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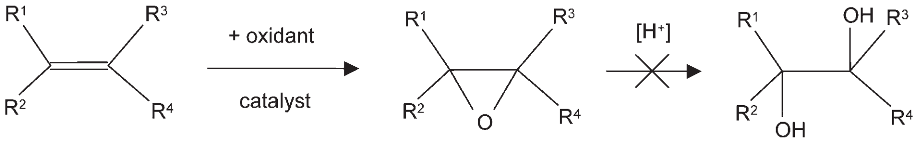
Novel Transition-Metal-Free Heterogeneous Epoxidation Catalysts Discovered by Means of High-Throughput Experimentation

Paolo P. Pescarmona,* Kris P. F. Janssen, and Pierre A. Jacobs[a]

Abstract: Various transition-metal-free oxides have been studied as catalysts for the epoxidation of cyclooctene with hydrogen peroxide by means of high-throughput experimentation. Different boron, aluminium, and gallium oxides were prepared according to various synthesis methods. A number of pure aluminium and gallium oxides showed very good catalytic performances, while the results obtained with boron oxides or mixed oxides were less positive. The best results were obtained with a gallium oxide catalyst, which gave an epoxide yield of 71 % and a selectivity of 99 % after reaction for 4 h at 80 °C. Gallium oxides had not been reported previously as active epoxidation catalysts. The use of high-throughput experimentation proved useful both for discovering new active catalysts and for identifying a number of relationships between the synthesis conditions and the catalytic properties of the transition-metal-free oxides.

Keywords: epoxidation · heterogeneous catalysis · high-throughput experimentation · sustainable chemistry · transition-metal-free oxides

Introduction



Scheme 1. Epoxidation of alkenes.

Epoxides are versatile compounds used in the synthesis of many fine chemicals with relevant industrial applications.[1] The most common way to prepare epoxides is by the catalytic oxidation of alkenes (Scheme 1).

A number of good homogeneous and heterogeneous catalysts for the epoxidation of alkenes has been reported.[2–4] However, none of them meets all of the requirements for efficient and sustainable chemistry. An ideal epoxidation catalyst should exhibit the following features:

- It should be active under mild reaction conditions for a wide range of substrates. It should also be selective, implying that it should not contain too strongly acidic sites that might cause further reaction of the formed epoxides.
- It should be usable in conjunction with hydrogen peroxide (H_2O_2) as the oxidant, since this readily available compound yields water as a by-product. The transfer of the reactive oxygen atom of H_2O_2 to the substrate should be catalysed in an efficient way, avoiding the formation of O_2.
- It should be a stable heterogeneous catalyst, to allow easy separation from the products and recycling without loss of activity.
- It should not release transition metals into the reaction medium, or preferably should not contain them at all.
- It should show optimum performance in environmentally acceptable solvents or in the absence of solvents.

Recently, it was discovered that partially hydroxylated aluminium oxides are active and selective heterogeneous catalysts for the epoxidation of a variety of alkenes with hydrogen peroxide.[5–7] The proposed catalytic cycle involves the formation of surface hydroperoxide groups (Al–OOH) by the reaction of surface hydroxyl functions (Al–OH) with hydrogen peroxide. The activities and stabilities of the aluminas strongly depend on the synthesis method used to prepare them.[8,9] The best catalytic performances are obtained

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[a] Dr. P. P. Pescarmona, K. P. F. Janssen, Prof. Dr. P. A. Jacobs
Centre for Surface Chemistry and Catalysis, K. U. Leuven
Kasteelpark Arenberg 23, 3001 Heverlee (Belgium)
Fax: (+32) 16-321-998
E-mail: paolo.pescarmona@biw.kuleuven.be

with aluminium oxides presenting a high number of acid sites combined with a moderate hydrophilicity, ensuring a good interaction with both the polar H_2O_2 and the apolar alkene.[10] Due to their reasonable stability in H_2O, these catalysts are active in epoxidation reactions with concentrated aqueous hydrogen peroxide, which represents the most suitable oxidant on environmental and economic grounds. Despite the aforementioned advantages, the catalytic parameters of these transition-metal-free oxides do not significantly exceed those of the known heterogeneous catalyst systems containing transition metals.[2]

Herein, we present a study of a new set of transition-metal-free catalysts for the epoxidation of alkenes with H_2O_2. It is anticipated that oxides of Group 13 elements with the capacity to form surface peroxide groups (B−OOH, Al−OOH, Ga−OOH) would be capable of serving as epoxidation catalysts. The catalytic performance of these oxides will be affected by the stability of the surface peroxide groups formed, which, in turn, depends on the nature of the metal[1] at the oxide surface and that of their close neighbours. The stability of the surface peroxide groups should not be too low, so as to avoid decomposition with O_2 generation, nor too high, which would be unfavourable for the transfer of the oxygen to the alkene. Finding the optimum balance is not trivial. On the basis of these considerations, it was decided to screen the composition triangle of three-component oxide mixtures (B, Al, and Ga oxides) with the aim of discovering improved transition-metal-free epoxidation catalysts. These materials can be prepared according to different procedures in order to tune their porosity and structure, as well as the strength and distribution of acid sites, to the desired catalytic behaviour.

High-throughput experimentation (HTE) techniques have been used to investigate the large parameter space defined by the various compositions of mixed B, Al and Ga oxides prepared by means of different synthesis methods. Combinatorial chemistry and high-throughput experimentation techniques are among the newest and most promising experimental methods in many fields of chemical research, including materials science and catalysis.[11–15] These methods are based on the investigation of broad sets of experimental parameters through the design, synthesis, and screening of large numbers of samples. The high throughput of these techniques is made possible by the use of automated workstations and fast-analysis equipment for the preparation and screening of the samples. The mixed oxides were synthesised and their catalytic properties were tested in parallel on an automated workstation equipped with a 60-well stirring and heating block. The epoxidation activities and selectivities were screened by means of a GC set-up equipped with a very fast heating and cooling system, which allowed rapid analysis of the samples.

When studying a system by means of HTE, an appropriate experimental strategy should be selected to deal effectively with the large number of results that will be produced. The choice of the HTE methodology depends on the features of the system under study, on the kind of information that is sought, and on the experimental equipment available.

The first step in an HTE experiment is the definition of the parameter space to be studied. This implies the use of personal knowledge and intuition, literature data, and computational modelling to identify the parameters that can be expected to have an influence on the generation of a system with the desired properties. The next step is to find the optimal strategy to study the selected parameter space. In a full factorial approach, all possible combinations of the parameters are studied. This strategy can be used if the number of experiments needed to investigate the entire selected parameter space is not too large compared with the number of experiments that may be performed with the available equipment. If the knowledge of the system under study is limited or if the system is very complex, the parameter space to be explored becomes too large for most HTE equipment. To overcome this problem, a variety of strategies for HTE experimental design have been developed in recent years.[16–18] Mathematical and statistical concepts are used to build search algorithms that allow a reduction in the number of experiments required to gain the desired information about the chosen parameter space. The selection of the experiments to be performed and the handling of the results become crucial and complex processes, which require the use of computational tools. Generally, the reliability of a search algorithm should be tested on a known system before applying it to a new one.[19]

The full factorial is the most suitable and flexible approach for focussed studies: in addition to the discovery of leads, it provides a clear correlation between parameters and properties, allowing the identification of trends and behaviours. The possibility of observing trends also minimises the risk of missing a lead in the event of experimental errors or technical problems. Compared to search algorithms, the use of a full factorial approach is more straightforward and allows intuitive and rational design of the experiments as well as analysis of the results. On the other hand, search algorithms permit the investigation of much larger parameter spaces and prevent the risk of incorrect or biased assumptions from the researcher by using computational techniques to select the experiments to be performed. Both a full factorial approach and search algorithms have found application in HTE studies of the catalytic epoxidation of alkenes.[20,21]

Results and Discussion

The composition diagram of boron, aluminium and gallium mixed oxides can be described using ternary arrays with a different number of points.[18] The higher the number of interval steps into which the array is divided, the more accurate the description of the three-component system. A ternary array with nine steps would offer a good coverage of the composition diagram and would require 45 sample

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[1] While aluminium and gallium are metals, boron is a semi-metal. The term "metals" is used in this article when referring to these three elements together.

points. This number of points is compatible with the throughput of the available HTE equipment, which allows performing up to 60 simultaneous parallel experiments. This means that a full factorial approach can be chosen to study the system.

The composition triangle formed by B, Al and Ga mixed oxides was screened for activity in the epoxidation of *cis*-cyclooctene[10] with a 50 wt % aqueous solution of H_2O_2 after reaction for 4 h at 80 °C. Three different synthesis methods were used to prepare the oxides; these were derived from the sol–gel procedures used to synthesise the aluminas with the highest epoxidation activity[10] or procedures used to prepare mixed Al and Ga oxides,[22] and were adapted so that they could be performed on the HTE workstation.

The epoxidation activities of the three sets of 45 mixed-oxide catalysts are reported in Figure 1. A number of observations can be made concerning these experiments:

- The catalytic properties of the oxides vary as a function of the method used for their synthesis: the epoxidation activity is proportional to the gallium content with method 1 (Figure 1a) and proportional to the aluminium content with method 3 (Figure 1c), while two zones of higher activity for a high gallium and high aluminium content are found with method 2 (Figure 1b). The influence of the method of synthesis is relevant to such a degree that pure aluminium oxide or pure gallium oxide can show alternatively the highest and almost the lowest activity according to the preparation route followed (compare plots (a) and (c) in Figure 1).
- Besides the good activity found for aluminium oxide, in agreement with literature data,[5–10] gallium oxide was identified as a new, promising epoxidation catalyst. This result can be explained by considering that gallium oxides have physicochemical properties similar to those of aluminium oxides and present a similar polymorphism.[23]
- Despite the good epoxidation activities shown by pure gallium and pure aluminium oxides, the activities of the mixed oxides of Al and Ga decrease as their composition moves away from that of the active pure oxides. This lack of synergy was observed with all of the synthesis methods employed and can be ascribed to the structural and textural features of the mixed oxides rather than to their chemical properties. Low or moderate activities were found for most of the tested ternary oxides. The best synergies were found for mixed oxides with very low or no Al content and with Ga/B molar ratios larger than 1. These catalysts showed moderate to good epoxidation activities when synthesised according to methods 1 and 2. However, the selectivities towards the epoxide of the most active of these catalysts were only around 50–60 %, as compared to values higher than 90 % for the pure gallium oxide and pure aluminium oxide catalysts.
- Catalysts with high boron content show very low epoxidation activities, regardless of the synthesis method employed.

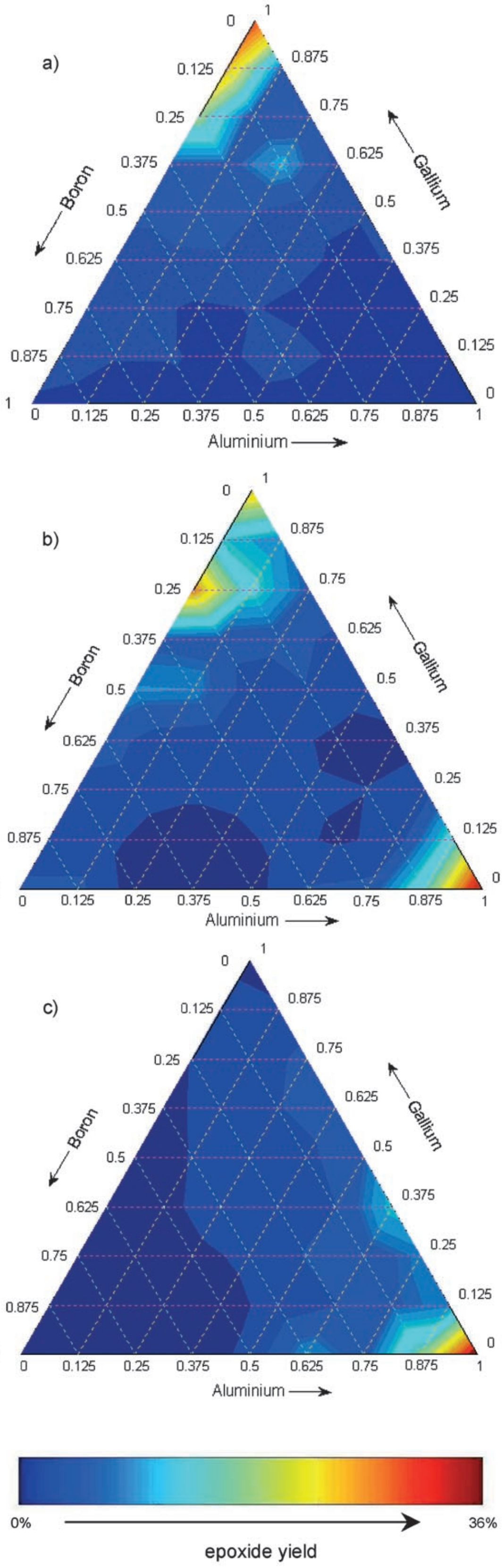

Figure 1. Activity in the epoxidation of cyclooctene with 50 wt % aqueous H_2O_2, after 4 h at 80 °C, of ternary arrays of B, Al, and Ga mixed oxides prepared according to different synthesis methods [a) method 1; b) method 2; c) method 3].

Besides the identification of gallium oxide as a new lead, this series of experiments indicated the decisive influence of the synthesis method on the final performance of the catalysts. The three synthetic methods employed differ from each other in the concentrations of the metal precursors in the reaction mixture, in the ratio between water and solvent, and in the pH of the medium (see the Experimental Section). These parameters are known to affect the hydrolytic condensation process that takes place in sol–gel syntheses.[24] On the basis of these considerations, it was decided to study in more detail the effects on the epoxidation activity of variations in the concentration of the metal precursors and in the amount of basic, neutral, or acid aqueous solution employed during the synthesis of aluminium and gallium oxides, that is, the two compositions that led to the best catalytic results in the first set of HTE tests.

For each metal oxide, four different concentrations of metal precursor and two different amounts of a basic, neutral, or acidic aqueous solution were selected. The combination of all these parameters defined a parameter space of 48 elements, which could again be studied with the available HTE equipment using a full factorial approach. The activities of the catalysts in the epoxidation of cyclooctene with H_2O_2 as a function of the variation of the above-mentioned synthesis parameters are reported in Figure 2. A more complete overview of the catalytic results, including the cyclooctene conversions and the selectivities towards epoxidation, can be found in Table 1 (first catalytic test).

The results confirm the relevance of the effects of the varied synthesis parameters on the epoxidation activities of the catalysts. Some leads can be identified and some general behaviour can be deduced from the analysis of these HTE data. The effects of the screened synthesis parameters on the aluminium oxides are quite different to those on the gallium oxides. Therefore, the results concerning each group of oxides will be discussed separately.

Aluminium oxides: The most active aluminas were obtained with small amounts of hydrolysing solutions (0.320 mL NH_3 in water/ethanol, 0.196 mL H_2O, 0.196 mL aqueous oxalic acid). The catalytic performances of these materials were not noticeably affected by variations in the concentration of the aluminium precursor. The activities of aluminium oxides synthesised with large amounts of hydrolysing solutions (1.600 mL NH_3 in water/ethanol, 0.980 mL H_2O, 0.980 mL aqueous oxalic acid) were found to be lower when a high water/solvent ratio was employed in their preparation. All syntheses involving the use of 0.980 mL of aqueous oxalic acid led to aluminas with low activities. These results indicate that too high a water concentration and too acidic an environment are detrimental to the formation of active aluminium oxides. A high water concentration in the reaction mixture increases the hydrolysis rate while retarding condensation reactions. Moreover, high acid to aluminium ratios in solution have been reported to hinder condensation reactions.[24,25] On the other hand, a basic or moderately

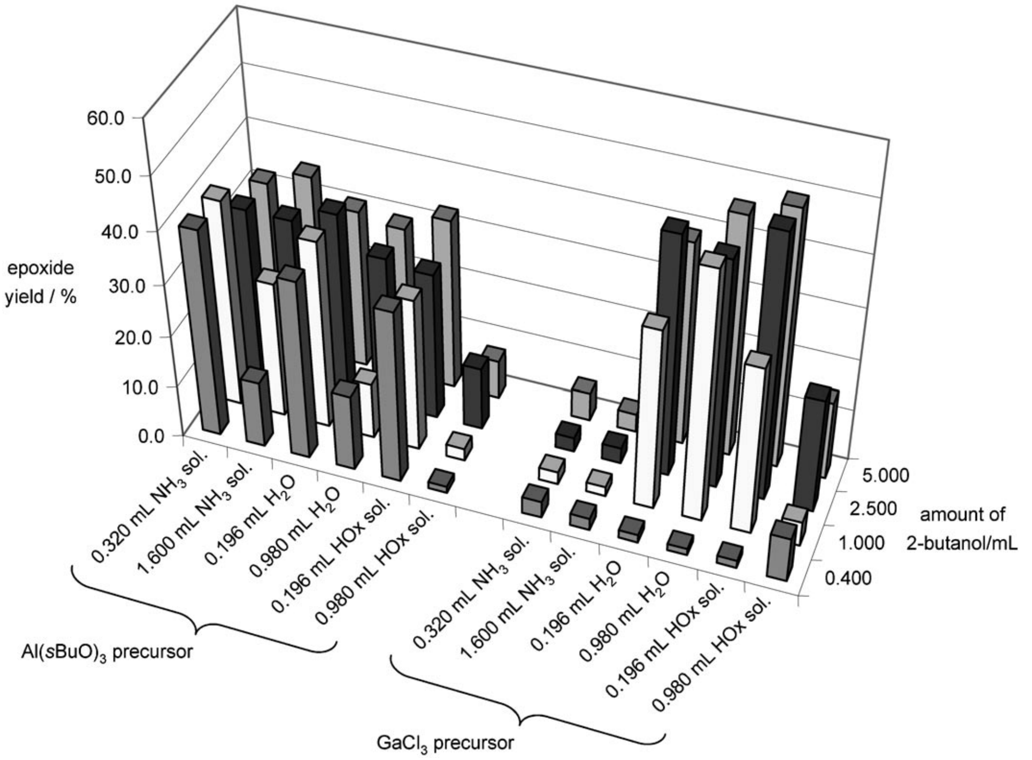

Figure 2. Activity in the epoxidation of cyclooctene with 50 wt % aqueous H_2O_2 after 4 h at 80 °C as a function of the concentration of the metal precursors and of the amount and type of hydrolysing solution employed during the synthesis of the aluminium oxide and gallium oxide catalysts [first catalytic test].

Table 1. Catalytic epoxidation of cyclooctene with 50 wt % aqueous H_2O_2 after 4 h at 80 °C: conversions, yields and selectivities against the concentration of the metal precursors and the amount and type of hydrolysing solution used during the synthesis of the aluminium oxide and gallium oxide catalysts.

	Synthesis conditions				First catalytic test				Second catalytic test			
	$Al(sBuO)_3$[a]	$GaCl_3$[a]	Amount of 2-butanol [mL]	Amount and type of aqueous solution	Cyclooctene conv. [%]	Epoxide yield [%]	By-products yield [%]	Epoxide sel. [%]	Cyclooctene conv. [%]	Epoxide yield [%]	By-products yield [%]	Epoxide sel. [%]
1	1	0	0.400	0.320 mL NH_3 sol.	43	40	3	93	45	42	4	92
2	1	0	0.400	1.600 mL NH_3 sol.	13	13	1	95	18	16	2	89
3	1	0	0.400	0.196 mL H_2O	38	35	3	92	34	32	2	93
4	1	0	0.400	0.980 mL H_2O	17	15	2	88	17	15	2	89
5	1	0	0.400	0.196 mL HOx sol.	36	33	3	92	32	30	2	93
6	1	0	0.400	0.980 mL HOx sol.	2	1	1	58	2	1	0.3	79
7	1	0	1.000	0.320 mL NH_3 sol.	43	40	3	93	36	34	2	95
8	1	0	1.000	1.600 mL NH_3 sol.	29	26	3	91	31	29	2	93
9	1	0	1.000	0.196 mL H_2O	40	36	4	91	39	35	5	88
10	1	0	1.000	0.980 mL H_2O	12	11	1	90	11	10	1	91
11	1	0	1.000	0.196 mL HOx sol.	34	29	5	86	26	23	3	89
12	1	0	1.000	0.980 mL HOx sol.	4	2	2	55	2	2	1	64
13	1	0	2.500	0.320 mL NH_3 sol.	36	33	3	91	38	35	2	94
14	1	0	2.500	1.600 mL NH_3 sol.	36	33	3	92	37	34	2	93
15	1	0	2.500	0.196 mL H_2O	39	36	3	92	36	33	2	94
16	1	0	2.500	0.980 mL H_2O	32	29	3	92	33	30	3	92
17	1	0	2.500	0.196 mL HOx sol.	32	28	3	89	30	27	3	91
18	1	0	2.500	0.980 mL HOx sol.	15	12	3	78	14	11	3	78
19	1	0	5.000	0.320 mL NH_3 sol.	36	32	4	90	40	38	3	93
20	1	0	5.000	1.600 mL NH_3 sol.	40	35	4	90	32	29	2	92
21	1	0	5.000	0.196 mL H_2O	34	31	3	90	35	33	2	94
22	1	0	5.000	0.980 mL H_2O	33	29	3	90	32	30	2	93
23	1	0	5.000	0.196 mL HOx sol.	37	33	4	89	31	28	3	91
24	1	0	5.000	0.980 mL HOx sol.	9	7	2	82	8	7	2	80
25	0	1	0.400	0.320 mL NH_3 sol.	5	3	1	70	6	5	0.2	97
26	0	1	0.400	1.600 mL NH_3 sol.	3	2	1	75	13	13	0.2	98
27	0	1	0.400	0.196 mL H_2O	2	2	1	73	2	2	1	70
28	0	1	0.400	0.980 mL H_2O	2	1	0.4	74	2	1	0.4	75
29	0	1	0.400	0.196 mL HOx sol.	2	1	1	67	2	2	1	73
30	0	1	0.400	0.980 mL HOx sol.	9	9	1	93	8	8	1	93
31	0	1	1.000	0.320 mL NH_3 sol.	6	2	2	57	5	4	0.1	98
32	0	1	1.000	1.600 mL NH_3 sol.	3	2	1	62	3	3	0.2	92
33	0	1	1.000	0.196 mL H_2O	45	35	11	77	27	26	1	98
34	0	1	1.000	0.980 mL H_2O	72	48	21	70	61	60	1	98
35	0	1	1.000	0.196 mL HOx sol.	41	32	8	80	27	27	0.2	99
36	0	1	1.000	0.980 mL HOx sol.	6	5	1	78	4	4	0.4	91
37	0	1	2.500	0.320 mL NH_3 sol.	5	3	2	57	5	4	0.3	94
38	0	1	2.500	1.600 mL NH_3 sol.	5	3	2	66	9	9	0.2	97
39	0	1	2.500	0.196 mL H_2O	76	46	26	64	68	66	1	98
40	0	1	2.500	0.980 mL H_2O	71	44	25	64	72	71	1	99
41	0	1	2.500	0.196 mL HOx sol.	67	51	13	80	56	55	1	99
42	0	1	2.500	0.980 mL HOx sol.	29	22	7	77	36	35	1	97
43	0	1	5.000	0.320 mL NH_3 sol.	8	5	2	69	7	5	1	81
44	0	1	5.000	1.600 mL NH_3 sol.	5	3	2	64	3	3	0.5	85
45	0	1	5.000	0.196 mL H_2O	74	39	32	55	71	69	2	97
46	0	1	5.000	0.980 mL H_2O	78	46	28	62	66	65	1	98
47	0	1	5.000	0.196 mL HOx sol.	76	49	27	65	69	68	1	98
48	0	1	5.000	0.980 mL HOx sol.	27	15	12	56	29	28	1	97

[a] Molar fraction.

acidic environment catalyses the hydrolytic condensation of aluminium alkoxides.[24] These considerations suggest that the condensation process is crucial for the formation of aluminium oxide catalysts with good epoxidation activity. If the hydrolysis is favoured over the condensation, the aluminium oxides will have highly hydroxylated surfaces: the degree of hydrophilicity would then be too high, preventing the alkenes from approaching the catalytic sites on the surface. This hypothesis is in agreement with data reported in the literature, which showed that aluminas synthesised with higher acid to aluminium ratios were the most hydrophilic and the least active.[10]

The best catalytic results were obtained with aluminium oxides **1** and **7** (Table 1, first catalytic test), synthesised from concentrated solutions of aluminium *sec*-butoxide in 2-butanol, hydrolysed with a solution of ammonia in water and ethanol, with a low water/solvent ratio. The cyclooctene conversion (43 %) and epoxide yield (40 %) obtained with these catalysts were significantly higher than those obtained with the aluminium oxide **5**, prepared according to a similar method to that employed for the synthesis of the best alumina epoxidation catalyst reported in the literature.[8,10] The selectivities in favour of the formation of the epoxycyclooctane were 90% or higher for the most active of the aluminium oxides. The main by-product was 2-cycloocten-1-one, accompanied by minor amounts of 2-cycloocten-1-ol.

Gallium oxides: Catalysts with high epoxidation activities were synthesised by the hydrolytic condensation of less concentrated solutions of $GaCl_3$ with water or with small amounts of aqueous solutions of oxalic acid (0.196 mL). Since the hydrolysis of $GaCl_3$ produces HCl, all of these syntheses take place in an acidic environment. Gallium oxides prepared with a high concentration of precursor or under basic conditions show very low activities. Similarly to the observations regarding the aluminium oxides, too high an acid/metal ratio (0.980 mL aqueous oxalic acid) is detrimental to the activity of the catalysts. However, the effect is less pronounced with gallium oxides, which still retain a good activity at low water/solvent ratios. These results suggest that a moderate acidity is the most suitable condition for the synthesis of active gallium oxide catalysts, probably by providing a good balance between hydrolysis and condensation reactions.

The best among the gallium oxide catalysts are in adjacent positions in the screened parameter space (Figure 2), indicating the range and limits of suitable synthesis conditions for the preparation of active gallium oxides. These catalysts showed cyclooctene conversions higher than 70% and epoxide yields of around 50% (Table 1, first catalytic test). These catalytic results represent a significant improvement compared to those obtained with the best aluminium oxides. Although the epoxidation activities of these catalysts are very promising, the epoxide selectivities are only between 55 and 80% (Table 1, first catalytic test), which are markedly lower values than those obtained with the aluminium oxides. The lower selectivity observed with the gallium oxides can be explained by considering the nature of the by-products formed during the epoxidation reaction. For the most active catalysts, the three main by-products are 1,2-cyclooctanediol, 3-chlorocyclooctene, and 5-chlorocyclooctene, with smaller amounts of other chlorinated products as well as of 2-cycloocten-1-one. The formation of 1,2-cyclooctanediol indicates the presence of strongly acidic species that cause hydrolytic ring-opening of the epoxide (Scheme 1). The presence of chlorinated products reveals that the catalysts still contain Cl atoms from the gallium source, $GaCl_3$. These Cl atoms at the surface may react directly with cyclooctene to produce the chlorinated species or may be hydrolysed when the aqueous H_2O_2 is added to yield HCl, which then catalyses the hydrolytic ring-opening of the formed epoxides.

An important feature of a good catalyst is its stability under the reaction conditions, which would imply that its activity is retained when it is reused in successive runs. The gallium oxides discussed above contained chlorine atoms that reacted during the first catalytic test. This change might generate a different catalytic performance of the recycled material. Therefore, it was of particular interest to re-evaluate the epoxidation activities of the 48 catalysts reported in Table 1 after washing them with ethanol and drying at 110 °C. The epoxide yields obtained in this second catalytic run are reported in Figure 3, while a more complete overview of the catalytic results is presented in Table 1.

All of the aluminium oxides showed similar catalytic performances in the first and the second runs, with a slight decrease in cyclooctene conversion and a slight increase in epoxide selectivity. On the other hand, the catalytic performances of the gallium oxides varied significantly between the first and second runs. The conversions of cyclooctene showed, on average, a slight decrease, while the epoxide yields and, consequently, the selectivities increased considerably. Sample **40** gave the best results, with an epoxide yield of 71% and a selectivity of 99% after reaction for 4 h at 80 °C (Table 1, second catalytic test): this represents a major improvement compared to the known alumina epoxidation catalysts.[10] The increased epoxide yields and selectivities of various recycled gallium oxides can be attributed to the absence of chlorine species in the recycled catalysts, as confirmed by the much reduced presence of 1,2-cyclooctanediol, 3-chlorocyclooctene, 5-chlorocyclooctene or other chlorinated compounds among the by-products. This indicates that the chlorine species present in the as-synthesised gallium oxides were almost completely removed during the first catalytic run and the subsequent washing procedure.

The HTE results presented so far have been based on a screening of the epoxidation activities of B, Al and Ga oxides as a function of their compositions and the conditions of their synthesis. The studied parameter spaces were selected as those expected to have the most marked influences on the catalytic properties of the oxides. The identification of new formulations for active catalysts has proved that these choices were consistent. However, the screening of other parameters not hitherto explored can prove useful for the optimisation of known catalyst formulations and opens the possibility of the serendipitous discovery of less expected leads. Among the parameters influencing the hydrolytic condensation leading to the formation of B, Al and Ga oxides, the nature of the anion of the metal precursor and the nature of the solvent in which the reaction takes place had not yet been investigated in this study. These two parameters are interrelated, since each metal precursor displays different degrees of solubility in different solvents. The best performing alumina catalysts reported in the literature have been prepared using 2-butanol as the solvent.[10] Therefore, 2-butanol was chosen as solvent for the preparation of all of the above-mentioned HTE samples. For this further study, a number of metal precursors of the type MX_3 were selected (where M is B, Al, or Ga and X is chloride, nitrate, or an alkoxy group). The group X reacts during the hydrolysis step of the synthesis and, therefore, influences the reaction rate. Most of the chosen metal precursors are soluble in eth-

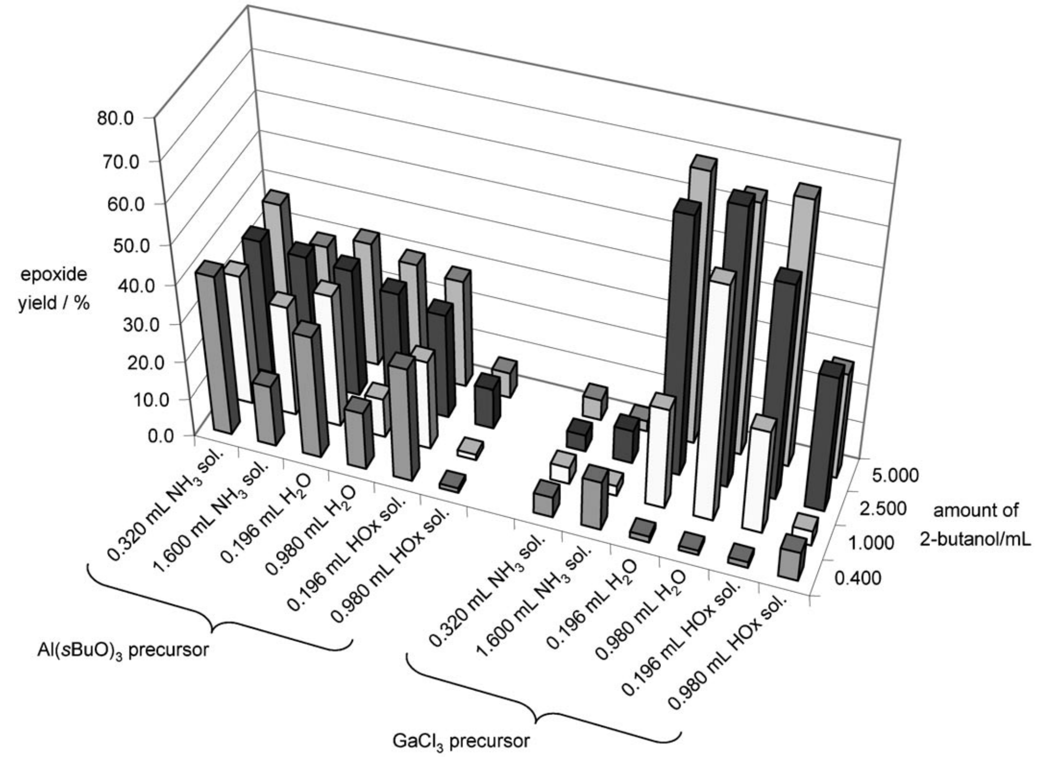

Figure 3. Activity in the epoxidation of cyclooctene with 50 wt % aqueous H_2O_2 after 4 h at 80 °C of the recycled aluminium and gallium oxides, as a function of the concentration of the metal precursors and of the amount and type of hydrolysing solution employed during their synthesis [second catalytic test].

anol, which was thus used as the solvent. Aluminium isopropoxide and aluminium *sec*-butoxide are only sparingly soluble in ethanol; consequently, 2-propanol and 2-butanol, respectively, were used as solvents for these two precursors (Table 2). Although boron-containing oxides and mixed aluminium and gallium oxides generally gave poor results in the previous HTE tests, it was decided to check whether using different precursors might bring about an improvement. Therefore, the selected metal precursors were combined in reduced-size ternary arrays (Figure 4). The other synthesis parameters were chosen to be as in the case of samples **15** and **39** (Table 1), that is, a set of conditions that led to very active catalysts for both aluminium and gallium oxides. A parameter space of 44 elements was generated. Each combination was tested for its activity in the epoxidation of cyclooctene with H_2O_2 (Table 2). Pure gallium oxides gave very poor results, in striking contrast with the very high activities found before. Sample **92** was prepared under the same conditions as sample **39**, the only difference being the use of ethanol instead of 2-butanol as solvent. The much better results obtained with 2-butanol instead of ethanol can be ascribed to the lower miscibility of 2-butanol with water: this can prevent too high a hydrolysis rate during the formation of the oxides, which has been proposed to be detrimental to the formation of active epoxidation catalysts (vide supra). Similarly, the effect of the interaction between water and the solvent or the group X can be used to explain the results obtained with the pure aluminium oxides: the highest and most satisfactory activities were found for the pure aluminium oxides **85** and **88** (equivalent to sample **15**), which were synthesised from Al(*i*PrO)$_3$ in 2-propanol and Al(*s*BuO)$_3$ in 2-butanol, respectively. As in the previous experiments, most of the mixed oxides showed low activities. However, some effect of the nature of the precursor could be observed. For instance, 1:1 boron to aluminium or 1:1 boron to gallium mixed oxides showed higher activities when $AlCl_3$ and $GaCl_3$ were used as precursors, probably owing to the fact that the chlorides rapidly hydrolyse to generate an acidic environment, which might favour the interaction with the boron species. Among these catalysts, the 1:1 boron to gallium mixed oxide **70** proved to be the most active mixed oxide identified in this work, with an epoxide yield of 32 % and a selectivity of 84 %. The best combination of precursors was found to be different for each molar ratio of boron, aluminium, and gallium: while aluminium and gallium chlorides proved to be the best precursors for 1:1 mixed oxides with boron, the only significant activities for an equimolar combination of boron, aluminium, and gallium were obtained with aluminium *sec*-butoxide and gallium nitrate as precursors (samples **62** and **77**).

The HTE study presented here led to the discovery of various promising epoxidation catalysts. Ideally, the results should have general validity and not be dependent on the equipment employed to obtain them.[26] However, the data generated using HTE might be affected by the small volume scale at which the experiments are performed and by techni-

Table 2. Catalytic epoxidation of cyclooctene with 50 wt% aqueous H_2O_2 after 4 h at 80 °C: conversions, yields and selectivities against the composition of the B, Al and Ga mixed-oxide catalysts and of the precursors and solvents used for their synthesis.

	$B(OMe)_3$[a] in ethanol	$B(iPrO)_3$[a] in ethanol	$Al(NO_3)_3$[a] in ethanol	$AlCl_3$[a] in ethanol	$Al(iPrO)_3$[a] in 2-propanol	$Al(sBuO)_3$[a] in 2-butanol	$Ga(NO_3)_3$[a] in ethanol	$GaCl_3$[a] in ethanol	Cyclooctene conversion [%]	Epoxide yield [%]	By-products yield [%]	Epoxide selectivity [%]
49	1	0	0	0	0	0	0	0	3	2	1	65
50	0.5	0	0.5	0	0	0	0	0	2	2	1	72
51	0.5	0	0	0.5	0	0	0	0	10	8	2	79
52	0.5	0	0	0	0.5	0	0	0	4	2	1	68
53	0.5	0	0	0	0	0.5	0	0	5	3	1	69
54	0.5	0	0	0	0	0	0.5	0	3	3	0.3	91
55	0.5	0	0	0	0	0	0	0.5	6	4	2	70
56	0.333	0	0.333	0	0	0	0.333	0	1	1	1	64
57	0.333	0	0.333	0	0	0	0	0.333	3	1	2	45
58	0.333	0	0	0.333	0	0	0.333	0	3	1	2	45
59	0.333	0	0	0.333	0	0	0	0.333	1	1	1	48
60	0.333	0	0	0	0.333	0	0.333	0	2	2	1	68
61	0.333	0	0	0	0.333	0	0	0.333	3	1	2	36
62	0.333	0	0	0	0	0.333	0.333	0	16	14	2	90
63	0.333	0	0	0	0	0.333	0	0.333	3	1	2	39
64	0	1	0	0	0	0	0	0	1	1	0.2	83
65	0	0.5	0.5	0	0	0	0	0	5	3	2	61
66	0	0.5	0	0.5	0	0	0	0	7	6	1	83
67	0	0.5	0	0	0.5	0	0	0	5	2	2	55
68	0	0.5	0	0	0	0.5	0	0	6	3	2	59
69	0	0.5	0	0	0	0	0.5	0	2	2	0.3	87
70	0	0.5	0	0	0	0	0	0.5	38	32	6	84
71	0	0.333	0.333	0	0	0	0.333	0	3	2	1	71
72	0	0.333	0.333	0	0	0	0	0.333	3	1	2	37
73	0	0.333	0	0.333	0	0	0.333	0	2	1	0.5	68
74	0	0.333	0	0.333	0	0	0	0.333	3	2	1	56
75	0	0.333	0	0	0.333	0	0.333	0	5	3	2	58
76	0	0.333	0	0	0.333	0	0	0.333	3	2	2	47
77	0	0.333	0	0	0	0.333	0.333	0	18	16	2	90
78	0	0.333	0	0	0	0.333	0	0.333	4	2	2	45
79	0	0	1	0	0	0	0	0	2	2	1	70
80	0	0	0.5	0	0	0	0.5	0	2	2	0.3	85
81	0	0	0.5	0	0	0	0	0.5	4	2	2	49
82	0	0	0	1	0	0	0	0	6	5	1	81
83	0	0	0	0.5	0	0	0.5	0	3	1	2	34
84	0	0	0	0.5	0	0	0	0.5	6	2	3	42
85	0	0	0	0	1	0	0	0	33	29	4	89
86	0	0	0	0	0.5	0	0.5	0	3	2	1	79
87	0	0	0	0	0.5	0	0	0.5	5	2	3	37
88	0	0	0	0	0	1	0	0	39	36	3	92
89	0	0	0	0	0	0.5	0.5	0	1	1	0.0	100
90	0	0	0	0	0	0.5	0	0.5	0.5	0.5	0.0	100
91	0	0	0	0	0	0	1	0	1	1	0.0	100
92	0	0	0	0	0	0	0	1	0.5	0.2	0.3	48

[a] Molar fraction.

cal features of the HTE equipment. For this reason, it is very important to check the reproducibility of the most interesting HTE results on a larger volume scale by repeating the experiments in a conventional manner. Therefore, gallium oxide was prepared under the same conditions as employed for the synthesis of the best catalyst discovered in this work (sample **40**) but on a tenfold larger volume scale. The material was tested over various cycles for the epoxidation of cyclooctene with 50 wt% aqueous H_2O_2 (Table 3). The results of the first two runs are in good agreement with those obtained by HTE, confirming the general validity of the HTE results reported here. After the second run, the cyclooctene conversion and the epoxide yield are seen to gradually decrease, while the selectivity towards the epoxide is retained. Calcination of the sample for 24 h at 400 °C did not serve to restore the features of the original catalyst (run 5). This slow deactivation upon recycling is similar to that observed for aluminium oxides, and is attributed to structural changes of the material during the catalytic process.[8,9] Alongside their epoxidation activity, transition-metal-free oxides might catalyse the unwanted decomposition of H_2O_2 into O_2 and H_2O. The amount of H_2O_2 decomposed during the catalytic test (run 2) was determined by means of titration with Ce^{4+} as 37% of the H_2O_2 employed, corresponding to a selectivity of H_2O_2 towards the epoxide of 49%. These values are of the same order as those found

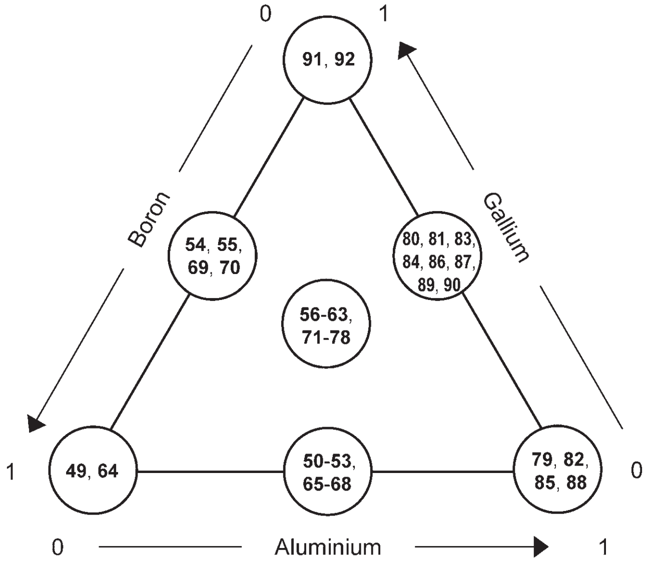

Figure 4. Ternary array representing the combination of the different boron, aluminium, and gallium precursors used to synthesise metal oxide catalysts for epoxidation reactions.

Table 3. Catalytic test of the larger volume scale version of catalyst **40** in the epoxidation of cyclooctene with 50 wt % aqueous H_2O_2 [conditions: 4 h at 80 °C; H_2O_2:cyclooctene = 2; solvent: ethyl acetate].

Run	Cyclooctene conversion [%]	Epoxide yield [%]	By-products yield [%]	Epoxide selectivity [%]
1	67	46	19	71
2	66	64	1	98
3	39	39	0.4	99
4	28	28	0.3	99
5	27	26	1	95

when using aluminium oxide as catalyst.[5,9] Finally, a leaching experiment was performed: the solid catalyst was filtered off from the reaction mixture after it had been stirred for 30 min while heating from room temperature to 80 °C. The clear filtrate was stirred for 4 h at 80 °C and epoxide formation was monitored by GC analysis. An extremely low epoxide yield was observed, proving that no active species had leached from the catalyst and confirming that the process is truly heterogeneous.

Conclusion

High-throughput experimentation techniques have been used to explore the synthesis and application of transition-metal-free oxides as epoxidation catalysts. The aim was to discover improved pathways for the effective and sustainable catalytic epoxidation of alkenes. Our study has yielded various interesting results. The most promising result is the discovery of gallium oxide as a very active heterogeneous catalyst for the epoxidation of alkenes using aqueous hydrogen peroxide. In this respect, the use of HTE proved to be particularly useful: the range of synthesis conditions under which active gallium oxides can be prepared is quite narrow and could have been overlooked if a conventional research approach had been followed. Another relevant result is the identification of new, improved formulations for the synthesis of aluminium oxides as active epoxidation catalysts. Finally, the screening of large parameter spaces characteristic of an HTE approach has provided an understanding of the effect of the synthesis parameters on the catalytic activity of the transition-metal-free oxides.

Gallium oxide is a promising heterogeneous catalyst for the sustainable epoxidation of alkenes, since it is active with aqueous H_2O_2, it is selective, and it does not contain transition metals. However, its stability and its efficiency in using H_2O_2 need to be improved before it can meet the requirements for industrial application. Future work can also be expected to extend the scope of application of the best catalysts discovered here to other alkenes. Furthermore, these catalysts will be fully characterised in order to shed more light on the relationship between their physicochemical features and their catalytic properties.

Experimental Section

The HTE samples were prepared by means of a Tecan Genesis RSP 100 liquid-handling robotic workstation coupled with a personal computer supplied with Gemini software enabling programming of the workstation. Liquids were dispensed and transferred using two kinds of needles: fixed metal needles to dispense water and organic solvents and disposable plastic needles suitable for handling viscous or contaminant liquids, that is, the solutions of the metal precursors. High accuracy of the operations performed with the needles was ensured by their prior calibration with different classes of liquid: the error was generally no higher than 1 %, even when dealing with volumes as small as 100 μL. The workstation was equipped with a reaction block developed in-house, consisting of a heating unit containing 60 wells for 10 mL glass vials (maximum working temperature of 80 °C) and a Variomag plate for individual magnetic stirring of the 60 parallel reaction vessels.

Chemicals used in the synthesis of the boron, aluminium, and gallium oxides were as follows: boron methoxide, $B(OCH_3)_3$ $[B(OMe)_3]$, boron isopropoxide, $B(OCH(CH_3)_2)_3$ $[B(i\text{PrO})_3]$, aluminium nitrate nonahydrate, $Al(NO_3)_3{\cdot}9H_2O$, aluminium chloride, $AlCl_3$, aluminium isopropoxide, $Al(OCH(CH_3)_2)_3$ $[Al(i\text{PrO})_3]$, aluminium *sec*-butoxide, $Al(OCH(CH_3)CH_2CH_3)_3$ $[Al(s\text{BuO})_3]$, gallium nitrate hydrate, $Ga(NO_3)_3{\cdot}x\,H_2O$, and gallium chloride, $GaCl_3$, as metal precursors; 2-butanol, 2-propanol, and ethanol as solvents; deionised water; oxalic acid [HOx]; and ammonia, NH_3, 25 wt % in aqueous solution. Chemicals used in the catalytic tests were as follows: *cis*-cyclooctene (95 %); di-*n*-butyl ether as an internal standard for the GC analyses; ethyl acetate as solvent; and hydrogen peroxide, H_2O_2, 50 wt % in aqueous solution, as oxidant.

All samples discussed in this article were prepared by the hydrolytic condensation of a metal precursor or of a mixture of two or three of them. The total amount of metal precursors was the same in all of the reported experiments (1.00 mmol per sample). The remaining synthesis conditions were different in the various experiments and will be discussed separately (see below).

The synthesis mixtures were prepared by using the HTE workstation to dispense the desired liquids into 10 mL glass vials placed in the 60-well reaction block. The vials were sealed with caps and heated to 80 °C for 3 h while their contents were stirred at 500 rpm. The vials were uncapped and left to stand at room temperature for 16 h in a fume hood. Next, the samples were transferred to an oven and calcined according to the following temperature program: 25 to 100 °C at 10 °C min^{-1}; 24 h at 100 °C;

100 to 200 °C in 30 min; 12 h at 200 °C; 200 to 400 °C in 60 min; 24 h at 400 °C. The samples were placed in the oven in special racks holding the 10 mL glass vials. It is considered that this arrangement might prevent the circulation of air inside the vials and, therefore, affect the calcination process.

The materials obtained were ground to fine powders and tested for their activities in the epoxidation of cyclooctene with hydrogen peroxide under similar conditions to those employed in the literature for testing aluminas.[9,10] However, a 50 wt % aqueous solution of hydrogen peroxide was used instead of a 70 wt % solution. Cyclooctene (2.50 mmol), di-*n*-butyl ether (1.25 mmol), ethyl acetate (2.50 g), and hydrogen peroxide (5.00 mmol) were added to each sample. First, a solution containing cyclooctene, di-*n*-butyl ether, and ethyl acetate was added to each solid catalyst with stirring. Then, the aqueous solution of hydrogen peroxide was added. Both solutions were dispensed using the HTE workstation. The reaction mixtures were stirred for 4 h at 500 rpm and 80 °C in capped vials placed in the 60-well reaction block. The rubber septa of the caps were pierced with a sharp needle to prevent the development of an overpressure in the reactors during the catalytic test.

Each HTE series of experiments, from the synthesis of the oxides to the catalytic tests, was carried out in a single set of glass vials, thus avoiding transfers of the samples that may have led to a loss of material.

Cyclooctene conversions and the epoxycyclooctane and by-product yields were determined by gas chromatography (GC) analysis on a Finnigan Trace GC Ultra chromatograph from Interscience, equipped with an RTX-5 fused silica column (10 m; 0.1 mm). The analysis time for each sample was just 2.25 min by virtue of the rapid heating and cooling system of the column (Ultra-Fast Module). The temperature profile during the analysis was as follows: 45 s at 70 °C, 70 to 250 °C at 180 °C min^{-1}, 30 s at 250 °C. The GC samples were prepared by adding an aliquot of the reaction mixture ($\approx$0.3 mL) to an equal volume of decane: any H_2O that might have been present in the sample would have separated in a phase at the bottom of the GC flask, preventing its injection into the chromatograph and consequent deterioration of the column. The conversions and yields were calculated by normalising the areas of the GC peaks by means of the area of the internal standard peak.

The by-products were identified by means of gas chromatography-mass spectrometry (GC-MS) analysis using an Agilent 6890 N gas chromatograph coupled with an Agilent 5973 MSD mass spectrometer. The GC was equipped with a WCOT fused-silica column (30 m; 0.25 mm) coated with a 0.25 µm thick HP-5 MS film. The temperature program was analogous to that employed for the GC analysis.

For recycling of the HTE samples, a washing procedure using the automated workstation was developed. After the catalytic tests, the reaction solution was removed from each of the samples. Ethanol (5 mL) was then added to each sample, and the suspensions obtained were stirred for 5 min. Next, the samples were centrifuged for 10 min to deposit the solid catalysts. The supernatant ethanolic solution was then removed from each sample; to avoid loss of solid during this operation, the liquid was aspirated from above the level of the solid, implying that a thin layer of ethanol could not be removed. This washing procedure was repeated four times. Finally, the samples were dried for 16 h in an oven at 110 °C. A similar but non-automated procedure was used to recycle larger volume scale samples.

The amount of H_2O_2 decomposed into H_2O and O_2 during the catalytic tests was determined by titrating the reaction solution (after 4 h at 80 °C) with a 0.1 M solution of $Ce(SO_4)_2$, obtained by dissolving $Ce(SO_4)_2{\cdot}4H_2O$ (50.0 mmol) in H_2SO_4 (28 mL) and doubly-distilled H_2O (28 mL) and diluting to a total volume of 500 mL with H_2O. The reaction solution was diluted with H_2O (18 mL) and with a 7 vol % aqueous solution of H_2SO_4 (2 mL). The obtained colourless solution was titrated with the 0.1 M Ce^{IV} solution until it turned yellow ($2Ce^{4+} + H_2O_2 \rightarrow 2Ce^{3+} + 2H^+ + O_2$).

Synthesis of the catalysts

Method 1: Three solutions of metal precursors were prepared by dissolving B(*i*PrO)$_3$, Al(*s*BuO)$_3$ or $GaCl_3$ (20.0 mmol) in 2-butanol to give a total volume of 100.0 mL in each case. The dissolution of $GaCl_3$ is a fast, exothermic process, accompanied by the evolution of HCl gas, and leads to the formation of a dark-brown solution.[27] An aqueous solution of oxalic acid was prepared by dissolving the acid (56.3 mmol) in deionised H_2O (75.0 mL). By means of the HTE workstation, 45 samples were prepared, each containing a solution of metal precursors (5.000 mL) to which an aliquot (1.000 mL) of the aqueous solution of oxalic acid was added with stirring. Each sample had a different ratio of the three metal precursors, in order to describe the desired ternary array (Figure 1). The preparation of the 45 samples required around 2 h. After calcination, the materials exhibited colours ranging from white to brown. Low yields of the final solid were observed for the samples with high boron content.

Method 2:[8,10] Three solutions of metal precursors were prepared by dissolving B(*i*PrO)$_3$, Al(*s*BuO)$_3$ or $GaCl_3$ (20.0 mmol) in 2-butanol (6.408 g; 8.000 mL). Each solution had a different density: 1.00 mmol of B(*i*PrO)$_3$ was contained in 0.633 mL of a clear, colourless solution; 1.00 mmol of Al(*s*BuO)$_3$ was contained in 0.667 mL of a clear, colourless solution; 1.00 mmol of $GaCl_3$ was contained in 0.487 mL of a dark brown solution. An aqueous solution of oxalic acid was prepared by dissolving the acid (11.3 mmol) in deionised H_2O (15.0 mL). By means of the HTE workstation, 45 samples were prepared, each containing a solution of the metal precursors (total 1.00 mmol) in 2-butanol (0.400 mL), to which an aliquot (0.196 mL) of the aqueous oxalic acid solution was added with stirring. Each sample had a different ratio of the three metal precursors, in order to describe the desired ternary array (Figure 1). The preparation of the 45 samples required around 40 min. After calcination, the materials exhibited colours ranging from white to brown, the intensity of the colour being proportional to the gallium content.

Method 3:[22] Three solutions of metal precursors were prepared by dissolving B(*i*PrO)$_3$, Al(*s*BuO)$_3$ or $GaCl_3$ (20.0 mmol) in 2-butanol to give a total volume of 100.0 mL in each case. $GaCl_3$ was used as gallium source in order to avoid the washing step that would be needed to remove the explosive NH_4NO_3 that would have been formed in the presence of aqueous NH_3 if $Ga(NO_3)_3$ had been used as gallium source.[22] By means of the HTE workstation, 45 samples were prepared, each containing a solution of the metal precursors (5.000 mL) to which a 1:1 (v/v) mixture of ethanol and a 25 wt % aqueous solution of ammonia (1.600 mL) was added with stirring. The total volume of 1.600 mL was added in separate aliquots of 0.160 mL each, over a period of 1 h, to mimic dropwise addition. Each sample had a different ratio of the three metal precursors, to describe the desired ternary array (Figure 1). The preparation of the 45 samples required around 3 h. After calcination, the materials displayed colours ranging from white for samples containing aluminium but no gallium, to dark brown and black for samples with high gallium content.

Samples 1–48: Two solutions of metal precursors were prepared by dissolving Al(*s*BuO)$_3$ or $GaCl_3$ (35.0 mmol) in 2-butanol (11.214 g; 14.000 mL). An aqueous solution of oxalic acid was prepared by dissolving the acid (11.3 mmol) in deionised H_2O (15.0 mL). By means of the HTE workstation, 48 samples were prepared. First, a solution of either Al(*s*BuO)$_3$ or $GaCl_3$ (1.00 mmol) in 2-butanol (0.400 mL) was dispensed into each glass vial. Some of the samples (see Figure 2) were diluted by adding 0.600 mL, 2.100 mL, or 4.600 mL of 2-butanol with stirring. Next, a basic, neutral, or acidic hydrolysing solution was added to each sample with stirring, that is, a 1:1 (v/v) mixture of ethanol and 25 wt % aqueous ammonia (0.320 mL; 2.14 mmol NH_3 or 1.600 mL; 10.7 mmol NH_3), deionised H_2O (0.196 mL or 0.980 mL), or aqueous oxalic acid (0.196 mL; 0.147 mmol HOx or 0.980 mL; 0.736 mmol HOx) (Figure 2). The hydrolysing solutions were dispensed in separate aliquots of 0.160 mL (basic solutions) or 0.196 mL (neutral and acidic solutions) to mimic dropwise addition. The preparation of the 48 samples required about 1 h. Gallium samples prepared with 0.980 mL of H_2O or aqueous HOx exhibited two distinctly separated liquid phases: a clear, colourless aqueous phase at the bottom and a dark-brown 2-butanol phase at the top. The volume of the aqueous phase progressively decreased as the volume of 2-butanol was increased from 0.400 to 5.000 mL. After calcination, the aluminium oxides were white or off-white while the gallium oxides displayed colours ranging from brown to dark grey and black. The yield of the final solid was approximately the same for all of the aluminium oxides, whereas lower yields were observed among the gallium oxides for the samples synthesised under basic conditions.

Samples 49–92: Solutions of boron and gallium precursors were prepared by dissolving $B(OMe)_3$, $B(i\text{PrO})_3$, $Ga(NO_3)_3\cdot xH_2O$ or $GaCl_3$ (8.00 mmol) in ethanol to give a total volume of 20.0 mL in each case. Solutions of aluminium precursors were prepared by dissolving $Al(NO_3)_3\cdot 9H_2O$ or $AlCl_3$ (6.00 mmol) in ethanol, $Al(i\text{PrO})_3$ (6.00 mmol) in 2-propanol, or $Al(s\text{BuO})_3$ (6.00 mmol) in 2-butanol to give a total volume of 15.0 mL in each case. By means of the HTE workstation, 44 samples were prepared, each containing a solution of metal precursors (2.500 mL), to which deionised H_2O (0.196 mL) was added with stirring. The precursors of each of the three Group 13 elements were combined with each precursor of the other two elements in the ratios indicated in Table 2. The preparation of the 44 samples required around 1 h. After calcination, the materials containing exclusively boron and those prepared using $AlCl_3$ and/or $GaCl_3$ displayed grey/brown colours, while all of the other solids were white. Very low yields of the final solid were observed for the samples containing exclusively boron.

Note: It is important to keep in mind that whereas the trends identified in high-throughput experiments can always be trusted, the level of reliability of each individual experiment constituting an HTE series is generally lower than that of a conventional laboratory experiment. This is due to many factors: the experimental errors that can arise during an HTE run can be specific to the HTE equipment being used (e.g., contamination with the liquid used to operate the syringes connected to the needles), but may also be similar to those occurring in standard laboratory experiments (e.g., due to inefficient stirring, leaching of volatile compounds through the septa of the reactor caps). Simple observations that help to prevent such errors are often more difficult when dealing with many simultaneous experiments performed in parallel vessels inside a reaction block. To increase the reliability of the HTE results, some samples were prepared in duplicate or in triplicate: in such cases, the average values of the catalytic results are reported. Another means of checking and improving the reliability of the HTE results is to include in each HTE series one or more individual experiments from the previous series: the level of reproducibility of the results obtained for the repeated experiments in different series can provide a measure of the consistency of the data in each series.

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