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$AlPO_4$-Catalysed Asymmetric Diels-Alder Reactions of Cyclopentadiene with Chiral Acrylates

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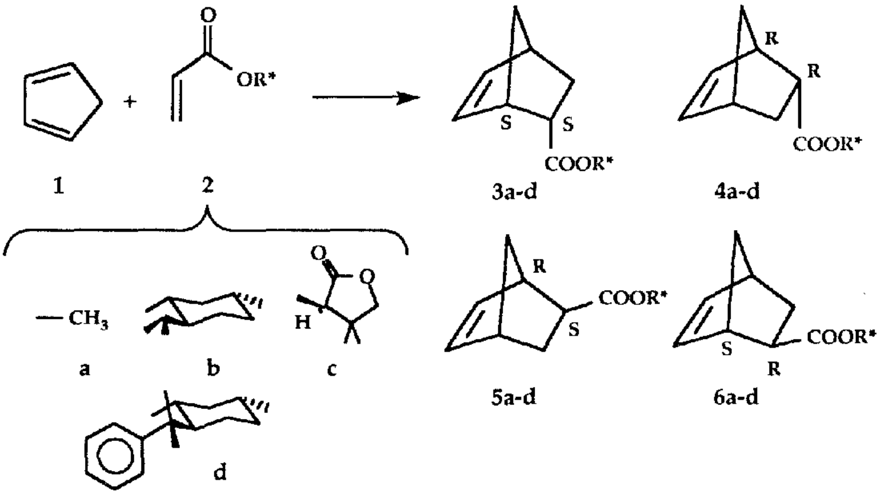
Abstract: Reactions of cyclopentadiene with several chiral acrylates are studied and compared with the same reactions catalysed by Zn(II)-exchanged K10 montmorillonite. In general, amorphous $AlPO_4$ is a more efficient catalyst than the clay. In particular, the reaction of cyclopentadiene with (-)-8-phenylmenthyl acrylate leads to 74% diastereomeric excess (d.e.) in methylene chloride at low temperatures. This result constitutes the highest asymmetric induction described to date for a solid-catalysed asymmetric Diels-Alder reaction. When the reactions are carried out in the absence of a solvent a noticeable decrease in selectivity is observed, probably due to an extensive competition of the non-catalysed reaction.

Introduction: The Diels-Alder adducts of acrylic acid derivatives constitute an important class of compounds as key intermediates for the total synthesis of a variety of natural products.[1] Excellent diastereofacial selectivities have been achieved in asymmetric Diels-Alder reactions between prochiral 1,3-dienes and chiral acrylates.[2] However, these good results are only obtained in the presence of a Lewis acid. This methodology has drawbacks, such as the disposal of environmentally hazardous residues. Heterogeneous catalysis is an interesting alternative which overcomes these problems.

Heterogeneous catalysis in Diels-Alder reactions of some chiral dienophiles has been studied by using clays,[3-5] alumina,[6] and silica and alumina modified by Lewis acids[7] as heterogeneous catalysts. The best asymmetric inductions (about 55% d.e.) have been obtained in the presence of clays (cation-exchanged K10 montmorillonites). However, the low catalytic activity of these solids, in comparison with homogeneous catalysts, precludes the use of better chiral auxiliaries than (-)-menthol and (R)-pantolactone.[5] Therefore, the above-mentioned 55% d.e. is probably the best asymmetric induction that can be achieved with these catalysts. So, the search for new solids capable of catalysing reactions of acrylates with better chiral auxiliaries is an interesting task. With regard to this, the surface acid-base character of synthetic $AlPO_4$ catalysts makes it possible to use them for a number of reactions in the field of selective organic synthesis.[8,9]

In this paper we describe the results obtained using $AlPO_4$[10] as a catalyst, in comparison with those obtained in the same reactions catalysed by Zn(II)-exchanged K10 montmorillonite calcined at 550 °C.[4]

Results and Discussion: The catalytic activities of both solids were compared in the reactions of cyclopentadiene with methyl acrylate, (-)-menthyl acrylate, and O-acryloyl-(R)-pantolactone (Scheme 1). The results obtained in these reactions are gathered in Table 1.



Scheme 1

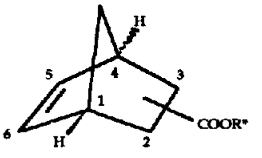
With the exception of the reaction between cyclopentadiene and O-acryloyl-(R)-pantolactone (**2c**), $AlPO_4$ is a better catalyst than the Zn(II)-exchanged K10 montmorillonite, leading to greater conversions and slightly higher selectivities. Specially noteworthy is the reaction between cyclopentadiene and (-)-menthyl acrylate (**2b**), where an almost total conversion, a high *endo/exo* ratio, and a reasonable asymmetric induction is achieved. $AlPO_4$ can be recovered once, by filtration and drying, with only a slight loss of catalytic activity. However, a second recovery considerably decreases the conversion, although both selectivities remain in about the same levels. Finally, the results obtained with **2b** and **2c** indicate that a right choice of the pair dienophile-catalyst is needed to get the best results.

Table 1. Results obtained in the reactions of cyclopentadiene (**1**) with methyl acrylate (**2a**), (-)-menthyl acrylate (**2b**) and O-acryloyl-(R)-pantolactone (**2c**) in CH_2Cl_2 at 20 °C

Dienophile	catalyst (g/mmol of **2**)	**1**: **2**	t (h)	conversion[a] (%)	*endo/exo*[a]	d.e.[a] (%)
2a	Zn(II)-K10 (0.17)[b]	3:1	2	92	14.7	–
	$AlPO_4$ (0.17)	3:1	2	98	21.0	–
2b	Zn(II)-K10 (0.50)[b]	3:1	2	67	11.0	41[c]
	$AlPO_4$ (0.50)	3:1	1	99	14.4	46[c]
	$AlPO_4$ (0.50)[d]	3:1	1	90	13.3	46[c]
	$AlPO_4$ (0.50)[e]	3:1	1	19	11.4	45[c]
2c	Zn(II)-K10 (0.50)f	3:1	2	50	-	-
		5:1	24	98	10.1	33[g]
	$AlPO_4$ (0.5)	3:1	2	44	–	–
			24	100	6.5	11[g]

[a] Determined by previously described methods (ref. 4 for **2a** and **2b**, and ref. 5 for **2c**); [b] Ref. 4; [c] **4b** is preferably obtained; [d] Recovered once by filtration and drying; [e] Recovered twice by filtration and drying; [f] Ref. 5; [g] **3c** is preferably obtained

In view of the excellent results achieved in the reaction between cyclopentadiene and (-)-menthyl acrylate (**2b**), we studied the reaction of the same diene with the acrylate of a better chiral auxiliary in the same family, namely (-)-phenylmenthyl acrylate (**2d**) (Scheme 1). The chiral auxiliary was obtained by the reaction of acryloyl chloride and (-)-8-phenylmenthol, according to the procedure described by Oppolzer et al.[11] Diels-Alder reactions were monitored by HPLC and final results were determined by ^{1}H-NMR and ^{13}C-NMR by integration of the signals indicated in Figure 1. Absolute configurations of **3d** and **4d** were assigned by comparison of the NMR spectra obtained in the heterogeneously-catalysed reactions, with those obtained in a Lewis acid-catalysed reaction, whose results had been previously described by Oppolzer and co-workers.[12]



Cycloadduct	δ (ppm) H-1	H-4	C-5	C-6	C=O
3d	2.78	2.69	137.6	132.0	173.8
4d	3.06	2.78	137.1	132.9	174.1
5d	2.78	2.65	137.9	-	175.3
6d	2.86	2.78	137.7	-	175.8

Note: **5d** and **6d** have been tentatively assigned on the basis of mechanistic considerations

Figure 1

Table 2 gathers the results obtained in the reaction between **2d** and cyclopentadiene. Zn(II)-exchanged K10 montmorillonite is not a very efficient catalyst for this reaction and reasonable rates can only be obtained if large amounts of diene and catalyst are used. This can be explained by an extensive oligomerization of the diene and the subsequent poisoning of the catalyst due to the low reactivity of the dienophile. In view of the low asymmetric inductions, it might be thought that, in these conditions, some of the non-catalysed reaction occurs which greatly decreases the % d.e. In fact, the non-catalysed reaction has been reported[13] to lead to **3d** as the major cycloadduct with a 43% d.e.

Table 2. Results obtained in the reactions of cyclopentadiene (**1**) with (-)-8-phenylmenthyl acrylate (**2d**) in CH_2Cl_2

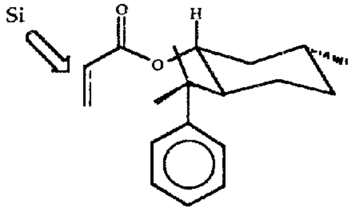
catalyst (g/mmol of **2d**)	**1**: **2**	T (°C)	t (h)	conversion[a] (%)	*endo*/*exo*[b]	d.e.[b,c] (%)
Zn(II)-K10 (0.75)	12:1[d]	20	26	52	6.7	40
Zn(II)-K10 (2.25)	12:1[e]	20	10	85	7.3	48
$AlPO_4$ (1.00)	3:1	20	16	100	11.1	54
$AlPO_4$ (1.00)	6:1	-25	24	72	14.0	74

[a] Determined by HPLC; [b] Determined by NMR; [c] **4d** is the major cycloadduct; [d] The diene is regularly added in portions of 3 eq throughout the reaction; [e] The diene is regularly added in portions of 2 eq throughout the reaction.

As occurs in the reactions of cyclopentadiene with 2a and 2b, $AlPO_4$ is a better catalyst than the Zn(II)-exchanged K10 montmorillonite, and high conversions are obtained using smaller amounts of diene and catalyst. This allowed us to decrease the reaction temperature, which increases both *endo/exo* and diastereofacial selectivities. The noticeable increase in diastereofacial selectivity by decreasing the reaction temperature seems to indicate that at -25 °C the competition of the non-catalysed reaction has been completely eliminated.

The asymmetric induction obtained at -25 °C parallels that obtained using homogeneous catalysts and is the best result described to date for heterogeneously-catalysed asymmetric Diels-Alder reactions.

Given that **4d** is preferably obtained in homogeneous- and heterogenenously-catalysed reactions, the direction of the asymmetric induction can be explained by the classical model used in the Lewis acid-catalysed reactions of chiral acrylates.[2] In this model, the dienophile displays an *anti* enoate conformation where the phenylisopropyl group of the chiral auxiliary shields the *Re* face of the double bond and the attack of the diene takes preferentially place on the *Si* face.



Some of the previous results[6] in heterogeneous catalysis of asymmetric Diels-Alder reactions have been obtained in reactions carried out without a solvent. Therefore, we decided to test the behaviour of $AlPO_4$ as a catalyst in the reactions of cyclopentadiene with **2b**, **2c** and **2d** in absence of a solvent. Table 3 gathers the results obtained in these reactions. As can be seen, the results are in general worse than those obtained in methylene chloride. Although total conversions are obtained in 24 h, a noticeable decrease in selectivity is observed in the reactions of **2b** and principally **2d**. It can be speculated that under these conditions, the non-catalysed reaction competes more favourably with the catalysed one. The increase in selectivity observed in the reaction of **2d** when the amount of catalyst is increased agrees with this hypothesis.

Table 3. Results obtained in the reactions of cyclopentadiene (**1**) with (-)-menthyl acrylate (**2b**) and O-acryloyl-(R)-pantolactone (**2c**), and (-)-8-phenylmenthyl acrylate (**2d**) in absence on solvent at 20 °C, catalysed by $AlPO_4$

Dienophile	amount of catalyst (g/mmol of **2d**)	1: 2	conversion (% after 24 h)	*endo/exo*	d.e.[a] (%)
2b	0.50	3:1	100	13.8	34
2c	0.50	3:1	100	9.8	15
2c	1.00	3:1	100	6.2	19
2d	2.00	3:1	100	8.0	25

[a] With **2b** and **2d**, **4** is the major cycloadduct, whereas in the case of **2c**, **3** is preferably obtained.

To sum up, $AlPO_4$ is a very efficient catalyst for Diels-Alder reactions of chiral acrylates. In particular, the reaction of (-)-8-phenylmenthyl acrylate with cyclopentadiene leads to the best asymmetric induction described for asymmetric Diels-Alder reactions with heterogeneous catalysts. A decrease in selectivity is observed when the reaction is carried out without a solvent, which is probably due to an efficient competition of the non-catalysed reaction.

Experimental

Preparation and characterization of the heterogeneous catalysts.- Zn(II)-exchanged K10 montmorillonite was obtained and characterised as previously described.[4,5]

Amorphous $AlPO_4$ was prepared by precipitation from aluminium chloride and phosphoric acid (aqueous solution 85% wt) using ammonium hydroxyde solution.[10] The solid was calcined at 650 °C for 3 hours. Surface area (156 m^2g^{-1}), pore volume (0.68 ml g^{-1}), and main pore diameter (3.6 nm) were determined from nitrogen adsorption by the BET method. Surface acidity was determined by a previously described[14] spectrophotometric method that allows the titration of the amount of irreversibly adsorbed pyridine (190 µm g^{-1}) and 2,6-ditertbutyl-4-methyl pyridine (53 µmol g-1).

Reaction between cyclopentadiene (**1**) *and methyl acrylate* (**2a**) *catalysed by $AlPO_4$*.- To a suspension of $AlPO_4$ of (1.25 g) in methylene chloride (15 ml) under argon atmosphere at 20 °C, methyl acrylate (0.645 g, 7.5 mmol) and freshly distilled cyclopentadiene (1.485 g, 7.5 mmol) were added via syringe, the flask was shaken and the reaction monitored by gas chromatography using the previously described procedure.[4]

Reactions between cyclopentadiene (**1**) *and (-)-menthyl acrylate* (**2b**) *catalysed by $AlPO_4$*.- To a suspension of $AlPO_4$ of (1.00 g) in methylene chloride (10 ml) under argon atmosphere at 20 °C, (-)-menthyl acrylate (0.420 g, 2 mmol) and freshly distilled cyclopentadiene (0.396 g, 6 mmol) were added via syringe, the flask was shaken and the reaction monitored by gas chromatography using the previously described procedure.[4]

In the reactions carried out in the absence of a solvent the same amounts of reagents and catalyst were used, the flask was shaken at 20 °C for 24 h, the catalyst repeatedly washed with methylene chloride, and the results determined by gas chromatography.[4]

Reactions between cyclopentadiene (**1**) *and O-acryloyl-(R)-pantolactone* (**2c**) *catalysed by $AlPO_4$*.- To a suspension of $AlPO_4$ of (1.00 g) in methylene chloride (10 ml) under argon atmosphere at 20 °C, O-acryloyl-(R)-pantolactone (0.368 g, 2 mmol) and freshly distilled cyclopentadiene (0.396 g, 6 mmol) were added via syringe, the flask was shaken and the reaction monitored by gas chromatography using the previously described procedure.[5] After shaking for 24 h, the catalyst was separated by filtration and washed with methylene chloride. The solvent was removed under reduced pressure and the composition of the mixture of cycloadducts determined by ^{1}H-NMR.[5]

Reactions between cyclopentadiene (**1**) *and (-)-8-phenylmenthy acrylate* (**2d**) *catalysed by $AlPO_4$*.- To a suspension of $AlPO_4$ of (1.00 g) in methylene chloride (10 ml) under argon atmosphere at working temperature (20 °C or -25 °C, Table 2), (-)-8-phenylmenthyl acrylate (0.276 g, 1 mmol) and freshly distilled cyclopentadiene (0.396 g, 6 mmol) were added via syringe, the flask was shaken and the reaction monitored by HPLC with diode array detection (4 µm silica column, eluent: hexane/tert-butyl methyl ether, gradient of 99% to 100% of hexane fom 2.5 to 3 min., flow rate 2.5 ml/min., detection at 210 nm). Retention times were: *exo* cycloadduct (**5d**+**6d**) 4.0 min., (-)-8-phenylmenthyl acrylate (**2d**) 4.6 min., and *endo* cycloadducts (**3d**+**4d**) 5.4 min. The catalyst was separated by filtration and washed with methylene chloride. The solvent was removed under reduced pressure and the mixture analysed by ^{1}H- and ^{13}C-NMR in $CDCl_3$ (Figure 1).

In the reactions carried out in the absence of a solvent the same amounts of reagents and two different amounts of catalyst (1 g or 2 g, Table 3) were used. The flask was shaken at 20 °C for 24 h, the catalyst repeatedly washed with methylene chloride and the solution analysed by HPLC. The solvent was then removed under reduced pressure and the mixture of cycloadducts analysed by ^{1}H- and ^{13}C-NMR.

Reactions between cyclopentadiene (**1**) *and (-)-8-phenylmenthy acrylate* (**2d**) *catalysed by Zn(II)-exchanged K10 montmorillonite.*- Pre-weighted exchanged montmorillonite (1.5 g) was calcined by the above-described method. The flask was charged with the catalyst and methylene chloride (15 ml) under argon atmosphere at 20 °C. (-)-8-Phenylmenthyl acrylate (0.552 g, 2 mmol) and freshly distilled cyclopentadiene (0.396, 6 mmol) were added via syringe. The flask was shaken and three additional amounts of 0.396 g (6 mmol) of freshly distilled cyclopentadiene were added at regular times until 24 h of reaction.

In a second reaction, 4.5 g of catalyst and 0.246 g (4 mmol) of diene were initially used. During the reaction time (10 h) five additional amounts of 0.264 g (4 mmol) od freshly distilled cyclopentadiene were added via syringe to the reaction flask.

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