

A New Variant of the Diels-Alder Reaction and Its Use in the Synthesis of Fragrance Materials

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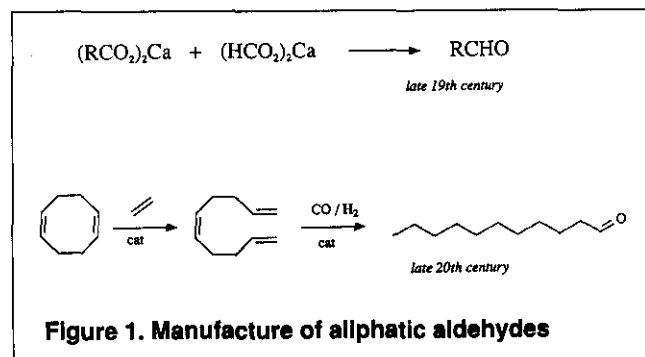
The use of perfumes can be traced back to the earliest recorded histories. Up until this century, the ingredients used were of natural origin and were therefore mostly expensive to produce and often uncertain as regards availability of supply.

In 1921, *Coco Chanel* introduced her now famous *No. 5* which owed its uniqueness to the use of synthetic aliphatic aldehydes. The success of this fragrance proved to be a water-shed in the perfume industry.

Nowadays, the fragrance ingredients market is dominated by synthetic materials which offer a reliable source of inexpensive building blocks for the creative perfumer.

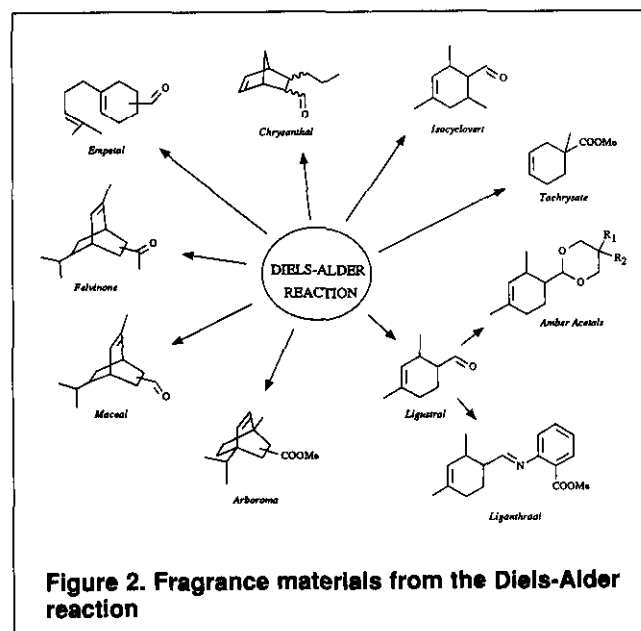
What is more, these materials usually offer improved performance over their natural counterparts when it comes to perfuming functional products such as detergents, hard surface cleaners or dishwashing powders.

The manufacturing methods used to produce today's fragrance materials have been the subject of much R&D effort over the last 150 years. The aliphatic aldehydes used in *Chanel's No. 5* for example, were originally produced by the pyrolysis of mixtures of calcium formate with the calcium salts of carboxylic acids, as proposed by Bertagnini in 1859.

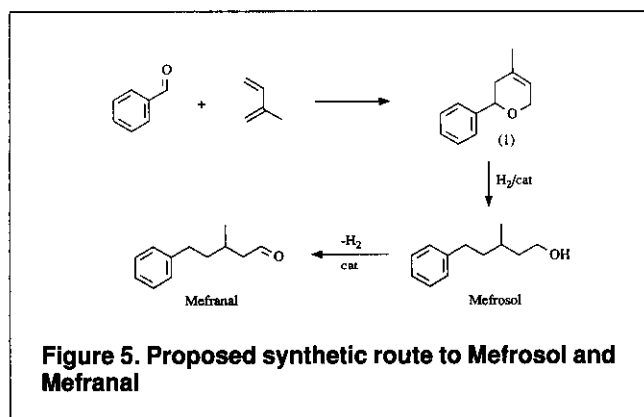
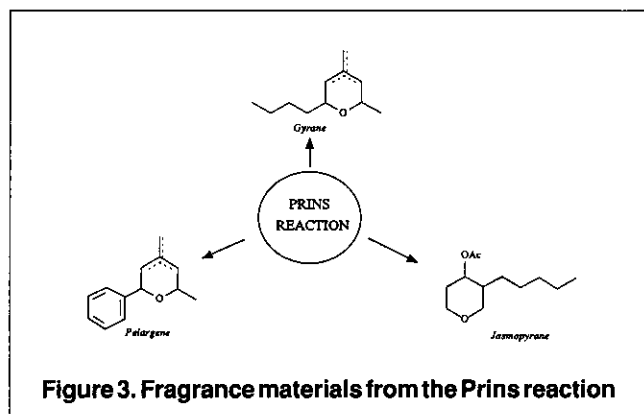


Nowadays, much higher yielding and cleaner processes, such as Shell's FEAST technology, are used, as illustrated in Figure 1. The search for clean chemistry has intensified recently because of growing concern about environmental pollution. At the same time, the commercial world is becoming steadily more competitive. Consequently, chemical process R&D has increasingly come under the twin constraints of cost and the "green" factor.

In response to this, our process R&D at Quest International has paid considerable attention to the building up of clean and efficient technologies and to product families based on them. Two such technologies are shown in Figures 2 and 3. Figure 2 shows some of the materials which we produce via the Diels-Alder reaction. A number of the



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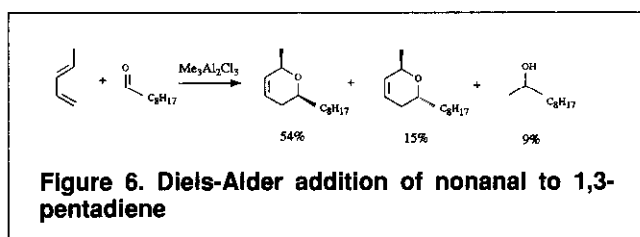
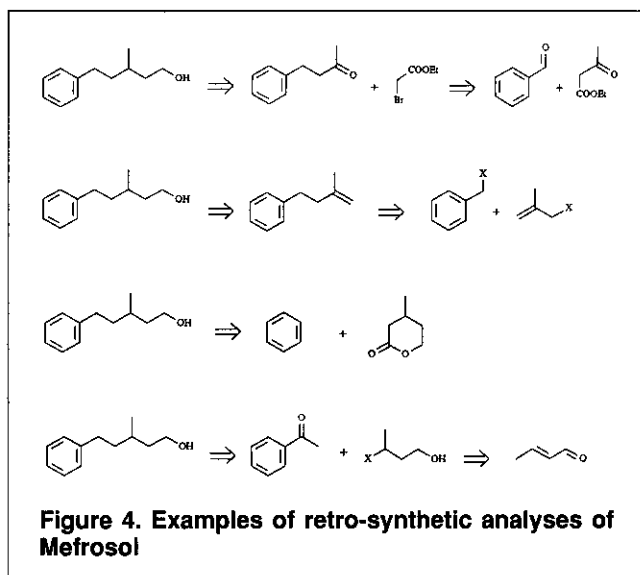


Diels-Alder adducts can be used both as fragrance materials in their own right and as intermediates for the preparation of others. Ligustral provides an illustration of this in this figure. Similarly, Figure 3 shows some of the products produced using our technology based around the Prins reaction.

3-Methyl-5-phenyl-1-pentanol is a well established fragrance material available from a number of suppliers under various trade names such as Mefrosol, Phenoxaflor and Rosaphen. Quest manufactures this material under the name Mefrosol and from it we also produce the corresponding aldehyde, which we call Mefranal. Mefrosol has a floral odor similar to that of citronellol in that it is predominantly rosy with some muguet character. Mefranal has a green aldehydic odor reminiscent of lily of the valley.

We felt that these two materials could be of even greater use to the fragrance industry if their cost could be significantly reduced. We therefore embarked on a research project with the objective of devising a new synthetic route to Mefrosol which would give an inexpensive product using clean technology.

The first stage of this project was to hold a "brainstorming session" in which over 70 ideas for novel synthetic routes were proposed. Four of the retro-synthetic analyses are shown in Figure 4. None of these were really satisfactory: they either used starting materials or reagents which were too expensive or they involved a large number of steps, thus incurring high process costs and the likelihood of a low overall yield.



Our current Mefrosol process comprises hydrogenation of the corresponding dihydropyran.¹ This pyran is produced using our Prins reaction technology. This led to the idea of combining the two families of processes shown in Figures 2 and 3 by preparing the pyran using a Diels-Alder reaction as shown in Figure 5.

The synthetic route outlined in Figure 5 offers the advantages of inexpensive starting materials and only two steps to Mefrosol, both of which are clean reactions, both in chemical as well as environmental terms. The disadvantage was that the proposed Diels-Alder reaction was unknown at the time.

Hetero Diels-Alder reactions in which the aldehyde is present as part of the "diene" rather than the dienophile are known¹ but examples in which the aldehyde function acts as a dienophile are rare. In a review, Weinreb gives some examples in which electron deficient aldehydes, such as chloral and p-nitrobenzaldehyde, behave as dienophiles but he reports that benzaldehyde failed to react with 2,3-dimethylbutadiene and reacted with 1-methoxybutadiene only at a pressure of 19.5 kbar.² Aldehydes have been found to react with very electron-rich dienes in the presence of Lewis acids³ and one intra-molecular example exists in which the constraints on the diene and dienophile are reduced by their enforced proximity.⁴

The closest literature example to the desired reaction is that shown in Figure 6 in which Snider et al. induced nonanal to add to 1,3-pentadiene under the influence of methyl aluminum sesquichloride.^{1c} This system would not

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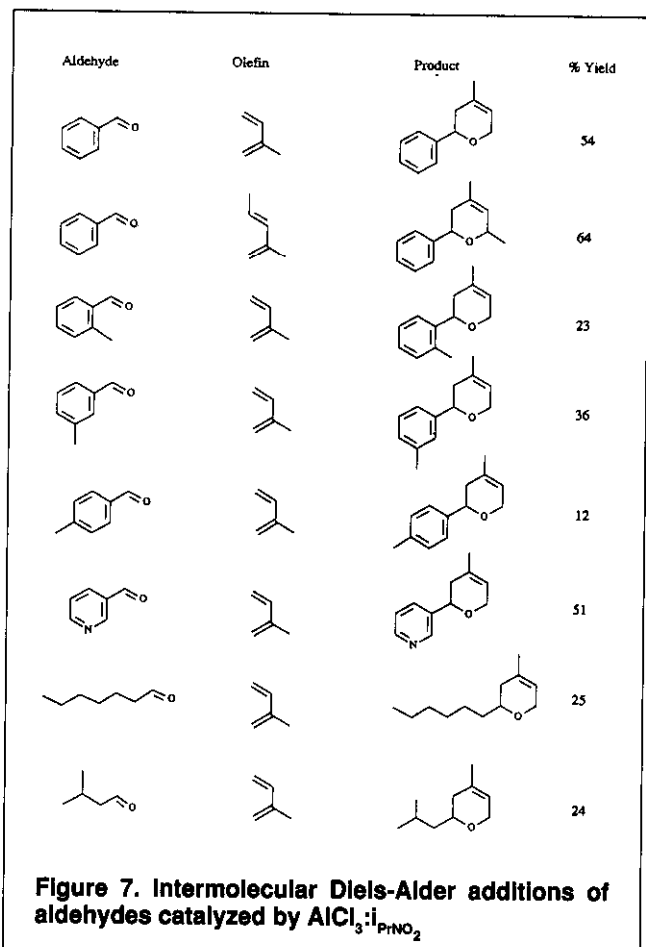


Table I. Effect of X on $\text{AlCl}_3 \cdot \text{X}$ catalyzed addition of benzaldehyde to isoprene

X	% yield pyran [1]
$i\text{-PrNO}_2$	54
Sulpholane	29
NH_4Cl	26
Ph Cl	16
$n\text{-BuOH}$	7
$i\text{-PrOH}$	3
DMF	0

be attractive as an industrial process because of the necessity for chlorinated solvents, the cost of the "catalyst," the stoichiometric requirement of the "catalyst" and the toxicity of the "catalyst."

Undeterred by the lack of close literature precedent, we attempted to add benzaldehyde to isoprene in the presence of Lewis acids. Using stannic chloride, we obtained yields of up to 32% of the desired pyran. This reaction took place in hydrocarbon solvents but reproducibility was poor. Higher temperatures gave increased conversion but at the expense of selectivity. Selectivity was not improved by increases in the proportions of either catalyst or isoprene with respect to

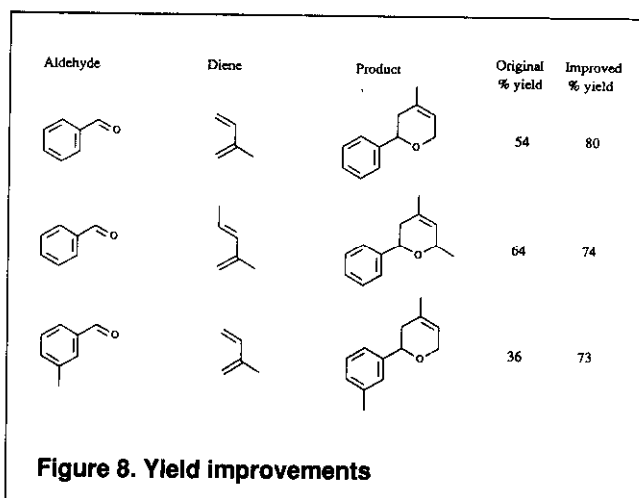


Table II. Effect of Lewis acid on $\text{M}:\text{Me}_2\text{CHNO}_2$ catalyzed addition of benzaldehyde to isoprene

M	% yield pyran [1]
AlCl_3	54
SnCl_4	8
TiCl_4	6

Table III. The effect on yield of pyran [1] from benzaldehyde and isoprene using different complexing agents

Catalyst $\text{AlCl}_3 \cdot \text{RNO}_2$	% yield [1]
R = Me	73
R = Et	73
R = $i\text{-Pr}$	77
R = C_6H_{11}	77
R = Ph	70

benzaldehyde. The use of stannic chloride as catalyst gave more reproducible results but lower yields. With stannic chloride, it was also found that dioxan could be used as a solvent. The use of boron trifluoride etherate as catalyst gave only 8% yield and ferric chloride gave none of the desired product.

Aluminum chloride is the most commonly used Lewis acid and so a large number of scouting experiments were carried out using it. It was found that, as expected, if the catalyst were added to isoprene in the absence of benzaldehyde, polymerization was so rapid that subsequent addition of the aldehyde was futile. Time and temperature were found to be key parameters with distinct optima, these being dependent on the exact choice of the other variables.

Interestingly, the reaction was found to be subject to quite marked solvent effects. Using hexane or cyclohexane as solvent, yields of up to 30% were obtained. When toluene

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was used as solvent, it was found that addition of isoprene to toluene to give 2-methyl-2,4-di-p-tolylbutane competed with the Diels-Alder reaction. In dichloromethane, selectivity was poor but in 2-nitropropane, the reaction was slowed down markedly and conversion was very poor. It seemed likely that this latter effect was due to moderation of the activity of the aluminum chloride by complexation with the 2-nitropropane. This then led to the suggestion of preparing a 1:1 complex of aluminum chloride with 2-nitropropane and studying its behavior in other solvents.

It was found that the aluminum chloride:2-nitropropane complex could be used effectively as a catalyst for the Diels-Alder addition of benzaldehyde to isoprene in either dichloromethane or hexane in yields of up to 54%. The use of dioxan as solvent gave lower yields. The reaction was best carried out at between -10°C and 0°C and the reaction was complete in 30 minutes. Under those conditions, a variety of complexing agents were tried and their effect on the yield of pyran [1] is shown in Table I.

Similarly, other Lewis acids were tried in combination with 2-nitropropane. The results are shown in Table II. The scope of the reaction in terms of substrate was then studied and the results are shown in Figure 7. From this figure it would seem that the reaction is strongly influenced by electronic effects. The variations in yield between benzaldehyde and the three tolualdehydes show that the electron donation by the methyl group is more important than any steric effect which it produces since the yields with benzaldehyde and m-tolualdehyde are much higher than those with o- or p-tolualdehyde.

Clearly, these results constituted an advance in the state of the art of Diels-Alder chemistry and accordingly, we obtained patent protection of our discovery.⁵ Since then, further development work has led to improved conditions and higher yields. A few examples are shown in Figure 8. We have also explored further the range of nitro derivatives which are capable of forming suitable catalyst complexes and some results under comparable conditions are shown in Table III.

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