

## ASYMMETRIC DIELS-ALDER REACTIONS ON CHIRAL $\alpha,\beta$ - UNSATURATED LACTAMS

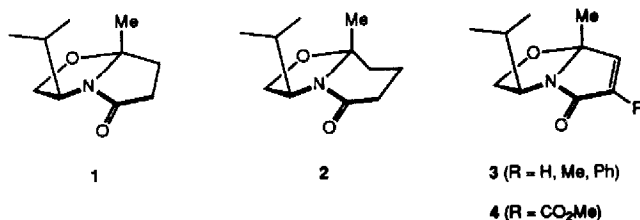
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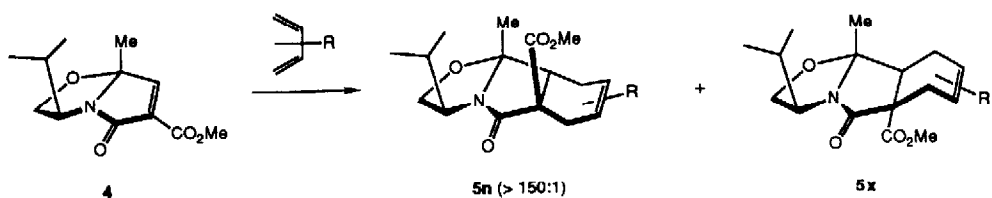
**Summary:** Cycloaddition of various dienes to **4** gives high yields and high regiochemistry and excellent de's of cycloadducts under thermal or Lewis acid conditions.

Asymmetric Diels-Alder reactions have long attracted the interest of organic chemists since the early pioneering effort of Walborsky.<sup>1</sup> Further developments by Corey,<sup>2</sup> Evans,<sup>3</sup> Masamune,<sup>4</sup> and Oppolzer,<sup>5,6</sup> have catapulted this methodology into one of today's most important synthetic tools.

In previous reports from this laboratory, we have shown that the readily available homochiral lactams **1** and **2** are very valuable vehicles for the construction of a number of enantiomerically pure substances ranging from alkaloids<sup>7</sup> to sesquiterpenes.<sup>8</sup> The unsaturated systems, **3** and **4**, have also been employed as substrates for 2 + 2 cycloadditions leading to chiral cyclobutanes<sup>9</sup> and 2 + 1 cycloadditions leading to cyclopropanes.<sup>10</sup>



We now can demonstrate the further utility of **4** by describing its Diels-Alder reactions with dienes affording the cycloadducts **5** accompanied by high levels of regio- and stereoselectivity. Our first attempts at asymmetric cycloadditions involved the unsaturated lactams **3** (R = H, Me, Ph) and resulted in a total lack of reaction with various dienes under many different conditions. However, when the ester **4** was employed, reaction with various dienes proceeded smoothly under mild conditions furnishing products **5n**, resulting from exclusive *endo* addition. The structure of **5n** (R = dimethyl) was confirmed by X-ray analysis (Fig. 1). No trace of the *exo*-isomer **5x** could be detected. Presumably, the extra carboxyl function provides a stronger electronic perturbation of the LUMO in **4** (over **3**) for this "normal electron demand process." From Table 1, where regiochemical



choices are possible (entries 1,3, and 5), *purely thermal conditions* leads to a single product in the case of the 2-siloxybutadiene (entry 1) but poor regioselectivity for isoprene (entry 3) and myrcene (entry 5). The electron-donating ability of the siloxy substituent on the diene and, therefore, the strong influence on regiocontrol was expected based upon earlier precedent.<sup>11</sup> When the isoprene and myrcene additions were examined *in the presence of various Lewis acids*, it was found that the regiochemical outcome (**A**:**B**) could be significantly improved<sup>12</sup> by addition of 1.0 equiv  $\text{ZnCl}_2$  and carrying out the process at 0 °C. Thus **A**:**B** ratios of 25:1 and 15:1, respectively, were reached (entries 4 and 6).

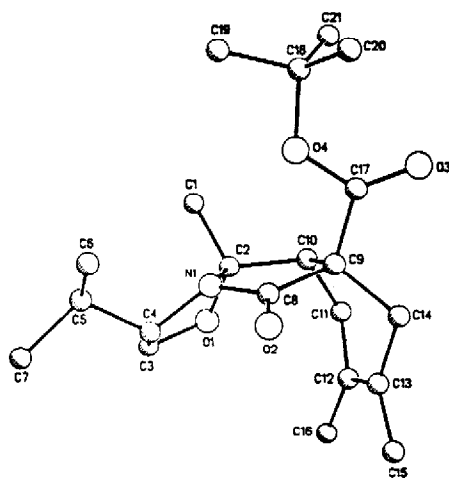


Fig. 1. X-ray structure of **5** (1-Butyl ester).

We also addressed the potential for secondary stereocontrol (Alder "*endo* selectivity") in this series and examined the behavior of *trans*, *trans*-2,4-hexadiene (entries 7-9). The thermal reaction gave exclusively the *endo* adduct in high yield but as a 1.3:1 ratio of **AB** diastereomers. Introduction of the Lewis acid,  $\text{ZnCl}_2$ , provided a slight increase in secondary selectivity with the methyl groups favoring the configuration in **A** by 2.2:1. The most dramatic increase, however, came when a catalytic amount of  $\text{SnCl}_4$  was utilized and the reaction performed at -60 °C. Under these conditions a 10:1 ratio of **A**:**B** was observed (entry 9). The chemical yield was lower for this run furnishing the product in 55% with the remainder being isomeric material. The structures of the latter products that accompanied the cycloadducts in entry 9 appear to be derived from double bond migration under the influence of the Lewis acid catalyst. Therefore, at this point of our study we are

TABLE I. DIELS-ALDER ADDITIONS TO LACTAM, 4

Entry	Diene <sup>a</sup>	Rxn Cond.	Product <sup>b,1</sup>	Yield %	A : B Ratio
1		neat 4 h, 70°		95	100:0
2		neat 8 h, 60°		89	--
3		neat <sup>c</sup> 24 h, 60°		74	2.0:1
4	" "	ZnCl <sub>2</sub> <sup>d</sup> 4 h, 0°	" "	71	25.0:1
5		neat 18 h, 75°		70	2.3:1
6	" "	ZnCl <sub>2</sub> <sup>d</sup> 36 h, 0°	" "	66	15.2:1
7		neat 15 h, 70°		87	1.3:1
8	" "	ZnCl <sub>2</sub> 24 h, 25°	" "	87	2.2:1
9	" "	SnCl <sub>4</sub> <sup>e</sup> 3 h, -60°	" "	55	10:1

<sup>a</sup>Ten equiv of diene were employed. <sup>b</sup>All compounds gave satisfactory spectral and combustion analyses. <sup>c</sup>Heated in a sealed tube. <sup>d</sup>Performed in a 0.1 M solution of CH<sub>2</sub>Cl<sub>2</sub>. <sup>e</sup>0.2 equiv SnCl<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub>. <sup>f</sup>Structure in entry 2 confirmed by X-ray crystallography, as the *t*-butyl ester (Fig. 1).

faced with the situation which affords high levels of secondary stereocontrol and moderate yields of cycloadduct. Although further effort will be put forward to improve the selectivity and yield of the products in entry 9, we have also extended this study to the preparation of novel carbocycles derived from these enantiomerically pure cycloadducts. These are presented in the accompanying paper.

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