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Viewpoint

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Heterogeneous Catalysis for Tandem Reactions

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Supporting Information

1. INTRODUCTION

As long as the molecular complexity increases, the number of chemical transformations will increase in parallel, becoming a highly demanding synthetic process in terms of time and resources. Since the loss of material after each purification step will also dramatically reduce the overall efficiency of a synthetic process, the conversion of such transformation into a practical and efficient process will be a great challenge for synthetic chemists.

Recent examples have shown that multifunctional catalytic systems can reduce the number of synthetic steps by leading sequential catalytic processes into one-synthetic operation.[1,2] These one-pot processes allow for different reactions to be carried out in a single vessel without purification between steps, hence avoiding stop-and-go syntheses and therefore producing an economical and environmental benefit.

Multienzymatic systems that perform multistep reactions in nature have been a model for the development of artificial systems in an attempt to mimic different aspects of synthetic strategies that operate in biological systems.[3−7] However, there has been significant progress in this direction over past decades, one-pot catalytic reactions are still not of general application. A primary reason is that controlling one-pot multistep reactions is rather difficult because, unlike for biocatalysts, the interactions arising between different active species and components involved in the global synthetic sequence can cause deactivation. In fact, an active center should be compatible with residual material (substrates, intermediates, solvents, additives) that coexists from preceding steps and should also exhibit reaction sequence selectivity. It is thus necessary to find a common operational window for connecting each individual reaction into a global process, hence creating difficulties that will increase gradually with the number of combined catalytic cycles.

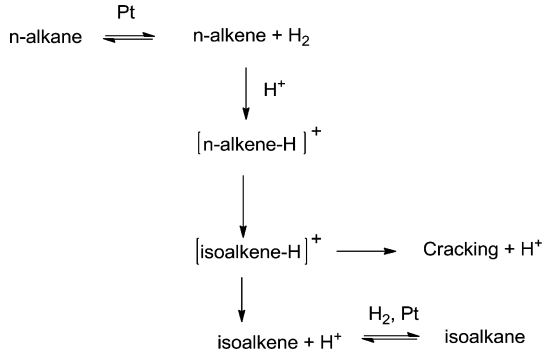
One way to approach the problem relies on the preparation of multisite solid catalysts in which a series of well-optimized isolated active sites able to catalyze the different reactions are immobilized on a support. For instance, if one considers a bifunctional catalyst, this can be designed in such a way that the two different catalytic functions (say, for example, an acidic and a basic site) act in a collaborative way in the transition state, or each one catalyzes a different reaction in a multistep catalytic process.

It becomes apparent that the design of an ideal multifunctional solid catalyst should involve generating the actives sites on a unique support; however, the material synthesis procedure to achieve this objective can sometimes be difficult. Then composite solids can be prepared in which a different catalytically active site is located in each component of the composite.

Although the conceptual methodology for using multifunctional catalysts to catalyze multistep reactions looks straightforward, this is not so straightforward in practice. Indeed, a common reaction window should be found in which the different reactions can operate on the different catalytic sites in a one-pot process. This involves searching for compatible reaction temperatures, pressures, solvents, etc. Therefore, the first step in the design of a one-pot multistep catalytic process is to perform a thermodynamic study to establish the thermodynamic compatibility of the different reactions. This study has to be made with an open mind since, in some cases, the use of multifunctional catalysts can help to perform in a one-pot sequential way reactions in which one of them is not occurring under optimal thermodynamic conditions to achieve maximum product yield. Consider, for instance, the well-known bifunctional alkane hydroisomerization on hydrocracking solid catalysts, formed by a metal function (for instance, Pt) supported on an acid carrier (for instance, amorphous silica−alumina or zeolites).[8] In this case, the first reaction step is the dehydrogenation of an alkane on the metallic function to give the corresponding olefin plus hydrogen. Then, when the olefin is formed, it adsorbs onto the acidic function to give a carbenium ion that undergoes branching isomerization (or cracking, or both), desorbing as an olefin that becomes hydrogenated on the metallic function (see Scheme 1).

The reactions are carried out under high H_2 pressure ($P \geq 30$ bar) and relatively low temperatures (180−400 °C), which are thermodynamically unfavorable for performing the first reaction

Scheme 1. Different Steps Involving the Hydroisomerization of *n*-Alkanes[9]



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in the sequential process, that is, the alkane dehydrogenation. Then from this point of view, the concentration of alkenes in the reaction media should be low and thermodynamically controlled. However, if the bifunctional catalyst is designed in such a way that the acid sites are close by the metal function and are acidic enough to perform very fast, the second step, that is, isomerization or isomerization-cracking, then the concentration of alkenes on the catalysts' surface will be rapidly depleted, and the dehydrogenation equilibrium will be shifted toward the production of more alkenes. By operating in this way, very high yields of the final product can be obtained, despite the fact that the optimum thermodynamic conditions are different for dehydrogenation of alkanes (high temperature and low pressures) and for isomerization (lower temperatures) and higher hydrogen pressures are required for maintaining catalyst life. In other words, it can be in many cases very useful for the design of one-pot multistep reaction to study the process in a multidisciplinary way involving organic chemistry, inorganic chemistry−materials design, and chemical engineering−process design. This type of multidisciplinary approach will be of much benefit for expanding multistep reactions beyond the one-pot batch reactor used frequently in organic synthesis and to expand it into fixed-bed uni- or multibed continuous reactors, catalytic distillation processes, and combinations of the above.

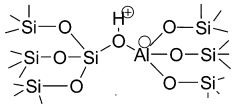
In this Viewpoint, we describe one-pot reactions that have been reported recently, grouped by number and type of catalytic active centers, with emphasis placed on the encountered difficulties, plausible solutions, and methodologies utilized for designing and optimizing these processes. Many examples of complex reaction sequences will consider a single active catalyst requiring minimal changes in reaction conditions, whereas in other cases, examples of multisite heterogeneous catalysts will be required, and setting the optimum reaction conditions will not be so straightforward.

We conclude the presentation with a section on future prospects that includes developmental approaches related to sequential transformations.

2. MULTISTEP SEQUENTIAL PROCESSES ON SINGLE-SITE SOLID CATALYSTS

2.1. Cascade Processes on Single-Site Bronsted Acid Catalysts. A large number of solid acids bearing Bronsted acid sites can be used as heterogeneous catalysts for promoting cascade reactions. For instance, successful materials in acid catalysis are crystalline and amorphous aluminosilicates, in which the existence in the structure of tetrahedrally coordinated aluminum generates a negative charge that is compensated by the positive charge associated with protons (see Scheme 2).

Scheme 2. Bronsted Acid Site in Crystalline Aluminosilicates



An important feature of these materials is the possibility to modify the strength and number of acid sites as well as the adsorption properties by changing the chemical composition, that is, the Si/Al ratio. Moreover, in the case of crystalline materials, specially zeolites, and short-range amorphous materials, they can be obtained with different pore dimensions and pore topologies, which allows achieving further stabilization of transition states through van der Waals interaction with the walls, with the corresponding decrease in activation energy as well as shape selectivity effects by selecting reactants and reaction transition states.[10−14]

Other materials containing Bronsted acid sites that have been effectively utilized in acid catalysis are high surface area heteropolyacids[15,16] and materials containing sulfonic groups. Sulfonic groups can be introduced on different carriers, such as organic polymers, as is the case for cation exchange resins,[17−19] introduced in the organic moiety of metal organic frameworks (MOFs)[20,21] or on carbon materials.[22,23] In addition, structured or amorphous silica-based organic−inorganic hybrid materials containing sulfonic groups can be prepared by supporting or interlinking sulfonated alkyl chains or aromatic molecules with silica precursors.[24−27]

As an example of cascade processes catalyzed by Bronsted acid sites, in this section, we present the synthesis of alkyl glucosides starting from cellulose, which involves as first step the hydrolysis of cellulose into glucose monomers, followed by acetalization of the glucose formed (glucosidation reaction) with fatty alcohols.

Long-chain alkyl glucosides are nonionic surfactants with low toxicity and good biodegradability[28] with a broad range of applications in detergents, cosmetics, and pharmaceutical formulations.[29] The acid-catalyzed Fischer glycosidation involving the acetalization of a sugar, frequently glucose, with a fatty alcohol is the main route to synthesize alkyl glucoside surfactants. Cellulose, which is a polymer of D-glucopyranoside units linked by β-1,4 glycosidic bonds, is the most important and inexpensive source of glucose, though, for acid hydrolysis. However, the hydrolysis process is difficult because of the strong crystalline structure of cellulose, and the hydrolysis of cellulose into glucose under mild conditions still remains an important challenge.[30]

Most hydrolysis processes to convert cellulose into glucose have been performed in water; however, several authors have showed that cellulose can be dissolved in ionic liquids,[31,32] and when an acid is present (mineral[33] or solid[34] acids), the cellulose can be depolymerized. Taking into account these findings, we have recently showed that by combining an ionic liquid that is able to dissolve cellulose with heterogeneous acid catalysts and adjusting the catalyst and reaction conditions, it is possible to couple cellulose hydrolysis with glucose acetalization with C_4−C_8 alcohols in a one-pot process to obtain alkyl-α,β-glycoside surfactants under very mild reaction conditions (Scheme 3).[35] The hydrolysis step, performed in the presence of an ionic liquid (butyl methyl imidazolium chloride, BMIMCl), was tested with different acid catalysts. Among them, the sulfonic resin Amberlyst 15Dry (A15) and $H_3PW_{12}O_{40}$ gave the best performances, and therefore, they were selected as catalysts for performing the one-pot process.

During the one-pot process, that is, hydrolysis of cellulose followed by Fischer glycosidation, there are two important variables to control. One of them is the amount of water, since the presence of water is required to promote the hydrolysis process while preventing the formation of HMF (formed by dehydration of hexoses). However, the water has a negative effect on the second step of the process, the Fischer glycosidation, in which a hemiacetal plus water are formed (Scheme 3). The second important variable to control is the reaction time during the hydrolysis step because long reaction times favor degradation of glucose. Then, to decrease the

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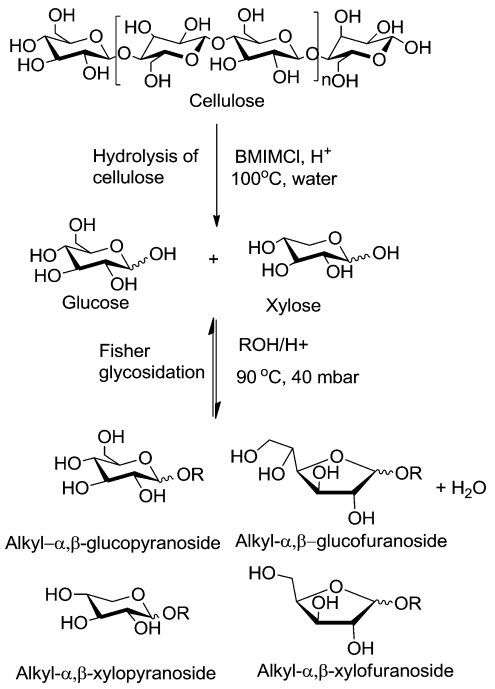
Scheme 3. Production of Alkyl-α,β-Glycoside Surfactants from Cellulose[35]



negative effect of water on the glucosidation step and glucose degradation, the alcohol was added after a shorter time of hydrolysis while the pressure of the system was reduced to 40 mbar. The results displayed in Table 1 (entries 5–9) show that

Table 1. One-Pot Production of Alkyl Glycoside Surfactants from Cellulose[a,35]

entry	alcohol	conv (%)[b]	alkyl-α,β-glucoside (yield mol %)[c]	alkyl-α,β-xyloside (yield mol %)[c]	total yield of surfactant (wt %)
1	butanol[d]	96	5.0 (7.2)	traces	7.2
2	hexanol[d]	96	5.8 (9.4)	1.2 (1.7)	11.1
3	hexanol[e]	95	17.1 (27.8)	4.8 (6.9)	34.7
4	octanol[e]	95	17.3 (31.3)	5.4 (8.7)	40.0
5	octanol[f]	98	24.3 (43.8)	2.8 (4.5)	48.3
6	octanol[g]	96	31.7 (57.1)	4.1 (6.7)	63.8
7	octanol[h]	94	33.9 (61.2)	5.4 (8.8)	70.0
8	octanol[i]	98	38.8 (70.0)	7.3 (11.7)	81.7
9	octanol[j]	96	27.7 (50.0)	6.6 (10.7)	60.7
10	octanol[k]	98	25.1 (45.2)	4.7 (7.6)	52.8
11	hexanol[i]	95	36.9 (60.1)	8.5 (12.3)	72.4
12	octanol[l]	99	39.7 (71.5)	0	71.5
13	octanol[m]	95	35.5 (64.0)	6.7 (10.9)	74.9

[a]α-Cellulose (300 mg, 1.85 mmol unity of glucose), A15 (160 mg, 0.74 mmol H^+), ionic liquid (6 g), water (315 μL), at 100 °C. Then for the hydrolysis, the alcohol (43 mmol) was added in the solution, and the temperature was decreased to 90 °C. The reaction was carried out at 40 mbar for 24 h. [b]Calculated by the weight difference of cellulose before and after reaction. [c]Determined by HPLC. [d]A15 (80 mg, 0.37 mmol H^+); hydrolysis time, 5h; Fisher glycosidation carried out at atmospheric pressure. [e]A15 (80 mg, 0.37 mmol H^+). [f]Hydrolysis time, 5h. [g]Hydrolysis time, 2.5 h. [h]Hydrolysis time, 2 h. [i]Hydrolysis time, 1.5 h. [j]Hydrolysis time, 1 h. [k]Fisher glycosidation carried out at atmospheric pressure. [l]Cellulose fibers (600 mg, 3.70 mmol unity of glucose, 67% crystallinity); water (760 μL); A15 (350 mg, 1.64 mmol H^+); hydrolysis time, 40 min. [m]$H_3PW_{12}O_{40}$ (710 mg, 0.74 mmol).

by using Amberlyst, there is an optimum at 1.5 h for the hydrolysis step with 98% total conversion and 82 wt % yield of octyl-α,β-glycosides (entry 8), whereas 5-hydroxymethyl furfural (HMF) produced by glucose degradation was only 6%. Under optimized conditions, $H_3PW_{12}O_{40}$ catalyst also gave good results (entry 13). In addition, the used A15 catalyst was reused in a second cycle previous regeneration of the acid sites with a H_2SO_4 solution, giving 77.8 wt % yield of octyl-α,β-glycosides. Moreover, alkyl glucosides and the ionic liquid could be separated by liquid chromatography using silica gel and a mixture of ethyl acetate and methanol, and the ionic was recycled.

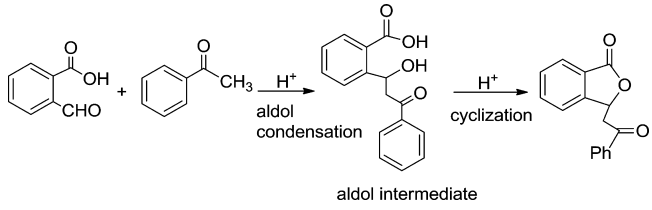
What becomes very clear from the above is that, for a successful multistep catalytic process, finding a good solid catalyst is as important as finding the optimum process conditions. The symbiosis of the two is absolutely necessary to achieve high conversions and selectivity as well as to reach a technologically and economically sound process.

Another example of a one-pot process catalyzed by heterogeneous Bronsted acid catalysts is the one-pot synthesis of 3-substituted phthalides, in which is shown the importance of selecting the more adequate operational conditions (particularly heating method and reaction time) to obtain good performances.

Substituted phthalides are important compounds with a variety of pharmacological activities, and particularly, 3-alkylidene phthalides derivatives have antispasmodic, insecticidal, and herbicidal properties.[36−38] A variety of synthetic methods have been developed to produce these compounds, among which the cyclization of carboxylic acid derivatives promoted by strong acids (trifluoroacetic acid)[37] or strong bases is the most used method.[39−41]

The synthesis of 3-substituted phthalides in one pot[42] was carried out by reacting phthalaldehydic acid with substituted ketones in the presence of Montmorillonite K10 as a heterogeneous Bronsted acid catalyst under microwave heating. The process follows two consecutive steps: first, the acid-catalized aldol condensation of the phthalaldehydic acid with the ketone that produces an aldol intermediate, which then cycles to the corresponding lactone (Scheme 4).

Scheme 4. Consecutive Steps Involved in the Formation of 3-Substituted Phthalides[42]



The authors showed that the process required high temperatures to achieve good yields, between 170 and 190 °C, while the time of microwave heating had to be optimized (20–30 min). Shorter times gave lower yields and longer reaction times gave a decrease in yield as a result of the promotion of secondary reactions and product decomposition. Reactions between phthalaldehydic acid and different ketones performed under optimized reaction conditions and in absence of solvent gave excellent yields (90–98%) of the corresponding 3-substituted phthalides. The benefit of microwave heating-initiated reaction conditions was evidenced by performing the

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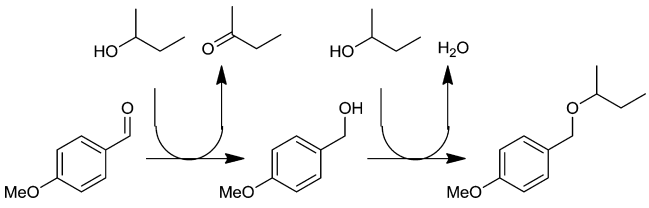
reaction under conventional heating, that is, at 170 °C, over 20 min. In this case, because of the formation of many byproducts, very poor selectivity to phthalide was observed.

This example shows that for processes that require high reaction temperatures, sometimes conventional heating methods are not the most adequate, particularly when the compounds involved have a limited thermal stability. In these cases, the use of microwaves, which allows it to achieve high temperature within a very short time, appears to be a good alternative for improving the process.

2.2. Cascade Processes on Single-Site Lewis Acid Catalyst. Salts or metals supported on high surface carriers, or materials such as zeolites with well-defined single Lewis acid sites, aluminophosphates, and mesoporous structured materials containing metals in its framework structure or in extraframework positions can be used successfully in cascade reactions. For instance, micro- and mesoporous molecular sieves allow incorporation of four-valent metals, such as Ti, Sn, Zr, Nb, and Ta, into their framework by isomorphic substitution of Si atoms, generating well-defined single isolated Lewis acid sites. One first example was titanium silicalite (TS-1),[43] which in combination with hydrogen peroxide resulted in an excellent catalyst for reactions such as phenol hydroxylation and cyclohexanone amoximation. However, the relatively small pore diameter of the 10-membered ring of TS-1 (5.5 Å) limits its use in processes in which bulky substrates are involved. Important efforts have been made to prepare large-pore 12-membered-ring Ti zeolites, such as Ti-Beta,[44] Ti-containing mesoporous materials,[45] Ti delaminated zeolites,[46] Ti-MWW,[47] and Ti-BEC,[48] which have shown good catalytic behavior for a number of reactions. Other four-valent metals, such as Sn,[49] Zr,[50] Nb, and Ta,[51] have also been successfully incorporated into pure silica zeolites, and particularly, Sn-Beta and Zr-Beta have shown excellent activity for Lewis acid catalyzed reactions.[50,52−55] Probably the most important property of these materials is that they can act as solid Lewis acids in the presence of water.[55] This fact has opened a series of possibilities to perform cascade reactions in processes in which water was generated during or introduced into the reaction. Following this, a cascade process was designed to synthesize 4-methoxybenzyl 1-methylpropyl ether (Scheme 5), which is a fruity pear odor fragrance. 4-Methoxybenzyl 1-methylpropyl ether is commercially prepared by etherification of 4-methoxybenzyl alcohol with 2-butanol. However, the 4-methoxybenzyl alcohol is obtained industrially by reduction of the corresponding aldehyde, 4-methoxybenzaldehyde, and the preparation process requires two separate steps. The first one involves the reduction of 4-methoxybenzaldehyde to the corresponding alcohol that produces undesired products and that has to be purified before the second step (etherification).[56] However, by selecting an adequate catalyst and operational conditions, both steps (aldehyde reduction and etherification) can be integrated into a one-pot process to produce the target compound in high yield and selectivity.

Scheme 5. Cascade Process for the Production of 4-Methoxybenzyl 1-Methylpropyl Ether[57]



Since it was found that Sn-Beta and Zr-Beta zeolites are water-resistant Lewis acid catalysts[55] and they can be made hydrophobic by direct synthesis,[49] they should then be able to promote efficiently the etherification of alcohols. In fact, the etherification of alcohols was performed on these materials possessing single isolated Lewis acid sites up to completion without requiring the removal of the water produced during the etherification process.[57] Then, an alternative process was designed that involves the Meerwein−Ponndorf−Verley (MPV) reduction step of the 4-methoxybenzaldehyde with an alcohol, followed by etherification of the produced alcohol in a tandem process with Sn- and Zr-Beta zeolites as Lewis acid catalysts.[57] The MPV reduction of the 4-methoxybenzaldehyde was performed using 2-butanol as the hydrogen donor, giving the corresponding 4-methoxybenzyl alcohol that in the second step undergoes etherification with the 2-butanol present in the medium (Scheme 5). The reaction proceeds under mild reaction conditions, and both catalysts proved very active for yielding the fragrance compound with excellent yield (see Table 2). Ta-Beta and Nb-Beta were also tested in the one-pot process.[51] Ta-Beta and Sn-Beta showed comparable activity and selectivity, whereas Nb-Beta gave a considerably lower selectivity for the target molecule.

Table 2. Results for the One-Pot Synthesis of 4-Methoxybenzyl 1-Methylpropyl Ether Using Solid Lewis Acid Catalysts[a,57]

catalyst (mg)	*t* (h)	total conv (%)	overall selectivity to ether (%)
Sn-Beta (50)	8	71	100
Sn-Beta (100)	24	99	99
Zr-Beta (50)	8	100	100

[a]Reaction conditions: *p*-methoxybenzaldehyde (1.1 mmol), 2-butanol (3 g) at 100 °C.

It is interesting to notice that, in principle, a conventional Lewis acid such as aluminum isopropoxide could be used in this process; however, the water formed during the etherification strongly limits its use.

In addition, a study of the isolated reactions showed that Zr-Beta was the most active catalyst for the MPV reduction, and Sn-Beta was the most active for etherification; therefore, the catalytic activity could be further maximized by using a Beta zeolite containing Zr and Sn in the framework.

2.3. Cascade Processes on Single-Site Base Catalysts. The substitution of conventional homogeneous basic catalysts, such as alkaline hydroxides, alkyl ammonium hydroxides, or carbonates, by solid bases in industrial processes is a difficult task, due mainly to the relatively low cost of such homogeneous catalysts. However, in recent years, important efforts have been made to develop high-surface-area, solid-base catalysts with different basic strengths capable of catalyzing a large variety of reactions, and extensive reviews on solid base catalysts and their catalytic applications have been reported.[58−63] Among them, basic metal oxides, such as high-surface magnesium oxides,[64] layered magnesium aluminates[65,66] bearing strong Lewis basic sites, nitrurated aluminum phosphates (ALPONs),[67] with medium basic strength sites and alkali cation exchanged zeolites[68] with weak basic strength sites, have been widely utilized for promoting base-catalyzed processes.

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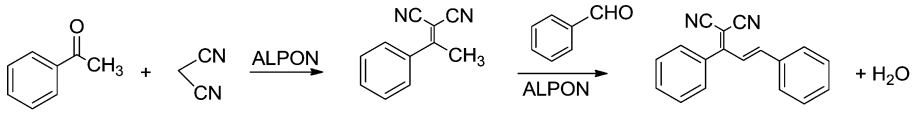
Scheme 6. One-Pot Synthesis of 1,1,-Dicyanomethylenebutadiene Derivatives[73]

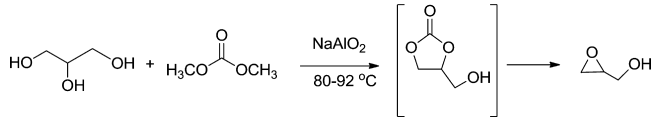


An example of a one-pot process on single-site base catalysts is the one-pot synthesis of 1,1-dicyano-2,4-diphenylbutadiene derivatives, which are compounds widely used as disperse dyes[69] and with interesting nonlinear optical properties.[70,71] 1,1-Dicyano-2,4-diphenylbutadiene derivatives are conventionally synthesized through two reaction steps. The first step is the synthesis of an α-methylbenzylidenemalonolnitrile derivative through the Knoevenagel condensation between acetophenone derivatives and malononitrile using a mixture of glacial acetic acid and ammonium acetate as catalyst. After separation and purification, the Knoevenagel adduct is reacted with benzaldehyde derivatives in the presence of a homogeneous base to give the corresponding 1,1-dicyano-2,4-diphenylbutadiene derivative;[70,72] however, this two-step synthesis of 1,1-dicyano-2,4-diphenylbutadiene derivatives can be performed successfully in one pot using heterogeneous base catalysts by adjusting catalyst basicity and operation conditions[73] (Scheme 6).

To optimize catalyst basicity, different solids with different basic strengths were tested for each individual step under different reaction conditions. It was found that the most active and selective catalyst for both steps was an aluminophosphate oxinitride[67] with a nitrogen content of 13.7 wt % (ALPON). The one-pot process was performed by reacting malononitrile with acetophenone at 100 °C up to a yield of α-methylbenzylidenemalonolnitrile above 90% (100% selectivity). Then, the required amount of benzaldehyde was added, and the temperature was increased to 150 °C. Under these reaction conditions, 100% conversion of α-methylbenzylidenemalonolnitrile with a 82% global yield of the 1,1-dicyano-2,4-diphenylbutadiene derivative was obtained after 6 h. This one-pot process is more efficient than the conventional method and has a much easier workup. This process has two interesting characteristics: first, the addition of one of the reactants, benzaldehyde, has to be in sequential mode after the first step is completed because malononitrile is more prone to react with benzaldehyde than with acetophenone. The second is that the α-methylbenzylidenemalononitrile intermediate is a more demanding molecule from the point of view of basic strength than malononitrile, and to achieve high yields of the target compound within a reasonable reaction time, the temperature has to be increased during the second step. This is a clear example of a one-pot reaction in which the sequential addition of one of the reactants and reaction temperature of the different steps has to be adjusted to achieve good performances.

Another example of a cascade process on solid basic catalysts has been recently reported and involves the one-pot synthesis of glycidol from glycerol and dimethyl carbonate[74] (Scheme 7). Glycidol is a glycerol derivative with a wide range of applications, for instance, in the preparation of polyglycerols, polyurethanes, glycidil ethers, and pharmaceuticals.[75−77] Glycidol is industrially produced through two main routes: reaction of 3-chloro-1,2-propanediol with bases[76] and epoxidation of allyl alcohol,[78] both of them requiring multistep synthesis with large production of wastes and raw materials derived from petrochemical resources. A promising alternative

Scheme 7. Cascade Process for the Synthesis of Glycidol from Glycerol and Dimethyl Carbonate[74]



route to production of glycidol is from the decarboxylation of glycerol carbonate, which is usually performed using homogeneous catalysts, such as Na_2SO_4 and $ZnSO_4$, under relatively harsh reaction conditions.[79−81] On the other hand, glycerol carbonate can be obtained from transesterification of glycerol with ethylene carbonate or dimethylcarbonate (DMC) in the presence of basic catalysts,[82,83] and it was observed that small amounts of glycidol were produced as a byproduct during the transesterification process. Taking into account these findings, the authors envisaged a one-pot process to produce glycidol from glycerol and DMC using a heterogeneous basic catalyst in which the global sequence (transesterification followed by decarboxylation) is conducted under the same experimental conditions. The process involves a first step of the transesterification of glycerol with DMC to produce glycerol carbonate, which subsequently decarboxylate into glycidol.

Since glycerol and glycidol are prone to polymerization, the basicity of the catalysts and, particularly, the reaction temperature have to be adjusted to maximize the yield of glycidol. The screening of different metal oxides as solid basic catalysts (see Table 3) under mild reaction conditions (90 °C, under atmospheric pressure) showed that the best performance was achieved with $NaAlO_2$, giving a selectivity to glycidol of 80.7% at 94.7 conversion of glycerol. These results are much better than the previously reported for the direct synthesis of glycidol using a basic ionic liquid as the catatalyst.[84] Moreover, it was found that the yield of glycidol is dependent on the dimethyl carbonate/glycerol molar ratio. Indeed, a molar ratio

Table 3. The Effect of the Different Catalysts on the Synthesis of Glycidol[a,74]

		selectivity (%)	
catalyst	conv. glycerol (%)	glycidol	glycerol carbonate
without			
ZnO	50.1	47.6	52.3
MgO	28.9	35.9	64.0
SrO	30.5	82.3	17.7
La_2O_3	45.2	10.0	90.0
$NaAlO_2$	94.7	80.7	19.3
$NaAlO_2$[b]	42.4	71.5	29.5
$NaAlO_2$[c]	89	1.3	98.7

[a]Reaction conditions: glycerol 0.1 mol; DMC/glycerol molar ratio 2:1; 0.3 wt % of catalyst (based on glycerol); at 80−92 °C, while removing the methanol formed by distillation; 90 min reaction time. [b]10 min. [c]At 60 °C.

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higher than 2:1 decreased the selectivity to glycidol because an excess of dimethyl carbonate favors the formation of glycerol dicarbonate under the reaction conditions. Moreover, it was found that the conversion of glycerol and the selectivity to glycidol slowly decreased with the number of reuses; however, after calcination of the catalyst at 400 °C, conversion of glycerol and selectivity to glycidol were 90% recovered with respect to the fresh catalyst.

An important drawback when using solid base catalysts is that they are easily poisoned by water and CO_2. Interestingly, in this case, exposure of $NaAlO_2$ to air showed that $NaAlO_2$ catalyst exhibited good tolerance to water and carbon dioxide and good recycling ability.

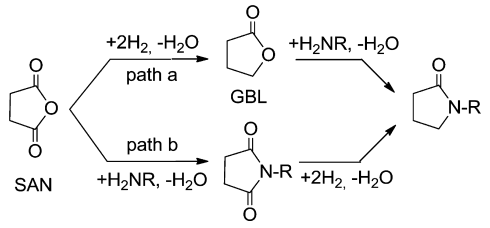
We would like to point out that one of the advantages of solid catalysts when competing with homogeneous bases can be the possibility of making use of the differential adsorption properties of solids and the possibility to work with them in a wide range of conditions. The above-described processes are clear examples in which the solid catalyst can introduce a plus for two-step reactions that is difficult to achieve with homogeneous counterpart catalysts.

2.4. Cascade Processes on Single-Site Metal Catalysts.

Pyrrolidones are molecules with a wide variety of applications as surfactants, solvents, and intermediates in the synthesis of pharmaceutical and bioactive compounds.[85−87] They are also included in the formulation of cleaning products and aerosols and are also useful as ink.[88]

Precisely, one of the few examples in which the global sequence is conducted under the same experimental conditions refers to the synthesis of pyrrolidone and pyrrolidone derivatives starting from succinic anhydride (SAN) and NH_4OH or phenylamine in the presence of Au/TiO_2 as catalyst (Scheme 8).[89]

Scheme 8. One-Pot Reaction for the Synthesis of Pyrrolidone and Pyrrolidine Derivatives from SAN: Possible Reaction Pathways[89]



The two reactions described in Scheme 8 were first studied separately. Thus, Au/TiO_2 was shown to be a very active and selective catalyst for the hydrogenation of SAN to γ-butyrolactone (GBL),[89−97] whereas the latter (GBL) has been described in numerous patents as the best starting reagent for the synthesis of pyrrolidone and its derivatives.[98−102] With these precedents, reaction conditions were studied to optimize the production of pyrrolidone, and the best results were obtained in aqueous medium at 120 bar and 250 °C. An 80% conversion and 99% selectivity were obtained with no overhydrogenated products (see Figure 1).[89]

In view of these results, the one-pot reaction for the synthesis of phenylpyrrolidone derivatives starting from SAN and phenylamine was also performed in dioxane at 110 bar and 250 °C, affording phenylpyrrolidone as the main product (Figure 2).[89]

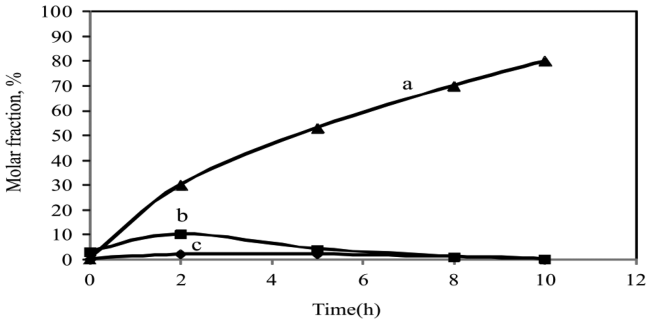


Figure 1. Hydrogenation of SAN catalyzed by Au/TiO_2 in the presence of ammonia at 250 °C and 120 bar: (a) pyrrolidone, (b) succinimide and (c) GBL.[89]

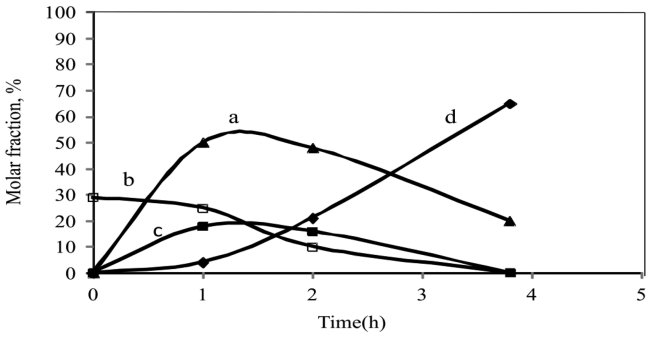


Figure 2. Hydrogenation of succinic anhydride in the presence of phenylamine with Au/TiO_2 as catalyst at 250 °C and 110 bar: (a) phenylpyrrolidone, (b) *N*-phenylsuccinimide, (c) GBL, and (d) phenylpyrrolidine.[89]

The reaction proceeded faster than in previous cases with ammonia, giving 52% yield of phenylpyrrolidone after 1 h, then the latter was hydrogenated to phenylpyrrolidine at longer reaction times.

In this case, two different pathways are proposed for the synthesis of these compounds: Path a consists of hydrogenation of SAN and ammination of the resulting GBL to pyrrolidone; the alternative, path b, consists of ammination of SAN, followed by hydrogenation of the pyrrolidine-2,5-dione intermediate (Scheme 8).[89]

Because succinimide has been detected as an intermediate product, usually in higher amounts than GBL, it has been proposed that the most likely reaction pathway will proceed through the synthesis of succinimide, which will be subsequently hydrogenated to pyrrolidone.[89] In this case, nothing is reported on the reusability and leaching studies of the Au/TiO_2 catalyst. Another important example refers to the synthesis of propargylamines, which are molecules of pharmaceutical interest and important building blocks for the synthesis of nitrogen-containing molecules.[103−105] Propargylamines have traditionally been prepared through nucleophilic attack of Grignard reagents or lithium acetylides on imine derivatives.[106,107] However, these compounds must be used in stoichiometric amounts because they are moisture-sensitive and require strictly controlled experimental conditions.

An alternative synthetic approach consists of performing a catalytic coupling of an alkyne, an aldehyde, and an amine (A_3 coupling) by C−H activation with gold nanoparticles supported on nanometric ceria (Au/CeO_2). This cycle can be connected to a N-monoalkylation reaction of amines with

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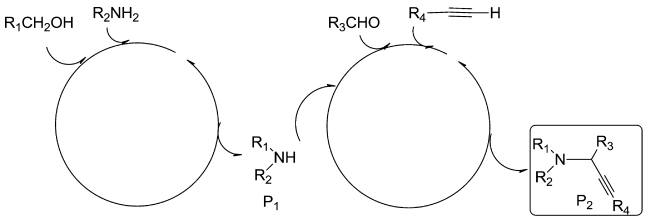
alcohols (through borrowing hydrogen methodology) in a sequential two-step process (Scheme 9).[108]

Scheme 9. Two-Step Process for Producing Propargylamines from Amines, Alcohols and Terminal Alkynes[108]



In principle, because previous and comprehensive studies have shown that Au/CeO_2 solid catalyst was the choice for the catalytic A^3 coupling,[109] the work focused initially on the N-monoalkylation reaction to look for the best catalyst and the nature of the active species involved in this step.[108] Fortunately, a preliminary screening showed that the same catalyst, Au/CeO_2, gave the highest conversions as well as the highest yields of the secondary amine ($\mathbf{P_1}$) when compared with Au deposited on other supports, hence, considerably simplifying the process. Nevertheless, identification of the active species involved in both steps will strongly help to design an optimum catalyst. For achieving this, kinetic and mechanistic studies were conducted by taking into account that the reaction steps involved in the N-monoalkylation are (a) alcohol dehydrogenation to afford an aldehyde and gold hydrides, (b) condensation between the amine and the aldehyde to give an imine, and (c) hydrogenation of the resulting imine by the gold hydrides formed on the surface (see reactions 1−3):

$$PhCH_2OH \xrightarrow{k_a} PhCHO \quad (1)$$

$$PhCHO + PhCH_2NH_2 \xrightarrow{k_b} PhCH{=}NCH_2Ph + H_2O \quad (2)$$

$$PhCH{=}NCH_2Ph \xrightarrow{k_c} PhCH_2 - NHCH_2Ph \quad (3)$$

From these equations and by varying the concentration of the reagents in a series of kinetic experiments, it was found that the dehydrogenation reaction was the slowest step in the Au-catalyzed monoalkylation of primary amines to secondary amines.

Because the XPS data of the fresh reduced catalyst confirmed that Au was almost exclusively in the form of Au^0 (BE Au $^4f_{7/2}$ = 83.7 eV; 100%), these experimental facts confirmed that in the case of reduced Au/CeO_2 catalyst, the hydrogen transfer was mediated by metallic Au^0 species. Moreover, because the TOF for dehydrogenation of benzyl alcohol increased when decreasing the gold crystal size, it could be concluded that the dehydrogenation of alcohol occurred preferentially on those Au atoms with lower coordination, that is, those gold atoms located at the corners and crystal edges. As a result, the size of the metal particle will be a very important variable to maximize the catalytic performance in the first catalytic cycle, that is, the formation of secondary amine $\mathbf{P_1}$.

Thus, since the active gold species responsible for the activity in the N-monoalkylation were Au^0 atoms at the crystal corners,

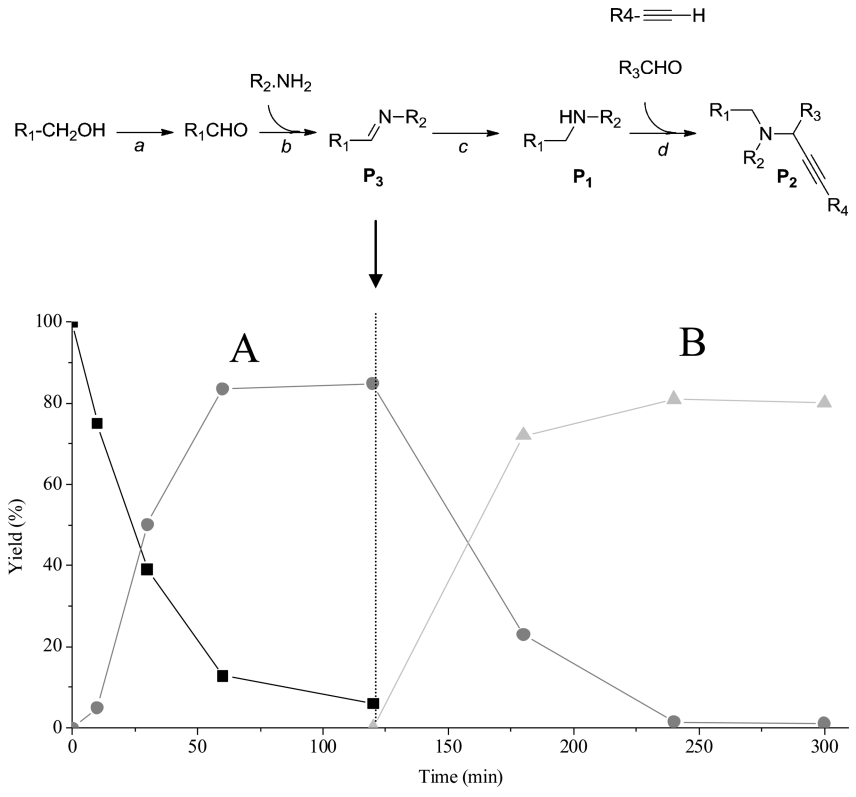


Figure 3. Plot showing the yield of products with time in the global one-pot reaction (cycles A and B) between benzyl amine, benzyl alcohol (■), cyclohexylcarboxaldehyde, and phenylacetylene to give propargylamine $\mathbf{P_2}$ (▲) in the presence of Au/CeO_2 (2.5% weight). Cyclohexylcarboxaldehyde and phenylacetylene were incorporated when almost all the imine $\mathbf{P_3}$ was hydrogenated to the amine $\mathbf{P_1}$ (●) (the arrow at the top of the chart illustrates this point).[108]

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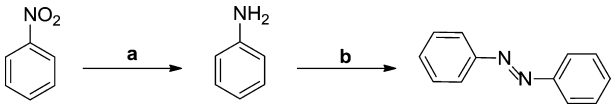
whereas cationic gold species (Au^{1+} and Au^{3+}) are the most active species for the second catalytic cycle, that is, the A^3 coupling,[108,109] it was necessary to adjust the synthesis of the catalyst as well as the experimental conditions (metal loading, temperature, and preparation of catalyst) to avoid a sharp decrease in the concentration of cationic gold species and sinterization of the gold particles (a relationship between activity and selectivity parameters of the catalyst with metal crystallite size was evidenced in the N-monoalkylation step).

When this was achieved, the two catalytic cycles could be connected in a cascade mode by working with Au/CeO_2 catalyst (2.5 wt %) prepared at 250 °C with H_2 flow and by turning down the temperature from 160 to 85 °C for performing the second cycle. Figure 3 shows the kinetic profile of the sequential reaction (cycles A and B) after adjusting the preparation of catalyst and the reaction conditions:

Reusability studies showed that $Au(2.5\%)/CeO_2$ could be reused without loss of activity and selectivity in subsequent cycles in this one-pot reaction. In this case, the strong interaction between different gold species and the carrier (CeO_2) will account for the observed high activity and stability of the catalytic active species during the overall tandem reaction.

Continuing with this compilation, we have found that the optimization of a process can gradually gain complexity because the same catalyst is capable of completing a two-step sequential transformation, albeit with changes in the experimental conditions in each reaction step. This is the case for Au nanoparticles on TiO_2 (Au/TiO_2), which was shown to catalyze the direct transformation of nitroaromatics to azo compounds (valuable chemicals widely used in industry as pigments, dyes, drugs, and food additives).[110−112] The process was devised through a two-step sequential reaction involving the formation of anilines as intermediates affording yields above 98% and working under mild reaction conditions (Scheme 10).[113]

Scheme 10. Two-Step, One-Pot Reaction from Nitroaromatics to Azocompounds Catalyzed by Au/TiO_2[113]



It was first observed that when aniline was put in contact with Au/TiO_2 prepared in the form of nanocrystallites, under mild oxidation conditions (i.e., P_{O_2} = 3−5 bar, T^a = 100 °C), azobenzene was obtained as the main product.

For completing this study, a series of catalysts prepared with different metals, loadings, and supports were tested in the oxidation of aniline to azobenzene, and their activity and selectivity data were compared with those obtained with Au/TiO_2 (Table 4).[113]

The catalytic results showed that Au/TiO_2 was superior over the rest of the catalysts assayed, whereas the support had an important influence on the activity of Au nanoparticles (Table 4). For example, whereas Au on TiO_2 proved to be active and selective for formation of azobenzene, Au with similar crystallite size on carbon (0.8% Au/C) or ferric oxide (4.4% Au/Fe_2O_3) was not active (Table 1). Similarly, the oxidation of aniline to azobenzene with carbon or titania-supported palladium (Pd/C and Pd/TiO_2) or even platinum nanoparticles (Pt/C) under the same reaction conditions was unsuccessful (Table 4). In addition to this, no catalytic improvement could be found when using, Au(core)−Pd(shell)/TiO_2 as catalyst (Table 4).[114]

At this point, it was clear that Au/TiO_2 was an excellent catalyst to convert aniline derivatives into azo compounds. Taking into account that Au/TiO_2 was also an excellent catalyst for reduction of nitroaromatics to anilines in a chemoselective way,[115] it was natural, therefore, to think that it should be possible to produce azo compounds in a single process starting with an industrially most convenient reactant, such as nitrobenzene. Then both reactions, that is, nitrobenzene (or its derivatives) hydrogenation to the corresponding anilines and the coupling of the anilines, were performed in a single-pot system by adjusting the reaction conditions (see Scheme 11). In this way, the nitro compound was hydrogenated at 120 °C, and after flushing out the H_2, oxygen was incorporated in the reactor, and the temperature was tuned down to 100 °C (Table 5) and the final azo compound was obtained with very high yield.

The wide scope of this process was confirmed because in general, the reaction was highly selective for the synthesis of azobenzene derivatives, regardless of the presence of electron acceptor or donor substituents at the aromatic position. Moreover, asymmetric azobenzenes could also be obtained, provided that the starting anilines present different reactivities. The reaction was proposed to occur through electron oxidation of aniline to the corresponding radical cation (detected by EPR) mediated by Au/TiO_2. Nothing was reported concerning the stability of the catalyst in ulterior uses.

Another example of a cascade process catalyzed by gold-supported nanoparticles is the synthesis of benzymidazoylquinoxaline derivatives by oxidative coupling of glycerol or glyceraldehyde with *o*-phenylenediamine derivatives.[116]

Benzymidazoylquinoxaline derivatives have shown properties as selective antagonists at human A1 and A3 adenosine receptors.[117] However, methods for the synthesis of these quinoxaline derivatives are limited and usually involve several synthetic steps, leading in general to low yields (lower than 50%).[118,119]

We then designed a new protocol to produce these types of compounds with excellent yield in a one-pot process using Au/CeO_2 as the catalyst. The oxidative coupling of glycerol with *o*-phenylenediamine derivatives performed at 140 °C using diglyme as a solvent leads to benzimidazoylquinoxaline compounds (**3aa**) through the formation of intermediates **4** and **5** (Scheme 12). In this case, the benzimidazoylquinoxaline possess the same substituents in both heterocycles. Then, with the aim to expand the synthetic scope, an alternative route that allows combining different substituens in both heteroaromatic moieties was designed.

This new process involves two sequential steps with very different reaction conditions. In the first one, glyceraldehyde is coupled with an *o*-phenylenediamine derivative in the presence of Au/CeO_2 to produce the intermediate **5** under very mild reaction conditions (room temperature, 3 bar O_2, and water as a solvent). Once the complete conversion of glyceraldehyde is achieved, a solution of the second *o*-phenylenediamine molecule (**1b**) in diglyme is added, and the temperature is increased to 140 °C while the water is removed by a Dean−Stark system. The main product observed under these conditions is the benzimidazoylquinoxalines **3ab** (Scheme 13), which is formed by oxidative coupling between the intermediate **5** and the *o*-phenylenediamine molecule (**1b**).

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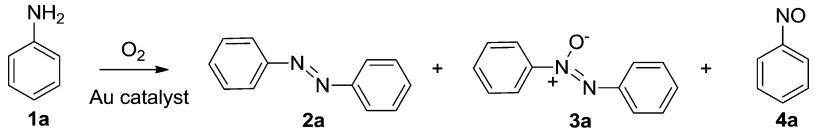
Table 4. Results on the Aerobic Oxidation of Aniline Catalyzed by Metal Nanoparticles Supported on Different Carriers[a,113]



		yield (%)				
catalyst	time (h)	2a	3a	4a	conv (%)	sel (%)
1.5% Au/TiO_2	9	90	0	10	100	90
	22	98	0.5	1.5	100	98
TiO_2	24	52.5	0	0.5	53	99
$Au(1.5\%)Pd(0.8\%)/ TiO_2$	34	8.4	0	0	8.4	99
$Au(1.5\%)Pd(1.8\%)/ TiO_2$	23	nr[b]	nr	nr	nr	nr
5% Pd/TiO_2	35	nr	nr	nr	nr	nr
4.4% Au/Fe_2O_3	47	nr	nr	nr	nr	nr
0.8% Au/C	69	nr	nr	nr	nr	nr
5% Pd/C	80	nr	nr	nr	nr	nr
0.2% Pt/C	40	nr	nr	nr	nr	nr
5% Pt/TiO_2	70	nr	nr	nr	nr	nr
0.44% Au/CeO_2	6	91	7	0	98	91
	10	93	7	0	100	93
$Au(0.44\%)Pd(10.15\%) /CeO_2$	20	83	6.5	0	100	83

[a]Reaction conditions: preheated anilines (93,13 mg) at 100 °C in toluene (2 mL), stirred magnetically in a reinforced glass vial (3 mL) at an initial O_2 pressure of 5 bar in the presence of the catalyst (metal/aniline mol ratio 1%). [b]nr = no reaction.

Scheme 11. Two-Step, One-Pot Process for the Synthesis of Azobenzene from Nitrobenzene[113]

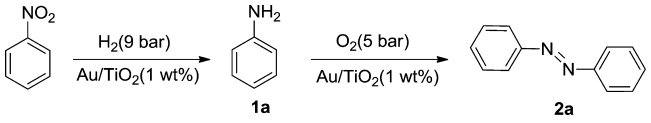


Table 5. Reaction Conditions for the Synthesis of Azobenzene Starting from Nitrobenzene through a Sequential Two-Step Process[113]

catalyst	T °C	P_{H_2} (bar)	t (h)	yield (%)	C (%)[a]	S (%)[b]
1.5% Au/TiO_2	120	9	6	95 (**1a**)	99	96
	100	5	9	92 (**2a**)	100	92

[a]C (%) refers to conversion of **1a**. [b]S (%) refers to selectivity toward azobenzene **2b**.

Both routes were applied to the synthesis of different benzimidazoylquinoxalines derivatives, which were obtained in yields between 60 and 80%.

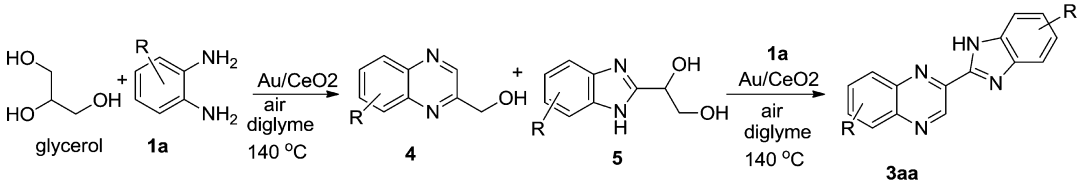
The recyclability of the catalyst was studied by performing consecutive reuses of the Au/CeO_2 under the same reaction conditions. Although no leached gold species were detected in the reaction media, some catalyst deactivation was observed, which was attributed to deposition of organic material on the catalyst surface. Therefore, to eliminate the organic deposits, the Au/CeO_2 catalyst was pretreated with oxygen flow at 250 °C for 2 h before each reuse. This pretreatment allowed regeneration of the initial activity in a large extension while selectivity to benzimidazoylquinoxaline was maintained.

3. CASCADE PROCESSES ON MULTIFUNCTIONAL CATALYSTS

3.1. Cascade Reactions on Bifunctional Bronsted and Lewis Acid Catalysts. Cascade reactions on bifunctional Bronsted and Lewis acid catalysts can be performed using materials that allow generating both types of acid sites on the same catalyst or by combining previously optimized Lewis and Bronsted acid catalysts. In this section, we present two interesting examples of the use of such catalytic systems in cascade reactions.

Amorphous and crystalline molecular sieves allow Bronsted and Lewis acid sites to be introduced simultaneously by performing isomorphous substitutions of silicon with trivalent atoms, such as Al, and other tetravalent elements, such as Ti and Sn. The Al atom generates a negative charge in the framework that is compensated by a proton that act as a Bronsted acid site while Ti and Sn act as Lewis acids able to catalyze oxidation reactions in the presence of peroxides. Consequently, by introducing these different active sites simultaneously, it should be possible to carry out tandem reactions involving, for instance, epoxidations followed by acid-catalyzed transformations of the epoxide formed.

Scheme 12. New One-Pot Two Steps Process for the Synthesis of Benzimidazoylquinoxalines Starting from Glycerol[116]



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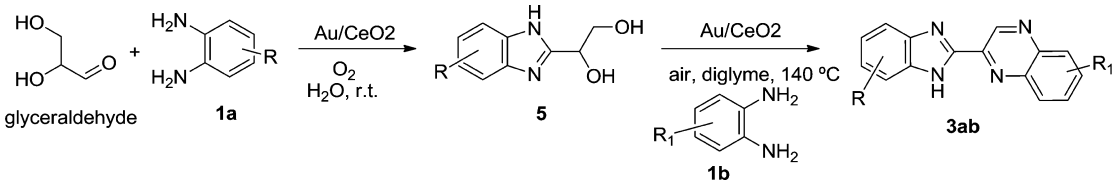
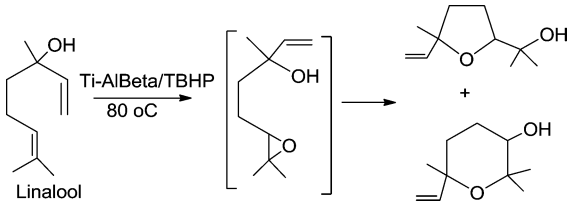
Scheme 13. New One-Pot, Two-Step Process for the Synthesis of Benzimidazoylquinoxalines Starting from Glyceraldehyde[116]



An interesting example is the formation of substituted tetrahydrofurans and tetrahydropyrans of interest in the flavors industry. For example, furan and pyran hydroxyl ethers, such as the ones presented in Scheme 14, exhibit a strong rose odor

Scheme 14. One-Pot Production of Pyran and Furan Hydroxyl Ethers by Epoxidation of Linalool[120]

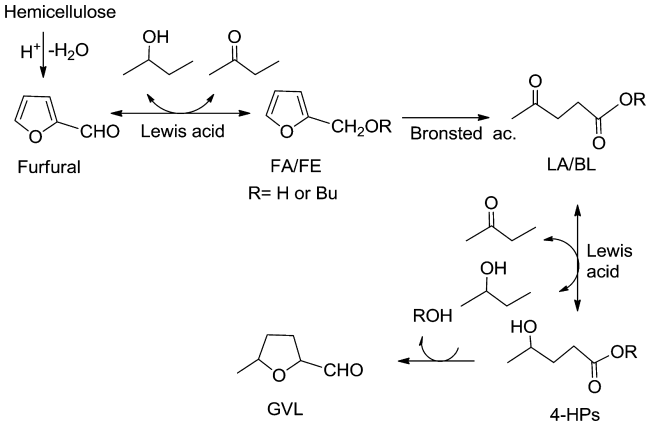


and can be selectively formed from linalool by the epoxidase enzyme, the 6,7-epoxylinalool intermediate being the natural precursor of the pyran and furan hydroxyl ethers. In an attempt to use an inorganic catalyst, it has been demonstrated that[120] bifunctional Bronsted−Lewis catalysts, such as Ti-AlBeta and Ti-AlMCM-41, with framework Ti^{4+} and Al^{3+}, are able to convert linalool into the hydroxyl ethers in one pot using TBHP as the oxidant at 80 °C. Conversions of linalool of 73 and 80% with 100% selectivity to the hydroxyl ethers were obtained with Ti-AlBeta and Ti- AlMCM-41, respectively. A proof that the reaction involves as a first step an epoxidation over Lewis acid sites (Ti^{4+}), followed by a rearrangement over the Bronsted acid sites associated to the aluminum atoms, was that the ratio of furans to pyrans was constant during the reaction.

On the other hand, an interesting example in which a physical mixture of a Bronsted and Lewis acid catalyst are required to perform a cascade process for obtaining Gamma-valerolactone from furfural has been presented recently by Román-Leshkov et al.[121]

Gamma-valerolactone (GVL) is a versatile biomass platform molecule that can be converted into liquid alkanes and renewable polymers and can also be used as a fuel additive and as a solvent for biomass processing.[122−126] Currently, biomass-derived GVL is obtained by treating carbohydrate fractions of lignocellulose with acid catalyst, which converts sugars into levulinic acid, which is subsequently hydrogenated on a noble metal catalyst into GVL.[126,127] However, the requirement of expensive noble metals (such as Pt or Ru) along with high hydrogen pressures for the reduction step may economically penalize this process for the large-scale production of GVL.[128,129] A recent alternative for the reduction of levulinic acid into GVL is the use of formic acid as a source of hydrogen; however, this strategy also requires noble metals, harsh conditions, or both to perform the reduction of levulinic acid.[130,131] However, the new approach to produce GVL from furfural through a cascade process introduced by Román-Leshkov et al.[121] does not require the use of noble metals or molecular hydrogen. Because levulinic acid can be produced from furfuryl alcohol, the process involves the conversion of furfural into a mixture of furfuryl alcohol and butyl furfuryl ether through a hydrogenation transfer process promoted by a Lewis acid catalyst, using 2-butanol as hydrogen donor. Furfuryl alcohol and butyl furfuryl ether are converted subsequently by hydrolytic ring-opening catalyzed by a Bronsted acid into a mixture of levulinic acid and butyl levulinate, which underwent a second transfer hydrogenation, producing 4-hydroxypentanoates which subsequently cyclize to GVL (Scheme 15). As can

Scheme 15. Cascade Reaction for the Synthesis of GVL from Hemicelluloses Using a Combination of Bronsted and Lewis Acids[a,121]



[a]FE, furfuryl ether; FA, furfuryl alcohol; LA, levulinic acid; BL, butyl levulinate, 4-HPs, 4-hydroxypentanoates; GVL, γ-valerolactone.

be observed, in this elegant process, two hydride transfer steps plus a ring-opening step have to occur in the same vessel under the same reaction conditions. In this case, optimization of Lewis and Bronsted catalysts as well as the operational window conditions have to be adjusted.

Concerning the selection of the Lewis acid catalyst, the authors took advantage of the fact that pure silica zeolites containing tetravalent metals, such as Sn-Beta or Zr-Beta, were shown to be solid Lewis acid catalysts able to promote efficiently the intermolecular MPV hydride transfer reaction between alcohols and ketones[53−55] as well as alcohol etherification.[57] Therefore, if diffusional limitations of reactants and products do not exist, these zeolites appear as excellent candidates to promote efficiently the two hydride-transfer steps involved in the one-pot process. Indeed, the screening of different solid Lewis acid catalysts performed in liquid phase in a batch reactor at 120 °C showed that particularly Zr-Beta exhibited the highest activity and selectivity both in the reduction of furfural into furfuryl alcohol and butyl furfuryl ether (formed by etherification of furfuryl alcohol and 2-butanol) (96% selectivity at 98% conversion) and the reduction of methyl levulinate into GVL(>99% selectivity at 97%

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Table 6. Results for the One-Pot Synthesis of GVL from Furfural in the Presence of Bronsted Acids and Zr-Beta (Si/Zr 127:1)[a,121]

						yield[c] (mol)		
entry	Bronsted acid	Fur/Al or Fur/H^{+}[b]	water content (wt %)	GVL	FE	BL	LA	MF
1	Al-beta	16:1		44	0	2	0	15
2	Al-MCM-41	16:1		34	0	0	0	4
3	Al-MFI	16:1		8	28	2	0	3
4	Amberlyst-70	10:1		66	0	0	0	0
5	Amberlyst-36	16:1		39	0	13	3	2
6	H_2SO_4	10:1		16	0	48	0	0
7	Al-MFI-ns	80:1		18	16	4	0	2
8	Al-MFI-ns	32:1		40	0	4	0	2
9	Al-MFI-ns	20:1		58	0	3	0	3
10	Al-MFI-ns	16:1		62	0	2	0	2
11	Al-MFI-ns	16:1	5	68	0	2	0	8
12	Al-MFI-ns	16:1	10	65	0	2	1	8
13	Al-MFI-ns	16:1	15	58	0	4	4	7
14[d]	Al-MFI-ns	16:1	5	78	0	1	0	8
15[e]	Al-MFI-ns	16:1	~6.5	70	0	2	0	5
16[e,f]	Al-MFI-ns	16:1	~6.5	62	0	6	0	4

[a]Reaction conditions: 1 mol %, Fur (5 wt %) in 2-butanol (Fur/Zr 100:1), 393 K, 24 h. [b]The amount of tetrahedrally coordinated Al was determined by a combination of ICP spectroscopy and solid-state ^{27}Al NMR spectroscopy. [c]Yield: ([mmol product]/[mmol (feed initial)]) × 100; GVL, γ-valerolactone; FE, butyl furfuryl ether; BL, butyl levulinate; LA, levulinic acid; MF, 5-methyl-2(5*H*)-furanone. [d]Reaction time: 48 h. [e]The reaction was carried out with a solution of Fur (5 wt %) in 2-butanol from a simulated biphasic system [2:1 (w/w) 2-butanol/water (30 wt % NaCl)]. [f]The reaction was carried out with the organic fraction of a biphasic system used for the dehydration of a 15 wt % xylose solution.

conversion). Comparatively, other Lewis acid catalysts, such as Sn-Beta, Al-Beta, and Ti-Beta, exhibited lower catalytic activity, showing the importance of the nature of the Lewis acid site on the hydride transfer process between the carbonyl compounds involved and 2-butanol. Interestingly, in the reduction of methyl levulinate into methyl 4-hydroxypentanoate, the thermodynamic equilibrium is less favored because both 2-butanol and methyl 4-hydroxypentanoate are secondary alcohols. However, the fast lactonization of methyl 4-hydroxypentanoate into GVL is the driving force that leads the reaction to completion. This last is an important point that was highlighted in the introduction of this manuscript for a cascade process in which one of the steps may be thermodynamically limited.

Concerning the ring-opening step of furfuryl alcohol and butyl furfuryl ether, the process occurs through a Bronsted acid-catalyzed hydrolytic cleavage of the furanic C−O bond. Typical heterogeneous catalysts that can promote this process are aluminosilicates and ion-exchange resins.[132] However, the Bronsted acid catalyst has to be carefully selected, because Bronsted acid sites also promotes secondary reactions, such as polymerization, formation of insoluble humins, and even self-etherification of 2-butanol. Studies of the one-pot transformation of furfural into GVL performed using a physical mixture of Zr-Beta and different Bronsted acid catalyst showed that an aluminosilicate with MFI topology and nanosheet morphology (Al-MFI-ns) exhibited the best performance in terms of yield and selectivity for the ring-opening step (see Table 6). Moreover it was found that the concentration of Bronsted acid sites had strong influence on GVL yield (see Table 6). Interestingly, composite catalyst formed by Zr-Beta and Al-MFI-ns works efficiently in the presence of water, achieving maximum yield of GVL when working in the presence of 5 wt % of water (see Table 6), which was attributed to the pore hydrophobicity of the Lewis acid zeolites, as was shown before.[55,57,133] Considering that when furfural is obtained from hemicellulose using biphasic systems with homogeneous catalyst, the organic phase may contain between 1 to 20 wt % of water, an important point is that this catalytic system and the operational conditions used are compatible with those required for the production of furfural from hemicellulose.[134]

Recyclability of the catalytic system is another central point to be considered. In this case, it was found that although the catalytic activity decreased over multiple cycles, probably as a result of the strong adsorption of organic material on the catalysts, the hydrothermal stability of the zeolites allows recovering full activity by calcinations.

This is an excellent example that shows the possibility of performing a multistep reaction in a cascade mode by properly designing an optimized multifunctional composite catalyst and optimizing the reaction conditions to find a window operation. Finally, success requires a combination of mechanistic and kinetic knowledge together with the ability to prepare an adequate solid material.

3.2. Cascade Reactions on Acid-Metal Bifunctional Catalyst. Acid−metal bifunctional catalysts are commonly prepared by supporting metals on acidic supports. Preferred supports are micro- and mesoporous molecular sieves because they allow selection between Lewis and Bronsted acidity, and acidity as well as adsorption properties can be tuned by changing its chemical composition.[10,135] In addition to the classical multistep reactions performed with bifunctional metal/acid catalysts that are widely used industrially in the oil refining industry (i.e. gasoline reforming, alkane isomerization, and hydrocracking of oil fractions),[136] and which were summarized before, we would like to describe here other less usual catalytic process more in the field of chemicals and fine chemicals.

An example is the stereoselective production of cis-4-*tert*-butylcyclohexanol, which is a fragrance chemical intermediate, that takes place through hydrogenation of 4-*tert*-butylphenol followed by MPV reduction over rhodium supported on Zr-

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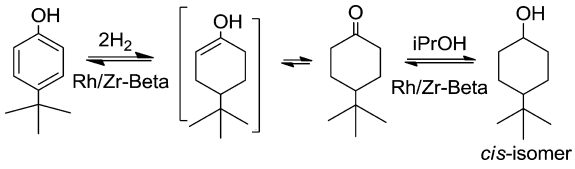
Beta zeolite.[137] An interesting aspect of Beta zeolites containing Lewis acid sites is that in addition to its capacity to promote the MPV reductions, they can introduce stereoselective effects imposed by the zeolite structure. Indeed, during the reduction of 4-alkylcyclohexanones, high stereoselectivity (>95%) to the kinetically favored but thermodynamically less stable *cis*-cyclohexanol isomer is obtained as a result of a transition-state selectivity imposed by the zeolite structure.[50,138] Thus, by supporting 0.5% of Rh on Zr-Beta, the hydrogenation activity of the Rh and the high stereoselectivity of Zr-Beta for *cis*-*tert*-butylcyclohexanol are combined in a bifunctional catalyst. As a result, a cascade process can be established that involves the metal-catalyzed hydrogenation of 4-*tert*-butylphenol into the corresponding intermediate 4-*tert*-butylcyclohexanone, which is subsequently stereoselectively reduced with isopropyl alcohol via MPV reduction over Zr Lewis acid sites into the *cis*-alcohol isomer (Scheme 16). Interestingly, the catalytic system

Scheme 16. One-Pot Synthesis of 4-Alkylcyclohexanols from 4-Alkylphenols[137]



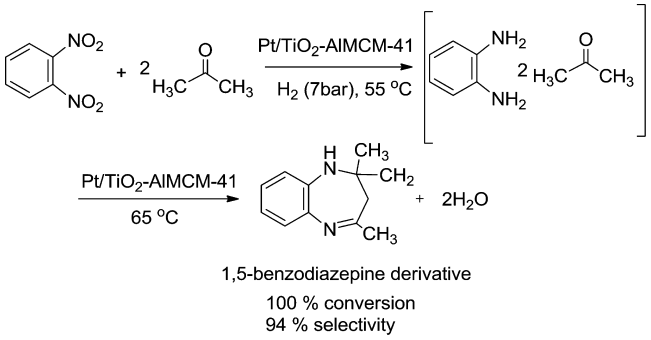
minimizes the competitive hydrogenation of the ketone into alcohol. Consequently, working under optimized reaction conditions (80 °C under 5 bar of hydrogen), *cis*-4-*tert*-butylcyclohexanol was obtained with 95% selectivity at 100% conversion of 4-*tert*-butylphenol. When Pd was used instead of Rh, a higher pressure and temperature for the hydrogenation was required. Moreover, the Rh/Zr-Beta is a stable and reusable catalyst, keeping its initial activity and selectivity after calcinations.

On the other hand, there are cascade processes in which optimized active sites for reduction (or oxidation) cannot be combined with the adequate acid sites on the same catalyst, and an optimized composite catalyst combining both functions has to be designed. A representative example is the synthesis of 1,5-benzodiazepines through a cascade process involving hydrogenation of 1,2-dinitrobenzene, followed by cyclocondensation with ketones.

Benzodiazepines and derivatives are important compounds that are used as anticonvulsants, analgesics, antianxieties, tranquilizers, hypnotics, antidepressives, and anti-inflammatories.[139,140] General methods for preparing 1,5-benzodiazepine derivatives involve the cyclocondensation of α,β-unsaturated carbonyl compounds,[141] β-haloketones,[142] or ketones with *o*-phenylenediamine in the presence of transition metal salts and Lewis acids as catalysts, the latter being the most general method for preparing 1,5-benzodiazepines.

Since nitroaromatics can be first converted into the corresponding amines by hydrogenation,[143] we envisaged a cascade process to produce 1,5-benzodiazepines starting from substituted nitroaromatics and ketones using a bifunctional acid/metal chemoselective catalyst.[144] In a first step, a chemoselective hydrogenation of the 1,2-dinitrobenzene in the presence of the ketone on the metal sites is required, whereas in a subsequent step, the cyclocondensation between the 1,2-diaminobenzene formed and the ketone will take place on the acid sites of the catalyst (Scheme 17).

Scheme 17. Cascade Process for the Synthesis of Benzodiazepines Starting from Nitroaromatics[144]



1,5-benzodiazepine derivative
100 % conversion
94 % selectivity

In this approach, there are two essential issues: the chemoselective hydrogenation of the nitro groups in the presence of the carbonyl compound, and avoiding the hydrogenation of the C═N double bound in the 1,5-benzodiazepine product. Then, to achieve good performances for the process, optimization of the two catalytic functions (i.e., the acid and the hydrogenation) has to be performed. First, a Pt-decorated TiOx catalyst was selected, which should be able to selectively hydrogenate the nitro groups in a large variety of 1,2-dinitrobenzene derivatives under mild reaction conditions[145] while the acidity of the TiO_2 support could promote the cyclocondensation step. This catalyst was prepared by supporting nanoparticles of Pt on TiO_2 and subsequent calcination at 450 °C in the presence of hydrogen. This treatment decorates the exposed (111) and (110) Pt crystal faces with TiO_2 from the support. However, when the cascade process starting from 1,2-dinitrobenzene and acetone was performed in the presence of decorated Pt/TiO_2, it was found that the weak acidity of the TiO_2 promoted the cyclocondensation step slowly, and reaction times of 14 h were required to achieve complete conversion, and the selectivity to the benzodiazepine was not optimum (73%). Then, an optimization of the acidic function was performed by selecting different aluminosilicates as acid catalysts for the cyclocondensation reaction between *o*-phenylenediamine and acetone. Among them, a structured mesoporous aluminosilicate (AlMCM-41) with a Si/Al ratio of 14, showed better activity and selectivity than Beta and ITQ-2 zeolites to form the corresponding 1,5-benzodiazepine working under mild reaction conditions. From this result, a composite catalyst was designed for performing the cascade process. It was prepared by combining 0.2 wt % Pt/TiO_2 and AlMCM-41. The reaction between 1,2-dinitrobenzene and acetone was performed under hydrogen pressure up to full hydrogenation of the 1,2-dinitrobenzene. At this point, the reactor was depressurized, and the temperature was increased to 65 °C, achieving 100% conversion with 94% selectivity to the corresponding 1,5-benzodiazepine in 2.5 h. An important point to achieve good selectivity to 1,5-benzodiazepine was to eliminate the hydrogen when nitro groups were completely reduced to avoid the hydrogenation of the C═N double bond of the target compound.

The composite Pt/TiO_2−AlMCM-41 catalyst was useful for the synthesis of different 1,5-benzodiazepines derivatives, achieving in all cases yields on the order of 90% under very mild conditions.

Because Au/TiO_2 has been reported to also be a chemoselective catalyst for the reduction of nitrobenzene deriva-

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tives,[145−147] the reaction was carried out with the composite AlMCM41−Au/TiO_2. In this case, excellent conversion (99%) and selectivity (93%) to 1,5-benzodiazepine were achieved within short reaction times (4 h), but a higher reaction temperature (120 °C) was necessary. In addition, when commercial 5 wt % Pt/C, Pt/Al_2O_3, Pt/C, or undecorated Pt/TiO_2 were used along with AlMCM-41, full conversions were also obtained; however, selectivities to the 1,5-benzodiazepines were considerably lower. It becomes evident that in the case of a composite catalyst, it becomes easier to optimize independently the different catalytic functions for each of the reaction steps. When this is achieved, it should not be a problem in practice to prepare the composite catalyst because catalyst manufacturers have developed much experience in this type of materials. Perhaps fluid catalytic cracking (FCC) catalysts are the most paradigmatic example of a composite catalyst.

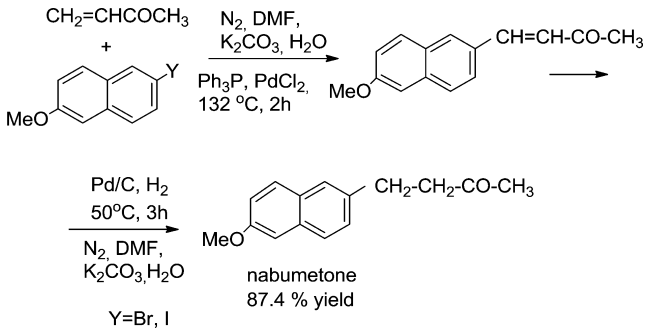
3.3. Cascade Reactions on Bifunctional Base-Metal Catalysts. Paradigmatic examples of cascade reactions on bifunctional base-metal catalysts are based on the aldol condensation of aldehydes and ketones, followed by dehydration, leading to an α,β-unsaturated carbonyl compound and subsequent hydrogenation of the C=C bond.[1]

The preferred heterogeneous multifunctional catalysts for performing these cascade processes are principally based on metals (Pd, Pt, Ni, Cu) acting as hydrogenating functions, supported on metal oxides, or metal mixed oxides, which possess $M^{+n}O^{2-}$ acid−basic pairs.[64] These supports possess strong Lewis basic sites associated with O^{2-} anions able to perform the aldol condensation, together with weak acid sites associated with M^{+n} cations. In the accepted mechanism for the base-catalyzed aldol condensation, the first step is a hydrogen abstraction by the basic site generating an enolate type species that is stabilized by the acid site. Then the nucleophilic attack of the enolate species to the carbonyl group of another molecule generates the aldol intermediate, which subsequently dehydrates on the weak acid site, yielding an α,β-unsaturated carbonyl compound.

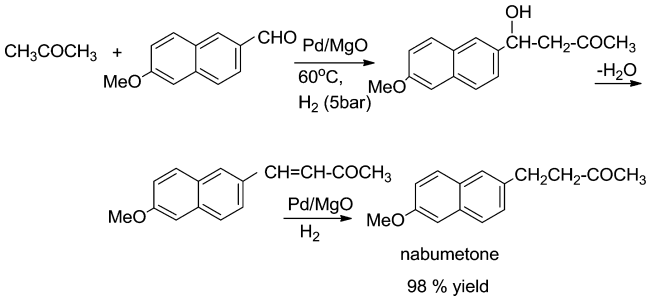
On the other hand, the selection of the hydrogenating function is of paramount importance to achieve the selective hydrogenation of the C=C bond, being Ni and particularly Pd the preferred metals. An interesting example of this approach is the one-pot synthesis of 4-(6-methoxy-2-naphthyl)-2-butanone. Nabumetone is a nonsteroidal anti-inflammatory drug generally utilized as an analgesic for several arthritic and rheumatic diseases.[148,149] The conventional synthesis involves as a first step the Heck coupling reaction of 6-methoxynaphthalene halide with methyl vinyl ketone using homogeneous palladium catalysts,[150,151] giving the corresponding α,β-unsaturated ketone intermediate, which is subsequently separated and hydrogenated in a second step to give nabumetone using Pd/C catalyst (Scheme 18). This approach gives nabumetone in 87.4% yield, while significant amounts of salts and other byproducts are formed by successive Heck reaction of the α,β-unsaturated ketone intermediate.

To introduce a green alternative to this process, we have designed a multifunctional solid catalyst bearing acidic, basic, and metal sites that is able to perform the synthesis of nabumetone with excellent yields through a cascade reaction.[152] Thus, the one-pot process involves the reaction of 6-methoxy-2-naphthaldehyde with acetone in the presence of hydrogen. The condensation step is promoted by a basic site, giving the aldol condensation intermediate, which is rapidly dehydrated on an acid site to the corresponding α,β-unsaturated ketone intermediate, the double bond of which is subsequently hydrogenated on the metallic site to produce nabumetone (Scheme 19). One has to consider that during the process, different secondary reactions can take place, such as consecutive aldol condensations, hydrogenation of reactants (acetone and 6-methoxy-2-naphtaldehyde) over hydrogenation of Nabumetone, and even C−O bond hydrogenolysis of the aldol intermediate. Therefore, minimization of the formation of byproducts is important to find the optimum catalyst that is able to efficiently work under mild reaction conditions.

Scheme 18. Synthesis of Nabumetone by Conventional Methods[150,151]



Scheme 19. One-Pot Synthesis of Nabumetone[152]



The synthesis of nabumetone was carried out using Pd (1 wt %) supported on different solids possessing both Lewis or Bronsted basic and Lewis acid sites (i.e., supports based on MgO, calcined Al−Mg hydrotalcite (HTc), and a rehydrated Al−Mg mixed oxide (HTr)). It was found that Bronsted bases (HTr) were more active than Lewis bases (MgO and HTc), although the latter was more selective to nabumetone. MgO could be further optimized by studying the influence of the crystal size on activity. The results showed that when decreasing the crystallite size of the MgO, the initial activity for the condensation step increases exponentially, indicating that the aldol condensation is structure-sensitive;[153] that is, the most basic sites, which are those associated with edges and corners, are also the most active for the condensation step. As a result, when the one-pot reaction was performed under mild reaction conditions (60 °C, under 5 bar of hydrogen) with a Pd/MgO sample (3 nm crystal size), nabumetone was obtained in 98% yield and 100% selectivity (after 1h), whereas Pd/MgO samples with higher crystal sizes (13 and 5 nm), exhibited lower catalytic activity. Moreover, MgO was regenerated and reused for several cycles and maintained its initial activity. Taking into account that the α,β-unsaturated ketone intermediate is a toxic compound,[149] the one-pot process described

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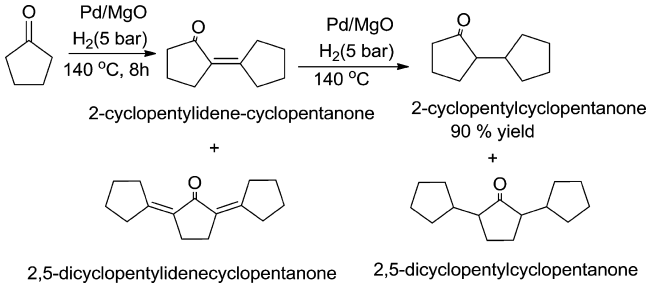
here for the synthesis of nabumetone can be considered as the best reported to date.

Following this protocol, another interesting example in which the multifunctional Pd/MgO is used with excellent success is the one-pot synthesis of 2-cyclopentylcyclopentanone. 2-Cyclopentylcyclopentanone (Scheme 20) with a

Scheme 20. Cascade Process for the Synthesis of 2-Cyclopentylcylopentanone[156]



jasmine aroma is a product utilized for perfume or flavouring[154] and as a wood preservative. The conventional method for the synthesis of 2-cyclopentylcyclopentanone involves the condensation of cyclopentanone in the presence of a homogeneous basic catalyst (NaOH, KOH, or sodium), yielding 2-cyclopentylidene-cyclopentanone, which is subsequently hydrogenated using a conventional hydrogenating catalysts, such as Pd/C.[154] However, the main problem of this approach is that under homogeneous catalysis, the yield of 2-cyclopentilydene-cyclopentanone intermediate is low as a result of its condensation with another cyclopentanone molecule to give the highly conjugated and thermodynamically stable trimer adduct (2,5-dicyclopentylidenecyclopentanone) in yields between 30 and 50%.[155] As a consequence, the target compound is obtained with a very low selectivity.

Nevertheless, when the reaction is carried out through a tandem process in the presence of hydrogen and Pd/MgO catalyst (Scheme 20), it is possible to adjust the relative rates of the different successive steps, achieving high selectivity to the 2-cyclopentylcylopentanone (91% selectivity at 98% cyclopentanone conversion).[156] Thus, in the one-pot process, a rapid hydrogenation of the 2-cyclopentylidene-cyclopentanone intermediate occurs, decreasing the reaction rate of the subsequent aldol condensation and suppressing the formation of the undesired trimer. These results demonstrate the advantage of the one-pot cascade process using a Pd/MgO catalyst with respect to the conventional method.

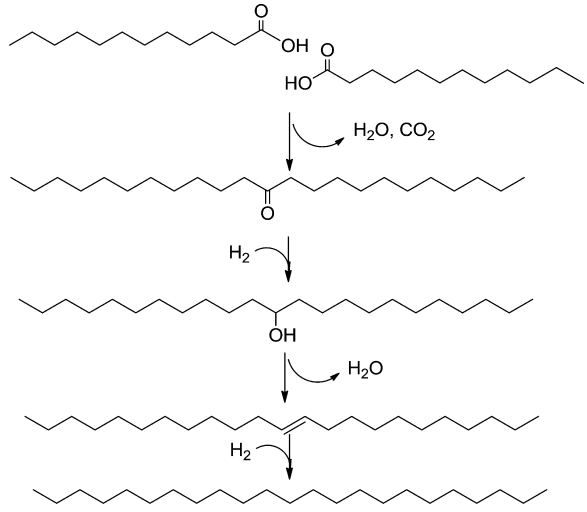
In some cases, the cascade process cannot be achieved with good success on the same bifunctional base-metal catalyst, and operational conditions have to be adjusted to achieve good performances. As an example of this, we discuss here a cascade process using bifunctional heterogeneous catalysts that are able to convert fatty acids into premium diesel and lubricants.

Sustainable development is an increasing demand of our society that has prompted researchers to develop processes that are capable of converting biomass and biomass-derived compounds into chemicals and liquid fuels.[157−164] Since a separation and purification intermediate process in the case of processes involving biomass are especially costly, the introduction of cascade processes for these types of transformations is of paramount importance to achieve process intensification.

The base-promoted coupling of two carboxylic acid molecules gives symmetrical ketones (ketonization) with $2n - 1$ carbon atoms, one molecule of water, and one molecule of CO_2.[165,166] Thus, fatty ketones can be obtained if the condensation takes place between two fatty acid molecules, which can be subsequently hydrogenated to the corresponding alcohols that by dehydration and subsequent hydrogenation of the resultant C=C give alkanes of interest as diesel fuel or biolubricants.

It was found that working in a fixed-bed continuous reactor at 400 °C, basic MgO or ZrO_2 were able to promote the ketonization of lauric acid ($C_{12}H_{24}O_2$) in high selectivity (97% at 95% conversion) to the corresponding ketone. Then, to perform a cascade reaction involving a ketonization−hydrogenation−dehydration−hydrogenation sequence (Scheme 21),

Scheme 21. Production of Tricosane from Lauric Acid by Ketonic Decarboxylation−Hydrogenation−-Dehydration−Hydrogenation Sequence[167]



a bifunctional catalytic system bearing basic sites and the hydrogenating function (Pt, Pd, Ru) is required.[167] However, when a cascade process is designed, one has to consider the capacity of the multifunctional catalyst to promote secondary reactions in any of the step in the process, which will decrease the selectivity to the target compound. Particularly in this case, if ketonization and hydrogenation are carried out on a single bifunctional base-metal catalyst, the reductive decarboxylation of the acid on the metal sites can also occur,[168] lowering the performance of the process. To overcome this problem, the cascade process was performed in a double-bed reactor in which the upstream catalyst bed (MgO) is used to perform the ketonization step and the downstream catalyst bed containing either a metal/MgO or a metal/Al_2O_3 is used to achieve the hydrogenation of the resulting ketone. Working at 400 °C and 30 bar hydrogen pressure, the MgO + Pt/MgO system gave the highest yield: up to 70% selectivity to total *n*-alkanes and 58% selectivity to the C_{23} *n*-alkanes at 98.8% conversion, which remained constant during at least 300 min of reaction time. Pd/MgO and Ru/MgO catalysts exhibited lesser catalytic activity in the hydrogenation step, the main product being the ketone. When Pt/Al_2O_3 catalyst was used, the hydrogenation activity was improved, although because of the acidity of alumina, products containing C_{13}−C_{22} *n*-alkanes resulting from the hydrocracking of the hydrocarbon chain were formed in

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considerable amounts. Using the MgO + Pt/Al_2O_3 system, the total yield of C_{10}−C_{23} *n*-alkanes was near 90%.

3.4. Cascade Processes on Bifunctional Acid−Base Catalysts. Acid−base-catalyzed cascade processes on homogeneous catalysts are difficult to perform because of rapid neutralization of the two catalytic functions; however, this can be avoided by putting them on solid carriers and controlling the spatial separation between the two incompatible functional sites.[169] In this sense, a variety of materials bearing acidic and basic sites that are capable of performing cascade reactions have been developed.[25,170] For instance, zeolitic hybrid organic−inorganic materials with acid sites located in the zeolitic counterpart and amino groups in the organic component (MWW-BTEB-NH_2),[171] ordered mesoporous hybrid silicas containing proton sponges as basic sites and sulfonic groups (DMAN-SO_3H-OMS),[172] organic porous materials containing amino and sulfonic groups (PAF-SO_3H-NH_2)[173] or mesoporous silicas with site-isolated amino and phosphotungstic acid groups[174] have been developed. They showed excellent activity in performing a cascade process that involves as a first step the hydrolysis of benzaldehyde dimethyl acetal into benzaldehyde catalyzed by the acid sites, which subsequently reacts with a methylene active compound (catalyzed by the basic sites), such as malononitrile, yielding the Knoevenagel adduct (benzylidene malononitrile) (see Scheme 22 and Table 7). The reaction is performed by mixing both reactants (benzaldehyde dimethyl acetal and malononitrile) and catalyst under mild reaction conditions and in the presence of a small amount of water. Water is necessary to initially promote the hydrolysis step; however, when the successive Knoevenagel condensation takes place, it produces water, which accelerates the hydrolysis of the dimethyl acetal. In addition, these bifunctional catalysts showed excellent recyclability, maintaining their activity during several consecutive cycles. This cascade process has also been performed with excellent success using layered materials bearing acid and basic sites (*H*-montmorillonite−NH_2)[175] and physical mixtures of an acidic layered clay (Ti + 4-montmorillonite) and a basic layered clay (Al−Mg hydrotalcite).[176] This protocol is particularly interesting when the reaction involves aldehydes having α-protons of carbonyl compounds, because this protocol allows one to maintain the concentration of the aldehyde at a low level during the reaction, depressing the self-aldol condensation of the aldehyde.

Metal organic frameworks (MOFs) are promising materials as heterogeneous catalysts because of their tunable pores, their atomistically well-defined structures, their uniformly accessible catalytic centers, and site isolation. In this example, the bifunctional MOF NH_2-MIL-101(Al),[177] with 2-aminoterephthalate ligands and trimeric Al^{3+} octahedral clusters, will catalyze the tandem epoxide ring-opening to aldehydes, followed by a Knoevenagel condensation and subsequent dehydration to 1,1-dicyanoalkene derivatives[178] (Scheme 23).

Scheme 22. One-Pot Hydrolysis of Acetal and Subsequent Knoevenagel Condensation[171−173]

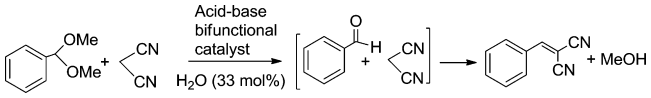
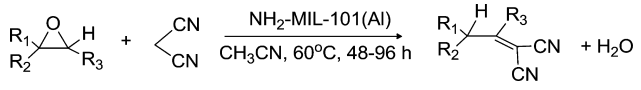


Table 7. Results of the One-Pot Acetal Hydrolysis Followed by Knoevenagel Condensation on Bifunctional Acid−Base Catalysts

cat.	cat. amt (mol %)[a]	solvent	*T* (°C)	*t* (h)	conv.[b] (%)	yield[c] (%)	ref
MWW-BTEB-NH_2	0.1	acetonitrile	82	7	99	96	171
DMAN-SO_3H-OMS[d]	0.1		82	6	100	98	172
PAF-SO_3H-NH_2	10	toluene	90	1	100	100	173

[a]Of basic sites. [b]Conversion of benzaldehyde dimethyl acetal. [c]Yield of Knoevenagel adduct. [d]DMAN is the proton sponge 1,8-bis(dimethylamino)naphthalene. MWW-BTEB-NH_2 is a material prepared by pillaring a MWW layered zeolite precursor with 1,4-bis(triethoxysilyl)benzene (BTEB), in which amino groups have been incorporated. DMAN-SO_3H-OMS is an ordered mesoporous silica containing DMAN and sulfonic groups. PAF-SO_3H-NH_2 is a structured porous polymer containing amino and sulfonic groups.

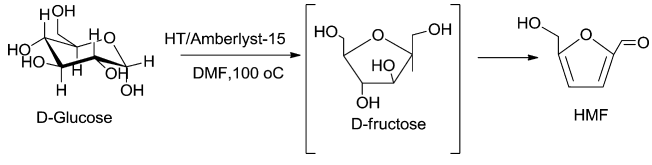
Scheme 23. Epoxide Ring-Opening to Aldehydes Followed by a Knoevenagel Condensation and Subsequent Dehydration Catalized by MOF[178]



The catalyst was recovered by centrifugation, and the pure product was isolated by column chromatography. The structural integrity of the catalyst remained unaffected even after two cycles.

Another catalytic alternative for performing acid−base catalyzed cascade processes involves a physical mixture of a solid acid and a solid base. An interesting example in the area of biomass valorization is the one-pot synthesis of 5-hydroxymethylfurfural (HMF) from glucose. HMF is an interesting biomass-derived molecule, useful as an intermediate for the production of a variety of alternative biofuels and chemicals.[159,179] Whereas HMF can be selectively formed by dehydration of fructose using liquid[180] or solid acid catalysts,[181,182] the reaction is ineffective starting from glucose because considerable amounts of byproducts are produced.[159] Because glucose can be isomerized into fructose using basic catalysts, Takagaki et al.[183] have reported a new one-pot process to obtain HMF directly from glucose. The process involves as the first step the isomerization of glucose into fructose catalyzed by a solid base that in a second step dehydrates to HMF on a solid acid. As a basic catalyst, an Al/Mg hydrotalcite (HT) consisting of layered clays with HCO_3^- groups was selected, and the acid catalyst was an ionic exchange resin bearing sulfonic groups (Amberlyst-15) (Scheme 24).

Scheme 24. Cascade Process for Synthesis of HMF from Glucose[183]



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Reactions were carried out using *N*,*N*-dimethylformamide as a solvent, and both steps occur under the same reaction conditions. However, the base/acid catalyst weight ratio and temperature had to be adjusted to obtain good performances. For instance, 64% conversion of glucose with 38% selectivity to HMF was obtained after 3 h using equal amounts of base solids and acid (0.1g) at 100 °C. However, selectivity could be improved up to 58% (at 73% conversion) by lowering the temperature to 80 °C and increasing the amount of the basic catalyst. Moreover, when the reaction was carried out in a sequential mode, that is, first performing the isomerization in the presence of HT over 2.5 h and then adding the Amberlyst-15, the selectivity of HMF was further improved up to 76% at 60% conversion. In addition, this catalytic system was useful for the direct transformation of disaccharides, such as sucrose and cellobiose, into HMF with high selectivity (see Table 8). In this case, three sequential steps are involved: first hydrolysis of disaccharides by acid sites, followed by isomerization of glucose into fructose by the base and then dehydration of fructose by the acid sites. In this case, it appears that the continuous formation of glucose from the disaccharide hydrolysis avoids side reactions, leading to a higher selectivity to HMF from disaccharides than from monosaccharides. Finally, it was shown that this catalytic system maintains full activity during three consecutive cycles.

Table 8. Results of the One-Pot Synthesis of HMF from Mono- and Disaccharides Using HT and Amberlyst-15 Catalysts[a,183]

substrate		conv (%)	HMF select. (%)
monosaccharide	fructose[b]	>99	76
	glucose[c]	73	58
disaccharide	sucrose[d]	58	93
	cellobiose[d]	52	67

[a]Reaction conditions: substrate (0.1g), HT (0.1g), Amberlyst-15(0.1g), *N*,*N*-dimethylformamide (3 mL). [b]100 °C, 3 h. [c]Using 0.2 g of HT, 80 °C, 9 h. [d]120 °C, 3 h.

More recently, and taking advantage of the excellent activity showed by Sn-Beta zeolite for the isomerization of glucose into fructose,[184,185] a combination of Sn-Beta and an acid catalyst (HCl) have been utilized to produce HMF from sugars (glucose, cellobiose, and starch) with good efficiency in one vessel.[186] In particular HCl and Sn-Beta were combined in aqueous media using single-phase and biphasic reactor systems. The single-phase system was a mixture of glucose, Sn-Beta, and HCl in water, whereas the biphasic system contained an organic phase and an aqueous phase of glucose, HCl, Sn-Beta, and (vs 1-butanol, THF, etc.). The best performances were obtained using this one-pot biphasic water/tetrahydrofuran (THF) reactor system with HMF selectivities over 70% at 180 °C. These results are promising because they demonstrate that Sn-Beta coupled with a homogeneous acid catalyst can be used for converting complex carbohydrates to HMF.

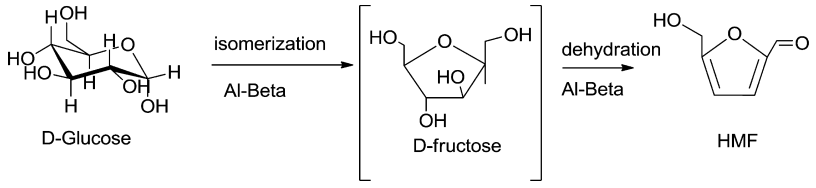
In addition to this, the catalytic performance of Beta zeolites bearing Bronsted and Lewis acid sites in the direct transformation of glucose into HMF through an isomerization/dehydration process has been studied[187] (see Scheme 25). In this case, isomerization of glucose to fructose was promoted by Lewis acid sites through intramolecular hydride transfer, and then fructose was dehydrated to HMF over Brønsted acid sites.

In this case, the effect of calcination and steam treatment on the structure of Al atoms of the Beta zeolite framework, as well as the acid properties, was examined in detail. ^{27}Al-MAS NMR measurement and IR observation revealed that a part of the Si−O−Al bonds in the framework were cleaved to form Al species out of the BEA framework during the treatments, and these species showed Lewis acidity. Especially when the ammonium-type Beta was calcined over 700 °C or treated with steam (50 kPa in N_2 balance) over 500 °C was the amount of Lewis acid sites increased at the expense of Brönsted acid sites. Thus, Beta zeolites having a sufficient number of Lewis and Bronsted acid sites were found to be effective bifunctional catalysts in the synthesis of HMF from glucose. For example, Beta zeolite prepared by the calcination at 750 °C showed 55% selectivity to HMF at 78% conversion of glucose. The mechanism as well as the role of Lewis and Brönsted acid sites on the direct transformation of glucose to HMF was clarified.

Another interesting example in the area of biomass valorization has been recently reported by Fraile et al.[188] It consists of the integrated production of biodiesel and solketal (2,2-dimethyl-4-hydroxymethyl-1,3-dioxolane), a glycerol derivative with a wide variety of applications, using a physical mixture of heterogeneous basic and acid catalysts. The process involves a heterogeneous base-catalyzed transesterification of triglycerides (sunflower oil) with methanol, followed by an acid-catalyzed acetalization of the glycerol formed during the transesterification with acetone promoted by the removal of water through a zeolite membrane (see Scheme 26). The process not only allows direct conversion of glycerol into a valuable and easily distillable compound (the solketal), but the equilibrium of the acetalization process, which is shifted by the membrane, also shifts the first equilibrium (transesterification), thus improving the global efficiency of the process.

The reaction was carried out using 1,5,7-triazabicycle[4.4.0]-dec-5-ene bound to polystyrene (TBD-PS) as the basic catalyst and Nafion NR-50 as the acid catalyst, while a zeolite A membrane grown on the external surface of a cylindrical α-alumina support was utilized to selectively eliminate the water from the reaction media. It was found that the presence of acetone and methanol from the beginning of the reaction was unfavorable to the kinetics of biodiesel formation because of the formation of byproducts coming from self-aldol condensation of acetone and acetalization of acetone with methanol promoted by the basic and acid catalysts, respectively. Then,

Scheme 25. Transformation of Glucose to HMF[187]



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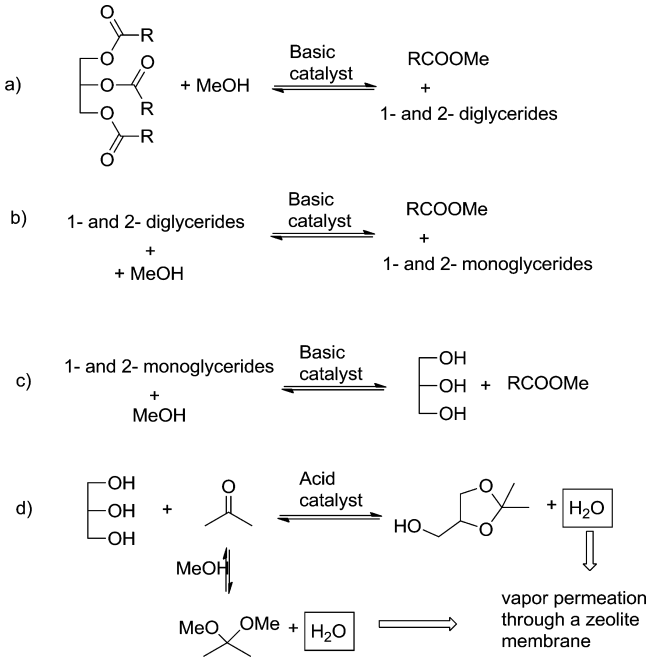
Scheme 26. Integrated Production of Biodiesel and Solketal Using Acid–Base Catalysts[188]

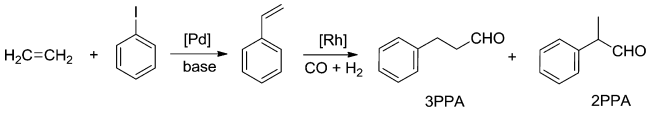


an improved method was to add acetone when the transesterification equilibrium was reached. Under these conditions, a membrane effect was clearly observed, reaching yields of 91% of fatty acid methyl ester and 85% for solketal working with a large excess methanol and acetone (methanol/oil molar ratio of 30/1 and acetone/glycerol molar ratio of 20/1). However, the most interesting aspect of this protocol is that the excess of reagents can be decreased. Indeed, in the absence of a membrane, a decrease in the acetone/glycerol ratio to 5/1 and methanol/oil ratio to 15/1 leads to a 50% yield of the fatty acid methyl ester and 38% yield of solketal, whereas using the membrane, a 90% yield of the methyl ester and an 84% yield of solketal were achieved. This is a clear example showing that the use of membranes to shift the sequential equilibria can considerably improve the performance of the process.

3.5. Cascade Processes on Bimetallic Catalysts. Usually, when two or more transition metal complexes are mixed together, their respective performances tend to decrease by some negative interactions occurring among them. To circumvent this problem, different strategies have been developed in the literature. Among them, the methodology of supported liquid-phase catalyst (SLPC) reported by Davis and co-workers[189] has been successfully applied to a Heck/hydroformylation sequential process for the synthesis of aldehydes (Scheme 27).[190]

The SLPC methodology consists basically of a thin hydrophilic liquid film, which contains such organometallic complexes supported on solids of high surface area. The SLPC will require the use of hydrophobic solvent that will not dissolve the film, being easily separated by simple filtration, and recycled (Figure 4).[189]

Scheme 27. Sequential Process Consisting of a Heck Coupling, Followed by Hydroformylation[190]



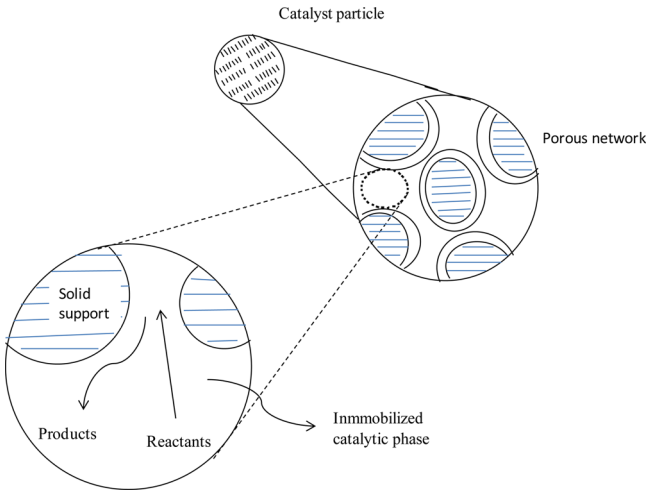


Figure 4. Schematic diagram of supported aqueous-phase catalyst.[189]

In addition to the obvious benefit for the catalyst separation and recycling, the SLPC methodology will keep two different supported catalysts separated, hence avoiding any interactions between them. The advantage of this concept has been corroborated by supporting two different metal complexes, such as Pd-SLPC and Rh-SLPC.[190] In that work, both catalysts remained separated by the solvent and any interactions between them occurred. This catalytic model system was applied to the Heck reaction, followed by subsequent hydroformylation in a single-pot process (Scheme 24).[190] Pd-SLPC and Rh-SLPC catalyzed the first and second steps, respectively.

In a first step, styrene was formed via Heck reaction from iodobenzene and ethylene. Then syngas (CO/H_2) was incorporated, and the hydroformylation took place under different reaction conditions to produce 3-phenylpropionaldehyde (3PPA) and 2-phenylpropionaldehyde (2PPA).

Results included in Table 9 show that the yields of the aldehydes 2PPA and 3PPA significantly decreased by using (Pd + Rh)-SLPC. The aforementioned catalyst was prepared from an ethylene glycol solution that contained the homogeneous catalysts palladium triphenylphosphine trisulfonate trisodium

Table 9. Sequential Heck Reaction of Iodobenzene and Ethylene and Hydroformylation of Styrene[a,190]

	Heck reaction	hydroformylation[b]		
	yield (%)	yield (%)		
catalyst	styrene	3PPA	2PPA	3PPA:2PPA
Pd-SLPC + Rh-SLPC	50.5	29.6	60.3	0.49
(Pd + Rh)-SLPC[c]	68.6	6.4	17.8	0.36

[a]Reaction conditions: ethylene glycol (0.3 mL), silica (0.5g), toluene (20 mL), ethylene (4 MPa), iodobenzene (5 mmol), triethylamine (5 mmol); CO (3 MPa), H_2 (3 MPa), 100 °C; time: 45 h (Heck), 6 h (hydroformylation). [b]Yields are based on the amount of **1** formed in the Heck reaction. [c]The catalyst was prepared from an ethylene glycol solution containing both Pd-TPPTS (palladium triphenylphosphine trisulfonate trisodium salt) and Rh-TPPTS (rhodium triphenylphosphine trisulfonate trisodium salt).

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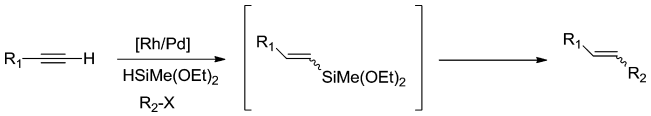
salt (Pd-TPPTS) and rhodium triphenylphosphine trisulfonate trisodium salt (Rh-TPPTS) in the same film on a silica gel.

Curiously, the Heck reaction was not influenced by the presence of both catalysts Rh and Pd in the same liquid film ((Pd + Rh)-SLPC in ethylene glycol), but the hydroformylation activity significantly lowered when both catalyst were included in the same system (Table 9). In addition the *n*/iso ratio (3PPA/2PPA) of the aldehydic compounds varied by the catalytic system used.

The results included in the table show that the efficient application of two homogeneous catalysts retaining their individual activities is possible by means of this methodology. Moreover, the concept of a multifunctional catalyst using different SLPC systems has wide applicability because it allows using two or more metal complexes in the SLPC form, apparently in any type of combination. Nothing is reported about plausible metal leaching and reusability experiments in this one-pot reaction.

In this last example, the concept of compartmentation of enzymes or biocatalysts occurring in Nature has been originally applied to a bimetallic-catalyzed reaction through immobilization of both active centers on an unexpected media. This is the case of the bimetallic catalyst [Rh−Pd], which has been immobilized on a polyionic gel and has been applied successfully to the obtention of (*E*)-alkenes through a one-pot process involving a hydrosilylation/Hiyama cross-coupling (Scheme 28).[191]

Scheme 28. One-Pot Hydrosilylation/Coupling Reaction[191]

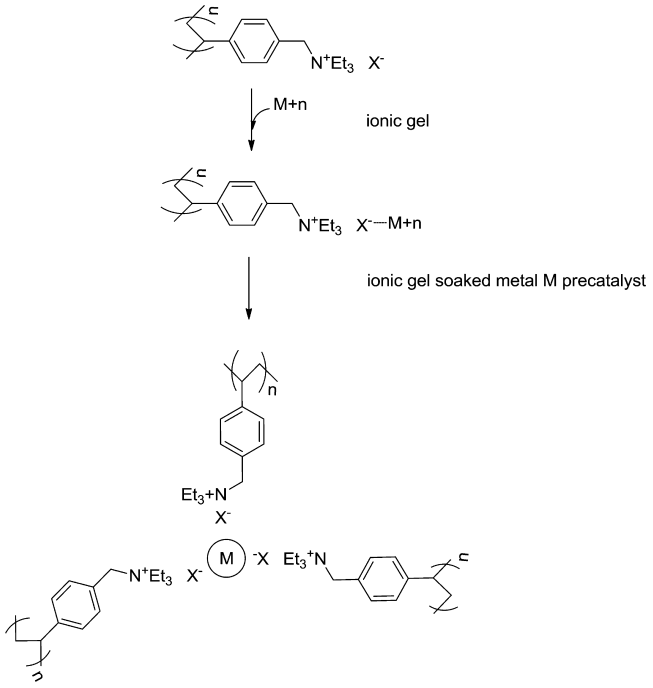


The bimetallic catalyst was prepared by using an ion-exchange resin, or polyionic gel provided the ability of this material to act as an effective heterogeneous media as a metal scavenger, as described by Thiot et al.[192] Indeed, polyionic gel beads will constitute a highly polar environment suitable for efficient metal scavenging and for heterogeneous catalyst preparation. Scheme 29 shows a schematic representation of the synthesis of metal loaded polyionic gel.

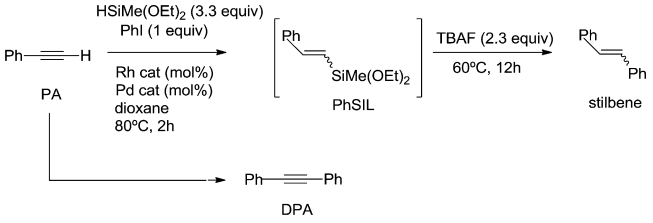
The properties of polyionic gels were exploited in this case by means of a bimetallic [Rh−Pd] catalyst. The bimetallic Rh−Pd catalyst was easily prepared by soaking it in an iodide ionic gel consisting of equimolar amounts of $Pd(OAc)_2$ and $RhCl(PPh_3)_3$ in CH_2Cl_2 to give the catalyst PL-1. Meanwhile, two other polyionic−based catalysts (PL-2 and PL-3) loaded with Rh and Pd, respectively, were also prepared by following this methodology (Scheme 29). Then the catalytic activity was evaluated in the sequential hydrosilylation/Hiyama cross-coupling of a series of terminal alkynes to (*E*)-alkenes (Scheme 30). In particular, the hydrosilylation/Hiyama coupling of phenylacetylene with catalyst PL-1 gave a very high stereo- and chemoselectivity to the corresponding (*E*)-alkene, thus giving very good yields of stilbene (entry 1, Table 10).

In addition, the bimetallic ionic gel (Rh−Pd) PL-1, which became remarkably dark orange after preparation, did not show any bleaching in the control experiments, illustrating the high affinity of these ionic gels for metal precursors. The (Rh−Pd) heterogeneous system PL-1 also exhibited much higher chemoselectivity than a mixture of homogeneous catalysts

Scheme 29. Schematic Representation of the Synthesis of a Polyionic Gel−Metal Heterogeneous Catalyst (PL)[192]



Scheme 30. Sequential Hydrosilylation/Hiyama Cross-Coupling[191]



$RhCl(PPh_3)_3$ and $Pd(OAc)_2$, provided no formation of Sonogashira side product could be detected with the bifunctional catalyst PL-1 (entries 1 and 2, Table 10). For comparison, a mixture of both polyionic gel systems prepared separately, PL-2 and PL-3, gave exclusively the (*E*)-alkene as the only product with complete conversion (entry 3, Table 10).

The high chemoselectivity of catalyst PL-1 (hydrosilylation versus Sonogashira reaction) was interpreted as due to a slower Sonogashira side coupling reaction when using the polyionic gel. In fact, competition between the Sonogashira and hydrosilylation reactions was remarkably high with the homogeneous systems (Table 10), whereas hydrosilylation was faster in the polyionic gel PL-1.

On the other hand, the remarkable stereocontrol was ascribed to a beneficial Pd-catalyzed isomerization from (*Z*)-PhSIL into the more stable *E* isomer obtained in the initial hydrosilylation step. Finally, the catalyst could be reused, displaying complete stereoselectivity to the *E* isomer, albeit a gradual decrease in yield was observed.

Another one-pot process recently reported using bifunctional metal organic framework (MOF) catalyst is the one-pot Sonogashira/click reaction from 2-iodobenzylbromide, sodium azide, and alkynes to produce 8*H*-[1,2,3]triazolo[5,1-*a*]-isoindoles[193] (Scheme 31). In this case, a bifunctional metal organic framework (MOF) containing palladium and copper-

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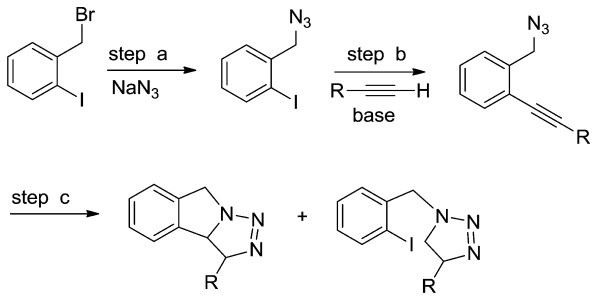
Table 10. Sequential Hydrosilylation/Coupling Reaction of Phenylacetylene[a,191]

entry	cat.	Rh/Pd (mol %)[b]	yield (%)[c]	stilbene (*E*/*Z*)[d]	DPA
1	PL-1	3.3: 9.0	>99	100 (>99:1)	0
2	$RhCl(PPh_3)_3/Pd(OAc)_2$, NaI[e]	3.3: 9.0	>99	43 (89:11)	57
3	PL-2/PL-3	2.7: 4.9	>99	100 (99:1)	0

[a]Reaction conditions: phenylacetylene, $HSiMe(OEt)_2$, PhI, catalyst, dioxane, 60 °C, 2 h. [b]Determined by elemental analysis. [c]Determined by GC/MS. [d]Values determined from the ^1H NMR spectrum of the crude reaction mixture. [e]NaI (1.6 equiv).

Scheme 31. Sonogashira/Click Reaction Starting from Sodium Azide, Alkynes and 2-Iodobenzylbromide[193]



(II) benzene-1,3,5-tricarboxylate-MOF-Cu(BTC)-[Pd] was prepared starting from $Cu_3(BTC)_2$ (BTC = benzene-1,3,5-tricarboxylate).[193] The presence of copper(II) in Cu_3BTC_2[194,195] will provide an intrinsic chelating property with electron-rich functional groups because it will lead to the formation of stable pyridine rings grafted onto the surface. This will provide the possibility to coordinate an additional metal complex (for example, by reaction of $Cu_3(BTC)_2$ with aminopyridine compounds and $PdCl_2(PhCN)_2$), leading to a pyridine-Pd-grafted CuBTC bifunctional catalyst.

Isoindolines are valuable molecules because of their diverse biological activity and clinical applications.[196−198] Similarly, the triazole nucleus is a structure found in a large number of compounds with anti-HIV, antimicrobial, and antibacterial activity.[199−201]

Once the bifunctional MOF was prepared and characterized, the reaction conditions were adjusted so that the experimental conditions were not varied during both reaction steps: 2 equiv K_2CO_3, 5 mol % catalyst, and 50 °C. Then, by changing the terminal alkyne, it was observed that the reaction was applicable to both aliphatic and aromatic acetylenes. Albeit the recyclability experiments showed that some leaching of Pd occurred together with CuBTC, most of the reaction still came from the heterogeneous MOF. The present study ensures the development and application of newly functionalized materials through the incorporation of organic molecules and the formation of transition metal complexes.

4. SUMMARY AND FUTURE OUTLOOK

In this Viewpoint, we have briefly emphasized the utility of one-pot processes through several representative examples of transformations carried out with mono- and multifunctional catalytic systems that have appeared in recent literature references.

The case of a unique catalytic system that performs the whole synthetic sequence has been elegantly applied to the production of alkyl glucosides starting from cellulose, the fragrance 4-methoxybenzyl 1-methylpropyl ether, glycerol derivatives, pyrrolidones, azobenzenes, etc., through efficient two-step processes with minimum changes in the reaction conditions. When this has not been possible, bifunctional catalysts have been applied to the simultaneous activation of substrates and reagents in different Lewis/Brönsted acid-, acid/base-, metal/base-, metal/acid-, or metal/metal-catalyzed processes, making possible multiple reactions in one pot. In this way, it has been possible to synthesize aldehydes, (*E*)-alkenes, furan and pyran hydroxyethers, the nonsteroidal anti-inflammatory Nabumetone, alkanes, etc.

Although the one-pot methodology has highly promising aspects for designing complex synthetic sequences, in practice, this methodology is still poorly exploited, surely because there are no definite rules for anticipating interactions and incompatibilities arising among the components involved in each reaction step. In fact, it is rather common to rely on the expertise and intuition of researchers for conducting these processes on the bases of a trial and error method.

Hence, despite the significant developments recently achieved in this field, the direct implementation of a one-pot process for synthesizing a desired molecule is still in the early stages so that future developments will require not only a more systematic design characterization and deep knowledge of a versatile catalyst but also a very thorough understanding of the physical−chemical features of the catalyst and reaction mechanisms to design more efficient processes with these complex catalytic systems.

■ ASSOCIATED CONTENT

Supporting Information

Summary of the most relevant information regarding the one-pot reactions presented in this Viewpoint. This information is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Climent, M. J.; Corma, A.; Iborra, S. *Chem. Rev.* **2011**, *111*, 1072.
(2) Climent, M. J.; Corma, A.; Iborra, S. *RSC Adv.* **2012**, *2*, 16.
(3) Khosla, C. *Chem. Rev.* **1997**, *97*, 2577.
(4) Leadlay, P. F. *Curr. Opin. Chem. Biol.* **1997**, *1*, 162.
(5) Staunton, J.; Wilkinson, B. *Chem. Rev.* **1997**, *97*, 162.
(6) Staunton, J.; Wilkinson, B. *Chem. Rev.* **1997**, *97*, 2611.
(7) Towsend, C. A. *Chem. Biol.* **1997**, *4*, 721.
(8) Calemma, V.; Peratello, S.; Perego, C. *Appl. Catal., A* **2000**, *190*, 207.

(9) Lónyi, F.; Kovács, A.; Szegedi, A.; Valyon, J. *J. Phys.Chem. C* **2009**, *113*, 10527.
(10) Corma, A. *Chem. Rev.* **1995**, *95*, 559.
(11) Derouane, E. G. *Catalysis for Fine Chemical Synthesis. Microporous and Mesoporous Solid Catalysts*; John Wiley & Sons Ltd.: Chichester, 2006, Vol. *4*.
(12) Fameth, W. E.; Gorte, R. J. *Chem. Rev.* **1995**, *95*, 615.
(13) Corma, A. *Chem. Rev.* **1997**, *97*, 2373.
(14) van Santen, R. A.; Kramer, G. J. *Chem. Rev.* **1995**, *95*, 637.
(15) Qiao, Y.; Hou, Z. *Curr. Org. Chem.* **2009**, *13*, 1347.
(16) Dupre, N.; Remy, P.; Micoine, K.; Boglio, C.; Thorimbert, S.; Lacote, E.; Hasenknopf, B.; Malacria, M. *Chem.—Eur. J.* **2010**, *16*, 7256.
(17) Busca, G. *Chem. Rev.* **2007**, *107*, 5366.
(18) Harmer, M. A.; Sun, Q. *Appl. Catal., A* **2001**, *221*, 45.
(19) Buttersack, C. *React. Polym.* **1989**, *10*, 143.
(20) Wee, L. H.; Alaerts, L.; Martens, J. A.; De Vos, D. *Met.-Org. Frameworks* **2011**, 191.
(21) Corma, A.; Garcia, H.; Xamena, F. X. L. I. *Chem. Rev.* **2010**, *110*, 4606.
(22) Suganuma, S.; Nakajima, K.; Kitano, M.; Yamaguchi, D.; Kato, H.; Hayashi, S.; Hara, M. *J. Am. Chem. Soc.* **2008**, *130*, 12787.
(23) Onda, A.; Ochi, T.; Yanagisawa, K. *Green Chem.* **2008**, 1013.
(24) Diaz, I.; Mohino, F.; Blasco, T.; Sastre, E.; Perez-Pariente, J. *Microporous Mesoporous Mater.* **2005**, *80*, 33.
(25) Diaz, U.; Brunel, D.; Corma, A. *Chem. Soc. Rev.* **2013**, *42*, 4083.
(26) Dufaud, V.; Davis, M. E. *J. Am. Chem. Soc.* **2003**, *125*, 9403.
(27) Alvaro, M.; Corma, A.; Das, D.; Fornes, V.; Garcia, H. *J. Catal.* **2005**, *231*, 48.
(28) von Rybinski, W.; Hill, K. *Angew. Chem., Int. Ed.* **1998**, *37*, 1328.
(29) Hughes, F. A.; Lew, B. W. *J. Am. Oil Chem. Soc.* **1970**, *47*, 162.
(30) Huang, Y.-B.; Fu, Y. *Green Chem.* **2013**, *15*, 1095.
(31) Swatloski, R. P.; Spear, S. K.; Holbrey, J. D.; Rogers, R. D. *J. Am. Chem. Soc.* **2002**, *124*, 4974.
(32) Pinkert, A.; Marsh, K. N.; Pang, S. S.; Staiger, M. P. *Chem. Rev.* **2009**, *109*, 6712.
(33) Li, C. Z.; Zhao, Z. K. B. *Adv. Synth. Catal.* **2007**, *349*, 1847.
(34) Rinaldi, R.; Palkovits, R.; Schuth, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8047.
(35) Villandier, N.; Corma, A. *Chem. Commun.* **2010**, *46*, 4408.
(36) Brady, S. F.; Wagenaar, M. M.; Sing, H. P.; Janso, J. E.; Clardy, J. *Org. Lett.* **2000**, *2*, 4043.
(37) Paradkar, M. V.; Gadre, S. Y.; Pujari, T. A.; Khandekar, P. P.; Kumbhar, V. B. *Synt. Commun.* **2005**, *35*, 471.
(38) Safari, J.; Naeimi, H.; Khakpour, A. A.; Jondani, R. S.; Khalili, S. D. *J. Mol. Catal.* **2007**, *270*, 236.
(39) Mal, D.; Pahari, P.; De, S. R. *Tetrahedron* **2007**, *63*, 11781.
(40) Pahari, P.; Senapati, B.; Mal, D. *Tetrahedron Lett.* **2004**, *45*, 5109.
(41) Pinto, D. C. G. A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Elguero, J. *Eur. J. Org. Chem.* **2003**, *4*, 747.
(42) Landge, S. M.; Berryman, M.; Toeroek, B. *Tetrahedron Lett.* **2008**, *49*, 4505.
(43) Perego, C.; Carati, A.; Ingallina, P.; Mantegazza, M. A.; Bellussi, G. *Appl. Catal., A* **2001**, *221*, 63.
(44) Blasco, T.; Camblor, M. A.; Corma, A.; Esteve, P.; Guil, J. M.; Martinez, A.; Perdigon-Melon, J. A.; Valencia, S. *J. Phys. Chem. B* **1998**, *102*, 75.
(45) Corma, A.; Navarro, M. T.; Pariente, J. P. *J. Chem. Soc.Chem. Comm.* **1994**, 147.
(46) Corma, A.; Diaz, U.; Domine, M. E.; Fornes, V. *Angew. Chem., Int. Ed.* **2000**, *39*, 1499.
(47) Wu, P.; Tatsumi, T. *Chem. Commun.* **2001**, 897.
(48) Moliner, M.; Serna, P.; Cantin, A.; Sastre, G.; Diaz-Cabanas, M. J.; Corma, A. *J. Phys. Chem. C* **2008**, *112*, 19547.
(49) Corma, A.; Nemeth, L. T.; Renz, M.; Valencia, S. *Nature* **2001**, *412*, 423.
(50) Zhu, Y.; Chuah, G.; Jaenicke, S. *J. Catal.* **2004**, *227*, 1.
(51) Corma, A.; Xamena, F. X.; Prestipino, C.; Renz, M.; Valencia, S. *J. Phys. Chem. C* **2009**, *113*, 11306.
(52) Zhu, Y. Z.; Liu, S. H.; Jaenicke, S.; Chuah, G. *Catal. Today* **2004**, *97*, 249.
(53) Boronat, M.; Corma, A.; Renz, M. *J. Phys. Chem. B* **2006**, *110*, 21168.
(54) Corma, A.; Domine, M. E.; Nemeth, L.; Valencia, S. *J. Am. Chem. Soc.* **2002**, *124*, 3194.
(55) Corma, A.; Domine, M. E.; Valencia, S. *J. Catal.* **2003**, *215*, 294.
(56) Bauer, K.; Garbe, D.; Suburg, H. *Common Fragrance and Flavor Materials*; Wiley-VCH: Weinheim, 1997; p 128.
(57) Corma, A.; Renz, M. *Angew.Chem., Int. Ed.* **2007**, *46*, 298.
(58) Sels, B. F.; De Vos, D. E.; Jacobs, P. A. *Catal. Rev.* **2001**, *43*, 443.
(59) Tichit, D.; Corma, A.; Iborra, S.; Brunel, D., Base-Type Catalysis. In *Catalysts for Fine Chemicals Synthesis. Microporous and Mesoporous Solid Catalysts*; Derouane, E., Ed.; Wiley & Sons Ltd: Lisbon, 2006; Vol. *4*; p 171.
(60) Ono, Y.; Baba, T. *Catal. Today* **1997**, *38*, 321.
(61) Weitkamp, J.; Hunger, M.; Rymsa, U. *Microporous Mesoporous Mater.* **2001**, *48*, 255.
(62) Hattori, H. *Chem. Rev.* **1995**, *95*, 537.
(63) Chen, L.; Zhao, J.; Yin, S.-F.; Au, C.-T. *RSC Adv.* **2013**, *3*, 3799.
(64) Corma, A.; Iborra, S. *Adv. Catal.* **2006**, *49*, 239.
(65) Cavani, F.; Trifiro, F.; Vaccari, A. *Catal. Today* **1991**, *11*, 173.
(66) Vaccari, A. *Catal. Today* **1998**, *41*, 53.
(67) Climent, M. J.; Corma, A.; Fornes, V.; Frau, A.; Guil-Lopez, R.; Iborra, S.; Primo, J. *J. Catal.* **1996**, *163*, 392.
(68) Corma, A.; Fornes, V.; Martin-Aranda, R. M.; Garcia, H.; Primo, J. *Appl. Catal.* **1990**, *59*, 237.
(69) Gokhale, U. V.; Seshadri, S. *Dyes Pigm.* **1986**, *7*, 389.
(70) Dworczak, R.; Fabian, W. M. F.; Pawar, B. N.; Junek, H. *Dyes Pigm.* **1995**, *29*, 65.
(71) Fabian, W. M. F.; Dworczak, R.; Junek, H.; Pawar, B. N. *J. Chem. Soc., Perkin Trans.* **1995**, *2*, 903.
(72) Mowry, D. T. *J. Am. Chem. Soc.* **1945**, *67*, 1050.
(73) Climent, M. J.; Corma, A.; Guil-Lopez, R.; Iborra, S. *Catal. Lett.* **2001**, *74*, 161.
(74) Bai, R.; Zhang, H.; Mei, F.; Wang, S.; Li, T.; Gu, Y.; Li, G. *Green Chem.* **2013**, *15*, 2929.
(75) Pagliaro, M.; Ciriminna, R.; Kimura, H.; Rossi, M.; Della Pina, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 4434.
(76) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.
(77) Sunder, A.; Mulhaupt, R.; Haag, R.; Frey, H. *Adv. Mater.* **2000**, *12*, 235.
(78) Wu, P.; Tatsumi, T. *J. Catal.* **2003**, *214*, 317.
(79) Bolivar-Diaz, C. L.; Calvino-Casilda, V.; Rubio-Marcos, F.; Fernandez, J. F.; Banares, M. A. *Appl. Catal., B* **2013**, *129*, 575.
(80) Uno, M.; Okutsu, M. U.S. PatentUS 7888517, 2011.
(81) Liu, X. M.; Chu, Z. N.; Liu, Z. W. *Chem. Ind. Eng. Prog.* **2009**, *28*, 1445.
(82) Climent, M. J.; Corma, A.; De Frutos, P.; Iborra, S.; Noy, M.; Velty, A.; Concepcion, P. *J. Catal.* **2010**, *269*, 140.
(83) Ochoa-Gomez, J. R.; Gomez-Jimenez-Aberasturi, O.; Ramirez-Lopez, C.; Maestro-Madurga, B. *Green Chem.* **2012**, *14*, 3368.
(84) Gade, S. M.; Munshi, M. K.; Chherawalla, B. M.; Rane, V. H.; Kelkar, A. A. *Catal. Commun.* **2012**, *27*, 184.
(85) Manzer, L. E. U.S. Patent US 6818593, 2004.
(86) Manzer, L. E. U.S. Patent US 6855731, 2005.
(87) Werpy, T.; Frye, J. G.; Wang, Y.; Zacher, H. U.S. Patent US 6670483, 2004.
(88) Schwarz, W., Schossig, J.; Rossbacher, R., Höke, H., Eds.; *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley Interscience: Weinheim, 2000.
(89) Budroni, G.; Corma, A. *J. Catal.* **2008**, *257*, 403.
(90) Budge, J. R.; Atting, T. G.; Graham, A. M. U.S. Patent US 5149836, 1993.
(91) Castiglioni, G. L. *Catal. Today* **1996**, *27*, 181.
(92) Conway, S. J.; Lundsford, J. H. *J. Catal.* **1991**, *131*, 512.

(93) de Thomas, W.; Taylor, P. D.; Tomfohrde, H. F. U.S. Patent US 5149836,1992.
(94) Herrmann, U.; Emig, E. *Chem. Eng. Technol.* **1998**, *21*, 285.
(95) Herrmann, U.; Emig, G. *Ind. Eng. Chem. Res.* **1997**, *36*, 2885.
(96) Kuksal, A.; Klemm, E.; Emig, G. *Appl. Catal., A* **2002**, *228*, 237.
(97) Messori, M.; Vaccari, A. *J. Catal.* **1994**, *150*, 177.
(98) Hara, Y.; Husaka, H.; Inagaki, H.; Takahashi, K.; Wada, K. *J. Catal.* **2000**, *194*, 188.
(99) Jung, S. M.; Godard, E.; Jung, S. Y.; Park, R. C.; Choi, J. U. *Catal. Today* **2003**, 171.
(100) Jung, S. M.; Godard, E.; Jung, S. Y.; Park, K.-C.; Choi, J. U. *J. Mol. Catal. A: Chem* **2003**, *198*, 297.
(101) Pillai, U. R.; Shale-Demessie, E. *Chem. Commun.* **2002**, *5*, 422.
(102) Rudloff, M.; Stops, P.; Henkes, E.; Schmidtke, H.; Fischer, R. H.; Julius, M.; Lebkücher, R.; Ross, K. H. EP 2002/012804, 2007.
(103) Boulton, A. A.; Davis, B. A.; Durden, D. A.; Dyck, L. E.; Juorio, A. V.; Li, X. M.; Paterson, I. A.; Yu, P. H. *Drug Rev. Res.* **1997**, *42*, 150.
(104) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.
(105) Naota, I.; Takaya, H.; Murahashi, S. I. *Chem. Rev.* **1998**, *98*, 2599.
(106) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968.
(107) Jung, M. E.; Huang, A. *Org. Lett.* **2000**, *2*, 2659.
(108) Corma, A.; Navas, J.; Sabater, M. J. *Chem.—Eur. J.* **2012**, *18*, 14150.
(109) Corma, A.; Zhang, X. *Angew.Chem. Int. Ed.* **2008**, *47*, 4358.
(110) Egli, R. *Colour Chemistry: The Design and Synthesis of Organic Dyes and Pigments*; Elsevier: London, 1991.
(111) Catino, S. C.; Farris, E. *Concise Encyclopedia of Chemical Technology*; Wiley: New York, 1985.
(112) Venkataraman, K. *The Chemistry of Synthetic Dyes*; Academic Press: London, 1970.
(113) Grirrane, A.; Corma, A.; Garcia, H. *Science* **2008**, *322*, 1661.
(114) Enache, D. I.; Edwards, J. K.; Landon, P.; Solsona-Espriu, B.; Carley, A. F.; Herzing, A. A.; Watanabe, M.; Kiely, C. J.; Knight, D. W.; Hutchings, G. J. *Science* **2006**, *311*, 362.
(115) Corma, A.; Serna, P. *Science* **2006**, *313*, 332.
(116) Climent, M. J.; Corma, A.; Iborra, S.; Martinez-Silvestre, S. *ChemCatChem* **2013**, *5*, 3866.
(117) Novellino, E.; Cosimelli, B.; Ehlardo, M.; Greco, G.; Ladanza, M.; Lavecchia, A.; Rimoli, M. G.; Sala, A.; Da Settimo, A.; Primofiore, G.; Da Settimo, F.; Taliani, S.; La Motta, C.; Klotz, K. N.; Tuscano, D.; Trincavelli, M. L.; Martini, C. *J. Med. Chem.* **2005**, *48*, 8253.
(118) Mamedov, V. A.; Zhukova, N. A.; Beschastnova, T. N.; Gubaidullin, A. T.; Balandina, A. A.; Latypov, S. K. *Tetrahedron Lett.* **2010**, *66*, 9745.
(119) Kalinin, A. A.; Isaikina, O. G.; Mamedov, V. A. *Chem. Heterocycl. Compd.* **2007**, *43*, 1307.
(120) Corma, A.; Iglesias, M.; Sanchez, F. *J. Chem. Soc., Chem. Commun.* **1995**, 1635.
(121) Bui, L.; Luo, H.; Gunther, W. R.; Roman-Leshkov, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 8022.
(122) Bond, J. Q.; Alonso, D. M.; Wang, D.; West, R. M.; Dumesic, J. A. *Science* **2010**, *327*, 1110.
(123) Bozell, J. J. *Science* **2010**, *329*, 522.
(124) Horvath, I. T.; Mehdi, H.; Fabos, V.; Boda, L.; Mika, L. T. *Green Chem.* **2008**, *10*, 238.
(125) Lange, J. P.; Price, R.; Ayoub, P. M.; Louis, J.; Petrus, L.; Clarke, L.; Gosselink, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 4479.
(126) Wrigth, W. R. H.; Palkovits, R. *ChemSusChem* **2012**, *5*, 1657.
(127) Alonso, D. M.; Wettstein, S. G.; Dumesic, J. A. *Green Chem.* **2013**, *15*, 584.
(128) Braden, D. J.; Henao, C. A.; Heltzel, J.; Maravelias, C. C.; Dumesic, J. A. *Green Chem.* **2011**, *13*, 3505.
(129) Sen, S. M.; Alonso, D. M.; Wettstein, S. G.; Gurbuz, E. I.; Henao, C. A.; Dumesic, J. A.; Maravelias, C. T. *Energy Environ. Sci.* **2012**, *5*, 9690.
(130) Heeres, H.; Handana, R.; Chunai, D.; Rasrendra, C. B.; Girisuta, B.; Heeres, H. J. *Green Chem.* **2009**, *11*, 1247.
(131) Kopetzki, D.; Antonietti, M. *Green Chem.* **2010**, *12*, 656.
(132) Lange, J. P.; van de Graaf, W. D.; Haan, R. J. *ChemSusChem* **2009**, *2*, 437.
(133) Gounder, R.; Davis, M. E. *AIChE J.* **2013**, *59*, 3349.
(134) Xing, R.; Qi, W.; Huber, G. W. *Energy Environ. Sci.* **2011**, *4*, 2193.
(135) Camblor, M. A.; Corma, A.; Iborra, S.; Miquel, S.; Primo, J.; Valencia, S. *J. Catal.* **1997**, *172*, 76.
(136) Biswas, J.; Maxwell, I. E. *Appl. Catal.* **1990**, *63*, 197.
(137) Nie, Y.; Jaenicke, S.; Van Bekkum, H.; Chuah, G. K. *J. Catal.* **2007**, *246*, 223.
(138) Creyghton, E. J.; Ganeshie, S. D.; Downing, R. S.; van Bekkum, H. *J. Mol. Catal. A: Chem.* **1997**, *115*, 457.
(139) Randall, L. O.; Kappel, B. *Benzodiazepines*; Ravpan Press: New York, 1973; p 27.
(140) Grossi, G.; Di Braccio, M.; Roma, G.; Ballabeni, V.; Tognolini, M.; Calcina, F.; Barocelli, E. *Eur. J. Med. Chem.* **2002**, *37*, 933.
(141) Ried, W.; Stahlhofen, P. *Chem. Ber.* **1957**, *90*, 815.
(142) Ried, W.; Torinus, E. *Chem. Ber.* **1957**, *92*, 2902.
(143) Werner, W.; Jungstand, W.; Gutsche, W.; Wohlrabe, K.; Romer, W.; Tresselt, D. *Pharmazie* **1979**, *34*, 394.
(144) Climent, M. J.; Corma, A.; Iborra, S.; Santos, L. L. *Chem.—Eur. J.* **2009**, *15*, 8834.
(145) Corma, A.; Serna, P.; Concepcion, P.; Calvino, J. *J. Am. Chem. Soc.* **2008**, *130*, 8748.
(146) Corma, A.; Concepcion, P.; Serna, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7266.
(147) Santos, L. L.; Serna, P.; Corma, A. *Chem.—Eur. J.* **2009**, *15*, 8196.
(148) Gondie, A. C.; Gaster, L. M.; Lake, A. W.; Rose, C. J.; Freeman, P. C.; Hughes, B. O.; Miller, D. J. *J. Med. Chem.* **1978**, *21*, 1260.
(149) Lai, C. S.; Wang, T. U.S. Patent US 2003220468, 2003.
(150) Fritch, J. R.; Aslam, M.; Rios, D. E.; Smith, J. C. Patent WO 9640608, 1996.
(151) Aslam, M.; Elango, V. U.S. Patent US 5225603, 1993.
(152) Climent, M. J.; Corma, A.; Iborra, S.; Mifsud, M. *J. Catal.* **2007**, *247*, 223.
(153) Boudart, M. *Chem. Rev.* **1995**, *95*, 661.
(154) Shiozaki, S.; Senuma, M.; Furumai, S.; Kawashima, H. Patent EP 16650, 1980.
(155) Rollin, P. *Bull. Soc. Chim. Fr.* **1973**, *4*, 1509.
(156) Climent, M. J.; Corma, A.; Iborra, S.; Mifsud, M.; Velty, A. *Green Chem.* **2010**, *12*, 99.
(157) Zhou, C. H.; Xia, X.; Lin, C. X.; Tong, D. S.; Beltramini, J. *Chem. Soc. Rev.* **2011**, *40*, 5588.
(158) Alonso, D. M.; Bond, J. Q.; Dumesic, J. A. *Green Chem.* **2010**, *12*, 1493.
(159) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411.
(160) Carrasquillo-Flores, R.; Kaeldstroem, M.; Schuth, F.; Dumesic, J. A.; Rinaldi, R. *ACS Catal.* **2013**, *3*, 993.
(161) Meine, N.; Rinaldi, R.; Schuth, F. *ChemSusChem* **2012**, *5*, 1449.
(162) Rinaldi, R.; Engel, P.; Buechs, J.; Spiess, A. C.; Schueth, F. *ChemSusChem* **2010**, *3*, 1151.
(163) Huber, G. W.; Iborra, S.; Corma, A. *Chem. Rev.* **2006**, *106*, 4044.
(164) Climent, M. J.; Corma, A.; Hernandez, J. C.; Hungria, A. B.; Iborra, S.; Martinez-Silvestre, S. *J. Catal.* **2012**, *292*, 118.
(165) Renz, M. *Eur. J. Org. Chem.* **2005**, 979.
(166) Pulido, A.; Oliver-Tomas, B.; Renz, M.; Boronat, M.; Corma, A. *ChemSusChem* **2013**, *6*, 141.
(167) Corma, A.; Renz, M.; Schaverien, C. *ChemSusChem* **2008**, *1*, 739.
(168) Mäki-Arvela, P.; Kubickova, I.; Snare, M.; Eränen, M.; Murzin, D. Y. *Energy Fuels* **2007**, *21*, 30.
(169) Boronat, M.; Climent, M. J.; Corma, A.; Iborra, S.; Monton, R.; Sabater, M. J. *Chem.—Eur. J.* **2010**, *16*, 1221.

(170) Li, H.; Wu, H.; Zhang, Q.; Liu, J.; Liu, X.; Liu, Y.; Yang, S. *Curr. Catal.* **2013**, *2*, 173.
(171) Corma, A.; Diaz, U.; Garcia, T.; Sastre, G.; Velty, A. *J. Am. Chem. Soc.* **2010**, *132*, 15011.
(172) Gianotti, E.; Diaz, U.; Velty, A.; Corma, A. *Catal. Sci. Technol.* **2013**, *3*, 2677.
(173) Merino, E.; Verde-Sesto, E.; Maya, E. M.; Iglesias, M.; Sanchez, F.; Corma, A. *Chem. Mater.* **2013**, *25*, 981.
(174) Shiju, N. R.; Alberts, A. H.; Khalid, S.; Brown, D. R.; Rothenberg, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 9615.
(175) Motokura, K.; Tada, M.; Iwasawa, Y. *J. Am. Chem. Soc.* **2009**, *131*, 7944.
(176) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2005**, *127*, 9674.
(177) Serra-Crespo, P.; Ramos-Fernandez, E. V.; Gascon, J.; Kapteijn, F. *Chem. Mater.* **2011**, *23*, 2565.
(178) Srirambalaji, R.; Hong, S.; Natarajan, R.; Yoon, M.; Hota, R.; Kim, Y.; Ko, Y. Y. H.; Kim, K. *Chem. Commun.* **2012**, *48*, 11650.
(179) Roman-Leshkov, Y.; Barrett, C. J.; Liu, Z. Y.; Dumesic, J. A. *Nature* **2007**, *447*, 982.
(180) Kuster, B. F. M.; Vanderbaan, H. S. *Carbohydr. Res.* **1977**, *54*, 165.
(181) Moreau, C.; Durand, R.; Razigade, S.; Duhamet, J.; Faugeras, P.; Rivalier, P.; Ros, P.; Avignon, G. *Appl. Catal., A* **1996**, *145*, 211.
(182) Carlini, C.; Giuttari, M.; Galletti, A. M. R.; Sbrana, G.; Armaroli, T.; Busca, G. *Appl. Catal., A* **1999**, *183*, 295.
(183) Takagaki, A.; Ohara, M.; Nishimura, S.; Ebitani, K. *Chem. Commun.* **2009**, 6276.
(184) Moliner, M.; Roman-Leshkov, Y.; Davis, M. E. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 6164.
(185) Roman-Leshkov, Y.; Moliner, M.; Labinger, J. A.; Davis, M. E. *Angew. Chem., Int. Ed.* **2010**, *49*, 8954.
(186) Nikolla, E.; Roman-Leshkov, Y.; Moliner, M.; Davis, M. E. *ACS Catal.* **2011**, *1*, 408.
(187) Otomo, R.; Yokoi, T.; Kondo, J. N.; Tatsumi, T. *Appl. Catal., A* **2014**, *470*, 318.
(188) Fraile, J. M.; Mallada, R.; Mayoral, J. A.; Menendez, M.; Roldan, L. *Chem. Eur. J.* **2010**, *16*, 3296.
(189) Arhancet, J. P.; Davis, M. E.; Merola, I. S.; Hanson, H. E. *Nature* **1989**, *339*, 454.
(190) Bhanage, B. M.; Fujita, S. I.; Yoshida, T.; Sano, Y. *Tetrahedron Lett.* **2003**, 3505.
(191) Thiot, C.; Schmutz, N.; Wagner, A.; Mioskowski, C. *Chem.—Eur. J.* **2007**, *13*, 8971.
(192) Thiot, C.; Schmutz, M.; Wagner, A.; Miokowski, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 2868.
(193) Arnanz, A.; Pintado-Sierra, M.; Corma, A.; Iglesias, M.; Sánchez, F. *Adv. Synth. Catal.* **2012**, *354*, 1347.
(194) Park, K.; Ni, Z.; Cote, A. P.; Choi, J. T.; Uribe-Romo, H. K.; Chae, R.; Huang, M.; Keeffe, O.; Yagh, O. M. *Proc. Natl. Acad., Sci., U.S.A.* **2006**, *103*, 10186.
(195) Baburin, I. A.; Leoni, S.; Seifert, G. *J. Phys.Chem. B* **2008**, *2008*, 9437.
(196) Alanine, A.; Burner, S.; Buettelmann, B.; Heitz, N. M.; Jaeschke, E.; Pinard, E.; Wyler, R. Patent EP1090917, 2001.
(197) Bhagwat, S. S.; Gayo, L. M.; Stein, Q.; Chao, A.; Gangloff, A.; Mckie, J.; Rice, K. Patent WO 0055137, 2000.
(198) Johnson, C. N.; Stemp, G. PatentWO 0021950, 2000.
(199) Alvarez, R.; Velázquez, S.; San, F.; Aquaro, S.; Declercq, C.; Perno, C. F.; Karlsson, A.; Balzarini, J.; Camarasa, M. J. *J. Med. Chem.* **1994**, *37*, 4185.
(200) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem.* **2000**, *43*, 953.
(201) Tatsuta, K.; Ikeda, Y.; Miura, S. *J. Antibiot.* **1996**, *49*, 836.