

Zeolite and Lewis Acid Catalysis in Diels–Alder Reactions of Isoprene

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The use of zeolites as catalysts in Diels–Alder reactions of isoprene, **2**, has been studied. The regioselectivity in zeolite-catalyzed reactions was compared with the regioselectivity of the same reaction using Lewis acid catalysts. The reaction was studied with seven dienophiles: but-3-en-2-one (**1a**), 3-bromobut-3-en-2-one (**1b**), methyl propenoate (**1c**), cyclohex-2-enone (**1d**), phenylethene (**1e**), ethyl propynoate (**1f**) and propenenitrile (**1g**). The following catalysts were investigated: zeolites: ZSM-5, mordenite, zeolite Y-152, zeolite Y-45, and zeolite beta; Lewis acids: aluminum tribromide, aluminum trichloride, antimony pentachloride, antimony triiodide, boron trifluoride–diethyl ether, manganese difluoride and zinc dichloride. The zeolite-catalyzed reactions afforded the Diels–Alder product with the dienophiles **1a–1d**, but not with the other dienophiles, **1e–1g**. The dienophiles which failed to undergo cycloaddition in the presence of zeolites also did so or afforded poor results with the Lewis acid catalysts. With the exception of the reaction of **1b** catalyzed by ZSM-5, which afforded a regioisomeric ratio of 13/87, the other zeolite-catalyzed reactions afforded regioisomeric ratios in the range 6/94–0/100 which is similar to that obtained by Lewis acid catalysis.

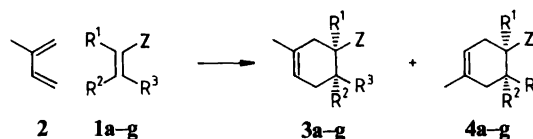
The experimental conditions were studied in detail for two zeolite catalysts (mordenite, zeolite beta) in the reaction of isoprene with **1d**. The optimum experimental conditions with respect to yield and selectivity were established by multivariate techniques. In this reaction, zeolite catalysis was found to afford high yields of *cis*-6-methyl-6(7)-1-octalone. Under Lewis acid catalyzed conditions, this product is rapidly epimerized into the *trans* isomer.

Full experimental details are given for the preparative use of the method. Examples are provided by the reactions with the dienophiles **1a**, **1c** and **1d** catalyzed by zeolite beta.

Factors determining the regioselectivity of zeolite-catalyzed Diels–Alder reaction are briefly discussed.

Uncatalyzed pericyclic reactions sometimes require high temperature and/or high pressure. It was therefore a major breakthrough when it was found that the [4 + 2] cycloaddition, known as the Diels–Alder reaction, could be conducted at low temperature in the presence of Lewis acid catalysts to afford often highly regioselective conversions.^{1,2} In a previous paper³ from this laboratory we reported that enhanced regioselectivity could be achieved in the Fischer indolization of dissymmetric arylhydrazones if the reactions were conducted in the presence of acid zeolite catalysts. The critical step that controls the regioselectivity in the Fischer indole reaction is the [3,3] sigmatropic rearrangement of an intermediate enehydrazine. It was also found that the nature of the zeolite catalyst has a large influence on the regioselectivity. The Fischer indole reaction occurs with the hydrazone sorbed on the solid zeolite catalyst. Selectivity must therefore depend on the interaction between the sorbed substrate and the catalyst so that one of two

possible regioisomeric transition states is favored. Such an effect must depend on the shape of the substrate and the structure of the zeolite crystal framework. It was therefore assumed that for certain substrates in pericyclic reactions, shape-selective catalysis can be achieved. To study whether these assumptions would also apply to the Diels–Alder reaction for achieving high regioselectivity we have studied the zeolite-catalyzed addition of seven dienophiles, **1a–1g**, (see Fig. 1) to 2-methylbuta-1,3-diene (isoprene), **2**, see Scheme 1. The products of these reactions exist as enantiomeric pairs. The results presented in this paper refer to racemic product mixtures.



Scheme 1.

Our reasons for choosing isoprene as a test substrate was that it is dissymmetric and acyclic. As acyclic dienes

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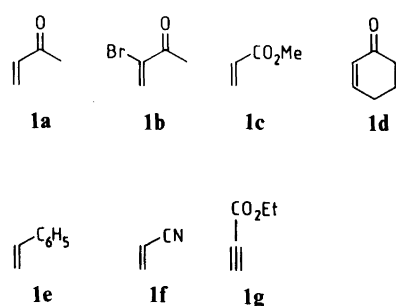


Fig. 1. Dienophiles used in the reactions.

usually undergo slower conversions in Diels–Alder reactions compared with cyclic ones in which the diene framework has a fixed *cis* orientation, catalysts and experimental conditions which afford high yields with isoprene would be of general synthetic interest.

The dienophiles were selected to afford a variation of the activating groups with a view to achieving some insight as to the scope of the reaction with respect to the dienophile.

Table 1. Properties of candidate zeolites. Items selected for experimental studies are marked with an asterisk.

No.	Zeolite		Property ^a			
	Class	Item	1	2	3	4
1*	Zeolite-Y	Y-152	758	5.6	7.4	7.4
2*		Y-45	820	30.0	7.4	7.4
3	ZSM-5	Y-25	787	57.9	7.4	7.4
4		Z-472	397	33.0	5.1	5.4
5		Z-332	422	51.0	5.1	5.4
6		Z-112	418	140.0	5.1	5.4
7*	Mordenite	Z-62	385	350.0	5.1	5.4
8		M-82	567	20.0	6.5	7.0
9*		M-56	545	28.0	6.5	7.0
10*	Beta	β-52	596	29.0	7.4	7.4

^a The property variables are: 1, the active surface ($\text{m}^2 \text{g}^{-1}$); 2, the ratio ($\text{SiO}_2/\text{Al}_2\text{O}_3$); 3 and 4, the dimensions of the cavities (Å).¹⁶

Table 2. Regioisomeric ratios and yields obtained in the screening experiment.

Dienophile ^a	Regioisomeric ratio 3/4 (% yield)				
	Catalyst				
	Zeolite ^b				
	Y-152	Y-45	ZSM-5	Mordenite	Beta
1a	5/95(55)	6/94(69)	2/98(100)	3/97(91)	3/97(62)
1b	6/94(40)	7/93(53)	13/87(23)	5/85(34)	6/94(39)
1c	3/97(48)	3/97(31)	0/100(11)	4/96(33)	1/99(100)
1d ^c	4/96(55)	1/99(38)	nr	0/100(62)	4/96(59)
1e	nr	nr	nr	nr	nr
1f	nr	nr	nr	nr	nr
1g	nr	nr	nr	nr	nr

^a See Fig. 1. ^b See Table 1. ^c Chlorination of the double bond of the cyclohexene moiety was also observed. ^d No reaction.

Our objective was thus to determine whether or not zeolites could be used to afford practically useful procedures with readily available catalysts. For this reason, only commercially available zeolites were included in the present study. To permit a comparison with the corresponding Lewis acid catalyzed reactions we also report our results obtained with a selection of Lewis acids.

A survey of the literature showed that the use of zeolites as catalysts in the Diels–Alder reaction is not a totally new concept, however. There is one paper⁴ which reports good regioselectivity in the reaction of isoprene with propenal, methyl propenoate, and but-3-en-2-one. However, the catalysts used in that study were special, metal-doped zeolites which must be prepared prior to use and such catalysts are therefore not readily available. Other papers⁵ on zeolite catalysis in Diels–Alder reactions have dealt with reactions of symmetrical diene systems and for this reason, the possibility of regioselective reactions has not been considered at all.

Methods and results

Scope of the study. The step-by-step lay-out of the present study was (1) (a) determine whether or not zeolite catalysis offers any advantages over Lewis acid catalysis both with respect to the observed regioselectivity and to the overall yield; (b) if the zeolites should yield promising results, *which ones* should then be selected for further development. To this end, run a large screening experiment which includes both zeolite catalysts and Lewis acid catalysts.

(2) Explore the experimental conditions with those zeolites which showed promising results and determine *which* experimental variables are important to control.

(3) Adjust these important variables to achieve optimum performance of the reaction.

(4) Apply the thus determined optimum experimental conditions to preparative scale runs so that the practical use of the reaction can be evaluated.

Selection of catalysts. Zeolites. Five zeolites were selected so that they covered four different structural families

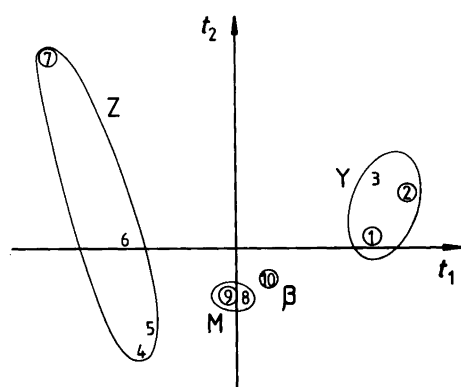


Fig. 2. Score plot used for the selection of zeolites. The plot was obtained from a principal component projection of the zeolite data in Table 1. Selected items are encircled. The different classes of the zeolites are shown in the plot: β (beta), M (mordenite), Y (Y), and Z (ZSM-5).

(ZSM-5, mordenite, Y, and β). The selection was based upon the principal component score plot shown in Fig. 2. This plot was obtained from a principal component projection of the data in Table 1. The following items were chosen (for the identification number, see Table 1). The structural class is given within parentheses: # 1, zeolite Y-152 (Y), # 2, zeolite Y-45 (Y), # 7, zeolite Z-62 (ZSM-5), # 9, mordenite-H M-56 (Mordenite), and # 10, zeolite beta (beta). As it was found in the study of the Fischer indole reaction³ that Y-type zeolites afforded excellent selectivity, two items from this structural class were chosen in such a way that they covered a range of variation within the class. For details on principal component analysis, see Refs. 6 and 7.

Lewis acids. Seven Lewis acids were selected according to their principal properties⁸ to yield a set of test items which spanned a large range of the molecular properties in the selected acids. A score plot which displays the principal properties of Lewis acids is shown in Fig. 3. The following Lewis acids were selected: aluminum trichloride, aluminum tribromide, boron trifluoride-diethyl ether,

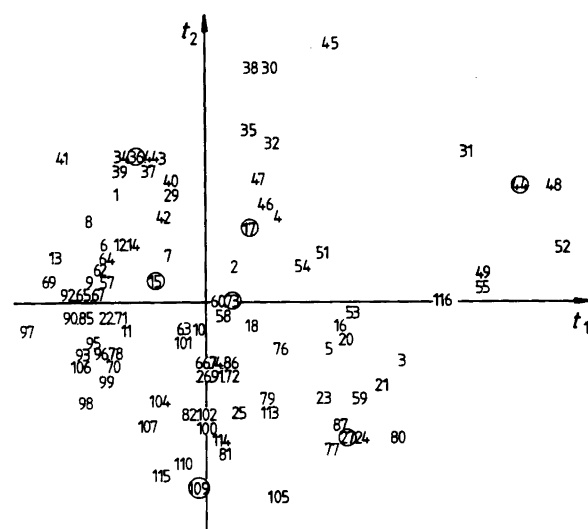


Fig. 3. Projection of the principal properties of Lewis acids used for the selection of Lewis acid catalysts. The selected items are encircled: AlBr_3 (73), AlCl_3 (17), SbCl_5 (27), SbI_3 (110), BF_3 (44), MnF_2 (36), and ZnCl_2 (15).

manganese difluoride, antimony triiodide, antimony pentachloride and zinc dichloride. A general discussion of experimental designs based upon principal properties in organic synthesis is given in Ref. 7 and we will not go into details here.

Screening of the performance of the selected catalysts. For each catalyst, the reactions between isoprene and each of the dienophiles were studied using dichloromethane as the solvent. We chose this solvent for the screening experiment to make it possible to compare our results with published work on zeolite-catalyzed and Lewis acid catalyzed Diels-Alder reactions for which dichloromethane was used as the solvent.^{4,9} The course of the reaction was monitored by high-resolution GLC of samples taken from the reaction mixture at regular time intervals. Integrated peak areas were used for determining the isomer distributions as well as the overall yields by the internal standard

Lewis acids

AlBr_3	AlCl_3	SbCl_5^c	SbI_3	$\text{BF}_3\text{-OEt}_2$	MnF_2	ZnCl_2
2/98(58)	0/100(26)	0/100(27)	0/100(42)	0/100(97)	nr ^d	5/95(80)
5/95(68)	4/96(36)	10/90(10)	13/87(8)	5/95(100)	18/82(5)	7/93(85)
5/95(42)	5/95(83)	nr	nr	5/95(10)	nr	nr
nr	3/97(73)	4/96(10)	nr	4/96(44)	nr	nr
tr ^e	tr	nr	nr	tr	nr	nr
5/95(14)	5/95(67)	nr	nr	nr	nr	6/94(9)
0/100(3)	5/95(30)	nr	nr	nr	nr	nr

^e Trace amounts of the Diels-Alder product were observed, the regioisomer distribution was not determined.

technique. A flame-ionization detector (FID) was used and it was assumed that the isomeric compounds have identical FID responses. The results of these experiments are summarized in Table 2.

The yields reported for the Lewis acid catalyzed reactions in Table 2 are the highest observed yields during the course of the reaction. This points to a problem which deserves comment. It was found that one disadvantage of using Lewis acids in Diels–Alder reactions is that the yields usually decreased over time, owing to decomposition of the product in the presence of aggressive catalysts. However, the timing for quenching the reaction mixture to destroy the catalyst and to achieve the maximum yield is critical and depends on the nature of the diene and the dienophile. The optimum timing must therefore be determined separately for each system and this makes it difficult to achieve a simple general procedure for carrying out Lewis acid catalyzed Diels–Alder reactions.

In the experiments using the zeolite catalysts reported in Table 2, the yields were observed to increase steadily with time. For convenience, a limiting reaction time of 24 h was set at which time the yields given in Table 2 were recorded. For the screening experiment this was considered to be sufficient since the purpose was to identify suitable catalysts for practical use. Catalysts which afford very slow formation of the product would not be very practical to use. Such catalysts would require excessively long reaction times to reach the final yield.

The observation of gradual product formation over time indicated that decomposition of the product in the presence of zeolites would not be an obstacle to the development of an experimental procedure for catalyzed Diels–Alder reactions.

As shown in Table 2, the zeolite-catalyzed reactions with dienophiles **1a–1d** afforded good to excellent results. We considered these results promising enough to motivate further studies with a view to developing a method for

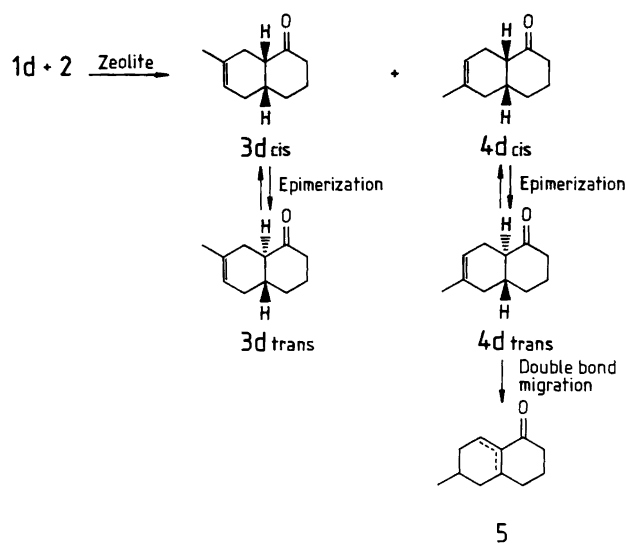
Table 3. Fractional factorial design, 2^{4-1} , for analyzing experimental variables with different zeolites.

Exp. No.	Variable ^a			
	x_1	x_2	x_3	x_4
1	-1	-1	-1	-1
2	1	-1	-1	1
3	-1	1	-1	1
4	1	1	-1	-1
5	-1	-1	1	1
6	1	-1	1	-1
7	-1	1	1	-1
8	1	1	1	1
9	0	0	0	0
10	0	0	0	0
11	0	0	0	0

^a The variables and their scalings are defined as follows: x_1 , definition, [-1 level, +1 level]; x_1 , amount of zeolite/g, [0.3, 3.0]; x_2 , reaction temperature/°C, [22, 80]; x_3 , addition time of isoprene/min, [0.01, 30]; x_4 , volume of solvent/ml, [10, 30].

zeolite-catalyzed Diels–Alder reactions. However, the failure of the dienophiles **1e–1g** to undergo the desired reaction in the presence of zeolites indicates a limitation of the scope of the method. These dienophiles also, however, afforded poor results in the Lewis acid catalyzed reactions.

Model system for developing the method. To explore the experimental conditions with a view to developing a synthetic method, the reaction of isoprene and cyclohex-2-enone, **1d**, was chosen as the model system. The reasons for this choice were that the products obtained are isomeric methyl-substituted octalones and, as such, they are useful for the synthesis of natural products containing fused six-membered ring systems. It would be of general interest for synthetic chemists if an efficient zeolite-catalyzed Diels–Alder procedure which affords high selectivity could be developed. The Diels–Alder reaction of the model system yields the *cis*-fused octalone system which, however, in the presence of acids (or bases) might epimerize into the *trans*-fused octalones, **3d_{trans}** and **4d_{trans}**, see Scheme 2. We were therefore interested to see how zeolite catalysis influences the yields of epimerized products. For this reason, the stereochemical outcome of the reaction was carefully analyzed. A discussion on the structural assignments of the isomers is given in the next section of this paper.



Scheme 1.

Mordenite and zeolite beta were considered the most promising candidates and were used as catalysts for the further development of the method.

To avoid the use of chlorinated solvents in the intended synthetic procedure, dichloromethane was replaced by cyclohexane in the subsequent experiments, with no significant difference in the outcome of the zeolite-catalyzed reactions.

Influence of the experimental variables. For the analysis of which experimental variables would have a significant

Table 4. Overall yields at different times of reaction, final yields of isomeric methyloctalones and observed selectivity, *S*, in the fractional factorial experiments with zeolite beta.

Exp. No.	Overall yield (%)						Final yields of methyloctalone isomers					Selectivity <i>S</i> (%)
	Reaction time <i>t</i> /min						3d_{cis}	3d_{trans}	4d_{cis}	4d_{trans}	5	
1	4.8	13.5	20.4	29.5	41.9	59.6	0.0	0.0	52.4	0.5	1.7	96.9
2	45.9	52.4	51.8	53.0	50.3	48.0	0.0	0.5	24.9	2.6	20.0	57.3
3	10.9	17.2	20.8	24.5	29.0	32.6	0.0	0.3	21.6	5.6	5.1	83.5
4	7.9	8.4	6.3	7.0	7.0	5.3	0.8	0.8	1.2	1.6	1.7	52.6
5	0.9	12.6	16.7	22.6	29.8	42.6	0.3	0.0	40.4	0.0	1.9	94.8
6	45.7	46.3	47.1	45.6	46.0	41.1	0.0	0.4	22.5	2.9	15.3	61.8
7	5.8	7.1	9.1	10.7	12.7	14.2	0.2	0.4	6.9	4.2	2.5	78.2
8	11.4	10.1	8.6	6.0	5.5	5.7	0.0	0.9	1.4	1.0	2.4	42.1
9	43.1	45.5	43.5	42.0	41.0	40.5	0.0	3.2	7.2	12.5	17.6	48.7
10	45.8	46.1	46.6	45.0	38.6	36.0	0.0	2.6	7.2	10.3	15.9	48.6
11	53.0	54.2	53.6	51.3	47.7	43.0	0.0	2.3	11.2	10.5	19.0	50.4

influence on the outcome of the reaction, a two-level fractional factorial design, 2^{4-1} , was used to vary the following variables: x_1 , the amount of zeolite; x_2 , the reaction temperature; x_3 , the rate of isoprene addition; x_4 , the amount of solvent. The experimental design is shown in Table 3. For a general discussion of fractional factorial designs, see Ref. 10, and for the use of such designs in organic synthesis, see Ref. 7.

As the influence of the experimental variables might be different with different zeolites, the design in Table 3 was used to define two series of experiments, one with each catalyst. The results are summarized in Tables 4, 5.

The results reported in Tables 4 and 5 show that an excellent regioselectivity ratio ($3\mathbf{d}_{cis} + 3\mathbf{d}_{trans}$)/($4\mathbf{d}_{cis} + 4\mathbf{d}_{trans}$) is obtained yielding the stereoisomeric regioisomers $4\mathbf{d}_{cis} + 4\mathbf{d}_{trans}$ as the almost exclusive products. It is also interesting to note that both the *cis*- and the *trans*-forms are formed and that the *cis*-isomer is the major one. This is in contrast with Lewis acid catalysis of the same reaction which has been reported to yield only the *trans*-isomers.¹¹

The fractional factorial experiments with the two zeolites were evaluated by fitting second-order interaction

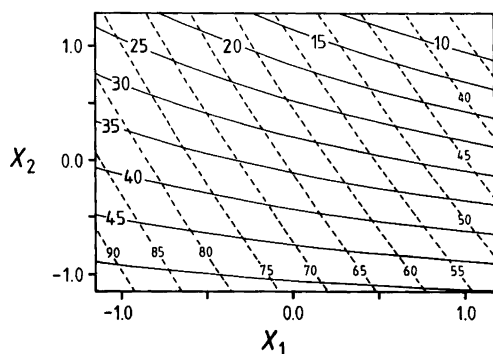


Fig. 4. Response surface contours showing the variation in yield (solid lines) and selectivity (dashed lines) when x_1 (the amount of zeolite) and x_2 (the reaction temperature) were varied in the fractional factorial study of zeolite beta. The variables x_3 and x_4 have been set to zero level.

response surface models (the coefficients of the interaction terms are aliased two-factor interactions) to the final yield (300 min), *Y*, and a measure of selectivity, *S*, defined as the abundance (%) of **4d** isomers in the final octalone mixture. The influence of the experimental variables was assessed by comparing the corresponding model parameter with its standard error. Variables for which the value of the parameter was close to the standard error were assumed to have a negligible influence on the result in the domain explored.

Zeolite beta yielded the models:

$$\begin{aligned}
 Y &= (33.3 \pm 2.4) - (5.1 \pm 2.9)x_1 - (15.9 \pm 2.9)x_2 \\
 &\quad - (4.2 \pm 2.9)x_3 + (1.9 \pm 2.9)x_4 \\
 &\quad - (3.3 \pm 2.9)(x_1x_2 + x_3x_4)/2 \\
 &\quad + (3.4 \pm 2.9)(x_1x_3 + x_2x_4)/2 \\
 &\quad + (0.3 \pm 2.9)(x_1x_4 + x_2x_3)/2 \\
 S &= (64.0 \pm 4.0) - (18.8 \pm 6.1)x_1 - (8.5 \pm 6.1)x_2 \\
 &\quad - (3.3 \pm 6.1)x_3 + (3.0 \pm 6.1)x_4 \\
 &\quad - (0.9 \pm 6.1)(x_1x_2 + x_3x_4)/2 \\
 &\quad - (3.0 \pm 6.1)(x_1x_3 + x_2x_4)/2 \\
 &\quad + (3.8 \pm 6.1)(x_1x_4 + x_2x_3)/2
 \end{aligned}$$

From the yield (*Y*) model it is seen that the important variables are: x_1 (the amount of zeolite), x_2 (the reaction temperature), and x_3 (the rate of addition of isoprene). The reaction temperature is found to be the most important variable. A negative sign of the coefficient of x_3 implies that a rapid addition of isoprene should be employed. An interaction effect with a negative sign between x_1 and x_2 is also indicated.

From the selectivity (*S*) model it is seen that the linear influence of x_1 and x_2 is important while other effects are probably negligible. A combined contour plot of the response surface projection of both yield and selectivity when x_1 and x_2 are varied is shown in Fig. 4.

Table 5. Overall yields at different times of reaction, final yields of isomeric methyloctalones and observed selectivity, S , in the fractional factorial experiments with mordenite.

Exp. No.	Overall yield (%)						Final yields of methyloctalone isomers					Selectivity S (%)
	Reaction time t /min						$3d_{cis}$	$3d_{trans}$	$4d_{cis}$	$4d_{trans}$	5	
	5	15	30	60	120	300						
1	0.4	1.1	1.5	2.4	3.8	6.5	0.1	0.0	6.3	0.0	0.1	97.9
2	2.5	6.9	9.8	15.1	24.6	40.1	0.4	0.0	34.7	3.3	1.7	194.8
3	1.1	1.5	2.7	4.6	6.8	11.1	0.2	0.0	8.7	1.3	0.9	90.1
4	7.0	14.5	22.1	30.6	39.0	48.0	0.6	2.5	18.5	14.2	12.4	68.1
5	0.8	1.0	1.2	1.6	2.3	3.7	0.0	0.0	3.7	0.0	0.0	100.0
6	13.0	16.2	20.9	27.7	39.3	60.9	1.0	0.0	51.5	5.9	2.5	95.3
7	2.0	2.5	3.6	4.6	6.8	9.6	0.3	0.0	7.8	0.9	0.6	90.6
8	21.3	24.7	29.3	37.0	45.6	59.9	0.6	3.7	20.4	18.1	17.1	64.3
9	8.0	12.1	16.5	23.8	31.5	45.5	0.8	0.3	33.4	6.3	4.7	87.3
10	6.4	12.6	16.2	25.0	34.1	45.8	1.1	0.4	34.6	6.6	4.8	88.7
11	9.5	13.6	17.9	25.2	34.0	47.7	1.1	0.4	34.0	6.9	4.7	87.0

It is seen in Fig. 4 that the best result is obtained when the settings of x_1 and x_2 are low and that a possible improvement might be obtained if the settings of these variables are further decreased. However, by decreasing x_1 and x_2 from their -1 levels (decreased amounts of zeolite and reaction temperatures below room temperature) the reaction proved to be too slow to be practically useful. Attempts further to improve the results by adjusting these variables were therefore not considered worthwhile. The experimental conditions corresponding to the settings in Exp. No. 1 of the design (all variables at their low levels) were therefore considered to be close to the optimum conditions.

An experiment was carried out under these conditions confirmed this conclusion. After 5 h which was the time limit of the experiment in the design, the yield was still increasing. A final yield of 90% was obtained after 24 h after which time no further increase in the yield could be observed. The following distribution of octalone isomer ($3d_{cis}/3d_{trans}/4d_{cis}/4d_{trans}/5$) was observed (0.9/0/93.6/2.5/3.0) which corresponds to a regioisomeric ratio $(3d_{cis} + 3d_{trans})/(4d_{cis} + 4d_{trans}) = 0.9/96.1$.

Mordenite yielded the models:

$$\begin{aligned}
 Y &= (34.4 \pm 4.2) + (22.3 \pm 4.9)x_1 + (2.2 \pm 4.9)x_2 \\
 &+ (3.6 \pm 4.9)x_3 - (1.3 \pm 4.9)x_4 \\
 &- (0.4 \pm 4.9)(x_1x_2 + x_3x_4)/2 \\
 &+ (4.6 \pm 4.9)(x_1x_3 + x_2x_4)/2 \\
 &- (1.0 \pm 4.9)(x_1x_4 + x_2x_3)/2 \\
 S &= (87.5 \pm 0.2) - (7.1 \pm 0.3)x_1 - (9.4 \pm 0.3)x_2 \\
 &- (0.1 \pm 0.3)x_3 + (0.3 \pm 0.3)x_4 \\
 &- (5.1 \pm 0.3)(x_1x_2 + x_3x_4)/2 \\
 &- (0.7 \pm 0.3)(x_1x_3 + x_2x_4)/2 \\
 &- (0.7 \pm 0.3)(x_1x_4 + x_2x_3)/2
 \end{aligned}$$

From the models it is seen that x_1 is the only variable

that has an influence on the yield. For the selectivity, the variables x_1 and x_2 have influence. These variables also show an interaction effect on the selectivity. The response surface contour projections shown in Fig. 5 indicate that both the yield and the selectivity might possibly be improved by adjustment of the experimental conditions in a direction defined by increasing x_1 from its high level in the fractional factorial design, and maintaining (or slightly decreasing) x_2 from its low level in the design. In order to explore this possibility, and more precisely to locate the optimum experimental conditions, a central composite rotatable response surface design¹² in these variables was laid out so that a second-order quadratic model could be fitted. For convenience, the low limit of the temperature variation was set at room temperature. The variation of the amount of zeolite was set to embrace the upper level used in the fractional factorial design. The response surface design and the results obtained are summarized in Table 6. A plot of the response surface contours is shown in Fig. 6.

However, these results show that further improvement with respect to the yield could not be achieved by increasing the amount of mordenite. We therefore conclude

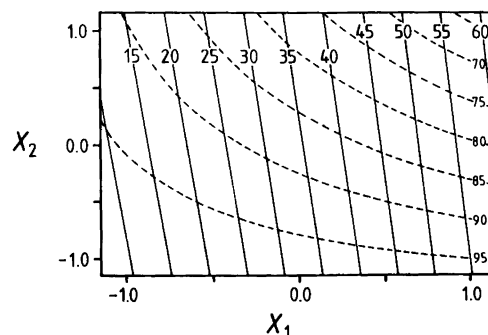


Fig. 5. Response surface contours showing the variation in yield (solid lines) and selectivity (dashed lines) when x_1 (the amount of zeolite) and x_2 (the reaction temperature) were varied in the fractional factorial study of mordenite. The variables x_3 and x_4 have been set to zero level.

Table 6. Response surface design for studying mordenite.

Exp. No.	Variable ^a		Yield of isomeric methyloctalones					Overall yield Y (%)	Selectivity S (%)
	x_1	x_2	3d _{cis}	3d _{trans}	4d _{cis}	4d _{trans}	5		
1	-1	-1	0.9	0.0	35.6	4.2	2.0	42.7	93.2
2	1	-1	1.0	0.5	49.9	9.5	4.9	65.8	91.8
3	-1	1	0.7	1.0	21.9	8.1	7.6	39.3	76.3
4	1	1	0.0	1.9	10.1	10.6	13.3	35.9	57.7
5	-1.414	0	0.7	0.2	26.6	3.5	1.9	32.9	91.5
6	1.414	0	0.0	1.4	23.9	11.7	14.2	51.2	69.5
7	0	-1.414	0.8	0.0	41.4	3.0	1.6	46.8	94.9
8	0	1.414	0.0	2.0	8.5	11.2	9.8	31.5	62.5
9	0	0	0.8	0.6	40.4	11.9	7.7	61.4	85.2
10	0	0	0.5	0.6	34.5	10.2	7.3	53.1	84.2
11	0	0	0.4	0.8	30.0	11.5	7.9	50.6	82.0

^a The variables and their settings [-1.414, -1, 0, 1, 1.414] were: x_1 , the amount of mordenite/g, [1.7, 2.3, 3.8, 5.4, 6.0], and x_2 , the reaction temperature/°C, [22, 30, 51, 72, 81].

that the optimum conditions, i.e., using the amount of mordenite corresponding to the high level of the fractional factorial design, and running the reaction at room temperature, had already been achieved in the fractional factorial experiments.

Preparative runs. The results obtained under the optimized experimental condition as determined above shows that zeolite beta afforded a better result compared with mordenite. Another result was that larger amounts of the zeolite were required for the optimum conditions with mordenite than with zeolite beta. For these reasons, zeolite beta was chosen for a preparative-scale synthesis of the octalone system.

In preparative scale runs using 1.0 g and 10.0 g of cyclohex-2-enone, respectively, in which work-up by flash chromatography was used to remove unchanged starting material, the product mixtures of isomeric octalones were obtained in 75 and 62% yield, respectively. Column chromatography of the crude product from the 1.0 g run afforded 45% isolated yield of analytically pure **4d**_{cis}.

A preparative-scale run using 5.0 g of cyclohex-2-enone afforded 85% conversion according to gas chromatography.

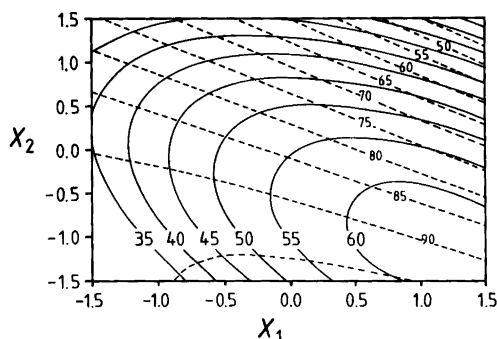


Fig. 6. Response surface contours showing the variation in yield (solid lines) and selectivity (dashed lines) when x_1 (the amount of zeolite) and x_2 (the reaction temperature) were varied in the response surface study of mordenite shown in Table 6.

Work-up by distillation afforded 68% of a mixture of isomeric octalones with the following distribution, **3d**_{cis}/**3d**_{trans}/**4d**_{cis}/**4d**_{trans}/**5** = 0.3/0/93.0/5.0/1.7.

Reactions with other dienophiles. According to the screening experiment (Table 2), all zeolites afforded fair to excellent yields and excellent selectivity in reactions where **1a–1d** were used as dienophiles. The other dienophiles failed or afforded poor yields when zeolites or Lewis acids were used as catalysts. After optimization of the experimental conditions for the reactions with **1d** for the use of mordenite and zeolite beta as the catalyst, excellent selectivity was obtained with both zeolites. With mordenite, however, the maximum conversion under the optimized conditions was ca. 60%. The optimized experimental conditions for zeolite beta afforded considerably higher conversion, 85–90%. Zeolite beta also afforded excellent results when methyl propenoate, **1c**, was used. Although the experimental conditions for zeolite beta were optimized for using **1d** as the dienophile, we considered it worth trying to extend these conditions to preparative-scale runs for **1a** and **1c**. The following results were obtained in experiments using 52 mmol of the dienophile and work-up of the crude product by flash chromatography.

But-3-en-2-one, **1a**, afforded a mixture of regioisomers (**3a/3b** = 5/95) in 59% isolated yield, and methyl propenoate, **1c**, afforded 41% isolated yield of a 7/93 mixture of regioisomers **3c/4c**.

Structural assignments of octalone isomers

Analysis by GLC-MS of the reaction mixtures from the octalone experiments generally showed, in addition to the peaks from unchanged starting material, five peaks which in their mass spectra had M^+ with m/z corresponding to the mass of methyloctalone. The spectra from these five different chromatographic peaks had very similar fragmentation patterns. We therefore concluded that the reaction yielded at least five isomeric products.

Careful column chromatography of the product mixture from the reaction made it possible to isolate one of the isomers in an analytically pure state. Upon treatment with sodium methoxide in methanol, this isomer was almost quantitatively converted into another isomer present in the reaction mixture. The isomer obtained by the base treatment afforded an identical ^{13}C NMR spectrum as has been reported for *trans*-6-methyl-6(7)-1-octalone, $4\mathbf{d}_{trans}$.¹¹ The isomer isolated by chromatography must be the *cis* isomer, $4\mathbf{d}_{cis}$, since it could be converted into the thermodynamically more stable *trans* isomer, $4\mathbf{d}_{trans}$, by treatment with base.

When the isolated product mixture with the five isomers present was dissolved in methanol and treated with sodium methoxide, GLC analysis showed that, in addition to the conversion $4\mathbf{d}_{cis} \rightarrow 4\mathbf{d}_{trans}$, two more isomers took part in an interconversion. Within a few minutes one of them had completely disappeared and the chromatographic peak of the other isomer had increased. Integration of the peak areas showed that the sum of the areas of the vanishing peak and the increasing peak was constant. We assign these changing peaks to the regioisomeric octalones $3\mathbf{d}_{cis}$ and $3\mathbf{d}_{trans}$; the thermodynamically more stable isomer obtained by treatment with base is the *trans*-fused octalone, $3\mathbf{d}_{trans}$.

The peak from the remaining isomer, 5 , was unchanged by treatment with base. We therefore conclude that it is not epimerizable and a tentative assignment is that this isomer is one in which the double bond has migrated into a position conjugated with the carbonyl group. We have not been able to isolate this isomer in a pure state and for this reason we have been able neither to elucidate the position of the double bond, nor unequivocally to determine the position of its methyl substitution. Support for a 6-methyloctalone structure 5 comes from the following observations. A mixture of $3\mathbf{d}_{trans}$, $4\mathbf{d}_{trans}$, and 5 was dissolved in cyclohexane and treated with an excess of zeolite beta at reflux temperature. Analysis of the reaction mixture by gas chromatography showed that the amount of $4\mathbf{d}_{trans}$ decreased with time with a concomitant increase in the amount of 5 . The amount of $3\mathbf{d}_{trans}$ remained unchanged. Upon prolonged heating under these conditions another isomeric peak emerged in the chromatogram close to the peak due to 5 . This emerging isomeric peak might come from the other possible conjugated isomer.

Discussion

The results presented above show that zeolites can conveniently be used as catalysts for Diels–Alder reactions of isoprene. The results of the screening experiment show that the performance of the zeolite is dependent on the nature of the dienophile. The choice of experimental material must be extended to permit any general conclusions to be drawn as to the roles played by the composition and the crystal structure of the zeolite for the catalytic activity. Some conclusions can, however, be

reached based on the nature of the interactions involved in the Diels–Alder reactions.

In Lewis acid catalyzed Diels–Alder reactions, the dienophile forms a complex with the Lewis acid. The complexation changes the degree of overlap in the π -system of the dienophile (the coefficients of the frontier orbital are changed). This decreases the HOMO–LUMO energy gap and hence reduces the activation energy of the reaction. Arguments like these have been invoked to explain the increased regioselectivity and the increased rate of Lewis acid catalyzed reactions compared with thermal Diels–Alder reactions in the absence of catalysts.

Lewis acid catalysis is also involved in the epimerization of the initially formed necessary *cis*-adduct to the *trans*-isomer in the Lewis acid catalyzed reaction forming the octalone system discussed above. The slow epimerization of the *cis*-adduct when zeolites are used to catalyze the Diels–Alder reaction indicates a weaker Lewis acid–carbonyl interaction with zeolites than with free Lewis acids. If this is true, as we assume, it would not be possible to explain the observed excellent regioselectivity in the zeolite-catalyzed reactions only in terms of acid–base catalyst–dienophile interactions. In several cases the selectivity was much better with zeolites than with added Lewis acids.

This is an argument which supports the assumption that the *shape* of the dienophile and the structure of the zeolite also play roles in determining the mode of approach of the diene to the dienophile. As the reaction occurs with the dienophile sorbed on the surface or in cavities of the zeolite, the effects of steric congestion will be much more pronounced than when the reaction occurs in solution. This may, at least, partially explain why zeolite catalysis affords very high regiocontrol in the Diels–Alder reaction, i.e., that some kind of shape- or size-selective catalysis is involved.

The results of the experiments with the zeolites in the screening experiment (Table 2) show that all of the zeolites afforded high regioselectivity with varying yields. Which zeolite should be used to afford a high conversion depends on the dienophile. There was no zeolite which afforded high yields with all dienophiles. These findings indicate that there are interactions between the zeolite and the dienophile which depend on the structure of both. We assume that such interactions with different combinations of zeolite and dienophile reagents will most likely respond differently to altered experimental conditions. The results obtained in the fractional factorial study of the influence of the experimental conditions on the performance of two zeolite catalysts support this assumption. For instance, see the very different shapes of the response surface projections shown in Figs. 4 and 5. Under such circumstances, the only way unequivocally to establish the best catalyst, is to establish the optimum experimental conditions for each candidate and then make the comparison of the results obtained. It is obvious that this would be quite cumbersome when there are several candidates to choose from.

Although the chemical outcome with respect to yield and selectivity is of prime concern when the feasibility of a chemical reaction for synthesis is evaluated there are other aspects that come into consideration when the reaction is to be adopted into a preparative *method*. One such aspect in the present case was how large an amount of the zeolite must be used in the reaction. Taking this aspect into account, mordenite was considered unsuitable since 1 kg per mol of the dienophile was required according to the optimized experimental conditions. For zeolite beta, only 100 g per mol of dienophile was required in the optimized condition and this catalyst was the preferred choice for use in the present case. However, the scaled-up experiments with the dienophiles **1a** and **1c** afforded lower yields than was obtained with **1d**. The procedure was optimized for **1d** and the results obtained with **1a** and **1c** illustrate that it is not always possible to extrapolate the optimum conditions determined for one reaction system to others.⁷

Conclusions

The use of zeolites as catalysts in Diels–Alder additions to isoprene affords highly regioselective reactions and good to excellent yields. An advantage of the method developed is that the experimental conditions are sufficiently mild to permit the isolation of the *cis*-fused octalone formed in the reaction with cyclohex-2-enone which has not been possible with Lewis acid catalysis. The present method is therefore complementary to methods based upon addition of a Lewis acid to promote the reaction. Another advantage is the very simple experimental procedure which comprises stirring of a mixture of the reactants and the catalyst in cyclohexane at room temperature and the equally simple work-up procedure in which the catalyst is removed by filtration.

Zeolites are used in large quantities as catalysts in large-scale industrial synthetic processes. Their use as catalysts in laboratory-scale synthesis and in fine-chemical synthesis has attracted little interest, however. The results presented in this paper show that zeolites, in certain respects, have unique properties as catalysts in the Diels–Alder reaction. We therefore conclude that the present method would be a useful alternative when a Diels–Alder cyclization is attempted.

Experimental

Chemicals. Isoprene, cyclohex-2-enone, methyl propenoate, zinc dichloride, boron trifluoride–diethyl ether, aluminum trichloride and antimony pentachloride were purchased from Janssen Chimica, antimony triiodide from the British Drug Houses Ltd., but-3-en-2-one and silica gel (Kieselgel 60, <0.063 mm) from Merck. Reagents were *puriss.* or *pro analysi* qualities and were used as received. All solvents were *pro analysi* quality and were stored over 4 Å molecular sieves. 3-Bromobut-3-en-2-one was synthesized from but-3-en-2-one, see below. Zeolites were obtained from EKA NOBEL AB. The

zeolite samples had the following designation given within parentheses: ZSM-5 (EZ-056), mordenite (EM-056), Y-152 (EY-152), Y-45 (EY-045), beta (EB-052).

General techniques. ¹H and ¹³C NMR spectra were recorded on a Bruker ACP 250 or a Bruker AM 500 instrument. IR spectra were recorded on a Perkin-Elmer 681 spectrometer. GLC analyses were carried out using a Carlo-Erba Fractovap 4130 instrument equipped with FID and a CP Sil-8 CB fused-silica capillary column (0.22 mm i.d. × 25 m). Peak areas were measured with a Milton Roy CI-10 integrator. Electron-impact ionization (EI) mass spectra were obtained via GC–MS analysis on an HP GC/MSD 5830/5970 system. Chemical ionization (CI) mass spectra were recorded using a Finnigan INCOS 500 instrument using methane as the ionizing gas. Zeolites were activated at 400 °C for 5 h in a PotteryCrafts P 5900 oven. For controlling the rate of addition of liquid reagents a Sage Instruments 355 syringe pump was used. All glassware was dried in an oven at 150 °C for several hours prior to use.

3-Bromo-3-buten-2-one, 1b. A typical procedure was as follows. A 500 ml two-necked flask was equipped with an air condenser and a dropping funnel. The flask was charged with freshly distilled but-3-en-2-one, (10.00 g, 142.7 mmol), and 200 ml of dichloromethane. The mixture was magnetically stirred and cooled in an ice-bath and bromine (14.6 ml, 285 mmol) was slowly added to the cooled solution. Towards the end of the addition a slightly yellow color persisted. When the addition was complete, the mixture was stirred for 15 min. The solvent was removed by evaporation under reduced pressure and the residue of crude 3,4-dibromo-2-butanone was dissolved in 100 ml of diethyl ether and transferred to a three-necked flask equipped with a Hershberg stirrer, a dropping funnel and an air condenser with a drying tube. The flask was immersed in an ice-bath and, with efficient stirring, triethylamine (14.45 g, 142.7 mmol) was rapidly added. Stirring was continued for 0.5 h, after which time the reaction mixture was filtered to remove the precipitated amine salt. The ether was removed by distillation under reduced pressure and the residual crude product was purified by Kugelrohr distillation, b.p. 80 °C (oven temperature)/10 mmHg, to yield 17.7 g (82%) of 3-bromobut-3-en-2-one, **1b**. The usual range of the yield by this procedure is 80–85%.

¹H NMR (80 Hz): δ 2.48 (s, 3 H), 6.47 (s, 1 H), 6.83 (s, 1 H). MS (EI 70 eV) 150 (9) [(M + 2)⁺], 148 (9) [M⁺], 135 (3), 133 (3), 107 (8), 105 (7), 81 (4), 79 (4), 43 (100), 26 (29).

General procedure for screening of zeolites and Lewis acids. Zeolites. A 25 ml round-bottomed flask was flushed with nitrogen and charged with 1.00 g of the zeolite, 3.67 mmol of the dienophile, an accurately weighed amount (ca. 0.25 g) of internal standard (see below), and 10 ml of dichloromethane. A magnetic

stirring bar was added and the flask was equipped with a reflux condenser. Under an atmosphere of dry nitrogen, the mixture was heated in an oil bath at reflux temperature for 0.5 h after which time isoprene (0.68 g, 9.9 mmol) was added in one portion. To monitor the course of the reaction, samples were withdrawn at regular intervals, filtered, diluted with dichloromethane and analyzed by GLC.

Lewis acids. The dienophile (3.67 mmol) and an accurately weighed amount (ca. 0.25 g) of internal standard (see below) was added to a magnetically stirred suspension of 0.92 mmol of anhydrous Lewis acid in 10 ml of dichloromethane contained in a 30 ml test tube fitted with a rubber septum. The mixture was stirred at room temperature under an atmosphere of dry nitrogen for 0.5 h after which time isoprene (0.68 g, 9.9 mmol) was added. Monitoring of the course of the reaction was as given above.

Internal standards. To avoid peak overlap between products and the internal standard and to ensure that the internal standard had a retention time as close as possible to those of the products, different internal standards were used for different dienophiles. The following compounds were used as internal standards: 1,2-dichlorobenzene, decane, hexadecane, phenylcyclohexane, and 1,2,4,5-tetramethylbenzene.

General procedure for the fractional factorial experiments with the octalone system. A 100 ml two-necked round-bottomed flask charged with a slurry of the given amount, x_1 , of the zeolite in the given volume, x_3 , of cyclohexane and a magnetic stirring bar was fitted with a reflux condenser and a rubber septum and flushed with dry nitrogen. The flask was placed in an oil bath at the given temperature, x_2 , and was allowed to reach temperature equilibrium. A mixture of cyclohex-2-enone (0.29 g, 3 mmol) and an accurately weighed amount (ca. 0.1 g) of cyclohexylbenzene (internal standard) dissolved in 2 ml cyclohexane was then added in one portion. The resulting mixture was stirred for 0.5 h after which time isoprene (0.61 g, 9.0 mmol), dissolved in 4 ml of cyclohexane, was added at the rate x_4 using a syringe pump for the slow addition. For the settings of the variables x_1 – x_4 , see Table 3.

Procedure for the experiments in the response surface design. The experiments were carried out as above with the settings of variables x_1 and x_2 as specified in Table 6. The variables x_3 and x_4 were set at levels which corresponded to the low level of the fractional factorial experiments, see note to Table 3.

Reaction of isoprene and cyclohex-2-enone: general procedure for preparative runs. In a 250 ml two-necked round-bottomed flask were placed 5.20 g of zeolite beta. The

flask was sealed with rubber septa, protected from moisture and heated with an electric heat-gun (400 °C) while being flushed with dry nitrogen. After cooling to room temperature, cyclohexane (100 ml), followed by cyclohex-2-enone (5.00 g, 52 mmol), was added to the flask. The resulting mixture was stirred for 0.5 h after which time isoprene (17.70 g, 269 mmol) was added in one portion. To monitor the course of the reaction, small samples were withdrawn at regular intervals. The samples were washed with ethanol, filtered through Celite and analyzed by gas chromatography. The reaction was stopped when no further change in the relation between the areas of the peak from cyclohex-2-enone and sum of the peaks from the products could be observed, in this case 32 h. The mixture was filtered by suction through a pad of Celite and washed with four 25 ml portions of ethanol. A pad of Celite was necessary to prevent the fine particles of the zeolite from clogging the filter. The filtrate was transferred to an evaporation flask and the volatiles were removed on a rotary evaporator under reduced pressure. The bright yellow residue was distilled under reduced pressure to yield 5.81 g (68 %) of the product, b.p. 115–130 °C/11 mmHg, as a mixture of isomeric octalones with the isomer distribution: *trans*-7-methyl-6(7)-1-octalone, **3d_{trans}** (0%), *cis*-7-methyl-6(7)-1-octalone, **3d_{cis}** (0.3%), *trans*-6-methyl-6(7)-1-octalone, **4d_{trans}** (5%), *cis*-6-methyl-6(7)-1-octalone, **4d_{cis}** (93%), and other isomers including **5** (1.7%).

Preparative run: reaction of isoprene and but-3-en-2-one. Using isoprene (18.68 g, 260 mmol), but-3-en-2-one, **1a** (3.64 g, 52.0 mmol), 52.0 g of zeolite beta in 100 ml of cyclohexane afforded the maximum yield after 1 h (GC). Flash chromatography (silica gel 60, heptane–ethyl acetate 10:1) of the crude product yielded 4.23 g (59 %) of a (5/95) mixture of **3a/4a**.

Preparative run: reaction of isoprene and methyl propenoate. Using isoprene (18.68 g, 260 mmol), methyl propenoate, **1c** (4.47 g, 52.0 mmol), 52.0 g of zeolite beta in 100 ml of cyclohexane afforded the maximum yield after 5.5 h (GC). Flash chromatography (silica gel 60, heptane–ethyl acetate 50:1) of the crude product yielded 3.31 g (41 %) of a (7/93) mixture of **3c/4c**.

Physical properties of compounds. NMR spectra were recorded in deuteriochloroform. Mass spectra are reported as m/z (% relative intensity) [assignment]. Boiling points and melting points are uncorrected. Boiling points at atmospheric pressure were determined by the Siwoloboff's method¹³ on a Büchi melting point apparatus.

4-Acetyl-1-methylcyclohexene, 4a. b.p. 207–209 °C/756 mmHg (lit.¹⁴ 204.5–206 °C/747 mmHg, 137–142 °C/12 mmHg). ¹H NMR (250 MHz): δ 5.39 (br s, 1 H), 2.45–2.60 (m, 1 H), 2.14 (s, 3 H), 1.99–2.00 (m, 4 H), 1.64–1.65 (m, 5 H). ¹³C NMR (63.0 MHz): δ 211.4, 133.5,

119.1, 47.0, 29.3, 27.7, 26.6, 24.7, 23.2. MS (EI 70 eV): 138 (27) [M^+], 123 (19), 105 (40), 95 (39), 79 (20), 67 (41), 55 (18), 43 (100). IR (neat): 1715 (C=O) cm^{-1} .

4-Acetyl-4-bromo-1-methylcyclohexene, **4b**. b.p. 112 °C/12 mmHg (decomp.). ^1H NMR (250 MHz): δ 5.30 (br s, 1 H), 2.66–2.83 (m, 2 H), 2.42 (s, 3 H), 2.23–2.28 (m, 2 H), 2.07–2.12 (m, 2 H), 1.67 (s, 3 H). ^{13}C NMR (63.0 MHz): δ 201.9, 133.5, 116.9, 66.8, 34.0, 32.4, 28.6, 23.7, 22.8. MS (CI): 217 (100) [$M^+ + 1$], 137 (42). IR (neat): 1720 (C=O) cm^{-1} .

Methyl 4-methylcyclohex-3-ene-1-carboxylate, **4c**. b.p. 231 °C/756 mmHg (lit.¹⁵ 83–86 °C/13 mmHg). ^1H NMR (250 MHz): δ 5.38 (br s, 1 H), 3.68 (s, 3 H), 2.47–2.48 (m, 1 H), 2.22–2.24 (m, 2 H), 1.98–2.02 (m, 2 H), 1.66–1.71 (m, 2 H), 1.63 (s, 3 H). ^{13}C NMR (63.0 MHz): δ 176.3, 133.6, 119.1, 51.4, 39.04, 29.2, 27.6, 25.4, 23.3. MS (EI 70 eV): 154 (18) [M^+], 139 (20), 122 (18), 95 (100), 79 (63), 67 (36), 55 (21). IR (neat): 1740 (C=O) cm^{-1} .

cis-6-Methyl-6(7)-1-octalone, **4d_{cis}**. m.p. 35–37 °C, b.p. 119–126 °C/11 mmHg. ^1H NMR (500 MHz): δ 5.34 (br s, 1 H), 2.68–2.66 (m, 1 H), 2.46–2.39 (m, 3 H), 2.31–2.26 (m, 1 H), 2.00–1.99 (m, 2 H), 1.91–1.75 (m, 5 H), 1.63 (s, 3 H). ^{13}C NMR (125.9 MHz): δ 213.0, 131.6, 118.2, 48.0, 39.9, 36.3, 32.2, 28.4, 24.5, 24.1, 23.7. MS (EI 70 eV): 164 (63) [M^+], 149 (42), 131 (64), 118 (80), 105 (51), 93 (75), 91 (71), 79 (63), 77 (65), 53 (36), 51 (24), 41 (72), 39 (100). IR (KBr): 1710 (C=O) cm^{-1} .

trans-6-Methyl-6(7)-1-octalone, **4d_{trans}**. b.p. 119–120 °C/11 mmHg. ^1H NMR (500 MHz): δ 5.39 (br s, 1 H), 2.42–2.38 (m, 2 H), 2.16–2.15 (m, 1 H), 2.08–2.04 (m, 2 H), 1.94–1.90 (m, 2 H), 1.71–1.65 (m, 3 H), 1.64 (s, 3 H), 1.49–1.42 (m, 2 H). ^{13}C NMR (125.9 MHz): δ 212.3, 132.3, 120.0, 50.3, 42.1, 40.5, 38.4, 32.7, 26.2, 24.7, 23.3. MS (EI 70 eV): 169 (94) [M^+], 149 (65), 131 (74), 118 (100), 105 (65), 93 (92), 91 (83), 79 (65), 77 (72), 53 (38), 51 (22), 41 (73), 39 (98). IR (neat): 1725 (C=O) cm^{-1} .

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