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REAGENT CONTROL IN THE ALDOL ADDITION OF CHIRAL BORON ENOLATES BASED ON THE 2,5-DIPHENYLBOROLANE LIGAND SYSTEM

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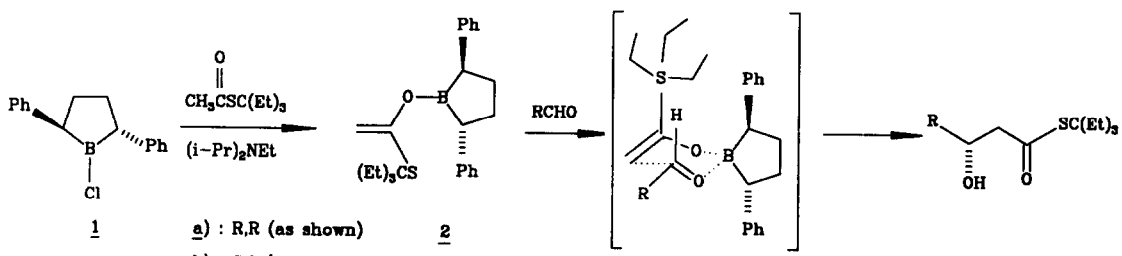
Summary: Thioesters can be O-borylated using optically active chloro-2,5-diphenylborolane to produce chiral boron enolates which show complete reagent control in aldol additions to chiral α-amino aldehydes.

Several versions of the "chiral acetate" have been developed for enantioselective aldol additions of enolates derived from acetic acid[1-3]. We have previously shown that the optically active chloro-borolane 1 can be utilized in the in situ preparation of boron enolates which in turn react enantioselectively with aldehydes[4]. Best results were obtained in the case of the boron enolates 2 which react via transition state 3 to form the aldol adducts 4 with ee-values of 92 to > 95 %[4,5]. Thus, enantioselectivity of 2 is a little higher than that of the 2,5-dimethyl analog[6].

In this communication we demonstrate reagent control[7] in the addition of 2 and its prochiral methyl derivative 11 to chiral α-amino aldehydes 5/8.



1

a) : R,R (as shown)
b) : S,S (opposite config.)

2

3a

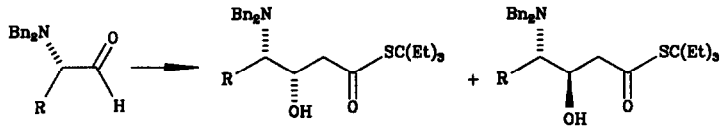
(3b : opposite config.)

4a

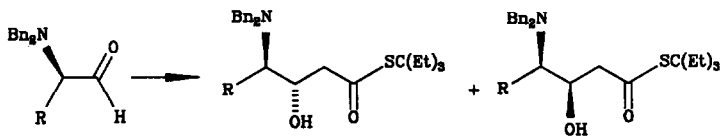
(4b : opposite config.)

Upon reacting pure R,R-configurated reagent 2a with the S- and R-configurated aldehydes 5a and 8a[8], the ratio of diastereomers 6a : 7a and 9a : 10a turned out to be 28 : 1 and 27 : 1, respectively (Table 1)[9]. Thus, in both cases the sense and extent of stereoselectivity at the newly created carbinol C-atom are the same, and in fact comparable to those observed in reactions of simple aldehydes (cf. 4a). This indicates complete reagent control and suggests that the chiral centers in the aldehydes 5a and 8a have little or no influence on the course of the reaction. Such a finding is

surprising, since N,N-dibenzyl protected α-amino aldehydes react highly stereoselectively with other C-nucleophiles such as Li-enolates, enolsilanes/$MgCl_2$, RLi, RMgX and $RTi(OiPr)_3$ to form adducts with 90-99 % non-chelation control[8]. In the present context such control should favor diastereomers 7a and 9a, which would then constitute the mismatched and matched cases, respectively. The above unexpected results also pertain in the case of aldehydes 5b and 8b, which were reacted with the S,S-reagent 2b (Table 1).



5 a) R = $PhCH_2$ 6 a) R = $PhCH_2$ 7 a) R = $PhCH_2$
b) R = Me_2CHCH_2 b) R = Me_2CHCH_2 b) R = Me_2CHCH_2



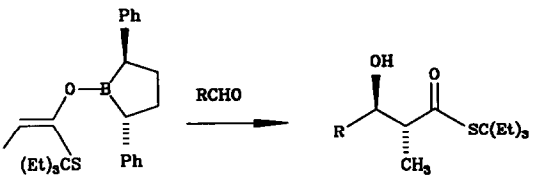
8 a) R = $PhCH_2$ 9 a) R = $PhCH_2$ 10 a) R = $PhCH_2$
b) R = Me_2CHCH_2 b) R = Me_2CHCH_2 b) R = Me_2CHCH_2

Table 1. Stereoselective Aldol Additions

Aldehyde	Reagent	Yield	Diastereomer ratio
5a	2a (R,R)	50	6a : 7a = 28 : 1
8a	2a (R,R)	65	9a : 10a = 27 : 1
5b	2b (S,S)	85	6b : 7b = 1 : 15
8b	2b (S,S)	80	9b : 10b = 1 : 14

In order to gain some insight into the phenomenon behind the above data, we reacted aldehyde 5a with the achiral boron enolates having diethyl and 9-BBN substituents. These reactions led to 6a : 7a ratios of 1 : 1 and 1 : 2, respectively. This contrasts with the reaction of the achiral Li-enolate from the same thioester, which affords a product ratio of 6a : 7a = 1 : 9, in line with non-chelation control observed in similar reactions[8]. Thus, the unexpected inherent stereorandom behavior of achiral boron enolates in reactions with N,N-dibenzyl amino aldehydes allows for complete reagent control in the chiral series of enolates 2. The readily accessible Braun Reagent[1], currently one of the most efficient chiral acetate synthons known, adds to N-BOC protected S-amino aldehydes to produce 11:1 diastereomeric mixtures (matched case), whereas the mismatched case (R-amino aldehydes) leads to 3:1 diastereomer ratios[10].

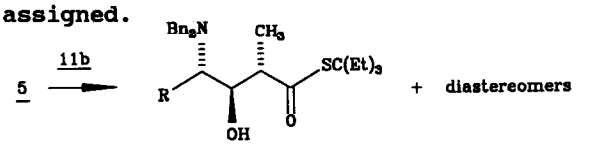
Upon reacting the prochirally pure enolate 11a (prepared from the thiopropionic acid ester using 92 - 93 % enantiomerically pure 1a), essentially one diastereomer 12 (anti : syn > 155 : 1) was obtained, the corrected ee-values being in the range 94 - 100 %. The latter values are thus a little lower than those observed for the analogous 2,5-dimethyl system[6], although the difference may be due to the analytical procedures used[11].



11 a) R,R (as shown)
b) S,S

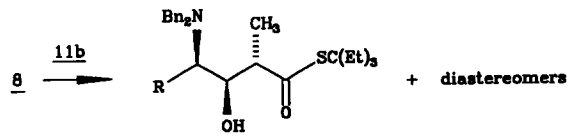
12 a) R = n-hexyl : 36% (ee = 100%)
b) R = i-propyl : 82% (ee = 99%)
c) R = t-butyl : 68% (ee = 94.3%)
d) R = cyclohexyl : 58% (ee = 98.7%)

In a final series of experiments, reagent control was tested in the reaction of enantiomerically pure 11b with the amino aldehydes 5 and 8, in which up to four diastereomeric products are possible. In all cases essentially only one product 13 or 14 was observed, simple diastereoselectivity being anti and the configuration of the carbinol C-atom being dictated by the absolute configuration of the reagent 11b. The configuration of traces of side products was not assigned.



13

a) R = $PhCH_2$ >46 : <1 : 0 : 0
b) R = Me_2CHCH_2 >130 : 1.5 : 1 : 0



14

a) R = $PhCH_2$ 76 : 3 : 1 : 0
b) R = Me_2CHCH_2 14 : 1 : 0 : 0

In summary, the 2,5-diphenylborolane ligand system in chiral boron enolates such as 2 and 11 is highly effective in aldol additions of simple aldehydes. In the case of chiral aldehydes such as 5 and 8 complete reagent control is possible, so that the (formal) chelation or non-chelation controlled aldol adducts are accessible, depending upon the absolute configuration of the reagent. On the negative side, borylating agents of the type 1 (and the 2,5-

dimethyl analog)[6] require an antipode separation, in contrast to those based on naturally occurring chiral auxiliaries[1,2,10]. However, detailed theoretical interpretations of stereoselectivity are likely to be easier in the case of C_2-symmetric ligands such as those presented here and elsewhere[6].

Acknowledgments

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References and notes

1. Review: M. Braun, Angew. Chem. 99 (1987) 24; Angew.Chem.Int.Ed.Engl. 26 (1987) 24.

2. R.O. Duthaler, P. Herold, W. Lottenbach, K. Oertle, M. Riedecker, Angew. Chem. 101 (1989) 490; Angew.Chem.Int.Ed.Engl. 28 (1989) 495.

3. S.G. Davies, Pure Appl. Chem. 60 (1988) 13.

4. M.T. Reetz, F. Kunisch, P. Heitmann, Tetrahedron Lett. 27 (1986) 4721; M.T. Reetz, Pure Appl. Chem. 60 (1988) 1607.

5. We have extended the list[4] of aldehydes tested; data for 4a: R = n-hexyl (78% yield, ee 95%); isobutyl (92% yield, ee > 95%); isopropyl (72% yield, ee 92%); cyclohexyl (87% yield, ee 95%). All reactions were carried out in CH_2Cl_2: borylation using pure 1a[4] at -40°C/5h and aldol additons at -78°C/15h. Determination of absolute configuration and of ee values: see lit[4,6].

6. S. Masamune, T. Sato, B.M. Kim, T.A. Wollmann, J.Am.Chem.Soc. 108 (1986) 8279; R.P. Short, S. Masamune, Tetrahedron Lett. 28 (1987) 2841.

7. S. Masamune, W. Choy, J.S. Petersen, L.R. Sita, Angew.Chem. 97 (1985) 1; Angew.Chem.Int.Ed.Engl. 24 (1985).

8. M.T. Reetz, M.W. Drewes, A. Schmitz, Angew.Chem. 99 (1987) 1186; Angew.Chem.Int.Ed.Engl. 26 (1987) 1141.

9. Typical procedure: To a solution of 178 mg (0.7 mmol) of 1a in 4 ml of dry CH_2Cl_2 at -40°C is added 72 mg (0.4 mmol) of thio-acetic acid S-3-(3-ethyl)-pentyl ester followed by 0.09 ml (0.5 mmol) of diisopropylamine. After 4-5 h the mixture is cooled to -78°C, 0.4 mmol of an amino aldehyde in 2 ml of CH_2Cl_2 are added and the mixture is stirred at -78°C overnight and finally at room temperature for a day. The mixture is treated with a buffer solution (pH 7), extracted several times with ether and dried over Na_2SO_4. Following removal of the solvents, the crude product is analyzed by HPLC and then purified by flash chromatography (pet. ether (40-60)/ether: 30:1). The configurational assignment was made, inter alia, by reduction of the aldol products to the diol with $LiAlH_4$ and comparison with known compounds.

10. R.M. Devant, H.E. Radunz, Tetrahedron Lett. 29 (1988) 2307; P.G.M. Wuts, S.R. Putt, Synthesis 1989, 951.

11. Masamune et al[6] used NMR shift reagents on the acylated aldol adducts to determine the ee values. In our hands this led to higher values (by 4-5%) than the use of R-1-phenylethyl-isocyanate (W. Pereira, Anal. Lett. 3 (1970) 23) on the aldol products followed by HPLC analysis of the carbamates.

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