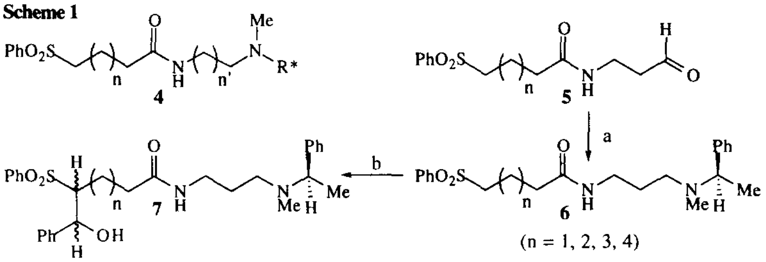
1 (n = 1, 2, 3 and 4)

3 (n = 1, 2, 3 and 4, n' = 1, 2 etc)

A simple variation is placement of the chiral auxiliary on the terminal nitrogen atom (*exo*-ligand) as depicted in **4**, **Scheme 1**. Through changes in n and n' some insights into inter- and intramolecular coordination leading to enhancements of diastereoselectivity at specific distances from the *sec*-amide linker might be forthcoming.

The series of aldehydes **5** (n = 1, 2, 3 and 4)[3] were reductively aminated with R(+) *N*-methyl-α-methylbenzylamine/$NaCNBH_3$/MeOH to give **6** (n = 1, 2, 3 and 4). The stereogenic carbon atom is 10, 11, 12 and 13 atoms respectively from the carbon atom adjacent to the $-SO_2Ph$ group. Treatment of each sulfone **6** (n = 1, 2, 3 and 4) with *n*-BuLi (2.2 equiv)/THF/-70°C, followed by cooling to -100°C, and addition of benzaldehyde gave **7** (n = 1, 2, 3 and 4).

Scheme 1



Conditions:- a) R(+) *N*-methyl-α-methylbenzylamine/NaCNBH$_3$/MeOH, **5** (40-50%).
b) *n*-BuLi/THF/-70°, cooled to -100°C/PhCHO.

Our previous results suggest that all four diastereomers should be formed, with a preference for the *erythro* (syn) pair. Consequently, we were surprised to find that in all cases of **7** (n = 1, 2, 3 and 4) we only observed one *erythro*- and one *threo*-diastereomer![4] ^{1}H NMR (crude product mixture) shows the PhC<u>H</u>(OH)-proton as a broad singlet for the *erythro* diastereomer, whereas in the *threo* diastereomer it appears as a doublet (J = 6-8 Hz).[5] **Figure 1**, shows this region of the ^{1}H NMR spectrum for **7** (n = 3, crude product). Conducting the above reactions (**6** into **7**) in the presence of excess LiCl (or HMPA) gave all four diastereomers of **7** (**A**:**A'**, 2:1, and **AA'**:**BB'**, 0.9:1).[6] **Figure 2**, shows the appearance of the other *erythro* diastereomer (PhC<u>H</u>OH singlet), and the other *threo* diastereomer. Decoupling one of the protons adjacent to the -SO$_2$Ph group collapsed the major *threo* doublet and revealed the other wing of the minor *threo* isomer, **Figure 3**.

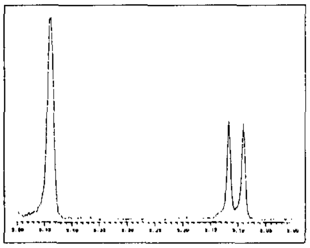


Fig. 1. 7 (n = 3), two-PhC<u>H</u>OH

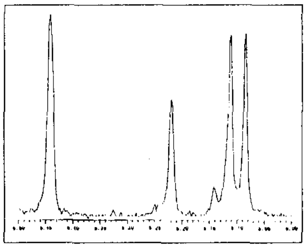


Fig. 2. 7 (n = 3), four PhC<u>H</u>OH

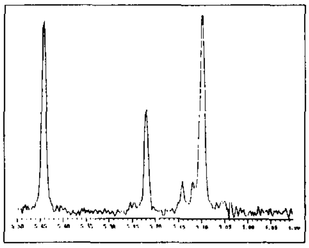
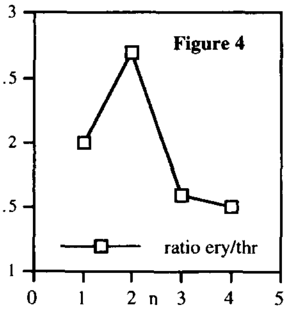
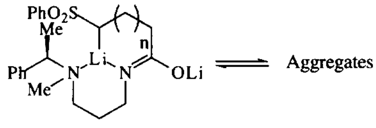


Fig. 3. 7 (n = 3), decoupled PhSO$_2$C<u>H</u>.



Consequently, we can be certain that in the absence of LiCl (or HMPA) only *two* of the four possible diastereomers of **7** are formed. The same holds true for the other homologs of **7** (n = 1, 2 and 4). **Figure 4** shows a plot of the *erythreo*:*threo* ratio as a function of n.

The remarkably long-range asymmetric induction (LAI) is operating as far as 1,13 and 1,14 for the case where n = 4. Supramolecular interactions of the intermediate dilithio species, either intramolecular or intermolecular (or both) must be responsible for the effective transmission of stereochemical information over such great distances.[7,8] We favor a bicyclic chelate such as **8** which positions the chiral auxiliary 1,3 to the C-Li



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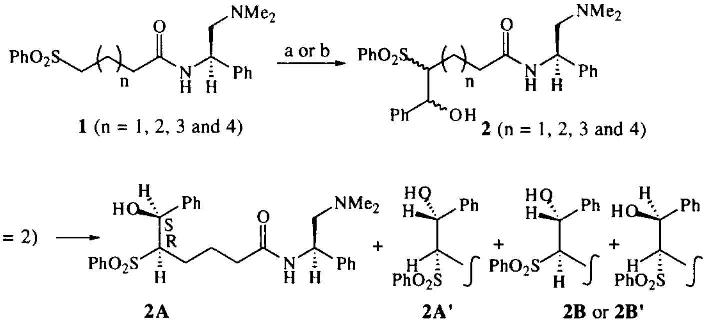
bond.[9] Dissociation of the chelate by LiCl or HMPA would be expected to reduce selectivity.[10] While these results show that it is possible to selectively obtain one pair of the possible two pairs of diastereomers, it should now be reasonable to modify the chiral inducing auxiliary to further favor the *erythro* isomer.

Acknowledgment. The National Science Foundation, Welch Foundation and Merck Frosst are thanked for their support of this research.

References and Footnotes

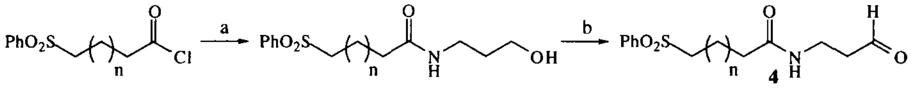
1. Linnane, P.; Magnus, N.; Magnus, P. *Nature* **1997**, *Vol 385*, 799. For example, for **1**, the n = 1 series did not show any notable stereoselectivity, whereas the n = 2 series exhibited dramatic diastereoselective enhancements. The ratio of the *erythro*-isomers **2A** and **2A'** is (2.2:1) in THF, and changes to 9:1 when HMPA (2.2 eq) is present. The amounts of *threo*-isomers **2B** and **2B'** was reduced such that the **2AA':2BB'** ratio changes from 2.7:1 in THF to 10:1 with HMPA (2.2 eq) additive. These effects disappear in the next homologous series n = 3, but are restored when n = 4; **2A:2A'** (4.5:1) (HMPA, 2.2 eq) and **2A/A':2B/B'** (5.5:1) (HMPA, 2.2 eq).



Conditions:- a) THF (0.1M in substrate)/2.2 equiv *n*-BuLi/0.5h/5.0 equiv PhCHO/-70°C.
b) THF (0.1M in substrate)/2.2 equiv *n*-BuLi/0.5h/2.2 equiv HMPA/0.5h/5.0 equiv PhCHO/-70°C.

2. For examples of "Long-Range Asymmetric Induction" (LAI) reactions see:- Magnus, P.; Frost, C.; Linnane, P.; Spyvee, M. *Tetrahedron Lett.* **1996**, *37*, 9139. McNeill, A. H.; Thomas, E. J. *Tetrahedron Lett.* **1990**, *31*, 6239. McNeill, A. H.; Thomas, E. J. *Tetrahedron Lett.* **1992**, *33*, 1369. Hallett, D. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1995**, 657 and references therein. Paetow, M.; Ahrens, H.; Hoppe, D. *Tetrahedron Lett.* **1992**, *33*, 5323. Beak, P.; Du, H. *J. Am. Chem. Soc.* **1993**, *115*, 2517. Mears, R. J.; Whiting, A. *Tetrahedron Lett.* **1993**, *34*, 8155. Molander, G. A.; Bobbitt, K. L. *J. Am. Chem. Soc.* **1993**, *115*, 7518. Molander, G. A.; Haar, Jr. J. P. *J. Am. Chem. Soc.* **1993**, *115*, 40. Zhang, H-C.; Harris, B. D.; Maryanoff, C. A.; Maryanoff, B. E. *Tetrahedron Lett.* **1996**, *37*, 7897. Denmark, S. E.; Marble, L. K. *J. Org. Chem.* **1990**, *55*, 1984. Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788.

3. The aldehydes **4** (n = 1, 2, 3 and 4) were made by the sequence of reactions below.



Conditions:- a) $H_2N(CH_2)_3OH$ (5 eq)/CH_2Cl_2/0°C, 100%. b) Dess-Martin periodane.

4. While we can assign relative stereochemistry (^{1}H NMR) to the newly formed stereogenic centers, we do not know their absolute stereochemistry. Even given the information in reference 1, it would be premature to hazard an educated guess based on the bicyclic chelate model.

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10. If we use racemic **6** (n = 3) in the dianion/PhCHO reaction, we obtained two diastereomers **7** in the same ratio (ca. 1.5:1) as in the enantiomerically enriched series. This can be viewed as circumstantial evidence for an intramolecular chelate, rather than an aggregate.

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