

## Clay-Catalysed Asymmetric Diels-Alder Reaction of Cyclopentadiene with Chiral Acrylates

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**Abstract:** Clay-catalysed Diels-Alder reactions of cyclopentadiene with several chiral acrylates are studied. The results obtained show that these solids are not efficient catalysts when chiral auxiliaries of large size are used. Clay-catalysed reactions between cyclopentadiene and (R)-O-acryloylpantolactone are compared with non-catalysed and TiCl<sub>4</sub> and EtAlCl<sub>2</sub>-catalysed reactions. With regard to diastereofacial selectivity, the clays studied behave like homogeneous aluminium catalysts. Clay-catalysed reactions of (R)-O-acryloylpantolactone lead to the (1S,2S,4S)-cycloadduct with good chemical yield, high % d.e. and excellent endo/exo selectivity. Given that (-)-menthyl acrylate leads to the (1R,2R,4R)-cycloadduct with about the same diastereofacial selectivity, (-)-menthol and (R)-pantolactone behave as complementary chiral auxiliaries.

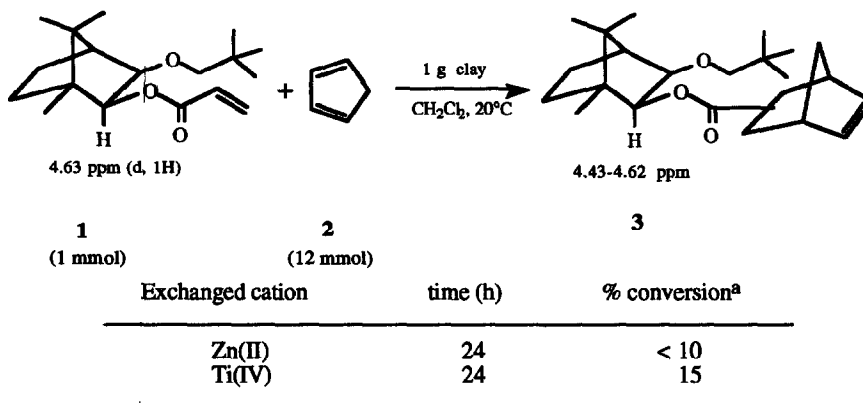
The Diels-Alder reaction of acrylic acid derivatives is an important reaction since the cycloadducts obtained are key intermediates for the total synthesis of a variety of natural products<sup>1</sup>. Excellent diastereofacial selectivities have been obtained in asymmetric Diels-Alder reactions of prochiral 1,3-dienes with chiral acrylates.<sup>2</sup> However, these good results are only obtained when a Lewis acid, necessary to control the *s-cis/s-trans* equilibrium of the enoate moiety of the dienophile, is used as a catalyst. This methodology has its drawbacks; namely a large amount of catalyst has to be used and necessitates the disposal of environmentally hazardous residues. Heterogeneous catalysis is an alternative which overcomes these problems.

It has been shown that several inorganic solids, such as silica gel,<sup>3,4</sup> magnesium silicate,<sup>4</sup> alumina,<sup>4-6</sup> zeolites<sup>7</sup> and clays<sup>8,9</sup> are efficient catalysts in Diels-Alder reactions. However, in the field of heterogeneous catalysis in Diels-Alder reactions of chiral dienophiles, only the reactions of cyclopentadiene with (-)-menthyl acrylate, catalysed by clays<sup>9</sup> and alumina,<sup>6</sup> and di(-)-menthyl fumarate, catalysed by alumina,<sup>6</sup> have been studied.

In the clay-catalysed reaction of (-)-menthyl acrylate with cyclopentadiene a 54 % d.e. was obtained at -20°C. Although the asymmetric induction can be increased to up to 58 % by lowering the reaction temperature, the reaction is too slow and only 33 % of conversion is obtained after 96 h.<sup>9</sup> As clay-catalysed Diels-Alder reactions are very sensitive to temperature, probably due to diffusion problems, this typical method of increasing asymmetric induction cannot be used.

Given the interest in improving diastereofacial selectivity, it is important to test other chiral auxiliaries than (-)-menthol, such as borneol and isborneol derivatives. The clay-catalysed Diels-Alder reaction between *cis*-3-

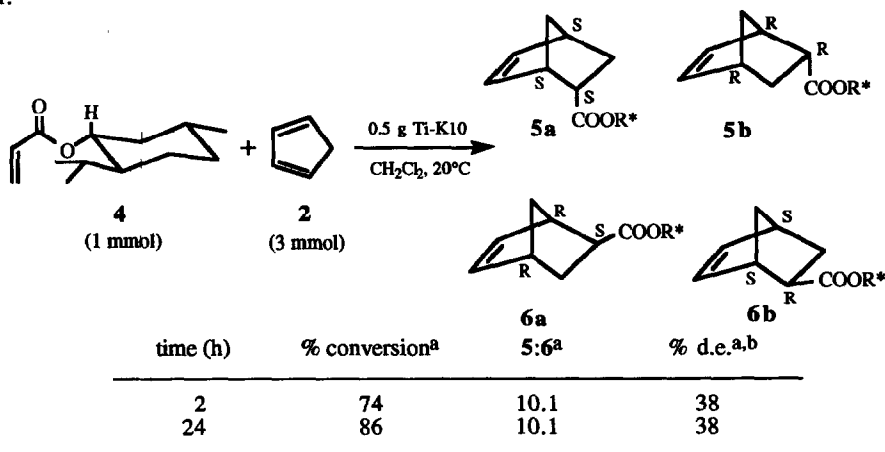
neopentoyisobornyl acrylate (**1**)<sup>10</sup> and cyclopentadiene (**2**) was tested with Zn(II) K10 montmorillonite which had been previously calcined at 550°C, but conversions smaller than 10 % (determined by <sup>1</sup>H-NMR) were obtained even with a great excess of diene (Figure 1).



<sup>a</sup>Determined by <sup>1</sup>H-NMR.

Figure 1

In order to solve the problem of reactivity we tried to obtain a more efficient clay than Zn(II)-K10. Ti(IV)-exchanged montmorillonite, calcined at 550°C, allowed us to obtain high conversions in the reaction between (-)-menthyl acrylate (**4**) and cyclopentadiene (**2**) with only a 3:1 excess of diene (Figure 2). Unfortunately, this catalyst only gives rise to a 15 % of conversion after 24 h in the reaction between *cis*-3-neopentoyisobornyl acrylate (**1**) and cyclopentadiene (**2**) (Figure 1). So Diels-Alder reactions of acrylates that incorporate chiral auxiliaries of large size are not effectively catalysed by clays. Again diffusion problems may account for this behaviour.

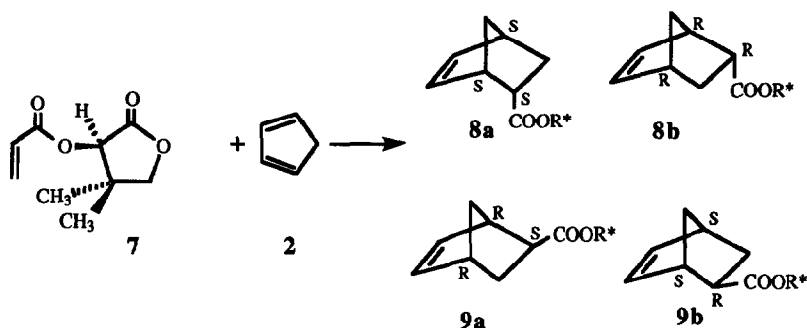


<sup>a</sup>Determined by gas chromatography. <sup>b</sup>5b is preferably obtained (see ref. 9).

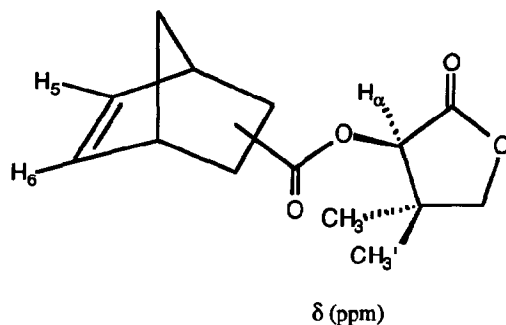
Figure 2

In view of the above limitations it was decided to examine the behaviour of these solids in Diels-Alder reactions of acrylates of smaller, chiral auxiliaries. (R)-O-acryloylpantolactone (**7**) is an interesting choice for two

reasons. First of all, (*R*)-pantolactone has proved to be an excellent chiral auxiliary when incorporated in several dienophiles.<sup>11,12</sup> Furthermore, it is able to form chelate complexes with suitable Lewis acids and the formation of these complexes strongly influences the diastereofacial selectivity. Therefore, it was considered that the study of this dienophile should provide some information about the catalytic role of heterogeneous catalysts. To this end the clay-catalysed reactions between (*R*)-*O*-acryloylpantolactone (**7**) and cyclopentadiene were studied and their results compared with those obtained from homogeneously-catalysed reactions.



(*R*)-*O*-acryloylpantolactone (**7**), obtained as described by Helmchen,<sup>11</sup> was reacted with cyclopentadiene (**2**) in the presence of cation-exchanged K10 montmorillonites. Prior to use, the corresponding amount of clay was weighed and dried in an oven at 120°C overnight or calcined by the following method: 20°C, 10°C/min, 120°C, 1°C/min, 550°C (10 h), -1°C/min, 40°C. Reactions were monitored by gas chromatography, which allowed an accurate determination of the percentage of conversion but only an approximate determination of selectivities, since one endo and one exo cycloadducts have the same retention time.



Cycloadduct	$\delta$ (ppm)				
	CH <sub>3</sub> '	CH <sub>3</sub>	H <sub><math>\alpha</math></sub>	H <sub>5</sub>	H <sub>6</sub>
<b>8a</b>	1.12	1.15	5.30	5.88	6.23
<b>8b</b>	1.07	1.13	5.27	6.06	6.17
<b>9a + 9b</b>	-	1.17	5.35	-	-

Figure 3

The diastereomeric composition of the mixture of cycloadducts and the absolute configuration of the major product could be determined by <sup>1</sup>H-NMR. (1*S*,2*S*,4*S*)-cycloadduct (**8a**) (98% d.e.) was obtained from a

TiCl<sub>4</sub>-catalysed reaction as previously described,<sup>11</sup> and its <sup>1</sup>H-NMR spectrum registered. The <sup>1</sup>H-NMR spectrum of the (1R,2R,4R)-cycloadduct (**8b**) was deduced from that of an approximately equimolecular endo pair (**8a**:**8b** = 53:47) obtained from a non-catalysed reaction. Finally, <sup>1</sup>H-NMR analysis of the mixture of cycloadducts, resulting from a non-catalysed reaction, allowed us to assign certain signals to exo-adducts. Figure 3 shows the peaks used to determine endo/exo and diastereofacial selectivities.

Table 1 summarises the results obtained from the reaction of (R)-O-acryloylpantolactone (**1**) with cyclopentadiene (**2**). As can be seen, the clay plays a catalytic role and makes the reaction faster with a noticeable increase in endo/exo and diastereofacial selectivities. The Fe(III)-clay activated at 120°C displays particular behaviour, the reaction with this catalyst is slower and considerable decreases in both selectivities were observed. This clay has the lowest Lewis-Brønsted acidity relationship (3:1), Brønsted acid sites catalyse the oligomerization of the cyclopentadiene and the oligomers formed poison the catalyst, with the result that the clay is partially deactivated and the percentage of the less selective reaction in solution increases. Ti(IV) clay is again the best catalyst and quasi total conversion is obtained after only 2 h.

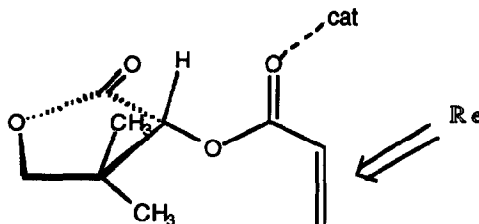
**Table 1.** Results obtained from the reactions of (R)-O-acryloylpantolactone (**7**) with cyclopentadiene (**2**) in methylene chloride.

Catalyst	Temp (°C)	2:7	Time (h)	Yield (%) <sup>a</sup>	endo/exo <sup>b</sup>	% d.e. <sup>b,c</sup>
-	20	6:1	3 24	21 100	75:25 75:25	6 6
TiCl <sub>4</sub> <sup>d</sup>	-10	1.5:1	0.5	100	99:1	92
EtAlCl <sub>2</sub>	-10	1.5:1	1	94	99:1	42
Zn-120	20	3:1 5:1	2 <sup>e</sup> 6	73 97	93:7	43
Fe-120	20	6:1	3 24	38 80	83:17	22
Zn-550	20	3:1 5:1	2 <sup>e</sup> 4 24	50 80 98	91:9	33
Fe-550	20	3:1 5:1	2 <sup>e</sup> 4 24	57 81 98	92:8	39
Zn-120	-20	3:1	2 6 <sup>f</sup> 24	17 32 83	95:5	53
Ti-550	20	3:1	2	94	90:10	43

<sup>a</sup>Determined by gas chromatography. <sup>b</sup>Determined by <sup>1</sup>H-NMR. <sup>c</sup>**8a** is preferably obtained. <sup>d</sup>Ref. 11. <sup>e</sup>At this time 2 eq. of diene were added. <sup>f</sup>At this time 3 eq. of diene were added.

Unlike that observed in the reaction between (S)-O-acryloyl ethyl lactate and cyclopentadiene,<sup>13</sup> aluminium and titanium homogeneous catalysts lead preferably to the same endo-cycloadduct (**8a**). Therefore, the formation of a TiCl<sub>4</sub>-dienophile chelate complex is only detected by the noticeable increase in asymmetric induction. With regard to diastereofacial selectivity, clays behave EtAlCl<sub>2</sub>. The direction of the asymmetric induction can be accounted for by involving a non-chelate dienophile-catalyst complex even with the Ti(IV) clay.

This is not completely surprising if the differences between  $\text{TiCl}_4$  and  $\text{TiCl}_2(\text{iPrO})_2$  in homogeneous catalysis<sup>13</sup> and the surrounding of  $\text{Ti(IV)}$  in the clay are taken into account. In this non-chelate complex the dienophile displays an anti-enoate conformation and the methyl groups in pantolactone shield the Si face of the double bond.



It can be concluded that the role of clays as catalysts in asymmetric Diels–Alder reactions is limited to the use of chiral auxiliaries of small size and the behaviour of these catalysts is comparable to that of homogeneous aluminium catalysts. Furthermore, it is important to notice that (-)-menthol leads to the (1R,2R,4R)-cycloadduct and (R)-pantolactone to the (1S,2S,4S), with the best diastereofacial selectivity (53–54 % d.e.) described for heterogeneously catalysed asymmetric Diels–Alder reactions, so they behave as complementary chiral auxiliaries.

## Experimental

### Preparation and characterization of the heterogeneous catalysts.

K10 montmorillonite was purchased from Aldrich. Cation exchange was performed by one of the following procedures:

- Fe(III) and Zn(II) clays: K10 montmorillonite (10 g) was gradually added to stirred ferric or zinc chloride solutions (125 ml, 1 M) at room temperature.<sup>8d</sup> The suspensions were stirred for 24 h, the solid filtered and washed chloride free with deionised water.

- Ti (IV) clay<sup>14</sup>: the solution of Ti(IV) was prepared by first adding  $\text{TiCl}_4$  (18.97 g, 100 mmol) to HCl (4 ml, 6 M) under argon atmosphere. This mixture was then diluted with deionised water (122 ml). Cation exchange was performed by gradually adding this solution of Ti(IV) to a suspension of K10 montmorillonite (10 g) in deionised water (2.5 l). The suspension was stirred at room temperature for 24 h, the solid filtered and washed chloride free with deionised water.

The resulting solids were dried overnight on a thin bed at 120°C in an oven and ground in a mortar. The catalysts were equilibrated over saturated salt solutions in order to give reproducible water contents. Clay calcination was carried out in dry air (25–30 ml/min) by the following temperature program: 20°C, 10°C/min, 120°C, 1°C/min, 550°C (10 h), -1°C/min, 40°C. Surface areas were calculated from BET isotherms determined at 77 K. In all cases the values obtained fall within the range of 220–240 m<sup>2</sup>/g. The micropore volume (pores  $\leq$  1 nm) is 0.1 ml/g.

### Reactions between (R)-O-acryloylpantolactone and cyclopentadiene

(R)-O-acryloylpantolactone was prepared by a previously described procedure.<sup>11</sup> Reactions were monitored by gas chromatography (FID from Hewlett-Packard 5890 II, cross-linked methyl silicone column 25 m x 0.2 mm x 0.33  $\mu\text{m}$ , helium as carrier gas 20 psi, injector temperature 230°C, detector temperature 250°C, oven temperature program 175°C (5 min) - 25°C/min - 200°C (8 min), retention times: **7** (3.9 min), **9** (11.1 min), **9+8b** (11.3 min), **8a** (11.7 min)). Endo/exo selectivity, diastereomeric excess in endo-cycloadducts and absolute configuration of the major product were determined by <sup>1</sup>H-NMR analysis of reaction mixtures.

$\text{TiCl}_4$ -catalysed reaction: By using the reaction and purification methods previously described by Helmchen<sup>11</sup> (1S,2S,4S)-bicyclo[2.2.1]hept-5-ene-2-carboxylate of (R)-pantolactone was obtained with a 98% d.e. <sup>1</sup>H-NMR ( $\text{CDCl}_3$ ,  $\delta$  ppm): 6.23 (dd, 1H), 5.88 (dd, 1H), 5.30 (s, 1H), 4.01 (m, 2H), 3.24 (bs, 1H), 3.13 (m, 1H), 2.92 (bs, 1H), 1.92 (m, 1H), 1.45 (m, 2H), 1.30 (d, 1H), 1.15 (s, 3H), 1.12 (s, 3H).

$[\alpha]_D^{25}(c = 30 \text{ mg/ml, CHCl}_3, 98\% \text{ d.e.}) = -113.3$

Non-catalysed reaction: A solution of (R)-O-acryloylpantolactone (0.184 g, 1 mmol) and freshly distilled cyclopentadiene (0.396 g, 6 mmol) in dry methylene chloride (10 ml) was stirred at 20°C for 24 h and the reaction monitored by gas chromatography. The solvent was evaporated under reduced pressure and 10 ml of methanol added. The cyclopentadiene insoluble polymers were then eliminated by filtration and the methanol

eliminated under reduced pressure. The composition of the resulting mixture was analyzed by  $^1\text{H-NMR}$  and passed through a chromatography column on silica-gel to afford 120 mg (48 %) of the endo pair. From this mixture the  $^1\text{H-NMR}$  of the (1R,2R,4R)-bicyclo[2.2.1]hept-5-ene-2-carboxylate of (R)-pantolactone was deduced.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ,  $\delta$  ppm): 6.17 (dd, 1H), 6.06 (dd, 1H), 5.27 (s, 1H), 4.00 (m, 2H), 3.26 (bs, 1H), 3.10 (m, 1H), 2.91 (bs, 1H), 1.92 (m, 1H), 1.44 (m, 2H), 1.27 (m, 1H), 1.13 (s, 3H), 1.07 (s, 3H).

$\text{EtAlCl}_2$ -catalysed reaction: To a solution of (R)-O-acryloylpantolactone (0.184 g, 1 mmol) in dry methylene chloride (5 ml) at  $-10^\circ\text{C}$ ,  $\text{EtAlCl}_2$  (0.15 ml of a 1 M solution in hexane, 0.15 mmol) was added under argon and the solution stirred for 30 min. Freshly distilled cyclopentadiene (0.1 g, 1.5 mmol) was then added and the solution stirred for an additional hour. The mixture was quenched by addition of  $\text{Na}_2\text{CO}_3 \cdot 10\text{H}_2\text{O}$ , filtered and the percentage of conversion determined by gas chromatography. The solvent was removed under reduced pressure and the composition of the mixture analyzed by  $^1\text{H-NMR}$ .

Clay-catalysed reactions: Preweighed exchanged montmorillonite (1.5 g) was dried at  $120^\circ\text{C}$  overnight or calcined by the above-described method. The flask was charged with the catalyst and methylene chloride (15 ml) under argon atmosphere at the working temperature (Table 1). (R)-O-acryloylpantolactone (0.552 g, 3 mmol) and freshly distilled cyclopentadiene (amount described in Table 1) were added via syringe, the flask shaken and the reaction monitored by gas chromatography. After shaking for the corresponding time (Table 1) the catalyst was separated by filtration and washed with methylene chloride. The solvent was removed under reduced pressure and the mixture analyzed by  $^1\text{H-NMR}$ .

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