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1,3-DIPOLAR CYCLOADDITION REACTIONS OF AZOMETHINE YLIDES ON ENANTIOMERICALLY PURE (E)-γ-ALKOXY-α,β-UNSATURATED ESTERS.

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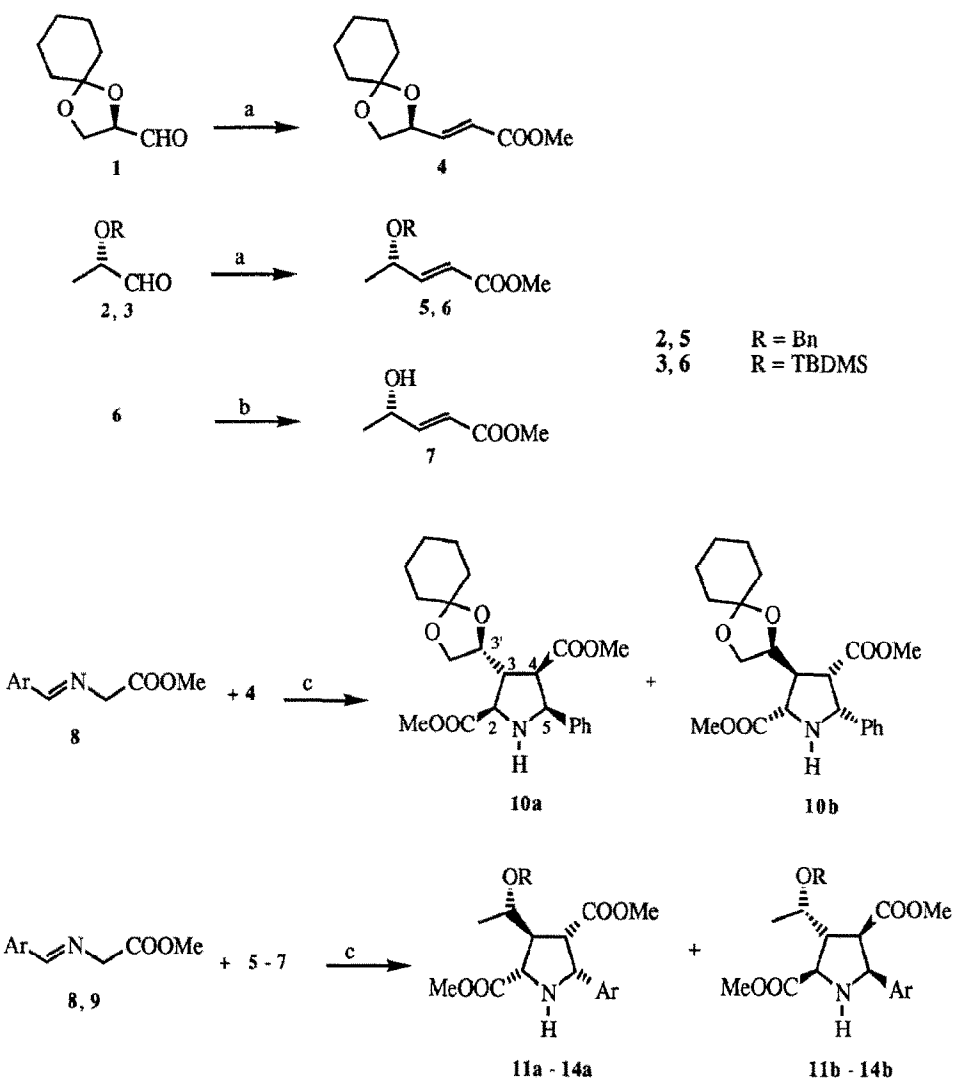
Abstract. Enantiomerically pure (E)-γ-alkoxy-α,β-unsaturated esters were reacted with azomethine ylides obtained from glycine imines in the presence of LiBr and diazabicycloundecene (DBU), to afford tetrasubstituted pyrrolidines with complete regiocontrol and fair to excellent diastereoselectivity (only two diastereoisomers formed in up to 96: 4 diastereoisomeric ratio). The results are compared with those of other 1,3-dipolar cycloadditions, and the origin of stereocontrol is discussed.

1,3-Dipolar cycloaddition reactions to alkenes have found wide synthetic application in organic chemistry, as they open access to polyfunctionalized five-membered heterocyclic rings, often in a highly regio- and stereoselective fashion. [1] Among the variety of 1,3-dipoles avaliable, the chemistry and stereochemistry of nitrone [1,2] and nitrile oxide [1,3] cycloadditions has been more intensively investigated, with particular focus on the variant of these reactions that secures control of the absolute stereochemistry of the products. [1,2,4] In the course of our studies [4] on the influence exerted by an allylic stereocenter on a chiral alkene to promote stereocontrolled nitrone and nitrile oxide cycloaddition, [5] we were able to test the validity of the model proposed by Houk [6] to rationalize the stereochemical outcome of these reactions. In view of the growing importance of azomethine ylide cycloadditions [1,7] for the assembly of biologically relevant heterocycles, we become interested in determining whether the factors ruling nitrile oxide and nitrone reactions to chiral alkenes could also be exploited to promote the stereoselection of an azomethine ylide cycloaddition. [8,9] The possibility of stereocontrolling the simultaneous formation of four stereocenters seemed a reasonable prize for this study. Here we present some experimental data obtained for the intermolecular reaction of azomethine ylides with (E)-γ-alkoxy-α,β-unsaturated esters, that nicely complement recent work by Kanemasa, *et al.* [8]

Scheme 1.



8 Ar = Ph
9 Ar = p-$MeOC_6H_4$
11 Ar = Ph; R = Bn
12 Ar = Ph; R = TBDMS
13 Ar = Ph; R = H
14 Ar = p-$MeOC_6H_4$; R = Bn

Reagents. a) $(MeO)_2POCH_2COOMe$, THF, NaH, -30°C; b) **6**, $Bu_4NF.3H_2O$, THF, r.t.;
c) LiBr, DBU, THF, -78°C.

Starting from (R)-O,O-cyclohexylideneglyceraldehyde **1**, (S)-O-benzyllactaldehyde **2** and (S)-O-t-butyldimethylsilyllactaldehyde **3**, (E)-(S)-esters **4-6** were prepared; [10] compound **7** was obtained from **6** via desilylation (Scheme 1). The esters were then reacted in different conditions with glycine-derived azomethine ylides **8** and **9**, generated in THF solution from the corresponding imines [11] with DBU in presence of lithium bromide. [7b] In each case a single regioisomer [1,7a] and only two diastereoisomers were obtained from the reaction mixture. No by-products were detected, only unreacted esters being isolated, together with the cycloadducts, by flash chromatography. Yields and diastereoisomeric ratios, as determined by proton NMR spectroscopy on the purified products, are collected in Table 1.

As can be seen from the experimental data, an increase in the reaction temperature caused a marked decrease in the diastereoisomeric ratio. The molar ratio between the reactants played a minor role in the outcome of the cycloaddition. With a 3:1 ylide: alkene ratio the chemical yields were slightly better than those observed with a 1:1 ratio in the case of lactaldehyde derivatives, while the diastereoisomeric ratios were almost unchanged. The glyceraldehyde-derived alkene **4** on the other hand exhibited a different behavior, the chemical yield decreasing and the diastereoisomeric ratio increasing on passing from a 1:1 to a 3:1 molar ratio. The cycloaddition reaction was also performed on ester **7** and was shown to proceed with low chemical yield but good selectivity. Differently substituted aryl groups on the dipole, when not sterically more demanding than a phenyl, [12] did not change significantly the yield and the diastereoselectivity of the reaction. The cycloadducts **14**, that containes a p-methoxy-phenyl substituent, are suitable for subsequent useful synthetic transformations.

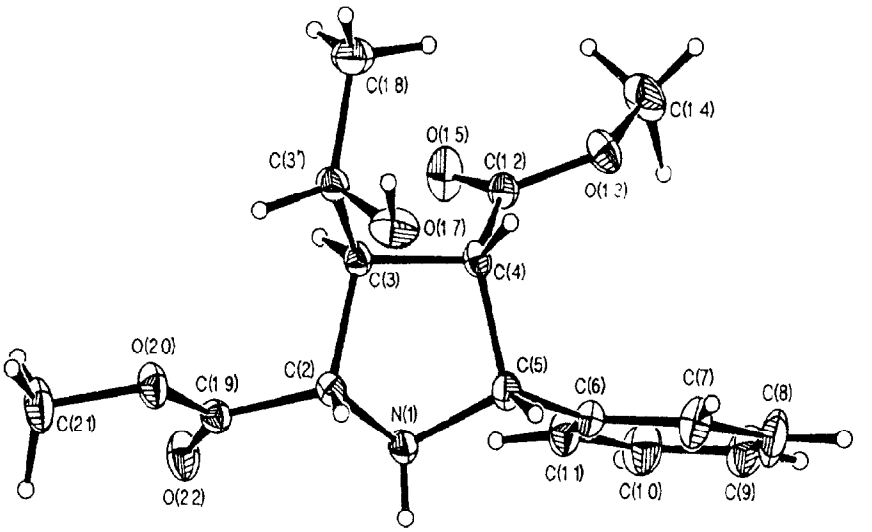
Table 1. Diastereoselective synthesis of pyrrolidines **10-14** from esters **4-7.** [a]

entry	ester	imine	products	dipole/alkene ratio	yield%	diastereoisomeric ratio **a/b**
1[b]	**4**	**8**	**10a,b**	1:1	39	75:25
2	**4**	**8**	**10a,b**	1:1	56	90:10
3	**4**	**8**	**10a,b**	3:1	40	95: 5
4	**5**	**8**	**11a,b**	1:1	40	78:22
5	**5**	**8**	**11a,b**	3:1	58	77:23
6	**6**	**8**	**12a,b**	1:1	65	90:10
7	**6**	**8**	**12a,b**	3:1	77	88:12
8	**7**	**8**	**13a,b**	1:1	24	96: 4
9	**5**	**9**	**14a,b**	1:1	52	79:21

a) all reactions performed at -78°C in THF as solvent.

b) reaction performed at room temperature.

Figure 1. An ORTEP plot of **13a**. The thermal ellipsoids are shown at 20% of probability level. Bond lengths in Å, bond and torsion angles in degrees.



N(1)-C(5)	1.470(4)	N(1)-C(2)	1.460(4)	C(2)-C(4)	1.565(4)
C(3)-C(4)	1.543(4)	C(2)-C(3)	1.542(2)	C(5)-C(6)	1.514(4)
C(4)-C(12)	1.504(4)	C(3)-C(3')	1.523(5)	C(2)-C(19)	1.510(4)
C(3')-O(17)	1.422(4)				

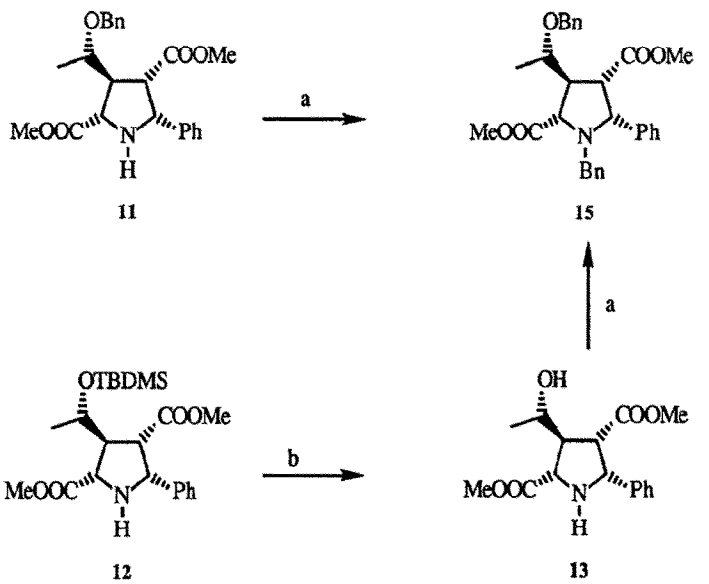
C(2)-N(1)-C(5)	104.3(2)	N(1)-C(5)-C(4)	102.7(2)
N(1)-C(5)-C(6)	113.5(3)	C(4)-C(5)-C(6)	115.4(2)
C(5)-C(4)-C(3)	105.1(2)	C(5)-C(4)-C(12)	112.2(2)
C(3)-C(4)-C(12)	113.0(2)	C(2)-C(3)-C(4)	103.4(2)
C(4)-C(3)-C(3')	113.1(2)	C(2)-C(3)-C(3')	114.1(2)
C(3)-C(2)-N(1)	103.4(2)	C(3)-C(2)-C(19)	112.5(2)
N(1)-C(2)-C(19)	111.6(2)	C(3)-C(3')-O(17)	106.8(3)

C(2)-N(1)-C(5)-C(4)	-42.2(3)	C(2)-N(1)-C(5)-C(6)	-167.4(2)
N(1)-C(5)-C(4)-C(3)	21.5(3)	N(1)-C(5)-C(4)-C(12)	-101.7(3)
C(5)-C(4)-C(3)-C(2)	5.5(3)	C(5)-C(4)-C(3)-C(3')	129.5(3)
C(4)-C(3)-C(2)-N(1)	-31.0(3)	C(4)-C(3)-C(2)-C(19)	-151.5(2)
C(3)-C(2)-N(1)-C(5)	46.5(3)	C(4)-C(3)-C(3')-O(17)	-56.7(3)

The structural assignment of diastereoisomers **10 a,b-14 a,b** was not a trivial accomplishment at all. The W-shaped dipole [7] and the (E)-geometry of the alkene, together with the complete regioselectivity of the cycloaddition, allow in principle the formation of four diastereoisomers, while only two were experimentally detected in all cases. The problem can be divided into two parts: the alkene can react in an endo or in an exo mode [1,7] (endo and exo being referred to the carbomethoxy group of the ester), while the diastereofacial selectivity of the chiral alkene can double the stereoisomers.

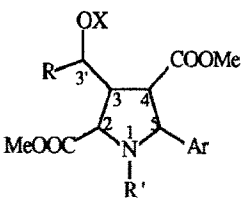
The absolute configuration of isomer **13a** was established by X-ray analysis. In Figure 1 we show the ORTEP plot of the molecule together with selected bond lenghts, bond angles and dihedral angles. The absolute configuration at the stereocenters is [2-(S), 3-(S), 3'-(S), 4-(S), 5-(R)] (for the numbering system, cfr. Scheme 1). Cycloadducts **11a** and **12a** were chemically correlated to **13a** as shown in Scheme 2. A 70:30 mixture of **11a,b** was N-benzylated to give a 70:30 mixture of **15a** and **15b**. Likewise, a 90:10 mixture of **12a** and **12b** afforded the same ratio of **13a,b** after desilylation and pure sample of **13a** was converted to pure **15a**. Proton and carbon NMR data trends, along with logical considerations, strongly suggest a related relative configuration for **10a**, i.e. [2-(R), 3-(R), 3'-(S), 4-(R), 5-(S)]; relevant NMR data for all the cycloadducts are collected in Table 2.

Scheme 2.



a: BnBr, Ag_2O, Et_2O, reflux; b: $Bu_4F.3H_2O$, THF, rt.

Table 2. Relevant ^{1}H and ^{13}C NMR data for pyrrolidines **10a,b-15a,b.** [a]



R = CH_3; X = Bn, TBDMS, OH;
R, X = CH_2O-$C(C_5H_{10})$-;
R' = H, Bn;
Ar = Ph, p-MeOPh.

product	H_2	H_3	H_4	H_5	R	$H_{3'}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{3,3'}$
10a	3.89	2.82	3.41	4.57	4.10; 3.67	4.38	7.0	3.9	7.5	4.0
10b	3.97	3.00	3.20	4.64	4.06; 3.87	4.33	6.5	4.7	7.3	5.0
11a	3.94	2.72	3.49	4.52	1.26	3.85	7.9	4.3	7.8	3.2
11b	3.97	3.28	3.18	4.59	1.29	3.76	7.2	4.6	7.5	4.6
12a	3.83	2.59	3.45	4.44	1.16	4.14	8.0	4.2	7.8	2.1
12b	3.83	2.82	3.21	4.54	1.22	4.10	7.0	4.0	7.5	4.0
13a	3.90	2.71	3.41	4.52	1.25	4.11	8.0	4.0	8.0	3.8
14a	3.91	2.71	3.43	4.45	1.24	3.83	8.0	4.5	8.0	3.0
14b	3.93	2.97	3.13	4.53	1.28	3.74	8.0	5.0	8.0	4.5
15a	3.48	3.08	3.32	4.06	1.08	3.58	9.0	8.0	10.0	4.0
15b	3.44	3.32	3.08	4.11	1.1	-	9.0	8.0	10.0	3.0

product	C_2	C_3	C_4	C_5	$C_{3'}$	C=O	R
10a	61.6	48.9	51.2	63.8	75.1	172.2	-
10b	60.3	48.3	55.7	63.85	75.6	-	-
11a	62.7	54.8	51.1	65.7	73.9	174.2;173.3	18.2
11b	61.8	53.2	54.1	65.7	75.3	173.7; 173.3	17.2
12a	62.7	56.4	50.0	65.9	67.6	174.2; 173.2	17.9
12b	60.6	54.7	54.3	65.5	69.1	-	-
13a	62.7	54.9	50.95	65.6	67.2	173.9; 173.3	22.5
14a	62.5	54.7	51.05	65.2	73.9	174.2	18.2
14b	61.8	53.1	54.95	65.2	75.3	173.3	17.2
15a	66.7	50.3	49.3	68.9	73.15	173.4; 172.5	17.4
15b	67.6	49.9	51.3	69.15	75.1	172.7; 172.0	16.9

a) ^{1}H: chemical shifts in ppm downfield from TMS; coupling constants in Hertz. C(3)-H and C(5)-H resonate at higher field in all **a** isomers and at lower field in all **b** isomers. For C(4)-H the opposite trend is observed.

^{13}C: chemical shifts in Hz. C(4) resonate at higher fields in the **a** isomers and at lower fields in the **b** isomers. The opposite trend is observed for C(2) and C(3).

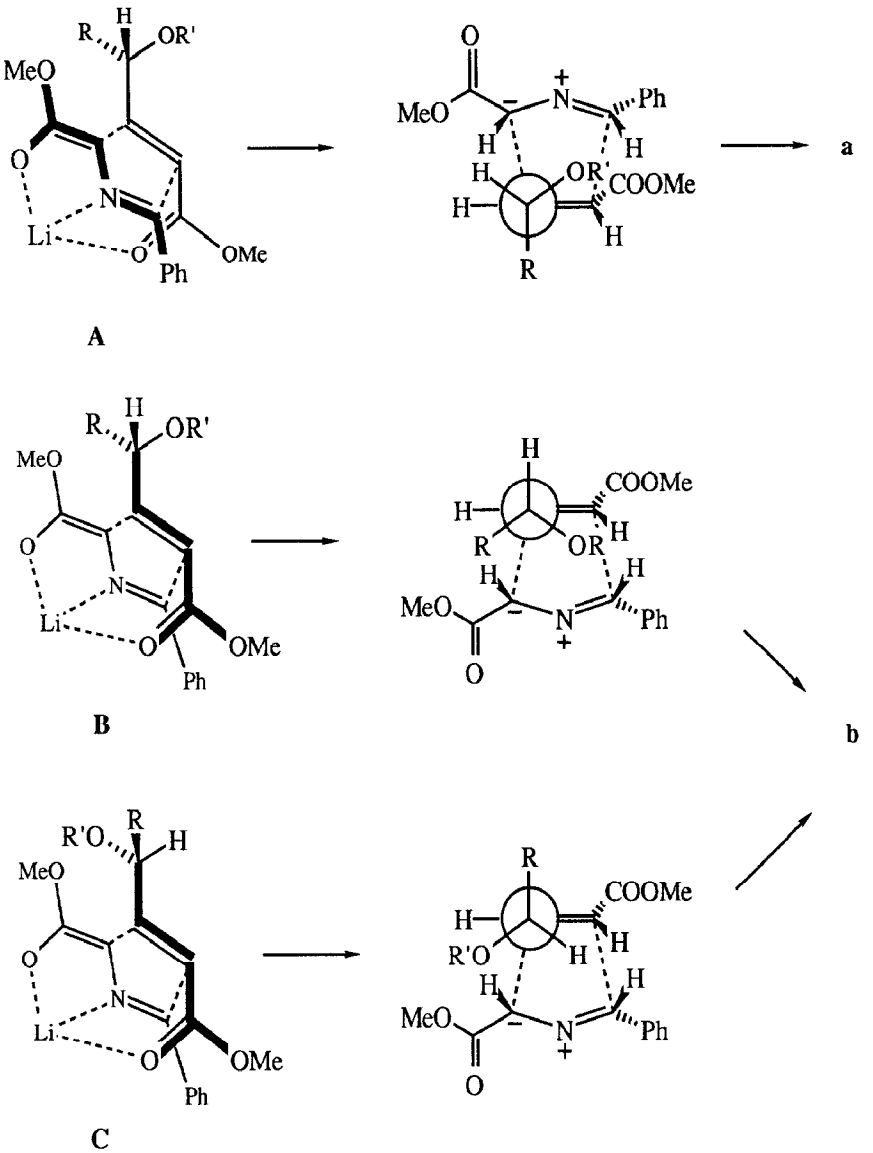
N.O.e. experiments allowed us to assign also the relative stereochemistry to isomers **b** as depicted in Scheme 1. In particular, both cycloadducts **11a** and **11b** showed high n.O.e.'s between the hydrogens at C-2, C-4 and C-5, thus suggesting a syn arrangement for these three hydrogens in both series. The examination of significant trends in the ^{1}H and ^{13}C NMR supported an identical relative stereochemistry at C-2, C-4, C-5 for all the cycloadducts in the **b** series. It follows that the minor isomers **b** can only have a reversed stereochemical relationship at the C-3/ C-3' carbons with respect to the corresponding major isomers **a**. If we consider the cycloadducts as drawn in Scheme 1, we can define the relative stereochemistry at C-3/ C-3' as anti for the **a** and syn for the **b** isomers respectively. Thus the cycloaddition proceeds with a complete endo selectivity, [1,7] while the **a:b** ratio is determined only by the diastereofacial preference of the alkene. [8]

Similar results were observed by Kanemasa [8] in his studies on azomethine ylide cycloaddition to α,β-unsaturated esters bearing either a diheterosubstituted allylic stereocenter, [8a,b] or a chirotopic but non-stereogenic γ-substituent imbedded in a chiral imidazoline ring. [8c] As in our case, in these reactions the formation of only two diastereoisomeric products was observed, resulting from a totally regioselective endo-cycloaddition of a W-shaped dipole. The diastereoselectivities ranged from good to excellent and were found to improve when the reaction temperature was lowered. The nature of the substitution pattern at the γ-carbon however prevents a meaningful comparison with the diastereofacial selectivities observed in our work. We think that our results could be conveniently compared with those obtained in nitrile oxide and nitrone cycloadditions to related alkenes bearing an oxygen-substituted allylic stereocenter. [4-6,13] There are few examples of nitrile oxide cycloadditions to unsaturated esters bearing a γ-stereocenter, [13] and in all but one example [13a] the dipolarophile was a lactone and therefore less pertinent to this work. Jaeger [13a] performed a nitrile oxide cycloaddition to an ester very similar to **4** and obtained two regioisomers in a 77:23 ratio. The major one, the isoxazoline bearing the ester group at C-4, was a 80:20 mixture of anti : syn products, and thus the sense and the extent of the diastereoselection is the same with both dipoles. Only intramolecular examples are available for comparison with nitrone cycloadditions: [5a] substrates related to **4** and **5** gave anti-selective reactions, with stereocontrol ranging from poor (for esters similar to **5**) to high (for esters similar to **4**), the major products deriving from the attack on the same diastereoface of the alkene.

Cycloadditions to electron-rich chiral allyl ethers have been studied in more detail, [4-6] and therefore offer another term of comparison. In the present study, we found that an increase in the bulkiness of the O-protecting group, as in passing from alkene **5** to **6**, secures a better stereoselectivity, exactly paralleling the data reported for nitrile oxide and nitrone reactions. [4-6] Moreover, as in the case of these dipoles, the presence of a homoallylic oxygen further improves the anti-selectivity of the azomethine ylide reaction. Thus for all these dipoles the anti-selectivity increases along the series **5** to **6** to **4**.

The nice agreement between the results obtained in this work with those of nitrile oxide and nitrone cycloadditions on similar substrates seems to indicate that Houk's "inside alkoxy effect"

Figure 2.



theory [6] is of general applicability to 1,3-dipolar cycloaddition to chiral allyl ethers. Combining this rationale with the transition state proposed by Kanemasa [8] we tentatively suggest that models **A** and **B** or **C** depicted in Figure 2 can account for the formation of the major and minor diastereoisomeric pyrrolidines. In model **A** the ylide attacks the Re/Re face of the ester away from the bulky alkyl residue at the stereocenter. This attack leads to a transition state where, in analogy with the case of nitrile oxide cycloadditions, [6] the OR' allylic substituent occupies the stereoelectronically favoured "inside" position and the small H group the more sterically demanding "outside" position, closer to the oncoming dipole. To account for the formation of **b** isomers, by analogy with Kanemasa's model [8] transition structure **B** can be invoked, featuring the attack at the Si/Si face antiperiplanar to the small H group, with the alkoxy group "inside" and an unfavourable steric interaction between the ylide OMe group and the allylic R group in the "outside" region. However, as in the case of nitrile oxide cycloadditions, [6] it seems more likely that the alkene reacts in a conformation different from that of the ground state. In model **C** the attack occurs antiperiplanar to the R group while the small H group occupies the "inside" position. The steric interaction between the "outside" OR group and the methoxy residue on the ylide destabilizes this transition structure with respect to **A**.

Thus very similar transition states seem capable rationalizing nitrile oxide, nitrone and azomethine ylide cycloadditions. The small but significant differences in diastereoselectivity observed for the three dipoles can very likely derive from the different dipole geometries. Theoretical work is underway to establish the importance of this factor in determining the course of the reaction. A strikingly different result is represented by ester **7** which reacts with azomethine ylide to give a good excess of anti product **13a**, while it is known that allylic alcohols lead to poor syn selective reactions with nitrile oxides and nitrones. [4-6] In the latter case the hydrogen bond formation between the allylic OH and the dipole oxygen was considered responsible for the stereochemical result. [4-6] In the azomethine ylide case such a directing effect does not seem possible and therefore the reaction maintains its anti-selectivity.

Having established the sense and the extent of the diastereoselection of these azomethine ylide cycloadditions, we turned our attention to the possibility of controlling the stereochemical outcome of the reaction by changing the nature of the metal salt. [7] On passing from LiBr to the more strongly chelating $MgBr_2$ we observed a slow reaction between **5** and **8** to afford 36% yield of **12a,b** in a 77:23 ratio. More Lewis acidic and chelating catalysts such as $ZnCl_2$ and $TiCl_4$ did not promote any cycloaddition between **5** and **8**, the ester being recovered almost quantitatively. These results have some precedents in other dipolar cycloadditions [4,14] and in azomethine ylide reactions. [7-9]

Further attempts to investigate the influence of the alkene geometry on the stereochemical results were thwarted by the almost complete lack of reactivity of (Z)-esters related to **4-6**. The poor chemical yields and the complex mixtures of cyclic and acyclic products obtained discouraged our efforts in this sense.

In conclusion we have shown that the 1,3-dipolar cycloaddition of an azomethine ylide to a chiral γ-alkoxy-α,β-unsaturated ester occurs with complete regiocontrol and fair to excellent stereocontrol. Houk's "inside alkoxy effect" nicely serves to rationalize the results, and this theory seems therefore of wide applicability to dipolar cycloadditions. The study of the intramolecular version [8b] of the reactions here described will be a useful test for this rationale.

Acknowledgments.

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Experimental.

^1H and ^{13}C NMR spectra were recorded with a Bruker WP80, a Bruker AC300 or a Varian XL300 instrument on $CDCl_3$ solutions. Chemical shifts are in ppm downfield from TMS. Melting points are uncorrected. Optical rotations were measured on a Perkin Elmer 241 spectrometer on $CHCl_3$ solutions. Elemental analyses were performed with a Perkin Elmer 240 instrument. Silica gel was used for flash chromatography. Usual work-up required addition of a saturated aqueous solution of NH_4Cl and extraction with an organic solvent; organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under vacuum. THF and Et_2O were distilled from $LiAlH_4$; CH_2Cl_2 was distilled from CaH_2. All reactions employing dry solvents were run under nitrogen.

General procedure for the synthesis of (E)-esters 4-6.

NaH (5 mmol, 240 mg of a 50% suspension in mineral oil) was washed with pentane and suspended in dry THF (10 ml). Dimethyl methoxycarbonylmethylphosphonate (5 mmol, 808 μl) was added dropwise at -30°C. After 30' stirring at that temperature, a solution of the required aldehyde (4.8 mmol) in dry THF (5ml) was slowly added, and the mixture stirred for an additional hour at -30°C. Usual work-up followed by flash chromatography gave stereoisomerically pure products.

(S)-Methyl-3-(1,4-dioxaspiro[4,5]-dec-2-yl)-(E)-propenoate **4** was obtained as an oil in 84% yield with a 8:2 hexane : diethyl ether as eluant (E:Z ratio 7:1). Found: C% 63.77; H% 7.98. $C_{12}H_{18}O_4$ requires: C% 63.70; H% 8.02. ^1H NMR: δ 6.90 (dd, 1H, J 16.5, 5.9 Hz, CH-C<u>H</u>=); 6.05 (dd, 1H, J 16.5, 1.2 Hz, CO-C<u>H</u>=); 4.50-4.80 (m, 1H, C<u>H</u>-O); 4.00-4.20 (m, 1H, 1 H of C<u>H</u>$_2$-O); 3.80 (s, 3H, C<u>H</u>$_3$-O); 3.50-3.80 (m, 1H, 1 H of C<u>H</u>$_2$-O); 1.00-2.00 (m, 10H, C_6H_{10}). $[\alpha]_D^{22}$ = +35.3 (c 0.6).

(S)-Methyl-4-phenylmethoxy-2-(E)-pentenoate **5** was an oil obtained in 80% yield with hexane : diethyl ether 9:1 as eluant (E/Z ratio 5:1). Found: C% 70.93; H% 7.30. $C_{13}H_{16}O_3$ requires: C% 70.89; H% 7.32. ^1H NMR: δ 7.25-7.35 (m, 5H, aromatic protons); 6.90 (dd, 1h, J 15.8, 6.0 Hz, CH-C<u>H</u>=); 6.00 (dd, 1H, J 15.8, 1.2 Hz, CO-C<u>H</u>=); 3.90-4.70 (m, 3H, C<u>H</u>$_2$-Ph and C<u>H</u>-O); 3.80 (s, 3H, C<u>H</u>$_3$-O); 1.10 (m, 3H, C<u>H</u>$_3$-CH). $[\alpha]_D^{22}$ = -34.8 (c 1.2).

(S)-Methyl-4-[(1,1-dimethylethyl)-dimethylsilyloxy]-2-(E)-pentenoate **6** was obtained as an oil in 80% yield with hexane : diethyl ether 95:5 as eluant (E/Z ratio 2:1). Found: C% 58.94; H% 9.92. $C_{12}H_{24}O_3Si$ requires: C% 58.97; H% 9.90. ^1H NMR: δ 6.80 (dd, 1H, J 15.3, 4.3 Hz, CH-C<u>H</u>=); 5.80 (dd, 1H, J 15.3, 1.8 Hz, CO-C<u>H</u>=); 4.30-4.50 (m, 1H, C<u>H</u>-O); 3.80 (s, 3H, C<u>H</u>$_3$-O); 1.10-1.35 (m, 3H, C<u>H</u>$_3$-CH); 0.80 (s, 9H, (C<u>H</u>$_3$)$_3$-Si); 0.10 (s, 6H, 2 C<u>H</u>$_3$-Si). $[\alpha]_D^{22}$ = +6.18 (c 1.6).

Synthesis of (S)-Methyl-4-hydroxy-2-(E)-pentenoate 7.

To a stirred solution of **6** (1 mmol, 244 mg) in 10 ml dry THF, was added $Bu_4NF.3H_2O$ (2 mmol, 630 mg) at room temperature. The mixture was stirred for 5 hours. After usual work-up, flash chromatography with a 2:1 mixture of diethyl ether : hexane afforded pure **7** as a colourless oil in 50% yield. Analytical data were in agreement with literature data [15].

General procedure for the synthesis of cycloadducts 10-14a,b.

To a suspension of LiBr (0.6 or 1.8 mmol, 48 or 144 mg; see text and Table 1) in dry THF (15 ml), was added crude imine **8** or **9** [10] (0.55 or 1.65 mmol). The solution was cooled at -78°C and DBU (0.55 or 1.65 mmol, 82 or 242 µl) was added. After 15 minutes stirring at that temperature, a solution of the unsaturated ester (0.55 mmol) in dry THF (5 ml) was added dropwise. After an additional 2-5 hours stirring at -78°C, usual work-up and flash chromatography afforded pure cycloadducts **10-14a,b**. Yields and diastereoisomeric ratios are summarized in Table 1. ^1H and ^{13}C relevant NMR data are collected in Table 2 respectively.

3-(1,4-Dioxaspiro[4.5]-dec-2-yl)-2,4-dicarbomethoxy-5-phenylpyrrolidines **10a,b** were obtained as a pale yellow oil (diethyl ether : hexane 7:3). Found: C% 65.53; H% 7.28; N% 3.48. $C_{22}H_{29}NO_6$ requires: C% 65.49; H% 7.24; N% 3.47. **10a**: $[\alpha]_D^{22}$ = -270.1 (c 0.6).

2,4-Dicarbomethoxy-3-(1-phenylmethoxyethyl)-5-phenylpyrrolidines **11a,b** were obtained as a pale yellow oil (diethyl ether : hexane 7:3). Found: C% 69.57; H% 6.82; N% 3.54. $C_{23}H_{27}NO_5$ requires: C% 69.50; H% 6.85; N% 3.52. A 10:1 mixture of **11a,b** had $[\alpha]_D^{22}$ = -3.87 (c 0.6).

2,4-Dicarbomethoxy-3-[1-(1,1-dimethylethyl)-dimethylsilyloxyethyl)-5-phenyl pyrrolidines **12a,b** were obtained (hexane : diethyl ether 6:4) as a colurless oil. Found: C% 62.70; H% 8.38; N% 3.29. $C_{22}H_{35}NO_5Si$ requires: C% 62.68; H% 8.37; N% 3.32. Chromatographic techniques did not allow satisfactory separation of **a** and **b** isomers for $[\alpha]_D$ measurement.

2,4-Dicarbomethoxy-3-(1-hydroxyethyl)-5-phenylpyrrolidines **13a,b** were obtained as a white solid (diethyl ether : hexane 98:2). Found: C% 62.50; H% 6.91; N% 4.53. $C_{16}H_{21}NO_5$ requires: C% 62.53; H% 6.89; N% 4.56. Recrystallization from AcOEt gave a sample of pure **13a**,

p.f. 130-132°C, $[\alpha]_D^{22}$ = +44.47 (c 1.7).

2,4-Dicarbomethoxy-3-(1-phenylmethoxyethyl)-5-(4-methoxyphenyl)pyrrolidines ***14a,b*** were obtained as a pale yellow oil (diethyl ether : hexane 7:3). Found: C% 67.40; H% 6.87; N% 3.30. $C_{24}H_{29}NO_6$ requires: C% 67.43; H% 6.84; N% 3.28. A purified mixture of **14a:b** 96:4 had $[\alpha]_D^{22}$ = +146.4 (c 0.6).

Conversion of 12a,b to 13a,b.

To a stirred solution of **12a,b** (0.5 mmol, 21 mg) in dry THF (10 ml) was added $Bu_4NF.3H_2O$ (1.6 mmol, 504 mg) at room temperature, and the mixture was stirred under nitrogen for 5 hours. Usual work-up and flash chromatography (diethyl ether : methanol 95:5) afforded **13a,b** in 40% yield.

Conversion of 11a,b to 15a,b and of 13a to 15a.

11a,b (0.2 mmol, 79 mg) and benzyl bromide (0.3 mmol, 36 µl) were dissolved in dry Et_2O, and freshly prepared Ag_2O (0.2 mmol, 46 mg) was added. The reaction mixture was refluxed for 2 hours, then filtered through a celite pad. Flash chromatography purification (diethyl ether : hexane 1:1) afforded **15a,b** in 68% yield. Found: C%: 73.93; H% 6.81; N% 2.88. $C_{30}H_{33}NO_5$ requires: C% 73.90; H% 6.82; N% 2.87. Relevant NMR data are collected in Table 2. A mixture 10:1 of **15a,b** had $[\alpha]_D^{22}$ = +6.57 (c 0.2).

Similarly, **13a** gave the corresponding N-benzyl-pyrrolidine that was not isolated but treated with Ag_2O and benzyl bromide to afford, after work-up, **15a**.

Single cristal X-ray analysis of 13a.

Crystallographic data and refinement parameters are summarized in Table 3.

Table 3. Crystal data and refinement parameters for compound **13a**.

Molecular formula	$C_{16}H_{21}NO_5$	Molecular weight	307.35
Crystal system	Monoclinic	Space group	$P2_1$
a, Å	8.497	b, Å	6.921
c, Å	14.009	β, deg.	92.15
V, Å^3	823.3	ρ_{calc}, g.cm^{-3}	1.240
Number of reflections for lattice parameters		25	
Range	10-17	Crystal size, mm	0.24 x 0.16 x 0.16
Scan type	ω - 2θ	θ range	1-27.5
No. of reflections	2040	'observed' [I>σ(I)]	1417
Maximum residue Δρ	0.18 eÅ^{-3}	$(\Delta/\sigma)_{max}$	0.04
$R = [\Sigma\|\Delta F\|/\Sigma\|F_o\|]$	0.044	$R_w = [\Sigma w(\Delta F)^2/\Sigma wF_o^2]^{1/2}$	0.045

$w = (2F_oL_p)^2/[\sigma^2(I)_{cs}+0.0009\ I^2]$

$\sigma(I)_{cs}$ = standard deviation from counting statistics.

The data were collected on a Enraf-Nonius CAD4 diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073). No decay was observed during the data collection. Data were corrected for Lorentz and polarization effects but not for absorption [μ(Mo-Kα) = 8.6 mm^{-1}]. The structure was solved by direct methods (MULTAN II, RANDOM option [16]). Atomic scattering factors were taken from *International tables for X-ray Crystallography*; [17] refinement was carried out by full-matrix least-squares, with anisotropic thermal parameters for all heavy atoms. [18] The pyrrolidine ring has an envelop conformation, [19] with q = 0.431(3) Å and φ = -7.3 (4)°.

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