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Diastereofacial Selectivity in the 1,3-Dipolar Cycloaddition of Chiral Azomethine Ylides

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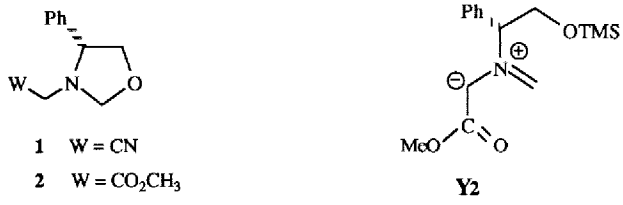
*Abstract : Diastereofacial stereoselectivity in the cycloaddition of azomethine ylides obtained from N-methoxycarbonylmethyloxazolidine **4** with N-phenylmaleimide is studied relative to R^1 and R^2 groups borne by the chiral auxiliary moiety.*

We recently described a new methodology for the facile generation of a chiral azomethine ylide from *N*-cyanomethyl-4-phenyloxazolidine **1** and *N*-methoxycarbonylmethyl-4-phenyloxazolidine **2**[4]. In reactions with *N*-phenylmaleimide as dipolarophile, **1** gave four cycloadducts whereas **2** underwent formation of only two compounds (ratio ~ 1:1) in 85% yield. The stereochemistry of these compounds was explained by an *exo* attack on each side of the stabilized U-shaped ylide $\mathbf{Y}_2$, derived from **2** (fig. 1), without facial stereoselectivity.



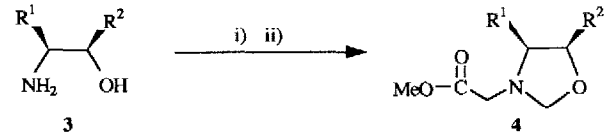
1 W = CN
2 W = CO_2CH_3

Y2

Figure 1

Studies on diastereofacial selectivity for 3 + 2 cycloaddition of chiral azomethine ylides have not received very much attention[1-4].

We were then prompted to investigate other chiral auxiliaries with the aim of improving the stereoselectivity. We undertook a systematic study with various *N*-methoxycarbonylmethyl oxazolidines **4a-e** (Table 1). These oxazolidines **4a-e** were prepared in two steps : *N*-alkylation of amino alcohols **3a-e**[5] with methyl bromoacetate (1.05 eq) in THF in the presence of iPr_2NEt (1.1 eq) was followed by condensation with paraformaldehyde in refluxing toluene (method A) or bromomethyl methyl ether at room temperature for 1 h (method B) (Table 1).



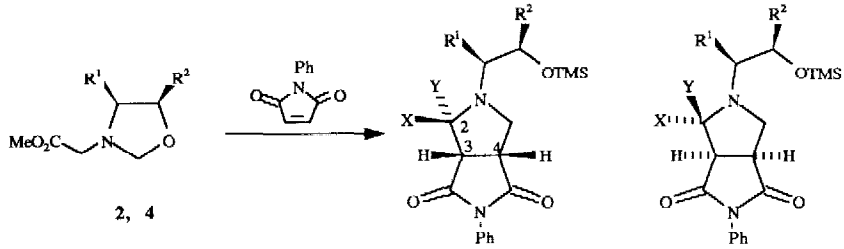
Reagents : i) $BrCH_2CO_2CH_3$, iPr_2NEt, THF, r.t.,15h. ii) Method A : $(CH_2O)_n$, toluene, Δ, 1h.
Method B : $BrCH_2OCH_3$, iPrNEt, THF, r.t., 1h.

	R^1	R^2	method	overall yield (%)	$[\alpha]_D^{20}$	(c, solvent)
4a	Ph	Ph	A	67	-(*)	
4b	iPr	H	B	62	+12	(c 2.5, $CHCl_3$)
4c	CH_2Ph	H	B	65	-13	(c 4, $CHCl_3$)
4d	H	Ph	A	36	-(*)	
4e	CH_3	Ph	A	59	-33	(c 1.2, $CHCl_3$)

(*) racemic aminoalcool was used as starting material

Table 1 : Preparation of oxazolidines 4 from aminoalcohols 3.

Cycloadditions were performed with *N*-phenylmalcimide using our standard procedure[4] (1.2 eq TMSOTf, 1.3 eq *N*-phenylmaleimide, 2 eq iPr_2NEt, -78°C, 4 h) to give, as expected, two cycloadducts in good overall yields. Examination of the stereochemistry of cycloadducts[6] showed that reaction with oxazolidines **4a-c** gave the two *exo*-adducts **5** and **7** with no facial diastereoselectivity (Table 2)[7]. This may be explained by the remote position of the chiral center which cannot interact with dipolarophile in this cycloaddition mode.



5 (exo) X = H, Y = CO_2Me **7** (exo)
6 (endo) X = CO_2Me, Y = H **8** (endo)

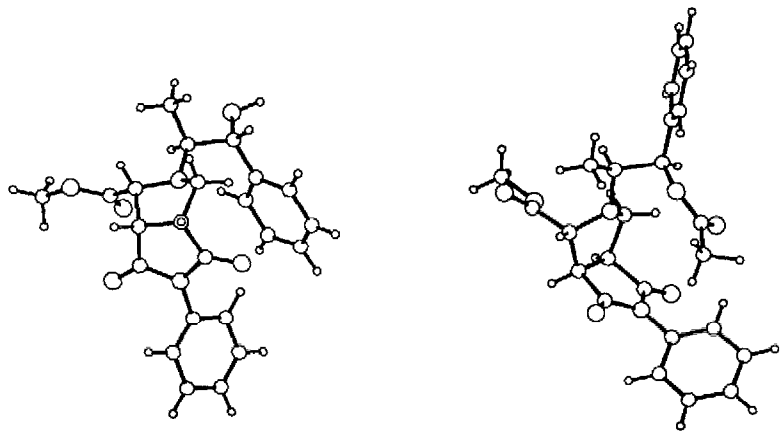
	R^1	R^2	overall yield (%)	**5** (%)	**6** (%)	**7** (%)	**8** (%)	d.e.
2(*)	Ph	H	85	52		48		4
4a	Ph	Ph	72	52		48		4
4b	iPr	H	66	51		49		2
4c	CH_2Ph	H	71	55		45		10
4d	H	Ph	62	39			61	>95
4e	CH_3	Ph	72	42			58	>95

Table 2 : Cycloaddition of oxazolidine 4 with *N*-phenylmaleimide in standard conditions (TMSOTf, iPr_2NEt, CH_2Cl_2, -78°C, 4h).

(*) R-(-)-phenylglycinol was used as starting material : the absolute configuration does not correspond with the stereochemistry shown above.

In contrast, oxazolidines **4d** and **4e** gave both *exo* and *endo* additions with excellent diastereoselectivity (table 2).

In these latter two cases the NMR data were insufficient to determine which pair of isomers had been formed among the four possible diastereomers. An X-ray analysis [8] of compounds **9** and **10** derived from the cycloaddition of **4e** established their stereochemistry demonstrating the formation of compounds **5e** and **8e**. These products might arise from an *exo* (**5e**) and an *endo* (**8e**) mode on the same face of the ylide thus with complete diastereoselectivity.



9 **10**

Figure 2 : Crystal structures of **9** (obtained from **5e**) and **10** (from **8e**)

This result was quite surprising and may be explained by stereochemically identical cycloaddition as in previous cases followed by an epimerization α to the ester group of **7** to **8**. However this possibility was rather unlikely because of the very high stability of compounds **5a-c** or **7a-c** in the reaction medium (no epimerization was observed after 1 week at room temperature).

It seems more reasonable to explain this result by both *endo* and *exo* cycloadditions. It has been shown that the *endo* mode is usually favoured for this type of ylide while the *exo* addition arises from increased bulk of the nitrogen substituent[9]. Then it may be considered that when large R^1 groups are present on the ylide the *exo* mode predominates without facial selectivity (**2**, **4a-c**) whereas when R^1 = H or CH_3 (**4d** and **4e**) an *endo* cycloaddition becomes possible and a complete diastereoselectivity is observed.

Despite a modest *endo/exo* ratio, the total diastereofacial stereoselectivity observed constitutes an unprecedented result in 3 + 2 cycloadditions using chiral azomethine ylides[1] encouraging us to continue our efforts in this field.

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5. Commercially available S-(+)-valinol (**3b**), S-(-)-phenylalalinol (**3c**) ; (1R,2S)-norephedrine (**3e**) and racemic 1-phenyl-2-aminoethanol (**3d**) were used. Racemic cis-1,2-diphenyl 2-aminoethanol (**3a**) was obtained by catalytic hydrogenation of benzoin oxime followed by recrystallization in EtOH according to Saigo, K.; Ogawa, S.; Kikuchi, S. *Bull. Chem. Soc. Jpn* **1982**, *55*, 1568.

6. The stereochemistry of each cycloadduct was determined by ^{1}H NMR at 250 MHz with the help of 2D correlation techniques (COSY HH, XH) on the separated derivatized alcohols obtained by desilylation (citric acid in MeOH). As an example data for alcohols derivatized from **5b** and **7b** are as follows : alcohol from **5b** : $(\alpha)_D^{20}$ = -65 (c 1.4, $CHCl_3$) ; ^{1}H NMR (400MHz, $CDCl_3$) : 0.9 (d, J=7Hz, 3H, CH_3), 0.95 (d, J=7Hz, 3H, CH_3), 1.65 (m, 1H, H-8), 2.5 (m, 1H, H-6), 3,.0 (dd, J=7Hz, 9Hz, 1H, H-5), 3.25 (t, J=7,5Hz, 1H, H-4), 3.4 (d, J=9Hz, 1H, H-5), 3,.45 (t, J=8Hz, 1H, H-3), 3.65 (s, 3H, OCH_3), 3.7 (m, 2H, 2H-7), 4.2 (d, J=8Hz, 1H, H-2), 7.2 à 7.4 (m, 5H, H arom) ; ^{13}C NMR ($CDCl_3$) : 20.5 (2 CH_3), 28.0 (C-8), 43.8 47.2 (C-3, C-4), 48.4 (C-5), 52.0 (OMe), 60.9 (C-7), 63.1 66.4 (C-6, C-2), 126.6 128.7 129.2 132.0 (C arom), 170.7 176.0 178.2 (C=O).
Alcohol from **7b** : $(\alpha)_D^{20}$ = +36 (c 0.5; $CHCl_3$) ; ^{1}H NMR (250MHz, benzene) : 0.75 (d, J=7Hz, 3H, CH_3), 0.95 (d, J=7Hz, 3H, CH_3), 1.7 (m, 1H, H-8), 2.6 (m, 1H, H-6), 2.65 (dd, J=7.5Hz, 9Hz, 1H, H-5), 2.8 (t, J=7, 5Hz, 1H, H-4), 3.2 (t, J=8, 5Hz, 1H, H-3), 3.55 (t, J=10Hz, 1H, H-7), 3.65 (d, J=9Hz, 1H, H-5), 3.7 (s, 3H, OCH_3), 3.75 (dd, J=4Hz, 10Hz, 1H, H-7), 4.1 (d, J=8,5Hz, 1H, H-2), 7.35-7.6 (m, 5H, H arom) ; ^{13}C NMR ($CDCl_3$) : 19.7 (CH_3), 22.2 (CH_3), 27.6 (C-8), 44.0 (C-4), 47.2 (C-3,C-5), 52.6 (OCH_3), 59.9 (C-7), 64.5 66.5 (C-6, C-2), 126.4 128.7 129.1 131.7 (C arom), 171.4 176.4 177.2 (C=O).

7. The ratio of diastereomers was determined by ^{1}H and ^{13}C NMR on the crude reaction mixture.

8 Suitable crystals were obtained for compound **9** (after desilylation of **5e**) and **10** (after desilylation of **8e** followed by acetylation). Crystal data for **9** : $C_{23}H_{24}O_5N_2$; M = 408.46, orthorhombic $P2_12_12_1$; a = 9.765(5), b = 10.884(6) , c = 19.947(8) Å , V =2120Å^3, d_c = 1.28 gcm^{-3}, λ(MoKα) = 0.7107 Å. 4098 Philips diffractometric registered reflexions of which 2145 unique. Least-squares refinement, R = 0.0453 for 1774 observed reflexions with I ≥ 3σ(I). **10** : $C_{25}H_{26}N_2O_6$; M = 450.49, orthorhombic, $P2_12_12_1$; a = 7.030(4), b = 15.271(8), c = 21.285 (9)Å, V = 2285 Å^3, dc = 1.31 gcm^{-3}, λ(MoKα) = 0.7107 Å 4284 Philips diffractometric registered reflexions of which 2316 unique ; least-squares refinement, R = 0.0429 for 1681 observed reflexions with I ≥ 3σ(I).

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