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Asymmetric Diels-Alder Reactions with Chiral 1-Azadienes

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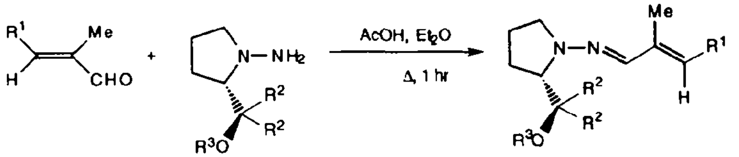
Abstract : Chiral 1-azadienes **1** derived from α,β-unsaturated aldehydes and Enders' hydrazines cycloadd to cyclic dienophiles with high facial selectivities. The adducts can be readily converted into enantiomerically pure piperidine derivatives.

The asymmetric Diels-Alder reaction is a powerful method of synthesis of enantiomerically pure six membered rings[1a-e]. The method has recently been extended to the preparation of enantiomerically pure heterocycles by using a chiral dienophile[1c] or a chiral Lewis acid coordinating to the dienophile[1b, 2]. We wish to present here the first examples of asymmetric hetero Diels-Alder reactions involving chiral 1-azadienes.

We have reported that N,N-dimethylhydrazones derived from α,β-unsaturated aldehydes reacted as electron-rich dienes with various dienophiles to give cycloadducts which could be converted into substituted pyridines or piperidines[3]. Several applications of this reaction have been reported by other groups[4].

We now report on the use of chiral hydrazones **1** as reagents for asymmetric [4+2] cycloadditions with activated dienophiles. Compounds **1** were readily prepared by condensation of α,β-unsaturated aldehydes **2** with enantiomerically pure hydrazines **3**[5] (Scheme 1).



2 **3**

1 a ; $R^1 = R^2 = H$, $R^3 = Me$ 81%
b ; $R^1 = H$, $R^2 = R^3 = Me$ 78%
c ; $R^1 = R^2 = R^3 = Me$ 73%

Scheme 1

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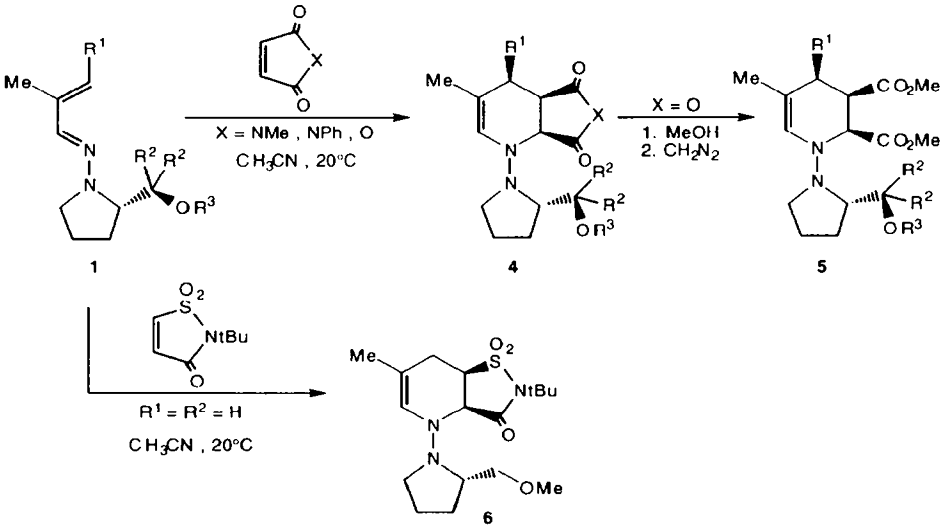
These new 1-azadienes smoothly reacted at room temperature in acetonitrile with cyclic dienophiles (Scheme 2, Table 1)[6]. Adducts **4** are sensitive compounds which can be purified by chromatography on neutral alumina but degrade easily at room temperature. When X=O, adducts **4** could not be purified but were rather transformed into the diesters **5**.



Scheme 2

Table 1 : Cycloadditions of Hydrazones **1** to Cyclic Dienophiles.

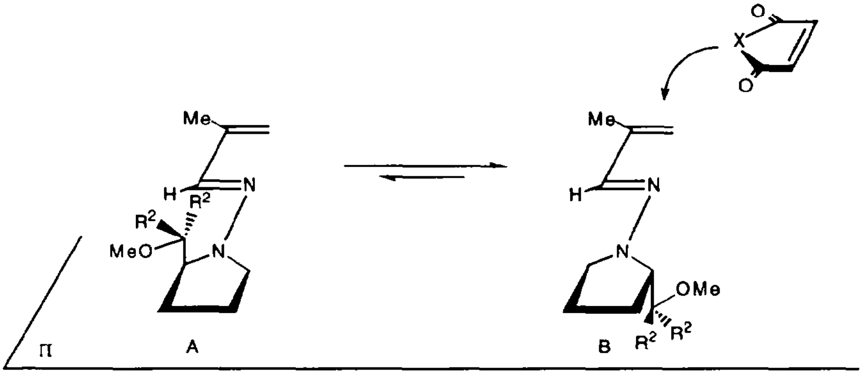
Dienophile	Diene	Yield %	de %(crude)[d]	de % (pure)
N-methylmaleimide	**1a**	81[a]	85	93
	1b	68[a]	≥98	≥98
	1c	65[a]	≥98	≥98
N-phenylmaleimide	**1a**	75[a]	76	≥98
	1b	70[a]	≥98	≥98
maleic anhydride	**1a**	58[b]	80	80
	1b	61[b]	96	≥98
isothiazol-3-(2H)-one	**1a**	51[c]	73	≥98

[a] Yield of **4** after purification by chromatography on neutral alumina (petroleum ether- ethyl acetate); [b] yield of **5** after chromatography on silica gel (petroleum ether-ethyl acetate); [c] yield of **6** after recrystallisation from ether- pentane; [d] measured on crude **4** and **6** in reactions run in CD_3CN.

Diastereoisomeric ratios were determined by examining the signals corresponding to the olefinic proton H_2 and the methine proton H_6 which are different for each diastereoisomer. A coupling constant $^3J=6.9$ Hz for the H_4 and H_5 protons of adduct **4** ($R^1=R^2=Me$, X=NMe) indicates a cis relationship between the two protons, thus establishing an endo approach of the reactants.

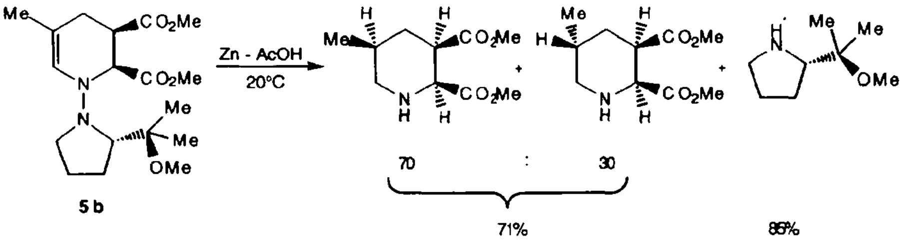
The absolute configuration of the crystalline adduct **6** was established on the basis of an X-ray diffraction analysis[7]. Since both **6** and adducts **4** show negative optical rotations, they were assigned the same absolute configurations.

Results of Table 1 clearly show that a substantial increase of facial selectivity was observed when the size of R^2 was increased. This can be easily rationalized on the basis of Scheme 3. Increasing the size of R^2 should bias the system towards conformation B and favours the attack of the dienophile from the β face.



Scheme 3

As demonstrated earlier in the racemic series[3], the cleavage of the N-N bond can be readily effected with zinc in acetic acid (Scheme 4). The reduction of the double bond leads to a mixture of epimers at C_3. The chiral auxiliary was recovered in high yield.



Scheme 4

These results represent the first examples of asymmetric hetero Diels-Alder reactions using a chiral 1-azadiene. We have been able to control the stereoselectivity of these reactions. Unfortunately, until now, we have not been able to apply the reaction to less reactive dienophiles such as methyl acrylate or dimethyl fumarate.

Acknowledgments

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6. Typical procedure : **1a** (0.963 g / 5.3 mmol) is treated with N-Phenylmaleimide (0.916 g / 5.3 mmol) in CH_3CN under Argon at 20°C for 20 hrs. After the removal of the solvent, the crude mixture is chromatographed on neutral alumina (Brockman II, petroleum ether-AcOEt 4 : 1) to give pure 4a (X = NPh; d.e. ≥98%) in 75% yield. $[\alpha]_D^{20}$: -249.7 ($CHCl_3$; c = 1.03); ^1H NMR (500MHz, $CDCL_3$, J(Hz) : 7.48-7.25 (m, 5H); 6.03 (s, 1H); 4.22 (d,^3J= 8, 1H); 3.62 and 3.35 (2xDxd, ^2J=9.2, ^3J=7.3, 3.7, 1H+1H); 3.30 (s, 3H); 3.12 (m, 2H); 3.05 (q, ^3J= 8.0, 1H); 2.85 (m, 1H); 2.42 (Dxd, ^2J=16.8, ^3J=8.0, 1H); 2.12 (Dxd, ^2J=16.8, ^3J=8.0, 1H); 1.98-1.65 (m, 4H); 1.69 (s, 3H); ^{13}C (125 MHz, $CDCl_3$) : 176.6; 175.2; 131.9; 129.0; 128.5; 126.3; 125.5; 105.9; 75.0; 60.0; 59.1; 58.8; 49.2; 37.8; 27.1; 26.3; 21.2; 20.3. M.S.(E.I., m/z) : 355 (100), 310 (55), 241 (35), 137 (44), 94 (37); I.R. (CH_2Cl_2, cm^{-1}) : 2950-2820, 1720, 1500, 1420, 1370, 1250, 1150, 1100, 890; Anal. Calcd for $C_{20}H_{25}N_3O_3$: C, 67.61; H, 7.04; N, 11.83. Found : C, 67.72; H, 6.61; N, 11.72.
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