High levels of diastereofacial selectivity have been achieved in asymmetric Diels–Alder additions of prochiral 1,3-dienes to dienophiles with a removable, chiral-directing auxiliary (1). However, it is interesting to test whether chiral reagents, both enantiomers of which are inexpensive and easily available, can be efficient chiral auxiliaries in this kind of reaction. In this context, reactions of acrylates (2) and fumarates (3) of several structural, these reagents differ from each other in the structural similarity between the dienophile used by these authors and N-acryloyl-L-phenylalanine methyl ester 1, in our case this catalyst gave low diastereofacial selectivity for all tested molar ratios of catalyst:dienophile.

To increase diastereofacial selectivity, a less effective titanium catalyst, Ti(PrO)₄, was tested. The relationship between the areas of the hplc peaks corresponding to the endo products 2a:2b followed an unexpected pattern, since it increased with increasing reaction temperatures. A careful analysis showed that the peak corresponding to 2a was contaminated with a new product, which was obtained by reaction of N-acryloyl-L-phenylalanine methyl ester with Ti(PrO)₄ and identified as

\[ 2a:2b = 1:6 \] (Scheme 1). The results of the reactions were determined by hplc and are shown in Table 1.

No significant solvent effect was found for the reaction of cyclopentadiene with dienophile N-acryloyl-L-phenylalanine methyl ester 1, the slight changes in both the reaction rate and endo/exo selectivity conforming to the pattern found by Berson et al. (9) for reactions of acrylates with cyclopentadiene.

As expected, the use of AlCl₃ as a catalyst caused a remarkable increase in both the reaction rate and endo/exo selectivity. When the reaction temperature was lowered the endo/exo ratio increased, but diastereofacial selectivity was not noticeably modified for reaction temperatures below 0°C.

Helmchen and co-workers have previously reported (2a) that the use of TiCl₃ to promote the reaction between cyclopentadiene and the acrylate of (S)-ethyl lactate causes a high diastereofacial differentiation, mainly with 0.75 equiv. of Lewis acid. In spite of the structural similarity between the dienophile used by these authors and N-acryloyl-L-phenylalanine methyl ester 1, in our case this catalyst gave low diastereofacial selectivity for all tested molar ratios of catalyst:dienophile.

To increase diastereofacial selectivity, a less effective titanium catalyst, Ti(PrO)₄, was tested. The relationship between the areas of the hplc peaks corresponding to the endo products 2a:2b followed an unexpected pattern, since it increased with increasing reaction temperatures. A careful analysis showed that the peak corresponding to 2a was contaminated by a new product, which was obtained by reaction of N-acryloyl-L-phenylalanine methyl ester with Ti(PrO)₄ and identified as
ester 1 and cyclopentadiene under the same conditions, a similar endo/exo ratio (35.4:1) but a lower diastereofacial selectivity (54:46) were obtained.

The low diastereofacial selectivities obtained with titanium catalysts suggest that the coordination of 1 with this kind of catalyst does not lead to a chelate complex, similar to that postulated by Helmchen et al. for the acrylate of (S)-ethyl lactate – TiCl₄ complex. However, the formation of N-acryloyl-

**Scheme 1**

N-acryloyl-L-phenylalanine isopropyl ester 4. The proportion of this product increases with the reaction time and temperature (Scheme 2).

When the reaction was carried out at −25°C the formation of the isopropyl ester 4 was minimized, and the ratio of 2a:2b approached that obtained with TiCl₄. Neither the Diels–Alder reaction nor ester formation occurred at still lower reaction temperatures.

N-Acryloyl-L-phenylalanine isopropyl ester 4 was made to react, in CH₂Cl₂ at −40°C, with 6 equiv. of cyclopentadiene using 1.1 equiv. of AlCl₃ to promote the reaction. In comparison to the reaction between N-acryloyl-L-phenylalanine methyl

**Scheme 2**

Time (h) | Ratio 4 : 1
---|---
25 | 19 : 79
0 | 66 : 91

**Scheme 3**

(a) SOCl₂, followed by L-H₂NCH(CO₂H)CH₂Ph and BF₃/MeOH (b) Column Chromatography on Silica gel using n-Hexane/Et₂O (1/3) as eluting agent; (c) H₂, Pd/C; (d) HCl 6N.
TABLE 1. Diels–Alder reactions of cyclopentadiene with N-acryloyl-L-phenylalanine methyl ester (2)

<table>
<thead>
<tr>
<th>Lewis acid (equiv.)</th>
<th>Solventa</th>
<th>T (°C)</th>
<th>Time (h)</th>
<th>Yield (%)b</th>
<th>endo/exo ratio of 2a:2b</th>
<th>Ratio of 2a:2b</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>70</td>
<td>63</td>
<td>2.8:1</td>
<td>52:48</td>
</tr>
<tr>
<td>—</td>
<td>Toluene</td>
<td>25</td>
<td>70</td>
<td>49</td>
<td>2.0:1</td>
<td>55:45</td>
</tr>
<tr>
<td>AlCl₃ (1.1)</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>5</td>
<td>99</td>
<td>7.3:1</td>
<td>60:40</td>
</tr>
<tr>
<td>AlCl₃ (1.1)</td>
<td>Toluene</td>
<td>25</td>
<td>5</td>
<td>99</td>
<td>4.5:1</td>
<td>57:43</td>
</tr>
<tr>
<td>AlCl₃ (1.1)</td>
<td>CH₂Cl₂</td>
<td>0</td>
<td>20</td>
<td>80</td>
<td>15.9:1</td>
<td>70:30</td>
</tr>
<tr>
<td>AlCl₃ (1.1)</td>
<td>CH₂Cl₂</td>
<td>-25</td>
<td>25</td>
<td>95</td>
<td>29.0:1</td>
<td>68:32</td>
</tr>
<tr>
<td>AlCl₃ (1.1)</td>
<td>CH₂Cl₂</td>
<td>-40</td>
<td>50</td>
<td>93</td>
<td>31.3:1</td>
<td>71:29</td>
</tr>
<tr>
<td>TiCl₄ (0.75)</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>20</td>
<td>95</td>
<td>14.9:1</td>
<td>51:49</td>
</tr>
<tr>
<td>TiCl₄ (0.75)</td>
<td>CH₂Cl₂</td>
<td>-15</td>
<td>65</td>
<td>91</td>
<td>12.5:1</td>
<td>51:49</td>
</tr>
<tr>
<td>TiCl₄ (1.1)</td>
<td>CH₂Cl₂</td>
<td>-15</td>
<td>65</td>
<td>86</td>
<td>3.0:1</td>
<td>49:51</td>
</tr>
<tr>
<td>TiCl₄ (1.7)</td>
<td>CH₂Cl₂</td>
<td>-15</td>
<td>65</td>
<td>86</td>
<td>4.0:1</td>
<td>52:48</td>
</tr>
<tr>
<td>Ti(PrO)₄ (1.1)</td>
<td>CH₂Cl₂</td>
<td>-25</td>
<td>65</td>
<td>40</td>
<td>5.1:1</td>
<td>58.42:1</td>
</tr>
<tr>
<td>Ti(PrO)₄ (1.1)</td>
<td>CH₂Cl₂</td>
<td>-40</td>
<td>190</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

a Twenty-five millilitres.


c The peak corresponding to 2a is contaminated by a small amount of N-acryloyl-L-phenylalanine isopropyl ester 4.

L-phenylalanine isopropyl ester 4 indicates that, in spite of the greater basicity of the amide moiety, there may be some degree of coordination to the ester moiety.

To determine the absolute configuration of the major product, endo- and exo-5-norbornen-2-carboxylic acids, which were prepared by reaction of acrylic acid with cyclopentadiene followed by iodolactone separation, were used to prepare endo and exo cycloadducts 2 and 3. The endo mixture was separated into its components by means of column chromatography on silica gel, using n-C₆H₁₄/Et₂O (1:3) as eluting agent. By treatment of 2a or 2b with 20% aqueous NaOH only the ester moiety was hydrolysed and, after 2 h, partial epimerization was observed. Treatment of 2a and 2b with aqueous mineral acids led to a complex mixture of products, probably due to Wagner–Meerwein type rearrangements (10). In view of this, 2a and 2b were hydrogenated and converted without epimerization into both enantiomers of the endo-norbornan-2-carboxylic acid, 6a and 6b, by acid hydrolysis. The absolute configurations of these acids were determined by comparing their specific rotations with those given in the literature (11). Under these conditions 2a gave (1S, 2R, 4R) norbornan-2-carboxylic acid and 2b (1R, 2S, 4S) norbornan-2-carboxylic acid, with optical rotations [a]₂⁰ D (EtOH) of +30° (c 1.2) and -30° (c 1.2) respectively (Scheme 3).

In all cases the Diels–Alder reaction led predominantly to the (1R, 2R)-endo diastereomer 2a, which comes from the attack of the cyclopentadiene on the Si face of the dienophile 1. This result can be explained on the basis of reactive conformer 1, with antiplanar enolate conformation, which is similar to those postulated for complexes (7) of “classical” chiral acrylates with only one center capable of coordination (12) (Scheme 4). The preferential attack on the Si face of the dienophile 1 suggests a possible electronic effect of the phenyl group (12).

**Experimental**

The ¹H nmr spectra were recorded at 80 MHz with a Bruker model WP 80 CW spectrometer and at 200 MHz with a Varian model XL 200 spectrometer in CDC₁₃ with Me₄Si as internal standard. High pressure liquid chromatography was performed using a Hewlett-Packard model 1090 M chromatograph; specific rotations were measured with a Perkin–Elmer model 241-MC polarimeter. Melting points were determined on a Buchi 510 apparatus and are uncorrected.

The chiral dienophile 1 was easily obtained by reaction of L-phenylalanine with acryloyl chloride (8) followed by methylation with BF₃–MeOH complex.

A. Diels–Alder reactions

1. Without a catalyst

One millimole of 1 and 6 mmol of cyclopentadiene were stirred under nitrogen in 25 mL of the appropriate solvent and at the temperature specified (Table 1). After the corresponding time the solution was filtered and evaporated under reduced pressure to give a solid, which was analyzed by hplc.

2. With a catalyst

One millimole of 1 and the corresponding amount of the catalyst were stirred in 20 mL of dry CH₂Cl₂ under nitrogen at the appropriate temperature for 1 h. A solution of cyclopentadiene (6 mmol) in 5 mL of dry CH₂Cl₂ at the same temperature was then added. The mixture was stirred for the adequate time (Table 1) and treated with a cold 10% aqueous NaOH solution in the case of AlCl₃ or 15% aqueous NaOH solution in the case of titanium catalyst. The organic layer was dried with anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to give a solid, which was analyzed by hplc.

B. Synthesis of N-acryloyl-L-phenylalanine isopropyl ester 4

One millimole of 1 and 1.1 mmol of Ti(PrO)₄ were stirred in 25 mL of dry CH₂Cl₂ under nitrogen at the appropriate temperature for the chosen time. The mixture was then treated with a 15% NaOH solution and the organic layer was dried with anhydrous sodium sulfate, filtered,
and evaporated under reduced pressure to give a solid, which was analyzed by hplc.

To obtain an analytically pure sample of 4, the reaction was carried out with 2 mmol of Ti(PrO)₄ at room temperature for 72 h, and the solid obtained after the treatment was recrystallized from diethyl ether/n-hexane; mp 81–83°C; nmr (CDCl₃) δ: 1.12 (d, 3H), 1.22 (d, 3H), 3.12 (dd, 2H), 4.9 (m, 2H), 5.5 (dd, 1H), 6.1 (m, 3H), 7.25 (m, 5H). Anal. calcd. for C₁₅H₁₉NO₃: C 68.94, H 7.33, N 5.36; found: C 69.29, H 7.07, N 5.43.

C. Alternative synthesis of methyl N-(endo-bicyclo[2.2.1]hept-2-carbonyl)-L-phenylalanine 2a and 2b

Ten millimoles of endo-bicycle[2.2.1]hept-5-en-2-carboxylic acid and 15 mmol of thionyl chloride in dry chloroform were refluxed for 3 h. After this time the solution was evaporated under reduced pressure to give a white oil appeared (yield 10%). After this time the solution was extracted with ether to give both diastereoisomers. These were recrystallized from water to give a 65% yield of N-(endo-bicycle[2.2.1]hept-5-en-2-carbonyl)-L-phenylalanine. Five millimoles of this compound were refluxed with BF₃-MeOH complex for 2 h. The solution was washed with sodium carbonate solution and extracted several times with ether. The organic layer was separated and dried over anhydrous sodium sulfate. After removing the organic solvent a white oil appeared (yield 90%), which was passed through a chromatographic column of silica gel, using n-hexane/CH₂Cl₂ = 1:3 as eluting agent, to give both diastereoisomers. These were recrystallized from n-hexane to give analytically pure samples of methyl N-(endo-bicycle[2.2.1]hept-5-en-2-carbonyl)-L-phenylalanine 2a and 2b. mp (2a) 114–116°C; nmr (2a) (CDCl₃) δ: 1.23–1.40 (m, 3H), 1.88 (m, 1H), 2.82–2.89 (m, 2H), 3.00–3.20 (m, 3H), 3.73 (s, 3H), 4.85 (m, 1H), 5.74 (m, 1H), 6.18 (m, 1H), 7.08–7.32 (m, 5H). Anal. calcd. for C₁₅H₁₉NO₃: C 72.22, H 7.69, N 4.15; found: C 71.96, H 7.20, N 4.93.

For 2b: mp 80–82°C; nmr (CDCl₃) δ: 1.23–1.40 (m, 3H), 1.92 (m, 1H), 2.81–2.90 (m, 2H), 3.00–3.20 (m, 3H), 3.73 (s, 3H), 4.85 (m, 1H), 5.75 (m, 1H), 6.18 (m, 1H), 7.06–7.38 (m, 5H). Anal. found: C 71.52, H 7.33, N 4.21.

Two millimoles each of 2a and 2b in 20 mL of methanol were hydrogenated at room temperature and atmospheric pressure using 10% Pd/C as catalyst until completion of the reaction (tlc). In 1 h the hydrogenation was completed, the catalyst filtered off, and the solvent removed under reduced pressure to give white solids, 5a and 5b, in quantitative yield. Anal. calcd. for C₁₅H₂₃NO₅: C 71.73, H 7.99, N 4.15; found for 5a: C 71.54, H 7.99, N 4.15; found for 5b: C 71.45, H 7.99, N 4.15.

To identify the major product in the Diels–Alder reaction, 1 millimole each of 5a and 5b in 5 mL of 6 N hydrochloric acid were refluxed for 24 h. After this time the solution was extracted with ether and the organic layer was dried over anhydrous sodium sulfate and evaporated to give both endo bicyclo[2.2.1]heptan-2-carboxylic acids 6a and 6b whose specific rotations were measured, [α]D°(6a) +30° (c 1.2, EtOH) and [α]D°(6b) −30° (c 1.2, EtOH), and compared with the literature value, [α]D 30.6° (c 1.2, EtOH) (11).

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