

STUDY OF THE ASYMMETRIC INDUCTION OF THE 1,3-DIPOLAR CYCLOADDITION OF CHIRAL AZOMETHINE YLIDES WITH UNACTIVATED DOUBLE BONDS

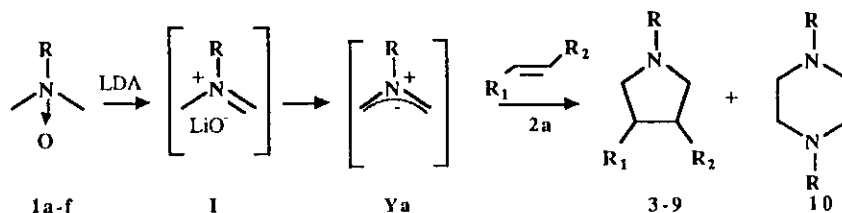
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Abstract-The asymmetric induction of the 1,3-dipolar cycloaddition reaction between **nonstabilized** azomethine ylides generated by deprotonation of the corresponding tertiary amine *N*-oxides (**1a-f**) with a base and various **unactivated** olefins (**2a-c**) or dienes (**2d-e**) has been studied. The results show that an important induction can be reached with valinol derived *N*-oxide (**1f**). The elimination of the chiral substituent in 3-phenyl-*N*-(1-hydroxymethyl-propyl)-pyrrolidine (**8b**) allowed to determine the absolute configuration of the major enantiomer (**12b**) in accordance with the proposed transition state.

The extensively studied 1,3-dipolar cycloaddition of azomethine ylides to olefins represents one of the most powerful access to pyrrolidine.¹ However, little is known about the asymmetric 1,3-dipolar cycloaddition of homochiral azomethine ylides to achiral dipolarophiles which showed modest diastereoselectivity ^{2a, b} until recently.^{2c, 3}

In connection with our discovery of an efficient access to nonstabilized azomethine ylides by deprotonation of tertiary amine *N*-oxides with a lithium base,⁴ we decided to study the effect exerted by the chiral substituent R in compounds (**1a-f**) on the asymmetric induction in the [3+2] dipolar cycloaddition reaction (Scheme I).



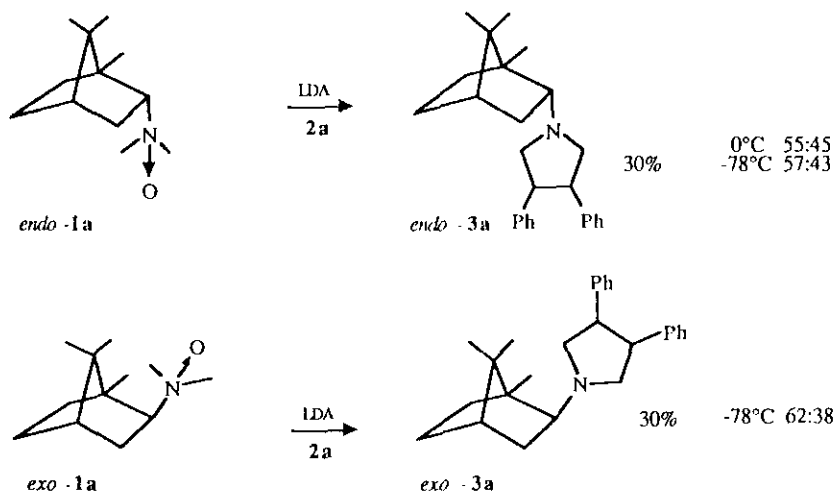
Scheme I

RESULTS AND DISCUSSION

The *endo*- and *exo*-aminocamphor *N*-oxides (**1a**) treated with LDA in the presence of *trans*-stilbene (**2a**), at 0°C

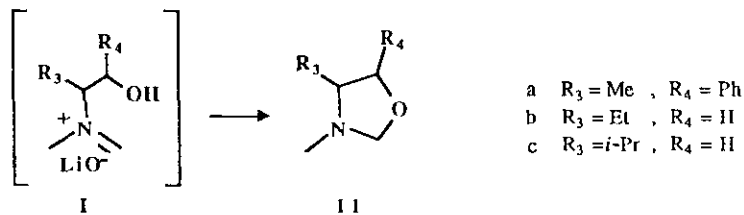
or -78°C , yielded a couple of diastereomeric pyrrolidines *endo*- and *exo*- (**3a**), respectively, with low selectivity (Scheme II).

The low yields of pyrrolidines can be due to the competitive ylide dimerization leading to the formation of the corresponding piperazine,^{4a} and the low selectivity observed is in accordance with the fact that the diastereofacial control by steric factors is balanced by the free rotation of the nitrogen-asymmetric carbon bond. This result confirms that steric factors are not determinant in the asymmetric induction and that it is of importance to use chiral groups able to induce electronic or polar effects in the transition state.



Scheme II

We turned then towards the *N*-oxides (**1b**) and (**1c**), in which the hydroxylic functions are protected as *t*-butoxy in order to avoid the competitive formation of the corresponding oxazolidines (**11**) by intramolecular trapping of the intermediate immonium salt [I] by the free hydroxylic group.^{4c}



These *N*-oxides were easily prepared by oxidation of the corresponding β -amino alcohol derivatives. The results are summarized in the Table I.

By treatment with LDA at 0°C in the presence of *trans*-stilbene (**2a**) or allyl alcohol (**2b**), the *N*-oxide (**1b**) yielded the corresponding pyrrolidines (**4**) and (**5**) as a mixture of diastereomers with a low selectivity. The reaction between the valinol *N*-oxide derivative (**1c**) and stilbene led to high yields of pyrrolidine (**6**).^{*} Similar lack of selectivity was observed at 0°C or -78°C.

These results can be due to the bulky *t*-butyl group which cancels the influence exerted by the hydro-

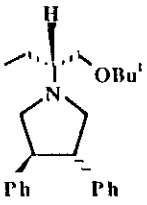
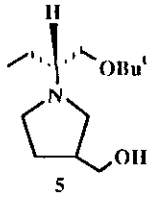
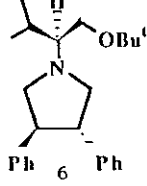
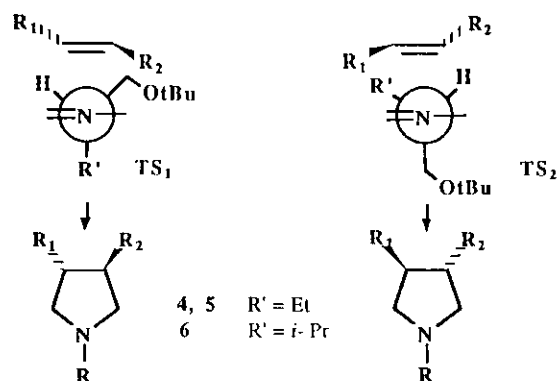
Entry	<i>N</i> -Oxides	Olefins		Temp. (°C)	Pyrrolidines	Yields (%)	Diastereomeric ratios
	R	R ₁	R ₂				
1	1-(<i>t</i> -butoxymethyl)- propyl 1b	Ph	Ph	0		63 ^{Ref. 4b}	57:43
2	1-(<i>t</i> -butoxymethyl)- propyl 1b	H	CH ₂ OH	0		35 ^{Ref. 4b}	57:43
3	1-(<i>t</i> -butoxymethyl)- 2-methylpropyl 1c			0 -78		80	58:42 58:42

Table I. Reaction between the *N*-oxides (**1b-c**) and olefins (**4b**)

xyloxy oxygen atom and by fact that the dipolarophile can approach *anti* to two large groups in the ylide (CH₂OBu^t and R') leading to two diastereomeric transition states TS₁ and TS₂ of close energy (Scheme III).

^{*}The high reactivity of the ylide generated from *N*-oxide (**1c**) was confirmed by the easy trapping with ethylene leading to the formation of the corresponding pyrrolidine in 80% yields.



Scheme III

We speculated that the less bulky *N*-oxides (**1d-f**) easily obtained respectively from 1-(*R*)-2-(*S*)-methyl-ephedrine, (*R*)-2-aminobutanol and (*S*)-valinol could behave differently.

Entry	<i>N</i> -Oxides R	Olefins R ₁ R ₂	Pyrrolidines	Yields (%)	Diastereomeric ratios
1	2-hydroxy-1-methyl- 2-phenylethyl 1d	2a Ph Ph		7 ^a 40	67:33
2	1-hydroxymethyl- propyl 1e	2a Ph Ph		8 ^a ^b 40	68:34
3		2b H Ph		8 ^b ^b 50	60:40
4		2c H CH ₂ OH		8 ^c ^b 20	65:35
5	1-hydroxymethyl- 2-methylpropyl 1f	2a Ph Ph		9 ^a 30	80:20
6		2d H isopropenyl		9 ^d 25	70:30
7		2e H isobutenyl		9 ^e 27	65:35

a. The corresponding piperazine (**10d**) and oxazolidine (**11a**) were concurrently formed in 20% yields.^{4b} b. See Ref. 4b.

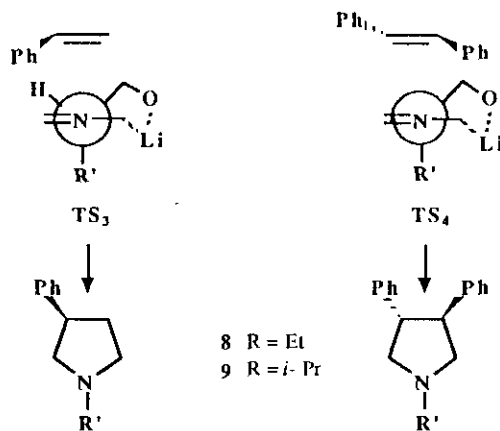
Table II. Reaction between the *N*-oxides (**1d-f**) and unsaturated compounds.^{4b}

These compounds were treated with LDA at 0°C in the presence of various olefins (**2a, c**) and conjugated dienes (**2d, e**) to yield the expected pyrrolidines as a mixture of diastereomers. The results are summarized in Table II. The decreased yields of pyrrolidines (**7-9**) are due to the competitive formation of oxazolidines (**11**) by the intramolecular trapping of the intermediate immonium salts [**I**] as we have shown in the case of the pyrrolidine **7**.^{4c}

The material balance could not be established in the case of the *N*-oxides (**1e, f**) because oxazolidines (**11b, c**) are volatile, and piperazines (**10e, f**) are soluble in water. The hydroxylic function appears to be of importance in the asymmetric induction, since the diastereomer ratios reached to 80:20 in the reaction between stilbene and the *N*-oxide (**1f**) (entry 5). The latter compound reacted exclusively with the terminal double bond of the butadiene derivatives (**2d, e**) to yield the diastereomeric pyrrolidines (**9d**) and (**9e**).

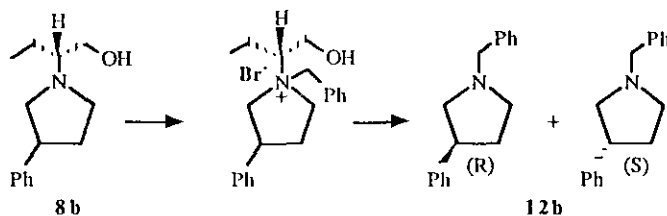
The increased selectivity can be due to a better diastereofacial control resulting from the chelation between lithium alkoxide and dipole termini, so that the transition state, in which the preferred configuration holds the largest group *anti* the dipolarophile, is rigid.

The preferential attack of stilbene (**2a**) could occur on transition state **TS₃** which is compatible with the increased selectivity observed with the valinol derivatives (R=*i*-Pr) where the isopropyl group enhanced the diastereofacial control of the dipolarophile approach (Scheme IV).



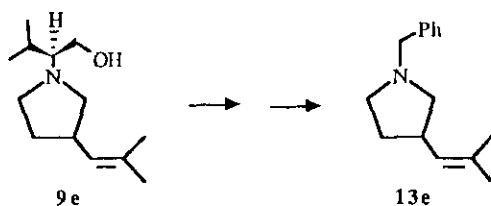
Scheme IV

Among the four possible transition states of the reaction between the *N*-oxide (**1e**) and the styrene (**2b**), the preferred one could be **TS₄**, in which the *exo* phenyl group minimizes the steric hindrance. The enantiomerically enriched NH pyrrolidine (**12b**) was easily obtained by the successive treatment of **8b** with benzyl bromide and potassium *t*-butoxide, according to the method we had recently proposed.^{4b}



The value and the rotation sign reported for the pure *N*-benzyl-3-phenylpyrrolidine (**12b**),⁵ allowed us to assign the absolute configuration 3R to the major enantiomer, in accordance with the proposed *exo* transition state **TS₄** rather than **TS₅** and confirmed the asymmetric induction value measured in the reaction leading to the formation of **8b**.

By the same way, the diastereomeric pyrrolidines (**9e**) were quantitatively transformed into the enantiomerically enriched *N*-benzyl derivatives (**13e**), of unknown absolute configuration.



CONCLUSION

Our results show that a good induction can be reached in the [3+2] cycloaddition reaction of **nonstabilized** azomethine ylide generated from *N*-oxide (**1f**) with **unactivated** olefins or dienes. The observed selectivity was due to a chelation between the lithium alkoxide and the dipole termini.

EXPERIMENTAL

¹H Nmr or ¹³C nmr spectra were recorded in CDCl₃, in Bruker WP 200-54 (200 MHz); chemical shifts from tetramethylsilane are given in δ. Ms spectra were obtained on a AEI-MS-50 spectrometer or INCOS-50 coupled with a vapor phase chromatograph (vpms). Cims were recorded on AEI-MS-9 spectrometer. The reactions were monitored by vapor-phase chromatography (vpc) and thin layer chromatography (tlc). Purifications were achieved by column chromatography (elution), preparative thin layer chromatography (tlc, elution), and high pressure liquid chromatography (hplc).

General procedure. The amine *N*-oxide (1 mmol) was dried for 6 h, just before use, by heating under vacuum at 30°C in a three necked flash equipped with rubber septum. The dipolarophile (1.1 mmol) in anhydrous THF

(50 ml) was then added *via* a syringe and the suspension was cooled to the desired temperature before LDA (4 equiv.) was introduced. The reaction was monitored by vpc and tlc. The determination of diastereomeric ratios was recorded on the crude mixture, by hplc, vpc or ^1H nmr.

Camphor-2-*endo*-dimethylamine *N*-oxide (*endo* 1a)

The oxidation of the corresponding amine (1.0 g) prepared according to the literature⁶ by 30% H_2O_2 (5 ml) in MeOH (5 ml) yielded (*endo* 1a) (0.54 g, 55%); ^1H nmr (CDCl_3): δ 0.93 (s, 3H), 1.02 (s, 3H), 1.20 (s, 3H), 1.32-3.12 (m, 8H), 3.52 (s, 3H), 3.65 (s, 3H); cims m/z 181.

Camphor-2-*exo*-dimethylamine *N*-oxide (*exo* 1a)

The oxidation of the corresponding amine (0.81 g) by 30% H_2O_2 (5 ml) in MeOH (5 ml) yielded (*exo* 1a) (0.59 g, 66%); ^1H nmr (CDCl_3): δ 0.83 (s, 3H), 1.20 (s, 3H), 1.30 (s, 3H), 1.36-2.66 (m, 6H), 3.05-3.5 (m, 2H), 3.10 (s, 3H), 3.26 (s, 3H); cims m/z 181.

(S)-1-(*t*-Butoxymethyl)-2-methylpropylamine-*N,N*-dimethylamine *N*-oxide (1c)

The oxidation of the corresponding amine (4.28 g) prepared according to the literature,⁷ by 30% H_2O_2 (20 ml) in MeOH (20 ml) yielded (1c) (2.50 g, 53%); ^1H nmr (CDCl_3): δ 1.06 (d, $J = 7$ Hz, 3H), 1.10 (d, $J = 7.0$ Hz, 3H), 1.22 (s, 9H), 2.73-2.93 (m, 1H), 3.06-3.23 (m, 1H), 3.20 (s, 3H), 3.30 (s, 3H), 3.63-3.90 (m, 2H); ms m/z 203, 100.

(S)-1-(Hydroxymethyl)-2-methylpropylamine-*N,N*-dimethylamine *N*-oxide (1f)

The oxidation, by 30% H_2O_2 (20 ml) in MeOH (20 ml), of the corresponding amine (5.30 g) yielded (1f) (4.00 g, 89%) after usual work up; ^1H nmr (CDCl_3): δ 0.98 (d, $J = 7$ Hz, 3H), 1.17 (d, $J = 7$ Hz, 3H), 1.93-2.19 (m, 1H), 3.15 (s, 3H), 3.25 (s, 3H), 3.22-3.43 (m, 1H), 3.69-3.87 (dd, $J = 13, 2$ Hz, 1H), 3.99-4.23 (dd, $J = 13, 2$ Hz, 1H); cims m/z 251, 236.

3,4-Diphenyl-*trans-N*-(*endo*-2-camphoryl)pyrrolidine (*endo* 3a)

N-Oxide (*endo* 1a) (0.28 g, 1.42 mmol) and *trans*-stilbene (0.28 g, 1.56 mmol) were treated with LDA (5.60 mmol) at 0°C to yield (*endo* 3) (0.15 g, 30%) as a 57:43 mixture of diastereomers; ^1H nmr (CDCl_3): δ 0.87 (s, 3H), 0.90 (s, 3H), 0.97 (s, 3H), 1.17-1.42 (m, 4H), 1.90-2.12 (m, 1H), 2.13-2.45 (m, 2H), 2.52-2.72 (m, 2H), 3.02 (s, 2H), 3.58-3.82 (m, 3H), 7.02-7.42 (m, 10H); cims m/z 360, 190, 182.

The same reaction run at -78°C yielded (*endo* 3) as a 57:43 mixture of diastereomers.

3,4-Diphenyl-*trans-N*-(*exo*-2-camphoryl)pyrrolidine (*exo* 3a)

N-Oxide (*exo* 1a) (0.20 g, 1.04 mmol) and *trans*-stilbene (0.21 g, 1.14 mmol) were treated with LDA (4.16 mmol) at -78°C to yield (*exo* 3) (0.11 g, 30%) as a 62:38 mixture of diastereomers; ^1H nmr (CDCl_3): δ 0.87 (s, 3H), 1.00 (s, 3H), 1.15 (s, 3H), 1.26-1.42 (m, 2H), 1.44-1.72 (m, 2H), 1.74-1.92 (m, 2H), 1.94-2.08 (m, 1H), 2.22-3.01 (m, 5H), 3.10 (s, 2H), 6.98-7.12 (m, 10H); ms m/z 360.

3,4-Diphenyl-*trans-N*-(1-*t*-butoxymethyl-2-methylpropyl)pyrrolidine (6)

N-Oxide (**1c**) (0.18 g, 0.90 mmol) and *trans*-stilbene (0.18 g, 1.02 mmol) were treated with LDA (4.82 mmol) at 0°C to yield pyrrolidine (**6**) (0.26 g, 80%) as a 58:42 mixture of diastereomers; ¹H nmr (CDCl₃): δ 1.05 (d, J = 7 Hz, 3H), 1.09 (d, J = 7 Hz, 3H), 1.18 (s, 9H), 1.82-2.05 (m, 1H), 2.10-2.20 (m, 1H), 2.33-2.50 (m, 1H), 2.65-2.80 (m, 1H), 2.96-3.05 (m, 1H), 3.32-3.53 (m, 5H), 7.02-7.38 (m, 10H); cims m/z 322, 278.

The same reaction run at -78°C, yielded (**6**) as a 58:42 mixture of diastereomers.

3,4-Diphenyl-*trans-N*-(1-hydroxymethyl-2-methylpropyl)pyrrolidine (**9a**)

N-Oxide (**1f**) (0.220 g, 1.67 mmol) and *trans*-stilbene (0.33 g, 1.84 mmol) were treated with LDA (7.28 mmol) at 0°C to yield (**9a**) (0.13 g, 25%), after chromatography on alumina (CH₂Cl₂-MeOH 99:1) as a 80:20 mixture of diastereomers.

(**9a**) Major compound: ¹H nmr (CDCl₃): δ 1.00 (d, J = 5.2 Hz, 3H), 1.10 (d, J = 5.6 Hz, 3H), 1.93-2.13 (m, 1H); 2.39-2.60 (m, 1H), 3.00-3.03 (m, 3H), 3.33-3.63 (m, 5H), 3.63-3.79 (m, 1H), 7.09-7.33 (m, 10H); cims m/z 278, 266.

The minor diastereomer (**9a**) was characterized by the presence of two doublets, (J = 5.4, and 5.5 Hz), centered at 1.02 and 1.16 ppm.

3-Isopropylidene-*N*-(1-hydroxymethyl-2-methylpropyl)pyrrolidine (**9d**)

N-Oxide (**1f**) (0.22 g, 1.67 mmol) and 2-methyl-1,3-butadiene (0.12 g, 1.84 mmol) were treated with LDA (7.8 mmol) at 0°C to yield (**9d**) (0.08 g, 25%), after silica gel chromatography (AcOEt-MeOH 98:2) as a 70:30 mixture of diastereomers.

(**9d**) Major isomer: ¹H nmr (CDCl₃): δ 0.94 (d, J = 6.9 Hz, 1H), 1.06 (d, J = 6.9 Hz, 1H), 1.57-1.83 (m, 1H), 1.75 (s, 3H), 1.84-2.23 (m, 2H), 2.27-2.47 (m, 1H), 2.52-2.70 (m, 1H), 2.72-3.03 (m, 4H), 3.23 (br s, 1H), 3.36-3.47 (m, 1H), 3.57-3.73 (m, 1H), 4.73 (br s, 1H), 4.75 (br s, 1H); ¹³C nmr (CDCl₃): δ 18.56, 20.03, 21.60, 28.65, 29.53, 44.78, 49.67, 54.43, 59.06, 67.47, 109.49, 146.94; cims m/z 198.

3-Isobutylene-*N*-(1-hydroxymethyl-2-methylpropyl)pyrrolidine (**9e**)

N-Oxide (**1f**) (0.49 g, 3.68 mmol) and 2-methyl-1,3-pentadiene (0.60 g, 7.36 mmol) were treated with LDA (12.57 mmol) at 0°C to yield (**9e**) (0.19 g, 27%) after column chromatography on alumina (CH₂Cl₂-MeOH 98:2) as a 70:30 mixture of diastereomers.

(**9e**) Major isomer: ¹H nmr (CDCl₃): δ 0.90 (d, J = 7 Hz, 3H), 0.99 (d, J = 7 Hz, 3H), 1.31-1.58 (m, 1H), 1.61 (s, 3H), 1.68 (s, 3H), 1.71-2.13 (m, 3H), 2.26-2.45 (m, 2H), 2.67-3.06 (m, 3H), 3.22-3.48 (m, 2H), 3.48-3.67 (m, 1H), 5.08 (d, J = 4 Hz, 1H); cims m/z 211, 180, 168.

(*R*)-3-Phenyl-*N*-benzylpyrrolidine (**12b**)

Pyrrolidine (**8b**) (0.09 g, 0.33 mmol) in MeOH (2ml) was treated at 0°C with benzyl bromide (0.17 g, 1.0 mmol) in the presence of NaHCO₃ (0.10g, 1.19 mmol). After complete consumption of the starting material, the methanol was distilled off, *t*-BuOK (0.08 g, 0.80 mmol) in *t*-BuOH (2 ml) was added and the mixture was heated to 60°C. Usual work up yielded (**12b**) (0.08 g, 90%); picrate (EtOH) mp 172-173°C; lit.,⁵ 172-173°C, [α]_D +5.3° (c 0.04, MeOH); lit.,⁵ [α]_D (c 0.04, MeOH) +37.3°.

3-Isobutenyl-N-benzylpyrrolidine (13e)

Pyrrolidine (**9e**) (0.09 g, 0.46 mmol) in MeOH (2ml) was treated at 0°C with benzyl bromide (0.22 ml, 2.31 mmol) in the presence of NaHCO₃ (0.17g, 2.0 mmol). After complete consumption of the starting material, the methanol was distilled off, *t*-BuOK (0.23 g, 2.05 mmol) in *t*-BuOH (10 ml) was added and the mixture was refluxed. Usual work up yielded (**13e**) (0.09 g, 93%); ¹H nmr (CDCl₃): δ 1.59 (s, 3H), 1.67 (s, 3H), 1.92-2.13 (m, 2H), 2.29-2.49 (m, 1H), 2.63-3.09 (m, 4H), 3.57 (s, 2H), 5.07 (d, J = 4.5 Hz, 1H), 7.07-7.53 (m, 5H); cims m/z 216, 167, 107.

REFERENCES

1. (a) R. Huisgen, "1,3-Dipolar Cycloaddition - Introduction, Survey and Mechanism" in "1,3-Dipolar Cycloaddition Chemistry", ed. A. Padwa, Wiley, New-York, 1986, *1*, pp.1-163; (b) E. Vedejs, *Advances in Cycloaddition*, 1988, *1* 33. (c) O. Tsuge and S. Kanemasa, *Advances Heterocycl. Chem.*, 1989, *45*, 231.
2. (a) A. Padwa, Y. Chen, V. Chiacchio, and W. Dent, *Tetrahedron*, 1985, *41*, 3529. (b) J. Rouden, J. Royer, and H-P. Husson, *Tetrahedron Lett.*, 1989, *30*, 5133. (c) Excellent diastereofacial and *endo/exo* stereoselectivities have been recently obtained in cycloaddition of the chiral azomethine ylide generated from 4-phenyloxazolidine acetic acid (-)-8-phenylmenthyl ester, see P. Deprez, J. Royer, and H-P. Husson, *Tetrahedron Asymmetry*, in press.
3. For recent results concerning 1,3-dipolar cycloaddition of achiral azomethine ylides to homochiral activated olefinic dipolarophiles, see A. G. H. Wee, *J. Chem. Soc., Perkin Trans. I*, 1989, 1363; S. Kanemasa and H. Yamamoto, *Tetrahedron Lett.*, 1990, *31*, 3633.
4. (a) R. Beugelmans, L. Benadjila-Iguertsira, J. Chastanet, G. Negron, and G. Roussi, *Can. J. Chem.*, 1985, *63*, 728. (b) G. Roussi and J. Zhang, *Tetrahedron*, 1991, *47*, 5161 and references cited therein. (c) G. Roussi and J. Zhang, *Tetrahedron Lett.*, 1991, *32*, 1443.
5. G. Bettoni, C. Cellucci, and V. Tortorella, *J. Heterocycl. Chem.*, 1976, *13*, 1053.
6. J. McKenna and J.B. Slinger, *J. Chem. Soc.*, 1958, 2759.
7. A. I. Meyers, D. Dickman, and T. Bailey, *J. Am. Chem. Soc.*, 1985, *107*, 7974.

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