

## Positive Cooperativity of Product Mimics in the Asymmetric Autoinduction of Diels–Alder Reactions Catalyzed by a VAPOL–Aluminum Catalyst

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It has been 18 years since Hashimoto, Komeshima, and Koga reported the first example of a Diels–Alder reaction catalyzed by a chiral Lewis acid.<sup>1</sup> This report served to galvanize the pre-existing interest in the Diels–Alder reaction in the synthetic community, and the number of reports on asymmetric Diels–Alder reactions with chiral Lewis acids has steadily increased until the present.<sup>2,3</sup> We have previously reported the preparation of the vaulted biphenanthrol ligand **3** (VAPOL) and the development of boron and aluminum complexes of VAPOL as catalysts for asymmetric Diels–Alder reactions.<sup>4</sup> We report herein that the asymmetric Diels–Alder reactions mediated by the aluminum catalyst exhibit an autoinduction<sup>5–7</sup> which is due to a cooperative interaction of the product with the catalyst to generate a more selective catalyst species. It is also shown that certain carbonyl compounds can mimic the auto-inductive effect of the product and surpass the inductions possible with the product to the point where nearly perfect positive cooperativities are observed.

An autoinduction is seen with both aldehyde and ester dienophiles, but we have chosen to focus our study on the reaction with esters since the reactions with aldehydes are too fast to conveniently monitor the asymmetric induction over time. Also, the effect that we have seen in our screening of several substrates reveals that the effect is much bigger for esters. This reaction was performed as indicated in Table 1 and was followed

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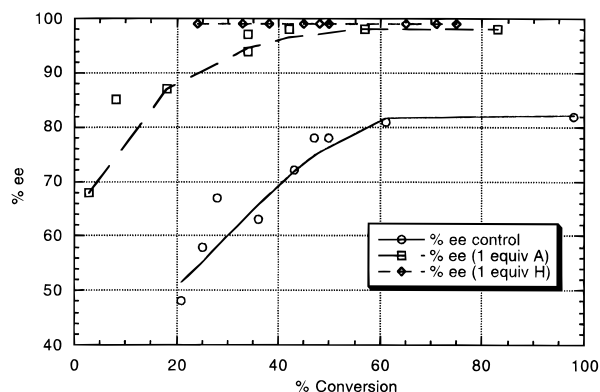
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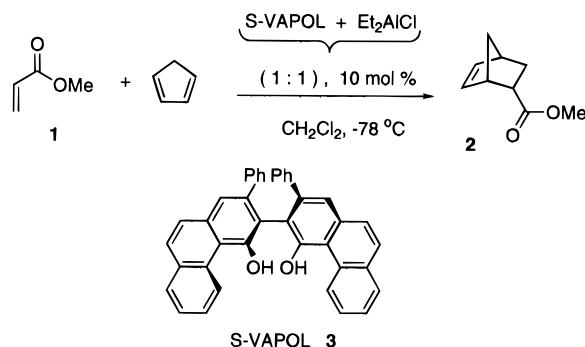
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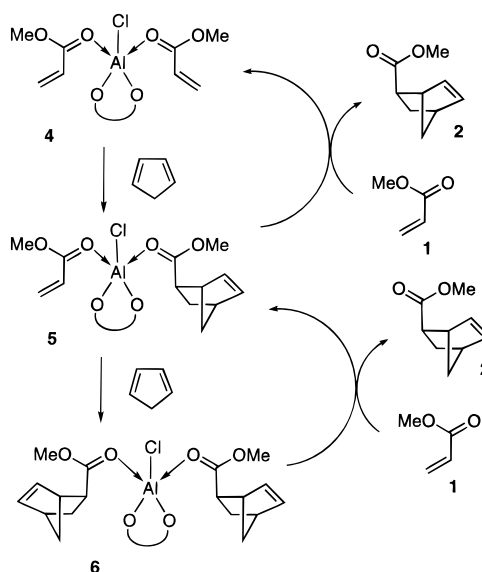


**Figure 1.** Dependence of induction of **2** on added aldehyde A and malonate H.

### Scheme 1



### Scheme 2



by analysis of withdrawn aliquots. The enantiomeric purity of the endo product **2** was determined by capillary GC analysis on a chiral cyclodextrin column. The first data point was collected after 5 min, and an induction of 48% ee was found for **2** (endo to exo >99:1). As shown in the plot in Figure 1, the % ee of **2** rose to 82% at the completion of the reaction (24 h). It was demonstrated that racemic **2** is still racemic after being treated with the catalyst and the dienophile under the reaction conditions for 24 h.

The basic tenant of our mechanistic hypothesis for this asymmetric induction is that more than one carbonyl compound is coordinated to the aluminum catalyst. One possible scenario is shown in Scheme 2 where the active catalyst species **4** and **5** involve pentacoordinate aluminum. Another scenario (not

shown) is that a similar set of tetracoordinate species is involved, which are cationic as the result of ionization of the chloride ligand.<sup>8</sup> Whatever the coordination number of aluminum, assuming carbonyl exchange is rapid, the autoinduction could be explained if it is hypothesized that the catalyst species **5** coordinated by one dienophile and one product molecule gives a higher induction in its Diels–Alder reaction than that of species **4** which contains two coordinated dienophiles. At the beginning of the reaction, species **4** would be more abundant and the selectivity would be lower than during the latter parts of the reaction where species **5** would be more abundant. Despite the now large body of work in the area of asymmetric catalytic Diels–Alder reactions, there is a unique observation of an enantioselective autoinductive effect reported by Rebiere, Riant, and Kagan, but no other experiments were performed to determine the source of this autoinduction.<sup>5</sup>

The mechanism in Scheme 2 requires that the product is incorporated into the catalyst and causes an increase in the induction. We decided to test this by performing an experiment in which 0.5 equiv (relatively to the dienophile) of enantiomerically pure **2** ( $\geq 99\%$  ee) was added to the beginning of a reaction (15 min after dienophile and before the diene) and from which it was found that the cycloadduct **2** was of 96.9% ee at 40% conversion (24 h). After allowance for the amount of enantiomerically pure **2** added, the product actually formed in this reaction is of much higher enantiomeric purity (92.8% ee) than the product from the unspiked reaction either at 40% conversion (70% ee) or at the end of the reaction (82% ee). With the knowledge that the product can interact with the catalyst in some fashion to give a more selective catalyst, the next question is whether the chirality or steric bulk of **2** is responsible for the positive cooperativity.

With the assumption that the autoinduction is a function of the size of the cycloadduct, adamantyl- and *tert*-butyl-substituted carbonyl compounds were evaluated since these compounds should be larger than the product or at least have a higher degree of substitution  $\alpha$  to the carbonyl. It was thus quite interesting to find that the induction could be increased from 82 to 96% ee with the addition of 0.5 equiv of pivaldehyde (relative to dienophile) and to 98% ee with 1.0 equiv. Increasing the size of the added ligand leads to increased induction as is illustrated with adamantyl aldehyde (98.5% vs 96% ee with pivaldehyde). Esters do not display positive cooperativity as high as that for their corresponding aldehydes, and this may be due to the smaller size of the aldehyde. The use of adamantyl amide **E** completely inhibits the reaction from taking place. This may be due to the fact that methyl acrylate may not be able to compete with the amide for coordination (pyridine and 2,6-lutidine will also stop the reaction).

It was quite surprising to find that the 1,3-dicarbonyl ligands **F**–**I** did not stop the reaction and, in fact, were more effective in enhancing the induction than monocarbonyl ligands, as evidenced by the data in Table 1. The overall effectiveness of the product mimics in the autoinduction can be seen in the fact that the induction for this reaction can be raised from 82 to 92% ee while at the same time the reaction temperature can be raised by 80 °C. This is even more dramatically evidenced in the cooperativities plotted in Figure 1 (under the conditions outlined in Table 1). The reaction in the presence of 1.0 equiv of pivaldehyde begins at a much higher induction and rises during the course of the reaction to give a much higher enantiomeric purity in the product than for the control reaction (98 vs 82% ee). Within the limits of detection, the cooperativity of 1.0 equiv of 2,2-dimethyl-di-*tert*-butyl malonate is perfect

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**Table 1.** Effect of Added Ligands on the Enantioselectivity of the Diels–Alder Reaction of Methyl Acrylate and Cyclopentadiene<sup>a</sup>

| ligand <sup>b</sup> | temp (°C) | yield of <b>2</b> <sup>c</sup> | endo:exo <sup>d</sup> | % ee <sup>d</sup> |
|---------------------|-----------|--------------------------------|-----------------------|-------------------|
| none                | −80       | 87                             | 99:1                  | 82                |
| A                   | −80       | 80                             | 99:1                  | 96                |
| A (1.0)             | −80       | 42 <sup>e</sup>                | 99:1                  | 98                |
| B                   | −80       | 65                             | 99:1                  | 89.7              |
| C                   | −80       | 60                             | 99:1                  | 98.5              |
| C (0.1)             | −80       | 75                             | 99:1                  | 87.3              |
| C (0.02)            | −80       | 73                             | 98.7:1                | 82                |
| D                   | −80       | 70                             | 98.9:1                | 87                |
| E                   | −80       | 0                              | —                     | —                 |
| F                   | −80       | 49                             | 99:1                  | 98                |
| G                   | −80       | 70                             | 99:1                  | 97.5              |
| H                   | −80       | 76                             | 99:1                  | >99               |
| none                | −40       | 76                             | 99:1                  | 47                |
| C                   | −40       | 80                             | 99:1                  | 88.4              |
| F                   | −40       | 80                             | 97.9:1                | 90.4              |
| G                   | −40       | 100                            | 98.4:1                | 90.5              |
| H                   | −40       | 100                            | 99:1                  | 91.6              |
| I                   | −40       | 100                            | 98.1:1                | 92.5              |
| none                | 0         | 84                             | 99:1                  | 36.6              |
| H                   | 0         | 67                             | 93.9:1                | 69.1              |
| I                   | 0         | 90                             | 95.3:1                | 85.1              |
| I (1.0)             | 0         | 80                             | 99:1                  | 91.6              |

<sup>a</sup> In all cases, 10 mol % catalyst was used generated from a 1:1 mixture of (*S*)-VAPOL and Et<sub>2</sub>AlCl and Et<sub>2</sub>AlCl in CH<sub>2</sub>Cl<sub>2</sub> at 25 °C for 30 min. Methyl acrylate was added to make a 0.6 M solution, and after 30 min 1.1 equiv of cyclopentadiene was added at the indicated temperature. All reaction times were 24 h except those at 0 °C which were for 2 h. <sup>b</sup> Unless otherwise specified, 0.5 equiv of ligand was used relative to dienophile. <sup>c</sup> Yield determined by NMR with VAPOL as internal standard. <sup>d</sup> Determined by capillary GC on a 0.25 mm × 30 M chiral cyclodextrin column. <sup>e</sup> 83% yield after 72 h.

as judged by the fact that the product is enantiomerically pure ( $\geq 99\%$  ee) at the first data point taken (24% conversion) and remains so during the course of the reaction.

A coordination number of 6 is not common for aluminum, and thus, the effect of malonates seen here is quite surprising.<sup>9</sup> Higher coordination numbers for aluminum are rarely evoked to explain the outcome of stereoselective reactions.<sup>10,11cd</sup> The effectiveness of malonates in enhancing the selectivities of the aluminum catalyst described here suggests that three carbonyls may coordinate to the aluminum in the active species. If the chloride is not lost during formation of the active species,<sup>8</sup> then a hexacoordinate aluminum complex would result.<sup>3h,11,12</sup> Future effort will be directed at obtaining information concerning the nature of the active catalyst species present under conditions where large positive cooperativity is seen with product mimics for this reaction.

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**Supporting Information Available:** Experimental procedures and spectral data for all new compounds (8 pages). See any current masthead page for ordering and Internet access instructions.

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