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# Fluorinated Alcohols as Solvents for Diels-Alder Reactions of Chiral Acrylates

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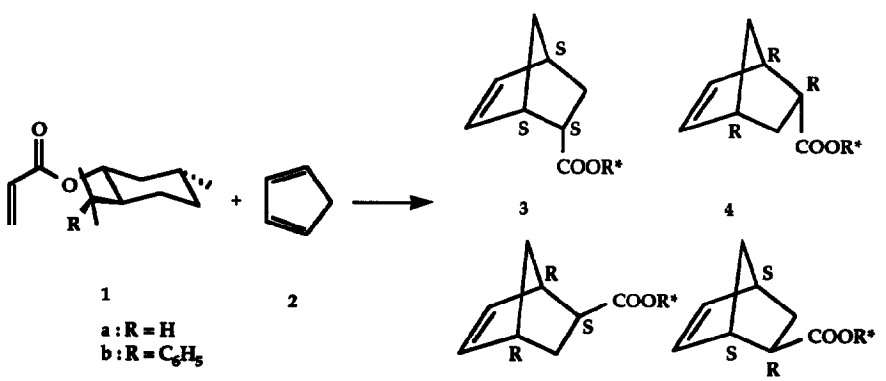
**Abstract:** Fluorinated alcohols increase the rates and *endo/exo* selectivities of the Diels-Alder reactions of cyclopentadiene with (-)-menthyl and (-)-8-phenylmenthyl acrylates. The use of fluorinated alcohols also increases the diastereofacial selectivity in the reactions of (-)-menthyl acrylate, but decreases it when the dienophile is (-)-8-phenylmenthyl acrylate. These facts are accounted for by the conformational preferences of the dienophile in non-HBD solvents and by the tendency of fluorinated alcohols to shift the conformational equilibrium towards the *s-trans* conformation.

Interest in the role of the solvent in Diels-Alder reactions has increased over the last few years because of the noticeable improvement in these reactions achieved by the use of aqueous solvents,[1] molten salts,[2] or lithium perchlorate solutions.[3] The influence of the solvent on rate and *endo/exo* selectivity has been explained by the use of empirical solvent parameters.[4] Recently, we have reported our results on the influence of the solvent on the benchmark asymmetric Diels-Alder reaction between (-)-menthyl acrylate and cyclopentadiene.[5] The results obtained showed that hydrogen bonding donor (HBD) solvents increase asymmetric induction, which was accounted for by the formation of an hydrogen bond between the solvent and the carbonyl oxygen, favouring the *s-trans* conformation of the dienophile. That is to say, HBD solvents behave as mild Lewis acids. In view of these results, it is interesting to test the influence of a family of highly HBD solvents, namely fluorinated alcohols, on model asymmetric Diels-Alder reactions. In this paper we describe the results obtained from the reactions of cyclopentadiene with (-)-menthyl and (-)-8-phenylmenthyl acrylates (Scheme 1).




**Scheme 1**

## Results and Discussion

**Reactions of (-)-menthyl acrylate.** The reactions were monitored by gas chromatography (GC) as previously described.[5]

Table 1 gathers the results obtained in the reaction between (-)-menthyl acrylate and cyclopentadiene. In the presence of high concentrations of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), extensive oligomerization of cyclopentadiene was experimentally observed, which precluded the calculation of accurate rate constant values. However, the specific effect of HFIP can be clearly stated, since the rate constant noticeably increases with the first addition of fluorinated alcohol, and then remains essentially constant within the experimental error. This specific effect of the solvent on the reaction rate is in accordance with the one previously described by Desimoni *et al.* for non-asymmetric Diels-Alder reactions.[6]

The behaviour of the *endo/exo* selectivity parallels the reaction rate. In this case, where the experimental values are more reliable, an important increase in *endo/exo* selectivity can be observed on going from toluene to a mixture toluene/HFIP 90:10, and then a slow, but progressive, further increase in *endo/exo* selectivity with the proportion of HFIP takes place.

It might be thought that the behaviour of the HFIP is due to the presence of traces of hydrogen fluoride. In order to discard this possibility, the reaction in pure HFIP was repeated in the presence of a small amount of triethylamine. The reactions with and without $NEt_3$ led to almost the same results, which indicates that a hydrogen fluoride-catalytic mechanism can be ruled out. On the other hand, the hyperbolic variation of rates and *endo/exo* selectivities with the HFIP concentration is consistent with a mechanism in which the dienophile is specifically solvated by the HBD solvent.

The use of a different fluorinated alcohol, namely trifluoroethanol (TFE), led to results quite similar to those obtained when HFIP was used (Table 1).

**Table 1. Results obtained in the reaction between cyclopentadiene and (-)-menthyl acrylate in several reaction media.**

| Solvent | k x $10^5$ (l $mol^{-1}$ $s^{-1}$)[a] | *endo/exo*[a] | 4a/3a | *de* (%) |
|---|---|---|---|---|
| toluene | 2.89 | 2.73 | 1.20 | 9.5 |
| toluene/HFIP 90:10 | 15.24 | 6.55 | 1.29 | 12.6 |
| toluene/HFIP 70:30 | 21.58 | 6.95 | 1.39 | 16.2 |
| toluene/HFIP 50:50 | 15.47 | 7.04 | 1.46 | 18.7 |
| toluene/HFIP 30:70 | 18.80 | 7.09 | 1.55 | 21.5 |
| HFIP[b] | 19.61 | 7.11 | 1.72 | 26.4 |
| HFIP + $NEt_3$[c] | 23.07 | 7.12 | 1.72 | 26.4 |
| HFIP at 0°C | 1.48 | 9.04 | 1.87 | 30.5 |
| TFE[d] | 20.09 | 6.57 | 1.46 | 18.7 |
| TFE at -20°C | 0.38 | 10.37 | 1.61 | 23.2 |
| $AlCl_3$-catalyzed[e] | - | 10.70 | 2.50 | 42.9 |

[a] Determined by GC [b] 1,1,1,3,3,3-hexafluoro-2-propanol [c] 2% of $NEt_3$ v/v [d] 2,2,2-trifluoroethanol [e] 1mmol in 30 ml of $CH_2Cl_2$ at room temperature.

The behaviour observed in the case of the diastereofacial selectivity is completely different. The variation of diastereofacial selectivity (represented by log (**4a/3a**) with the mole fraction of HFIP in the solvent mixture. shows an excellent linear correlation (r=0.994).

It is generally accepted that in asymmetric Diels-Alder reactions of prochiral 1,3-dienes with chiral acrylates, the diastereofacial selectivity obtained depends on the shielding effect of the chiral auxiliary and, given that *s-cis* and *s-trans* conformers display reverse topicity on their top and bottom faces, on the conformational equilibrium of the acrylate.[7] In fact, it has been suggested that the solvent can modify this equilibrium, and hence the diastereofacial selectivity, through hydrogen bonding.[5] However, this model would lead to a hyperbolic relationship between asymmetric induction and HFIP concentration (similar to that described for rate and *endo/exo* selectivity). The linear relationship experimentally found indicates that the influence of the non-specific effects of the HFIP on diastereofacial selectivity cannot be neglected.

In order to test the influence of the non-specific effects of the HFIP, several reactions were carried out in the presence of $AlCl_2Et$. It is assumed that the coordination of the dienophile to the metal complex completely shifts the conformational equilibrium to the *s-trans* conformation.[8] The simultaneous presence of HFIP and $AlCl_2Et$ gave rise to extensive polymerization of the cyclopentadiene. In order to overcome this problem, at least partially, mixtures of toluene and hexane were used as co-solvents. In spite of these difficulties, it could be observed that the diastereofacial selectivity increases with the concentration of HFIP, even in the presence of $AlCl_2Et$ (Table 2). This result indicates the existence of a non-specific effect of the HFIP, probably due to modifications induced by the fluorinated alcohol in the bulk of the solvent.

**Table 2. Results obtained in the reaction between cyclopentadiene and (-)-menthyl acrylate catalyzed by $AlCl_2Et$ in several reaction media containing HFIP.**

| Solvent Mixture | | | percentage of | *endo/exo*[a] | 4a/3a[a] | *de* (%) |
|---|---|---|---|---|---|---|
| toluene (%) | hexane (%) | HFIP (%) | conversion at 10 h[a] | | | |
| 50 | 50 | 0 | 98 | 13.0 | 1.86 | 30.1 |
| 45 | 45 | 10 | 88 | 11.1 | 2.11 | 35.7 |
| 35 | 35 | 30 | 14 | 10.8 | 2.38 | 40.8 |
| 25 | 25 | 50 | <4 | - | - | - |

[a] Determined by GC after treatment of the reaction with $NaHCO_3$

Given that fluorinated alcohols have proved to be excellent reaction media for carrying out the asymmetric Diels-Alder reaction of (-)-menthyl acrylate with cyclopentadiene, we tried to improve the selectivity of this reaction by lowering the temperature. The *endo/exo* selectivities obtained in HFIP at 0°C and in TFE at -20°C are comparable to those obtained by using conventional Lewis acid catalysts (Table 1). The diastereofacial selectivities improve slightly, the corresponding values being located halfway between those obtained in an "inert" solvent, such as toluene, and with the use of a conventional Lewis acid, such as $AlCl_3$ (Table 1).

The results obtained using (-)-menthol as a chiral auxiliary seemed very promising, so we decided to consider the asymmetric Diels-Alder reaction of cyclopentadiene with the acrylate of a better chiral auxiliary, namely (-)-8-phenylmenthol.

**Reactions of (-)-8-phenylmenthyl acrylate.** The reactions were monitored by HPLC. Compounds **3b** and **4b**, and **5b** and **6b** could not be resolved as separate peaks, so HPLC could only be used to determine the degree of conversion and the *endo/exo* selectivity, the final results being determined by NMR. HPLC analysis of the $AlCl_2Et$-catalysed reactions shows a 89:11 *endo/exo* ratio. NMR analysis of the mixture of cycloadducts obtained from this reaction allowed us to assign several signals to *endo* and *exo* diastereoisomers. Absolute configurations of the *endo* cycloadducts were determined by comparison with the

previously described results for the Lewis acid-catalysed reactions between **1b** and **2**.[8] Absolute configurations of the *exo* cycloadducts were assigned by mechanistic considerations, taking into account that **4b** is the major *endo* diastereoisomer in the catalysed reaction, **6b** (coming from the approach of the diene on the same face of the double bond) must be the major *exo* product. Given that only one *exo* cycloadduct is obtained from the catalysed reaction, the signals corresponding to **5b** were assigned from NMR analyses of the non-catalysed reactions. The signals used to determine *endo/exo* and diastereofacial selectivities are given in Table 4.

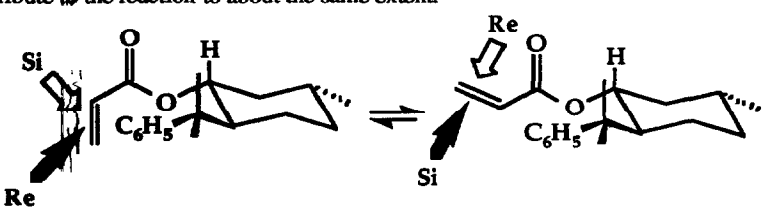
(-)-8-phenylmenthyl acrylate (**1b**), obtained as previously described,[9] was made to react with cyclopentadiene in several solvents and solvent mixtures (Table 3). *Endo/exo* selectivity increases with the HBD-ability of the solvent, in accordance with a specific solvation of the dienophile. However, asymmetric inductions in the *endo* pair obtained using fluorinated alcohols (mainly HFIP) are surprisingly lower than those obtained when (-)-menthyl acrylate is used as a dienophile (Table 1). Furthermore, the absolute configuration of the major cycloadduct (**3b**) is reversed in relation to that of the catalysed reaction (**4b**), and the percentage of **3b** increases when non-highly HBD or non-HBD solvents are used.

**Table 3. Results obtained in the reaction between cyclopentadiene and (-)-8-phenylmenthyl acrylate in several reaction media.**

| Solvent (ml) | days | 2:1 | mmol of **1** | % conversion | *endo/exo* | *endo de*(%)[a] | *exo de*(%)[a] |
|---|---|---|---|---|---|---|---|
| $CH_2Cl_2$ (3.2) | 6 | 3 | 0.10 | 42 | 2.8 | 41.3 (**3b**) | 35.0 (**5b**) |
| toluene (5.0) | 6 | 3 | 0.37 | 80 | 3.2 | 38.8 (**3b**) | 37.3 (**5b**) |
| acetone/water 80:20 (5.0) | 8 | 3 | 0.37 | 95 | 4.2 | 39.7 (**3b**) | 27.5 (**5b**) |
| methanol/water 60:40 (250.0) | 5 | 3 | 0.27 | 35 | 5.4 | 44.0 (**3b**) | 37.0 (**5b**) |
| $CH_2Cl_2$/HFIP 70:30 (3.2) | 6 | 3 | 0.10 | 75 | 5.8 | 21.0 (**3b**) | 5.0 (**6b**) |
| TFE (5.5) | 3 | 8 | 0.35 | 100 | 5.8 | 17.8 (**3b**) | 8.5 (**6b**) |
| HFIP (5.0) | 2 | 8 | 0.39 | 95 | 7.5 | 8.0 (**3b**) | 37.0 (**6b**) |
| $AlCl_2Et$-catalyzed[b] | 3 h | 2.5 | 1.00 | 50 | 7.9 | 79.0 (**4b**) | 100.0 (**6b**) |

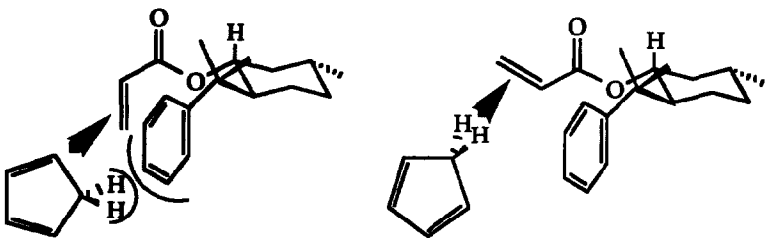
[a] Major product is given in brackets [b] 1.5 mmol in $CH_2Cl_2$ at 0°C

The dependence of the asymmetric induction on the *s-cis/s-trans* conformational equilibrium of the dienophile (Scheme 2) accounts for these results. The catalysed reaction takes place through the *s-trans* conformation, so that **4b** (coming from the attack of the diene on the less-hindered *Si* face of the double bond) is preferably obtained. In non-catalysed reactions **3b** (coming from the attack of the diene on the *Re* face of the double bond) is the major cycloadduct. Given that the *Re* face is the less hindered in the *s-cis* conformation, this result suggests that, unlike the situation of the (-)-menthyl acrylate (**1a**), this conformer is the one favoured in the absence of a catalyst. As previously discussed, fluorinated alcohols behave as mild Lewis acids, and they shift the conformational equilibrium towards the *s-trans* form. Therefore, the low asymmetric induction obtained in HFIP indicates that the *s-cis/s-trans* conformational equilibrium is shifted in such a way that both conformers contribute to the reaction to about the same extent.




**Scheme 2**

Changes in diastereomeric excess of the *exo* pair follow a similar pattern, but in this case Lewis acids and fluorinated alcohols lead preferably to the same cycloadduct (**6b**) and the lowest asymmetric induction is not obtained in HFIP but in TFE. The $AlCl_2Et$-catalysed reaction shows that the *exo* attack on the *s-trans* conformer is more discriminating than that of the *endo*. This can be rationalized by the interaction of the methylene hydrogens of the cyclopentadiene with the chiral auxiliary, which greatly disfavours the *exo* attack of the diene on the *Re* face (Scheme 3). This interaction is not present in the *s-cis* conformation, so *endo* and *exo* attacks lead to similar discriminations, as shown by the reactions carried out in non-HBD solvents. Consequently, if *s-cis* and *s-trans* conformers are present in the same proportion (as probably happens in HFIP), the major *exo* adduct **6b** comes from the attack of the diene on the less-hindered face of the *s-trans* form.



**Scheme 3**

## Conclusions

Fluorinated alcohols greatly increase the rate and *endo/exo* selectivity of the Diels-Alder reactions of cyclopentadiene with chiral acrylates. These solvents influence the asymmetric induction through a shift of the conformational equilibrium of the dienophile towards the *s-trans* conformation. So, they behave as mild Lewis acids.

The conformational equilibrium of the chiral acrylate is strongly dependent on the chiral auxiliary. Thus, closely-related dienophiles, such as (-)-menthyl and (-)-8-phenylmenthyl acrylates, display reversal preferences in the absence of a Lewis acid catalyst. In particular, catalysed and non-catalysed reactions of the (-)-8-phenylmenthyl acrylate display reversal topicity. Therefore, fluorinated alcohols increase the asymmetric induction when the *s-trans* conformation of the dienophile is already preferred in non-HBD solvents. The diastereofacial discrimination depends on both the conformation of the dienophile and the way of approach (*endo* or *exo*) of the diene.

## Experimental

$^1$H-NMR and $^{13}$C-NMR were recorded at 300 and 75 MHz, respectively. All organic solvents were purified and dried according to standard procedures. (-)-Menthyl and (-)-8-phenylmenthyl acrylates were prepared according to previously described procedures.[9]

**Reactions of (-)-menthyl acrylate.** In a typical run, 0.396 g (6 mmol) of freshly distiled cyclopentadiene (**2**) dissolved in the corresponding organic solvent (4 ml) was added to a thermostated (30±1 °C) solution of 0.42 g ( 2 mmol) of (-)-menthyl acrylate (**1a**) in the same solvent (28 ml) and the solution obtained was stirred magnetically and monitored by GC.[5]

The catalysed reactions were carried out as follows. The (-)-menthyl acrylate (0.105 g, 0.5 mmol) and freshly distiled cyclopentadiene (0.100 g, 1.5 mmol) were added via syringe to a flask charged with the aluminium catalyst (0.5 ml of $AlCl_2Et$ or 0.067 g of $AlCl_3$) in the corresponding reaction medium (10 ml, see Tables 1 and 2) under argon atmosphere. The reaction was monitored by GC.

**Reactions of (-)-8-phenylmenthyl acrylate.** Freshly distiled cyclopentadiene (**2**) was added to a solution of (-)-8-phenylmenthyl acrylate (**1b**) in the corresponding reaction medium (amounts given in Table III). Reactions were monitored by HPLC with diode array detection (4 μm silica column, eluent: hexane-tert-butylmethyl ether, gradient of 99% to 100% of hexane from 2.5 to 3 min, flow rate 2.5 ml/min, detection at 210 nm). Retention times were: *exo* cycloadducts (**5b+6b**) 4.0 min, (-)-8-phenyl-menthyl acrylate (**1b**) 4.6 min and *endo* cycloadducts (**3b+4b**) 5.4 min.

The solvent was eliminated under reduced pressure and the resulting solid was analyzed by $^1H$ and $^{13}C$-NMR (Table 4).

**Table 4. Selected $^1H$- and $^{13}C$-NMR chemical shifts of compounds 3b, 4b, 5b and 6b.**

| Cycloadduct | H-1 | H-4 | C=O | C-5 | C-6 |
|---|---|---|---|---|---|
| **3b** | 2.78 | 2.69 | 173.8 | 137.6 | 132.0 |
| **4b** | 3.06 | 2.78 | 174.1 | 137.1 | 132.9 |
| **5b** | 2.78 | 2.65 | 175.3 | 137.9 | - |
| **6b** | 2.86 | 2.78 | 175.8 | 137.1 | - |

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